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KIDNEYWEEK 2017

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Abstract Supplement

Abstract Publication
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- Special Sessions
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TH-OR001

Comorbid Disease Trends in Hemodialysis and Peritoneal Dialysis Patients Rita L. McGill,[3] Jennifer L. Bragg-Gresham,[2] Kevin He,[2] Eduardo K. Lacson,[1] Dana Miskulin,[1] Rajiv Saran.[2] *[1]Tufts University School of Medicine, Boston, MA; [2]University of Michigan, Ann Arbor, MI; [3]University of Chicago, Chicago, IL.*

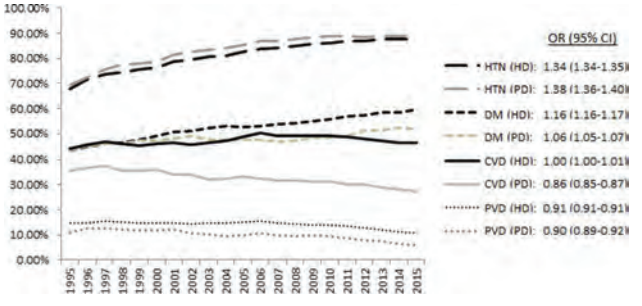
Background: The US Renal Data System has collected comorbid conditions data on incident hemodialysis (HD) and peritoneal dialysis (PD) patients since 1995. We evaluated the prevalence of several comorbid conditions over 20 years, and compared trends in both groups.

Methods: All first-time HD and PD patients 1996-2015 were included, and analyzed by year of initiation. Diabetes (DM) and cardiovascular disease (CVD) were condensed into single variables, to align data obtained from the 1995 and 2005 Medical Evidence forms. The proportions of co-morbid conditions were evaluated with logistic regression, treating year of initiation as a continuous variable, stratifying by dialysis type, and adjusting for age, sex, and race. Five year prevalence trends were expressed as odds ratios (OR) and 95% confidence intervals, with OR > 1 representing increasing prevalence.

Results: Among 1,864,386 HD and 157,395 PD patients, the mean age increased by 3 years; PD patients were consistently 5-6 years younger than HD patients. CVD decreased in PD but remained flat in HD. In HD patients, hypertension (HTN), DM and lung disease (COPD) increased and peripheral vascular disease (PVD) decreased. PD patients had a smaller increase in DM, and COPD and PVD decreased, but HTN increased. Stroke and cancer did not change significantly over time. Five-year OR's are shown below.

Conclusions: While HD and PD patients in the United States are both becoming older, and increasingly hypertensive and diabetic, the comorbid disease burdens have been diverging over the past 20 years, resulting in PD patients having less DM, CVD, and COPD than their counterparts receiving HD.

Funding: NIDDK Support



Time trends in Comorbid Diseases over 20 years, for HD and PD Patients

TH-OR002

Racial Disparities in Coronary Artery Bypass Graft Surgery in Maintenance Dialysis Patients Robert Nee,[3,4] Keith C. Norris,[2] Christina M. Yuan,[3,4] Lawrence Agodoa,[1] Kevin C. Abbott.[1] *[1]NIDDK, National Institutes of Health, Bethesda, MD; [2]Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA; [3]Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; [4]Medicine, Uniformed Services University, Bethesda, MD.*

Background: Racial disparities in invasive cardiac procedures such as coronary artery bypass graft (CABG) in the general population are well documented. However, contemporary national-level data on such disparities in the end-stage renal disease (ESRD) population are lacking. Herein we assessed racial differences in the receipt of CABG between Blacks and Whites with ESRD, after the start of maintenance dialysis.

Methods: Using the US Renal Data System database, we identified 281,464 Medicare primary patients initiated on maintenance dialysis from 1 January 2009 through 1 June 2013, and followed until 31 December 2013. We abstracted Medicare hospital claims for CABG among patients who had primary diagnoses of either native coronary atherosclerosis (NCA) or acute myocardial infarction (AMI). We conducted logistic regression analyses, adjusted for demographic characteristics, Hispanic ethnicity, cause of ESRD, comorbidities, socioeconomic factors (insurance type to include Medicare-Medicaid dual eligibility as a proxy measure of individual-level poverty, employment status, and ZIP code-level median household income [MHI] obtained from the 2010 US Census).

Results: 8,004 patients underwent CABG surgery during the study period, of whom 19.4% were Blacks and 74.6% were Whites. Fully adjusted models demonstrated that, among patients with primary diagnoses of NCA or AMI, Blacks were significantly less likely to undergo CABG compared to Whites (odds ratio [OR] 0.76, 95% CI 0.64-0.90, p=0.002). The odds were similar in non-Hispanic Blacks vs. non-Hispanic Whites (OR 0.74, 95% CI 0.62-0.88, p=0.001). There were no significant interactions between race and ZIP code-level MHI (p=0.31), or dual-eligibility status (p=0.60).

Conclusions: Similar to the general population, there exists a racial gap among incident dialysis patients undergoing CABG surgery despite having comprehensive coverage with Medicare. These findings persisted despite accounting for demographic, clinical and socioeconomic factors. *Disclaimer: The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of the Army/Navy/Air Force, the Department of Defense, National Institutes of Health, or the United States government.*

TH-OR003

Clinical Effects of Molecular Hydrogen (H2) Delivery during Hemodialysis in Chronic Dialysis Patients: Five Years Prospective Observational Study Masaaki Nakayama,[4] Wan-Jun Zhu,[4] Tae Yamamoto,[2] Mariko Miyazaki,[3] Sadayoshi Ito.[1] *[1]Tohoku Graduate School of Medicine, Sendai Miyagi, Japan; [2]Tohoku University, Sendai, Japan; [3]Tohoku University Hospital, Sendai, Japan; [4]Tohoku University, Tohoku University Hospital, Sendai City, Japan.*

Background: Enhanced oxidative stress and inflammation are supposed to play a crucial role for poor clinical outcomes in patients on chronic hemodialysis (HD) treatment. Recent studies have revealed unique biological characteristics of molecular hydrogen (H_2) as an anti-inflammatory agent. Thus, we developed a novel hemodialysis (E-HD) system which delivers H_2 (30 to 80 ppb)-enriched dialysis solution by water electrolysis technique, and conducted a prospective study (UMIN000004857) to study the clinical impact of E-HD as compared to the conventional-HD (C-HD).

Methods: Prevalent chronic HD patients (n=309, mean HD vintage, 7.8 years; age, 66 years old; male, 57%; history of cardio- and cerebro-vascular disease (CVD), 29%) were registered from 7 HD centers in Japan (from Mar 2011 to Dec 2012), and allocated to either E-HD (n= 161), orC-HD (n=148). They had been treated by the respective HD treatments during the study. Primary end-point was composite of all-cause of mortality, and development of non-lethal CVDs (apoplexy, cardiac diseases, and peripheral artery disease).

Results: During the five-year observation periods (end of Oct 2016), no differences were found in dialysis parameters between the two groups. However, there were uniquechanges in clinical profiles in patients on E-HD, i.e. significant reduction in post-HD systolic BP in those who had remained hypertensive state after HD at baseline, which was accompanied by significant reductions ofprescriptions of anti-hypertensive agents. There were 91 events during the mean observation periods of 3.28 years. The number of primary events were 50 cases in C-HD (17 in death and 29 in CVD: Event Rate; 107.1 /1000 patients-year:95%CI:81.2-141.1), and 41 cases in E-HD (20 in death and 20 in CVD:Event Rate;75.4:55.6-102.2), respectively. Multivariate analysis of Cox proportional hazard model revealed that E-HD was an independent significant factor for the primary event (HR 0.59, 95%CI:0.38-0.92) after adjusting for confounding factors (age, history of CVD, serum albumin, and CRP).

Conclusions: The data indicates E-HD could improve prognosis of chronic HD patients, through the unique BP control effect during HD treatment.

Funding: Commercial Support - Nihon Trim. Co, Government Support - Non-U.S.

TH-OR004

Increased Risk of Premature Cerebral Small Vessel Diseases in Dialysis Patients: A Cross-Sectional Controlled Study Ke Zheng, Haiyun Wang. *Peking Union Medical College Hospital, Beijing, China.*

Background: Growing evidence suggests a higher prevalence of cerebrovascular diseases in patients with end-stage renal disease and undergoing dialysis. As an important cause of stroke, dementia or disability, cerebral small vessel disease (CSVD) has been recognized recently. However, discovery of CVSD needs brain resonance imaging (MRI) scan. There were only small sample size non-controlled study in this field. These limited us to get a further understanding of CSVD in dialysis population. By now, a comprehensive controlled assessment of CSVD in a dialysis cohort of large sample size is lacking.

Methods: In this cross-sectional controlled study, we enrolled a total of 179 dialysis patients (116 in hemodialysis (HD) and 63 in peritoneal dialysis (PD)) and 351 matched non-chronic kidney disease (CKD) controls. We collected detailed clinical characteristics and all participants underwent brain MRI. We assessed and compared the presence and location of CSVD in the dialysis patients and controls, including lacunes, microbleeds, and white matter hyperintensities (WMH). We used univariable and multivariable logistic regression to investigate the risk factors.

Results: Prevalence of the CSVD lesions were significantly higher in the dialysis patients compared with non-CKD controls (OR: 1.86 (95% CI 1.23–2.81) in lacunes; 3.61 (95% CI2.32–5.61) in microbleeds; 1.92 (95% CI 1.31–2.82) in WMH). In dialysis patients, the majority of lacunes were detected in the subcortical white matter and basal ganglia, while the majority of the microbleeds were found in the lobes and basal ganglia. After adjusting age, dialysis vintage, hypertension, diabetes mellitus (DM), hyperlipidemia, smoking and drinking habits, significantly increased risk was observed in the dialysis patients for microbleeds (OR 2.82, 95% CI1.70-4.65) and WMH with total Fazekas larger than two (OR 2.04,95% CI1.25-3.34). Finally, the age of lesion detection was significantly smaller in dialysis patients ((p=0.017, 0.004 and 0.020 for lacunes, microbleeds and WMH). In our dialysis cohort, these was no significant differences in all three types of CSVD lesions between HD and PD modality.

Conclusions: Patients on dialysis were associated with significantly increased risk of CSVD comparing with controls, they also demonstrated a tendency premature CSVD.

Funding: Government Support - Non-U.S.

TH-OR005

Intradialytic Hypertension Frequency and Short-Term Clinical Outcomes among Hemodialysis Patients Magdalene M. Assimon, Jennifer E. Flythe. *University of North Carolina, Chapel Hill, NC.*

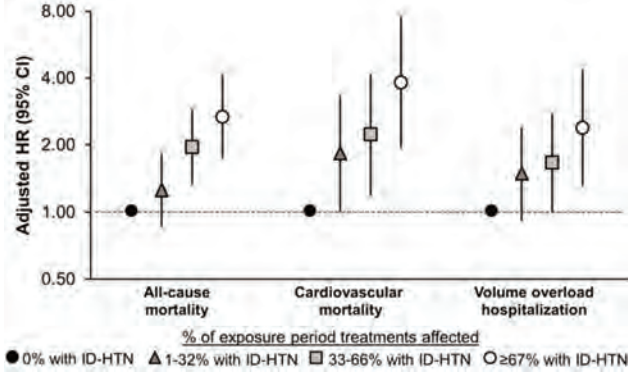
Background: Intradialytic hypertension (ID-HTN) occurs in 5-20% of hemodialysis treatments. Observational data support an association between ID-HTN and increased long-term mortality. However, the short-term cardiovascular (CV) consequences of recurrent ID-HTN are unknown.

Methods: Data were taken from a cohort of prevalent hemodialysis patients receiving treatment at a large U.S. dialysis organization on 01/01/2010. Using a retrospective cohort design with a 180-day baseline, 30-day exposure assessment and 30-day follow-up period, we estimated the association between ID-HTN frequency and: 1) 30-day mortality and 2) 30-day hospitalizations. We defined ID-HTN frequency during the 30-day exposure period as the proportion of hemodialysis treatments with a pre- to post-dialysis systolic blood pressure (BP) rise >0 mmHg. Multivariable Cox proportional hazards models, adjusting for numerous clinical, laboratory and dialysis treatment covariates, were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: Of 37,094 study patients, 5,242 (14%), 17,965 (48%), 10,821 (29%), 3,066 (8%) had ID-HTN in 0%, 1-32%, 33-66% and ≥67% of exposure period treatments, respectively. More frequent ID-HTN was associated with incremental increases in 30-day mortality and volume overload hospitalizations (**Figure**). Patients with ID-HTN in ≥67% (vs. 0%) of exposure period treatments had the highest risk of all-cause death, adjusted HR [95% CI]: 2.6 [1.7-3.9]; CV death, 3.7 [1.9-7.1]; and volume overload hospitalizations, 2.3 [1.3-4.2]. Analogous incremental associations were observed for all-cause and CV hospitalizations. In sensitivity analyses, use of alternative BP thresholds (≥5 and ≥10 mmHg) to define ID-HTN yielded similar results (data not shown).

Conclusions: Among prevalent hemodialysis patients, ID-HTN frequency is incrementally associated with short-term morbidity and mortality. Randomized trials are needed to determine if ID-HTN frequency mitigation improves patient outcomes.

Funding: NIDDK Support



TH-OR006

Pre ESRD Coronary Artery Revascularization and Post ESRD Mortality Abduzhappar Gaipov,[4] Miklos Z. Molnar,[4] Praveen Kumar Potukuchi,[4] Keiichi Sumida,[2] Robert B. Canada,[4] Oguz Akbilgic,[4] Kairat Kabulbayev,[1] Kamyar Kalantar-Zadeh,[3] Csaba P. Kovesdy.[4] *[1]Kazakh national medical university, Almaty, Kazakhstan; [2]Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; [3]University of California Irvine, School of Medicine, Orange, CA; [4]University of Tennessee Health Science Center, Memphis, TN.*

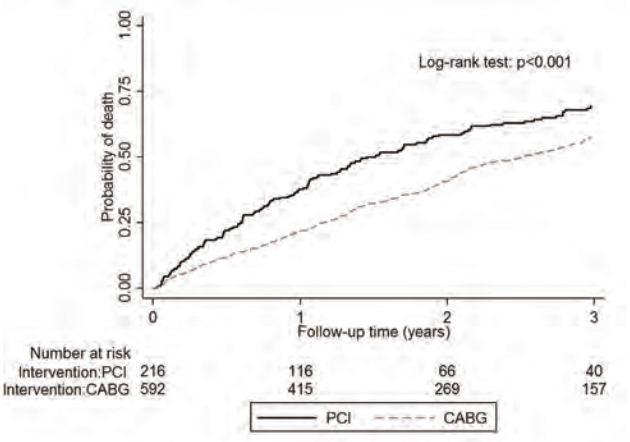
Background: Coronary artery bypass grafting (CABG) is associated with better survival than percutaneous coronary intervention (PCI) in patients with mild-to-moderate CKD and ESRD. However, the optimal strategy for coronary artery revascularization in advanced CKD patients who transition to ESRD is unclear.

Methods: We examined a contemporary national cohort of 815 US veterans with incident ESRD, who underwent first CABG or PCI up to 5 years prior to dialysis initiation. We examined the association of CABG versus PCI with all-cause mortality following transition to dialysis, using Cox proportional hazards models adjusted for time to dialysis start, sociodemographics, comorbidities and medications.

Results: 596 patients underwent CABG and 219 patients underwent PCI. The mean age was 66±8 years, 99% of patients were male, 78% were white, 20% were African Americans, and 84% were diabetic. The all-cause post-dialysis mortality rates after CABG and PCI were 301/1000 patient-years (PY) [95% CI=271–333] and 436/1000PY [95% CI=371–512], respectively. Mortality was lower after CABG (Figure). The multivariable adjusted hazard ratio of all-cause mortality in patients who underwent CABG compared to PCI was 0.72 (95% CI=0.58–0.89, p=0.003).

Conclusions: In patients with advanced CKD CABG is associated with lower risk of post-ESRD death compared to PCI.

Funding: NIDDK Support



TH-OR007

Association of Peridialytic Systolic Blood Pressure Change and Pre-Dialysis Systolic Blood Pressures on Mortality among Hemodialysis Patients Hanjie Zhang,[6] Priscila Preciado,[7] Yuedong Wang,[2] Anna Meyring-Wosten,[6] Alice Topping,[6] Jochen G. Raimann,[6] Jeroen Kooman,[4] Frank van der Sande,[5] Len A. Usvyat,[3] Dugan Maddux,[3] Franklin W. Maddux,[1] Peter Kotanko.[6] *[1]Fresenius Medical Care, Waltham, MA; [2]University of California - Santa Barbara, Santa Barbara, CA; [3]Fresenius Medical Care North America, Melrose, MA; [4]Maastricht University Medical Centre, Maastricht, Netherlands; [5]Maastricht University Medical Centre, Maastricht, Netherlands; [6]Renal Research Institute, New York, NY; [7]Renal Research Institute, New York, NY.*

Background: Pre-dialysis systolic blood pressure (pre-SBP) and peridialytic SBP change (ΔSBP) had been associated with mortality in former studies, but the nature of this interaction is still not fully explained.

Methods: Pre-SBP and ΔSBP (post-HD – pre-HD) were analyzed between 1/2001 and 12/2012 in HD patients treated in Fresenius Medical Care (FMC) facilities. Baseline was defined as months 4-6 in the first year of HD, the primary outcome was all-cause mortality. Censoring events were renal transplantation, modality change, or study end. Only patients who survived the baseline and had no missing covariates were included. We fitted Cox proportional hazard model with a bivariate spline for the primary predictors, pre-SBP and ΔSBP, with adjustment for age, gender, race, diabetes, access-type, relative interdialytic weight gain (IDWG), body mass index (BMI) and albumin, enPCR, and ultrafiltration rate (≥13 or <13 mL/kg body weight/hour).

Results: A total of 191 491 patients were included. We found that a peridialytic SBP increase in the presence of high pre-SBP was associated with an increased mortality, while in patients with low pre-SBP a peridialytic SBP increase was associated with better survival **(Fig. 1)**.

Conclusions: We showed association of pre-SBP and peridialytic SBP changes with all-cause mortality in a large and diverse HD population. Patients with low pre-SBP may benefit from an increase in peridialytic SBP, while an increase in SBP may be detrimental in patients with a high pre-SBP.

Funding: Commercial Support - Fresenius Medical Care

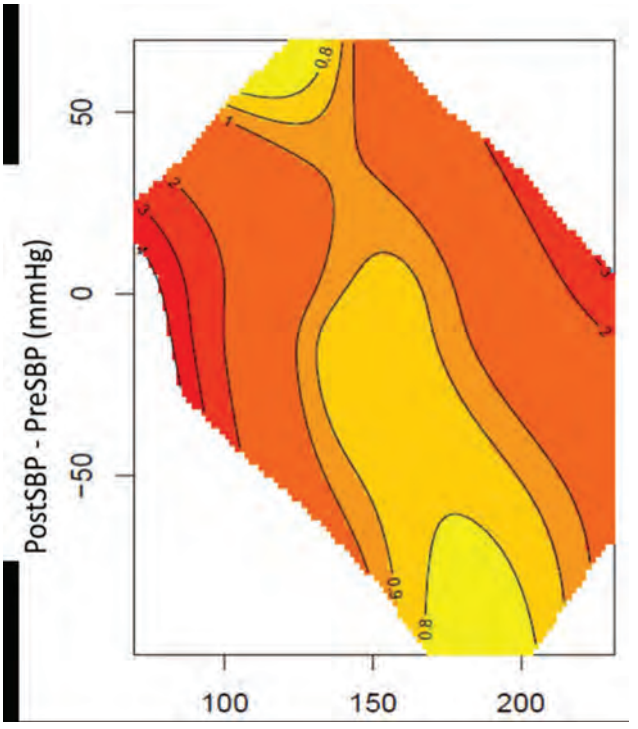


Figure 1: Contour plot showing the relationship between pre-SBP, ΔSBP and hazard ratios (HR) for all-cause mortality. Contour lines indicate discrete HR levels.

TH-OR008

Individualized Cool Dialysate as an Effective Therapy for Intradialytic Hypotension Alexander Bullen,[2,1] Dena E. Rifkin,[2,1] Danuta Trzebinska.[3] *[1]La Jolla, CA; [2]UCSD, San Diego, CA; [3]UCSD Medical Center, SAN DIEGO, CA.*

Background: Intradialytic hypotension (IDH) is the most common dialytic complication identified in 15-20% of all dialysis encounters. Cool dialysate by promoting peripheral vasocontriction leads to decreased IDH and may be an effective approach to reduce IDH. However, only small studies have been done to date using a cool dialysate and they have not typically used an individualized cool dialysate temperature. Therefore, we designed a study to determine if cool dialysate would decrease the number of episodes of IDH in a high-comorbidity dialysis population served within our hospital.

Methods: We conducted a single center study at the UCSD dialysis unit. Baseline characteristics were obtained from the electronic medical record including age, race, and co-morbidities. The study consisted of baseline and intervention phases, with patients serving as their own controls. In the first phase, core baseline temperature (CBT) was determined as an average of oral temperature prior to three sessions of hemodialysis. During this phase hemodynamic parameters during dialysis were recorded for 6 HD sessions. In the second phase, the CBT was then decreased by 0.5 degrees Celsius and hemodynamic parameters were then collected again for 6 more HD sessions. Parameters during the control phase and cool phase were compared.

Results: 93 participants with mean age was 56.7±1.5 were included. 53% were women, and 53.8% were Hispanic. The average years on HD were 4.7±0.5 years. The number of IDH episodes between the control and the cool phase, decreased significantly (P<0.001) from 3.27±0.29 per patient to 1.96±0.23. The lowest recorded intradialytic MAP increased from 78.22±1.60 mmHg to 85.60±1.20 mmHg, the mean increase was of 4.75±2.12 (P=0.028). No correlation was found between a change in UF and improved hemodynamics (P=0.22). Adequacy of HD (Kt/v) did not change significantly (P=0.75).

Conclusions: Individualized cool dialysate is an effective and easy to implement method to decrease intradialytic hypotension and it may ameliorate clinical symptoms and ease nursing burden in patients with frequent IDH.

BP (mm Hg)	Control phase	Cool Dialysate phase	Mean Difference	P-value
Pre-HD (standing)				
-SBP	149.9	155.5	5.59	0.15
-DBP	80.41	81.9	1.48	0.54
-MAP	103.6	106.4	2.85	0.25
Pre-HD (sitting)				
-SBP	149.3	155.3	6.01	0.08
-DBP	79.8	83.0	3.24	0.12
-MAP	103.1	107.1	4.02	0.06
Lowest Intradialytic Pressure				
-SBP	106.3	112.6	6.3	0.03
-DBP	63.2	75.9	4.0	0.04
-MAP	78.2	85.6	4.8	0.03
Post-HD (standing)				
-SBP	125.5	138.5	13.0	<0.001
-DBP	69.25	75.9	6.6	0.001
-MAP	88.0	96.7	8.7	<0.001
Post-HD (sitting)				
-SBP	132.7	140.4	7.6	0.02
-DBP	72.9	76.2	3.3	0.09
-MAP	92.9	97.6	4.8	0.02

TH-OR009

Ratio of Early Mitral Inflow Velocity to Global Diastolic Strain Rate and Global Left Ventricular Longitudinal Systolic Strain Predicts Overall Mortality and Cardiovascular Events in Hemodialysis Jiun-Chi Huang,[1,2] Szu-Chia Chen,[1,2] Jer-Ming Chang.[2,3] *[1]Department of Internal Medicine, Kaohsiung Municipal Hsiao-Kang Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [2]Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan; [3]Department of Internal Medicine, Kaohsiung Municipal Cijin Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan, Kaohsiung, Taiwan.*

Background: The associations between the ratio of early mitral inflow velocity (E) to global diastolic strain rate (E'sr) and global left ventricular longitudinal systolic strain (GLS) obtained from two-dimensional speckle-tracking echocardiography with cardiovascular (CV) outcomes remain unclear in patients undergoing hemodialysis (HD). This study aimed to examine the ability of E/E'sr ratio and GLS to predict overall mortality and CV events in maintenance HD patients.

Methods: Echocardiography was performed in 190 HD patients. E'sr and GLS were measured from three standard apical views using the index beat method. CV events were defined as CV death, non-fatal stroke, coronary artery disease, peripheral artery disease and heart failure.

Results: During the mean follow-up period of 2.7 years, 28 patients died and 28 CV events were recorded. After multivariate adjustment, the E/E'sr ratio (hazard ratio [HR]: 1.561; 95% confidence interval [CI], 1.221–1.995) and GLS (HR: 1.229; 95% CI, 1.061–1.423) were associated with overall mortality. Furthermore, the E/E'sr ratio (HR: 1.233; 95% CI, 1.001–1.518) and GLS (HR: 1.299; 95% CI, 1.104–1.529) were both associated with CV events in multivariate analysis. The E/E'sr ratio and GLS had a better predictive ability of overall mortality and CV events than the ratio of E to early diastolic mitral annular velocity (E') and left ventricular ejection fraction (LVEF). Moreover, adding the E/E'sr ratio and GLS to a clinical model with conventional echocardiographic parameters improved the prediction of both mortality ($p = 0.002$) and CV events ($p < 0.001$).

Conclusions: The E/E'sr ratio and GLS are stronger than the E/E' ratio and LVEF in predicting unfavorable outcomes, and may provide additional prognostic value to conventional clinical and echocardiographic parameters in maintenance HD patients.

Predictive values of echocardiographic parameters in relation to overall and cardiovascular events

Parameters	Overall mortality		Cardiovascular events	
	difference in likelihood ratio	p	difference in likelihood ratio	p
Basic model + ABI < 0.9, baPWV, CTR, AoAC	17.667	0.001	21.900	<0.001
Basic model + ABI < 0.9, baPWV, CTR, AoAC + LAVI, LVMI, LVEF, E/E'	16.212	0.003	31.541	<0.001
Basic model + ABI < 0.9, baPWV, CTR, AoAC + LAVI, LVMI, LVEF, E/E' + E/E'sr, GLS	12.195	0.002	97.735	<0.001

p value was based on the incremental value compared with the basic model which was adjusted for demographic, clinical, and biochemical risk factors

TH-OR010

Hemodialysis Induces Decline in Cerebral Blood Flow in Elderly Patients: A Quantitative [15O]H2O-PET-CT Study Harmke A. Polinder-Bos,[3] David Vállez,[3] Johanna J. Kuipers,[4] Jan willem Elting,[3] Marcel Aries,[5] Henk Groen,[3] Wim Krijnen,[2] Antoon Willemsen,[3] Peter Jan van Laar,[3] Fijanne Strijkert,[3] Gert Luurtsema,[3] Riemer hja Slart,[3] Ralf Westerhuis,[1] Ron T. Gansevoort,[3] Carlo A. Gaillard,[3] Casper F. Franssen.[3] *[1]Dialyses Center Groningen, Groningen, Netherlands; [2]Hanze University of Applied Sciences, Groningen, Netherlands; [3]University Medical Center Groningen, Groningen, Netherlands; [4]Dialyse Centrum Groningen, Groningen, Netherlands; [5]Maastricht University Medical Center, Maastricht, Netherlands.*

Background: The transition to hemodialysis (HD) is associated with a decline of cognitive function and an increased incidence of cerebrovascular accidents and white matter lesions. It has been hypothesized that the repetitive circulatory stress of

HD induces ischemic injury to the brain, but the mechanism is unclear. Despite the sophisticated regulation of the brain to keep the cerebral blood flow (CBF) steady, HD might induce a fall in CBF. We evaluated whether a change in CBF occurred during a HD session, measured by [^{15}O]H_2O-PET-CT, which is considered the gold standard for measuring CBF.

Methods: Twelve maintenance HD patients aged ≥65 years, (5 females, 7 males) with a median dialysis vintage of 3.8 years, participated in this observational study. During a single HD session three [^{15}O]H_2O-PET-CT scans were performed: before, early after the start, and at the end of HD. For each PET-CT scan a bolus injection of [^{15}O]H_2O was administered intravenously in the non-dialysis access arm, and arterial blood was continuously sampled from the arteriovenous fistula. Dialysate temperature was 36.5°C. Mixed linear models were used to study global and regional CBF change during HD.

Results: Mean arterial pressure declined non-significantly from 101±11 before HD to 93±17mmHg at the end of HD, whereas pCO_2 remained stable. The PET-CT scan at the end of the HD session showed a significant 10 (±15)% decline in global CBF from a mean of 34.5 to 30.5 ml/100g/min (difference: -4.0 ml/100g/min [-7.3; -0.7], P=0.01). CBF fell significantly in all regions of interest: the frontal, parietal, temporal, and occipital lobes, cerebellum and thalamus. The largest CBF reductions were observed in the thalamus (-5.2 ml/100g/min [-8.8; -1.6], P=0.001) and frontal lobe (-5.1 ml/100g/min [-7.7; -2.5], P<0.0001).

Conclusions: Conventional HD induces a significant reduction in CBF in elderly patients. This finding fits well into the hypothesis that HD induces ischemic injury to the brain, which in the long-term might contribute to cognitive function decline, especially in elderly HD patients.

TH-OR011

New Intravital Imaging Technique Visualizes Renal ATP Dynamics during AKI Predicting Renal Prognosis Shinya Yamamoto,[1] Masamichi Yamamoto,[1,2] Motoko Yanagita.[1] *[1]Nephrology, Kyoto University Graduate School of Medicine, Kyoto, Japan; [2]Japan Science and Technology Agency, PRESTO, Tokyo, Japan.*

Background: The kidney constantly produces and consumes adenosin 5' triphosphate (ATP), and mitochondrial dysfunction, which leads to ATP depletion, plays an important role in the pathogenesis of renal diseases. In spite of importance of ATP dynamics, however, lack of technology has hindered further analysis. Here we established a novel ATP intravital imaging technique and analyzed whether the ATP dynamics during acute kidney injury (AKI) could predict the renal prognosis.

Methods: To enable intravital imaging of ATP dynamics, we generated a novel mouse line, which expressed the FRET-based ATP biosensor in all tissues. We visualized renal ATP dynamics at a single cell level in the physiological condition as well as in ischemic reperfusion (IR) model with two-photon microscope. Furthermore, we performed the quantification of fibrosis two weeks after IR, and assessed the correlation between the ATP recovery and fibrosis.

Results: The ATP levels in proximal tubules (PTs) rapidly decreased to the basal level in only 2 minutes after induction of ischemia, whereas the ATP levels in distal tubules (DTs) were maintained even after 30 minutes. The ATP dynamics in PTs after reperfusion was variable depending on the duration of ischemic time. The ATP recovery in PTs after 15, 30, and 60 minute-IR took 2, 5, and 30 minutes to reach a peak plateau, and the % ATP recovery (recovery ATP/ initial ATP levels) were 90%, 83%, and 69%, respectively. The longer ischemic time led to slower and more insufficient ATP recovery in PTs. Interestingly, ATP recovery time and the % ATP recovery in DTs were 4 minutes and 90% even after 60 minute-IR, indicating the tolerance of DTs to ischemia. The longer ischemic led to more significant renal fibrosis in chronic phase, and the fibrosis was inversely well correlated with the ATP recovery slopes in PTs in acute phase.

Conclusions: We, for the first time, succeeded in visualizing the spatiotemporal ATP dynamics in the kidney by generating a novel FRET-based ATP biosensor mice. We demonstrated the rapid reduction of ATP in PTs and the slow reduction in DTs after ischemia. After reperfusion, the rate and sufficiency of ATP recovery were dependent on the severity of injury, and the ATP dynamics in the acute phase might determine the outcome in chronic phase. We also confirmed the tolerance of DTs to ishemia from the point of ATP dynamics.

TH-OR012

Activated CD47 Promotes AKI by Limiting Autophagy Natasha M. Rogers, Barkha Sanganeria, Maryam El-Rashid. *Westmead Institute for Medical Research, Sydney, NSW, Australia.*

Background: Renal ischemia reperfusion injury (IRI) initiates a complex pathophysiological cascade leading to epithelial cell death manifesting as acute kidney injury. Recent studies identify autophagy, the mechanism of intracellular degradation of cytoplasmic constituents, as important in protection against injury. We have reported that the protein thrombospondin-1 (TSP1), and its receptor CD47, are induced in renal IRI, however the mechanism underlying the regulation of renal injury is unknown.

Methods: Age and gender-matched wild-type (WT) and CD47$^{-/-}$ mice were challenged with bilateral renal IRI. All animals underwent analysis of renal function and biomolecular phenotyping. Human and murine WT and CD47$^{-/-}$ renal tubular epithelial cells (rTEC) were studied *in vitro*.

Results: CD47$^{-/-}$ mice were resistant to renal IRI at multiple time-points following reperfusion (24 h, 72 h, 168 h), with significantly decreased urea and creatinine (2.1±0.5 *vs* 0.9±0.3 mg/dl at 24 h, p<0.001), and ameliorated histological changes compared to WT animals. CD47$^{-/-}$ mice demonstrated concurrent upregulation of key autophagy genes, including Atg5, Atg7, Beclin-1, and LC3 at baseline and at all reperfusion time-points. WT mice consistently demonstrated negligible autophagy expression in the kidney. However, p62 expression was not significantly different between WT and CD47$^{-/-}$ mice. rTEC from CD47$^{-/-}$ mice displayed basal upregulation of autophagy genes that was preserved under exogenous stress (hypoxia, FiO_2 1%, or treatment with TSP1, 2.2nM for 24 h), and this correlated with enhanced viability when compared to WT cells. Treatment of WT rTEC with an oligonucleotide to block TSP1-CD47 signalling increased autophagy. Human rTEC similarly demonstrated downregulated autophagy in response to exogenous TSP1, which was mitigated in conjunction with a CD47-blocking antibody. Finally, in a syngeneic mouse kidney transplantation model, treatment with a CD47-blocking antibody improved renal function and decreased histologic damage compared to control mice, and this was associated with increased autophagy.

Conclusions: These data suggest activated CD47 is a proximate promoter of renal IRI through inhibition of autophagy and cell viability, and point to CD47 as a target to restore renal function following injury.

Funding: Government Support - Non-U.S.

TH-OR013

JNK1 Promotes Renal Ischaemia-Reperfusion Injury Keren Grynberg,[1] Elyce Ozols,[1] William R. Mulley,[1] Kate Blease,[2] David J. Nikolic-Paterson,[1] Frank Y. Ma.[1] *[1]Department of Nephrology, Monash Medical Centre, Monash, Victoria, Austria; [2]Celgene, San Diego, CA.*

Background: Tubular activation of the c-Jun amino-terminal kinase (JNK) pathway is prominent in most forms of acute and progressive tubulointerstitial damage, including renal ischaemia/reperfusion (I/R) injury. Both *Jnk1* and *Jnk2* genes are expressed in most cells of the kidney resulting in considerable redundancy. Combined blockade of JNK1/2 is known to be protective in renal I/R injury; however, the relative contribution of each isoform is unknown. The aim of this study is to determine the relative contribution of JNK1 versus JNK2 in renal I/R injury.

Methods: Preferential pharmacological inhibition of JNK1 (CC90001) was compared to mice with global deletion of *Jnk1* or *Jnk2* and mice with combined global Jnk2 deletion plus Jnk1 deletion in proximal tubular cells (*Jnk-PT* mice). Bilateral warm renal ischaemia injury was induced with vascular clamps and animals killed 24hr after reperfusion. Controls were sham operated. Sprague-Dawley rats (n=8-10/group) were treated 3 times with CC-90001 (10mg/kg) or vehicle starting 1 hour prior to surgery. Renal I/R injury studies were also performed in *Jnk1-/-* (n=10), *Jnk2-/-* (n=8), *Jnk PT* (n=8) and wild type (WT) mice (n=10).

Results: Treatment with CC-90001 provided significant protection in rat I/R injury (8±0.5 vs 20±2 fold increase in serum creatinine (sCR), drug versus vehicle, respectively; P<0.001). In a separate study, *Jnk1-/-* mice also showed significant protection from I/R injury compared to WT mice (4±0.5 vs 8±1 fold increase in sCr respectively; p=0.01); however, this was not replicated in *Jnk2-/-* mice (16±0.5 vs 15±2 fold increase in sCr, *Jnk2-/-* versus WT, respectively; p=NS). *Jnk-PT* mice exposed to renal I/R injury showed significant protection from injury compared to WT mice (5.5±0.7 vs 15±2 fold increase in sCr respectively p<0.01). CC-90001 treatment reduced tubular damage and macrophage infiltration. This protection was replicated in *Jnk1-/-* and *Jnk-PT* mice.

Conclusions: Using complementary approaches, we have established that JNK1 in the proximal tubule is crucial for renal IR injury. Prophylactic JNK1 inhibition may have clinical utility in anticipated renal IR injury.

Funding: Commercial Support - Celgene, Government Support - Non-U.S.

TH-OR014

A Snapshot of RNA Expression in a Single Segment of the Kidney Reveals Stimulus Specific Responses Katherine Xu,[3] Jacob Stauber,[2] Jonathan M. Barasch.[1] *[1]Columbia Presbyterian, New York, NY; [2]Columbia University, New York, NY; [3]None, East Elmhurst, NY.*

Background: The identification of acute kidney disease at the time of patient encounter remains a central problem in clinical medicine. A single analyte, the serum creatinine (sCr) is currently in use as a surrogate for tubular, vascular, or interstitial cellular damage. Nonetheless the sCr test is not specific to kidney injury, but rather might reflect physiological responses to a the primary disease in a distant organ. In addition, while cellular events occur over minutes or hours, sCr requires 24 hours or more to reach a worrisome clinical threshold or demonstrate further deterioration of tissue function and architecture.

Methods: To examine the cell and stimulus specific responses, we have adapted the method of Gay et al, (2013) to allow cell specific labelling of RNA at the time of our choosing after injury. The technique involves cre driven, cell specific expression of a uracil phosphoribosyltransferase (Uprt) and the subsequent purification of 4-thio-uracil labelled nascent RNAs. We used this technique with Atp6b1v1-Cre and Hoxb7-Cre to perform transcriptional profiling of the new newly synthesized RNA in the cell types in mouse models of iAKI (intrinsic-AKI) and vAKI volume (volume depleted-AKI).

Results: We found hundreds of genes responding in each cell specific and stimulus specific RNA pool. There was almost no overlap between vAKI and iAKI, although they both raise sCr, and limited overlap between Atp6b1v1-Cre and Hoxb7-Cre RNA pools. To validate this technique, we show that collecting duct marker genes are enriched and genes from the other segments of the kidney are deenriched in the tagged RNA. In addition, we validated the technique by independently using a GFP-Hoxb7 mouse and FAC-sorting out the collecting duct cells for gene expression.

Conclusions: Hence, a snapshot of newly synthesized RNA reveals the complexity subsumed by diagnostic classifications dependent on sCr. We suggest that the Uprt technique will allow characterization of each cell type in the nephron at multiple time

points after the onset of injury. These data will replace our current diagnostic strategies with Precision Medicine approach to AKI.

Funding: NIDDK Support

TH-OR015

Parabiosis Reveals Renal Resident Leukocytes in Quiescence and AKI Jeremie M. Lever,[1] Ravindra Boddu,[1] Oreoluwa O. Adedoyin,[1] Zhengqin Yang,[1] Lingling Guo,[1] Amie Traylor,[1] Reny Joseph,[1] James F. George,[1] Anupam Agarwal.[1,2] *[1]University of Alabama at Birmingham, Birmingham, AL; [2]VA Medical Center, Birmingham, AL.*

Background: Inflammation drives damage and promotes tissue regeneration in AKI, but the origin of inflammatory cells found in renal tissue (infiltrative versus tissue-resident) has remained elusive. In this study, we developed a novel model of AKI in parabiosis chimeras to study exchange of inflammatory cells with the circulation. Our goal was to discern which renal leukocyte populations are tissue-resident and how this may change in the setting of injury-induced inflammation.

Methods: Parabiosis was established between C57BL/6J adult congenic mice with differing CD45 allotypes, allowing identification of cells from each individual. After 28d, chimeras were subject to 30m of renal ischemia-reperfusion injury (IRI) or sham surgery and harvested at 24 and 72h. Kidney, peripheral blood, and spleen were analyzed by multicolor flow cytometry.

Results: After 28d of parabiosis, chimerism for intrarenal neutrophils was 24.2% (95% CI, 14.2 to 34.2). In contrast, F4/80^{Hi}CD11b^{Low}CX3CR1^{Hi}CD11c^{+} macrophages, CD3^{+}CD4^{-}CD8^{-} T lymphocytes, and NK1.1^{+}CD3^{+} NKT cells in the kidney demonstrated low exchange with the blood, with chimerism equal to 2.4% (95% CI, 1.0 to 3.8%; p = 0.002 compared with blood), 2.3% (95% CI, 0.6 to 4.1%; p = 0.02), and 2.3% (95% CI, 0.7 to 3.9%; p = 0.002), respectively in uninjured kidneys. In injured kidneys, a trend toward chimeric CD45.1^{+} leukocyte infiltration was observed relative to sham control ($6.6 \times 10^5 \pm 1.1 \times 10^4$ vs $1.8 \times 10^5 \pm 8.4 \times 10^4$ cells/g tissue, p = 0.10, n = 3 pairs, 24h after injury). However, absolute numbers of chimeric F4/80^{Hi}CD11b^{Low}CX3CR1^{Hi}CD11c^{+} macrophages were not different, indicating bone marrow precursors from the peripheral blood do not supplement expansion of this population, *even* in the setting of acute inflammation.

Conclusions: Certain renal leukocyte populations exhibit low or no exchange with the peripheral blood, indicating they are long-lived or undergo self-renewal *in situ*. Kidney resident macrophages do not appear to be supplemented by infiltrating cells during acute inflammation. These findings may be important in targeting inflammation after AKI with small molecule drugs or development of cell-based therapeutics.

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TH-OR016

Endothelial Marker Expressing Stromal Cells Are Important Regulators of Recovery from AKI Katherine V. Maringer,[3] Elina Mukherjee,[2] Sunder Sims-Lucas.[1] *[1]Children's Hospital of Pittsburgh, Pittsburgh, PA; [2]None, Pittsburgh, PA; [3]Pediatric Nephrology, University of Pittsburgh, Pittsburgh, PA.*

Background: Acute Kidney Injury (AKI) is characterized by an abrupt decrease in renal function that can lead to renal failure, contributing to morbidity and mortality. We have identified a subset of endothelial marker expressing stromal (EMES) cells that contribute to peritubular capillary endothelium. The peritubular capillaries are the primary sites of damage during AKI. We have previously shown that EMES cells are important during the injury phase of AKI. Subsequently, we hypothesize that EMES cells are important contributors to recovery after AKI.

Methods: To determine the importance of EMES following ischemia reperfusion injury (IRI) we utilized lineage tracing, using a TdTomato reporter (labeling all EMES cells) and interrogated the percentage of EMES cells present in IRI and contralateral kidneys. We then interrogated re-expression of stromal genes using RT-PCR. Furthermore, we generated mice with a conditional deletion of Flk1 (Vegfr2, essential for vascular development) in Foxd1cre positive renal stroma (*Flk1*$^{ST-/-}$), and evaluated tissue after blood flow dependent AKI, utilizing (IRI), and blood flow independent/nephrotoxic AKI utilizing cisplatin and focused on the recovery phase (7, or 28 days) post injury.

Results: We determined that EMES cells were upregulated 7 days after IRI contributing to vascular recovery. We next determined following both AKI models that developmental stromal genes were re-expressed, suggestive of stromal de-differentiation, which may drive EMES proliferation. To interrogate the importance of EMES cells after AKI, we used *Flk1*$^{ST-/-}$ animals subjected to IRI or cisplatin, and found mutants had less perfusion and increased HIF1a expression at 7 days in IRI models while cisplatin treatment had no change in perfusion but increased HIF1a. In both models, persistent proximal tubule de-differentiation was observed in mutants. Furthermore, 28 days after injury mutants contained significant fibrosis, and damage compared to controls.

Conclusions: Following AKI the renal stroma requires de-differentiation and re-expression of developmental stromal genes prior to proliferation and re-differentiation. This coupled with EMES cell proliferation, reestablishes normal oxygen concentrations and regulates HIF signaling to modulate repair and recovery from AKI.

Funding: NIDDK Support

TH-OR017

Kidney PANX1 Releases ATP to Mediate Ischemia-Reperfusion Injury Jakub Jankowski,[1] Heather M. Perry,[1] Liping Huang,[1] Diane L. Rosin,[2] Christopher B. Medina,[3] Brant Isakson,[4] Kodi S. Ravichandran,[3] Mark D. Okusa.[1] *[1]Department of Medicine, University of Virginia, Charlottesville, VA; [2]Department of Pharmacology, University of Virginia, Charlottesville, VA; [3]Department of Microbiology, Immunology, and Cancer Biology, Center for Cell Clearance, University of Virginia, Charlottesville, VA; [4]Robert M. Berne Cardiovascular Research Center, Department of Molecular Physiology and Biological Physics, University of Virginia, Charlotesville, VA.*

Background: Extracellular ATP, a DAMP molecule, is deleterious in a number of kidney disease models. There is little data on its source and impact in AKI. We hypothesize that ATP is released from injured kidney cells by transmembrane pannexin1 (PANX1) channels and mediates ischemia-reperfusion injury (IRI). Earlier we reported that global PANX1 KO mice are protected against kidney IRI. We hypothesize that PANX1 expression on specific cell types in the kidney can contribute to injury by different mechanisms.

Methods: Proximal tubule (PT) and endothelial cell (EC) specific PANX1 KO mice (*PepckCrePanx1*$^{f/f}$ and *VECadCrePanx1*$^{f/f}$, n=7 and 9 respectively) and appropriate controls were subjected to 26m bilateral kidney IRI or sham operation and 24h of reperfusion. To generate bone marrow chimeras global PANX1 KO and control mice (n=18 and 20) were lethally irradiated and $1x10^7$ donor bone marrow cells were administered i.v. and after 9 weeks mice were subjected to IRI. Kidney function and injury were assessed by plasma creatinine (PCr) and stereological quantification of acute tubular necrosis (ATN). Markers of kidney injury were quantified by real-time PCR of whole kidney lysates. Murine proximal tubule cell line (TKPTS) was transfected using CRISPR/Cas9 to create stable PANX1 deficiency. Injury after in vitro hypoxia/reoxygenation (H/R) was assessed by fluorescent ATP release assay and qPCR.

Results: PANX1 KO mice receiving PANX1 KO bone marrow (KO→KO) had lower PCr levels compared to WT→WT group after injury (0.57 vs.1.67; p<0.0001). KO→WT chimeras had increased level of plasma creatinine compared to WT→KO (1.67 vs. 0.38; p<0.0001), suggesting importance of parenchymal PANX1 deficiency in mediating tissue protection. The increase in PCr in WT mice subjected to IRI was attenuated in both PT (1.73 vs. 0.28; p<0.0001) and EC specific PANX1KO (1.3 vs. 0.16; p<0.0001). Histological injury scores were also lower in both PT (28.7% vs 87.8%; p<0.01) and EC PANX1KO (22.5% vs. 89.3%; p<0.001) compared to their respective controls. In TKPTS cells subjected to H/R medium ATP content and *TNFa* expression correlated positively with *Panx1* expression.

Conclusions: These results show that loss of PANX1 from both PT and endothelium protects mouse kidneys from IRI. Targeting parenchymal PANX1 may lead to new therapeutic agents in the treatment of AKI.

Funding: NIDDK Support

TH-OR018

Towards Single Cell RNA-Sequencing of Tubular Epithelium in AKI Haojia Wu,[1] Erinn L. Donnelly,[1] Samantha A. Morris,[2] Benjamin D. Humphreys.[1] *[1]Division of Nephrology, Washington University in St. Louis, Saint Louis, MO; [2]Department of Developmental Biology, Washington University in St Louis, Saint Louis, MO.*

Background: A complete transcriptional atlas of epithelial states and dynamics during AKI and repair is a goal of the Kidney Precision Medicine Project. Here, we apply DropSeq, a microfluidic single cell RNA sequencing (scRNA-seq) technique, to characterize kidney tubule single cell transcriptional signatures. We additionally asked if MeOH fixation allows storage of single cells for subsequent scRNA-seq.

Methods: Mouse kidney was dissociated with Liberase TL and DNase I. Single cells were fixed by methanol and stored in -80°C for 4 days. Rehydrated cells were purified by FACS and DropSeq performed according to Macosko et al. Unsupervised clustering was performed to group the kidney cells into separate clusters based on the biological variations on gene expression. Cell types were annotated with known markers or by comparing to a published tubular cell transcriptional profiling dataset.

Results: High quality DropSeq cDNA libraries (average insert size of 1284bp) was generated from MeOH fixed kidney cells. We sequenced 3130 fixed cells at a depth of 7795 reads/cell, detecting an average of 2283 transcripts and 961 genes per cell. Unbiased clustering revealed 12 separate cell types in kidney. This included six tubular cell types, including proximal tubule (PT), Loop of Henle (LOH), distal tubule, connecting tubule and collecting duct. A majority of the cells (67.7%) expressed proximal tubular markers (Slc34a1 and Lrp2), highlighting the preference of PT cell type dissociation with the current protocol. Reclustering analysis of Slc34a1 expressing cells further revealed 5 separate subtypes within the PT cluster. These included three distinct PT subtypes that correspond to S1, S2 and S3 segments. Interestingly, we identified two distinct PT subtypes co-expressing LOH markers (e.g. Wfdc2 and Jun).

Conclusions: DropSeq can be performed on MeOH fixed mouse kidney cells. This will facilitate future analysis of human kidney, whose availability is unpredictable, and allow generation of biobanks for downstream scRNA-seq analysis. Our approach enriches for tubular cell types, including S1, S2 and S3 segments of the proximal tubule, making it well suited for analysis of acute tubular injury and repair at cellular resolution.

Funding: NIDDK Support

TH-OR019

Inhibition of Endothelial PHD2 Protects against Ischemic Kidney Injury through HIF-1 Dependent Suppression of Neutrophilic Inflammation Ganeshkumar Rajendran,[1] Michael P. Schonfeld,[2] Rafael Torosyan,[3] Pinelopi P. Kapitsinou.[3] *[1]KANSAS UNIVERSITY MEDICAL CENTER, KANSAS CITY, KS; [2]KUMC - University of Kansas Medical Center, Kansas City, KS; [3]University of Kansas Medical Center, Kansas City, KS.*

Background: Peritubular endothelial cells (ECs) are major determinants in renal ischemia reperfusion injury (IRI) but the molecular mechanisms remain undefined. Key regulators of hypoxic vascular responses are Hypoxia-Inducible-Factors (HIF)-1 and -2, transcription factors whose activity is inhibited by prolyl-hydroxylase domain proteins 1 to 3 (PHD1 to PHD3), PHD2 being the main oxygen sensor. We previously reported that deficiency of endothelial HIF-2 exacerbated renal IRI, while inactivation of endothelial PHD2 provided renoprotection. Here, we investigated the contribution of HIF1/HIF2 in renoprotection induced by endothelial PHD2 loss.

Methods: EC-specific HIF activation was achieved by crossing Vecadherin (Cdh5)-Cre transgenics to Phd2 floxed mice (*ePHD2*), while the contribution of each HIF isoform was assessed by generating double mutants lacking PHD2 and HIF-2 (*ePHD2HIF2*) or PHD2 and HIF-1 (*ePHD2HIF1*) in ECs. IRI was induced by unilateral renal artery clamping.

Results: Deletion of HIF-1 in endothelial PHD2 deficient background completely reversed the renoprotection conferred by endothelial PHD2 loss as indicated by histological injury scores and *Kim1* mRNA levels in kidney homogenates (Day 3 post IRI, n=8 mice). In contrast, double ePHD2HIF2 mutants had attenuated kidney injury with ~1.7 fold down-regulation in *Kim1* transcript levels compared to controls. CD45 staining showed comparable inflammatory cell infiltration in ePHD2HIF1 injured kidneys with Cre-, while ePHD2HIF2 kidneys had significantly less $CD45^{+ve}$ area than their corresponding controls. Consistently, FACs analysis indicated significant reduction in neutrophils in ePHD2HIF2 kidneys while no difference was detected in ePHD2HIF1 compared to controls. To assess how endothelial PHD2/HIF-1 suppressed post-ischemic inflammation, we examined the expression of EC-adhesion molecules and chemokines known to regulate neutrophil recruitment. We found that *Icam1*, *Tnfa*, *Cxcl1* and *Cxcl2* mRNA levels were significantly reduced in *ePHD2HIF2* post-ischemic kidneys compared to controls, while no differences were noted for ePHD2HIF1 kidneys.

Conclusions: Our data establish that endothelial HIF-1 mediates the renoprotective effects generated by endothelial PHD2 deficiency through suppression of leukocyte recruitment and adhesion to endothelium.

Funding: Other NIH Support - NIH/NIGMS9P20GM104936, Private Foundation Support

TH-OR020

MicroRNA-709 Mediates Acute Tubular Injury by Negatively Regulating the TFAM/Mitochondria Axis Aihua Zhang,[1] Yan Guo,[2] Yue Zhang,[1] Songming Huang,[1] Zhanjun Jia.[1] *[1]Nephrology Departement, Children's Hospital of Nanjing Medical University, Nanjing, China; [2]Nanjing Medical University, Nanjing, China.*

Background: Mitochondrial dysfunction (MtD) plays important roles in the pathogenesis of acute kidney injury (AKI), whereas therapeutic approaches to improve mitochondrial function are still limited. In the present study, we investigated the pathogenic role of miR-709 in mediating mitochondrial impairment and tubular cell death in AKI.

Methods: We used cisplatin-induced AKI mouse model and renal tubular cells to investigate the role of miR-709 in AKI, as well as the mechanisms. The mitochondrial function was determined by the examination of mitochondrial DNA copy number, mitochondrial membrane potential, mitochondrial ROS production, oxygen consumption and the expressions of mitochondrial proteins.

Results: In cisplatin-treated mice, renal miR-709 was significantly upregulated by more than 2 folds. In proximal tubular cells (PTCs), cisplatin led to 6-fold increase of miR-709. Notably, overexpression of miR-709 in mouse PTCs significantly induced MtD and cell apoptosis (>50%), whereas inhibition of miR-709 ameliorated cisplatin-induced MtD and cell apoptosis (about 50%). Further analyses showed that TFAM (mitochondrial transcriptional factor A) is a target gene of miR-709 and that genetic restoration of TFAM blocked the MtD and cell injury induced by cisplatin or miR-709 overexpression. More importantly, miR-709 antagonism with a miR-709 antagomir dramatically attenuated cisplatin-induced kidney injury and MtD in mice. Finally, we verified the overexpression of miR-709 in renal PTCs of 21 patients with AKI of various etiologies (ischemia, nephrotoxins et al), and found a close correlation between the expression of miR-709 and the severity of kidney injury.

Conclusions: These results suggest that miR-709 plays an important role in mediating cisplatin-induced AKI via negative regulation of TFAM and subsequent MtD.

TH-OR021

DNAJ Homolog Subfamily B Member 9 Is a Putative Autoantigen in Fibrillary Glomerulonephritis Nicole K. Andeen, Han-Yin Yang, Dao-Fu Dai, Michael Maccoss, Kelly D. Smith. *University of Washington, Seattle, WA.*

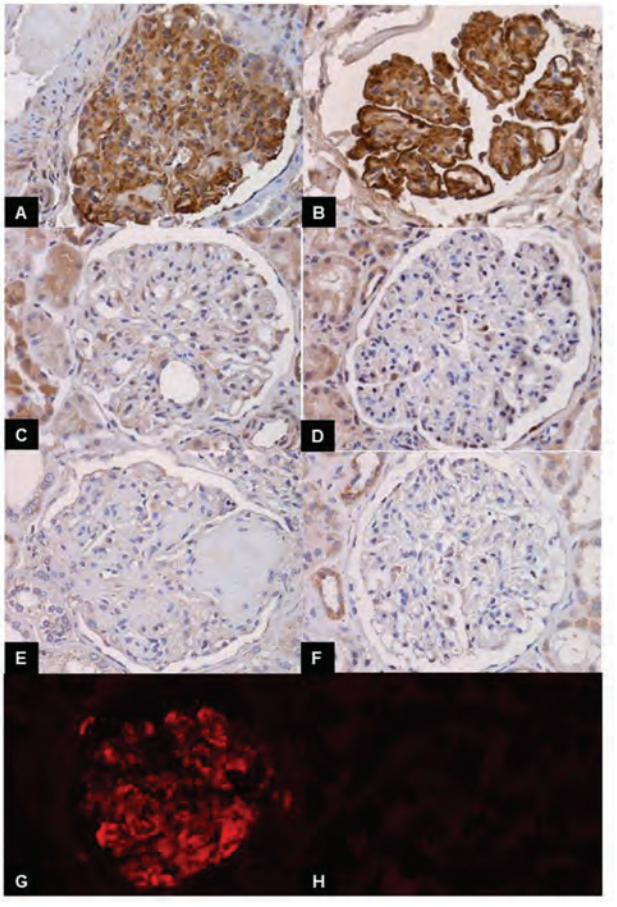
Background: Fibrillary glomerulonephritis (FGN) is a rare form of glomerulonephritis of uncertain pathogenesis, which is characterized by the glomerular accumulations of non-branching, randomly arranged fibrils composed of immunoglobulin and complement proteins. In this study, we utilized mass spectrometry to comprehensively define the glomerular proteome in FGN compared to controls and non-FGN renal diseases.

Methods: Glomeruli from formalin-fixed and paraffin-embedded biopsies were isolated using laser capture microdissection (LCM) and analyzed with liquid chromatography and data-dependent tandem mass spectrometry (LC MS/MS). Findings were correlated with immunohistochemistry (IHC).

Results: These studies identified DNAJ homolog subfamily B member 9 (DNAJB9) as a frequently sampled protein by mass spectrometry in FGN cases that was not detected in other samples. The glomerular proteome of FGN cases also contained IgG1 as the dominant immunoglobulin and proteins of the classical complement pathway. Immunostaining with anti-DNAJB9 demonstrated strong and specific staining of the glomerular tufts in a distribution that mimicked the immune deposits of FGN cases.

Conclusions: Our results identify DNAJB9 as a putative autoantigen in FGN and IgG1 effector pathways as likely mediators for the destructive glomerular injury in FGN.

Funding: Other NIH Support - This work was supported by NIH grants: R21 CA192983, P41 GM103533, and P30 AG013280 (MM), and the University of Washington Department of Pathology (KS, NA).



Anti-DNAJB9 shows strong, discrete peripheral capillary wall and mesangial staining in fibrillary glomerulonephritis (A, B), but not in membranous nephropathy (C), immunotactoid glomerulopathy (D), diabetic glomerulopathy (E), or normal controls (F, H) (IHC). By immunofluorescence microscopy, anti-DNAJB9 shows bright peripheral capillary wall and mesangial staining in fibrillary glomerulonephritis (G), but is negative in normal controls (H).

TH-OR022

Antibody Guided Therapy with Cyclophosphamide and Prednisone in Patients with Membranous Nephropathy Anne-Els van de Logt,[2] Coralien Vink- van Setten,[2] Julia M. Hofstra,[1] Jack F. Wetzels.[2] *[1]Hospital Gelderse Vallei, Ede, Netherlands; [2]Radboud University Medical Center, Nijmegen, Netherlands.*

Background: The discovery of anti-PLA2R antibodies provides options for individualized therapy in patients with membranous nephropathy (MN). We previously showed that monitoring of aPLA2R allowed shortening of the overall duration of cyclophosphamide (Cyc) treatment (van de Logt, Kidney week 2015). Here we present longer-term follow-up data.

Methods: Cyc-therapy (combined with steroids) is started in patients with aPLA2R positive MN and high risk of progression. In our antibody guided cohort aPLA2R are repeatedly monitored (IFT test) at 8, 16, and 24 weeks after start of treatment. If

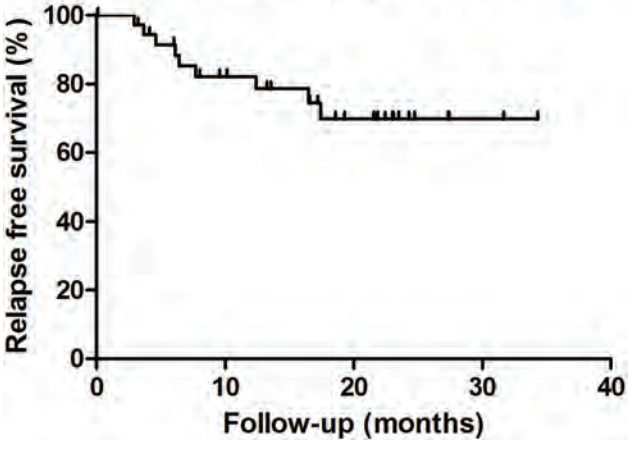
antibodies become negative, Cyc is stopped and prednisone is tapered. Otherwise, therapy is continued after 24 weeks with MMF and prednisone.

Results: Thus far 46 patients (30 males) are included; mean age was 57 ± 13 years, median creatinine 122 μmol/l (IQR 96-159), mean albumin 21.6 ± 6.8 g/l and protein-creatinine ratio 8.6 ±4.3 g/10 mmol. Follow-up duration was 22 ± 11 months. Time to disappearance of aPLA2R was on average short (median 2.1 month), however ranged from 1.4 to 14.6 months. As a consequence the median duration of treatment was 3.2 (range 1.4 to 16.6) months. Cumulative remission rates (PCR <3.0 g/10 mmol) were 52% and 76% respectively 6 and 12 months after start of therapy, not significantly different from historical controls (40% and 60%). The cumulative incidence of relapses at 12 months after onset of remission was 21% and after 24 months 30% in our cohort (respectively 16 % at 24 months in historical controls, van den Brand JASN 2014).

Conclusions: Overall, this strategy shortens the duration of Cyc therapy, maintaining remission rates. The relapse rate however is increased. Still, 70 % of patients remain in remission beyond two years after start of therapy (Figure 1).

Funding: Government Support - Non-U.S.

Figure 1: Relapse free survival



TH-OR023

Immunological Remission in PLA2R-Antibody Associated Membranous Nephropathy (MN): Cyclophosphamide versus Rituximab Anne-Els van de Logt,[4] Karine Dahan,[2] Alexandra Rousseau,[1] Hanna Debiec,[3] Pierre M. Ronco,[2] Jack F. Wetzels.[4] *[1]AP-HP, Paris, France; [2]Hospital Tenon, Paris, France; [3]INSERM UMR S702, Paris, France; [4]Radboud University Medical Center, Nijmegen, Netherlands.*

Background: Rituximab (cumulative dose 750 mg/m2) induces remissions in patients with MN (Kahan JASN2017). However, efficacy is limited in patients with high anti-PLA2R (aPLA2R) levels. Cyclophosphamide therapy is effective independent of aPLA2R levels (van de Logt SA-PO 631, kidneyweek 2016). Incidence of partial remissions was higher with Cyclophosphamide vs Rituximab (van de Brand JASN2017). We questioned if differences in the immunological (aPLA2R) response could explain these observations. We therefore evaluated the change in aPLA2R levels during treatment with Cyclophosphamide (1.5mg/kg/day, duration 8-24 weeks; Nijmegen cohort) and Rituximab (the GEMRITUX cohort (rituximab 375 mg/m2 at day 1 and 8).

Methods: We included 30 anti-PLA2R positive patients treated with Cyclophosphamide and 27 patients treated with Rituximab. In stored samples (baseline, and at the end of therapy or after 6 months) aPLA2R were measured with ELISA (Euroimmun®).

Results: In the Cyclophosphamide cohort 19 patients were male, mean age was 56 ± 13 years, median serum creatinine level was 1.3 g/dl (IQR 1.1-1.6) and median protein creatinine ratio 7.7 g/g (IQR 5.5-11.3). In the Rituximab cohort, 21 patients were male, mean age was 51 ± 14 years, median serum creatinine level was 1.1 g/dl (IQR 0.93-1.3) and median protein creatinine ratio 8.4 g/g (IQR 4.4-11.0). aPLA2R disappeared in all but one patient treated with Cyclophosphamide, and in 13 of 27 patients treated with Rituximab. The reponse was associated with baseline titers (table 1). Rituximab did not induce immunological remission in patients in the highest tertile of aPLA2R levels.

Conclusions: Rituximab in a dose of 750mg/m2 is less effective than Cyclophosphamide in inducing an immunological remission in patients with MN and high antibody levels. Our study highlights the potential role of PLA2R antibody measurements in predicting outcome to therapy. Higher doses of Rituximab must be evaluated.

Funding: Government Support - Non-U.S.

Disappearance of aPLA2R during treatment with Cyclophosphamide and Rituximab

aPLA2R titer in Cyc group	Lowest Tertile n=10	Middle Tertile n=10	Highest Tertile n=10
ElISA titer RU/ml (range)	15-67	86-134	136-776
Cumulative percentage samples negative after 24 wk	100 %	100 %	90 %
aPLA2R titer in RTX group	Lowest Tertile n=9	Middle Tertile n=9	Highest Tertile n=9
ElISA titer RU/ml (range)	17-41	62-276	314-2900
Cumulative percentage samples negative after 24 wk	89 %	56 %	0 %

TH-OR024

Presence of Cellular or Fibrocellular Crescent Is Important for a Long-Term Renal Prognosis in Patients with IgA Nephropathy Followed for 10 Years or Longer on Average Takayuki Fujii, Satoshi Suzuki, Noriko Terasaki, Kaiji Saito, Mizuki Shinozaki, Mayu Morimoto, Tanaka Hiroaki. *Seirei Sakura Citizen Hospital, Sakura-shi Chiba, Japan.*

Background: Regarding the prognosis of patients with IgA nephropathy, the addition of the crescent score: C0 (no crescent), C1 (crescents in more than zero but less than one fourth of glomeurli), and C2 (crescents in one fourth or more of glomeruli), to the conventional factors of the Oxford classification: M, E, S, T score has been proposed (J Am Soc Nephrol 2017). However, the observation period in the above study was relatively short (mean: 4.7 years) and it is unclear whether the C score, which may be modified by treatment, serves as a factor associated with the long-term prognosis of patients followed for more than 10 years on average. We investigated the influence of the C score on the long-term prognosis.

Methods: The subjects were 658 patients with biopsy-proven IgA nephropathy who could be followed up for one year or longer, or reached end stage kidney disease and required renal replacement therapy within one year. A single-center retrospective cohort study was performed involving these patients. Setting the outcome at 50% reduction of eGFR, the influence of the C score on the prognosis was investigated using the Kaplan-Meier method and Cox proportional hazard model. Model A was adjusted with the clinicopathological data including time average proteinuria (TAP) and time average mean blood pressure (TAMAP) during the course, and the M, E, S, and T scores, and model B was adjusted with model A + treatment with or without steroid and RAS inhibitors for analysis.

Results: The mean observation period was 10.9±8.8 years, eGFR at the time of kidney biopsy was 75.8±26.4 mL/min/1.73 m^2, TAP was 0.8±1.2 g/day, C1 and C2 accounted for 18.2% and 1.5%, respectively, and the outcome was reached in 18.0%. On analysis using the Kaplan-Meier method, the outcome was significantly more favorable in the order of C0, C1, and C2 (log-rank $p<0.0001$). Regarding C0 as the reference, HR of C1 or higher was 1.68 (95% CI: 1.04-2.64) in model A and 1.81 (95% CI: 1.11-2.87) in model B, showing that the score was applicable as a prognostic predictor in addition to the Oxford T score, TAP and TAMAP, and eGFR at the time of kidney biopsy.

Conclusions: The C score was important for a long-term renal prognosis even when treatment was included in the analysis.

TH-OR025

Prognosis of Henoch-Schönlein Purpura Nephritis among Adult and Elderly Patients: Nationwide Cohort Study Based on the Japan Renal Biopsy Registry Hiroyuki Komatsu,[4] Shouichi Fujimoto,[5] Hitoshi Sugiyama,[2] Hiroshi Sato,[3] Hitoshi Yokoyama.[1] *[1]Kanazawa Medical University, Ishikawa, Japan; [2]Okayama University Graduate School, Okayama, Japan; [3]Tohoku University, Sendai, Japan; [4]University of Miyazaki, Miyazaki, Japan; [5]University of Miyazaki, Miyazaki, Japan. Group/Team: HSPN study group of J-RBR in Japan.*

Background: The clinical presentation and prognosis of adult and elderly patients with Henoch-Schönlein purpura nephritis (HSPN) has not been investigated in detail. We therefore surveyed the features and outcomes of HSPN based on nationwide data from the Japan Renal Biopsy Registry (J-RBR).

Methods: This multi-center cohort study compared the clinico-pathological parameters at diagnosis, initial therapies and outcomes between 106 adult (age 19 - 64 years), and 46 elderly (age ≥ 65 years) patients with HSPN who were registered in the J-RBR between 2007 and 2012. The primary end-points comprised a 50% increase in serum creatinine (sCr) values or end-stage kidney disease. Factors affecting a decrease in renal function were assessed using a Cox proportional hazards model.

Results: The rates of hypertension, impaired renal function, hypoalbuminemia, and crescentic glomerulonephritis were significantly higher among the elderly, compared with the adult patients. About 80% and 60% of the patients in both groups were respectively treated with corticosteroid and renin-angiotensin system (RAS) inhibitors. Both groups had favorable renal survival rates for nine years (93.6% and 91.4% of the adult and elderly patients, respectively). Significantly more elderly than adult patients developed a 50% increase in sCr during a mean observation period of 3.9 years (21.7% vs. 4.7%, $p = 0.012$). In addition, significantly fewer elderly than adult patients achieved clinical remission (24% vs. 46%, $p = 0.016$). Multivariate analysis revealed that advanced age (≥ 65 years) was an independent prognostic factor for a decline in renal function (HR, 6.08; $p = 0.018$).

Conclusions: The renal prognosis of adult and elderly patients with HSPN was favorable when treated aggressively with corticosteroid and RAS inhibitors. However, the course of renal function should be carefully monitored in patients aged over 65 years.

TH-OR026

Renal Complications during Pregnancy Before and After Glomerulonephropathy Diagnosis Andrea L. Oliverio,[3,6] Monica L. Reynolds,[5,6] Laura H. Mariani,[3,6] Michelle M. O'Shaughnessy,[2,6] Jarcy Zee,[1,6] Michelle A. Hladunewich.[4,6] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]Stanford University Medical Center, Palo Alto, CA; [3]University of Michigan, Ann Arbor, MI; [4]University of Toronto, Toronto, ON, Canada; [5]University of North Carolina, Chapel Hill, NC; [6]CureGN Women's Health Working Group, Bethesda, MD.*

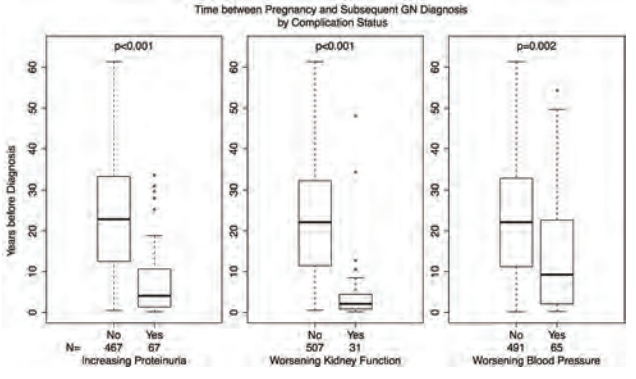
Background: Pregnancy studies in women with glomerulonephropathy (GN) are limited to single centers and small samples. Delineating pregnancy-associated risks would better inform counseling and determine safe management strategies.

Methods: CureGN is an ongoing 64-center prospective cohort study of children and adults with biopsy-proven MCD, FSGS, MN, or IgAN/IgAV. Patient-reported pregnancy outcomes and maternal/fetal complications are collected at each study visit. Descriptive statistics were used to assess complications of pregnancies before and after GN diagnosis. Among pregnancies prior to diagnosis, a generalized estimating equation model was fit to compare time to diagnosis for those with and without pregnancy complications.

Results: As of May 2017, 273 out of 427 adult women enrolled in CureGN reported 585 pregnancies prior to GN diagnosis and 30 after diagnosis, excluding elective terminations. Of pregnancies after GN diagnosis, 13.3% were in women with MCD, 40% FSGS, 13.3% MN, 33.3% IgAN. Of those with pregnancies prior to GN diagnosis, 12.5% reported increasing proteinuria, 5.8% worsening kidney function, 11.7% worsening blood pressure and 88.5% full term delivery compared to 48.1%, 35.7%, 25.9 % and 57.1%, respectively among pregnancies after diagnosis. Women with pregnancy complications prior to diagnosis had a significantly shorter time between pregnancy and subsequent GN diagnosis than those with uncomplicated pregnancies (Figure).

Conclusions: Pregnancies in women with GN diagnosis had high rates of maternal/fetal complications, necessitating high-risk care. Decreased latency between complicated pregnancies and subsequent GN diagnosis suggests that diagnosis may have been missed during pregnancy or that the physiologic stress of pregnancy may have unmasked a smoldering glomerular disease. While currently at 73% of target enrollment, CureGN is projected to be the largest multi-center international cohort poised to study pregnancy outcomes in women with GN.

Funding: NIDDK Support



TH-OR027

Similarities between THSD7A and PLA2R Antigens in Autoimmune Membranous Nephropathy (AMN) Samuel Rhoden,[3] Maryline Fresquet,[3] Thomas A. Jowitt,[3] Jennet O. Gummadova,[3] Ian Roberts,[1] Rachel Lennon,[3] Paul E. Brenchley.[2] *[1]John Radcliff Hospital, Headington, United Kingdom; [2]Manchester Royal Infirmary, Manchester, United Kingdom; [3]University of Manchester, Manchester, United Kingdom.*

Background: Patients with AMN either have autoantibodies against PLA2R (75%) or THSD7A (2%). PLA2R and THSD7A proteins share similar structural and biochemical properties. Both proteins are large transmembrane receptors expressed on podocytes with multiple disulfide-bonded and N-glycosylated extracellular domains. We previously described the major epitope within PLA2R but the dominant epitope in THSD7A is still unknown. **Hypothesis:** The major epitope in THSD7A may share shape homology with PLA2R.

Methods: Recombinant full length extracellular domains of THSD7A (FL 180kDa) and a fragment (NT 120kDa) were expressed, purified and used to screen 1400 AMN sera by ELISA for anti-THSD7A. Clinical phenotype on 10 cases was collected. Biopsies were stained for THSD7A and PLA2R. Sera were characterised by western blotting, ELISA and slot blotting on various THSD7A fragments and peptides. The homology model of the PLA2R CysR domain was used to thread the THSD7A epitope peptide.

Results: 22 cases negative for anti-PLA2R were found anti-THSD7A positive (2%). We selected the 10 highest titre sera from the MN group (6F/4M mean age= 64yr). All 10 sera could be inhibited by the THSD7A NT fragment indicating an epitope(s) within this region. Interestingly a short sequence within the NT fragment shares homology with the PLA2R epitope. This short sequence peptide bound antibodies by slot blotting and inhibited binding to the antibodies by ELISA in all patients' sera suggesting a potential epitope in THSD7A. Homology modelling of these two epitopes in PLA2R and THSD7A revealed two regions important for antibody binding.

Conclusions: We describe the first ELISA for anti-THSD7A and report an incidence of 2% positivity in a large cohort of anti-PLA2R negative AMN patients. We identified a specific region on THSD7A with structural homology to the major epitope in PLA2R and show this sequence to be a potential epitope in THSD7A. These results suggest a pathological epitope structure common to autoantigens involved in MN.

Funding: Private Foundation Support

TH-OR028

The Microbiota Is a Central Determinant in IgA Nephropathy as Its Modulation Prevents Disease Development Jonathan M. Chemouny,[2,1] Patricia Lepage,[3] Patrick J. Gleeson,[1] Lilia Abbad,[1] Agnes Jamin,[1] Eric Daugas,[2,1] Francois Vrtovsnik,[2,1] Sanae Ben mkaddem,[1] Laureline Berthelot,[1] Marion Leclerc,[3] Renato C. Monteiro.[2,1] *[1]INSERM U1149 & ELR8252 CNRS, Paris, France; [2]AP-HP, Hopital Bichat, Paris, France; [3]INRA, Jouy-en-Josas, France.*

Background: IgA nephropathy (IgAN) is associated with microbiota dysbiosis when compared to healthy individuals (De Angelis et al. PLoS One 2014). Here, we studied the composition of fecal microbiota of IgAN patients compared with non-IgAN glomerular disease (non IgAN-GD). An IgAN mouse model (α1KI-CD89Tg) was used to study the effect of gut microbiota modulation in disease development.

Methods: We collected feces from patients with IgAN and non-IgAN-GD. Fecal microbiota compositions were studied through 16S rRNA pyrosequencing. For the experimental part of the study, 31 four-week old male α1KI-CD89Tg mice were fed an antibiotic mix (ATB) or vehicle twice a week for 8 weeks. Urine samples were collected before the first administration. At the end of experiments, urine, blood samples and kidneys were collected. Proteinuria and creatininuria were measured.

Results: IgAN and non-IgA-GN patients showed significant differences in proportions of the main phylum Firmicutes (p=0.020) and in Lentispherae (p=0.019). As the data suggest an IgAN-linked dysbiosis, we targeted the gut microbiota in a mouse model of IgAN to modulate disease expression. As expected total bacterial load was significantly lesser in the ATB group (p<0.001). Protein/creatinine ratio (PCR) did not rise over the course of 12 weeks in the ATB group (p=0.436) whereas there was a significant increase (p<0.001) in the PCR in the vehicle control group. Markedly less mesangial IgA1 deposits was seen in the ATB group. While no differences were seen in serum human IgA1 levels in the mice, there were significantly fewer lymphoid follicles in Peyer's patches (PP) among ATB treated as compared to vehicle group.

Conclusions: Our data suggest the gut dysbiosis in IgAN patients may be independent of the effect of CKD. Moreover, gut commensal bacteria may have a pathogenic role in IgAN as gut microbiota modulation through the administration of antibiotics prevented disease development in mice. Finally, nephrotoxic IgA1 may originates from the gut mucosa, as despite the presence of PP alterations in ATB group, serum IgA1 levels remained unaffected.

Funding: Government Support - Non-U.S.

TH-OR029

Ubiquitin Carboxyl-Terminal Hydrolase L1 Is a Podocyte Target of IgG Antibodies in Idiopathic Nephrotic Syndrome (INS) Georges Deschênes,[2] Agnes Jamin,[3] Laureline Berthelot,[4] Renato C. Monteiro.[1] *[1]Bichat Medical School, Paris, France; [2]Hospital Robert Debre, Paris, France; [3]INSERM U1149 & ELR8252 CNRS, 75018 Paris, France; [4]INSERM U699, Paris, France.*

Background: The efficiency of B cell-depleting treatments highlights the involvement of B cells in INS. This study searched for identifying antibodies (Abs) directed against podocytes in patients with INS.

Methods: The study was performed using a biobank including 86 patients sampled at various stages of INS and 76 controls. Fractions of plasma obtained by size exclusion chromatography and tested on cultured podocyte adhesion; specificities of IgG Abs contained in the plasma fraction of interest were studied through immunoprecipitation of a podocyte lysate then identification of cognate antigens by liquid chromatography-mass spectrometry.

Results: Cultured podocyte detachment was observed with one specific plasma fraction in 16/34 INS relapsing patients, 1/11 INS patients in remission and 0/25 controls. IgG were isolated from this specific plasma fraction in 3 INS relapsing patients (all detaching cultured podocytes), 3 from the same INS patients in remission (all not detaching cultured podocytes) and in 3 controls, then used to immunoprecipitate a podocyte lysate. Comparative proteomic analysis allowed selecting 5 proteins according to statistical and biological criteria. Specific Abs were tested and only anti-Ubiquitin Carboxyl-Terminal Hydrolase L1 (UCHL1) IgG led to podocyte detachment. Pre-incubation of either anti-UCHL1 IgG Abs or plasma fractions with recombinant UCHL1 prevented podocyte detachment. Plasma levels of anti-UCHL1 IgG Abs were increased in 18/42 relapsing INS patients over the highest level of 38 controls (median=0.20 AU/*g of total IgG;IQ0.15-0.29;range0.07-0.85). For those 18 patients, the level of anti-UCHL1 IgG Abs in 43 samples available at various stage of INS was confirmed to be significantly higher in relapse (n=23;median=1.22AU/µg of total IgG; IQ 0.92-1.90) compared to remission (n=20;median=0.51;IQ 0.33-0.77;p<0.001). In those 18 INS patients, proteinuria correlated with anti-UCHL1 IgG Abs level (n=43,r=0.57,p<0.001).

Conclusions: UCHL1 is involved in the adhesion of cultured podocytes. UCHL1 is a target of circulating IgG Abs in a subset of relapsing INS patients.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-OR030

Circulating Serum miR-148b and let-7b Are Inherited in IgA Nephropathy (IgAN) Trios Grazia Serino,[7] Sharon N. Cox,[5,9] Massimiliano Copetti,[3] Luigi Bisceglia,[8] Gianluigi Zaza,[6] Isabella Squarzoni,[1] Martina Ferraresi,[4] Luigi Biancone,[2] Francesco P. Schena.[5,9] *[1]Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy; [2]Department of Medical Science, Turin, Italy; [3]IRCCS, San Giovanni Rotondo, Italy; [4]Nephrology, Dialysis and Transplantation, Turin, Italy; [5]University of Bari, Bari, Italy; [6]University of Verona, Verona, Italy; [7]IRCCS "S. de Bellis", Castellana Grotte (BA), Italy; [8]IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG), Italy; [9]Schena Foundation, Valenzano (BA), Italy.*

Background: IgA nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide characterized by aberrant O-glycosylation in the hinge region of IgA1. Our recent work demonstrates that serum levels of the combined miRNA biomarker, let-7b and miR-148b, appears to be a novel, reliable, and non-invasive test to predict the probability of having IgAN (Kidney International, 89, 683-692; 2016). In this study our aim was to evaluate if the serum levels of the combined biomarker are heritable.

Methods: Serum miRNA was extracted using QIAzol Lysis Reagent and miRNeasy Mini Kit (Qiagen) according to the manufacturer's protocol. Using quantitative real-time PCR, we detected the expression of circulating miRNAs (let-7b and miR-148b) in 90 trios that consists of one IgAN patient and their two parents. Heritability was estimated using the approach proposed in Rabe-Hesketh et al. (Biometrics, 64, 280-288, 2008) implemented in R package "gap".

Results: We found that serum levels of the combined biomarker (let-7b and miR-148b) were elevated in the first-degree relatives of IgAN patients compared with healthy blood donors (IgAN 0.31±0.23; IgAN relatives 0.29±0.18; HBD -1.04±0.09). In addition, serum level of the combined biomarker did not differ between IgAN patients and their relatives (p=0.93). The estimated heritability (h2) of the serum biomarkers was 37,54% (95%CI: 13.57%-61,51%; p= 0.001) in crude (unudjasted) model. Age- and gender-adjusted heritability improved at 52.94% (95%CI=22.28%-83.59%, p=0.000356).

Conclusions: These results suggest that serum levels of the combined biomarker are, in part, genetically determined and may constitute a helpful tool for screening of relative at risk for IgAN development.

Funding: Government Support - Non-U.S.

TH-OR031

EXPEDITION-4: Efficacy and Safety of Glecaprevir/Pibrentasvir in Patients with Chronic Hepatitis C Genotype 1-6 Infection by Dialysis Status Csaba P. Kovesdy,[1] Emily Dumas,[9] Alexander Thompson,[2] Yves Horsmans,[3] Hendrik Reynaert,[4] Peter Ghali,[5] Laurent Alric,[6] Dominique Larrey,[7] Giuliano Rizzardini,[8] Caroline Park,[9] Yang Lei,[9] David Pugatch,[9] Federico Mensa,[9] Magdy Elkhashab,[10] Meghan E. Sise.[1] *[1]University of Tennessee Health Science Center, Memphis, TN; [2]St. Vincent's Hospital Melbourne and the University of Melbourne, Fitzroy, NSW, Australia; [3]Université Catholique De Louvain, Louvain-la-Neuve, Brussels, Belgium; [4]University Hospital UZBrussel, Brussels, Belgium; [5]McGill University, Montreal, QC, Canada; [6]CHU Toulouse, Toulouse, France; [7]Hôpital Saint Eloi CHRU Montpellier, Montpellier, France; [8]Ospedale Luigi Sacco, Milan, Italy; [9]AbbVie, Chicago, IL; [10]Toronto Liver Centre, Toronto, ON, Canada.*

Background: Hepatitis C (HCV)-infected patients with late-stage kidney disease have limited treatment options. The ribavirin-free regimen of glecaprevir/pibrentasvir (coformulated as G/P; glecaprevir identified by AbbVie and Enanta) has a renal excretion <1% and has yielded sustained virologic response (SVR) >97% in clinical trials. Here we report efficacy and safety by dialysis status from a Phase 3 study of G/P in HCV genotype (GT) 1-6-infected patients.

Methods: HCV GT1-6 patients with an eGFR <30 mL/min/1.73 m^2, without cirrhosis or with compensated cirrhosis, received G/P (300 mg/120 mg) once daily for 12 weeks. Outcomes were analyzed by predialysis (CKD stages 4-5) and dialysis status.

Results: The trial enrolled 104 patients (predialysis, 19; dialysis, 85): 76% were men, 58% treatment-naïve, 19% cirrhotic, and 52% GT1-infected. The overall SVR12 and SVR24 rates were 98% and 96%, respectively, without virologic failures. The rates of serious AEs were 26% (predialysis) and 24% (dialysis); none was considered G/P-related. In predialysis patients, mean ± SD change in creatinine clearance from baseline to Week 12 was -1.4 ± 3.6 mL/min (median: -1.0 mL/min).

Conclusions: G/P is an all-oral pangenotypic anti-HCV treatment with high efficacy and a favorable safety profile, regardless of patients' dialysis status. AbbVie sponsored the studies, contributed to their design, collection, analysis, and interpretation of the data, and participated in the writing, review, and approval of the abstract. All authors had access to relevant data. This abstract contains information on the investigational products glecaprevir (ABT-493) and pibrentasvir (ABT-530). Medical writing support, was provided by Vojislav Pejovic of Medical Expressions, Chicago, IL, funded by AbbVie.

Funding: Commercial Support - Abbvie

TH-OR032

Intensive Systolic Blood Pressure (SBP) Control and Incident CKD in Persons with and without Diabetes Mellitus (DM) Srini Beddhu,[1] Alfred K. Cheung,[1] Glenn M. Chertow,[2] Paul K. Whelton,[3] R. E. Boucher,[1] Guo Wei,[1] Paul L. Kimmel,[4] William C. Cushman,[5] Tom Greene.[1] *[1]Univ of Utah, SLC, UT; [2]Stanford Univ, Palo Alto, CA; [3]Tulane Univ, New Orleans, LA; [4]NIDDK, Bethesda, MD; [5]VAMC, Memphis, TN.*

Background: In Systolic Blood Pressure Intervention Trial (SPRINT), higher incidence of CKD with intensive SBP control in persons without DM was reported. It is unclear whether intensive SBP control has similar effects in DM.

Methods: SPRINT tested the effects of SBP goal < 120 vs. < 140 mm Hg on CV outcomes in persons without DM whereas Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP trial tested the same in type 2 DM. In separate Cox models, we related the interventions to incident CKD (defined as a >30% decrease in eGFR to a value <60 ml/min/1.73 m^2) in participants without CKD at baseline (N = 6677 in SPRINT; N = 4305 in ACCORD).

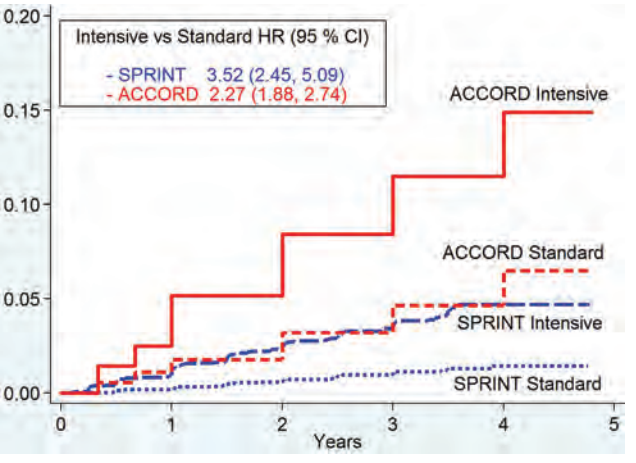
Results: Baseline characteristics are summarized. (table) The absolute risks of incident CKD estimated by Kaplan Meier (KM) curves at 3 years of follow-up in standard vs. intensive arms were 1.0 vs. 3.5% in SPRINT and 4.6 vs. 11.5% in ACCORD with an absolute risk increase % (95% CI) at 3-years of 2.5 (1.8 to 3.2) in SPRINT and 6.9 (5.2 to 8.5) in ACCORD. KM failure curves and hazard ratios are presented in the figure.

Conclusions: Intensive SBP control increased the risk of incident CKD in persons with and without DM, however, absolute risk increase is higher in DM. The long-term implications of these findings need to be established.

Funding: NIDDK Support, Other NIH Support - NHLBI

Baseline Characteristics

	SPRINT		ACCORD	
	Intensive (N=3332)	Standard (N=3345)	Intensive (N=2148)	Standard (N=2157)
Age (yr)	66.3 ± 9.0	66.3 ± 9.0	62.3 ± 6.5	62.4 ± 6.6
Male (%)	66	67	54	53
Black (%)	34	35	28	29
SBP (mm Hg)	140 ± 16	140 ± 15	139 ± 16	139 ± 15
DBP (mm Hg)	79 ± 12	79 ± 12	76 ± 10	76 ± 10
BMI(kg/cm^2)	30.1 ± 5.8	30.0 ± 5.7	32.1 ± 5.6	32.1 ± 5.3
eGFR (ml/min/1.73 m^2)	81.1 ± 15.5	81.3 ± 15.5	94.2 ± 20.7	94.0 ± 20.8
Urine ACR (mg/g)	9 (5, 17)	9 (5, 17)	15 (7, 44)	14 (7, 45)



KM failure curves for incident CKD by treatment arm in SPRINT and ACCORD BP

TH-OR033

Autologous Hematopoietic Stem Cell Transplantation for Refractory Lupus Nephritis Xiang-hua Huang, Wencui Chen, Weixin Hu, Zhi-Hong Liu. *National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing China, Nanjing, China.*

Background: To evaluate the efficiency and safety of the treatment of autologous hematopoietic stem cell transplantation (ASCT) for patients with refractory lupus nephritis (LN).

Methods: From Jul 2011 to Jan 2015,a total of twenty-two patients with refractory LN relapse or had no response to standard immunosuppressive therapies were enrolled in this study. Peripheral blood stem cells were mobilized with cyclophosphamide (CTX) and granulocyte colony-stimulating factor (G-CSF),and reinfused after treatment with CTX and antithymocyte globulin(ATG). The primary end point was remission rate,and secondary end points included the survival and relapse rate, changes in proteinuria, renal function and serology immunologic test. All the complications were recorded for safety access.

Results: Twenty-two patients were enrolled and underwent stem cell mobilization. They were 9 males and 13 females with a median LN duration of 45.5(33-71) months. The mean number of $CD34^+$ cells was $(7.3 \pm 3.8) \times 10^6$ /kg. All patients had successful engraftment,and the median time of granulocyte and platelet engraftment was 8 and 9 days, respectively. The major complications of ASCT were fever and symptom of gastrointestinal tract. The treatment-related mortality was 4.5% (1/22). After a median follow-up of 53 months,eighteen patients (81.8%) achieved completed remission,one patient (4.5%) achieved partial remission,and one had no response and received peritoneal dialysis at 12 months after ASCT. One patient died for sepsis at 5 month after ASCT. The median time of renal response was 3 months. The 5-years overall survival was 90%. The probability of disease-free survival at 5 years following ASCT was 52.9%. Six patients had relapse during the follow-up and the relapse rate was 27.3%.

Conclusions: Our preliminary data shows that ASCT is a safe and effective treatment of refractory LN, the completed response rate was high and the complications was manageable. Infection is still an important cause of treatment failure, the long-term efficacy still need further observation.

TH-OR034

Influence of Baseline Diastolic Blood Pressure (DBP) Level on the Effects of Intensive Blood Pressure Lowering on Incident CKD in SPRINT Srini Beddhu,[1] Glenn M. Chertow,[2] Alfred K. Cheung,[1] Mahboob Rahman,[3] Tom Greene,[1] Guo Wei,[1] William E. Haley,[4] William C. Cushman,[5] Paul K. Whelton.[6] *[1]Univ Utah, SLC, UT; ; [2]Stanford, Palo Alto, CA; [3]CWRU, Cleveland, OH; [4]Mayo Clinic, Jacksonville, FL; [5]Memphis VA Medical Center, Memphis, TN; [6]Tulane Univ, New Orleans, LA. Group/Team: For SPRINT Research Group.*

Background: Lowering systolic blood pressure (SBP) in persons with low DBP might affect kidney perfusion and thereby, ↑ risk for incident CKD.

Methods: SPRINT tested the effects of SBP goal < 120 vs. < 140 mm Hg on CV outcomes. We tested for effect modification by baseline DBP of the intervention on incident CKD (defined as a >30% decrease in eGFR to a value <60 ml/min/1.73 m^2) in participants without CKD at baseline (N = 6677).

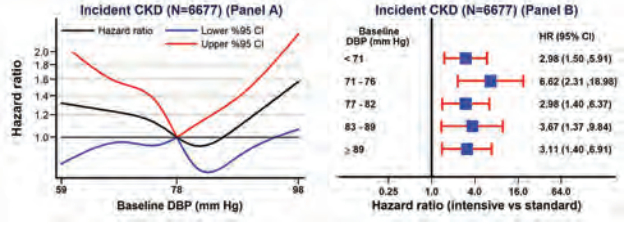
Results: Participants with lower baseline DBP were older, had ↑ prevalence of CV disease and ↓ eGFR (table). There was a U-shaped relation between baseline DBP and incident CKD (Fig Panel A). Within each baseline DBP quintile, participants randomized to the intensive arm had a higher hazard ratio of incident CKD (Fig Panel B). P-value for comparison of hazard ratios in the lowest quintile to the upper 4 quintiles was non-significant (p = 0.79). P-value for the linear treatment by baseline DBP interaction was also non-significant (p = 0.94).

Conclusions: Lower baseline DBP was associated with ↑ risk of incident CKD, but there was no evidence that the effects of intensive SBP lowering on incident CKD differed by baseline DBP.

Funding: NIDDK Support, Other NIH Support - NHLBI

Baseline characteristics by baseline quintiles of DBP in non-CKD subgroup in SPRINT (N=6677)

Variable name	1st quintile <71 (N=1460)	2nd quintile 71-76 (N=1283)	3rd quintile 77-82 (N=1365)	4th quintile 83-89 (N=1356)	5th quintile >89 (N=1251)	P value
DBP (mm Hg)	64 ± 5	73 ± 2	80 ± 2	86 ± 2	96 ± 6	
Age (year)	72.5 ± 8.5	67.9 ± 8.2	65.9 ± 8.3	63.6 ± 7.7	60.9 ± 7.6	<0.001
Female (%)	37.9	32.7	31.6	31.6	34.5	0.002
Black race (%)	25.7	29.6	32.4	37.0	48.1	<0.001
History of cardiovascular disease (%)	26.6	18.9	15.3	15.2	15.0	<0.001
Never smoked	43.3	42.7	44.9	45.3	41.2	0.20
Antihypertensive agents (# / patient)	2.0 ± 1.0	1.8 ± 1.0	1.7 ± 1.0	1.6 ± 1.0	1.5 ± 1.1	<0.001
SBP (mm Hg)	131 ± 14	135 ± 13	139 ± 13	142 ± 13	153 ± 15	<0.001
BMI (kg/m^2)	28.5 ± 5.3	29.9 ± 5.8	30.2 ± 5.8	30.6 ± 5.7	31.0 ± 6.0	<0.001
eGFR (ml/min/1.73 m^2)	79 ± 15	80 ± 15	81 ± 16	82 ± 16	83 ± 17	<0.001
Urine ACR (mg/g)	9.1(5.7,17.0)	8.3(5.3,16.7)	8.0(5.2,15.7)	8.4(5.4,16.0)	9.6(5.9,20.0)	<0.001



TH-OR035

Empagliflozin (EMPA) and Incidence of Rapid Decline in eGFR in Patients with Type 2 Diabetes (T2D) and Established Cardiovascular Disease (CVD): An Exploratory Analysis from the EMPA-REG OUTCOME Trial Samy Hadjadj,[1] Merlin C. Thomas,[2] Mark E. Cooper,[2] Audrey Koitka-Weber,[4] Stefan Hantel,[4] Maximilian von Eynatten,[5] Christoph Wanner.[6] *[1]University Hospital Centre, Poitiers, France; [2]Department of Diabetes, Monash University, Melbourne, VIC, Australia; [4]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; [5]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; [6]Dept of Medicine, Würzburg Univ Clinic, Würzburg, Germany.*

Background: The eGFR progressively declines in most patients with T2D. In some patients a more rapid decline in eGFR is observed, putting them at risk for the consequences of uremia and ultimately end-stage renal disease. In the EMPA-REG OUTCOME® trial, EMPA was associated with slower progression of kidney disease. In this *post-hoc* analysis, we evaluated the effect of EMPA on the incidence of patients experiencing a more rapid decline in eGFR.

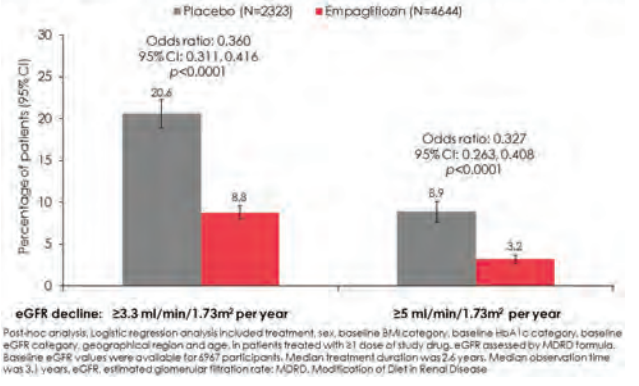
Methods: 7020 patients with T2D and established CVD were randomized (1:1:1) to EMPA 10 mg, 25 mg or placebo (PBO) in addition to standard of care. Change in eGFR decline over the study period (from baseline to follow-up) was calculated by utilizing linear regression models. A rapid decline in eGFR was defined by an annual decline in eGFR ≥5 ml/min/1.73m^2. Logistic regression analysis was used to investigate differences between EMPA vs PBO groups.

Results: At baseline, mean (SD) eGFR was 74.0 (21.4) ml/min/1.73m^2. Over the study period, 354 participants (5.1%) experienced a rapid decline in eGFR, including 8.9% in the PBO group and 3.2% in participants receiving EMPA. After adjusting for other risk factors, this equated to two-thirds reduction in risk (Figure, odds ratio 0.33 [95% CI 0.26, 0.41]; $p<0.0001$) among participants receiving EMPA. A similar reduction among EMPA-treated participants in the incidence of patients experiencing a rapid decline in eGFR was also observed using a lower threshold (Figure).

Conclusions: Patients treated with EMPA were significantly less likely to experience a rapid decline in eGFR over approximately 3 years of treatment. This finding suggests that EMPA may have the potential to reduce the incidence of chronic renal failure in T2D in the long term.

Funding: Commercial Support - Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance

Figure: Rapid decline in eGFR over the course of the EMPA-REG OUTCOME trial



Post-hoc analysis. Logistic regression analysis included treatment, sex, baseline BMI category, baseline HbA1c category, baseline eGFR category, geographical region and age. In patients treated with ≥1 dose of study drug. eGFR assessed by MDRD formula. Baseline eGFR values were available for 6967 participants. Median treatment duration was 2.6 years. Median observation time was 3.1 years. eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease

TH-OR036

Diffusion MRI for Assessment of Kidney Fibrosis Lena Berchtold,[2] Iris Friedli,[2] Karine Hadaya,[3] Pierre-Yves F. Martin,[1] Jean-Paul Vallée,[2] Sophie M. De Seigneux.[2] *[1]Hospital Universitaire de Geneve, Geneva City, Switzerland; [2]Hôpitaux Universitaire de Genève, Geneva, Switzerland; [3]University Hospital of Geneva, Geneva, Switzerland.*

Background: Renal interstitial fibrosis (IF) is a process common to all kidney diseases and is predictive of renal prognosis. IF can currently only be assessed by biopsy, an invasive procedure associated with complications and focal sampling. There is currently no clinically available noninvasive method to assess IF. Diffusion Magnetic Resonance Imaging (MRI) is emerging as a promising tool to evaluate kidney fibrosis non invasively. The aim of this study was to validate in a mixed CKD population a novel renal MRI diffusion sequence that we recently developed and to create a new non-invasive score for assessment of IF.

Methods: In this prospective study, we included 124 CKD patients having undergone a kidney biopsy (native or transplant). Optimized Diffusion-Weighted Imaging (DWI) and T1 sequences were compared to histological assessment of IF. Differences between cortical and medullary Apparent Diffusion Coefficient (ΔADC) and T1(ΔT1) values were assessed and compared to gold standard histopathology. We then combined routinely measured serum markers and ΔADC to create a new score for assessment of IF.

Results: In CKD patients, ΔADC correlated well with IF ($r=-0.55$, $p<0.001$). This good correlation was observed in both CKD and kidney transplant patients. ΔADC showed a better discrimination to IF than cortical ADC values, T1 values and ΔT1. To optimize fibrosis prediction, we combined ΔADC values to routinely obtained markers

known to correlate to fibrosis (phosphate, hemoglobin, eGFR) to obtain a score of predicted fibrosis. We observed a strong correlation between our score and histological IF($r=0.8$, $p<0.001$). We further built receiver operating characteristic curves and reported area under the curve (AUC) to discriminate between patients with high levels of fibrosis (≥40%). Analysis revealed that the new score was predictive of fibrosis ≥40% with an AUC was 0.99. The sensitivity and specificity to detect IF of more than 40% were 76.2% and 100% respectively, implying that our scoring system is able to identify patients with more than 40% without false positive.

Conclusions: In summary, we validated the use of the ΔADC to predict IF non invasively in CKD and kidney transplant patients. We further derive a scoring system from ΔADC and commonly obtained laboratory values and showed a high specificity to identify non invasively patient harboring extensive fibrosis (≥40%).

TH-OR037

A Pilot Pragmatic Randomized Trial of CKD Screening to Improve Care Among Hypertensive Veterans Carmen A. Peralta,[7] Martin J. Frigaard,[1] Anna Rubinsky,[8] Leticia Rolon,[6] Lowell J. Lo,[2] Santhi Voora,[5] Delphine S. Tuot,[8] Neil R. Powe,[3] Michael Shlipak.[4] *[1]Kidney Health Research Collaborative, Oakland, CA; [2]None, San Francisco, CA; [3]Priscilla Chan and Mark Zuckerberg San Francisco General Hospital & University of California SF, San Francisco, CA; [4]San Francisco VA Medical Center, San Francisco, CA; [5]UC San Francisco, San Francisco, CA; [6]UCSF Medical Center, San Francisco, CA; [7]University of California San Francisco/SFVAMC, San Francisco, CA; [8]University of California, San Francisco, San Francisco, CA.*

Background: It is uncertain whether screening for chronic kidney disease (CKD) can improve care of persons at high risk for complications.

Methods: We conducted a 3-arm randomized controlled trial within an integrated primary care clinic at the San Francisco VA (SFVA). The electronic health record (EHR) was used to identify eligible participants (from administrative codes), deliver interventions and ascertain outcomes. Non-diabetic hypertensive veterans without known CKD who receive primary care at SFVA were enrolled and cluster-randomized (41 clusters by provider) to Usual Care (UC), CKD Screening with patient-provider Education (SE) or CKD Screen-Educate plus clinical Pharmacist management (SEP). CKD screening included creatinine, cystatin C and albuminuria and CKD was defined as $eGFR_{creat\text{-}cys}$ <60 ml/min/1.73m^2 or albumin to creatinine ratio ≥30mg/g. Consent was written for providers and opt-out by mail for veterans.

Results: We mailed 2,012 consent letters and 133 veterans opted out. After exclusions, we randomized 1,819 veterans. Of 1,142 veterans randomized to intervention, 525 were identified with an upcoming appointment and had CKD screening ordered, among whom 371 (71%) completed testing. The yield of new CKD cases was 73 (20%, 95% CI 16-24%). Overall, proportions of participants who initiated ACE/ARB by end of study were 4.3% for UC, 6.0% for SE and 6.3%, for SEP. Proportions who initiated diuretics were 3.6% (UC), 4.8% (SE) and 6.0% (SEP). Among participants with screen-detected CKD, proportions who initiated ACE/ARB were 14.6% (SE) and 12.5% (SEP), and proportions who initiated diuretics were 7.3% (SE) and 9.4% (SEP). Differences were not statistically significant (all $p>0.2$). No adverse events were reported by providers.

Conclusions: We successfully implemented an EHR-based pragmatic trial of CKD screening with high rates of participation, and a 20% yield of undetected CKD among those screened. A larger study is required to test whether CKD screening would impact process of care and clinical outcomes.

Funding: NIDDK Support

TH-OR038

Ferric Citrate Reduced FGF23 in Patients with Non-Dialysis Dependent Chronic Kidney Disease (NDD-CKD) and Iron Deficiency Anemia (IDA) Irrespective of the Change in Serum Phosphate (P) Geoffrey A. Block,[3] Pablo E. Pergola,[2] Katrin Uhlig,[1] John F. Neylan,[1] Steven Fishbane,[4] Glenn M. Chertow.[5] *[1]Keryx Biopharmaceuticals, Boston, MA; [2]Renal Associates PA, San Antonio, TX; [3]Denver Nephrology, Denver, CO; [4]Hofstra Northwell Health, Commack, NY; [5]Stanford University School of Medicine, Palo Alto, CA.*

Background: Ferric citrate (FC), an oral iron-based P binder approved for control of serum P in patients (pts) with CKD on dialysis, has also been shown to improve hemoglobin (Hb) and iron parameters in pts with NDD-CKD with IDA. FGF23 is a key phosphate-regulating hormone and known to be elevated in patients with iron deficiency. Here, in a post hoc analysis of a phase 3 study, we examine effects of FC on FGF23 in pts stratified by baseline (BL) P and transferrin saturation (TSAT).

Methods: 233 pts with NDD-CKD and IDA were randomized 1:1 to receive FC (n=117) or placebo (n=116) for 16 wks. FC was initiated at 3 1-g tablets/day and titrated to achieve an increase in Hb ≥1 g/dL from BL (max 12 g/day). The effect of FC on both intact (i) and c-terminal (c)-FGF23 are reported by BL strata of P and TSAT, and the effect of FC on serum P are shown stratified by BL P.

Results: BL levels of iFGF23 and cFGF23 were positively related to BL P. After 16 wks of FC treatment, iFGF23 concentrations significantly decreased in both TSAT strata and across all strata of BL P except in pts with BL P <3.5 mg/dL. cFGF23 significantly decreased in both TSAT strata, and in all BL P strata except the highest (≥5.5 mg/dL). Changes in FGF23 did not consistently track with P changes [Table].

Conclusions: In pts with NDD-CKD and IDA, 16 wks of treatment with FC significantly reduced iFGF23 except in pts with the lowest BL P, while cFGF23 was significantly reduced except in pts with the highest BL P. iFGF23 and cFGF23 reductions occurred irrespective of BL TSAT, BL P and P change. These data suggest that FC reduces FGF23 via several, potentially independent pathways in pts with CKD and IDA.

Funding: Commercial Support - Keryx Biopharmaceuticals

		BL P <3.5 mg/dL	BL P 3.5 - <4.5 mg/dL	BL P 4.5 - <5.5 mg/dL	BL P ≥5.5 mg/dL	BL TSAT <20%	BL TSAT ≥20%
i-FGF23 (pg/mL) [n=117]	BL median (IQR) [n]	89.7 (66.6, 109.4) [16]	118.1 (86.3, 176.7) [65]	205.3 (127.4, 347.9) [25]	250.2 (177.4, 1612.5) [11]	117.1 (84.3, 246.4) [58]	143.5 (95.1, 227.6) [59]
	16 wks median (IQR) [n]	85.0 (57.1, 92.5) [13]	102.2 (66.7, 154.9) [46]	152.0 (93.2, 309.1) [20]	156.6 (101.4, 255.2) [7]	101.4 (59.7, 156.6) [41]	113.0 (75.3, 192.2) [45]
	p-value*	0.340	0.004	0.012	0.031	<0.001	0.019
c-FGF23 (RU/mL) [n=116]	BL median (IQR) [n]	266.0 (155.3, 406.7) [16]	330.5 (153.4, 546.9) [64]	415.8 (231.7, 931.7 [25]	576.8 (474.1, 1554.1) [11]	427.4 (215.4, 934.5) [57]	297.8 (164.9, 474.1) [59]
	16 wks median (IQR) [n]	173.1 (136.1, 256.9) [13]	198.3 (117.3, 293.5) [45]	328.0 (210.8, 588.7 [20]	592.1 (332.2, 898.5) [7]	259.3 (156.3, 409.2) [40]	207.1 (121.3, 385.8) [45
	p-value*	0.021	<0.001	0.027	0.297	<0.001	0.009
Serum P (mg/dL) [n=115]	Δ (BL to wk 16) mean±SE	+0.24±0.14	-0.26±0.08	-0.97±0.15	-1.74±0.63	-	-
	p-value†	0.115	0.002	<0.001	0.032	-	-

* p-values are from a non-parametric (Wilcoxon signed-rank) test; †p-values are from a parameter t-test; IQR = Interquartile Range

TH-OR039

Subclinical Coronary Artery Calcification Predicts Future Risk of Acute Coronary Syndrome Among Non-Dialysis CKD: A 5-Year Prospective Analysis Angela Y. Wang,[1] Henry H. Wu,[1] Sharon Yui Ling Cheung,[1] Sharon S. Wong,[1] Yat Y. Yau,[2] Sharbat Ryskaliyeva.[1] *[1]Medicine, University of Hong Kong, Queen Mary Hospital, HONG KONG, China; [2]Radiology, Biomedical Imaging Center, Hong Kong, Hong Kong.*

Background: Vascular calcification is highly prevalent in chronic kidney disease (CKD) and is considered to be largely a medial type of arterial calcification, secondary to deranged mineral metabolism as a result of impaired kidney function. This is in contrast to studies in the general population suggesting that vascular calcification is a marker of atherosclerotic burden. The current study aims to determine if subclinical coronary artery calcification may predict future risk of acute coronary syndrome (ACS) in non-dialysis CKD.

Methods: Two hundred and seventy-two asymptomatic CKD 3-5 subjects with no known history of coronary artery disease (age: 60 ± 10 years, 56% men) were recruited from a University Teaching Hospital. All subjects underwent plain multi-slice computed tomography to estimate coronary artery calcium score (CACS) and blood collection.

Results: All subjects were followed up prospectively for a median duration of 69 months, during which 18% of subjects developed ACS or died from other causes. Having a CACS ≥ 400 was independently associated with an increased risk of ACS and mortality [adjusted hazard ratio (HR), 4.66, 95% confidence intervals (CI), 1.37 - 15.83] controlling for Framingham risk factors. Further adjusting for eGFR, proteinuria, hemoglobin, serum albumin, phosphate, low density lipoprotein-cholesterol, and C-reactive protein did not alter the independent association between CACS ≥ 400 with ACS and death [adjusted HR, 4.31, 95% CI, 1.22 – 15.27]. The area under the receiver-operator characteristics curve for CACS in predicting a composite outcome of ACS and mortality in CKD was 0.74 (95% CI, 0.67 - 0.82). Having a CACS ≥ 400 showed a specificity of 86% in predicting a future risk of ACS and mortality.

Conclusions: This study for the first time demonstrates the importance of subclinical coronary artery calcification in predicting future risk of ACS and mortality among asymptomatic non-dialysis CKD subjects. These novel findings suggest that coronary artery calcification reflects atherosclerotic disease burden other than 'mineral stress' among CKD subjects. The potential value of CACS as a screening tool to early identify CKD subjects at future risk of ACS warrant further large scale evaluation.

Funding: Commercial Support - Sanofi Renal Co.

TH-OR040

Comparative Performance of Longitudinal Measures of Change in Kidney Function in Predicting ESRD and Death Benjamin C. Bowe,[2] Yan Yan,[2,4] Yan Xie,[2] Hong Xian,[2,1] Tingting Li,[2,3] Ziyad Al-Aly.[2,3] *[1]Department of Biostatistics, Saint Louis University College for Public Health & Social Justice, St. Louis, MO; [2]Clinical Epidemiology Center, Research and Development Service, Veterans Affairs St Louis Health Care System, St. Louis, MO; [3]Department of Medicine, Washington University School of Medicine, St. Louis, MO; [4]Department of Surgery, Washington University School of Medicine, St. Louis, MO.*

Background: Four different methods are commonly used in the evaluation of longitudinal changes of eGFR: ordinary least square (OLS), annualized change (AC), group-based trajectory models (GBT), and empirical Bayes slopes (EBS). Their comparative predictive performance for ESRD and death is unknown.

Methods: We built a development (N=274,277) and five validation cohorts (N~54,857 each) of US Veterans with stage 3a CKD and aimed to comparatively evaluate risk discrimination and reclassification of Cox proportional hazard regression models using the various longitudinal eGFR change measurement methods.

Results: For the outcome of death, when eGFR change was captured over a 5-year period, risk discrimination improved gradually from base model, OLS, AC, GBT, and EBS with a corresponding c-statistic of 0.698 (0.696-0.700), 0.702 (0.700-0.704), 0.703

(0.701-0.705), 0.706 (0.704-0.708), and 0.707 (0.705-0.709), respectively. Similarly, for the outcome of ESRD, the base, OLS, AC, GBT, and EBS models had a c-statistic of 0.699 (0.693-0.705), 0.710 (0.704-0.716), 0.711 (0.705-0.717), 0.716 (0.710-0.722), and 0.718 (0.712-0.724), respectively. EBS models offered the largest net reclassification improvement of 4% and 5% for death and ESRD, respectively, and they offered the largest integrated discrimination improvement of 0.56%, and 1.27% for death and ESRD, respectively. Results were reproduced in 5 validation cohorts, and were consistent when change in eGFR was captured over 1-year period.

Conclusions: Longitudinal eGFR change contributed to risk discrimination; measuring change using empirical Bayes slopes offered the most risk discrimination, and the largest improvement in net reclassification, and integrated discrimination for the outcomes of death as well as ESRD.

Funding: Veterans Affairs Support

TH-OR041

NPHP1 Gene Deletions Cause ESRD in 0.9% of Adult-Onset Cases Rozemarijn Snoek,[2] Jessica Van setten,[2] Bert Van der zwaag,[2] Brendan Keating,[3] Nine V. Knoers,[2] Martin H. De Borst,[1] Albertien M. van Eerde.[2] *[1]University Medical Center Groningen, Groningen, Netherlands; [2]University Medical Center Utrecht, Utrecht, Netherlands; [3]University of Pennsylvania, Philadelphia, PA. Group/Team: International Genetics & Translational Research in Transplantation Network* .

Background: Nephronophthisis (NPH) is the most prevalent (15%) genetic cause for end-stage renal disease (ESRD) in children. ~16% is caused by homozygous full gene deletions of the autosomal recessive *NPHP1* gene. However, little is known about the prevalence of these mutations in adult-onset ESRD. With data generated to perform genome-wide association studies in adult-onset ESRD patients, we aimed to determine the prevalence of homozygous *NPHP1* full gene deletions.

Methods: Renal transplant recipients were genotyped using the Affymetrix *Axiom Tx GWAS Array*, containing ~780,000 markers accross the genome with probes to cover *a priori* copy number variant (CNV) regions. CNVs (e.g. deletions and duplications) were determined based on median log2 ratios and B-allele frequency patterns. All findings were independently validated. In this abstract we report on 1272 cases, all Caucasian, from the TransplantLines-Genetics cohort. As we are currently analyzing ~4300 additional samples of various ethnicities, from the DeKAF Genomics, GoCAR, Dublin and Vienna cohorts (part of iGeneTRAiN), we will soon be able to report on ~5500 cases. Cases are included in the analysis when they had adult-onset ESRD, defined as start of renal replacement therapy (RRT) at any age ≧18 years.

Results: 1250 cases in the TransplantLines-Genetics cohort met the age criteria, of whom 11 (0.9%) showed a homozygous deletion of the *NPHP1* gene. Median age at start of RRT was 35 years (range 18-42), with eight cases aged ≧30. Notably only three out of 11 cases (27%) were diagnosed as having NPH. The other cases (8/11, 73%) were noted as chronic kidney disease with unknown etiology (n=5), glomerulonephritis (n=1), sporadic primary reflux nephropathy (n=1) and autosomal dominant polycystic kidney disease (n=1).

Conclusions: NPH is a classical pediatric kidney disease. However, we show that homozygous *NPHP1* full gene deletions alone cause 0.9% of all adult-onset ESRD in our dataset, with the majority of *NPHP1* cases ≧30 years of age. Considering that other types of mutations in *NPHP1* were not analyzed, and the other 19 known NPH genes were not even investigated, NPH is a relatively frequent cause of adult-onset ESRD. As only 27% of *NPHP1* cases were registered clinically as NPH, these results warrant wider application of genetic testing in adult-onset ESRD.

TH-OR042

Mutations of DNAJB11 Cause Autosomal Dominant Polycystic Kidney Disease Emilie Cornec-Le Gall,[1,2] Vladimir Gainullin,[1] Binu Porath,[1] Christina M. Heyer,[1] Marie-Pierre Audrezet,[2] Yannick Le Meur,[2] Francois Jouret,[3] Dominique A. Joly,[4] Claude Ferec,[2] Alan S. Yu,[5] Vicente E. Torres,[1] Peter C. Harris.[1] *[1]Mayo Clinic, Rochester, AL; [2]University Hospital, Brest, France; [3]University of Liege Hospital (ULg CHU), Liege, Belgium; [4]Assistance Publique Hôpitaux de Paris, Paris, France; [5]University of Kansas Medical Center, Kansas City, KS.*

Background: Seven to 10% of ADPKD patients remain genetically unresolved (GUR). Mutations of *GANAB*, *ALG8* and *SEC61B* impair polycystin-1 (PC1) maturation and were recently identified in ADPKD or Autosomal Dominant Polycystic Liver Disease families (ADPLD). We hypothesized that other genes processing PC1 may cause ADPKD.

Methods: We performed whole exome sequencing (WES) in a multiplex pedigree and analyzed 600 other GUR families (508 PKD, 92 PLD) by targeted NGS sequencing (TNGS; 55 candidate genes involved in N-linked glycosylation and/or identified by WES). TNGS enrichment was performed using the Agilent SureSelect Target Enrichment Kit and sequenced on the Illumina HiSeq4000.

Results: WES identified a missense variant (p.P54R) in *DNAJB11* in a 78y mother and her 47y daughter, both presenting with unenlarged polycystic kidneys; and CKD4 in the mother (eGFR=28ml/min/1.73m^2). *DNAJB11* is a protein of the endoplasmic reticulum (ER) functioning as a co-chaperone of BiP, a key player in the control of the protein folding and the regulation of ER stress. p.P54R occurs in the hallmark HPD motif of the highly conserved J domain of the protein, likely disrupting its interaction with BiP. TNGS led to the identification of 3 other *DNAJB11* mutations (p.R206*(3), c.479delC(1), p.L77P(1)) in 5 additional families. Ages at diagnosis ranged from 35 to 84y. Clinical presentation was consistent in the 12 affected members (35-92y, 3 males), with normal-sized polycystic kidneys and evolution to kidney atrophy; 5 patients (3 families) reaching ESRD (60y to 92y). Only 5 patients were hypertensive, all after age 50; PLD was mild or absent. Analysis of *DNAJB11-/-* cells showed a disruption of maturation of polycystin-1 (PC1), while reduced mature PC1 was seen in *DNAJB11+/–* cells.

Conclusions: Our findings extend the spectrum of genetic causes of ADPKD. DNAJB11 differs from typical ADPKD, with no renal enlargement but progressive tubulointerstitial fibrosis leading to ESRD. In addition to inhibiting PC1 maturation and leading to cystogenesis, mutations of *DNAJB11* may inhibit responding appropriately to ER stress in the kidney. Recognizing this further genetic heterogeneity is important since these patients may not benefit from the same therapeutic strategies.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-OR043

Highly Efficient Organoid Cystogenesis Reveals a Critical Role for Physical Microenvironment in Human Polycystic Kidney Disease Nelly M. Cruz,[1] Xuewen Song,[2] York P. Pei,[2] Benjamin S. Freedman.[1] *[1]University of Washington, Seattle, WA; [2]University Health Network and University of Toronto, Toronto, ON, Canada*.

Background: Polycystic kidney disease (PKD) is a life-threatening disorder in which tubular epithelia form fluid-filled cysts, disrupting organ architecture. A major barrier to understanding the pathophysiology of PKD is the absence of human cellular models that accurately and efficiently recapitulate cystogenesis. Previously, a genetic model of PKD has been generated using human pluripotent stem cells (hPSCs) and derived kidney organoids. Here we show that systematic substitution of physical components in this system can be used to dramatically increase or decrease cyst formation, unveiling a critical role for microenvironment in PKD.

Methods: Genome-modified *PKD1$^{-/-}$*, *PKD2$^{-/-}$*, or isogenic control hPSCs were differentiated *in vitro* into kidney organoids and subsequently cultured in the presence or absence of extracellular matrix and stroma. To directly test the effect of PKD mutations on the matrix microenvironment, individual organoids were embedded into larger collagen droplets. Structure and composition of organoid cysts were analyzed by immunofluorescence, microarray and immunoblot, and compared histologically to disease tissue from PKD patients.

Results: Removal of adherent cues increased cystogenesis 10-fold, producing cysts that phenotypically resembled human PKD cysts and expanded massively to 1-centimeter diameters. Non-PKD control organoids of identical genetic background did not form cysts. Cysts derived from hyperproliferative kidney tubular epithelial cells and showed upregulation of known PKD signaling pathways. Removal of stroma enabled proliferation and outgrowth of PKD cell lines, which revealed PC1 deficiency as a common molecular endpoint. Collagen droplets implanted with organoids furthermore contracted dramatically over a period of 2 weeks in a PKD-dependent manner.

Conclusions: Culture conditions have a significant impact on rates of cystogenesis in PKD organoids, enabling us to establish a highly efficient model of PKD cystogenesis. Collagen contraction could not be explained by differences in proliferation alone. Our findings directly implicate the microenvironment as a critical component at the earliest stages of PKD, with PC1 likely functioning as an adhesive or signaling molecule to control tissue contractility.

Funding: NIDDK Support, Commercial Support - Northwest Kidney Centers (unrestricted gift), Private Foundation Support

TH-OR044

Loss of Cep120 Disrupts Centriole Maturation and Ciliary Assembly and Function and Causes Cystic Kidney Disease Ewelina Betleja, Tao Cheng, Moe Mahjoub. *Washington University, St Louis, MO*.

Background: Jeune asphyxiating thoracic dystrophy (JATD) is a skeletal dysplasia characterized by a small thoracic cage, shortened bones in the limbs, and polydactyly. Infants develop difficulties with breathing due to abnormal development of their thoracic cage, but may survive into early childhood following surgery to correct these defects. However, these children develop life-threatening renal abnormalities, namely cystic kidneys. Whole-exome sequencing of JATD patients recently identified mutations in CEP120, which we previously showed to be important for centriole duplication. What remains unknown is the functional *in vivo* role of Cep120 during embryonic kidney development and adult kidney homeostasis.

Methods: Two complementary approaches were used to characterize the loss-of-function of Cep120. First, siRNA-mediated depletion of Cep120 was performed in mouse embryonic fibroblasts and epithelia to analyze its role *in vitro*. Next, we utilized a transgenic mouse model harboring a conditional allele (Cep120$^{f/f}$) to delete Cep120 in the developing kidney. Cep120$^{f/f}$ mice were crossed with Six2-Cre animals to delete the gene in the metanephric mesenchyme, and with Hoxb7-Cre animals to knock out Cep120 in the ureteric bud epithelium.

Results: Here we show that Cep120 plays a critical inhibitory role at the daughter centriole. Depletion of Cep120 in quiescent cells causes accumulation of pericentriolar material (PCM) components at the daughter centriole including pericentrin, Cdk5Rap2, ninein and Cep170. The elevated PCM levels result in an overall increase in microtubule-nucleating capacity at the centrosome. Consequently, loss of Cep120 leads to aberrant dynein-dependent trafficking of centrosomal proteins, dispersal of centriolar satellites, and defective ciliary assembly and function. Finally, we show that deletion of Cep120 in the developing mouse kidney recapitulates the *in vitro* cellular phenotypes, and results in rapid renal cystogenesis that is evident at birth.

Conclusions: Our results indicate that Cep120 inhibits untimely maturation of the daughter centriole, and defines a novel mechanism that regulates the asymmetric properties of the two centrioles in quiescent cells. These data provide the first detailed

characterization of the role of Cep120 (and potentially other daughter centriolar proteins) in renal cystogenesis of patients with JATD.

Funding: NIDDK Support

TH-OR045

Defective Mitochondrial Structure and Function Might Explain the Metabolic Derangement in Polycystic Kidney Disease Laura Cassina, Marco Chiaravalli, Christine Podrini, Isaline Rowe, Gianfranco Distefano, Alessandra Boletta. *San Raffaele Scientific Institute, Milan, Italy. Group/Team: Molecular basis of Polycystic Kidney Disease Unit*.

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a common genetic disorder characterized by bilateral renal cyst formation. By metabolomic profiling, we showed that *Pkd1* mutations result in enhanced glycolysis in cells and murine models of PKD. Moreover, inhibition of mitochondrial ATP synthase only mildly decreased ATP content in $Pkd1^{-/-}$ cells, indicating a weak mitochondrial contribution to total ATP production (Rowe et al, *Nat Med* 2013). Interestingly a recent study implicated a role for the Polycystins in mitochondrial function (Padovano et al, *Mol Cell Biol* 2017). We are investigating the role of mitochondria in the metabolic alterations in PKD.

Methods: Mitochondrial size, shape, and structural organization were analyzed by transmission electron microscopy (TEM). Mitochondrial oxygen consumption rate (OCR) was measured using Seahorse XFe96 Analyzer, and mitochondrial network morphology by live imaging of mitochondria-targeted EYFP.

Results: TEM images of the cystic epithelia showed evidence of grossly altered mitochondrial structure in kidneys of $Pkd1^{flox/-}$:Ksp-Cre mice at P4, as compared to control littermates. We have also observed mitochondria with altered cristae and decreased matrix electron density scattered among apparently normal mitochondria. Morphometric analysis of TEM images from $Pkd1^{flox/-}$:Ksp-Cre indicated decreased mitochondrial area and length. Time course analysis of mitochondrial shaping-proteins by western blot showed that the structural alterations seem to precede the biochemical ones. In parallel, we are assessing mitochondrial morphology in $Pkd1^{-/-}$ MEFs and CRISPR/Cas9-mediated *Pkd1* knockout IMCD cells and preliminary findings indicate that the absence of PC-1 affects mitochondrial network morphology. In line with this, functional analysis indicated that both basal and maximal OCRs are severely affected in cells lacking *Pkd1*.

Conclusions: Our data indicate that alteration in mitochondrial structure might explain the severe metabolic alterations in PKD models. Alternatively, the mitochondrial structural impairment might be secondary to metabolic defects. Our investigations along with ongoing genetic interaction studies will clarify whether mitochondria are players or modifiers in the pathophysiology of ADPKD.

TH-OR046

The Long Noncoding RNA Hoxb3os Is Dysregulated in Autosomal Dominant Polycystic Kidney Disease and Regulates mTOR Signaling Karam S. Aboudehen,[1] Mohammed S. Kanchwala,[3] Shayan A. Farahani,[1] Sophia M. Vrba,[1] Siu Chiu Chan,[1] Svetlana Avdulov,[1] Alan Mickelson,[1] Vishal Patel,[2] Chao Xing,[2] Peter Igarashi.[1] *[1]University of Minnesota, Minneapolis, MN; [2]University of Texas Southwestern Medical Center, Dallas, TX; [3]UT Southwestern Medical Center, Dallas, TX*.

Background: Polycystic kidney disease (PKD) is a debilitating disease that is characterized by the accumulation of numerous fluid-filled cysts in the kidney. Autosomal dominant polycystic kidney disease (ADPKD), is primarily caused by mutations in two genes, *PKD1* and *PKD2*. The pathophysiology of PKD is incompletely understood, and no FDA-approved treatment currently exists. Long noncoding RNAs (lncRNAs) are single-stranded RNA molecules that are >200 nucleotides in length, lack a long open-reading-frame, and have recently emerged as epigenetic regulators of development and disease; however, their involvement in PKD has not been explored previously.

Methods:

Results: Here, we performed deep RNA sequencing to identify lncRNAs that are deregulated in two orthologous mouse models of ADPKD (kidney-specific *Pkd1* and *Pkd2* mutant mice). We identified a kidney-specific and highly conserved lncRNA, called *Hoxb3os*, that was down-regulated in cystic kidneys from *Pkd1* and *Pkd2* mutant mice as well as in a *Pkd2* mutant renal cell line. Its human ortholog *HOXB3-AS* was down-regulated in kidneys from PKD patients. *Hoxb3os* was normally highly expressed in renal tubules in adult wild-type mice, whereas its expression was lost in the cyst epithelium of mutant mice. To investigate the function of *Hoxb3os*, we performed RNA-seq analysis on *Hoxb3os* knockdown mIMCD3 cells. Knockdown of *Hoxb3os* resulted in >2-fold dysregulation of 77 genes, 40 of which were similarly dysregulated in PKD mouse models. Pathway analysis suggested that *Hoxb3os* activated mTOR signaling, a pathway that has been implicated in PKD. Consistent with this result, ablation of *Hoxb3os* in mIMCD3 cells with CRISPR/Cas9 resulted in hyperactivation of mTOR signaling, as evidenced by enhanced phosphorylation of mTOR and ribosomal protein S6. Compared to wild-type cells, *Hoxb3os* knockout cells had increased rates of cell proliferation. Conversely, overexpression of *Hoxb3os* in wild-type mIMCD3 cells decreased phosphorylation of mTOR and S6. Collectively, these findings identify *Hoxb3os* as a novel lncRNA that is dysregulated in human and mouse PKD.

Conclusions: Down-regulation of Hoxb3os may underlie transcriptional abnormalities and hyperactivation of mTOR signaling in PKD.

Funding: NIDDK Support

TH-OR047

A Ketogenic Diet Slows Disease Progression in a Rat Model of Polycystic Kidney Disease Jacob A. Torres, Caroline M. Broderick, Samantha Kruger, Margaret F. Schimmel, Thomas Weimbs. *University of California, Santa Barbara, Goleta, CA*.

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a slowly progressing, life-threatening disease wherein normal healthy kidney tissue is replaced with fluid-filled cysts, decreasing renal function and leading to eventual renal failure. Cyst-lining cells have been shown to exhibit a metabolic shift towards aerobic glycolysis which may be exploited as a therapeutic approach. We have recently demonstrated that a reduction of food intake leads to a decrease in disease progression in a mouse model of ADPKD but the exact mechanism remained to be elucidated.

Methods: Here we show that the reduced food intake regimen leads to a partial state of ketosis and increased levels of beta-hydroxybutyrate (BHB). To test whether ketosis, rather than caloric reduction per se, leads to inhibition of renal cyst growth we treated the Han:SPRD rat model of PKD with a ketogenic diet regimen fed ad libitum.

Results: The high-fat, ketogenic diet leads to strong ketosis, elevation of BHB and concomitant reduction in blood glucose levels. Remarkably, Han:SPRD rats on the ketogenic diet exhibit strongly reduced disease progression with marked reduction in their cystic phenotype including significant reductions in kidney/body weight ratio, cystic index, proliferation and fibrosis.

Conclusions: These results suggest that cyst-lining cells may be dependent on glucose as their main energy source and are unable to switch to the use of ketone bodies and fatty acids under conditions of ketosis. These findings raise the exciting possibility that ketogenic diets may be a viable therapy for ADPKD.

Funding: Private Foundation Support

TH-OR048

Canonical Wnt Inhibitors Ameliorate Cystogenesis in a Mouse Orthologue of Human ADPKD Ao Li, Yuchen Xu, Song Fan, Jialin Meng, Xufeng Shen, Dongyue Ma, Li Zhang, Xiansheng Zhang, Guanqing Wu, Chaozhao Liang. *Anhui Province PKD Center, Institute/Department of Urology, The First Affiliated Hospital of Anhui Medical University, Hefei, China*.

Background: ADPKD is a heterogeneous disease which is caused by mutations in the *PKD1* or *PKD2* genes. Our previous study indicated that lack of *Pkd2* causes elevated β-catenin signaling in mouse tissues and cells (Kim et al. *JASN* 2009;20:2556). However, it remains unclear if β-catenin signaling plays a role in PKD phenotypes and if Wnt inhibitor halts the cyst formation in the disease models.

Methods: In this study, we crossed a newly generated standardized ADPKD mouse model for *Pkd2* (*Vil*-Cre;$Pkd2^{f3/f3}$) (Li et al *J. Cell Mol. Med.* 2017) with $Ctnnb1^{+/-}$ mice to generate the mouse model that haploinsufficiency of *Ctnnb1* (*Vil*-Cre;$Pkd2^{f3/f3}$;$Ctnnb1^{+/-}$). In addition, we also explored the effects of canonical Wnt signaling inhibitors (XAV939 and LGK974) on amelioration of disease phenotypes. XAV939-treated group and its solvent DMSO control group (n≥5/group) were intraperitoneally treated by 50 mg/kg/d and the same amount of DMSO from postnatal days 10 (P10) to 60 (P60); while LGK974-treated group and its solvent control group were intragastrically treated by 3mg/kg/d from postnatal days 30 (P30) to 90 (P90). The XAV939 and LGK974 treated animals were sacrificed at P65 and P95, respectively.

Results: *Vil*-Cre;$Pkd2^{f3/f3}$ mice with $Ctnnb1^{+/-}$ allele and the mice treated with XAV939 or LGK974 exhibit significantly prolonged lifespan, decreased cyst index, kidney/body ratio and improved renal function (BUN and Cr). All treated mice also showed significantly decreased proliferation, but no change for apoptosis, in renal cyst-lining epithelial cells. Canonical Wnt signaling targeted genes, including *Axin2*, *Ccnd1* and *c-Myc*, were also significantly downregulated in the treated ADPKD mouse kidney.

Conclusions: Our study provides clear evidence for the importance of β-catenin signaling in *Pkd2*-associated ADPKD phenotypes and develops new Wnt inhibitors XAV939 and LGK974, which affects at different targets of Wnt signaling, as a potential therapeutic modality for ADPKD that currently lacks effective therapy.

Funding: Government Support - Non-U.S.

TH-OR049

A Novel Strategy to Identify an Effective Treatment for Juvenile Nephronophthisis Hugo Garcia,[1] Flora Silbermann,[1] Esther Porée,[1] Clementine Mahaut,[2] Berangere M. Deleglise,[2] Pamela C. Rodriguez,[2] Soraya Sin-Monnot,[2] Luis Briseno-Roa,[2] Jean-Philippe M. Annereau,[2] Corinne Antignac,[1] Remi Salomon,[1,3] Marion H. Delous,[1] Sophie Saunier.[1] *[1]Imagine Inst, INSERM UMR1163, Paris, France; [2]Alexion R&D France, Paris, France; [3]Pediatric Nephrology, Necker Hospital, Paris, France*.

Background: Nephronophthisis (NPH) is an autosomal recessive tubulointerstitial nephropathy and the most common cause of hereditary end-stage renal disease in children and young adults. No specific treatment is currently available. Almost all the 21 identified *NPHP* genes encode proteins localized in the primary cilium.

Methods: We designed an *in vitro* high-throughput drug-screen strategy based on the Prestwick Chemical Library that includes more than 1120 compounds (mostly FDA-approved). We first evaluated migration and ciliogenesis in mammalian renal epithelial cells invalidated for either *Nphp1* or *Nphp4*, the two main genes involved in juvenile NPH, and identified 78 modulating drugs in these models. Then we selected 30 molecules

based on pharmacodynamics and assessed their effect on ciliogenesis of immortalized renal tubular cells derived from urine samples of *NPHP1*-deleted patients (URECs).

Results: We validated the positive effects of one compound (ARDF006) that increases the percentage of ciliated cell from and normalizes cilia length distribution. A similar rescue was observed when using specific agonists and antagonists targeting ARDF006 receptors. These G protein–coupled receptors partially localize at primary cilia. We could confirm *in vivo* effects of ARDF006 and a structural analog by using the *nphp4*-ATG morphant zebrafish model, which present a classical ciliopathy-related phenotype: body curvature and pronephric cysts. By using semi-automated imaging and analysis tools, we observed that ARDF006 treatment of morphant embryos does not have a significative impact on body curvature; however, it leads to a 27% relative reduction of pronephric cysts formation and an increase of ciliated cells percentage and cilia length in the distal part of the pronephros.

Conclusions: URECs and zebrafish represent useful and fast models to recapitulate patients' ciliogenesis defects and implement a pharmacologic approach for genetic deletion-related disease such as NPH.

Funding: Commercial Support - Alexion Pharmaceuticals, Private Foundation Support, Government Support - Non-U.S.

TH-OR050

Fenofibrate, a PPARA Agonist, Enhances Mitochondrial Metabolism and Slows Kidney and Liver Cyst Progression in a 6 Month Pre-Clinical Trial Ronak Lakhia, Matanel Yheskel, Andrea N. Flaten, Ezekiel Quittner-Strom, Vishal Patel. *University of Texas Southwestern Medical Center, Dallas, TX.*

Background: Impaired fatty acid oxidation (FAO) and oxidative phosphorylation (OXPHOS) are thought to underlie ADPKD progression. Peroxisome proliferator activated receptor alpha (PPARA) is a key regulator of FAO and OXPHOS. PPARA is downregulated in mouse and human ADPKD kidney cysts. We recently showed that deletion of *Ppara* aggravates cyst formation in an ADPKD model. The goal of this study was to determine if augmentation of FAO using the PPARA agonist fenofibrate can slow cyst growth.

Methods: Q-PCR, Western blot, and immunofluorescence staining confirmed downregulation of Ppara and its FAO-related target genes in 200-day-old *Pkd1*$^{RC/RC}$ mice. Sixteen 50-day-old *Pkd1*$^{RC/RC}$ mice were randomized to receive either standard chow diet or standard chow diet supplemented with fenofibrate. All mice underwent MRI to determine total kidney volume and total cyst volume at 180 days of age and were subsequently sacrificed at 200 days of age for molecular and histological analysis. An additional cohort of mice underwent *in-vivo* FAO assessment by ^{3}H-triolein assay.

Results: Fenofibrate treatment upregulated PPARA and enhanced FAO and OXPHOS in the kidneys of *Pkd1*$^{RC/RC}$ mice as evidenced by upregulation of FAO/OXPHOS genes, improved mitochondrial biogenesis, and increased oxidation of ^{3}H-triolein. MRI-assessed total kidney volume and total cyst volume was reduced by 30% and 60%, respectively, in fenofibrate-treated *Pkd1*$^{RC/RC}$ mice compared to *Pkd1*$^{RC/RC}$ mice on control diet. Moreover, kidney-weight-to-body-weight ratio, cyst index and serum creatinine were also reduced in the fenofibrate-treated *Pkd1*$^{RC/RC}$ mice. Fenofibrate treatment was associated with reduced kidney cyst proliferation and M2-like macrophages infiltration in *Pkd1*$^{RC/RC}$ mice treated with fenofibrate compared to *Pkd1*$^{RC/RC}$ mice on control diet. Fenofibrate treatment also reduced liver cyst burden, cyst proliferation, and liver inflammation and fibrosis.

Conclusions: Fenofibrate augments Ppara expression, improves FAO, and slows kidney and liver cyst growth, in *Pkd1*$^{RC/RC}$ mice. Our studies suggest that normalizing Ppara activity may be a useful therapeutic strategy for ADPKD.

Funding: NIDDK Support

TH-OR051

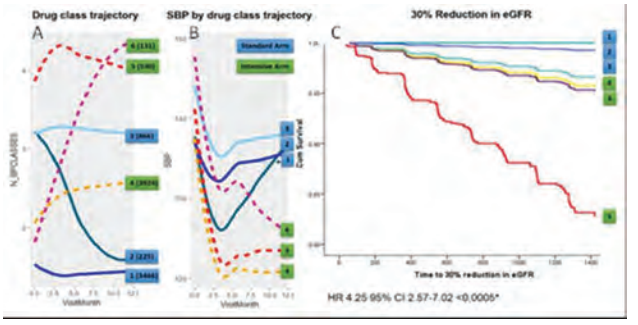
The Use of Four or More Drugs for Intensive Control of Blood Pressure Is Associated with Detrimental Renal Effects in the SPRINT Indranil Dasgupta,[1,2] Linsay Mccallum,[3] Alan G. Jardine,[4] Sandosh Padmanabhan.[4] *[1]Renal Medicine, Heartlands Hospital, Birmingham, United Kingdom; [2]University of Birmingham, Birmingham, United Kingdom; [3]Univeristy of Glasgow, Glasgow, United Kingdom; [4]University of Glasgow, Glasgow, United Kingdom.*

Background: In the SPRINT trial, A Randomized Trial of Intensive versus Standard Blood-Pressure Control, achievement of target SBP in the intensive arm required a higher number of drugs. Intensive treatment was associated with lower CV events and death but an increased incidence of adverse events. In this analysis we assessed the relationship between number of antihypertensive drugs classes used to achieve blood pressure target and renal adverse events.

Methods: Number of drug classes prescribed at randomisation and at 1,2,3,6,9,12 months were used to identify distinct trajectory groups in the standard and intensive arm using Latent Class Mixed Modelling, in 8,449 participants. Cox-PH models, adjusted for age, sex, SBP (AUC 0-12 months), prevalent CVD, prevalent CKD and number of drug classes at randomisation, were used to assess the association between drug class trajectories and renal adverse events.

Results: The 6 groups based on the trajectories of drug classes prescribed over the first year are shown in the panel A with corresponding SBP by drug class groups in panel B. Cox-PH model (reference category: Int-4, SBP <125 on 2.5 drug classes) showed that, in those without CKD at baseline, in Int-5 (125 on 4 drug classes) there was a higher risk of 30% reduction in eGFR (HR 4.25 [2.57-7.02]; p <0.0005) whilst those in Std-1 (SBP 133 on 1.5 drugs) had a lower risk (HR 0.17[0.10-0.29]; p <0.0005) (panel C. Those in Int-5 had a higher risk of hyperkalaemia (HR 1.64 [1.03-2.61]; p 0.036) with trend towards higher risk of AKI (HR 1.42 [0.95-2.12]; p 0.09).

Conclusions: Within the intensive arm of the SPRINT, treatment with ≥4 antihypertensive drug classes was associated with adverse renal events, independent of BP achieved in the first year.



Trajectories of number of antihypertensive drug classes used and GFR decline

TH-OR052

Dietary Sodium Restriction versus Diuretics for Salt-Sensitive Hypertension in CKD Dominique M. Bovee, Alexander H. Danser, Robert Zietse, Ewout J. Hoorn. *Erasmus Medical Center, Rotterdam, Netherlands.*

Background: Fluid overload and salt-sensitive hypertension are hallmarks of advanced chronic kidney disease (CKD) and associated with worse outcomes. Dietary sodium (Na^+) restriction is an accepted intervention, but longterm adherence remains a challenge. Distal diuretics could provide an alternative approach but they are considered less effective in advanced CKD because of reduced tubular secretion. Here, we compared both approaches head-to-head.

Methods: Twenty-two patients with CKD stage 3 or 4 and hypertension were included in this single-center, open-label, randomized cross-over trial (baseline eGFR 38 ± 13 ml/min/1.73 m2). Renin-angiotensin inhibitors and diuretics were discontinued (2 weeks prior to interventions and during study period). Subsequently, we compared dietary Na^+ restriction (60 mmol/day) versus amiloride/hydrochlorothiazide (5/50 mg once daily). Both interventions lasted for two weeks and were separated by a 2-week wash-out period. The primary endpoint was 24h systolic blood pressure (SBP).

Results: Urinary Na^+ excretion was successfully lowered with dietary Na^+ restriction (156 ± 66 to 60 ± 26 mmol/day, p<0.001), and remained similar with diuretics (147 ± 46 to 135 ± 39 mmol/day, p=0.3). Dietary Na^+ restriction lowered 24-hour SBP moderately (134 ± 13 to 131 ± 14 mmHg, p=0.08), whereas diuretics had a strong effect (137 ± 12 to 124 ± 13 mmHg, p<0.01 both for within intervention and between interventions). Both maneuvers significantly lowered indices of fluid overload, including body weight (-1.4 ± 1.1 kg with dietary Na^+ restriction and -1.8 ± 1.5 kg with diuretics), NT-pro-BNP (median -13 and -5 pmol/L), and overhydration as assessed by bioimpedance (-0.5 ± 0.6 and -1.4 ± 0.7 L). Finally, both interventions lowered eGFR (-3 ± 4 and -5 ± 4 ml/min/1.73 m2, p<0.05 for both) and showed a trend towards albuminuria reduction (median -25 mg/day for both interventions).

Conclusions: Distal diuretics but not dietary Na^+ restriction effectively lowers blood pressure in CKD 3 or 4 in the absence of renin-angiotensin inhibitors. Both interventions are equally effective in lowering indices of fluid overload, including body weight, NT-pro-BNP, and overhydration. These beneficial effects may outweigh the (hemodynamic) reduction in eGFR.

TH-OR053

Bilateral Renal Cryo-Denervation Decreases Blood Pressure and Improves Insulin Sensitivity in Fructose-Fed Sprague Dawley Rats Tyler Soncrant,[1] William H. Beierwaltes,[1] Haiping Chen,[1] Min Wu,[1] Noreen F. Rossi.[1,2] *[1]Wayne State University, Detroit, MI; [2]John D. Dingell VAMC, Detroit, MI.*

Background: Consumption of foods with fructose content is highly prevalent in modern diets with the average western intake at 17% of total calories. In combination with high salt intake, an elevated fructose diet leads to increased blood pressure and renal sympathetic nerve activity even prior to development of frank metabolic syndrome. Renal denervation reportedly improves glycemic control. We tested the hypothesis that bilateral cryo-denervation of the renal nerves will decrease mean arterial pressure (MAP) and improve insulin sensitivity in prediabetic fructose-fed rats on high salt diet.

Methods: Male Sprague Dawley rats were equipped with radiotransmitters to measure hemodynamics. They were given 20% fructose in their drinking water and 0.4% NaCl diet. After 7 days, they were either kept on 0.4% (LS) or switched to 4% NaCl (HS) diet for an additional 10-12 days. Control rats (C) were given plain water and 0.4% NaCl diet throughout. Rats were then subjected either to sham denervation (shamDNX) or bilateral denervation by alternately freezing (-150°C) and thawing the nerve 3 times (cryoDNX).

Results: One week later, MAP was unchanged in C or fructose-fed LS rats but had risen significantly in the fructose-fed HS rats from 110 ± 1 to 117± 2 mmHg; $P < 0.05$). Norepinephrine content decreased by 85% in cryoDNX vs shamDNX kidneys ($P < 0.01$).

MAP did not change in shamDNX but returned to pre-diet levels cryoDNX fructose-fed HS rats ($P < 0.05$). Blood glucose (BG) was 100 ± 9 mg/dL in C rats vs 131 ± 8 mg/dL in conscious fructose-fed rats ($P < 0.02$). Glucose:insulin ratio in shamDNX rats was lower (47 ± 8) than in cryoDNX rats (105 ±18; $P < 0.05$) regardless of sodium intake, consistent with improved insulin sensitivity in the cryoDNX rats.

Conclusions: We conclude that bilateral renal denervation normalizes MAP in prediabetic fructose-fed rats on high salt diet and also improves insulin sensitivity in fructose-fed rats regardless of sodium intake. Further studies are needed to identify whether afferent inputs from or efferent sympathetic inputs to the kidney are involved. Thus, the renal nerves likely play important role in glucose disposal.

Funding: Veterans Affairs Support

TH-OR054

In Two-Kidney One-Clip Hypertensive Sheep Cardiac and Contralateral Renal Sympathetic Nerve Activity Are Differentially Controlled

Tycho R. Tromp,[2,1] Jaap A. Joles,[2] Rohit Ramchandra.[1] *[1]The University of Aucklad, Auckland, New Zealand; [2]University Medical Center Utrecht, Utrecht, Netherlands.*

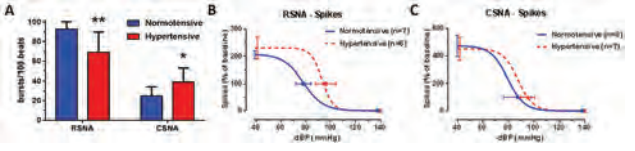
Background: Hypertension is often initiated and maintained by elevated sympathetic tone. We investigated changes in directly recorded sympathetic nerve activity (SNA) to the heart and nonclipped kidney in two-kidney one-clip (2K-1C) hypertensive sheep.

Methods: Adult ewes either underwent unilateral renal artery clipping (n=12) or sham surgery (n=15). Two weeks later, the carotid artery was cannulated and electrodes were placed in the (nonclipped) renal and/or cardiac nerve. Blood pressure (BP), heart rate (HR) and baseline and baroreflex control of SNA were recorded in the conscious sheep one week later.

Results: Unilateral renal artery clipping induced hypertension (systolic blood pressure 130±3 vs 111±4 mmHg in shams, p<0.001) after 21±5 days, and shifted the heart rate baroreflex curve rightwards (BP_{50} 120±13 vs 104±16 mmHg, p<0.01). HR was unchanged. The renal SNA (RSNA) baroreflex curve was also shifted rightwards (BP_{50} 93±3 vs 78±2, p<0.01) and showed increased gain (p<0.05). In the hypertensive group, cardiac SNA (CSNA) burst incidence (bursts/100 beats) was increased (39±14 vs 25±9 in normotensives, p<0.05), whereas RSNA burst incidence was decreased (69±20 vs 93±8 in normotensives, p<0.01).

Conclusions: In this ovine model of 2K-1C renovascular hypertension we show that cardiac and contraleteral renal sympathetic nerve activity were differentially controlled three weeks after clipping: baseline CSNA was increased whilst RNSA to the nonclipped kidney was decreased. We speculate that the observed contralateral RSNA decrease is a homeostatic response to increased blood pressure and the sodium avid state of the clipped kidney.

Funding: Private Foundation Support, Government Support - Non-U.S.



Differential control of contralateral renal and cardiac sympathetic nerve activity (SNA). Baseline contralateral renal SNA was decreased whereas cardiac SNA was increased (A). Baroreflex control of contralateral renal (B) and cardiac SNA (C) was differentially regulated.

TH-OR055

Sodium-Sensitive Blood Pressure Response in Type 1 Diabetes Is Accompanied by Impeded Skin Lymphangiogenesis

Eliane F. Wenstedt, Nienke M. Rorije, Rik H. Olde Engberink, Bert-jan Van den born, Jan Aten, Liffert Vogt. *Academic Medical Center, Amsterdam, Netherlands.*

Background: Studies showed that sodium can be non-osmotically stored within the skin. In response to high sodium diet (HSD), skin sodium content increases and macrophages are attracted, inducing lymphangiogenesis. Disruption of this system has been shown to lead to sodium-sensitive hypertension. This study investigates the effects of HSD on skin lymphatic and blood capillaries as well as blood pressure (BP) in type 1 diabetic patients (DM1).

Methods: We performed a randomized crossover study in males with DM1 and healthy controls. All subjects pursued an 8-day low sodium diet (LSD: <50 mmol Na^+/day) and HSD (>200 mmol Na^+/day). Diet order was randomized and time in-between diets was 1-2 weeks. After each diet, BP measurements and skin biopsies were obtained. Macrophages (CD68), vascular endothelium (CD31) and lymphatic endothelium (D2-40) were identified through immunohistochemistry.

Results: This study included 8 patients with DM1 and 12 controls who were similar regarding age, BMI and eGFR. In DM1 patients, mean arterial pressure was higher after HSD as compared to LSD (mean (SE) 85(2) vs. 80(1) mmHg, p=0.03) whereas in controls no differences were observed (78(1) vs. 78(2) mmHg, p=0.66). HSD increased lymphatic cross sectional surface area in controls (p=0.01) but not in DM1 patients (fig 1a). Less $CD68^+$ macrophages were present in DM1 patients compared to controls (p<0.001) (fig 1b). In both groups, there was a strong association between lymphatic capillary density and macrophage density (DM1 r=0.57 p=0.02; controls r=0.71 p=0.02).

Conclusions: The sodium-sensitive BP increase in DM1 patients is accompanied by impeded skin lymphangiogenesis and reduced skin macrophage content. Lymphangiogenesis may help to prevent sodium-sensitive hypertension.

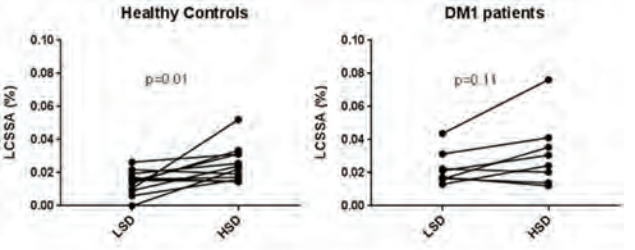


Fig 1A. Lymphatic cross sectional surface area (LCSSA) expressed as a percentage of the histological slice. LSD = low sodium diet, HSD = high sodium diet.

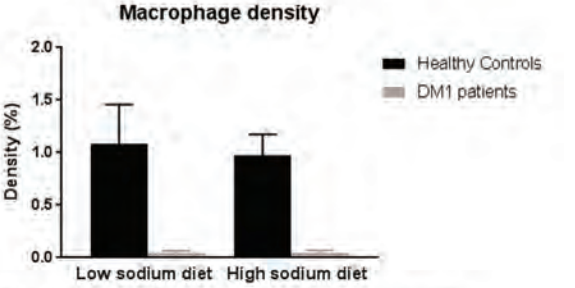


Fig 1B. Macrophage density in healthy controls and DM1 patients after low and high sodium diet, expressed as the percentage of the histological slice that is positively stained with CD68. Data are presented as median with interquartile range.

TH-OR056

Renal Medullary Interstitial Cell COX-2 Protects against Salt-Sensitive Hypertension and Papillary Necrosis

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Background: Cycloxygenase 2 (COX-2)-derived prostaglandins regulate renal hemodynamics and salt and water homeostasis. COX-2 is highly expressed in renal medullary interstitial cell (RMICs). COX-2 inhibition causes blood pressure elevation and papillary necrosis and COX-2 sustains RMIC survival in response to hypertonicity in vitro. However, the role or RMIC COX-2 *in vivo* in response to stimuli has not yet been definitively studied. We investigated the effect of COX-2 deletion in RMICs on blood pressure and papillary integrity in response to high salt intake.

Methods: We used inducible COX-2 deletion in RMICs in adult mice to avoid any potential developmental abnormalities of the inner medulla/papilla. Male $COX\text{-}2^{f/f}$ (WT) and Tenascin-C-CreER2;$COX\text{-}2^{f/f}$ (RMIC COX-2-/-) mice were fed a high salt diet, and blood pressure was monitored with tail cuff plethysmography. Mice were sacrificed at 2, 4, 9 weeks. For acute salt loading, mice were IP injected with isotonic saline equivalent to 10% of body weight, placed in metabolic cages, and 4-h urine was collected.

Results: Tamoxifen efficiently induced COX-2 deletion in inner medulla/papilla of the Tenascin-C-CreER2; $COX\text{-}2^{f/f}$ mice. Blood pressure was similar between RMIC COX-2-/- mice and WT mice on a normal salt diet. Although blood pressure was not altered in WT mice on a high salt diet, it increased gradually in RMIC COX-2-/- mice, peaked at 4-5 weeks (131 ± 5 vs. 121 ± 4 mmHg, $P < 0.05$, n = 7), and then progressively decreased to levels significantly lower than corresponding WT. After return to a normal salt diet for 3 weeks, RMIC COX-2-/- mice still had lower blood pressure (101 ± 4 vs. 116 ± 3 mmHg, $P < 0.05$, n = 4) and a urine concentrating defect (2535 ± 97 vs. 3080 ± 120 mOsm/kg H_2O of WT, $P < 0.01$, n = 6), in association with striking loss of papillae. Increased apoptotic cells in papillae of high salt treated RMIC COX-2-/- mice were seen 2 weeks after high salt intake. In addition, RMIC COX-2-/- mice had impaired pressure natriuresis one week after high salt diet (% of sodium excretion: 69.6 ± 8.9 vs. 98.4 ± 4.7 of WT, $P < 0.05$, n = 4).

Conclusions: These studies indicate that RMIC COX-2 plays an important role in salt and water homeostasis and provides cytoprotection for papillary structures in response to chronic high salt intake.

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TH-OR057

Loss of Salt Sensing Kinase, SGK1, in T Cells Abrogates Memory Cell Formation, Hypertension, and End-Organ Damage Hana A. Itani, Arvind K. Pandey, David G. Harrison. *Clinical Pharmacology, Vanderbilt University Medical Center, Nashville, TN.*

Background: Accumulating evidence indicates that NaCl can be concentrated in tissues with high salt-intake, age and in the setting of hypertension. Elevated NaCl has been shown to promote T_H17 cell formation in an SGK1-dependent fashion. We have previously shown that Memory T cells play a major role in the genesis of hypertension. These long-lived cells remain responsive to repeated hypertensive stimuli, such as salt feeding, and can be mobilized to enter the kidney where they release cytokines that promote renal dysfunction. To examine mechanisms by which T cells sense salt and contribute to salt-sensitivity, we tested the hypothesis that SGK1 in T cells is necessary for formation of memory T cells and their activation in salt-sensitive hypertension.

Methods: To study the role of SKG1 in hypertension, we produced mice with T cell specific deletion of SGK1, $SGK1^{fl/fl}$ x tg^{CD4cre} mice and used $SGK1^{fl/fl}$ mice as controls. To impose repeated episodes of hypertension, we treated these mice with L-NAME (0.5mg/ml) in drinking water for two weeks, allowed a two-week normotensive interval and a then fed high salt (4% NaCl) for three weeks.

Results: L-NAME followed by high salt increased memory T cells in the kidney, aorta and bone marrow of $SGK1^{fl/fl}$ control mice but not in $SGK1^{fl/fl}$ x tg^{CD4cre} mice, as identified by the surface marker $CD44^{hi}$. To assess markers of renal injury, we measured albumin in 24-hour urine samples collected at the end of the L-NAME/high salt. L-NAME/high salt caused striking albuminuria in $SGK1^{fl/fl}$ mice and was absent in $SGK1^{fl/fl}$ x tg^{CD4cre} mice. In additional studies, we found that loss of SGK1 in T cells abrogates renal and vascular inflammation and protects against hypertensive renal and vascular injury in the L-NAME/high salt model.

Conclusions: Thus, our data provide a potential mechanism by which SGK1 in T cells promotes their development of salt sensitivity and their mediation of renal and vascular dysfunction in hypertension.

TH-OR058

Angiotensin II Type 2 Receptor Contributes to Hypertension in Elastin Insufficiency Carmen M. Halabi. *Washington University School of Medicine, Saint Louis, MO.*

Background: Hypertension and vascular stiffness are major consequences of elastin insufficiency, as seen in patients with Williams syndrome and animals models of elastin insufficiency. Altered reactivity of resistance vessels was recently proposed to contribute to hypertension in elastin insufficiency. Specifically, mesenteric arteries of elastin insufficient mice were shown to be hypercontractile to angiotensin II (AngII) *ex vivo*. Interestingly, this hypercontractile response to AngII was partially mediated by AngII type 2 receptors (AT2R) as blockade of AT2R by PD123319 abrogated the hypercontractile response to AngII. The purpose of this study was to determine whether AT2R contributes to the hypertension seen with elastin insufficiency *in vivo*.

Methods: Elastin haploinsufficient (Eln^{het}) mice were bred to AT2R knock-out ($Agtr2^{KO}$) mice. Arterial blood pressure measurement and large artery compliance studies were performed on three month-old male littermate progeny with the following genotypes ($Agtr2^{WT}/Eln^{WT}$; $Agtr2^{KO}/Eln^{WT}$; $Agtr2^{WT}/Eln^{het}$; *and* $Agtr2^{KO}/Eln^{het}$). Structural examination of ascending aorta and mesenteric arteries was done via Alexa-633 hydrazide staining and transmission electron microscopy, respectively.

Results: As expected, compared to wild type (WT) mice, loss of AT2R had no effect on blood pressure or large vessel compliance in the presence of WT elastin ($Agtr2^{KO}/Eln^{WT}$), while elastin insufficiency resulted in elevated systolic blood pressure, pulse pressure, and reduced large vessel compliance in the presence of AT2R ($Agtr2^{WT}/Eln^{het}$). Loss of AT2R in elastin insufficient mice ($Agtr2^{KO}/Eln^{het}$) resulted in significant reduction of systolic and diastolic blood pressures, but no change in pulse pressure or large artery compliance. There were no structural changes in either the ascending aortae or mesenteric arteries of $Agtr2^{KO}/Eln^{het}$ compared to $Agtr2^{WT}/Eln^{het}$.

Conclusions: These results provide *in vivo* evidence for a role of AT2R in mediating elastin insufficiency-associated hypertension. Furthermore, these data suggest distinct mechanisms for the development of hypertension and vascular stiffness in elastin insufficiency, as loss of AT2R reduced blood pressure, but had no effect on large artery stiffness in this mouse model. Studies are underway to determine the effect of AT2R loss on resistance artery reactivity.

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TH-OR059

Interference with COP9 Signalosome Mimics FHHt Effects on WNK/NCC Signaling Ryan J. Cornelius, Chao-Ling Yang, David H. Ellison. *Oregon Health and Science University, Portland, OR.*

Background: The Familial Hyperkalemic Hypertension (FHHt) cullin 3 (CUL3) mutant is unable to degrade WNK kinases normally, activating the thiazide-sensitive NaCl cotransporter (NCC). Previous work showed that the CUL3 mutant does not bind to the COP9 signalosome (CSN), a deneddylase involved in regulating cullin-RING ligases. We sought to determine whether this impaired binding was the cause of the increased WNK protein abundance in FHHt by inhibiting the CSN *in vivo*.

Methods: The Pax8 mouse system was used to generate mice in which the catalytically active CSN subunit, JAB1, was deleted only along the nephron, after full development (KS-$JAB1^{-/-}$).

Results: JAB1 protein abundance was 62% lower in KS-$JAB1^{-/-}$ kidney vs WT. Western blot analysis demonstrated that loss of JAB1 caused enhanced neddylation of CUL3. Moreover, total CUL3 expression was reduced by 37%, indicating decreased CUL3 stability, as reported by other groups for the FHHt CUL3 mutant. As expected, KLHL3 protein abundance was lower and total WNK1 and WNK4 protein abundance were higher. Phosphorylated WNK4 levels and the ratio of pNCC to total NCC were also higher, but, surprisingly, total NCC protein abundance was dramatically reduced. Consistent with the low total NCC, KS-$JAB1^{-/-}$ mice did not develop an FHHt phenotype. KS-$JAB1^{-/-}$ mice were hypokalemic ($[K^+]$: 3.20 ± 0.07 vs 3.55 ± 0.06 mM, $P < 0.01$), hyperchloremic ($[Cl^-]$: 117.5 ± 1.7 vs 112.7 ± 1.3 mM; $P < 0.05$), and acidemic ([TCO]: 11.83 ± 0.87 vs 18.00 ± 0.57 mM, $P < 0.001$). Urine output was approximately twice as high in KS-$JAB1^{-/-}$ (9.4 ± 1.6 vs 4.7 ± 0.50 ml/day, $P < 0.05$) and there was Na^+ and K^+ wasting (Na^+ clearance: 0.135 ± 0.013 vs 0.088 ± 0.006 ml/day/g, $P < 0.01$; K^+ clearance: 4.90 ± 0.40 vs 3.68 ± 0.28 ml/day/g, $P < 0.05$). As we reported with CUL3 deletion, chronic JAB1 deletion also led to kidney tubule damage, as determined by H&E staining.

Conclusions: CUL3 in KS-$JAB1^{-/-}$ mice was highly neddylated, with increased WNK protein abundance, consistent with impaired degradation; Na^+ and K^+ wasting was observed, however, due to decreased levels of total NCC. In conclusion, KS-$JAB1^{-/-}$ mice mimic many, but not all, aspects of the FHHt phenotype.

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TH-OR060

Pannexin 1 Channels in Renin Expressing Cells Regulate RAAS and Blood Pressure Leon DeLalio,[2,4] Ester Masati,[4] Thu H. Le,[3] Paula Q. Barrett,[2] Roberto Ariel Gomez,[2] Brant Isakson.[5,4] *[2]Child Health Research Center, University of Virginia, Charlottesville, VA; [3]University of Virginia School of Medicine, Charlottesville, VA; [4]Robert M. Berne Cardiovascular Research Center, University of Virginia, Charlottesville, VA; [5]Molecular Physiology and Biological Physics, University of Virginia, Charlottesville, VA.*

Background: The homeostatic regulation of blood pressure (BP) by renin lineage-cell differentiation in the renal vasculature and the adrenal zona glomerulosa (ZG) is crucial for controlling renin expression and aldosterone synthesis. In the renal vasculature, renin lineage cells respond to changes in blood pressure by differentiating and re-expressing a fetal renin gene program, termed recruitment. In the adrenal cortex, ZG cells of the renin lineage centripetally turnover, differentiating from an aldosterone synthetic program to a glucocorticoid synthetic one, thus maintaining steady state aldosterone production. The cellular signals coordinating these responses is unclear, but evidence from our lab posits a potential role for purinergic signaling mediated by Pannexin 1 channels. **We hypothesized that Pannexin 1 (Px1) channels regulate purinergic communication and cell differentiation in the renal vasculature and adrenal ZG cells to maintain blood pressure homeostasis.**

Methods: Blood pressure radiotelemtry, hormone specific RIA and ELISA, immunohistological staining, qPCR, and pressure myography.

Results: To test this hypothesis, we generated a novel renin cell Panx1 knockout mouse (Ren1-Px1 KO). At baseline, mice exhibit no differences in kidney size, morphology, or plasma renin concentration. However, KO mice have enhanced vasoconstriction responses and a significant elevation in aldosterone levels (1737 compared to 1172 pg/mL; $p<0.5$), which corresponded with aberrant ZG cell differentiation in the adrenal cortex. By radiotelemetry, Ren1-Px1 KO mice displayed increased baseline BP (110 compared to 100 mmHg; $p<0.5$). Lastly, we assessed renal renin dynamics in response to BP lowering with captopril. Ren1-Px1 KO mice retain adequate capacity to secrete renin at baseline, but fail to adequately upregulate renin expression in the juxtaglomerular afferent arteriole, determined by quantitative immunostaining, after BP lowering.

Conclusions: We conclude that loss of Panx1 from renin lineage cells causes activation of RAAS primarily by influencing differentiation responses in ZG cells, despite changes in renal renin dynamics. Thus, Pannxin 1 channels may regulate complex adrenal cell differentiation events important for long term BP control.

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TH-OR061

Single-Cell Transcriptome Profiling of Glomeruli from Healthy and Nephritic Mice Jun-Jae Chung,[1] Jasmine Chen,[2] Leonard Goldstein,[2] Zora Modrusan,[2] Andrey S. Shaw.[1] *[1]Research Biology, Genentech, South San Francisco, CA; [2]Molecular Biology, Genentech, South San Francisco, CA.*

Background: Disruption of glomerular homeostasis leads to filtration barrier damage and kidney disease. Determining the gene expression profiles of cells that comprise the glomerulus will facilitate understanding of the processes involved in kidney diseases. Single-cell RNA-seq analysis can provide information not attainable using bulk RNA-seq, such as cell subpopulations and heterogeneity of cellular responses to injury.

Methods: Single cell suspensions of glomerular cells were prepared via magnetic bead isolation followed by enzymatic digestion from healthy C57BL/6J mice or mice with anti-GBM glomerulonephritis. The individual transcriptome of thousands of cells in the mouse glomeruli were obtained using the droplet-based 10x Genomics Chromium™ technology and Next-Generation Sequencing.

Results: Principle component analysis (PCA) of cells from healthy glomeruli clearly distinguished the three major cell types in the glomerulus (podocytes, mesangial cells, endothelial cells). Analysis of differentially expressed genes identified novel candidates for mesangial cell markers. After induction of anti-GBM glomerulonephritis, we detected

accumulation of immune cells and significant changes in the gene expression patterns of glomerular cells. After resolution of the heterologous phase, global gene expression pattern of podocytes largely reverted back to its original state, whereas the transcriptome profile of mesangial cells and endothelial cells remained altered. We observed heterogeneous expression of CCL2 in the mesangium of a CCL2-reporter mouse, which was increased after induction of glomerulonephritis. CCL2 expression was enriched in mesangial cells that had higher levels of immediate early genes, suggesting these cells may act as sentinels during glomerular injury. Comparing the transcriptomes of each cell type from healthy and nephritic glomeruli reveal candidate genes for further functional studies.

Conclusions: Single-cell RNA-seq reveals previously undetected heterogeneity in the injury response of glomerular cells.

TH-OR062

Human iPSC-Derived Glomeruli Facilitate Accurate Modeling of Podocytopathy Lorna J. Hale,[2] Sara E. Howden,[2] Belinda Phipson,[2] Irene Ghobrial,[2] Pei Xuan Er,[1] Santhosh V Kumar,[3] Alicia Oshlack,[2] Melissa H. Little.[2] *[1]Murdoch Children's Research Institute, Parkville, NSW, Australia; [2]Murdoch Childrens Research Institute, MELBOURNE, NSW, Australia; [3]Murdoch childrens research institute, Melbourne, NSW, Australia*.

Background: Numerous kidney diseases leading to proteinuria result from alterations to the podocyte which leads to foot process effacement and loss of slit diaphragms. Immortalised cell lines have been the gold standard in podocyte biology, however, this model has inherent limitations. Consequently, validation of novel disease-associated mutations is most often performed in animal models which may not replicate the human condition. The advent of iPSC organoids now provides a new avenue for the study of human podocyte disease *ex utero*.

Methods: Sieved glomeruli isolated from human iPSC kidney organoids were characterised and compared to conditionally immortalised human podocytes by RNA-sequencing. The capacity of organoid-derived glomeruli to recapitulated podocytopathy through introduction of clinically relevant mutations into iPSC was assessed using CRISPR-Cas9 technology.

Results: Organoid-derived glomeruli showed superior podocyte-specific gene expression when compared to conditionally immortalised podocytes, with an upregulation of 2187 genes. GO terms associated with slit diaphragm development, and glomerular epithelial cell differentiation and development were significantly enriched. Glomeruli isolated from homozygous MAFB mutant organoids accurately recapitulated anticipated disease related transcriptional changes.

Conclusions: We provide the first evidence that human iPSC kidney organoids can accurately model podocytopathy. Organoid podocytes which are allowed to form in 3D via the patterning and segmentation seen during normal nephrogenesis are superior to the current gold standard conditionally immortalised podocyte cell system. The capacity to readily generate such an accurate model of the human glomerulus from iPSC will facilitate patient-specific functional genomics to validate novel podocytopathy genes and further interrogate the pathogenic mechanisms of existing podocytopathies *in vitro*.

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TH-OR063

Calcium/Calmodulin-Dependent Kinase IV Compromises Podocyte Function in Autoimmune and Non-Autoimmune Kidney Diseases Kayaho Maeda,[1] Kotaro Otomo,[3] Nobuya Yoshida,[1] Sean D. Bickerton,[4] Tarek Fahmy,[4] Maria Tsokos,[2] George C. Tsokos.[1] *[1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Keio University School of Medicine, Tokyo, Japan; [4]Yale School of Medicine, New Haven, CT*.

Background: Podocyte dysfunction is a common feature of renal injury in autoimmune or non-autoimmune renal diseases and the good target of proteinuric kidney diseases. We previously reported that calcium/calmodulin-dependent kinase IV (CaMK4) was upregulated as a result of exposure to IgG from the patients with lupus nephritis (LN). Since podocytes from patients and mice with lupus have increased levels of CaMK4 linked to decreased nephrin expression, we considered that targeted delivery of a CaMK4 inhibitor (KN93) to podocytes should preserve podocyte function.

Methods: We treated lupus-prone MRL.*lpr* mice starting at 8 weeks age, mice injected lipopolysaccharide (LPS) or adriamycin with anti-podocin or nephrin tagged nanolipogels (nlg) loaded with KN93 intraperitonealy (i.p.). We also used immortalized differentiated human podocytes to examine the actin structure and function under LPS or lupus IgG treatment.

Results: Podocytes from lupus-prone or LPS-or adriamycin-treated mice and patients with LN or focal segmental glomerulosclerosis (FSGS) displayed increased expression of CaMK4. Targeted delivery of KN93 to podocytes suppressed proteinuria, immune complex deposition and crescent formation in lupus-prone mice and proteinuria in mice with LPS-or adriamycin-induced podocyte injury by preserving podocyte structure, nephrin and synaptopodin expression. In animals exposed to adriamycin, podocyte-specific delivery of KN93 prevented and reversed renal disease. Similarly, CaMK4 deficiency also protected from those podocyte injuries. Inhibition or silencing of CaMK4 protected from LPS-induced the actin cytoskeleton injury and synaptopodin degradation in human podocytes. Activated CaMK4 interacted with 14-3-3β and disrupted the binding of synaptopodin with 14-3-3β leading to actin cytoskeleton rearrangement of podocytes.

Conclusions: We conclude that inhibition of CaMK4 preserves podocyte structure and function and targeted delivery of a CaMK4 inhibitor to podocytes should have therapeutic value in lupus nephritis and podocytopathies including FSGS.

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TH-OR064

Ex Vivo Induced Neutrophil Extracellular Traps Are Intrinsically Different in ANCA-Associated Vasculitis- and Systemic Lupus Erythematosus Laura S. van Dam,[1] Tineke Kraaij,[1] Sylvia Kamerling,[1] Hans Ulrich Scherer,[1] Charles D. Pusey,[2] Ton J. Rabelink,[1] Cees van Kooten,[1] Yoe Kie Onno Teng.[1] *[1]LUMC, Leiden, Netherlands; [2]Imperial College London, London, United Kingdom*.

Background: Neutrophil extracellular traps (NETs) are immunogenic, extracellular DNA structures that harness important autoantigens to be recognized by the adaptive immune system. NETs are thought to play a pivotal role in the pathogenesis of AAV and SLE. However it is still unclear how and if NETs act as a common pathway in the pathophysiology of these clinically divergent autoimmune diseases. The aim of the present study is to characterize AAV- and SLE-induced NETs.

Methods: Healthy neutrophils were stimulated with 10% serum of AAV (n=101) and SLE (n=59) patients to induce NETs. Ex vivo NET induction by serum and IgG-depleted serum was measured by a novel, highly-sensitive NET quantification assay using 3D-confocal microscopy. Qualitative characteristics of NETs were studied by immunofluorescence to detect NET-related auto-antigens. Additionally, the morphology and kinetics of AAV- and SLE-induced NETs were visualized by live cell imaging and electron microscopy.

Results: Ex vivo NET induction by AAV sera was 20.74 [9.56 – 74.14], (median [Q1 - Q3]) fold higher than sera of healthy controls (n=10) and also significantly higher than NET induction by SLE sera 5.02 [1.88 – 14.33]). Depletion of IgG from serum did not reduce NET induction in AAV, whereas it was significantly decreased in SLE. Colocalisation of NET-related auto-antigens was different: citrullinated histon-3 (CitH3) was predominantly found on AAV-induced NETs, whereas high mobility group box protein-1 (HMGB1) was exclusively found on SLE-induced NETs. Live cell imaging demonstrated that the kinetics of SLE-induced NETs peaked at 30 minutes, while AAV-induced NETs peaked at 4 hours. Intriguingly, SLE sera induced immediate clustering of neutrophils surrounding NETs whereas AAV sera induced NETs composed of long, thin DNA-fibres through lytic expulsion.

Conclusions: We demonstrate distinct features of ex vivo AAV- and SLE-induced NETs, indicating that NET formation in AAV and SLE is based on different mechanisms. Future studies should be directed at unravelling how different NETs are involved in causing SLE- or AAV-associated glomerulonephritis.

TH-OR065

The Co-Inhibitory Molecule PD-L1 Contributes to Regulatory T Cell-Mediated Protection in Murine Crescentic Glomerulonephritis Katrin Neumann, Annett Ostmann, Philippe C. Breda, Hans-Joachim Paust, Ulf Panzer, Gisa Tiegs. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany*.

Background: Glomerular diseases such as crescentic glomerulonephritis (cGN) are mediated by inappropriate cellular and humoral immune responses towards autoantigens subsequently leading to the development of end-stage renal failure. Previously, we demonstrated a crucial role for regulatory T cells (Tregs) in suppressing pro-inflammatory Th1 and Th17 cell-mediated immune responses during nephrotoxic nephritis (NTN), the murine model of cGN. However, mechanisms of immune regulation in cGN are insufficiently understood. Here, we aim at investigating the role of the co-inhibitory molecule PD-L1 in Treg-mediated protection from NTN.

Methods: NTN was induced in PD-L1$^{-/-}$ mice by injection of the nephritogenic serum. Disease severity was investigated at day 8 after NTN induction and compared to C57BL/6 wild type (WT) mice. Kidney damage was quantified by crescent formation in PAS-stained tissue sections and determination of albumin-to-creatinine ratio by ELISA. PD-L1 was blocked in WT mice by injection of an anti-PD-L1 antibody. To neutralize IFNγ, PD-L1$^{-/-}$ mice were treated with an anti-IFNγ antibody. Tregs from nephritic PD-L1$^{-/-}$ or WT mice were adoptively transferred into Rag1$^{-/-}$ mice one day before NTN induction. Gene and protein expression analysis was done by quantitative RT-PCR and flow cytometry.

Results: PD-L1$^{-/-}$ mice developed more severe NTN compared to WT mice. Histological analysis revealed increased numbers of T cells, macrophages/DCs but also Foxp3^{+} Tregs in the kidneys of nephritic PD-L1$^{-/-}$ mice. Moreover, renal and systemic IFNγ-mediated Th1 immune response as well as systemic humoral immune response were strongly enhanced in nephritic PD-L1$^{-/-}$ mice. Blockage of PD-L1 in WT mice amplified renal Th1 response and aggravated disease pathogenesis. Furthermore, neutralization of IFNγ ameliorated NTN in PD-L1$^{-/-}$ mice. In co-culture, renal DCs from nephritic PD-L1$^{-/-}$ mice strengthened expression of IFNγ in CD4^{+} T cells. Interestingly, PD-L1$^{-/-}$ Tregs were not able to suppress activation and proliferation of responder CD4^{+} T cells *in vitro* and they also failed to protect from NTN *in vivo*.

Conclusions: PD-L1 displays a protective role in NTN, which is related to Treg- and DC-dependent suppression of the Th1 immune response. Thus, targeting PD-L1 may represent a novel therapeutic option in cGN.

TH-OR066

DNA-Aptamer Raised against RAGE Improves the Development of Lupus Nephritis in MRL/lpr Mice Kensei Taguchi,[1,5] Akito Maeshima,[2] Sho-ichi Yamagishi,[3] Yosuke Nakayama,[1] Yusuke Kaida,[1] Yuichiro Higashimoto,[4] Craig R. Brooks,[5] Kei Fukami.[1] *[1]Division of Nephrology, Department of Medicine, Kurume University, Kurume, Japan; [2]Gunma University Graduate School of Medicine, Maebashi, Japan; [3]Kurume University, Kurume, Japan; [4]Kurume University School of Medicine, Kurume, Japan; [5]Vanderbilt University Medical Center, Nashville, TN.*

Background: Lupus nephritis (LN) affects 60% of patients with systemic lupus erythematosus (SLE). Although immunosuppressive drugs are used as a first-line therapy, LN still negatively impacts the survival and quality of life in SLE patients. The Receptor for advanced glycation endproducts (RAGE), which belongs to the immunoglobulin superfamily, is strongly associated with innate immune responses. In this study, we examined whether RAGE could be involved in LN development in lupus prone MRL/lpr mice. Further, we explored the therapeutic impact of RAGE DNA-aptamer on renal damages on these mice.

Methods: Renal expression levels and urinary RAGE excretion (uRAGE) were determined in female mice at 8, 12, 16, 18, 20 weeks of age by IHC and ELISA, respectively. A DNA-aptamer raised against RAGE (RAGE-apt) or Control-aptamer (Ctrl-apt) was subcutaneously administered to MRL/lpr mice for 10weeks. Histological and serological analyses were performed.

Results: uRAGE levels, but not urinary protein excretion, were significantly increased in 8-week-old MRL/lpr mice compared with control MRL/MPJ mice. In addition, glomerular RAGE expression was markedly increased starting at 12 weeks and was associated with the increased glomerular extracellular matrix accumulation and cellular crescents. RAGE expression was dramatically increased in endothelium and infiltrating macrophages of the glomeruli. Administration of RAGE-apt significantly ameliorated mesangial expansion, wire-loop and crescent formation, and macrophage infiltration into the glomeruli in MRL/lpr mice. In addition, RAGE-apt, but not Ctrl-apt, significantly reduced the levels of pro-inflammatory cytokines gene expression such as IL-6, TNF-a, and MCP-1 in renal cortex of MRL/lpr mice.

Conclusions: RAGE is involved in the pathogenesis of LN, and the treatment with RAGE-apt represents a promising therapeutic strategy for preventing the development of LN.

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TH-OR067

Urine Neutrophil Gelatinase-Associated Lipocalin to Predict Renal Response after Induction Therapy in Active Lupus Nephritis Bancha Satirapoj,[2] Chagriya Kitiyakara,[3] Yingyos Avihingsanon,[1] Ouppatham Supasyndh.[2] *[1]King Chulalongkorn Memorial hospital, Chulalongkorn University, Bangkok, Thailand; [2]Phramongkutklao hospital, Bangkok, Thailand; [3]Ramathibodi Hospital, Bangkok, Thailand.*

Background: Tubulointerstitial injury is important to predict the progression of lupus nephritis (LN). Urine neutrophil gelatinase-associated lipocalin (NGAL) has been reported to detect worsening LN disease activity. Thus, urine NGAL may predict renal outcomes among lupus patients.

Methods: We conducted a prospective multi-center study among active LN patients with biopsy-proven. All patients provided urine samples for NGAL measurement by ELISA collected from all patients at baseline and at 6-month follow-up after induction therapy.

Results: In all, 75 active LN patients were enrolled (mean age 31.8±9.9 years, median UPCR 4.8 g/g creatinine level with interquartile range (IQR) 2.5 to 8.4 and mean estimated glomerular filtration rate (GFR) 89.1±36.3 mL/min/1.73 m2). At baseline measurement, median urinary NGAL in complete response, partial response and nonresponse groups was 11.8 (IQR; 6.2, 23.5), 18.9 (IQR; 8.9, 43.1), and 78.9 (IQR; 23.2, 118.4) ng/mL, respectively (P=0.004). Urinary NGAL (ng/mL) correlated positively with proteinuria and correlated negatively with serum complement C3 level. Based on ROC analysis, urinary NGAL (AUC; 0.769, 95%CI 0.603-0.935) outperformed conventional biomarkers (serum creatinine, urine protein, and GFR) in differentiating complete and partial response groups from the nonresponse group. The urine NGAL cutoff value in the ROC curve, 28.07 ng/mL, discriminated nonresponse with 75% sensitivity and 66.7% specificity.

Conclusions: Urine NGAL at baseline performed better than conventional markers in predicting a clinical response to treatment of active LN except serum complement C3 level. It may have the potential to predict poor response after induction therapy.

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TH-OR068

Molecular Profiling of Renal Compartments from Serial Lupus Nephritis Kidney Biopsies to Identify Markers of Response Samir V. Parikh,[4] Ana Malvar,[1] Huijuan Song,[4] John P. Shapiro,[4] Valeria G. Alberton,[5] Juan M. Mejia-Vilet,[4] Isabelle Ayoub,[4] Anjali A. Satoskar,[4] Jianying Zhang,[4] Lianbo Yu,[4] Paolo Fadda,[4] Michael T. Eadon,[2] Daniel J. Birmingham,[3] Brad H. Rovin.[4] *[1]HOSPITAL FERNANDEZ, Buenos Aires, Argentina; [2]Indiana University Division of Nephrology, Indianapolis, IN; [3]Ohio State University Medical Center, Columbus, OH; [4]Ohio State University Wexner Medical Center, Columbus, OH; [5]hospital Fernandez, Buenos Aires, Argentina.*

Background: Molecular profiling of kidney compartments from serial renal biopsies of proliferative lupus nephritis (LN) may provide novel information to improve treatment. Here we present results of molecular profiling of the glomeruli and tubulointerstitum (TI).

Methods: A kidney biopsy was done at flare (Bx1) and after induction therapy (Bx2) in 56 LN patients. Controls were living donor transplant biopsies (n=7). Glomeruli and TI were isolated using laser capture microdissection, RNA was extracted and analyzed by Nanostring. Transcript expression of LN flares was compared to controls, and complete renal responders (CR, n=28) were compared to non-responders (NR, n=9).

Results: The top upregulated glomerular transcripts were *TGFBI(*fold-change (FC): 10.6, P=6x10^{-9}*), FCER1G (FC:8.2, P=2x10^{-7}), CCL2(FC:3.5, P=0.001), FN1(FC:3.5, P=2x10^{-7}), ICAM1(FC:3.2, P=0.0001)* and *VCAM1 (FC:2.7, P=6x10^{-13}).* The top upregulated TI transcripts were *CCR10*(FC:2.8, P=5x10^{-9}), *STAT1*(FC:2.8, P=6x10^{-8}), *HLA-DRB3(FC:2.6, P=2x10^{-12}), CCL19*(FC:2.8, P=2x10^{-7}), *CD74*(FC:2.3, P=1x10^{-15}) and *CFD*(FC:2.2, P=0.00001). At Bx1 26 glomerular and 39 TI transcripts differentiated CR from NR. After treatment several glomerular and TI transcripts differentially-expressed in Bx1 trended toward control levels in Bx2, but 15 transcripts significantly increased in expression, suggesting increased infiltration of T cells (*CD5, CD7, ICOS, CD45*), NK cells (*CD2, KLRB1*), and neutrophils (*CSF3RB*) in NR TI.

Conclusions: The inflammatory profiles of glomeruli and TI at LN flare and after treatment are different. CR and NR also have unique profiles at flare that may be helpful in predicting response to therapy. After treatment NR are characterized by increased infiltration of T cells, NK Cells and neutrophils in the TI compared to CR. These transcripts may be used to refine subsequent treatment of NR and convert these patients to CR.

Funding: Other NIH Support - CCTS - Stragegic Pharma-Academic Research Consortium Grant

TH-OR069

Effects of Blisibimod, a Selective Inhibitor of B-Cell Activating Factor, on Urinary Protein:Creatinine Ratio (UPCR) in Subjects with Renal Manifestations of Systemic Lupus Erythematosus (SLE) Joan T. Merrill,[1] Renee Martin,[2] William Shanahan,[2] Kenneth Kalunian,[3] David Wofsy.[4] *[1]Oklahoma Medical Research Foundation, Oklahoma City, OK; [2]Anthera Pharmaceuticals, Inc., Hayward, CA; [3]UCSD, La Jolla, CA; [4]University of California, San Francisco, CA.*

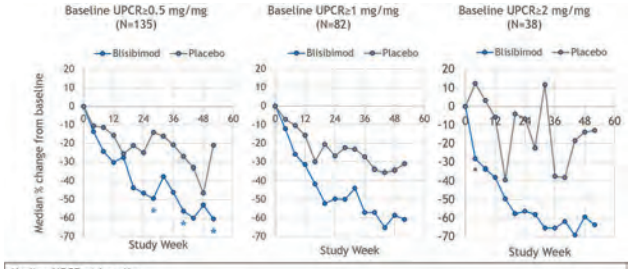
Background: The CHABLIS-SC1 trial (NCT01395745) was a Phase 3 trial of blisibimod in 442 patients with active systemic lupus, 135 of whom had UPCR≥0.5 mg/mg at study entry.

Methods: Subjects in the CHABLIS-SC1 trial were randomized to receive weekly subcutaneous blisibimod (200 mg) or placebo. All subjects had anti-nuclear or anti-dsDNA antibodies and SLEDAI score ≥10 on standard of care medications. Patients with renal manifestations were eligible unless proteinuria exceeded 6 g/24hour or disease severity was likely to require escalation of immunosuppressive therapy. This report evaluates the effects of blisibimod in the subgroup of subjects with baseline UPCR≥0.5 mg/mg.

Results: In the renal subgroup, greater decreases in UPCR from baseline were observed in the blisibimod arm (Figure). Significantly more subjects who received blisibimod achieved >50% reduction in UPCR from baseline (59.7% vs 30.8%, p=0.006). A higher proportion also achieved UPCR<0.5 (53.2% and 30.8%, p=0.021). No treatment effects were noted on eGFR and serum creatinine, which typically were within normal ranges throughout the trial. Across all 442 enrolled subjects, adverse events were balanced between treatment arms excepting mild or moderate injection site erythema and injection site reaction which occurred more frequently with blisibimod.

Conclusions: The reduction in proteinuria in SLE subjects with clinical evidence of nephritis suggests that blisibimod may have therapeutic potential in lupus nephritis and, perhaps, other B-cell-associated renal diseases.

Funding: Commercial Support - Anthera Pharmaceuticals



Median UPCR at baseline			
blisibimod	1.2	1.6	2.8
placebo	1.2	1.7	3.1

Treatment Effects on UPCR

TH-OR070

Treatment and Outcomes of the ANCA Associated Vasculitis in the Very Elderly – A Single Centre Experience Turren tarun S. Chaggar. *Epsom and St Helier NHS Trust, London, United Kingdom.*

Background: ANCA-associated vasculitis has a peal incidence between 65-74 years of age, and not uncommonly presents in the very elderly (>80yrs). Decisions regarding immunosuppression in the very elderly can be challenging, given likely co-morbidities and general frailty, and on treatment and outcomes in this age group is lacking.

Methods: Patients were identified retrospectively from the local renal database. A total of 231 patients presented with ANCA associated vasculitis between 2006 and 2015. Data from patients >= 80 years during the study period were collected. Follow-up was until May 2017. The collected data were analysed with respect to age, sex, renal function at diagnosis, patient and renal survival, induction and maintenance treatment and disease relapse

Results: We identified 32 patients from this cohort, mean age of 83.5 yrs (range 80- 90 years), mean follow-up period of 35.5 months (range 0.2 – 106). Of these, 14 were PR3 positive and 18 were MPO positive. Overall survival to completion of induction therapy at 3 months was 91% (29/32) and 1 year survival was 90% (26/29). Mean creatinine at presentation was 406 µmol/L and 38% (12/32) required renal replacement therapy (RRT) within 72 hours of presentation. Induction of remission was achieved using corticosteroids with either cyclophosphamide (25/32), MMF (1/32) or rituximab (1/32). In two patients azathioprine was used with corticosteroids as first line therapy. N=6 had Plasma Exchange in addition to RRT. Of these, 4 were RRT independent at 3 months. Renal survival was 79% (23/29) at 3 months and 85% (22/26) at 1 year. No patients progressed to ESRD after 3 months. Disease relapse occurred in 2 patients, with a mean time to relapse of 21.5 months.

Conclusions: AAV is a disease with substantial mortality and morbidity among elderly patients. The results of this retrospective study showed that very elderly patients can benefit from immunosuppressive therapy with good outcomes to 3 month and 1 year survival. Relapse rates are low. Dialysis independence can be achieved in those patients requiring RRT on admission and this treatment ensures that patients are maintained off RRT upto a median of 35.5 months follow-up.

TH-OR071

Single-Cell RNA-Seq Reveals Distribution of Na, K, and Cl Transporters among the Major Cell Types of the Collecting Duct Lihe Chen,[3] Chung-Lin Chou,[3] Maurice B. Burg,[3] Jill W. Verlander,[2] Susan M. Wall,[1] Mark A. Knepper.[3] *[1]Emory University School of Medicine, Atlanta, GA; [2]University of Florida, Gainesville, FL; [3]National Heart Lung and Blood Institute, Bethesda, MD.*

Background: Fine control of water, ion, and acid-base homeostasis is maintained by transport processes in the collecting duct. Collecting ducts are made up of at least 3 cell types: type A intercalated cells (A-ICs), type B intercalated cells (B-ICs) and principal cells (PCs). To identify transcriptomes for A-ICs, B-ICs and PCs, it is necessary to carry out RNA-Seq at a single-cell level.

Methods: We used cell-surface markers for A-ICs (c-Kit), B-ICs (PNA) and PCs (DBA), allowing these cell types to be enriched from kidney cell suspensions from untreated mice using fluorescence-activated cell sorting (FACS). The enriched fractions were used for microfluidic-based single-cell RNA-Seq. We performed a t-distributed stochastic neighbor embedding (t-SNE) analysis and resolved cell clusters. Based on the gene expression patterns, three major clusters are identified as A-ICs, B-ICs and PCs.

Results: In the table below, we present transcript abundances in TPM values for major Na, K and Cl transporters and associated regulators in the three major cell types of the collecting duct (largest value in bold). Our data confirm the selective expression of *Hsd11b2, Scnn1b* and *Scnn1g*, and major potassium channels (*Kcnj1, Kcne1, Kcnj10, Kcnj16*) in PCs. We also found AE1 (*Slc4a1*) and pendrin (*Slc26a4*) are mutually exclusive in A-IC and B-IC, respectively. Interestingly, we found that ENaC alpha (*Scnn1a*) and Na-K-ATPase (*Atp1a1*) transcripts are more abundant in B-ICs than in PCs or A-ICs. In addition, the mineralocorticoid receptor is predominantly expressed in B-ICs, while glucocorticoid receptor is expressed in all three cell types. AE4 (*Slc4a9*) was expressed in both IC cell types (confirmed by immunohistochemistry).

Conclusions: In conclusion, the single-cell RNA-Seq profiling results revealed a distinct distribution pattern of transporters and their regulators in A-ICs, B-ICs and PCs. The identification of transcripts related to Na^+ transport and its regulation in B-ICs is consistent with a direct role of B-ICs in regulated Na reabsorption.

Funding: Other NIH Support - NHLBI

Gene Symbol	*Atp1a1*	*Clcnkb*	*Hsd11b2*	*Kcne1*	*Kcnj1*	*Kcnj10*	*Kcnj16*	*Nedd4*	*Nedd4l*
Common Name	Na/K-ATPase	CLCKB	11-beta HSD	ISK	ROMK	KCNJ10	KCNJ16	NEDD4	NEDD4-2
A-IC	2.61	506.8	1.31	0.56	0.41	0.03	0.15	10.49	4.01
B-IC	**50.97**	**659.83**	0	0	0.07	0	0.01	**55.41**	2.95
PC	6.22	122.98	**770.22**	**553.91**	**426.33**	**7.12**	**24.42**	12.15	**6.51**

Gene Symbol	*Nr3c1*	*Nr3c2*	*Scnn1a*	*Scnn1b*	*Scnn1g*	*Slc4a1*	*Slc4a9*	*Slc26a4*	*Stk39*
Common Name	GR	MR	alpha ENaC	beta ENaC	gamma ENaC	AE1	AE4	pendrin	SPAK
A-IC	0.02	0.06	1.03	2.6	0.19	**94.14**	76.42	0	0.3
B-IC	0.02	**2.11**	**19.83**	0.01	0	0.01	**423.73**	**1134.51**	0.03
PC	**0.05**	0.06	7.82	**307.88**	**101.67**	0.07	0.31	0	**15.92**

TH-OR072

Interleukin 6 Regulates the Epithelial Sodium Channel Brandi M. Wynne,[1] Qiang Yue,[1] Gillian G. Hecht,[1] Henrieke J. van Elst,[1] Hayley C. Moyer,[1] Douglas C. Eaton,[1] Robert S. Hoover.[1,2] *[1]Emory University, Atlanta, GA; [2]Veteran's Administration, Decatur, GA.*

Background: Hypertension is characterized by increased sodium (Na^+) reabsorption along the aldosterone-sensitive distal nephron (ASDN), as well as a chronic systemic inflammation. Interleukin-6 (IL-6) is a mediator of this inflammatory process. We have previously demonstrated that IL-6 activates the mineralocorticoid receptor (MR), and increases sodium chloride cotransporter expression and activity. We hypothesized that IL-6 will increase ENaC activity and/or expression.

Methods: We used mpkCCD cells to determine amiloride-sensitive transepithelial voltage and resistance (EVOM) with IL-6 (100ng/mL, 18hrs). C57Bl6 (Wt) mice were perfused with IL-6 (16ng/min, intrarenal, 3d) or vehicle, and/or treated with spironolactone. Kidney cortex homogenates were used to determine ENaC (α, γ) expression. SGK1 immunofluorescence was determined in tissue slices. ENaC channel density (N) and activity (NP_o) was obtained using split open tubules (cortical collecting duct, CCD) from IL-6 KO and Wt mice. Data are expressed as mean±SEM.

Results: Using EVOM, IL-6-mediated amiloride-sensitive current (7.4±0.7 *vs.* 6.2±0.7µAmp/cm², n=6, p<0.0001) was increased. IL-6 perfusion increased ENaCα (≈1.49, n=3, p<0.05) and γ (≈3.14, n=8, p<0.05) protein expression, as compared to vehicle. SGK1 pixel intensity (PI) was increased following IL-6 perfusion (306±4.7 *vs.* 263±4.4PI, n=6, p<0.0001); spironolactone reduced this response (224.3±4.5PI *vs.* vehicle, n=6, p<0.0001). Baseline ENaC activity (NP_o) was less than half in split open tubules from IL-6 KO mice, as compared to Wt (0.337±0.01 *vs.* 0.151±0.04, n=3, p<0.001).

Conclusions: Here, we show that IL-6 infusion increases ENaCα and γ protein expression, as well as SGK1 levels in an MR-dependent manner. Amiloride-sensitive current was also increased, corroborating the increased ENaC expression found following IL-6 perfusion. With whole animal IL-6 depletion, there was a significant reduction in ENaC activity. Together, our data suggest that a basal level of IL-6 is necessary to for adequate ENaC activity and that increased IL-6 levels may contribute to increased ENaC protein expression. Our data reveal a possible role for IL-6 mediated increases in ENaC expression and/or activity, which is especially important during hypertension.

Funding: NIDDK Support, Veterans Affairs Support

TH-OR073

Potassium Acts through mTORC2 to Regulate SGK1 and ENaC Directly in Collecting Duct Cells Bidisha Saha,[2] Prasanna K. Allu,[2] Peng Wu,[1] WenHui Wang,[1] David Pearce.[2] *[1]New York Medical College, Valhalla, NY; [2]University of California San Francisco, San Francisco, CA.*

Background: The control of K+ excretion is critical to the maintenance of blood [K+]. Aldosterone controls renal tubule K+ secretion substantially by increasing SGK1 expression, which in turn stimulates ENaC. In addition to expression, SGK1 must be activated by the kinase, mTORC2. The key physiological inputs that control this phosphorylation are poorly characterized. We postulated that [K+] itself might directly regulate SGK1 activity through effects on mTORC2-dependent phosphorylation.

Methods: mpkCCD cortical collecting duct (CCD) cells were grown on Transwell filters, and treated for 4 h with aldosterone to stimulate SGK1 expression and adapted to either 1 mM or 5 mM [K+]. At t = 0, basolateral [K+] was changed from 1 to 5 mM or from 5 mM to 1 mM, followed by a return to 5 mM in the presence or absence of either an SGK1 or mTOR inhibitor. Additional experiments were performed using patch clamp to detect ENaC currents in mice subjected to low sodium diet for 7 days, followed by acute change in bath [K+] from 5 mM to 1 mM.

Results: In mpkCCD cells, raising basolateral [K+] from 1 to 5 mM increased SGK1 phosphorylation approximately 3-fold, while lowering [K+] from 5 mM to 1 mM decreased SGK1 phosphorylation approximately 4.5-fold ($p < 0.01$). The stimulatory effects were dependent on mTORC2 in that they were inhibited by a global mTOR inhibitor (AZD 8055) but not by the mTORC1-specific inhibitor, rapamycin. Changing apical [K+] had no significant effect. Further, shifting basolateral [K+] from 5 mM to 1 mM markedly reduced ENaC-dependent Na+ current, and returning [K+] to 5 mM

induced a rapid increase in Na+ current. This latter effect was blocked by SGK1 or mTOR inhibitor. Finally, in mice subjected to patch clamp, ENaC currents were significantly greater in the presence of 5 mM (330 +/-25 pA, N=5) than in the presence of 1 mM (250 +/- 20 pA, N=5) [K+] ($p < 0.05$).

Conclusions: Changes in extracellular [K+] rapidly modulate mTORC2-dependent SGK1 phosphorylation resulting in altered ENaC-mediated Na+ transport. In light of recent evidence that Na-Cl cotransporter (NCC) phosphorylation and activity are regulated in distal convoluted cells directly by extracellular fluid [K+], these data support a new model of coordinated regulation of Na+ transport between distal convoluted tubule and CCD, which is directly modulated by local renal [K+].

Funding: NIDDK Support

TH-OR074

Aldosterone Is Essential for Angiotensin II-Induced Upregulation of Pendrin Daigoro Hirohama,[1] Nobuhiro Ayuzawa,[1] Kohei Ueda,[1] Mitsuhiro Nishimoto,[1] Wakako Kawarazaki,[1] Atsushi Watanabe,[1,2] Tatsuo Shimosawa,[3] Takeshi Marumo,[1] Shigeru Shibata,[1,4] Toshiro Fujita.[1] *[1]Research Center for Advanced Science and Technology, The University of Tokyo, Tokyo, Japan; [2]Department of Nephrology and Endocrinology, National Defense Medical College, Tokorozawa, Saitama, Japan; [3]Department of Clinical Laboratory, School of Medicine, International University of Health and Welfare, Narita, Chiba, Japan; [4]Division of Nephrology, Department of Internal Medicine, Teikyo University School of Medicine, Tokyo, Japan.*

Background: The renin-angiotensin-aldosterone system (RAAS) is known to play an important role in the control of fluid homeostasis and blood pressure during volume depletion. Dietary salt restriction elevates circulating angiotensin II (AngII) and aldosterone levels, which increase levels of the Cl^-/HCO_3^- exchanger (pendrin) in β-intercalated cells and Na^+-Cl^- cotransporter (NCC) in distal convoluted tubules; however, the independent roles of AngII and aldosterone in regulating these levels remain unclear.

Methods: In both C57BL/6J mice receiving a low-salt diet or AngII infusion and adrenalectomized mice receiving either AngII or co-administration of AngII and aldosterone, we evaluated membrane-protein abundance of pendrin, NCC and mineralocorticoid receptor (MR) phosphorylation, which selectively inhibits aldosterone binding in intercalated cells. We also measured blood pressure (BP) by radiotelemetry in pendrin-knockout and wild-type mice.

Results: A low-salt diet as well as AngII infusion upregulated NCC and pendrin levels, associated with decreased MR phosphorylation. Notably, a low-salt diet did not alter BP in wild-type mice, but significantly decreased BP in pendrin-knockout mice, suggesting the important role of pendrin in the regulation of BP. In adrenalectomized mice, AngII infusion again upregulated NCC, but did not affect pendrin expression despite the decreased MR phosphorylation. By contrast, AngII and aldosterone co-administration markedly elevated pendrin levels in adrenalectomized mice. AngII and aldosterone co-administration induced enhanced translocation of the MR to the nucleus in β-intercalated cells, whereas AngII alone did not.

Conclusions: Our results indicate that aldosterone is necessary for AngII-induced pendrin upregulation, and suggest that pendrin contributes to maintaining normal BP in cooperation with NCC during activation of the RAAS by dietary salt restriction.

TH-OR075

The Cystic Fibrosis Transmembrane Regulator (CFTR) and the Na+/H+ Exchanger NHE-2 Play Important Roles in Compensatory Salt Absorption in Kidneys of Na-Cl Cotransport (NCC) Deficient Mice Manoocher Soleimani,[1,2] Sharon L. Barone,[1,2] Jie Xu,[1] Marybeth Brooks,[1] Kamyar A. Zahedi.[1,2] *[1]University of Cincinnati, Cincinnati, OH; [2]Research Services, Veterans Administration, Cincinnati, OH.*

Background: Background: The ablation of the Na-Cl cotransporter NCC (Slc12a3) does not cause any significant salt wasting in mice, in part due to activation of the Cl^-/HCO_3^- exchanger pendrin and the epithelial sodium channel ENaC. However, whether other transporters/channels contribute to compensatory salt absorption in NCC null mice remains speculative.

Methods: To better identify the compensatory salt absorptive mechanisms in NCC deficient mice RNA-Seq analysis was performed on kidney cortices of wild type, NCC KO and pendrin KO mice. Results were verified by expression studies in kidneys and complemented by functional studies in live animals.

Results: One notable transporter/channel, which was significantly upregulated in NCC KO but downregulated in pendrin KO mice was CFTR. Another transporter, which was upregulated in NCC KO mice was NHE-2. Northern hybridizations verified enhanced expression of CFTR and NHE-2 in the kidney cortex of NCC KO mice and immunofluorescence labeling studies indicated the upregulation of CFTR and NHE-2 in the CCD and DCT, respectively. To ascertain the role of CFTR in compensatory salt absorption in NCC KO mice, WT and NCC KO mice were placed in metabolic cages and injected twice/ day with the CFTR inhibitor GlyH-101 for 4 days. Urine volume increased by ~60% and urine sodium increased by 35% vs. baseline in response to GlyH-101 treatment ($p<0.05$ for both parameters). Wild type mice showed no significant increase in urine output or sodium excretion in response to GlyH. NCC KO, but not WT mice showed enhanced salt excretion in response to amiloride injection which was likely resulting from combined inhibition of NHE-2 and ENaC.

Conclusions: CFTR is upregulated in the distal nephron and plays an important role in compensatory salt absorption in NCC deficient mice. In addition, NHE-2 is activated in the distal nephron and facilitates the absorption of sodium. We propose that CFTR may facilitate the activity of the Cl^-/HCO_3^- exchanger pendrin and ENaC in B intercalated cells and principal cells, respectively, leading to enhanced salt absorption in NCC KO mice. We further propose that NHE-2 is activated and works in tandem with pendrin to facilitate the electroneutral absorption of sodium and chloride.

Funding: Veterans Affairs Support, Private Foundation Support

TH-OR076

Role of ClC-K and Barttin in Low-Potassium Induced Sodium-Chloride Cotransporter Activation and Hypertension in Mouse Kidney Naohiro Nomura, Wakana Shoda, Yuanlong Wang, Daiei Takahashi, Moko Zeniya, Eisei Sohara, Tatemitsu Rai, Shinichi Uchida. *Tokyo Medical and Dental University, Tokyo, Japan.*

Background: The sodium-chloride cotransporter (NCC) was identified as a key molecule regulating potassium balance. The mechanisms of NCC regulation during low extracellular potassium concentrations have been investigated *in vitro* showing that the hyperpolarization induced by low potassium concentrations increased chloride efflux through the ClC-K chloride channels, leading to the activation of chloride-sensitive WNK kinases and their downstream molecules including SPAK and NCC. However, this mechanism was not investigated *in vivo*.

Methods: We used the barttin hypomorphic mouse (*Bsnd*$^{neo/neo}$ mice), expressing very low levels of barttin and ClC-K channels since barttin is an essential ß-subunit of ClC-K. Mice were fed a normal diet or a low-potassium diet *in vivo*. Kidney slices were incubated in different potassium concentration buffer *ex vivo*. Then, SPAK and NCC phosphorylation was evaluated by Western blotting.

Results: In contrast to *Bsnd*$^{-/-}$ mice, *Bsnd*$^{neo/neo}$ mice survived to adulthood, which enabled us to investigate the role of ClC-K in NCC activation. When mice were fed a normal diet, there was no significant difference in total and phosphorylated NCC between wild-type mice and *Bsnd*$^{neo/neo}$ mice. In *Bsnd*$^{neo/neo}$ mice, SPAK and NCC activation (phosphorylation) after consuming a high-salt and low-potassium (HSLK) diet was clearly impaired compared to that in wild-type mice. In *ex vivo* kidney slice experiment, the increase in phosphorylated NCC in low-potassium medium was also blunted in *Bsnd*$^{neo/neo}$ mice. Furthermore, the increase in blood pressure was observed in wild-type mice fed a HSLK diet, which was not evident in the *Bsnd*$^{neo/neo}$ mice.

Conclusions: Our study provides *in vivo* evidence that ClC-K and barttin play important roles in the activation of the WNK4-SPAK-NCC cascade and the blood pressure regulation, in response to a low-potassium diet.

Funding: Government Support - Non-U.S.

TH-OR077

Paracellular Properties of the Cortical Collecting Duct Nina Himmerkus,[2] Julian Isermann,[2] Lieske Jarck,[2] Yongfeng Gong,[1] Susanne Milatz,[2] Jianghui Hou,[1] Markus Bleich.[2] *[1]Washington University School of Medicine, Saint Louis, MO; [2]Christian-Albrechts-University Kiel, Kiel, Germany.*

Background: Collecting duct salt and water transport is involved in the regulation of extracellular volume and blood pressure. Ions are transported either transcellularly or through the paracellular pathway following electrochemical driving forces. Claudins are the major determinants of tight junction permeability. They form the paracellular pathway and claudin-4 and -8 have been discussed to be involved in paracellular chloride transport.

Methods: Cortical collecting ducts (CCD) from principal cell-specific claudin-4 knockout animals (KO) and their respective controls (Ctrl) were investigated under normal diet and low salt diet. CCD were isolated by manual dissection, perfused *in vitro* and investigated for their basic trans- and paracellular transport properties. Transepithelial voltage (V_{te}), transepithelial resistance (R_{te}) and equivalent short circuit current (I'_{sc}) were measured before and after luminal application of 50 μM amiloride and 100 μM hydrochlorothiazide to inhibit transcellular ion transport. A diffusion potential was generated by changing the basolateral solution from 145 to 30 mM NaCl (isotonic) to test for paracellular ion selectivity and the permeability ratio P_{Cl}/P_{Na} was calculated. Immunofluorescence was used to localize and quantify claudin-4 expression along the nephron and particularly in the collecting duct.

Results: Under normal diet CCDs of Ctrl as well as of KO showed similar transcellular amiloride dependent lumen negative V_{te}. Under inhibition of transcellular transport, however, R_{te} was lower in KO CCD (111±8 Ωcm²) vs. Ctrl CCD (151±11 Ωcm²), respectively. P_{Cl}/P_{Na} values showed chloride selectivity in Ctrl CCD (1.36±0.08) but hardly any selectivity in KO CCD (1.07±0.03). Low salt diet increased amiloride dependent V_{te} in both genotypes to a similar extend, however, with increased R_{te} in KO CCD (192±16 Ωcm²) vs. in Ctrl CCD (147±11 Ωcm²), under inhibition of transcellular transport, respectively. P_{Cl}/P_{Na} did neither change in Ctrl CCD (1.24±0.05) nor in KO CCD (1.04±0.03). Immunofluorescence confirmed claudin-4 knockout with residual low expression of claudin-4 in intercalated cells.

Conclusions: In summary, claudin-4 is expressed in both, principal and intercalated cells of CCD and claudin-4 deficiency leads to the loss of Cl^- selectivity.

Funding: Other NIH Support - RO1DK084059

TH-OR078

HIF Regulation of Nephron Progenitor Metabolic State Mediates Cell Fate Decisions Anjana Murali,[3] Kasey Cargill,[3] Elina Mukherjee,[3] Zubaida R. Saifudeen,[2] Sunder Sims-Lucas.[1] *[1]Children's Hospital of Pittsburgh, Pittsburgh, PA; [2]Tulane University School of Medicine, New Orleans, LA; [3]University of Pittsburgh, Pittsburgh, PA.*

Background: Hypoxia inducible factors (HIFs) are transcription factors involved in the differentiation of nephron progenitors (NP) into functional nephrons. Alterations in nephron differentiation lead to renal abnormalities. As renal oxygen increases, von Hippel-Lindau (VHL) marks HIF-1α for degradation and facilitates normal nephron differentiation. Alternatively, pathological hypoxia results in HIF-1α accumulation and initiation of processes including cellular survival and metabolism. Previous *in vitro* studies have also linked HIF-1α stabilization to mitochondrial pathologies suggesting that HIF-1α plays a role in cellular and mitochondrial respiration. Therefore, we hypothesize that HIF-1α alters mitochondrial function, mediating a metabolic switch to determine NP fate.

Methods: To determine the role of HIFs in the NPs we utilized VHL floxed mice bred with the *Six2EGFPcre* line, to generate Six2creVHL$^{lox/lox}$ mutant mice. RNA sequencing was conducted on E14 whole kidneys to look at differential gene expression, and validated via RT-PCR. We also performed a metabolic assessment using seahorse extracellular flux analysis, and coupled this with immunofluorescence (IF) and western blot analysis to analyze metabolic markers.

Results: RNA sequencing of Six2creVHL$^{lox/lox}$ mutant mice revealed metabolic gene dysregulation. Furthermore, seahorse extracellular flux analysis suggested that mutants with HIF-1α stabilization in the NPs remained in a glycolytic state, and were subsequently unable to switch to oxidative phosphorylation, which drives NP differentiation. IF staining and western blot analysis supported these results revealing fewer mature nephron structures and decreased mitochondrial content in mutant kidneys.

Conclusions: HIFs are critical in determining the metabolic state of the NPs. In the absence of VHL, HIF1α is stabilized. This stabilization maintains NPs in a state of glycolysis and in turn blocks the switch to oxidative phosphorylation causing NP differentiation defects and kidney malformations.

Funding: NIDDK Support

TH-OR079

Cadherin-11 Is Induced by BMP7 and Stimulates Cap Mesenchyme Formation Midori Awazu,[1] Michio Nagata,[2] Mariko Hida.[1] *[1]Keio University School of Medicine, Tokyo, Japan; [2]Renal Vascular Pathology, University of Tsukuba, Tsukuba, Japan.*

Background: Cadherin-11 (CDH11) is an adhesion molecule specific to mesenchymal cells, which has been shown to promote cell migration and compaction and be involved in the differentiation of progenitor cells. In the developing kidney, CDH11 is expressed in cap mesenchyme and the interstitium. We investigated the role of CDH11 in kidney development and its relationship to BMP7, a growth factor necessary for maintaining and priming nephron progenitors.

Methods: Mice embryonic day 12 (E12) and E13 kidneys were transfected with two different siRNA against CDH11 (a or b) or irrelevant siRNA and cultured. Ureteric bud and cap mesenchyme were stained with pancytokeratin and Six2, respectively. An immortalized metanephric mesenchymal cell line MS7 was generated from the metanephroi of E11.5 homozygous mouse transgenic for H-2Kb-tsA (*J Am Soc Nephrol* 12:964, 2001). The effect of different concentrations of BMP7 (0.25, 1, and 10 nM) on CDH11 expression in MS7 was assessed by quantitative real-time PCR and immunoblot.

Results: Cap mesenchyme, marked by Six2, was well observed around ureteric tips in control metanephroi and those transfected with irrelevant siRNA. In metanephroi transfected with siRNA a or b, on the other hand, Six2-positive cells were diffusely distributed and condensation around the ureteric tips was faint. CDH11 expression, assessed by whole mount staining, was distinctly observed in cap mesenchyme in controls, but was diffuse and reduced in metanephroi transfected with siRNAs. Ureteric bud tip number was significantly reduced by siRNAs (a 6.3±1.5, b 5.8±0.2) compared with controls (7.3±2.4/kidney). Kidney size cultured with siRNAs also tended to be smaller (a 6.3±1.5, b 5.8±0.2, control 7.3±2.4). Incubation of MS7 with BMP7 for 24 h dose-dependently increased mRNA and protein expression of CDH11 with the maximal effect at 1 nM. Cadherin 6 and E-cadherin were not expressed by MS7 nor induced by BMP7. As previously reported by us, BMP7 1 nM stimulated both ERK and p38 at 24 h. While BMP7-stimulated proliferation of MS7 was suppressed by a MEK inhibitor PD98059 5 μM or a p38 inhibitor SB203580, BMP7-induced CDH11 expression was not inhibited by PD98059 or SB203580 alone but by combination of both.

Conclusions: CDH11 is induced by BMP7 *via* ERK and p38, and stimulates cap mesenchyme formation.

Funding: Government Support - Non-U.S.

TH-OR080

Single-Cell Analysis of Progenitor Cell Dynamics and Lineage Specification of the Human Fetal Kidney Cristina Cebrian Ligero,[1] Rajasree Menon,[1] Edgar A. Otto,[1] Austin Kokoruda,[1] Jian Zhou,[2] Zidong Zhang,[2] Olga Troyanskaya,[2] Jason R. Spence,[1] Matthias Kretzler.[1] *[1]University of Michigan Medical School, Ann Arbor, MI; [2]Princeton University, Princeton, NJ.*

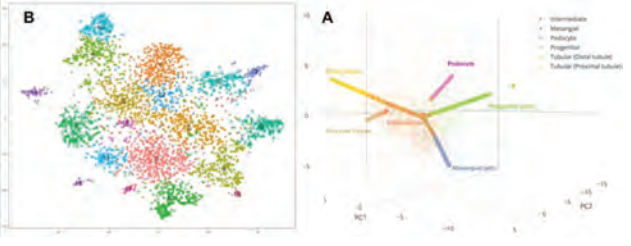
Background: The study of animal models has identified a plethora of genes and pathways driving the repetitive and reciprocal interactions between the Ureteric Bud (UB) and the Metanephric Mesenchyme (MM) that give rise to the collecting system and the nephron pool. However, these expression patterns and how they drive differentiation have not been systematically characterized in the human kidney. We have used single-cell transcriptomics to study individual cell dynamics and characterize the expression profile of the human kidney.

Methods: Fetal kidneys (105 to 115 days of gestation) were dissociated to single cells and processed for DropSeq workflow as described by the McCarroll lab. Individual cells were identified by barcodes, and transcripts were tagged with Unique Molecular Identifiers. Paired-end RNASeq was performed on a HiSeq2500 platform. Bioinformatics analysis employed the Picard tools developed by the Broad Institute and unsupervised clustering algorithms were executed with the R package toolkit "Seurat". RNA profiles were mapped into trajectories derived using a nonparametric ridge estimation statistical framework. Gene expression was confirmed by immunofluorescence on fetal kidneys.

Results: Single cell transcriptome analyses of 3,865 cells (fig.A) enabled the distinction of UB-4 and MM-1 progenitors as well as their intermediate and differentiated lineages including the mature collecting ducts-18, the renal vesicle and comma- and s-shaped bodies-2, immature-9 and mature podocytes-13, proximal tubules-6, Henle's loop and distal tubules-8, as well as mesangium-5 and cortical-5 and medullary interstitium-10. Importantly, known as well as novel markers for these cell types were revealed in the analysis.

Conclusions: We have generated an accurate map of gene expression and lineage relationships (fig.B) in the human fetal kidney. These results confirm the expression of genes identified by studying animal models. New gene-expression patterns have also been identified that may help understand human renal development.

Funding: NIDDK Support, Other NIH Support - GM



TH-OR081

Profiling and Mathematically Modelling Cell and Tissue Morphogenesis during Renal Development Ian Smyth,[3] Kieran M. Short,[3] James Lefevre,[1] Timothy Lamberton,[5] Alexander N. Combes,[6] Andrew P. McMahon,[2] Melissa H. Little,[4] Nicholas A. Hamilton.[5] *[1]Institute for Molecular Bioscience, The University of Queensland, Highgate Hill, NSW, Australia; [2]Keck School of Medicine of the University of Southern California, Los Angeles, CA; [3]Monash University, Melbourne, NSW, Australia; [4]Murdoch Childrens Research Institute, Melbourne, VIC, Australia; [5]The University of Queensland, Brisbane, NSW, Australia; [6]University of Melbourne, Parkville, NSW, Australia.*

Background: While cell, tissue and even organism level analyses of morphogenesis are feasible in invertebrates, the size, opacity and complexity of mammalian organs has impeded systematic analyses of developmental processes critical to organ function.

Methods: Here, we integrate optical projection tomography, single-cell resolution confocal microscopy and quantitative image analysis to comprehensively document mouse kidney organogenesis across time. Using mathematical modeling, we develop a framework for generating and comparing modes of branching morphogenesis and compare these models with datasets derived from fetal mouse kidneys.

Results: Our tissue and cell based analysis reveals a previously unappreciated structurally stereotypic organ architecture undergoing a temporally non-uniform process of development with respect to rates of cellular proliferation, dominant morphogenetic processes and spatial relationships between key cellular compartments. Mathematical modelling was able to determine base patterning programs operant in driving branching of the ureteric epithelium, facilitating the analysis of different genetic and morphological impacts on the development of the organ.

Conclusions: Integrating cell, tissue and organ level datasets facilitates quantitative analysis of even subtle perturbations to kidney development and is also applicable to other organ systems. Our data describes a mechanism of branching morphogenesis which is highly patterned when comparing one organ to the next, and across developmental time. The existence of such distinct phases of development and patterning of branching morphogenesis predicts temporal sensitivity to genetic and environmental insults, potentially enhancing our understanding of the mechanism by which developmental anomalies and normal variation in renal anatomy arise.

Funding: Government Support - Non-U.S.

TH-OR082

Polycomb Repressive Complex-2 (PRC2) Fine-Tunes Timing of the Final Wave of Nephrogenesis Samir S. El-Dahr,[2] Zubaida R. Saifudeen,[2] Hongbing Liu.[1] *[1]Tulane, New Orleans, LA; [2]Tulane University School of Medicine, New Orleans, LA.*

Background: The mechanisms that control cessation of nephrogenesis are not well understood. Heterochronic transplantation and epigenome profiling suggest that old nephron progenitor cells (NPC) are poised for differentiation limiting their lifespan. In stem cells, Enhancers of Zeste, Ezh1 and Ezh2, the catalytic components of PRC2, mediate H3K27 methylation to maintain lineage-specific genes in a silent yet poised state. We hypothesized that PRC2 activity restrains NPC aging and is essential for timely cessation of nephrogenesis.

Methods: We generated conditional Six2$^{Ezh2-/-}$; ROSA26^{Tomato} and compound Six2$^{Ezh2-/-}$;Ezh1$^{-/-}$;ROSA26^{Tomato} mice. Molecular and phenotypic analyses were accomplished by section IF and ISH at E15.5, E17.5, and P0, and transcriptome profiling of Six2-GFP^{+} cells at E17.5. Results were integrated with genome-wide maps of accessible chromatin, Six2 and histone mark occupancy, and scRNA-seq databases.

Results: Six2$^{Ezh2-/-}$ and germline Ezh1$^{-/-}$ kidneys are morphologically normal. In contrast, **E17.5** Six2$^{Ezh2-/-}$;Ezh1$^{-/-}$ and Six2$^{Ezh2-/-}$;Ezh1$^{+/-}$ NPC fail to form the cap mesenchyme and display a unique gene expression signature consisting of the cell cycle inhibitor Cdkn2a/p16, Lin28B (inhibitor of Let-7 miRNA upregulated in Wilm's tumor), Six1 (normally expressed in early metanephric mesenchyme but absent in mouse cap mesenchyme), Hoxd13 and Wnt5A/10A genes. In wild-type NPC, these aberrantly expressed genes are silent and heavily methylated on H3K27, yet display small peaks of accessible chromatin suggesting a state of epigenetic poising. At **P0**, Six2$^{Ezh2-/-}$;Ezh1$^{+/-}$ NPC undergo en mass differentiation into ectopic Tomato^{+}/Wnt4^{+}/Pax2^{+}/Lef1^{+}/Lhx1^{+} renal vesicles located dorsal to the UB tips, akin to the final wave of nephrogenesis that normally occurs at P2-P4. There was complete loss of H3K27me3 in double Ezh1/Ezh2 mutant NPC and their derived epithelial tubules.

Conclusions: We conclude that H3K27 methylation fine-tunes timing of the last wave of nephrogenesis by restraining Cdkn2a/p16 and unscheduled activation of canonical Wnts in NPC. Ectopic induction of Lin28B, Hox and Six1 in mutant progenitors suggests a state of arrested differentiation of metanephric mesenchyme. Interventions targeting PRC2 function may be beneficial for nephron progenitor maintenance and regeneration.

Funding: NIDDK Support

TH-OR083

DNA Methylation Changes in Human Kidney Development and Disease Revealed by Whole Genome Bisulfite Sequencing of Tissue Samples Jihwan Park, Szu-Yuan Li, Matthew J. Seasock, Joshua S. Bryer, Rojesh Shrestha, Katalin Susztak. *Renal-Electrolyte and Hypertension Division, University of Pennsylvania, Philadelphia, PA.*

Background: Numerous epidemiologic studies have confirmed the associations between "fetal programming" and development of chronic kidney disease (CKD) and hypertension. The epigenetic system is not only heritable but also under the influence of the environment, therefore proposed to mediate the environmental "programming effect". Cytosine methylation is important epigenetic signal, however limited data is available in kidneys of different conditions. In addition, most prior reports have examined epigenetic changes in only < 1% of about 1 billion cytosines in the genome.

Methods: Here, we generated base pair resolution methylome maps of early (11.5 weeks) and late (18.5 weeks) human fetal kidneys and microdissected tubules from healthy and CKD adult subjects (n=12). Our whole genome bisulfite sequencing (WGBS) data cover 96~98% of all CpGs with 15x mean genome coverage. Computational analysis included WGBS alignment and methylation extract followed by differential methylation analysis and PCA. Functional regions were mapped using histone modification ChIP-Seq datasets.

Results: In fetal kidneys we identified low methylated regions (LMRs) and unmethylated regions (UMRs) which are enriched in enhancers and promoters, respectively inferring their functional activity. Transcription factor motif analysis indicates enrichment for CTCF in early and SIX1 in late fetal kidneys in the LMRs. We also identified differentially methylation regions (DMRs) in adult CKD tubule samples when compared to the controls. DMR-genes were associated with immune and Notch signaling (VEGFA, TNF, STAT5A and NOTCH1). We finally compared fetal and adult kidneys, and found that (1) PC1 separates fetal from adult kidneys and (2) PC2 separates early fetal and adult fibrosis from late fetal and normal kidneys. The DMRs between the groups separated by PC2 are associated with developmental genes such as HNF1B, MTSS1, NOTCH1, PAX2 and SIX1. HNF1 binding motif is highly enriched in the DMRs and expression of HNF1B and its potential target, MTSS1, are reduced in fibrosis samples of human and mouse CKD models.

Conclusions: Our study provides a novel comprehensive epigenome map of human fetal kidneys and identified common DNA methylome changes in normal development and fibrosis, which offers new insight into injury repair processes in CKD.

Funding: NIDDK Support

TH-OR084

TFAP2A Is a Novel Regulator of Renal Progenitor Fate during Kidney Ontogeny Brooke E. Chambers, Rebecca A. Wingert. *University of Notre Dame, Notre Dame, IN.*

Background: Occurring in 1 in 500 births, Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) are the primary cause of pediatric end-stage renal disease. The central etiology of these conditions involves aberrant development of nephrons, which are the functional units of the kidney.

Methods: Zebrafish have emerged as a powerful genetic system to study the molecular coordination of cell fate decisions during vertebrate nephron formation. Here, through a forward ENU screen, we isolated a nephron mutant with abrogated distal tubules. Whole genome sequencing revealed a lesion that disrupts splicing of *transcription factor AP-2 alpha* (*tfap2a)*, thereby truncating essential transcriptional activation and DNA binding domains. Until now, *tfap2a* has been known as essential for neural crest and epidermis differentiation but was not appreciated to act during renal ontogeny.

Results: We found that *tfap2a* was dynamically expressed in zebrafish renal progenitors, eventually restricting to the distal tubules. During mouse embryogenesis, *tfap2a* expression was abundant within the developing urogenital tract encompassing structures such as the ureteric tip and distal tubules. Human *tfap2a* mutations result in branchio-oculo-facial syndrome (BOFS), which primarily affects craniofacial tissue, though case reports have linked *tfap2a* lesions to multicystic dysplastic kidney. Complementation tests between our mutant line and *tfap2a*^{m819}, which encodes a nonsense allele, as well as knockdown studies similarly abolished the distal tubule. Conversely, overexpression of *tfap2a* caused a striking expansion of distal cells. Through a subsequent suite of functional studies, we have determined that *tfap2a* acts upstream of several key lineage factors necessary for distal tubule formation, like the T-box transcription factor *tbx2b*. In addition, our data suggests *tfap2a* interplays with Iroquois homeobox genes *irx1a* and *irx3b* to pattern distal nephron structures.

Conclusions: Taken together, our studies have revealed novel mechanisms by which *tfap2a* directs cell fate during nephrogenesis. Examining the molecular activities of this conserved transcription factor in renal progenitors will shed light on the regulatory role of the mammalian homologue, *AP-2α*, in congenital diseases.

Funding: NIDDK Support

TH-OR085

Transcription Factor 21 (TCF21) Controls Branching Morphogenesis via GDNF Signaling and Has Pleiotropic Roles in Kidney Development Gal Finer,[4] Shintaro Ide,[1] Tomokazu Souma,[2] Minghao Ye,[3] Jing Jin,[3] Yoshiro Maezawa,[1] Susan E. Quaggin.[3] *[1]Chiba University Graduate School of Medicine, Chiba, Japan; [2]None, Chicago, IL; [3]Northwestern University, Chicago, IL; [4]Kidney Diseases, Northwestern University, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL.*

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading cause of chronic kidney disease in children. Although the pathogenesis of CAKUT is incompletely understood and heterogeneous, many cases arise from alterations in genes critical for kidney development. We previously showed that absence of *Tcf21* causes CAKUT in the mouse but the mechanisms remain obscure.

Methods: We utilized systemic and conditional *Tcf21* knockout mouse models and employed immunohistochemistry, in-situ hybridization, RT qPCR and kidney explant studies.

Results: Global deletion of *Tcf21* showed abnormal UB branching and arrested mesenchymal to epithelial transition with resultant severe renal dysplasia. These kidneys had markedly reduced expression of *Gdnf*, *Wnt11* and *Ret* mRNA to 16%, 29% and 52% of normal levels respectively. When *Tcf21* was specifically deleted from the cap mesenchyme and its progenitors (Tcf21$^{fl/fl}$;Six2-Cre), mutant kidneys showed abnormal UB branching at early developmental stages (E11.5-13.5) but normal appearing collecting ducts subsequently. Importantly however, when *Tcf21* was selectively deleted from kidney stromal cells (Tcf21$^{fl/fl}$;FoxD1-Cre), the mice developed diabetes insipidus-like phenotype suggestive of functional defect in the collecting ducts. This was also supported by findings of severe defect in UB branching at early stages of kidney development and by the absence of collecting ducts at P0 in Tcf21$^{fl/fl}$;FoxD1-Cre mice. Mechanistically, deletion of *Tcf21* from renal stromal cells was again associated with down-regulation of *Gdnf* and *Wnt11* supporting impaired branching signaling. Moreover, the stromal factor BMP4, a known inhibitor of GDNF, was up-regulated in *Tcf21* null kidneys both at the mRNA and protein levels. This suggested that TCF21 controls UB branching by regulating BMP4.

Conclusions: Taken together, these results suggest that TCF21 is essential for normal branching morphogenesis via regulation of *Gdnf-Wnt11-Ret* axis, likely via control of BMP4 in the renal stroma. Further study is required to identify direct gene targets for TCF21.

Funding: Private Foundation Support

TH-OR086

Identification of GREB1L as a Novel Causative Gene for Bilateral Kidney Agenesis Lara De tomasi,[1] Pierre David,[2] Flora Silbermann,[1] Christelle Arrondel,[1] Olivier Alibeu,[3] Cecile Fourrage,[4] Brigitte Lelongt,[5] Joëlle Roume,[6] Christine Pietrement,[7] Bertrand Isidor,[8] Philippe Khau van kien,[9] Robert Novo,[10] Jelena Martinovic,[11] Marie Gonzales,[12] Laurence Heidet,[13] Sophie Saunier,[1] Cecile Jeanpierre.[1] *[1]Inserm UMR1163 - Imagine Institute, Paris, France; [2]Transgenesis Platform, Imagine Institute, Paris, France; [3]Genomic Platform, Imagine Institute, Paris, France; [4]Bioinformatics Platform, Imagine Institute, Paris, France; [5]UMR_S1155 - Tenon Hospital, Paris, France; [6]Department of Genetics, CHI POISSY ST GERMAIN EN LAYE, POISSY, France; [7]Pediatric Nephrology Department, American Memorial Hospital, Reims, France; [8]Department of Genetics, CHU Nantes, Nantes, France; [9]Department of Genetics, University Hospital Nîmes, Nîmes, France; [10]Department of Pediatric Nephrology, CHRU, Lille, France; [11]Unit of Fetal Pathology, Antoine Béclère University Hospital, Clamart, France; [12]Department of fetal pathology, AP-HP A Trousseau Hospital, Paris, France; [13]Pediatric Nephrology Department, Reference Center MARHEA, APHP - Necker Hospital, Paris, France.*

Background: Renal hypodysplasia (RHD) is a heterogeneous condition encompassing a spectrum of developmental kidney defects, i.e. renal agenesis, hypoplasia, and cystic and non-cystic dysplasia. Many studies have identified genes involved in kidney development. Heterozygous mutations in several of these genes have been shown to lead to various forms of RHD. However, the pathophysiological mechanisms leading to bilateral renal agenesis (BKA) remain largely elusive.

Methods: In order to identify novel RHD genes, we used whole exome/targeted exome sequencing and analysed familial and severe cases including 68 families/cases with BKA. *Greb1l* knock-out mice were generated using CRISPR/Cas9 and immunostaining analysis was performed in cleared kidneys.

Results: Through whole exome sequencing we identified heterozygous loss-of-function variants in *GREB1L* (Growth Regulation By Estrogen In Breast Cancer 1-Like) in two families with BKA fetuses. Targeted exome sequencing revealed *GREB1L* variations in 14 additional families, including 10 with BKA fetuses. Altogether, two nonsense, one frameshift, one splice and twelve damaging missense variants were identified. All these variants were absent from the ExAC database. *GREB1L* encodes an uncharacterised target of retinoic acid, never yet associated with kidney abnormalities. Embryonic lethality was observed in *Greb1l* knock-out mice in the homozygous state. Analysis at E13.5 revealed that all *Greb1l*$^{-/-}$ embryos were smaller and presented with exencephaly and lack of kidneys. Light-sheet imaging of cleared kidneys did not reveal any differences in size or branching in *Greb1l*$^{+/-}$ embryos compared to wild-type. We also showed that the fetal kidney was the major site of GREB1L expression. Analyses are in progress to more precisely characterize the pattern of expression within fetal kidney. In parallel, we generated *Greb1l* KO IMCD3 cells that are currently being used to analyse the role of Greb1l in epithelialization and branching. These cells will also be useful to validate the pathogenicity of the missense variations.

Conclusions: These data demonstrate that *GREB1L* represents a novel RHD gene with a crucial role in kidney development.

Funding: Government Support - Non-U.S.

TH-OR087

Protein Kinase 2b (PTK2b): A Novel Marker That Controls Urinary Pacemaker Cell Function Norman D. Rosenblum,[1,2] Samir M. Iskander.[1,2] *[1]Paediatrics, The Hospital for Sick Children, Toronto, ON, Canada; [2]University of Toronto, Toronto, ON, Canada.*

Background: Congenital non-obstructive hydronephrosis occurs in 0.5-1% of pregnancies. Previously, we demonstrated that murine congenital non-obstructive hydronephrosis is associated with absent expression of HCN3 and cKIT, which mark distinct populations of urinary tract pacemaker cells (utPMCs) located in the pelvis-kidney junction and ureter, respectively (*JCI*, 2011). Further, we showed that utPMCs are derived from the *Wnt1*+ neural crest (NC) cell lineage (Feeney M, ASN, 2015). Elucidation of the ontogeny and function of utPMCs in health and disease are limited by the lack of known cellular markers expressed earlier than the onset of expression of cKIT/HCN3 (E15.5). The goal of these studies is to identify novel utPMC proteins that control their function.

Methods: HCN3+ and cKIT+ cells were isolated and purified using FACS. RNAs differentially expressed in HCN3+ and HCN- cells were identified by RNA sequencing (Seq) and validated by quantitative (q) PCR. Protein expression was analyzed by immunoflouresence in situ. Contractile function was analyzed in murine pyeloureteric explants with time-lapse imaging. NC derived-cells were identified by TOMATO expression in *Wnt1-Cre;ROSA*$^{tdTomato+}$ mice.

Results: RNASeq of FACS-isolated murine E18.5 HCN3+ utPMCs versus adjacent HCN3- cells, identified *Ptk2b*, a regulator of Ca2+ signaling and ion channel activity, among seven other novel gene transcripts enriched in HCN3+ cells (P<0.0001, n=3/group). Validation of RNASeq results by qPCR revealed 11.5- and 2.5-fold higher *Ptk2b* mRNA in FACS-isolated HCN3+ and cKIT+ utPMCs, respectively, compared to their adjacent HCN3- and cKIT- cells (P<0.05, n=3). Co-localization with TOMATO in *Wnt1-Cre;ROSA*$^{tdTomato+}$ mice demonstrated PTK2B expression in NC cells as early as E12.5. Immunofluorescence in situ showed colocalization of PTK2b with HCN3 and cKIT as early as E15.5 with sustained PTK2B expression in cKIT+ and HCN3+ cells until P8 and adulthood, respectively. Treatment of murine pyeloureteric explants with the PTK2b inhibitors, PF431396 and Leflunomide (associated with human fetal non-obstructive hydronephrosis), decreased contraction frequency by 50% compared to vehicle-treated controls (P<0.01, n=3).

Conclusions: PTK2b is a novel marker of utPMCs that: (i) is expressed in neural crest cells before the onset of and coincident with HCN3 and cKIT expression, and (ii) controls pelvic-ureteric contraction.

Funding: Government Support - Non-U.S.

TH-OR088

Survival and Kidney Transplant Incidence on Home versus In-Center Hemodialysis, Following Peritoneal Dialysis Technique Failure Sheru Kansal,[1] Jose A. Morfin,[3] Eric D. Weinhandl.[2,4] *[1]None, Cleveland, OH; [2]NxStage Medical, Inc., Victoria, MN; [3]University of California Davis, El Dorado Hills, CA; [4]University of Minnesota, Minneapolis, MN.*

Background: Peritoneal dialysis (PD) technique failure is often accompanied by complications that increase risks of hospitalization and death. Planned transition to hemodialysis may improve outcomes. Transitioning patients from PD to home hemodialysis (HHD) may improve continuity of lifestyle and facilitate delivery of more frequent treatment. However, data about transfer from PD to HHD are sparse.

Methods: We analyzed United States Renal Data System (USRDS) data from to compare incidence of death and kidney transplant in patients that transferred from PD to HHD in 2006-2012 and matched patients that transferred from PD to in-center hemodialysis (IHD). We used propensity score matching, with scores as a function of demographics and comorbidity; for each patient that transferred from PD to HHD, we selected 3 matched patients that transferred from PD to IHD. We used Fine-Gray regression to estimate intention-to-treat hazard ratios (HRs) of death and transplant for HHD versus IHD, in aggregate and stratified by insurance status (non-Medicare, Medicare).

Results: We identified 521 patients who transferred to HHD and 32,871 patients who transferred to IHD. Before matching, mean hospitalized days during the 6-month interval surrounding PD technique failure were 9.1 in Medicare patients who transferred to HHD and 18.5 in Medicare patients who transferred to IHD. Survival in HHD patients was 89.1% at 1 year and 80.5% at 2 years. The HR of death for HHD versus matched IHD patients was 0.76 (95% confidence interval, 0.65-0.90). In subsets of non-Medicare and Medicare patients, corresponding HRs were 0.57 (0.43-0.75) and 0.92 (0.75-1.13), respectively. In Medicare patients, lower hazard of death with HHD was evident only after 2 years of follow-up. Kidney transplant incidence in HHD patients was 10.6% at 1 year and 21.0% at 2 years. The HR of transplant for HHD versus matched IHD patients was 1.36 (1.14-1.61).

Conclusions: Transfer to HHD after PD technique failure was rare, but associated with lower risk of death and higher incidence of transplant than transfer to IHD. Heterogeneity in relative risks by insurance status suggests uncertainty about the magnitude of benefit. Still, the high hospitalization rate that typifies the transfer from PD to IHD suggests that clinical outcomes after PD technique failure can be improved.

TH-OR089

Contemporary Anemia Management in Peritoneal Dialysis Patients: Results from the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) Rachel Perlman,[1,2] Junhui Zhao,[2] Douglas S. Fuller,[2] Brian Bieber,[2] Yun Li,[3] Ronald L. Pisoni,[2] Bruce M. Robinson,[2] David W. Johnson,[4] Hideki Kawanishi,[5] Simon J. Davies,[6] Martin J. Schreiber,[7] Jeffrey Perl.[8] *[1]University of Michigan Health Center, Ann Arbor, MI; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]University of Michigan, Ann Arbor, MI; [4]Princess Alexandra Hospital, Brisbane, QLD, Australia; [5]Tsuchiya General Hospital, Hiroshima, Japan; [6]University Hospital of North Midlands, Stoke-on-Trent, United Kingdom; [7]DaVita HealthCare Partners Inc., Denver, CO; [8]St. Michael's Hospital, Toronto, ON, Canada.*

Background: Gaps in knowledge exist regarding anemia management among peritoneal dialysis (PD) patients. We sought to understand international variation in anemia management among patients receiving PD.

Methods: PDOPPS is an international prospective cohort study based on randomly selected national samples of PD patients. Hemoglobin (Hgb), TSAT, and ferritin levels, as well as erythropoiesis stimulating agent (ESA) and iron use collected between 2014-16 were compared in cross-sections of PD patients at study enrolment. Results were analysed by country: Australia and New Zealand (A/NZ), Canada, Japan, United Kingdom (UK), and United States (US).

Results: Mean Hgb ranged from 10.9-11.2 g/dL across countries (table). ESA use was higher in Japan (93%) vs. 65-71% elsewhere, with ESA type varying by country. Median epoetin dose ranged from 2500-7250 units/week. In US and Japan, 87-88% of patients had a TSAT≥20%, compared to 72-76% of patients in other countries. Ferritin >500 ng/mL was most common in US, at 60% compared to 7-35% in other countries. IV iron use was higher in US (53%) than elsewhere (5-18%).

Conclusions: In the largest international study to date of anemia and iron management in PD patients, we have demonstrated comparable Hgb levels across countries but significant variations in markers of iron adequacy and ESA and iron use. Notably, US PD patients have higher ferritin levels, iron saturation and IV iron use than other countries. Future analyses will investigate whether these differences persist after patient- and facility-level adjustments, and will evaluate associations between anemia management practices and clinical and patient-reported outcomes.

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Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, Association of German Nephrology Centres, Societies for Nephrology in Germany, Italy, & Spain., Private Foundation Support, Government Support - Non-U.S.

Table: Anemia labs and treatments, by PDOPPS country

	A/NZ	Canada	Japan	UK	US
Patients, N	303	379	521	168	2439
Age, years	64.2(13.9)	61.6(14.5)	64.8(13.0)	61.9(15.3)	57.5(15.0)
ESRD vintage, years	2.38(2.82)	3.11(3.63)	3.02(3.33)	2.71(3.92)	3.05(3.33)
Labs					
Hgb, g/dL	11.2(1.6)	11.0(1.6)	10.9(1.3)	11.1(1.5)	11.1(1.5)
<10.0	16%	23%	21%	20%	21%
10.0-11.9	54%	53%	59%	49%	55%
≥12.0	29%	24%	20%	31%	24%
TSAT[a], %	26.7(11.5)	26.4(12.5)	32.0(12.0)	27.0(10.9)	33.3(13.5)
<20	24%	28%	12%	27%	13%
≥20	76%	72%	88%	73%	87%
Ferritin[a], ng/mL	291[171,526]	242[118,465]	111[60,203]	336[202,589]	635[330,980]
<100	11%	22%	44%	10%	6%
100-500	63%	57%	50%	56%	33%
>500	26%	21%	7%	35%	60%
Anemia treatment					
ESA use[b], %	67%	66%	93%	65%	71%
ESA type among users, % (median dose[c], units/week)					
Darbepoetin	69% (30.0)	72% (24.4)	40% (26.9)	70% (20.0)	11% (25.0)
Epoetin	22% (6000)	28% (4000)	1% (3000)	30% (2500)	87% (7250)
Pegylated epoetin beta	9% (18.8)	0% (-)	59% (25.0)	0% (-)	2% (29.2)
IV iron use[b], %	12%	10%	5%	18%	53%
Oral iron use[b], %	8%	38%	19%	7%	11%

Results are shown as mean (std), median [IQR], or %.
[a]Among patients with measurements in 4 months prior to study enrollment. 58-84% patients have TSAT measured, and 79-96% have Ferritin measured.
[b]Any use in last 4 months.
[c]Weekly dose averaged over 4 months, excluding months without ESA use.

TH-OR090

Randomized Trial on Adjunctive Lavage for Severe Peritonitis Steve Siu-Man Wong,[1] Yuk L. Cheng,[1] Alex W. Yu.[2] *[1]Alice Ho Miu Ling Nethersole Hospital, N.T., Hong Kong; [2]Hong Kong Baptist Hospital, Kowloon, Hong Kong.*

Background: No adjunctive therapy has been shown to improve the antibiotic response in peritoneal dialysis (PD)-related peritonitis. This study was conducted to assess if adjunctive lavage is useful for severe cases, as it may enhance the removal of bacteria and inflammatory cells from the peritoneal cavity.

Methods: Intraperitoneal (IP) cefazolin/ ceftazidime were the empirical treatment for PD peritonitis. Severe cases were defined as persistent symptoms with PD effluent (PDE) leukocyte count >1090/mm^3 on day 3. We excluded patients with concurrent exit site infection (ESI), or known fungal/ mycobacterial growth from the PDE. Recruited patients with severe peritonitis were randomized into the lavage or control group. While both groups involved empirical antibiotics escalation (vancomycin/ gentamicin) before the microbiology report became available, continuous lavage by a cycler PD machine was applied in the lavage group for 2-3 days, during which the antibiotics were given intravenously. Usual PD regimen and IP administration of antibiotics were resumed after lavage completed. Primary endpoint was the treatment outcome: success (cleared PDE) or failure (catheter removed).

Results: Between March 2014 and May 2017, there were 399 peritonitis episodes in our center. A total of 39 episodes, involving 36 patients, were recruited. The other 360 episodes were not recruited mostly because of their mild severity or treatment initiated in other units. Among the recruited patients, 5 were excluded due to later development of ESI (n=1), fungal (n=3) or mycobacterial growth (n=1) from the PDE. The peritonitis details and outcome are shown in the Table.

Conclusions: Adjunctive lavage did not bring additional merit. Yet, the high treatment success rates in both groups indicated that an early antibiotic escalation could be beneficial in severe PD peritonitis with poor clinical response.

Patients' characteristics & peritonitis details

	Lavage group (n=17)	Control group (n=17)	P values
Age, years	64.1 ± 9.2	58.8 ± 10.2	0.12
Male gender, n (%)	12 (70.6)	5 (29.4)	0.04
Peritoneal dialysis vintage, years	4.2 ± 2.7	4.7 ± 3.6	0.57
Dialysate leukocyte count on day 3, /mm^3	6804 ± 5164	5297 ± 3876	0.34
Gram-positive peritonitis, n (%)	6 (35.3)	10 (58.8)	0.30
Gram-negative peritonitis, n (%)	8 (47.1)	4 (23.5)	0.28
Mixed gram-positive & gram-negative peritonitis, n (%)	3 (17.6)	2 (11.8)	1.00
Culture-negative peritonitis, n (%)	0 (0.0)	1 (5.9)	1.00
Treatment success, n (%)	12 (70.6)	14 (82.4)	0.69

TH-OR091

Retroperitoneal Leakage as an Important Cause of Acute Ultrafiltration Failure in Peritoneal Dialysis Patients Min Zhang,[4] Qionghong Xie,[3] Da Shang,[1] Chuan-Ming Hao,[2] Tongying Zhu.[1] *[1]Division of Nephrology, Huashan Hospital, Fudan University, Shanghai, China; [2]Huashan Hosp., Shanghai, China; [3]Huashan Hospital of Fudan University, Shanghai, China; [4]Huashan Hospital, Fudan University, SHANGHAI, China.*

Background: Acute ultrafiltration failure (AUFF), characterized by a sudden reduction in ultrafiltration, is one of the causes of technique failure in peritoneal dialysis (PD). AUFF can lead to fluid overload, which is a high risk factor for mortality in PD patients. Retroperitoneal leakage (RPL) is one of the causes of AUFF. In this study, we aimed to analyze the risk factors of RPL in PD patients and observe the outcomes.

Methods: RPL was determined by magnetic resonance (MR) peritoneography in the patients with AUFF. Non-AUFF patients were chosen as controls. Demographic and PD related characteristics were analyzed between these two groups and treatment outcome was observed in RPL patients.

Results: During a 6-year observational period, 142 out of 421 PD patients developed AUFF, and 49 (34.5% in AUFF) of them were diagnosed as RPL by MR Peritoneography. None of RPL patients had hernia, pleural fistula or PD tube exit fistula, while one patient had scrotal fistula. Twenty-one (42.9%) of the RPL cases occurred in the first 3 months, while 16 (32.7%) occurred after 2 years' PD therapy. The percentage of male patients was significantly higher in the RPL group than in the controls (75% vs. 51%, P=0.003). RPL patients were younger than non-RPL patients (48.42±14.64 vs. 55.86±16.99, P<0.001). No child-bearing experience was a risk factor for RPL in female PD patients (3/12 vs. 10/119, P=0.002). While multi-variants analysis showed that only younger age was a risk factor (P=0.017). After 8 weeks' intermittent peritoneal dialysis (IPD) or hemodialysis, four patients turned to hemodialysis permanently because of severe and persistent leakage, while others improved remarkably confirmed by MR peritoneography and resumed CAPD.

Conclusions: RPL is common in PD patients and an important cause of AUFF. MR peritoneography is an ideal diagnostic method to detect RPL. Risk factors for RPL include younger age and probably no child-bearing experience in females. RPL is reversible after transitional therapy of IPD or hemodialysis.

Funding: Government Support - Non-U.S.

TH-OR092

Bio Impedance Measurements Taken Over a Period of Time May Be Better Predictors of Survival Than Baseline Measurements in Peritoneal Dialysis Patients Hari Dukka,[3] Mark Lambie,[1] Simon J. Davies.[2] *[1]Keele University, Crewe, United Kingdom; [2]University Hospital of North Midlands, Stoke-on-Trent, United Kingdom; [3]Nephrology, University Hospital North Midlands, Stoke on Trent, United Kingdom.*

Background: Numerous recent studies have shown that a single measure of body composition estimated from bioimpedance (BI) in dialysis patients is predictive of survival. However, fluid status varies with time and it is not known whether repeated measures improve predictions when compared to a single measure.

Methods: We analysed the long-term predictive value of baseline and longitudinal (5 measures over 12 months). BI measurements obtained from 289 patients enrolled into the UK and Shanghai BI trial (4 centres, 2009-2010). Patients were followed up until a censor date of 30 April 2016 and events such as death, Haemodialysis and transplantation were recorded. Analysis was performed using Cox model stratified for centre.

Results: On univariate analysis, increased extracellular water to total body water ratio (ECW/TBW) and lower phase angle (PA) predicted worse survival with HR's of 1.063 (95% CI 1.030-1.097) and 0.792 (95% CI 0.671-0.933) respectively. In an analysis adjusted for age, co-morbid score, albumin and urine volume, baseline values of both ECW/TBW and PA provided estimated hazard ratios closer to 1 (HR 1.023, 95% CI 0.984-1.063, and HR 0.913, 95% CI 0.761-1.095 respectively). When time varying rather than baseline values were used in the same adjusted analysis, the goodness of fit statistics improved significantly (ECW/TBW Δ-2LL 7.7, PA Δ-2LL 6.2) and estimated HR's were further from 1 (ECW/TBW HR 1.063, 95%CI 1.023-1.106, PA HR 0.726, 95%CI 0.577-0.913).

Conclusions: Our analysis demonstrates that repeated BI measurements over a period of time increases the predictive value compared to baseline measurements.

Variables in the Equation

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B) Lower	Upper
T_COV_	.062	.020	9.775	1	.002	1.064	1.023	1.106
age	.050	.011	22.496	1	.000	1.052	1.030	1.074
score	.269	.124	4.692	1	.030	1.309	1.026	1.670
urinevolume	.000	.000	.162	1	.687	1.000	1.000	1.000
albumin	.001	.001	.635	1	.425	1.001	.999	1.004

Survival analysis of Longitudinal ECW/TBW measures.

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B) Lower	Upper
T_COV_	-.321	.117	7.458	1	.006	.726	.577	.913
age	.050	.011	21.464	1	.000	1.051	1.029	1.073
score	.286	.124	5.326	1	.021	1.331	1.044	1.696
urinevolume	.000	.000	.145	1	.704	1.000	1.000	1.000
albumin	.001	.001	.535	1	.465	1.001	.998	1.003

Survival analysis of longitudinal phase angle measures.

TH-OR093

Effects of Long-Term Treatment with Low GDP, pH Neutral Solution on the Peritoneal Functions and Morphological Changes in PD Patients Mitsuhiro Tawada,[1,2] Yasuhiko Ito,[3,2] Chieko Hamada,[4] Masashi Mizuno,[2] Yasuhiro Suzuki,[2] Fumiko Sakata,[2] Shoichi Maruyama.[2] *[1]Koujyukai Kasugai Hospital, Kasugai, Japan; [2]Nagoya University Graduate School of Medicine, Nagoya, Japan; [3]Aichi Medical University, Nagakute, Japan; [4]Juntendo University, Tokyo, Japan.*

Background: Effects of long-term treatment with acidic solution on the peritoneal membrane are well known. However, the peritoneal membrane damage induced by long-term peritoneal dialysis low GDP, pH neutral solution (neutral solution) has not been

reported in detail. The aim of this study was to investigate the effects of neutral solutions on peritoneal functions and morphological changes.

Methods: This study used pathological and immunopathological techniques to assess peritoneal membrane biopsy samples from peritoneal dialysis patients treated with acidic solution or neutral solution. And we investigate the D/P Cr changes by long-term neutral solution treatments.

Results: The morphological changes were compared between the acidic solution group (n=54) and neutral solution group (n=67). According to the analyses, the ratio of lumen diameter to vessel diameter (L/V ratio) was significantly smaller ($p<0.01$), peritoneal membrane was thicker ($p<0.01$) and accumulation of advanced glycation end-products (AGEs) was higher in the acidic solution group than in the neutral solution group ($p<0.01$). In addition, acidic solution group (n=33) and neutral solution group (n=31) who were treated for 4 to 10 years were compared. In this study, the L/V ratio was significantly smaller ($p<0.01$) and peritoneal membrane was thicker ($p=0.034$), and there were no significant differences in number of CD31 positive vessels and CD68 positive cells between the two groups. Furthermore, the L/V ratio in the acidic solution group significantly decreased over time ($p<0.01$), no such change was seen in the neutral solution group. According to the results of peritoneal equilibration tests for long term neutral solution treatments, D/P Cr also did not change over time.

Conclusions: These findings suggest that neutral peritoneal dialysis solutions prevent morphological changes and keep peritoneal functions with no changes in D/P Cr after long term PD treatment.

TH-OR094

Socioeconomic Factors and Racial/Ethnic Disparities in PD Initiation Jenny I. Shen,[1] Holly Wilhalme,[3] Sitaram Vangala,[3] Anjali B. Saxena,[2] Keith C. Norris.[3] *[1]LaBiomed at Harbor-UCLA, Torrance, CA; [2]Stanford University / Santa Clara Valley Med Ctr, Los Altos, CA; [3]UCLA, Los Angeles, CA.*

Background: Peritoneal dialysis (PD) has been underutilized in the US. The discrepancy is most pronounced in black and Hispanic patients who, despite having a higher prevalence of chronic kidney disease than non-Hispanic White and Asian patients, are less likely to use PD. We investigated the association of socioeconomic factors with racial and ethnic disparities in the initiation of dialysis with PD in the US.

Methods: We identified from the USRDS all adult patients who initiated dialysis on Day 1 with either hemodialysis (HD) or PD from 2005-13 and categorized them as either non-Hispanic White, Hispanic White, non-Hispanic Black, or non-Hispanic Asian. We then used logistic regression to estimate the odds ratio (OR) of initiating dialysis with PD vs. HD for each of the minority groups compared to non-Hispanic White patients.

Results: Of 522,767 patients, 55% were non-Hispanic White, 28% black, 13% Hispanic white, and 4% Asian; 8% started dialysis on PD. In unadjusted analyses, Blacks and Hispanics were 30% and 21% less likely and Asians were 32% more likely to start on PD than whites (Table). The gap for Blacks and Hispanics widened and for Asians lessened when adjusted for age, sex, and calendar year of dialysis initiation. However, the disparities narrowed when adjusted for individual and neighborhood level socioeconomic factors.

Conclusions: Black and Hispanic patients are less likely to start on PD than White patients, especially given their age, sex, and era of dialysis initiation. This disparity is reduced, but still statistically significant when adjusted for socioeconomic factors. More research is needed to determine whether these variables are associated with potentially modifiable factors such as physician or patient bias against starting PD in patients of a certain socioeconomic background.

Funding: NIDDK Support, Other NIH Support - NCATS

OR (95%CI) of starting dialysis on PD (vs. non-Hispanic Whites)

Model	Blacks	Hispanic Whites	Asians
unadjusted	0.69 (0.68-0.71)	0.81 (0.78-0.84)	1.32 (1.26-1.38)
1: adjusted for age, sex, calendar year	0.56 (0.55-0.58)	0.66 (0.64-0.68)	1.17 (1.12-1.22)
2: adjusted for 1+comorbidities+labs	0.66 (0.64-0.68)	0.69 (0.67-0.72)	1.01 (0.69-1.05)
3: adjusted for 2+socioeconomic factors*	0.76 (0.74-0.79)	0.90 (0.87-0.94)	1.00 (0.95-1.05)

*SES factors: early referral, insurance, employment, neighborhood poverty, neighborhood education, neighborhood % black/Hispanic, neighborhood linguistic isolation, rural/urban, # of nephrologists & large PD units/population, census division

TH-OR095

Quasi-Continuous Monitoring of intraperitoneal Volume Using Segmental Bioimpedance in Peritoneal Dialysis Patients Fansan Zhu,[1] Samer R. Abbas,[1] Roxana M. Bologa,[2] Nathan W. Levin,[1] Peter Kotanko.[1,3] *[1]Renal Research Institute, New York, NY; [2]The Rogosin Institute, New York, NY; [3]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Ultrafiltration failure (UFF) is a frequent complication in peritoneal dialysis (PD) patients. The peritoneal equilibration test (PET) is the standard method for assessing peritoneal transport characteristics. However, dynamic changes in intraperitoneal volume (IPV) during the dwell cannot be determined by PET. The aim of this pilot study was to explore the feasibility of segmental bioimpedance analysis (SBIA) to quasi-continuously monitor IPV during dwell periods.

Methods: 10 PD patients (7 females, age 59±8.8 years, weight 71.9±12 kg) with standard 4 hours PET using 2 L of 2.5 % dextrose PD solution were studied. Eight electrodes were placed as shown in Figure 1. At 5 kHz resistance (R_5, Ohm) was measured from each pair of electrodes minute-by-minute with the Hydra 4200 device. During the PET IPV was calculated from the average R_5 of the left and right sides of the abdomen (Zhu et al., *Am J Kidney Dis*, 42:167-172, 2003). This setting allowed us to follow the IPV time course and determine the maximum IPV from visual inspection of the recordings.

Results: In 9 patients the IPV measurements were technically successful; in 1 patient signal quality was poor. Figure 2 shows a typical IPV measurement. Average (SD) drain volume at 4 hours was 0.5±0.3 L by SBIA compared to weight loss (ΔWt) of 0.54±0.27 kg. Maximal IPV indicated by SBIA was 1.0±0.4 L. The difference between maximal IPV and drain volume was 0.5±0.4 L (95% confidence interval: 0.2 to 1.2; $P<0.01$ in a paired t-test) L. Maximal IPV was reached after a dwell time of 157±57 minutes (range 113 to 200 min).

Conclusions: This pilot study demonstrates the feasability of segmental bioimpedance to quasi-continuoously monitor IPV and to identify the time point of maximum IPV. These insights may help to optimize individual PD treatments and improve ultrafiltration efficiency. While these results are encouraging, additional validation studies, to automatically detect maximum IPV, and efforts to improve measurement convenience are required.

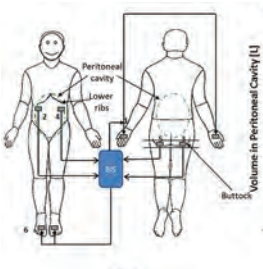


Fig.1

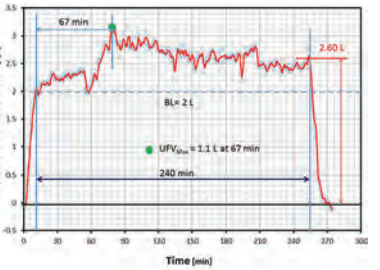


Fig.2

Fig1 and Fig2

TH-OR096

Low Serum Potassium Is Associated with Indicators of Under-Nutrition and Reduced Residual Kidney Function: Results from the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) Simon J. Davies,[1] Junhui Zhao,[2] Brian Bieber,[2] Douglas S. Fuller,[2] James A. Sloand,[3] Andreas Vychytil,[4] Hideki Kawanishi,[5] David W. Johnson,[6] Angela Y. Wang,[7] Sarinya Boongird,[8] Thyago P. Moraes,[9] Sunil V. Badve,[10] Jeffrey Perl.[11] *[1]University Hospital of North Midlands, Stoke-on-Trent, United Kingdom; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]Baxter Healthcare Corporation, Deerfield, IL; [4]Medical University of Vienna, Vienna, Austria; [5]Tsuchiya General Hospital, Hiroshima, Japan; [6]Princess Alexandra Hospital, Brisbane, QLD, Australia; [7]University of Hong Kong, Queen Mary Hospital, Hong Kong, China; [8]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [9]Pontificia Universidade Catolica do Parana, Curitiba, Brazil; [10]St. George Hospital, Kogarah, NSW, Australia; [11]St. Michael's Hospital, Toronto, ON, Canada. Group/Team: On behalf of PDOPPS dialysis prescriptiOn and fluid management working group.*

Background: Serum potassium <4mmol/L is associated with increased all-cause mortality risk and possibly increased risk of peritonitis in PD patients. We evaluated the relationship between serum potassium (K) and patient characteristics and clinical practices in PDOPPS.

Methods: PDOPPS is a prospective cohort study of PD treatment and outcomes in Australia, Canada, Japan, New Zealand, Thailand, the UK, and the US. Using the most recent value within 8 months of study enrollment, we defined low K as <4 mEq/L. We assessed demographic and clinical associations with low K using logistic regression generalized estimating equations.

Results: Among 2486 incident and prevalent patients analyzed, 69% had K <4 mEq/L. Demographic variables were similar in patients with or without low K. Low K was associated with several indicators of poorer nutritional status, including lower levels of serum phosphorus, creatinine, and albumin, but higher levels of serum bicarbonate. Patients with greater residual kidney function were less likely to have low K. Low K was associated with higher prescribed glucose concentrations and systolic blood pressure.

Conclusions: Low K is associated with indicators of reduced muscle mass and/or protein intake and reduced residual kidney function rather than increased dialytic clearance. Increased blood pressure and prescription of glucose in patients with K≥4 mEq/L group likely reflects their higher oral salt and fluid intake but could reflect increased calorie contribution from dialysate. Clinicians should recognize that lower K levels, even within the normal range, may reflect under-nutrition particularly when associated with reduced residual function and that could contribute to increased mortality risk.

Funding: Commercial Support - Amgen, AstraZeneca, Baxter Healthcare, Kyowa Hakko Kirin, Hexal AG, Janssen, Keryx, Proteon, Relypsa, Roche, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, Association of German Nephrology Centres, Societies for Nephrology in Germany, Italy, & Spain., Private Foundation Support, Government Support - Non-U.S.

Table: Patient characteristics by serum potassium (K), with odds ratios estimated from logistic model

Patient characteristics	K ≥4 mEq/L (N=1469)	K <4 mEq/L (N=1017)	Adjusted Odds Ratio (95% CI)* for K <4 mEq/L	
Age, years	60.3 (14.5)	61.0 (14.8)	1.01(0.94,1.09)	per 10 years
Male, %	60.0%	53.9%	0.98(0.84,1.15)	vs. female
Diabetic, %	44.2%	47.6%	0.94(0.76,1.16)	vs. non-diabetic
BMI, kg/m^2	26.1 (5.7)	24.9 (5.8)	1.03(0.93,1.14)	per 5 kg/m^2
CAPD, %	42.4%	57.5%	1.02(0.79,1.32)	vs. APD
Caregiver(s) involved in PD exchanges, %	20.8%	32.9%	0.98(0.78,1.23)	vs. not involved
24 hour urine volume, L	0.85 (0.73)	0.58 (0.60)	0.75(0.67,0.83)	per 0.5 L
Peritoneal Kt/V urea	1.37(0.56)	1.52(0.63)	1.05(0.83,1.32)	per 1
Phosphorus, mg/dL	5.36 (1.52)	4.59 (1.35)	0.78(0.73,0.84)	per 1 mg/dL
Albumin, g/dL	3.38 (0.67)	3.24 (0.70)	0.84(0.73,0.98)	per 1 g/dL
Serum creatinine, mg/dL	9.33 (3.69)	8.71 (3.54)	0.95(0.92,0.98)	per 1 mg/dL
Bicarbonate, mEq/L	25.5 (3.4)	26.9 (3.2)	1.05(1.02,1.09)	per 1 mg/dL
Diastolic blood pressure, mm Hg	78.7 (14.1)	76.9 (14.2)	1.02(0.93,1.11)	per 10 mm Hg
Systolic blood pressure, mm Hg	139 (24)	136 (25)	0.93(0.89,0.97)	per 10 mm Hg
2.27% or 2.5% PD solution use, %	62.6%	57.8%	1.34(1.05,1.71)	vs. non user
Diuretic, %	52.5%	55.1%	1.12(0.91,1.39)	vs. non user
Residual Kt/V urea	0.78(0.79)	0.57(0.71)	–	
Residual GFR, mL/min	3.49(3.83)	2.52(3.45)	–	

Percent prevalence or mean (SD) are shown. Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; APD, automated peritoneal dialysis. GFR, Glomerular filtration rate.
*Multivariate model adjusted for variables listed in table, additionally adjusted for country.

TH-OR097

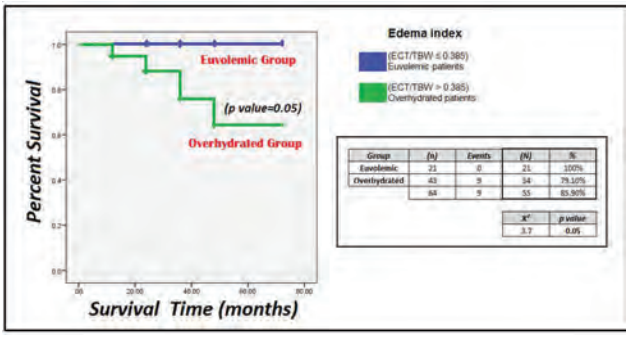
New Overhydration Definition and Mortality Risk Assessment in Automated Peritoneal Dialysis Mexican Patients Julio C. Arriaga,[2] Gabriela Leal,[3] Bernardo Moguel.[1] [1]*Instituto Nacional de Cardiologia, Mexico City, Mexico;* [2]*Instituto Nacional de Cardiologia Ignacio Chavez, Tlalpan, Mexico;* [3]*Instituto Nacional de Cardiología, México, Mexico.*

Background: CKD prevalence in Mexico is about 33% and peritoneal dialysis (PD) represents 66% of renal replacement therapy. Overhydration assessment with bioimpedance in APD patients may be a key point predictor for mortality.

Methods: We analyze an APD cohort of 64 Mexican patients. Anthropometric, blood and nutritional profiles, time in APD, dialysis prescription, use of medication and bioimpedance analysis was assessed and reported as the average of 3 repeated samples during the last 6 months. Inclusion criteria were age ≧18 years, clinical and biochemical stability and adherence to dialytic therapy. Patients with other systemic comorbidities were excluded. Edema index *(Ei)* was defined as ECW/TBW (extracellular water/ total body water) ≧0.385 and phase angle (*Pa*)⟨4.8. Euvolemic and overhydrated groups were compared in mortality, regression, correlation and risk factor analysis.

Results: Mean age was 38.9 ±15 years. BMI was normal in half of the patients; 43 patients were overhydrated and 21 euvolemic, we observed significant differences between groups (p⟨0.05) for *Ei*, *Pa*, albumin, residual urine volume and RDW. Survival analysis at 48 months was 100% for euvolemic arm and 79.1% for overhydrated patients (*p=0.05*). Regression model showed an *r2= 0.6*. Correlation coefficient analysis for overhydration was 0.85 for *Pa* and 0.52 for low albumin both with p⟨0.05. Risk factors for mortality were *Ei* OR=1.26 (IC 1.08-1.47), *Pa*⟨4.8 OR=6.13 (IC 1.16-32.3), albumin ⟨3.5 OR=5.8 (IC 1.29-26.5), Age ≧50 years OR=5.0 (IC 1.15-21.7) and RDW ≧14.5% OR=1.38 (1.12-1.69).

Conclusions: Bioimpedance analysis is a practical, useful, cheap, easy and relevant evaluation that impacts on mortality. Cut point values for Mexican PD population *(Ei*=0.385 and *Pa*=4.8*)* are proposed as a new overhydration definition in stable normotensive and non-clinical edema patients. Overhydration, albumin and RDW model predicts 60% of mortality risk in this population.



TH-OR098

Development of an AKI Prediction Model Using Machine Learning Jay L. Koyner, Kyle Carey, Matthew M. Churpek. *University of Chicago, Chicago, IL.*

Background: Early identification of hospitalized patients at risk for the development of AKI prior to changes in serum creatinine(SCr) may improve patient outcomes. We aimed to develop an AKI risk prediction algorithm using electronic health record(EHR) data across ward and ICU patients

Methods: All hospitalized patients at the University of Chicago who had SCr measured from 11/2008 to 1/2016 were eligible. Patients with a first SCr>3.0mg/dl, those who had an ICD9 code for CKD Stage 4 or higher, or received renal replacement therapy(RRT) within 48 hours (hrs) of admission were excluded. Demographics, vital signs, lab results, interventions, medications, blood transfusion & diagnostic testing were utilized in a gradient boosted machine learning algorithm to predict SCr-based KDIGO stage 2 AKI, with 60% of the data used for derivation and 40% for validation. Area under the curve (AUC) was calculated in the validation cohort, and subgroup analyses were conducted across admission SCr, AKI severity, and hospital location

Results: Among the 121,158 included patients, 17,481(14.4%) developed KDIGO AKI, with 4,251(3.5%) developing Stage 2 and 1,997(1.6%) Stage 3. The AUC(95%CI) of the model in the validation cohort was 0.90(0.90-0.90) for predicting Stage 2 AKI within 24 hrs and 0.87(0.87-0.87) within 48 hours. The AUC was 0.95(0.95-0.95) for Stage 3 in 24 hrs and 0.92(0.92-0.93) for 48 hrs. Accuracy was excellent for predicting RRT(n=821) in the next 72 hrs 0.94(0.94-0.94). AUCs for the subgroups can be found in the table. At a threshold with a sensitivity of 85% and a specificity of 85%, the median time from first reaching the threshold to stage 2 AKI was 42(IQR 12,140) hrs

Conclusions: Readily available EHR data can be used to predict impending AKI prior to changes in SCr with excellent accuracy across different patient locations and admission SCr. Real-time use of this model would allow early diagnostic and therapeutic interventions for those at high risk of AKI and may improve cost and outcomes

	AUC(95%CI) for Predicting Stage 2 AKI within 24 hrs
Patient Location	
Ward	0.88(0.88-0.88)
ICU	0.88(0.88-0.89)
Admission SCr (mg/dL)	
<1.0	0.88(0.88-0.89)
1.0 to 1.9	0.92(0.92-0.92)
2.0 to 2.9	0.92(0.92-0.92)

TH-OR099

The Effect of Early Initiation of Renal Replacement Therapy Guided by Furosemide Stress Test on Clinical Outcomes: A Multicenter Randomized Controlled Trial (FST Trial) Nuttha Lumlertgul,[1] Sadudee Peerapornratana,[1] Karjbundid -. Surasit,[2] Thananda Trakarnvanich,[3] Wanjak Pongsittisak,[3] Pleumjit Tankee,[4] Kriang Tungsanga,[1] Somchai Eiam-Ong,[1] Kearkiat Praditpornsilpa,[1] Nattachai Srisawat.[1] [1]*Chulalongkorn University, Bangkok, Thailand;* [2]*Nakornping hospital, Chiangmai, Thailand;* [3]*Vajira Hospital, Bangkok, Thailand;* [4]*Vachira Phuket Hospital, Phuket, Thailand.*

Background: Recently, furosemide stress test (FST) has been introduced as a novel acute kidney injury(AKI) test. Furosemide-nonresponsive AKI patients have poor outcomes. There are unavailable data whether early initiation of renal replacement therapy (RRT) in furosemide non-responsive AKI patients could provide better outcomes than standard RRT. This FST trial **(NCT02730117)** was conducted to determine whether early initiation of RRT in furosemide-nonresponsive patients could improve 28-day mortality.

Methods: AKI patients were recruited from 5 tertiary care hospitals. FST was performed by giving intravenous furosemide (1 mg/kg in furosemide-naïve or 1.5 mg/kg in previous furosemide use). Furosemide non-responsive patients (urine output less than 200 mL in 2 hours) were randomized into early or standard RRT group. With the early strategy, RRT was initiated within 12 hours after randomization. With the standard strategy, RRT was started when standard criteria were met. We also collected blood samples for testing plasma NGAL, NT-proBNP and angiopoietin-2 on day 0, 3, and 7.

Results: Among 87 furosemide-nonresponsive patients, 97.7% in the early RRT group and 70.5% in the standard RRT group received RRT. The 28-day mortality in the early RRT and the standard RRT were comparable (65.1 VS 56.8%, P=0.33). There was no difference in the dialysis dependence rate (35.3 VS 45%, P=0.55). Interestingly, urine output on day 7 in the early RRT group was lower than the standard RRT group (498.5 VS 1,560 mL, P=0.035). There was a trend of more hemodynamic instability related to RRT in the early RRT group than the standard group (32.6 VS 15.9%, P = 0.07). Of interest, time to renal recovery occurred significantly earlier in the standard than the early RRT group (2 VS 7 days; P=0.018). There were no differences in plasma NGAL, NT-proBNP, and angiopoietin-2 levels between 2 groups.

Conclusions: This was the first study to test the role of FST in guiding RRT initiation. Early RRT in furosemide-nonresponsive patients is not recommended since it could not improve 28-day mortality and might prolong time to renal recovery.

Funding: Government Support - Non-U.S.

TH-OR100

Urinary Matrix Metalloproteinase-7 Predicts Severe AKI and Poor Outcomes after Cardiac Surgery Xiaobing Yang,[2] Fan Fan Hou.[1] [1]*Nanfang Hospital, Guangzhou, China;* [2]*Nanfang Hospital, Southern Medical University, Guangzhou, China.*

Background: Urinary matrix metalloproteinase (uMMP)-7 levels faithfully reflect the activity of intrarenal Wnt/β-catenin which is activated in AKI models. uMMP-7 level might be used as a noninvasive biomarker for early predicting AKI after cardiac surgeries.

Methods: we performed a prospective, multicenter, two-stage cohort study in 721 patients undergoing cardiac surgery. In stage 1, 323 children were recruited from 3 academic medical centers. In stage 2, 398 adults were enrolled at 6 centers. The levels

of uMMP-7 and other injury biomarkers were analyzed during the perioperative period. Severe AKI was defined as Kidney Disease Improving Global Outcomes stage 2 or 3.

Results: uMMP-7 peaked within 6 hours after surgery in patients who subsequently developed severe AKI. After multivariate adjustment, the highest quintile of uMMP-7 was associated with 17-fold (in adults) and 36-fold (in children) higher odds of severe AKI compared with the lowest quintile. Elevated uMMP-7 associated with increased risk of composite events (severe AKI, acute dialysis, and in-hospital death) and longer stay in intensive care unit and hospital. For predicting severe AKI, uMMP-7 had an area under the receiver-operating characteristic curve (AUC) of 0.81 (in children) and 0.76 (in adults), outperforming urinary interleukin-18, urinary angiotensinogen, urinary neutrophil gelatinase-associated lipocalin, urinary albumin to creatinine ratio, urinary tissue inhibitor metalloproteinase-2×IGF-binding protein-7, and the clinical model. uMMP-7 significantly improved risk reclassification over the clinical model alone as measured by net reclassification improvement and integrated discrimination improvement.

Conclusions: uMMP-7 is a promising predictor for severe AKI and poor in-hospital outcomes in patients after cardiac surgery.

Funding: Government Support - Non-U.S.

TH-OR101

Urine Insulin like Growth Factor Binding Protein1 (IGFBP1): Novel Prognostic Biomarker in AKI Nithin Karakala,[1,2] Ricky Edmondson,[1] Christian Herzog,[1] John M. Arthur.[1,2] *[1]Nephrology, University of Arkansas for Medical Sciences, Little Rock, AR; [2]Nephrology, Central Arkansas VA, Little Rock, AR.*

Background: Serum creatinine (Cr) is a poor prognostic marker in early AKI. Prognostic urine biomarkers could be valuable tools to detect high risk patients in early AKI. We identified urine IGFBP1 as a potential biomarker using discovery proteomics and validated it in a larger cohort.

Methods: We performed liquid chromatography/ tandem mass spectrometry on urine from patients who developed stage 1 AKI within 48 hours after cardiac surgery. 10 patients that required renal replacement therapy within 7 days after surgery were matched to 20 patients with similar comorbities, baseline Cr, surgical type, bypass status and change in Cr at urine collection. The biomarker concentration was subsequently measured in 213 patients by ELISA to validate the prognostic ability. The primary outcome in the validation set was the composite of death, renal replacement therapy (RRT) and KDIGO stage 3.

Results: In the discovery phase we identified 2065 high confidence proteins of which 126 had p values of less than 0.01 between groups. IGFBP1 had the largest fold increase in RRT (14.8-fold). Median amino acid coverage of IGFBP1 in controls was 0% (range 0-15%) and 26% (0-38%) in RRT. Based on these data, we performed validation with ELISA in a larger cohort. Of the 213 patients included in the validation set, 27 met the primary outcome. The median time to urine collection from cardiac surgery was 22 hours (range:19-43). There were no significant differences between the outcome groups with respect to demographics, underlying medical conditions, type of surgery or pre-op Cr. The median concentration of IGFBP1 was significantly higher in the primary outcome group at 40 (95%CI:10-244) vs 3 (1-11) ng/ml; p<0.05. Median concentration of IGFBP1 was significantly higher in those that met secondary outcomes of mortality (40, 95%CI: 10-333 vs 3: 1-16 ng/ml; p<0.05) and RRT (81: 13-353 vs 4: 1-17 ng/ml; p<0.05) compared those who did not meet these outcomes. Urine IGFBP1 levels were highly discriminative for identifying the primary outcome (ROC AUC: 0.85) and the secondary outcomes death (0.82) and dialysis (0.85). The results did not significantly change when urine IGFBP1 concentrations were normalized to urine Cr.

Conclusions: Urinary IGFBP1 is a prognostic biomarker of AKI after cardiac surgery and can predict adverse outcomes early in the course of disease.

Funding: NIDDK Support, Veterans Affairs Support, Clinical Revenue Support

TH-OR102

Polymyxin-B Induces Fas-Mediated Apoptosis in a Human Kidney Proximal Tubule Microphysiological System (Organ-on-a-Chip) Pavan K. Bhatraju,[2] Elijah Weber,[2] Jonathan Himmelfarb,[1] Edward J. Kelly.[2] *[1]Kidney Research Institute, Seattle, WA; [2]University of Washington, Seattle, WA.*

Background: In response to the emergence of multi-drug resistant gram negative infections, polymyxin-B (PMB) use has increased despite the clinical observations of severe nephrotoxicity. Our lab is modeling PMB-induced nephrotoxicity in 2D proximal tubule epithelial cells (PTECs) and in a 3D microphysiological system (MPS) to identify biological pathways in the development of renal epithelial cell injury.

Methods: PTECs were treated in 2D with escalating doses of PMB (0 uM to 800 uM). Cellular viability (cell cytotoxicity assay) and caspase 3, 7 activation (fluorescent caspase detection) were measured. The minimal concentration that led to cell death in 2D cultured PTECs was used in the MPS. The MPS system was treated with 50 uM for 48 hours. Effluent was collected at 24 hours and analyzed for caspase cleaved cytokeratin 18 (CK-18). Additionally, transcriptional response was analyzed via RNA-sequencing (RNA-seq) of PMB treated MPS.

Results: In two separate donors, PMB-induced toxicity was observed in 2D in a concentration dependent manner with decreasing cellular viability with increasing PMB concentrations. The EC50 for PMB was 130 uM (SD +/- 12.3) and the minimal concentration that led to cell death was 50 uM. Additionally, we observed increasing caspase activation with decreasing cellular viability (one way ANOVA p-value <0.0015). In the 3D MPS, PMB significantly increased CK-18 effluent levels (control 70 +/- 11 U/l versus PMB 207 +/- 24 U/l, p < 0.001). RNA-seq demonstrated increased transcription of Fas/FasL related genes including Fas cell surface receptor (*FAS*), Fas associated death domain (*FADD*) as well as others. The RNA seq response was distinct compared to MPS treated with cadmium, another known nephrotoxicant.

Conclusions: We have demonstrated that in 2D and in 3D, PMB induced injury is mediated through apoptosis. Furthermore, transcriptional response data demonstrates upregulation of Fas pathways in human PTECs after PMB exposure. This study supports continued study of apoptosis and the Fas-pathway to potentially develop therapies that ameliorate PMB induced nephrotoxicity. Clinically, CK-18 may be useful as a biomarker of PMB induced-AKI. This research was supported by an unrestricted gift from the Northwest Kidney Centers to the Kidney Research Institute, F32DK112532, UH3TR000504.

Funding: NIDDK Support, Private Foundation Support

TH-OR103

Precision Medicine in Renal Failure: Role of Lanosterol Synthase Gene and Endogenous Ouabain in AKI Marco Simonini,[4] Chiara Lanzani,[4] Elena Bignami,[4] Nunzia Casamassima,[4] Lorena Citterio,[8] Rossella Iatrino,[9] Roberta Meroni,[2] Laura Zagato,[2] Simone Fontana,[7] Simona Delli carpini,[3] Elisabetta Messaggio,[6] Elena Brioni,[10] John Hamlyn,[5] Paolo Manunta.[1] *[1]HSR-Nefrologia, Milano, Italy; [2]Ospedale San Raffaele, Milano, Italy; [3]San Raffaele Hospital, Milano, Italy; [4]San Raffaele Scientific Institute, Milan, Italy; [5]University of Maryland, Baltimore, Baltimore, MD; [6]Università San Raffaele, Milano, Italy; [7]Università Vita Salute San Raffaele, Milan, Italy; [8]Università Vita-Salute - Ospedale San Raffaele, Milano, Italy; [9]Vita-Salute San Raffaele University, Milan, Italy; [10]ospedale San Raffaele, Milan, Italy.*

Background: A key question in renal failure concerns the mechanism(s) that underlie the decline in renal function. Endogenous Ouabain (EO) has been proposed as predictive biomarker for acute kidney injury (AKI), and effector of glomerular damage in salt-sensitive hypertensive rats. Lanosterol Synthase (LSS) is a key enzyme in the EO biosynthesis. This work explores the association of LSS genotypes and kidney EO with renal damage and its progression.

Methods: Three different conditions were investigated: 1. Renal EO: we analyzed EO contents of the cortex and medulla of healthy kidneys derived from nephrectomised patients genotyped for LSS genetic variants. 2. Essential Hypertension: 338 naïve hypertensive (f 162, m 176, age 44.5±0.42 years) were enrolled for a prospective follow-up study, in which BP was maintained in similar range and changes in renal function were followed. 3. AKI: 1097 individuals undergoing elective cardiovascular surgery were enrolled for a prospective, observational study, investigating the genetic predisposition to AKI.

Results: Among LSS genotypes, individuals with LSS AA variant had higher renal cortical content of EO (2.14±0.29 ng/g), than their LSS CC (1.25±0.08 ng/g; p=0.0009) counterparts. The follow-up study revealed a genotype-dependent decline in renal function over time. LSS AA exhibited greater eGFR decay than LSS CC (AA -2.02±1.22 vs CC 2.24±0.76 ml/1.73m2/yr; p=0.027), despite similar blood pressure values. Likewise, the incidence of AKI following cardiovascular surgery was greater among LSS AA individuals, and proportional to the number of A alleles (AA 30.7% vs AC 26.0% vs CC 17.4%; p=0.001).

Conclusions: Our findings support the view that LSS drives a common mechanism of renal damage in hypertension and AKI and this appears to be mediated in part by EO. LSS-based risk stratification can be used for the timely preoperative recognition and improved management of acute kidney failure.

TH-OR104

Cell-Cycle Arrest Biomarkers TIMP2*IGFBP7 Predict Worse Outcomes in Septic Patients without Clinical Evidence of AKI Marco Fiorentino,[1,2] Christopher M. Keener,[1] Ali Smith,[1] John A. Kellum.[1] *[1]Center for Critical Care Nephrology, CRISMA, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA; [2]Department of Emergency and Organ Transplantation, Nephrology, Dialysis and Transplantation Unit, University of Bari, Bari, Italy.*

Background: Acute kidney injury (AKI) is associated with both short and long-term adverse outcomes in patients with sepsis. Standard criteria for AKI, like serum creatinine (sCr) and urine output (UO), are poor, late and non-specific diagnostic tools. The aim of this study is to analyze the performance of several biomarkers in addition to standard criteria for early prediction of sepsis-associated AKI.

Methods: We analyzed data from 1243 patients with septic shock enrolled in the ProCESS trial of early goal-directed therapy, for which biomarkers at admission were available. TIMP2*IGFBP7, uNGAL and uKIM1 at the time of admission were independently combined with clinical parameters for AKI (sCr and UO). Our primary endpoint was the development of severe AKI (KDIGO stage 3), renal replacement therapy (RRT) or death in the first 7 days of enrollment. We analyzed the frequency of the outcome and the odds ratios (ORs) for each combination, compared to a reference (normal sCr, UO and negative biomarkers). We also examined the effect of different resuscitation strategies on the endpoint.

Results: Excluding patients with stage 3 AKI at admission and those with missing data, we analyzed 493 patients with availability of biomarkers at time 0. No significant differences in the outcome were found when uNGAL and uKIM1 were added to sCr and UO. By contrast, in patients with normal sCr and UO, the proportion of patients who developed the endpoint was significantly higher in those with positive (>0.3 ng/ml^2/1000) urine TIMP2*IGFBP-7 (16.2% vs 5.7%, p=0.02) and the odds ratio for developing the

endpoint was 3 times greater (OR 3.03, 95%CI 1.27-7.22). Similar results were found in sensitivity analyses using the highest cut-off for TIMP2*IGFBP7 (>2 ng/ml²/1000; OR 2.8, 95%CI 1.14-6.84) and using different outcomes (death/dialysis at 30 days OR 3, 95%CI 1.26-7.15, p=0.005; death/dialysis at 1 year OR 3.32, 95%CI 1.41-7.85, p=0.002). Moreover, the effect of the protocolized resuscitation vs usual care on the endpoint was negative and not different across TIMP2*IGFBP7 strata.

Conclusions: Early assessment of TIMP2*IGFBP7 at the time of admission in ICUs may significantly improve the ability to predict hard outcomes (severe AKI, RRT and death within 7 days) in apparently "asymptomatic" septic patients (normal sCr and UO).

Funding: Other NIH Support - R01DK083961

TH-OR105

AKI Severity and Risk of Adverse Pregnancy Outcomes in Women with Recovered AKI Jessica S. Tangren,[1] Wan Ahmad Hafiz Wan Md Adnan,[2] Elizabeth D. Ankers,[1] Ravi I. Thadhani.[1] [1]*Massachusetts General Hospital, Boston, MA;* [2]*University Malaya, Kuala Lumpur, Malaysia.*

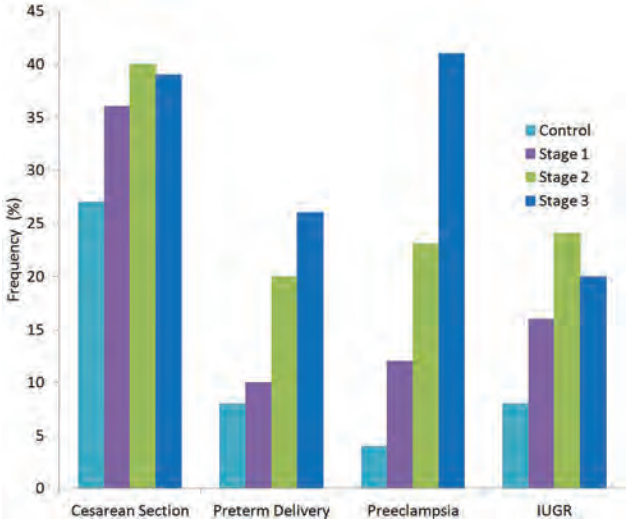
Background: We previously reported that an episode of clinically recovered AKI (rAKI) before pregnancy was associated with increased rates of pregnancy complications including preeclampsia. Our initial study was not powered to determine if stage of AKI was associated with adverse outcomes. Using an expanded cohort of women with recovered AKI with 8 years of additional data, we aimed to identify if AKI severity prior to pregnancy was associated with adverse pregnancy outcomes.

Methods: We conducted a retrospective cohort study of women who delivered infants from 1998 to 2016 at the Massachusetts General Hospital. Pregnancy outcomes in women with a history of Stage 1 (S1, n=98), Stage 2 (S2, n=99) and Stage 3 (S3, n=49) AKI were compared to women without a history of AKI (controls, n=24,460).

Results: Pre-pregnancy serum creatinine measurements were similar between women with rAKI and controls (0.63 ± 0.1 vs 0.69 ± 0.1 mg/dl). Women with rAKI had an increased rate of preeclampsia (22% versus 4%, p<0.01). Infants of women with r-AKI were born earlier (38.2±3.1 vs. 39.2±2.2 weeks, p<0.01). Increasing AKI stage was associated with higher rates preterm delivery and preeclampsia (Table 1). Rates of IUGR were higher in women with rAKI but did not show a dose-response effect (p for trend = 0.40). After multivariate adjustment women with S3 AKI were at increased risk for preeclampsia compared to women with S1 AKI (OR 3.7 95%CI 1.5-9.1) Longer duration (years) from AKI to pregnancy was associated with decreased risk for preeclampsia (OR 0.7 95% CI 0.6-0.9).

Conclusions: Severity of AKI demonstrated a dose-response relationship with many adverse pregnancy outcomes. Longer duration between AKI episode and pregnancy was protective against adverse outcomes. Further research is needed to determine how best to counsel young women with AKI planning pregnancy.

Funding: Private Foundation Support



TH-OR106

Potential Impact of CMS Payment Policy on Misclassification of Dialysis-Requiring AKI (AKI-D) as ESRD: A National Temporal Trend Analysis Benjamin J. Lee,[1] Kirsten L. Johansen,[1,2] Charles E. McCulloch,[1] Chi-yuan Hsu.[1] [1]*University of California, San Francisco, San Francisco, CA;* [2]*San Francisco VA Medical Center, San Francisco, CA.*

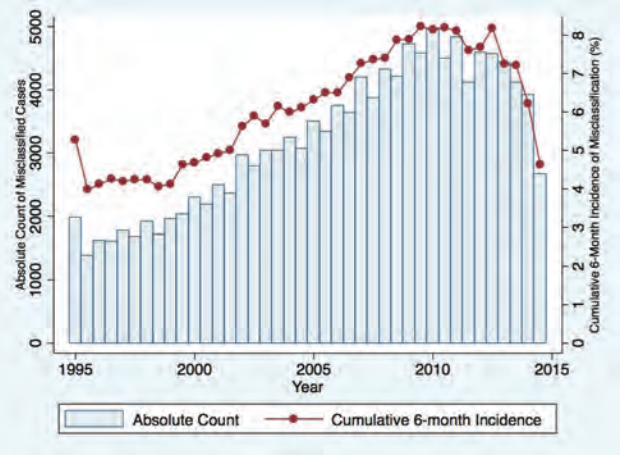
Background: Difficulty in predicting which patients with AKI-D will recover to discontinue dialysis may result in misclassification of such patients as having ESRD, which may be detrimental to patient well-being and may falsely inflate estimates of national ESRD incidence. External factors such as reimbursement policies may influence misclassification.

Methods: Using US Renal Data System (USRDS) Standard Analytic Files, we studied all patients registered as having incident ESRD from 1995 to 2014 (n=2,049,212). Patients subsequently reported to be alive ≥90 days without continued dialysis treatments or kidney transplant were considered misclassified AKI-D and not true ESRD cases. We used linear regression and interrupted time-series (ITS) regression to estimate temporal trends in AKI-D misclassification, with particular attention to mid-2012 when the Centers for Medicare & Medicaid Services (CMS) changed reimbursement policy to forbid ESRD facilities from providing dialysis to AKI-D outpatients.

Results: The overall AKI-D misclassification rate was 6.2%, but with a distinct temporal trend (**Figure**). AKI-D misclassification increased on average 0.36% (95% CI 0.33-0.38%) per year from 2000 to 2010. It then abruptly changed in July 2012, when our univariate ITS model estimated that misclassification incidence decreased 2.14% (1.11-3.18%).

Conclusions: Approximately 1 in every 16 patients in the ESRD registry is actually misclassified AKI-D, a much higher proportion than reported previously. The incidence of misclassification increased throughout the first decade of the 21st century but subsequently decreased around the time of a key Medicare reimbursement policy change.

Funding: NIDDK Support



6-month absolute count (bar graph) and 6-month cumulative incidence (%, line graph) of AKI-D misclassification in the USRDS.

TH-OR107

Mitochondria Homing Drug MA-5 Protects against Contrast Induced AKI Takehiro Suzuki, Tetsuro Matsuhashi, Akihiro Matsuo, Koichi Kikuchi, Eikan Mishima, Chitose Suzuki, Sadayoshi Ito, Takaaki Abe. *Tohoku university, Sendai, Japan.*

Background: Contrast induced acute kidney injury (CI-AKI) is the common cause of the iatrogenic and drug-induced kidney injury, but the therapeutic procedures have not been established. The renal hypoxia and the toxic effects on renal tubular cells are postulated as the pathophysiologic mechanisms of CI-AKI. Recently we reported mitochondria homing drug, mitochonic acid-5 (MA-5) increased intracellular ATP, decreased mitochondrial ROS and improved cell survivals of fibroblasts form mitochondrial disease patients by binding mitochondrial protein Mitofilin and promoting oligomelization of ATP synthases (Suzuki T. *Tohoku J Exp Med* 2015, Matushashi T. *EBioMedicine* 2017). MA-5 improved the renal function and tubular cell injuries in murine renal ischemia reperfusion and cisplatin induced nephropathy models (Suzuki T. *JASN* 2016). The aim of this study is to examine the protective effects of MA-5 on CI-AKI.

Methods: Human proximal tubular cell line HK-2 cells were cultured to 80% confluent and MA-5 at 10uM final concentration for 24hr without serum and then added radiocontrasts sodium ditrizoate, Iopamidol and iohexol at 75mg iodine /ml for another 1hr. Cell viability and cytotoxicity were accessed by WST-8 assay and LDH assay respectively. Male CD-1 and C57/BL6 mice, 10-12 week old were left-nephrectomized (Nx) and MA-5 was administrated, at 50mg/kg body weight by gavage, to mice 2hr before they injected with an inhibitor of prostaglandin synthesis (indomethacin, 10 mg/kg) intraperitoneally and iohexol (300 mg iodine/ml, 2 g iodine/kg) intravenously. 24hr after iohexol injection, mice were sacrificed, serum creatinine (Cr), urinary Neutrophil gelatinase-associated lipocalin (NGAL) and renal pathology were examined.

Results: MA-5 improved cell viabilities and reduced injured cell derived LDH activity in culture medium in Sodium ditrizoate, Iopamidol and iohexol treated HK2 cell culture. Serum Cr at 24hr after iohexol injection showed tendency to improve but not significant in MA-5 treated mice comapred to control group. Urinary NGAL was significantly decreased in MA-5 treated animals compared to vehicle gavaged mice.

Conclusions: MA-5 exhibited improved viability in contrast medium treated HK-2 cells as well as decrease renal injury marker NGAL in CI-AKI model mice. MA-5 might have the therapeutic potency on CI-AKI.

Funding: Government Support - Non-U.S.

TH-OR108

ADAM17 Induces Sustained Pro-Fibrotic EGFR Activation via a Positive Feedback Loop Involving YAP1-Dependent Transcription of Pro-AREG Eirini Kefalogianni, Andreas Herrlich. *Washington University in St. Louis, St. Louis, MO.*

Background: We recently showed that the cell-surface metalloprotease ADAM17 and its substrates, including in particular the epidermal growth factor receptor (EGFR) ligand pro-amphiregulin (pro-AREG) are highly upregulated after kidney injury and that inducible proximal tubule (PT)-specific knockout of ADAM17 confers protection against fibrosis in ischemic and obstructive kidney injury mouse models. To clarify the role and function of ADAM17 and its substrate AREG in PT cells *in vivo*, we have now genetically labeled (tdTomato) PT cells in ADAM17 *wt* or ADAM17 PT-KO mice and studied them after kidney ischemia-reperfusion injury (IRI). We have also examined the transcriptional regulation and function of pro-AREG in PT cells *in vitro*. Finally, we investigated the activation of these pathways in acute kidney injury (AKI) and chronic kidney disease (CKD) in human samples.

Methods: We used SLC34a1-Cre-ERt2;R26tdTomato;ADAM17fl/fl (PT-KO) and respective littermates and subjected them to unilateral IRI. tdTomato positive cells were isolated by FACS. ADAM17 and downstream pathways were studied in human and mouse PT cells *in vitro* and in human AKI and CKD samples.

Results: IRI induces the transcriptional upregulation of ADAM17 and pro-AREG in PT cells (tdTomato+ cells). This upregulation is diminished in PT cells lacking ADAM17, suggesting that a positive feedback loop exists in which ADAM17 activity drives not only the release of soluble active AREG but also the upregulation of pro-AREG. This positive feedback is also observed *in vitro*; soluble AREG causes sustained (profibrotic) activation of EGFR that requires Yap1-dependent upregulation of pro-AREG expression, followed by ADAM17-mediated release of soluble AREG. AREG is unique among other EGFR ligands in inducing a panel of proinflammatory and profibrotic cytokines *in vitro*. PT cells isolated from injured mice and lacking ADAM17 show diminished production of these factors as compared to controls. Finally, levels of urinary and serum soluble AREG are upregulated in human AKI and CKD samples, suggesting that this pathway is also active in human kidney disease.

Conclusions: Injury-induced ADAM17-dependent release of soluble AREG drives a profibrotic positive feedback loop of further AREG release via Yap1-dependent transcriptional upregulation of pro-AREG.

Funding: NIDDK Support

TH-OR109

Macrophage Mitophagy Modulates Pro-Fibrotic Response in Renal Fibrosis Divya Bhatia, Mary E. Choi. *Division of Nephrology and Hypertension, Weill Cornell Medicine, New York, NY.*

Background: Kidney injury involves infiltration of pro-inflammatory macrophages and oxidative stress induced mitochondrial dysfunction, and pro-fibrotic macrophages driving progression of renal fibrosis. Mitophagy, the selective autophagy of dysfunctional mitochondria, is important for cellular homeostasis. We examined the role of PTEN-induced kinase1 (PINK1), major mediator of mitophagy, in regulating macrophage derived fibrotic response.

Methods: Wild type (WT) and PINK1-KO mice, subjected to unilateral ureteral obstruction (UUO), a model of progressive renal fibrosis, were sacrificed at day 3. Peritoneal and bone marrow-derived macrophages were isolated. The expression levels of CD11b, Ly6C, F4.80, CD206 and CX3CR1 were detected by flow cytometry. Arginase1 (Arg1), TGFβ type I receptor (TGFβRI), fibronectin and α-smooth muscle actin (α-SMA) expression was determined by western blot. MitoSox staining was used to assess mitochondrial derived superoxide production. Mitophagy was suppressed in RAW264.7 cells through transfection of PINK1 small interfering RNA (siRNA).

Results: UUO-induced increase in the expression of circulating Ly6C++ CD11b+ pro-inflammatory monocytes was higher in PINK1-KO mice compared to WT. PINK1-KO mice displayed higher expression of F4.80+ CD206+ pro-fibrotic macrophages and chemokine receptor CX3CR1 in obstructed kidneys compared to WT and contralateral kidneys. Flow cytometric data revealed increase in the Ly6C++ pro-inflammatory cells in kidney post-UUO at day 3. However, their expression was comparable in kidneys from KO and WT mice. The expression of Arg1 and fibronectin was higher in kidneys of KO mice after UUO. Furthermore, PINK1 deficient macrophages (both primary PINK1-KO and siRNA knockdown RAW264.7) exhibited enhanced polarization towards pro-fibrotic phenotype. Primary PINK1-KO macrophages also showed higher expression of Arg1, TGFβRI, fibronectin and α-SMA. The expression levels of Arg1, fibronectin and α-SMA were further increased after stimulation with TGFβ. In addition, PINK1 deficient macrophages displayed higher mitochondrial superoxide levels upon TGFβ stimulation compared to WT.

Conclusions: PINK1-mediated mitophagy deficiency results in increased oxidative stress and enhanced pro-fibrotic response by macrophages. Macrophage mitochondrial superoxide production might play critical role in activation of their pro-fibrotic phenotype and progression of renal fibrosis.

Funding: NIDDK Support

TH-OR110

Therapeutic Angiogenesis in CKD Alejandro R. Chade, Gene L. Bidwell. *University of Mississippi, Jackson, MS.*

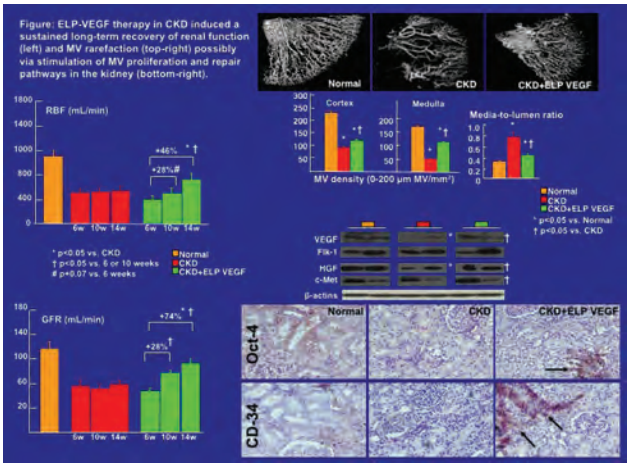
Background: Renal microvascular (MV) loss in CKD correlates with progressive loss of renal function. However, whether this is an association or a cause-effect relation is unclear. We developed a drug-delivery construct of an elastin-like polypeptide (ELP) fused to VEGF-A and showed that intra-renal infusion of ELP-VEGF in CKD improved renal function. We tested the hypothesis that ELP-VEGF therapy may induce long-term recovery in CKD by stimulation of MV proliferation and repair.

Methods: CKD was induced in 8 pigs by bilateral renal artery stenosis and diet-induced dyslipidemia. Blood pressure was continuously measured (telemetry). Bilateral RBF and GFR were quantified *in vivo* using multi-detector CT after 6 weeks of CKD, and then pigs randomly treated with a single intra-renal administration of ELP-VEGF (100 μg/kg) or placebo (n=4 each). *In vivo* studies were repeated 4 and 8 weeks after treatment, pigs were then euthanized, and *ex vivo* studies performed to quantify renal MV density (micro-CT), MV remodeling, and angiogenic signaling

Results: RBF and GFR were reduced in CKD, accompanied by hypertension, cortical and medullary MV remodeling and loss, and blunted expression of VEGF, HGF, specific VEGF/HGF receptors, and markers of cell progenitors (Oct-4 and CD-34). However, CKD+ELP-VEGF pigs showed 28% and 53% improvement in RBF and GFR 4 weeks after treatment, and 46% and 74% recovery after 8 weeks, respectively (compared to pre-treatment), followed by increased expression of angiogenic and progenitor cell markers, reduced MV loss and remodeling [Figure]

Conclusions: Therapeutic angiogenesis via single-dose ELP-VEGF therapy stimulates renal neovascularization and MV repair, which likely drove recovery of renal function and improved CKD stage from 2 to 1. CKD recovery was progressive, and our data imply that underlying mechanisms of the long-term effects may involve sustained stimulation of cell progenitors to and within the kidney.

Funding: Other NIH Support - AHA and NHLBI



TH-OR111

The Impact of a Young Circulation on Renal Injury and Fibrosis in Aged Mice David A. Ferenbach,[1,2] Cuiyan Xin,[1] Julia Wilflingseder,[1] Jeremy Hughes,[2] Joseph V. Bonventre.[1] *[1]Brigham and Women's Hospital, Boston, MA; [2]MRC Centre for Inflammation Research, University of Edinburgh, Edinburgh, United Kingdom.*

Background: Aging is associated with an increased risk of acute kidney injury (AKI) and higher rates of subsequent fibrotic chronic kidney disease (CKD). The mechanisms accounting for these changes in injury and fibrosis susceptibility remain poorly understood. We conducted studies using heterochronic parabiosis to test whether the young circulation can influence injury imposed on an older mouse.

Methods: Parabiotic pairs were established between young (Y, 8 weeks old) and old (O, 14 months old) female C57BL6 mice to generate YY, OO, OY and YO pairings, and a shared microcirculation was allowed to develop for 28 days. Baseline and post-injury renal characteristics were assessed by immunofluorescence, western blotting, microarray analysis and Somascan measurement of circulating protein levels. AKI was induced via 20 minutes bilateral renal ischaemia/reperfusion injury (IRI), and chronic fibrosis via unilateral ureteric obstruction. Animals were followed for 24hrs for peak IRI severity, and for up to 14 days for UUO-induced fibrosis

Results: Baseline renal function was equivalent in all groups. At d28 of parabiosis, old animals in both OO and OY pairings had increased levels of baseline fibrosis ($p<0.05$) compared to the young in YO and YY pairs. In the acute injury model on the Old mice, OY animals demonstrated significantly lower 24 hr serum creatinine compared with OO animals ($p<0.05$). In the UUO model of chronic renal fibrosis, Old animals in OY pairs showed reduced scarring, macrophage infiltration and inflammatory gene transcription compared to Old paired with Old mice (OO) (all $p<0.05$). Microarray studies revealed multiple transcriptional processes which alter with aging and injury and revert to 'young' patterns after OY pairing. Bulk proteomics on >1000 circulating proteins identified 11 compounds which track with the protected phenotype.

Conclusions: Our data show that normal aged kidneys exhibit differences from the young kidney at a transcriptomic and proteomic level even with well maintained renal function. Furthermore, connection to a young circulation modifies the transcriptional signature in the aged kidney at baseline and protects against subsequent AKI and progressive renal scarring, indicating the presence of a circulating factor which modifies renal aging. Therapeutic targeting of these compounds is ongoing.

Funding: Private Foundation Support

TH-OR112

5-Lipoxygenase Promotes Renal Interstitial Injury and Fibrosis John R. Montford,[1] Colin D. Bauer,[1] Evgenia Dobrinskikh,[1] Katharina Hopp,[1] Moshe Levi,[1] Raphael A. Nemenoff,[1] Seth B. Furgeson.[1,2] *[1]University of Colorado Denver, AMC, Aurora, CO; [2]Denver Health, Denver, CO.*

Background: Although macrophages promote renal fibrosis, the mechanism is incompletely understood. Macrophages may exert tissue damage through activation of 5-lipoxygenase (5-LO). 5-LO and 5-LO associated protein (FLAP) initiate leukotriene synthesis; the downstream enzymes LTA_4 hydrolase (Lta4h) and LTC_4 synthase (Ltc4s) catalyze the production of LTB_4 and cysteinyl leukotrienes, respectively. We hypothesized that leukotriene inhibition would decrease renal fibrosis after unilateral ureteral obstruction (UUO).

Methods: C57Bl/6 mice undergoing UUO were treated with zileuton (5-LO antagonist) or vehicle. UUO was also done in wild type, Flap knockout (ko), Lta4h ko and Ltc4s ko mice. Renal fibrosis was measured using both a biochemical assay (hydroxyproline) and microscopy to detect second harmonic generation (SHG) signal from collagen. To measure metabolic changes in renal tubular epithelial cells, fluorescent lifetime imaging microscopy (FLIM) was performed to determine alterations in free and bound NADH levels.

Results: We found a large induction in 5-LO-expressing interstitial leukocytes in kidneys of UUO mice. Treatment of mice with zileuton before UUO significantly decreased hydroxyproline content at 7 days (37% reduction vs. vehicle). SHG microscopy also confirmed a significant decrease in renal fibrosis in zileuton-treated mice (40% reduction). Compared to littermate controls, Flap ko mice had less interstitial fibrosis as measured by hydroxyproline assay (33% reduction). Ltc4s ko mice, but not Lta4h ko mice, were significantly protected from UUO-induced fibrosis (44% reduction in hydroxyproline content and 41% reduction in fibrotic area by SHG). We then performed FLIM for NADH to determine if 5-LO inhibition led to metabolic changes in renal tubular epithelial cells. We found that there was significant shift to glycolytic metabolism after UUO in control mice; this was partially abrogated in zileuton-treated mice. To validate these findings, we tested whether 5-LO is induced in other models of chronic kidney disease and found increased numbers of 5-LO expressing leukocytes in mice with polycystic kidney disease.

Conclusions: 5-lipoxygenase and LTC_4 synthase are potent inducers of renal fibrosis after UUO. The pathologic effects of leukotrienes may be partially mediated through changes in renal tubular epithelial metabolism.

Funding: Other NIH Support - NHLBI K08 - HL103774

TH-OR113

MicroRNA-214 Confers the Pathogenesis of CKD by Disrupting the Mitochondrial OXPHOS Aihua Zhang, Mi Bai, Yue Zhang, Songming Huang, Zhanjun Jia. *Nephrology Department, Children's Hospital of Nanjing Medical University, Nanjing, China.*

Background: Mitochondria are critical in determining the energy hemostasis and cell fate. Mitochondrial dysfunction (MtD) presenting with aberrant mitochondrial oxidative phosphorylation (OXPHOS) and other abnormalities is involved in the chronic kidney disease (CKD). Here we investigated the role of miR-214 in mediating the MtD and kidney injury in CKD.

Methods: The CKD patients' renal biopsy tissues, three CKD animal models (UUO, albumin-overload, and post-AKI), and tubular cells challenged with several insults were used to define the role of miR-214 in CKD, as well as the potential mechanisms.

Results: In CKD patients, the renal tubules presented more abundant miR-214 expression compared with the healthy controls, which was accompanied by a positive correlation with the severity of proteinuria and renal fibrosis. Meanwhile, several lines of CKD animal model of UUO, albumin-overload, and post-AKI and renal tubular cell models induced by IL-1β, hypoxia, albumin, or TGF-β displayed similar enhancement of miR-214. Importantly, systemic inhibition or specific tubular deletion of miR-214 strikingly attenuated CKD pathology in line with the ameliorated responses of apoptosis, inflammation, and fibrosis in CKD models mentioned above. In contrast, overexpressing miR-214 induced tubular cell apoptosis. Moreover, in the mechanistic study, we proved that cytoplasm miR-214 could be translocated into the mitochondria to target mitochondrial gene ND4L and ND6 to disrupt mitochondrial OXPHOS, leading to mitochondrial dysfunction and subsequent tubular injury and fibrosis in CKDs.

Conclusions: These results not only demonstrated a pathogenic role of miR-214 in CKDs by targeting mitochondrial gene ND4L and ND6 to disrupt mitochondrial OXPHOS but also suggested the potential of this microRNA as the therapeutic target and diagnostic biomarker of CKDs.

TH-OR114

Biopsy Transcriptome Expression Identifies Loss of FRMD3 as a Mediator of Declining Renal Function in CKD Eoin P. Brennan,[2] Caitriona M. McEvoy,[2] Oisín Gough,[2] Susan M. McAnallen,[2] Mohd R. Rodzlan Akib,[1] Anthony M. Dorman,[1,3] Peter J. Conlon,[1] Denise M. Sadlier,[2,4] Catherine Godson.[2] *[1]Department of Nephrology and Pathology, Beaumont Hospital, Dublin, Ireland; [2]Diabetes Complications Research Centre, UCD Conway Institute & School of Medicine UCD, University College Dublin, Dublin, Ireland; [3]Royal College of Surgeons Ireland, Dublin, Ireland; [4]Mater Misericordiae University Hospital, Dublin, Ireland. Group/Team: GENIE Consortium.*

Background: We have generated global transcriptome profiles of renal biopsies from patients with chronic kidney disease (CKD). Here, we investigated the relationship between renal gene expression and clinical parameters of kidney function, and identify an association between loss of Ferm domain-containing protein 3 (FRMD3) and a decline in renal function.

Methods: We performed RNA-Seq gene expression profiling on material obtained from patients undergoing clinically indicated biopsy (n=44). Using this phenotypically heterogenous cohort of patients, the association of gene expression with clinical parameters [tubulointerstitial fibrosis (TIF) score, eGFR, serum creatinine, glomerular basement membrane thickness] was investigated. Follow-up clinical data (serum creatinine measurements 3-6 years post-biopsy) was used to identify gene expression profiles predictive of disease progression. Subsets of genes were identified that were significantly associated (FDR $P<0.05$) with these parameters of kidney disease.

Results: Pathway analyses identified enrichment for pro-inflammatory signalling (e.g. T-cell infiltration, TNF-α, NF-κB, IFN-γ, CD3) in patients with severe CKD. 1,590 genes were significantly associated with renal decline in these patients during a 3-6 year follow-up period (FDR $P<0.05$), including loss of FRMD3 expression (FDR $P=0.006$). Interestingly, large scale genome-wide association studies have recently implicated FRMD3 as a genetic candidate in kidney disease. Using functional studies we investigated the role of FRMD3 in renal cells using *in vitro* models of renal fibrosis. Here, FRMD3 knockdown caused exaggerated fibrotic responses to TGF-β1 in renal tubule epithelial cells. Finally, mass spectrometry analysis of FRMD3 binding partners indicated interactions with mitochondrial respiratory chain components (complex I, III and V).

Conclusions: Taken together, these data implicate FRMD3 as a novel regulator of renal function in CKD.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-OR115

Rescue of Reno-Protective BMP7 by Low-Dose Hydralazine Protects Functional Parenchyma with Restoration of Solute and Solvent Transporters Bjoern Tampe, Desiree Tampe, Gerhard A. Mueller, Michael Zeisberg. *University Medical Center Goettingen, Goettingen, Germany.*

Background: CKD progression remains an unsolved problem in clinical Nephrology since approaches to reverse or repair chronic renal injury are not yet available. BMP7 and its agonists are among leading compounds currently under clinical testing and widely accepted to facilitate regeneration of the injured kidney, ultimatively associated with attenuation of disease progression. The impact of restoring intrarenal BMP7 with regard of renal excretory function on a molecular level remains elusive.

Methods: In multiple mouse models of acute (moderate IRI), acute-on-chronic (severe IRI) and chronic kidney disease (UUO, 5/6 Nx, FAN, NTN), dynamic regulation of BMP7 and signaling (pSmad1/5/8) were analyzed by qRT-PCR, Western blotting and immunostaining. Furthermore, *BMP7* promoter methylation was assessed by MeDIP in cohorts of mice treated with low-dose Hydralazine and corresponding cell culture models of EMT program in TECs. Finally, impact on expression of solute and solvent transporters was analyzed by qRT-PCR, immunostaining and functional monitoring of transporter function.

Results: Based on a genome-wide transcriptional expression dataset for bioactive small molecules, transcriptional induction of *BMP7* was among top induced candidate genes in response to Hydralazine. Low-dose Hydralazine mediates TET3-dependent normalization of *BMP7* promoter methylation in multiple rodent CKD models and human cell lines. On a mechanistic level, transcriptional induction of reno-protective BMP7 attenuates intratubular EMT program commonly observed during CKD progression, ultimatively associated with protection from G2/M arrest of TECs and attenuation of renal fibrogenesis. We provide evidence that protection of functional parenchyma restores solute and solvent transporter function, including AQP1, AQP3 and Na^+/K^+-ATPase, supporting a protective role also for renal excretory function on a molecular level. Based on existing transciptional profiling datasets, decline of renal excretory function is commonly associated with loss of intrarenal BMP7 expression, suggesting that reno-protection mediated by Hydralazine may also have promise among CKD patients.

Conclusions: In summary, low-dose Hydralazine induces reno-protective BMP7 and protects functional parenchyma with restoration of solute and solvent transporters.

TH-OR116

SIRT6-Knockout Mice Exhibit Marked Type IV Collagen Deposition, Causing Phenotypes Similar to Those of Diabetic Tubulopathy Hirokazu Muraoka, Kazuhiro Hasegawa, Shu Wakino, Hiroshi Itoh. *Keio University, Tokyo, Japan.*

Background: The class of NAD-dependent deacetylase and longevity genes called sirtuins comprises seven isoforms (SIRT1 to SIRT7). Here we investigated the role of SIRT6 in the kidneys.

Methods:

Results: We investigated the intrarenal distribution of SIRT6 expression in different physiological conditions using wild-type mice and human renal biopsy specimens. High Sirt6 levels were detected in the nucleus of proximal tubules (PTs), whereas low levels were observed in glomeruli and other tubules. To assess the temporal changes in SIRT6 expression in different physiological conditions, we modeled several kidney injuries. Among these, diabetic nephropathy models demonstrated marked alterations. We next evaluated the temporal changes in SIRT6 expression every 8 weeks (8W, 16W, 24W, and 32W) in STZ and db/db models. At 8W and 16W, SIRT6 expression exhibited no difference. However, SIRT6 expression was conspicuously downregulated at 24W and was further augmented at 32W in both STZ and db/db models. To delineate the endogenous role of SIRT6 in the kidneys, we newly created PT-specific SIRT6-conditional knockout (CKO) mice by crossbreeding SIRT6 flox/flox[Editor1] mice with g-GT Cre mice. PT-SIRT6-CKO mice exhibited marked proximal tubular basement membrane (TBM) thickening and widespread peri-proximal tubular fibrosis. We next tested the molecular mechanisms underlying tubulopathy augmentation caused by SIRT6 knockdown. By performing DNA microarray and confirmatory real-time PCR analyses after microdissecting PT-injured regions together with immunostaining and immunogold electron microscopy, we could demonstrate that tissue inhibitor metalloproteinase 1 (TIMP-1) mRNA levels were elevated, leading to decreased MMP-9 activity and upregulated type IV collagen protein levels. These changes were consistent with the phenotypes of PT-SIRT6-CKO mice. Lastly, we analyzed in detail the mechanisms whereby SIRT6 knockdown directly elevated TIMP-1 mRNA levels and revealed that SIRT6 deficiency in PTs directly hyperacetylated histone H3 lysine K9 and RELA at these target regions within the TIMP-1 promoter.

Conclusions: PT Sirt6 is suggested to be involved in type IV collagen-related TBM thickening and peritubular fibrosis, which directly regulates TIMP-1 expression and plays a crucial role in tissue fibrosis, especially in diabetic nephropathy.

TH-OR117

Aging Phenotype(s) in Kidneys of Diabetic Mice Are p66ShcA Dependent Himanshu Vashistha,[1] Allyson E. Bradley,[1] Bronwyn Leblanc,[1] Frank C. Abbruscato,[1] Ashwani Malhotra,[2] Pravin C. Singhal,[2] Leonard G. Meggs.[1] *[1]Ochsner Health System, New Orleans, LA; [2]Feinstein Inst.Med research and NSLIJ, Manhasset, NY.*

Background: Hyperglycemia constitutively activates the p66ShcA protein, which controls cellular responses to oxidative stress, aging and apoptosis. Here, we test the hypothesis aging phenotype(s) in kidneys of diabetic mice, that are commonly associated with the broad category of chronic kidney disease (glomerulosclerosis, interstitial fibrosis, tubular atrophy), are linked to the p66ShcA locus.

Methods: Stem cell antigen-1^{+} (Sca-1+) mesenchymal stem cells (MSCs) were isolated from kidneys of WT and p66 KO mouse, and plated in media containing normal or high glucose. Parameters evaluated were ROS metabolism, apoptosis, cellular and molecular markers of senescence and DNA microarray gene profiles. p66 KO diabetic mice, were generated by crossing Akita (Ins2+) with p66 KO mouse. Kidneys were examined at 12 mo of age by light microscopy and deconvolution microscopy.

Results: WT-MSCs exhibit an exponential increase in ROS metabolism, upregulation of senescence associated proteins (p21; p16^{INK4a}; p53) and enter apoptotic or senescent phenotypes. DNA microarray detected downregulation of Wnt regulatory genes, implicated in self renewal and differentiation. By contrast, p66KO-MSCs are resistant to HG-stress signals, apoptosis/cell senescence and express increase levels of intracellular b-catenin, mimicking canonical Wnt signaling. Small clusters of Sca-1+MSCs in kidneys of p66 KO Akita were captured by deconvolution microscopy scattered in the interstitium adjacent to tubules, but were only rarely seen in kidneys of WT and Akita. Furthermore, the senescent biomarker p16^{INK4a} was upregulated in proximal tubular epithelial cells of Akita, whereas expression levels did not differ between p66 KO-Akita and WT (non-diabetic); indicative p66ShcA participates in activation of p16^{INK4a} in diabetic kidneys. Histologic markers of aging were prominent in Akita kidneys, whereas these aging phenotypes were barely detectable in kidneys of p66 KO-Akita. Taken together, p66 ShcA is necessary and sufficient for the expression of aging phenotypes in kidneys of diabetic mice.

Conclusions: Our results establish a genetic link between diabetes, constitutive p66ShcA expression and accelerated aging phenotype(s) in the kidney, that may serve as precursors to diabetic nephropathy.

Funding: Private Foundation Support

TH-OR118

Kidney Allografts with High Risk APOL1 Genotypes Have Worse Outcomes: Association with Decreased Podocyte Density Dhruti P. Chen,[5] Ziad S. Zaky,[1] Jesse D. Schold,[1] Leal C. Herlitz,[1] Rasha El-Rifai,[3] Paul E. Drawz,[4] Leslie A. Bruggeman,[3] John R. Sedor,[2] Emilio D. Poggio,[1] John F. O'Toole.[5] *[1]Cleveland Clinic, Cleveland, OH; [2]MetroHealth Medical Center, Cleveland, OH; [3]None, Cleveland, OH; [4]University of Minnesota, Minneapolis, MN; [5]Case Western Reserve University, Cleveland, OH.*

Background: Variants in *APOL1 gene* (G1 or G2), which encodes apolipoprotein L1(APOL1), associate with non-diabetic kidney diseases in African Americans (AA) but the mechanisms driving this association remain unclear. Kidney diseases only develop in a subset of individuals with high risk *APOL1* genotypes, consistent with a need for a "second hit" or stress to initiate disease. Mice transgenic for G2 have a podocyte depletion phenotype compared to wild-type mice or mice expressing the reference allele (G0). We hypothesized that variant APOL1 generates subclinical, prodromal podocyte injury that is a "first hit."

Methods: A cohort of 107 AA kidney donors, living (LD) and deceased (DD), with available implant biopsy tissue and DNA were genotyped for *APOL1* risk variants and evaluated for baseline kidney phenotypes, histology, and podocyte density in implant biopsies. Recipients were genotyped for APOL1 and outcomes collected, including graft loss and rate of eGFR decline.

Results: Donor demographic data and clinical phenotypes at graft implant were similar between high risk (HR, 2 risk variants, n=16) and low risk groups (LR, <2 risk variants, n=91). Glomerular volume was lower in HR group (2.58 um^{3}X10^6 vs. 3.13 um^{3}X10^6, p=0.03) of implant biopsies. Podocyte density was significantly less in HR compared to LR (108 ± 26 vs 127±40 podocytes/10^{6}um^3, p=0.03). Similarly, podocyte coverage of glomerular area was reduced in HR vs. LR donors (30% vs. 39%, p=0.05). Recipients were 64% AA and 36% White or not specified;38% of AA recipients had HR *APOL1*. Recipients were followed for 48 months, and increased graft loss of HR donor was noted using a multivariate model (Hazard Ratio = 2.7; 95% CI, 0.9-7.8) and Kaplan Meier graft survival (HR 61% vs. LR 91%, log rank p-value=0.049). eGFR decline was also greater in recipients of HR APOL1 allografts with slope of overall decline statistically significant (p<0.001), eGFR(mL/min) at 60 months was 27 in HR vs. 51 in LR.

Conclusions: In living and deceased donors, outcomes of *APOL1* HR allografts were significantly worse. Importantly, variant APOL1 generates subclinical, prodromal podocyte depletion, which only becomes clinically evident when subsequent stress supervenes and initiates progressive CKD in African Americans with *APOL1* HR.

Funding: Other NIH Support - T32

TH-OR119

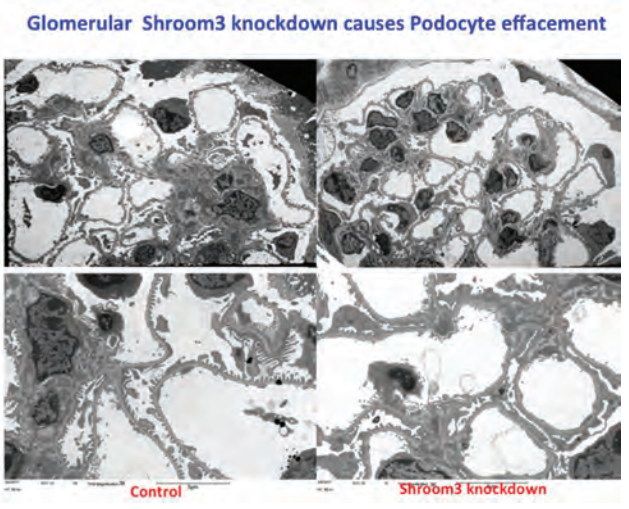
Interaction of SHROOM3 with FYN Impacts Phosphorylation of Nephrin Causing Proteinuria with Foot Process Effacement Madhav C. Menon,[4] Nimrod Philippe,[2] Chengguo Wei,[1] Ruijie Liu,[3] Jenny Wong,[4] Zhengzi Yi,[1] Weijia Zhang,[4] John C. He,[4] Barbara T. Murphy.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Mount Sinai Hospital, New York, NY; [3]Mount Sinai Medical School, New York, NY; [4]Mount Sinai School of Medicine, Forest Hills, NY.*

Background: In the GoCAR study, we identified that a CKD-associated SHROOM3-SNP, and tubular *Shroom3* expression correlated with the development of renal fibrosis post-transplant. We showed that SHROOM3 facilitated TGF-B signaling suggesting its potential role as a therapeutic target. However, recent data suggest a *protective* role for SHROOM3 in glomerular development.

Methods: To study the role of SHROOM3 in adult glomeruli, we used doxycycline-inducible (DOX), shRNA-mediated SHROOM3 knockdown, Podocin- and tubular-specific (PAX8)-RTTA mice, comparing these to non-transgenic DOX-fed littermates.

Results: Adult Podo-RTTA mice, but not PAX8-RTTA, developed significant albuminuria compared to littermates with DOX. Albuminuria was reversible on DOX-withdrawal, and reappeared on re-initiation. EM revealed diffuse foot process effacement (Fig1). Glomerular RNA-seq identifed downregulated intracellular signaling/actin-cytoskeleton among Gene-ontology terms in knockdown mice. We performed mass spectrometry on protein lysates of 293-T cells overexpressing SHROOM3 immunoprecipitated (IP) with either anti-V5, -SHROOM3 or IgG. Among 491 unique interactions, we identified FYN – a src-kinase – as a top ranking candidate. Podocyte FYN is crucial for NPHS1-phosphorylation, and FYN-deficient mice show a proteinuria phenotype. In human podocytes, we confirmed the interaction of endogenous SHROOM3 and FYN by IP. Glomerular protein extracts of Shroom3-knockdown mice showed decreased phosphorylation of FYN, and NPHS1. In human allografts from GoCAR, we identifed a corresponding reduced albuminuria (>1year post-transplant) associated with homozygosity of the risk allele in the donor.

Conclusions: In summary, Podocyte-specific SHROOM3 knockdown causes a reversible proteinuria phenotype in adult mice, by interacting with FYN, a mechanism distinct from its effect on renal fibrosis in allografts.



TH-OR120

Polygenic Risk Score as a Determinant of Risk of Non-Melanoma Skin Cancer Post-Renal Transplantation Caragh P. Stapleton,[9] Kelly A. Birdwell,[8] Patrick B. Mark,[6] M. Lee Sanders,[7] Paul J. Phelan,[10] Alexander P. Maxwell,[5] A.J. McKnight,[5] Claire Kennedy,[1] Alan G. Jardine,[6] Jamie P. Traynor,[3] Fiona A. Chapman,[4] Brendan Keating,[2] Peter J. Conlon,[1] Gianpiero Cavalleri.[9] *[1]Beaumont Hospital, Dublin 9, Dublin, Ireland; [2]University of Pennsylvania, Philadelphia, PA; [3]NHS Greater Glasgow and Clyde, Glasgow, United Kingdom; [4]NHS Scotland, Glasgow, United Kingdom; [5]Queen's University Belfast, Belfast, United Kingdom; [6]University of Glasgow, Glasgow, United Kingdom; [7]University of Iowa Hospitals and Clinics, Iowa City, IA; [8]Vanderbilt University, Nashville, TN; [9]Department of Molecular and Cellular Therapeutics, Royal College of Surgeons, Dublin, Ireland; [10]Royal Infirmary of Edinburgh, NHS Lothian, Edinburgh, United Kingdom. Group/Team: International Genetics & Translational Research in Transplantation Network.*

Background: Multiple genetic loci have been identified for non-melanoma skin cancer (NMSC) in the general population. Polygenic risk score (PRS) was defined as the sum of all alleles associated with a trait weighted by the effect size of that allele as determined by a previous genome-wide association study (GWAS). We tested whether PRS, calculated using a GWAS of NMSC in a non-transplant population, can be used to determine risk of developing and time to NMSC post-kidney transplant.

Methods: Post-kidney transplant NMSC cases (n=155) and controls (n=442) were collected from Tennessee, Ireland and Scotland. Genetic variants that reached pre-defined levels of significance were chosen from a squamous cell carcinoma (SCC), and a basal cell carcinoma (BCC) GWAS, both conducted in non-transplant populations. Using these GWAS results, BCC and SCC PRSs were calculated at each p-value threshold (pT) for each sample in the renal transplant cohorts. PRSs were normalized so mean = 0 and standard deviation = 1. PRSs were tested as a predictor of case: control status in a logistic regression model and time to NMSC post-transplant in a survival model. Age of recipient at transplant, recruitment centre, azathioprine exposure and the first four principal components were included as covariates in both models.

Results: SCC PRS calculated at pT of $1x10^{-6}$ was the most significant predictor of case: control status of NMSC post-transplant (OR per 1 standard deviation increase in PRS = 2.3; corrected P (P_c) =0.04). When we subdivided NMSC into SCC and BCC, SCC PRS pT $1x10^{-6}$ was a significant predictor of case:control SCC (OR = 2.5, P_c = 0.02) and BCC status (OR = 7.6, P_c = 0.02). SCC PRS pT $1x10^{-5}$ was also a significant predictor of time to post-transplant BCC (P_c = 0.007, HR = 1.8) and SCC (P_c = 0.05, HR = 1.4).

Conclusions: PRS of non-transplant NMSC can be used to predict case:control status of post-transplant NMSC, SCC and BCC as well as time to developing BCC and SCC post-transplant.

Funding: Government Support - Non-U.S.

TH-OR121

Effect of Conversion to Belatacept on Tacrolimus-Induced Diabetes Mellitus Chul Woo Yang,[1,2] Sun Woo Lim,[2] Kang Luo,[2] Yoo-Jin Shin.[2] *[1]Department of Internal Medicine, Seoul St. Mary's Hospital, Seoul, Republic of Korea; [2]Transplant Research Center, The Catholic University of Korea, Seoul, Republic of Korea.*

Background: The effect of belatacept conversion on tacrolimus (TAC)-induced diabetes mellitus (DM) is still undetermined. In the present study, we first tested the dose-dependent effect of belatacept on pancreatic islet function and viability in rats. Second, in an experimental model of TAC induced DM, TAC was switched to belatacept and parameters of glucose control were measured. In addition, the direct effect of belatacept on TAC-induced pancreatic islet cell injury was evaluated in vitro.

Methods: The first study was designed to evaluate whether belatacept has a diabetogenic effect in rats. We tested the dose-dependency of belatacept (0.25, 0.5, 1, 2, and 4 mg/kg) on pancreatic islet function and viability. The second study aimed to evaluate the effect of conversion from TAC to belatacept on pancreatic islet function in established TAC-induced DM. After the establishment of TAC-induced DM (three weeks), TAC was continued, withdrawn, or replaced by belatacept treatment (1 or 2 mg/kg). Rats were treated with vehicle or subcutaneous TAC daily, and belatacept was injected weekly via the tail vein. The effect of belatacept on TAC-induced diabetes was evaluated by assessing pancreatic islet function, histopathology. The protective effect of belatacept was evaluated by measuring markers of oxidtive stress, apoptosis, and infiltrating macrophage. Reactive oxygen species production using MitoSOX red and cell death using Annexin V were also evaluated in INS-1 cells.

Results: Pancreatic islet function and islet cell death were not affected by any of the tested doses of belatacept. TAC withdrawal ameliorated pancreatic islet dysfunction compared with that in the group in which TAC treatment was continued, and conversion to belatacept further improved pancreatic islet function compared with that in the TAC withdrawal group. TAC-induced oxidative stress, apoptotic cell death, and infiltration of macrophages decreased with TAC withdrawal, and belatacept conversion further reduced those values. In an in vitro study, belatacept decreased TAC-induced pancreatic islet cell death and reactive oxygen species production.

Conclusions: The results of these studies suggest that conversion to belatacept is an effective approach to reduce TAC-induced DM. Moreover, belatacept has a protective effect against TAC-induced pancreatic islet injury.

TH-OR122

Tacrolimus Prevents Von Willebrand Factor Exocytosis from Human Glomerular Endothelial Cells Treated with Anti-HLA Antibodies Stephanie Beland, Olivier Desy, Patrice Vallin, Sacha A. De Serres. *University Health Center (CHU) of Quebec, Laval University, Quebec, QC, Canada.*

Background: Mechanistic knowledge about the direct effect of DSA on the endothelium is lacking. Von Willebrand factor (vWF) is a glycoprotein involved in endothelial hemostasis. Previous studies reported that anti-HLA-I antibodies promote vWF exocytosis. It is known that higher CNI levels associates with better outcomes in patients with DSA. We hypothesized that TAC prevents endothelial damage by inhibiting vWF exocytosis from cells exposed to anti-HLA antibodies.

Methods: We measured *in vitro* the vWF expression of human glomerular endothelial cells treated with anti-HLA-I or II, in the presence and absence of TAC. Cell viability was confirmed in all experiments. vWF was quantified by immunofluorescence and ELISA. Platelet adhesion on the endothelial cells was assessed by immunofluorescence. We next measured the association between vWF and TAC blood levels in 71 samples from 69 kidney recipients.

Results: Anti-HLAs antibodies increased surface expression of vWF as well as vWF levels in cell supernatants (anti-HLA I 36±4, anti-HLA-II 40±5 vs. NS 22±4%, both $p<0.05$). vWF release in the supernatant following anti-HLA-II stimulation was higher than with anti-HLA-I (3.4±2.5 vs. 5.6±3.2 ng/mL; p=0.03). Treatment with TAC (5, 10 ng/mL) abrogated the percentage of vWF-positive cells after anti-HLA stimulation (for anti-HLA-I, TAC0 vs. TAC5 vs. TAC10 : 32±5 vs. 5±3 vs. 5±3% respectively; for anti-HLA-II, TAC0 vs. TAC5 vs. TAC10 36±7 vs. 7±3 vs. 2±1% respectively; all $p<0.01$) and led to a decrease in platelet adhesion (all $p<0.01$). In patients, TAC was a significant negative predictor of vWF blood levels (-768±239 ng/mL per 1ng/mL increase in TAC); this association was robust to adjustment for clinical and histological predictors.

Conclusions: Direct disruption of endothelial hemostasis through vWF exocytosis is a potential mechanism for the higher occurrence of transplant glomerulopathy in patients with DSA. Mechanistic studies are underway to better understand these observations, given that TAC is seldom associated with thrombotic microangiopathy.

TH-OR123

B Cell Deficiency Inhibits Chronic Antibody Mediated Rejection in a Th1 and IL-10 Dependent Pathway in a Rat Kidney Transplant Model Sarah E. Panzer, Shannon Reese, Nancy A. Wilson, Lucille D. Ptak, Isabelle S. Renteria, Arjang Djamali. *University of Wisconsin Madison, Madison, WI.*

Background: The pathologic role of B cells in chronic antibody mediated rejection (cAMR) remains unclear.

Methods: We generated B cell deficient Lewis rats ($B^{-/-}$) via CRISPR technology. Kidney transplantation was performed in 4 groups: syngeneic (Lewis to Lewis), allogeneic (Fisher to Lewis), sensitized (Fisher to Lewis 3 weeks following donor-specific blood transfusion), and allogeneic B cell deficient recipients (Fisher to $B^{-/-}$ Lewis). All animals were harvested at 6 months.

Results: cAMR was reduced in $B^{-/-}$ recipients compared to allogeneic and sensitized recipients based on Banff scores for microvascular inflammation (allogeneic: 3.0±1.7, sensitized: 4.6±0.5, $B^{-/-}$: 1.5±0.6; P=0.001) and C4d staining (allogeneic: 1.5±0.6, sensitized: 2.2±0.8, $B^{-/-}$: 0.5±0.6; P=0.05). Allograft deposition of IgM was significantly reduced in $B^{-/-}$ compared to allogeneic recipients (Fig1A). Intragraft macrophages and fibrosis by Picrosirius red stain demonstrated no differences among allogeneic, sensitized, and $B^{-/-}$ recipients (Fig1B). Th1 (IL-2 and IFN-gamma) and IL-10 cytokines by RT PCR were significantly reduced in $B^{-/-}$ compared to allogeneic recipients, but not Th2 (IL-4 and IL-6) or Th17 (Fig1C). Chronicity scores (Banff chronicity score = cg + ct + ci + cv)

were elevated in allogeneic, sensitized, and $B^{-/-}$ recipients (3.0±1.7, 4.6±0.5, and 1.5±0.6, respectively).

Conclusions: B cell deficiency inhibits cAMR in a Th1 and IL-10 dependent pathway. Further studies are needed to determine the contributions from non-B cell mediated factors, such as innate immunity, to the development of fibrosis in chronic rejection.

Funding: Other NIH Support - This project was supported by the Clinical and Translational Science Award (CTSA) program, through the NIH National Center for Advancing Translational Sciences (NCATS), grant UL1TR000427, and the KL2 training Award (KL2TR000428).

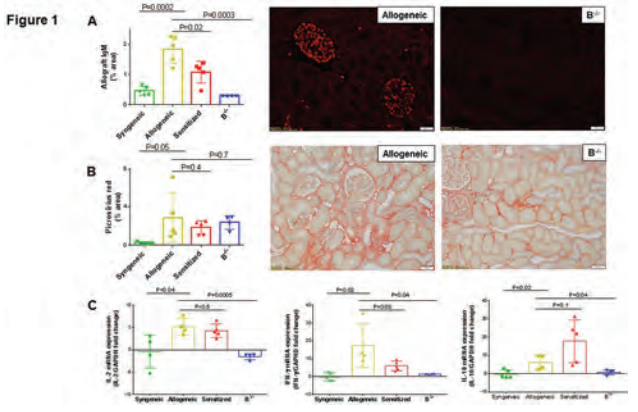


Figure 1. B cell deficient recipients demonstrated reduced allograft inflammation. (A) Immunoflourescence showed absent antibody deposition in the allografts of $B^{-/-}$ recipients. (B) Fibrosis, as determined by Picorsirius red stain, was unchanged among allogeneic, sensitized, and $B^{-/-}$ recipients. (C) RT PCR of allografts demonstrated a reduction in Th1 cytokines (IL-2, IFN-gamma) and IL-10.

TH-OR124

Absence of MFGE8 Promotes Rejection in a Murine Model of Transplant Vasculopathy

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Background: Transplant vasculopathy (TV) is the major cause of long-term allograft dysfunction in renal and heart transplantation. TV is characterized by persistent endothelial and epithelial apoptosis, leading to neointima formation and release of mediators in the microenvironment. Amongst them, we found that Milk Fat Globule Epidermal growth factor-8 (MFG-E8) can reprogram macrophages from a pro-inflammatory to a pro-repair phenotype. We hypothesize that MFG-E8 from the allograft is crucial to dampen local and systemic inflammation; attenuating the initial pro-inflammatory macrophage program resulting in better transplant outcomes.

Methods: We used a filly mismatched murine aortic transplant model. Abdominal aorta from MFG-E8 KO and WT mice (C57BL/6J background) were transplanted into Balb/C recipients. Following transplantation, each group received MFG-E8 or vehicle (PBS) twice a week. 4 groups (8-10 mice in each) were constituted (KO+PBS, KO+MFG-E8, WT+PBS, WT+MFG-E8). Isografts were performed between Balb/C mice as control. Intimal proliferation of the transplant was evaluated at week 9. Leukocyte phenotypes and activation status were assessed by flow cytometry, weekly in blood and at week nine in spleen. Variation overtime was evaluated using mixed linear models to account for repeated measurement and time effect when appropriate.

Results: At week nine, intimal proliferation was higher in the KO+PBS group than in all the others groups. CD8+ T cell activation in spleen was higher in the KO+PBS group compared with the KO+MFG-E8 and with the WT+PBS. In circulating blood, the variations over time of activated CD4+ T cells, regulatory T cells, B cells and plasmablasts were significantly different between groups.

Conclusions: The absence of MFG-E8 is associated with increased intimal proliferation in the transplant, increased activation of T cells in spleen and significant variation of T and B cells subpopulation in circulating blood. The addition of recombinant MFG-E8 dampened this proliferation and activation.

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TH-OR125

A Proteomic Analysis of Kidneys Subjected to Normothermic Ex-Vivo Kidney Perfusion Demonstrates Metabolism and Energy Production Are Important Determinants of Kidney Function Following Warm Ischemia

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Background: Organ shortage remains a problem for kidney transplantation, leading to an increased use of marginal grafts. These grafts tolerate cold storage poorly, resulting in more severe ischemia-reperfusion injury (IRI) and a higher rate of delayed graft function (DGF). This has led to the development of alternative preservation techniques that aim to reduce IRI and the rate of DGF. Normothermic ex-vivo kidney perfusion (NEVKP) is a storage method that may result in improved kidney function and limit IRI compared to traditional static-cold-storage (SCS).

Methods: Porcine kidneys were explanted, subjected to 30-minutes of warm ischemia, and stored via NEVKP or SCS for 8 hours, followed by re-implantation. Creatinine and BUN were measured in serum samples daily, until post-operative day (POD) 10. Kidney biopsies were taken at time of explant, 30 minutes following anastomosis and on POD3. Biopsy tissue was subjected to proteomic analysis on Q-Exactive mass spectrometer. Cytoscape software was used for enrichment analysis of differentially expressed proteins.

Results: Serum creatinine and BUN measurements demonstrated lower values in NEVKP grafts compared with SCS kidneys with POD10 levels in the NEVKP group comparable to their baseline values. Proteomic analysis allowed for quantification of 6179 proteins in total. Eighty proteins were differentially expressed ($p<0.05$; paired t-test) between NEVKP and SCS biopsies at 30 minutes following anastomosis with top enriched pathways relating to regulation of metabolism in NEVKP and energy production in SCS ($p<0.05$; Cytoscape pathway analysis). Analysis of samples from POD3 revealed 112 differentially expressed proteins with top enriched pathways relating to metabolism and catabolism in both groups.

Conclusions: NEVKP leads to improved kidney function compared to traditional SCS. Metabolism, energy production and catabolism represent key biological processes differentiating NEVKP from SCS proteome. Better understanding and manipulation of metabolism in kidney grafts may lead to amelioration of IRI and prevention of DGF.

TH-OR126

Normothermic Ex-Vivo Kidney Perfusion Improves Function of Marginal Renal Grafts That Were Subjected to Prolonged Ischemia prior to Preservation

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Background: Normothermic ex-vivo kidney perfusion (NEVKP) is an emerging technique for renal graft preservation. We investigated whether NEVKP could promote improved marginal graft function compared to cold storage in a model of donation after cardiac death.

Methods: Kidneys from 30kg Yorkshire pigs were removed following 30, 60, 90, or 120 minutes of warm ischemia (WI). These grafts were then preserved in either cold histidine-tryptophan-ketoglutarate solution (CS) or subjected to pressure-controlled NEVKP for 8 hours prior to heterotopic autotransplantation.

Results: Prolonging WI time prior to kidney retrieval and subsequent storage in CS resulted in grafts that demonstrated incremental posttransplant increases in serum creatinine with grafts subjected to 120min of WI having persistent elevation (POD7: 13.45±3.50mg/dl vs baseline: 1.1±0.33mg/dl $p<0.01$, n=4). During NEVKP perfusion, 120min WI grafts cleared lactate from perfusion solution (0hr: 10.48±0.93mmol/L vs 7hr: 1.48±0.85mmol/L, $p<0.01$, n=5), had decreasing intra-renal resistance (0hr: 2.26±0.9mmHg/mL/min vs 7hr: 0.37±0.6mmHg/mL/min, $p<0.01$), and continuous urine production. Posttransplantation, 120min WI grafts with NEVKP, compared to CS, demonstrated significantly decreased serum creatinine peak values (POD4: 12.62±2.34mg/dl vs POD5: 18.95±1.11mg/dL, p=0.001) and higher creatinine clearance (POD4: 6.61±4.03mL/min vs 0.35±0.30mL/min, p=0.02 and POD7: 26.31±11.54mL/min vs 9.78±4.6mL/min, p=0.03). On POD7, serum creatinine returned to baseline values in the NEVKP group (POD7: 4.88±5.57mg/dL vs baseline: 1.02±0.16mg/dL, p=0.16) but not the CS group (POD7: 13.45±3.50mg/dl vs baseline: 1.1±0.33mg/dl $p<0.01$, n=4). Histology from 120min WI NEVKP grafts at POD7 demonstrated decreased tubular injury scores compared to cold CS grafts (1.8+/-0.8 vs. 3.0+/-0.0, p=0.03) as assessed by a blinded pathologist.

Conclusions: Kidney grafts subjected to 120min of WI before retrieval showed significant improvement in function following 8hrs of continuous pressure-controlled NEVKP compared to CS. This suggests NEVKP could be utilized to expand the donor pool through the consideration of extreme marginal grafts for transplantation.

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TH-OR127

Bioengineering a Kidney in Secondary Lymphoid Tissues: A LTβR Dependent Pathway for Ectopic Organogenesis Maria G. Francipane,[1] Bing Han,[1] Leif Oxburgh,[2] Sunder Sims-Lucas,[3] Carlton M. Bates,[3] Eric Lagasse.[1] *[1]University of Pittsburgh, Pittsburgh, PA; [2]Maine Medical Center Research Institute, Scarborough, ME; [3]Children's Hospital of Pittsburgh, Pittsburgh, PA.*

Background: Kidney diseases are rising rapidly worldwide. While further work needs to be done before induced pluripotent stem cells (iPSCs) technology can be used to generate transplantable kidneys, disease modeling using iPSCs can facilitate the development of targeted therapies benefiting kidney patients. Unfortunately, while organoids expressing markers of kidney cells have been generated in vitro from mouse nephron progenitors and human iPSCs, there is little evidence that these cells exhibit phenotypic and functional aspects in vivo. Paradoxically, orthotopic engraftment of kidney tissue in the adult does not provide an environment conducive to vascularization and functional differentiation. Among potential endogenous bioreactors, the lymph node (LN) stands out, having permissive properties for kidney rudiments. Understanding LN remodeling and adaptation upon tissue transplantation could prove valuable in future endeavors to create a niche for human kidney cells. We hypothesize that LTβR signaling in LN fibroblastic reticular cells (FRCs) drives ectopic organogenesis.

Methods: Human fetal kidneys, mouse nephron progenitor- or human iPSC-derived kidney organoids were transplanted into mouse LNs. The maturation of transplanted cells and tissues was investigated through immunofluorescence. Three-dimensional reconstructions and Dextran uptake assay were used to test graft architecture and glomerular filtration, respectively. To investigate the molecular mechanism contributing to ectopic organogenesis, mice bearing grafts were treated with LTβR-Fc fusion protein. $LT\beta R^{-/-}$ mice were also used to confirm that LTβR ablation negatively affects ectopic kidney organogenesis (as $LT\beta R^{-/-}$ mice do not have LNs, omentum was used as an alternative secondary lymphoid organ for transplantation).

Results: Our preliminary data show engraftment of human fetal kidneys as well as efficient maturation of mouse nephron progenitor- and iPSC-derived kidney organoids in LN. Importantly, in the absence of an active LTβR pathway grafts exhibited impaired vascularization and structure.

Conclusions: The LN act as an innovative bioreactor to organize kidney progenitors into vascularized and functional renal structures. Our study has a wide-ranging impact for tissue engineering approaches for the rebuilding of functional kidneys in vivo.

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TH-OR128

Single Cell Transcriptome Atlas of the Mouse Kidney Reveals Important Cell Diversity Jihwan Park, Rojesh Shrestha, Chengxiang Qiu, Ayano Kondo, Szu-Yuan Li, Katalin Susztak. *Renal Electrolyte and Hypertension Division, University of Pennsylvania, Philadelphia, PA.*

Background: A revolution in cellular measurement technology is under way: For the first time, we have the ability to monitor global gene regulation in thousands of individual cells in a single experiment. They overcome fundamental limitations inherent in measurements of bulk cell population that have frustrated efforts to resolve precise cellular states. These methods also provide a stunningly high-resolution view of transitions between states. Single-cell transcriptomics will allow us to identify cell type specific expression changes, discover novel disease associated cell types and trace cell composition changes in complex disease such as diabetic kidney disease (DKD).

Methods: Using droplet-based single-cell barcoding and sequencing methods we cataloged mouse kidney cell types in an unbiased manner. We have developed a novel cell isolation method and individually profiled over 30,000 cells from the kidneys. Computational analysis included normalization, quality control, dimension reduction and clustering followed by identification of cell types using known markers and bulk RNAsequencing data of kidney segments.

Results: Main clustering analysis identified 15 major cell populations in normal mouse kidneys; three distinct ureteric bud- and 7 metanephric mesenchyme-derived epithelial clusters, in addition to endothelial cells, fibroblasts, different immune cell types and two novel epithelial cell populations that have not been described before. Cell trajectory analysis highlighted cell type conversion in the collecting duct and discovered novel transient cell type. Furthermore we have developed methods for single cell marker based in silico deconvolution of bulk RNAsequencing datasets. We found that most transcript level changes previously reported in kidney disease are resulted from cell type proportion changes in kidney samples, such as accumulation of immune cells and fibroblasts and decrease of tubule epithelial cells in disease development. Finally, we identified key transcription factors, mapped GWAS candidates, known drug targets, and nephrotic syndrome genes in the clusters showing their cell type-specific expression patterns.

Conclusions: In conclusion, our first single cell transcriptome of the entire mouse kidney could have a transformative impact to understand transcriptional networks maintaining cell identity and development of DKD.

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TH-OR129

SH3D21 Dysregulation May Cause Disruption of the Actin Cytoskeleton in Diabetic Nephropathy Heiko J. Schenk, Irini Schaefer, Patricia Bolanos-Palmieri, Beina Teng, Janina Müller-Deile, Hermann G. Haller, Mario Schiffer. *Department of Nephrology, Hannover Medical School, Hannover, Germany.*

Background: Diabetes is the most common cause of end-stage renal disease. The onset of albuminuria and podocyte damage is associated with disruption of the actin cytoskeleton. We identified SH3D21 as a potential key regulator of the actin cytoskeleton in podocytes which changes its expression in diabetes.

Methods: Cultured murine and human podocytes under glucose- and VEGF-stimulation were used to mimic diabetic conditions and compared to osmolality controls with mannitol. To model type I diabetes, C57BL/6J mice were treated for 5 days either with intraperitoneal injections of streptozotocin (STZ) or sodium citrate buffer as control while blood glucose levels were determined for 16 weeks. WB analysis of STZ-injected mice and buffer-injected mice was carried out. Immunofluorescence (IF) staining on cryosections of STZ- or buffer-injected mice was performed. IF of SH3D21 was performed on kidney cryosections of STZ- or buffer-injected mice as well as human and murine cultured podocytes. To identify protein interaction partners of SH3D21, we performed co-affinity purification mass spectrometry (MS) of murine whole kidneys as well as human cultured podocytes. Knockdown of sh3d21 was performed in zebrafish and proteinuria was measured using transgenic zebrafish line Tg*(l-fabp*:eGFP-DBP).

Results: Reduction of SH3D21 protein expression was detected in murine kidney and cultured podocytes under diabetic conditions. IF of diabetic murine kidney cryosections showed reduced Sh3d21 expression associated with the absence of Sh3d21-Nephrin co-expression. In murine and human podocytes we could document a shift from a membrane to a perinuclear or cytosolic speckled expression pattern which paralleled actin disruption under glucose- or VEGF-treatment. In murine and human podocytes SH3D21 primarily interacts with cytoskeletal proteins. Knockdown of sh3d21 in zebrafish caused proteinuria and foot process effacement.

Conclusions: SH3D21 is a novel interaction partner of nephrin which appears to be an important regulator of the actin cytoskeleton impacting slit diaphragm functions in diabetes.

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TH-OR130

Amelioration of Diabetic Nephropathy in miR-379 Knockout Mice Mitsuo Kato,[3] Maryam Abdollahi,[3] Linda L. Lanting,[2] Mei P. Wang,[4] Rama Natarajan.[1] *[1]Diabetes Complications and Metabolism, Beckman Research Institute of City of Hope, Duarte, CA; [2]Diabetes Complications and Metabolism, Beckman Research Institute of City of Hope, Duarte, CA; [3]Diabetes Complications and Metabolism, Beckman Research Institute of City of Hope, Duarte, CA; [4]Diabetes Complications and Metabolism, Beckman Research Institute of City of Hope, Duarte, CA.*

Background: Major features of diabetic nephropathy (DN) include extracellular matrix (ECM) accumulation, glomerular hypertrophy and fibrosis. Evidence shows that key microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) are involved in DN development. Recently we found that miR-379 megacluster of miRNAs and its host transcript lncRNA are regulated by endoplasmic reticulum (ER) stress, increased in glomeruli of diabetic mice and mediate early DN. Therefore, here we developed miR-379-knockout (KO) mice using CRISPR-Cas9 system to examine the hypothesis that miR-379, the first miRNA in the cluster, has an in vivo role in DN progression.

Methods: miR-379KO mice were generated by CRISPR-Cas9 nickase and dual guideRNA strategy. Diabetes was induced with streptozotocin (STZ) in 10 wk old wild type (WT-STZ) and miR379-KO (miR379-KO-STZ) C57BL/6 mice (n=6). Non-diabetic age/gender matched mice acted as control (WT-Con and miR379-KO-Con; n=6). Urine albumin excretion and urinary albumin/creatinine ratio (ACR) were measured before euthanization at 24 wks post diabetes induction. Renal glomeruli were isolated for measuring miRNAs, profibrotic and miR379 target genes. Cortical sections were stained for histopathology. Expression of TGFß1 and ER stress regulator EDEM3, a target of miR-379, were examined by immunohistochemical staining.

Results: miR-379KO mice did not depict any abnormalities, and developed diabetes to the same extent as WT mice. On the other hand, miR379-KO-STZ mice did not lose body weight like WT-STZ mice. Increased urine albumin and ACR in WT-STZ mice were attenuated in miR-379KO-STZ mice. Glomerular hypertrophy, ECM accumulation and fibrosis observed in WT-STZ mice were all significantly reduced in miR-379KO-STZ mice. Other candidate miRNAs in the miR-379 cluster (miR-495 and miR-377) were increased in glomeruli of WT-STZ, but not miR-379KO-STZ mice. Furthermore, increases in expression of profibrotic genes Col4α1, Col1α2, and TGF-ß1 seen in WT-STZ mice were significantly attenuated in miR-379KO-STZ mice. Conversely, decreased expression of EDEM3 in WT-STZ mice was not observed in miR-379KO-STZ mice.

Conclusions: Genetic deletion of miR-379 in mice by CRISPR-Cas9 system prevents glomerular hypertrophy and ECM accumulation associated with early DN. miR-379 and its target EDEM3 may play key roles in inducing ER stress and TGFß1 in diabetes to increase glomerular damage.

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TH-OR131

Comprehensive Renoprotective Mechanisms of Ipragliflozin against Diabetic Nephropathy Michitsugu Kamezaki,[1,2] Tetsuro Kusaba,[2] Noriyuki Yamashita,[2] Masahiro Uehara,[2] Keiichi Tamagaki.[2] *[1]Kyoto Chubu Medical Center, Nantan, Japan; [2]Kyoto Prefectural University of Medicine, Kyoto, Japan.*

Background: Clinical and experimental investigations showed that sodium glucose co-transporter 2 inhibitors (SGLT2i) potentiate glucose-lowering and natriuretic effects and contribute to the prevention of diabetic kidney disease progression. Amelioration of glomerular hyperfiltration is one of the candidate, but the other molecular mechanisms are not fully understood.

Methods: To distinguish these different pharmacological effects on the molecular mechanisms underlying the development of diabetic kidney disease, we administered different doses of SGLT2i, ipragliflozin, (low dose: Ipra-LD, high dose: ipra-HD or vehicle) into type 2 diabetic, *db/db* mice for 8weeks through oral gavage.

Results: Though body fluid volume was depleted in both Ipra-LD and Ipra-HD, only high dose Ipra significantly lowered blood glucose and reduced urinary albumin excretion. 3-nitrotyrosine (3-NT) immunostaining demonstrated that oxidative stress in the kidney was ameliorated by Ipra at dose-dependent manner. qPCR showed that expressions of tubular injury marker and NADPH oxidase 4 (Nox4) was improved in both Ipra-LD and Ipra-HD. Electron microscopy showed that Ipra improved the diabetes induced-abnormal mitochondrial cristae formation. Regarding kidney hypoxia, pimonidazole immunostaining showed that both high and low dose Ipra ameliorated the tubular hypoxia in the renal cortex where SGLT2i act. Regarding glomerulus, increased glomerular area in diabetic kidney reflecting hyperfiltration was ameliorated by both Ipra-LD and -HD. 3-NT immunostaining in glomerulus demonstrated the dose-dependent amelioration of oxidative stress in podocyte by Ipra. We further assessed the molecular mechanisms by using a glomeruli isolation technique, and found that high dose ipra preserved podocyte markers and reduced Nox4 expressions.

Conclusions: We verified the dose-dependent difference in the effect of ipra on diabetic nephropathy *in vivo*. Especially even low dose ipra improved the renal cortical hypoxia and abnormal hemodynamics in early diabetic nephropathy. In addition to these effects, high dose ipra exhibited renoprotective effects through the reduction of oxidative stress in both tubular epithelia and glomerular podocytes.

TH-OR132

Transcriptome of Urinary Extracellular Vesicles in Diabetic Kidney Disease Karina A. Barreiro,[3] Om Dwivedi,[7] Maija Puhka,[2] Carol Forsblom,[1] Per-Henrik Groop,[6] Leif Groop,[4] Tobias B. Huber,[5] Harry B. Holthofer.[7,8] *[1]Helsinki University Central Hospital, Helsinki, Finland; [2]Institute for Molecular Medicine Finland FIMM, Helsinki, Finland; [3]Institute for Molecular Medicine Finland FIMM, University of Helsinki, Helsinki, Finland; [4]Lund University, Maimo, Sweden; [5]University Medical Center Hamburg, Hamburg, Germany; [6]University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [7]Finnish Institute of Molecular Medicine, University of Helsinki, Helsinki, Finland; [8]III Dept of Medicine, University Clinic Hamburg-Eppendorf, Hamburg, Germany.*

Background: We compared methods for the urinary extracellular vesicle (uEV) harvest and respective transcriptomes in diabetic kidney disease (DKD). This also included study of storage conditions, in -20°C vs. -80°C, to find out whether existing large sample collections stored at -20°C can be successfully used.

Methods: Patients: Type 1 diabetic patients (T1D) and normoalbuminuric controls were included. **Main Measurables**: EVs were isolated from 40ml of 24h urines by differential centrifugation, Hydrostatic Filtration Dialysis (HFD) or kit-based isolation. Quality of the EV yield was analyzed with EM and Western blotting. Isolated RNAs were profiled with Bioanalyzer Pico kit and subjected to RNAseq after cDNA library preparation using ultra-low amount protocols. RNAseq was performed using HiSeq 2000 (Illumina) pair-end (2X100) protocol. Output reads were aligned to human reference genome and counted using GENCODE gene annotations. We used gene length normalized values FKPM (Fragments Per Kilobase Of Exon Per Million) as expression measurement for genes.

Results: Results: The isolated EVs appeared typical at EM. All samples had >15 million RNA eads. On average, expression (FKPM >1) of 13,161 genes and a high expression (FPKM≥5) of key kidney specific genes (e.g. *SLC12A3, SLC12A1, LGALS1, ATP6V1B1, NPHS2, AQP3, AQP2, SLC22A12*). A comprehensive analysis of 182 kidney specific genes revealed >70% (total 132) of the genes in urine EVs. Principal component analysis of these discriminated macro-albuminuric from normoalbuminuric T1D patients. Six genes were differentially expressed in DKD ($P_{uncorrected}$ <0.001 and fold change >1.5 or <0.66). The highest expressed genes were enriched ($P>10^{-11}$) in pathways of cellular metabolism (oxidative phosphorylation and TCA cycle), mitochondrial, ribosomal and vesicle trafficking functions. Pathway and gene enrichment analyses implicate (P<0.002) TGF-beta signaling, PI3K-Akt signaling and immune pathway in DKD.

Conclusions: uEV transcriptome captures a significant kidney specific transcriptome which differentiates macroalbuminuric from normoalbuminuric T1D patients. Technically, samples stored at different temperatures cannot be directly compared with each other. Our results show high value of urinary EV transcriptome for biomarker search and call for meticulous standardization of protocols used.

TH-OR133

Deletion of Adaptor Protein p66Shc Decreases Afferent Arteriolar KATP Channel Activity and Decreases Renal Damage in Diabetic Dahl SS Rats Andrey Sorokin,[1] Bradley S. Miller,[1] Shoshana R. Blumenthal,[1] John D. Imig.[2] *[1]Medicine, Medical College of Wisconsin, Milwaukee, WI; [2]Pharmacology & Toxicology, Medical College of Wisconsin, Milwaukee, WI.*

Background: Increased expression of adaptor protein p66Shc has been associated with progression of diabetic nephropathy. Afferent arteriolar dilation and glomerular hyperfiltration in diabetes are due to increased K_{ATP} channel availability and activity.

Methods: This study tested the hypothesis that p66Shc KO Dahl SS rats with STZ-induced diabetes are protected from glomerular injury because afferent arterioles do not exhibit enhanced K_{ATP} channel activity. Afferent arteriolar responses to the K_{ATP} channel opener pinacidil and the K_{ATP} channel blocker glibenclamide were assessed in Dahl SS, Dahl SS p66Shc KO, Dahl SS with STZ-induced diabetes, and Dahl SS p66Shc KO with STZ-induced diabetes rats. Afferent arteriolar diameter responses were determined using the juxtamedullary nephron technique six weeks following induction of STZ diabetes. Hyperglycemia, excessive urination, body weight, albuminuria and glomerular injury was evaluated in all rat groups to monitor the progression of diabetic nephropathy.

Results: Afferent arteriolar diameters at 100 mmHg averaged 22.9 ± 0.9 μm (n=8) in Dahl SS rats, 21.1 ± 0.8 μm (n=6) Dahl SS p66Shc KO. Dahl SS with STZ-induced diabetes rats had a significant increase in the afferent arteriolar diameter (24.7 ± 1.3 μm; n=6). Inversely, Dahl SS p66Shc KO with STZ-induced diabetes rats did not have increased afferent arteriolar diameters (22.1 ± 1.2 μm; n=6). Afferent arteriolar dilator responses to pinacidil were not different between Dahl SS rats and Dahl SS p66Shc KO. However; Dahl SS with STZ-induced diabetes but not Dahl SS p66Shc KO with STZ-induced diabetes rats had an increased vasodilator response to pinacidil. Likewise, the K_{ATP} inhibitor gibenclamide (30 μM) resulted in a greater decrease in afferent arteriolar diameter in Dahl SS & STZ-induced diabetes (23 ± 4%, n =6) compared to Dahl SS p66Shc KO & STZ-induced diabetes (13 ± 2%, n =6). The glomerular injury was mitigated in Dahl SS p66Shc KO with STZ-induced diabetes.

Conclusions: Taken together, these results indicate that increased afferent arteriolar K_{ATP} channel activity contributes to increased diameters and renal injury in Dahl SS & STZ-induced diabetes. Moreover, deletion of the adaptor protein p66Shc decreases afferent arteriolar K_{ATP} channel activity and decreases renal damage in diabetic Dahl SS rats.

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TH-OR134

Genetic Ablation of Vasohibin-2 Prevents the Progression of Diabetic Nephropathy in an Experimental Mouse Model Kana Masuda, Katsuyuki Tanabe, Haruyo Ujike, Norikazu Hinamoto, Hiromasa Miyake, Hitoshi Sugiyama, Yohei Maeshima, Jun Wada. *Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science, Okayama, Japan.*

Background: Diabetic nephropathy has been reported to be associated with abnormal angiogenesis and increased glomerular VEGF, which could represent potential therapeutic targets. Vasohibin-2 (VASH2) is a novel pro-angiogenic factor and has shown to be involved in tumor enlargement. In the present study, we investigated whether VASH2 was involved in the progression of diabetic nephropathy in vivo and in vitro experiments.

Methods: Eight to ten weeks old male C57BL/6 wild type (WT) or VASH2-knockout ($VASH2^{LacZ/LacZ}$) mice received intraperitoneal injections of 50mg/kg STZ or vehicle on five consecutive days. The experimental subgroups included 1) non-diabetic WT, 2) non-diabetic $VASH2^{LacZ/LacZ}$, 3) diabetic WT and 4) diabetic $VASH2^{LacZ/LacZ}$. Blood glucose (BG) and urine albumin excretion (UAE) were evaluated every other week, and 16 weeks after the injections, blood pressure (BP) was measured and blood and kidney samples were obtained. Conditionally immortalized human mesangial cells were stimulated by high glucose (25mM) or TGF-β1 (10 ng/ml) under the presence of control or VASH2 siRNA.

Results: There were no differences in BP, BG and serum creatinine between diabetic WT and $VASH2^{LacZ/LacZ}$ group. However, increased UAE and creatinine clearance observed in diabetic WT mice were significantly decreased in diabetic $VASH2^{LacZ/LacZ}$ mice. In addition, increased glomerular CD31 positive area induced by diabetes was also suppressed in $VASH2^{LacZ/LacZ}$ group. VASH2 deficiency did not affect renal level of VEGF but suppressed diabetes-induced elevation of renal VEGFR2 expression. Increased glomerular type IV collagen accumulation and renal TGF-β1 mRNA in diabetic WT mice were prevented in diabetic $VASH2^{LacZ/LacZ}$ mice. Endogenous VASH2 level was increased by diabetes, and immunostaining suggested that VASH2 was localized in mesangial cells in glomeruli. Knockdown of VASH2 using siRNA suppressed the increased mRNA level of type IV collagen and α-SMA in cultured mesangial cells treated with high glucose or TGF-β1 stimulation.

Conclusions: Deletion of VASH2 had protective effects in diabetic nephropathy through the suppression of excessive VEGF action on endothelial cells and extracellular matrix production in mesangial cells.

TH-OR135

Soluble Nogo-B Overexpression Ameliorates Diabetic Glomerulopathy Ivan Hernandez,[1] Carlo alberto Ricciardi,[1] Kathryn E. White,[3] Anthea E. Hayward,[1] Xiaoyan Bai,[2] Fan Fan Hou,[2] David A. Long,[4] Luigi Gnudi.[1] *[1]King's College London, London, United Kingdom; [2]Nanfang Hospital, Southern Medical University, Guangzhou, China; [3]Newcastle University, Newcastle upon Tyne, United Kingdom; [4]University College London, London, United Kingdom.*

Background: Diabetic glomerulopathy (DG) is characterized by altered vascular remodelling, increased vascular permeability. Neurite Outgrowth Inhibitor (Nogo)-B and its soluble form (sNogo-B) bind to NgBR and have been implicated in vascular remodelling. Full-length Nogo-B is expressed in glomerular endothelial cells and podocytes and is downregulated in experimental model of diabetic nephropathy and in patients with diabetic nephropathy (DN). Our aims were to investigate whether overexpression of sNogo-B could ameliorate DG in an experimental animal model of diabetes.

Methods: 8-10 weeks-old male DBA/2J mice were made diabetic (streptozotocin), and administered (12-14 week-old) an adeno-associated viral vector (AAV) expressing sNogoB or GFP (control). Animals were divided into four groups: non-diabetic (ND) and diabetic (D) mice treated with either GFP-AAV or sNogo-B-AAV followed by 12-14 weeks of diabetes. Blood pressure was assessed with tail-cuff methodology, plasma sNogo-B levels by ELISA, full-length Nogo-B and AKT phosphorylation with immunoblotting, creatinine by mass spectrometry, albuminuria by fluorescence, and glomerular ultrastructure by electron microscopy.

Results: sNogo-B-AAV allowed a sustained expression of sNogoB in the circulation ($p<0.05$). Diabetes-mediated albuminuria ($p<0.01$) was ameliorated by sNogo-B upregulation ($p=0.04$). Similarly, increase in creatinine clearance was corrected by sNogo-B overexpression to control ND mice levels ($P<0.006$). Blood pressure was similar in all groups. sNogo-B overexpression ameliorated diabetes-mediated mesangial expansion ($p<0.05$), full-length Nogo-B downregulation ($p=0.02$), and blunted Akt-Serine phosphorylation ($p=0.01$) in diabetic mice in kidney cortex lysate.

Conclusions: Overexpression of sNogo-B ameliorates DG via prevention of diabetes-mediated Nogo-B downregulation. Ongoing work is dissecting the major molecular mechanisms involved. sNogo-B could represent a potential novel future treatment for DG.

TH-OR136

A Small Molecule Inhibitor of ASK1 Modulates Biomarkers and Pathways Associated with Diabetic Kidney Disease (DKD) Shawn S. Badal,[1] Haichun Yang,[2] Li Li,[1] Henry Liu,[1] Agnes B. Fogo,[2] David G. Breckenridge,[1] John T. Liles.[1] *[1]Gilead Sciences, Foster City, CA; [2]Vanderbilt University, Nashville, TN.*

Background: Apoptosis signal-regulating kinase 1 (ASK1) promotes inflammation, apoptosis, and fibrosis via activation of MAPK kinases p38 and c-Jun N terminal kinase (JNK). ASK1 pathway activation has been demonstrated in human DKD biopsies and in kidneys of db/db eNOS$^{-/-}$ mice. Clinically relevant urinary biomarkers associated with kidney damage and GFR decline in DKD patients have not been investigated in this animal model. This study evaluated effects of a selective, small molecule ASK1 inhibitor on urinary biomarkers and expression of DKD-related genes in db/db eNOS$^{-/-}$ mice.

Methods: db/db eNOS$^{-/-}$ mice were treated with a structural analog of the ASK1 inhibitor, Selonsertib, (GS-444217, 0.3% in chow) or vehicle for 8 weeks, starting at 10 weeks of age (baseline) (n=8-10 mice/group). At 18 weeks of age EGF, KIM-1 and TIMP1 levels in urine were quantified at end of study by ELISA and values normalized to urine creatinine levels. GFR was measured by FITC-inulin clearance. Kidney cortex mRNA was isolated and gene expression analyzed by qPCR and RNA-Seq.

Results: At 18 weeks, vehicle-treated mice had significant reductions in GFR (212± 21 vs 296±27 ml/min, $p=0.0265$) and uEGF levels (1.38 ± 0.11 vs 2.17± 0.27 μg/mg, $p=0.0067$) compared to baseline. ASK1 inhibition halted GFR decline (365± 31 vs 212± 21 ml/min, $p=0.0007$), prevented decreases in uEGF (2.51± 0.23 μg/mg vs 1.38±0.11, $p=0.0003$) and preserved kidney *Egf* mRNA levels. ASK1 inhibition reduced urinary TIMP1 (481.5± 96.3 vs 903.4± 158.8 pg/mg, $p=0.0473$) and *Timp1* mRNA, compared to vehicle. Additionally, urinary KIM-1 as well as *Havcr1* (KIM-1), *Lcn2* (NGAL), *Mcp1*, and *Tnf* mRNA were all significantly reduced by ASK1 inhibition. Gene set enrichment analysis (GSEA) of RNA-Seq data revealed that TNFα signaling and inflammatory response pathways were enriched in db/db eNOS$^{-/-}$ mice and down-regulated by treatment with an ASK1 inhibitor.

Conclusions: Biomarkers related to kidney injury, inflammation, fibrosis and GFR decline in DKD patients are dysregulated in db/db eNOS$^{-/-}$ mice. The administration of an ASK1 inhibitor improved these biomarker levels and kidney function. These data establish db/db eNOS$^{-/-}$ mice as a relevant model to evaluate drug effects on biomarkers associated with GFR decline.

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TH-OR137

Increased Podocyte SIRT1 Function Attenuates Diabetic Kidney Injury Quan Hong,[1,4] Lu Zhang,[3,4] Bhaskar Das,[4] Guangyan Cai,[1] Xiangmei Chen,[1] Peter Y. Chuang,[2,4] John C. He,[4] Kyung Lee.[4] *[1]Chinese PLA General Hospital, Bei Jing, China; [2]Connecticut Kidney Center, LLC, Orange, CT; [3]Xiamen University Affiliated The First Hospital, Amoy, China; [4]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: We previously found that the glomerular expression of Sirtuin-1 (SIRT1) was reduced in human diabetic kidneys and the loss of SIRT1 aggravated albuminuria and worsened kidney disease progression in diabetic mice. SIRT1 encodes an NAD-dependent deacetylase that modifies the activity of key transcriptional regulators affected in diabetic kidneys, including NF-κB and STAT3. Consistent with reduced SIRT1, acetylation of NF-κB and STAT3 was reduced in diabetic kidneys, resulting in their increased activities. In this study we employed genetic and pharmacological means to interrogate whether the increased SIRT1 function is sufficient to attenuate diabetic kidney injury.

Methods: For the genetic approach, we generated doxycline-inducible podocyte-specific overexpression of SIRT1 (Pod-SIRT1^{OV}) mice, which were further crossed with diabetic OVE26 mice to generate OVE26;Pod-SIRT1^{OV}. Littermates without SIRT1 transgene (OVE26;WT) and age-matched nondiabetic mice were used as controls. Healthy control, OVE26;WT and OVE26;Pod-SIRT1^{OV} mice were given dox-supplemented chow starting at 16 weeks of age, at which time the OVE26 mice exhibit pronounced hyperglycemia and proteinuria. For the pharmacological approach, OVE26 mice at 16 weeks of age were treated with either vehicle or novel SIRT1 inhibitor, BF175 (0.4mg/kg daily). All mice were sacrificed at 22 weeks of age for analysis.

Results: 6 weeks of Dox administration led to significant reduciton in kidney-to-body weight ratio and urinary albumin excretion in OVE26;Pod-SIRT1^{OV} in comparison to OVE26;WT mice. Glomerular hypertrophy, mesangial matrix expansion, and podocyte foot process effacement were also markedly reduced in OVE26;Pod-SIRT1^{OV} mice. Administration of SIRT1 agonist BF175 for 6 weeks similarly led to significant reductions in albuminuria, mesangial matrix expansion, and podocyte foot process effacement in OVE26 mice compared to vehicle treatment. Both OVE26;Pod-SIRT1^{OV} and OVE26 mice treated with BF175 showed increased podocyte number compared to control OVE26, suggesting that increased SIRT1 function protected against podocyte loss in OVE26 glomeruli.

Conclusions: Our data demonstrates that increased podocyte SIRT1 expression is sufficient to significantly mitigate early diabetic injury and that BF175 is a novel SIRT1 agonist that can be further developed as a potential therapy for early DKD.

Funding: NIDDK Support

FR-OR001

Mentorship in the Digital Age: Nephrology Social Media Collective Internship – 2 Year Experience Silvi Shah,[8] Matthew A. Sparks,[2] Scherly Leon,[6] Hector M. Madariaga,[4] Kenar D. Jhaveri,[5] Edgar V. Lerma,[1] Timothy Yau,[7] Paul J. Phelan,[6] Nikhil A. Shah,[6] Ali Poyan-Mehr,[6] Michelle N. Rheault,[3] Swapnil Hiremath,[9] Joel M. Topf.[6] *[1]Associates in Nephrology, Berwyn, IL; [2]Duke University and Durham VA Medical Centers, Durham, NC; [3]University of Minnesota, Minneapolis, MN; [4]Good Samaritan Medical Center, Brockton, MA; [5]Hofstra Northwell School of Medicine-Northwell health system, Great neck, NY; [6]Detroit, MI; [7]Washington University School of Medicine, Saint Louis, MO; [8]University of Cincinnati, Cincinnati, OH; [9]University of Ottawa, Ottawa, ON, Canada. Group/Team: Nephrology Social Media Collective Internship Group.*

Background: Although social media use by healthcare professionals is increasing, formal education is lacking. The Nephrology Social Media Collective (NSMC) internship is a worldwide collaboration among nephrologists to cultivate leaders in the use of social media in medicine by instilling knowledge, competence, and professionalism.

Methods: he NSMC internship was established in 2015. The NSMC faculty consists of 21 individuals who are clinicians, educators, and scientists. The internship is 1 year. Interns are selected on the basis of their curriculum vitae, personal statement, and interest. There is an entrance discussion with each intern to discuss goals followed by quarterly online meetings. Interns are paired with 2 faculty mentors and are expected to contribute 3-4 hours/month. Interns attend NephJC (online nephrology journal club) and participate in NephJC administrative activities (curating a Twitter chat, constructing a visual abstract, writing blog posts or moderating a session). Interns participate in the two required projects - the annual NephMadness contest and the Renal Fellow Network blog. Assessment are based on participation in NephJC, timely completion and quality of projects.

Results: The initial class of 2015 class enrolled 4 interns. The subsequent class of 2016 included 7 interns. The classes were near gender balanced with 6/11 male. There were 6 fellows, 2 medical students, 1 practising physician and 1 nurse. 8 were from USA, 2 from the United Kingdom and 1 from Canada. NSMC internship increased exposure and opportunities for engagement in other social media activities. Following completion, interns became part of NephJC team (N=5) and NephMadness editorial team (N=2). Interns were invited to join International Society of Nephrology's Social Media Task force (N=2), Women in Nephrology's communications' committee (N=2) and ASN's media and communication committee (N=1). The current class of 2017 has enrolled 9 interns.

Conclusions: NSMC internship provides modern communication skills and opportunities to improve skills in social media. It resulted in successful recruitment of the graduated interns in various social media forums. NSMC internship can be included as a part of nephrology fellowship training curriculum.

FR-OR002

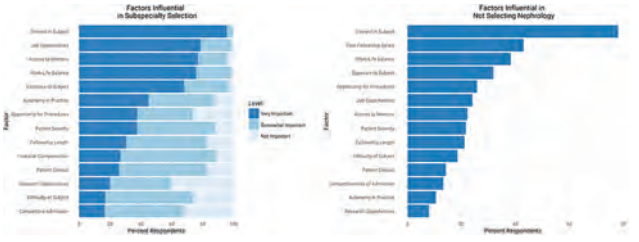
Specialty Choice and Nephrology: Perceptions Among Medical Students and Internal Medicine Residents Devika Nair,[1] Kurtis Pivert.[2] [1]*Vanderbilt University, Nashville, TN;* [2]*American Society of Nephrology, Washington, DC.*

Background: Fewer medical trainees are choosing to pursue nephrology. Only 60.8% of nephrology fellowship positions filled in the AY 2017 nephrology Match, especially concerning in the setting of a growing number of patients with kidney disease.

Methods: To understand perceptions about nephrology and assess factors influencing specialty choice among trainees, an anonymous survey was distributed to medical students and internal medicine residents at 30 US medical schools and residencies. Of 4199 recipients, 648 (15.4%) trainees responded, including 333 upper-level medical students, 304 residents, and three chief residents.

Results: Interest in the subject matter was the most critical factor in choosing to pursue a specialty (92% of participants). Other key considerations included a suitable post-fellowship work-life balance (73%), access to mentors (70%), and adequate exposure to the subject (66%). Lack of interest was the most common reason to forgo a nephrology fellowship (79% of responses). Concerns about remuneration (43%), perceptions of an unsatisfactory work-life balance (39%), and inadequate exposure to nephrology during earlier training (32%) were frequently cited dissuading factors. Several respondents expressed a desire for a combined nephrology-critical care or nephrology-interventional radiology fellowship. Interest in renal physiology and access to mentors were noted as highly influential to those who considered a nephrology career at any point.

Conclusions: Lack of interest in nephrology was the leading factor in respondents' decision to not pursue the specialty. Innovative ways to expose trainees to the meaningful rewards and worthwhile challenges of kidney care are needed to continue to attract qualified applicants.



FR-OR003

Best Practices to Increase Resident Interest in Nephrology: A Mixed Methods Study Stephen M. Sozio,[3,7] Kurtis Pivert,[6] Hitesh H. Shah,[1] Abdo Asmar,[4] Benjamin D. Morrow,[2] Nancy D. Adams.[5] [1]*Hofstra Northwell School of Medicine, Great Neck, NY;* [2]*Uniformed Services University of the Health Sciences (USUHS), San Antonio, TX;* [3]*Medicine, Johns Hopkins University School of Medicine, Baltimore, MD;* [4]*University of Central Florida Shool of Medicine, Orlando, FL;* [5]*University of Connecticut Health Center, Hartford, CT;* [6]*American Society of Nephrology, Washington, DC;* [7]*Welch Center for Prevention, Epidemiology, and Clinical Research, Baltimore, MD.*

Background: Interest in nephrology careers has declined. Understanding practices of internal medicine (IM) residency programs that successfully generate nephrology interest is sorely needed.

Methods: The *Best Practices Project* is an ASN Workforce and Training Committee project to increase nephrology interest. Residents graduating 2002-2012 were identified with the AMA Masterfile; programs were ranked by number of residents ultimately choosing nephrology. Nephrology training program directors (TPDs) from the top 30 institutions were sent a survey about their renal elective and educational experience for IM residents. Directed focus groups were conducted among IM-PDs (top 15 programs) probing key factors in each program's success. Survey results were analyzed across program ranking and compared to a previously-reported national survey. Transcripts from focus groups were analyzed using thematic content analysis.

Results: 19 nephrology TPDs (68%) responded to our survey and 4 IM-PDs (27%) directed focus group sessions were conducted. Most programs were in large tertiary centers. Nephrology TPDs noted faculty mentoring (78%), elective experience (72%), research opportunities (56%), and exposure to nephrology fellows (56%) were most effective in fostering interest. All programs offered renal electives; 33% were mandatory. 53% of programs' typical electives incorporate outpatient experiences, higher than the national average (42%). Programs with more IM residents choosing nephrology were significantly more likely to offer ambulatory experiences in general nephrology in their elective (p=0.042) and have residents mentored in more impactful research projects (p=0.025). IM-PDs noted faculty exposure, quality of nephrology teaching, and demonstrating nephrology as a viable field were keys to success. One exemplar quote: *[Faculty] work hard and play hard. This group of faculty always hosts dinners at the end of the rotation. They actually make their own t-shirts. They kind of have their own branding of what they are*

Conclusions: Integrating outpatient experiences in nephrology electives and mentoring residents in high quality research projects likely increase interest in nephrology. Faculty contact and teaching in both electives and core resident areas also contribute to generating nephrology interest. Interventions to enhance these activities are needed.

FR-OR004

Breaking Bad News: An Objective Structured Clinical Examination (OSCE) of Renal Replacement Therapy (RRT) and Kidney Biopsy Communication Skills Lisa K. Prince, Anna M. Howle, Christina M. Yuan. *Walter Reed National Military Medical Center, Silver Spring, MD. Group/ Team: NERDC.*

Background: There are few reported simulation-based assessments for nephrology-specific interpersonal communication skills (ICS) and professionalism (PROF). We developed a "Breaking Bad News" OSCE that assesses fellow competence in counseling a surrogate decision maker for acute RRT, a patient with advanced chronic kidney disease for RRT, and a patient for kidney biopsy.

Methods: The OSCE was designed for the 2-year nephrology fellowship cycle, with 2 sets of scenarios. Fellows are provided with a brief clinical summary before counseling a simulated patient (SP). SP are trained to portray a nephrology patient with a specific condition, to provide feedback and rate fellows. SPs receive a medical and social history designed to stimulate fellows to demonstrate ICS. After each encounter SPs rate ICS and PROF using the Essential Elements of Communication-Global Rating Scale 2005 (EEC-GRS). Faculty assess performance using a 5-point Likert Mini-Clinical Examination Exercise (Mini-CEX). The two scenario sets were beta-tested in Spring 2015 (3 second year fellows and 2 first year fellows) and 2016 (2 second year fellows and 1 first year fellow).

Results: The OSCE is being evaluated prospectively at 5 training programs (16 first-year; 10 second-year fellows) over a two year period. There are 3 faculty per training site. Primary outcome is overall score on the EEC-GRS for each scenario (first vs. second year fellow performance for each scenario, and individual fellow scores between first and second year). Secondary outcomes include score < 3 (Satisfactory for level of training) on any subsection of the mini-CEX and overall score < 3 on the EEC-GRS. Preliminary satisfaction survey data indicate that 100% of faculty (6/6) and fellows (7/7) rated the OSCE as having met objectives, and 86% (6/7) fellows rated the experience as being "good" or better.

Conclusions: The Breaking Bad News OSCE, designed for a 2-year fellowship cycle, uses previously validated instruments (EEC-GRS; MiniCEX) to assess nephrology-specific ICS and PROF skills. Fellows and faculty report satisfaction with the OSCE, and indicate that it meets objectives. *The views expressed are those of the authors and do not reflect the official policy of the Department of the Army, the Department of the Navy, the Department of Defense or the United States Government.*

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FR-OR005

Renal Fellows' Point-of-Care Lung Ultrasound Curriculum Nathaniel C. Reisinger,[2] Anubhav Kumar,[2,1] Vishnu S. Potluri,[2] Jehan Z. Bahrainwala,[2] Jeffrey S. Berns.[2] [1]*None, Philadelphia, PA;* [2]*Penn, Philadelphia, PA.*

Background: Fluid overload (FO) is a prevalent risk factor for death in patients on hemodialysis (HD) and is underdiagnosed. Lung ultrasound (US) B-line score is a tool to quantify extravascular lung water and measure FO. B-lines are reverberation artifacts that correlate with lung congestion and disappear with ultrafiltration during HD. B-line score is superior to physical exam in detection of asymptomatic pulmonary congestion. B-line score correlates with cardiovascular outcomes, death, and readmissions for patients on HD. A prospective clinical trial is ongoing which uses a web-based tutorial to ensure interobserver agreement among attending physicians. Competency among nephrology fellows is not known.

Methods: To assess and improve the current state of knowledge and ability of nephrology fellows in obtaining and interpreting lung US we employed a mobile-optimized, app-supported curriculum for didactic learning as well as pre- and post-course surveys (using a 5-point Likert Scale) and knowledge assessments. Trainees had a hands-on, one-on-one teaching session with a peer-user to hone psychomotor skills in point-of-care lung US. Images were obtained using a commercially available curvilinear US probe and a tablet computer. A panel of expert trainers reviewed representative images remotely, provided feedback on image acquisition, and adjudicated B-line scores. Scores were compared using a paired two sample means t-Test with a one-tailed p value. Interclass correlation coefficients were calculated in Stata.

Results: Surveys demonstrated statistically significant increases in confidence in five domains critical to point-of-care US. Mean knowledge assessment score was 4% before the course and 92% after the course. Interclass correlation coefficients averaged 0.90 with no scores below 0.7 demonstrating excellent agreement in interpreting B-line scores which was confirmed on regression analysis. Bland-Altman plot showed good agreement and low bias. User images were well-reviewed by the expert trainers.

Conclusions: Point-of-care US to quantify lung water by B-line score can be taught to nephrology fellows quickly and reliably combining a web-based curriculum and hands-on training.

FR-OR006

Point of Care Echocardiography and Ultrasound-Guided Volume Assessment Training for Nephrologists and Trainees to Teach Point of Care ECHO Skills Nithin Karakala,[1,2] Gerren Hobby,[1] Kelly W. Bulloch,[1] Krishna siva sai Kakkera,[1] John T. Huggins.[1] *[1]Medicine, University of Arkansas for Medical Sciences, Little Rock, AR; [2]Medicine, Central Arkansas VA, Little Rock, AR.*

Background: Intravascular volume assessment is an extremely important in the care of patients with acute kidney injury (AKI), chronic kidney disease, and patients needing intermittent and continuous renal replacement therapy. The current volume assessment tools like, MAP, heart rate, clinical examination are unreliable in assessing intravascular (IV) volume. The accuracy of invasive methods like central venous pressure, and pulmonary artery pressure measurements in assessing responsive to volume have been questioned in recent years. Nephrologists play a pivotal role in volume assessment and management. Point of care (echocardiogram) ECHO is a very valuable non-invasive tool for volume assessment.

Methods: During an intense 8 hour workshop, participants were trained by an experienced intensivist and a trained nephrologist. There were 2 stations which utilized live standardized patients and a preceptor. Station 1 covered basics of ECHO, cardiac para-sternal short and long axis views, and measurement of Inferior VenaCava (IVC) diameter and variability; second 2 station was cardiac apical 4 and 5 chamber views and lung parenchymal exam. The preceptors initially demonstrated the techniques, and then the participants were allowed to practice under supervision. We conducted a 20 multiple choice question (5 basics of ECHO, 9 cardiac ECHO, and 6 IVC and lung parenchymal volume assessment) per and post-test. There were 5 five-scale questions assessing procedural confidence.

Results: Twenty two participants (5 nephrologists, 16 trainees) attended and completed the test. There was a significant improvement in mean percentage of correct answers for the post compared to pre-test 78% (SD:17) vs 46% (SD:11); $p<0.0001$. The improvement during post compared to pre-test was observed in all 3 categories: basics of ECHO (79%, SD:22 vs 53%, SD:21; $p<.001$), cardiac ECHO (77%: 19 vs 40%: 19; $p<0.0001$) and IVC and lung (77%: 12 vs 46: 28; $p<0.001$). After attending the workshop the participants answered that they were either confident or extremely confident in acquiring or interpreting basic images 62% (SD: 17) vas 4% (SD:8) pre workshop.

Conclusions: Point of care ECHO training can help nephrologists learn and improve bedside volume assessment skill and reignite passion for nephrology among residents.

Funding: Clinical Revenue Support

FR-OR007

Project Nephron: Teaching Medical Students Physiology and Histology Lena Vaynberg. *FAU Charles E Schmidt College of Medicine, Highland Beach, FL, FL.*

Background: The objective of PBL in the FAU COM curriculum is to foster self-directed learning, communication skills, and teamwork among the students as well as linking these skills to basic sciences and patient problems. Students have a difficult time with the physiology of the nephron with regard to channels, transporters, pumps and diuretics. Since 2014, at the start of the renal course, each of eight case inquiry groups received a poster of a nephron with the objective of understanding he functions of the cells in different portions of the nephron.

Methods: Each group of students received a poster of a nephron with the cells of different parts of the glomerulus and tubule drawn in. The pathways for anion and cation transfer were left blank. They were directed to search through the 8th edition of *Vander's Renal Physiology* and fill in the functions of the different cells. They did so and following the final session, they were given a nephron with the labeled pathways (Fig. 1)

Results: Following the end of the renal course, the students were surveyed as to whether or not the poster was useful to them in learning the physiology and histology of the nephron. Sixty three of the 65 students responded to the survey. The questions were phrased for a yes or no response as well as a degree of helpfulness that ranged from 1 (not helpful) to 5 (extremely helpful). There was also a section for comments. To the question "did the nephron help you learn the histology of the nephron"? The students gave it an average helpfulness of 4. To the question "did the nephron help you learn the physiology of the nephron"? The students gave it an average helpfulness of 3.5. To the question "did you continue to use nephron in subsequent cases"? The students gave it an average helpfulness of 4.1. As for the comments, the students found it a useful learning tool which they reviewed in subsequent IQ cases.

Conclusions: The students found the poster helpful in understanding renal (nephron) physiology and histology. Once the poster was complete, it was helpful in understanding the pathophysiologic and the pathologic anatomy of the nephron. Coming before the lectures and the IQ cases, it gave them a frame of reference for understanding the function of the nephron and the mechanisms of action of the diuretics.

FR-OR008

NephMadness: 5 Years' Experience Joel M. Topf,[5] Anna M. Burgner,[3] Timothy Yau,[4] Swapnil Hiremath,[2] Matthew A. Sparks.[1] *[1]Duke University and Durham VA Medical Centers, Durham, NC; [2]University of Ottawa, Ottawa, ON, Canada; [3]Vanderbilt University Medical Center, Nashville, TN; [4]Washington University School of Medicine, Saint Louis, MO; [5]Medicine, Oakland University William Beaumont School of Medicine, Rochester, MI.*

Background: NephMadness (NM) is an educational game that takes place entirely on the internet through blog-based review articles, participatory interactive website, and Twitter-based discussion. NM leverages social media and Free Open Access Medical Education (FOAMed) to highlight advances and neglected issues in nephrology. NM began in 2013 and has completed 5 iterations. NM has evolved as the organizers have experimented with the medium. This review of the evolution of NM provides lessons to organizers of other online educational campaigns.

Methods: The NM curriculum takes the form of an online game that mimics the March Madness basketball tournament. The field consists of 32 nephrology concepts in 8 topics. The concepts and topics change every year. The field initially consisted of 64 concepts but this was reduced to 32 to encourage participation. Each concept is reviewed in a blog post providing the core educational content of the game. Independent content experts help select the concepts and fact check the blog posts. During the 3-week contest, additional commentaries are published from other experts. In 5 years NM has covered 256 nephrology concepts and posted 185 reviews and commentaries.

Results: Participants attempt to predict the winners of all 31 matchups. Initially the winners of each single elimination contest was scripted by the organizers. After significant push back by the users, winners were selected by participant voting. NM now uses a panel of experts to determine the winners. The NM team encourages training programs to participate using a flipped classroom model. In 2017, 32 training programs participated. NM encourages participation from all levels, ranging from lay people, to medical students, to attendings. Prizes are awarded for the most accurate predictions and for programs with the greatest participation. 1481 individuals from 55 countries, two thirds from the US, have played NM in the last 4 years.

Conclusions: NM is a unique forum to present medical education that takes nephrology education out of the classrooms and textbooks and transforms it into a gamified, interactive campaign that populates social media channels. The mixture of free, evidence-based, expert content with twitter and blogs is a novel method of delivering high quality continuing medical education that could serve as a template for future projects.

FR-OR009

GlomCon – International Web-Based Glomerular Disease Case Conferences: Connecting Peers to Enhance Clinical Experience Nikhil Agrawal,[14,15] Rhea Bhargava,[9] Roger A. Rodby,[11] Mihran V. Naljayan,[7] Kenar D. Jhaveri,[5] Stewart H. Lecker,[2] Johannes S. Schlondorff,[3] Meghan E. Sise,[8] Timothy Yau,[13] Isaac E. Stillman,[3] Franco H. Cabeza Rivera,[12] Jorge L. Castaneda,[9] Arley F. Diaz,[6] Michael J. Germain,[10] Francesco Iannuzzella,[9] Olufunmilola A. Olubukola,[1] Adam M. Segal,[9] Jonathan Slater,[9] Joseph Kupferman,[3] David J. Friedman,[9] John Danziger,[15] Jeffrey H. William,[3] Bradley M. Denker,[9] Martin R. Pollak,[4] Ali Poyan-Mehr.[9] *[1]BIDMC, CONCORD, NH; [2]Beth Israel Deaconess Medical Center, Boston, MA; [3]Beth Israel Deaconess Medical Center, Boston, MA; [4]Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA; [5]Hofstra Northwell School of Medicine- Northwell health system, Great neck, NY; [6]Kidney Care and Transplant Associates of New England, Springfield, MA; [7]LSUHSC School of Medicine, New Orleans, LA; [8]Massachusetts General Hospital, Boston, MA; [9]None, Boston, MA; [10]Renal and Transplant Assoc of New England, Hampden, MA; [11]Rush University Medical Center, Chicago, IL; [12]University of Mississippi Medical Center, Ridgeland, MS; [13]Washington University School of Medicine, Saint Louis, MO; [14]Nephrology, Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA; [15]Harvard Medical School, Boston, MA.*

Background: Gaining enough exposure to glomerular diseases is a challenge and may lead to uncertainties in the management of these patients. The aim of our Glomerular Disease Case Conferences (GlomCon) is to increase nephrologist's/nephropathologist's exposure to patients with glomerular disorders and to create a forum to discuss diagnosis and management of individual cases in detail with colleagues.

Methods: We have created a web-based, secure video platform at Glomcon.org where nephrologists/nephropathologists can connect worldwide and participate in live "peer-to-peer" clinical exchange. Participants submit challenging cases from their daily practice. Cases are reviewed by a volunteering nephropathologist/nephrologist and clinico-pathological correlation and therapeutic options discussed in bi-monthly live web sessions. All participants were surveyed in April 2017 for feedback.

Results: Since inception in July 2016, the conferences have seen a steady increase in worldwide participation. As of April 2017, GlomCon includes over 100 participants from 27 countries. A survey of 113 participants yielded the following results: 54% responded. Of these, 100% were "Very satisfied" or "Satisfied", 86% noted that participation impacted their care, for 31% knowledge about glomerular kidney disorders improved "extremely" and for 54% "very". 100% believe that the conferences improve the care of patients with glomerular kidney disease.

Conclusions: GlomCon is a new platform which enables nephrologists/ nephropathologists to share their experience and solicit peer-to-peer opinion and expertise. The majority of participants feel it has improved their clinical knowledge and with this impacted and improved patient care. Through this inclusive and open-access initiative, new opportunities for raising awareness and enhancing education in glomerular kidney disease has been created.

FR-OR010

The Use of a Medical Application Improves the Identification and Classification of AKI Rolando Claure-Del Granado,[2,4] Maria F. Iturricha caceres,[4] Etienne Macedo,[1] Ravindra L. Mehta.[3] *[1]UCSD, San Diego, CA; [2]Universidad Mayor de San Simon, School of Medicine, Cochabamba, Bolivia, Plurinational State of; [3]University of California San Diego Medical Center, San Diego, CA; [4]Hospital Obrero #2 - C.N.S., Cochabamba, Bolivia, Plurinational State of.*

Background: The use of mobile devices by health care professionals (HCPs) has transformed many aspects of clinical practice. Mobile devices and apps provide many benefits for HCPs, perhaps most significantly they increase the access to point-of-care tools, which has been shown to support better clinical decision-making and improved patient outcomes. In this study we tested the hypothesis that the use of an app specifically designed for recognition and management of AKI will help HCPs to better identify and classify AKI.

Methods: We included 20 AKI cases from our center that were part of the 0by25 Global Snapshot study report. Twenty clinical vignettes of these patients (including baseline serum creatinine (sCr) and a second sCr that was measure in a 7 day period) were presented to 50 last year medical students and ask two simple questions: 1) Did the patient develop AKI? and 2) To classify the stage of AKI; before and after providing them with an app that was developed for early identification, classification and management of AKI (IRA SLANH app, Island of the Moon® V.1, 2014; Cochabamba-Bolivia). We analyzed if the use of a medical app could improve correct identification and stage classification of AKI.

Results: Before the IRA SLANH app was introduce to the 50 medical students, the mean number of correct answers were 14.7±4.7 with a minimum of 3 correct answers and a maximum of 20 correct answers; and only in 6.7±4.4 of the cases the correct stage of AKI was identified. After the app was presented to the medical students the number of correct answers improved to 20 and in all cases AKI stage was correctly classified. Before the medical app was presented to the medical students, only 22% of them were able to correctly identify all AKI cases, and 0% of them could correctly classify all cases of AKI.

Conclusions: Medical applications are useful tools in the practice of evidence-based medicine at the point of care. The use of a medical application specifically developed for the identification and staging of AKI could play a very important role in early identification and correct classification of AKI potentially allowing earlier intervention with preventive and treatment strategies to reverse kidney injury and improve recovery.

FR-OR011

The Risk of Stroke with Atrial Fibrillation in CKD Patients Manish M. Sood,[4] Ngan Lam,[5] Megan K. Mccallum,[1] Amit X. Garg,[2] Amber O. Molnar.[3] *[1]Institute for Clinical Evaluative Sciences, London, ON, Canada; [2]London Health Sciences Centre, London, ON, Canada; [3]McMaster University, Hamilton, ON, Canada; [4]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [5]University of Alberta, Edmonton, AB, Canada.*

Background: Both atrial fibrillation (AF) and chronic kidney disease (CKD) are known to increase the risk of ischemic and hemorrhagic stroke. However the relative contribution of albuminuria and eGFR level on stroke risk in patients with and without AF remains unknown.

Methods: From a total cohort of 736,666 patients from Ontario, Canada from 2002-2015, 35024 patients developed incident AF with an ACR and eGFR measure within 12 months prior. AF and stroke were determined by hospital diagnostic codes at admission. We used propensity-score matched Cox proportional and Fine and Grey sub-distribution hazards ratio models to determine the time to first event of ischemic, hemorrhagic or any stroke.

Results: After matching to examine exposure to incident AF, 35,024 matched pairs were identified. There were a total of 1781 (5.1%) strokes (85% ischemic) with an average time to stroke for patients with CKD + AF of 2.7 years (+/- 2.4) compared to 3.4 years (+/- 2.4) in patients with no AF. Among the entire cohort the presence of AF was associated with an increased risk of stroke with a HR of 2.93 (95%CI 2.67, 3.2). The crude rate of ischemic, hemorrhagic and any stroke were 16.24 (95%CI 15.43-17.08), 2.79 (95%CI 2.46-3.15) and 19.03 (95%CI 18.15-19.93) with AF and 4.38 (95%CI 4.01-4.78), 0.94 (95%CI 0.78-1.14) and 5.32 (95%CI 4.92-5.76) with no AF per 1000 person-years of follow up, respectively. Higher ACR and lower eGFR were associated with ischemic, hemorrhagic and any stroke compared to those with no AF, eGFR > 90 and ACR < 3 ($p<0.0001$ for all). The adjusted HR of stroke was higher across all categories of ACR and eGFR with the presence of AF compared to those without AF (ACR X stroke interaction $p <0.0001$, eGFR X stroke interaction $p <0.0001$).

Conclusions: CKD patients with atrial fibrillation are at a high risk of total, ischemic and hemorrhagic stroke and this risk is higher with lower eGFR and higher ACR.

FR-OR012

The Association of Beta-Blockers and All-Cause Mortality by eGFR in Patients with Heart Failure Amber O. Molnar,[2] Amit X. Garg,[1] Manish M. Sood.[3] *[1]London Health Sciences Centre, London, ON, Canada; [2]McMaster University, Hamilton, ON, Canada; [3]Ottawa Hospital Research Institute, Ottawa, ON, Canada.*

Background: Congestive heart failure (CHF) and CKD are strongly interrelated and when occurring concurrently, are associated with very high mortality, especially in the elderly. Whether the mortality benefit of beta-blockers (BB) extends to patients with CHF and lower levels of eGFR remains unknown.

Methods: A population-level administrative database study using linked datasets in Ontario, Canada. Incident CHF cases age > 66 years from April 2002 to March 2014 were included. The date of the first prescription for a BB was the date of inclusion (index date). Patients without evidence of a BB prescription were randomly assigned an index date based on the distribution of index dates for those prescribed a BB. Individuals without an eGFR measure within 1 year prior to the index date, or a prior history of kidney or heart transplant or chronic dialysis were excluded. We matched BB users to non-users (1:1) based on age, sex, eGFR grouping, and a high dimensional propensity score. We examined all-cause mortality using Cox proportional hazards models with BB prescription at baseline and as a time-varying covariate.

Results: Results: After matching, a total of 3,574 pairs were identified. By eGFR category, the number of all-cause mortality events in the BB versus the no beta-blocker (NBB) groups were eGFR > 90: BB 44 (12.7%) vs. NBB 188 (38.6%), eGFR 60-90, BB 357 (14.0%) vs. NBB 1352 (22.2%), eGFR 30-60, BB 274 (19.0%) vs NBB 917 (47.7%), eGFR < 30 BB 47 (20.4%) vs. NBB 166 (53%). Examining baseline BB use, there was no mortality benefit with BB usage in lower eGFR categories [eGFR >90: HR 0.67 (0.48-0.94), eGFR 60-90: HR 0.96 (0.85-1.08), eGFR 30-60: HR 0.96 (0.88-1.05), eGFR <30: HR 0.87 (0.68-1.13), eGFR category X BB interaction p=0.225]. When examining time-varying BB use, it was associated with a similar reduction in all-cause mortality across all eGFR categories [eGFR 90: HR 0.56 (0.39-0.79), eGFR 60-90: HR 0.63 (0.55-0.73), eGFR 30-60: HR 0.59 (0.52-0.66), eGFR <30: HR 0.47 (0.33-0.66), eGFR category X beta-blocker interaction p=0.458].

Conclusions: In elderly patients with CHF, BB use was associated with a similar reduction in mortality across all eGFR categories. Our findings suggest that mortality benefits of BB's observed in CHF patients included in randomized trials could be extended to patients with eGFR < 30 not on dialysis.

Funding: Government Support - Non-U.S.

FR-OR013

Assessing the Impact of CKD Progression on Cardiovascular Disease in a Contemporary UK Cohort of 30,222 Diabetics Claudia S. Cabrera. *AstraZeneca R&D, Mölndal, Sweden.*

Background: We evaluated the association between Chronic Kidney Disease (CKD) progression, based on glomerular filtration (eGFR) slope estimates and the risk of cardiovascular disease (CVD) in a contemporary cohort of persons with Type 2 diabetes mellitus (T2DM).

Methods: Incident CKD subjects were selected from a prevalent population of T2DM between Jan 1, 2005 and Dec 31, 2015. Subjects were retrieved from the Clinical Practice Research Data Link (CPRD) in England and followed from CKD diagnosis until event of heart failure (HF), myocardial infarction (MI), ischemic stroke (IS), a composite endpoint including all three event types (MACE plus), mortality, drop out from the database, or end of study. The association between CKD and CVD was estimated using adjusted proportional hazard models (HR 95% CI) in this cohort (n=30,222). The main variables of interest were the updated eGFR slope calculated over multiple overlapping 2 year periods throughout the follow-up time and the updated mean eGFR during these periods with ~ 5 over-lapping slopes/subject and a mean of 11 eGFR values per patient.

Results: The updated eGFR slope predicted CVD outcomes independently of current renal risk (updated mean eGFR) and key risk factors: CVD treatment, smoking, comorbidity, and metabolic risk factors. Both updated mean eGFR (ref ≥60, >30 to 60, ≤30) and the updated eGFR slope (ref ≥3, ≥0 to <3, ≥-3 to <0, ≤ -3) were monotonically associated with MACE plus and HF. Updated eGFR slope decline of ≤- 3 significantly increased the risk of MACE plus (HR 1.45; 95% CI 1.26 - 1.67), HF (HR 1.49; 95% CI 1.27 - 1.76), and MI (HR 1.39; 95% 1.01 - 1.91).

Conclusions: These results indicate that CKD is an independent risk factor for CVD and that rate of progression and cumulative status of CKD elucidate important but distinct aspects of this risk independently of underlying disease such as hypertension and obesity.

Funding: Commercial Support - AstraZeneca R&D Sweden

FR-OR014

Continuation of Statin Therapy Initiated in Pre-ESRD Period and All-Cause and Cardiovascular Mortality after Transition to Dialysis Elvira Gosmanova,[3] Miklos Z. Molnar,[5] Praveen Kumar Potukuchi,[5] Elani Streja,[1] Keiichi Sumida,[2] Kamyar Kalantar-Zadeh,[4] Csaba P. Kovesdy.[5] *[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [2]Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; [3]Stratton VA Medical Center, Albany, NY; [4]University of California Irvine, School of Medicine, Orange, CA; [5]University of Tennessee Health Science Center, Memphis, TN.*

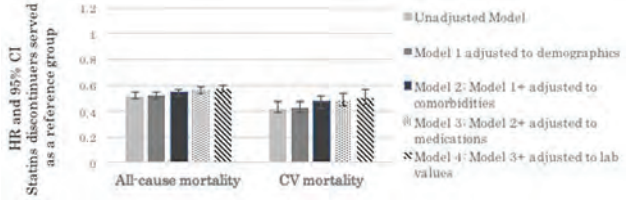
Background: *De novo* statin therapy in ESRD patients failed to demonstrate significant cardiovascular (CV) protection in randomized clinical trials and, therefore, it is not recommended. However, whether continuation of statins from late-stages of non-dialysis dependent CKD to the post-ESRD period is associated with improved all-cause and CV mortality in dialysis patients is unknown.

Methods: We identified 14,939 US veterans transitioning to dialysis between 2007-2011 who were receiving statins during the 1 year prior to dialysis initiation and had adequate adherence, defined as proportion of days covered (PDC) of ≥80%. Subsequently, dialysis patients were characterized as statin continuers (N=5,066) if statin therapy was continued with PDC ≥80% during up to 1 year following dialysis initiation, and statin discontinuers (N=9,874) if statins were stopped or adherence to statins was inadequate (PDC <80%). Associations of statin continuation with all-cause and CV mortality following dialysis initiation was examined using Cox regressions adjusted for demographics, comorbidities, medications, and laboratory parameters.

Results: All-cause and CV mortality rates were 285 [95% CI 279-291]/1000 patient-years and 116 [95% CI 112-121]/1000 patient-years, respectively, during a mean ± SD 2.01±1.38 years of follow-up. Statin continuation after ESRD onset was associated with lower all-cause and CV mortality in unadjusted and various adjusted analyses (figure).

Conclusions: Extension of statin therapy following dialysis transition was associated with reduced all-cause and CV mortality. This data support experts' opinion in the current lipid guidelines that statins started prior to dialysis should be continued after dialysis initiation.

Funding: NIDDK Support



FR-OR015

Incident Atrial Fibrillation and Risk of Subsequent Cardiovascular Events and Mortality: The CRIC Study Nisha Bansal,[5] Dawei Xie,[11] Daohang Sha,[11] Lawrence J. Appel,[3] Rajat Deo,[11] Harold I. Feldman,[11] Jiang He,[7] Kenneth A. Jamerson,[10] John W. Kusek,[6] Steven R. Messe,[11] Sankar D. Navaneethan,[1] Mahboob Rahman,[2] Ana C. Ricardo,[9] Elsayed Z. Soliman,[14] Raymond R. Townsend,[11] Alan S. Go.[4] *[1]Baylor College of Medicine, Houston, TX; [2]Case Western Reserve University, Cleveland, OH; [3]Johns Hopkins Medical Institutions, Baltimore, MD; [4]Kaiser Permanente Northern California, Oakland, CA; [5]Kidney Research Institute, Seattle, WA; [6]NIDDK, Bethesda, MD; [7]Tulane School of Public Health and Tropical Medicine, New Orleans, LA; [9]University of Illinois at Chicago, Chicago, IL; [10]University of Michigan Health System, Ann Arbor, MI; [11]University of Pennsylvania, Philadelphia, PA; [14]Wake Forest University School of Medicine, Winston Salem, NC.*

Background: Atrial fibrillation (AF) is the most common sustained arrhythmia in patients with chronic kidney disease (CKD) and may be associated with poor clinical outcomes. We examined the association of incident AF with the risk of subsequent incident cardiovascular (CVD) events and mortality.

Methods: We studied participants enrolled in the prospective Chronic Renal Insufficiency Cohort (CRIC) Study without AF at baseline. Incident AF was identified by ECGs and physician-adjudicated hospitalizations. Outcomes included: incident heart failure (HF), myocardial infarction (MI), stroke and death after diagnosis of AF. Cox regression models (with time-updated AF) and marginal structural models (MSM, to account for time-dependent confounding) were used to examine the association of incident AF with outcomes, adjusting for demographics, clinical characteristics and ECG measures.

Results: Among 2,814 participants, 288 (9.2%) developed incident AF. During a mean (SD) follow-up of 7.0 (2.1) years, rates of HF, MI, stroke and death were higher in those who developed AF versus those who did not (**Table**). Cox and MSM models demonstrated that incident AF was associated with greater than 4-fold increased risk of subsequent incident HF, MI and death. Cox models also showed a significant association of incident AF with stroke (**Table**). These associations remained robust with additional adjustment for biomarkers of inflammation, cardiac stress and mineral metabolism as well as left ventricular mass, ejection fraction and left atrial diameter.

Conclusions: Incident AF is associated with increased risk of developing subsequent CVD and death in adults with CKD. Further study is needed to determine whether treatment of AF mitigates this risk.

Table. Adjusted* association of incident atrial fibrillation with subsequent incident cardiovascular events and death

*adjusted for age, sex, race, ethnicity, site, diabetes, hypertension, history of cardiovascular disease, eGFR, proteinuria, BMI, tobacco use, physical activity, systolic blood pressure, LDL, HDL, number of anti-hypertensive medication classes, lipid lowering agents, diuretics, warfarin, anti-platelet use, PR duration, RR interval

	Incident Heart Failure			Incident MI			Incident stroke			Death		
	IR (per 100 py), (# events)	Cox model HR (95% CI)	MSM model HR (95% CI)	IR (per 100 py), (# events	Cox model HR (95% CI)	MSM model HR (95% CI)	IR (per 100 py), (# events	Cox model HR (95% CI)	MSM model HR (95% CI)	IR (per 100 py, (# events)	Cox model HR (95% CI)	MSM model HR (95% CI)
No AF	1.86 (256)	ref	ref	0.72 (106)	ref	ref	0.4 (65)	ref	ref	2.21 (415)	ref	ref
Incident AF	8.16 (48)	4.7 (3.4, 6.6)	4.4 (2.9, 6.6)	3.68 (19)	4.6 (2.7, 7.8)	4.5 (2.5, 8.0)	1.40 (10)	3.6 (1.4, 6.1)	1.9 (0.9, 4.3)	11.9 (105)	5.5 (3.7, 4.3)	4.4 (3.4, 5.7)

FR-OR016

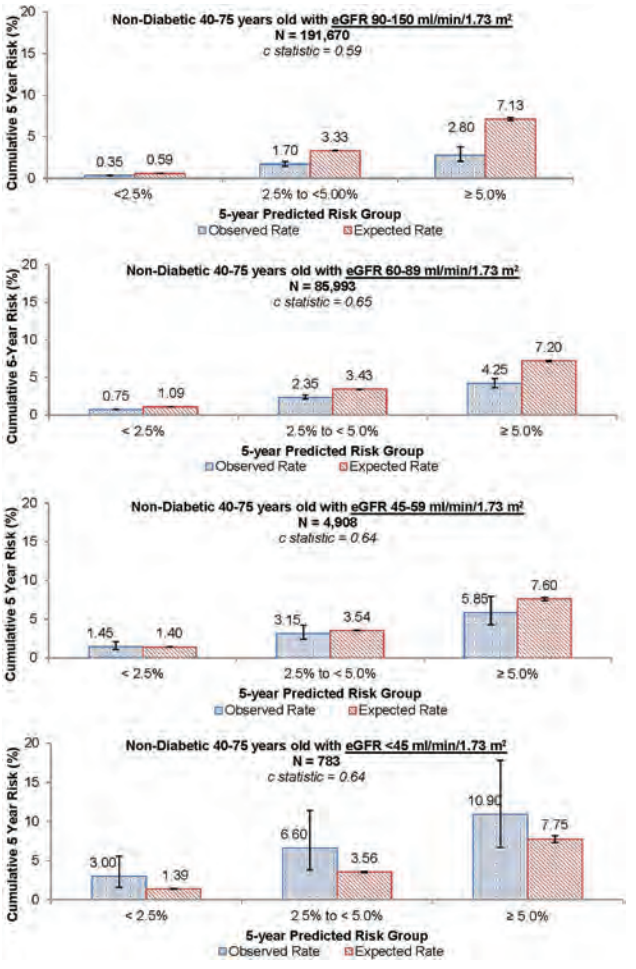
Accuracy of ACC/AHA ASCVD Risk Estimator by eGFR in a Large, Multiethnic Non-Diabetic Population Alan S. Go, Grace H. Tabada, Tracy Y. Jonelis, Sue hee Sung, Jamal S. Rana. *Kaiser Permanente Northern California, Oakland, CA.*

Background: Earlier atherosclerotic cardiovascular disease (ASCVD) prediction equations have limited utility in adults with kidney disease. The ACC/AHA ASCVD Risk Estimator has been recommended to assist with primary prevention planning, but its accuracy varies in contemporary populations and little is known about its performance by level of kidney function. We evaluated its accuracy and discrimination in a large community-based population across the range of eGFR.

Methods: Within Kaiser Permanente Northern California, we identified members age 40-75 years in 2008 who had LDL-C 70-189 mg/dL, no prior ASCVD or lipid-lowering therapy, no diabetes, available eGFR, and full 5-year follow-up. Non-fatal and fatal ASCVD events through 2013 were ascertained from electronic health records using validated algorithms. We compared observed vs. ACC/AHA Risk Estimator-based 5-year risk of ASCVD events by baseline eGFR (90-150, 60-89, 45-59 and <45 ml/min/1.73m^2) with associated c statistics.

Results: In 283,354 non-diabetic adults, mean age was 55 years, 61% women and 32% minorities. Overall, the distribution of 5-year predicted ASCVD risk was <2.5% (55%), 2.5% to <5.0% (21%) and ≧5.0% (24%), with higher proportions of patients at high predicted ASCVD risk with lower eGFR. Going from eGFR 90-150 to 45-59, there was progressively less overestimation of actual 5-year ASCVD risk using the ACC/AHA ASVD Risk Estimator, with underestimation of risk for eGFR <45 (Figure). Discrimination was only modest across eGFR levels (c=0.59-0.65).

Conclusions: Accuracy of the ACC/AHA ASCVD Risk Estimator varies by eGFR level, and recalibration in contemporary, ethnically diverse populations would increase its utility to assist with primary prevention strategy decision-making.



Utility of ACC/AHA ASCVD Risk Estimator by Category of eGFR

FR-OR017

Incident Atrial Fibrillation and the Risk of Subsequent Adverse Outcomes in Patients with a Decreased eGFR David Massicotte-Azarniouch,[7] John Paul Kuwornu,[1] Juan J. Carrero,[2] Ngan Lam,[8] Amber O. Molnar,[4] Deborah Lynn Zimmerman,[5] Megan K. Mccallum,[1] Ron Wald,[6] Amit X. Garg,[3] Manish M. Sood.[5] *[1]Institute for Clinical Evaluative Sciences, London, ON, Canada; [2]Karolinska Institutet, Stockholm, Sweden; [3]London Health Sciences Centre, London, ON, Canada; [4]McMaster University, Hamilton, ON, Canada; [5]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [6]St. Michael's Hospital, Toronto, ON, Canada; [7]Medicine, University of Ottawa, Ottawa, ON, Canada; [8]University of Alberta, Edmonton, AB, Canada.*

Background: The effect of atrial fibrillation (AF) among patients with decreases in eGFR and its subsequent effect on adverse outcomes remain unknown.

Methods: In this population-based retrospective cohort study, we determined the association of AF with congestive heart failure (CHF), myocardial infarction (MI), end stage kidney disease (ESKD) and all-cause mortality in patients with reduced renal function. Among 1,422,978 million adult residents with an eGFR measure < 90 ml/min/1.73m², we identified 93,414 with AF. We used propensity-score matched, competing risk models to determine the risk of CHF, MI and ESKD accounting for the competing risk of mortality. The eGFR level was examined using interaction terms for each adverse outcome.

Results: All adverse events were more frequent in individuals with atrial fibrillation compared to no atrial fibrillation [CHF: AF 9.9% vs. No AF 3.1%, HR 3.88 (95% confidence interval, CI 3.69-4.07)], [ESKD: AF 0.7% vs. No AF 0.4%, HR 2.10 (95%CI 1.89-2.32)], [MI: AF 3.2% vs. No AF 2.0%, HR 1.60(95% CI 1.54-1.67)], [all-cause mortality: AF 21.7% vs. No AF 17.6%, HR 1.32 (95%CI 1.29-1.35)]. The eGFR level was an effect modifier for all outcomes (p<0.05 for eGFR X outcome interaction). The risk of CHF, MI and ESKD were highest within the first 6 months of AF onset.

Conclusions: Incident AF is associated with a high risk of adverse outcomes in patients with an eGFR < 90ml/min/1.73m² and the risk differs by eGFR level. As the risk is highest within the first 6 months after AF diagnosis, therapeutic interventions and monitoring may improve outcomes.

Funding: Government Support - Non-U.S.

FR-OR018

Are RAASi Underused in Moderate to Advanced CKD? Early Findings from CKDopps Roberto Pecoits-Filho,[1] Charlotte Tu,[2] Jarcy Zee,[2] Lindsay Zepel,[2] Brian Bieber,[2] Michelle M. Wong,[2] Friedrich K. Port,[2] Christian Combe,[3,4] Danilo Fliser,[5] Ricardo Sesso,[6] Ichiei Narita,[7] Bruce M. Robinson,[2] Ziad Massy.[8] *[1]Pontificia Universidade Catolica do Parana, Curitiba, Brazil; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]CHU de Bordeaux, Bordeaux, France; [4]Université de Bordeaux, Bordeaux, France; [5]Saarland University Medical Centre, Homburg/Saar, Germany; [6]Escola Paulista De Medicina, Unifesp, Sao Paulo, Brazil; [7]Niigata University, Niigata, Japan; [8]Ambroise Pare University Hospital and Inserm U1018 Eq5, Boulogne Billancourt/ Paris cedex, France. Group/Team: On behalf of CKDopps and CKD REIN investigators.*

Background: Current guidelines support prescription of RAASi for CKD patients (pts) with comorbidities such as diabetes and heart failure (HF). These drugs may be underused, particularly due to hyperkalemia as a side effect of RAASi. We hypothesize that the use of RAASi in advanced CKD is influenced by the presence of hyperkalemia and the use of potassium (K) binders, diuretics, and bicarbonate.

Methods: We used data from CKDopps (2013-2017), a multinational cohort study of pts with eGFR <60 ml/min/1.73m² to describe RAASi prescription patterns by country and patient subgroups. Brazil (BR), Germany (GER), and the US are shown; data from France and Japan are forthcoming.

Results: Among 2,817 pts, ranges by country were: mean age 66-74 years; eGFR <30 69%-74%; HF 17%-19%; diabetes 41-58%; serum potassium ≥5 21-35%; albuminuria 50-69%. RAASi prescription was more common in GER (80%) than BR (66%) and US (54%); less common in CKD stage 5 in all countries; less common with higher serum K in US; and lower with albuminuria in GER and US (Table 1). RAASi use was higher among pts with (vs. without) CHF/diabetes in BR, but only for diabetes in US. Among pts prescribed RAASi, prescriptions of loop or thiazide diuretics were 68-74%; resins were 6% in GER, almost absent in BR and US; and bicarbonate was 6-8%.

Conclusions: RAASi prescription patterns in CKD vary by country, demographic, and clinical characteristics. RAASi may be underused**,** especially in the US where only half were prescribed a RAASi even among pts with strong class-specific recommendations including albuminuria, diabetes, or heart failure. Antihyperkalemia measures, such as dietary restriction, loop diuretics, bicarbonate and K binders may raise RAASi use.

Funding: Commercial Support - Amgen, AstraZeneca, Baxter Healthcare, Kyowa Hakko Kirin, Hexal AG, Janssen, Keryx, Proteon, Relypsa, Roche, Vifor Fresenius Medical Care Renal Pharma, Private Foundation Support

Table 1. Prevalence of RAASi use in patient subgroups

	% prescribed RAASi[a]		
	Brazil	Germany	US
Patients, N	575	1419	823
Overall % RAASi use	66%	80%	54%
Demographics			
Age, years			
<45	74%	70%	51%
45-65	71%	82%	57%
>65	63%	80%	53%
CKD stage			
3a	89%	88%	63%
3b	75%	80%	69%
4	68%	79%	52%
5	42%	67%	32%
Comorbidities			
Coronary artery disease			
No	64%	-	55%
Yes	74%	-	52%
Congestive heart failure			
No	65%	-	56%
Yes	75%	-	46%
Diabetes			
No	65%	79%	50%
Yes	68%	82%	57%
Labs			
Serum Potassium, mEq/L			
<5.0	65%	79%	56%
5.0+	69%	84%	47%
Albuminuria[b]			
Normal to mildly increased	68%	89%	60%
Moderately increased	65%	82%	60%
Severely increased	73%	82%	50%

[a] Renin-angiotensin-aldosterone system inhibitors including ACEi, ARB, direct renin inhibitors and aldosterone antagonists

[b] Urinary albuminuria excretion or equivalent < 30 mg/g: normal or mildly increased; 30-300 mg/g: moderately increased; ≥300 mg/g: severely increased

FR-OR019

Electronic Health Records-Based Computable Phenotype for CKD Diagnosis and Staging Ning Shang,[1] Paul E. Drawz,[2] Robert J. Carroll,[3] Adelaide M. Arruda-Olson,[4] Sumit Mohan,[5] Iuliana Ionita-Laza,[6] Ali G. Gharavi,[5] Chunhua Weng,[1] George Hripcsak,[1] Krzysztof Kiryluk.[5]
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Background: Chronic Kidney Disease (CKD) diagnosis can be made by blood, urine, or imaging tests. This study is to design and evaluate a portable electronic phenotype for automated detection and staging of CKD based on electronic health records (EHR).

Methods: With urine tests data of 68,617 patients from three major health care systems (Columbia, Minnesota, and Vanderbilt), we used machine learning to design a universal albuminuria (A-stage) classifier that accommodates five common methods for quantification of urinary protein excretion, including two urine dipstick scales in combination with urine specific gravity. The performance of the classifier for each type of urine test was assessed by a 10-fold cross-validation procedure against matched UACR data. By integrating our A-stage classification with kidney-related diagnostic codes and serum Cr-based eGFR, a rule-based method, each individual is automatically assigned as CKD case or control. Each CKD case is additionally placed on a "staging grid" of albuminuria (A-stage) by eGFR (G-stage).

Results: The CKD algorithm has been designed, implemented and tested at Columbia University, achieving 100% and 83% PPVs for cases and controls respectively by manual chart review. We then performed external validation at Vanderbilt University and Mayo Clinic; where our electronic phenotype had PPVs of 85% and 98% for cases and controls, respectively. Based on expert review of 265 charts across all three sites, the PPVs to diagnose CKD Stage 1, 2, 3a, 3b, 4, and 5 were 75%, 98%, 95%, 93%, 89%, and 79%, respectively.

Conclusions: Using machine learning and rule-based methods, we developed and validated a portable CKD diagnosis and staging algorithm in a large multi-center effort. The electronic phenotype follows the latest guidelines and can be applied to both pediatric and adult patients. This algorithm can be implemented within any EHR to enable real-time automated detection and staging of CKD, enabling the implementation of stage-specific clinical decision support tools.

Funding: Other NIH Support - National Human Genome Research Institute, National Institutes of Health (Grant U01HG008680)

FR-OR020

Comparison of Estimated versus Measured GFR Decline in the Association with ESRD and Mortality Marieke van Rijn,[4] Karen Leffondre,[7] Marie Metzger,[2] Martin Flamant,[1] Jean-philippe Haymann,[6] Benedicte Stengel,[3] Jan A. van den Brand.[5] *[1]APHP, Paris, France; [2]CESP U1018, INSERM, Villejuif, France; [3]Inserm – DRPA11, Le Kremlin-Bicêtre Cedex, France; [4]Radboud Univ Medical Centre, The Netherlands; Inserm U1018, France, Nijmegen, Netherlands; [5]Radboud University Nijmegen Medical Center, Nijmegen, Netherlands; [6]UPMC, INSERM UMRS 702, AH-HP, Paris, France; [7]University of Bordeaux, Bordeaux, France. Group/Team: On behalf of NephroTest study group.*

Background: There is growing interest for GFR decline as an alternative endpoint for end-stage renal disease (ESRD), but whether using estimated GFR (eGFR) instead of measured GFR (mGFR) is appropriate has not been evaluated. We compared the association of eGFR and mGFR decline with risk for ESRD and mortality in patients with CKD.

Methods: We included 1734 adult patients with CKD stage 1 to 4 who had a total of 4790 simultaneous eGFR and mGFR measurements, over a median 3.3-year follow-up (IQR: 2.0-5.4). mGFR was measured with 51Cr-EDTA renal clearance and CKD-EPI eGFR was based on IDMS-traceable creatinine. We used shared parameter joint models to estimate the association between current value and slope of eGFR or mGFR and ESRD or death, adjusted for baseline age, gender, and albumin to creatinine ratio (ACR).

Results: Patients (mean age 59±15 yrs, 31% women) had a median of 2.0 (IQR 1.0-4.0) visits, a mean mGFR of 43.5 mL/min/1.73m², and a median ACR of 8.0 mg/mmol (IQR: 1.5-46.2). eGFR and mGFR decline was comparable, 1.87 (2.02-1.73) *versus* 1.88 (2.04-1.73) mL/min/1.73m2/year, respectively. HRs for death were similar for both current value and slope of mGFR or eGFR. In contrast, HRs for ESRD were lower when using current value and slope of mGFR than eGFR.

Conclusions: This study shows that the association of GFR slope with mortality is similar whether using eGFR or mGFR, but not that with ESRD. The hazard ratio of ESRD is lower with mGFR than eGFR. Therefore, mGFR decline may be considered as an alternative endpoint for ESRD rather than eGFR in clinical trials.

	HR for death (95% CI)		HR for ESRD (95%CI)	
	mGFR	CKD-EPI eGFR	mGFR	CKD-EPI eGFR
Current GFR (ml/min/1.73m2)	0,98 (0,97 – 0,99)	0,98 (0,97 – 0,99)	0,84 (0,81- 0,87)	0,86 (0,83 – 0,88)
Current GFR slope (ml/min/1.73m2 per year)	0,89 (0,78 – 1,02)	0,89 (0,79 – 0,99)	0,80 (0,66 – 0,97)	0,85 (0,73 – 0,99)
2log ACR (mg/mmol)	1,04 (0,99 – 1,09)	1,05 (1,00 – 1,09)	1,23 (1,14 – 1,33)	1,26 (1,17 – 1,36)

FR-OR021

Plasma Zonulin Levels in Childhood Nephrotic Syndrome (NS) Howard Trachtman,[3] Debbie S. Gipson,[7] Kevin V. Lemley,[1] Jonathan P. Troost,[7] Christian Faul,[6] Debra J. Morrison,[4] Suzanne M. Vento,[2] Judith D. Goldberg,[5] Dong-hyun Ahn.[5] *[1]Children's Hospital Los Angeles, Los Angeles, CA; [2]NYU Langone Medical Center, New York, NY; [3]NYU Langone Med Ctr, New York City, NY; [4]NYU Medical Center, New York, NY; [5]New York University School of Medicine, New York, NY; [6]The University of Alabama at Birmingham, Birmingham, AL; [7]University of Michigan, Ann Arbor, MI.*

Background: Case reports suggest that NS is responsive to dietary modifications including a gluten-free diet (GFD). In celiac disease, zonulin is released from enterocytes after exposure to gliadin, activates protease activated receptor 2 (PAR2), and perturbs the actin cytoskeleton and cell-cell junctions in the gut. PAR2 is present on podocytes and, therefore, zonulin may increase glomerular permeability in NS. We conducted this study to test the hypothesis that plasma zonulin levels are elevated in pediatric patients with NS.

Methods: Plasma specimens collected from patients ≤18 yr old with minimal change disease or FSGS enrolled in the NEPTUNE study, were tested. Clinical and laboratory data were retrieved coincident with the visit when the zonulin level was measured. Samples were available for testing from the 4 or 8 month visit. Plasma zonulin levels were measured by ELISA. Results (mean±SD or median (IQR)) were analyzed by t-test, Wilcoxon, Kruskal-Wallis, or linear regression and considered significant if $P<0.05$

Results: There were 113 patients, 9.5±4.9 yr, 53% male, 42% white, 40% black and 18% other. Disease classification was infrequent relapser in 27%, frequent relapser/steroid dependent 42% and steroid resistant 30%. The mean BP, eGFR, and serum albumin were normal. Urine protein:creatinine (UPC) ratio was 3.9±6.9 (g:g). The plasma zonulin level in NS children was 14.2±6.0 vs 10±2.5 ng/ml in healthy adults ($P<0.01$) and was >3 standard deviations above the mean in 27%. There was a trend toward lower zonulin levels in children with UPC ≥2 vs <2, 12.9(7.4) vs 16.7(8.0) ($P=0.051$). Plasma zonulin levels did not differ by eGFR, disease classification, or BP. Plasma zonulin and serum albumin concentrations were directly correlated, $r=0.24$, $P=0.04$.

Conclusions: The plasma zonulin level was significantly elevated in more than a quarter of children with NS and was unrelated to BP or eGFR. We observed a significant relationship between zonulin values and serum albumin but not proteinuria. There was a trend to lower zonulin levels in children with nephrotic-range proteinuria. Further study is needed to determine the relationship between plasma zonulin levels and proteinuria and to test whether the plasma zonulin level can be used to predict response to a GFD in children with NS.

Funding: NIDDK Support

FR-OR022

Rhinovirus-Induced Defect of CTLA-4 Expression Plays a Critical Role in Relapse of Childhood Idiopathic Nephrotic Syndrome Ching-Yuang Lin.
China Medical University Children's Hospital, Taichung, Taiwan.

Background: The onset of minimal change disease (MCD) in idiopathic nephrotic syndrome(INS) is often preceded by an upper respiratory tract infection(URI) such as human rhinoviruses (HRVs). Transient spontaneous remission of nephrotic syndrome after intercurrent measles infection has also been reported. Upregulation of CD80 with an altered podocyte shape has been reported to result in proteinuria. CTLA-4 is the natural inhibitor of CD80, and the suppressive function of Tregs is dependent on CTLA-4. The aim of this study was to investigate whether an increase in systemic $CD4^+$ $CD80^+/CD4^+$ $CTLA\text{-}4^+$, Th17/Treg ratio and podocyte CD80/CTLA-4 ratio after HRV infection would result in a higher urinary CD80/CTLA-4 ratio and proteinuria.

Methods: Of the 123 URI were proven to be caused by HRV, Thirty-two patients with relapsing INS and biopsy-proven MCD were enrolled. Peripheral blood mononuclear cells (PBMCs) from the INS patients and six age-matched normal controls were exposed to either one infectious unit/cell of HRV or measles virus for 48 h. The surface expressions of CD80, CTLA-4, IL-17 and FoxP3 in the PBMCs and cultured podocytes were evaluated by flow cytometry.

Results: Systemic $CD4^+$ $CD80^+/CD4^+$ $CTLA\text{-}4^+$ T cell and Th17/Treg ratios significantly increased during the nephrotic phase and returned to normal during remission. The urinary CD80/CTLA-4 ratio increased significantly during relapse and decreased in remission. Histologically, strongly positive staining of CD80 and weak staining of CTLA-4 were found in all renal biopsy specimens of the patients with MCD. In vitro HRV infection on PBMCs of relapsing INS patients induced a significantly higher CD80/CTLA-4 expression than in the controls. In contrast, in vitro measles infection caused an slightly increase in CD80 and a 6-fold increase in CTLA-4 on $CD4^+$ T cells and significantly down-regulated the $CD4^+$ $CD80^+/CD4^+$ $CTLA\text{-}4^+$ T cell ratio in the PBMCs of the normal controls. It was also upregulated CD80 and down regulated CTLA-4 in cultured podocyte treated with HRV.

Conclusions: Systemically high levels of the $CD4^+$ $CD80/CD4^+$ CTLA-4 ratio in PBMCs induced by HRV infection in patients with MCD may result in an enhanced Th17/Treg ratio, thereby leading to altered endogenous podocyte autoregulation of the CD80/CTLA-4 ratio and the development of proteinuria.

FR-OR023

Tissue Transcriptomic Profiles Perform Similarly to Clinical and Pathology Features for Nephrotic Syndrome Outcome Prediction Laura H. Mariani, Huateng Huang, Brad A. Godfrey, Matthias Kretzler, Yuanfang Guan. *University of Michigan, Ann Arbor, MI.*

Background: Clinical parameters do not accurately predict outcomes in nephrotic syndrome (NS). Traditional statistics are not well equipped to identify predictors from many potential parameters across the genotype-phenotype continuum. Machine learning techniques have been developed to address this, but have not been widely applied to NS.

Methods: NEPTUNE is a cohort study of NS patients enrolled at the time of biopsy. Clinical data, pathologic features and kidney tissue genome wide mRNA expression levels are collected. Elastic net regularization was used to build Cox proportional hazards models for time to (1)composite of ESRD/40% eGFR decline and (2)complete remission (UPCR <0.3mg/mg) using different sets of predictors: clinical+pathology data, gene expression modules, all variables. In 200 bootstrap replicates, models were built in training sets and time-dependent area under the curve (tAUC) was computed in test sets. Paired t-test of mean tAUCs across replicates was used to compare prediction accuracy between models.

Results: 432 patients were in clinical/pathology models [mean age 33(21), eGFR 83(36), UPCR 3.7(5.5), 41% male, 27% black, 18% MN, 31% MCD, 13% IgA, 38% FSGS]. 198 patients in gene expression models had similar characteristics. Elastic net models had higher tAUC than simple cox models(Table). Signifcant predictors are shown(Fig).

Conclusions: Machine learning elastic net models had highest accuracy and identified novel predictors. Tissue mRNA expression modules were more accurate predictors of composite outcome than routine clinical parameters and may better capture the underlying biologic heterogeneity of NS.

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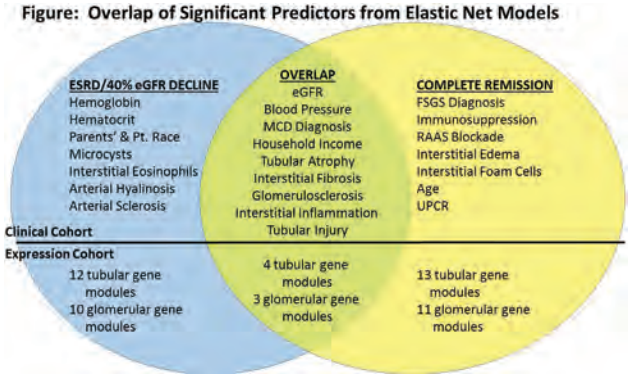
Model Comparison of Prediction Accuracy

Cohort	Model (p-value comparison is default model)	tAUC Composite	tAUC Complete Remission
Clinical Cohort	Simple Cox Model (Default: demographics, eGFR, UPCR)	0.68	0.71
	Elastic Net Clinical and Pathology	0.76 (p=0.02)	0.73 (p<0.01)
Gene Expression Cohort	Elastic Net Clinical and Pathology (Default)	0.73	0.71
	Elastic Net Gene Expression Modules	0.75 (p<0.01)	0.70 (p=0.03)
	Elastic Net Clinical, Pathology, Gene Expression Modules*	0.77 (p<0.01)	0.72 (p<0.01)

*Composite:14 clinical, 7 pathology, 14 modules; Remission: 27 clinical, 2 pathology, 24 modules

Figure: Overlap of Significant Predictors from Elastic Net Models



FR-OR024

Response to Second-Line Immunosuppressive Treatments in Genetically Stratified Steroid-Resistant Nephrotic Syndrome Ethan S. Sen,[1,2] Agnieszka Bierzynska,[1] Gavin I. Welsh,[1] Moin Saleem.[1,2] *[1]University of Bristol, Bristol, United Kingdom; [2]Bristol Royal Hospital for Children, Bristol, United Kingdom.*

Background: Steroid-resistant nephrotic syndrome (SRNS) is a heterogeneous condition with significant numbers of patients progressing to end-stage renal failure. Response to second-line immunosuppression is variable. This study aimed to evaluate effectiveness of second-line treatment according to genetic aetiology and pattern of steroid resistance.

Methods: Paediatric patients with SRNS were recruited into the United Kingdom Renal Registry. We have previously reported whole exome sequencing of these patients (Bierzynska et al. *KI* 2017;91:937-947). The current study included subjects from this group with available data on response to immunosuppression. Complete response (CR) was defined as urine protein:creatinine ratio (PCR) < 20mg/mmol or negative/trace dipstick proteinuria within 6 months of starting therapy. Partial response (PR) was PCR > 20mg/mmol or dipstick ≥ 1+ but plasma albumin > 25g/L.

Results: Of 177 genetically-sequenced patients, 140 (72 male, median age at onset 4.4 years, 80 FSGS on first biopsy) received 298 second-line medications. These included ciclosporin in 64%, tacrolimus 51%, cyclophosphamide 33%, mycophenolate mofetil 29% and rituximab 27%. In 21 monogenic patients (33 treatments), overall CR was 9.1% and PR was 36.4% compared with 31.4% and 25.2% respectively in 119 non-genetic patients (242 treatments). Within the non-genetic group, among 92 patients with presumed or primary steroid resistance (SR) (178 treatments), overall CR was 27.0% and PR was 26.4% compared with 43.3% and 21.7% respectively in 25 patients with secondary SR (60 treatments). Fifteen patients suffered post-transplant disease recurrence among whom pre-transplant CR and PR were both 5.9% (34 treatments). When considering only first immunosuppressive treatments in non-genetic patients, there was CR to ciclosporin in 36.5% (19/52), to tacrolimus in 33.3% (9/27) and to cyclophosphamide in 11.5% (3/26).

Conclusions: CR occurred most frequently in patients with secondary SR, followed by non-genetic primary SR and then patients with genetic disease. Subjects retrospectively identified as having circulating factor disease based on post-transplant recurrence had a particularly poor response to immunosuppression.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-OR025

The Effectiveness of a Short-Term Steroid Regimen for Adult Steroid Sensitive Nephrotic Syndrome Takaya Ozeki, Takayuki Katsuno, Sawako Kato, Yoshinari Yasuda, Tomoki Kosugi, Naotake Tsuboi, Shoichi Maruyama. *Nagoya University Graduate School of Medicine, Nagoya, Japan.*

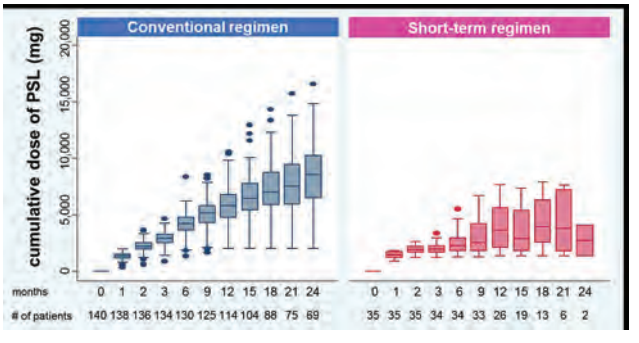
Background: In pediatric patients with steroid sensitive nephrotic syndrome, recent trials have revealed that 2 months short-term steroid regimen (STSR) is not inferior to the extending steroid course. However, the optimal duration of the initial steroid therapy for adult patients remains unclear.

Methods: Adult MCD or FSGS cases (n=35) who had started STSR from Jan. 2015 through Jun. 2016 were included in this study. Control MCD patients (n=140) who were treated with conventional regimen were also enrolled from our retrospective cohort. All patients fulfilled the criteria below: biopsy proven MCD or FSGS, over 20 years old, first time episode of nephrotic syndrome, and complete remission achieved within 4 weeks. The detail of STSR was as below; (1) prednisolone started 0.8-1.0 mg/kg/day as initial dose and continued for 4-6 weeks. (2) reduced to 0.5-0.6 mg/kg/alternative day and continued for 4 weeks. STSR cases were compared with the control patients who were treated with conventional regimen.

Results: Throughout the observation period (median, 469 days), 23 (65.7%) of 35 STSR patients developed at least one relapse. In survival analysis, STSR associated with earlier first relapse (p<0.001, logrank test) but not with frequent relapse (p=0.21, logrank test). Among STSR group, none had symptom of adrenal insufficiency. The cumulative steroid doses during observational period were significantly smaller in patients with STSR than those with conventional regimen (Figure).

Conclusions: Although the timing of the first relapse in STSR group was earlier compared with conventional group, there was no difference in the occurrence of frequent relapse. Furthermore, STSR achieved lower steroid exposure. The present study suggest that STSR could be an effective treatment option for adult steroid sensitive MCD or FSGS.

Funding: Commercial Support - Alexion, Asahi Kasei Pharma, Astellas Pharma Inc, Baxter, Bristol-Myers Squibb, Chugai Pharmaceutical Co. Ltd, Daiichi Sankyo Co., Ltd, Kyowa Hakko Kirin Co. Ltd, Mercj Sharp and Dohme, Mitsubishi Tanabe Pharma Co, Mochida Pharmaceutical Co. Ltd, Novartis Pharma, Otsuka Pharmaceutical Co. Ltd, Pfizer Japan Inc, Sanwa Kagaku Kenkyusho Co. Ltd, Sumitomo Dainippon Pharma Co. Ltd, Takeda Pharmaceutical Co. Ltd, Teijin Pharma Ltd, Torii Pharmaceutical Co. Ltd



FR-OR026

Long-Term Effect of Sparsentan (SPAR), a Dual Angiotensin and Endothelin Receptor Antagonist, on Proteinuria in Patients with Primary FSGS: Interim Analysis of the DUET Trial Howard Trachtman,[3] Ivan Rychlik,[1] Robert M. Haws,[2] Carla M. Nester,[5] Alessia Fornoni,[6] Radko Komers.[4] *[1]Charles University, 3rd Faculty of Medicine, Prague 10, Czech Republic; [2]Marshfield Clinic, Marshfield, WI; [3]NYU Langone Med Ctr, New York City, NY; [4]Retrophin, Inc., Portland, OR; [5]University of Iowa, Iowa City, IA; [6]University of Miami, Miami, FL.*

Background: In the ongoing DUET trial, SPAR (200, 400, 800 mg/day) resulted in greater reduction in proteinuria vs. irbesartan (IRB, 300 mg/day) over the 8-week double-blind (DB) period. Generally, SPAR was safe and well tolerated. After DB, patients

were treated in an open-label extension (OLE). We present interim results of OLE for sustainability of the antiproteinuric effect of SPAR.

Methods: In the OLE, patients [biopsy-proven FSGS, baseline (BL) urine protein/creatinine ratios (Up/C)>1g/g, age 8-75 y (U.S.), eGFR>30 ml/min] randomized to SPAR continued (SPAR:SPAR), and those randomized to IRB received SPAR (IRB:SPAR). Up/C, eGFR and blood pressure (BP) were measured every 12 weeks to Week 48 and compared to BL (Week 0 for SPAR:SPAR; Week 8 for IRB:SPAR).

Results: Results of patients with available Up/C are below. In SPAR:SPAR, SPAR resulted in rapid reduction of Up/C and BP which remained sustained over 48 weeks, while eGFR remained stable. In IRB:SPAR group, transition to SPAR resulted in a significant reduction in Up/C (Week 16), which was sustained until the end of follow-up. In contrast to SPAR:SPAR, IRB:SPAR was associated with mild, temporary, but significant reduction in eGFR, while SPAR-induced BP reduction was less apparent.

Conclusions: SPAR was well tolerated and achieved a sustained antiproteinuric effect in primary FSGS with early BP reduction and stable eGFR over 48 weeks. Transition to SPAR from IRB led to significant, sustained reduction of proteinuria and a temporary, mild reduction in eGFR without long-term impact on BP.

Funding: Commercial Support - Retrophin, Inc.

	Week	N at Baseline	0	4	8	16	24	36	48
SPAR:SPAR	Median Up/C (g/g)	50	2.7	1.7*	1.6*	1.7	1.0*	0.9*	0.7
	eGFR (ml/min)†	50	70±38	68±35	69±34	66±32	65±35	65±33*	64±37
	Systolic BP (mmHg)†	50	132±11	119±11*	120±13*	121±11*	121±13*	121±15*	121±14*
IRB:SPAR	Median Up/C (g/g)	33			2.3	1.8*	1.9	1.7*	1.7
	eGFR (ml/min)†	33			76±44	72±44*	71±42*	77±38*	84±43
	Systolic BP (mmHg)†	33			124±13	121±16	117±12*	119±12	118±11

†Data noted as mean±SD; *p<0.05 vs. BL

FR-OR027

Diagnosing Recurrent FSGS Using a Novel Cell-Based Assay Pankaj Srivastava,[1] Ehtesham Arif,[2] Ashish K. Solanki,[2] Kenneth Kwon,[2] Michael G. Janech,[2] Deepak Nihalani.[2] *[1]MEDICAL UNIVERSITY OF SOUTH CAROLINA, CHARLESTON, SC; [2]Medical University of South Carolina, Charleston, SC.*

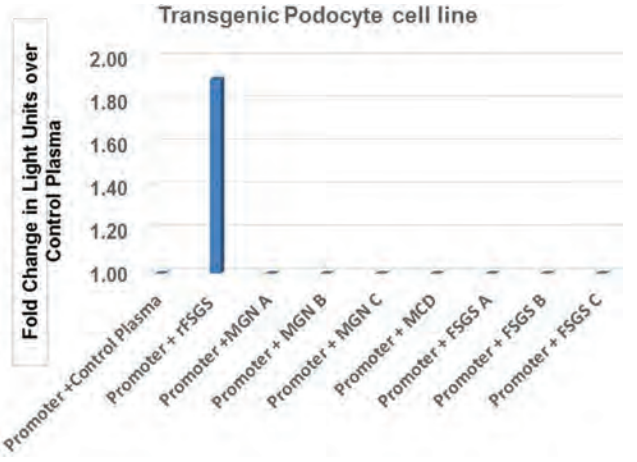
Background: Here we report a novel human podocyte cell-based assay that will serve as a non-invasive diagnostic clinical tool to detect rFSGS (recurrent focal and segmental glomerulosclerosis), which provides rapid and accurate identification of rFSGS patients. The concepts and approaches demonstrated in this proposal are widely applicable in designing assays for other forms of FSGS (or ESRD) whose diagnosis and treatment options remains inadequate. This assay is aimed at specifically diagnosing rFSGS to avert the ineffective renal transplant in FSGS patients.

Methods: As a first step, we identified rFSGS responsive genes by mRNA profiling of human podocytes treated with plasma derived from human rFSGS and control patients, which also induced significant alterations to podocyte actin cytoskeleton partially mimicking the disease processes. Two unique candidate genes (**proprietary information**) based on profiling data from control, non-FSGS and rFSGS patients were selected. In second step, the promoter regions for these genes were cloned into a promoterless reporter vector and transduced into podocytes to generate two stable podocyte cell lines, where expression of reporter was under the control of these promoters. This assay allowed us to measure plasma-induced increase in luminescence in these cells.

Results: Remarkably, both cell lines showed similar results, where only rFSGS patient plasma showed ~2-fold induction, whereas no induction was observed with plasma from other nephropathies including minimal change disease (MCD), membranous glomerulonephritis (MGN) and FSGS (Fig1).

Conclusions: Multiple centers within the country including CureGN and NEPTUNE have been solicited to analyze many rFSGS and non-rFSGS patient plasma using this assay and studies are being planned for conducting clinical trials to utilize its full diagnostic potential.

Funding: NIDDK Support



FR-OR028

IgM Bound to the Surface of T Cells: A Novel Prognostic Marker of Steroid Dependence in Idiopathic Nephrotic Syndrome Manuela Colucci, Francesco Emma, Marina Vivarelli. *Bambino Gesù Children's Hospital - IRCCS, Rome, Italy.*

Background: The pathogenesis of non-genetic forms of idiopathic nephrotic syndrome (INS) is unknown, but the therapeutic success of rituximab suggests a role of B cells and possibly immunoglobulins. During the characterization of the T and B cell phenotype of INS patients pre-rituximab, we observed an unexpected presence of IgM on the surface of T lymphocytes of some patients. Therefore, we investigated the role of IgM on the T cell surface of patients with INS.

Methods: We evaluated by FACS analysis the presence of IgM on the surface of T lymphocytes (T-cell IgM intensity) in 103 healthy donors (HD, 78 adults and 25 children) and 113 INS pediatric patients at onset (44 patients) or subdivided between steroid-sensitive (SSNS, 28) and steroid-dependent (SDNS, 41) patients, in relapse or in remission. We compared T-cell IgM intensity with other predictive parameters of response to steroid treatment and explored *in vitro* the mechanism responsible for this unexpected finding and its potential pathogenic role.

Results: At disease onset (before treatment) 34% patients showed an intense presence of IgM on the surface of T cells as compared to HD, and individuals with higher T-cell IgM intensity showed a significantly increased risk of relapse by Log Rank test ($p<0.03$). Furthermore, T-cell IgM intensity discriminated between SDNS and SSNS patients by ROC analysis (AUC, 0.85; $p<0.001$). *In vitro*, serum IgM from INS patients bound healthy T cells more than serum IgM from HD ($p<0.001$) and showed a reduced sialylation of their N-linked glycan residues, more evident in the steroid-dependent group. Commercially available desialylated IgM bind to T cell surface and fail to be internalized, causing elevated T-cell IgM intensity. Interestingly, whereas commercially available sialylated IgM inhibit the induction of T-cell activation and proliferation, desialylated IgM fail to exert this immunomodulatory effect, reduce the T-cell response to steroid inhibition and allow production of T-cell-derived podocyte damaging factors.

Conclusions: The presence of IgM on T cells may be a prognostic marker of steroid dependence in INS at disease onset. Desialylated IgM in some INS patients may bind to T cell surface and contribute to T cell dysregulation, possibly playing a role in INS pathogenesis.

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FR-OR029

Development and Validation of an EHR-Based Computable Phenotype to Rapidly Identify Glomerular Disease in Large Populations Michelle Denburg,[2] Charles Bailey,[2] Hanieh Razzaghi,[2] Danielle Soranno,[3] Ari Pollack,[4] Donna J. Claes,[5] Vikas R. Dharnidharka,[6] William E. Smoyer,[7] Michael J. Somers,[8] Joshua Zaritsky,[9] Joseph T. Flynn,[4] Mark Mitsnefes,[5] Maryjane Benton,[2] Laura H. Mariani,[10] Christopher B. Forrest,[2] Susan L. Furth.[2] *[2]The Children's Hospital of Philadelphia, Philadelphia, PA; [3]Children's Hospital Colorado, Aurora, CO; [4]Seattle Children's Hospital, Seattle, WA; [5]Cincinnati Children's Hospital, Cincinnati, OH; [6]Washington University School of Medicine, St Louis, MO; [7]Nationwide Children's Hospital, Columbus, OH; [8]Children's Hospital, Boston, MA; [9]Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE; [10]University of Michigan, Ann Arbor, MI.*

Background: The objective of this study was to develop and validate a computable phenotype algorithm to identify all patients with glomerular disease (GD) using PEDSnet, a pediatric clinical research network (CDRN) that aggregates and standardizes electronic health record (EHR) data on >5 million children from multiple pediatric health systems.

Methods: A systematic review of EHR data from 231 patients with GD seen at the Children's Hospital of Philadelphia (CHOP) from April-December 2013 was used to develop, iterate, and validate a computerized algorithm comprised of Systematized

Nomenclature of Medicine (SNOMED) diagnosis codes, kidney biopsy and transplant procedure codes, and pediatric nephrologist encounters. The algorithm identified 6138 cases of GD from 7 PEDSnet institutions. For validation, non-cases were defined as patients with ≥3 pediatric nephrologist encounters (n=42,186). Random samples of cases (n=694) and non-cases (n=697) were evaluated at each site using a standardized chart review form, and with the reviewer blinded to case status.

Results: When first implemented at CHOP, the computable phenotype identified GD with a sensitivity (SENS) of 100%, specificity (SPEC) of 93%, positive predictive value (PPV) of 92%, and negative predictive value (NPV) of 100%. When implemented across 7 health systems in PEDSnet, the performance characteristics were: SENS 97%, SPEC 80%, PPV 76%, and NPV 97%. One SNOMED code contributed considerably to the false positives, and refining the algorithm to exclude it as a qualifying code improved performance: SENS 96%, SPEC 87%, PPV 83%, and NPV 97%. The most common biopsy-based diagnoses were focal segmental glomerulosclerosis (18%), minimal change disease (17%), lupus nephritis (16%), and IgA nephropathy (13%). The most common non-biopsy diagnosis was nephrotic syndrome (41%).

Conclusions: We developed and validated an EHR-based computerized algorithm that identifies virtually all patients with GD within the PEDSnet CDRN. This method for rapid cohort identification is critcal for population-based comparative effectiveness and outcomes research in GD and other rare diseases across large health system populations.

Funding: NIDDK Support, Commercial Support - Mallinckrodt

FR-OR030

Mobile Text Messaging for Disease Activity, Stressors, and Treatment Adherence Monitoring in Pediatric Nephrotic Syndrome

Chia-Shi Wang,[1] Jonathan P. Troost,[2] Larry A. Greenbaum,[1] Tarak Srivastava,[3] Keisha L. Gibson,[4] Howard Trachtman,[5] Emily G. Herreshoff,[2] Debbie S. Gipson.[2] *[1]Emory University, Atlanta, GA; [2]University of Michigan, Ann Arbor, MI; [3]Childrens's Mercy Hospital, Kansas City, MO; [4]University of North Carolina Kidney Center, Chapel Hill, NC; [5]NYU Langone Med Ctr, New York City, NY. Group/Team: cNEPTUNE Working Group*.

Background: There is limited information on the role of medication adherence or infectious/other stressors on the response to corticosteroids (IST) or risk of relapse in childhood nephrotic syndrome (NS). Mobile text messaging (SMS) technology may capture the impact of these factors on childhood NS disease course.

Methods: SMS data were collected on incident pediatric NS patients enrolled in the Nephrotic Syndrome Study Network (NEPTUNE) within 30 days of IST initiation. Parents or patients ≥12 years old responded to daily messages on the results of their urine protein testing and weekly messages on the presence of stressors (infections, allergies, or other) and adherence to NS medications. Non-adherence was defined as self-/parent-report of not taking prescribed NS medications in the first week of SMS. Time to remission was described using Kaplan-Meier method, stratified by adherent/non-adherent groups. Stressors were examined for relationship to disease relapses within a 7 day window via Chi-squared test.

Results: 69 pediatric NS patients were included in this analysis. Response rate to messages was 95%. Median follow-up was 364 days. 52 (76%) patients reached complete remission during follow-up. Among those who remitted, 25 (48%) later relapsed, with 47 relapse events. Median time to remission was 7 days among adherent patients and 34 days among non-adherent patients (Figure; p=0.01). The frequency of stressor occurrence in the week prior to relapse did not differ from other weeks while a patient was in remission (6/47 (13%) vs. 171/1,641 (10%) *p*=0.63).

Conclusions: Mobile text messaging was an effective method to monitor disease activity and adherence in childhood NS. Non-adherence to medications was associated with a longer time to remission. Allergies, infections, or other stressors were not found to be associated with disease relapse.

Funding: NIDDK Support

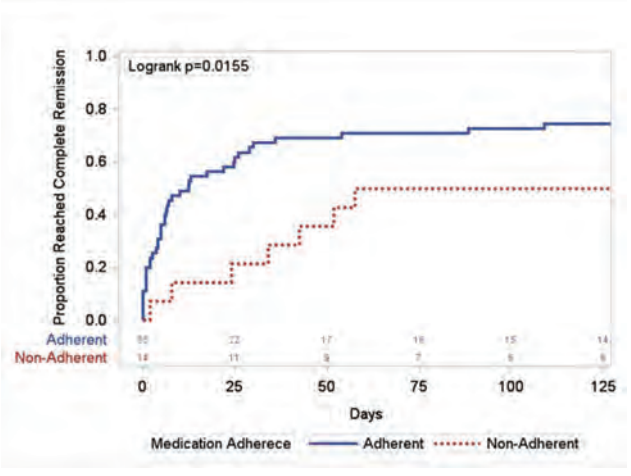

FIGURE. Time to remission among incident pediatric NS patients: adherent vs. non-adherent to medications.

FR-OR031

Conserved Transcriptional Changes in Drosophila and Mouse Models of APOL1 Nephropathy

Zhe Han,[1,2] Yulong Fu,[1] Peng Zhang,[1] Jun-yi Zhu.[1] *[1]Children's National Health System, Washington, DC; [2]Dept. of Pediatrics, George Washington University, Washington, DC*.

Background: African Americans are at higher risk for developing chronic kidney diseases due to APOL1 risk alleles (RA), but the mechanism remains unclear. Expression of APOL1-RA in both the fly nephrocytes (a cell type similar to human podocytes) and the mouse podocytes led to cellular toxicity and renal disease phenotypes, but whether APOL1-RA induces similar transcriptional changes in kidney cells across different species is unknown.

Methods: We performed RNA-seq analysis for Drosophila nephrocytes with APOL1-G0, G1 or G2 expression, and compared the results with the recently published RNA-seq data from mouse kidney with induced expression of APOL1-G0, G1 or G2 in podocytes. Significant number of common target genes were identified. We characterized these genes into different groups based on molecular function and biological processes. Using the fly APOL1 model together with nephrocyte-specific gene knock down, we tested these common target genes of APOL1-RA for genetic interaction. We also examined the expression level changes of some common target genes in human patient samples.

Results: We found strikingly similar transcriptional profile changes in the genes that are dramatically up- or down-regulated from the RNA-seq analysis of the fly and mouse APOL1 nephropathy models. Among the significantly up-regulated genes in both fly nephrocytes and mouse podocytes are genes involved in gluconeogenesis, oxidation-reduction process, proton transport and cell adhesion. The most down-regulated common target genes are involved in glycogen biosynthesis, fatty acid metabolic process, cell trafficking, and mitochondria coenzymes. Genetic interaction assays demonstrated that knocking down of many common down-regulated genes in APOL1-RA expressing nephrocytes made the phenotype worse, whereas knocking down some of the up-regulated common target genes could partially rescue the nephrocyte phenotype caused by APOL1-RA. We found similar transcriptional changes for some common target genes in human APOL1 nephropathy patient samples.

Conclusions: Our findings suggest that the fly and mouse APOL1 nephropathy models share highly similar transcriptional profile changes, and some of these changes can be found in human patients, indicating conserved APOL1 toxicity mechanism in flies, mice and humans. We also showed that some common target genes of APOL1-RA could be used as potential therapeutic targets.

Funding: NIDDK Support

FR-OR032

Rare Exonic Variants in Idiopathic Nephrotic Syndrome

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Background: Idiopathic nephrotic syndrome (NS) is a major cause of end stage renal disease and the molecular diagnosis in the majority of drug-resistant and hereditary forms remains unknown.

Methods: We performed whole exome sequencing in 310 patients with idiopathic NS from 259 independent families. 116 (44%) of these cases were familial and 143 (56%) were sporadic. A case-control exome-wide collapsing analysis for rare functional variants (i.e. burden tests) was performed, comparing 259 index affected by familial or sporadic idiopathic NS with 6,905 controls.

Results: We identified diagnostic or likely pathogenic mutations in 28 cases (10.8%; 15.5% of familial 7.0% of sporadic NS): these included variants in *INF2*, *WT1*, *LMX1B*, and *TRPC6*. To identify novel susceptibility genes for NS we conducted a rare variant collapsing analysis comparing 259 cases and 6,905 controls. The analysis yielded 25 genes at a p-value $<2.5\times10^{-3}$ with minimal genomic inflation. Among these top-ranking signals, we identified 6 genes implicated in Mendelian forms of NS or structural kidney disease: *TRPC6* (rank 3; $p=2.01\times10^{-4}$; OR 12.1); *COL4A3* (rank 7; $p=5.39\times10^{-4}$; OR 6.98); *UMOD* (rank 17; $p=1.53\times10^{-3}$; OR 19.9); ACE (rank 18; $p=1.53\times10^{-3}$; OR 7.0); *LMX1B* (rank 19; $p=1.53\times10^{-3}$; OR 19.9); and *WT1* (rank 24; $p=2.39\times10^{-3}$; OR 15.9). Aggregate analysis of 12 known genes involved in adult-onset NS identified qualifying variants in 30 (11.6%) cases and 152 (2.2%) controls (OR 5.8, $p=1.6\times10^{-12}$). The estimated fraction of disease explained by variants at these genes was 9.4%, similar to that explained by variants identified by prioritization, expert inspection, and segregation tests.

Conclusions: Rare variants collapsing analysis represent a powerful approach to identify known and novel monogenic forms of NS in absence of large pedigrees or segregation data, and holds promises to help dissecting the complex genetic architecture of NS.

Funding: Other U.S. Government Support

FR-OR033

Connectivity Mapping in Experimental Alport Syndrome Identifies Lysine Deacetylase Inhibition as a Potential Therapy Vanessa R. Williams,[2] Ana Konvalinka,[1,2] Xuewen Song,[1] Rohan John,[1,2] York P. Pei,[1,2] James W. Scholey.[2,1] *[1]University Health Network, Toronto, ON, Canada; [2]University of Toronto, Toronto, ON, Canada.*

Background: Alport syndrome (AS) is a hereditary progressive nephropathy caused by mutations in type IV collagen genes. Currently there are few effective therapies for AS. We applied a drug repurposing strategy based on gene expression to identify a novel treatment.

Methods: Wild-type (WT) and *Col4a3*$^{-/-}$ (KO) mice on a 129/SvJ background were studied. Global RNA expression profiling was performed on whole kidney cortex at 4 and 7 weeks of age. Differential gene expression was determined with Significance Analysis of Microarrays (SAM). A disease progression signature was generated and then subsequently used to query the Connectivity Map (CMAP). CMAP identified vorinostat, a lysine deacetylase inhibitor, as a potential treatment. KO mice were treated with vorinostat at a dose of 50 mg/kg/day in DMSO by oral gavage from 4 to 7 weeks of age. DMSO-treated KO mice served as the control group. Mice were sacrificed at 7 weeks of age for analysis of kidney structure, function, inflammation, and fibrosis. Separate groups were followed out to 12 weeks of age.

Results: Pilot studies showed that vorinostat increased the acetylation of lysine in the kidney. Vorinostat led to a significant increase in survival (n = 19/group). This effect was associated with a trend toward decreased mean values in serum creatinine and urinary protein excretion rates that did not reach statistical significance (n = 6-10/group). There was no effect of vorinostat treatment on glomerulosclerosis scores. mRNA for the cytokines *Ccl2*, *Il6*, *Cxcl2* were reduced in cortical tissue from treated animals (n = 6/group). Western blot analysis showed that vorinostat lowered α-SMA expression in kidney cortex. This was associated with a trend toward decreased urinary excretion rates of TGF-β1. The urinary excretion rate of NGAL, a marker of tubular injury, was significantly reduced by vorinostat treatment.

Conclusions: CMAP can be used to identify new treatments for kidney disease based on expression profiling. Vorinostat was identified by CMAP analysis. We found that it extended the lifespan of KO mice but had modest effects on kidney function. It did not impact on glomerular injury but reduced kidney inflammation and excretion of a tubular injury marker. Future studies will provide more insight into the role of lysine acetylation in the progression of AS nephropathy.

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FR-OR034

Glomerular and Tubulointerstitial eQTLs of Patients with Nephrotic Syndrome R Putler, Xiaoquan Wen, Matt G. Sampson. *University of Michigan, Ann Arbor, MI. Group/Team: NEPTUNE.*

Background: Using intrarenal mRNA expression as a molecular phenotype in expression quantitative trait loci (eQTL) studies of nephrotic syndrome (NS) can lead to discovery of transcripts under significant genetic control, reveal novel NS-related biology, and identify loci associated with clinically meaningful outcomes. To describe the intrarenal eQTL landscape of NS, we paired whole genome sequencing with glomerular (GLOM) & tubulointerstitial (TI) transcriptomes from patients in the Nephrotic Syndrome Study Network (NEPTUNE).

Methods: NEPTUNE is a prospective, longitudinal study of NS enrolling affected adults and children receiving a clinically indicated biopsy. Rich demographic, clinical, and genomic data is collected and GLOM & TI transcriptomes are derived from a microdissected research biopsy core. We performed a cis-eQTL study to identify GLOM & TI transcripts under genetic regulation by SNPs within 1Mb of the gene. We used the Bayesian "Deterministic Approximation of Posteriors" (DAP), which uses linkage disequilibrium and annotation information, to discover & fine-map eQTL signals within each locus while controlling for multiple testing. We included appropriate covariates for each dataset. We utilized MatrixEQTL for the same data to gain insight into direction of effect for these signals.

Results: At genome-wide significance, we discovered 340 independent eQTL signals in 313 unique genes in GLOM and 862 independent signals in 772 unique genes in TI. *PLCG2*, previously implicated in steroid sensitive NS via burden testing, was one of the strongest GLOM eQTLs. Five of 30 Mendelian NS genes had both a GLOM eQTL and a significant association with eGFR. This suggests that non-coding variants regulating Mendelian NS gene expression can impact clinical outcomes. 14% and 28% of significant eQTLs were GLOM- and TUB-specific, respectively. 58% of eQTLs were shared between GLOM & TI. When we compared the significance of GLOM- & TI-eQTLs with blood-derived eQTLs (from GTeX), 19% of eQTLs had more significant minimum p-value in GLOM & TI vs blood, despite smaller sample size.

Conclusions: In our glomerular & tubulointerstitial eQTL study of NS patients, we discovered 100s of genes under significant genetic control. We can now pursue their biologic & clinical correlates. Making this NS eQTL database publicly available should be a useful resource to inform future molecular & epidemiologic studies of NS.

Funding: NIDDK Support, Private Foundation Support

FR-OR035

Clinical Utility of Whole-Exome Sequencing for CKD Emily Groopman, Maddalena Marasa, Hila Milo Rasouly, Adele Mitrotti, Krzysztof Kiryluk, Simone Sanna-Cherchi, David B. Goldstein, Ali G. Gharavi. *Columbia University, New York, NY.*

Background: Whole-exome sequencing (WES) has recently been introduced into clinical diagnostics, but its value for adult constitutional disorders requires further evaluation. We are assessing the diagnostic yield of WES in a large cohort of adults with all-cause CKD or ESRD recruited at Columbia University (N=1920).

Methods: WES was performed in 1920 patients evaluated at Columbia University for various forms of CKD. To date, the exomes of 765 patients have been analyzed using American College of Medical Genetics (ACMG) guidelines for clinical sequence interpretation.

Results: 97.4% of 765 patients were adults and 51.0% were non-Caucasian; 54% had glomerulopathy, 7% had congenital defects, and 17.5% had CKD of unknown etiology. In total, 82 (10.7%) patients had a diagnostic variant for a genetic form of nephropathy. Among these diagnosed cases, 19.5% had presented with "CKD of unknown origin" and 41.5% noted no family history of nephropathy. In 47.6% of diagnosed cases, the molecular diagnosis confirmed the clinical diagnosis (e.g., Alport syndrome); in 52.4% it clarified the diagnosis (e.g., UMOD mutation in a patient with tubulointerstitial nephropathy) or provided an alternative diagnosis (e.g., Dent disease in a case of suspected glomerulopathy). Diagnostic variants were mainly found in genes for glomerulopathies (65.9%), followed by those for cystic disease (11.0%), tubulointerstitial disease (9.8%), other nephropathies (9.8%), and congenital anomalies (3.7%). In addition, 6 patients (0.8%) had a secondary, pathogenic variant in one of the 59 ACMG actionable genes. In the majority of cases, the results impacted clinical decision-making, through aspects such as initiation of targeted surveillance, family counseling, selection of transplant donors, and changes in therapy.

Conclusions: In a large all-cause CKD cohort, WES gave a molecular diagnosis for 1 in 10 patients, and in 52.4% of positive cases, pinpointed an etiology not detected using traditional diagnostics, impacting clinical care. The completion of this study will inform the utility of genetic testing for nephropathy across broad demographic subgroups and etiologic subtypes.

Funding: NIDDK Support

FR-OR036

Effect Modification Detected in a Genome-Wide Comparison of Kidney Function Variants between Over 270,000 Diabetic and Non-Diabetic Participants: The Million Veterans Program Adriana Hung,[5,3] Ayush Giri,[3] Digna R. Velez edwards,[3] Jacklyn N. Hellwege,[3] Otis D. Wilson,[3] Eric S. Torstenson,[3] Csaba P. Kovesdy,[2] Kelly A. Birdwell,[3,5] Edward D. Siew,[3,5] Christianne Roumie,[5,3] Christopher J. O'Donnell,[1] Todd L. Edwards.[4] *[1]Boston Veterans Administration, Boston, MA; [2]University of Tennessee Health Science Center, Memphis, TN; [3]Vanderbilt University, Nashville, TN; [4]Vanderbilt University Medical Center, Nashville, TN; [5]VA TVHS Nashville, Nashville, TN. Group/Team: On behalf of VA Million Veteran Program.*

Background: Diabetes is the number one cause of end stage kidney disease worldwide and diabetic kidney disease is often thought to be distinct from non-diabetic kidney disease. To investigate the extent of shared genetic etiology between these two subgroups in relation to kidney function

Methods: We conducted two genome-wide association studies (GWAS) in the Million Veteran Program (MVP) cohort to detect associations with eGFR: in self-reported black and white, non-diabetic veterans (N = 181,315) and diabetic veterans (N = 91,523).

Results: In total, 1,991 SNPs at 36 loci reached genome-wide significance (p-value $<5x10^{-8}$) in the diabetic subgroup, of which 15 were novel loci. *UMOD* represented the most striking signal in diabetics (p-value = $2.43x10^{-82}$). In the non-diabetic group, 7,357 SNPs at 101 loci, of which 52 were novel loci, reached genome-wide significance, with *SPATA5L1* having the strongest association (p-value = $6.39x10^{-106}$). Notably, 24 genome-wide significant loci were shared between diabetics and non-diabetics, including 5 novel loci: *TPPP*, *NRIP1*, *MAS1L*, *HFE*, and *C15orf54*. Comparison of effect estimates for significant loci showed a positive correlation between estimates across diabetics and nondiabetics (R^2 = 0.69). Correlations were strongest for known loci *SPATA5L1* and *UMOD* (r^2=0.93 and 0.98, respectively). Differences in effect sizes between diabetics and non-diabetics were also observed at two distinct loci: *MAF* and *C2*. Index SNP rs11644758 near *MAF* was associated with eGFR in non-diabetics (beta: 0.018; p-value = $1.1x10^{-9}$), but not in diabetics (beta = -0.003; p-value = 0.54), while index SNP rs644045 in *C2* was only associated in diabetics

Conclusions: In the largest comparative investigation of GWAS loci for eGFR between diabetics and non-diabetics known to date, this study reports numerous known and novel loci for eGFR, with mostly shared, and a few distinct loci across the two groups.

Funding: Veterans Affairs Support

FR-OR037

Analysis of Humans and Mice with DSTYK Mutations Reveals Complex Association with Urinary Tract Malformations and Neurological Phenotypes Jeremiah Martino,[3] Shouhong Xuan,[3] Alejandra Perez,[2] Katarina Vukojevic,[5] Qingxue Liu,[3] Rik Westland,[4] Adele Mitrotti,[3] Cathy Mendelsohn,[3] David B. Goldstein,[1] Ali G. Gharavi,[1] Simone Sanna-Cherchi.[1] *[1]Columbia University, New York, NY; [2]Columbia University College of Physicians & Surgeons, New York, NY; [3]Columbia University Medical Center, New York, NY; [4]VU University Medical Center, Amsterdam, Netherlands; [5]Department of Anatomy, Histology and Embryology, University of Split School of Medicine, Split, Croatia.*

Background: Our previous work has shown that dominant splice-site or premature termination mutations in DSTYK produce urinary tract malformations associated with epilepsy/ataxia in humans.

Methods: We queried exome sequencing data from large datasets of epilepsy patients and controls. We analyzed Dstyk null mice and human DSTYK null 293T cells generated using CRISPR technology.

Results: We queried exome sequencing data for 11,081 epilepsy patients, and 36,952 in house controls. The disease-implicated splice variant c.654+1G>A is present in ~1 in 3,300 European individuals from ExAC, and in 12/36,952 house controls and 3/11,081 epilepsy patients, suggesting it may be an incompletely penetrant allele. Healthy controls were completely depleted of any *DSTYK* loss-of-function (LOF) mutations. We also identified a new splice mutation, absent in ExAC and all our controls, in monozygotic twins with bilateral congenital hydronephrosis, and two premature termination mutations in two epilepsy patients for whom renal history is not yet available. Inactivation of *Dstyk* in the mouse showed perinatal lethality at P0/P1 and CAKUT. We observed unilateral renal agenesis and hypoplasia, shortened ureters and pelvic kidneys, and bladder diverticuli. Age-dependent obstructive uropathy was observed in ~70% of *Dstyk*$^{-/-}$ embryos. Hydronephrosis, papillary septation and maldevelopment increased in severity with age. To gain more insight into molecular pathogenesis, we generated two compound heterozygous *DSTYK*-null clones in 293T cells. Analysis of RNA-seq data of WT and *DSTYK* null cells show alterations in cell adhesion and neurogenesis pathways, including altered signaling by BMP, FGF, NOTCH, and WNT pathways. Genes associated to monogenic forms of epilepsy (*GABRB3*, *PCDH19,* and *PRRT2)* and CAKUT (*GDNF*, *ITGA8, GPC3)* were also downregulated. Finally, DOK6, an adaptor protein that interacts with RET was also downregulated in the *DSTYK* null cells.

Conclusions: In summary, we identified novel LOF mutations in patients with epilepsy confirming a new potential clinical association, provide evidence for genetic causality for CAKUT based on gene inactivation in the mouse, and identified cellular pathways perturbed by *DSTYK* inactivation.

Funding: NIDDK Support

FR-OR038

The Multi-Phenotype Derived Nephrotic Syndrome Severity (NS2) Score Empowers Genomic Discovery C. Gillies,[1] K Yasutake,[2] Xiaoquan Wen,[2] Matt G. Sampson.[1] *[1]University of Michigan, Ann Arbor, MI; [2]University of Michigan, Ann Arbor, MI. Group/Team: NEPTUNE.*

Background: Among patients with nephrotic syndrome (NS), we are interested in discovering genomic factors associated with disease severity over time. This requires creating accurate models of NS biology and a statistical strategy that takes advantage of deep phenotypic data while accounting for modest sample sizes and multiple testing. Thus, we developed a Nephrotic Syndrome Severity ("NS2") score for patients in the Nephrotic Syndrome Study Network (NEPTUNE).

Methods: NEPTUNE is a prospective, longitudinal study of NS enrolling affected adults and children receiving a clinically indicated biopsy. Rich demographic and clinical data are collected at baseline and over time. Genomic and histologic data are collected at baseline. We used the following parameters to create the multi-phenotype NS2 score: interstitial fibrosis, eGFR, protein/creatinine ratio, eGFR slope, time to complete remission, and time to a composite endpoint. We modeled the relationships between these variables and meaningful covariates using a Bayesian network (BN). The NS2 score represents a latent factor explaining the correlations in the observed data. The BN's parameters were inferred from 616 patients NEPTUNE participants using Markov chain Monte Carlo.

Results: Compared to existing multi-phenotype methods, NS2 score increased power for discovery without inflating Type I error. With regards to known biomarkers of NS severity, a worse NS2 score was significantly associated with the *APOL1* high-risk genotype in black patients ($p< 2.2$ e-5) and lower tubulointerstitial expression of *EGF* ($p< 5.7$ e-10). After FDR control, 1,040 glomerular transcripts were significantly associated with NS2 score. Using geneset enrichment analysis, kidney development genes were among the most enriched NS2-associated glomerular transcripts in adults ($p<5.3$ e-9), including 15 known Mendelian SRNS genes. In children, TNF alpha induced protein 3's glomerular expression was most associated with NS2 score.

Conclusions: The NS2 score is a robust metric created by capitalizing on extensive clinical data and NS-specific knowledge. As a robust multi-phenotype method, it improved statistical power for discovery without inflating false positives and replicates known genomic associations. Ultimately, using NS2 score as an outcome measure in analyses ranging from gene expression correlation to GWAS may empower genomic discoveries.

Funding: NIDDK Support

FR-OR039

Novel Loci for Renal Decline in Type 1 Diabetes (T1D) Marcus G. Pezzolesi,[9,6] Jan Skupien,[6,8] Chunyi Wu,[2] Adam Smiles,[6] Tarunveer S. Ahluwalia,[1] Niina Sandholm,[4,5] Erkka A. Valo,[4,5] Beáta György,[7] Suna Onengut-Gumuscu,[3] Wei-Min Chen,[3] Carol Forsblom,[4,5] Josyf Mychaleckyj,[3] Michel Marre,[7] Stephen Rich,[3] Andrzej Galecki,[2] Samy Hadjadj,[7] Peter Rossing,[1] Per-Henrik Groop,[4,5] Andrzej S. Krolewski.[6,10] *[1]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [2]University of Michigan, Ann Arbor, MI; [3]University of Virginia School of Medicine, Charlottesville, VA; [4]Folkhälsan Institute of Genetics, Folkhälsan Research Center, Helsinki, Finland; [5]University of Helsinki and Helsinki University Hospital, Helsinki, Finland; [6]Joslin Diabetes Center, Boston, MA; [7]INSERM, Poitiers, France; [8]Jagiellonian Univiversity Medical College, Krakow, Poland; [9]University of Utah, Salt Lake City, UT; [10]Harvard School of Medicine, Boston, MA.*

Background: Progressive renal decline is the predominant clinical feature of diabetic kidney disease (DKD) that leads to end-stage renal disease. Although genetic factors are known to contribute to DKD's susceptibility, despite intense effort, the identification of variants that underlie its risk has proven challenging. To advance this area of research, as part of the JDRF-sponsored Diabetic Nephropathy Collaborative Research Initiative, we recently performed the first genome-wide association study (GWAS) aimed at identifying variants associated with progressive renal decline in T1D.

Methods: We performed a linear mixed-effects model (LMM) meta-GWAS using serial measures of estimated glomerular filtration rate (eGFR) to estimate the effects of genetic variants on eGFR slope in 1,614 T1D patients with proteinuria assembled from 4 cohorts of European ancestry (Boston, Finland, Denmark and France). In total, more than 38,000 longitudinal eGFR measures collected over 5-20 years of follow-up were used to establish eGFR slopes in these patients.

Results: Our LMM meta-GWAS identified several novel loci that were strongly associated with eGFR decline. Our top finding was a variant in *LRP1B* that approached genome-wide significance (P=7.3x10^{-8}). In total, 37 variants across 20 distinct loci achieved P<1x10^{-4}, including 6 variants with P<1x10^{-6} in genes not previously associated with DKD. In addition to novel loci for progressive renal function decline, our LMM meta-GWAS replicated an association at *FRMD3*, a gene that we initially identified as part of our GWAS in the GoKinD collection.

Conclusions: Using a LMM meta-GWAS approach and longitudinal measures of renal function, we discovered several novel loci that contribute to progressive renal decline in patients with T1D and, thereby, further our understanding of the biology underlying DKD.

Funding: Private Foundation Support

FR-OR040

GSTM1 Deficiency Exaggerates Hypertension, Oxidative Stress, and Kidney Injury in Experimental Mouse Models of Hypertension and CKD Thu H. Le,[4] Gabor Bodonyi-Kovacs,[1] Phillip Ruiz,[2] Sylvia Cechova.[3] *[1]Renal Division, George Washington University, Washington, DC; [2]University Of Miami, Miami, FL; [3]University of Virginia, Charlottesville, VA; [4]Medicine, University of Virginia, Charlottesville, VA.*

Background: *GSTM1* encodes the glutathione S-transferase m-1 (GSTM1) enzyme that belongs to a superfamily of phase II antioxidant enzymes. In humans, a common deletion mutation, the null allele *GSTM1(0)*, results in decreased GSTM1 enzymatic activity and is associated with higher levels of oxidative stress. We reported that *GSTM1(0)* is associated with accelerated kidney disease progression in the African Americans Study of Kidney Disease (AASK). This has been confirmed in the Atherosclerosis Risk in Communities (ARIC) Study, in which *GSTM1(0)* is associated with incident kidney failure in both European Americans and African Americans.

Methods: To directly determine the impact of loss of GSTM1 enzyme on kidney disease development, we deleted *Gstm1* in the mouse to determine its consequence in the angiotensin II model of hypertension (Ang II-HTN) and the surgical remnant model of chronic kidney disease (Nx-CKD).

Results: Compared to wild-type mice, *Gstm1-/-* mice display higher levels of urinary 8-isoprostane and a modest but significantly higher BP at baseline. In both Ang II-HTN and Nx-CKD models, *Gstm1-/-* mice have exaggerated HTN, increased superoxide levels and worse kidney injury, independent of activation of Nox2 and Nox4 NADPH oxidases. In AngII-HTN, *Gstm1-/-* mice display increased renal expression of genes involved in inflammation - CXCL-1, MCP-1, IL-1b and IL-6 – and increased renal macrophage infiltration. In the Nx-CKD model, deletion of *Gstm1* resulted in early mortality, and significantly higher plasma creatinine and increased albuminuria. Isolated primary podocytes from *Gstm1 KO* mice also displayed a higher rate of migration in wound-healing assay.

Conclusions: In hypertension and CKD, GSTM1 enzyme may be protective by modulating oxidative stress and inflammation. Therapy directed at *GSTM1* pathway in those genetically most susceptible may ameliorate kidney disease progression.

Funding: NIDDK Support

FR-OR041

Early Transcriptional Changes Associated with the Altered Flow Environment and Intimal Hyperplasia Following AVF Creation Kyle M. Staton,[1] Jared Rozowsky,[2] Qiongyao Hu,[1] Sarah Barbey.[1] *[1]The University of Florida, Gainesville, FL; [2]University of Florida, Gainesville, FL.*

Background: While recent clinical studies have provided insights into factors that dictate success or failure in arteriovenous fistula (AVF) maturation, advances in our understanding of the fundamental biology within the fistula vein wall that controls these events has been limited to animal models. Two-stage basilic vein transposition (BVT) fistula offer the unique opportunity for collection of vein wall sample at initial placement and 4-6 weeks following AVF creation. This study utilizes high-throughput genomics to evaluate the transcriptional changes associated with the independent effects of vein wall pathology versus the altered flow environment on mRNA expression.

Methods: Vein samples were collected from patients at Stage 1 and Stage 2 of BVT creation (n=14). mRNA was isolated and analyzed for 44,699 genes using the HTA 2.0 microarray. BRB ArrayTools and Ingenity Pathway Analysis was used to identify genome changes, relevant ontologies, and upstream regulators. Histomorphometry was evaluated using Movat's stain.

Results: Substantial heterogeneity was identified at the time of AVF creation (intimal thickness: range =42-260 µm; mean = 133 µm). 86% of the Stage 2 samples demonstrated an increase in intimal thickness from baseline, with 50% of these veins exhibiting a greater than 2-fold increase in intima. A linear mixed model demonstrated 150 genes associated with the stage of fistula creation and 51 genes associated with extent of intimal disease (>1.5-fold change, p<0.01; Figure). Genes regulating AVF creation/local flow environment were associated with cell cycle progression, metabolism, and inflammation (with IL1, IL12, and CCL4 as extracellular regulators). Genes related to the extent of intimal disease were related to cell migration, cell cycle progression, and cell death (with ADAMTS1, PDGF, and TGFβ as regulators).

Conclusions: Within the vein wall of patients undergoing AVF creation, independent genomic signatures related to alterations in flow and intimal hyperplasia can be identified. These differences offer the opportunity for development of target interventional strategies to improve AVF maturation and durability.

Funding: Other NIH Support - RO1

FR-OR042

A Randomised Controlled Trial of Early Cannulation Grafts (ecAVGs) versus Tunneled Central Venous Catheters in Patients Requiring Urgent Vascular Access for Haemodialysis: One Year Follow-Up Data Emma L. Aitken, Peter C. Thomson, David Kingsmore. *NHS Greater Glasgow and Clyde, Glasgow, United Kingdom.*

Background: Early cannulation arteriovenous grafts (ecAVGs) are proposed as an alternative to tunnelled central venous catheters (TCVCs) in patients requiring immediate vascular access for haemodialysis (HD). We compare bacteraemia rates in patients treated with ecAVG and TCVC. Early follow-up data was recently published in *The Journal of Vascular Surgery*. One-year follow-up is now presented.

Methods: 121 adult patients requiring "urgent" vascular access for HD were randomised in a 1:1 fashion to receive either ecAVG+/-AVF (n=60) or TCVC+/-AVF (n=61). Patients were excluded if they had active systemic sepsis, no anatomically suitable vessels or anticipated life expectancy <3months. The primary end-point was culture-proven bacteraemia rate at 6 months, with the trial powered to detect a reduction in bacteraemia from 24% to 5% (alpha=0.05, beta=0.8). Secondary end points included thrombosis, re-intervention and mortality rates at 6 months and bacteraemia and mortality rates at 12 months (ISRCTN 8058854).

Results: Ten patients in the TCVC+/-AVF arm (16.4%) developed culture-proven bacteraemia within 6 months compared to two (3.3%) in the ecAVG+/-AVF arm (risk ratio 0.2 95% CI 0.12, 0.56; P=0.02). Six-month mortality was also higher in the TCVC+/-AVF cohort (16.4% [n=10] vs. 5% [n=3]; risk ratio 0.3 95% CI 0.08, 0.45; P=0.04). At 1-year follow-up 14 patients (23.3%) in the ecAVG+/-AVF arm and 16 patients (26.2%) in the TCVC+/-AVF arm were dialysing via AVF. Fewer patients in the ecAVG+/-AVF cohort were dialysing via TCVC (18.3% [n=11] vs. 41.0% [n=25]. Eleven patients in the TCVC arm (18.0%) had developed culture-proven bacteraemia at 12 months compared to six (10.0%) in the ecAVG+/-AVF arm (risk ratio 0.55 95% CI 0.24, 0.77; P<0.001). 12-month mortality was also higher in the TCVC+/-AVF cohort (18.0% [n=11] vs. 10.0% [n=6]; risk ratio 0.55 95% CI 0.24, 0.77; P<0.001.

Conclusions: Compared to TCVC+/-AVF, a strategy of ecAVG+/-AVF reduced the rate of culture-proven bacteraemia and mortality in patients requiring urgent vascular access for HD. The previously described early benefits of a strategy of ecAVG+/-AVF have now been demonstrated to persist to at least a year following "urgent" access creation.

FR-OR043

Procedural Burden Following Successful Arteriovenous Fistula Maturation in the United States Kenneth J. Woodside,[1] Kaitlyn Ratkowiak,[2] Purna Mukhopadhyay,[2] Douglas E. Schaubel,[1] Vahakn B. Shahinian,[1] Rajiv Saran,[1] Ronald L. Pisoni.[2] *[1]University of Michigan, Ann Arbor, MI; [2]Arbor Research Collaborative for Health, Ann Arbor, MI.*

Background: Over the last decade, the number of arteriovenous fistula (AVF) in the prevalent US hemodialysis (HD) population has increased. We have previously reported that just under half of patients required interventional procedures for successful maturation of AVF. Herein, we sought to determine the procedural burden following successful AVF maturation (defined as first-use) among newly placed AVF in United States.

Methods: Using the United States Renal Data System (USRDS), Medicare claims and CROWNWeb data, we analyzed patients new to HD from 7/1/12 to 6/30/13 who had first-time AVF placements (after HD start) between 7/1/12 and 6/30/2014. Successful maturation was defined as documentation of first AVF use in the CROWNWeb monthly reporting of vascular access in use. Patients were followed until 12/31/2015.

Results: Among the 102,703 incident HD patients, there were 24,416 first-time AVF placements of which 72.6% were successfully utilized, 24.0% had no recorded use, and 3.4% were lost to follow-up. Of those AVF that successfully matured, 30.0% required interventions during the maturation phase ("assisted maturation"), with about half (55.1%) of these interventions requiring angioplasty. Rates of interventions during the maintenance phase, expressed as a rate per patient per year (ppy), are summarized in the Table. AVF that required interventional assistance to mature also had higher procedural burden for AVF maintenance.

Conclusions: While there have been improvements in AVF prevalence in the HD population, interventions on these AVF were exceedingly common. Future work will examine factors predisposing to greater requirements for intervention, cost effectiveness, patient outcomes, and comparisons with alternative vascular access types.

Funding: NIDDK Support

	Natural Maturation	Assisted Maturation	P	Total
Patients	9,631	7,561		17,192
Patients with Interventions After Maturation	5,412	5,166		10,578
Interventional Procedures	14,365 (0.40 ppy)	17,112 (0.52 ppy)	P < 0.0001	31,477 (0.46 ppy)
Diagnostic Fistulogram Only	3,949 (0.11 ppy)	4,316 (0.13 ppy)	P < 0.0001	8,265 (0.12 ppy)
Any Therapeutic Intervention (Excluding Fistulogram Only)	10,416 (0.29 ppy)	12,796 (0.39 ppy)	P < 0.0001	23,212 (0.34 ppy)
Angioplasty	7,358 (0.21 ppy)	9,423 (0.29 ppy)	P < 0.0001	16,781 (0.25 ppy)
Thrombectomy	1,693 (0.05 ppy)	1,820 (0.06 ppy)	P = 0.0013	3,513 (0.05 ppy)
Revision	535 (0.02 ppy)	441 (0.01 ppy)	P < 0.0001	976 (0.01 ppy)
Stent	830 (0.02 ppy)	1,112 (0.03 ppy)	P = 0.0081	1,942 (0.03 ppy)

FR-OR044

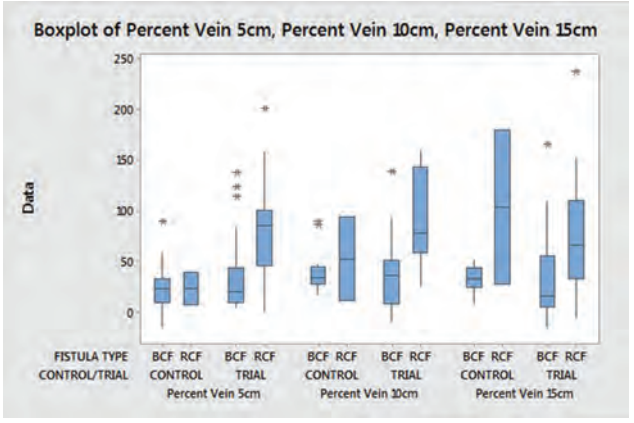
Intermittent Pneumatic Compression Increases Forearm AV Fistula Dilation: The First Medical Wearable for the Renal Community Tej M. Singh.[1,2] *[1]Vascular Surgery, El Camino Hospital, Mountain View, CA; [2]Fist Assist Devices, LLC, Los Altos Hills, CA.*

Background: Delays in AV fistula (AVF) maturation cause increased catheter dependency and costs. Forearm fistulas have very poor maturation rates compared to upper arm AVF. Increased distention pressure, nitric oxide release, and intermittent wall shear stress may help dilate forearm veins after AVF creation. Early use of non-invasive devices may help assist clinical AVF maturation and dilation.

Methods: One week after AVF creation, a novel, intermittent pneumatic compression device [Fist Assist (FA)] was applied 15 cm proximal to the AVF in order to apply intermittent, cyclic compression for 60 mm Hg for six hours daily for 30 days. Fourty (n=46) AVF patients were enrolled in an IRB approved study to test vein maturation at baseline and with the FA. Controls (n=17) used a sham device. Vein size was measured and recorded at baseline and after 30 days by duplex measurement. Clinical results (percentage increase) were recorded and tested for significance using standard t-tests.

Results: No patients experienced immediate thrombosis or adverse effects. Patient compliance and satisfaction was high. After one month, the mean percentage increase in vein diameter in the FA treatment group for all fistulas was significantly larger (p=0.05) than controls in the first 5 mm segment of the AVF vein. Forearm AVF veins dilated in all segments of the veins compared to upper arm veins. In the midportion alone, veins dilated compared to upper arms (39±35% vs. 94±44%) (p<.05). No fistulas had complications on dialysis or after needle placement.

Conclusions: Early application of an intermittent pneumatic compression device may assist in AVF maturation and success. Novel, non-invasive devices like Fist Assist may have clinical utility to create functional fistulae development and decrease costs as they may assist in maturation. FA may assist in forearm vein dilation and may provide the first wearable for the renal community to assist in AVF dilation especially at the forearm vein region.



FR-OR045

VasQ™ External Support Device Improves Functionality of Arteriovenous Fistulas: Randomized Controlled Study Results Nikolaos Karydis,[1] Paul Bevis,[2] Gary Maytham,[3] Moshe Halak,[4] Noam Zilberman.[5] *[1]Guy's Hospital, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [2]Bristol, Bath and Weston Vascular Network, Bristol, United Kingdom; [3]Vascular Institute, St Georges University Hospital NHS Foundation Trust, London, United Kingdom; [4]Vascular Surgery, Sheba Medical Center, Ramat - Gan, Israel; [5]Laminate Medical Technologies, Tel-Aviv, Israel.*

Background: Inadequate maturation is a major drawback of the Arteriovenous Fistula (AVF). Non-laminar flow at the peri-anastomotic area and venous exposure to arterial circulation are associated with development of neo-intimal hyperplasia, impairing venous remodeling. VasQ™ is a novel external support device designed to optimize anastomosis geometry, regulate flow patterns and support the venous wall, thus improving AVF outcomes. Interim results of a randomized controlled study designed to evaluate VasQ™ usability, safety and efficacy are presented here.

Methods: Sixty patients referred for a Brachiocephalic AVF (BCAVF) in 4 different hospitals were recruited and randomized to the 'Device' group (End-to-side BCAVF + VasQ™, n=40), or the 'Control' group (End-to-side BCAVF, n=20). Patients were followed up 1, 3, and 6 months post AVF creation.

Results: Device implantation easily integrated with the BCAVF procedure. All patients were free from device related complications. Of patients with patent AVFs undergoing hemodialysis, significantly higher rates of AVF use, larger diameter veins, and less stenosis were seen in the 'Device' group 3 months post AVF creation (Table 1) Primary patency rates 6 months post AVF creation were 79% vs. 67%, and the secondary patency rates were 88% vs. 79% in the 'Device' and 'Control' groups respectively. Average blood flow rates (mL/min) were 1214 vs. 1208 at 1 month, 1426 vs. 1173 at 3 months, and 1269 vs. 1175 at 6 months post AVF creation, for the 'Device' and 'Control' groups respectively.

Conclusions: A significant increase in functionality 3 months post AVF creation was observed in the Device group. This may be associated with an increase in laminar flow and a decrease in venous wall tension promoted by VasQ™.

Funding: Commercial Support - Laminate Medical Technologies

Table 1 - AVF functionality 3 months post creation

	Access used for dialysis (%) (p=0.0126)		Average vein diameter (mm) (p=0.0273)	AVF with reported stenosis (%)
	AVF	Catheter		
Device (n=18)*	95	5	8.76	16.66
Control (n=10)*	50	50	7.04	30

* Patients with a patent AVF, on active hemodialysis

FR-OR046

Does Regional Compared to Local Anaesthesia Influence Outcome after Arteriovenous Fistula Creation? One Year Follow-Up of a Randomised Controlled Trial Emma L. Aitken,[2] Andrew J. Jackson,[3] Rachel J. Kearns,[3] John Kinsella,[4] Alan J. Macfarlane,[1] Marc J. Clancy.[2] *[1]Glasgow Royal Infirmary, Glasgow, United Kingdom; [2]NHS Greater Glasgow and Clyde, Glasgow, United Kingdom; [3]NHS Greater Glasgow & Clyde, Glasgow, United Kingdom; [4]University of Glasgow, Glasgow, United Kingdom.*

Background: AVF are the optimal form of vascular access but have a high early failure rate. Although regional compared to local anaesthesia produces vasodilation and increases short-term blood flow there is no evidence that anaesthesia modality influences long-term fistula patency. This study investigated whether regional compared to local anaesthesia improved long-term AVF patency. The early (3 month) patency rates were recently published in *The Lancet.* 1 year follow-up data is now presented.

Methods: An observer-blinded randomised controlled trial was performed at three university hospitals in Glasgow, UK. Adults undergoing primary radiocephalic (RCF) or brachiocephalic (BCF) AVF creation were randomly assigned (1:1; in blocks of eight) using a computer-generated allocation system to receive either local anaesthesia (LA) or regional (brachial plexus block (BPB)) anaesthesia. Patients were excluded if they were coagulopathic, had no suitable vessels or had a previous failed ipsilateral fistula. The primary end point was AVF patency at 3 months. Secondary end points included functional patency at 3 months and 1 year, vessel diameters and brachial artery blood flow before and after anaesthesia (NCT01706354).

Results: 163 patients were assessed for eligibility and 126 patients were randomly assigned to LA (n=63) or BPB (n=63). All patients completed follow-up on an intention-to-treat basis. Primary patency at 3 months was higher in the BPB group than the LA group (53 [84%] vs 39 patients [62%]; odds ratio [OR] 3.3, p=0.005) and was greater in RCF (20 [77%] vs 12 patients [48%]; OR 3.6, p=0.03). In the subsequent year, 18 revisional procedures aimed at improving functional patency were performed on 10 patients. Functional patency at 1 year was higher in the BPB group than the LA group (51 [81%] vs 35 patients [56%]; OR 3.4, p<0.001). This difference remained more marked for RCF than BCF.

Conclusions: BPB significantly improved 3 month primary and functional patency and 12 month functional patency rates. This difference was more marked in RCF. The low early functional patency rates observed in our previously published data are not reproduced in 1 year follow-up data.

FR-OR047

Locking Solutions Impact on Biofilm Formation in Tunneled Hemodialysis Catheters (T-HDC) and Activation of the Inflammatory Response Mario Jimenez Hernandez. *Nephrology, Hospital Clinic of Barcelona, BARCELONA, Spain.*

Background: The surface of the T-HDC proves an optimal environment for the development of bacterial biofilm. The presence of these biofilms facilitates the generation of catheter-related infections (CRI) and possibly thrombosis, which can significantly reduce catheter life as well as its relationship with higher inflammatory state. Use locking solutions into catheter with antibacterial and anticoagulant activity seems reduced those complications. To date, there are no studies comparing locking solutions and biofilm formation on catheter surface and their possible relation with inflammatory response.

Methods: Objetive: To analyze biofilm formation into THDC locked with heparin solution 10%, citrate 4% or taurolidine + heparin 500UI + citrate al 4% mix solution through confocal microscopy and activation of the inflammatory response Prospective study, 35 patients in HD were included in whom the catheter was removed for non–infection-related reasons, according to the lock solution used in T-HDC were divided in three groups: 1) heparin 1:1000, 2) citrate 4% and 3) taurolidine+citrate 4%+heparin 500UI. Microbiological growth were determined in each catheter. C- reactive protein, IL-6, IL-10 and Tumoral Necrosis Factor alfa were determined. We use confocal microscopy to determine the characteristics of biofilm.

Results: 35 patients were included, mean age was 67.06±4.41 y.o, 80% were male sex; no significant differences were found related with clinical and demographical variables. Both catheters and blood cultures were negative. Catheter locking with taurolidine had lower thickness of biofilm compared with citrate 4% and heparin (28.85±6.86 *vs* 49.99 ±16.56 vs 56.2 ±15.67*mm*; p<0.001) respectively, as well as volume of biofilm (1013967.2 ±1184812.3 vs 3706378,3 ±2152223,8 vs 5553246,791 ±2448121,8 mm^3; *p<0.001).* No significant differences were found in the inflammatory markers studied among the 3 locking solutions

Conclusions: The presence of biofilm was found in all catheters, even in the absence of bacteremia and regardless of the type of locking solution used, however, biofilm was thiner in those catheters locked with the taurolodine-based solution which could be related with better outcome and lower bacteremia rates. No statistical differences were found in inflammatory response between citrate 4% años taurolidine based solution.

Funding: Private Foundation Support

FR-OR048

Changes in Biomarker Profile a nd L eft Ventricular Hypertrophy Regression: Results from the Frequent Hemodialysis Network Trials Christopher T. Chan,[6] George A. Kaysen,[3] Gerald J. Beck,[1] Minwei Li,[1] Joan C. Lo,[2] Michael V. Rocco,[5] Alan S. Kliger,[7] The FHN Trial Group.[4] *[1]Cleveland Clinic Foundation, Cleveland, OH; [2]Kaiser Permanente Northern California, Oakland, CA; [3]UC Davis, Davis, CA; [4]NIDDK, NIH, Bethesda, MD; [5]Wake Forest School of Medicine, Winston-Salem, NC; [6]Toronto General Hospital, Toronto, ON, Canada; [7]Yale New Haven Health System, New Haven, CT. Group/Team: FHN Trials Group.*

Background: Regression of left ventricular hypertrophy (LVH) has been shown to be feasible with more frequent hemodialysis. We aimed to ascertain potential biological pathways associated with regression of left ventricular mass (LVM) in patients enrolled in the Frequent Hemodialysis Network (FHN) Trials.

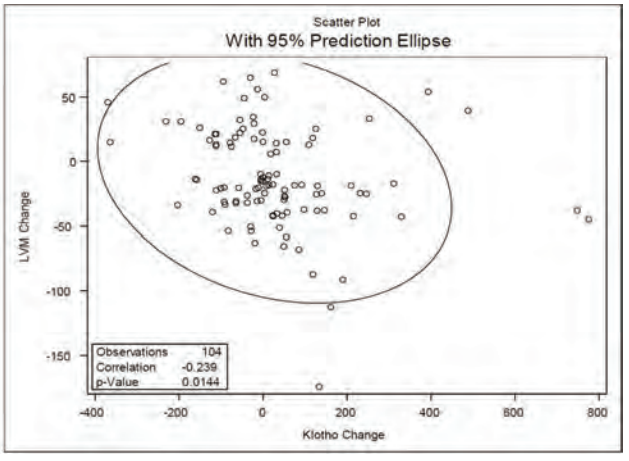
Methods: FHN participants were stratified according to LVM response. Regressors were defined as patients who achieved a reduction of more than 10% in LVM at 12 months. Progressors were defined as patients who had a minimum of 10% increase in LVM at 12 months.

Results: Among 332 randomized patients, there were 77 regressors and 45 progressors. LVM change differed between the 2 groups by -65.6(-74.0, -57.2) g, p < 0.001). Regressors had a median increase in dialysis frequency (from 3 (3,3) to 4.9 (3, 5.7) per week, p = 0.001) and median reductions in pre-dialysis systolic (from 149 (136, 162) to 136 (123, 152) mmHg, p <0.001) and diastolic (from 83 (71, 91) to 76 (68,

84) mmHg, p<0.001) BP. Amongst the various pre-defined cardiac biomarkers, Klotho levels increased significantly in patients with LVM regression versus those who had LVM progression (76.9 (10.5; 143.3) pg/ml, p = 0.024). Similarly, tissue inhibitors of metalloproteinase - 2 (TIMP – 2) levels fell in patients who had LVM regression than in the progressors (-7853 (-14653; -1052) pg/ml, p = 0.024). TIMP – 1 and LogBNP levels also tended to fall in patients with LVM regression. Changes in LVM correlated inversely with changes in Klotho (r = -0.24, p = 0.014). Amongst patients with LVH at baseline, copeptin tended to differ between progressors and regressors (-87.2 (-178.8; 4.4) pmol/L, p =0.06).

Conclusions: Our results demonstrated that markers of collagen turnover and changes in klotho levels are novel pathways, which may provide mechanistic insights into the regression of LVH in dialysis patients.

Funding: NIDDK Support



FR-OR049

A Light Dialysis Session Makes a Heavy Heart: Extended Haemodialysis Offers Cardio-Protection Darren R. Churchward,[3,2] Katherine L. Hull,[2] Daniel S. March,[3,2] Matthew P. Graham-Brown,[2,1] James Burton.[3,2] *[1]None, Leicestershire, United Kingdom; [2]University Hospitals of Leicester NHS Trust, Coventry, United Kingdom; [3]University of Leicester, Leicester, United Kingdom.*

Background: Internationally, there is a growing body of observational data that extended hours haemodialysis (HD) improves morbidity, mortality and quality of life. Limited experimental data are available comparing conventional HD (CD) to in-centre programmes of extended HD. This study examined the effects of extended in-centre nocturnal HD (INHD) on left ventricular geometry and circulating markers of cardiac injury, compared to CD.

Methods: : The MIDNIGHT trial (ISCTRN16672784) is a non-randomised controlled trial of INHD (3x5-8hours, n=10) vs CD (3x4hours, n=12), with patients matched for age, gender and HD vintage. Left ventricular mass index (LVMI) was assessed by cardiac magnetic resonance imaging; levels of heat shock protein 70 (HSP70), fibroblast growth factor-23 (FGF-23) and troponin-I (Trop-I) were analysed from blood samples taken prior to HD. All measures were completed at baseline and 6-months. LVMI results are shown as mean with standard deviation (*Mean*±*SD*); blood markers are presented as median with lower and upper quartiles (*Mdn*[LQ,UQ]).

Results: LVMI significantly reduced in the INHD group (63.6±20.7 vs 55.0±17.3, *p*=0.02) and tended to increase in the CD group (51.4±8.6 vs 54.6±11.1, *p*=0.46). No change to HSP70 was seen in either group. Reductions in FGF-23 were seen in the INHD group (489.7[156.3, 1515.0] vs 88.3[49.7,400.6], *p*=0.043) but not the CD group (399.24[174.1,4670] vs 657.3[158.9,1099.7], *p*=0.735). Similarly, no change to Trop-I in the INHD group (15[5.3,20.5] vs 6.5[0.0,25.0], *p*=0.917) but a trend to increase in the CD group (11.0[6.3,20.3] vs 15.0[8.8,38.8], *p*=0.066).

Conclusions: In this study, INHD patients demonstrated favourable changes in circulating biomarkers of cardiovascular disease as well as regression of left ventricular hypertrophy, compared to controls. These results provide further evidence that extended HD regimens may improve cardiovascular outcomes and therefore warrant further investigation.

FR-OR050

Reduction in Post-Dialysis Recovery Time in the FREEDOM Study of Frequent Home Hemodialysis Bertrand L. Jaber,[2] Eric D. Weinhandl,[1,4] Allan J. Collins,[1,4] Fredric O. Finkelstein.[3] *[1]NxStage Medical, Inc., Victoria, MN; [2]St. Elizabeth's Medical Center, Boston, MA; [3]Yale University, New Haven, CT; [4]University of Minnesota, Minneapolis, MN.*

Background: Long post-dialysis recovery time (RT) is associated with higher risk of death and lower quality of life. Increasing treatment frequency reduced RT in the Frequent Hemodialysis Network trials. The FREEDOM (Following Rehabilitation, Economics and Everyday-Dialysis Outcome Measurements) Study was a 12-month prospective cohort study of short daily home hemodialysis (SDHHD). Interim analysis of the FREEDOM Study indicated that SDHHD led to decreased RT. We sought to confirm these findings in a final analysis.

Methods: We analyzed RT, as elicited by the question, "How long does it take you to recover from a dialysis session and resume your normal, usual activities?", in intention-to-treat (ITT), conditional ITT (cITT), and as-treated (AT) cohorts. The ITT, cITT, and AT cohorts comprised all patients who initiated SDHHD, those who completed 2 months of follow-up, and those who completed 12 months of follow-up, respectively. RT was measured at baseline, 4 months (if the patient remained on SDHHD), and 12 months (if the patient remained on SDHHD). Patients were censored at death or kidney transplantation. We used mixed models to analyze changes in RT, with adjustments for demographics and comorbidity.

Results: The ITT, cITT, and AT cohorts included 487, 407, and 247 patients, respectively. In the ITT cohort, mean RT decreased from 494 minutes (min) at baseline to 227 and 198 min at 4 and 12 months, respectively, while median RT decreased from 180 min at baseline to 60 and 45 min at 4 and 12 months. In the AT cohort, mean RT decreased from 512 min at baseline to 132 and 96 min at 4 and 12 months, while median RT decreased from 180 min at baseline to 30 min at both 4 and 12 months. Adjusted differences in mean RT between baseline and 4 months were -263 min, -306 min, and -380 min in the ITT, cITT, and AT cohorts, respectively, and corresponding adjusted differences between baseline and 12 months were -287 min, -339 min, and -416 minutes ($P < 0.001$ for all differences).

Conclusions: In a 12-month prospective cohort study, SDHHD was associated with large reductions in mean and median post-dialysis recovery time. Reductions were evident after 4 months on SDHHD and sustained after 12 months. Increasing treatment frequency likely reduces recovery time, but the physiologic mechanisms underlying this effect remain uncertain and merit further research.

FR-OR051

Determinants of Interdialytic Volume Overload During More Frequent Hemodialysis: Time-Integrated Estimate of Fluid Load (TIFL) J. Ken Leypoldt,[3] Allan J. Collins,[1] Eric D. Weinhandl.[2] *[1]Chronic Disease Research Group, Minneapolis, MN; [2]NxStage Medical, Inc., Victoria, MN; [3]None, San Clemente, CA.*

Background: The Frequent Hemodialysis Network has recently demonstrated that a novel measure of interdialytic volume overload, the time-integrated estimate of fluid load (TIFL), is inversely associated with left ventricular mass reduction and could therefore be used to evaluate the effect of volume overload on cardiac stress (Raimann et al, Blood Purif 2016). The relative importance of clinical factors, such as dietary sodium intake (NaI), interdialytic weight gain (IDWG) and dialysate sodium concentration (dialNa), on TIFL during conventional and more frequent hemodialysis (HD) are incompletely understood.

Methods: We compared the effect of clinical factors on the mean interdialytic excess of extracellular fluid volume (eECV) and TIFL using mathematical model simulations. A conventional model of sodium and fluid kinetics was used to simulate intradialytic and interdialytic changes in serum sodium and extracellular fluid volume (Kimura & Gotch, Int J Artif Organs 1984). TIFL was calculated using the approach of Raimann et al (Blood Purif 2016) that assumes rapid post-dialysis fluid intake to maintain the sodium set-point and accounts for the length of the interdialytic interval. Residual kidney urine volume was assumed negligible. We compared eECV and TIFL for conventional HD, daily HD and nocturnal HD.

Results: As expected, eECV and TIFL were strongly and positively associated with IDWG. In contrast, eECV and TIFL were inversely associated with NaI when not accompanied by increased IDWG. The effects of treatment modality and dialNa are tabulated.

Conclusions: More frequent (daily and nocturnal) HD result in substantial reductions in eECV and TIFL. Similar reductions in these measures cannot be achieved with reductions in dietary Na intake or dialysate Na concentrations. The use of increased HD frequency for reduction of interdialytic fluid overload should be preferred over stringent dietary Na restriction or reductions in dialysate Na concentration.

Funding: Commercial Support - NxStage Medical

HD	Treatments/wk	Treatment Time (min)	dialNa (meq/L)	eECV (L)	TIFL (L-days)
Conventional	3	220	136	1.27	12.4
			140	1.25	12.8
Daily	6	180	136	0.76	8.5
			140	0.75	8.7
Nocturnal	6	480	136	0.61	5.4
			140	0.60	5.6

FR-OR052

Preservation of Residual Renal Function in a European Cohort of Frequent Home Hemodialysis Patients Sunita Nair,[2] Maria Fernanda Slon.[1] *[1]Complejo Hospitalario de Navarra, Pamplona, Spain; [2]Shrewsbury and Telford Hospital NHS Trust, Shrewsbury, United Kingdom. Group/Team: KIHDNEy Investigators.*

Background: Residual renal function (RRF) in dialysis patients promotes clearance of phosphate and middle molecules, permits more liberal fluid intake, and associates with improved survival. Intensive hemodialysis (HD) may accelerate loss of RRF, but whether all intensive HD schedules are similarly associated with deterioration of RRF is uncertain. We assessed the trajectory of 24-hour urine volume (UVol) in a European cohort of frequent home hemodialysis (HHD) patients.

Methods: We analyzed data from the KIHDNEy (Knowledge to Improve Home Hemodialysis Network in Europe) cohort, which comprises HHD patients at 9 centers in 5 Western European countries. All patients used the NxStage System One. Data about the HD prescription and 24-hour urine volume were collected at HHD initiation, 6 months, and 12 months. We retained patients with 24-hour UVol ≥500 mL at baseline and ≥4 sessions/week. We used generalized estimating equations to model changes in UVol between HHD initiation and 12 months.

Results: Baseline UVol was recorded in 98 (54%) of 182 patients, 44 (45%) of 98 had UVol ≥500 mL, and 43 (98%) of 44 dialyzed ≥4 sessions/week. Mean age was 51 years, 49% were female, median dialysis duration before HHD was 11.5 months, 9% had diabetes, and 19% had glomerulonephritis. Treatment frequencies were 5 and 6 sessions/week in 70% and 30% of patients, respectively, and mean treatment time was 12.2 hours/week. Mean UVol decreased (P = 0.001) from 1310 mL at baseline to 1080 mL at 6 months and 910 mL at 12 months. Cumulative incidence of anuria (UVol ≤50 mL) was 6% at 6 months and 18% at 12 months. Concurrently, mean ultrafiltration volume increased from 0.69 L at baseline to 0.85 L at 6 months and 0.96 L at 12 months. Antihypertensive medication use declined from 1.62 agents/day at baseline to 1.35 agents/day at 12 months. Concurrently, use of ACE inhibitors or ARBs declined from 28% to 16% of patients, while use of loop diuretics in non-anuric patients remained between 30% and 40%.

Conclusions: RRF decreased during 12 months of frequent HHD, with treatment time per week comparable to conventional HD. However, cumulative incidence of anuria was lower than with nocturnal HD in FHN (Daurgidas, Kidney Int, 2013), as well as lower than with peritoneal dialysis in NECOSAD (Michels, CJASN, 2011). Further research should assess whether specific approaches to intensive HD better preserve RRF.

FR-OR053

A Comparison of Patient and Technique Survival on Peritoneal Dialysis and Home Hemodialysis in Canada

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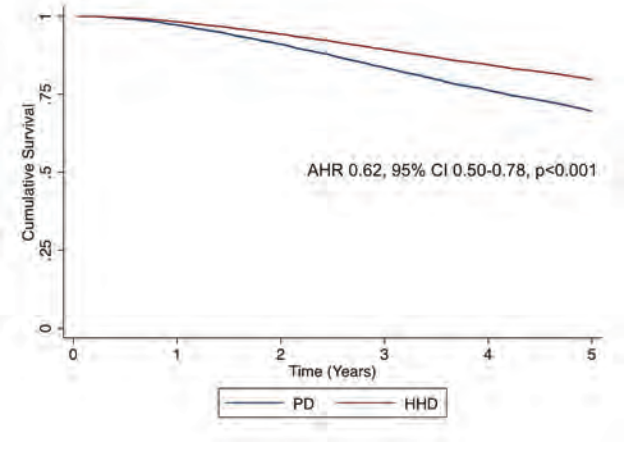
Background: Improved outcomes and superior cost effectiveness among home dialysis patients compared to conventional hemodialysis has led to greater utilization of home dialysis in Canada. Little is known about survival comparisons among home dialysis modalities. This study aimed to compare the survival and technique failure of patients treated with either peritoneal dialysis (PD) or home hemodialysis (HHD).

Methods: All incident dialysis patient treated with PD or HHD within 180 days of renal replacement therapy start in Canada between January 2000 and December 2013 were analyzed. The primary outcome of death was assessed in a Cox proportional hazards model adjusting for baseline demographics, comorbidities, dialysis vintage, era and geographic region, and censored at time of transplantation or loss to follow-up. A sensitivity analysis was performed using a 2:1 propensity score matched (PSM) model. Secondary outcomes included the composite of home dialysis technique failure and death.

Results: The study included 14 589 PD patients and 721 HHD patients. Unadjusted 5-year survival was 77% for HHD patients and 52% for PD patients. In the adjusted analysis, patient mortality was lower with HHD compared to PD (adjusted hazard ratio [AHR] 0.62, 95% confidence interval [CI] 0.50-0.78, p<0.001) and the association was consistent in the PSM model (HR 0.73, 95% CI 0.56-0.95, p=0.02). The composite of on-treatment mortality and technique failure was also lower with HHD compared to PD (AHR 0.48, 95% CI 0.42-0.72, p<0.001).

Conclusions: In Canada, incident HHD was associated with a lower mortality compared to PD. Whether or not this association is related to the impact of dialysis modality or due to differences in patient selection remains uncertain and should be evaluated in further prospective studies.



Adjusted survival

FR-OR054

Vascular Audit Checklist in Home Hemodialysis: A Prospective Cohort Study

Miten Dhruve,[2] Christopher T. Chan.[1] *[1]Toronto General Hospital, Toronto, ON, Canada; [2]University Health Network, Toronto, ON, Canada.*

Background: Vascular access related infections lead to increased morbidity and mortality in the home hemodialysis (HHD) population. We had previously reported that errors made on nurse – administered vascular access audit were associated with higher rate of access-related infection. In the present study, we hypothesize that repeat administration of vascular audit, will result in a decrease in the number of errors performed. Furthermore, increase in errors will augment the future risk of vascular related infection.

Methods: We conducted a prospective cohort study of all HHD patients from 2013 to 2016. Vascular access audits errors were obtained from checklists that were nurse administered and occurred on average every six and a half (0 – 32) months.

Results: 370 audits were performed on 122 patients with an average HHD vintage of 6.7 (0.8 – 19.5) years. At baseline the mean number of errors was 1.24 ± 1.75. This decreased significantly to mean of 0.33± 0.49 by 8th audit. Patients with multiple audits demonstrated a significant decrease in median number of errors (baseline median 1, (0-2) end of study median 0, (0-1) p= 0.01). There was a significant relation between ≥ 2 errors and future risk of infection, p<0.001 (**Table 1**). The overall infection rate was 0.57 infections per patient year.

Conclusions: Vascular access audits have a significant role to play in identification of errors in HHD population with repeat audits leading to a decrease in the number of errors. There exists a strong relation between 2 or more errors and increased risk of future infection. Vascular audit tool should be utilized in HHD programs to identify patient errors in aspiration of decreasing infection rates.

TABLE 1: Chi Square analysis to assess relation between 2 or more errors and future risk of infection.

No. of Errors	No. of Patients with Infection	No. of Patients without Infection
2 or More	24	34
Less than 2	39	54
		$\chi^2(4) = 152$ ($p < 0.001$)

FR-OR055

Therapy Attrition on Nocturnal versus Diurnal Home Hemodialysis

Eric D. Weinhandl,[1,2] Allan J. Collins.[1,2] *[1]NxStage Medical, Inc., Victoria, MN; [2]University of Minnesota, Minneapolis, MN.*

Background: Nocturnal hemodialysis offers several clinical advantages over diurnal hemodialysis, including slower ultrafiltration rate and increased cumulative phosphorus clearance. In addition, because nocturnal hemodialysis transfers treatment time to overnights, patients may gain daytime hours for activity unrelated to health care. Recently, the NxStage System One (NSO) was cleared by the US Food and Drug Administration for nocturnal home hemodialysis (NHHD). We aimed to identify the relative risk of all-cause and cause-specific therapy attrition in NHHD patients and diurnal HHD patients using the NSO.

Methods: We analyzed data in prescription records maintained by NxStage Medical (Lawrence, MA). We identified all US patients who initiated NHHD between April 1, 2015, and December 31, 2016. We also identified all US patients who initiated HHD between April 1, 2006, and December 31, 2016. For all patients, we collected age, race, sex, and year of HHD initiation with the NSO. We followed NHHD patients from the date of NHHD initiation, followed diurnal HHD patients from HHD initiation with the NSO, and followed all patients until the earlier of HHD cessation or January 15, 2015. We used stratified Cox regression to estimate hazard ratios of all-cause and cause-specific (transplant, technique failure, death) attrition for nocturnal versus diurnal HHD, with adjustment for age, race, and sex, and stratification by year of HHD initiation; in models, follow-up time was enumerated in days from HHD initiation with the NSO, in order to address HHD vintage.

Results: We identified 406 patients who initiated NHHD. Mean age was 53.3 years, 72% with known race were white, and 68% were male. During follow-up, there were 21 transplants, 43 technique failures, and 21 deaths. Cumulative incidence of HHD attrition at 12 months after NHHD initiation was 24.9% (95% confidence interval [CI], 20.0-30.0%). Compared to diurnal HHD, hazards ratios of HHD attrition for NHHD were 0.63 (95% CI, 0.52-0.78) for all causes, 0.70 (0.45-1.08) for transplant, 0.54 (0.40-0.73) for technique failure, and 0.77 (0.54-1.12) for death.

Conclusions: Nocturnal HHD with the NSO was associated with lower risk of HHD attrition, with significantly lower risk of technique failure, compared to diurnal HHD. Lower risks of both transplant and death on NHHD merit further analysis, including adjustment for the comorbidity profile of NHHD patients.

FR-OR056

Improvement in Health-Related Quality of Life in the FREEDOM Study of Frequent Home Hemodialysis

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Background: Poor health-related quality of life (HRQOL) is common in dialysis patients. Increasing treatment frequency improved physical HRQOL in the Frequent Hemodialysis Network trials. The FREEDOM (Following Rehabilitation, Economics and

Everyday-Dialysis Outcome Measurements) Study was a 12-month prospective cohort study of short daily home hemodialysis (SDHHD). Interim analysis of the FREEDOM Study indicated that SDHHD led to improvements in HRQOL. We sought to confirm these findings in a final analysis.

Methods: We analyzed HRQOL in intention-to-treat (ITT), conditional ITT (cITT), and as-treated (AT) cohorts. The ITT, cITT, and AT cohorts comprised all patients who initiated SDHHD, those who completed 2 months of follow-up, and those who completed 12 months of follow-up, respectively. HRQOL was measured with the Short Form-36 health survey at baseline, 4 months (if the patient remained on SDHHD), and 12 months (if the patient remained on SDHHD). Patients were censored at death or kidney transplantation. We used adjusted mixed models to analyze changes in HRQOL domains, the physical-composite summary (PCS), and the mental-composite summary (MCS).

Results: The ITT, cITT, and AT cohorts included 487, 408, and 247 patients, respectively. In the ITT cohort, mean PCS increased from 34.8 at baseline to 37.1 at 12 months, while mean MCS increased from 45.8 to 48.0. In the AT cohort, mean PCS increased from 35.5 to 38.6, while mean MCS increased from 48.4 to 50.4. Modeled changes in HRQOL domains between baseline, 4 months, and 12 months are displayed in the table. Changes were uniformly positive.

Conclusions: In a 12-month prospective cohort study, SDHHD was associated with widespread improvements across domains of both physical and mental HRQOL.

HRQOL domain	ITT cohort		cITT cohort		AT cohort	
	4 months	12 months	4 months	12 months	4 months	12 months
PCS	+1.9*	+2.0*	+2.2*	+2.2*	+3.1*	+3.0*
MCS	+1.9*	+1.8*	+2.2*	+2.1*	+2.2*	+2.0*
Physical functioning	+1.4*	+1.4*	+1.5*	+1.6*	+1.9*	+1.8*
Role-physical	+2.9*	+3.0*	+3.2*	+3.4*	+3.9*	+4.2*
Bodily pain	+1.0*	+1.2*	+1.2*	+1.4*	+1.7*	+1.6*
General health	+1.8*	+1.5*	+2.1*	+1.8*	+2.6*	+2.1*
Vitality	+3.4*	+2.9*	+4.0*	+3.3*	+4.9*	+3.9*
Social functioning	+2.3*	+2.6*	+2.7*	+3.1*	+3.6*	+4.0*
Role-emotional	+1.0*	+1.0	+1.0*	+1.2	+0.3	+0.3
Mental health	+1.5*	+1.7*	+1.7*	+2.0*	+1.7*	+1.9*

*P < 0.05, with adjustments for demographics and comorbidity

FR-OR057

Comparing Mortality between Incident Peritoneal Dialysis and Home Hemodialysis Patients Soo Jeong Choi,[1] Yoshitsugu Obi,[1] Miklos Z. Molnar,[2] Connie Rhee,[1] Elani Streja,[1] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine, Orange, CA; [2]University of Tennessee Health Science Center, Memphis, TN.*

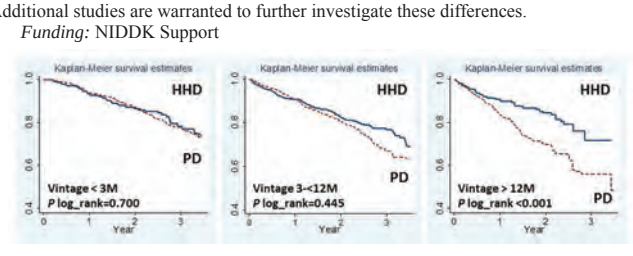
Background: The use of home dialysis modalities, including peritoneal dialysis (PD) and home hemodialysis (HHD), has recently increased. Although HHD differs from PD in terms of setting, frequency and patient preference, prior studies have shown that HHD patients have lower mortality risk than PD, in which we sought to examine using propensity scores in a large contemporary cohort of home dialysis patients.

Methods: We retrospectively examined a cohort of 1,993 HHD and 16,515 PD patients who initiated home dialysis from 2007-2011. HHD patients were matched with 2 PD patients using propensity score (PS) matching. Demographics, comorbidities, vintage and body mass index were included in logistic regression model for PS matching. We matched 1,988 HHD with 3,876 PD patients. Patients were stratified by vintage at the time of home modality initiation (<3 months (M), 3-<12M, and >12M).

Results: In the matched cohort, 244 and 699 deaths occurred in HHD and PD patients, respectively (cumulative incidence rate: 9.4 vs 12.0/100 patient year, p = 0.002). But, PD patients who transitioned within 12M of vintage had similar mortality risk. Only PD patients who transitioned after 12M of vintage had higher risk for mortality (HR, 1.62; 95% CI, 1.18-2.20).

Conclusions: Whereas there appears to be no survival difference among those who started home dialysis in the first 12 M, patients who transitioned to PD after 12 M of vintage had worse survival than those who transitioned to HHD after 12 M of vintage. Additional studies are warranted to further investigate these differences.

Funding: NIDDK Support



FR-OR058

A Novel Nephrotic Syndrome Circulating Factor Disease Model Based on PAR-1 Activation Carl J. May, Sarah Higgins, Fern Barrington, Richard Coward, Gavin I. Welsh, Moin Saleem. *University of Bristol, Bristol, United Kingdom.*

Background: There is strong evidence for the role of a circulating factor in the pathogenesis of idiopathic nephrotic syndrome (iNS). Several candidates have been put forward over the years, however, none have been definitively proved. Work previously published by this group has suggested a role for Protease Activated Receptor 1 (PAR-1). Cultured podocytes respond to treatment with nephrotic syndrome relapse plasma (and not paired remission plasma) by phosphorylating VASP and increasing motility. Furthermore, the response can be blocked by knocking down the PAR-1 receptor with siRNA. A transgenic mouse was developed that expressed a podocyte specific constitutively active form of PAR-1. We hypothesise that this replicates over exposure to a circulating protease and hence causes idiopathic nephrotic syndrome.

Methods: Transgenic mice were generated by Genoway (Lyon, France). The transgene was inserted at the Rosa 26 locus. These mice were crossed with Pod- Cre mice for the developmental line and Pod- rtTA Tet- O- Cre mice for the inducible line. Kidneys were harvested and processed for histological staining and EM as indicated.

Results: The developmental PAR-1_{active} mice were born normal, and died consistently between the ages of 39 and 45 days. They demonstrate proteinuria from the age of 14 days. The level of proteinuria increases considerably over time. By day 40 they have significantly higher blood urea and creatinine (mean 70mMol/L, 60μMol/L respectively), suggesting the mice die of renal failure. EM analysis showed a significantly thickened GBM and foot process effacement. PAS and Masson's Trichrome staining over a time-course ranging from 8 to 40 days demonstrated an initial hypercellualrity within the Bowman's capsule at 8 days that appear to reduce by 14 days. By 30 days there is clear evidence of fibrosis and by 40 days there is both fibrosis and sclerosis. The inducible PAR-1 Active mice show a similar phenotype although less severe. These mice die around 6 months old. We have also seen increased staining for activated PAR-1 in human iNS, compared to IgAN control biopsies.

Conclusions: This work demonstrates a clear role for the PAR-1 receptor in proteinuria, and strengthens the hypothesis that circulating factor(s) may act via this receptor. Additionally, this is a novel model for circulating factor NS, to test therapies *in vivo*.

Funding: Government Support - Non-U.S.

FR-OR059

Angiomotin Knockout in Rats Causes Proteinuria Yaochun Zhang,[2] Jerrold m. Ward,[3] Zakir Hossain,[2] Sik Yin Foo,[2] Isaac Liu,[2] Chang-Yien Chan,[2] Zi Jin Sun,[2] Hui Kim Yap,[1] Kar Hui Ng.[2] *[1]National University Hospital, Singapore, Singapore; [2]National University of Singapore, Singapore, Singapore; [3]Global VetPathology, Montgomery Village, MD.*

Background: Angiomotins were originally identified as angiostatin binding proteins and implicated in the regulation of endothelial cell migration and tube formation. Recent studies have shown that Angiomotion plays a central role in tight junction maintenance via the complex formed with ARHGAP17, which acts by regulating the uptake of polarity proteins at tight junctions. This study aimed to investigate the renal functions of *Angiomotin* with an *Angiomotin* knockout (Amot KO) rat model.

Methods: Using CRISPR/Cas9 system, we created an Amot KO founder rat with a 5 bp insertion in the coding region, which produced a premature stop codon, resulting in a truncated protein of 63 amino acids. The founder was crossed with wild type rats to establish Amot KO rat line. The phenotypes of Amot KO (n = 11) male rats were studied and compared with wild type control (n = 11). Body weight, serum and urine albumin:creatinine ratios were monitored monthly. Total RNA were extracted from peripheral blood mononuclear cells and sent for RNA-Seq. The rats were euthanized at different time points. Kidney cortex samples were obtained for pathological examinations.

Results: Increased urine albumin:creatinine ratio was found as early as 4 month age in the Amot KO rats. The ratio increased progressively with age and reached 547.7 ± 254.6 μg/mg in the 6 month old Amot KO rats, while the ratio is 150.4 ± 117.4 μg/mg for the wild type control (p < 0.01). Pathological changes in the rat kidneys were systemically examined with H&E and PAS staining. While wild type control rats showed normal renal glomeruli and proximal tubules, prominent thickened GBMs, thickened Bowman's capsule, casts or crystal in distal tubule, thicker tubular basement membrane and hyperplastic epithelium as well as podocyte atypia can be seen in the 6 and 10 month old Amot KO rats. RNA-Seq results showed more than 300 differentially expressed genes including Smad7, Rac1 and pdlim1. Analysis using IPA revealed altered effector pathways in glomerular injury, renal necrosis, and nephritis.

Conclusions: AMOT appears to play important roles in regulating renal functions. AMOT may exert its function through Rich1/Gap complex affecting activation status of Rho GTPases or via interactions with slit diaphragm and actin cytoskeleton proteins.

Funding: Government Support - Non-U.S.

FR-OR060

CCR2 Inhibitor Improves Renal Function and Structure in Murine Models of Focal Segmental Glomerulosclerosis (FSGS) Zhenhua Miao, Linda Ertl, Jeffrey P. Mcmahon, Bin N. Zhao, James J. Campbell, Xiaoli Liu, Ton H. Dang, Shichang Miao, Thomas J. Schall, Rajinder Singh. *ChemoCentryx, Mt View, CA.*

Background: FSGS is the most common primary glomerular disorder causing in at least 4% of patients with ESRD. The current SOC includes renin-angiotensin-aldosterone (RAAS) inhibitors, steroids and/or immunosuppresants. Several lines of evidence support a role for chemokine receptor 2 (CCR2) positive monocyte/macrophages in the pathogenesis of FSGS, and inhibition of CCR2 presents a potential therapeutic treatment of FSGS.

Methods: Two murine models of FSGS, 5/6 nephrectomy and Adriamycin nephropathy were used to investigate the efficacy of either CCR2 antagonist alone or in combination with RAAS inhibitor candesartan (CST). Kidney injury was assessed by proteinuria (UAER), UACR, BUN, serum creatinine and histopathology.

Results: In the 5/6 nephrectomy model, mice had a rapid reduction in UAER when treated with either the CCR2 antagonist (42% reduction by week 1) or RAAS inhibitor (69% reduction). Addition of the CCR2 antagonist to RAAS inhibitor further reduced the UAER (92% reduction; $p < .005$ versus RAAS inhibitor alone). The same renal protective effects of CCR2 blockade were seen in the Adriamycin nephropathy model. UAER was significantly reduced by administration of CCR2 antagonist (66% reduction; $p = .05$ versus vehicle), but not by RAAS inhibitor alone. Furthermore, the combination of the CCR2 antagonist and RAAS inhibition resulted in an additive effect (74% reduction; $p = .027$ versus vehicle) in Adriamycin nephropathy model. The combination of the CCR2 antagonist and RAAS inhibitor significantly reduced serum creatinine and BUN. Histological parameters also improved with CCR2 antagonist treatment and/or RAAS inhibitor. The combination of the CCR2 antagonist and RAAS inhibition reduced tubulointerstitial injury (including inflammation, fibrosis, tubular casts and dilatation) and glomerular injury (including glomerular hypertrophy, mesangial expansion and glomerular sclerosis).

Conclusions: CCR2 inhibition provides significant and rapid renal protection in two models of FSGS, as measured by renal functions and histological parameters, and thus represents a novel and mechanistically distinct approach for the treatment of FSGS. We are moving forward to initiate a clinical trial in the treatment of FSGS with our late stage drug candidate CCR2 antagonist CCX140.

Funding: Commercial Support - ChemoCentryx

FR-OR061

A New Mouse Model of Chronic Proteinuria Due to a Glomerular Basement Membrane Laminin-521 Polymerization Defect Steven D. Funk, Raymond H. Bayer, Jeffrey H. Miner. *Washington University School of Medicine, St. Louis, MO.*

Background: The glomerular basement membrane (GBM) is a dense extracellular matrix that separates endothelium from podocytes. The GBM is thought to stabilize foot processes and slit diaphragms and, together with podocytes and endothelium, forms the glomerular filtration barrier. GBM integrity is maintained by: 1) polymerization of laminin $\alpha5\beta2\gamma1$ (LM-521) via tripartite α-β-γ chain NH2-terminal LN domain interactions; 2) attachment of the LMα5 C-terminal LG domain to podocyte & endothelial cell integrins; and 3) linkage of the laminin network to the type IV collagen network by nidogen. Null and missense mutations in the LMβ2 chain of LM-521 cause nephrotic syndrome. In previous studies of *Lamb2-/-* mice proteinuria preceded both foot process effacement and loss of slit diaphragms. Thus, LAMB2 LN domain missense mutations found in nephrotic patients may cause disease by impairing laminin polymerization.

Methods: In vivo CRISPR gene editing was used to generate a point mutation in the LN domain of mouse LAMB2, but DNA analysis of 1 founder showed an unexpected in-frame, 44 amino acid deletion within the LN domain. Homozygous LAMB2-d44 mice were observed for up to 8 months. Urine, blood, and tissues were taken at select time points to evaluate albuminuria, BUN, histopathology, and GBM composition and ultrastructure.

Results: The unexpected LAMB2-d44 mutation is analogous to the dy-2J mutation in mouse LMα2 that causes severe muscular dystrophy due to defective LM-211 polymerization. The GBM of LAMB2-d44 mice contained a normal level of LAMB2, but the mice exhibited modest proteinuria between 4-6 wks of age and nephrotic range by 8 wks. Foot process swelling was observed at 6 wks of age, with effacement at 8 wks. LAMB2-d44 mice died spontaneously from 4 months onward, but some lived over 8 months. Moderate glomerulosclerosis, tubular dilations, protein casts, and occasional immune infiltrates were commonly observed features.

Conclusions: LAMB2-d44 mice exhibit modest proteinuria early but have intact foot processes. Chronic nephrotic range proteinuria is accompanied by effacement. This mutant will serve as a tool to test innovative protein-based methods for strengthening the GBM's laminin network and reducing proteinuria. More generally, this new genetic model of nephrotic syndrome will useful for investigating disease progression.

Funding: NIDDK Support

FR-OR062

The miRNA-29a to Claudin-1 Pathway Is an important Regulator of Glomerular Albumin Permeation in Diabetic Nephropathy Yongfeng Gong,[3] George Jarad,[4] Ming-Zhi Zhang,[2] Raymond C. Harris,[1] Jianghui Hou.[4] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Vanderbilt University Medical School, Nashville, TN; [3]Washington University Renal Division, Saint Louis, MO; [4]Washington University School of Medicine, St. Louis, MO.*

Background: Diabetic nephropathy (DN) is characterized by alteration in glomerular filtration barrier, which include thickening of the the glomerular basement membrane (GBM), podocyte foot process effacement, reduced slit width and loss of slit diaphragm (SD). The disappearance of the SD is associated with the appearance of the tight junction (TJ) and re-expression of claudin-1 in podocytes, suggesting a previously unknown role for TJ in DN. Hyperglycemia has been shown to suppress the expression of miRNA-29 family in podocytes, which is known to modulate the expression of claudin-1 and extracellular matrix (ECM). These data suggest that miRNA-29a family might play roles in the development of podocyte dysfunction and glomerular phenotype of DN.

Methods: We have generated a series of transgenic mouse models to study the role of claudins and microRNAs in DN. Using a nephrin-rtTA mouse model, we have generated podocyte specific overexpression of claudin-1 in tetracycline inducible manner. Using gene targeting approach, we have generated a miRNA-29a knockout mouse model in the kidney.

Results: 1. Expression of miRNA-29a is downregulated in the podocytes from the *db/db-eNOS* mouse model of DN. 2. Knockout of miRNA-29a, the innate regulator of claudin-1 and ECM in podocytes, resulted in progressive proteinuria, accompanied by destabilization of podocyte SD and thickening of the GBM, which are the hallmarks of DN. Mechanistically, such pathologic changes are derived from increased expression of cell junction gene - claudin-1, and in GBM genes - collagen IV alpha3,4,5 and laminin beta2, all of which are direct targets of miRNA-29a. 3. Induction of claudin-1 gene expression in mature podocytes caused albuminuria. Using freeze fracture techniques, we confirmed the cell junction induced by claudin-1 overexpression, which culminate in the transformation of podocyte SD into TJ. Immunolabeling of SD proteins revealed that claudin-1 overexpression destabilized the SD protein complex, with significant reduction and altered localization of nephrin and podocin.

Conclusions: Our data attest to a novel concept that a central signaling pathway from microRNA to claudin-1 may coordinately regulate a wide spectrum of podocyte lesions important to DN. Such a pathway may lead to a new therapeutic aproach to treat DN by manipulating mircoRNA expression.

Funding: NIDDK Support

FR-OR063

The Potential Significance of Complement Factor D Bypass in fD-Targeted Treatment for C3G Yuzhou Zhang,[1] Adam C. Keenan,[1] Margaret A. Lindorfer,[3] Carla M. Nester,[1] Ronald P. Taylor,[3] John Lambris,[2] Richard J. Smith.[1] *[1]University of Iowa, Iowa City, IA; [2]University of Pennsylvania School of Medicine, Philadelphia, PA; [3]University of Virginia School of Medicine, Charlottesville, VA.*

Background: C3 glomerulopathy (C3G) is characterized by predominant deposition of complement C3 in the glomerulus in the absence or sparse presence of immunoglobulins. The underlying disease mechanism is uncontrolled activity of the C3 convertase of the alternative pathway (AP). Convertase activity is normally tightly controlled by the fluid-phase AP regulator factor H (fH). Mice with a targeted deletion of fH (*Cfh-/-*) develop features of C3G, with intense C3 deposition along glomerular capillary walls accompanied by subendothelial electron-dense deposits. The rate-limiting protease, fD, is the only enzyme known to cleave fB. Several AP inhibiting small-molecule antagonists against fD have been developed.

Methods: To assess fD-targeted therapy, we backcrossed *Cfh-/-* mice with *Cfd-/-* mice for >10 generations and evaluated complement dysregulation and renal pathology in *Cfh-/-* mice, *Cfd-/-* mice and *Cfh-/-*;*Cfd-/-* mice. We developed an *in vitro* fB-cleavage assay using a recombinant protein that contains the active catalytic domain of mannose-binding lectin-associated serine protease 3 (MASP-3).

Results: *Cfh-/-*;*Cfd-/-* mice have abundant mesangial and capillary deposition of C3 and C5b-9 with scant densities on electron microscopy consistent with ongoing complement dysregulation even in the absence of fD. Serum from *Cfh-/- mice* was devoid of complement activity due to depletion of complement proteins. Circulating C3 levels in *Cfd-/-* mice were 40% higher than in wild type mice however serum from *Cfd-/-* mice could not initiate AP activity without the addition of human fD. C3 levels in *Cfh-/-*;*Cfd-/-* and wild-type mice were comparable however even without fD serum from *Cfh-/-*;*Cfd-/-* mice was able to initiate AP activity based on hemolysis of rabbit erythrocytes and a positive C3-deposition assay. In the absence of fD, we found that the MASP-3 catalytic domain was capable of cleaving fB in the presence of C3b.

Conclusions: In the absence of fD, AP convertase assembly and activation can be initiated by the fB-cleavage activity of the lectin pathway serine protease MASP-3. This *in vivo* fD-bypass activation mechanism is always present but only becomes operational when the complement system is 'pushed' by the absence of both fH and fD. The implications of this bypass mechanism should be considered in fD-targeted treatment for C3G.

Funding: NIDDK Support

FR-OR064

Ex Vivo Formation of C5b9 on Endothelial Cells Differentiates Complement-Mediated Renal Failure from Hypertensive Nephrosclerosis in Severely Hypertensive Patients Sjoerd Timmermans,[2] Chris Reutelingsperger,[1] Pieter V. Paassen.[2] *[1]Maastricht University, Maastricht, Netherlands; [2]Maastricht University Medical Center, Maastricht, Netherlands. Group/Team: Limburg Renal Registry.*

Background: Severe hypertension (HTN) can induce renal failure due to hypertensive nephrosclerosis, a diagnosis rarely confirmed by biopsy assuming that the kidney is the victim rather than culprit of HTN. Underlying acute thrombotic microangiopathy (TMA) can therefore be missed, particularly in patients not presenting with microangiopathic hemolysis and thrombocytopenia. Moreover, it is critical to distinguish TMA due to shear stress from TMA dominantly caused by complement dysregulation, having major impact on treatment and prognosis.

Methods: To differentiate complement-mediated from shear stress-induced kidney injury in patients with severe HTN (blood pressure >180/120 mmHg) and renal failure, we analyzed serum-induced C5b9 formation on resting and ADP activated human microvascular endothelial cells (HMEC) by using samples from patients with severe HTN either with active TMA or hypertensive nephrosclerosis on kidney biopsy. Serum from patients with atypical hemolytic uremic syndrome (aHUS) and dense deposits disease (DDD) were used as positive and negative controls; all samples were compared with normal human serum run in parallel.

Results: Serum from 12 patients with HTN-associated TMA induced extensive C5b9 formation on resting (293%, $P<0.001$) and activated HMEC (318%, $P<0.001$), identical to aHUS samples ($n=3$; 344% and 394%, respectively). In contrast, samples from 5 patients with hypertensive nephrosclerosis induced scanty C5b9 formation on both resting (98%, $P=1.0$) and activated HMEC (108%, $P=0.7$), identical to DDD ($n=5$; 89% and 90%, respectively). C3c and C5b9 staining on kidney sections linked complement activation to TMA but not to nephrosclerosis. Moreover, genetic analysis confirmed complement defects in 6 (50%) out of 12 patients with HTN-associated TMA.

Conclusions: In conclusion, intrarenal solid phase complement dysregulation and ongoing TMA appears the dominant cause of renal failure in a subset of patients with severe HTN. The HMEC test differentiates complement-mediated TMA from other causes of HTN associated kidney injury, such as shear stress.

FR-OR065

Stem Cell-Derived Extracellular Vesicles Protect from VEGF-Induced Endothelial Damage in the Kidney Sargis Sedrakyan,[1] Valentina Villani,[1] Stefano Da Sacco,[1] Nikita Tripuraneni,[1] Stefano Porta,[2] Andrea Achena,[1] Maria J. Lavarreda-Pearce,[1] Astgik Petrosyan,[1] Hasmik Soloyan,[1] Roger E. De Filippo,[1] Benedetta Bussolati,[2] Laura Perin.[1] *[1]Children's hospital Los Angeles, Los Angeles, CA; [2]University of Torino, Torino, Italy.*

Background: Tight regulation of paracrine VEGF signaling between podocytes and glomerular endothelial cells (GEC) is required for maintenance of the glomerular filtration barrier structure and function. Disruption of VEGF signaling has been implicated in various types of glomerular diseases. However, current therapies neither specifically target the glomerulus nor the local VEGF but in addition, present multiple side effects. Therefore, identification of new approaches that will restore local VEGF signaling remains a potential therapeutic target to treat glomerular disease. We previously showed that amniotic fluid stem cells (AFSC) are renoprotective in Alport Syndrome (AS), a model of CKD. They home within the diseased glomeruli and secrete extracellular vesicles (EVs). EVs play a key role in stem cell-mediated paracrine function, including the kidney. Herein, we demonstrate that AFSC derived EVs regulate VEGF/VEGFRs signaling balance in AS GEC via a trapping mechanism involving VEGFR1 expressed on the surface of EVs.

Methods: We measured VEGF activity in AS glomeruli by WB. We also assessed VEGF/VEGFRs activity in GEC. We characterized AFSC-EVs cargo by FACS and by miRs arrays and evaluated their potential to affect VEGF biology in GEC and kidney function. EVs silenced for VEGFR1 were used to confirm VEGF trapping by VEGFR1.

Results: Glomeruli from AS mice at 3-months showed increased VEGF activity that was associated with GEC damage and subsequent onset of proteinuria. Treatment with EVs ameliorated the damage and improved kidney function by trapping and sequestration of VEGF. We found VEGFR1, present on the surface of EVs, responsible for this mechanism of action. EVs lacking both the full and soluble VEGFR-1 failed to rescue GEC from VEGF inflicted damage.

Conclusions: We demonstrated for the first time the aberration of VEGF signaling within AS glomeruli. We further showed that AFSC derived EVs play important role in maintaining glomerular homeostasis of VEGF signaling, presenting with a potential for new targeted therapies in CKD.

Funding: Private Foundation Support

FR-OR066

NG2 Lineage Cells Migrate onto the Glomerular Tuft and Bowman's Capsule with Expression of PEC Markers in Experimental FSGS Taihei Suzuki,[2] Jeffrey W. Pippin,[1] Diana G. Eng,[1] Stuart J. Shankland.[2] *[1]University of Washington, Seattle, WA; [2]Nephrology, University of Washington, Seattle, WA.*

Background: Glomerular regeneration typically relies on local stem/progenitor cells. After podocyte loss, parietal epithelial cells (PECs) and cells of renin lineage serve as adult podocyte progenitors. Although Neural/glial antigen 2 (NG2) cells are considered to have progenitor potency, their ability to participate in regeneration following podocyte loss is not fully understood. We sought to determine if NG2 lineage cells serve as adult glomerular stem/progenitors in disease.

Methods: We generated *NG2CreER tdTomato* reporter mice (n=11). Tamoxifen was given to 8 week-old mice to permanently label cells of NG2 lineage with the red fluorescent protein (RFP) tdTomato. After a washout period, podocytes were depleted with a cytopathic anti-podocyte antibody. Serial biopsies were taken at baseline, D14, and D28, to assess and fate map the behavior of NG2 lineage cells in individual mice.

Results: Podocyte number decreased by ~35% on D14 from baseline, and partially recovered on D28 ($p<0.05$ vs D14). Following podocyte loss, the percentage of glomeruli with RFP^+ cells increased two-fold on D14 and D28 ($p<0.05$ vs baseline). RFP^+ cells in glomeruli did not co-express podocyte proteins (synaptopodin, nephrin, podocin). Glomeruli with RFP^+ cells along Bowman's capsule increased significantly accompanied by increased PEC density, (PAX8 staining), at D14 and D28. Co-staining for PAX8 and src-suppressed C-kinase substrate to determine if the RFP+ cells along Bowman's capsule transdifferentiated to adult PECs showed that within individual mice, the percentage of glomeruli with $RFP^+/PAX8^+$, and $RFP^+/SSeCKS^+$ on Bowman's capsule increased significantly from baseline at both D14 and D28 following podocyte loss. Double-staining for RFP and BrdU for cell proliferation revealed that RFP^+ cells in glomerular tuft and capsule did not co-express BrdU.

Conclusions: We showed that after an abrupt loss of podocytes in an inducible reporter mouse, NG2 lineage cells migrated onto the glomerular tuft, but did not express podocyte proteins. However, a majority of NG2 labeled cells that migrated to Bowman's capsule co-expressed the PEC markers PAX8 and SSeCKS, which was accompanied by a higher PEC density. These results suggest that a subset of cells of NG2 lineage might serve as adult PEC stem/progenitors in glomerular disease.

FR-OR067

Krüppel-Like Factor 4 Is a Negative Regulator of Aberrant Glomerular Epithelial Cell Proliferation Chelsea C. Estrada,[4] Yiqing Guo,[4] Praharshasai Paladugu,[4] Stephanie Cardona,[4] Monica P. Revelo Penafiel,[3] David J. Salant,[1] John C. He,[2] Sandeep K. Mallipattu.[4] *[1]Boston University Medical Center, Boston, MA; [2]Mount Sinai School of Medicine, New York, NY; [3]University of Utah, Murray, UT; [4]Stony Brook Medicine, Stony Brook, NY.*

Background: Pathologic glomerular epithelial cell (GEC) proliferation is characteristic of both RPGN and subtypes of FSGS. Although initial podocyte injury resulting in activation of signal transducer and activator of transcription (STAT) 3 signals GEC proliferation in both diseases, mechanism(s) regulating this process are largely unknown. Krüppel-Like Factor 4 (KLF4), a zinc finger transcription factor, is a negative regulator of proliferation and has recently been shown to inhibit STAT3 activation in neurons. Furthermore, KLF4 was previously shown to be renoprotective in proteinuric kidney disease. Based on these data, we hypothesize that podocyte-specific *Klf4* deletion exacerbates pathologic GEC proliferation by activation of STAT3 signaling.

Methods: Podocyte-specific *Klf4* knockout mice ($Klf4^{\Delta Pod}$) were generated on *C57BL/6* background by crossing $Klf4^{fl/fl}$ mice with *Podocin-Cre* mice. Nephrotoxic serum (NTS) nephritis was used to induce RPGN. $Klf4^{\Delta Pod}$ mice were backcrossed to a background susceptible to FSGS (*FVB/n*). Finally, human podocytes with stable knockdown of *KLF4* (*KLF4-shRNA*) and overexpression of *KLF4* (*lentiORF-KLF4*), with appropriate controls, were generated.

Results: Glomerular KLF4 expression was increased 7 days after NTS treatment. NTS-treated $Klf4^{\Delta Pod}$ (*C57BL/6*) mice exhibited increased crescent formation, parietal epithelial cell (PEC) proliferation (Claudin1, Ki67), serum creatinine, and STAT3 signaling (phospho-STAT3, *Il-6, Socs3* expression) as compared to NTS-treated wildtype mice. Untreated backcrossed $Klf4^{\Delta Pod}$ (*FVB/n*) mice exhibited STAT3 activation, cellular FSGS with PEC proliferation, renal failure, and a 50% increase in mortality as compared to wildtype mice at 12 weeks of age. Furthermore, basal STAT3 activation was significantly increased in wild-type *FVB/n* as compared to the *C57BL/6* strain. Differentiated *KLF4-shRNA* podocytes also exhibited increased STAT3 activation with mitotic catastrophe (re-entry into cell cycle, actin destabilization) leading to reduced survival as compared with *EV-shRNA* podocytes. Conversely, these changes were rescued with re-induction of *KLF4* (*lentiORF-KLF4)* in cultured podocytes.

Conclusions: Collectively these data suggest that KLF4 is a key regulator of STAT3-mediated aberrant GEC proliferation in RPGN and FSGS.

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FR-OR068

Effects of the Potassium Binding Polymer Patiromer on Markers of Mineral Metabolism David A. Bushinsky,[2] David M. Spiegel,[3] Jinwei Yuan,[3] Suzette Warren,[3] Pablo E. Pergola.[4] *[2]Division of Nephrology, University of Rochester Medical Center, Rochester, NY; [3]Relypsa, Inc., a Vifor Pharma Company, Redwood City, CA; [4]Renal Associates, PA, San Antonio, TX.*

Background: Patiromer is a non-absorbed potassium (K)-binding polymer approved for treatment of hyperkalemia (HK), which uses calcium (Ca) as the counter-exchange ion. The 4-week TOURMALINE study in patients with HK demonstrated that patiromer once-daily (QD) reduces serum K when given without food similarly to when given with food. Here we report data from TOURMALINE on markers of mineral metabolism.

Methods: Initial patiromer dose was 8.4 g QD and was adjusted to achieve and maintain serum K between 3.8-5.0 mEq/L. In this prespecified analysis, baseline and week 4 (wk 4) serum and 24-hour urine (u) markers of mineral metabolism normalized for u-creatinine (Cr) excretion, to correct for collection errors, are reported for the overall population of 112 patients. All values are mean ± SE; p values are for change from baseline by paired t-test.

Results: Baseline serum Ca and phosphate (P) were 9.31 ± 0.06 and 4.10 ± 0.07 mg/dL, respectively, and were not different at wk 4 (9.34 ± 0.06 and 3.99 ± 0.07 mg/dL, respectively). In the 16 patients with elevated serum P (> 4.8 mg/dL) at baseline, patiromer decreased P from 5.32 ± 0.11 to 4.68 ± 0.26 mg/dL at wk 4 ($p<0.02$). In the overall population, Cr-normalized uP decreased from 628.2 ± 28.2 at baseline to 573.6 ± 29.4 mg/24 hr at wk 4 ($p<0.01$). Cr-normalized uCa was 50.8 ± 6.4 at baseline and did not change at wk 4 (58.5 ± 6.7 mg/24 hr; $p=0.1$). Serum $1,25(OH)_2D$ levels decreased from 37.3 ± 1.6 at baseline to 34.1 ± 1.7 pg/mL at wk 4 ($p<0.05$), while PTH decreased from 85.1 ± 5.6 at baseline to 65.2 ± 4.5 pg/mL at wk 4 ($p<0.0001$). There were no changes in mean levels of FGF-23 or 25(OH)D.

Conclusions: In addition to lowering serum K, patiromer decreased mean uP excretion in the overall population and mean serum P in patients with hyperphosphatemia, while not changing mean uCa or mean serum Ca. PTH and $1,25(OH)_2D$ both decreased. These findings suggest that when patiromer exchanges intestinal K for Ca, some of the released Ca binds to intestinal P lowering uP and serum P in hyperphosphatemic patients and some of the Ca is absorbed, lowering PTH and $1,25(OH)_2D$ without changing serum Ca.

Funding: Commercial Support - Relypsa, Inc., a Vifor Pharma Company

FR-OR069

Erythropoietin Is Associated with Total FGF23 Levels in Mice and Humans with CKD Mark R. Hanudel,[1] Maxime Rappaport,[1] Victoria R. Gabayan,[2] Tomas Ganz,[2] Elizabeta Nemeth,[2] Isidro B. Salusky.[1] *[1]Department of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA; [2]Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA.*

Background: We have previously demonstrated that exogenous erythropoietin (EPO) acutely increases bone and circulating FGF23 levels in mice and humans with normal kidney function. It is unknown if EPO has similar effects on FGF23 in the setting of CKD.

Methods: We administered a single dose of EPO to wild type mice with adenine diet-induced CKD. We evaluated associations between serum EPO levels and circulating FGF23 in adult and pediatric non-dialysis CKD patients, and between recombinant human EPO (rhEPO) doses and circulating FGF23 in adult and pediatric dialysis patients.

Results: At six hours post-injection, compared to CKD mice injected with saline, CKD mice intraperitoneally injected with 70 U/g rhEPO demonstrated a 10-fold increase in bone *Fgf23* mRNA expression and a 5-fold increase in plasma C-terminal (total) FGF23 (cFGF23) levels, but only a 3-fold increase in plasma intact FGF23 (iFGF23) levels, with a 40% decrease in percentage iFGF23 (iFGF23/total FGF23 x 100%). These data suggest that EPO-induced increases in *Fgf23* mRNA expression are coupled with increased FGF23 proteolytic cleavage. In 70 adult and pediatric non-dialysis CKD patients, after adjustment for eGFR ($p<0.001$) and phosphate ($p<0.001$), serum EPO levels positively associated with Log cFGF23 (std. coeff. 0.25, $p=0.010$; model adjusted $R^2=0.44$). The association remained significant ($p=0.023$; model adjusted $R^2=0.42$) after further adjustment for age, calcium, Log PTH, TSAT, Log ferritin, Hgb, and Log CRP, none of which were independently associated with Log cFGF23. Unlike cFGF23, Log iFGF23 was not significantly associated with EPO levels. In 79 adult and pediatric dialysis patients, after adjustment for age ($p<0.001$), phosphate ($p<0.001$), calcium ($p=0.013$), Log CRP ($p=0.015$), and Log ferritin ($p=0.018$), Log rhEPO dose positively associated with Log cFGF23 (std. coeff. 0.23, $p=0.013$; model adjusted $R^2=0.44$). The association remained significant ($p=0.016$; model adjusted $R^2=0.43$) after further adjustment for Log PTH, TSAT, and Hgb, none of which were independently associated with Log cFGF23. Similar to the non-dialysis CKD patients, Log rhEPO dose was not significantly associated with Log iFGF23.

Conclusions: In CKD patients, erythropoietin has stronger associations with total FGF23 than intact FGF23, suggesting coupling of increased production with increased cleavage.

Funding: NIDDK Support, Other NIH Support - NIH Loan Repayment Program

FR-OR070

Ferric Citrate Administration Reduces FGF23 Production and Improves Renal Function in a Mouse Model of CKD Connor Francis,[2] Guillaume Courbon,[2] Samantha Neuburg,[2] Claire Gerber,[2] Xueyan Wang,[2] Corey Dussold,[2] Lixin Qi,[2] Aline Martin,[2] Myles S. Wolf,[1] Valentin David.[2] *[1]Duke University, Durham, NC; [2]Northwestern University - Feinberg School of Medicine, Chicago, IL.*

Background: Elevated levels of fibroblast growth factor 23 (FGF23) are strongly associated with cardiovascular disease, mortality, and progression of chronic kidney disease (CKD). Hyperphosphatemia and iron deficiency are powerful stimuli of FGF23 production. This suggests that reducing dietary phosphate intake or absorption and increasing serum iron may lower FGF23 levels and improve clinical outcomes in CKD.

Methods: We tested the hypotheses that ferric citrate treatment will simultaneously correct iron deficiency and also bind to dietary phosphate in the $Col4a_3^{ko}$ mouse model of progressive CKD. We fed 4 week-old wild-type (WT) and $Col4a_3^{ko}$ (CKD) mice, a control (Ctr) or a 5% Ferric Citrate enriched (FC) diet for 6 weeks and performed biochemical, molecular and histological analyses.

Results: At ten weeks, Ctr-CKD animals displayed a decline in renal function, as shown by a 8 fold increase in Blood Urea Nitrogen (BUN) and urinary albumin, signs of iron deficiency anemia, evidenced by low serum iron (99±12 vs 128±5 mg/dL) and hemoglobin (15±1 vs 19±1 g/dL), as well as a 2 fold increase in serum phosphate ($p<0.05$ vs WT). This was concomitant with a marked increase in both total (tFGF23, which includes intact and cleaved proteins) and intact FGF23 (iFGF23) serum levels, compared to WT (11426±2623 vs. 433±32 and 7312±1749 vs. 207±57 pg/mL respectively, $p<0.05$). In addition, serum 1,25 Vitamin D levels were low (34±7 vs 143±45 pg/mL) in Ctr-CKD animal ($p<0.05$, vs. Ctr-WT). Ferric citrate increased serum iron levels by 1.6 fold in CKD mice and resulted in a 1.5 fold serum phosphate reduction ($p<0.05$, vs. Ctr-CKD). In addition, tFGF23 and iFGF23 were reduced by 4 and 3 fold respectively and serum 1,25 Vitamin D levels increased by 2 fold in FC-CKD mice ($p<0.05$ vs. Ctr-CKD). Interestingly, the FC diet also decreased BUN (127±21 vs. 218±24 mg/dL) and 24h urine albumin (101±69 vs. 586±91 µg) ($p<0.05$ vs. Ctr-CKD). Reductions in interstitial fibrosis and tubular dystrophy were also evident by histology in FC-CKD animals compared to Ctr-CKD group.

Conclusions: Our data show that ferric citrate administration in CKD mice reduces the magnitude of FGF23 increase and slows disease progression. This suggests that ferric citrate might mitigate renal injury.

Funding: Commercial Support - Keryx Biopharmaceuticals

FR-OR071

Occurrence of Hypophosphatemia Following IV Iron Treatment: Results from a Randomized Controlled Trial Myles S. Wolf,[2] William Strauss,[1] Kristine Bernard,[1] Naomi V. Dahl,[1] Robert F. Kaper,[1] Julie S. Krop.[1] *[1]AMAG Pharmaceuticals, Inc., Waltham, MA; [2]Duke University, Durham, NC.*

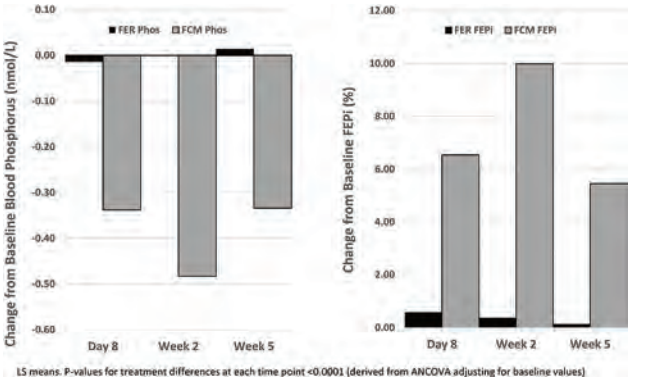
Background: Hypophosphatemia is a common complication of administration of certain IV irons. For example, 32.1% of patients with gastrointestinal disorders who received treatment with ferric carboxymaltose (FCM) developed hypophosphatemia, <0.6 mmol/L (1.9 mg/dl) (Schaefer et al., PLoS ONE 2016). Acute increases in circulating levels of intact fibroblast growth factor 23 (FGF23) mediate hypophosphatemia due to renal phosphate wasting in response to FCM, but not iron dextran, suggesting that the specific carbohydrate moieties might be involved in the differential FGF23 response to IV iron (Wolf et al., Bone Min Res, 2013). While initially considered a transient and benign laboratory finding, reports are accumulating of significant clinical sequelae associated with chronic FCM-associated hypophosphatemia.

Methods: In a large RCT (NCT02694978) that compared the safety and efficacy of standard courses of ferumoxytol (FER, 510mg x 2 doses; N=997), vs. FCM (750mg x 2 doses; N=1000) in patients with iron deficiency anemia of any etiology except dialysis-dependent CKD, we measured serum phosphate and fractional excretion of phosphate (FEPi) at baseline, day 8 (prior to dose 2), week 2 and week 5.

Results: Mean baseline serum phosphate was 1.22 mmol/L (3.8 mg/dl) and FEPi was 15.7% in both groups. Among patients receiving FCM, serum phosphate decreased significantly, and FEPi increased significantly at all time points compared to ferumoxytol-treated patients ($P<0.0001$; Figure). Serum phosphate <0.6 mmol/L (1.9 mg/dl) occurred in 38.7% of FCM patients, and only 0.4% of FER patients.

Conclusions: FCM induced a marked drop in blood phosphorus occurring as soon as 8 days following 750mg of FCM secondary to a significant increase in FEPi. Almost 40% of patients developed at least moderate hypophosphatemia. These changes did not occur following FER.

Funding: Commercial Support - AMAG Pharmaceuticals, Inc.



FR-OR072

Cardiac Hypertrophy Elevates Serum FGF23 Karin Shimada, Isao Matsui, Tatsufumi Oka, Daisuke Mori, Nobuhiro Hashimoto, Ayumi Matsumoto, Satoshi Yamaguchi, Keiichi Kubota, Sayoko Yonemoto, Yusuke Sakaguchi, Takayuki Hamano, Yoshitaka Isaka. *Osaka University Graduate School of Medicine, Suita, Japan.*

Background: FGF23 is a potent phosphaturic hormone predominantly produced by the bone. Although several studies have revealed FGF23 induces left ventricular hypertrophy (LVH), effect of LVH on FGF23 remains uncertain.

Methods: The activation of calcineurin/NFAT pathway plays pivotal roles in the development of pathological LVH. Therefore, we performed experiments using cardiomyocyte-specific calcineurin A transgenic (TG) mice.

Results: The TG mice at 6-week-old showed severe LVH. Body weight, systolic blood pressure, food intake, water intake, urinary volume, and creatinine clearance were not different between wild type (WT) and the TG mice. We found that serum intact FGF23 (iFGF23) in the TG mice were elevated (TG 125.6 ± 16.1 vs. WT 87.5 ± 10.1 pg/mL, $P=0.0107$). Both real time PCR and immunohistochemistry revealed that the elevation of iFGF23 in the TG mice was derived from hypertrophic cardiomyocytes but not from the bone. The promoter region of the FGF23 gene contained two putative NFAT-biding sites. Luciferase assay showed that NFAT1 activates the promoter in a proximal NFAT-binding site dependent manner. Although serum level of iFGF23 was elevated in the TG mice, all parameters — serum, urinary, and fractional excretion of calcium/phosphate, and serum $1,25(OH)_2$ vitamin D — were not different between the WT and the TG mice. Renal levels of α-klotho were also at comparable levels between the two groups. We found that plasma ADH levels of the TG mice were higher than those of the WT mice (TG 1.01 ± 0.68 vs. WT 0.40 ± 0.46 pg/mL, $P=0.0306$). To investigate the effects of ADH on the function of FGF23, we injected ADH and/or FGF23 into WT mice. As previously reported, FGF23 suppressed renal mRNA levels of CYP27B1. The suppression of CYP27B1 was restored by ADH. In addition, FGF23-dependent elevation of CYP24 was suppressed by ADH. Both FGF23 and ADH did not affect expression levels of α-klotho in the kidney.

Conclusions: Hypertrophic cardiomyocyte produces FGF23. Proximal NFAT-binding site in the FGF23 gene promoter was important for the transcriptional regulation of FGF23. ADH causes FGF23-resistance in the kidney.

Funding: Private Foundation Support

FR-OR073

Different Outcome of Cardiac Remodeling in Two Mouse Models with FGF23 Excess and Klotho Deficiency Beatrice Richter,[5] Melis Basaran,[6] Ioana Alesutan,[7] Jakob Voelkl,[4] Florian C. Lang,[1] Dieter Haffner,[3] Maren Leifheit-Nestler.[2] *[1]Department of Cardiology, Vascular Medicine and Physiology, University of Tuebingen, Tuebingen, Germany; [2]Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; [3]Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; [4]Department of Internal Medicine and Cardiology, Center for Cardiovascular Research, Charité University Medicine, Berlin, Germany; [5]Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; [6]Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; [7]Department of Internal Medicine and Cardiology, Center for Cardiovascular Research, Charité University Medicine, Berlin, Germany.*

Background: High levels of fibroblast growth factor-23 (FGF23), phosphate and parathyroid hormone (PTH) as well as deficiency in active vitamin D (1,25D) and klotho are strongly associated with the development of cardiovascular disease, including left ventricular hypertrophy and myocardial fibrosis. *In vivo*, klotho and 1,25D improve cardiac hypertrophy and *in vitro*, klotho inhibits fibroblast activation and collagen synthesis in the heart and protects against FGF23-induced oxidative stress.

Methods: Heart tissue from two mouse models with high FGF23 serum levels and klotho deficiency was analyzed: 1) klotho hypomorphic ($KL^{-/-}$) mice displaying both high phosphate and 1,25D levels, but low PTH; 2) *Hyp* mouse presenting high PTH, but low plasma levels of phosphate and 1,25D.

Results: For both mouse models an enhanced relative heart weight and raised cross-sectional area of cardiomyocytes were detected when compared to respective wild type controls. In $KL^{-/-}$ mice, a clear increase of cardiac Fgf23, Fgfr4, activation of calcineurin/NFAT signaling and induction of pro-hypertrophic genes *Rcan1, BNP, ANP* and *bMHC* was seen. Furthermore, $KL^{-/-}$ mice showed an enhanced expression of transcription factors (Cebpb, Gata4) and fibrosis-related factors (*Tgfb1, collagen 1, Mmp2*) that are involved in cardiac remodeling events. In contrast, *Hyp* mice presented a strong increase of cardiac *Fgf23* mRNA and intact cardiac Fgf23 protein as well, but missed the induction of the Fgfr4/calcineurin/NFAT pathway. Moreover, the expression of the pro-hypertrophic markers *BNP, ANP, bMHC* and pro-fibrotic factors was absent in *Hyp* mice.

Conclusions: Despite the FGF23 excess, high PTH, low 1,25D and reduced klotho, it seems that *Hyp* mice are protected from the development of pathological heart changes may be due to hypophosphatemia. Contrary, $KL^{-/-}$ mice show induced cardiac hypertrophy and fibrosis though high 1,25D plasma levels.

FR-OR074

Fibroblast Growth Factor 23 (FGF23) Regulates PTH Levels through FGF Receptor Signaling In Vivo at Normal, but Not at Low, Plasma Calcium Maria L. Mace,[2] Eva Gravesen,[3] Anders Nordholm,[2] Jacob Hofman-Bang,[3] Klaus Olgaard,[1] Ewa Lewin.[2] *[1]Copenhagen University, Copenhagen, Denmark; [2]Herlev Hospital, Herlev, Denmark; [3]Rigshospitalet, Copenhagen, Denmark.*

Background: The regulation of PTH secretion is primarily mediated by calcium. FGF23 is a bone derived phosphatonin that requires klotho as a co-receptor for binding to the FGF receptors (FGFR). Parathyroid cells express both Klotho and FGFRs, however, the physiological function of FGF23 in the parathyroid gland is not fully clarified. Parathyroid cells lose rapidly their calcium-sensing responsiveness *ex vivo*, and no functional parathyroid cell line has been established. Therefore the aim of the present investigation was to study FGF23's regulation of PTH levels *in vivo*.

Methods: Wistar rats were randomized to FGFR inhibition by PD173074 (20-40mg) or vehicle. Acute hypocalcemia was induced by a continuous intravenuous EGTA infusion (40mM, 3ml/h) in normal rats and rats after prior FGFR inhibition. Increasing doses (0.1, 1, and 10 μg) of recombinant FGF23 were given to normal rats and rats after prior FGFR inhibition. Plasma Ca^{++}, phosphate, FGF23 and PTH were measured.

Results: Acute inhibition of FGFR resulted in a decrease in p-FGF23 (364±22 to 154±18 pg/ml, $p<0.05$) and a concomitant increase in p-PTH levels (134±34 to 685±285 pg/ml, $p<0.01$). The PTH secretory response was challenged by acute severe hypocalcemia (p-Ca^{++} decreased from 1.37±0.01 to 0.98±0.03 mmol/l, $p<0.01$). Again at normocalcemia PTH increased in FGFR inhibited rats (85±13 to 182±10 pg/ml), while the maximal PTH secretion at low p-Ca^{++} was not different in FGFR inhibited rats compared to vehicle treated rats (347±61 vs. 316±22 pg/ml). Exogenous rFGF23 0.1 μg inhibited rapidly, at 20 min, PTH levels in normal rats (137±71 to 10±4 pg/ml, $p<0.05$). In FGFR inhibited rats 0.1 μg rFGF23 did not suppress PTH levels (270±50 vs. 347±62 pg/ml). Higher doses of rFGF23 resulted in very high levels of p-FGF23 (12,000 & 120,000 pg/ml), still these high levels had no effect on PTH levels when the FGFR was inhibited.

Conclusions: FGF23 regulates PTH tonus in vivo via the FGF receptor. The inhibitory effect of FGF23 on PTH is present at normal range of plasma Ca^{++}, but not at low Ca^{++} levels, when increased PTH secretion is needed.

Funding: Government Support - Non-U.S.

FR-OR075

Acute and Mid-Term Mineral Disturbances Following Kidney Donation Kenneth Lim,[1,4] Jane C. Smith,[4] Carmel M. McEniery,[4] Laurie A. Tomlinson,[2] Ian Wilkinson,[4] Thomas F. Hiemstra.[3,4] *[1]Division of Nephrology, Massachusetts General Hospital, Harvard Medical School, Boston, MA; [2]London School of Hygiene and Tropical Medicine, London, United Kingdom; [3]University of Cambridge, Cambridge, United Kingdom; [4]School of Clinical Medicine, University of Cambridge, Cambridge, United Kingdom.*

Background: Unilateral nephrectomy performed for live transplant donation is increasing due to a greater demand for available organs. To counteract the growing transplant waiting list, the opportunity to donate organs has been extended to a broader population. However, these expanded criteria donors (ECDs) maybe at greater risk from a fall in GFR following unilateral nephrectomy. While emerging studies have demonstrated profound mineral disturbances that occur following kidney donation, whether acute disturbances in mineral homeostasis occur following unilateral nephrectomy is currently unknown.

Methods: We conducted the KARMA (Effect of Kidney Donation on Bone and Mineral Metabolism) study, a prospective controlled observational cohort study. Biochemical parameters were determined before and acutely after kidney donation on days 1-3 with mid-term follow-up at 6 weeks and 12 months in the donor group and at baseline, 6 weeks and 12 months in the control group.

Results: We enrolled 34 donors (59% male) and 34 healthy controls (47% male). Both groups had similar characteristics: mean (±SD) age (53±10 vs 50±14 years, p=0.33), BMI (26±2.8 vs 25.9±3.7, p=0.59), systolic BP (128±13 vs 130±6, p=0.59), diastolic BP (80±9 vs 81±9, p=0.68) and baseline GFR (84.4±20.2 vs 83.6±25.2 ml/min/1.73m^2, p=0.89). Kidney donation reduced eGFR significantly from 84.4±20.2 to 52.3±17.5 ($p<0.001$) acutely by day 1 and remained lower than baseline by 6 weeks (60.0±20.0; $p<0.001$) and 12 months (88.6±24.3; $p<0.001$). Phosphate levels increased from baseline by day 1 (1.1[0.9,1.2] to 1.3[1.1, 1.4], $p<0.001$) and then declined to 0.8[0.8, 1.0] by day 2 ($p<0.001$) before normalizing by 6 weeks. Albumin-corrected calcium declined on day 1 (p=0.003) but did not differ at 6 weeks or 12 months after donation. PTH levels did not rise significantly from baseline until 1 year (4.77[3.39, 5.8] vs 5.8[4.56, 8.7]; p=0.018). FGF-23 levels were statistically unchanged at all time points. However, soluble α-Klotho levels were significantly reduced by day 1 (p=0.001) and remained low at 6 weeks (p=0.02) and 1 year (p=0.04).

Conclusions: Profound mineral disturbances occur acutely after kidney donation. Acute mineral disturbances in phosphate and calcium occur independently of changes in the phosphaturic hormones, PTH and FGF-23. Serum α-Klotho levels decline acutely following unilateral nephrectomy.

Funding: Private Foundation Support

FR-OR076

Quantitative Systems Pharmacology (QSP) Model of Metabolic Bone Disease in ESRD Michael E. Brier,[1] Matthew J. Graves,[1] Eleanor D. Lederer,[2] Adam E. Gaweda.[1] *[1]University of Louisville, Louisville, KY; [2]University of Louisville; Robley Rex VA Medical Center, Louisville, KY.*

Background: Metabolic bone disorder (MBD), a universal complication of chronic kidney disease (CKD), is a recognized contributor to the accelerated mortality of CKD patients but achieving established goals for therapy is challenging. We tested the hypothesis that a QSP model of MBD-CKD could provide a precision medicine tool to guide pharmacologic interventions for MBD.

Methods: We modified the Peterson-Riggs (Bone 2010) model of phosphate (PO4), calcium (Ca), PTH, and Calcitriol (CTL) in CKD to apply to end-stage renal disease patients. The model consists of a set of nonlinear differential equations describing the regulation of serum PO4, Ca, PTH, and CTL, implemented in Matlab, and includes the effect of intermittent hemodialysis and the administration of phosphate binders, cinacalcet, and vitamin D analogs. We tested the model by simulating the administration of different agents and performed a Sensitivity Analysis to identify key model components. Data were obtained from in-center dialysis patients at the University of Louisville.

Results: The QSP model accurately predicts the concentration time profile of PTH following repeated administration of cinacalcet and CTL and the impact of intermittent hemodialysis on the serum concentrations of Ca and PO4. Sensitivity Analysis results for the top 5/100 parameters along with the contribution of each of the individual components are shown. The table entries represent the correlation between the model parameters and goodness of fit for an individual patient. The model is most sensitive to flux of PO4, kidney PO4 excretion, and Ca absorption and hydroxyapatite conversion.

Conclusions: We conclude that a QSP model of MBD-CKD accurately predicts the serum concentrations of PO4, Ca, PTH, and CTL and that these predictions are heavily influenced by PO4 flux, PO4 excretion sensitivity, and availability of Ca.

Parameter	PTH	Ca	PO4	CTL	Total
k85	0.01	-0.06	0.11	-0.39	0.57
d59	-0.04	-0.01	-0.08	0.42	0.55
T13	-0.34	-0.08	-0.06	-0.06	0.54
k58	-0.05	-0.02	-0.08	0.38	0.54
T15	0.33	0.03	0.08	0.05	0.49

k85 and k58 PO4 transfer rate between serum and intracellular compartment; d59 kidney phosphate excretion sensitivity; T13 normalized calcium absorption rate; and T15 hydroxyapatite conversion rate

FR-OR077

FGF23 Trajectories Among Patients Undergoing Chronic Hemodialysis in the HEMO Study Anna J. Jovanovich,[2] Zhiying You,[5] Kristen L. Nowak,[8] Lilia Cervantes,[1] Tamara Isakova,[4] Myles S. Wolf,[3] Michel Chonchol,[6] Jessica B. Kendrick.[7] *[1]Denver Health, Denver, CO; [2]Denver VA / University of Colorado, Denver, CO; [3]Duke University, Durham, NC; [4]Feinberg School of Medicine, Northwestern University, Chicago, IL; [5]UC Denver, Aurora, CO; [6]University of Colorado, Aurora, CO; [7]University of Colorado Denver and Denver Health Medical Center, Denver, CO; [8]University of Colorado Denver: Anschutz Medical Campus, Aurora, CO.*

Background: Single measurements of elevated circulating levels of fibroblast growth factor 23 (FGF23) are associated with all-cause mortality in patients with end stage kidney disease (ESKD); however, long-term patterns in FGF23 levels have been poorly characterized. The objective of this study was to identify common FGF23 trajectories in patients with ESKD, and to evaluate predictors and outcomes among trajectories.

Methods: The HEMO Study was a randomized multicenter study evaluating the effects of high-dose versus standard-dose and high-flux versus low-flux hemodialysis. Serum intact FGF23 (iFGF23) levels were measured in stored serum samples obtained at baseline and annually in this cohort. Among 919 HEMO participants with at least two measurements of iFGF23, latent mixture modeling was used to identify trajectories of iFGF23 over time. Logistics regression models were employed to identify demographics, cardiovascular risk factors, markers of mineral metabolism and other variables associated with trajectory group membership. Cox regression models were used to examine the association between trajectory group and all-cause mortality.

Results: We identified 5 distinct FGF23 trajectories during the initial 2 years of the HEMO study: low-stable (16.8%; n=154), moderate-increasing (17.3%; n=159), elevated-increasing (27.5%; n=253); elevated-stable (25.4%; 233) and moderate-decreasing (13.1%; n=120). The only predictors of the moderate decreasing trajectory versus the low-stable trajectory were lower serum calcium (OR: 0.50; 95% CI 0.35-0.71; p <0.0001), lower serum phosphorus (OR: 0.64; 95% CI 0.53-0.78; p=0.0001), and lower serum interleukin-6 (0.58; 95% CI 0.39-0.87; p=0.009). In fully adjusted analyses, participants with elevated-stable FGF23 trajectory were at higher risk of death (HR: 1.61 95% CI 1.10-2.40; p=0.01) compared with the low-stable group trajectory.

Conclusions: FGF23 trajectories in patients undergoing hemodialysis vary and higher FGF23 trajectories are associated with an increased risk of death. Lower serum calcium and interleukin-6 appear to be important predictors of decreasing FGF23 levels.

Funding: NIDDK Support

FR-OR078

Athena Study Outcomes on Allograft Function after 12 Months with Everolimus-Based versus Tacrolimus-MPA Regimen in De Novo Renal Transplant Recipients Friedrich Thaiss,[9] Barbara M. Suwelack,[3] Claudia Sommerer,[11] Duska Dragun,[10] Ingeborg A. Hauser,[2] Peter Schenker,[6] Oliver Witzke,[8] Christian Hugo,[12] Nassim Kamar,[7] Pierre Merville,[5] Martina Junge,[4] Björn Nashan.[1] *[1]Bundesärztekammer, Hamburg, Germany; [2]University Clinic Frankfurt (UKF), Frankfurt Main, Germany; [3]Muenster, Germany; [4]Novartis Pharma GmbH Germany, Nuremberg, Germany; [5]PELLEGRIN HOSPITAL, Bordeaux, France; [6]Ruhr-University Bochum, Bochum, Germany; [7]Toulouse University Hospital, Toulouse, France; [8]University Duisburg-Essen, Essen, Germany; [9]University Hospital, Hamburg, Germany; [10]University Hospital Charite, Campus Virchow, Berlin, Germany; [11]University Hospital of Heidelberg, HEIDELBERG, Germany; [12]University of Dresden, Dresden, Germany, Dresden, Germany. Group/Team: Athena Study Group.*

Background: The ATHENA study was designed to compare efficacy, safety and outcomes on renal function [GFR] of everolimus [EVR] combined with tacrolimus [TAC] or cyclosporine A [CyA] vs. a standard regimen of mycophenolic acid [MPA] +TAC in de novo kidney transplant [KTx] recipients.

Methods: In this 12 months [M], prospective, randomized study with 15 German and 12 French sites, 612 patients [pts] were randomized 1:1:1 at time of Tx to either EVR (3-8ng/ml M1-M12) +TAC (4-8ng/ml M1-M3; 3-5ng/ml M3-M12), or EVR (3-8ng/ml M1-M12) + CyA (75-125ng/ml M1-M3; 50-100ng/ml M3-M12) or control TAC (4-8ng/ml M1-M3; 3-5ng/ml M3-M12) +MPA. Steroids were to be continued. Here we report M12 outcomes on allograft function from ITT full analysis set with 208 EVR+TAC vs 199 EVR+CyA vs 205 TAC+MPA pts.

Results: From rdz to M12 allograft recovery was good in all 3 treatment groups with increase in GFR (Nankivell) as ΔeGFR M1-M12: a) EVR+TAC +6.6ml/min, b) EVR +CyA +9.6ml/min, c) TAC+MPA +7.6 ml/min (not significantly different). Analysis of donor age categories [<35; 35-49; 50-64; >65 years] showed that donor age >65years had worst renal allograft outcomes, regardless of treatment. Urinary protein excretion at M12 was not different between groups with a category analysis showing only 3.7% of TAC+MPA vs 1.3% of TAC+EVR vs 0.7% of CyA+EVR pts had proteinuria in nephrotic range [>339mg/mmol] at M12.

Conclusions: ATHENA, the largest European KTx study, showed comparable improvement in renal allograft function between all treatment groups with no difference in measured urinary protein excretion after 12 Mo drug exposure. Strongest impact on post Tx GFR appears to be determined by donor age, which is shown here for the first time in a large prospective study.

Funding: Commercial Support - Novartis Pharma GmbH, Germany

FR-OR079

HLA-DQ Mismatching and Kidney Transplant Outcomes: A UNOS/OPTN Analysis Napat Leeaphorn, J. ryan Pena, Natanong Thamcharoen, Eliyahu V. Khankin, Martha Pavlakis, Francesca Cardarelli. *Beth Israel Deaconess Medical Center, Brookline, MA.*

Background: Recent evidence suggests that HLA epitope-mismatching at HLA-DQ loci is strongly associated with the development of anti-DQ donor-specific antibodies (DSA) and adverse graft outcomes. However, the clinical significance of broad antigen HLA-DQ mismatching (MM) in predicting graft outcomes is not well examined. Using UNOS/OPTN data, we analyzed the effect of HLA-DQ MM on graft outcomes.

Methods: Patients with primary kidney transplants performed between 2007 and 2015 were included. Patients were classified as having either zero HLA-DQ MM, one or two HLA-DQ MM. Primary outcomes were death-censored graft survival (DCGS), and incidence of acute rejection.

Results: 95,664 patients were included in the analysis, with median follow-up time of 3.45 years. Of these, 22,379 (23.39%) and 73,294 (76.61%) received zero and one or two HLA-DQ MM kidneys, respectively. After adjusting for HLA-ABDR, various recipient and donor variables and initial immunosuppression, HLA-DQ MM was associated with an increased risk of graft loss in living donor kidney transplant (LDKT) recipients with an adjusted hazard ratio (HR) of 1.12 (95% CI, 1.01-1.26; p=0.042), but not in deceased donor kidney transplant (DDKT) recipients (HR 1.07, 95% CI, 0.99-1.53; p=0.066). When taking cold ischemic time (CIT) into account, HLA-DQ MM was an independent factor for an increased risk of graft loss in DDKT recipients with CIT ≤ 17 hours (HR 1.15, 95% CI 1.03-1.27; p=0.010), but not in DDKT recipients with CIT > 17 hours (HR 1.00, 95% CI, 0.90-1.11; p=0.971). Compared with recipients who received zero HLA-DQ MM kidneys, those who received one or two HLA-DQ MM kidneys had a higher incidence of acute rejection at 1-year with adjusted odd ratios of 1.12 (95% CI, 1.02-1.22; p=0.012) in DDKT and 1.14 (95% CI, 1.03-1.28; p=0.016) in LDKT, respectively.

Conclusions: HLA-DQ mismatching is a predictor for graft survival and acute rejection independent of mismatching of HLA-ABDR and initial immunosuppression. Cold ischemic times of longer than 17 hours appear to obviate the benefit of zero HLA-DQ MM.

FR-OR080

Donor-Derived Cell-Free DNA Improves DSA-Informed Diagnosis of ABMR in Kidney Transplant Patients Stanley C. Jordan,[1] Arthur J. Matas,[2] Suphamai Bunnapradist,[3] Anthony J. Langone,[4] David Hiller,[5] Robert Woodward,[5] Marica Grskovic,[5] John J. Sninsky,[5] Jim Yee.[5] *[1]Cedars-Sinai Medical Center, Los Angeles, CA; [2]University of Minnesota, Minneapolis, MN; [3]UCLA, Los Angeles, CA; [4]Vanderbilt University Medical Center, Nashville, TN; [5]CareDx, Brisbane, CA.*

Background: Donor-derived cell-free DNA (dd-cfDNA) discriminates active T cell mediated (TCMR) and antibody mediated rejection (ABMR) in kidney transplant patients. Many transplant patients are monitored with donor-specific antibodies (DSA), which is a risk factor for ABMR. This study assesses the combined use of dd-cfDNA and DSA to diagnose active rejection and subtypes of rejection.

Methods: dd-cfDNA (AlloSure) was assayed in 107 blood samples with paired clinically indicated biopsies from 102 kidney transplant patients from the DART multicenter study (NCT02424227). Patients were divided into those who had prior or current positive DSA (DSA+, n=33 samples) and those who did not (DSA-, n=74 samples). DSA+ cutoffs were determined by center. Prevalence of biopsy-based diagnosis of rejection was computed. Mixed rejections were included in the ABMR group. Samples were further divided into dd-cfDNA > 1% (dd-cfDNA+) and dd-cfDNA ≤ 1% (dd-cfDNA-), and PPV of dd-cfDNA to predict ABMR and TCMR within DSA+ and DSA- patients were computed.

Results: DSA+ patients were 47 ± 14 years old, 48% Caucasian, and 58% male. DSA- patients were 53 ± 13 years old, 51% Caucasian, 62% male. 40% of DSA+ and no DSA- patients had ABMR. PPV of dd-cfDNA+ to detect ABMR in DSA+ patients is 76% (95% CI, 63%-100%). 14% of DSA+ and 13% of DSA- patients had TCMR. PPV of dd-cfDNA to detect TCMR in DSA+ patients is 25% (95% CI, 0%-54%) and in DSA- patients is 22% (95% CI 0%-44%). 13/16 DSA+, dd-cfDNA+ patients had ABMR and 1/16 had TCMR. 3/17 DSA+, dd-cfDNA- patients had ABMR and 3/17 had TCMR. 2/12 DSA-, dd-cfDNA+ patients had TCMR. 5/62 DSA-, dd-cfDNA- patients had TCMR.

Conclusions: Donor-derived cell free DNA may be used in conjunction with DSA status to improve the diagnosis of rejection in kidney transplant patients. Patients with dd-cfDNA+/ DSA+ have highest probability of rejection, most likely ABMR. Patients with dd-cfDNA-/DSA+ have a medium probability of rejection, either TCMR or ABMR. Since DSA is required to diagnose ABMR (Banff 2013), DSA- patients can only have TCMR. Patients with dd-cfDNA+/DSA- have a medium probability of TCMR and patients with dd-cfDNA-/DSA- have a low probability of TCMR.

Funding: Commercial Support - CareDx

FR-OR081

A Substantial Fraction of Standard-of-Care Transplant Biopsies Have Clinically Actionable Findings Evan A. Farkash, Ali K. Shammout. *University of Michigan, Ann Arbor, MI.*

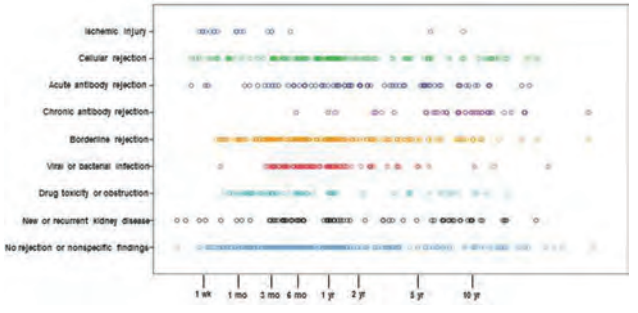
Background: Standard-of-care (SOC) or "protocol" biopsies may detect subclinical disease impacting renal allograft longevity. Transplant recipients at our center have SOC biopsies at 3, 6, and 12 months after implantation. Indication biopsies are also performed in the setting of graft dysfunction or *de novo* DSA. We hypothesize that a substantial percentage of SOC biopsies identify pathologic processes that trigger patient management changes.

Methods: An Access database was populated with pathology reports on all renal biopsies over a 40 month period, obtained from a pathology laboratory information system (Soft) and a transplantation clinical database (Otis). Biopsies were categorized by type (native vs. allograft, indication vs. SOC) and time after transplantation. Natural language diagnoses were standardized. Rejection (antibody and cellular), infection (bacterial and viral), recurrent disease, calcineurin inhibitor toxicity, and obstruction were identified as clinically actionable diagnoses.

Results: 2410 of the 3724 biopsies over this time period were allograft biopsies. At 3, 6, and 12 months after transplant, 15.1%, 17.8%, and 17.8% of SOC biopsies had clinically actionable diagnoses, respectively. 47.9% of indication biopsies had clinically actionable diagnoses ($p<0.0001$ compared to SOC, chi-squared). Cellular rejection tended to be diagnosed earlier than antibody mediated rejection diagnoses in this population (Figure 1). About 1 in 20 biopsies at or before 6 months had evidence of viral or bacterial infection, many of which were SOC biopsies.

Conclusions: The SOC biopsy program frequently identified findings affecting patient management and is a valuable addition to post-transplant patient care. The temporal spectrum of rejection related diagnoses in all biopsies over this time period is consistent with the literature. Infectious diagnoses, particularly subclinical infections, are frequent and can occur early after transplantation.

Funding: Other NIH Support - NIAID



The primary diagnosis for 2410 consecutive indication and SOC renal transplant biopsies are plotted together on a logarithmic timescale after transplantation.

FR-OR082

Notch Receptor Expression Is Significantly Increased during Human Kidney Transplant Rejection Amy Bowes,[5] Kirsten Morris,[5] Naoka Murakami,[1] Paul Bass,[4] Alan D. Salama,[4,2] Hans J. Stauss,[3] Leonardo V. Riella,[1] Ciara N. Magee.[4] *[1]Brigham and Women's Hospital, Harvard Medical School, Brookline, MA; [2]None, Boston, MA; [3]UCL, London, United Kingdom; [4]UCL Centre for Nephrology, Royal Free Hospital, London, United Kingdom; [5]Royal Free London NHS Foundation Trust, London, United Kingdom.*

Background: Despite significant advances in transplantation, our ability to appropriately modify the immune response therein remains limited. Development of therapies that promote regulation while suppressing effector immunity is imperative to improve graft survival and minimize immunosuppression. Notch receptor signaling is crucial to cell development and plays a key role in T cell activation and differentiation, though limited data exist on its importance in immune regulation. In this study, we investigated the pattern of Notch receptor expression in human renal transplantation.

Methods: Transplant kidney biopsy samples obtained from patients enrolled in an immune monitoring study in our institution were evaluated. All patients had a routine time zero biopsy; a subset of patients underwent further biopsy post-transplant due to episodes of graft dysfunction, and were classified as acute rejection (n=12), or non-rejection (n=15). Immunohistochemical analysis was performed to identify intact and activated (cleaved) Notch receptor expression (measured as % threshold area using ImageJ) on paraffin-embedded sections. Cellular samples were collected from another cohort of renal transplant patients during times of clinical quiescence or acute rejection and analyzed for T cell subset expression of Notch using flow cytometry.

Results: Renal expression of cleaved Notch1, cleaved and intact Notch2 was significantly increased in patients with acute rejection when compared to their baseline biopsies and post-transplant patients without rejection ($p<0.0001$, $p<0.0001$ & $p<0.0001$, respectively). Next, we investigated the expression of Notch1 in T conventional cells (T_{conv}: $CD4^+Foxp3^-$) and T_{regs} ($CD4^+Foxp3^+$) in transplant recipients. During clinical quiescence, a significantly higher proportion of T_{regs} expressed Notch1 compared to T_{conv} cells. However, there was a 100-fold increase in the proportion of T_{conv} expressing Notch1 during a rejection episode, with a slight reduction in the proportion of T_{regs} expressing Notch1.

Conclusions: We found that there is significant upregulation of both celluar and tissue Notch receptor expression during immune activation. Given the importance of Notch signaling in T cell activation, treatment with Notch inhibition may provide a novel means of attenuating cellular responses in transplantation.

Funding: Other NIH Support - National Institute of Health Research (UK), Private Foundation Support

FR-OR083

GWAS of Time to Renal Allograft Failure after Transplantation of African American Deceased-Donor Kidneys Jasmin Divers,[5] Lijun Ma,[5] William M. Brown,[5] Nicholette D. Palmer,[5] Ajay K. Israni,[3] Stephen O. Pastan,[1] Bruce A. Julian,[4] Robert S. Gaston,[4] Pamela J. Hicks,[2] Amber M. Reeves-Daniel,[5] Barry I. Freedman.[5] *[1]Emory University School of Medicine, Atlanta, GA; [2]Wake Forest Baptist Health, Winston Salem, NC; [3]Hennepin County Medical Center, Minneapolis, MN; [4]University of Alabama at Birmingham, Birmingham, AL; [5]Wake Forest School of Medicine, Winston-Salem, NC.*

Background: Two apolipoprotein L1 gene (*APOL1*) renal-risk variants in African American (AA) deceased donors (DD) associate with shorter renal allograft survival after transplantation. Modifying factors are likely involved because not all deceased donor kidney transplants (DDKT) from AA donors with *APOL1* risk genotypes fail early.

Methods: To identify genes contributing to allograft failure in addition to *APOL1*, a genome-wide association study (GWAS) was performed using the Illumina 5M chip in 477 AA DD, yielding 880 DDKTs. Association tests were performed using Cox proportional hazard on the genotyped and 1000 Genomes-imputed markers, using death-censored allograft survival as the outcome with each single nucleotide polymorphism (SNP), and accounting for donor African ancestry proportion, sex and age, and recipient sex, age, HLA match, cold ischemia time and peak panel reactive antibodies, using data collected from the Scientific Registry of Transplant Recipients (SRTR). SNP-by-*APOL1* interaction effects on allograft survival were also assessed.

Results: Seven SNPs near the Nudix Hydrolase 7*(NUDT7)* gene, a coenzyme A diphosphatase, were among the top hits showing independent effects after accounting for *APOL1* ($p=1.6x10^{-8}$ -$3.8x10^{-8}$). *NUDT7* is expressed in human renal tubule cells. Two SNPs in the *SEC63* gene modified the effect of *APOL1* on allograft survival (interaction $p=2x10^{-9}$ - $3.7x10^{-8}$). *SEC63* encodes a protein translocation regulator, which appears at the endoplasmic reticulum (ER) and ER-mitochondria contact sites, and is expressed in human renal tubules and glomeruli.

Conclusions: Genetic associations were detected with 41 SNPs ($p= 2x10^{-9}$ - $5x10^{-8}$) contributing independently or interacting with *APOL1* to impact renal allograft survival after DDKT from AA deceased donors. Replication and functional validation efforts are needed to elucidate these associations.

Funding: Other NIH Support - National Institute on Minority Health and Health Disparities (NIMHD)

FR-OR084

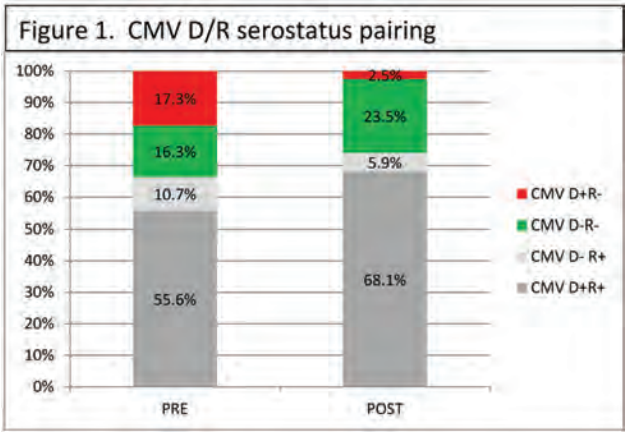
Kidney Transplant Allocation with CMV Seromatching Reduces CMV Infection Douglas J. Norman,[2] Eric D. Langewisch,[3] Joseph B. Lockridge.[1] *[1]None, Tualatin, OR; [2]Oregon Health and Science University, Portland, OR; [3]University of Nebraska Medical Center, Omaha, NE.*

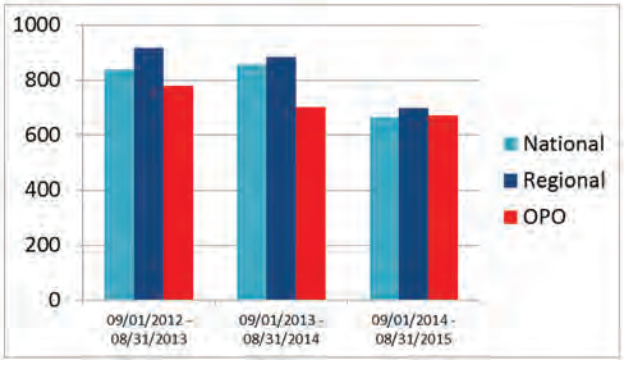
Background: Cytomegalovirus (CMV) infection is a major cause of morbidity in kidney transplant recipients. A pre-transplant allocation strategy by matching deceased kidney donors and recipients by CMV serostatus may reduce CMV infection. .

Methods: We adopted a CMV seromatching allocation policy within our Organ Procurement Organization (OPO) beginning 09/01/2012. In this retrospective analysis of 400 consecutive deceased donor kidney transplant recipients, we compared rates of CMV syndrome between a historical control (PRE: 1/1/2010 – 8/31/2012) versus after the CMV matching protocol (POST: 9/1/2012 – 12/3/2014). Wait times in the OPO were reviewed after the protocol was implemented.

Results: CMV matching decreased the number of high CMV risk (donor seropositive / recipient seronegative) transplants from 17.3% to 2.5% ($p<0.001$) and increased the number of low CMV risk (donor seronegative / recipient seronegative) transplants from 16.3% to 23.5% ($p=0.072$) (Figure 1). CMV viremia was reduced from 13.3% to 5.9% ($p=0.0118$) while CMV syndrome or disease decreased from 9.2% to 2.9% ($p=0.008$). After the allocation change, median waiting times for all deceased donor recipients in the OPO did not increase and appeared to be consistent with national and regional trends (Figure 2).

Conclusions: CMV seromatching optimizes high and low risk CMV profiles and significantly reduces the rate of CMV infection without appearing to disadvantage wait times for recipients





Median Wait Times For Deceased Donor Kidney Recipients(days) after CMV Allocation Change

FR-OR085

Increased Expression of the Co-Inhibitors PD-1 and BTLA on CMV-Specific T-Cells Is Associated with Symptomatic CMV Infection in Renal Transplant Patients Benjamin Wilde,[2] Sebastian Dolff,[3] Oliver Witzke.[1] *[1]Department of Infectious Diseases, University Duisburg-Essen, Essen, Germany; [2]Department of Nephrology, University Duisburg-Essen, University Hospital Essen, Essen, Germany; [3]Department of Infectious Diseases, University Duisburg-Essen, University Hospital Essen, Essen, Germany.*

Background: Cytomegalovirus (CMV) infections occur frequently in renal transplant patients due to immunosuppressive therapy inhibiting CMV-specific T-cell immunity. Prophylaxis with antiviral agents or pre-emptive strategies to monitor viral load and then treat do not prevent infections sufficiently. It was the aim of this study to investigate if the expression of inhibitory molecules on CMV specific T-cells is associated with the clinical course of renal transplant patients.

Methods: 30 renal transplant patients were recruited. Peripheral blood was sampled and stimulated with CMV lysate, SEB or control serum. The coinhibitors PD-1 and BTLA were determined on CMV-specific T-cells. Clinical data was collected retrospectively from patient files. Symptomatic CMV infection was defined as CMV syndrome or tissue invasive disease. Asymptomatic CMV infection was defined as detectable CMV replication in peripheral blood and absence of signs indicating CMV syndrome/tissue invasive disease.

Results: Two renal transplant patients were at low risk for CMV infection according to donor /recipient CMV IgG sero-status at the time of transplantation (D neg / R neg). Seven patients had a high risk according to sero-status (D pos /R neg) and the remaining 21 patients were confined to the intermediate risk group (D pos /R pos or D neg / R pos). Patients with low risk were excluded for further analysis. PD-1 expression was significantly enhanced on CMV-specific CD3+ T-cells in patients with a history of symptomatic CMV infection (n=6) as compared to patients with asymptomatic CMV (n=14) infection ($CD3^+CD154^+$: % of $PD\text{-}1^+$ 63.8 ±16.0% vs. 37.2 ±19.4%, p=0.006). Likewise, expression of BTLA on CMV-specific T-cells was significantly increased in patients with symptomatic versus asymptomatic CMV infection ($CD3^+CD154^+$: % of $BTLA^+$ 89.3 ±9.5% vs. 66.0 ±22.0%, p=0.003).

Conclusions: Patients with symptomatic CMV infection had enhanced expression of PD-1/BTLA on virus-specific T-cells. The coinhibitors PD-1/BTLA usually promote T-cell suppression. Therefore, increased expression of PD-1/BTLA on CMV-specific T-cells may compromise viral control and could serve as biomarker to stratify patients at risk.

FR-OR086

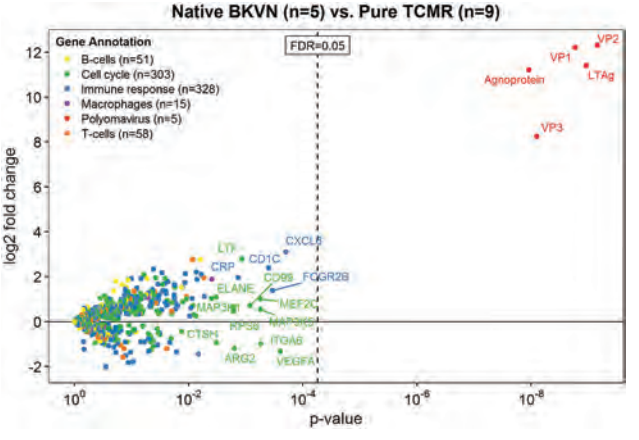
The Molecular Phenotype of Polyomavirus Nephropathy and Its Discrimination from T-Cell Mediated Rejection Benjamin A. Adam,[8] Siegfried Wagner,[8] Jan H. Braesen,[5] Verena Broecker,[2] Vivette D. D'Agati,[1] Cinthia Drachenberg,[9] Evan A. Farkash,[10] Alton B. Farris,[3] Laurette Geldenhuys,[6] Volker Nickeleit,[7] Parmjeet S. Randhawa,[11] Heinz Regele,[4] Michael Mengel.[8] *[1]Columbia University College of Physicians and Surgeons, New York, NY; [2]Sahlgrenska University Hospital, Gothenburg, Sweden; [3]Emory University, Atlanta, GA; [4]Medical University of Vienna, Vienna, Austria; [5]Medizinische Hochschule Hannover, Hannover, Germany; [6]Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada; [7]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [8]University of Alberta, Edmonton, AB, Canada; [9]University of Maryland School of Medicine, Baltimore, MD; [10]University of Michigan, Ann Arbor, MI; [11]University of Pittsburgh, Pittsburgh, PA.*

Background: Improved immunosuppression protocols have reduced the incidence of T-cell mediated rejection (TCMR) but still carry a significant risk of BK polyomavirus nephropathy (BKVN). Despite requiring opposite treatments, BKVN and TCMR often have overlapping clinical and histological presentations. Molecular testing may allow for more precise diagnosis.

Methods: NanoString® was used to measure the expression of 800 genes in 40 formalin-fixed paraffin-embedded human samples. The genes included 795 human immune-related genes and 5 polyomavirus (PV) genes (Agnoprotein, LTAg, VP1, VP2, VP3). The samples included native kidney BKVN (n=5), pure TCMR (n=9), SV40 immunohistochemistry-positive carcinoma (tumor BK, n=9), and normal implant kidney biopsies (n=8). Using six additional nephrectomies with mixed BKVN and TCMR, regions showing histologic features of only BKVN (mixed BKVN, n=6) and only TCMR (mixed TCMR, n=3) were isolated with laser capture microdissection. Differential gene expression and diagnostic performance were assessed.

Results: All five PV genes were significantly increased (FDR<0.05) in native BKVN versus pure TMCR but no human genes were differentially expressed (Figure 1). PV gene expression was also significantly higher (versus pure TCMR) in tumor BK (p<0.01), mixed BKVN (p<0.001), and mixed TCMR (p<0.05, except VP1). ROC analysis revealed excellent discrimination between BK-positive (including mixed TCMR) and BK-negative cases (AUC=0.96-1.00). As a 5-gene set, the PV genes demonstrated near-perfect diagnostic performance (AUC=0.99) with improved sensitivity (0.96) over histology (0.87).

Conclusions: These data suggest that PV gene expression is more sensitive than histology and can more precisely discriminate BKVN and TCMR. However, at the molecular level, no significant difference in immune response was identified.



FR-OR087

Comparison of Outcomes after DAA Therapy among HCV Infected Kidney Transplant Recipients Who Received Grafts from Either HCV Positive or Negative Donors Mai Sedki,[4] Camilo Cortesi,[4] Paul Martin,[2] David Roth,[3] Kalyan R. Bhamidimarri.[1] *[1]University of Maimi, Miami, FL; [2]University of Miami, Miami, FL; [3]University of Miami Miller School of Medicine, Miami, FL; [4]University of Miami/Jackson Memorial Hospital, Miami, FL.*

Background: Direct acting antivirals (DAA) have transformed hepatitis C virus (HCV) treatment. In the kidney transplant (KT) setting, HCV-infected patients (R+) can now receive deceased donor KT (DDKT) from HCV positive donors (D+) and undergo treatment in the post-transplant period. However, a few cases of rejection have been reported in this HCV D+R+ cohort. We sought to compare outcomes among R+ receiving grafts from HCV negative donors (D-) versus D+.

Methods: This is a case series of 39 KT recipients of which 14 R+ have been transplanted with a kidney from D- and the rest from D+. All patients completed a full course of DAA. Time to transplantation, efficacy of DAA therapy, rejection episodes, tacrolimus dose adjustments, and renal function were assessed in both groups.

Results: The average age of our cohort was 56.7±8.8 and 59.1±10.5 years with 64% and 77% male in D-R+ and D+R+, respectively. In both groups the predominant genotype was 1A. The median METAVIR fibrosis stage was 2.0 in D-R+ and 1.0 in D+R+. The SVR at 12 weeks was 100% in D-R+ and 96% in D+R+. The median waiting time to transplantation was 802 days for D-R+ and 58 days in D+R+. Additionally, the median time between transplantation and start of DAA therapy was 405 days and 124 days in D-R+ and D+R+, respectively. There were 4 antibody mediated rejection episodes in D+R+ and 1 mixed rejection in D-R+. Tacrolimus dose adjustments were required in 64% of D-R+ and 52% of D+R+. When comparing kidney function before and after treatment with DAA, 42% of D-R+ and 28% of D+R+ had a significant change, defined as a change in creatinine by ≥ 0.3mg/dL.

Conclusions: Acceptance of a D+ kidney resulted in a significant decrease in transplant waiting time in R+ candidates without marked compromise. The response to DAA therapy was excellent and the SVR rates were similar to those reported in the general population. In both groups, tacrolimus dose adjustments were necessary. Our data suggests that KT recipients should be closely monitored during and immediately following HCV therapy with DAAs.

	D-R+	D+R+
Age (years) mean ± SE Gender (%) Genotype (1, 2, 3)	57.6 ± 8.8 64% male, 36% female 83%, 7%, 0%	59.1 ± 10.5 77% male, 23% female 92%, 4%, 4%
SVR12 (%) Time to DDKT (days) median Time from DDKT to start DAA (days) median Rejection Episodes (%)	100% 806 405 7%	96% 58 124 16%
Tacrolimus Dose Changes (%)	43% increase 22% decrease 26% no change	48% increase 28% decrease 4% no change
Changes in Creatinine (%) (defined as change ≥ 0.3mg/dL)	21% increase 21% decrease 58% no change	20% increase 8% decrease 72% no change

FR-OR088

Dulaglutide Treatment Is Associated with Less eGFR Decline and Greater Reduction in Albuminuria in Type 2 Diabetes and CKD Stages 3-4 (AWARD-7) Katherine R. Tuttle,[2] Mark C. Lakshmanan,[4] Jorge L. Gross,[5] Brian Rayner,[3] Robert S. Busch,[1] Brad Woodward,[4] Alan G. Zimmermann,[4] Fady T. Botros.[4] *[1]Albany Medical Center Division of Community Endocrinology, Albany, NY; [2]Providence Health Care, University of Washington School of Medicine, Spokane, WA; [3]Division of Nephrology and Hypertension, Groote Schuur Hospital and University of Cape Town, Cape Town, South Africa; [4]Eli Lilly and Company, Indianapolis, IN; [5]Centro de Pesquisas em Diabetes, Porto Alegre, Rio Grande do Sul, Brazil.*

Background: The AWARD-7 phase 3 trial compared weekly dulaglutide (DU 1.5 or 0.75 mg) to daily insulin glargine (IG), both with insulin lispro, in participants with type 2 diabetes (T2D) and chronic kidney disease (CKD) stages 3-4.

Methods: Baseline (BL) characteristics (N=576) were: estimated glomerular filtration rate (eGFR CKD-EPI): 38±13 mL/min/1.73m^2 [mean±SD], urine albumin/creatinine ratio (UACR, mean [median]): 847.2 (209.3), age: 65±9 years, A1c: 8.6±1.0%, duration of T2D: 18±9 years.

Results: After 52 weeks, mean eGFR was not statistically different from BL with DU 1.5 mg, while it decreased with DU 0.75 mg and IG; UACR decreased from BL with both DU doses (table). DU 1.5 mg vs IG differences were statistically significant in participants with UACR >300 mg/g. Both doses of DU were noninferior to IG for the change in A1c.

Conclusions: In participants with T2D and CKD stages 3-4, overall effects on eGFR and UACR were mainly driven by lesser eGFR decline and greater UACR reduction in the DU 1.5 mg group vs IG in participants with UACR >300 mg/g.

Funding: Commercial Support - Eli Lilly and Company

Table. Effects of DU and IG on eGFR and albuminuria after 52 weeks

Study Group	All (N=576)		UACR >300 mg/g (n=258)		UACR ≤300 mg/g (n=317)	
	Δ eGFR, mL/min/1.73m^2	%Δ UACR	Δ eGFR, mL/min/1.73m^2	%Δ UACR	Δ eGFR, mL/min/1.73m^2	%Δ UACR
DU 1.5 mg (N=192)	-1.1 (-2.4, 0.2)	-22.5* (-35.1, -7.5)	-3.4**# (-5.4, -1.4)	-29.0*# (-43.0, -11.5)	-0.4 (-2.0, 1.3)	-3.4 (-24.0, 22.8)
DU 0.75 mg (N=190)	-1.5* (-2.8, -0.2)	-20.1* (-33.1, -4.6)	-5.2** (-7.1, -3.2)	-12.3 (-29.0, 8.5)	0.2 (-1.4, 1.9)	-15.3 (-33.6, 8.0)
IG (N=194)	-2.9** (-4.2, -1.6)	-13.0 (-27.1, 3.9)	-6.3** (-8.2, -4.4)	0.1 (-18.8, 23.4)	-1.3 (-2.9, 0.4)	-9.9 (-29.0, 14.4)

Data are change from BL least squares mean (95% confidence interval). *2-sided p<0.05 and **2-sided p<0.001 change from BL, #2-sided p<0.05 and ##2-sided p<0.001 vs IG

FR-OR089

Effect of SGLT-2 Inhibitors on Proximal Tubular Function and Injury in Patients with Type 2 Diabetes: A Randomized Controlled Trial Pattharamon Korkiatpitak,[2] Bancha Satirapoj,[2] Naowanit Nata,[2] Amnart Chaiprasert,[1] Pamila Tasanavipas,[1] Theerasak Tangwonglert,[2] Ouppatham Supasyndh.[1] *[1]Phramongkutklao Hospital, Pathumthani, Thailand; [2]Phramongkutklao hospital, Bangkok, Thailand. Group/Team: phramongkutklao.*

Background: Intensive glucose control reduces the risk for microvascular complications in type 2 diabetes (T2DM). Recently, sodium glucose cotransporter 2 (SGLT2) inhibitors have the potential to exert renoprotection beyond glycemic control, the effects of SGLT2 inhibitors on the organs are not well known. There is limited data of SGLT2 inhibitors on biomarkers of kidney injury in T2DM patients.

Methods: T2DM patients with persistent HbA1c > 7% randomly assigned to add dapagliflozin 10 mg/day or standard treatment for 12 weeks. Proximal tubular injury biomarkers including urine kidney injury molecule-1 (KIM-1), urine cystatin-C, urine albumin to creatinine ratio (UACR), fraction excretion of phosphate (FEPO4) and uric acid (FEUric) were measured at baseline and the end of study.

Results: Patients were randomized to receive dapagliflozin (N=28) and control (N=29). Baseline characteristics were comparable across treatment groups. After 12 weeks, dapagliflozin-treated versus standard-treated patients showed reductions in HbA1c (-0.75 ± 0.21 vs -0.07 ± 0.25 %, p-value=0.882), fasting plasma glucose (-19.59 ± 8.26 vs -11.07 ± 8.71 mg/dL, p-value=0.481) and serum uric acid -0.06 ±0.18 vs 0.18 ± 0.12 mg/dL). There were significant between-group differences in the reduction of UACR (-23.31 ± 10 vs 19.88 ± 11.54 mcg/mgCr., p-value=0.010) and urine KIM-1 to creatinine ratio (-26.70 ± 98.2 vs 422.19 ± 181.05 mcg/mgCr, p-value=0.036), but no significant in changes of urine cystatin-C to creatinine ratio between two groups. There was no significant change of glomerular filtration rate, serum phosphorus, FEUric and FEPO4 in the dapagliflozin. No serious renal-related adverse events were observed in any group.

Conclusions: This study indicates that dapagliflozin in T2DM patients can decrease urinary proximal tubular injury biomarkers which refer to renoprotective effects. SGLT2-Inhibitors may be useful in treating T2DM for protect renal tubular injury and may lead to a reduced long-term renal outcome.

Funding: Other NIH Support - This study was supported by a grant from the National Science and Technology Development Agency (NSTDA, P-13-00505), Bangkok, Thailand.

FR-OR090

Effect of the SGLT-2 Inhibitor Dapagliflozin on Glomerular and Tubular Injury Markers Claire Dekkers,[4] Sergei Petrykiv,[1] Gozewijn D. Laverman,[2] Ron T. Gansevoort,[3] Hiddo J. Lambers Heerspink.[4] *[1]None, Groningen, Netherlands; [2]ZGT Almelo, Almelo, Netherlands; [3]UMC Groningen, Groningen, Netherlands; [4]University Medical Center Groningen, Groningen, Netherlands.*

Background: Sodium-glucose co-transporter 2 (SGLT2) inhibitors have been shown to delay progression of kidney function decline in type 2 diabetes. However, an FDA communication reported potential risk of acute kidney injury (AKI) particular during the first weeks of treatment, potentially due to tubular injury. Here we assessed effects of the SGLT2 inhibitor dapagliflozin (DAPA) on markers of subclinical tubular injury.

Methods: Data was used from a randomized controlled cross-over trial in 33 patients with type 2 diabetes and albuminuria ≥100 mg/g designed to assess the albuminuria lowering effect of 6-weeks treatment with DAPA 10 mg/d. IgG and IgG4 were measured as markers of glomerular damage and fractional excretion of the IgG to IgG4 ratio was used as proxy of charge selectivity. Urinary KIM-1, NGAL and LFABP were assessed as tubular damage markers, whereas urinary MCP-1 and urinary IL-6 were measured as inflammation markers.

Results: Compared to placebo, DAPA decreased IgG and IgG4 excretion, but did not change the glomerular charge selectivity index (table 1). Compared to placebo, DAPA decreased urinary KIM-1 excretion, whereas no change in NGAL and LFABP was observed. The inflammatory marker IL-6 significantly decreased during DAPA therapy. DAPA also decreased albuminuria (36.2% [95%CI 22.9, 47.2]) and eGFR (5.3 ml/min/1.73m^2 [8.0, 2.7]). Albuminuria change tended to correlate with eGFR change during DAPA (r=0.34; p=0.06). Tubular injury markers did not correlate with change in eGFR. Changes in IgG, MCP-1 and IL-6 significantly correlated with change in albuminuria (all p<0.02).

Conclusions: DAPA lowers urinary excretion of glomerular and tubular injury markers as well as inflammation markers. These data indicate that the fall in eGFR after start of dapagliflozin reflects a hemodynamic response and not (subclinical) tubular injury.

Table 1

Injury markers	Mean change % from baseline compared to placebo (95% CI)	P-value
IgG	-28.4 (-7.2, -44.7)	0.01
IgG4	-34.6 (-3.0, -55.9)	0.04
IgG/IgG4	17.8 (-25.2, 85.4)	0.46
KIM-1	-22.6 (-0.3, -39.8)	0.05
NGAL	-13.4 (-35.6, 16.6)	0.33
LFABP	0.9 (-13.2, 17.2)	0.91
IL-6	-23.5 (-1.4, -40.6)	0.04
MCP-1	-14.1 (-32.2, 8.8)	0.20

FR-OR091

Effect of the SGLT2 Inhibitor Dapagliflozin in Patients with Type 2 Diabetes and Stages 3b-4 CKD David C. Wheeler,[3] Claire Dekkers,[4] David Sjostrom,[2] Bergur V. Stefansson,[1] Valerie Cain,[5] Hiddo J. Lambers Heerspink.[4] *[1]AstraZeneca, Molndal, Sweden; [2]AstraZeneca LP, Molndal, Sweden; [3]University College London, London, United Kingdom; [4]University Medical Center Groningen, Groningen, Netherlands; [5]Bogier Clinical and IT Solutions, Inc, Haddonfield, NJ.*

Background: Dapagliflozin, an anti-diabetic drug targeting the sodium-glucose co-transporter 2, decreases HbA1c, body weight, blood pressure (BP), and albuminuria (UACR) in patients with type 2 diabetes. Although the glucose lowering capacity of dapagliflozin is diminished in patients with reduced kidney function, the effects of this drug on body weight, BP, and UACR as well as its safety have not been properly defined in patients with type 2 diabetes and stages 3b-4 chronic kidney disease (CKD).

Methods: In a pooled analysis of 11 phase 3 randomized controlled clinical trials, we determined changes in HbA1c, body weight, BP, hematocrit, eGFR, and UACR over 24 weeks in patients with type 2 diabetes and an eGFR <45 ml/min/1.73m^2 receiving placebo (n=70) or dapagliflozin 5 mg or 10 mg (n=151). Effects on UACR were determined in a subgroup of patients with baseline UACR ≥ 30 mg/g (n=137).

Results: Placebo-corrected changes in HbA1c with dapagliflozin 5 and 10 mg were -0.02 (95% CI: -0.36, 0.33) and -0.03 (95% CI: -0.34, 0.28). Dapagliflozin 5 and 10 mg compared to placebo changed eGFR after 24 weeks by -1.5 (95% CI: -4.6, 1.5) and -2.6 (95% CI: -5.3, 0.2) and UACR by -48.3% (95% CI: -67.4, -17.8), and -32.7% (95% CI: -56.2, 3.5), respectively. Additionally, dapagliflozin at both 5 and 10 mg compared to placebo increased hematocrit and decreased body weight and BP. The overall frequency of adverse events was similar among treatment groups. Adverse events associated with renal function occurred more frequently in the dapagliflozin 10 mg group. These events included many asymptomatic increases in serum creatinine of which none qualified as a serious adverse event.

Conclusions: Dapagliflozin does not decrease HbA1c in patients with type 2 diabetes and stages 3b-4 CKD. However, the drug decreases UACR, BP, and body weight to a clinically meaningful extent without major side effects. These actions of dapagliflozin support a large outcomes trial in this population to confirm long-term safety and efficacy in reducing adverse clinical end points.

Funding: Commercial Support - AstraZeneca

FR-OR092

Are the Renal Effects of Empagliflozin Consistent in Patients Already Using Medications That Alter Renal Hemodynamics? An Exploratory Analysis from EMPA-REG OUTCOME Gert J. Mayer,[1] Christoph Wanner,[2] Matthew R. Weir,[3] Silvio E. Inzucchi,[4] Audrey Koitka-Weber,[5] Stefan Hantel,[5] Maximilian von Eynatten,[6] Bernard Zinman,[7] David Cherney.[8] *[1]Dept of Internal Medicine IV (Nephrology and Hypertension), Medical University Innsbruck, Innsbruck, Austria; [2]Dept of Medicine, Würzburg Univ Clinic, Würzburg, Germany; [3]Dept of Nephrology, University of Maryland School of Medicine, Baltimore, MD; [4]Yale University School of Medicine, New Haven, CT; [5]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany; [6]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany; [7]Lunenfeld-Tanenbaum Research Inst, Mount Sinai Hospital, Toronto, ON, Canada; [8]Toronto General Hospital, Univ of Toronto, Toronto, ON, Canada.*

Background: Among patients with type 2 diabetes (T2D) at high cardiovascular (CV) risk, the SGLT2 inhibitor empagliflozin (EMPA) decreases progression of kidney disease, likely via reduction in intraglomerular pressure. These patients often receive other agents to prevent development or progression of both CV disease (CVD) and chronic kidney disease (CKD). Some of these agents may also alter renal hemodynamics, such as RAS inhibitors, diuretics, NSAIDs and CCBs. We investigated whether the renal effects of EMPA are consistent in those already using these background medications.

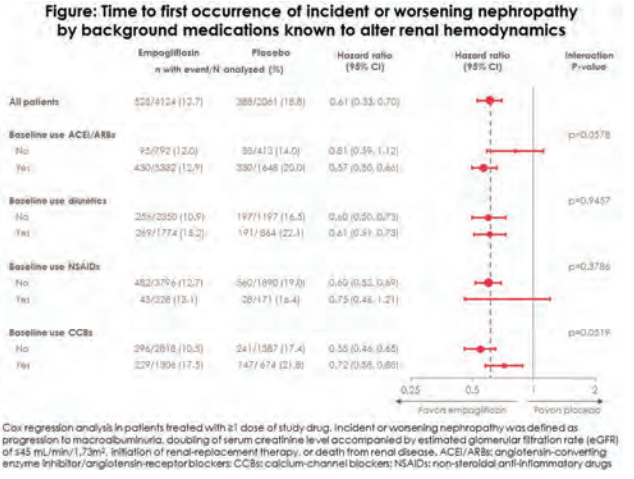
Methods: 7020 patients with T2D and established CVD were randomized (1:1:1) to EMPA 10 mg, 25 mg or placebo (PBO) in addition to standard of care. Differences in risk of incident or worsening nephropathy for EMPA vs PBO across subgroups by baseline background medications were assessed using a Cox proportional hazards model. Acute renal failure (ARF) events were assessed based on the MedDRA narrow standardized query.

Results: Risk reductions in incident or worsening nephropathy seen with EMPA were consistent across background medication subgroups, with no heterogeneity of treatment effect (Figure). RAS inhibitors were the most commonly used background medication group and there was an overall increased risk for ARF with ACEi/ARBs in the PBO group (ACEi/ARB yes: 7% vs ACEi/ARB no: 5.2%) but no imbalance was seen with EMPA 10 mg and 25 mg, respectively (ACEi/ARB yes: 5.3% and 5.9%; ACEi/ARB no: 4.5%, 2.7%).

Conclusions: Addition of EMPA resulted in a consistent reduction in CKD progression in T2D patients at high CV risk, irrespective of commonly used background medications that also alter renal hemodynamics.

Funding: Commercial Support - Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance

Figure: Time to first occurrence of incident or worsening nephropathy by background medications known to alter renal hemodynamics



Cox regression analysis in patients treated with ≥1 dose of study drug. Incident or worsening nephropathy was defined as progression to macroalbuminuria, doubling of serum creatinine level accompanied by estimated glomerular filtration rate (eGFR) of ≤45 mL/min/1.73m^2, initiation of renal-replacement therapy, or death from renal disease. ACEi/ARBs: angiotensin-converting enzyme inhibitor/angiotensin-receptor blockers; CCBs: calcium-channel blockers; NSAIDs: non-steroidal anti-inflammatory drugs

FR-OR093

Effects of SGLT2 Inhibition on Fibroblast Growth Factor 23 and 25(OH) Vitamin D Maarten A. de Jong,[1] Sergei Petrykiv,[1] Gozewijn D. Laverman,[2] Dick de Zeeuw,[1] Stephan J. Bakker,[1] Hiddo J. Lambers Heerspink,[1] Martin H. De Borst.[1] *[1]University Medical Center Groningen, Groningen, Netherlands; [2]ZGT Almelo, Almelo, Netherlands.*

Background: Sodium glucose co-transporter 2 (SGLT2) inhibitors like dapagliflozin are novel drugs for the treatment of diabetes mellitus, which also promise to slow the progression of kidney disease. Previous studies found that SGLT2 inhibition increases serum phosphate and PTH. However, the effects on fibroblast growth factor 23 (FGF23) and vitamin D are less well studied.

Methods: This is a post-hoc analysis of a double-blind, randomized, cross-over trial, enrolling patients on stable RAAS blockade, albumin:creatinine ratio between 100 and 3500 mg/g, eGFR ≥ 45 ml/min/1.73m^2 and HbA1c ≥ 55 and <100 mmol/mol. Patients were treated with dapagliflozin 10 mg/d (DAPA) or placebo during 2 consecutive periods of 6 weeks each, with a 6-week wash-out in between. Plasma C-terminal FGF23 was measured with ELISA (Immutopics Inc), 25(OH) vitamin D with LC-MS/MS. Data are shown as mean (95%CI). Endpoints were assessed with linear mixed models.

Results: Thirty-three patients (age 61±9 yrs; 24% female; median 24h UAE 470 mg/24hr) completed the study. Baseline characteristics and results are shown in table 1. DAPA increased serum phosphate, PTH and FGF23 compared to both baseline and placebo. Serum calcium and 25(OH)D did not change (p=0.9, p=0.8). DAPA reduced eGFR, but change in eGFR and change in bone and mineral parameters were not correlated (all P>0.5). All effects of DAPA were reversed 6 weeks after discontinuation.

Conclusions: Dapagliflozin treatment induced a significant rise in serum phosphate, PTH and FGF23 levels, independent of concomitant effects on eGFR. Serum calcium and 25(OH)D levels remained unchanged. In light of the high prevalence of bone and mineral disorders in patients with diabetes and kidney disease, future studies should assess the clinical significance of these alterations.

Funding: Commercial Support - Astra Zeneca provided study medication., Government Support - Non-U.S.

Plasma parameter	Baseline	Δ Placebo	Δ DAPA
Phosphate (mg/dL)	3.37 (3.19;5.59)	0.03 (-0.12;0.19)	0.25 (0.09;0.40)*‡
PTH (pg/mL)	48.3 (40.5;55.4)	1.9 (-2.2;6.1)	10.4 (5.7;14.1)*‡
FGF23 (RU/mL)	124.3 (100.6;153.6)	4.9% (-5.3;16.2%)	24.9% (12.3;38.8%)*‡
Calcium (mg/dL)	9.42 (9.26;9.58)	0.06(-0.04;0.20)	0.06 (-0.04:0.19)
25(OH)D (ng/mL)	19.29 (16.21;22.37)	-1.44 (-3.27;0.39)	-1.25 (-3.13;0.63)
eGFR (ml/min*1.73m2)	69.7 (63.5;76.4)	0.9 (-1.6;3.4)	-4.4 (-7.0;-1.9)*‡

Table 1: baseline values and mean change (95%CI) vs. baseline during Dapa and Placebo study periods. * denotes P < 0.01 vs baseline. ‡ denotes P< 0.01 vs placebo.

FR-OR094

AKI in Patients on SGLT2 inhibitors: A Propensity Matched Analysis Girish N. Nadkarni,[2] Rocco Ferrandino,[3] Alex R. Chang,[1] Aditya L. Surapaneni,[5] Kinsuk Chauhan,[3] Priti Poojary,[6] Aparna Saha,[4] Bart Ferket,[3] Morgan Grams,[5] Steven G. Coca.[3] *[1]Geisinger Medical Center, Danville, PA; [2]Icahn School of Medicine, New York, NY; [3]Icahn School of Medicine at Mount Sinai, New York, NY; [4]Icahn school of medicine at Mount Sinai, NEW YORK, NY; [5]Johns Hopkins University, Baltimore, India; [6]Icahn School of Medicine at Sinai, New York, NY.*

Background: Sodium-glucose co-transporter-2 inhibitors (SGLT2i) improve both renal and cardiovascular outcomes in type 2 diabetes (T2D) patients. However, the FDA has issued alerts regarding increased acute kidney injury (AKI) with canagliflozin/dapagliflozin. We aimed to assess real world AKI risk with SGLT2i separately in two health-care cohorts.

Methods: We utilized the Mount Sinai chronic kidney disease (MSCKD) registry and Geisinger Health System (GHS) cohort. We selected SGLT2i users/non-users and determined AKI by KDIGO definition (AKI_{KDIGO}). We used nearest neighbor 1: 1 propensity matching and calculated unadjusted and adjusted (accounting for covariates poorly balanced in the propensity match) hazard ratios (HRs).

Results: We analyzed 377 SGLT-2i users: non-user pairs in MSCKD, and 1242 SGLTi users: non-user pairs in GHS. During median follow-up time of 14 months, 4% in Mount Sinai and 3% of SGLTi users experienced an AKI_{KDIGO} event, vs. 10% and 7% of non-users, respectively. Unadjusted HRs for AKI_{KDIGO} were 0.46 (95% CI 0.26-0.82) and 0.43 (95% CI 0.29-0.63) in MSCKD and GHS, respectively. After adjustment, decreased risk persisted (aHR 0.48; 95% CI: 0.25-0.91, and aHR 0.63, 95% CI: 0.39-1.00, respectively). These estimates did not qualitatively change across sensitivity analyses, including by SGLTi type. (Table 1)

Conclusions: These pharmacoepidemiologic findings suggest there may not be increased AKI risk in SGLT2i users vs. comparable T2D patients. In fact, all three SGLTi were associated with lower AKI risk, similar to empagliflozin trial results. Our results suggest that perceived AKI risk with canagliflozin/dapagliflozin may be attributable to the high-risk population taking these medications and not to inherent nephrotoxicity.

Funding: NIDDK Support

Table 1. Hazard Ratios for AKI in SGLT2 Users vs. Propensity Matched Non-users in Mount Sinai and Geisinger Cohorts

	Mount Sinai		Geisinger	
	Unadjusted HR [95% CI]	Adjusted HR [95% CI]	Unadjusted HR [95% CI]	Adjusted HR [95% CI]
Primary analysis				
AKI defined by KDIGO	0.4 (0.2-0.8)	0.4 (0.2-0.9)	0.4 (0.3-0.6)	0.6 (0.4-1.0)
Sensitivity analyses				
AKI defined by ICD	0.5 [0.3-0.8]	0.5 [0.3-0.9]	0.5 [0.3–0.8]	0.8 [0.4-1.5]
Including only User/Non users with complete covariate data	0.7 [0.3-1.3]	0.7 [0.3-1.4]	0.5 [0.3–0.8]	0.7 [0.5-1.2]
Canagliflozin	0.5 [0.3-0.8]	0.5 [0.3-1.00]	0.5 [0.3-0.8]	0.8 [0.4-1.3]
Dapagliflozin	0.8 [0.3-1.9]	0.8 [0.3-1.9] 0.5 [0.2-1.7]	0.1 [0.02-1.1]	0.2 [0.02-2.5
Empagliflozin	NA	NA	0.3 [0.1-0.8]	0.4 [0.1-1.6]

NA= Insufficient Sample Size for estimation

FR-OR095

Organelles in Organoids: Live Imaging of Human Mini-Kidneys Using Targeted Tracers Reveals Dynamic Intracellular Responses to Kidney Injury Angela J. Churchill,[2] Jonathan Himmelfarb,[1] Benjamin S. Freedman.[2] *[1]Kidney Research Institute, Seattle, WA; [2]University of Washington, Seattle, WA.*

Background: Cellular subcompartments, known as organelles, play critical roles in cell biology, but little is known about the dynamics of organelles in complex tissues and organs. Mini-kidney organoids derived from human pluripotent stem cells (hPSCs) are complex structures *in vitro* that resemble nephrons and can be genetically modified to study regeneration and disease. We used human mini-kidneys to model organelle dynamics in complex tissues and acute kidney injury.

Methods: CRISPR-modified hPSC lines encoding fluorescently-tagged microtubules, nuclear envelopes, mitochondria, or desmosomes were differentiated into kidney organoids. Whole organoids were imaged every 5 minutes with a spinning disk confocal microscope over the course of 16 hours, and organelle dynamics were quantified. Organoids were physically disrupted or chemically treated to simulate kidney injury. Organelle distributions in tubule and podocyte populations were compared to fixed organoids and kidney tissue *in vivo* by fluorescence and electron microscopy.

Results: Live movies of human kidney organoids captured tubule movements, cell rearrangements, and mitotic events at high temporal and spatial resolution. Organelle distribution in diverse nephron segments closely resembled kidney tissue *in vivo*. Organelles exhibited a range of behaviors, from highly dynamic microtubules and nuclear envelopes, to relatively static desmosomes forming regularly-spaced foci. Quantitative time-lapse analysis revealed extended cell division duration and fragmented mitochondrial morphology under acute kidney injury conditions.

Conclusions: Live imaging of fluorescently-labeled kidney organoids reveals that organelle distributions and dynamics depend on nephron segment identity and environmental cues, approximating tissues *in vivo*. Furthermore, kidney injury induces changes in cell cycle length and mitochondrial structure, recapitulating and revealing aspects of the tubular injury/repair process. The study of organelles in organoids provides a new framework for elucidating the intracellular mechanisms underlying kidney injury, disease, and regeneration.

Funding: NIDDK Support, Other NIH Support - NCATS Tissue Chips, Commercial Support - Northwest Kidney Centers (unrestricted gift), Private Foundation Support

FR-OR096

Dissecting Lineage Relationships in Kidney Organoids Sara E. Howden, Jessica M. Vanslambrouck, Sean Wilson, Melissa H. Little. *Murdoch Childrens Research Institute, Parkville, NSW, Australia.*

Background: The capacity to create a model of the developing human kidney in vitro provides a unique opportunity to better understand nephrogenesis at the molecular level in human cells. Here we begin to characterise lineage relationships during human nephrogenesis through the generation of complex 3D kidney organoid cultures from human pluripotent stem cells (PSCs) that have been genetically modified to permit fate-mapping of specific cell lineages in real-time.

Methods: Human PSCs lines suitable for fate-mapping studies were generated by inserting a dual fluorescence cassette (loxP-flanked EGFP and adjacent mCherry reporter genes) within the "safe-harbor" GAPDH locus (GAPDHdual). Upon expression of Cre recombinase, cells switch from constitutive EGFP (green) expression to constitutive mCherry (red) expression. To interrogate the nephron lineage within human kidney organoids and validate the utility of GAPDHdual PSCs for fate-mapping studies, we used CRISPR/Cas9 to insert the Cre recombinase gene within the endogenous SIX2 locus of GAPDHdual PSCs (GAPDHdual:SIX2Cre). Kidney organoids were generated from GAPDHdual:SIX2Cre PSCs and monitored for mCherry expression.

Results: Following the derivation of kidney organoids from GAPDHdual:SIX2Cre PSCs, mCherry-expressing cells arise from day 10 of differentiation, coinciding with endogenous SIX2 expression. The proportion of mCherry+ cells increased steadily thereafter with a corresponding loss of EGFP-expressing cells. Importantly, subsequent analysis by immunofluorescence revealed that mCherry+ cells predominantly contributed to ECAD+ epithelial structures characteristic of the developing nephron. In constrast, mCherry+ cells were excluded from GATA3+ collecting duct. This is consistent with the lineage relationships previously demonstrated in murine kidney development.

Conclusions: Our findings validate lineage relationships of nephrons during human development and demonstrate the feasibility of using reporter/Cre-driver PSCs for fate-mapping studies in developing kidney organoids. We are currently using CRISPR/Cas9 mediated knock-out of specific genes in these GAPDHdual:SIX2Cre PSCs to interrogate the requirement for specific genes in the formation of human nephrons. We also propose to generate several other Cre-drivers to interrogate lineage relationships of other cellular compartments within the developing kidney that remain largely unknown.

FR-OR097

Ureteric Bud Organoids Derived from Human Pluripotent Stem Cells Facilitate Self-Organization of Nephron Organoids Navin R. Gupta,[1,2] Joseph V. Bonventre,[1,2] Ryuji Morizane.[1,2] *[1]Brigham and Women's Hospital, Boston, MA; [2]Harvard Stem Cell Institute, Cambridge, MA.*

Background: Renal epithelia arise from the reciprocal induction between two populations of cells, the ureteric bud (UB) of the anterior intermediate mesoderm (aIM) and nephron progenitor cells (NPCs) of the posterior intermediate mesoderm (pIM). We previously generated nephron organoids through the efficient induction of SIX2+ NPCs from human pluripotent stem cells (hPSCs). By design the nephron organoids were optimized for formation from pIM and hence lacked the organized collecting duct system derived from the UB, an outpouching of the Wolffian duct (WD).

Methods: A 4-step directed differentiation protocol over 7 days was designed to mimic mammalian UB development *in vivo*. Differentiation efficiency was evaluated by immunostaining at key intermediate cell stages. Quantification of aIM induction efficiency was performed using quantitative morphometric analysis of protein expression. hPSC-GFP lines, generated from the transduction with a CMV-GFP lentiviral construct, permitted lineage tracing in co-culture experiments with distinction between UB and nephron organoids.

Results: Following induction of mesendoderm, addition of retinoic acid, FGF2, and BMP4 induced aIM expressing up to 95% GATA3, 88% HOXB4, 78% PAX2, 74% WT1, and 71% LHX1 in both human embryonic stem cells and induced pluripotent stem cells. Subsequent treatment of aIM with noggin generated $CDH1^+PAX2^+GATA3^+$ tubular epithelia consistent with putative Wolffian Duct (WD). Ensuing treatment of WD with GDNF and retinoic acid to induce ret signaling upregulated SALL4 in tubular epithelial structures, consistent with ureteric bud (UB) induction. Using an hESC-GFP line, 3D culture of aIM-GFP cells treated with noggin and FGFs (2, 7,10) generated presumptive WD organoids. Co-culture of WD-GFP and nephron organoids induced $GFP^+CDH1^+GATA3^+$ tubular epithelial structures connected in series with $CDH1^+GFP^-$ distal segments of MM organoids, consistent with the addition of an in-series distal tubule-collecting duct structural linkage. Moreover, UB organoids provided Wnt signaling to the nephron organoids, negating the need for a transient CHIR pulse.

Conclusions: hPSC-derived UB organoids, whether alone or in co-culture with nephron organoids, will provide a human tissue tool for the study of kidney development and human disease modeling with implications for drug discovery and regenerative medicine.

Funding: Other NIH Support - T32

FR-OR098

Fluidic Shear Stress Induces Vascular and Glomerular Development in Kidney Organoids Kimberly Homan,[4] Navin R. Gupta,[1] Katharina T. Kroll,[4] David Kolesky,[4] Mark A. Skylar-Scott,[4] Tomoya Miyoshi,[2] M. Todd Valerius,[2] Joseph V. Bonventre,[2] Jennifer A. Lewis,[3] Ryuji Morizane.[2] *[1]Brigham & Women's Hospital/Massachusetts General Hospital, Brighton, MA; [2]Brigham and Women's Hospital, Brookline, MA; [3]Harvard School of Engineering and Applied Sciences, Cambridge, MA; [4]Harvard University, Cambridge, MA.*

Background: Kidney organoids, derived from human pluripotent stem cells (hPSCs), provide a novel platform to study basic kidney development, drug toxicity, and disease modeling. The cellular heterogeneity and tubular architectures recapitulated in these systems are noteworthy, and recent studies demonstrated that vascularized glomeruli can be formed with host endothelial cells upon transplantation of organoid-derived podocytes to SCID mice. However, in current organoid systems *in vitro*, glomerular development is

imperfect and vasculature is neither perfusable nor remains viable longitudinally, limiting both the degree of relevant applications and potential extent of translatability to human physiology *in vivo*.

Methods: Early nephron organoids (renal vesicle stage) derived from both human embryonic stem cells (hESCs) and induced pluripotent stem cells (hiPSCs) were embedded on extracellular matrix (ECM) in 3D perfusable chips. The degree, distribution, and maturation of vascular networks were evaluated by immunostaining, RT-qPCR, and flow cytometry for FLK1, CD146, and CD31 at regular intervals when subject to variable degrees of fluidic shear stress as well as of growth factors including VEGF, as compared to controls in static chips.

Results: By subjecting renal organoids to the right combination of underlying ECM, medium components, and fluidic shear stress, the abundance of vasculature, the incidence of capillary invasion of glomerular clefts, and the number of vascularized glomerular structures as well as peritubular vasculature are significantly enhanced. We also demonstrate that the vasculature contains open lumens which can be visualized with fluorescent beads, indicating that vasculature in the organoids is perfusable.

Conclusions: Culturing renal organoids under fluidic shear stress has the potential to unlock new opportunities for glomerular disease modeling, podocyte/vascular maturation, and development of a glomerular filtration barrier *in vitro*.

Funding: NIDDK Support

FR-OR099

A Microfluidic Kidney Organoid System Reveals Real-Time Dynamics of Nutrient Absorption Ramila E. Gulieva,[2] Jonathan Himmelfarb,[1] Benjamin S. Freedman.[2] *[1]Kidney Research Institute, Seattle, WA; [2]University of Washington, Seattle, WA.*

Background: Human mini-kidney organoids derived from pluripotent stem cells have great potential for kidney disease modeling and regeneration. Microfluidic flow is an essential component of the nephron for reabsorption and filtration, but is absent from existing organoid cultures. To more accurately model nephron functions *in vivo,* we tested whether introduction of fluid flow into kidney organoids could be used to visualize absorption of transport cargoes and nutrients in real time.

Methods: Human mini-kidneys were either differentiated *de novo* from hPSCs or transferred into chambers from cryopreserved stocks in microfluidic flow chambers. Fluorescence-labeled glucose, albumin and dextran were introduced and monitored live every 15 minutes over the course of 24 hours, under constant perfusion conditions. Absorption was quantified using image intensity analysis with background subtraction, compared to static conditions without flow, or in the presence of glucose transport inhibitors. Transporter expression was determined by immunofluorescence.

Results: Organoid proximal tubules, distal tubules, and podocytes differentiated normally, expressed SGLT2 and LRP2 transporters, and remained stable under flow for as long as two weeks. Accumulation of glucose occurred very rapidly, while absorption of albumin and dextran increased gradually in a linear fashion and eventually reached a plateau over 24 hours. The magnitude of absorption was significantly increased and featured increased signal to noise under flow conditions, compared to static conditions where absorption was minimal. Inhibition of SGLT transporters blocked glucose absorption in a dose-dependent manner.

Conclusions: The combination of kidney organoids with microfluidics enables visualization of nutrient and transport cargo absorption in nephron-like structures with high spatial and temporal resolution. Organoids under flow exhibit increased ability to absorb nutrients, relative to other cells in these cultures or organoids without flow. Our results indicate that this system can be utilized to accurately model absorption dynamics of specific substrates and to test the effects of therapeutic compounds, such as SGLT2 inhibitors. As flow is an essential component of the nephron, these experiments also build towards more sophisticated organoid microphysiological systems and artificial kidney devices.

Funding: NIDDK Support, Other NIH Support - NCATS Tissue Chips, Commercial Support - Northwest Kidney Centers (Unrestricted Gift), Private Foundation Support

FR-OR100

Multi-Segmented Kidney Organoids Derived from Human ES Cells by Stepwise Transcription Factor Administration Ken Hiratsuka,[2] Toshiaki Monkawa,[2] Shintaro Yamaguchi,[2] Ryuji Morizane,[1] Shigeru B. Ko,[2] Hiroshi Itoh,[2] Minoru S. Ko.[2] *[1]Brigham and Women's Hospital, Boston, MA; [2]Keio University School of Medicine, Tokyo, Japan.*

Background: We have recently reported a method to differentiate renal tubule-like cells from human Embryonic Stem Cells(hESCs) by a combinatorial administration of defined transcription factor(TF) mRNAs. However, a critical problem of this protocol, referred as direct reprogramming, is that it generates only proximal and distal tubular cells, but not other cell types. Here, we identified TFs that can induce the formation of SIX2+ metanephric mesenchyme/renal vesicles, which can be further differentiated into all other renal linages.

Methods: We utilized the human ES lines with doxycycline-inducible transcription factors (~700 genes), analyzed correlation of gene expression response to the induction of human TFs with tissue-specific gene expression in silico, and identified candidate TFs for differentiating towards renal lineages. Modified mRNAs for TFs were synthesized by in vitro transcription. hESCs were transfected with several combinations of synthetic mRNAs for four days by lipofection and cultured for up to 14 days to form kidney organoids, mimicking renal developmental stage. hESCs-derived kidney organoids were used for RNA sequencing analysis(RNA-Seq) and were tested functional assays to model kidney injury.

Results: Based on in-silico analysis, we identified a set of four TFs that induce SIX2+ metanephric mesenchyme and another set of four TFs that help differentiate toward renal vesicles. Two days after the transfection of the first set of four TFs together into hESCs, metanephric mesenchyme cell populations ($SIX2^+$, $SALL1^+$) were induced efficiently (~95%). Subsequent administration of the second set of four TFs transfection induced differentiation into renal vesicles($PAX8^+LHX1^+$). On day 14, epithelial characteristic changes and multi-segmented kidney structures containing podocyte(PNA+PODXL+), proximal tubules(AQP1+KSP+), and distal tubules(CDH1+BRN1+) were observed in both 2D and 3D cultures. RNA-Seq analysis also showed the global expression profile closely resembled kidney profile in renal developmental stages. Moreover, treatment with gentamicin, nephrotoxic agent, induced KIM-1 expression.

Conclusions: We have identified specific TFs for the differentiation of hESCs toward renal lineage via SIX2+ metanephric mesenchyme, and generated multi-segmented functional kidney organoids.

FR-OR101

Nephron Organoids Derived from Patients with ARPKD Model Polycystic Kidney Disease Respond to a cAMP Inducer and an Src Inhibitor and Provide a Platform for Drug Screening In Vitro Ryuji Morizane,[1,3] Tomoya Miyoshi,[1] Navin R. Gupta,[1,3] Koichiro Susa,[1] Edgar Garcia,[2] Albert Q. Lam,[1] Jing Zhou,[1,3] M. Todd Valerius,[1,3] Joseph V. Bonventre.[1,3] *[1]Brigham & Women's Hospital/Harvard Medical School, Boston, MA; [2]Brigham and Women's Hospital, Boston, MA; [3]Harvard Stem Cell Institute, Cambridge, MA.*

Background: Nephron organoids, derived from human pluripotent stem cells (hPSCs), represent a method to study inherited kidney diseases and perform drug screening *in vitro*. Previously, we established proof of concept by modeling autosomal dominant PKD (ADPKD), an adult-onset form, using PKD1 or PKD2 CRISPR-mutant hPSC lines that generated 6% cystic organoids. Here, we sought to model autosomal recessive PKD (ARPKD), an early-onset form, using patient derived induced pluripotent stem cell lines (hiPSCs) to generate cystic organoids with greater efficiency, establishing a suitable platform for studying cystogenic mechanisms and therapeutic screens *in vitro*.

Methods: Nephron organoids were generated in 96-well culture plates from a human embryonic stem cell (hESC) line and a hiPSC line derived from subjects without cystic kidney disease (controls), and 2 ARPKD patient-derived hiPSC lines using our established protocol. Cyst formation was evaluated by bright field imaging and staining for LTL and CDH1. Organoids were treated with forskolin, a cAMP inducer, and tubular cell proliferation assessed by Ki67 staining. Abnormal polarization of cystic epithelia was determined by NaK-ATPase staining. The effect of Src inhibition on cystogenesis was assessed by organoid size.

Results: Patient-derived ARPKD nephron organoids spontaneously formed cysts and demonstrated enhanced cystogenesis with forskolin treatment. Bright field imaging detected cysts in >90% of ARPKD organoids, while control hESC and hiPSC organoids formed very few cysts. Forskolin increased the number of $Ki67^+$ tubular epithelial cells in ARPKD organoids, but not in controls. Mislocalization of the NaK-ATPase to the apical membrane was observed in ARPKD organoids, while control organoids demonstrated NaK-ATPase basolateral restriction. Src inhibition decreased the size of ARPKD organoids.

Conclusions: Patient-derived ARPKD organoids efficiently demonstrated cystic phenotypes that retain known pathophysiology: proliferative response to cAMP and loss of tubular epithelial cell polarity. Src treatment suppressed cystogenesis in a 96-well format, indicating the feasibility of drug screening *in vitro*.

Funding: NIDDK Support, Commercial Support - AJINOMOTO, TORAY

FR-OR102

Defining Cellular Ontologies in Inducible Pluripotent Stem Cell (iPSC)-Derived Kidney Organoids by Mapping into Human Nephrogenesis via ssRNAseq Jennifer L. Harder,[1] Edgar A. Otto,[1] Rajasree Menon,[1] Cristina Cebrian Ligero,[1] Jizhong Zou,[2] Benjamin S. Freedman,[4] Robert G. Nelson,[3] Matthias Kretzler.[1] *[1]University of Michigan, Ann Arbor, MI; [2]NHLBI, NIH, Bethesda, MD; [3]National Institutes of Health, Phoenix, AZ; [4]University of Washington, Seattle, WA.*

Background: Generation of kidney organoids from iPSCs offers a novel method to study genetic effects on kidney cell phenotypes, and may provide useful models of kidney development and disease. Techniques to address the variable cell heterogeneity of these organoids will enhance their value as model systems.

Methods: iPSCs were derived from peripheral blood mononuclear cells from individuals with diabetic kidney disease and kidney organoids were generated using a Matrigel sandwiching technique. Droplet-based single cell RNA-Seq (ssRNAseq) was performed on dissociated cells and sequencing data were aligned to the human genome. Downstream clustering and further analyses were performed using various R statistical packages (Seurat, SC3, Limma). Organoid single cell gene expression was compared to human fetal kidney ssRNAseq data and to publically available expression datasets.

Results: SsRNAseq signatures of cells from iPSC-derived organoids separated into 3 clusters with distinct patterns of differential gene expression reflecting differentiated kidney cell lineages: podocyte (PODXL, NPHS1, NPHS2, CLIC5), tubular (IGFBP7, SLC3A1, VILLIN1, CUBN, CLDN16), and stromal/mesangial (COL3A1, TAGLN, ACTA2). Gene expression of these clusters mapped to cell clusters from ssRNAseq analysis of early second trimester human fetal kidney. When compared to bulk RNA expression patterns of human fetal and adult tissues, iPSC-derived kidney organoid

clusters overlapped prominently with microdissected developing and adult murine kidney tissues and showed kidney specificity.

Conclusions: Human iPSC-derived kidney organoid cultures contain subsets of cells with unique gene expression patterns that recapitulate distinct tissue states of developing and adult human kidney. Identification of individual cells with specific markers of interest provides both the ability to analyze co-expression of genes within an individual cell in a heterogeneous environment and a method to isolate cells of interest within organoid experiments. These results highlight the benefits of modeling human kidney disease with human iPSCs in a kidney organoid culture system and provide strategies to address the system's inherent cellular heterogeneity.

Funding: NIDDK Support

FR-OR103

Defining the Cellular Composition of Human Kidney Organoids Using High Throughput Single Cell Sequencing Alexander N. Combes,[2,1] Luke Zappia,[1] Belinda Phipson,[1] Pei Xuan Er,[1] Alicia Oshlack,[1] Melissa H. Little.[1,3] *[1]Murdoch Children's Research Institute, Melbourne, VIC, Australia; [2]Anatomy and Neuroscience, University of Melbourne, Parkville, VIC, Australia; [3]Peadiatrics, University of Melbourne, Parkville, VIC, Australia.*

Background: Single cell sequencing is a rapidly developing method for transcriptional analysis that has resulted in new insight into the cellular composition of complex tissues. Our lab and others have recently established protocols to direct the differentiation of human pluripotent cells to a kidney fate. This resulted in the formation of self-organizing structures that contain the basic components of the developing kidney. Understanding the cellular composition of these organoids is important to clarify the extent of tissue-specific diseases that may be modelled in this system, and to determine whether all known renal progenitors have been generated.

Methods: Kidney organoids were generated as previously described and harvested after 18 days of culture. We used the 10x Genomics Single Cell platform to profile ~7000 cells from three independent organoids.

Results: Clustering the single cell data identified multiple cell types enriched for markers of early proximal tubule, podocyte, pre-podocyte, collecting duct, ureter, vasculature, neural cells, and multiple interstitial populations. Cell types such as the vasculature and podocytes expressed multiple markers that enable unequivocal identification and give an insight into the state of maturity and fidelity of those cell types. Two distinct populations were identified which were enriched for podocyte markers such as PODXL, NPHS1, NPHS2, PTPRO, and SYNPO. While these both suggest podocyte identity, this may infer distinctions between early visceral and parietal epithelial cell types. Nephron segments such as the loop of Henle and distal tubule were not clearly identified. However, remaining epithelial clusters may represent progenitors of mature nephron segments. This is consistent with organoid morphology, which suggests nephron segmentation equivalent to Stage III/capillary-loop formation.

Conclusions: The analysis of organoid cellular composition using single cell transcriptional profiling has enabled a rapid survey of cellular diversity and fidelity of the cell types generated. The major cell types previously identified in kidney organoids were confirmed and extended with gene expression profiles for each. This data suggests that our kidney organoids will be useful for modelling development and disease of the early proximal tubule, collecting duct, and podocytes.

Funding: Government Support - Non-U.S.

FR-OR104

Defining Kidney Organoid Cell Diversity by scRNA-Seq Haojia Wu,[1] Kohei Uchimura,[1] Erinn L. Donnelly,[1] Samantha A. Morris,[2] Benjamin D. Humphreys.[1] *[1]Division of Nephrology, Washington University in St. Louis, Saint Louis, MO; [2]Department of Developmental Biology, Washington University in St. Louis, Saint Louis, MO.*

Background: Kidney organoids differentiated from pluripotent stem cells hold great promise for understanding organogenesis, disease modeling and ultimately as a source of replacement tissue. Realizing this potential requires a comprehensive evaluation of organoid cell diversity and differentiation state.

Methods: We generated kidney organoids from human BJFF iPS cells (Little protocol). Proper organoid differentiation was confirmed by histology and immunofluorescence. Day 26 organoids were processed for single cell RNA-Sequencing (scRNA-Seq) using DropSeq. We sequenced 4958 cells to a final read depth of 9086 mapped reads/cell with 2137 transcripts and 1185 unique genes detected per cell. Single cell data was visualized by an unsupervised approach combining dimension reduction and graph-based clustering embedded in Seurat. Clusters were annotated by examining known markers and gene ontology analysis. Gene correlation was visualized after data transformation by diffusion based imputation.

Results: Unsupervised clustering revealed 12 separate cell types present in d26 organoids. Kidney cell types made up 61% of all cells: podocytes, proximal tubule (PT), Loop of Henle (LOH), distal convoluted tubule, myofibroblasts and fibroblasts. The epithelial cell types were immature. For example, PT cells expressed terminal differentiation markers SLC3A1, SLC34A1 but coexpressed anterior intermediate mesoderm markers LHX1 and EMX2. LOH also expressed differentiation markers (SLC12A1) and developmental markers (ID1, ID2, and ID4). Surprisingly, many known neural markers (e.g. CRABP1, MAP2, PCP4 and CNTNAP2) were uniquely expressed in four cell clusters and were absent from all kidney cell clusters, indicating distinct neuronal populations. In fact neuronal cell types made up 20.5% of the cell total. Re-analysis of the bulk RNA-seq data in Takasato *et al* confirmed the presence of these neuron-specific genes suggesting that neural differentiation may be a common outcome using this differentiation protocol.

Conclusions: We provide the first comprehensive scRNA-Seq analysis of 4958 kidney organoid cells. We reveal diverse kidney cell types that are immature and the unexpected emergence of neuronal identity with the kidney organoid.

Funding: NIDDK Support

FR-OR105

Transcription Factor Meis1 Is Upregulated in Kidney Stroma after Injury and in Aging and Regulates Tubulointerstitial Cross-Talk Monica Chang Panesso,[4] Farid F. Kadyrov,[2] Flavia G. Machado,[3] Benjamin D. Humphreys.[1] *[1]Washington University School of Medicine, Clayton, MO; [2]Washington University in St Louis, St Louis, MO; [3]Washington University in St Louis, School of Medicine, St Louis, MO; [4]Washington University in St. Louis, St Louis, MO.*

Background: $P16^{INK4a}$, a cell cycle regulator and mediator of cellular senescence, accumulates during aging including in kidney. Meis1 is a transcription factor known to regulate $p16^{INK4a}$ and other cyclin-dependent kinases. We hypothesized that Meis1 may mediate cell senescence in kidney and investigated the expression and function of Meis1 in kidney injury and aging.

Methods: We used Meis1ECFP reporter mice and antibody-based detection of endogenous Meis1. We also deleted Meis1 from kidney stroma by crossing a FoxD1-GFPCre with the Meis1-floxed allele.

Results: Meis1 was strongly expressed in PDGFRβ+ pericytes and fibroblasts based on both immunofluorescence and Meis1ECFP reporter mice. Meis1 mRNA and protein was upregulated after bilateral ischemia-reperfusion injury (IRI). It was also strongly upregulated in myofibroblasts of aged (23 mo) mice. To examine the functional role of Meis1 in kidney stroma, we generated bigenic $Meis1^{f/f}$;$FoxD1GC^{+/-}$. Examination by qPCR and IF staining showed efficient Meis1 deletion of approximately ~90% compared to controls. There was no gross histological abnormality at either P0 or P30 in the $Meis1^{f/f}$;$FoxD1GC^{+/-}$ compared to littermate controls. However by P30, kidneys of $Meis1^{f/f}$;$FoxD1GC^{+/-}$ mice weighed less compared to controls and had a higher BUN. Further histological evaluation at P30, revealed unexpected expression of Kidney Injury Molecule-1 (Kim1) protein expression in the outer medulla, indicating tubular injury. Kim1 upregulation was confirmed by qPCR. There was no NGAL expression indicating that the injury pattern was restricted to the S3 proximal tubular segment. Meis1 knockout mice had normal peritubular capillary density, normal numbers of glomeruli and no albuminuria.

Conclusions: Meis1 is upregulated in myofibroblasts during kidney fibrosis and in aging. Surprisingly, conditional deletion of Meis1 in the stromal lineage led to focal injury of the S3 segment of the proximal tubule in the absence of structural kidney abnormalities. These findings suggest that Meis1 expression in kidney stroma regulates proximal tubule health by a non cell-autonomous mechanism.

Funding: NIDDK Support

FR-OR106

Renal Tubular-Specific Jagged1 Deletion Ameliorates Kidney Fibrosis via Mitochondrial Transcription Factor A (TFAM) Regulation and Metabolic Reprogramming Shizheng Huang, Jihwan Park, Chengxiang Qiu, Szu-Yuan Li, Katalin Susztak. *University of Pennsylvania, Philadelphia, PA.*

Background: Notch is a basic cell-cell communication pathway where expression of the ligand, Jagged1,2 or Delta1,3,4 on signal-sending cells, Notch1-4 on the signal-receiving cell. Our group previously established that tubular epithelial cell (TEC) Notch signaling plays a key role in kidney fibrosis development. However, the precise ligand and receptor pairs that contribute to kidney fibrosis still remain unknown. Here we performed a systematic analysis to define the specific ligands and molecular pathways of Notch-induced fibrosis development in TEC.

Methods: To examine Notch ligands and receptors expression profiles, we used genome wide gene expression arrays from well phenotyped microdissected human kidney tubule samples (n=94). Mechanistic studies were performed by generating mice with tubule-specific deletion of Jagged1 (Ksp^{cre}/$Jagged1^{flox/flox}$). Kidney injury was induced by administering folic acid (FA) intraperitoneally. In vitro studies were performed using a co-culture system of rat tubule epithelial cells (NRK52E) and mouse stromal cells that express Jagged1. Direct targets of Notch signaling were identified by ChIP-Seq with co-transcription factor Rbpj.

Results: In microdissected human kidney tissue samples, of the ligands, Jagged1 showed the best correlation with the degree of interstitial fibrosis. Increased Jagged1 expression was recapitulated in the FA-induced kidney fibrosis model and in primary cultured TEC treated with TGFB1. Mice with tubule specific deletion of Jagged1 mice showed no kidney specific alterations at baseline, but were protected from FA-induced kidney fibrosis. There was marked reduction in inflammatory and profibrotic gene expression and improvement of histology in the Jagged1 knock-out mice following FA injection. In vitro co-culture studies indicated that Jagged1 expression induces proliferation and dedifferentiation of TEC. We found that mitochondrial transcription factor A (TFAM) is a direct target gene for Notch signaling by ChIP-seq. Expression of TFAM could rescue the metabolic defect and protect from Jagged1-induced fibrosis development in co-culture system.

Conclusions: The effect of Notch in TEC induced fibrosis development is mediated by Jagged1. Jagged1 induces epithelial dedifferentiation and fibrosis via TFAM mediated metabolic reprogramming.

Funding: NIDDK Support

FR-OR107

Myokines Mediate Muscle-Kidney Crosstalk Suppressing Metabolic Reprogramming and Fibrosis in Damaged Kidneys Hui Peng,[3,1] Yanlin Wang,[1] William E. Mitch,[1] Sandhya S. Thomas,[2] Zhaoyong Hu.[1] *[1]Baylor College of Medicine, Houston, TX; [2]None, Houston, TX; [3]The third affiliated hospital of Sun Yat-sen University, Guangzhou, China*.

Background: Kidney injury initiates metabolic reprogramming in tubule cells that contributes to the development of chronic kidney disease (CKD). Because exercise might benefit the outcomes of CKD, we hypothesized that the induction of myokines will improve kidney energy metabolism and suppress kidney damage.

Methods: we investigated how a substitute for exercise, overexpression of PGC-1α only in skeletal muscles (mPGC-1a), affects recovery from kidney tubule cell damage in three mouse models including folic acid nephropathy (FAN); unilateral ureteral obstruction (UUO); or subtotal nephrectomy (CKD).

Results: Despite injury from folic acid, unilateral ureteral ligation or subtotal nephrectomy, kidney tubules from mPGC-1α mice resisted progressive cellular damage and subsequent fibrogenesis. Metabolomics analysis revealed improved energy metabolism and ATP production in injured kidneys from mPGC-1α mice. A myokine-enriched serum fraction from mPGC-1α mice (<50 kDa but > 10 kDa) improved energy metabolism in primary cultures of tubule cells. Specifically, the myokine, irisin, protected kidney cells from injury by suppressing metabolic reprogramming. A neutralizing anti-irisin antibody blocked improvements in kidney cell metabolism engendered by serum from mPGC-1a mice. Recombinant irisin administration to mice with kidney injury attenuated kidney damage and fibrosis. The mechanism underlying irisin-initiated improvements is that irisin competes with TGF-β1 for binding to the TGF-b type 2 receptor, thereby impeding activation of the TGF-β type 1 receptor and Smad2/3 signaling, as result, suppression of metabolic reprogramming and fibrogenesis.

Conclusions: myokine-mediated crosstalk between muscle and kidney can protect kidney tubule cell from damage. Myokine, irisin counteracts metabolic reprogramming in injured kidney cells with improvement in kidney function and suppression of kidney fibrosis.

Funding: Other NIH Support - NIASM, Government Support - Non-U.S.

FR-OR108

RNA of APOL1 Risk Alleles Causes Cellular Toxicity through the PKR Pathway Zhe Han,[1,2] Yulong Fu,[1] Jun-yi Zhu.[1] *[1]Children's National Health System, Washington, DC; [2]Dept. of Pediatrics, George Washington University, Washington, DC.*

Background: African Americans are at higher risk for developing chronic kidney diseases due to APOL1 risk alleles (RA), but the mechanism of the cellular toxicity remains unclear. We generated *Drosophila* models of APOL1 nephropathy by expressing APOL1-RA in nephrocytes, which shares striking similarities with podocytes. Using fly genetic screen, we identified genes that interact with APOL1-RA. One of these genes is Pyk, homolog of human protein kinase R (PKR). PKR was suggested to interact with APOL1-RA RNA. Here we test the hypothesis that the APOL1-RA RNA induce toxicity through activating the PKR pathway.

Methods: A series of transgenic flies carrying APOL1-RA with different mutations were generated. Some carry an early stop codon so that these APOL1 proteins are gone but RNA remains same (STOP mutations), some carry synonymous mutations so that the APOL1 RNA no longer interacts with the Pyk protein, but proteins are same (Synonymous mutations). These transgenic lines, together with controls, were tested in different cell types. We also tested how Pyk knocking down affect the phenotype of these transgenes in different cell types, and whether the PKR inhibitor is beneficial for fly models of APOL1 nephropathy.

Results: We found that expression of either STOP or Synonymous mutations of APOL1-RA lead to cellular toxicity. In the fly wing, phenotypes caused by APOL1 RNA and protein appear different, suggesting that APOL1 RNA and protein have different molecular mechanism of cellular toxicity. In the nephrocytes, however, APOL1 STOP and Synonymous mutations cause similar phenotype, characterized as nephrocyte hypertrophy followed by functional decline and cell death. Knocking down of Pyk could rescue the toxicity caused by APOL1-RA with STOP mutations but not by APOL1-RA with Synonymous mutations, suggesting that PKR interaction is uniquely required for the APOL1 RNA toxicity. Feeding with PKR inhibitor reduced the overall toxicity of APOL1-G1 and G2, suggesting that inhibiting the PKR pathway is beneficial for reducing the cellular toxicity caused by the RNA of APOL1-RA.

Conclusions: Our findings demonstrated that both the RNA and the protein of APOL1-RA contribute to the overall cellular toxicity. We provided the *in vivo* evidence for the mechanism of APOL1 RNA toxicity through the PKR pathway, and showed that PKR inhibitor could be used as a potential therapeutic treatment to reduce APOL1 RNA toxicity.

Funding: NIDDK Support

FR-OR109

Potential Therapeutic Targets for CKD by Comparative Analysis of Conserved Transcriptional Changes in Human and Mouse Kidney Fibrosis Rojesh Shrestha,[1] Jihwan Park,[1] Chengxiang Qiu,[1] Shizheng Huang,[1] Szu-Yuan Li,[1] Yi-An Ko,[1] Thomas Bell,[2] Aaron Donner,[2] Emily Brand,[2] Katalin Susztak.[1] *[1]University of Pennsylvania, Philadelphia, PA; [2]Ionis Pharmaceuticals, Carlsbad, CA.*

Background: Kidney fibrosis is the histological manifestation of chronic kidney disease (CKD). Kidney fibrosis is associated with global gene expression changes and while some of them might be causally related to disease development, others could be a consequence of the disease. While not all aspect of CKD is recapitulated in mouse models, changes that consistent in a different species could have a higher likelihood to be causal. Furthermore, genetic modification of mouse models can be used to understand causality.

Methods: We performed expression profiling for a large cohort (n=95) of human microdissected normal and CKD tubule samples. Using an adjusted linear regression model, we identified genes whose expression levels were significantly associated with phenotypic changes including GFR and tubulointerstitial fibrosis. By using RNA sequencing, we examined gene expression changes in four mouse fibrosis models; folate induced fibrosis (FA), unilateral ureteral obstruction (UUO), tubule specific Notch transgenic and podocyte specific risk allele APOL1 transgenic mice.

Results: We identified 761 conserved expression changes and 10 transcription factors between mouse and human kidney disease. Here, we focused on E74-like factor 4 (Elf4), which is mainly expressed in immune cells and fibroblasts. It is also an important transcription factor that mediates the effect of interferon response. Then, we developed and tested the effectiveness of antisense oligonucleotide (ASO) both in vitro and in vivo for Elf4 knock-down. ASO mediated knockdown of ELF4 in kidney prevented interstitial fibrosis in FA model. Mice injected with Elf4 ASO showed lower expression of fibrosis markers (vimentin, fibronectin, collagen) compared to control FA injected mice. In addition, Elf4 ASO mice also showed marked histological improvement in fibrosis.

Conclusions: Thus, comparative analysis of human and mouse kidney fibrosis have identified conserved genes and pathways in kidney fibrosis. These genes can serve as potential new biomarkers or therapeutic targets for kidney disease development.

Funding: NIDDK Support, Commercial Support - Ionis pharmaceuticals

FR-OR110

Smad Anchor for Receptor Activation (SARA) Overexpression in Pericytes Prevents Renal Fibrosis Tomoko Hayashida,[2,3] Zhe Han,[1] Constance Runyan,[2] H. William Schnaper,[2,3] Xiaoyan Liang.[2] *[1]Children's National Medical Center, Washington, DC; [2]Northwestern University, Chicago, IL; [3]Lurie Children's Hospital, Chicago, IL.*

Background: We previously reported that overexpressing SARA in cultured proximal tubular epithelial cells prevents transforming growth factor (TGF)-β-induced mesenchymal phenotypic transition, and SARA knockdown alone is sufficient to induce such changes, suggesting that SARA is critical for maintenance of cellular phenotype. Here we tested whether maintaining SARA levels could ameliorate mouse and fly models of kidney fibrosis.

Methods: A SARA-overexpressing (SARA-Tg) mouse was generated by inserting full-length human cDNA for SARA1 preceded by a lox-stop-lox cassette at the ROSA26 locus, and was crossed with either PDGFRβ-Cre or tamoxifen-inducible Cre-ERT2 mice to induce ectopic SARA expression specifically in pericytes or systemically, respectively. Aristolochic acid (AA), 5 mg/kg, was given intraperitoneally 3x week for 4 weeks beginning at 8 weeks old, to SARA Tg-Cre mice and their Cre-negative littermates. The mice were sacrificed for analysis one week after AA treatment was stopped. Drosophila heart tube/nephrocyte fibrosis model was generated using a 4xHand-Gal4 driver and iRNA for Wds or Ada2b.

Results: Severe interstitial fibrosis was observed in wild-type mice subjected to AA and whole-kidney SARA expression was significantly lower than in non-AA control mice. On the other hand, SARA levels remained similar even after AA administration to SARA-Tg Cre-ERT2 mice treated with tamoxifen. Cre expression in PDGFRβ-Cre mice starts approximately at E12.5, but SARA-Tg PDGFRβ-Cre mice developed normally and were fertile. PDGFRβ-Cre expression was detected in pericytes and in some mesangial cells as expected. AA-induced fibrosis as detected by COL1A2 and α-smooth-muscle actin staining and mRNA levels were significantly less in PDGFRβ-Cre+ SARA-Tg mice compared to their Cre-negative littermates. In Drosophila, cardioblast/nephrocyte-specific knockdown of Wds or Ada2b caused fibrosis around the heart tube as shown by increased pericardin expression. SARA knockdown significantly enhanced, and SARA overexpression virtually prevented, pericardin expression.

Conclusions: SARA maintains renal cell phenotype in murine kidney disease and decreases the collagen-producing response in mice and flies. Our data support the recent findings by others that pericytes are essential for renal fibrosis, and suggest a role for SARA in ameliorating fibrogenesis.

Funding: NIDDK Support

FR-OR111

Erythrocyte Adenosine A2B Receptor (ADORA2B) Promotes Oxygen Release to Counteract Renal Tissue Damage Zhangzhe Peng,[3,5] Renna Luo,[1] Lijian Tao,[4] Yang Xia.[2] *[1]The First Affiliated Hospital of Dalian Medical University, Dalian, China; [2]Universith of Texas-Medical School, Houston, TX; [3]Xiangya Hospital, Central South University, Changsha, China; [4]Xiangya hospital, Central South University, Changsha, China; [5]Departments of Biochemistry and Molecular Biology, McGovern Medical School, the University of Texas Health Science Center, Houston, TX.*

Background: Hypoxia, defined as inadequate oxygen supply to the whole body or a region of the body, is commonly seen in patients with chronic kidney disease(CKD), and frequently promotes renal failure. As the only cell type responsible for delivering oxygen, erythrocytes quickly respond to hypoxia by increasing their oxygen delivery ability. However, there is an enormous gap in our understanding of the role of erythrocytes in renal tissue damage.

Methods: Non-biased metabolomics screening was conducted in the whole blood of Angiotensin II(Ang II) treated WT mice. Subsequently, we infused Ang II to mice with specific deletion of ADORA2B in erythrocytes (ADORA2B$^{f/f}$/EpoR-Cre^{+}), and examined tissue hypoxia, damage, and erythrocyte function. Human studies were conducted on CKD patient samples.

Results: First, metabolomics profiling revealed that 2,3-BPG, an erythrocyte-specific metabolite regulating oxygen release, was highly elevated in the whole blood of Ang II treated mice. Erythrocyte-specific ADORA2B deficiency suppressed Ang II-induced 2,3-BPG production and 2,3-BPG mutase activity. After Ang II infusion, erythrocyte oxygen release ability (P50) was significantly elevated in EpoR-Cre^{+} mice but not in ADORA2B$^{f/f}$/EpoR-Cre^{+}. Moreover, renal and cardiac hypoxia was more severe in ADORA2B$^{f/f}$/EpoR-Cre^{+} mice. Ang II also significantly increased proteinuria in ADORA2B$^{f/f}$/EpoR-Cre^{+} mice. In addition, both the protein and mRNA levels of HIF-1α in heart and kidney were further increased in kidneys and hearts of ADORA2B$^{f/f}$/EpoR-Cre^{+} mice infused with Ang II, together with the mRNA levels of collagen I, fibronectin, indicating significantly more severe tissue damages. Mechanistically, we revealed that AMPK is an intracellular signaling molecular which functions downstream of ADORA2B underlying elevated 2,3-BPG production by inducing BPG mutase activity. Subsequently, we translate our mouse study to human and confirmed that the levels of 2,3-BPG, P50 and p-AMPK were elevated in erythrocytes of mild CKD patients and further increased in severe CKD patients, indicating a compensation mechanism in response to hypoxia.

Conclusions: Our findings reveal a previously unrecognized beneficial role of erythrocyte ADORA2B signaling in Ang II-induced systemic hypoxia and renal tissue damage and thereby identify novel and important therapeutic possibilities for hypoxia-induced tissue damage.

FR-OR112

Pik3c3-Dependent mTORC1 Signaling Mediates Compensatory Nephron Hypertrophy Ting Liu,[1] Jinxian Xu,[1] Benjamin D. Humphreys,[2] Caihong Dai,[1] Jian-Kang Chen.[1] *[1]Augusta University, Augusta, GA; [2]Washington University School of Medicine, Clayton, MO.*

Background: Nephron loss stimulates the residual nephrons to undergo compensatory nephron hypertrophy (CNH), which is implicated in progressive nephron damage. Activation of the mechanistic (formerly mammalian) target of rapamycin complex 1 (mTORC1) mediates uninephrectomy (UNX)-induced CNH. We recently observed class 3 phosphatidylinositol 3-kinase (Pik3c3) activation in the remaining kidney after UNX. However, whether Pik3c3 activation is essential for mTORC1 activation and CNH remains undefined.

Methods: We created homozygous *Pik3c3*-hypomorphic (*Hypo*) mice to compare with gender-matched heterozygous (*Het*) and wild type *(WT)* littermates. We also created tamoxifen-inducible proximal tubule-specific *Pik3c3* knockout (*KO*) mice, which have a genotype of *Pik3c3*$^{flox/flox}$;*SLC34a1.CreER*^{T2}(+). Gender-matched *Pik3c3*$^{flox/flox}$;*CreER*^{T2}(-) littermates were used as controls (*Ctrl*) mice.

Results: *Hypo* mice express markedly less Pik3c3 than *Het* littermates, which already express a lower level of Pik3c3 than *WT* littermates. Interestingly, when subjected to UNX, *Hypo* mice developed less CNH than both *WT* and *Het* mice, revealed by UNX-induced increases in kidney-to-body weight ratio (*WT*: 31.78±1.89 vs. *Hypo*: 18.10±1.31%, p<0.0001; *Het*: 27.14±1.04 vs. *Hypo*: 18.10±1.31%, p<0.001; n=5-7). Consistently, UNX induced significantly less CNH in *KO* mice than in *Ctrl* mice, indicated by UNX-induced increases in kidney-to-body weight ratio (*Ctrl*: 33.15±1.97 vs. *KO*: 15.81±2.82%, p<0.001; n=7) as well as protein-to-DNA ratio (*Ctrl*: 25.00±4.01 vs. *KO*: 9.78±2.88%, p<0.05; n=7). Signaling studies with immunoblotting and immunostaining unveiled that UNX-induced mTORC1 activation in the remaining kidney was markedly inhibited in both *Pik3c3*-hypomorphic and *Pik3c3-KO* models.

Conclusions: The present study using two genetically engineered mouse models provides unequivocal evidence that Pik3c3-dependent mTORC1 activation is a major mechanism underlying nephron loss-induced residual nephron hypertrophy.

Funding: NIDDK Support

FR-OR113

Dysfunction of Proteasome in Podocytes Results in CKD Shinichi Makino,[2] Naritoshi Shirata,[4] Kanae Nonaka,[3] Motoko Yanagita,[3] Katsuhiko Asanuma.[1] *[1]Chiba University Graduate School of Medicine, Chiba, Japan; [2]Kyoto University Graduate School, Kyoto, Japan; [3]Kyoto University Graduate School of Medicine, Kyoto, Japan; [4]Mitsubishi Tanabe Pharma Corporation, Toda, Japan.*

Background: Ubiquitin-proteasome(UP) and autophagy had been known as major intracellular degradation systems. The importance of autophagy in podocyte has already been reported, however, the role of UP has not well been understood.

Methods: To investigate the role of UP in podocyte, we generated podocyte-specific proteasome knockout mice (Rpt3^{pdKO}) by deletion of Rpt3, which is essential for construction of 26S proteasome, using Cre-loxP system under the regulation of the podocyte specific podocin promoter. To evaluate autophagy activity, LC3 was visualized by crossing with GFP-LC3 transgenic mice.

Results: Rpt3^{pdKO} mice developed albuminuria starting at 4 weeks of age and increased significantly higher levels compared with their Rpt3^{Ctrl} littermates on 8weeks of age. The ratio of sclerotic glomeruli and serum creatinine levels were significantly increased. The KO mice exhibited a significantly lower survival ratio than the littermates due to severe renal failure. Ubiquitinated proteins were accumulated and the oxidative stress marker 8OHdG intensity was increased in podocytes of Rpt3^{pdKO} mice. Expressions of p53 and cleaved caspase3 to regulate apoptosis were increased in podocytes of the KO mice. On the other hand, LC3 positive dots in the KO podocytes were not increased, and accumulation of p62 which is detected in autophagy failure, was seen in the KO podocytes.

Conclusions: Ubiquitin-proteasome plays an important role in podocytes, resulting in severe renal failure.

Funding: NIDDK Support, Veterans Affairs Support, Commercial Support - Mitsubishi Tanabe Pharma

FR-OR114

Keap1/Nrf2 Signaling Reveals Homeostatic Function in Renal and Cardiovascular Physiology Soma Jobbagy,[1] Dario A. Vitturi,[1] Sonia R. Salvatore,[1] Scott Hahn,[1] Adam Straub,[1] Arohan R. Subramanya,[2] Bruce Freeman,[1] Francisco J. Schopfer.[1] *[1]Pharmacology & Chemical Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA; [2]Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA.*

Background: Keap1/Nrf2 signaling is well-established as a master regulator of cellular responses to oxidative stress; however, recent findings suggest that this pathway additionally performs key functions in renal solute and water homeostasis. Herein we study the functional consequences of constitutive graded Nrf2 activation on renal salt and water handling and integrate renal and cardiovascular endpoints.

Methods: Wild-type, Keap1 hypomorphic (Keap1$^{f/f}$), and Nrf2$^{-/-}$ mice were studied under control conditions or in response to dietary sodium maneuvers, and renal and plasma biomarkers were assayed by IF, PCR, immunoblot, and HPLC-MS/MS. Cardiovascular function was assessed by radiotelemetry and wire myography.

Results: Keap1$^{f/f}$ mice exhibited 5-fold upregulation of Nrf2 target gene NQO1 in the kidney and were polyuric. Consistent with a urine concentrating defect and volume depletion, hematocrits were higher in the Keap1$^{f/f}$ cohort (45.5% vs 37.2% WT). The latter was not attributable to upregulation of renal EPO expression or increased RBC antioxidant enzyme production, and resolved after salt loading. 2-fold down-regulated expression of total NKCC2 and NCC by western blot implicated a distal nephron defect. Compensatory activation of WNK signaling was consistent with 2-fold elevation in plasma renin activity and led to 3-fold increase in phospho-to-total NCC ratio in Keap1$^{f/f}$ mice after sodium depletion. Finally, 2-fold reduction in renal cycolooxygenase-1 and -2 in Keap1$^{f/f}$ mice suggests crosstalk between Nrf2 and prostaglandin signaling, and resulted in reduction in vasodilatory PGI_2. Blood pressure was unchanged between WT and Keap1$^{f/f}$ mice, however heart rate was significantly depressed in the Keap1$^{f/f}$ cohort. Wire myography revealed impaired vasodilation of resistance arteries in response to ACh.

Conclusions: Mice with genetic Keap1 hypomorphism were studied as a pharmacomimetic model of chemical Nrf2 inducers to delineate physiologic effects of this pathway. Keap1$^{f/f}$ mice display distal nephron defect with reduced urine concentrating function and volume depletion. Compensatory activation of RAS- and WNK-signaling likely serves to mitigate solute and water loss in this model. Differences in prostanoid biosynthesis suggest a mechanism underlying renal and vascular effects of constitutive Nrf2 activity.

Funding: NIDDK Support, Private Foundation Support

FR-OR115

The Prevalence of Mesoamerican Nephropathy in Larreynaga-Malpaisillo, Leon, Nicaragua Stefano Bianchi,[1] Elba M. Jimenez penado,[2] Andrea Grillo,[1] Francesca Nistri,[1] Giada G. Santini,[1] Elisa Poderelli,[1] Eva D'Aurizio,[1] Sara Samoni,[1] Filippo Cellai,[1] Roberto Bigazzi.[1] *[1]ASL NO, Livorno, Italy; [2]Blood bank - Health MInister, León, Nicaragua.*

Background: An unrelenting epidemic of unexplained chronic kidney disease (CKD) affecting primarily young individuals has been observed throughout Central America. This condition has been called Mesoamerican Nephropathy (MeN). This disease is characterized by elevated serum creatinine, hyperuricemia, leukocyturia, and minimal

proteinuria and hematuria. Kidney biopsies are consistent with chronic tubulointerstitial nephritis. The causes of this epidemic remain obscure and systematic epidemiological data are scarse.

Methods: In the context of a joint effort between Regione Toscana and the Department of Leon we performed a screening of the population in the city of Malpaisillo-Larreynaga, in the Department of León, Nicaragua *. Out of a general population of 23885 inhabitants we selected 18510 subjects, age ≥ 12 years, (mean age (± SD) 36.3 ± 18 years, 8771 M, 9739 F), and extracted a sample of 2768 subjects (1310 M, 1458 F), of these 1915 subjects (723 M and 1192 F; mean age 38.9 ± 18) were enrolled. All participants filled a questionnaire and in all of them we collected blood and urine samples to estimate glomerular filtration rate (eGFR) (CKD-EPI mL/min/1.73m^2), and urine albumin excretion (UAE= albumin, mg / creatinine, g).

Results: Among participants, 1410 (73.6%; 483 M and 927 F) had normal eGFR, and 505 (26.4%; 240 M and 265 F) manifested CKD (Stage 1=21.6%; Stage 2=14.8%; Stage 3a= 25.5%; Stage 3b=15.8%; Stage 4=16%; Stage 5=6.3%). Males (33.2%) were more affected than females (22.2%). Among participants with CKD Stage 3-5, 160 (~50%) had UAE < 30 and 162 (~50%) had UAE > 30. Among the latter, only 40 (25%) of subjects manifested UAE > 300. No patient manifested nephrotic syndrome.

Conclusions: For the first time a systematic epidemiological approach to estimate the prevalence of MeN has been used. We report an alarming prevalence of CKD affecting a relatively young population in Malpaisillo-Larreynaga, Leon, Nicaragua. The disease is in large part asymptomatic and characterized by minimal proteinura in keeping with a diagnosis of tubulointerstitial disease. The cause(s) of this disease remain to be determined. *Perfil epidemiologico de la enfermedad renal cronica y sus principales factores de riesco en el municipio Larreynaga-Malpaisillo, Leon, Nicaragua.

Funding: Government Support - Non-U.S.

FR-OR116

CKDu in Mexico: The Case of Poncitlán, Jalisco Guillermo Garcia-Garcia, Evelyn F. Morraz Mej?a, José M. Montalban, Jonathan Chavez, Luz E. Vazquez martinez, Eduardo N. Pacheco, Karina Renoirte. *Hospital Civil De Guadalajara, University of Guadalajara, Guadalajara, Mexico.*

Background: An elevated prevalence of CKD of unspecified cause (CKDu) has been documented in various developing countries. It has been reported by the media a high prevalence of CKDu in towns located by Chapala Lake, Mexico, particularly in the communities of San Pedro Itzican, Agua Caliente, and Mezcala, in Poncitlan, Mexico. Environmental factors have been blamed as the probable cause of the pandemia.

Methods: Since 2006, we pioneered screening people at risk for the presence of CKD using mobile units that travel to rural and urban communities of Jalisco. Trained personnel collected demographic and clinical data, and obtained blood and urine for serum chemistry and dipstick urinalysis. Those individuals who were aware they had kidney disease were not assessed; all others were eligible to participate. GFR was estimated with the MDRD formula. CKD was defined as an eGFR < 60 ml/min/1.73m2.

Results: Between 2007-2016, 50,909 adults were screened with the mobile units. Findings in individuals residing in Poncitlan were compared with those living in other Jalisco municipalities (Table)

Conclusions: CKD and proteinuria were highly prevalent among individuals living in communities of Poncitlan, Mexico. CKD prevalence was two-fold higher among the adult population in comparison with other Jalisco municipalities. Prevalence of proteinuria was three-fold higher than in other communities of Jalisco. Undergoing studies will provide information on the causes of this epidemic

Funding: Private Foundation Support

Results

	All n=50,909	Poncitlan n=283	Other municipalities n= 50,626	p
Age, y	52.33±14.82	50.92±17.16	52.32±14.80	0.173
Male, %	32.0	21.9	32.1	0.000
Known DM, %	22.5	15.9	22.5	0.03
Known HTN, %	32.7	26.9	32.7	0.113
SBP ≥ 140, %	39.5	47.9	39.4	0.005
DBP ≥ 90, %	20.4	20.7	20.4	0.888
% with IMC ≥ 30	35.4	26.8	35.4	0.001
% with eGFR < 60 ml/min/1.73 m2	10.6	20.1	10.4	0.002
% with dipstick + proteinuria	11.2	36.1	11.0	0.000

FR-OR117

SPRINT Trial: Intensive Hypertension Treatment and CKD Incidence Rita Magriço,[1] Miguel Bigotte Vieira,[2] Catarina Viegas dias,[3] Lia Leitão,[4] João Sérgio Neves.[5] *[1]Nephrology Department, Hospital Garcia de Orta, Almada, Portugal; [2]Nephrology and Renal Transplantation Department, Centro Hospitalar Lisboa Norte, Lisboa, Portugal; [3]Dafundo Family Health Unit, Agrupamento de Centros de Saúde Lisboa Ocidental e Oeiras, Lisboa, Portugal; [4]Neurology Department, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal; [5]Department of Endocrinology, Diabetes and Metabolism, Hospital de São João, Faculdade de Medicina, Universidade do Porto, Porto, Portugal.*

Background: The Systolic Blood Pressure Intervention Trial (SPRINT) showed that in non-diabetic patients with high cardiovascular risk, intensive systolic blood pressure treatment (<120 mmHg) was associated with lower rates of major cardiovascular events and mortality. However, intensive treatment was associated with increased CKD incidence. We evaluated the association between mean arterial pressure (MAP) reduction and CKD incidence in the intensive-treatment group.

Methods: We performed a secondary analysis of the SPRINT trial. We categorized patients in the intensive-treatment group according to MAP reduction: <20 mmHg; 20 to <40 mmHg; ≥40 mmHg. We defined the primary outcome as ≥30% reduction in eGFR to <60 ml/min/1.73m2, and the secondary outcome as cardiovascular events or death. We also performed a propensity score analysis, matching patients in each MAP reduction category from the intensive-treatment group with patients from the standard-treatment group, in order to calculate the number needed to treat (NNT) regarding cardiovascular events or mortality and the number needed to harm (NNH) regarding CKD incidence.

Results: 1138 (34.4%) patients presented MAP reduction <20 mmHg, 1857 (56.3%) presented 20 to <40 mmHg and 309 (9.4%) ≥40 mmHg. Adjusted hazard ratios for CKD incidence were 2.14 (95% CI, 1.25-3.66) for MAP reduction between 20 and 40 mmHg and 6.35 (95% CI, 2.82-14.29) for MAP reduction ≥40 mmHg. In the propensity score analysis, MAP reduction <20 mmHg presented a NNT of 43.5 and a NNH of 65.4; MAP reduction between 20 and <40 mmHg presented a NNT of 41.7 and a NNH of 35.1 and MAP reduction ≥40 mmHg presented a NNT of 95.2 and a NNH of 15.9.

Conclusions: Higher categories of MAP reduction were associated with increased risk of CKD incidence. The benefit-risk balance of intensive treatment was less favourable as MAP reduction increased.

FR-OR118

The Effect of Intensive Blood Pressure Lowering on Kidney Tubule Injury among Participants with CKD in the SPRINT Trial Rakesh Malhotra,[9] Timothy Craven,[10] Walter T. Ambrosius,[2] Anthony A. Killeen,[4] William E. Haley,[1] Alfred K. Cheung,[8] Michel Chonchol,[7] Mark J. Sarnak,[6] Chirag R. Parikh,[5] Joachim H. Ix,[9] Michael Shlipak.[3] *[1]Mayo Clinic, Jacksonville, FL; [2]Wake Forest School of Medicine, Winston-Salem, NC; [3]San Francisco VA Medical Center, San Francisco, CA; [4]University of Minnesota, Minneapolis, MN; [5]Yale University, New Haven, CT; [6]Tufts Medical Center, Boston, MA; [7]University of Colorado, Aurora, CO; [8]University of Utah, Salt Lake City, UT; [9]UCSD, San Diego, CA; [10]Wake Forest, Winston-Salem, NC.*

Background: Randomization to the intensive (SBP<120 mm Hg) arm in SPRINT resulted in more rapid decline in estimated glomerular filtration rate (eGFR) than in the standard arm (SBP <140 mm Hg). Whether this change reflects hemodynamic effects or accelerated intrinsic kidney damage is unknown.

Methods: In a subset of SPRINT with CKD (eGFR<60 ml/min/1.73m^2), we compared changes in kidney tubule biomarkers over 4 years between the intensive and standard arms. Among these 978 participants (519 in intensive and 459 in the standard arm), we measured urine biomarkers of tubule cell injury (KIM-1, IL-18), repair (YKL-40) and inflammation (MCP-1) at baseline, year 1 and year 4. Biomarkers were assayed *en bloc* in multiplex panels. Biomarker changes were evaluated using linear mixed-effects models in an intention-to-treat design.

Results: Mean age was 72± 8.6 and eGFR 46.1 ± 9.4. Clinical characteristics, eGFR, urinary albumin-to-creatinine ratio (ACR), and all 4 biomarkers were similar between arms at baseline. Compared to the standard arm, eGFR was 2.9 and 3.3 ml/min/1.73m^2 lower in the intensive arm at year 1 and year 4, and ACR was also lower in the intensive arm. All urinary biomarkers, except YKL-40, were significantly lower at year 1 in the intensive arm, and none differed between arms at year 4 (**Figure 1**).

Conclusions: Among CKD participants in SPRINT, intensive BP control reduced eGFR but did not increase urine markers of tubule cell injury. These findings may support the hypothesis that eGFR decline in the intensive arm of SPRINT reflects hemodynamic changes.

Funding: NIDDK Support

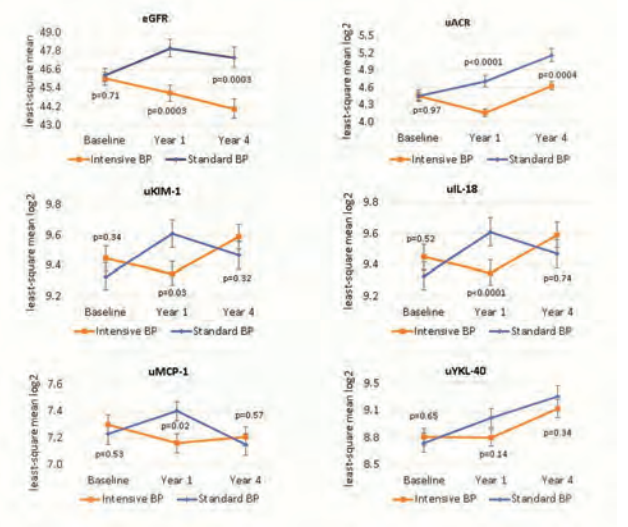


Figure 1. Unadjusted least-square means and standard error of eGFR, urinary ACR and urinary biomarkers at baseline and the 4-year follow-up

FR-OR119

Longitudinal Changes in Plasma Biomarkers Strongly Associate with Risk for DKD Progression in the VA NEPHRON-D Trial Steven G. Coca,[1] Yuan Huang,[2] Dennis G. Moledina,[3] Veena Rao,[3] Divya A. Verghese,[1] Wassim Obeid,[3] Girish N. Nadkarni,[1] Bart Ferket,[1] Linda F. Fried,[4] Chirag R. Parikh.[5] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]VA Cooperative Studies Program, West Haven, CT; [3]Yale School of Medicine, New Haven, CT; [4]VA Pittsburgh Healthcare System, Pittsburgh, PA; [5]Yale University and VAMC, New Haven, CT.*

Background: While baseline levels of plasma TNFR-1, TNFR-2, and KIM-1 are independently associated with risk for renal function decline in diabetic kidney disease (DKD), the prognostic value of longitudinal changes in these biomarkers is unknown.

Methods: In this ancillary study of the Veterans Affairs Nephropathy in Diabetes Trial (VA NEPHRON-D) that included 759 participants with plasma samples at both baseline and 1 year, we measured plasma TNFR1, TNFR2 and KIM-1 *via* MesoScale Discovery multiplex assay. We assessed the association between the change in plasma biomarker concentrations at 12 months from baseline with the renal endpoint (decline in eGFR or ESRD as defined in the trial) using Cox Proportional Hazards Models with adjustment for study arm, biomarker, eGFR and albuminuria at baseline and change in eGFR and albuminuria by 12 months.

Results: In the 123 (16%) participants who experienced the renal endpoint after 12 months, plasma TNFR1, TNFR2 and KIM-1 increased by 34%, 17%, and 6%, respectively by 12 months (**TABLE**). In the 636 participants that did not reach the renal endpoint, plasma TNFR1 and TNFR2 increased by 11% and 3%, respectively, whereas KIM-1 decreased by 6%. After multivariable adjustment, including baseline biomarker concentration eGFR, urine albumin at baseline and change in eGFR and albuminuria at 12 months, increases in TNFR1, TNFR2 and KIM-1 over time were associated with increased hazards of developing the renal end point (**TABLE**). There were no statistically significant differences in the change in the three biomarkers or interactions on the outcomes between the combination-therapy group vs. the monotherapy arms.

Conclusions: Longitudinal changes in plasma TNFR1, TNFR2 and KIM-1 add additional prognostic information to baseline concentrations of these markers, even after accounting for clinical variables, including changes in eGFR and albuminuria.

Funding: NIDDK Support, Veterans Affairs Support

	Median ([Q1, Q3]) change (pg/ml) at 12 months from baseline		Adjusted HR (95% CI)					
Biomaker	No renal event (n=636)	Renal event (n=123)	Baseline Biomarker (log2)	Change in biomarker at 12 month (log2) from baseline (log2)	Baseline eGFR	Change in eGFR at 12 months from baseline	Baseline UrAlb (log)	Change in UrAlb at 12 months (log) from baseline (log)
TNFR1	442 [-371, 1373]	1423 [94, 2916]	3.9 (2.5-6.4)	2.4 (1.4-4.0)	1.03 (1.01-1.04)	0.93 (0.91-0.95)	2.4 (1.8-3.0)	1.9 (2.5-6.4)
TNFR2	270 [-969, 1683]	1797 [232, 4056]	2.3 (1.4-3.7)	3.5 (1.9-6.3)	1.01 (0.99-1.03)	0.93 (0.91-0.95)	2.5 (1.9-3.2)	2 (1.5-2.6)
KIM-1	-25 [-115, 51]	24 [-142, 292]	1.5 (1.2-1.8)	1.6 (1.1-2.2)	0.99 (0.98-1.01)	0.92 (0.90-0.94)	2.2 (1.6-2.8)	1.7 (1.3-2.3)

FR-OR120

suPAR Serum Levels Predict Progression of Kidney Disease in Children Franz S. Schaefer,[7] Howard Trachtman,[3] Marietta Kirchner,[6] Salim Hayek,[1] David C. Wei,[5] Sanja Sever,[2] William E. Smoyer,[4] Jochen Reiser.[5] *[1]Emory University School of Medicine, Atlanta, GA; [2]Massachusetts General Hospital, Charlestown, MA; [3]NYU Langone Med Ctr, New York City, NY; [4]Nationwide Children's Hospital, Columbus, OH; [5]Rush University Medical Center, Chicago, IL; [6]University Heidelberg, Heidelberg, Germany; [7]University of Heidelberg, Heidelberg, Germany. Group/Team: ESCAPE Trial Consortium and the 4C Study Group.*

Background: Renal disease progression rate in chronic kidney disease (CKD) children is highly variable, and no serum markers exist today that aid with prediction of renal function decline. Even within individual age and disease groups, progression rate varies widely, defining a need for informative prognostic biomarkers predicting disease progression and the need for early intervention in an individual patient. Recently, soluble urokinase receptor (suPAR) has been shown to be a strong predictor of CKD incidence and progression. Here we determine whether elevated suPAR levels are associated with renal disease progression in children with CKD.

Methods: *Post-hoc* analysis of two prospectively followed pediatric CKD cohorts (ESCAPE trial and 4C Study) including 898 children (mean age 11.9±3.5 years) with serum suPAR level measured at enrollment and longitudinal eGFR measured prospectively. Renal diagnoses included CAKUT (70%), tubulointerstitial nephropathies (10.2%), glomerulopathies (7.7%), post-ischemic (4.7%), and other CKD (6.5%). Mean eGFR was 34±16 ml/min/1.73m^2, median follow-up 3.1 (0 to 7.9) years. The primary renal endpoint was a composite of 50% eGFR loss, eGFR<10 ml/min/1.73 m^2 or start of renal replacement therapy.

Results: 5-year endpoint-free renal survival was 64.5% (95%CI 57.4-71.7%) in children with suPAR in the lowest quartile as compared to 35.9% (95%CI 28.7-43.0%) in those with levels in the highest quartile (P<0.0001). In multivariable analysis, the risk of attaining the endpoint was higher in children with glomerulopathies and increased with age, blood pressure, proteinuria and lower eGFR at baseline. In patients with baseline eGFR>40 ml/min/1.73 m^2, higher log-transformed suPAR levels were independently associated with a higher risk of CKD progression (HR 5.12, 95% CI 1.56-16.7, P=0.007).

Conclusions: Elevated suPAR levels are independently associated with disease progression in children with mild to moderate CKD.

Funding: NIDDK Support

FR-OR121

Soluble Urokinase Plasminogen Activation Receptor and Cardiovascular Mortality in Persons Undergoing Coronary Angiography Claudia Sommerer,[5] Marcus E. Kleber,[1] Christian Morath,[6] Jochen Reiser,[3] Martin G. Zeier,[2] Winfried März.[4] *[1]Heidelberg University, Mannheim, Germany; [2]None, Heidelberg, Germany; [3]Rush University Medical Center, Chicago, IL; [4]Synlab Services GmbH, Mannheim, Germany; [5]Nephrology, University Hospital of Heidelberg, HEIDELBERG, Germany; [6]University of Heidelberg, Heidelberg, Germany.*

Background: Soluble urokinase plasminogen activation receptor (suPAR) is an emerging biomarker for prediction and progression of kidney disease and cardiovascular outcomes. To further validate the value of suPAR as a cardiorenal biomarker we studied German persons undergoing coronary angiography having a follow-up of ten years.

Methods: suPAR was measured in baseline samples of participants of the Ludwigshafen Risk and Cardiovascular Health (LURIC) study. We estimated overall risk of cardiovascular death by Cox proportional hazards regression according to quartiles of suPAR, including age, sex, use of lipid-lowering drugs, body mass index, diabetes mellitus, hypertension, smoking, LDL cholesterol, HDL cholesterol, triglycerides, as well as eGFR (CKD-EPI), NT-proBNP, IL-6 and CRP as covariates.

Results: A total of 2922 participants (69 % males, mean age 62.7 ± 10.5) having a median GFR of 81ml/min/1.73 m^2 were included. 393 patients had a GFR<60ml/min /1.73 m^2. Median suPAR levels 3000 pg/ml (interquartile range, 2250-3980 pg/ml). Using the lowest quartile of suPAR as the reference, crude HRs for cardiovascular mortality were 1.58 (95% CI 1.16-2.16), 1.85 (95% CI 1.37-2.52) and 2.75 (95% CI 2.03-3.71) in the second, third and fourth quartile, respectively. Adjusting for eGFR or inflammation (IL-6 and CRP) did not materially alter this relationship. In a fully adjusted model HRs for cardiovascular death were 1.52 (95% CI 1.11-2.09), 1.56 (95% CI 1.14-2.15), and 1.78 (95% CI 1.28-2.46) in quartiles two to four.

Conclusions: suPAR predicts cardiovascular death over a period of ten years in persons undergoing coronary angiography, independent of kidney function and markers of systemic inflammation. su-PAR has the potential to stratify the risk in patients with cardiovascular disease and kidney disease. su-PAR could be a useful and additional biomarker in cardiovascular and renal medicine.

Funding: Private Foundation Support

FR-OR122

Treatment of Metabolic Acidosis in CKD with Fruits and Vegetables Yields Better Overall Health Outcomes Than Oral NaHCO3 Nimrit Goraya,[4,5] Jan Simoni,[3] Yolanda Munoz Maldonado,[1] Donald E. Wesson.[2,4] *[1]Biostatistics, Baylor Scott & White Health, Temple, TX; [2]Diabetes Health and Wellness Institute, Dallas, TX; [3]Surgery, Texas Tech University Health Sciences Center, Lubbock, TX; [4]Internal Medicine, Baylor Scott and White Health, Temple, TX; [5]Internal Medicine, Texas A and M School of Medicine, Temple, TX.*

Background: Dietary acid reduction added to pharmacologic anti-angiotensin II therapy appears to provide adjunctive kidney protection and KDIGO guidelines recommend Na^+-based alkali for treatment of metabolic acidosis in chronic kidney disease (CKD). Nevertheless, base-producing fruits and vegetables (F+V) also improve metabolic acidosis and might yield better overall health outcomes in patients with CKD than Na^+-based alkali. We tested the hypothesis that F+V compared to oral $NaHCO_3$ (HCO_3) treatment of metabolic acidosis in CKD yielded better long-term (five years) health outcomes.

Methods: One hundred eight macroalbuminuric, non-diabetic CKD 3 subjects with metabolic acidosis but with serum [HCO_3] between 22-24 meq/L were randomized to receive F+V (n=36) in amounts to reduce dietary potential renal acid load by half, oral $NaHCO_3$ (HCO_3, n=36) 0.3 meq/Kg bw/day, or to Usual Care (UC, n=36). All had a systolic blood pressure (SBP) goal < 130 mm Hg using drug regimens including ACE inhibition and were followed with annual assessments for five years. A score of 1 for improved, 0 for no change, and -1 for worsened at 5 years was assigned to the following 4 parameters: plasma total CO_2 ($PTCO_2$), LDL, HDL, and change in medication dose (a decrease in dose among the 7 possible medications was considered improved; an increase in dose was considered worsened). A score of 1 for met goal and 0 for not meeting goal was assigned to eGFR (goal > 30 ml/min/m^2) and SBP (goal < 130 mm Hg) at five years.

Results: All three groups showed improved health outcomes during follow up ($p<0.05$) but the health score was greater than UC (1.17 ± 1.44) for both HCO_3 and F+V (2.89 ± 1.70 and 7.39 ± 1.61, respectively, $p<0.01$). Additionally, the F+V health score was greater than HCO_3 ($p<0.01$) due mostly to greater F+V than HCO_3 reductions in medication (predominately anti-hypertensive) dosage, lower LDL, and a greater proportion of patients achieving SBP goal.

Conclusions: Treatment of metabolic acidosis in CKD with F+V and $NaHCO_3$ yielded better overall health outcomes in CKD 3 patients than Usual Care but health outcomes were dramatically better in F+V than HCO_3. The data support an overall long-term health advantage of F+V compared to HCO_3 as a dietary acid reduction strategy for the treatment of metabolic acidosis in CKD 3.

FR-OR123

Blood Pressure Lowering and Risk of Mortality in CKD: A Meta-Analysis of Randomized Controlled Trials Rakesh Malhotra,[10] Hoang Anh Nguyen,[5] Oscar Benavente,[6] Mihriye Mete,[2] Jonathan Mant,[8] Michelle Odden,[3] Carmen A. Peralta,[7] Alfred K. Cheung,[9] Girish N. Nadkarni,[1] Ruth L. Coleman,[11] Holman Rury,[11] Alberto Zanchetti,[12] Ruth Peters,[13] Nigel Beckett,[14] Jan A. Staessen,[4] Joachim H. Ix.[10] *[1]Ichan School of Medicine, New York, NY; [2]Medstar Health Research Institute, Hyattsville, MD; [3]Oregon State University, Corvallis, OR; [4]Studies Coordinating Centre, Division of Hypertension and Cardiovascular Rehabilitation, Department of Cardiovascular Diseases, University of Leuven, Leuven, Belgium; [5]UCSD Department of Nephrology and Hypertension, San Diego, CA; [6]University of British Columbia, Vancouver, BC, Canada; [7]University of California San Francisco/SFVAMC, San Francisco, CA; [8]University of Cambridge, Cambridge, United Kingdom; [9]University of Utah, Salt Lake City, UT; [10]UCSD, San Diego, CA; [11]University of Oxford, Oxford, United Kingdom; [12]Istituto Auxologico Italiano, University of Milan, Milan, Italy; [13]Imperial College London, London, United Kingdom; [14]Guys and St Thomas' NHS Foundation Trust, London, United Kingdom.*

Background: Trials in hypertensive patients demonstrate that intensive blood pressure (BP) lowering reduces CVD and mortality risk, but may increase risk of chronic kidney disease (CKD) progression. Whether intensive BP lowering is associated with a lower mortality in patients with prevalent CKD remains uncertain.

Methods: We conducted a meta-analysis of randomized controlled trials (RCTs) that enrolled patients with CKD stage 3-5 and determined whether randomization to more vs. less intensive BP control was associated with mortality. Ovid Medline, Cochrane Library, Embase, Pubmed, and ClinicalTrials.gov electronic databases were searched. All RCTs that compared two defined BP targets (either active treatment vs. placebo or no treatment, or intensive vs. less intensive BP control) and enrolled persons with CKD stages 3-5 exclusively or as CKD subgroup between January 1950 and June 2016 were included. The main outcome was mortality during the active phase of each trial.

Results: We identified 31 RCTs, among which we were able to extract the CKD subset mortality data in 19 trials. There were 1300 deaths among 15,861 participants with CKD. More vs. less-intensive BP control resulted in 14% lower risk of all-cause mortality (Odds Ratio (OR) 0.86; 95% CI 0.76- 0.96, p = 0.009) (**Figure 1**); a finding that was without significant heterogeneity (p=non-sig) across subgroups including type of treatment in the comparator arm (placebo vs. less intensive BP target), length of follow-up, presence of diabetes, baseline SBP, achieved SBP during the trial and degree of SBP differences across the treatment arms.

Conclusions: Randomization to more intensive BP control is associated with lower mortality risk among CKD trial participants.

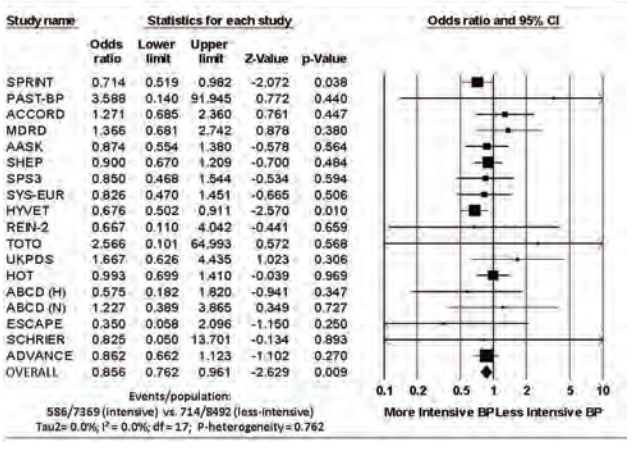


Figure 1. Effect of Intensive BP Lowering on Risk of Mortality in Participants with CKD

FR-OR124

Influence of Altitude of Residence on the Prevalence of Anemia of CKD Christos Argyropoulos,[4] V. Shane Pankratz,[3] Orrin Myers,[4] Mark L. Unruh,[4] Keith C. Norris,[2] Joseph A. Vassalotti.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]UCLA, Marina Del Rey, CA; [3]UNM Health Sciences Center, Albuquerque, NM; [4]University of New Mexico, Albuquerque, NM.*

Background: Hypoxia is the major regulator of erythropoietin production in the kidney. There are currently minimal data about the prevalence of anemia in patients with varying degrees of CKD who reside in high altitudes.

Methods: We undertook an exploratory analysis of the National Kidney Education Kidney Early Evaluation Program. Participant's address were geocoded to geographic coordinates using National Elevation US Database and the altitude of the residence of each participant in KEEP was determined. We examined prevalence of anemia (Hemoglobin, Hgb < 10g/dL) against the severity of CKD (eGFR) and other predictors after weighting the KEEP participants to the US census, in order to account for the self-selection bias in KEEP.

Results: In multivariate analyses, race, ACR, personal history of anemia (Table), age (a relationship that differed between women Figure A and men Figure B), eGFR and altitude were significant predictors of the odds of anemia (p<0.001). Predicted prevalence of anemia was half at 2.0 km elevation vs. sea level for all eGFR values (Figures C,D). There was no interaction between altitude and eGFR.

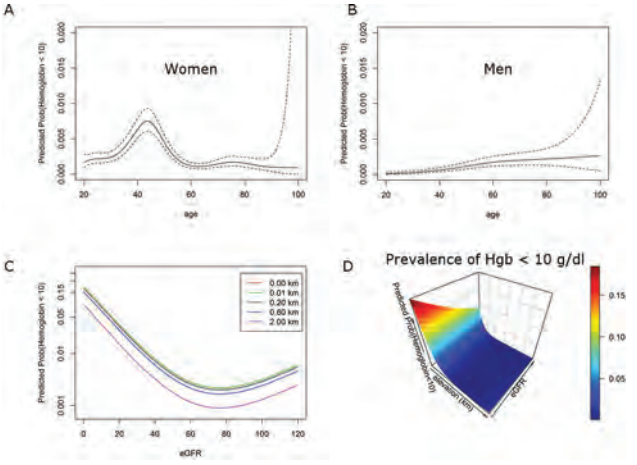
Conclusions: The odds of anemia differ for individuals residing at different altitudes. This relationship likely contributes to geographic disparities of CKD complications. Further studies should examine the response to iron and ESA according to altitude.

Funding: Commercial Support - Dialysis Clinic Inc

Categorical associations with anemia

Variable	Odds Ratio (95% CI)
Race (Caucasian = ref)	1
Black	3.53 (2.89 – 4.31)
American Indian	3.47 (2.30 – 5.24)
Other	2.25 (1.79 – 2.82)
ACR (<30 = ref)	1
ACR 30-300 mg/g	1.79 (1.41 – 2.27)
ACR >300 mg/g	2.02 (1.18 – 3.48)
Personal Hx of Anemia	10.7 (7.68 – 15.0)

ACR : Albumin-Creatinine Ratio (random urine)



FR-OR125

The A-Splice Variant of NBCe1 (NBCe1-A) Is Necessary for the Renal Ammonia and K Response to Hypokalemia Hyun-Wook Lee,[1] Gunars Osis,[1] Autumn N. Harris,[1] Kierstin L. Webster,[1] Heather L. Holmes,[2] Adam J. Rossano,[2] Michael F. Romero,[2] Jill W. Verlander,[1] I. D. Weiner.[1,3] *[1]Nephrology, University of Florida, Gainesville, FL; [2]Mayo Clinic College of Medicine, Rochester, MN; [3]Nephrology, NF/SGVHS, Gainesville, FL.*

Background: Hypokalemia is associated with increased ammonia excretion, but neither the specific proteins that signal this response nor the functional role of increased ammonia excretion are known. This study's purpose was to determine NBCe1-A's role in the effect of hypokalemia on renal ammonia metabolism and potassium homeostasis.

Methods: We used mice with NBCe1-A deletion generated using TALEN techniques. We compared mice with homozygous deletion (KO) to wild-type (WT) littermates. Hypokalemia was induced by feeding a K-free diet for 7 days.

Results: A K-free diet caused persistently increased urinary ammonia excretion in WT mice, whereas in KO mice urinary ammonia increased only on day 1 and 2, and then returned to baseline. In proximal convoluted tubule (PCT), NBCe1-A KO had significantly lower expression, compared to WT, of key ammoniagenic proteins, phosphoenolpyruvate carboxykinase (PEPCK) and phosphate-dependent glutaminase (PDG), and greater expression of the ammonia-recycling protein, glutamine synthetase (GS). In contrast, in the proximal straight tubule (PST) in the outer medulla, where relatively little NBCe1-A expression is found compared to the PCT, hypokalemic KO mice exhibited PEPCK and PDG expression that was greater and GS expression that was less than in hypokalemic WT. NBCe1-A deletion also altered renal K handling during hypokalemia. Serum K did not differ on normal diet, but was lower in KO mice on K-free diet (KO 1.8±0.1; WT 3.2±0.1 mM, P<0.01). Despite more severe hypokalemia, urinary K was significantly higher, 75%±16% greater in KO than WT during days 3-7, when maximal K conservation occurred in both WT and KO. Total NCC expression was unchanged, but phospho-NCC, which decreases renal K excretion, was significantly less in hypokalemic KO than WT mice.

Conclusions: 1) NBCe1-A is essential to the signaling pathway that increases ammonia excretion in response to hypokalemia; 2) KO mice partially compensate to NBCe1-A deletion with supranormal responses in PST; and, 3) NBCe1-A is critical for PT signaling to distal sites to conserve K through a mechanism that may involve NCC phosphorylation. Thus, hypokalemia's induction of ammonia metabolism via NBCe1 may be a critical signaling mechanism regulating distal epithelial K transport.

Funding: NIDDK Support, Private Foundation Support

FR-OR126

Expression, Localization, and Role of Slc4a8 (NDCBE) in Acid Base Transport in Kidney Tubules Jie Xu,[1,2] Sharon L. Barone,[1,2] Marybeth Brooks,[1] Manoocher Soleimani.[1,2] *[1]University of Cincinnati, Cincinnati, OH; [2]Research Services, Veterans Administration, Cincinnati, OH.*

Background: The sodium-dependent bicarbonate transporter Slc4a8, also known as NDCBE, mediates the cotransport of sodium and bicarbonate in exchange for chloride (Na-dependent Cl^-/HCO_3^- exchanger). NDCBE is abundantly detected in the brain, with very low expression levels in the kidney. The cell distribution, subcellular localization and role of NDCBE in acid/base and electrolyte homeostasis in the kidney have been the subject of conflicting reports. There are no localization studies (such as immunolabeling and/or in situ hybridization) and no functional studies to pinpoint the location and demonstrate the function of NDCBE in the kidney.

Methods: Molecular techniques including RT-PCR, Northern Hybridization and in situ hybridization were employed in kidney sections and tagged epitopes were used to examine the membrane localization of NDCBE in transfected polarized kidney epithelium. Crispr/Cas9 approach was used to generate and examine NDCBE KO mice.

Results: Zonal distribution (cortex, outer medulla and inner medulla) studies by northern hybridization and RT-PCR and in situ hybridization experiments using FISH (Fluorescence *In Situ* Hybridization) showed very little to no expression for NDCBE in the cortex or in cortical collecting ducts (CCD). NDCBE was predominantly detected in the kidney medulla with significant expression in medullary collecting ducts. NDCBE was targeted to the basolateral membrane of MDCK cells when grown in hypertonic medium, a physiologic environment for cells in medullary collecting duct. NDCBE deficient mice show no salt, bicarbonate or fluid wasting phenotype under baseline condition, and their urine pH remained comparable to wild type mice in response to bicarbonate loading or salt restriction. Expression levels of pendrin and NCC were comparable in kidney cortices of NDCBE KO and wild type mice.

Conclusions: Slc4a8 (NDCBE) is predominantly detected in mouse medullary collecting duct, is targeted to the basolateral membrane, shows increased activity in hypertonic environment and its deletion does not cause any noticeable acid base perturbation either under baseline conditions or in response to bicarbonate loading or salt restriction.

Funding: Veterans Affairs Support, Private Foundation Support

FR-OR127

Robust Circadian Clock Oscillation and Osmotic Rhythms in the Inner Medulla Reflecting Cortico-Medullary Osmotic Gradient Rhythm in Rodent Kidney Masayuki Hara,[1,2] Yoichi Minami,[1] Nobuya Koike,[1] Tetsuro Kusaba,[2] Keiichi Tamagaki,[2] Kazuhiro Yagita.[1] *[1]Physiology and Systems Bioscience, Kyoto Prefectural University of Medicine, Kyoto, Japan; [2]Nephrology, Kyoto Prefectural University of Medicine, Kyoto, Japan.*

Background: Circadian clocks in mammals function in most organs and tissues throughout the body. Various renal functions such as the glomerular filtration and excretion of electrolytes exhibit circadian rhythms. Although it has been reported that the expression of the clock genes composing molecular oscillators show apparent daily rhythms in rodent kidneys, functional variations of regional clocks are not yet fully understood.

Methods: 1. To monitor the molecular clock work and localization, we applied the macroscopic bioluminescence imaging method of the PER2::Luciferase knock-in mouse kidney. 2. We analyzed the circadian fluctuation of the cortico-medullary osmotic pressure gradient. 3. We analyzed diurnal expression patterns of genes contributing to high osmotic pressure and reabsorption of water in mice kidneys. 4. To analyze the effect of molecular clock on diurnal variations of osmotic pressure gradient, we measured osmotic pressure gradient in systemic *Bmal1* deficient mice which completely lack a functional clock.

Results: 1. PER2::Luciferase knock-in mice exhibited strong and robust circadian clock oscillation in the medulla. 2. Significant diurnal rhythm of the tissue osmolality with peaking at night (active phase) was found in the medulla but not in the cortex. This suggests that cortico-medullary osmotic pressure gradient changes diurnally depending on osmotic pressure rhythm in the inner medulla. 3. Vasopressin receptors (*V1aR, V2R*), urea transporter (*UT-A2*) and water channel (*Aqp2*) show diurnal variations in the inner medulla. 4. Systemic *Bmal1* deficient mice impaired circadian rhythm of osmotic pressure gradient and of expression of genes (*V1aR, V2R, UT-A2, and Aqp2*) in the inner medulla.

Conclusions: The circadian clocks in the medulla of the kidney regulate the circadian rhythm of gene expressions related to the water reabsorption and subsequent cortico-medullary osmotic pressure gradient, resulting in the physiological day-night rhythm of urination.

FR-OR128

Global Identification of Protein Phosphorylation Changes Following CRISPR/Cas9-Deletion of cAMP-Dependent Protein Kinase (PKA) in Collecting Duct Cells Kiyoshi Isobe, Hyun Jun Jung, Chin-Rang Yang, Maurice B. Burg, Viswanathan Raghuram, Mark A. Knepper. *NHLBI/NIH, Bethesda, MD.*

Background: Vasopressin regulates water and sodium transport in collecting duct principal cells by binding to the V2 receptor and increasing cAMP, thereby activating cAMP-regulated protein kinase PKA catalytic subunits PKA-Cα and/or PKA-Cβ. Signaling downstream from PKA is poorly understood.

Methods: To identify PKA-dependent phosphorylation changes, we deleted both PKA catalytic subunits using CRISPR-Cas9 in vasopressin-sensitive mpkCCD cells. Indel mutations were confirmed by Sanger sequencing. We carried out large-scale quantitative phosphoproteomic analysis using protein mass spectrometry in three pairs of PKA-knockout (KO) vs. control clones. The cells were grown on permeable supports in the presence of 0.1 nM dDAVP.

Results: The PKA-KO cells maintained viability and polarity. Phosphoproteomics identified 229 PKA substrate sites. These sites contained the motif R-(R/K)-X-pS and were significantly decreased in PKA-KO. Most of these PKA targets are not annotated in public databases. Surprisingly, a large number of phosphorylation sites with the motif X-(pS/pT)-P showed increased phospho-occupancy, pointing to increased activity of one or more MAP kinases in PKA-KO cells. Indeed, a marked increase in phosphorylation of ERK2 at T183 and Y185 (which activates ERK2) was seen in PKA-KO cells. The ERK2 site is downstream from a direct PKA site in Sipa1l1, which indirectly inhibits Raf1 through Rap1 inactivation. Aquaporin-2 phosphorylation at S256 was **not** decreased in PKA-KO cells. The datasets were integrated to identify a causal network describing PKA signaling that explains vasopressin's actions to regulate membrane trafficking and gene transcription. The model predicts that, through PKA activation and inhibition of MAP kinase signaling, vasopressin stimulates AQP2 exocytosis (confirmed by immunofluorescence microscopy), induces nuclear translocation of the transcriptional co-activator/acetyltransferase EP300 (confirmed by immunoblotting of nuclear fractions) and increases histone H3K27 acetylation of vasopressin-responsive genes (confirmed by ChIP-Seq).

Conclusions: We conclude that PKA-dependent signaling is more complex than previously believed with both primary and secondary effects on phosphorylation that explain vasopressin responses.

Funding: Other NIH Support - NHLBI

FR-OR129

Proteomics and Water Channel Function of AQP2-Rich Extracellular Vesicles in Human Urine Yuko Miyazawa,[1] Saki Mikami,[1] Masaki Sakai,[1] Tatsuya Saito,[1] Kenichi Ishibashi,[1] Sei Sasaki.[1,2] *[1]Meiji Pharmaceutical University, Kiyose-shi, Japan; [2]Tokyo Medical and Dental University, Tokyo, Japan.*

Background: AQP2 water channel is a key membrane protein which determines urine concentrating ability. AQP2 is excreted in urine in a form of extracellular vesicles (EVs), mostly in exosomes and urine AQP2 is now measured as a useful biomarker for diagnosis and treatment of water-balance disorders. However, proteomic and functional analysis of AQP2-bearing EVs have not been performed.

Methods: Urine EVs were obtained from heathy volunteers by the differential centrifugation. Membrane-disrupted (freeze-thaw) AQP2-bearing EVs were obtained by immunoprecipitation with an AQP2-specific antibody and the proteins were digested with trypsin and applied to LC-MS/MS proteomic analysis. The proteins were also analyzed by Western blots. Osmotic water permeability (Pf) of the AQP2-enriched EVs was measured by a stopped flow method monitoring 90 degree scattered light intensity in response to outwardly directed osmotic gradient created by glycerol.

Results: 1) The MS analysis of the EVs co-immunoprecipitated with the AQP2 antibody identified 137 proteins, surprisingly, 103 of these 137 proteins have been shown to express in collecting duct cells, suggesting that our co-immunoprecipitation successfully gather AQP2-bearing EVs membranes. Pathway analysis show the presence of late endosome and multiple vesicular body-related proteins such as TSG101, ALIX, CHMP1-6, VPS4,7,9,25. MS analysis of urine EVs showed the phosphorylation of AQP2 at Ser256 and Ser261. Western blot analysis confirmed the presence of these proteins and S256, S261, and S269 phosphorylated AQP2. 2) Pf of 160,000 xg EVs was $4.75 \pm 0.38 \times 10^{-4}$ cm/s which was inhibited by 63% by 0.3 mM HgCl2 pretreatment. The activation energy was 3.51 kcal/mol which is consistent with a water channel activity. Pf was not detectable when EVs membranes were disrupted by extensive sonication. The measured Pf values of EVs samples were proportional to the protein amounts of AQP2 ($r=0.95$, $p<0.014$). A positive correlation was also observed between the EVs Pf and osmolality of the urine from which urine EVs were prepared ($r=0.879$, $p<0.049$).

Conclusions: Urine AQP2 excretion is mediated by late endosome-multiple vesicular body pathway, and AQP2 at EVs preserve the original water channel function.

Funding: Government Support - Non-U.S.

FR-OR130

RNA-Seq in Microdissected Rat Cortical Collecting Ducts during Development of Lithium-Induced Nephrogenic Diabetes Insipidus Chih-chien Sung,[1,2] Chung-Lin Chou,[1] Lihe Chen,[1] Hyun Jun Jung,[1] Mark A. Knepper.[1] *[1]NHLBI/NIH, Bethesda, MD; [2]Tri-Service General Hospital, Taipei, Taiwan.*

Background: Lithium has been widely used to treat bipolar disorder, but many patients develop nephrogenic diabetes insipidus (NDI). Our previous studies in rats have demonstrated rapid activation of ERK1/ERK2 in collecting ducts after oral lithium administration (Trepiccione et al., KI, 2014). Associated gene expression changes early in the development of lithium-induced NDI have been incompletely explored.

Methods: Cortical collecting ducts (CCDs) were microdissected from rats 72 hrs after beginning treatment with lithium (lithium chloride, 40 mmol/kg of dry food) versus time controls. Single-tubule RNA-Seq was carried out independently in 3-5 CCD samples per rat (4 lithium-treated rats versus 4 controls) using the methods of Lee et al. (JASN, 2015). Cortical thick ascending limbs (cTALs) were also microdissected for RNA-Seq at 72 hrs.

Results: Lithium-treated rats showed increased water intake within 24 hrs, concomitant with a fall in AQP2 protein abundance (western blotting). RNA-Seq data at 72 hr revealed moderate decreases in AQP2, AQP3, and AQP4 mRNA. The three subunits of ENaC showed more profound decreases. A large number of transcripts coding for other transporters and receptors were decreased with lithium treatment including the vasopressin V2 receptor and the chloride channel ClC-Kb. Several known aldosterone-regulated genes showed decreases in mRNA including Sgk1, αENaC, and Gadd45g. Immediate early genes (typical of MAP kinase activation) and transcriptional targets of NF-κB were significantly more frequent among transcripts increased with lithium than among all expressed genes (Chi-square). Similar over-representation among lithium-affected transcripts were seen for two other pathways, e.g. cell cycle signaling, and Wnt signaling. No association with lithium treatment was found for several pathways including cyclic AMP signaling, estrogen receptor signaling and insulin signaling. In contrast to the CCD, no significant changes were found in mRNA levels in cTALs in response to lithium, indicating the effect of lithium was selective for CCD.

Conclusions: Cellular signaling during development of lithium-induced NDI is consistent with known responses to increased MAP kinase activation and includes major gene expression changes characteristic of NF-κB-dependent inflammatory signaling.

Funding: Other NIH Support - NHLBI

FR-OR131

Identification of miRNAs Regulating the Water Transport in the Collecting Duct Federica Petrillo,[5] Anna Iervolino,[3] Alfonso De Falco,[4] Federica Prosperi,[3] Luigi R. De la motte,[5] Sabina K. Jelen,[1] Robert A. Fenton,[2] Giovambattista Capasso,[5] Francesco Trepiccione.[6] *[1]Biogem S.C.R.L, Ariano Irpino, Italy; [2]University of Aarhus, Aarhus, Denmark; [3]Biogem scarl, Ariano Irpino, Italy; [4]Laboratoire National de Santè, Dudelange, Luxembourg; [5]University of Campania Luigi Vanvitelli, Napoli, Italy; [6]Dpt of Cardio-Thoracic and Respiratory Science, University of Campania, Naples, Italy*.

Background: Principal cells (PC) contribute to water reabsorption in the collecting duct (CD). In response to vasopressin, they express on their apical membrane the AQP2, and so increase water permeability of the CD. Finally, an interstitium driven osmotic gradient leads the water to be reabsorbed. Although several molecular mechanisms have been identified as master regulators of this process, both dependent and independent by vasopressin stimulation, no miRNAs involved in the water reabsorption are known. miRNas are post-trascriptional regulators of gene expression and, thus, they are appealing targets for new therapy. We aim to identify the miRNAs involved in urinary concentrating mechanism to fill this gap.

Methods: To identify whether the miRNAs are crucial for the water reabsorption in the CD, we generate a mouse model deficient of dicer selectively in the AQP2 expressing cells. By microarray analysis we compared the miRNAs expressing profile of the inner medulla from Dicer cKO and their littermate control mice. miRNAs target prediction and IPA analysis was used to build a network of interaction between miRNAs and target proteins and to select candidate miRNAs, master regulators of the AQP2 expression. In vitro assay of miRNAs activity has been performed to validate bio-informatic data.

Results: Single segment evaluation of Dicer expression confirmed its ablation only in the CD. Dicer-AQP2 cKO mice present with a severe water concentrating defect that is resistant to dDAVP administration. Loss of expression of AQP2 all along the PC made these mice consistent with an experimental model of neprhogenic diabetes insipidus. Since principal cells keep expressing other cellular markers such as AQP4 and ENaC, our hypothesis was that Dicer suppression targets mostly AQP2 expression. Microarray screening of the miRNas profile reveals potential candidate miRNA, able to directly interfere with the V2R-AQP2 axis. In vitro validation in mpkCCD cells confirms the role of 3 miRNAs in regulating the expression of target mRNA crucial for the water reabsorption.

Conclusions: We identify for the first time miRNAs able to regulate the AQP2 expression in the PC. This is the first step to build a miRNA-based therpy to potentially approach the nephrogenic diabetes insipidus.

FR-OR132

ILDR1 Expression in the Tricellular Junction Regulates Epithelial Water Impermeability Nina Himmerkus,[1] Yongfeng Gong,[2] Susanne Milatz,[1] Cosima Merkel,[1] Jianghui Hou,[2] Markus Bleich.[1] *[1]Christian Albrechts University Kiel, Kiel, Germany; [2]Washington University School of Medicine, Saint Louis, MO*.

Background: The ability to produce a wide range of urine osmolality depends on epithelial water tightness of the thick ascending limb (TAL). The collecting duct (CD) uses the corticomedullary concentration gradient for controlled transcellular water absorption under control of anti-diuretic hormone (AVP). Water tightness of the space in between epithelial cells is determined by the properties of bicellular and tricellular tight junctions. ILDR1 is expressed in the tricellular junction and ILDR1 knockout mice (KO) show high urine production with nearly plasma isotonic urine osmolality.

Methods: ILDR1 expression was investigated in isolated tubular segments along the nephron by qPCR and immunofluorescence. Transepithelial water permeability was assessed in isolated perfused tubules of KO and control mice (CTRL). Tubules were freshly isolated and microperfused with FITC-dextran as indicator of luminal concentration. Transepithelial water flux was measured as changes in fluorescence intensity of the luminal perfusate after application of a transepithelial osmotic gradient and closure of the open tubular end. In addition, CD transcellular water permeability was measured under unstimulated conditions and after stimulation by basolateral application of AVP. Relative fluorescence intensity increment per time was calculated as correlate of transepithelial water transport.

Results: ILDR1 was localized in the tricellular junctions of TAL and CD but was absent in proximal tubules. TAL of KO showed a water leak in comparison to the watertight TAL of Ctrl. Also CD of KO showed a significant water permeability already under unstimulated conditions whereas CD of Ctrl were water tight in the absence of AVP. The effect of basolateral AVP on CD water permeability was additive in ILDR1 knockout animals and not different to controls.

Conclusions: In summary, ILDR1 is part of the tricellular junction in the nephron segments TAL and CD and it confers paracellular water tightness. Impaired water tightness in the TAL by ILDR1 knockout impedes the dilution of the luminal fluid as well as the concentration of the medullary interstitium. ILDR1 might therefore be a new target to regulate renal concentrating ability.

Funding: Other NIH Support - RO1DK084059

FR-OR133

Renal Phenotype of P2Y12 Receptor Knockout Mice Bellamkonda K. Kishore,[5] Kenny M. Hansson,[1] Tao Liu,[4] Kerstin Magnell,[2] Noel G. Carlson,[6] Yue Zhang.[3] *[1]AstraZeneca, Cardiovascular and Metabolic Diseases iMED, Mölndal, Sweden; [2]AstraZenecaR&D, Mölndal, Sweden; [3]Univ. of Utah & VA Medical Center, Salt Lake City, UT; [4]Internal Medicine, Univ. of Utah & VA Med Ctr, Salt Lake City, UT; [5]Univ. of Utah and VA Medical Center, Salt Lake City, UT; [6]VA Salt Lake City Health Care System, Salt Lake City, UT*.

Background: Previously we reported that pharmacological blockade of P2Y12 receptor (R) potentiates the action of arginine vasopressin (AVP) on renal medullary collecting duct (mCD). To establish that the observed effect is mediated through P2Y12-R, we evaluated the renal phenotype of P2Y12-R global knockout (KO) mice.

Methods: The P2ry12 gene was disrupted by targeted homologous recombination in ES cells. Urinary excretion of AVP, cAMP, PGE2, Na and K was assayed in adult homozygous KO and syngeneic C57/Bl6 wild type (WT) mice under basal conditions. Primary cultures of mCD cells from KO and WT mice were stimulated with 0.1 nM of dDAVP for 24 h, and assayed for cAMP generation, and mRNA expression of AQP2.

Results: The urine from KO mice showed significant increases in cAMP, PGE2 and K compared to WT mice (see Table). Comparisons between mCD cells derived from KO and WT mice showed significantly higher production of cAMP in response to stimulation with dDAVP (16-fold vs. 4-fold, $P < 0.006$, $N = 6$). Significantly higher level of mRNA expression of AQP2 was observed in mCD from KO vs. WT mice after dDAVP stimulation (2.43-fold, $P < 0.04$).

Conclusions: These findings are consistent with our previous observations and show that loss of P2Y12-R by either pharmacological blockade or genetic deletion potentiates the action of AVP/dDAVP on mCD. These data also reveal that P2Y12-R may play a role in renal handling of sodium and potassium.

Funding: Veterans Affairs Support, Commercial Support - AstraZeneca AB, Clinical Revenue Support

Urine	WT	P2Y12 KO	P Value
AVP*	432 ± 55 (5)	518 ± 67 (5)	= 0.175
cAMP**	23 ± 2 (6)	35 ± 6 (6)	< 0.050
PGE2↑	377 ± 25 (5)	566 ± 98 (5)	< 0.050
Sodium#	131 ± 13 (4)	184 ± 17 (6)	= 0.057
Postassium#	289 ± 34 (4)	426 ± 45 (6)	< 0.040

Values are mean ± se (N): Statistical analysis by ANOVA

*pmoles/24 h/20 g body weight;

**nmoles/24 h/20 g body weight;

↑pg/24 h/20 g body weight;

#µmol/24 h/20 g body weight;

FR-OR134

Novel Imaging Techniques Reveal Axial Differences in Endo-Lysosomal Uptake Capacity along the Kidney Proximal Tubule Claus D. Schuh,[1] Marcello Polesel,[1] Dominik Haenni,[1] Evgenia Platonova,[1] Urs Ziegler,[2] Olivier Devuyst,[1] Andrew Hall.[1] *[1]University of Zurich, Zurich, Switzerland; [2]University of Zurich, Center for Microscopy and Image Analysis, Zurich, Switzerland*.

Background: The kidney filters low-molecular weight proteins (LMWPs) and albumin, which are reclaimed by the proximal convoluted tubule (PCT) to prevent wasting in urine. PCT cells take up proteins across the apical membrane by receptor-mediated endocytosis, which involves binding to megalin/cubilin, internalization into early endosomes (EE), and subsequent trafficking to late endosomes (LE) and lysosomes. Early (S1) and late (S2) PCT segments show ultrastructural differences in the endo-lysosomal system by EM, but how these might relate to differences in uptake capacity is unclear.

Methods: Confocal microscopy of immuno-stained mouse kidney. Multiphoton intravital imaging and 3-D analysis of cleared post-mortem tissue.

Results: Using established antibody markers for EEs (Rab5), LEs (Rab 7), recycling endosomes (Rab11) and lysosomes (LAMP1), we found that expression levels of these 4 markers were far higher in S1 than in S2 segments. In contrast, expression of megalin was similar in both. Intravital imaging revealed that uptake of dye-labeled albumin and

LMWP lysozyme occurred exclusively in S1, whereas uptake of 10 kDa dextran – a substrate for fluid phase endocytosis - was observed in S1 and S2. Experiments were repeated using two different fluorescent labels for each ligand to exclude a confounding effect on substrate handling. Real-time imaging of lysozyme uptake revealed the expected dynamic progression from brush border to EEs, and then LEs/lysosomes. Following saturation of S1 uptake capacity with a high concentration of injected lysozyme, some uptake was observed in S2 segments, but it remained far lower than in S1. Antibody staining in tissue fixed post-lysozyme injection revealed that the uptake pattern closely matched the expression of endo-lysosomal proteins, but not megalin. A major constraint of intravital kidney microscopy is limited depth of imaging. We therefore treated fixed kidneys chemically with a modified CLARITY protocol to increase transparency. Using this approach, we were able to image through the entire cortex and confirm that lysozyme uptake was confined to early segments in all PCTs, whereas dextran uptake was more diffuse.

Conclusions: We have found evidence for major axial differences in endo-lysosomal uptake capacity along the PCT, independent of megalin expression.

Funding: Government Support - Non-U.S.

SA-OR001

Novel Imaging Technique Reveals Changes in the Podocyte Actin Network after Injury Hani Suleiman,[2] Andrey S. Shaw,[1] Jeffrey H. Miner.[3] *[1]Genentech, South San Francisco, CA; [2]Washington University, Saint Louis, MO; [3]Washington University School of Medicine, St. Louis, MO.*

Background: Actin stress fibers are abundant structures in cultured cells, including podocytes, yet no clearly equivalent structures have been observed *in vivo.* This discrepancy has been thought to be the result of current tissue preparation methods that do not preserve actin structures in their intact forms. Here we developed a new method that allows us to view actin stress fibers in their native state in the whole kidney glomerulus using focused ion beam scanning electron microscopy (FIB-SEM).

Methods: Kidney glomeruli from wild-type and *Col4a3-/-* (Alport) mice were isolated, the cytoskeleton was stabilized, and at the same time all cell membranes were extracted with detergent. Samples were processed and imaged using FIB-SEM using the serial block-face imaging mode.

Results: Block-face imaging of membrane-extracted healthy glomeruli showed all nuclei and basement membranes as electron dense material, similar to their appearance by transmission electron microscopy. In contrast, the cellular edges were completely gone, leaving behind only the contours of the cytoskeleton. This method allowed us to view the cytoskeleton of the foot processes (FPs), which formed a continuous electron dense sheet incorporating the slit diaphragms (SDs) and covering the glomerular basement membrance (GBM). Tracking this dense material across serial sections in the FPs revealed continuity with the central actin cables in individual FPs that fuse together to form thick actin bundles in the podocyte's major processes (MP). These bundles, in turn, appear to anchor at the periphery of podocyte cell bodies. In contrast, analysis of Alport glomeruli revealed thick actin bundles running in different directions juxtaposed to the GBM as part of the cytoskeletal transformation that accompanies podocyte injury.

Conclusions: Here, we imaged the complete cytoskeleton of the podocytes in both health and disease. Our data indicate that in the normal podocyte, actin filaments in the FPs are connected to the SDs to form one continuous network enclosing the capillary wall, like a wire mesh, suggesting that podocyte FPs and the SDs work as one unit to form the outer structure of the glomerular filtration barrier. Our data also indicate that in injured podocytes, foot process effacement changes the orientation of the actin cables and affects the SDs, thus disrupting the integrity of the wire mesh, leading to proteinuria.

Funding: NIDDK Support, Private Foundation Support

SA-OR002

Deep Mapping of the Podocyte Proteome Unravels Altered Protein Dynamics during Differentiation Christina B. Schroeter,[2] Thomas Benzing,[3] Markus M. Rinschen,[1] Paul T. Brinkkoetter.[2] *[1]CECAD, Cologne, Germany; [2]University Hospital Cologne, Cologne, Germany; [3]University of Cologne, Köln, Germany.*

Background: Podocytes are epithelial postmitotic cells which maintain the renal filtration barrier. Immortalized podocyte cell lines are widely utilized tools to estimate podocyte injury and cytoskeletal rearrangement processes *in vitro*. We intended to generate a comprehensive map of proteins expressed in proliferating and differentiated cultured human podocytes *in vitro* thereby providing a thorough database and useful tool for researchers in the podocyte field.

Methods: We analysed 7637 proteins in depth and quantified 7230 of them. We performed additional in-depth analyses of the cultured human podocyte proteome in order to characterize changes regarding protein expression, protein synthesis and proteostatic mechanisms during differentiation of the cells. We included a detailed analysis on the expression of podocyte-specific proteins that govern the function and dysfunction of the slit diaphragm, and of gene products mutated in hereditary nephrotic syndrome. Finally, we compared the resulting proteomic dataset to data obtained from the previously published murine cultured podocyte proteome. We also performed comparative analysis with transcriptomic data from cultured human podocytes.

Results: Cultured podocytes express abundant copy numbers of endogenous receptors. Some protein classes associated with podocyte disease, such as slit-diaphragm associated proteins and ion channels, were hardly detected. Differentiation-induced changes were comparable in mouse and human podocytes, but slight differences, e.g. in proteins associated with lipid metabolism were detected. Also, there were distinct differences in expression of genes commonly thought to be associated with podocyte function. Notably, this data set detected general perturbations in proteostatic mechanisms as a dominant alteration during podocyte differentiation irrespectively of the species: Proteasome activity and kinetics were high in the undifferentiated state and lysosomal activity was high in the differentiated state.

Conclusions: In conclusion, podocyte differentiation *in vitro* is largely associated with a proteostatic shift, and the deep proteomic mapping approach utilized here may demonstrate the limitations, but also the potential of podocyte cell culture.

SA-OR003

Super Resolution Microscopy and Automatized Digital Image Processing as a Novel and Rapid Diagnostic Tool for Podocyte Foot Process Effacement Nicole Endlich,[1] Florian Siegerist,[1] Silvia Ribback,[2] Frank Dombrowski,[2] Kerstin U. Amann,[3] Karlhans Endlich.[1] *[1]Anatomy and Cell Biology, University Medicine Greifswald, Greifswald, Germany; [2]Pathology, University Medicine Greifswald, Greifswald, Germany; [3]Nephropathology, University Medicine Erlangen, Erlangen, Germany.*

Background: Podocyte foot process morphology plays an essential role for proper glomerular filtration. In glomerular diseases like *minimal change disease*, interdigitating foot processes are replaced by flattened cellular protrusions. Since foot processes are around 200-300nm in width, morphometrics could only be performed by time consuming electron microscopy. Recently, super resolution microscopy techniques have been developed which allow lightmicroscopic imaging beyond *Abbe's* optical resolution limit of ~200nm. Using one of those techniques, structured illumination microscopy (SIM), it is now possible to double the optical resolution limit. We hypothesized that SIM would allow the analysis of podocyte morphology and to diagnose foot process effacement.

Methods: 4µm sections were obtained from formalin fixed and paraffin embedded renal tissue of human and murine origin and stained with an antibody against the slit diaphragm protein nephrin. Morphometrics of SIM-reconstructed podocyte foot processes were manually measured using ImageJ. For automatic evaluation of the slit diaphragm density, meaning slit diaphragm length / glomerular capillary area, we programmed a specific ImageJ plugin. The plugin automatically segments the nephrin positive slit diaphragm and measures the total length and the glomerular capilarry area.

Results: In human samples, we measured a mean foot process width of 0.249±0.68µm in healthy, and 0.675±0.246µm in MCD patients. By the use of our custom made software we measured a slit diaphragm density of 3.099±0.268µm/µm² in healthy compared to 1.825±0.493µm/µm² in MCD patients. Using both methods we found statistically significant differences between the MCD patients in comparison to the healthy control subjects. As we found out that the both results highly correlate (R^2=0.91) we show that the techniques can be used equivalently. Furthermore, we show that we can image and measure foot process morphology in murine kidneys.

Conclusions: Taken together, we have established a novel method which allows quick analysis of kidney sections for foot process effacement in an automated fashion. Including this technique into the diagnostic routine could effectively shorten the time until diagnosis of podocyte foot process effacement in patients and in animal models.

SA-OR004

Intravital Imaging Reveals the Important Role of A-Synuclein in Podocytes Georgina Gyarmati, Anne Riquier-brison, Janos Peti-Peterdi. *University of Southern California, Los Angeles, CA 90033, CA.*

Background: Podocytes are known to functionally express a number of neuron-specific proteins. Recent studies predicted the Parkinson's and Alzheimer's disease amyloid a-synuclein (SNCA) to be among 136 top podocyte genes (PMID23950145), and top 5 phosphoproteins with increased expression in Fabry disease podocytes (PMID27681560). SNCA was also recently linked to disruption of the autophagy-lysosome pathway and neuropathology in Fabry disease (PMID24529306). The present study aimed to establish the functional importance of SNCA in podocytes.

Methods: Constitutive or tamoxifen-inducible podocyte-specific SNCA knockout mice (i/Pod-SNCA KO) were generated that also expressed the intensely green calcium indicator GCaMP5/Tomato or the green/red mTmG reporter only in podocytes. Serial high resolution intravital multiphoton microscopy (MPM) of the same glomeruli in the same intact living kidney consecutively for three weeks was performed non-invasively via a dorsal abdominal imaging window to directly visualize and track the changes in glomerular and podocyte function including cell [Ca^{2+}] after SNCA deletion.

Results: Immunohistochemistry of human and mouse kidney tissue sections confirmed the podocyte-specific expression of SNCA. Intact podocyte and glomerular functions were found at baseline in iPod-SNCA mice. However, within one week of tamoxifen-induced SNCA KO, podocytes developed an enlarged cell body with balled-up appearance, which gradually progressed within two additional weeks to the appearance of focally increased cell [Ca^{2+}], podocyte detachment and shedding into the tubular fluid and migration to the parietal Bowman's capsule, leakage of plasma albumin-Alexa594 into the filtrate and tubular fluid, and glomerular capillary microthrombi blocking blood flow. High magnification MPM found widened podocyte primary and secondary processes and foot process effacement. Histology of constitutive Pod-SNCA kidney sections found numerous tuft adhesions and detached podocytes.

Conclusions: This study visually demonstrated the development and progression of glomerular pathology after SNCA knockout, suggesting the important role of SNCA in maintaining normal podocyte and glomerular functions.

Funding: NIDDK Support

SA-OR005

aPKC Independent Signaling Events of Par3 at the Glomerular Slit Diaphragm Sybille Köhler,[4] Carien M. Niessen,[1] Sandra Iden,[5] Wilhelm Bloch,[3] Bernhard Schermer,[4] Thomas Benzing,[5] Barry Denholm,[2] Paul T. Brinkkoetter.[4] *[1]CECAD University clinic of Cologne, Cologne, Germany; [2]Edinburgh University, Edinburgh, United Kingdom; [3]German Sport University, Cologne, Germany; [4]University Hospital Cologne, Cologne, Germany; [5]University of Cologne, Köln, Germany*.

Background: Polarity signaling through the aPKC-Par polarity complex is essential for the development and maintenance of the podocyte architecture and the function of the glomerular filtration barrier of the kidney. Despite its well-established role in aPKC-mediated signaling, Par3A appears to be dispensable for the function of the glomerular filtration barrier.

Methods:

Results: mRNA seq data from primary podocytes revealed high levels of Par3B in podocytes, which were much higher in comparison to Par3A levels. Interestingly, loss of Par3B also did not cause glomerulosclerosis or albuminuria. To study a potential compensatory mechanism between Par3A and Par3B, we generated podocyte-specific Par3A/B double knockout mice. Par3A/B double knockout mice were born following Mendelian rules. Within 8 weeks of age Par3A/B DKO mice developed severe proteinuria in comparison to control mice. To further study the interplay between the different Par3 proteins, we utilized *Drosophila* nephrocytes. Here, we show co-localization of the Par3A/B homolog bazooka and the nephrocyte diaphragm proteins Sns (nephrin) and Duf (NEPH1) in different developmental stages at the nephrocyte diaphragm. Second, we analyzed the role of bazooka on nephrocyte function. Silencing bazooka expression resulted in a disturbed nephrocyte diaphragm morphology and severe filtration defects. To study the mammalian Par3 proteins in greater detail, we used the UAS-GAL4 system to re-express different murine Par3 variants in a *bazooka* knockdown background. Although the rescue capacity differed between the different mammalian Par3A isoforms, none of the isoforms resulted in a complete rescue. Even the 100kDa isoform, lacking the aPKC-binding domain, resulted in partial rescue, suggesting an aPKC-independent function for Par3A in nephrocyte filtration. In line with these findings, an aPKCiota interactome from immortalized mouse podocytes, revealed Lgl2 and Par6 as predominant interactors of aPKCiota.

Conclusions: Taken together, the data establish an important role for Par3 function in podocytes and reveal this function is, at least partially, independent from aPKC.

SA-OR006

The Interaction between MAGI2 and RapGEF2 Sustains Podocyte Rap1GTPase Signaling and Is Critical for Glomerular Filter Function Bingbing Zhu,[1,2] Jianhua Li,[1] Jenny Wong,[1] Kirk N. Campbell,[1] Shazia Ashraf,[3] Agnieszka Bierzynska,[4] Moin Saleem,[4] Charles Sawyers,[5] John C. He,[1] Friedhelm Hildebrandt,[3] Vivette D. D'Agati,[6] Wen Peng,[2] Lewis Kaufman.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Putuo Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China; [3]Boston Childrens Hospital, Harvard Medical School, Boston, MA; [4]University of Bristol, Bristol, United Kingdom; [5]MSKCC, New York, NY; [6]Columbia University College of Physicians and Surgeons, New York, NY*.

Background: The essential role of MAGI2 in proper podocyte function is reflected by the severe FSGS phenotypes of both MAGI2 knockout mice and of humans with congenital nephrotic syndrome (CNS) caused by mutations in MAGI2.

Methods:

Results: In the current work, we perform co-immunoprecipitation experiments that show MAGI2 directly binds the Rap1 guanine nucleotide exchange factor, RapGEF2, and that this interaction is lost when expressing MAGI2 variants that cause CNS. In cultured cells, co-expression of RapGEF2 with wild-type MAGI2, but not MAGI2 variants known to cause CNS, dramatically enhanced activation of the small GTPase Rap1, a pathway we previously demonstrated to be essential for normal podocyte function. Furthermore, in mice, podocyte specific deletion of RapGEF2 resulted in spontaneous proteinuria with FSGS, substantiating the critical importance of RapGEF2 to sustain normal podocyte function. Although the FSGS phenotype of MAGI2 knockout mice is considerably more severe than that of RapGEF2, both models show comparable qualitative glomerular features including mesangial expansion, focal segmental and global sclerosis, podocyte loss, and glomerular epithelial cell proliferation, suggesting mechanistic similarities. Indeed, knockdown of either RapGEF2 or MAGI2 in cultured podocytes caused nearly identical reductions in levels of Rap1GTPase activation, dramatic reductions in many Rap1 downstream signaling targets, and similarly high rates of podocyte apoptosis. Finally, immunostaining of kidney sections from CNS patients with MAGI2 mutations also suggested reduced glomerular Rap1GTPase mediated signaling.

Conclusions: We conclude that Rap1 activation induced by the complex of MAGI2 and RapGEF2 is indispensable for normal podocyte homeostasis.

Funding: NIDDK Support

SA-OR007

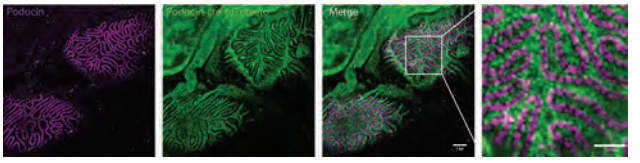
Confocal Imaging of the Glomerular Filtration Barrier in Expanded Kidney Tissue Samples David Unnersjö-Jess,[2] Lena Scott,[1] Sonia Zambrano Sevilla,[1] Jaakko Patrakka,[1] Hans Blom,[2] Hjalmar Brismar.[2] *[1]Karolinska Institutet, Solna, Sweden; [2]Royal Institute of Technology, Solna, Sweden*.

Background: When studying the glomerular filtration barrier (GFB), one is normally restricted to electron microscopy (EM). However, using EM, it is not trivial to perform volumetric imaging and multiple labelling of different epitopes. We have recently demonstrated an optical clearing protocol that in combination with super-resolution STED microscopy enables epitope-specific nanoscale imaging of the GFB. STED microscopy is presently an expensive and complex technique, and thus it would be highly relevant to develop more conventional bioimaging methods which resolve the GFB.

Methods: We apply a sample preparation protocol which isotropically expands kidney tissue samples approximately 5 times, while making them optically transparent. We then use immunofluorescence and confocal microscopy to image components of the GFB.

Results: Kidney samples were sufficiently expanded to allow for nanoscale localizations of different parts of the GFB (e.g. glomerular basement membrane, podocyte foot processes and the slit diaphragm), at an effective resolution below 70 nm. 2-color z-stacks of glomeruli were acquired, giving the unique possibility to study the 3D localizations of GFB proteins in intact tissue samples, including the detection of foot process effacement in mice with induced glomerulonephritis. Additionally, by applying super-resolution STED microscopy on expanded kidney samples, a resolution below 20 nm could be obtained.

Conclusions: We show that an expansion protocol in combination with confocal microscopy can be used to perform sub-70 nm resolution imaging of the GFB using standard lab equipment and reagents. This finding has an impact for researchers and clinical pathologists, since conventional light microscopy can for the first time be used to study kidney fine-morphology and protein topology on the effective nanometer-scale.



Expanded kidney sample stained for podocin (magenta) and cytosolic podocyte-specific tdTomato (pod-cre-tdTomato, green), showing podocyte foot processes and the filtration slit. The sample was imaged using confocal microscopy.

SA-OR008

APOL1 Risk Variant Induced Kidney Injury in Podocytes Is Mediated by Caspase-1 Dorottya Laczko, Pazit Beckerman, Jing Bi Karchin, Frank S. Chinga, Katalin Susztak. *University of Pennsylvania, Philadelphia, PA*.

Background: Coding variants of APOL1 (termed as G1 and G2) are associated with increased risk of kidney disease in African Americans. Recently, we developed a new mouse model that recapitulates APOL1 associated renal disease by conditional inducible expression of G1 and G2 APOL1 variants in podocytes. While these animals develop albuminuria, glomerulosclerosis and azotemia, the exact pathomechanism of APOL1 variant induced kidney disease remains poorly understood. Here, we tested whether caspase-1 (Cas1) / IL-1β mediated pyroptotic cell death play a role in disease development.

Methods: Podocyte specific G2 APOL1 transgenic mice was generated by crossing TRE-G2 APOL1 animals with mice carrying the nephrin rtTA. Transgene expression was controled by doxycycline. To test the role of Cas1, we crossed nephrin rtTA/TRE-G2 APOL1 with Cas1 knock-out (KO) mice. To test the role of IL-1β we treated mice with IL-1β neutralizing antibody Anakinra. Histological changes were evaluated by PAS staining and the level of proteinuria was determined by albumin specific ELISA. The mRNA levels of kidney injury markers (KIM1, Col4a1, SMA) were analyzed by qPCR. For in vitro testing cells with inducible G2 APOL1 expression were generated, and the effect of pan-caspase, Cas1 and -3 were tested.

Results: In vitro expression of G2 APOL1 resulted in increased cleaved Cas1 and IL-1β levels. Pan-caspase and Cas1 inhibitors ameliorated cell death induced by G2 APOL1. In vivo, Anakinra injection for 21 days failed to significantly reduce albuminuria or glomerulosclerosis of G2 APOL1 mice. In line with these findings, no change in the transcript level of kidney injury markers was observed after neutralization of IL-1β compared to their control saline injected littermates. In contrast, renal disease was ameliorated in G2 APOL1 Cas1 KO mice as evidenced by decreasing level of proteinuria over the 21 days doxycycline treatment period as opposed to their Cas1 wild type littermates. In addition to this, Cas1 KO mice displayed marked reduction of kidney fibrosis confirmed by PAS staining.

Conclusions: Our initial data suggest that Cas1 plays a crucial role in the development of G2 APOL1 induced kidney damage, albeit the mechanism still needs to be elucidated. We propose that inhibition of Cas1 can offer a potential therapeutic target for APOL1 associated kidney damage.

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SA-OR009

COSMC, the Molecular Chaperone of O-Linked Glycosylation, Is Essential for Podocyte Function Brian R. Stotter,[1,2] Brianna Talbot,[1] Johannes S. Schlondorff.[1] *[1]Div of Nephrology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; [2]Div of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston, MA.*

Background: Proper podocyte function is required to maintain the glomerular filtration barrier. Many podocyte proteins undergo post-translational O-linked glycosylation (OLG), which requires T-synthase and its molecular chaperone Cosmc. Prior studies have shown that global *COSMC* knockout produces immature glycoproteins that express Tn antigen. We hypothesize that podocyte-specific *COSMC* deletion causes albuminuria, renal failure, and glomerulosclerosis due to aberrant OLG.

Methods: Male podocin-Cre mice were bred with female *COSMC*$^{fl/fl}$ mice to produce males devoid of *COSMC* in podocytes (Podo-*COSMC*$^{Y/fl}$) and females with mosaic *COSMC* loss in podocytes (Podo-*COSMC*$^{+/fl}$). Serum creatinine (SCr) and urine albuminuria were measured at 1 and 2 months of life for experimental and control mice. Kidneys were harvested for histology, immunofluorescence (IF), electron microscopy (EM), and biochemical analysis. Immature OLG was detected by staining for Tn antigen with lectin HPA.

Results: Podo-*COSMC*$^{Y/fl}$ males have heavy albuminuria by 1 month, with mesangial expansion and glomerulomegaly on histology and diffuse foot process effacement by EM. By 2 months, SCr is elevated compared to controls and histology shows extensive glomerulosclerosis, interstitial fibrosis, and tubular atrophy. Podo-*COSMC*$^{+/fl}$ females have mosaic glomerular Tn antigen expression, mild albuminuria, and normal SCr by 1 and 2 months. Podo-*COSMC*$^{+/fl}$ females have normal histology at 1 month but both rare segmental sclerosis and foot process effacement by 2 months. IF shows diffuse lectin HPA staining in Podo-*COSMC*$^{Y/fl}$ male podocytes and mosaic staining in Podo-*COSMC*$^{+/fl}$ female podocytes. Podocalyxin, an O-linked podocyte glycoprotein, is normally expressed in 1 month Podo-*COSMC*$^{Y/fl}$ males and 1 and 2 month Podo-*COSMC*$^{+/fl}$ females, but is lost in 2 month Podo-*COSMC*$^{Y/fl}$ males. In contrast, staining of O-linked glycoprotein podoplanin is reduced in *COSMC*-deficient podocytes by 1 month, confirmed by Western blot of glomerular lysates.

Conclusions: Loss of *COSMC* in podocytes causes albuminuria and renal failure with glomerulosclerosis, interstitial fibrosis, and tubular atrophy. This phenotype is most severe in male mice that have complete *COSMC* excision, and less severe in mosaic females. The mechanism of podocyte injury may be due to aberrant function of podocalyxin, podoplanin, and other O-linked glycoproteins.

Funding: NIDDK Support

SA-OR010

Dissociation-Induced Maff and Egr1 Upregulation Triggers Dedifferentiation of Podocytes Masahiro Okabe,[1,2] Masaru Motojima,[1] Yoichi Miyazaki,[2] Takashi Yokoo,[2] Taiji Matsusaka.[1] *[1]Tokai University School of Medicine, Isehara, Japan; [2]Jikei University School of Medicine, Tokyo, Japan.*

Background: Podocytes quickly lose their characteristics when they are cultured *in vitro*, suggesting that detachment from the glomerular basement membrane (GBM) may trigger dedifferentiation. We aimed to explore gene expression changes induced by podocyte dissociation from the GBM.

Methods: We obtained podocyte-specific RNAs by two methods. One method was to dissociate glomerular cells and purify RNAs from FACS-sorted podocytes that are transgenically labeled with fluorescent protein. The other was to utilize RiboTag transgenic mice, in which podocyte ribosomes are tagged with HA epitope, and podocyte RNAs were obtained by immunoprecipitation without dissociating glomerular cells. We then analyzed them (each n=4) with Agilent 8X66K array and compared the two profiles.

Results: Array and qRT-PCR analyses confirmed that known podocyte-specific mRNAs were similarly concentrated in both samples. Among 39,430 probes, 554 were downregulated (<0.125-fold) in dissociated podocytes, including *Itga8* and *Icam2* (0.019 and 0.12-fold, respectively). 1,013 probes were upregulated (>8-fold), including *Fos* and *Fosb* (720 and 2,000-fold, respectively). We next searched for mRNAs that were commonly upregulated by both dissociation and injury. For this, we analyzed mRNA profiles of injured podocytes in NEP25 mice (n=4) 7 days after injection with podocyte-targeted immunotoxin. Expression of 55 genes was increased more than 16-fold by both dissociation and injury. Among them, we focused on transcription factors, *Maff* and *Egr1*. MafF and MafB, as well as EGR-1 and WT-1, share the same DNA binding sequence, but not transcriptional activation domain. MafB and WT-1 are indispensable for maintaining podocyte differentiation state. In baseline primary cultured podocytes, *Maff* and *Egr1* mRNAs were increased 15 and 4.2-fold compared to *in vivo* podocytes of RiboTag mice, respectively. *Maff* knockdown increased MafB target- *Nphs2* mRNA (2.4-fold) without change of *Mafb* mRNA. *Egr1* knockdown increased Wt-1 target- *Ptpro* mRNA (2.2-fold) without change of *Wt1* mRNA.

Conclusions: These findings indicate that detachment from the GBM activates MafF and EGR-1 in podocytes, which actively facilitate dedifferentiation by competing with MafB and WT-1, respectively. These molecules may be novel drug targets for preventing progressive podocyte deterioration.

Funding: Government Support - Non-U.S.

SA-OR011

Impact on Blood Pressure of Mobile-Based Application (eKidneyCare) in Patients with CKD: A Randomized Controlled Trial Stephanie W. Ong,[2] Sarbjit V. Jassal,[2] Kelly Min,[2] Akib Uddin,[2] Eveline C. Porter,[2] George Tomlinson,[2] Alexander G. Logan.[1,2] *[1]Mount Sinai Hospital, Toronto, ON, Canada; [2]University Health Network, Toronto, ON, Canada.*

Background: We have previously demonstrated feasibility and acceptability of an integrated app (eKidneyCare) used for CKD management (CJASN 2016). It allows patients to monitor blood pressure (BP), manage medication, assess symptoms and track laboratory results. Customizable algorithms provide real-time personalized patient feedback and alerts to providers. Currently we are performing a one-year randomized controlled trial comparing eKidneyCare (intervention) to MyMedRec (control). The latter is a commercially available app that records medical information without providing feedback. Study midpoint results are presented.

Methods: Consenting patients with CKD 3b-5 or 5D were recruited from 6 out-patient renal clinics or dialysis units at University Health Network (UHN) and randomized to eKidneyCare or MyMedRec monitoring. Outcome assessments include BP at 6 and 12 months and medication reconciliation, questionnaires on self-management and, at study end, in-person interviews.

Results: A total of 182 patients were enrolled and randomly allocated to the intervention (n=89) or the control (n=93) group. A total of 157 patients completed the 6 month BP assessment using the automated oscillometric device, BpTRU. Premature withdrawals included 11 transferred or incomplete data, 8 who withdrew consent and 6 withdrawn after medical complications. At 6m, the fall in BP of patients with uncontrolled hypertension at baseline was greater in the active (eKidneyCare) group (median reduction in systolic BP mmHg -18 vs 13 mmHg respectively, p =0.05; diastolic BP 9 vs 5.5 mmHg p=0.03). There was no between group difference in normotensive patients.

Conclusions: Hypertensive patients allocated to the eKidneyCare app had a significantly lower BP than those using the commercially available app. This preliminary analysis suggests that real time patient feedback and integrated mobile apps are critical components for success with mHealth monitoring.

Funding: Other NIH Support - Canadian Institute for Health Research, Government Support - Non-U.S.

SA-OR012

Reducing Health Disparity – PCORI Supported Home Based Kidney Care Approach in Zuni Indians Vallabh O. Shah,[2] Robert G. Nelson,[1] V. Shane Pankratz,[2] Donica M. Ghahate,[2] Jeanette Bobelu.[2] *[1]National Institutes of Health, Phoenix, AZ; [2]University of New Mexico Health Science Center, Albuquerque, NM.*

Background: To conduct a randomized trial of home based kidney care (HBKC) of patient activation measure (PAM) with lifestyle intervention to reduce risk factors for chronic kidney disease (CKD) in Zuni Indians.

Methods: Randomized families with more than one individual with CKD (1:1) to a usual care (UC) or an HBKC intervention group. After initial lifestyle coaching in both groups, the HBKC received reinforcement of healthy behaviors through alternate weekly home visits by the community health representatives, and with quarterly group sessions. The primary outcome was change in PAM. The secondary outcomes were changes in measures of T2D, CKD, BP, lipid profiles, BMI, Morisky score), KDQOL and diet. Tests for significance were performed using mixed models analysis of variance with a per-household random effect and while adjusting for baseline levels of the variables being examined.

Results: Patients in the HBKC group increased PAM total score by 9.5±26.1 points, compared to a decrease of 0.7±14.0 points in the UC (p=0.04). Similarly, 16.7% more of the HBKC group were in the PAM "activated" group (PAM level >3) at the study's end, while 12.5% fewer of the UC group were in the PAM "activated" group at the study's end. In our secondary analyses, progression of multiple risk factors for kidney disease, especially BMI, A1C, and hsCRP, slowed by the HBKC intervention. We also observed greater improvements in QOL in the HBKC group; SF12 mental scores significantly increased in the HBKC compared to the UC (p=0.02), with an average±S.D. point change in the HBKC group of 7.5±11.0 compared to a -0.2±9.0 point change in the control group

Conclusions: A HBKC intervention of continuous patient engagement, a potentially scalable approach to providing care to patients with CKD, was effective in improving PAM levels and in reducing risk factors for CKD.

Funding: Other U.S. Government Support

SA-OR013

Loss of Renal Function and Benefits of Measured GFR among Lung Transplant Patients Nans Florens,[1,2] Laurence Dubourg,[1,2] Agathe Senechal,[1] François Philit,[1] Laurent Juillard,[1,2] Sandrine Lemoine.[1,2] *[1]Hospices Civils de Lyon, Lyon, France; [2]University of Lyon, Lyon, France.*

Background: There are about 4000 lung transplant patients over the world. Renal dysfunction and chronic kidney disease among this population are underestimated. The aim of our study was to evaluate the loss of glomerular filtration rate (GFR) after a lung transplantation.

Methods: All the lung transplant patients in the university hospital of Lyon between January 2012 and April 2016 were studied retrospectively. Patients had a pre- and/or post-transplantation measurement of their GFR (mGFR) either by the inulin gold standard

method or by iohexol clearance. Estimation of the GFR was achieved with CKD-EPI equation.

Results: 111 lung transplantations were performed between January 2012 and April 2016. 91 patients had a pre-transplantation mGFR. Among those patients, 13 deceased during the follow-up period, 28 had a mGFR after 1 or 2 years of their transplantation and 6 patients underwent maintenance hemodialysis after their transplantation. Mean pre-transplantation mGFR was 106 mL/min/1.73m^2 and 58 mL/min/1.73m^2 after transplantation ($p<0.05$) with a mean loss per patient of 48 mL/min/1.73m^2. 6 % of the patients had a CKD stage 3 or more before the transplantation while 66% after. In pre-transplantation patients, eGFR and mGFR were significantly different (16 ± 6 mL/min/1.73m^2, $p<0.05$) while not in post-transplantation. The risk of developing a CKD stage 3 after the transplantation was higher for patients with a pre-transplantation mGFR under 90 mL/min/1.73m^2 (RR = 2,1; IC 95% 1,2 – 3,6). Patients undergoing a maintenance hemodialysis had a lower pre-transplantation mGFR than all the other patients with a post-transplantation CKD (74 ± 7 mL/min/1.73m^2 *vs* 108 ± 5, $p<0.05$).

Conclusions: The prevalence of CKD among lung transplant patients is important as the loss of kidney function is about 50 mL/min/1.73m^2 per patient. Lung transplant candidates with a mGFR under 90 mL/min/1.73m^2 need an increased monitoring of their renal function and patients with an initial GFR< 50 mL/min/1.73m^2 had to be discussed for a double-lung and kidney transplant.

SA-OR014

Racial and Ethnic Disparities in Access to Predialysis Nephrology Care in the US: Have We Made Any Progress over the Last Decade? Tanjala S. Purnell, Xun Luo, Sunjae Bae, Deidra C. Crews, Lisa A. Cooper, Dorry L. Segev. *Johns Hopkins School of Medicine, Baltimore, MD.*

Background: Over the past decade, there has been increased attention and efforts to improve overall access and redress racial and ethnic disparities in access to predialysis nephrology care in the US. The goal of this study was to investigate whether these efforts have been successful.

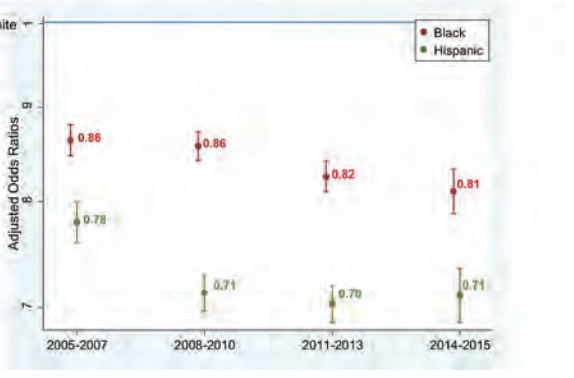
Methods: Using USRDS patient data, we performed multivariable logistic regression models to quantify temporal changes in racial and ethnic disparities in receipt of predialysis nephrology care among 934,599 adults who initiated chronic dialysis treatment between 2005 and 2015. We adjusted regression models for differences in patient sociodemographic factors.

Results: Over the last decade, racial and ethnic disparities in access to predialysis nephrology care slightly worsened. In 2005-2007, Blacks were 14% (aOR: 0.86, 95% CI: 0.85-0.88) and Hispanics were 22% (aOR: 0.78, 95% CI: 0.76-0.80) less likely to receive predialysis nephrology care than Whites. In 2008-2010, Blacks were 14% (aOR: 0.86, 95% CI: 0.84-0.87) and Hispanics were 29% (aOR: 0.71, 95% CI: 0.70-0.73) less likely than Whites. In 2011-2013, Blacks were 18% (aOR: 0.82, 95% CI: 0.81-0.84) and Hispanics were 30% (aOR: 0.70, 95% CI: 0.69-0.72) less likely than Whites. In 2014-2015, Blacks were 19% (aOR: 0.81, 95% CI: 0.79-0.83) and Hispanics were 29% (aOR: 0.71, 95% CI: 0.69-0.73) less likely than Whites. **(Figure 1)**

Conclusions: Disparities in access to predialysis nephrology care worsened (versus narrowed) over the past decade. Targeted interventions to effectively reduce these disparities should be identified and adopted widespread to improve outcomes for patients with ESRD in the US.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIMHD, AHRQ, Other U.S. Government Support

Figure 1. Racial-Ethnic Disparities in Predialysis Nephrology Care in the US



SA-OR015

Disease-Specific Stress Experienced by Patients with CKD Julie A. Wright Nunes,[3] Eve Kerr,[2] Emily P. Chen,[1] Gunjan Garg,[2] Angela Fagerlin.[4] *[1]University of Michgan, Ann Arbor, MI; [2]University of Michigan, Ann Arbor, MI; [3]University of Michigan Health System, Ann Arbor, MI; [4]University of Utah, Salt Lake City, UT.*

Background: Increased psychological stress is independently associated with decreased social functioning, poor quality of life and morbidity. We developed a new scale to assess patient psychological stress about a chronic kidney disease (CKD) diagnosis and examined whether stress varies across different patient demographics.

Methods: Adults with CKD Stages 1-5 were enrolled to take a cross-sectional survey from April 2015-May 2016. Eight questions (stress scale) assessed how often patients thought about their CKD, had trouble sleeping because of it, and felt fearful and worried (scale 0="not at all" to 3="often"). We also asked patients to rank CKD importance compared to other conditions. An *a priori* model was used to examine for validity. Reliability was calculated using Cronbach's alpha. Associations were examined using linear regression.

Results: 203 patients were enrolled with a mean (SD) age 59 (16) years; 49% were men, 78% Caucasian, 16% African American (AA), 5% other races, 73% had CKD Stage 3-5, 48% had an annual income < $50K, and 95% had ≥ H.S. education. Cronbach's alpha was 0.89 (excellent reliability). The mean (SD) of the 8-item scale was 1.1 (0.6), range 0.0 – 2.8. Sixty-seven percent ranked CKD as either very important or their top health priority. Age was negatively associated [β = -0.01 (CI -0.02, -0.005); $p<0.01$] and AA race positively associated [β=0.4 (0.1, 0.6); $p<0.01$] with CKD stress scores. In adjusted analysis, age remained independently and negatively associated with stress scores [β = -0.01 (-0.02, -0.001); p=0.03], while AA race and CKD stage trended towards a positive association [β=0.33 (-0.004, 0.7); p=0.05] and [β=0.2 (-0.02, 0.5); p=0.08], respectively.

Conclusions: Our scale exhibits excellent internal reliability and evidence of validity assessing disease-specific stress in patients with CKD. Despite the majority of patients ranking CKD as very important/top health priority, overall patients reported low stress about their diagnosis. African American race conferred more perceived stress related to CKD. Future education and awareness interventions must consider the impact that disease knowledge has on patient stress, in particular for African American patients--and integrate individualized psychosocial support for all patients into education programs.

Funding: NIDDK Support

SA-OR016

Reported Kidney Disease Awareness and Medical Subspecialty Use before and after the Affordable Care Act Implementation among National Health Interview Survey Participants Anna J. Jovanovich,[1] Michel Chonchol,[3] Zhiying You.[2] *[1]Denver VA / University of Colorado, Denver, CO; [2]UC Denver, Aurora, CO; [3]University of Colorado, Aurora, CO.*

Background: In the U.S., individual awareness of chronic kidney disease (CKD) is low. Nephrology referral improves CKD awareness and clinical outcomes. The Affordable Care Act (ACA) implementation on January 1, 2014 increased insurance coverage and access to health care for people with chronic disease. It is unknown if the ACA has impacted people with CKD.

Methods: Utilizing National Health Interview Survey (NHIS) data, we compared kidney disease awareness and medical subspecialty use during 2012, a full year before the ACA implementation, and 2015, a full year after. The sample included 66,624 non-institutionalized U.S. citizens ages 19-64. In this quasi-experimental analysis, we used logistic regression to examine whether kidney disease awareness and medical subspecialty use increased after the ACA implementation, using weights as appropriate.

Results: Baseline characteristics among NHIS participants in the years 2012 and 2015 were similar: age 47 years, 52% female, and 80% white. The percentage of participants reporting no health insurance coverage decreased from 17% in 2012 to 10% in 2012 ($p<0.0001$). Kidney disease awareness, medical subspecialty use, and a combination of both increased from 2012 to 2015: 1.6% to 2.0% (p = 0.002), 26% to 28% (p = 0.002), and 1.0% to 1.3% (p = 0.006), respectively. After adjustment for age, sex, race, ethnicity, marital status, education, income, and region, 2015 NHIS participants were 27% (odds ratio [OR] 1.27 [95% CI, 1.10-1.46]) more likely to report kidney disease awareness, 6% (OR 1.06, [95% CI, 1.00 to 1.11]) more likely to report medical subspecialty use, and 27% (OR 1.27 [95% CI, 1.07 to 1.50]) more likely to report both. When insurance status was added to the models, the magnitude of all the odds ratios was attenuated suggesting that insurance status influences reported kidney disease awareness and medical subspecialty use.

Conclusions: Kidney disease awareness and medical subspecialty use reported by NHIS participants significantly increased from 2012 to 2015, after the ACA implementation, while participants reporting no health insurance significantly decreased. These data suggest that the ACA improves access to care among people with CKD, and thus, may be key to improving clinical outcomes.

Funding: Veterans Affairs Support

SA-OR017

The Association between Participation in a Specialized Renal Disease Management Program and Economic Outcomes Changhung A. Chien, Kael Haig, Matt Ruyter, Ana R. Stankovic. *OptumHealth, Minneapolis, MN.*

Background: A 2016 meta-analysis of efficacy of chronic kidney-focused disease management (DM) programs demonstrated improved quality of life among chronic kidney disease (CKD) patients. However, published evaluations of DM program impact on medical spend, utilization, and transplantation have been inconsistent. We measured the association between participation in a specialized renal disease management (DM) program and all-cause medical spend, utilization outcomes, and transplantation among patients with Stage 4 or 5 CKD or ESRD.

Methods: The study included commercially insured members 18 years or older identified as having Stage 4 or 5 CKD or ESRD during January 2013 – December 2016. All members included in the study were eligible for the DM program. We compared members who participated in a nurse-based telephonic DM program (CKD = 1,428 and

ESRD = 4,144) to members who did not participate in the DM program (CKD = 8,179 and ESRD = 5,825). Kaplan-Meier curves were used to estimate the probability of kidney transplant evaluation and transplant among CKD and ESRD patients. Chi-square and t-tests were used to compare differences in average inpatient admission rate, inpatient length of stay, and all-cause medical spend between DM program participants and non-participants.

Results: CKD patients who participated in the DM program were more likely to be evaluated for transplant than non-participants (25.8% vs. 7.1%) and to receive a preemptive transplant (4.8% vs. 1.5%). Similarly, ESRD patients who participated in the DM program were more likely to be evaluated for transplant than non-participants (32.5% vs. 4.5%) and also to receive a transplant (5.6% vs. 0.7%). ESRD program participants had fewer annual inpatient admissions (1.2 vs. 1.4) and fewer inpatient days per year (10.5 vs. 14.4) than non-participants. All reported differences were significant with $p < 0.05$. There were no significant differences in inpatient length of stay and all-cause medical expenditures between the study groups.

Conclusions: Participation in a specialized DM program was associated with higher transplant evaluation rate, higher preemptive and non-preemptive transplant rate, fewer inpatient admissions, and fewer inpatient days per year among patients with Stage 4 or 5 CKD or ESRD.

Funding: Commercial Support - UnitedHealth Group

SA-OR018

Interaction of Socioeconomic Status with Genetic Factors in Kidney Function Outcomes Chris H. Thio,[2] Harold Snieder,[1] Ute Bültmann,[3] Ron T. Gansevoort.[4] *[1]Epidemiology, UMCG, Groningen, Netherlands; [2]Epidemiology, UMCG, Groningen, Netherlands; [3]Health Sciences, UMCG, Groningen, Netherlands; [4]Nephrology, UMCG, Groningen, Netherlands.*

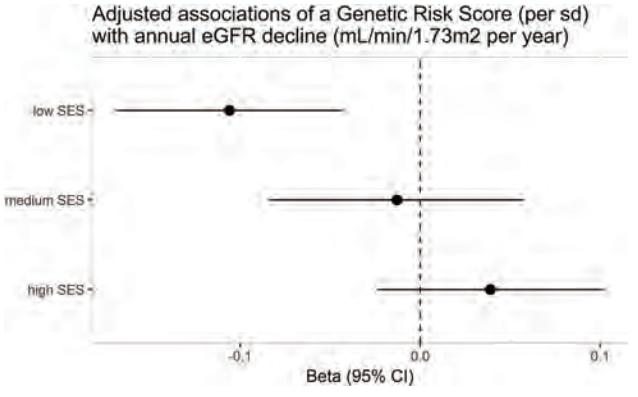
Background: Chronic kidney disease (CKD) is potentially caused by genetic and environmental factors. Previous studies suggested joint effects of socio-economic status (SES) and genetic risk in obesity and diabetes, but this issue has not been investigated in CKD. We therefore tested whether SES and genetic risk interact in their association with eGFR decline and incident CKD (CKDi).

Methods: In the community-based PREVEND cohort, we calculated eGFR from creatinine and cystatin C at five examinations. We defined CKDi as eGFR<60 mL/min/1.73m^2 during follow-up in those without baseline CKD. SES was measured by educational level and categorized into low, medium, and high (<secondary; secondary/equivalent; >secondary school). To quantify genetic risk, we used a genetic risk score (GRS) comprising 53 eGFR SNPs, weighted for published effects. In longitudinal analyses, we tested main effects of SES and GRS, as well as their interaction. Covariates were age, sex, smoking, BMI, urinary albumin, diabetes, hypertension, high cholesterol, and cardiovascular disease.

Results: We included 3,393 subjects (Caucasian, 52% male, median age 49 yrs [IQR 40-60], median follow-up duration 11 yrs [IQR 4.7-12], N=109 baseline CKD, N=190 CKDi). Mean GRS did not differ between SES levels. In univariate analyses, both high GRS and low SES were associated with lower eGFR levels. Low SES was associated with steeper eGFR decline, but higher GRS was not. However, their interaction was significant (SES*GRS*time, p=0.01). A higher GRS was associated with steeper decline only in those with low SES (see Figure). Covariate adjustment did not affect these conclusions. Both SES and GRS were univariately associated with CKDi, but their interaction was not significant.

Conclusions: Our data suggest that in subjects with low SES the effects of genetic risk for kidney function decline are stronger, independent of CKD risk factors. Future studies need to corroborate these findings in larger samples and focus on aspects of SES that mediate this relation.

Funding: Government Support - Non-U.S.



SA-OR019

Qualitative Assessment of an Online Peer Mentoring Platform for Patients with CKD Awais Ammar,[1] Mary Morrow-Sutton,[1] Tabitha Semancik,[2] Tara Liaghat,[1] Umar Farooq,[1] Nasrollah Ghahramani.[1] *[1]Penn State College of Medicine, Hershey, PA; [2]Kidney Foundation of Central Pennsylvania, Harrisburg, PA.*

Background: Peer mentoring (PM) is an effective model for patients with the same chronic disease to share knowledge and experience to which others often cannot relate. PM occurs in various settings, including face-to-face, via telephone or online. This study is a qualitative assessment of the communications in an online PM platform designed for patients with chronic kidney disease (CKD).

Methods: Twenty-one patients were assigned to trained peer mentors with whom they had regular online communication in a PM relationship. The interactive online platform allowed patients to post their concerns and questions about specific symptoms or treatment decisions through a private network. Patients used an intuitive user interface, utilizing mood and symptom icons, to indicate their current status. The program coordinator monitored the patients' and mentors' updated posts. Stress Score (SS: 1-10), as subjectively indicated by the patients, were used to quantitatively assess the severity of their concerns.

Results: A total of 213 posts, initiated by 21 patients, were included in the analysis. The posts were categorized into 15 general topic areas. The largest number of posts (n=34) related to family relationship concerns, followed by posts regarding weakness and lack of energy (n=25), weight change (n=19), overall prognosis (n=18) and financial stressors (n=16). Quantitatively, the most stressful concerns related to financial matters (SS: 7/10) and family relationships (SS: 6.5/10).

Conclusions: Patients communicate with their peers via an online platform regarding a variety of concerns and questions. Concerns about finances and family relationships form a significant aspect of the communication. These findings underscore the patients' concern about the impact of their disease on their families. Funding source: Patient Centered Outcomes Research Institute

Funding: Other U.S. Government Support

SA-OR020

Trajectories of HRQOL in Children with CKD Arlene C. Gerson,[1] Matthew Matheson,[2] Rebecca J. Johnson,[3] Stephen R. Hooper,[4] S. Shinnar,[5] Bradley A. Warady,[6] Susan L. Furth,[7] Cynthia Wong,[8] Amy Kogon,[9] Marc Lande,[10] Lyndsay Harshman,[11] Susan R. Mendley.[12] *[1]Johns Hopkins School of Medicine, Baltimore, MD; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [3]Children's Mercy Kansas City, Kansas City, MO; [4]University of North Carolina School of Medicine, Chapel Hill, NC; [5]Montefiore Medical Center, Albert EInstein College of MEdicine, Bronx, NY; [6]The Children's Mercy Hospital, Kansas City, MO; [7]The Children's Hospital of Philadelphia, Philadelphia, PA; [8]Stanford University, Stanford, CA; [9]Nationwide Children's Hospital, Columbus, OH; [10]University of Rochester, Rochester, NY; [11]University of Iowa Children's Hospital, Iowa City, IA; [12]University of Maryland, Baltimore, MD.*

Background: Trajectories of health related quality of life (HRQOL) may offer valuable insights into psychosocial aspects of disease progression in children with chronic kidney disease (CKD). Few longitudinal studies have evaluated the impact of CKD duration on HRQOL. The aim of this study was to determine how HRQOL changes over the time course of CKD.

Methods: The subjects in this study were participants in the Chronic Kidney Disease in Children (CKiD) cohort who completed the Pediatric Quality of Life Inventory (PedsQL) on three or more occasions over the course of two or more years. Generalized gamma (GG) mixed effects models were applied to assess the effect of CKD duration on HRQOL while controlling for confirmed covariates from previous cross-sectional analyses.

Results: 660 children (median age: 11.3) with a median of 8.5 years duration of CKD were evaluated. GG models with child self-report PedsQL data indicated that longer CKD duration was associated with improved Overall, Physical, Emotional, Social and School HRQOL. GG models with parent-proxy PedsQL data indicated that longer duration was associated with worse School HRQOL. Increasing trajectories of child self-report HRQOL were observed in the majority of subjects (ranging from 64% to 96% depending on subscale and baseline HRQOL level), while lower percentages of increasing trajectories were observed on parent-proxy scales. In the overall group there was no significant relationship between HRQOL and time varying GFR.

Conclusions: Longer duration of disease is associated with improved HRQOL on all child self-report scales. This finding may be a function of changes in internal standards, values or conceptualization of illness.

Funding: NIDDK Support, Other NIH Support - NICHD, NHLBI

CHILD SELF-REPORT SCALES (562 subjects, 2637 observations)	OVERALL	PHYSICAL	EMOTIONAL	SOCIAL	SCHOOL*
PedsQL Scores at 25th percentile for CKD Duration 5 vs 15 years	68.7 vs 75.7	74.2 vs 78.9	60.4 vs 70.4	76.2 vs 84.4	54.3 vs 59.3
P value for effect of CKD duration on full distribution of PedsQL scores	<0.0001	0.005	<0.0001	<0.0001	0.007
PARENT PROXY SCALES (660 subjects, 3372 observations)	**OVERALL**	**PHYSICAL**	**EMOTIONAL**	**SOCIAL**	**SCHOOL****
PedsQL Scores at 25th percentile for CKD Duration 5 vs 15 years	70.3 vs 68.8	72.7 vs 72.5	64.7 vs 67.5	76.4 vs 76.2	57.9 vs 52.5
P value for effect of CKD duration on full distribution of PedsQL scores	0.26	0.89	0.051	0.94	0.002

*School subscale uses 557 subjects, 2612 observations
**School subscale uses 650 subjects, 3277 observations

Table 1. Significance of CKD duration from generalized gamma mixed effects models and effects on PedsQL scores at the 25th percentile

SA-OR021

Protective Role of Type III Sodium-Dependent Phosphate Transporter, PiT-2, in Uremic Vascular Calcification Shunsuke Yamada, Elizabeth M. Soberg, Timothy C. Cox, Mei Y. Speer, Cecilia M. Giachelli. *University of Washington, Seattle, WA.*

Background: Vascular calcification (VC) is prevalent in patients with chronic kidney disease (CKD) and increases the risk of cardiovascular deaths. PiT-2 is a type III sodium-dependent phosphate (Pi) transporter expressed in various tissues and a causative gene for familial basal ganglion arterial calcification. However, it is unknown whether PiT-2 plays a role in the pathogenesis of VC related to CKD.

Methods: To determine the role of PiT-2 in VC, wild-type (WT) and global PiT-2 heterozygous (HET) knockout mice were challenged with CKD. At two weeks after the two-step 5/6th nephrectomy, mice were fed a normal (0.5%) or high (1.5%) Pi diet for 11 days and terminated. At termination, blood, aorta, kidney, and femur were collected. Serum chemistry, histology, and micro CT analyses were performed. Primary vascular smooth muscle cells (VSMCs) isolated from the aortas of WT and PiT-2 HET mice were used for *in vitro* Pi-induced calcification and P-uptake assays. WT-derived VSMCs were also treated with scramble or PiT-2 small interfering RNA (siRNA) and used for gene and protein expression analysis.

Results: Uremic mice fed a high Pi diet developed VC in the medial layer of the aorta, which was exemplified by Alizarin red staining and calcium quantification of the blood vessel. PIT-2 haploinsufficiency greatly enhanced VC in the setting of CKD and high Pi diet. No differences were observed in the serum levels of calcium, Pi, and FGF23, kidney function, and renal mRNA expression of SLC34A1 and SLC34A3 between the WT and PiT-2 HET mice with CKD. MicroCT analyses showed that haploinsufficiency of PiT-2 decreased trabecular bone mineral density and thickness in CKD. *In vitro*, Pi uptake activity was decreased in the cultured VSMCs isolated from the PiT-2 HET mice compared with those from the WT mice. Under high Pi medium condition, PiT-2 haploinsufficiency increased calcification of the cultured VSMCs. Similar results were also found in WT VSMCs treated with PiT-2 siRNA. Finally, mRNA expression and protein levels of osteoprotegerin, an inhibitor of VC, were decreased in VSMCs treated with PiT-2 siRNA compared to scramble controls.

Conclusions: PiT-2 plays a protective role in the pathogenesis of VC and bone disorders in CKD mice, and can be a promising therapeutic target in the CKD population.

Funding: NIDDK Support, Government Support - Non-U.S.

SA-OR022

Large Secondary Calciprotein Particles Are Associated with Vascular Calcification Wei Chen,[1] Viktoriya Anokhina,[1] Benjamin L. Miller,[1] Gregory Dieudonne,[1] Matthew K. Abramowitz,[2] Randeep Kashyap,[1] Chen Yan,[1] Tong tong Wu,[1] David A. Bushinsky.[1] *[1]University of Rochester School of Medicine, Rochester, NY; [2]Albert Einstein College of Medicine, Bronx, NY.*

Background: Vascular calcification (VC) is common and contributes to cardiovascular mortality in patients with CKD. Calcification propensity as measured by the serum assay of Pasch et al. using nephelometry is associated with cardiovascular events; however, whether it is a biomarker for VC is unknown. We modified this assay through the use of microplate-based dynamic light scattering, which allowed us to measure both time for half-maximal transformation (T_{50}) of 1° to 2° calciprotein particles (CPPs) and size of 2°CPPs (CPP2) (instead of only T_{50} with nephelometry). A fast T_{50} and/or a large CPP2 appears to reflect a procalcific milieu. Here we tested the hypothesis that a fast T_{50} and/or a large CPP2 would be associated with VC.

Methods: We measured T_{50} and CPP2 in 46 subjects with stage 4-5 CKD and 17 healthy volunteers. T_{50} and CPP2 were examined as continuous and categorical variables (dichotomized at the median). VC was measured on plain radiographs and defined as a Kauppila score >6 (lumbar aorta) or Adragao score ≥3 (iliac, femoral, radial and digital arteries). Logistic regression was used to examine the association of T_{50} and CPP2 size with VC, adjusting for age, gender, eGFR and diabetes.

Results: Compared to healthy volunteers (age 24±5 yr, eGFR 114±13ml/min/1.73m^2), CKD patients (age 65±12 yr, eGFR 19±8ml/min/1.73m^2) had lower mean T_{50} (191±40 vs. 221±31 min, p=0.008) and higher median CPP2 [305 (187-477) vs. 168 (145-352) nm, p=0.02]. T_{50} was correlated inversely with CPP2 (r=-0.50, p<0.001). No healthy volunteers had VC, while 51% of CKD patients did. In all subjects, compared to those without VC, those with VC had a higher median CPP2 [370 (272-566) vs. 195 (153-327) nm, p=0.001] with no difference in mean T_{50} (191±39 vs. 203±41 min, p=0.27). Compared to those with CPP2 in the lower half (median=305nm), those with CPP2 in the upper half had 10.7 times higher odds of having VC (95% CI 1.4, 79.1, p=0.02). Similar results were obtained when analysis was limited to CKD patients.

Conclusions: CKD patients had larger CPP2 and faster T_{50} indicating greater calcification propensity compared with healthy volunteers. While a faster T_{50} was associated with larger CPP2, only a large CPP2 was associated with VC suggesting that CPP2 may be a useful biomarker for VC.

Funding: Other NIH Support - KL2 TR000095, Private Foundation Support

SA-OR023

The Effect of Increasing Dialysate Magnesium on Serum Calcification Propensity in Subjects with ESRD: A Randomised Double-Blind Controlled Trial Iain B. Bressendorff,[2,5] Ditte Hansen,[2] Morten Schou,[1] Andreas Pasch,[4] Lisbet Brandi.[3] *[1]Department of Cardiology, Herlev Hospital, Herlev, Denmark; [2]Department of Nephrology, Herlev Hospital, Copenhagen, Denmark; [3]Department of Cardiology, Nephrology and Endocrinology, Nordsjællands Hospital, Hillerød, Denmark; [4]University Hospital Bern, Bern, Switzerland; [5]Department of Cardiology, Nephrology and Endocrinology, Nordsjællands Hospital, Hillerød, Denmark.*

Background: Patients undergoing haemodialysis (HD) for end-stage renal disease (ESRD) have an enormously high risk of cardiovascular disease. Serum calcification propensity (T_{50}) is a novel functional test, which quantifies the functionality of the humoral system of calcification control. Low T_{50} values are associated with increased risk of cardiovascular events and death in patients with ESRD. Increasing magnesium (Mg) in serum increases (i.e. improves) T_{50} *in vitro*, but so far no clinical trials have investigated whether increasing serum Mg increases T_{50} in subjects with ESRD.

Methods: We conducted a single-centre, randomised, double-blinded, controlled clinical trial, in which we examined the effect of increasing dialysate Mg from 0.5 mmol/L to 1.0 mmol/L compared to maintaining dialysate Mg at 0.5 mmol/L on T_{50} in subjects undergoing HD for ESRD. Fifty-nine subjects underwent 28 days of intervention followed by 14 days of observation.

Results: After increasing dialysate Mg from 0.5 mmol/L to 1.0 mmol/L for 28 days the difference in serum Mg between the two groups was 0.351 mmol/L (between-group difference, 95% confidence interval 0.263 - 0.440, p < 0.001). In parallel to the increase in serum Mg, the difference in T_{50} between the two groups was 72 min (between-group difference, 95% confidence interval 29 - 114, p < 0.001). One subject withdrew consent (high dialysate Mg group) and two subjects died (one in each treatment group). There were no adverse events considered to be related to the intervention.

Conclusions: Increasing dialysate Mg increased T_{50} in subjects undergoing maintenance HD. Improving T_{50} might lead to reductions in cardiovascular events and death in subjects with ESRD.

Funding: Government Support - Non-U.S.

SA-OR024

Monocyte Chemoattractant Protein-1 (MCP-1) Is Associated with Atherosclerotic (ASCV) Events and Death in CKD Maria Clarissa Tio,[1] Lucile Parker Gregg,[3,2] Xilong Li,[4] Beverley Adams-Huet,[4] James Delemos,[5] Susan Hedayati.[3,2] *[1]Department of Medicine, University of Texas Southwestern Medical Center, Dallas, TX; [2]VA North Texas Health Care System, Dallas, TX; [3]Division of Nephrology, University of Texas Southwestern Medical Center, Dallas, TX; [4]Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, TX; [5]Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, TX.*

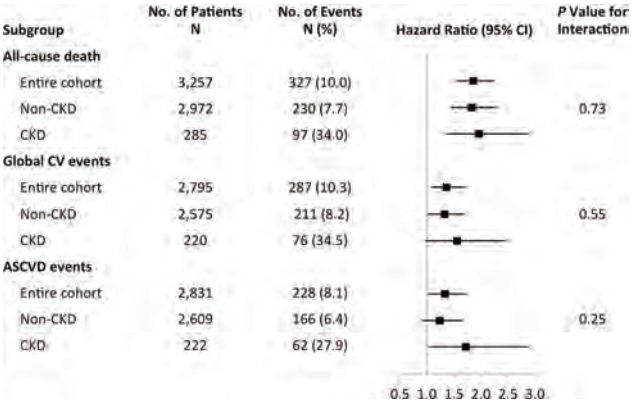
Background: MCP-1, an inflammatory chemokine involved in atherogenesis, is associated with CV events in individuals with known coronary artery disease. Few data exist regarding its association with hard outcomes in CKD.

Methods: We studied 3,257 participants of the Dallas Heart Study, 285 (8.8%) of whom had CKD (eGFR <60 mL/min/1.73m^2 or albuminuria), followed for a median of 12.5 years for all-cause death, global CV events (CV death, MI, stroke, CV revascularization, hospitalization for heart failure or atrial fibrillation), and ASCV events (CV death, MI, stroke, CV revascularization). Cox proportional hazards regression assessed associations between log MCP-1 levels and outcomes, unadjusted and adjusted for traditional CV risk factors (age, sex, race, hypertension, diabetes, current smoking, total and HDL cholesterol) and eGFR.

Results: There were 327 deaths, 287 global CV and 228 ASCV events in the entire cohort. In the CKD group, there were 97 (34%) deaths, 76 (34.5%) global CV and 62 (27.9%) ASCV events. Median (IQR) MCP-1 was 164.7 (120.3, 220.9) pg/mL in non-CKD vs. 192.2 (143.6, 269.8) in CKD individuals, P<0.001, and negatively correlated with eGFR, r=-0.23, P<0.0001. In the CKD group, MCP-1 was associated with death (HR 1.96, 95% CI 1.35-2.85) and ASCV events (HR 1.72, 95% CI 1.04-2.87) but not global CV events in unadjusted models (**Figure**). Adjustment for CV risk factors attenuated the association between MCP-1 and ASCV events, but the association with death remained significant in non-CKD (aHR=1.65, 95% CI 1.32-2.07) and CKD (aHR=1.49, 95% CI 1.01-2.19) groups. There were no significant CKDxMCP-1 interactions on outcomes.

Conclusions: While MCP-1 does not predict global CV and ASCV events after adjusting for CV risk factors, it is an independent predictor of all-cause death in both CKD and non-CKD individuals. Future directions include exploring its inclusion in outcome prediction models in the CKD population.

Funding: NIDDK Support, Commercial Support - J. A. de Lemos has received grant support and consulting income from Roche Diagnostics and Abbott Diagnostics and has served on endpoint committees for Siemen's Health Care Diagnostics and Radiometer.



SA-OR025

Metabolic and Hypertensive Complications of Pregnancy in Women with Nephrolithiasis Jessica S. Tangren, Elizabeth D. Ankers, Ravi I. Thadhani. *Massachusetts General Hospital, Boston, MA.*

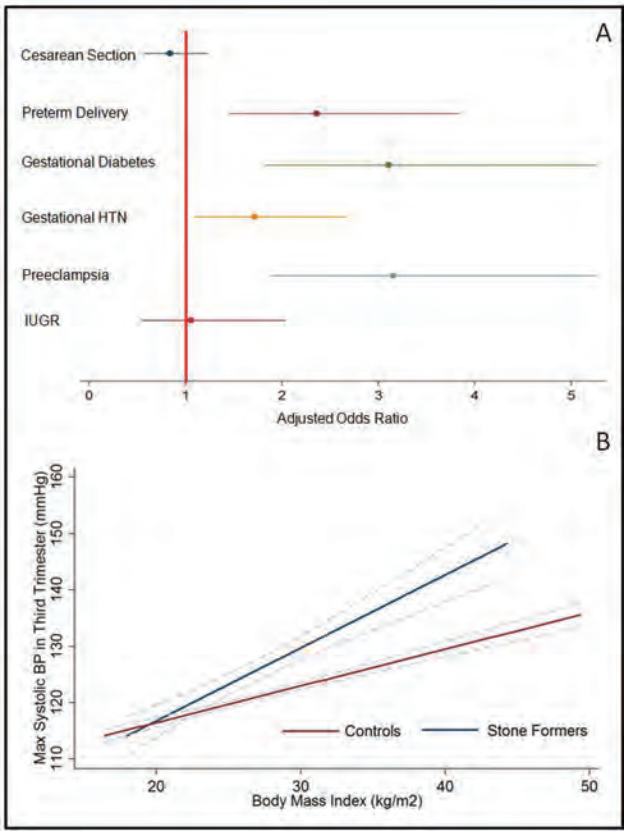
Background: Kidney stones are associated with future development of hypertension, diabetes and the metabolic syndrome. The relationship between nephrolithiasis and pregnancy complications, including gestational dysglycemia and gestational hypertension has not previously been evaluated. We assessed whether stone formation *prior to pregnancy* was associated with metabolic and hypertensive complications in pregnancy. We hypothesized that stone formation is a marker of metabolic disease and associated with increased risk for maternal complications in pregnancy.

Methods: We conducted a retrospective cohort study of women who delivered infants at the Massachusetts General Hospital from 2006 to 2016. Women with abdominal imaging (CT or ultrasound) prior to pregnancy were included in the analysis. Pregnancy outcomes in women with documented stones on imaging (stone formers, n=174) were compared to women without stones on imaging (controls, n=1,330). Women with pre-existing CKD, hypertension and diabetes were excluded.

Results: Maximum systolic blood pressure (mSBP) in pregnancy was increased in stone formers versus controls despite similar first trimester blood pressure. Gestational diabetes and gestational hypertension were more common in stone formers (18% vs. 6%, p<0.01 and 19% vs. 13%, p=0.04). After multivariate adjustment, stones were associated with increased risk of preterm delivery, gestational diabetes and preeclampsia (1A). Stone formation was an effect modifier of the relationship between mSBP and BMI (1B).

Conclusions: In women without preexisting diabetes and hypertension, a history of nephrolithiasis was associated with gestational dysglycemia and hypertension. Nephrolithiasis may be a marker of increased metabolic risk in women without traditional risk factors for pregnancy complications.

Funding: Private Foundation Support



SA-OR026

Antibiotic Use and Risk of Incident Kidney Stones Eric N. Taylor,[3] Gary C. Curhan,[1] Pietro Manuel Ferraro.[2] *[1]Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA; [2]Fondazione Policlinico Universitario A. Gemelli, Rome, Italy; [3]Maine Medical Center, Portland, ME.*

Background: Intestinal microbiota may play a role in the formation of kidney stones. Antibiotics alter the gut microbiome and therefore represent a potential risk factor for kidney stones.

Methods: We prospectively examined the independent associations between antibiotic use at age 20 to 39 and age 40 to 59 with risk of a subsequent symptomatic, incident kidney stone in the Nurses' Health Study I (NHS I; N=67,051 women). We also examined antibiotic use at age 20 to 39 and age 40 to 49 in the Nurses' Health Study II (NHS II; N=74,467 women). Medical record review of a subset of cases confirmed ≥ 95% of self-reported incident kidney stones in each cohort, and the majority of stones (≥ 77%) were predominantly calcium oxalate. Validated food frequency questionnaires were used to update dietary intakes every four years. Cox proportional hazards regression was used to adjust for age, body mass index, thiazide use, family history of kidney stones, hypertension, diabetes, fluid intake, supplemental calcium, and dietary factors.

Results: We documented 1,318 incident kidney stones over a combined 14 years of follow-up. At baseline, mean age was 68 in NHS I and 50 in NHS II. Compared with non-users, women who used antibiotics for ≥ 2 months between age 20 to 39 had a multivariable relative risk (MVRR) for kidney stones of 1.41 (95% CI 0.95 to 2.09) in NHS I and 1.28 (95% CI 0.87 to 1.89) in NHS II. Compared with non-users, women who used antibiotics for ≥ 2 months between age 40 to 59 in NHS I and between age 40 to 49 in NHS II had MVRRs for kidney stones of 1.62 (95% CI 1.01 to 2.60) and 1.35 (95% CI 1.00 to 1.84), respectively. Excluding women with self-reported urinary tract infections before the symptomatic kidney stone event did not change the results. There was no statistically significant interaction between dietary oxalate, antibiotic use, and kidney stone risk.

Conclusions: Long-term antibiotic use in early and middle adulthood may be independently associated with a higher risk of kidney stones later in life.

Funding: NIDDK Support

SA-OR027

Effect of Dietary Phosphate Intake on Blood Pressure in Healthy Humans Reto Krapf,[2] Lukas Bestmann,[1] Roberto Scanni,[4] Henry N. Hulter.[3] *[1]Bioanalytica Labs, Lucerne, Switzerland; [2]Medicine, University of Basel, Lucern, Switzerland; [3]University of California San Francisco, San Rafael, CA; [4]Istituto Oncologico Veneto, Padova, Italy.*

Background: Despite strong epidemiologic evidence for CV toxicity of high dietary phosphate (Pi) in humans with normal renal function, controlled Pi intervention effects on systemic human hemodynamics have not been reported. Vitamin D is known to increase intestinal Pi absorption, thereby increasing Pi load. Conversely, vitamin D supply has been associated with better CV outcome.

Methods: Prospective outpatient study with blinded assessment in 20 young healthy humans with normal renal function randomly assigned to high (HP, regular diet, RD, + 1 mmol/kg bw/d of Pi as neutral NaPO4) or to low Pi (LP, RD + lanthanum 750 mg p.o. TID plus 0.7 mmols/kg bw/d NaCl to correct for excess Na intake in HP group) for 11 weeks (w). At end of w6, each subject received 600 000 U of vitamin D3 (i.m.) and continued on HP and LP for another 5w. Recovery visits on RD were performed 2 months after w11. Plasma and 24h urinary assays were performed at BL, w6 and w11. CV endpoints: 24h ABPM. endothelial function (reactive hypoxia index), arterial elasticity (pulse wave velocity). Data are means of 3 consecutive daily measurements/period.

Results: Mean fasting [Pi]p increased significantly by 0.23±0.11 (SEM) mmol/l in HP group as did 24h SBP and DBP, both in comparison to own baseline and to the LP group: + 4.1 (range 2.1-6.1) and 3.2 (1.2-5.2) mmHg, respectively. 24h U Pi was 14.6 ± 1.8, 21.9 ± 2.4 and 41.5 ± 4.1 mmol/24h in LP, RD and HP. Mean 24h pulse rate increased significantly by + 4.0 (2.0-6.0) bpm. Plasma renin/aldosterone concentrations and 24h urinary excretion rates of Na, aldosterone and free cortisol did not differ among the 2 groups. 24h urinary excretion of metanephrin increased significantly (intra- and intergp) in the HP group by + 60 (50-70) ugr/24h. Vitamin D had no effect on the HP-induced increases in BP, pulse rate, metanephrin or renin/aldosterone values and increased U Pi/24h only in the LP group. Serum FGF23, PTH, a-Klotho and urinary Klotho increased significantly in HP vs. LP. Recovery RD visits showed reversal of the elevated 24h ABPM and pulse rates in the HP group. Neither modulation of Pi intake nor vitamin D affected endothelial and arterial function tests significantly.

Conclusions: Increased Pi intake (controlled for sodium intake) significantly increases SBP, DBP and pulse rate in normal humans, an effect explained at least in part by increased sympathoadrenergic activity.

Funding: Government Support - Non-U.S.

SA-OR028

Understanding the Metatranscriptome and Metagenome Regulating Oxalate Metabolism in the Human Gut Lama Nazzal,[2] Tom W. Battaglia,[2] Menghan Liu,[2] David S. Goldfarb,[1] Kelly Ruggles,[2] Martin J. Blaser.[2] *[1]New York Harbor VAMC, Hastings on Hudson, NY; [2]New York University School Of Medicine, New York, NY.*

Background: Multiple bacterial species are capable of degrading oxalate in vitro. Certain taxa degrade oxalate as their sole source of energy and carbon (e.g. *Oxalobacter formigenes*), whereas others use oxalate as an auxiliary carbon source. For oxalate metabolism, it is not yet well-understood how genomic potential relates to transcriptional regulation. We asked whether the human gut could have a community of oxalate-degrading taxa working synergistically to diminish the effects of this toxic metabolite. Our hypothesis is that oxalate metabolism is regulated by a multi-organism oxalate-degrading community (oxalobiome) that is dominated by specialist oxalate degraders.

Methods: We used data from 2 public databases: (i)8 healthy subjects in the USA; and (ii)471 healthy subjects in the Netherlands as part of the Human Functional Genomic Project (HFGP). Both collected fecal samples for metagenomic and/or metatranscriptomic high throughput sequencing. Using HUMAnN2 with customized settings, we profiled the metabolic activity of oxalate-degrading bacterial species. Output from these analyses was expressed as Reads per Kilobase per Million mapped reads (RPKM).

Results: We identified the oxalate degradation pathway (ODP) in the metagenome and metatranscriptome of all 8 subjects. Mean ODP is 35.3±28.1 and 90.1±43.5 RPKM in the metagenome and the metatranscriptome, respectively, indicating active expression. *O. formigenes, E. coli,* and unclassified bacteria were present in metagenomic and metatranscriptomic reads. *B. dentium* had detectable ODP in its genome but was not transcribing it. In the HFGP database, we identified ODP in 328 subjects of the 471 tested (70%) (Mean=18.1±2.1 RPKM). ODP was detected in *B. animalis, B. dentium, B. pseudocatenulatum, E.coli/Shigella, L. acidophilus, L. gasseri, L. mucosae, O. formigenes* and unclassified bacteria. ODP was examined in the metagenome of 265 females (Mean ODP= 21.7±3.3) and 200 males (Mean ODP=13.3±1.9 RPKM; p=0.04 by unpaired t test).

Conclusions: We have identified a community of bacteria with the potential to degrade oxalate in healthy humans and species actively transcribing ODP. These include *E.coli*, which might be a common contributor of oxalate degradation in humans. The sex differences in ODP is consistent with the ~ 2:1 male/female incidence and prevalence of calcium oxalate stones.

Funding: NIDDK Support

SA-OR029

The L530R Variation Found in Kidney Stone Patients Impacts the Structure and Function of TRPV5 Lingyun Wang, Ji-Bin Peng. *Div of Nephrology, Dept of Medicine, Nephrology Research and Training Center, University of Alabama at Birmingham, Birmingham, AL.*

Background: TRPV5 is a Ca^{2+}-selective channel that plays a key role in the reabsorption of Ca^{2+} ions in the kidney. Recently, a L530R variation in TRPV5 was found in some kidney stone formers. This variation introduces a positive charged residue into a hydrophobic region of the pore helix and may alter the Ca^{2+} transport activity of TRPV5. However, it is unclear to what extent this variation alters the structure and function of TRPV5.

Methods: To evaluate the function and expression of the TRPV5 variant, Ca^{2+} uptake in *Xenopus* oocytes and western blot analysis were performed. To assess the structural effects of L530R, TRPV5 was modeled using MODELLER based on the core structure of TRPV6 containing all the six transmembrane (TM) helices and the TRP domain. The L530R variation was introduced into TRPV5 using PyMOL. The modeled TRPV5 was embedded in a lipid bilayer composed of 299 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) lipids using CHARMM-GUI, and water molecules were added on both sides of the bilayer. Two 400 ns molecular dynamics simulations were performed using AMBER14.

Results: The L530R variation abolished the Ca^{2+} uptake activity of TRPV5 in *Xenopus* oocytes. The variant protein was expressed with abnormal complex glycosylation. Simulation results show that the L530R variation breaks the hydrophobic interaction between L530 and L502, damaging the secondary structure of TM5. The variation also alters its interaction with membrane lipid molecules. Compared to the electroneutral L530, the positively charged R530 residue shifts the surface electrostatic potential towards positive. R530 is attracted to the negatively charged phosphorus atoms rather than the hydrophobic carbon atoms of membrane lipids. This shifts the pore helix where R530 is located and the D542 residue in the Ca^{2+}-selective filter towards the surface of membrane where phosphorus atoms are located.

Conclusions: Our results indicate that the L530R variation damages the secondary structure of TM5 of TRPV5 and alters the interaction between TRPV5 and membrane lipids. This may lead to misfolding of TRPV5 or impaired translocation of the channel to the plasma membrane, and ultimately disrupt TRPV5-mediated Ca^{2+} reabsorption.

Funding: NIDDK Support

SA-OR030

Chlorthalidone Is Superior to Potassium Citrate in Reducing Calcium Phosphate Stone Formation in Genetic Hypercalciuric Stone-Forming Rats Nancy S. Krieger,[2] John R. Asplin,[1] Ignacio Granja,[1] Felix M. Ramos,[2] Courtney A. Flotteron,[2] Luojing Chen,[2] David A. Bushinsky.[2] *[1]Litholink Corp, Chicago, IL; [2]Univ. of Rochester, Rochester, NY.*

Background: To study human idiopathic hypercalciuria (IH) we developed an animal model, genetic hypercalciuric stone-forming (GHS) rats, whose pathophysiology parallels that found in human IH. All GHS rats form calcium phosphate (CaP) kidney stones while there is no stone formation in the founder Sprague-Dawley (SD) rats. Previously, in GHS rats, we have shown that potassium citrate (KCit) increases urine supersaturation (ss) with respect to CaP but does not alter stone formation. In this study we tested the hypothesis that chlorthalidone (CTD) and KCit combined would reduce CaP stone formation in the GHS rats.

Methods: 111th generation GHS rats were fed a fixed amount of a normal Ca (1.2%) and P (0.65%) diet, housed in metabolic cages and divided into four groups. Diets were supplemented with KCit (4 mmol/d) or CTD (4-5mg/kg/d), alone, or combined. Rats not receiving KCit were given KCl (4 mmol/d). Urine (u) was collected at 6, 12, and 18 wks for electrolyte analyses and kidney stone formation was determined by X-ray at 18 weeks.

Results: Compared to KCl, KCit reduced uCa (KCl=17.2±0.6 mg/d, KCit=14.9±0.3), CTD reduced it further (CTD= 12.4±0.5) and KCit+CTD reduced it even further (KCit+CTD=10.5±0.4). CTD raised uCit (KCl=112.1±3.6 mg/d, CTD=133.9±2.5) KCit raised it further (KCit=182.2±2.5) while KCit+CTD did not increase it further (KCit+CTD=171.7±3.2). KCit alone increased uP (KCl=20.4±0.6 mg/d, KCit=26.7±1.0). CTD did not change uCaP ss (KCl= 4.1±0.2 vs CTD=3.2±0.3), while KCit alone, or in combination with CTD, increased it (KCit=8.0±0.5, KCit+CTD=9.5±0.8). Compared to KCl (stone formation range of 0-4: KCl=2.6±0.3), KCit did not alter stone formation (3.3±0.3), while there was no stone formation in the GHS rats fed with CTD alone (CTD=0). The combination of KCit+CTD (2.0±0.3) resulted in more stones than CTD alone. All changes were significant to $p<0.05$.

Conclusions: Thus in GHS rats, who universally spontaneously form CaP stones, CTD alone is superior to KCit alone or in combination with CTD, in reducing stone formation.

Funding: NIDDK Support

SA-OR031

Dementia and Alzheimer's Disease Among Older Adults Initiating Hemodialysis Mara McAdams-DeMarco,[1] Matthew Daubresse,[4] Sunjae Bae,[2] Dorry L. Segev.[3] *[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [2]Johns Hopkins School of Medicine, Baltimore, MD; [3]Johns Hopkins University, Baltimore, MD; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.*

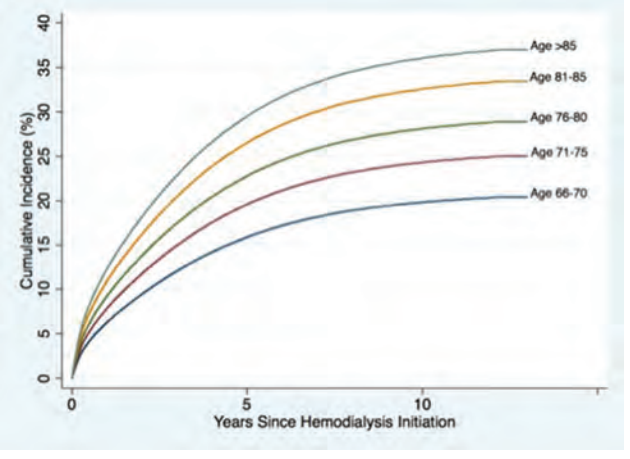
Background: Older end-stage renal disease (ESRD) patients experience rapid declines in executive function after initiating hemodialysis; these impairments might lead to high rates of dementia and Alzheimer's disease (AD) in this population. We estimated incidence, risk factors, and sequelae of dementia and AD among older ESRD patients initiating hemodialysis.

Methods: We studied 356,668 older (age≥66) hemodialysis patients (1/1/2001-12/31/2013) from national registry data [United States Renal Data System] linked to Medicare. We estimated dementia and AD risk (cumulative incidence), studied factors associated with these disorders using competing risks models, and estimated the risk of subsequent mortality using Cox proportional hazards models.

Results: The 1-year, 10-year, and lifetime dementia risks were 4.6%, 22.1%, 25.1% for women and 3.7%, 18.9%, and 21.3% for men. The corresponding AD risks were 0.6%, 4.3%, and 5.4% for women and 0.4%, 3.4%, and 4.2% for men. The strongest independent risk factors for dementia and AD were age≥86 years (dementia: HR=2.11, 95%CI:1.99-2.23; AD: HR=2.33, 95%CI:2.06-2.63), African American race (dementia: HR=1.70, 95%CI:1.64-1.75; AD: HR=1.92, 95%CI:1.79-2.06), and institutionalization (dementia: HR=1.50, 95%CI:1.41-1.59; AD: HR=1.49, 95%CI:1.31-1.69). Older HD patients with dementia were at 2.17-fold (95%CI:2.15-2.19) increased risk of subsequent mortality; those with AD were at 1.92-fold (95%CI:1.88-1.95) increased mortality risk.

Conclusions: Older hemodialysis patients are at substantial risk of dementia and AD, and these disorders increase subsequent mortality risk 2-fold. Hemodialysis may be inadequate to treat ESRD patients; the role of renal replacement therapy, particularly in older adults, should be expanded to protect cognitive function.

Funding: Other NIH Support - NIA



Cumulative Incidence of Dementia After Hemodialysis Initiation

SA-OR032

Randomized, Placebo-Controlled Study on the Efficacy of CR845 in Improving the Quality of Life of Hemodialysis Patients with CKD-Associated Pruritus Frederique Menzaghi, Catherine Munera, Maria S. Oberdick, Joseph W. Stauffer, Robert H. Spencer. *Cara Therapeutics, Inc., Stamford, CT.*

Background: Chronic kidney disease-associated pruritus is a serious itching disorder associated with poor quality of life (QOL), linked to sleep disturbance, depressed mood and increased mortality. The present trial evaluated the anti-pruritic efficacy of the novel kappa-opioid receptor agonist CR845 and its impact on QOL in hemodialysis (HD) patients suffering from moderate-to-severe pruritus.

Methods: 174 HD patients with a mean baseline numerical rating score (NRS) for worst itching intensity >4 were enrolled [0=no itching up to 10=worst itching imaginable]. Patients were randomized to receive one of 3 intravenous doses of CR845 (0.5 mcg/kg, n=44; 1 mcg/kg, n=41 and 1.5 mcg/kg, n=44) or placebo (n=45) at the end of each dialysis over an 8-week treatment period. Worst itching intensity (NRS, primary endpoint) and QOL measures due to itching (secondary/exploratory endpoints) were recorded, with efficacy being defined as the change from baseline to the last week of the treatment (i.e. Week 8). Changes in QOL was assessed using multidimensional questionnaires including the Skindex-10 (with measures of emotional distress and social functioning), 5-D itch scale (with measures of sleep and social functioning) and the MOS sleep disturbance subscale.

Results: CR845 was well tolerated and reduction in itch NRS scores over placebo was observed at all doses, with a change from baseline ≥3 NRS points by end of Week 8 for 64% of the patients treated with CR845 0.5 mcg/kg vs 29% of the placebo patients (p<0.001). Improvement in QOL measures was significantly different from placebo for all doses of CR845 with respect to the Skindex-10 and the 5-D itch scale (p values ranging from <0.001 to <0.026), along with a significant improvement in sleep at doses of 0.5 and 1 mcg/kg (p=0.006). The mean change in QOL measures correlated with the change in itch intensity (Pearson's correlation ranging from r=0.67 to 0.74, p<0.0001).

Conclusions: CR845 produced a substantial improvement in multiple measures of itch-related QOL associated with a clinically important reduction in itch intensity in HD patients with moderate-to-severe pruritus that was sustained over 2 months of treatment.

Funding: Commercial Support - Cara Therapeutics, Inc.

SA-OR033

Conservative Kidney Profile Prior to Transitioning to Dialysis and Early Dialysis Outcomes in US Veterans: A Transition of Care in CKD Study Melissa Soohoo,[1] Elani Streja,[1] Yoshitsugu Obi,[1] Connie Rhee,[1] Daniel L. Gillen,[1] Keiichi Sumida,[2] Danh V. Nguyen,[1] Csaba P. Kovesdy,[3] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine, Orange, CA; [2]Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; [3]University of Tennessee Health Science Center, Memphis, TN.*

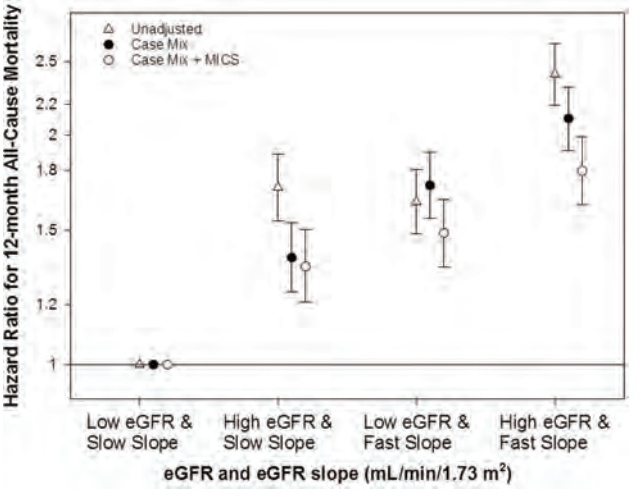
Background: National data has shown that more patients transition to end-stage renal disease (ESRD) at a higher estimated glomerular filtration rate (eGFR), yet mortality is high in the first months upon ESRD transition and studies have questioned the contribution of aggressive dialysis initiation to this outcome. We hypothesized that among US veterans transitioning to ESRD, a more conservative kidney profile in the pre-ESRD (prelude) period, including lower kidney function level and slower eGFR slope, is associated with better outcomes.

Methods: In 19,985 veterans transitioning to ESRD in 2007-2014, we examined the association of eGFR at transition and its slope over the final 12 months of the prelude period with 12-month post-ESRD mortality and hospitalization rates, using Cox and Poisson regression models, respectively. Two groups of low vs. high eGFR (dichotomized at 10 mL/min/1.73m^2) and slow vs. fast slope (dichotomized at -10 mL/min/1.73m^2/year) were combined into four groups.

Results: Patients had a median[IQR] of eGFR at transition and slope of 9.7[7.1,13.3] mL/min/1.73m^2 and -10.5[-18.8,-5.9] mL/min/1.73m^2/year, respectively. Patients with a conservative kidney profile (low eGFR and slow slope), had the lowest 12-month all-cause and cardiovascular (CV) mortality risks (Figure), and hospitalization rate. Conversely, patients with a high eGFR and fast slope had the highest adjusted all-cause (HR [95% CI]: 1.80 [1.62, 1.99]) and CV mortality risks (1.57 [1.32,1.88]) and hospitalization rate (IRR [95% CI] 1.39 [1.34, 1.44]) compared to conservative kidney profile patients.

Conclusions: A kidney profile characterized by slower chronic kidney disease progression and a later transition to ESRD is associated with more favorable early dialysis outcomes. Trials to examine a more conservative approach to dialysis are warranted.

Funding: NIDDK Support



SA-OR034

Residual Kidney Function and Ultrafiltration Rate: Their Association with Mortality Jason A. Chou,[1] Yoshitsugu Obi,[1] Connie Rhee,[1] Elani Streja,[1] Danh V. Nguyen,[1] Melissa Soohoo,[1] Csaba P. Kovesdy,[2] John J. Sim,[3] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine, Orange, CA; [2]University of Tennessee Health Science Center, Memphis, TN; [3]Kaiser Permanente Southern California, Pasadena, CA.*

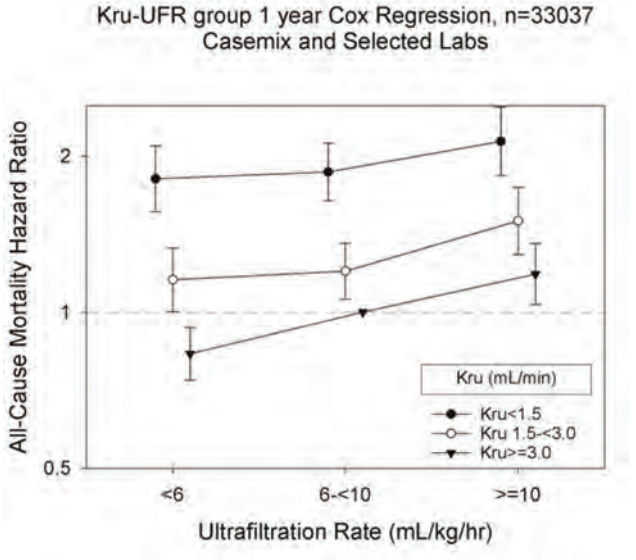
Background: Residual kidney function (RKF) among both peritoneal dialysis and hemodialysis (HD) patients has been associated with improved survival. Although faster ultrafiltration rates (UFR) with HD have been observed to have greater mortality risk among incident HD patients with RKF, the ideal UFR goals are unknown. We hypothesize that in incident HD patients with RKF, a lower UFR will have improved survival.

Methods: We examined the association of RKF measured as Kru (mL/min/1.73m^2) and UFR (mL/kg/hr) in combined groups with 1- and 5-year all-cause mortality in a cohort of 34,546 incident HD patients with Cox regression models adjusted for case-mix, comorbidities and selected lab covariates. A total of 9 groups were analyzed, composed of the following groups: Kru <1.5, 1.5-<3.0 and ≥3.0 mL/min/1.73m^2 and UFR <6, 6-<10, and ≥10 mL/kg/hr with reference group of Kru ≥3.0 and UFR 6-<10.

Results: We found that Kru-UFR groups with a higher Kru and lower UFR demonstrated a graded association with survival where the Kru ≥3.0 mL/min/1.73m^2 and UFR <6 ml/kg/hr group had a 1 year mortality HR (CI 95%) of 0.83 (0.74-0.93) (p-for-interaction 0.002) in the fully adjusted model. All associations were robust to all levels of adjustment on both 1- and 5- year mortality outcomes.

Conclusions: Among incident HD patients with RKF, lower UFR rates were associated with improved survival. Targeting different UFR goals may be a focus of intervention given its potential impact on RKF and mortality.

Funding: NIDDK Support



Figure

SA-OR035

Renal Function Recovery in Incident US Dialysis Patients
Paul L. Kimmel,[1] Chyng-Wen Fwu,[3] Kevin C. Abbott,[4] Paul Eggers.[2] *[1]National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; [2]Retired, Olney, MD; [3]Social & Scientific Systems, Inc., Silver Spring, MD; [4]The National Institutes of Health, NIDDK, Bethesda, MD.*

Background: Recovery of renal function (RRF) in ESRD patients is thought to be uncommon, but there are few recent descriptive data. Factors associated with RRF as well as outcomes after RRF are unknown.

Methods: Using USRDS data, we included incident dialysis patients between 2006 and 2015, followed until 6/30/2016. RRF was physician-determined and reported by dialysis facility. Logistic regression examined associations of RRF 6m after dialysis initiation with demographic characteristics and diagnoses causing ESRD. Percent of RRF patients who died, returned to ESRD, and alive and not on ESRD therapy 3y after RRF were determined.

Results: 1,087,954 incident dialysis patients from 2006 through 2015 were included. 68,711 patients (6%) recovered renal function during the study. The incidence of RRF within 6m, accounting for 77% of all RRF, was 9.0 cases/1,000 person-months (95% CI, 8.9-9.1). Mean patient age with RRF was 62±15 y compared with 63±15 y for those without RRF (p<0.001). Males, non-Hispanic Whites, younger patients, those receiving hemodialysis as first modality, patients with higher eGFR, and patients with central catheters had greater likelihood of RRF, compared with their counterparts (all p<0.001). Acute interstitial nephritis (AIN; percent with RRF, odds ratio and 95% CI: 40%, 12.8, 11.7-14.0), acute tubular necrosis (ATN; 35%, 8.8, 8.6-9.1), nephrotoxins (18%, 5.1, 4.7-5.5), traumatic or surgical loss of kidney (19%, 4.8, 4.1-5.6), and multiple myeloma (16%, 3.5, 3.3-3.7) had higher odds of RRF, while patients with cystic kidney (1%, 0.4, 0.3-0.4) had lower odds of RRF, compared with patients with diabetes (4%) as primary cause of ESRD. AIN and ATN patients together account for 3% of incident patients, but comprised 18% of all recoveries. At 3y, 53% of recovered patients were still alive and not on ESRD therapy, 32% had died, and 15% were living on ESRD therapy.

Conclusions: RRF is not uncommon, occurs later than previously reported, and is associated with acute kidney injury diagnoses. A majority of patients survive after RRF, but more than 45% of patients with RRF return to ESRD and/or die within the following 3y. To better detect RRF earlier, for the benefit of patients, practitioners and dialysis providers, patients with acute diagnoses and abrupt presentations should receive more intensive monitoring after initiation of dialysis than is currently practiced.

Funding: NIDDK Support

SA-OR036

Impact of Transition of Care Visits on Readmission Rates in Dialysis Patients
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Background: End stage renal disease (ESRD) patients discharged from an acute care facility have 30-day readmission rates that approach 30% (USDS, 2015). In a fee for service environment, the Centers for Medicare & Medicaid Services (CMS) Transitional Care Management Services cannot be submitted by a physician billing for ESRD Monthly Capitation Payment services. Through the Comprehensive ESRD Care (CEC) Model, FMCNA has partnered with CMS to identify, test, and evaluate new ways to improve care for Medicare beneficiaries with ESRD. Utilizing the ESRD Seamless Care Organization (ESCO) care coordination waiver, we hypothesized that nephrology providers could feasibly conduct ESRD specific Transition of Care (TOC) visits that would lower readmission rates. We are obligated to disclose that the statements contained in this document are solely those of the authors and do not necessarily reflect the views or policies of CMS. The authors assume responsibility for the accuracy and completeness of the information contained in this document.

Methods: We established an ESRD specific TOC template. Nephrology providers were paid a care coordination fee for completing the TOC within 14 days of discharge. We analyzed claims data from May-2016 to Dec-2016 using a 3 month claims run out for 6 ESCOs representing 7,248 discharges. We determined the frequency of TOC visits conducted by the nephrology practice within 14 days of discharge. We measured 30-day readmission rates for each ESCO for the patients who had a TOC visit within 14 days of discharge.

Results: Completion of the TOC visits varied among the 6 ESCOs from a low of 11% to a high of 36%; TOC completion rates were inversely correlated with the ESCOs number of discharges (correlation coefficient -0.95). Among 5 ESCOs, 30-day readmission rates were 0.6% to 4.2% lower in patients who received a TOC visit; at one ESCO there was 0.9% increase.

Conclusions: Conducting a formal TOC visit within 14 days of discharge is associated with reductions in 30-day readmission rates. Smaller ESCOs completed TOC visits at a higher rate as compared to larger ESCOs.

Funding: Commercial Support - Fresenius Medical Care North America

SA-OR037

Pre-ESRD Nephrology Care Associated with Larger Survival Benefit for Black Compared to White Patients on Hemodialysis (HD)
Jennifer L. Bragg-Gresham,[3] Shervin Assari,[3] Kevin He,[2] Austin G. Stack,[1] Rajiv Saran.[3] *[1]Graduate Entry Medical School, University of Limerick, Limerick, Ireland; [2]Kidney Epidemiology and Cost Center, University of Michgian, Ann Arbor, MI; [3]University of Michigan, Ann Arbor, MI.*

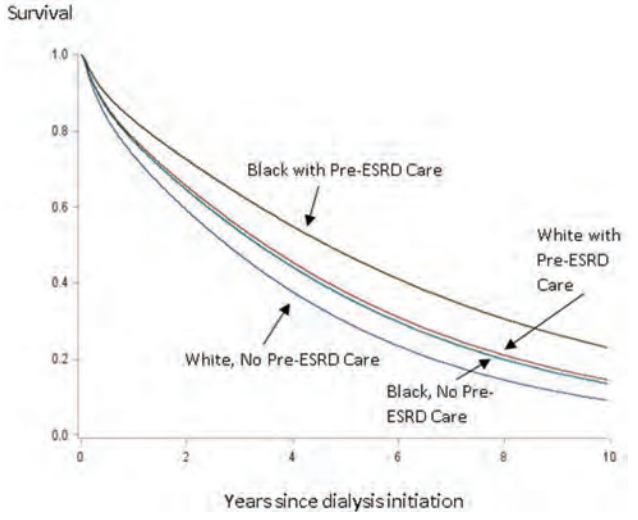
Background: Recent literature suggests that psychosocial resources, medical risk factors, and treatments may have differential effects across racial groups. We sought to compare the potential impact of pre-ESRD Nephrology care on all-cause mortality by race (Black versus White) among patients newly enrolled in the United States Renal Data System (USRDS) over the last decade.

Methods: Using data on 791,248 incident HD patients initiating treatment from 2006-2015, we examined the association between pre-ERSD Nephrology care (defined as 'no care' versus 'any pre-ESRD nephrology care') on long-term survival, adjusting for age, sex, and comorbidities for both Black and White race groups. Cox regression was used to test the multiplicative effect of race and pre-ESRD care, by interaction. Patients were followed for mortality through 2015 (average follow-up was 2.8 years).

Results: Overall, fewer Black patients had pre-ESRD Nephrology care compared to White patients (53.1% vs. 60.1%). Although pre-ESRD care was associated with lower hazard of mortality in both race groups (p<0.0001), a significant interaction was found, i.e., lower hazard for mortality was associated with Pre-ESRD care for Black (HR=0.73) versus White patients (HR=0.81; p for interaction <0.0001). Survival curves are shown in the Figure.

Conclusions: This finding advocates for promotion of Pre-ESRD care for Black patients, particularly given their lower chance of getting such services, compared to Whites. Future work will expand this to study other race categories and Hispanic ethnicity to gain insight into differential health gain across sub-populations to guide public health priorities toward reducing disparities.

Funding: NIDDK Support



SA-OR038

Scheduled versus Emergency Dialysis in ESRD Saves Lives and Lowers Utilization: A Quasi-Randomized Study Oanh K. Nguyen,[1] Miguel A. Vazquez,[1] Lakeesha Charles,[2] Joseph R. Berger,[1] Henry Quinones,[1] Richard C. Fuquay,[3] Ethan Halm,[1] Anil N. Makam.[1] *[1]UT Southwestern Medical Center, Dallas, TX; [2]Parkland Health & Hospital System, Dallas, TX; [3]Dallas Nephrology Associates, Dallas, TX.*

Background: In many states across the U.S., individuals with end-stage renal disease (ESRD) lacking federal funding for scheduled dialysis instead receive intermittent emergency dialysis only for life-threatening indications. The effects on health outcomes and utilization compared to scheduled dialysis are unknown. We sought to compare these strategies through a natural experiment among individuals with ESRD on emergency dialysis who were newly eligible and applied for private insurance coverage for scheduled dialysis, with nearly half receiving coverage in a quasi-randomized fashion.

Methods: Retrospective cohort study of 193 adults on emergency dialysis in Dallas, Texas who applied for private insurance in February 2015. Patient characteristics and outcomes were ascertained using medical record and all-payer regional claims data. Overall, 112 were enrolled in scheduled dialysis; 81 were declined for non-patient-related reasons (i.e., their dialysis center declined to participate) and remained on emergency dialysis (control). We compared emergency department (ED) visits and hospitalizations in a 6-month baseline and a 12-month follow-up period after enrollment with a 1-month washout, using intention-to-treat negative binomial difference-in-differences (DiD) regression analyses.

Results: At baseline, the scheduled group was younger (45 vs. 52 yrs., p<0.001), had more frequent dialysis (1.0 vs 0.6 sessions/week, p=0.04), more ED visits (7.6 vs. 4.3 median visits/month, p<0.001), and similar hospitalizations (median 2.5 vs. 3.2 per 6 months, NS) vs. controls. After enrollment, the scheduled group had fewer deaths (6% vs. 16%, p<0.01). In adjusted analyses, compared to baseline, the scheduled group had a larger net decrease in ED visits (-6.7 vs. -0.1 visits/month, p<0.001; DiD of 6.6 fewer visits/month, 95% CI 5.5-7.7) and similar net decrease in hospitalizations (-1.7 vs. -1.4 per 6 months, p=0.46) during follow-up vs. controls.

Conclusions: In this quasi-randomized controlled study, individuals enrolled in a scheduled dialysis program had far lower rates of death and ED utilization in the year after enrollment compared to those remaining on emergency dialysis, despite being sicker at baseline. Universal scheduled dialysis improves health outcomes and may also be more cost-effective.

Funding: Other NIH Support - NIH/NCATS KL2 TR001103

SA-OR039

Opiate Analgesics and Adverse Outcomes in Hemodialysis Patients Julie H. Ishida, Charles E. McCulloch, Michael Steinman, Barbara A. Grimes, Kirsten L. Johansen. *UCSF, San Francisco, CA.*

Background: Pain is a highly prevalent symptom in hemodialysis patients and has been associated with worse quality of life and survival. Hemodialysis patients may be particularly vulnerable to adverse events from the use of opiate analgesics, but studies evaluating their risk are scare and have not examined associations with dose or specific agents.

Methods: From the USRDS, we identified 140,899 Medicare-covered adults on in-center hemodialysis with Part D coverage in 2011. Using Cox regression models in which we adjusted for demographics, comorbidities, number of medications, and use of potentially confounding concomitant medications (e.g., sedatives/hypnotics), we investigated the association between receipt of opiate analgesics, modeled as a time-varying exposure, and time to first emergency room visit or hospitalization for altered mental status (AMS), fall, and fracture defined by ICD-9 and CPT codes. We evaluated risk according to average daily dose (high >60 mg, low <=60 mg, and per 10 mg) and specific agents (hydrocodone, oxycodone, tramadol, codeine, hydromorphone, fentanyl, morphine, methadone per 10 mg). Doses are expressed in standardized oral morphine equivalents (OME), and exposure was time-lagged (i.e., ascertained from the prior day) for fall and fracture to account for the possibility of effect/cause.

Results: There were 90,124 (64%) patients who received opiate analgesics and 39,173 (28%) who had an episode of AMS, fall, or fracture in 2011. Opiate use was associated with risk of AMS, fall, and fracture in a dose-dependent manner (Table). Agents were associated with significantly higher rates of adverse outcomes (hazards per 10 mg OME): all agents for AMS (2-22% higher hazard); hydromorphone, hydrocodone, oxycodone, tramadol, and morphine for fall (2-7% higher hazard); and hydrocodone, oxycodone, and tramadol for fracture (3-10% higher hazard).

Conclusions: Opiate analgesics are associated with a high risk of adverse outcomes in hemodialysis patients, even at lower doses and for agents recommended by guidelines. Future research intended to predict and mitigate risks of opiate use in this population is warranted.

Funding: NIDDK Support

Adverse Outcomes by Opiate Dose

	Hazard Ratio (95% Confidence Interval)		
	AMS	Fall	Fracture
<=60 mg vs. none	1.30 (1.24-1.35)	1.30 (1.22-1.38)	1.50 (1.38-1.62)
>60 mg vs. none	1.79 (1.68-1.90)	1.51 (1.37-1.65)	1.75 (1.54-1.99)

SA-OR040

Utilizing Symptom Targeted Intervention to Help Dialysis Patients Remain Vocationally Active Deborah S. Evans, Duane V. Dunn, Kathryn M. Aebel-Groesch, Jay Gervens, Deborah A. Benner. *DaVita, Inc, Denver, CO.*

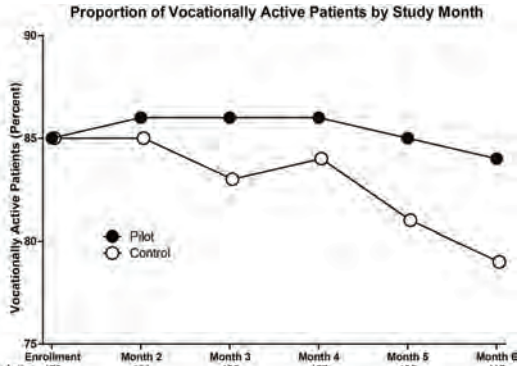
Background: Ongoing vocational activity among patients with end-stage renal disease receiving dialysis is associated with considerable benefits, including better financial/insurance status, higher quality of life, and greater likelihood of receiving a kidney transplant. In spite of these benefits, most dialysis patients are not vocationally active. Perceived barriers to vocational activity include lack of access to transportation, depression, and lack of motivation. Here, we tested the utility of social workers applying Symptom Targeted Intervention (STI) to mediate psychosocial challenges and support ongoing vocational activity among dialysis patients.

Methods: In this pilot study (2016-2017), 85 specifically trained social workers at a large US dialysis organization provided 6 or more STI counseling sessions, delivered over a period of ~10 weeks, to dialysis patients who were either vocationally active (employed, student/trainee, volunteer) or interested in becoming vocationally active. Following completion of STI, each patient was matched to a control subject (no STI) based on geographic area, vocational status, and dialysis vintage. Subjects were followed until the earliest of transplant, death, loss to follow-up, or 6 months post-enrollment.

Results: Of 246 patients who received STI in the pilot study, 210 were matched to eligible controls (15 were withheld from matching due to enrollment in additional intervention programs; appropriate controls could not be identified for the remainder). A larger proportion of pilot patients were vocationally active during follow-up as compared to controls.

Conclusions: Previous work has shown that STI benefits patients who display difficulty with adjustment to dialysis. Here, we demonstrate that proactive incorporation of STI by social workers may support ongoing vocational activity among patients on dialysis.

Funding: Commercial Support - DaVita, Inc



		Enrollment	Month 2	Month 3	Month 4	Month 5	Month 6
Pilot	Vocationally Active	179	181	180	157	132	117
	Vocationally Inactive	31	29	29	26	23	22
	Total	210	210	209	183	155	139
Control	Vocationally Active	179	178	174	158	126	112
	Vocationally Inactive	31	32	35	30	30	29
	Total	210	210	209	188	156	141

SA-OR041

Haemodiafiltration (HDF) Improves the Cardiovascular Risk Profile Compared to Conventional Haemodialysis (HD) in Children – The HDF, Heart, and Height (3H) Trial Rukshana Shroff,[1] Colette J. Smith,[2] Karolis Azukaitis,[3] Constantinos J. Stefanidis,[4] Nur Canpolat,[5] Saoussen Krid,[6] Mieczys?aw P. Litwin,[7] Franz S. Schaefer.[8] *[1]Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom; [2]University College London, London, United Kingdom; [3]Vilnius University, Lithuania, Vilnius, Lithuania; [4]A. and P. Kyriakou Childrens Hospital Athens, Greece, Athens, Greece; [5]Istanbul University Cerrahpasa Faculty of Medicine, Istanbul, Turkey; [6]Hôpital, Paris, France; [7]The Children's Memorial Health Institute, Warsaw, Warsaw, Poland; [8]University of Heidelberg, Heidelberg, Germany. Group/Team: On behalf of International Pediatric Hemodialysis Network and 4C study investigators.*

Background: Fluid overload, hypertension and cardiovascular disease are common in children on dialysis. In adults, HDF is shown to reduce cardiovascular mortality, but causes for this are not clear and data in children are scarce.

Methods: We performed a non-randomized parallel-arm clinical trial within the International Pediatric Hemodialysis Network registry to assess changes in fluid status, BP, biochemistry and cardiovascular measures in children on HDF compared with conventional HD. The primary outcome measure was change in carotid intima media thickness standard deviation score (cIMT SDS) at 1-year. (ClinicalTrials.gov NCT02063776)

Results: 190 children (from 28 centres across Europe and North America) were recruited, and 179 fulfilled inclusion criteria. 134 children (78 on HD and 56 on HDF) completed one-year follow-up. There was no difference between HD and HDF groups in age, gender, underlying renal disease, dialysis vintage, access type, blood flow or residual renal function. There were 45 drop-outs, mainly (75%) due to transplantation; there were no deaths. The median convective volume achieved in the HDF group was 13.3 (inter-quartile range 12.4 to 14.5) ml/m^2/session. At 1-year, children on HDF had lower cIMT SDS and lower pulse wave velocity-SDS compared to those on conventional HD (1.88 vs 2.64; p=0.007 and 0.77 vs 1.99, p<0.001 respectively). Annualised change in cIMT SDS was 10-fold lower in HDF compared to HD (0.013 vs 0.48; p=0.002). 24-hour mean arterial pressure, left ventricular mass index and parathyroid hormone level were also significantly lower on HDF (p<0.01 for all). On univariable analysis the HDF vs HD group, serum phosphate and PTH and dialysate water quality significantly associated with cIMT SDS. On multivariable linear regression analysis, the annualised change in cIMT SDS was 0.3 higher (95%CI -0.01 to 0.61) and PWV SDS was 0.26 higher (95%CI -0.4 to 0.9) in children on HD compared to those on HDF. All data were adjusted for centre and baseline cIMT-SDS.

Conclusions: In children, HDF attenuates the progression of vascular disease compared to conventional HD. This may be due to improved fluid and BP control as well as normalisation of phosphate and PTH levels.

SA-OR042

Using KDIGO Criteria, Beta-2 Microglobulin Predicts the Development of AKI Kevin T. Barton, Hongjie Gu, Charles Goss, Dennis Dietzen, Aadil K. Kakajiwala, Vikas R. Dharnidharka. *Washington University School of Medicine, St Louis, MO.*

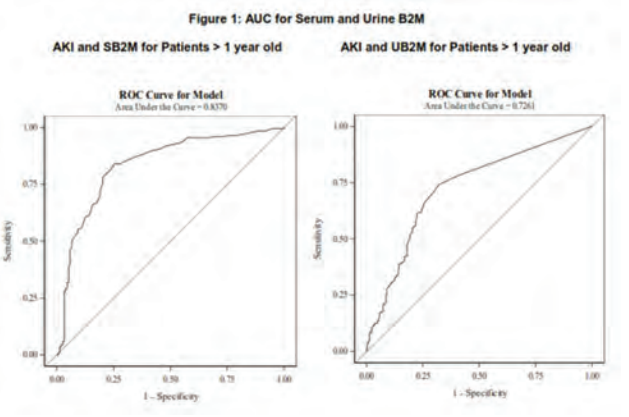
Background: Beta-2-microglobulin (B2M) is a functional marker of proximal tubular injury and glomerular filtration. Analyses using older/non-standardized definitions have shown low efficacy of B2M as a predictor of AKI. We assessed if elevated levels of B2M would predict the diagnosis of or recovery from AKI.

Methods: We performed a retrospective study including children >1 year, between 01/2011 and 12/2015, who had urine (UB2M) and/or serum B2M (SB2M) measured by immunoturbidometry. We defined AKI using changes in serum creatinine (sCr) based on KDIGO criteria and urine output <0.5 mL/kg/hr for 24 hours. We defined recovery from AKI as return to baseline serum creatinine within six months of AKI. We gathered data on baseline, maximum and recovery sCr, SB2M, and UB2M. We calculated receiver-operating-characteristic (ROC) area under curves (AUC).

Results: 245/529 patients developed AKI. SB2M and UB2M predicted AKI development with an ROC-AUC of 0.84 and 0.73 respectively (Figure 1). Patients had a graded higher median SB2M and UB2M with each higher AKI Stage. SB2M and UB2M differentiated between Stage I and Stage III AKI (both p-value <0.0001). Serum B2M also differentiated between Stage II and Stage III AKI (p-value <0.0001). However, neither UB2M nor SB2M levels predicted recovery from AKI. Only older age and need for dialysis predicted less than complete recovery after AKI (HR: 0.97 (CI 0.94, 0.99) and 0.39 (CI 0.23, 0.61) respectively).

Conclusions: Using the latest AKI definition, serum B2M performs well to predict AKI. Given the relative ease and lower cost of B2M we suggest more widespread use of B2M for the detection of AKI.

Variable	AKI (Median [IQR])	No AKI (Median [IQR])	p-value
Serum B2M (mg/L)	4.3 (2.8,9.6)	1.7 (1.3,2.5)	< 0.0001
Urine B2M (mg/L)	3.2 (0.4, 16.8)	0.2 (0.2, 0.9)	< 0.0001



SA-OR043

The Effect of Prenatal Lead Exposure and Gestational Age on Blood Pressure among Children Alison P. Sanders,[2] Katherine Svensson,[2] Chris Gennings,[2] Chitra Amarasiriwardena,[2] Priyanka Basnet,[2] Maria L. Pizano,[5] Lourdes Schnaas,[5] Marcela Tamayo y ortiz,[4] Lisa M. Satlin,[2] Andrea A. Baccarelli,[3] Martha M. Tellez-Rojo,[1] Robert O. Wright.[2] *[1]National Institute of Public Health, Cuernavaca, Mexico; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]Columbia University, New York, NY; [4]National Council of Science and Technology (CONACYT) - National Institute of Public Health (INSP), Cuernavaca, Mexico; [5]National Institute of Perinatology, Mexico City, Mexico.*

Background: Prenatal metal exposure occurs during a susceptible period of renal development and may program later life cardiovascular and renal disease. Our objective was to evaluate the association between prenatal lead exposure and gestational age on childhood blood pressure measured at 4 years of age.

Methods: Maternal blood lead levels (BLLs) collected in the second trimester were analyzed via inductively coupled plasma-mass spectrometry. Resting blood pressure was obtained using a Dinamap automated oscillometer from 565 children between 4 and 6 years of age in the PROGRESS cohort located in Mexico City, Mexico. We performed nonlinear piecewise regression to examine the association between prenatal lead levels and gestational age on children's systolic blood pressure (SBP) adjusting for child's age, sex, and height.

Results: Maternal second trimester BLLs ranged from 0.7 to 17.8 μg/dL with 112 (20%) above the CDC guideline level of 5 μg/dL. We identified a threshold lead level of concern of 2.5 μg/dL. When data were stratified at this lead level, shorter gestations were associated with increased SBP for subjects with BLLs ≥ 2.5 μg/dL, whereas shorter gestations were not associated with SBP for BLLs < 2.5 μg/dL. Specifically, for BLLs ≥ 2.5 μg/dL, SBP was 1.6 (95%CI: 0.4, 2.9) mmHg higher per each week shorter gestation among gestations shorter than 36.9 weeks; and among gestations longer than 36.9 weeks, this relationship was attenuated yet remained significant [β: 0.9, 95%CI (0.2, 1.6)].

Conclusions: Prenatal lead exposure may contribute to subclinical changes in the developing kidney or cardiovascular system leading to elevated SBP in childhood. We found that higher prenatal blood lead modified the association between shorter gestation and higher blood pressure. Ongoing studies will assess renal molecular changes due to early life lead exposure.

Funding: Other NIH Support - NIEHS

SA-OR044

Long-Term Renal Outcomes in Children Who Had Surgical Repair of Congenital Heart Disease Chirag R. Parikh,[7] Jason H. Greenberg,[6] Eric McArthur,[1] Heather Thiessen Philbrook,[6] Ron Wald,[5] Michael Zappitelli,[3] Rahul Chanchlani,[4] Amit X. Garg.[2] *[1]Institute for Clinical Evaluative Sciences, London, ON, Canada; [2]London Health Sciences Centre, London, ON, Canada; [3]McGill University Health Centre, Montreal Children's Hospital, Montreal, QC, Canada; [4]None, Hamilton, ON, Canada; [5]St. Michael's Hospital, Toronto, ON, Canada; [6]Yale University, New Haven, CT; [7]Yale University and VAMC, New Haven, CT.*

Background: The risk of mortality in children who require surgery for congenital heart disease (S-CHD) has markedly reduced in recent years due to advances in pediatric and surgical care. However, there are limited data on long-term kidney outcomes in children after S-CHD compared with the general population of children.

Methods: A registry-based, matched-cohort study was conducted across 7 administrative Canadian databases. Children were included if they were born between April 1, 2002 and March 31, 2015 and underwent surgery for CHD. Follow-up and comorbidity data were collected until March 2015. Children serving as controls (10 controls for each patient with S-CHD), were matched for age, sex, neighborhood income quintile, and county, and were randomly selected from the general population. Survival analyses were performed with Cox proportional hazards models.

Results: Of the 3600 patients with a diagnosis of S-CHD, 1595 were female (44.3%). Median age at first surgery was 150 (IQR, 40-252) days and 21.8% of the children were low birthweight (<2500 grams). The median (IQR) follow-up time was 5.9 (2.9-9.0) years. 52 (1.4%) children reached ESRD in follow-up. The 10-year cumulative incidences of hypertension and CKD were 12.9% and 2.1%, respectively. The hazard ratios for renal outcomes and mortality in children with S-CHD compared with controls were significantly higher (Table). According to RACHS-1 severity classifications, the group of patients with the most severe complex defects (RACHS-1 category 4) had the highest risk for death and renal outcomes. Trends in relative increase in risk of renal outcomes and mortality were also seen associated with younger age at surgery (<150 days), but not with income quintile or preterm status at birth.

Conclusions: Despite dramatic recent improvements in outcomes after S-CHD, the incidence of long-term hypertension, CKD, ESRD and mortality remains high in these patients compared to matched controls. Further interventions aimed at improving renal outcomes in this vulnerable group are required.

Funding: NIDDK Support, Veterans Affairs Support

Table: Long-Term Outcomes following Surgical Repair of Congenital Heart Disease

Outcome	Status	N	No. of events	%	Incidence rate per 10000 person-years	Hazard Ratio (95% CI)	P Value
Hypertension	No CHD	34520	260	0.75%	12.53	Ref	<0.0001
	S-CHD	3452	336	9.73%	180.60	14.3 (12.1-16.9)	
CKD	No CHD	35740	42	0.12%	1.96	Ref	<0.0001
	S-CHD	3574	48	1.34%	23.32	12.3 (8 -18.7)	
ESRD	No CHD	36000	6	0.02%	0.28	Ref	<0.0001
	S-CHD	3600	52	1.44%	25.80	86.5 (37.5-201.6)	
Death	No CHD	36000	35	0.10%	1.62	Ref	<0.0001
	S-CHD	3600	140	3.89%	69.04	42.3(28.2-61.4)	

SA-OR045

Amniotic Fluid Peptide Biomarkers for In Utero Prediction of Postnatal Renal Function in CAKUT Julie Klein,[1] Benedicte Buffin-Meyer,[1] Franck Boizard,[1] Pedro Magalhães,[2] Petra Zürbig,[2] Benjamin Breuil,[1] Elena N. Levtchenko,[3] An Hindryckx,[3] Lounis Nadia,[4] Francoise Auriol,[4] Jean-loup Bascands,[1] Stéphane Decramer,[4] Joost Schanstra.[1] *[1]Inserm U1048, Toulouse, France; [2]Mosaiques Diagnostics GmbH, Hannover, Germany; [3]University Hospitals Leuven, Herent, Belgium; [4]Hopital des Enfants, Toulouse, France. Group/Team: Bioman-consortium.*

Background: Clinical management of fetuses with bilateral CAKUT is hampered by the lack of methods able to predict evolution towards kidney failure. Here we explored the amniotic fluid (AF) peptidome of 152 bilateral CAKUT pregnancies in order to identify biomarkers predictive of disease progression.

Methods: Using capillary electrophoresis coupled to mass spectrometry, comparison of the AF peptidome from 32 fetuses with normal postnatal renal function at 2 years and 18 fetuses with early renal failure allowed the identification of 59 differentially abundant peptides, including fragments from extracellular matrix proteins, osteopontin, proSAAS or thymosin beta-4.

Results: Modelling the 59 peptides into a random forest classifier combined with clinical features (AF volume and the age of the fetus at the time of sampling) predicted the renal outcome at 2 years in a separate validation cohort of 68 CAKUT fetuses with 89% sensitivity, 98% specificity and a positive likelihood ratio of 44. Next, we used the classifier to discriminate 34 CAKUT fetuses subjected to termination of pregnancy (TOP) but where fetopathology analysis either failed to demonstrate severe renal damage or was absent or inconclusive. The classifier scores suggested that TOP without severe renal damage could have been avoided in 80% of the cases. In addition, the classifier predicted 55% of absent/inconclusive fetopathology as having severe postnatal outcome and 45% with normal function. Taking into account likelihood ratio and sensitivity, we can speculate that approximately 40% of these fetuses with non-interpretable fetopathology were subjected to TOP while most likely evolving to normal postnatal renal function.

Conclusions: We believe that identification of the 59 AF peptide biomarkers is a significant step forward for antenatal prediction of the postnatal renal function outcome in CAKUT fetuses and should be of great help for early prenatal counsellingand improved clinical management of CAKUT pregnancies, hence alleviating the psychological burden imposed on the parents. [Equal contribution JK and BBM].

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-OR046

Survival and Morbidity of Children with Posterior Ureteral Valves Gina Lockwood,[1,2] Katherine W. Herbst,[1] Cynthia J. D'Alessandri-Silva.[1,3] *[1]Connecticut Children's Medical Center, Hartford, CT; [2]Urology, University of Connecticut Health Center, Farmington, CT; [3]Pediatrics, University of Connecticut Health Center, Farmington, CT.*

Background: Posterior urethral valves (PUV) is a severe urologic condition causing a spectrum of sequelae. PUV can lead to end-stage renal disease, dialysis, renal transplantation, and premature death. Predicting outcomes is challenging as prognostic measures remain imprecise. We aimed to describe outcomes for children with PUV in United States children's hospitals.

Methods: The Pediatric Health Information System (PHIS) database was searched for children diagnosed with PUV (ICD-9 code 753.6; congenital urethral stenosis) with initial hospitalization between 1992 and 2006 in their first year of life. Valve ablation or mortality following urinary drain placement was used to confirm diagnosis of PUV. Primary outcomes of dialysis catheter placement, renal transplant and mortality were determined by disposition and ICD-9/ICD-10 codes found in subsequent hospitalizations through 12/31/2016. Dialysis catheter insertion was used as a proxy for dialysis treatments, as these are not generally captured in the PHIS dataset. Subjects from hospitals without a transplant program were excluded from transplant analysis.

Results: Our cohort included 754 males with median age upon hospitalization of 7 days (IQR 1-38 days). Over 90% were discharged at one month of age or less. The majority (621; 82%) did not experience any of the outcomes described, and 232 (37%) did not have a subsequent PHIS hospitalization. Of 60 (7.9%) subjects who underwent dialysis catheter placement, 34 (57%) did so during their initial hospitalization. Only 10 (16.7%) underwent placement at >5 years. Thirty-six (6.5%) subjects underwent renal transplant at a median age of 3.2 years (IQR 2.0-8.1 years), with 26 (43%) of those who underwent dialysis catheter placement undergoing transplantation. Twelve (33%) subjects underwent transplant after five years of age. Of 33 (4.4%) patients who died, 32 (97%) did so at <5 years, with 19 (58%) expiring during their initial hospitalization.

Conclusions: Relatively small but significant proportions of children with PUV at PHIS hospitals undergo dialysis, renal transplantation and/or premature death. Most outcomes occur at <5 years of age, as expected in those born with severe nephropathy. As risk factors for renal deterioration are studied, these statistics from a large cohort can help to counsel parents and guide physician management.

Funding: Clinical Revenue Support

SA-OR047

IL-6/Stat3 Signaling Promotes Antimicrobial Peptide Expression and Limits Epithelial Invasion and Ascending Infection by Uropathogenic Escherichia coli Sudipti Gupta,[6] Christina B. Ching,[4] Birong Li,[1] Hanna H. Cortado,[2] Ashley R. Jackson,[3] Kirk M. McHugh,[5] Brian Becknell.[5] *[1]Nephrology, Nationwide Children's Hospital, Columbus, OH; [2]Nephrology, Nationwide Children's Hospital, Columbus, OH; [3]Nephrology, Nationwide Children's Hospital, Columbus, OH; [4]Urology, Nationwide Children's Hospital, Columbus, OH; [5]Anatomy, Ohio State University, Columbus, OH; [6]Urology, Nationwide Children's Hospital, Columbus, OH.*

Background: The signaling networks regulating host antimicrobial activity during UTI are incompletely understood. Bacterial virulence varies inversely with IL-6 production during UTI, suggesting IL-6 signaling plays an important role in bacterial containment in infection. The specific contributions of IL-6 to host immunity against uropathogens, however, are unknown. We hypothesized that IL-6 activates the Stat3 transcription factor in infected urothelium, driving an antimicrobial program of gene expression with consequences on bacterial colonization of the urinary tract.

Methods: C57BL/6J, IL-6 deficient, or Stat3 conditional knockout mice were transurethrally inoculated with uropathogenic *E. coli* (UPEC). IL-6 production, Stat3 phosphorylation (pStat3), and antimicrobial peptide (AMP) mRNA expression were analyzed by ELISA, Western blotting, and qRT-PCR, respectively. Intracellular bacterial communities (IBC) were enumerated by beta-galactosidase staining. Bacterial invasion assays were performed in IL-6 or carrier treated human urothelial cells. The role of Tlr4 signaling in IL-6 signaling was established using C3H/HeJ mice (Lps-hyporesponsive) and C3H/HeOuJ (Lps-sensitive) controls. Chronic IL-6 depletion was evaluated by systemic administration of IL-6 neutralizing or isotype control antibody.

Results: Transurethral inoculation of UPEC leads to IL-6 secretion, urothelial pStat3, and activation of AMP transcription, in a Tlr4-dependent manner. Recombinant IL-6 elicits pStat3 and suppresses UPEC invasion in human urothelial cells. Systemic IL-6 administration promotes urothelial pStat3 and AMP expression in vivo. IL-6 deficiency leads to decreased urothelial pStat3 and AMP mRNA expression following UTI, accompanied by increased IBC formation and persistent bacteriuria. Moreover, chronic IL-6 depletion leads to increased renal bacterial burden and severe pyelonephritis in C3H/HeOuJ mice. Conditional Stat3 deletion results in reduced AMP mRNA levels and increased IBC formation following experimental UTI.

Conclusions: IL-6/Stat3 signaling drives a transcriptional program of antimicrobial gene expression in infected urothelium, with key roles in limiting epithelial invasion and ascending infection.

Funding: NIDDK Support, Private Foundation Support

SA-OR048

Large-Scale CNV Analysis Provides Insight into the Genomic Architecture of Congenital Anomalies of the Kidney and Urinary Tract Miguel Verbitsky,[8] Rik Westland,[18,8] Alejandra Perez,[8] Priya Krithivasan,[8] David Fasel,[8] Matt G. Sampson,[16] Friedhelm Hildebrandt,[1] Velibor Tasic,[12] Francesco Scolari,[15] Joanna Van Wijk,[18] Loreto Gesualdo,[14] Cecile Jeanpierre,[10] Marijan Saraga,[13] Ana cristina Simões e silva,[7] Susan L. Furth,[11] Craig S. Wong,[2] Anna Materna-Kiryluk,[19] Krzysztof Kiryluk,[8] Hakon Hakonarson,[3] Gian Marco Ghiggeri,[6] Feng Zhang,[5] Virginia Papaioannou,[8] Cathy Mendelsohn,[8] Ali G. Gharavi,[8] Simone Sanna-Cherchi.[8] *[1]Boston Children's Hospital, Boston, MA; [2]UNM, Albuquerque, NM; [3]Children's Hospital of Philadelphia, Philadelphia, PA; [5]Fudan University, Shanghai, China; [6]G. Gaslini Children Hospital, Genoa, Italy; [7]UFMG, Brazil, Belo Horizonte, Brazil; [8]Columbia University, New York, NY; [10]Inserm UMR1163/Imagine Institute, Paris, France; [11]The Children's Hospital of Philadelphia, Philadelphia, PA; [12]University Children's Hospital, Skopje, Macedonia (the former Yugoslav Republic of); [13]University Hospital in Split, Split, Croatia; [14]University of Bari, Altamura, Italy; [15]University of Brescia, Montichiari (Brescia), Italy; [16]University of Michigan, Ann Arbor, MI; [18]Vrije Universiteit University Hospital Amsterdam, Amsterdam, Netherlands; [19]Poznan University of Medical Sciences, Poznan, Poland.*

Background: Copy number variations (CNVs) play an important role in the pathogenesis of human birth defects.

Methods: We performed a genome-wide CNV study in 2,824 cases compared to 21,498 controls to elucidate the genomic landscape of disease across the whole phenotypic spectrum of CAKUT.

Results: CAKUT cases carried a significant increased burden of rare CNVs and were highly enriched for known genomic disorders (GD) compared to controls (OR 6.6, P=7.5x10^{-41}). Renal hypodysplasia (RHD) showed the highest enrichment (OR 12.7, P=8.5x10^{-50}), followed by obstructive uropathy (OU; OR 3.5, P=6.0x10^{-4}), and posterior urethral valves (PUV; OR 5.9, P=2.2x10^{-3}). The most frequent GD loci in cases were 17q12 (n=26), 22q11.2 (n=17), the 1q21 (n=10), and 16p11.2 (n=9). While the 17q12, 22q11.2, and 1q21 were specific for RHD, the 16p11.2 showed high pleiotropy. At the loci where deletions were associated to RHD, duplications were associated to PUV or duplicated collecting system. Deletion mapping and *in silico* annotation identified *TBX6* as a candidate driver gene for CAKUT in the 16p11.2 deletion syndrome. We identified a *de novo* frameshift mutation in *TBX6* in a case with scoliosis and CAKUT. Analysis of mouse models for two different *Tbx6* alleles identified highly penetrant CAKUT recapitulating the high pleiotropic effect observed in humans with 16p11.2 deletions.

Conclusions: Our study describes the genomic landscape across the phenotypic spectrum of CAKUT, identifies recurrent CNVs for urinary tract developmental phenotypes and identifies *TBX6* as a genetic driver of CAKUT in the 16p11.2 deletion syndrome.

Funding: NIDDK Support

SA-OR049

Loss of Dicer Activity in the Peri-Wolffian Duct Stroma Leads to Increased Rates of Vesicoureteral Reflux Melissa J. Anslow,[3] Jacqueline Ho,[1] Carlton M. Bates,[2] Andrew J. Bodnar,[1] Sunder Sims-Lucas.[2] *[1]Children's Hosp of Pittsburgh of UPMC, Pittsburgh, PA; [2]Children's Hospital of Pittsburgh, Pittsburgh, PA; [3]Pediatric Nephrology, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA.*

Background: Vesicoureteral reflux (VUR) is associated with urinary tract infections, hypertension, and reflux nephropathy, which is the 4th most frequent cause of end-stage renal disease in children. The formation of the vesicoureteral junction occurs during development through induction of the ureteric bud from the Wolffian duct, which requires signaling factors from both the Wolffian duct and surrounding stroma. VUR is known to be heritable, but very little is known about which specific genes are involved. miRNAs are small, noncoding RNAs that regulate gene expression post-transcriptionally. We hypothesize that miRNAs are also important in vesicoureteral junction development and play a role in VUR.

Methods: We generated a transgenic mouse model with loss of Dicer in the peri-Wolffian duct stroma. Dicer is a key component in the production of mature, functional miRNAs. Euthanized cystograms and 3D reconstructions of the ureters and bladder were performed on mutants (Tbx18Cre+:Dicerflx/flx) and controls (Tbx18Cre negative littermates).

Results: Euthanized cystograms demonstrated significantly higher rates of VUR in the mutant mice compared to control, ~42% (5/12) of Dicer mutants as opposed to ~5% (2/37) of controls ($p < 0.01$). Of the mutant mice, two had bilateral VUR and three had unilateral VUR. Preliminary 3D reconstruction data suggests lower ureteral insertion into the bladder in mutants compared to control mice.

Conclusions: Together, these data suggest for the first time that miRNAs play a role in VUR, and that this may be due to lower ureteral insertion into the bladder in mutant mice. Future work will further assess for ureteric bud induction abnormalities and explore other potential etiologies of increased VUR in the mutant mice.

Funding: NIDDK Support, Other NIH Support - T32 Grant, Private Foundation Support

SA-OR050

Conditional Ablation of the Prorenin Receptor (PRR) in Nephron Progenitor Cells (NPCs) Results in Developmental Programming of Hypertension Renfang Song, Adam T. Janssen, Laura R. Kidd, Ihor V. Yosypiv. *Tulane University, New Orleans, LA.*

Background: The PRR is a receptor for renin and prorenin, and an accessory subunit of the vacuolar proton pump V-ATPase. Previously, we demonstrated that conditional ablation of the *PRR* in *Six2*$^{+}$ NPCs in mice (cKO) causes reduced congenital nephron endowment and early neonatal death (Song et al., 2016).

Methods: Here, we: 1) Investigated PRR-regulated genes and pathways in *Six2*$^{+}$ NPCs FACS-isolated from cKO and control (Co) kidneys on embryonic day E15.5 (n=3 pooled samples/genotype) using whole-genome-based analysis of gene expression; 2) Tested whether reduced *PRR* gene dosage in heterozygous *Six2*$^{PRR+/-}$ mice (Het) is associated with development of hypertension during later life; and 3) Tested the hypothesis that soluble PRR (sPRR), PRR cleavage product generated subcellularly and secreted into the urine by renal tubular cells, can contribute to BP programming in Het mice.

Results: Top 10 genes downregulated in cKO included *Hoxb8*, *Mspt*, *Mdfi* and *Gpc2*. The functional groups of differentially expressed genes within the altered gene set in cKO mice included genes involved in embryonic development, tissue/cell morphology, cellular assembly and organization, cell death and survival. While the number of glomeruli per kidney section was reduced at 2 months of age (69±4.0 vs. 178±4.9, $p<0.001$), conscious tail-cuff mean (95.5±2.8 vs. 70.4±3.8, $p<0.01$), systolic (143±5.3 vs. 113±6.5, $p<0.01$) and diastolic (67±4.5 vs. 51±4.0, $p<0.05$) arterial blood pressure was increased in Het compared with Co mice. Electron microscopy showed segmental thickening of the GBM with focal podocyte foot process effacement in Het mice. Urine sPRR levels measured by ELISA at 2 months of age were increased in Het compared to Co mice (262±28 vs. 146±13 pg/ml, $p<0.01$).

Conclusions: These data demonstrate that NPC PRR performs essential functions during nephrogenesis *via* control of hierarchy of genes that regulate critical cellular processes. Reduced nephron endowment, glomerular injury and augmented urine sPRR likely contribute to programming of hypertension in Het mice.

SA-OR051

Circulating miRNAs Profile and Risk of ESRD in Type 1 Diabetes Eiichiro Satake,[1] Marcus G. Pezzolesi,[2] Adam Smiles,[1] Monika A. Niewczas,[1] Andrzej S. Krolewski.[1] *[1]Joslin Diabetes Center, Boston, MA; [2]University of Utah, Salt Lake City, UT.*

Background: MicroRNAs (miRNAs) are short endogenous, non-coding RNA molecules which are expressed in a variety of human biofluids. These molecules are involved in gene regulation and play important roles in the pathogenesis of various renal diseases including diabetic nephropathy. However, miRNA signatures associated with diabetic nephropathy in Type 1 diabetes (T1D) has not been fully established. The objective of this study was to determine the circulating miRNA signature that is associated with risk of end- stage renal disease (ESRD) in T1D patients with chronic kidney disease (CKD).

Methods: The expression levels of 2,083 miRNAs from the human miRNA genome were measured in baseline plasma samples from 196 T1D patients with CKD3. We applied a new technology, High Throughput Genomics (HTG) Edge Sequence platform for miRNA sequencing and quantitation. Data were normalized by quantile normalization with sample weights.

Results: Among 196 patients, there were 90 patients who progressed to ESRD within 10 years follow- up. After filtering out miRNAs with low expression level, a total of 988 miRNAs were detectable in plasma samples from these study participants. To identify miRNAs associated with risk of ESRD, we performed fold change analysis and Cox model analysis. In total, there were 28 miRNAs significantly correlated to risk of ESRD (p-value <10^{-4}). For these candidate miRNAs, we divided them into 5 groups according to the Cox model analysis, and selected 5 representative miRNAs (exemplars) from each group. Multivariate Cox analysis showed that 4 of them were still associated with risk of ESRD after adjusting for baseline ACR and eGFR. Pathway analysis revealed that 3 exemplars were associated with insulin signaling pathway and/or the TGF-β pathway.

Conclusions: We discovered a profile of circulating miRNAs that is a very strong predictor/determinant of progression to ESRD in patients with T1D. This profile is represented by exemplar miRNAs which can be used to develop a multi-miRNA prognostic biomarker to predict time to onset of ESRD. Furthermore, some of these miRNAs can be used as therapeutic targets to prevent or treat progressive renal decline that leads to ESRD in diabetes.

Funding: NIDDK Support, Commercial Support - Novo Nordisk, Private Foundation Support

SA-OR052

Immunolocalization of Apolipoprotein L1 with Specific Antibodies Suzie J. Scales, Nidhi Gupta, Kathy J. Hotzel, Andrew A. Pierce, Georgios Koukos, Paul Moran, Michael T. Lipari, Xinhua Wang, Daniel Kirchhofer, Randall J. Brezski, Oded Foreman, Andrew S. Peterson. *Genentech, Inc., South San Francisco, CA.*

Background: Human Apolipoprotein (ApoL1) is the only secreted member of the apolipoprotein (ApoL) family (ApoL1-ApoL6), with 53% amino acid identity (63% similarity) to its closest relative, ApoL2. ApoL1 has been widely studied because of its protective role against *Trypanosoma* infections and the association of its variants G1 and

G2 with chronic kidney disease. To better understand the role of ApoL1 in kidney disease, it is important to identify its localization within the kidney. By immunohistochemistry, ApoL1 is reportedly strongest in proximal tubules but only just detectable in podocytes, the susceptible kidney cell type in ApoL1 nephropathies. There are conflicting reports of immunofluorescent ApoL1 subcellular localization using different commercially available antibodies: in the endoplasmic reticulum, on the plasma membrane, endosomes and even mitochondria. However, these antibodies have not been well characterized for cross-reactivity with other members of the ApoL family, giving rise to misleading results.

Methods: We generated monoclonal antibodies to ApoL1 and characterized their cross-reactivity with all members of the ApoL family in parallel with the commercially available polyclonal antibodies. ApoL family expression in podocytes was determined by Taqman analysis. ApoL1-specific antibodies were used to determine the true localization of ApoL1 in kidney and liver by immunohistochemistry, and in cultured podocytes by dual immunofluorescence labeling.

Results: All the commercially available antibodies previously published for localization studies cross-react with ApoL2, as did half of our monoclonals. Human podocytes express ApoL1, 2 and 6 mRNAs. In tissues, ApoL1 was specifically and robustly detected in serum, liver hepatocytes and kidney podocytes, but not in most proximal tubules. In cells, overexpressed ApoL1 and ApoL2 were found on opposite faces of the endoplasmic reticulum. Endogenous ApoL1 was also detected inside the endoplasmic reticulum (but not endosomes or mitochondria) of wild type podocytes and was enhanced by gamma interferon. The specificity of the staining was proven by its absence from ApoL1 knockout (CRISPR) podocytes.

Conclusions: Non-ApoL2 cross-reactive antibodies are essential for determining the true localization of endogenous ApoL1.

Funding: Commercial Support - Genentech

SA-OR053

Metabolomic Profiling of APOL1 Risk Alleles Adrienne Tin,[10] Girish N. Nadkarni,[3] Cheryl A. Winkler,[7] Erwin P. Bottinger,[1] Lesley Inker,[8] Andrew S. Levey,[8] Michael S. Lipkowitz,[2] Lawrence J. Appel,[4] Dan Arking,[6] Josef Coresh,[9] Morgan Grams.[5] *[1]Berlin Institute of Health, Berlin, Germany; [2]Georgetown University Medical Center, Washington, DC; [3]Ichan School of Medicine, New York, NY; [4]Johns Hopkins Medical Institutions, Baltimore, MD; [5]Johns Hopkins University, Baltimore, MD; [6]Johns Hopkins University School of Medicine, Baltimore, MD; [7]NCI, NIH, Frederick National Laboratory, Frederick, MD; [8]Tufts Medical Center, Boston, MA; [9]Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; [10]Epidemiology, Johns Hopkins University, Baltimore, MD.*

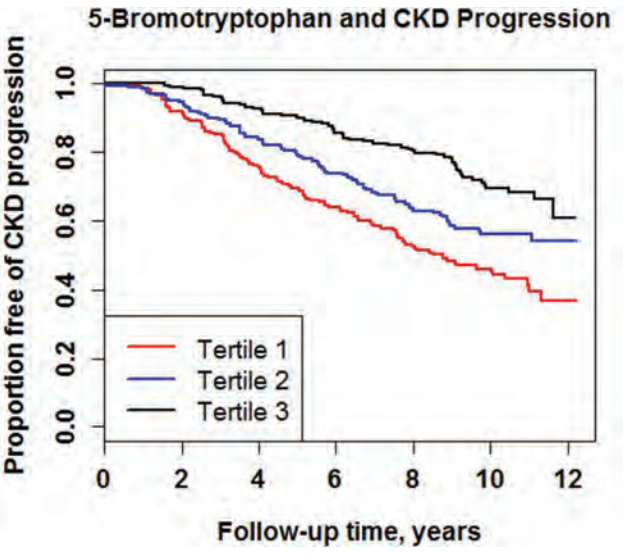
Background: Apoliprotein L1 (*APOL1*) risk alleles have been associated with chronic kidney disease (CKD) progression. Metabolomic profiling by *APOL1* risk allele status may inform our understanding of the pathogenesis of *APOL1*-associated kidney disease.

Methods: We evaluated the association between 1,133 serum metabolites identified via an untargeted approach at Metabolon and the number of *APOL1* high risk alleles (0,1, or 2) in the African American Study of Kidney Disease (AASK) (N=609). The significance threshold was set at 2.4e-4 based on principal component analysis. Significantly associated metabolites were then tested in a second cohort of African American patients with CKD (BioMe; N=680). Metabolites that replicated were evaluated as risk factors for CKD progression, defined as ESRD or at least doubling of serum creatinine.

Results: Of the six metabolites significantly associated with *APOL1* in AASK, one, 5-bromotryptophan, was also significant in BioMe, with lower levels associated with higher number of risk alleles (beta per *APOL1* risk allele, AASK: -0.23, p=2.5e-5; BioMe: -0.14, p=4.1e-3). In further analysis in AASK, lower levels of 5-bromotryptophan, a product of tryptophan metabolism, were associated with CKD progression adjusting for demographics, study assignments, baseline GFR, proteinuria, and *APOL1* high-risk status (adjusted HR by tertile [T]: T2 vs T1 (lowest): 0.86 (95% CI: 0.64, 1.16); T3 (highest) vs T1: 0.63, 95% CI: 0.45, 0.88, p for trend: 0.008, figure).

Conclusions: Metabolomic profiling identified an association of *APOL1* high risk alleles with lower 5-bromotryptophan levels, which was also associated with CKD progression, a finding which was consistent in two cohorts.

Funding: NIDDK Support



Kaplan-Meier estimates of proportion free of CKD progression by tertile of 5-bromotryptophan

SA-OR054

Apolipoprotein L1 Risk Variants and Soluble Urokinase Plasminogen Activator Receptor Synergistically Mediate CKD in African Americans Salim Hayek,[1] Kwi Hye Koh,[12] Morgan Grams,[4] David C. Wei,[11] Hyun Lee,[2] Ranadheer Dande,[12] Ha Won Lee,[12] Eunsil Hahm,[12] Vasil Peev,[12] Nicholas J. Tardi,[12] Vineet Gupta,[12] Mehmet M. Altintas,[11] Nikolina Stojanovic,[5] Cheryl A. Winkler,[7] Michael S. Lipkowitz,[3] Adrienne Tin,[9] Lesley Inker,[13] Andrew S. Levey,[13] Martin G. Zeier,[16] Barry I. Freedman,[14] Jeffrey B. Kopp,[8] Karl Skorecki,[10] Josef Coresh,[15] Sanja Sever,[6] Jochen Reiser.[12] *[1]Emory University School of Medicine, Atlanta, GA; [2]Univ. of Illinois at Chicago, Chicago, IL; [3]Georgetown University Medical Center, Washington, DC; [4]Johns Hopkins University, Baltimore, MD; [5]MGH, Charlestown, MA; [6]Massachusetts General Hospital, Charlestown, MA; [7]NCI, NIH, Frederick National Laboratory, Frederick, MD; [8]NIDDK, NIH, Bethesda, MD; [9]None, Baltimore, MD; [10]Rambam Health Care Campus, Haifa, Israel; [11]Rush University, Chicago, IL; [12]Rush University Medical Center, Chicago, IL; [13]Tufts Medical Center, Boston, MA; [14]Wake Forest University School of Medicine, Winston-Salem, NC; [15]Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; [16]Division of Nephrology, Ruprecht Karls University, Heidelberg, Germany.*

Background: Apolipoprotein L1 (APOL1) gene variants G1 and G2 but not the reference allele G0 are associated with an increased risk for chronic kidney disease (CKD) in African Americans, but the mechanisms are unknown. Soluble urokinase plasminogen activator receptor (suPAR) strongly predicts CKD.

Methods: We characterized *APOL1* genetic variants and plasma suPAR levels in two separate cohorts of African-American patients, the Emory Cardiovascular Biobank (EmCAB; $n = 487$) and the African American Study of Kidney Disease and Hypertension (AASK; $n = 607$). We studied the biochemical interaction between ApoL1, suPAR, and integrin β3 by immunoprecipitation and surface plasmon resonance (SPR).

Results: Here we show that individuals carrying the high-risk APOL1 genotype, i.e. 2 copies of risk variants, manifest a steeper decline in kidney function with increasing suPAR levels compared to individuals harboring low-risk genotypes. SPR identified high affinity interactions between ApoL1, suPAR and αvβ3 integrin. ApoL1 protein variants G1 and G2 exhibited higher affinity for suPAR-activated αvβ3 integrin than ApoL1 G0, and activated podocyte αvβ3 integrin. APOL1 G1 or G2 expression causes proteinuria in mice in a suPAR dependent manner.

Conclusions: The synergistic activation of αvβ3 integrin by circulating factor suPAR and ApoL1 G1 or G2 is a mechanism for CKD in patients of recent African ancestry.

Funding: NIDDK Support

SA-OR055

Metabolites Associated to Mortality and ESRD in a Brazilian CKD Cohort: The Progredir Study Silvia M. Titan,[3] Gabriela Venturini,[2] Kallyandra Padilha,[2] Paulo Lotufo,[4] Isabela M. Bensenor,[4] Ravi I. Thadhani,[1] Eugene P. Rhee,[1] Alexandre C. Pereira.[5] *[1]Nephrology Division, Massachusetts General Hospital, Boston, MA; [2]Laboratório de Cardiologia Molecular, Incor, Hospital das Clínicas, Faculty of Medicine, University of Sao Paulo, Sao Paulo, Brazil; [3]Nephrology Division, Faculty of Medicine, Sao Paulo University, Sao Paulo, Brazil; [4]Clinical Research Center, Universitary Hospital, Sao Paulo University, Sao Paulo, Brazil; [5]Laboratorio de Cardiologia Molecular, Incor, Hospital das Clínicas, Faculty of Medicine, University of Sao Paulo, Sao Paulo, Brazil.*

Background: Recent studies have evaluated metabolomics in relation to eGFR and to incident CKD. However, very few studies have evaluated metabolomics biomarkers in the setting of prevalent CKD and hard outcomes. **Objective**: To evaluate metabolites related to death, ESRD and a composite outcome of both in a CKD population (n=454).

Methods: Metabolomics was performed by GC and Mass Spectrometry. Metabolites were identified using Agilent Fiehn GC/MS Metabolomics and NIST libraries (Agilent MassHunter Work-station Quantitative Analysis, version B.06.00). From initial 10940 metabolites, we excluded those present <50% of the samples, leaving 293. We selected candidate metabolites by applying a FDR q value <0.05 in a Cox model on the composite outcome adjusted only for batch. Among the 34 selected metabolites, Cox regression models were built on death (n=93), ESRD (n=36) and composite outcome (n=126). Competing risk analysis was also performed for ESRD.

Results: Mean age was 68(±12)y, mean eGFR-CKDEPI was 38.4 (±14.6) ml/min/1.73m^2 and 57% were diabetic. After adjustment for batch, sex, age, DM and eGFR, 18 metabolites remained significantly related to the composite outcome, with lactose, D-threitol, docosahexaenoic acid (DHA), butanoic acid and mannitol among the top. For mortality only, 9 metabolites remained significantly associated with death, with D-malic acid (TCA cycle, OR 1.84, 95%CI1.32 – 2.56, p=0.0003), butanoic acid (colon microbiota; 1.59, 95%CI1.17 – 2.15, p=0.003), and DHA (omega3 fatty acid, OR 0.58, 95%CI0.39 – 0.88, p=0.009) among the top 3. For ESRD, 4 metabolites remained significantly associated to its risk: lactose, 2-O-glycerol-α-D-galactopyranoside, D-threitol and tyrosine (Table1), findings confirmed by the competing analysis except for D-threitol.

Conclusions: Our results identify specific metabolites related to hard outcomes in a CKD population. These results require confirmation.

Funding: Government Support - Non-U.S.

Table1. Cox proportional hazard models on the risk of ESRD after adjustment for batch, sex, age, eGFR and DM.

Metabolite (log2)	HR	95%CI HR		p
Lactose	1.68	1.21	2.34	.002
2-O-Glycerol-α-d-galactopyranoside	1.77	1.11	2.84	.02
D-threitol	2.74	1.04	7.20	.04
Tyrosine	0.59	0.35	0.98	.04

SA-OR056

The Global Burden of Kidney Disease Attributable to Air Pollution Benjamin C. Bowe,[1] Yan Xie,[1] Hong Xian,[1,2] Tingting Li,[3,4] Ziyad Al-Aly.[1,4] *[1]Clinical Epidemiology Center, Research and Development Service, Veterans Affairs St Louis Health Care System, St. Louis, MO; [2]Department of Biostatistics, Saint Louis University College for Public Health & Social Justice, St. Louis, MO; [3]Washington University in St. Louis, Saint Louis, MO; [4]Department of Medicine, Washington University School of Medicine, St. Louis, MO.*

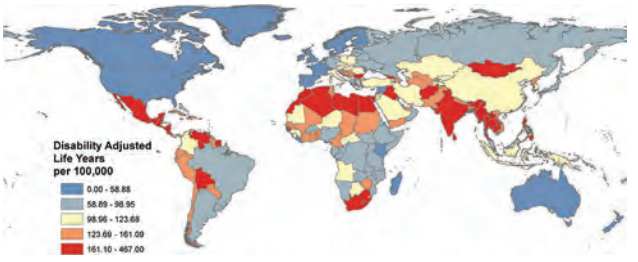
Background: We previously described an association between increased levels of fine particulate matter of <2.5 μm in aerodynamic diameter ($PM_{2.5}$) and risk of incident chronic kidney disease (CKD). This work aims to provide a quantitative assessment of the global burden of CKD attributable to elevated levels of $PM_{2.5}$.

Methods: We used the Global Burden of Disease (GBD) study methodologies to estimate the burden of CKD attributable to air pollution using the following measures: attributable burden of disease (ABD), years living with disability (YLD), years of life lost (YLL), and disability-adjusted life years (DALY). Relative risk was derived from our prior work. Population weighted $PM_{2.5}$ levels and incident rates of CKD for each country were curated from the GBD study publicly available data sources.

Results: Our estimate for the global annual burden of incident CKD attributable to elevated $PM_{2.5}$ was 10,784,514 (95% Uncertainty Interval: 7,821,109-13,857,623). YLD, YLL, and DALYs of CKD attributable to elevated $PM_{2.5}$ were 2,185,317 (1,418,442-3,061,477), 7,897,941 (5,471,081-10,514,433), and 10,083,258 (7,064,399-13,323,685), respectively. Standardized ABD in the 10 most populated countries showed Nigeria, Bangladesh, Pakistan, and India having high ABDs, exceeding 200 incident cases of CKD per 100,000 population. Populations in Mexico, Central America, Southeast Asia, India, and Northern Africa were amongst those with highest DALYs. For example, DALYs per 100,000 were 366.71 (251.05, 498.01) in Nicaragua and 353.93 (260.05-449.24) in Mexico, compared to 44.59 (24.07-65.74) in the United States.

Conclusions: The global toll of CKD attributable to air pollution is significant. The burden varies substantially by geography. Air pollution might at least partially explain the rise in incidence of CKD of unknown cause in many geographies around the world, and the rise in Mesoamerican nephropathy in Mexico, and Central America.

Funding: Veterans Affairs Support



The global burden of chronic kidney disease attributable to elevated $PM_{2.5.}$ expressed in disability adjusted life years (DALY) per 100,000 population.

SA-OR057

A Machine Learning Approach to Predicting ESRD Girish N. Nadkarni,[1] Edward Lee,[2] Oliver L. Fielding,[2] Teddy Cha,[2] Hai po Sun,[2] Chris Kipers,[2] William D. Paiva,[3] Elvena Fong,[3] Steven G. Coca.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]pulseData, Inc., New York, NY; [3]Center for Health Systems Innovation (Oklahoma State University), Stillwater, OK.*

Background: Risk prediction of end stage renal disease (ESRD) for population management and care intervention is both a research priority and unmet public health need. The use of electronic medical records (EMR) can be leveraged for improved assessment of ESRD onset. However, traditional risk scoring may not provide accurate risk prediction or complete population coverage if EMR data is incomplete. To handle missing data we developed a machine learning (ML) approach and compared it to traditional risk scoring in two EMR cohorts.

Methods: We utilized longitudinal data from the Mount Sinai Chronic Kidney Disease registry and a data set from the Center for Health Systems Innovation at Oklahoma State University provided by the Cerner Corporation. Using a random forest ML technique and imputation we can predict risk of ESRD (defined as administrative codes for dialysis or transplant). We then compared it to the Tangri 4-Variable kidney failure risk equation (KFRE) by comparing area under curve (AUC) measures and the percent of the population on which each metric can be calculated.

Results: We analyzed data from 318,292 patients. The median age was 65 years, 54% were female and 20% were African American. 60% of the cohort had at least one estimated glomerular filtration rate (eGFR) measurement before ESRD onset, however, only 6% had both an eGFR measurement and a urine albumin creatinine ratio (UACR) value before failure. The AUC of the 4-Variable KFRE was 0.89 (95% CI [0.88, 0.91]), while the ML approach had an AUC of 0.94 (95% CI [0.94, 0.95]). Importantly, the improvement in AUC was achieved while risk-scoring 10 times more of the population.

Conclusions: The ML approach outperformed traditional risk scoring such as the 4-Variable KFRE both in risk discrimination and in population coverage. Therefore, future efforts to risk stratify for population management and care intervention will benefit from utilizing ML approaches.

Table. Comparison of 4-Variable KFRE and ML approach

	4 Variable KFRE	Machine Learning Approach
Population coverage, n (%)	19,880 (6.3)	191,435 (60.1)
ESRD events, n(%)	846 (4.3)	12,870 (6.7)
eGFR, Mean (SD)	67.6 [49.6, 88.4]	65.3 [47.2, 86.9]
Follow Up in Years, Mean (SD)	3 [1.3, 5.3]	3.4 [1.4, 6.0]
AUC (95% Confidence Interval)	0.89 (0.88-0.90)	0.94 (0.93-0.95)
Number of features considered	4	>20,000

SA-OR058

Association between Pre-ESRD RAAS Blockade and Post-ESRD Mortality Miklos Z. Molnar,[4] Adnan Naseer,[6] Keiichi Sumida,[2] Ariel R. Riezenman,[5] Praveen Kumar Potukuchi,[4] Abduzhappar Gaipov,[4] Elani Streja,[1] Kamyar Kalantar-Zadeh,[3] Csaba P. Kovesdy.[4] *[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [2]Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; [3]University of California Irvine, School of Medicine, Orange, CA; [4]University of Tennessee Health Science Center, Memphis, TN; [5]University of Tennessee Health Science Center - Memphis, Memphis, TN; [6]VAMC, Germantown, TN.*

Background: Renin-Angiotensin-Aldosterone system inhibitor (RAASi) use is associated with slower progression of chronic kidney disease (CKD) and lower mortality in patients with CKD. However, the association between pre-end stage renal disease (ESRD) RAASi use and post-ESRD mortality is unclear.

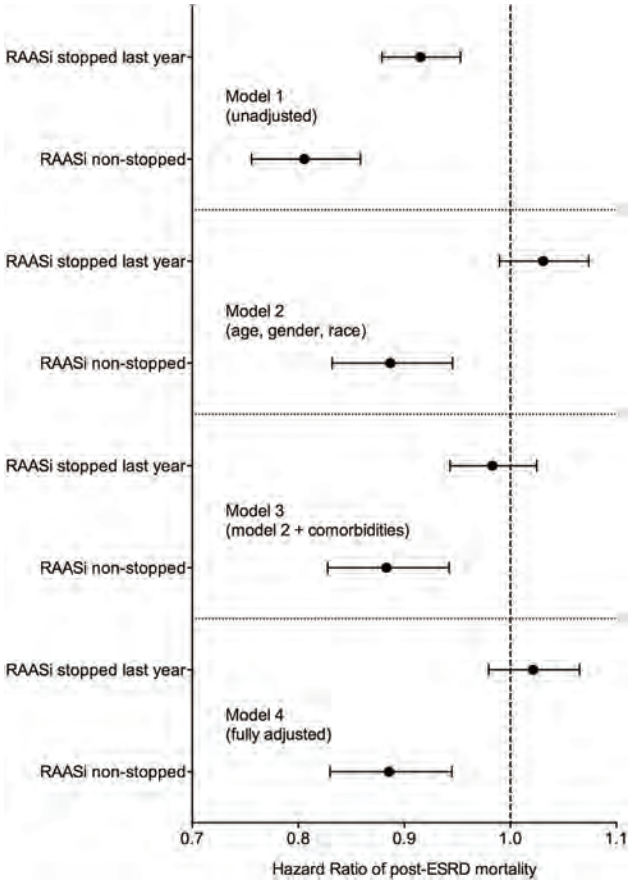
Methods: We examined 15,966 US veterans initiating dialysis during 2007-2014. We divided patients into three groups of RAASi use pattern in the last 3 pre-dialysis years: never exposed (n=7,294), exposed but discontinued in the last pre-dialysis year (n=6,833) and uninterrupted use (n=1,839). Associations of RAASi use patterns with all-cause mortality were examined in multivariable adjusted Cox models.

Results: Patients were 72±11 years old, 98% male, 23% African-American, and 65% diabetic. The all-cause mortality rates were 303 [95% CI 294-311]/1000 patient-years (PY) in patients never exposed to RAASi, 276 [95% CI 268-284]/1000PY in patients who discontinued RAASi and 240 [95% CI 227-254]/1000PY in patients on uninterrupted

RAASi, respectively, during a median of 2.2 years of follow-up. Uninterrupted RAASi use was associated with lower risk of death after dialysis start in unadjusted and various adjusted analyses (Figure).

Conclusions: Uninterrupted RAASi use prior to dialysis is associated with lower risk of death after dialysis start. There was no post-ESRD survival benefit observed in patients who discontinued RAASi in the final year before MHD initiation.

Funding: NIDDK Support



SA-OR059

High FGF-23 Is Associated with Coronary Calcification Only in Patients with High Adiponectin: From the KNOW-CKD Study Young Youl Hyun,[6] Kook-Hwan Oh,[4] Curie Ahn,[4] Yong-Soo Kim,[3] Tae-Hyun Yoo,[5] Soo Wan Kim,[1] Yeong Hoon Kim.[2] *[1]Chonnam National University Medical School, Dongku, Republic of Korea; [2]Inje University Medical School, Busan, Republic of Korea; [3]The Catholic University of Korea College of Medicine, Seoul, Republic of Korea; [4]Seoul National University Hospital, Seoul, Republic of Korea; [5]Yonsei University College of Medicine, Seoul, Republic of Korea; [6]Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea. Group/Team: KNOW-CKD Study Group.*

Background: Both FGF-23 and coronary artery calcification (CAC) are known as predictors of high cardiovascular and all-cause mortality. However, previous studies on the association between FGF-23 and CAC were inconclusive. Recently, it has been shown that adiponectin modulates renal handling of phosphate and calcium, important factors in vascular calcification. We hypothesized that adiponectin play a role in the effect of FGF-23 on CAC, and explored whether this association between FGF-23 and CAC is modified by serum adiponectin level in CKD patients.

Methods: This cross-sectional study analyzed 1,153 predialysis CKD patients from the KNOW-CKD cohort who measured coronary artery calcium scores (CACS), serum FGF-23 and serum adiponectin. Participants were divided into three groups according to their FGF-23 levels as follows: low <5.0 RU/ml, middle =5.0-29.9 RU/ml, and high ≥30.0 RU/ml. We evaluated the association between FGF-23 and CACS by multivariate Tobit regression and multivariate logistic regression in each group with lower half and upper half of adiponectin.

Results: Median [interquartile range] CACS were not different between low and high adiponectin group (2.0 [0.0-91.8] vs 0.4 [0.0-103.5], P=0.536). The CACS ratio comparing the high FGF-23 to the low FGF-23 was significantly increased in high adiponectin group, but not in low adiponectin group [3.25 (1.53-6.91) vs 1.07 (0.50-2.29), P for interaction=0.029). Similarly, the ORs for CAC in the high FGF-23 group compared to the low group were significantly increased only in the high adiponectin group (Table).

Conclusions: High serum FGF-23 was associated with CAC only in CKD patients with high adiponectin, but not in those with low adiponectin. Further studies are warranted to verify the role of adiponectin in FGF-23-related coronary calcification.

Funding: Government Support - Non-U.S.

ORs (95% CI) for CAC in different FGF-23 groups according to adiponectin level

	Low adiponectin			High adiponectin			P for interaction
	FGF-23			FGF-23			
CAC definition	low (n=252)	middle (n=202)	high (n=123)	low (n=181)	middle (n=206)	high (n=189)	
CACS>0	reference	0.88 (0.54-1.45)	1.11 (0.62-2.02)	reference	1.11 (0.67-1.87)	2.15 (1.21-3.80)	0.028
CACS≥100	reference	0.98 (0.56-1.74)	0.88 (0.45-1.73)	reference	1.62 (0.88-2.98)	2.34 (1.24-4.42)	0.070
CACS≥400	reference	1.25 (0.63-2.48)	0.68 (0.29-1.55)	reference	1.65 (0.74-3.67)	4.03 (1.82-8.91)	0.009

Adjusted for age, sex, BMI, hypertension, diabetes, dyslipidemia, current smoking, eGFR, hsCRP, urine protein to creatinine ratio, calcium, phosphorus, ALP, 25-OH-vit D, intact PTH

SA-OR060

HDL Cholesterol and Its Associations with Cause-Specific Mortality in Patients with CKD Sankar D. Navaneethan,[1] Jesse D. Schold,[2] Susana Arrigain,[2] Stacey Jolly,[2] Carl P. Walther,[1] Wolfgang C. Winkelmayer,[1] Joseph V. Nally.[2] *[1]Baylor College of Medicine, Houston, TX; [2]Cleveland Clinic, Cleveland, OH.*

Background: Recent data suggest a U-shaped association between HDL cholesterol (HDL-c) and death in CKD. However, whether the increased mortality in patients with extreme levels is driven by specific causes of death remains unclear. Herein, we examined the associations between HDL-c and cause-specific mortality in a large CKD population.

Methods: We included 38,377 patients with eGFR 15-59 ml/min/1.73 m² who had lipid levels measured within 1 year of CKD diagnosis. We ascertained overall and cause-specific deaths from the State mortality data and classified deaths into 3 major categories: a) cardiovascular; b) malignancy; and c) non-cardiovascular/non-malignancy causes. We fitted Cox regression models for overall mortality and separate competing risk models for each major cause of death category to evaluate their respective associations with categories of HDL-c (≤30, 31-40, 41-50 [referent], 51-60, >60 mg/dl). Separate analyses were conducted for men and women.

Results: During a median follow-up of 4.5 years, 9,665 patients died. HDL-c ≤30 mg/dl was associated with higher risk of all-cause and cardiovascular mortality in both sexes and higher risk of malignancy-related deaths in women (Table 1). HDL-c >60 mg/dl was associated with lower all-cause mortality in women only. HDL-c >60 mg/dl was associated with higher risk of non-cardiovascular/non-malignancy related deaths in men but not women. Exclusion of those with malignancy yielded results similar to primary analyses.

Conclusions: In a non-dialysis dependent CKD population, HDL-c ≤30 mg/dl was associated with higher all-cause and cardiovascular mortality, but not with non-cardiovascular mortality. HDL-c >60 mg/dl was associated with higher risk of non-cardiovascular/non-malignancy related deaths in men only. Additional studies examining the reasons for these different associations between HDL-c and cause-specific mortality, and potential effect modification by sex, are needed.

Funding: Commercial Support - Development of CCF CKD registry was suppoerted by an unrestricted educational fund to the Department of Nephrology and Hypertension from Amgen, Inc

Table 1. Associations between HDL-c (in mg/dl) and cause-specific mortality in CKD

	Women HR (95% CI)	Men HR (95% CI)
All-cause mortality^		
≤30	**1.40 (1.22, 1.60)**	**1.17 (1.04, 1.30)**
31-40	1.03 (0.93, 1.13)	0.99 (0.91, 1.07)
41-50	ref	ref
51-60	0.94 (0.86, 1.02)	1.04 (0.95, 1.14)
≥60	**0.89 (0.82, 0.98)**	1.07 (0.96, 1.19)
	Women SHR (95% CI)	**Men SHR (95% CI)**
Cardiovascular mortality^		
≤30	**1.39 (1.11, 1.73)**	**1.25 (1.05, 1.49)**
31-40	1.01 (0.86, 1.19)	1.11 (0.98, 1.27)
41-50	Ref	ref
51-60	0.94 (0.82, 1.08)	0.95 (0.82, 1.10)
≥60	0.96 (0.83, 1.11)	0.93 (0.79, 1.11)
Malignancy-related mortality^		
≤30	**1.44 (1.05, 1.96)**	1.26 (0.99, 1.59)
31-40	1.12 (0.91, 1.39)	1.09 (0.92, 1.29)
41-50	ref	ref
51-60	1.00 (0.83, 1.20)	1.09 (0.90, 1.32)
≥60	0.88 (0.72, 1.07)	1.21 (0.97, 1.51)
Non-cardiovascular/non-malignancy mortality^		
≤30	1.19 (0.94, 1.50)	0.95 (0.78, 1.14)
31-40	0.98 (0.84, 1.15)	0.82 (0.71, 0.94)
41-50	ref	ref
51-60	0.96 (0.84, 1.10)	1.16 (1.00, 1.35)
≥60	0.97 (0.84, 1.11)	**1.30 (1.09, 1.54)**

^Models adjusted for age, sex, race, eGFR, diabetes, hypertension, pre-existing cardiovascular disease, malignancy, congestive heart failure, peripheral vascular disease, cerebrovascular disease, BMI, ACE/ARB use, beta blocker use, statin use, albumin, hemoglobin, cholesterol, log triglycerides, smoking, and insurance.

SA-OR061

Differential Effects of STCH and HSP70 on the Stability and Maturation of NKCC2 Elie Seaayfan,[2] Sylvie Demaretz,[2] Martin Kömhoff,[1] Kamel Laghmani.[2] *[1]Philipps Univ Marburg, Marburg, Germany; [2]Centre de Recherche des Cordeliers, INSERM-U1138, UPMC, CNRS-ERL8228, Paris, France.*

Background: Mutations in the apically located Na-K-2Cl cotransporter, NKCC2, lead to type I Bartter syndrome, a life-threatening kidney disorder associated with salt wasting, hypokalemia, and metabolic alkalosis. Conversely, increased expression of NKCC2 promotes hypertension. We previously showed that export from the ER constitutes the limiting step in the maturation and cell surface expression of NKCC2 and its disease causing mutants. Yet the molecular mechanisms involved in this process remain obscure.

Methods: To identify the protein partners involved in ER associated degradation of NKCC2, we screened a kidney cDNA library through yeast two-hybrid using NKCC2 C-terminus as bait. NKCC2 protein expression was monitored in transiently transfected HEK cells, using immunoblot and confocal imaging. NKCC2 stability was assessed by cycloheximide chase assay.

Results: We identified STCH, a *constitutively* expressed member of the heat shock protein 70 family, as a specific binding partner of NKCC2. STCH is known to be a microsome-associated chaperone. Co-immunoprecipitation and co-immunolocalization experiments confirmed NKCC2-STCH interaction in HEK cells. Interestingly, they also identified the cytoplasmic and *stress-inducible* heat shock protein 70 (HSP70) as an interactor with NKCC2. STCH and HSP70 binding to NKCC2 involve mainly the immature form of the co-transporter and takes place at the ER. STCH co-expression heavily decreased total cellular WT NKCC2 protein and its disease associated folding mutants, in a dose dependent fashion, whereas HSP70 co-expression had the opposite effect. Cycloheximide chase assay showed that in cells over-expressing STCH, NKCC2 stability and maturation are heavily impaired. In contrast to STCH, HSP70 co-expression increased strikingly NKCC2 expression and maturation.

Conclusions: Our results are consistent with STCH and HSP70 having differential and antagonistic effects with regard to NKCC2 biogenesis, in particular under ER stress conditions. Most importantly, they may have an impact on our understanding and potential treatment of diseases related to aberrant NKCC2 trafficking and expression.

Funding: Government Support - Non-U.S.

SA-OR062

Modeling the Structural and Dynamical Changes of TRPV5 Caused by the A563T Variation Based on the Structure of TRPV6 Lingyun Wang, Ji-Bin Peng. *Div of Nephrology, Dept of Medicine, Nephrology Research and Training Center, University of Alabama at Birmingham, Birmingham, AL.*

Background: TRPV5 is an epithelial Ca^{2+} channel that plays a key role in the active Ca^{2+} reabsorption process in the kidney. The single nucleotide polymorphism (SNP) rs4252499 in TRPV5 gene has a minor allele frequency of around 0.17 in African descendants. This SNP results in an A563T variation in the sixth transmembrane (TM) domain of TRPV5. Our previous study indicates that the variation increases Ca^{2+} uptake and alters Mg^{2+} sensitivity of TRPV5. To understand the molecular mechanism, molecular simulations have been performed based on the structure of TRPV1. Recently, the structure of TRPV6 was determined. Since TRPV5 is much more similar to TRPV6 than TRPV1, new molecular simulation based on TRPV6 structure would provide more accurate information on the A563T variation in TRPV5.

Methods: Using MODELLER, TRPV5 model was set up based on a newly deposited structure of TRPV6 which shares 75% amino acid identity with TRPV5. This model contains all the six TM helices and the TRP domain of TRPV5. The A563T variation was introduced into TRPV5 using PyMOL. To mimic the membrane environment, the modeled TRPV5 was embedded in a lipid bilayer composed of 299 1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine (POPC) lipids using CHARMM-GUI, and then water molecules were added on both sides of the bilayer. Two 400 ns molecular dynamic simulations were performed using AMBER14.

Results: Consistent with TRPV1-based simulation, the current simulation indicates that the A563T variation results in increased contacts between residues 563 and V540, enhanced stability for the secondary structure of TM helix 6, and reduced correlated motion among monomers. The stable secondary structure of the variant mainly results from the stabilized hydrogen bond between T563 and T567. In contrast to TRPV1-based simulation, no significant changes in the pore size or in the electrostatic potential for the pore region were observed between the two forms of TRPV5 in this study.

Conclusions: Simulations based on the newly determined TRPV6 structure confirm that the A563T variation affects the structure and dynamics of TRPV5 through increased interactions with V540, which is one residue away from the key residue D542 in the Ca^{2+} filter.

Funding: NIDDK Support

SA-OR063

Transcriptional Activation of Kir5.1 by HNF1B – Implications for Autosomal Dominant Tubulo-Interstitial Kidney Disease Joost Hoenderop,[1] Andreas Kompatscher,[1] Karam S. Aboudehen,[2] Peter Igarashi,[2] Jeroen H. De Baaij,[1] René J. Bindels.[1] *[1]Radboud University Medical Center, Nijmegen, Netherlands; [2]University of Minnesota, Minneapolis, MN.*

Background: Hepatocyte nuclear factor 1 homeobox B (*HNF1B)* is an essential transcription factor for the development and functioning of the kidney. Mutations in HNF1b cause autosomal dominant tubulointerstitial kidney disease (ADTKD-HNF1B). Patients often suffer from a severe electrolyte phenotype consisting of hypomagnesemia and hypokalemia. Until now, known genes regulated by HNF1B do not fully explain the phenotype of the patients.

Methods: Therefore, a chromatin immunoprecipitation and sequencing (chIP-seq) was conducted in immortalized mouse kidney cells (mpkDCT) to identify HNF1B binding sites at a genome-wide scale. Luciferase-promoter assays, siRNA-mediated knockdown of *Hnf1b* in DCT cells and RT-qPCR on HNF1B mutant mouse kidneys were performed to assess the transcriptional regulation of *Hnf1b* on candidate genes *in vitro* and *in vivo*.

Results: In total 7,421 HNF1B binding sites were identified, including several genes involved in electrolyte transport and diabetes. A highly conserved HNF1B site was identified in the promoter of *Kcnj16*, encoding the potassium channel Kir5.1. Luciferase-promoter assays showed a 2.2 fold increase in *Kcnj16* expression when HNF1B was present. Expression of the *Hnf1b* p.Lys156Glu mutant that was identified in a ADTKD-HNF1B patient, did not activate *Kcnj16* expression. Knockdown of *Hnf1b* in mpkDCT cells significantly reduced the expression of *Kcnj16* (Kir5.1) and *Kcnj10* (Kir4.1) by 38% and 37%. These results were confirmed in a HNF1B renal knockout mouse, exhibiting downregulation of *Kcnj16, Kcnj10* and *Slc12a3* transcripts in the kidney by 78%, 83% and 76%, respectively, compared to HNF1B wild-type mice.

Conclusions: HNF1B has been identified as a transcriptional activator of *Kcnj16*. Consequently patients with *HNF1B* mutations may have reduced Kir5.1 activity in the kidney, resulting in hypokalemia and hypomagnesemia.

Funding: Government Support - Non-U.S.

SA-OR064

CLDN10 Mutations Cause a Novel Autosomal Recessive Hypokalemic-Alkalotic Salt-Losing Tubulopathy Tom Nijenhuis,[2] Ernie M. Bongers,[2] Luke M. Shelton,[2] Susanne Milatz,[1] Sjoerd Verkaart,[2] Anneke Bech,[2] Jeroen Schoots,[2] Elisabeth A. Cornelissen,[2] Markus Bleich,[1] Joost Hoenderop,[2] Jack F. Wetzels,[2] Dorien Lugtenberg.[2] *[1]Christian Albrechts University Kiel, Kiel, Germany; [2]Radboud university medical center, Lent, Netherlands.*

Background: Hypokalemic alkalosis result from acquired causes or rare (genetic) tubular disorders. Salt-losing nephropathies, due to mutations affecting transcellular sodium reabsorption, induce hypokalemic alkalosis by increasing distal tubular flow and sodium delivery. However, the importance of paracellular transport across tight junctions, involving the claudin protein family, is increasingly acknowledged.

Methods: We phenotyped two unrelated patients with hypokalemic alkalosis, including tubular function testing, performed whole exome sequencing and characterized the identified *CLDN10* sequence variations *in vitro*.

Results: The first patient was diagnosed with Bartter syndrome (BS) over 30 years ago. Re-evaluation demonstrated hypocalciuria and hypercalcemia, suggesting Gitelman syndrome (GS). However, serum magnesium was in the upper-normal to hypermagnesemic range, thiazide responsiveness was not blunted, and genetic analyses did not show mutations in genes associated with either GS or BS. A reduced urinary concentrating ability with a preserved aquaporin-2 response to desmopressin was demonstrated, with an intact to exaggerated response to furosemide. These findings are not in line with any known salt-losing nephropathy. Whole exome sequencing revealed compound heterozygous *CLDN10* sequence variants. A second unrelated patient was thereafter identified demonstrating a similar phenotype and compound heterozygous *CLND10* sequence variants. Both patients' phenotypes resemble a mouse model lacking distal tubular Claudin-10, that demonstrates a reduced TAL paracellular sodium permeability leading to a urine concentrating defect, and enhanced paracellular magnesium and calcium permeability. Cell surface biotinylation and immunofluorescence experiments in cells expressing the Claudin-10 mutants showed that the phenotype is not explained by mere lack of Claudin-10 membrane localization or tight junction strand formation.

Conclusions: Pathogenic *CLDN10* mutations cause a novel tight junction disease, possibly affecting TAL paracellular ion transport, characterized by a non-Bartter non-Gitelman hypokalemic-alkalotic salt-losing phenotype and a renal concentration defect, with hypocalciuria and unexpectedly normal to high serum magnesium levels.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-OR065

Effect of Sodium-Glucose Cotransporter 2 Inhibitor on Fluid Distribution: Comparison with Furosemide and Tolvaptan Ken Ohara, Takahiro Masuda, Takuya Murakami, Toshimi Imai, Saki Nakagawa, Mari Okada, Hiromichi Yoshizawa, Atsushi Miki, Kentaro Oka, Maki Asakura, Taro Sugase, Akira Onishi, Tetsu Akimoto, Osamu Saito, Shigeaki Muto, Daisuke Nagata. *Divison of Nephrology, Department of Internal Medicine, Jichi Medical University, Oyama, Japan.*

Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitor is a new antihyperglycemic drug that increases urinary glucose excretion. Recently, the diuretic property of SGLT2 inhibitors has been reported, but the effect on fluid distribution remains unclear. We therefore examined the change of fluid distribution after the administration of SGLT2 inhibitor dapagliflozin (DAPA), and compared with loop diuretic furosemide (FR) and vasopressin V2 receptor antagonist tolvaptan (TLV).

Methods: Forty chronic kidney disease (CKD) patients with fluid retention (average eGFR 29.0±3.3 mL/min/1.73 m^2) were enrolled in this study. The patients were divided into the three groups: DAPA (n=15, dose 5 mg/day), FR (n=15, dose 55.7±12.4 mg/day) and TLV (n=10, dose 7.5 mg/day). The fluid volume was measured using a bioimpedance

analysis (BIA) device day 0 and 1 week after the administration. One-way ANOVA was performed to measure differences between the groups.

Results: After 1 week, changes in body weight (DAPA -3.1±0.8, FR -4.6±0.8, TLV -2.6±1.0 kg, p=0.22) and urine volume (+81±220, +451±243, +187±230 mL/day, p=0.52) were not significantly different among the groups. BIA showed changes in intracellular water (-6.2±1.3, -7.3±1.2, -7.1±1.4 %, p=0.82) were similar among the groups, and changes in extracellular water (ECW) tended to increase in FR (-8.5±1.6, -12.6±1.6, -7.9±1.8 %, p=0.10). Changes in the ratio of ECW to total body water (ECW/TBW) were significantly different (-1.3±0.5, -3.4±0.5, -0.3±0.6 %, p<0.001). Changes in estimated glomerular filtration ratio were not significantly different during the treatment (-2.0±3.3, 3.9±3.3, 0.4±4.1 %, p=0.46).

Conclusions: SGLT2 inhibitor dapagliflozin predominantly decreases ECW, but the reduction rate of ECW/TBW differs from furosemide and tolvaptan. These results indicate that SGLT2 inhibitor has a novel property on fluid distribution not found in conventional diuretics.

Funding: Government Support - Non-U.S.

SA-OR066

Mobilization of Nonosmotically Stored Sodium after Water Loading in Healthy Individuals Rosa D. Wouda,[4] Shosha Dekker,[2] Joelle Reijm,[3] Rik H. Olde Engberink,[1] Liffert Vogt.[1] *[1]Academic Medical Center, Amsterdam, Netherlands; [2]AMC Amsterdam, Amsterdam, Netherlands; [3]Academic medical center, Amsterdam, Netherlands; [4]Academic Medical Center, Amsterdam, Amsterdam, Netherlands.*

Background: Recently it was discovered that significant amounts of sodium (Na^+) can be stored without concurrent water retention. These observations indicate the presence of a third compartment for Na^+ distribution. The role of this compartment under hypotonic conditions is not known. In this study we investigated whether Na^+ can be released from its nonosmotic stores after a hypotonic fluid load.

Methods: Twelve healthy male subjects had a water loading test (WL; 20 ml water/kg in 20 min). During a 240 min follow-up, we compared the observed plasma [Na^+], fluid and cation excretion with values predicted by the Barsoum-Levine and Nguyen-Kurtz formula. These formulas are used for guidance of fluid therapy during dysnatraemia and do not account for nonosmotic Na^+ stores.

Results: 30 min after WL plasma [Na^+] was decreased with -3.2±0.5 mmol/L (mean (SE)), after which plasma [Na^+] increased gradually. The observed maximal decrease in plasma [Na^+] after WL was significantly overestimated by the Barsoum-Levine (-4.4±0.3 mmol/L) and Nguyen-Kurtz formula (-5.2±0.4 mmol/L)(p<0.05). In addition, 120 min after WL the Barsoum-Levine and Nguyen-Kurtz formula overestimated urine volume, while cation excretion was significantly underestimated with a cation gap of 51±18 mmol and 60±19 mmol, respectively (p<0.05). At 240 min, this gap was 29±18 mmol and 5±23 mmol, respectively (p=NS).

Conclusions: These data demonstrate that healthy individuals are able to mobilize osmotically inactivated Na^+ after a hypotonic fluid load. Further research is needed to expand knowledge on the Na^+ buffer and asses its impact on therapy of dysnatremia.

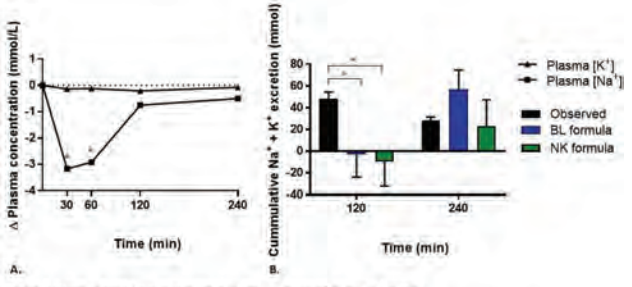


Figure 1. Expected and observed urinary cation excretion after water loading
A. In healthy subjects plasma [Na^+] reached nadir only 30 min after initiation of WL, while plasma [K^+] remained stable. **B.** 120 min after WL the corresponding changes in urinary cation excretion were largely underestimated compared to the observed values by both the Barsoum-Levine and Nguyen-Kurtz formula. Data are presented as mean ± SE. *p<0.05

SA-OR067

Expression Pattern of Renal Transporters in Urinary Exosomes from Patients with Edematous States Silvana Bazua-Valenti,[1,2] Lorena L. Rojas,[1] Fabiola Gallardo,[1] Diego L. Carrillo Perez,[1] Braulio A. Marfil,[1] Pablo E. Galindo,[1] Gerardo Gamba.[1,2] *[1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Tlalpan, Mexico City, Mexico; [2]Instituto de Investigaciones Biomédicas, UNAM, Mexico City, Mexico.*

Background: The use of urinary exosomes (UE) is a non-invasive powerful tool to study the pathophysiology of renal diseases and also as a diagnostic tool for assessment of human samples. For instance, we have shown that in renal transplant patients, tacrolimus increases expression and phosphorylation of NCC in UE. Here we analyzed UE from patients with liver cirrhosis or chronic kidney disease (CKD) with and without edema to assess the expression of a variety of renal transporters.

Methods: We conducted a prospective and observational study. We obtained clinical and biochemical data, and urinary samples from adult patients with liver cirrhosis (Child B) (N=6 with, N=6 no-edema), with CKD (KDIGO G3-G5) (N=6 with, N=6 no-edema) and healthy subjects (N=5), as controls. UE from 8 ml of urine were obtained by ultracentrifugation for western blot analysis of SGLT2, NHE3, NKCC2, NCC and CaSR. The amount of UE used per patient was adjusted to urinary creatinine.

Results: We found no significant differences in laboratory findings of cirrhotic patients with or without edema, except for higher serum Na^+ in the edema group (133.9±4.9 vs. 140.1±2.1 p<0.05). In CKD patients, however, we found differences in the BMI (31±6.9 vs. 25±3 p<0.01), serum K^+ (5.2±0.39 vs. 4.6±0.55 p<0.01) and serum Ca^{2+} (8.6±0.47 vs. 9.3±0.75 p<0.05) in the edema vs. no-edema group, respectively. Analysis of UE showed a significant increase in NCC phosphorylation, SGLT2, NHE3 and CaSR expression in both cirrhotic and CKD patients when compared to healthy controls. In the cirrhotic patients, those with edema showed increased expression of SGLT2, NHE3 and CaSR vs. the non-edema group. In CKD patients, although the expression of these transporters looks higher in the edema group, the difference did not reach significance. Interestingly, NKCC2 expression showed no changes in any group.

Conclusions: We observed different expression patterns for five proteins in UE of cirrhotic and CKD patients. Moreover, in cirrhotic patients the expression of the transporters was higher in the edema group. These results suggest that the analysis of renal transporters using UE can give insights into the molecular mechanisms of salt retention in patients with edematous states and may contribute to the design of early therapeutic strategies.

Funding: Government Support - Non-U.S.

SA-OR068

Low Dietary Acid Intake May Help the Kidneys Improve Exercise Capacity Enni-Maria Hietavala,[2] Lynda A. Frassetto.[1] *[1]University of California San Francisco, San Francisco, CA; [2]University of Jyväskylä, Jyväskylä, Finland.*

Background: Diet composition influences the acid-base status of the body. The effects of differing acid balances may become more relevant as renal functional capacity declines with aging. We examined the effects of low (LD) versus high dietary acid load (HD) on blood bicarbonate and exercise performance.

Methods: The 88 healthy volunteers who participated - 22 adolescents (AD), 33 young adults (YA) and 33 elderly (EL) - followed a 7-day LD and HD in a randomized order. At the end of both diet periods the subjects performed a cycle ergometer test (3x10 min at 35%, 55%, 75%, and (except EL) until exhaustion at 100% of VO_2peak). At the beginning of, and after the diet periods, blood samples were collected at rest and after all workloads. Oxygen consumption, respiratory exchange ratio and heart rate were monitored during cycling. Glomerular filtration rate (GFR) was calculated with CKD-EPI equation. Two-way repeated measure ANOVA and Pearson correlation analyses were done on SPSS Statistics 22.0.

Results: Bicarbonate (HCO_3^-) decreased over the HD period in YA women (p<0.001), YA men (p=0.027), EL women (p<0.001) and EL men (p<0.001). HCO3- increased over the LD period in AD girls (p=0.005) and EL men (p=0.039). HCO_3^- was lower at rest after HD compared to LD in YA women (p<0.001), YA men (p=0.042) and in both EL groups (p<0.001). HCO_3^- was lower at submaximal workloads after HD compared to LD in YA women (p≤0.022) and EL women (p≤0.020). In young women, the maximal workload was 19 % shorter (p=0.001) and maximal cardiorespiratory measures (p≤0.029) lower after HD compared to LD.

Conclusions: Our data uniquely suggests that better renal function is associated with higher availability of bases, which may diminish exercise-induced acidosis and improve performance. Glomerular filtration rate decreased with aging and was higher in men compared to women, likely explaining the larger effects of dietary acid load on acid-base status in the elderly compared to younger subjects and in women compared to men. The diet composition along with renal functional capacity affects acid-base status of the body at rest and in exercise.

Funding: Private Foundation Support

SA-OR069

Impact of Fluid Balance on One-Year Mortality of Patients with Septic Shock Tsering Dhondup,[1] Jong-Chie Claudia Tien,[1] Hon Liang Tan,[2] Alberto E. Marquez,[1] Kianoush Banaei-Kashani.[1] *[1]Mayo Clinic, Rochester, MN; [2]Singapore General Hospital, Singapore, Singapore.*

Background: Septic shock patients require early and aggressive volume resuscitation. However, current evidence shows higher risk with the intensity and duration of fluid overload in critically ill patients. In this report, we outline the impact of fluid balance and timing of volume de-resuscitation on outcomes in septic shock patients.

Methods: We retrospectively identified adult septic shock/ severe sepsis patients admitted to the ICU of Mayo Clinic Hospital from January 1st, 2007 to December 31st, 2009. Data was abstracted electronically and validated manually. We collected basic demographic, clinical, laboratory and outcome variables. Social security death index was used for missing mortality information. De-resuscitation day was defined as the 1st day with the negative fluid balance, and KDIGO criteria were used for AKI definition.

Results: A total of 633 patients were included with mean age of 68 years, with 348(55%) being males. Median ICU length of stay was 2.4 (IQR of 1.3-5.5) days, and median daily fluid balance in ICU was 2352 (IQR of 990-4323) ml. The median day-1 SOFA score was 7, and 57 (9%) patients had pre-existing ESRD. In ICU, de-resuscitation was achieved in 443 (70%) patients within [median (IQR)] 2 (1-3) days of ICU admission. Among those starting de-resuscitation in ICU, the average cumulative fluid balance was -1.4 (±5.7) liters. 371 of 576 non-ESRD (64%) patients developed AKI of which 291 patients were admitted with AKI. Eighty (22%) of those with AKI required initiation of dialysis with 63 patients being initiated on CVVH and 17 on intermittent hemodialysis.

Adjusted for age, Charlson Comorbidity Index, APACHE III score and day 1 SOFA score, every 1 liter positive cumulative fluid balance was associated with increased hospital mortality (OR of 1.10; 95% CI: 1.06-1.16) in patients who achieved de- resuscitation phase. More interestingly, every 1 liter positive cumulative fluid balance was also associated with increased 1-year mortality (OR of 1.07; 95% CI: 1.03-1.12). Association of positive cumulative fluid balance with increased risk of Hospital and 1-year death remained significant irrespective of pre-existing ESRD or AKI development.

Conclusions: In our cohort of patients with septic shock who achieved de-resuscitation, positive cumulative fluid balance was associated with increased hospital and 1-year mortality.

SA-OR070

TRC101, a Novel Hydrochloric Acid Binder, Increases Serum Bicarbonate in Acidemic Patients with CKD David A. Bushinsky,[5] Thomas H. Hostetter,[1] Robert J. Alpern,[4] Gerrit Klaerner,[3] Yuri Stasiv,[3] Claire Lockey,[3] Sarah McNulty,[3] Angela A. Lee,[3] Dawn Parsell,[6] Vandana S. Mathur,[2] Jerry M. Buysse.[3] *[1]Case Western Reserve Univ., Cleveland, OH; [2]Mathur Consulting, Woodside, CA; [3]Tricida, Inc., South San Francisco, CA; [4]Yale School of Medicine, New Haven, CT; [5]Univ. of Rochester, Rochester, NY; [6]Parsell Associates, Cedar Park, TX.*

Background: Metabolic acidosis is common in patients with chronic kidney disease (CKD) and has significant adverse effects on renal function, muscle, and bone. TRC101 is a novel, orally-administered, non-absorbed, metal and counterion-free polymer that selectively binds hydrochloric acid. In this study of acidemic CKD patients we evaluated the safety and tolerability of TRC101, and its effectiveness in increasing serum bicarbonate.

Methods: In this randomized, double-blind, placebo-controlled study, 135 acidemic CKD patients (eGFR 20 to <60 mL/min/1.73m^2) were admitted to an in-patient unit and treated for 14 days with placebo (BID or QD) or one of four TRC101 dosing regimens (1.5, 3.0, or 4.5 g BID; 6.0 g QD), while on a controlled diet. After completion of treatment, patients were discharged and followed for up to 14 days.

Results: Patients had a mean baseline eGFR of 34.8 mL/min/1.73m^2 and a mean baseline serum bicarbonate of 17.7 mEq/L. Comorbidities included hypertension (93%), diabetes (70%), and heart failure (22%). Within 72 hours of the first TRC101 dose, mean serum bicarbonate increased in each of the four TRC101 treatment groups by >1.4 mEq/L and was significantly increased ($p<0.0001$) by 3.1 - 3.8 mEq/L at the end of treatment compared to placebo. Mean serum bicarbonate continued to increase in all treatment groups over the course of the study while the mean bicarbonate in the placebo group remained stable. In the combined TRC101 treatment groups, serum bicarbonate was in the normal range (22 - 29 mEq/L) at the end of treatment in 34.6% of patients and increased by >4 mEq/L in 38.5% of patients. After discontinuation of TRC101, serum bicarbonate decreased nearly to baseline levels within 2 weeks. All adverse events were mild or moderate in intensity and there were no serious or severe adverse events. All patients completed the study.

Conclusions: In this 14-day study of acidemic CKD patients TRC101 was safe and well-tolerated and led to a significant increase in the level of serum bicarbonate.

Funding: Commercial Support - Tricida

SA-OR071

Economic Evaluation of Contemporary Kidney Transplant Practice David A. Axelrod,[2] William Irish,[1] Mark Schnitzler,[3] Janet E. Tuttle-newhall,[5] Krista L. Lentine.[4] *[1]CTI, Raleigh, NC; [2]Lahey Hospital and Clinic, Burlington, MA; [3]Saint Louis Univ, St Louis, MO; [4]Saint Louis University, St. Louis, MO; [5]St Louis University Center for Outcomes Research, St Louis, AL.*

Background: Kidney transplantation (KT) has been established as the optimal therapy for medically suitable patients with end-stage renal disease, prolonging survival and reducing health care spending. However, KT economics using Markov models have assumed compatible donors of average or better quality. The economic implication of KT in contemporary practice including the use of high kidney donor profile index (KPDI) and public health service high risk (PHS) deceased donors, as well transplantation from ABO or HLA incompatible living donors, has not been assessed.

Methods: Using contemporary modeling techniques including Discrete Event Simulation (DES) over a 10-year time horizon, we compared the cost effectiveness of KT from varying donor types and dialysis for patients with kidney failure. DES models were constructed using data drawn from the United States Renal Data System, the national transplant registry, University HealthSystem Consortium, and literature review. Graft failure rates, transplant cost, and disease transmission events were adjusted for donor characteristics.

Results: All KT options resulted in improved patient survival compared to long term dialysis; however, the relative benefits and costs differed substantially (**Table**). Over a 10 year period, living donor KT with 0-3 HLA mismatches (mm) yielded 77.3 Quality Adjusted Life Months (QALM) at a cost of $53,982 per quality adjusted life year (QALY). By comparison, dialysis provided only 56.4 QALMs at a cost of $110,580 per QALY. HLA incompatible living donor KT was more expensive than dialysis, but resulted in an additional 12 QALM of survival over 10 years. Sensitivity analysis suggests that these results are robust over a clinically relevant range of inputs

Conclusions: KT is cost effective over across a spectrum of donor characteristics, despite higher costs for marginal organs and innovative living donor KT practices.

Funding: Private Foundation Support

COSTS, SURVIVAL & COST-EFFECTIVENESS BY RENAL REPLACEMENT MODALITY

Modality	Total Cost	Quality Adjusted Life Months	Cost per Quality Adjusted Life Year
Dialysis	$519,748	56.4	$110,589
KDPI > 85%	$452,772	64.2	$84,669
KDPI <= 85%	$394,690	72.3	$65,502
PHS High Risk Deceased Donor	$425,604	72.8	$70,206
HLA Incompatible Living Donor	$622,436	68.4	$109,132
ABOi Living Donor	$513,487	75.0	$82,158
HLA mm 4-6 Living Donor	$363,481	77.3	$56,467
HLA mm 0-3 Living Donor	$348,193	77.4	$53,983

Economic Evaluation of Renal Replacement Therapy Options

SA-OR072

Association of Dialysis Facility Ownership on Access to Kidney Transplant Waitlist or Living Donor Transplant Jennifer C. Gander,[3] Katherine Ross,[3] Sumit Mohan,[1] Stephen O. Pastan,[4] Rachel E. Patzer.[2] *[1]Columbia University, New York, NY; [2]Emory Transplant Center, Atlanta, GA; [3]Emory University, Atlanta, GA; [4]Emory University School of Medicine, Atlanta, GA.*

Background: Past studies have shown for-profit facilities have lower rates of kidney transplantation (KT), but used older data that did not account for differences in facility ownership. Our aim was to examine the relationship between dialysis facility ownership and access to KT.

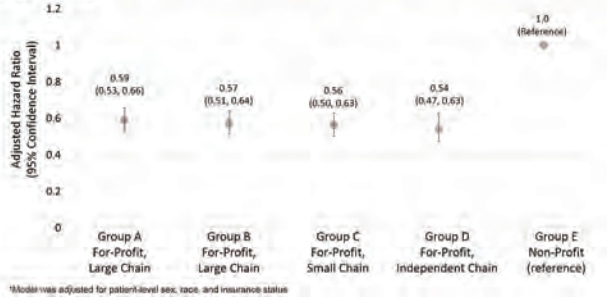
Methods: We linked adult, incident ESRD, United States Renal Data System (2000-2014) patient data with facility ownership (Dialysis Facility Compare) and facility-level characteristics (Dialysis Facility Report). Access to KT was defined as incident waitlisting or receipt of living donor KT. Facility ownership was categorized into one of five groups as either for-profit, large company (Groups A and B), for-profit small clinics(Group C), for-profit independent clinics (Group D), or non-for profit clinics (Group E). Hierarchical survival analysis assessed the association between access to KT and dialysis facility ownership while controlling for patient- and facility-level characteristics and patient-level clustering.

Results: Among 1,137,113 patients in our study cohort, 166,240 (14.6%) were waitlisted or received a living donor KT and among 6,263 U.S. facilities. In adjusted survival analysis, patients waitlisted or receiving a living donor KT were more likely to be Hispanic (HR=1.45; 95% CI 1.40, 1.51) and male (HR=1.39; 95% CI 1.33, 1.46), and less likely to have heart disease (HR=0.46; 95% CI 0.46, 0.47), and Medicaid insurance (HR=0.44; 95% CI 0.43, 0.45). ESRD patients receiving treatment from Group A and Group B facilities were less likely (HR=0.59; 95% CI 0.53, 0.66 and HR=0.57; 95% CI 0.51, 0.64; respectively) to be waitlisted or receive a living donor KT compared to non-profit facilities (Figure 1).

Conclusions: Dialysis facility ownership was found to be significantly associated with a patient's access to KT. Facilities can influence their patients' access to the KT waitlist and living donor KT. We urge CMS to adopt quality measures that hold dialysis facilities accountable for patient access to KT.

Funding: NIDDK Support

Figure 1. Adjusted* hierarchical survival analysis to determine the association between dialysis facility chain ownership and access to kidney transplantation, measured by a patient's placement on the waitlist or receipt of living donor kidney transplantation. (Reference group was Non-profit dialysis facilities)



SA-OR073

Significantly Lower Rates of Transplantation and Increased Wait List Mortality among Kidney Transplant Candidates with VA Insurance Joshua J. Augustine,[1,2] Susana Arrigain,[1] Krishna P. Balabhadrapatruni,[2] Niraj Desai,[2] Jesse D. Schold.[1] *[1]Cleveland Clinic, Cleveland, OH; [2]Cleveland VAMC, Case Western Reserve University, Cleveland, OH.*

Background: Military veterans do not incur cost for kidney transplantation within the VA system, but transplant availability has historically been limited to just four VA

centers nationwide. Recent SRTR reports show a lower observed vs. expected rate of transplant in VA centers. Because VA centers are affiliated with non-VA academic centers within the same donor service area (DSA), we sought to compare transplantation rates nationally and also between the four VA centers and their non-VA (NVA) affiliates.

Methods: SRTR data was used to identify adult patients listed for a primary kidney transplant from 2004 through 2016. Patients with VA insurance (n=3663) were compared to those with private insurance (PI) (n=141,523), Medicaid (n=25,245) and Medicare (n=132,026). Analyses were conducted using multivariable Cox and competing risks regression models for time to transplantation, and unadjusted cumulative incidence functions of death with transplant as a competing risk.

Results: Compared to PI, VA patients were older and mostly male, with more black patients, diabetes, and vascular disease. VA patients lived much further from the transplant center compared to other groups (med. 282 vs. 23 miles). VA patients had a lower likelihood of transplantation compared to PI nationally (HR: 0.72(95% CI:0.69,0.76)), and compared to PI patients within the four NVA programs (HR: 0.78(95% CI:0.71,0.85). This difference with NVA centers persisted after excluding living donors (HR of 0.84(95% CI:0.76,0.93)), and in a model with death as a competing risk. VA patients also had a lower rate of transplantation vs. Medicare nationally (HR of 0.86(95% CI:0.82,0.91)) but did not differ from Medicare in the NVA centers. The HR of VA vs. Medicaid was not different nationally (HR 1.01(0.95,1.06)). The unadjusted cumulative incidence of waitlist mortality at 2 years was 7.0(95% CI:6.1,7.9) in VA patients, 5.8(5.6,5.9) in PI nationally, and 4.6(3.9,5.3) in PI within NVA centers.

Conclusions: VA patients had a lower rate of transplantation and greater waitlist mortality compared to PI patients both nationally and within four paired NVA academic centers that shared DSAs. The reasons for this discrepancy require further study, but may include differences in patient availability and organ acceptance between VA and non-VA centers.

SA-OR074

Hospitalizations for AKI in Kidney Transplant Recipients in the United States, 2004–2014 Tripti Singh, Nilay Kumar, Sana Waheed, Arjang Djamali, Neetika Garg. *School of Medicine and Public Health, University of Wisconsin, Madison, WI.*

Background: There is little information on the incidence of acute kidney injury (AKI) and mortality associated with AKI in hospitalized kidney transplant recipients.

Methods: We used the National Inpatient Sample 2004 – 2014 to identify hospitalizations with a primary or secondary diagnosis of AKI in the setting of known history of kidney transplantation. Survey analysis techniques were used to generate national estimates. Linear and logistic regression were used to test trends in outcomes.

Results: There were 36,457 hospitalizations for AKI representative of 176,128 hospitalizations nationally in renal transplant recipients during the study period. Mean age of kidney transplant recipients admitted for AKI was 55.5 years and 43.4% were females. There was a significant increase in the comorbidity burden during the period of study (Charlson comorbidity index 1.3 in 2004 to 2.8 in 2014, p<0.001). There was a nearly threefold increase in hospitalization rate for AKI (52 to 135/1000 transplant recipients, p<0.001) over 10 years. We found a concomitant decline in in-hospital mortality, dialysis requirement and length of stay (LOS) along with a modest but significant negative trend in cost. Utilization for intubation and mechanical ventilation increased during the study period.

Conclusions: Hospitalizations for AKI have increased in the kidney transplant recipients but in-hospital outcomes and resource utilization have improved significantly. Further study is warranted to understand the reasons for increasing rate of hospitalizations for AKI in renal transplant patients.

Hospitalizations in kidney transplant recipients for AKI

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	P-trend
Hospitalization rate (per 1000 renal transplant recipients)	51.6	58.6	69.4	81.3	91.6	105.1	111.2	109.0	114.2	122.6	134.8	<0.001
In-hospital mortality (%)	5.2	4.9	4.4	3.8	4.3	4.2	3.0	3.6	3.7	3.4	3.6	0.001
Intubation and mechanical ventilation (%)	8.0	7.8	8.3	8.6	8.7	9.5	8.8	9.3	9.1	9.4	9.3	0.002
Dialysis-requiring AKI (%)	6.8	7.2	8.0	6.9	6.6	6.6	6.2	6.2	5.3	5.0	5.2	<0.001
LOS (mean)	7.8	7.6	7.6	7.1	7.5	7.4	6.8	6.9	6.5	6.6	6.7	<0.001
Inflation-adjusted cost (mean)	18,629	19,451	19,851	18,084	19,451	20,403	19,141	18,274	15,982	16,736	19,326	0.01

SA-OR075

Consequences of Declining a Public Health Service Increased Risk (PHS-IR) Donor Kidney Hilda E. Fernandez, Mariana C. Chiles, Marcus Pereira, Syed A. Husain, Sumit Mohan. *NYP-CUMC, NYC, NY.*

Background: The risk of disease transmission from PHS-IR kidney donors is extremely low but the perception increased risk by patients may adversely impact their willingness to accept these organs.

Methods: We performed a retrospective, single-center study of all PHS-IR kidney offers made to patients at Columbia University Medical Center (CUMC) from 6/2004 to 5/2015 to 1) identify who was likely to accept these organs and 2) assess the potential consequences of declining such offer.

Results: Among 2423 candidates who received a PHS-IR kidney offer, 358 accepted and 2065 declined. On multivariate analysis, higher estimated post-transplant survival (EPTS) score (OR=1.005, p=0.025), male sex (OR=1.345, p=0.035), and higher educational achievement (OR=0.693, p=0.025) appear to influence organ offer acceptance. Among those who declined, 57.5% subsequently received a non-PHS-IR transplant while 16.5% remained on the waitlist. Acceptance of a PHS-IR offer was associated with a lower mortality (3.63% vs 11.6%; adjusted HR 0.467, p=0.0008) and PHS-IR allografts were associated with lower death censored allograft failure rates (HR = 0.677, p=0.041).

Conclusions: Declining a PHS-IR kidney offer appears to be associated with a survival disadvantage at our center. This underscores the importance of patient education regarding the risks and benefits of PHS-IR organs. Efforts must be made to increase acceptance of PHS-IR organs in order to improve outcomes for those on the waitlist.

Funding: NIDDK Support

SA-OR076

Abstract Withdrawn

SA-OR077

Obesity Is a Risk Factor for New-Onset Diabetes Mellitus after Living Kidney Donation Krista L. Lentine,[8] Farrukh M. Koraishy,[8] Abhijit S. Naik,[4] Ngan Lam,[9] David A. Axelrod,[3] Mark Schnitzler,[5] Zidong Zhang,[8] Gregory P. Hess,[2] Amit X. Garg,[7] Bertram L. Kasiske,[1] Daniel C. Brennan,[10] Dorry L. Segev.[6] *[1]Hennepin County Medical Center, Minneapolis, MN; [2]LDI University of Pennsylvania/IMS, Plymouth Meeting, PA; [3]Lahey Hospital and Clinic, Burlington, MA; [4]None, Ann Arbor, MI; [5]Saint Louis Univ, St Louis, MO; [6]Johns Hopkins University, Baltimore, MD; [7]London Health Sciences Centre, London, ON, Canada; [8]Saint Louis University, St. Louis, MO; [9]University of Alberta, Edmonton, AB, Canada; [10]Washington University in St. Louis, St. Louis, MO.*

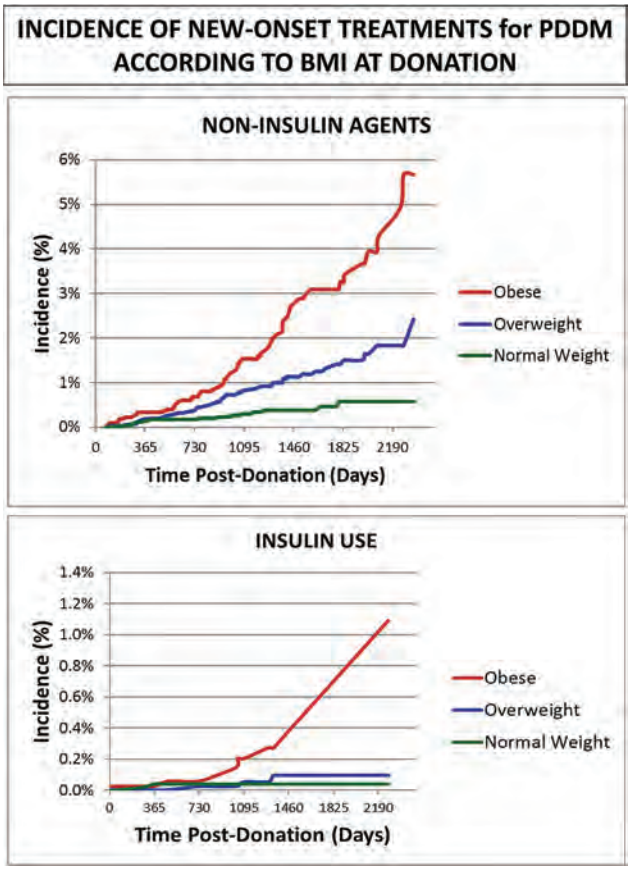
Background: End-stage renal disease is uncommon in living kidney donors (LKD), but most kidney failure developing late after donation appears to be due to diabetes or hypertension. To improve understanding of the relationship of obesity and post-donation diabetes mellitus (PDDM), we examined a novel linkage of national transplant registry data with records from a pharmacy claims clearinghouse that identifies diabetes treatments.

Methods: Among 20,238 LKD with at least 1 year of pre-donation pharmacy records, fills for insulin and non-insulin diabetes agents were examined as measures of new-onset PDDM. Time to first fill of insulin or other diabetes agents in relation to body mass index (BMI), age, sex, race, and other clinical factors in the registry was examined by Kaplan-Meier analysis and Cox regression (adjusted hazard ratio, $_{LCL}$ aHR $_{UCL}$).

Results: Mean age at donation was 42.7 years. Of LKD, 67.5% were women; 75% white, 10.5% black, and 10.9% Hispanic; 40.8% were overweight (BMI 25-<30 m2) and 22.8% were obese (BMI ≥30 kg/m2). The 5-year risk of non-insulin PDDM treatments rose in a graded manner with higher BMI, from 0.6% in normal weight to 3-fold increased risk in overweight (1.5%, aHR, $_{1.76}3.05_{5.27}$) and 3.4% in obese (3.4%, aHR, $_{3.70}6.45_{11.03}$) LKDs. Adjusted 5-year risk of insulin use after donation was 5 times higher in obese than in normal weight LKDs (1.1% vs 0.04%, aHR, $_{1.09}5.24_{25.3}$). **[Fig1].** Once PDDM treatments were started, use of non-insulin agents and insulin continued over 99% and 30% of remaining observation.

Conclusions: Obesity is a strong correlate of PDDM treatments in LKD. Future research should define relationships of obesity and PDDM with outcomes including kidney failure after donation.

Funding: NIDDK Support



SA-OR078

Early Post-Donation eGFR and ESRD in Living Kidney Donors <u>Allan Massie</u>,[3] Lara Fahmy,[2] Macey L. Henderson,[1] Jon J. Snyder,[5] Courtenay M. Holscher,[4] Sandra R. Dibrito,[1] Dorry L. Segev.[4] *[1]Johns Hopkins, Baltimore, MD; [2]Johns Hopkins University School of Medicine, Detroit, MI; [3]Johns Hopkins School of Medicine, Baltimore, MD; [4]Johns Hopkins University, Baltimore, MD; [5]Minneapolis Medical Research Foundation, Minneapolis, MN.*

Background: Several studies have shown higher ESRD risk in living kidney donors (LKDs) compared to healthy nondonors. All LKDs may not equally tolerate nephrectomy. Identifying post-donation risk factors for ESRD would improve post-donation counseling and care. We studied the association between early post-donation eGFR and subsequent ESRD risk.

Methods: Using SRTR data, we studied 64,989 LKDs 1999-2015 who were ESRD-free 9 months post-donation and who had at least one valid post-donation SCr value reported to OPTN between 3-30 months post-donation. When eGFR measured between 3-9 months post-donation (6-month eGFR) was missing, we multiply imputed based on pre-donation eGFR and other post-donation eGFR values. We studied the association between 6-month eGFR and post-donation ESRD (via CMS linkage) using Cox regression, adjusting for age, sex, race (black vs nonblack), pre-donation eGFR, BMI, and 1st-degree biological relationship to recipient.

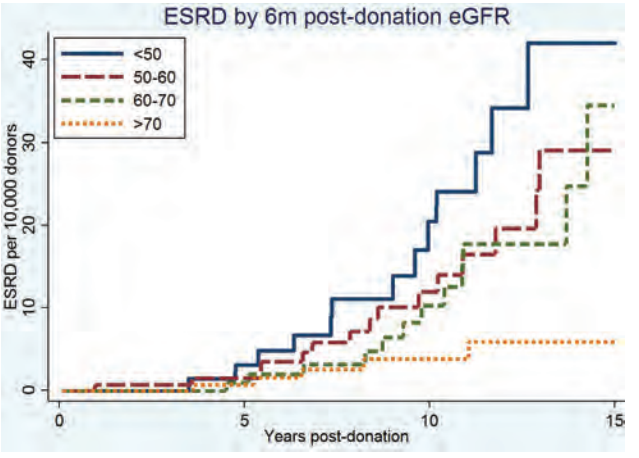
Results: Median (IQR) 6-month eGFR was 63.2 (54.2-74.3) mL/min/1.73 m^2. Out of 64,989 donors, 50 progressed to ESRD during the study period. Donors with lower 6-month eGFR had greater incidence of ESRD (Figure). There was no evidence of association between pre-donation eGFR and post-donation ESRD risk (p=0.3, Table). A 10-unit difference in 6-month eGFR was associated with 32% decreased risk of ESRD (aHR=$_{0.53}$ 0.68 $_{0.87}$, p<0.01, Table).

Conclusions: Lower eGFR in the first 6 months post-donation is associated with higher subsequent risk of post-donation ESRD in living kidney donors. Careful monitoring of early post-donation eGFR is essential to provide adequate post-donation care and counseling.

Funding: NIDDK Support

	Model 1	Model 2	Model 3
pre-donation eGFR	0.77 0.91 1.08	-	0.87 1.06 1.29
6m post-donation eGFR	-	**0.53 0.68 0.87**	**0.49 0.65 0.87**

aHRs per 10 units eGFR. **Bold** p<0.05



SA-OR079

Estimated GFR before Living Kidney Donation as a Predictor of Postdonation Measured GFR <u>Marco van Londen</u>, Jessica V. Weijden, Robert Pol, Jan-Stephan Sanders, Stefan P. Berger, Stephan J. Bakker, Gerjan Navis, Martin H. De Borst. *University Medical Center Groningen, Groningen, Netherlands.*

Background: In living kidney donor screening, precise renal function measurement is vital to ensure adequate postdonation renal function. Measured GFR (mGFR) is the gold standard, but costly and laborious. We tested the capacity of predonation estimated GFR (eGFR) equations to predict postdonation mGFR.

Methods: In a single-center prospective cohort study in 750 living kidney donors, we determined predonation mGFR (continuous iothalamate) including dopamine stimulation, and creatinine-based eGFR (CKD-EPI, Cockcroft-Gault and MDRD equations), as well as mGFR at 3 months postdonation. We used linear regression, Receiver Operating Characteristic curves, and Bayesian statistics to test the performance of eGFR equations.

Results: Mean donor age was 51±11 years, 48% of donors were male. Predonation mGFR was 102±16 ml/min/1.73 m^2, stimulated mGFR was 110±18 ml/min/1.73 m^2, $eGFR_{CKD\text{-}EPI}$ was 88±14 ml/min/1.73 m^2, $eGFR_{CG}$ was 93±19 ml/min/1.73 m^2, and $eGFR_{MDRD}$ was 86±16 ml/min/1.73 m^2. Postdonation mGFR was 65±11 ml/min/1.73 m^2. Predonation mGFR and the results of the three eGFR formulas were positively associated with postdonation mGFR (mGFR R^2=0.49, dopamine stimulated mGFR R^2=0.34, $eGFR_{CKD\text{-}EPI}$ R^2=0.21, $eGFR_{CG}$ R^2=0.22, $eGFR_{MDRD}$ R^2=0.14). A predonation $eGFR_{CKD\text{-}EPI}$ >102 ml/min/1.73 m^2 (present in 16% of donors) excludes a postdonation mGFR <60 ml/min/1.73 m^2 with a specificity of 100% (AUC 0.74), for predonation $eGFR_{CG}$ this threshold is 114 ml/min/1.73 m^2 (AUC 0.78) and for $eGFR_{MDRD}$ 114 ml/min/1.73 m^2 (AUC 0.70). A predonation $eGFR_{CKD\text{-}EPI}$ of 95 ml/min/1.73 m^2 (present in 30% of donors) excludes a postdonation mGFR of <50 ml/min/1.73 m^2 with 100% specificity (AUC 0.78), for predonation $eGFR_{CG}$ this threshold is 105 ml/min/1.73 m^2 (AUC 0.82) and for $eGFR_{MDRD}$ 97 ml/min/1.73 m^2 (AUC 0.74).

Conclusions: We provide cut-off values for predonation donor eGFR to select donors with a high probability of good renal function postdonation without requiring mGFR measurement. In order to avoid incorrect exclusion of a large proportion of donors, additional renal function tests such as measured GFR are warranted in donors with an $eGFR_{CKD\text{-}EPI}$ <95 ml/min/1.73 m^2.

Funding: Government Support - Non-U.S.

SA-OR080

Predonation Recruitment of Renal Functional Reserve Capacity Is Associated with Early Renal Adaptation after Living Kidney Donation <u>Marco van Londen</u>, Jessica V. Weijden, Jan-Stephan Sanders, Stefan P. Berger, Stephan J. Bakker, Martin H. De Borst, Gerjan Navis. *University Medical Center Groningen, Groningen, Netherlands.*

Background: Early renal adaptation after kidney donation results in a GFR above 50% of the predonation value. This is probably due to early hemodynamic changes, whereas long-term renal adaptation, which may further increase GFR in the months thereafter is likely more structural in nature. Recruitment of Renal Reserve Capacity assessed by the renal response to dopamine infusion (RRC) is considered to reflect functional reserve capacity, but it is unknown whether it predicts short- or long-term renal adaptation or both. In this study we investigate the association between pre-donation RRC and GFR changes after donation.

Methods: In 750 living kidney donors between 1984 and 2017, we prospectively measured mGFR (^{125}-Iothalamate clearance) and RRC. We performed multivariable linear regression analysis with short-term postdonation mGFR as dependent variable. In a subgroup with 5 year follow-up after donation we assessed the association with long-term mGFR.

Results: Mean donor age was 52±11 years, 48% were male. Mean predonation mGFR was 107±28 ml/min, $mGFR_{Dopamine}$ was 115±30 ml/min, resulting in a RRC of 9 ±10 ml/min. Three months postdonation, mGFR was 73±15 ml/min and $mGFR_{Dopamine}$ was 76±15 ml/min, indicating that donors still had RRC (2.7±5.8 ml/min, p<0.001). Predonation RRC was associated with mGFR preservation, independent of age, mGFR, blood pressure and BMI (st. β 0.12, p<0.001, final model R^2=0.63). In the subgroup of donors of whom 5-year follow-up data was available, RRC was neither associated with absolute mGFR at 5 years postdonation (st. β 0.02, p=0.78), nor with compensatory mGFR increase between 3 months and 5 year after donation (st. β 0.03, p=0.67).

Conclusions: Dopamine-recruited renal reserve capacity is independently associated with preservation of mGFR early after donation, but not with long-term mGFR. This indicates that $RC_{Dopamine}$ is a marker of early, hemodynamic-driven, adaptation to kidney donation rather than long-term mGFR changes. More long-term follow-up data are needed to provide conclusive results about the use of dopamine in living kidney donors.

Funding: Government Support - Non-U.S.

SA-OR081

Role of COUP-TFII in Pericyte Activation and Kidney Fibrosis Li Li, Xiaoyan Xiao, Takaharu Ichimura, Julia Wilflingseder, Joseph V. Bonventre. *Brigham & Women's Hospital/Harvard Medical School, Boston, MA.*

Background: Genetic fate mapping studies suggest that pericytes are the main source of myofibroblasts enriched in injury-induce kidney fibrosis. The transcriptional network that controls the pericyte-myofibroblast transdifferentiation is poorly understood. Chicken Ovalbumin Upstream Promoter-Transcription Factor II (COUP-TFII) is a transcription factor critical to the kidney development. It is broadly detected in the mesenchyme of developing organs and has a profound impact on organogenesis and cell fate determination.

Methods: We measured COUP-TFII mRNA by quantitative real-time PCR (qRT-PCR) and protein by Western Blot from normal C57BL/6 mouse kidneys and at different times after unilateral ureter obstruction (UUO). To assess the origin of COUP-TFII+ cells, we crossed Forkhead Box D1 (Foxd1)-Cre driver mice to tdTomato reporter mice to genetically label the Foxd1-derived stromal cells. In vitro, knockdown of COUP-TFII was attained by transfecting a small interfering RNA (siRNA) into CH310T1/2 (pericyte-like cells). COUP-TFII and αSMA expression was evaluated in tissue by immunostaining and in siRNA-transfected CH310T1/2 by RT-PCR.

Results: In non-injured kidney, expression of COUP-TFII is sparsely distributed in interstitial cells, Bowman's capsule and to a lesser extent in tubules. Cells expressing COUP-TFII are PDGFRβ+ (pericytes/fibroblasts) and are adjacent to CD31+ (endothelial) cells. Most COUP-TFII+ cells are localized in the region of Foxd1-derived stromal cells. Upon injury, COUP-TFII expression is significantly increased in αSMA+ cells (myofibroblasts) localized within the fibrotic region. COUP-TFII expression did not overlap with F4/80 (macrophages) staining. Both mRNA and protein levels of COUP-TFII increased at 5, 7 and 10 days after UUO and are associated with increased levels of αSMA at the same time point. In vitro, knockdown of COUP-TFII by siRNA results in decreased αSMA expression in pericyte-like cells.

Conclusions: COUP-TFII is expressed at basal levels in non-injured kidney in Foxd1-derived stromal cells. Upon injury, COUP-TFII expression increased in αSMA+ cells localized within the fibrotic region. Attenuation of COUP-TFII expression is associated with reduced expression of αSMA in pericyte-like cells. These data suggest that COUP-TFII may play a role in the regulation of pericyte-myofibroblast transdifferentiation in injury-induce kidney fibrosis.

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SA-OR082

The Breast Cancer Type 1 Susceptibility Protein (BRCA1) Mediates Fibrotic Kidney Disease Akinwande A. Akinfolarin, Amrendra K. Ajay, Venkata Sabbisetti, Joseph V. Bonventre. *Brigham and Women's Hospital, Boston, MA.*

Background: Repetitive tubular injury leads to chronic fibrotic kidney disease (CKD). Chemical, ischemic and obstructive kidney injuries lead to replication fork arrest (RFA) and double strand DNA breaks (DSB), triggering the DNA damage response. *BRCA1* is a breast tumor suppressor gene with a role in homologous recombination (HR) and maintenance of genome integrity by DNA repair. Here we deplete BRCA1 in the adult mouse proximal tubule (PT) to examine its effect on the development of interstitial fibrosis

Methods: *SLC34A1 Cre* mice were crossed to mice with floxed *BRCA1 exon 11* allele yielding models of inducible PT *BRCA1* gene deletion. After Tamoxifen-induced *Cre* activation, we subjected mice to bilateral ischemia/reperfusion (I/R), unilateral ureteric obstruction (UUO), or aristolochic acid (AA)-induced injury. Kidney extracts were evaluated by western blot, real time PCR and Masson's trichrome (MT) and Picrosirius Red (PS) staining for markers of interstitial fibrosis. Markers of DNA damage, cell cycle arrest and senescence were examined by immunofluorescence. BRCA1 was also down regulated in PT cells using short-hairpin RNA against *BRCA1* and cells were treated with AA and cisplatin to explore the relationship between injury and cell cycle stage, apoptosis and secretory senescence

Results: There was reduced kidney fibrosis in mice heterozygous ($BRCA1^{WT/\Delta11}$) and homozygous ($BRCA1^{\Delta11/\Delta11}$) for PT *BRCA1* deletion compared to wild type ($BRCA1^{WT/WT+}$) littermate controls by MT and PS staining after I/R, UUO or AA. There was a corresponding decrease in fibrogenic factors including CTGF, COL4A1, fibronectin and ACTA2 in the $BRCA1^{WT/\Delta11}$ and $BRCA1^{\Delta11/\Delta11}$ mice. There was a decrease in the markers of cell cycle arrest and senescence ($p16^{ink4a}$ and GATA4) and an increase in apoptosis among $BRCA1^{WT/\Delta11}$ or $BRCA1^{\Delta11/\Delta11}$ mice when compared to WT mice. These murine data were supported by in vitro experiments with AA and Cisplatin after depleting BRCA1 in PT cells which caused less G2 cell cycle arrest and secretion of fewer fibrogenic factors

Conclusions: BRCA1 facilitates interstitial fibrosis following kidney tubular injury in mice through its role in DNA damage response and induction of senescence. We have thus identified a novel role of BRCA1 in non malignant pathobiology.

Funding: NIDDK Support, Private Foundation Support

SA-OR083

Bone Marrow Stromal Cell Antigen-1 Identified by RNA-Seq and ChIP-Seq Is important for Inducing Renal Ischemia-Reperfusion Injury and Fibrosis Tsuyoshi Inoue,[2] Liping Huang,[2] Diane L. Rosin,[2] Katsuhiko Ishihara,[3] Youichiro Wada,[1] Mark D. Okusa.[2] *[1]University of Tokyo, Tokyo, Japan; [2]University of Virginia, Charlottesville, VA; [3]Kawasaki Medical School, Kurashiki, Japan.*

Background: Sphingosine kinase 2-deficient mice (SphK2KO) develop less fibrosis after unilateral kidney ischemia-reperfusion injury (IRI). Sphingosine 1-phosphate (S1P) produced by SphK2 inhibits histone deacetylase (HDAC) and changes in histone acetylation status, which can lead to an altered target gene expression. The aim of this study is to elucidate new mechanisms of kidney fibrosis through epigenetic changes.

Methods: RNA-seq and ChIP-seq of H3K9ac and H3K27ac using primary renal fibroblasts from WT, Sphk1KO and Sphk2KO mice were performed. Flow cytometry was used to identify bone marrow stromal cell antigen-1 (BST-1/CD157) expression in hematopoietic cells. In addition, bone marrow chimeric mice were created to evaluate the role of BST-1 in bone marrow-derived cells. Unilateral IRI was used as a renal fibrosis model and bilateral IRI was used as an acute kidney injury (AKI) model.

Results: The combination of RNA-seq and ChIP-seq analysis yielded 30 candidate genes that might be regulated by SphK2 through epigenetic change. We applied SphK2 knock down to WT fibroblasts and overexpression to fibroblasts from SphK2KO to determine if the selected genes are regulated by SphK2. Gene expression was also evaluated using an in vivo fibrosis model. *Bst1* was identified as a gene that is regulated by SphK2 through a change in histone acetylation level. *Bst1*-deficient mice (*Bst1*KO) developed less fibrosis after renal unilateral IRI and were protected against renal bilateral IRI in the AKI model. Bone marrow chimera experiments further revealed that BST-1 expression on hematopoietic, but not parenchymal cells, is responsible for inducing renal IRI and fibrosis. BST-1 was found mainly in B cells and neutrophils by flow cytometry of spleen and bone marrow. The migration of neutrophils from *Bst1*KO was suppressed, and adoptive transfer of neutrophils from *Bst1*WT mice abolished the renal protective effect in *Bst1*KO mice.

Conclusions: *Bst1* is a gene that is regulated by SphK2 through epigenetic change and is critical in kidney injury and fibrosis. *Bst1*KO mice are protected against renal IRI and develop less fibrosis. Furthermore *Bst1* expression in neutrophils plays an important role in inducing renal ischemia-reperfusion injury and fibrosis.

Funding: NIDDK Support

SA-OR084

BET Protein Family Member BRD4 Promotes Transcription through Super-Enhancer Activation in Kidney Repair and Progression of Fibrosis Julia Wilflingseder,[1,2] Michaela Willi,[2] Chaochen Wang,[2] Hannes Olauson,[1,3] Takaharu Ichimura,[1] M. Todd Valerius,[1] Lothar Hennighausen,[2] Joseph V. Bonventre.[1] *[1]Renal Division, Brigham & Women's Hospital/Harvard Medical School, Boston, MA; [2]Laboratory of Genetics and Physiology, NIDDK/NIH, Bethesda, MD; [3]Division of Renal Medicine, Karolinska Institutet, Stockholm, Sweden.*

Background: The mammalian kidney can repair after acute kidney injury (AKI) through robust proliferation of tubular epithelial cells. Maladaptive repair can however lead to kidney fibrosis and chronic kidney disease (CKD). There is currently limited understanding of which transcriptional regulators activate these repair programs and how transcriptional deregulation leads to CKD. Here we investigate the existence of enhancer regulatory elements occupied by BRD4 that are activated in regenerating mouse kidney.

Methods: RNA-Seq and CHIP-Seq (H3K27ac, H3K4m3, BRD4, MED1, POL2) were performed on samples from repairing kidney cortex day 2 after ischemia reperfusion injury (IRI) to identify activated genes, transcription factors, enhancer and super-enhancers associated with kidney repair. Further we investigated the role of super-enhancer activation in kidney repair through pharmacological BET inhibition via the small chemical compound JQ1 in vitro and in three kidney injury models in vivo.

Results: Here we establish the enhancer and super-enhancer landscape associated with kidney injury and repair. Furthermore, we identify key transcription factors, which cooperate with BRD4 and MED1 at enhancer sites, likely activating repair programs in tubular epithelial cells. Loss of BRD4 function by systemic administration of the

BET inhibitor JQ1 (50mg/kg/d) before IRI leads to impaired recovery after AKI and increased mortality between day 2 and 3 after injury. By contrast, inhibition of prolonged transcriptional responses during repair, through blockade of BRD4 at enhancer sites via JQ1 starting at day 2 and day 7 after injury, ameliorates interstitial fibrosis in UUO, unilateral IRI and aristolochic acid (AA) kidney injury models at day 10 and day 21, respectively.

Conclusions: These results are the first demonstration of BRD4 enhancer and super-enhancer function in the repairing kidney, providing a critical link between AKI and CKD. In addition, our data call attention to potential caveats for use of small molecule inhibitors of BET proteins that are already being tested in clinical trials in patient at risk for AKI. Our comprehensive analysis of epigenetic changes after kidney injury in vivo has the potential to identify new targets for therapeutic intervention.

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SA-OR085

Endocycle-Mediated Hypertrophy and Progenitor Proliferation as Central Mechanisms of Response to AKI Elena Lazzeri, Maria Lucia Angelotti, Anna J. Peired, Carolina Conte, Laura Lasagni, Paola Romagnani. *Center of Excellence DENOthe, Department of Biomedical Experimental and Clinical Sciences, University of Florence, Florence, Italy.*

Background: Acute kidney injury (AKI) is considered a reversible disease because of the capacity of all tubular cells to proliferate as demonstrated by proliferation markers. As AKI can be followed by chronic kidney disease (CKD), we questioned the high intrinsic regenerative capacity of tubules.

Methods: To investigate the proliferative capacity of tubules after AKI, we developed 2 conditional transgenic mouse models: 1. *Pax8.rtTA;TetO.Cre;R26.FUCCI2aR* (Pax8/FUCCI2aR) to track all tubular cells; 2. *Pax2.rtTA;TetO.Cre;R26.FUCCI2aR* (Pax2/FUCCI2aR) to track a putative scattered tubular progenitor population. After doxycycline administration, we investigated the reporter expression in Pax8 and Pax2 cells (cells in G1 phase are mCherry+, in S/G2/M phase are mVenus+) in healthy and at 30 days after unilateral ischemia reperfusion injury (IRI).

Results: Confocal analysis of Pax8/FUCCI2aR mice demonstrated that immunostaining for proliferation markers (KI-67, PCNA and p-H3) didn't mirror exactly cell-cycle phase as indicated by FUCCI2aR reporter. This suggests that cell-cycle markers indicate cell-cycle activation but not cell division after IRI. We, therefore, explored aberrant cell-cycles such as endocycle, where G1 and S proceed repeatedly wihout mitosis, generating cells arrested in G1 phase with a doubled DNA content and an increased size. To detect these cells, we combined FUCCI2aR expression and DNA content assessment by flow-cytometry. This analysis revealed that 11.5±0.8% of Pax8+tubular cells underwent endocycles at day 30 after IRI. Most of endocycling cells were in S1-S2 segments of the cortex with a higher cell surface area in comparison to cells in G1 phase. Accordingly, tubular cell hypertrophy *via* endocycle is the dominant feature in the cortex of human biopsies with CKD after AKI. By contrast, Pax2+tubular cells didn't undergo endocycle but rather complete mitosis at day 30 after IRI. Automatic quantification analysis by flow-cytometry demonstrated that while Pax8+tubular cells are irreversibly lost, Pax2+tubular cells are the only proliferating cells, generating new tubular cells after AKI.

Conclusions: These results demonstrate that, although limited regeneration occurs *via* Pax2 cell proliferation, persistent tubular cell loss and tubular cell hypertrophy *via* endocycle are the dominant features after AKI.

SA-OR086

YAP, Not TAZ, Mediates EGF Receptor Dependent Renal Recovery from AKI Jianchun Chen, Raymond C. Harris. *Vanderbilt University Medical Center, Nashville, TN.*

Background: Both EGFR and the Hippo signaling pathway are implicated in cell proliferation and differentiation. Our previous studies have shown that activation of EGFR in renal proximal tubule epithelial cells (RPTC) plays a critical role in functional and structural recovery from Ischemia-reperfusion injury (IRI). YAP and TAZ, two key downstream effectors of Hippo pathway, are activators for multiple gene transcriptional factors in the nucleus. The goal of these studies was to determine whether YAP and/or TAZ play a role in mediating EGFR's effects in AKI.

Methods: Mice with EGF receptor deletion ($Egfr^{ptKO}$), inducible $SLC34a1^{GCE}$-Cre mediated Yap/Taz double deletion ($Yap/Taz^{l\text{-}ptDKO}$) or Taz single deletion ($Taz^{l\text{-}ptKO}$) specifically in renal proximal tubule epithelial cells (RPTC) or their wild type littermates (WT) were subjected to ischemia-reperfusion injury (IRI). We also determined the effects of silencing EGFR, AKT1 and YAP gene expression by specific siRNAs in a human renal proximal tubule epithelial cell line (hRPTC) on cellular responses to hypoxia exposure for 3 h followed by reoxygenation for either 3 h or 8 h.

Results: Deletion of EGFR specifically in RPTC or administration of an EGFR tyrosine kinase inhibitor, Erlotinib, markedly inhibited YAP expression and nuclear translocation and the YAP downstream target gene, amphiregulin, in response to IRI. Deletion in renal proximal tubule of both *Yap* and *Taz* but not *Taz* alone delayed renal recovery from IRI. BUN remained elevated in $Yap/Taz^{l\text{-}ptDKO}$ mice at day 7 (64 ± 2.5 mg/dl, n=3, P<0.05), while decreasing to 39 ± 3.8 mg/dl or 32 ± 2.5 mg/dl in the $Taz^{l\text{-}ptKO}$ mice or the WT mice after IRI. Upregulation of amphiregulin and cyclin D and phosphorylation of retinoblastoma protein (Rb) in response to IRI were inhibited in $Egfr^{ptKO}$ and the $Yap/Taz^{l\text{-}ptDKO}$ mice. Exposure of the hRPTC to hypoxia followed by reoxygenation increased YAP nuclear translocation, amphiregulin expression, cyclin D expression and Rb phosphorylation, which were inhibited by an EGFR tyrosine kinase or PI3K inhibitor treatments or transfection of EGFR, AKT1 or YAP specific siRNAs.

Conclusions: This study demonstrates that EGFR-PI3K-Akt dependent YAP activation plays an essential role in mediating epithelial cell regeneration during kidney recovery from AKI.

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SA-OR087

Gli1+ Pericytes Are Required for AKI Recovery and Regulate Renal Function Flavia G. Machado,[3] Eoghainín O hAinmhire,[1] Benjamin D. Humphreys.[2] *[1]Washington University, Lake St. Louis, MO; [2]Washington University School of Medicine, Clayton, MO; [3]Washington University in St Louis, School of Medicine, St Louis, MO.*

Background: Gli1+ pericytes support the peritubular vasculature, and their ablation causes transient tubular injury and permanent, subclinical, capillary rarefaction. Whether Gli1+ pericytes are required for renal repair after AKI is unknown.

Methods: We evaluated distribution and density of Gli1+ pericytes after bilateral IRI (bIRI) using Gli1-nLacZ reporter mice. We tested whether the Gli1+ population is fixed or dynamic using Gli1-nLacZ;Gli1CreERT2;R26-tdTomato triple transgenic mice. We asked whether Gli1+ pericytes are required for AKI repair by ablating them and measuring GFR by FITC-sinistrin, then performing biIRI. We also tested the effect of pharmacologic blockade of hedgehog signaling on biIRI recovery with the smoothened inhibitor LDE225.

Results: Gli1+ cells expand in the cortex and outer medulla during AKI recovery. There is substantial de novo Gli1+ expression, as well as loss of Gli1 expression in previously Gli1+ cells, as assessed with Gli1-nLacZ; Gli1CreERT2; R26-tdTomato mice. tdTom single positive and tdTom/nLacZ double positive cell populations increased 3-fold by two weeks after IRI. By contrast, nLacZ single positive cells increased 7-fold. Genetic ablation of Gli1+ cells spontaneously reduced GFR of 242±108ml/min/100gBW (delta baseline vs. after DTX). Mice with ablated Gli1+ pericytes had substantially increased mortality after biIRI (50% 7d after injury, p<0.05 vs. PBS injected mice with 100% survival). Surviving mice 7 days after bIRI had poorer renal recovery compared to controls (434±69 ml/min/100gBW) with 35% of their baseline renal function (vs. 62% on PBS group, p<0.05). Inhibition of hedgehog signaling had a similar effect: 3 days after bIRI mice that received LDE225 exhibited 60 – 80% mortality whether drug was given before or after IRI. Mice receiving vehicle had no mortality.

Conclusions: The Gli1+ pericyte population is not fixed but expands after AKI through both recruitment and proliferation. These cells are required for repair from AKI since their ablation increases mortality and reduces GFR during repair. We suggest that the mechanism is via the hedgehog-Gli signaling pathway itself, since inhibition of smoothened had the same effect after biIRI as Gli1+ cell ablation.

SA-OR088

Myeloid Mineralocorticoid Receptor Controls Inflammatory and Fibrotic Responses after Renal Ischemic Injury via Macrophage Interleukin-4 Receptor Jonatan Barrera-Chimal,[3] Sebastian M. Lechner,[1] Soumaya El moghrabi,[1] Peter Kolkhof,[2] Frederic Jaisser.[1] *[1]INSERM U1130, Centre de Recherche des Cordeliers, Paris, France; [2]BAYER AG, Wuppertal, Germany; [3]Instituto de Investigaciones Biomédicas, UNAM, ----Mexico City, Mexico.*

Background: Pharmacological mineralocorticoid receptor (MR) antagonism is useful to prevent chronic kidney disease (CKD) after an episode of ischemic acute kidney injury (AKI) in the rat. We aimed to test the involvement of myeloid MR in the development of kidney fibrosis after an ischemic AKI episode.

Methods: We included 18 male C57/B6 mice that were divided in: sham, renal ischemia for 22.5 min and IR plus treatment with the non-steroidal MR antagonist finerenone (10 mg/kg) at -48, -24 and -1 h before IR. MR inactivation in myeloid cells (MR^{MyKO}) was achieved by crossing mice with the MR alleles flanked by loxP sites ($MR^{f/f}$) with mice expressing the Cre recombinase under the LysM promoter activity. In $MR^{f/f}$ and MR^{MyKO} mice we induced renal IR of 22.5 min or sham surgery. The mice were followed-up during 4 weeks to test for AKI to CKD transition. In another set of mice, the macrophages were sorted from kidneys after 24 h of reperfusion for flow cytometry analysis or mRNA extraction. Thyoglycolate elicited peritoneal macrophages were used for *in vitro* studies.

Results: The progression of AKI to CKD after 4 weeks of renal ischemia in the untreated C57/B6 and $MR^{f/f}$ mice was characterized by a 50% increase in plasma creatinine, a 2-fold increase in the mRNA levels of TGF-b and fibronectin as well as by severe tubule-interstitial fibrosis. The mice that received finerenone or MR^{MyKO} mice were protected against these alterations. Increased expression of M2-anti-inflamatory markers in kidney-isolated macrophages from finerenone-treated or MR^{MyKO} mice was observed. The inflammatory population of $Ly6C^{high}$ macrophages was reduced by 50%. In peritoneal macrophages in culture, MR inhibition promoted increased IL-4 receptor expression and activation, facilitating macrophage polarization to an M2 phenotype.

Conclusions: MR antagonism or myeloid MR deficiency facilitates macrophage polarization to an M2, anti-inflammatory phenotype after kidney IR, preventing maladaptive repair and chronic kidney fibrosis. MR inhibition acts through the modulation of IL-4 receptor signaling to facilitate macrophage phenotype switching.

Funding: Government Support - Non-U.S.

SA-OR089

Biodistribution and Homing of Human Endothelial Colony Forming Cell-Derived Exosomes in Ischemia-Reperfusion AKI Jose L. Vinas,[1] Matthew Spence,[4] William A. Knoll,[1] Alex Gutsol,[4] Dylan Burger,[1] David Allan,[2] Kevin D. Burns.[3] *[1]Kidney Research Centre, Ottawa, ON, Canada; [2]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [3]Medicine, Ottawa Hospital Research Institute, Ottawa, ON, Canada; [4]University of Ottawa, Ottawa, ON, Canada.*

Background: Infusion of human cord blood endothelial colony forming cell (ECFC)-derived exosomes prevents ischemia/reperfusion acute kidney injury (AKI) in mice, via the transfer of microRNA-(miR)-486-5p, which is highly enriched within these exosomes. Whether exosomes selectively home to the kidneys, and possible targeting mechanisms, are unclear.

Methods: Exosomes were isolated from ECFC conditioned media by serial centrifugation. Ischemia-reperfusion injury was induced in mice by bilateral renal vascular clamp (30 min), with i.v. infusion of DiR-labeled ECFC exosomes at the time of reperfusion, followed by optical imaging. miR-486-5p levels were measured by qPCR in various tissues. Cy3-labeled-pre miR-486-5p was used to study the transfer of exosomal miR-486-5p from ECFCs to cultured human umbilical vein endothelial cells (HUVECs). The potential role of the chemokine SDF1-α and its receptor CXCR4 in exosome homing was studied in HUVECs using a blocking antibody to SDF1-α.

Results: In mice, i.v. infusion of exosomes at the time of reperfusion increased kidney miR-486-5p levels after 30 min ($p<0.01$ vs AKI alone, n=3), with no significant change in miR-486-5p levels in liver, spleen, heart or lungs. After 24 hrs, a further significant increase in miR-486-5p levels was observed only within kidneys ($p<0.01$, n=3). Optical imaging revealed selective homing of exosomes to the kidneys 30 min after reperfusion ($p<0.01$, n=4). Conditioned media from ECFCs transfected with Cy3-pre-miR-486-5p induced an increase in cytoplasmic fluorescence within HUVECs, which was blocked when ECFCs were first treated with the exosome release inhibitor GW4869 or when HUVECs were incubated with the inhibitor of pinocytosis, ethylisopropyl amiloride ($p<0.001$, n=3). By immunoblot, ECFC exosomes expressed CXCR4, and incubation of HUVECs with blocking antibody to SDF1-α prevented exosome uptake (n=3).

Conclusions: ECFC exosomes selectively home to the kidneys after infusion in mice with ischemia-reperfusion AKI, associated with early and sustained increases in kidney levels of miR-486-5p. Endothelial cells are targeted by exosomes, possibly via interaction of CXCR4 with SDF1-α, leading to transfer of miR-486-5p. The results suggest that ECFC exosomes may have therapeutic potential in human AKI due to selective kidney targeting.

Funding: Private Foundation Support

SA-OR090

Role of Cyclin G1 in Maladaptive Repair and Kidney Fibrosis Adam W. Scott,[1,3] Craig R. Brooks,[2] Takaharu Ichimura,[3] Joseph V. Bonventre.[3] *[1]Boston Children's Hospital, Boston, MA; [2]Vanderbilt University Medical Center, Nashville, TN; [3]Brigham & Women's Hospital/ Harvard Medical School, Boston, MA.*

Background: Survivors of acute kidney injury (AKI) have an increased risk for the development of chronic kidney disease (CKD). Previous work from our lab has demonstrated that G2/M cell cycle arrest is an important driver for the maladaptive repair process that leads to renal fibrosis. Using unbiased gene expression profiling, one of the major pathways upregulated following injury is the p53 pathway, and within this pathway cyclin G1 expression was increased. While the exact function of cyclin G1 is not well known, it is known to interact with p53 and is involved in cell cycle arrest at G2/M. We hypothesize that cyclin G1 plays a critical role in the maladaptive repair process following AKI that leads to progressive fibrosis and CKD.

Methods: We transfected HK-2 cells with the mouse (mCG1) or human form of cyclin G1 (hCG1), and analyzed cell cycle markers as well as inflammatory cytokines. Using a global knockout murine model of cyclin G1 compared with wild-type mice, we performed bilateral IRI to evaluate the effect of cyclin G1 on AKI. Animals were sacrificed at 48 hours and 7 days. We then analyzed markers of renal dysfunction and routine histology. We also performed immunofluorescence experiments staining for KIM-1 to compare proximal tubule injury between the two groups.

Results: Transfection with either mCG1 or hCG1 in vitro induced a higher percentage of cells into G2/M phase. These cells also demonstrated increased production of TGF-beta and CTGF. At 48 hours after ischemic kidney injury, there was a tendency towards increased KIM-1 staining by immunofluorescence in the wild-type animals compared to cyclin G1 knockout animals. At 7 days, KIM-1 staining by immunofluorescence was decreased in the knockout animals compared to wild-type mice. Histologically, there was a decreased amount of tubular injury, including reduced inflammatory response and tubular vacuolization, in the knockout animals compared to the wild-type animals.

Conclusions: Cyclin G1 overexpression leads to an increase in the number of cells in the G2/M phase of the cell cycle, and is associated with a pro-inflammatory phenotype. In vivo, cyclin G1 is associated with a more severe injury phenotype in an animal model of AKI. In vivo knockout of cyclin G1 expression led to decreased proximal tubular injury and suggests a role for cyclin G1 in promoting maladaptive repair following AKI that leads to renal fibrosis.

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SA-OR091

Neutrophils Induce Endothelial Cell Injury through the Release of Extracellular Vesicles Containing miRNA in ANCA-Associated Renal Vasculitis Alexandre Glemain,[1,2] Mélanie Néel,[1,2] Rozenn Le Bloas,[1,2] Fadi Fakhouri,[1,2] Sarah Bruneau.[1,2] *[1]Centre de Recherche en Transplantation et Immunologie UMR1064, INSERM, Université de Nantes, Nantes, France; [2]Institut de Transplantation Urologie Néphrologie (ITUN), CHU Nantes, Nantes, France.*

Background: To date, the pathophysiological mechanisms by which neutrophils cause endothelial damage in anti-neutrophil cytoplasm antibodies (ANCA)-associated renal vasculitis (AARV) are not fully elucidated. Some data suggest that neutrophil-derived extracellular vesicles (EV) may contribute to endothelial cell (EC) activation, but the mechanisms by which these EV can induce EC damage in the context of AARV, and the role of miRNA they may contain have not been studied.

Methods: In these studies, we used TaqMan Low Density Arrays to identify miRNA released in EV by ANCA-activated neutrophils that are internalized by microvascular EC in vitro. The consequences of this miRNA transfer were analyzed using an overexpression approach in microvascular EC.

Results: We identified three particular miRNA transferred from ANCA-activated neutrophils to microvascular EC in vitro: miR-223, miR-142-3p and miR-451. The overexpression of miR-142-3p and/or of miR-451 in EC led to profound cell damage, especially in inflammatory conditions (TNFα). This was characterized by the induction of EC apoptosis by miR-142-3p (n=8, $P<0.01$), the inhibition of EC proliferation by miR-451 (n=8, $P<0.05$) and as a result, impairment of EC repair and angiogenesis by these two miRNA as observed in wound-healing (n=6, $P<0.05$) and tube formation (n=7, $P<0.05$) assays. Using phosphokinase protein arrays, we found that miR-142-3p inhibits the mTORC1, ERK1/2 and eNOS signaling pathways in EC, which may explain its strong effect on EC injury. Moreover, miR-142-3p and miR-451 overexpression in EC resulted in marked activation responses, characterized by induced expression of the leukocyte chemoattractant chemokines CXCL10 (2- to 5-fold), CXCL11 (2- to 3-fold) and IL8 (6-fold), as well as the proinflammatory cytokine IL6 (4-fold), as assessed by mRNA expression arrays. In contrast, miR-223 overexpression had no significant impact on EC responses in our studies.

Conclusions: Collectively, these findings identify miR-142-3p and miR-451 as critical mediators of neutrophil-induced endothelial damage in the course of AARV, and suggest that specific targeting of these miRNA in EC may have implications for the prevention of microvascular injury in AARV patients.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-OR092

CKD-induced Hedgehog/PDGFRα Signaling Activates Mesenchymal Stem Cells, Accelerating Arteriovenous Fistula Failure Ke Song, William E. Mitch, Jizhong Cheng. *Baylor College of Medicine, Houston, TX.*

Background: we find that ~50% of neointima cells in failing arteriovenous fistulas (AVF), originate from vascular smooth muscle cells (VSMCs) of the arterial anastomosis. Other sources of VSMCs are unclear. One contributor is the adventitial $Gli1^+$-mesenchymal stem cells (MSCs) that transdifferentiate into fibroblasts or VSMCs. How MSCs contribute to AVF neointimal formation in CKD mice is unknown.

Methods: in mice, we created CKD and then, AVFs in order to study how Hedgehog/PDGFRα signaling stimulates activation and differentiation of MSCs. We also examined crosstalk between MSCs and VSMCs assessed both *in vivo* and *in vitro*. This was possible because we labelled VSMCs and MSCs by using SMMHC-ERCre and Gi1-ERCre reporter mice, respectively.

Results: in AVFs, created in Gli1-CreER uremic mice, few GFP-labelled MSCs were in the neointima. Most of these MSCs were in the adventitia and they expressed fibroblast markers. Using VSMC reporter mice (SMMHC-ERCre mice), we found that VSMCs migrated into the AVF adventitia. Consequently, adventitial MSCs were able to interact with VSMCs, promoting activation and proliferation of VSMCs. What accounts for these interactions? First, we found that CKD stimulates MSCs to differentiate into either myofibroblasts or VSMCs via TGF-β1. MSCs isolated from CKD showed increased potential for differentiation into myofibroblasts with the expense of adipogenesis. Secondly, there was increased hedgehog signaling in MSCs that increased the expression of PDGFRα which is required for activation of TGF-b1 signaling. Notably, an inducible-specific KO of PDGFRα in MSCs led to reduced MSCs differentiation into adventitial fibroblasts. This process impairs VSMC activation resulting in reduced neointima area with increased AVF patency despite CKD.

Conclusions: CKD activates hedgehog/PDGFRα signaling in adventitial MSCs, promoting their differentiation into myofibroblasts or VSMCs. Interfering with the Hedgehog/PDGFRα signaling pathway in MSCs could suppress neointima formation with improvement in AFV maturation.

Funding: NIDDK Support, Other U.S. Government Support

SA-OR093

Genetic Risk for Scleroderma Renal Crisis in RNA-Polymerase III Antibody Positive Patients Edward Stern,[1,2] Sandra G. Guerra,[2] Mark Harber,[1] Aine Burns,[1] Carmen Fonseca,[2] Christopher P. Denton.[2] *[1]Centre for Nephrology, UCL, London, United Kingdom; [2]Centre for Rheumatology and Connective Tissue Diseases, UCL, London, United Kingdom.*

Background: Scleroderma renal crisis (SRC), characterised by accelerated hypertension and AKI, is a life-threatening complication of systemic sclerosis (SSc). Most SSc cases have a disease-specific circulating antibody, including the anti Scl-70, anti-centromere or anti RNA polymerase III (ARA) antibodies. Previous studies confirm ARA as a powerful serological predictor of SRC, and cases of SRC more than 5 years after the diagnosis of SSc are rare. We developed an innovative approach to identify genetic susceptibility loci for SRC, comparing ARA positive patients with and without the occurrence of SRC.

Methods: From a well-characterised SSc cohort (n=415), we selected 100 ARA+ patients with more than 5 years of follow-up data. 50 had a history of SRC and 50 had not developed SRC. Cases were genotyped using the Illumina Human Omni-express chip. Quality control checks were performed in PLINK (Hardy-Weinberg equilibrium p < 0.001; genotyping rate >90%). Based on the results of logistic regression analysis, ten SNPs were put forward for validation in a separate US cohort of 256 ARA+ patients (40 SRC+), using ThermoFisher TaqMan genotyping probes. Immunohistochemistry (IHC) was performed on SRC biopsy samples to identify proteins associated with our genes of interest.

Results: After quality control checks, 641,489 SNPs were analysed in the first cohort. In logistic regression analysis of our initial cohort, the SNPs within genes and gene regions most strongly associated with SRC were for POU2F1 ($p=4.12 \times 10^{-5}$), CTNND2 ($p=2.92 \times 10^{-5}$), HECW2 ($p=2.71 \times 10^{-5}$), GRIA3 ($p=2.16 \times 10^{-5}$) and GPATCH2L ($p=2.06 \times 10^{-5}$). The SNP within the GPATCH2L region was also significantly associated with SRC in our validation cohort (p=0.025). GPATCH2L polymorphisms have been associated with arterial hypertension in previous GWAS analyses. Polymorphisms in the CTNND2 gene have been demonstrated to be associated with pulmonary arterial hypertension, another vasculopathic complication of SSc, in previous studies. We performed IHC for this protein, and confirmed altered staining of mesangial cells in SRC biopsy samples compared with controls.

Conclusions: A novel autoantibody-based extreme phenotype method identifies risk alleles for SRC within a rare disease cohort. In particular we identify CTNND2 and GPATCH2L as candidates for investigation of SRC aetiopathogenesis.

Funding: Government Support - Non-U.S.

SA-OR094

Upregulation of Lysyl Oxidase Activity in Vascular Smooth Muscle Underlies Increased Vascular Stiffness in CKD Rajesh Mohandas,[2,3] Brandon To,[1] William W. Hahn,[1] Philip Ferns,[1] Cody Kilar,[1] Mark S. Segal.[2,3] *[1]University of Florida, Melbourne, FL; [2]University of Florida, Gainesville, FL; [3]Renal Section, North Florida/South Georgia Veterans Health System, Gainesville, FL.*

Background: Introduction: Individuals with chronic kidney disease (CKD) have increased vascular stiffness which correlates with adverse cardiovascular outcomes and mortality. This increase in stiffness is thought to be a consequence of the metabolic derangements of CKD. However, our data shows that vascular smooth muscle dysfunction occurs early in CKD and is not completely explained by endothelial dysfunction. Lysyl oxidase is an amine oxidase that crosslinks collagen and elastin and contributes to stiffness of extracellular matrix. LOX is upregulated by reactive oxygen species, which is increased in CKD. **Hypothesis:** We hypothesized that increased vascular stiffness in CKD is due to upregulation lysyl oxidase and increases in collagen and elastin cross linking.

Methods: Method: In vitro: Aortic smooth muscle cells were treated with serum from uremic patients or healthy controls. Lysyl oxidase mRNA and activity was measured by a colorimetricassay. In vivo: 6-8 week old C57BL6 mice were subject to a 5/6 nephrectomy model of CKD or sham surgery. 6 weeks later mice were sacrificed. Serum levels of lysyl oxidase were assayed. Mesenteric arteries were mounted in an arteriograph chamber and denuded of endothelium. Passive compliance was determined by measuring changes in luminal diameter to step wise increments in luminal pressure. Aortic smooth muscle lysates were assayed for lysyl oxidaseactivity.

Results: Results: Treatment with uremic serum resulted in an upregulation of lysyl oxidase in cell culture supernatant 22.5 vs 15.58 (n=6 p=0.001). Mice subjected to the CKD model demonstrated increased vascular stiffness. Aortic smooth muscle lysates demonstrated increased lysyl oxidase activity in CKD mice as compared to sham surgical controls [15.67 vs. 12.75 (n=5, p=0.02)]. There was no change in serum lysyl oxidase activity.

Conclusions: Conclusion: Upregulation of lysyl oxidase in vascular smooth muscle cells occurs early in CKD and may be a key mediator of increased vascular stiffness. Lysyl oxidase is a potential novel therapeutic target for CV disease in CKD.

Funding: Other NIH Support - NHLBI

SA-OR095

Mitoprotection Preserves the Renal Microvasculature in Porcine Metabolic Syndrome Alfonso Eirin, Ahmad F. Hedayat, Christopher M. Ferguson, Kyra L. Jordan, Stephen C. Textor, Amir Lerman, Lilach O. Lerman. *Mayo Clinic, Rochester, MN.*

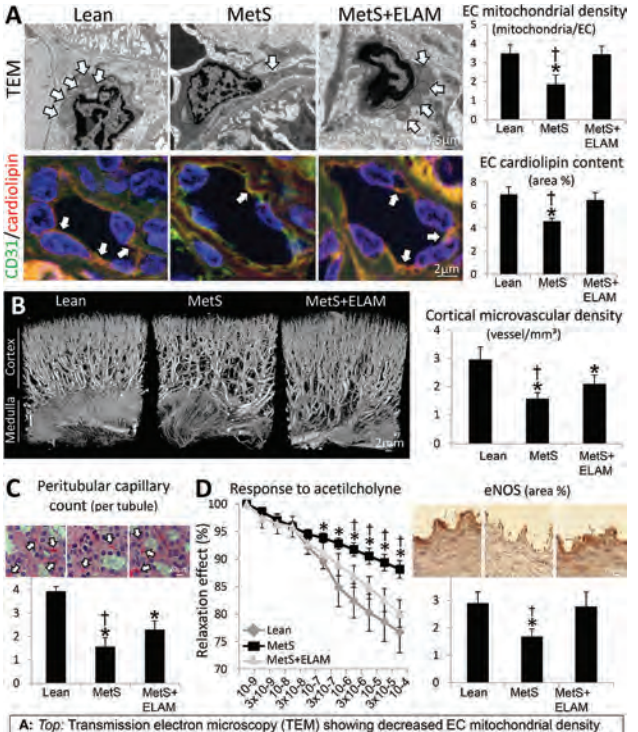
Background: The metabolic syndrome (MetS) induces intra-renal microvascular disease, which may involve mitochondrial injury. The mitochondrial cardiolipin-targeting peptide elamipretide (ELAM) improves the microcirculation in post-stenotic kidneys, but its potential for attenuating MetS-induced microvascular dysfunction is unknown. We hypothesized that chronic treatment with ELAM would decrease vascular remodeling and dysfunction in swine MetS.

Methods: Pigs were studied after 16 weeks of diet-induced MetS, MetS after 4 weeks of ELAM treatment (0.1mg/kg SC q.d), and Lean controls (n=6 each). Vascular endothelial cell (EC) mitochondrial density (electron microscopy) and cardiolipin content (10N-nonyl acridine orange staining) were assessed in situ. The density of peritubular capillaries (PTC, H&E staining) and renal microvessels (20-500μm, 3D micro-CT), and the function of renal artery segments (organ bath, endothelial nitric oxide (eNOS) expression) were characterized.

Results: MetS pigs developed obesity, hypertension, hyperlipidemia, and insulin resistance. Mitochondrial density and cardiolipin content in EC were diminished in MetS, but improved in ELAM-treated pigs. Furthermore, ELAM improved PTC and microvascular density, and restored eNOS expression and endothelial-dependent relaxation of renal artery segments.

Conclusions: MetS-induced mitochondrial alterations might contribute to renal PTC and microvascular loss, and impair renal artery endothelial function in pigs. These observations suggest a potential role for mitoprotection in preserving the renal microvasculature in MetS.

Funding: NIDDK Support, Commercial Support - Stealth BioTherapeutics, Inc.



A: *Top:* Transmission electron microscopy (TEM) showing decreased EC mitochondrial density (arrows) in MetS that improved in MetS+ELAM. *Bottom:* Double immunofluorescence staining of CD31 and cardiolipin (arrows). **B:** Representative 3D micro-CT images of the pig kidney, showing decreased number of cortical microvessels in MetS that improved in MetS+ELAM. **C:** Peritubular capillary density (arrows) decreased in MetS, but improved in ELAM-treated pigs. **D:** ELAM restored endothelial-dependent relaxation and eNOS expression in renal artery segments. *p<0.05 vs. Lean; †p<0.05 vs. MetS+ELAM.

SA-OR096

Targeting STUB1-Tissue Factor Axis Normalizes the Hyperthrombotic Uremic Phenotype without Increasing Bleeding Risk Moshe Shashar,[3] Mostafa Belghasem,[3] Shinobu Matsuura,[3] Faisal F. Alousi,[3] Keshab Rijal,[3] Vijaya B. Kolachalama,[4] Joel M. Henderson,[3] Amitabh Gautam,[1] Jean M. Francis,[3] Katya Ravid,[2] Vipul C. Chitalia.[4] *[1]Boston Medical Center, Boston, MA; [2]Boston University, Boston, MA; [3]Boston University Medical Center, West Roxbury, MA; [4]Boston University School of Medicine, Boston, MA.*

Background: Atherothrombosis remains one of the major complications in CKD patients despite their treatment with antithrombotic/antiplatelet therapies. Though associations of uremic solutes (e.g. indolic solutes) and vascular wall protein, such as

tissue factor (TF) and Aryl Hydrocarbon Receptor (AHR) have been defined, the specific mechanisms that drive the thrombotic and bleeding risks have not been fully understood, nor means by which they might be therapeutically manipulated. We further probed the uremic solute-AHR-TF axis for it's role in uremic hyperthrombogenicity.

Methods: TF expression and activity and half-life were examined. Indoxyl sulfate was detected in animals using LC/MS approach. Adenine-induced CKD model and a novel uremic-solute injected mice were generated. Customized object-level intensity estimation algorithms were developed to quantify TF and carboxy terminus Hsc70 interacting protein (CHIP/STUB1) expressions in human arteriovenous fistulae (AVF) explants.

Results: We demonstrate that indolic solutes mediate the hyperthrombotic phenotype across all CKD stages in AHR- and TF-dependent manners in a mouse model *in vivo*. We demonstrate further that AHR regulates TF through STUB1, by interacting and degrading TF through ubiquitination, dependent on the uremic status. TF regulation by STUB1 is substantiated in humans by an inverse relationship between STUB1 and TF expression, and reduced STUB1-TF interaction in AVF explants. AHR and STUB1 modulations normalized the uremic hyperthrombotic phenotype to non-CKD range in both the animal models of CKD without prolonging the bleeding time. This finding is in stark contrast to Heparin, the standard-of-care antithrombotic in CKD patients

Conclusions: Our data implicate indolic solutes as bonafide mediators of the hyperthrombotic uremic *milieu*. Importantly, targeting the STUB1-TF axis reverses the thrombosis risk to the non-CKD range, importantly, without altering the hemostatic balance. Overall, we have significantly expanded the understanding of the interconnected relationships of thrombosis and hemostasis that drive the fragile thrombotic state in CKD.

Funding: Other NIH Support - NATIONAL HEART, LUNG, AND BLOOD INSTITUTE, Private Foundation Support

SA-OR097

Renin Cell Precursors Require B1 Integrin for Normal Vascular Development and Renal Function Tahagod Mohamed, Rajwinderjit Kaur, Roberto Ariel Gomez, Maria Luisa S. Sequeira Lopez. *University of Virginia, Charlottesville, VA.*

Background: Integrins are the largest family of cell adhesion molecules that mediate cell-to-cell and cell-to-matrix interactions. β1-Integrin (Itgb1) is the most abundantly expressed β subunit and is present in almost every cell type. Previous studies showed that Itgb1 is required for normal development of the ureteric bud and podocytes and for the function of the proximal tubule. However, its role in the kidney vasculature has not been explored. Renin cells are crucial for blood pressure homeostasis and for normal nephrovascular development. The mechanisms involved in their morphogenetic functions are not well understood. We found that Itgb1 is highly expressed in renin expressing cells throughout development.

Methods: To study the role of Itgb1 in renin cells we generated a conditional deletion (cKO) of Itgb1 in cells of the renin lineage by crossing floxed Itgb1 mice with mice expressing *cre recombinase* driven by the *renin* locus

Results: Itgb1 cKO mice were smaller in size (20.32 ± 4.35 g *vs* 29.55 ± 7.39 g, *p=0.016*), had smaller kidney to body weight ratio (0.92 ± 0.30 *vs* 1.31 ± 0.30, *p=0.017*), hypotension (MABP 82.33 ± 4.00 mmHg *vs* 92.55 ± 7.72 mmHg, *p=0.02*), anemia (hemoglobin 11.26 ± 1.48 g/dL *vs* 15.07 ± 1.31 d/dL, *p=0.003*; hematocrit 40.39 ± 5.48% *vs* 53.8 ± 4.21%, *p=0.002*), renal failure (BUN 71.44 ± 32.81 mg/dL *vs* 29.4 ± 7.67mg/dL, *p=0.004),* and lower plasma renin levels (6664.58 ± 3251.92 *vs* 43357.09 ± 17032.63 pg/ml, *p*=0.001*).* Mutants also developed hyposthenuria (urine osmolality 452 ± 138.98 mOsm/kg *vs* 1460.5 ± 482.09 mOsm/kg, *p<0.02*). Histological analysis revealed excessive collagen deposition in the interstitium and peri-glomerular areas; fibrocystic glomeruli; tubular dilatation and protein casts in the tubules. Immunostaining for renin and α-smooth muscle actin showed a marked decrease in renin protein expression and abundant α-smooth muscle actin expression in the interstitium. Microdissection of the renal arterial tree combined with renin immunostaining confirmed the marked decrease in renin and evidenced the overall vascular abnormalities including fewer and shorter arterial and arteriolar branches.

Conclusions: Overall, this study shows that β1-Integrin in cells of the renin lineage is crucial for renin expression, morphogenesis of the renal vasculature and maintenance of the normal kidney architecture and function.

Funding: NIDDK Support

SA-OR098

Liraglutide Treatment Improves Renal Vascular Function in Zucker Rats as Visualized by Microangiography Vijayakumar Sukumaran,[2,3] Takashi Sonobe,[3] Hirotsugu Tsuchimochi,[3] Eisuke Tatsumi,[2] Mikiyasu Shirai,[1] James T. Pearson.[3,4] *[1]Department of Advanced Medical Research for Pulmonary Hypertension, National Cerebral and Cardiovascular Center, Suita, Japan; [2]Department of Artificial Organ, National Cerebral and Cardiovascular Center, Suita, Japan; [3]Department of Cardiac Physiology, National Cerebral and Cardiovascular Centre, Osaka, Japan; [4]Department of Physiology, Monash Biomedicine Discovery Institute, Monash University, Clayton 3800, ACT, Australia.*

Background: Metabolic syndrome is a cluster of conditions that synergistically increase the risk of cardiovascular disease, type 2 diabetes, and premature mortality. In this present study, we investigated whether chronic liraglutide (LIRA) treatment affects the metabolic profile and renal vascular function in Zucker rats on a high-salt diet (6%NaCl).

Methods: Eight-week old Zucker lean and Zucker obese (fa/fa) rats were treated with vehicle or LIRA (0.1mg/kg/day) for 8 weeks. Glomerular filtration rate (GFR) was measured at 0 and 8 weeks by using fluorescein isothiocyanate (FITC)-sinistrin method in conscious rats. Further, we used X-ray microangiography to measure the renal arterial diameter (70-350 μm) and vessel number in the anaesthetised rats. Renal protein expression levels of nitrotyrosine and transforming growth factor (TGF)-beta 1 were detected by Western blotting.

Results: After 8 weeks of high-salt diet, systolic blood pressure was significantly increased, renal function and structure were impaired, and collagen deposition was abundant in renal tissues of vehicle-treated Zucker fa/fa rats. We found that in comparison to the untreated Zucker fa/fa rats, rats treated chronically with LIRA showed improved GFR and nitric oxide-mediated vasodilation in response to acetylcholine in small artery and arterioles (<200 μm diameter). Further, vessel internal diameter and visible vessel number (%) were greater in LIRA treated fa/fa rats compared to vehicle-treated rats (Figure 1). Moreover, LIRA treatment decreased the protein expression of nitrotyrosine and TGF-β1 compared to those of vehicle-treated rats.

Conclusions: These results suggest that LIRA treatment improved renal vascular function through dilation of small intrarenal arteries and arterioles.

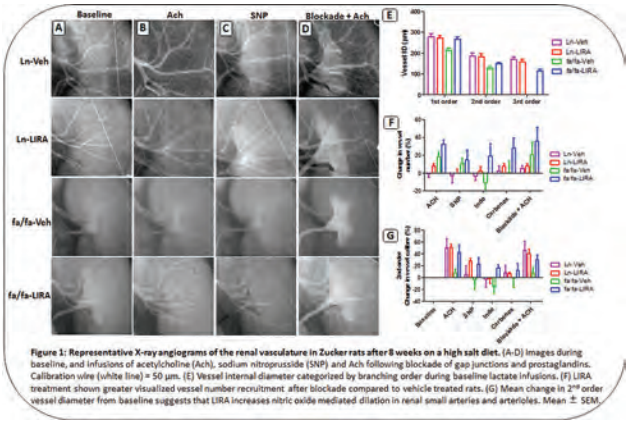


Figure 1: Representative X-ray angiograms of the renal vasculature in Zucker rats after 8 weeks on a high salt diet. (A-D) Images during baseline, and infusions of acetylcholine (Ach), sodium nitroprusside (SNP) and Ach following blockade of gap junctions and prostaglandins. Calibration wire (white line) = 50 μm. (E) Vessel internal diameter categorized by branching order during baseline lactate infusions. (F) LIRA treatment shown greater visualized vessel number recruitment after blockade compared to vehicle treated rats. (G) Mean change in 2nd order vessel diameter from baseline suggests that LIRA increases nitric oxide mediated dilation in renal small arteries and arterioles. Mean ± SEM.

SA-OR099

Indoxyl sulfate Promotes Macrophage Activation via Novel Crosstalk between OATP2B1 and Dll4-Notch Signaling Toshiaki Nakano,[2] Julius L. Decano,[2] Shunsuke Katsuki,[2] Mario S. Boff,[2] Whitney S. Irvin,[2] Hideyuki Higashi,[2] Sasha Singh,[2] Elena Aikawa,[1] Masanori Aikawa.[2] *[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA.*

Background: CKD increases cardiovascular risk, however, its underlying mechanisms remain obscure. We previously reported the role of the Notch signaling ligand Delta-like 4 (Dll4) in macrophages. We tested the novel hypothesis that Dll4-Notch mediates macrophage activation stimulated by indoxyl sulfate.

Methods: We examined the effects of indoxyl sulfate (0.25–1.0 mM) on pro-inflammatory responses and Notch signaling in macrophages and the roles of organic anion transporters / polypeptides (OATs/OATPs). To determine the contribution of OATP2B1 to pro-inflammatory activation of macrophages *in vivo*, we used macrophage-targeted lipid nanoparticles to deliver siRNA to mice. To address the role of Dll4 in atherogenesis in CKD, we used 5/6 nephrectomy and Dll4 neutralizing antibody in mice.

Results: [In vitro] In human primary macrophages, indoxyl sulfate induced pro-inflammatory molecules IL-1β, TNFα, and MCP-1 and Notch signaling components Dll4, Notch1 and Hes1. Decreased degradation by ubiquitin-proteasome pathway appears to promote rapid induction of Dll4 < 1 hour by indoxyl sulfate (FACS, Western blotting, immunofuorescence), which in turn triggers Notch signaling. Notch inhibition with the γ-Secretase inhibitor, Dll4 siRNA or Dll4 antibody indeed suppressed indoxyl sulfate-induced macrophage activation. We identified previously unreported 9 OATs/OATPs in macrophages, among which human and mouse commonly expressed OATP2B1. Suppression of OATP2B1 suppressed macrophage uptake of indoxyl sulfate (HPLC), Notch signal components Dll4 and Hes1, and pro-inflammatory genes. [In vivo] Indoxyl sulfate administration in mice promoted expression of IL-1β and MCP-1 in peritoneal macrophages. Co-administration of Dll4 antibody or OATP2B1 siRNA encapsulated in macrophage-targeted nanoparticles suppressed these responses ($p<0.05$, n=6-8). In LDL receptor-deficient mice, 5/6 nephrectomy enhanced Notch signaling and the development of atherosclerosis, macrophage burden, calcification, and pro-inflammatory responses, which were abrogated by Dll4 antibody ($p<0.01$ vs. IgG; n=20/group).

Conclusions: These lines of in vitro and in vivo evidence suggest that crosstalk between OATP2B1 and Dll4-Notch signaling mediates indoxyl sulfate-induced macrophage activation and vascular disease.

SA-OR100

Autologous Mesenchymal Stem Cells Decrease Blood Pressure and Kidney Injury in Human Renovascular Disease Ahmed Saad, Sandra Herrmann, LaTonya J. Hickson, James Glockner, Allan B. Dietz, Lilach O. Lerman, Stephen C. Textor. *Mayo Clinic, Rochester, MN.*

Background: Atherosclerotic renovascular disease (RVD) reduces blood flow (RBF), glomerular filtration rate (GFR) and accelerates both systemic hypertension and post-stenotic kidney (SK) tissue injury. Preclinical studies indicate that MSCs stimulate angiogenesis and modify immune function in experimental RVD. We assessed the safety and clinical effects of intrarenal autologous MSCs in a phase 1/2A study of human subjects with RVD.

Methods: Adipose tissue-derived MSCs were collected from 21 RVD patients (age 73.7 ± 4.3; 13 male and 8 females). Inpatient studies were performed during fixed Na+ intake and ACE/ARB Rx before and 3 months after unilateral intra-arterial single infusion of MSC of either 1.0, 2.5 or 5 x 10^5 cells/kg into the SK (n=7 each). SK cortical/medullary perfusion and RBF were measured using multidetector CT, GFR by iothalamate clearance, Injury markers including NGAL and VEGF-C were measured in the renal veins and renal tissue oxygenation was assessed by BOLD-MRI at 3T.

Results: Intra-arterial MSC infusions were tolerated without adverse effects. Tissue perfusion and RBF increased after 3 months ($p<0.05$ vs. baseline), and fractional hypoxia (%R2*>30 sec-1) decreased in the treated kidneys. Renal vein levels of NGAL and VEGF-C decreased (Table). Systolic blood pressure fell ($P<0.05$) and iothalamate-GFR marginally increased ($P=0.053$) 3 months after MSC (Table). These changes were of similar magnitude among the 3 doses.

Conclusions: In this "first-in-human" dose escalation study in 21 patients with atherosclerotic RVD, a single intraarterial infusion of autologous adipose tissue-derived MSCs into the SK decreased systolic blood pressure and increased RBF after three months. These were associated with a reduction in tissue hypoxia and renal injury cytokines, while GFR tended to improve. Our results demonstrate the capability of intrarenal MSC to increase tissue oxygenation and RBF in the human kidney, and support a potential role for MSC in the management of ischemic renal disease.

Funding: NIDDK Support

N=21	*Baseline*	*3 months after MSC infusion*
Systolic blood pressure (mmHg)	143.4 ± 12.8	136.4 ± 14.6*
Iothalamate clearance GFR (mL/min)	52.7 ± 16.5	55.6 ± 16.4
NGAL (ng/ml)	192 ± 63.7	179.5 ± 49*
VEGF-C (pg/ml)	644.7 ± 277	576.7 ± 247*
Cortical perfusion, mL/min/mL tissue	2.21 ± 0.79	2.5 ± 1.02*
RBF, mL/min	151.9 (68.5, 232)	197.3 (71.8, 255)*
Cortical flow, mL/min	125.6 (55, 202)	156.4 (60.4, 217)*
Medullary flow, mL/min	28.7(13.6, 34)	30.9 (15.8, 38.8)
Renal hypoxia (% R2* > 30 sec^{-1})	10.5 (4.6, 14.7)	7.3 (2.5, 9.9)*

*P< 0.05 vs baseline (Wilcoxon signed-rank test). Values are presented as mean ± SD or median (IQR).

SA-OR101

Causes of Death in Patients Who Survive a Hospitalization with AKI Samuel A. Silver,[6] Ziv Harel,[4] Eric McArthur,[1] Danielle M. Nash,[3] Rey R. Acedillo,[2] Abhijat Kitchlu,[7] Amit X. Garg,[3] Glenn M. Chertow,[5] Ron Wald.[4] *[1]Institute for Clinical Evaluative Sciences, London, ON, Canada; [2]Kingston Health Sciences Centre, Kingston, ON, Canada; [3]London Health Sciences Centre, London, ON, Canada; [4]St. Michael's Hospital, Toronto, ON, Canada; [5]Stanford University School of Medicine, Palo Alto, CA; [6]Queen's University, Kingston, ON, Canada; [7]University of Toronto, Toronto, ON, Canada.*

Background: Mortality after an acute kidney injury (AKI) episode is high, but the causes of death are not well described. We sought to better understand causes of death in patients who survive a hospitalization with AKI, and hypothesized that cardiovascular disease would account for most deaths after hospital discharge.

Methods: We conducted a population-based study of residents in Ontario, Canada, who survived a hospitalization with AKI from 2003-2013. We defined AKI with validated ICD-10 diagnosis codes. Using linked administrative databases, we categorized cause of death in the year following hospital discharge as cardiovascular, cancer, infection-related, or other. We calculated standardized mortality ratios (SMR) to compare the cause of death in survivors of AKI to the general adult population, and used Cox proportional hazards modeling to estimate determinants of death.

Results: Of the 156,690 patients discharged after an AKI episode, 43,422 (28%) died in the subsequent year. The most common causes of death were cardiovascular disease (28%) and cancer (28%), with respective SMRs nearly six-fold (5.81, 95% CI 5.70-5.92) and nearly eight-fold (7.87, 95% CI 7.72-8.02) higher relative to the general population. The highest SMRs were for cancer-related mortality, specifically bladder cancer (18.24, 95% CI 17.10-19.41), gynecologic cancer (16.83, 95% CI 15.63-18.07), and leukemia (14.99, 95% CI 14.16-15.85). In addition to older age and nursing home residence, factors most strongly associated with one-year mortality were cancer (hazard ratio [HR] 1.62, 95% CI 1.58-1.65) and inpatient chemotherapy (2.03, 95% CI 1.90-2.17).

Conclusions: Among survivors of a hospitalization with AKI, cancer-related death was as common as cardiovascular death; moreover, cancer-related deaths occurred at the highest rates relative to the general adult population. In addition to modifying the risk of subsequent cardiovascular disease, strategies are needed to care for and counsel patients with cancer who experience AKI.

SA-OR102

Ultrasonography-Based Volume Status Assessment Unveils Misclassification of AKI in Cirrhotics as Hepatorenal Syndrome Juan Carlos Q. Velez,[3] Nithin Karakala,[2] John T. Huggins.[1] *[1]Division of Pulmonary and Critical Care, Medical University of South Carolina, Charleston, SC; [2]Division of Nephrology, University of Arkansas for Medical Sciences, Little Rock, AR; [3]Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA.*

Background: The International Ascites Club criteria for the diagnosis of hepatorenal syndrome (HRS) requires documentation of failure to respond to 2 days of intravenous (IV) volume expansion and/or diuretic withdrawal. We hypothesized that ultrasonography (US)-based bedside techniques to assess volume status may provide clinically significant information to ascertain or disprove the clinical diagnosis of HRS.

Methods: A pilot prospective study was conducted to determine the feasibility and clinical utility of US examination of inferior vena cava (IVC) diameter and collapsibility and echocardiographic measurement of velocity time integral (VTI) to assess intravascular volume status in hospitalized adult patients with cirrhosis and acute kidney injury (AKI) who had been deemed adequately volume resuscitated and assigned a clinical diagnosis of HRS.

Results: A total of 52 patients completed the study (mean age 56.2 years, 48% women, 88% white). Mean serum creatinine (sCr) at the time of volume status assessment was 2.9 ± 1.4 mg/dL, and mean Model for End-Stage Liver Disease (MELD) score was 29.8. Twenty-two (42%) patients had an IVC diameter < 1.3 cm and were reclassified as volume depleted, 13 (25%) had an IVC diameter between 1.3 to 2 cm and 17 (33%) had an IVC > 2 cm and were reclassified as volume overloaded. Twenty-four hours later, 12 (55%) of patients reclassified as volume depleted exhibited ≥ 20% decrease in sCr along with improvement in VTI following additional IV volume expansion with ≥ 25 g/day of albumin, whereas 11 (65%) of those reclassified as volume overloaded had ≥ 20% decrease in sCr and improvement in VTI following loop diuretic therapy and/or large volume paracentesis (≥ 5 L). Altogether, 21 (40%) of patients labeled *a priori* as having HRS partially improved kidney function as a result of a therapeutic intervention guided by US-based volume status assessment.

Conclusions: Utilization of bedside US-based assessment of volume status in cirrhotic individuals with AKI may reduce the likelihood of incorrectly assigning a diagnosis of HRS. Further exploration of the clinical applicability of this approach is warranted.

SA-OR103

Prospective Evaluation of AKI and Risk of Heart Failure: The ASSESS-AKI Study Alan S. Go,[2] Talat Alp Ikizler,[6] Vernon M. Chinchilli,[3] Jonathan Himmelfarb,[4] Paul L. Kimmel,[1] James S. Kaufman,[5] Chirag R. Parikh.[7] *[1]NIDDK, Bethesda, MD; [2]Kaiser Permanente Northern California, Oakland, CA; [3]Penn State University, Hershey, PA; [4]Kidney Research Institute, Seattle, WA; [5]VA New York, New York, NY; [6]Vanderbilt University, Nashville, TN; [7]Yale University, New Haven, CT. Group/Team: ASSESS-AKI Study Investigators.*

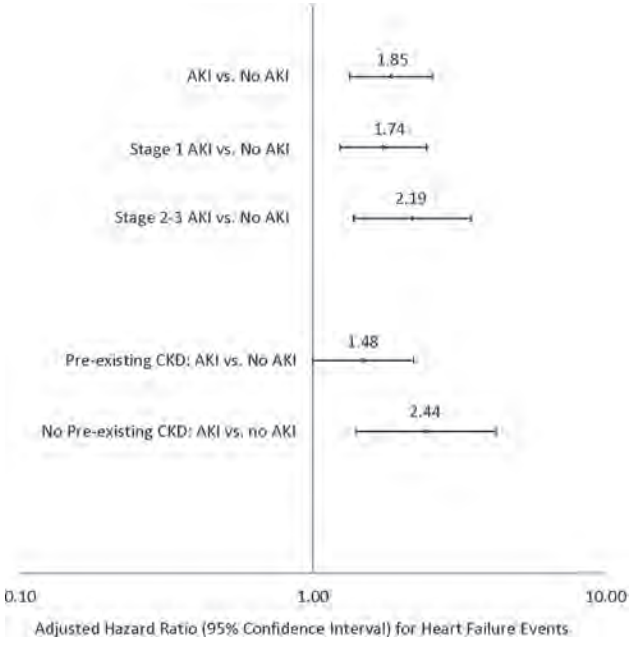
Background: Several retrospective studies suggest that acute kidney injury (AKI) is associated with excess risk of heart failure (HF), but have important methodological limitations. We prospectively evaluated whether AKI impacts subsequent risk of HF.

Methods: Individually-matched hospitalized adults with and without AKI were enrolled in a parallel cohort study from 4 centers between 2009-2015 and completed an outpatient baseline visit within 3 months of discharge. Potential hospitalized HF events were adjudicated through Feb 2017 using medical records and standardized criteria. Demographics, clinical characteristics and kidney function were obtained at baseline. Multivariable Cox proportional hazards regression was used to examine the association of AKI with HF events, overall and stratified by AKI severity and by pre-existing chronic kidney disease (CKD) status.

Results: Among 769 AKI and 769 matched non-AKI adults, baseline characteristics were similar except for higher prevalence of prior cardiovascular disease, diabetes mellitus and diagnosed sepsis during the index admission in AKI patients. During follow-up, the rate (per 100 person-years) of HF was 3.90 in AKI compared with 1.83 in matched non-AKI adults ($P<0.0001$). In multivariable analyses, AKI was associated with a nearly 2-fold higher rate of HF (adjusted hazard ratio [aHR] 1.85, 95% CI:1.34-2.56), with stronger associations with greater AKI severity and in those without pre-existing CKD (aHR 2.44, 1.41-4.22) vs. with pre-existing CKD (aHR 1.48, 1.00-2.21) (Figure).

Conclusions: AKI independently increases the risk of being hospitalized for HF in the presence or absence of pre-existing CKD. Studies should evaluate underlying mechanisms and whether early surveillance and intervention can prevent HF after an episode of AKI.

Funding: NIDDK Support



Multivariable associations of AKI with subsequent HF events in the ASSESS-AKI Study.

SA-OR104

AKI and CKD Incidence and Progression: The ASSESS-AKI Study Talat Alp Ikizler,[6] Alan S. Go,[1] Vernon M. Chinchilli,[4] Jonathan Himmelfarb,[2] Paul L. Kimmel,[3] James S. Kaufman,[5] Chirag R. Parikh.[7] *[1]Kaiser Permanente Northern California, Oakland, CA; [2]Kidney Research Institute, Seattle, WA; [3]National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; [4]Penn State College of Medicine, Hershey, PA; [5]VA New York Harbor Healthcare System, New York, NY; [6]Vanderbilt University Medical Center, Nashville, TN; [7]Yale University and VAMC, New Haven, CT. Group/ Team: ASSESS-AKI.*

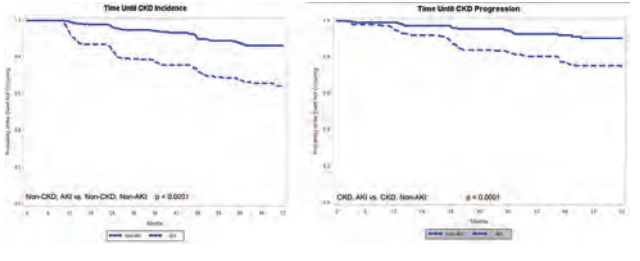
Background: Retrospective studies suggest AKI associates with risk of CKD and faster CKD progression, but there are few prospective data. We prospectively evaluated whether AKI independently increases risks of incident and progressive CKD.

Methods: Hospitalized adults with and without AKI were enrolled in a parallel matched cohort from 4 centers between 2009-2015 and had an outpatient baseline visit within 3 months post-discharge. AKI (≥50% relative or absolute increase ≥ 0.3mg/dL in peak inpatient SCr compared to baseline outpatient SCr) was identified during the index hospitalization. AKI and non-AKI participants were matched on center and baseline CKD status (using eGFR<60ml/min/1.73m^2). CKD incidence was defined as ≥25% decrease in baseline eGFR and eGFR <60 ml/min/1.73m^2. In patients with CKD at index hospitalization, CKD progression was defined as ≥50% decrease in eGFR from baseline, reaching eGFR <15 ml/min/1.73m^2 or receiving renal replacement therapy. Multivariable Cox regression was used to examine association of AKI with CKD.

Results: A total of 769 AKI and 769 well-matched non-AKI adults were enrolled. During follow-up, CKD incidence rate was 66 per 1000 p-y in AKI group compared with 26 per 1000 p-y in matched non-AKI adults (P<0.0001). In patients with underlying CKD, CKD progression rate was 35 per 1000 p-y in AKI group compared with 14 per 1000 p-y in matched non-AKI adults (P<0.0001). In multivariable analyses, AKI was associated with an over threefold higher adjusted rate of CKD incidence (adjusted hazard ratio [aHR] 3.17, 95% CI: 2.25-4.46), and an over twofold higher adjusted rate of CKD progression (aHR 2.03, 1.11-3.74).

Conclusions: AKI independently increases the post-discharge risks of incident CKD and CKD progression. Future studies should assess if early surveillance of and intervention in AKI patients with or without underlying CKD can prevent CKD incidence and progression post-AKI.

Funding: NIDDK Support



SA-OR105

Defining Renal Recovery Following Postoperative AKI Thorir E. Long,[2,1] Sólveig Helgadóttir,[4] Dadi Helgason,[2,1] Runolfur Palsson,[1,2] Tomas Gudbjartsson,[1,2] Gisli H. Sigurdsson,[1,2] Martin I. Sigurdsson,[3] Olafur S. Indridason.[1] *[1]Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland; [2]Faculty of Medicine, Univeristy of Iceland, Reykjavik, Iceland; [3]Duke Univeristy, Durham, NC; [4]Akademiska Hospital Uppsala Univeristy, Uppsala, Sweden.*

Background: Consensus on the definition of renal recovery after acute kidney injury (AKI) is lacking. The aim of this study was to examine the association of different definitions of renal recovery with survival among individuals with AKI following surgical procedures.

Methods: This was a retrospective study of all adult patients who underwent abdominal, cardiothoracic, vascular or orthopedic surgery at the University Hospital in Reykjavik in 1998-2015. Clinical data was extracted from electronic medical records. AKI was diagnosed according to the serum creatinine (SCr) part of the KDIGO criteria. Association between 1-year survival and renal recovery of varying degree (SCr reduction to less than 1.5, 1.25 and 1.1 x baseline SCr) and at various time points (10, 20 and 30 days following AKI) was examined by logistic regression. We excluded patients with baseline eGFR <15 mL/min/1.73 m^2, those who died during the index admission, and recurrent AKI episodes

Results: A total of 2,410 patients had AKI. All recovery definitions, namely SCr <1.5, 1.25 or 1.10 x baseline SCr at 10, 20 or 30 days after surgery, were significantly associated with 1-year survival. Reaching SCr <1.5 x baseline within 30 days had the strongest relationship with 1-year survival (OR 0.37; 95% CI, 0.29-0.48, p<0.001) in a multivariable logistic model adjusting for age, AKI stage, year of the AKI episode, previous diagnoses of congestive heart failure, chronic pulmonary disease or neoplasm, preoperative eGFR<60 mL/min/1.73 m^2 and type of surgery. Increased odds of 1-year mortality was observed for those who had persistent SCr 1.5 x baseline following AKI compared with patients whose SCr returned to <1.1 x baseline (Table).

Conclusions: Among patients with postoperative AKI surviving to hospital discharge, achieving SCr <1.5 x baseline within 30 days had the strongest association with 1-year survival. This might therefore be a useful definition of renal recovery after AKI

Funding: Government Support - Non-U.S.

Odds ratio for one-year mortality according to renal recovery at 30 days

Recovery at 30 days, (SCr compared to baseline SCr)	Unadjusted	p-value	Adjusted	p-value
<1.10 (N=1,430)	1.0	-	1.0	-
1.10 – 1.25 (N=218)	0.7 (0.4-1.1)	0.16	0.8 (0.5-1.2)	0.22
1.25 – 1.50 (N=195)	1.3 (0.9-1.9)	0.15	1.2 (0.8-1.8)	0.33
> 1.50 (N=567)	2.3 (1.8-2.9)	<0.001	2.5 (1.9-3.2)	<0.001

SA-OR106

Intensity of Ultrafiltration and Mortality in Critically Ill Patients with AKI and Fluid Overload Vikram Balakumar,[1] Raghavan M. Murugan,[3] Paul M. Palevsky,[2] John A. Kellum.[2] *[1]Department of Critical Care Medicine, , University of Pittsburgh, Pittsburgh, PA; [2]University of Pittsburgh, Pittsburgh, PA; [3]Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA.*

Background: We examined the association between ultrafiltration intensity and risk-adjusted one-year mortality among critically ill patients with fluid overload and receiving renal replacement therapy (RRT).

Methods: We analyzed a large intensive care unit (ICU) dataset involving adults admitted to a tertiary academic medical center over 8-year period. Acute kidney injury (AKI) was defined according to KDIGO criteria and only patients with AKI and fluid overload ≥ 5% of body weight prior to initiation of RRT were included. UF intensity was calculated as volume removed per day from initiation of either continuous or intermittent RRT until end of ICU stay adjusted for patient hospital admission body weight as follows: high >25ml/kg/day; moderate ≤25 - >20ml/kg/day, and low ≤20ml/kg/day. We constructed a propensity score to account for indication bias for UF intensity using age, sex, body mass index, race, surgery, baseline estimated GFR, first RRT modality, pre-RRT fluid balance, duration of RRT, time to RRT initiation as well as risk factors measured in the first 24 hours of ICU admission such as APACHE-III score, vasopressor use, mechanical ventilation use, suspected sepsis and severity of hypotension. We examined Kaplan-Meir failure plots in the propensity-matched cohort and fitted multivariable logistic regression for mortality.

Results: Of 1,075 patients with ≥5% fluid overload and receiving RRT, the distribution of high, moderate and low intensity UF were 40.4%(n=434), 15.2%(n=166) and 44.2%(n=475), respectively. The crude mortality was 59.4%, 60.2% and 69.7%, respectively. After combining low and moderate intensity groups (n=322) and propensity matching with high intensity group (n=322) in a 1:1 ratio, the high intensity UF groups had lower mortality compared with moderate and low intensity UF (56.5% vs. 70.2%, P<0.001). In the overall cohort, mortality was lower in high intensity UF group compared with low intensity UF (adjusted OR, 0.51, 95% CI, 0.35 - 0.73; P<0.001), whereas, there was no difference in mortality between moderate, compared with low intensity UF group (adjusted OR, 0.67; 95% CI, 0.42-1.05; P=0.08).

Conclusions: Higher intensity ultrafiltration of >25mls/kg/day compared with low intensity ultrafiltration of <20mls/kg/day is associated with lower one-year mortality in critically ill patients with fluid overload.

SA-OR107

The Epidemiology and Impact of Fluid Balance on Outcomes in Critically Ill Preterm Neonates: A Report from the AWAKEN Study

David T. Selewski,[14] Ayse Akcan Arikan,[1] Elizabeth Bonachea,[8] Katja M. Gist,[12] Stuart Goldstein,[5] Mina Hanna,[13] Catherine Joseph,[15] John D. Mahan,[9] Arwa Nada,[6] Amy Nathan,[4] Kimberly J. Reidy,[3] Amy Staples,[15] Pia Wintermark,[7] Louis J. Boohaker,[2] Russell Griffin,[11] David J. Askenazi,[10] Ronnie Guillet.[16] *[1]Baylor College of Medicine, Houston, TX; [2]Children's of Alabama, Hoover, AL; [3]Children's Hospital at Monte iore/ Albert Einstein College of Medicine, Bronxville, NY; [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [5]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [6]LeBonheur Children's Hospital, Memphis, TN; [7]McGill University, Montreal, QC, Canada; [8]Nationwide Children's hospital, Columbus, OH; [9]Nationwide Children's Hospital, Columbus, OH; [10]University of Alabama at Birmingham, Birmingham, AL; [11]University of Alabama at Birmingham, Birmingham, AL; [12]University of Colorado, Children's Hospital Colorado, Aurora, CO; [13]University of Kentucky, Lexington, KY; [14]University of Michigan, Ann Arbor, MI; [15]University of New Mexico, Albuquerque, NM; [16]University of Rochester, Rochester, NY.*

Background: Critically ill preterm neonates are at risk of AKI and disorders of fluid balance(FB). Very little data exist on the association between FB and outcomes in this population. We aim to evaluate the epidemiology of FB over the first week of life and impact on outcomes in a multi-center cohort of premature neonates.

Methods: The Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWAKEN) study included neonatal ICU admissions at 24 institutions from 01/14-03/14. Inclusion criteria: intravenous fluids for ≥48 hrs. Exclusion criteria: congenital heart disease repair at ≤7 days of life (DOL), lethal chromosomal anomaly or death ≤48 hrs. This analysis includes infants <36 weeks gestational age admitted by DOL 7. FB during the first week of life was defined by percent change in weight from birthweight. Outcomes: Mechanical ventilation(MV) at DOL 7, mortality

Results: 1136 preterm neonates were enrolled. Median peak FB was 0%(IQR -2.9, 1.9) at median DOL 2 (IQR 1,5). The pattern of peak FB over the first week included: < birthweight in 510(44.8%), 0-5% in 458(40.2%), 5-10% in 83(7.3%), 10-15% in 34(3.0%) and >15% in 51(4.9%). 155(13.6%) were on MV at DOL 7 and 46(4%) died. Table 1 describes the association of variables, including FB, with MV at DOL 7. Peak FB was higher in non-survivors (0%(IQR -2.9,1.7) v 0%(IQR-1.2, 9.3), p=0.002).

Conclusions: The AWAKEN study describes the impact of FB in the first week of life on outcomes in preterm infants. Over half of the cohort had a positive peak FB in the first week of life. Peak FB was associated with MV at DOL 7 and mortality in this cohort.

Conclusions: The AWAKEN study describes the impact of FB in the first week of life on outcomes in preterm infants. Over half of the cohort had a positive peak FB in the first week of life. Peak FB was associated with MV at DOL 7 and mortality in this cohort.

	MV at 7 days (N=155)	No MV at 7 days (N=981)	*P*-value
22–<29 weeks	108 (69.7%)	136 (13.9%)	<0.001
29–<36 weeks	47 (30.3%)	845 (86.1%)	
BW ≤ 1000 gm	103 (66.4%)	102 (10.4%)	<0.001
BW 1001 – 1500 gm	20 (12.9%)	252 (25.8%)	
BW 1501 – 2500 gm	22 (14.2%)	516 (52.8%)	
BW ≥ 2501 gm	10 (6.4%)	108 (11.0%)	
Apgar 1 Minute*	3 (1, 6)	7 (5, 8)	<0.001
Apgar 5 Minutes*	6 (4, 8)	8 (7, 9)	<0.001
AKI	51 (32.9%)	117 (11.9%)	<0.001
Diagnosis			
Respiratory failure	128 (82.6%)	528 (53.8%)	<0.001
Sepsis evaluation	97 (62.6%)	534 (54.4%)	0.06
Hypoxic Ischemic Encephalopathy	11 (7.1%)	14 (1.4%)	<0.001
Fluid Balance			
Peak Fluid Balance *	1.1%(-1.2, 9.3)	0%(-3.0, 1.3)	<0.0001
Fluid Balance DOL 3 *	-2.7%(-7.0,1.2)	-4.3%(-7.0, -2.0)	0.001
Fluid Balance DOL 7 *	-2.6%(-9.4, 4.9)	-4.6%(-8.0, -0.7)	0.01

* Median (IQR)

Table 1: Association of variables with Mechanical Ventilation at day of life 7

SA-OR108

Development and Validation of a Risk Prediction Model for AKI Following the First Course of Cisplatin

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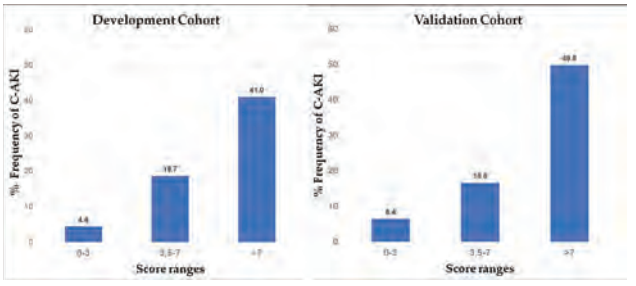
Background: Cisplatin-associated acute kidney injury (C-AKI) remains a frequent problem occurring in up to 30% of patients who have received cisplatin (Cis). Candidacy for Cis has largely been determined by renal function alone. We sought to develop and validate a predictive model for C-AKI for patients who received Cis.

Methods: Clinical and demographic data were collected on patients who received Cis between 2000-2016 at two large independent cancer centers in Boston. C-AKI was defined as a 0.3mg/dl rise in creatinine from baseline to peak measurement within 14 days of the first course of Cis. Multivariable (MV) logistic regression models using C-AKI as the primary outcome were created and a scoring model was developed using one cohort (Ct). The score-based model was then tested in the validation Ct.

Results: C-AKI occurred in 13.2% of 2049 patients and 11.6% of 2362 patients after the first course of Cis in the development and validation Cts respectively. The following factors were associated with C-AKI in the development Ct: age 61-70 years (OR=1.72, 95% CI 1.26, 2.35, p=0.0007) and age 71-90 years (OR=3.21, 95% CI 2.21, 4.66, p<0.0001) when compared with age ≤60 years; Cis dose 101-150mg (OR= 1.62, 95% CI 1.16, 2.27; p=0.005) and >150mg (OR=3.77; 95% CI 2.69, 5.30; p<0.0001) when compared with ≤100mg; history of hypertension (OR= 2.24; 95% CI 1.67, 3.01; p<0.0001) when compared with no hypertension; serum albumin 2.0-3.5 g/dl (OR=1.95; 95% CI 1.39, 2.73; p=0.0001) when compared with serum albumin >3.5 g/dl; and low blood pressure within 14 days of Cis (OR=1.47; 95% CI 1.07, 2.05; p=0.02) when compared with those without low blood pressure during that interval. The c-statistics of the score-based model in the development Ct and validation Ct were 0.73 and 0.70, respectively.

Conclusions: A score-based model using the patient's age, Cis dose, history of hypertension, serum albumin, and low blood pressure after infusion is predictive of cisplatin-associated acute kidney injury.



Frequency of C-AKI across various score ranges.

SA-OR109

AKI Precipitating Initiation of Chronic Maintenance Hemodialysis

Csaba P. Kovesdy,[6] Adnan Naseer,[7] Keiichi Sumida,[2] Miklos Z. Molnar,[6] Praveen Kumar Potukuchi,[6] Fridtjof Thomas,[6] Elani Streja,[1] Michael Heung,[5] Kevin C. Abbott,[3] Rajiv Saran,[5] Kamyar Kalantar-Zadeh.[4] *[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [2]Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; [3]The National Institutes of Health, NIDDK, Bethesda, MD; [4]University of California Irvine, School of Medicine, Orange, CA; [5]University of Michigan, Ann Arbor, MI; [6]University of Tennessee Health Science Center, Memphis, TN; [7]VAMC, Germantown, TN.*

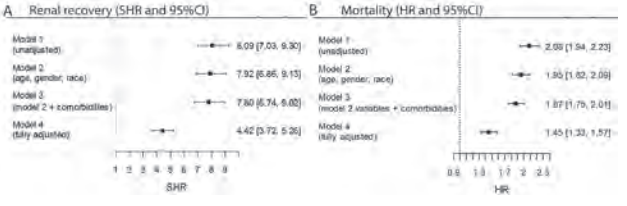
Background: Acute kidney injury (AKI) often occurs in patients with advanced chronic kidney disease (CKD) and may hasten the need to initiate maintenance hemodialysis (MHD) treatment. It is unclear how frequently AKI occurs in patients transitioning to MHD, and what outcomes it leads to.

Methods: We examined a national cohort of 23,349 US veterans initiating MHD during 2007-2014. We defined AKI as a 50% decrease in eGFR at the time of MHD start, compared to the expected eGFR estimated from the disease trajectory recorded in the last year before dialysis. Associations of AKI with all-cause mortality and with recovery of kidney function (per USRDS records) in the first 6 months after MHD start were examined in multivariable adjusted Cox models and competing risk regression models.

Results: Patients were 67±11 years old, 98% male, 33% African-American, and 72% diabetic. 4,804 (21%) of all patients had AKI. Renal recovery occurred in 12.2% of patients with AKI vs. 1.6% of those without AKI (adjusted subhazard ratio, 95%CI: 4.42, 3.72-5.27, p<0.001) (Fig A). AKI was associated with 45% higher multivariable adjusted mortality (hazard ratio and 95% CI: 1.45, 1.33-1.57) (Fig B).

Conclusions: Nearly 1 in 8 patients experienced AKI during transition to MHD, and this was associated with higher mortality in the immediate post-transition period. Patients with AKI also experience a much higher rate of renal recovery, hence careful attention to residual kidney function is warranted in these patients.

Funding: NIDDK Support



SA-OR110

Kidney Tubular Dysfunction among HIV-Negative Persons Receiving Tenofovir-Based Pre-Exposure Prophylaxis Vasantha Jotwani,[4] Rebecca Scherzer,[4] David V. Glidden,[4] Steven G. Coca,[1] Chirag R. Parikh,[2] Robert M. Grant,[4] Michael Shlipak.[3] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Yale University and VAMC, New Haven, CT; [3]San Francisco VA Medical Center, San Francisco, CA; [4]UCSF, San Francisco, CA.*

Background: Pre-exposure prophylaxis (PrEP) with once-daily tenofovir disoproxil fumarate (TDF) and emtricitabine (FTC) has been adopted by the World Health Organization and the United States Centers for Disease Control as a global strategy for HIV prevention. Tenofovir can cause proximal tubular damage and chronic kidney disease in HIV-infected persons, but little is known regarding its nephrotoxicity in persons without HIV. We evaluated the effects of PrEP on kidney health using a panel of urinary biomarkers.

Methods: Biomarker levels were measured in urine specimens collected before and after PrEP initiation in 109 HIV seronegative participants of the iPrEx-OLE study, a longitudinal cohort of former PrEP trial participants who received open-label TDF/FTC. Cross-sectional correlations of hair drug concentrations with post-TDF urine biomarker levels were evaluated.

Results: After 24 weeks on PrEP, we observed statistically significant increases in proteinuria and α1-microglobulin, a marker of proximal tubule dysfunction, whereas monocyte chemoattractant protein-1 (MCP-1), a marker of renal repair, and eGFR declined (112 ml/min/1.73m2 pre-TDF vs 108 ml/min/1.73m2 post-TDF). Higher tenofovir concentrations, measured in hair, were associated with lower concentrations of uromodulin (r=-0.404; p<0.001), a protein secreted by healthy tubular cells.

Conclusions: PrEP with TDF/FTC was associated with changes in renal tubular health, captured by urine biomarker levels. Urine biomarkers may be useful indicators of nephrotoxicity in PrEP users.

Funding: NIDDK Support, Other NIH Support - NIAID - University of California San Francisco-Gladstone Center for AIDS Research

Biomarkers levels before and after initiation of PrEP

Biomarker	Pre-TDF Median (IQR)	Post-TDF Median (IQR)	Relative change	P-value
Proteinuria (mg/g)	72.0 (53.1, 97.8)	85.3 (65.0, 110.8)	14%	0.002
Albuminuria (mg/g)	5.2 (3.4, 8.6)	4.8 (3.2, 7.6)	1.0%	0.77
α1-microglobulin (mg/dL)	0.50 (0.50, 0.80)	0.70 (0.50, 1.10)	26%	<0.001
β2-microglobulin (ng/mL)	87.9 (60.3, 139)	101 (48.4, 167)	7.2%	0.48
Interleukin-18 (pg/mL)	44.1 (25.5, 70.4)	36.6 (17.2, 72.6)	-19%	0.12
Kidney injury molecule-1 (pg/mL)	995 (355, 1711)	715 (315, 1659)	-12%	0.48
Neutrophil gelatinase-associated lipocalin (ng/mL)	18.2 (10.0, 37.7)	13.1 (5.9, 39.7)	-14%	0.20
Monocyte chemoattractant protein-1 (pg/mL)	200 (103, 308)	169 (74, 292)	-15%	0.04
Uromodulin (μg/mL)	7.7 (3.9, 12.8)	7.5 (3.3, 14.6)	-5.6%	0.70

P-values from Wilcoxon Signed-Rank test.

SA-OR111

Complement System and Rapid Renal Function Decline in Type 1 (T1D) and Type 2 Diabetes (T2D) – Application of Novel SOMAscan-Based Proteomic Technology John J. Tsay,[2,3] Adam Smiles,[2] Stephanie E. Croall,[2] Joseph V. Bonventre,[1,4] Andrzej S. Krolewski,[2,4] Monika A. Niewczas.[2,4] *[1]Brigham and Women's Hospital, Boston, MA; [2]Joslin Diabetes Center, Boston, MA; [3]Veterans Administration, West Roxbury, MA; [4]Harvard Medical School, Boston, MA.*

Background: We aimed to investigate inflammatory protein signatures in the urine associated with rapid renal function loss in subjects with diabetes.

Methods: In a case-control study of 60 subjects nested within the Joslin Kidney Study cohort of subjects with T1D, proteinuria and CKD 3 (discovery panel), we performed urinary baseline measurements of 194 inflammatory proteins using the SOMAscan platform. Subjects with a Rapid Renal Function Decline (eGFR loss >40% within 5 years) were defined as cases (n=29). Eighteen out of 29 subjects developed ESRD within this time period. Further, we performed urinary proteomic measurements in the validation panel of T2D patients. The 2nd nested case-control study group consisted of 26 T2D subjects with eGFR loss >40% within 5 years (cases); 11 of these progressed to ESRD, and 26 controls remained alive with preserved renal function during the follow-up.

Results: Six major inflammatory classes of proteins were measured within the array. We identified 26 proteins that were concordantly associated with rapid eGFR loss in the discovery panel (Bonferroni corrected nominal *p* value) and in the validation panel (nominal *p* value < 10^{-2}). Candidate inflammatory proteins were particularly enriched for proteins from the complement system ($\chi^2 = 21.5$; p<0.0001). Complements C3a, C5a and factor H were among the top proteins associated with an increased renal risk.

Conclusions: In our study we identified a robust inflammatory signature enriched for proteins of the complement system that are associated with rapid renal function decline in both types of diabetes. Our findings suggest that local kidney disturbances of the complement pathway are etiologically linked to the development of kidney complications in diabetes.

Funding: NIDDK Support, Private Foundation Support

Inflammatory Classes	Total N	Proteins Associated with Increased Renal Risk
Chemokines	41	6 (14.6%)
Complement System	26	12 (46.2%)*
Interferons	2	0 (0%)
Interleukins	60	3 (5%)
Tumor Necrosis Factor Family	41	1 (2.4%)
Others	24	4 (16.7%)
Total	194	26 (13.4%)

SA-OR112

Systems Methylome Analysis Identifies CTCF Regulated Pathways in Disease Progression to Diabetic Nephropathy Ishant Khurana,[1] Mark E. Cooper,[1] Per-Henrik Groop,[2] Assam El-Osta.[1] *[1]Department of Diabetes, Central Clinical School, Monash University, Melbourne, VIC, Australia; [2]University of Helsinki and Helsinki University Hospital, Helsinki, Finland. Group/Team: Finnish Diabetic Nephropathy study.*

Background: Despite extensive GWAS by multiple groups and consortia, including the The Finnish Diabetic Nephropathy Study (FinnDiane), only a few genes that explain <5% of susceptibility to nephropathy in type 1 diabetes (T1D) have been identified. With increased awareness of epigenetics as it pertains to human disease, there remains scepticism whether the signalling pathways in diabetes are an association or represent a direct pathogenic state. Therefore, we used a global approach to characterize methylation-mediated function in clinical samples combined with integrative molecular studies to define mechanisms implicated in hyperglycemia and diabetes.

Methods: Leukocyte DNA isolated from case and control groups were fragmented and DNA precipitated using methyl-CpG capture followed by massive parallel sequencing (methyl-seq). We have mapped the methylome of (FinnDiane) participants selected based on the presence or absence diabetic nephropathy. The case group included 25 participants with T1D characterized into three groups, normoalbuminuria (Normo), macroalbuminuria (Macro) and end stage renal disease (ESRD). The control group consisted of 14 non-diabetic participants with no proteinuria.

Results: We show for the first time DNA methylation sequence changes derived from leukocytes for genes important in insulin signaling, integrin interactions and lipid metabolism. Methylation sequencing identified mechanistic target of rapamycin (mTOR) gene regulation was subject to differential CpG methylation in the genebody at CTCF binding sites. *Ex vivo* cell experiments confirm transition from normal to high glucose conditions reduced DNA methylation and increased mTOR gene expression. The significance of DNA methylation on mTOR was also validated using the DNA methylation inhibitor, 5-aza-2'-deoxycytidine (5adC). We show exon-specific mTOR expression is DNA methylation dependent and hypothesize alternative splicing of mTOR is mediated by Pol II pausing conferred by DNA methylation. CTCF binding is dependent on DNA methylation and regulates mTOR in primary cells stimulated by hyperglycemia and, 5adC.

Conclusions: These results highlight glucose-derived changes to CTCF binding sites are sensitive to loss-of-methylation with gain-of-function of mTOR in diabetes with strengthens the evidence base against DNA methylation changes just being an epiphenomenon.

Funding: Government Support - Non-U.S.

SA-OR113

Fasting Plasma Trimethylamine-N-Oxide as a Risk Marker of Poor Renal Outcomes, Cardiovascular Disease, and Mortality in Patients with Type 1 Diabetes with Diabetic Nephropathy Signe Abitz Winther,[4,6] Jens C. Øllgaard,[2] Hans-Henrik Parving,[5] Stanley L. Hazen,[1] Oluf Pedersen,[3] Peter Rossing.[4,7] *[1]Center for Cardiovascular Diagnostics and Prevention, Cleveland, OH; [2]None, Køge, Denmark; [3]Novo Nordisk Foundation Center for Basic Metabolic Research, København Ø, Denmark; [4]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [5]National Hospital, Copnehagen, Denmark; [6]Novo Nordisk A/S, Maaløv, Denmark; [7]University of Copenhagen, Copenhagen, Denmark.*

Background: Trimethylamine-N-Oxide (TMAO) is a metabolite of phosphatidylcholine, choline and carnitine produced by the gut microbiota from ingested animal foods. It has been suggested as an independent gut microbiota derived risk factor for renal and cardiovascular disease (CVD). Patients with type 1 diabetes are at increased risk of renal and cardiovascular disease and early mortality. We investigated associations between plasma TMAO and outcomes in a prospective study.

Methods: TMAO was measured at baseline in 384 patients with type 1 diabetes with diabetic nephropathy (u-AER > 300 mg/g), 61 % were male, mean age was 42 years and eGFR 66 ml/min/1.73m². Fasting plasma levels of TMAO were measured using stable isotope dilution tandem mass-spectrometry. Endpoints included mean yearly decline in ^{51}Cr EDTA GFR (follow-up (FU) up to 12 years), ESRD (n=65; mean FU: 7.2 years), fatal and non-fatal CVD (n=154; mean FU: 7.5 years) and all-cause mortality (n=134; mean FU: 9.0 years). Associations between TMAO and the endpoints were tested using linear regression or Cox proportional hazard regression in uni- and multivariate analyses adjusting for conventional risk factors at baseline.

Results: Plasma TMAO was inversely associated with baseline eGFR (R^2: 0.42; p<0.001). In univariate analysis higher TMAO was associated with all endpoints (p≤0.002). All endpoints remained significant associated with higher TMAO after adjustment for baseline age, diabetes duration, sex, smoking, systolic blood pressure, cholesterol, HbA_{1c} and u-AER (p ≤ 0.014). After further adjustment for baseline eGFR

significance was lost for all endpoints, except for CVD events (HR per doubling: 1.22, [1.05-1.41]; p=0.010).

Conclusions: In type 1 diabetes patients with diabetic nephropathy, higher fasting plasma TMAO level was predictive of poor renal outcomes, CVD events and mortality independent of conventional risk factors. Only the relation to CVD events remained after further adjustment for baseline eGFR. This elucidated the close relationship between TMAO and renal function.

Funding: Private Foundation Support

SA-OR114

Identification of Novel Urinary Biomarkers for Predicting the Renal Prognosis in Patients with Type 2 Diabetes by Glycan Profiling in a Multicenter Cohort Study: U-CARE Study 1 Koki Mise,[1] Hitoshi Sugiyama,[2] Haruhito A. Uchida,[3] Jun Wada.[1] *[1]Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; [2]Department of Human Resource Development of Dialysis Therapy for Kidney Disease, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan; [3]Department of Chronic Kidney Disease and Cardiovascular Disease, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.*

Background: Recent studies have demonstrated that alterations of glycosylation are critically involved in the development of diabetes and in the progression of diabetic nephropathy (DN). However, the association between changes of glycosylation and the renal prognosis of DN patients remains unclear because of difficulty in quantifying glycans due to their complex structures.

Methods: A total of 680 patients with type 2 diabetes admitted to 8 affiliated hospitals in Okayama during 2012 were enrolled in this study. At baseline, we measured urinary levels of Cy3-labeled glycans that bound to 45 lectins with different specificities. The endpoint was a decrease of the estimated glomerular filtration rate (eGFR) by ≥ 30% from baseline or commencement of dialysis for end-stage renal disease (ESRD). Cox proportional hazards analysis was employed to calculate hazard ratios (HRs) and 95% confidence interval (CIs) for the death-censored endpoint.

Results: During a median follow-up period of 4.0 years (IQR: 3.9-4.0), the primary endpoint was reached in 60 patients. Baseline mean eGFR was 71.0 ± 17.7 ml/min/1.73 m^2, and 594 patients (87%) showed either normoalbuminuria (63%) or microalbuminuria (24%). After adjustment for known indicators of DN, including baseline eGFR and albuminuria, the urine levels of glycans binding to some lectins (including SNA, SSA, ABA, ACA, and MPA) were significantly associated with the primary endpoint (+1SD for log[glycan signal intensity/urinary creatinine concentration], HR for SNA: 1.43[95% CI: 1.07-1.89], HR for SSA: 1.43 [1.07-1.90], HR for ABA: 1.37 [1.05-1.80], HR for ACA: 1.37 [1.03-1.81], and HR for MPA: 1.33 [1.01-1.76], respectively). The glycan Siaα2-6Gal/GalNAc was reported to bind with SNA and SSA, while Galβ1-3GalNAc was reported to bind with ABA, ACA, and MPA.

Conclusions: Urinary Siaα2-6Gal/GalNAc and Galβ1-3GalNAc may be novel predictors of the renal prognosis in patients with type 2 diabetes.

Funding: Private Foundation Support

SA-OR115

ACE Inhibitor, ARB, or Combined Therapy in Patients with Diabetes and Microalbuminuria: The Long-term Impact of RAS Inhibition on Cardiorenal Outcomes (LIRICO) Randomized Clinical Trial Giovanni F. Strippoli,[1] Suetonia Palmer,[2] Valeria M. Saglimbene,[1] Marinella Ruospo,[1] Jorgen B. Hegbrant,[1] Jonathan C. Craig.[3] *[1]Diaverum, Bari, Italy; [2]University of Otago, Christchurch, New Zealand; [3]University of Sydney/Children's Hospital, Sydney, NSW, Australia. Group/Team: LIRICO trial Investigators*.

Background: Combination ACE inhibitor/ARB therapy may increase risks of end-stage kidney disease without evidence of improved cardiovascular outcomes. The Long-term Impact of RAS Inhibition on Cardiorenal Outcomes (LIRICO) randomized clinical trial evaluated the comparative efficacy of combined ACEi/ARB therapy versus monotherapy on cardiovascular and renal outcomes in patients with diabetes and microalbuminuria.

Methods: The LIRICO trial was a phase III, prospective, randomized, open-label, blinded-endpoint (PROBE) trial funded by the Italian Medicines Agency. Patients with microalbuminuria (ACR ≧30mg/g) or macroalbuminuria and diabetes were randomly assigned to an ACEi (n=427), ARB (n=428) or combination (n=432) titrated to full doses. Non-randomized antihypertensive therapy was administered to achieve blood pressure <130/80. The primary outcome was all-cause mortality. Secondary outcomes were cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, hospitalization for cariovascular causes. end-stage kidney disease, and surrogate renal outcomes (doubling serum creatinine, chronic kidney disease [eGFR<60 ml/min/1.73 m2, development of macroalbuminuria, or normoalbuminuria).

Results: During a median follow-up of 2.8-3.0 years, the number of all-cause mortality events was similar between groups (15 deaths [3.6%] in the ACEi group (hazard ratio 0.84 versus combination group, 0.42-1.67), 20 [4.8%] in the ARB group (HR 1.11, 0.59-2.10), and 18 [4.3%] in the combination group). The secondary outcome end-stage kidney disease was similar between groups (6 events [1.5%, HR 1.53, 0.43-5.44], 7 events [1.7%, HR 0.50, 0.09-2.76] and 4 events [1.0%], respectively). There was no difference between groups for cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or renal outcomes.

Conclusions: In patients with diabetes and microalbuminuria, there was no evidence that combination ACEi and ARB therapy had different effects on all-cause mortality, and cardiovascular or renal outcomes compared with ACEi or ARB alone.

Funding: Government Support - Non-U.S.

SA-OR116

Biomarkers Protective against ESRD in Advanced Diabetic Nephropathy Adam Smiles, Monika A. Niewczas, Jan Skupien, Bozena Krolewski, Andrzej S. Krolewski. *Joslin Diabetes Center, Boston, AL.*

Background: A population of patients with type 1 diabetes, persistent proteinuria and CKD stage 3 was followed for progression to End Stage Renal Disease (ESRD). From the group of 219 subjects, 119 were identified as cases, based on their progression to ESRD within 10 years. The control group was the remaining 100 subjects who did not progress to ESRD.

Methods: Baseline plasma from these subjects was assayed on the SOMAscan platform. Relative concentrations were measured for 568 proteins. A protein fold change was calculated as the ratio of mean protein concentration for cases dived by concentration in controls. 16 potentially protective proteins were identified by having a fold change < 1 and a p<0.001. This list was reduced to 12 proteins that also had nominal significance in a similar cohort of Type 2 patients.

Results: In Yamanouchi et al. (KI 2017) we have shown that plasma level of TNFR1 is the primary predictor of ESRD and accounts for most of the traditional risk factors. As such, we performed a Cox proportional hazards model for each protein, adjusting for TNFR1 concentration. Hazard Ratios and p values are reported in the table below. Cluster analysis grouped the proteins into 4 clusters.

Conclusions: Clusters of protective proteins might have similar physiological relevance, be part of common or related pathways or be under the same genetic regulation. Identification of proteins that protect patients from ESRD in the face of such advanced diabetic nephropathy may be useful targets for the development of therapeutics for preventing or delaying the onset of ESRD.

Funding: NIDDK Support, Private Foundation Support

Cluster	Biomarker Gene Name	Fold Change ESRD / CONTROL	Hazard Ratio Adjusted for TNFR1	p Value
1	CAPN1	0.69	0.722	0.009
	PA2G4	0.64	0.738	0.018
	GSK3 a/b	0.69	0.709	0.004
2	CAMKK1	0.79	0.708	0.008
	STIP1	0.73	0.737	0.018
	SBDS	0.68	0.690	0.005
3	CLIC1	0.69	0.711	0.005
	NMT1	0.77	0.748	0.025
	SPHK1	0.72	0.767	0.023
4	AK1	0.56	0.776	0.034
	ESD	0.73	0.769	0.031
	PGD	0.25	0.846	0.155

SA-OR117

Diabetic Kidney Disease (DKD) Alters the Transcriptome in Adipose Tissue-Derived Mesenchymal Stromal/Stem Cells (MSC) LaTonya J. Hickson, Alfonso Eirin, Ahmed Saad, Sandra Herrmann, Hui Tang, Stephen C. Textor, Lilach O. Lerman. *Mayo Clinic, Rochester, MN.*

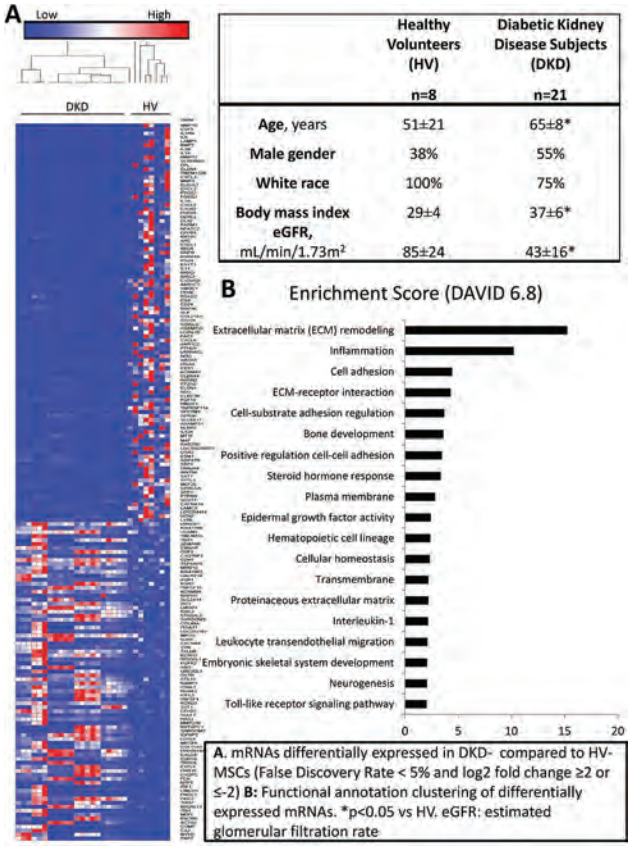
Background: Cellular therapy applying autologous MSC may be a viable option for the treatment of DKD. However, patient-related factors, including hyperglycemia and uremia, may alter their reparative capacity. To explore the effect of these biological factors on MSC, we characterized the MSC transcriptome and compared to a set of healthy volunteers (HV).

Methods: MSCs were harvested from subcutaneous abdominal adipose tissue of DKD (n=21) and HV (n=8 kidney donors) subjects. Next-generation sequencing (RNA-seq) of MSC (3rd passage) and functional annotation analysis (DAVID 6.8 database) were then performed to identify differentially expressed mRNAs and rank the primary gene ontology categories.

Results: DKD subjects were older, had higher body mass indices, and lower glomerular filtration rates compared to HV (Table). RNA-seq generated reads for 13,182 mRNAs, of which180 were differentially expressed in DKD-MSC vs. HV-MSC (False Discovery Rate <5% and log2 fold change ≥2 or ≤-2) [Figure]. Functional analysis identified extracellular matrix remodeling and inflammation as the most prominent categories (enrichment score >10), followed by genes capable of modulating cellular pathways linked to tissue repair.

Conclusions: DKD and associated comorbidity modulate the expression of genes involved in inflammation, matrix remodeling, and tissue repair in adipose tissue-derived MSC. These alterations may impact the endogenous repair capacity of MSC and may have clinical implications for the capacity of exogenous autologous MSC delivery to repair DKD.

Funding: NIDDK Support, Private Foundation Support, Clinical Revenue Support



	Healthy Volunteers (HV)	Diabetic Kidney Disease Subjects (DKD)
	n=8	n=21
Age, years	51±21	65±8*
Male gender	38%	55%
White race	100%	75%
Body mass index	29±4	37±6*
eGFR, mL/min/1.73m²	85±24	43±16*

A. mRNAs differentially expressed in DKD- compared to HV-MSCs (False Discovery Rate < 5% and log2 fold change ≥2 or ≤-2) **B:** Functional annotation clustering of differentially expressed mRNAs. *p<0.05 vs HV. eGFR: estimated glomerular filtration rate

SA-OR118

Symmetric and Asymmetric Dimethylarginine as Risk Markers of Cardiovascular Disease, All-Cause Mortality, and Deterioration in Kidney Function in Patients with Type 2 Diabetes and Microalbuminuria Frederik Persson,[4] Emilie Hein Zobel,[2] Bernt Johan Von Scholten,[3] Tine Hansen,[2] Hans-Henrik Parving,[1] Peter Rossing.[2] *[1]Rigshospitalet, Copenhagen, Denmark; [2]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [3]Novo Nordisk A/S, Soborg, Denmark; [4]Steno Diabetes Center Copenhagen, Gentofte, Denmark.*

Background: To evaluate symmetric dimethylarginine (SDMA) and asymmetric dimethylarginine (ADMA) as risk markers of cardiovascular disease, all-cause mortality and deterioration in renal function in a well characterised type 2 diabetic population with microalbuminuria and without symptoms of coronary artery disease.

Methods: 200 participants followed for 6.1 years. SDMA and ADMA were measured at baseline. Endpoints included 1) composite cardiovascular endpoint (n=40); 2) all-cause mortality (n=26); and 3) decline in eGFR of >30% (n=42). Cox models were unadjusted and adjusted for traditional risk factors (sex, age, systolic blood pressure, LDL-cholesterol, smoking, HbA_{1c}, creatinine and urinary albumin excretion rate). To assess if SDMA or ADMA improved risk prediction beyond traditional risk factors we calculated c-statistics and relative integrated discrimination improvement (rIDI).

Results: Higher SDMA was associated with increased risk of all three endpoints (unadjusted: p≤0.001; adjusted: p≤0.02). Higher ADMA was associated with all-cause mortality (unadjusted: p=0.002; adjusted: p=0.006), but not cardiovascular disease or decline in eGFR(p≥0.29). The c-statistics was not significant for any of the endpoint for either SDMA or ADMA (p≥0.11). The rIDI for SDMA was 15.0%(p=0.081) for the cardiovascular endpoint, 52.5%(p=0.025) for all-cause mortality and 48.8%(p=0.007) for decline in eGFR; for ADMA the rIDI was 49.1%(p=0.017) for all-cause mortality.

Conclusions: In patients with type 2 diabetes and microalbuminuria higher SDMA was associated with incident cardiovascular disease, all-cause mortality and deterioration in renal function. Higher ADMA was associated with all-cause mortality. SDMA and ADMA significantly improved risk prediction for all-cause mortality, and SDMA for deterioration in renal function beyond traditional risk factors.

Funding: Private Foundation Support

SA-OR119

SGLT2 Inhibitors Induce Local Mitochondrial Unfolded Protein Responses in the Proximal Tubules by Suppressing Mitoribosome Proliferation and Influencing Mitonuclear Imbalance in Diabetic Nephropathy Hiroyuki Umino, Kazuhiro Hasegawa, Shu Wakino, Hiroshi Itoh. *Keio University School of Medicine, Tokyo, Japan.*

Background: We have previously reported a molecular mechanism by which SGLT2 inhibitors maintain the anti-aging gene *SIRT1*. The findings that mitoribosome blockage causes mitonuclear imbalance and induces mitochondrial unfolded protein responses (UPRs) are reportedly linked to longevity. These changes also underlie the elongation occurring from modulation of NAD metabolism and SIRT1. In this study, we analyzed whether SGLT2 inhibition and SIRT1 retention would produce this effect in the proximal tubules.

Methods: Canagliflozin (Cana), a SGLT2 inhibitor, was administered to 8-week-old *db/m* and *db/db* mice, and the following parameters were evaluated at 16 weeks of age: (1) SGLT2 and SIRT1 expression; (2) mitoribosome and cytoplasmic ribosome (cytoribosome) numbers on electron microscopy; and (3) COX1, representing mitoribosome function, which is encoded by mitochondrial DNA and translated in mitoribosomes, and ATP5A, a marker protein reflecting cytoribosome function, which is encoded by nuclear DNA and translated in cytoribosomes.

Results: In *db/db* mice, SGLT2 expression was elevated and SIRT1 expression was decreased; these changes were suppressed in *db/db* mice treated with Cana. In *db/db* mice, an elevated mitoribosomal number was observed despite no marked change in the cytoribosomal number in the proximal tubules observed on electron microscopy. Consistent with mitoribosomal proliferation, a significant increase in COX1 was detected in *db/db*, whereas ATP5A was not changed. The elevation in mitoribosomal number and function was suppressed in *db/db* + Cana. Such specific inhibition of mitoribosome protein expression can lead to mitonuclear protein imbalance and associated UPR^{mt}. One of the marker proteins induced by UPR^{mt} is heat shock protein 60 (HSP60). Indeed, elevation of HSP60 was detected in *db/db* + Cana.

Conclusions: A mitoribosome synthesizes the enzyme complexes of the electron transport system in the inner membrane (Complexes I–IV). Its increase suggests excessive ATP and ROS production and is a sign of metabolic regulation failure. However, a SGLT2 inhibitor induces an apt stress response caused by UPR^{mt}. This newly identified organelle change occurs in early-stage diabetic nephropathy, and the mitoribosome may serve as a novel therapeutic target.

SA-OR120

Genetic Deletion of Myo-Inositol Oxygenase (MIOX) Rescues ob/ob Mice from the Progression of Tubulo-Interstitial Injury Isha Sharma,[1] Yashpal S. Kanwar.[2] *[1]NORTHWESTERN UNIVERSITY, CHICAGO, IL; [2]Northwestern University Medical School, Chicago, IL.*

Background: MIOX, a proximal tubular enzyme, is up-regulated in diabetic state and is involved in the pathogenesis of tubulo-interstitial injury. Previously, we reported that MIOX over-expressing mice with STZ-induced diabetes have remarkable tubulo-interstitial changes. These were largely attributed to excessive generation of ROS leading to increased activity of fibrogenic cytokines, especially in the tubulo-interstitial compartment. Such phenotypic changes were not observed in $MIOX^{-/-}$ mice.

Methods: Aim of this study was to assess if genetic ablation of MIOX ameliorates the progression of tubulo-interstitial injury in *ob/ob* mice by reducing the oxidant stress in proximal tubules. $MIOX^{-/-}$ mice were cross bred with *ob/ob* mice to generate mice with double mutation ($MIOX^{-/-}$/*ob/ob*). Animals were sacrificed at age of 20 weeks and kidneys were harvested for various studies. Prior to sacrifice blood and urine samples were obtained.

Results: The $MIOX^{-/-}$/*ob/ob* mice had improved levels of serum creatinine, urea and insulin compared to *ob/ob* mice. No change was observed in blood glucose levels. The double mutants had decreased urinary excretion of high molecular weight proteins. The MIOX expression was highly accentuated in kidneys of *ob/ob* mice compared to WT, and it was absent in $MIOX^{-/-}$ and mice with double mutation. The renal interstitial compartment had notable decreased staining of fibronectin, collagen I and III in mice with double mutation compared to *ob/ob* mice. The generation of ROS in the kidney tissues was notably less in $MIOX^{-/-}$/*ob/ob* mice compared *ob/ob* mice, as indicated by decreased DHE staining. Analyses of various metabolic sensors revealed revival of the expression of SIRT1, AMPK, YY-1, and of the master regulator of mitochondrial biogenesis, i.e., PGC-1alpha. In vitro, HK-2 cells treated palmitate-BSA had decreased expression of various metabolic sensors with increased ROS generation, and these aberrant parameters of metabolic sensors were normalized with the treatment of MIOX-siRNA.

Conclusions: In conclusion, these findings suggest that ablation of MIOX gene ameliorates the progression of tubulo-interstitial injury in the settings of diabetic nephropathy by reducing the oxidant stress and improving the status of various metabolic sensors.

Funding: NIDDK Support

TH-PO001

DNA Methylation Changes of Aging-Related Genes in Renal Proximal Tubular Epithelial Cells Are Regulated by Complement: A Whole-Epigenome Analysis Giuseppe Castellano,[2] Rossana Franzin,[2] Fabio Sallustio,[2] Alessandra Stasi,[2] Claudia Curci,[2] Chiara Divella,[2] Giuseppe Grandaliano,[1] Loreto Gesualdo.[2] *[1]Nefrologia/Dialisi/Trapianto, Foggia, Italy; [2]University of Bari, BARI, Italy*.

Background: Complement, in particular C5a, is the major player of Ischemia Reperfusion injury. Renal Proximal Tubular Epithelial Cells (RPTEC) express the C5aR, however the underlying mechanisms of C5a-C5aR interaction remain poorly understood. We aimed to investigate the impact of C5a exposition on DNA methylation profile in RPTEC.

Methods: Genome-wide array-based DNA methylation levels were measured in several RPTEC lots stimulated with C5a for 24h by the Illumina 450 BeadChips. The analysis was performed on site and region level considering the difference in mean methylation levels both in gene centric regions (promoter, 5'UTR, first exon, gene body, and 3'UTR) and in CpG islands regions (CpG islands and CpG islands shore and shelves). Gene Ontology tools were used to determine genes interaction. qPCR, WB, SA-β Gal staining and MTT were performed for validation analysis.

Results: Compared to basal, 144 sites were hypomethylated and 24 sites were hypermethylated by C5a. Several sites differentially methylated were located in CpG island regions and promoters of genes involved in DNA damage checkpoints in response to genotoxic events, in cell cycle regulation, apoptosis, Hedgehog, Wnt and p53 pathways. The most representative protein classes were: nucleic acid binding proteins (DNA topoisomerase), enzyme modulators, transcription factors and cytoskeletal protein (classification analysis: 21,9%, 9,40%, 7,80% and 7,70% respectively). qPCR analysis confirmed that the hypermethylated genes were downregulated and hypomethylated genes were upregulated. Interestingly, among these genes we found several effectors involved in acquirement of a SAPS (Senescent-Associated Secretory Phenothype). In accordance, 3h of exposure of RPTEC to C5a induced cellular senescence as observed by up-regulating SA-β Gal and by cell proliferation reduction ($p<0.05$). Moreover, senescent RPTEC showed a significant increase in p53 and p21 protein level, as sign of cell cycle arrest ($p<0.05$).

Conclusions: These results suggest a role of complement in inducing tubular senescence affecting epigenetic programs, in particular the DNA methylation profile. Targeting epigenetic mechanisms may represent a strategy to protect tubular cells from aging.

TH-PO002

Renal Crisis in Scleroderma: A Renal Complementopathy? Cybele Ghossein,[2] Yashpal S. Kanwar,[3] John Varga.[1] *[1]Rheumatology, Northwestern University Medical School, Chicago, IL; [2]Nephrology Division, Northwestern University FSM, Chicago, IL; [3]Pathology, Northwestern University FSM, Chicago, IL*.

Background: Scleroderma renal crisis (SRC) is an abrupt-onset and unpredictable complication of systemic sclerosis (SSc) generally presenting with acute kidney injury and severe hypertension. Despite the introduction of ACE inhibitors, the 5-yr survival of these patients remains<50%. The pathogenesis of SRC is still incompletely understood. Current paradigms implicate activation of renin- angiotensin system leading to accelerated hypertensive pathophysiology. Recently there has been an enhanced understanding of the role of acquired and/or genetic complement pathway dysregulation in the pathogenesis of thrombotic microangiopathies (TMA) such as in preeclampsia and aHUS. Pathologically SRC shares many similarities to TMA. We hypothesized that complement may play a role in SRC

Methods: We retrospectively reviewed all SRC patients who had a renal biopsy at our institution between the years of 1990 -2015. 19 renal biopsies of SSc patients with diagnosed SRC, defined as a clinical presentation and pathologic findings consistent with this diagnosis were evaluated. Light microscopy, immunofluorescence and electron microscopy were assessed with specific focus on vascular injury

Results: 14 out 19 renal biopsies had C3 deposition in arteriolar walls along with immunoglobulin reactivity. Biopsies with complement staining had active severe vascular lesions.5 out of the 19 renal biopsies showing no complement staining were more likely to have significant interstitial fibrosis with vessel undergoing impending hyalinosis.

Conclusions: C3 small vessel reactivity in renal biopsies of patients with SRC reflects the active role of complement in the pathogenesis of SRC. Once in the chronic phase of the disease, complement is no longer an important component of disease activity. These findings challenge the current dogma for SRC pathogenesis, and raise the possibility of alternative treatment approaches to SRC.

Funding: Clinical Revenue Support

Table 1

	C3+ (n= 14)	C3 - (n=5)	
Average Age at SRC onset (years)	48	55	
Male/Female	4/10	0/5	p=0.5
Hypertension on presentation (# of patients)	10	4	p=0.9
RNA Polymerase 3 + (# of patients)	5	2	p=0.9
>50% interstitial fibrosis (# of patients)	2	4	p=0.0173

TH-PO003

Presentations, Outcomes, and Complement Gene Analysis in a Single-Center Cohort of Patients with Atypical Hemolytic Uremic Syndrome Sindhura Bobba, Jason M. Kidd, Daniel E. Carl, Dhiren Kumar, Anne L. King, Gaurav Gupta. *Virginia Commonwealth University, Richmond, VA*.

Background: Previous data suggests that up to 50% of patients with atypical hemolytic uremic syndrome (aHUS) might not have detectable complement gene mutations. In this single-center analysis of the aHUS registry we report our experience on 15 consecutive patients with aHUS.

Methods: Patients were enrolled between 2012-2017 at variable time points after initial presentation. The exonic regions of 12 genes including Complement Factor FH (CFH), MCP (CD46), CFI, C3, CFB, CFHR1, CFHR3, CFHR4, CFHR5, Thrombomodulin, Plasminogen and DGKE were analyzed using commercially available testing.

Results: The mean age at diagnosis was 42±18 years. A majority were females (10/15; 67%) and 40% (6/15) were African-Americans. Seven (47%) presented with thrombotic microangiopathy (TMA) and renal failure, of these 4 (out of 7; 57%) recovered kidney function with C5 blockade therapy (eculizumab). Only one patient did not respond to eculizumab therapy and progressed to end-stage renal disease (ESRD). Of the remaining eight, 6 (40%) were diagnosed in the setting of a pre-transplant evaluation or allograft failure. Of these six, 3 (50%) got transplanted. Two patients (13%) were diagnosed with aHUS post-transplant. All 5 patients with kidney transplants have been maintained on indefinite eculizumab and have intact graft function at a median follow-up of 2.5 years (range1-3 years). Genetic analysis of these 15 patients revealed 39 mutations. A majority of patients (13/15; 87%) were noted to harbor complement mutations with seven (47%) having mutations in more than one gene. CFH mutations and Complement Factor H-related protein (CFHR3- CHFR1) deletions were the most frequent (8 patients each; 61%). Three patients (20%) had MCP/CD46 mutations (IVS9-78 G>A). Patients with homozygous mutations had a trend towards presentation at a younger age (mean 35 vs 50 years; $p=0.1$) compared with those with heterozygous mutations.

Conclusions: In this single-center analysis of 15 consecutive aHUS patients, we report that a large majority (87%) had complement gene mutations. This might represent increasing knowledge of identifiable mutations in the contemporary era. A large majority of patients had an excellent response to C5 blockade. Patients being evaluated for kidney transplants with a history of unexplained TMA should be screened for aHUS.

TH-PO004

Abnormalities of Alternative Pathway of Complement in C3 Glomerulopathy Aishwarya Ravindran, Fernando C. Fervenza, Sanjeev Sethi. *Mayo Clinic, Rochester, MN*.

Background: C3G, comprising C3 glomerulonephritis (C3GN) and dense deposit disease (DDD), is characterized by glomerular accumulation of complement proteins due to abnormal regulation of the alternative pathway (AP) of complement. Large scale studies describing genetic and acquired abnormalities of AP associated with C3G are lacking. We describe our institutional experience of the abnormalities of AP associated with C3G.

Methods: Of the 114 C3G patients seen at the Mayo Clinic, 76 (66.7%) patients (65 C3GN/11 DDD) were evaluated for abnormalities of the AP of complement during the period 2007-2016.

Results: C3 levels were low in only 44.6% patients, while 11.8% patients also had low C4 levels. Overall, 29 (43.9%) were positive for mutations of complement factors/ complement regulating proteins, the most common (15.2%) was a heterozygous mutation in complement factor H (*CFH*). Other less common heterozygous mutations included mutations in *CFI, C3, C5, C8* and *C9*, and in the CFH-related genes, *CFHR2* and *CFHR5*. Forty-five (97.8%) patients were positive for genetic polymorphisms associated with C3G, the most common being *CFH* allele variants, which were present in 44 (95.7%) patients; CFH V62 (78.2%) and H402 (73.9%) were the most common. C3 nephritic factor was present in 29 (43.9%) patients; 1 patient also had a positive C5 nephritic factor. Seven (10.9%) patients were positive for other auto-antibodies, 3 (4.7%) to CFH and 4 (6.3%) to CFB. These findings are quite distinct from atypical HUS, where antibodies to CFH are frequently detected. There was no significant difference in prevalence of polymorphisms/ mutations or C3 nephritic factors/autoantibodies between C3GN and DDD.

Conclusions: Our studies show that the common drivers for C3G are: 1) C3 nephritic factor, and 2) mutations in complement regulating proteins, in particular CFH. Almost all patients carried allele polymorphisms of complement regulating proteins associated with C3G. Autoantibodies to other complement regulating proteins were less commonly present. Our study provides insight into the genetic and acquired abnormalities associated with C3G underscoring that appropriate treatment should be based on treating the abnormality driving the C3G.

TH-PO005

Clinicopathological Features, Triggers, Complement Abnormalities, Treatment, and Outcomes of C3 Glomerulopathy Aishwarya Ravindran, Fernando C. Fervenza, Sanjeev Sethi. *Mayo Clinic, Rochester, MN*.

Background: C3 glomerulopathy (C3G), comprising C3 glomerulonephritis (C3GN) and dense deposit disease (DDD), is characterized by glomerular accumulation of complement proteins due to over activation of the alternative pathway of complement.

Most of the reports on C3G are based on individual cases or small series of C3GN/DDD patients.

Methods: We provide a comprehensive evaluation of 114 patients seen at Mayo Clinic during a 10-year period (2007-2016), of which 102 (89.5%) had C3GN and 12 (10.5%) had DDD.

Results: The median age at diagnosis of C3G was 42 years; C3GN patients were older (median age 42 years) while DDD patients were younger (median age 23.5 years). The median serum creatinine and proteinuria at presentation was 1.6 mg/dL and 2605 mg/24 hours. Hematuria was present in 100 (87.7%) patients. C3 levels were low in only 44.6% patients. Monoclonal gammopathy was present in 37.9% patients; 65.1% of the patient's ≥ 50 years had a monoclonal Ig. 28.9% patients had a history of infection and 23.7% patients had an associated autoimmune abnormality. Mutations in complement regulating proteins including CFH, C3 nephritic factor, and other autoantibodies (anti-CFH and CFB) were detected in 43.9%, 43.9% and 10.9% patients, respectively. All patients tested carried C3G risk-associated polymorphisms, the most common being *CFH* allele variants. Membrano- and mesangial proliferative glomerulonephritis were most common patterns of injury on kidney biopsy. Most patients received steroids and other immunosuppressive drugs. After a median follow-up of 34.6 months, the median serum creatinine was 1.4 mg/dL and the median proteinuria was 809 mg/24 hours. Eighteen patients (15.8%) progressed to ESRD. The predictors of ESRD on univariate analysis were serum creatinine >1.5 mg/dL, proteinuria >3 g/24 hours at diagnosis, severity of global glomerulosclerosis and the extent of tubular atrophy and interstitial fibrosis.

Conclusions: C3G is a heterogeneous disease entity that affects both children and adults. In younger patients, both mutations and autoantibodies to complement regulating proteins are present, while in older patients, a monoclonal Ig, which presumably acts as an autoantibody to complement regulating proteins, is most frequently identified.

TH-PO006

Dysregulation of the Alternative Complement Pathway in C3GN and IgAN Yifu Li,[2] Maddalena Marasa,[1] Nicholas J. Steers,[1] Vivette D. D'Agati,[3] Pietro A. Canetta,[4] Andrew S. Bomback,[1] Gerald B. Appel,[3] Krzysztof Kiryluk,[1] Ali G. Gharavi.[1] *[1]Columbia University, New York, NY; [2]Columbia University, New York, NY; [3]Columbia University College of Physicians and Surgeons, New York, NY; [4]None, New York, NY.*

Background: Dysregulation of the alternative pathway plays an important role in glomerular disease, including IgA nephropathy (IgAN) and *C3 Glomerulopathy (C3GN). These disorders share some clinical manifestations,* such as microscopic hematuria and episodes of synpharyngitic flares. Both are characterized by variable mesangial deposits of C3.

Methods: In this cross-sectional study, we collected plasma from 55 participants with IgAN, 105 diagnosed with C3GN, as well as from 62 unrelated healthy controls. All cases of IgAN and C3GN were diagnosed by biopsy. Major components of the alternative pathway, including C3, CFH and CFD levels, were measured by ELISA.

Results: Compared to controls, plasma CFD levels were higher in IgAN and C3GN groups. When compared to the IgAN group, the C3GN group has a significantly lower level of plasma C3 and CFH levels.

Conclusions: These data demonstrate dysregulation of the alternative complement pathway in both IgAN and C3GN. Lower C3 and CFH levels are characteristic of C3GN and differentiate it from IgAN. Analysis of larger cohorts during both active and inactive stages of the disease will better clarify shared and distinct complement profiles between these disorders.

Complement	Ctrls (N=62)	IgAN (N=55)	C3GN (N=105)
C3 (ug/ml)	1051.4±247.1	908.6±142.3	682.1±333.5**††
CFD (ng/ml)	1120.3±446.2	2050.1±1341.0 **	1592.6±1169.0 *
CFH (ug/ml)	817.4±429.2	938.8±485.1	788.3±366.5††

* <0.05, ** <0.01 compared to ctrls;

† <0.05, †† <0.01 compared to IgAN.

TH-PO007

The Complement System and Hemodialysis: Activity of the Lectin Pathway Philip De laval,[1] Katrine Pilely,[3] Peter Garred,[3] Bo Nilsson,[2] Bengt C. Fellstrom,[1] Inga Soveri.[1] *[1]Department of Medical Sciences, Uppsala university, Uppsala, Sweden; [2]Department of Immunology, Genetics and Pathology, Uppsala university, Uppsala, Sweden; [3]Department of Clinical Immunology, Rigshospitalet, Copenhagen, Denmark.*

Background: Complement activation occurring during hemodialysis (HD) has been put forward as a driving force for inflammation in HD patients, but the importance of the lectin complement pathway in HD is largely unknown. Aim: To quantify complement activity through the lectin pathway in contemporary HD.

Methods: Blood was sampled from 20 consecutive HD-patients before, at 30, 60, 120, 180 and 240 minutes and after the prescribed HD-session using either polysulphone or polyarylethersulfone/polyamide/polyvinylpyrrolidone dialyzers. Enzyme-linked immunosorbent assays were used to quantify plasma concentration of the lectin pathway initiator molecules, ficolin -1, -2, -3, mannose-binding lectin (MBL), lectin pathway regulator MAP-1 and enzyme MASP-3 as well as the soluble form of the terminal complement complex, sC5b-9.

Results: Plasma concentrations of ficolin-2, MAP-1 and MASP-3 decreased significantly after 30 minutes and remained low for the rest of the HD session. MBL decreased after 30 minutes and returned to baseline levels after 2 hours, while no change was seen for ficolin-1 and ficolin-3. Concentrations of sC5b-9 increased after 30 minutes and remained elevated for the rest of the HD session.

Conclusions: Complement activation occurs during HD as indicated by increase in sC5b-9. LP complement factors decrease, in particular ficolin-2 which is almost depleted, likely due to dialyzer adsorption and/or consumption. Further studies are needed to investigate the long-term kinetics and half-life of the changes and to examine their clinical impact.

Plasma Concentration of lectin pathway complement factors during hemodialysis

Factor	Pre-dialysis	1 h	p (Pre vs 1 h)	4 h	p (Pre vs 4 h)
Ficolin-1 (ng/ml)	271 (162 - 1200)	317 (142 - 1200)	0.952	267 (154 - 1200)	0.338
Ficolin-2 (µg/ml)	4.85 (1.44 - 12.5)	0.964 (0.246 - 5.1)	< 0.001	0.712 (0.156 - 2.94)	< 0.001
Ficolin-3 (µg/ml)	26 (13 - 45.9)	22.2 (14.5 - 35.2)	0.312	27.2 (12.5 - 55)	0.465
MBL (ng/ml)	314 (11.1 - 4348)	269 (11.4 - 3991)	0.007	284 (16.2 - 2629)	0.113
MAP-1 (ng/ml)	259 (143 - 524)	176 (70.7 - 321)	< 0.001	190 (99.5 - 388)	0.005
MASP-3 (ng/ml)	9499 (4737 - 10000)	3048 (1608 - 5749)	< 0.001	4772 (1743 - 10000)	0.008
sC5b-9 (AU/ml)	0.502 (0.317 - 0.967)	0.74 (0.442 - 2.41)	< 0.001	0.705 (0.446 - 1.37)	0.001

Data presented as median (range).

TH-PO008

Modeling Glomerular Complement Activity In-Vitro Using a Novel Human Glomerular Endothelial Cell Assay Qin Ruan, Kishor B. Devalaraja-Narashimha, Shu Mao, Joshua R. Broden, Lori Morton, Scott Macdonnell. *Regeneron Pharmaceuticals, Tarrytown, NY.*

Background: Reproducible methods for evaluating inhibitory effects of drug candidates on complement activation are essential for preclinical development and potential clinical translation. Due to the complexity of complement activation pathways, an in-vitro assay should use relevant cells and endpoints to the given therapeutic indication. Here, using primary human glomerular endothelial cells (HGECs), we validated a complement C3 & C5 deposition model for use evaluating the blocking activity of C5 monoclonal antibodies (mAb).

Methods: Resting or adenosine 5′-diphosphate (ADP)-activated confluent HGECs were incubated for 4 hours with 50% normal human serum, C3 or C5 depleted human serum, or pretreated with anti-C5 mAbs. Thereafter, HGECs were fixed with BD Cytofix, stained with ThermoFisher anti-human C3/C3b or Abcam anti-human C5b-9 antibodies and complement deposits were analyzed (9 sites per well in duplicated wells) by ImageXpress.

Results: C3 and C5b-9 deposition was observed on ADP-activated HGECs exposed to normal human serum but not on non-activated HGECs (C3: $1.5x10^7±1.0x10^7$; C5: $7.9x10^6±6.6x10^6$, P<0.05 vs non-ADP-activated HGEC). The deposition of C3 and C5b-9 were significantly reduced on ADP-activated HGEC exposed to C3 or C5 depleted serum (C3: $3.3x10^5±4.8x10^4$; C5: $1.5x10^6±6.0x10^5$, P<0.05). Addition of a blocking anti-C5 mAb significantly reduced normal human serum derived C5b-9 deposition onto ADP-activated HGEC, deposition was comparable to C5 depleted sera (C5 mAb: $1.02x10^6±6.0x10^5$, Control mAb $3.7x10^6±1.6x10^6$, P<0.05 vs. control mAb).

Conclusions: These data demonstrate utility of an *in vitro* primary human glomerular endothelial cell assay to model complement C3 & C5 deposition. In addition to in-vitro screening, this assay offers potential as a translational model to evaluate anti-complement strategies in renal disease using patient derived serum samples.

Funding: Commercial Support - Regeneros Pharmaceutics Inc.

TH-PO009

Complement Factor D, a New Predictor of Renal Allograft Dysfunction and Rejection? Christoph Daniel,[3,2] Steffen Bobka,[1,2] Maike J. Buettner,[1,2] Kerstin U. Amann.[1,2] *[1]FAU Erlangen-Nürnberg, Erlangen, Germany; [2]Institute of Pathology, Dept. of Nephropathology, Erlangen, Germany; [3]University Erlangen-Nürnberg, Erlangen, Germany.*

Background: The complement system is part of innate immunity and thus important for graft function and survival. Here we focused on complement Factor D (CFD) that initiates alternative complement activation by cleavage of factor B. Triggers of CFD upregulation are unknown and it is unclear if CFD is already upregulated in zero-biopsies of transplanted kidneys. In addition, we assessed whether the alternative complement pathway is upregulated in the setting of delayed graft function.

Methods: CFD was investigated in renal zero- and corresponding transplant-biopsies of patients receiving a cadaveric kidney transplant using immunohistochemistry. Specimens were selected from patients with delayed graft function (DGF, n=12), T-cell mediated rejection (TCMR, n=10) and antibody mediated rejection (ABMR, n=8) and evaluated with regard to localization and degree of expression of CFD. Furthermore, renal complement factor D reactivity was correlated with renal function and transplantation conditions.

Results: CFD was located in different compartments of renal transplants. In 0-biopsies prominent CFD-staining was found in tubules in comparable amounts in all investigated groups. In contrast, glomerular CFD reactivity in 0-biopsies was at least 4-times lower compared to tubular staining but showed significant differences between groups. Highest glomerular CFD was detected in patients that later develop ABMR, being about 5-times higher compared to 0-biopsies from patients that developed DGF. Interestingly, CFD staining was prominent in glomerular, tubular and interstitial localization in post-transplant biopsies without clear differences between groups. The amount of glomerular CFD in 0-biopsies strongly correlated with renal changes including

glomerulitis (r=0.628; p<0.001), chronic transplant glomerulopathy (r=0.659; p<0.001) and mesangial matrix expansion (r=0.771; p<0.001) in transplant-biopsies taken after at a later timepoint. Furthermore, donor serum creatinine correlated with tubular CFD in post-transplant biopsies (r=0.463; p=0.006).

Conclusions: CFD is upregulated in DGF and in antibody as well as T-cell mediated rejection compared to zero-biopsies. Our findings implicate CFD reactivity in 0-biopsies as a potentially useful predictor of pathophysiologic changes in transplanted kidneys in the post-transplantation time course.

Funding: Government Support - Non-U.S.

TH-PO010

Increased Expression of Complement Receptor C5aR1 in Macrophages Contributes to Kidney Fibrosis Ranjit K. Sahu,[1,2] Sandhya Xavier,[1] Susan G. Landes,[1] Ronald P. Taylor,[1] Joerg Koehl,[3,4] Didier Portilla.[1,2] *[1]University of Virginia Health System, Charlottesville, VA; [2]Department of Veterans Affairs, Salem Veterans Affairs Medical Center, Salem, VA; [3]University of Luebeck, Luebeck, Germany; [4]Division of Immunobiology, Cincinatti Children's Hospital Medical centre, Cincinatti, OH.*

Background: We recently demonstrated increased expression and activation of the complement system with increased expression of C5 and C5aR1 in whole kidney tissue homogenates of mice subjected to folic acid and Unilateral ureteral obstruction (UUO) injury. Given the central role of complement activation product C5a in the development of the inflammatory response through interaction with C5aR1, in the present studies we examined the cellular localization of C5aR1 during injury, and the potential mechanism(s) by which its activation contributes to kidney fibrosis.

Methods: C5aR1 expression was studied by immunohistochemistry, flow cytometry, qPCR, and by western blot analysis of wild type, GFP-C5aR1-floxed, and C3$^{-/-}$ mice subjected to the UUO model. RAW264.7 cells were used as an in vitro model to study how increased C5aR1 expression on macrophages was linked to the process of fibrosis.

Results: Immunohistochemistry studies localized expression of C5aR1 to proximal tubules in sham mice but increased expression was seen mostly in interstitial cells after UUO. C5aR1 mRNA levels were increased in CD45+ cells isolated from UUO mice. Flow cytometry analysis using GFP/C5aR1-Floxed mice demonstrated a 75-fold increase of GFP+C5aR1+CD11b+, F4/80+, LyC6- macrophages after UUO. Reduced staining of GFP+-C5aR1+ Prominin-1+ cells by flow suggests loss of renal tubular epithelial cells during UUO. C5aR1 expression as well as kidney fibrosis were significantly reduced in C3 null mice when compared to wild type mice subjected to UUO. Our studies suggest that increased C5aR1 expression on macrophages during UUO is associated with increased kidney fibrosis. In vitro studies using RAW 264.7 cells treated with LPS showed increased C5aR1 protein expression associated with increased production of IL1β and IL6, as well as inflammasome activation, all indicative of an increased inflammatory response.

Conclusions: Our results are the first to report that increased expression of C5aR1 on CD11b+ F4/80+ LyC6- macrophages correlates with the advent of kidney fibrosis. Increased cytokine production and inflammasome activation represent cellular mechanisms by which increased C5aR1 expression contributes to kidney fibrosis.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO011

Role of Complement C1r and C1s Serine Proteases in Kidney Fibrosis Sandhya Xavier,[1] Ranjit K. Sahu,[1] Susan G. Landes,[1] Judit Megyesi,[2] Jing Yu,[3] Ronald P. Taylor,[3] Didier Portilla.[1,4] *[1]University of Virginia Health System, Charlottesville, VA; [2]University of Arkansas for Medical Science, Little Rock, AR; [3]University of Virginia, Charlottesville, VA; [4]Salem Veteran Affairs Medical Center, Salem, VA.*

Background: Complement C1 complex consists of C1q, and proteases C1r and C1s. Our previous studies of UUO (Unilateral Ureteral Obstruction) demonstrated complement activation with increased synthesis of C1q, C1r and C1s in whole kidney tissue homogenates. To better understand the cellular processes leading to increased classical complement activation we examined the cellular localization and potential mechanisms leading to increased expression of C1r and C1s in kidney cells.

Methods: We performed real time-PCR, immunohistochemistry, in situ hybridization in wild type and in C1ra-/- mice subjected to sham or UUO injury. Cultured Raw 264.7 macrophages were treated with interferon gamma to induce C1r/C1s expression.

Results: We show increased synthesis of C1q in pericytes and CD45 positive cells, but C1r/C1s was only increased in CD45 positive and PDGFRβ negative cells during UUO. In situ hybridization and immunohistochemistry showed that C1s is induced following UUO injury in cortical thick ascending loops (cTALs) and dilated collecting ducts (CDs). C1r immunostaining was increased in cTALs, distal tubules and dilated CDs. Cultured RAW 264.7 macrophages treated with Interferon gamma had increased expression of C1r and C1s mRNA due to activation of the IFN-regulatory factor-1 (IRF-1) binding site present in the C1r promoter. Expression of C1r mRNA was absent in kidney tissue from C1ra-/- mice as compared to wildtype littermates. The ablation of C1r also leads to reduced or no expression of C1s mRNA in kidney tissue from C1ra-/- mice. Preliminary studies in these mice suggest that protection against kidney fibrosis is dependent on the expression levels of C1s and C3, and this needs to be further investigated.

Conclusions: The results support the role of complement activation with de novo increased synthesis of C1r/C1s expression by tubular epithelial and immune cells as an important mechanism leading to tubulointerstitial fibrosis.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO012

The Relationship between Renal Arteriosclerotic Lesions in CKD and the Serum Levels of Complement C3 and Uric Acid Tsuyoshi Miyagi,[1] Chisato Fukuhara,[1] Ryo Zamami,[1] Kentaro Kohagura,[1] Yusuke Ohya,[1] Kunitoshi Iseki.[2] *[1]University of the Ryukyus, Okinawa, Japan; [2]Tomishiro Central Hospital, Okinawa, Japan.*

Background: We previously reported that hyperuricemia (HUA) was related to renal arteriosclerosis in patients with chronic kidney disease (CKD). Serum complement C3 (C3), which is also an adipocytokine, has also been suggested to be related to renal arteriosclerosis. Here we examined the significance of concurrent occurrence of HUA and elevated C3 levels in renal arteriosclerosis.

Methods: This study involved 172 CKD patients whose biopsies were taken at our department. Of these patients, we excluded those who were receiving corticosteroids or calcineurin inhibitors, those with hypocomplementemia, and patients affected by disease which could cause morphological change in the renal arterioles. Arteriosclerosis was analyzed in renal pathological specimens obtained from renal biopsy using arteriolar hyalinization grade, which represents the mean grade obtained following semiquantitative assessment of the degree of hyalinization. Scores equal to or higher than the C3 median were classified into a high (HC3) group. The definition of HUA was determined as those taking antihyperuricemic drugs or those with serum uric acid levels ≥7 mg/dL for men and ≥6 mg/dL for women. The subjects were divided into four subgroups of HC3–/HUA–, HC3+/HUA–, HC3–/HUA+ and C3+/HUA+ by the presence or absence of HC3 and HUA and we then compared their arteriolar hyalinization grades.

Results: The mean arteriolar hyalinization grade after HC3/HUA subgrouping, and after logarithmic transformation, was highest for the HC3+/HUA+ subgroup, and a significant difference was observed with that for HC3–/HUA–. However, the differences between the HC3–/HUA– and HC3+/HUA– or HC3–/HUA+ subgroups were relatively small. We performed multivariate analysis of the determination factors of high arteriolar hyalinization (median grade or higher) including age, sex, pulse pressure, HbA1c, LDL-cholesterol level, and HC3/HUA subgroups (Ref: HC3–/HUA–). We found that HC3+/HUA+ (OR, 4.3; 95%CI, 1.2–15.9) was a significant factor. Furthermore, in comparison to the HC3–/HUA– subgroup, the flow-mediated dilation (%FMD) in the HC3+/HUA+ subgroup was significantly decreased.

Conclusions: In CKD patients, the relationship between HUA and renal arteriosclerosis may become more notable in patients with high levels of serum complement C3.

TH-PO013

An Association of Renal Arteriolopathy with Combination of Hypertriglyceridemia and Increased Serum Complement Component 3 in CKD Chisato Fukuhara, Ryo Zamami, Tsuyoshi Miyagi, Masanobu Yamazato, Akio Ishida, Kentaro Kohagura, Yusuke Ohya. *University of the Ryukyus, Nishihara-cho, Japan.*

Background: Metabolic syndrome, which is characterized by adiposity, is a risk factor for progression of chronic kidney disease (CKD). Complement component 3 (C3), one of adipocytokines correlated with serum triglyceride (TG) levels. We previously reported that combination of hypertrigriceridemia (hTG) and increased serum C3 related to proteinuria via unknown mechanism. Arteriolar hyalinosis may relate to proteinuria via disrupted autoregulation of glomerular hemodynamics. In the present study, we examined the association between this combination and renal arteriolopathy, oxidative stress and inflammation in patients with CKD.

Methods: A total of 139 patients with non-nephrotic CKD who underwent renal biopsy were enrolled in this study. Renal arteriolar hyalinosis was semi-quantitatively assessed via arteriole grading. Oxidative stress and inflammation was assessed by d-ROMs (Diacron-Reactive Oxygen Metabolites) test that mainly evaluating the level of hydroperoxides and high-sensitivity C-reactive protein (hs-CRP), respectively. We examined a cross-sectional association between arteriolar hyalinosis and clinical factors such as serum TG and C3. To evaluate the effect of the combination of hTG and high C3, patients were divided into four groups based on the presence of hTG and high C3 levels (hC3), defined as equal or higher than their median values.

Results: The mean values for age, estimated glomerular filtration rate (eGFR), serum TG and C3 were as follows: 44 years, 74 ml/min/1.73m^2, 169 mg/dl and 106. Serum TG, but not C3 was significantly correlated with arteriolar hyalinosis index. Subgroup analysis showed that hTG+/ hC3+ group was characterized by higher levels of body mass index, urine protein, hs-CRP and dROMs. In multivariate regression analysis, hTG+/hC3+ as well as age, systolic blood pressure and HbA1c was positively associated with arteriolar hyalinosis.

Conclusions: These findings suggest that coexistence of hTG and hC3 may relate enhanced oxidative stress and inflammation, which may cause proteinuria in association with arteriolosclerosis.

TH-PO014

Association of Renal Artery Sclerosis with Serum Complement C3 and Triglyceride–Glucose Index in CKD Chisato Fukuhara, Tsuyoshi Miyagi, Ryo Zamami, Masanobu Yamazato, Akio Ishida, Kentaro Kohagura, Yusuke Ohya. *University of the Ryukyus, Nishihara-cho, Japan.*

Background: An association between serum complement C3 (C3) and renal artery sclerosis has been suggested to exist. We investigated the influence of triglyceride–glucose index (TyG), a marker of insulin resistance, in regard to this association.

Methods: Arteriolosclerosis was semiquantitatively evaluated from hyalinized arterioles of pathological specimens obtained from kidney biopsies, and average scores (grading of arteriole hyalinization) were calculated. Patients with median or higher C3 levels were classified as the high-C3 (HC3) group. TyG was calculated as fasting triglycerides (mg/dL) × fasting glucose (mg/dL) / 2, and patients with median or higher TyG value were classified as the high-TyG (HTyG) group. Patients were then divided into subgroups based on the presence or absence of HC3 and HTyG (HC3–/HTyG–, HC3+/HTyG–, HC3–/HTyG+, and HC3+/HTyG+).

Results: The average score for arteriole hyalinization grading after applying a subgroup-specific logarithmic transformation was significantly higher in the HC3+/HTyG+ group than in the other groups. A multivariate analysis was conducted wherein high degree of arteriole hyalinization (median grade or higher) was the determinant, and age, sex, systolic blood pressure, serum uric acid levels, presence or absence of diabetes, and HC3/HTyG subgroup (Ref: HC3–/HTyG–) were explanatory variables. Results indicated that HC3+/HTyG+ was significant but HC3+/HTyG– was non-significant. The HC3+/HTyG+ group also had the lowest percent flow-mediated dilatation.

Conclusions: An association between C3 and renal artery sclerosis in patients with chronic kidney disease may be prominent in terms of endothelial dysfunction under conditions of high insulin resistance.

TH-PO015

Complement C5a Moderates Renal Lipid Metabolism and Fibrosis in Diabetic Nephropathy Wai Han Yiu,[1] Ruixi Li,[1] Dickson W. Wong,[1] Haojia Wu,[1] Kam wa Chan,[1] Loretta Y.Y. Chan,[1] Joseph C K Leung,[1] Kar Neng Lai,[1] Steven H. Sacks,[2] Wuding Zhou,[2] Sydney C. Tang.[1] *[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China; [2]Medical Research Council Centre for Transplantation, King's College London, Guy's Hospital, London, United Kingdom*.

Background: Complement C5 activation has been implicated in tubulointerstitial injury with increased levels of tubular C5a in renal biopsies from patients with diabetic nephropathy. We investigated whether administration of a C5a inhibitor would confer protection against the progression of diabetic nephropathy in an animal model of type 2 diabetes.

Methods: Uninephrectomized diabetic *db/db* mice were administrated with novel C5a inhibitor, NOX-D21 (10 mg/kg, a kind gift from NOXXON) or an equal volume of saline for a total of 12 weeks. Non-diabetic *db/m* mice were used as control.

Results: In *db/db* mice, treatment with NOX-D21 for 12 weeks did not affect hyperglycemia, but significantly prevented the increase in serum creatinine and BUN levels. These NOX-D21 treated mice had reduced glomerulosclerosis and tubular damage compared to the vehicle-treated diabetic mice. In addition, blockade of C5 signaling reduced the overexpression of TGF-β1, activation of Akt signaling and interstitial expression of fibronectin and collagen type I in the diabetic kidney. NOX-D21 also ameliorated lipid abnormalities in *db/db* mice and resulted in significant decrease in serum triglycerides and expression of lipid metabolism-related genes (DAGT1 and SREBP-1) in the diabetic kidney.

Conclusions: Our findings suggest a pathogenic role of C5a in diabetic nephropathy, especially in regulating TGF-β-driven renal fibrosis. Inhibition of C5a signaling partially improves renal function and ameliorates dyslipidemia in diabetic animals. **Funding:** Hong Kong Society of Nephrology and Hong Kong Kidney Foundation Research Grant (2016).

TH-PO016

C-Terminal Oligomerization of Podocin Can Mediate Interallelic Complementation Eszter Balogh,[8,6] Pal Straner,[1] Gusztáv Schay,[4,6] Christelle Arrondel,[5] Ágnes Mikó,[8,6] Gerda L'aune,[8,6] Alexandre Benmerah,[2] Andras Perczel,[1] Dora K. Menyhard,[1] Corinne Antignac,[3] Geraldine Mollet,[7] Kalman Tory.[8,6] *[1]MTA-ELTE Protein Modeling Research Group, Eötvös Loránd University, Budapest, Hungary; [2]INSERM U1163, Imagine Institute, Paris, France; [3]Imagine Institute, Paris, France; [4]Department of Biophysics and Radiation Biology, Semmelweis University, Budapest, Hungary; [5]INSERM, Paris, France; [6]Semmelweis University, Budapest, Hungary; [7]Inserm U1163, Paris, France; [8]MTA-SE Lendulet Nephrogenetic Laboratory, Hungarian Academy of Sciences, Budapest, Hungary. Group/Team: MTA-SE Lendulet Nephrogenetic Laboratory*.

Background: Podocin, a membrane-anchored component of the slit diaphragm, is encoded by *NPHS2*, the major gene of steroid-resistant nephrotic syndrome. We formerly showed that its most frequent non-silent variant, R229Q, is pathogenic only when trans-associated to specific 3' missense mutations and suggested that an altered dimerization mediates their dominant negative effect. Here we aimed to determine the membrane targeting and the oligomerization capacity of podocin in function of its C-terminal integrity.

Methods: Podocin localization was studied in cultured podocytes co-transfected with GFP- and HA-tagged podocin variants. The role of endocytosis was studied by the coexpression of a dominant negative dynamin. Binding capacity of the dimers was measured as the FRET efficiency between podocin variants expressed either in HEK293 cells or in E.coli, extracted and stained with fluorescent maleimides. Oligomerization was studied by size exclusion chromatography.

Results: We found neither colocalization, nor FRET between the membranous R286Tfs*17 podocin lacking the C-terminal tail (CTT) and other podocin variants indicating that oligomerization occurs exclusively through the CTT. Podocin variants containing the first helix (H1) of the CTT (273-313) dimerized, and those also containing the 332-348 region, oligomerized. Truncated podocin variants with an intact H1 were significantly influenced in their localization by the coexpressed missense podocin variants. We found the F344Lfs*4 and F344* podocin mutants to be endocytosed. Interestingly, it was inhibited by the coexpression of some membranous podocin variants with an intact CTT. We found the F344Lfs*4 podocin, the first frameshift mutation that is pathogenic with R229Q to similarly retain R229Q podocin as other pathogenic associations. Its dominant negative effect was exerted through the FDL344_346LTY amino acid changes encoded by the frameshift sequence.

Conclusions: Oligomerization of podocin is mediated exclusively by the CTT. Though oligomerization is not prerequisite for membrane-targeting, it may mediate not only a dominant negative effect between podocin variants, but also normalization of the localization, i.e. interallelic complementation. Such a complementation can also modify the pathogenicity of *NPHS2* alleles.

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TH-PO017

Complement Activation Is Not Required for MPO-ANCA Induced Pulmonary Granulomatosis in Mice Hong Xiao, Peiqi Hu, Marco A. Alba, Ronald J. Falk, J. Charles Jennette. *University of North Carolina at Chapel Hill, Chapel hill, NC*.

Background: We previously developed an animal model of human pauci-immune crescentic glomerulonephritis (CGN) caused by myeloperoxidase (MPO) specific antineutrophil cytoplasmic autoantibodies (MPO-ANCA) by i.v. injection of mice with antibodies specific for mouse MPO. The induction of CGN by injection of anti-MPO IgG required activation of the alternative complement pathway, and was prevented in deficient in complement factor B (CFB) or C5. We now have developed a model of ANCA pulmonary granulomatosis that mimics granulomatosis with polyangiitis caused by i.v. injection of anti-MPO IgG after intratracheal spray of lipopolysacarride (LPS).

Methods: 9-11 wk-old B6 WT, CFB-/- and C5-/- mice were treated with an intratracheal spray of LPS (5ug) at day 0, plus two doses of anti-MPO IgG, i.v. (75ug/g BW) at day0 and day1. Mice were sacrificed at day7. Kidney and lung tissues were obtained for pathologic examination.

Results: With this regimen, all B6 WT mice (n=5) developed CGN (mean 20% glomeruli with crescents) and pulmonary necrotizing granulomatous lesions (mean scores = 2.6 out of 3). All CFB-/- (n=3) and C5-/- (n=4) mice developed pulmonary necrotizing granulomatous lesions (mean scores = 3) but none developed CGN. Negative control WT mice that received LPS alone (n=6), and MPO-/- mice that received LPS and anti-MPO (n=3) developed no CGN or pulmonary granulomatosis.

Conclusions: Absence of CFB or C5 protects from anti-MPO induced CGN but not anti-MPO induced pulmonary granulomatosis, indicating complement activation is not required for MPO-ANCA induced pulmonary granulomatosis in mice. These interesting and potentially impactful observations suggest that although both necrotizing CGN and necrotizing pulmonary granulomatosis are caused by MPO-ANCA, the mediators are different, and, thus optimum therapy for the kidney disease may differ from optimum therapy for the lung disease. For example, although blockade of alternative pathway activation may be effective adjunct therapy for ANCA CGN, it may have no effect on ANCA granulomatous disease.

Funding: NIDDK Support

TH-PO018

The Role of Complement C9 as a Marker for Therapeutic C5 Blockade in Lupus Nephritis Hannah R. Wilson,[2] Alyssa C. Gilmore,[2] Nicholas R. Medjeral-Thomas,[2] Pritesh Trivedi,[2] Kathleen I. Seyb,[1] Ramin Farzaneh-Far,[1] Tom Cairns,[2] Liz Lightstone,[2] Matthew C. Pickering,[2] H. Terence Cook.[2] *[1]Ra Pharmaceuticals, Inc., Cambridge, MA; [2]Imperial College Lupus Centre, Imperial College Healthcare NHS Trust, London, United Kingdom*.

Background: Complement plays an important role in the pathogenesis of lupus nephritis (LN) and there are reports of therapeutic benefit with eculizumab, a C5 inhibitor. However, LN can also develop in complement-deficient individuals. With the emergence of therapeutic C5 inhibition, there is a need to identify patients in whom complement-driven inflammation, attributable to C5a, C5b-9, or both, is a major cause of kidney injury in LN.

Methods: Clinical and histopathological data from 54 patients with class III, IV and V LN were obtained retrospectively. Staining for C9, C5b-9, C3c and CD68 was performed and intensity assessed. Response was defined using urine protein-creatinine ratio and estimated glomerular filtration rate.

Results: C9 staining was equivalent to C5b-9 staining. C9 was detected in the mesangium of both active and chronic proliferative (class III and IV) LN in the majority of patients and in the capillary wall of class V LN in all patients. C9 staining intensity in the tubular basement membrane correlated with creatinine levels at the time of biopsy and with markers of tubulo-interstitial damage. C9 staining intensity did not correlate with C3c staining intensity or glomerular CD68 count. C9 staining also did not correlate with serological markers of activity, however C3c and CD68 staining did. Although not statistically significant, a low C9 staining intensity appears to indicate a greater chance of complete remission in active disease.

Conclusions: The widespread presence of glomerular C9 in LN supports a role for the C5b-9 membrane attack complex in renal injury. Importantly, the lack of correlation with C3c intensity suggests that the kinetics of glomerular C9 and C3c staining differ. Understanding the kinetics of complement deposition will be important in identifying patients most likely to benefit from C5 inhibition.

Funding: Commercial Support - Ra Pharmaceuticals

TH-PO019

Decay Accelerating Factor (DAF), Local Complement Inhibitor, Protects from Adriamycin (ADR)-Induced FSGS Andrea Angeletti,[2,3] Chiara Donadei,[2,3] Vivette D. D'Agati,[1] Jenny Wong,[2] Kirk N. Campbell,[2] Gaetano La Manna,[3] Miguel L. Fribourg,[2] Peter S. Heeger,[2] Paolo Cravedi.[2] *[1]Columbia University College of Physicians and Surgeons, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]Nephrology, DIMES, Bologna, Italy.*

Background: The impact of DAF, a cell surface expressed complement regulator, in the pathogenesis of proteinuric glomerular disease, including Adr-induced nephropathy is unknown.

Methods: We injected 20mg/kg Adr into B6 WT, and congenic DAF$^{-/-}$, DAF$^{-/-}$C3$^{-/-}$, DAF$^{-/-}$C3aR$^{-/-}$ mice and DAF$^{fl/fl}$ crossed to Cre-transgenics; the B6 strain is known to be resistant to Adr nephropathy. We serially measured urine albumin/creatinine (A/C) and at 35 weeks we quantified histological injury and stained sections for complement activation products.

Results: : Adr caused proteinuria in B6 DAF$^{-/-}$ but not in WT (Fig 1A), DAF$^{-/-}$C3$^{-/-}$, or DAF$^{-/-}$C3aR$^{-/-}$ mice, mechanistically implicating DAF-dependent restraint on complement activation and ensuing C3a/C3aR signaling in the disease process (Fig 1B). Using newly developed DAF conditional KOs, absent DAF from podocytes (DAF$^{fl/fl}$-podocin-Cre^{+}) conferred Adr-sensitivity, while DAF$^{fl/fl}$-CD11c-Cre^{+} did not develop disease (Fig 1A). DAF-deficiency-induced proteinuria correlated with higher histological scores (Fig 1C) and glomerular staining for C3b, without C1q, C4b, and MAC. Kidneys from Adr-treated DAF$^{-/-}$, DAF$^{fl/fl}$-CD11c-Cre^{+} but not control mice showed Claudin-1^{+} parietal epithelial cells (PECs) in the glomerulus.

Conclusions: Podocyte-expressed DAF mediates resistance to Adr-induced glomerular injury in B6 mice. In the absence of DAF, Adr-induced kidney injury is propagated by local C3a/C3aR signaling that likely contributes to PEC recruitment and glomerulosclerosis. Studies addressing a role for DAF/complement in human FSGS and related diseases are warranted.

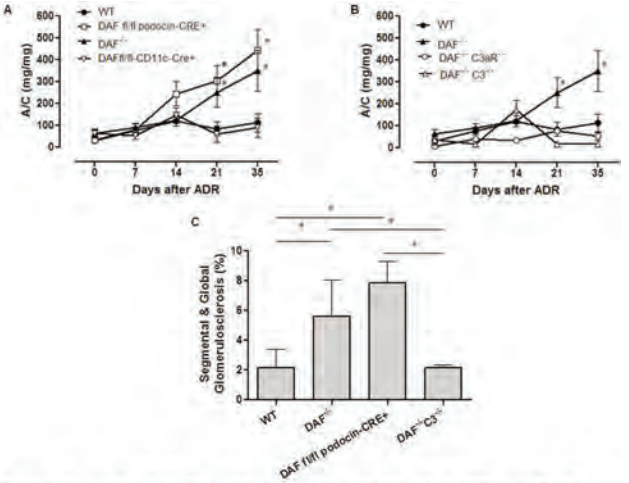

Figure 1. Urinary albumin/creatinine (A/C) WT, DAF$^{-/-}$, and DAF$^{fl/fl}$ podocin-CRE^{+} and in B) WT, DAF$^{-/-}$, DAF$^{-/-}$C3aR$^{-/-}$ and DAF$^{-/-}$C3$^{-/-}$ mice. C) Histological scores.

TH-PO020

An In Vitro Model of Idiopathic Membranous Nephropathy Reveals PLA2R- and Complement-Dependent Pathways of Podocyte Injury George Haddad,[2] Andreas D. Kistler.[1] *[1]None, Winterthur, Switzerland; [2]University of Zurich, Zurich, Switzerland.*

Background: Idiopathic membranous nephropathy (iMN) is an autoimmune kidney disease that usually manifests as nephrotic syndrome through damage of podocytes and leads to progressive renal failure in a significant proportion of patients. Recently, the target antigen of autoantibodies in the majority of patients with iMN has been identified as the phospholipase A_2 receptor (PLA_2R). The definitive proof for pathogenicity of PLA_2R antibodies, however, is still lacking. Furthermore, mechanisms of podocyte injury remain elusive, although sublytic complement injury has been proposed. In this study, we aim to develop an *in vitro* model for iMN to determine downstream mechanisms of anti-PLA2R-antibody mediated injury to podocytes.

Methods: PLA_2R expression levels in conditionally immortalized human podocytes were modulated by infection with a lentivirus vector carrying FLAG-tagged full length human PLA2R or by siRNA-mediated knock down. These cells were then pretreated with sera from PLA_2R-positive iMN patients or control sera and subsequently, human complement was added. Cell lysates were collected and analyzed by qPCR, Western blot, and IF.

Results: Podocytes overexpressing PLA_2R treated with a high-titer (1:1000) PLA2R antibody positive sera and complement in sublytic concentration resulted in decrease synaptopodin and NEPH1 expression with a noticeable synaptopodin rearrangement. The complement sublytic effect on podocytes is likely to involve the activation of the lectin pathway and C3aR1 and C5aR1 signaling as knock down of these receptors rescued synaptopodin and NEPH1. Synaptopodin and NEPH1 degradation appeared to occur via two independent pathways that require cysteine and aspartate proteases, respectively.

Conclusions: Podocyte injury by iMN serum and sublytic complement includes synaptopodin and NEPH1 degradation. In addition, we have developed an in vitro assay to specifically assess the complement-dependent podocytopathic effect of iMN sera that will allow to screen for protective compounds.

TH-PO021

Abstract Withdrawn

TH-PO022

Calcineurin Inhibitor-Induced Endothelial Cell Injury – A Role for Complement Chia Wei Teoh,[2] Magdalena Riedl,[2] Valentina Bruno,[1] Lisa Robinson,[2] Christoph Licht.[2] *[1]None, Toronto, ON, Canada; [2]The Hospital for Sick Children, Toronto, ON, Canada.*

Background: Calcineurin inhibitors (CNI) are associated with nephrotoxicity, endothelial cell (EC) dysfunction and thrombotic microangiopathy (TMA). Evolving evidence suggests a central role for complement dysregulation in the pathogenesis of CNI-induced TMA. However, the exact mechanism of CNI-induced complement-mediated injury remains unknown. We hypothesize that CNIs induce complement-mediated EC injury and impair complement regulation on EC surfaces.

Methods: Complement activation (C3c, C9) and regulation (CD46, CD55, CD59), and complement factor H (CFH) surface binding were assessed by flow cytometry. CFH surface cofactor activity was assessed by a surface cofactor assay. EC cytotoxicity was detected via LDH assay. Blood outgrowth EC (BOECs) from healthy donors and an aHUS patient with MCP mutation were incubated with cyclosporine (CsA) and subsequently exposed to 50% normal human serum (NHS) as source for complement. EC glycocalyx was assessed with wheat germ agglutinin staining on confocal microscopy.

Results: The sequence of CsA incubation and 50% NHS resulted in a dose and time dependent enhancement of EC complement deposition and EC death, exacerbated by serum starvation and sensitization with anti-CD59 antibody. An optimal balance of EC survival and CNI effect was obtained with CsA 10 mcg/ml for 24 hours. CsA led to upregulation of CD46, CD55 and CD59 on EC surface. CsA diminished the EC glycocalyx with subsequent decreased CFH surface binding and surface cofactor activity. In further support of our in-vitro findings, MCP-deficient BOECs exposed to CsA had significantly higher surface complement deposition compared to healthy controls.

Conclusions: Our findings suggest a role for complement-mediated EC injury induced by CsA, with CFH surface dysregulation playing a key role in CsA-induced complement activation on EC surfaces. MCP-deficient BOECs were genetically predisposed to be more susceptible to CsA-induced endothelial complement deposition. CsA-induced abolishment of EC glycocalyx may be the key mechanism leading to alternative pathway dysregulation, and warrants further studies.

TH-PO023

The RS6677604 in Complement Factor H Is Associated with Long Term Graft Function in Transplant Recipients with IGA Nephropathy Francesco Pesce,[2] E. D. Stea,[2] Anna lucia Crispino,[1] Matteo Accetturo,[2] Francesca Cianciotta,[2] Chiara Divella,[2] M. Rossini,[2] Paola Laghetti,[2] Paola Pontrelli,[2] Donata Mininni,[1] Marcella Margiotta,[1] G. Lucarelli,[2] Michele Battaglia,[2] Loreto Gesualdo,[2] Giuseppe Castellano.[2] *[1]Policlinico di Bari, Bari, Italy; [2]University of Bari, Bari, Italy.*

Background: BACKGROUND The rs6677604 in Complement Factor H (CFH) and the deletion of complement factor H-related genes 1 and 3(CFHR3-1Δ), which is in linkage disequilibrium (LD) with rs6677604-A, have been associated with the development of IgA nephropathy (IgAN). IgAN has a negative outcome on renal transplantation. We tested the role of CFHR3-1Δ using rs6677604 as proxy, in IgAN patients who received a kidney transplant assessing the impact on long-term graft survival.

Methods: Our cohort consisted of 67 patients with a biopsy-proven diagnosis of IgAN on native kidneys that received a kidney transplant at the University of Bari (D.E.T.O.) between 1993 and 2017. Genomic DNA was extracted using standard techniques. The complement factor H (CFH) region containing the SNP rs6677604 was amplified through PCR and sequenced by Sanger technology. Relevant clinical parameters were retrieved from patients' files and periodically recorded during the follow-up. Univariate and multivariate survival analyses were performed with eGFR < 60mL/min/1.73m^2 as endpoint.

Results: Of 67 patients, 22 (32.8%) had the rs6677604-AG genotype and 45 (67.2%) the rs6677604-GG genotype. These two groups were comparable in terms of demographic characteristics, donor features and transplant-related factors such as the occurrence of delayed graft function, episodes of acute rejection and therapeutic regimen. No difference was found when we analyzed the progression of the disease before the

transplant. However, we observed a significantly worse outcome of the graft in patients with the rs6677604-GG genotype by univariate survival analysis (P=5.81E-05) during the follow-up (69 ± 62 months). A multivariate Cox survival analysis revealed that the rs6677604-GG genotype (HR 30.8; 95% IC 3.3-285.5; P=0.003) is the strongest independent predictor for the graft outcome in a model adjusted for age, gender, delayed graft function, episodes of acute rejection, HLA match and donor specific antibodies.

Conclusions: Our study suggests a major impact of CFHR3-1Δ on long term graft function in kidney transplant recipients with IgAN and that rs6677604 typing can be used to predict the outcome in these patients.

TH-PO024

IL-17C/IL-17 receptor E Signaling in CD4+ T Cells Is Required to Promote TH17 Cell-Driven Glomerular Inflammation Jasper Nies,[1] Sonja Krohn,[5] Hans-Joachim Paust,[2] Jan-Hendrik Riedel,[3] Christian F. Krebs,[1] Silke R. Brix,[4] Sonja Kapffer,[7] Tilman Schmidt,[1] Rolf A. Stahl,[6] Ulf Panzer.[5] *[1]Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; [2]Hamburg University Hospital, Hamburg, Germany; [3]UKE, Hamburg, Germany; [4]University Hospital Hamburg-Eppendorf, Hamburg, Germany; [5]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [6]University of Hamburg, Hamburg, Germany; [7]Universitätsklinikum Hamburg Eppendorf, Hamburg, Germany. Group/Team: Panzer Lab.*

Background: The IL-17 cytokine family (IL-17A-F) and their cognate receptors (IL-17RA-RE) play a unique role in organ-specific autoimmunity. So far, most studies focused on the IL-17 founding member, IL-17A, as the critical mediator of diseases. The specific function of the other IL-17 family members in immunity and inflammatory diseases is largely unclear. The aim of our study was to examine the potential role of these cytokines in human and experimental immune-mediated glomerular diseases.

Methods: Serum IL-17A/C/E/F levels of 70 patients with acute ANCA-associated crescentic GN (biopsy proven) and 20 healthy control subjects were analyzed by multiplex technology (Meso Scale Discovery). The function of IL-17 cytokines and their receptors was assessed in experimental models of glomerulonephritis.

Results: Serum IL-17C levels were significantly elevated in patients with acute ANCA-associated crescentic GN compared to healthy controls ($p < 0.001$). In contrast, no significant differences in serum IL-17A/F/E levels were detected between patient groups and controls. Using mouse models of crescentic GN (NTN) and pristane induced lupus nephritis, we showed that the lack of IL-17C and its unique receptor IL-17RE significantly ameliorated the course of the GN in terms of renal tissue injury and kidney function. Interventional studies using an anti-IL-17A neutralizing antibody demonstrated that this protective effect was due to a reduced Th17 response in IL-17C and IL-17RE gene-deficient mice. GN induction in bone marrow chimeric mice lacking IL-17C in either hematopoietic or tissue cells revealed that systemic and renal IL-17C is expressed by tissue resident cells and not by lymphocytes. Finally, we demonstrated that IL-17RE was predominantly expressed by $CD4^+$ Th17 cells and that this expression is instrumental for the induction / maintenance of the Th17 responses with subsequent tissue injury in crescentic GN.

Conclusions: Our findings indicate that IL-17C promotes Th17 cell responses and autoimmune kidney disease via IL-17RE signaling on $CD4^+$ Th17 cells. Targeting the IL-17C/IL-17RE pathway may present an intriguing therapeutic strategy for Th17 driven autoimmune disorders.

Funding: Government Support - Non-U.S.

TH-PO025

Amphiregulin Aggravates Glomerulonephritis via Recruitment and Activation of Myeloid Cells Simon Melderis,[1] Georg R. Herrnstadt,[1] Anna Nosko,[1] Gisa Tiegs,[2] Oliver M. Steinmetz.[1] *[1]III. Medical Clinic, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [2]Institute of Experimental Immunology and Hepatology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*

Background: Amphiregulin (AREG), a member of the epidermal growth factor family, plays a role in development and tumorigenesis. Recently AREG has also emerged as novel player in immune responses. Both, pro- and anti-inflammatory functions have been postulated, leaving the role of AREG in inflammatory diseases widely unclear. In particular, nothing is known about the role of AREG in glomerulonephritis (GN). Given that EGF-receptor directed therapies have recently become available, we aimed to clarify the function of AREG in an experimental model of crescentic GN.

Methods: Nephrotoxic nephritis (NTN) was induced in AREG-KO mice and wild type controls. Time course and tissue specific AREG expression was assessed. Renal histology, function and leukocyte influx were analyzed. Broad analyses of renal and systemic immune responses were performed.

Results: Renal AREG expression was undetectable under homeostatic conditions. After induction of NTN AREG mRNA levels increased within the first 5 days and peaked at day 7. Expression subsequently decreased to baseline levels at day 20. In contrast, splenic expression remained below detection level at all time points. Importantly, the course of NTN was significantly attenuated in AREG-KO mice in terms of kidney function, albuminuria and histological damage. In search of a potential mechanism, we found reduced renal expression of the pro-inflammatory cytokine IL-1β, the macrophage attracting chemokine monocyte chemotactic protein 1 (MCP-1), as well as granulocyte attracting C-X-C motif chemokine ligands 1 (CXCL1) and 5 (CXCL5). As a consequence, renal infiltration of macrophages and neutrophils was significantly impaired in AREG-KO mice. Furthermore, characterization of renal macrophage markers revealed a less inflammatory phenotype in the absence of AREG.

Conclusions: Our data strongly suggest that AREG has pro-inflammatory effects in acute GN. As one mechanism, we hypothesize, that AREG induces renal chemokine expression. This in turn results in enhanced recruitment and activation of inflammatory myeloid cells. AREG is thus a potential new therapeutic target for crescentic GN.

Funding: Government Support - Non-U.S.

TH-PO026

Erythroid ACKR1 Expression Has Profound Impact on the Development of Experimental Glomerulonephritis Katharina Artinger,[1] Igor Novitzky-Basso,[3] Alexander H. Kirsch,[1] Corina Schabhüttl,[1] Elin Hub,[2] Leah Etheridge,[2] Philipp Eller,[1] Alexander R. Rosenkranz,[1] Antal Rot,[2] Kathrin Eller.[1] *[1]Medical University of Graz, Graz, Austria; [2]University of York, York, United Kingdom; [3]Queen Elizabeth University Hospital, Glasgow, United Kingdom.*

Background: The majority of individuals of West African ancestry carry a polymorphic "erythroid silent" FyB(ES) variant of *ACKR*1. Individuals with FyB(ES) express ACKR1 on endothelial cells but not on erythroid cells. The FyB(ES) polymorphism is of special interest for understanding human kidney disease as the individuals of West African ancestry have higher incidence of chronic kidney diseases. Moreover, chemokine ligands of ACKR1 are involved in driving the inflammatory pathology in the experimental model of nephrotoxic serum nephritis (NTS).

Methods: We developed humanized transgenic mouse strains, which do not express mouse ACKR1 but instead either West African FyB(ES) or Caucasian FyB polymorphic *ACKR1* variants. These strains as well as ACKR1-deficient and WT mice were subjected to NTS, a murine model of immune complex glomerulonephritis. The parameters of immunepathogenesis and kidney phenotype were evaluated after 14 days.

Results: Albuminuria, PAS and tubular injury scores were significantly increased in FyB(ES)tg and ACKR1-deficient mice as compared to their respective control strains. While monocytes were unchanged in peripheral blood, we found significantly increased numbers of macrophages and neutrophils infiltrating the kidneys of FyB(ES)tg and ACKR1-deficient mice. Interestingly, T cell numbers in the draining lymph nodes were comparable between FyB(ES)tg and ACKR1-deficient mice and their respective controls.

Conclusions: We found that NTS was more severe in ACKR1-deficient and FyB(ES) mice as compared to their respective controls. Our results show that ACKR1 expression in the erythroid compartment has a significant impact on the development of kidney disease. These findings have important implications for the pathomechanisms of glomerulonephritis in individuals of West African ancestry who lack ACKR1 selectively in the erythroid lineage.

TH-PO027

Upregulation of Matrix Metalloproteinase-10 in Glomerular Cells and Macrophages by Inflammation Keisuke Osaki,[2] Yukiko Kato,[2] Naohiro Toda,[2] Akira Ishii,[2] Keita P. Mori,[2] Shoko Ohno,[2] Kiyoshi Mori,[3] Moin Saleem,[5] Taiji Matsusaka,[4] Masashi Mukoyama,[1] Motoko Yanagita,[2] Hideki Yokoi.[2] *[1]Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan; [2]Kyoto University Graduate School of Medicine, Kyoto, Japan; [3]School of Pharmaceut Sci, University of Shizuoka, Shizuoka, Japan; [4]Tokai University School of Medicine, Isehara, Japan; [5]University of Bristol, Bristol, United Kingdom.*

Background: Recently, we and others have unveiled the novel renal function of natriuretic peptide receptor/guanylyl cyclase-A (GC-A) system on antagonizing aldosterone-induced podocyte injury as well as the conventional effects on natriuresis and reducing blood pressure. High salt-fed systemic or podocyte-specific GC-A knockout mice with aldosterone and uninephrectomy showed accelerated glomerular injury with massive albuminuria. However, genes involved in glomerular injury are elusive.

Methods: By using microarray analysis, we compared gene expression in the glomeruli of systemic GC-A knockout mice and wild-type mice with aldosterone and examined gene expression by glomerular cells and macrophages with TNF-α. We performed immunohistochemical study for an identified protein.

Results: We identified matrix metalloproteinase-10 (MMP-10) in glomeruli of aldosterone-induced systemic GC-A KO mice. We confirmed that the expression of MMP-10 from the glomeruli in systemic and podocyte-specific GC-A knockout mice was 50 and 3 times higher than that from control mice by real-time PCR, respectively. Immunostaining revealed that aldosterone–infused systemic or podocyte-specific GC-A knockout mice exhibited a mild increase in MMP-10-positive cells in glomeruli and distal tubular cells. MMP-10 staining of renal biopsy samples in human IgA nephropathy also demonstrated the increase of MMP-10 staining intensity in glomerular cells. *In vitro*, mRNA expression of MMP-10 was increased in human podocytes as well as murine mesangial cells with TNF-α stimulation. In murine macrophages (RAW264.7 cells), the expression of MMP-10 wasn't increased with TNF-α alone, but was upregulated when both TNF-α and connective tissue growth factor (CTGF) were given at the same time. Additionally, TGF-β stimulation induced MMP-10 overexpression in podocytes.

Conclusions: These results suggest that glomerular MMP-10 in podocytes, mesangial cells and macrophages is increased in aldosterone-infused GC-A KO mice, and could play a role on inflammation during glomerular injury.

TH-PO028

Podocyte-Specific Knockout of the Neonatal Fc Receptor (FcRn) Does Not Protect against Induction of Immune Complex Mediated Glomerular Disease James F. Dylewski,[2] Evgenia Dobrinskikh,[3] Linda Lewis,[4] Gabriela E. Garcia,[1] Judith Blaine.[1] *[1]University of Colorado Denver, Aurora, CO; [2]University of Colorado Hospital, Aurora, CO; [3]University of Colorado, Denver, Aurora, CO; [4]University of Colorado Denver, Aurora, CO.*

Background: Podocytes have been postulated to act as non-hematopoietic antigen presenting cells (APCs). In typical APCs the neonatal Fc receptor is required for antigen presentation and induction of an immune response. Global knockout of FcRn has been shown to protect against immune-mediated kidney disease. Podocytes express FcRn and the aim of this study was to determine whether knockout of FcRn in podocytes ameliorates immune complex mediated kidney disease.

Methods: MHC II and costimulatory marker expression in wild type (WT) and FcRn knockout (KO) podocytes was characterized at baseline and after stimulation with IFNg using flow cytometry. We compared antigen presentation in WT and FcRn KO podocytes using an in vitro antigen presentation assay. We created a podocyte-specific FcRn KO mouse and examined albuminuria, renal histology, intraglomerular neutrophil accumulation, and C3 deposition after induction of anti-glomerular basement membrane (anti-GBM) nephritis. Fluorescence lifetime imaging (FLIM) was used to examine metabolic changes in the glomeruli of KO and control mice after induction of nephritis.

Results: We found that treatment with IFNg upregulated MHC II expression in both WT and FcRn KO podocytes. At baseline, WT podocytes expressed significantly more CD80 than FcRn KO podocytes and there was no increase in CD80 expression in the KO after treatment with IFNg. Neither WT nor KO podocytes expressed CD86 at baseline or after treatment with IFNg. When treated with immune complexes in an in vitro antigen presentation assay, WT podocytes induced a very modest increase in T-cell IL-2 production whereas KO podocytes did not stimulate T cells at all. There was no difference in BUN, albuminuria, intraglomerular neutrophil infiltration, C3 deposition, glomerulosclerosis score, or percent crescents in control versus podocyte-specific FcRn KO mice after induction of anti-GBM disease. FLIM demonstrated a decreased shift in glycolysis in KO mice compared to control after disease induction.

Conclusions: This study demonstrates that podocytes are inefficient antigen presenting cells and podocyte specific KO of FcRn does not prevent induction of anti-GBM disease.

Funding: NIDDK Support

TH-PO029

Absence of RORyt+ Foxp3+ biTregs Aggravates Glomerulonephritis Torben Ramcke, Anna Nosko, Rolf A. Stahl, Malte A. Kluger, Oliver M. Steinmetz. *Nephrology, University Hospital Hamburg Eppendorf, Hamburg, Germany.*

Background: Recently, cells expressing the unusual combination of the Treg transcription factor Foxp3, together with the Th17 charateristic RORyt were identified (biTregs). In models of glomerulonephritis, we found protection by transfer of exogenous biTregs. However, selective deletion of RORyt in biTregs revealed additional pro-inflammatory effects, including IL-17 secretion and suppression of Th2 immunity. The net effect of complete absence of RORyt+ biTregs, as opposed to sole knockout of RORyt in Tregs, remains unknown to date.

Methods: CD4+ T cells, containing or lacking biTregs, were sorted from RORyt Foxp3 double reporters and transferred into RAG1-/- recipients. Development of transfer colitis and nephrotoxic nephritis (NTN) were assessed at varying time points after cell transfer. Immune responses and renal outcome parameters were studied. Finally, immunosuppressive mechanisms of biTregs were analysed by adoptive transfer and in vitro assays.

Results: BiTregs were readily detectable at all time points after transfer. In contrast, they failed to develop de-novo in mice receiving biTreg depleted T cells. Furthermore, the Treg/Th17 balance was not disturbed, underlining their independent character. Selective absence of biTregs did not cause generalized lymphoproliferation or accelerated transfer colitis. Importantly, however, nephritis was aggravated in mice lacking biTregs with enhanced renal inflammatory mRNA expression, leukocyte infiltration and tissue damage. Interestingly, while selective ablation of RORyt in Tregs resulted in enhanced Th2 immunity, complete absence of biTregs did not. Transfer of exogenous biTregs into immunocompetent mice revealed broad immunosuppressive capacity with no preference for Th2 responses.

Conclusions: We developed a new model, which mimicks knockout of biTregs. Absence of biTregs did not accelerate transfer colitis but significantly aggravated glomerulonephritis. In contrast to isolated deletion of RORyt in Tregs, complete lack of biTregs did not result in selectively enhanced Th2 responses. In summary, we provide further evidence that biTregs are novel and independent regulators of inflammation with broad immunosuppressive capacity.

Funding: Government Support - Non-U.S.

TH-PO030

Group 1 Innate Lymphoid Cell Is Involved in the Progress of Experimental Glomerulonephritis Inhibited by PPAR-Alpha Yusuke Okabayashi,[1,2] Shinya Nagasaka,[1] Anri Sawada,[1] Sae Aratani,[1] Ai Katsuma,[1,2] Michiko Aoki,[1] Yusuke Kajimoto,[1] Dedong Kang,[1] Go Kanzaki,[2] Nobuo Tsuboi,[2] Takashi Yokoo,[2] Akira Shimizu.[1] *[1]Department of Analytic Human Pathology, Nippon Medical School, Tokyo, Japan; [2]Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan.*

Background: Both $CD8^+$ lymphocytes ($CD8^+$Lym) and macrophages (Mϕ) associate with the progress of the anti-glomerular basement membrane glomerulonephritis (anti-GBM GN) in a rat model. However, the profile of $CD8^+$Lym has not been fully evaluated except that they do not express T-cell receptor. Previous studies have shown that peroxisome proliferator activated receptors (PPARs) have anti-inflammatory effects. This study evaluated the profile of $CD8^+$Lym and the effect of PPARs on $CD8^+$Lym.

Methods: Male Wister-Kyoto rats at 4 weeks of age were intravenously injected with 50μg anti-GBM antibodies on day 1 and divided into 7 groups and received fenofibrate (30, 100, 300mg/kg/day; PPARα agonist), pioglitazone (12.5, 50, 100mg/kg/day; PPARγ agonist) or vehicle once-daily from day 0. 24-hr urine samples were collected and the kidneys were harvested on day 8. Isolated glomeruli were analyzed by flow cytometry and quantitative RT-PCR (qRT-PCR) analysis.

Results: In immunofluorescence and flow cytometric analysis of isolated glomeruli, $CD8^+$Lym that infiltrated into glomerulus were lineage negative cells (negative for T-cell, B-cell, dendritic cell, NK cell, Mϕ and granulocyte markers). Both the treatments of PPAR agonists reduced the level of proteinuria, and the number of crescentic lesions and infiltrating Mϕ dose dependently. Notably, fenofibrate showed greater reduction in infiltration of $CD8^+$Lym than pioglitazone, which was associated with the decrease of *T-bet* and *IFN*-γ mRNA expression. Moreover, fenofibrate down-regulated inflammatory cytokines and chemokines mRNA expression. qRT-PCR analysis of $CD8^+$Lym harvested by cell sorting revealed that $CD8^+$Lym expressed *IFN*-γ mRNA more than Mϕ.

Conclusions: The phenotype of $CD8^+$Lym was consistent with characters of group 1 innate lymphoid cell (ILC) which were recently identified as the novel subset of innate immune cells that were lineage negative population and express T-bet and IFN-γ. In conclusion, we first identified that $CD8^+$Lym involved in the progression of a rat anti-GBM GN is group 1 ILC and PPARα attenuates the crescent formation in anti-GBM GN through the inhibition of group 1 ILC infiltration into glomerulus.

TH-PO031

Inhibition of the TLR4/NF-κB Axis Attenuated Glomerular Inflammation and Injury in Long Term Experimental Diabetic Kidney Disease Orestes Foresto-Neto, Amanda H. Albino, Simone C. Arias, Viviane D. Faustino, Victor F. Avila, Claudia R. Sena, Camilla Fanelli, Vivian L. Viana, Marcos A. Cenedeze, Flavia G. Machado, Denise M. Malheiros, Niels O. Camara, Clarice K. Fujihara, Roberto Zatz. *University of Sao Paulo, Sao Paulo, Brazil.*

Background: The TLR4/NF-κB signaling pathway promotes the transcription of inflammatory interleukin genes. There is evidence that activation of this innate immunity pathway is involved in the pathogenesis of diabetic kidney disease (DKD). We investigated whether NF-κB inhibition with pyrrolidinedithiocarbamate (PDTC) exerts long term renoprotection in experimental DKD.

Methods: Diabetes (DM) was induced in 27 Munich-Wistar rats by a single streptozotocin injection (65 mg/kg, iv). Blood glucose (BG) was kept between 300 and 400 mg/dL with daily NPH insulin. Rats were divided into Groups **DM** (untreated) and **DM+PDTC** (receiving PDTC, 60 mg/kg/day vo). Untreated nondiabetic rats (**C**, n=12) were also studied. After 12 months, we assessed: urinary albumin/creatinine (Ualb/Ucr); kidney/body weight (KW/BW); glomerular sclerosis (GS, %); glomerular zonula occludens-1 (gZO-1, %); glomerular macrophage infiltration (gMΦ, cells/mm^2); glomerular TLR4, IL-1β and NLRP3 positive staining (%), renal content of heme oxigenase-1 (HO-1) and nuclear p65 (NF-κB) (fold change).

Results: After 12 months, the untreated DM group exhibited high Ualb/Ucr, renal hypertrophy, high GS, loss of gZO-1, and more intense gMΦ than C. gTLR4 and NF-κB were activated in association with increased gIL-1β and HO-1 content, whereas gNLRP3 was similar to the C value. PDTC treatment inhibited NF-κB activation and prevented the augmentation of the gTLR4, gIL-1β and HO-1 contents. In addition, PDTC attenuated renal hypertrophy and prevented the increase in Ualb/Ucr, GS, gMΦ, as well as the loss of gZO-1, without interfering with BG.

Conclusions: TLR4/NF-κB inhibition with PDTC exerts glomerular protection in long-term DKD, without changing the abundance of the NLRP3 inflammasome. These findings suggest a specific involvement of the TLR4/NF-κB axis in the pathogenesis of DKD and the possibility that this signaling pathway becomes a therapeutic target. FAPESP/CNPq

Funding: Government Support - Non-U.S.

	BG	Ualb/Ucr	KW/BW	GS	gZO-1	gMΦ	gTLR4	NF-κB	gIL-1β	HO-1	gNLRP3
C	98±2	1.5±0.2	0.5±0.0	2.6±0.4	77±1	16±3	1±0	1.0 ±0.3	10±1	1.0±0.1	1.4±0.2
DM	378±24^a	5.1±1.2^a	0.7±0.0^a	7.9±1.9^a	61±2^a	54±15^a	3±0^a	3.6±0.5^a	25±2^a	2.3±0.4^a	1.4±0.4
DM+PDTC	386±7^a	1.3±0.3^b	0.6±0.0^{ab}	2.1±0.7^b	75±2^b	33±10^b	1±0^b	1.7±0.3^b	13±1^b	1.4±0.2^b	1.2±0.2

Mean±SE; ^{a}p<0.05 vs C, ^{b}p<0.05 vs DM.

TH-PO032

Glomerular Mechanical Tension Promotes Activation of the NLRP3 Inflammasome Pathway in Experimental Diabetic Kidney Disease: Role of Podocytes

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Background: We showed previously (ASN 2016) that in the 5/6 ablation the estimated glomerular capillary mechanical tension (GCMT) was increased along with activation of the TLR4/NLRP3/CASP1/IL1β innate immunity (InIm) axis, helping to explain the link between hemodynamic insult and glomerular inflammation. Here we investigated whether such effect of cell agression also manifests in streptozotocin diabetes mellitus (DM), and the possible role of podocytes in this response.

Methods: We analyzed retrospectively, by immunohistochemistry, renal tissue from male Munich-Wistar rats divided into Control (C), Uninephrectomy (UNx) and UNx+DM groups. Mean arterial pressure (MAP, mmHg) had been measured 60 days after DM induction, whereas GCMT (mmHg×μm) was estimated from glomerular pressures and mean glomerular radii. Glomerular infiltration by macrophages (MΦ, cells/mm^2) was also assessed. The protein content of TLR4, NLRP3, CASP1, and IL-1β was evaluated in DM glomeruli (% area), as well as in cultured murine podocytes in the presence or absence of 15% stretching.

Results: In UNX, MAP was elevated without change in GCMT or Inlm components. In UNx+DM, hypertension was associated with increased GCMT, MΦ and InIm components, whereas a positive correlation was observed between NLRP3 and IL-1β. Under stretching, the protein content of ERK 1/2 was increased in endothelial cells, mesangial cells and podocytes. However, only podocytes exhibited a significant effect of stretching regarding the TLR4/NLRP3/CASP1/IL1β axis.

Conclusions: Inlm activation may mediate the inflammatory effects of GCMT, thus participating in the initiation and perpetuation of progressive glomerular injury in both diabetic and nondiabetic kidney disease. FAPESP/CNPq.

Funding: Government Support - Non-U.S.

	MAP	GCMT	MΦ	TLR4	NLRP3	CASP1	IL-1β
C (n=10)	113±2	146±4	1.1±0.2	0.3±0.1	0.9±0.6	0.3±0.1	1.2±0.3
UNx (n=6)	123±3 [a]	164±5	1.9±0.2 [a]	1.4±0.3 [a]	0.5±0.2	0.9±0.2	1.8±0.8
UNx+DM (n=5)	126±4 [a]	225±11 [ab]	3.1±0.2 [ab]	1.9±0.3 [a]	2.4±0.6 [ab]	1.9±0.3 [ab]	5.3±2.4 [a]

Mean±SE. [a]p<0.05 vs C; [b]p<0.05 vs UNx

TH-PO033

RNA-Seq Profiling of Microdissected Glomeruli in Clinically Early IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common primary glomerular disease worldwide and also a leading cause of chronic kidney disease and renal failure. Although recent studies have shed light on genetic variants associated with IgAN, transcriptomic changes in the glomerulus and their relevance to the pathophysiology of IgAN have been poorly defined. To identify early gene-expression changes in IgAN, we profiled the transcriptome in microdissected human glomeruli using deep sequencing of RNA species (RNA-seq).

Methods: Glomeruli were microdissected from the biopsy specimen obtained from 6 IgAN patients with preserved renal function (eGFR > 60 mL/min/1.73m^2 and proteinuria < 1 g/d). As negative controls, normal glomeruli were obtained from patients undergoing nephrectomy (n=3). Glomerular mRNAs were captured using oligo-dT primers and made into cDNA libraries for Illumina sequencing. After mapping to the human reference genome (GRCh38 primary assembly), reads mapping to Ensembl genes were counted. Wald test for a negative binomial model was used to call differentially expressed genes.

Results: Each library produced 29-43 million pairs of reads, more than 70% of which were uniquely aligned to the human genome. Of 17,833 Ensembl genes with >10 reads, 285 were upregulated and 434 downregulated in the IgAN glomeruli. Downregulated genes included transcription factors (FOS, FOSB, ZFP36, EGR1, ATF3, JUNB, NR4A2, JUN, SKI, POU5F1, KLF9, KLF8, KLF4, KLF2, CTNNB1, DMTF1, and CREBBP), periostin (POSTN), cytoskeletal proteins (MYO15A and TPM2), and C-X-C motif chemokine ligand 2 (CXCL2). Among upregulated genes were integrin subunits (ITGAV, ITGA4, and ITGB3), histone deacetylase (HDAC5), adenylate cyclase 7 (ADCY7), cyclin D2 (CCND2), homeobox D1 (HOXD1), and interleukin-6 receptor (IL6R). None of the genes positively reported in the GWAS studies on IgAN have been found to be differentially expressed in our dataset.

Conclusions: In human glomeruli obtained from patients with clinically early IgAN, RNA-seq revealed altered expression of DNA-binding transcription factors, cytoskeletal proteins, and integrin subunits that are potentially important for maintaining the integrity of the glomerular filtration barrier.

TH-PO034

Fecal Microbiome Profiles and Pathogenesis of IgA Nephropathy

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Background: Mucosal immune system plays a role in pathogenesis of Immunoglobulin A nephropathy (IgAN); however, little has been known about the relationship between IgAN and the intestinal microbiome.

Methods: We prospectively enrolled 30 biopsy-proven IgAN patients at 3 centers and collected fecal specimens at the time of renal biopsy. Feces from thirty healthy volunteers were used as control. The composition of microbiota was analyzed using extracted metagenomic DNA from the feces by Illumina MiSeq system. Downstream analyses were performed using SPSS, Phylogenetic reconstruction of unobserved states (PICRUSt), and Linear discriminant analysis Effect Size (LEfSe).

Results: The age, sex, and BMI were comparable between the groups. The fecal microbiota of both IgAN and control group were dominated by two bacterial phyla, Firmicutes and Bacteroidetes. Compared to control group, fecal microbiota of IgAN patients showed significantly lower OTUs and Shannon diversity index. The relative abundances of Firmicutes and Acinetobacteria were higher, whereas those of Bacteroidetes and Proteobacteria were lower in IgAN patients than healthy subjects. At Genus level, the abundances of Blautia were higher and those of Bacteriodetes, Prevotella, and Escherichia were lower in the fecal specimens from IgA nephropathy patients compared to healthy subjects. PICRUSt analysis showed that genes involved in galactose metabolism were enriched in IgAN while those responsible for glycosyltransferases were significantly associated with the controls. By dividing patients on the basis of 3 g/day proteinuria, bacterial diversity was significantly lower in severe group compared to less severe group.

Conclusions: The fecal microbiota of IgAN patients differed from those of control group. We also showed that microbial difference was possibly related to galactose metabolism or glycosyltransferases. Such differences might be related with pathogenesis of IgAN.

TH-PO035

Dysregulation of Mucosal Immune Response in IgA Nephropathy

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Background: IgA nephropathy (IgAN) is associated with dysregulation of mucosal immune system, which manifests as mesangial IgA deposition leading renal impairment. However, it is not unclear which gut-associated lymphatic tissue (GALT) or nasal-associated lymphoid tissue (NALT) is more involved in the pathogenesis of IgAN. Indeed, the origin of nephritogenic IgA has been obscure. Several studies demonstrated the efficacy of tonsillectomy and corticosteroid therapy, whereas recent NEFIGAN study suggested that the novel targeted-release formulation of budesonide targeting intestinal mucosal immunity reduced proteinuria in IgAN patients. In present study, we focused on the role of GALT in murine IgAN using IgAN-prone "ddY mice".

Methods: Mesenteric lymph node (MLN) is considered to be a key function of GALT in murine. Levels of aberrantly glycosylated IgA and IgA-IgG immune complexes (IC) in serum and supernatant from cultured MLN and splenocytes were measured using IgAN onset and quiescent ddY mice (each n=15). Level of aberrantly glycosylated IgA was measured by the binding of Sambucus nigra bark lectin and Ricinus communis agglutinin I.

Results: Serum levels of aberrantly glycosylated IgA and IgA-IgG IC in IgAN onset ddY mice were significantly higher than those in quiescent ddY mice (P<0.01). However, there were no significant differences in the levels of aberrantly glycosylated IgA and IgA-IgG IC produced by MLN between IgAN onset and quiescent mice. Serum levels of aberrantly glycosylated IgA and IgA-IgG IC correlated with those in culture supernatant of splenocytes (P<0.05). However, the sugar component of IgA produced by MLN was different from those in circulation in IgAN onset ddY mice. Furthermore, serum IgA-IgG IC levels did not associate with those levels produced by cultured MLN.

Conclusions: Serum levels of aberrantly glycosylated IgA and IgA-IgG IC elevated in IgAN onset ddY mice. Glycosylation pattern of circulatory IgA was different from those originated from GALT. Therefore, IgA originated from GALT did not form immune complexes with IgG. Present study suggested that the GALT may not be involved in the pathogenesis of murine IgAN.

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TH-PO036

Tonsillar Microbiome in IgA Nephropathy Ji In Park,[1] Hyunjeong Cho,[5] Hajeong Lee,[4] Dong Ki Kim,[5] Seung Hee Yang,[2] Jung Pyo Lee,[3] Yon Su Kim.[4] *[1]Kangwon National University Hospital, Chuncheon-si, Republic of Korea; [2]Kidney Research Institute, Seoul National University, Seoul, Republic of Korea; [3]Seoul National University Boramae Medical Center, Seoul, Republic of Korea; [4]Seoul National University College of Medicine, Seoul, Republic of Korea; [5]Seoul National University Hospital, Jongno- gu, SEOUL, Republic of Korea.*

Background: Mucosal immune system plays a role in pathogenesis of Immunoglobulin A nephropathy (IgAN); however, little has been known about the relationship between IgAN and the microbiome reside in tonsil.

Methods: We prospectively enrolled 29 biopsy-proven IgAN patients at 3 centers and collected tonsil swabs at the time of renal biopsy. Tonsil swabs from 29 healthy volunteers who visited hospital for a medical check-up were used as control. The composition of microbiota was analyzed using extracted metagenomic DNA from the tonsil swabs by Illumina MiSeq system. Downstream analyses were performed using SPSS, Phylogenetic reconstruction of unobserved states (PICRUSt), and Linear discriminant analysis Effect Size (LEfSe).

Results: The mean age was 32.4 and 42.9 in control group and IgAN patients group, respectively. Though the age was significantly different between the groups, there was no trend or clustering according to the age groups. Compared to control group, tonsil microbiota of IgAN patients showed significantly higher Shannon diversity index. The relative abundances of Firmicutes and Bacteroidetes were higher, whereas those of Proteobacteria were lower in IgAN patients than healthy subjects. At Genus level, relative abundances of Granulicatella were higher, whereas those of Acinetobacter and Veillonella were significantly lower in the tonsil specimens from IgAN patients compared to healthy subjects. PICRUSt analysis showed that genes involved in galactose metabolism were enriched in IgAN. By dividing patients on the basis of 3 g/day proteinuria, we tried to figure the microbial difference according to disease severity. However, the bacterial diversity or composition were not differed between severity groups.

Conclusions: The tonsillar microbiota of IgAN patients differed from those of control group although it was not associated with disease severity. In addition, these differences showed possible relation with galactose metabolism which was involved in pathogenesis of IgAN.

TH-PO037

Racial Comparison of IgA1 Hinge-Region O-Glycoforms by High-Resolution Mass Spectrometry Yukako Ohyama,[1] Kazuo Takahashi,[1] Shoko Matsushita,[1] Hisateru Yamaguchi,[2] Kazuki Nakajima,[3] Tomohiro Mizuno,[4] Hiroki Hayashi,[1] Shigehisa Koide,[1] Daijo Inaguma,[1] Midori Hasegawa,[1] Jan Novak,[5] Yoshiyuki Hiki,[1] Yukio Yuzawa.[1] *[1]Nephrology, Fujita Health University School of Medicine, Toyoake, Japan; [2]Institute for Comprehensive Medical Science, Fujita Health University, Toyoake, Japan; [3]Fujita Academy, Fujita health university, Toyoake, Japan; [4]Analytical Pharmacology, Faculty of Pharmacy, Meijo university, Nagoya, Japan; [5]University of Alabama at Birmingham, Birmingham, AL.*

Background: Prevalence of IgAN varies among racial groups, being more common in Asians, moderately prevalent in Europeans, and rare in Africans. IgA1 with galactose (Gal)-deficient hinge-region (HR) *O*-glycans (Gd-IgA1) plays a key role in the pathogenesis of IgAN. Relationship of serum Gd-IgA1 levels and race-specific susceptibility to IgAN is not known. To understand race-specific IgA1 *O*-glycan heterogeneity, we determined serum Gd-IgA1 levels in healthy volunteers of different races and profiled the corresponding IgA1 *O*-glycoforms.

Methods: Serum Gd-IgA1 was determined by ELISA using novel monoclonal antibody specific for Gd-IgA1 (35A12, Tomiyama Laboratory Co. Ltd., Tokyo, Japan). Human serum IgA1 was purified by affinity chromatography. After neuraminidase treatment and trypsin digestion, IgA1 *O*-glycan HR heterogeneity was analyzed by liquid chromatography-high-resolution mass spectrometry (LC-MS). To increase the throughput of the analysis, we developed an in-house automated program, Glycan Analyzer. The attachment site(s) of the Gal-deficient *O*-glycan chain(s) were identified by electron-transfer dissociation (ETD) tandem MS after selective removal of galactosylated *O*-glycans.

Results: Serum Gd-IgA1 levels were determined in 50 healthy subjects recruited from White, Black, Hispanic, Asian, and Japanese. Gd-IgA1 levels were lower in Asians, including Japanese subjects. His^{208}-Arg^{245} HR was present in 12 different glycoforms with 3-6 *O*-glycans. Approximately 58% of HR *O*-glycoforms contained one to three Gal-deficient *O*-glycans in IgA1 samples from the subjects of all races. ETD tandem MS revealed that Gal-deficient *O*-glycans were consistently attached at specific sites.

Conclusions: Despite high susceptibility to IgAN in Asians, Gd-IgA1 levels in Asians were lower compared to other races. Furthermore, HR *O*-glycoforms with Gal-deficient *O*-glycans were found also in healthy subjects. Detailed analysis of IgA1 HR *O*-glycoforms, including sites of glycan attachment, will be important for investigation of pathogenic form(s) of IgA1 in IgAN.

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TH-PO038

Expression of CD71 Mesangial IgA1 Receptor Predicts Progression of IgA Nephropathy Jong Hyun Jhee,[1] Seohyun Park,[1] Seong yeong An,[1] Ki Heon Nam,[1] Boyoung Nam,[2] Meiyan Wu,[2] Sukyung Kang,[2] Arum Choi,[2] Tae-Hyun Yoo,[1] Shin-Wook Kang,[1,2] Seung Hyeok Han.[1] *[1]Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea; [2]Department of Internal Medicine, College of Medicine, Severance Biomedical Science Institute, Brain Korea 21 PLUS, Yonsei University, Seoul, Republic of Korea.*

Background: The transferrin receptor (CD71) is known as a receptor for IgA1 on mesangial cells and plays a key role in the pathogenesis of IgA nephropathy. However, little is known about the association between clinical outcomes and the level of CD71 expression.

Methods: We studied the clinical implication of mesangial CD71 in 282 patients with biopsy-proven IgAN between 2005 and 2014. Glomeruli were obtained from biopsy tissues by manual microdissection. The expression of glomerular CD71 was determined by real-time polymerase chain reaction. Disease progression was defined as a ≥ 30% decline in estimated glomerular filtration rate (eGFR).

Results: During a mean follow up of 51.6 months, 40 (14.2%) patients developed disease progression. The mRNA expression of CD71 was significantly higher in progressors than in non-progressors (P = 0.01). Immunnohistochemial study also confirmed the higher expression of CD71 in the former. In a multivariable Cox model adjusted for confounders, enhanced transcript level of CD71 was significantly associated with an increased risk of disease progression (P = 0.018). Furthermore, CD71 expression level independently predicted the development of persistent proteinuria of ≥ 1 g/g creatinine (P = 0.003). Among 4 components of the Oxford classification, only M1 score was significantly associated with a higher transcript level of CD71.

Conclusions: We showed that glomerular CD 71 expression is significantly associated with various clinically important parameters in IgA nephropathy. This finding suggests that incorporation of CD71 into risk stratification is helpful in determination of adverse outcomes.

TH-PO039

IgA Nephropathy Patients B Cells Producing IgA Exhibit High Epstein-Barr Virus Infection Rate in Comparison to Disease and Healthy Controls Katerina Zachova,[1] Milan Raska.[2] *[1]Palacky University Olomouc, Olomouc, Czech Republic; [2]University of Alabama at Birmingham, Birmingham, AL.*

Background: IgAN is the most common form of primary glomerulonephritis worldwide and is typical for deposition of immune complexes mostly of IgA-IgG in the glomerular mesangium. The mesangial IgA is exclusively of the IgA1 subclass and is aberrantly glycosylated in its hinge region (galactose deficient IgA1 – gd-IgA1). EBV infects preferentially B cells, mostly the precursors of IgA-producing cells in peripheral blood. That implies the possibility that EBV infection is somehow involved in Gd-IgA1 production. Relations between some autoimmune diseases (multiple sclerosis, diabetes mellitus) and Epstein Barr virus (EBV) infection were already described in several papers. Therefore it was obvious to focus on the impact of EBV infection on IgA nephropathy (IgAN).

Methods: By cell surface staining with monoclonal antibodies we analyzed B cell subpopulations to naive, regulatory, memory, plasmablast, and plasma cell and surface immunoglobulin subpopulations IgA, IgG from peripheral blood of IgAN patients, disease controls and healthy subjects. Using a specific approach combining cell surface staining with *in situ* hybridisation for EBV RNA (EBER) followed by flow cytometry analyses we made several observations.

Results: EBV infects preferentially IgA+ B cells followed by IgG+ B cells in either IgAN patients and in controls. **Nevertheless, the incidence of EBV^+ IgA and also EBV^+ IgG B cells in peripheral blood of the IgAN patients is more than 10x higher than in non IgAN patients.** Furthermore plasmablasts are the most EBV-infected cells (65%) following with memory cells (35%) in IgAN patients in contrasts to 100% of plasmablasts in non IgAN patients. No naive and regulatory B cells were observed to be EBV positive in any groups. These explorations were confirmed on IgA deficient patients, having low amounts of IgA in serum but still having IgA B cells (naive and memory) in peripheral blood. Analysis of those patients showed 10x lower co-incidence of IgA-EBV^+ cells. That clearly corresponds with our analysis showing that 2/3 of EBV^+ cells are plasmablasts.

Conclusions: Our data confirmed an important impact of EBV infection on IgA nephropathy. From these results it is clear that B cells producing IgA of IgAN patients exhibit high Epstein-Barr virus infection rate in comparison to disease and healthy controls.

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TH-PO040

The Immunoglobulin Repertoire in IgA Nephropathy Revealed by Deep Sequencing Nicholas J. Steers, Zizhang Sheng, Jason Mccutchan, Lawrence Shapiro, Ali G. Gharavi. *Columbia University, New York, NY.*

Background: Dysregulated IgA1 response is a central defect in the development of IgA nephropathy (IgAN), but it is not clear if the altered IgA1 response is attributable to a monoclonal or polyclonal expansion of the dysregulated of IgA plasma B-cells.

Methods: Our cohort consisted of 15 healthy controls (HC), 16 IgAN patients. IgA plasma cells were phenotyped by flow cytometry, IgA1, IgA, and IgG were measured by ELISA. The immunoglobulin repertoire was sequenced and analyzed using SONAR software.

Results: We studied peripheral B-cells in 16 IgAN patients, and 15 HC, in the steady state. Increased numbers of IgA plasma cells (88 per 1000 activated B-cells) were detected in the peripheral blood of IgAN patients compared to HC (20 per 1000 activated B-cells), correlating with increased levels of IgA and IgA1 detected in the plasma. Following *in vitro* stimulation, IgA cells from IgAN patients have a greater proliferative capacity compared to HC. We next asked if the increased number of peripheral IgA B-cells in IgAN patients arose by monoclonal or polyclonal expansion. We used NGS to sequence the immunoglobulin repertoire to determine if there were differences in usage of immunoglobulin heavy chain variable (V), heavy chain joining (J), kappa and lambda genes. We observed no differences in the heavy chain V, J and kappa usage, however we detected an enhanced usage of the IGLV2-8 lambda chain in IgAN patients compared to controls (12.9% Vs 7.9% respectively, p<0.01). Examination of the complementary determining region (CDR) 3 length or the somatic hypermutation (SHM) levels in the immunoglobulin sequences showed no differences between the IgAN patients and the HC.

Conclusions: We did not detect any consistent differences in usage of immunoglobulin heavy V and J chains, CDR3 length, or SHM levels between IgAN patients and HC at the repertoire level, with the exception of lambda IGLV2-8 usage. This indicates a global expansion of IgA plasma cells rather than a monoclonal expansion in IgA Nephropathy. Future studies will be directed towards identification of intrinsic and extrinsic regulatory factors leading to globally enhanced proliferative potential in IgA plasma cells.

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TH-PO041

TLR9 Activation Induces Overproduction of Aberrantly Glycosylated IgA through the APRIL Mediated Pathway in IgA Nephropathy

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Background: Involvement of Toll-like receptor 9 (TLR9) that play a key role in the innate immune system has been discussed in the pathogenesis of IgA nephropathy (IgAN). There are increasing evidences that galactose-deficient IgA1 (Gd-IgA1) and Gd-IgA1 containing immune complexes (ICs) have critical roles in the pathogenesis of IgAN. We recently demonstrated that interleukin-6 (IL-6) can enhance the production of Gd-IgA1 by IgA1-producing cells. Moreover, A proliferation-inducing ligand (APRIL) may be involved in the overproduction of the nephritogenic IgA1. However, the mechanisms leading to overproduction of Gd-IgA1 and subsequent formation of Gd-IgA1 containing ICs are still unclear.

Methods: IgAN prone ddY mice were divided into two groups with CpG-ODN (TLR9 ligand) immunization (n=19) or without (n=19). CpG-ODN was injected intraperitoneally 3 times a week for 12 weeks. Renal pathology and serum levels of aberrantly glycosylated IgA (Gd-IgA), IgG-IgA ICs, IL-6 and APRIL were evaluated after 12 weeks. We also examined the mechanisms of production of Gd-IgA1 in human IgA1-secreting cells through TLR9 activation and stimulation with IL-6 and APRIL.

Results: Mice immunized with CpG-ODN, but not non-immunized mice, showed mesangioproliferative glomerulonephritis accompanied by mesangial deposition of IgA, and C3. Immunization with CpG-ODN elevated serum levels of Gd-IgA, IgG-IgA IC and APRIL (P<0.05). Serum levels of APRIL significantly correlated with serum level of Gd-IgA and IgG-IgA IC (P<0.05). The activation of TLR9 induced production of IL-6, and IL-6 stimulation induced overexpression of APRIL in splenocytes. Moreover, in human IgA1-secreting cells, TLR9 activation enhanced Gd-IgA1 production through overexpressions of IL-6 and APRIL. Production of Gd-IgA1 was reduced by anti-IL-6 and/or siRNA for APRIL. However, anti-IL-6 could not inhibit overproduction of APRIL completely.

Conclusions: TLR9 activation exacerbated murine IgAN by enhancing production of aberrantly glycosylated IgA and nephritogenic ICs. TLR9 activation induced overproduction of IL-6 and APRIL. Present study suggested that TLR9-induced overproduction of both IL-6 and APRIL resulted in enhancing production of Gd-IgA1 and subsequent formation of Gd-IgA1 containing ICs in IgAN.

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TH-PO042

O-Glycan Profiling of High Molecular Weight Forms of IgA1 in Archival Plasma Samples from IgAN Patients and Controls

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Background: IgA nephropathy (IgAN) is the most common form of glomerulonephritis worldwide. The hallmark of the disease is deposition of IgA1 in the glomerular mesangium. These deposited IgA1 are mainly polymeric in nature. Serum polymeric forms of IgA1 are diverse and may include homodimeric IgA, homodimeric secretory IgA, and heterodimeric complexes of IgA covalently bound to other plasma proteins. Abnormalities in *O*-glycosylation of circulating IgA1, resulting in increased Tn antigen, are hypothesized to be involved in IgAN pathogenesis, and *O*-glycan structures of monomeric and homodimeric form of IgA1 have been described before in great details. However, so far, very little information is available concerning the *O*-glycosylation patterns of heterodimeric and other polymeric forms of IgA1 present in the circulation of IgAN patients.

Methods: IgAs were affinity purified from serum samples from 16 patients with IgAN and 16 control subjects. Various molecular forms of IgA1 were size-separated by gel electrophoresis. Proteins were either visualized by Coomassie blue staining or transferred to nitrocellulose membranes for Western blotting. IgA1-containing bands were in-gel digested with trypsin, and the released glycopeptides were analyzed by electrospray ionization liquid mass spectrometry.

Results: Approximately 25 % of IgA1 in archival samples from IgAN patients and controls was found as high molecular mass complexes linked through disulfide bonds. Immunobloting demonstrated 1:1 complexes between IgA and albumin, alpha-1-antitrypsin, or alpha-1-microglobulin. Quantitative analysis of *O*-linked glycosylation showed no significant differences in glycan composition between different types of circulating IgA1 complexes and no significant difference between glycan composition of IgA1 complexes from IgAN patients and from healthy controls.

Conclusions: These data indicate that, in addition to homodimeric forms of IgA, a significant fraction of IgA1 molecules in the circulation of IgAN patients and healthy controls exist as heterodimeric complexes of IgA covalently bound to other plasma proteins. It is still unclear to what extend the galactose-deficient IgA present in these heterodimeric complexes play a role in the pathogenesis of IgA nephropathy.

Funding: NIDDK Support

TH-PO043

Circulating Levels of Tumor Necrosis Factor Alpha Correlate with Clinicopathological Features and Progression of IgA Nephropathy

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Background: Tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) are considered to play an important role in IgA nephropathy (IgAN). However, it is still unknown whether circulating TNF-α or IL-6 is a prognostic marker of IgAN.

Methods: Circulating levels of TNF-α and IL-6 of 147 patients with IgAN and 20 healthy subjects were measured by chemiluminescence assay. Absolute renal risk (ARR) score was used to evaluate the dialysis/death risk. This study explored the relationship between the levels of serum TNF-α or IL-6 with clinicalopathological features and progression of IgAN.

Results: Circulating levels of TNF-α were higher in patients with IgAN than that in healthy controls (HC) (P=0.02). However, circulating levels of IL-6 in patients with IgAN did not differ from HC (P=0.54). Circulating levels of TNF-α, but not IL-6, were positively correlated with male (r=0.20, P=0.02), mean arterial pressure (r=0.26, P<0.01), 24 hour urine protein (r=0.22, P<0.01), urinary protein to serum creatinine ratio (r=0.26, P<0.01), serum creatinine (r=0.49, P<0.0001) and Cystatin C (r=0.51, P<0.0001) in IgAN. Circulating levels of TNF-α were negatively correlated with estimated glomerular filtration rate (r= -0.47, P<0.0001). According to Oxford classification, circulating levels of TNF-α were higher in patients with mesangial hypercellularity grade M1 than that in M0 (P=0.03). Circulating levels of TNF-α with tubular atrophy/interstitial fibrosis grade T2 were higher than that in T1 (P=0.02). Circulating levels of TNF-α in patients of Haas grade III~V were higher than Haas grade I~II (P<0.01). Circulating levels of TNF-α in patients of Lee grade III~V were higher than Lee grade I~II (P=0.02). Furthermore, circulating levels of TNF-α steadily increased with the ARR level (ARR=3 > ARR=2, P<0.001; ARR=2 > ARR=1, P=0.04).

Conclusions: Circulating levels of TNF-α, but not IL-6, detected by chemiluminescence immunoassay, were closely associated with main prognostic clinicopathological features and progression of IgAN.

Funding: Government Support - Non-U.S.

TH-PO044

Discovery and Engineering of VIS649, a First-in-Class Humanized IgG2 Targeting APRIL for the Treatment of IgA Nephropathy

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Background: IgA nephropathy (IgAN) is one of the most prevalent, chronic glomerular diseases worldwide. No disease-specific therapeutic modalities currently exist. APRIL (A PRoliferation Inducing Ligand; TNFSF13) has recently emerged as a potentially key immunobiological factor in disease pathogenesis and progression. We describe here the discovery and lead identification of VIS649, a highly potent, humanized IgG2κ antibody targeting human APRIL. A molecular description of the unique VIS649 epitope and correlation of its mode of target engagement to its potent neutralizing activity and pharmaceutical properties are described

Methods: VIS649 was derived from parental mouse antibody 2419 following immunization with recombinant APRIL. Parental mAb 2419 was humanized with conversion to an IgG2κ with full retention of *in vitro* activity. The VIS649 binding epitope on APRIL was mapped using an integrated platform approach that incorporated X-ray crystallography, deep mutational scanning with an APRIL yeast display library, and computationally driven structural modeling. Antibody effector function (ADCC, CDC) was assessed using recombinant human Fc receptor binding and cell-based assays.

Results: VIS649 binds to human APRIL with low picomolar affinity and possesses subnanomolar blocking potency of APRIL binding and signaling through both its receptors, BCMA and TACI. VIS649 also exhibits potent inhibition of relevant APRIL-mediated B-cell activities including B cell proliferation, IgA production, and terminal B-cell survival. VIS649 targets a critical quaternary epitope within APRIL that overlaps with the high affinity (CRD2) receptor binding site and spanning the interface between

two monomers to effectively neutralize oligomeric APRIL, the biologically relevant form of APRIL. VIS649 engages with Fc receptors reflecting the expected canonical binding characteristics of a human IgG2 isotype and binds only minimally to complement (C1q).

Conclusions: This work highlights the integrated platform used for the discovery, lead optimization, and structure-activity characterization of VIS649, a first-in class anti-APRIL antibody currently in development for the treatment of IgA nephropathy.

Funding: Commercial Support - Visterra, Inc.

TH-PO045

Pharmacokinetics/Pharmacodynamics of VIS649, a First-in-Class Humanized IgG2 Targeting APRIL for the Treatment of IgA Nephropathy, in Healthy Cynomolgus Monkeys Kristy J. Szretter, James R. Myette, Emily A. Helger, Bharathi L. Sundaresh, Ketan Deotale, Jose Trevejo, Susan E. Sloan, Brian J. Pereira. *Visterra, Inc., Cambridge, MA.*

Background: VIS649 is a humanized IgG2 monoclonal antibody that targets A PRoliferation-Inducing Ligand (APRIL), a cytokine that is part of the TNF superfamily that has been implicated in IgA nephropathy (IgAN) pathogenesis and progression. Because of its role in IgA class switching and plasma cell survival, targeting APRIL in IgAN patients may substantially reduce circulating levels of aberrantly glycosylated IgA and alter disease progression.

Methods: Cynomolgus monkeys (NHP; n = 4/group) were administered VIS649 (25 mg/kg) or vehicle alone once weekly for eight weeks by intravenous injection, and were then followed for an additional 3 weeks without treatment. Study endpoints included serum VIS649 and immunoglobulin (Ig) levels. In order to characterize the temporal relationship between circulating VIS649 and IgA, a population pharmacokinetic/pharmacodynamic (popPK/PD) model was developed. Temporal changes in IgA concentration following VIS649 administration was described with an indirect response model.

Results: Treatment of NHP with VIS649 resulted in significantly lower serum levels of IgA (up to 70%) and IgG (~40%), and minimal modulation of serum IgM levels. The changes in serum Ig levels were not reversed during the 3 week no-dose period, which was attributed to the saturating levels of VIS649 at the dose administered. Analysis of the VIS649 pharmacokinetic data revealed that serum levels of VIS649 accumulated following weekly dose administrations at 25 mg/kg, and estimated the VIS649 half-life in NHP as 15 days. The popPK/PD model fit available PK and PD data well. Simulations were performed over a range of doses to inform dose selection and frequency in a follow-on study that will test lower VIS649 doses. Model simulations predict that approximately 50% reduction in IgA levels may be achieved with lower dose levels.

Conclusions: VIS649, a humanized IgG2 monoclonal antibody that targets APRIL, reduced serum IgA levels significantly in healthy NHP following 8 weekly doses at 25 mg/kg. The specific targeting of APRIL confirmed its important role in the homeostasis of IgA, and confirmed our rationale for targeting it for the treatment of IgAN.

Funding: Commercial Support - Visterra, Inc.

TH-PO046

Preclinical Safety Profile of VIS649, a First-in-Class Humanized IgG2 Targeting APRIL for the Treatment of IgA Nephropathy Kristy J. Szretter, James R. Myette, Emily A. Helger, Jose Trevejo, Susan E. Sloan, Brian J. Pereira. *Visterra, Inc., Cambridge, MA.*

Background: IgA Nephropathy (IgAN) is the most common cause of glomerulonephritis worldwide, with no disease-specific therapies currently available. VIS649 is a humanized IgG2 monoclonal antibody targeting the cytokine named A PRoliferation Inducing Ligand (APRIL) that has been implicated in the pathophysiology of IgAN disease and progression. The preclinical effect of inhibiting APRIL activity by VIS649 was evaluated in nonhuman primates (NHP) to better understand the safety and tolerability profile of this development candidate.

Methods: Preclinical safety assessments of VIS649 included off-target binding analysis, cytokine release, and *in vivo* tolerability in a NHP study. Off-target binding analysis utilized the Retrogenix cell microarray platform, in which human plasma membrane proteins were transiently expressed on HEK293 cells and therapeutic antibody binding was measured by fluorescent staining. Cytokine release was assessed with whole blood from human donors and cytokines were measured by Luminex. *In vivo* safety and tolerability were evaluated in cynomolgus monkeys administered 25 mg/kg of VIS649 intravenously weekly for 8 weeks, followed by a 3 week recovery period. Clinical chemistry, clinical pathology, hematology, immune cell profiling by flow cytometry, and histopathology were assessed.

Results: VIS649 did not demonstrate off-target binding in the Retrogenix cell microarray platform including over 3,300 unique membrane-associated human proteins. Preliminary cytokine release assays demonstrated that compared to negative controls, VIS649 did not induce secretion of cytokines. Treatment of NHP with VIS649 as compared to the control group resulted in no significant abnormalities in clinical observations, clinical chemistry, clinical pathology, hematology, or pathology. Despite a ~70% reduction in serum IgA levels, no perturbations in immune cell populations in peripheral blood or lymphoid organs were observed.

Conclusions: VIS649 has a preclinical safety profile that supports its further development as a therapeutic monoclonal antibody candidate for the treatment of IgAN. Furthermore, targeting APRIL at a dose that reduced IgA levels by 70% did not result in any safety or tolerability findings in NHP.

Funding: Other U.S. Government Support, Commercial Support - Visterra, Inc.

TH-PO047

Sympathetic Renal Denervation Locally Aggravates Kidney Inflammation in Crescentic Glomerulonephritis Alexander M. Böhner,[2] Christian Kurts.[1] *[1]Institute of Experimental Immunology, Bonn, Germany; [2]Institute of Experimental Immunology, University Clinic Bonn, Bonn, Germany. Group/Team: Research-Group Kurts.*

Background: Nephrotoxic nephritis (NTN) is a murine model of crescentic glomerulonephritis, a serious immune-mediated type of kidney disease. There is evidence that the autonomous nervous system can regulate immune responses in general, but its role in NTN is unknown. In the present study we performed unilateral sympathetic renal denervation (RDN), by depriving the left murine kidney of its sympathetic fibers using a mixture of ethanol and cyclic aromatic chemicals applied to the renal hilus. We compared the inflammatory response in the denervated and the contralateral kidney and studied consequences for renal function.

Methods: Renal denervation was performed by application of a mixture of ethanol and cyclic aromatic chemicals to the left renal hilus. We induced the nephrotoxic nephritis by intraperitoneal injection of nephrotoxic serum. Analytic methods included flow-cytometry, ELISA and histology. Furthermore we utilized light sheet microscopy in which we made use of fluorescent tracers, kidney tissue clearing and algorithm-based full kidney reconstruction and measurement.

Results: Unilateral renal denervation caused neither albuminuria nor tubular damage in healthy mice. But already at d3 after NTN initiation, proteinuria was exacerbated. We noted an an increased influx of neutrophils, which can directly mediate glomerular damage during the early phase of NTN, into the denervated inflamed tissue. Furthermore, we detected a more proinflammatory phenotype in dendritic cells of the denervated kidney, which might be causative for the increased PMN influx. Examination of histological sections showed stronger inflammation in the cortex of the denervated kidney. To distinguish effects on the glomerular function in denervated and contralateral kidney, we perfomed light sheet microscopy of cleared kidneys after injecting fluorescent tracers. This revealed that proteinuria commenced on d3 in the denervated kidneys, while the contralateral kidney fulfilled its function without noticeable alterations at this time point. Finally, we noted significant swelling of glomeruli in the denervated kidney.

Conclusions: Neuronal signals locally attenuate harmful inflammatory responses in experimental glomerulonephritis. Our findings suggest that renal denervation, for example in the treatment of arterial hypertension, might aggravate preexisting chronic inflammation in nephritis patients.

Funding: Commercial Support - Fresenius Medical Care, Government Support - Non-U.S.

TH-PO048

Annexin A1 Promotes the Resolution of Inflammation in Murine Crescentic Glomerulonephritis Robert Labes,[1] Ralf Mrowka,[2] Christian Hugo,[4] Sebastian Bachmann,[1] Sibylle Von Vietinghoff,[3] Alexander Paliege.[4] *[1]Charité Universitätsmedizin Berlin, Berlin, Germany; [2]Friedrich-Schiller-Universität, KIM III, Jena, Germany; [3]Hannover Medical School, Hannover, Germany; [4]University of Dresden, Dresden, Germany, Dresden, Germany.*

Background: Resolution of acute inflammation occurs in an active and tightly regulated process which involves the suppression of pro-inflammatory signals and a cessation of leukocyte influx. The glucocorticoid-inducible protein annexin A1 has been suggested to function as key-regulator of the resolution process but its role in acute crescentic glomerulonephritis has not been studied so far.

Methods: Acute crescentic nephritis was induced in annexin A1 deficient (n=8) and wildtype mice (n=8) using a sheep serum raised against rat glomerular basement membrane constituents. Animals were sacrificed 10 days after induction of the nephritis. Renal morphology was analyzed using routine histological techniques. Renal leukocyte abundance was studied by fluorescence activated cell sorting (FACS). Alterations in gene expression were determined by RNA-Seq and gene ontology analysis. Renal levels of eicosanoids and related lipid products were measured using lipid mass spectrometry.

Results: Histological analysis revealed an increased number of sclerotic glomeruli and aggravated tubulointerstitial damage in the kidneys of annexin A1 deficient mice as compared to the wildtype controls. FACS analysis confirmed an increased number of CD11b+/Gr1+ myeloid cells (+ 110 ± 32%; $p < .01$). Lipid mass spectrometry showed elevated levels of the proinflammatory prostaglandins PGE2 (+140 ± 62%, $p < .05$), and PGD2 (+78 ± 39%, $p < .05$) whereas the abundance of the anti-inflammatory and anti-fibrotic epoxy-derivates of docosapentaenoic acid (EDP) were reduced (10,11-EDP: -34 ± 2%; 13,14-EDP: -34 ± 5%; 16,17-EDP: -27 ± 4%; 19,20-EDP: -16 ± 5%; $p < .05$ each). RNA-Seq analysis demonstrated a higher abundance of several pro-inflammatory cytokines (IL-1b: +112 ± 62%; IL-5: +90 ± 29%; IL-6: +178 ± 58%; IL-12b: +70 ± 24%; IL-13: +260 ± 70%; TNF-:+82 ± 8%; $p < .05$ each) and Gene ontology analysis revealed induction of gene products related to neutrophil- (GO:0030593) and monocyte-(GO:0002548) chemotaxis ($p < .01$ each).

Conclusions: Deficiency of annexin A1 results in a defective resolution process of renal inflammation with a persistence of pro-inflammatory signals, infiltration of myeloid cells, and aggravated tissue damage. The annexin A1 signaling cascade may therefore provide novel targets for the treatment of inflammatory kidney disease.

Funding: Government Support - Non-U.S.

TH-PO049

CD4+ T Cells Control TH17 Responses in an IL-17 Receptor A-Dependent Manner Tilman Schmidt, Hans-Joachim Paust, Sonja Krohn, Sonja Kapffer, Christian F. Krebs, Ulf Panzer. *Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany*.

Background: The characterization of IL-17A producing $CD4^+$ T_H17 cells has substantially improved our understanding of organ-specific autoimmunity including crescentic glomerulonephritis. The biological effects of IL-17A are mediated via the IL-17 receptor A. Recent clinical trials targeting the IL-17 signaling pathway by IL-17RA antibodies, have been remarkable effective for the treatment of some autoimmune disorders (psoriasis) but even led to the exacerbation of colitis in patients with inflammatory bowel diseases. The reason for these controversial results are unknown.

Methods: We generated conventional and conditional IL-17RA deficient mice to analyze the effect of IL-17 signaling in models of inflammatory kidney and gut diseases. Cytokine production was analyzed using multi-color flow cytometry.

Results: Using the T_H17 dependent model of crescentic GN (nephrotoxic nephritis), we found that IL-17RA gene-deficiency, as well as IL-17RA antibody treatment, did not ameliorated the clinical course of the GN in terms of glomerular crescent formation, albuminuria, and renal function. Of note, Citrobacter rodentium induced colitis, that triggers a potent T_H17 cell response in the gut, was significantly aggravated in IL-$17RA^{-/-}$ mice. Mechanistically, we identified a unique pattern of dysregulated CD4 T cell immunity in these animals. Production of IL-17A, IL-17F and in particular the T_H17 associated cytokines IL-22 and GM-CSF were highly upregulated in the inflamed organs accompanied by tissue injury in the absence of IL-17 signaling. Competitive adoptive transfer experiments of wildtype and IL-$17RA^{-/-}$ CD4 T cells into nephritic $Rag1^{-/-}$ mice revealed that T_H17 genes were upregulated in cells lacking the IL-17RA. Using IL-17A reporter mice and cell-specific IL-$17RA^{-/-}$ mice we finally demonstrated, that IL-17RA is highly expressed by $CD4^+$ T_H17 cells and that this expression is critical for the control of the T_H17 response and subsequent tissue injury in crescentic GN and colitis.

Conclusions: Our findings indicate that IL-17RA expression on CD4 T cells control T_H17 immune response and production of IL-22 and GM-CSF via a self-inhibitory loop. This knowledge might help to understand organ specific outcome after anti-IL-17RA antibody treatment in immune-mediated disorders and indicate that IL-17RA blockade might be ineffective for treatment of RPGN or colitis.

Funding: Government Support - Non-U.S.

TH-PO050

Staphylococcus aureus Sepsis Drives a Highly Flexible TH17 Immune Response in the Kidney Patricia Bartsch,[1] Michael Zinke,[1] Christoph Kilian,[1] Hans-Joachim Paust,[1] Thorsten Wiech,[2] Jan-Eric Turner,[1] Ulf Panzer,[1] Samuel Huber,[3] Holger Rohde,[4] Christian F. Krebs.[1] *[1]III. Medizinische Klinik, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; [2]Nephropathologie, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; [3]I. Medizinische Klinik, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; [4]Medizinische Mikrobiologie, Virologie und Hygiene, Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany*.

Background: $CD4^+$ T cells play an important role in autoimmunity and infections. IL-17A expressing T_H17 effector cells are involved in autoimmune diseases and in the immune response to bacterial infections. Plasticity within the $CD4^+$ T cell system seems to be a critical factor for their pathogenicity in autoimmune diseases. T_H17 cells have a high degree of plasticity in experimental autoimmune encephalomyelitis (EAE) a mouse model for multiple sclerosis (MS), while renal T_H17 cells in crescentic glomerulonephritis (cGN) show a high degree of stability (70% maintain IL-17 expression). However, the knowledge about the T_H17 cell immune response and their plasticity in bacterial infections in the kidney is very limited.

Methods: To investigate the $CD4^+$ T cells response in infections, we established a mouse model of *Staphylococcus aureus* (*S.aureus*) sepsis induced by intravenous injection of *S. aureus* SH1000 (10^8 cfu). Renal tissue was analyzed by histology and flow cytometry. To analyze T cell plasticity, we used fluorescent reporter mice (IL-17A fate reporter and $FoxP_3$-IL-10-IL-17 acute reporter).

Results: Viable *S. aureus* were detected in kidneys at day 3-6 after infection, while no live bacteria were found after 10 days. Infection resulted in abscess formation in the kidney with infiltration of neutrophils and T cells. Intracellular cytokine staining displayed a high abundance of IL-17 producing $CD4^+$ T cells specifically in the kidney (IL17-A^+:5.7%±0.64) as compared to liver (IL17-A^+:1.84%±0.05) and spleen (IL17-A^+:1.1%±0.06). Interestingly, renal T_H17 cells revealed a high degree of plasticity in septic animals (IL-17-A^+:43.7%±0.62;IFN-γ^+:8.8%±1.31; IL17-A^+ IFN-γ^+:35.7%±4.16). However, IL-10 expression of T_H17 cells was very low (<1%), indicating a proinflammatory phenotype of renal T_H17 cells in response to *S. aureus.*

Conclusions: Here, we demonstrate a high degree of plasticity of T_H17 cells in the kidney in a *S. aureus* sepsis model. In contrast, T_H17 cells in crescentic GN are rather stable, thus suggesting that T_H17 cell plasticity is not tissue specific but might rather depend on the trigger of inflammation. Further understanding of T_H17 cell plasticity will allow more specific targeting of beneficial and detrimental T cell populations in settings of autoimmunity and infection.

Funding: Government Support - Non-U.S.

TH-PO051

Azithromycin Modulates Giant Cell Formation in Granulomatosis with Polyangiitis (GPA) Scott R. Henderson, Nixon Phua, Alan D. Salama. *University College London, London, United Kingdom*.

Background: Macrolides have immunomodulatory properties influencing both innate and adaptive immune responses. Anti-inflammatory effects have been established on neutrophils, CD4 positive T cells and monocytes and macrophages. Monocytes are central to disease pathogenesis in GPA, with critical importance in the development of granulomatous inflammation which remains one of the hardest manifestations to treat. We have established a novel *in vitro* giant cell/granuloma model with GPA patients' cells and established the significance of persistent PR3 exposure on giant cell and granuloma formation in GPA patients. Upper and lower airway manifestations of GPA are often treated with macrolide adjuvant therapy and we described a case of apparent recovery from more severe vasculitic features with azithromycin alone. Therefore, we set out to evaluate whether modulating monocyte responses to PR3 with azithromycin would result in reduced giant cell formation in GPA patients.

Methods: Monocytes were isolated from healthy controls, GPA and microscopic polyangiitis (MPA) patients and stimulated with either proteinase-3 (PR3) (10ug/ml) or myeloperoxidase (MPO) (10ug/ml) and varying concentrations of azithromycin (0.5, 2, 5ug/ml) for 72 hours. Semi-automated fusion index was calculated, a measure of MGC formation, using imaging software. Cytometric bead assays were used to evaluate modulation of cytokine production.

Results: Spontaneous rates of giant cell formation were greatest in GPA patients (n=4). The addition of PR3 but not MPO significantly increased giant cell formation in GPA patients compared to healthy controls (n=4) and MPA patients (n=4) (p 0.02). Addition of Azithromycin decreased giant cell formation in GPA patients (p 0.001) with the greatest effect seen at a concentration of 5ug/ml (p 0.03), but was also observed at 2ug/ml (p 0.003). IL-6 was important in the formation of giant cells. Although levels remained unchanged despite a reduction in giant cell formation at 72 hours in the presence of azithromycin and PR3, a reduction in IL-1b and an increase in IL-10 levels were observed.

Conclusions: Anti-inflammatory and anti-bacterial treatment is important in the maintenance therapy of GPA. Azithromycin may therefore offer a new alternative adjunctive treatment to this strategy whilst being a cost-effective, safe therapeutic option.

TH-PO052

Alkylating Histone Deacetylase Inhibitor Treatment in Animal Models of MPO-ANCA Vasculitis Dearbhaile Dooley,[5] Eóin O'Brien,[5] Barbara Fazekas,[4] Charles D. Pusey,[3] Frederick W. Tam,[2] Fionnuala B. Hickey,[5] Thomas Mehrling,[1] Peter Heeringa,[6] Mark A. Little.[5] *[1]EDO GmbH, Basel, Switzerland; [2]Imperial College Kidney and Transplant Institute, London, United Kingdom; [3]Imperial College London, London, United Kingdom; [4]Trinity College Dublin, Dublin, Ireland; [5]Trinity Health Kidney Centre, Tallaght Hospital, Trinity College Dublin, Dublin, Ireland; [6]University Medical Center Groningen, Groningen, Netherlands*.

Background: Anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) is a systemic inflammatory, autoimmune condition that affects the microvasculature. The lungs and kidneys are most frequently affected, leading to lung haemorrhage and glomerulonephritis (GN). When left untreated, AAV has a mortality rate of around 80% in year one and a 25% five-year mortality rate with current conventional treatments consisting of cyclophosphamide and steroids. However, these therapies do not prevent disease relapse and patients often require long-term treatment which is associated with severe morbidity. Recently, histone deacetylase inhibitors (HDACi) were shown to have beneficial effects in inflammatory rodent models and have been found to act synergistically with a diverse range of pharmacological agents including cyclophosphamide.

Methods: EDO-S101, a small molecule compound developed by Mundipharma EDO GmbH, is an alkylating HDACi fusion molecule which combines the strong DNA damaging effect of bendamustine, with a fully functional pan-HDACi, vorinostat. In this study, we investigated the effects of EDO-S101 in 2 well established rodent models of AAV. These consisted of a passive mouse model of anti-myeloperoxidase (MPO) IgG-induced GN and an active rat model of MPO-ANCA microscopic polyangitis: experimental autoimmune vasculitis (EAV).

Results: Our data indicate that although pre-treatment with EDO-S101 reduced circulating leukocyte populations, it did not affect development of anti-MPO IgG-induced GN in mice. On the other hand, EDO-S101 in EAV significantly reduced the degree of lung haemorrhage, severe GN and almost completely abolished crescent formation. EDO-S101 treatment in EAV also significantly depleted B and T cells compared with vehicle-treated controls, suggesting a selective effect on the adaptive immune response.

Conclusions: Taken together, we have demonstrated that EDO-S101 is a promising novel therapy for treatment of AAV that operates primarily through its effects on the adaptive immune response to the autoantigen MPO.

Funding: Commercial Support - Mundipharma EDO GmbH

TH-PO053

Transcriptional Profile Distinguishes Two Groups of ANCA Vasculitis Patients Independent of Serotype Britta E. Jones,[1] Joshua Starmer,[4] Caroline J. Poulton,[2] J. Charles Jennette,[4,1] Ronald J. Falk,[1,3] Dominic J. Ciavatta.[4,1] *[1]UNC Kidney Center, UNC Chapel Hill, Chapel Hill, NC; [2]UNC Kidney Center, Chapel Hill, NC; [3]University of North Carolina Hospitals, Chapel Hill, NC; [4]University of North Carolina at Chapel Hill, Chapel Hill, NC.*

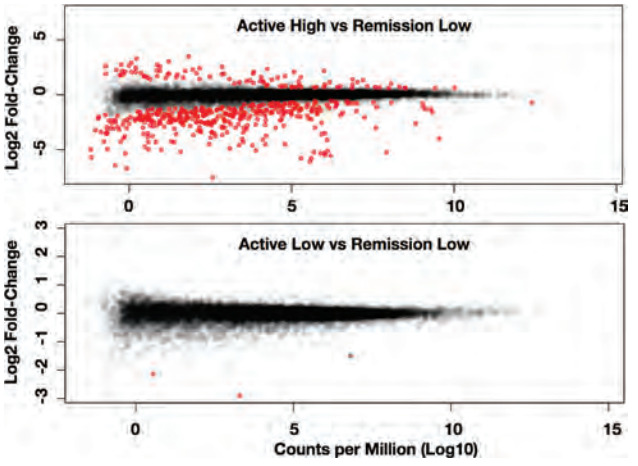
Background: Increased expression of ANCA autoantigen genes myeloperoxidase (*MPO*) and proteinase 3 (*PRTN3*) has been observed in several cell types, but global transcriptional changes are less well defined in ANCA vasculitis patients.

Methods: We isolated neutrophils, CD14+ monocytes and CD4-enriched cells, from 30 healthy controls and 75 patients during active disease or remission, including 25 longitudinal patient pairs. Expression of *MPO* and *PRTN3* in these purified cell populations was determined by quantitative real-time PCR. RNA-seq was performed on the CD4-enriched cell population from 12 active-remission pairs, 7 MPO-ANCA and 5 PR3-ANCA, to identify differentially expressed genes (DEGs) between active disease and remission.

Results: Expression of the autoantigen genes was elevated in patients with active disease compared to healthy controls in all three cell populations. A non-significant fold change in expression was seen in monocytes while the mean fold-change in expression for *MPO* and *PRTN3*, respectively, was 2.6; 3.6 in neutrophils and 7; 15.8 in the CD4-enriched cell population. Analysis of autoantigen gene expression in the CD4-enriched cell fraction and neutrophils in active-remission pairs revealed two groups of patients: patients with decreased expression from active disease to remission and those in which *MPO* and *PRTN3* mRNA did not change. RNA-seq of active-remission pairs detected three DEG in patients where *MPO* and *PRTN3* expression did not change. In patients who decreased autoantigen expression from active disease to remission, 468 significantly DEGs were detected including granulocyte genes [Figure 1].

Conclusions: The transcriptional profile that divides ANCA vasculitis patients into two categories suggests a molecular signature can distinguish disease status.

Funding: NIDDK Support



Summary of RNAseq analysis on active remission pairs. Red dots indicate differentially expressed genes.

TH-PO054

Monocytes Promote Crescent Formation in Anti-Myeloperoxidase Antibody-Induced Glomerulonephritis Anthony Rousselle,[2] Ralph Kettritz,[1,3] Adrian Schreiber.[1,3] *[1]Charite Berlin, Berlin, Germany; [2]ECRC, Berlin, Germany; [3]Charite, Experimental and Clinical Research Center, Berlin, Germany.*

Background: Neutrophils and monocytes express ANCA antigens, and activation of these cells by ANCA is central to ANCA-associated vasculitis (AAV) and necrotizing crescentic glomerulonephritis (NCGN). The importance of neutrophils is established; however, any role of monocytes is less clear. We tested the hypothesis that depletion of $CCR2^{+}$ inflammatory monocytes and their derivatives would abrogate anti-MPO antibody-induced NCGN in a mouse model.

Methods: We used anti-MPO IgG (50 µg/g body weight, BW) transfer to induce NCGN in LPS-challenged wild-type (WT) mice and in mice expressing the CCR2 promoter-controlled diphtheria toxin receptor (CCR2-DTR). Diphteria toxin (DT) then allows depletion of $CCR2^{+}Ly6C^{high}$ inflammatory monocytes in DTR mice. Urine was analyzed by dipstick, albuminuria by ELISA, glomerular necrosis and crescents by histology, and circulating and renal cell influx by flow cytometry.

Results: Both mouse strains showed similar circulating $Ly6C^{hi}$ and $-^{lo}$ monocytes and neutrophils at baseline. Diphtheria toxin robustly depleted circulating monocytes only in CCR2-DTR mice, whereas neutrophil numbers were similar. Anti-MPO antibody transfer resulted in nephritic urine by dipstick and albuminuria by ELISA, and monocyte depletion had no effect. However, monocyte depletion significantly reduced glomerular necrosis and crescent formation (21.4±10.5 vs. 4.3±2.2 for crescents and 12.0±7.1 vs. 3.0±1.1 for necrosis, $p<0.05$ for both) and abrogated monocyte, macrophage and dendritic cell increase in the affected kidneys, whereas renal neutrophil numbers were not affected. Soluble CD163 increased in serum, but not in urine with anti-MPO antibody treatment and was completely abolished with monocyte depletion.

Conclusions: Our findings provide novel experimental evidence that monocytes are important disease contributors in ANCA-mediated NCGN. Whereas neutrophils are sufficient to induce nephritic urine abnormalities, albuminuria, and some NCGN, inflammatory monocytes clearly enhanced necrosis and crescent formation.

Funding: Government Support - Non-U.S.

TH-PO055

Detecting Autoreactive Cells and Pathogenic Epitopes in MPO-ANCA Vasculitis Katherine G. Stember,[2] Jacob Hess,[1] Candace D. Henderson,[1] Simon Mallal,[3] J. Charles Jennette,[5] Ronald J. Falk,[4] Dominic J. Ciavatta,[5] Meghan E. Free.[1] *[1]UNC Kidney Center, Chapel Hill, NC; [2]University of North Carolina Chapel Hill, Chapel Hill, NC; [3]Vanderbilt University Medical Center, Nashville, TN; [4]University of North Carolina Hospitals, Chapel Hill, NC; [5]University of North Carolina at Chapel Hill, Chapel Hill, NC.*

Background: Anti-neutrophil cytoplasmic autoantibody (ANCA) vasculitis is an autoimmune disease that damages blood vessels throughout the body, and treatment regimens include immunosuppression. Previous studies demonstrated dysregulation of the adaptive immune system and identified two autoantigens: myeloperoxidase (MPO) and proteinase 3 (PR3). GWAS studies found an association between ANCA vasculitis and human leukocyte antigen (HLA). Mouse and human studies identified pathogenic MPO epitopes. Our lab sought to investigate MPO epitopes recognized by autoreactive B and T cells in patients.

Methods: We used an in-house ELISA to test antibody reactivity to a previously identified linear MPO epitope. We HLA sequenced 203 patients to identify disease-associated alleles and used predictive and in vitro binding studies to assess MHC-peptide binding. MHC II tetramers were produced for DPB1*04:01 and DRB4*01:01 containing MPO epitopes and controls. Patient PBMCs were incubated with tetramers, stained with surface markers, and analyzed by flow cytometry day 1 ex vivo.

Results: Our ELISA revealed 53% percent of patients have autoantibodies that bind $MPO_{447\text{-}461}$, most often at disease onset. Patients carrying HLA of interest demonstrate specific CD4+ T cell recognition of tetramers containing MPO epitopes. The majority of tetramer positive cells are $CD25^{intermediate}$ cells, and are positive for CD45RO and CCR7 memory markers. Additionally they secrete IL-17 when stimulated.

Conclusions: Recently, it was shown that $MPO_{409\text{-}428}$ induced tolerance and attenuated disease in a mouse model of anti-MPO GN. Patient CD4+ T cells show significant reactivity to tetramers carrying the human homolog of this epitope. Ideally, we will use this region of MPO to inform the development of new therapies for patients with ANCA vasculitis.

Funding: NIDDK Support

TH-PO056

Neutrophil-Gelatinase Associated Lipocalin (NGAL) Attenuates ANCA-Induced Glomerulonephritis by Inhibiting Th17 Immunity Adrian Schreiber,[1,5] Ulf Panzer,[3] Anthony Rousselle,[2] Ralph Kettritz.[4,5] *[1]Charite Berlin, Berlin, Germany; [2]ECRC, Berlin, Germany; [3]None, Hamburg, Germany; [4]Universitatsmedizin Berlin, Berlin, Germany; [5]Charite, ECRC, Berlin, Germany.*

Background: ANCA activate neutrophils and monocytes and thereby participate in vasculitis and necrotizing crescentic glomerulonephritis (NCGN). NGAL is a marker of intrinsic kidney injury and is expressed by neutrophils and renal tubular cells. Whether or not NGAL is merely a diagnostic marker or participates mechanistically in renal damage is not known. We hypothesized that neutrophil NGAL plays a pathogenic role in ANCA-induced NCGN.

Methods:

Results: Patients with active ANCA disease demonstrated strongly increased NGAL serum levels by western blot analysis (47.3±13.1 optical density, OD) compared to patients in remission (19.4±8.1OD) and healthy controls (2.1±0.4OD). By ELISA, both PR3-ANCA and MPO-ANCA stimulated NGAL release from human neutrophils (887±72 and 961±70 ng/ml, respectively), whereas control IgG induced much lower levels (105±21ng/ml). In addition, mice with anti-MPO-induced NCGN demonstrated upregulated NGAL serum levels. To assess the role of neutrophil NGAL in vivo, we used a murine model of anti-MPO induced NCGN, where mMPO-immunized MPO-deficient mice were transplanted with either WT- or NGAL-deficient BM. NCGN was significantly aggravated in mice that received NGAL-deficient BM (34.8±6.1% crescents in NGAL-KO versus 13.4±2.8% in WT mice). With respect to intrinsic neutrophil function, migration, ROS generation, degranulation and apoptosis were similar in NGAL-KO and WT neutrophils. In addition, humoral immunity to MPO did not differ between both groups. In contrast, flow cytometry demonstrated significantly increased renal T-cells in NGAL-deficient mice: TH17 cells were 21.7±7.6% of renal CD4 cells versus 5.7±1.0%. Splenocytes from NGAL-deficient mice demonstrated a higher proliferation rate than splenocytes from WT mice. Finally, to assess the specific role of TH17 immunity in anti-MPO-induced NCGN, immunized MPO-KO and MPO-/IL17A-double-KO mice were transplanted with either WT or IL17A-KO BM, respectively. NCGN was significantly attenuated in IL17A-KO mice compared to WT mice as assessed by urine pathology and

renal histology (2.5±1.3% crescents in MPO-/IL17A-double-KO versus 29.6±7.2% in MPO-KO mice).

Conclusions: Our findings indicate that neutrophil NGAL down-regulates inflammation in ANCA-induced NCGN by inhibiting TH17 immunity and TH17 cells are clearly necessary for induction of ANCA-mediated NCGN.

Funding: Government Support - Non-U.S.

TH-PO057

Microparticle Tissue Factor Activity Dominates Venous Thromboembolism Signature in ANCA Vasculitis Carmen E. Mendoza,[4] Elizabeth J. Brant,[1] Matthew L. Mcdermott,[4] Anne B. Froment,[2] Yichun Hu,[2] Susan L. Hogan,[8] J. Charles Jennette,[7] Ronald J. Falk,[5] Patrick H. Nachman,[6] Vimal K. Derebail,[3] Donna O. Bunch.[2] *[1]Dartmouth-Hitchcock Medical Center, Lebanon, NH; [2]UNC Kidney Center, Chapel Hill, NC; [3]University North Carolina at Chapel Hill, Chapel Hill, NC; [4]University of North Carolina, Chapel Hill, NC; [5]University of North Carolina Hospitals, Chapel Hill, NC; [6]University of North Carolina School of Medicine, Chapel Hill, NC; [7]University of North Carolina at Chapel Hill, Chapel Hill, NC; [8]University of North Carolina, Chapel Hill, Chapel Hill, NC.*

Background: Venous thromboembolism (VTE) is a complication of ANCA vasculitis whose mechanism remains incompletely elucidated. We tested biomarkers associated with disease activity in ANCA vasculitis and/or VTE in other diseases, including microparticle tissue factor activity (MPTFa) and anti-plasminogen (anti-Plg) to devise a thrombotic signature. We hypothesized that elevated MPTFa and anti-Plg may identify patients at risk for VTE.

Methods: Patients were enrolled during active disease. Twelve patients experienced a VTE (VTE^{pos}) and were compared to patients without VTE (VTE^{neg}, n=29) and 56 healthy controls (HC). Platelet free plasma and serum samples were assayed for MPTFa and anti-Plg. IL-6 was measured by a commercial ELISA; positivity was defined as 2 standard deviations above the HC mean. D-dimer, high sensitivity CRP (hs-CRP) and serum creatinine were measured by our clinical laboratory. Measures were assessed at active disease and remission. Univariate and bivariate analyses were performed by Cox regression.

Results: Demographics were similar in patients and HC. VTE^{pos} and VTE^{neg} patients did not differ in ANCA serotype, titer or BVAS. In univariate analysis, elevated MPTFa during active disease was associated with VTE (HR=1.06, 95%CI 1.01, 1.10; p=0.009). For every 10 units increase of MPTFa during active disease, the risk of VTE increased by 60%. This is a significant unit of measure as the threshold for positivity was set at 11% of the positive control. Assuming remission values before and after VTE are comparable, MPTFa at remission was also associated with VTE (HR=1.4, 95%CI 1.11, 1.77; p=0.005). Similarly, increased anti-Plg during remission was associated with VTE (HR=1.17, 95%CI 1.03, 1.33; p=0.02) but not at active disease. Per unit increases of both hs-CRP (HR=1.21, 95%CI 1.02, 1.45; p=0.04) and serum creatinine (HR=1.29, 95%CI 1.0, 1.66; p=0.05) were associated with VTE. IL-6 and D-dimer were not associated with VTE. In bivariate analysis, MPTFa adjusted for serum creatinine was still significantly associated with VTE (HR=1.05, 95%CI 1.01, 1.10; p=0.01).

Conclusions: Our data suggest that of the variables evaluated, elevated MPTFa provides the best marker of VTE and may identify patients at high risk for VTE in ANCA vasculitis.

Funding: NIDDK Support, Private Foundation Support

TH-PO058

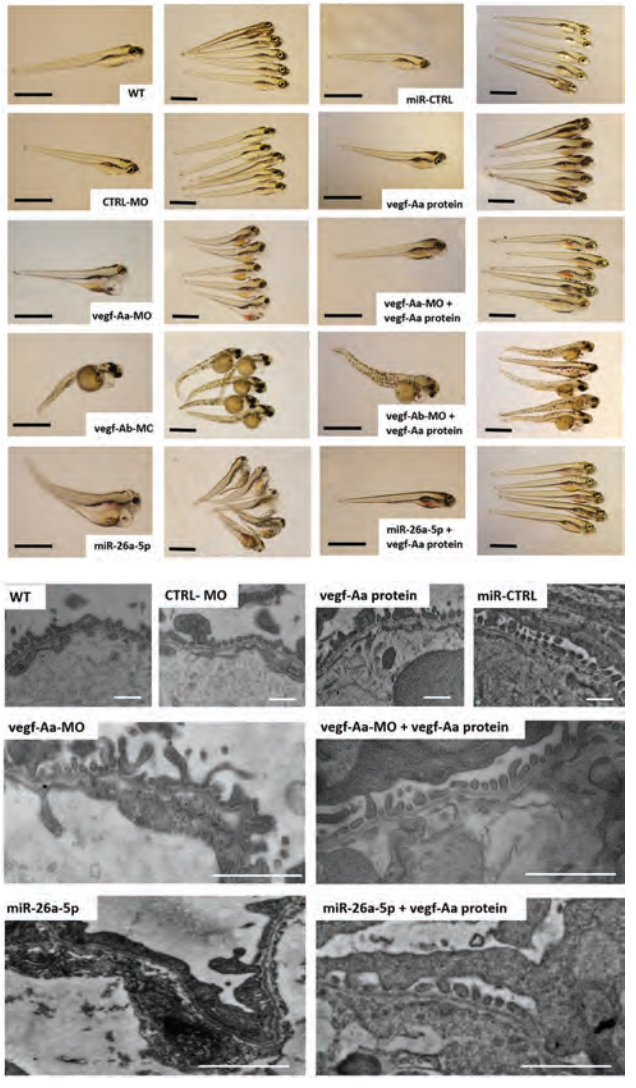
Overexpression of Preeclampsia Induced miR-26a-5p Leads to Proteinuria in Zebrafish Janina Müller-Deile,[1] Patricia A. Schroder,[3] Jenny C. Nystrom,[4] Hermann G. Haller,[2] Mario Schiffer.[2] *[1]Hypertention and nephrology, Hannover medical school, Hanover, Germany; [2]Hannover Medical School, Hannover, Germany; [3]Mount Desert Island Biological Laboratory, Salisbury Cove, ME; [4]University of Gothenburg, Goteborg, Sweden.*

Background: So far the pathomechanism of preeclampsia in pregnancy is focussed on increased circulating levels of sFLT1 that neutralizes glomerular VEGF-A expression and prevents its signalling at the glomerular endothelium. MiR-26a-5p is upregulated in the preeclamptic placenta.

Methods: We analyzed miR-26a-5p expression in podocytes and microinjected zebrafish eggs with a miR-26a-5p mimic. We analysed phenotype, proteinuria and ultrastructural changes of the glomerular filtration barrier.

Results: We found that miR-26a-5p targets VEGF-A expression in cultured podocytes and that its overexpression in zebrafish causes proteinuria, edema, glomerular endotheliosis and podocyte foot process effacement. Recombinant zebrafish vegf-Aa protein could rescue glomerular changes induced by miR-26a-5p. Preeclamptic patients with podocyte damage identified by podocyturia, expressed significantly more urinary miR-26a-5p compared to controls.

Conclusions: Thus, functional and ultrastructural glomerular changes after miR-26a-5p overexpression can resemble the findings seen in preeclampsia and indicate a potential pathophysiological role of miR-26a-5p in addition to sFLT-1 in this disease.



TH-PO059

Protective Effect of TRPC6 Knockout in Chronic PAN Nephrosis in Sprague-Dawley Rats Stuart E. Dryer, Eunyoung Kim. *University of Houston, Houston, TX.*

Background: Mutations in TRPC6 channels give rise to rare forms of focal and segmental glomerulosclerosis (FSGS). A possible role of wild-type TRPC6 channels in the progression of acquired forms of FSGS is not firmly established, and it is important to examine this in multiple species. Here we examined the role of TRPC6 channels in chronic puromycin aminonucleoside (PAN) nephrosis in Sprague-Dawley rats. Chronic PAN nephrosis is one of the most extensively studied models of secondary FSGS. A major advantage of this model is that experimental animals get a severe glomerular disease.

Methods: A global constitutive $TRPC6^{-/-}$ rat was generated on the Sprague-Dawley background using CRISPR/Cas9 technology. Experiments were carried out using $TRPC6^{+/+}$ and $TRPC6^{-/-}$ littermates. Rats were given two i.p. injections of PAN at 30 day intervals. Renal phenotypes were characterized by standard histological, ultastructural, and biochemical methods. All experiments were approved by the University of Houston IACUC.

Results: Nephrotic range albuminuria was present 9-10 days after the first PAN injection and there was no difference in 24-hour urine albumin excretion in $TRPC6^{+/+}$ and $TRPC6^{-/-}$ rats at that time. In marked contrast to the acute phase, at 30 and 60 days after the initial PAN injection, $TRPC6^{-/-}$ rats had biologically and statistically significantly reduced urine albumin excretion, reduced serum cholesterol and triglycerides, and improved BUN compared to $TRPC6^{+/+}$ littermates. Glomerulosclerosis was severe during chronic PAN nephrosis in $TRPC6^{+/+}$ rats, but was markedly reduced in $TRPC6^{-/-}$ littermates. TRPC6 knockout rats also had less severe tubulointerstitial fibrosis, and reduced foot process effacement and glomerular basement thickening compared to $TRPC6^{+/+}$ controls. $TRPC6^{-/-}$ rats also had reduced infiltration of monocytes or macrophages into glomeruli, and reduced expression of α-smooth muscle actin in renal cortex compared to $TRPC6^{+/+}$ littermates. Basal TRPC3 abundance in renal cortex was increased in $TRPC6^{-/-}$ rats compared to $TRPC6^{+/+}$ controls. However TRPC3 did not increase further in chronic PAN nephrosis. None of the manipulations in this study affected TRPC5 channels.

Conclusions: TRPC3/6 family channels may represent useful therapeutic targets for acquired forms of FSGS.

Funding: NIDDK Support

TH-PO060

Calpain Activation by TRPC6 in the Podocyte Louise K. Farmer, Gavin I. Welsh, Moin Saleem. *University of Bristol, Bristol, United Kingdom.*

Background: TRPC6 mutations have been shown to cause Focal Segmental Glomerulosclerosis (FSGS). Previously the pathology of these mutations was thought to be due to an increased calcium conductance of this membrane channel. However, several disease-causing mutations have been reported to have no change in, or decreased, calcium conductance. We have investigated whether these mutations affect protein interactions.

Methods: Conditionally immortalised podocyte cell lines were generated from TRPC6 KO C57Bl/6 mice. GFP tagged WT/mutant TRPC6 was stably reintroduced into the KO cell line using a lentiviral construct. Cell lines were then characterised to determine motility and adhesion using scratch and adhesion assays. GFP TRAP beads were used to immunoprecipitate TRPC6 and proteomics was performed to identify novel binding partners. Calpain assays were performed using a commercially available kit.

Results: TRPC6 KO (T6K) podocytes are less motile and more adhesive than those expressing WT TRPC6. Calpain 1 and 2, ERK 1/2 and caldesmon were identified as novel TRPC6 binding partners using GFP-TRAP pull down, proteomics and verified through co-immunoprecipitation experiments. Calpain is a protease with a variety of targets including focal adhesion kinase (FAK). T6K cells have decreased FAK cleavage and increased FAK phosphorylation compared to cells containing WT TRPC6. The cleavage of the calpain targets talin-1 and caldesmon was also decreased in T6K cells. Calpain assays demonstrated a loss of calpain activity in T6K cells. This suggests that in WT cells TRPC6 is responsible for calpain activation. The disease causing mutant form of TRPC6, K874*, has normal calcium conductance, however, as with T6K cells, cells expressing this mutant have decreased calpain activity and decreased cleavage of calpain targeted proteins. Co-IP experiments have shown that there is decreased binding of TRPC6 K874* to calpain compared to WT. We have also shown that treatment of WT cells with plasma from nephrotic syndrome patients during relapse, but not remission, causes an increase in calpain activity. This suggests that TRPC6 mediated activation of calpain could be playing an important role in disease.

Conclusions: TRPC6 mediated activation of calpain plays an important role in podocyte motility and detachment. Disease causing mutations in TRPC6 could be acting by preventing the binding of calpain 1/2 to TRPC6, decreasing calpain activation

TH-PO061

Targeting Podocyte Endoplasmic Reticulum Calcium Depletion to Treat Nephrotic Syndrome Sun-Ji Park,[1] Yeawon Kim,[1] Jeffrey H. Miner,[1] Fumihiko Urano,[2] Ying M. Chen.[1] *[1]Division of Nephrology, Washington University School of Medicine, St. Louis, MO; [2]Division of Endocrinology, Metabolism, and Lipid Research, Washington University School of Medicine, Saint Louis, MO.*

Background: Emerging evidence has demonstrated that podocyte endoplasmic reticulum (ER) stress caused by gene mutations contributes to the pathogenesis of nephrotic syndrome (NS). ER stress-mediated calcium efflux from the ER to the cytosol can activate calcium-dependent protease calpain 2, which underlies the development of proteinuria. Here for the first time, we have shown that a novel ER calcium stabilizer can inhibit podocyte calpain activation.

Methods: We have developed a NS mouse model in which C321R mutation of the glomerular basement membrane constituent laminin β2 (LAMB2), a mutation identified in human patients, leads to podocyte ER stress. We isolated mouse glomeruli and cultured primary podocytes at the early stage of the disease to investigate the functional impact of ER stress. Meanwhile, we generated human podocytes stably expressing WT or C321R β2. Moreover, a *Gaussia* luciferase (GLuc)-based assay utilizing secreted ER calcium-monitoring proteins (SERCaMPs), and fluorescent calcium indicator Fluo-4 detected by flow cytometry were employed to monitor ER calcium leak in live cells and to measure cytosolic calcium levels, respectively.

Results: Podocyte ER stress triggered by the C321R mutation induced calpain activation, as indicated by the cleavage of its substrate spectrin. In addition, calpain 2 hyperactivation in mutant podocytes activated the caspase 12 apoptotic pathway, cleaved the podocyte cytoskeletal protein talin, and downregulated the podocyte slit diaphragm proteins nephrin and podocin. Furthermore, cytosolic calcium levels were increased in human podocytes expressing C321R-LAMB2 compare to WT-LAMB2, directly demonstrating ER calcium depletion in the mutant podocytes. RNAseq further highlighted dysregulated ER calcium signaling pathways in C321R podocytes compared to controls. Most excitingly, by utilizing GLuc-SERCaMP as a high throughput drug screening tool, a novel ER calcium stabilizer was identified to suppress calpain 2 activation in C321R podocytes.

Conclusions: Currently there is no treatment for most genetic forms of NS. Our study may open up a new avenue for treatment of NS caused by podocyte ER calcium depletion.

Funding: NIDDK Support, Private Foundation Support

TH-PO062

TRPM4 Is Expressed at the Apical Surface of Podocyte Just Above Slit Diaphragm, and Its Altered Expression Is Involved in Podocyte Injury Ying Zhang, Yoshiyasu Fukusumi, Hiroshi Kawachi. *Department of Cell Biology, Kidney Research Center, Niigata University, Niigata, Japan.*

Background: TRPC6, a member of TRP channels is reported to play an important role in regulating the slit diaphragm (SD) function. To explore novel molecules involved in the development of proteinuria, we performed cDNA subtraction assay and RNA-seq analysis. 293 molecules were identified to be decreased to less than 20 % in PAN nephropathy. We found transient receptor potential melastatin 4 (TRPM4), another member of TRP channels was clearly downregulated. In this study we examined the expression and localization of TRPM4 in glomeruli and its possible roles in pathogenesis of proteinuria.

Methods: The expression and the localization of TRPM4 under the physiological and pathological conditions were analyzed by real-time PCR, dual-labeling immunofluorescence and Western blot. We prepared three rat models, PAN nephropathy, a mimic of MCNS, ADR nephropathy, a mimic of FSGS and anti-nephrin antibody (ANA) induced nephropathy, which is characterized as a slit diaphragm specific dysfunction.

Results: The mRNA expression of TRPM4 in glomeruli was more extensive than that in renal cortex and other tissues. The expression of TRPM4 was also detected in cultured mouse podocytes. Immunostaining of TRPM4 in renal cortex was restricted to glomeruli, and it was observed to be a discontinuous linear pattern along the glomerular capillary loops. TRPM4 staining was slightly aside from nephrin, an extracellular component of the SD, and some portions of TRPM4 were colocalized with podocyte apical membrane marker podocalyxin. TRPM4 first appeared in the presumptive podocytes in early S-shaped body stage, when nephrin was not detected yet. The mRNA expression of TRPM4 was evidently decreased immediately after disease induction (1h: 10 % in ANA, 31 % in PAN) and the decrease was still detected when proteinuria peaked (42 %, 57 %). The immunostaining of TRPM4 shifted to a discontinuous patchy pattern in PAN nephropathy. The staining intensity of TRPM4 was lowered in ANA nephropathy and ADR nephropathy.

Conclusions: TRPM4 is expressed at the apical surface of podocyte just above slit diaphragm. The mRNA expression of TRPM4 was clearly decreased before the onset of proteinuria. The immunostaining of TRPM4 was altered in proteinuric states. It is conceivable that the altered expression of TRPM4 is involved in initiating the slit diaphragm dysfunction.

Funding: Government Support - Non-U.S.

TH-PO063

Brevin R-SNARES Provide a Cellular Address to Localize APOL1 to Podocyte Endosomal Compartments Sethu M. Madhavan,[2] John F. O'Toole,[1] Martha Konieczkowski,[1] Leslie A. Bruggeman,[1] John R. Sedor.[1] *[1]Case Western Reserve University, Cleveland, OH; [2]MetroHealth Medical Center, Cleveland, OH.*

Background: Genetic variants in *APOL1* (G1 and G2) associate with non-diabetic kidney diseases in individuals with African ancestry. Kidney-expressed, but not circulating APOL1 variants, confer risk for CKD. Most subjects with high risk *APOL1* genotypes do not develop kidney disease, suggesting a second hit is necessary. Sites of APOL1 synthesis in kidney, its subcellular localization and the identity of its cognate binding partners as well as mechanisms by which variant APOL1s promote nephropathy remain unclear.

Methods: In situ hybridization (ISH) was performed in normal human kidney tissue to detect APOL1 transcripts. APOL1 subcellular localization was examined by immunoelectron (IEM) and confocal immunofluorescence microscopy. Co-immunoprecipitation (Co-IP) experiments to study APOL1-SNARE protein interaction was performed in 293T cells ectopically expressing tagged proteins. Bacterially expressed proteins purified by metal affinity and size-exclusion chromatography were used to study protein interaction by surface plasmon resonance (SPR).

Results: ISH demonstrated that APOL1 is synthesized in podocytes of human kidney and less so in tubules. In kidneys of mice transgenic for APOL1 and human nephrectomy samples, IEM localized the protein to double membrane vesicles and endocytic compartments in podocytes. APOL1 did not localize to plasma membrane in podocytes. By immunofluorescence, podocyte APOL1 did not localize with either a mitochondrial marker, beta-subunit of ATP synthase, or a lysosomal marker, LAMP1. APOL1 interacted with the R-SNAREs, VAMP8 and VAMP1 in Co-IPs. APOL1 colocalized with VAMP8 in podocytes of normal human kidney and Co-IP and SPR experiments confirmed that APOL1-G1 and -G2 interact with VAMP8 with lower affinity than -G0.

Conclusions: Reference APOL1 is expressed in the podocyte, localizes with vesicular structures and directly interacts with VAMP8, consistent with regulation of podocyte vesicular trafficking. APOL1 variants attenuate interaction with VAMP8. We propose that reference APOL1, by interacting with VAMP8 or other R-SNAREs, identifies vesicles containing cargo capable of mediating cellular damage, and activates a cellular response, which mitigates the pathogenic potential of these cargos. Variant APOL1 proteins fail to do so, disrupting vesicular trafficking and permitting kidney disease progression.

Funding: NIDDK Support

TH-PO064

The Effects of Mechanical Strain on Adhesion in MYH9- Ablated Podocytes Keith H. Keller,[3,4] Mostafa Belghasem,[3] Hui Chen,[1] Joel M. Henderson.[2,3] *[1]BMC, Boston, MA; [2]Boston University Medical Center, Boston, MA; [3]Boston University School of Medicine, Boston, MA; [4]Brigham and Woman's Hospital, Boston, MA.*

Background: Myh9 is a gene that encodes for non-muscle myosin IIA (NM-IIA), an actin cytoskeleton component and protein involved in cell movement and adhesion in most cells, including podocytes. Autosomal dominant mutations in NM-IIA have been associated with focal segmental glomerulosclerosis (FSGS). Podocyte specific Myh9 knockout in mice showed that this gene alone was not enough to cause proteinuria or glomerulosclerosis. However, in our own laboratory we have found that when these same mice are exposed to models of glomerular hypertension, glomerular damage is promoted. This damage was preceded by evidence of podocyte loss in urine and tissue. Podocyte loss is a hallmark of kidney disease, and while it is known to occur in vivo, the mechanisms behind this phenomenon are unknown. It is believed that increase in glomerular capillary blood pressure is likely to be a strong contributing factor. Here we investigated the effect of mechanical strain on adhesion and cell morphology in Myh9 ablated podocytes.

Methods: Myh9 was knocked down, using RNAi, in immortalized mouse podocytes cultured on flexible silicone 6-well plates at a density of 6000 cells per well. Cells were mechanically stretched in a step-change fashion for 24hrs then cells were fixed or lysed for protein. Each experiment included three groups with two conditions (stretch/no stretch): WT; lentiviral control; KD. Changes in adhesion were assessed using cell counts, and morphologic changes were evaluated using immunofluorescence and quantified using imageJ.

Results: Transfected cells showed marked decrease in cellular attachment (V.CTL: -53%; V.CTL-ST: -53%; KD: -50%; KD-ST: -60%), compared to control cells (CTL: +77%; CTL-ST: +120%). Mean focal adhesion area increased with stretch in each experimental treatment group except KD (CTL: 1.41+ 1.62 μm2; CTL-ST: 2.12+ 3.13μm2; V.CTL: 0.54+ 0.47μm2; V.CTL-ST: 2.77+ 3.59μm2; KD: 3.04+ 2.57μm2; KD-ST: 2.09+ 1.13μm2). KD-ST cells showed large decrease in focal adhesion number compared to all other groups. Mean cell size was drastically larger in the KD groups (CTL: 773.6+489.μm2; CTL-ST: 505.5+377.7μm2; V.CTL: 817.6+1008,5μm2; V.CTL-ST: 1306.9+787μm2; KD: 3576.5+2694.7μm2; KD-ST: 5461.7+13,456.3μm2)

Conclusions: Myh9/NM-IIA may necessary for cells to bolster cell adhesion structures during events of mechanical stress, and its loss may compromise this protective adaptation.

TH-PO065

MicroRNA671-5p Mediates Wnt/β-Catenin-Triggered Podocyte Injury by Targeting WT1 Chunhong Wang,[1] Wenjuan Zhu,[1] Lili Zhou,[1] Youhua Liu.[2] *[1]Division of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China; [2]Department of Pathology, University of Pittsburgh, Pittsburgh, PA.*

Background: Podocyte injury is the major pathological feature of many proteinuric kidney diseases. It has been shown that dysregulated activation of Wnt/β-catenin signaling in podocytes can lead to podocyte dedifferentiation and mesenchymal transition, causing impaired glomerular filtration and proteinuria. MicroRNAs (miRNAs) are a class of short non-coding RNAs, which regulates specific genes by targeting and fine-tuning their expression. To study whether miRNA is involved in mediating Wnt/β-catenin-triggered podocyte injury, we performed a comprehensive miRNA expression profiling and sought to identify the miRNAs that may play a crucial role in this process.

Methods:

Results: Mouse podocytes were transiently transfected with expression vector encoding constitutively activated β-catenin (pDel-β-cat) or empty vector (pcDNA3). The differential expression of miRNAs was identified through a microarray analysis. Among several dozens of miRNAs which expression levels were altered after β-catenin activation, miR-671-5p was on the top of the list. Subsequent qRT-PCR confirmed that miR-671-5p was upregulated in cultured podocytes after β-catenin activation, as well as in the kidneys of proteinuric CKD. Bioinformatics analysis predicted that miRNA671-5p could target WT1 mRNA for degradation. Indeed, over-expression of miR671-5p induced down-regulation of WT1 protein and promoted podocyte injury, whereas it had no effect on the level of WT1 mRNA. Inhibition of miRNA671-5p mitigated podocyte injury caused by β-catenin activation. In mouse model of remnant kidney after 5/6 nephrectomy (5/6NX), miR671-5p was specifically up-regulated in glomerular podocytes, as shown by in situ hybridization. Furthermore, over-expression of miR671-5p in vivo promoted β-catenin activation, inhibited WT1, worsened podocyte injury and kidney fibrotic lesions in remnant kidney after 5/6NX.

Conclusions: These studies identify miR-671-5p as a novel mediator that plays a crucial role promoting podocyte injury through down-regulation of WT1. The study also provides new insights into the pathogenic mechanisms of Wnt/β-catenin in podocyte dysfunction. Therefore, miR-671-5p may be a potential therapeutic target for ameliorating podocyte injury in the proteinuric kidney diseases.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-PO066

Isthmine-1, a New Podocyte Protein Involved in the Progression of Nephrotic Syndrome Jean-Jacques Boffa,[5,3] Lu Zhang,[2,1] Sahiri V. Marie aude,[6] Khalil A. Ghachem,[1] Placier Sandrine,[7] Chantal Jouanneau,[8] Christos Chatziantoniou.[4,3] *[1]INSERM U1155, Paris, France; [2]Jiangsu Province Hospital of Chinese Medcine, Nanjing, China; [3]INSERM UNIT 1155, Paris, France; [4]Tenon Hospital, Paris, France; [5]Tenon Hospital, AP-HP, Paris, France; [6]INSERM U1155 / UPMC, Paris, France; [7]INSERM 1155 - UPMC, Paris, France; [8]inserm, Paris 20, France.*

Background: Using differential transcriptomic analysis in renal cortical slices from hypertensive rats with nephrotic level of proteinuria, we identified and studied isthmine-1 (ISM-1), a new player of renal diseases.

Methods:

Results: Under control physiological conditions, ISM-1 is strongly expressed and colocalized with nephrin in rodents and humans as well. Immunogold electron microscopy revealed that ISM-1 localizes on podocyte foot processes. Because its two receptors, avb5integrin and grp78 (Bip) are involved in podocytopathy, we induced nephrotic syndrome in rats by PAN and doxorubicine injection. In both experimental models, we found increased expression of ISM-1 mRNA and protein on isolated glomeruli. Likewise, the expressions of its two receptors were increased and contrasted to the decrease of nephrin protein expression. In addition, ISM-1 expression increased after doxorubicine stimulation in primary cultured podocytes in vitro. To determine the role of ISM-1, ISM-1 antisens ODN were administered in experimental models of nephrotic syndrome in vivo. Although ISM-1 antisens administration blunted ISM-1 expression, no difference was observed in the progression and severity of the disease in PAN rats. Because, ISM-1 has been shown to act as a permeability factor during lung sepsis, we are pursuing our studies by examining its role on glomerular membrane permeability.

Conclusions: Our results show the discovery of a novel protein ISM-1 specifically expressed in podocyte in normal conditions. This expression is further increased in the progression of nephrotic syndrome. We are currently investigating the physiopathological role of this increase.

TH-PO067

Loss of Robo2 Rescues Podocyte Number and Ultrastructure Defects in Adult Ilk Knockout Mice Richa Sharma, Hila Milo Rasouly, Xueping Fan, Sudhir Kumar, Arielle R. Strzelewicz, Mostafa Belghasem, Joel M. Henderson, David J. Salant, Weining Lu. *Boston University Medical Center, Boston, MA.*

Background: Previous studies showed that ROBO2 signaling functions as a negative regulator on podocyte actin polymerization and podocyte adhesion. Our data shows that ROBO2 forms a complex with integrin-linked kinase (ILK) and loss of *Robo2* improves the survival of *Ilk* podocyte-specific knockout (cKO) mice. However, the mechanism of this renoprotective role of *Robo2* loss in *Ilk* cKO is not clear.

Methods: *Robo2* and *Ilk* single cKO were crossed to generate *Robo2-Ilk* podocyte specific double knockout mice (dKO). Glomerular histology, podocyte number, and podocyte ultrastructure of single cKO and double dKO mice were analyzed at 4 weeks and 16 weeks of age. Glomerular histology was evaluated by PAS staining. Podocyte numbers were quantified using WT1 staining. Podocyte ultrastructure was analyzed and quantified by transmission electron microscopy (TEM). Quantitative data were analyzed using SPSS statistics software.

Results: Results: At 4 weeks old, the podocyte number and glomerular sclerotic index are almost the same in both *Ilk* single cKO and *Robo2-Ilk* dKO mice. However, analyses of podocyte number, glomerular histology, and TEM in 16 weeks old mice showed a significant improvement in podocyte number (p=0.02), sclerotic index (p=0.006), glomerular basement membrane width (p=0.03), podocyte foot process width (p=0.002), and slit diaphragm density (p=0.04) in *Robo2-Ilk* dKO as compared to *Ilk* single cKO mice.

Conclusions: Loss of *Robo2* improves the survival of *Ilk* podocyte-specific knockout mice by rescuing podocyte number and podocyte ultrastructure defects in adult mice. Our findings suggest that inhibition of ROBO2 signaling could be beneficial for glomerular disease associated with podocyte loss and be a potential therapeutic target.

Funding: NIDDK Support, Commercial Support - Pfizer Centers for Therapeutic Innovation

TH-PO068

In Vivo Characterization of Podocin Variants Based on a CRISPR/Cas9 Based Genome Editing Approach Linus Butt,[1,2] Lena K. Ebert,[1,2] Markus M. Rinschen,[1,2] Martin Höhne,[1,2] Branko Zevnik,[2] Paul T. Brinkkoetter,[1,2] Bernhard Schermer,[1,2] Thomas Benzing.[1,2] *[1]Department II of Internal Medicine and Center for Molecular Medicine Cologne, University of Cologne, Cologne, Germany; [2]Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, University of Cologne, Cologne, Germany.*

Background: *NPHS2* encodes for Podocin, a membrane protein at the inner leaflet of the plasma membrane of podocytes, and is the most frequently mutated gene in patients with Steroid-Resistant Nephrotic Syndrome (SRNS). Analyzing the role of posttranscriptional and -translational regulations of Podocin in the maintenance of the architecture and functional integrity of the slit diaphragm will contribute to the understanding of the underlying pathomechanisms. In previous studies, we confirmed the expression of a short isoform of Podocin in the human kidney, characterized its

biochemical properties *in vitro* and showed an altered localization of the protein. In addition, we identified phosphorylation sites within Podocin by analyzing the glomerular phosphoproteome and found evidence for their biological significance, e.g. for Podocin multimerization (p.T234).

Methods: We used different CRISPR/Cas9 based genome editing strategies that enabled us to alter the murine *Nphs2* gene in a targeted manner. The endonuclease Cas9 forms a complex with a guide RNA which selectively binds to DNA and induces double strand breaks. Subsequently, repair mechanisms can either lead to random indel mutations via Non-Homologous End-Joining (NHEJ) or precise mutations via Homology-Directed Repair (HDR). By pronuclear injection we generated a mouse line that, in analogy to the human short isoform, lacks the entire exon 5. In an additional approach we eliminated a phosphorylation site within the PHB domain (p.T234I) by integrating a point mutation.

Results: Strikingly, *in vivo* data of compound-heterozygous animals show a rapid development of proteinuria and elevated retention parameters indicating a loss of kidney function. Histological examinations reveal Fokal-Segmental Glomerulosclerosis (FSGS), a hallmark of glomerular disease. Mice homozygous for the T234I allele do not display an overt phenotype and up to now we did not observe living offspring homozygous for the short isoform allele.

Conclusions: CRISPR/Cas9 technology allows us to create a fast and efficient pipeline to generate mutant alleles mimicking human genetic diseases and our pioneer project already provided novel insights into the pathogenesis of SRNS.

TH-PO069

Par6β Interaction with Ephrin-B1 at the Slit Diaphragm Could Be a Differential Diagnostic Marker of Nephrotic Syndrome: Interaction of the Par-Complex Molecules with Ephrin-B1/Nephrin in Podocyte Sayuri Takamura,[1,2] Yoshiyasu Fukusumi,[1] Ying Zhang,[1] Ichiei Narita,[2] Hiroshi Kawachi.[1] *[1]Dept. Cell Biology, Kidney Research Center, Niigata University, Niigata, Japan; [2]Division of Clinical Nephrology and Rheumatology, Niigata University, Niigata, Japan.*

Background: Par-complex, Par3/Par6/Cdc-42/aPKC is reported to be a component of the slit diaphragm (SD) and to play a role in maintaining the podocyte function. However, the precise differential roles of the Par-complex molecules in podocyte are not fully understood. We have reported that ephrin-B1 is a novel component of the SD. Although ephrin-B1 is reported to control cell-cell junctions of vascular endothelial cells through Par-complex, no studies on the interaction of the Par-complex molecules with ephrin-B1 at the SD have not been analyzed.

Methods: The expressions of the Par-complex molecules in podocyte were analyzed in the normal adult and developing glomeruli and in the rat nephrotic models of MCNS and FSGS by immunofluorescence, Western blot and RT-PCR. The interactions of Par3 and Par6 with ephrin-B1 and nephrin were analyzed by the IP analyses with glomerular lysates and HEK-293 transfected cells. The expressions of the Par-complex molecules in the podocyte-specific ephrin-B1 conditional KO (CKO) mouse were analyzed.

Results: mRNA expressions of Par6β and Par3 decreased from the early phase in the MCNS model and the decreases were detected when proteinuria peaked in both models. mRNA of Par6α increased in both models. Western blot analyses showed Par6β decreased in both models and Par3 decreased in the MCNS model. Immunostainings of Par3 and Par6β clearly decreased in both models. The decrease of Par6β was more evident in the FSGS model than in the MCNS model (IF score: 2.1 in FSGS model vs control 5.0). By contrast Par3 staining decreased more evidently in the MCNS model. The Par6β staining in normal glomeruli was co-localized with ephrin-B1, whereas no co-localization of Par3 and ephrin-B1 was observed. Whereas, some portions of the Par6β staining were apart from nephrin, and the Par3 staining was almost co-stained with nephrin. The IP study showed Par6β was interacted with ephrin-B1. The expression of Par6β was altered in the ephrin-B1 CKO mice.

Conclusions: Altered expressions of Par3 and Par6β are involved in the pathogenesis of both nephrotic models, and these molecules could be differential diagnostic markers of nephrotic syndrome. Not Par3 but Par6β is highly associated with ephrin-B1 at the SD.

TH-PO070

Soluble Form of VCAM-1 Ameliorates Podocyte Phenotypic Change by Plasma Membrane PTEN Recruitment Shun Manabe,[5,6] Kazuo Sakamoto,[4] Naoko Ito,[3] Nobuyuki Saga,[7] Kosaku Nitta,[2] Michio Nagata.[1] *[1]Department of Renal Pathology, University of Tsukuba, Tsukuba, Japan; [2]Medicine, Kidney center, Tokyo Women's Medical University, Shinjuku-ku, Japan; [3]Department of Renal Pathology, University of Tsukuba, Tsukuba, Japan; [4]Department of Renal Pathology, University of Tsukuba, Tsukuba, Japan; [5]Department of Renal Pathology, University of Tsukuba, Tsukuba, Japan; [6]Medicine, Kidney Center, Tokyo women's medical university, Shinjuku, Japan; [7]Department of Renal Pathology, University of Tsukuba, Tsukuba, Japan.*

Background: Podocyte stresses are the hallmark of glomerular diseases. The stresses cause podocyte phenotypic change and detachment. Podocyte has self-defense mechanism to resist and adapt against stresses by expressing several stress induced proteins. Vascular cell adhesion molecule-1 (VCAM-1) is a well-known stress induced protein that principally expressed in vascular endothelial cells. The VCAM-1 exerts physiological effects in membrane-bound form and soluble form. The membrane-bound form of VCAM-1 works as a pro-inflammatory molecule, whereas the soluble form of VCAM-1, that is generated by the cleavage of membrane-bound VCAM-1, antagonize the pro-inflammatory effect. However, the links between stress induced VCAM-1 and stress adaptation in podocyte remain largely unknown. Here, we aimed to investigate the role of VCAM-1 in podocyte stress adaptation.

Methods: We induced podocyte stress using NEP25 transgenic mice that develop podocyte specific injury by LMB2 toxin injection. We assessed glomerular VCAM-1 and protease expression eight days after the LMB2 injection. Immortalized podocyte with or without TGF-β1 stimulation was used to study the role of soluble VCAM-1.

Results: The glomerular staining of NEP25 mice indicated aberrant podocyte VCAM-1 expression. VCAM-1 and ADAM-13 (VCAM-1 cleavage enzyme) was simultaneously up regulated in isolated glomeruli that suggest the generation of soluble VCAM-1. Immortalized podocyte constitutively expressed integrin alpha 9 and beta 1, that works as receptor of soluble VCAM-1. The soluble VCAM-1 suppressed TGF-β1 induced podocyte migration and podocyte mRNA expression of EMT markers. The soluble VCAM-1 suppressed podocyte phenotypic change. Western blot analysis of Akt phosphorylation indicate soluble VCAM-1 to suppress the TGF-β1 induced Akt phosphorylation. Next, the treatment with soluble VCAM-1 recruited PTEN to plasma membrane by cell staining and western blot analysis of plasma membrane fraction. The soluble VCAM-1 suppressed PI3K/Akt pathway by plasma membrane PTEN recruitment.

Conclusions: We demonstrated stress induced podocyte VCAM-1 expression. The soluble form of VCAM-1 ameliorates podocyte phenotypic change by suppression PI3K-Akt pathway via plasma membrane PTEN recruitment. Podocyte VCAM-1 expression is one of the intrinsic stress adaptation mechanisms.

TH-PO071

Proteasomal or Lysosomal Degradation System Failures Have Different Consequences on Renal Cell Protein Homeostasis Wiebke Sachs,[2] Giorgia Di Lorenzo,[2] Marlies Sachs,[1] Sandra Pohl,[2] Catherine Meyer-Schwesinger.[3] *[1]UKE, Hamburg, Germany; [2]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3]University of Hamburg, Hamburg, Germany.*

Background: Protein degradation plays an important role in protein quality control and therefore in cell homeostasis. Two different degradation systems are responsible for clearance of disused or defective proteins, the ubiquitin-proteasome system (UPS) and the autophagy-lysosome system (ALS), which are interconnected and influence each other. The aim of the project is to understand the significance of the proteasomal and lysosomal degradation systems for proteostasis of renal cells such as podocytes.

Methods: In order to dissect the significance of the UPS and ALS for renal cells, Balb/C mice were treated with epoxomicin (proteasomal inhibitor) and leupeptin (lysosomal inhibitor) respectively over 4 days. Furthermore, mice with general lysosomal dysfunction due to defective targeting of all newly synthesized lysosomal enzymes (Mucolipidosis type II, MLII) were analyzed. The effects of altered proteasomal and lysosomal functions were investigated clinically, morphologically and biochemically.

Results: Epoxomicin treatment resulted in a successful proteasomal inhibition. Mice developed proteinuria with abnormal glomerular protein accumulations in the subepithelial space and in podocytes. The tubulointerstitium was morphologically inconspicuous. Leupeptin treatment successfully reduced lysosomal function. Mice did not develop proteinuria. Morphological analyses were significant for abnormal accumulations in tubular cells and the mesangium of glomeruli. MLII mice showed severe lysosomal dysfunction in combination with proteasomal dysfunction in glomeruli and tubulointerstitial cells. Clinically, MLII mice showed slight proteinuria. Morphologically, MLII mice exhibited accumulations of enlarged lysosomes in interstitial cells, in the mesangium of glomeruli and in podocytes, with abnormal protein accumulations in podocytes.

Conclusions: Based on our results we conclude that the UPS and ALS interplay in renal cells and are compensatory upregulated when the other is inhibited. Failure of the proteasomal degradation system has a greater impact on renal cell proteostasis and renal function that cannot be compensated by the lysosomal degradation system.

TH-PO072

Altered Hydrolysis Function of Ubiquitin C-Terminal Hydrolase L1 (UCH-L1) by Oxidative Modification Affects Protein Homeostasis in Podocytes Julia Reichelt,[6] Anna Reinicke,[2] Julia M. Fehlert,[4] Marlies Sachs,[1] Gunther Zahner,[5] Catherine Meyer-Schwesinger.[3] *[1]UKE, Hamburg, Germany; [2]University Clinic Eppendorf Hamburg, Hamburg, Germany; [3]University of Hamburg, Hamburg, Germany; [4]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [5]University hospital hamburg, Hamburg, Germany; [6]Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.*

Background: The ubiquitin proteasome system (UPS) represents the major system for protein degradation and is important for maintenance of protein homeostasis. Ubiquitin C-terminal hydrolase L1 (UCH-L1) regulates the pool of monoubiquitin required for tagging target proteins. The hydrolase-deficient mutant UCH-L1^{I93M} is highly associated with the development of neurodegenerative disease in humans and structurally resembles oxidative-modified UCH-L1. During podocyte injury UCH-L1 is *de novo* expressed resulting in proteasomal impairment and accumulation of polyubiquitinated proteins by unknown mechanisms. Aim of this project is to investigate the toxic gain of function of UCH-L1.

Methods: In order to dissect UCH-L1 hydrolysis versus UCH-L1 hydrolase-independent mechanisms transgenic mice with podocyte-specific overexpression of UCH-L1 wildtype or an enzymatic-deficient form UCH-L1^{I93M} were generated. The effects of altered degradation were investigated in cultured podocytes and in 5-7 week old naïve mice morphologically, clinically and biochemically. By use of PAS

and immunofluorescent stainings for podocyte-specific proteins and by measurement of proteinuria the glomerular integrity was characterized. To analyze the biochemical properties of UCH-L1 (such as expression levels or proteolytic capacity) quantitative real-time PCR, Western blot, activity assays and immunohistochemical stainings were executed.

Results: In cultured podocytes UCH-L1 expression was induced following oxidative stress. UCH-L1^{I93M} induced accumulations of polyubiquitinated as well as oxidative modified proteins in cultured podocytes and isolated glomeruli of transgenic mice. This conglomeration resulted from impaired proteasomal activity despite an enhanced proteasomal capacity. UCH-L1^{WT} mice on the other hand were characterized by increased proteasomal activity and a dedifferentiated phenotype. This was indicated by decreasing levels of podocyte-specific proteins nephrin and α-actinin-4 influenced by declining amount of WT-1 which seems to be regulated by the proteasome.

Conclusions: *De novo* expression of UCH-L1 in podocyte injury could mediate two effects: first, dedifferentiation of the podocyte and second, accumulation of polyubiquitinated proteins conditioned by defective enzymatic function.

TH-PO073

Lipoproteins Modulate Podocyte Damage and Proteinuria Yohei Tsuchida,[3] Jianyong Zhong,[3] Talat Alp Ikizler,[3] Agnes B. Fogo,[3] Taiji Matsusaka,[1] Haichun Yang,[2] Valentina Kon.[3] *[1]Tokai University School of Medicine, Isehara, Japan; [2]Vanderbilt University, Nashville, TN; [3]Vanderbilt University Medical Center, Nashville, TN.*

Background: Although high density lipoprotein (HDL) and its main protein, apolipoprotein AI (apoAI) have established benefits in various cell types, their effects on renal cells remain unclear. We investigated the consequences of exposing normal and damaged podocytes to normal apoAI/HDL (HDL^{Cont}), apoAI mimetic (L-4F), and HDL from patients with established CKD known to have dysfunctional (HDL^{CKD}).

Methods: *In vitro*, primary mouse podocytes were injured by puromycin (PAN) and cellular viability, proliferation, migration and cellular production of reactive oxygen species (ROS) assessed. *In vivo*, transgenic mice expressing human CD25 in podocytes that can be selectively injured by injection of immunotoxin were used as the proteinuric model. At injury, half the mice recieved L-4F x 2 wks. Urinary albumin-creatinine ratio (ACR) was measured and expression of podocyte markers, synaptopodin and WT1 assessed.

Results: PAN reduced podocyte viability, proliferation, migration and increased ROS production *in vitro*. Each of these perturbations was significantly lessened by apoAI and HDL^{Cont} but not HDL^{CKD} (Table). Critically, while maximum proteinuria was similar in treated and untreated mice, L-4F significantly accelerated ACR reduction and preserved podocyte expression of synaptopodin and WT1-positive cell density.

Conclusions: The results indicate that normal apoAI and HDL, but not dysfunctional HDL^{CKD} protect against podocyte damage. ApoAI mimetic provides *in vivo* benefits to podocytes culminating in reduced albuminuria. We suggest supplemental apoAI may be a novel candidate to lessen podocyte damage and proteinuria.

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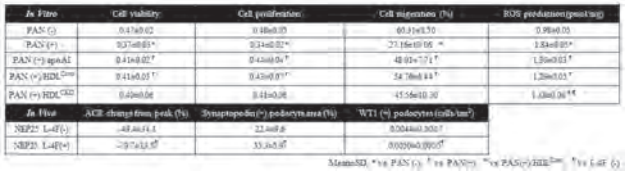


In Vitro	Cell viability	Cell proliferation	Cell migration (%)	ROS production/pixel*sec
PAN (-)	0.47±0.02	0.48±0.05	60.0±13.50	0.98±0.05
PAN (+)	0.37±0.03*	0.24±0.02*,	23.16±10.06 *,	1.83±0.05*,
PAN (+) apoAI	0.41±0.02†	0.44±0.04,†	48.03±7.71†	1.38±0.03†
PAN (+) HDL^{Cont}	0.41±0.03 †,	0.43±0.03†,	54.78±8.44 †,	1.28±0.03 †,
PAN (+) HDL^{CKD}	0.49±0.04	0.41±0.04	45.56±10.30	1.48±1.04 ††,

In Vivo	ACR change from peak (%)	Synaptopodin(+) podocyte area (%)	WT1 (+) podocytes (cells/mm^2)
NEP25 L-4F(-)	48.46±9.1	22.4±9.6	0.004±0.003*
NEP25 L-4F(+)	-39.7±13.8†	33.6±5.6†	0.020±0.005†

Mean±SD. *vs PAN (-). †vs PAN(+). ††vs PAN(+) HDL^{Cont}. ‡vs L-4F (-).

TH-PO074

Novel Role for Podocyte SIRPα and Pulmonary Surfactants in Minimal Change Disease Miguel A. Lanaspa, Ana Andres-hernando, Christina Cicerchi, Richard J. Johnson. *University of Colorado Denver, Aurora, CO.*

Background: Minimal change disease (MCD) is the most common cause of proteinuria and nephrotic syndrome in children whose primary cause is unknown. Recent studies identified podocyte CD80 as a key deleterious player in MCD. SIRPα is a receptor that regulates cell growth and differentiation by controlling phosphatases like PTPN11. SIRPα agonists include soluble surfactants SP-A and SP-D, produced by an anti-inflammatory response in the lungs. Here, we propose that MCD is associated with the elevation of serum SP-A and SP-D. that stimulate podocyte SIRPα to activate a signaling cascade mediated by PTPN11, nephrin dephosphorylation, CD80 expression and actin reorganization causing the activation of the podocye, loss of foot processes, proteinuria and nephrotic syndrome.

Methods: Serum, renal and urinary levels of surfactants are determined in MCD subjects in relapse and remission and correlated with albumin excretion and urinary CD80. To test the role of surfactants in podocyte activation, podocytes are exposed to serum from patients in relapse or in remission in which surfactants are added back and SIRPα, PTPN11 activity, nephrin phosphorylation, CD80 expression, actin re-organization and proteinuria is determined in these podocytes and in a mouse model of intranasal exposure to LPS.

Results: Human subjects with MCD in relapse but not remission and intranasal exposure to LPS in mice have elevated serum SP-A/D suggesting a crosstalk between lungs and kidneys. The stimulation of SIRPα in cultured podcytes with serum from MCD patients in relapse or by addition back of surfactants to serum of patients in remission releases PTPN11 from SIRPα to interact and dephosphorylate nephrin. This action results in NfkB activation and transcription of CD80 and pro-inflammatory cytokines, Similarly, nephrin loss results in loss of cell polarity that combined with the pro-inflammatory response re-organizes actin structure leading to the podocyte activation

Conclusions: Based on our data and the observation that 70% of the cases of MCD relapses are preceded by respiratory tract infections, we conclude that MCD is associated with the deregulation of podocyte SIRPα signaling leading to its activation characterized by PTPN11-mediated nephrin dephosphorylation, CD80 expression and actin reorganization ultimately causing loss of foot processes, proteinuria and nephrotic syndrome.

Funding: NIDDK Support

TH-PO075

Apoptosis Signal-Regulating Kinase 1 (ASK1) Inhibitor GS-444217 Mitigates Progression of HIV-Associated Nephropathy Kyung Lee,[1] Jin Xu,[1] Anqun Chen,[1] John T. Liles,[2] John C. He.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Gilead Sciences, Inc., Foster City, CA.*

Background: Renal inflammation is the major pathology in chronic kidney diseases, including HIV-associated nephropathy (HIVAN) that ultimately progresses to end stage renal disease. Activation of apoptosis signal-regulating kinase 1(ASK1) has been shown to drive renal inflammation, apoptosis, and fibrosis by downstream activation of MAPK kinases p38 and c-Jun N terminal kinase (JNK). Recent studies have shown that a potent selective ASK1 inhibitor substantially reduced renal p38MAPK activation and halted the disease progression in mouse models of diabetic kidney disease. Thus we sought to determine whether the blockade of ASK1 would also attenuate renal injury and impede the progression of HIVAN.

Methods: A well-established transgenic model of HIVAN, Tg26 mice on FVB/N background, was used for the study. Tg26 mice typically start to develop proteinuria and mild glomerulosclerosis (GS) at 4 weeks of age, moderate GS and mild tubulointerstitial injury by 8 weeks of age, and advanced GS and tubulointerstitial fibrosis, tubular atrophy and dilatation by 12 weeks of age. 4-week old Tg26 mice received either standard control chow or chow supplemented with selective ASK1 inhibitor GS-444217 (0.1% or 0.2% in chow). There were 7 to 10 mice in each group. Urine and blood were collected weekly to assess their kidney functions, and kidneys were harvested for analysis after 6 weeks of treatment.

Results: Administration of ASK1 inhibitor GS-444217 at both 0.1% and 0.2% concentrations significantly reduced p38 activation and albuminuria, and improved renal function in Tg26 mice after 6 weeks of treatment. Histological analysis revealed a marked reduction in GS and tubular damage in mice treated with GS-444217 compared to control Tg26 mice. GS-444217 administration increased the expression of differentiated podocytes markers and significantly curtailed podocyte loss in Tg26 mice. GS-444217 also reduced marker expressions of inflammation and apoptosis. Furthermore, GS-444217 administration resulted in significant reduction in collagen deposition and renal fibrosis.

Conclusions: Selective ASK1 inhibition reduced both glomerular and tubular injury and mitigated the progression of HIVAN in Tg26 mice, suggesting that blockade of ASK1 pathway is a potential therapeutic approach against progression of CKD, including HIVAN.

Funding: Commercial Support - Gilead Sciences, Inc., Foster City, CA

TH-PO076

Sox-9 Is a Marker for Activated Parietal Epithelial Cells and Potentially Involved in Podocyte Regeneration in a Rat Anti-GBM Nephritis Model Christoph Daniel,[2] Ania Prochnicki,[1] Jeffrey W. Pippin,[3] Stuart J. Shankland,[3] Kerstin U. Amann.[1] *[1]FAU Erlangen, Erlangen, Germany; [2]University Erlangen-Nürnberg, Erlangen, Germany; [3]University of Washington, Seattle, WA.*

Background: In healthy kidneys parietal epithelial cells (PECs) line out the Bowman's capsule. During renal disease PECs are thought to be involved in crescent formation as well as in podocyte regeneration. However, the activation of PECs during crescent formation and its potential role in scar formation or podocyte regeneration is not well understood. The aim of the study was to investigate a potential role of the transcription factor Sox9 as a marker of activated PECs in renal development, healthy adult kidneys and during anti-GBM nephritis.

Methods: Renal Sox9 expression was investigated in different species including mouse, rat, pig and humans using immunohistochemistry. Glomerular Sox9 expression was characterized in more detail in healthy (n=11) and anti-glomerular basement membrane (anti-GBM) nephritic (n=11) rats on days 7 and 14 after model induction as well as in newborn rats (n=3) using immunofluorescence double staining and confocal laser scanning microscopy.

Results: In glomeruli from healthy rat kidneys Sox9 expression is restricted to approx. 30% of PECs nuclei. During anti-GBM nephritis the number of glomerular Sox9-positive cells was increased 2-fold on day 7 and about 5-fold on day 14 after disease induction. In nephritic glomeruli Sox9 expression was not restricted to Bowman's capsule lining but was also found on cells of the glomerular tuft. Nearly all Sox9-positive cells also expressed the parietal epithelial marker Pax8 whereas Ox7-positive mesangial cells, CD31-positive endothelial cells and CD68-positive macrophages lacked Sox9 expression. While in healthy glomeruli only 4% of Sox9-positive cells showed proliferative activity, during anti-GBM nephritis more than 60% on day 7 and about 40% on day 14 of glomerular Sox9 positive cells also expressed PCNA, a proliferation marker. Of note, on day 7 0.8±0.9 and on day 14 1.6±1.3 cells per glomerular cross-section express both Sox9

and the podocyte marker podocalyxin. In addition, during glomerulogenesis Sox9 was expressed in parietal epithelial cells as well as podocytes.

Conclusions: Our data are in line with Sox9 being a marker of activated parietal epithelial cells and may further point to a potential role in podocyte regeneration.

Funding: Government Support - Non-U.S.

TH-PO077

Morphometric Quantitation of Parietal Epithelial Cells in Human Kidneys Christopher L. O'Connor,[1] Mohamed A. Elshayeb,[1] Jeffrey B. Hodgin,[3] Roger C. Wiggins,[2] Markus Bitzer.[1] *[1]University of Michigan, Ann Arbor, MI; [2]University of Michigan Health System, Ann Arbor, MI; [3]Pathology, University of Michigan, Ann Arbor, MI.*

Background: Parietal epithelial cells (PECs) play a key role in glomerulosclerosis. We therefore developed a method for quantitation of PECs usable in routine FFPE archival histologic sections. Initial data are reported.

Methods: PECs were identified by anatomic position, lining the inner aspect of Bowman's Capsule (BC), and positive immune-peroxidase nuclear staining for PAX8. The morphometric method used principles previously reported for podocyte quantitation in which observed PEC nuclear number per glomerular tuft profile is corrected according to nuclear size, shape and section thickness (Venkatareddy et al. JASN 2014). 600 glomerular profiles were assessed in 12 normal human kidneys obtained at nephrectomy (mean age: 64.9, range: 46-82y). Glomerular and tubule-interstitial parameters were assessed through quantitative computer-assisted image analysis on 50 glomeruli per case. Qualitative glomerular characteristics were assessed in all glomeruli (mean 198 glomeruli per sample, range 71-392). Quantitative morphometric parameters were evaluated in 50 randomly selected glomeruli per sample.

Results: PECs identified as cells lining the inner aspect of BC were >99% PAX8 positive. In contrast <5% of glomerular tufts contained PAX8-positive nuclei. In the normal human kidney sample tested the BC surface area was 159 (range 110-216) $x10^3 \mu m^2$). The number of PECs per glomerular tuft (total BC surface area) was 407 (range 70-722). The estimated average PECs per area of BC was 25.3 (range 5.2-43.6) PECS/$10^6 \mu m^2$. Average PEC cell area was 578μm^2 (range 247-2103 μm^2). PEC density correlated with podocyte nuclear density (p=0.02; r=0.64), mean podocyte volume (p=0.001; r=-0.82), podocytes per glomerulus (p=0.01; r=0.69), % of normal glomeruli (p=0.01, r=0.70), fractional interstitial area (p=0.002; r=-0.78), number of globally (p=0.03; r=-0.55) and segmentally sclerotic glomeruli (p=0.004; r=-0.76), and eGFR (p=0.05; r=0.75).

Conclusions: We report a method for quantitatively evaluating PECs. PEC number per glomerulus, density and estimated cell size varies substantially between individual samples. Furthermore, these PEC parameters significantly correlate with both podocyte parameters and clinical phenotype in the small sample evaluated. Additional samples from our human kidney biobank (n>150) will be used to confirm and extend these data.

TH-PO078

Microecological Imbalance of Intestinal Microflora Activates Renal Renin-Angiotensin System to Contribute to the Progression of Early Diabetic Nephropathy Chenchen Lu,[2,1] Kun ling Ma,[1] Yang Zhang,[1] Gui hua Wang,[1] Zebo Hu,[1] Peipei Chen,[1] Jian Lu.[1] *[1]Zhongda Hospital, Southeast University Medical School, Nanjing City, China; [2]Institute of Nephrology, Zhong Da Hospital, Nan Jing City, China.*

Background: It is well-known that activated renal rennin-angiotensin (RAS) plays a key role in the development of early diabetic nephropathy (DN). However, the initiating factors and potential mechanisms led to RAS activation have not been fully elucidated. This study aimed to investigate the underlying mechanisms of how abnormal intestinal microenvironment activates RAS to contribute to early renal injuries of DN.

Methods: Streptozotocin-induced diabetic rat model was randomly divided into three groups: Control group, diabetic group (DM), and diabetic+antibiotics (DM+AB) group. The rats of DM+AB group were fed for 8 weeks with regular chow and antibiotic mixed liquor (ampicillin 1g/L + vancomycin 0.5g/L + neomycin 1g/L + amphotericin B 0.1g/L). Gene sequencing of intestinal microflora was carried out using 16S-rDNA pyrosequencing technique. The morphological changes to the renal pathology and ultra-microstructures were checked by pathological staining and electron microscopy. The plasma RAS components were determined by radioimmunoassay. The protein expressions of RAS components in the kidneys were determined by immunohistochemical staining and Western blot.

Results: Compared with control group, DM group showed with abnormal intestinal microflora, which significantly increase the production of acetate in the plasma. There were increased ACR, thickened glomerular basement membrane, podocyte foot process effacement in kidneys of DM group compared with the controls. The plasma levels of angiotensin II and the protein levels of angiotensinogen, angiotensin II, renin, angiotensin-converting enzyme, and angiotensin II type 1 receptor in the kidneys of DM group were significantly increased compared to the controls, which were positively associated with kidney injuries of DM group. However, in DM+AB group, after intestinal microflora were completely killed by antibiotics, kidney damage and RAS activation were weakened accordingly compared with the DM group.

Conclusions: These findings suggest that microecological imbalance of intestinal microflora might be a potential mechanism for the progression of early DN, which leads to kidney injuries via the RAS activation.

TH-PO079

Glomerular Enhancer of Zeste Homolog-2 (EZH2) Histone Methyltransferase Reduces Glomerular Endothelial Glycocalyx during Diabetic Nephropathy by Regulating Hyaluronan Synthesis Marloes Sol,[2] Jiedong Qiu,[3] Johan Van der vlag,[1] Jacob van den Born,[4] Benito Yard,[3] Jan-luuk Hillebrands,[2] Jan A. Kamps,[2] Guido Krenning.[2] *[1]Dept. of Nephrology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; [2]Dept. of Pathology and Medical Biology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; [3]Dept. of Nephrology, Endocrinology and Rheumatology, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany; [4]Dept. Internal Medicine, Div. Nephrology, University Medical Center Groningen, University of Groningen, Groningen, Netherlands.*

Background: Diabetic nephropathy (DN) is the leading cause of end-stage renal failure worldwide. The glomerular endothelial glycocalyx is the first barrier that prevents leakage of circulating proteins. Injury to the glycocalyx evokes proteinuria and kidney failure. The polycomb group methyltransferase Enhancer of Zeste Homolog 2 (EZH2) inhibits expression of its target genes through methylation of lysine 27 on histone 3 (H3K27Me3). We recently performed a target screen for genes involved in glycocalyx turnover, which indicated that EZH2 inhibits glycocalyx synthesis in glomerular endothelial cells. We hypothesized that EZH2 activity is increased in the glomerular endothelium during DN thereby reducing glycocalyx synthesis.

Methods: H3K27me3 was analyzed in glomerular endothelial cells by immunofluorescence in $BTBR^{ob/ob}$ mice, a mouse model for DN. Glycocalyx in these mice was measured by the binding of fluorescently-labeled wheat germ agglutinin. In glomerular endothelial cells, EZH2 was silenced by RNAi. Gene expression was assessed by Quantitative Real-time PCR.

Results: H3K27me3 in glomerular endothelial cells was increased 1.5-fold compared to non-diabetic mice (p=0.026). Albumin-creatinine ratios of $BTBR^{ob/ob}$ mice correlated with the increase in H3K27me3 (p=0.044; r^2=0.674). A 2-fold loss of glomerular glycocalyx was observed in $BTBR^{ob/ob}$ mice (p=0.002). Silencing of EZH2 in glomerular endothelial cells led to a decrease in H3K27me3 and an 8-fold increase in the hyaluronan synthesizing enzyme HAS1 (p<0.001). ENCODE database analysis revealed a binding site for EZH2 in the HAS1 gene, suggesting that HAS1 is a direct target of EZH2. Interestingly, the hyaluronan degrading enzymes, HYAL1 (p=0.002), HYAL2 (p=0.015), and HYAL3 (p=0.014) were all decreased upon knockdown of EZH2.

Conclusions: In conclusion, our data suggests that EZH2-mediated epigenetic changes reduce endothelial glycocalyx via reduction of hyaluronan in DN.

TH-PO080

Depletion of Gprc5a Promotes Development of Diabetic Nephropathy Jaakko Patrakka,[2] Mark Lal,[1] Sonia Zambrano Sevilla.[3] *[1]AstraZeneca, Gothenburg, Sweden; [2]Karolinska Institutet, Huddinge, Sweden; [3]None, Seville, Spain.*

Background: Renal glomeruli are the primary target of injury in diabetic nephropathy (DN). In the glomerulus, damage to podocyte cells plays a critical role in the disease progression. Transforming growth factor beta (TGF-β) signaling is involved in the pathogenesis but mechanisms regulating this pathway in podocytes are poorly understood. G-protein coupled receptors (GPCRs) have been the most successful protein class for drug discovery as 20-40% of currently clinically approved drugs are targeting them. In this study, we investigated glomerular GPCRs in DN with the aim of identifying novel molecular targets for pharmaceutical intervention.

Methods:

Results: We performed high throughput molecular profiling of GPCRs in human glomeruli and identified an orphan GPCR, Gprc5a, as a novel highly podocyte-specific molecule whose expression was significantly down-regulated in patients with DN. Inactivation of Gprc5a in mouse resulted in thickening of the glomerular basement membrane and activation of mesangial cells, which are two hallmark features of DN in humans. Gprc5a-deficient animals were susceptible to diabetic glomerular damage as demonstrated by higher albuminuria and more severe histological changes after induction of diabetes with streptozotocin. Mechanistically, we show that Gprc5a modulates TGF-β signaling pathway in podocytes through activation of epidermal growth factor receptor (EGFR).

Conclusions: We conclude that depletion of Gprc5a promotes the progression of DN. Gprc5a can provide us a possibility to develop pharmaceutical tools to manipulate pathogenic signaling pathways in a podocyte-specific manner.

Funding: Commercial Support - AstraZeneca, Private Foundation Support, Government Support - Non-U.S.

TH-PO081

Palovarotene, Selective Retinoic Receptor-γ Agonist, Inhibited Both BMP4 and TGF-β Signaling Pathways in Diabetic Nephropathy Yui Fujita, Tatsuya Tominaga, Masanori Tamaki, Taichi Murakami, Seiji Kishi, Kojiro Nagai, Hideharu Abe, Toshio Doi. *Tokushima University, Graduate School of Biomedical Sciences, Tokushima, Japan.*

Background: We have reported that the BMP4 / Smad1 signaling pathway play a key role for development of diabetic nephropathy (DN). In recent years, retinoic acid receptor

agonists have been focused as therapeutic targets for progressive fibrosis. In this study, we examined the effect of palovarotene, selective retinoic acid receptor-γ agonist, on DN.

Methods: 12-15 weeks old ICR mice were rendered diabetic by streptozotocin (STZ). Palovarotene was administered 2 times per week intraperitoneally at 60 μg / kg from 4 weeks after STZ injection. Histological analysis was performed at 12 weeks after administration of palovarotene. BMP4 and TGF-βsignaling pathways were analyzed with *in vitro* mouse mesangial cells to reveal the mechanism of palovarotene treatment.

Results: Diabetic mice showed significant extracellular matrix expansion associated with increased expressions of phosphorylated (p) Smad1 and type 4 collagen (Col4). The administration of palovarotene in DN reduced the expressions of pSmad1 and Col4 as well as mesangial matrix expansion. Phosphorylated Smad2/3 were increased in DN. Palovarotene administration decreased pSmad2/3. In cultured mesangial cells, the expressions of BMP4, pSmad1 and Col4 were increased by AGE stimulation. Palovarotene suppressed the increased expressions of BMP4 and Col4 under AGE stimulation. In addition, palovarotene decreased pSmad1 and pSmad2/3 signaling under BMP4 or TGF-β treatment.

Conclusions: Palovarotene has regulated the downstream molecules of the BMP type I receptors, and inhibited pSmad1 and reduced expression of Col4 in mesangial cells. The study has unveiled that palovarotene exerts the suppressive effect for both BMP4 and TGF-β signaling pathways. The findings suggest that the chemicals that targeted a retinoic acid receptor are useful as new therapy for DN.

TH-PO082

Plasminogen Activator Inhibitor-1 (PAI-1) Modulates Parietal Epithelial Cell (PEC) Activation and Migration after Podocyte Injury Xin Li,[1] Marcus J. Moeller,[3] Taiji Matsusaka,[2] Haichun Yang,[4] Agnes B. Fogo.[4] *[1]The Medicine College of Shanghai JiaoTong University, Shanghai, China; [2]Tokai University School of Medicine, Isehara, Japan; [3]University of Aachen, RWTH, Aachen, Germany; [4]Vanderbilt University Medical Center, Nashville, TN.*

Background: Parietal epithelial cells (PECs) can migrate on to the glomerular tuft and serve as either progenitor cells to replace podocytes or profibrotic cells to secret matrix in response to injury. Claudin-1 is expressed on all PECs, while CD44 is expressed on activated PECs. PAI-1 affects matrix turnover, cell migration and mediates renal fibrosis. After glomerular injury, PAI-1 expression on PECs increases. We aimed to study effects of PAI-1 on PECs migration, activation and transdifferentiation after podocyte injury.

Methods: NEP25 mice express human CD25 only on podocyte, and podocyte injury is induced by exogenous immunotoxin (LMB2). By mating *NEP25/PAI-1*^{loxP} with *PEC-rtTA/ PAI-1*^{loxP} transgenic mice, we generated inducible PEC specific PAI-1 knockdown mice (PAI-1 KD, n=8) and control (WT, n=10). All mice underwent doxycycline induction at 9 weeks old followed by LMB2 injection at 10 weeks, and were sacrificed 10 days later.

Results: LMB2 induced similar albuminuria and segmental glomerular sclerosis in WT and PAI-1 KD mice. Podocyte density, measured by WT-1 staining, was similar in the two groups (WT 3.9±0.8 vs PAI-1 KD 3.7±0.5 /10^4 um^2), but synaptopodin expression was higher in PAI-1 KD (18.7 ±16.7%) than WT (5.3±2.4%, P<0.05). PAI-1 KD induced more CD44+ PECs on glomerular tuft (2.8±0.8 vs WT 1.3±1.2%, P<0.05), while WT showed more claudin-1+ cells on the tuft (4.14±1.57% vs. 2.51±0.87%, WT vs. PECs PAI-1 KD *P*<0.05). By double staining, we assessed the proportion of PECs expresses nephrin, a podocyte differentiation marker, finding 14.1±4.4% of claudin-1+ cells also expressing nephrin in WT, similar in PAI-1 KD (11.0±4.0%, pNS). CD44+ cells expressing nephrin were also similar in the two groups (WT 17.7±9.2 vs. PAI KD 13.0±5.9%, pNS).

Conclusions: We conclude that knockdown of PAI-1 increased the presence of activated PEC on the tuft and preserved podocyte differentiation, but does not affect PECs transdifferentiation to podocyte.

Funding: NIDDK Support

TH-PO083

Epigenetics-Induced Down-Regulation of MicroRNA (miR)193a Determines APOL1 Expression in Parietal Epithelial Cells Vinod Kumar,[4] Xiqian Lan,[1] Seyedeh Shadafarin Marashi Shoshtari,[7] Sheetal Chowdhary,[3] Manali Bhooplapur,[2] Catherine Meyer-Schwesinger,[8] Ashwani Malhotra,[9] Karl Skorecki,[6] Pravin C. Singhal.[5] *[1]Feinstein Institute for Medical Research, Great Neck, NY; [2]Feinstein Institute for medical research, Dix Hills, NY; [3]Feinstein Institute of Medical Research, New Hyde Park, NY; [4]Immunology, Fienstine Institute for Medical Research, New York, NY; [5]North Shore LIJ Health System, Great Neck, NY; [6]Rambam Health Care Campus, Haifa, Israel; [7]The Feinstein Institute for Medical Research, Manhasset, NY; [8]University of Hamburg, Hamburg, Germany; [9]Immunolgy and Inflammation, Feinstein Inst. Med research and NSLIJ, Manhasset, NY.*

Background: APOL1 is expressed in kidneys of some primate species, including humans. Its trypanolytic effect has been well studied. Podocytes express APOL1 and overexpression of APOL1G1 and G2 has been demonstrated to be cytotoxic to podocytes, both *in vitro* and *in vivo* studies. Parietal epithelial cells (PECs) do not express APOL1; however, HIV has the potential to induce APOL1 expression in PECs (submitted abstract ASN, 2017). We hypothesize an epigenetic mechanism for the induction of APOL1 in PECs.

Methods: Immortalized human PECs (at 33°C) were transduced with either vector (V) or HIV (NL4-3) (n=4); PECs were incubated in media containing variable concentration of IFN-γ (0, 5, 10, and 20 nM) for 48 hours (n=4); PECs were treated with either buffer, azacytidine (5 μM, a demethylating agent), or SAHA (10μM, an histone deacetylation inhibitor) for 48 Hours (n=4). Protein blots were probed for APOL1, DNMT 1-3, HDAC 1-4, H3K27me3, H3K4me3, H3K8/9ac, and reprobed for actin. cDNAs were amplified for DNMT1-4, HDAC1-4, and *APOL1.* RNAs were assayed for miR193a. To confirm histone acetylation at miR193a gene promoter, ChiP assay was carried out. To confirm binding of miR193a to *APOL1* gene promoter, RIP-ChIP assay was performed. To measure methylation of CpG islands at miR193a gene, Bisulphite sequencing was carried out in PECVs and PECHIVs.

Results: Both HIV and IFN-γ induced APOL1 expression in PECs. PECHIV and IFN-γ-treated PECs showed 2 to 2.5-fold decrease in miR193a expressions, respectively; on the other hand, miR193a knockout PECs displayed induction of APOL1expression in PECs. Both azacytidine and SAHA not only induced APOL1 expression but also decreased (3-fold) miR193a levels in PECs. Both HIV and IFN-γ-treated PECs displayed enhanced DNMT3b, HDAC4, HK4me3, and H3K27me3 but down-regulation of H3K8/9ac expressions. RIP-ChIP assay confirmed binding of miR193a to the APOL1 gene promoter. Bisulphite sequencing displayed enhanced methylation of CpG islands at miR193a gene in PECHIV. These findings suggest that HIV down regulates miR93a through methylation at CpG islands and at histone 3 lysine 27 residues.

Conclusions: HIV induces APOL1 expression in PECs through down-regulation of miR193a via epigenetic mechanisms.

Funding: NIDDK Support

TH-PO084

VDR Agonist (VDA) Facilitates Transition of Parietal Epithelial Cells (PECs) to Podocytes (PDS) Molecular Phenotype through Induction of APOL1 Vinod Kumar,[3] Xiqian Lan,[1] Seyedeh Shadafarin Marashi Shoshtari,[6] Rukhsana Aslam,[2] Kamesh R. Ayasolla,[1] Catherine Meyer-Schwesinger,[7] Ashwani Malhotra,[8] Karl Skorecki,[5] Pravin C. Singhal.[4] *[1]Feinstein Institute for Medical Research, Great Neck, NY; [2]Feinstein Institute for medical research, Glenoaks, NY; [3]Immunolgy and Inflammation, Fienstine Institute for Medical Research, New York, NY; [4]North Shore LIJ Health System, Great Neck, NY; [5]Rambam Health Care Campus, Haifa, Israel; [6]The Feinstein Institute for Medical Research, Manhasset, NY; [7]University of Hamburg, Hamburg, Germany; [8]Immunolgy and Inflammation, Feinstein Inst.Med research and NSLIJ, Manhasset, NY.*

Background: APOL1 is expressed intracellularly and also a minor component of circulating lipid-rich trypanolytic multiprotein complexes in certain primate species including humans. However, the role of kidney cell, both i*n vitro* and *in vivo* studies. We hypothesize that VDA is an inducer of APOL1 in PECs and plays an important role in the maintenance of PD homeostasis.

Methods: Immortalized human PECs proliferate at 33°C but enter into a transition mode (differentiated to PDs) after incubation in special media and collagen/fibronectin substrate at 37°C. PECs and differentiated PECs molecular phenotype (WT1 and podocalyxin vs. PAX2 and Claudin 1) was characterized. To determine the effect of VDA on the entry of PECs transition at 33°C, PECs were incubated in media containing either buffer or VDA (EB1089, 10 nM) for 48 hours at 33°C (n=4). TO evaluate the dose response effect, PECs were incubated in media containing different concentratios of VDA (0, 1, 10, 25, 50 and 100 nM) for 48 hours at 33°C (n=4). To determine the effect of other APOL1 stimulants, PECs were incubated in media containing variable concentrations of IFN-Y (0, 5, 10, and 20 nM) for 48 hours at 33°C. To examine a causal relationship, PECs were transfected with either control of miR193a plasmids/siRNA APOL1, followed by treatment with/without VDA (10 nM) or IFN-y (10 nm). Proteins and RNAs were extracted. Protein blots were probed for APOL1 and reprobed for WT1, podocalyxin, podocin, PAX2, Claudin 1, and GAPDH. cDNAs were probed for *APOL1, WT1, and podocalyxin*. RNAs were assayed for microRNA193a.

Results: VDA induced APOL1 protein expression in PECs in a dose dependent manner. IFN-y also induced APOL1 expression in PECs. Both VDA and IFN-γ also enhanced (2 to 3 fold) transcription of APOL1 in PECs. VDA-induced APOL1 expression was associated with down regulation of miR193a (2.3 fold), PAX2 (1.8 fold) and enhanced expression of WT1 (2.2 fold), podocalyxin (2.5 fold), and podocin (1.8 fold) (both mRNA and protein levels). However, the effects of VDA were partially reversed both by increasing miR193a or silencing APOL1 expressions.

Conclusions: VDA stimulates PECs transition through induction of APOL1 and down regulation of miR193a.

Funding: NIDDK Support

TH-PO085

HIV Activates Epithelial Mesenchymal Transition (EMT) and Mammalian Target of Rapamycin (mTOR) Pathway in Parietal Epithelial Cells (PECs) via Down Regulation of MicroRNA193a Vinod Kumar,[4] Xiqian Lan,[1] Rukhsana Aslam,[2] Ali Hussain,[3] Seyedeh Shadafarin Marashi Shoshtari,[6] Manali Bhooplapur,[2] Sheetal Chowdhary,[3] Catherine Meyer-Schwesinger,[7] Ashwani Malhotra,[8] Pravin C. Singhal.[5] *[1]Feinstein Institute for Medical Research, Great Neck, NY; [2]Feinstein Institute for medical research, Glenoaks, NY; [3]Feinstein Institute of Medical Research, New York, NY; [4]Immunolgy and Inflammation, Fienstine Institute for Medical Research, New York, NY; [5]North Shore LIJ Health System, Great Neck, NY; [6]The Feinstein Institute for Medical Research, Manhasset, NY; [7]University of Hamburg, Hamburg, Germany; [8]Immunolgy and Inflammation, Feinstein Inst.Med research and NSLIJ, Manhasset, NY.*

Background: Micro-RNA (miR) 193a has been considered to be a tumor suppressor gene and its down regulation has been reported to stimulate EMT and mTOR pathways in cancer cells. HIV-associated nephropathy is characterized by collapsing variant of focal segmental glomerulosclerosis; in this glomerular phentype, proliferating cells in Bowman's space are considered to be of PEC lineage; however, the involved mechanism for PECs proliferation in HIV milieu is not clear. We asked whether HIV was inducing PECs proliferation through down regulation of miR193a.

Methods: Vector (PECV) - and HIV (NL4-3; PECHIV)-transduced human immortalized PECs were growth arrested and then incubated media (containing 1% serum) for 48 hours (n=4). In another set of experiments, PECs were incubated in media containing either buffer (control) or a microRNA193a inhibitor (25 nM) for 48 hours (n=4). To examine a causal relationship, PECV and PECHIV were transfected with either control or miR193a plasmids (n=4). *In vivo* studies, kidneys were harvested from 4- week old control (FVB/N) and HIV-transgenic (Tg26) mice. Proteins and RNAs were extracted. Protein blots were probed for EMT (α-SMA, SNAIL, and fibronectin), mTOR (p-mTOR, p-P70S6k, p-4EBP, and p-eEF)) markers and reprobed for actin. RNAs were assayed for miR193a. Renal cortical sections were immunolabeled for α-SMA, SNAIL, and p-mTOR.

Results: PECHIV and renal tissues of HIVAN mice displayed enhanced (P<0.05 vs. PECV/FVB/N) expression of EMT markers including alpha-SMA, fibronectin, and SNAIL. Similarly, PECHIV and renal tissues of HIVAN mice showed enhanced (P<0.05 vs. PECV/FVB/N) expression of p-mTOR, p-P70S6K, and p-4EBP and down regulation (P<0.05 vs.PECV/FVB/N) of p-eEF, indicating activation of mTOR pathway. PECHIV and renal tissues of HIVAN mice displayed 4 fold decreases in miR193a levels when compared to respective controls. Inhibition of miR193a in PECs, stimulated EMT and mTOR pathways. On the other hand, overexpression of miR193a in PECHIV attenuated activation of EMT and mTOR pathways.

Conclusions: HIV induces activation of growth pathways in PECs. This effect of HIV is mediated through down regulation of miR193a in PECs.

Funding: NIDDK Support

TH-PO086

Ultrastructural Descriptors for Clinically Relevant Categorization of MCD/FSGS NEPTUNE Patients Jarcy Zee,[3] Q Liu,[3] A R. Smith,[3] Carmen Avila-Casado,[2] Jeffrey B. Hodgin,[6] Lawrence B. Holzman,[1] Brenda W. Gillespie,[6] L. Barisoni,[5] Virginie Royal.[4] *[1]University of Pennsylvania, Philadelphia, PA; [2]University of Toronto, Toronto, ON, Canada; [3]Arbor Research Collaborative for Health, Ann Arbor, MI; [4]Université de Montréal, Montréal, QC, Canada; [5]University of Miami, Miami, FL; [6]University of Michigan, Ann Arbor, MI.*

Background: Ultrastructural features of renal biopsies are rarely used in conventional classification systems, and their reporting is often limited to a few parameters. The aim of this study was to investigate the prognostic value of 12 electron microscopy (EM) descriptors from the NEPTUNE Digital Pathology Scoring System (NDPSS).

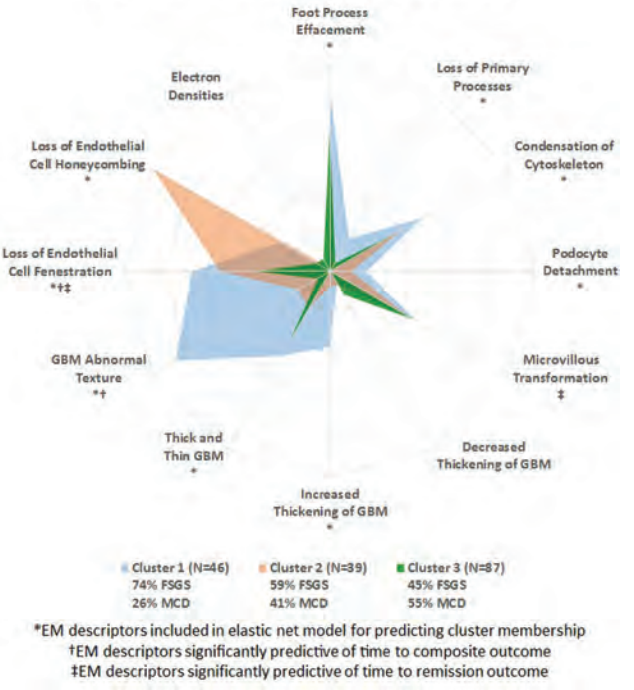
Methods: Study pathologists scored digital EM images from 172 MCD/FSGS patients using the NDPSS. We performed hierarchical clustering of patients based on EM descriptors. We compared demographics, clinical characteristics, time to proteinuria remission, and time to the composite of 40% reduction in eGFR or ESRD across the clusters. We used penalized multinomial regression with cross-validation to test descriptors driving cluster membership and Cox proportional hazards models to link EM descriptors to clinical outcomes.

Results: Of the 3 clusters found [figure], cluster 1 patients had the most EM damage, were older (p=0.018), had lower eGFR (p<0.001) and higher urine protein creatinine ratio (p=0.029) at baseline, had higher rates of the composite outcome (p=0.005) and lowest rates of remission (p=0.033). Clusters 2 and 3 did not have significantly different demographics, baseline clinical characteristics, or outcomes. Microvillous transformation was not predictive of clusters, but was independently predictive of remission (p=0.001).

Conclusions: The NDPSS descriptor-based assessment of EM uncovered the significance of ultrastructural parameters usually under-reported in clinical practice. EM descriptor-based patient clusters predicted remission and progression outcomes, reflecting quantifiable transitional vs. permanent damage.

Funding: NIDDK Support

Figure: Mean EM descriptor values in each of three clusters



*EM descriptors included in elastic net model for predicting cluster membership
†EM descriptors significantly predictive of time to composite outcome
‡EM descriptors significantly predictive of time to remission outcome

TH-PO087

Laser Capture Microdissection and Liquid Chromatography Tandem-Mass Spectrometry for Small Amounts of Formalin-Fixed Paraffin Embedded Kidney Tissue Sophie I. Nagelkerken,[1] George Janssen,[2] Kimberley Veraar,[1] Peter Van veelen,[2] H. J. Baelde,[1] Jan A. Bruijn,[1] Ingeborg M. Bajema.[1] *[1]Department of Pathology, Leiden University Medical Center, Leiden, Netherlands; [2]Center for Proteomics and Metabolomics, Leiden University Medical Center, Leiden, Netherlands.*

Background: Liquid chromatography tandem-mass spectrometry (LC-MS/MS) is a sensitive and specific technique for in depth protein identification but diagnostic kidney material is scarce, limiting the number of protein identifications. Only a few studies have used this technique for protein identification in formalin fixed paraffin embedded (FFPE) glomerular material and only one used a practical amount that can be used for diagnostic biopsies. Therefore, we optimized a work-flow of laser capture microdissection (LCM) of glomeruli, followed by LC-MS/MS on FFPE tissue for a minimal amount of tissue with a maximum protein yield.

Methods: One FFPE tissue block of a normal human kidney was utilised. Cross-sections of randomly selected kidney and glomeruli were collected from 6 µm sections, mounted on a 1.0 PEN membrane, using LCM. Protein extraction and digestion was performed using filter aided sample preparation (FASP) with polyethylene glycol (PEG) as a carrier, adapted from previously described methods for microdissected colon tissue. Samples were purified using mixed anion exchange solid phase extraction (MAX-SPE) and analysed using LC-MS/MS.

Results: Using the PEG-FASP protocol, we established the optimum amount of tissue to be 3 nl, based on 605 protein identifications, compared to 216 and 693 identifications in 1 and 10 nl tissue respectively. In a reproduction analysis of 5 experiments, using both random kidney and glomerular tissue, an average of 457 and 228 proteins were identified respectively. The method was able to distinguish glomerular samples from random kidney samples, as demonstrated by differentially identified proteins and clustering of glomerular and random kidney samples.

Conclusions: The relative number of proteins detected was comparable to or higher than reported in previous studies using FFPE glomerular tissue. The presented work-flow expands the potential for novel protein identification in glomerular diseases, while keeping the amount of tissue small enough for diagnostic practicality. Therefore, the combination of LCM followed by LC-MS/MS, using PEG-FASP and MAX-SPE for sample preparation, is a suitable and promising technique for diagnostic applications, especially when specific proteins are overexpressed or abundant within glomeruli.

Funding: Private Foundation Support

TH-PO088

Identification of Glomeruli for Improved Enumeration in Renal Biopsies Using Convolutional Neural Networks and Deep Learning Jonathan Street,[2] Tiffany R. Bellomo,[2] Erik H. Koritzinsky,[2] Stephen M. Hewitt,[1] Peter S. Yuen,[2] Robert A. Star.[2] *[1]National Cancer Institute, Bethesda, AL; [2]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD.*

Background: Accurate detection and counting of glomeruli in renal biopsies is important to assess biopsy adequacy, and for diagnostic accuracy (for example, the percentage of sclerotic glomeruli). A recent evaluation indicates that traditional methods can under-count glomeruli by ~50% when compared to more labor-intensive annotation methods. In recent years, deep learning has significantly advanced in a variety of tasks including image recognition, classification, and segmentation. To improve the accuracy of glomerular enumeration in renal biopsy evaluation, we are developing a convolutional neural network/deep learning model to locate glomeruli.

Methods: Twenty-two biopsy sections stained with hematoxylin and eosin were imaged using whole slide scanners (Aperio and Hamamatsu) for use in training and validation of the model. A custom application was developed to record the position of glomeruli in each biopsy with masks processed as geometries (boundaries stored rather than each pixel). This approach minimized file sizes and supported complex operations. Training and validation was conducted at the NIH high-performance computing facility employing multiple NVidia K20 GPU equipped nodes. The keras software package was used to define and train the neural network. Data augmentation and a modestly sized network (3 convolutional layers, a single hidden fully connected layer and an output layer) were used to optimize performance without overfitting the dataset.

Results: The accuracy of the neural network model was 91%. The model performance was robust to changes in stain intensity and the scanner used for imaging. Importantly, manual review of disagreements revealed errors in annotation (the model correctly identified glomeruli that had been missed by the human annotator).

Conclusions: Deep learning techniques can be utilized to accurately identify glomeruli in renal biopsies and can be scaled to handle the large images generated by whole slide scans. A convolutional neural network may help to improve the accuracy of glomeruli localization and enumeration, without the need for human intervention. This model could be leveraged for classification of glomerular morphology.

Funding: NIDDK Support

TH-PO089

Body Composition Parameters Do Not Contribute to Glomerular Hypertrophy Satoshi Aoki, Tasuku Nagasawa. *Nephrology, Japanese Red Cross Ishinomaki Hospital, Miyagi, Japan.*

Background: Glomerular hypertrophy is often observed in diabetic nephropathy and obesity-related glomerulopathy. A correlation between body-mass indices (BMI) and glomerulomegaly has been reported. However, specific contributing factors remain unknown. The aim of this study is to investigate relations between glomerular hypertrophy and clinical parameters.

Methods: We measured glomerular major axis length (GMAL) of 157 patients who underwent percutaneous renal biopsy from July 2013 to July 2015 in Japanese Red Cross Ishinomaki Hospital. Body composition parameters, subcutaneous fat area (cm^2), visceral fat area (cm^2), psoas major area (mm^2/m^2), and muscles of back proper area (mm^2/m^2) were calculated based on CT images. We performed a multiple regression analysis with GMAL as the dependent variable.

Results: 157 cases were separated into 4 groups depending on the primary diseases: diabetic nephropathy (DN, n = 25), focal segmental glomerular sclerosis (FSGS, n = 20), hypertensive nephrosclerosis (HNS, n = 36) and the others (n = 76). Hypertrophic glomeruli (GMAL ≥ 250 μm) were observed in 76% of DN, 75% of FSGS, 66.7% of HNS and 56.6% of the others. The average GMAL was significantly greater in DN and FSGS. BMI, body weight, subcutaneous fat area, visceral fat area, psoas major area, and muscles of back proper area were not correlated with GMAL. As for blood and urine parameters, only eGFR had an inverse correlation (β = -0.657, $p < 0.01$). Glomerular density, the number of glomeruli that did not present global sclerosis per renal cortical area ($/m^2$) was not interrelated to BMI.

Conclusions: eGFR was the significant contributor to enlargement of GMAL. Glomerular hypertrophy may arise as a result of compensatory mechanism to eGFR decline.

TH-PO090

Ultrastructural Examination of Glomerular Fibrillary Deposits in Diabetic Nephropathy Sophie I. Nagelkerken, P.h. Neeskens, Jan A. Bruijn, Ingeborg M. Bajema. *Department of Pathology, Leiden University Medical Center, Leiden, Netherlands.*

Background: In diabetic nephropathy (DN), glomerular fibrillary deposits have been observed but there are no large-scale, ultrastuctural examinations in the literature about the nature of these deposits. We here report our investigation of fibrillary deposits found by transmission electron microscopy (TEM) in DN, and compare results to those in fibrillary glomerulonephritis (FGN).

Methods: Twenty-two patients with autologous biopsy confirmed DN were selected and routine light microscopic evaluation, classification and clinical data were reviewed. TEM was performed and fibril diameter was calculated from 60-90 measurements per glomerulus. For comparison, 7 non-diabetic FGN patients were selected.

Results: For detailed results we refer to Table 1. There were 7 cases with class II, 10 with class III and 5 with class IV DN. Irrespective of class, small, randomly organised fibrils with a diameter of 7-14 nm were present in glomeruli of all cases, while additionally, straight or curved, organised fibrils with a diameter of 17-37 nm were present in 11 cases. No renal comorbidity at time of biopsy or at clinical follow up that could explain fibrillary deposits was present. FGN patients had similar fibrillary deposits that were either small and randomly organised or had a more organised aspect and a diameter of 13-32 nm. None of the patients had diabetes. IF findings did not contribute to differentiate between DN and FGN, but patients with DN did have a significantly thicker GBM than those with FGN.

Conclusions: Fibrillary deposits found in glomeruli of all 22 DN patients are morphologically similar to those in FGN patients. The widespread presence of fibrils in DN was an unexpected finding; their similarity to fibrils in FGN may complicate the histological diagnosis, especially in patients with clinically overlapping symptoms. Therefore, we are currently investigating their composition using mass spectrometry.

Funding: Private Foundation Support

Table 1. Patient characteristics

		DN (n=22)	FGN (n=7)
Age (years)		55 ± 14	55 ± 10
Gender = male		17 (77%)	3 (43%)
DM type	Type 1	5 (23%)	Not applicable
	Type 2	16 (73%)	
	MODY	1 (5%)	
DM duration (years)		15 ± 14	Not applicable
Clearance (ml/min/1.73m<2>)		43 ± 28	41 ± 27
Proteinuria (g/day)		6 ± 3	7 ± 6
Follow-up (years)		3 [0 -19]	0 [0-7]

Values are depicted as mean ± SD, median [min-max] or as number of patients(%).

TH-PO091

Serum IgA/C3 Ratio May Be a Useful Serologic Marker to Predict Remission and Disease Progression in Patients with Adult Onset IgA Vasculitis Takeyuki Takamura,[1] Fumihiko Furuya,[1] Kenichiro Kitamura.[2] *[1]University of Yamanashi, Chuo, Japan; [2]University of Yamanashi School of Medicine, Chuo, Japan.*

Background: In adult cases**,** IgA vasculitis (IgAV) typically represents severe renal dysfunction. Various clinical and histological parameters have been associated with an increased risk of progressive renal disease in several studies. However, there are no serologic markers that can be employed to assess disease activities or to predict renal outcome in IgAV. On the other hand, recently the serum IgA/C3 ratio has been suggested to serve as a marker for the progression of IgA nephropathy.

Methods: The aim of this study was to examine whether the serum IgA/C3 ratio serves as a marker to predict remission and disease progression in adult onset IgAV. We studied 37 patients with adult onset IgAV (mean follow-up of 34.2±5.3 months) with a mean age of 50.8±3.7 years old. Based on the available medical records, we retrospectively evaluated clinical data, IgA/C3 ratio, and kidney biopsy findings according to the ISKDC classification.

Results: The serum IgA/C3 ratio at the renal biopsy was significantly lower in patients with remission (no hematuria and U-TP/Cr <0.15g/gCr) compared to those with non-remission group (2.52±0.16 vs 3.69±0.52, $p<0.05$); there were no differences in ISKDC classification. In addition, patients with small reduction in eGFR (<25%) showed significantly lower serum IgA/C3 ratio than those with large decline in eGFR (≧25%) (2.57±0.18 vs 4.42±0.77, $p<0.05$).

Conclusions: To our knowledge, this is the first report to demonstrate that the serum IgA/C3 ratio can be a good marker to predict remission and disease progression in patients with adult onset IgAV. However, long-term follow-up and further studies are required to clarify the validity of the serum IgA/C3 ratio.

TH-PO092

Clinical Impact of Modified MESC Classification for Renal Outcome among Japanese IgAN Patients Ahmad B. Kaihan,[1] Yoshinari Yasuda,[4] Takayuki Katsuno,[2] Sawako Kato,[2] Takahiro Imaizumi,[5] Takaya Ozeki,[3] Manabu Hishida,[1] Naotake Tsuboi,[2] Shoichi Maruyama.[2] *[1]Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [2]Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [3]Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [4]Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [5]Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan.*

Background: Our previous study revealed that MES and crescent (C) in the Oxford classifications could not predict real outcome among adult Japanese IgA nephropathy (IgAN) patients, probably because that Japanese IgAN patients were diagnosed in earlier and more active stage. The purpose of this study was to modify the cutoff point of MESC scores adequate for Japanese patients with IgAN.

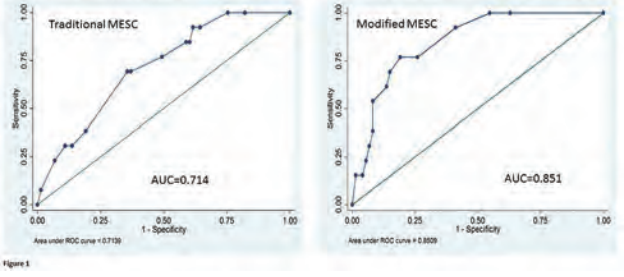
Methods: A total of 86 adult IgAN patients diagnosed from 2001 to 2009 by renal biopsy retrospectively evaluated at Nagoya University Hospital by seven nephrologists. The ROC curve analyses were used to modify the traditional cutoff points for MESC. Then the modified and traditional MESC score was analyzed in association with renal outcome, defined as a 50% increase in serum creatinine.

Results: Baseline characteristics [median and IQR] of study subjects were: age 36 [24-46] years, 41 female, proteinuria 1.2 [0.7-1.8] g/day, and serum creatinine (sCr) 0.9 [0.7-1.1] mg/dL. The modified cutoff point for MESC was ≥ 40%, ≥ 10%, ≥ 20%, and ≥ 10% in glomeruli respectively. Number and proportion of traditional vs modified MESC were M1: 24 (27.9%) vs 30 (34.9%), E1: 35 (40.7%) vs 17 (19.8%), S1:57 (66.3%) vs, 20 (23.3%) and C1:45 (52.3%) vs 32 (37.2%). During a median follow-up period of 6.8 years, 13 (15%) patients achieved the renal outcome. In univariate analyses, the traditional MESC was not associated with renal outcome, while in modified cutoff point M (HR 2.99, p= 0.05), E (HR 4.94, p= 0.004), S (HR 3.51, p= 0.03), and C (HR 3.67, p= 0.03) were significantly associated with renal outcome. ROC curve analyses (Fig 1) revealed significant predictive value in modified MESC classification (AUC=0.851).

Conclusions: The modified cutoff points for MESC significantly improved predictive value for renal outcome in Japanese patients with IgAN.

Funding: Other U.S. Government Support

ROC analyses by traditional and modified MESC in the Oxford classification



TH-PO093

The GRACE IgA Nephropathy in Indians (IgANI) Study

Suceena Alexander,[1] Vijayakumar Theophilus-Sunder,[1] Vinoi G. David,[1] Anjali Mohapatra,[1] Anna T. Valson,[1] Shailesh T. Kakde,[1] Charles D. Pusey,[3] Mohamed R. Daha,[5] Jonathan Barratt,[2] John Feehally,[2] George John,[4] Santosh Varughese.[1] *[1]Christian Medical College, Vellore, India; [2]University of Leicester, Leicester, United Kingdom; [3]Imperial College London, London, United Kingdom; [4]Royal Brisbane and Womens Hospital, Brisbane, NSW, Australia; [5]Leiden University Medical Center, Leiden, Netherlands.*

Background: In India, about 30-40% IgAN patients present with nephrotic syndrome and renal dysfunction and progress rapidly.

Methods: Prospective longitudinal single center cohort. **Inclusion Criteria:** Age ≥18 years. Renal biopsy proven primary IgA nephropathy. CKD EPI eGFR > 10ml/min/1.73m^2. Treatment naïve. **Definitions:** Rapid Progresser (RP): IgAN patients with ≥5ml/min/1.73m^2/year fall in glomerular filtration rate (GFR) as estimated by the CKD EPI equation. Slow/Non Progresser (S/NP): IgAN patients with <5ml/min/1.73m^2/year fall in CKD EPI eGFR. End of study outcome (EOS): Composite end-point of 50% decline in eGFR with eGFR <10ml/min/1.73m^2, RRT or death whichever occurs earlier.

Results: 165 patients were included. Refer table for baseline parameters. Average in-center follow-up duration of 135 patients was 5.0 ± 4.4 months. There were 82/135 (60.7%) S/NPs and 53/135 (39.3%) RPs at follow-up. EOS outcome was reached in 1.2% of S/NPs vs. 30.2% of RPs. The significant predictors of EOS outcome for the cohort by Cox Regression analysis are given in the figure.

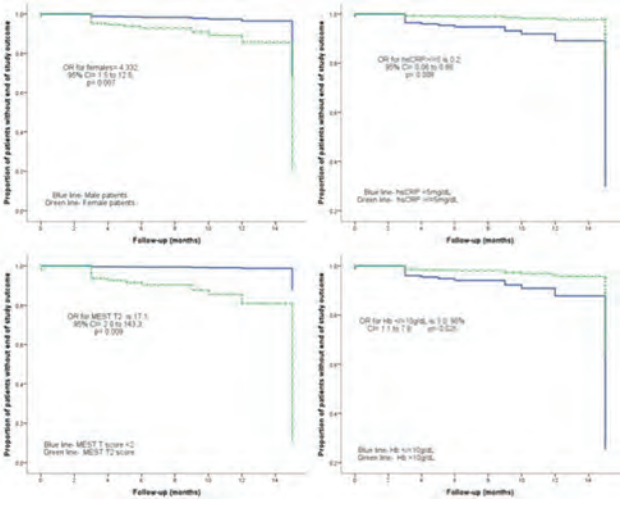
Conclusions: 28% of patients were RPs at follow-up. Higher hsCRP levels were protective whereas female gender, Hb <10g/L and MEST T2 score were significant risk factors for EOS outcome.

Funding: Government Support - Non-U.S.

Baseline Characteristics

Parameters	Total, n=165	Slow/non-progressors, n=82/135	Rapid progressors, n=53/135
Gender M: F	121: 44	67:15	35:18
Age (years) mean ± SD	36.9 ± 10	36.3 ± 9.3	34 ± 11.1
Serum albumin (g/dL) mean ± SD	4.0 ± 0.5	4.0 ± 0.5	4.5 ± 0.4
Proteinuria ≥3g/day, n (%)	56 (34.1%)	24/81 (29.6)	25/53 (47.2)
Serum hsCRP <0.99 mg/dL n (%)	22/157 (14)	11/81 (13.6)	7/53 (13.2)
1-9.99 mg/dL n (%)	85 (54.1)	37/81 (45.7)	31/53 (58.5)
10 mg/dL n (%)	50 (31.8)	33/81 (40.7)	15/53 (28.3)
CKD EPI creatinine eGFR (ml/min/1.73m2) mean ± SD	46.6 ± 30.9	56.9 ± 27.8	82 ± 34.4
Percent crescentic glomeruli mean ± SD	0.7 ± 3.7	0.7 ± 3.7	0
MEST S1 n (%)	123/154 (79.9)	19/27 (70.4)	65/80 (81.3)
MEST T2 n (%)	76/155 (49)	38/80 (47.5)	29/48 (60.4)

135 patients had in-center follow-up till date



Cox Regression Curves

TH-PO094

IgA Dominant Membranoproliferative Glomerulonephritis

Nicole K. Andeen,[4] J. Ashley Jefferson,[4] Shreeram Akilesh,[4] Charles E. Alpers,[6] Laura S. Finn,[5] John P. Higgins,[2] Neeraja Kambham,[1] Behzad Najafian,[4] Roberto F. Nicosia,[7] Megan L. Troxell,[3] Kelly D. Smith.[4] *[1]Stanford Medical Center, Stanford, CA; [2]Stanford University, Stanford, CA; [3]Stanford University School of Medicine, Stanford, CA; [4]University of Washington, Seattle, WA; [5]University of Washington / Seattle Children's Hospital, Seattle, WA; [6]University of Washington Medical Center, Seattle, WA; [7]VA Puget Sound HCS, Seattle, WA.*

Background: IgA dominant membranoproliferative glomerulonephritis (MPGN) has morphologic and clinical features distinct from IgA nephropathy, lupus, and IgA dominant infection related glomerulonephritis. We sought to better understand the clinical and pathologic characteristics of this disease.

Methods: Native kidney biopsies from 2000 through 2016 with IgA dominant deposition by IF and diffuse MPGN features were retrospectively identified. Cases with only focal or segmental MPGN features, exudative features, prominent subepithelial deposits, other significant nephropathies, or findings of Henoch Schonlein purpura were excluded.

Results: 25 biopsies from 21 patients were identified from 5 institutions. The cases were subclassified into two groups: 1) patients without known underlying medical conditions (idiopathic, n=12) and 2) patients with significant gastrointestinal disease or cirrhosis from various etiologies (GI, n=9). The idiopathic group consisted of 9 men and 3 women, with a median age of 38 (range 11-68) years, who typically presented with nephrotic range proteinuria, hematuria, mild renal insufficiency, normal lupus serologies and serum complement levels, and no history of bacterial infection. At a median time of 3 years, 7 had available follow-up. Two progressed to end stage kidney disease, one of whom had recurrent IgA dominant glomerulonephritis in the allograft less than one year post transplant; two had persistent disease with increasing chronic features on repeat biopsy, and three had persistent renal insufficiency and/or proteinuria. From the GI group, follow up was available for 7 patients. At a median time of 2 months after biopsy (range 9 days – 13 months), 6 died and the 7th became dialysis dependent.

Conclusions: IgA dominant MPGN represents a rare but distinct pathologic entity that occurs as an idiopathic form or in association with significant gastrointestinal disease or cirrhosis. The idiopathic form has a poor prognosis, with persistent or progressive disease despite immunosuppressive therapy and recurrence post-transplant. The GI-associated form is associated with death or renal failure within a year of biopsy due to underlying complex medical conditions. Recognition of IgA dominant MPGN may help better define prognostic factors and therapeutic interventions.

TH-PO095

Thrombotic Microangiopathy Like Lesions in IgA Nephropathy: A Cohort Study

Qingqing Cai,[1] Sufang Shi,[1] Jicheng Lv,[2] Hong Zhang.[1] *[1]Peking University First Hospital, Beijing, China; [2]Peking University, Beijing, China.*

Background: Background: Thrombotic microangiopathy (TMA)-like lesion often occurs in IgA nephropathy (IgAN), but its role in disease progression is not well established, and recent Oxford MEST-C score system doesn't include this lesion. In this study, we aim to investigate TMA-like lesions in IgAN using a prospective IgAN database cohort in Peking University.

Methods: Methods: Patients with IgAN from 2003 to 2014 who were followed at least 1 year enrolled in this study. Kidney biopsies from all participants were re-reviewed by two investigators independently blinded to the clinical data. The TMA-like lesions

were graded according to criteria by El Karoui K et al (JASN 2012, 23(1):137) under light microscope(LM). The primary outcome was time to 50% decline in estimated glomerular filtration rate (eGFR), end-stage kidney disease(ESRD) or death. Multivariable Cox regression model was used to evaluate TMA-like lesions for prognosis of IgA nephropathy.

Results: Results: Among the 1052 patients, 985(93.6%) patients with pathological slides available entered the study. Overall 194 (19.7%) had TMA-like lesions. Patients with TMA-like lesions presented a higher proportion of malignant hypertension (9.8 vs 1.0%, p<0.001), a higher blood pressure (130±19 *vs* 122±15 mmHg, p<0.001), severer proteinuria [2.3(1.4-4.1) *vs* 1.4(0.7-2.8) g/d, p<0.001] and lower eGFR (58.8±26.8 *vs* 86.2±28.9 ml/min per 1.73 m^2, p<0.001) at baseline compared to those without TMA-like lesions. After a mean follow-up of 4.1 years, 75(38.7%) patients with TMA-like lesions and 89(11.3%) with non-TMA-like lesions reached end points (p<0.001). In a multivariable Cox regression model, after taking into account clinical and pathological indicators available at the time of biopsy, TMA-like lesion was an independent risk factor for kidney progression in IgAN (HR 1.88, 95%CI:1.30-2.72, P=0.001). Moreover, the risk for kidney failure rose as the severity of TMA-like lesions increased (mild: HR 1.66, 95%CI:1.11-2.48; moderate: 2.53, 1.49-4.30; severe: 2.99, 1.27-7.04). Other renovascular sclerosis (arterial intimal fibrosis and arteriolar hyalinosis) were not risk factors of the progression of IgAN (HR: 0.84, 95%CI:0.54-1.31, p=0.441).

Conclusions: Conclusion: TMA-like lesions were frequent in IgA nephropathy and were associated with high risk of renal failure. Future pathological score of IgA nephropathy should include TMA-like lesions.

Funding: Government Support - Non-U.S.

TH-PO096

Immunoglobulin A-Dominant Glomerulopathy and Thrombotic Microangiopathy after Chemotherapy: A Report of Three Cases Zeljko Dvanajscak,[2] Bethany E. Karl,[4] Vighnesh Walavalkar.[1] *[1]Pathology, University of California San Diego, San Diego, CA; [2]University of California San Diego, San Diego, CA.*

Background: Chemotherapeutic agents are a well-known cause of renal dysfunction and are known to cause injury to all compartments of the kidney. Amongst the glomerular diseases, immune complex mediated glomerulonephritis (usually IgG-dominant) and thrombotic microangiopathy (TMA) are the most commonly reported patterns of injury. We have recently encountered three unusual cases of IgA-dominant glomerulonephritis with superimposed TMA occurring after chemotherapy.

Methods: All three had an unusual pattern of IgA dominant immune complex deposition, not entirely compatible with known IgA-dominant immune complex mediated glomerulopathies like IgA nephropathy or IgA-dominant infection associated glomerulonephritis. All three cases had superimposed TMA. The patients were closely followed prior to and after renal biopsy. In each case there was no suggestion of pre-existing renal disease prior to initiation of chemotherapy; and presenting symptomology leading to biopsy occurred after initiation of the drug, suggesting contemporaneous relationship/association to the drug. All patients were successfully treated by cessation of the drug and steroid therapy. Several months of follow-up shows stable renal function without proteinuria or active urinary sediment in both patients.

Results:

Conclusions: We present these cases to discuss the differential diagnosis, approach to biopsy, potential mechanisms of injury, treatment considerations and to spread awareness of this unique pattern of renal injury seen after chemotherapy.

TH-PO097

Glomerular FHR5 Associates with Severity in IgA Nephropathy Nicholas R. Medjeral-Thomas, Nicholas Constantinou, Hannah J. Lomax-Browne, H. Terence Cook, Matthew C. Pickering. *Imperial College London, London, United Kingdom.*

Background: Serum factor H-related protein 5 (FHR5) levels are higher in IgA nephropathy (IgN) patients than healthy controls and correlate with histological severity. We hypothesised that glomerular FHR5 deposition would associate with IgAN severity.

Methods: 37 IgAN patients had stored tissue available from diagnostic renal biopsy and were categorised as progressive (n=19) or stable (n=18) disease. Immunohistochemistry protocols to detect complement C3c/C3b/iC3b, C3d, C4d, C5b9, factor H (fH) and FHR5 were developed and glomerular staining intensity graded on a scale: 0 (absent), 0.5 (minimal), 1, 2 or 3.

Results: Glomerular FHR5 deposition was present in 31 and absent in 6 patients. All cases with FHR5 staining showed glomerular C3 staining. A greater proportion of progressive than stable patients had detectable glomerular FHR5 (18/19 progressive and 13/18 stable patients, p=0.09). Of the 6 patients with absent FHR5, 5 (83%) had stable IgAN. We next sub-divided our cohort into those with negative(0)/minimal(0.5) glomerular FHR5 staining (FHR5-) and those with staining intensity scores of 1-3 (FHR5+). Features of IgAN severity were more common in the FHR5+ cohort (Table). After median 51 months follow up (range 13-296 months), four of the FHR5+ but none of the FHR5- patients reached end stage renal failure (p<0.0001). A greater proportion of the FHR5+ cohort showed glomerular complement deposition (Table) with a positive correlation between FHR5 staining and C3c/C3b/iC3b (r=0.57, p<0.0001), C3d (r=0.74, p<0.0001), and C5b9 (r=0.68, p<0.0001).

Conclusions: We conclude that glomerular FHR5 associates with disease severity and glomerular complement activation and represents a novel IgAN biomarker.

Clinical feature	FHR5+(n=24), median	FHR5– (n=13), median	Difference of medians	95% CI	p value
eGFR (ml/min per 1.73m2)	63	89	-26	-50.2 to -3.2	0.03
UPCR (mg/mmol)	155	59	96	2 to 123	0.04
Serum C3 (g/L)	1.13	1.37	-0.24	-0.46 to -0.05	0.02
Histology feature	FHR5+, proportion	FHR5–, proportion	Odds Ratio	95% CI	p value
Mesangial hypercellularity	18/24	3/13	10	1.9 to 39.7	0.005
Tubular atrophy	12/24	2/13	5.5	0.97 to 27.8	0.07
Cellular Crescents	12/24	2/13	5.5	0.97 to 27.8	0.07
C3c/C3b/iC3b	24/24	11/13			0.11
C3d	17/20	3/12	17	3.0 to 77.6	0.002
C4d	15/22	4/13	4.8	1.1 to 17.0	0.04
C5b9	20/21	3/10	66.7	6.5 to 743	<0.0001
fH	3/22	4/12			0.21

TH-PO098

Utility of Subgroups of the Japanese Histological Grade Classification of IgA Nephropathy to Evaluate Effectiveness of Therapy Kensuke Joh,[1] Akinori Hashiguchi,[2] Satoshi Hisano,[3] Akira Shimizu,[4] Ritsuko Katafuchi,[5] Tetsuya Kawamura.[6] *[1]Tohoku University Graduate School of Medicine, Sendai, Japan; [2]Keio University School of Medicine, Tokyo, Japan; [3]Fukuoka University School of Medicine, Fukuoka, Japan; [4]Nippion Medical School, Tokyo, Japan; [5]National Fukuoka-Higashi Medical Center, Fukuoka, Japan; [6]The Jikei University School of Medicine, Tokyo, Japan.*

Background: Japanese Histological Grade Classification (JHGC; HG1-HG4) (J Nephrol, 2013) is a lumped system grading glomerular lesions constituting of active crescent, global sclerosis, segmental sclerosis (S) and fibrous crescent. Each group is divided into subgroups constituting of active lesion (A), chronic lesions (C), and mixed lesions (A/C) The purpose was to investigate a utility of these subgroups to evaluate an effectiveness of therapy in a cohort of a Japanese IgA nephropathy (IgAN) prospective cohort study.

Methods: Sequential clinical data as well as renal biopsies were obtained from 847 Japanese patients (pts) with IgAN (male 49%) collected from 32 centers in Japan. The pts, whose median age was 36 years old, were prospectively followed for a median of 42 months. The average amount of proteinuria at the time of the biopsy was 1.1 g/day. Mean eGFR was 76±29 ml/min/1.73m^2. Pts was divided into group A or A/C (320 pts), group C (410pts), and group without A, A/C, or C (117 pts). Percent of the cases receiving steroid therapy with/without tonsillectomy (ST) and those receiving tonsillectomy with/without ST (Tons) were 79% and 41%, respectively in group A or A/C, whereas ST and Tons were 58% and 31% in group C, respectively. An effectiveness of these choices of therapy was evaluated by multivariate Cox regression analysis to predict renal functional decline (RFD) for 1.5 time's increase of serum creatinine (sCr) and proteinuric remission (PUR) for an endpoint of proteinuria as 0.3 g/day.

Results: In group A or A/C**,** ST or Tons besides HG3 and HG4 were selected as independent parameters for RFD, whereas HG2, HG3 and HG4 but not ST or Tons were selected in group C, even after adjustment by RAS blockade, initial mean arterial pressure (MAP), initial proteinuria, and initial eGFR (p<0.05). For PUR, ST besides HG 3 were selected as independent predictors **i**n group A or A/C**,** whereas ST besides HG3, and HG4 were selected in in group C after adjustment by aforementioned clinical parameters (p<0.05).

Conclusions: A utility of the subgroups of JHGC was appraised for an evaluation of an effectiveness of therapy. The cases with A or A/C but not C is a target of ST and Tons for RFD, whereas for PUR, ST can be applied not only for the pts with A or A/C but also for the pts with C.

Funding: Government Support - Non-U.S.

TH-PO099

Clinicopathological Findings of IgA Nephropathy with Subepithelial Deposits Mineaki Kitamura, Yoko Obata, Tomoya Nishino. *Nagasaki University Hospital, Nagasaki, Japan.*

Background: Approximately 10% of patients with adult IgA nephropathy (IgAN) show subepithelial deposits, although their clinical significance remains unknown. A few clinical analyses performed for IgAN with subepithelial deposits (IgAN-SD) were reported long ago, but were relatively small sized. We studied a large number of IgAN patients focusing on atypical findings of IgAN to elucidate clinicopathological features of IgAN-SD.

Methods: We examined 464 cases diagnosed as IgAN at Nagasaki University Hospitals and affiliated hospitals between 1996 and 2013. Clinicopathological findings were compared between patients with IgAN-SD and IgAN with no subepithelial deposits (IgAN-NSD). Complement levels, localization of immunoglobulins, light chain staining pattern, and intramembranous deposits were evaluated, besides typical IgAN features.

Results: Patient characteristics were: age 38 ± 18 years, 214 men and 250 women. Subepithelial deposits were noted in 51 cases (11%). Compared to IgAN-NSD, mean serum protein (6.4 g/dL vs. 6.7 g/dL; P=0.020), albumin (3.7 g/dL vs. 3.9 g/dL; P=0.018) and complement (C3) (94 mg/dL vs. 103 mg/dL; P=0.020) were significantly lower in IgAN-SD patients. Diffuse mesangial proliferation (M) (65% vs. 45%; P < 0.01), endothelial hypercellularity (E) (43% vs. 28%; P=0.029), IgA staining in glomerular capillary walls (22% vs. 8.2%; P < 0.01) were higher in IgAN-SD patients. The incidence of light chain lambda predominance was lower in IgAN-SD patients (47% vs. 63%; P=0.028). Seven cases of IgAN-SD showed intramembranous deposits.

Conclusions: We found IgAN-SD showed the tendency to display atypical findings for IgAN, viz., low C3, and light chain staining pattern. Subendothelial deposits, low C3

and not light chain lambda predominance are also observed in IgA dominant-infection related nephropathy (IgA-IRGN). Therefore, some cases of IgAN-SD might in reality be IgA-IRGN, but not get diagnosed as IgA-IRGN owing to lack of clinical history of infection. Secondary IgA nephropathy, resulting from other etiology of IgAN, could be refractory and therapeutic strategy differs from that for IgAN. Secondary IgA deposition should be considered and careful history and clinical course be monitored if we find atypical findings for IgAN.

TH-PO100

Galactose-Deficient IgA1 Monoclonal Antibody Specifically Identifies Primary IgA Nephropathy and IgA Vasculitis with Nephritis Hitoshi Suzuki,[2] Junichi Yasutake,[1,2] Yuko Makita,[2] Kohei Yamasaki,[1,2] Toshiki Kano,[2] Yusuke Suzuki.[2] *[1]Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan; [2]Nephrology, Juntendo University Faculty of Medicine, Tokyo, Japan.*

Background: Galactose-deficient IgA1 (Gd-IgA1) has been proposed as an important effecter molecule in patients with IgA nephropathy (IgAN) and IgA vasculitis with nephritis (IgAV-N). Our previous study revealed that Gd-IgA1-specific monoclonal antibody KM55 (KM55 mAb) could be a new tool for detecting circulatory Gd-IgA1 in patients with IgAN, which enabled us to study molecular roles of Gd-IgA1. In this study, we further examined pathophysiological significance of Gd-IgA1 in glomerular deposits of patients with IgAN and IgAV-N by immunohistochemical analysis with KM55 mAb.

Methods: Kidney biopsy specimens were obtained from 2013 to 2016 at Juntendo University Hospital with the informed consent from patients. Double Immunofluorescent staining of Gd-IgA1 with KM55 mAb and anti-human IgA antibody was performed in paraffin embedded sections of renal biopsy specimens from patients with IgAN (n=43), and other renal diseases (n=30); such as lupus nephritis, HCV-related nephropathy and IgAV-N.

Results: Glomerular Gd-IgA1 was specifically detected by KM 55 mAb in all patients with IgAN and IgAV-N. In patients with IgAN and IgAV-N, Gd-IgA1 was localized predominantly in the mesangial region as IgA deposition. Gd-IgA1 could not be detected even in patients with lupus nephritis accompanied by glomerular IgA deposition. Furthermore, HCV-related nephropathy with secondary IgA deposition after HCV infection did not show any glomerular Gd-IgA1.

Conclusions: This is the first observation to clearly indicate that Gd-IgA1 could be specifically deposited in glomeruli of IgAN and IgAV-N, strongly suggesting the pathophysiological function of Gd-IgA1 in those diseases. Further studies are necessary to clarify the underlying mechanisms of Gd-IgA1 deposition and induction of renal injuries in IgAN and IgAV-N. Monoclonal antibody against Gd-IgA1 could be a novel powerful tool to distinguish primary IgAN and IgAV-N from other renal diseases with glomerular IgA.

Funding: Government Support - Non-U.S.

TH-PO101

Glomerular Glucocorticoid Receptor Expression Associates with Treatment Response and Prognosis in Patients with IgA Nephropathy Boyoung Nam,[1] Youn kyung Kee,[2] Sukyung Kang,[1] Arum Choi,[1] Seung Hyeok Han.[2] *[1]Department of Internal Medicine, College of Medicine, Severance Biomedical Science Institute, Brain Korea 21 PLUS, Yonsei University, Seoul, Republic of Korea; [2]Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea.*

Background: Corticosteroid is a potential therapeutic option in patients with IgA nephropathy (IgAN) who have persistent proteinuria of ≥ 1g/day after 3-6 months of maximal supportive care. Responsiveness to steroid is highly variable and unpredictable in patients receiving steroid treatment. Glucocorticoid receptor (GCR) is present in glomerular cells such as mesangial cells and podocytes. However, it is unknown on the association between GCR and steroid responsiveness in management of glomerular diseases. Therefore, this study aimed to evaluate whether steroid responsiveness may differ depending on GCR expression level in patients with IgAN.

Methods: Among 504 patients of biopsy-proven IgAN between 2010 and 2015, 78 patients had received steroid treatment. After excluding patients who did not give an informed consent and had estimated glomerular filtration rate (eGFR) of < 30 ml/min/1.73 m^2, nephrotic syndrome, and inadequate biopsy samples, a total of 35 patients were included in the analysis. Glomeruli were obtained from biopsy tissues by manual microdissection. Glomerular mRNA expression of GCR was assessed by real-time polymerase chain reaction. Complete (CR) was defined as random urine protein-to-creatinine ratio (UPCR) < 0.3 g/g creatinine and partial (PR) remission was defined as a ≥ 50% reduction of proteinuria from baseline and UPCR of ≥ 0.3 g/g creatinine. Disease progression was defined as a ≥ 30% decrease in eGFR during follow-up period.

Results: The mean age of study patients was 43.9 years and 74.3 % were men. All patients responded to steroid treatment; CR and PR occurred in 14 (40.0%) and 21 (60.0%) patients, respectively. There were no significant differences in baseline eGFR and proteinuria level between CR and PR groups. The mRNA expression of GCR was significantly higher in the patients with CR than those with PR (P = 0.008). Immunohistochemal study also confirmed the enhanced expression of GCR in the former. During a median follow-up of 21.2 months, disease progression occurred only in 1 patient (7.1%) in CR group, as compared to 10 patients (47.6%) in PR group (P = 0.013).

Conclusions: This study shows that higher expression level of glomerular GCR is associated with a higher probability of steroid-induced CR and better renal outcome in IgAN.

TH-PO102

Diffusional Kurtosis Imaging in Assessing Renal Function and Pathology of IgA Nephropathy: A Preliminary Clinical Study Yan Liu,[1] Gu-Mu-Yang Zhang,[2] Xiaoyan Peng,[1] Hao Sun,[2] Limeng Chen.[1] *[1]Nephrology, Chinese Academy of Medical Science, Peking Union Medical College Hospital, Beijing, China; [2]Radiology, Chinese Academy of Medical Science, Peking Union Medical College Hospital, Beijing, China.*

Background: Renal fibrosis is the strongest predictor of ESRD in IgA nephropathy, but noninvasive and repeatable imaging markers are missing. Magnetic resonance imaging (MRI) has higher range of applications in renal parenchyma diseases, and diffusion kurtosis imaging (DKI) is a new promising noninvasive method of MRI which can potentially provide more information about non-Gaussian diffusion using a polynomial model, but still not used to assess renal fibrosis. This study first applied this novel technique to evaluate renal fibrosis, compared with pathological findings of kidney in patients with IgAN.

Methods: Twenty patients with biopsy-proven IgAN were enrolled and divided into two groups (eGFR≥45ml/min and eGFR≥45ml/min). The clinical data were documented, and DKI was performed on a clinical 3T MR scanner. Region-of-interest (ROI) measurements were performed to determine apparent diffusion coefficient (ADC), mean kurtosis (MK) and mean diffusivity (MD) of the cortex of the kidneys. Renal biopsy specimens were scored based on the severity of renal fibrosis. The values of DKI metrics were compared between two groups and the association between DKI data and clinicopathologic data were investigated.

Results: Twenty patients consisted of 9 males and 11 females with mean age of 34.6±13.0 years. The pathologic indicators showed significant correlation with eGFR. In DKI model, both renal ADC and MK values not only correlated well with eGFR (ADC: r=0.713,p=0.000; MK: r=-0.622, p=0.003), but also significantly associated with glomerular sclerosis index (GSI) (ADC: r=-0.577, p=0.008; MK: r=0.634, p=0.003) and the percentage of tubular atrophy/interstitial fibrosis (TAIF) (ADC: r=-0.699, p=0.001; MK: r=0.611, p=0.004). The ADC and MK values between two groups were also significantly different (p=0.002 and p=0.007, respectively). But the MD values showed no correlation with all clinicopathologic features and no significant differences were found in MD values between two groups. Further multiple linear regression analysis showed that only eGFR and ADC values was related and only glomerular sclerosis index (GSI) and MK values was related.

Conclusions: Renal ADC and MK values obtained from DKI showed significant correlation with pathologic sclerosis scores of IgAN, could be a promising noninvasive technique in patients follow-up.

TH-PO103

Urine Biomarkers' Efficacy as a Disease-Activity Parameter for Children with IgA Nephropathy Taketsugu Hama,[1] Yu Tanaka,[1] Masashi Sato,[1] Hironobu Mukaiyama,[1] Hiroko Togawa,[1] Yuko Shima,[1] Hiroyuki Suzuki,[1] Koichi Nakanishi,[2] Norishige Yoshikawa.[3] *[1]Wakayama Medical University, Wakayama, Japan; [2]Graduate School of Medicine, University of the Ryukyus, Nishihara-cho, Japan; [3]Clinical Research Center, Wakayama Medical University, Wakayama, Japan.*

Background: Although there have been several reports of biomarkers in adults, few studies have reported their use in pediatric patients, especially non-invasive methods. Several biomarkers are thought to be useful for differential diagnosis in kidney diseases. However, it is still unknown which biomarkers are more reliable in childhood IgA nephropathy (IgAN). Moreover, there are few reports about the efficacy of biomarkers, especially non-invasive methods as a disease-activity parameter in IgAN.

Methods: We compare several biomarkers from cells in urine samples between patients with IgAN and other renal diseases. And we assess the correlation between biomarkers from urine of pediatric patients with IgAN and their clinical and pathological status. Fifty consecutive patients with kidney diseases (18 nephrotic syndrome, 13 IgAN, 3 Henoch-Schönlein Purpura Nephritis, 1 Lupus, 1 Membranoproliferative Glomerulonephritis, 5 isolated hematuria, 2 isolated proteinuria, 7 others) at our hospital were enrolled. We examined by quantitative real time PCR and compared the expression levels of urine liver fatty acid-binding protein (L-FABP), kidney injury molecule-1 (KIM-1), Cubilin, interleukin-18 (IL-18), neutrophil gelatinase-associated lipocalin (NGAL), Megalin, podocin and Thy1 between IgAN patients and others.

Results: IgAN patients showed significantly lower levels of L-FABP1 (p<0.01), Megalin (p=0.03), Thy1 (p=0.02) and Cubilin (p<0.01) than other patients. Only KIM-1 expression in IgAN patients correlated with proteinuria (p=0.01) and hematuria (p=0.03). IgAN patients with crescents expressed a significantly higher level of IL-18 (p=0.03) than IgAN patients with no crescent pathologic changes.

Conclusions: Some kinds of biomarkers from urine of IgAN patients have potential to diagnose IgAN, predict disease-activity and pathological findings of glomerular crescents. Urine biomarkers are effective invasive tools for long-term follow up for IgAN patients.

Funding: Government Support - Non-U.S.

TH-PO104

The Oxford IgA MEST Score Is Associated with Worse Kidney Outcomes in Childhood Onset Henoch Schönlein Purpura Nephritis Sally A. Kellett,[1] Paul S. Thorner,[1] Rose Chami,[1] Natasha Jawa,[2] Rulan S. Parekh,[1] Damien G. Noone.[2] *[1]The Hospital For Sick Children, Toronto, ON, Canada; [2]The Hospital for Sick Children, Toronto, ON, Canada.*

Background: Henoch-Schönlein Purpura (HSP) is one of the commonest forms of systemic small vessel vasculitis in children, with kidney involvement occurring in 40-50% of children. Current pathology classification systems have not proved useful in determining long-term kidney outcomes in children with HSP nephritis. Aim: Determine if Oxford IgA MEST score is associated with long-term outcomes in childhood onset HSP.

Methods: This was a single-center, retrospective cohort study of children aged 0 to 18 yrs who presented with HSP nephritis between 2002 and 2016. Initial renal biopsies were scored based on the MEST criteria (M=mesangial hypercellularity, E=endocapillary hypercellularity, S=segmental glomerulosclerosis, T=tubular atrophy/interstitial fibrosis) and also for presence of crescents (C=cellular or fibrocellular crescents) and level of C3 deposition. Analyzed by logistic regression, we determined if MEST score was associated with clinical outcomes at last clinical follow-up with a composite outcome of proteinuria (protein:creatinine ratio >20mmol/mmol and/or eGFR <90ml/min/1.73m^2) controlling for age at presentation and sex.

Results: We identified 44 children (F=63.6%) with biopsy data who were followed for at least 6 months. At presentation, median age was 8.3 yrs (IQR 5.8 – 11.5yrs) median protein:creatinine ratio was 239.6mg/mmol (IQR 151.5 – 608.9 mg/mmol). Median length of follow-up was 3 yrs (0.5 to 11yrs). Pathology review determined 34.1% had a combined MEST score ≥3, 63.6% had crescents (of those, 85.7% <50%) and 61.4% C3 staining >1+. A total of 79.5% were treated with steroids and 45.5% with an ACE inhibitor or angiotensin II receptor blocker. Median GFR at last follow up was 107.4ml/min/1.73m^2 (IQR 83.6 to 146.2). A MEST score ≥3 had an adjusted odds of 8.3 [95% CI 1.3-52.2] of having a poor kidney outcome when adjusted for age and sex. The presence of crescents gave an adjusted odds of 5.4 [95% CI 1.2-25.5] of reaching the composite outcome. C3 was not significantly associated with the composite outcome with adjusted odds of 1.9 [95% CI 0.5-7.3].

Conclusions: MEST pathological score of ≥3 and presence of crescents on first biopsy in children with HSP nephritis is associated with a worse outcome by 3 years. This study suggests that Oxford IgA MEST score may be useful for disease prognosis.

TH-PO105

Prognostic Evaluation of Pediatric IgA Nephropathy Using Histological Criteria Including Macrophage Accumulation Yohei Ikezumi,[1] Yuji Matsumoto,[1] Hiroya Hasegawa,[3] Takeshi Yamada,[3] David J. Nikolic-Paterson.[2] *[1]Fujita Health University School of Medicine, Toyoake, Japan; [2]Monash Medical Centre, Clayton, VIC, Australia; [3]Niigata University Medical and Dental Hospital, Niigata-City, Japan.*

Background: There is no histological classification to predict disease flare in children with IgA nephropathy (IgAN). As macrophage (MQ) accumulation correlates with histological injury, we investigated new histological criteria to predict disease flare in pediatric IgAN.

Methods: A total of 73 children with biopsy proven IgAN underwent 2 years of steroid treatment followed by a protocol biopsy and then steroid tapering. The non-flare group successfully discontinued steroid treatment (N=61, 20.1±9.2 years at biopsy); the flare group exhibited increased proteinuria during the taper or cessation of treatment (N=12, 11.6±2.3 years at biopsy, p<0.05). Histological findings were evaluated using Oxford classification. Macrophage number and phenotype was assessed by immunofluorescence.

Results: At first (diagnostic) biopsy, urine findings were comparable between the two groups, but the flare group had a higher serum IgA level (279±83 vs 214±87 mg/dL; P<0.05). Biopsies revealed no difference in mesangial proliferation (M), endocapillary proliferation (E), glomerulosclerosis (S), tubulointerstitial fibrosis (T), and crescent formation (C); however, the flare group had more total MQ (CD68+ cells) (p<0.05) and M1 MQ (CD68+CD86+ cells) (p<0.05). In addition, M1 MQ correlated with glomerular M, E, S, C lesions (all P<0.01). At second (protocol) biopsy, the flare group had more severe S (p<0.01) and T (p<0.05) lesions, and more glomerular and interstitial M2 MQ (CD68+CD163+ cells) (both p<0.01 vs non-flare group). In addition, M2 MQ correlated with S and T lesions (both p<0.001). ROC analyses revealed glomerular MQ number >2.2 cells at first biopsy could predict disease flare by sensitivity of 83%.

Conclusions: MQ accumulation is a potential marker to predict disease flare in pediatric IgAN. The number of glomerular M1 MQ in active lesions at the first biopsy was related to flare occurrence, while glomerular and interstitial accumulation of M2 MQ in chronic lesions may predict disease flare in pediatric IgAN.

Funding: Government Support - Non-U.S.

TH-PO106

Clinical and Pathological Differences in Patients with IgA Nephropathy with IgG Deposit and Position in Glomeruli Chang Ying Xing, Yanfang Zheng. *First Affiliated Hospital of Nanjing Medical University, Nanjing, China.*

Background: It is not clear the clinical data, pathological changes in patients with IgA Nephropathy with or without IgG deposition in glomeruli. This paper is to explore the significance of IgG deposit in glomeruli in patients with IgA Nephropathy.

Methods: There were 327 patients with IgA nephropathy diagnosed by renal biopsy in our hospital in the past 2 years. All renal biopsy samples were examined by light microscopy and immunofluorescence. IgA nephropathy patients were divided into two groups: IgA+IgG group (n=82) with IgG deposit in glomerli, and IgA group (n=245) without IgG deposit. Patients in IgA+IgG group were divided 2 subgroups according to the position of IgG deposit, deposit in mesangial area(10) and along glomerular basement membrane(72).

Results: Patients with IgA Nephropathy in IgA+IgG group had more 24 hours urine protein, higher serum creatinine, uric acid, hypertension and lower complement C4, eGFR than those in IgA group(P<0.05). The score of renal tubular atrophy/interstitial fibrosis (T) was higher IgA+IgG group than that in IgA group (P<0.05). There was no significant difference in proliferation of mesangial cells, mesangial hypercellularity, segmental glomerulosclerosis or adhesion, hyperplasia of endocapillary cell (P>0.05). Patients with IgG deposits along glomerular basement membrane(GBM) subgroup had more numbers, younger age, higher blood pressure than those in patients with IgG deposit in mesangial area subgroup(P<0.05). The eGFR, urea nitrogen and uric acid in IgG along GBM deposit subgroup were lower than those in the IgG deposit in mesangial area subgroup (P<0.05). There was no significant difference in the pathological changes between the two subgroups (P>0.05).

Conclusions: The patients with IgA nephropathy with IgG deposition are younger, more 24 hours urine protein, higher serum creatinine, and hypertension. Even the different position of IgG deposit in glomeruli may also have different clinical significance. We should strengthen the understanding of IgA nephropathy with IgG deposition and delay the progress of IgA nephropathy.

TH-PO107

Crescentic Lesions and Renal Outcomes in IgA Nephropathy: Validation of the Updated Oxford Classification in Brazilian Patients Precil D. Neves,[2] Rafaela B. Pinheiro,[5] Cristiane B. Dias,[4] Luis Yu,[3] Leonardo A. Testagrossa,[5] Viktoria Woronik,[1] Lectícia Jorge.[5] *[1]None, Salvador, Brazil; [2]University of S?o Paulo, S?o Paulo, Brazil; [3]University of Sao Paolo School of Medicine, Sao Paulo, Brazil; [4]University of Sao Paulo, Brazil, São Paulo, Brazil; [5]University of São Paulo, São Paulo, Brazil.*

Background: Background: IgA Nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide. The Oxford Classification (OC) of IgAN has been recently updated and crescentic lesions were recognized as histological features related to worst renal outcomes. **Objectives:** Evaluation of crescentic lesions impact in renal outcomes in IgAN patients and validation of the new Oxford Classification of IgAN (MEST-C) in brazilian patients.

Methods: Methods: Analysis of medical reports database and kidney biopsy of patients with diagnosis of IgAN. Kidney biopsy were classified according new OC (MEST-C). Composite outcome was doubling of baseline serum creatinine concentration or end stage kidney disease. We performed comparative analyses between groups with and without crescentic lesions in kidney biopsy.

Results: Results: In the following image we describe baseline clinical data and kidney biopsy features of patients with IgAN as well comparative analysis of groups with (C1/C2) and without (C0) crescentic lesions in kidney biopsy.

Conclusions: Conclusion: Crescentic lesions were associated with both worst renal function at biopsy and outcomes in brazilian patients. These data ratify previous findings in the literature.

	Baseline (n=111)	C0 (n=80)	C1/C2 (n=31)	p
Male (%)	35	46	58	0.29
Age (years)	36 (25;44)	33 (25;47)	32 (24;42)	0.54
Hypertension (%)	65.5	60.6	79.1	0.13
Hematuria (%)	85.5	81	96.7	0.03
Serum creatinins (mg/dl)	1.4 (0.9;2.4)	1.2 (0.9;2.0)	1.9 (1.4;2.9)	0.0007
Estimated GFR ml/min/1,73m2 (CKD-EPI)	53 (30;80)	65 (33.5;88.7)	36 (23;54.9)	0.0007
Proteinuria (g/day)	1.95 (1.1,3.4)	1.5 (1.1; 3.1)	2,38 (1,4; 4,1)	0.09
Serum Albumin (g/L)	3.5 (3;3.8)	3.5 (3;3.9)	3.3 (3.2;3.6)	0.2
High serum IgA level (%)	44.7	43.1	47.8	0.79
Kidney Biopsy				
M1 (%)	77.5	75	83	0.44
E1 (%)	38.7	28.7	64.5	0.009
S1 (%)	76.6	68.7	96.7	0.001
T1/T2 (%)	41.4	35	58	0.03
Treatment				
ACE or ARA (%)	68.4	72.5	58	0,17
Corticosteroid therapy (%)	43.2	37.5	58	0.05
Other Immunosuppressive drug (%)	29.1	13.7	38.7	0.01
Follow-up (months)	63 (17;108)	70 (35;121)	11 (4; 65)	<0.0001
Doubling serum creatinine and/or ESRD (%)	29.7	21.2	51.6	0.002
Evolution Time to ESRD (months)	12 (2;64)	39 (17;79)	4.5 (1;10)	0.0014

TH-PO108

Urinary Excretion of C5a in Membranous Nephropathy Isabelle Ayoub,[5] Daniel J. Birmingham,[1] Jessica M. Nelson,[4] Lee A. Hebert,[2] Brad H. Rovin.[3] *[1]Ohio State University, Columbus, AL; [2]Ohio State University Medical Center, Columbus, OH; [3]Ohio State University Wexner Medical Center, Columbus, OH; [4]Ohio State Wexner Medical Center, Columbus, OH; [5]Medicine/ Nephrology, The Ohio State University Wexner Medical Center, Columbus, OH.*

Background: Using proteomic analysis we previously showed that glomeruli from patients with membranous nephropathy (MN) express increased levels of complement components C3 and C4 and decreased levels of the complement receptor CR1 compared to glomeruli from healthy kidneys. Here we measured complement component C5a in the urine of MN patients as a non-invasive surrogate of intra-renal complement activation.

Methods: Urine samples were collected at the time of first kidney biopsy of patients with active MN (n=13). These patients had primary MN as suggested by dominant (n=5) or co-dominant (n=6) IgG4 glomerular immunofluorescence. Two patients only had IgG1 glomerular immunofluorescence, usually seen in secondary MN, but no underlying etiology was found in either case, so they were treated as primary MN. Urine C5a levels were measured by a sandwich ELISA.

Results: Urine protein to creatinine ratios (uPCR) in this group of MN patients ranged from 2.2-11 g/g with a median of 4 g/g. Urine C5a levels were undetectable in 2 two patients. The median value for the group was 4 ng/mg urine creatinine with a range of 0-11 ng/mg. Patients with Ig4 dominant or co-dominant MN had a higher level of C5a (5.1±3.3 ng/mg) than patients who were IgG1 dominant (1.3±1.8). C5a levels correlated with spot uPCR (r=0.68, p= 0.01), however the correlation was mainly driven by those with heaviest proteinuria.

Conclusions: In immunologically active primary MN, C5a is present in the majority of urine samples. In secondary (IgG1-dominant) MN C5a levels were much lower than in primary MN, but this is difficult to interpret due to small sample size. The presence or absence of urinary C5a could be useful in differentiating immunologically active proteinuric patients with an historic diagnosis of MN from proteinuria driven by hemodynamic or other factors, facilitating decisions regarding immunosuppressive therapy without repeating kidney biopsy. The relationship between urinary C5a and anti-PLA2R levels remains to be determined.

TH-PO109

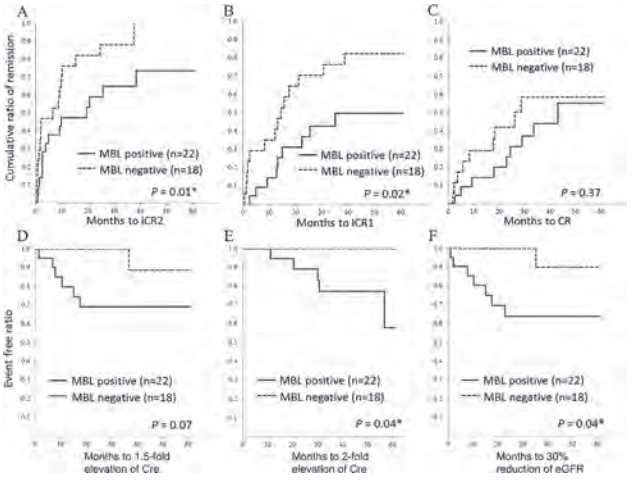
Clinical Impact of Glomerular Mannose-Binding Lectin Deposition in Intrinsic Antigen-Related Membranous Nephropathy Norifumi Hayashi,[1] Yuki Matsui,[1] Keiji Fujimoto,[1] Hiroki Adachi,[2] Hideki Yamaya,[1] Hitoshi Yokoyama.[1] *[1]Kanazawa Medical University, Kanazawa, Japan; [2]Kanazawa medical university, Kanazawa, Japan.*

Background: The M-type phospholipase A2 receptor (PLA2R) and thrombospondin type-1 domain-containing 7A (THSD7A) were identified as intrinsic antigens in primary membranous nephropathy (MN). Complement activation via the lectin pathway in intrinsic antigen-related MN is still unclear.

Methods: We retrospectively enrolled 60 primary MN patients and detected activated complement pathways by staining complement proteins in glomerular deposition. According to the findings of PLA2R and THSD7A staining in glomeruli, they were classified into intrinsic antigen-related or -unrelated MN. We evaluated clinicopathological characteristics and predictors of clinical outcomes in intrinsic antigen-related MN.

Results: Thirty-nine patients (65%) had PLA2R in glomerular deposits and 2 patients (3.3%) had THSD7A. One of them had both PLA2R and THSD7A (double positive). Forty patients were classified into the intrinsic antigen-related group. The other 20 patients were negative for both antigens (unrelated group). The prevalence and staining intensity of mannose-binding lectin (MBL) deposits was much higher in the intrinsic antigen-related group (55% vs. 20%, P<0.010, 1.0 [1.0-2.0] vs. 1.0 [0.0-1.0], p=0.01, respectively). The staining intensity of MBL in glomeruli also correlated with the IgG4 staining intensity. In intrinsic antigen-related MN, MBL staining intensity was an unfavorable predictor for remission of proteinuria (HR 0.40, p<0.01) and renal dysfunction (HR 3.81, p=0.01) in Cox proportional hazards analysis. Moreover, the glomerular MBL-positive group showed more severe interstitial fibrosis and worse clinical outcomes.

Conclusions: Intrinsic antigen-related MN was more strongly associated with complement activation by the lectin pathway, and was an unfavorable predictor for clinical outcomes.



TH-PO110

Clinicopathological Characteristics of Thrombospondin Type 1 Domain–Containing 7A-Positive Membranous Nephropathy Shigeo Hara,[2] Shinichi Nishi,[3] Akihiro Yoshimoto.[1] *[1]Kobe City Medical Center General Hospital, Kobe, Japan; [2]Diagnostic Pathology, Kobe University Graduate School of Medicine, Kobe, Japan; [3]Nephrology, Kobe University Graduate School of Medicine, Kobe, Japan.*

Background: Recent studies suggested the possible association of Thrombospondin type 1 domain–containing 7A (THSD7A)-positive membranous nephropathy (MN) and malignancy; however, the clinicopathological characteristics of THSD7A-positive MN have been still poorly characterized.

Methods: Among 164 consecutive cases of pathologically-proven MN, 7 cases were immunohistologically positive for THSD7A (4.2%) and defined as THSD7A-positive MN. Clinical characteristics including renal function, proteinuria levels, and incidence of specific disease entities such as malignancy and other disorders were obtained from the data base record. IgG subclass profiles were examined in 6 cases using frozen sections. PLA2R1 immunostaining were evaluated in all cases.

Results: The patient age ranged from 42 to 73 (mean 63.7). Male-female ratio was 5:2. The median levels of serum creatinine and proteinuria were 0.84 mg/dl (range 0.53 – 1.4) and 7.41 g/gCr (0.37 – 16.1), respectively. Two patients had cancer concomitantly at the time of renal biopsy; one had small cell carcinoma in the lung and the other had prostatic adenocarcinoma. THSD7A immunostaining was available in the lung cancer case, which was negative for THSD7A. Two patients had concurrent incidence of inflammatory diseases; one had Kimura's disease, a chronic eosinophilic inflammatory disorder of unknown etiology, and the other had eosinophilic pneumonia in addition to asthma. Remaining three patients had no specific disease entity at the time of MN diagnosis, classified as primary MN. IgG subclass showed IgG4-dominant or co-dominant phenotype in 5 cases. One case with prostatic cancer had IgG2 and IgG3-dominant distribution. One case showed PLAR1 positivity (dual positive for PLA2R1 and THSD7A).

Conclusions: In contrast to the major distribution of IgG4-dominant/co-dominant phenotype, THSD7A-positive MN tends to be associated with various disease entities.

Funding: Government Support - Non-U.S.

TH-PO111

Urine Anti-PLA2R Antibody Is a Biomarker for Diagnosis and Activity in Idiopathic Membranous Nephropathy Bing Li. *Department of Nephrology, 2nd Affiliated Hospital of Harbin Medical University, Harbin, China.*

Background: Detection of the serum anti-PLA_2R antibody ($sPLA_2R$-Ab) and the glomerular PLA_2R antigen ($gPLA_2R$) has been widely used as a diagnostic tool for idiopathic membranous nephropathy (IMN) and for the evaluation of IMN activity and severity. Since urine samples more directly reflect kidney damage and alterations than blood samples, we evaluated whether urine anti-PLA_2R antibody ($uPLA_2R$-Ab) could be utilized as a noninvasive biomarker for IMN.

Methods: In this study, we completed a qualitative analysis through indirect immunofluorescence test (IIFT) and measured $uPLA_2R$-Ab and $sPLA_2R$-Ab concentrations by enzyme-linked immunosorbent assay (ELISA) in 28 patients with biopsy-proven IMN and 12 patients with secondary membranous nephropathy (SMN).

Results: Overall, 64.3% (n=18) of patients with IMN had IIFT-positive $sPLA_2R$-Ab, 67.9% (n=19) of patients with IMN had IIFT-positive $uPLA_2R$-Ab IIFT, and none of the SMN patients had IIFT-positive $sPLA_2R$-Ab or $uPLA_2R$-Ab. The titers of the anti-PLA_2R antibody from the IMN patients in the urine (10.72±22.24 RU/mmol, presented as $uPLA_2R$-Ab/urine creatinine) or the serum (107.36±140.93 RU/ml) were higher than those from the SMN patients (0.51±0.46 RU/mmol, p<0.001; 0.008±0.029 RU/ml, p=0.02, respectively). Statistical analyses indicated that there were positive correlations between $uPLA_2R$-Ab and $gPLA_2R$, $sPLA_2R$-Ab or urinary protein and negative correlations between $uPLA_2R$-Ab and serum albumin in patients with IMN.

Conclusions: Our results indicate that uPLA$_2$R-Ab might serve as a biomarker, like sPLA$_2$R-Ab, for IMN diagnosis and that the antibody titer, as measured by ELISA, might reflect IMN activity and severity.

Funding: Government Support - Non-U.S.

TH-PO112

The Exact Time Difference between PLA2R Antibody and Proteinuria in Reflecting Disease Activity Change in Idiopathic Membranous Nephropathy Weifeng Lin,[2,4] Hang Li,[3,1] Xuemei Li,[1] Limeng Chen,[1] Xuewang Li.[1] *[1]Peking Union Medical College Hospital, Beijing, China; [2]Department of Nephropahty, Peking Universty Third Hospital, Beijing, China; [3]Peking Union Medical college hosiptal, Beijing, China; [4]Peking Union Medical College Hospital, Chinese Academy of Medicine Sciences & Peking Union Medical College, Beijing, China.*

Background: According to most studies, PLA2R antibody was faster than proteinuria in reflecting disease activity in idiopathic membranous nephropathy. However, the exact time difference is still unknown. This study was to reveal the precise time difference between them, which could guild clinical practice.

Methods: A total of 102 patients with IMN proven by kidney biopsy at Peking Union Medical College Hospital from January 1, 2014 to December 31, 2015 were enrolled. An observationally prospective follow-up was conducted monthly to monitor the changes in PLA2R antibody titer and disease activity changes based on proteinuria in IMN. The study end point was clinical remission based on proteinuria or the research deadline.

Results: The average follow-up time was (13.83±3.14) months, with a minimum time of 7 months and a maximum time of 21 months. The overall average time of PLA2R antibody turning negative in clinical remission group based on proteinuria was (3.11±2.97) months. In subgroups,the average time of antibody turning negative in the complete remission (CR) group and partial remission (PR) group were (3.17±3.23) months and (3.13±3.05) months, respectively. Importantly, our study showed that PLA2R antibody was (1.91±2.51) months earlier turning negative than proteinuria reaching clinical PR in IMN. Also, there was (6.91±3.33) months earlier for antibody to turn negative than proteinuria to achieve clinical CR. There was (3.09±4.66) months earlier for antibody turning positive again than proteinuria recurrence.

Conclusions: The PLA2R antibody changes was faster than proteinuria in reflecting disease activity changes in IMN,about 2 months ahead of proteinuria PR, about 7months ahead of proteinuria CR and about 3 months ahead of proteinuria recurrence.

TH-PO113

Plasma C4d Differentiates PLA2R Positive Membranous Nephropathy from Other Primary Glomerular Diseases Congcong Jiao,[3] Junjun Luan,[3] Guangying Guo,[3] Wei Qu,[5] Ying Chen,[5] Weiwei Kong,[3] Yani Zhang,[3] Jingqi Fu,[1] Jingbo Pi,[1] Jeffrey B. Kopp,[4] Lining Wang,[2] Hua Zhou.[3] *[1]Chinese Medical University, Shenyang, China; [2]Department of Nephrology, First Affiliated Hospital of China Medical University, Shenyang, P. R. China, Shenyang, China; [3]Nephrology department, The first hospital of China medical university, Shenyang, China; [4]NIDDK, NIH, Bethesda, MD; [5]China Medical University, Shenyang, China.*

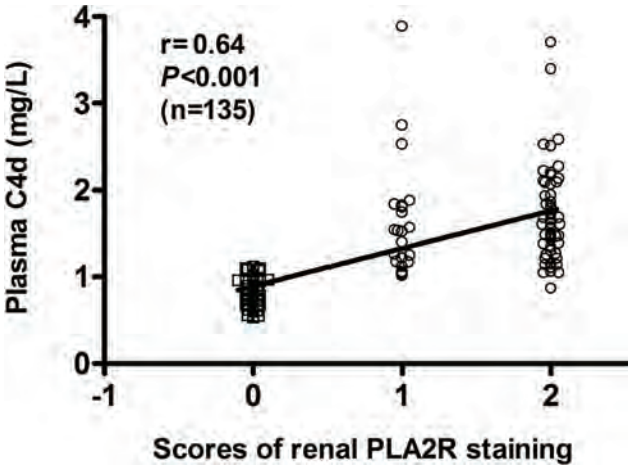
Background: Renal C4d staining is a potential diagnostic biomarker for immune complex-mediated glomerular diseases. Positive M-type phospholipase A2 receptor (PLA2R) staining on kidney biopsy is specific for primary membranous nephropathy (pMN) diagnosis. We aimed to assess whether plasma C4d can differentiate PLA2R positive MN from other primary glomerular diseases and to correlate plasma C4d level with renal PLA2R staining.

Methods: Plasma C4d levels were measured by ELISA in 16 healthy volunteers and 187 untreated patients with biopsy-proven glomerular diseases, including 80 PLA2R positive and 55 PLAR negative MN cases, 20 IgA nephropathy, 18 minimal change disease, and 14 focal segmental glomerulosclerosis cases. There were 123 nephrotic and 26 nephritic cases among subjects with primary glomerular diseases. PLA2R negative MN cases included atypical pMN (n=17), hepatitis B virus (HBV)-associated MN (n=23) and autoimmune-associated MN (n=15).

Results: Plasma C4d levels significantly increased in pMN compared with each of the other groups. C4d differentiated pMN from these three primary glomerular diseases either in nephrotic (AUC=0.7, p<0.001, n=111) or nephritic diseases (AUC=1.0, p<0.001, n=21). C4d also distinguished PLA2R positive MN from PLA2R negative MN (AUC=0.98, p<0.001, n=135). Interestingly, C4d was significantly decreased in autoimmune-associated MN compared with HBV-associated MN and PLA2R negative MN without identified primary causes. Plasma C4d was positively correlated with the extent of renal PLA2R staining (r=0.64, p<0.001, n=135).

Conclusions: Plasma C4d differentiates PLA2R positive MN from other primary glomerular diseases and correlated with renal PLA2R staining. Plasma C4d may serve as a supplementary biomarker, together with circulating PLA2R antibody, as a measurement panel for diagnosing pMN in patients with a contraindication to renal biopsy.

Funding: NIDDK Support, Government Support - Non-U.S.



TH-PO114

Clinical Significance of Urinary Podocyte-Derived Microparticle Detection in Idiopathic Membranous Nephropathy Jian Lu, Kun ling Ma, Yang Zhang, Zebo Hu. *Zhongda Hospital, Southeast University Medical School, Nanjing City, China.*

Background: Microparticles (MPs) are a type of extracellular vesicles (EVs) shed from the outward budding of cytoplasma membranes during cell apoptosis and/or activation. These microsized particles release specific contents (lipids, proteins, microRNAs, etc.) and are active participants in a wide range of both physiological and pathological processes at molecular levels. This study aimed to observe the change of urinary podocyte-derived microparticle level and to explore its potential clinical significance in idiopathic membranous nephropathy(IMN).

Methods: We prospectively enrolled patients with IMN (n = 24) before initial Immunosuppressive therapy to study renal tissue pathology using Periodic acid–Schiff staining by light microscope and ultrastructural observation by transmission electron microscope. After isolation from urine samples, podocalyxin-positive podocyte-derived microparticles were characterized by flow cytometry. Twenty IMN patients were studied again 6 months after Glucocorticoids in combination with tacrolimus intervetion. Health Volunteers (n= 15) served as controls. The correlation of urinary podocyte microparticles and clinical and pathological factors in IMN patients was analyzed.

Results: Compared with the control group, there were increased serum PL2AR antibody tite and 24-hour urinary protein (all P<0.05). The fraction of podocyte microparticles among urinary microparticles was elevated in IMN compared with health volunteers (P<0.01) and decreased after 6 months therapy and after controlling for clinical parameters.

Conclusions: The excretion of urine podocyte-derived microparticles might reflect podocyte injury and might be closely associated with the progression of IMN.

TH-PO115

Practice Patterns in Management and Outcomes of Primary Membranous Nephropathy: A Single Centre Experience Martin E. Durcan, Mohamed Elsayed, Arvind Ponnusamy. *Royal Preston Hospital, Preston, United Kingdom.*

Background: Membranous nephropathy is a common glomerular disease. In the last number of years there has been many clinical trials addressing its management. These trials have altered the treatment patterns of this condition by giving the physician more treatment options. The aim of this study was to review the practice patterns in management and outcomes of primary membranous nephropathy at a single U.K centre.

Methods: Clinical demographics, relevant laboratory values and modalities of treatments were collected on all patients with biopsy proven membranous nephropathy between 2004 and 2011. Patients were followed up until November 2016. The following outcomes were of interest; complete remission (proteinuria less than 30mg/mmol and stable renal function), partial remission (at least 50% reduction in proteinuria from baseline and uPCR <300mg/mmol with stable renal function (<15% drop in eGFR), relapse (recurrence of proteinuria with ≥ 300mg/mmol) and a composite outcome of the following endpoints; doubling of baseline creatinine, start of renal replacement therapy or death.

Results: 129 incident patients were followed up for a median of 5.56 years. Mean age of patients was 56.5 ±16.7 years of age. 66.6% of patients were male and remainder were female. Prevalence rate of hypertension was 60.6% while 17.4% had diabetes. Mean baseline eGFR was 62.9 ± 34.6 ml/min/1.73m^2. Mean PCR and albumin at diagnosis was 769.83 mg/mmol and 27.9 ± 6.6 g/L, respectively. 56 (43.4%) received immunosuppressive therapy overall. 24 (19%) patients were treated with the Ponticelli regime.36 (28%) received a calcineurin inhibitor.12 (9.52%) received mycophenolate mofetial (MMF). Patient and renal survival at last follow up was 71.20%. 51% of study population obtained complete remission. 27% achieved partial remission. 40.17% achieved the composite outcome. Achieving remission (whether partial or complete)

decreases hazards of developing composite outcome by 64%. P=0.0007. Please see figure 1. for survival outcomes related to each treatment modality.

Conclusions: Outcomes are comparable and better than what is reported in the literature. Treatment of patients with a calcineurin inhibitor seems to be superior to treatment with other modalities. Further analysis of this finding is needed.

TH-PO116

Clinicopathological Manifestation in Patients of Idiopathic Membranous Nephropathy Assigned to a Heterogeneous Group with Nephrotic Syndrome Shinji Kitajima,[1] Tadashi Toyama,[1] Akinori Hara,[1] Yasunori Iwata,[1] Norihiko Sakai,[1] Miho Shimizu,[1] Kengo Furuichi,[1] Hitoshi Yokoyama,[2] Takashi Wada.[1] *[1]Division of Nephrology, Kanazawa University Hospital, Kanazawa, Japan; [2]Division of Nephrology, Kanazawa Medical University Hospital, Uchinada, Japan.*

Background: The 20-year renal survival of Idiopathic membranous nephropathy (IMN) in Japanese adults with nephrotic syndrome was reported around 60%. Based on the electron microscopic findings, we reported that there are two distinct types, homogeneous type and heterogeneous type; synchronous electron dense deposits or various phases of dense deposits in basement membrane, respectively. (Kidney International in 2004). Our previous analysis revealed that the rate of renal death was around 20 times higher in heterogeneous group (heterogeneous group; 25.6%, homogeneous group; 1.3%). In this study, we evaluated the predisposing clinicopathological factors for IMN patients assigned to heterogeneous group with nephrotic syndrome (NS).

Methods: Forty patients of NS (24 males and 16 females; mean age 45.7 years) with heterogeneous type IMN were evaluated in this study who were collected in Kanazawa University Hospital and affiliated hospitals from 1965 to 2013. The patients were followed for more than three years, or until renal or patient death. Clinicopathological factors, which might affect renal death were evaluated.

Results: Renal death was observed 12 out of 40 patients (30%). We divided two groups; renal death group and renal survival group. The renal death group showed lower remission rate (CR or ICRI;renal death group; 16.7%, renal survive group; 60.7%, p=0.01), and higher sustained NS rate (renal death group; 50.0%, renal survive group; 10.7%, p=0.006). There was no difference in clinical background at onset between two groups. In renal death group, two patients achieved remission, but relapsed after the remission and became renal death. The median duration to renal death after kidney biopsy was 107 months, and patients of sustained NS had a tendency to shorter duration (NS group; 76.5months, non-NS group; 139.1months, p=0.10).

Conclusions: These findings suggest that electron microscopic findings demonstrating heterogeneous type and no-remission of nephrotic syndrome was susceptible to renal death in patients with nephrotic IMN.

TH-PO117

Serological and Immunohistological Characteristics of Membranous Nephropathy in Children Anne K. Dettmar,[1] Thorsten Wiech,[4,3] Markus J. Kemper,[5] Jun Oh,[1] Rolf A. Stahl,[3] Elion Hoxha.[2,3] *[1]Pediatric Nephrology, University Medical Center Hamburg- Eppendorf, Hamburg, Germany; [2]III. Department of Internal Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3]SFB1192, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [4]Department of Pathology, University Medical Center Hamburg Eppendorf, Hamburg, Germany; [5]Department of Pediatrics, Asklepios Nord-Heidberg, Hamburg, Germany. Group/Team: Pediatric MN Study Group.*

Background: In adult patients with membranous nephropathy (MN) phospholipase A_2 receptor 1 (PLA_2R1) and thrombospondin type 1 domain containing 7A (THSD7A) are the target antigens in 80% and 2-3% of patients, respectively. In children MN is less common and two more antigens are involved in disease development: neutral endopeptidase (NEP) and cationic bovine serum albumin (cBSA). In this study we performed a clinical, serological and immunhistological characterization of MN in children.

Methods: Twelve children with biopsy-proven MN were included. We analyzed the sera for PLA_2R1, THSD7A, NEP and cBSA-Antibodies (Ab). Clinical data and blood samples were evaluated every three months. Immunohistochemical analyses for all antigens and IgG subclasses were performed in five biopsies. The median follow-up time was 24 months.

Results: Six (50%) children had a PLA_2R1-associated MN. There were no antibodies against THSD7A, NEP or cBSA in any of the sera. To detect further potential antigens, all sera were analyzed by Western blot against human glomerular extracts, showing no further specific reactions. Immunohistochemical analyses of renal biopsies identified no THSD7A, NEP or cBSA-associated case in our cohort. Two biopsies from PLA_2R1-associated patients showed enhanced staining for PLA_2R1, but not for the other antigens. Both biopsies were positive for IgG2 and IgG4. In contrast, all three biopsies from patients with non-PLA_2R1-associated MN stained negative for IgG2 and IgG4. IgG1 and IgG3 staining was not different between PLA_2R1- and non-PLA_2R1-associated MN cases. Four PLA_2R1-Ab positive and five PLA_2R1-Ab negative patients had a remission of proteinuria. In PLA_2R1-associated cases remission was preceded by decline of PLA_2R1-Ab levels. In one patient a relapse of proteinuria occurred and was preceded by PLA_2R1-Ab reappearance in serum.

Conclusions: PLA_2R1-Ab levels are associated with disease activity and outcome in pediatric MN. PLA_2R1-associated MN is a common form of pediatric MN, however, in a considerable number of patients the pathogenesis of the disease remains unclear.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO118

The Relationship between Interstitial Fibrosis and Tubular Atrophy Scores and Adverse Renal Outcomes among Patients with Primary Membranous Nephropathy: A Retrospective Study Martin E. Durcan, Mohamed Elsayed, Arvind Ponnusamy. *Royal Preston Hospital, Preston, United Kingdom.*

Background: Primary Membranous Nephropathy (MGN) is a major cause of adult onset nephrotic syndrome. The severity of interstitial fibrosis and tubular atrophy (IF/TA) has long been used in the prognostication of some glomerulopathies and renal allografts, little is known about their effect on MGN outcomes. The aim of this study was to investigate the association of IF/TA with adverse renal outcomes among a cohort of patients with biopsy-proven primary MGN.

Methods: A cohort of all patients diagnosed with biopsy-proven primary MGN between 2004 to 2011 was constructed. Follow up was until November 2016. Data was retrieved retrospectively. Renal biopsies were scored for (IF/TA) as 0 (absent/focal), 1(moderate) and 2(severe). Primary outcome was a composite of the following endpoints; doubling of baseline creatinine, start of renal replacement therapy or death. Achieving remission was a secondary outcome. Univariate and adjusted Cox regression models were used to calculate hazard ratios with 95% CI for each IF/TA group.

Results: 129 incident patients were followed for a median of 5.56 years. 33.3% were females with the remainder being male. Mean age was 56.4 ±16 years. Baseline mean eGRF was 62.9 ± 34.6 ml/min/1.73m^2 and PCR was 769.83 mg/mmol. Patients with IF/TA scores of 0,1 and 2 represented 72.5%, 17.5%and 6.8%, respectively. Unadjusted analysis revealed that patients with IF/TA scores of 1 and 2, in reference to IF/TA=0, were at elevated risk to develop the study primary outcome, HR 2.05 [95% CI, 1.04-4.17] and HR 2.73, [95% CI, 1.03-7.26], respectively. However, when adjusted for potential confounders, higher IF/TA scores were no longer associated with adverse outcomes, HR 1.78 [95% CI, 0.39-8.20] for IF/TA=1 and HR 1.62 [95% CI, 0.09-12.95] for IF/TA=2. Furthermore, those with lower scores didn't have greater likelihood to achieve remission, HR 0.69 [95%CI, 0.31-1.56] for IF/TA=1 and HR 0.34 [95%CI, 0.47-2.52] for IF/TA=2 (reference: IF/TA=0).

Conclusions: The degree of IF/TA on renal biopsy did not predict adverse outcomes among patients with primary membranous nephropathy. Moreover, it was not associated with a higher likelihood to attain remission. We propose that management not be dictated by IF/TA scores. Patients with severe IF/TA should still be considered for treatment.

TH-PO119

Kidney and Patient Survival in Glomerulonephritis: Results from a Mexican Cohort Petra Martínez,[1] Liliana Mondragon,[4] Benjamin Gomez-Navarro,[5] Arisbeth Villanueva-Perez,[6] Alfonso M. Cueto-Manzano,[3] Enrique Rojas-Campos.[2] *[1]Nephrology, Hospital of Specialties, CMNO, IMSS, Guadaljara, Mexico; [2]INSTITUTO MEXICANO DEL SEGURO SOCIAL, GUADALAJARA, Mexico; [3]None, Zapopan, Jalisco, Mexico; [4]IMSS, Guadalajara, Mexico; [5]IMSS, HECMNO, Zapopan, Jalisco, Mexico; [6]Patologia y nefropatologia, Guadalajara, Mexico.*

Background: Background: There is scarce information of glomerulonephritis (GN) survival in our setting. Objective: To evaluate kidney and patient survival in GN.

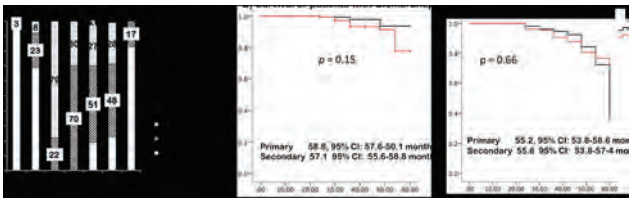
Methods: Methods: Retrospective cohort. From kidney biopsy records, all cases with GN diagnosis, ≥16 yrs, and any gender, were included; transplant biopsies excluded. Data were obtained from medical charts. At the end of follow-up, patient status was registered as alive, dead or lost, and kidney status as functioning or failure. Statistical Analysis: Kaplan Meier and Log-rank analysis used to evaluate mortality, and Cox Hazard Proportional Model to evaluate mortality risk factors.

Results: Results: 328 biopsies were analyzed; age 33±13 yrs, 67% female, follow-up 35±11 months. Comparison between primary vs secondary GN is shown in Table. Figure A, show the most common clinical presentation. Type of GN: Lupus nephritis 41%, Focal segmental glomerulosclerosis 23%, Membranous nephropathy 12%, other 24%. Figure B and C, shows patient and kidney survival; 32 (10%) developed ESRD, and 15 (5%) died at follow-up. In multivariate analysis, final systolic blood pressure (SBP, RR 1.29, 95%CI: 1.00-1.06, p=0.04), and age (RR 1.03, 95%CI: 0.99-1.07, p=0.06) predicted death, whereas baseline SBP (RR 1.45, 95%CI: 0.83-250, p=0.01) and baseline creatinine (RR 3.09, 95%IC: 1.03-9.26, p=0.02) predicted kidney survival.

Conclusions: Conclusions: Primary GN had lower SBP and higher cholesterol, CrCl and proteinuria at baseline than Secondary GN; however these differences disappeared at the end of follow-up. Patient and kidney survival were similar to other series, and were not different between Primary and Secondary GN.

Variable	GN primary		GN Secondary	
	Baseline	Final	Baseline	Final
SBP (mmHg)	122±15	120±16	125±16*	123±15
DBP (mmHg)	77±10	76±10	77±10	77±10
Cholesterol (mg/dL)	230 (180-270)	213 (154-254)£	220 (176-265)*	214 (152-247)£
CrCl (ml/min/1.73m2)	80 (60-107)	82 (55-97)	69 (42-92)	75 (48-94)*
Proteinuria (g/day)	3100 (1100-6500)	573(228-1400)£	1800 (595-3500)*	499 (210-1500)£

*p<0.05 vs same evaluation of primary GN; £p<0.05 vs baseline of the same-group.



TH-PO120

A Single Center Observation Study on Findings in Indication Biopsies and Autopsies after Stem Cell Transplantation Michael Y. Girsberger,[1] Helmut Hopfer,[3] Michael Dickenmann,[2] Thomas Menter.[3] *[1]None, Basel, Switzerland; [2]Universita Hospital, Basel, Switzerland; [3]University Hospital Basel, Basel, Switzerland.*

Background: Haematopoietic stem cell transplantation (HSCT) is a now widely used therapy both in the treatment of haematolymphoid malignancies as well as other malignant or autoimmune diseases. Renal impairment is an important problem after HSCT, yet its pathophysiology still needs more investigation, especially regarding the correlation of clinical findings and morphologic changes.

Methods: We retrospectively analysed indication renal biopsies and autopsies after HSCT of the HSCT patient cohort of the University Hospital of Basel, Switzerland. Data of patients' characteristics were retrospectively collected from the clinical records.

Results: The pathology reports of 17 indication biopsies and 137 autopsies were analysed. In the autopsy cohort, the most common changes were due to acute kidney injury (55/137) most likely as a consequence to the deteriorated state of the patients and thrombotic microangiopathy (14/137). In the indication biopsy cohort the most common changes were therapy related (12/17), with thrombotic microangiopathy (5/17) and Calcineurin-Inhibitor toxicity (4/17) representing the majority within this category.

Conclusions: This study gives a comprehensive overview on potential renal complications in HSCT patients and broadens the spectrum of diseases which have to be expected to occur in this special clinical setting.

Renal Findings

Diagnosis	Indication biopsy cohort (n=17)	Autopsy cohort (n=137)
Acute tubular damage/necrosis	2 (12%)	55 (40%)
Chronic vascular and interstitial changes	2 (12%)	20 (15%)
Thrombotic microangiopathy	5 (29%)	14 (10%)
Tumour infiltrates	1 (6%)	9 (7%)
Cholaemic nephrosis	0	8 (6%)
Presence of fungi or bacteriae in the glomeruli/kidney parenchyma	0	6 (4%)
Infarction	0	5 (4%)
Amyloidosis	0	2 (1%)
Fibrillary glomerulonephritis	0	1 (1%)
Membranous glomerulonephropathy	3 (18%)	1 (1%)
Renal vein thrombosis	0	1 (1%)
Calcineurin-Inhibitor toxicity	4 (24%)	0
IgG4 related interstitial nephritis	1 (6%)	0

TH-PO121

Clinicopathologic Features of Biopsy-Proven Kidney Diseases in Korean Elderly Patients over 65 Years Old Seong Sik Kang,[1,2] Woo Yeong Park,[1,2] Hayeon Park,[1] Sang Mok Yeo,[1] Kyubok Jin,[1,2] Sung Bae Park,[1,2] Seungyeup Han.[1,2] *[1]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Republic of Korea; [2]Keimyung University Kidney Institute, Daegu, Republic of Korea.*

Background: As the life expectancy increases and the aging society comes, the incidence of kidney disease (KD) is increasing in the elderly population. The purpose of this study was to evaluate the clinical and pathological spectrums of KD in the elderly population.

Methods: We retrospectively investigated 101 patients aged over 65 years with biopsy-proven KD. We analyzed the clinicopathologic manifestation, treatment strategy, and clinical course of KD.

Results: The mean age at the time of kidney biopsy was 71 ± 4 years, and 44.6% of patients had hypertension and 10.9% had diabetes. The median serum creatinine was 1.4 mg/dL (interquartile rage 0.9, 2.3). The most common clinical diagnosis was nephrotic syndrome (NS, 55%), followed by asymptomatic urinary abnormality (AUA, 12%). The most common primary glomerular disease was membranous nephropathy (MN, 33%) and, secondary glomerular disease was anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis (AGN, 24%). The most common pathologic diagnosis classified based on clinical diagnosis was MN (33%) in NS, IgA nephropathy (IgAN, 33%) in AUA, AGN (67%) in rapidly progressive glomerulonephritis (RPGN), IgAN (88%) in acute nephritic syndrome, and hypertensive nephropathy (25%) in chronic GN. Treatment strategies for KD were angiotensin converting enzyme inhibitor or angiotensin receptor blocker (48%), and immunosuppressants (48%) such as steroid, cyclosporine, mycophenolate mofetil, or cyclophosphamide. The most common disease that was completely responded among NS was minimal change disease (39%). Of the 21 (21%) patients who received dialysis, 11 (52%) received dialysis due to the onset of acute kidney injury (AKI), and received maintenance dialysis without recovery. The most common cause of dialysis was AGN (38%). Death rate was 17%, and the most common cause was infection (53%).

Conclusions: KD in elderly patients showed various patterns in our study. The most common indication for kidney biopsy in elderly patients was NS. NS in elderly patients should be actively performed for kidney biopsy because of the high rate of complete remission when treated. All elderly patients with AKI were dialyzed and progressed to end-stage renal disease without recovery. RPGN in elderly patients should be diagnosed and treated early because the prognosis is poor.

TH-PO122

Primary Nephrologist Procedural Status Impact on Kidney Biopsy Findings Christopher B. McFadden,[2] Krystal Hunter,[2] Manjula J. Naik.[1] *[1]Clinical renal Associates, Phoenixville, PA; [2]Cooper Medical School of Rowan University, Camden, NJ.*

Background: A kidney biopsy is an important diagnostic procedure in the field of Nephrology. It generally yields information regarding multiple components of a patient's kidney problems including the diagnosis, therapeutic options, and prognosis. The decision to perform a kidney biopsy represents a balance of relevant risks and benefits by the provider (typically nephrologist) and patient. Frequently, the decision to perform a biopsy is guided most by the the likelihood the findings will alter patient care.

Methods: We performed a retropsective study of 99 native kidney biopsies perfromed within the last 10 years at our institution. Our primary hypothesis was the status of the primary nephrologist (performs biopsy or does not perform biopsy) had a signficant impact on the kidney biopsy findings as assessed by whether immune based therapy was used in the next 3 months after time of kidney biopsy (yes or no). A chi square test was used to compare the outcome (immune therapy or not) in the two referring nephrology groups. The study was reviewed and approved by the Cooper University Hospital IRB.

Results: A significantly higher rate of immune therapy (65.9 vs 29.3%, p <0.01) was noted in the group whose primary nephrologist performed biopsies (3 nephrologists) compared to the group whose primary nephrologist did not perform biopsies (6 nephrologists). The groups were similar in terms of their age, serum creatinine, and urine protein to creatinine ratio as presented in Table 1. The patient characteristics reported represent data from 30 and 46 subjects, respectively, in the biopsy/ non biopsy groups.

Conclusions: This retropepctive chart review suggests the status of the primary nephrologist (performing biopsy or not performing a biopsy) impacts which patients get a kidney biopsy. These potential biases should be considered as the decision to perform a biopsy is made. This study is limited by its single center design, retrospective nature, and lack of information about patient outcomes.

Nephologist Procedural Status Impacting Bx. Findings

	Nephologist performs Bx	Nephrologist does not perform Bx.
Biopsy Led to Immune Therapy	27/41 (65.9%)	17/58 (29.3%)
Patient Characteristics		
Age (years)	52.2	56.1
Serum Creatinine (mg/dl)	1.88	1.75
Urine protein/creatinine	4.4	5.1

TH-PO123

Histopathologic Findings and Mortality in Fibrillary Glomerulonephritis Ayman Hallab, Ranjani N. Moorthi, Jwalant R. Modi, Carrie L. Phillips, Pierre C. Dagher, Michael T. Eadon. *Indiana University, Indianapolis, IN.*

Background: Fibrillary glomerulonephritis (GN) is a rare glomerular disease with a paucity of literature. We present a retrospective collection of our single-center fibrillary GN experience.

Methods: We reviewed 7,579 kidney biopsies performed at our institution between 2001 and 2015 and identified 51 cases of fibrillary GN. Histopathologic features and clinical variables were recorded from the medical record by a nephrologist. Data is presented as mean (SD). Chi-squared test assessed correlation between histologic and categorical clinical variables.

Results: Fibrillary GN constituted 0.7% of kidney biopsies. Average age at diagnosis was 59.9 (8.8) years. Female to male ratio was 1.4:1 with 77% Caucasian patients. On light microscopy, mesangial proliferative/sclerosing GN was present in 62% of cases. Membranous (MGN), membranoproliferative GN (MPGN), and endocapillary proliferative GN accounted for 10%, 20%, and 8% of cases respectively. Mesangial changes were present in 92% of cases. Crescents were present in 7 cases (14%). Interstitial fibrosis and tubular atrophy IFTA was mild, moderate, and severe in 30%, 45%, and 21% respectively. The mean glomerular obsolescence was 30%. Immunofluorescence revealed universal staining for IgG and C3. IgM, IgA, C1q were positive in 56%, 12%, and 16% respectively. No Kappa or Lambda restriction was present. The average positivity (0-4) scale for IgG, IgM, IgA, C3, C1q was 2.6, 0.9, 0.1, 2.7, and 0.2 respectively. The pattern was granular in 38% and smudged in 62%. Electron dense deposits were seen in 7 of 51 cases (14%), mostly subepithelial. Podocyte effacement, seen in 100% of the cases, ranging from patchy to widespread. The average fibril diameter was 15.5 ± 3.4 nm [9 – 28]. Fibrils were deposited in both mesangium and GBM in 82% of the cases, and in either for the rest. Mortality was 15.7% (8 of 51). No histopathological features were associated with mortality.

Conclusions: Our fibrillary GN analysis confirms the results of prior cohorts. Histopathological features alone are insufficient to predict mortality. As this disease is infrequently reported, these cases will prove vital to pool with other cohorts in order to correlate pathologic features with outcomes.

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TH-PO124

Predictive Factors of Renal Involvement in Cryoglobulinemia: A Retrospective Study of 153 Patients Vladimir Coliche, Jean-Christophe Lega, Maurice Laville, Clemence THERY-CASARI, Pierre Trolliet, Mathilde Nouvier, Basse Grégoire, Marie N. Sarda, Denis Fouque. *Hospices Civils de Lyon, Lyon 1 University, Lyon, France.*

Background: The course of cryoglobulinemia varies widely, from asymptomatic patients to severe vasculitis. Renal involvement (RI) is a major prognostic factor, and frequently occurs several years after diagnosis. Twenty to 56% of patients will develop RI. Predictive factors of RI have not been studied. The aim of our study was to identify factors associated with RI occurence in patients with cryoglobulinemia.

Methods: We retrospectively reviewed the clinical charts of a consecutive series of 153 patients positive for cryoglobulinemia (from January 2012 to December 2014) in the University Hospital of Lyon (France). Immunoglobulin (Ig) G, IgM and IgA concentrations as well as rheumatoid factor (RF) activity were assessed in cryoprecipitate. Complement fractions C3 and C4, CH50 activity and RF were simultaneously assayed in sera. RI was defined either histologically, or biologically if cryoglobulinemia was the only possible cause of nephropathy (proteinuria > 0.5 g/24h or hematuria > 10/mm3 or eGFR < 60 ml/min/1.73m^2 CKD-EPI).

Results: Among the 153 positive measures (mean age 55 years, male gender 37%), cryoglobulinemia was associated with RI in 45 pts (29.4%). The presence of IgA in cryoprecipitate was very significantly associated with RI (22% in RI group vs 1% in control group, p<0.0001) contrary to IgG or IgM. Type 3 cryoglobulinemia was more frequent in controls than in RI group (35% vs 11%, p=0.006). Regarding etiology, only B-cell lymphoma was statistically associated with RI (22% vs 9%, p=0.03), there was no difference for hepatitis C virus. RF activity was more frequent (42% vs 24%, p=0.03) and cryoglobulin total Ig concentration was higher (137 mg/l vs 39 mg/l, p=0.001) in case of RI, whereas C3 and C4 were similar. There were more men in RI group (60% vs 27%, p<0.0001), and slightly more patients had cutaneous purpura (38% vs 22%, p=0.048).

Conclusions: Several factors may be associated with the occurrence of RI in cryoglobulinemia (IgA, B-cell lymphoma, purpura), whereas type 3 cryoglobulinemia appears to be protective. In these at risk patients, kidney function monitoring and nephroprotection might be intensified. Further studies are needed to confirm these findings and understand mechanisms of theses associations with RI.

TH-PO125

Prevalence of Occult Hepatitis C Infection in Patients with Glomerulopathies and Chronic Renal Disease: A Pilot Study Luis H. Sette,[1] Savio Augusto vieira de oliveira,[3] Nathalia C. dos Anjos,[2] Norma Lucena-Silva,[3] Edmundo P. Lopes.[1] *[1]UNIVERSIDADE FEDERAL DE PERNAMBUCO, Recife, Brazil; [2]Nephrology, University Federal of Pernambuco, RECIFE, Brazil; [3]Instituto Aggeu Magalhães, Laboratório de Imunogenética, RECIFE, Brazil.*

Background: The Occult Hepatitis C Infection (OHCI) is characterized by the presence of the genetic viral material on polymorphonuclear cells (PMNC), plasma ultracentrifugation or hepatic tissue in the absence of antibodies in the serum. It has been demonstrated a high prevalence of OHCI in patients with glomerulopathies (GP), suggesting a pathophysiological association between the virus and GP. It is also known that there is a higher prevalence of chronic HCV infection in patients with dialytic chronic kidney disease (CKD) and that IOHC can be acquired before renal replacement therapy initiation. Therefore, this study aimed to evaluate the prevalence of OHCI in patients with GP and with CKD.

Methods: Patients were evaluated from April to August 2016. Patients younger than 18 years of age, pregnant, infected with HBV, HCV and HIV and less than 3 months of follow-up were excluded. PCR for hepatits C RNA were investigated in serum, plasma ultracentrifuged and PMNC.

Results: We evaluated 126 of which 56 were excluded. Of the 64 remaining patients, 32 were GP patients. Demographic and clinical data are shown in Table 1. When analyzing patients for OHCI, a prevalence of 18.2% was observed in patients with GP. Among the patients with CKD, the prevalence was 6.25%. Although there is almost 3-fold prevalence among cases of OHCI in patients with GP it was not statistically significant (p=0.35), probably due to the small number of patients enroled.

Conclusions: The existence of OHCI was observed in patients with GP and in pre-dialytic CKD. The prevalence in patients with GP was about three times higher than that observed in patients with CKD.

Baseline characteristics

	GP (n=32)	CKD (n=32)	p
Gender, female (%)	62.5	43.7	
AGE (SD)	38.7 ± 13.6	60.9 ± 15.2	
BMI (Kg/m2), ± SD	25.5 ± 5.8	27.2 ± 4.4	p<0.001
Acumputure (n,%)	2 (6.2)	0	
Tatoo (n,%)	5 (15.6)	1 (3.1)	p=0.19
Hemotransfusion, n (%)	12 (37.5)	9 (28.2)	p=0.18
Sexual transmited disease(n,%)	6 (18.7)	11 (34.4)	p=0.004
Piercing n,%	6 (18.7)	0	
Previous Dialysis (n, %)	3 (9.3)	2 (6.2)	p=0.28
eGFR (mL/min/1.73m2) ± SD (CKD-EPI)	78.1 ± 33.5	23.5 ± 11.8	p<0.001
OHCI n (%)	6 (18.2)	2 (6.2)	p=0.34

OHCI: occult HCV infection;

TH-PO126

The Characteristics of Membranoproliferative Glomerulonephritis (MPGN) at a Single Center in Japan Marie Nakano, Kazunori Karasawa, Saeko Kumon, Takahiro Kamiyama, Takahito Moriyama, Kosaku Nitta. *Tokyo Women's Medical University Hospital, Tokyo, Japan.*

Background: MPGN has been recently proposed new classification, and alternative pathway (AP) mediated MPGN (C3 glomerulopathy), which was defined as isolated C3 deposition and absent of immunoglobulin deposition, has been recognized as a different glomerulonephritis from Immune complex (IC) mediated MPGN. However, there was no report analyzed about the difference of these two nephritis in Japan.

Methods: We reclassified 87 MPGN patients diagnosed between 1977 and 2014 in our institution according to the new classification. The clinical, pathological features and outcomes of patients between IC mediated MPGN and AP mediated MPGN were analyzed.

Results: Among 55 MPGN patients except 32 secondary MPGN, there were 42 IC mediated MPGN patients and 13 AP mediated. In the baseline clinical findings, the estimated glomerular filtration rate were similar between both groups (89.69 vs. 76.19, p=0.2581). The amount of proteinuria (2.34 vs. 5.20 d/day, p=0.0063), C3 (39.0 vs. 67.25, p=0.0317), and CH50 (22.4 vs. 36.4, p=0.0404) were significantly lower, and serum albumin was significantly higher (3.40 vs. 2.70, p=0.0186) in AP mediated MPGN than IC mediated MPGN. In the pathological findings, there were no significance in light microscopical findings, but all immunofluorescence staining except C3 were significantly higher in IC mediated MPGN. Immunosuppression therapy was used in 92.3% patients in AP mediated MPGN, and 90.5% in IC mediated. The 400 months renal survival rate were similar between both groups (70.0 vs. 74.0%, P=0.445).

Conclusions: We have shown that AP mediated MPGN had similar prognosis in comparison to IC mediated MPGN, though proteinuria at baseline was lower than IC mediated MPGN. Lower serum complements were resulted from higher alternative pathway activation, and this phenomenon might induce the poor prognosis in AP mediated MPGN, though their lower proteinuria.

TH-PO127

Glomerulopathies Secondary to Schistosomiasis: Histological Forms and Follow-Up Cristiane B. Dias,[4] Lectícia Jorge,[5] Leonardo A. Testagrossa,[5] Denise M. Malheiros,[3] Viktoria Woronik,[1] Precil D. Neves,[2] Ramaiane A. Bridi.[5] *[1]None, Salvador, Brazil; [2]University of S?o Paulo, S?o Paulo, Brazil; [3]University of Sao Paulo, Sao Paulo, Brazil; [4]University of Sao Paulo, Brazil, São Paulo, Brazil; [5]University of São Paulo, São Paulo, Brazil.*

Background: Schistosomiasis mansoni (MS) is a parasitosis caused by Schistosoma mansoni that is endemic in several Brazilian states. Gastrointestinal involvement is the most frequent, but the kidney can also be injured, especially in the form of glomerulopathies. The aim of this study is to show the MS-related glomerulopathies and evaluation of the long-term follow-up

Methods: Evaluation of clinical data and renal biopsies of patients diagnosed with MS-related glomerulopathies in the period 1992-2017, in addition to clinical-evolutionary follow-up.

Results: Twenty eight patients, predominantly male (78.5%), white (64.2%), median age 38 (33; 44), all cases from the endemic area, most of them from Bahia (32,2%). The most common form of MS diagnosis was through fecal examination (94%), and 60.7% presented the hepatosplenic form of the disease. The most common clinical presentation was mixed syndrome (64.3%), with Cr: 1.51 ± 0.77mg / dL, MDRD: 69.3 ± 39ml / min / 1.73m2, 24h proteinuria: 6.56 ± 3.5g, serum albumin: 2.35 ± 0.91g / dL, low serum complement in 42.8% of patients. The distribution of the histological diagnoses to renal biopsy was: membranoproliferative glomerulonephritis (MPGN) 60.7%; focal segmental glomerulosclerosis (FSGS) 21.4%; membranous nephropathy 10.7% and proliferative mesangial 7.2%. The patients' follow-up time was 70 (14-124) months, after which 32.1% of the patients had started dialysis. Comparing the patients with MPGN vs non-MPGN, they differed in proteinuria of 24h (g) (5.19 vs 8.67, p = 0.04) and serum albumin (g / dL) (2.6 vs 1.0, P = 0.04), frequency of hypertension (%) (70.5 vs 9.0, p = 0.002) and hematuria (%) (94.1 vs 45.4, p = 0.007). Comparing patients that evolved and did not evolve to dialysis, they differed in the initial creatinine (1.99 vs 1.28, p = 0.05), MDRD (55/78, P = 0.03), renal response to anti-parasitic use (%) (0 vs 77, p = 0.0007) and follow-up time (months) (45.7 vs 9.7, p = 0, 03).

Conclusions: The glomerulopathies secondary to MS are still a reality in Brazilian daily life. Histological presentation as GNMP did not determine a worse prognosis for the patients in this series, but rather the severity of the initial clinical presentation and non-response to the use of antiparasitics.

TH-PO128

An Automated Immunoassay for High-Throughput Measurement of Symmetric Dimethylarginine (SDMA) in Human Serum Joe M. El-Khoury,[2] Parker C. Wilson,[2] Shay Toohey,[2] Chirag R. Parikh,[3] Daniel Patch,[1] Maha Yerramilli,[1] Giosi Farace,[1] Murthy V. Yerramilli.[1] *[1]IDEXX Laboratories, Westbrook, ME; [2]Yale University, New Haven, CT; [3]Yale University and VAMC, New Haven, CT.*

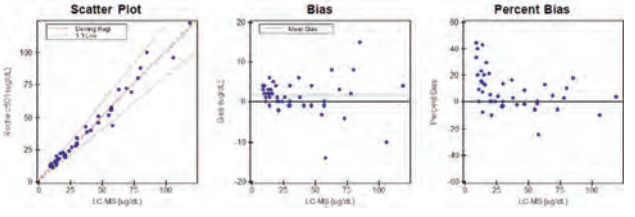
Background: Symmetric dimethylarginine (SDMA) is a byproduct of protein methylation and degradation that is primarily eliminated by the kidneys. It is freely filtered at the glomerulus, with no active secretion or reabsorption by the renal tubules. As a result, SDMA plasma concentrations are affected by changes in GFR and it is emerging as a kidney function biomarker that has outperformed serum creatinine in several studies. SDMA has traditionally been measured using liquid chromatography tandem mass spectrometry (LC-MS/MS), which is a major limitation for its widespread application as a screening marker for kidney function. The objective of this study is to validate a high throughput automated immunoassay for measuring SDMA in human serum.

Methods: Left-over serum samples were used for this study. SDMA was measured using novel immunoassay reagents manufactured by IDEXX Laboratories (Westbrook, ME) loaded on a Roche c501 analyzer (Indianapolis, IN). The assay was evaluated to establish its analytical measurement range (AMR), imprecision, specificity and accuracy. Method comparison with a separate LC-MS/MS was performed using serum collected from 50 adults with varied kidney function.

Results: The analytical measurement range of the SDMA immunoassay was 4.2 to 100.5 µg/ml. Total coefficient of variation (CV) was less than 13.1% at the three different concentrations tested. Hemolysis did not affect assay performance up to a hemolysis index of 186 and common drugs tested did not interfere. Deming regression analysis of the method comparison with the LC–MS/MS revealed a slope of 1.001, intercept of 1.4, and correlation coefficient of 0.99

Conclusions: A novel immunoassay for measuring SDMA with comparable performance to LC-MS/MS is now validated for use in humans and better suited for high-throughput clinical laboratory testing. This assay will facilitate further research and widespread clinical adoption of this emerging biomarker.

Funding: Commercial Support - IDEXX



Comparison between IDEXX SDMA immunoassay on Roche c501 and an LC-MS/MS method

TH-PO129

Factors Influencing Initial Treatment Options for Idiopathic Membranous Nephropathy Huaiya Xie,[1] Xin Zhang,[3] Zhen Wu,[2] Yubing Wen,[1] Jianfang Cai,[1] Hang Li,[4] Xuemei Li,[5] Xuewang Li.[1] *[1]Peking Union Medical College Hospital, Beijing, China; [2]Beijing Frendship Hospital, Capital Medical University, Beijing, China; [3]Peking University First Hospital, Beijing, China; [4]Peking Union Medical college hosiptal, Beijing, China; [5]Peking Union Medical College Hospital, Chinese Academy of Medicine Sciences & Peking Union Medical College, Beijing, China.*

Background: This study aimed to analyze factors which may influence the initial therapy option for idiopathic membranous nephropathy (IMN) diagnosed in a tertiary center of China.

Methods: In this retrospective study, we consecutively enrolled 875 IMN patients diagnosed in a single tertiary center between 2004 to 2015. Data on age, sex, body mass index, presence of hypertension and diabetes mellitus, and laboratory tests at renal biopsy and treatment options after diagnosis of IMN were retrospectively retrieved from medical records. We retrospectively classified the initial therapy as glucocorticoids plus cyclophosphamide, calcineurin inhibitors alone or plus corticosteroids, corticosteroids alone or plus other immunosuppressives, and supportive treatment. Multinomial multiple logistic regression was employed to analyze the factors influencing the selection of a therapeutic regimen.

Results: The presence of diabetes(OR=5.06, 95% CI 2.90-8.84, P<0.001) and age <50 years was associated with selection of calcineurin inhibitors(OR=1.48, 95% CI 1.00-2.17, P=0.048), whereas a 24 hour urine total protein(24h-UP)<8g and a serum albumin> 25g/L were associated with selection of supportive treatment (OR=15.2, 95% CI 3.53-65.1, P<0.001 and OR=21.3, 95% CI 5.09-89.5, respectively) and corticosteroids alone or plus other immunosuppressives(OR=4.93, 95% CI 2.52-9.64, P<0.001 and OR=1.69, 95% CI 1.05-2.74, respectively) as opposed to selection of cyclophosphamide. When we restricted the analyses in non-diabetes patients, age <50 years was also associated with selection of calcineurin inhibitors as compared with selection of cyclophosphamide(OR=1.69, 95% CI 1.12-2.54, P=0.012).

Conclusions: Serum albumin level, amount of 24h-UP, presence of diabetes, and age may influence a physician's decision on initial treatment options for IMN.

TH-PO130

Clinical Advantage of Concomitant Use of Low Dose Mizoribine and Prednisolone on Primary Membranous Nephropathy in the Elderly Hajime Hasegawa,[1,2] Tetsuya Mitarai,[1,2] Yasuhiko Tomino,[1] Hitoshi Yokoyama,[1] Kunihiro Yamagata,[1] Masayuki Iwano,[1] Shin'ichi Akiyama,[1] Kaori Takayanagi.[1,2] *[1]Study group for nephrotic syndrome in the elderly, Kawagoe, Japan; [2]Nephrol and Hypertens, Blood Purification Center, Saitama Med Center, Saitama Med Univ, Kawagoe, Japan.*

Background: Initial therapeutic strategy of membranous nephropathy (MN) in Japan is sole administration of Prednisolone (PSL) of 1 mg/kg for 4 weeks, and then addition of immunosuppressant such as Cyclosporin. However, long-term administration of high dose PSL and immunosupressant in elder patients is controversial because of their multiple adverse effects. Here, we show the clinical efficacy of concomitant use of lower dose of Mizoribine (MZB) and PSL in terms of earlier induction to the remission by multicentered prospective cohort study.

Methods: Thirty-six patients diagnosed primary MN showing nephrotic syndrome were enrolled from 24 independent facilities. The patients, being older than 65 of age and preliminary obtained none of therapy, were randomly assigned to two groups, solely administered 30 mg of PSL (P group, n=18), or concomitantly administered 150 mg of MZB (MP group, n=18) and observed for 12 months. Remission rate was evaluated by remission score (RS) as follows: 1: Urine protein-to-Cr ratio (PCR)≥3.5, 2: 3.5>PCR≥1.0, 3: 1.0>PCR≥0.3 and 4: PCR<0.3 g/gCr. In some cases, anti-phospholipase A2 receptor antibody (PLA2R-Ab) titer was qualitatively measured.

Results: Mean ages of MP and P groups were 73.3 and 72.8. PCR at 12M was not different in the two groups. However, %PCR vs baseline and RS at earlier phase of MP were better than P (%PCR: 3M 50.0±47.0% vs 55.6±57.0%, 6M 31.4±27.2% vs 39.9±33.1%, RS: 3M 1.24±1.20 vs 1.00±0.93, 6M 1.69±1.03 vs 1.07±1.00). Those results were confirmed by the logistic analysis showed estimated odds ratio of the high responder in MP group was 1.50 (95%CI=0.33-6.83), suggesting that the concomitant use of MZB might accelerate the remission. Additionally, in cases showing qualitatively negative PLA2R antibody, the odds ratio of high responder cases was 2.67 (95% CI: 0.28-25.64) in MP vs 1.00 in P whereas the odds ratio was 0.33 (MP) and 0.40 (P) in cases showing positive PLA2R-Ab, suggesting that concomitant use of MZB might be more effective in PLA2R-Ab negative cases.

Conclusions: Concomitant use of low dose of MZB and PSL might contribute to save time until remission in elder patients with MN-based NS.

TH-PO131

Long Term Outcome of Apparent Treatment Resistant Patients with Idiopathic Membranous Nephropathy Coralien Vink- van Setten, Anne-Els van de Logt, Jack F. Wetzels. *Radboud University Medical Center, Nijmegen, Netherlands.*

Background: Cyclophosphamide is effective in idiopathic membranous nephropathy (iMN). Still, some patients do not respond timely, and do not develop remission at the end of therapy. We evaluated the outcome of these "apparent treatment resistant" (ATR) patients.

Methods: We selected patients with iMN, treated with cyclophosphamide (6-12 months), persistent proteinuria (PCR > 3g/10 mmol) at 12 months after start of therapy, and a minimum follow-up of 24 months. Renal failure was defined as > 50% increase in serum creatinine concentration. Remission was defined as PCR of less than 3.0g/10mmol and stable renal function.

Results: Between 1995 and 2016, we evaluated 518 patients with iMN. 219 high risk MN patients were treated with cyclophosphamide. 110 with outcome data were followed for at least 24 months. At 12 months 84 (76.4%) patients achieved partial remission, one (0.9%) patient developed renal failure and 25 (22.7%) patients fulfilled ATR criteria. Of these 25 patients, 20 were males, mean age was 55 (± 12) years, median serum creatinine was 149 umol/L (108.5-195), median PCR 11g/10mmol (6.7-15.3). During follow-up (median 80 months (34.5-126), 16 patients developed partial or complete remission without additional therapy. A relapse has occurred in 4 patients, necessitating a second course of immunosuppressive therapy. Nine patients had persistent proteinuria. Five of these were treated with a second course of immunosuppressive therapy, which resulted in a remission of proteinuria in 4. Two patients with persistent proteinuria and no additional immunosuppressive therapy have developed renal failure after 60 and 237 months respectively.

Conclusions: Persistent proteinuria at 12 months after start of cyclophosphamide therapy is not evidence of treatment resistance. Most patients will develop remission of proteinuria. Patients with persistent proteinuria respond favourably to a second course of therapy. Risk of end stage renal is low.

Funding: Government Support - Non-U.S.

TH-PO132

Role of Rituximab in Primary Membranous Nephropathy Refractory to Modified Ponticelli/Calcineurin Based Treatment Jasmine Sethi, Harbir S. Kohli, Raja Ramachandran. *Post Graduate Institute of Medical Education and Research (PGIMER), CHANDIGARH, India.*

Background: Rituximab is emerging as a promising therapeutic agent particularly in the management of refractory primary membranous nephropathy. What should be dosage schedule to avoid toxicity without compromising the efficacy is a matter of concern and data to this regard is limited. This is a single center prospective study to evaluate the role of B cell titrated protocol of rituximab in adults with PMN who failed treatment with conventional immunosuppressive agents and its possible association with $aPLA_2R$ antibodies.

Methods: 14 patients aged 14-65 years of refractory PMN were given intravenous rituximab at a dose of 375mg/m^2 in a tertiary center in northern India. Following rituximab injection, CD19 counts were monitored weekly for 4 weeks followed by monthly for 6 months. If CD19 count was >5/μL (or >1%), repeat doses of rituximab were given. The change in laboratory parameters (24 urinary protein, serum albumin and serum creatinine) were recorded at the baseline, and monthly till 6 months after rituximab administration. Serum sample drawn just before rituximab infusion and at the end of 6th month post-infusion were tested for $aPLA_2R$ by ELISA

Results: At the end of 6 months, 6 out of 14 patients (42.8%) responded, with 1/14 (7.1%) achieving CR and 5/14 (35.7%) achieving PR. Eight out of 14 (57.1%) patients showed no response to rituximab at the end of the 6 months. Mean proteinuria decreased from 4.6 ±1.7 g/day at baseline to 3.3 ±2.1 g/day at 3 months, and 3.2 ±2.3 g/day at 6 months (p=0.29). Mean serum albumin also increased from 2.4 ±0.6 g/dl at baseline to 2.8 ±0.6 g/dl at 3 months, and 3.2 ±0.6 g/dl at 6 months. (p=0.002). Average time to CD19 reconstitution was 3.1± 0.8 (2-4) months. Rituximab dose administered during 6 month period was 1289±720 (600-2800) mg. $aPLA_2R$ antibody testing was done in 13 patients. Among these, all 13 patients presented with high levels of antibodies before the treatment, eight of them experienced a reduction of aPLA2R antibody titer, while 5 patients experienced no change after treatment (all five patients continued to have resistant disease).

Conclusions: CD19 titrated rituximab therapy is effective in achieving remission in 42.85% of patients of PMN refractory to prior immunosuppression. Titrated therapy might enhance the safety without compromising the efficacy of the therapy.

TH-PO133

Improvement of Clinical Outcomes in Kidney Diseases via the On-line Thai Glomerular Disease Registry: Membranous Nephropathy Pantipa Tonsawan,[5] Sakkarn Sangkhamanon,[4] Boonyarit Cheunsuchon,[3] Warangkana Pichaiwong,[2] Mongkon Charoenpitakchai,[6] Bancha Satirapoj.[1] *[1]Medicine, Phramongkutklao hospital, Bangkok, Thailand; [2]Medicine, RAJAVITHI HOSPITAL, Bangkok, Thailand; [3]Pathology, Siriraj hospital, Bangkok, Thailand; [4]Pathology, Khon Kaen University, Khon Kaen, Thailand; [5]Division of Nephrology, Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand; [6]Pathology, Phramongkutklao Hospital and College of Medicine, Bangkok, Thailand. Group/Team: Thai Glomerular Disease Collaborative Network (TGCN).*

Background: The primary membranous nephropathy (MN) is the common cause of adult onset nephrotic syndrome. The Thai glomerular disease registry was established by Thai Glomerular Disease Collaborative Network (TGCN) to evaluate the prevalence, clinical features and outcomes in Thai glomerular disease patients. This study focused especially on MN.

Methods: We conducted a prospective cohort study in the adults with native kidney biopsy proven glomerular diseases between July 2014 and Mar 2017 from TGCN registry. The clinical features and laboratory parameters at the time of biopsy, pathologic findings, treatment regimens and clinical outcomes were monitored.

Results: MN was presented 111 (7.1%) of total 1,556 patients and 111 (15.5%) of total 742 patients with primary glomerular diseases. Mean age was 52.6±15 years. The clinical features of MN were identified; 86 % nephrotic syndrome, 46 % hypertension, 5.4 % acute kidney injury and 4.5% asymptomatic proteinuria. At the time of renal biopsy, median serum creatinine was 0.98 mg/dL (0.42-7.4), median urine protein creatinine ratio was 3.5 g/g. Cr (0.14-21.9), mean serum albumin was 2.5±0.7 g/dL, and median interstitial fibrosis was 5% (5-90). Median time to remission was 5.6 months. At 24 weeks of follow up, complete remission and partial remission were observed in 20.7% and 59%, respectively. The predicting factors for clinical remission were identified as young patients, low serum creatinine, high hemoglobin, and high serum albumin at time of kidney biopsy. After the multivariate analysis, high serum albumin and low serum creatinine were the independent factors for clinical remission. Doubling of serum creatinine was observed in only 1.6 % during this period.

Conclusions: This study suggested that the clinical course and outcomes of Thai MN were favorable with low incidence of end stage renal disease. Baseline serum albumin and renal function were significantly predict the renal remission. *Funding: Health Systems Research Institute, and Nephrology Society of Thailand support*

Funding: Private Foundation Support

TH-PO134

The Investigative Burden of Membranous Nephropathy in the UK Fiona Wilson,[2] Patrick Hamilton,[3] Rajkumar Chinnadurai,[4] Malinder Singh,[6] Smeeta Sinha,[5] Durga A. Kanigicherla,[1] Paul E. Brenchley.[2] *[1]Central Manchester University Hospitals, Manchester, United Kingdom; [2]Manchester Royal Infirmary, Manchester, United Kingdom; [3]NHS, Manchester, United Kingdom; [4]SALFORD ROYAL NHS FOUNDATION TRUST, Manchester, United Kingdom; [5]Salford Royal NHS Foundation Trust, Salford, United Kingdom; [6]LTHTR, Preston, United Kingdom.*

Background: Membranous Nephropathy (MN) represents two distinct disease entities. Primary MN (PMN) is now recognized as an autoimmune condition associated with the anti-PLA_2R antibody and secondary MN occurs in tandem with malignancy, infection or drug therapy. Prior to the discovery of anti-PLA_2R antibody in 2009 and the development of accessible ELISAs, the diagnosis of MN was a diagnosis of exclusion. We investigated the investigative burden for patients with MN and the diagnostic yield of these tests

Methods: Patients from 2 UK centres with a diagnosis of MN between 2009 and 2014 were identified. Across the Northwest of England, anti-PLA_2R testing became readily available in 2012. Therefore patients were divided into those receiving a diagnosis 2009-2011 (pre-ELISA) and 2012-2014 (post-ELISA). Records were reviewed for the investigations which took place 6 months prior and 6 months following the biopsy date to see if these were normal or identified a secondary cause of MN. Investigations included viral and autoimmune screens, X-rays, CT, MRI, PET scan, ultrasound, upper and lower GI endoscopies and cystoscopies. Hypothesis The introduction of anti-PLA_2R testing leads to a modification of the investigative pathway for MN patients.

Results: 121 patients were identified, 104 with PMN and 17 with secondary MN. Patients went through an average of 7.38 tests with only 18 of 893 (2.0%) tests proving to be instrumental in helping with the diagnosis of secondary versus primary MN. For patients diagnosed with PMN they had an average of 7.48 tests, all of which were negative. With the introduction of anti-PLA_2R testing in 2012 there appears to be a trend towards a reduction in the investigative profile of patients with the average number of tests falling from 7.73 to 7.29. A significant reduction was noted in Hepatitis B and C (p=0.029 for both) and colonoscopies (p=0.012). There was also a reduction in the total cost of investigation per patient with PMN from an average of £553.41 in 2009-2011 to £366.02 in 2012-2014.

Conclusions: Patients with a diagnosis of MN undergo multiple investigations, many of which are negative, at a significant cost to both the healthcare system and patients quality of life. The anti-PLA_2R test has the potential to reduce this burden as its use becomes more widespread.

TH-PO135

Association of Presence of Diabetes with Failure to Complete Remission of Idiopathic Membranous Nephropathy Huaiya Xie,[1] Zhen Wu,[2] Xin Zhang,[3] Yubing Wen,[1] Jianfang Cai,[1] Hang Li,[1] Xuemei Li,[1] Xuewang Li.[1] *[1]Peking Union Medical College Hospital, Beijing, China; [2]Beijing Friendship Hospital, Capital Medical University, Beijing, China; [3]Peking University First Hospital, Beijing, China.*

Background: This study aimed to assess whether the presence of diabetes will influence renal outcomes in patients with idiopathic membranous nephropathy (IMN).

Methods: In this retrospective study, a total of 875 patients with pathology-proved IMN were consecutively enrolled. Among them, 101 were diagnosed as type 2 diabetes mellitus (T2DM) prior to their diagnosis of IMN. Data on age, sex, body mass index (BMI), presence of hypertension and diabetes mellitus, laboratory tests, and therapeutic regimens were retrospectively retrieved from medical record. Complete remission (CR) was defined as urinary protein excretion<0.3g/d with stable estimated glomerular filtration (eGFR). COX regression was used to analyze risks of failure to CR and renal function deterioration associated with the presence of T2DM.

Results: A total of 810 patients were followed at least once with a median follow-up of 23.6 (IQR 9.9-42) months, of whom 292 achieved CR and 95 developed a 30% decline in eGFR. Presence of T2DM was associated with failure to reach CR of IMN (*HR*=0.53, 95% *CI* 0.37-0.77, *P* =0.001), independently of age, sex, hypertension, therapeutic regimen, serum albumin, proteinuria, and baseline eGFR. The association remained statistically significant when we further excluded 103 patients with corticosteroid-induced diabetes(*HR*=0.49, 95% *CI* 0.34-0.71,*P* <0.001), or restricted the analyses in patients with nephrotic syndrome(*HR*=0.46,95% *CI* 0.28-0.67,*P* =0.002) or in those using calcineurin inhibitors(*HR*=0.58,95% *CI* 0.37-0.91, *P* =0.017). However, patients with and without T2DM did not differ in developing a 30% decline in eGFR, adjusting for age, sex, BMI, state of smoking, hypertension, therapeutic regimen, serum albumin, proteinuria, and baseline eGFR(*HR*=0.67,95% *CI* 0.39-1.16,*P* =0.156).

Conclusions: Presence of T2DM may be independently associated with failure to remission but not eGFR decline in IMN patients.

TH-PO136

Treatment of Membranous Glomerulopathy with Ponticelli's Modified Scheme and with Cyclosporine Are Comparable after 1 Year of Follow-Up: Retrospective Cohort

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Background: The standard treatment recommended by KDIGO in patients with membranous glomerulopathy (MN) is performed with corticosteroids and cyclophosphamide (modified Ponticelli's scheme). However, there are few studies in the Latin American population about the comparative efficacy of an alternative regimen using oral cyclosporine (CSA). The hypothesis is CSA presents therapeutic equivalence and lower side effects when compared to Ponticelli's scheme. Therefore, this study sought to evaluate the response of these two therapeutic regimens in patients with MN.

Methods: a retrospective cohort was conducted from 1998 to 2016. Data from patients older than 18 years with idiopathic MN for at least 6 months without previous treatment, were analyzed. In addition to the clinical and epidemiological profile, the response to the treatment was evaluated (CyA and Ponticelli), in a period of 6 months and 1 year after initiation of therapy. Definitions of partial response, complete response, relapse, and therapeutic failure were based on KDIGO.

Results: Thirty patients were evaluated 16 were treated with CSA and 14 with Ponticelli's scheme. The baseline characteristics of the two groups treated with IMS are described in **Table 1**. After 6 and 12 months the partial and complete response rate was 50% and 69% in the cyclosporine group and 57% and 50% in the Ponticelli's group. There was no difference between response rates (complete response and parcial response) between groups after 6 months (p = 0.69); 12 months (p = 0.64).

Conclusions: the therapeutic regimens of immunosuppression evaluated showed similar response rates after the 6-month and 12-month follow-up.

	Cyclosporine (n=16)	Ponticelli (n=14)	p
Age (mean ± SD)	40 ± 14.8	39 ± 16.2	p=0.32
Gender, male n(%)	12 (75)	9(64)	p=0.53
Race			
White	10 (62.5)	9 (64.2)	p=0.56
non-white	6 (37.5)	5 (35.7)	p=0.42
Proteinuria(g/24h)	5.3 ± 4.7	5.2 ± 3.9	p=0.58
Serum albumin (g/dL)	2.0 ± 0.7	1.8 ± 0.8	p=0.36
Scr (mg/dL)	1.0 ± 0.4	1.1 ± 0.2	p=0.32
ACEi/ARBs	100%	100%	p=1
Total colesterol (mg/dL)	323±193	373 ± 119	p=0.22

TH-PO137

HLA-DR3 Impact on Graft Survival in Membranous Nephropathy: A Tricontinental Registry Study

Patrick Hamilton,[4] Kay V. Poulton,[3] Lisa L. Mumford,[5] Laura H. Mariani,[6] Nathan P. Goodrich,[2] Robert Merion,[2] Stephen P. McDonald,[1] Paul E. Brenchley.[3] *[1]ANZDATA Registry, Adelaide, SA, Australia; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]Manchester Royal Infirmary, Manchester, United Kingdom; [4]NHS, Manchester, United Kingdom; [5]NHS Blood and Transplant, Bristol, United Kingdom; [6]University of Michigan, Ann Arbor, MI.*

Background: Membranous nephropathy (MN) is a rare disease in which a third of patients will need a kidney transplant. The strong genetic predisposition to MN was initially associated with HLA-DR3, and more recently HLA-DQA. It is unknown whether a relation to graft survival is based on presence in the recipient, donor or both.

Methods: We investigated HLA-DR3 mismatching effects on graft survival using data on adult renal transplant recipients with MN from US, UK and Australasian renal transplant registries. Univariate and multivariable Cox proportional hazard regression (donor age, donor type, registry, recipient ethnicity and transplant year) analyses were fitted to compare overall and death-censored graft survival (GS & DCGS respectively) in the 9 combinations of HLA-DR3 mismatch. Analysis was repeated by grouping HLA-DR3 with other HLA-DR antigens to examine any combined effect that may implicate antigen presentation by HLA-DQ.

Results: There were 6660 MN patients. Using HLA-DR3 homozygous recipient/donor pairs as the reference group, multivariate analysis showed two combinations associated with significantly lower overall and death-censored graft survival: HLA-DR3 homozygous recipients with an HLA-DR3 negative donor (GS - HR 1.92, 95%CI 1.04-3.56, p=0.037 & DCGS - HR 2.18, 95%CI 1.13-4.21, p=0.020), and HLA-DR3 negative recipients with a donor homozygous for HLA-DR3 (GS - HR 2.83, 95%CI 1.01-7.95, p=0.049 & DCGS - HR 3.36, 95%CI 1.16-9.7, p=0.025). In combination with HLA-DR1, HLA-DR6, or HLA-DR7, the same two groups became more significant, with HLA-DR1 appearing to provide the greatest impact. HLA-DR3 +/- DR1 homozygous recipients with an HLA-DR3 +/- DR1 negative donor – HR 1.55, 95%CI 1.05-2.29, p=0.027 and for HLA-DR3 +/- DR1 negative recipients with an HLA-DR3 +/- DR1 homozygous donor – HR 2.36, 95%CI 1.4-3.98, p=0.001

Conclusions: HLA matching at HLA-DR3 does not appear to be associated with graft survival. However graft survival is reduced in HLA-DR3 negative recipients if the donor is HLA-DR3 homozygous, and in HLA-DR3 homozygous recipients receiving an HLA-DR3 negative donor kidney. These results become more significant if HLA-DR1, HLA-DR6 or HLA-DR7 is combined with HLA-DR3, suggesting an association with HLA-DQB polymorphisms

TH-PO138

Patients with Membranous Nephropathy (MN): A Real-World (RW) Clinical and Economic Analysis

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Background: MN is one of the most common causes of nephrotic syndrome (NS) in adults. Given varying clinical course and treatment response, where 1/3 of patients progress to end-stage renal disease, MN represents a high-risk population where management strategies can alter and improve outcomes (van den Brand et al., 2014). We describe RW outcomes in a prevalent MN cohort using US administrative healthcare claims data.

Methods: A retrospective analysis was conducted using Truven Marketscan®, among commercially-insured patients ≥ 18 years during 1/1/12-12/31/15. MN was identified using ≥2 MN diagnoses (Dx ICD-9-CM=581.1, 583.1; ICD-10-CM= N052, N062 and N072). The date of first Dx was designated the index date. Patients with Dx indicating secondary causes of NS were excluded. Patients were followed for 1 year post-index and evaluated with regards to demographics, clinical outcomes, all-cause healthcare resource utilization [HCRU: inpatient (IP), emergency room (ER), outpatient (OP), medications (Rx)], and all-cause costs using Dx, procedure and drug codes. Costs were assessed in patients enrolled in fee-for-service plans (FFS).

Results: 701 patients were identified [54.8% male, mean age=48.7 years, hematuria (7.6%), mean Charlson Comorbidity Index score=2.3, from South (37.5%) and North Central US (23.0%)]. 15.3% of patients had urinary tract infections, 3.9% pneumonia, and 1.1% septicemia. Treatment with dialysis and renal transplant occurred in 4.3%, and 1.1% of patients, respectively. 25.1% used the ER and 12.6% had IP stays; 20.0 mean Rx were dispensed. Among FFS patients (n=562), total and mean (SD) costs were $17.6 million and $31,412.3 ($97,654.3), respectively. 5% of patients (n=28) were responsible for 57.4% of costs or $10.1 million, for a mean (SD) cost per patient of $362,064.1 ($259,261.3); as a proportion of cost, OP and IP were responsible for 89.3%, while Rx and ER comprised 10.0% and <0.8%, respectively.

Conclusions: Our analysis characterizes 1-year RW outcomes among commercially-insured patients with MN, revealing a subset responsible for a large portion of costs incurred largely by IP and OP use. This group should be studied further to focus identification and treatment strategies. Burden of illness and costs over a longer–term horizon should be examined.

Funding: Commercial Support - This study was funded by Mallinckrodt Pharmaceuticals.

TH-PO139

Can THSD7A Be a New Marker for Diagnosing Idiopathic Membranous Nephropathy? A Systematic Review and Meta-Analysis of the Diagnostic Value of THSD7A in IMN

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Background: Thrombospondin type 1 domain–containing 7A (THSD7A) is a new target antigen in patients with idiopathic membranous nephropathy. Moreover, malignancies are also found in THSD7A-positive membranous nephropathy patients. We aimed to systematically evaluate prevalence of THSD7A in the IMN patients and malignancies in THSD7A-postive patients.

Methods: We searched English database including MEDLINE, Embase, Cochrane Library and Chinese database including CNKI, VIP and Wanfang database to Jan 4, 2017 with the term "THSD7A" or "thrombospondin type 1 domain-containing 7A". Meta analysis was used to explore the positive rate of THSD7A in the patients with idiopathic membranous nephropathy. Subgroup analysis was done according to the race, sample size, and detecting method of THSD7A. The incidence of malignancies in THSD7A positive patients was also summarized.

Results: Ten studies involving 3061 participants were eventually included in this review. The prevalence of THSD7A was 3% (95% CI, 3%–4%). In the anti-phospholipase A2 receptor (PLA2R)-negative patients, the prevalence of THSD7A was 10% (95% CI, 6%–15%). A total of 77 patients were detected for positive circulating antibodies, and the prevalence of THSD7A was lower at 3% (95% CI, 2%–4%). Overall 72 patients were THSD7Apositive detected by renal biopsy with immunohistochemistry, and the prevalence was 3% (95% CI 3%-4%). Subgroup analysis did not show significant differences in the prevalence of THSD7Abetween races and study sample sizes. Among THSD7A-postive patients, 2/10 studies reported malignancies with the incidence varied from 20% to 25%.

Conclusions: The prevalence of THSD7A is not uncommon in the patients with IMN, but more common in the PLA2R-negtive patients. Malignancies should be screened and closely monitored in THSD7A-positvie membranous nephropathy patients.

TH-PO140

Late Relapses of Membranous Nephropathy (MN) Yonatan A. Peleg,[4] Andrew S. Bomback,[1] Pietro A. Canetta,[3] Gerald B. Appel,[2] Wooin Ahn.[3] *[1]Columbia University, New York, NY; [2]Columbia University College of Physicians and Surgeons, Scarsdale, NY; [3]None, New York, NY; [4]Nephrology, New York Presbyterian-Columbia University Medical Center, New York City, NY.*

Background: Most patients (pts) with MN who achieve remission carry a risk of relapse that diminishes over time. Relapse of disease after 5 years of sustained remission is considered a rare event.

Methods: We reviewed 15 idiopathic MN pts, who relapsed after a median time of 11 years of disease remission.

Results: 10/15 pts were male. All were white, and one was Hispanic. Median age at diagnosis was 34 y (range 3-71). Median baseline eGFR was 79.4 ml/min/1.73m^2 (range 26.8-110). 9 went into complete remission (CR) and 6 pts went into partial remission (PR). CR was achieved with immunosuppression (IS) in 6 pts. Median age at first relapse was 51 y (range 20-80), representing a gap of 11 y (range 6-36) from initial remission. Relapses presented as nephrotic syndrome in 8, while the other 7 were diagnosed by lab surveillance. 10/15 pts underwent repeat biopsy 12 y (range 8-33) after first biopsy: all showed pattern of primary MN. 12 pts received IS after relapse and 1 died prior to treatment. 8/14 surviving pts had PR after their initial relapse, 3 had CR, and 3 had no remission (NR). CR was not associated with IS use. 5 pts had additional relapse episodes after their first relapse, and all were treated with IS. Experiencing PR vs. CR did not predict risk of subsequent relapse. The results of the most recent relapse for these 5 patients are 1 in CR, 1 in PR, and 3 in NR. Median follow up duration was 19 y (range 9-56). The median most recent eGFR was 60.8 (range 16.8-105.6), and median yearly change in eGFR was -0.32 (range -2.73 to +2.82). None reached ESRD. Of 10 available biopsies during clinical relapse, 6 were stained for PLA2R with all staining positive. Serum PLA2R Ab was tested in 10 pts, with some surveilled with serial titers: 2 had positive titers during relapse, 5 had negative titers during relapse, and 3 had negative values during PR. In all, 8/10 pts were positive for either tissue PLA2R or serum PLA2R Ab while in clinical relapse.

Conclusions: We present 15 MN pts with proteinuric relapse a median time of 11 years after initial remission. Repeat biopsies, even as long as 33 years after complete remission, all showed MN, and 80% of pts were PLA2R positive by tissue or serum testing. Thus repeat biopsy to reestablish a diagnosis of MN may be unnecessary. There was no significant decline in renal function despite relapses and median follow up time of 19 years.

TH-PO141

Clinical and Pathological Analysis of Renal Tubulointerstitial Injury in Idiopathic Membranous Nephropathy Zilong Li,[1] Yibo Zhang,[4] Juan Wang,[1] Linlin Liu,[3] Jianfei Ma,[2] Li Yao.[2] *[1]Department of Nephrology, First Affiliated Hospital of China Medical University, Shenyang, P. R. China, Shenyang, China; [2]The First Affiliated Hospital of China Medical University, Shenyang, China; [3]The First Hospital of China Medical University, ShenYang, China; [4]the first affiliated hospital of China Medical University, Shenyang, China.*

Background: It has been revealed that renal tubulointerstitial injury (TII) plays important roles in the progression of chronic kidney diseases, while how TII affects idiopathic membranous nephropathy (IMN) remains unclear. Herein, we retrospectively studied the clinical and pathological data of 134 IMN patients, to investigate the characteristics of TII in IMN.

Methods: 134 patients diagnosed as IMN via renal biopsy from January 2014 to December 2015 in our department were enrolled. All the patients didn't administrate with either corticosteroid or immunosuppressants before undergoing renal biopsy, and accepted appropriate therapy according to the clinical and pathological features after renal biopsy. The patients were divided into two groups: TII group and non-TII group. Clinical and pathological data were accumulated after 12-month follow-up.

Results: Among the 134 IMN patients, 79 were males (58.96%) and 55 were females(41.04%), age from 14 to 74 years. The pathological results suggested 65 cases (48.51%) existed TII in IMN. Compared to non-TII group, TII group appeared significantly higher levels of 24-hour urinary protein,urinary α1-microglobulin,urinary β2-microglobulin, urinary albumin, serum creatinine and cystatin C ($p<0.05$), and significantly declined eGFR ($p<0.05$). Renal tubulointerstitial injury score was positively associated with serum creatinine($r=0.304$,$p=0.00$), cystatin C($r=0.372$,$p=0.00$), 24-hour urinary protein($r=0.207$,$p=0.016$), α1-microglobulin($r=0.174$,$p=0.044$), β2-microglobulin($r=0.246$,$p=0.004$) and urinary albumin($r=0.206$,$p=0.017$), and negatively associated with eGFR($r=-0.304$,$p=0.00$). After 12-month follow-up, patients in TII group showed higher incidence of eGFR decrease.

Conclusions: TII occurs in IMN patients, which may be prompted by some clinical indicators. TII may affect the the progression and prognosis of IMN, and further researches are needed to elaborate the mechanisms and explore effective therapies.

TH-PO142

Initial States of Circulating Anti-Phospholipase A2 Receptor Antibody and Cigarette Smoking Predict a Clinical Outcome in Japanese Patients with Idiopathic Membranous Nephropathy Asaka Hachiya, Shin'ichi Akiyama, Shoichi Maruyama. *Nagoya University Graduate School of Medicine, Nagoya, Japan.*

Background: Idiopathic membranous nephropathy (iMN) is the leading cause of nephrotic syndrome in adults, the clinical outcomes in iMN is difficult to predict. We reported that the prevalence of anti-PLA2R in Japanese patients with iMN is approximately 50%, which was lower than reports from any other countries (approx. 75%). In addition, we reported that cigarette smoking is a significant and dose-dependent risk factor for progression of Japanese patients with iMN. In this study, we had tried to reveal that the association of initial states of anti-PLA2R and cigarette smoking to clinical outcomes in Japanese patients with iMN.

Methods: We retrospectively enrolled consecutive 78 biopsy-proven iMN Japanese patients with nephrotic syndrome (# of male, 57; median age, 64 [IQR 60-70] years old; # of Current/Ex-smoker, 34) who admitted our hospitals between January 2003 and December 2012, and followed these patients for at least 3 months (median [IQR], 56 [35-81] months). All patients were not treated with any immunosuppressive therapies at renal biopsy, whose serum were collected at the same time of renal biopsy. Duration of complete remission (CR) and predictors of prolongation of CR were assessed and anti-PLA2R in serum was measured by ELISA.

Results: Anti-PLA2R was positive in 53% (41 of 78) of all patients with iMN. The prevalence of anti-PLA2R in current/ex-smokers (59%, 20 of 34) higher than that in never-smokers (47%, 21 of 44). In the follow-up period, CR was observed in 55 patients (anti-PLA2R positive, 27; negative, 28). In patients with anti-PLA2R positive and/or ex/current smoker, the period to CR tended to prolong. Duration of CR with anti-PLA2R positive and ex/current smoker was significantly longer than that of the other groups (log rank, $p = 0.009$). Multivariate Cox proportional hazards models revealed anti-PLA2R positive and current/ex-smokers (adjusted hazard ratio, 0.16 [95% confidence interval, 0.05–0.51]) associated with prolongation of CR.

Conclusions: The smoking experience and anti-PLA2R positive at diagnosis are risk factor for prolongation of complete remission. Our data suggested that check the initial states of circulating anti-PLA2R and cigarette smoking is useful and easy method to predict a clinical outcome of patient with iMN.

TH-PO143

Low Dose Rituximab Is Non-Inferior to Higher or Multiple Dose Schedules in the Treatment of Steroid Sensitive, Frequently Relapsing Nephrotic Syndrome in Children Ben C. Reynolds,[4] Rebecca A. Dalrymple,[2] Andrew P. Maxted,[6] Denise Chisholm,[6] John H. Mccoll,[5] Yincent Tse,[1] Martin Christian.[3] *[1]Great North Children's Hospital, Newcastle upon Tyne, United Kingdom; [2]Greater Glasgow and Clyde NHS, Glasgow, United Kingdom; [3]NHS, Nottingham, United Kingdom; [4]Royal Hospital for Children, Glasgow, Glasgow, United Kingdom; [5]University of Glasgow, Glasgow, United Kingdom; [6]Pediatric Nephrology, Nottingham Children's Renal and Urology Unit, Nottingham, United Kingdom.*

Background: Rituximab is an effective treatment for children with steroid dependent or frequently relapsing nephrotic syndrome. Dosing schedules vary between centres and are based on anecdotal evidence and non randomised controlled data. We hypothesised that a single low dose of 375mg/m^2 would be non-inferior to higher or multiple doses, in maintaining remission and time to B-cell reconstitution.

Methods: This was a retrospective, observational cohort study of children from three paediatric nephrology centres in the United Kingdom. Children with steroid sensitive, frequently relapsing nephrotic syndrome who received Rituximab since January 2007 were included. Data were extracted from clinical records on the dates of diagnosis, treatment and relapses; lymphocyte subset profiling pre-and post-rituximab administration; and the use of concomitant immunosuppression. The primary outcome was an absence of clinically confirmed relapse 12 months after Rituximab administration. Secondary outcomes were median time to relapse, probability of being relapse free at 6 and 24 months and time to reconstitution of $CD19^+$ B cells (CD 19^+ B cells $>0.2 \times 10^9$).

Results: 60 patients received 143 courses of Rituximab. Patients were grouped according to the dose of Rituximab received; those in group 1 (15 courses) received a higher total dose of 1.5g/m^2, group 2 (25 doses) received an intermediate dose between 750mg/m^2 – 1g/m^2, and group 3 (103 courses) received our current low dose regimen of a single dose of 375mg/m^2. There was no difference in event-free survival at 6, 12, or 24 months between groups. Of those who relapsed, the median time to relapse was not significantly different between the high and low dose groups, 317 days in group one and 299 days in group three. The median time to reconstitution of B-cells was not significantly different between groups at 175, 226 and 196 days for groups 1, 2 and 3 respectively.

Conclusions: We conclude that usage of a single low dosage of Rituximab in the management of frequently relapsing nephrotic syndrome does not affect the probability of relapse at 6 and 12 months, or the time to B-cell reconstitution in our cohort of patients.

TH-PO144

Initial Response to Corticosteroid Therapy and Native Kidney Biopsy Findings Predict Disease Recurrence Following Kidney Transplantation in Childhood Nephrotic Syndrome Adam R. Bensimhon, Jonathan H. Pelletier, Karan Kumar, Michelle N. Rheault, Tarak Srivastava, Caroline E. Straatmann, Thomas K. Davis, Cynthia J. D'Alessandri-Silva, Scott E. Wenderfer, Rachel M. Engen, Keisha L. Gibson, Christoph Licht, David T. Selewski, Larry A. Greenbaum, Rasheed A. Gbadegesin. *Pediatrics, Duke University Medical Center, Durham, NC.*

Background: Steroid resistant nephrotic syndrome (SRNS) is a leading cause of ESKD in children. Disease recurrence following kidney transplantation is the single most important cause of renal allograft loss in SRNS. Previous studies have not consistently identified risk factors associated with recurrence of disease. This study aims to determine predictors of disease recurrence in children with SRNS after renal transplantation.

Methods: A 10 year multicenter review of kidney transplants performed for SRNS in MWPNC participating centers. Data were collected on patients' demographics, clinical course, and biopsy findings. Patients with primary SRNS (PSRNS) were defined as those initially resistant to steroid therapy at diagnosis, and patients with late SRNS (LSRNS) were defined as those initially responsive who subsequently developed resistance. Groups were compared by chi-square tests or Fisher's exact test, and multivariate regression analysis was used to identify predictors of recurrence.

Results: We identified 116 patients (67 with PSRNS, 17 with LSRNS, and 32 with genetic SRNS/undetermined pattern of response). Disease recurrence occurred in 35.8% of patients with PSRNS compared to 70.6% of those with LSRNS ($p < 0.001$). Age at diagnosis and ESKD, sex, race, and ethnicity were similar in patients with and without recurrence. Patients with minimal change disease histology (MCD) on initial kidney biopsy had an 80% recurrence rate compared with a 31% recurrence rate in those with focal segmental glomerulosclerosis (FSGS) ($p = 0.005$). Unadjusted multivariate analysis identified MCD (OR 8.9; 95% CI 1.8-45.3, $p = 0.008$) and LSRNS (OR 4.3; 95% CI, 1.4 to 13.7, $p = 0.013$) as predictors of disease recurrence, but in adjusted analysis, only LSRNS predicted disease recurrence (OR 4.3; 95% CI 1.1-16.1, $p = 0.032$).

Conclusions: Pediatric patients with LSRNS and MCD histology are at significantly higher risk of disease recurrence following kidney transplantation. These findings may be useful for designing studies to test strategies for preventing recurrence.

Funding: NIDDK Support

TH-PO145

Management of Children With Congenital Nephrotic Syndrome: Challenging Treatment Paradigms Stephanie Dufek,[1] Elisa Ylinen,[2] Agnes Trautmann,[4] Enrico Vidal,[3] Tuula M. Holtta,[2] Rukshana Shroff.[1] *[1]Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom; [2]University Hospital Helsinki, Helsinki, Finland; [3]University-Hospital of Padova, Padova, Italy; [4]Center for Pediatrics and Adolescents Medcine, University Hospital Heidelberg, Heidelberg, Germany. Group/Team: On behalf of ESPN Dialysis Working Group.*

Background: Management of children with congenital nephrotic syndrome (CNS) is challenging and ranges from antiproteinuric treatment to uni- or bilateral nephrectomies followed by dialysis and transplantation. Early bilateral nephrectomies followed by dialysis and transplantation is currently practised in most centres, but conservative treatment may also be effective.

Methods: We conducted a 6-year survey across members of the European Society for Paediatric Nephrology Dialysis Working Group to compare management strategies and their outcomes in children with CNS.

Results: 81 children (51% male) across 17 tertiary nephrology units in Europe were included (NPHS1 n=57; NPHS n=2, WT1 n=10, others n=12; details of mutations were not examined). Antiproteinuric treatment was given in 48 (59%) with an increase in S-albumin in 68% by median 6 (interquartile range 3-8) g/L ($p<0.001$) and decrease of weekly albumin infusion dose by median 1 (0-3) g/kg/week ($p=0.021$). Unilateral nephrectomy (or first kidney removal) was performed in 16 children. In those, S-albumin increased by median 3 (1–7) g/L ($p=0.021$) and weekly albumin infusion dose decreased by median 4 (0-7) g/kg/week ($p=0.018$). The median age at bilateral nephrectomy was 9 (7-15) months. Dialysis was initiated in 53 (65%) at a median age of 9 (5.5-15) months, with PD in 91% of children. Children with NPHS1 mutations and >12 months follow-up were divided into two groups and their outcomes were compared: bilateral nephrectomy (n=26) versus conservative management (no nephrectomy; n = 17). Nephrectomised children presented earlier (3 vs 29 days; $p=0.01$), with comparable S-albumin ($p=0.21$) and S-creatinine ($p=0.19$). There was no difference in the number of septic or thrombotic episodes and growth was comparable. At final follow-up (median age 34 months) 9 (53%) children in the conservative group remained without renal replacement therapy, 4 (24%) received a renal transplant and 2 died. Amongst nephrectomised children 21 (81%; $p<0.01$) were transplanted and 1 died.

Conclusions: An individualised, stepwise approach, with prolonged conservative management, followed by unilateral nephrectomy may be a reasonable alternative to early bilateral nephrectomies in children with CNS and NPHS1 mutation.

TH-PO146

Medication Adherence and Perceived Difficulties in Pediatric Nephrotic Syndrome Chia- Shi Wang,[1] Jonathan P. Troost,[2] Tarak Srivastava,[3] Darcy K. Weidemann,[3] Larry A. Greenbaum.[1] *[1]Emory University, Atlanta, GA; [2]University of Michigan, Ann Arbor, MI; [3]Children's Mercy Hospital, Kansas City, MO, Group/Team: cNEPTUNE Working Group.*

Background: In children with nephrotic syndrome (NS), there is limited information on the prevalence of medication nonadherence and the role of perceived barriers in determining nonadherence.

Methods: We surveyed a large cohort of prevalent pediatric NS patients enrolled in an international, prospective study, the Nephrotic Syndrome Study Network (NEPTUNE). Self-reports for patients ages 8-18 years and caregiver-reports for patients ages 0-10 years were administered to prevalent patients between 2015-2016. The surveys contained 2 questions on whether medications were taken/missed and 17 questions on difficulties with medication ingestion, regimen adaptation, and disease frustration. All responses were reported in a 5-item Likert-type scale. Non-adherence was defined as responses of "not sure" or affirmative responses to not taking all medications or having missed medications. Patients were noted to have perceived barriers to medication adherence if an affirmative answer was given to one of the seventeen questions on medication difficulties. Association between perceived barriers and adherence was assessed by Chi-square test.

Results: 129 patients/caregivers completed medication adherence surveys, and 113 responded to medication difficulties surveys. Median time of study enrollment at time of survey was 521 days (interquartile range = 10-1221 days). 51 (39.5%) of patients were non-adherent to medications by self-/caregiver-report. 56 (49.6%) reported difficulties with ingestion, 45 (39.8%) with regimen adaptation, and 69 (61.1%) with disease frustration. 86 (76.1%) patients reported difficulties within at least one domain. Report of perceived barriers was not significantly associated with medication nonadherence (odds ratio = 1.63, 95% confidence interval = 0.64-4.14).

Conclusions: Self-/caregiver-reported medication nonadherence was common among pediatric NS patients. The majority of patients and caregivers reported experiencing barriers to adherence, including difficulties with medication ingestion, adaptation to medication regimen, or frustration with the disease. Prospective studies are needed to assess the effects of reported difficulties on long-term medication adherence and disease outcome.

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TH-PO147

Cardiovascular Disease Risk Factors in Pediatric Glomerular Disease: An Early Analysis of the Cure Glomerulonephropathy (CureGN) Study Isa Ashoor,[1] Donald J. Weaver,[2] Amy Kogon,[3] Rulan S. Parekh,[4] Tetyana L. Vasylyeva,[5] Aftab S. Chishti,[6] Michelle N. Rheault,[7] Christine B. Sethna,[8] Michelle M. O'Shaughnessy,[9] Margaret Helmuth.[10] *[1]Children's Hospital of New Orleans, New Orleans, LA; [2]Levine Children's Hospital at Carolinas Medical Center, Charlotte, NC; [3]Nationwide Children's Hospital, Columbus, OH; [4]The Hospital For Sick Children, Toronto, ON, Canada; [5]Texas Tech University Health Sciences Center, Amarillo, TX; [6]University of Kentucky, Lexington, KY; [7]University of Minnesota, Minneapolis, MN; [8]Cohen Children's Medical Center of NY, New Hyde Park, NY; [9]Stanford University Medical Center, Palo Alto, CA; [10]Arbor Research Collaborative for Health, Ann Arbor, MI. Group/Team: CureGN Study Cardiovascular Working Group.*

Background: Chronic kidney disease (CKD) is major risk factor for subsequent development of cardiovascular disease (CVD). We sought to describe the burden of CVD risk factors in pediatric glomerular disease.

Methods: CureGN is a prospective multi-center cohort of biopsy-confirmed primary glomerular diseases (minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), membranous nephropathy (MN), and IgA Nephropathy/Vasculitis (IgAN/IgAV)). Descriptive statistics are used to assess CVD risk factors (hypertension, obesity, dyslipidemia, prematurity, and second hand tobacco exposure) and management practices among 578 participants under age 18. Data were obtained at enrollment.

Results: The *Table* summarizes baseline characteristics and prevalence of CVD risk factors overall and by primary glomerular disease. Prevalent cardiac disease was rarely reported. Overall, 20% had a history of hypertension. Enrollment BPs were hypertensive in 21% and pre-hypertensive in 14% of patients compared to 1.6% and 9.6% of general pediatric population. Among those with hypertensive readings, and those with UPCR>3.5, less than a third received RAAS blockers overall. Obesity was present in 31% and elevated total cholesterol (TC > 200 mg/dL) was present in 30% compared to 17% and 7.4% of general pediatric population. Use of lipid lowering medications in children with TC > 200 was infrequent (7%). Prematurity and second hand smoke exposure were similar to general population.

Conclusions: In this pediatric glomerular disease cohort, prevalence of traditional CVD risk factors is high, particularly hypertension and dyslipidemia. Further study is needed to optimize screening and management of CVD risk factors in this population.

Funding: NIDDK Support

Baseline Characteristics at Enrollment Median (IQR) or n (%)		Overall N=578	MCD[1] N=187	FSGS[2] N=144	MN[3] N=29	IgAN/IgAV[4] N=218	P-Value[5]
Age (years)		11 (7-14)	7 (5 -11)	11.5 (7 -15)	15 (13-17)	12 (8-14)	<0.0001
Race:	White	406 (70%)	115 (62%)	91 (63%)	16 (55%)	184 (84%)	<0.0001
	African American	84 (15%)	35 (19%)	36 (25%)	8 (28%)	5 (2%)	
Ethnicity: Hispanic or Latino		73 (13%)	23 (12%)	19 (13%)	8 (28%)	23 (11%)	0.007
Sex: Male		342 (59%)	113 (60%)	81 (56%)	12 (41%)	136 (62%)	0.01
CKD duration (days)		257 (37-772)	777 (310 -1404)	447 (189 -1083)	208 (73 -632)	337 (97-858)	<0.0001
Serum albumin (g/dL)		3.8 (3.1-4.2)	3.6 (2.6-4.1)	3.6 (2.8-4.2)	3.1 (2.3-3.8)	4.0 (3.6-4.3)	<0.0001
eGFR (mL/min/1.73[2])		110 (89-129)	117 (101-141)	99 (70-126)	108 (88 -122)	108 (87-124)	<0.0001
UPCR (mg/mg)		0.6 (0.2-3.1)	0.7 (0.1-4.7)	1.5 (0.2-4.4)	1.5 (0.4-5.9)	0.4 (0.2-1.2)	<0.0001
Cardiovascular Risk Factors Burden		**Overall N=578**	**MCD N=187**	**FSGS N=144**	**MN N=29**	**IgAN/IgAV N=218**	**P-Value**
Exposure to Second Hand Smoke at home		133 (23%)	48 (26%)	30 (21%)	9 (31%)	46 (21%)	0.5
Premature (Born <=37 wks)		65 (11%)	19 (10%)	16 (11%)	2 (7%)	28 (13%)	0.4
Prevalent cardiac disease		9 (2%)	3 (2%)	3 (2%)	1 (3%)	2 (1%)	0.4
Prevalent hypertension		116 (20%)	38 (20%)	39 (27%)	9 (31%)	30 (14%)	<0.0001
Weight Status	Overweight	106 (18%)	38 (20%)	21 (15%)	10 (35%)	37 (17%)	0.01
	Obese	180 (31%)	56 (30%)	54 (38%)	11 (38%)	59 (27%)	
Measured blood pressure at enrollment	Pre-hypertensive[7] Hypertensive	83 (14%)	32 (17%)	25 (17%)	6 (21%)	20 (9%)	0.008
		121 (21%)	44 (24%)	33 (23%)	8 (28%)	36 (17%)	
Total Cholesterol (TC) > 200 mg/dL	Yes	172 (30%)	91 (49%)	39 (27%)	15 (52%)	27 (12%)	<0.0001
	Not measured	304 (53%)	71 (38%)	71 (49%)	11 (38%)	151 (69%)	
Practice Patterns		**Overall N=578**	**MCD N=187**	**FSGS N=144**	**MN N=29**	**IgAN/IgAV N=218**	**P-Value**
Among patients with TC >200 (N), number prescribed lipid lowering medication, n/N (%)		12/172 (7%)	3/91 (3%)	4/39 (10%)	5/15 (33%)	0/27 (0%)	0.0001
Among hypertensive patients (N), number prescribed RAAS blockade, n/N (%)		35/121 (29%)	8/44 (19%)	11/33 (33%)	3/8 (38%)	13/36 (36%)	0.3
Among patients with UPCR > 3.5 (N), number prescribed RAAS blockade, n/N (%)		37/121 (31%)	8/47 (17%)	15/39 (39%)	6/12 (50%)	8/23 (35%)	0.07

1) Minimal Change Disease 2) Focal Segmental Glomerulosclerosis 3) Membranous Nephropathy 4) IgA Nephropathy/ IgA Vasculitis 5) Categorical variables are tested using chi-squared tests and continuous variables are tested using non-parametric Kruskal-Wallis tests 6) Pre-hypertensive BP includes 90th to < 95th% or > 120/80 7) Hypertensive BP includes =/> 95th %

TH-PO148

Pregnancy in Women with Relapsing Minimal Change Disease – Experience of a Tertiary Centre Iolanda Godinho,[1,2] Philip Webster,[1,2] Liz Lightstone.[1,2] *[1]Imperial College London, London, United Kingdom; [2]Imperial College Healthcare NHS Trust London, London, United Kingdom.*

Background: Recent data suggest even patients with CKD stage 1 have an increased risk of pregnancy complications when compared to the general population. However, data on outcomes specifically in pregnant women with relapsing minimal change disease (MCD) are lacking. We now report the largest series to date.

Methods: Women with MCD were identified from our obstetric renal database from 1996-2016. We report maternal outcomes: relapse, AKI & worsening of renal function, HTN; & obstetric outcomes: number of successful pregnancies, preeclampsia, preterm delivery & low birth weight.

Results: Out of 797 pregnancies, we identified 14 in 10 women with MCD. Median maternal age: 35 years (19-40). Two patients had chronic HTN – one with relapsing MCD with IgM deposition for 11 years & 8 years of FK treatment; the other patient had dysmetabolic syndrome and MCD diagnosis made on post-partum biopsy. All women were in remission with no proteinuria at the time of conception & normal creatinine with CKD1 in 8, CKD2 in 6 using CKD-EPI eGFR. The majority (71%) of women were on immunosuppression (FK (n-7), CsA (n-2) or steroids (n-2) & one had an unplanned pregnancy diagnosed very soon after maintenance rituximab. None of the women developed worsening renal function. Relapses were seen in 2 pregnancies in women who stopped their maintenance immunosuppression. One hypertensive patient had worsening HTN during pregnancy. The majority of babies (69%, n=9) delivered at term (median gestation 38 weeks (range 28-40)). Preterm (35 & 36 weeks) & very preterm (28 weeks) were seen in 3 & 1 pregnancies respectively. Birth weight was 2923±622g. Just 1 baby had low birth weight (<2.5kg) & 1 very low (1.5kg). There was one miscarriage at 18 weeks. No women developed pre eclampsia & no congenital abnormalities were seen.

Conclusions: In this series, the largest reported to date, of women with CKD1/2 due to relapsing MCD, despite high rates of immunosuppression, pregnancies were largely uncomplicated (69%) & relapse rare unless maintenance immunosuppression stopped. Our data suggest pregnancies in MCD in remission are safe & that establishing secure remission especially with tacrolimus, is key to pregnancy planning. Our good results rely on pre-pregnancy counselling to optimise timing & medications & a highly experienced MDT obstetric renal antenatal clinic.

TH-PO149

Utility of Renal Biopsy for Proteinuria in Pregnancy Eri Kawashima, Yoshihiko Inoue, Kiyoko Inui, Fumihiko Koiwa, Ashio Yoshimura. *Showa University Fujigaoka Hospital, Yokohama, Japan.*

Background: We are often referred patients who have proteinuria in pregnancy. The patients present various clinical conditions; superimposed preeclampsia, normotensive nephrotic syndrome, complicating hematuria. These clinical conditions sometimes become the risk of pregnancy termination. The patients with proteinuria in pregnancy had renal biopsies, and were discussed utility of the biopsies based on histopathological findings and clinical courses.

Methods: 17 patients who had proteinuria in pregnancy had postpartum needle biopsies of their kidneys. Then we analyzed clinical findings to need aggressive treatments, based on histopathological diagnosis and onset of proteinuria.

Results: Before 20 weeks' gestation, the timing of onset of proteinuria, nine of 11 patients were diagnosed kidney diseases to need treatments. Histopathological diagnoses were IgA nephropathy (n = 6), focal segmental glomerular sclerosis (n = 2), mesangial proliferative nephritis (n = 1). Other 2 patients were thin basement membrane disease and minor abnormality. After 20 weeks' gestation, two of 6 patients were diagnosed kidney diseases to need treatments, there were IgA nephropathy (n = 1), membranous nephropathy (n = 1). Other 4 patients were histopathological findings of pregnancy induced hypertension (PIH). Compared histopathological PIH with non-PIH about clinical characters, gestational age (PIH; 28.7 ± 2.87, non-PIH; 30.7 ± 4.11 y.o., p = 0.32), maximum proteinuria (9.9 ± 3.03, 1.8 ± 2.71 g/day, p = 0.006), continuous hematuria (p = 0.00002), serum creatinine (0.75 ± 0.21, 0.68 ± 0.23 mg/dl, p = 0.59), eGFR (80.5 ± 26.8, 94.3 ± 43.0 ml/min/1.73m^2, p = 0.46), systolic blood pressure (156 ± 8.0, 141 ± 17.7 mmHg, p = 0.03). Significant clinical character of non-PIH was continuous hematuria.

Conclusions: The patients who have proteinuria in pregnancy with continuous hematuria were suspected kidney disease to need aggressive treatments, and renal biopsies were utility as early diagnoses and treatments.

TH-PO150

Factors Associated with the Initiation of renin-Angiotensin-Aldosterone System Blockade in Patients with Sustained Proteinuria Elaine S. Kamil,[9] Matthew Elliott,[5] Patrick E. Gipson,[4] Susan F. Massengill,[10] Sharon G. Adler,[1] Anne Pesenson,[8] Meg Modes,[7] Gia J. Oh,[3] David T. Selewski,[4] Lauren Lee,[6] Debbie S. Gipson,[4] Xuhui Zhong,[2] Anne Waldo,[4] Jonathan P. Troost,[4] Richard A. Lafayette.[3] *[1]Harbor-UCLA Medical Center, Torrance, CA; [2]Peking University First Hospital, Beijing, China; [3]Stanford University, Stanford, CA; [4]University of Michigan, Ann Arbor, MI; [5]Metrolina Nephrology Associates, Charlotte, NC; [6]NephCure Kidney International, King of Prussia, PA; [7]Patient Advocate, Livonia, MI; [8]The Polyclinic, Seattle, WA; [9]Cedars Sinai Medical Center, Los Angeles, CA; [10]Levine Children's Hospital, Charlotte, NC.*

Background: Renin-angiotensin-aldosterone system (RAAS) blockade plays an important role in the treatment of sustained proteinuria. The goal of this study was to investigate the time from the onset of sustained proteinuria to initiation of RAAS blockade therapy and associated characteristics.

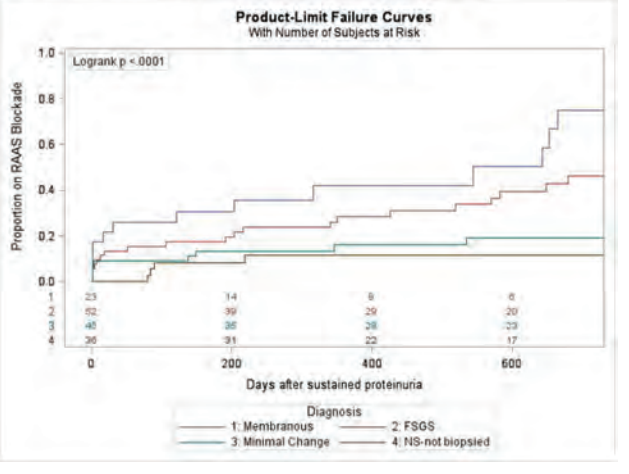
Methods: Electronic health record derived NephCure Accelerating Cures Institute cohort data were used. Patients with primary proteinuric kidney disease and onset of sustained proteinuria, defined as two or more days within 6 months with measurements of UP:C>1 or dipstick proteinuria ≥2+, were eligible. Kaplan-Meier analysis was used to evaluate the time to initiation of RAAS blockade from the date of the second qualifying proteinuria measurement.

Results: Of 848 registry patients, 147 patients were excluded due to prior RAAS therapy and 496 due to intermittent proteinuria. 205 patients were eligible for this analysis. 89 (43%) patients were prescribed RAAS blockade, 64 of 110 adults and 25 of 95 children. The median time from onset of sustained proteinuria until initiation of RAAS blockade was 241 days (IQR 35 to 653). Patients with Focal Segmental Glomerulosclerosis (FSGS) or Membranous Nephropathy (MN) were more likely to receive RAAS blockade and receive it earlier than Minimal Change or NS-not biopsied patients (Figure). In a multivariable Cox-proportional hazards model, diagnosis but not age or sex, was a significant factor associated with time to initiation of therapy.

Conclusions: Following onset of sustained proteinuria, RAAS blockade was initiated within a median of 8 months. Patients with a diagnosis of FSGS or MN were more likely to be treated and to be treated earlier. This study highlights opportunities for improvements in health care delivery.

Funding: Private Foundation Support

Figure. Time to initiation of RAAS blockade after sustained proteinuria by diagnosis



TH-PO151

Time to Initiation of Anti-Hypertensive Therapy after Onset of Elevated Blood Pressure in Patients with Primary Proteinuric Kidney Disease Susan F. Massengill,[1] Cheryl D. Courtlandt,[1] Matthew Elliott,[3] Patrick E. Gipson,[7] Elaine S. Kamil,[8] Anne Pesenson,[6] Meg Modes,[5] David T. Selewski,[7] Gia J. Oh,[9] Debbie S. Gipson,[7] Richard A. Lafayette,[9] Hailey Desmond,[7] Jonathan P. Troost,[7] Lauren Lee,[4] Sharon G. Adler.[2] *[1]Levine Children's Hospital, Charlotte, NC; [2]Harbor-UCLA Medical Center, Torrance, CA; [3]Metrolina Nephrology Associates, Charlotte, NC; [4]NephCure Kidney International, King of Prussia, PA; [5]Patient Advocate, Livonia, MI; [6]The Polyclinic, Seattle, WA; [7]University of Michigan, Ann Arbor, MI; [8]Cedars Sinai Medical Center, Los Angeles, CA; [9]Stanford University, Stanford, CA.*

Background: Past research suggested a significant lag between onset of hypertension (HTN) and initiation of antihypertensive therapy (AHRx). The aim of this study was to evaluate the time to initiation of AHRx in patients with proteinuric kidney disease identified as hypertensive based on standard guidelines.

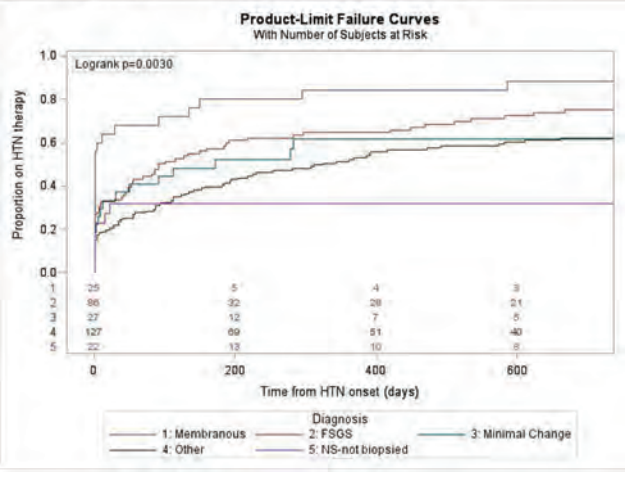
Methods: Longitudinal outpatient blood pressure (BP) measurements were available on 858 patients, 71% adults and 29% children, in the NephCure Accelerating Cures Institute cohort. Patients were defined as hypertensive either by ICD9/ICD10 diagnosis code or having 3 or more elevated BPs in a 6-month period. Patients already on AHRx at first observation were excluded. Kaplan-Meier and cox-proportional hazards analyses were used to evaluate the time to initiation of AHRx.

Results: Of the 858 patients available, 482 had evidence of HTN. 195 of these patients were excluded due to prior AHRx. Of the 287 remaining patients, 234 (82%) were subsequently started on AHRx. The median time from diagnosis or third qualifying BP until therapy initiation was 92 days (IQR=1 to 535). Adults were more likely to receive AHrx than children (87% vs 60%, p=0.04). Patients with Membranous Nephropathy had a shorter time to therapy initiation than those with other diagnoses (Figure). Patients with HTN by coded diagnosis were more likely to receive therapy compared to those with HTN by BP readings alone (83% vs 33%, p=0.03).

Conclusions: Patients with HTN in the setting of primary proteinuric kidney disease are prescribed AHRx a median of 3 months after HTN diagnosis. Having a coded diagnosis of HTN increased the likelihood of AHRx. Overall only 11% of the proteinuric patients in the NACI patient registry have HTN without the benefit of AHRx.

Funding: Private Foundation Support

Figure. Timing of antihypertensive therapy initiation in relation to onset of hypertension



TH-PO152

Steroid Associated Side Effects in Patients with Glomerular Disease Gia J. Oh,[1] Patrick E. Gipson,[8] Anne Pesenson,[2] David T. Selewski,[8] Elaine S. Kamil,[4] Susan F. Massengill,[5] Richard A. Lafayette,[1] Meg Modes,[6] Sharon G. Adler,[3] Lauren Lee,[7] Debbie S. Gipson,[8] Richard Eikstadt,[8] Samara Attalla,[8] Zubin J. Modi,[8] Anne Waldo,[8] Jonathan P. Troost.[8] *[1]Stanford University, Stanford, CA; [2]The Polyclinic, Seattle, WA; [3]Harbor-UCLA Medical Center, Torrance, CA; [4]Cedars Sinai Medical Center, Los Angelos, CA; [5]Levine Children's Hospital, Charlotte, NC; [6]Patient Advocate, Livonia, MI; [7]NephCure Kidney International, King of Prussia, PA; [8]University of Michigan, Ann Arbor, MI.*

Background: Steroid therapy is a common treatment for chronic glomerular disease with a goal of delaying or preventing end-stage kidney disease, but patients and families often express concerns about steroid-associated side effects (SA-SE). The goal of this study was to assess the occurrence of SA-SE in patients with primary proteinuric kidney disease.

Methods: 736 patients with preserved native kidney function enrolled in NephCure Accelerating Cures Institute registry within electronic health record sourced database were available for analysis. ICD-9 and ICD-10 code sets were generated for SA-SEs including HTN, obesity, diabetes, short stature, cataracts, glaucoma, and psychosis. Measures (elevated BP > 3 times and BMI) were also used to identify HTN and obesity. These side effects were identified through analysis of inpatient and outpatient encounter data. Events were considered steroid-associated if they occurred after the onset of steroid exposure.

Results: 413 of 736 (56%) registry patients were treated with steroids during study observation. Of these 413, 67% were adults, median age 41y, and 33% children, median age 11y, and the diagnoses were FSGS 26%, Membranous 11%, Minimal Change 19%, NS-not biopsied 16%, and other 29%. Median observation was 35 (IQR: 18-59) months. Table 1 presents SA-AE frequencies. 79% developed any SA-AE and 54% developed an event other than HTN. No episodes of glaucoma or psychosis were documented.

Conclusions: This study evaluated the incidence of medical encounter documented SA-AEs in patients with primary proteinuric kidney disease. The majority of patients treated with steroids developed at least one SA-AE. An accounting of the full patient experience of SA-AEs will likely require direct patient reported information to enrich the medical documentation.

Funding: Private Foundation Support

Table 1. Frequencies of SA-AEs among steroid treated proteinuric kidney disease patients by age group

	All Patients on steroids (n=413)	Patients < 18 y on steroids (n=159)	Patients >=18 y on steroids (n=254)	P value
Hypertension	289 (70)	131 (82)	158 (62)	<0.01
Obesity	173 (42)	76 (48)	97 (38)	0.05
Diabetes	44 (11)	8 (5)	36 (14)	<0.01
Short stature	16 (4)	10 (6)	6 (2)	0.04
Cataracts	11 (3)	2 (1)	9 (4)	0.16
>=1 SA-AE beyond HTN	221 (54)	128 (50)	93 (58)	0.11

TH-PO153

Tacrolimus as Monotherapy for Relapsing Minimal Change Disease in the Adult Population Anthony T. Chan, Tom Cairns, Jack W. Galliford, Charles D. Pusey, Megan Griffith. *Imperial College Renal and Transplant Centre, London, United Kingdom.*

Background: Minimal change disease (MCD) in adults is usually steroid responsive but the relapse rate is high, and some patients may develop steroid dependent disease. Tacrolimus has been used for relapsing/ steroid dependent MCD, however, the relapse rate during treatment has not been studied in adult population.

Methods: This is a retrospective cohort study of 27 patients with relapsing MCD treated with tacrolimus from 2011-2017. 21 males and 6 females with average age of 40.7 years old (Range 16- 80 years old). All patients had relapsing disease and 5 of 27 patients were steroid dependent. Prior to treatment with tacrolimus, 16 patients had 1 relapse, 3 patients had 2 relapses and 8 patients had 3 or more relapses. 23 patients had previously been treated with prednisolone alone, 2 patients had cyclophosphamide and prednisolone and 2 patients received cyclosporine and prednisolone.

Results: 15 of 27 patients remained in remission after receiving tacrolimus, with an average treatment time of 28 months (Range 3 to 69 months) and all these patients remain on maintenance therapy. 12 of 27 patients had a further relapse after commencing treatment with tacrolimus, average treatment time of 23.6 months (Range 3-65 months). 8 of 12 patients relapsed while still taking tacrolimus, with average treatment time of 21.3 months (Range 5-65 months), but 5 of these 8 patients had sub-therapeutic levels at time of relapse (<5 ng/ml). 4 of 12 patients relapsed after stopping tacrolimus with average time to relapse after stopping of 2.25 months (Range 2-3 months). The average estimated glomerular filtration rate before tacrolimus was 83.9 ml/min/1.73m^2 (Range 24-90 ml/min/1.73m^2) and during treatment was 85.73 ml/min/1.73m^2 (Range 48-90 ml/min/1.73m^2).

Conclusions: Tacrolimus is an effective treatment for relapsing MCD in adult. Patients often require long term maintenance treatment with careful drug level monitoring to avoid relapse. In this cohort all patients who had stopped tacrolimus went on to relapse. Retrospective extension of the study cohort is ongoing to investigate the optimal length of treatment with tacrolimus required to prevent future relapse, to facilitate design of a randomised controlled trial.

TH-PO154

Initial Therapy of Primary FSGS with Calcineurin Inhibitors Decreases Steroid Exposure without Compromising Renal Response Carlos A. Ch?vez-Mendoza, Jose A. Nino-Cruz, Ricardo Correa-Rotter, Juan M. Mejia-Vilet. *Nephrology and Mineral Metabolism, National Medical Sciences and Nutrition Institute Salvador Zubirán, Mexico City, Mexico.*

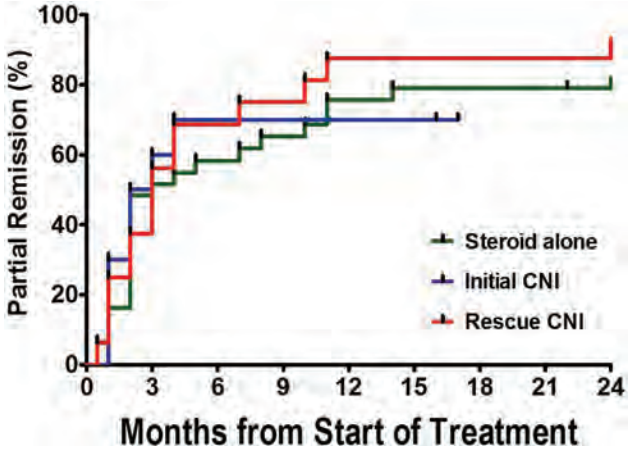
Background: Reduction of corticosteroid exposure has been a relevant focus in the management of glomerular diseases. High-dose glucocorticoid remains first-line therapy in primary FSGS, reserving calcineurin inhibitors (CNI) to patients with resistant disease or contraindication to corticosteroids.

Methods: Observational cohort. Sixty-two patients were segregated into 3 groups: high-dose steroid (n=35), initial CNI+low-dose steroids (n=11), rescue CNI+steroids (n=16). Groups were compared by survival analysis for complete (CR) and partial remission (PR), time to relapse (TTR), doubling of creatinine (DCr), end-stage renal disease (ESRD). Factors associated with each outcome were obtained by Cox-regression.

Results: Median follow-up was 44 months (IQR 24-69). There were no differences in time to CR/PR between steroid and initial CNI group (p=0.592 and p=0.962). Initial

CNI group had a shorter time to prednisone taper<10mg and lower cumulative steroids. There were no differences between the groups in TTR, DSCr, and renal survival. Although the rescue-CNI represented a steroid-resistant/dependent population, this group had no differences when compared to steroid and initial CNI groups. No differences in hospitalizations for infectious events between were observed in the three groups. The factors associated with lower renal survival were higher baseline creatinine, proteinuria, and chronicity score in the renal biopsy.

Conclusions: Treatment of FSGS with CNI as a first-line therapy may reduce exposure to steroids with similar response.



Multivariate Cox regression survival curves for partial remission according to the group of induction therapy for primary FSGS.

TH-PO155

Five Year Outcome of Steroid Resistant Focal Segmental Glomerulosclerosis (FSGS) Treated with Tacrolimus Harbir S. Kohli,[2] Raja Ramachandran,[1] Krishan Lal L. Gupta.[3] *[1]Nehru Hospital, Chandigarh, India; [2]Post Graduate Institute of Medical Education and Research (PGIMER), CHANDIGARH, India; [3]Postgraduate Institute of Medical Education & Research, Chandigarh, India.*

Background: Calcineurin inhibitors (CNIs) are recommended for steroid-resistant (SR) nephrotic syndrome (NS) due to focal segmental glomerulosclerosis (FSGS) by KDIGO as the 1st line agents. We reported earlier a remission in 52% at 1year. CNI use is limited by relapse after stopping and nephrotoxicity on prolonged use. The objective of the study was to report the 5 year outcome of patients treated initially with tacrolimus (TAC) for SR-FSGS.

Methods: Patients were treated with TAC (trough level 5–10 ng/ml) and prednisolone (0.15 mg/kg/d). TAC was discontinued in nonresponders at 24 weeks(TAC resistant). TAC was continued for 48 weeks in responders. After completing the study period, patients were managed as per treating physicians discreetion. Patients were followed up furthur for 4 years or till end stage renal disease (ESRD)/death. Primary outcomes, doubling of serum creatinine, ESRD or death and secondary outcomes remission rate (CR and PR) and persistent NS were studied.

Results: Of 44 who received TAC, at 48 weeks, CR and PR were achieved in 17 (38.6%) and 6 (13.6%) respectively, 21 (47.7%) patients were TAC resistant. At end of 5 years of starting therapy, 2 patients were lost to follow up 1 in each group. Of 22 responders14 (61%) had relapse on stopping TAC, they were restarted on TAC for another year. Four had sustained remission, while 4 became TAC dependent and 6 TAC resiatant. Of 4 Tac dependent, 3 responded to rituximab, only 2 of 6 TAC resistant received rituximab of which 1 responded. while others took ACE inhibitors or indigenous drugs. Kidney biopsy done in 8 patients after 2 years of TAC showed chronicity. Of 20 TAC resistant 2 of 3 who received rituximab responded. At the end of 5 years of starting TAC, in responders CR, PR, persistent NS, CKD, ESRD and death were seen in 3 (13.6%), 13 (59.1%), 5 (22.7%), none, 1 (4.6%) and none respectively, and amongst resistant patients1 (5%), 2 (10%), 3(15%), 3 (15%), 7 (35%) and 4 (20%). Fourteen (70%) patients with resistant disease had attained primary outcome compared to 1 (4.5%) in the remission group (p=0.0001).

Conclusions: TAC resistance portends poor prognosis with 70% having doubling of serum creatinine, ESRD or death at the end of 5 years. TAC dependency was seen in 60% of the initial TAC responders. Rituximab appears to be promising agent in both TAC dependent and resistant patients.

TH-PO156

Repeat Rituximab Dosing Is Often Necessary but Effective in Relapsing Minimal Change Disease in Adults Nikki L. Wong,[3] Tom Cairns,[1] Jack W. Galliford,[2] Charles D. Pusey,[3] Megan Griffith.[3] *[1]IMPERIAL COLLEGE HEALTHCARE, LONDON, United Kingdom; [2]Imperial College Kidney and Transplant Institute, London, United Kingdom; [3]Imperial College London, London, United Kingdom.*

Background: Rituximab (RTX) is increasingly being used for relapsing minimal change disease (MCD) in adults, but data is lacking on the need for and efficacy of multiple dosing regimens.

Methods: We retrospectively reviewed 19 patients treated with RTX for relapsing, or steroid resistant MCD between 2006-2017. Median age at treatment was 35 years (20-66), mean time from diagnosis 15 years (1-39), and mean relapse rate was 4/last 3 years. Previous maintenance treatment included steroids (17/19), tacrolimus (19/19), ciclosporin (6/19), mycophenolate (1/19), cyclophosphamide/chlorambucil (8/19) and levamisole (3/19).

Results: 19 patients received RTX. 8 patients were nephrotic, and 11 were in complete or partial remission at time of treatment. B-cell depletion was achieved in all patients. 10 patients had more than one RTX course [mean 2 (1-4)], the mean follow-up was 34 months (1-127). Of 8 patients who were nephrotic at RTX initiation, 6 achieved complete or partial remission and 2 failed to respond. 1/2 was steroid resistant and on subsequent rebiopsy was found to have FSGS, the other was steroid intolerant. Of 17 patients in remission post RTX, 9 had no further relapse at mean follow-up of 17 months (1-60). 3/9 received a second course of RTX after a mean 13 months (9-16). At last follow-up 5/9 have reconstituted B-cells (>10) at a mean of 6 months post RTX (1-11), while 4/9 remain B-cell deplete. 8/17 patients relapsed post RTX, at a mean 13 months (5-35). All relapsed patients had B-cell reconstitution at time of relapse. 7/8 who relapsed had a second course of RTX. 6 of these 7 relapsed again at a mean of 22 months (7-53) post redosing, 5 of these 6 patients received a third course of RTX. All 5 are now in remission and relapse free at a mean 7 months (1-14). 1 patient received a prophylactic fourth RTX course at B-cell reconstitution. There were no serious infusion reactions; and one case of *Pneumocystis* infection requiring hospitalization.

Conclusions: RTX is effective for relapsing MCD in adults, but repeated treatment courses may be required. B-cell reconstitution is associated with relapse and may be helpful in guiding prophylactic redosing in some patients. Nonresponse to RTX may suggest underlying FSGS. Further trials are needed to determine which patients will relapse and appropriate dosing regimens for maintenance RTX therapy.

TH-PO157

Rituximab Treatment of Minimal Change Disease (MCD) and Focal Segmental Glomerulosclerosis (FSGS) in Adults Renu Regunathan-Shenk, Andrew S. Bomback, Pietro A. Canetta, Wooin Ahn, Gerald B. Appel. *Columbia University College of Physicians and Surgeons, New York, NY.*

Background: Previous retrospective and prospective studies have suggested that rituximab may be an effective therapy for patients (Pts) with MCD and FSGS who have failed other therapies. Most studies have had small numbers of Pts and consisted largely of children.

Methods: We reviewed the charts of 58 adults (41 male) evaluated at Columbia University Medical Center between 2014 - 2017 who received rituximab for MCD or FSGS. We analyzed clinical, biopsy, and laboratory data pre-infusion and at follow up (F/U). We categorized Pts as frequently relapsing/steroid dependent (FRSD), infrequently relapsing (IR), steroid resistant (SR), and multi-drug resistant (MDR) based on their clinical course prior to rituximab.

Results: On renal biopsy, 31 Pts had MCD, 22 had FSGS, and 5 had podocytopathy associated with another diagnosis (e.g. IgA Nephropathy with MCD). There were 34 Whites, 13 Latinos, 6 Blacks, and 5 Asians. Disease category included 33 FRSD, 2 IR, 6 SR, and 17 MDR. Three patients (all FRSD) were excluded from further analysis; 2 Pts had <1 month (mo) of F/U and 1 was unable to complete treatment due to infusion reaction. The median number of immunosuppressant (IS) medications used prior to rituximab was 3 (range 1-6). The median number of concurrent IS was 1 (range 0-3) at time of infusion and 0 (range 0-2) at F/U. The median F/U was 15.8 mo (range 1.4-159). 62% (37/55) achieved a complete remission (CR, UPC <0.5 g/gCr) or partial remission (PR, UPC 0.5-3.5 g/gCr) during the F/U period; 32 remained in CR or PR and 5 relapsed by last F/U. Of patients in remission at last F/U, 13/22 Pts in CR and 5/10 Pts in PR were off all other IS. Of 23 Pts not in remission at last F/U, 12 never achieved CR or PR, 5 had relapsed, and 6 had progressed to ESRD. Of 17 MDR Pts, 3 achieved CR or PR after rituximab, 3 achieved CR or PR on other IS, and 11 never achieved CR or PR, with 3 progressing to ESRD. 18 Pts repeated rituximab treatment, 9 prophylactically, and 9 for treatment of relapse with all responding.

Conclusions: This is the largest study showing the benefit of rituximab in achieving remission of proteinuria and reduction of immunosuppression in adults with MCD or FSGS. Pts with MDR disease were less likely to respond to rituximab.

TH-PO158

Continuous B Cell Depletion for Resistant, Steroid Dependent, and Relapsing Nephrotic Syndrome in Adults Frank B. Cortazar, Colleen B. Dunbar, Karen A. Laliberte, John Niles. *Nephrology, MGH, Boston, MA.*

Background: The clinical course of minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) can be complicated by resistance to treatment, steroid dependence, and frequent relapses. Treatment options for such patients are limited. We present a retrospective series of patients with these phenotypes treated with rituximab (RTX)-induced continuous B cell depletion.

Methods: Patients were included if they had biopsy proven MCD or FSGS that was resistant, steroid dependent, or relapsing. All patients had a UPCR ≥ 3.5 g/g and were treated with RTX-induced continuous B cell depletion. Resistant disease was defined as failure to achieve a partial remission (PR) with prednisone at 1 mg/kg per day for 3 months or a calcineurin inhibitor or mycophenolate mofetil. Steroid dependence was defined as relapse during or within 2 weeks of steroid tapering. Relapsing disease was defined as at least two prior relapses. PR was defined as a urine protein:Cr ratio (UPCR) of ≤ 3.5 g/g and a 50% reduction from baseline, while CR was defined as a UPCR ≤ 0.3 g/g. Relapse after any remission was a UPCR ≥ 3.5 g/g.

Results: We identified 11 patients who met the inclusion criteria (Table). Over a median followup of 4.5 years (IQR, 2-5), patients received a median of 9 RTX doses (IQR, 8-15) and were in a state of B cell depletion for 3.7 years (IQR, 2-5). All patients entered PR at a median time of 89 (IQR, 34-144) days and 7 patients entered CR at a median of 362 (IQR, 34-1208) days. Prednisone dose was tapered from 60 mg/d (IQR, 15 to 60) at entry to 5 mg/d (IQR 0-7.5) at 1 year. Three patients sustained a relapse after PR, but all subsequently obtained a remission. No relapses occurred following CR.

Conclusions: Continuous B cell depletion is an effective treatment strategy for complicated cases of MCD and FSGS. Additional studies are needed.

Patient	Age	Sex	Disease	Phenotype	Failed Therapies
1	49	M	MCD	Resistant	Pred, CsA
2	40	M	MCD	Resistant	Pred
3	30	M	MCD	Resistant	Pred, CsA
4	66	F	FSGS	Resistant	Pred, MMF, Cyc
5	56	M	FSGS	Dependent	Pred, CsA, Tac, MMF
6	60	M	MCD	Dependent	Pred, CsA, MMF
7	23	F	MCD	Dependent	Pred, Tac, MMF
8	67	M	FSGS	Dependent	Pred, MMF
9	45	M	MCD	Dependent	Pred, Cyc, Aza
10	31	M	MCD	Relapsing	Pred
11	33	M	MCD	Dependent	Pred

CsA, cyclosporine, Cyc, cyclophosphamide; MMF, mycophenolate mofetil; Pred, prednisone; Tac, tacrolimus

TH-PO159

High Doses of Rituximab Are Ineffective in Adult Patients with Focal Segmental Glomerulosclerosis Dario Roccatello,[1] Savino Sciascia,[2] Roberta Fenoglio.[1] *[1]Ospedale San GIovanni Bosco, Torino, Italy; [2]Center of Research of Immunopathology and Rare Diseases (CMID), Division of Clinical Immunology, Giovanni Bosco Hospital and University of Turin, Ita, Torino, Italy.*

Background: a beneficial effect of rituximab on Focal Segmental Glomerulosclerosis (FSGS) in pediatric patients or in transplant recipients has been reported in isolated cases. However, the use of Rituximab in adult patients with idiopathic FSGS needs further investigation.

Methods: Eight patients who had biopsy-proven FSGS (63.9±14.0, range 40-81 yr, 4 women, 4 men) with major risk factors precluding corticosteroids or conventional immunosuppression were treated with high dose of rituximab (8 weekly doses of 375mg/m^2) and prospectively followed up for at least 2 years (29.1 ± 8.8 mo, range 24 to 42 mo).

Results: Rituximab failed to improve proteinuria in seven out of 8 patients, who had persistent nephrotic proteinuria. In one case, a rapidly deteriorating renal function was also observed. Only one patient showed an improvement of renal function and a remarkable proteinuria reduction. There were no differences in clinical or laboratory characteristics or in the CD20 B lymphocyte count after rituximab between the responder and the 7 non responders patients

Conclusions: Only a minority (one of eight) in our series of adult patients with FSGS showed positive effects of high doses of rituximab. Future studies are warranted to investigate more promising therapeutic options in the management of FSGS.

TH-PO160

Cetirizine and Montelukast Combination Therapy in Patients with Minimal Change Nephrotic Syndrome Concomitant with Allergic Disorders: A Single Center Study Yoichi Oshima,[1] Keiichi Sumida,[1] Masayuki Yamanouchi,[1] Junichi Hoshino,[1] Yoshifumi Ubara.[1,2] *[1]Nephrology Center, Toranomon Hospital, Kawasaki, Japan; [2]Okinaka Memorial Institute for Medical Research, Tokyo, Japan.*

Background: In minimal change nephrotic syndrome (MCNS) glucocorticoid treatment is a major therapeutic option; however glucocorticoid may cause many adverse effects since most patients with MCNS are dependent on glucocorticoid. It is known that MCNS often complicates with allergic diseases. We investigated if anti-allergy therapy with cetirizine and montelukast have therapeutic effect in disease control for MCNS.

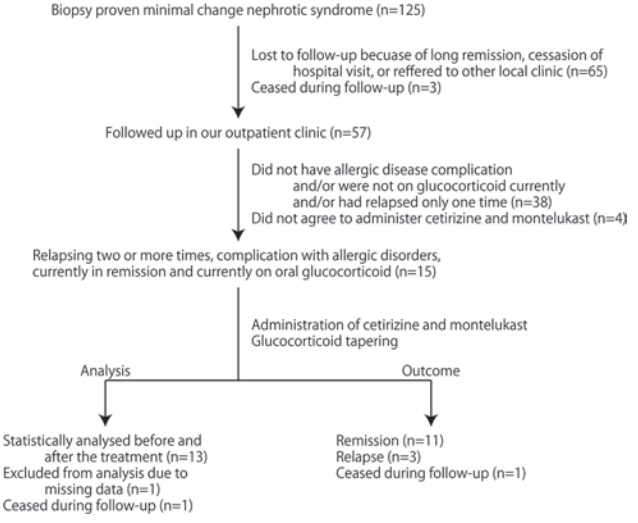
Methods: We identified 125 patients who were diagnosed as MCNS by renal biopsy in our hospital between 1985 and 2015. As shown in figure 1, 15 patients were included in this study. Patients were evaluated by minimum glucocorticoid maintenance dose.

Results: Average age at the time of onset was 33.2 years. Nine out of 15 patients were men (60%). Average number of relapses was 4.3 times. Average duration of corticosteroid treatment before the study was 211.3 months. Complicated allergic disorders were allergic rhinitis in ten patients (66.7%), atopic dermatitis in eight (53.3%), sinusitis in five (33.3%), drug allergy in four (26.7%), food allergy in three (20%), and asthma in two (13.3%). Average predonisolone dose at the start of the study was 3.78 (range: 0.5-10) (mg/day). Eleven patients (73%) became glucocorticoid free without relapse for more than 28 months, while only three relapsed (20%). After the treatment, minimum predonisolone maintenance dose was 0.038 (mg/day) compared to 0.858 (range: 0-4) (mg/day) before the treatment (p=0.042, Wilcoxon nonparametric paired test).

Conclusions: Cetirizine and montelukast therapy may have steroid sparing effect in allergy concomitant relapsing MCNS.

Funding: Private Foundation Support

Figure 1



TH-PO161

Dyslipidemia and Outcomes in NEPTUNE Christine B. Sethna,[2] Kevin E. Meyers,[5] Tammy M. Brady,[3] Crystal A. Gadegbeku,[4] Tarak Srivastava,[1] Keisha L. Gibson,[8] Matthias Kretzler,[6] Laura H. Mariani.[7] *[1]Childrens's Mercy Hospital, Kansas City, MO; [2]Cohen Children's Medical Center of NY, New Hyde Park, NY; [3]Johns Hopkins University, Baltimore, MD; [4]Temple University, Philadelphia, PA; [5]The Children Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA; [6]U.Michigan, Ann Arbor, MI; [7]University of Michigan, Ann Arbor, MI; [8]University of North Carolina Kidney Center, Chapel Hill, NC. Group/Team: NEPTUNE Cardiovascular Working Group.*

Background: Patients with nephrotic syndrome (NS) have a pronounced alteration in lipoprotein metabolism. Dyslipidemia is a major risk factor for cardiovascular disease and may be associated with progression of renal disease; however, this has not been well characterized in NS.

Methods: Baseline lipid studies from the Nephrotic Syndrome Study Network (NEPTUNE) were collected. Dyslipidemia was defined as total cholesterol ≥200 mg/dL, HDL <40 mg/dL, LDL ≥130 mg/dL or triglycerides ≥100 mg/dL (0-9 yr), ≥130 mg/dL (10-17 yr), ≥50 mg/dL (≥18 yr). Cox regression adjusted for age, sex, race, disease, disease duration, baseline eGFR and urine protein:creatinine [UPC] examined the association of lipids (per 10 unit increase) with the Composite Outcome (End Stage Renal Disease or eGFR decline by ≥40%) and first Complete Remission (UPC ≤0.3).

Results: 271 adults (45.4±16.1 yr, 62% M) and 123 children (10.2±4.8 yr, 59% M) were evaluated. At baseline, 85% of participants had dyslipidemia (table). In the overall group, lower HDL and greater triglycerides were associated with increased hazard of the composite outcome (HR 0.91, 95%CI 0.83-0.98, p=0.02 and HR 1.02, 95%CI 1.001-

1.03, p=0.001, respectively). Greater HDL (HR 1.05, 95%CI 1.001-1.1, p=0.045) was associated with increased hazard of Complete Remission. Similar relationships were found in adults for Composite Outcome (HDL: HR 0.88, 95%CI 0.79-0.98, p=0.03; triglycerides: HR 1.01, 95%CI 1.001-1.03, p=0.04) and Complete Remission (HDL: HR 1.1, 95%CI 1.03-1.18, p=0.006). In children, greater triglycerides (HR 1.05, 95%CI 1.02-1.08, p=0.001) were associated with increased hazard of the Composite Endpoint. Lipids were not associated with Complete Remission.

Conclusions: In NEPTUNE, dyslipidemia is common and is an independent predictor of renal outcomes.

Funding: NIDDK Support, Other NIH Support - Office of Rare Diseases Research (ORDR), NCATS, Private Foundation Support

N (%) or Median (IQR)	Adults N =271	Children N = 123	P
Dyslipidemia	231 (85)	103 (84)	0.7
Total Cholesterol (mg/dL)	239 (192, 302)	242 (192, 330)	0.1
Total Cholesterol abnormal	192 (71)	89 (72)	0.76
HDL (mg/dL)	61 (49, 77)	73 (60, 98)	<0.001
HDL abnormal	29 (11)	10 (8)	0.43
LDL (mg/dL)	138 (95, 186)	148 (102, 236)	0.12
LDL abnormal	146 (54)	69 (56)	0.68
Triglycerides (mg/dL)	164 (113, 263)	144 (91, 255)	0.17
Triglycerides abnormal	154 (57)	77 (63)	0.28
eGFR (ml/min/1.73m^2)	69.5±33.1	98.5±32.6	<0.0001
UPC (g/g)	2.5±1	1.6±0.35	0.03
Focal Segmental Glomerulosclerosis/ Minimal Change/ Membranous (%)	30/ 15/ 23	35/ 42/ 2	<0.0001
Follow-up months	33.4±16	33.4±22.9	1.0
Composite Endpoint	82 (30)	26 (21)	0.06
Complete Remission Ever	124 (46)	86 (70)	<0.0001

TH-PO162

Cross Sectional Study on the Clinical Manifestations of Focal Segmental Glomerular Sclerosis (FSGS) in Japan from the Data of the Japan-Renal Biopsy Registry (J-RBR) Takaya Ozeki,[2] Shoichi Maruyama,[2] Takehiko Kawaguchi,[4] Toshiyuki Imasawa,[4] Ritsuko Katafuchi,[3] Hiroshi Sato.[1] *[1]Clinical Pharamacology and Therapeutics, Graduate School of pharmaceutical Sciences, Tohoku University, Sendai, Japan; [2]Nagoya University Graduate School of Medicine, Nagoya, Japan; [3]National Fukuoka-Higashi Medical Center, Koga, Fukuoka, Japan; [4]National Hospital Organization Chiba-East Hospital, Chiba, Japan.*

Background: Even though the clinical manifestations of FSGS varies amomg the underlying etiology, few reports had described the detail of its features comparing with MCD. J-RBR: Japanese nationwide registry started in 2007 and it has 32870 biopsy cases until December 2016. The aim of this study was to clarify the clinical characteristics of FSGS through analyzing the data of J-RBR.

Methods: A cross sectional study; patients were diagnosed with FSGS or MCD and were registered in J-RBR during 2007-2016. **<Analysis 1>** 1409 cases who were registered with histopathological diagnosis of FSGS were divided to 3 subgroups by age; Children (<18)/ Adult (18-64)/ Elderly (65≤), and clinical parameters were compared between subgroups. **<Analysis 2>**To compare the clincal features between nephrotic FSGS and MCD, patients who filfilled the criteria below were selected from the database. Criteria; histopathological diagnosis as FSGS or MCD, clinical diagnosis of nephrotic syndrome and over 18 years old.

Results: **<Analysis 1>**Among the 3 groups; Children (n=166), Adult (n=904), Elderly (n=339), the percentages of clinical diagnosis of nephrotic syndrome was 62.1, 32.9, 56.1 respectively. Adult group showed the lowest incidence of nephrotic syndrome. **<Analysis 2>**As compared with MCD (n=1522), FSGS (n=419) patients had higher age (FSGS: 59 vs MCD: 47.5) and higher rate of hypertension. And FSGS patients showed lower kidney finction (creatinine: 1.03 vs 0.83 mg/dL), higher serum albumin (2.2 vs 1.8 g/dL) and lower unine protein level (5.40 vs 6.28 g/day) at biopsy.

Conclusions: The incidence of nephrotic syndrome in FSGS patients was different among the age groups. Although FSGS patients showed lower kidney function and relatively milder proteinuria compared with MCD, it seemed to be difficult to distinguish these diseases only by initial clinical informations.

Comparison among 3 age groups in FSGS patients

	Obs	Children (n=166)		Adult (n=904)		Elderly (n=339)		P-value
		Median, n	[IQR] (%)	Median, n	[IQR] (%)	Median, n	[IQR] (%)	
age	1409	11	[5-15]	44	[33-55]	72	[68-77]	<0.001
sex (male)	1409	100	(60.2)	535	(59.2)	220	(64.9)	0.184
nephrotic syndrome	1409	103	(62.1)	297	(32.9)	190	(56.1)	<0.001
BMI	1387	18.5	[16.2-21.9]	24.2	[21.0-28.1]	23.7	[21.4-25.9]	<0.001
systolic BP	1180	113	[104-122]	130	[120-142]	136	[125-150]	<0.001
anti-hypertension drugs	1159	39	(32.2)	383	(50.6)	200	(71.1)	<0.001
HbA1 c (NGSP)	998	5.5	[5.3-5.9]	5.7	[5.4-6.0]	5.8	[5.5-6.2]	0.014
total protein	1396	6.2	[5.2-7.0]	6.7	[5.5-7.1]	5.9	[5.0-6.9]	<0.001
albumin	1391	3.9	[2.7-4.3]	3.9	[2.8-4.2]	2.9	[2.3-3.8]	<0.001
total cholesterol	1371	227	[173-284]	224	[191-263]	229	[186-300]	0.63
creatinine	1403	0.51	[0.34-0.72]	0.96	[0.72-1.29]	1.28	[0.94-1.70]	<0.001
eGFR	1395	100.4	[74.3-129.1]	62.5	[44.9-82.1]	39.5	[28.3-55.7]	<0.001
urinary protein (g/gCr)	718	4.1	[2.27-13.66]	3.05	[1.76-6.04]	5.58	[3.02-9.47]	<0.001
urinary protein (g/day)	700	2.97	[1.54-7.16]	2.74	[1.54-5.40]	3.7	[1.90-6.50]	0.034
urine RBC present	1409	41	(24.7)	205	(22.7)	65	(19.2)	0.29

Comparison between nephrotic FSGS and MCD patients

	FSGS (n=419)			MCD (n=1522)			P-value
	obs	Median, n	[IQR] (%)	obs	Median,n	[IQR] (%)	
age	419	59	[39-71]	1522	47.5	[30-66]	<0.001
sex (male)	419	251	(59.9)	1522	892	(58.6)	0.23
BMI	417	23.3	[20.8-26.2]	1507	23.6	[21.2-26.3]	0.39
systolic BP	392	135	[121-148]	1336	123	[112-135]	<0.001
anti-hypertension drugs	352	191	(54.3)	1329	395	(29.7)	<0.001
HbA1 c (NGSP)	300	5.6	[5.4-6.0]	1103	5.6	[5.4-6.0]	0.97
total protein	415	4.9	[4.3-5.7]	1516	4.2	[4.2-5.3]	<0.001
albumin	409	2.2	[1.7-2.6]	1439	1.8	[1.4-2.4]	<0.001
total cholesterol	412	308	[239-394]	1509	383	[291-478]	<0.001
creatinine	417	1.03	[0.79-1.52]	1521	0.83	[0.66-1.09]	<0.001
eGFR	417	54.2	[35.4-72.8]	1521	81.7	[61.8-89.5]	<0.001
urinary protein (g/gCr)	291	6.69	[4.00-9.95]	1076	7.52	[4.60-11.00]	0.008
urinary protein (g/day)	294	5.4	[3.50-8.10]	1067	6.28	[3.84-9.53]	0.001
urine RBC present	419	92	(22.0)	1522	239	(15.7)	0.008

TH-PO163

Improvement of Clinical Outcome in Kidney Diseases via the On-line Thai Glomerular Disease Registry: Focal Segmental Glomerulosclerosis Noppanit Pattanachaiwit,[2] Suchin Worawichawong,[1] Boonyarit Cheunsuchon,[5] Ngoentra Tantranont,[5] Warangkana Pichaiwong,[4] Pornpen Sangthawan.[3] *[1]Pathology, Ramathibodi Hospital, Bangkok, Thailand; [2]Medicine, Bhumibol Adulyadej hospital, Bangkok, Thailand; [3]Medicine, Prince of Songkla University Hospital, Songkhla, Thailand; [4]Medicine, RAJAVITHI HOSPITAL, Bangkok, Thailand; [5]Pathology, Siriraj hospital, Bangkok, Thailand.*

Background: Focal segmental glomerulosclerosis (FSGS) is one of the most common cause of end stage renal disease (ESRD) in adults. FSGS is more common in African-Americans than Asians. In Thailand, the data of FSGS have not been well determined. This study was conducted to investigate the prevalence and outcomes of FSGS via using the data from the on-line registry from Thai Glomerular Disease Collaborative Network (TGCN).

Methods: The data of biopsy-proven FSGS in adults were collected by the on-line registry from July 2014 to March 2017. Patients' clinical data including histopathological diagnosis at baseline, and clinical outcomes at 24, 48 and every 48 weeks after renal biopsy were analyzed.

Results: FSGS was diagnosed in 170 patients (10.9%) from 1,556 renal biopsy specimens. At the time of biopsy, 44.2% of FSGS was male, the mean age was 47.5±16.9 years, median serum creatinine level was 1.7 mg/dL (0.42-8.33), median urine protein creatinine ratio (UPCR) was 4.36 g/g. Cr (0.08-25.3), mean serum albumin (sAlb) was 2.8±0.9 g/dL. Nephrotic syndrome was 75%, whilst nephrito-nephrotic syndrome was only 2%. Most common histologic variant was not-otherwise-specified (NOS) (80.7%) followed by tip lesion (10.0%), perihilar variant (3.6%), cellular variant (3.6%), and collapsing FSGS (2.1%). At 24-week follow up, 22.9% of patients had complete remission and 62.7% had partial remission. The median time to all remission was 5.7 months. The only factor that was significantly associated with the remission rate was the percentage of tubular atrophy more than 50% with HR 0.24 (95%CI 0.07-0.81, *p = 0.021*) Three patients developed ESRD during the period of study.

Conclusions: The prevalence of FSGS in our study was 10.9%. NOS was the most common histologic variant. The severity of tubular atrophy was the only significant poor prognostic factor. *Funding: Health Systems Research Institute, and Nephrology Society of Thailand support*

Funding: Private Foundation Support

TH-PO164

Incidence of Focal Segmental Glomerulosclerosis in Olmsted County Musab S. Hommos,[2] An S. De Vriese,[1] Mariam P. Alexander,[2] Sanjeev Sethi,[2] Lisa E. Vaughan,[2] Kharmen A. Bharucha,[2] Ladan Zand,[2] Nicola Lepori,[3] Andrew D. Rule,[2] Fernando C. Fervenza.[2] *[1]AZ Sint-Jan, Bruges, Belgium; [2]Mayo Clinic, Rochester, MN; [3]Ospedale Brotzu, ----Cagliari, Italy.*

Background: Focal segmental glomerulosclerosis (FSGS) incidence is increasing. However, previous studies reported trends in relative disease frequencies and presented FSGS as a single disease entity. We now know that FSGS is a histological pattern of injury caused by a variety of conditions. Thus, we evaluated the incidence of primary vs. secondary FSGS in a population-based study.

Methods: Olmsted County residents with native kidney biopsy between 1994 and 2013 that showed FSGS as the only glomerulopathy were identified. Primary FSGS was defined as having nephrotic syndrome (serum albumin ≤3.5g/dl and proteinuria ≥3.5g/24h), foot process effacement ≥ 80% and no identifiable causes. Age and sex adjusted incidence rate per 100,000 person-years was calculated. Poisson regression models estimated the change in incidence rate over time.

Results: Among 370 adults biopsied during this period, 281 had glomerular disease of which 46 (16%) had FSGS as the only glomerulopathy.(Table 1) Estimated native

kidney biopsy incidence rates were significantly higher in 2004-2013 compared to 1994-2003 (22.9 vs. 14.7 per 100,000 person-years, 17% increase per 5 years, p<0.001). Total FSGS incidence rates also increased over the same time period from 1.4 in 1994-2003 to 3.2 per 100,000 person-years in 2004-2013 (41% increase per 5 years, p=0.02). Secondary FSGS accounted for 9/12 (75%) of cases during 1994-2003 and 25/34 (74%) of cases during 2004-2013.

Conclusions: The majority of cases are secondary FSGS. While the incidence of FSGS has increased over the past two decades, the proportion of primary and secondary FSGS has remained stable. Further studies are needed to understand the causes of this increasing Incidence though increasing biopsy rates may be a contributor. Importantly, primary FSGS rate remains low (0.85 per 100,000 person-years).

Table 1: Characteristics of FSGS patients by FSGS subtype and decade of biopsy

	1994-2003		2004-2013	
Characteristics at time of biopsy	**Primary FSGS N=3**	**Secondary FSGS N=9**	**Primary FSGS N=9**	**Secondary FSGS N=25**
	Mean ± SD or N (%)		Mean ± SD or N (%)	
Demographics				
Age, yr	37 ± 21	53 ± 21	55 ± 20	52 ± 18
Male	1 (33%)	5 (56%)	6 (67%)	13 (52%)
White	1 (33%)	5 (56%)	8 (89%)	21 (84%)
Clinical characteristics				
Hypertension	2 (67%)	8 (89%)	6 (67%)	20 (80%)
Diabetes	0 (0%)	2 (25%)	0 (0%)	7 (28%)
Body mass index > 30 kg/m²	0 (0%)	2 (29%)	6 (67%)	15 (60%)
ACEi/ARB at time of biopsy	0 (0%)	4 (44%)	5 (56%)	16 (64%)
Laboratory data				
eGFR, ml/min/1.73²	43 ± 67	48 ± 28	48 ± 19	55 ± 32
Albumin, g/dl	3.4 ± 0.1	4 ± 0.2	3 ± 0.4	4 ± 0.3
Proteinuria, g/day	6.1 ± 0.8	2.4 ± 2.1	8.6 ± 3.6	3.4 ± 2.8
Total cholesterol, mg/dl	233 ± 92	267 ± 44	255 ± 26	205 ± 63

TH-PO165

Improvement of Clinical Outcome in Kidney Diseases via the On-line Thai Glomerular Disease Registry: Minimal Change Disease Pattharawin Pattharanitima,[6] Ratana Chawanasuntorapoj,[3] Warangkana Pichaiwong,[2] Pornpen Sangthawan,[1] Ngoentra Tantranont,[4] Boonyarit Cheunsuchon.[5] *[1]Prince of Songkla University Hospital, Songkhla, Thailand; [2]RAJAVITHI HOSPITAL, Bangkok, Thailand; [3]Siriraj Hospital, Bangkok, Thailand; [4]Siriraj Hospital, Mahidol University, Bangkok, Thailand; [5]Siriraj hospital, Bangkok, Thailand; [6]Thammasat University, Pathumthani, Thailand. Group/Team: Thai Glomerular Disease Collaborative Network (TGCN).*

Background: The data on prevalence, clinical characteristics and outcomes of minimal change disease (MCD) in Thailand is sparse. The available data came from few medical schools which might not represent the entire Thai population. The Thai Glomerular Disease Collaborative Network (TGCN) was established to determine the prevalence, clinical characteristics, outcomes and prognosis in Thai glomerular disease patients.

Methods: The data collected prospectively from TGCN included adult patients with biopsy-proven glomerular disease from institutes in Thailand participating in TGCN from July 2014 to March 2017. The clinical and renal pathology characteristics, treatment regimens at the time of renal biopsy, clinical outcomes, and complications at 24, 48 and every 48 weeks after renal biopsy were obtained via online data collection forms.

Results: Among 1,556 patients, 115 (7.4%) had MCD. At baseline, 53% of MCD patients were male, the mean age was 46.5 ± 17.2 years, median serum creatinine (sCr) was 1.02 mg/dL (0.5-10.7), mean urine protein creatinine ratio (UPCR) was 5.99±4.72 g/g. Cr, mean serum albumin (sAlb) was 2.4±0.9 g/dL, and mean serum cholesterol (sChol) was 422±194 mg/dL. At 24 weeks, 62% had complete remission, and 19% had partial remission. Median time to remission was 1.5 months. The odd ratio of remission was 3.13 in patients with UPCR >5 *(P=0.047)*. The age, sAlb, sChol, sCr at time of biopsy and pathological characteristics were not different between remission and non-remission groups. The 1.5% of them had doubling serum creatinine, none of them developed ESRD and 1.4% of patient died during the study.

Conclusions: Conclusions: The outcome of the adults with MCD was excellent. The patients with UPCR >5 at baseline had more favorable outcome. *Funding*: Health Systems Research Institute and Nephrology Society of Thailand support

Funding: Private Foundation Support

TH-PO166

Health Related Quality of Life (HRQOL) in Primary Glomerular Disease: The Initial CureGN Experience Pietro A. Canetta,[1] Sharon M. Bartosh,[2] Yi Cai,[3] Hilda E. Fernandez,[1] Alessia Fornoni,[4] Rasheed A. Gbadegesin,[5] Emily G. Herreshoff,[6] Amy Kogon,[7] John D. Mahan,[7] Shannon L. Mahoney,[8] Patrick H. Nachman,[8] David T. Selewski,[6] Tarak Srivastava,[9] Katherine R. Tuttle,[10] Chia- Shi Wang,[11] Jonathan P. Troost,[6] Debbie S. Gipson.[6] *[1]Columbia University, New York, NY; [2]University of Wisconsin Children's Hospital, Madison, WI; [3]Helen DeVos Children's Hospital, Grand Rapids, MI; [4]University of Miami, Miami, FL; [5]Duke University, Durham, NC; [6]University of Michigan, Ann Arbor, MI; [7]Nationwide Children's Hospital, Columbus, OH; [8]University of North Carolina, Chapel Hill, NC; [9]Childrens's Mercy Hospital, Kansas City, MO; [10]University of Washington, Spokane, WA; [11]Emory University, Atlanta, GA. Group/Team: CureGN Consortium.*

Background: There is little published data on HRQOL in patients with primary glomerular diseases.

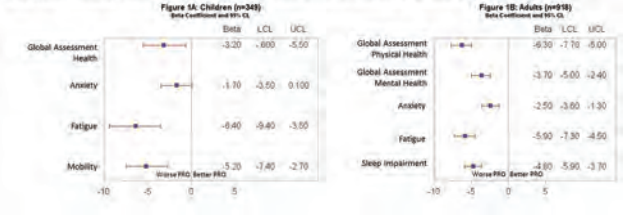
Methods: We studied HRQOL in subjects enrolled in CureGN, an international cohort of participants with minimal change disease, FSGS, membranous nephropathy, and IgA nephropathy or IgA vasculitis. HRQOL was assessed at enrollment using the Patient Reported Outcomes Measurement Information System (PROMIS). Domains measured in adults were: Global Assessment of Physical Health, Mental Health, Fatigue, Sleep, and Anxiety; domains in children were: Global Health, Mobility, Fatigue, and Anxiety. Minimally important differences have been defined as score change of 3 for the pediatric domains and have not been defined for adult domains. Immunosuppression (IS) in the past 60 days was classified as None, Glucocorticoids alone, or Other IS. Differences in HRQOL scores are reported as mean [95% confidence interval]. Multivariable analysis was conducted by linear regression with backwards selection.

Results: Data were available from 349 children and 918 adults. In children, multivariable analyses revealed PROMIS Global Health scores were worse with edema (-3.2 [-5.5 to -0.9]) and obesity (-4.5 [-6.9 to -2.1]) but were not significantly different across levels of proteinuria or eGFR. In adults, PROMIS Global Physical Health scores were worse with edema (-6.3 [-7.7 to -5.0]), log UPC (-0.6 [-0.9 to -0.2]), eGFR per -30 ml/min (-1.1 [-1.6 to -0.5]), female sex (-1.8 [-3.1 to -0.5]), and obesity (-3.2 [-4.8 to -1.7]). Race, ethnicity, diagnosis, disease duration, hematuria, and IS were not associated with HRQOL. In multivariable analysis, edema was the strongest predictor of HRQOL across both age groups and PROMIS domains (Figure).

Conclusions: Children and adults with glomerular diseases report a range of HRQOL. Edema was a consistent predictor of poor HRQOL across all measured domains of Global Health, Anxiety, Fatigue, Sleep, and Mobility.

Funding: NIDDK Support

Figure: The impact of edema on PROMIS domain scores at enrollment into the CureGN study: adjusted linear regression coefficients (*Beta*), Lower Confidence Limits (LCL) and Upper Confidence Limits (UCL) in (A) children and (B) adults. No edema = reference



TH-PO167

Cost Analysis on the Use of Rituximab and Calcineurin Inhibitor in Children and Adolescents with Steroid Dependent Nephrotic Syndrome Oluwatoyin F. Bamgbola,[2] Diego H. Aviles,[3] Franca M. Iorember.[1] *[1]Phoenix Children's Hospital, Scottsdale, AZ; [2]SUNY Downstate Medical Center, Brooklyn, NY; [3]Dept. of Pediatrics, Louisiana state university health science center, New Orleans, LA.*

Background: To minimize adverse effects, steroid sparing agents are used in steroid dependent nephrotic syndrome (SDNS). Although effective, the main drawback of calcineurin inhibitors (CNI) is the need for therapeutic drug monitoring (TDM). Apart from proven efficacy, Rituximab produces a long lasting remission after 1 or 2 single intravenous doses. To reduce frequency of clinic visits and cost efficiency, we introduced rituximab particularly in patients living remotely from laboratory facilities.

Methods: A retrospective analysis of pediatric patients with SDNS treated with either CNI &/ or Rituximab from Jan 2008 to Dec 2012 at Children's Hospital of New Orleans, Louisiana. All patients were followed up for a minimum of 12 months. We compared the cost effectiveness, efficacy, and safety profiles of the 2 groups.

Results: Ten patients were treated with Rituximab while 8 received CNI. Baseline data were comparable. Annual cost of treatment was lower with Rituximab ($197,031 vs. $189,856; p > 0.05). Amount expended on Rituximab arm was mostly due to drug cost and mandatory hospitalization for infusion. Due to frequent clinic visits for TDM, cost of outpatient care was more for the CNI ($4383 vs. $7534). There was marginally better control of SDNS with use of Rituximab. Duration of freedom from steroid was twice longer for those treated with Rituximab (p > 0.05). This accounted for twice the annual gain in body mass index in the CNI arm (1.5 kg/m² vs. 0.8 kg/m²). There was no significant side effect in either group. Retrospective design & small sample size limited ability to demonstrate significant findings. In addition, study outcome may vary with

regional differences in health care financial system. Nevertheless, we believe this is the first study of this kind in the pediatric population.

Conclusions: Although Rituximab is marginally more efficacious than CNI, short-term safety profiles are comparable. The annual cost of health care for patients on Rituximab is essentially similar to that of CNI. By cutting the need for frequent outpatient visits, Rituximab may curtail number of school absences, parental loss of wages, and the burden of health care on family. By minimizing the need for steroids and CNI, Rituximab use may avoid hypertension, dyslipidemia, short stature and impairment in renal function.

TH-PO168

Patients with Focal Segmental Glomerulosclerosis (FSGS): A Claims Analysis of Clinical and Economic Outcomes Tara A. Nazareth,[2] Furaha Kariburyo,[4] Aaron Kirkemo,[2] Lin Xie,[4] Anna Pavlova-Wolf,[1] Laura Bartels-Peculis,[2] Neel Vaidya,[4] John J. Sim.[3] *[1]Mallinckrodt, Henderson, TX; [2]Mallinckrodt Pharmaceuticals, Hampton, NJ; [3]None, Los Angeles, CA; [4]STATinMED Research, Ann Arbor, MI.*

Background: FSGS is the leading cause of idiopathic nephrotic syndrome (NS) in the US, accounting for 35% of cases (Haas et al., 1997; Kitiyakara et al., 2004). Given the complexity of diagnosis and treatment, many patients with FSGS have renal insufficiency at clinical presentation. Within 10 years, >50% develop kidney failure; post-transplant, FSGS can recur in 30-40% of patients (MedlinePlus FSGS; NephCure FSGS fact sheet). We studied a prevalent cohort to quantify the burden of illness with FSGS.

Methods: Commercially-insured patients ≥18 years with ≥2 diagnoses of FSGS [Diagnosis (Dx) code ICD-9=582.1 or ICD-10: N031, N033, N020, N040] were identified from Truven Marketscan® US healthcare claims data during 1/1/12-12/31/15; the first Dx date was denoted the index date. Patients with claims for secondary causes of NS (Dx) were excluded. During 1 year follow-up, demographics and clinical characteristics, clinical health outcomes, and all-cause healthcare resource utilization [HCRU: emergency room (ER), inpatient (IP), outpatient (OP), and medications (Rx)] were assessed using diagnosis, procedure and drug codes. Costs attributable to HCRU were evaluated in all patients enrolled in fee-for-service plans (FFS), as well as in the top 5% specifically.

Results: 1,187 patients were identified [59.0% male, mean age=45.1 years, with hematuria (17.7%), mean Charlson Comorbidity Index score=2.5, from South and North Central US (62.3%)]. 14.7% of patients had urinary tract infections, 4.6% pneumonia and 2.7% septicemia. 12.5% were placed on dialysis and 4.1% received a renal transplant. 29.0% of patients used the ER and 20.6% had IP stays. 21.9 mean Rx were dispensed. Among FFS patients (n=949), total and mean (SD) costs were $42.1 million and $44,397 ($102,481.8), respectively. 5% of patients (n=47) were responsible for 44.4% of total costs equaling $18.7 million, for a mean (SD) per patient cost of $397,973.8 ($219,457.3); OP, IP, Rx and ER represented 57.2%, 30.5%, 11.8%, and 0.5% of total costs, respectively.

Conclusions: Our study characterizes the 1-year burden of illness with FSGS and identifies a small group of patients incurring high cost, mostly via IP and OP use. Understanding this subset and their unmet needs, as well as their longer-term outcomes and costs, is a priority.

Funding: Commercial Support - This study was funded by Mallinckrodt Pharmaceuticals.

TH-PO169

Clinical Features and Outcomes of Collapsing Glomerulopathy Giulia gabriela B. Figueiredo,[2] Lucas B. Mota,[3] Luanne F. Soares,[2] Precil D. Neves,[2] Hady S. Miguel,[4] Leonardo A. Testagrossa,[3] Cristiane B. Dias,[2] Luis Yu,[2] Viktoria Woronik,[1] Lectícia Jorge.[3] *[1]None, Salvador, Brazil; [2]University of Sao Paulo, Brazil, São Paulo, Brazil; [3]University of São Paulo, São Paulo, Brazil; [4]Univertty of sao Paulo, São Paulo, Brazil.*

Background: The collapsing variant of focal and segmental glomerulosclerosis (FSGS) has usually been associated with poor renal outcomes. The aim of our study was to evaluate clinical features and renal outcomes associated with collapsing FSGS.

Methods: A retrospective analysis was carried out on all collapsing FSGS diagnosed by kidney biopsy between 1996-2016. Clinical and laboratory data were collected at baseline and at the end of follow up. Primary outcome (PO) was defined as ESRD or doubling of baseline creatinine.

Results: Clinical features are summarized in table 1. The PO occurred in 54.8% of patients. Pathology data analysis showed a higher prevalence of acute tubular necrosis (ATN) in patients who did not achieved PO, 14,3% versus 0%, with a p value of 0.03. The percentage of interstitial fibrosis was similar in both groups.

Conclusions: Collapsing glomerulopathy is an aggressive disease, and patients who reached the PO had greater baseline proteinuria and less partial or complete remission. As baseline creatinine was not a predictor of PO, perhaps the therapy should not be withheld in patients with high creatinine at presentation.

Clinical aspects of Collapsing FSGS patients

	Baseline	With PO	Without PO
Patients	77	34 (54.8%)	28 (45.2%)
Age (Y)	28.5 (21-38)	24.5 (21-38)	23.5 (30-50.5)
Male	43 (55.1%)	21 (61.8%)	15 (53.6%)
Creatinine (mg/dL)	1.98 (1.2-3.16)	1.6 (1.2-2.2)*	2.2 (1.3-3.7)
Proteinuria (g/day)	5.4 (3.36-10.4)	8.8 (3.8-13.3)*	5.0 (3.6-7.9)
AKI (n.%)	47 (68%)	23 (67%)	20 (71%)
Hematuria	34 (50%)	15 (44%)	14 (50%)
Hypertension	24 (48%)	11 (52%)	12 (43%)
Albumin (g/dL)	2.26 ±0.9	2.0 ±0.8	2.4 ±0.9
Hb (g/dL)	12.5 ±2.2	13.1 ±2.2*	11.9 ±2.1
Final creatinine (mg/dL)	2.8 (1.1-8.5)	8.1 (2.7-12.8)‡	1.2 (0.9-2.3)
Final proteinuria (g/day)	2.8 (0.7-6.16)	4.4 (2.1-9.8)*	0.79 (0.36-3.08)
Follow up (mo)	18.5 (7.8-43.8)	15 (7.3-34.8)	21 (10-52.3)
Corticorsteroid	36 (70.6%)	14 (61%)	22 (78%)
Remission†	28 (47,5%)	12 (35.3%)	22 (78.5%)

Data showed as mean (+/-SD) or median (IQR).

* p<0.05 versus without PO.

† <3.5g/day of proteinuria.

TH-PO170

Intermittent Dosing of Rituximab Induces Long-Term Remission in Children with Steroid Dependent Nephrotic Syndrome Cheryl P. Sanchez, Rita D. Sheth, Drew C. Cutler, Shobha Sahney. *Loma Linda University Children's Hospital, Loma Linda, CA.*

Background: Rituximab is frequently used as an alternative therapy in pediatric patients with nephrotic syndrome.

Methods: 17 children, 10.7 ± 3.4 years old, received rituximab infusion at 375 mg/m^2 per dose weekly x 4 weeks. Renal biopsy showed minimal change, n=10; IgM nephropathy, n=2; FSGS, n=3; C1Q, n=1; no biopsy n=1. All patients were taking prednisone and prograf at the time of rituximab infusion. Prior to rituximab, five out of 17 patients had ≥ 5 relapses per year, 4/17 ≥ 4 relapses per year, 3/17 ≥ 3 relapses per year, 5/17 without remission.

Results: After 4 weekly doses of rituximab, 12 patients (70%) had complete remission, 2/17 had partial remission and 3/17 did not respond to rituximab. Five of 12 relapsed within 6-12 months of receiving rituximab, 4/10 relapsed 12 months after rituximab, 3/13 remained in remission. CD20 levels decreased at 3 months after rituximab compared to baseline (10 ± 8% vs 0.03 ± 0.07%, p<0.05), and started to increase at 6 months, 2.3 ± 3.8%. There was no correlation noted between CD20 levels and proteinuria. Nine out of 12 patients who relapsed received 1.7 ± 0.8 additional doses of rituximab at 12 ± 3.2 months after last relapse, and remained in remission for an additional 6.4 ± 3.4 months. Five out of 9 children were off prednisone and prograf, and 4/9 remained on low dose prograf. One patient who had partial remission developed anaphylaxis to rituximab, but successfully treated with ofatumumab. There were no complications associated with repeated rituximab therapy.

Conclusions: Intermittent doses of rituximab can be used to maintain remission in steroid dependent nephrotic syndrome to avoid long term complications associated with prolonged prednisone and calcineurin therapy.

TH-PO171

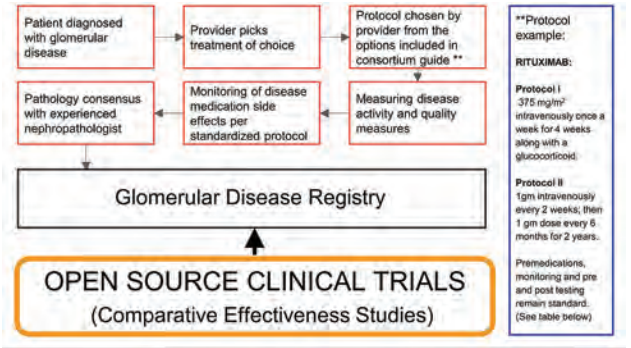
Enabling Large Observational Comparative Effectiveness Studies in Glomerular Disorders Rhea Bhargava,[6] Elizabeth J. Brant,[3] Jorge L. Castaneda,[4] David J. Friedman,[4] Neetika Garg,[6] Michael J. Germain,[5] Martin R. Pollak,[1] Johannes S. Schlondorff,[6] Tripti Singh,[4] Nikhil Agrawal,[6] Isaac E. Stillman,[6] Franco H. Cabeza Rivera,[2] Ali Poyan-Mehr.[4] *[1]Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA; [2]University of Mississippi Medical Center, Ridgeland, MS; [3]Dartmouth-Hitchcock Medical Center, Lebanon, NH; [4]None, Watertown, MA; [5]Renal and Transplant Assoc of New England, Hampden, MA; [6]Beth Israel Deaconess Medical Center, Boston, MA.*

Background: The heterogeneous presentation of glomerulopathies contributes to ambiguity in diagnosis and management making large comparative studies difficult

Methods: We created a network of nephrologists and nephropathologists in private practice and academic institutions, leveraging collective power to enroll patients to conduct comparative effectiveness studies(The Glomerular Disease Study and Trial Consortium)

Results: Major requirements identified for registry A Consensus on treatment standards & disease monitoring while preserving freedom of treatment selection B Standardized follow up laboratory studies and evaluations at predefined intervals C Review of tissue diagnosis by experienced nephropathologists, pathological work up and classification systems D Cloud-based clinical data repository A web-based, HIPAA secure system has been created for provider referral or patient self-referral for enrollment. Clinical data will be collected and updated quarterly. De-identified data will be available for research to collaborators. **Other opportunities**: Quality improvement measure development(e.g. TB surveillance, pregnancy counselling, diabetes, cancer screening) Active surveillance for therapy-related adverse outcomes (e.g. quality of life, osteoporosis, infection, malignancy)

Conclusions: Developing a synchronized approach for treatment of glomerular disorders will permit large scale comparative effectiveness studies on observational data. We refer to this as "Open Source Clinical Trial" initiative, where each nephrologist may treat patients per individual decision making while following similar protocols, enabling comparative studies of different treatment strategies. www.glomcon.org



Medication	Dosage protocol (questions to be answered by consensus)	Therapy-specific Surveillance, Prophylaxis, and Disease Monitoring (to be determined by consensus after review of current evidence and best practice recommendations)
Steroids	High-dose, low-dose regimen. Taper regimen	TB screening, baseline HbA1c, baseline bone density. Antibiotic prophylaxis, vitamin D, calcium, bisphosphonate, H2 blocker,
Azathioprine	Monitoring and titration protocol. Taper regiment	TMPT activity and genotype. Baseline and serial LFTs, interval CBC.
Rituximab	Dosage and interval of administration	CBC, HBV, B-Cell population. Vaccine status before and during maintenance phase.
Mycophenolate mofetil, Mycophenolate sodium	Up and down titration regimens. Dose equivalency and therapeutic interchange rules	Pre-treatment pregnancy test; contraceptive use; sun prophylaxis, interval blood and urine studies
Methotrexate	Dosage and maintenance therapy protocol	Interval blood and urine studies
CNI: Cyclosporine and tacrolimus	Default regimen and therapeutic interchange rules	Counsel and monitoring for drug-drug interaction, LFT, BMP, lipid panel and HbA1c monitoring
ACEI/ARB	Contraindications and additional interventions (e.g. potassium binder, diuretics)	Counsel about teratogenicity and ensure contraceptive use. Check BP and BMP 7-14 days post initiation
Cyclophosphamide	Harmonization of dosage, route and time course	Assessment of infertility and malignancy risk. Contraception use, and standardized preinitiation screening (pregnancy, Hep B, Hep C, TB (PPD or IGRA), HPV, cervical cancer screening, prophylaxis for PCP; Standardized follow up, including CBC, LFT, annual urine cytology, and long-term cancer surveillance.
Leflunamide		CBC, CMP, BP, contraception use, counselling against pregnancy, Urine pregnancy test. CBC, CMP, BP monitoring every 4 weeks, Neuropathy testing every 4-8 weeks
Bortezomib	New protocol determination	Contraception use , pregnancy test, Cardiac ECHO, pulmonary function test, peripheral neuropathy (monofilament test)
Hydroxychloroquine	Timing and dose titration	Muscle strength (especially proximal), Annual retinal exam

TH-PO172

Development of Nephrotic Syndrome and Tip-Variant Focal Segmental Glomerulosclerosis during Antiviral Therapy for Hepatitis C Virus Infection Arun Rajasekaran,[1] Edward T. Casey,[2] Mario A. Mendoza.[2] *[1]University of Central Florida College of Medicine, Kissimmee, FL; [2]Nephrology, Orlando VA Medical Center, Orlando, FL.*

Background: Focal segmental glomerulosclerosis (FSGS), associated with focal glomerular damage and podocytopathy, is classically accompanied by proteinuria and high rates of renal progression over time. We describe a patient with Hepatitis C virus (HCV) infection who developed nephrotic syndrome during treatment with direct acting antiviral (DAA) therapies, and a kidney biopsy that demonstrated FSGS-Tip variant.

Methods: A 51-year-old white male with treatment-naïve chronic HCV infection (Genotype-2b) was started on velpatasvir and sofosbuvir. After initiation of DAA therapy, he developed myalgias and lower extremity swelling on day 3, after one month his serum albumin was 1.5 mg/dl (previously 3.9 mg/dl) and at week fourteen a 24-hour-urine collection showed 3469 mg of protein. Evaluation revealed a serum creatinine of 0.8 mg/dl, normal ESR and complement levels. HIV, ANA, ANCA, and cryoglobulins were negative. He was started on lisinopril and atorvastatin. A renal biopsy 5 months after start of DAA treatment showed normal sized glomeruli that exhibited segmental increase in mesangial matrix and cellularity. Half of the glomeruli displayed segmental glomerulosclerosis, with cellular features that projected into the initial segment, and adherent to the origin of the proximal tubule segment, fulfilling criteria for glomerular tip lesions. Immunofluorescence revealed negative staining for IgG, IgM, IgA, C3, C1q, albumin, fibrinogen, and lambda and kappa light chains. Electron microscopy depicted visceral epithelial cells with severe diffuse foot process effacement, with no immune-type electron dense deposits. These findings were consistent with FSGS with glomerular tip lesions. High-dose steroids were initiated, and his proteinuria markedly improved in 3 weeks, with a urine protein-to-creatinine ratio of 0.431. He attained sustained virological response at 12 weeks post DAA therapy.

Results:

Conclusions: FSGS is a disease of podocyte injury that leads to proteinuria. We describe a patient with treatment-naïve HCV infection who developed nephrotic syndrome within days after starting DAA therapy and a kidney biopsy 5 months later revealed tip-variant FSGS. His proteinuria markedly improved after high-dose steroid therapy. Physicians should be aware of this newly emerging renal adverse effect associated with DAA therapy.

TH-PO173

Effects of Rituximab in Adult Patients with Minimal Change Disease Dario Roccatello, Savino Sciascia, Roberta Fenoglio. *Ospedale San GIovanni Bosco, Torino, Italy.*

Background: Minimal change disease (MCD) accounts for 15-20 % of adult nephrotic syndrome cases; adult-MCD patients (pts) may have more severe clinical features than pediatric pts. Therefore, active therapy and remission are very relevant for these patients. In children, rituximab (RTX) has been used since 2006 to treat frequently relapsing NS. In adults, data about the efficacy of RTX for MCD is limited. It is still not clear whether RTX is best used to induce remission or to maintain it, what the optimal dose should be and whether repeated doses improve response rates and prolong remission. We report a monocentric experience on the use of RTX in adult biopsy-proven MCD

Methods: Our series includes 5 adult pts (2 males and 3 females), aged 27-73 yrs treated with RTX (4 weekly doses of RTX 375 mg/m2 or 1 gr two weeks apart). RTX was administrated as a rescue therapy in 2 pts (1 pt with previous long term corticosteroid therapy; 1 pt received corticosteroids and immunosuppressive drugs in infancy). 3 pts with major risk factors precluding corticosteroids or conventional immunosuppression received RTX as a first-line treatment.

Results: Proteinuria decreased from 8.4 (19.5-4.8) g/24 h to 0.03 g/24 h after 6 months; creatinine decreased from 1.44 (0.7-3.2) mg/dl to 0.86 (0.7-1.1) mg/l. 3 pts achieved a complete renal remission, in 1 pt proteinuria decreased by 50%. 1 pt didn't achieved any response at 10 months; a ri-biopsy showed a focal-segmental-glomerulosclerosis. RTX successfully depleted CD19 lymphocytes in 100% of pts for at least 6 months. The follow-up ranged from 3 months to 24 months. No clinically relevant adverse events have been observed.

Conclusions: Our study shows a remarkable efficacy of RTX in treatment of MCD. RTX can be an attractive alternative as induction therapy or to manage recurrent forms of MCD. RTX may be preferentially used in pts at a high risk of development of the adverse effects of corticosteroids and should be considered as an important treatment alternative in patients with recurrent nephrotic syndrome. Randomized controleld trials are needed to confirmed our observations.

TH-PO174

IgA Nephropathy in a Patient with Alcoholic Cirrhosis Itunu O. Owoyemi,[2] Negiin Pourafshar,[1] Julia Iezzoni,[3] Tushar Chopra.[2] *[1]None, Gainesville, FL; [2]University of Virginia, Charlottesville, VA; [3]University of Virginia Health System, Charlottesville, VA.*

Background: Impaired removal of IgA-containing complexes in the liver is thought to predispose to IgA deposition in the kidney. Portal hypertension has been implicated in IgA nephropathy in cirrhotic patients through various mechanisms leading to decreasing hepatic processing of IgA Immune complexes. Despite the frequency of glomerular IgA deposits in advanced liver disease, most adults have no clinical signs of glomerular disease. There is a dearth of literature regarding differentiation of primary and secondary IgA nephropathy (IgAN) in cirrhotic patients.

Methods: We report a 52-year-old male with alcoholic liver cirrhosis complicated by portal hypertension who presented with a recent history of fatigue and skin rash for three weeks. The serum creatinine (SCr) had increased from baseline 2.1mg/dl to 3.2 mg/dl with proteinuria of 6.5 g/g. Measured serum IgA level was elevated at 599.2 mg/dL (68-378 mg/dL). He had a MELD score of 17. Urinalysis was significant for microscopic hematuria. His kidney biopsy revealed a mild increase in mesangial cellularity, lambda mesangial predominance, endocapillary hypercellularity with moderate tubular atrophy and moderate interstitial fibrosis consistent with a diagnosis of IgA nephropathy. Skin rash was in line with psoriasis. The patient was eventually discharged home on conservative management with losartan, and fish oil. On follow-up, his SCr was 3.1mg/dl, and proteinuria decreased to 2 g/g.

Results:

Conclusions: Our case highlights the inherent difficulty in recognition of primary and secondary IgA nephropathy in the setting of liver cirrhosis which would result in difficulty in decision making regarding proper management. We present a case of primary IgAN with diffuse staining of IgA in the glomeruli, and lambda mesangial dominance. In IgAN, lambda is usually, but not invariably, stronger than kappa. Kappa dominance and focal IgA staining not involving all the glomeruli, slightly favors secondary IgAN. Primary IgAN is rarely associated with nephrotic syndrome. Given his multiple co-morbidities, conservative management of IgA nephropathy was implemented. Cirrhotic glomerulonephritis is usually a clinically silent disease; however, the diagnosis can be suspected by finding proteinuria or abnormalities of the urine sediment. The pathogenesis may relate to defective hepatic processing and portocaval shunting of circulating immune complexes.

TH-PO175

A Unique Case of IgA Cryoglobulinemia in the Setting of Staphylococcus aureus Infection Stephen L. Jenkins, Pace Romney, Catreena Marji, Laith Al-Rabadi. *University of Utah Hospital, Salt lake, UT.*

Background: IgA cryoglobulinemia is a rare entity with scarce literature regarding its pathogenesis and management. Herein, we describe a case of IgA cryoglobulinemia in the setting of Staphylococcus aureus infection.

Methods: A 75-year-old Caucasian man presented to the hospital with a two-week history of progressive weakness, lower extremity edema and decreased urine output. He was in acute renal failure with a serum creatinine of 8 mg/dL and serum potassium of 7

mmol/L. Urinalysis upon presentation was strongly positive for protein and blood. Urine microscopy revealed many red blood cells that were normal in shape with no cellular casts. Acute hemodialysis was initiated for hyperkalemia. His history was relevant for a chronic left foot ulcer infected with methicillin-sensitive Staphylococcus aureus (MSSA), for which he was receiving antibiotics. He was found to have a low serum C3 level of 41 mg/dL and a normal C4 at 28 mg/dL. Serum cyroglobulins were detected. Further workup was negative for ANA, ANCA, anti-GBM antibody and hepatitis serologies. Immunofixation serum testing revealed a polyclonal increase in IgA without monoclonal proteins. Biopsy of the kidney was performed and revealed glomeruli with diffuse endocapillary proliferation, frequent luminal neutrophils, few weakly PAS-positive hyaline thrombi, and more than 50% cellular crescents. Immunofluorescence showed capillary wall deposits in a mesangial and intraluminal distribution that were predominantly positive for C3 and, less intensely, for IgA and light chains. Electron microscopy revealed several mesangial, subendothelial and intraluminal deposits. The frequent intraluminal deposits suggested possible cryoglobulinemic glomerulonephritis, which can rarely be IgA-related. The patient did not receive steroids given his ongoing infection. He continued to require intermittent hemodialysis.

Results:

Conclusions: The presence of frequent glomerular neutrophils and C3 staining of higher intensity than IgA should raise concern for infection-related glomerulonephritis. Intraluminal deposits forming hyaline pseudo-thrombi and prominent hypercellularity should lead to consideration for cryoglobulinemic glomerulonephritis. There are no current recommendations for treating infection-related IgA cryoglobulinemia. Management should focus on supportive care while treating the primary infectious process.

TH-PO176

Atypical Hemolytic Uremic Syndrome Associated with Complement Factor H Mutation: First Case Report on a Patient with IgA Nephropathy Yukiya Iimura, Hironori Nakamura, Anayama Mariko, Yasushi Makino, Masaki Nagasawa. *Nephrology, Shinonoi General Hospital, Nagano, Japan.*

Background: Several types of glomerulopathy, including focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, C3 glomerulonephritis, and Henoch–Schönlein purpura, can be complicated by atypical hemolytic uremic syndrome (aHUS). Although immunoglobulin (Ig) A nephropathy (IgAN) has been associated with HUS or thrombotic microangiopathy, no report on its association with aHUS has been published. A recent study has found that rare variants of complement factor H (*CFH*)-related protein 5 may contribute to the genetic susceptibility to IgAN.

Methods: Here we present the first case of a 76-year-old man with IgAN who developed aHUS and was confirmed of harboring a *CFH* gene mutation.

Results: This patient was admitted with thrombotic microangiopathy findings. On admission, he was afebrile without diarrhea. His blood pressure was 178/109 mmHg. Blood analysis data demonstrated platelets counts of $1.1 \times 10^4/\mu L$; hemoglobin level, 9.6 g/dL; lactate dehydrogenase level, 3270 IU/L; and creatinine level, 4.2 mg/dL. Schistocytes were detected on blood smears. The patient was suspected of having thrombotic thrombocytopenic purpura or aHUS and was treated with plasma exchange, hemodialysis, and methylprednisolone. The level of a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, was not decreased. The patient was definitively diagnosed with aHUS, and subsequently, plasma exchange and hemodialysis were discontinued. Eculizumab (900 mg/week) was initiated on day 18. Light microscopy findings were consistent with those of HUS, and an immunofluorescence analysis revealed IgA and C3 in the mesangial area. A hemolytic assay using sheep red blood cells revealed increased hemolytic activity. A genetic analysis revealed a p.Arg1215Gln mutation in *CFH*. Eculizumab therapy was effective for 5 months. The serum creatinine level was approximately 2 mg/dL without hemodialysis, and the hemoglobin level was 9 g/dL without proteinuria or hematuria.

Conclusions: We report the first case of a patient with IgAN who developed aHUS and was confirmed of harboring a *CFH* gene mutation. Both IgAN and aHUS activate the alternate pathway. Accordingly, this chronic trigger, namely IgAN, might have facilitated aHUS development in our genetically predisposed patient.

TH-PO177

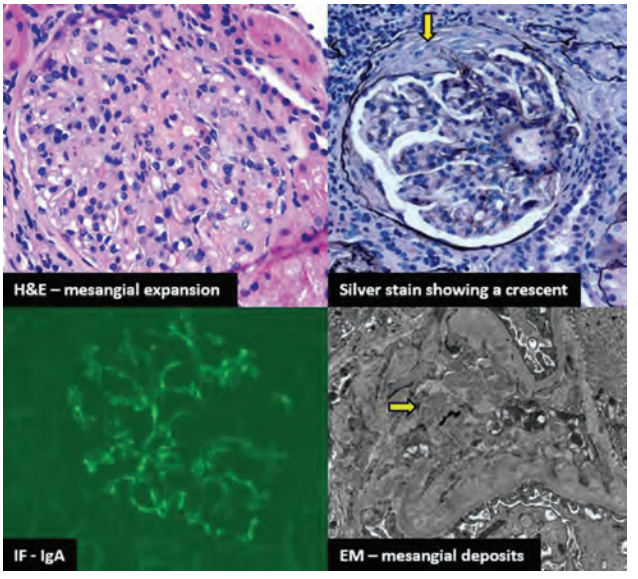
Does Your Differential for Glomerulonephritis in African Americans Include IgA Nephropathy? Abhilash Koratala,[2] Don H. Esprit,[1] William L. Clapp,[1] Jogiraju V. Tantravahi.[1,3] *[1]University of Florida, Gainesville, FL; [2]University of Florida, Gainesville, FL; [3]North Florida/South Georgia Veterans Health System, Gainesville, FL.*

Background: Despite being the commonest primary glomerulonephritis in the world, IgA Nephropathy (IgAN) is rarely reported among African Americans (AAs), who otherwise have high renal disease burden. As nephrologists, we have been taught that IgAN should be considered as the last differential for GN in AA patients unless they have HIV. This assumption is based on the 'reported' rarity of this disease in AAs and the fact that AAs make up more than 50% of the new cases of HIV infection in the US. However, IgAN is being increasingly recognized in the non-HIV AA population. Factors such as level of disease awareness, access to appropriate diagnostic facilities and referral patterns may play a role in the underdiagnosis of IgAN in AAs. Moreover, there are reports suggesting that these patients may have more severe disease at presentation.

Methods: A 48-year-old woman was seen for IgAN. Her baseline serum creatinine (Scr) of 1.2 mg/dL. She was evaluated at an outside facility 3 months ago, when the Scr was 1.4 mg/dL with a UPCR of 1.7 g/g and 60/hpf RBCs in the urine. A month later, her Scr increased to 1.7mg/dL, which prompted a renal biopsy. It was suggestive of crescentic IgAN but the sample was inadequate. ANA, ANCA, HIV and hepatitis serologies were negative and complements normal. In our clinic, BP was 110/78mmHg, Scr 1.35 mg/dL and PCR ~1g/g. We elected to rebiopsy her to confirm the diagnosis of crescentic IgAN in an AA patient and possible treatment with an alkylating agent. It was surprisingly consistent with IgAN [Fig.1]. As there were fibrocellular crescents in only 2 of 11 glomeruli and the Scr remained stable, we chose to manage her conservatively.

Results:

Conclusions: Our case serves as a reminder that IgA nephropathy does occur in AAs and needs to be considered in the differentials when they present with nephritic picture.



TH-PO178

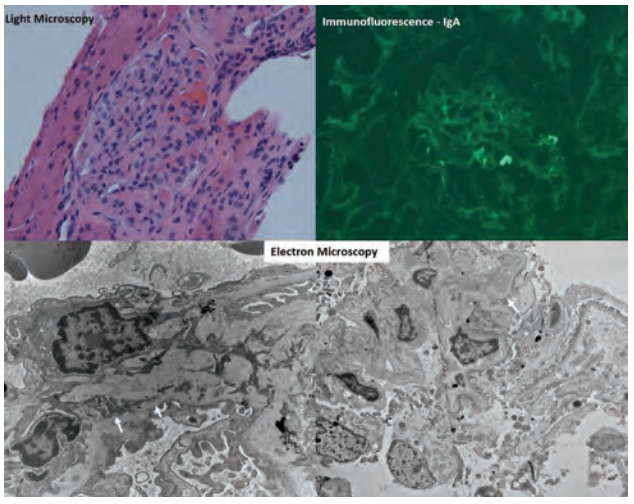
ANCA-Positive IgA Nephropathy: A Benign Coincidence or a Ticking Bomb? Abhilash Koratala, Xu Zeng, Amir Kazory. *University of Florida, Gainesville, FL.*

Background: There have been a few reports of patients with IgA nephropathy (IgAN) who presented with circulating antineutrophil cytoplasmic autoantibodies (ANCAs). It remains unclear whether the presence of these antibodies reflects a mere incidental finding or a novel overlap entity with possibly untoward impact on the outcomes.

Methods: A 29-year-old woman referred for microscopic hematuria (MH) in the setting of positive ANCAs. She was first noted to have MH 2 years ago followed by mild hemoptysis and infiltrates on chest CT a few months later, which prompted a comprehensive autoimmune work up. Interestingly, both C-ANCA and P-ANCA were positive with anti-MPO and negative anti-PR3. Moreover, ANA and anti-dsDNA antibodies were found positive. Bronchoscopy ruled out diffuse alveolar hemorrhage. Serum creatinine was normal at 0.8 mg/dL, and urine studies revealed MH and mild proteinuria of 350 mg/g of creatinine. Renal biopsy was consistent with IgAN with mesangial expansion and electron dense mesangial deposits without cellular crescents or segmental necrosis [figure]. In the absence of histologic findings compatible with pauci-immune glomerulonephritis, the decision was made not to use immunosuppression and to follow expectantly.

Results:

Conclusions: There have been a few previous reports of ANCA positivity in the setting of IgAN; most cases presented with nephritic sediment, histologic picture of crescentic glomerulonephritis, and rapidly worsening renal function. ANCA-positive IgAN without these features is extremely rare. As the timeline of appearance of ANCAs need not correlate with that of crescentic IgAN, we opine that such patients should be closely monitored and a repeat biopsy be considered if there is any change in their renal manifestations.



TH-PO179

A Case of RPGN with Dual Positive Anti-GBM and PR3-ANCA Antibodies Nawsheen Chowdhury,[2] Shayan Shirazian,[1] Nobuyuki (Bill) Miyawaki,[1] James Drakakis.[1] *[1]Winthrop University Hospital, Mineola, NY; [2]Winthrop university hospital, Mineola, NY.*

Background: Anti-GBM disease and ANCA associated vasculitis are the major differentials for patients presenting with RPGN and pulmonary involvement. We report a case of unusual double positivity of both anti-GBM and PR3-ANCA antibodies, as most of the patients with both ANCA and anti-GBM antibodies are MPO-ANCA positive.

Methods: A 47-year-old female presented to the hospital with fatigue, malaise, and hemoptysis. Imaging of the chest revealed patchy consolidations and cavitary lesions. Initial creatinine was 1.1 mg/dL, but during the hospital course she developed rapidly progressive renal failure (peak creatinine of 2.6 mg/dL) in the setting of proteinuria and microscopic hematuria. An anti-GBM antibody titer was 135 units/mL and anti-proteinase 3 (PR3) antibody titers were > 100 units. Anti-myeloperoxidase (MPO) antibody titers were negative. Therapy was initiated with pulse steroids and plasmapharesis. Renal biopsy (done after having already received significant immunosuppression) revealed a focal crescentic glomerulonephritis with cellular crescents involving 29% of glomeruli. The patient received a dose of IV Cyclophosphamide and continued on tapering doses of prednisone. She was discharged with a creatinine of 1.5 mg/dL and negative PR3-ANCA and anti-GBM antibody titers. She completed 4 months of oral Cyclophosphamide and currently has a creatinine of 0.7 mg/dL on Azathioprine.

Results:

Conclusions: About 30% of patients with anti-GBM disease will have concurrent ANCA seropositivity, most of which are MPO-ANCA associated (74%). Our patient belonged to a smaller subset of patients with anti-GBM and PR3-ANCA antibodies. The reason for the emergence of dual antibody production is not known, however there have been some pathophysiological hypotheses for how MPO-ANCA may injure the glomerular basement membrane, expose antigens and lead to the development of an anti-GBM antibody. Most of the literature on patient and renal survival in dual positivity involves anti-GBM and MPO-ANCA antibodies. It is not clear that these descriptions of mechanism and outcome also apply to an overlap with PR-3-ANCA and more literature is required to help elucidate the potential clinical implications.

TH-PO180

Dual-Positive Anti-Myeloperoxidase and Anti-Glomerular Basement Membrane Antibody Vasculitis Muhammad Afzal, Krishna M. Baradhi. *OU Tulsa, Tulsa, OK.*

Background: Vasculitis secondary to the combination of anti-glomerular basement membrane (GBM) antibody and antineutrophil cytoplasmic antibodies (ANCA) is not common occuring up to 14% in patients with primary ANCA vasculitis and in up to 38% of patients with primary anti-GBM disease and moreover ANCA is usually directed against myeloperoxidase (MPO). Histologically, both are characterised by crescentic necrotizing glomerulonephritis. Immunofluorescence in anti-GBM disease reveals linear IgG staining, while ANCA vasculitis is pauci-immune.

Methods: 69 yr-old-male presented with abdominal pain & diarrhea and found to have acute oliguric renal failure. Labs showed BUN of 80 mg/dl and creatinine 8.34 mg/dl with associated hematuria and proteinuria. Serology revealed elevated MPO-ANCA (116.9 AU/ml) as well as anti-GBM antibodies (101 U). Renal biopsy showed diffuse necrotizing and crescentic glomerulonephritis with 1+ linear Ig G staining. Patient was started on plasmapheresis concurrently with hemodialysis and immunosuppressive therapy (cyclophosphamide and pulse steroids). Plasmapheresis was continued until Anti-GBM titers were < 20 U. Unfortunately his renal function did not recover and was discharged on tapering steroids, while continuing hemodialysis.

Results:

Conclusions: This is a unique case of rapidly progressive nephritis due to dual MPO-ANCA antibodies and anti-GBM antibodies (DAV). Clinical presentation of DAV may vary from isolated ANCA related vasculitis and mortality usually tends to be higher. Renal survival in dual-positive patients is not better than that in anti-GBM-positive patients and is inferior compared to patients with MPO-ANCA only. Relapse with Dual-antibody vasculitis is higher than in anti-GBM disease, hence clinical vigilance is necessary to detect relapse. Treatment of DAV is similar to anti-GBM disease with plasmapheresis, cyclophosphamide, and steroids. Patients with either ANCA-related disease or anti-GBM disease, whether diagnosed serologically or histologically, should be tested for the second antibody. This dual serological approach provides better prognostication and dictates appropriate management, as goal is to limit further immunosupression in dialysis dependent patients.

TH-PO181

ANCA Associated Vasculitis in Scleroderma: A Renal Perspective Sam Kant,[2] Duvuru Geetha.[1] *[1]John Hopkins Bayview Medical Center, Baltimore, MD; [2]University of Maryland, Baltimore, MD.*

Background: Overlap syndrome of ANCA associated vasculitis (AAV) and scleroderma (SS) is rare with conflicting data on renal outcomes. We describe the clinical characteristics and treatment outcome of ANCA glomerulonephriitis(GN) in SS patients followed at a single center

Methods: We conducted a retrospective study of 3840 patients in our SS database to identify SS patients who subsequently developed AAV with renal involvement. Patient demographics, serology, renal function with renal histology and treatment outcomes were assessed.

Results: Of the 3840 patients, we identified 5 patients who had ANCA GN. The median age at SS diagnosis was 52 years, all 5 patients were female and 4 had diffuse scleroderma. ANA was positive in all, with 3 of them having anti Scl 70 antibodies. Four patients had interstitial lung disease and gastrointestinal dysmotility as a part of the constellation of clinical characteristics of SS. Median time of onset of AAV from time of diagnosis of SS was 12 years and all of 5 patients were MPO positive. All patients had acute kidney injury, with biopsy proven crescentic glomerulonephritis and none requiring dialysis. One patient had sinus involvement while AAV was renal limited in the remaining 4 patients. Two patients were treated with cyclophosphamide(CYC) and steroids(GC) and three were treated with rituximab (RTX) and steroids. All patients achieved disease remission. The median follow up was 24 months, The mean GFR at diagnosis was 39 ml/min and at last follow up was 38 ml/min. Of the 5 patients, 2 did not receive maintenance immunosuppression and both experienced vasculitis relapse. None of the patients reached ESRD. Three patients died and of these 2 experienced relapse with fulminant alveolar hemorrhage

Conclusions: ANCA GN in SS is rare with disease manifestation and course similar to AAV. This case series demonstrates that disease remission can be achieved with standard induction therapy. However vasculitis relapse is common and associated with high mortality without remission maintenance therapy

Patient Characteristics

Patient	Induction Rx	Maintenance Rx	Vasculitis Relapse	ESRD	Death
1	GC + RTX	AZA	No	No	No
2	GC + CYC	MMF	No	No	Yes
3	GC + RTX	None	Yes (GN + DAH)	No	Yes
4	GC + CYC	None	Yes (DAH)	No	Yes
5	GC + RTX	AZA	No	No	No

AZA- Azathioprine; MMF- Mycophenolate mofetil; DAH- Diffuse alveolar hemorrhage

TH-PO182

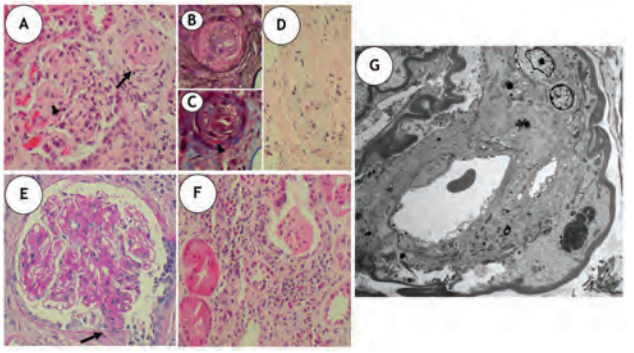
Renal Biopsy Teaching Case: A Patient with Scleroderma, Hypertension, AKI, and PR3 ANCA Positivity Sam Kant,[2] A Z. Rosenberg,[1] Duvuru Geetha.[1] *[1]Johns Hopkins University Hospital, Baltimore, MD; [2]University of Maryland Medical Center, Baltimore, MD.*

Background: A 65 year old African-American male, with a history of limited scleroderma for 16 years complicated by severe gastrointestinal dysmotility and interstitial lung disease, presented to the clinic with elevated blood pressure of 190/100 mm Hg, on a background of previously well controlled blood pressure. He was found to have an acute kidney injury with a serum creatinine of 2.5 mg/dL, compared to his baseline of 1.3 mg/dL. Urine studies demonstrated microscopic hematuria, with 3.4 grams of proteinuria. His hemoglobin was 7.4 and he had no evidence of hemolysis and platelet count was normal. Serologies revealed a positive c-ANCA serology with PR3 positivity at 97.4 IU/mL with negative ANA, ds-DNA, Scl-70, anti-smith, anti-Ro, Anti-La, and RNP. A renal biopsy was performed which demonstrated arteriolar microangiopathy with fibrinoid necrosis and concentric lamellation with no evidence of ANCA GN (Fig1). He was treated with ACE inhibitor with improvement of his BP and improved serum creatinine of 1.7 mg/dl.

Methods:

Results:

Conclusions: This case of late onset scleroderma renal crisis highlights that atypical presentations of scleroderma renal crisis can exist and ANCA positivity can be misleading in such situations. Therefore, clinical decisions for further management should be predicated on expedient renal biopsy.



A) Glomerulus (HE) and glomerular arteriole with entrapped RBCs (arrow) with vessel wall and surrounding interstitial edema and a consolidated ischemic glomerular appearance with potential entrapped RBCs (arrowhead).

B and C) Glomerular arteriole (b, silver stain) shows lamination of the vessel wall and fibrinoid material entrapped within the vessel wall (Masson's trichrome).

D) Small artery with subintimal mucoid change (HE)

E) Glomerulus (PAS) with synechial adhesion and associated glomerular solidification

F) Foci of interstitial inflammation including eosinophils (HE)

G) Ultrastructural evidence of microvascular injury including subendothelal widening with prominent cellular interposition.

TH-PO183

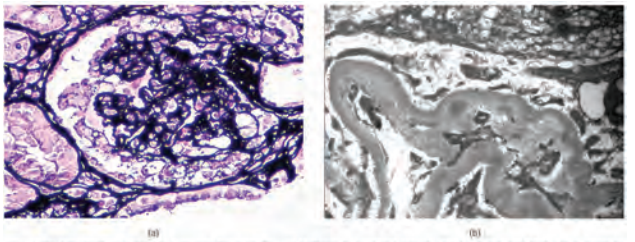
A Case of Collapsing FSGS Presenting with ANCA Positive Pulmonary Renal Syndrome George C. Bonifant, Steven D. Smith, Karim El Hachem, Mubasshar Rehman. *Icahn School of Medicine at Mount Sinai/St Luke's-Roosevelt Hospital Center, New York, NY.*

Background: Most cases of HIV-negative collapsing FSGS are idiopathic. However, a growing list of disorders, including mixed connective tissue diseases such as Sjogrens syndrome and SLE, are being reported to cause this lesion

Methods: A 22 y/o female with Sjogren's syndrome and pericarditis presented with dyspnea and cough. She complained of chronic nasal congestion, anosmia, pleurisy, dry mouth and Raynauds. There were basilar rales, facial acne, pale conjunctiva but no edema or arthritis on exam. Serum creatinine was 1.47 mg/dl (0.6 six months prior). Chest x-ray showed bibasilar airspace consolidations. She developed hemoptysis and respiratory failure requiring intubation. Bronchoscopy showed blood throughout the tracheobronchial tree thought due to diffuse alveolar hemorrhage. Urine protein creatinine ratio was 6.8g/g with an active urine sediment: dysmorphic RBCs and RBC casts. Negative serologies: HIV, parvo B virus, dsDNA, anti-GBM, anti-PR3, C3, C4. Positive serologies: anti SSA/SSB, anti-MPO. She received pulse steroids, cytoxan and plasmapheresis for presumed ANCA vasculitis. Creatinine peaked at 3.6 and improved to 2.0mg/dl with treatment. Renal biopsy showed focal and segmental glomerulosclerosis with collapsing features. Electron microscopy showed podocyte foot process effacement and no immune-type electron dense deposits or tubuloreticular inclusions. Outpatient treatment continues with oral prednisone

Results:

Conclusions: The patient presented as pulmonary renal syndrome and an active urine sediment with high titer anti-MPO Ab. Suspicion was high for ANCA vasculitis with expected pauci-immune crescentic GN on biopsy. Instead, collapsing glomerulopathy was diagnosed. Collapsing lesions can resemble crescents (pseudocrescents) and our case was reviewed by several renal pathologists to confirm the diagnosis. This challenges the notion that biopsy isn't necessary when pretest probability for pauci-immune glomerulonephritis is high. We propose that this patient's collapsing glomerulopathy is due to her collagen vascular disease (Sjogren's) and is analogous to lupus podocytopathy



Renal biopsy highlighting key features of Glomerular Podocytopathy. (a) Methenamine silver stain showing Focal Segmental and Diffuse Global sclerosing glomerulopathy with collapsing features. (magnification x200). (b) Electromicroscopy showing widespread attenuation and wrinkling of Basement Membranes with detachment of Podocyte foot processes. (magnification x1500).

TH-PO184

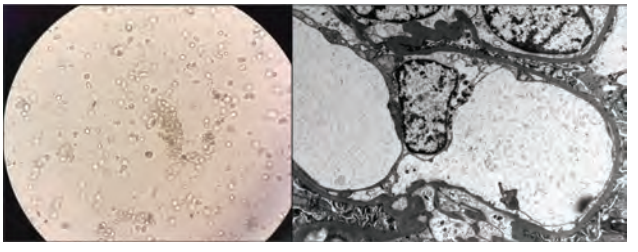
A Sheep in Wolf's Clothing: Hematuria in GPA Stefan C. Hemmings,[3] Duvuru Geetha,[1] Paul E. Segal,[2] Stephen M. Sozio.[3] *[1]John Hopkins Bayview Medical Center, Baltimore, MD; [2]Johns Hopkins Bayview Medical Center, Baltimore, MD; [3]Johns Hopkins University School of Medicine, Baltimore, MD.*

Background: Performing a renal biopsy in a patient with RBC casts, rising serum creatinine (sCr) and positive ANCA serology is justifiable to evaluate for crescentic glomerulonephritis and determine best management strategies. Nonrenal involvement has a better prognosis in patients with ANCA-vasculitis. Finding underlying unrelated benign pathology in such instances can make future clinical decision-making challenging.

Methods: A 51 year-old man visited the rheumatology clinic in May 2017 for ongoing unexplained multisystem symptoms. He had been in good health until 10 months earlier when he started having recurrent bouts of sinusitis, cough, fatigue, otitis media leading to deafness and a 40lbs weight loss. Serology for cANCA was positive [1:40 titer; PR3: 87], this was negative earlier in his clinical course. He was noted to have microscopic hematuria and was seen in nephrology clinic within 24 hours for evaluation. His sCr notably had risen from 0.7 to 1.0 mg/dL over a 5 month-period, he had normal serum complements, and his random urine protein to creatinine ratio was 280 mg/g. Urine microscopy revealed RBC casts (Figure-left). An urgent renal biopsy was performed and pulse IV steroids initiated for presumed renal involvement of granulomatosis with polyangiitis (GPA). On biopsy, the 19 glomeruli sampled were histologically normal on light microscopy and immunofluorescence was unremarkable. Electron microscopy revealed thin basement membranes of width 218nm (Figure-right). Alport's immunostaining was negative.

Results:

Conclusions: Thin Basement Membrane Nephropathy (TBMN) likely explained his microscopic hematuria and RBC casts. This diagnosis portends a good clinical renal prognosis. However, finding benign pathology, including TBMN, does pose challenges in diagnosing a GPA relapse clinically as the hematuria and RBC casts can be intermittent and from the benign condition. Nevertheless, this case highlights the utility of performing renal biopsy even when there is a high index suspicion of renal involvement from ANCA-associated vasculitis.



RBC cast on microscopy (Right) and Electron Microscopy with TBMN (Left).

TH-PO185

Henoch-Schönlein Purpura Nephritis: Not Only a Childhood Disease Krystahl Z. Andujar,[1] Ileana E. Ocasio Melendez,[1] Nicolle M. Canales-Ramos,[2] Sharlene Medina aviles,[2] Fatima B. Cintron-Rosa,[1] Naomi Collazo Gutierrez,[2] Luis F. Alvarez,[4] Phillip Ruiz.[3] *[1]Nephrology, University of Puerto Rico, Medical Sciences Campus, San Juan, PR; [2]Internal Medicine, University of Puerto Rico, Medical Sciences Campus, San Juan, PR; [3]University Of Miami, Miami, FL; [4]Internal Medicine, VA Caribbean Healthcare System, San Juan, PR.*

Background: Henoch-Schönlein Purpura Nephritis (HSPN) is often regarded as a childhood disease. As adults are at more risk for developing chronic kidney disease (CKD) if treatment is delayed, it is vital for clinicians to be aware of this rare disease.

Methods: A 51-year-old Puerto Rican man without medical history presented with abdominal pain associated with bloody stools, a rash on lower extremities and arthralgias. Palpable purpura was visible on legs, back and buttocks. Vital signs were normal. Laboratories were remarkable for a creatinine of 2 mg/dl. Urine protein:creatinine ratio revealed proteinuria of 1,988 mg/g. Urine microscopy showed dysmorphic red blood cells. Abdomino-pelvic computer tomography scan was diagnostic of colitis. Skin lesions biopsied demonstrated leukocytoclastic vasculitis. A renal biopsy was performed revealing increased mesangial cellularity on light microscopy and mesangial staining with IgA on immunofluorescence. In the presence of palpable purpura, arthralgias, colitis, proteinuria and renal biopsy evidence of IgA deposition, he was diagnosed with HSPN. After a three-day course of intravenous methylprednisolone, he was started on oral prednisone and azathioprine. Two weeks later, creatinine returned to baseline of 1 mg/dL, proteinuria improved and skin lesions and abdominal complaints resolved. He was started on losartan and a decision for immunosuppression weaning was reached.

Results:

Conclusions: HSPN is most prevalent in the first decade of life, making our adult case unusual. Renal involvement in adults with HSPN is worse than in children and up to forty percent of patients can progress to CKD. A challenge the clinician must face is balancing the cost of immunosuppressive treatment versus the actual risk of developing CKD. Also, the difficult decision of choosing which immunosuppressive agent is most beneficial for the patient. A clinical trial by Bergstein *et al* suggest that corticosteroid and azathioprine therapy is beneficial in treating HSPN. In our case, treatment with this

immunosuppressive therapy proved to be effective in eliminating abdominal complaints, decreasing proteinuria and improving renal function. Nonetheless, more evidence-based recommendations are needed to pinpoint which immunosuppressive agent is the choice of therapy for HSPN.

TH-PO186

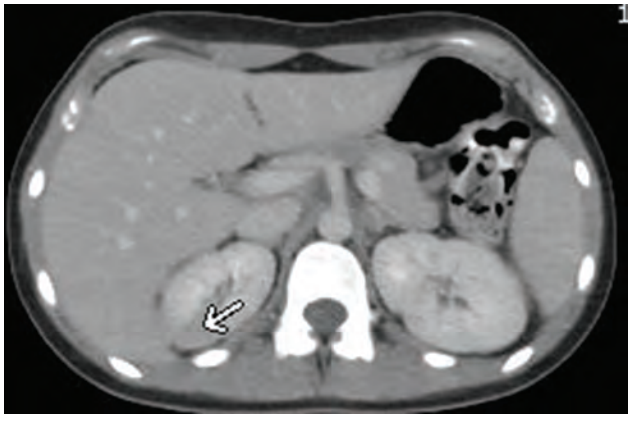
Unusual Cause of Visceral Infarcts Amar Pandit,[2] Aditya S. Pawaskar,[2] Randy A. Goldberg.[1] [1]*New York Medical College, Valhalla, NY;* [2]*Westchester Medical Center, White Plains, NY.*

Background: Thrombosis is an increasingly recognized feature of ANCA vasculitis

Methods: An 18 year old lady with history of celiac disease presented with high grade fevers, 10 lb. weight loss, nausea and epigastric tenderness. Physical exam was negative for lymphadenopathy, murmur, adventitious lung sounds, hepatosplenomegaly, joint swelling/tenderness or rash. Labs revealed anemia, elevated ESR and CRP and normal white count, renal and liver function tests. Infectious vs. inflammatory processes were considered and she was started on antibiotics. CT abdomen revealed renal and splenic infarcts. Infective endocarditis was ruled out by negative blood cultures and a normal echocardiogram, following which antibiotics were stopped. Urinalysis showed microscopic hematuria and 2+ proteinuria (Urine protein/creatinine ratio of 961), consistent with nephritic syndrome, likely due to collagen vascular disease vs. thrombotic disease. ANA and anti-PR3 were positive, and dsDNA, anti-Sm, anti-RNP, C3, C4, cryoglobulins, anti-GBM, anti-SS-A and anti-SS-B were negative. Hypercoagulable workup revealed decreased Protein S activity and negative anti-phospholipid antibodies. CT chest revealed a hemorrhagic infarct, but no nodules. Renal biopsy confirmed the presence of pauci-immune necrotizing crescentic glomerulonephritis, indicating GPA. She was started on IV methylprednisolone, rituximab and rivaroxaban with resolution of her symptoms.

Results:

Conclusions: Venous (DVT, PE) and arterial thrombosis are being increasingly recognized in GPA, although arterial involvement has predominantly been described in the coronaries. This predisposition to thrombosis is multifactorial: 1) Activation of neutrophils by antibodies and the interaction of activated neutrophils with the endothelium. There is also release of tissue factor which activates thrombosis. 2) Elevated thrombomodulin levels activate thrombosis and inhibition of conversion of plasminogen to plasmin inhibits fibrinolysis. There are no recommendations on use of anti-platelets or anti-coagulants at present.



TH-PO187

Be Brash: Name That Rash Amir Kazerouninia, Azka Afzal, Natasha N. Dave, Rajeev Raghavan. *Baylor College of Medicine, Houston, TX.*

Background: Granulomatosis with polyangiitis (GPA), is a relatively rare, potentially fatal anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. It is characterized by necrotizing granulomatous inflammation and vasculitis, affecting predominantly small to medium vessels. Here, an uncommon manifestation of vasculitis—livedo racemosa—was not addressed and the patient suffered a stroke.

Methods: A 60-year-old woman with hypothyroidism presented to her PCP for rash, progressive weakness, stocking/glove numbness, and intermittent fevers. The rash was not described or addressed, but EMG was ordered. Within a week, she presented to the ED for the same complaints. She was febrile and studies were notable for leukocytosis, 1+ blood on urinalysis, anemia, and hypoalbuminemia. General medicine diagnosed polyneuropathy, began gabapentin, and discharged her from the ED. Shortly thereafter, she re-presented to the ED with a left fronto-temporal hemorrhagic stroke. Renal was consulted for AKI and noticed a purplish, lace-like, mottled, reticulated rash on both legs, suggestive of livedo reticularis, but with irregularities within the thickness of the reticulations, more consistent with livedo racemosa. Family noted the rash had been present for several months. Her urine had RBC casts, serum was positive for MPO-ANCA, and kidney biopsy showed interstitial granulomas and focal partial artery necrosis, all evidencing GPA. Given hemorrhagic stroke at an uncommon site, brain angiography was performed showing subtle luminal irregularities in the bilateral small cerebral vessels consistent with CNS vasculitis. Chest CT and EMG were consistent with pulmonary and PNS GPA, respectively. She was given pulse dose steroids and started weekly rituximab infusions. The patient's kidney function improved somewhat, but dysarthria continues, with only about 60% of her speech understandable by family members.

Results:

Conclusions: Livedo racemosa is always due to a secondary disorder and warrants further evaluation. Multiple clinicians missed the importance of her rash; any livedo-like rash in the setting of active urinary sediment, nondiabetic polyneuropathy, intermittent fevers, leukocytosis, anemia, and hypoalbuminemia should be biopsied allowing for early diagnosis of systemic illnesses such as vasculitis. If identified early, GPA remission is possible with immunosuppressive therapy, and may have prevented this patient's hemorrhagic stroke.

TH-PO188

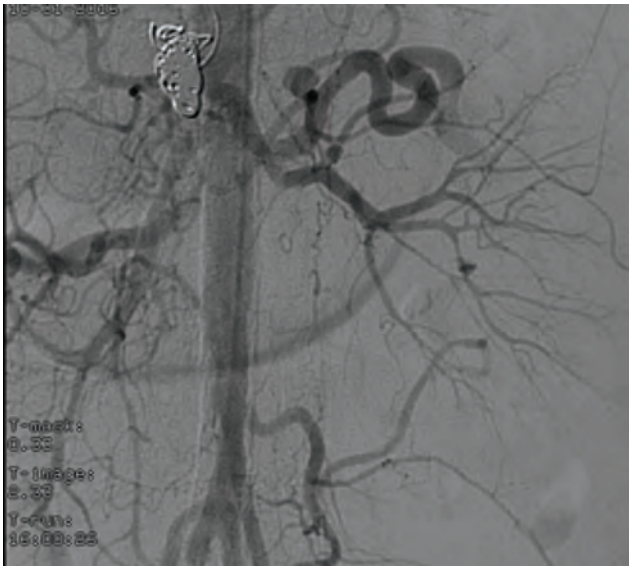
From a Complicated Biopsy to an Unexpected Diagnosis Haris F. Murad,[1] Randy L. Luciano.[2] [1]*Yale School of Medicine, New Haven, CT;* [2]*Yale University School of Medicine, New Haven, CT.*

Background: Polyarteritis Nodosa (PAN) is a rare systemic necrotizing vasculitis targeting medium sized arteries and can involve any organ in the body except for the lungs. Arterial inflammation causes tissue ischemia and hemorrhage and may present with a wide spectrum of clinical manifestations ranging from neuropathies and rashes to renal failure and bowel ischemia. Renal failure is thought to be secondary to ischemia from rupture of microaneurysms. Diagnosis requires an integration of clinical, radiographic and pathological findings, but the presence of medium vessel microaneurysms can suffice in the absence of tissue confirmation. We present a case in which the diagnosis was made in unusual circumstances.

Methods: A 46 year old lady with non-cirrhotic hepatoportal sclerosis presents with a gradually uptrending creatinine over two years reaching 4.1mg/dL, worsening proteinuria up to 5.6gm/day and a urine sediment showing granular casts. Renal ultrasound showed bilateral echogenic kidneys and elevated velocities in renal arteries and the aorta. She underwent a renal biopsy which was challenging and on the second pass she had severe abdominal pain. A color doppler demonstrated a pulsatile jet originating from the lower renal pole. She immediately passed a large amount of blood from her urethra. An emergent angiography showed several aneurysms in the liver, kidney and spleen (see figure) along with two pseudoaneurysms, consistent with a diagnosis of PAN. Unfortunately the biopsy sample was insufficient for interpretation. Subsequent labs showed elevated inflammatory markers, negative rheumatoid factor, cryoglobulins, hepatitis B and C titers.

Results:

Conclusions: This case demonstrates that a complication from a kidney biopsy was able to provide an important, and previously unthought of diagnosis in a patient. In addition it highlights the safety concerns of patients with vasculitis undergoing biopsy.



TH-PO189

Bartonella Endocarditis Mimicking ANCA-Associated Glomerulonephritis (GN) Joseph Vercellone, Lisa J. Cohen, Saima Mansuri, Ping L. Zhang, Paul S. Kellerman. *Oakland University/William Beaumont School of Medicine, Royal Oak, MI.*

Background: *Bartonella henselae* is a fastidious organism causing cat scratch disease, commonly associated with fever and lymphadenopathy. Rarely, *B. henselae* results in culture-negative endocarditis (IE). Herein, we describe a case of *B. henselae* IE mimicking ANCA-associated GN.

Methods: A 47-year-old male presented with 2 weeks of flank pain and four days of cola-colored urine. Exam revealed a soft murmur over the left-sternal border and severe CVA tenderness, with no fever. Labs showed a Hgb of 7.7 mg/dL, a creatinine of 2.36 mg/dL (up from 0.89 mg/dL), and UA showed 3+ blood, 1+ protein, 51-100 RBC/HPF,

0-5 WBC/HPF, and RBC casts. Kidneys were normal on ultrasound, but MRI noted wedge-shaped splenic infarcts. Pending serologic studies and biopsy, the patient was initially pulsed with steroids with no further immunosuppression. Serologies revealed normal C_3, C_4, ASO, ANA, anticardiolipins, IgA, and hepatitis panel. ANCA and anti-MPO were negative, but anti-PR3, CRP and ESR were markedly elevated. On biopsy, light microscopy showed focal proliferative injury with two non-necrotic crescents. Immunoflourescence was positive for IgM, IgA, C_3, and C1q. Electron microscopy showed subtle mesangial and subendothelial deposits without "humps". With possible immune complexes on kidney biopsy and a murmur, TEE was performed showing a bicuspid aortic valve with vegetation. A diagnosis of culture-negative endocarditis was made, doxycycline and rifampin were started, and valve replacement performed, with pathology identifying *B. henselae*. On antibiotics, the patient's symptoms resolved and creatinine decreased to 1.4 mg/dL with normalization of ESR and CRP over two months.

Results:

Conclusions: Culture-negativity comprises 3-48% of all endocarditis cases. This case highlights how *Bartonella* IE can present with crescentic GN and falsely elevated anti-PR3 antibodies mimicking ANCA-associated GN. Literature review revealed approximately 50 cases of *Bartonella*-induced IE with GN with ANCA and PR-3 positivity. Unique to our case was a negative ANCA with very high anti-PR3 antibody titer. Because of culture negative IE and false vasculitis titers, *Bartonella* can mimic ANCA-associated GN, thus kidney biopsy showing immune complex deposition is critical to diagnosis and appropriate therapy.

TH-PO190

An Unexpected Finding of Post Infectious Glomerulonephritis Superimposed on Cryoglobulin Mediated Membranoproliferative Glomerulonephritis in a Patient with Influenza

Sara Syeda, Jie Tang. *Div of Kidney Diseases and Hypertension, Brown University, Providence, RI.*

Background: Active glomerulonephritis with hypocomplementemia has a limited differential. Here we present an interesting case of acute kidney injury (AKI) with influenza, in which kidney biopsy showed cryoglobulinemic membranoproliferative glomerulonephritis (MPGN) and evidence of post-infectious glomerulonephritis (PIGN).

Methods: A 62-year-old man with history of clinically inactive low-grade B cell lymphoma (LGBL), presented with cough, myalgias, and tested positive for Influenza A. He was found to have AKI with a serum creatinine of 11.9mg/dL (baseline 1.1mg/dL), sub-nephrotic proteinuria and microscopic hematuria. Serologic studies showed low complements (C3, C4) and a weak monoclonal IgG lambda light chain on serum electrophoresis. All other infectious and rheumatologic work up were negative. Kidney biopsy revealed pattern of MPGN, with prominent sub-endothelial deposits and intra-capillary hyaline pseudo thrombi, staining predominantly for IgG and lambda light chain on immunofluorescence. By electron microscopy, he also had many sub-epithelial "humps" along with sub-endothelial and mesangial deposits. This was consistent with type 1 cryoglobulinemic glomerulonephritis with superimposed PIGN. In the interim, he was started on a course of steroids and over the next 2-3 weeks his kidney function returned to baseline with resolution of proteinuria and hematuria. He was eventually taken off steroids and his kidney function has remained normal.

Results:

Conclusions: This case is unique in several aspects. First of all, although his history of LGBL could explain weak paraproteinemia, our patient showed no clinical evidence of lymphoma on routine monitoring by Hematology. Moreover, we had no compelling reason to believe that he had an indolent lymphoproliferative disease causing his renal failure. Secondly, his quick and full recovery is consistent with a self-limiting acute process, possibly from Influenza. Thirdly, this case represents a rare finding of PIGN associated with influenza. We think concurrent findings of type 1 cryoglobulinemic MPGN associated with paraproteinemia and PIGN in this case, are likely a manifestation of the disease spectrum related to Influenza.

Funding: Clinical Revenue Support

TH-PO191

Incidental Finding of CFHR5 Mutation in a Case of Hemolytic Uremic Syndrome

Matthew H. Shapiro, Diego H. Aviles, Isa Ashoor. *LSUHSC Pediatrics, New Orleans, LA.*

Background: Hemolytic-uremic syndrome (HUS) is a triad of microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency. It's divided into two categories, diarrhea-positive (D+HUS) or typical HUS and diarrhea-negative or atypical HUS (aHUS).

Methods: A previously healthy 7 year old boy presented with several days of abdominal pain, emesis and bloody diarrhea. Admission labs were notable for Hgb 13.7 gm/dL, Platelets 485k/mm3 and creatinine 0.5 mg/dL. Stool culture, C. diff and Shiga toxin assays were negative. He subsequently developed oliguria and acute kidney injury. Urine was positive for blood (+3), protein (+3) and granular casts. Hgb and platelets fell to 7.1 gm/dL and 22K/mm3, respectively. Creatinine peaked at 4 mg/dL at which point hemodialysis was started. aHUS was suspected and additional labs were drawn. Complement C3/C4 and ADAMST13 levels were normal. Genetic testing for 11 genes implicated in thrombotic microangiopathy identified a mutation of unknown significance in the intron of Complement Factor H Related Protein 5 (CFHR5) gene. Renal function returned to baseline within a week without complement inhibition therapy and remains normal 3 months later.

Results:

Conclusions: We present a case of likely D+HUS where we were unable to isolate shiga toxin. This is further complicated by the incidental finding of a mutation in a complement regulating gene of unknown significance in aHUS, that has other known associations with disease. CFHR5 is associated with protection of glomerular cells against complement activation, yet mutations in the CFHR5 gene do not necessarily cause HUS, as they are also present in control populations. CFHR5 exon mutations have been described in association with various nephropathies, particularly in Cypriot patients, but few mention HUS, and none have described an intron mutation or its relationship to HUS. Importantly, CFHR5 mutations described in aHUS patients are in coding regions, not the in intron. This CFHR5 intron mutation is not predicted to alter or affect splicing, therefore it is unlikely to play a role in this particular case. Hence, complement inhibition with eculizumab is perhaps not indicated. Long-term monitoring is warranted.

TH-PO192

Complement Factor C4d Staining in Gemcitabine-Induced Thrombotic Microangiopathy: A Case Series

Koji Muro, Hideki Yokoi, Kaoru Sakai, Shuichiro Endo, Takeshi Matsubara, Motoko Yanagita. *Department of Nephrology, Kyoto University Hospital, Kyoto, Japan.*

Background: Complement factor C4d staining is a common finding in thrombotic microangiopathy (TMA), regardless of the underlying clinical condition. However, there are few reports in the literature investigating C4d staining of drug-toxicity-induced TMA, especially of gemcitabine (GEM)-induced TMA (GCI-TMA). We aim to examine the pattern of C4d staining in renal biopsy specimens from three patients with GCI-TMA.

Methods: Case 1 A 52-year-old man was diagnosed with hilar cholangiocarcinoma at the age of 46. Following surgery, he had been treated with GEM therapy (cumulative dose of 64,400 mg). His serum creatinine (Cr) level started increasing to 3.5 mg/dL from a baseline of 0.8 mg/dL within 22 months. Proteinuria appeared and his urinary protein-to-Cr ratio reached 2.5 g/g Cr. **Case 2** A 64-year-old woman was diagnosed with pancreatic cancer. She was treated with concurrent chemoradiotherapy and GEM was administered. Four months later, cumulative dose of GEM was 23,800 mg and her serum Cr level started increasing to 1.69 mg/dL from a baseline of 0.7 mg/dL within 5 months. Her urine dipstick revealed 2+ proteinuria, and her urinary protein-to-Cr ratio was 1.5 g/g Cr. **Case 3** A 70-year-old woman with recurrent angioimmunoblastic T-cell lymphoma was referred to our hospital. She had started to receive GEM since the age of 69. After cumulative dose of 15,250 mg, her serum Cr level was elevated to 1.4 mg/dL from a baseline of 0.6 mg/dL within 17 months, and proteinuria appeared reaching to 3.4 g/day. **Result** Light microscopy showed mesangiolysis and double contours in glomeruli. Immunofluorescence study demonstrated segmental deposits of C4d along glomerular capillaries (GBM-C4d) in all cases. Electron microscopy showed glomerular basement membraine (GBM) duplication and no dense deposit. In all three cases, GEM was discontinued. Renal function of these patients partially improved but did not fully recover.

Results:

Conclusions: A recent study showed that isolated strong GBM-C4d can highlight architectural glomerular remodeling. In our cases, segmental GBM-C4d and GBM duplication were observed, and their renal function did not fully recover. GBM-C4d staining in GCI-TMA might imply relatively poor renal prognosis.

TH-PO193

Thrombotic Microangiopathy and AKI Associated with MT-3724

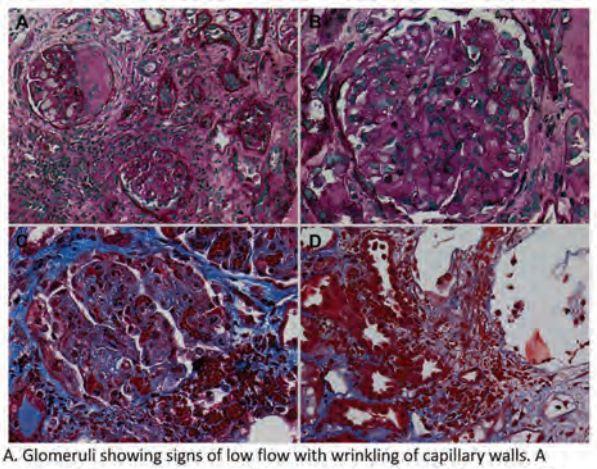
Mona Shaban,[3] Abhijit V. Kshirsagar,[2] Alexei V. Mikhailov.[1] *[1]University of North Carolina, Chapel Hill, NC; [2]University of North Carolina at Chapel Hill, Chapel Hill, NC; [3]Nephrology, University of North Carolina at Chapel Hill, Chapel Hill, NC.*

Background: Study drug MT-3724 is a CD20-targeting immunotoxin consisting of a recombinant fusion protein with a CD20 binding variable fragment fused to the enzymatically active Shiga-like toxin-I A1 subunit (SLT-I A1). Upon binding to the surface of CD20, SLT-I A1 leads to MT-3724 internalization, which inactivates cell ribosomes and causes cell death. MT-3724 is currently being studied in relapsed diffuse B cell lymphoma (DLBCL). Here, we report a case of acute kidney injury (AKI) secondary to thrombotic microangiopathy after administration of MT-3724 and leading to dialysis dependence.

Methods: A 70-year-old female with relapsed DLBCL presented with lower extremity swelling during the second cycle of study drug, MT-3724. Each cycle of MT-3724 is 75 mg/kg dosed on days 1,3,5,8,10, and 12. Exam was remarkable for significant peripheral edema. Serum creatinine (SCr) was 3.2 mg/dL from a baseline of 1.0-1.2 mg/dL. Urine protein to creatinine ratio (U P/C) was 20 g/g. Urine sediment revealed multiple oval fat bodies, hyalofatty casts, and dysmorphic red blood cells. Renal biopsy was performed and revealed thrombotic microangiopathy with evidence of fragmented red blood cells in the mesangium and interstitium. Glomeruli had signs of low flow and 1 fibrocellular crescent was observed. There was moderate to severe interstitial fibrosis and tubular atrophy (Figure 1, Panel A-D). 22 days after last dose of MT-3724, SCr continued to rise to 10 mg/dL associated with uremic symptoms and oliguria. Hemodialysis was initiated and patient continues to require outpatient dialysis.

Results:

Conclusions: The pathogenesis of this acute kidney injury is currently unclear, however we can speculate on the role of Shiga-like toxin given the clear association between Shiga toxin and hemolytic uremic syndrome (HUS). Novel targeted therapies in the treatment of DLBCL can potentially be nephrotoxic and early recognition and cessation of offending agent may prevent progression of kidney injury.



A. Glomeruli showing signs of low flow with wrinkling of capillary walls. A fibrocellular crescent observed in one glomerulus (upper left corner). The interstitial compartment demonstrates diffuse, moderate to severe fibrosis and tubular atrophy. Hematoxylin and Eosin, 20x.
B. Glomerular endothelial cells are diffusely and globally swollen; rare polymorphonuclear leukocytes are seen. Hematoxylin and Eosin, 40x.
C. A glomerulus with fragmented red blood cells in the mesangium. Trichrome, 40x.
D. Evidence of edematous interstitial regions with microscopic foci of hemorrhage with fragmented red blood cells are noted. Trichrome, 40x.

TH-PO194

Recurrent Venous Thromboembolism (VTE) in Membranous Nephropathy despite Direct Xa Inhibitor Therapy Monica L. Reynolds, Vimal K. Derebail. *University North Carolina at Chapel Hill, Chapel Hill, NC.*

Background: In membranous nephropathy, the risk of VTE is high and increases significantly with a serum albumin of <2.8 g/dl. Apixaban, a direct factor Xa inhibitor, is non-inferior to warfarin for VTE treatment in the general population but has not been studied in the nephrotic syndrome. We report a patient with recurrent VTE while on therapeutic dosing of apixaban.

Methods: A 51-year-old Caucasian male presented with new hypertension and lower extremity edema. Imaging studies demonstrated bilateral pulmonary emboli and acute DVT of the left external iliac, femoral and popliteal vein with extension to the IVC. After mechanical thrombectomy and catheter-directed thrombolytics, he was placed on apixaban 2.5mg BID. Edema recurred two months later and CT demonstrated extension of clot. He was switched to fondaparinux and referred to Hematology. Serum albumin was 2.1 g/dl and urinalysis showed proteinuria. Urine protein to creatinine ratio was 13 g/g. Catheter-directed thrombolytics and mechanical thrombectomy were repeated. Thrombophilia work-up was negative for Antithrombin and Protein C/S deficiency. He was discharged on apixaban 5 mg BID as prior dosing was thought to be sub-therapeutic. Anti-Phospholipase A2 receptor (PLA2R) antibody titers were 424 RU/ml, and he was presumed to have membranous nephropathy. Given the need for anticoagulation and recent thrombolytics, renal biopsy was deferred. He was treated with alternating monthly corticosteroids and oral cyclophosphamide. Six months later, UPC was 5 g/g and serum albumin was 2.6 g/dl. Repeat PLA2R antibody was <2 RU/ml. However, D-dimer was elevated to 2345 ng/mL and doppler ultrasonography revealed left acute mid femoral DVT and acute on chronic proximal femoral DVT. Four-hour apixaban drug level was 50.4 ng/ml (mean peak value in healthy volunteers- 128.5 ng/ml). He was switched back to fondaparinux. At one year, he had no further VTE's and serum albumin was 3.3 g/dl.

Results:

Conclusions: Despite appropriate dosing of apixaban, our patient developed recurrent VTE. A four-hour drug level was below the range reported for healthy volunteers at the same dose. Due to its high protein binding, apixaban may have altered pharmacokinetics and pharmacodynamics in patients with nephrotic syndrome and hypoalbuminemia. More data is needed to determine appropriate use of novel oral anticoagulants in the nephrotic syndrome.

TH-PO195

Spontaneous Cerebral Venous Thrombosis as a Presenting Manifestation of Secondary Membranous Nephropathy Srijan Tandukar,[1] Helbert Rondon Berrios.[2] *[1]University of Pittsburgh Medical Center, Pittsburgh, PA; [2]University of Pittsburgh School of Medicine, Pittsburgh, PA.*

Background: Membranous nephropathy is one of the most common causes of nephrotic syndrome in adults and accounts for the glomerulopathy associated with the highest rate of thromboembolic complications. We present a case of an otherwise healthy man who presented with spontaneous cerebral venous thrombosis and ultimately was diagnosed with a form of secondary membranous nephropathy.

Methods: A 40 year-old previously healthy man presented with progressively worsening generalized headache and nausea. He had been taking occasional ibuprofen for headaches for 2 weeks. He was afebrile and hemodynamically stable at presentation. On examination, he was in moderate distress due to headaches without neck stiffness, temporal artery tenderness or other focal neurological deficit. Laboratory data revealed normal blood counts, chemistry profile and renal function but low serum albumin of 2.3 g/dL, high total cholesterol of 263 mg/dL and high LDL of 191 mg/dL. Urine protein-to-creatinine ratio was elevated at 10 g/g. CT angiography of the brain revealed bilateral transverse venous sinus thrombosis. Patient was initiated on warfarin with heparin bridging. Thrombophilia workup could not be performed since acute thrombosis and warfarin reduce levels of antithrombin, protein C, and protein S. However, antiphospholipid antibodies were negative. Serological workup demonstrated low normal serum complement (C3 95, C4 22) with positive ANA (1:320), anti-U1RNP, anti-SSA, anti-Smith and anti-dsDNA. Hepatitis screen was negative. Kidney biopsy was performed. Light microscopy revealed a diffuse thickening of the glomerular basement membrane with "spikes". Immunofluorescence studies showed a negative PLA2R staining and a classic "full house" staining pattern (IgG1-4, C3, C1q). Electron microscopy revealed subepithelial, subendothelial and mesangial deposits with tubuloreticular inclusions. Based on the above findings a diagnosis of mixed connective tissue disease with lupus overlap was made and patient was initiated on prednisone and mycophenolate mofetil.

Results:

Conclusions: Cerebral venous thrombosis is a rare but potentially fatal complication of nephrotic syndrome. Increased risk of thromboembolism has been classically demonstrated in primary, but is also commonly seen in secondary membranous nephropathy. The risk increases with the level of decline in serum albumin.

TH-PO196

Incidental Thin Basement Membrane Associated with Primary Membranous Nephropathy Felipe Naranjo Sanchez,[2] Helmut G. Rennke,[1] Kelly A. Burdge.[2,3] *[1]Brigham and Women's Hospital, Boston, MA; [2]North Shore Medical Center, Salem Hospital, Cambridge, MA; [3]Masschusetts General Hospital Danvers, Danvers, MA.*

Background: Thin basement membrane nephropathy (TBMN) is a benign recessive genetic condition caused by defects of α3 or α4 type IV collagen, presenting with hematuria. A thin BM can also be found in Alport syndrome, an x-linked disease affecting α5 type IV collagen, which presents with early renal failure and has poor prognosis.

Methods: 52 yo F, PMHx of HTN, CKD3, GERD and Takasubo cardiomyopathy, presented to the ER with severe headache and nausea, there she had one episode of seizure, lasting 45 secs, in the setting of PRES. In her workup, a UA demonstrated proteinuria, confirmed to be 8g/g creatinine in a random sample, but no hematuria. Medications included: amlodipine, lisinopril, metoprolol, atorvastatin and omeprazole. She denied NSAIDs, herbal or illicit drugs, smoking, travel. No family history of kidney or autoimmune diseases. She had negative cervical, breast and colon cancer screening. Physical exam demostrated stable vital signs and edema in lower extremities. Urine sediment findings: few muddy brown casts and several fat bodies. Laboratory showed: SCr 2 mg/dl (previous 1mg/dl); hypercholesterolemia, hypoalbuminemia, Alb/Cr 8,583 mg/g; negative serology for HBV, HVC, HIV and RPR; normal C3 and C4, negative ANCA, ANA, SPEP and positive PLA2r antibody; low IgG, normal IgA. Kidney biopsy reported membranous glomerulonephropathy (MGN) stage II. Immunofluorescence microscopy revealed co-dominant reactivity for IgG3 and IgG4, weakly reactive to PLA2r. Electronic microscopy showed diffuse attenuation and fraying of lamina densa and effacement of foot processes of the glomerular basement membrane (GBM); thickness of the GBM could not be measured due to marked distortion of the capillary wall; changes suggestive of TBMN, an inherited abnormality of the GBM, possibly involving collagen IV genes. Patient was started on rituximab, cyclophosphamide and steroids, with improvement Alb/Cr ratio to 89 mg/g. The underlying etiology for her proteinuria was primary MGN, but a concomitant TBMN was incidentally observed, probably heightened the primary glomerular disease.

Results:

Conclusions: Diagnosing female patients with TBMN should raise awareness to screen for GBM collagen-related inherited disorders in the patient's family members, especially in males. Careful clinical assessments and repeated urinalysis should be offered to discover the genetic basis of the disease.

TH-PO197

Primary Membranous Nephropathy and AKI Jessica D. Morris,[1] Tazeen H. Jafar.[2] *[1]Duke University, Durham, NC; [2]Duke-NUS Graduate Medical School, Singapore, Singapore.*

Background: Over 90% of patients with primary membranous nephropathy present with preserved renal function with only 10-20% of patients progressing to ESRD. Here we present a case of respiratory failure and acute anuric renal failure requiring renal replacement therapy found to have primary membranous nephropathy.

Methods: Our patient was a 60 year old man with hypertension, baseline serum Cr of 0.7-0.9 mg/dl who presented to an outside hospital with fevers, cough, and shortness of breath. Two months prior he had presented to his primary care physician with lower extremity edema and was found to have 10 g of proteinuria on a24 hour urine collection. During evaluation at the outside hospital he was hypoxic requiring supplemental oxygen and serum Cr was 1.4 mg/dl. Chest imaging demonstrated bilateral infiltrates and pleural effusions. Within three days hypoxic respiratory failure progressed and he required BIPAP with increasing serum Cr to 3.0 mg/dl, he was subsequently transferred. On arrival to our hospital he was intubated within first 24 hours of presentation. He was anuric despite

diuretics with increasing serum Cr to 4.0 mg/dl and was then started on dialysis. Given presentation of rapidly progressive pulmonary and renal failure, along with active urine sediment, methylprednisolone was started. Renal biopsy demonstrated findings consistent with membranous nephropathy and tubular injury. He was eventually extubated with negative influenza, bronchoscopy and blood cultures. Later, anti-PLA2R returned positive at 578 RU/mL and he was discharged on steroids. He continued to require dialysis at discharge. At follow up 2 months later renal function returned to baseline and dialysis was discontinued.

Results:

Conclusions: The AKI in this case was likely the combination of contrast, ARB therapy, NSAIDs, and hemodynamic insults in setting of hypoalbuminemia. This case highlights the importance of biopsy in determination of etiology of underlying diagnosis.

TH-PO198

Gastric Stimulator Infection Complicated by Post-Infectious Glomerulonephritis Tyler Woodell, Rupali S. Avasare. *Oregon Health & Science University, Portland, OR.*

Background: Acute poststreptococcal glomerulonephritis, though considered rare among adults in developed countries, remains a serious health concern. In contrast to the typical skin or throat infection preceding acute poststreptococcal glomerulonephritis, here we report to our knowledge the first case of infection-related glomerulonephritis associated with intraabdominal infection after gastric stimulator placement.

Methods: A 24 year-old woman with type 1 diabetes mellitus complicated by gastroparesis and proteinuric stage IIIa chronic kidney disease undergoes placement of a gastric stimulator after multiple emergency room visits for intractable vomiting. She develops severe abdominal pain on postoperative day 27 and presents to the emergency room. On physical exam she is febrile to 102.5 °F, tachycardic to 135 beats per minute and hypotensive to 80s/40s mmHg. Diagnostic studies are remarkable for a serum creatinine of 2 mg/dL (increased from 1.5 mg/dL one month prior), a white blood cell count of 29,000/mL (94% neutrophils) and a CT scan of the abdomen and pelvis that reveals a fluid collection adjacent to the gastric stimulator; blood cultures are negative. She is started on vancomycin and piperacillin-tazobactam and, on postoperative day 30, diagnostic laparoscopy reveals purulent fluid around the stimulator for which it is removed. Intraoperative cultures grow group A *Streptococcus pyogenes*. The patient's antibiotics are narrowed and her clinical status improves. Despite rapid initial improvement in renal function, the patient develops recurrent kidney injury four days after removal of the gastric stimulator characterized by a rise in creatinine from 1.4 mg/dL to 2.9 mg/dL over the subsequent two weeks and oliguria; C3 is reduced and C4 is normal. She is started on hemodialysis for volume overload. A kidney biopsy is performed and findings are significant for mesangial proliferation, exudative endocapillary hypercellularity and interstitial eosinophilia. Electron microscopy reveals mesangial and subepithelial deposits. A diagnosis of infection-related glomerulonephritis is established and, after two months of supportive care, she is able to discontinue hemodialysis.

Results: Clinicians should maintain suspicion for post-infectious glomerulonephritis in the absence of classic infection and, when appropriate, perform a kidney biopsy for its confirmation.

Conclusions:

TH-PO199

Possible Contribution of Vascular Endothelial Growth Factor A (VEGF-A) to the Pathogenesis of Membranous Nephropathy (MN) Ayumi Matsumoto, Isao Matsui, Tomoko Namba, Yusuke Sakaguchi, Masayuki Mizui, Takayuki Hamano, Yoshitaka Isaka. *Osaka University Graduate School of Medicine, Suita, Japan.*

Background: Autoantibody against thrombospondin type-1 domain-containing 7A (THSD7A) is responsible for primary MN, but the mechanisms how is THSD7A-expression controlled and how is THSD7A recognized by the immune system remain uncertain.

Methods: Two cases of THSD7A-associated MN accompanying subcutaneous tumors were transferred to our hospital. Hypereosinophilia was evident in both cases. Histological analyses of forehead tumors of Case 1 revealed that the tumors were formed by swollen arteries. The arteries were nearly occluded due to small vessels lined by CD31-positive plump endothelial cells, which were surrounded by eosinophils. These findings indicated that the patient suffered from intra-arterial angiolymphoid hyperplasia with eosinophilia (ALHE). The right axillary tumor of Case 2 indicated that Case 2 also suffered from ALHE. Plasma VEGF-A before the initiation of prednisolone therapy was elevated to 109 pg/mL in Case 1 (normal level: 42 ± 20 pg/mL). Serum level of IL-5, a cytokine that upregulates VEGF-A production and secretion by eosinophils, was also elevated to 15.5 pg/mL in Case 1 (normal level: <3.9 pg/mL). These parameters were not measured in Case 2. Flow cytometric analysis of peripheral blood revealed that a substantial number of the circulating eosinophils was positive for VEGF-A in Case 1, and eosinophils infiltrated into the ALHE tumor were also positive for VEGF-A in both cases. Prednisolone therapy dramatically decreased the number of VEGF-positive eosinophils and plasma VEGF-A levels (57.3 pg/mL). We found that plump endothelial cells in ALHE strongly expressed THSD7A in both cases. VEGF-A upregulated THSD7A expression in a dose-dependent manner in cultured human umbilical-vein endothelial cells. Furthermore, double-positive cells for THSD7A and CD83, a molecule involved in antigen-presentation activity, surrounded the proliferated small vessels. These findings suggested that VEGF-A-induced THSD7A was presented to the immune system at ALHE foci.

Results:

Conclusions: Our study clearly demonstrated that VEGF-A induced THSD7A expression. The existence of THSD7A/CD83 double-positive cells in ALHE tumors suggested that THSD7A was immunized at ALHE foci. Therefore, VEGF-A-induced THSD7A-expression outside of the kidney plays important roles in MN pathogenesis.

Funding: Private Foundation Support

TH-PO200

A Refractory Case of Membranous Nephropathy Concurrent with IgG4-Related Kidney Disease Hiroyuki Arai,[1] Ryo Kamimatsuse,[1] Naohiro Toda,[1] Keisuke Nishioka,[2] Shuichiro Endo,[1] Takeshi Matsubara,[1] Hideki Yokoi,[1] Motoko Yanagita.[1] [1]*Department of Nephrology, Kyoto University Hospital, Kyoto city, Japan;* [2]*Department of Nephrology, Osaka red cross hospital, Osaka city, Japan.*

Background: IgG4-related kidney disease (IgG4-RKD) is a recently recognized clinical entity characterized by IgG4-positive plasma cell infiltration and characteristic 'storiform' fibrosis. Tubulointerstitial nephritis is the most common finding, which responds well to corticosteroid therapy. However, it is uncertain whether the treatment for IgG4-RKD is equally effective for membranous nephropathy (MN), which occasionally coincides with IgG4-RKD. We present a refractory case of IgG4-RKD accompanied with MN, which warrants the combination therapy of prednisone (PSL) and cyclosporine (CyA).

Methods: A 58-year-old male was referred to our hospital for recently diagnosed nephrotic syndrome. He had a history of autoimmune pancreatitis (AIP), and was maintained on PSL 10 mg/day. Laboratory results revealed serum albumin 2.2 g/dL, creatinine 0.80 mg/dL, IgG4 473 mg/dL, and urinary protein 13.6 g/gCr. Anti-PLA2R antibody was undetectable. Renal biopsy revealed tubulointerstitial lymphoplasmacytic infiltration and storiform fibrosis with increased ratio of IgG4/IgG positive plasma cells (44.8%), predominant subepithelial granular deposits of IgG1 and IgG2 in glomeruli, and electron dense deposits in subepithelial and subendothelial regions along glomerular basement membrane. As other causes of secondary MN were excluded, we diagnosed secondary MN concurrent with IgG4-RKD. Although PSL was increased to 35 mg/day, proteinuria did not resolve. CyA was initiated, and urinary protein started decreasing. While serum IgG4 level increased by tapering PSL, urinary protein remained suppressed. After 1 year of follow-up, urinary protein decreased to 0.34 g/gCr and AIP did not recur under PSL 12.5 mg/day.

Results:

Conclusions: Renal biopsy findings and negative anti-PLA2R antibody argued for secondary MN concurrent with IgG4-RKD. While PSL was effective for the extrarenal lesion of IgG4-RKD, proteinuria was refractory to PSL and the addition of CyA was required. Generally IgG4-RKD responds well to PSL, in great contrast to our case. Moreover, our case is interesting in that serum IgG4 level did not correlate with proteinuria, indicating that serum IgG4 level does not reflect the activity of MN. These findings suggest that the underlying etiology of secondary MN concurrent with IgG4-RKD is different from other lesion of IgG4-RKD.

TH-PO201

Hepatitis C Virus-Associated Glomerulonephritis Following Sustained Virological Response with Direct-Acting Antiviral Therapy Bogdan Obrisca,[1] Roxana A. Jurubita,[1] Vlad T. Berbecar,[2] Bogdan M. Sorohan,[1] Andreea Andronesi,[1] Gener Ismail.[1] [1]*Fundeni Clinical Institute, Bucharest, Romania;* [2]*University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania, Bucharest, Romania.*

Background: Cryoglobulinemic membrano-proliferative glomerulonephritis (MPGN) is the most frequent type of renal involvement in HCV infection. The newer direct-acting antiviral (DAA) agents have been associated with sustained virological response (SVR) in over 95% of cases. However, the efficacy of this therapy on extrahepatic manifestations of HCV infection is still unknown. We report two cases of persistent and new-onset mixed cryoglobulinemia (MC) after successful eradication of HVC infection.

Methods: New onset MC. A 57 year-old male is admitted for purpuric rash and acute nephritic syndrome. His past medical history included psoriatic arthritis diagnosed 35 years ago and cirrhosis due to HCV infection (genotype 1b) for the past 11 years. Six months ago he received the ritonavir-boosted paritaprevir, ombitasvir and dasabuvir regimen and obtained SVR. Prior to this admission serum cryoglobulins were undetectable and urinalysis was unremarkable. The clinical exam revealed a purpuric rash on lower extremities, hepatomegaly and splenomegaly. Laboratory results are shown in table 1. The kidney biopsy was compatible with type I MPGN with extracapillary proliferation and the patient was started on cyclophosphamide and prednisone. After 6 months of immunosuppressive therapy the patient experienced a complete remission. **Persistent MC.** A 50 year-old male presented with nephrotic syndrome (NS). He was known with HCV infection and MC with renal involvement for the past 15 and 2 years, respectively. Initially he received Rituximab and corticosteroids without a clinical response. Three months ago he received the ritonavir-boosted paritaprevir, ombitasvir and dasabuvir regimen and obtained SVR, but with persistence of NS. He underwent a kidney biopsy that showed MPGN with extracapillary proliferation after which he was started on cyclophosphamide. Baseline laboratory results are shown in table 1.

Results:

Conclusions: Despite successful viral eradication with the newer DAA agents there is increasingly recognition that clonal B cell expansion associated with HCV infection can still persist, thus maintaining the autoimmune manifestations.

Table 1

	eGFR (ml/min)	Serum Albumin (g/dl)	Proteinuria (g/day)	Serum C3 (mg/dl)	Serum C4 (mg/dl)	Cryoglobulins
Case 1	68	3.7	1.9	55	1.6	Present
Case 2	63	3.1	9.6	98	3.6	Present

TH-PO202

Daclatasvir Plus Asunaprevir Treatment Ameliorated Proteinuria in Patients with HCV-Related Nephropathy in the Absence of Immunosuppressant Yoshihito Nihei, Hitoshi Suzuki, Maiko Nakayama, Masao Kihara, Tomohito Gohda, Yusuke Suzuki. *Nephrology, Juntendo University Faculty of Medicine, Tokyo, Japan.*

Background: The standard therapy of a chronic HCV infection is IFN monotherapy or IFN combined with ribavirin; however, after the introduction of direct-acting antivirals (DAAs), the standard therapy for patients with HCV genotype 1 has dramatically changed. However, the effects of DAAs on extra-hepatic manifestations such as HCV-related nephropathy (HCV-RN), especially in cases with renal dysfunction, are not well elucidated. We report a case of HCV-RN successfully treated by Daclatasvir and Asunaprevir, which are IFN-free DAAs for HCV.

Methods: A 66-year-old man was diagnosed as having chronic hepatitis C. Blood examination revealed a high copy number of HCV-RNA (genotype 1b). He presented with microscopic hematuria and proteinuria at the age of 56. After 7 years from the onset of urinary abnormalities, levels of urinary protein increased up to 5 g/gCr, and kidney biopsy was performed. Pathological findings of kidney biopsy specimens revealed mesangioproliferative glomerulonephritis with IgA deposition, and he was diagnosed as HCV-RN. He developed severe nephrotic syndrome with pleural effusion due to the hypoalbuminemia, therefore, we initiated treatment with oral corticosteroid (PSL). However, liver dysfunction was exacerbated and a copy number of HCV-RNA increased after treatment with PSL. Then, we changed medication from PSL to antiviral treatment with Daclatasvir/Asunaprevir. Clearance of HCV-RNA was obtained by 4 weeks and sustained, and microhematuria turned negative, proteinuria decreased (1.5 g/gCr) by 24 weeks. After 2 years from treatment with Daclatasvir/Asunaprevir, level of proteinuria was 0.8 g/gCr.

Results:

Conclusions: Patients with HCV infection have a higher risk of end-stage renal disease. This case offers original evidence for the application of newer generation of IFN-free DAAs in the treatment of HCV-RN.

Funding: Clinical Revenue Support

TH-PO203

Diagnostic Dilemma of a Vasculitic Rash in a Patient with Hepatitis C Infection Arjun Ghodasara,[2] Neha Jaswal,[1] Narottam Regmi,[3] Krishna M. Baradhi.[3] *[1]Family Medicine, University of Oklahoma, Tulsa, Tulsa, OK; [2]Internal Medicine, University of Oklahoma, Tulsa, Tulsa, OK; [3]Nephrology and Hypertension, University of Oklahoma, Tulsa, TULSA, OK.*

Background: Diagnosing ANCA vasculitis in patients with hepatitis C is challenging due to similarity of clinical presentation; moreover, treatment can worsen infection. We present a unique case of vasculitic rash in a patient with hepatitis C that, to our knowledge, has been reported only once previously in literature.

Methods: A 31-year-old man with history of intravenous drug use presented with fever, rash, malaise, and arthralgias. He was initially treated with antibiotics but when fever and rash did not subside was admitted to the hospital for further evaluation. Physical examination was pertinent for temperature of 102 F and a non-blanching purpuric rash on his extremities bilaterally including his palms and soles. Initial labs showed leukocytosis without bacteremia and hematuria and proteinuria on urine microscopy. Further evaluation revealed hepatitis C viral PCR load above 3 million IU/ml, negative cryoglobulins, normal complements, and elevated rheumatoid factor. Skin biopsy revealed leukocytoclastic vasculitis. Our presumptive diagnosis was hepatitis C-related mixed cryoglobulinemia. However, additional findings of C-ANCA 1:160 with positive proteinase-3 antibody and lung nodule on CT chest lead us to the kidney biopsy, revealing focal necrotizing and crescentic glomerulonephritis. Lung nodule biopsy showed necrotizing granulomatous inflammation. Patient was diagnosed with granulomatosis with polyangiitis (GPA). He was initiated on pulse steroids and rituximab along with concomitant treatment with ledipasvir and sofosbuvir for hepatitis C and was discharged with outpatient follow-up.

Results:

Conclusions: The diagnosis and treatment of GPA can be challenging in a patient with hepatitis C. Cryoglobulinemia and GPA may both present with renal dysfunction, hematuria, vasculitic rash, and arthralgia. Treatment of GPA with immunosuppresion can be complicated in a patient with an active infection. ANCA should be evaluated in patients with hepatitis C presenting with rash or other systemic symptoms. Determination of target ANCA antigens is invaluable as false positives are common in hepatitis C. Similarly, hepatitis C-associated infection should be considered in patients with positive ANCA in an appropriate clinical context.

TH-PO204

HCV-Associated Glomerulopathy and Cryoglobulinemia Despite Sustained Remission of Hepatitis C Viremia after Treatment with Oral Direct-Acting Antiviral Agents Rabia Akhtar,[1] Cory Handelsman,[2] John A. Walker.[2] *[1]Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ; [2]Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ.*

Background: Millions of people are infected with chronic hepatitis C worldwide. Aside from hepatic injury, hepatitis C virus infection may be associated with a multitude of extrahepatic complications. These include lymphoproliferative disorders (including essential mixed cryoglobulinemia, monoclonal gammopathies and lymphoma), dermatologic conditions such as lichen planus and porphyria cutanea tarda, and glomerular disease.

Methods: We present a case of a 47 year old woman who developed worsening azotemia, nephrotic-range proteinuria, hypocomplementemia, and mixed cryoglobulinemia nearly one year after demonstrating a sustained remission of hepatitis C viremia (genotype 1A) following treatment with the oral direct acting anti-viral agent Harvoni (ledipasvir/sofosbuvir). Kidney biopsy revealed extensive duplication of the glomerular basement membrane on light microscopy, predominant mesangial and capillary wall IgA deposits on immunofluorescence, and extensive dense subendothelial deposits on electron microscopy, consistent with a histologic diagnosis of a hepatitis C virus associated membranoproliferative glomerulonephritis with immune complex deposition. Hepatitis C RNA PCR was negative at the time of the biopsy

Results:

Conclusions: This case is noteworthy in that our patient developed a hepatitis C virus associated membranoproliferative glomerulonephritis with immune complex deposition in the setting of mixed cryoglobulinemia despite achieving a sustained remission of hepatitis C viremia 1 year earlier. Another intriguing and unusual feature of our case is that in membranoproliferative glomerulonephritis, immune complex depositions typically consist of IgG and C3, whereas in our patient the predominant immunoglobulin present was IgA. This case suggests that the immunostimulatory effects of hepatitis C infection may persist or recur despite a successful course of antiviral therapy, and these effects may be responsible for post-treatment glomerular injury.

TH-PO205

Response to Intravenous Immunoglobulin in Acute Parvovirus B19-Associated Nephrotic Syndrome from Collapsing Focal Segmental Glomerulosclerosis Nupur N. Uppal, Nishita Parikh, Hitesh H. Shah. *Hofstra Northwell School of Medicine, Great Neck, NY.*

Background: Human parvovirus B19 (HPV B19) has been associated with collapsing focal segmental glomerulosclerosis (c-FSGS). However, the optimal therapy for HPV B19-associated c-FSGS is currently unknown. While intravenous immunoglobulin (IVIG) therapy has been used for treatment of c-FSGS in immunocompromised patients, its role in immunocompetent patients remains unclear. We report the response to IVIG treatment in 2 immunocompetent patients with HPV B19-associated c-FSGS.

Methods: Case 1: 37-year-old African American (AA) female with sickle cell disease was hospitalized and treated for transient aplastic crisis secondary to acute HPV B19 infection. Five days later, patient presented with worsening lower extremity (LE) edema. She was found to have massive proteinuria (spot urine TP/CR: 56), hypoalbuminemia (serum albumin: 1.8 g/dL) and serum creatinine (Scr) of 1.8 mg/dL. HPV B19 DNA by PCR was markedly elevated (1.8 X 108 IU/ml). Other serological work up for nephrotic syndrome including HIV infection was negative. Kidney biopsy subsequently revealed c-FSGS. In addition to diuretics, patient received trial of 2 doses of IVIG therapy. Despite IVIG treatment, HPV B19 viral load remained elevated and our patient progressed to ESRD within 11 months of initial presentation. **Case 2**: 18-year-old AA male presented for evaluation of AKI (Scr: 2.74 mg/dL) and acute onset nephrotic syndrome. Patient was found to have significant proteinuria (spot urine TP/CR: 14.9) and hypoalbuminemia (serum albumin: 1.9g/dL). HPV B19 DNA by PCR was elevated (95,600 IU/ml). Other serological work up for nephrotic syndrome including HIV infection was negative. Kidney biopsy showed c-FSGS. Patient subsequently received trial of 2 doses of IVIG treatment. HPV B19 viral load remained elevated despite IVIG treatment. Patient did not respond to IVIG treatment and continues to have significant nephrotic syndrome and progressive renal failure.

Results:

Conclusions: Optimal therapy for HPV B19-associated c-FSGS is currently unknown. Role of IVIG treatment in immunocompetent patients with acute HPV B19-associated c-FSGS remains unclear. Our patients continued to have elevated HPV B19 viral load and progressive renal failure despite IVIG treatment. Well-designed studies are needed to understand the mechanisms and treatment of this devastating medical condition.

TH-PO206

Parvovirus Infection Mimicking Atypical Hemolytic Uremic Syndrome in an Immunocompetent Adult Gerald Shovlin,[2] Mark A. Kleman,[1] Joseph Vadakara,[2] Syam Prasad Mallampalli,[2] maria bermudez.[2] *[1]Geisinger Health System, Danville, PA; [2]Geisinger Medical Center, Danville, PA.*

Background: Human parvovirus B19 (PB19) has been associated with thrombotic microangiopathies (TMA) including hemolytic uremic syndrome (HUS) both in immunocompetent and immunosuppressed individuals. To our knowledge, specific pathophysiologic mechanisms for this association is unclear. We present a case of acute

PB19 infection presenting as atypical HUS and discuss potential pitfalls in the diagnosis and implications for therapy.

Methods: A 20-year-old female presents with anuric AKI, thrombocytopenia, and MAHA (low haptoglobin, presence of schistocytes and high LD 1500). Autoimmune diseases including lupus, antiphospholipid syndrome and cryoglobulinemia were ruled out. Her mono test, hepatitis panel, and HIV were negative. C3 complement level was low at 78. Bone marrow biopsy showed reactive neutrophilia and occasional RBC fragments. ADAMTS13 and alternate complement studies were sent and patient was started on dialysis and plasmapheresis (PLEX) for presumed diagnosis of HUS. Reticulocyte count was inappropriately normal for which PB19 PCR was checked and found to be > 600,000 copies. ADAMTS13 came back normal so the patient was started on Eculuzimab (900 mg weekly for 4 doses, then 1200 mg every two weeks) for possible atypical HUS. Alternate complement pathway (TMA functional panel) returned normal, without identifiable mutations predisposing the patient to aHUS. She completely recovered, came off dialysis, and Eculizumab was discontinued.

Results:

Conclusions: Our patient presented with features of atypical HUS in the setting of acute PB19 infection. Her ADAMTS13 and alternate complement pathway were normal making the exact pathophysiologic mechanism of this association unclear. Prompt search for PB19 as a potential trigger of her clinical picture and rapid initiation of PLEX appeared to favor her rapid improvement. Potential role of Eculizumab remains unclear but likely prudent until alternate pathway studies are available. Further studies to better understand this association and approach to therapy are mandated.

TH-PO207

Cytomegalovirus-Associated Collapsing Glomerulopathy and Tubulointerstitial Nephritis in an African American Patient with T-Cell Lymphoma Edgar Hernandez- Montalvo,[2] Sixto G. Giusti,[2] Agnes B. Fogo,[1] Paisit Paueksakon,[1] Juan Carlos Q. Velez.[2] *[1]Department of Pathology, Vanderbilt University Medical Center, Nashville, TN; [2]Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA.*

Background: Collapsing glomerulopathy (CG) may occur in association with human immunodeficiency virus (HIV) and parvovirus B19 (PVB19) infections. However, published reports of CG associated with cytomegalovirus (CMV) infection are sparse.

Methods: We describe a case of a 69 year-old African American woman with T-cell lymphoma who presented with 1-week history of fever, anorexia and delirium. She was on chemotherapy with alemtuzumab. On arrival, blood pressure was 110/64 mmHg, temperature 38.0 ºC. Physical examination was remarkable for 2+ pitting leg edema. She was pancytopenic with serum creatinine 2.6 mg/dL. Urinalysis revealed 3+ protein and 3+ blood without red blood cell (RBC) casts or dysmorphic RBCs. The urine protein-to-creatinine ratio was 24.8 g/g. Anti-nuclear, hepatitis C, HIV and PVB19 antibodies, polymerase chain reaction (PCR) for HIV RNA, complement levels, hepatitis B antigen and antibodies were all negative or normal. Acute CMV infection was subsequently diagnosed upon detection of serum CMV DNA PCR of 3,450,814 copies/mL. Renal ultrasound revealed normal sized kidneys with hyperechoic parenchymal echotexture. Her kidney function deteriorated and hemodialysis was initiated on hospital day 10. A kidney biopsy was performed. The biopsy showed 10-20% interstitial fibrosis, tubular dilatation, acute tubular injury and multifocal lymphocytic interstitial infiltrates with positive tubular CMV immunostaining. Glomeruli (2 out of 3) showed collapse of the glomerular tuft, overlying visceral epithelial cell hyperplasia and diffuse foot process effacement without immune complexes, characteristic of CG. Despite treatment with valgancyclovir, the patient progressed to require permanent hemodialysis.

Results:

Conclusions: Although CMV immunostaining was negative in glomeruli, we suspect that the glomerular lesion was induced by the viral infection. The patient described herein, as well as those described in the only 3 published cases of CMV-associated CG in the literature, are individuals of African descent. Therefore, we speculate that an interaction between CMV and apolipoprotein L1 risk alleles could trigger cases of CMV-associated CG.

TH-PO208

Recovery of Kidney Function Following Autologous Hematopoietic Stem Cell Transplant in a Patient with C3 Glomerulonephritis Associated with Monoclonal Gammopathy Nicola Lepori,[1] Wisit Cheungpasitporn,[1] Sanjeev Sethi,[2] Nelson Leung,[1] David L. Murray,[3] Fernando C. Fervenza.[1] *[1]Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [2]Anatomic Pathology, Mayo Clinic, Rochester, MN; [3]Laboratory Medicine, Mayo Clinic, Rochester, MN.*

Background: C3 glomerulopathy is associated with presence of monoclonal immunoglobulin (MIg) in almost 60% of cases after 50 years of age. Overall renal prognosis is poor with frequent progression to ESRD.

Methods: A 55 y/o man was referred to our clinic for renal insufficiency (serum creatinine [sCr] from 1.0 to 2.7 mg/dl in the previous 16 months) with a recent episode of gross hematuria. Urinalysis showed hematuria with dysmorphic RBCs and 24h proteinuria was 643 mg. Serology tests showed elevated soluble membrane attack complex (sMAC) and CBb levels, with normal C3, C4, CH50. SPEP with immunofixation showed an Ig kappa M spike of 2.0 g/dL with kappa free light chains of 10.2 mg/dL. Kidney biopsy showed mesangial proliferative glomerulonephritis with bright C3 staining on IF (negative for all immunoglobulins), supporting a diagnosis of C3 glomerulonephritis (C3GN). A bone marrow biopsy revealed 5% to 10% kappa restricted plasma cells; diagnostic work up for multiple myeloma was negative. Patient was treated with 12 cycles of CyBorD based regimen; renal function significantly improved (Table), but after discontinuation of cyclophosphamide and dexamethasone, C3GN relapsed. VRD based regimen was ineffective to induce remission. Thus the patient subsequently underwent high-dose melphalan (HDM) followed by autologous hematopoietic stem cell transplant (ASCT). Three months following ASCT, sCr had fallen to 1.3 mg/dL with M-spike of 0.8 g/dL and kappa free light chains of 2.31 mg/dL

Results:

Conclusions: Recent evidences indicate that treatment direct against underlying monoclonal disorder improves renal survive in MIg-associated C3 GN. As we described in our case, ASCT may potentially be an emerging treatment option for patients with MIg-associated C3GN, especially in those with poor response to classical chemotherapy.

Laboratory testing	Presentation	CyBorD regimen	Maintenance Bortezomib	VRD regimen	3 months following ASCT
sCr (mg/dL)	2.7	1.1	1.5	2.1	1.3
Hb (g/dL)	9.8	n/a	12.5	10.5	12.2
24 h Urine Proteine (mg)	643	347	n/a	280	224
Urinary RBC's (n/hpf)	>100	11-20	21-30	51-100	11-20
M spike (g/dL)	2.0	1.2	1.3	0.8	0.8
Kappa free light chain (0.33-2.63 mg/dL)	10.2	2.92	3.44	3.36	2.31
Lambda free light chain (0.57-2.63 mg/dL)	1.23	0.92	0.98	1.08	0.76
C3 (75-175 mg/dL)	112	116	n/a	n/a	113
C4 (14-40 mg/dL)	21	23	n/a	n/a	17

TH-PO209

Crescentic C3 Glomerulonephritis in HIV Disease Muhammad Y. Jan, Jwalant R. Modi, Carrie L. Phillips, Tarek M. El-Achkar, Michael T. Eadon. *Indiana University School of Medicine, Indianapolis, IN.*

Background: Crescentic C3 Glomerulonephritis (C3GN), a subtype of C3 glomerulopathy, presents a diagnostic and therapeutic challenge, especially in the setting of HIV infection.

Methods: A 24-year-old African-American male with no past medical history presented with leg swelling, upper respiratory tract symptoms and hematuria of 2 weeks duration. Physical exam showed signs of volume overload and uncontrolled hypertension. Lab showed serum creatinine of 3.01 mg/dl and urine with dysmorphic RBCs and spot proteinuria of 2.4 g/g. He was found to be HIV+ with viral load of 64,000 copies and CD4 count of 355 cells/µl. C3 and C4 levels were within normal limits. Clinical course showed worsening kidney injury and proteinuria. Anti-GBM IgG, ANA, ASO titer, hepatitis B and C, ANCA titers, cryoglobulins were all negative. A Kidney biopsy revealed crescentic glomerulonephritis with diffuse mesangial and capillary hypercellularity with patchy basement membrane duplication. Immunofluorescence staining revealed 4+ C3 and 1+ IgG. Work-up for other infections was negative. Alternate complement pathway analysis showed borderline low level of Factor H, normal C3 nephritic factor and low levels of Factor B and I confirming the diagnosis of C3GN. He was initiated on HIV treatment, pulse steroids, and Cellcept®. This lead to stabilization and subsequent improvement of renal function.

Results:

Conclusions: Diagnosis of glomerulonephritis with predominant C3 deposits in the setting of HIV disease is very challenging. The differential includes C3GN, infection related GN, and HIV immune complex disease (HIVICK). The overlap between these entities and the relevance to disease pathogenesis and management is still unclear. Correlation between isolated strong C3 staining on biopsy and normal C3 complement levels may be more suggestive of C3 glomerulopathy. Testing for abnormalities in the complement pathway is crucial to establish a firm diagnosis. The low levels of Factors B and I in this case suggest inhibited C3 activation, which could be related to HIV disease itself. We report a case of crescentic C3GN with altered factors B and I in a patient with HIV disease. Further investigation is required to determine whether HIV may dysregulate complement and precipitate C3 glomerulopathy.

TH-PO210

Congestive Glomerulopathy: An Uncommon Primary Finding in Nephrotic Syndrome Michael D. Donnan,[1] Yashpal S. Kanwar,[2] Daniel Batlle,[1] Shubhada N. Ahya.[1] *[1]Nephrology, Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Pathology, Northwestern University Feinberg School of Medicine, Chicago, IL.*

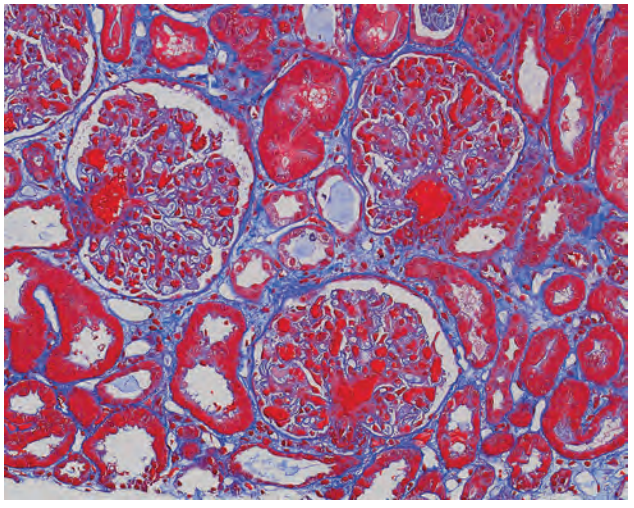
Background: Congestion of the intra-glomerular feeding arterioles is a pathologic feature uncommonly reported as a primary finding on renal biopsy. Here we present a case of significant congestion of the intra-glomerular arterioles in a man with nephrotic syndrome and oliguric renal failure.

Methods: A 42 yo man presented with 2 weeks of weight gain and dyspnea. His symptoms were preceded by arthralgias for which he was taking regular ibuprofen. Exam demonstrated anasarca. Labs showed a rising serum creatinine from 0.9 to 6.4mg/dl. Serum albumin was 1.9g/dl, urinalysis with blood and protein, and 24 hour urine protein collection was 8.4g. Serologies revealed a low C3 / C4 and positive ANA. A renal biopsy showed minimal mesangial proliferation, marked dilation of the intra-glomerular portion of the feeding arterioles with significant congestion in a majority of the glomeruli by light microscopy. No other vascular pathology or micro-thombi seen. Final pathology was consistent with class V lupus nephritis. Renal artery duplex did not show renal vein thrombosis. Patient developed an acute deep vein thrombosis of the right brachial vein; hypercoagulable studies were unremarkable. Initiated on steroids and mycophenolate

mofetil. One month after presentation, serum creatinine returned to baseline with <1g proteinuria.

Results:

Conclusions: Marked intra-glomerular congestion is an atypical pathologic finding whose mechanism and significance is not yet known. It has been reported concurrently with visible micro-occlusions, as in the setting of thrombotic microangiopathy or sickle cell crisis. It rarely has been reported with renal vascular flow limitations, such as states of shock and renal vein thrombosis. In the setting of nephrotic syndrome one may postulate smaller venous thrombembolisms may have been present. While not previously reported, we surmise the possibility that the use of NSAIDs may have contributed to these findings.



TH-PO211

Polycythemia Vera: An Unusual Cause of Proteinuria

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Background: Introduction: Polycythemia vera (PV) is a myeloproliferative disease which is typpified by increased red cell mass; rarely it has been associated with renal manifestations, including nephrotic syndrome. Here, we present a case of PV associated with glomerular basement membrane thickening and consequent proteinuria.

Methods: Case Description: Patient is a 46 year-old male with a history of mild hypertension on lisinopril monotherapy who presented to nephrology clinic after urinalysis performed as part of a life insurance examination revealed proteinuria. He was otherwise asymptomatic. He was thin and muscular with mild rubot and blood pressure 148/81. Initial laboratory examination was notable for a hematocrit of 56%, creatinine of 1.0 mg/dL, and a urine protein-to-creatinine ratio (PCR) of 3.2 g/g. Renal ultrasound demonstrated normal appearing kidneys but raised concern for hepatatic pathologiy. Magnetic resonance imaging showed mild diffuse hepatic steatosis and splenic vein thrombosis. Laboratory examination was negative except for a mildly postive antinuclear antibody ratio of 1:80. Renal biopsy was pursued. This revealed diffusely thickened glomerular basement membranes concerning for dysmetabolic injury. Given his splenic vein thrombosis and increased hematocrit, he was referred to hematology for PV. He underwent JAK2 mutation testing which was positive. He was initiated on maximal renin-angiotensin-aldosterone blockade and his PCR decreased to 1.9 g/g. As his hematocrit decreased with phlebotomy, his PCR has continued to decrease, most recently to 1.5 g/g.

Results:

Conclusions: Discussion: Previous reports have shown an association between myeloproliferative disorders and various glomerulopathies. In the largest published series of these patients, though, only 1 of the 11 reported patients had PV as an explanation for nephrotic syndrome. While the natural history of this condition is uncertain, in a patient being evaluated for new proteinuria with the right clinical findings, PV should be included in the differential diagnosis. Further study of these patients will help us further understand the pathophysiology of the disease and whether treatment of the PV improves renal outcomes.

TH-PO212

Rituximab as Rescue Therapy for Difficult to Treat Lupus Nephritis: A Case Series

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Background: Conventional treatment of lupus nephritis with antimetabolites, calcineurin inhibitors, and steroids may be associated with intolerable adverse events or treatment resistance. We present a case series of patient characteristics and treatment response to rituximab therapy in three patients with resistance or intolerance to conventional lupus nephritis therapy at our center.

Methods: Patient data for three lupus nephritis patients who were treated with rituximab was obtained from retrospective chart review. Student t-test was used for comparison of means. Demographic serological, clinical characteristics and indications for rituximab therapy are presented in (Table 1). There was a non-statistically significant improvement between pre-rituximab serum creatinine (sCr) (1.26 ± 0.18 mg/dl) and post-rituximab sCr (1.00 ± 0.3 mg/dl, p=0.153) and pre and post rituximab degree of proteinuria (1664 ± 1278 vs 739 ± 595 mg/g, p=0.18). There was a statistically significant improvement in pre and post rituximab serum complement C3 (66 ± 45 vs 94 ± 42 mg/dl, p=0.003) and serum complement C4 levels (10.7 ± 5.5 vs 22.3 ± 11.2 mg/dl, p=0.04). The average time to treatment response, defined as 50% reduction in proteinuria, and serological increase in complement levels, was 7 months. There were no adverse events reported. There was a clinically significant reduction in immunosuppression and medication side effects as well as tolerance (Table 1).

Results:

Conclusions: In conclusion, rituximab as a "rescue" therapy was efficacious and well tolerated in our patients. More research is required to ascertain the clinical and serological characteristics of patients with lupus nephritis who may benefit from rituximab therapy.

Table 1: Demographic, Serological and Clinical characteristics

Case Number	Demographics: age(years), ethnicity, gender	Lupus Nephritis Class	Pre-Rituximab Regimen, Total daily dose in mg (miligrams)	Post-Rituximab Regimen, Total daily dose in mg (miligrams)	Rituximab Indication*,**	Time to Peak Response (months)	Serology Profile
1	27, White, Female	4	Prednisone 10 mg Mycophenolate 3000 mg Tacrolimus 3 mg	Prednisone 1mg Mycophenolate 1000 mg	Treatment failure, osteoporosis, cushing syndrome	8	ANA (-), dsDNA (-)
2	54, Black, Male	4	Prednisone 5 mg Mycophenolate 2000mg - intolerant* Azathoprine 100mg - intolerant* Hydroxychloroquine 800mg	Prednisone 5mg Hydroxychloroquine 400mg	Multiple infections, Treatment failure	10	ANA (+), dsDNA (+), RNP (+), SSa/SSb (+)
3	25, Black, Male	4+5	Prednisone 10 mg Mycophenolate 2000 mg Tacrolimus 3 mg	Prednisone 5 mg Mycophenolate 2000mg Tacrolimus 1.5 mg	Multiple infections, Treatment failure	4	ANA (+), dsDNA (+)

*Intolerance secondary to multiple infections (empyema, pyelonephritis)

**All patients were given rituximab 1gram IV x 2 doses

TH-PO213

Unusual Case of Lupus Nephritis with Negative Serology

Eddy J. De jesus, Bindu Goel, Rabih Nasr. *Bronx Lebanon Hospital, Bronx, NY.*

Background: Lupus Nephritis (LN) is a common complication of Systemic Lupus Erythematous (SLE) and occurs in 43-55% of the cases, usually in first year of the disease. It is one of the highest predictors of morbidity and mortality, and thus requires prompt diagnosis and treatment

Methods: We report a case of a 25 year old hispanic female presenting to the nephrology clinic referred due to episodes of gross hematuria for 2 months followed by persistent asymptomatic microhematuria and proteinuria of 2g/day, In the initial workup she was found to have proteinuria up to 2 grams/day and further autoimmune workup revealed positive anti-myeloperoxidase of 115. She did not have any history of diabetes or hypertension, no edema, serum creatinine of 0.8 mg/dl, urinalysis 1-2+ protein microhematuria, no RBC cast, urine total protein/creatinine ratio 2.0 gm, serum albumin 3.6 g/dl, with positive anti-MPO ANCA, negative ANA, Hepatitis B Virus(HBV) and Hepatitis C. Initially she was suspected to have microscopic polyangiitis however kidney biopsy was done and revealed membranous and focal segmental endocapillary and extra capillary proliferative and sclerosis glomerulonephritis, immune complex type, suggestive of class V and III of moderate activity and moderate chronicity, and mild tubulointerstitial atrophy with P-ANCA/Anti MPO antibody associated/clinical. Since biopsy was suggestive of Lupus Nephritis, comprehensive serologies were sent once again and reported as negative for ANA, anti-ds DNA, Sm, RNP, SSA-SSB, cardiolipin and included normal complements. Patient was started on Mycophenolate Mophetil and prednisone (tapering) One year after diagnosis patient still denies any constitutional symptoms, rashes, photosensitivity, oral ulcers, joint pain/swelling or weight loss

Results:

Conclusions: Lupus Erythematous (SLE), is a heterogeneous autoimmune disease that affects multiple organs and particularly the kidneys. Fortunately anatomical and pathologic markers of Lupus nephritis are quite specific. Rare cases such as the one from Chi Young Park et al, where there is pathological confirmation of LN but negative serology have been reported. Nephrologists should still have high suspicion of Lupus nephritis in any patient that presents with proteinuria and hematuria and negative serology as limited data is available as it has shown poor prognosis.

TH-PO214

Podocytes Contact with the Mesangial Cells at the Mesangial Interposition in a Case of Human Lupus Nephritis: Three-Dimensional Observation by Serial Block-Face Scanning Electron Microscopy Takashi Takaki,[1] Nobuhiko Ohno,[2] Sei Saitoh,[3] Masaaki Nagai,[4] Kensuke Joh.[5] *[1]Showa University, Tokyo, Japan; [2]Jichi Medical University, Shimotsuke-shi, Japan; [3]National Institute for Physiological Sciences, Okazaki, Japan; [4]Narita Memorial Hospital, Toyohashi-shi, Japan; [5]Tohoku University Graduate School of Medicine, Sendai-city, Japan.*

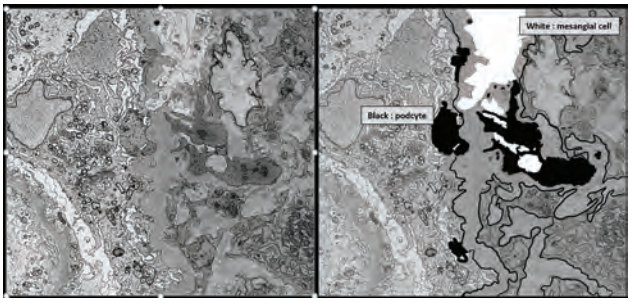
Background: We employed serial block-face scanning electron microscopy (SBF-SEM) to examine the three-dimensional relationships among the cells and extracellular matrix in a case of human lupus nephritis.

Methods: A 25 year-old female, who presented nephrotic syndrome, microscopic hematuria 10-20/hpf, and hypocomplementemia with C3 47 mg/dl and C4 4 mg/dl. Anti-nuclear antigen titer and anti ds-DNA titer were x640 and 191 mg/dl, respectively. Renal biopsy revealed membranoproliferative glomerulonephritis like lesion of lupus nephritis, Class IV A/C in light microscopy. The detail of ultrastructural morphology was almost similar to that of TEM excepting a thicker staining on the nuclear membrane and thinner staining of immune deposits. Using SBF-SEM, we followed the localization of the cytoplasmic processes of the podocyte, which invaded into the lamina densa of the glomerular basement membrane (GBM) and penetrated finally into the mesangial matrix. On the other hand, mesangial interposition was seen of varying length beneath the lamina densa of the GBM along the glomerular capillary loop. The mesangial cells, which were recognized in the extended mesangial matrix as having dense patch on the cytoplasmic membrane, showed a proliferative change. We followed the cytoplasmic process of the podocyte penetrating into the mesangial matrix and have succeeded to find a manifestation of direct cytoplasmic contact of the podocytes with the cytoplasm of the mesangial cells (Figure).

Results:

Conclusions: Since a direct contact between podocytes and mesangial cells was found, it is easier to understand an effect of podocytes on the mesangial cells by assuming an intercellular signaling communication, which may result in a proliferation of the mesangial cells and an overproduction of the extracellular matrix. This finding provides a new insight on a mechanism of a progression of glomerular sclerosis via podocyte-mesangial interaction.

Funding: Government Support - Non-U.S.



TH-PO215

Primary Tubulointerstitial Lupus Nephritis Complicated by Diffuse Alveolar Hemorrhage Farhan Qadeer,[1,2] George P. Bayliss,[1,2] Sairah Sharif.[1,2] *[1]Alpert Medical School, Brown University, Providence, RI; [2]Rhode Island Hospital, Providence, RI.*

Background: Lupus nephritis (LN) most often affects the glomerulus. While tubulointerstitial nephritis (TIN) commonly accompanies glomerular lesions, predominant and isolated TIN is extremely rare. Here we describe the case of a woman with systemic lupus erythematosus (SLE) who presented with respiratory failure and acute kidney injury due to isolated TIN.

Methods: A 39 year old Caucasian woman with history of SLE for 7 years without renal involvement was admitted with complaints of abdominal pain, vomiting, diarrhea, fevers up to 103 F for 3 days. She took ibuprofen for symptoms. Physical examination revealed blood pressure 110/57, heart rate 116, temperature 98.6 F. She had right-sided basilar crackles and no edema. Lab data showed white blood cell 1.0/μl, platelet 200 x10^4/μl, hemoglobin 10.2gm/dl, blood urea nitrogen 58mg/dl, creatinine 3.7mg/dl, elevated titers of anti-ANA (1:10240) and anti-double stranded-DNA antibodies (25IU/ml); low C3 and C4. Urine sediment showed granular casts, no dysmorphic red blood cells. She was treated with penicillin for streptococcus bacteremia and received empiric high-dose corticosteroids after undergoing a renal biopsy. On hospital day 4 she developed respiratory distress and hypotension, requiring intubation and ICU transfer. Diffuse alveolar hemorrhage was suspected on the basis of hemoptysis, and she was started on cyclophosphamide. Creatinine rose to 5.8mg/dL; she required hemodialysis for worsening metabolic acidosis, oliguria. Renal biopsy showed normal glomeruli, patchy interstitial inflammation on light microscopy; tubular basement membranes stained positive for IgG, IgM, C3, kappa and lambda on immunofluorescence. After 4 dialysis sessions, renal function improved to baseline and dialysis was stopped. She was extubated and eventually discharged on prednisone with stable renal function.

Results:

Conclusions: TIN along with glomerular lesions has been reported in SLE in up to 66% of biopsy samples, but isolated TIN LN without glomerular lesions is a rare entity. The pathogenesis may be due to circulating immune complexes or cytotoxic T-cell mediated injury. Patients usually present with subnephrotic-range proteinuria, renal tubular acidosis and hypocomplementemia. Most patients have been treated with corticosteroids with reasonable response. To our knowledge this is the first reported case of SLE-TIN with diffuse alveolar hemorrhage.

Funding: Clinical Revenue Support

TH-PO216

Novel PLG Gene Mutation with Heterozygous CHFR1-R3 Deletion in a Patient with Atypical Hemolytic Uremic Syndrome and Lupus Nephritis Huzair Ali,[2] Taseen A. Syed,[3] Joe Ghata,[1] Mubasher Abbas.[4] *[1]OUHSC, Oklahoma City, OK; [2]University of Oklahoma, Oklahoma City, OK; [3]University of Oklahoma Health Sciences Center, Oklahoma cty, OK; [4]University of Oklahoma College of Medicine, Oklahoma City, OK.*

Background: Thrombotic Microangiopathy (TMA) is a disease characterized by intravascular thrombosis, hemolytic anemia, and endothelial cell damage, often contributing to renal failure. Atypical Hemolytic Uremic Syndrome (aHUS) is a complement mediated TMA. Most genetic abnormalities linked to aHUS relate to dysregulation of these complement and coagulation pathways. We describe a case of aHUS with lupus nephritis in a patient with a unique set of mutations, including the plasminogen (PLG) gene, recently linked to aHUS.

Methods: 19 yo male presented with facial swelling, rash and fever for three days. On evaluation, he was in hypertensive emergency (>200/100mmHg), hypopigmented facial lesions with vitiligo on right ear. Labs demonstrated acute renal failure (Creatinine (Cr) 7.80mg/dL) requiring intermittent hemodialysis Work up revealed pancytopenia, ANA titer 1:320, positive schistocytes, low C3/C4 levels, normal ADAMTS13 activity, and negative infectious work up. Kidney biopsy showed diffuse proliferative glomerulonephritis consistent with Lupus nephritis (Class IV-A). Moreover, TMA affected the afferent arterioles. Renal Failure was refractory to PLEX, Steroids, Cellcept, and Rituximab. Renal Failure and hemolytic anemia only improved after Eculizumab, with Cr nadir to 2mg/dL upon discharge. Genetics later showed: **(1)** Heterozygous missense mutation of exon 2 & 10 of PLG gene, **(2)** Two polymorphisms in CFH gene, **(3)** Heterozygous polymorphism within an intron in MCP/CD46 **(4)** Heterozygous for the large CFHR1-CFHR3 deletion.

Results:

Conclusions: Mutations in the complement pathway have been described with atypical HUS. Coagulation pathway mutations are being linked with the pathogenesis of aHUS. Our patient developed renal TMA through complement dysregulation (via both classical & alternative pathways) likely through a double hit from Lupus nephritis flare, as well as underlying heterozygous genetic mutations (CHFR, CFH, & MCP/CD46 genes). In addition, dysregulation of the coagulation pathway through his PLG gene mutation likely contributed to his persistent renal TMA. This case suggests heterozygotes for these mutations may benefit from Eclizumab, especially in refractory cases of aHUS.

TH-PO217

A Unique Case of Sjogren's Syndrome-Associated Cryoglobulinemic Glomerulonephritis Brad Long, Ryan Morton, Catreena Marji, Monique E. Cho, Laith Al-Rabadi. *University of Utah Hospital, Salt lake, UT.*

Background: Cryoglobulinemic Glomerulonephritis is rare and not well described in the absence of Hepatitis C virus. Sjogren's syndrome continues to be the second most common cause of mixed cryoglobulinemia after hepatitis C virus (HCV). We present a unique case of Sjogren's disease and cryoglobulinemic glomerulonephritis

Methods: Patient is a 65 year old male patient with medical history relevant for Sjogren's disease and hepatitis C, in remission after treatment with interferon 10 years ago, presented to the outside hospital with a 5-day history of fatigue, headache, facial swelling and lower extremity rash. His physical exam was relevant for petechial rash involving his low extremities. Initial investigation revealed well preserved renal function with creatinine of 1 mg/dL. Urine protein was 1346 mg per gram of creatinine. Urine microscopy showed many non-dysmorphic RBCs with no cellular casts. Further workup showed ANA 1:2560, with positive SSA/SSB. The antibodies for GBM, dsDNA, RNP, ASO, Smith Ab, and ANCA were all negative. Complement 3 and 4 levels were 44 mg/dL and undetectable, respectively. HCV PCR was undetectable. Cryoglobulin from outside hospital was negative. Rheumatoid factor was elevated at 411 IU/mL. Immunofixation showed a faint band in the IgM kappa region. Light microscopy showed 15 glomeruli, many with lobular membranoproliferative pattern, mesangial and endocapillary hypercellularity. There was also evidence of focal intra-capillary eosinophilic material and hyaline pseudothrombi. Immunofluorescence showed granular mesangial and capillary wall staining for the following: 3+ IgM, 1-2+ IgG (segmental), 2+ C3, trace C1q, 2+ Kappa, and trace lambda. Electron microscopy revealed segmental immune-type subendothelial and mesangial electron dense deposits with no definite substructural organization. Repeat Cryoglobulin done at our hospital was positive. Patient was started on prednisone 60 mg and Azathioprine 100 mg daily. He had complete resolution of proteinuria and hematuria in one month

Results:

Conclusions: Elevated rheumatoid factor, and very low complement 4 level were the key for suspecting cryoglobulinemic glomerulonephritis despite the absence of impaired GFR. Cryoglobulinemia in this case is likely related to Sjogren's syndrome, not hepatitis C, given the undetected Hepatitis C PCR. Early treatment is crucial in preserving renal function

TH-PO218

Cryoglobulinemic Glomerulonephritis in a Patient with Sjögren Syndrome Ramon Noriega,[2] Tina Kochar,[2] Hania Kassem,[2] Adam J. Ward,[1] Marjan Afrouzian.[2] *[1]UTMB, Galveston, TX; [2]University of Texas Medical Branch, Galveston, TX.*

Background: Background: Sjögren's Syndrome (SS) is a disease characterized by lympho-plasmacytic infiltration of exocrine glands. Interstitial nephritis is the most common form of renal involvement in SS. Glomerular involvement including Membranoproliferative glomerulonephritis (MPGN) is relatively rare.

Methods: Case Description: A 73 yr old Caucasian female with past medical history of uncontrolled hypertension and SS presented with fluid overload. Physical examination revealed pulmonary crackles and peripheral edema. Laboratory analysis was significant for a creatinine of 1.5 mg/dL and urine protein to creatinine ratio of 2.5g/g. Urine microscopy revealed dysmorphic red blood cells. Serologies for hepatitis B, C, HIV, cryoglobulins and ANA were negative. Serum complements were low. **Pathology:** Light microscopy revealed 14 glomeruli with the following findings: global sclerosis (1), segmental sclerosis (4), endocapillary proliferation (5), and intracapillary coagula of cryoglobulins (4). Mild tubular atrophy/ interstitial fibrosis/ inflammation, mild arteriosclerosis and arteriolar onionskin pattern were also present. By immunofluorescence microscopy 12 glomeruli showed granular mesangial and capillary loop staining with IgG/Kappa/Lambda (+++), IgA and IgM (++), and C1q (+). Electron microscopic findings in 2 glomeruli included thickened glomerular basement membrane, mesangial interposition, subendothelial, subepithelial, and mesangial deposits of cryoglobulins. Cryoglobulinemic GN (secondary MPGN) in the background of SS was diagnosed.

Results:

Conclusions: Discussion: In our patient, glomerular involvement by MPGN, an uncommon pathologic manifestation of SS, was complicated by mixed cryoglobulinemia which was not detected in serum but noted on renal biopsy. This reflects the high incidence of false-negativity of serum cryoglobulin testing due to suboptimal specimen collection and handling. Our case highlights the importance of SS as a non-HCV-related cause of mixed cryoglobulinemia, and the significant role of renal biopsy. Renal insufficiency in patients with SS may not always be secondary to acute/chronic tubulo-interstitial nephritis or primary MPGN, but rather a secondary glomerular disease such as Cryoglobulinemic GN. Patient was started on prednisone with significant improvement in her symptoms and renal function and resolution of proteinuria.

TH-PO219

Necrotizing Crescentic Glomerulonephritis after Allogenic Stem Cell Transplant Shehryar Anjum, Lin Liu, Luis Bent-shaw. *Nephrology, University at Buffalo, Buffalo, NY.*

Background: Renal disease in Allogenic stem cell recipients involves glomerular, tubular /vascular injury triggered by chemo/radiation/infection/ischemia/GVHD & Immunosuppression. Rare reports of collapsing FSGS, Fibrillary GN & Anti GBM noted.

Methods: 61 y/o female with Myelodysplastic Syndrome treated with Azacitidine & Decitabine, complicated by refractory thrombocytopenia & anemia. Allogenic stem cell transplant (Brother) June, 2016, complicated by GVHD (Skin, GI and likely Lung). Hospital admissions for seizures due to PRES likely to Tacroliumus use, Influenza A & RSVpneumonia with subsequent pulmonary GVHD. She developed non oliguric AKI. Creatinine 1.1 -> 1.5. ROS -ve, v/s stable. Physical exam revealed no JVD, Chest with bibasilar crackles. S1, S2 noted, no S3. Abdomen benign, non tender. Lower extremity +2 pitting edema. Urine under light micro. revealed many WBC/ RBCs but no dysmorphic RBC or cast noted. U/S Renal reveals RT. kid12.8 cm & LT. kid 14 cm, minimal increased echogenicity. No hydronephrosis. Subsequent large epistaxis relieved with nasal packing & transfusing platelets. Transferred to ICU for seizures/confusion. With current picture, concerns for TTP/HUS. Plasmapheresis started. Received 3 sessions + steroids with improved mental status. Cr 1.15 --> 4.5. ADAMST13 in limits. HIT +ve. Urine again revealed no casts however some dysmorphic RBC suspected. Initiated Hemodialysis due to her worsening renal parameters and oliguric state. She underwent Renal Biopsy which revealed 6/6 Glom. with Necrotizing Crescentic pattern, granulomatous interstit. inflammation & necrotizing vasculitis, moderate interstitial fibrosis and tubular atrophy, no glomeruli for IF. EM reveals disrupted, corrugated Basement membrane. Serologic studies negative except for anti-GBM(179). Started on oral Cyclophosphamide & prednisone, plasmapheresis resumed with no recovery. Treatment subsequently stopped & Steroids tapered off. Per Oncology team started weekly Rituximab 800 mg IV for chronic GVHD. Patient remains dialysis dependent for>8 weeks now deemed ESRD.

Results:

Conclusions: Rare case of RPGN with anti-GBM following allogenic stem transplant as a potential complication of GVHD. Interestingly our patient had clinical Pulmonary GVHD. Exposure of collagen type Iv alpha 3 epitope due to immune injury is speculated mechanism however unclear if true relation with Stem cell transplant/GVHD & Anti GBM disease.

TH-PO220

A Rare Case of Crescentic Glomerulonephritis Mimicking Multiple Myeloma Alinda M. Sarma,[1] Mohammad Alomari,[1] Anca C. Vlasie.[2] *[1]Cleveland Clinic, Cleveland, OH; [2]Comprehensive Kidney Care, Westlake, OH.*

Background: We describe a unique case of biopsy proven crescentic glomerulonephritis with an earlier presumptive diagnosis of multiple myeloma.

Methods: A 58 year old male with past medical history of hyperlipidemia and enlarged prostate was admitted to the hospital with worsening shortness of breath(SOB) and new onset generalized petechial non-pruritic rash. Vitals signs were temperature of 97.2 F, heart rate of 100 beats per minutes, and blood pressure of 112/64 mm Hg. Physical exam showed diffuse, raised, non-blanching, rash involving palms and soles, diffuse crackles on lung auscultation and bilateral foot drop. Initial laboratory studies showed hemoglobin of 8.3 g/dl, leukocytosis of 28,000(k/uL), severe acute kidney failure with creatinine of 12 mg/dl, and uric acid of 15 mg/dL. Urinalysis showed many RBCs and mild proteinuria without any cast. Based on sudden bilateral foot drop, anemia, axonal acute to sub-acute sensorimotor peripheral polyneuropathy on electromyography and elevated kappa to lambda ratio in blood workup, a presumptive diagnosis of multiple myeloma was made as an outpatient. On the day of bone marrow biopsy, patient developed severe SOB, confusion, and was brought to the hospital. On further inquiry, he endorsed a history of recurrent sinusitis for many years. Imaging studies including chest radiography, chest CT scan, brain CT scan and renal US were unremarkable. Bronchoscopy was done due to ongoing SOB, which showed diffuse alveolar hemorrhage. Further work-up showed a positive C-ANCA titer and elevated proteinase 3 antibodies. Subsequently kidney biopsy was done which was consistent with pauci-immune necrotizing crescentic glomerulonephritis(CrGN) with necrotizing arteritis. He responded very well to plasmapheresis, pulse dose steroid and cyclophosphamide.

Results:

Conclusions: Both ANCA –positive CrGN and mutiple myeloma can present with systemic manifestations of renal failure, peripheral neuropathy and skin lesions. An elevated kappa lambda ratio in this context can often perplex the clinical scenario. Careful history and serologic markers often aid in separating one from another. However, a kidney biopsy remains the gold standard in distinguishing amongst variants of RPGN to guide therapy and estimate prognosis. Prompt and aggressive plasmapharesis in addition to pulse therapy with cyclophosphamide can reverse kidney injury to a large extent.

TH-PO221

The "M" Factor: An Insight into IgM Nephropathy Divyanshu Malhotra, Randy L. Luciano. *Yale New Haven Hospital, New Haven, CT.*

Background: Nephrotic syndrome is an important clinical entity with multiple manifestations and a variety of causes. In addition to MCD, three other disorders causing a picture of nephrotic syndrome present initially with minimal changes on light microscopy. These include idiopathic mesangial proliferative glomerulonephritis, IgM nephropathy and C1q nephropathy. There is a controversy regarding these being a part of the spectrum of MCD/FSGS versus being separate clinical entities. We present a series of 2 patients with IgM nephropathy and their interesting clinical course.

Methods: Case 1 61 y/o male with DM who had initially presented with lower extremity edema, scrotal swelling and was found to have 3+ proteinuria. His further w/u revealed Hepatitis C Genotype 1b infection. He had a kidney biopsy which was consistent with IgM nephropathy and early diabetic nephropathy. Initially it was thought that this was secondary to the hepatitis C. He received Ledipasvir/Sofosbuvir for the Hepatitis C with SVR. This led to proteinuria resolution but recurrence in 3 months. Started on prednisone which controlled the proteinuria but with recurrence when he tapered off steroids. He had a another biopsy which showed evidence of IgM nephropathy again. He was then started on Cellcept and currently remains in remission on the same. Case 2 22 y/o male who came to our clinic with a diagnosis of FSGS and nephrotic syndrome. He had been steroid dependent with frequent relapses off prednisone. Repeat biopsy showed evidence of IgM nephropathy concomitant with FSGS. He was switched to Cellcept leading to remission but with relapse requiring steroids. His course waxes and wanes on cellcept and we have planned for an extended genetic testing panel for podocyte specific genes.

Results:

Conclusions: IgM nephropathy is a rare condition and has been a controversial entity since its first description. It is characterized by prominent diffuse mesangial deposits of IgM +/- complement, along with electron dense deposits in the mesangium. Limited case series suggest that it is typically more steroid resistant than idiopathic MCD. Progression to FSGS is possible in a number of cases. Exact pathophysiology and relationship to FSGS is not well defined. Clinical progression is intermediate between MCD and FSGS. Multiple steroid sparing immunosuppressants have been tried with variable responses thus it can be a challenging disease to manage as seen in our cases too.

TH-PO222

A Case of Low-Dose Rituximab for the Treatment of Steroid Resistant Nephrotic Syndrome Marie Murata,[5] Daisuke Ichikawa,[2] Tomo Suzuki,[6] Shiika Watanabe,[4] Mikako Hisamichi,[3] Yugo Shibagaki.[1] *[1]Division of Nephrology and Hypertension, St Marianna University Hospital, Kawasaki, Japan; [2]St Marianna University of Medical School, Yokohama City, Japan; [3]St.Marianna university school of medicine, Kawasaki, Japan; [4]the Kawasaki Municipal Tama Hospital, Kawasaki Citiy Tama Ward, Japan; [5]St.Marianna medical school of medicine, Kawasaki, Japan; [6]Kidney and Vascular Pathology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan.*

Background: The efficacy of rituximab for frequent relapsing nephrotic syndrome has been reported. Some reports have a use of low dose rituximab for treatment of the ABO incompatible kidney transplant patients. Rituximab dosage of 100 mg/body was administered, which led to immediate depletion of CD20-positive cells. Therefore, a low dose rituximab may have a possibility of same effect compared to the normal dose rituximab.

Methods: A 22-year-old Japanese man presented with severe peripheral edema within several days after onset. His past history is not in particular. Nephrotic syndrome was diagnosed and minimal change disease was diagnosed by renal biopsy.

Methyl-prednisolone was administered at 500mg/day for 3 days and prednisolone was administered at 1mg/kg/day. Nephrotic syndrome become a remission at 7 days, however nephrotic syndrome was replaced at 28 days. After that methyl-prednisolone was administered at 500mg/day for 3 days two times and cyclosporine was added however, nephrotic syndrome was not improved. An initial rituximab dosage of 100 mg/body was administered. Two weeks later, urinary protein was 1g or less. Rituximab dosage of 100 mg/body was administered. Two months later, it became possible to taper prednisolone by 5mg. Six months later, it became possible to taper off prednisolone. He maintains remission of nephrotic syndrome by administering of rituximab dosage of 100 mg/body every four months.

Results:

Conclusions: Low dose rituximab might be an option for the treatment of steroid-resistant nephrotic syndrome. It was expected a reduction of the cost-effectiveness and side effect of rituximab. This case could be steroid dependent nephrotic syndrome from this history, therefore low dose rituximab might be an option for maintenance of steroid dependent nephrotic syndrome.

TH-PO223

A Case of Rapid Remission Proteinuria with Ace Inhibitor Monotherapy in HIV Associated Minimal Change Disease Alfonso D. Moreno, Janice B. Desir, Juan P. Vera-Gomez, Libardo Rueda prada. *St Barnabas Hospital, Bronx, NY.*

Background: The use of antiretroviral drugs among HIV patients has been associated with a number of renal toxicities including proteinuria. Minimal-change disease (MCD) with nephrotic syndrome in this population has also been described, though uncommon. First line therapy includes corticosteroids with a need for prompt and efficient management since this is linked with increased mortality and poor outcomes. However, there is a higher chance for opportunistic infections with HIV. Here we report an atypical case of HIV associated MCD on Atripla (tenofovir/emtricitabine/efavirenz) with rapid remission of proteinuria on monotherapy with angiotensin converting enzyme (ACE) inhibition.

Methods: A 45-years old man with HIV-1/AIDS (diagnosed 2011) initially presented July 2016 to HIV clinic with three-week bilateral lower extremity edema. Screening labs showed creatinine 0.9 mg/dl, albumin 2.2 mg/dl, proteinuria >500 mg/dl and total cholesterol 274 mg/dl. His antiretroviral therapy with Atripla was switched to Triumeq (abacavir/dolutegravir/lamivudine). He returned September 2016 with temporal resolution of his peripheral edema and nephrotic range proteinuria at 13 g/L. He was hospitalized October 2016 with an unremarkable physical exam, and negative autoimmune workup. Pertinent findings included albumin 1.1 mg/dl and creatinine 0.9 mg/dl. Nephrology was consulted for ongoing nephrotic syndrome and renal biopsy showed podocytes with 90% foot process effacement consistent with MCD. The patient was discharged home with Lisinopril 2.5 mg and Lasix 40 mg daily. On November 2016 labs showed significant improvement of his proteinuria to 0.74 g/L. His Lisinopril was increased to 10 mg daily and he continued with Lasix. Recent follow up documented on April 2017 showed a urinalysis with 100 mg/dl.

Results:

Conclusions: In closing, it is important to consider optimization of ACE inhibitors or angiotensin II blockers as alternate therapy to corticosteroids among HIV infected patients with MCD. One isolated case of rapid decline of proteinuria exists in a diabetic patient with no literature seen in HIV. This case illustrates the need for additional research into the impact of therapy with sole ACE inhibition in lieu of corticosteroids for the treatment of MCD and other glomerular diseases associated with nephrotic proteinuria among this group.

TH-PO224

Role of DJ-1(PARK7) in Hepcidin-Mediated Protection of AKI in a Murine Model of Sepsis (LPS) Joseph T. Leeds,[3] Yogesh M. Scindia,[2] Saleh Mohammad,[3] Valentina Loi,[1] Ewa U. Mandziak,[3] Sundararaman Swaminathan.[3] *[1]AO Brotzu Cagliari, Cagliari, Italy; [2]Univerisity of Virginia, Charlottesville, VA; [3]University of Virginia, Charlottesville, VA.*

Background: Acute Kidney injury is a frequent complication of Sepsis and is associated with increased comorbidity and mortality. A new paradigm of sepsis-induced AKI suggest that responses to tubular injury with an uncontrolled pro-inflammatory response (TNFα, IL-6, IL-10) can further renal damage. Previously we have shown that Hepcidin (Hamp), an endogenous peptide which controls systemic and local iron homeostasis, ameliorates ischemia-reperfusion injury and LPS induced AKI, by reducing renal oxidative stress, inflammation and apoptosis. DJ-1 is an anti-oxidant protein that is expressed in the brain and kidney and known to reduce oxidative stress via multiple mechanisms. Importantly it is a positive regulator of glutathione peroxidase 4 (GPX-4) a protein implicated in Ferroptosis (Iron-mediated cell death).

Methods: C57BLK/6 (WT) and DJ-1 knockout mice on B6 background were injected with PBS or 50 ug of Hamp (i.p) and 24 hours later administered 6.5mg/kg LPS (i.p). Tissue were harvested 24 hours after LPS administration for measuring renal function, injury, and inflammation.

Results: Compared to PBS, Hamp pretreated WT mice were protected against LPS-induced AKI as indicated by significantly lower plasma creatinine (WT PBS+ LPS 1.11 ± 0.17 Vs Hamp + LPS 0.41 ± 0.03; p= <0.0001), NGAL and KIM-1 levels. Hamp + LPS treated animals also had less infiltrating neutrophils and CD11b positive cells compared to PBS + LPS treated ones. Hamp + LPS treated mice had significantly lower splenic IL-6, IL-10 and IL-22 mRNA levels compared to PBS + LPS. In contrast to WT mice, Hamp failed to protect DJ-1 KO mice against LPS induced AKI. DJ-1 KO mice treated with PBS or Hamp had comparable plasma creatinine (DJ-1 KO PBS + LPS; .95 ± 0.06 Vs Hamp + LPS 0.85 ± 0.15; p= 0.7776), NGAL, KIM-1 and infiltrating cells. The splenic inflammatory signature was also comparable between the two groups.

Conclusions: Hepcidin protects against LPS-induced AKI by reducing systemic inflammation. The protective effect of Hamp seems to be dependent DJ-1, as loss of DJ-1 in mice abrogated Hamp's protective effect.

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TH-PO225

Mitophagy Is Activated to Protect against Iodionated Contrast-Induced AKI Shaobin Duan,[1] Rong Lei,[1] Fei Zhao,[1] Min Luo,[1] Wei X. Li,[1] Wei Cheng,[1] Chengyuan Tang,[1] Zheng Dong,[2] Lin Sun,[1] Hong Liu.[1] *[1]Department of Nephrology, The Second Xiangya Hospital, Central South University, Changsha410011, China, Changsha, China; [2]Georgia Regents University, Augusta, GA.*

Background: Contrast induced-acute kidney injury (CIAKI) is one of the most commmon causes of acute kidney injury in hospitalized patients, but the underlying pathogenesis is poorly understood. And there are little reports about the regulation and role of mitophagy in CIAKI.

Methods: The establishment of damaged cells model was performed. The cell viability, expression of LC3II/I and parkin, cleaved caspase 3, mitochondrial ROS, mitochondrial membrane potential, colocalization of LC3-FITC and parkin-FITC with mitotracker-red mitochondria, formation of autophagosome and mitophagy were measured. The Rapamycin (Rap) and 3-Methyladenine (3-Ma) were used to enhance and inhibit the formation of autophagososmes respectively. Male SD rats were deprived of water for 48 h and followed by furosemide (10 ml/kg) for 20 minutes before iohexol (15 ml/kg) administration to build CIAKI models. Pretreatmemt with Rap or 3-Ma was used at 1 h before iohexol injection. Serum creatinine were measured before and 24 h after the injection of iohexol. Kidney tissues were collected for HE staining, electron microscope examination and expression of LC3II/I, P62, Cleaved Caspase3, Parkin.

Results: Iohexol and iodixanol dose-dependently decreased cell ciability, also induced mitochondrial damage, cell apoptosis and mitophagy. Enhancing mitophagy with Rap markedly increased expression of LC3II, Parkin and formation of autophagosome and mitophagy, reversed iohexol induced apoptosis. Rap also significantly decreased expression of cleaved caspase 3 and serum creatinine. LC3-FITC and parkin-FITC puncta colocalization with mitotracker-red mitochondria were increased. In contrast, inhibiton of mitophagy with 3-Ma displayed increased serum creatinine, apoptosis and expression of cleaved caspase 3, decreased expression of LC3II and formation of autophagosome and mitophagy, compared with iohexol group.

Conclusions: Autophagy and mitophagy play an important role in mitochondrial quality control, tubular cell survival, and renal function during CIAKI. Enhancing mitophagy may offer a novel therapy for CIAKI.

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TH-PO226

Deletion of Sirtuin-5 (Sirt5) Protects Mice Against Ischemia-Reperfusion Kidney Injury Eric S. Goetzman,[1,2] Katherine V. Maringer,[1,2] Sivakama S. Bharathi,[1,2] Elina Mukherjee,[1,2] Sunder Sims-Lucas.[1,2] *[1]Children's Hospital of Pittsburgh, Pittsburgh, PA; [2]University of Pittsburgh, Pittsburgh, PA.*

Background: Sirtuin-5 (Sirt5) is a deacylase enzyme that reverses the post-translational succinylation of lysine residues. Sirt5 is highly expressed in the kidney. In liver Sirt5 promotes function of the respiratory chain and of the mitochondrial fatty acid oxidation (FAO) pathway. While mitochondrial FAO is a critical source of energy for the proximal tubule, the role of Sirt5 in regulating kidney FAO during acute kidney injury (AKI) has not been investigated.

Methods: Sirt5 knockout mice (Sirt5KO) were subjected to ischemia-reperfusion kidney injury followed by contralateral nephrectomy on Day 6 and tissue harvest on Day 7. The oxidation of ^{14}C-palmitate was used to follow FAO. Immunofluorescence was used to visualize mitochondria and peroxisomes, the two intracellular sites of FAO, in proximal tubules. Kidney injury markers were assessed by immunofluorescence and real-time PCR.

Results: Sirt5KO kidneys had reduced mitochondrial staining and reduced mitochondrial FAO at baseline. Conversely, peroxisome staining and peroxisomal FAO were increased. Despite compromised mitochondrial function, Sirt5KO mice exhibited significant protection against AKI. Day 7 post-injury serum creatinine was significantly lower than in wild-type mice. Tissue staining indicated less tubular damage, less fibrosis, and less inflammation. There was markedly less expression of kidney injury molecule-1 (Kim1) and activated caspase-3. Day 7 wild-type tubules showed abundant mitochondrial staining but a near-complete loss of peroxisomes, while Sirt5KO tubules showed peroxisomes but a loss of mitochondria. Peroxisomal FAO in Sirt5KO kidney was several-fold higher than in wild-type kidney. Finally, we observed Sirt5 protein in purified wild-type kidney peroxisomes suggesting that Sirt5 may serve to coordinate FAO between intracellular compartments.

Conclusions: Deletion of Sirt5 limits kidney injury in response to ischemia-reperfusion, the opposite of what has been reported in in knockouts of other sirtuins such as Sirt1 and Sirt3. Absence of Sirt5 compromises mitochondria but stabilizes peroxisomes. Given previously published obserations that peroxisomal abundance is associated with better outcomes from AKI, we propose that metabolic switching from mitochondria to peroxisomes is the mechanism by which deletion of Sirt5 is beneficial during ischemia-reperfusion injury.

Funding: NIDDK Support

TH-PO227

PINK1-Parkin Pathway of Mitophagy Is Activated to Protect against Renal Ischemia/Reperfusion Injury Chengyuan Tang,[1] Fuyou Liu,[1] Zheng Dong.[1,2] *[1]Department of Nephrology, The Second Xiangya Hospital of Central South University, Changsha, China; [2]Department of Cellular Biology & Anatomy, Medical college of Georgia at Augusta University and Charlie Norwood VA Medical Center, Augusta, GA.*

Background: Mitochondrial damage contributes to the pathogenesis of acute and chronic kidney diseases. Damaged or dysfunctional mitochondria are toxic to the cell by producing reactive oxygen species and releasing cell death factors. Therefore, timely removal of these organelles is critical to cellular homeostasis and viability. Mitophagy is the mechanism of selective degradation of mitochondria via autophagy. A major mitophagy pathway in mammalian cells is mediated by PINK1 and Parkin. The significance of mitophagy in kidney diseases, including ischemic acute kidney injury (AKI), has yet to be established, and the involved pathway of mitophagy remains poorly understood. In this study, we examined PINK1- and Parkin- mediated mitophagy in the acute kidney injury (AKI) model of renal ischemia-reperfusion.

Methods: PINK1 and Parkin single or double knockout mice were compared to their matched wild-type mice for the response to 30 minutes of bilateral renal ischemia followed by 48 hours of reperfusion. Renal function, histopathology, biochemical analysis and electron microscopy analysis were performed to evaluate the effect of PINK1 and Parkin deletion. In *vitro*, HK-2 cells were subjected to ATP depletion/repletion treatment with CCCP (mitochondrial uncoupler) to examine the effects of PINK1 and Parkin knockdown.

Results: Mitophagy was induced in renal proximal tubular cells in both *in vitro* and in *vivo* models of ischemic AKI, as evidenced by: (1) increased autophagy flux, (2) decreased expression of mitochondrial membrane proteins TOM20 and TIM23, and (3) increased formation of mitophagosomes. Mitophagy under these conditions was abrogated by *PINK1* and *Parkin* deficiency, supporting a critical role of the PINK1/Parkin pathway in tubular cell mitophagy. Moreover, ischemic AKI was deteriorated in *PINK1* and *Parkin* single as well as double knockout mice, as indicated by aggravated functional or structural renal damage, and enhanced tubular cell death. Mechanistically, *PINK1* and *Parkin* deficiency enhanced mitochondrial damage, ROS production, and inflammatory response.

Conclusions: These results indicate that PINK1/Parkin-mediated mitophagy plays an important role in mitochondrial quality control, tubular cell survival, and renal function during AKI.

TH-PO228

HDAC2 Deletion Mitigates Renal Ischemia-Reperfusion Injury by Stabilizing the CoREST Complex David D. Aufhauser,[3] Douglas R. Murken,[3] Zhonglin Wang,[5] Guanghui Ge,[6] Seth Concors,[4] Tricia Bhatti,[2] Wayne W. Hancock,[1,3] Matthew H. Levine.[3] *[1]Children's Hospital of Philadelphia, Philadelphia, PA; [2]The Children's Hospital of Philadelphia, Philadelphia, PA; [3]University of Pennsylvania, Philadelphia, PA; [4]University of Pennsylvania Health System, Philadelphia, PA; [5]University of Pennvania, Philadelphia, PA; [6]Surgery, University of Pennsylvania, Philadelphia, PA.*

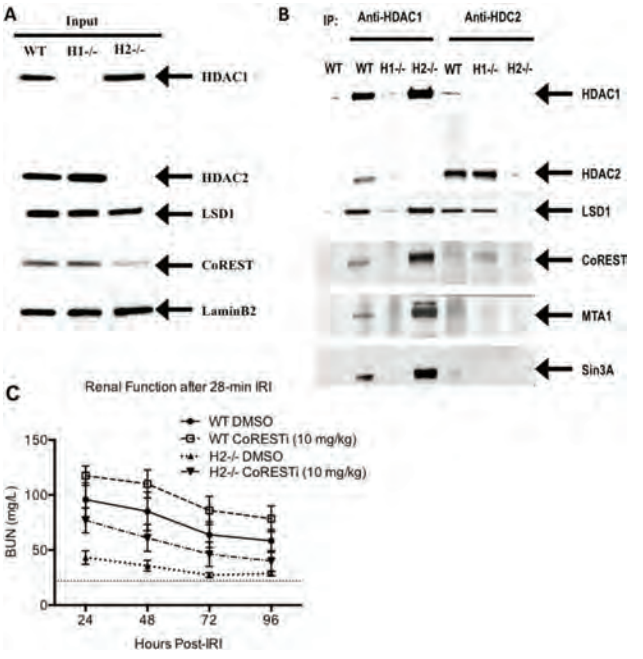
Background: Class I histone/protein deacetylases (HDAC) 1 and 2 have reciprocal effects on renal ischemia-reperfusion injury (IRI) with HDAC1 deletion increasing vulnerability and HDAC2 protection providing profound protection. HDAC1 and 2 typically interact as heterodimers in multimeric corepressor complexes and are conventionally been viewed as functionally redundant.

Methods: Wild type C57BL/6 (WT) and whole animal-inducible HDAC1- or 2- gene deleted mice (HDAC1-/- or HDAC2-/-) were used in this study. Primary renal tubular epithelial cell (RTEC) cultures were derived from each genetic strain for protein analysis via Western blot. Standardized warm renal IRI was achieved through unilateral clamping of the renal pedicle and contralateral nephrectomy.

Results: In nuclear extracts, HDAC1 and 2 deficient RTEC have compensatory enhanced protein expression of the other (Fig 1a). HDAC1 pulldown in HDAC2 deficient RTEC demonstrated enhanced association with CoREST and LSD1 compared to wild type RTEC (Fig 1b). HDAC2 pulldowns in HDAC1 deficient RTECs showed no enhanced association with CoREST. *In vivo* CoREST inhibition increased vulnerability to renal IRI injury in both WT and HDAC2-/- mice and returned HDAC2-/- mice to a WT renal IRI phenotype (Fig 1c).

Conclusions: HDAC2 deletion leads to increased associated between HDAC1 and other members of the CoREST complex, indicating increased complex stability. Inhibition of the CoREST complex *in vivo* reverses the protection seen with HDAC2 deletion.

Funding: NIDDK Support



TH-PO229

Lysophosphatidic Acid Regulates FGF23 via LPAR1 in Response to AKI Petra Simic,[4] Wondong Kim,[4] Paola Divieti Pajevic,[1] Andrew M. Tager,[2] Harald Jüppner,[4] Marc N. Wein,[3] Eugene P. Rhee.[4] *[1]Boston University, School of Dental Medicine, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]MGH Endocrine Unit, Boston, MA; [4]Massachusetts General Hospital, Brookline, MA.*

Background: Lysophosphatidic acid (LPA) is one of the simplest phospholipids with a range of signaling actions throughout the body. It has been implicated as an important cofactor for calcitriol's effect on osteoblast differentiation *in vitro*, and LPA receptor 1 knock-out (*Lpar1*-/-) mice are known to have osteoporosis.

Methods: As FGF23 is a predominantly bone-derived hormone modulated by calcitriol, we have tested the effect of LPA on FGF23 production *in vivo* in C57Bl6 and *Lpar1*-/- mice and *in vitro* in a conditionally immortalized osteocyte cell line (Ocy454 cells).

Results: Exogenous LPA (50 mg/kg i.p. single dose) stimulated intact and C-terminal FGF23 production 2.4 fold in C57Bl6 mice as compared to vehicle treated mice (n=8 per group) at 24 hours (P=0.02). This effect was corroborated in Ocy454 cells, with a 10 fold increase in C-terminal and intact FGF23 protein levels 24 hrs following LPA treatment (P=0.05); this effect was specifically dependent on the LPAR1 receptor, as the effect of LPA on FGF23 was abolished in CRISPR generated *Lpar1*-/- Ocy454 cells but not in *Lpar4*-/- cells (the other major LPA receptor expressed in osteocytes). Next, we tested *in vivo* whether the effect of LPA on FGF23 is dependent on LPAR1, injecting *Lpar1*-/- mice or WT littermates with a single dose of LPA (50 mg/kg i.p.) or vehicle (n=8 per group). LPA increased serum FGF23 levels in WT, but not in *Lpar1*-/- mice (1215 ± 200 pg/ml vs. 664 ± 98 pg/ml, respectively, P=0.01) after 24 hrs. Finally, we subjected *Lpar1*-/- mice or WT littermates (n=4 per group) to AKI by performing 35 minutes of bilateral ischemia reperfusion injury (IRI). Circulating levels of FGF23 were 1.5 fold greater in WT mice as compared to Lpar1-/- mice following IRI (P=0.04).

Conclusions: In summary, LPA stimulates FGF23 production *in vitro* and *in vivo* via the LPAR1 receptor and the effects of AKI on FGF23 are attenuated in LPAR1 deficient mice.

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TH-PO230

Proximal Tubular Epithelial Expression of Kim-1 Causes Progressive Kidney Injury in Mice Wenqing Yin, M. Todd Valerius, Joseph V. Bonventre. *Brigham and Women's Hospital, Boston, MA.*

Background: Acute kidney injury (AKI) predisposes to the progression of chronic kidney disease (CKD) and the development of end stage renal failure. Previously, we had reported that early and persistent epithelial expression in nephrons of kidney injury molecule-1 (KIM1) causes murine kidney fibrosis, and zebrafish tubule damage through a mechanism involving mTOR. Since prenatal activation also decreases nephron number we tested the hypothesis that postnatal activation of KIM-1 expression specifically in renal proximal tubular epithelial cells would lead to fibrosis independent of any potential effect on kidney development.

Methods: We created proximal tubular cell specific KIM-1 transgenic mice by treating the Slc34a1 Cre-ERT2 mouse with tamoxifen to express KIM-1 in proximal tubules in a postnatal context. The resulting KIM-1^{PTCtg} transgenics (and non-KIM1

expressing controls) were subjected to bilateral renal ischemia-reperfusion injury for 26 minutes or sham surgery.

Results: KIM-1 was expressed on the proximal tubular cells after tamoxifen-induced Cre-ERT2 recombination starting at 4 weeks of age. Without any further intervention KIM-1^{PTCtg} mice developed fibrosis with progressive renal insufficiency at 6 months of age, while the kidney function and histology were close to normal at 3 months of age. Bilateral renal ischemia reperfusion injury in KIM-1^{PTCtg} kidneys at 3 months of age cause impaired repair with remained renal insufficiency, leading to progressive kidney fibrosis and renal failure.

Conclusions: Chronic activation of KIM-1 expression promotes kidney fibrosis and accelerates the progression of chronic kidney disease after acute kidney injury. Persistent expression of KIM-1 may play an important role on the link between acute kidney injury and progressive chronic kidney disease.

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TH-PO231

Dimethyl Fumarate Attenuates Renal Ischemia/Reperfusion Injury Yingchuan Li,[2,3] Junhui Li,[2,3] Hong Xue,[1] Feng Wang,[2] Julian H. Lombard,[1] Aron M. Geurts,[1] Kristie Usa,[1] Niansong Wang,[2] Mingyu Liang.[1,3] *[1]Medical College of Wisconsin, Milwaukee, WI; [2]Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China; [3]Physiology, Center of Systems Molecular Medicine, Medical College of Wisconsin, Milwaukee, WI.*

Background: Fumarate is an intermediary in the tricarboxylic acid cycle and can activate NRF2 and HIF-1a. Emerging evidence suggests fumarate might be involved in ischemia-reperfusion injury (IRI). It remains unclear whether fumarate is protective against acute kidney injury (AKI) resulting from renal IRI and what mechanisms might be involved.

Methods: Male SD or *Nrf2*$^{-/-}$ rats (~250g) were anaesthetized with ketamine. Sham operation (controls) or bilateral renal artery occlusion for 30 min followed by reperfusion (IRI) were performed. For pre-IRI treatment, dimethyl fumarate (DMF, 30mg/Kg), a fumarate precursor, or Vehicle was administered via intraperitoneal injection twice daily for 5 days before surgery. For post-ischemia treatment, DMF (30mg/Kg) or Vehicle was administrated at the time of 0 and 3 hours after reperfusion. Serum was collected 6 h or 24 h post-reperfusion and kidney collected 24 h post-reperfusion for analysis of renal function and kidney injury.

Results: Pre-treatment with DMF for 5 days attenuated subsequent renal IRI in rats. Serum creatinine (Scr) was 1.05±0.26 mg/dl and 1.42±0.42 mg/dl in DMF- and vehicle-treated rats, respectively (n=11, $p<0.05$). Tubular injury score (TIS) was 2.76±0.64 and 4.00±0.88 in the two groups (n=5, $p<0.05$). The attenuation of renal injury was associated with up-regulation of mRNA expression of *HIF-1a, NRF2* and their target genes *Hmox1* and *Nqo1* in kidney tissue. However, the effect of DMF pre-treatment on renal IRI was preserved in *Nrf2*$^{-/-}$ rats. Post-ischemia Treatment with DMF also significantly attenuated renal IRI. Scr was 1.08±0.46 mg/dl and 1.76±0.74 mg/dl in DMF- and vehicle-treated rats, respectively (n=8, $p<0.05$). TIS was 2.82±0.71 and 4.06±0.92 in the two groups (n=5, $p<0.05$). The post-ischemia treatment with DMF resulted in up-regulation of *NRF2, Hmox1* and *Nqo1,* but not *HIF-1a*. The protective effect of post-ischemia treatment with DMF on renal IRI was significantly attenuated in *Nrf2*$^{-/-}$ rats.

Conclusions: These results suggest fumarate could have preventive as well as therapeutic effects on AKI induced by IRI. The therapeutic, but not preventive, effect of fumarate depends on the presence of NRF2.

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TH-PO232

Identification of the RNA Interactome of Ciliated Tubular Cells and Its Modulation by Hypoxia Roman-Ulrich Mueller,[2] Rainer Kaiser,[2] Constantin Rill,[2] Francesca Fabretti,[2] Michael Ignarski,[2] Markus M. Rinschen,[2] Ilian Atanassov,[1] Bernhard Schermer,[2] Thomas Benzing.[2] *[1]Max Planck Institute for Biology of Aging, Cologne, Germany; [2]Renal Unit, University Hospital Cologne, Koeln, Germany.*

Background: RNA-binding proteins (RBPs) control the fate of all RNA species and every step of messenger RNA generation and processing. Through specific binding of their targets, RBPs heavily influence the cellular transcriptome and proteome. The scale of their impact has been shown by recent studies that have linked RBPs to a number of human pathologies, ranging from neurological disorders to tumor growth. The global effect of RBPs in kidney physiology has never been assessed until now. Here, we identify RNA binding proteins in renal epithelial cells under both hypoxic and normoxic growth conditions as well as candidate RBPs that may play key roles in hypoxia signaling of of the kidney.

Methods: Using an oligo(dT) capture approach to precipitate mRNA-protein complexes in ciliated mIMCD-3 cells, we aimed to identify the kidney-specific mRNA interactome using mass spectrometry. UV-crosslinked samples were either exposed to hypoxia (1% O_2) or grown under normoxic conditions. In parallel, the proteome of whole cell lysates was identified to assess the total amount of protein in comparison to RBPs detected under different conditions. Using TALEN-mediated genome engineering for the creation of transgenic human cell lines, specific candidates were validated as RNA binding protein with the Polynukleotide (PNK) assay. Subsequent immunofluorescence studies on the same cell lines revealed the localization pattern of these RBPs.

Results: Our data revealed over 350 significant mRNA interactors and more than 300 additional candidate RBPs, 84 of which have not been described as RNA binding proteins in common data bases. We define these proteins as the renal epithelial cell mRNA interactome. Based on whole cell proteome analyses we hypothesize that the increased detection of RBP candidates in the hypoxia-treated Oligo(dT) captured samples is indeed due to differential binding to their target transcripts.

Conclusions: RNA binding proteins are important players in general cell biology and may also play a key role in the cellular response to hypoxia of kidney cells. Our data identify the first set of RBPs specific to renal epithelial cells and aid to understand their role in both kidney physiology and pathology, adding another regulatory layer to the diverse biology of the kidney.

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TH-PO233

Reduced Heat Shock Protein 90α/Endothelial Nitric Oxide Synthase Interaction in the Heart Contributes to Cardiovascular Injury in the AKI to CKD Transition Isabel Amador-Martinez, Rosalba Pérez-villalva, Norma Bobadilla, Jonatan Barrera-Chimal. *Molecular Physiology Unit, Instituto de Investigaciones Biomédicas, UNAM and INNSZ, Mexico City, Mexico.*

Background: Acute kidney injury (AKI) is a recognized risk factor for chronic kidney disease (CKD) development. CKD is associated with cardiovascular alterations and the associated mechanisms remain largely unexplored. CKD patients display reduced nitric oxide (NO) levels. The endothelial nitric oxide synthase (eNOS) is regulated by phosphorylation and by its interaction with proteins such as heat shock protein 90α (Hsp90α). We investigated some modifications in the eNOS activation pathway that occur in the heart during the AKI to CKD transition.

Methods: We included 50 male Wistar rats that were divided into sham surgery (n=25) or rats subjected to bilateral renal ischemia-reperfusion (IR) of 45 min (n=25). The rats were studied at 1, 2, 3, 4 or 5 months post-surgery (n=5). Urinary protein excretion was monitored every month. After each experimental period, plasma creatinine, renal blood flow, mean arterial pressure levels and heart and renal weights were determined. The apical part of the heart was snap frozen for western blot analyses.

Results: CKD progression in the IR group was characterized by proteinuria that went from 26.5±8 at month-1 to 127.6±24 mg/24h at month-5. The renal dysfunction was only manifested after five months of follow-up as shown by a 50% increase in the plasma creatinine levels and a 30% reduction in the renal blood flow. In contrast, heart hypertrophy was observed since the 4th month after IR, as evidenced by a 24% increase in the heart/body weight ratio. Heart dysfunction and fibrosis were determined by a significant increase in brain natriuretic peptide and collagen I levels, respectively ($p<0.05$). Moreover, an increase in the phosphorylation of eNOS at threonine 495 (inactivating eNOS) was observed. This effect was associated with reduced eNOS/Hsp90α interaction.

Conclusions: The AKI to CKD transition is characterized by cardiac hypertrophy, dysfunction and fibrosis, even before the renal dysfunction is manifested. These alterations were associated with fewer eNOS activation and reduced eNOS/Hsp90α interaction in the heart, which may result in reduced NO bioavailability and endothelial dysfunction. PAPIIT: IA200117

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TH-PO234

Klotho Reduces Necroptosis by Inhibiting Oxidative Stress Involved in Renal Ischemic-Reperfusion Injury Yingying Qian, Leyi Gu, Zhaohui Ni. *Renji Hospital, Shanghai, China.*

Background: Klotho is mainly expressed in kidney, but its functional relevance with AKI remains largely unclear. Although necroptosis has been suggested as a hallmark of the pathological progress of renal IRI, it is currently unknown what triggers this death mode during I/R induced AKI and whether the protective actions of Klotho have any relationship to necroptosis.

Methods: Male BALB/c mice were grouped as AKI and sham group. AKI model was generated by bilateral renal pedicles clamping. For the therapeutical investigation, recombined Klotho protein or nec-1 was intraperitoneal applied at 30 min or 0 min of reperfusion respectively. Besides, TCMK-1 cell was suffered to hypoxia/reoxygenation or H_2O_2 insult for pre-determined time. Recombinant Klotho protein or NAC was pre-applied for 1 h. Klotho levels in serum and urine were determined using ELISA. Expression of Klotho, RIP1, RIP3, Il-1 ß, 3-nitrotyrosine and SOD2 were assessed by Western Blot or/ and Real-Time PCR. TUNEL staining and immunohistochemistry for Kim-1 and Klotho were performed. The release of LDH was measured to assess the membrane integrity. Urinary 8-OHdG, renal MDA levels and SOD activity were determined to detect oxidative injury.

Results: Klotho levels were decreased in serum and kidney, but increased in urine post-IRI, accompanied by enhancement of oxidative stress and necroptosis. In contrast, Klotho administration ameliorated AKI. Klotho application reduced the expression of RIP1, RIP3, and Il-1 ß, and the number of TUNEL positive cells. In TCMK-1 cell, Klotho downregulated the expression of RIP1 and RIP3, and attenuated the release of LDH induced by H/R or H_2O_2 insult by dose dependent. These functional effects of Klotho on necroptosis can also be duplicated by NAC application. These indicate a critical role of ROS in triggering necroptosis in tubular epithelial cell, which can be partly abolished by Klotho. In support of this, Klotho exerted an anti-oxidant role evidenced by reducing the levels of u-8-OHdG, renal MDA and 3-Nitrotyrosine, and upregulating SOD2 expression and total SOD activity in AKI mice. Meanwhile, Klotho also abolished the generation of ROS and increased the expression of SOD2 in TCMK-1 cell when exposed to H/R injury.

Conclusions: Klotho protects tubular epithelial cell from I/R-induced necroptosis, which may be attributable to its inhibition of oxidative stress.

TH-PO235

Nucleophosmin (NPM) Phosphorylation Mediates Renal Cell Death: A New Therapeutic Target for Ischemic AKI Zhiyong Wang,[1] Chinaemere Igwebuike,[3] Erdjan Salih,[5] Andrea Havasi,[4] Ramon G. Bonegio,[5] John H. Schwartz,[2] Steven C. Borkan.[1] *[1]BOSTON MEDICAL CENTER, BOSTON, MA; [2]Boston Medical Center-Evans Biomedical Center, Boston, MA; [3]Boston Univerisity School of Medicine, Boston, MA; [4]Boston University Medical Center, Boston, MA; [5]Boston University School of Medicine, Boston, MA.*

Background: We hypothesize that renal ischemia alters site-specific NPM phosphorylation, converting NPM from an essential protein synthesis promoter to a killer Bax chaperone that causes renal cell death and AKI.

Methods: To detect site-specific phosphorylation and de-phosphorylation events, NPM was subjected to mass spectrometry before and after ischemic stress in both cell and cortical lysates harvested from: (1) normal vs. ATP deplete primary mouse and primary human proximal tubule epithelial cells (PTEC), (2) sham vs. ischemic mouse kidneys and (3) two pairs of human donor kidneys rejected for transplantation. One of the paired human kidneys was normally perfused, whereas the other was grossly ischemic due to perfusion pump malfunction. Site-specific NPM phosphorylation events were correlated with NPM alterations that mediate its cell death including: nuclear translocation, de-oligomerization, NPM-Bax complex formation, and mitochondrial complex accumulation. To confirm their biologic significance, NPM mutants with site-specific phospho-changes were generated in lentivirus and introduced into PTEC. Peptides that interfere with NPM phosphorylation were tested for their ability to prevent ischemic PTEC death.

Results: Mass spectrometry identified 92% of NPM residues that included all known serine, tyrosine and threonine residues capable of undergoing phosphorylation or de-phosphorylation. Five serine/threonine phosphorylation and de-phosphorylation events differed between NPM harvested from normal vs. ischemic conditions. NPM phosphorylation events were identical in both murine and human NPM harvested from either primary PTEC or intact renal cortex. Only the NPM phospho-mutant that mimicked phosphorylation events detected during renal ischemia caused cytosolic NPM translocation and de-oligomerization, NPM interaction with conformationally active Bax, mitochondrial complex accumulation, and increased PTEC death. In contrast, 2 distinct NPM peptides designed to interfere with NPM phosphorylation protected PTEC against ATP depletion-induced death.

Conclusions: Ischemia-induced NPM phosphorylation regulates Bax-induced cell death and contributes to human AKI. This study identifies a new, modifiable cell death pathway and reveals novel therapeutic approach for preventing and treating ischemic AKI.

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TH-PO236

TSA Can Induce Autophagy to Protect against Cisplatin-Induced Apoptosis Jing Liu,[1,2] Man J. Livingston,[2] Zheng Dong.[2,1] *[1]Department of Nephrology, The Second Xiangya Hospital, Central South University, Changsha, China; [2]Augusta University Medical College of Georgia, Augusta, GA.*

Background: HDAC inhibitors have protective effects against tubular cell injury and death in acute kidney injury (AKI). However, the underlying mechanism remains elusive. Autophagy is known to be an important protective mechanism in AKI. Whether HDAC inhibitors regulate autophagy and protect renal tubular cells from injury via autophagy is currently unknown.

Methods: In vitro, rat proximal tubular cells (RPTCs) were treated with cisplatin to induce apoptosis. In vivo, C57BL/6 mice were injected with cisplatin to induce nephrotoxic AKI. The effect of the HDAC inhibitor Trichostatin A (TSA) was examined both in vitro and in vivo models. Chloroquine and kidney proximal tubule-specific ATG7 knockout (PT-ATG7-KO) mice were used to determine the involvement of autophagy in the protective effect of TSA.

Results: In RPTC, cisplatin induced autophagy in 8 hours, which decreased at 20 hours of treatment as indicated by the analysis of LC3 II accumulation and autophagic vesicle formation. At 20 hours, cisplatin induced significant apoptosis in RPTC as indicated by cell morphology and caspase activation. TSA treatment increased autophagy at both 8 and 20 hours of cisplatin treatment. TSA also attenuated cell apoptosis. Importantly, the protective effect of TSA in RPTC was suppressed by the autophagy inhibitor chloroquine and also by ATG7 knockdown. In mice, cisplatin induced autophagy and AKI. TSA further increased autophagy in kidneys during cisplatin treatment and protected against AKI. The protective effect of TSA was suppressed by chloroquine. Moreover, the protective effect of TSA was diminished in PT-ATG7-KO mice.

Conclusions: TSA induces autophagy in renal tubular cells, which accounts for the protective effect of TSA during cisplatin-induced AKI.

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TH-PO237

Extracellular Signal-Regulated Kinase 1/2 Regulates Kidney Injury Molecule-1 Following Renal Injury through STAT3 Phosphorylation Justin B. Collier,[1,2] Rick G. Schnellmann.[2] *[1]Medical University of South Carolina, Charleston, SC; [2]University of Arizona, Tucson, AZ.*

Background: Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein that is highly upregulated during injury and is a renal injury biomarker. Because KIM-1 transcription is highly induced, we explored the role of extracellular signal-regulated kinase 1/2 (ERK1/2) in KIM-1 expression in cells and in different mouse models of acute kidney injury.

Methods: Mouse kidney proximal tubule cells (TK) were treated with varying concentrations of hydroxyurea, hydrogen peroxide, and tert-butyl-hydroperoxide with and without pretreatment with the MEK1/2 inhibitor trametinib (10nM). Trametinib (1mg/kg) was administered 1 h before renal I/R injury to mice. Trametinib was administered 1 h prior to I/R injury or LPS (10 mg/kg) exposure to TLR4 KO and WT mice and euthanized 18 h later, respectively. KIM-1 mRNA was measured by RT-qPCR.

Results: Trametinib blocked ERK1/2 phosphorylation in all experiments. Toxicant exposure to TK cells for 24 h upregulated KIM-1 mRNA and was blocked by trametinib. At 3 and 24 h post renal I/R cortical KIM-1 mRNA increased 4- and 600-fold, and pretreatment with trametinib resulted in a 50% and 66% decrease, respectively, in induced KIM-1 mRNA. Trametinib also decreased KIM-1 protein 24 h post I/R. ERK1/2 phosphorylated the transcription factor STAT3 at sites, Y705 and S727, following I/R and was prevented by trametinib. WT mice pretreated with trametinib before LPS had decreased KIM-1 mRNA and protein. In contrast to TLR4 KO mice subjected to I/R, TLR4 KO mice injected with LPS did not exhibit increased KIM-1 mRNA or protein, nor activated ERK1/2 after 18 h.

Conclusions: We have linked ERK1/2 to KIM-1 transcriptional upregulation in the kidney cortex through STAT3 Y705/S727 phosphorylation following renal injury. In I/R and LPS-induced kidney injury KIM-1 mRNA and protein increased and ERK1/2 inhibition attenuated this increase. However, ERK1/2 mediated KIM-1 upregulation was dependent on TLR4 in LPS treated mice but not mice subjected to I/R. These results demonstrate that ERK1/2 is a key initiator of renal KIM-1 expression and that KIM-1 expression is regulated by different ERK1/2 pathways following renal injury.

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TH-PO238

Hypoxia Induces Tubular Autophagy by Preventing Oxygen-Dependent Prolyl Hydroxylation and Degradation of Stress-Responsive Transcriptional Factor FoxO3 Ling Li, Catherine Ha, Qais Al-Awqati, Fangming Lin. *Collumbia University College of Physicians and Surgeons, New York, NY.*

Background: Renal hypoxia results in metabolic perturbations and cell stress which likely leads to CKD following AKI. Autophagy is an evolutionally conserved cellular response to stress. Recent finding in our lab has shown that the stress-responsive transcription factor, FoxO3, can activate renal epithelial autophagy.

Methods: We used the autophagy reporter line (*CREL* mouse), which expresses a tandem RFP and EGFP fused with LC3 protein, to study molecular regulation of autophagy during the AKI to CKD transition.

Results: At 2-4 weeks following left renal ischemic injury for 35 min and right nephrectomy, we found progressive increases in proximal tubular autophagy in areas of low capillary density and thus hypoxia. Concomitantly, FoxO3 was activated with a 4-fold increase in nuclear expression over controls in the hypoxic tubules. To test whether hypoxia is an upstream activator for FoxO3 leading to autophagy, we exposed primary cultures of proximal tubular cells to 1%O_2 and found an increase in FoxO3 protein levels (50% increase at 30 min and 115% increase at 60 min), as well as its prominent nuclear localization. In renal tubular cells isolated from *CREL* mice, hypoxia or nutrient deprivation (a potent stimulator for autophagy) led to a time-dependent appearance of autophagic dots and increased conversion of LC3I to LC3II proteins. How could hypoxia activate FoxO3? We found that FoxO3, like Hif proteins, is prolyl hydroxylated, which leads to its degradation. Immunoprecipitation with FoxO3 antibody followed by immunoblot analyses with pan-hydroxyl proline antibody showed that prolyl hydroxylated FoxO3 diminished in hypoxic or starved conditions. Treating tubular epithelial cells grown in normal conditions with a prolyl hydroxylase (Phd) inhibitor, dimethyloxalylglycine (DMOG), caused a 60% reduction in OH-FoxO3 and a 39% increase in FoxO3 protein abundance. Conversely, treating starved cells with DMKG, a cell permeable analogue of α-ketoglutarate, the Phd substrate, resulted in a 57% decrease in FoxO3 protein abundance.

Conclusions: Taken together, our results indicate that FoxO3 can be regulated by the O_2- and α-ketoglutarate-dependent Phd enzymes in the kidney. Hypoxia and metabolic perturbations inactivate Phd enzymes to inhibit FoxO3 degradation, thus allowing it to induce tubular autophagy.

Funding: NIDDK Support

TH-PO239

Flow Cytometric Detection of Urinary Renal Tubular Epithelial Cells Directly Reflects Kidney Damage and Predicts Recovery from AKI Philipp Enghard,[1] Valerie S. Langhans.[2] *[1]Charité, Berlin, Germany; [2]Charité Universitätsmedizin Berlin, Berlin, Germany.*

Background: Acute kidney injury (AKI) is among the most frequent causes for renal damage and associated with significant increase of morbidity and mortality. Renal Tubular epithelial cells (TEC) are arguably the main target cell of AKI. The objective of our study was to establish flow cytometry based detection of different TECs in the urine and assess these cells as a biomarker for AKI.

Methods: Urine samples of 28 patients with AKI and 5 healthy controls were collected, immediately washed and the cells fixed using 2% formaldehyde. Proximal and distal TECs were identified using a staining for Cytokeratine (all TECs), CD10 (proximal TECs) and EPCAM (distal TECs). The amount of TECs per 100ml urine was correlated to AKIN stadium and subsequent recovery/non-recovery from AKI.

Results: Urinary numbers of TECs were increased upon kidney injury and only slowly decreased during recovery. TEC counts correlated with AKIN stadium of the patients (p=0.0006, r=0.57 proximal and p< 0.0001, r=0.67, for distal TECs, Spearman). TEC numbers were significantly higher in patients with AKI than in healthy donors and enabled to distinguish between different AKIN stadia. Importantly, the amount of distal TECs (Cytokeratine+EPCAM+) upon AKI was able to predict subsequent recovery/non-recovery from AKI. Applying a cut-off of 200.000 cells/100ml urine separated patients with and without recovery (Cytokeratine+EPCAM+, p= 0.0068).

Conclusions: Urinary cell counts of renal epithelial cells directly reflect the amount of tissue damage in human AKI. Our findings suggest proximal and distal TECs as biomarkers to diagnose and estimate the severity of kidney damage and to predict the outcome of patients with AKI.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO240

Genetic Screening Reveals Potential Therapeutic Targets in Gentamicin-Induced AKI Chinaemere Igwebuike,[4] Zhiyong Wang,[1] Andrea Havasi,[5] Michael Y. Sherman,[6] Julia Yaglom,[6] Yongmei Wang,[6] John H. Schwartz,[2] Steven C. Borkan.[3] *[1]BOSTON MEDICAL CENTER, BOSTON, MA; [2]Boston Medical Center-Evans Biomedical Center, Boston, MA; [3]Boston Medical Center, Boston, MA; [4]Boston Univerisity School of Medicine, Boston, MA; [5]Boston University Medical Center, Boston, MA; [6]Boston University School of Medicine, Boston, MA.*

Background: Gentamicin is a highly effective, nephrotoxic antibiotic that accounts for >20% of AKI, a complication that increases morbidity and mortality but lacks effective therapy. We propose that high throughput genetic screening can characterize the signal pathways that mediate gentamicin-induced proximal tubule epithelial cell (PTEC) injury and that once identified, pharmaceuticals that favorably alter these signal pathways will ameliorate gentamicin-induced AKI.

Methods: Human proximal tubule cells (HK2) were exposed to gentamicin sulfate under conditions that replicate the human disease. An shRNA library directed against 5,000 signal genes was introduced into human PTEC exposed to gentamicin for 10 ("low stringency") or 11 days ("high stringency"). shRNA that were over-represented *vs*. luciferase control were considered "protective" and under-represented genes were considered "sensitizing" to gentamicin-induced death measured by image cytometry of Hoechst and propidium iodide stained cells. Signal pathways that mediate gentamicin toxicity were identified using Ingenuity Pathway Analysis based on genes with a similar change in expression under both low and high stringency conditions. PTECs were then exposed to drugs that either stimulate protective or inhibit sensitizing pathways during gentamicin exposure.

Results: Genetic screening detected 406 genes in gentamicin exposed *vs*. control PTEC with at least a 1.8-fold change in expression. Pathways analysis showed that these genes were involved in cell metabolism, survival and inflammatory pathways. Three distinct pathway modifying drugs, including metformin, an FDA approved agent, were found to be non-toxic to normal PTEC. Approximately 59% and 88% of PTEC died after 10 or 11 days exposure to 26 mM gentamicin, respectively. In contrast, pre-incubation with metformin, a CAMP and AMP kinase mediator, significantly prevented PTEC death ($P<0.05$).

Conclusions: Genetic screening successfully identifies modifiable pathways responsible for gentamicin-induced nephrotoxicity that can be selectively targeted using existing pharmaceuticals. Together, studies define an effective strategy for gaining mechanistic insight into the pathogenesis of nephrotoxic AKI, facilitating the selection of agents to prevent and treat its devastating consequences.

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TH-PO241

Endogenous Fructose Production and Fructokinase Activation Mediate Rhabdomyolysis-Induced AKI Yuka Sato, Carlos A. Roncal-jimenez, Ana Andres-hernando, Thomas Jensen, Masanari Kuwabara, Richard J. Johnson, Miguel A. Lanaspa. *Renal Disease and Hypertension, University of Colorado Denver, Aurora, CO.*

Background: Acute kidney injury (AKI) is associated with high mortality. Treatment of AKI is limited to supportive care, and no interventions to improve recovery from AKI have yet been developed. The cause of AKI is diverse including ischemia, nephrotoxic agents and rhabdomyolysis. Endogenous fructose production from glucose by the polyol pathway, and its metabolism by fructokinase (KHK) leads to ATP depletion, oxidative stress and inflammation. We have reported that the metabolism of endogenous fructose is a key deleterious step in the pathogenesis of ischemic AKI, and KHK blockade showed protective role. However, to further validate if the blockade of this pathway is clinically relevant for the treatment of other types of AKI, here, we tested the hypothesis that the endogenous fructose production and metabolism contributed to rhabdomyolysis related AKI.

Methods: To establish the rhabdomyolysis-induce AKI, male wild-type mice (WT) and KHK-deficient mice (KHK-KO) were injected with 50%v/v glycerol or saline (for control) of 6 ml/kg body weight to the two hind limbs intramuscularly. Mice were sacrificed at 24 hours after glycerol injection, and blood, urine, kidney and muscle collected for histological and biochemical analyses.

Results: Serum creatinine elevation was significantly suppressed in KHK-KO mice. (WT sham; 0.23mg/dL, KHK-KO sham; 0.10mg/dL, WT glycerol (Gly); 2.03 mg/dL, KHK-KO Gly; 1.47 mg/dL, $p<0.01$; WT sham vs WT Gly, $p<0.01$; WT Gly vs KHK-KO Gly). Serum creatine phosphokinase (CPK) levels were similar between WT and KHK-KO mice on glycerol (WT Gly; 207.5 IU/L vs KHK-KO Gly; 227.0 IU/L) suggesting equivalent muscle injury and the protective effect for rhabdomyolysis-induced AKI in KHK-KO was mediated locally at kidney. Consistently, renal endogenous fructose production and metabolism was activated in the kidney of WT Gly compared to WT sham as denoted by the up-regulation of aldose reductase and KHK.

Conclusions: Endogenous fructose production in kidney by activation of polyol pathway had a deteriorative role for rhabdomyolysis-induced AKI. The blockade of KHK could be the target for preventive and recovery for AKI.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-PO242

Temporal Changes in Histone Deacetylases after Renal Ischemia/Reperfusion Injury Kelly A. Hyndman, Malgorzata Kasztan. *University of Alabama at Birmingham, Birmingham, AL.*

Background: Histone deacetylases (HDACs) are epigenetic regulators of transcription through deacetylation of histone lysines. Increased HDAC activity causes uncontrolled proliferation, inflammation, and/or fibrosis. Moderate ischemia/reperfusion (IR) of the kidney results in an immediate decline of renal function and injury including fibrosis followed by a stage of repair and improvement of renal function. The aim of this study was to determine if renal HDACs are dysfunctional during injury and repair after IR.

Methods: Male and female 10 week old mice underwent sham or bilateral ischemia for 27 minutes, followed by reperfusion for 1, 24, 48 or 72 h.

Results: Abnormal tubular morphology and reduced nuclei number were evident after 1 h, followed by significant reduction by 24-48 h, and reappearance of larger nuclei by 72 h. Western blots of cortical samples showed the following effects of IR on class I HDACs compared to sham: HDAC1 was increased 2.5-fold by 48 h, HDAC2 was not affected, HDAC3 initially increased 50% but returned to sham levels by 48 h, and HDAC8 was significantly reduced 40% over the study period. The class II HDAC4 was significantly increased 4-fold over the study period. To determine if the increase in HDAC promoted renal damage and fibrosis, we delivered a class I inhibitor (MS275, 20 mg/kg/day) or a class I/II inhibitor (trichostatin A, TSA, 1 mg/kg/day) by i.p. osmotic minipump 3 days prior IR. In both sexes, plasma creatinine was 2-3-fold greater in MS275 and TSA mice compared to vehicle, suggesting that inhibition of HDACs during IR results in a worsening of renal function. Histological analyses revealed reduced fibrosis in the MS275 and TSA mice, however there was an increase in protein casts in these groups. In vitro studies in primary and immortalized proximal tubular (PT) cells determined that only class I/II inhibitors led to reduced proliferation. Overexpression of HDAC4, but not HDAC1, resulted in 55% greater PT proliferation.

Conclusions: From this study, we conclude that class I and II HDACs are significantly affected during IR and display isoform specific expression patterns. Our data suggest that class I HDACs may promote fibrosis, while class II HDACs, likely HDAC4, are critical for PT proliferation and repair.

Funding: NIDDK Support

TH-PO243

Modulation of PPARδ with MTB-2 Post-Reperfusion Attenuates IR-Induced AKI Injury Biomarkers and Histopathology in Rats Christina Bracken, Katelyn Pulito, Effie Tozzo. *Mitobridge, Cambridge, MA.*

Background: Ischemic acute kidney injury (AKI) is characterized by persistent proximal tubule mitochondrial dysfunction. Due to their highly oxidative metabolism, proximal tubule cells utilize fatty acids to generate the energy required for their specialized function. We hypothesized that enhancing fatty acid oxidation with a PPARδ modulator will restore mitochondrial function, offering a potential therapeutic treatment for AKI.

Methods: Sprague-Dawley (SD) rats underwent a 45 minute bilateral ischemia-reperfusion (IR) AKI. Following reperfusion rats were treated with 2 IV doses of selective PPARδ modulator MTB-2 at doses varying from 0.3 to 10 mg/kg or vehicle. Plasma and urinary kidney injury biomarkers were measured at 10h, 24h and 48h post reperfusion. Histology assessment of kidney cortex was done 48h post AKI.

Results: MTB-2 treatment resulted in significantly lower plasma creatinine (up to 69% reduction), BUN (up to 60% reduction) and cystatin C (up to 69% reduction) levels at 24 and 48 hours post AKI compared to vehicle animals. Importantly, this translated to an improvement of renal function marked by increased creatinine clearance (up to 800%) and normalization of fractional excretion of Na^+ (FENa) (up to 90%) suggesting improved tubular function. Modulation of PPARδ after AKI also led to significantly reduced urinary levels of [TIMP-2]*[IGFBP-7], FABP-1 and NGAL. Assessment of kidney histopathology at 48 hours post reperfusion confirmed that MTB-2 reduced tubular injury and normalized renal tubular architecture, resulting in improvement of histopathology scores.

Conclusions: Our data demonstrates that selective PPARδ modulation after an ischemic AKI event in rats is sufficient to recover renal and tubular function, reduce clinically relevant urinary and plasma injury biomarkers and improve kidney histopathology.

TH-PO244

Identification of Urinary Activin A as a Novel Biomarker for AKI Shunsuke Takahashi,[2] Yoshinori Takei,[4] Masao Nakasatomi,[1] Toru Sakairi,[3] Hidekazu Ikeuchi,[5] Yoriaki Kaneko,[2] Keiju Hiromura,[2] Yoshihisa Nojima,[1] Akito Maeshima.[2] *[1]Gunma University, Maebashi, Japan; [2]Gunma University Graduate School of Medicine, Maebashi, Japan; [3]Gunma University Graduate School of Medicine, Japan, Maebashi, Japan; [4]Gunma University School of Medicine, Maebashi, Japan; [5]Gunma university graduate school of medicine, Maebashi, Japan.*

Background: Activin A, a member of TGF-beta superfamily, is known to regulate cell growth and differentiation in various tissues. We previously reported that activin A, which was absent in normal kidney, was increased in the ischemic rat kidney and negatively regulates the repair process of the kidney after injury (Maeshima et al. J Am Soc Nephrol 2001). To further investigate the role of activin A in acute kidney injury (AKI), we examined whether activin A can be detected in the urine of mice and humans with AKI.

Methods: Ischemia-reperfusion injury (I/R) was induced in C57BL/6 mice. At the indicated periods after operation, the kidneys and urine were collected for analysis. Expression and localization of activin A in ischemic kidneys (real-time PCR, immunostaining, and in situ hybridization) and urinary activin A (ELISA) were examined. Urine samples were also collected from fifteen patients with AKI as well as from eight healthy volunteers. Correlations of urinary activin A with other parameters were analyzed.

Results: Expression of activin A was markedly increased in the ischemic mouse kidney and peaked at 24 hours after I/R. Immunoreactive activin A was detected in proximal tubular cells of the outer medulla in ischemic kidneys, but not in normal kidneys. Activin A was absent in the urine of normal mice. In contrast, activin A was detectable in the urine of ischemic mice and bimodal peak (3 hours and 48 hours after I/R) was observed. In situ hybridization demonstrated that activin mRNA was expressed in tubular cells of the ischemic kidney, but was not in normal kidneys. Urinary activin A level became higher according to the ischemic periods. Urinary activin A was almost undetectable in healthy volunteers, but was significantly increased in patients with renal-AKI (7.2 ± 2.6 vs. 48.6 ± 15.3 pg/ml, $p<0.05$). Interestingly, urinary activin A was absent in the urine from patients with pre-renal AKI due to dehydration. There was a significant correlation of urinary activin A level with urinary follistatin (activin antagonist), but not with urinary KIM-1, urinary protein and serum creatinine.

Conclusions: Urinary activin A can be detected in mice and humans with AKI and might be a useful biomarker reflecting the severity of AKI.

Funding: Commercial Support - Astellas Pharm Inc.

TH-PO245

Mapping the Spatiotemporal Transcriptional Landscape of the Collecting Duct During Ischemic Injury Using Non-Invasive Optical Guidance Neal A. Paragas, Tomoaki Miyazaki, Yun-Wei A. Hsu, Sina Gharib. *University of Washington, Seattle, WA.*

Background: Collecting duct (CD) cells are sensitive to acute kidney injury (AKI) before an appreciable rise in serum creatinine. CD cells are mitochondrial rich and sensitive to oxidative stress (OS), so we specifically targeted them to monitor H_2O_2 generation along with changes in gene expression.

Methods: To interrogate genetic changes at the peak of OS, we non-invasively monitored H_2O_2 generation to identify the most relevant time points tissue acquisition for CD specific RNA-seq. We created a CD, HoxB7-luciferase (CD-Luc) bioluminescent reporter animal, to monitor OS. CD-Luc cell-specific reporter mice were injured by 30 min bilateral ischemia reperfusion injury (IRI) and H_2O_2 activity monitored non-invasively. A H_2O_2 sensitive caged-luciferin substrate was used to quantify cell specific changes of H_2O_2 after IRI. In parallel, we created a CD, HoxB7-riboTRAP (CD-riboTRAP) RNA isolation animal, to selectively immuno-precipitate (ip) RNA transcripts from CD cells. CD population was RNA sequenced and analyzed.

Results: In vivo measures of CD-Luc H_2O_2 activity were in agreement with MDA levels (lipid peroxidation), and qPCR of biomarkers of hypoxic stress (Hspa1b and Hmox1) with all peaking at 6-9 h after IRI. In the parallel, CD-riboTRAP IRI animals 9 h after injury had ip RNA-seq. We identified over 14,000 transcripts with many up- and down-regulated genes between IRI vs. sham CD-riboTRAP populations. Previously validated biomarkers of renal injury to the medulla were upregulated (Lcn2, Clu, and Spp1). Pathways involved in mitochondrion-associated processes were down-regulated. We pretreated CD-Luc before IRI with a targeted mitochondrial antioxidant and were able to reverse the CD OS in vivo.

Conclusions: In sum, using our novel integrative approach we: (i) non-invasively and longitudinally imaged the peak time point of OS in the CD; (ii) used ip to isolate CD RNAs at that time point; (iii) successful carried out RNA sequencing; (iv) performed differential gene expression and pathway analysis to reveal mitochondrial OS as a potential target pathway; (v) reversed the acute OS state with a targeted mitochondrial antioxidant with reduced lipid peroxidation in the kidney; and (vi) validated the reversal of mtROS induction in ROS reporter animal model and as a result suppressed the strong inflammatory stimulus of IRI.

Funding: NIDDK Support

TH-PO246

Iron Deficiency Sensitizes the Kidney to Acute Injuries Xueqiao Wang,[3] Wenjun Shang,[2] Xiaoqing Zheng,[4] Zhigang Wang,[2] Juanlian Zhang,[3] Jushan Zhang,[3] Jing Nie,[3] Jonathan M. Barasch,[1] Andong Qiu.[3,1] *[1]Columbia Presbyterian, New York, NY; [2]Zhengzhou University, Zhengzhou, China; [3]School of life science and technology, Tongji University, Shanghai, China; [4]School of life science and technology, Tongji University, Shanghai, China.*

Background: Iron deficiency is the most common micronutrient deficiency in both the developing and developed countries, and it causes defective development of organogenesis in embryos. However, it remains unknown whether iron deficiency impacts acute kidney injuries (AKI) during postnatal life. Here we studied the effects of iron deficiency on AKI in murine models.

Methods: Mice were fed either iron deficient (22ppm), moderate iron deficiency (60ppm) or iron-replete (260ppm) diets for 3 weeks, and then subject to cisplatin or rhabdomyolysis AKI. sCR and BUN were analyzed three days after i.p. injection of cisplatin and one day after muscular injection of glycerol. Pro-oxidant and antioxidant, cell death and iron proteins and inflammatory factors were analyzed by Q-PCR, western blot or immunofluorescence and CBA.

Results: We found that iron deficiency markedly exacerbate cisplatin- and rhabdomyolysis-induced AKI when compared with iron-replete condition, and even moderate iron deficiency had similar impacts. Nox4 and inflammatory factors were largely upregulated while catalase was markedly downregulated in the cisplatin-injured kidneys of iron-deficient mice when compared with iron-replete control. Further studies showed that the exacerbation of cisplatin-induced kidney injuries in iron deficient mice could be reversed by Fer-1, a ferroptosis inhibitor, demonstrating that the increased ferroptosis was a major mechanism for the aggravation of AKI. In contrast, Fer-1 failed to rescue the exacerbation of AKI induced by rhabdomyolysis, indicating the existence of a different mechanism for the impacts of iron deficiency on kidney injuries in this model.

Conclusions: Iron deficiency and even moderate iron deficiency markedly exacerbated AKI induced by either cisplatin or rhabdomyolysis, and increased ferroptosis represented a major mechanism of the exacerbation of kidney injuries in iron deficient cisplatin-induced AKI model.

Funding: Government Support - Non-U.S.

TH-PO247

Omega-3 Fatty Acids Attenuate Cisplatin Nephrotoxicity via Enhancement of Autophagy Flux Youngrok Ham,[1] Jin young Jeong,[2] Hong jin Bae,[1] Chang hun Song,[1] Kiryang Na,[3] Kang Wook Lee,[1] Jwajin Kim,[3] Jiwon M. Lee,[4] Dae Eun Choi.[1] *[1]Nephrology, School of Medicine, Chungnam National University, Daejeon, Republic of Korea; [2]Department of Medical Science, Chungnam National University, Daejeon, Republic of Korea; [3]Anatomy, School of Medicine, Chungnam national university, Deajeon, Republic of Korea; [4]Pediatrics, School of Medicine, Chungnam National University, Daejeon, Republic of Korea.*

Background: Various studies demonstrated that omega-3 polyunsaturated fatty acids (PUFAs) attenuate kidney injuries through anti-apoptotic and antioxidant properties. Recently, several studies showed that omega-3 PUFAs enhance induction of autophagy. We evaluated whether administration ω-3 PUFAs may induce autophagy in cisplatin nephrotoxicity, and investigated the role of autophagy in attenuating cisplatin nephrotoxicity by ω-3 PUFAs.

Methods: 10-week- old male C57BL/6 mice were divided into 4 groups; control, control plus omega 3, cisplatin, cisplatin plus omega 3; they were injected with a vehicle or single dose of cisplatin (16 mg/kg body weight) intraperitoneally. Omega 3 and vehicle were administered orally using an NG tube (Omega 32,000 μg/kg/day) from pre-injection day to 3 days after injection of cisplatin. Mice were sacrificed at 4 days after administration of cisplatin and kidney tissue were collected. Real time PCR, western blot and immunohistochemistry for molecular study and H&E stain and PAS stain for histologic examination were performed.

Results: Omega 3 treated cisplatin-mice showed improvement of renal cell survival, renal function, and pathologic damage compared to vehicle treated cisplatin-mice. Omega-3 treatment also reduced the renal expression of MCP-1 (Monocytye chemotactic protein-1) and OPN (Osteopontin) in cisplatin-treated kidney. Cisplatin-mice kidney showed that higher amounts of LC3, Beclin-1 and p62 compared to sham mice. Omega 3 treated cisplatin kidney showed higher amounts of LC3 and Beclin-1 and lower amounts of p62 compared to vehicle treated cisplatin kidney. Moreover, renal cathepsin D and ATP6E were also increased in omega 3 treated cisplatin-mice compared to vehicle treated cisplatin-mice.

Conclusions: Omega 3 fatty acids attenuate renal injury in cisplatin nephrotoxicity through stimulating autophagy flux

TH-PO248

Shroom3 Contributes to a More Severe AKI after Ischemia Reperfusion Darren Bridgewater, Thomas A. Drysdale. *McMaster University, Hamilton, ON, Canada.*

Background: Acute kidney injury (AKI) is a severe complication of ischemia reperfusion injury. Individuals who survive AKI have an increased risk of developing chronic kidney disease, end stage renal disease, and death. While several clinical risk factors are associated with AKI, the genetic contributions are limited. Genome-wide

association studies (GWAS) identified 53 novel single nucleotide polymorphisms (SNPs) robustly associated with variations in kidney function. *SHROOM3* is the second most significant gene identified in these studies. Shroom3 is an actin-associated protein that regulates tissue morphogenesis by regulating epithelial cell shape. In the kidney, Shroom3 is expressed in the parietal and visceral epithelial cells, in some tubular epithelial cells, and distal collecting ducts. While Shroom3 heterozygous mice develop chronic kidney disease at 1 year, the role of Shroom3 in AKI is not known.

Methods: Bilateral renal ischemia/reperfusion (I/R) procedure was performed in Shroom3 heterozygous mutant (*Shroom3*$^{Gt/+}$) and wild type (WT) mice at 12 weeks to mimic the I/R renal injury experienced during transplant and cardiac surgery. Serum creatinine and urine protein at baseline, days 1, 2, 3, 5, 7, and 10 were measured. Kidneys were collected 48 hours and 10 days after I/R the procedure to compare the histopathological changes of the initial AKI insult and the kidneys ability to recover.

Results: Twelve-week old *Shroom3*$^{Gt/+}$ and WT mice had similar serum creatinine and urinary protein levels at baseline. Twenty-four hours after I/R, *Shroom3*$^{Gt/+}$ mice had a 1.5 fold (P=0.038) increase of serum creatinine from baseline (Fold Mean±SD, 3.89±1.35, N=10) compared to WT mice (Fold Mean±SD, 2.58±1.01, N=8). The *Shroom3*$^{Gt/+}$ mice demonstrated worse histopathology as measured by tubular changes and cell death. Ten days after I/R, the serum creatinine in *Shroom3*$^{Gt/+}$ and WT mice returned to baseline levels. However, the histopathological changes in *Shroom3*$^{Gt/+}$ mice were markedly worse when compared to WT mice.

Conclusions: Our results demonstrate that genetic anomalies or aberrant expression of Shroom3 could lead to worse renal outcomes in patients after an I/R injury.

Funding: Government Support - Non-U.S.

TH-PO249

Paricalcitol Ameliorates Radiocontrast-Induced Nephropathy by Regulating Mitophagy Dong Jun Park,[3,4] Tae won Lee,[3] Eunjin Bae,[3] Hyun Seop Cho,[1] Ha nee Jang,[5] Hee jung Park,[2] Se-Ho Chang.[1,4] *[1]Gyeongsang National University Hospital and Gyeongsang National University, Jinju-si, Gyeongsangnam-do, Republic of Korea; [2]Gyeongsang national university hospital, Jinju, Jinju-si, Republic of Korea; [3]Internal Medicine, Changwon Gyeongsang National University Hospital and Gyeongsang National University, Changwon-si, Republic of Korea; [4]Institute of Health Science, Gyeongsang National University, Jinju-si, Republic of Korea; [5]Gyeongsang National Univ. Hospital, Jinju-si, Republic of Korea*.

Background: Radiocontrast-induced nephropathy (RCIN) is an important problem in clinical settings. However, strategies to prevent RCIN have been suboptimal. Paricalcitol was recently found to be effective in a variety of renal animal models, so it was hypothesized that paricalcitol would prevent RCIN

Methods: RCIN was induced in rats by injection of the radiocontrast medium Ioversol in addition to inhibition of prostaglandin and nitric oxide synthesis. Rats were randomly assigned to four groups: healthy controls (Con, n=10), received paricalcitol only (Parical, n=10), ioversol (CONT, n=10), and received paricalcitol before ioversol injection (Parical+CONT, n=10). Rats were treated with either paricalcitol (0.3 mg/kg, i.p) or saline (equal volume, i.p.) at 24 h and 30 minutes prior to ioversol injection.

Results: Administration of two doses of paricalcitol before the induction of nephropathy significantly reduced the renal dysfunction and histologic tubular injury. The apoptosis of renal tubular cells was inhibited by paricalcitol. Oxidative stress markers such as 8-OhdG and NOX-2, NADPH oxidase, were highly expressed in nephropathy rat model, but attenuated by paricalcitol administration. β-galactosidase, one of markers of cellular senescence, increased in tubules after contrast infusion. This was alleviated by paricalcitol. Furthermore, the expression of LC3, PINK1, and Parkin, representatives of mitochondrial autophagy, after radiocontrast injection was highly attenuated by administration of paricalcitol, suggesting that the effects of paricalcitol might be mediated by the autophagy pathway.

Conclusions: These findings suggest that paricalcitol may have potential as a new therapeutic approach to prevent RCIN.

TH-PO250

Histone Deacetylase 6 Inhibition Protects Against Cisplatin-Induced AKI Yingfeng Shi,[2] Na Liu,[1] Liuqing Xu,[4] Jinhua Tang,[1] Shougang Zhuang.[3] *[1]Department of Nephrology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China; [2]Department of Nephrology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China; [3]Rhode Island Hospital, Alpert Medical School of Brown University, Providence, RI; [4]Department of Nephrology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China*.

Background: The function of histone deacetylase 6 **(**HDAC6**)** has been demonstrated in various pathophysiological events, including cancer, neurodegenerative disorders and inflammatory diseases. Its role in cisplatin-induced acute kidney injury (AKI) is still unclear.

Methods: We used a murine model to investigate the role and mechanism of HDAC6 in cisplatin-induced AKI.

Results: HDAC6 expression levels were markedly increased in the kidneys of cisplatin-treated mice. Blocking HDAC6 activity with tubastatin A (TA), a high selective inhibitor, protects against cisplatin-induced AKI as demonstrated by improved renal dysfunction, attenuated renal pathological changes, reduced expression of AKI biomarkers (NGAL and Kim-1), and decreased tubular cell apoptosis. Administration of TA also enhanced tubular cell dedifferentiation and regeneration as evidenced by increased expression of Pax2 and proliferating cell nuclear antigen protein in the injured kidney. In vitro studies demonstrated that TA increased acetylation of histone H3 and a-tubulin and decreased cell apoptosis in cultured human proximal tubular cells. Mechanistic studies demonstrated that TA treatment enhanced AKT phosphorylation and induced autophagy. Moreover, HDAC6 blockage restrained renal oxidative stress by raising superoxide dismutase activity and lessening malondialdehyde level. Finally, TA treatment inhibited NF-κB phosphorylation as well as expression of multiple cytokines/chemokines, thereby reducing macrophage infiltration in the injured kidney.

Conclusions: These data provide strong evidence that HDAC6 inhibition protects against cisplatin-induced AKI and suggest HDAC6 as a potential therapeutic target for AKI treatment.

Funding: Government Support - Non-U.S.

TH-PO251

Involvement of Sirtuins 1 and 3 during the Acute Phase of Aristolochic Acid Nephropathy Inès Jadot,[3] Pauline F. Mosseray,[3,4] Blanche Martin,[3] Olivia Botton,[3] Joelle L. Nortier,[1] Anne-Emilie Decleves,[2] Thierry Arnould,[4] Nathalie Caron.[3] *[1]Hospital Erasme, Brussels, Belgium; [2]Laboratory of Molecular Biology, University of Mons, Belgium, NIMY (MONS), Belgium; [3]Molecular Physiology Research Unit (URPHYM), University of Namur, Namur, Belgium; [4]Laboratory of Biochemistry and Cell Biology (URBC), University of Namur, Namur, Belgium*.

Background: Aristolochic acid (AA) nephropathy (AAN) is a rapidly progressive tubulointerstitial nephritis induced by intoxication with AA and is usually associated with end-stage renal disease and urothelial malignancy. While the carcinogenic mechanisms of AA have been well documented, the mechanisms by which AA exert cytotoxic effects on proximal tubular epithelial cells, AA's primary target, are poorly characterized. Since oxidative stress and mitochondrial damage are known to be drivers of acute kidney injury, the goal of this study is to characterize oxidative stress and mitochondrial dysregulation with a particular emphasis on sirtuins (SIRT) during the acute phase of experimental AAN. Indeed, SIRT1 and SIRT3 have been previously described to be protective in different models of kidney disease. Therefore, this study aims to investigate for the first time the involvement of SIRT1 and SIRT3 in the pathophysiology of AAN.

Methods: C57BL/6J male mice were randomly subjected to daily i.p. injection of AAI (3,5mg/kg) for 4 days. Mice were euthanized 24 hours, 5 days and 10 days after the beginning of AA intoxication.

Results: Polyuria and proteinuria were observed 5 days after AA intoxication as well as an increase in plasma creatinine and in blood urea nitrogen confirming renal failure. Histological analysis revealed early alterations of proximal tubules 24 hours after AA intoxication. At day 5, necrotic tubules with cellular debris in the tubular lumen were observed thereafter evolving at day 10 to atrophic tubules. Tubular injury was confirmed by upregulation of relative mRNA expression of *NGAL*. Along with renal failure, inflammation developed with upregulation of mRNA of inflammatory cytokines (*MCP1, MIP2, IL1*β, *IL6* and *TNF*α) and with macrophage infiltration. Antioxidant pathways were also downregulated as attested by decrease in mRNA expression of *NRF-2* and *SOD* at day 5 and day 10. Finally, relative mRNA expression of *SIRT1* and *SIRT3* was found to be downregulated from day 5 until day 10, the protein expression of SIRT3 being also reduced at the same time-points.

Conclusions: The downregulation of SIRT1 and SIRT3 observed in the acute phase of AAN could constitute a key event in AAN pathogenesis. Therefore, this observation could lead to a new potential strategy for improving outcomes of AAN.

Funding: Government Support - Non-U.S.

TH-PO252

Characterization of the Metabolome and Renal Tubular Cisplatin Disposition in Cisplatin Induced AKI Yong Jin (James) Lim,[1] Emily D. Hartjes,[1] Brad Urquhart.[1,2] *[1]Physiology and Pharmacology, Schulich School of Medicine & Dentistry, University of Western Ontario, London, ON, Canada; [2]Department of Medicine, Division of Nephrology, University of Western Ontario, London, ON, Canada*.

Background: Cisplatin induces acute kidney injury (AKI) in approximately 1/3 of patients. It is currently unknown why some patients develop AKI and others do not. Cisplatin AKI is diagnosed by increases in serum creatinine (SCr), but nephrotoxicity develops before rises in SCr can be detected. Novel diagnostic/predictive markers of AKI may help explain why some cisplatin patients get AKI while others are resistant. FVB mice have greater susceptibility to cisplatin AKI than C57BL/6 mice. These two mouse strains were used to model the variability of cisplatin response observed in humans. We aim to: 1) Determine the effects of AKI on expression of renal transporters and enzymes involved in cisplatin disposition; 2) Investigate metabolic differences between FVB and C57BL/6 mice using metabolomics, with the goal of biomarker discovery.

Methods: FVB and C57BL/6 strains were treated with 15 mg/kg cisplatin or saline by intraperitoneal injection. Mice were sacrificed 1 and 3 days following treatment, and blood, urine and kidneys were collected. Gene expression was assessed using RT-PCR. Liquid chromatography-mass spectrometry was used for untargeted metabolomics.

Results: In FVB mice, expression of renal uptake transporter Oct2 and metabolizing enzyme Ggt1 were 51% and 66% lower 3 days following cisplatin treatment compared to saline ($p<0.05$, $p<0.01$ respectively). Oct1 trended towards lower expression in day 3 cisplatin-treated FVB mice. Principle component analysis (PCA) of untreated FVB and C57BL/6 plasma samples showed clustering based on mouse strain. PCA of day 3 plasma samples clearly separated cisplatin and saline groups for both mouse strains. Multivariate

analysis revealed indoxyl sulfate and p-cresyl sulfate to be two metabolites associated with cisplatin AKI.

Conclusions: mRNA expression results suggest that cisplatin alters expression of drug disposition genes in FVB, but not C57BL/6 mice. PCA clustering of baseline mice indicates metabolic differences between the strains, while separation by treatment groups suggests that cisplatin administration alters the metabolic profile of the mice. Our preliminary data suggests possible mechanisms why FVB mice show increased susceptibility to cisplatin AKI compared to the C57BL/6 mice. Further work will to be done to identify additional metabolic changes associated with cisplatin AKI.

TH-PO253

Blockade of Sonic Hedgehog Signaling in Fibroblasts Protects against AKI Dong Zhou,[1] Haiyan Fu,[1,2] Yuan Tian,[1] Hongyan Mo,[1] Youhua Liu.[1] *[1]Department of Pathology, University of Pittsburgh, Pittsburgh, PA; [2]Division of Nephrology, Southern Medical University, Guangzhou, China.*

Background: Sonic Hedgehog (Shh), an evolutionarily conserved, secreted and extracellular signal protein, is an inducible, tubule-derived growth factor specifically promoting fibroblast proliferation and expansion through its receptor by the so-called canonical pathway in chronic kidney disease. However, whether activation of Shh signaling in fibroblast plays any role in acute kidney injury (AKI) remains to be defined.

Methods:

Results: Here we show that Shh, Smoothened (Smo) and fibroblasts were concomitantly activated after ischemic AKI. To investigate the potential role of activation of fibroblast-specific Shh signaling in AKI, we generated conditional knockout mice, designated as FC-Smo-/-, in which the Smo gene was specifically disrupted in renal fibroblasts by using the inducible Cre-LoxP system. The FC-Smo-/- mice are phenotypically normal and displayed no appreciable defects in kidney morphology and function. However, in AKI induced by ischemia reperfusion injury (IRI), loss of fibroblasts Smo substantially ameliorated renal dysfunction and lesions. Compared with controls, FC-Smo-/- mice displayed lower serum creatinine and reduced morphologic injury. Fibroblast-specific ablation of Smo significantly blocked the expression of pro-inflammatory cytokines including TNF-α and MCP-1, and retarded renal infiltration of inflammatory cells such as CD3+ T cells and F4/80+ macrophages after AKI. Less apoptosis was detected in FC-Smo-/- kidneys, accompanied by a decreased expression of Bax and Fas-associated protein with death domain (FADD). Interestingly, loss of Smo in fibroblast in turn caused an increased expression of Shh in tubules by feedback control, Shh then promoted activation of canonical Wnt signaling pathway including upregulation of the majority of 19 Wnt family members after AKI which is strongly associated with AKI recovery.

Conclusions: Collectively, these results suggest that loss of fibroblast-specific Shh receptor, Smo, is crucial in conferring renal protection after AKI, primarily via a reduced renal inflammation, as well as activation of Wnt signaling through cell-cell communication.

Funding: NIDDK Support

TH-PO254

Sex Differences in Renal Toxicity of the Neurotoxin Domoic Acid Robert G. Thompson,[1] Hernan E. Grenett,[1] Lan He,[3] P. Darwin Bell.[2] *[1]University of Alabama at Birmingham, Birmingham, AL; [2]University of Alabama at Birmingham, Birmingham, AL; [3]University of Alabama at Birmingham, Birmingham, AL.*

Background: The algae-derived neurotoxin, domoic acid (DA), is an ionotropic receptor agonist and is currently considered an increasing threat to mammals and other species. Intraperitoneal administration (IP) of 4-5 mg/Kg/BW in mice has been found to cause neurological symptoms\damage. However, we recently reported (Funk, JASN 2014) that the kidney was 100 times more susceptible to injury with DA compared to brain. With IP injection, the kidney has a 4-fold higher concentration of DA compared to brain and prior probenecid treatment leads to even greater accumulations of DA, suggesting that DA is both filtered andis secreted by the kidney. Organic Anion Transporters such as OAT-1, OAT-2, and OAT-3 participate in helping mediate drug and toxin removal by the kidney through the process of secretion. In epithelial tissues, OAT-1 and OAT-3 are located at the basolateral membrane, and OAT-2 is located at the apical membrane (Nigam SK, Physiological Review 2015). The purpose of these studies was to determine if there is a gender sex difference in the renal injury response to DA.

Methods: Doses of 0.05 mg/Kg and 0.005 mg/Kg were IP injected into C57BL6 mice and 30 mins later the early injury-response genes *c-fos*, *Junb*, and *EGR-1* were quantified using RT-qPCR. RT-qPCR was also performed to assess the mRNA levels for organic anion transporters in both male and female mice at 0.05mg/Kg DA.

Results: After 30 minutes both male and female mice exhibited an increase in gene expression. Surprisingly, female mice expression of early response genes was significantly higher compared to male mice. OAT-1, OAT-2, and OAT-3 in males were slightly upregulated; however, female mice showed no change in mRNA expression for OAT-1, OAT-2, and OAT-3.

Conclusions: These results demonstrate that female mice are more susceptible to renal injury compared to male mice in response to very low doses of DA. This difference may be due to a reduced ability for the renal secretion of DA though organic anion transport pathways.

Funding: Other NIH Support - P30 awarded to Dr. Darwin Bell, Veterans Affairs Support

TH-PO255

Thrombospondin-1 (TSP-1) and Microparticles in AKI Begoña Campos,[2] Brittany N. Gleich,[2] Sonam S. Singh,[2] Karen M. Domenico,[1] Charuhas V. Thakar.[2,3] *[1]Shriners Hospitals for Children, Cincinnati, OH; [2]University of Cincinnati, Cincinnati, OH; [3]Cincinnati VAMC, Cincinnati, OH.*

Background: We have previously shown (Thakar et al, JCI, 2005) that TSP-1 is up-regulated and mediates kidney damage (AKI) in murine ischemia reperfusion injury. TSP-1 exposure to renal epithelial cells is also known to induce apoptosis/necrosis. TSP-1 exerts its inflammatory modulating effects through signaling of CD36 (pro-inflammatory) and CD47 (anti-inflammatory) ligands. Microparticles (MP's) are released in response to stress or injury from various cells and can serve as markers of type and state of cell activation. Whether TSP-1 induced inflammatory ligands can be detected as MP's, and could play a role in organ cross-talk in models of AKI is unknown.

Methods: By studying *in vitro* models of AKI using immortalized human renal proximal tubular epithelial cell (RPTEC) line, we incubated cells with and without TSP-1 (1 μg/ml for 24 hours) (N = 3 sets). MP's were isolated and evaluated by flow cytometry techniques and with CD36 and CD47 flourescent antibodies. Analyses of microparticles was performed using flow-jo software and levels of MP's was expressed as mean and standard deviation times 10^{5}. Unpaired t-tests were used for comparison.

Results: Morphological assessment of TSP-1 treated cells confirmed characteristics assocaited with apoptosis. CD36 MP's were significnatly higher in TSP-1 treated cells vs controls (92.66 +/- 11.06 vs 229 +/-69.77; p = 0.007). CD47 MP's were statistically similar in TSP-1 and control cells (715.33 +/- 248 vs 759.6 +/- 220; p = 0.88). CD10 and CD13 MP's, as putative markers of RPTEC were also detected in response to TSP-1 exposure.

Conclusions: Our results show that MP's containing CD36 and CD47 are released from RPTEC upon exposure to TSP-1. CD36 MP's are significantly increased after TSP-1 exposure, whereas CD47 MP's are statistically similar. It is known that CD-36 serves as a pro-inflammatory ligand for various inflammatory proteins including TSP-1; thus raising the possibility that TSP-1 exposure could initiate a cross-talk between renal epithelium and other targets/tissues mediated thru CD-36 ligand interactions. This is the first report that demonstrates the release of CD36 and CD47 postive MP's in response to TSP-1 exposure. We propose that MP's originating from kidney under pathological conditions could release pro-inflammatory signals to other remote organs.

Funding: Clinical Revenue Support

TH-PO256

HIF-1-Mediated Production of Exosomes during Hypoxia Is Protective in Renal Tubular Cells Wei Zhang,[5,6] Xiangjun Zhou,[3] Hao Zhang,[4] Jin Wen,[2] Zheng Dong.[1] *[1]Georgia Regents University, Augusta, GA; [2]Sichuan University, Augusta, GA; [3]Taihe Hospital, Hubei University of Medicine, ----Shiyan, China; [4]The Third Xiangya Hospital of Central South University, Changsha, China; [5]Cellular Biology, Augusta University, Augusta, GA; [6]Nephrology Department, the Third Xiangya Hospital, Central South University, Changsha, China.*

Background: Exosomes are nano-sized vesicles produced and secreted by cells to mediate intercellular communication. The production and function of exosomes in kidney tissues and cells remain largely unclear. Hypoxia is a common patho-physiological condition in kidneys. This study was designed to characterize exosome production during hypoxia of rat renal proximal tubular cells (RPTC), investigate the regulation by hypoxia-inducible factor-1 (HIF-1), and determine the effect of the exosomes on ATP-depletion induced tubular cell injury.

Methods: RPTCs were treated with or without hypoxia. Exosomes were isolated by ultracentrifugation. Transmission electron microscopy and Nanoparticle Tracking Analyzer (NTA) Zeta View as well as Immunoblot analysis were used to qualify and quantify exosomes. HIF-1α inducer DMOG and its inhibitor YC-1 were used for HIF-1α induction or inhibition. A stable HIF-1α knockout MEF cell line and HIF-1α siRNA induced kknockdownRPTC cells were used to verify the role of HIF-1α in exosomes production. Conditioned exosomes were administrated as a pretreatment before Azide induced ATP-depletion injury in RPTC cells. Hoechst staining, morphology images and caspase-3 expression by immunoblot were conducted to evaluate the death and survival rate of the cells.

Results: The average size of exosome secreted in hypoxia condition was comparable to the normal condition by the NTA measurement. Hypoxia significantly increased exosome production in a time-dependent manner. HIF-1α induction by DMOG also slightly promoted exosomes secretion. Pharmacal or genomic inhibition of HIF-1α abrogated exosome increase under hypoxia condition; Pretreatment with hypoxic exosomes from tubular cells attenuated the apoptosis of RPTCs after Azide induced ATP-depletion. Exosomes form HIF-1α knock down cells failed to decrease cell apoptosis rate and caspase-3 expression.

Conclusions: Hypoxia stimulates exosome production and secretion in renal tubular cells. The exosomes from hypoxic cells are protective against renal tubular cell injury. HIF-1 mediates exosome production during hypoxia and contributes to the cytoprotective effect of the exosomes.

Funding: NIDDK Support

TH-PO257

Non-Classical MHC Class I Molecules Regulate Development and Maintenance of Kidney Double Negative αβ T Cells Mohanraj Sadasivam, Sanjeev Noel, Sul A Lee, Abdel Hamad, Hamid Rabb. *Johns Hopkins University School of Medicine, Baltimore, MD.*

Background: Despite strong evidence that immune cells mediate early injury and repair from ischemic acute kidney injury (AKI), the underlying mechanisms are poorly understood. A recently characterized subset of αβ T cells that is double negative (DN) for both CD4 and CD8 coreceptors is present in significant numbers in normal mouse and human kidney. Unlike $CD4^+$ and $CD8^+$ T cells, DN T cells divide actively in the steady state and rapidly increase in response to AKI. In addition, kidney DN T cells secrete anti-inflammatory cytokines IL-10 and IL-27, possess an in vitro and in vivo regulatory function and ameliorate AKI in mice. However, the exact MHC restriction element(s) required for homeostatic DN T cells development and maintenance is not known.

Methods: C57BL/6J (WT), B6.129P2-B2m^{tm1Unc}/J (β2m KO), B6.129S2-H2$^{dlAb1\text{-}Ea}$/J (MHC II KO) and B6.129P2-H2-K1^{tm1Bpe} H2-D1^{tm1Bpe}/DcrJ (KD KO) mice were used for analyses. The lymphocytes from the kidney, lymph node and thymus were isolated and analyzed for activation (CD69, CD44, CD62L & CD28), proliferation (Ki67) and apoptosis (annexin V). In vitro functional analysis of cytokines were performed by flow cytometry. Adoptive transfer of T and B cells were performed to assess the regulation of kidney DN T cells.

Results: Our data demonstrate that lack of β2m, but not classical MHC class Ia or class II molecule significantly reduces the frequency (WT, 28.8±3 vs. β2m KO, 9.5±2 vs. MHC II KO, 32.3±2; $P<0.05$) and the absolute number (WT, 3,355±1,077 vs. β2m KO, 1,016±471 vs. MHC II KO, 1,538±639; $P<0.05$) of kidney DN T cells. Subsequent studies show the reduction is due to impaired activation ($P<0.001$) and proliferation ($P<0.05$), and increased apoptosis ($P<0.05$) by kidney DN T cell. Further, most of the defects were restored by adoptive transfer of CD8 T cell from wild type mice, leading to activation and expansion ($P<0.001$) of endogenous DN T cells in β2m KO mice.

Conclusions: Our data indicate a critical role of β2m dependent MHC class Ib molecules in regulating homeostasis and activation of kidney DN T cells. Furthermore, CD8 T cells are appearing to be a source of MHC class Ib molecules and one strong candidate (Qa2) is being investigated using knockout mice, bone marrow chimera and adoptive transfer in the steady state and ischemic AKI.

Funding: NIDDK Support

TH-PO258

Loss of the Stress-Responsive Transcription Factor FoxO3 Accelerates AKI to CKD Transition Ling Li, Catherine Ha, Julia D. Liu, Qais Al-Awqati, Fangming Lin. *Columbia University College of Physicians & Surgeons, New York, NY.*

Background: AKI increases the risk for developing or worsening CKD. Capillary drop out and hypoxia occurs in kidneys transitioning from AKI to CKD. We recently found that hypoxia activated a stress-responsive transcription factor FoxO3 in mouse kidneys by the mechanism of preventing its oxygen-dependent degradation.

Methods: To test the function of FoxO3 activation during the AKI to CKD transition, we specifically deleted FoxO3 with high efficiency in tubular epithelial cells using *Pax8-rtTA;Tet-O-cre;FoxO3$^{f/f}$* mice.

Results: Ischemia-reperfusion injury (IRI) of a 35 min duration to the left kidney and right nephrectomy was performed. One week later, FoxO3 was deleted by giving mice doxycycline in the drinking water to study its role after the acute injury and recovery phase. Deletion of FoxO3 aggrevated renal damage 4 weeks post IRI indicated by significantly higher scores of brush border loss in proximal tubules, renal tubular atrophy and tubular cast formation (229 ± 5.3 vs. 22 ± 3.6 in wild type, n= 5). Furthermore, FoxO3 deleted mice had more prominent tubular cell apoptosis. However, neither interstitial fibrosis and inflammation nor microvascular density were significantly different compared with FoxO3 wild type mice. Mice with FoxO3 deletion also had higher urinary albumin:creatinine (53.2 ± 8.3 mg/g vs. 18.4 ± 4.6 mg/g in wild type, n=4) indicating that worse morphology was associated with functional decline. One potential mechanism for repair and survival of renal tubules is autophagy, a well-known cellular stress response. To examine the role of FoxO3 in renal autophagy, we examined the conversion of the core autophagy-related protein LC3I to LC3II, which is a key event in the formation of autophagic vesicles. Kidneys with FoxO3 deletion showed a 52% reduction in the ratio of LC3II to LC3I, suggesting lower level of autophagy.

Conclusions: In summary, our results indicate that FoxO3 activation induces renal autophagy as a stress response, which attenuates CKD development and progression.

Funding: NIDDK Support

TH-PO259

Optogenetic Stimulation of Specific Neural Circuits in the Neuroimmune Reflex Control of Inflammation in AKI Shinji Tanaka,[1] Tsuyoshi Inoue,[1] Diane L. Rosin,[2] Patrice G. Guyenet,[2] Mark D. Okusa.[1] *[1]Div of Nephrology and Center for Immunity, Inflammation and Regenerative Medicine, Dept of Medicine, University of Virginia, Charlottesville, VA; [2]Dept of Pharmacology, University of Virginia, Charlottesville, VA.*

Background: We recently reported that electrical vagus nerve stimulation (VNS) protects mouse kidneys from ischemia-reperfusion injury (IRI) by activating the cholinergic anti-inflammatory pathway (CAP). A limitation of this study is the bidirectional stimulation of both the efferent and afferent vagus nerve fibers. We used optogenetics to begin to distinguish the specific functions of vagus efferent and afferent fibers within the vagus nerve bundle in controlling inflammation by the CAP. Optogenetic stimulation involves the expression of light-reactive ion channels, such as channelrhodopsin-2 (ChR2), in relevant neurons using the Cre/loxP system. When light of a specific wavelength is applied to the target nerve, the ion channels open, resulting in selective activation of the neurons.

Methods: We crossed *loxP-STOP-loxP ChR2-eYFP* mice with choline acetyltransferase (*Chat*)-*cre* and vesicular glutamate transporter 2 (*Vglut2*)-*cre* mice to generate *Chat-ChR2* and *Vglut2-ChR2* mice expressing ChR2 in vagal efferent and afferent fibers, respectively.

Results: ChR2 expression was confirmed by direct observation of the eYFP signal in the cervical vagus nerve. When blue laser (wavelength 473 nm, 50 Hz) was applied to the cervical vagus nerve of *Chat-ChR2* mice, heart rate decreased markedly (300→180 bpm) without a change in respiratory rate. Blue laser application to the intact vagus nerve or the central end of the cut vagus nerve of *Vglut2-ChR2* mice completely paused breathing by activation of Hering-Breuer inflation reflex, while application to the distal end of the cut vagus nerve did not affect the respiratory rate, which reflects the fact that Hering-Breuer inflation reflex needs afferent vagal input to the brain. In a preliminary experiment, optogenetic VNS (5 Hz to minimize the effect on respiration) in *Vglut2-ChR2* mice protected kidneys from IRI.

Conclusions: We have successfully created transgenic mice expressing ChR2 in vagus efferent (*Chat-ChR2*) and afferent fibers (*Vglut2-ChR2*) and validated their expression and functional effect following optogenetic stimulation. Our preliminary data showed that selective stimulation of the vagus afferent fibers was protective against kidney IRI. Optogenetics will be useful in identifying selective neural circuits of the CAP that control systemic inflammation and other neural circuits of the kidney.

Funding: NIDDK Support

TH-PO260

Dendritic Cell Expression of Rictor, but not Raptor, Protects Against AKI Natasha M. Rogers,[3] Helong Dai,[2] Daniel Fantus,[1] Alicia Watson,[2] Angus W. Thomson.[2] *[1]Comprehensive Transplant Center, Northwestern University, Chicago, IL; [2]University of Pittsburgh, Pittsburgh, PA; [3]Westmead Institute for Medical Research, Sydney, NSW, Australia.*

Background: Dendritic cells (DC) are critical to innate immunity in the kidney and orchestrate inflammation fundamental to the pathophysiology of acute kidney injury (AKI). The mechanistic target of rapamycin (mTOR) functions as 2 independent complexes: Raptor and Rictor. The role of mTOR in AKI pathophysiology has been poorly characterized, and the influence of DC-based alterations in mTOR signalling has not been investigated.

Methods: CD11c-specific Raptor$^{-/-}$ or Rictor$^{-/-}$ mice were generated by crossing respective floxed mice with mice expressing CD11c-Cre. Age- and gender-matched DC-mTOR-null mice or littermate controls underwent bilateral renal ischemia-reperfusion injury (IRI), followed by assessment of renal function, histopathology, and biomolecular analysis. Dendritic cells (DC) from WT control, Raptor$^{-/-}$ or Rictor$^{-/-}$ mice were isolated and assessed *ex vivo*.

Results: CD11c-specific Raptor$^{-/-}$ mice demonstrated no difference in renal function compared to control mice following IRI. However, CD11c-specific Rictor$^{-/-}$ displayed significantly worse renal function and histologic damage at 24 h reperfusion compared to littermate controls. Deterioration in renal function also reflected an aggravated pro-inflammatory cytokine profile (TNFα, IL-1β, IL-6), with kidney-specific increases in $CD11b^+Ly6G^+$neutrophil, $CD3^+$ T cell, $CD11b^+F4/80^+$macrophage and $MHCII^+CD11c^+$DC infiltrates. Increased splenic neutrophil and macrophage infiltrates were also demonstrated in Rictor$^{-/-}$ mice post-IRI. Renal Rictor$^{-/-}$ DC displayed enhanced expression of maturation markers CD40 and CD86, and decreased PD-L1 post-IRI. *Ex vivo* isolated Rictor$^{-/-}$ DC also demonstrated an enhanced maturation profile compared to WT DC, which was augmented by hypoxia-reoxygenation, and associated with depressed oxidative phosphorylation and increased glycolytic phenotype. Tracking of WT and Rictor$^{-/-}$ DC simultaneously adoptively transferred into B6 mice at the time of renal IRI showed increased numbers of Rictor$^{-/-}$ DC migrating to the injured kidney.

Conclusions: These novel data show that DC-targeted elimination of Rictor promotes IRI, highlighting the regulatory role of both DC and mTOR complex 2 in the pathophysiology of AKI.

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TH-PO261

Activation of the Cholinergic Anti-Inflammatory Pathway by GTS-21 Attenuates Cisplatin-Induced AKI Prodyot K. Chatterjee,[1] Michael M. Yeboah,[3] Malvika H. Solanki,[2] Gopal Kumar,[4] Xiangying Xue,[1] Valentin A. Pavlov,[1] Yousef Al-Abed,[5] Christine N. Metz.[1] *[1]The Center for Biomedical Sciences, Feinstein Institute for Medical Research, Manhasset, NY; [2]The Department of Pathology and Laboratory Medicine, Medical College of Wisconsin, Milwaukee, WI; [3]Dept. Division of Nephrology, Medical College of Wisconsin, Milwaukee, WI; [4]Elmezzi Graduate School of Molecular Medicine, Northwell Health, Manhasset, NY; [5]The Center for Molecular Innovation, Feinstein Institute for Medical Research, Manhasset, NY.*

Background: Acute kidney injury (AKI) is the most common side effect of cisplatin, a widely used chemotherapeutic agent. Although AKI occurs in up to 1/3 of patients treated with cisplatin, effective protective strategies are lacking. Cisplatin targets renal proximal tubular epithelial cells leading to the production of reactive oxygen species

(ROS), inflammation, tubular cell injury, and eventually cell death. The cholinergic anti-inflammatory pathway is a vagus nerve-mediated physiological mechanism that suppresses inflammation via α7nicotinic acetylcholine receptors (α7nAChRs). Our previous studies demonstrated the renoprotective effects of α7nAChR agonists (e.g. GTS-21) in murine renal ischemia reperfusion injury and sepsis-induced AKI. Therefore, we examined the effect of GTS-21 on cisplatin-AKI.

Methods: Male C57BL/6 mice were treated with either saline or GTS-21 (4mg/kg, i.p.) twice daily for 4 days before cisplatin (20mg/kg, i.p.); 72 hrs later mice were euthanized and their plasma and kidneys were analyzed for markers of renal injury, ROS, and inflammation, as well as renal ATP levels, renal cisplatin accumulation and the expression of cisplatin influx and efflux transporters.

Results: GTS-21 significantly reduced cisplatin-induced renal dysfunction and injury. GTS-21 significantly attenuated renal *Ptgs2*/COX-2, IL-6, IL-1β, and CXCL1 expression, as well as neutrophil infiltration and MPO activity after cisplatin. GTS-21 blunted cisplatin-induced ERK1/2 activation, oxidative stress, as well as renal ATP depletion and apoptosis ($p<0.05$). GTS-21 suppressed cisplatin influx transporter CTR1 expression and enhanced the expression of cisplatin efflux transporters MRP2, MRP4, and MRP6 ($p<0.05$). Using cancer cell lines we showed that GTS-21 did not inhibit cisplatin's tumor killing activity.

Conclusions: GTS-21 protects against cisplatin-AKI by attenuating renal cytokine/chemokine expression, ROS, and mitochondrial dysfunction, as well as by decreasing renal cisplatin influx and increasing efflux. GTS-21 does not impair cisplatin-mediated tumor cell killing. Our results support further exploring the cholinergic anti-inflammatory pathway for preventing cisplatin-induced AKI.

Funding: Private Foundation Support

TH-PO262

Implications of Short-Term Coxsackievirus Infection in Non-Obese Diabetic Mouse Kidneys Debra L. Walter, Rosemary J. Oaks, Ramiro Malgor, Frank L. Schwartz, Kelly D. Mccall, Karen T. Coschigano. *Ohio University, Athens, OH.*

Background: End stage renal disease (ESRD) can result from four primary diagnoses, diabetes, hypertension, glomerulonephritis and cystic kidney disease, all of which have viruses implicated as causative agents. Enteroviruses, like coxsackievirus (CV), are a common genus of viruses that have been implicated in both diabetes and cystic kidney disease, however, little is known about early CV infection in the kidney and how that infection may contribute to ESRD. This study, therefore, evaluates short-term CV infection in the kidneys of non-obese diabetic (NOD) mice; a strain of mice with a genetic predisposition to develop type 1 diabetes mellitus (the most common primary ESRD diagnosis), a condition which can be accelerated by CV infection in these mice. Characterizing the short-term effects of CV on the kidneys will define our understanding of how "innocent" viruses like CV may have a more significant impact on chronic kidney disease than previously described.

Methods: Eight-week-old NOD mice were infected with CV and euthanized 3, 7, 10 and 14 days post infection. Kidneys were collected and processed for histological and gene expression analyses.

Results: CV RNA in the kidney peaked 3 days post infection and was identified in both the glomerulus and tubulointerstitial regions. Virus was no longer detectible by real-time RT-PCR or *in situ* hybridization 14 days post infection. Percent kidney weight and urinary albumin creatinine ratio, hallmarks of kidney injury, did not demonstrate significant alterations in NOD mouse kidneys at these timepoints. Histological evaluation of PAS and H&E stained tissue did not reveal any significant pathological changes between infected and non-infected kidneys at any time point. However, gene expression of TLR3 and its signaling products TNFα, IL-6 and CXCL10 were found to be upregulated 3 days post CV infection, indicating a potential kidney cell response to virus infection. Further evaluation will be performed to determine in which cells of the kidney TLR3 is upregulated.

Conclusions: Together, these data will help identify initial kidney gene expression changes in response to virus infection that may play a role in later ESRD.

TH-PO263

Natural IgM and TLR Agonists Switch Murine Splenic Pan-B to "Regulatory" Cells That Suppress Ischemia Induced Innate Inflammation via Regulating NKT-1 Cells Peter I. Lobo, Kailo H. Schlegel, Amandeep Bajwa, Mark D. Okusa. *University of Virginia, Charlottesvillle, VA.*

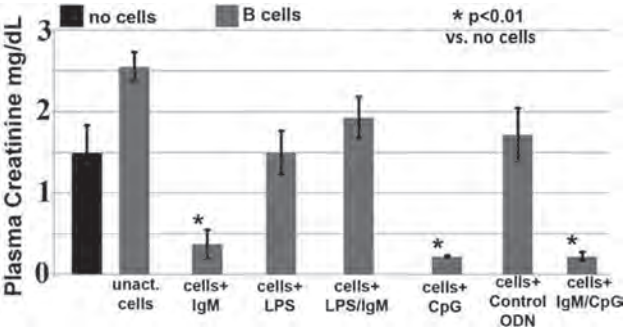
Background: Innate inflammation after reperfusion of ischemic organ has a significant role in ischemic acute kidney injury (AKI). In prior studies, we showed that natural IgM anti-leucocyte autoantibodies (IgM-ALA) inhibit inflammation. Here we show that pan-B cells are switched to regulatory cells when pretreated *ex-vivo* with either IgM or CpG.

Methods: C57BL/6 mice were i.v. infused with 0.5X10^6 B cells that were cultured for 48h with either IgM or CpG and 24h later these mice underwent bilateral renal ischemia. Plasma creatinine and other studies were preformed 24h after ischemia.

Results: Pre-treatment with regulatory pan-B cells (IgM or CpG treated) protected kidneys from AKI via regulation of *in-vivo* NKT-1 cells which amplify the innate inflammatory response to DAMPS released after ischemia. Such *ex-vivo* induced regulatory pan-B cells express low CD1d and inhibit inflammation by regulating *in-vivo* NKT-1 in the context of low lipid antigen presentation and by a mechanism that involves either PDL1. CpG induced regulatory B cells, but not IgM induced regulatory B cells, also require IL10 for their regulatory activity. LPS, unlike CpG, fails to down-regulate CD1d and switch pan-B to regulatory cells that inhibit ischemia induced AKI despite increased IL10 production.

Conclusions: *Ex-vivo* induced regulatory pan-B cells could have therapeutic relevance as these easily available cells can be pre-emptively infused to prevent AKI that can occur during open heart surgery or in transplant recipients receiving deceased donor organs.

Funding: NIDDK Support



TH-PO264

Genetic and Pharmacologic Blockade of Prostaglandin Transporter Attenuates Cisplatin Nephrotoxicity Molly Fisher, Victor J. Pai, Run Lu, Victor L. Schuster. *Albert Einstein College of Medicine, Bronx, NY.*

Background: Cisplatin (CP) is used to treat a variety of malignancies but nephrotoxicity limits its use. CP nephrotoxicity is characterized by renal vasoconstriction and proximal tubular damage. Underlying molecular mechanisms include inflammation, reactive oxygen species, and apoptotic pathways. Prostaglandins have been shown to be cytoprotective in many tissues including the kidney. Prostaglandins are metabolized by the prostaglandin transporter, PGT. We have developed a PGT knockout mouse and a high-affinity PGT inhibitor, PV02076 ("PV"). Both have been shown to raise endogenous levels of PGE_2 and may be useful therapeutically. We hypothesized that genetic and pharmacologic blockade of PGT would prevent CP nephrotoxicity.

Methods: PGT wildtype and knockout mice were given a single dose of CP 20mg/kg intraperitoneally (IP). C57BL/6 wildtype mice were given vehicle or PV 20mg/kg IP 24 and 1 hour prior to, 24 and 48 hours after, one dose of CP 20mg/kg IP. All mice were sacrificed 72 hours after CP. Renal function was evaluated by serum creatinine, cystatin C, KIM-1 immunohistochemistry, and tissue histology by tubular injury score. Quantitative polymerase chain reaction (Q-PCR) and serum cytokine dot-blot assay were used to identify differences in the expression of inflammatory, oxidative stress, and apoptotic genes. TUNEL assay was performed to assess for cell apoptosis. Urine PGE_2 levels were measured by ELISA.

Results: Urine PGE_2 excretion was increased in KO and PV-treated mice, confirming blockade of PGE_2 metabolism. KO mice had reduced serum creatinine after CP. Pharmacologic blockade of PGT with PV significantly attenuated CP nephrotoxicity as assessed by serum biomarkers of renal injury (creatinine, cystatin C) and histologic measurements of tubular injury and cell apoptosis (KIM-1, tubular injury score, TUNEL assay). Serum biomarkers (TNF-alpha) and renal gene expression studies (IL-6, IL-1beta, bcl2, SOD-1, SOD-2) revealed decreased inflammation, apoptosis, and oxidative stress in CP mice given PV.

Conclusions: Genetic and pharmacologic blockade of PGT attenuates cisplatin nephrotoxicity. We hypothesize the mechanism involves PGE_2-mediated vasodilation and/or cytoprotection through reduction of inflammation, oxidative stress, and apoptosis. Pharmacologic blockade of PGT may be a novel renoprotective strategy for cisplatin nephrotoxicity.

Funding: Other NIH Support - T32 Research Training Grant

TH-PO265

A Distinct Kidney CD45intCD11bintF4/80+MHCII+Ly6C- Macrophage Population in Mice and Humans Sul A Lee, Sanjeev Noel, Mohanraj Sadasivam, Abdel Hamad, Hamid Rabb. *Johns Hopkins University School of Medicine, Baltimore, MD.*

Background: Kidney mononuclear phagocytic cells (MPCs) play important roles in the pathogenesis of acute kidney injury (AKI) and other inflammatory diseases. However, renal MPCs are incompletely understood. While focusing on murine kidney $TCR\alpha\beta^+CD4^-CD8^-$ [double negative (DN)] T cells, we identified a distinct kidney macrophage subset which differed from conventional renal macrophages in many key aspects.

Methods: MPCs were isolated from different lymphoid and non-lymphoid organs of C57BL6 male mice at baseline or following ischemic AKI and analyzed for the frequency and phenotypic markers. Macrophage ablation was performed by intraperitoneal injection of liposomal clodronate. MPCs in human kidney were analyzed in normal tissue from nephrectomies for renal cell carcinoma.

Results: While focusing on kidney DN T cells, we identified a cell population that binds only to TCRβ and CD8β antibodies but not to CD8α antibody. Further studies using Fc receptor blockers disclosed that this population was a renal macrophage subset which was different from conventional macrophages by its intermediate (int) expression

of CD45 and CD11b. These $CD45^{int}CD11b^{int}$ macrophages were further characterized as $F4/80^{+}MHCII^{+}Ly6C^{-}$ cells, comprising 16.8%±0.4% of total $CD45^{+}$ cells in normal kidney ($P = 0.002$), 4.5%±1.0% in heart but <1% of total $CD45^{+}$ cells in thymus, lymph node, spleen, lung, liver, lamina propria and intraepithelial layer. Systemic clodronate treatment had greater depletive effect on $CD45^{int}CD11b^{int}$ population than conventional $CD45^{high}CD11b^{+}$ population (77.1% vs. 19.3%) in mouse kidney, suggesting higher phagocytic function of $CD45^{int}CD11b^{int}$ population. $CD45^{int}CD11b^{int}$ cells increased rapidly after AKI and decreased after 48 hours compared to a persistent increase in $CD45^{high}CD11b^{+}$ population ($P < 0.05$). We also found $CD45^{int}CD11b^{int}$ macrophages (1.4% to 9.3%) in human kidney samples (n=3) compared to conventional $CD45^{high}CD11b^{+}$ population that comprised 12.5% to 42.4% of total $CD45^{+}$ cells.

Conclusions: Our data suggest that $CD45^{int}CD11b^{int}F4/80^{+}MHCII^{+}Ly6C^{-}$ macrophages are primarily found in kidney and have distinct pattern of phenotypic markers and response to ischemic AKI compared to traditional macrophages. We are currently studying functional characteristics of this population by analyzing their phagocytosis functions, cytokines, and role in kidney diseases.

Funding: NIDDK Support

TH-PO266

Antisense Oligonucleotide Mediated Inhibition of NLRP3 Expression Attenuates Aristolochic Acid Induced AKI Aaron Donner,[2] Thomas Bell,[1] Mark Graham,[4] Rosanne M. Crooke.[3] *[1]Ionis Pharmaceuticals, Carlsbad, CA; [2]Antisense Drug Discovery, Ionis Pharmaceuticals, Carlsbad, CA; [3]Ionis Pharmaceuticals, Inc, Carlsbad, CA; [4]Isis Pharmaceuticals, Carlsbad, CA.*

Background: In addition to its role in innate immunity, there is increasing evidence that the inflammasome pathway is a crucial driver of pathology in immune, metabolic and renal diseases. Genetic and pharmacologic inhibition of components of the NLRP3-containing inflammasome (NLRP3, ASC and Caspase-1) or its downstream effectors (IL-1b, IL-18) has been shown to provide therapeutic benefit in animal models of disease. We have sought to target the upstream node, the inflammasome, using ASOs directed against NLRP3 in a mouse model of acute kidney disease. We demonstrated the ability to prevent aristolochic acid I induced acute kidney injury (AAI AKI) with prior administration of an ASO targeting NLRP3, a key component of the inflammasome. The NLRP3 ASO attenuated disease based on plasma and urinary biomarkers, renal expression of inflammatory and pro-fibrotic mRNA markers and histological changes. Disease-induced increases in plasma creatinine and BUN and urinary increases in protein:creatinine ratios were reduced by prior administration of NLRP3 ASO. AAI dependent induction of renal inflammatory (e.g. nlrp3, kim1, ngal) and pro-fibrotic (e.g. timp1, mmp2, col1a1) mRNAs was also reduced by the NLRP3 ASO. Histologically, the NLRP3 ASO protected from AAI induced morphological changes throughout the nephron. Based on our findings, ASO mediated inhibition of NLRP3 expression could provide therapeutic benefit for those suffering from kidney disease.

Methods:

Results:

Conclusions:

TH-PO267

Microparticles in Oxidative Stress and Inflammatory Models of Kidney Injury Begoña Campos,[2] Brittany N. Gleich,[2] Keith L. Saum,[2] Karen M. Domenico,[1] Charuhas V. Thakar.[2,3] *[1]Shriners Hospitals for Children, Cincinnati, OH; [2]University of Cincinnati, Cincinnati, OH; [3]Cincinnati VAMC, Cincinnati, OH.*

Background: Acute kidney injury (AKI) is associated with significant morbidity, including remote organ dysfunction. In response to stress or injury cells release phenotypically and quantitatively distinct microparticles (MP's), representing both the cell type and metabolic stage (e.g. apoptosis, activation, proliferation). The *objective* of this study was to evaluate relelase of MP's from renal proximal tubular epithelial cells (RPTEC) in inflammatory and oxidative stress. We also examined MP's as putative biomarkers, and their role in remote organ cross-talk.

Methods: We used in vitro models of injury to human immortalized RPTEC line. Exposures of H_2O_2 (0.03 mM for 1 hour) and TNF-α (50 and 100 ng/ml for 72 hours were compared to controls (N = 3 sets). The presence of CD10, CD13 and CD146 proteins on the cells was evaluated by western blot and confocal microscopy. Flow cytometric analysis was used to detect the release of MP's containing CD10, CD13, and CD146. Analysis of MP's was performed using FlowJo software. MP levels were expressed as mean and standard deviations times 10^5 and compared by unpaired t-tests.

Results: Western blot and confocal microscopy, in controls and treated cells, confirmed the presence of CD10, CD13 and CD146 proteins on RPTEC. Under both oxidative stress (H_2O_2) and inflammatory stress (TNF-α) cells showed morphological changes associated with apoptosis. Compared to controls MP's were significantly increased in H_20_2 treated cells: CD10 (0.456 vs 9.842; p = 0.013), CD13 (3.190 vs 53.882; p = 0.0001) and CD146 (5.991 vs 142.474; p = 0.0018). TNF-α treated cells at both concentrations also released CD10, CD13 and CD146 MP's; however, only CD13 MP's were statistically higher than controls at 100 ng/ml of TNF-α (26.67 vs 56.911; p 0.02). CD146 MP's showed a trend at both concentrations of TNF-α.

Conclusions: This is the first report of detection of microparticles (CD10 and CD13) specific to and derived from human RPTEC. Furthermore, we demonstrate a significant increase in the level of MP's derived from renal cells that is specific to oxidative and inflammatory stress. Additionally, release of CD146 MP's by stressed RPTEC could serve as ligand for endothelial activation, suggesting renal origins of organ cross-talk. Thus, MP's expressed by RPTEC could serve as putative biomarkers for AKI, and once released, may mediate organ cross-talk.

Funding: Clinical Revenue Support

TH-PO268

Loss of Melanocortin 5 Receptor Exacerbates Endotoxic AKI via Impairing Regulatory T Cell Response Yahong Xu,[1,2] Rong Zhou,[1] Rujun Gong.[2] *[1]Yangpu Hospital, Tongji University, Shanghai, China; [2]Brown Medical School, Providence, RI.*

Background: Pituitary melanocortin neuropeptides, exemplified by α-melanocyte-stimulating hormone, have long been recognized to possess a remarkable renoprotective activity in diverse forms of acute kidney injury (AKI). However, the molecular mechanism responsible for this beneficial action has been illusive and exactly which type of melanocortin receptor conveys the renoprotective effect remains to be defined. Lately, there is growing evidence suggesting that melanocortin 5 receptor (MC5R) signaling confers a protective effect in multiple organ systems. The role of MC5R in kidney injury was examined in this study.

Methods: MC5R knockout mice (KO) and congenic wild-type (WT) littermates were injured with lipopolysaccharides (LPS) and AKI examined. Bone marrow derived cells were prepared from WT or KO mice and adoptively transferred to KO mice followed by LPS injury.

Results: Mice with global knockout of MC5R were phenotypically indistinguishable from their WT littermates, and exhibited normal development with undetectable difference in kidney physiology, function and histology. As compared with WT controls, KO mice developed much severer AKI upon LPS injury, as evidenced by higher serum creatinine levels, more urinary excretion and renal expression of lipocalin-2, exacerbated renal histologic damages and tubular cell death, and amplified renal inflammation. This worsened AKI in KO mice was unlikely attributable to a tubular cell-autonomous mechanism, because primary cultures of proximal tubular epithelial cells derived from KO and WT mice demonstrated similar cellular injury and death and comparable inflammatory response following LPS injury. Instead, the amount of CD4+Foxp3+ regulatory T cells in the injured kidney from KO mice was strikingly diminished, concommitant with a drastic amplification of renal inflammatory infiltrations, thus underscoring an impaired immune tolerance to LPS injury. Moreover, adoptive transfer of bone marrow derived cells derived from congenic WT littermates to KO mice substantially replenished CD4+Foxp3+ regulatory T cells in the kidney following LPS injury, resulting in a substantial improvement of the LPS-invoked AKI and renal inflammation.

Conclusions: Collectively, MC5R is likely essential for regulatory T cell response to LPS injury and thereby conveys a protective activity in endotoxic AKI.

TH-PO269

The Yes Associated Protein (YAP) Facilitates Kidney Fibrosis in a Kidney Injury Molecule-1 (KIM-1) Dependent Manner Akinwande A. Akinfolarin, Venkata Sabbisetti, Amrendra K. Ajay, Emily Christie, Joseph V. Bonventre. *Brigham and Women's Hospital, Boston, MA.*

Background: The Salvador-Warts-Hippo (SWH) pathway controls organ size by modulating cell proliferation and apoptosis. The nuclear localization of the YAP drives cell proliferation through the transcriptional co-activation of the TEA domain family, a regulator of TGF-β signaling. Following cell confluence, the SWH pathway acts as a negative feedback system to cause nucleo-cytoplasmic shuttling, phosphorylation and inactivation of YAP. Chronic epithelial expression of the KIM-1 is associated with the development of murine kidney fibrosis. In this study we show that the presence of epithelial KIM-1 is associated with nuclear accumulation of YAP and development of kidney fibrosis in mice

Methods: C57B6 wild type (WT) mice or mice with a mutation of the mucin domain of KIM-1 ($KIM\text{-}1^{\Delta mucin}$) were examined either 14 days after 26 min of bilateral ischemia (I/R) or 10 days after unilateral ureteral obstruction (UUO). LLC-PK1 and HEK cells were transduced with human *KIM-1* full length cDNA (LLC-PK1-KIM1 and HEK-KIM1) or an empty pcDNA3 vector (PK1-pcDNA and HEK-pcDNA). Experiments with short hairpin RNA against *YAP* and inhibition of YAP signaling with a small molecule, verteporfin was also done in PK1 and HEK cells. These kidney cells were then examined for proliferation after TGF-β stimulation and Cisplatin treatment

Results: Proximal tubule (PT) expression of YAP was increased in WT mice that had more kidney fibrosis as compared to their $KIM\text{-}1^{\Delta mucin}$ littermates when examined by Masson's trichrome (MT) and Periodic Acid Schiff (PAS) staining after I/R and UUO. Western blot analysis of whole kidney cortex revealed greater levels of fibrogenic factors including CTGF, fibronectin and ACTA2 in the WT mice as compared with the $KIM\text{-}1^{\Delta mucin}$ mice. These animal data were supported by in vitro experiments which revealed less cell proliferation and production of pro fibrotic factors with either YAP knock down or inhibition when compared with WT, following TGF-β stimulation. KIM-1 expressing cells had increased nuclear YAP and CTGF levels as compared to cells expressing the control vector

Conclusions: YAP is up regulated in murine kidney fibrosis, more so in proximal tubule cells expressing KIM-1. Pharmacologic depletion of YAP or enhancement of SWH signaling may be of therapeutic importance in attenuating kidney fibrosis

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TH-PO270

Orai1 Mediated Ca+2 Signaling Influences IL-17 Expression in CD4+ T Cells Following I/R Purvi Mehrotra,[1] David P. Basile.[2] *[1]Indiana School of Medicine, Indianapolis, IN; [2]Indiana University School of Medicine, Indianapolis, IN.*

Background: T-helper 17 (Th17) cells have been implicated in the pathogenesis of acute kidney Injury (AKI). Renal Th17 cells transiently increase for up to 3-days post ischemia/reperfusion (I/R) and return to basal levels within a week. Exposure of post AKI rats to elevated dietary salt (4%) stimulates sustained induction of renal Th17 cells, which is associated with CKD progression. The store-operated calcium channel (SOCC), Orai-1 plays a role in models of inflammatory disease such as colitis or autoimmune encephalopathy, which may be influenced by dietary salt. We hypothesized that AKI primes CD4+ T cells to increase IL17 expression secondary to Orai1 dependent Ca^{2+} signaling.

Methods: FACs analysis demonstrated increased Orai1 protein in renal CD4+ T-cells 7 days following I/R (MFI:221644±3567) relative to sham operated controls (MFI:106924±467; p<0.05). To evaluate the role of Orai1 mediated Ca^{2+} influx in the progression of AKI, rats were subjected to bilateral I/R and the dependency of AKI primed T cells on Ca^{2+} entry was evaluated using an in vitro assay of renal CD4+ cells, which resulted in ~5 fold increase in IL17 expression in response to Ang II (10^{-7}M) and elevated extracellular Na^{+} (170 mM).

Results: The IL17 induction of AKI primed CD4+ cells in vitro was attenuated by > 95% (p<0.05) by 3 inhibitors that target Orai-1 (2-ABP (20mm), AnCoA4 (50mm) or YM58483 (120nm)). A significant percentage (40-50%) of AKI-primed CD4+ cells, but not sham-derived CD4 cells, manifested increased intracellular Ca^{2+} in response AngII+170 mM Na^{+}, a response that was completely abrogated by co-incubation with AnCoA4. Furthermore, treatment with YM58483 in vivo (1mg/Kg), reduced renal Th17 cells 2 days post I/R compared to vehicle treated rats (15,3076±1265 vs 7390±439 cells/gram of kidney; p<0.05). Interestingly, YM58483 had no effect on renal Th1 or Th2 cells. In addition, YM58483 significantly reduced the extent of renal injury by attenuating the increase in serum creatinine by ~66% (p<0.05) vs vehicle treated post AKI rats.

Conclusions: Taken together, these data suggest that I/R leads to increased Orai-1 mediated Ca^{2+} influx thereby enhancing IL-17 expression and may influence the severity of AKI.

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TH-PO271

Mutation of the RORγC Gene in Rats Attenuates Th17 Cell Activity, Renal Injury, and Inflammation in Response to Ischemia Reperfusion Purvi Mehrotra,[1] Jason A. Collett,[2] David P. Basile.[2] *[1]Indiana School of Medicine, Indianapolis, IN; [2]Indiana University School of Medicine, Indianapolis, IN.*

Background: T cells have been implicated in initiation of renal damage following I/R injury, while recent studies have also suggested that a specific T helper subset, Th17 cells, is associated with both initiation of AKI and the AKI-to-CKD progression. To evaluate the direct role of Th17 cells in AKI, RoRgc (RAR orphan receptor gamma), a transcription factor considered the master regulator for Th17 cell differentiation and IL-17 gene expression was targeted for mutation in Lewis rats.

Methods: Using a CRISPR-CAS9 approach, an 8 bp deletion was introduced into the rat RoRgc gene. The verified sequence analysis predicted a mis-sense mutation at a.a.31 and premature truncation relative to the 508 a.a. protein in wild-type rats. Lewis$^{RORγT-/-}$ rats appear normal and healthy but show moderate growth retardation relative Lewis $^{RORγT+/+}$ control rats.

Results: Under basal conditions, reduced percentages of CD4+ (50±2.4 vs 24.45±1.7; p<0.05), B cells (21.4±7.2 vs 13.85±0.85; p<0.05) and Macrophages (13.07±3.5 vs 7.7±0.97; p<0.05) in the spleen of 6-8-week old Lewis$^{RORγT-/-}$ rats compared to wildtype controls. To evaluate the effect of RORgC mutation on the induction of Th17 cells during AKI, both mutant and wild type rats were subjected to bilateral renal I/R for 40 min. Renal Th17 cells were enhanced 2 days following I/R in wild type rats but were significantly reduced in Lewis$^{RORγT-/-}$ rats (63094±10498 vs 24434±4830; p<0.05) post I/R with no effect on Th1 and Th2 cells. In addition, Lewis$^{RORγT-/-}$ were resistant to AKI as measured by serum creatinine (4.5±0.4 vs 2.6±0.4; p<0.05) as well as reduced renal inflammation as indicated by total CD4+ (40%; p<0.05) and CD8+ (48%; p<0.05). After 7 days of recovery, AKI primed lymphocytes from wild type rats manifested an IL-17 mRNA induction in response to Ang II +170 mM Na+ in vitro, however AKI primed lymphocytes from Lewis$^{RORγT-/-}$ rats showed no increase in IL-17 mRNA expression.

Conclusions: Taken together these data that mutation of RORγC in rats impairs Th17 cell activity in response to renal I/R and modulates the sensitivity to the development of AKI.

Funding: NIDDK Support

TH-PO272

CC-Chemokine Receptor 7 Deficient Mice Are Resistant to Renal Ischemia Reperfusion Injury Hiroshi Kojima,[1] Xuzhen Hu,[1] Erik H. Koritzinsky,[1] Myung-gyu Kim,[1] Jonathan Street,[1] Timothy J. Break,[2] Michail Lionakis,[2] Peter S. Yuen,[1] Robert A. Star.[1] *[1]National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; [2]National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, MD.*

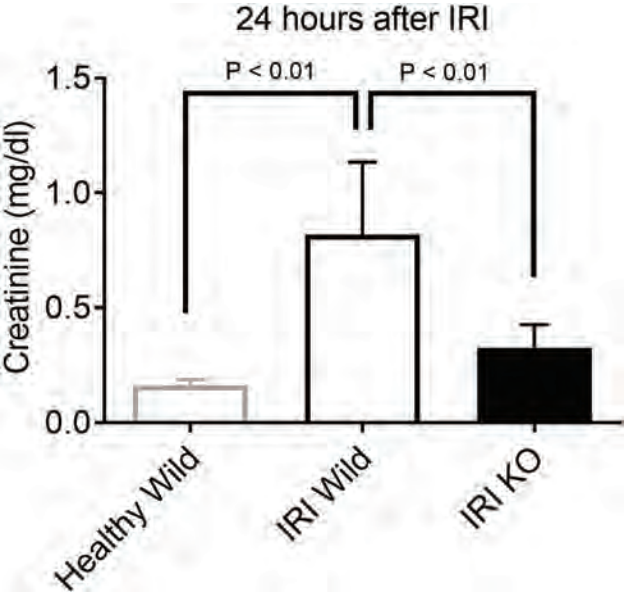
Background: One of the most prominent chemokine receptors in the adaptive immune system is CC-chemokine receptor 7 (CCR7), which has been established as an important component of lymphocyte-driven immune function. CCR7 promotes homing of T cells and Dendritic Cells (DCs) to T cells areas of lymphoid tissues where T cells priming occur. Apart from chemotaxis, CCR7 controls cytoarchitecture, rate of endocytosis, survival, migratory speed, and maturation of the DCs. Manipulation of CCR7 axis has either protective or deleterious role in mouse kidney injury models. We sought to clarify the role of CCR7 in the pathogenesis of renal injury after ischemia reperfusion injury (IRI).

Methods: CCR7 deficient mice (*CCR7*$^{-/-}$) or wild-type mice (*CCR7*$^{+/+}$) underwent IRI. Mice were euthanized at 1, 3 and 7 days after the surgery. Kidney & serum were collected for biochemical analysis & histological evaluation.

Results: Blood urea nitrogen, cystatin C, & creatinine levels in *CCR7*$^{-/-}$ were lower than *CCR7*$^{+/+}$ throughout experimental periods. Similarly, *CCR7*$^{-/-}$ developed milder tubulointerstitial injuries than *CCR7*$^{+/+}$. There was a significant correlation between serum markers & histology score.

Conclusions: *CCR7*$^{-/-}$ mice are resistant to IRI. We speculate that dendritic cells (DCs) are involved the reno-protective property in *CCR7*$^{-/-}$. In *CCR7*$^{+/+}$, IR induced danger signals induce normal maturation/activation of DCs, causing the development of effector T cell response. In *CCR7*$^{-/-}$, DC maturation is prevented; DCs would remain in the state of immune tolerance despite the presence of danger signals. **Implications:** Targeting DCs through CCR7 may have therapeutic potential for IRI.

Funding: NIDDK Support



TH-PO273

CD4 T Cells Activated by Ultrasound or Vagus Nerve Stimulation Protect Kidneys from Ischemia-Reperfusion Injury through β2 Adrenergic Receptor Tsuyoshi Inoue,[1] Chikara Abe,[2] Liping Huang,[1] Diane L. Rosin,[1] Patrice G. Guyenet,[1] Mark D. Okusa.[1] *[1]University of Virginia, Charlottesville, VA; [2]Gifu University, Gifu, Japan.*

Background: We recently showed that prior ultrasound (US) treatment and vagus nerve stimulation (VNS) protect kidneys from ischemia-reperfusion injury (IRI) through the cholinergic anti-inflammatory pathway (CAP). Although β2 adrenergic receptor-positive CD4+ T cells are thought to be components of the CAP, they have yet to be tested in mediating the protective effect of CAP activation following IRI.

Methods: Kidney IRI (bilateral, 26 mins) was used as an acute kidney injury (AKI) model and IRI was performed 24 hr after US (bilateral, 2 mins) or VNS (left side, 5 Hz, 50 μA for 10 min) treatment. Kidney injury was evaluated 24 hr later using plasma creatinine (PCr), kidney Kim-1 mRNA expression and histology (H&E). CD4+ splenocytes (MACS-enriched) were isolated from donor mice and transferred i.v. to recipient mice. Butoxamine was used as a β2 adrenergic receptor antagonist, and salbutamol was used as a β2 adrenergic receptor agonist.

Results: When butoxamine (15 mg/kg) was administered 30 mins prior to US and VNS, the renal protective effect of US and VNS was abolished (PCr: 0.20 and 1.76 mg/dl (P<0.001) for vehicle+US and butoxamine+US, respectively, n=7). Salbutamol (15 mg/kg) administration 24 hr prior to IRI protected the kidney. Adoptive transfer of CD4+

splenocytes (1x10^5 cells) from US-treated or VNS-treated mice to recipient mice subjected to IRI provided greater protection than CD4+ splenocytes from mice who received sham US or sham VNS (PCr: 0.44 and 1.31 mg/dl (P<0.001) for VNS- and sham VNS-treated CD4+ splenocytes from spleen, respectively, n=9). In addition, the kidney was protected when salbutamol-treated CD4+ splenocytes were transferred 24 hr prior to IRI.

Conclusions: These data demonstrate that activation of CD4+ splenocytes through β2 adrenergic receptors is important for the protective effect of US and VNS in AKI.

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TH-PO274

AKI Stimulates Inflammation Associated Lymphangiogenesis

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Background: The lymphatic system is crucial for maintaining fluid balance, transporting lipids, and aiding in immune function. The functions of the lymphatic system are further accentuated during pathological conditions such as inflammation, the latter a key component of acute kidney injury (AKI). Inflammation induces lymphangiogenesis through expression of vascular endothelial growth factors (VEGFs), particularly VEGF-C, VEGF-D, and their receptor VEGF-R3. While recent studies have shown lymphangiogenesis to be an active participant in a number of inflammatory diseases, very little is known about the role of the lymphatic system and more importantly, lymphangiogenesis, in the pathogenesis of AKI. Based on the prominent role of lymphangiogenesis in various inflammation induced disease models, this delicate and crucial pathway could serve as a novel target to be exploited for therapeutic interventions in AKI.

Methods: To study the role of lymphangiogenesis in the pathophysiology of AKI, we induced renal injury in mice via bilateral ischemia-reperfusion injury (I/R), a well characterized model of AKI and measured lymphatic vessel content as well as mRNA and protein levels of growth factors and inducers of lymphangiogenesis.

Results: We observed increased lymphatic vessel content in kidneys of mice that had undergone I/R compared to uninjured controls via LYVE1 (a cell surface receptor on lymphatic endothelial cells) immunohistochemistry. RT-PCR analysis revealed increased levels of lymphatic markers, LYVE1 and Podoplanin in kidneys 7 days after I/R. We also observed increased VEGF-R3 protein levels after injury peaking at day 3 post I/R in kidney lysates. ELISA analysis of VEGF-C levels showed a decrease in kidney VEGF-C with a simultaneous increase in serum levels of VEGF-C. VEGF-C protein was also detected in the urine at day 1 post I/R. VEGF-C immunofluorescence staining revealed expression in proximal tubule cells in uninjured kidneys. After I/R, VEGF-C is seen in the apical side of proximal tubule cells. This together suggests a mechanism in which VEGF-C is secreted from the tubules into the blood and urine following injury.

Conclusions: These results suggest that lymphangiogenesis is stimulated in kidneys after AKI and may represent a target for intervention in the pathogenesis of AKI.

TH-PO275

STAT5 Knockouts Are More Susceptible Than Wildtype Mice to Streptozotocin-Induced AKI

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Background: We have previously shown that mice deleted for the first coding exon of the Signal Transducer and Activator of Transcription 5 genes (STAT5 A/B knockout or SKO) exhibit more kidney damage in comparison to wildtype (WT) littermates when examined 12 weeks after treatment with streptozotocin (STZ) to induce diabetes. However, it was not clear whether the kidney damage was a result of the STZ treatment or the resulting hyperglycemia. To try to address this question, this study sought to investigate the acute effects of STZ treatment on kidneys of SKO and WT mice.

Methods: SKO and WT mice received, on five consecutive days, an intraperitoneal injection of either vehicle (citrate buffer, V), STZ (50 mg/kg, M) or four daily injections of vehicle followed on the fifth day by a single dose of STZ (250 mg/kg, H). All mice (n=7/group) were euthanized three days after the last injection and serum and kidneys collected. A portion of each kidney was fixed in formalin and then embedded in paraffin for morphometric and *in situ* hybridization analyses. The remaining portions of kidneys were flash frozen in liquid nitrogen for gene expression analyses (real-time reverse transcription – polymerase chain reaction; RT-RT/PCR). Two-way (genotype vs. treatment) analysis of variance followed by Tukey post-hoc analysis was used to determine statistical significance at p<0.05.

Results: At the end of the study, blood glucose levels were significantly elevated in the four STZ treatment groups in comparison to the two vehicle groups (WT-V and SKO-V), with the high dose STZ SKO group (SKO-H) being significantly higher than the other three STZ treatment groups (WT-M, SKO-M, WT-H). Blood urea nitrogen and creatinine levels were significantly elevated in the SKO-H group in comparison to the other two SKO treatment groups and to the WT-H group. Histochemical analyses revealed the greatest degree of damage, mainly tubular necrosis with no glomerular damage, in the SKO-H group, with corresponding increased RNA expression of the genes for neutrophil gelatinase-associated lipocalin (NGAL) and cytokines interleukin-6 (IL6) and -1beta (IL1beta).

Conclusions: SKO mice are more susceptible than WT mice to the acute effects of STZ, especially when administered in a single high dose.

TH-PO276

Transcriptional Response of the Intercalated Cells to UTI

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Background: Urinary tract infections (UTI) are among the most prevalent bacterial infections acquired in US hospitals, and complications can lead to urinary obstruction, bacteremia, urosepsis. We found that uropathogenic E. coli (UPEC) require iron for infection: loading with iron dextran resulted in significantly more urinary colony forming units (CFUs) than mice without prior iron loading; conversely iron-deficient mice (4 weeks of iron-deficient chow) demonstrated markedly reduced CFUs compared with iron-sufficient mice (regular chow). The form of iron was also important, heme iron was stoichometrically more powerful as a stimulant than ferric iron. These data raise the question as to how the nephron controls luminal and interstitial iron content and how bacteria disrupt these homeostatic mechanisms.

Methods: To study the process by which UPECs interact with the kidney to obtain iron, we generated a novel cell- and time-specific in-vivo RNA-labeling technique to purify specific RNA species from the intercalated cells (IC) in a UTI model.

Results: We analyzed newly synthesized RNA. RNA-sequencing demonstrated a robust transcriptional response of ICs 12 hours after UTI (95% of induced genes). Many of these upregulated genes were involved in iron and heme transport and storage, such as heme-responsive gene 1 (Hrg1), heme oxygenase (Ho1), and ferritin heavy chain (Fth1), suggesting that heme metabolism is a critical component of UTI and a mechanism of immune defense. After 24hrs these transcripts were no longer expressed.

Conclusions: A thorough investigation of iron transporters throughout the nephron revealed megalin in the proximal tubule, TfR1 in the thick limb of Henle, DMT1 in the distal convoluted tubule but remarkably none of these proteins were found in the collecting duct. In summary, we suggest that the nephron is able to recover iron using many different transport mechanisms, but the collecting duct is unique in its mechanisms of iron capture focused on heme transport. Consequently, the nutritional requirement of the collecting duct IC matches an essential component of innate defense, namely heme sequestration.

Funding: NIDDK Support

TH-PO277

Myeloid Specific H-Ferritin Mediates Sepsis Induced Inflammation and Organ Injury

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Background: Sepsis is a severe clinical syndrome that is characterized by profound and dysregulated inflammatory response to infection resulting in end-organ dysfunction distant from the primary site of infection. Despite fundamental findings that have expanded our understanding into the mechanisms that instigate and propagate sepsis and its deleterious effects on various organs including kidney, novel therapeutic agents and modalities have remained elusive. In fact, sepsis remains a leading cause of mortality and acute kidney injury in patients admitted to the intensive care unit. We previously demonstrated that macrophage polarization depends on expression of ferritin heavy chain (FtH) and such expression plays a key role to regulate the cross-talk between macrophages and renal epithelial cells during kidney injury and repair. This led to our hypothesis that macrophage specific FtH may be involved in development and consequences of sepsis.

Methods: Using transgenic mice with conditional deletion of FtH in myeloid cells (FtH LysM$^{-/-}$), we induced sepsis by a well characterized cecal ligation and puncture method.

Results: Our results demonstrate that myeloid FtH deficiency is associated with hyporesponsiveness to sepsis. We show that specific deletion of FtH in myeloid cells led to ~90% improved survival when compared to FtH LysM$^{+/+}$ littermates. Furthermore, renal function supported by serum creatinine was significantly more preserved in the FtH LysM$^{-/-}$ mice. In addition, we found decreased level of several pro-inflammatory cytokine expression in major organs, including the kidney. Our mechanistic studies show that myeloid FtH deletion causes derangements in pathways that are crucial in innate immunity and inflammation including NF-κβ, and hypoxia inducible factor.

Conclusions: Overall, our results for the first time signify the paramount importance of myeloid system iron metabolism in sepsis mediated organ injury and identify the central role of FtH in this context. As such, we propose a novel target to mitigate sepsis mediated inflammation and consequent organ injury that is urgently needed given the unacceptable rate of mortality and morbidity related to this devastating clinical condition.

Funding: NIDDK Support, Private Foundation Support

TH-PO278

Sensing of Bacterial Infection by Nerves and the Induction of Inter-Organ Communication during the First Hours of Pyelonephritis Svava E. Steiner,[1] Ferdinand X. Choong,[1] Anette Schulz,[1] Keira Melican,[1] Camilla Svensson,[2] Agneta Richter-Dahlfors.[1] *[1]Swedish Medical Nanoscience Center, Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden; [2]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden.*

Background: Tissue microbiological studies have revealed that inter-organ communication occurs within the first hours of pyelonephritis. IFN-γ released from the spleen is known to modulate the host responses at the site of renal infection within 8 h. We hypothesize that this rapid inter-organ signaling is, at least in part, mediated by the nervous system. Here we investigate nervous sensing of the bacterial infection and implicate nervous signals as mediators of the inter-organ communication between infected kidney and the responding spleen.

Methods: GFP$^+$-expressing uropathogenic *Escherichia coli* (UPEC) were microinfused into single proximal tubules in exposed kidneys of anesthetized rats. After 4 h the infection site was examined by *ex vivo* immunofluorescence (IF) analysis. Nervous projections in the renal cortex were identified through IF analysis of fixed, uninfected rat renal tissue. Splenic *Ifng* mRNA expression was determined by qPCR on splenic tissue. Cytokine and ATP release of UPEC infected renal epithelial cells (A498) were investigated in cell culture *in vitro*. Primary sensory nerve cells from mice were used to determine immune and nervous responses to UPEC infection.

Results: Despite the very localized nature of the infection, splenic *Ifng* expression was found to be upregulated already within 4 h of kidney infection. We found that sensory nerves are present in the basement membrane of proximal tubules, where they can come into close contact with infection related products. *In vitro* we found that primary mouse sensory nerves can detect pathogen-associated molecular patterns and damage-associated molecular patterns during infection and have both immunological IL-6, and nervous CGRP, responses. In cell culture, nervous responses were found to only occur during infection with bacteria that produce the toxin α-haemolysin. Translating this finding *in vivo*, we found that inter-organ communication was abrogated in animals infected with a UPEC strain that does not produce α-haemolysin.

Conclusions: Our work shows the role of the sensory nervous system in sensing a local infection in the kidney and alerting distal organs to alter the systemic host response. Bacterial production of the α-haemolysin toxin plays an important role in initiating such an alerting signal.

Funding: Government Support - Non-U.S.

TH-PO279

C5aR1 Promotes the Pathogenesis of Acute Pyelonephritis Ke Li,[2] Steven H. Sacks,[1] Wuding Zhou.[1] *[1]King's College London, London, United Kingdom; [2]Xi'an Jiaotong University, Xi'an, China.*

Background: Our recent work in a murine mode of chronic pyelonephritis has shown that C5a/C5aR1 interaction play an important role in the pathogenesis of chronic renal inflammation and tubulointerstitial fibrosis. However, the role of C5aR1 in acute pyelonephritis is presently unknown.

Methods: To investigate this, we employed a murine mode of acute pyelonephritis, induced by human UPEC strain J96, in combination with either C5aR1 deficiency (*C5aR1*$^{-/-}$ mice), or chemical blockade of C5a/C5aR1 interactions, to determine the roles of C5aR1 in acute renal infection. In addition, we performed a serious of *ex vivo* (renal tissue) and *in vitro* (primary cultures of renal tubular epithelial cells [RTEC]) experiments to examine the relationship between C5a/C5aR1 and mannosyl residue expression and UPEC adhesion/colonisation in RTEC. We also explored the signal transduction mechanisms by which C5a regulates mannosyl residue expression in RTEC. Bone marrow chimera experiments were performed to specifically evaluate the relative contributions of C5aR1 expressed on renal and myeloid cells.

Results: *In vivo* analysis showed that C5aR1 deficient mice or C5aR1 antagonist treated mice displayed reduced bacterial load and tissue destruction in the kidney, which is associated with reduced expression of mannosyl residues (a ligand for type 1 fimbriae of E coli) at luminal surface of renal tubules and early bacterial colonization of the tubular epithelium. Chimera experiments suggest that C5aR1 on renal cells plays a more prominent role in this model. In vitro analysis of renal tubular epithelial cells showed that mannosyl-dependent adhesion and invasion were enhanced by C5a-mediated ERK1/2 and NF-kB phosphorylation and TNF-α production.

Conclusions: Our data demonstrate a pathogenic role for C5a/C5aR1 in acute pyelonephritis and define novel mechanism by which C5aR1 signalling enhances mannosyl residue-dependent colonisation of renal tubular epithelium that increases susceptibility to a common and harmful urinary pathogen, opening up a new avenue for therapeutic targeting.

Funding: Government Support - Non-U.S.

TH-PO280

AKI Increases Gut Permeability and Provokes Dysregulation of Mucosal Immunity: Effect of Probiotics on AKI Severity Jihyun Yang,[1] Yoon kyung Choi,[1] Taeyeon Hwang,[1] Woori C. Cho,[3] Myung-gyu Kim,[2] Won-Yong Cho,[1] Sang-Kyung Jo.[1] *[1]Korea University Hospital, Seoul, Republic of Korea; [2]National Institutes of Health, North Bethesda, MD; [3]Korea University hospital, Seoul, Republic of Korea.*

Background: Emerging evidence indicate the presence of kidney-gut crosstalk in diverse pathological conditions. In normal condition, healthy microbiome help to maintain gut barrier and mucosal immune tolerance. In this study, we investigated kidney-gut crosstalk in AKI by assessing the effect of AKI on gut barrier integrity and mucosal immunity.

Methods: C57BL/6 mice underwent bilateral ischemia-reperfusion injury (IRI) or sham operation. In the probiotic treatment group, Bifidobacillus was administered via oral gavage once daily, started 3 weeks prior to the injury. The gut barrier integrity was assessed by measuring orally administered fluorescein isothiocyanate-dextran (FITC-dextran) activity in blood and western blot for various tight junction proteins was performed. Flow cytometric analysis of colonic macrophages as well as Foxp3 expression was performed.

Results: Following AKI, gut permeability increased significantly and it was accompanied by decreased claudin-1, occludin expression and increased number of apoptosis in colon. Ly6G$^+$ neutrophil infiltration and MPO activity increased after kidney IRI and the number of Ly6C^{high} CX3CR1.^{intermediate} macrophages also increased. Colonic Foxp3 mRNA expression showed a slight but statistically significant increase. Preconditioning with probiotics prior to IRI significantly attenuated functional, histological kidney injury and the renoprotective effect was accompanied by partial restoration of claudin-1, occludin expression and also by decreased number of colon epithelial cell apoptosis. Colon Foxp3 expression significantly increased in probiotic treated group

Conclusions: In conclusion, AKI induced gut barrier disruption and colonic inflammation might be one mechanism leading to systemic inflammation, kidney and other remote organ injury. Probiotic mediated renoprotective effect might be mediated by strengthening gut barrier and also mucosal immune tolerance mechanisms. Probiotics might be one promising strategy aiming for reducing AKI severity or remote organ injury.

TH-PO282

A Furosemide Excretion Stress Test (FEST) Predicts AKI Progression and Mortality after Sepsis Jonathan Street,[2] Tiffany R. Bellomo,[2] Erik H. Koritzinsky,[2] Hiroshi Kojima,[2] Lakhmir S. Chawla,[1] Peter S. Yuen,[2] Robert A. Star.[2] *[1]George Washington University, San Diego, CA; [2]NIDDK, Bethesda, MD.*

Background: The furosemide stress test (FST) measures urine production (diuresis) after a furosemide bolus. FST is a sensitive and specific predictor of a need for renal replacement therapy and mortality in the ICU. Furosemide causes a diuresis via 2 steps: 1) active secretion into the proximal tubule lumen, then 2) inhibition of thick ascending limb NKCC2. We hypothesize that tubule damage should reduce furosemide excretion (FEST) and prevent a subsequent increase in urine volume (FST). We developed FST and FEST protocols for a septic mouse model in which mortality is poorly predicted by filtration markers, and also tested the predictive performance of FEST in a human cohort.

Methods: We developed a sensitive reverse phase HPLC assay for urine furosemide. Male CD-1 mice underwent cecal ligation and puncture (CLP) to induce sepsis. 42 hrs post-CLP 1 mg/kg furosemide was given s.c. and urine was collected for the next 12 hrs to allow for intermittent urination. The mice were monitored every 8 hrs and euthanized if their clinical score exceeded the protocol threshold. Furosemide concentration was also measured in the post-furosemide challenge samples of 49 patients from the PASSKI cohort.

Results: A moderate severity of CLP injury was used; 32 mice survived to 42 hr and underwent FST/FEST, 19 mice survived 7 d. Urine production during 12 hr varied from 0.08 to 2.62 ml. Both urine production and the fraction of furosemide recovered in the urine predicted mortality [AUC ROC values of 0.92 ($p<0.0001$) for FST and 0.87 ($p<0.001$) for FEST]. In the human cohort, the fraction of furosemide recovered predicted progression to AKIN stage III and was comparable to FST [AUC ROC values of 0.864 for FST and 0.848 for FEST].

Conclusions: The furosemide excretion stress test and furosemide stress test strongly predict post-sepsis mortality in mice, allowing for early stratification by severity in future drug studies of late treatment or enhancing recovery. FEST performs comparably to FST in the human PASSKI cohort.

Funding: NIDDK Support

TH-PO283

LPS-Binding Protein (LBP)/TLR4 Signaling Mediates Pericyte (PC) to Myofibroblasts Trans-Differentiation (PMT) in Endotoxemic AKI Giuseppe Castellano,[1] Alessandra Stasi,[1] Rossana Franzin,[1] Fabio Sallustio,[1] Chiara Divella,[1] Alessandra Spinelli,[1] Giuseppe Grandaliano,[2] Giovanni B. Pertosa,[1] Loreto Gesualdo.[1] *[1]University of Bari, Bari, Italy; [2]University of Foggia, FOGGIA, Italy.*

Background: During sepsis, LBP/TLR4 signaling is central in the inflammatory cascade and its activation impairs renal function, leading to AKI. Renal fibrosis induced by PMT is a common pathological feature of chronic kidney disease but little is known in AKI.

Methods: AKI was induced by i.v. LPS infusion in 8 pigs (LPS). After 3h from LPS infusion, 8 pigs were treated with coupled plasma filtration adsorption (CPFA). Renal biopsies, performed at 9h from LPS infusion (T9), were analyzed by IHC and IF. Serum LBP and TGFβ were quantified by ELISA. In vitro, PC (PDGFRβ+) were analyzed by FACS, IF and WB. TGFβ-Receptor(R) neutralizing antibody was added to the cultures 30' before LPS or TGFβ stimulation.

Results: We found the occurrence of acute PMT in endotoxemic AKI by the reduction of PDGFRβ expression and αSMA increase in peritubular PC. CPFA treatment restored PDGFRβ expression ($p=0.03$) and significantly decreased $\alpha SMA^{+}PC$ ($p=0.001$), in accordance with reduced serum levels of LBP ($p<0.05$). In vitro, activation of PC with LPS or endotoxemic sera led to PMT with CollagenI synthesis and αSMA reorganization in contractile fibers ($p<0.05$). The removal of LBP from septic plasma maintained CollagenI and αSMA expression at basal level ($p<0.05$). On the contrary, exogenous LBP supplementation reversed CPFA effects. LPS increased phosphorylation of Smad2/3 and ERK1, respectively ($p<0.05$) suggesting that PMT was induced by both canonical TGFβ-Smad2/3 dependent and non-canonical TGFβ-Smad independent signaling (MAPK). Moreover, the serum levels of TGFβ increased in endotoxemic pigs and were reduced after CPFA treatment ($p<0.05$). It is well known that TGFβ induces PMT contributing to renal fibrosis. Interestingly, in vitro TGFβR-signaling blockade, did not affect LPS-induced PMT and phosphorylation of SMAD2/3 and ERK1, underlying a fibrotic role of LPS independently of TGFβ synthesis and release.

Conclusions: PC might be pivotal in the generation of myofibroblasts by PMT during AKI upon the activation of LBP/TLR4 signaling. Disrupting the persistent TLR4 signaling activation by the removal of LBP may represent a therapeutic option to prevent PC dysfunction and acute renal fibrosis.

TH-PO284

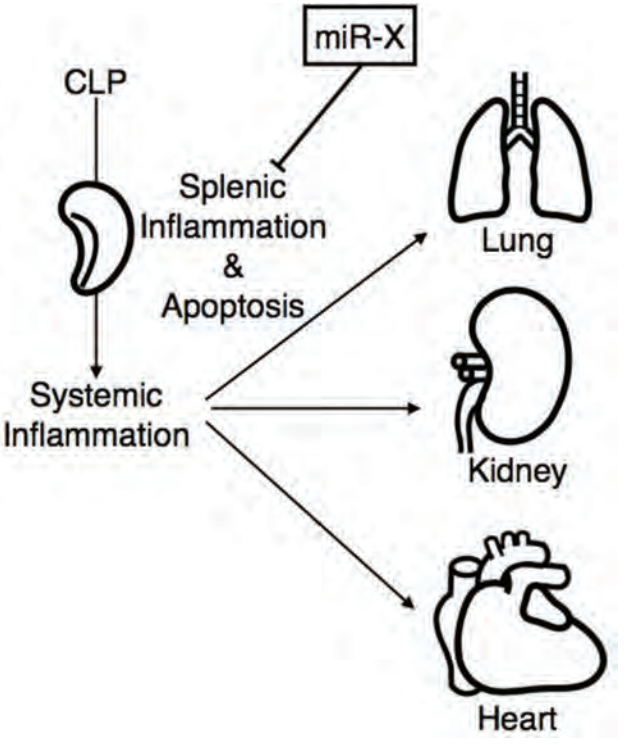
Indirect Therapeutic Role of Immunosuppressive Micro-RNA for Sepsis Induced AKI via Spleen Yoshio Funahashi. *Nagoya University, Nagoya,AICHI, Japan.*

Background: Sepsis is life-threatening organ dysfunction caused by dysregulated immune response to infection. It is known that sepsis with acute kidney injury (AKI) shows high mortality rate. However, therapies to treat sepsis and AKI are largely ineffective because of its pathophysiological complexity. Several studies have reported that some micro-RNAs (miRNAs) acted as a regulator of systemic inflammation. Here, we revealed the significance of spleen to regulate septic state by induction of immunosuppressive miRNA.

Methods: In vitro study, miR-X, which targeting toll like receptor/NF-kB pathway, was transfected into RAW264.7 cells. After transfection, cells were treated with lipopolysaccharide (LPS) for 6h, then RNA, protein, and supernatant were purified. In vivo study, 8-12 week-old C57BL/6 male mice, with or without splenectomy, were treated with miR-X expression plasmid combined with polyethyleneimine (PEI), 7 days before sepsis. Sepsis was induced by cecal ligation and puncture (CLP). Organs were harvested at 24h after CLP.

Results: In vitro study, miR-X transfected cells were tolerant toward LPS stimulation, and showed low NF-kB activity. In vivo study, miR-X expression plasmid/PEI complex was mainly detected in splenic macrophages. miR-X plasmid group showed the improvement of survival rate, inflammatory cytokine production, renal dysfunction, and renal tubular damage. In addition, less apoptotic cells were observed in spleen of miR-X expression plasmid group, than that of empty plasmid group. Interestingly, anti-inflammatory effect of miR-X was rarely observed in splenectomized mice.

Conclusions: Splenic induction of miR-X prevented dysregulated systemic inflammation in sepsis and attenuated AKI. In addition, we provided the new treatment strategy for sepsis induced AKI by targeting spleen with specific miRNA.



TH-PO285

Interleukin-10 Alleviates Ureteral Obstruction-Induced Renal Fibrosis by Reduction of Inflammation, Oxidative Stress, and Endoplasmic Reticulum Stress Kyong-Jin Jung. *Yeungnam University College of Medicine, Nam-gu, Daejeon, Republic of Korea.*

Background: Imbalance of oxidative stress, endoplasmic reticulum (ER) stressand accumulation of extracellular matrix results in renal fibrosis contributes to progressive renal failure. Recent studies suggested that interleukin (IL)-10 plays potent impacts on the fibrosis-related immunomodulation. However, the role of IL-10 against unilateral ureteral obstruction (UUO)-induced ER stress remains poorly understood.

Methods: Here, we investigated the mechanisms of IL-10 on ER stress-induced renal fibrosis by UUO model in IL-10 knockout (KO) mice and a normal kidney cell line (TMCK-1). Age-matched 10 weeks old male IL-10 KO mice and wild-type (WT) mice were divided into control (CON) and UUO groups. The mice were sacrificed at 3 days or 7 days after UUO. ER stress and profibrotic protein levels were evaluated by, western blotting. Periodic acid Schiff and Masson's trichrome stain were used for analyzed histologic changes and collagen deposition. To evaluate oxidative stress levels checked production of O_2^-, H_2O_2, malondihydrogenase and expression of 4-HNE. To investigate correlation among the IL-10, CHOP and α-SMA expression, immunofluorescence staining was used.*In vitro,* treatment of ER stress inducer (tunicamycin, thapsigargin and brefeldin A)with or without transfected siRNA (IL-10and CHOP) or CHOP overexpression in TMCK-1 cells.

Results: In this study, we found IL-10 KO UUO mice promoted renal fibrosis by more excessive tubular damage (tubular dilatation, cast formation andtubular cells infiltration), collagen deposition and oxidative stress production. We also confirmed IL-10 KO mice express higher level of profibrotic genes (α-SMA, COL1 and FN) and ER stress genes (GRP78/Bip and CHOP) after UUO. We observed IL-10, CHOP and α-SMA were highly expressed in tubulointerstitial lesion of UUO mice than CON mice. *In vitro,* transient depletion of CHOP attenuated expression of profibrotic genes.

Conclusions: Present study shows that IL-10 protecting was opposed to ER stress mediated-renal fibrosis. Combination of IL-10 and ER stress therapy could be a strong protective effect for patients with chronic kidney diseases.

TH-PO286

Keap1 Specific CRISPR/Cas9 Gene Editing in Primary Human T Cells Increases Nrf2 Activity and Anti-Inflammatory Phenotype Sanjeev Noel,[1] Sul A Lee,[1] Mohanraj Sadasivam,[2] Abdel Hamad,[2] Hamid Rabb.[1] *[1]Department of Medicine, Johns Hopkins University, Baltimore, MD; [2]Department of Pathology, Johns Hopkins University, Baltimore, MD.*

Background: T lymphocytes are established mediators of acute kidney injury (AKI) and other immune mediated kidney diseases. Previous work demonstrated significant protection from AKI in mice with enhanced T lymphocyte specific nuclear factor erythroid-derived 2-like 2 (Nrf2) activity, via deletion of kelch like-ECH-associated protein 1 (Keap1). In this study we applied CRISPR technology to edit *Keap1*, and

enhance Nrf2 activity, in human Jurkat and primary T cells to develop immune cell based therapy for humans.

Methods: We targeted *Keap1* exon 2 using site specific guide RNA. Briefly, $5X10^5$ cells were electroporated with cas9:guide RNA complex. Control cells were electroporated without cas9:guide RNA complex. Cells were harvested 72h after electroporation and assessed for *Keap1* editing and qPCR based analysis of Nrf2 target genes. Edited cells were further enriched using ATTO 550 positive sorting and analyzed for *Keap1* editing and immunological changes.

Results: Genomic cleavage analysis showed *Keap1* editing in up to 70% Jurkat cells and 40% primary T cells. qPCR analysis in Jurkat cells showed significant ($p \leq 0.05$) increase in Nrf2 regulated antioxidant genes, *Nqo1* (~11 fold), *Ho-1* (~11 fold) and *Gclm (*~2 fold) mRNA in *Keap1* edited cells compared to control cells. In primary T cells, CRISPR mediated *Keap1* editing resulted in significant ($p \leq 0.04$) increase in *Nqo1* (~16 fold), *Ho-1* (~9 fold) and *Gclm* (~2 fold) compared to control cells. Enrichment of ATTO 550 positive cells improved *Keap1* editing from 40% to 55% cells. qPCR analysis found significantly ($p \leq 0.01$) higher expression of *Nqo1* (~7 fold) in ATTO 550 positive cells compared to control cells. *Keap1* edited cells had increased ($p \leq 0.01$) frequency of CD4, CD25 and CD69 and reduced frequency of CD8 ($p \leq 0.01$) and IL-17 ($p \leq 0.05$) compared to control cells.

Conclusions: Gene editing using CRISPR/Cas9 successfully augments Nrf2 activity in primary human T lymphocytes resulting in increased expression of antioxidant genes and reduction in IL-17 expression. This sets the stage for immune cell therapy for AKI and other inflammation mediated diseases.

Funding: NIDDK Support

TH-PO287

Antioxidant Regulation of Alarmin Redox and Function during Sepsis Wasan Abdulmahdi,[3] Devika Patel,[3] May M. Rabadi,[1] Tala F. Azar,[3] Edson Jules,[3] Anastasios Papanagnou,[2] Brian B. Ratliff.[3] *[1]Columbia University Medical Center, New York, NY; [2]Westchester Medical Center, Bayside, NY; [3]New York Medical College, Valhalla, NY.*

Background: During sepsis, oxidative stress is enhanced and the alarmin High Mobility Group Box 1 protein (HMGB1) is released into the circulation from immune, endothelial and kidney epithelial cells. Once in the circulation, HMGB1 can promote systemic inflammation, with the kidney particularly susceptible to damage. However, the severity of the pro-damage signal mediated by HMGB1 is dependent on the alarmin's redox state. Thus, we examined HMGB1 redox in kidney cells during sepsis and the ability of endogenous antioxidants to regulate HMGB1 oxidation.

Methods: Lipopolysaccharide (LPS) was administered at different doses to cells and animals to mimic different severities of sepsis. During LPS treatment, reactive oxygen species (ROS) generation was examined in cell cultures and in animals. After 24 hours of LPS treatment, HMGB1 redox state was examined in the nuclear and cytoplasmic compartments of kidney cells and in the plasma using a HMGB1 redox detection assay and also by mass spectrometry (LC-MS/MS) analysis. Glutathione and thioredoxin inhibitors were administered to endothelial and proximal tubule cell cultures to determine their impact on HMGB1 redox during LPS treatment. In addition, HMGB1 (of varying redox state) was isolated from mice that had received high or low LPS dose and was re-introduced to healthy mice for analysis of the alarmin's pro-inflammatory effects.

Results: CellROX and MitoSOX labeling of LPS-stressed endothelial and proximal tubule cells demonstrated increased ROS generation in cells as sepsis severity increased. Consequently, HMGB1 oxidation increased in the cytoplasm of kidney cells and was maintained after its release into the circulation, with the degree of oxidation dependent on the severity of sepsis. The greater the oxidation of HMGB1, the greater the ability of the alarmin to stimulate pro-inflammatory cyto-/chemokine release. Highly oxidized HMGB1 also increased mitochondrial ATP production. Administration of glutathione and thioredoxin inhibitors to cell cultures enhanced HMGB1 oxidation during sepsis in endothelial and proximal tubule cells.

Conclusions: In conclusion, as sepsis severity increases, ROS generation and HMGB1 oxidation increases in kidney cells, which enhances HMGB1's pro-inflammatory signaling. Conversely, the glutathione and thioredoxin systems work to maintain the protein in its reduced state

TH-PO288

Protective Effects of Brazilian Green Propolis in Sepsis-Induced AKI Marcelo D. Silveira,[1] Jose Manuel Condor Capcha,[1] Talita R. Sanches,[1] Roberto D. Moreira,[1,2] Margoth R. Garnica,[1] Maria H. Shimizu,[1] Flavio Teles de Farias Filho,[3] Lucia Andrade.[1] *[1]Nephrology, University of Sao Paulo School of Medicine, Sao Paulo, Brazil; [2]Federal University of Goias, Catalão, Brazil; [3]UNCISAL, Maceio, Brazil.*

Background: The pathophysiology of sepsis involves oxidative stress, as well as inflammatory mediator networks, to which NF-κB and TLR4 activation is central. The pharmacological benefits of propolis have been extensively explored, because it might be an important resource for the prevention and treatment of systemic diseases. Brazilian green propolis (BGP) has garnered attention for its promising anti-inflammatory, antioxidant and immunomodulatory properties. We used a cecal ligation and puncture (CLP) model to analyze the role of BGP in sepsis-related organ dysfunction.

Methods: We divided Wistar rats into groups: sham-operated; CLP; and CLP+BGP (500 mg/kg BW ip, 6 h after CLP). Studies were performed at 24 h post-CLP. Data are mean±SD.

Results: Blood GSH was higher in CLP+BGP rats than in CLP rats (0.87±0.4 vs. 0.33±0.1 mg/ml; $p<0.001$) as was protein expression of MnSOD and eNOS in kidney tissue (138.1±27.4 vs. 100.5±19.7%; $p<0.01$ and 109.3±14.1 vs. 81.2±26.4%; $p<0.05$, respectively). In kidney tissue, protein expression of TLR4 and NF-κB was lower in CLP+BGP rats than in CLP rats (111.9±11.9 vs. 164±26.6; $p<0.001$ and 93.50±7.1 vs. 132±11.3; $p<0.001$, respectively). Renal expression of CD68 (positive cells/mm^2) was lower in CLP+BGP rats than in CLP rats (5.1±1.0 vs. 7.1±2.0; $p<0.05$). Apoptosis (TUNEL) in kidneys and lungs was lower in CLP+BGP rats than in CLP rats (2.9±2.2 vs. 7.6±3.46 positive cells/0.087 mm^2; $p<0.05$ and 0.04±0.03 vs. 0.08±0.06 positive cells/Total Cells; $p<0.001$, respectively). BAX protein expression in kidney was lower in CLP+BGP rats than in CLP rats (97±10.9 vs. 135±24.7; $p<0.01$). BGP also improved kidney mitochondrial morphology (electron microscopy). Myeloperoxidase activity (AU/g) was lower in CLP+BGP rat lungs than in CLP rat lungs (2.32±3.4 vs. 3.62±4.7; $p<0.05$), as was the number of TLR4-positive cells (0.20±0.07 vs. 0.27±0.10; $p<0.001$).

Conclusions: In sepsis, BGP protects kidneys and lungs by attenuating oxidative stress and decreasing expression of NF-κB and TLR4. (FAPESP)

Funding: Government Support - Non-U.S.

Biochemical parameters and NKCC2 protein expression

	Cl_{in} (ml/min)	$UVNa_i$ (mEq/day)	UVK (mEq/day)	OSM_U mOsm/kg	NKCC2 (%)
Sham	0.82±0.13	0.51±0.22	0.88±0.17	695.4±215.8	113.0±23.0
CLP	0.23±0.08	1.05±0.51	1.47±0.52	487.8±204.4	47.22±31.0
CLP+GP	0.68±0.36*	0.64±0.53*	1.13±0.22*	873.3±430.7*	83.0±27.4*

*$p<0.05$ vs. CLP

TH-PO289

Antioxidant-Mediated Improvement of Kidney Function in the Adult LBW Neonate Wasan Abdulmahdi,[3] Edson Jules,[3] Noor Marji,[3] Lauren M. Nesi,[2] May M. Rabadi,[1] Magdi Abdelrahman,[3] Brian B. Ratliff.[3] *[1]Columbia University Medical Center, New York, NY; [2]NYMC, Scarsdale, NY; [3]New York Medical College, Valhalla, NY.*

Background: Low birth weight (LBW), as defined by the World Health Organization, is a birth weight of less than 5.5 pounds. Maternal malnourishment during pregnancy impairs nephrogenesis in the developing embryo and is a major cause of LBW. As a result, the LBW neonate has a decreased nephron compliment and is susceptible to kidney disease and hypertension. However, investigation is still required to fully understand disease progression in LBW neonates and the underlying causes. Hence, we established a pregnant mouse malnourishment model to further investigate the causes that promote kidney disease in LBW neonates and to examine potential therapeutic treatments.

Methods: Pregnant CD-1 mice were started on a food restricted diet on day 9 of gestation and were maintained on the diet throughout the rest of gestation. The malnourished diet consisted of a 50% daily caloric reduction combined with administration of a low protein chow (6%, vs control chow composed of 26% protein). We measured body weight, blood pressure, renal blood perfusion, glomerular filtration rate (GFR) and blood glucose levels in LBW mice 1, 3 and 6 months postpartum. We also included a direct analysis of gender differences in the aforementioned parameters. Since preliminary experiments indicated a dramatic increase of reactive oxygen specious (ROS) in the circulation of adult LBW neonates, we examined the therapeutic efficacy of tempol, a ROS quencher, which was administrated (via drinking water) to these animals.

Results: Our results showed that female and male LBW mice at 1, 3 and 6 months have higher blood pressure and blood glucose levels, while body weight, GFR and renal blood perfusion are reduced, as compared to controls. Conversely, tempol treatment improved GFR and renal blood flow, while it decreased blood glucose levels and blood pressure. Body weight was unaffected by tempol treatment. We did not observe any gender based differences in LBW mice.

Conclusions: In conclusion, our results confirmed the validity of our mouse model and indicated our model develops pathologies within 6 months postpartum that closely resemble pathologies observed in human LBW neonates. The potential efficacy of antioxidant based therapies was also highlighted when tempol treated mice showed improved kidney function, decreased blood pressure and blood glucose levels.

TH-PO290

Identification of the Oliguric Patient Using a Novel Electronic Device for Measuring Urine Output Mor Grinstein,[2] Aliza D. Goldman,[2] Hagar Azran,[2] Tal Stern,[2] Dafna Willner.[1] *[1]Hadassah-Hebrew University Hospital, Efrat, Israel; [2]RENALSENSE LTD, Brookline, MA.*

Background: The AKIN and KDIGO criteria for acute kidney injury (AKI) define oliguria as urine output (UO) over 6 hours of less than 0.5ml/kg/hr. While UO is an available biomarker of kidney function, only a small percentage of AKI studies incorporate UO criteria. In these retrospective studies, hourly UO is often inaccessible, and corresponds to the nursing shift. We developed a prospective observational study using real-time electronic monitoring of UO, and applied the AKIN criteria of UO to identify the oliguric patient in the intensive care unit (ICU).

Methods: 57 General ICU patients in Hadassah Hospital, Israel were electronically monitored for hourly UO using The RenalSense® *Clarity RMS™ sterile sensor kit.* The drainage bag was connected to the Foley catheter and placed on a scientific scale for measurement validation. Patient data was analyzed as follows: AKI defined by the AKIN criteria for oliguria only: NON-AKI UO (n=26), AKI UO Stage 1(n=10), AKI UO Stage 2 (n=21). AKI defined by AKIN criteria for SCr only (where available): NON-AKI SCr (n=44) and all stages AKI SCr (n=12). Additional analysis using both SCr and UO criteria was performed on all patients.

Results: 54% of patients had AKI according to UO criteria only. Patients with AKI UO Stage 2 received more fluid boluses than NON-AKI UO and AKI UO Stage 1 in the first two 12 hour periods of UO monitoring (p=0.0051 and 0.0091, respectively). 9 out of 21(43%) patients with AKI UO Stage 2 also had increased SCr. NON-AKI UO had an average ICU stay of 5.7 days, and AKI UO Stage 1 and 2 had 8.6 and 9.9 days respectively (p= 0.1048). Using only SCr criteria, NON-AKI SCr averaged 7.1 days in the ICU vs. all stages of AKI SCr of 10.8 days. When both UO and SCr were applied, 40% of patients were NON-AKI and averaged 5.9 days in the ICU. 15% of patients had AKI by both criteria and averaged 13.3 days (p=0.1002).

Conclusions: Studies have shown worse outcomes in patients that fulfill AKIN criteria for both SCr and UO versus SCr alone. Increased SCr alone may be an insufficient indicator of AKI, as ICU patients tend to be fluid overloaded. Our data shows a trend of increased ICU stay when AKI is analyzed according to UO. This unique study presents a tool for future research using reliable real time UO monitoring, where early intervention and appropriate treatment of oliguria may improve outcomes.

Funding: Commercial Support - RenalSense ltd

TH-PO291

Dose Finding Safety Study for Bardoxolone Methyl and 6-Gingerol as Nephroprotectants against Cisplatin Induced Kidney Injury Stacey Tuey, Carolyn N. Brown, Charles L. Edelstein, Melanie S. Joy. *University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: Nephrotoxicity is a major adverse effect that limits cisplatin (CIS) clinical use. CIS induced kidney injury is in part due to reactive oxygen species. Bardoxolone methyl (BARD) and 6-gingerol (6GNG), have shown nephroprotective potential through antioxidant properties. The purpose of this study was to conduct a dose finding safety study for use of BARD and 6-GNG as nephroprotectants against CIS induced kidney in a mouse model of cancer and cisplatin nephrotoxicity.

Methods: Study mice were injected with CMT167 lung cancer cells. In the first study, BARD (5, 10, or 20 mg/kg) or BARD vehicle (VEH) was given daily for 6 days and one dose of CIS (25mg/kg) was given on day 3 of BARD treatment. In the second study, mice were dosed with 6GNG (25, 50, or 100 mg/kg) or 6GNG VEH 3x weekly and CIS (12.5 mg/kg) or CIS VEH was given 1x weekly for 2 weeks. Treatments were compared to VEH using one-way analysis of variance with Dunnett's post-hoc test.

Results: See Table 1

Conclusions: The 10 mg/kg BARD and 50 mg/kg 6GNG demonstrated the best performance in terms of no potential adverse effects on ALT, BUN, and hematocrit and no discernable increases in tumor size. Additionally, these doses appear promising for protection of kidney function and cisplatin-induced anemia as demonstrated by the reduction in BUN and increase in hematocrit, respectively. Future studies will be conducted to confirm safety and efficacy in this mouse model relevant to human CIS induced nephrotoxicity.

Funding: NIDDK Support

Results:

	BARD				6GNG			
	CIS+VEH	CIS+5mg/kg	CIS+10mg/kg	CIS+20mg/kg	CIS+VEH	CIS+25mg/kg	CIS+50mg/kg	CIS+100mg/kg
ALT (mU/mL)	14±5.3	21±9.1	7±2.3	56±12.3*	56±8.4	51±14.7	31±2.6	25±5.3
BUN (mg/dL)	37.5±2.22	25.3±3.84*	29.0±2.65	175.5±3.50*	30.3±2.10	26.3±0.47	25.6±1.15	30.7±5.66
Hematocrit (%)	34±0.7	35±2.9	41±0.8	38±1.2	37±1.9	40±1.2	40±3.3	38±1.8

*: $p<0.05$ compared to CIS+VEH

TH-PO292

Prothymosin Alpha-Derived Peptide Prevents Cisplatin-Induced AKI Kenta Torigoe,[1] Yoko Obata,[1] Miki Torigoe,[1] Takehiko Koji,[2] Hiroshi Ueda,[3] Tomoya Nishino.[1] *[1]Department of Nephrology, Nagasaki University Hospital, Nagasaki, Japan; [2]Department of Histology and Cell Biology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan; [3]Department of Pharmacology and Therapeutic Innovation, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan.*

Background: Cisplatin is one of the most used drugs for cancer treatment. However, cisplatin induces nephrotoxicity via apoptosis, necrosis or vasoconstriction, and this side effect limits clinical application of cisplatin. Prothymosin alpha (ProTα) is reported to exert protective effects against ischemia-induced necrosis and apoptosis in the brain and retina. Recently, the 6-amino acid peptide/P_6Q (NEVDQE), modified active core 6-amino acid peptide (a.a.51-56) in ProTa, also showed protective effect against retinal ischemia. Therefore, in this study, we investigated the renoprotective effect of P_6Q against cisplatin-induced acute kidney injury (AKI).

Methods: *In vitro* study, HK-2 cells were treated with cisplatin (12.5μM) for 24hrs to evaluate the cell viability by MTT assay. ProTα protein (0-40nM) or P_6Q (0-100μM) was added 30 minutes before cisplatin treatment. *In vivo* study, 8 week old male Wistar rats were divided into 3 groups: vehicle-treated group, cisplatin (8mg/kg)-treated group, cisplatin-treated group with P_6Q (30mg/kg) injection. P_6Q was injected 30 minutes before cisplatin treatment. Renal function was assessed by measuring serum creatinine. Renal histological change was assessed by PAS staining, and apoptosis of renal tubular cell was assessed by active caspase 3 and TUNEL staining. Renal hypoxia was assessed by HIF1α staining.

Results: Cisplatin treatment reduced the viability of HK-2 cells *in vitro*. Administration of ProTα improved cell viability dose-dependently. Furthermore, P_6Q administration was more effective to suppress the cytotoxicity by cisplatin compared with ProTa. Thus, we focused to investigate the protective effect of P_6Q against cisplatin-induced AKI *in vivo*. Serum creatinine level peaked at 5 days after cisplatin treatment. Histologic examination revealed extensive tubular damage in cisplatin-treated rats. Cisplatin treatment also increased the active caspase 3 positive area, number of TUNEL-positive apoptotic cells and HIF1α positive area at day 5. P_6Q injection significantly suppressed cisplatin-induced AKI and apoptosis of tubular cells, but not HIF1α expression.

Conclusions: We showed the renoprotective effect of ProTα-derived peptide against cisplatin-induced AKI via suppression of apoptosis. Our results suggest that ProTa-derived peptide may become a preventive drug for cisplatin-induced AKI.

TH-PO293

Ischaemic Preconditioning of the Kidney: Total RNA Sequencing and Ingenuity Pathway Analysis David A. Foxwell,[1] Usman Khalid,[2] Robert Andrews,[1] Gilda Pino-Chavez,[1] Rafael E. Chavez,[2] Timothy Bowen,[1] Donald Fraser.[1] *[1]Cardiff University, Cardiff, United Kingdom; [2]University Hospital of Wales, Cardiff, United Kingdom.*

Background: Ischemia-Reperfusion Injury (IRI) is a common cause of Acute Kidney Injury (AKI). Clinical trials and animal models shows that Ischemic Preconditioning (IPC), delivered directly (to the tissue) or indirectly (to other tissues), may confer protection. However, reported efficacy is variable, and development of IPC as a therapy is hampered by the current lack of detailed mechanistic understanding. The purpose of the current study was to establish the main IPC response pathways in the protected kidney, and the extent of similarity between direct and indirect IPC.

Methods: Stepwise variation in warm ischemic time was used to develop moderate AKI in the rat (defined as Creatinine ≥1.5 x sham baseline creatinine; negative control) and pulsatile, continuous, direct and indirect IPC approaches were systematically compared.

Results: Optimum benefit was observed with direct pulsatile IPC and indirect aortic IPC. Subsequently, an unbiased transcriptomic profiling of whole kidney was performed using RNA-Sequencing in animals treated with these optimum direct and indirect approaches. Six animals were compared per experimental group (n=24), at a mean paired end sequencing depth of 23.2 million reads, mapping to 16.780 unique genes. Robust differences between groups were observed (IRI vs Sham; 2,193 genes differentially regulated to a Log2FC ≥1 or ≦-1 and a corrected p ≤1.0 E-04). Ingenuity Pathway Analysis revealed upregulation of pathways linked to inflammatory response, oxidative stress and cell cycle regulation in response to IRI, and reduction in oxidative stress, inflammation and cell cycle checkpoint regulation with IPC.

Conclusions: Together, the results displayed a molecular signature of IRI consistent with previous studies and, for the first time, uncovered a detailed signature of IPC protection that was shared between direct and indirect approaches. Our data provide novel insights into the pathogenicity of IRI injury and IPC signal, highlighting possible therapeutic targets for future investigation.

TH-PO294

Elucidation of Mechanism for Indoxyl Sulfate (IS)-Promoted Renal Fibrotic Response in HK-2 Cells under Hypoxic Condition and Mice with Ischemia-Reperfusion (IR)-Induced AKI Mami Yamashita,[1] Moe Eto,[1] Go Yoneda,[1] Rika Fujino,[2] Hirofumi Jono,[2,1] Hideyuki Saito.[2,1] *[1]Kumamoto University Graduate School of Pharmaceutical Sciences, Kumamoto, Japan; [2]Kumamoto University Hospital, Kumamoto, Japan.*

Background: IR-induced acute kidney injury (AKI) is known to be a trigger for the development of renal fibrosis followed by the progression to chronic kidney disease. Under ischemia-caused hypoxia of the kidney, tubulointerstitial fibrosis is enhanced with the increased accumulation of matrix proteins such as collagen. A typical sulfate-conjugated uremic solute, IS, is known to be produced in the liver and accumulated in serum and renal tissue under IR-induced AKI, thereby promoting fibrotic responses. However, precise molecular mechanisms involved in IS-promoted renal fibrosis under hypoxia has not been elucidated. In this study, we examined the molecular biological effect of IS on fibrotic responses under hypoxic condition using HK-2 cells and IR-induced AKI model mice.

Methods: C57/BL6 mice (8-weeks old) were treated with IS or vehicle (control) intraperitoneally, after subjected to 20 min of renal IR. In IR-AKI mice, serum creatinine (SCr), BUN and serum IS levels were determined. HK-2 cells were cultivated in the medium with or without IS or vehicle. Hypoxic treatment of HK-2 cells was performed using AnaeroPack System™. mRNA expression of fibrosis-related gene including transforming growth factor (TGF)-β and plasminogen activator inhibitor (PAI)-1 were determined in the kidney of AKI mice and HK-2 cells cultivated under normal oxygen or hypoxic condition.

Results: IR treatment of murine kidney caused a marked elevation in SCr and BUN 24 hr after surgery. Administration of IS in IR-AKI mice synergistically enhanced these increases in SCr (2.2-fold vs control) and BUN (1.5-fold). Expression of PAI-1 mRNA was enhanced in IR-AKI mice (3.4-fold), and HK-2 cells (1.7-fold) under both hypoxic condition and IS treatments, compared with those under normal oxygen condition. GLUT1 mRNA expression, a downstream gene of hypoxia-inducible factor, was also elevated significantly under both hypoxia and IS treatments. By hypoxia and IS treatments, TGF-β expression was accelerated, whereas LY2157299, a TGF-β receptor inhibitor, suppressed dose-dependently PAI-1 expression induced by hypoxia with simultaneous addition of IS.

Conclusions: IS could play important roles in promoting renal fibrosis via TGF-β-mediated up-regulation of fibrotic gene expression under hypoxic condition.

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TH-PO295

Early Terlipressin Treatment for Hemorrhagic Shock-Induced AKI Leticia U. De Castro, Denise A. Otsuki, Talita R. Sanches, Débora R. Maia, Jose Manuel Condor Capcha, Denise M. Malheiros, Luiz M. Malbouisson, Lucia Andrade. *University of Sao Paulo School of Medicine, Sao Paulo, Brazil.*

Background: Although hemorrhagic shock (HS) remains the leading cause of mortality, early vasopressor use might restore hemodynamic parameters and vital organ perfusion, thereby reducing the need for aggressive fluid therapy and avoiding fluid overload. However, that strategy has yet to be included in the Advanced Trauma Life Support guidelines. This study aimed to compare the effects of three different levels of lactated Ringer's (LR) fluid therapy—aggressive (3× the blood volume removed, 3LR), conservative (2× the blood volume removed, 2LR) and low (1× the blood volume removed, 1LR)—with or without terlipressin (TLP), on acute kidney injury (AKI) in rats with HS.

Methods: We induced rats to HS, maintaining mean arterial pressure (MAP) at 30-40 mmHg for 60 min and thereafter submitting them to 30 min of LR fluid therapy, some rats also receiving TLP (10 μg/100 g BW, iv). Rats with HS were divided into 3 groups: 3LR, 1LR+TLP and 2LR+TLP. At 15 min after the end of the fluid therapy, the rats were resuscitated with the blood drawn previously. With the exception of MAP, which was measured at various time points, all studies were performed 24 h after HS induction. Data are mean±SEM.

Results: Mortality was 28%, 16% and 0% in 3LR, 1LR+TLP and 2LR+TLP rats, respectively. Creatinine clearance was higher in 2LR+TLP rats than in 1LR+TLP and 3LR rats (1.2±0.13 vs. 0.72 ± 0.1 and 0.53±0.2 ml/min/100 g BW, $p<0.05$). At 45 min after HS induction, MAP was higher in 2LR+TLP and 1LR+TLP rats than in 3LR rats. The acute tubular necrosis score was lower in 2LR+TLP rats than in 1LR+TLP and 3LR rats (5.8±0.8 vs. 14.2±3.5 and 18±4.3%, $p<0.05$). Protein expression of MnSOD was higher in 2LR+TLP rats than in 1LR+TLP and 3LR rats (130±7.1 vs. 110±4.5 and 103±4.3%, $p<0.05$). AQP2 expression was higher in 2LR+TLP and 1LR+TLP rats than in 3LR rats. TLR4 protein expression was lower in 2LR+TLP rats than in 1LR+TLP and 3LR rats (95±4.2 vs. 134±6.8 and 115±5.0%; $p<0.05$). There was less apoptosis (TUNEL-positive cells/0.087 mm2) in 2LR+TLP rats than in 1LR+TLP and 3LR rats (0.6±0.1 vs. 4.5±2.5 and 1.6±0.3; $p<0.05$).

Conclusions: Combining TLP with conservative fluid therapy appears to be a viable therapy for HS-induced AKI. We speculate that TLP attenuates AKI by modulating the inflammatory response via the TLR4 pathway. (FAPESP)

Funding: Government Support - Non-U.S.

TH-PO296

ZO-1 Protein Is Required for H2O2-Induced, ERK 1/2-Dependent Increase in MDCK Cell Paracellular Permeability Sahar Bilal,[2] Shirin Jaggi,[2] Angelina Voronina,[2] Jessica Watari,[2] Josephine Axis,[1] Danielle Janosevic,[3] Kurt Amsler.[1] *[1]Biomedical Sciences, NYIT College of Osteopathic Medicine, Old Westbury, NY; [2]NYIT College of Osteopathic Medicine, Old Westbury, NY; [3]Indiana University School of Medicine, Indianapolis, IN.*

Background: Tight Junctions (TJ) are complexes of multiple proteins on the apicolateral membranes of adjacent epithelial cells that interact to form a selectively permeable paracellular barrier. Hydrogen peroxide (H_2O_2) treatment increases renal epithelial paracellular permeability but the mechanism(s) mediating this effect are unclear. Previous studies suggest kinase-mediated regulation may influence paracellular permeability. In this study, we examined the roles of ERK 1/2 activation and of specific TJ proteins (occludin, ZO-1, ZO-2) in H_2O_2-induced paracellular permeability in renal epithelial cell monolayers.

Methods: Paracellular permeability via the leak pathway (large solutes) was measured as transepithelial movement of calcein, a fluorescent dye, across monolayers of wild type and knockdown MDCK cells grown on permeable membrane filters. H_2O_2 and inhibitors were added prior to measurement of calcein flux. ERK 1/2 activation and TJ protein content were monitored by immunoblot.

Results: Treatment of MDCK cells with H_2O_2 at non-toxic concentrations increased both ERK 1/2 activation and paracellular calcein flux rate in a concentration-dependent manner. ERK 1/2 activation occurred within 30'. Inhibition of ERK 1/2 activation by U0126 blocked the ability of H_2O_2 to increase paracellular calcein movement. Knockdown of either occludin or ZO-2 protein did not block the ability of H_2O_2 to increase paracellular calcein movement nor its inhibition by U0126. In contrast, knockdown of ZO-1 protein, which links the TJ to the actin cytoskeleton, blocked the ability of H_2O_2 to increase paracellular calcein flux. H_2O_2 treatment also altered F-actin organization of confluent MDCK cells, including disruption of actin stress fibers.

Conclusions: We demonstrate that H_2O_2 treatment of renal epithelial cells activates ERK 1/2 which is required for H_2O_2 to increase MDCK cell paracellular permeability. ZO-1 protein, but not ZO-2 or occludin protein, is required for H_2O_2 to increase MDCK cell paracellular permeability. Since ZO-1 protein links the TJ to the actin cytoskeleton, these results may implicate ERK 1/2 modulation of the actin cytoskeleton in mediating the ability of H_2O_2 to increase MDCK cell paracellular permeability.

Funding: NIDDK Support

TH-PO297

RNA-Seq Analysis of Mice Exposed Acutely to Low Levels of Domoic Acid Hernan E. Grenett,[1] Robert G. Thompson,[2] Lan He,[4] P. Darwin Bell.[3] *[1]Universiy of Alabama at Birmingham, Birmingham, AL; [2]University of Alabama at Birmingham, Birmingham, AL; [3]University of Alabama at Birmingham, Birmingham, AL; [4]University of Alabama at Birmingham, Birmingham, AL.*

Background: Domoic acid (DA) is produced by diatoms of the genus Pseudo-nitzschia. Exposing mammals to this glutamate analog causes a neurologic condition known as amnesic shellfish poisoning. Recently we reported that very low levels of DA (Funk, JASN 2014) are highly toxic to the kidney. DA activates ionotropic receptors in the kidney which could have multiple cellular effects on renal epithelial cells. To begin a mechanistic understanding of the renal effects of DA on kidney, we undertook RNA sequencing (RNA-Seq) studies designed to investigate how acute exposure to low levels of DA affects kidney gene expression.

Methods: Mice were injected IP with 0.05 mg/kg DA and their kidneys were harvested after 0, 15, 30, and 60 min. Total kidney RNA was isolated for RNA-Seq analysis and a sequencing library was generated using the SureSelect Stranded mRNA kit (Agilent Technologies).

Results: RNA-Seq analyses showed DA treatment affected 41 differentially-expressed-genes (DEG) that were at least 2-fold up- or down-regulated ($p<0.05$). In particular systems analyses indicate that genes involved in (i) lipid metabolism [Angptl4, Star], (ii) terminal cellular oxidation [Cyp11a1, Cyp11b1, Cyp21a1, Cyp24a], and (iii) plasma membrane transport [Slc22a6, Scl22a22, Slc22a26, Slc25a25] respond to DA.

Conclusions: These data reveal a complex mechanistic response by the kidney to DA. Future studies will build on and expand this intriguing preliminary data to unravel the untoward biological effects of DA.

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TH-PO298

NAD+ Augmentation Ameliorates Cisplatin Toxicity via Enhanced Autophagy Matthew R. Lynch, Kenneth M. Ralto, Mei T. Tran, Samir M. Parikh. *Nephrology, Beth Israel Deaconess Medical Center, Boston, MA.*

Background: We recently reported that renal NAD+ (nicotinamide adenine dinucleotide) concentrations decline markedly in diverse etiologies of AKI and showed that nutritional NAD+ augmentation can treat experimental post-ischemic AKI. Downstream salutary mechanisms of NAD+ augmentation are incompletely understood. Based on evidence linking impaired autophagy to cisplatin-induced renal tubular injury, we hypothesized that NAD+ augmentation may enhance resistance to cisplatin by increasing autophagy.

Methods: Murine intermedullary collecting duct (IMCD3) cells were pre-treated with the NAD+ precursor NMN (nicotinamide mononucleotide) or vehicle for one hour before cisplatin. Cell survival was assessed by automated trypan blue. RNA and protein were isolated for quantitative PCR measurement of autophagy related genes and autophagocytic flux by western blot, respectively. Acidified lysosomes were imaged using Lysotracker DND-99.

Results: NMN supplementation increased NAD+ levels at baseline and preserved NAD+ levels despite cisplatin exposure. NMN-treated cells better tolerated cisplatin stress whereas the lysosomal inhibitor chloroquine exacerbated cisplatin toxicity. NMN enhanced expression of autophagy genes ($p < 0.05$). Finally, NMN-supplemented cells maintained lysosomes in a favorable low-pH-state (Figure 1).

Conclusions: Addition of NMN enhanced cell survival after cisplatin exposure. Autophagic gene and protein levels, along with lysosomal imaging, implicate NMN-related increase in autophagy. NAD+ augmentation may therefore counteract cisplatin-induced renal injury by promoting autophagy.

Funding: NIDDK Support

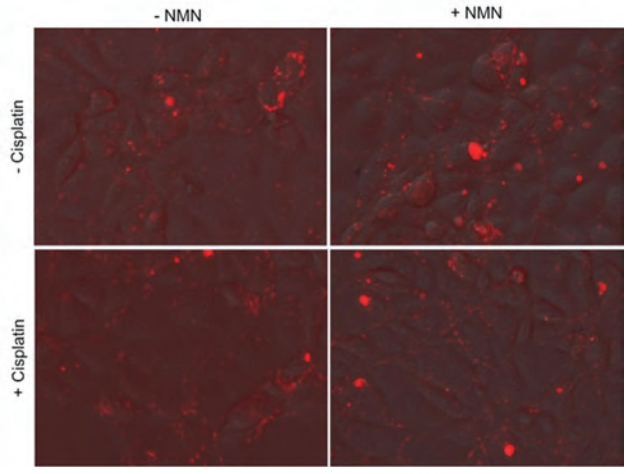

Figure 1. Lysotracker imaging reveals preservation of low pH state of lysosomes with NMN and cisplatin. Representative images (20X).

TH-PO299

Chronic Tempol Treatment Preserves Afferent Arteriole Autoregulatory Behavior in Renal Ischemia-Reperfusion Rats Zhengrong Guan, Wenguang Feng, Ijeoma E. Obi, Jennifer S. Pollock, Paul W. Sanders, Edward W. Inscho. *University of Alabama at Birmingham, Birmingham, AL.*

Background: Inflammation and increased reactive oxygen species (ROS) contribute to impaired renal autoregulatory capability under pathological conditions. We showed that renal ischemia-reperfusion (IR) impairs renal autoregulation in rats 24 hours after IR, but it was restored by acute exposure to the ROS scavenger, tempol. We postulated that chronic tempol treatment would reduce renal inflammation and preserve autoregulation in IR rats.

Methods: Renal IR was induced by bilateral renal artery occlusion (60 min). Renal cortical mRNA expression was measured for NADPH oxidase subunits, cytokines and adhesion molecules. Autoregulation was assessed with the *in vitro* blood-perfused juxtamedullary nephron preparation on day 7 post IR.

Results: Renal IR significantly increased mRNA expression for p47phox, p67phox, Gp91phox, MCP-1, TGF-β, TNF-α, P-selectin, VCAM and ICAM vs. sham kidneys (n=6/each group). Tempol pre-treatment (2 mM in drinking water) suppressed the IR-induced increase in mRNA expression for all parameters except TGF-β and TNF-α. IR also impaired afferent arteriole autoregulatory behavior. Baseline arteriole diameters were similar in sham, IR and tempol-treated IR kidneys at a renal perfusion pressure (RPP) of 100 mmHg and averaged 13.4±0.3, 11.7±0.8 and 13.4±1.2 μm (n=4-5/each), respectively. Decreasing RPP from 100 to 65 mmHg increased diameter in sham rats by 18±6%. Subsequent increases in RPP (15 mmHg) caused pressure-dependent vasoconstriction and reduced diameter by 30±5% at 170mmHg. In contrast, pressure-mediated diameter changes were blunted in IR rats. Diameter increased by 5±2% and decreased by just 8±9% at 65 and 170 mmHg, respectively (P<0.05 vs. sham), indicating impaired autoregulation. In different IR rats, chronic tempol treatment improved autoregulatory capability. Arteriole diameter increased by 12±1% and decreased by 33±6% at RPP of 65 and 170 mmHg, respectively (P>0.05 vs sham).

Conclusions: In conclusion, these results demonstrate that IR causes renal inflammation and impaired afferent arteriole autoregulatory capability. Scavenging ROS accumulation with tempol preserves normal autoregulatory reactivity, indicating that excessive ROS accumulation contributes importantly to impaired renal autoregulation in IR rats.

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TH-PO300

Inhibition of Bromodomain Protein BRD4 Suppresses Cisplatin Induced p53 Activation and Apoptosis in Renal Tubular Cells Xia Zhou, Xiaogang Li. *University of Kansas Medical Center, Kansas City, KS.*

Background: Bromodomain protein BRD4 recognizes and binds acetylated histones to regulate gene transcription. Inhibitor of bromodomain protein, JQ1, has been reported to be effective in treating a variety of cancers. Cisplatin has been used for the chemotherapy of cancers for decades with the side effect of nephrotoxicity and acute kidney injury. One of the mechanisms of nephrotoxicity is p53 mediated apoptosis. However, whether JQ1 has a cytoprotective effect during cisplatin treatment of renal tubular cells is unknown.

Methods: To understand the effect of JQ1 on cisplatin induced acute kidney injury, we treated rat renal proximal tubule cells (RPTC) and mice with cisplatin with or without the presence of JQ1, and analyzed the cells and kidneys by flow cytometry, western blot, TUNEL and immunohistochemistry staining.

Results: We found that BRD4 positively regulated the mRNA and protein expression of p53, and BRD4 bound with p53 promoter in renal epithelial cells as examined by ChIP-PCR analysis. Cisplatin treatment induced 16.5% of cell apoptosis in RPTC cells at the concentration of 20 μM. JQ1 at the concentration of 60 nM did not induced apoptosis. However, co-treatment with cisplatin (20 μM) and JQ1 (60 nM) decreased the percentage of apoptotic cells to 4.1% as analyzed by FACS. JQ1 treatment decreased cisplatin induced RPTC cell apoptosis was further confirmed by TUNEL assay. We further found that cisplatin treatment increased the expression of p53 and its downstream pro-apoptotic protein Bax, as well as the apoptotic cell markers, cleaved PARP and active caspase 3. Cisplatin induced upregulation of p53 and apoptotic associated proteins could be down-regulated by the co-treatment with JQ1. In consistent with the results *in vitro*, JQ1 treatment attenuated cisplatin induced nephrotoxicity *in vivo*. We found that JQ1 treatment preserved renal function as seen by decreased the serum BUN level in cisplatin treated mice, the cortical and medullary tubular necrosis, and the TUNEL positive tubular cells.

Conclusions: This is the first report that BRD4 regulated p53 transcription in renal tubule cells. Inhibition of BRD4 with JQ1 attenuates cisplatin induced acute kidney injury by suppressing cisplatin induced p53 activation and apoptosis in renal tubular cells.

Funding: NIDDK Support, Private Foundation Support

TH-PO301

Gender Differences in Renal Ischemia/Reperfusion Injury and the Protective Role of Sigma-1 Receptor Adam Hosszu,[1,2] Zsuzsanna Antal,[3] Lilla Lenart,[3,2] Edgar Szkibinszkij,[1,2] Dora B. Balogh,[3,2] Ádám Vannay,[4,3] Attila J. Szabo,[3,4] Laszlo J. Wagner,[1] Andrea Fekete.[2,3] *[1]Dept. of Transplantation and Surgery, Semmelweis University, Budapest, Hungary; [2]MTA-SE "Lendulet" Diabetes Research Group, Budapest, Hungary; [3]1st Dept. of Pediatrics, Semmelweis University, Budapest, Hungary; [4]MTA-SE Pediatrics and Nephrology Research Group, Budapest, Hungary.*

Background: Gender differences in the susceptibility to renal ischemia/reperfusion injury (IRI) is a known phenomenon. Tubular dysfunction following IRI can be prevented by heat shock proteins. We recently showed that Sigma-1 receptor (S1R) activation is protective in IRI through inducing the Akt-nitric oxide synthase molecular pathway. 17β-estradiol is known to have estrogen receptor-independent effects, possibly through modulating S1R which could explain superior outcomes in females. We aimed to describe gender differences in S1R expression and the heat shock response; to prove that S1R activation by 17β-estradiol or dehidroepiandrosterone (DHEA) induces the heat shock response and is thus involved in gender differences in renal IRI.

Methods: Adult female (F), male (M), ovariectomized female (Ovx), and S1R agonist DHEA-treated male (DHEA) Wistar rats (n=8/group) were subjected to 50 min renal ischemia. Kidneys were harvested 2 hours (T2) or 24 hours (T24) after reperfusion. Renal function and structural damage were assessed. Renal protein levels of S1R, phospho-Akt (Ser473), HSF-1, HSP72, HSP27 and Na^+/K^+-ATP-ase (NKA) were determined. Protein localization was determined by fluorescent immunohistochemistry.

Results: Renal function of F and DHEA rats was less impaired compared to M and Ovx. Structural lesions were less prominent in F, Ovx and DHEA rats than in M. S1R protein increased only in F and DHEA at T2, but returned to baseline by T24. Akt phosphorylation was induced in F and after DHEA treatment at T2. Heat shock response proteins (HSF-1, HSP72 and HSP27) were induced after IRI and were markedly more increased in F and DHEA rats than M and Ovx. Baseline NKA protein levels were higher in F rats. NKA disruption after IRI was suppressed in F and DHEA rats. In M and Ovx females NKA translocated from the basal membrane of tubular cells, thereby losing its function, while in F and DHEA rats it was mainly preserved in its physiological location colocalized with HSP72.

Conclusions: We confirmed previous data indicating that females are less prone to IRI than males. We showed that ovariectomy diminishes the protection that female rats enjoy. We identified S1R activation by 17β-estradiol or DHEA as a possible mediator of protective mechanisms in renal IRI by inducing the heat shock response.

TH-PO302

Minimal Volume of Urine for Analysis of Urinary Extracellular Vesicles Recovered at Low Relative Centrifugation Force Luca Musante,[1] Sai Vineela Bontha,[1] Christine Rudy,[1] Sabrina La salvia,[1] Joanne Lannigan,[1] Valeria Mas,[1] Uta Erdbruegger.[2] *[1]University of Virginia, Charlottesville, VA; [2]University of Virginia Health System, Charlottesville, VA.*

Background: Urinary extracellular vesicles (uEVs) provide a relative novel source of valuable biomarkers for kidney and urogenital diseases. Although the bulk of the research has focused mainly on exosomes as the primary source of extracellular vesicles (EVs). Only recently have uEVs recovered at low relative centrifugation force (RCF) been regarded as an additional important fraction of EVs carrying biomarkers. The number of MVs released by podocytes has shown to be higher in the urine of patients with diabetes mellitus type 1 without any kidney complications. This study aims to investigate what is the minimal amount of urine which enables the detection and characterization uEVs in the low RCF pellet.

Methods: First morning urine was centrifuged at RCF of 3,200 g. The supernatant was split in 0.5, 1.0, 1.5, 3.0, 4.5, 9.0 and 13.5 ml fractions to enrich uEVs by centrifugation at RCF of 21,000g. Tunable Resistive Pulse Sensing (TRPS), imaging flow cytometry, Cryo-Transmission Electron Microscopy and quantitative real time PCR were employed to establish the minimal volume of urine to provide uEVs for analysis.

Results: uEVs could be detected by TRSP and imaging flow cytometry, and it was possible to quantify selected miRNA starting from 0.5 ml of urine. Cryo-Transmission Electron Microscopy provided adequate images starting from a minimal volume of 1.5 ml of urine, showing uEVs of different size (60-500 nm) and morphology. Finally, western blot detection of uEVs proteins listed in Vesiclepedia like TSG101, TMEM27,

IGFB-7 and TIMP-2 could be detected starting from 3.0-4.5 ml of urine. Interestingly, the detection of IGFB-7 and TIMP-2, approved early biomarkers of acute kidney injury (AKI), underlines the important role of uEVs in the detection and assessment of urinary biomarkers.

Conclusions: Depending on the sensitivity of the technique in use, a minimal volume of 0.5 ml urine is sufficient for a single analysis; however for multi analysis the volume of urine depends on the limit of detection of the techniques in use.

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TH-PO303

Outer Stripe of the Outer Medulla in Human and Pig Kidney Is Markedly Reduced or Absent Compared to Rat

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Background: In the rat inner and outer stripes of the outer medulla (ISOM, OSOM), there are clear, functionally defined architectural features that lead to physiologically significant nephron and vascular flows. The dynamics of these flows define, in part, our views of basic renal physiology, such as diabetic nephropathy, progression of kidney injury, oxygen delivery and the urine concentrating mechanism. The human and pig medullary architecture differ from the rat in distinct ways, consistent with published observations from the first decade of the 20th century that suggested that the human OSOM, along the corticomedullary axis, has minimal depth.

Methods: We investigated architecture of the human, pig and rat medulla near the corticomedullary junction using tissue embedded in paraffin or resin, followed by sectioning and staining with conventional histochemical (H&E) and immunohistochemical techniques (antibodies for aquaporin1, smooth muscle actin, CD34 and urea transporter UTB and wheat germ lectin). Sections were viewed and photographed using conventional microscopy.

Results: The rat OM has two distinct zones (ISOM, OSOM). The human equivalent of the OM is a single zone whose tubular/vascular structure is largely similar to the rat ISOM. The human basal cortex is almost completely composed of medullary rays, which merge confluently with this single zone (ISOM). The human glomerular efferent arterioles cluster to form the most superficial aspect of the outer medullary vasa recta, which descend, accruing a venous component to form an exclusively arteriolar-venous structure, in contrast to the rat, which also includes thin limbs. The ascending vasa recta bundles of the deeper ISOM become, in the superficial ISOM, composite groupings of venous vasa recta, collecting ducts and thick ascending limbs fusing with medullary rays.

Conclusions: Our studies suggest that in human and pig, the OSOM, as defined by rat medullary architecture, is minimal or absent. Importantly, vascular perfusion of nephron segments in the OM and the deep cortex follows patterns that differ from rat. Re-evaluation of vascular architecture and expected blood flows in human and pig models may provide insights into a number of renal disorders that have resisted advances in treatment and may challenge the use of rat and mouse experimental models that regard outer stripe injury as parallel to human AKI.

Funding: NIDDK Support, Other U.S. Government Support

TH-PO304

Cisplatin-Induced AKI: Proteomic and Transcriptomic Analysis Unravels Molecular Correlates of the Protective Effect of Caloric Restriction and Hypoxic Preconditioning

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Background: Acute kidney injury (AKI) is a strong risk factor for cardiovascular morbidity and chronic kidney disease, but causal treatment is still missing. In animal models it can be reduced by preconditioning protocols, but little is known about the underlying molecular mechanisms. We aimed for identifying these in two modes of preconditioning.

Methods: 20-week-old C57Bl6-wildtype mice were treated intraperitoneally with cisplatin comparing mice preconditioned by hypoxia (HP) or caloric restriction (CR) to controls. All mice were phenotyped (plasma creatinine, blood urea nitrogen, histology) and a proteomic and transcriptomic analysis of the renal cortex was done. Additionally we analyzed the whole-cell proteome in cultured proximal tubular cells after cisplatin-damage.

Results: CR completely prevented AKI and HP showed a significant damage reduction. Cisplatin-administration led to a significant increase of extracellular matrix-, complement- and MHC-proteins, in addition to several known markers for AKI. Kinases, receptors and ubiquitin ligases, potential therapeutic targets, were increased in cisplatin-treated kidneys. Brush-border and transport proteins were reduced. Treatment of tubular cells showed that the above mentioned findings can be partly recapitulated in-vitro. The integration of the proteomic with the transcriptomic data showed the largest posttranscriptional changes in mice only treated with cisplatin. The proteomic data was correlated with plasma kidney function values. A positive correlation of extracellular proteins and a negative correlation of brush-border proteins with the damage were shown. A bioinformatical integration of a text-mining-analysis with the correlation-analysis led to a prediction of new "damage-associated-molecular-patterns" partially strongly correlating (R>0.8) with the kidney function. Proteins related to fatty acid synthesis were increased in kidneys of calorie restricted animals, suggesting that increased renal fatty acid synthesis may be involved in renoprotection.

Conclusions: In conclusion these data shows mechanistic insights of the protective effect of preconditioning in cisplatin-induced AKI and the potential of proteome-phenotype-correlations in nephrological basic science.

TH-PO305

Activation of Endoplasmic Reticulum Stress Response by Enhanced Polyamine Catabolism Plays an Important Role in Cisplatin-Induced AKI

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Background: Cisplatinis a commonly used and highly effective chemotherapeutic agent utilized for the treatment of a variety of solid tumors. Despite its effectiveness, cisplatin usage is limited due its nephrotoxic side effects. More than 25% of patients treated with cisplatin develop renal failure and have to discontinue treatment. The expression of enzymes involved in polyamine catabolism, spermidine/spermine N^1-acetyltransferase (SSAT) and spermine oxidase (SMOX) increase in the kidneys of mice treated with cisplatin. We hypothesized that enhanced polyamine catabolism contributes to tissue damage in cisplatin acute kidney injury (AKI).

Methods: Using knockout mice and chemical neutralization of toxic products of polyamine degradation, the role of polyamine catabolism in cisplatin AKI was examined.

Results: Deficiency of SSAT, SMOX or neutralization of the toxic products of polyamine degradation, H_2O_2 and aminopropanal, significantly diminished the severity of cisplatin AKI. *In vitro* studies demonstrated that the induction of SSAT and elevated polyamine catabolism in cells increases the phosphorylation of eukaryotic translation initiation factor 2a (eIF2a), and enhances the expression of binding immunoglobulin (BiP/GRP78) and CCAAT-enhancer-binding protein homologous protein (CHOP/GADD153). The increased expression of endoplasmic reticulum stress response (ERSR) markers was accompanied by the activation of caspase-3. These results suggest that enhanced polyamine degradation in cisplatin AKI may lead to tubular damage through the induction of ERSR and the consequent onset of apoptosis. In support of the above, we show that the ablation of the SSAT or SMOX gene, as well as the neutralization of polyamine catabolism products modulate the onset of ERSR (e.g. lower BiP and CHOP) and apoptosis (e.g. reduced activated caspase-3).

Conclusions: These studies indicate that enhanced polyamine catabolism and its toxic products are important mediators of ERSR and critical to the pathogenesis of cisplatin AKI.

Funding: Veterans Affairs Support

TH-PO306

NHERF1 Deficiency Increases Susceptibility to Cisplatin-Induced AKI

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Background: Acute kidney injury (AKI) develops in 30% of patients who receive cisplatin (CIS), a widely used chemotherapeutic agent. We have demonstrated that NHERF1 deficiency results in differences in mitochondrial protein expression and function. We hypothesize that NHERF1-deficiency increases susceptibility to AKI through an underlying metabolic stress.

Methods: To test this hypothesis, we treated 2 month old male and female wild type (WT) C57BL/6 and NHERF1 knock out (KO) mice with vehicle or CIS (20 mg/kg dose IP) and euthanized after 72 hours. Blood was collected for blood urea nitrogen (BUN) levels. Kidneys were harvested for histology, TUNEL assay, RT-qPCR of Kidney Injury Molecule-1 (KIM-1), and Western Blot for eIF2α, GRP78, and AMPK.

Results: Significantly greater severity of injury was seen in CIS treated NHERF1 KO mice compared to WT mice as demonstrated by semi-quantitative injury score ($p<0.001$) and by BUN levels (WT 97.8 mg/dL +/- 10.01 vs KO 151.8 mg/dL +/- 17.2) ($p<0.05$). KIM-1 mRNA expression was significantly increased in both CIS treated WT (2063.7 fold control +/- 864.4) and NHERF1 KO mice (3802.1 +/- 2132.0) ($p<0.05$) in comparison to vehicle treated mice. TUNEL assay analysis showed significant increases in both NHERF1 KO (12.5 no. nuclei/ no. visual fields +/- 3.2) and WT (10.3 +/- 1.4) CIS treated mice ($p<0.001$) in comparison to vehicle treated mice. Neither KIM-1 expression nor apoptosis differed between CIS treated WT and NHERF1 KO mice. There was no difference in expression of GRP78 and p-eIF2α between WT and NHERF1 KO mice or in proximal tubule cell expression of pAMPK. There were no significant gender differences found between WT and NHERF1 KO mice for any of the measured parameters.

Conclusions: We conclude that NHERF1-deficient mice show an increase in susceptibility to CIS-induced AKI that is not due to an underlying increase in ER stress or a decrease in cell energy levels.

Funding: Veterans Affairs Support, Clinical Revenue Support

TH-PO307

Experimental Confirmation of the Toxico-Pharmacological Role of Sulfate-Conjugated Uremic Solutes in Cisplatin Nephropathy Rika Fujino,[2] Shohei Unoki,[1] Hitomi Tanaka,[1] Keisuke Matsushita,[1] Go Yoneda,[1] Shunsuke Miyake,[1] Hirofumi Jono,[2,1] Hideyuki Saito.[2,1] *[1]Kumamoto University Graduate School of Pharmaceutical Sciences, Kumamoto, Japan; [2]Kumamoto University Hospital, Kumamoto, Japan.*

Background: The toxicological process leading to cisplatin-induced nephropathy is known to be caused by several mechanisms, including inflammatory responses, oxidative stress, DNA damage and apoptosis in renal tubules. We have reported that indoxyl sulfate (IS), a typical uremic toxin generated by hepatic sulfotransferase-mediated sulfation of indoxyl, accumulates markedly in serum and several tissues of animal models with cisplatin-induced acute kidney injury (AKI). AST-120, an orally administered spherical carbon adsorbent, suppressed the renal IS accumulation in association with a significant nephropreventive effect. The present study was aimed to confirm the toxico-pharmacological role of sulfate-conjugated uremic solutes, IS and p-cresylsulfate (PCS), in cisplatin-induced AKI models.

Methods: SD rats or C57BL/6 mice were treated with cisplatin (20 mg/kg body weight) by intraperitoneal injection. Serum and tissues were collected periodically after cisplatin administration. IS and PCS levels in serum and tissues were determined by LC-MS. Accumulation of IS and 4-Hydroxy-2-nonenal (4-HNE), an oxidative stress marker, in renal tissue was examined by immunohistochemical method.

Results: We developed an in vitro screening system for exploring inhibitors of hepatic production of IS. By using the screening system, we found that some compounds had a potent inhibitory effect on hepatic IS production. Administration of these compounds to rats with cisplatin-induced AKI ameliorated the disturbed renal function with the suppression of serum and tissue IS levels. In C57BL/6 wild type (WT) mice and sulfotransferase 1A1 gene-deficient mice (Sult1A1$^{-/-}$) treated with cisplatin, renal function was preserved (BUN, 193.5 mg/dl in WT vs 84.7 mg/dl in Sult1A1$^{-/-}$, $p<0.01$; sCr, 1.40 mg/dl in WT vs 0.42 mg/dl in Sult1A1$^{-/-}$, $p<0.01$) in association with the marked suppression of serum IS and PCS levels (IS, 88.3 μM in WT vs 20.0 μM in Sult1A1$^{-/-}$, $p<0.001$; PCS, 41.0 μM in WT vs 0.1 μM in Sult1A1$^{-/-}$, $p<0.01$). Renal accumulation of IS, PCS and 4-HNE were markedly reduced in Sult1A1$^{-/-}$ compared with those in WT.

Conclusions: IS and PCS appeared to be key progression factors in cisplatin-induced AKI *via* producing oxidative stress, suggesting that hepatic Sult1A1 could be a therapeutic target for cisplatin nephropathy.

Funding: Government Support - Non-U.S.

TH-PO308

Renal Selective Mesoscale Nanoparticles to Treat AKI Edgar A. Jaimes,[4,5] Ryan M. Williams,[3] Janki Shah,[2] Elizabeth Mercer,[1] Daniel A. Heller.[3,5] *[1]Indiana University School of Medicine, Evansville, IN; [2]MSKCC, NY, NY; [3]Memorial Sloan Kettering Cancer Center, New York, NY; [4]Memorial Sloan-Kettering Cancer Center, New York, NY; [5]Weill Cornell Medical College, New York, NY.*

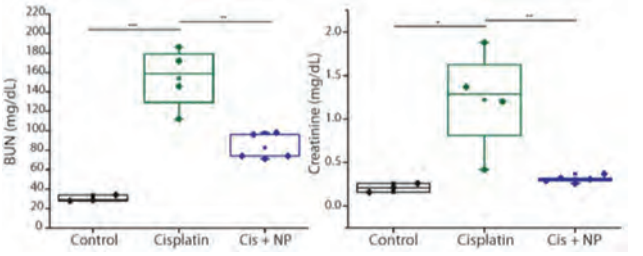
Background: Acute kidney injury (AKI) accounts for 1% of hospital admissions and up to 25% of patients in intensive care develop AKI. As many as 25% of these patients require renal replacement therapy and have high mortality rates. Despite the incidence and associated morbidities, there are no proven or effective therapies for AKI of different etiologies including cisplatin induced AKI, which occurs in 30% of patients receiving this chemotheraputic agent.

Methods: We synthesized nanoparticles from poly(lactic-*co*-glycolic acid) and polyethylene glycol (PLGA-PEG) encapsulating an antioxidant small molecule. The particles are 400 nm in diameter with a negative surface charge and when injected systemically they accumulate predominantly in the proximal tubules as we have shown (Williams, Nanoletters, 2015). Therapy experiments were performed in a mouse model (C57BL6, N = 4 to 6) of cisplatin induced AKI (25 mg/kg I.P.). MNPs (0.2 mg/kg nano-encapsulated drug) were injected IV 24 hours after AKI induction with cisplatin. Mice were sacrificed at 72 hours post-injury and blood urea nitrogen and creatinine measurements, and kidneys were fixed and saved for histology.

Results: MNPs exhibited significant therapeutic efficacy in cisplatin-induced AKI. In vivo, MNPs caused a significant decrease in serum biomarkers and histopathological hallmarks of AKI. AKI mice treated with therapeutic MNPs exhibited a 50% decrease in blood urea nitrogen and an 80% decrease in creatinine, with a marked decrease in tubular necrosis as assessed in PAS stained slides.

Conclusions: These studies demonstrate that targeted delivery of small molecules to the proximal tubule is an effective method of treatment for AKI. In future studies we will investigate the mechanisms of localization and optimization of therapy. This novel strategy may result in the development of novel strategies for the treatment and prevention of AKI of different etiologies.

Funding: Other NIH Support - P30 CA008748, DP2HD075698



In vivo AKI therapy with anti-oxidant-loaded nanoparticles. AKI mice treated with MNPs 24 hours after cisplatin administration. **(A)** BUN and **(B)** creatinine measurements show significant decrease in injury with MNP treatment.

TH-PO309

Systemic Effects of Long-Acting Albumin-Thioredoxin Fusion Protein against Distant Organ Injury Following AKI Kento Nishida,[1] Hiroshi Watanabe,[1] Masafumi Fukagawa,[2] Toru Maruyama.[1] *[1]Department of Biopharmaceutics, School of Pharmacy, Kumamoto University, Kumamoto-shi, Japan; [2]Tokai University School of Medicine, Isehara, Japan.*

Background: The high mortality of acute kidney injury (AKI) is associated with distant organ injury such as lung and liver injury. Therefore, an effective strategy is highly desirable for preventing AKI-associated distant organ injury induced by increasing oxidative stress and inflammatory response. Thioredoxin-1 (Trx) is a redox-active protein that has anti-oxidative and anti-inflammatory properties. Although, Trx has great potential for use as a therapeutic agent against several types of oxidative stress-related diseases, its short half-life limits its clinical application. To overcome this problem, we produced a recombinant fusion protein that is comprised of human serum albumin and Trx (HSA-Trx), and examined its preventive effect against AKI-induced distant organ injury.

Methods: Recombinant HSA-Trx was expressed using *Pichia* expression system. AKI-induced distant organ injury mice were produced by renal ischemia reperfusion injury (IRI).

Results: A pharmacokinetic study of HSA-Trx or Trx in mice showed that the plasma retention of Trx was markedly increased by fusion with HSA. HSA-Trx treatment attenuated the renal IRI-induced decline in renal function and histological alterations. HSA-Trx also attenuated not only lung injury, including increased neutrophil infiltration, vascular hyper-permeability and alveolar expansion, but also liver injury, including elevated aspartate aminotransferase and alanine aminotransferase following renal IRI. In plasma, the elevation of inflammatory cytokine was suppressed by HSA-Trx treatment. In kidney, lung and liver, HSA-Trx suppressed the number of apoptosis-positive cells, cytokine and chemokine mRNA expression and oxidative stress. The administration of HSA-Trx resulted in a significant increase in survival rate, with 55% of the mice being alive at 7 days after the renal IRI.

Conclusions: HSA-Trx has potential for use in the treatment of AKI-induced distant organ injury via its extended effects of modulating oxidative stress and inflammation.

TH-PO310

Worsened Renal Fibrosis in Kras4bG12D Lung Adenocarcinoma-Bearing Mice Treated with Repeated Dosing of Cisplatin May Be EGFR-Mediated Cierra Sharp,[2] Mark A. Doll,[2] Tess Dupre,[2] Levi J. Beverly,[1,3] Leah J. Siskind.[2,3] *[1]University Of Louisville, Louisville, KY; [2]University of Louisville, Louisville, KY; [3]James Graham Brown Cancer Center, Louisville, KY.*

Background: Cisplatin (CDDP) is a first choice therapy for many solid cancers, but 30% of patients develop nephrotoxicity leading to acute kidney injury (AKI). AKI is defined as the rapid loss of renal function, marked by an increased mortality rate. Recent large-scale, longitudinal studies have indicated that AKI can progress to chronic kidney disease (CKD), which also has an increased mortality rate. Currently, there are no therapeutic interventions for AKI or CKD sustained from CDDP treatment. This may be due to the fact that the mouse model used to study CDDP AKI utilizes non cancer mice that are treated with one, high dose of CDDP leading to death 3-4 days after injection. Clinically, only cancer patients receive CDDP, and it is administered in low doses over an extended period of time to curtail CDDP nephrotoxicity.

Methods: We optimized a repeated dosing model of CDDP (7 mg/kg 1x/wk for 4wks), which induces fibrosis indicative of CKD. To incorporate cancer into our model, we utilized a Kras4bG12D transgenic mouse that develops lung adenocarcinoma within 6 months, and treated non cancer and cancer mice with repeated CDDP dosing.

Results: CDDP treated cancer mice had significantly decreased survival (25%) compared to CDDP treated non cancer mice. In urine, NGAL levels in CDDP treated cancer mice increased after Dose 1 (34.9 pg/ml) and Dose 2 (51.5 pg/ml), but not in CDDP treated non cancer mice. CDDP treated cancer mice had significantly worsened fibrosis as indicated by Sirius red (SR) staining (25.4% SR +), levels of myofibroblasts (α-SMA IHC; 4.6% +), and TGFβ protein levels as compared to CDDP treated non cancer mice (11.6% SR +, 2.2% α-SMA +). We hypothesized that CDDP treated cancer mice have worsened fibrosis due to the activation of different pathways involved in renal fibrosis. Indeed, CDDP treated cancer mice had increased EGFR and pEGFR Y1068 protein

levels. The role of EGFR was further supported by differential activation of downstream signaling pathways in these mice (JNK and NFκB).

Conclusions: These data suggest that worsened renal outcomes in CDDP treated cancer mice may be EGFR-mediated, and that targeting EGFR may prevent renal fibrosis.

Funding: NIDDK Support

TH-PO311

The Protective Effect of Transplanting Bone Marrow Mesenchymal Stem Cells with Over Expressed Klotho Gene for Kidney Injury Xin Wan,[1] Changchun Cao.[2] *[1]Nanjing Hospital Affiliated to Nanjing Medical University (Nanjing First Hospital), Nanjing, China; [2]Sir Run Run Hospital Affiliated to Nanjing Medical University, Nanjing, China.*

Background: The bone marrow mesenchymal stem cell (BMSC) is a kind of cell with multi-directional differentiation ability and has potent immuno-regulation ability which was confirmed in alleviating acute kidney injury(AKI). Klotho is a protein associated with aging and thought as an antagonist of Wnt/β-catenin pathways which can induce renal fibrosis. Thus a hypothesis was make that modify BMSCs with over expressed Klotho gene and then transplant the BMSCs to individuals with AKI can protect the kidney more efficiency.

Methods: BMSCs was isolated from mice and was cultured to the third generation, the BMSCs were transfected with adenovirus carrying Klotho gene in three days and harvested Klotho-BMSCs. A total of 18 healthy C57BL/6 male mice were used to establish renal IRI model by clamping unilateral renal pedicle for 60 minutes followed by reperfusion. The IRI mice were divided into three groups which was transplanted with PBS, BMSCs and Klotho-BMSCs separately. Kidney tissue and blood samples were collected at 3,14 days after AKI. Renal histological changes were estimated by HE staining and Masson staining. The expression of collagen III and IDO were determined by immunohistochemistry, the location of CD68 was observed by immunofluorescence.

Results: Compared with normal mice, classical tubular damage was found in IRI groups,accompanied by a lot of macrophage infiltrate. The mice transplant with Klotho-BMSCs have the lowest BUN and Cr serum level, while the PBS injected mice have the highest BUN and Cr serum level. The extent of kidney fibrosis at 14 days showed that the Klotho-BMSCs group was the mildest while the fibrosis of BMSCs group was better than PBS group. Compared with normal groups, the injury kidney expressed CD68 significantly which means macrophage infiltrated in kidney, and the infiltration was downregulated by transplanting BMSCs or Klotho-BMSCs. In vivo, Klotho-BMSCs showed more obviously proliferative capacity compared with BMSCs, while the Wnt pathway was significantly suppressed in Klotho-BMSCs.

Conclusions: Over expression of Klotho in BMSCs can improve the proliferative capacity of the BMSCs. That leads to potent down-regulated effect to macrophage cells. At the same time, secrete Klotho is an antagonism to kidney fibrosis. So Klotho-BMSCs exhibit synergistic effect and it can be a new medicine in therapy of kidney fibrosis after AKI.

TH-PO312

Limiting Reperfusion Pressure Protects against Renal Ischemia Reperfusion Injury Jin Wei,[2] Jie Zhang,[2] Lei Wang,[2] Shan Jiang,[2] Jacentha L. Buggs,[1] Ruisheng Liu.[3] *[1]Tampa General Hospital, Tampa, FL; [2]USF, Tampa, FL; [3]University of South Florida College of Medicine, Tampa, FL.*

Background: The role of hemodynamics in renal ischemia reperfusion injury (IRI) is not defined. We hypothesized that lowering renal perfusion pressure during the initial phase of reperfusion protects against renal IRI.

Methods:

Results: First, we evaluated renal autoregulation by measuring changes of renal blood flow (RBF) while elevating 20 mmHg in renal artery pressure (RAP). RBF increased by 94.4±8.1% (n=5, p<0.01) in mice with 15 min renal ischemia while kept constant without significant change in sham. Then, in isolated perfused afferent arteriole, we measured myogenic response by increasing perfusion pressure from 60 to 120 mmHg, which was 1.6±0.08 μm at basal but decreased to 0.9±0.06 μm following 20 min hypoxia (n=6, p<0.01). In isolated perfused juxtaglomerular apparatus, we measured tubuloglomerular feedback (TGF) *in vitro*, which was 3.7±0.6 μm at basal and blunted to 1.2±0.3 μm (p<0.01) following hypoxia. TGF *in vivo* measured using micropuncture was 4.7±0.5 mmHg in sham and inhibited to 0.8±0.6 mmHg right after 15 min renal ischemia (n=5, p<0.01). We next measured tubular free flow pressure (P_f) using micropuncture. P_f was 11.8±1.6 mmHg at basal and decreased to 2.4±0.5 mmHg during ischemia phase, then significantly elevated to 38.2±4.1 mmHg at the beginning of reperfusion and gradually decrease to 19.8±3.7 mmHg after 45 min of reperfusion (n=5, p<0.01). We adjusted the RAP at the initial 45 min of reperfusion to 66±3 mmHg by partially clamping aorta above renal arteries (LP group) and to 102±6 mmHg by clamping superior mesentery artery (HP group), compared with normal RAP 83±4 mmHg (NP group). Accordingly, P_t was significantly lower in LP group (9.4±1.1 mmHg) (n=4, p<0.05) and higher in HP group (30.8±2.5 mmHg) (n=4, p<0.05) at 45 min compared with NP group (22.6±3.5 mmHg) (n=6). Plasma creatinine was significantly decreased in LP group (0.21±0.04 mg/dl, n=5, p<0.05) and increased in HP group (1.95±0.2 mg/dl, n=5; p<0.01) compared with NP group (0.48±0.01 mg/dl, n=6) at 24h after IRI. The percentage of necrotic tubules in histology with PAS staining was decreased in LP (9.1±3.7%) and increased in HP (32.7±2.4%) compared with NP (20.3±2.9%) (n=5, p<0.05).

Conclusions: In conclusion, intratubular pressure is elevated during the initial phase of reperfusion. Attenuation of the increase in intra-tubular pressure by limiting RAP protects against renal IRI.

Funding: NIDDK Support

TH-PO313

Lack of Vasohibin-1, a Negative Feedback Regulator of Angiogenesis, Exacerbates Renal Injury in a Murine Cisplatin Nephropathy Model Satoshi Tanimura, Katsuyuki Tanabe, Kana Masuda, Hiromasa Miyake, Hitoshi Sugiyama, Jun Wada. *Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.*

Background: Vasohibin-1 (VASH1) was originally identified as an endothelium-derived anti-angiogenic factor. In contrast to other anti-angiogenic factors, VASH-1 has been shown to enhance stress-tolerance and survival of endothelial cells via upregulation of Sirt1 and SOD2. We previously reported that VASH1 deficiency resulted in the exacerbation of renal inflammation and interstitial fibrosis in murine unilateral obstruction model (Watatani et al., Phys Rep 2012), and increased albuminuria and marked glomerular alterations in murine type 1 diabetes model (Hinamoto et al., PLoS ONE 2014). In the present study, we examined the effect of VASH-1 deficiency on cisplatin-induced AKI.

Methods: Nine-week-old male VASH1$^{+/-}$ (C57BL/6 background) and wild type (WT) mice received once intraperitoneal injection of 20mg/kg of cisplatin or saline (vehicle). Mice were divided into four groups; 1) WT-control (n=5), 2) VASH1$^{+/-}$-control (n=5), 3) WT-cisplatin (n=7), and 4) VASH1$^{+/-}$-cisplatin (n=7). 72 hours after the injection, these mice were sacrificed and blood and kidney samples were collected.

Results: There were no differences in renal function and histology between WT and VASH1$^{+/-}$-control mice. Renal dysfunction induced by cisplatin injection was more prominent in VASH1$^{+/-}$-cisplatin compared with WT-cisplatin mice (serum creatinine 1.18 ± 0.52 vs 0.39 ± 0.11 mg/dl; BUN 140.9 ± 16.1 vs 92.4 ± 14.0 mg/dl, respectively). Increased renal tubular injury scores and number of TUNEL positive nuclei were also greater in VASH1$^{+/-}$-cisplatin mice. Furthermore, loss of peritubular capillaries observed in WT-cisplatin mice was exacerbated in VASH1$^{+/-}$-cisplatin mice. Renal accumulation of oxidative stress markers, malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) were markedly increased in VASH1$^{+/-}$-cisplatin mice compared with WT mice. Along with the results, decreased level of antioxidative enzyme SOD2 in WT-cicplatin mice was significantly accelerated in VASH1$^{+/-}$-cisplatin mice.

Conclusions: VASH1 deficiency exacerbated renal dysfunction and tubular injury as well as increased oxidative stress. SOD2 may influence the number of PTCs and renal function. These results suggest that VASH1 exerts renal protective effect in AKI through preserved peritubular capillaries and SOD2 expression.

Funding: Government Support - Non-U.S.

TH-PO314

Treatment with the SGLT2 Inhibitor Luseogliflozin after Ischemia/Reperfusion Attenuated Renal Fibrosis through Reversing the Endothelial Rarefaction in Mice Daisuke Nakano, Akira Nishiyama. *Kagawa University, Kagawa, Japan.*

Background: Sodium-glucose cotransporter (SGLT) 2 inhibitors increase glucose excretion in the urine by inhibiting glucose reabsorption in proximal tubules. However, the effects of SGLT2 inhibition on the severity of proximal tubular injury or on the efficiency of repair after injury have not been examined.

Methods: We investigated the effects of the SGLT2 inhibitor luseogliflozin on acute kidney injury and subsequent development of renal fibrosis in mice. Luseogliflozin (30 mg kg^{-1} day^{-1}, p.o.) was administered at 6 hours after renal ischemia/reperfusion (I/R), and the treatment was continued daily until day 7.

Results: Luseogliflozin did not affect blood urea nitrogen increases, histopathological damage, or autophagy induction at day 1 or 3 after I/R. In contrast, luseogliflozin significantly suppressed the development of renal fibrosis at day 7 and week 4 after I/R. Additionally, luseogliflozin prevented peritubular capillary congestion/hemorrhage, and attenuated renal CD31-positive cell loss after I/R injury. These changes were accompanied by an increase in renal VEGF-A mRNA levels. Furthermore, luseogliflozin failed to attenuate the renal I/R injury-induced fibrotic changes in the animals co-treated with sunitinib, a VEGF receptor inhibitor. Finally, low glucose concentration in the medium increased VEGF-A mRNA levels in cultured proximal tubular cells, and an in vivo glucose uptake analysis showed that luseogliflozin after I/R suppressed glucose uptake in the proximal tubules.

Conclusions: These results indicate that luseogliflozin prevented endothelial rarefaction and the development of renal fibrosis after renal I/R injury through a VEGF-dependent pathway.

Funding: Commercial Support - Taisho-Toyama Pharma. Inc

TH-PO315

Youthful Systemic Milieu Alleviates Renal Ischemia Reperfusion Injury in Elderly Mice Xiangmei Chen. *Department of Nephrology, Chinese PLA General Hospital, Beijing, China.*

Background: The incidence of acute kidney injury (AKI) is high in elderly people. Parabiosis is an experimental model that surgically joins the muscle and hypoderm of two organisms to develop a shared circulatory system. Within this common blood circulation, blood cells and soluble factors can exchange continuously at physiological levels. Parabiosis has been used to study the different internal environmental factors that affect organ function and recovery from damage. A young systemic environment may prevent the senescence of old organs.

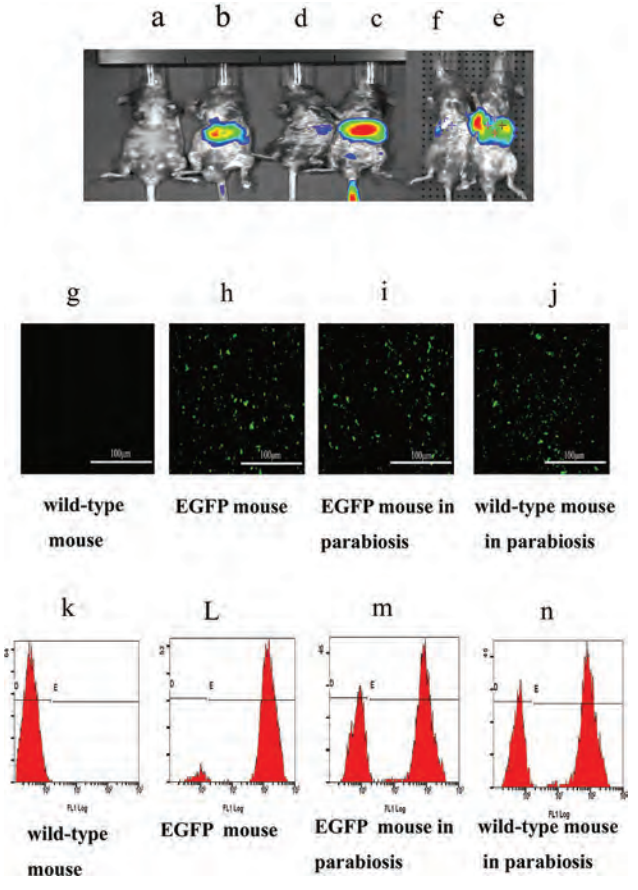
Methods: The mice were divided into four groups at random.1). old sham group (O:sham), 2). old IRI group (O:IRI). 3). old-old parabiosis IRI group (O-O:IRI). 4).

young-old parabiosis IRI group (Y-O:IRI). The parabiosis model was established first. Then 3 weeks, the bilateral renal pedicles were clamped in the old recipient mouse.

Results: It was verificated that cross-circulation in the parabiosis model with the IVIS Spectrum Imaging System, fluorescence microscopy, flow cytometry analysis. At 24 hours after IRI, compared to old wild-type mice, the old IRI mice had significantly damaged renal histology, decreased renal function, and increased renal tissue apoptosis. Compared to old IRI mice, old-old parabiosis IRI mice did not show differences in renal histological damage, renal tissue apoptosis. Compared to the old-old parabiosis IRI mice, the old IRI mice in the young-old parabiosis showed less renal histological injury and better renal function. In addition, the renal tissue expression levels of proteins related to apoptosis were significantly decreased.

Conclusions: These results indicate that a young systemic milieu may ameliorate renal ischemia reperfusion injuries in old mice.

Funding: Government Support - Non-U.S.



TH-PO316

The Impact of Uninephrectomy on Subsequent AKI Outcomes Myung-gyu Kim, Hiroshi Kojima, Jonathan Street, Erik H. Koritzinsky, Xuzhen Hu, Peter S. Yuen, Robert A. Star. *NIH/NIDDK, Bethesda, MD.*

Background: The long-term risk of kidney donation (uninephrectomy) is controversial, but appears modest (hypertension; ESRD very rarely). However, the short-term risks including acute kidney injury (AKI) are not well studied. Although uninephrectomy (uni-Nx) alone causes a clinically silent hyperfiltration, the impact of hyperfiltration on AKI outcomes is still unknown. Here, we examine whether uni-Nx alone could be a risk factor for AKI development and recovery.

Methods: In C57BL/6 mice, uni-Nx or sham operation was performed and then renal and tubular function was assessed by transcutaneous measurement of glomerular filtration rate (GFR) using FITC-sinistrin and furosemide simulation test (FST), respectively. At 2 wks after uni-Nx or sham, animals were subjected to 28 min ischemia reperfusion injury (IRI) then followed for 4 wks.

Results: Uni-Nx induced renal hypertrophy and increased expression of tubular transporter in the remaining kidney. These structural changes were accompanied by functional compensation. GFR recovered to more than 70% of normal after 1 wk. Interestingly, urinary output in response to furosemide remained unchanged during 2 wks after uni-Nx, suggesting that hyperfiltration also increased tubular secretion and action of furosemide. Two weeks after uni-Nx, animals were subjected to IRI. The GFR one day post-IRI was lower and BUN was higher in uni-Nx than sham mice. Uni-Nx also significantly delayed recovery of renal function over the next 4 wks. Interestingly, a higher urine production in response to furosemide, but not GFR, just before IRI was strongly correlated with more ischemic renal damage in uni-Nx mice. This suggests that the changes in tubular function, rather than changes in GFR, after uni-Nx could be risk/protective factors for subsequent AKI development.

Conclusions: Mice with a single kidney 1) have the expected compensatory changes in GFR and tubular function; 2) an unexpectedly severe functional deterioration to IRI 2 wks after uni-Nx; and 3) an unexpectedly delayed recovery over the next 4 wks. In addition, the baseline tubular function (and not baseline GFR) can better predict the risk of subsequent AKI. These results may provide important clues in developing new risk stratification and management strategies in patients with a single kidney.

Funding: NIDDK Support

TH-PO317

Role of MIF2 in Proximal Tubular Cell Proliferation and Survival after Ischemia-Reperfusion Injury Akinobu Ochi,[2] Dong Chen,[2] Luisa Averdunk,[1] Marta Piecychna,[2] Xin Du,[2] Lin Leng,[2] Richard Bucala,[2] Gilbert W. Moeckel.[2] *[1]RWTH Aachen University, Aachen, Germany; [2]Yale University School of Medicine, New Haven, CT.*

Background: Macrophage migration inhibitory factor (MIF) is a cytokine with pleiotropic actions including cell proliferation and survival. MIF is expressed in kidney tubular cells and released by various stimuli such as hypoxia. Renal tubular cells express MIF receptors: CD74/44, CXCR2/4. Recently D-dopachrome tautomerase, also known as MIF2 was characterized as a homologue of MIF. MIF2 is thought to exert more selective tissue protective action via CD74 activation than MIF. We examined the role of MIF2 in renal tubular cell proliferation and survival after ischemia-reperfusion (I/R) injury.

Methods: *Mif-/-*, *Mif2-/-*, *Cd74-/- and* wild type (*WT*) mice were subjected to 30 minutes bilateral I/R surgery. We then injected MIF2 intraperitoneally every 12 hours. We collected kidney and blood samples 48 hours after I/R surgery, and evaluated tubular damage and performed comprehensive RNAseq analysis. For *in vitro* modeling of I/R injury, we used mouse MPT proximal tubular cells incubated in a hypoxic chamber (0.1% O_2, 6 hrs, low nutrient medium). The cells then were cultured in normal condition with/without 100 ng/ml of MIF2 for different time points.

Results: *Mif-/-, Mif2-/-* and *CD74-/-* mice had more severe tubular injury compared to *WT* mice. MIF2 injection promoted proximal tubular cell proliferation and improved renal function. RNAseq analysis showed that MIF2 injection increased cell cycle associated genes (cyclinD1, D2, E1, E2), secretory leukocyte proteinase inhibitor (SLPI) and survivin expression. In MPT cells, MIF2 promoted cell proliferation via cyclin D1 upregulation following SLPI upregulation in 36 hours. The short time (30-120 min) impact of MIF2 on hypoxic MPT cells included activation of eIF2α and ATF4, which are involved in the integrated stress response. MIF2 also induced autophagy and inhibited apoptosis.

Conclusions: MIF2 promoted renal tubular cell proliferation and survival after I/R injury. MIF2 may be of therapeutic utility as a regenerative agent in the clinical setting of ischemic acute kidney injury.

Funding: Other NIH Support - RO1 AR049610 to R.B., Private Foundation Support

TH-PO318

CNT/CD-Specific Injury Triggers Serial Proliferation of Aqp2+ Progenitor Cells in Adult Mouse Kidney Long Zhang,[1] Chao Gao,[1] Lihe Chen,[2] Ye Zhang,[1] Enuo Chen,[1] Qiaoling Zhou,[3] Wenzheng Zhang.[1] *[1]Albany Medical College, Albnay, NY; [2]NIH, Bethesda, MD; [3]Xiangya Hospital, Changsha, China.*

Background: The existence of stem/progenitor cells in adult kidneys and their function in kidney injury repair remain very controversial.

Methods: Hence, *iDTR$^{f/f}$ Aqp2Cre* mice were generated to selectively activate expression of the simian diphtheria toxin (DT) receptor in Aqp2$^+$ progenitor cells, which generate all known cell types of the connecting tubule/collecting duct (CNT/CD). Adult *iDTR$^{f/f}$ Aqp2Cre* and *iDTR$^{f/f}$* mice were injected with DT at 2-10 μg/kg to induce acute injury in CNT/CD.

Results: *iDTR$^{f/f}$ Aqp2Cre* mice died at a time- and dose-dependent manner, with 80% mice being dead by day 15 post DT injection. However, all *iDTR$^{f/f}$* mice survived the time course. To accurately label two sequential cell divisions, thymidine analogs, 5-chloro-2-deoxyuridine (CldU) and 5-iodo-2-deoxyuridine (IdU) were injected, either alone or sequentially. IdU$^+$ CldU$^+$ cells were exclusively detected in mice that received both IdU and CldU, verifying the labeling specificity. *iDTR$^{f/f}$ Aqp2Cre vs. iDTR$^{f/f}$* mice significantly increased the number of labeled cells (CIDU$^+$, IdU$^+$, or both) (88.3 vs. 0.4 cells/section, n=5-9 mice). Triple IF combining CIdU and IdU with various markers was performed with kidneys from 10 DT-induced, CIdU and IdU-chased *iDTR$^{f/f}$ Aqp2Cre* mice. For each marker, one section/mouse was completely examined for labeled cells that were positive for the marker. For Aqp2$^+$ cells, the double-labeled rate (CldU$^+$ IdU$^+$ / (CldU$^+$ + IdU$^+$ + CldU$^+$ IdU$^+$) was significantly higher (74.8%, 595/795) than the expected (19.4% CldU$^+$ × 5.8% IdU$^+$ = 1.1%) if cell division were stochastic. The high double-labeled rate was also seen in labeled V-ATPase B1B2$^+$ (84.3%, 118/140), Pendrin$^+$ (100%, 10/10), NCC$^+$ (87%, 174/200), THP$^+$ (75%, 18/24), Megalin$^+$ (61%, 183/300) and Aqp1$^+$ (73.5%, 189/257) cells. Only 87 of 31071 Aqp2$^+$ cells were labeled (0.28%). Among 595 double labeling cells, Aqp2$^+$ and Aqp2$^-$ cells were 25% and 75%, respectively.

Conclusions: The non-stochastic pattern argues against the notion that all surviving CNT/CD cells are capable of proliferating through self-duplication and suggests that adult Aqp2$^+$ progenitor cells selectively proliferate after injury resulting in a high double-labeled rate after sequential CldU and IdU pulses. CNT/CD-targeted injury induces a global effect within the kidney and invokes proliferation of other progenitor cells.

Funding: NIDDK Support

TH-PO319

Role of CD133 Molecule in WNT Response and Renal Repair Benedetta Bussolati, Elli Papadimitriou, Alessia Brossa. *Molecular Biotechnology and Health Sciences, University of Torino, Torino, Italy.*

Background: The renal CD133$^+$ cells have been indicated as a resident scattered population able to survive and proliferate after injury. However, the biological function of CD133 molecule along with its possible modulation during damage are currently unknown. In the present study, we evaluated the role of stem cell marker CD133 in renal cellular repair at both molecular and functional level.

Methods: CD133 was silenced by two different shRNA against CD133. RNA sequencing was performed on CD133+ and CD133Kd cells after cisplatin damage. Functional Enrichment analysis tool and PANTHER software were used for pathways enrichment analysis. Wnt pathway activation was studied by Western Blot analysis of beta-catenin expression and Luciferase reporter assay for the TCF/LEF promoter. Proliferation, sphere formation, telomere length and senescence were evaluated in CD133+ and CD133Kd cells.

Results: We found that CD133+ cells dedifferentiated after damage, loosing the CD133 signature and acquiring metanephric mesenchymal genes such as SNAIL1 and KLF4 and regenerative genes such as SOX9 and WNT3. CD133 was reacquired in the recovery phase. Lack of CD133 limited cell proliferation after injury and was correlated with deregulation of Wnt signaling pathway. In parallel, CD133-Kd cells showed lower β-catenin levels and TCF/LEF promoter activation in respect to CD133+ cells. Finally, the lack of CD133 impaired clonal generation of spheres while favored senescence.

Conclusions: These data indicate that CD133 may act as a permissive factor for Wnt/beta-catenin signaling, regulating the cell proliferative response after damage, and may limit cell senescence. In addition, CD133 are not stable during damage, but rather undergo a mesenchymal dedifferentiation showing a plastic phenotype.

Funding: Government Support - Non-U.S.

TH-PO320

Tubule Interconnection after Zebrafish Kidney Injury Caramai N. Kamei,[1] Iain A. Drummond.[1,2] *[1]Massachusetts General Hospital, Charlestown, MA; [2]Genetics, Harvard Medical School, Boston, MA.*

Background: Cell-based therapies for kidney regeneration propose the use of renal epithelial or progenitor cells to generate new nephrons and replace damaged nephrons in injured kidneys. For cell-based approaches to fulfill their promise, newly made nephrons must establish tubule lumen interconnections with the collecting system.

Methods: The zebrafish adult kidney regenerates after gentamicin injury from an adult progenitor cell population, forming 20-100 new nephrons that subsequently invade and "plumb into" to the pre-existing collecting system and restore renal function. Using the zebrafish adult kidney as a model of synchronous nephron-collecting duct fusion, we investigated the role of growth factor signaling pathways in this process.

Results: *Tg(TCFLef-miniP:dGFP)* Wnt reporter expression revealed that new nephron aggregates are patterned by canonical Wnt signaling. High canonical Wnt signaling cells formed a single cell thick dome within cell aggregates and polarized to form rosettes with an apical constriction predicting the site of future tubule lumen formation. Cells under the dome exhibiting low levels of canonical Wnt signaling and low proliferation appear to invade the tubular epithelium, while cells corresponding to the dome flatten into a segment of the forming new nephron and continue to maintain high levels of canonical Wnt signaling activity and proliferation until lumen formation. *Tg(lhx1a:GFP)* reporter expression is maintained at high levels in the entire distal end of the new nephron, allowing visualization of the invasion process. Cells at the distal end of the new nephron extend invasive processes or invadopodia into the underlying tubular epithelium. Short term inhibition of Wnt signaling using the chemical inhibitors IWR1 and IWP2 inhibited invadopodia formation and blocked tubule interconnection events. Newly generated kidney cell-type specific transgenics will allow spatially and temporally controlled modulation of Wnt signaling to identify the cells responsible for generating and interpreting tubule interconnection signals.

Conclusions: Canonical Wnt signaling is required for tubule interconnection during adult zebrafish kidney regeneration.

Funding: NIDDK Support, Private Foundation Support

TH-PO321

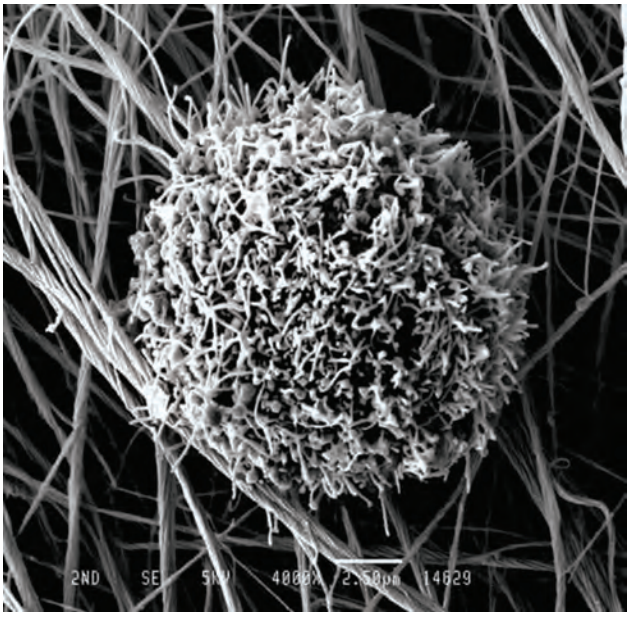
Synthesized Basement Membrane Substratum Provided Cultured Renal Tubular Cells with Scaffold upon Which They Aggressively Developed Filolpodia/Lamellipodia Needed for Cell Motility Kiyoko Inui,[1] Hiroyuki Morita,[2] Yoshihiko Inoue,[1] Eri Kawashima,[1] Fumihiko Koiwa,[1] Katsumi Mochitate,[3] Ashio Yoshimura.[1,4] *[1]Division of Nephrology, Department of Medicine, Showa University Fujigaoka Hospital, Yokohama, Japan; [2]Division of Endocrinology and Metabolism, Aichi Medical University School of Medicine, Nagakute, Japan; [3]BM Matrix Laboratory, National Institute for Environmental Studies, Tsukuba, Japan; [4]Shin-Yokohama Dai-ichi Clinic, Yokohama, Japan.*

Background: Little is known about the ultrastructure of renal tubular epithelium in culture. We previously reported imaging obtained by the use of scanning electron microscopy (SEM) for cultured cell allowed curious aspects of cellular morphology for discussion. In this study, we aimed to capture SEM images of synthesized basement membrane (sBM) we developed and see how it created conditions favorable for cellular proliferation.

Methods: The collagenous substrata, "fib", were prepared on 2 chamber culture dishes interconnected with pores. Type I collagen solution was cast on the second chamber, polymerized, air-dried and used as fib. SV40-T2 cells were seeded on fib, and cocultured with EHS tumor matrigel in the first chamber. During a week of culture, a lamina densa structure formed beneath the cells. The cells were removed and used as sBM substrata.

Results: In subculturing the cells, *rattus norvegicus* kidney tubular epithelialium, NRK-52E, attached fib substrata (Figure), formed lamellipodia, assembled, and proliferated until they became confluent. Application of sBM substrata increased the growth rate of NRK-52 3-fold. SEM images disclosed formation of filopodia / lamellipodia and cell flattening were much more aggresive with sBM substrata.

Conclusions: In vitro, sBM substratum provided NRK-52E cell with scaffold upon which it easily developed cellular structures needed for cell motility and proliferation.



TH-PO322

Analysis of Molecular Mechanisms of Human Kidney Tubulointerstitial Disease Driven by Interleukin 1β Dario R. Lemos,[5,2] Ryuji Morizane,[5,2] Navin R. Gupta,[5,2] Edgar Garcia,[1] Julia Wilflingseder,[5] Tomoya Miyoshi,[5] Koichiro Susa,[5,2] Guanghai Wang,[3,5] Jeremy S. Duffield,[4] Joseph V. Bonventre.[5,2] *[1]Brigham and Women's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Southern Medical University, Guangzhou, China; [4]Vertex Pharmaceuticals, Boston, MA; [5]Renal Division, Brigham and Women's Hospital, Boston, MA.*

Background: Tubulointerstitial disease is characterized by tubular damage with interstitial fibrosis and persistent inflammation. While the deleterious effect of the whole inflammatory response is well documented, contribution of specific cytokines is virtually impossible to study *in vivo*.

Methods: Combined whole genome human data analysis with hPSC-derived organoid technology, experimental mouse models and CRISPR/CAS9 technology.

Results: Whole genome analysis of patients with severe kidney fibrosis indicated a correlation between inflammatory cytokines, mitochondria damage and elevated levels of glycolytic enzymes suggesting that inflammatory and metabolic pathways are mechanistically related. To overcome the limitations of studying inflammatory signals *in vivo*, we tested the effect of single inflammatory cytokines on human kidney organoids. Among other damage mechanisms, we found that IL1β stimulation resulted in cell cycle arrest in proximal tubule epithelial cells after 48hr, and KIM1-expressing damaged proximal tubules with near complete absence of brush borders 96hr post stimulation. Simultaneously, IL1β induced the proliferation and differentiation of stromal fibrogenic cells, resulting in hypertrophic expansion of the interstitium, and interstitial fibrosis. Further investigation into the mechanisms of fibrosis revealed the activation of MYC in organoid stromal PDGFRβ+ cells. Nuclear localization of MYC in interstitial fibrogenic cells was confirmed in Col1a1-GFP mice 72hs after acute damage in vivo. IL1β stimulation of human PDGFRβ+ fibrogenic precursor cells purified from human kidneys in vitro induced autophagy, loss of SQSTM1/P62 reduced mTOR signaling and triggered a MYC-dependent metabolic proliferative program encompassing upregulation of glycolysis enzymes and cyclin kinases. Mechanistically, in the absence of IL1β, SQSTM1/P62 interacts directly with MYC, driving its proteasomal degradation to keep MYC levels low. That interaction is interrupted by IL1β through induction of autophagy, resulting in SQSTM1/P62 degradation and MYC stabilization.

Conclusions: By studying components of the inflammatory response separately, we identified a novel molecular mechanism for tubulointerstitial disease triggered by one single inflammatory cytokine, namely IL1β.

Funding: Other NIH Support - T32 DK007527-26 NIH/NIDDK, Commercial Support - Biogen

TH-PO323

TLR3 Activation Enhances the Renoprotective Effect of Low Serum Cultured Adipose Derived Stromal Cell for Anti-GBM Nephritis Yutaka Kamimura, Naotake Tsuboi, Akimitsu Kitagawa, Takayuki Katsuno, Shoichi Maruyama. *Nagoya University Graduate School of Medicine, Nagoya, Japan.*

Background: We established human adipose tissue-derived stromal cells (hASC) cultured in low (2%) serum (LASC), which demonstrated great therapeutic potential for inflammatory diseases. We have already reported that LASC significantly attenuated rat anti-GBM glomerulonephritis than did hASCs cultured in high (20%) serum (HASC) by promoting the phenotypic conversion of macrophages to immunoregulatory cells. However, the mechanism for LASC to exert greater anti-inflammatory function than HASC was partly evaluated. Based on our DNA microarray data in hASCs, we identified TLR3 as a candidate gene that underlies LASC-mediated immuneregulation. In the current study, we investigated the effect of TLR3 activation of ASC in vitro and in vivo.

Methods: Human abdominal subcutaneous adipose tissue was obtained from patients underwent liposuction or gynecological surgery. Cells were cultured under the two conditions; a low serum culture medium containing 2% fetal bovine serum (FBS) and a high serum culture medium containing 20% FBS. ELISA for HGF, IL-6 and MCP-1 were performed on hASC supernatant cultured with or without poly(I:C) for TLR3 ligand or LPS for TLR4 ligand. Anti-GBM model rats were administered 1×10^6 hASC primed by poly(I:C) or not on days 0, 2 and 4 via the tail vain and we evaluated BUN, sCr, proteinuria and histologic assessment of glomerular crescent formation on day 7.

Results: LASC secreted more HGF, IL-6 and MCP-1 in response to poly(I:C) than HASC, but not to LPS, and these growth factor and cytokines were increased in a dose dependent manner of poly(I:C). In rat anti-GBM model, significant disease amelioration was verified in less elevation of BUN and sCr, and was further evidenced in significant reduction of glomerular crescent formation in animals treated with TLR3-activated LASCs compared to others.

Conclusions: Our data suggest that LASC can be characterized by immune response through TLR3 activation, and that poly(I:C) priming may enhance LASC-mediated renoprotective effects for anti-GBM nephritis.

TH-PO324

Tenascin-C Mediates the Protective Effect of HIF in AKI Xiaoyi Mao, Qionghong Xie, Min Zhang, Da Shang, Chuan-Ming Hao. *Division of Nephrology, Huashan Hospital, Shanghai, China.*

Background: Accumulating evidence suggests that the hypoxia-inducible factor (HIF) mediates cellular adaptions to hypoxia and has a protective effect in acute kidney injury, but the mechanism is not completely understood. The matricellular protein tenascin-C(TNC) which is transiently expressed during development can be re-induced after tissue injury and may be involved in creating a microenvironment that facilitates cell proliferation, adhesion and inflammation. The present study examined the role of TNC in mediating the protective effect of HIF in acute kidney injury using ischemia-reperfusion (IR) model.

Methods: A tenascin-C promoter driven inducible CreER2 knock-in mouse line with an eGFP reporter was generated. TNC-CreER$^{+/+}$ (TNC$^{-/-}$) mice were used to examine the role of TNC in of AKI. RNA sequencing was performed to analyze differentially expressed genes between TNC$^{-/-}$ mice and their wild type littermates.

Results: Following IR, TNC was markedly induced in the interstitium of corticomedullary junction of the kidney as early as 3 hours and peaked at 24-48 hours. Increased TNC expression was also observed in biopsy tissues from patients with AKI. Deletion of TNC in mice significantly aggravated IR induced AKI, showing lower survival rate, higher BUN and more severe tubular injury comparing to their wild type littermates. Then the mechanism underlying TNC induction following injury was investigated. Since 4 hypoxic response elements (HRE) were identified in the promoter region of TNC, we examined the effect of HIF on TNC induction. DMOG, a HIF stabilizer, significantly induced TNC expression both in mice and in primary cultured renal interstitial cells. Luciferase reporter assay showed that hif-2α promoted the transcription of TNC, while mutation of the HRE of the TNC luciferase reporter abolished this effect. To explore the mechanism by which TNC protects kidney from AKI, we did RNA sequencing using renal tissues of TNC$^{-/-}$ mice and their wild type littermates 2 days after IR. RNA-Seq data showed that TNC$^{-/-}$ mice had lower levels of pro-inflammatory cytokines, chemokines and their receptors than wild type mice. Our data suggested that TNC might play an important role in the recovery phase of IR by activating inflammatory response.

Conclusions: Hif-2α induced expression of TNC after ischemia-reperfusion and TNC facilitated recovery from IR injury by activating inflammatory response.

TH-PO325

Ala-Apelin, an Apelin Receptor Antagonist, Ameliorates Contrast-Induced Nephropathy in Rats Seda Kutlug Agackiran,[2] Abdullah Shbair,[2] Zarife Ozdemir,[3] Ozlem Tugce Cilingir Kaya,[1] Naziye Ozkan,[1] Sule Cetinel,[1] Berrak Yegen,[3] Mehmet Koc.[2,3] *[1]Marmara University Medical Faculty, Department of Histology, Istanbul, Turkey; [2]Marmara University Medical Faculty, Department of Internal Medicine, Istanbul, Turkey; [3]Marmara University Medical Faculty, Department of Physiology, Istanbul, Turkey.*

Background: With a dramatically increasing incidence in today's medicine, contrast-induced nephropathy (CIN) is the third common cause of acute kidney injury. Mechanisms of CIN include renal vasoconstriction, medullary hypoxia, endothelial injury, oxidative stress and direct tubular toxicity of contrast agents. Apelin (Ap) is a vasodilatatory molecule and has been shown to prevent cardiac ischemia-reperfusion injury. On the contrary, ala-apelin (Ala-Ap), an apelin receptor antagonist, has anti-fibrotic effects on CCl_4 induced liver fibrosis. In this study, we aimed to demonstrate the effects of Ap and Ala-Ap on CIN.

Methods: Male Sprague-Dawley rats were injected intraperitoneally with only saline (control group, n=8), while CIN groups were treated with either saline (SL, n=9) or Ap (100 mcg/kg/day, n=8) or Ala-Ap (100 mcg/kg/day, n=8) at 0, 24 and 48 hours of the experiment. CIN was established by intravenously injecting indomethacin (10 mg/kg), L-NAME (10 mg/kg) and a high-osmolar contrast agent (Urografin 76%, 6 ml/kg) at 24th h of the experiment. On the 72nd h, kidneys were removed for the assessment of histopathological changes and the determination of glutathione levels and myeloperoxidase activity. Data were analyzed using ANOVA and Student's t-test.

Results: Serum creatinine and BUN levels in SL, Ap and Ala-Ap-treated groups were elevated as compared to control group ($p<0.05$, 0.001 and 0.001), while the increases in serum creatinine in Ala-Ap-treated group was significantly lower as compared to Ap-treated group ($p<0.05$). In contrast to depressed 24-h creatinine clearance in SL and Ap-treated groups ($p<0.01$), creatinine clearance in Ala-Ap-treated group was similar to control group ($p=0.25$). CIN-induced increase in renal myeloperoxidase activity in SL-treated group ($p<0.01$) was abolished in Ala-Ap-treated group ($p<0.05$), while renal glutathione content was increased with Ala-Ap treatment ($p<0.01$). However, histopathological damage scores obtained by light microscopic examination were lower in both Ap and ala-Ap-treated groups as compared to SL-treated group ($p<0.01$).

Conclusions: The present data demonstrate that CIN is ameliorated by administration of Ala-Ap, which appears to act, in part, by diminishing oxidative stress via the inhibition of neutrophil infiltration.

Funding: Government Support - Non-U.S.

TH-PO326

Onset and Resolution of Renal Inflammation Is Orchestrated by YB-1 Tammo Ostendorf,[3] Sonja Djudjaj,[7] Daniel M. Breitkopf,[7] Thomas Rauen,[6] Daniela Hermert,[5] Ina V. Martin,[4] Peter Boor,[2] Jürgen Floege,[4] Ute Raffetseder.[1] *[1]Div. of Nephrology, University Hospital Aachen, Aachen, Germany; [2]RWTH University Aachen, Aachen, Germany; [3]RWTH University Aachen, Nephrology, 52074 Aachen, Germany; [4]RWTH University of Aachen, Aachen, Germany; [5]Uniklinik Aachen, Aachen, Germany; [6]University Hospital Aachen, Aachen, Germany; [7]University Hospital RWTH Aachen, Aachen, Germany.*

Background: The Y-box-binding protein (YB)-1 plays a non-redundant role in both, systemic and local inflammatory responses. During the onset of inflammation, YB-1 upregulates the expression of pro-inflammatory factors such as interleukin (IL)-6 and CCL5. However, anti-inflammatory properties of YB-1 *via* a trans-repressive capacity on the *Ccl5* promoter upon macrophage differentiation have also been described. Thus, YB-1 influences the early phase of inflammation and also seems to contribute to its termination in the later phase.

Methods: We analyzed YB-1-mediated expression of the anti-inflammatory cytokine IL-10 in cell culture assays and *in vivo* in both, LPS induced inflammation and sterile inflammation induced by unilateral renal ischemia-reperfusion (I/R) in mice with half-maximal expression of YB-1 (*Yb1*$^{+/-}$ mice) and their wild type (WT) littermates. Parameters of renal inflammation/fibrosis were determined by immunohistochemistry and qRT-PCR. *Il10* gene regulation was investigated by *ex vivo* chromatin immunoprecipitation in kidney tissues.

Results: Within a decisive *cis*-regulatory region of the *IL10* gene locus, the 4th intron, we identified and characterized an operative YB-1 binding site *via* gel shift experiments and reporter assays in immune and different renal cells. *In vivo*, YB-1 phosphorylated at serine 102 localized to the 4th intron, which was paralleled by enhanced *Il10* mRNA expression in mice following LPS challenge and in I/R. *Yb1*$^{+/-}$ mice had diminished IL-10 expression upon LPS challenge. In I/R, *Yb1*$^{+/-}$ mice exhibited reduced kidney injury/inflammation in the early phase (days 1 and 5), however they exhibited aggravated long-term damage (day 21) with increased expression of *Il10* together with known mediators of renal injury and inflammation compared to their WT littermates.

Conclusions: In conclusion, these data support the notion that there are context-specific decisions concerning YB-1 function and that a fine-tuning of YB-1 e.g. *via* a post-translational modification regulates its activity and/or localization that is crucial for systemic processes such as inflammation.

TH-PO327

A Novel Hybrid Multifunctional Cytokine IL233 Promotes Regeneration Following Kidney Injury Vikram Sabapathy, Nardos T. Cheru, Rebecca L. Corey, Saleh Mohammad, Rahul Sharma. *University of Virginia, Charlottesville, VA.*

Background: Nephrotoxicity remains a principle concern among complications arising due to chemotherapy. For many chemotherapeutic agents and their metabolites, kidney remains the main pathway for elimination. Inflammation amplifies the renal injury and studies have demonstrated that regulatory T-cells (Treg) play a vital role in restricting inflammation thus facilitating recovery following injury. Based on our studies that interleukin IL-2 and IL-33 synergize to increase the number and function of Tregs, we generated a hybrid cytokine (IL233) bearing the activities of both cytokines in one molecule. Pretreatment with IL233 increased Tregs and protected mice from ischemia reperfusion injury (J Am. Soc. Neph., 2017). Here, we investigated, whether the IL233-mediated increase in Tregs can be used therapeutically in nephrotoxic injury model and whether it promotes renal repair.

Methods: The cytokine overexpressed in *E.coli* were purified using affinity and ion-exchange chromatography. A murine model of doxorubicin-induced renal injury was developed to investigate the therapeutic effect of the cytokine. BALB/cJ male mice were injected with doxorubicin (iv) and the protective effect of the cytokine treatment (ip) was examined both pre- and post- doxorubicin administration. The structure and function of the kidney were probed using flow cytometry, histology, immunohistochemistry, quantitative gene expression analysis and biochemical analysis.

Results: As expected, cytokine treatment rapidly increased Treg numbers in blood and spleen. Mice treated with IL233 hybrid cytokine either before or after doxorubicin treatment had lower kidney injury and inflammation scores. Plasma creatinine and blood urea nitrogen values also indicate that IL233 pretreatment significantly protected renal function. Importantly, IL233 administration post doxorubicin treatment restored the kidney function. The level of renal fibrosis was also significantly less in the treated group than saline group. Treatment with hybrid cytokine led in augmenting the levels of Th2 and anti-inflammatory cytokines but attenuating the pro-inflammatory cytokines.

Conclusions: The data from this study provides that IL233 hybrid cytokine bears strong therapeutic potential to rescue kidney injury associated with nephrotoxic drugs and promote repair.

Funding: Other NIH Support - 1R01 DK105833

TH-PO328

Human Renal Tubular Cells and Their Exosomes in Rat Ischemic Renal Injury Jesus H. Dominguez,[2,3] Katherine J. Kelly,[1] James M. Dominguez.[1] *[1]Indiana University, Indianapolis, IN; [2]VAMC, Indianapolis, IN; [3]Medicine, IUMC, Indianapolis, IN.*

Background: We previously showed that intravenous infusion of 3E10 rat renal cells, previoulsy subjected to ischemia preconditioning, prevented rat acute kidney injury (AKI) one day after severe ischemia. The donor cells were found anchored to recipient kidney tubules in relatively small numbers.

Methods: We hypothesized that the relatively small number of donated cells amplified their action by releasing their exosomes in situ. Thus, a local spread of exosomes derived from ischemia preconditioned cells potentially amplified the effect. Therefore, normal human kidneys declined for transplantation were digested and their tubules stored frozen and then cultured, representing 70 % proximal tubular cells. These human cells or their exosomes were given intravenously to nude rats, and comparisons were made.

Results: We compared the protective effects of normal human kidney cells (HuCell) or their exosomes (HuExo) (from declined human kidneys) given intravenously, against untreated ischemia (Isch) 1 and 2 days after 50 minutes of bilateral renal ischemia in nude rats. A sham group was also included (Sh). We estimated each rat nephron received a maximum of 47 renal cells or 2E06 exosomes per injection. We found that 1 day after ischemia serum creatinine increased from 0.23 ± 0.02, n = 4-5, mean ± SE, to 1.23 ± 0.07 in all ischemic groups. After 2 days, Isch continue to rise 2.26 ± 0.36, but Huexo, 0.41 ± 0.05 was similar to Sh, 0.36 ± 0.02, and lower than HuCell ± 0.85 ± 0.17, p <0.02. After 6 days, % damaged tubules in Isch 89 ± 2 was higher than HuCell 49 ± 4 ; HuExo 23 ± 2 and Sh 1.5 ± 0.2 ; p < 0.001. Fibrosis (% area) was also higher in Isch 26 ± 1.5 than HuCell 12 ± 0.7, HuExo 8.5 ± 0.5 and Sh 5.5 ± 0.9, p < 0.001.

Conclusions: We conclude that HuExo are superior agents than HuCell, although the latter were also effective. However, the probability for larger numbers of HuExo to reach all affected nephrons is likely higher. Also, HuExo were effective 1 day after severe ischemia, which greatly enhances their therapeutic advantage over all other therapies in AKI. Finally HuExo therapy of AKI is a very feasible therapy in the clinical setting.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO329

Regenerative Effects of Stem Cell Derived Nano-Extracellular Vesicles in AKI in Mice Ciro Tetta,[1] Daniel Gau,[2] John W. Larkin,[3] Franklin W. Maddux.[3] *[1]Fresenius Medical Care, Waltham, MA; [2]Unicyte AG, Oberdorf, Switzerland; [3]Fresenius Medical Care North America, Waltham, MA.*

Background: The use of nano-extracellular vesicles (n-EVs) to treat several pathologies including cancers, inflammatory and heart disease has increased in the recent years (Ref). Various adult stem cells, including mesenchymal stromal cells (MSCs) and human liver stem cells (HLSCs), are known to promote regeneration involving n-EVs. We studied the regenerative potential of MSC- and HLSC-derived n-EVs in acute kidney injury (AKI) models.

Methods: We utilized two mouse models of AKI: glycerol-induced in severe-combined immune-deficient (SCID) mice and an ischemia reperfusion injury (IRI) model. One IV injection of n-EVs was administered 3 days after induction of AKI. The study was also performed *in vitro* using HLSC derived EV cell model of IRI induced by ATP depletion. miRNA-depleted n-EVs from MSCs were created by knocking down Drosha as a negative control.

Results: In glycerol-induced AKI, both MSC- and HLSC-derived n-EV injections accelerated injured kidney recovery. n-EVs localized only in injured kidney cells. In the IRI model, MSC n-EV treatment prevented damage and inhibited chronic functional and morphological sequelae. n-EVs treatment up-regulated anti-apoptotic genes (BCL-XL, BIRC8 & BCL2), down-regulated pro-apoptotic genes (LTA, CASP1 & CASP8), and inhibited transcription of pro-inflammatory genes, extracellular matrix-receptor interaction, cell adhesion molecules, and inhibition of cell cycle. In an HLSC EV model of IRI, n-EV administration reverted RNA changes in renal tubular epithelial cells and inhibited tubular cell apoptosis. In a miRNA-depleted n-EV model, the n-EV's protective effect in AKI was significantly decreased. MSC n-EVs treatment significantly improved survival in a lethal model of cisplatin-induced AKI in SCID mice.

Conclusions: The findings indicate that MSC- and HLSC- derived n-EVs have regenerative effects in AKI mouse models. n-EVs may be promising for the development of stem cell free therapies.

Funding: Commercial Support - Fresenius Medical Care North America

TH-PO330

Adipose-Derived Mesenchymal Stem Cells Employed Exosomes to Attenuate AKI-CKD Transition through Tubular Epithelial Cell Dependent Sox9 Activation Rui Zeng,[1] Ying Yao,[2] Fengming Zhu.[2] *[1]Tongji Hospital, Wuhan, China; [2]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.*

Background: Acute kidney injury (AKI) predisposes patients to an increased risk into progressive chronic kidney disease (CKD). Mesenchymal stem cells (MSCs) have been shown to promote recovery of injured tubular epithelial cells (TECs) in many kidney diseases. The transcription factor Sox9 is critical for renal development and has been reported to be activated within TECs upon renal injury. However, all these studies focused solely on AKI, whether MSCs can prevent AKI-CKD transition and what is the relationship of Sox9 activation to this process are largely unknown. This study aimed to investigate the therapeutic efficacy of human adipose-derived MSCs (hAD-MSCs) in the prevention of AKI-CKD transition, and illuminate the role of Sox9 in this process.

Methods: 1. C57BL/6 mice were subjected to unilateral renal ischemia/reperfusion (I/R) with or without hAD-MSC treatment. 2. Exosomes derived from hAD-MSCs were extracted and injected into I/R mice through tail vein. 3. GW4869 was used to inhibit the release of exosomes. 4. The changes of kidney pathology, infiltration of inflammatory cells, hallmarks of kidney injury and repair were detected. 5. The activation of tubular Sox9 was assessed.

Results: We found that hAD-MSC treatment activated tubular Sox9, promoted tubular regeneration, attenuated AKI, and mitigated subsequent renal fibrosis. However, these beneficial effects were abolished by a drug inhibiting the release of exosomes from hAD-MSCs. Further, we verified that hAD-MSCs activated tubular Sox9 and prevented TGF-β1-induced transformation of TECs into pro-fibrotic phenotype through exosome shuttling in vitro, but the cells did not inhibit TGF-β1-induced transition of fibroblasts into myofibroblasts.

Conclusions: hAD-MSCs employed exosomes to mitigate AKI-CKD transition through tubular epithelial cell dependent activation of Sox9.

Funding: Government Support - Non-U.S.

TH-PO331

Intravenous Exosomes Decrease Apoptotic Cell Death Following Rat Ischemic Renal Injury Jesus H. Dominguez,[2] James M. Dominguez,[1] Katherine J. Kelly.[1] *[1]Indiana University, Indianapolis, IN; [2]VAMC, Indianapolis, IN.*

Background: In acute kidney injury with ischemia (AKI), multiple, redundant pathways promote inflammation, sustained ischemia tubular cell death. The most common interpretation of cell death in AKI is by necrosis. However, death by apoptosis is an important process that may evolve over longer time after the initial injury. There is no treatment that can prevent the implementation of the dying process in AKI.

Methods: We infused renal tubular cells to treat two rat models of AKI: SD rats (given rat kidney exosomes) and Nude rats (NR) (given normal human kidney exosomes) subjected to 50 min of bilateral renal ischemia. Cells were given 24 and 48 hrs post-ischemia, and prevented injury after 6 days. The broad benefit of a few donor renal cells led to the hypothesis that their exosomes (EX) are the therapeutic effector.

Results: Hence, we infused EX from renal cells, 24 and 48 hrs post-ischemia. In ischemic NR, renal apoptosis was 4.4 fold higher in untreated AKI, as compared to sham controls, and it was prevented by EX, n = 5-4, p <0.05, for all. Equally ischemic SD showed upregulation of renal pro-apoptosis transcripts, casp4, casp8, fas, apaf1, bak, bax, p53 and TRAIL, fold increase 2.7, 2.1, 2.86, 2.05, 1.84, 1.43, 1.53 and 1.91 fold, respectively, and these were blunted by EX treatment, n = 5, p <0.05 for all. Ischemia also activated the anti-apoptotic genes bag2, birc 3 and birc5, 1.8, 3.5 and 3.1 fold, respectively, and EX suppressed this activation as well, p <0.05. Renal function and structure was markedly compromised after 6 days in untreated AKI. In contrast, EX treatment protected renal function and structure to a level similar to that of sham control rats in both sets.

Conclusions: We conclude, the apoptotic transcriptome is stimulated in untreated AKI, promoting renal apoptosis after 24 hrs of the initial injury. The concurrent activation of anti-apoptosis genes is not sufficient to reverse the apoptotic process triggered by AKI. EX prevented ischemic renal apoptosis by interfering with pro and anti-apoptotic activation, and prevented long-term functional and structural renal compromise. The 24 hour lag time after injury is an opportunity for intervention with EX intravenous infusions in AKI.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO332

Superiority of Mesenchymal Stem Cell-Derived Exosomes versus Parent Cells for Rescue Therapy of Advanced Stage AKI Anna Gooch, Ping Zhang, Zhuma Hu, Christof Westenfelder. *University of Utah and VA Medical Centers, Salt Lake City, UT.*

Background: Bone marrow and Adipose-derived Mesenchymal Stem Cells (MSCs and ASCs) have proven both pre-clinically and clinically to be effective for prevention of Acute Kidney Injury (AKI). Yet studies in which MSCs are given 48 hrs. post-insult, a time at which most patients with severe AKI are diagnosed and when no rescue therapy is available, show them to be ineffective or potentially damaging due to compromised renal blood flow, where introduction of large cells (~50μm) causes further deterioration of renal function. ASCs' paracrine actions, including release of exosomes, are largely responsible for their protective effects, and others have shown that administration of ASC-derived exosomes can prevent AKI. Thus, we hypothesized that ASC-derived exosomes (40-150 nm), which can easily move through the microvasculature, may be effective rescue therapy for late stage AKI. Accordingly, we compared the therapeutic efficacy of ASC-derived exosomes vs. ASCs given late to rats with severe, non-spontaneously recovering AKI.

Methods: ASCs were isolated from Sprague Dawley (SD) rats and characterized by standard protocols. Exosomes were isolated from cultured ASCs using the ExoQuick TC kit (SBI), quantified (Nanosight and Bradford assay), and characterized by FACS for CD44 and CD29 surface protein expression. Adult, female SD rats were subjected to I/R AKI (52 min bilateral renal pedicle clamp). Serum Creatinine (SCr) was assessed at baseline, Days (D) 1, 2 and 3. If the SCr value on D2 was greater than that on D1, rats were treated via left carotid artery with either 1 ml of 1) 1x10e6 SD MSCs, 2) 200 ug protein-equivalent of SD MSC-derived exosomes (~4x10e10 exosomes), or 3) vehicle (1xPBS).

Results: SCr increased between D1 and D2 in all rats 1.6 ± 0.35 mg/dL (mean ± SD). As hypothesized, exosome administration on D2 caused a significant -1.7 ± 0.34 mg/dL drop in SCr by D3 vs. vehicle (+0.4 ± 1.1 mg/dL), while ASC administration did not, and in 25% of animals caused further functional deterioration.

Conclusions: Exosome therapy 2 days post-insult is superior to ASC therapy for rescue of AKI. Further optimization of the exosome therapy is expected to identify optimal treatment doses for advanced AKI.

Funding: Veterans Affairs Support

TH-PO333

Urinary Extracellular Vesicles in Tubular Cell Repair Benedetta Bussolati,[2] Veronica Dimuccio,[1] Cristina Grange,[4] Elli Papadimitriou.[3] *[1]Univerity of Turin, Turin, Italy; [2]University of Torino, Torino, Italy; [3]University of Turin Italy, Turin, Italy; [4]University of Turin, Turin, Italy.*

Background: Extracellular vesicles (EVs) are emerging as an integral component of the cell-to-cell communication network. EVs may actively transfer to target cells various molecules including proteins, mRNAs and microRNA, with stable epigenetic changes. Urinary EVs in particular, released by cells lining the nephron, are abundantly present in urine and may be involved in intra-nephron communication among cells. We here evaluate the possible role of urinary EVs in repair of renal tissue after AKI.

Methods: EVs were isolated by urine of normal subjects by ultracentrifugation and gradient sedimentation. CD133+ and CD133neg EVs were separated by magnetic sorting. EV populations were subjected to nanoparticle tracking analysis to define their dimension and profile and measure EV mean, distribution and concentration. EVs were characterized by marker expression using Western Blot and FACS analysis. MicroRNA content was assessed by qRT-PCR using a MicroRNA Assay Human Panel Early Access kit to profile 754 human mature miRNAs. EVs from mesenchymal stem cells were used as control. Urinary EVs were injected in mice undergoing AKI (day 1) by intramuscle injection of glycerol.

Results: CD133+ and CD133neg vesicles obtained from urine showed similar expression of exosomal markers. CD133+ and CD133neg EVs showed selective expression of a panel of microRNAs. Functional Enrichment analysis tool showed enrichment in pathways related to matrix-receptor interaction, adhesion as well as pathways regulating pluripotency in CD133+ EVs, where pathways involved in TGF-beta signalling, cell cycle and mTor signalling in CD133 negative EVs. EV administration to AKI mice showed a selective improvement of renal function and histology. In particular, CD133neg EVs promoted repair in a comparable level to MSC-EVs. CD133+ EVs did not show repairing effect. This was confirmed by administration of CD133+ EVs isolated by CD133+ cells in culture. Bioimaging of injected CD133neg EVs showed their rapid localization and internalization within tubules in AKI mice.

Conclusions: These data indicate that EVs within urine may support repair of tubular cells, indicating a possible paracrine action of EVs released within urine to damaged cells in lower tubular compartments. This was not obtained by CD133+ EVs suggesting selective effects of cells within tubules in its repair.

Funding: Government Support - Non-U.S.

TH-PO334

β-Hydroxybutyrate Attenuates Renal Ischemia-Reperfusion Injury Takaya Tajima, Ayumi Matsui, Tomoaki Ito, Kiyotaka Uchiyama, Shu Wakino, Hiroshi Itoh. *Keio University School of Medicine, Tokyo, Japan.*

Background: An endogenous ketone, β-hydroxybutyrate(βOHB) is used as an energy source in organs including kidney. It has been reported that βOHB has therapeutic benefits against stress conditions. In this study, we evaluated its protective effects and potential mechanisms in renal ischemia/reperfusion injury(IR).

Methods: Male C57BL/6J mice and human proximal cell line, HK-2 cells were used in this study. Two weeks before the study, the right kidney was removed and mice were separated into 4 groups: saline-treated sham-operated mice (n=6), βOHB-treated sham-operated mice (n=6), saline-treated mice with IR (n=8), βOHB-treated mice with IR (n=8). In IR injury mice were subject to clamping of both renal arteries and veins for 45 min and to reperfusion. βOHB was administered continuously by osmotic mini-pump at the dose of 8 mg/h. Kidneys were harvested 24 h after IR injury, and functional and molecular parameters were evaluated. In vitro studies, HK-2 cells were incubated for 1 h with mineral oil to induce hypoxic injury, and incubated for 24 h after medium replacement. These HK-2 cells were treated with various doses of βOHB and molecular parameters were evaluated.

Results: In mouse study, blood urea nitrogen, serum creatinine levels, and renal tissue injury scores in βOHB-treated IR mice were significantly lower than those of saline-treated IR mice. βOHB increased histone acetylation due to the inactivation of histone deacetylase, which increased the expression of anti-oxidative factors including FOXO3, MnSOD, Catalase, Nrf2 in IR-injured kidneys and hypoxic HK-2 cells. Consistently, βOHB decreased ROS production, decreased the MDA content in IR-injured kidneys as well as in hypoxic HK-2 cells. Moreover, βOHB decreased markers of inflammasome activation including NLRP3, ASC, caspase-1, and the proinflammatory cytokines IL-1β and IL-18 expression in IR-injured kidneys as well as in hypoxic HK-2 cells. Finally, βOHB decreased Bax expression and increased Bcl-2 expression in IR-injured kidneys as well as in hypoxic HK-2 cells. Consistently, βOHB improved cell survival in hypoxic HK-2 cells and reduced the numbers of TUNEL-positive cells in IR-injured kidneys.

Conclusions: βOHB attenuates renal IR injury. The anti-oxidation, anti-inflammation and anti-apoptosis effects by βOHB, may play a role in renoprotection against renal IR injury.

TH-PO335

Inhibition of the Transcriptional Activator Etv4 in Proximal Tubule Cells Protects Kidneys from Tubular Injury Susanne V. Fleig,[7] Flavia G. Machado,[5] Monica Chang Panesso,[6] Chia-Chun Wu,[1] Kohei Uchimura,[6] Rafael Kramann,[3] Motoko Yanagita,[2] Benjamin D. Humphreys.[4] *[1]Chi Mei Medical Center, Tainan, Taiwan; [2]Kyoto University Graduate School of Medicine, Kyoto, Japan; [3]RWTH Aachen University, Lemiers, Netherlands; [4]Washington University School of Medicine, Clayton, MO; [5]Washington University in St Louis, School of Medicine, St Louis, MO; [6]Washington University in St. Louis, St Louis, MO; [7]Nephrology and Hypertension, Hannover Medical School, Hannover, Germany.*

Background: The transcription factor Etv4 regulates developmental programs in several organs including kidney, but roles for Etv4 in kidney injury are poorly defined. Here we have investigated the expression, function and regulation of Etv4 during dedifferentiation and repair after AKI.

Methods: We generated a novel mouse model with inducible expression of a dominant-negative Etv4 (DN-Etv4) in proximal tubule cells. NDRG1CreERT2; R26-DN-Etv4 bigenic mice were subject to moderate and severe bilateral IRI and tissue histology, gene expression and kidney function was monitored. Primary human proximal tubule cultures (RPTEC) and iPS-derived kidney organoids were used to assess regulation of Etv4 expression.

Results: At 24h after IR injury, mice with proximal specific DN-Etv4 expression had a significantly lower increase in creatinine and BUN than controls; a functional difference is not seen at 3 and 5 days past injury. DN-Etv4 expressing mice have a much lower tubular injury score at 24h than controls. Caspase 3 staining shows a significantly lower amount of apoptotic cells at 24h. The metabolic intermediate α-ketoglutarate (aKG) is upregulated in ischemia due to lack of decarboxylation via PHD2 (Olenchock BA et al, Cell 2016). aKG inversely controls etv4 expression in cancer, and high etv4 was linked to hypoxia-induced apoptosis (Keenan M. et al, PLoS Genetics 2015); we observed strong downregulation of Etv4 expression in human RPTECs after exposure to aKG. Finally, gentamicin treatment of human iPS-derived kidney organoids potently induced Etv4 mRNA.

Conclusions: The transcriptional activator etv4 is induced in dedifferentiatied proximal tubule after AKI. Our results suggest that it normally acts to induce apoptosis in the hypoxic postischemic tubule, as blocking its function improved cell survival, tubular injury scores and BUN after IRI. This pathway is conserved in humans, since gentamicin induced Etv4 mRNA in human iPS-derived kidney organoids. Finally, aKG downregulated Etv4 expression in vitro, suggesting a novel therapeutic strategy.

Funding: NIDDK Support

TH-PO336

Role of Sirt2 in a Murine Cisplatin Induced AKI Model Woong Park,[2] Yujin Jung,[3] Won Kim,[1] Kyung Pyo Kang.[2] *[1]Chobuk National Univeristy Medical School, Jeonju, Republic of Korea; [2]Chonbuk National University Medical School, Jeonju, Republic of Korea; [3]chonbuk national university medical school, Jeonju, Republic of Korea.*

Background: Cisplatin based chemotherapy is commonly used in therapeutic strategies for solid tumor. However, limitation of this agent is adverse effect on normal tissue such as kidney, ear, and peripheral nerves. Mechanisms of cisplatin nephrotoxicity are proposed as oxidative stress, inflammation, cellular apoptosis and death, and cell cycle regulation. Sirt2 is one of sirtuins family, which is NAD^+ (nicotinamide adenine dinucleotide)-dependent deacetylase. However, there are a few reports about the role of Sirt2 on cisplatin-induced renal injury. In this study, we evaluated the effect of Sirt2 on renal injury induced by cisplatin.

Methods: We used *Sirt2* knockout mice (B6.129-*Sirt2*$^{tm1.1Fwa}$/J, *Sirt2*KO) and their wild type mice (C57BL/6, WT mice). Cisplatin nephrotoxicity was induced by intraperitoneal injection of cisplatin (20 mg/kg). After 3 days after cisplatin injection, blood and kidney tissues were harvested. Renal function and histology were evaluated. Tubular apoptosis and reactive oxygen species were evaluated by immunohistochemistry. Intercellular adhesion molecule (ICAM)-1 and acetyl-p65 were evaluated by Western blot analyses.

Results: After induction of cisplatin nephrotoxicity, renal function measured by serum BUN and creatinine was significantly improved in *Sirt2*KO mice group at 72 h after cisplatin treatment compared to WT mice. At 72 h after cisplatin treatment, tubular injury score was significantly decreased in *Sirt2*KO mice compared to WT mice. TUNEL positive tubular cells and renal caspase-3 expression were decreased in *Sirt2*KO mice compared to WT mice after cisplatin treatment. Cisplatin-induced increases of dihydrorhodamine-123 (DHR, a reactive oxygen species marker)-positive tubular cells were significantly suppressed in *Sirt2*KO mice compared to WT mice. Finally, cisplatin-induced increases of ICAM-1 and acetyl-p65 expression in Western blot or immunohistochemistry were decreased in *Sirt2*KO mice.

Conclusions: Sirt2 KO might have important pathophysiologic role in cisplatin-induced renal injury with regulation of apoptosis, a reactive oxygen species and inflammation.

Funding: Government Support - Non-U.S.

TH-PO337

Par1b Is Protective to Cisplatin Induced Renal Tubular Injury Abhijeet Pal,[2] Philip Chu,[1] James M. Pullman,[5] Frederick J. Kaskel,[3] Kimberly J. Reidy.[4] *[1]Albert Einstein College of Medicine, New York, NY; [2]Pediatric Nephrology, Children's Hospital at Montefiore, Bronx, NY; [3]Albert Einstein College of Medicine, Children's Hospital at Montefiore, Bronx, NY; [4]Children's Hospital at Montefiore/ Albert Einstein College of Medicine, Bronxville, NY; [5]Montefiore Medical Center, Bronx, NY.*

Background: Nephrotoxic injury is an important contributor to childhood acute kidney injury (AKI). Partitioning defective(Par)1b is a serine threonine kinase member of Par polarity protein family. Dual loss of Par1b and its paralogue Par1a in mice leads to defects in Notch expression and glomerular and proximal tubule development. We identified increased expression of Par1b in proximal tubules in mouse models of AKI and in human kidney tissue with acute tubular necrosis(ATN). We hypothesized that Par1 proteins are protective and promote renal epithelial repair.

Methods: To test this, we used in vivo and in vitro approaches. We induced AKI in *Par1b*$^{-/-}$ (Par1b KO) mice with the proximal tubular nephrotoxin, cisplatin. In addition, loss of function was studied using primary proximal tubular cultures from Par1b KO and WT mice. For gain of function, adenoviral constructs were used to overexpress Par1b or control constructs in primary proximal tubular cultures.

Results: Par1b KO mice developed more severe ATN, with higher tubular injury scores and higher Kim-1 levels. Cytoskeletal architecture and cell-extracellular matrix structures were severely disrupted in cisplatin injected Par1b KO kidneys compared to WT as demonstrated by immunostaining of adhesion molecules (e-cadherin, β-catenin, and β1-integrin). To identify the mechanisms underlying the increased injury, we examined the effect of loss of Par1b on apoptosis and necrosis. Par1b deletion led to increased apoptosis following cisplatin treatment, as demonstrated by increased TUNEL staining in vivo and increased cleaved caspase 3 staining in vitro. Increased necroptosis was also demonstrated by increased RIP-1 levels in the Par1b KO kidneys. In WT kidneys, cisplatin exposure induced renal repair pathways, as evidenced by increased expression of Wnt4 and its effectors Axin2 and Lhx1 along with increased levels of activated cleaved Notch2 receptor and increased expression of its effectors Hes1 and Hes5. This effect was attenuated in Par1b KO kidneys. Par1b overexpression in proximal tubular cells showed increased cell viability following cisplatin treatment, demonstrating a protective role for Par1b.

Conclusions: Both in vivo and in vitro studies support the protective role for Par1b in cisplatin induced ATN. Further defining Par1b targets may lead to therapeutic options to prevent cisplatin induced AKI in the future.

TH-PO338

TWEAK and RIPK1 Mediate Secondary Cell Death During AKI Diego Martin-Sanchez,[1] Miguel Fontecha,[1] Susana Carrasco,[1] Maria Dolores Sanchez-Nino,[1] Marta Ruiz-Ortega,[2] Jesus Egido,[1,2] Andreas Linkermann,[3] Alberto Ortiz,[1,2] Ana B. Sanz.[1] *[1]IIS-Fundación Jiménez Díaz, Madrid, Spain; [2]Universidad Autonoma, Madrid, Spain; [3]University Hospital Carl Gustav Carus Dresden, Dresden, Germany.*

Background: TWEAK is a member of the TNF superfamily that, in a proinflammatory environment, induces renal tubular cell death. TWEAK, TNFα and IFNγ (TTI)-induced cell death has features of apoptosis and is associated to activation of caspases and mitochondrial stress. However, inhibition of caspases with zVAD in vitro and in vivo was not protective. Recently, it was reported that ferroptosis plays a key role in the initial wave of tubular cell death in AKI, and beyond cell death, it mediates upregulation of inflammatory molecules, as Fn14, and of necroptosis proteins. We hypothesized that TWEAK in collaboration with RIPK1 could contribute to a secondary wave of inflammation-related cell death during AKI.

Methods: Fn14 knockout (Fn14-KO), RIPK3 KO mice or wild type (WT) mice received a single i.p. injection of folic acid. Some WT mice were pretreated with Nec-1. In vitro studies were performed in murine proximal tubular MCT cells.

Results: Fn14-KO mice were protected from AKI, as assessed by serum BUN and creatinine levels, and reduced cell death, assessed by TUNEL, at 72h, while, at 24 hours there is not protection. This suggests that TWEAK contributes to secondary cell death in AKI. In cultured cells, TTI induces caspase activation, but zVAD changed the mode of cell death from apoptosis to necroptosis. The RIPK1 inhibitor Nec-1 prevented both cell death induced by TTI and by TTI+zVAD (TTI/Z), suggesting that RIPK1 is implicated in both apoptosis and necroptosis. Specifically, Nec-1 prevented features of apoptosis as caspase activation. By contrast, RIPK3 and MLKL siRNA only prevented TTI/Z-induced cell death suggesting that this process is mediated by necroptosis. Both Nec-1 and RIPK3 deficiency protected from AKI at 96h, showing the implication of necroptosis. This suggests that TWEAK/RIPK1 may mediate the secondary wave of cell death during AKI.

Conclusions: TWEAK in association with RIPK1, plays a key role in secondary, inflammation-related cell death in AKI. In vitro experiment showed that TTI-induced cell death has features of apoptosis but is dependent on the kinase activity of RIPK1. By contrast, caspase inhibition changed the mode of cell death to necroptosis. These results open a new therapeutic window to treatment of AKI once it has been established.

TH-PO339

PPARδ Modulator MTB-2 Enhances FAO In Vitro and Attenuates Ischemia-Reperfusion-Induced Gene Expression Changes In Vivo 48 Hours and 14 Days Post AKI Christina Bracken, Jeff H. Stanwix, Hien G. Hoang, Eric Bell, Effie Tozzo. *Mitobridge, Cambridge, MA.*

Background: Ischemic acute kidney injury (AKI) is characterized by persistent proximal tubule mitochondrial dysfunction. Due to their highly oxidative metabolism, proximal tubule cells (PTC) utilize fatty acids to generate the energy required for their specialized function. We hypothesized that enhancing fatty acid oxidation (FAO) with a PPARδ modulator will restore mitochondrial function, offering a potential therapeutic treatment for AKI.

Methods: Human hTERT RPTECs were treated with MTB-2 and analyzed for PPARδ target gene expression and their ability to utilize palmitate. Sprague-Dawley rats underwent a 45 minute bilateral ischemia-reperfusion (IR) AKI. Following reperfusion, rats were treated with 2 IV doses of selective PPARδ modulator MTB-2 at doses varying from 0.3 to 10 mg/kg or vehicle. At 48 hours and 14 days post reperfusion kidney cortex gene expression was assessed by qPCR.

Results: MTB-2 significantly increased expression of PPARδ-target genes associated with mitochondrial FAO (such as Cpt1a) and resulted in enhanced palmitate oxidation in hTERT RPTECs. In vivo, MTB-2 reduced plasma and urinary biomarkers of AKI at 24 and 48 hours. To elucidate the mechanism by which MTB-2 modulation of PPARδ improved AKI we measured expression of proximal tubulec abundance, mitochondrial homeostasis, kidney injury and fibrosis genes at 48 hours and 14 days post AKI. At 48 hours MTB-2 resulted in partial restoration of proximal tubules denoted by increased expression of PTC genes; this effect was maintained through 14 days post AKI. At the same time points, PPARδ modulation mitigated IR-induced reduction of genes regulating mitochondrial transcription such as PGC1α and many nuclear and mitochondrial-encoded transcripts of electron transport chain proteins. At both 48 hours and 14 days post AKI MTB-2 decreased the expression of kidney injury genes KIM-1and NGAL. Genes associated with fibrosis, such as, Col1a1, were induced at 14 days post AKI and MTB-2 treatment attenuated their upregulation.

Conclusions: Selective PPARδ modulation by MTB-2 after AKI in rats recovered renal function through preservation of proximal tubular and mitochondrial gene expression and reduction of kidney injury and profibrotic genes.

TH-PO340

Proximal Tubule DRP1 Deletion after AKI Promotes Recovery Heather M. Perry, Amandeep Bajwa, Liping Huang, Mark D. Okusa. *Medicine, University of Virginia, Charlottesville, VA.*

Background: Mitochondrial dysfunction plays a crucial role in the pathogenesis of kidney disease. A key mediator of mitochondrial function is the GTPase, dynamin related protein 1 (DRP1). The cell specific role of DRP1 during recovery from acute kidney injury (AKI) is unknown. Proximal tubule (PT) cells are highly dependent on

promoting mitochondrial function in proximal tubule cells during recovery from AKI may prevent kidney dysfunction and progressive fibrosis. Thus, we hypothesize that the spatio-temporal genetic deletion of DRP1 in proximal tubules after ischemia-reperfusion injury (IRI) promotes kidney recovery in mice.

Methods: *iSLC34a1CreER*^{T2} *Drp1*$^{fl/fl}$ (iDrp1 PTKO, n = 8) and littermate control *iSLC34a1CreER*^{T2} *Drp1*$^{wt/wt}$ (n = 5) mice were subjected to unilateral renal ischemia. Tamoxifen was initiated 3d later to induce deletion of DRP1 followed by a nephrectomy of the un-operated kidney at 13d and mice were euthanized on day 14. Plasma was collected for creatinine (PCr) measurement and kidneys were prepared for histology to assess renal injury by H&E, fibrosis by picro-sirius red and Masson's trichrome, and detection of myofibroblasts, macrophages and endothelial rarefaction by IF. Total kidney tissue mRNA levels of fibrosis markers, *SMA, Col1a1, Col3a1, Fn,* and *Vim* were measured by RT-qPCR. Mitochondrial function was assessed by Seahorse.

Results: iDrp1 PTKO mice had attenuated IRI-induced PCr levels compared to control mice (1.10 vs. 0.21 mg/dl respectively, $p < 0.05$). Consistent with preserved kidney function, iDrp1 PTKO mice had attenuated renal injury compared to controls. Histological measures of fibrosis and transcript levels of fibrosis markers were also reduced in IRI kidneys of iDrp1 PTKO mice compared to controls. Hallmarks of fibrosis including myofibroblast formation, macrophage infiltration and capillary rarefaction were attenuated in IRI kidneys of iDrp1 PTKO mice compared to control mice. Lastly, primary proximal tubule cells lacking DRP1 had enhanced mitochondrial function.

Conclusions: Loss of DRP1 after IRI allows for epithelial cells to recover and prevent kidney dysfunction and progressive fibrosis. Targeting DRP1 and mitochondrial function may be an effective therapeutic strategy to allow for epithelial recovery after AKI.

Funding: NIDDK Support

TH-PO341

Tubular BMPR1A-SMAD1/5/8-ID Signaling Mediates Renal Recovery via Inhibition of Profibrotic Processes after Ischemia-Reperfusion Injury Emilia Vigolo,[2] Lajos Marko,[1,4] Christian Hinze,[2,3] Dominik N. Müller,[2,1] Ruth Schmidt-ullrich,[2] Kai M. Schmidt-Ott.[2,3] *[1]Experimental and Clinical Research Center, Berlin, Germany; [2]Max Delbrueck Center for Molecular Medicine, Berlin, Germany; [3]Charité University, Berlin, Germany; [4]Berlin Institute of Health (BIH), Berlin, Germany.*

Background: The signaling pathways that mediate renal recovery after acute kidney injury (AKI) constitute potential targets of pharmacologic intervention. Bone morphogenetic protein (BMP) signaling has been previously implicated in preventing profibrotic responses in the injured kidney, but its detailed role and molecular targets after AKI are incompletely understood. We therefore addressed the time course, molecular targets and cellular functions of BMP signaling after experimental AKI.

Methods: A unilateral ischemia reperfusion injury (IRI) mouse model was used to investigate renal regeneration. The modulation of BMP signaling after IRI was monitored in kidney tissue by examined the nuclear expression pattern of phosphorylated BMP-specific transcription factors SMAD1/5/8 (pSMAD1/5/8) using immunostaining and Western blotting. To study the role of BMP signaling in tubules, we generated a tubular-specific and injury-dependent BMP type 1A receptor (BMPR1A) knock-out (*Bmpr1a cKO*) mouse model. Tubular injury and inflammation were evaluated by renal histology, and immunostaining for infiltrating neutrophils and macrophages. Tubulointerstitial fibrosis was examined by Masson's trichrome staining and collagen IV Western blotting. pSMAD1/5/8 chromatin immunoprecipitation (ChIP-) and RNA-sequencing were performed to discover novel BMP targets during renal recovery.

Results: We observed that BMP signaling was transiently down-regulated during early injury phases and re-activated 7 days (d) after IRI, when the kidney is undergoing recovery. However, the *Bmpr1a cKO* kidneys failed to re-activate pSMAD1/5/8 and displayed an aggravated tubular injury and increased inflammation when compared to controls. 21 d after IRI the *Bmpr1a cKO* kidneys presented enhanced tubulointerstitial fibrosis. Comparative analyses between ChIP- and RNA-sequencing data revealed genes encoding inhibitor of DNA-binding (ID) proteins *Id1, Id2, and Id4* as direct targets of BMP signaling during regeneration. Down-regulation of *Id* genes in *Bmpr1a cKO* kidneys was associated with activation of profibrotic factors, including P38 mitogen-activated kinase (MAPK), P21 and P27.

Conclusions: Successful recovery after ischemia-induced AKI is mediated by BMPR1A-SMAD1/5/8-ID signaling that prevents activation of profibrotic pathways.

TH-PO342

Sphingosine-1 Receptor Agonist SEW2871 Ameliorates Contrast-Induced Nephropathy in Rats Abdullah Shbair,[3] Seda Kutlug Agackiran,[3] Zarife Ozdemir,[2] Ozlem Tugce Cilingir Kaya,[1] Naziye Ozkan,[1] Sule Cetinel,[1] Berrak Yegen,[2] Mehmet Koc.[3,2] *[1]Marmara University Medical Faculty, Department of Histology, Istanbul, Turkey; [2]Marmara University Medical Faculty, Department of Physiology, Istanbul, Turkey; [3]Marmara University Medical Faculty, Department of Internal Medicine, Istanbul, Turkey.*

Background: With a dramatically increasing incidence in today's medicine, contrast-induced nephropathy (CIN) is the third common cause of acute kidney injury (AKI). Mechanisms of CIN include renal medullary hypoxia, endothelial injury, oxidative stress and direct tubular toxicity of contrast agents. A sphingosine-1 receptor agonist SEW2871 has been shown to prevent ischemia-induced AKI. In this study, we aimed to demonstrate the effects of SEW2871 on CIN.

Methods: Male Sprague-Dawley rats were injected intraperitoneally with only saline (control group, n=8), while CIN groups were treated with either saline (SL, n=9) or SEW2871 (10 mg/kg/day, n=7) at 0, 24 and 48 hours of the experiment. CIN was established by intravenously injecting indomethacin (10 mg/kg), L-NAME (10 mg/kg) and a high-osmolar contrast agent (Urografin 76%, 6 ml/kg) at 24th h of the experiment. On the 72nd h, kidneys were removed for the assessment of histopathological changes and the determination of glutathione levels and myeloperoxidase activity. Data were analyzed using ANOVA and Student's t-test.

Results: Serum creatinine and BUN levels in SL- and SEW2871-treated CIN groups were elevated as compared to control group ($p<0.05$-0.01), while the increases in SEW2871-treated group were relatively lower. In contrast to depressed 24-h creatinine clearance in SL-treated CIN group ($p<0.05$), clearance in SEW2871-treated group was not different than that of the control group. CIN-induced increase in renal myeloperoxidase activity ($p<0.01$) was abolished in SEW2871-treated group ($p<0.05$), while renal glutathione content was increased with SEW2871 ($p<0.001$). However, histopathological damage scores obtained by light microscopic examination were similar in SEW2871- or SL-treated CIN groups.

Conclusions: The present data demonstrate that CIN is ameliorated by administration of SEW2871, which appears to act, in part, by diminishing oxidative stress via the inhibition of neutrophil infiltration.

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TH-PO343

Renal Cholesterol Rafts Blockade Ameliorates Septic Multiorganic Failure Alberto Lazaro Fernandez,[3,4] Maria angeles GONZALEZ-NICOLAS GONZALEZ,[3,4] Blanca Humanes,[3,4] Raquel Herrero,[1,5] Mario Arenillas,[2] Antonio Ferruelo,[1,5] José Á. Lorente,[1,5] Alberto Tejedor jorge.[3,6] *[1]Critical Care Department, Hospital Universitario de Getafe, Madrid, Spain, Getafe, Madrid, Spain; [2]Hospital Universitario de Getafe, Madrid, Spain, Getafe, Spain; [3]Renal Physiopathology Lab, Instituto de Investigación Sanitaria Gregorio Marañón, Hospital G.U. Gregorio Marañón, Madrid, Spain, Madrid, Spain; [4]REDinREN, Madrid, Spain, Madrid, Spain; [5]CIBERES, Madrid, Spain, Madrid, Spain; [6]Department of Medicine, Universidad Complutense, Madrid, Spain, Madrid, Spain.*

Background: Sepsis is a potentially life-threatening condition that occurs due to systemic inflammatory response to infection that leads to organ failure and death. Acute kidney injury (AKI) has been reported as a particularly serious complication in patients with severe sepsis, where it is the leading cause of death among critically ill patients. In fact, the mortality of septic patients with AKI is about 75%, while those with severe sepsis without AKI ranges between 27 and 32%. Cilastatin, a renal dehydropeptidase-I inhibitor has shown its usefulness in the protection of AKI induced by nephrotoxic drugs due to disruption of lipid rafts cycling. Here, we evaluated the utility of cilastatin as a protector against renal damage induced by sepsis and its effect on survival.

Methods: Sepsis was developed on male Sprague-Dawley rats by cecal ligation puncture model (CLP). The animals were divided into 4 groups: SHAM, CLP, SHAM+cilastatin and CLP+cilastatin. Cilastatin (150 mg/kg bw, i.p.) was administered immediately and at 24h after induction of sepsis. Renal damage was evaluated 48h after surgery by measuring serum creatinine, BUN, glomerular filtration rate (GFR), proteinuria, renal injury biomarker KIM-1 and renal morphology. Survival was evaluated in another CLP model with greater perforation thickness, in the presence and absence of cilastatin.

Results: Sepsis increased serum creatinine, BUN and proteinuria levels and decreased the GFR in comparison with the sham groups. These renal effects of sepsis were confirmed by the increased of the acute kidney injury biomarker KIM-1 at protein level and the presence of severe morphological changes such as swelling of tubular cells, and hyaline cast in the tubular lumen. Treatment with cilastatin completely prevented renal dysfunction, restored KIM-1 into control levels, and reduced many of the histologic symptoms of renal damage. Importantly, these protective effects of cilastatin at the renal levels caused a decrease in mortality by 33%.

Conclusions: Our findings support the potential use of cilastatin as a useful drug in the treatment of sepsis, improving the AKI induced by it and preventing its lethality. Therefore, it could be a very beneficial therapeutic strategy for septic patients susceptible to renal damage in clinical practice.

Funding: Government Support - Non-U.S.

TH-PO344

Autophagy Activation in Circulating Proangiogenic Cells (PAC) Aggravates Interstitial Fibrosis Post-AKI in Type I Diabetes Mellitus Daniel Patschan,[2] Gerhard A. Mueller.[1] *[1]Georg-August University, Gottingen, Germany; [2]Department of Cardiology, Pulmology, Angiology and Nephrology, Brandenburg Medical School, Brandenburg an der Havel, Germany.*

Background: Diabetes mellitus increases the risk for AKI under experimental and clinical conditions. Circulating proangiogenic cells (PAC) have been proven as effective tool in ischemic AKI in recent years. Autophagy (AP) serves as endogenous mechanism of self-defense in situations of increased metabolic stress. Aim of the study was to analyze consequences of AP activation in syngeneic murine PAC, administered to diabetic animals suffering from ischemic AKI.

Methods: Insulin-dependent diabetes was induced in male, 8-12 weeks old C57/Bl6N mice by repeated i.p. injection of streptozotocin. Six weeks later, AKI was induced by bilateral renal ischemia of 45 minutes. Animals were injected with either untreated or pharmacologically preconditioned murine PAC (10^6) at the time of reperfusion.

Preconditioning was performed with zVAD or MD132, two established AP inducers. Animals were analyzed 48 hours and 6 weeks later.

Results: Excretory function (serum cystatin C) – ischemia induced significant kidney dysfunction in the short-term (48 h), IDDM aggravated this situation even further. Cell therapy did neither attenuate nor aggravate AKI. At week 6, excretory dysfunction remained affected in non-diabetic and diabetic mice without cell therapy. Administration of both, zVAD and MD132 pretreated PAC resulted in aggravated dysfunction in non-diabetic animals, serum cystatin C was lower in diabetic mice receiving zVAD treated PAC. Fibrosis – at 48 h, significant interstitial matrix accumulation was exclusively detected in diabetic mice receiving MD132 treated cells. At week 6 however, fibrosis occurred in almost every group with two exceptions (non-diabetic and diabetic AKI +native PAC). The morphological findings were most pronounced in diabetic mice undergoing treatment with preconditioned cells. EndoMT – mesenchymal transition of endothelium cells was detected in a significant manner in the following groups: 48 h – IDDM + zVAD and + MD132; 6 weeks – IDDM + MD132.

Conclusions: zVAD-/MD132-induced AP activation in PAC does not result in any functional improvement in diabetic AKI. Postischemic structural abnormalities however are being aggravated. Thus, pharmacological stimulation of autophagy in PAC has not been identified as effective strategy for improving the cells′ renoprotective capacity in diabetic AKI.

TH-PO345

The Striking Finding of Multiciliated Proximal Tubular Cells in Patients with Tubular Injury Jennifer Eymael,[1] Brigith Willemsen,[1] Fieke Mooren,[1] Jack F. Wetzels,[2] Henry Dijkman,[1] Johan Van der vlag,[2] Bart Smeets.[1] *[1]Pathology, Radboudumc, Nijmegen, Netherlands; [2]Nephrology, Radboudumc, Nijmegen, Netherlands.*

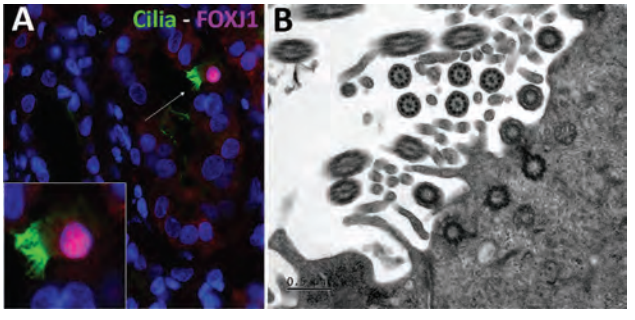
Background: Cilia are evolutionary highly conserved antennae-like structures with important functions in cell signaling and homeostasis. In kidney epithelial cells, one primary cilium per cell can be detected, which serves as flow sensor and consists of 9 peripheral microtubular doublets. Motile cilia can be found on multiciliated cells and additionally express a central microtubule pair, dynein arms and radial spoke proteins (e.g. RSPH4A) required for ciliary motion. Motile cilia assembly involves activation of the transcription factors FOXJ1 and RFX3. In this study, the unexpected detection of multiciliated cells in patients with tubular injury was evaluated.

Methods: Immunofluorescent staining was performed on patient biopsies with markers for cilia, specific tubular segments and for motile cilia (RSPH4A). In addition the expression of FOXJ1 and RFX3 was studied. The ciliary ultrastructure was analyzed by transmission electron microscopy.

Results: Multiciliated cells were initially detected in five patients. All patients were affected by tubular injury with different underlying pathologies. Multiciliated cells were localized in the proximal tubule. Furthermore, cilia on multiciliated cells stained positive for RSPH4A and the motile cilia structure (9+2) was detected by transmission electron microscopy. Co-expression of FOXJ1 and RFX3 in multiciliated cells was observed, indicating activation of motile cilia assembly. Analysis of additional biopsies from 20 patients with severe tubular injury revealed the presence of multiciliated cells in 4 cases (20%).

Conclusions: Multiciliated proximal tubular cells with motile cilia were frequently observed in patients with tubular injury. The mechanism underlying this phenomenon and the possible function of multiciliated cells in the kidney, need further investigation.

Funding: Private Foundation Support



A) Immunofluorescence showing multicilia (green, arrow) and FOXJ1 expression (purple).B) TEM showing a multiciliated proximal tubule cell with motile cilia (9+2 structure).

TH-PO346

Highly Specific RIPK1 Inhibition Significantly Improves Renal Ischemia Reperfusion Injury in Mice Kevin M. Gallagher,[5] Ewen M. Harrison,[4] Jeremy Hughes,[3] James A. Ross,[4] Lorna Marson,[2] Sheryl Beh,[4] Allison M. Beal,[1] John Bertin,[1] Stephen J. Wigmore.[4] *[1]GlaxoSmithKline, Collegeville, PA; [2]Queen's Medical Research Institute, Edinburgh, United Kingdom; [3]The Queens Medical Research Institute, Edinburgh, United Kingdom; [4]University of Edinburgh, Edinburgh, United Kingdom; [5]University of Edinburgh, Edinburgh, United Kingdom.*

Background: Non-specific RIPK1 inhibition with Nec-1, is beneficial in murine ischemia reperfusion injury (IRI). It is not known if tubular epithelial cells (TECs) undergo necroptosis nor how RIPK1 inhibition is beneficial. We aimed to determine if a novel, highly specific RIPK1 inhibitor (GSK963a) is beneficial in murine IRI and determine if TECs undergo necroptosis during IRI.

Methods: Mice were subjected to 23m (severe injury) bilateral renal vascular clamp then 24h reperfusion. Outputs included: Serum urea and creatinine; acute tubular necrosis(ATN) scoring and immunofluorescent(IF) staining of phosphorylated mixed lineage kinase like domain protein (pMLKL) (end effector of necroptosis) using MLKL phospho-S345 specific antibody. Dephosphorylation controls confirmed phospho-specific staining. The effect of GSK963a on TEC (HK2 cell line) viability, cytotoxicity and mitochondrial health (mito-tracker red) was also assessed in in-vitro models of TEC ischemic injury.

Results: GSK963a significantly reduced creatinine (131 umol/L (95%CI 134-175) vs 174 umol/L (154-194) p=0.01 N=7) and ATN score (Mean 3.29/4 (95% CI 2.83-3.74) vs 1.75/4 (1.16-2.34)p=0.008) compared to vehicle. Results with Nec-1s were similar. pMLKL was detected extensively with IF in injured moderately injured tubules (15m ischemia) but not glomeruli. With severe IRI (23 minutes), pMLKL was also detected within glomeruli. In-vitro, GSK963a significantly decreased TEC death in an ATP depletion and glucose deprivation model (12h injury % cell death (CellToxGreen) was: Vehicle: 67.2% (95%CI 62.8-71.5) vs GSK963a: 40.4% (34.3-46.5) N=6 p=<0.001). GSK963a also reduced mitochondrial perinuclear condensation and loss of membrane potential after 1.5 hours of physical hypoxia and glucose deprivation in HK2 cells (N=3).

Conclusions: Highly specific RIPK1 inhibition significantly improves biochemical and histological injury in severe murine IRI. We provide preliminary evidence that renal tubular cells undergo necroptosis in IRI.

Funding: Commercial Support - GlaxoSmithKlein, Private Foundation Support, Government Support - Non-U.S.

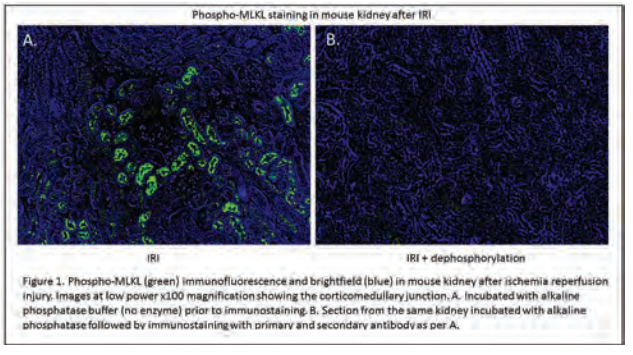


Figure 1. Phospho-MLKL (green) immunofluorescence and brightfield (blue) in mouse kidney after ischemia reperfusion injury. Images at low power x100 magnification showing the corticomedullary junction, A. Incubated with alkaline phosphatase buffer (no enzyme) prior to immunostaining. B. Section from the same kidney incubated with alkaline phosphatase followed by immunostaining with primary and secondary antibody as per A.

TH-PO347

Controlled Blood Pressure Increases the Appearance of Angiogenic Hemodialysis Patient-Derived Cells In Vitro Brooke M. Huuskes,[2] Ryan J. Debuque,[3] Kevan Polkinghorne,[1] Peter G. Kerr,[1] Chrishan S. Samuel,[4] Sharon D. Ricardo.[2] *[1]Department of Medicine, Monash Medical Centre and Monash University, Melbourne, VIC, Australia; [2]Biomedical Discovery Institute, Department of Anatomy and Developmental Biology, Monash University, Clayton, VIC, Australia; [3]Australian Institute of Regenerative Medicine, Monash University, Clayton, NSW, Australia; [4]Biomedical Discovery Institute, Department of Pharmacology, Monash University, Clayton, VIC, Australia.*

Background: Endothelial progenitor cells (EPCs) are present in lower numbers in kidney disease patients who are dialysis-dependent and can be used to predict adverse cardiovascular events. The function of EPCs can be measured using colony forming unit (CFU) assays and the appearance of late outgrowth endothelial cells (OECs) *in vitro.* Specific clinical parameters can affect EPC function, yet less is known about the relationship between clinical observations and OEC function. Therefore the aim of this study was to determine if the appearance of OECs derived from dialysis-dependent patients was influenced by their clinical history.

Methods: Dialysis-dependent patients (n=20) were recruited to this study; and their age, time on dialysis, blood pressure (BP), erythropoietin (EPO), statin use and smoking status was collected as these parameters have previously demonstrated to affect circulating EPC levels. Blood (10mls) was obtained prior to a single dialysis session and peripheral blood mononuclear cells isolated and cultured. After 7 days CFU was

assessed, then cells were further cultured for 21 days or until OECs appeared (identified by cobblestone morphology).

Results: The patient cohort had a mean age of 64.2(±15.5) years and 80% were male. The mean time on hemodialysis was 46 months (±69.6) and blood pressures of 139.1(±27.1)/75.2 (±18.9). Half of the patients received EPO, 30% were administered statins and 65% had a history of or were current smokers. Circulating %EPC of patients receiving EPO was significantly lower then patients who were not (mean diff. 1.487±0.538, 95% CI 0.3-2.7. p=0.0184) and high systolic blood pressure was negatively correlated with %EPC (r=-0.59, p=0.033). We observed a 45% conversion of EPCs to OECs, which was not dependent on starting %EPC (p=0.19). Both systolic (mean diff. 24.95mmHg, 95% CI 1.7-48.1, p=0.0365) and diastolic (mean diff. 18.9, 95%CI 3.2-34.6, p=0.0208) blood pressures were significantly lower in patients when OECs appeared.

Conclusions: BP affects dialysis-dependent patient-derived OEC numbers in culture, suggesting that controlling BP may be key to maintaining vascular health in patients on dialysis.

Funding: Government Support - Non-U.S.

TH-PO348

Associations of Biomarkers of Angiogenesis with AKI and Mortality Post-Cardiac Surgery Sherry Mansour,[6] William R. Zhang,[4] Dennis G. Moledina,[6] Steven G. Coca,[1] Yaqi Jia,[7] Heather Thiessen Philbrook,[7] Jay L. Koyner,[5] Michael Shlipak,[3] Francis P. Wilson,[6] Amit X. Garg,[2] Chirag R. Parikh.[8] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]London Health Sciences Centre, London, ON, Canada; [3]San Francisco VA Medical Center, San Francisco, CA; [4]UCSF School of Medicine, San Francisco, CA; [5]University of Chicago, Chicago, IL; [6]Yale School of Medicine, New Haven, CT; [7]Yale University, New Haven, CT; [8]Yale University and VAMC, New Haven, CT.*

Background: Angiogenesis is a process of new blood vessel formation after renal injury. We hypothesize that unimpeded angiogenesis following acute kidney injury (AKI) leads to maladaptive repair resulting in poor long-term outcomes.

Methods: We tested the association of a panel of angiogenesis biomarkers with AKI and 1-year mortality in 1444 adult participants who underwent cardiac surgery from the TRIBE-AKI cohort. Using Mesoscale Discovery multiplex assay, we measured adaptive repair biomarkers, placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), and maladaptive repair biomarker VEGF receptor 1 (VEGFR1) from plasma samples collected before (preoperative) and 0-6 hours after (postoperative) surgery. We defined AKI using AKIN stage 1 criteria, and evaluated 1-year all-cause mortality.

Results: A total of 492 developed AKI and at one year 81 died. Among the preoperative biomarkers, VEGF was independently associated with higher odds of AKI OR 1.19 (95% CI: 1.02, 1.39) but none of the preoperative biomarkers were associated with mortality. Each log increase of postoperative PlGF and VEGF was independently associated with lower odds of AKI, whereas each log increase of postoperative VEGFR1 had higher odds of AKI (**Table**). Each log increase of postoperative PlGF and VEGF was also independently associated with 44% and 20% lower odds of one-year mortality, respectively, whereas each log increase of postoperative VEGFR1 had a 2-fold increase in odds of mortality (**Table**). There was no interaction between angiogenesis biomarkers and mortality by AKI status. Preoperative and postoperative biomarkers were weakly correlated.

Conclusions: Although there was a slight increase in odds of AKI with higher preoperative VEGF, higher postoperative levels of adaptive repair biomarkers PlGF and VEGF were significantly associated with improved renal outcomes and reduced mortality whereas higher postoperative levels of maladaptive repair biomarkers VEGFR1 were associated with worse renal outcomes and higher mortality.

Postoperative Biomarkers	Adjusted odds ratio for each log increase in biomarker (95% Confidence Interval)	
	AKI*	1-year all-cause mortality^
Adaptive Repair	-	-
PlGF	0.69 (0.55, 0.87)	0.56 (0.38, 0.83)
VEGF	0.89 (0.82, 0.98)	0.80 (0.66, 0.96)
Maladaptive Repair	-	-
VEGFR1	1.56 (1.31, 1.87)	1.84 (1.28, 2.65)

*Adjusted for 13 clinical variables + pre-operative biomarker concentration.

^Above + change in serum creatinine from baseline to peak post-operative

TH-PO349

A Rare Case of Secondary Amyloidosis with Kidney and Colon Involvement in Chordoma Ali Ziaolhagh,[4] Umut Selamet,[1] William F. Glass,[5] Amanda Tchakarov,[3] Ala Abudayyeh.[2] *[1]MD Anderson Cancer Center, Houston, TX; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]University of Texas Medical School at Houston, Houston, TX; [4]University of Texas health Science Center at Houston, Housotn, TX; [5]University of Texas – Houston Medical School, Houston, TX.*

Background: Amyloidosis is characterized by extracellular deposition of abnormal proteins. Secondary Amyloidosis (AA) is associated with infectious, inflammatory and malignant diseases. Among neoplastic diseases, AA is mostly associated with renal cell carcinoma, Gastrointestinal (GI) stromal tumors, and intestinal carcinomas

Methods: We present a case of AA with GI and kidney involvement due to sacral chordoma. Patient presented with diarrhea and proteinuria. Colonoscopy showed severe colitis. Pathology findings suggested amyloidosis. He had nephrotic range proteinuria, renal biopsy showed amyloidosis with no monoclonal deposition and confirmed to be secondary with mass spectrometry. He had extensive diarrhea and history of recurrent ileus. He presented with normal renal function, but due to ongoing diarrhea, he had hypotension and developed acute renal failure.

Results:

Conclusions: Secondary amyloidosis in association with cancers are reported as case-reports in the literature. However, to the best of authors' knowledge, chordoma has never been reported as a cause of AA with severe systemic disease.

TH-PO350

A Case of Drug-Induced Acute Tubular Necrosis Associated with Focal Necrotizing Vasculitis in Veins and Periglomerular Arterioles Shintaro Masuko, Miho Karube, Hikaru Kukimoto, Hideki Shimizu, Shinya Kaname. *Kyorin University School of Medicine, Tokyo, Japan.*

Background: Although NSAIDs-induced acute tubular necrosis and tubulointerstitial nephritis are well known, drug-induced vasculitis including veins is rarely reported.

Methods: A 38 year-old female noticed headache and slight fever a week ago and received several medication including NSAIDs and antibiotics. Afterwards, she developed leg edema and oliguria and was admitted to a local hospital because of acute kidney injury with serum UN 87.4 mg/dL and Cr 9.06 mg/dL. The urinalysis showed urine protein 1+, RBC 0-1/HPF, WBC 20-29/HPF and some granule casts, with increased urinary NAG 13.6 U/L and β2-microglobulin 1,266 μg/L. The renal function deteriorated and hemodialysis was begun. She was transferred to our hospital and kidney biopsy was performed, showing acute tubular injury with diffuse tubular cell ballooning and atrophy, peritubular capillaritis and interstitial changes with a focal infiltration of lymphocytes and plasma cells. Interestingly, periglomerular vasculitis of efferent arteries and also granulomatous vasculitis in a part of the veins. The immunofluorescence study was negative. Renal function improved, and later DLST test for loxoprofen turned out to be positive.

Results:

Conclusions: We here reported a rare case of acute tubular necrosis and tubulointerstitial nephritis with vasculitis that is localized in periglomerular arterioles and veins with granulomatous lesion that may be induced by NSAIDs.

TH-PO351

Endothelial STAT3 Modulates Protective Mechanisms in a Mouse Model of AKI Shataakshi Dube,[3,1] Tejasvi Matam,[1] Jessica Yen,[2,1] Pierre C. Dagher,[1] Takashi Hato,[1] Timothy A. Sutton.[1] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Jackson Memorial Health Systems, Miami, FL; [3]Duke University, Durham, NC.*

Background: Acute kidney injury (AKI) is a common clinical entity with devastating consequences. STAT3 is a transcriptional regulator that plays an important role in coordinating inflammation and there is a growing appreciation of the role STAT3 signaling plays in the response to organ injury following diverse insults. Since it is well recognized that endothelial alterations contribute to organ dysfunction in AKI, in this study we examine the role of endothelial STAT3 in a model of ischemic AKI.

Methods: A mouse with the genetic deletion of Stat3 restricted to the endothelium (eStat3-/-) was used to examine the role of endothelial STAT3 signaling in a bilateral renal artery clamp (BAC) model of ischemic AKI.

Results: Mean serum creatinine 24 hours after BAC was significantly higher in eStat3-/- mice (3.0+0.2 mg/dL) as compared to background C57BL/6 mice (1.2+0.9 mg/dL; $p<0.05$). Histologic damage was also significantly greater in the eStat3-/- mice with mean tubular damage scores of 3.7+5 in the eStat3-/- mice and 2.3+0.9 in the background C57BL/6 mice ($p<0.05$). Proximal tubular oxidant stress as determined by intravital imaging of carboxy-DCFDA fluorescence was 25% higher in eStat3$^{-/-}$ mice as compared to C57BL/6 mice ($p<0.05$). Heme oxygenase-1 (HO-1), a critical mediator of protective adaptations in the proximal tubule exposed to oxidant stress, and the expression of IL-22, a key promoter of tubular HO-1, were both significantly decreased in eStat3-/- mice as compared to C57BL/6 mice ($p<0.05$). Given the contribution of inflammation to oxidant stress and tubular injury during AKI and the coordinating role the microvascular endothelium plays in these responses, we examined the impact of endothelial Stat3 deletion on microvascular leukocyte trafficking and tissue leukocyte composition in this model of AKI. Leukocyte adherence to the microvascular endothelium as measured by intravital microscopy was 2-fold greater in eStat3-/- mice as compared to C57BL/6 mice ($p<0.05$); however, there was no significant difference in macrophage tissue infiltration between eStat3-/- and C57BL/6 mice.

Conclusions: These findings suggest the endothelial STAT3 signaling plays an important role in limiting kidney dysfunction in ischemic AKI and that selective pharmacologic activation of endothelial STAT3 signaling could serve as a potential therapeutic target.

Funding: NIDDK Support

TH-PO352

Contrast-Enhanced Ultrasound for Assessing Renal Perfusion Impairment and Predicting AKI to CKD Progression Wei Cao. *Division of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China.*

Background: Acute kidney injury (AKI) is increasing recognized as a major risk factor leading to progression to chronic kidney disease (CKD). However, the diagnostic tools for predicting AKI to CKD progression are particularly lacking. Here, we tested the utility of contrast enhanced ultrasound (CEUS) for predicting progression to CKD after AKI.

Methods: Mice treated with 20 or 45 min ischemia-reperfusion injury (IRI) was served as mild or severe AKI. Renal perfusion was evaluated by CEUS. Kidney morphological injury and function were assessed. We further measured renal perfusion by CEUS in patients who admitted for acute decompensated heart failure (ADHF) with or without AKI-CKD progression.

Results: Renal perfusion measured by CEUS reduced to 25%±7% and 14%±6% of the pre-ischemic levels in mild and severe AKI 1 hour after ischemia ($P<0.05$). Renal perfusion returned to pre-ischemic levels 1 day after mild AKI followed by restoration of kidney function. While severe AKI caused persisted renal perfusion impairment (60%±9% of baseline levels) accompanied by progressive renal fibrosis and sustained decrease in renal function. Renal perfusion at day 1-21 significantly correlated with tubulointerstitial fibrosis 42 days after AKI. For predicting renal fibrosis at day 42, the area under receiver operating characteristics curve of renal perfusion impairment at day 1 was 0.84. Similar changes in renal image of CEUS were observed in patients with AKI-CKD progression. By using microbubbles targeted to P-Selectin, CEUS was able to quantify the severity of renal microvascular injury after AKI.

Conclusions: These results indicate that CEUS enables the evaluation of renal perfusion impairment associated with CKD after ischemic AKI and may serve as a noninvasive technique for assessing AKI-CKD progression.

Funding: Government Support - Non-U.S.

TH-PO353

Tubule Specific Deletion of Cullin 3 Causes Cell Cycle Dysregulation and Kidney Fibrosis Turgay Saritas,[7,6] Catherina A. Cuevas,[8] Christoph Kuppe,[5] Rafael Kramann,[4] Marcus J. Moeller,[3] Jeffrey Singer,[2] Jürgen Floege,[1] James A. McCormick.[7] *[1]University Hospital RWTH Aachen, Aachen, Germany; [2]Portland State University, Portland, OR; [3]University Hospital RWTH Aachen, Aachen, Germany; [4]University Hospital RWTH Aachen, Aachen, Germany; [5]University Hospital RWTH Aachen, Aachen, Germany; [6]University Hospital RWTH Aachen, Aachen, Germany; [7]Oregon Health & Science University, Portland, OR; [8]Oregon Health & Science University, Portland, OR.*

Background: Cell cycle dysregulation is involved in the pathogenesis of acute kidney injury and kidney fibrosis, but the molecular details are still poorly understood. Cullin 3 (Cul3) is part of an E3 ubiquitin ligase which controls protein abundance by promoting proteasomal degradation. Cul3-dependent ubiquitination has emerged as a key mechanism to control various critical cellular processes including cell cycle progression.

Methods: We characterized the time-course of kidney fibrosis after tubule-specific deletion of Cul3 in adult mice (doxycyline-inducible Pax8-rtTA-LC1 system) using Western blot, immunofluorescence (IF) and immunohistochemistry (IHC). In addition, Cul3 expression was analysed in different mouse models of kidney fibrosis (unilateral ureteral obstruction (UUO), ischemia/reperfusion injury (IRI) and nephrotoxic nephritis (NTN)).

Results: Cul3 deletion caused progressive loss of kidney function within weeks and death at around 7-8 months. At 2 weeks after induction of Cul3 deletion, mice developed progressive tubular injury and were positive for NGAL and KIM-1 staining. At the same time-point, Cul3 substrates cyclin E (+62%, $p<0.05$) and p21 (+474%, $p<0.005$) were significantly increased, but p27 was reduced (-75%, $p<0.05$) by Western blot analysis. This was associated with increased tubular expression of cell cycle proliferation markers (cyclin D1 (5.2-fold), Ki67 (3.9-fold), PCNA (17.6-fold)), and also the G2/M pH3 (5.8-fold), using IF and IHC. 4 weeks after induction of Cul3 deletion, PAS/H&E-stained sections revealed loss of brush borders, tubule dilation, necrotic cell cast formation, caspase-3-positive apoptosis and interstitial inflammation (e.g. CD3-positive cells (14.7-fold)). Cul3-deficient tubules were adjacent to areas of increased extracellular matrix accumulation (30% and 18% of area positive for picrosirius red and alpha-smooth muscle actin (aSMA), respectively, $p<0.001$). In UUO, IRI and NTN, we observed reduced tubular Cul3 expression in areas where peritubular expression of aSMA was increased.

Conclusions: These data suggest a critical role for Cul3 in epithelial cell cycle dysregulation, dedifferentiation and the development of kidney fibrosis. Thus, Cul3 might be a promising novel therapeutic target in AKI to CKD transition and fibrosis development.

Funding: Government Support - Non-U.S.

TH-PO354

Extracellular YB-1, as Signal of Tissue Damage, Induces Mesangial Cell Migration and Proliferation Sabine Brandt, Florian G. Scurt, Jonathan A. Lindquist, Peter R. Mertens. *Otto-von-Guericke University, Magdeburg, Germany.*

Background: The Y-box protein-1 (YB-1) is the prototypic member of the cold shock protein family of RNA/DNA binding proteins. Recent findings indicate acetylation-dependent secretion of YB-1 via a non-classical pathway and profound extracellular effects mediated by Notch-3 receptors.

Methods: Here we determined changes in gene expression and proliferation in rat mesangial cells following stimulation with recombinant YB-1, truncated YB-1, and peptides corresponding to domains of YB-1.

Results: Stimulation of mesangial cells with recombinant YB-1 resulted in an up-regulation of defined target genes and surprisingly even YB-1 itself. Further analysis revealed that recombinant YB-1 is capable of enhancing proliferation and migration rates. We also confirmed the chemokine activity using human peripheral blood mononuclear cells in a Boyden chamber assay. YB-1 significantly increases the specific migration of cells compared to the basal rate. Additionally, subcutaneous injection of recombinant YB-1 induced immune cell infiltration. Furthermore activation of monocytes with pro-inflammatory stimuli induces the secretion of YB-1.

Conclusions: Taken together, our results indicate a feed-forward loop with activation of signaling cascades by extracellular YB-1 that results in the phosphorylation of Akt, MAPK/ERK, and STAT proteins, up-regulation of YB-1 expression and target gene regulation, as well as an increase in cell proliferation and migration. Thus, we identify extracellular YB-1 as potent extracellular mediator of cell activation in inflammatory diseases.

Funding: Government Support - Non-U.S.

TH-PO355

Proximity-Ligation Assay Identified the Rho Guanine Nucleotide Exchange Factor, β-PIX, as a Rac1-Interactor in Podocytes Mirela Maier,[1] Lamine Aoudjit,[1] Cindy Baldwin,[2] Tomoko Takano.[3] *[1]McGill University, Montreal, QC, Canada; [2]McGill university, Montreal, AB, Canada; [3]None, Montreal, QC, Canada.*

Background: Hyperactivity of Rac1 (a small GTPase) in podocytes has been implicated in the development of proteinuria and focal segmental glomerulosclerosis (FSGS). We sought to identify guanine nucleotide exchange factors (GEFs) that activate Rac1 in podocytes.

Methods: BioID, a proximity-based ligation assay, was used to identify Rac1-GEFs in human podocytes (HP). This assay consists of HP expressing a bait, Rac1G15A (a mutant of Rac1 reported to have high affinity to active GEFs), conjugated to a biotin ligase, BirA (BirA-Rac1G15A). BirA alone was used as control. HP were incubated with biotin for 18 hours in the culture medium, and biotinylated proteins (i.e. proteins that have come in close proximity of Rac1G15A) were isolated with streptavidin-beads and identified by mass spectroscopy. Active Rac1 was visualized with immunofluorescence staining (IF) and quantified using CRIB pulldown (PD). β-PIX binding to Rac1 was determined by PD with GST-Rac1, followed by immunoblotting (IB).

Results: BioID identified 5 GEFs in BirA-Rac1G15A expressing HP; β-PIX was by far the most abundant and the only one whose quantity was consistently enriched (20-fold or more) in three independent experiments, as compared with control cells expressing BirA alone. Thus, we proceeded to characterize β-PIX in podocytes. By IB, HP expressed only one isoform of β-PIX (75 kDa), whereas mouse podocytes (MP) expressed an additional isoform of 88kDa. These isoforms were verified by RT-PCR. By IF of kidney sections, β-PIX was expressed in human, mouse, and rat glomeruli, largely overlapping with nephrin and/or β1-integrin. By IF of un-stimulated MP, β-PIX was localized diffusely in the cytosol and at cell periphery, which, upon stimulation with epidermal growth factor (EGF), shifted to the tip of cellular projections, co-localizing with active Rac1. Biochemically, EGF increased Rac1 activity, and β-PIX binding to Rac1 by 5 and 10 minutes (5min: 1.56-fold ±0.24; 10min: 1.34-fold ±0.13, $n=5$, $p<0.05$).

Conclusions: BioID using RacG15A as bait identified β-PIX as a predominant Rac1-interactor in HP. β-PIX is expressed in podocytes, and its binding to Rac1 is modulated by EGF. Together, this data warrants further studies on the functional role of β-PIX in podocyte health and disease.

Funding: Government Support - Non-U.S.

TH-PO356

Toll-Like Receptor 8 and 10 Are Possibly Associated with Pathogenic Mechanisms of Idiopathic Nephrotic Syndrome Eriko Tanaka,[2] Miyuki Takagi.[1] *[1]Division of Nephrology, Tokyo, Japan; [2]Department of Pediatrics, Tokyo Medical and Dental University, Tokyo, Japan.*

Background: Idiopathic nephrotic syndrome (ISN) is still a disease of unknown cause, though many studies have been done to elucidate pathogenic mechanisms. Some studies suggest that disorder of immune system derived by toll-like receptor (TLR) is involved, however, expressions of TLRs in ISN patients are not fully examined.

Methods: We investigated RNA expressions of TLRs and its pathways in ISN patients. Total RNA was extracted from kidney biopsy specimens of each ISN patients. We performed RNA-sequencing and analyzed RNA expressions of TLRs and molecules related to TLR pathways.

Results: Three patients with ISN were enrolled in this study (P1, P2, and P3). At the time of kidney biopsy, proteinuria of P1 was decreasing and she achieved remission a few days after the biopsy. P2 and P3 had nephrotic range of proteinuria when they received kidney biopsy. Pathological diagnosis of both P1 and P2 was minor glomerular abnormality, while that of P3 was focal segmental glomerulosclerosis. We analyzed RNA expressions of patients and found that TLR 8 and TLR 10 were significantly low in P1 compared to those in P2 and P3. (Fold Change (FC) of P1 vs P2 and P1 vs P3 in TLR8 were -6.59 and -4.62, respectively, and FC in TLR10 were -25.38 and -40.03, respectively.) RNA expressions in TLR1, 2, 3, 4 and 9 showed no differences among the three patients. We explored the molecules in pathway of TLR8 and found that IRF7 and IRAK2, which

are the downstream molecules leading to type 1 interferon activation, are significantly low in P1 in comparison to those in P2 and P3. We next investigated expressions of molecules related to TLR10. On contrary to previous reports, RNA expressions of pro-inflammatory cytokines such as IL1β and IL-6 were significantly low in P1 who showed lower expression of TLR10, suggesting that TLR10 expression was secondary suppressed because of activation of pro-inflammatory cytokines.

Conclusions: The profile of RNA expressions in INS patients implies the possibility of TLR pathways' involvement in pathogenic mechanisms. Comparing the RNA expressions in INS patient in remission phase to INS patient in nephrotic phase revealed that pathways related to TLR8 and TLR10 may be associated with onset and remission of INS.

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TH-PO357

PolyIC Induces the Expression of Retinoic Acid-Inducible Gene I and Melanoma Differentiation-Associated Gene 5 in Podocytes and Modulates Inflammatory Responses and Podocyte Damage

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Background: Viral infection often exacerbates proteinuria and activation of innate immunity in renal cells is suggested as pathogenesis. As well as some of the toll-like receptors, retinoic acid-inducible gene-I (RIG-I)-like helicase receptors (RLRs) recognize double-stranded RNA (dsRNA) produced during viral replication. RLRs are located in the cytoplasm, and RIG-I and melanoma differentiation-associated gene 5 (MDA5) are the members of RLRs. It is reported that dsRNA induces the expression of RIG-I and MDA5 in mesangial cells, however, the effect on podocytes is not well elucidated. In this study, we tested the effect of polyinosinic polycytidylic acid (polyIC) on the expressions of RIG-I and MDA5 and on the down-stream inflammatory responses and podocyte damages.

Methods: Conditionally immortalized human podocytes were grown in 33 degrees centigrade and differentiated in 37 degrees centigrade, then treated with 2 to 500 μg/ml of polyIC, synthesized dsRNA for 3 to 36h. The expression levels of RIG-I and MDA5 were assessed by quantitative RT-PCR and western blotting. The expression of IFN-β, TNFα and IL-6 were assessed by quantitative RT-PCR. We further tested the role of RIG-I and MDA5 by the temporal knockdown utilizing siRNA. F-actin staining was performed to assess actin re-organization as a feature of podocyte damages.

Results: PolyIC induced the expression of RIG-I and MDA5 in podocytes in dose and time dependent manners, as demonstrated by quantitative RT-PCR and western blotting. PolyIC also increased mRNA expression of IFN-β, TNFα and IL-6. PolyIC induced actin re-organization by F-actin staining. Temporal knockdown of RIG-I by siRNA resulted in decreased expression of IFN-β and TNFα induced by polyIC, while temporal knockdown of MDA5 by siRNA inhibited IFN-β, TNFα and IL-6.

Conclusions: PolyIC dramatically induced the expression of RIG-I and MDA5 in podocytes in dose and time dependent manners. Temporal silencing of RIG-I and MDA5 by siRNA significantly suppressed the expression of inflammatory cytokines induced by polyIC leading to podocyte damages. These results suggest that not only TLRs but also RLRs play an important role in podocyte damage during viral infection.

TH-PO358

The Impact of Sirtuin 3 in Renal Tubular Cell Apoptosis under Diabetic Conditions

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Background: Reactive oxygen species (ROS) play roles in kidney diseases including diabetic nephropathy (DN). Central to tubular injury is mitochondrial dysregulation resulting in ROS overproduction. The role of mitochondrial sirtuins (SIRTs) has been reported to be implicated in numerous ROS-mediated diseases. Since SIRT3 is mainly localized in the mitochondria and regulates mitochondrial function via deacetylation of mitochondrial proteins, SIRT3 has been suggested to be involved in the pathogenesis of kidney diseases. However, the impact of SIRT3 on tubular cell apoptosis under diabetic conditions has never been elucidated.

Methods: *In vitro*, rat proximal tubular epithelial cells (NRK-52Es) were cultured in DMEM media containing 5.6 mM glucose (normal glucose, NG) or NG + TGF-β1 (10 ng/ml) with or without plasmid SIRT3 transfection. After 48 hours, cells were harvested and mitochondrial fraction was isolated. *In vivo*, 12 C57BL/6 mice were intraperitoneally injected with saline (Control, C) (N=6) or STZ (50 mg/kg/d) for 5 consecutive days (Diabetes, DM) (N=6), and were sacrificed after 6 weeks. The protein expression of SIRT3, MnSOD, and apoptosis-related proteins (Bax, Bcl-2, cleaved-caspase 3, cytochrome C, and p53) were determined by western blot analysis. Immunofluorescent staining for SIRT3 and Mitotracker staining were also performed with cultured cells, TUNEL assay was conducted with mice renal tissues.

Results: Compared to NG cells, the protein expression of mitochondrial SIRT3 was significantly decreased in TGF-β1-stimulated renal tubular cells, while SIRT3 protein expression in the cytoplasm was comparable between the two groups. Bax, cleaved-caspase 3, and p53 protein expression were significantly increased, whereas the protein expression of Bcl2, MnSOD, and cytochrome C were significantly decreased in tubular cells exposed to TGF-β1. In contrast, transfection with plasmid SIRT3 significantly abrogated the changes in apoptosis-related protein expression in TGF-β1-stimulated cells. A significant decrease in SIRT3 expression was also demonstrated in the kidney of DM mice compared to the C kidney along with a significant increase in TUNEL-positive tubular epithelial cells in the DM kidney.

Conclusions: These results suggest that SIRT3 plays a protective role in tubular injury under diabetic conditions and that SIRT3 can be a promising therapeutic target in patients with DN.

TH-PO359

Effects of High-Glucose Induced Epithelial to Mesenchymal Transition by Sulforaphan in Human Renal Tubule Cells

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Background: Epithelial-to-mesenchymal transition (EMT) of tubular epithelial cells in the kidney is associated with the progression of renal tubulointerstitial fibrosis and contributes to the renal matrix protein accumulation that is associated with diabetic nephropathy.

Methods: In this study, we examined the role of Nrf2 and heme oxygenase-1 (HO-1) protein on EMT induced by high glucose (HG) in the human renal tubular epithelial cells (HK2 cells). We treated HK2 cells with HG and Nrf2 activator, Sulforaphan. EMT was assessed by the expression of mesenchymal markers such as α-smooth muscle actin (α-SMA) and vimentin, and epithelial marker, E-cadherin.

Results: Exposure of HK2 cells to HG (50 mM) resulted in an increase of the expression of α-SMA and vimentin, and was associated with a decrease in the expression of E-cadherin. Treatment of HK2 cells with Nrf2 activator, Sulforaphan, showed a dosage-dependent amelioration of HG induced changes in markers of EMT with an increase of HO-1 expression. We found that SFN ameliorated experimental diabetic nephropathy, at least in part, via GSK3β /Nrf2 signaling pathway. We observed NRF2 activator inhibited high glucose-induced generation of reactive oxygen species (ROS), phosphorylation of PI3K/Akt at serine 473, and phosphoratory inhibition of serine/therionine kinase gycogen synthase kinase-3β (GSK-3β) at serine 9. These signaling resulted in the down-regulation of Snail transcriptional factor and recovery of E-cadherin. The Nrf2 activation attenuates high glucose-induced epithelial-to-mesenchymal transition via modulation of GSK-3β activity in human renal tubular cells.

Conclusions: Taken together, our results suggest that Nrf2-HO-1 has a critical role in the regulation of EMT through modulation of GSK-3β activity, highlighting Nrf2-HO-1 and GSK-3β as a potential therapeutic target in diabetic nephropathy.

TH-PO360

Constitutive Akt1 Activation in Renal Tubule Cells Ameliorates TGF-β Induced Oxidative Stress and Pro-Fibrotic Signaling by Preserving NF-E2 Expression

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Background: TGF-β-induced renal fibrosis is mediated by p38 and JNK MAPK activation. Preliminary laboratory studies found TGF-β (10 ng/ml; 24 h) treatment of human renal proximal tubule (HK-11) cells decreased Akt1 activation and Nuclear Factor-Erythroid derived 2 (NF-E2) protein expression and increased CTGF and PAI-1 expression. Current studies identified signaling mechanisms by which TGF-β regulates NF-E2 and renal fibrosis which may lead to generation of new therapies.

Methods: *In vitro* Akt kinase assay was performed using active Akt, recombinant NF-E2 and γ-^{32}P-ATP. Real-time NF-E2 PCR was performed on total RNA from control and TGF-β treated HK-11 cells. HK-11 cells were transfected with pUse vector or pUse-NF-E2 or pUse-AktCA (c-myc tagged), or scrambled or NF-E2 siRNA and treated with TGF-β for 24 h. Cell lysates were subjected to immunoblotting for pp38 MAPK, cleaved caspase-3, pJNK, NF-E2, CTGF, PAI-1, c-myc, and GAPDH antisera. Additionally, HK-11 cells were pre-treated (1 h) with DMSO or p38 MAPK inhibitor, 3 μM SB203580, or transfected with pUse or pUse-NF-E2 or pUse-AktCA followed by treatment with/without TGF-β for 24 h. Following day cell were stained with dihydroethidium (DHE) (10 μg/ml) for 30 m. Cells were washed and viewed by confocal microscopy for superoxide generation.

Results: RT-PCR and immunoblotting demonstrated that NF-E2 transcript was significantly induced after TGF-β treatment for 24 h but protein expression was down-regulated. NF-E2 was identified as an Akt substrate *in vitro* and over-expression of AktCA preserved NF-E2 expression in presence of TGF-β (24 h). NF-E2 overexpression, AktCA overexpression, or SB203580 inhibited TGF-β-induced superoxide in HK-11 cells. AktCA over-expression inhibited TGF-β-induced pp38 activation, pJNK activation, caspase-3 cleavage, CTGF and PAI-1 expression. NF-E2 over-expression inhibited CTGF and PAI-1 expression while silencing NF-E2 expression significantly increased CTGF expression in presence of TGF-β.

Conclusions: Akt1 substrate NF-E2, serves as a putative negative regulator of oxidative stress and pro-fibrotic signaling and its expression is regulated by post-translational modification in TGF-β treated HK-11 cells.

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TH-PO361

Differential Effects of Two Nrf2 Inducers on Renal Tubule Cells Austin King,[1] Shruti Wadhwa,[1] Kayvon Ghayoumi,[1] Susan M. Isaacs,[1] Michael Merchant,[2] Madhavi J. Rane,[1] Michelle T. Barati.[1] *[1]University of Louisville, Louisville, KY; [2]University of Louisville Medicine, Louisville, KY.*

Background: A variety of compounds inducing the cytoprotective transcription factor Nrf2 have shown promise to reduce renal injury in experimental murine models. However, comparison of mechanisms of action of these agents on renal cell biology is limited. This study examined effects two Nrf2 inducing compounds on renal tubule cells: Dimethyl fumarate (DMF), an FDA approved and clinically used drug, and Protandim, a dietary supplement with no previously reported findings in renal cells.

Methods: Human proximal tubule cells (HK11 cells) were treated with DMF (10-80μM) or Protandim (5-80μg/ml; comprised of Milk Thistle, Bacopa, Ashwagandha, turmeric, and green tea extracts) for various time points. Cell viability was analyzed by reduction of MTT and cell counting. Immunoblotting used to analyze Nrf2 expression/localization, phosphorylation of kinases known to regulate Nrf2 activation (Akt, GSK3β, ERK and p38 MAPK), and expression of Nrf2 transcriptional targets (NQO1 and SOD-1). Apoptosis was analyzed by immunostaining for cleaved caspase 3.

Results: MTT reduction and number of adherent cells was decreased with ≧40μM DMF and ≧40μg/ml Protandim, and DMF caused cells to round up while Protandim caused cell shrinkage, at these concentrations. The lowest concentration of Protandim (5μg/ml) and DMF (10μM)) increased nuclear localization of Nrf2, indicative of Nrf2 activation. Both inducers increased expression of NQO1 at multiple concentrations whereas expression of SOD1 was induced more by DMF. Protandim caused a concentration-dependent increase in p38 phosphorylation. Neither compound altered Akt phosphorylation whereas phospho-ERK and GSK3β-Ser9 phosphorylation (inactive GSK3β) were increased by Protandim. High concentrations of Protandim (80μg/ml) increased caspase3 cleavage and nuclear condensation, indicating apoptosis, while 80μM DMF caused nuclear swelling.

Conclusions: Activation of p38 by Protandim may activate Nrf2 through direct phosphorylation and inhibition of GSK3β, a cellular Nrf2 inhibitor. Alternatively, p38 may play a role in high concentration Protandim-induced cell death. The results suggest that differential effects on tubule cell morphology, kinase signaling, and induction of Nrf2 transcriptional targets by DMF and Protandim may result in different tubule cell responses during stress stimuli or kidney injury.

Funding: NIDDK Support

TH-PO362

NF-E2 Is Induced in the Lungs of ABIN1-(D485N) Mice David W. Powell,[3] Sanjana Rane,[3] Shunying Jin,[2] Erik Korte,[1] Michelle T. Barati,[3] Madhavi J. Rane.[3] *[1]None, Louisville, KY; [2]UNIVERSITY OF LOUISVILLE, LOUISVILLE, KY; [3]University of Louisville, Louisville, KY.*

Background: Inflammation caused by systemic lupus erythematosus (SLE) can affect the kidneys and lungs. Variants for the ABIN1 gene (*TNIP1*) are risk factors for glomerulonephritis (GN) in SLE and a knock-in mouse expressing an inactive form of ABIN1-(D485N) spontaneously developed systemic autoimmunity and progressive GN. IL-8 increases in plasma of ABIN1 (D485N) mice, a target of Nuclear Factor-Erythroid derived 2 (NF-E2). Inflammatory mediators in the lungs, bronchoalveolar lavage fluid (BALf), and plasma of WT and ABIN1-(D485N) mice were examined in the current study.

Methods: Three and six month old wild-type (WT) and ABIN1-(D485N) mouse lung homogenates, BALF, and plasma samples were immunoblotted for Myeloperoxidase (MPO), Thrombospondin 1 (TSP1), Nuclear Factor-Erythroid derived 2 (NF-E2) and CRP. Six-month old WT and ABIN1-(D485N) mouse kidneys were also subjected to H&E staining and MPO immunohistochemistry.

Results: Increased pulmonary MPO, TSP1 and NF-E2 expression was detected in 3 m old ABIN1-(D485N) mice. Concurrently, increased TSP-1, NF-E2 and CRP were detected in the plasma of 3 m old ABIN1-(D485N) mice. Cleaved caspase-3 was detected in lungs of ABIN1-(D485N) mice suggesting increased pulmonary apoptosis. In 6 m old ABIN1-(D485N) mice, H&E and MPO staining demonstrated immune cell recruitment in lung tissue sections. CRP and NF-E2 expression persisted in ABIN1-(D485N) mice at 6 m of age. NF-E2 and CRP was detected in the BALf of 6 m old ABIN1-(D485N) mice. To examine the role of NF-E2 in BALf, recombinant purified NF-E2 protein or control vector protein was intratracheally administered to long evans rats and 2 h after administration the rats were sacrificed and BALf, lung homogenates and lung tissue sections were obtained. Neutrophils were recruited into the BALf of rats treated with recombinant NF-E2 but not control protein and H&E staining of tissue demonstrated lung damage. Moreover, recombinant NF-E2 was shown to promote human neutrophil actin polymerization, chemotaxis, and survival.

Conclusions: Thus, an inactive form of ABIN1-(D485N) leads to induction of NF-E2 in the lungs. Neutrophil recruitment in the lungs and *ex-vivo* activation of neutrophils by recombinant NF-E2 suggests that NF-E2 may serve as a novel immune modulator and a potential therapeutic target.

Funding: Other NIH Support - NIAID

TH-PO363

Manganese Promotes Intracellular Accumulation of AQP2 via Modulating F-Actin Polymerization and Reduces Urinary Concentration in Mice Ming Huang,[1] Lei Lei,[1,2] Teodor G. Paunescu,[1] Baoxue Yang,[2] Hua A. Lu.[1] *[1]Massachusetts General Hospital, Boston, MA; [2]Department of Pharmacology, School of Basic Medical Sciences, Peking University, Beijing, China.*

Background: Aquaporin-2 (AQP2) is a water channel protein expressed in principal cells (PCs) of the kidney collecting ducts (CDs) and plays a critical role in urine concentration. F-actin polymerization through Rho phosphorylation is one of the key determinants for the cytoskeletal dynamics controlling AQP2 trafficking. Preliminary studies have shown that manganese stabilizes F-actin nuclei and decreases the concentration of its monomers at the steady state. We report in this study that manganese chloride ($MnCl_2$) is a novel and potent regulator of AQP2 trafficking in cells and in the kidney. We observed aperinuclear accumulation of AQP2 in both cultured cells and kidney CDs in response to $MnCl_2$ treatment. This effect of $MnCl_2$ on AQP2 distribution was associated with an increase in the rate of AQP2 endocytosis without alteration of the overall exocytosis. This perinuclear accumulation of AQP2 induced by $MnCl_2$ was resistant to vasopressin (VP) simulation. Although the level of total and phosphorylated AQP2 did not change, $MnCl_2$ treatment impeded VP-induced phosphorylation of AQP2 at its serine residues 256, 264, 269 and dephosphorylation at serine 261. In addition, $MnCl_2$ significantly promoted F-actin polymerization along with downregulation of RhoA activity, and prevented VP-induced AQP2 membrane accumulation. Finally, $MnCl_2$ treatment caused significant polyuria and reduced urinary concentration in mice, likely by promoting intracellular accumulation of AQP2. More importantly, this reduced urinary concentration induced by $MnCl_2$ was resistant to VP treatment. In summary, our study identified a novel effect of $MnCl_2$ on AQP2 trafficking, and proved its potent impact on regulating urinary concentration in animals.

Methods:

Results:

Conclusions:

TH-PO364

Oxidative Stress-Induced Intracellular Fatty Acids Imbalance Contributes to Renal Tubular Cell Damage Tadashi Imafuku,[1] Hiroshi Watanabe,[1] Masafumi Fukagawa,[2] Toru Maruyama.[1] *[1]Department of Biopharmaceutics, School of Pharmacy, Kumamoto University, Kumamoto, Japan; [2]Tokai University School of Medicine, Isehara, Japan.*

Background: Although chronic kidney disease (CKD) is one of the oxidative stress related diseases, the mechanism by which oxidative stress contributes to pathophysiology of CKD still remains unclear. Previous reports indicated that the addition of exogenous saturated fatty acid induced lipotoxicity in renal tubular cell, whereas co-incubation with unsaturated fatty acid attenuated saturated fatty acid-mediated tubular damage. However, the relationship between oxidative stress and fatty acid composition in proximal tubular cells has not been investigated.

Methods: Intracellular fatty acids composition in immortalized proximal tubule epithelial cells (HK-2 cells) was measured by GC-MS.

Results: In HK-2 cells, hydrogen peroxide treatment decreased the expression of both elongation of long chain fatty acid member 6 (Elovl6), which elongates saturated and unsaturated fatty acid with 12, 14, and 16 carbons, and stearoyl-CoA desaturase-1 (SCD1), which catalyzes the formation of monounsaturated fatty acids. At that time, intracellular unsaturated fatty acids content was significantly decreased, while cellular ER stress/apoptosis was increased. Co-treatment of anti-oxidant, N-acetylcystein recovered the reduction of Elovl6 and SCD1 expression and consequently, enhanced cellular ER stress/apoptosis were reduced. This was further confirmed by the inhibition of these enzymes using siRNA and inhibitor in which these treatments caused to the increases of cellular ER stress/apoptosis via the reduction of intracellular contents of unsaturated fatty acids. Interestingly, co-incubation with exogenous unsaturated fatty acids with siRNA for Elovl6 and inhibitor of SCD1 attenuated tubular toxicity.

Conclusions: Oxidative stress-induced intracellular fatty acids imbalance contributes to renal tubular cell damage.

TH-PO365

TGFβ Signals to Chromatin via Direct Interaction of Smad3 with the Polycomb Repressive Complex during the Determination of Renal Epithelial Cell Fate Darrell C. Andrews,[2] Thomas K. Dodd,[2] Jessica Davis,[2] Ciarán F. Kennedy,[2] Eoin P. Brennan,[2] Caitriona M. McEvoy,[2] Peter J. Conlon,[1] Catherine Godson,[2] John Crean.[2] *[1]Beaumont Hospital, Dublin 9, Co Dublin, Ireland; [2]Diabetes Complications Research Centre, UCD Conway Institute of Biomolecular and Biomedical Science, Belfield, Dublin 4, Ireland.*

Background: TGFβ resides at the centre of therapeutic approaches for the treatment of renal fibrosis, however despite significant efforts in this area, few intervention studies have demonstrated clinical efficacy. At the core of this issue remains a fundamental gap in our knowledge of how TGFβ signalling converges and interacts with transcriptional machinery to regulate gene expression. We recently demonstrated that silencing of the TGFβ type II receptor and repression of Smad2/3 signalling by miR302 promotes the acquisition of plasticity, suggesting that TGFβ signalling to chromatin plays a critical role in determining renal cell fate decisions.

Methods:

Results: Here, we have identified and characterized a novel direct interaction between Smad3 and EZH2, the enzymatic component of the PRC2 complex, during fate specification and TGFβ mediated epithelial dedifferentiation. Using iPSC derived renal organoids we established that targeting the interaction between Smad3 and EZH2 protected against TGFβ mediated tubular epithelial differentiation and loss of apical basolateral polarity. We interrogated the ChIP-Seq data (GSE75297) in which embryonic stem cells were differentiated by exposure to activin, identifying 2882 Smad3 peaks after 48h treatment with Activin of which 1618 mapped to Gene IDs. Smad3 peaks were significantly enriched for Oct/Sox motifs in ESCs whereas in ESCs treated with Activin, Smad3 peaks were prominently enriched for Nanog; 816/2112 peaks contained Nanog motifs, 243 of which mapped to known superenhancers, suggesting cooperativity between Smad3/PRC2 and superenhancer repression in the determination of cell fate. A number of these genes were also identified by RNA-seq as significantly differentially regulated in patients with chronic kidney disease (CKD).

Conclusions: We propose that this complex forms a molecular switch that regulates promoter access through epigenetic mechanisms and controls gene silencing, informing the fundamental mechanisms through which subsets of genes are switched on and off during fate specification and the pathogenesis of CKD.

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TH-PO366

RNA Sequencing of Enriched Collecting Duct Specific Cells Reveals Novel Immune Cell Signature in Intercalated and Principal Cells

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Background: The collecting duct is well known to be involved with acid-base and water balance, but other functions are relatively unexplored. Recently we generated two reporter mice models to enrich collecting duct specific principal cell (PC) and intercalated cell (IC) and reported targeted gene expression of anti-microbial peptide genes because these cells are the "1st responders" to ascending pathogens. In this study, we performed global unbiased gene expression profiling on enriched ICs and PCs using RNA sequencing.

Methods: In this study, we performed global unbiased gene expression profiling on enriched ICs and PCs using RNA sequencing and performed pathway analysis with Ingenuity software.

Results: Lineage marker expression analysis indicated enrichment of ICs and PCs. IC lineage marker (*Atp6v1b1, Slc4a1 and Slc26a4*) normalized read counts were 11-27 fold higher in ICs compared to non-ICs, while PC lineage marker (*Aqp2, Elf2, Scnn1a, Scnn1b* and *Scnn1g*) normalized read counts were 24-198 fold higher in PCs compared to non-PCs. In direct comparison between ICs and PCs, IC marker expression was 2-3 fold higher in ICs while PC marker expression was 2-fold higher in PCs. The genes upregulated in ICs included innate immune receptor *Il1r1,* tight junction protein such as *Cldn4* and electrolyte exchanges such as *Slc8a1*. Ingenuity analysis of upstream regulators revealed ICs involvement in proliferation, inflammation and anti-bacterial response. PC's top predicted upstream regulators with a Z-score > 2 were TGFβ1, TP53, and cisplatin (a drug which is reported to cause polyuria). The top PC functions are cellular assembly and organization, and organismal survival. In direct comparison, both IC and PCs revealed overlapping innate immune function with expression of nod like receptors such as *Nlrp6, Nod1, Nod2*, toll like receptor such ad *Tlr1, Tlr3 and Tlr12,* interleukin receptor such as *Il13ra1, Il17r, Il1r1, Il15r*, and chemokine receptor such as *Cxcl10, Cxcl12, Cxcr4* - which are shown to be involved in response to pathogen challenge. Both cells had expression of beta defensin 1, 11, 29, and 42, as well as secretogranin V (*Scg V*), while lipocalin 2 (*Lcn2*) was also highly enriched in principal cells.

Conclusions: This study identifies collecting duct cells as innate immune effector cells with overlapping function.

Funding: NIDDK Support

TH-PO367

Identification of Circular RNAs Underlying Circadian Cycling in Mouse Kidney Samples

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Background: Over the past years circular RNAs have emerged as a new species of noncoding RNAs and a subject of intense research efforts. They are more stable than linear stranded RNA species and seem to be involved in post transcriptional gene regulation. Only last year, the first dataset of circular RNAs expressed in the murine kidney was published, yet we are far from understanding the precise involvement and bio molecular functions of these nucleic acids. Furthermore the question whether their expression is partially regulated in a timely or circadian manner has not been addressed so far.

Methods: 10 week old wild type mice were sacrificed for their organs every three hours starting at 12pm for an overall period of 48 hours. We isolated RNA from the extracted kidneys, pooled samples of three mice per time point and performed RNA Sequencing. Using bioinformatics analyses of backsplicing events we identified circular RNA sequences. Furthermore, we analyzed quantitative changes of these backsplicing events during the circadian cycle. qPCR was used to further validate the rhythmicity of the cycling circular RNAs as well as their host genes.

Results: We identified more than 4000 distinct backsplicing events in our data set. A subset of these circles showed a distinct circadian rhythmicity. Of the 35 top cycling circular RNAs, we validated the circadian expression pattern for two circular RNAs derived from the *Strn3* and *Smad4* gene locus. Interestingly both host genes did not display a circadian expression pattern.

Conclusions: Our data set yields further insight into the expression pattern of circular RNAs in the murine kidney. Especially we present the first evidence for a circadian expression of certain circular RNA species. Ongoing experiments will focus on the analysis of potential miRNA binding sites on the two circadian circular RNAs and the rhythmicity of the potentially bound miRNAs.

TH-PO368

MicroRNA-200c Is Involved in Klotho Reduction by Oxidative Stress in Human Tubular Cells

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Background: Klotho deficiency is reportedly associated with the progression of kidney dysfunction, whereas its overexpression exerts renoprotective effects. Previous studies report that oxidative stress suppressed Klotho expression in renal epithelial cells, and that microRNA-200c (miR-200c) is upregulated by oxidative stress in human umbilical vein endothelial cells. In this study, we investigated whether oxidative stress-induced miR-200c is implicated in Klotho reduction in human tubular cells (HK-2).

Methods: HK-2 were stimulated with hydrogen peroxide before Klotho expression was evaluated using western blotting (WB) and quantitative PCR (qRT-PCR). MiR-200c expression was determined by qRT-PCR and the miR-200c binding site at the *klotho* mRNA 3′-untranslated region (3′-UTR) was characterized using an online prediction tool (microRNA.org). After miR-200c mimic or inhibitor was transfected into HK-2, Klotho expression was examined using WB and qRT-PCR. Luciferase reporter plasmid containing *klotho* 3′-UTR was transfected into HK-2 to investigate the inhibitory effect of miR-200c on Klotho expression. Histological analysis was performed to examine the correlation between Klotho and oxidative stress markers (8-OHdG, 4-HHE). *In situ* hybridization was performed to reveal the localization of miR-200c in human kidney biopsy specimens.

Results: Hydrogen peroxide suppressed Klotho expression without any reduction in *klotho* mRNA levels but upregulated miR-200c expression. Similarly, transfection of miR-200c mimic reduced Klotho expression as well as luciferase activity without any reduction in *klotho* mRNA levels. In contrast, transfection of miR-200c inhibitor maintained Klotho expression. In human kidney biopsy specimens, Klotho expression inversely correlated with oxidative stress markers (8-OHdG: $\rho=-0.44$, $P=0.010$; 4-HHE: $\rho=-0.39$, $P=0.021$). MiR-200c was expressed in distal tubular cells whose renal function was lowered.

Conclusions: Oxidative stress-induced miR-200c binds to *klotho* mRNA 3′-UTR, resulting in a reduction in Klotho expression.

TH-PO369

Palmitate Aggravates Proteinuria-Induced Cell Apoptosis and Inflammation via CD36-NLRP3-Caspase-1 Axis in the Proximal Tubular Cells of Obese Mice

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Background: Dyslipidemia is common in obesity and elevated free fatty acid (FFA) is prominent in these patients. Palmitate, a long-chain saturated FA, accounts for the majority of FFA and causes renal injury in obesity. CD36 is a class B scavenger with widespread tissue distribution, including renal proximal tubular cells. The NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome is a multi-protein complex, which contains NLRP3, apoptosis-associated speck-like protein containing a CARD (caspase recruitment domain)(ASC), and caspase-1, that forms upon exposure to pathogens or danger signals to activate IL-1β and IL-18 secretion and lead to cell death. Our aims are to investigate whether CD36 and NLRP3 inflammasome contribute to FFA-induced inflammation and cell death in obesity-related tubulopathy.

Methods: High fat diet (HFD)-fed C57BL/6 mice and palmitate-treated renal tubular cells were used as *in vivo* and *in vitro* models in the current study. Sulfo-N-succinimidyl oleate (SSO) was used to treat mice and cells as a CD36 inhibitor. Stable knockdown of caspase-1 using shRNA were developed in HK2 cells (a proximal tubular cell line). The protein expressions of IL-1β, IL-18, and NLRP3 were assessed by immunohistochemistry in the renal tissues and western blotting in the cells. The expression and colocalization of NLRP3 and ASC were examined by immunofluorescent staining. The cell death and apoptosis of HK2 cells were checked by cell viability assay and TUNEL staining, respectively.

Results: The expressions of CD36, IL-1β, and IL-18 were increased progressively in the kidney of HFD-fed mice. SSO attenuated HFD-induced upregulation of IL-1β, IL-18 and NLRP3 and also decreased the colocalization of NLRP3 and ASC in the proximal tubular cells of mouse kidney. In HK2 cells, palmitate induced the maturation of IL-1β, IL-18 and caspase-1 in a dose-dependent manner, while SSO ameliorated it. SSO also abolished palmitate-induced cell death and apoptosis in a dose-dependent manner. Furthermore, knockdown of caspase-1 abrogated palmitate-induced cell death and apoptosis in HK2 cells.

Conclusions: FFA causes renal tubular cells inflammation and cell death/apoptosis via CD36-NLRP3-caspase-1 axis, which may explain, at least partly, the mechanism of obesity-related nephropathy.

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TH-PO370

K-Cadherin Protein Transfer from Proximal to Distal Tubule Cells Is Associated with the Release of BMP-7 Kameljit K. Kalsi,[2] Seema Jain,[2] Mysore K. Phanish,[1] Mark E. Dockrell.[2] *[1]SW Thames renal and transplantation unit, London, United Kingdom; [2]South West Thames Institute for Renal Research, London, United Kingdom.*

Background: Cadherins are structural trans-membrane proteins that maintain the epithelial integrity by homodimerization. In the human kidney K-Cadherin (CDH6) is exclusively expressed in proximal tubular epithelial cells (PTEC) as opposed to the mouse, where K-Cadherin is only expressed in embryonic tubular cells. K-Cadherin exhibits low homology to N-(38%) & E-cadherin (35%) and the loss of K-Cadherin is associated with progression of kidney disease. Loss of K-Cadherin could suggest that it is a signal of proximal tubular damage and is involved in intercellular signalling between proximal and distal cells within the kidney which may prevent progression of epithelial remodelling.

Methods: Tissue from 3 months post-transplant human biopsies was probed for K-Cadherin by immunohistochemistry. Epithelial cells from mice kidneys were separated into predominantly distal and proximal fractions and cultured to confluence. Conditioned human PTEC media taken from confluent PTEC cells was added to mice cells, allowed to incubate for 24h; cells treated with conditioned media were compared to cells treated with control media. Media was collected and cells were lysed for western blot analysis.

Results: Analysis of human biopsy tissue identified vesicular K-Cadherin in distal tubules (in addition to membrane staining identified in proximal tubules). We identified the presence of full length K-Cadherin in the medium of primary human (PTEC) cultures and investigated the effects of conditioned media from human PTEC on mice distal or proximal tubular epithelial cells. *De novo* K-Cadherin expression was detected ($p<0.05$, n=3) in distal mice cells treated with PTEC media compared to treatment with control media, K-cadherin in mice proximal cells (megalin positive) treated with PTEC media was not as pronounced. Expression of the kidney specific cadherin (ksp-cadherin, CDH16) followed the same pattern. Media was analysed for the distal anti-fibrotic factor Bone Morphogenetic Protein 7 (BMP7) release from distal and proximal tubular cells treated with PTEC media, both were positive for BMP7 compared to treatment with control media.

Conclusions: Release of K-cadherin from PTECs is incorporated into distal cells is associated with BMP-7 secretion, possibly enhancing epithelial integrity and may represent a previously unrecognised trans-nephron communication.

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TH-PO371

Angiotensin II Selectively Activates SGK1, but Not Akt, via PKC-Dependent Modulation of mTORC2 in Renal Tubule Epithelial Cells Catherine Gleason, David Pearce. *University of California San Francisco, San Francisco, CA.*

Background: Angiotensin II (AngII) is a potent regulator of fluid balance and blood pressure homeostasis. In volume depletion, AngII stimulates production of the sodium retaining hormone, aldosterone, but also directly effects salt reabsorption through regulation of ion transporters located in various segments of the kidney tubules. Elevated circulating and local tissue AngII levels are a significant factor in the development of sodium and fluid retention and hypertension. Serum- and glucocorticoid-regulated kinase 1(SGK1) is implicated as a mediator of Ang II action, however, the molecular mechanisms underlying activation of SGK1 by AngII are not completely understood. SGK1 plays an important role in regulation of sodium and potassium transport in renal tubules of the kidney through activation of ENaC and NCC (in the cortical collecting duct (CCD) and distal connecting tubule (DCT), respectively), and NHE3 (in the proximal tubule (PT)).

Methods:

Results: SGK1 and the highly related kinase, Akt, are activated by mTOR through phosphorylation of a critical, homologous residue within their hydrophobic motif (HM). mTOR, an atypical serine/threonine kinase, is the catalytic core of two functionally distinct multi-protein complexes, mTORC1 and mTORC2. mTORC1 consists of mLST8, DEPTOR, PRAS40, and RAPTOR. mTORC2, also contains mLST8 and DEPTOR, but is defined by the presence of RICTOR, SIN1 and PROTOR. We find that AngII triggers selective mTORC2-dependent activation of SGK1 but not Akt. PKC activity is required for the AngII-stimulated SGK1 S422 phosphorylation and is mediated in part by PKC-induced SIN1 phosphorylation at three serine residues: S128, S315 and S356.

Conclusions: Our findings provide a mechanism for selective regulation of the mTORC2 substrate, SGK1, which is dependent on cPKC. Considering the well-described roles of SGK1 and Akt in regulation of ion and glucose homeostasis, respectively, these findings have important implications for defining molecular mechanisms that specify selective control of ion balance and glucose metabolism. Our results are particularly compelling in the context of metabolic diseases such as diabetes and obesity, which are frequently associated with impaired ion balance and hypertension.

Funding: NIDDK Support

TH-PO372

Resveratrol Attenuates Epithelial to Mesenchymal Transition of Human Renal Proximal Tubular Epithelial Cells by Induction of M2 Macrophages Polarization with High Expression of HO-1 Jun Li,[1,3] Ya-Fen Yu,[3] Ting Zhang.[2] *[1]Jiangnan University, Wuxi, China; [2]Department of tumor research, Affiliated hospital of Jiang nan university, Wu xi, China; [3]Department of nephrology, Affiliated hospital of Jiangnan University, Wuxi, China.*

Background: The aim of this study was to investigate the effect and mechanism of M2 macrophages with high expression of HO-1, which were induced with resveratrol, on TGF-β1 induced chronic tubular injury.

Methods: THP-1 cells (human leukemic monocyte) were treated with resveratrol concentration. HK-2 cells (human renal tubular epithelial cells) were treated with TGF-β1 to induce the chronic tubular damage. Co-culture technique was used to clarify the role of HO-1 positive M2 macrophages, which were induced by resveratrol, in the amelioration of chronic tubular injury.

Results: 1. THP-1 cells were treated with resveratrol, ICC showed the positive staining of HO-1 and the markers of M2 macrophage(CD206 and Macrophage mannose receptor 2, Mrc-2), and the supernatant showed increased IL-10 levels and decreased IL-12 levels. The western blot of the THP-1 cells protein showed the increased expression of p-STAT3 and IL-10. 2. After co-cultured of injured HK-2 cells with THP-1 cells intervened by resveratrol, the ratio of G2/M phase was lower than that treated with TGF-β1 alone. The ICC of HK-2 cells showed the increased expression of E-cadherin and the decreased expression of α-smooth muscle actin(α-SMA). The western blot of the HK-2 cells protein also showed the decreased p-STAT3 expression.

Conclusions: Small doses of resveratrol can induce the expression of HO-1 and M2 macrophages polarization, which might help to attenuate the progression of fibrosis in HK-2 cells by STAT3 signaling pathway.

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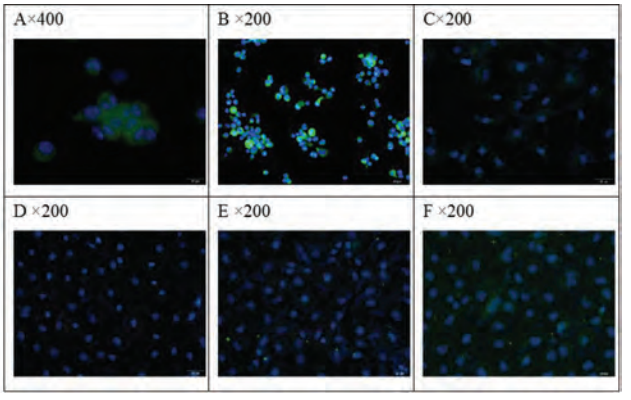

Figure 1 Co-cultured of TGF-β1 damaged HK-2 cells with THP-1 cells treated with resveratrol(20μmol/l)A B. CD206, HO-1 of THP-1 cells; C D.α-SMA of injured HK-2 without/with co- culture with THP-1; E F. E-cadherin of injured HK-2 without/with co-culture with THP-1;

TH-PO373

Aldosterone-Induced Epithelial-to-Mesenchymal Transition (EMT) in Peritoneal Mesothelial Cells: Differential Role of NADPH Oxidase and Mitochondrial Dysfunction Duk-Hee Kang,[1] Eun sun Ryu,[3] Dal-ah Kim,[2] Hyun-Jung Kang.[4] *[1]Ewha University College of Medicine, Seoul, Republic of Korea; [2]Ewha Womans University Medical Center, Seoul, SEOUL, Republic of Korea; [3]Ewha Womans University School of Medicine, Seoul, Republic of Korea; [4]Ewha Womans University, Seoul, Republic of Korea.*

Background: Peritoneal fibrosis is one of the major causes of technical failure in patients on peritoneal dialysis. Epithelial-to-mesenchymal transition (EMT) of peritoneum has been known as an early and reversible mechanism of peritoneal fibrosis. Human peritoneal mesothelial cell (HPMC) is known to have its own renin-angiotensin-aldosterone system (RAAS), however it has not been investigated whether aldosterone, an end product of RAAS induces EMT in HPMC and which mechanisms are responsible for aldosterone-induced EMT

Methods: EMT of HPMCs was evaluated by comparing the expression of epithelial cell marker, E-cadherin and mesenchymal cell marker, α-smooth muscle actin (α-SMA) after the stimulation with aldosterone (1-100 nM) or spironolactone. Activation of Src, epidermal growth factor receptor (EGFR), phosphoinositide 3-kinase (PI3K), Akt and generation of reactive oxygen species (ROS) were assessed by Western blotting, DCF-DA and Mito-SOX staining. Effect of kinase inhibitors or anti-oxidants (N-acetyl cysteine, DPI, and MitoQ) on aldosterone-induced EMT was evaluated.

Results: Aldosterone induced EMT in cultured HPMC, which was blocked by spironolactone. Aldosterone induced an activation of both Src and EGFR from 15 and 30 minutes, followed by an activation of PI3K and Akt from 1 and 3 hours, respectively. The inhibitors of Src (PP2, 5 uM) and EGFR (Erlotinib, 10 uM) alleviated aldosterone-induced EMT. Aldosterone induced ROS in HPMCs from 5 minutes with an increase in NOX

activity and NOX-1, -2, -4 mRNA expression. Aldosterone also increased mitochondrial ROS production. Anti-oxidant treatment ameliorated the aldosterone-induced EMT. NAC an DPI alleviated an activation of Src/EGFR and PI3K/Akt pathways whereas mitoQ did not alter the phosphorylation of EGFR and PI3K in HPMCs

Conclusions: Aldosterone induced EMT in HPMC by acting through mineralocorticoid receptor. Aldosterone-induced generation of ROS followed by an activation of Src/EGFR and PI3K/Akt pathways served as the mechanism of aldosterone-induced EMT of HPMC via differential regulation of NOX and mitochondrial ubiquitone

TH-PO374

Uromodulin Is Essential for Correct Insertion of Uric Acid Transporter GLUT9 in the Plasma Membrane Eva Koenigshausen, Clara Porwoll, Paul Probst, Lars C. Rump, Lorenz Sellin. *Medical Faculty Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany.*

Background: Uromodulin (UMOD) mutations cause autosomal dominant tubulointerstitial kidney disease (ADTKD). Patients with ADTKD-UMOD usually show hyperuricemia in childhood and progressive renal failure in the course of the disease. The pathogenesis of hyperuricemia by mutation in UMOD is scarcely understood so far. In microdissection analyses of tubular structures, UMOD has been localized also to the proximal tubulus and uric acid transporters have been localized to the distal proximal tubulus.

Methods: HEK293T cells expressing UMOD WT and uric acid transporters ABCG2, Urat1, OAT4, GLUT9, NPT1, NPT4 and UAT were lysed and UMOD was precipitated. On western blot, uric acid transporters were visualized. Subcellular fractionation experiments with UMOD WT or its mutant P236L and GLUT9 were performed. Cos7 cells were transfected with UMOD WT and P236L. Immunofluorescent labeling with markers for the endoplasmic reticulum (calnexin), Golgi (giantin), endosomes (EEA1) and the plasma membrane (WGA) were performed. In addition, a triple staining for UMOD WT or P236L, GLUT9 and organelle markers were done.

Results: UMOD WT interacts with the uric acid transporters ABCG2, URAT1, OAT4 and GLUT9. In the subcellular fractionation experiment GLUT9 is localized to the membrane fraction if UMOD WT is expressed. However, if UMOD P236L is expressed, GLUT9 localizes to the vesicular fraction. UMOD WT colocalizes with WGA (plasma membrane), while UMOD P236L colocalizes in the ER (calnexin). UMOD WT and GLUT9 colocalize at the plasma membrane and UMOD P236L localizes with GLUT9 in the ER.

Conclusions: UMOD WT interacts with several uric acid transporters and is essential for the proper insertion of uric acid transporters in the plasma membrane. With UMOD mutation P236L, mutated UMOD and uric acid transporters are trapped in the ER. This retention of uric acid transporters could explain the reduced fractional uric acid excretion with resulting hyperuricemia in patients with ADTKD-UMOD.

TH-PO375

ANCA Stimulation of Monocytes Changes Their Cellular Metabolism Eóin O'Brien, Carla A. White, Safa H. Mohamed, Mark A. Little, Fionnuala B. Hickey. *Trinity College Dublin, Dublin, Ireland.*

Background: Anti-neutrophil cytoplasmic antibody (ANCA) vasculitis causes rapidly progressive glomerulonephritis and is characterised by autoantibodies against myeloperoxidase (MPO) or proteinase-3 (PR3). We have previously shown that stimulation of monocytes with anti-MPO, but not anti-PR3, antibodies results in increased pro-inflammatory cytokine release, suggesting a pathogenic role for this cell type. Cellular metabolism (particularly a switch to aerobic glycolysis), has recently been shown to be important in the immune response, and targeting metabolic pathways postulated as a potential treatment in autoimmunity. We investigated the effect of ANCA on the metabolism of monocytes.

Methods: Monocytes were isolated from healthy donors. Following stimulation with anti-MPO/PR3 antibodies, with or without a range of metabolic pathway inhibitors, changes in metabolism were measured using Seahorse extracellular flux analysis. Changes in cytokine production were assessed by ELISA.

Results: In accordance with prior data indicating that pro-inflammatory leukocytes preferentially use glycolysis for metabolism, we found increased glycolysis in ANCA-stimulated monocytes. However, we also observed upregulated oxidative respiration. These changes occur within minutes of exposure to ANCA. Cells treated with anti-PR3 antibodies displayed different oxygen consumption kinetics compared to those treated with anti-MPO; changes in these metabolic pathways were linked to the previously observed differences in cytokine production. To further investigate the mechanism by which metabolic pathways are involved in the response to ANCA, we used pharmacological inhibitors to block elements of glucose metabolism. Blocking oxidative phosphorylation, as measured by reduced oxygen consumption, resulted in no change in IL-1β production, but blocking glycolysis resulted in complete inhibition. Pyruvate dehydrogenase, a major point-of-no-return in the metabolism of glucose, was required for IL-1β production. In addition, using a specific scavenger of mitochondrial reactive oxygen species (mROS) we showed an inhibition of the IL-1β induced by anti-MPO treatment indicating that mROS has a role in activation of this inflammatory pathway.

Conclusions: These data indicate an important role for the upregulation of cellular metabolism in the pro-inflammatory activation of monocytes in response to ANCA.

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TH-PO376

The Role of Chaperones and ROS in Trafficking of the mitoBK Channel in Response to Renal Cold Storage and Transplantation Stephen A. Shrum, Lee Ann MacMillan-Crow, Nirmala Parajuli, Julia Tobacyk. *University of Arkansas for Medical Sciences, Little Rock, AR.*

Background: Patients with renal failure require a kidney transplant in order to avoid dialysis with high mortality. Deceased donor kidneys regularly undergo cold storage (CS) preservation while a recipient is matched. However, the process of CS damages kidneys and greatly increases the chance of transplant failure. Our lab and others have previously reported that renal CS induces oxidative stress, mitochondrial dysfunction, and renal dysfunction. The mitochondrial isoform of the large-conductance Ca^{2+}-activated K^+ channel (mitoBK) is dynamically involved with ROS and is a promising therapeutic target in ischemia-reperfusion injury. Mitochondrial chaperone proteins, such as mortalin, are involved in protein trafficking, thus our goal was to investigate how CS+Tx alters the mitoBK channel and if ROS and chaperones are involved.

Methods: Rat kidneys or rat renal proximal tubular (NRK) cells were exposed to CS for 18h, followed by transplantation into syngeneic recipient rats (*in vivo;* CS+Tx) or rewarming (*in vitro; CS+RW*). Protein expression of mitoBK and chaperones was evaluated by western blot. Immunocytochemistry and confocal microscopy were used to assess intracellular localization of mitoBK with co-labeled organelle-specific dyes. The mechanistic relationships between mitoBK, chaperone proteins, and ROS during CS were examined using knockdown (siRNA), overexpression (plasmid), and relevant pharmacological agents (activators, inhibitors).

Results: Results show that the mitoBK channel is expressed in rat kidney *in vivo* and in NRK cells *in vitro* and that CS reduces its expression. Interestingly, CS substantially alters the intracellular localization of mitoBK. In addition, mortalin expression was decreased after CS+RW or CS+Tx. Molecular studies suggest that mortalin and ROS are involved with trafficking of mitoBK due to CS. Ongoing experiments are further examining these relationships in the context of CS+Tx.

Conclusions: Our results suggest that CS-/+Tx alters expression and trafficking of mitoBK and that ROS and mortalin are involved. Future studies will address whether mitochondrial targeted antioxidants restore mitoBK channel expression which may be informative for investigating therapeutic interventions for renal CS+Tx.

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TH-PO377

C-C Chemokine Receptor 2 (CCR2) Genetic Deletion Protects Against Gadolinium-Induced Skin Lesions by Preventing Recruitment of Bone Marrow-Derived Fibrocytes in a Novel Mouse Model Brent Wagner,[4,3] Chunyan Tan,[2] Catherine Do,[4,3] Viktor Drel,[2] Doug Y. Lee,[3] Yves C. Gorin.[1] *[1]University of Texas Health Science Center, San Antonio, TX; [2]University of Texas Health Science Center at San Antonio, San Antonio, TX; [3]UTHSCSA, San Antonio, TX; [4]Medicine, South Texas Veterans Health Care System, San Antonio, TX.*

Background: Gadolinium-based contrast is now associated with a number of conditions, including 'nephrogenic' systemic fibrosis/gadolinium-associated systemic fibrosis (NSF) and gadolinium deposition disease. Bone marrow-derived fibrocytes and the monocyte chemoattractant protein 1 (MCP1) inflammatory pathway have been implicated as mediators in rats but mechanistic studies in this model have been limited. In the present work, we establish a mouse models of NSF.

Methods: Lethally-irradiated mice with 5/6 nephrectomies were salvaged with bone marrow from green fluorescent protein- (GFP-) expressing donors. Next, GFP-positive marrow was transplanted into wild-type and mice deficient of the C-C chemokine receptor 2 (CCR2), the prime effector of MCP-1. After an engraftment period, recipients were randomized to control or gadolinium-based contrast treatment.

Results: Dermal cellularity was increased in contrast-treated mice. Compared to control, skin GFP, fibronectin, and type I collagen were all increased in the contrast-treated animals as assessed by Western blot and immunofluorescence. Importantly, CD45RO, a marker for myeloid fibrocytes, was abundant in the dermis of contrast-treated animals, frequently expressed by the myeloid cells. Many of these cells expressed cytoplasmic α-smooth muscle cell actin, a marker of myofibroblast activation. Importantly, the markers of myofibroblast activation and fibrosis colocalized with GFP-positive cells in contrast-treated animals. MCP-1 and CCR-2 were increased in the tissues from contrast-treated mice. Recipients devoid of CCR2 had an abrogation of gadolinium-induced pathology and displayed fewer GFP-positive cells in the skin.

Conclusions: Systemic fibrosis can be induced by gadolinium contrast in mice. That GFP levels and expression increase in an involved organ, the skin, in tandem with a fibrocyte marker—CD45RO—supports the blood-borne circulating fibrocyte hypothesis of the disease. *This is the first demonstration of fibrocyte trafficking ever demonstrated in mice.* Importantly, similar to what is observed in a rat model, our data demonstrate that the monocyte chemoattractant protein 1/C-C chemokine receptor 2 axis plays a critical role in the pathogenesis of gadolinium-induced systemic fibrosis.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO378

Sexual Dimorphic Response of Murine Kidneys to Dietary Cadmium and Fat Mitchell A. Jacobs,[1] Michelle T. Barati,[1] Madhavi J. Rane,[1] Adam E. Gaweda,[1] Alfred A. Jacobs,[1] Jon B. Klein,[1,2] Gavin E. Arteel,[1] Jonathan H. Freedman,[1] Lu Cai,[1] Michael Merchant.[1] *[1]University of Louisville, School of Medicine, Louisville, KY; [2]Robley Rex VA Medical Center, Louisville, KY.*

Background: Obesity and cadmium (Cd) are associated with CKD. This study examined the longer-term effects of heavy metal exposure and high dietary fat on kidneys of male and female mice.

Methods: C57B/6J mice were maintained/bred on normal or 5ppm Cd drinking water and normal chow. Offspring were maintained on identical drinking water as parents but split into male and female groups fed low fat or high fat (42% saturated fat) diets. Upon sacrifice (10wks) tissue was collected for histochemical and biochemical analysis. Tissue Cd levels were measured by ICP-MS. Cortical tissue phosphoproteome was studied using LCMS-based proteomics. Phosphopeptide data were compared using GO annotation, kinase motif enrichment (Motif-x, Phosphosite), fuzzy-c means clustering, protein-protein interaction (PPI) networks (StringDB) and Ingenuity Pathways Analysis (IPA).

Results: At 10wks, no gross effects of diet or Cd were observed in female kidneys. In contrast, Cd exposed male kidneys demonstrated cortical tubular vacuolization. Kidney wet weight was higher in males by diet or Cd. Cd levels (ngCd/g kidney) were significantly higher in females and high fat increased female Cd levels almost two fold. By LCMS 1,787 unique phosphopeptides were detected, including 14 unique kinase phosphorylation motifs. Clustering and GO analysis suggested high-fat and Cd effected FGF- & EGF-signaling in both sexes. PPI analyses identified effected molecular signaling pathways for gene transcription, protein translation, and cytoskeletal/cell junction maintenance. IPA identified the insulin signaling pathway as the most significantly affected pathway.

Conclusions: Cd and/or HFD affects the insulin signaling suggesting that these environmental factors may be contributors to diabetic CKD. The renal response to 5ppm Cd and/or a high fat diet suggests strong sexual dimorphism at the tissue and molecular signaling levels.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO379

Modulation of Oxidative Stress by Inhibition of Angiotensin II Type 1 Receptors in Cardiorenal Syndrome Firoozeh Farahmand. *Richmond Heights, MO.*

Background: Cardiorenal syndrome (CRS) has a complex pathophysiology that is still not completely understood. Oxidative stress is one of the key mediators of CRS. The aims of this study were to examine if an experimental model of CRS type 1 is associated with oxidative stress and whether blocking of the renin-angiotensin system (RAS) at the angiotensin II type 1 (AT1) receptor site is accompanied by changes in the oxidative stress parameters and attenuates CRS.

Methods: Rats were randomized into 4 groups: control, myocardial infarction (MI), MI group treated with losartan and control group treated with losartan. MI was induced by the ligation of the left coronary artery. At 4 weeks post-MI, animals were examined for hemodynamic function including left ventricle (LV) systolic pressure (LVSP), aortic systolic (AS)pressure, LV diastolic pressure, LV hypertrophy (LVH), and LV function. Hearts and the kidneys were analyzed for antioxidant enzyme activities including superoxide dismutase, glutathione peroxidase, catalase and oxidative stress. After sacrificing the animals, the renal cortex and the heart were removed for histology.

Results: At 4 weeks post MI there was a significant drop in LVSP and ASP associated with increased renal and myocardial lipid peroxidation to 63%, and 57% respectively. In MI group there was a decerase in in antioxidants enzymes activities in the kidney including catalase (34%), glutathione peroxidase (43%) and superoxide dismutase (51%). In the MI+ Losartan group losartan improved hemodynamic function and decerase oxidative stress in the kidney to 59% compared with MI group.(p-value less than 0.05).

Conclusions: In CRS type 1 congestive heart failure and acute kidney injury (AKI) in rats after MI correlates with a decrease in antioxidant and increase in oxidative stress in the heart and the kidney. Inhibition of the RAS with losartan improves cardiac function and survival in MI rats as well as oxidative stress parameter in the kidney. This study suggest the beneficial effects of angiotensin II type 1 (AT1) receptor blocker in the treatent of CRS.

TH-PO380

Multiple Roles for NHERF1 in Forward Trafficking and Apical Membrane Anchoring of NPT2a Kenneth Gagnon,[1] Michelle T. Barati,[1] Michael Merchant,[2] Barbara Clark,[1] Eleanor D. Lederer.[3] *[1]University of Louisville, Louisville, KY; [2]University of Louisville Medicine, Louisville, KY; [3]University of Louisville; Robley Rex VA Medical Center, Louisville, KY.*

Background: Loss of NHERF1 (Na-H Exchanger Regulatory Factor Isoform 1), a PDZ domain scaffolding protein, results in phosphate wasting and stone formation in animals and humans. NHERF1 knockout mice show diminished proximal tubule apical membrane expression of the sodium-phosphate cotransporter IIa (NPT2a). We have previously demonstrated in cell culture that NHERF1 and NPT2a exhibit a dynamic association between the Golgi and apical membrane, leading to the hypothesis that NHERF1 regulates trafficking and apical membrane anchoring of NPT2a through assembly of accessory protein partners.

Methods: To test this hypothesis, we immunoprecipitated (IP) NPT2a from kidney cortex lysate of wild-type (Wt) and NHERF1 KO (KO) littermates, compared the expression of associated proteins by mass spectrometry (MS), and performed western blot (WB) of proteins in cortex lysates. We compared mouse NPT2a localization and glycosylation status in HEK293 cells transfected with either a GFP-tagged full-length mouse NPT2a construct (NPT2a-FL) or a GFP-tagged mouse NPT2a construct lacking the PDZ binding motif required for interaction with NHERF1 (NPT2a-TRL).

Results: We identified 164 proteins having greater and 8 proteins having lower expression levels in Wt vs KO IPs. Expression of the F-actin binding protein ezrin decreased 75% in KO vs Wt, while total ezrin expression was similar in both pre-IP cortex lysates. WB's revealed a 2-fold increase in PDZK1 (a.k.a. NHERF3) and a 4-fold decrease in the SNARE accessory protein Munc18-2 in KO versus Wt. WB's for NPT2a in Wt revealed multiple bands at 35, 75-100, and 150-200 kDa and a 3-fold decrease in expression of the largest band in KO. WB from the NPT2a-TRL transfected cells showed a 41% decrease in expression of the larger band compared to the NPT2a-FL. F-glycosidase treatment of the NPT2a-FL and NPT2a-TRL lysates reduced the expression of the larger protein band by 68% and 44%, respectively. Confocal microscopy of transfected HEK293 cells showed NPT2a-FL localized at the plasma membrane, while NPT2a-TRL expression was cytosolic.

Conclusions: We conclude that NHERF1 is essential for the forward trafficking of NPT2a through direct PDZ domain interaction and through coordinated assembly of accessory proteins responsible for glycosylation, vesicle fusion, and membrane anchoring.

Funding: Veterans Affairs Support

TH-PO381

Characterizations of HSP90-Interacting Complex in Renal Cells Using Tandem Affinity Purification and Its Potential Role in Kidney Stone Formation Visith Thongboonkerd, Juthatip Manissorn. *Siriraj Hospital, Mahidol University, Bangkok, Thailand.*

Background: Heat shock protein 90 (HSP90) is a highly abundant molecular chaperone that interacts with many other intracellular proteins to regulate various cellular processes. However, compositions of the HSP90-interacting complex remain largely unknown. This study thus aimed to characterize such complex in renal cells by tandem affinity purification (TAP) followed by ultrahigh-resolution tandem mass spectrometry (Qq-TOF MS/MS).

Methods: The full-length *HSP90AB1* gene was constructed and subcloned into pGLUE vector, which was designed to express streptavidin- and calmodulin-binding affinity tags at the N-terminus of HSP90, whereas TAP-tag without HSP90 fusion served as the control for TAP purification system. Expression of TAP-tag fusion with HSP90 (TAP-HSP90) in the transfected HEK293T cells was confirmed by immunoblotting. The HSP90-interacting complex was purified by TAP-tag method and subjected to in-solution tryptic digestion and identification by Qq-TOF MS/MS. Functional significance of this complex was then addressed by using small-interfering RNA (siRNA) targeting to HSP90 (siHSP90).

Results: A total of 40 proteins, including four forms of HSP90 and 19 novel HSP90-interacting partners, were successfully identified from this complex using TAP control to subtract non-specific binders. Co-immunoprecipitation followed by immunoblotting and immunofluorescence co-staining confirmed the association of HSP90 with known (HSP70, α-tubulin, and β-actin) and novel (vimentin, calpain-1, and importin-β1) partners. Knockdown of HSP90 by siRNA (siHSP90) caused significant changes in levels of HSP70, α-tubulin, β-actin, vimentin, and calpain-1, all of which are calcium oxalate (CaOx) crystal-binding proteins that play significant roles in kidney stone formation. CaOx crystal-cell adhesion assay revealed that crystal-cell adhesion was significantly decreased in siHSP90-transfected cells as compared to non-transfected control and siControl-transfected cells.

Conclusions: We report herein a number of novel HSP90-interacting proteins in renal cells and demonstrate the potential role of HSP90-interacting complex in kidney stone formation.

Funding: Government Support - Non-U.S.

TH-PO382

Increased Expression of Soluble Fas in Patients with CKD Miguel A Goes,[2] Maria Eugenia F. Canziani,[1] Silvia R. Manfredi,[3] Maria Dalboni.[3] *[1]Federal University of Sao Paulo, Sao Paulo, Brazil; [2]Hospital Israelita Albert Einstein, Sao Paulo, Brazil; [3]Universidade Federal de São Paulo, São Paulo, Brazil.*

Background: Fas (CD95) is a cellular receptor for apoptosis in leukocytes and other cells. A soluble form of Fas (sFas) is an anti-apoptotic molecule devoid of the transmembrane domain from alternative splicing of CD95. Serum sFas levels are higher in CKD patients and associated with inflammation, anemia, and cardiovascular disease.

Objective: To investigate whether the expression of CD95mRNA and sFasmRNA is increase in leukocytes of CKD patients and their respective correlation with serum soluble Fas levels.

Methods: We performed the dosage of Hb concentration, serum creatinine and urea by conventional methods and serum sFas levels measured using an enzyme-linked immunosorbent assay from 51 CKD patients (eGFR 15 to 59 ml/min; CKD group) and 18 healthy volunteers (control group). We extracted leukocytes to measure the mRNA expression of CD95 and sFas. Total RNA was isolated from 5 x 10^6 leukocytes from each subject using TRIzol reagent, and cDNA was synthesized from 1 μg RNA using reverse transcriptase synthesis system. Relative levels of mRNA transcripts of sFas were

quantified by real-time PCR. We used the Epi-CKD formula. We perform correlations and comparisons between groups.

Results: When analyzed both groups together we observed negative correlation between eGFR serum sFas levels (r=-0.30, p=0.01), between eGFR and sFasmRNA expression (r= - 0.28, p= 0.02). Serum sFas levels correlated positively with sFasmRNA copies (r = 0.32, p = 0.007). The CD95mRNA did not correlate with eGFR (r= - 0.04, p= 0.9). The main etiologies of CKD were diabetes and hypertension. We observed lower concentration of Hb in the CKD group (10.8 ± 2.1, 14.2 ±1.7, p <0.001). There was a higher serum sFas levels in CKD group (3161± 1000, 1686± 996, p <0.001) and higher copies of sFasmRNA in the CKD group (32.3 + 2.3 x 10^6, 23.3 + 5.9 x 10^6, p <0.001). There was a negative correlation between CD95mRNA and sFasmRNA copies in CKD patients (r= - 0.49, p <0.001).

Conclusions: Serum sFas levels and sFasmRNA expression are elevated in patients with CKD. We observed correlation between sFasmRNA expression and serum levels of sFas

TH-PO383

Protein Bound Uremic Toxins p-Cresyl Sulfate and Indoxyl Sulfate Modulate the Human Endothelial Cells' Transcriptome Regiane S. Cunha,[1] Giane Favretto,[1] Paulo C. Gregório,[1] Rayana A. Maciel,[1] Valentina Busato,[1] Roberto Pecoits-Filho,[2] Fellype C. Barreto,[3] Wesley M. Souza,[4] Andréa M. Stinghen.[1] *[1]Basic Pathology Department, Universidade Federal do Paraná, Curitiba, Brazil; [2]School of Medicine, Pontifícia Universidade Católica do Paraná, Curitiba, Brazil; [3]Internal Medicine Department, Universidade Federal do Paraná, Curitiba, Brazil; [4]Clinical Analysis Department, Universidade Federal do Paraná, Curitiba, Brazil.*

Background: *p*-Cresyl sulfate (PCS) and indoxyl sulfate (IS) are protein bound uremic toxins associated with endothelial dysfunction in chronic kidney disease (CKD). Thus, PCS and IS could activate signaling pathways leading to changes in the cellular transcriptome. This study evaluated the effect of PCS and IS on the expression of Organic Anion Transporter (OAT) 1 and 3 and their transcription factors cAMP responsive element binding protein-1 (CREB1), activating transcription factor-1 (ATF1) and hepatocyte nuclear factor-4α (HNF4α).

Methods: Human endothelial cells were treated for 24 h at normal, uremic and maximal uremic concentration of PCS (0.08, 1.75 and 2.6 mg/L) and IS (0.6, 53 and 236 mg/L). Probenecid (Pb) and benzilpenicilin (Bp) were used as OATs inhibitors, vitamin C (Vit C) as antioxidant and the N-nitro-Larginine methyl ester (L-NAME) as the inhibitor of nitric oxide (NO) synthase in order to evaluate the NO pathway production. Cell viability was assessed by MTT. The protein levels of OAT1 and OAT3 was evaluated by Western blotting. CREB1, ATF-1 and HNF4α expression were evaluated by RT-qPCR.

Results: The cell viability was reduced (P<0.001) after PCS and IS treatments in dose-dependent manner, being restored with Pb or Bp (P<0.001). An increased OAT1 and OAT3 protein expression was observed after PCS treatment at maximal uremic concentration (P<0.05). The RT-qPCR analysis showed an increase (P<0.01) in the CREB1 and ATF1 expression in cells treated with PCS and IS, which was restored with Pb, Bp, Vit C and L-NAME (P<0.05). The HNF4α expression was increased (P<0.05) only after PCS treatments at maximal uremic concentration.

Conclusions: PCS and IS are able to modulate differentially the gene expression of transcription factors which could affect the OATs expression. These changes in the cellular transcriptome could lead to the pathological phenotype found in CKD.

TH-PO384

Multispectral Fluorescence Unmixing for Large-Scale Three-Dimensional Imaging and Quantitative Tissue Cytometry of Human Kidney Tissue Seth Winfree,[4] Katherine J. Kelly,[2] Carrie L. Phillips,[4] Michael T. Eadon,[3] Timothy A. Sutton,[4] Ken Dunn,[1] Pierre C. Dagher,[1] Tarek M. El-Achkar.[1] *[1]Indiana University, Indianapolis, IN; [2]Indiana University, Indianapolis, IN; [3]Indiana University Division of Nephrology, Indianapolis, IN; [4]Indiana University School of Medicine, Indianapolis, IN.*

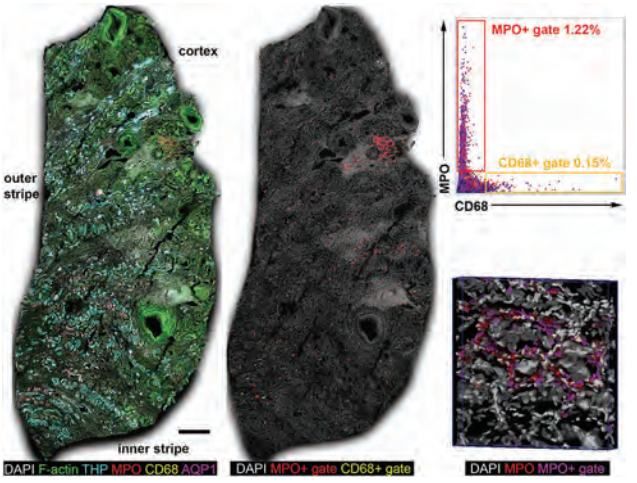
Background: Large-scale confocal fluorescence microscopy combined with three-dimensional tissue cytometry (3DTC) has the potential to provide quantitative data like flow cytometry, while preserving the localization and distribution of cells in intact kidney tissue. Confocal imaging is typically limited to 4 markers, dictated by available lasers and spectral bleed-through, limiting cell identification to 2 or 3 types.

Methods: To extend the palette of simultaneously distinguishable fluorophores (up to 8 colors), we implemented fluorescence spectral unmixing. Using this approach, we labeled proximal and distal tubular cells along with 4 basic types of immune cells in single human kidney tissue sections.

Results: Large-scale 3D imaging of these sections generated data suitable for 3DTC with our recently developed Volumetric Tissue Exploration and Analysis (VTEA) software tool. Using VTEA, we determined the abundance and localization of each labeled cell type. Furthermore, we explored the distribution of leukocytes in relation to nephron sub-segments and showed clustering of neutrophils around proximal tubules.

Conclusions: Multi-fluorescence labeling with spectral unmixing enhances our ability to simultaneously visualize and detect various cell types withn the kidney in 3D, and quantify the association of immune cells with nephron sub-segments *in situ*.

Funding: NIDDK Support, Veterans Affairs Support



Large-scale 3D multi-fluorescence imaging of a human nephrectomy section (≈ 7 x 3 x 0.05 mm^3, left), and tissue cytometry analysis (middle and right) using VTEA. Gates on the scatter plot identify CD68+ (macrophages) and MPO+ cells (neutrophils). The gated cells were mapped to the original volume to identify their spatial distribution (middle). A 3D rendered sub-volume demonstrates the resolution and precision of gating (lower right, gated cells identified by nuclear overlays). Scale bar = 500μm.

TH-PO385

FRMD3/Protein 4.1O Is a Novel Nephrin Adaptor to F-Actin Regulated by MAPK- and Src-Kinases and Linked to Diabetes Eva Koenigshausen,[1] Aida Bajraktarevic,[1] Sinja Ohlsson,[1] Klaus Stahl,[3] Marie Schönberger,[1] Thorsten Wiech,[2] Hermann G. Haller,[3] Lars C. Rump,[1] Mario Schiffer,[3] Lorenz Sellin.[1] *[1]Medical Faculty Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany; [2]Department of Pathology, University Hospital Hamburg Eppendorf, Hamburg, Germany; [3]Hannover Medical School, Hannover, Germany.*

Background: FRMD3 has been proposed as a candidate gene for diabetic nephropathy (DN). FRMD3 encodes for protein 4.1O, a member of the 4.1 protein family. In erythrocytes, protein 4.1R links membrane proteins to the actin cytoskeleton. The molecular function of protein 4.1O is unknown so far.

Methods: Expression and interaction of protein 4.1O were investigated by qPCR, IF and western blot in podocytes. Zebrafish larvae were treated with morpholinos against *moe* the orthologue of FRMD3. The loss of 78 kD-GFP tagged protein using the Tg(l-fab:DBP-eGFP) fish line was measured. Human 4.1O truncations were reexpressed in *moe* knockdown zebrafish larvae. Electronmicroscopy was performed. Cells expressing protein 4.1O, its truncations, its point mutations and nephrin or nck were subjected to co-immunoprecipitation. Cells were incubated with kinase inhibitors PP2 (10 μM) and SB202190 (50 μM). Kidney samples from patients with T1DN or T2DN and from streptozotocin treated mice were stained for protein 4.1O.

Results: Protein 4.1O is expressed in human podocytes and interacts with nephrin, GLEPP1, IQGAP1, Neph1 and actin in vitro and in vivo. Injection of *moe* morpholinos leads to zebrafish edema, complete loss of slit diaphragm, complete foot process effacement and increase in glomerular permeability. The phenotype can be rescued by expression of human protein 4.1O AA 506-553, the nephrin binding domain. AA 506-553 contain a MAPK and DEF (SFK phosphorylation) site. Inhibition of SFK and p38 attenuate significantly nephrin protein 4.1O interaction. 4.1O and nck compete for the binding to nephrin. Mutations of protein 4.1O at the DEF site reduces significantly nephrin protein 4.1O interaction. Protein 4.1O expression is increased in human DN, interestingly is reduced in streptozotocin treated mice.

Conclusions: Protein 4.1O is a novel podocyte protein that interacts with nephrin, GLEPP1, IQGAP1, Neph1 and the actin cytoskeleton. Protein 4.1O is essential for the intact glomerular filtration barrier. Knockdown of *moe* in zebrafish leads to nephrotic phenotype that is rescued by expression of human protein 4.1O AA 506-553. Nephrin protein 4.1O binding is regulated by SFKs and MAPK. The expression of protein 4.1O is increased in human DN and reduced in a mouse model.

TH-PO386

Regulation of Actin Cytoskeletal Remodeling in Glomerular Podocytes by Testis Specific Protein Kinase 1 (TESK1) Liming Wang,[2] Anne Buckley,[1,3] Robert F. Spurney.[2,3] *[1]Duke University, Durham, NC; [2]Duke University Medical Center, Durham, NC; [3]Durham VA Medical Center, Durham, NC.*

Background: In published studies, we found that expression of a constitutively active Rho A construct (V14Rho) in glomerular podocytes *in vivo* induced albuminuria and foot process (FP) effacement (Kidney Int 81:1075, 2012). We postulated that these effects might be mediated by the Rho A effector Rho kinase (ROK).

Methods: V14Rho mice were treated with the ROK inhibitor Y27632. We then examined the effects of ROK inhibition on albuminuria and FP effacement. These *in vivo*

studies were supplemented with cell culture experiments using an immortalized mouse podocyte cell line.

Results: Treatment with the ROK inhibitor Y27632 failed to attenuate albuminuria or FP effacement in V14Rho mice. An important target phosphorylated and inhibited by ROK is the actin depolymerizing factor cofilin 1 (CFL1). Sustained phosphorylation of CFL1 is implicated in human nephrotic diseases. In V14Rho mice, Y27632 did not inhibit phosphorylation of CFL1 despite effective ROK inhibition in vivo. CFL1 is also phosphorylated by testis-specific kinase 1 (TESK1) on the same serine residue. While the cell type specific expression of TESK1 is restricted, TESK1 was expressed in podocytes. Integrins activate TESK1, and plating podocytes on fibronectin to activate integrins increased CFL1 phosphorylation. Fibronectin induced CFL1 phosphorylation was not blocked by Y27632 but was inhibited by the β1-integrin agonist pyrintegrin. To examine the role of TESK1 in podocytes, we created TESK1 knockout (KO) cells. In contrast to podocytes expressing TESK1, Y27632 inhibited phosphorylation of CFL1 in KO cells. TESK1 KO did not affect actin polymerization under basal conditions, but reduced actin polymerization in the presence of Y27632. ROK inhibition also promoted podocyte motility, which was blocked by either TESK1 KO or pyrintegrin.

Conclusions: TESK1 plays a key role in regulating podocyte cytoskeletal dynamics. Because glomerular filtration barrier integrity requires an intact podocyte cytoskeleton, TESK1 may be a novel target for the treatment of glomerular diseases.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO387

Endocytosis and Intracellular Trafficking of AQP2 Is Regulated by the Notch Signaling Pathway

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Background: The Notch signaling pathway plays important roles in development and pathological processes in multiple tissues, including the kidney. A role of Notch signaling in regulating trafficking of nephrin in podocytes and of monocarboxylic acid transporter 1 in brain endothelial cells has recently been reported, implicating an emerging function for Notch in protein trafficking. Aquaporin-2 (AQP2) is a water channel that mediates water reabsorption in the collecting ducts (CDs) of the kidney. It plays a predominant role in regulating water balance in mammals. In this study, we investigate the function of Notch signaling in AQP2 trafficking and urinary concentration. Our data show that inhibiting Notch signaling either by Notch inhibitors DAPT and LY-411575, or by siRNA knock down in cultured cells increases AQP2 membrane accumulation. A similar increase in AQP2 membrane accumulation is observed in CD principal cells (PCs) in cultured mouse kidney slices treated with DAPT or LY-411575. Notch inhibition causes AQP2 accumulation on the apical membrane in CDs from both cortex and medulla. Membrane accumulation of AQP2 induced by Notch inhibition does not affect AQP2 expression, and is independent of AQP2 phosphorylation. Further analysis reveals that Notch inhibition reduces the endocytosis of AQP2 without affecting the overall exocytosis, and Notch inhibition negatively impacts F-actin polymerization. The role of Notch signaling in water transport was next investigated in vivo. DAPT treatment of mice attenuates the polyuria and increases urinary concentration in lithium treated mice by promoting apical membrane accumulation of AQP2 in CD PCs. Further supporting this idea, increased membrane accumulation of AQP2 was observed in the hemizygous PC-specific rbpj $^{flox/+}$/aqp2 cre mice (recombination signal binding protein for immunoglobulin kappa J (RBPJ)-deficient mice). We further challenged the hemizygous rbpj $^{flox/+}$/aqp2 cre mice with lithium. We found that the hemizygous rbpj $^{flox/+}$/aqp2 cre mice are resistant to lithium induced nephrogenic diabetes insipidus. Our studies collectively show that AQP2 trafficking is regulated by the Notch signaling pathway both in vitro and in vivo, therefore uncovering a novel role of Notch signaling in modulating water homeostasis through regulating AQP2 trafficking.

Methods:

Results:

Conclusions:

TH-PO388

Activated Renal Tubular Wnt/β-Catenin Signaling Triggers Renal Inflammation during Proteinuria

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Background: Imbalance of Wnt/β-catenin signaling in renal cells is associated with renal dysfunction, yet the precise mechanism is poorly understood. Previously we observed activated Wnt/β-catenin signaling in renal tubules during proteinuric nephropathy with an unknown net effect (rescue vs. damage?) (*Cell Death Dis* 2016; 24;7:e2155).

Methods: To identify the definitive role of tubular Wnt/β-catenin, we generated a novel transgenic "Tubcat" mouse, which conditionally expresses stabilized β-catenin specifically in renal tubules after tamoxifen administration.

Results: Four weeks after tamoxifen induction, Tubcat mice displayed proteinuria and elevated BUN levels, implying a detrimental effect of the activated signaling. This was associated with tubulointerstitial infiltration predominantly by M1 macrophages and overexpression of the inflammatory chemocytokines CCL-2 and RANTES. Induction of overload proteinuria by low-endotoxin BSA injection for 4 weeks aggravated proteinuria and increased BUN levels to a significantly greater extent in Tubcat mice. Renal dysfunction correlated with the degree of M1 macrophage infiltration in the tubulointerstitium and renal cortical up-regulation of CCL-2, IL-17A, IL-1β, CXCL1 and ICAM-1. Finally, there was overexpression of cortical TLR-4 and NLRP-3 in Tubcat mice, irrespective of BSA injection.

Conclusions: Conditional activation of renal tubular Wnt/β-catenin signaling enhances intrarenal inflammation via the TLR-4/NLRP-3 inflammasome axis in overload proteinuria. **Funding support:** National Natural Science Fund (NSFC) of China (grant no. 81570647)

TH-PO389

Local Inflammatory Mechanism Aggravated by Intraglomerular Crosstalk in Diabetic Kidney

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Background: We previously reported that the myeloid-related protein 8 (MRP8, S100A8)/toll-like receptor 4 (TLR4) signaling activated by glucolipotoxicity-associated ER stress plays an important role in the progression of diabetic nephropathy. Although local activation of the renin-angiotensin system (RAS) in the kidney has been observed in concurrence with the MRP8/TLR4 activation in the diabetic-hyperlipidemic model mice, the relationship between these signals remains obscure.

Methods: In vivo studies were performed using diabetic-hyperlipidemic mice (by streptozotocin plus high-fat diet, STZ-HFD) and db/db mice, treated with olmesartan (Olm) and angiotensin II (AngII), respectively. In vitro experiments were done with mouse macrophages (MΦ) that were co-cultured with rat mesangial cells (MC), or stimulated by MC-conditioned media (MC-sup). Expressions of the pro-inflammatory and profibrotic genes were analyzed by qPCR. Inflammation and ER stress were evaluated using a THP1-dual reporter cell line monitoring NF-κB and IRF pathways. Effects of a TLR4 antagonist on this crosstalk were also examined.

Results: Angiotensinogen (Agt) mRNA was upregulated in the glomeruli of STZ-HFD mice. Olm effectively suppressed upregulation of glomerular MRP8/TLR4 and Agt in STZ-HFD mice, which was associated with the reduction of albuminuria. In contrast, a subpressor dose of AngII markedly worsened albuminuria and increased glomerular infiltrated MRP8-positive cells in db/db mice. Glomerular MΦ showed obviously high MRP8 positivity compared to tubulointerstitial ones, suggesting intraglomerular crosstalk. MRP8 and TNFα in MΦ were dramatically induced by co-culture with MC, which was reproduced by stimulation with MC-sup. Dual reporter assay revealed that MC-sup stimulation activated IRF, which could cause ER stress, as well as NF-κB in a concentration-dependent manner. Such induction was partially abrogated by the TLR4 antagonist.

Conclusions: RAS activation should contribute to progression of diabetic nephropathy through promoting intraglomerular crosstalk, which may trigger MRP8 production in glomerular MΦ. Humoral factors secreted from MC could contribute to the crosstalk partly in a TLR4-dependent manner, thus facilitating local inflammation and ER stress.

TH-PO390

Engineered Immune Complexes with Galactose-Deficient IgA1: A New Model for IgA Nephropathy

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Background: IgA nephropathy (IgAN) is an autoimmune disease characterized by circulating immune complexes (CIC) that deposit in the kidney and incite kidney injury. These CICs contain galactose-deficient IgA1 (Gd-IgA1) bound by Gd-IgA1-specific autoantibodies. Development of models of IgAN has been hindered because only humans and hominoid primates have IgA1 with its *O*-glycans. To address these issues, we developed an animal model by using *in vitro*-formed, engineered immune complexes (EIC) from human Gd-IgA1 and recombinant Gd-IgA1-specific IgG. In this study, we profiled kidney transcriptomes from mice injected with these EIC, controls, and human IgAN kidney biopsies.

Methods: EICs were formed from Gd-IgA1 and recombinant Gd-IgA1-specific antibody. EIC or Gd-IgA1 only were injected intravenously 3 times every other day in 8-week old immunodeficient mice. Kidneys were harvested 1d after last injection, and either snap frozen in liquid nitrogen for RNAseq analysis or fixed for pathologic analysis. RNAseq data sets were compared against published data from IgAN patient kidney biopsy samples, and pathway analysis was performed using the Broad Institute GSEA tool.

Results: Mice injected with EIC exhibited glomerular matrix expansion and hypercellularity, with no morphological changes observed in the control group. Using 0.5 log2 fold-change parameter, gene expression analysis found 118 genes up-regulated and 165 down-regulated in the EIC-injected vs. control mice. Pathway analysis between the EIC model and IgAN biopsies identified multiple pathways in common, including estrogen early and late response, matrisome, interferon gamma response, and epithelial

to mesenchymal transition. In addition, similar genes between the EIC animal model and biopsies were found to be modified in a similar pattern and SDS/Western blotting of kidney tissue for selected targets showed protein expression followed mRNA changes for some genes.

Conclusions: Using EICs, we generated an IgAN passive mouse model that replicates some of the pathologic changes observed in renal biopsies of IgAN patients. This model thus provides a unique platform for testing disease-specific drugs for efficacy in reducing kidney damage from CICs.

Funding: NIDDK Support

TH-PO391

TWEAK Increases CD74 Expression and Sensitizes to DDT Proinflammatory Actions in Tubular Cells Lara Valiño rivas,[3] Richard Bucala,[6] Lin Leng,[5] Ana B. Sanz,[4] Laura Gonzalez-Lafuente,[2] Alberto Ortiz,[1] Maria Dolores Sanchez-Nino.[1] *[1]Nephrology, Fundacion Jimenez Diaz, Madrid, Spain; [2]IIS-Fundacion Jimenez Diaz, Madrid, Spain; [3]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain; [4]Instituto de Investigacion Sanitaria Fundacion Jimenez Diaz, Madrid, Spain; [5]Yale School of Medicine, New Haven, CT; [6]Yale University School of Medicine, New Haven, CT.*

Background: TWEAK is a proinflammatory cytokine that promotes kidney injury. CD74 is a multifunctional protein upregulated in diabetic kidney disease another chronic nephropathies. One function of CD74 is being a receptor for Macrophage Migration Inhibitory Factor (MIF) and for the recently described MIF-2 / D-dopachrome tautomerase (DDT) cytokine. However, the molecular mechanisms of TWEAK-induced kidney injury, the drivers of CD74 expression and the function of DDT function in kidney cells are poorly characterized.

Methods: Wild type (WT) mice received a single i.p. injection of TWEAK. Cell culture studies were performed in murine proximal tubular MCT cells. TWEAK, DDT and MIF expression was determined by immunohistochemistry in kidney tissue from mice. The effects of TWEAK in mice and in cultured tubular cells was assessed by qRT-PCR, Western blot and flow cytometry.

Results: We have now identified CD74 gene expression as upregulated in the kidneys in response to systemic TWEAK administration in mice in a transcriptomics analysis, and have characterized the in vivo CD74 expression and the functional consequences in cultured cells. TWEAK administration to mice resulted in a progressive time-dependent (up to 24h) upregulation of kidney CD74 mRNA (RT-PCR) and protein (Western blot). Furthermore, the CD74 ligands MIF and DDT were also upregulated at the protein level 24h after TWEAK administration. Immunohistochemistry localized the increased CD74, MIF and DDT expression to tubular cells. In cultured tubular cells, TWEAK increased CD74 mRNA and protein expression dose-dependently, with the temporal pattern similar to the in vivo experiments. TWEAK-induced CD74 localized to the cell membrane, where it can function as a cytokine receptor. For the first time, we explored the actions of DDT in tubular cells and found that DDT amplified the increase in MCP-1 and RANTES expression in response to TWEAK. By contrast, DDT did not significantly modify TWEAK-induced Klotho downregulation.

Conclusions: In conclusion, TWEAK upregulates CD74 and its ligands MIF and DDT in renal tubular cells. This may have functional consequences for kidney injury since DDT amplified the inflammatory response to TWEAK.

TH-PO392

TGF-Beta Exposure Represses Fibroblast Transcription of the Anti-Fibrotic Molecule Slit2: A Novel Fibrogenic Mechanism? Monica F. Tolosa,[1,2] Darren A. Yuen.[1,2] *[1]Keenan Research Centre for Biomedical Science, St. Michael's Hospital, Toronto, ON, Canada; [2]Department of Laboratory Medicine & Pathobiology, Faculty of Medicine, University of Toronto, Toronto, ON, Canada.*

Background: Recent work has demonstrated that the molecular guidance ligand Slit2 may also serve as an important anti-fibrotic signal in the kidney. Specifically, we have previously shown that Slit2 is reduced following renal injury, and bioactive N-terminal Slit2 attenuates fibrosis following both ischemia-reperfusion injury and unilateral ureteral obstruction (UUO). While this provides early evidence that Slit2 could be a possible adjunct therapy for chronic kidney disease, the regulation of endogenous Slit2 during fibrosis—as well as its role in downstream injury—remains largely uncharacterized. **Objective:** To study the endogenous regulation of Slit2 expression by fibroblasts in fibrotic disease, and further characterize the role of Slit2 on fibroblast activation and renal injury.

Methods: Using real-time PCR and immunofluorescence, we measured Slit2 expression in primary human dermal fibroblasts in response to TGF-beta. *In vitro* tools, including siRNA-mediated knockdown and pharmacological inhibition, were used to further identify and characterize novel regulators of Slit2 expression.

Results: Here, we demonstrate that fibroblast exposure to TGF-beta, a master regulator of fibrosis, causes a downregulation of the anti-fibrotic factor, Slit2. Furthermore, we determined that TGF-beta mediated repression of Slit2 occurred at the level of transcription, by observing a corresponding downregulation of Slit2 pre-mRNA transcript levels. *In silico* analysis showed putative binding sites for TGF-beta-regulated transcription factors in the Slit2 promoter region, suggesting that repression may occur through proximal *cis*-acting elements. Finally, we determined that Slit2 repression occurs through a Smad- and YAP-dependent mechanism, as loss of each of these transcriptional regulators by siRNA reversed the repressive effect of TGF-beta.

Conclusions: While many forms of chronic kidney disease are characterized by fibrosis, few strategies exist to effectively suspend fibrotic progression. Here, we determined that fibroblast exposure to TGF-beta leads to a marked decrease in Slit2 expression, suggesting that loss of Slit2 may facilitate fibroblast activation in a disease context. Further studies will help to clarify the mechanism of Slit2 repression and how this may be targeted to potentially reduce fibrotic injury.

Funding: Government Support - Non-U.S.

TH-PO393

Calcium Dobesilate Reduces VEGF Signaling in Endothelial Cells, Preserves Cell Function, and Improves Vascular Complications in Diabetic Mice Florence Njau,[1] Nelli Shushakova,[3] Joon-Keun Park,[1] Jan Menne,[2] Hermann G. Haller.[1] *[1]Hannover Medical School, Hannover, Germany; [2]Medical School Hannover, Hannover, Germany; [3]Nephrology and Hypertensiology, 30625 Hannover, Germany.*

Background: Calcium dobesilate is a small molecule with vasoprotective properties. Preliminary evidence suggests that calcium dobesilate interferes with heparan-sulfate binding sites of growth factors such as FGF and VEGF. We therefore tested the hypothesis that calcium dobesilate (1) ameliorates diabetic nephropathy and (2) directly and/or indirectly inhibits VEGF signaling in the microcirculation.

Methods: In vitro HUVECs were used for analysis of VEGF signaling as well as migration and proliferation. Streptozotocin-treated mice (STZ) were treated with calcium dobesilate and analyzed after 4 and 8 weeks of hyperglycemia. Diabetic neuropathy was assessed by thermal sensitivity Urinary albumin was measured by. ELISA and immunohistochemistry performed on cryostat or on paraffin sections.

Results: Dobesilate (100 and 200 μM) decreased VEGF (20 ng/ml)-induced migration by 50% and inhibited assembly of F-actin in lamellipodia-like structures and phosphorylation of focal adhesion kinase (FAK). Dobesilate reduced HUVECs proliferation by 30% and enhanced apoptosis of HUVECs induced by serum deprivation in a dose-dependent manner as evidenced by a decrease in Bcl-2/Bax ratio, and phosphorylation of Bad. It inhibited VEGF-induced phosphorylation of VEGFR2 kinase by 50% in concentration dependent manner and suppressed the phosphorylation of pERK1/2, pMEK1/2 and Pp38 MAPK. Diabetic mice treated with calcium dobesilate showed a decrease in albuminuria, less phosphorylation of VEGF-R2 and an increased thermal sensitivity as compared to sham-treated diabetic animals.

Conclusions: Calcium dobesilate ameliorates both hyperglycemia-induced nephropathy and neuropathy in mice. *In vitro* the signaling of VEGF in endothelial cells is reduced. Our findings suggest that calcium dobesilate is a VEGF inhibitor at high concentrations. The specific inhibition of FGF and VEGF signaling by blockading heparin sulfate binding sites may be a novel therapeutic strategy for diabetic vascular complications.

Funding: Government Support - Non-U.S.

TH-PO394

Urinary Activin A Is a Novel Biomarker Reflecting Renal Inflammation and Tubular Damage in ANCA-Associated Vasculitis Yoshinori Takei,[4] Shunsuke Takahashi,[2] Masao Nakasatomi,[1] Toru Sakairi,[3] Hidekazu Ikeuchi,[5] Yoriaki Kaneko,[2] Keiju Hiromura,[2] Yoshihisa Nojima,[1] Akito Maeshima.[2] *[1]Gunma University, Maebashi, Japan; [2]Gunma University Graduate School of Medicine, Maebashi, Japan; [3]Gunma University Graduate School of Medicine, Japan, Maebashi, Japan; [4]Gunma University School of Medicine, Maebashi, Japan; [5]Gunma university graduate school of medicine, Maebashi, Japan.*

Background: Activin A, a member of TGF-beta superfamily, is known to regulate cell growth and differentiation in various tissues. It has been reported that activin A is involved in kidney development, tubular regeneration, and renal fibrosis in rodents. However, the role of activin A in kidney diseases remains unknown in human. To address this issue, we analyzed renal biopsy specimens and urine from patients with ANCA-associated vasculitis (AAV).

Methods: Thirty-seven patients with biopsy-proven AAV who were treated in our department from 2011 and 2015 were included in this study. Serum activin A, urinary activin A, urinary follistatin (an activin antagonist), and urinary KIM-1 were measured by ELISA. Urine from healthy volunteers and rheumatic disease patients with normal urinalysis (control patients) were also used. The localization of activin A in renal biopsy specimens from AAV patients was examined by immunostaining. Normal kidney specimens from patients who underwent nephrectomy were used as a control.

Results: Urinary activin A was almost undetectable in healthy volunteers, but was significantly increased in AAV patients (7.2 ± 2.6 vs. 122.0 ± 38.6 ng/gCr, $p<0.001$). Urinary activin A levels of these patients was rapidly decreased after treatment. There was a significant correlation of urinary activin A level with urinary KIM-1 and urinary protein. On the other hand, compared with control patients, urinary follistatin levels were decreased in AAV patients (673.1 ± 135.3 vs. 291.7 ± 38.8 ng/gCr, $p<0.05$). Activin A was localized in the cytoplasm of distal tubules of normal kidneys. In contrast, activin A was present not only in distal tubules, but also in the apical lumen of proximal tubules, and infiltration macrophages in patients with AAV.

Conclusions: These data suggest that urinary activin A reflects renal inflammation and tubular damage in ANCA-associated vasculitis.

Funding: Commercial Support - Astellas Pharm Inc.

TH-PO395

Osmotic Pressure Increases TGFβ1-Mediated Loss of SGLT2 Expression in Human Proximal Tubule Cells Xinlu Pan,[4,3] Deborah L. Baines,[3] Mysore K. Phanish,[2] Mark E. Dockrell.[1] [1]*South West Thames Institute for Renal Research, London, United Kingdom;* [2]*SW Thames renal and transplantation unit, London, United Kingdom;* [3]*St George's, University of London, London, United Kingdom;* [4]*St Helier Hospital, London, United Kingdom*.

Background: Approximately 90% of glucose is reabsorbed by the low affinity Na+/glucose co-transporter SGLT2, predominantly expressed in the early proximal tubule. This transporter has received renewed interest in the light of anti-diabetic drugs targeting its activity. Although reports suggest an increase in SGLT2 expression in diabetic nephropathy (DN), we hypothesised that the loss of phenotype of proximal tubule epithelial cells (PTEC) observed in DN may result in a decrease in SGLT2 expression.

Methods: Primary human PTEC were cultured on plain or collagen IV coated plastic-ware in supplemented medium. Cells at 80% confluence were treated with: 5mM D-Glucose (normoglycaemia), 25mM D-Glucose (hyperglycaemia), or 5 mM D-Glucose + 20mM L-Glucose (osmotic control) +/-TGFβ1(0.75ng/ml). After 24h, medium was collected and cells lysed. Western blot was used to detect protein expression; membranes were probed with antibodies against: SGLT2, SGLT1, K-Cadherin and tubulin.

Results: Primary PTEC expressed mature SGLT2, molecular weight of ~ 73KDa, indicating appropriate post-translational processing and membrane localisation. Probing with the SGLT1 antibody only identified bands of 60 KDa or lower, indicating an immature protein not expressed at the membrane. TGFβ1 treatment (24h) resulted in a decrease in SGLT2 expression in all treatments; this effect was more pronounced in cells grown on collagen and in osmotic control containing non-transported/non-metabolised L-glucose. K-Cadherin protein expression was not reduced by TGFβ1 at this time point; in fact there was a tendency to increased expression in cells treated with D-Glucose + TGFβ1.

Conclusions: Our data demonstrates that TGFβ1 reduced the expression of mature SGLT2 protein in human primary PTEC. This is not consistent with recent reports of a TGFβ1-induced increase in SGLT2 expression using transformed cells grown on plastic, less representative of the in vivo situation. SGLT2 was decreased prior to any measurable loss of K-Cadherin, suggesting that SGLT2 could be a more sensitive phenotypic marker than cadherin in PTEC. An increase in K-Cadherin expression in response to D-Glucose + TGFβ1 may be secondary to cellular hypertrophy observed in DN. In the other presentation from our group on this topic we investigate whether there is a metabolic interaction between TGFβ1 and SGLT2 activity.

Funding: Private Foundation Support

TH-PO396

Inhibition of Erythropoiesis by Soluble Fas in Cell Culture Miguel A Goes.[1,2] [1]*Wake Forest Institute for Regenerative Medicine, Wake Forest University, Winston Salem, NC;* [2]*Division of Nephrology, Federal University of São Paulo (UNIFESP), São Paulo, Brazil*.

Background: Serum soluble Fas (sFas) levels are associated with anemia in CKD patients. Cord blood cells (CBc) can generate hematopoietic stem cells ($CD34^+$). **Objective:** To investigate whether sFas interferes with erythropoiesis in cell culture

Methods: We studied $CD34^+$-cell culture after sorting from CBc. Analyzed on flow cytometry for glycophorin A, CD 34^+, CD 38^+ and CD 171^+. The $CD34^+$ cells were incubated for 14 days in methylcellulose medium containing growth factors added with sFas or without sFas. They were divided in 18 wells from 6 plates. We divided in 2 groups. Each group consisted in 9 wells with different concentrations of sFas (H group- [2, 4 and 8 ng/mL]; L group-[0, 0.5, and 1 ng/mL]). We performed counting of colony-forming unit (CFU) numbers in all wells for red series (B/CFU-E), white series (CFU-GM) and mixed series (CFU-GEMM) under inverted light microscopy. We performed correlations and comparisons.

Results: We found that CD34+ was the major marker after sorting. We observed a negative correlation between sFas concentration and B/CFU-E ($r=-0.74$; $p<0.001$) when analyzed all 18 wells together. We observed lower amount of B/CFU-E in plate with sFas-8ng/ml than in the plates with sFas-1ng/ml, 0.5 ng/ml and non-sFas, 3.7±1.1, 4.3±2.0, 5±1.7, respectively; $p=0.02$). There was a negative correlation between B/CFU-E and CFU-GM ($r=-0.69$; $p=0.03$) in the H-$CD34^+$ group. We observed lower number of B/CFU-E in H-$CD34^+$ group than in the L-$CD34^+$ group (1.5±0.9, 4.3±1.6; $p=0.008$).

Conclusions: We observed that higher concentrations of sFas interfere with erythropoiesis in $CD34^+$ cell culture.

TH-PO397

Differential Expression of Myogenic Regulators Following Aerobic or Combined Exercise in Non-Dialysis CKD Douglas W. Gould,[1] Emma L. Watson,[1] Matthew P. Graham-Brown,[1] Soteris Xenophontos,[1] Thomas J. Wilkinson,[1] Joao L. Viana,[2] Alice C. Smith.[1] [1]*University of Leicester, Leicester, United Kingdom;* [2]*University Institute of Maia, Porto, Portugal*.

Background: CKD is associated with satellite cell (SC) dysfunction and reduced expression of myogenic regulatory factors (MRFs), which contribute to muscle wasting. SCs are skeletal muscle stem cells responsible for muscle repair and regeneration following 'injury'. Such 'injury' occurs following exercise; this leads to SC activation, a process controlled by the MRFs MyoD and Myogenin. The effect of exercise on the expression of MRFs in CKD is currently unknown.

Methods: 19 CKD patients (62±14 years; 12 female; eGFR: 27±7ml/min/kg/1.73m^2) completed supervised aerobic exercise (AE) (n=10), or combined aerobic plus resistance exercise (CE) (n=9) 3x/week for 12 weeks. Muscle biopsies were obtained from the vastus lateralis at baseline (B1) and 24h (B2) post the first and final exercise sessions (B3). Gene expression of MyoD and Myogenin were analysed by RT-PCR and data reported as percentage change from B1. Data was analysed using repeated measures ANOVA with post-hoc paired t-tests.

Results: Analysis revealed effects between biopsy time-points ($F=5.795$, $p=.016$) and groups ($F=4.630$, $p=.031$) for MyoD expression. Post-hoc analysis revealed AE had a negligible effect on MyoD expression with a change of +0.5% ($p=.988$) at B2 and +14% ($p=.511$) at B3. Following CE, MyoD was downregulated by -70% ($p=.050$) at B2, but up regulated by +54% ($p=.123$) from baseline at B3, which was +429% ($p=.012$) from B2. No interactions were observed for Myogenin expression ($F=.492$, $p=.615$).

Conclusions: We report differential effects of AE and CE on MyoD gene expression in non-dialysis CKD. In the general population, exercise acts as a potent stimulus for SC activation, which is mediated by MRFs. We observed a small increases at both biopsy time points following AE. In contrast, CE suppressed MyoD gene expression following the initial bout of exercise, indicating a possible abnormal response. However, this appeared to be reversed following 12-weeks, where expression was increased above baseline. This demonstrates that regular exercise incorporating resistance training has the potential to overcome CKD induced abnormalities in SC activation.

TH-PO398

A New Deleterious Role for AMPD1 in the Pathogenesis of CKD-Dependent Muscle Waste Ana Andres-hernando, Richard J. Johnson, Miguel A. Lanaspa. *University of Colorado Denver, Aurora, CO*.

Background: Chronic Kidney Disease (CKD) reflects an overall catabolic state with significant loss of muscle mass. Mortality in CKD closely relates to muscle atrophy and no reliable methods to prevent CKD-induced muscle wasting currently exist. Proper glucose and phosphate uptake is essential for maintaining muscle mass which is controlled by the regulation of the Akt/As160/glut4 axis. AMP Deaminase 1 (AMPD1) is a muscle-specific protein inhibited by intracellular phosphate that negatively regulates the activation of the energy sensor protein AMPK and thus, AKt-signaling and glucose uptake. Based on this, we hypothesize that AMPD1-deficient mice by having an over-activation of AMPK and glucose uptake in the skeletal muscle will demonstrate a significant amelioration in CKD-dependent loss of muscle mass.

Methods: CKD-dependent muscle waste was induced in wild type and AMPD1 knockout mice by subtotal nephrectomy followed by a 5-week high protein diet. Body weight loss –a marker of muscle mass loss- in sham and nephrectomized mice was monitored weekly and renal function, muscle mass, intramuscular activation of AMPD1 and its signaling –AMPK and Akt activities, phosphate and uric acid levels- determined at sacrifice.

Results: AMPD1 activation in muscle of wild type mice undergoing CKD/High protein feeding is denoted by reduced intramuscular phosphate, increased AMP-dependent ammonia production and accumulation of AMPD-dependent products –uric acid and inosine-. Wild type but not AMPD1 deficient mice on CKD/high protein demonstrated significant weight and muscle –tibialis anterior, gastrocnemius and soleus- loss with elevation of serum creatinine kinase and glutamate –markers of muscle protein loss-. AMPD1 deficiency in mice results in AMPK activation leading to increased energy levels (ATP) and improved glucose uptake as reflected by the activation of the Akt/AS160/glut4 axis thus preventing protein loss and intramuscular catabolic processes. As a result, AMPD1 knockout mice on CKD demonstrated significant improved renal function with lower serum creatinine levels than wild type counterparts. .

Conclusions: AMPD1 activation in the skeletal muscle is a key step in the pathogenesis of CKD-dependent muscle wasting. Thus, AMPD1 blockade represents a new therapeutic approach for the prevention of this condition and to accelerate the recovery of muscle loss in subjects with CKD.

Funding: NIDDK Support

TH-PO399

Abnormal Lipid Metabolism in Skeletal Muscle Mediates CKD-Induced Sarcopenia Yuki Niida,[1] Masashi Masuda,[1] Aika Yoshizawa,[1] Yuichiro Adachi,[1] Yilimulati Yimamu,[1] Serina Kabutoya,[1] Risa Yoshida,[1] Hisami Okumura,[1] Yoshichika Kawai,[2] Makoto Miyazaki,[4] Hironori Yamamoto,[1,3] Yutaka Taketani.[1] [1]*Department of Clinical Nutrition and Food management, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan;* [2]*Department of Food Science, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan;* [3]*Dept. of Health and Nutrition, Jin-ai University, Echizen city, Fukui, Japan;* [4]*Division of Renal Diseases and Hypertension, Department of Medicine, University of Colorado Denver, Aurora, CO*.

Background: Sarcopenia is defined by decreased skeletal muscle mass and strength. Chronic kidney disease (CKD)-induced sarcopenia is associated with degraded quality of life and poor prognosis of the patient. However, there is currently no effective therapy available because the mechanisms of its pathogenesis are largely unknown. Recent evidence indicates that CKD increases circulating levels of the major saturated fatty acid stearic acid through repression of stearoyl-CoA desaturase (SCD), which induces lipotoxicities such as ER stress in tissues, including cardiovascular tissues. Several reports have also indicated that ER stress plays a causative role in sarcopenia and cahexia.

In this study, we examined the role of ER stress via abnormal lipid metabolism in the skeletal muscles of CKD rats with muscle atrophy.

Methods: Eight-week-old male Wistar rats were treated with either adenine diet (0.4%) (CKD rats) or vehicle (normal rats) for 6 weeks. Gastrocnemius muscles(GM), soleus muscles, tibialis anterior muscles, and extensor digitorum longus muscles were weighed and atrophy was evaluated by hematoxylin and eosin (H&E) staining. Gene expression of gastrocnemius muscles was evaluated by real-time qPCR. Fatty acid composition of gastrocnemius muscles was determined by the gas-liquid chromatography method.

Results: GM tissue weight was significantly decreased in CKD rats compared with normal rats. We confirmed infiltration of inflammatory cells and increased connective tissue in the GM of CKD rats by H&E staining. mRNA expression of muscle atrophy-related genes and ER stress responsive genes were increased in the GM of CKD rats compared with normal rats. Inversely, CKD rats presented a decrease in SCD1 mRNA expression of the GM compared with normal rats. In addition, the unsaturated fatty acid ratio (UFA/SFA) was significantly lower in the GM of CKD rats compared with normal rats. In mouse myoblasts, administration of SCD inhibitor increased mRNA expression of muscle atrophy-relating genes and ER stress response genes.

Conclusions: We suggest that the unbalanced SFA/UFA ratio in skeletal muscles due to a decrease in SCD activity induced by CKD causes lipotoxicity and sarcopenia via activation of various muscle atrophy systems.

TH-PO400

Plant versus Animal Protein Improves Anti-Inflammatory Effects of HDL and Lessens CKD-Induced Atherosclerosis Ryohei Kaseda,[1] Michihiro Hosojima,[1] Shoji Kuwahara,[1] Hideyuki Kabasawa,[1] Hiroyuki Aoki,[1] Yuki Higuchi,[1,3] Valentina Kon,[2] Kentaro Maruyama,[3] Ichiei Narita,[1] Akihiko Saito.[1] *[1]Niigata University, Niigata, Japan; [2]Vanderbilt University, Nashville, TN; [3]Rice Research Center, Kameda Seika Co., Ltd, Niigata, Japan.*

Background: Although CKD is known to cause endothelial injury that contributes to the many adverse consequences of CKD, few interventions specifically target endothelial cell injury. Little is known about the potential of nutritional effects on endothelial cell health, especially the impact of different dietary proteins. We and others have shown that in the CKD setting, HDL loses its anti-inflammatory effects, and even potentiates inflammation. Our aim was to determine whether differences in dietary protein source, namely animal protein versus plant protein can modulate renal injury-acceleration of atherosclerosis and anti-inflammatory properties of HDL.

Methods: 12-week-old ApoE-deficient hyperlipidemic mice underwent uninephrectomy. The mice were pair-fed the usual casein-based diet (animal protein) or rice protein-based diet (plant protein extracted from rice endosperm by alkaline extraction method) for 6 weeks. We compared atherosclerotic lesions by en-face Sudan IV staining. HDL fraction was obtained by eliminating Apo B by polyethylene glycol precipitation. Human umbilical vein endothelial cells (HUVEC) were exposed to TNF-α together with HDL for 6 hours. Cellular expression of inflammatory markers (MCP-1, IL-6, and IL-1β) was assessed by real time RT-PCR.

Results: Atherosclerotic lesions were significantly reduced in rice protein-fed group compared to casein-fed mice (en-face atherosclerotic lesions 0.28±0.06 vs. 0.67±0.15mm^2, p=0.038, N=5 and 5, respectively). HDL of rice protein-fed mice suppressed HUVEC's inflammatory response compered to casein-fed mice (MCP-1, 3.83±0.73 vs. 7.42±0.39, p=0.003; IL-1β, 1.54±0.19 vs. 5.70±1.32 p=0.02; and IL-6, 0.52±0.07 vs. 0.98±0.06, p<0.001, N=5 and 5, respectively)

Conclusions: Plant protein-based diet significantly reduced kidney-injury driven atherosclerosis compared to animal protein-based diet. This anti-atherogenic effect is associated with anti-inflammatory effects of HDL. The results underscore the potential utility of nutritionally-based intervention in affecting atherosclerosis for CKD.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO401

HDL from CKD Rabbits and Hemodialysis Patients Exhibit Impaired Anti-Aggregative Activity on Human Platelets through CD36 Pathway Nans Florens,[2,1] Catherine Calzada,[1] Dan Yi,[1] Sandrine Lemoine,[2,1] Laurent Juillard,[2,1] Christophe O. Soulage.[1] *[1]CarMeN, INSERM, U1060, INSA Lyon, Villeurbanne, France; [2]Hospices Civils de Lyon, Lyon, France.*

Background: Recent studies have shown altered biological properties of HDL in chronic kidney disease (CKD). As cardiovascular mortality remains the major cause of death in CKD and as oxidative stress is raised in CKD, we aimed to explore the specific role of oxidative modifications of HDL in CKD and their impact on anti-aggregant phenotype of HDL.

Methods: Rabbits were surgically 5/6-nephrectomized. Blood from healthy volunters (control) were sampled during their live-donor evaluation visit. Hemodialysis (HD) patients were sampled before the HD session. HDL were separated from plasma by potassium bromide stepwise density gradient ultracentrifugation. In rabbits, Malondialdehyde (MDA), 4-hydroxy-nonenal (HNE) and 4-hydroxy-2-hexenal (HHE) protein adducts levels were assayed. Platelet aggregation was measured after 5 min of incubation with HDL from each group in an aggregometer with or without anti-CD36 blocking antibody (Ab-CD36). HDL from control rabbits were modified by an incubation overnight at 37°C with 100mM of HNE.

Results: 8 CKD were compared with 9 Sham operated rabbits. CKD rabbits exhibited a higher creatinine level than the control group (93 ± 12 vs 214 ± 25 μM, p<0.001). MDA contents were significantly higher in the HDL from CKD group (0.89 ± 0.18 vs 2.64 ± 0.67 nmol/mg, p<0.05). HNE-adducts were also increased in HDL from CKD animals while HHE-adducts levels were not different. Percentage of platelet aggregation (PA) compared to collagen alone was 65% when were incubated with HDL from CKD group while it was 30% with HDL from the control group (p<0.05) evidencing a blunted anti-aggregative effect. PA in presence of HNE-modified HDL was 85% (p<0.05 compared to Control group). Incubation with Ab-CD36 decreased the PA with CKD and HNE-modified HDL to 27 and 23%, respectively (p<0.05). 5 control patients were compared with 6 HD patients. Percentage of PA compared to collagen alone with HDL from HD patients was higher than in the control group (63 vs 24%, p<0.01).

Conclusions: CKD is associated with oxidative modifications of HDL among which HNE-adducts. HDL from CKD rabbits and HD patients exhibited an impaired ability to inhibit platelet aggregation suggesting that altered HDL properties could contribute to the increased cardiovascular risk in this population.

TH-PO402

IL-1 Inhibition Improves HDL Functionality in CKD Adriana Hung,[4,6] Yohei Tsuchida,[4] Kristen L. Nowak,[3] Sudipa Sarkar,[4] Thomas G. Stewart,[5] Michel Chonchol,[1] Jiansheng Huang,[4] Macrae F. Linton,[2] Talat Alp Ikizler,[5,6] Valentina Kon.[4] *[1]University of Colorado, Aurora, CO; [2]Vanderbilt University School of Medicine, Nashville, TN; [3]University of Colorado Denver: Anschutz Medical Campus, Aurora, CO; [4]Vanderbilt University, Nashville, TN; [5]Vanderbilt University Medical Center, Nashville, TN; [6]VA TVHS, Nashville, TN.*

Background: Cardiovascular disease (CVD) is the most prominent cause of morbidity and mortality among patients with chronic kidney disease (CKD). Inflammation and oxidative stress are considered to contribute to CVD in CKD. Both of these factors are also known promote HDL malfunction in CKD. Whether interventions that modulate systemic inflammation can improve anti-inflammatory aspects of HDL in the setting of advanced CKD or ESRD is unknown.

Methods: We conducted a post-hoc analysis to evaluate if IL-1 blockade could improve the anti-inflammatory and anti-oxidant functions of HDL in patients with CKD. We used serum samples from two pilot randomized clinical trials; one in CKD stages 3 & 4 patients (CKD3/4) and one in maintenance hemodialysis (MHD) patients. HDL was isolated from each participant's serum at baseline and at the end of the study. The anti-inflammatory and anti-oxidant function of HDL was measured as the response of LPS-activated THP-1 macrophages exposed to the participant's HDL (IL-6, TNF-α, NLRP3 response were measured by RT-PCR and cellular oxidant production by HPLC). Biomarkers were log transformed and repeated measures ANCOVA was used to estimate the percent change in biomarker expression with the intervention (btween group comparison).

Results: The mean age of the participants was 60±13, 72% (n=33) were male, 38% (n=17) were black. There were 32 CKD patients (16 intervention and 16 placebo) and 14 MHD (7 intervention and 7 CKD). IL-1 blockade down-regulated hsCRP and IL-6 in both studies (*Nowak et al 2017 and Hung et al 2011*). IL-1 blockade effectively improved HDL functionality: compared to baseline, IL-1 blockade reduced TNF expression by 30% (p=0.006) [18% in CKD (p=0.03) and 61% in MHD (p=0.06)], IL-6 by 40% (p=0.02) [36% in CKD (p=0.006) and 50% in MHD (p=0.3)], and NLRP3 by 17% (p=0.02) [15% in CKD (p=0.02) and 25% in MHD (p=0.02)]. Cellular superoxide production fell by 15% (p<0.001) [17% in CKD (p< 0.001) and 12% in MHD (p=0.004)].

Conclusions: IL-1 blockade improved the anti-inflammatory and anti-oxidative properties of HDL in patients with CKD stage 3 or stage 4 and MHD. Larger scale and longer term prospective studies are needed to confirm the utility of this intervention in clinical settings. (Hung and Tsuchida are first co-authors)

Funding: Veterans Affairs Support, Private Foundation Support

TH-PO403

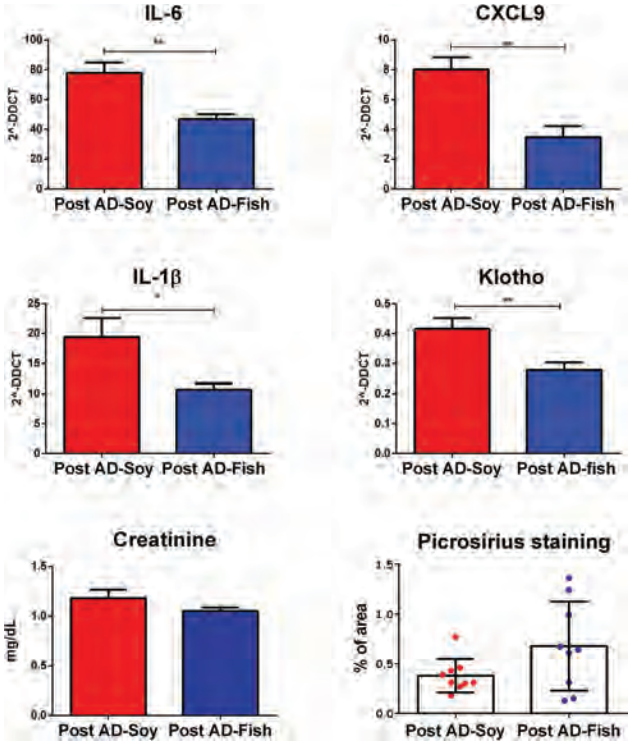
Fish Oil Supplementation Reduces Inflammation but Does Not Restore Renal Function and Klotho Expression in an Adenine-Induced CKD Model Juan S. Agudelo,[2] Leandro C. Baia,[1] Milene S. Ormanji,[2] Amandda rakell Peixoto dos santos,[2] Niels O. Camara,[2] Gerjan Navis,[1] Martin H. De Borst,[1] Ita P. Heilberg.[2] *[1]University Medical Center Groningen, Groningen, Netherlands; [2]Nephrology Division, Universidade Federal de São Paulo, São Paulo, Brazil.*

Background: CKD and inflammation promote loss of klotho expression. Given the well-established anti-inflammatory effects of n-3 fatty acids, we aimed to investigate the effect of fish oil supplementation in an experimental model of inflammatory renal damage.

Methods: Male C57BL/6 mice were fed an adenine-enriched diet (**AD-10days**) to induce inflammatory renal damage or standard chow (**CTL**) for 10 days, and in the subsequent 7 days received either fish oil (**Post AD-Fish**) or soybean oil (**Post AD-Soy**). Renal function, pro-inflammatory and profibrotic markers (picrosirius staining) were assessed and the expression of Klotho was evaluated by qPCR and Western-blot.

Results: When compared to **CTL,** the **AD-10days** group exhibited significantly higher mean serum creatinine (1.3±0.4 vs 0.8±0.1mg/dL), IL-6, CXCL10 and IL-1β (68.0±17.7 vs 1.0±0.2, 6.6±0.3 vs 1.0±0.2 & 3.5±1.5 vs 1.2±0.7, respectively), reduced renal klotho expression (0.2±0.0 vs 1.0±0.1), confirmed by Western-blot and a non-significant trend for increased fibrosis. As shown in the Figure, IL-6, CXCL9 and IL-1β were significantly decreased in **Post-AD-Fish** group but klotho expression was unaltered (also demonstrated by Western-blot). Serum creatinine and fibrosis did not differ statistically between **Post-AD-Fish** and **Post-AD-Soy** groups.

Conclusions: Fish oil supplementation reduced pro-inflammatory markers, but was not able to restore renal function or klotho expression in a model of inflammatory renal damage.



TH-PO404

Erythropoietin Pathway Dysregulation in Anemia of CKD Daniel Landau,[1] Lital London,[2] Inbar Bandach,[1] Yael Segev.[1] *[1]Microbiology and Immunology, Ben Gurion University of the Negev, Beer Sheva, Israel; [2]Ben Gurion University of the Negev, Beer-Sheva, Israel.*

Background: Anemia is a known driver for hypoxia inducible factor (HIF) which leads to increased renal erythropoietin (EPO) synthesis. Bone marrow (BM) EPO receptor (EPOR) signals are transduced through a JAK2-STAT5 pathway. Anemia of CKD is considered to be of multifactorial origin, including impaired renal EPO synthesis and intestinal iron absorption. EPO resistance in CKD may be an additional factor but its mechanisms are poorly understood. We investigated the HIF- EPO- EPOR axis in kidney, BM and proximal tibia in anemic juvenile CKD rats.

Methods: CKD was induced by 5/6 nephrectomy in young (20 days old) Sprague-Dawley rats while C group was sham operated. An additional control anemic (C-A) group was daily bled for 7 days. Rats were sacrificed 4 weeks after CKD induction and 5 minutes after a single bolus of IV rhEPO (25 U/kg).

Results: Hemoglobin levels were similarly reduced in CKD and C-A (11.7 ± 0.4 and 10.8±0.2 Vs 14.3±0.2 g/dL in C, p<0.0001). Liver hepcidin mRNA was decreased in CA but increased in CKD. Serum iron and transferrin levels were unchanged in CKD. Kidney HIF2α was elevated in C-A but unchanged in CKD. Remnant kidney EPO protein and mRNA levels were unchanged between groups. However, BM EPO protein (which reflects circulating EPO) was increased in C-A but remained unchanged in CKD. BM and proximal tibia EPOR were unchanged in C-A but decreased in CKD. Proximal tibial phsopho-STAT5 increased in C but not in CKD.

Conclusions: Compared to chronic blood loss, anemia in young CKD rats is associated with inappropriate responses: kidney HIF2α and BM EPO are not increased, BM and bone EPOR levels, as well as bone pSTAT5 response to EPO are reduced. This may allow the introduction of additional therapeutic avenues for CKD related anemia beyond iron and EPO supplementation.

TH-PO405

Hepcidin Response to IV Iron Is Different in CKD Compared with Pregnancy and Healthy Controls Lawrence P. McMahon,[1] Louis L. Huang,[1] Darren H. Lee,[1] Iain C. Macdougall.[2] *[1]Department of Renal Medicine, Eastern Health, Box Hill, VIC, Australia; [2]Department of Renal Medicine, King's College Hospital, London, United Kingdom.*

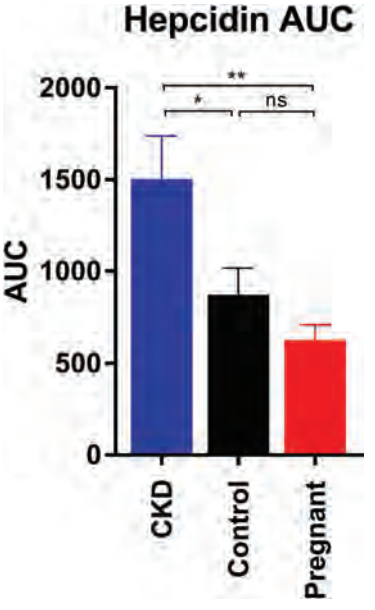
Background: The IDENTIFY Study investigated the effects of IV ferric carboxymaltose (FCM) on markers of bone metabolism in chronic kidney disease (CKD), pregnancy, and healthy controls, but data on iron status were also collected. When the results of the latter were analysed, it became clear that there were differences among the three groups of patients, and the aim of this analysis was to examine this in more detail.

Methods: IDENTIFY was a prospective observational study comprising 1g of IV FCM administered to 3 patient populations: CKD (n=25); healthy Controls (n=20); and Pregnancy (n=20). The following markers of iron status were collected on days 0, 2, 7 and 21: serum iron, ferritin, transferrin saturation (TSAT) and hepcidin (by mass spectrometry).

Results: Following IV FCM, there was a similar increase in serum iron and TSAT in all groups, which peaked at day-2, and returned to baseline at day-7. Ferritin increased to the same extent in all groups, reaching a maximum at day-7, and remaining significantly above baseline at day-21. Serum hepcidin peaked at day-2 in all groups, but the zenith varied (127±61 vs. 106±62 vs. 61±44 ng/mL, p=0.001) and the AUCs differed (1503±1173 vs. 953±718 vs. 629±360, p=0.004) in the CKD, Controls and Pregnancy groups, respectively.

Conclusions: Despite receiving the same dose of FCM, and with comparable levels of haematinics, the rise in hepcidin was significantly greater in CKD patients compared to healthy controls and pregnant women. The reason for this novel finding is unclear, and requires further study. Finally, the ferritin response observed in this study supports a recommendation that following administration of 1g FCM, serum ferritin should not be rechecked for at least 1-month.

Funding: Commercial Support - Vifor



TH-PO406

Oxidative Stress after Intravenous Iron in Dialysis Patients – A Real Phenomenon or an In Vitro Artifact? Jaromir Eiselt,[1] Daniel Rajdl,[2] Lukas Kielberger,[1] Ladislav Trefil.[2] *[1]Dept. of Internal Medicine I, Charles University, Faculty of Medicine in Pilsen, Pilsen, Czech Republic; [2]Inst. of Clinical Biochemistry and Hematology, Charles Univversity, Faculty of Medicine in Pilsen, Pilsen, Czech Republic.*

Background: Intravenous iron can aggravate oxidative stress. However, the presence of the iron preparation in the serum sample may interfere with the determination of oxidative stress markers. The aim of the study was to measure markers of oxidative stress and serum iron after administration of i.v. iron.

Methods: A total of 10 patients on chronic hemodiafiltration (HDF) received in a random order physiological solution (CONTR), 200 mg of ferric carboxymaltose (FC) and 200 mg of iron succrose (IS). Infusions were given from min. 60 to min. 90 of 4 h HDF. In minutes 60, 90, 150 and 240 were measured thiobarbituric acid reacting substances (TBARS), 8-isoprostane (8-iso) and iron in serum. Iron was determined by a routine photometric method (Fe-PHOT) and by an atomic absorption spectrometry (Fe-AAS).

Results: We detected increase of TBARS after both FC and IS, while 8-iso rose only after administration of IS. Levels of serum iron were dramatically higher when using Fe-AAS, than Fe-PHOT. The Fe-AAS method, unlike Fe-PHOT, detects all plasmatic iron, including the one bound in iron-sugar complexes. Results are summarized in table. Changes in TBARS strongly correlated with serum iron measured by Fe-AAS after infusion of both IS (r=0.92, p<0.001) and FC (r=0.79, p<0.0001), but not after CONTR (r=0.23, p=0.133). On the other hand, 8-isoprostane did not correlate with Fe-AAS in any of the three tested treatments.

Conclusions: Immediate effect of i.v. administration of ferric carboxymaltose and iron succrose on oxidative stress of dialysis patients is probably small and difficult to prove with the respect to artifacts in analyses. Measurement of 8-isoprostane does not seem to be affected, compared to TBARS, by a false *in vitro* interference with intravenously administered iron-sugar complexes.

Funding: Government Support - Non-U.S.

	Ferric carboxymaltose	Iron sucrose	Physiol. sol.	P (AUC by ANOVA)
8-iso [ng.h/L]	62 (57-68) [a]	87 (79-93) [b]	69 (52-86)	<0.001
TBARS [µmol.h/L]	4.0 (3.5-4.5) [a,b]	3.1 (2.8-3.5) [b]	2.2 (1.7-2.5)	<0.001
Fe(PHOT) [µmol.h/L]	73 (56-93) [a,b]	139 (107-165) [b]	27 (19-42)	<0.001
Fe(AAS) [µmol.h/L]	1984 (1704-2141) [a,b]	1610 (1214-1729) [b]	59 (44-70)	<0.001

Values are medians (95 % CI) of serial measurements in serum; groups were compared using area under the curve (AUC) by ANOVA; Student-Newman-Keuls test was used for post-hoc pairwise comparisons; a P<0.05 vs. iron suc., b P<0.05 vs. physiol. sol.

TH-PO407

Erythropoietin (Epo) Inhibits Sodium-Driven Pro-Inflammatory Effects Andrea Angeletti,[2,4] Chiara Donadei,[3,4] Vivette D. D'Agati,[1] Miguel L. Fribourg,[2] Gaetano La Manna,[4] Paolo Cravedi.[2] *[1]Columbia University College of Physicians and Surgeons, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]Icahn School of Medicine at Mt. Sinai, New York, NY; [4]Nephrology, DIMES, Bologna, Italy*.

Background: High sodium concentrations promote T cell IL-17 production and injury by increasing intracellular pSGK1. We tested whether EPO, which we previously showed has immune-modulating effects, can counteract sodium-induced human Th17 production in vitro, and in a murine kidney disease model, in which sodium and EPO concentrations are elevated.

Methods: We added EPO or vehicle to human PBMC (n=3-8 donors per experiment) cultured in vitro +/- high [NaCl] or [urea] (osmotic control) and measured T cell proliferation, IL-17/IFNg production, pSGK1 (flow cytometry) and Foxp3 expression. To assess in vivo effects we fed WT B6 mice with normal or high NaCl diet, treated them aristolochic acid (ArA) to induce T cell-mediated interstitial nephritis ± EPO and measured proteinuria and immune responses 6 weeks later.

Results: EPO (but not urea) inhibited human NaCl-driven SGK1 phosphorylation, T cell proliferation (Fig. 1A), and IFNg production (6.7±1.2% vs. 1.8±0.4%, vehicle vs. EPO in the presence of NaCl; P<0.05), without affecting apoptosis/necrosis. EPO prevented Na-driven Th17 induction (1.6±0.3% vs. 0.7±0.3%, vehicle vs. EPO; P<0.05) and increased $CD4^+CD25^+Foxp3^+$ Treg induction/function (Fig. 1B), while maintaining Treg stability. In mice fed a normal or a high NaCl diet, EPO reduced ArA-induced splenic Th1 and Th17 cells, increased Treg and reduced proteinuria (Fig. 1C).

Conclusions: EPO inhibits NaCl-induced proinflammatory T cell immunity in vitro and in vivo, in humans and mice. Our data support the concept of EPO is an immune-modulatory hormone that could physiologically counteract the proinflammatory effects of high intrarenal [NaCl].

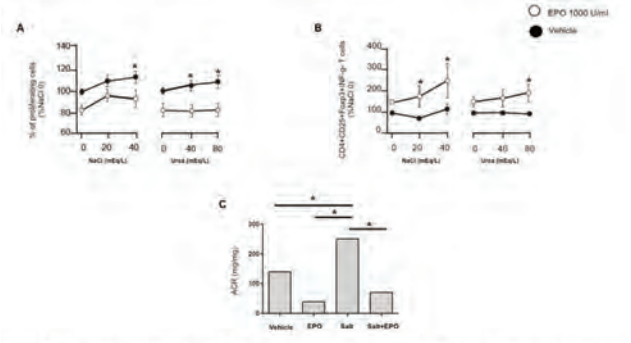


Figure 1. A) Number of human CD4+ T cells at 5 days after activation with aCD3/aCD28 and cultured in the presence of increasing concentrations of NaCl or Urea +/- EPO (data are mean +/- SD of 5 donors, normalized to untreated samples). B) Human naïve CD4+ T cells were cultured in the presence of monocytes, IL-2, and eCD3 in the presence of increasing concentrations of NaCl or Urea +/- EPO. At 5 days, we quantified the percentages of $CD4+CD25+Fxp3+IFNg-$ Treg (data are mean +/- SD of 8 donors, normalized to untreated samples). C) Albumin/creatinine ratio in WT B6 mice fed with regular diet or diet supplemented with NaCl at 3 weeks after aristolochic acid +/- EPO (median values of 3 animals per group).

TH-PO408

The Role of Nrf2/HO-1 Signaling Pathway in Mild Hyperuricemia Promoting the Progress of CKD Zhihong Zhao,[1] Qin Zhou,[1] Hequn Zou.[2] *[1]The Third Affiliated Hospital of Southern Medical University, Guangzhou, China; [2]The 3rd Affiliated Hospital of Southern Medical University, Guangzhou, China*.

Background: Previously it was believed that mild hyperuricemia had no pathogenic effect. However recently it is recognized that mild hyperuricemia can accelerate the progression of chronic kidney disease. The aim of this study was to investigate the role of Nrf2/HO-1 signaling pathway in mild hyperuricemia promoting the progress of chronic kidney disease in a rat model of 5/6 nephrectomy.

Methods: Rats were randomely dividided into five groups (n=8 in each group): Control Group, RK Group (5/6 nephrectomy), OA Group (750mg/kg/d oxonic acid treatment for 6 weeks), RK+OA Group and RK+OA+SFN Group (5mg/kg/d sulforaphane treatment for 6 weeks). Renal function, malondialdehyde (MDA) level, and SOD activity were determinated. Renal pathology was observed by light microscope. Western blot and immunohistochemical assays were used to test the expression of Nrf2, HO-1, P38/p-P38, ERK/p-ERK protein.

Results: Compared with the controls, the level of serum uric acid was increased in the OA Group and RK+OA Group respectively (P<0.05), but not significantly changed in the RK Group (P>0.05). Compared with RK Group, either the level of blood urea nitrogen (BUN), serum creatinine (Scr), 24-h urinary protein output or MDA was increased, the SOD activity was decreased in the RK+OA group(P<0.05). Compared with the RK+OA group, those blood and urine biochemical indices were decreased, MDA level was decreased, the SOD activity was increased, and the renal histological damage was ameliorated in the RK+OA+SFN group (P<0.05). The expression of Nrf2 nuclear protein and HO-1 protein were decreased in RK+OA group compared with either control or RK group, SFN increased the expression of Nrf2 and HO-1 in RK+OA+SFN group, the expression of P-p38 protein and p-ERK protein were decreased (P<0.05).

Conclusions: It is indicated by the results of our present study that mild hyperuricemia accelerated the progression of chronic kidney disease. Furthermore it is suggested by our results that the mechanism of mild hyperuricemia in inducing renal damage might be promoting oxidative stress by inactivating Nrf2/HO-1 signal pathway. It is also suggested that SFN could attenuate the renal injury induced by mild hyperuricemia and its mechanism might be allivateing the oxidative stress injury through activating Nrf2/HO-1 signal pathway. SFN may also affect the activity of ERK signaltransduction pathway.

Funding: Government Support - Non-U.S.

TH-PO409

pNaKtide Attenuates Kidney Dysfunction and Systemic Inflammation by Blocking Na/K-ATPase/Reactive Oxygen Species Amplification in ApoE -/- Mice Athar Nawab,[1] Brian J. Snoad,[2] Hari Vishal Lakhani,[2] Komal Sodhi,[2] Joseph I. Shapiro.[3] *[1]Marshall Health, Morgantown, WV; [2]Marshall University, Huntington, WV; [3]Marshall University School of Medicine, Huntington, WV*.

Background: We have previously reported that the alpha-1 subunit of the sodium potassium adenosine triphosphatase (Na/K-ATPase) acts as an amplifier for reactive oxygen species (ROS) in addition to its ion pumping function. We have also shown that blockade of this amplification with a novel peptide, pNaKtide, ameliorates oxidative stress and obesity in mice subjected to a high-fat diet.

Methods: pNaKtide was administered in ApoE knockout mouse fed western diet. 25 mg/Kg pNaKtide was administered intraperitoneally once every 7 days for 2 months. Lipid profile, ROS levels and plasma creatinine were measured Also, kidney fibrosis was quantified.

Results: pNaKtide administered to these mice significantly decreased plasma triglycerides, FFA, and LDL levels (p<0.05). Further, our results show that ApoE -/- mice fed a western diet had decreased plasma HDL levels and this decrease was reversed by pNaKtide. Plasma ROS levels were also significantly attenuated by pNaKtide treatment. Our results show that pNaKtide improved plasma creatinine and kidney fibrosis in in ApoE-/- mice fed a western diet (p<0.05

Conclusions: This study suggests that the Na/K-ATPase/ROS signaling cascade is a possible mechanism for the development of kidney dysfunction and systemic inflammation associated with the metabolic syndrome phenotype and pNaKtide presents a potential novel treatment for these pathologies.

TH-PO410

Factors Affecting Plasma Linoleic Acid in CKD Malgorzata Sikorska-Wisniewska,[1] Adriana Mika,[2] Tomasz Sledzinski,[1] Alicja Debska-Slizien,[1] Michal Chmielewski.[1] *[1]Medical University of Gdansk, Gdansk, Poland; [2]University of Gdansk, Gdansk, Poland.*

Background: Previous studies have shown that plasma linoleic acid (LA, 18:2n-6) is inversely associated with inflammatory markers and all-cause mortality in dialysis patients. The purpose of the present evaluation was to assess plasma LA percentage content in chronic kidney disease (CKD) subjects, and to evaluate factors that could affect it.

Methods: The study included a cohort of 224 participants, comprised of a group of controls free from any kidney disease (n=54), CKD stage 3-5 patients (n=86), dialysis subjects (n=60), and transplanted patients (n=24). LA amount was analyzed by gas

chromatography with a mass spectrometer detector, and expressed as percentage of total fatty acids of serum lipids. Intake of products rich in LA (nuts, seeds) was evaluated with a validated FFA-6 questionnaire.

Results: LA content decreased with CKD, as it equalled 26.2 ± 0.5% in controls, 24.2 ± 0.4% in CKD stage 3-5 patients, 22.6 ± 0.5% in dialysis subjects, and 24.2 ± 0.8 in kidney transplant recipients (ANOVA F = 7.75; p<0.001). As in previous studies, chronic inflammation, defined here as a persistently elevated hsCRP > 5 mg/L, was associated with decreased plasma LA, as compared to the group with hsCRP within the normal range (22.7 ± 3.6% vs. 25.1 ± 4.1%; p < 0.001). LA content was also inversely correlated with age and BMI. Ingestion of nuts and seeds showed a considerable linear relationship with the plasma LA content (Sperman rho = 0.22; p<0.05). Nevertheless, CKD turned out as an independent predictor of serum LA content, following adjustment for the abovementioned confounders (adjusted R^2 = 0.19; p<0.01).

Conclusions: Serum LA content is decreased in the course of CKD. Taking into account the potential impact of low LA on mortality, increased intake of products reach in this essential fatty acid could be of benefit for CKD patients.

Funding: Government Support - Non-U.S.

TH-PO411

AT2R Deficiency Accelerates Renal Dysfunction in Diabetic Progeny in a Sex-Dependent Manner Min-Chun Liao,[1] Shiao-Ying Chang,[1] Xin-Ping Zhao,[1] Chao-Sheng Lo,[1] Isabelle Chenier,[1] Julie R. Ingelfinger,[2] Shao-Ling Zhang.[1] *[1]CRCHUM, University of Montreal, Montreal, QC, Canada; [2]The New England Journal of Medicine, Boston, MA.*

Background: Angiotensin type 2 receptor (AT_2R) deficient mice (AT_2RKO) exhibit a spectrum of congenital abnormalities of the kidney and urinary tract. We aimed to study whether AT_2R deficiency in dams that also had diabetes mellitus would result in offspring with even more abnormalities in the urinary tract.

Methods: The offspring (male/female) of non-diabetic and diabetic dams of wild-type (WT) and AT_2RKO mice were followed until 20 weeks of age. Systolic blood pressure, insulin sensitivity test (IST), albumin/creatinine ratio (ACR), glomerular filtration rate (GFR), renal morphology and gene expression including angiotensin converting enzyme (ACE), angiotensin converting enzyme 2 (ACE2), synaptopodin (Synpo) and tyrosine phosphatase SHP-1 (qPCR and immunohistochemistry) were assessed.

Results: Compared to the age- and sex-matched offspring of non-diabetic dams, diabetic progeny of both WT and AT_2RKO mice developed more evidence of nephropathy (higher GFR and apparent glomerulosclerosis with podocyte loss) at 20 weeks of age, which were further aggravated in the offspring of AT_2RKO diabetic dams, particularly female mice. Female offspring from diabetic AT_2RKO dams developed insulin resistance, while male diabetic progeny of AT_2RKO dams had normal IST. Renal ACE2, Synpo and SHP-1 gene expression were downregulated in both sex's progenies of diabetic WT dams as well as male offspring of diabetic AT_2RKO dams. In contrast, female offspring of AT_2RKO dams had significant lower basal expression of ACE2, Synpo and SHP-1 genes in their kidneys, and those genes were completely blunted in female progeny of diabetic AT_2RKO dams.

Conclusions: AT_2R deficiency accelerated features of nephropathy in female progeny of diabetic dams, which might be due to loss of the protective effects of ACE2 and SHP1 expression in the kidney.

Funding: Government Support - Non-U.S.

TH-PO412

Therapeutic Targeting of Melanocortin 5 Receptor: A Novel Approach for Protection against AKI Rong Zhou,[1] Yahong Xu,[1,2] Rujun Gong.[2] *[1]Yangpu Hospital of Tongji University, Shanghai, China; [2]Brown Medical School, Providence, RI.*

Background: Melanocortin peptides belong to a neuroimmunoendocrine hormone system that sustains the homeostasis of diverse organ systems. Burgeoning evidence suggests that activation of melanocortin 5 receptor (MC5R) by melanocortin neuropeptides plays a pivotal role in immunoregulation and confers a protective effect in various disease models. Nevertheless, how therapeutic targeting of MC5R affects kidney injury was unknown and explored here.

Methods: Mice were treated with MC5A, a highly selective agonist of MC5R, or with PG20N, a highly selective antagonist, prior to folic acid injury. *In vitro*, primary renal proximal tubular cells (PTC) were injured with tumor necrosis factor (TNF) after MC5A or PG20N treatment. Kidney or cellular injuries were assessed.

Results: Selective activation of MC5R by MC5A strikingly improved the folic acid-elicited acute kidney injury (AKI), as evidenced by a mitigated elevation of serum creatinine, reduced urinary excretion and renal expression of lipocalin-2, diminished tubular damages and tubular cell death, and attenuated renal inflammation. Conversely, selective blockade of MC5R by PG20N exacerbated the folic acid induced AKI. In normal kidney tubulointerstitium, MC5R was sporadically expressed by some renal interstitial cells but absent from renal tubules, as demonstrated by immunohistochemistry, thus underscoring a possible non-tubular cell autonomous effect of MC5R on regulating kidney injury. In support of this, in primary renal PTC, the TNF-instigated apoptosis and production of proinflammatory cytokines, like CCL2, were barely altered by MC5A or PG20N. Rather, inflammatory infiltrations in the folic acid-injured kidney, as probed by CD45 staining, was mitigated by MC5A but amplified following PG20N treatment. In parallel, CD11b+Gr-1+ myeloid-derived suppressor cells (MDSC), which have been shown to mediate a renoprotective tolerogenic response in various types of AKI, were prominently expanded after MC5A treatment but remarkably diminished by PG20N in the injured kidney. Moreover, the kidney protective effect of adoptive transfer of MDSC in folic acid-injured mice was reinforced by MC5A pretreatment of MDSC, but blunted by PG20N, thus denoting a direct modifying effect of MC5R on MDSC.

Conclusions: Altogether, therapeutic targeting of MC5R protects against folic acid AKI likely *via* modulating the tolerogenic MDSC response.

Funding: NIDDK Support

TH-PO413

RhoA Effector mDia1 Contributes to Kidney Injury in the Early Stage of High-Fat Diet Induced Obesity Makiko Naitoh,[4] Hirobumi Tokuyama,[1] Shu Wakino,[2] Hiroshi Itoh.[3] *[1]Internal Medicine, Keio University, Tokyo, Japan; [2]Keio University, Tokyo, Japan; [3]Keio University School of Medicine, Tokyo, Japan; [4]Keio university, Tokyo, Japan.*

Background: Obesity is a critical contributor to kidney damages that are reported to be structurally characterized by glomerulomegaly, tubular hypertrophy and renal hypertrophy. We have previously demonstrated that proximal tubular (PT) hypertrophy occurred in obese mice fed with high-fat diet (HFD) for twelve weeks, which activated RhoA/ROCK signaling leading to inflammatory reaction. However, the early changes which precede this renal tubular cell change and RhoA activation was unclear.

Methods: We used male C57Bl/6J mice with overexpressed dominant negative RhoA genes selectively expressed in the PT ($dnRhoA^{Tg/Tg}$) to suppress RhoA activation. Morphological and biochemical changes were compared between $dnRhoA^{Tg/Tg}$ mice and their wild-type littermates (WT) fed with HFD or low-fat diet (LFD) for 2 weeks. To investigate the molecular mechanism, we utilized tissue culture system with human kidney-2 (HK-2) cells.

Results: Although the body weight, serum insulin and lipid levels were increased in HFD-fed WT mice, fasting glucose levels were not altered as compared with LFD-fed WT mice. HFD-fed WT mice showed no significant renal morphological changes except increased tubular proliferation even two weeks after the initiation of HFD as assessed by Ki67 staining. Although urinary albumin excretion was not altered, the excretion of NGAL was increased in HFD-fed WT mice. Immunoblot analysis revealed increased expression level of one of the RhoA effectors, Diaphanous-related formin-1 (mDia1) and decreased expression level of negative cell cycle regulator p27 in HFD-fed WT mice, while the activity of another RhoA downstream target ROCK was unaltered. Compared with WT on HFD, $RhoA^{Tg/Tg}$ on HFD exhibited less tubular cell proliferation and NGAL excretion. The upregulation of mDia1 and the downregulation of p27 in HFD-fed mice was restored in HFD-fed $RhoA^{Tg/Tg}$ mice. In cultured HK-2 cells, treatment with insulin upregulated mDia1 and downregulated p27, which were ameliorated by siRNA-mediated knockdown of mDia1.

Conclusions: The activation of RhoA/mDia1 pathway in PT promotes PT proliferation in early stage of obesity probably through insulin stimulation. The early activation of RhoA/mDia1 pathway may precede the activation of RhoA/ROCK pathway and may play a critical roles in the initiation process of obesity-induced renal damages.

TH-PO414

Activation of Browning in White Adipose Tissue during CKD Mathilde Luce,[2,1] Nyam Elsa,[3] Christophe O. Soulage,[1] Denis Fouque,[2] Laetitia Koppe.[2,1] *[1]CarMeN, INSERM u1060, INSA LYON, VILLEURBANNE, France; [2]Nephrology, Hospices Civils of Lyon, Lyon, France; [3]Montreal Diabetes Research Center, CRCHUM and Department of Medicine, University of Montréal, Montréal, QC, Canada.*

Background: In patients with chronic kidney disease (CKD), protein energy wasting (PEW) is characterized by an increased resting energy expenditure (REE) although the underlying mechanisms remain poorly understood. Browning corresponds to the activation of inducible brown adipocytes in white adipose tissue (WAT) and participates in cachexia associated with hypermetabolic diseases such as cancers. **The objective of this study is to highlight a phenomenon of browning associated with CKD and to study the potential role of uremic toxins in the activation of this phenomenon.**

Methods: 3T3L1 mouse adipocytes were incubated for 24h with plasma (20% v/v) from healthy volunteers or chronic haemodialysis patients; or with two major uremic toxins (p-Cresyl sulfate and Indoxyl-sulfate). We quantitated the content of uncoupling protein 1 (UCP-1) recognized as a hallmark of browning and studied the adipocytes differentiation. *In vivo*, study was carried out on 5/6 nephrectomy mice with measurement of indirect REE, WAT UCP-1 expression and content after 3 weeks of uremia.

Results: The incubation of 3T3L1 adipocytes with plasmas of uremic patients led to an increase of UCP-1 (+ 153%, p<0.001) compared to the control plasma and inhibited by cycloheximide, a protein synthesis inhibitor. Incubation of adipose cells with uremic toxins at concentrations found in CKD patients failed to alter UCP-1 synthesis or adipocytes differentiation. CKD mice exhibited an increase in REE compared to sham mice consistent with a possible transformation of WAT into brown adipose tissue (BAT) and activation of thermogenesis. Moreover, UCP-1 content is significantly higher in CKD WAT compared to sham mice (p = 0.02) with an increase in the expression of several thermogenesis genes in the WAT of CKD mice (e.g. UCP-1, PGC1α and PRMD16).

Conclusions: Taken together, these data, suggest the activation of a browning phenomenon during CKD. Uremic toxins do not appear to participate in this phenomenon although p-Cresyl sulfate was previously shown to induce adipocyte dysfunction *in vitro*. **The activation of browning in WAT could contribute to malnutrition associated with CKD through an increase in thermogenesis and REE. Further works are needed to decipher the molecular determinants of the browning associated with CKD.**

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO415

Oral NaHCO3 Activates the Splenic Anti-Inflammatory Pathway Promoting M2-Macrophage Polarization Paul O'Connor, Babak Baban, Sarah C. Ray, Matthew Tucker, Ryan A. Harris. *Augusta University, Augusta, GA.*

Background: Oral sodium bicarbonate ($NaHCO_3$) may slow decline in kidney function in CKD, yet the mechanisms mediating this beneficial effect remain unclear. In the current study we tested the hypothesis that oral $NaHCO_3$ intake promotes anti-inflammatory-M2 macrophage polarization by activating the splenic anti-inflammatory pathway in both rats and humans.

Methods: 8-10 week old male Sprague Dawley rats maintained on a standard pellet diet with water *ad libitum* were utilized. To determine the effect of oral $NaHCO_3$ on macrophage polarization, drinking water was replaced with solutions of $NaHCO_3$ in tap water containing (0, 0.01, 0.05 or 0.1M $NaHCO_3$; n=3 per treatment group) with all solutions made equimolar (0.1M) with the addition of NaCl. Following 4 days of drinking $NaHCO_3$, rats were anesthetized, the left kidney and spleen harvested and prepared for flow cytometry analysis. In a separate study, 7 healthy volunteers were given a single dose of $NaHCO_3$ following an overnight fast. Venous blood was drawn for flow cytometry analysis, at baseline and 1 and 2 hours following ingestion of 2g of $NaHCO_3$ in 250 ml of bottled water.

Results: We found that addition of $NaHCO_3$ to the drinking water of rats resulted in a dose dependent increase in renal macrophage polarization away from an M1 (inflammatory) and toward an M2 (anti-inflammatory) phenotype with as little as 3 days of drinking 0.01M $NaHCO_3$ solution (P_{DOSE}=0.02). Most of the polarization effect could be attributed to an increase in renal M2 macrophages, with the % of renal cells identified as M2's increasing from 2% to 8% at the highest dose of $NaHCO_3$ (0.1M; P_{DOSE}=0.006). The effect of 0.1M $NaHCO_3$ on renal macrophage polarization was confirmed in a separate group of rats (n=5/5; P=0.007) and was abolished with prior splenectomy. In human blood, T-cells were reduced from 15.6±0.8 at baseline to 13.0±0.8% of all leukocytes at 2 hours post $NaHCO_3$ ingestion; (P=0.01). Inflammatory cells, M1 macrophages (P=0.054) and Th17+ cells (P=0.06), tended to decrease, whereas, M2 macrophages tended to increase from 48.4±1.2 at baseline to 50.9±0.4% of all macrophages 2 hours post $NaHCO_3$ (p=0.054).

Conclusions: Our data indicate that oral $NaHCO_3$ may activate the splenic anti-inflammatory pathway in rats and humans. Activation of these pathways may underlie part of the beneficial effects of $NaHCO_3$ observed in CKD patients.

Funding: NIDDK Support

TH-PO416

Expression of T Regulatory Cells in the Kidneys of Guanylyl Cyclase/Natriuretic Peptide Receptor-A Gene-Knockout Mice Venkateswara R. Gogulamudi, Umadevi Subramanian, Kailash N. Pandey. *Department of Physiology, Tulane University Health Sciences Center, School of Medicie, New Orleans, LA.*

Background: Background: Guanylyl cyclase/natriuretic peptide receptor-A (GC-A/NPRA) gene (*Npr1*) disruption activates the pro-inflammatory responses in null mutant mice. There is increasing evidence that imbalanced immune responses play important role in physiological changes and complications of hypertension leading to organ damage. T Regulatory cells are defined as vital immune cellular population and they are likely to aid in immune tolerance by dampening the harmful effects of the other immune cellular population. The objective of our study was to elucidate the role of T regulatory cell markers and their expression levels in *Npr1* gene-disrupted mice.

Methods: Methods: In the present study, 0-copy (*Npr1*$^{-/-}$), 1-copy (*Npr1*$^{+/-}$), and 2-copy (*Npr1*$^{+/+}$) mice were pre-treated with rapamycin (2mg/kg/day) for 14 days. Spleen was collected, T cells were pre-enriched from spleen by using magnetic separation columns, and phenotypic expression of T regulatory subsets ($Foxp3^+$, $CD25^+$ and $CD4^+$) were determined by flow cytometry.

Results: Results: The *Npr1* gene-disrupted mice displayed the significant reduction of $Foxp3^+$ expression in 0-copy (77.5%) and 1-copy (71.5%) mice compared with 2-copy wild-type mice. Similarly, $CD25^+$ expression was reduced in 0-copy (75%) and in 1-copy (60%) mice compared with wild-type controls. In contrast, the total $CD4^+$ count was potentially up-regulated by 40% in 0-copy and 31% in 1-copy mice compared with 2-copy control mice. Treatment with rapamycin showed a substantial increase of $Foxp3^+$ cells by 17.38% (P<0.001) in 0-copy and 8.23 % (P<0.001) in 1-copy mice and $CD25^+$ T cells by 62.2% (P<0.001) in 0-copy and 38.1 % (P<0.001) in 1-copy mice.

Conclusions: Conclusions: The present results demonstrate that plummeting levels of T regulatory cells in *Npr1* gene-disrupted 0-copy and 1-copy mice provoke inflammatory responses in the kidney compared with wild-type mice. The treatment of 0-copy and 1-copy mice with rapamycin renders elevation of Tregs, suggesting the potential roles of *Npr1* in down-regulation of pro- inflammatory renal immune conditions.

Funding: Other NIH Support - NIH/NHLBI

TH-PO417

Tissue-Type Plasminogen Activator Modulates Macrophage M2 to M1 Phenotypic Change through Annexin A2-Mediated NF-κB Pathway Ling Lin, Kebin Hu. *Penn State University College of Medicine, Hershey, PA.*

Background: Macrophage accumulation is one of the hallmarks of progressive kidney disease. In response to injury, macrophages undergo a phenotypic polarization to become two functionally distinct subsets: M1 and M2 macrophages. Macrophage polarization is a dynamic process, and recent work indicates that macrophages, in response to kidney injury, can shift their polarity. However, the underlying mechanisms remain largely unknown. Tissue-type plasminogen activator (tPA), a protease up-regulated in the chronically injured kidneys, has been shown to preferably promote M1 macrophage accumulation and renal inflammation. We hypothesized that tPA may be an endogenous factor that modulates macrophage M2 to M1 phenotypic change contributing to the accumulation of M1 macrophages in the injured kidneys.

Methods: We used integral *in vivo* and *in vitro* approaches to investigate the role of tPA in macrophage polarity shift, and clarified the underlying signaling mechanim.

Results: It was found that obstruction-induced renal M1 chemokine expression was alleviated in tPA knockout mice, and these knockout mice displayed increased M2 markers. *In vitro*, resting J774 macrophages were treated with IL-4 to induce M2 phenotype as indicated by de novo expression of arginase 1, Ym1, and IL-10, as well as suppression of iNOS, TNF-α, and IL-1β. Intriguingly, these IL-4-induced M2 macrophages, after tPA treatment, not only lost their M2 markers such as arginase 1, Ym1, and IL-10, but also displayed increased M1 chemokines including iNOS, TNF-α, and IL-1β. Possible endotoxin contamination was also excluded as heat-inactivated tPA lost its effect. Additionally, tPA-mediated macrophage M2 to M1 phenotypic change required its receptor annexin A2, and SN50, a specific NF-κB inhibitor, abolished tPA's effect.

Conclusions: It's clear that tPA promotes macrophage M2 to M1 phenotypic change through annexin A2-mediated NF-κB pathway.

Funding: NIDDK Support, Other NIH Support - American Heart Association

TH-PO418

Rubicon Deficiency Leads to Obesity by Promoting Excessive Lipid Efflux in Proximal Tubular Epithelial Cells Jun Matsuda,[4] Atsushi Takahashi,[5] Yoshitsugu Takabatake,[4] Takeshi Yamamoto,[4] Tomonori Kimura,[2] Tomoko Namba,[4] Satoshi Minami,[3] Shinsuke Sakai,[2] Ryuta Fujimura,[1] Jun-Ya Kaimori,[4] Isao Matsui,[4] Fumio Niimura,[6] Taiji Matsusaka,[6] Yoshitaka Isaka.[4] *[1]Osaka University Graduate School of Medicine, Suita, Japan; [2]Osaka University Graduate School of Medicine, Suita, Japan; [3]Osaka University Graduate School of Medicine, Suita, Osaka, Japan; [4]Osaka University Graduate School of Medicine, Suita, Japan; [5]Osaka University Graduate School of Medicine, Suita, Japan; [6]Tokai University School of Medicine, Isehara, Japan.*

Background: Autophagy is a lysosomal degradation system which contributes to maintain nutritional status. It has been known that Rubicon (Run domain Beclin-1 interacting and cysteine-rich containing protein) negatively regulates autophagic activity by inhibiting the fusion of autophagosomes and lysosomes. However, its physiological role in proximal tubular epithelial cells (PTECs) remains poorly understood.

Methods: We analyzed the phenotype of newly generated PTEC-specific Rubicon-deficient mice (KO mice). We crossed KO mice with GFP-MAP1LC3 transgenic mice, in which GFP-positive puncta reflect autophagosomes, and evaluated autophagic flux by comparing the number of GFP-positive dots with or without chloroquine administration. We finally investigated the role of Rubicon in lipid metabolism using isolated Rubicon-deficient PTECs.

Results: The number of autophagosomes was increased after chloroquine administration even during the fed state in the PTECs of 3-month-old KO mice, indicating sustained high autophagic flux. When fed standard mouse chow, KO mice began to exhibit a significant increase in body weight compared with controls after the age of 4 months (12-month-old KO mice: 45.9 ± 5.2 kg vs controls: 38.5 ± 6.8 kg, P<0.01). At 12 months of age, we observed a gain of weight in liver and adipose tissue, fatty liver, impaired glucose tolerance, and hypercholesterolemia. Immunohistochemical and electron microscopic analysis revealed expanded lysosomes containing multi-layered phospholipids in the PTECs of 12-month-old KO mice. Isolated Rubicon-deficient (KO) and wildtype (WT) PTECs were loaded oleic acid (OA)-bound albumin to induce the formation of lipid droplets (LDs). Rubicon KO PTECs showed more rapid degradation of LDs compared with WT PTECs. Furthermore, cultured hepatocytes (BNL-CL2 cells) exhibited a significant increase in LD formation when co-cultured with OA-loaded KO PTECs compared with OA-loaded WT PTECs. These results suggest an accelerated lipid efflux from KO PTECs to blood circulation.

Conclusions: Rubicon deficiency in PTECs leads to systemic lipid accumulation and obesity by promoting excessive lipid efflux. Rubicon in PTECs can be a therapeutic target for metabolic syndrome.

TH-PO419

Knockdown of Ugcg Induces Kidney Autoimmune Disease Tess Dupre,[6] Cierra Sharp,[6] Mark A. Doll,[6] Ying Sun,[2] Judit Megyesi,[5] Levi J. Beverly,[4] Tamara Nowling,[3] Deanna L. Davis,[7] Leah J. Siskind,[6] Richard R. Drake,[3] Wujuan Zhang.[1] *[1]CCHMC, Cincinnati, OH; [2]Cincinnati Children's Hospital, Cincinnati, OH; [3]Medical University of South Carolina, Charleston, SC; [4]University Of Louisville, Louisville, KY; [5]University of Arkansas for Medical Science, Little Rock, AR; [6]University of Louisville, Louisville, KY; [7]Virginia Commonwealth University, Richmond, VA.*

Background: Glycosphingolipids (GSLs) play a role in autoimmune kidney diseases, including lupus nephritis. Autoimmune kidney diseases are associated with chronic inflammation and recruitment of immune cells into the kidney. N-glycans play a role in regulating inflammatory pathways in autoimmune diseases. Importantly, data in the literature suggest interplay between GSL and N-glycan biosynthetic pathways that may be important in regulating inflammatory responses.

Methods: We generated transgenic mice containing an inducible shRNA that targets expression of Ugcg (Tet-O-shUgcg). Ugcg is the gene that encodes for glucosylceramide synthase, the enzyme that catalyzes synthesis of glucosylceramide from ceramide. Tet-O-shUgcg mice were bred with $CAG^{+/-}$rtTA3 mice (CAG-rtTA3-Tet-O-shUgcg) for universal expression of the shRNA in the presence of doxycyline.

Results: Following Ugcg knockdown (KD), organized accumulations of $CD19^+$ B cells and $CD3^+$ T cells formed in the kidneys, which are defining features of tertiary lymphoid organs (TLOs). TLOs are ectopic accumulations of lymphoid cells that can arise in areas of chronic inflammation via lymphoid neogenesis. Data indicate that knockdown of Ugcg in kidney results in significant increases in levels of biantennary N-glycans relative to control, and decreases in branched multi-fucosylated glycans normally present in control kidneys. KD of Ugcg increases serum levels of total IgG and IgA.

Conclusions: KD of Ugcg alters N-glycan signatures in the kidney, induces TLO formation, and autoimmunity. This transgenic mouse model is novel tool for studying the role of GSLs and N-glycans in kidney inflammation and autoimmunity and may represent a new mouse model of autoimmune kidney disease.

Funding: NIDDK Support

TH-PO420

ACF-TEI, a Novel Oral Adsorbent, Shows Potent Adsorption Effect on Uremic Toxin in the Rat Model and the System Mimicked Human Gastrointestinal Tract

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Background: Uremic toxins (UTs), such as indoxyl sulfate (IS) and *p*-cresyl sulfate (PCS), accumulate in the blood of patients with impaired renal function. Since several studies have demonstrated a link between serum UTs levels and clinical outcomes, they draw much attention as key factors in the progression of chronic kidney diseases (CKDs) and cardiovascular diseases. Thus, adsorbing UTs in the intestinal tract and excreting with feces is effective for inhibiting the progression of CKDs and delaying the introduction of dialysis treatment. We have identified a novel oral UTs adsorbent, ACF-TEI, which has more potent adsorption profiles to UTs than existing adsorbents. In this study, we examined *in vitro* adsorption capacities of ACF-TEI to several UTs and the reducing effect of ACF-TEI on serum UTs in CKD model rats. In addition, to estimate the effectiveness of ACF-TEI in human, we evaluated the effect of ACF-TEI on UT adsorption in a system that mimicked human gastrointestinal (GI) tract.

Methods: ACF-TEI was mixed with solutions of indole, the precursor of IS produced by enterobacteria, or other UTs and reacted, then the adsorption capacity was calculated. ACF-TEI was administered orally to bilateral nephrectomized rats, and then concentrations of serum IS and PCS were measured. Adsorption of indole in the human GI tract was estimated using dynamic multi-compartmental GI tract model.

Results: ACF-TEI showed higher adsorption capacity to indole and other UTs than existing adsorbent. In the bilateral nephrectomized rats, ACF-TEI dose-dependently reduced serum IS and PCS levels and the effects were more potent than the existing adsorbents. In the dynamic multi-compartmental GI tract model, ACF-TEI reduced colonic indole concentration at lower doses than the existing adsorbents.

Conclusions: ACF-TEI adsorbed various UTs and showed the potent effects not only in the rodent model but also in the human GI tract mimicked system. Therefore, in clinical, ACF-TEI is expected to show potent UTs reducing effect and to be beneficial for patients with CKDs.

TH-PO421

Gut Microbiota-Dependent Trimethylamine-N-Oxide and Inflammatory Biomarkers in Patients with Diabetic Nephropathy

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Background: Trimethylamine N-oxide (TMAO) is a product of diet, gut microbiome, and tissues metabolism. Elevated TMAO levels associated with heart attack, stroke and chronic kidney disease (CKD). We investigated the gut microbiome composition and TMAO levels in the serum of patients with type 2 diabetes mellitus (T2DM) and advanced stages of diabetic nephropathy (DN); and TMAO association with serum IL-6, TNFα, CRP, ET-1, LPS, and zonulin.

Methods: Twenty adult patients with T2DN and CKD 3-4 secondary to DN and 20 healthy subjects (HS) participated in the study. The analysis included: nutrition, metabolic parameters, trimethylamine (TMA) producing gut microbiota, and TMAO, LPS, zonulin and serum biomarkers of inflammation and endothelial dysfunction. The gut microbiota diversity identified by amplified V5-V6 region of the 16S ribosomal RNA (rRNA) genes and DNA sequencing by the MiSeq (Illumina Inc., San Diego, CA) using a 600 cycle v3 sequencing kit. The TMAO quantified by LC/MS method and serum biomarkers by ELISA.

Results: Dietary analysis showed that patients with T2DM and DN consumed less protein and more fat compared to HS and had more than two-fold elevated levels of triglycerides. The gut microbiome in DN patients exhibited a higher abundance of TMA-producing bacteria, $p < 0.05$. The serum level of TMAO in patients with DN was significantly higher (2.7 ± 0.52 μg/ml) compared to HS (0.43 ± 0.1 μg/ml), $p < 0.05$. The IL-6 and ET-1 also showed higher levels in the DN patients and positive correlation with TMAO. A positive correlation also observed between zonulin and LPS in both DN and HS groups.

Conclusions: Gut microbiota in patients' with T2DM-CKD has increased abundance of TMA-producing bacteria, which together with excessive dietary TMAO and increased gut permeability possess substantial risk for cardiovascular health through increased level of chronic inflammation and endothelial dysfunction. The pilot study findings are worth perusing further evaluation.

Funding: Clinical Revenue Support

TH-PO422

Homocysteine Aggravates Intestinal Permeability Increase and Tight Junction Destruction In Vivo and In Vitro

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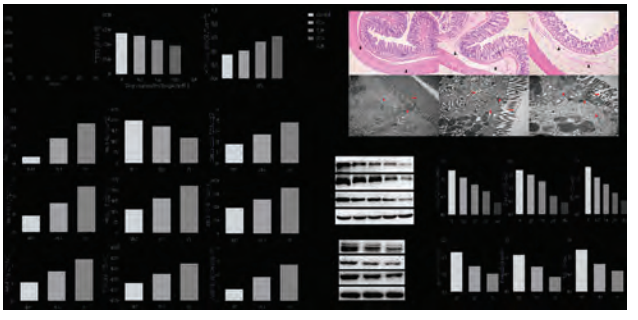
Background: Intestinal injury is a common complication of uremia. Homocysteine (Hcy), as an important intestinal derived uremic toxin and pro-inflammatory molecule, whether it is involved in the increased intestinal permeability and epithelial barrier dysfunction in uremia remains unclear. This study aimed to investigate the effect of Hcy on intestinal epithelial in vitro and in vivo.

Methods: In vitro experiment, Caco2 cells were seeded on transwell plates and utilized when transepithelial electrical resistance (TEER) exceeded 500Ω*cm^2 to ensure full polarization and TJ formation. Cells were then incubated with Hcy (0.5 to 5.0mmol/L) for 24h. Paracellular permeability was determined by TEER and the fluorescent Lucifer yellow dye (FLY) flux across cell monolayers. In vivo experiment, SD rats were divided into control, uremia (induced by adenine) and uremia + vitamin B compounds (folate, vitamin B6 and B12) group. Serum Hcy levels, colon homogenate of Hcy, inflammatory factors (CRP, IL-6 and TNF-α), SOD, MDA, endotoxin and intestinal permeability were assessed. H&E and transmission electron microscopy were used for pathological analysis. TJ proteins of claudin-1, occludin, and ZO-1 were assessed by western blot.

Results: Fig.1 showed the TEER changes of Caco-2 cells during 21 days and the decreased TEER as well as the gradually increased FLY flux rates after Hcy incubation. Hcy down regulates TJ protein abundance in a concentration-dependent manner (Fig 4A), which was accompanied with the increased epithelial permeability. In animal experiments, uremia group showed elevated Hcy levels, oxidized inflammatory factors and intestinal permeability (Fig 2). The pathological changes of colon were obviously observed (Fig 3) with TJ protein levels decreased (Fig 4B). Fortunately, these parameters were improved in varying degrees after vitamin B compounds treatment.

Conclusions: Hcy aggravates intestinal permeability increase and epithelial barrier destruction by stimulating oxidative inflammatory damage. Supplementation of folate, vitamin B6 and B12 can improve the damage to some extent by reducing Hcy.

Funding: Government Support - Non-U.S.



TH-PO423

Inhibition of Glycolysis Attenuates Ischemia-Reperfusion Injury via Metabolic and Redox Changes in Proximal Tubular Cells

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Background: Proximal tubular cells utilize fatty acid oxidation (FAO) more than glycolysis for ATP production in the physiological state. However, it remains largely unknown whether their metabolism affects pathophysiology of renal diseases. In this study, we investigated effects of glycolysis inhibition with 2DG, a representative glycolysis inhibitor, on murine renal ischemia-reperfusion injury (IRI), to which proximal tubular cell (PTC) injury by oxidative stress is central.

Methods: Eight-week-old male C57BL/6J mice were treated with 500 mg/kg 2DG or vehicle by i.p. 24 hours before bilateral IR, and renal injury was evaluated on day 1. We also examined effects of 2DG on PTCs, using HK-2 in vitro. HK-2 cells were treated with 5 mM 2DG for 6 hours and exposed to oxidative stress with 4 mM hydrogen peroxide. Cytotoxicity was measured with generation of reactive oxygen species (ROS) assessed by flow cytometry using dihydroethidium and LDH assay.

Results: Glycolysis inhibition by 2DG ameliorated renal dysfunction on day 1: serum creatinine was 1.4 ± 0.4 mg/dL in the vehicle group and 0.9 ± 0.1 mg/dL in the 2DG group. The reduced IRI was also demonstrated by a decrease in histological tubular injury score and mRNA expression of Kim-1 in the 2DG group. 2DG-preconditioned kidney cortex showed far less phospho-AMPK in immunoblot, indicating increased ATP in PTCs, which can suppress cell injury and death in IRI. We investigated its mechanism and found that

2DG increased free fatty acid in serum and PPARα expression in the kidney, suggesting that activated FAO promoted ATP production in PTCs. In vitro, treatment with 2DG suppressed generation of ROS and cell death. We focused on pentose phosphorylation pathway (PPP), because glycolysis inhibition can promote PPP as a bypass of glucose metabolism, and its key function is generation of reducing equivalents of NADPH. Indeed, PPP enzymes, including glucose-6-phosphate dehydrogenase and transketolase, were up-regulated, and NADPH/NADP ratio was increased by 2DG. We also found that glutathione peroxidases, key antioxidative enzymes, were induced by 2DG.

Conclusions: In conclusion, glycolysis inhibition ameliorated renal IRI via an ATP increase by enhanced FAO and a favorable redox state by promoted PPP in PTCs, implicating the importance of PTC metabolism in renal diseases.

TH-PO424

Combined Treatment with Cholecalciferol and Omega-3 Fatty Acid Modulates Molecules Associated with Sarcopenia and Cardiac Hypertrophy in 5/6 Nephrectomy Rats

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Background: Cardiac hypertrophy and sarcopenia are common in dialysis patients and result in high probability for morbidity and mortality. Akt-mTOR axis is related with cardiac hypertrophy and muscle atrophy. The present study aimed to investigate whether omega-3 fatty acid (O-3FA) and cholecalciferol (Vit. D) affect on molecules associated with cardiac hypertrophy and sarcopenia in 5/6 Nx. rats.

Methods: Male Sprague Dawley rats were divided into 5 groups and treated for 6 weeks: sham control, 5/6 subtotal Nx control, 5/6 Nx treated with Vit.D, 5/6 Nx treated with O-3 FA, 5/6 Nx treated with Vit. D and O-3 FA. The expression of myostatin, myogenin, MyoD, Akt, phosphrylated(p) Akt and mTOR were examined by western blot analysis.

Results: Serum BUN and creatinine were the lowest in 5/6 Nx group treated with O-3 FA and Vit. D among other 5/6 Nx groups. Compared with sham control, 5/6 Nx control significantly up-regulated myostatin and down-regulated myogenin and MyoD in both cardiac and skeletal muscle. Increased expression of myostatin and decreased expression of myogenin and MyoD of cardiac and skeletal muscle were recovered by combined treatment with O-3 FA and Vit. D. Phosphorylated Akt and mTOR were up-regulated in the cardiac muscle but down-regulated in the skeletal muscle of 5/6 Nx control compared to sham control. Combined therapy of O-3 FA and Vit. D decreased p-Akt and mTOR expression in cardiac muscle and increased p-Akt and mTOR expression in skeletal muscle of 5/6 Nx rats.

Conclusions: Combined therapy of O-3 FA and Vit. D may be helpful for decreasing cardiac hypertrophy and sarcopenia by increasing myogenin and MyoD, decreasing myostatin and modulating Akt-mTOR axis in both cardiac and skeletal muscle of 5/6 Nx rats.

Funding: Private Foundation Support

Laboratory results

	Normal control	5/6 Nx	5/6 Nx with Vit. D	5/6 Nx with O-3 FA	5/6 Nx with O-3 FA and Vit. D	P value
BUN(mg/dL)	17.7±1.5	77.7±28.4*	75.3±22.1*	63.9±17.0*a	51.3±8.7*ab	0.003
Creatinine(mg/dL)	0.4±0.0	1.3±0.6*	1.2±0.3*	1.0±0.3*	0.8±0.1*abc	0.002

Data are expressed as mean ± SD

*P value < 0.05 (mean values are significantly different from control)

aP value < 0.05 (mean values are significantly different from 5/6 nephrectomy group)

bP value < 0.05 (mean values are significantly different from 5/6 nephrectomy c Vitamin D group)

cP value < 0.05 (mean values are significantly different from 5/6 nephrectomy c omega-3 FA group)

TH-PO425

Combination of Cholecalciferol and Omega-3 Fatty Acid Increases 1, 25 Dihydroxy Vitamin D Level by Inhibiting 24-Hydroxylase of Kidney and Liver in 5/6 Nephrectomized Rats

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Background: The 1α-hydroxylase (CYP27b1) and 24-hydroxylase (CYP24) in renal proximal tubules primarily involve vitamin D metabolsim. Increased activity of CYP24 contributes vitamin D metabolism in chronic kidney disease (CKD). Recent reports showed that CYP27b1 was strongly expressed in monocytes developing into hepatic macrophages and omega-3 fatty acid (FA) elevated 1, 25-dihydroxy vitamin D level in dialysis patients with scanty renal function. In this study, we evaluated whether the effect of omega-3 FA and cholecalciferol on vitamin D metabolism are related with the activity of CYP27b1 and CYP24 in liver and kidney of 5/6 nephrectomy (Nx) rat model.

Methods: Male Sprague Dawley rats were divided into five groups and treated for 6 weeks: sham control (0.9% saline), 5/6 Nx control (0.9% saline), 5/6 Nx treated with vitamin D (cholecalciferol 3000 IU/kg/week by gastric gavage), 5/6 Nx treated with omega-3 FA (300 mg/kg/day by gastric gavage), 5/6 Nx treated with vitamin D and omega-3 FA. CYP27b1 and CYP24 in remnant kidney and liver were measured by western blot analysis.

Results: Serum BUN and creatinine were the lowest in 5/6 Nx group treated with omega-3 FA and vitamin D among other 5/6 Nx groups. The levels of serum 1, 25-dihydroxy vitamin D and 25-hydroxy vitamin D were the highest in 5/6 Nx group treated with omega-3 FA and vitamin D among other 5/6 Nx groups. The expression of CYP24 was significantly increased in remnant kidney and liver of 5/6 Nx control compared to sham control. Increased expression of CYP24 in remnant kidney and liver of 5/6 Nx control was significantly decreased by combined treatment with omega-3 FA and cholecalciferol. The expression of CYP27b1 was significantly increased in remnant kidney and significantly decreased in liver of 5/6 Nx control compared to sham control. The increased expression of CYP27b1 in remnant kidney and decreased expression of CYP27b1 in liver of 5/6 Nx control was nearly normalized by combined treatment with omega-3 FA and vitamin D.

Conclusions: Combined treatment with omega-3 FA and cholecalciferol definitely increases 1, 25-dihydroxy vitamin D level by inhibiting expression of 24-hydroxylase in remnant kidney and liver and activating expression of 1 α-hydroxylase in liver of 5/6 Nx rats.

TH-PO426

Correlation between Vitamin D Deficiency and Hematuria: Korean National Health and Nutrition Examination Survey

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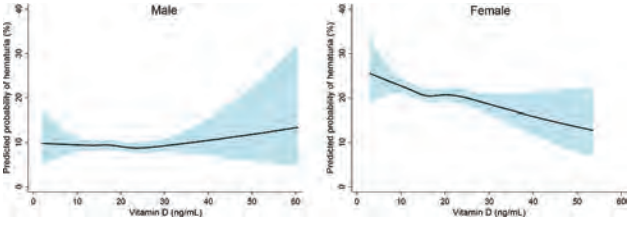
Background: Vitamin D deficiency is an important health concern because it is related with several comorbidities and mortality. However, its relationship with the risk of hematuria remains undetermined in the general population.

Methods: Cross-sectional analysis was applied to the subjects (n=20,240, aged ≥18 years old) using Korean National Health and Nutrition Examination Survey (KNHANES) 2010–2014. Serum 25-hydroxyvitamin D [25(OH)] levels were measured in a central laboratory and hematuria was defined as ≥1+ on a dipstick test. Multivariate logistic regression was conducted to calculate the odds ratio (OR) of hematuria risk according to the 25(OH)D quartiles, after adjusting 10 covariates, such as comorbidities and laboratory findings.

Results: Of study subjects, 10,847 (53.6%) were female and 5,388 (26.6%) were identified as menopause. The mean age and estimated glomerular filtration rates were 49±16.3 year old and 88±17.4 mL/min/1.73m^2, respectively. The number of subjects with hematuria was 3,144 (15.5%). The mean 25(OH)D level was 17.4±6.2 ng/ml [median, 16.6 ng/ml (interquartile range, 13.1–20.8 ng/ml)]. The 3rd and 4th quartiles had a higher risk of hematuria than the 1st quartile, as following adjusted ORs; 1.1 (1.02-1.29) and 1.3 (1.12-1.42) in the 3rd and 4th quartiles, respectively. However, this relationship was only significant in the female subjects, not in the male subjects [Figure]. Subsequent analyses were stratified according to the menopausal status. For the premenopausal females, there was no significant increase of hematuria risk according to the quartiles. However, for the postmenopausal females, the increased risk of hematuria was shown in all the higher quartiles, compared with the 1st quartile.

Conclusions: Vitamin D deficiency was correlated with hematuria in female subjects, particularly after menopause. Further interventional studies are warranted to address whether the correction of vitamin D deficiency lowers the hematuria risk.



TH-PO427

Restriction of Both P and Caloric Intake Decrease Renal Damage Induced by Cafeteria-Style Diet

Ignacio Lopez,[1] Paula Esquinas,[3] Rafael Rios-Varo,[1] Carmen Pineda,[1] Ana isabel Raya bermudez,[1] Mariano Rodriguez,[2] Escolastico Aguilera-tejero.[1] *[1]Animal Medicine and Surgery, University of Cordoba, Cordoba, Spain; [2]Hospital Universitario Reina Sofia, Cordoba, Spain; [3]Universidad Nacional de Colombia, Bogota, Colombia.*

Background: Energy dense diets, which also tend to be rich in P (cafeteria-style diets), are associated to metabolic syndrome, diabetes and kidney disease. In this study, renal damage after feeding a diet rich in P and calories was investigated. In addition, the influence of P and caloric intake restriction on renal pathology was assessed.

Methods: Wistar rats (n=32) were divided in 4 groups (n=8) and fed either: normocaloric (3518 kcal/kg) with normal P (0.6%) diet (NC-NP), hypercaloric (5241 kcal/kg) with high P (1.2%) diet (HC-HP), HC with low P (0.2%) diet (HC-LP), and hypocaloric (1314 kcal/kg) with HP diet (hC-HP). After 210 days, renal tissue was obtained and processed for optical (OM) and electronic microscopy (TEM). Lesions were

graduated with a semi-quantitative scale of 0-3: 0 (absent), 1 (mild), 2 (moderate) and 3 (severe) or in percentage.

Results: The table 1 shows OM scores. Feeding HC-HP diet resulted in significant renal lesions. Both P and caloric restriction attenuated renal damage. P restriction was more effective at preventing nephrocalcinosis while caloric restriction was more effective at preventing glomerular damage. Ultrastructurally, TEM lesions correlated to OM lesions. The main alterations observed in the HC-HP group by TEM were: hyperactivity of the epithelial and mesangial cells, capillary remodeling, tubular atrophic changes and increased fibroblast and cell inflammatory activity. These lesions were attenuated in the HC-LP and hC-HP groups.

Conclusions: In conclusion, the results suggest a synergistic deleterious effect of high caloric and high phosphorus intake on the kidney. Both P and caloric restriction can attenuate renal damage although their influence on renal pathology show differential characteristics.

Funding: Government Support - Non-U.S.

Table1

	Glomerular Retraction (%)	Basal Membrane Thickness (0-3)	Tubular Dilatation (0-3)	Tubular Atrophy (0-3)	Fibrosis (0-3)	Calcification (0-3)
NC-NP	10,00±3,77a	0,00±0,00a	0,75±0,46a	0,12±0,33a	0,00±0,00a	0,00±0,00a
HC-HP	38,5 ± 4,81b	1,88 ± 0,35b	2,25 ± 0,70b	1,75 ±0,46b	2,25 ± 0,70b	2,25 ± 0,70b
HC-LP	16,5±2,26c	1,50±0,53c	1,25± 0,46a	0,75±0,70c	0,75±0,46c	0,00±0,00a
hC-HP	12,50±3,29a	1,12±0,35c	1,12±0,83a	0,96±0,35c	1,12±0,64c	0,625±0,51c

Values are mean ±SE; a,b,c For each parameter, data with different superscripts are significantly ($P < 0.05$) different between diets.

TH-PO428

Calciprotein Particle Contributes to the Synthesis and Secretion of Fibroblast Growth Factor 23 Induced by Dietary Phosphate Intake Kenichi Akiyama.[1,2] *[1]Tokyo Women's Medical University, Tokyo, Japan; [2]Center for Molecular Medicine, Jichi Medical University, Shimotsuke, Japan.*

Background: It has been reported that the synthesis and secretion of fibroblast growth factor 23 (FGF23) induced by phosphate also require calcium. However this mechanism is still unclear. Highly concentrated phosphate and calcium are crystallized and formed calciprotein particle (CPP) with some proteins including fetuin-A in extracellular fluid. CPP is considered the pathogenesis of some complications such as an inflammatory response in chronic kidney disease. The role of CPP on the synthesis and secretion of FGF23 was investigated.

Methods: Rat osteoblastic cell line (UMR-106 cell) was treated by various dose of phosphate or artificially made CPP for 4 and 24 hours. Protein level of FGF23 in the medium and mRNA expression level of FGF23 were analyzed. Serum phosphate, FGF23 and CPP levels and FGF23 mRNA expression level in cranial bone were also evaluated in C57BL/6J mice 2 and 6 hours after phosphate administration using a feeding tube and 10 days after switching to the high phosphate diet.

Results: Both phosphate and artificial CPP treatments for 4 and 24 hours significantly increased FGF23 protein level in the medium of UMR-106 cell at dose-dependent manner. The upregulation of FGF23 mRNA expression level was observed only 24 hours after both treatments. The supplementation of citrate as an inhibitor of CPP formation canceled all of these findings. The significant increases of serum CPP and serum FGF23 levels compared with control treatment were observed 2 and 6 hours, respectively after the gavage of phosphate. However FGF23 mRNA expression level in cranial bone did not change in these mice. Significant increases of serum phosphate, CPP and FGF23 levels and upregulation of FGF23 mRNA expression level in cranial bone were confirmed in mice fed high phosphate diet for 10 days.

Conclusions: These findings suggest CPP but not phosphate itself might be contributing to the dietary phosphate-induced both postprandial secretion and sustained high level of serum FGF23 level.

TH-PO429

In Vivo Responses of Phosphorus-Based Food Additives with Different Forms Toru Fujii, Yuka Kawabata, Hiroko Segawa, Ai Hanazaki, Kayo Ikuta, Aoi Kushi, Ichiro Kaneko, Sawako Tatsumi, Ken-ichi Miyamoto. *Tokushima University, Tokushima, Japan.*

Background: Hyperphosphatemia causes hyperparathyroidism and ectopic calcification in patients with chronic kidney disease, and dietary management for blood phosphate levels in patients with kidney disease is considered to be important. Both organic and inorganic phosphorus (Pi) are present in regularly consumed foods, such as eggs, and daily products. Pi is included in foods as an additive. Phosphorus-containing food additives were included with several forms (mono/polyphosphate-salt e.t.c.). In the small intestine, the luminal mono-phosphate can be available for absorption following ingestion of a food. Previous report suggested that polyphosphate salt have more harmful effects than those of monophosphate salt on bone physiology and renal function. The mechanism, however, has not been clarified. Recent studies suggested the presence of an gastro-renal signaling axis for dietary Pi as well as the existence of a mechanisms of intestinal Pi sensing, however, unknown. We focused that different forms of phosphorus-containing food additives have different effects in the body. In the present study, to clarify the mechanism, we investigated several responses of diet containing mono or polyphosphate on whole body.

Methods: C57B6 male mice were fed a test diet (low Pi diet, control Pi diet, high Pi diet 1 and 2) for short, middle and long periods. KH2PO4 (CP and HP1), and K5P3O10 (HP2) were used for phosphate additives.

Results: There were remarkable differences on blood, fecal, and urine biochemical analysis data between HP1 and HP2 diet group. Though HP1 and HP2 diet significantly increased inflammatory markers mRNA levels in several tissues, only HP2 diet increased fibrosis marker mRNA level in the kidney, urinary volume, and renal calcification. To identify the different response between HP1 and HP2 diet, renal and intestinal Pi regulating factors expression and activity were examined. There were no significantly differences on renal Pi regulating molecules between HP1 and HP2. However, we found differences on several intestinal molecules expression and activity levels between HP1 and HP2.

Conclusions: Intestine might detects difference luminal monophosphate and triphosphate form. It is necessary to consider about not only the phosphorus content but also the form of the phosphorus-containing food additives.

Funding: Government Support - Non-U.S.

TH-PO430

Narrowing the Phosphate Divide: A Comparison between UK and Chinese Haemodialysis Patients Yan Song,[1] Patrick J. Highton,[2] Barbara P. Vogt,[3] Annabel Biruete,[4] Ken Wilund,[4] Alice C. Smith,[1] James Burton.[1] *[1]University of Leicester, Leicester, United Kingdom; [2]Loughborough University, Leicester, United Kingdom; [3]Universidade Estadual Paulista UNESP, Botucatu, Brazil; [4]University of Illinois, Urbana, IL.*

Background: Management of hyperphosphataemia requires a multi directional approach. Dietary restriction of phosphate (Ph) is often inadequate by itself; other strategies such as extended dialysis and Ph binders are often necessary. Designing an effective intervention to manage hyperphosphataemia, whilst balancing Ph restriction and maintaining adequate protein intake, requires a thorough understanding of dietary Ph. In addition, perception and habits related to dietary behaviour may be influenced by ethnicity and culture. The aim of the study was to contrast data about Ph intake on dialysis and non-dialysis days with haemodialysis (HD) patients from UK and China.

Methods: In this cross-sectional study, 24-hour diet recall interviews were undertaken with patients in UK and China during four normal dialysis sessions distributed evenly in two consecutive weeks. Patients were asked to recall food intake for the previous 24 hours on dialysis and non-dialysis days. Demographic and clinical data were collected from patients' medical records. Nutritics and China Food Composition were used as nutrition database for UK and Chinese dietary data respectively.

Results: A total of 83 patients were recruited (UK, n=40; China, n=43). The UK patients were older (56.8±16.1 vs. 42.4±9.1 years; P=0.001) with a higher body mass index (BMI) than the Chinese cohort (26.6±5.9 vs. 21.3±2.7 kg/m^2; P<0.001). Although energy intake was comparable between populations (UK, 25.3±1.5Kcal/kg/d; China, 23.0 ±1.3 kcal/kg/d, P=0.12), UK patients reported higher Ph intake on both dialysis (0.91g/d vs 0.72g/d, P=0.039) and non-dialysis days (0.90g/d vs. 0.73g/d, P=0.004) than their Chinese counterparts. Despite higher dietary intake, serum Ph levels in UK patients were lower compared to those in China (1.59±0.44 mmol/L vs 2.11±0.53 mmol/L, P<0.001). There was no difference in the number of patients prescribed Ph binders between two groups (UK, n=8; China, n=9, P=0.567).

Conclusions: Despite higher BMI and dietary intake, and with no difference in prescribed Ph binding medications, UK patients had lower serum Ph concentrations than their Chinese counterparts. Strategies to improve compliance with medications and increasing dialysis phosphate removal would have a greater impact on hyperphosphataemia than increased nutritional support in Chinese HD patients.

TH-PO431

Use of Urinary Metabolomics to Identify Potential Pathways Associated with Hyperuricemia in Hispanic Children: The Viva La Familia Study V. Saroja Voruganti,[7] Itzel Vazquez-Vidal,[4] Baba B. Mass,[6] Robert P. Mohney,[3] Nitesh R. Mehta,[2] Anthony G. Comuzzie,[5] Shelley A. Cole,[5] Nancy F. Butte.[1] *[1]Baylor Coll Medicine, Houston, TX; [2]Baylor College of Medicine, Houston, TX; [3]Metabolon, Inc., Durham, NC; [4]Nutrition Research Institute, University of North Carolina at Chapel Hill, Kannapolis, NC; [5]Texas Biomedical Research Institute, San Antonio, TX; [6]UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL, CHARLOTTE, NC; [7]University of North Carolina at Chapel Hill, Kannapolis, NC.*

Background: Hyperuricemia (elevated serum uric acid) is associated with increased risk for gout, cardiovascular and kidney disease. Studies have shown hyperuricemia in children to be predictive of hypertension in adulthood. Our aim in this study was to identify urinary metabolites and pathways associated with hyperuricemia in a cross-sectional study of 260 Hispanic children from the Viva La Familia Study.

Methods: Urinary metabolomics profiling was conducted in 130 hyperuricemic and 130 normouricemic children using ultrahigh performance liquid chromatography mass spectroscopy. Hyperuricemia was characterized using upper most quartile of serum uric acid.

Results: A total of 703 urinary metabolites were identified, of which 377 metabolites were significantly different between the two groups. Key differences were found in amino acid, steroids and xenobiotics metabolic pathways, with 262 metabolites being higher in hyperuricemic than normouricemic group. Metabolites that were significantly higher in hyperuricemia group belonged to histidine (formimimoglutamate and methylhistidine), methionine (S-adenosylhomocysteine (SAH)), nicotinate and nicotinamide (nicotinamide

N-oxide and 1-metylnicotinamide), steroid (epiandrosterone glucuronide and cortisol glucuronide) and purine (1,3 dimethylurate and xanthosine) metabolic pathways. The metabolites that were significantly lower in hyperuricemia group were derivatives of glycine, serine, threonine, N-acetylglycine, N-acetylserine, glutamate and gamma-aminobutyrate, and xenobiotics (ferulate, caffeine acid sulfate, vanillate, saccharin, etc). Interestingly, xanthine oxidase, a key enzyme that catalyzes the conversion of xanthine to uric acid and nicotinamide N-oxide to nicotinamide, is also a major enzyme in xenobiotics metabolism. Elevated levels of formimimoglutamate indicate folate deficiency whereas folate is thought to inhibit xanthine oxidase.

Conclusions: Our global urinary metabolomics profiling not only revealed different pathways in hyperuricemic and normouricemic children, but also demonstrated a link between xanthine oxidase, xenobiotics and folate in hyperuricemia

Funding: NIDDK Support

TH-PO432

Targeted Metabolomics of Adolescent CKD Ellen Brooks,[1,5] Shannon Haymond,[2] Craig B. Langman,[1,5] Bradley A. Warady,[4] Susan L. Furth.[3] *[1]Feinberg School of Medicine, Northwestern University, Chicago, IL; [2]Northwestern University, Chicago, IL; [3]The Children's Hospital of Philadelphia, Philadelphia, PA; [4]The Children's Mercy Hospital, Kansas City, MO; [5]Kidney Disease, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, IL.*

Background: Dysregulation of amino acids, biogenic amines, and phosphatidylcholines (PCs) have been described in advanced chronic kidney disease (CKD) in adults. Metabolic alterations related to oxidative stress and inflammation in children with mild to moderate CKD may have greater significance for risk of secondary morbidities since growth and development are not complete.

Methods: In this cross-sectional study, 2 CKD groups were matched for age and gender but had differing measured (*m*)GFR by iohexol clearance and CKD stage [n=20 per CKD group with 10 glomerular (G) and 10 non-glomerular (NG) disorder per group]. Targeted plasma metabolomics were completed at the Proteomics and Metabolomics Shared Resource, Duke University (Durham, NC) using the Biocrates Absolute*IDQ*® p180 panel-ultra-HPLC-tandem mass spectrometry and integrated software (Biocrates Life Sciences AG, Austria).

Results: The median (Md) and interquartile range (IQR) *m*GFR of the groups differed as planned: 74.3 (67.4, 82.9) CKD 2 vs. 32.8 (24.3, 35.5) ml/min/1.73m^2 CKD 3b ($p<0.001$) but age was similar 14.7 (11.7, 16.0) vs. 15.0 (12.7, 15.7) yrs. Plasma symmetric dimethylarginine (SDMA), creatinine, kynurenine (Kyn), sarcosine, trans-4-OH-proline, aspartic acid, alanine, and glycine were higher in CKD 3b (biogenic amines and amino acids p range=5.5E^{-7} to 0.04) but long chain PCs were lower (p=0.01-0.035). In CKD 3b, SDMA/asymmetric DMA, Kyn/tryptophan (tryp), and phenylalanine/tryp were higher (p=6.79E-7 to 4.4E-4), Kyn was greater in NG vs. G (p=0.009) and alanine was higher in G vs. NG (p=0.045).

Conclusions: The aberrant metabolic patterns in adolescents with CKD 3b infer augmented amino acid catabolism, including alanine via pyruvate and tryp via indoleamine 2,3-dioxygenase 1 (IDO-1). The Kyn pathway is upregulated by IDO-1 and -2 in acute/chronic infection to inhibit bacterial growth and amplify immunosuppression, which may occur in CKD 3b NG. The higher SDMA and SDMA/ADMA ratio are likely related to decreased GFR while PC derangement may be due to phospholipase A_2 increased mass and activity. Low plasma PCs can result from PC accumulation in LDLs and may signify increased cardiovascular risk, while CKD-MBD may be related to enhanced collagen turnover. Correlations with clinical and biochemical parameters will provide further evidence of altered metabolomic contributions to the excess morbidity of pediatric CKD.

TH-PO433

Systemic Oxalosis with Retinopathy Secondary to Vitamin C in a Patient on Peritoneal Dialysis Matthew R. D'Costa, Nelson S. Winkler, Dawn S. Milliner, Suzanne M. Norby, LaTonya J. Hickson, John C. Lieske. *Mayo Clinic, Rochester, MN.*

Background: We report a case of systemic oxalosis involving the eyes and joints due to long-term use of high-dose vitamin C in a peritoneal dialysis (PD) patient.

Methods: A 76-year-old female presented to the hospital with a 1-month history of decreasing vision and polyarthralgias. She had developed ESRD secondary to autosomal dominant polycystic kidney disease and underwent living unrelated kidney transplant 10 years earlier. Due to declining allograft function, biopsy was performed 1 year prior to admission revealing severe arteriosclerosis, focal segmental glomerulosclerosis, and early transplant glomerulopathy but no calcium oxalate (CaOx) crystals. She initiated hemodialysis (HD) 6 months later and transitioned to PD 2 months prior to admission. At presentation, ophthalmologic exam revealed crystalline retinopathy consistent with CaOx deposition. Fluorescein angiography demonstrated significant retinal non-perfusion, and optical coherence tomography showed hyperreflective deposits throughout the inner and outer retina. Plasma oxalate (POx) was markedly elevated at 187 μmol/L (normal < 1.7 μmol/L). Urine oxalate/creatinine ratio was high (0.18 mg/mg) while urine glycolate, glycerate and 4-hydroxy-2-oxoglutarate were normal. Genetic testing confirmed absence of pathogenic changes in *AGXT, GR/HPR* and *HOGA1*. Stool analysis did not suggest significant fat malabsorption and she had no previous gastrointestinal surgery, diarrhea, or other gastrointestinal symptoms. While excessive intake of high oxalate foods was not identified, she reported chronic use of high-dose vitamin C of up to 4 grams per day for many years. With discontinuation of vitamin C and nearly daily HD for 2 weeks, predialysis POx fell markedly to 30-50 μmol/L. Serial funduscopic examinations remained stable in the setting of mild improvement in visual acuity and marked improvement in joint pain. She was discharged on standard thrice weekly HD. Three months later, her most recent predialysis POx was 35.2 μmol/L.

Results:

Conclusions: This case demonstrates that *in vitro* conversion of vitamin C to oxalate can occur in patients with significant renal impairment producing significant hyperoxalemia. Therefore, high-dose vitamin C should be avoided in later stage CKD patients, especially those on PD which does not clear oxalate effectively.

TH-PO434

Lipidogenic Actions of Insulin in Patients with CKD Aseel Alsouqi,[5] Serpil muge Deger,[2] Feng Sha,[1] Aihua Bian,[4] Thomas G. Stewart,[5] Charles D. Ellis,[3] Adriana Hung,[4] Talat Alp Ikizler.[5] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Vanderbilt University Medical Center, Nashville, TN; [3]Vanderbilt University Medical Center, Nashville, TN; [4]Vanderbilt University Medical Center, Nashville, TN; [5]Vanderbilt University Medical Center, Nashville, TN.*

Background: Resistance to the metabolic actions of insulin is common in patients with CKD. We examined the acute effects of hyperinsulinemia on free fatty acid (FFA) levels during hyperinsulinemic euglycemic clamp (HEGC) study in patients with CKD and controls without kidney disease.

Methods: All participants underwent HEGC, where a fixed insulin infusion was started to achieve hyperinsulinemia with subsequent IV dextrose administration to maintain euglycemia (steady state). Peripheral resistance to insulin actions on glucose was assessed by Glucose Disposal Rate (GDR). Free fatty acid levels were measured at baseline and during steady state.

Results: We studied 165 individuals; 73 controls (59% females, 51% AA, median age 50 [IQR 38,65]) and 92 patients with CKD (31.5% females, 51% AA, median age 60, IQR[46,67]). FFA levels decreased similarly in response to insulin in all four groups: 88% in the control group, 89% in CKD Stages 3-4, 90% in HD and 86% in PD patients ($p < 0.05$ only for PD vs controls). Higher body mass index, fat mass, lean mass and Leptin Adiponectin Ratio were associated with lower rates of decrease in FFA levels. Increased age, higher baseline FFA levels, higher baseline adiponectin, higher GDR were significantly associated with higher rate of decrease in FFA levels. Leptin, C- reactive protein and interleukin-6 were not significantly associated with the change in FFA.

Conclusions: Body composition and adipocytokines are the primary determinants of actions of insulin on FFA metabolism in CKD patients. Patients on PD might have an underlying abnormality related to FFA metabolism, potentially related to excessive glucose exposure.

Funding: NIDDK Support, Veterans Affairs Support

Correlations of different variables with the ratio of change in FFA levels during HEGC

Variable	Rho	p value
BMI	0.263	<0.001
Fat Mass	0.266	0.022
Lean Mass	0.404	<0.001
LAR	0.583	<0.001
Age	-0.169	0.035
Baseline FFA	-0.377	<0.001
Adiponectin	-0.705	<0.001
GDR	-0.363	<0.001
Leptin	0.179	0.107
CRP	-0.076	0.446
IL-6	0.03	0.837

TH-PO435

An Epigenetic Mechanism Controls Muscle Protein Synthesis in Mice with CKD Liping Zhang,[2] William E. Mitch.[1] *[1]Baylor College of Medicine, Houston, TX; [2]Nephrology, Baylor College of Medicine, Houston, TX.*

Background: For patients with chronic kidney disease (CKD), loss of muscle mass is frequent leading to morbidity. Unfortunately, there are no approved, regularly effective treatments that overcome muscle wasting in part because mechanisms causing muscle protein losses are still being uncovered. Previously, we showed that CKD induces loss of muscle via increased protein degradation with decreased protein synthesis. The former is due to activation of caspase-3 and the ubiquitin-proteasome system (UPS) but mechanisms impairing muscle protein synthesis are unknown. Now, we show that CKD stimulates a chromatin modifying protein, NO66, in muscle resulting in reduced protein synthesis.

Methods: Mice with whole body deletion of NO66 (NO66$^{-/-}$) were created by crossing transgenic, Sox2-cre mice with NO66$^{flox/flox}$ mice. Mice with muscle-specific NO66 knockout (NO66^{mko}) were created by crossing tamoxifen-inducible, Pax7-cre mice with NO66$^{flox/flox}$ mice. CKD (subtotal nephrectomy) was created in mice and those with BUN >80 mg/dL were studied

Results: Our hypothesis is that expression of NO66 in muscles suppresses protein synthesis. During testing of this hypothesis, we found that NO66$^{-/-}$ mice exhibited a 20-30% increase in muscle mass *vs.* responses in NO66$^{flox/flox}$ control mice. Secondly, in NO66$^{-/-}$ mice the muscle wasting from CKD was blocked. To test the role of NO66 in muscle, we studied mice with muscle-specific NO66 KO (NO66^{mko}) and found there was an increase in muscle mass. To determine the mechanism underlying NO66-induced regulation of muscle mass in mice with CKD, we performed mass spectrometry assays and found that NO66 forms a repressive complex with two histone-modifying proteins, retinoblastoma binding protein 4 (RBBP4) and histone deacetylase 2 (HDAC2). This

complex represses expression of muscle genes and the transcription of ribosomal DNA via a demethylase mechanism. Lastly, we performed a RNA-seq analysis using soleus muscles and identified that absence of NO66 stimulates a ribosomal biogenesis signaling pathway

Conclusions: We have uncovered a new CKD-initiated pathway that proceeds *via* a novel epigenetic mechanism that regulates muscle protein synthesis

Funding: NIDDK Support, Other U.S. Government Support, Commercial Support - Atara Biotherapeutics, Private Foundation Support

TH-PO436

Eliminating SIRPα Replicates Exercise Induced Remodeling and Prevents Cardiac Dysfunction in CKD Jiao Wu,[1] Giovanni Davogustto,[2] Zhaoyong Hu,[1] Yanlin Wang,[1] Heinrich Taegtmeyer,[2] William E. Mitch,[1] Sandhya S. Thomas.[3,1] *[1]Baylor College of Medicine, Houston, TX; [2]The University of Texas Health Science Center at Houston, Houston, TX; [3]Michael E. Debakey Veteran Affairs Medical Center, Houston, TX.*

Background: A major consequence of chronic kidney disease (CKD) is uremic cardiomyopathy characterized by left ventricular hypertrophy (LVH), systolic and diastolic dysfunction. Even at early stages of CKD with near normal GFR, and normal blood pressure, LVH is present, which suggests an unidentified trigger unrelated to pressure overload. We now find that elevations of a novel protein, signal regulatory protein alpha (SIRPα) in CKD cardiac muscle not only adversely influences insulin signaling cardiac fibrosis, but also cardiac dysfunction classically associated with CKD. Suppression of SIRPα reverses CKD-induced cardiac dysfunction and promotes exercise induced cardiac remodeling.

Methods: SIRPα whole body mutant (Mt) mice and wild type mice (WT) were compared after 8 weeks of subtotal nephrectomy. Cardiac function was analyzed *in vivo* with M-mode and doppler echocardiography. N=8-9 mice/group, results are presented as mean±SD.

Results: Hearts of SIRPα Mt sham mice exhibit eccentric LVH compared with WT sham (LV mass/height 1.532±0.167 vs 1.329±0.216, p=0.04; Relative wall thickness 0.519±0.052 vs 0.608±0.098, p=0.03), preserved systolic function (EF 70.649±6.826 vs 65.901±5.304) as well as diastolic function (E/A 1.812±0.521 vs. 1.499±0.254). However, in WT Sham vs. WT CKD mice there is evidence of cardiac dysfunction characterized by reduced ejection fraction (EF) % (65.901±5.304 vs. 53.112±11.302, p =0.016) and reduced cardiac output (CO) ml/min (19.4±3.942 vs. 15.493±2.474, p=0.03). Doppler analysis revealed diastolic dysfunction in WT CKD as well (E/A: 1.499± 0.254 vs. 1.146±0.102, p=0.008). In WT CKD mice systolic blood pressure was not different than WT sham, suggesting changes observed are not due to pressure overload. On the contrary, in SIRPα Mt mice, induction of CKD did not significantly affect cardiac function (EF 70.649± 6.826 vs. 65.816±2.568, CO: 24.702±3.247 vs. 23.6±5.765, E/A 1.812±0.521 vs. 1.483±0.3, p > 0.05 for all).

Conclusions: In conclusion, suppression of SIRPα replicates exercise induced cardiac remodeling, similar to marathon-runners, as evidenced by eccentric LVH, preserved EF and diastolic function. Furthermore, hearts of SIRPα Mt mice were protected against CKD-induced cardiac dysfunction. Therefore, SIRPα may prove to be a key mediator for prevention of CKD-associated cardiomyopathy.

Funding: Other NIH Support - Dr. and Mrs. Harold Selzman, Veterans Affairs Support

TH-PO437

Biased Mortality Risk Associated with Change in Normalized Protein Catabolic Rate Due to Residual Kidney Function among Hemodialysis Patients Yoshitsugu Obi,[1] Elani Streja,[1] Rieko Eriguchi,[2] Melissa Soohoo,[1] Connie Rhee,[1] Csaba P. Kovesdy,[3] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine, Orange, CA; [2]Kaizuka Hospital, Fukuoka, Japan; [3]University of Tennessee Health Science Center, Memphis, TN.*

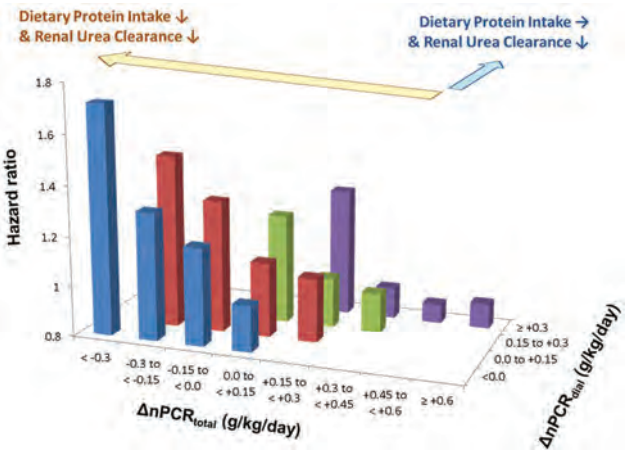
Background: Dietary protein intake among hemodialysis (HD) patients is estimated by dialysis urea clearance-based normalized protein catabolic rate (nPCR) in clinical practice, without accounting for renal urea clearance (rCL_{urea}). Decreases in rCL_{urea} directly increase nPCR by imposing greater dialysis clearance, and hence, patients appear to maintain nPCR values with decreased rCL_{urea} and decreased protein intake, both of which are associated with mortality.

Methods: We identified 10,066 HD patients with data on rCL_{urea} at both the 1st and 3rd quarters after dialysis initiation in a large U.S. dialysis organization (2007-2011). We calculated their 6-month change in nPCR with and without accounting for rCL_{urea} (i.e., $\Delta nPCR_{total}$ and $\Delta nPCR_{dial}$), and created 15 groups of combined $\Delta nPCR_{total}$ and $\Delta nPCR_{dial}$. All-cause mortality risk was estimated using Cox models with adjustment for 25 clinically relevant factors.

Results: Median (IQR) $\Delta nPCR_{dial}$ and $\Delta nPCR_{total}$ were 0.12 (-0.01, 0.26) and 0.11 (-0.06, 0.28) g/kg/day, respectively. $\Delta nPCR_{dial}$ and ΔrCL_{urea} explained 61% and 10% of the variation in $\Delta nPCR_{total}$ respectively. Within the same category of $\Delta nPCR_{dial}$, adjusted mortality risk was incrementally higher across lower $\Delta nPCR_{total}$ (P_{trend} <0.001). Contrary, within the same category of $\Delta nPCR_{total}$, mortality risk was paradoxically higher across higher $\Delta nPCR_{dial}$ (P_{trend} <0.001).

Conclusions: In the absence of data on rCL_{urea}, $\Delta nPCR$ does not adequately capture true changes in protein intake, leading to a biased evaluation of associated mortality risk among HD patients with rCL_{urea}.

Funding: NIDDK Support



TH-PO438

Relationship between Body Mass Index, Inflammation, and Mortality in Hemodialysis Patients Rakesh Malhotra,[4] Xiaoling Ye,[3] Jochen G. Raimann,[3] Len A. Usvyat,[1] Joachim H. Ix,[4] Frank van der Sande,[2] Peter Kotanko,[3] Jeroen Kooman.[2] *[1]Fresenius Medical Care North America, Melrose, MA; [2]Maastricht University Medical Centre, Maastricht, Netherlands; [3]Renal Research Institute, New York, NY; [4]UCSD, San Diego, CA.*

Background: High body mass index (BMI) is associated with improved survival in hemodialysis (HD) patients. Mechanisms responsible are unknown. Here, we evaluate whether neutrophil-lymphocyte ratio (NLR) and serum albumin - markers of inflammation - affect the relationship of BMI with mortality in dialysis subjects.

Methods: We evaluated HD patients enrolled in MONDO (MONitoring Dialysis Outcomes) among whom measurements of neutrophil and lymphocyte counts, albumin, body weight and height were available (n=6162). BMI was categorized by quintiles:<21.3 kg/m^2, 21.3 to 24.0 kg/m^2, >24.0 to 26.7 kg/m^2, >26.7 to 30.4 kg/m^2 and >30.4 kg/m^2. Patients were classified as inflamed if NLR ≥5.0 or albumin ≤3.1 mg/dL. The main outcome was all-cause mortality over 2 years.

Results: The median (IQR) age was 66 (55-76) years, 57% were male, 46% white and median vintage 4-6 months. During 2-year follow-up, there were 2641(42.9%) deaths(864 in inflamed;1777 in non-inflamed). The protective effect of high BMI was observed in inflamed patients(HR (95% CI) Q1:2.48 (2.10-2.94); Q2:1.73 (1.44-2.09); Q3:1.77 (1.44-2.17); Q4:1.44 (1.16-1.80); and Q5:1.46 (1.18-1.81)); however this effect was mitigated in non-inflamed HD patients(HR (95% CI) for Q1:1.27 (1.08-1.49); Q2:1.06 (0.91-1.24); Q3:0.99 (0.85-1.16); Q4:0.93 (0.80-1.09); and Q5:1.0 (ref)). Further analysis showed that these findings were restricted to Europeans but not in Asians and United states subjects (**Fig1**).

Conclusions: Our results showed that inflammation may impact the relationship between BMI and survival. Further studies are needed to better understand the interaction between inflammation and the BMI in HD patients.

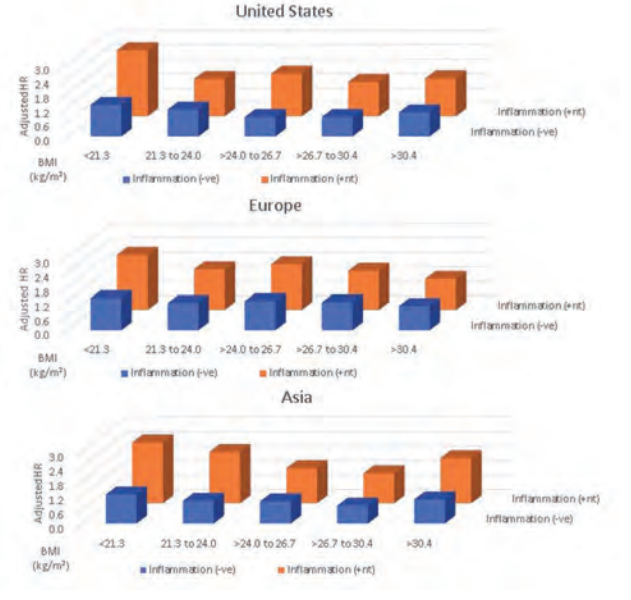


Figure 1. All-cause mortality by BMI and inflammation stratified by Region; adjusted Cox regression analysis

TH-PO439

Eculizumab and ECMO Rescue-Therapy of Most Severe ARDS in a Young Boy with Goodpasture's Syndrome Oliver Gross. *University Medicine Goettingen, Goettingen, Germany.*

Background: Goodpasture's syndrome is a life-threatening autoimmune disease characterized by the presence anti–glomerular basement membrane (GBM) antibodies, rapid progressive glomerulonephritis and/or pulmonary hemorrhage.

Methods: In a 17-year old boy, hydrocarbon exposure and additional severe bacterial infection triggered pulmonary hemorrhage due to Goodpasture's syndrome resulting in acute respiratory distress syndrome (ARDS). Within one day after hospital admission, the patient required extracorporeal membrane oxygenation (ECMO).

Results: Despite steroid-pulse and plasmapheresis, ARDS further deteriorated. Eleven days after admission, the boy was in a pre-final stage. At last, we decided to block the complement-driven lung damage by a single dose of Eculizumab. Three days after, lung-failure has stabilized in a way allowing us to initiate Cyclophosphamide-therapy. As mechanical ventilation further triggers Goodpasture-epitope exposure, the boy was taken from pressure support - breathing spontaneously by the help of maximal ECMO therapy. After a total of 24 days, ECMO could be stopped and pulmonary function further recovered within three weeks.

Conclusions: Our findings suggest that [1] Eculizumab can halt complement-driven organ-damage in life-threatening Goodpasture's syndrome and [2] lung-protective early withdrawal from pressure support by the help of ECMO can prevent further harm to the lung-tissue. Both therapeutic options take Goodpasture's pathogenesis into account and might serve as an important tool in otherwise hopeless situations to prevent further organ-damage and to gain time until the established immunosuppressive therapy works in otherwise fatal autoimmune-diseases.

TH-PO440

Latent CMV reinforces Myeloid Inflammation in the Kidney and Other Organs Following a Septic Episode William Nash, Sundararaman Swaminathan, Michael G. Brown. *University of Virginia, Charlottesville, VA.*

Background: Although CMV reactivation is a well-known complication of renal transplant, the impact of CMV infection outside of the transplant field is relatively understudied. Reactivation of latent viral infections is a common occurrence in ICU patients diagnosed with sepsis and this coincides with high frequency of kidney dysfunction and failure. To date, such viral reactivation has been mostly viewed as a symptom of lympho-depression that can occur alongside or following the hyperinflammatory stage of sepsis. However, recent studies have indicated that CMV reactivation during sepsis is associated with longer hospital stays and increased risk of death.

Methods: We are designing a two-hit model to investigate the impact of latent CMV infection on sepsis. Mice are infected with MCMV for 60+ days to establish a latent infection. Naïve mice are used as comparators. A sepsis-like state is then induced by intraperitoneal injection of a cecal slurry prepared from naïve mice. Mice are monitored for 15 days post-septic insult and then serum and tissues are analyzed.

Results: All mice lost weight following cecal slurry injection, but we observed greater fluctations in body weight during recovery from sepsis in CMV(+) mice. In addition, of the 6 CMV(+) mice, one developed a massively cystic kidney and another exhibited aberrantly high numbers of monocytes in the lung and kidney. Mice that were previously infected with CMV displayed a greater proportion of Ly6C-hi inflammatory monocytes in the kidney as well as in the spleen, liver, and lung. Kidney and lung tissue from CMV+ mice also had a greater concentration of neutrophils per gram of tissue. At the time point investigated, we did not detect differences in histology, serum creatinine, or serum BUN between CMV(+) and CMV(-) mice, but the cecal slurrly dose used was generally well tolerated since all mice survived.

Conclusions: Our study shows that CMV may reinforce the myeloid inflammation occuring during sepsis. The tissues of mice previously infected with CMV maintain an inflammatory-skewed environment out to 15 days post-septic insult, even when mice are recovering body weight. It will be interesting to know if this skew predisposes mice to increased pathology in the kidney and lung upon additional infection and to determine the effects of CMV during more severe septic episodes.

Funding: NIDDK Support

TH-PO441

Beverage Consumption and Kidney Disease Risk Casey Rebholz,[1] Bessie A. Young,[2] Ronit Katz,[6] Brandon J. Auerbach,[6] Katherine L. Tucker,[3] Teresa C. Carithers,[4] Arnita F. Norwood,[5] Victoria I. Okhomina,[5] Adolfo Correa.[5] *[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [2]Uniiversity of Washington, Seattle, WA; [3]University of Massachusetts Lowell, Lowell, MA; [4]University of Mississippi, Oxford, MS; [5]University of Mississippi Medical Center, Jackson, MS; [6]University of Washington, Seattle, WA.*

Background: Sugar-sweetened beverages have been the target of health policies to reduce obesity and related cardiometabolic diseases. Identifying beverages that are associated with chronic kidney disease (CKD) risk could inform dietary guidelines.

Methods: We conducted a prospective analysis of participants in the Jackson Heart Study, a cohort of African-American men and women in Jackson, Mississippi. Beverage intake was assessed using a food frequency questionnaire administered at baseline (2000-04). Incident CKD was defined as eGFR <60 mL/min/1.73 m^2 and ≥30% eGFR decline at follow-up (2009-13) relative to baseline among those with baseline eGFR ≥60 mL/min/1.73 m^2. Logistic regression was used to estimate the association between the consumption of each individual beverage (energy-adjusted using the residual method), beverage patterns, and incident CKD. Beverage patterns were empirically-derived using principal components analysis (PCA) in which components were created based on the linear combinations of beverages consumed.

Results: Among 3,402 participants, 220 (6.5%) developed incident CKD over a median follow-up of 8 years. At baseline, median age was 54 years, 63% were female, and median eGFR was 98 mL/min/1.73 m^2. After adjusting for total energy intake, age, sex, income, body mass index, smoking, physical activity, hypertension, diabetes, high density lipoprotein cholesterol, history of cardiovascular disease, and baseline eGFR, higher intake of sweetened fruit drinks was significantly associated with increased risk of CKD (OR=1.12, 95% CI: 1.00, 1.27, p=0.05). A PCA-derived beverage pattern consisting of higher consumption of soda, sweetened fruit drinks, and water was more strongly associated with incident CKD (OR=1.23, 95% CI: 1.08, 1.41, p=0.002) than any beverage alone. No other individual types of beverages or beverage patterns were associated with CKD.

Conclusions: Higher consumption of sweetened fruit drinks was associated with elevated risk of subsequently developing CKD in this community-based population of African-Americans.

Funding: NIDDK Support

TH-PO442

Vitamin D Supplementation Increases Nephrocalcinosis but Not Bone Density in Preterm Infants Sabrina R. Malone jenkins,[2] Matthew M. Grinsell,[2] Kimberlee A. Weaver lewis,[1] Gary M. Chan.[2] *[1]Intermountain Medical Center, Murray, UT; [2]University of Utah, Salt Lake City, UT.*

Background: Vitamin D (VitD) supplementation is recommended for infants to maintain VitD status and improve bone density. One possible complication of VitD supplementation is nephrocalcinosis (NC), which is the calcification of renal tissue and is reported in 7-64% of infants with gestational age (GA)<32 wks or birth weight (BW)<1500g. Hypercalciuria and urine calcium crystal formation may also be complications of VitD supplementation. The relationship between VitD supplementation, NC, and the effect on bone density in preterm infants remains unknown. We hypothesize that VitD supplementation is associated with higher incidence of NC and hypercalciuria without improving bone density in preterm infants.

Methods: Prospective observational cohort study of 56 infants with GA≤32wks or BW≤1800g. We collected data on demographics, dietary intakes, and serum VitD levels until 40 wks corrected GA. Weekly urinalyses with microscopy were performed from 2 wks of age. NC was identified by renal ultrasound (US). Bone mineral density and content was assessed using DXA scan. Bone strength and elasticity was assessed by measuring speed of sound (SOS) through tibial US.

Results: 26/56 (46%) infants were diagnosed with NC. Infants with NC had a lower GA (28±2 vs 31±2wks, p<0.01) and BW (1102±305 vs 1449±428g, p<0.01) compared to Non-NC. There were no differences in VitD intake or urine calcium/creatinine ratios in NC vs NonNC infants. However, 69% of NC infants vs 40% NonNC had urinary calcium oxalate (CaOx) crystals on microscopy (p<0.03; PPV=60% & NPV=60%). Near discharge, 25-OH VitD levels were higher in the NC group compared to the NonNC group (46±24 vs 34±20ng/ml, p=0.03). DXA scan showed no difference in bone mass and density. However, tibial bone US demonstrated lower SOS (2774±159 vs 2910±158 m/s, p<0.01) and percentile (9±15 vs 28±27, p<0.01) in the NC group consistent with reduced bone strength and elasticity.

Conclusions: Infants born at an earlier GA and lower BW are at increased risk of NC. Our study shows that infants with NC had higher VitD levels and more frequent urine CaOx crystals. VitD supplementation did not increase bone density or mass on DXA but did have lower bone elasticity and strength on tibial US. We speculate that VitD supplementation may not improve bone density but may increase the risk for development of NC in preterm infants.

Funding: Private Foundation Support

TH-PO443

Time-Updated Analysis of Potassium Intake, Serum Potassium, and Outcomes after Kidney Transplantation Lara C. Verschuur,[2] Antonio Gomes Neto,[2] Michele F. Eisenga,[1] Gerjan Navis,[1] Stephan J. Bakker,[2] Martin H. De Borst.[2] *[1]None, Groningen, Netherlands; [2]University Medical Center Groningen, Groningen, Netherlands.*

Background: Low potassium (K+) intake has been associated with an increased risk of hypertension, cardiovascular events, and mortality in patients with chronic kidney disease and in the general population. Kidney transplant recipients (KTRs) may nevertheless refrain from increasing K+ intake because of fear for hyperkalemia, which may be often unjustified.

Methods: We assessed the relationship between paired measurements of 24-hour urinary K+ excretion, as a proxy for K+ intake, and serum K+ in 1,108 with eGFR >15 mL/min/1.73 m^2. We subsequently analyzed associations of K+ intake with death-censored graft failure (DCGF) and all-cause mortality using time-updated Cox regression, adjusted for potential confounders, including age, sex, time-matched estimated GFR (eGFR, CKD-EPI), systolic blood pressure, and use of diuretics or RAAS-inhibitors.

Results: KTRs (55% men) were 44±13 yrs old at transplantation. Data from 8,904 paired urinary and serum K+ measurements were available. When considering intra-individual median K+ excretion, K+ excretion was 2.6 [2.0-3.1] g/d (median [IQR]). K+

intake was below the WHO-recommended intake (90-120 mmol/d, 3.5-4.7 g/d) in 87.4% of KTR. K+ intake decreased with advancing stages of CKD (P-trend<0.001). Overall, K+ intake explained 1.3% of the variation in serum K+; in stage 4 CKD it explained 1.0%. In multivariable linear regression, eGFR, diuretics use, sex, BMI, and ACE-inhibitor use (all P<0.05) were the main independent determinants of serum K+ (R^2=0.12), whereas K+ excretion was no significant independent determinant (P=0.16). During median follow-up for 14.3 [9.2-20.3] years, 291 patients developed DCGF and 676 patients died. In time-updated multivariable Cox regression analysis, K+ intake was inversely associated with the risk of DCGF (fully adjusted HR 0.60 [95% CI 0.49-0.74] per 1 g/d increase in K+ intake, P<0.0001) and mortality (0.76 [0.63-0.91], P<0.0001). Adjustment for serum K+ did not materially change the results.

Conclusions: K+ intake is low in the vast majority of KTR. The minimal impact of K+ intake on serum K+ and the association of low K+ intake with an increased risk of adverse outcomes suggest that dietary K+ intake should be stimulated in most KTRs.

TH-PO444

Effects of Diet and Exercise on Adipocytokine Levels in Patients with Moderate to Severe CKD Aseel Alsouqi,[1] Jacob M. Taylor,[1] Charles D. Ellis,[2] Aihua Bian,[3] Thomas G. Stewart,[1] Cassianne Robinson-Cohen,[6] Katherine R. Tuttle,[4] Michael J. Germain,[7] Elizabeth E. Evans,[5] Sam A. Headley,[5] Chutatip Limkunakul,[8] Jonathan Himmelfarb,[9] Talat Alp Ikizler.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Vanderbilt University Medical Center, Nashville, TN; [3]Vanderbilt University Medical Center, Nashville, TN; [4]University of Washington School of Medicine, Spokane, WA; [5]Springfield College, Wilbraham, MA; [6]University of Washington, Seattle, WA; [7]Renal and Transplant Assoc of New England, Hampden, MA; [8]Srinakharinwirot University, Nonthaburi, Thailand; [9]Kidney Research Institute, Seattle, WA.*

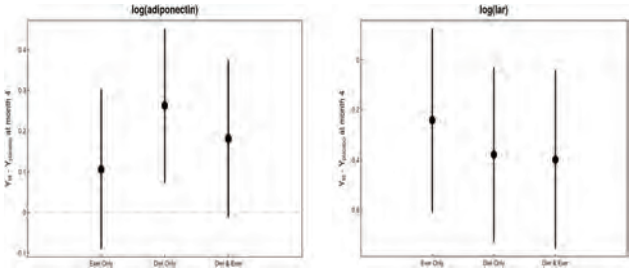
Background: Obesity is a pro-inflammatory risk factor for progression of CKD and cardiovascular disease. We hypothesized that implementation of caloric restriction and aerobic exercise improves adipocytokine profiles in patients with moderate to severe CKD.

Methods: We enrolled patients with moderate to severe CKD through a multi-center pilot randomized trial of diet and exercise in a 4-arm design (dietary restriction of 10%-15% reduction in caloric intake, exercise three times/week, combined diet and exercise and control) (NCT01150851). A total of 122 participants were consented, 111 were randomized (42% female, 25% diabetic, and 91% hypertensive), 104 started intervention and 92 completed the study. Adipocytokines (adiponectin, leptin and resistin) were measured at the beginning and end of the study period as secondary outcomes. Treatment effect was analyzed in a multivariable model adjusted for baseline outcome values, age, gender, site and diabetes.

Results: Adiponectin and resistin levels increased statistically significantly in response to diet whereas leptin levels did not change by either treatment (Figure-1). Leptin-Adiponectin Ratio (LAR) decreased statistically significantly in response to both interventions (Figure-2).

Conclusions: Our data suggest that dietary caloric restriction improves adiponectin and resistin levels in Stage 3-4 CKD patients with limited effect on leptin levels. LAR improved in response to both interventions indicating a potential beneficial effect of exercise intervention to the overall metabolic milieu.

Funding: Veterans Affairs Support



Effect of diet and exercise on Adiponectin and LAR levels in study groups compared to usual care.

TH-PO445

Cardiovascular Outcomes in CKD Patients with Sickle Cell Disorders Kabir O. Olaniran, Nwamaka D. Eneanya, Andrew S. Allegretti, Dihua Xu, Ravi I. Thadhani. *Massachusetts General Hospital, Boston, MA.*

Background: Sickle cell disease (SCD) patients are known to be at risk for ischemic stroke (CVA), heart failure (HF) and chronic kidney disease (CKD). However, cardiovascular (CV) outcomes in SCD CKD patients have not been described. Additionally, sickle cell trait (SCT) is independently associated with CKD. However, the effect of SCT with concurrent CKD on CV outcomes has not been explored.

Methods: We performed a multi-hospital retrospective cohort study in Boston using adult KDIGO criteria CKD patients between 2005-2017. Chart review was used to ascertain the following exposures: SCT with CKD, SCD with CKD and the reference group (RG; black race with CKD with normal hemoglobin electrophoresis). Outcomes were identified using diagnosis codes and defined as incident coronary heart disease (CHD), HF and CVA. Exposures and outcomes confirmed by diagnosis code only were then added for sensitivity analysis.

Results: 960 CKD subjects were initially included (241 SCT CKD, 45 SCD CKD, 674 RG). The mean baseline GFR in SCD CKD patients was higher vs the RG despite similar proportions per CKD stage (80±50 vs 70±36ml/min, p=0.17). SCD CKD patients were significantly younger (41±14 vs 52±17yrs, p<0.01), had lower mean systolic blood pressure (129±21 vs 137±23mmHg, p=0.03), fewer co-morbidities and less CV risk treatment vs the RG. No other significant differences in the baseline characteristics of the SCT CKD vs the RG were noted. Initial analysis showed an increasingly positive trend towards CHD risk from the RG to SCT CKD to SCD CKD which did not persist with HF and CVA. After adjustment for age, co-morbidities and medications, we found significantly increased odds for CHD in SCT CKD (OR 1.6, 95% CI 1.1-2.4) and SCD CKD (OR 3.2, 95% CI 1.2-8.3) compared to the RG. SCD CKD patients also had significantly increased odds for CVA (OR 3.8, 95% CI 1.2-12.3) and HF (OR 2.5, 95% CI 1.2-5.2) after multivariable analysis. Sensitivity analysis of 9,078 CKD subjects (360 SCT CKD, 498 SCD CKD, 8,220 RG) revealed similar findings.

Conclusions: Patients with CKD and either concurrent SCT or SCD have increased odds for adverse CV outcomes. Larger studies are needed to confirm these findings and to determine best practices for CV disease prevention in this patient population.

TH-PO446

The Association between Cardiac Troponin T and Coronary Artery Calcification in CKD: Result from the Korean Cohort Study for Outcomes in Patients with CKD Eunjeong Kang,[1] Hyo Jin Kim,[2] Hyunjin Ryu,[1] Miyeun Han,[3] Hyun suk Kim,[4] Curie Ahn,[1] Kook-Hwan Oh.[1] *[1]Seoul National University Hospital, JongNo-Gu, SEOUL, Republic of Korea; [2]Internal medicine, Dongguk University Gyeongju Hospital, Gyeongju, Republic of Korea; [3]Internal medicine, Busan National University Hospital, Busan, Republic of Korea; [4]Internal Medicine, Chuncheon Sacred Heart Hospital, Chuncheon, Republic of Korea.*

Background: Although cardiac troponin T (cTnT) is one of the biomarkers for the diagnosis of acute coronary syndromes, the association between cTnT and coronary artery calcification (CAC) in chronic kidney disease (CKD) patients are less well known, especially in Asian population.

Methods: We conducted a cross-sectional study and data were collected from the KNOW-CKD cohort. cTnT was measured by the highly sensitive assay and were categorized into 4 groups by quartiles (≤6.0, >6.0-10.0, >10.0-16.0, >16.0 pg/mL). CAC was evaluated through Agatston score calculated based on the extent of CAC detected by an electron-beam computed tomography scan. CAC scores were divided into 3 groups: 0-100, >100-400, and >400. We conducted multinomial logistic regression to evaluate the relationship between cTnT and CAC. Age, sex, CKD stage, diabetes, body mass index, hemoglobin, low density lipoprotein, and high density lipoprotein were included as covariates. We carried out subgroup analysis which divided into 2 groups based on estimated glomerular filtration rate (eGFR) 60mL/min/1.73m^2.

Results: Total 2,061 patients were included. The mean age was 53.5±12.3 years; 61.0% of patients were men, 5.3 % were diabetic and 1.4% were had history of myocardial infarction. CAC score was 183.2±523.1. After multivariable adjustments, compared to the lowest cTnT group, the highest cTnT group tended to have higher CACS in a fully adjusted multivariable model (CACS >100-400, odds ratio [OR] 2.460, 95% confidential interval [CI] 0.920-6.574, *P*=0.073; CACS >400, OR 10.175, 95% CI 2.076-49.878, *P*=0.004; reference group CACS 0-100). In a subgroup analysis according to eGFR, statistical significance was weakened in lower eGFR group with full adjustment. In receiver operating curve analysis, area under the curve was above 0.8, regardless of the eGFR subgroup.

Conclusions: Elevated concentration of cTnT was independently associated with the degree of severity of CAC in the CKD population of Korea. In subgroup analysis according to eGFR, the statistical significance regarding coronary artery calcification was weakened in lower eGFR group. Circulating cTnT levels is a fair screening test for the detection of coronary artery calcification in a subgroup with eGFR over 60 mL/min/1.73m^2.

Funding: Government Support - Non-U.S.

TH-PO447

Hypertension (HTN) Modifies the Association of Coronary Artery Calcification (CAC) with CV Events in CKD and Non-CKD Individuals Lucile Parker Gregg, Beverley Adams-Huet, Xilong Li, James Delemos, Susan Hedayati. *UT Southwestern, Dallas, TX.*

Background: Few studies examine whether HTN and CKD modify the association of CAC with CV events. We evaluated these associations at various CAC cutoffs with fatal or nonfatal CV events.

Methods: We studied 2,288 asymptomatic participants of the Dallas Heart Study followed for 12.5 years. Cox proportional hazards determined associations of CAC with CV events (CV death, myocardial infarction, stroke, CV revascularization, or hospitalization for heart failure or atrial fibrillation), adjusted for age, sex, race, smoking, HTN, diabetes, hyperlipidemia, HDL cholesterol, and CKD. Interactions for CKD (defined as eGFR<60 mL/min/1.73m^2 or albuminuria) and HTN (blood pressure >140/90 mmHg or on medication therapy for HTN) with CAC were tested at various CAC cutoffs, with *P*<0.1 considered significant.

Results: There were 170 (7.4%) participants with CKD and 811 (35.4%) with HTN. There were 232 CV events: 161 (19.9%) in those with HTN vs. 71 (4.8%) without HTN, and 60 (35.3%) in those with CKD vs. 172 (8.1%) without CKD, *P*<0.01 for each. CAC was associated with CV events in all non-CKD and non-HTN groups for each CAC cutoff point, but was not associated with CV events at any cutoff in individuals with both CKD and HTN. There was a CKDxCAC interaction for a CAC cutoff of 10 Agatston units, aHR 3.12 (2.20, 4.42) in non-CKD and 1.17 (0.68, 1.99) in CKD, *P*=0.001, but no CKDxCAC interaction for other CAC cutoffs. There was a significant HTNxCAC interaction at all tested cutoffs of CAC, such that CAC was less predictive of CV events in individuals with HTN (**Figure**).

Conclusions: CAC was more strongly predictive of CV events in individuals without HTN, but did not add to traditional risk factors for predicting CV events in hypertensive CKD participants.

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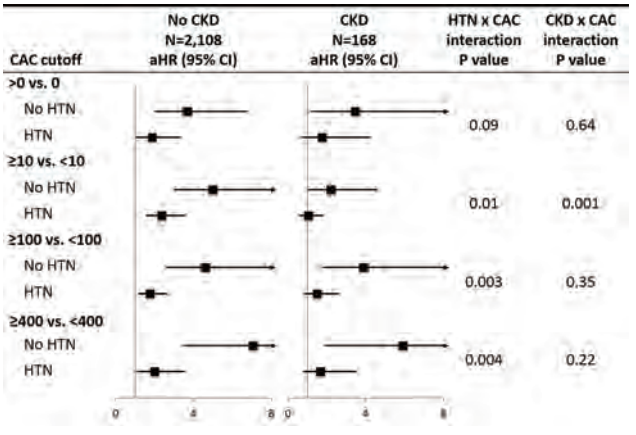


Figure. Adjusted hazard ratios for CV outcomes at multiple CAC cutoffs in CKD and non-CKD individuals, stratified by HTN status

TH-PO448

Differential Effects of Arterial Stiffness versus Fluid Overload on High Blood Pressure According to Renal Function in Patients at a Risk of Cardiovascular Disease Jaeyeol Kwon,[1] Seung Hyeok Han,[1] Meiyan Wu,[2] Boyoung Nam.[2] *[1]Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea; [2]Department of Internal Medicine, College of Medicine, Severance Biomedical Science Institute, Brain Korea 21 PLUS, Yonsei University, Seoul, Republic of Korea.*

Background: Pathogenesis of hypertension is multifactorial in patients with chronic kidney disease (CKD). In this study, we explored the relative contribution of arterial stiffness and fluid overload to blood pressure (BP) in these patients. We evaluated 1531 patients of Cardiovascular and Metabolic Disease Etiology Research Center-High Risk (NCT02003781), a prospective observational cohort study of high risk patients with cardiovascular disease.

Methods: BP, arterial stiffness, and volume status expressed as an extracellular water/total body water ratio (ECW/TBW) were measured by 24-h BP monitoring, pulse wave velocity (PWV) and bioelectrical impedance analysis measurement, respectively.

Results: In patients with CKD, multiple linear regression analysis showed that both PWV and ECW/TBW were significantly associated with 24-h systolic BP (SBP). The area under the receiver operating characteristic curves (AUCs) for predicting 24-h SBP ≥130 mmHg significantly increased after PWV was added to conventional factors regardless of CKD status. However, the AUCs did not increase in ECW/TBW-based models. When a cut-off level of 24-h SBP was defined as 140 mmHg, predictability of ECW/TBW for elevated BP significantly improved in patients with CKD, but not in those without CKD. This association was further confirmed by the net reclassification and integrated discriminant improvements, RMSE with adjusted R^2, and interaction effects. In summary, as kidney function declines, fluid overload significantly contributes to high BP. The impact of fluid overload on BP is only observed in late stage of hypertension in patients with CKD.

Conclusions: Our findings suggest that a stepwise approach is required in the management of hypertension, depending on CKD stages.

TH-PO449

Determinants of Change in Arterial Stiffness over 5 Years in Early CKD Natasha J. Mcintyre,[2] Adam Shardlow,[2] Richard J. Fluck,[4] Christopher W. McIntyre,[1,3] Maarten W. Taal.[2,4] *[1]Division of Nephrology, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON, Canada; [2]Centre for Kidney Research and Innovation, Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, The University of Nottingham, Derby, United Kingdom; [3]Department of Nephrology, London Health Sciences Centre, London, ON, Canada; [4]Department of Renal Medicine, The Royal Derby Hospital, Derby, United Kingdom.*

Background: Arterial stiffness (AS) is an established risk factor for cardiovascular disease (CVD) associated with CKD but there have been few studies to evaluate progression of AS over time or factors that contribute to this, particularly in early CKD, where most care is carried out in a primary care based setting. We therefore investigated AS in an elderly population with CKD stage 3 over 5 years.

Methods: 1741 persons with estimated GFR 59-30mL/min/1.73m^2 were recruited into the Renal Risk in Derby (RRID) study from Primary Care practices. Clinical assessments were completed at baseline, year 1 and 5. Carotid to femoral pulse wave velocity (PWV) was measured as a marker of AS, using a Vicorder™ device (Skidmore Medical Ltd, Bristol, UK). 978 participants had PWV assessments at baseline and 5 years and are included in this analysis.

Results: Changes in important variables over time are shown in the table. In our population, PWV increased significantly by 1.1m/sec over 5 years. Univariate analysis revealed significant correlations between ΔPWV at year 5 and previously identified risk factors for CVD. Multivariable linear regression analysis identified independent determinants of ΔPWV (R^2=0.37 for equation). These were Baseline Age (β=0.152, p<0.0001); Diabetes Mellitus (β=0.075, p=0.004); Baseline Systolic BP (β=0.112, p<0.0001); Baseline PWV (β= -0.342, p<0.0001); ΔPWV at year 1 (β=0.318, p<0.0001); ΔSerum Protein at year 5 (β=0.059, p=0.027); ΔSystolic BP at 5 years (β=0.214, p<0.0001).

Conclusions: We observed a clinically significant increase in PWV over 5 years in a primary care based cohort of elderly persons with early CKD. Systolic BP was identified as the most important modifiable determinant of change in PWV suggesting that interventions to prevent arterial disease should focus on control of blood pressure in this population.

Characteristics at 5 year follow up n=978

	Baseline	Year 1	Year 5
Age(years)	70±9	71±9	75±9‡
Gender Male	378(39)		
Diabetes Mellitus	134(14)		
eGFR EPI(mL/min/1.732)	55.7±11.7	55±12.7	54.3±15.2‡
Systolic BP(mmHg)	133±17	130±16	139±20‡
Diastolic BP(mmHg)	74±11	71±10	75±11‡
Pulse Wave Velocity(m/sec)	9.7±1.9	9.5±1.8	10.8±2.1‡
UACR(mg/mmol)	0.23(0.0-1.1)	0.50(0.2-1.6)	0.67(0.0-3.2)

‡P<0.05 versus baseline value

TH-PO450

Elevated Pulse Amplification in Advanced Kidney Diseases Tsuneo Takenaka. *International University of Health and Welfare, Sanno Hospital, Tokyo, Japan.*

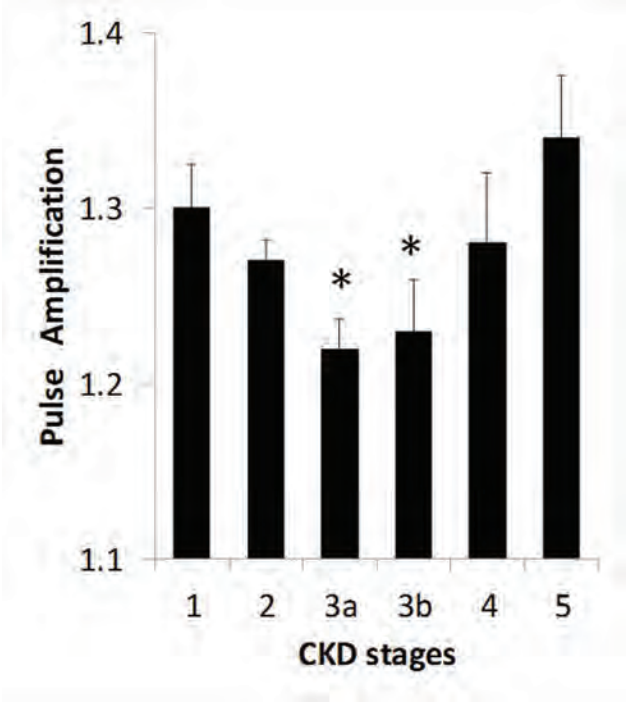
Background: The progression of chronic kidney disease (CKD) inverts arterial stiffness gradient. However, central haemodynamic pressure profiles in CKD have not been fully examined. A cross-sectional study was performed to assess the relationship between CKD stage and central haemodynamic processes.

Methods: The subjects were 2020 hypertensive patients who had undergone echocardiography and had their serum creatinine levels. Radial tonometry was applied in all patients to measure central blood pressure, and they were classified according to six CKD stages based on their estimated glomerular filtration rate (eGFR).

Results: Central (PP2) and brachial pulse pressure (PP) were elevated at stages 3a and 3b, respectively. Diastolic blood pressure (DBP) at stage 1 was higher than at the other stages. The left ventricular mass index (LVMI) was greater at CKD stages 3b-5 than that at stage 1. Either PP or PP2 is sensitive in detecting the presence of left ventricular hypertrophy (LVH), raising the possiblity that central hemodynamic changes in CKD progression participate in lowering the power of PP2 in predicting LVH in treated hypertensive patients. Age, weight, pulse rate, brachial blood pressures, and antihypertensive medication differed among the six stages. As shown in figure, pulse amplification adjusted with these confounders was the lowest in CKD stages 3a and 3b.

Conclusions: The present observations that LVMI was increased at CKD stages 3b-5 support that cardiovascular risk is higher in CKD stages 3b and later. Our findings indicate that pulse amplification is inverted in CKD stages 4 and 5, and suggest that aortic stiffening inadequately reduces PP in advanced CKD, which accounts for a high prevalence of micro- as well as macrovascular diseases of the brain and kidney. Taken together, these results implicate that CKD3b comes of age as an index for timely cardiovascular screening.

Funding: Government Support - Non-U.S.



TH-PO451

Body Composition Is Associated with Clinical Outcomes in Patients with Nondialysis-Dependent CKD Szu-Chun Hung,[1] Ting-yun Lin.[2] *[1]Taipei Tzu Chi Hospital, Taipei County, Taiwan; [2]Teipai Tzu Chi Hospital, Taipei City, Taiwan.*

Background: An inverse relationship between body mass index (BMI) and mortality (the"obesity paradox") has been demonstrated in patients with nondialysis-dependent chronic kidney disease (CKD). However, it is unclear whether increased muscle mass or body fat confers the survival advantage. We investigated the impact of body composition on the composite outcome of death or cardiovascular events in a prospective cohort of 326 patients with stage 3–5 CKD who were not yet on dialysis.

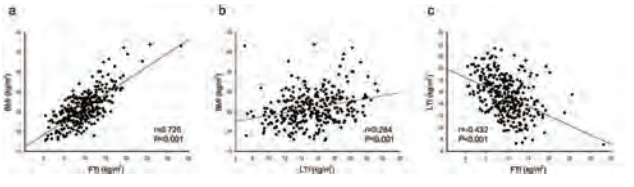
Methods: Lean mass and body fat were determined using the Body Composition Monitor (BCM), a multifrequency bioimpedance spectroscopy device, and were expressed as the lean tissue index (LTI) and fat tissue index (FTI), respectively. Patients were stratified as High (above median) or Low (below median) BMI, as High or Low LTI, or as High or Low FTI.

Results: During a median follow-up of 4.6 years, there were 40 deaths and 68 cardiovascular events. In Cox proportional hazards models, High LTI, but not High BMI or High FTI, predicted a lower risk of both the composite and its components (reference: below median). When patients were further stratified into 4 distinct body composition groups based on both LTI and FTI, only the High LTI/High FTI group had a significantly lower risk of the composite outcome (hazard ratio 0.38, 95% confidence interval 0.15–0.96; reference: Low LTI/Low FTI group).

Conclusions: LTI can provide better risk prediction than can BMI alone in nondialysis-dependent CKD patients. High LTI/High FTI appears to be associated with best outcomes. The optimal body composition for improving the prognosis of CKD needs to be determined.

Cox proportional hazards model for time to primary composite outcome

Body composition	Unadjusted		Model 1		Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
BMI (H vs L)	0.72 (0.47–1.11)	0.136	0.87 (0.57–1.33)	0.517	0.91 (0.58–1.43)	0.687
FTI (H vs L)	1.41 (0.92–2.17)	0.116	1.06 (0.67–1.68)	0.803	0.96 (0.59–1.55)	0.860
LTI (H vs L)	0.31 (0.19–0.49)	0.000	0.45 (0.26–0.78)	0.005	0.52 (0.30–0.91)	0.021



TH-PO452

Serum Bicarbonate and Pulse Wave Velocity in CKD – A Report from the CRIC Study Mirela A. Dobre,[1] Raymond R. Townsend,[9] Wei Yang,[8] Amanda H. Anderson,[8] Vecihi Batuman,[6] Jing Chen,[5] Bernard G. Jaar,[4] Radhakrishna R. Kallem,[8] Hernan Rincon-Choles,[2] Stephen M. Sozio,[3] Susan P. Steigerwalt,[7] Harold I. Feldman,[8] Thomas H. Hostetter,[1] Mahboob Rahman.[1] *[1]Case Western Reserve University, Cleveland, OH; [2]Cleveland Clinic, Cleveland, OH; [3]Johns Hopkins University School of Medicine, Baltimore, MD; [4]Johns Hopkins University and Nephrology Center of Maryland, Baltimore, MD; [5]Tulane School of Medicine, New Orleans, LA; [6]Tulane University, New Orleans, LA; [7]University of Michigan, Ann Arbor, MI; [8]University of Pennsylvania, Philadelphia, PA; [9]University of Pennsylvania School of Medicine, Villanova, PA.*

Background: Vascular stiffness is an important phenotype of cardiovascular disease (CVD) in patients with CKD. Though common in CKD, acid base disturbances as risk factors for CVD are not well studied. We aimed to test the association between serum bicarbonate and vascular stiffness as expressed by carotid femoral pulse wave velocity (cfPWV).

Methods: Serum bicarbonate and cfPWV were simultaneously measured in 3206 participants enrolled in the Chronic Renal Insufficiency Cohort (CRIC) at study year 2. Serum bicarbonate was analyzed as a categorical variable using the following groups: <22 mEql/L, 22-26 mEq/L (reference group) and >26 mEq/L, and as a continuous variable using restricted cubic splines to accommodate potential nonlinear associations. The models were adjusted for age, sex, race, diabetes, smoking, CVD, hypertension, FGF 23, Calcium, eGFR and proteinuria.

Results: The mean eGFR was 43.3±17ml/min per 1.73m2 and mean serum bicarbonate was 23.9 mEq/L. Participants with serum bicarbonate < 22 and > 26 mEq/L had significantly higher cfPWV (10.04 and 9.84 m/s respectively) compared to reference group (9.47 m/s, p=0.004) ((Figure- Panel A). In non-linear models, we found a U-shaped association between serum bicarbonate and cfPWV (p<0.05), (Figure- Panel B).

Conclusions: In a large cohort of patients with CKD, serum bicarbonate below 22 or above 26 mEq/L was associated with higher cfPWV. Further studies are needed to determine if there is a direct causal link between acid base abnormalities and vascular stiffness and to define the optimal range of serum bicarbonate in CKD to prevent adverse clinical outcomes.

Funding: Private Foundation Support

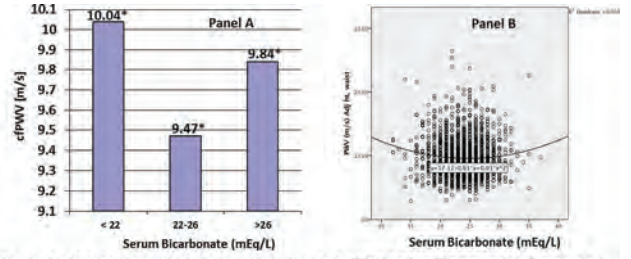


Figure - Panel A. Mean carotid femoral pulse wave velocity (cfPWV) (m/s) by serum bicarbonate strata (*p=0.004). Panel B. Association between serum bicarbonate and cfPWV: adjusted restricted cubic spline model. The solid line represents the effect (p <0.05).

TH-PO453

Renal Hyperfiltration and Central Blood Pressures: A Populational Cohort Study Marie-Eve Dupuis,[2] Francois Madore,[2] Mohsen Agharazii,[1] Remi Goupil.[2] *[1]CHUQ-HDQ, Quebec City, AB, Canada; [2]Hopital du Sacre-Coeur, Montreal, QC, Canada.*

Background: Renal hyperfiltration (RHF) in non-diabetic individuals is linked to mortality and cardiovascular events. Whether increased central blood pressure (BP) plays a role in this association is unknown.

Methods: Of the 20,004 CARTaGENE participants, 14,580 non-diabetics with central BP were identified. From these, a group with RHF (eGFR >95th percentilestratified for sex and age) was compared to a control group (eGFR 25th to 75th percentile). Central BP parameters adjusted for known confounding factors were compared using multivariate regression and propensity score matching analyses.

Results: Baseline characteristics between RHF [eGFR 108.4 (IQR 105.3, 113.3) ml/min/1.73m^2] and control [eGFR 89.9 (IQR 84.2, 95.9)] groups were similar apart from age, smoking status and BMI. All adjusted central BP parameters were higher with RHF on regression analyses. These results were replicated using propensity score matching (1:1 matching, n=721), apart from central systolic BP (113.2 ± 14.6 vs 112.3 ± 14.8, p=0.2).

Conclusions: In this populational cohort of non-diabetic individuals, RHF was associated with higher central BP parameters, independently of peripheral BP and other confounders. Whether this explain, at least in part, the increased cardiovascular morbidity and mortality associated with RHF remains to be determined.

Demographic characteristics	RHF (n=727)	Controls (n=7,292)	p
Age	52.1 ± 7.7	54.0 ± 7.7	<0.001
Sex	48%	48%	1.0
Cardiovascular disease	3.6%	3.2%	0.6
Hypertension	18%	18%	1.0
Smoking	27%	19%	<0.001
BMI	26.5 ± 5.4	27.1 ± 4.9	0.007
Brachial systolic BP	122.9 ± 15.3	123.5 ± 15.5	0.4
Brachial pulse pressure	49.7 ± 10.0	49.8 ± 10.6	0.8
Adjusted central BP parameters*			
Central systolic BP	114.9 (114.5, 115.3)	114.2 (113.9, 114.5)	<0.001
Central pulse pressure	40.7 (40.0, 41.4)	39.6 (39.2, 40.1)	<0.001
Augmentation index	28.7 (27.9, 29.5)	28.0 (27.4, 28.5)	0.03
Pulse pressure amplification	1.277 (1.268, 1.286)	1.287 (1.280, 1.293)	0.01
Augmented pressure	12.1 (11.7, 12.5)	11.6 (11.3, 11.9)	0.001

*Adjusted for age, sex, smoking, cardiovascular disease, mean BP, heart rate, total cholesterol, HDL, glucose, weight, height, bio-impedance lean body mass, aspirin, statins, beta-blockers, renin-angiotensin blockers, calcium channel blockers and diuretics.

TH-PO454

Obstructive Sleep Apnea and Cardiovascular Outcomes in CKD Patients Claudio P. Loivos, Julia F. Fernandes, Vagner S. Meira, Carla C. Lemos, Sergio E. Kaiser, Márcia R. Klein, Maria Ines Barreto-Silva, Rachel Bregman. *State University of Rio de Janeiro, Rio de Janeiro, Brazil.*

Background: Chronic kidney disease (CKD) is a non-traditional risk factor for cardiovascular disease (CVD). The frequency of obstructive sleep apnea (OSA) in this population is not well established. CVD and hypertension are related to OSA. The aim was to investigate the presence of OSA in CKD patients, its relation with blood pressure (BP) and cardiovascular outcomes.

Methods: Longitudinal study including 74 CKD patients stages 3b-4 (eGFR: CKD-EPI) under regular treatment, for 21 months. Sleep study was performed with the equipment Watch-PAT200®. OSA diagnosis: apnea-hipopnea index (AHI) ≥ 5 events/h, mild: AHI ≥ 5 ≤ 15, moderate: AHI > 15 ≤ 30, severe: AHI > 30 events/h. Blood pressure (BP) evaluated in office and by 24-hour ambulatory BP monitoring (ABPM). Statistics: SPSS 20

Results: Mean age 63.2 ± 9.3 years, 55% men. Mean eGFR: 28.7 ± 8.3 ml/min/1.73m^2, 64% CKD stage 4. All patients were under regular treatment for at least 6 months. OSA was present in 70.3% (OSA group, n=52), of which mild form: 50%, moderate: 33%, severe: 17%. Office BP in OSA group, showed higher systolic (SBP) values (153 ± 23 vs 140 ± 17 mmHg, p=0.016) and pulse pressure (PP) (71 ± 21 vs 60 ± 15 mmHg, p=0.034). ABPM showed higher values for SBP and PP in all periods (p < 0.05). When comparing patients from stages 3b and 4, no differences were observed in office BP and ABPM. AHI showed a correlation with: 24-hour mean PP (R=0.274, p=0.033), daytime PP (R=0.281, p=0.028), SBP and diastolic BP in all periods (p<0.05) regardless eGFR values. Among nondippers 77.8% presented OSA. All cardiovascular events (n=7, acute myocardial infarction and/or cerebrovascular accident) occurred in patients with OSA

Conclusions: CKD patients 3b-4 presented high OSA frequency. OSA was associated with higher SBP and PP, both in office measurements and in ABPM, despite a higher usage of antihypertensive drugs in this group. We suggest that the presence of OSA as well as systolic hypertension might be modifiable risk factors for CVD in CKD (3b-4) patients.

TH-PO455

The Association of Body Mass Index (BMI) with Mortality and Institution of Renal Replacement Therapy (RRT) in CKD Patients in the CKD-QLD Registry: Queensland, Australia Samuel S. Chan,[1,2] Anne Cameron (Salisbury),[2,3] Zaimin Wang,[2,3] Helen G. Healy,[1,2] Wendy E. Hoy.[2,3] *[1]Kidney Health Service, Royal Brisbane and Women's Hospital, Metro North Hospital and Health Service, Herston, Queensland, NSW, Australia; [2]CKD.QLD and the NHMRC CKD.CRE, The University of Queensland, Brisbane, QLD, Australia; [3]Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia.*

Background: Dialysis patients who are overweight and obese are reported to have better survival compared with those with lower BMI. We do not know if this is so in CKD patients.

Methods: A retrospective analysis of preterminal CKD patients from two major sites enrolled in the CKD. QLD registry was undertaken between May 2011 and July 2015. Associations of WHO BMI categories with subsequent death without RRT and with RRT were examined using Cox regression modelling, adjusting for hospital site, demographic variables, CKD stage, primary renal disease and co-morbidities.

Results: Of the 2,059 patients (median age 68, IQR 56–77 yr), median (IQR) BMI was 29.7 (25.9-35.0)kg/m^2. 216 died without RRT (10%) and 151 started RRT (7%). Median (IQR) ages at death and start of RRT were 78 (IQR 71-84) and 61 (IQR 49-69) yr, respectively. The incidence rates for death and start of RRT was 41.8 and 34.4 per 1000 person-years, respectively. With normal BMI (<25) persons as the referent group, the adjusted hazard ratios (HR) (95% CI) for death were 0.57 (0.40-0.81) p=0.002, for overweight subjects, 0.59 (0.41-0.85) p=0.004, for obese subjects, and 0.94 (0.56-1.60) p=0.83, for morbidly obese subjects. The adjusted HR for RRT were 1.08 (0.69-1.70) p=0.73, for overweight subjects, 1.09 (0.69-1.73) p=0.71, for obese subjects, and 1.04 (0.56-1.92) p=0.90, for morbidly obese subjects.

Conclusions: Demographic and clinical characteristics of CKD patients who die without RRT are different to patients who commence RRT. Overweight and obese, but not morbidly obese, subjects appear to be protective against death, compatible with the phenomenon observed in dialysis patients. In some patients, lower BMI may mark ill health and advanced age. However, with adjustments, there is no significant association of BMI with the likelihood of starting RRT.

Funding: Government Support - Non-U.S.

TH-PO456

Association between Body Mass Index and In-Hospital Mortality in Emergently Hospitalized Dialysis-Independent CKD Patients: A Nationwide Retrospective Cohort Study in Japan Hiroaki Kikuchi,[5] Eiichiro Kanda,[4] Fumiaki Ando,[5] Hidehiko Sato,[1] Kiyoshi Isobe,[1] Takayasu Mori,[5] Soichiro Iimori,[1] Naohiro Nomura,[5] Shotaro Naito,[5] Eisei Sohara,[5] Tomokazu Okado,[2] Shinichi Uchida,[5] Kiyohide Fushimi,[5] Tatemitsu Rai.[3] *[1]Department of Nephrology, Tokyo Medical and Dental University, Tokyo, Japan; [2]Department of Nephrology, Tokyo medical and dental university, Tokyo, Japan; [3]TOKYO MEDICAL & DENTAL UNIV, TOKYO, Japan; [4]Tokyo Kyosai Hospital, Meguro, Japan; [5]Tokyo Medical and Dental University, Tokyo, Japan.*

Background: The relationship between high body mass index (BMI) and in-hospital mortality in emergently hospitalized dialysis-independent chronic kidney disease (DI-CKD) patients is unknown.

Methods: The study cohort was comprised of 7936 emergently hospitalized DI-CKD patients (stages 3–5) age 20-70 years old who were treated in hospitals participating in the Diagnosis Procedure Combination (DPC) system. Data for patients hospitalized from April 2015 to March 2016 were collected. Patients were classified by presence (n=2427) or absence (n= 5509) of inflammation (coexistence with malignancy and/or infectious diseases). Patients were divided into tertiles by BMI: group 1, low BMI (< 20.5 kg/m^2); group 2, normal BMI (20.5-25.0 kg/m^2); group 3, high BMI (> 25.0 kg/m^2). Non-inflamed patients in BMI group 3 formed the reference group. The primary outcome was the occurrence of in-hospital death.

Results: Logistic regression analysis adjusted for baseline characteristics showed that among both inflamed and non-inflamed patients, group 1 was significantly associated with the highest risk of in-hospital mortality. For inflamed patients, the adjusted odds ratio (aOR) for group 1,2 and 3 were 3.62 [95% confidence interval (CI) (2.69, 4.86)], 2.88 (95% CI 2.13, 3.90), 2.34 (95% CI 1.68, 3.24), respectively. For non-inflamed patients, aOR for groups 1 and 2 were 2.00 (95% CI (1.51, 2.64), and 1.20 (95% CI 0.89, 1.62), respectively.

Conclusions: This study suggests that high BMI leads to better in-hospital mortality in emergently hospitalized dialysis-independent CKD patients irrespective of presence of inflammation.

Model	BMI tertile (kg/m^2)	Adjusted odds ratio (95% Confidence Interval)	
		Inflammation Present	Inflammation Absent
1[a]	1 (< 20.5 kg/m^2)	4.86 (3.65, 6.47)	2.28 (1.73, 2.99)
	2 (20.5-25.0 kg/m^2)	3.53 (2.63, 4.76)	1.26 (0.94, 1.70)
	3 (> 25.0 kg/m^2)	2.65 (1.92, 3.67)	1
2[a]	1 (< 20.5 kg/m^2)	3.55 (2.65, 4.77)	1.98 (1.50, 2.62)
	2 (20.5-25.0 kg/m^2)	2.84 (2.10, 3.84)	1.20 (0.89, 1.62)
	3 (> 25.0 kg/m^2)	2.31 (1.66, 3.20)	1
3[a]	1 (< 20.5 kg/m^2)	3.62 (2.69, 4.86)	2.00 (1.51, 2.64)
	2 (20.5-25.0 kg/m^2)	2.88 (2.13, 3.90)	1.20 (0.89, 1.62)
	3 (> 25.0 kg/m^2)	2.34 (1.68, 3.24)	1

[a] Model 1 adjusted for age and sex.
[b] Model 2 adjusted for all variables in model 1 plus history of DM and history of HTN.
[c] Model 3 adjusted for all variables in model 2 plus history of CAD and heavy smoking.

DM, diabetes mellitus; HTN, hypertension; CAD, coronary artery disease.

TH-PO457

Intensity of Statin Therapy and All-Cause Mortality in CKD Carl P. Walther, Peter Richardson, Jingbo Niu, Wolfgang C. Winkelmayer, Salim S. Virani, Sankar D. Navaneethan. *Baylor College of Medicine, Houston, TX.*

Background: KDIGO guidelines recommend statin therapy for primary or secondary prevention of vascular events in most persons with non-dialysis CKD, at doses which would be categorized as moderate-intensity by the 2013 AHA/ACC lipid guideline. It is unclear whether persons with CKD would benefit from higher intensity statin therapy given the potential higher risks of adverse events. We examined the association between incident statin therapy intensity and all-cause mortality in a non-dialysis CKD population.

Methods: Incident statin users were identified from a cohort of persons with sustained low eGFR (<60 for ≥90 days) receiving care through the Veterans Administration from 2005-08. The cohort was limited to those with filled prescriptions covering ≥67% of days in the first year of use. Exposure was categorized by preponderant dose intensity (high, moderate, low by AHA/ACC guideline) during the first year. The outcome was all-cause mortality following the exposure period. Patients were censored at last VA follow-up or 5 years. We used Cox proportional hazards regression adjusted for relevant covariates.

Results: Of 40,241 persons included, 33.9% received low-, 59.9% received moderate-, and 6.2% received high-intensity statin therapy. Median age [IQR] was 76 [66-82] years, 32.2% had diabetes, and 91.4% were CKD stage 3. High-intensity users were younger (median age 74) and more likely to have diabetes (34.6%). During 167,850 person-years of follow up 10,753 persons (26.7%) died. Unadjusted mortality was lower in the high-dose group. After multivariable regression adjustment, mortality risk did not differ across the high-, medium-, and low-intensity groups.

Conclusions: In an older, non-dialysis CKD population of US Veterans, statin therapy intensity over one year was not independently associated with all-cause mortality. This real-world analysis supports the KDIGO lipid guideline, which recommends doses of moderate intensity, although the question of whether lower intensity therapy might be equally effective is raised.

Statin intensity	Patients (N)	Events (N [%])	Event rate (per 100 person-years)	HR* (95% CI)
Low	13629	3756 (27.6)	6.44	1 (ref)
Moderate	24119	6461 (26.8)	6.41	1.03 (0.99-1.07)
High	2493	536 (21.5)	6.19	1.05 (0.96-1.15)

*Adjusted for age, CKD stage, BMI, SBP, DBP, ACEI/ARB, LDL, trig., DM, CHD, cerebrovasc. dis., PVD, COPD, CHF, malignancy

TH-PO458

Pre-ESRD Systolic Blood Pressure Trajectory and Post-ESRD Mortality Keiichi Sumida,[2] Miklos Z. Molnar,[5] Praveen Kumar Potukuchi,[5] Fridtjof Thomas,[5] Elvira Gosmanova,[3] John J. Sim,[1] Kunihiro Yamagata,[6] Kamyar Kalantar-Zadeh,[4] Csaba P. Kovesdy.[5] *[1]Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA; [2]Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; [3]Stratton VA Medical Center, Albany, NY; [4]University of California Irvine, School of Medicine, Orange, CA; [5]University of Tennessee Health Science Center, Memphis, TN; [6]University of Tsukuba, Tsukuba, Japan.*

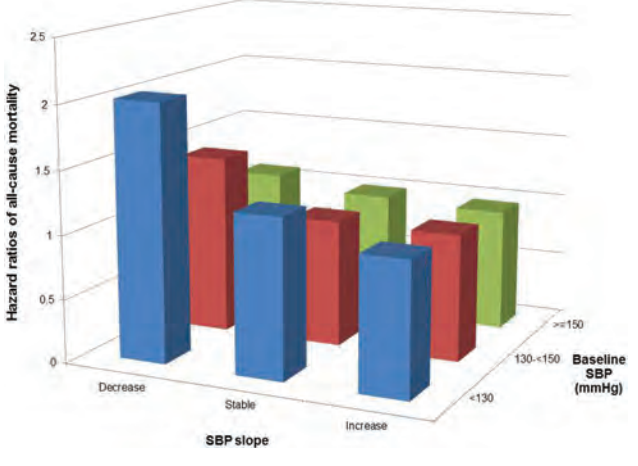
Background: Pre-ESRD systolic blood pressure (SBP) shows a reverse J-shaped association with post-ESRD mortality. However, the pre-ESRD association of SBP trajectories (decrease vs. increase vs. stable over time) with post-ESRD mortality is unknown.

Methods: We assessed SBP measurements in the last 3 years prior to dialysis in 39,383 US veterans with incident ESRD. SBP slopes and baseline levels were categorized (<-5, -5-<5, and ≥5 mmHg/year for slopes; and <130, 130-<150, and ≥150 mmHg for baseline) and combined into 9 mutually exclusive groups with slope of -5-<5 mmHg/year and baseline of 130-<150 mmHg as referent. Associations with all-cause post-ESRD mortality were examined in multivariable-adjusted Cox models.

Results: The median (interquartile interval) SBP slope and baseline SBP were -0.1 (-2.4-1.9) mmHg/year and 140 (133-149) mmHg. Decrease in SBP was associated with higher mortality, with the highest risk seen with SBP slope of <-5 mmHg/year combined with baseline SBP of <130 mmHg (adjusted hazard ratio [95% CI]: 2.02 [1.70-2.40], vs. referent; Figure). Increase in SBP was associated with lower mortality independent of baseline SBP, as was stable SBP in patients with baseline SBP ≥130 mmHg.

Conclusions: Decrease in SBP prior to dialysis start is associated with higher post-ESRD mortality, especially in patients with lower baseline SBP. Increasing SBP is associated with better outcomes independent of baseline SBP. Further studies are needed to test whether modification of pre-ESRD SBP trajectories can improve clinical outcomes in incident ESRD patients.

Funding: NIDDK Support



TH-PO459

Clinical Characteristics and Outcomes Associated with Resistant Hypertension in the VA Million Veteran Program Csaba P. Kovesdy,[3] Todd L. Edwards,[4] Otis D. Wilson,[4] Philip S. Tsao,[5] Peter W. Wilson,[2] Christopher J. O'Donnell,[1] Adriana Hung.[4] *[1]Boston Veterans Administration, Boston, MA; [2]Emory University, Atlanta, GA; [3]University of Tennessee Health Science Center, Memphis, TN; [4]Vanderbilt University, Nashville, TN; [5]Stanford University, Nashville, TN. Group/Team: On behalf of VA Million Veteran Program.*

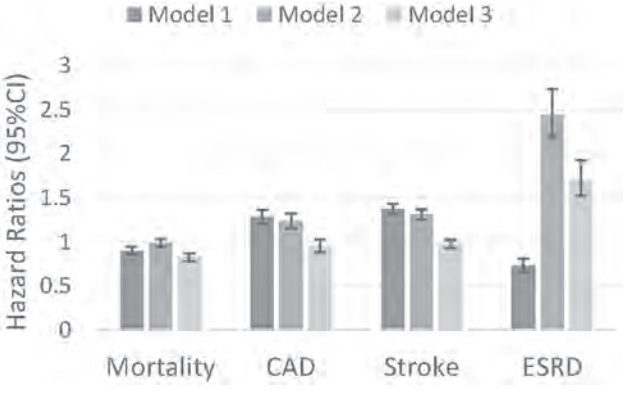
Background: The prevalence of resistant hypertension (RH), the characteristics of patients with RH and the association of RH with clinical outcomes is unclear.

Methods: Methods: From among 510,167 veterans enrolled in the Million Veteran Program (MVP), we identified 27,381 patients with the RH phenotype by using clinical data: failure to achieve outpatient BP <140/90 mmHg with three antihypertensive drugs (AHD), one being a thiazide, or success with 4 or more drugs, excluding BP measurements when pain score was >5, when interfering medications were prescribed and excluding patients with confounding medical conditions (CKD, secondary HTN, sleep apnea, urinary obstruction, adrenal, thyroid and parathyroid over-activity). Patients with RH were compared to 268,520 patients with non-resistant HTN (NRH). We examined associations with all-cause mortality, heart attacks (MI), strokes and ESRD in crude (Model 1) and multivariable Cox proportional hazards models adjusted for baseline demographics, comorbid conditions and estimated GFR (Model 2). The role of BP control was examined by additional adjustment for SBP, DBP and number of antihypertensive drugs (AHD) (Model 3).

Results: The SBP/DBP (mean/SD) and number of AHD (median/IQR) in RH vs. NRH patients were 143±18/81±13 vs. 134±12/79±11 mmHg and 4 (3-4) vs. 1 (1-2), respectively. In Model 2 RH (referent: NRH) was associated with similar mortality but significantly higher risk of MI, stroke and ESRD (Figure). The higher risks of MI and stroke were mediated by the higher BP seen in RH patients, and became non-significant after additional adjustment in Model 3. The higher risk of ESRD persisted in Model 3 (Figure). [figure1]

Conclusions: RH is associated with higher risk of incident MI, stroke and ESRD. Better BP control in patients with RH may alleviate the higher risk of MI and stroke. Further studies are needed to explain the mechanisms underlying the higher risk of ESRD in RH.

Funding: Veterans Affairs Support



TH-PO460

Apixaban versus Warfarin in Patients with Atrial Fibrillation (AF) and Stage 4 CKD John W. Stanifer,[3] Glenn M. Chertow,[6] Stefan H. Hohnloser,[4] Daniel Wojdyla,[2] Samira Garonzik,[1] Wonkyung Byon,[5] Renato D. Lopes,[2] John H. Alexander,[2] Lars Wallentin,[7] Christopher B. Granger.[2] *[1]BMS, Princeton, NJ; [2]Duke Clinical Research Institute, Durham, NC; [3]Duke University, Durham, NC; [4]J. W. Goethe University, Division of Clinical Electrophysiology, Frankfurt, Germany; [5]Pfizer, Groton, CT; [6]Stanford University School of Medicine, Palo Alto, CA; [7]Uppsala Clinical Research Center, Uppsala, Sweden.*

Background: Limited safety data exist for direct-acting oral anticoagulants in patients with advanced CKD. In Apixaban for Reduction of Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, we evaluated the effects of apixaban vs. warfarin in stage 4 CKD.

Methods: ARISTOTLE included patients with AF with a serum creatinine ≤2.5 mg/dL and estimated CrCl ≥25 mL/min. Apixaban dose was 5 mg bid or 2.5 mg bid if 2 of 3 criteria were met: age ≥80, weight ≤60 kg or serum creatinine ≥1.5 mg/dL. We used Cox proportional hazard models to analyze treatment effect stratified by CrCl category (< 30 vs ≥ 30mL/min). We also evaluated drug exposure by apixaban dose for patients with CrCl <30mL/min.

Results: Overall 269 patients (median age 81; 61% women) had a CrCl <30 mL/min. The effect of apixaban vs warfarin on stroke or systemic embolism was similar across CrCl categories (p interaction=0.50). For those with CrCl <30 mL/min, major bleeding occurred in 7 patients with apixaban and 19 with warfarin (HR 0.34; 95% CI 0.14-0.79), and the median apixaban drug exposure was 5512 ng/mL*hr (n=12) for 5mg and 2792

ng/ml*hr (n=19) for 2.5mg. The relative safety of apixaban was similar across CrCl categories (**Table**).

Conclusions: Among patients with Stage 4 CKD in ARISTOTLE, those randomized to apixaban experienced lower bleeding rates compared with warfarin, consistent with the overall population. Studies evaluating the safety and efficacy of apixaban in patients with advanced CKD, including end-stage kidney disease, are needed.

Funding: Commercial Support - Bristol-Myers Squibb/Pfizer

Bleeding rates per 100 patient-years and hazard ratios for apixaban vs. warfarin

		Bleeding Rates (n/N) CrCl <30 mL/min			Bleeding rates (n/N) CrCl ≥30 mL/min			Interaction p-value
		Apixaban	Warfarin	HR (95% CI)	Apixaban	Warfarin	HR (95% CI)	
Apixaban 2.5 mg*/placebo	Major bleeding	3.42 (4/87)	11.1 (11/85)	0.34 (0.11-1.07)	3.25 (16/337)	5.75 (26/317)	0.57 (0.31-1.07)	0.41
	Major or CRNM bleeding	4.28 (5/87)	17.9 (17/85)	0.27 (0.20-0.73)	5.14 (25/337)	8.08 (36/317)	0.64 (0.38-1.06)	0.12
Apixaban 5.0 mg/placebo	Major bleeding	4.39 (3/48)	13.3 (8/47)	0.34 (0.09-1.29)	2.08 (303/8578)	2.91 (415/8567)	0.72 (0.62-0.83)	0.26
	Major or CRNM bleeding	7.45 (5/48)	15.0 (9/47)	0.51 (0.17-1.53)	4.01 (575/8578)	5.83 (812/8567)	0.69 (0.62-0.77)	0.56

*For those who met 2 of 3 dose-reduction criteria
CrCl=creatinine clearance; CRNM=clinically relevant non-major; HR=hazard ratio.

TH-PO461

Cause-Specific Mortality among Patients with CKD and Atrial Fibrillation Sankar D. Navaneethan,[1] Jesse D. Schold,[2] Stacey Jolly,[2] Susana Arrigain,[2] Medha Airy,[1] Nisha Bansal,[3] Wolfgang C. Winkelmayer,[1] Joseph V. Nally.[2] *[1]Baylor College of Medicine, Houston, TX; [2]Cleveland Clinic, Cleveland, OH; [3]Kidney Research Institute, Seattle, WA.*

Background: Atrial fibrillation (AF) is associated with death in patients with chronic kidney disease (CKD). However, whether the increased mortality in patients with CKD is due to cardiovascular or other causes is unclear. We examined the associations between AF and cause-specific mortality in a large CKD population.

Methods: We included 62,459 patients with eGFR 15-59 ml/min/1.73 m² with AF (based on the presence of ≥2 ICD-9 codes for AF). Using the State mortality registry data, we classified deaths as follows: a) cardiovascular; b) malignancy-related; and c) non-cardiovascular/non-malignancy causes. We fitted Cox regression models for overall mortality and separate competing risk models for each cause of death category to evaluate their respective associations with AF. We conducted a separate analysis after excluding those with pre-existing malignancy.

Results: During a median follow-up of 4.1 years, 19,094 patients died; cause of death data was available for 18,854 patients. After adjusting for covariates, AF was associated with 23% increased risk of all-cause mortality, 45% increased risk of cardiovascular mortality and 13% lower risk of malignancy-related mortality in this CKD cohort (Table 1). Proportion of deaths due to ischemic heart disease (23.1% vs 16.5%) and heart failure (5.3% vs 2.4%) were higher in those with AF than among those without AF. Deaths due to cerebrovascular diseases were similar in those with and without AF. Exclusion of those with malignancy at baseline yielded similar results except that no association between AF and malignancy-related deaths was noted. Results were consistent across various stages of CKD.

Conclusions: In a non-dialysis dependent CKD population, presence of AF was associated with higher all-cause and cardiovascular mortality.

Funding: Commercial Support - Development of CCF CKD registry was suppoerted by an unrestricted educational fund to the Department of Nephrology and Hypertension from Amgen, Inc

Table 1. Associations of Atrial fibrillation with all-cause and cause-specific mortality

	Unadjusted HR (95% CI)	Adjusted* HR (95% CI)	Excluding those with malignancy Adjusted* HR (95% CI)
All-cause death	1.69 (1.62, 1.76)	1.23 (1.18, 1.29)	1.31 (1.25, 1.39)
	Unadjusted SHR (95% CI)	Adjusted* SHR (95% CI)	Adjusted* SHR (95% CI)
Cardiovascular deaths^	2.40 (2.26, 2.55)	1.45 (1.36, 1.56)	1.48 (1.37, 1.60)
Malignancy-related deaths^	0.80 (0.73, 0.89)	0.87 (0.78, 0.97)	1.01 (0.86, 1.20)
Non-CV non-malignancy deaths^	1.33 (1.23, 1.42)	1.05 (0.96, 1.13)	1.02 (0.93, 1.12)

*adjusted for age, sex, race, diabetes, hyperlipidemia, body mass index, albumin, hemoglobin, malignancy, hypertension, CAD, CHF, cerebrovascular disease, peripheral vascular disease, insurance type, ACEI/ARB, beta blocker use, smoking, eGFR

Hazard and sub-hazard ratios presented in adjusted models were pooled using Mianalyze from 5 multiply imputed datasets. ^N = 62,219 due to some missing cause of death

TH-PO462

White Matter Hyperintensities and Risk for Kidney Function Decline with Intensive Blood Pressure (BP) Lowering: The Secondary Prevention of Subcortical Strokes (SPS3) Trial Jesse C. Ikeme,[1] Michael Shlipak,[1] Oscar Benavente,[2] Carmen A. Peralta.[1] *[1]The Kidney Health Research Collaborative at SF VAMC and UCSF, San Francisco, CA; [2]University of British Columbia, Vancouver, BC, Canada.*

Background: Intensive BP lowering may help prevent stroke recurrence, but it can also cause rapid kidney function decline (RKFD). White matter hyperintensities (WMHs) on brain MRI are a marker of cerebral small vessel disease and may suggest small vessel disease in kidneys. We hypothesized that high WMH burden could identify stroke survivors susceptible to RKFD with intensive blood pressure (BP) lowering.

Methods: SPS3 randomized 3,020 participants with lacunar stroke to target systolic BPs 130-150 mmHg vs. <130 mmHg. We included 2,454 participants with baseline WMHs from brain MRI. We defined RKFD as ≥30% decline in eGFR from baseline to year 1. We tested for interaction between BP intervention and WMH severity on the incidence of RKFD in one year.

Results: At randomization, mean age was 63 years and eGFR 81 mL/min/1.73m². Two hundred thirty-four (9.5%) had RKFD at one year—100 (8.1%) in the usual BP and 134 (11.0%) in the intensive BP arm (p = 0.01). The proportion with RFKD increased with higher WMH tertile (8%, 10%, and 11% from lowest to highest tertile). The association of BP target with RKFD was qualitatively higher with increasing WMH tertile (Table), but the interaction was not significant (p = 0.65).

Conclusions: Higher WMH burden was not adequate to distinguish persons most susceptible to rapid kidney function decline in the setting of intensive BP lowering after stroke.

Funding: Other NIH Support - NIH-NIMHD grant R25MD006832 and NIH-NIA grant R01AG046206

Rapid kidney function decline (RKFD) among persons randomized to usual vs. intensive BP lowering in SPS3, stratified by WMH tertile.

BP intervention arm	Participants with RKFD at year 1	Odds ratio	(95% CI)	P
Lowest WMH tertile (n=1013)				
Usual BP arm (n=498)	7.2%	Referent		
Intensive BP arm (n=515)	9.0%	1.26	(0.80 - 1.98)	0.32
Medium WMH tertile (n=770)				
Usual BP arm (n=381)	8.7%	Referent		
Intensive BP arm (n=389)	11.3%	1.34	(0.84 - 2.16)	0.22
Highest WMH tertile (n=671)				
Usual BP arm (n=357)	8.7%	Referent		
Intensive BP arm (n=314)	14.0%	1.71	(1.05 - 2.80)	0.03

TH-PO463

Association of SNPs on FGFR4 and Klotho Genes with LVH and Cardiovascular Outcome in CKD Patients Alexander Sellier,[4] Sarah Seiler,[3] Insa E. Emrich,[1] Danilo Fliser,[5] Adam M. Zawada,[4] Gunnar H. Heine.[2] *[1]None, Haschbach, Germany; [2]Saarland University Faculty of Medicine, Homburg, Germany; [3]Saarland University Hospital, Homburg, Germany; [4]Saarland University Medical Center, Homburg (Saar), Germany; [5]Saarland University Medical Centre, Homburg/Saar, Germany.*

Background: High circulating levels of fibroblast growth factor 23 (FGF23) predict future cardiovascular events in CKD patients even after adjustment for baseline GFR. Recent rodent studies suggest that FGF23 may directly induce left ventricular hypertrophy by activating FGF-receptor 4 (FGFR4) independently from its co-receptor klotho. Opposing studies however reported a deficiency of soluble klotho, rather than high serum FGF23, to aggravate LVH. To compare the clinical relevance of these pathophysiological pathways, we examined whether SNPs within the FGFR4 and klotho gene affect the risk of prevalent LVH and incident cardiac events in our prospective CARE FOR HOMe study.

Methods: The ongoing CARE FOR HOMe study recruits chronic kidney disease G2-G4 patients, of whom 519 patients consented to DNA isolation and genotyping using qualitative real-time PCR (*Gly388Arg* for FGFR4 and *Phe352Val* for klotho). Echocardiography was conducted at baseline by one single physician following American Society of Echocardiography guidelines. All patients were followed for the occurrence of the primary endpoint cardiac decompensation for 4,2 ± 2,1 years.

Results: Carriers of the different alleles of *Gly388Arg* and *Phe352Val* did not differ significantly in their left ventricular mass index (*Gly388Arg*: Gly/Gly: 91.7 ± 28.5 g/m², Gly/Arg: 91.4 ± 24.4 g/m², Arg/Arg: 93.9 ± 28.7 g/m², p = 0.861; *Phe352Val*: Phe/Phe: 91.1 ± 25.4 g/m², Phe/Val: 92.8 ± 28.2 g/m², Val/Val: 100.9 ± 48.0 g/m², p = 0.379). During follow up, cardiovascular events occurred in 104 patients. Neither *Gly388Arg* nor *Phe352Val* was significantly associated with risk of cardiac decompensation in univariate analysis (log rank test: *Gly388Arg*: p = 0.241; *Phe352Val*: p = 0.817).

Conclusions: In CKD patients, SNPs of FGFR4 and Klotho are neither associated with LV mass, nor with the risk of future cardiac decompensation. We suggest to analyze the association between SNPs, LV hypertrophy and incident cardiac events in independent large CKD collectives before findings from rodent studies should be transferred to clinical nephrology.

TH-PO464

Renal Resistive Index in Cortical but Not in Segmental Arteries Reflects Renal Perfusion in Hypertensive CKD Patients Arkadiusz Lubas, Stanislaw Niemczyk. *Military Institute of Medicine, Warsaw, Poland.*

Background: Renal Resistive Index in segmental arteries (RI-S) is a well known marker of cardiovascular and renal organ damage. In many studies it is used as a marker of Renal Perfusion (RP). However this relation was not proved. Renal Resistive Index in cortical arteries (RI-C) is erroneously used as RI-S, because the difference between these indexes is unclear. The aim of the study was to investigate relations between segmental and cortical renal Resistive Indexes and Renal Perfusion.

Methods: Fifty patients (3F; 47M; age 56.6 ±13.3) with stable CKD (CKD-EPI 57.4 ±28.4 ml/min/1.73m^2) and a history of hypertension were enrolled in the study. Ultrasonic color and duplex Doppler examinations of intrarenal arteries in the right kidneys were performed. RI-S was calculated as a mean of 3 measurements. RI-C and RP (arterio-venous mean perfusion [mL/s]) were calculated with the use of Dynamic Tissue Perfusion Method (PixelFlux software). Echocardiographic Cardiac Index (CI), IMT, 24-h Pulse Pressure (PP) and renal function expressed as Creatinine and Cystatin based CKD-EPI formula were estimated.

Results: Renal Resistive Indexes were significantly correlated (r=0.63; R^2=0.40; p<0.001), but RI-S was lower than RI-C (0.684 ±0.075 vs 0.728 ±0.131; p=0.004). In the univariable analysis RI-S and RI-C both were significantly correlated with age, IMT, PP, CI, CKD-EPI, and RP. The multivariable regression analysis adjusted to age and BMI showed that CKD-EPI (p<0.001), CI (p=0.005) and PP (p=0.014) independently influenced RI-S (R^2=0.55, p<0.001). The same analysis for RI-C revealed an independent relation (R^2=0.41, p<0.001) with PR (p<0.001) and CI (p=0.024). When RI-S was added to the regression equation PR (p<0.001) and RI-S (p<0.001) independently modified RI-C (R^2=0.51, p<0.001).

Conclusions: Renal Resistive Index in segmental arteries is independently modified by cardiovascular and renal organ damage parameters with the exclusion of the Renal Perfusion. Although RI-S and RI-C correlate with each other, their values differ significantly. Renal cortical Resistive Index reflects both Renal Perfusion and segmental Resistive Index. Segmental and cortical renal Resistive Indexes cannot be used interchangeably.

Funding: Government Support - Non-U.S.

TH-PO465

Analysis of Genome-Wide Arterial Media-Specific DNA Methylation Demonstrates No Epigenetic Evidence of Aging but Reveals New Targets in CKD Associated Cardiovascular Pathology Athina Dritsoula,[1] Amin Oomatia,[1] Maria Kislikova,[1] Amy P. Webster,[2] Stephan Beck,[2] Jill T. Norman,[1] David C. Wheeler,[1] Thomas Oates,[1] Ben Caplin.[1] *[1]Centre for Nephrology, University College London, London, United Kingdom; [2]Cancer Institute, University College London, London, United Kingdom.*

Background: Cardiovascular disease (CVD) is the primary cause of morbidity and mortality among patients with chronic kidney disease (CKD). In CKD-related CVD, structural and morphological changes occur in the vascular bed leading to arterial stiffness, matrix deposition and calcification that have been described as accelerated arterial aging. These changes are mediated by the activation of vascular smooth muscle cells. Altered DNA methylation has been proposed to mediate the aging process and is also a manifestation of CKD. We aim to investigate tissue specific changes in DNA methylation that occur in CKD-related CVD.

Methods: DNA methylation analysis was performed (Illumina EPIC array) in bisulfite converted genomic DNA, isolated from the arterial media of 25 recipients (CKD patients; epigastric artery) and 7 donors (controls; renal artery) during kidney transplantation procedures, after the advintitia was removed and the endothelium was brushed away. Bioinformatics analysis was performed using Bioconductor packages in R (SNP and XY chromosome-related CpGs were excluded). BMIQ and Combat analysis were used for normalization and to correct technical variation respectively. DNA methylation age (DMAge) was estimated using the algorithm by Horvath *et al*. Methylation-specific PCR was used to validate the array data. P-values were adjusted for multiple comparisons.

Results: 3x10^5 differentially methylated CpGs encompassing 703 differentially methylated regions (DMR) were identified (adj p<0.05) spread across all autosomal chromosomes. Significant enrichment was found in promoters, exons, introns and 5' UTRs. DMRs were found in or in proximity to interfering RNAs (miR-196b) along with genes associated with vascular remodelling and ECM production (*COL6/7/9, ADAMTS8/9, MMP2, LOXL1*), and signalling mechanisms involved in fibrosis and vascular pathologies (*TGFβ1, FGF1/6, SMAD3, GATA3/4/5)*. DMAge and chronological age were highly correlated but there was no evidence of higher DMAge in CKD cases.

Conclusions: Overall, these data implicate altered arterial media-specific DNA methylation in CKD-related CVD, but this methylation profile does not reflect a process of accelerated aging.

TH-PO466

Methylarginines in CKD Insa E. Emrich,[7] Adam M. Zawada,[4] Jens Martens-lobenhoffer,[6] Stefan Wagenpfeil,[2] Danilo Fliser,[5] Gunnar H. Heine,[3] Stefanie M. Bode-Böger.[1] *[1]Institute of Clinical Phamacology, Medical Faculty, Otto-von Guericke University, Magdeburg, Germany; [2]Saarland University, Homburg, Germany; [3]Saarland University Faculty of Medicine, Homburg, Germany; [4]Saarland University Medical Center, Homburg, Germany; [5]Saarland University Medical Centre, Homburg/Saar, Germany; [6]University Magdeburg, Magdeburg, Germany; [7]Medical Center, Saarland University, Homburg, Germany.*

Background: Patients suffering from chronic kidney disease (CKD) have a substantial burden of cardiovascular disease, whose underlying pathophysiological mechanism cannot fully be explained by traditional risk factors. Therefore, non-traditional cardiovascular risk factors have to be taken into account. As such potential non-traditional risk factors, asymmetric dimethylarginine (ADMA) & symmetric dimethylarginine (SDMA) have been a focus of cardiorenal research for several years. It has recently been revealed that ADMA & SDMA become acetylated during their degradation. In murine models the acetylated ADMA (Ac-ADMA) & the acetylated SDMA (Ac-SDMA) were significantly associated with kidney function. We now hypothesize that (a) a similar accumulation of Ac-ADMA & Ac-SDMA occurs in humans & (b) Ac-ADMA & Ac-SDMA are more prominent predictors of incident cardiovascular events than ADMA & SDMA.

Methods: Blood samples of 528 CKD patients KDIGO stage G2 to G4 who participated in our CARE FOR HOMe study were analyzed. ADMA, SDMA & acetylated metabolites were measured by liquid chromatography – tandem mass spectrometry. All patients were followed annually with standardized interviews during a follow up period of 4.6 ± 2.0 years.

Results: Mean plasma ADMA concentration was 0.49 [0.44; 0.55] µmol/l, mean plasma SDMA concentration was 0.72 [0.59; 0.98] µmol/l, mean plasma Ac-ADMA concentration was 1.24 [0.74; 2.16] nmol/l & mean plasma Ac-SDMA concentration was 8.42 [3.60; 19.12] nmol/l. All four metabolites accumulated in patients with more advanced CKD. While Ac-ADMA was more strongly correlated with eGFR than ADMA, Ac-SDMA was less strongly correlated with eGFR than SDMA. During follow up, 144 patients suffered from a cardiovascular event. In univariate Cox-regression analyses, high plasma levels of all four metabolites were significantly associated with incident cardiovascular events. However, after adjustment for confounders including eGFR & traditional cardiovascular risk factors, only high plasma SDMA remained significantly associated with incident cardiovascular events.

Conclusions: In the future, we need further investigations to analyze the underlying acetylation's mechanism & we have to clarify the role of SDMA in cardiorenal pathophysiology.

TH-PO467

The Role of Neprilysin in CKD Insa E. Emrich,[2] Nicolas Vodovar,[1] Kathrin Untersteller,[2] Hélène Nougué,[1] Sarah Seiler,[4] Danilo Fliser,[5] Alexandre Mebazaa,[1] Jean-Marie Launay,[1] Gunnar H. Heine.[3] *[1]Inserm UMR-S 942, Paris, France; [2]None, Haschbach, Germany; [3]Saarland University Faculty of Medicine, Homburg, Germany; [4]Saarland University Hospital, Homburg, Germany; [5]Saarland University Medical Centre, Homburg/Saar, Germany.*

Background: Since the introduction of sacubitril in clinical cardiology, neprilysin has become a major treatment target for patients suffering from heart failure. Neprilysin inhibition with sacubitril prolongs survival of patients with systolic heart failure, and elevated plasma neprilysin concentrations predict adverse cardiac outcome in non-nephrological cohorts. However, natriuretic peptides were recently shown to inhibit plasma neprilysin. As natriuretic peptides accumulate in chronic kidney disease (CKD), we hypothesized that high plasma neprilysin loses its predictive role in patients with impaired renal function.

Methods: We measured plasma levels of neprilysin concentration, neprilysin activity and brain natriuretic peptide (BNP) in 542 CKD G2 - G4 patients within the CARE FOR HOMe study. Patients were followed annually for predefined endpoints (a) hospitalization for acute decompensated heart failure, and (b) atherosclerotic cardiovascular events.

Results: During 5.1 ± 2.1 years, 63 hospitalizations for acute decompensated heart failure and 125 incident atherosclerotic cardiovascular events occurred. Plasma BNP was inversely correlated with neprilysin activity (before adjustment for glomerular filtration rate: r = -0.118; p = 0.006; after adjustment: r = -0.193; p < 0.001), but not with neprilysin concentration (r = -0.022; p = 0.603 and r = 0.065; p = 0.132, respectively). Both in univariate Kaplan-Meier and in multivariate Cox regression analyses, high plasma BNP and low, rather than elevated, neprilysin activity predicted future hospitalization for acute decompensated heart failure, whereas neprilysin concentration was not predictive. Further, BNP was an independent predictor of incident atherosclerotic cardiovascular events, while neprilysin concentration and activity were not.

Conclusions: In line with experimental studies, high natriuretic peptides may inhibit neprilysin activity in CKD. In accordance, high neprilysin activity and concentrations are no predictors of adverse cardiovascular outcome in CKD patients. Thus, neprilysin inhibitors should be implemented with caution in patients with advanced CKD, and further studies are needed to better understand the benefits and risks of neprilysin inhibitors in these patients.

TH-PO468

Plasma Phospholipid Remodeling Associates with Stroke in CKD Adil Jadoon,[2] Thekkelnaycke Rajendiran,[1] Jaeman Byun,[2] Tanu Soni,[2] Subramaniam Pennathur,[2] Farsad Afshinnia.[2] *[1]Univeraity of MIchigan, Ann Arbor, MI; [2]University of Michigan, Ann Arbor, MI.*

Background: Stroke is a prevalent co-morbidity in chronic kidney disease (CKD). Systematic identification and quantification of complex lipids in stroke are lacking. This study is aimed at comparison of 17 different lipid classes in patient with and without a history of stroke.

Methods: This is a cross-sectional study of CKD patients from Clinical Phenotyping Resource and Biobank Core. Inclusion criteria were age greater than 18 years from all stages of CKD, frequency matched by gender and race among the CKD stages. Baseline demographic and clinical characteristics at the time of enrolment were background variables. Predictors were plasma lipid features identified by an untargeted liquid chromatography/mass spectrometry-based lipidomics platform from plasma samples obtained at the time of enrolment. Outcome was history of stroke. Lipids were internal standard normalized, log2 transformed, underwent calculation of percentage contribution to the corresponding lipid class, logit transformed, and z-score standardized for the downstream analyses.

Results: Overall 214 patients were included consisting of 184 patients without and 30 patients with stroke. Mean age was 60 years (SD=16). There were 104 females (48.6%); 64 patients (29.9%) were African-American and 150 (70.1%) were Caucasians. Distribution of body mass index, blood pressure, serum albumin, total cholesterol, lipoprotein, total triglycerides, and urine albumin-creatinine ratio was not different in patients with and without stroke. Overall we identified 330 lipid features of which 106 (32.1%) consisted of phospholipids including Phosphatidylcholines (PC, n=50), Phosphatidylethanolamine (PEs, n=28), Plasmenyl-Phosphatidylcholine (pPCs, n=6), and Plasmenyl-phosphatidylethanolamine (pPEs, n=12). Using a t-test, 36 lipids passed the nominal threshold of $p<0.05$ comparing patients with and without stroke, of which 23 lipids belonged to one of the phospholipid classes (over representation enrichment p=0.00004). Accordingly, PC-38:4 was the top ranking lipid with 0.73 SD higher level (95% confidence interval: 0.35 to 1.10) in stroke as compared to no stroke.

Conclusions: These findings reveal sustained significant alterations and remodeling in major plasma phospholipid subclasses in stroke in CKD patients. Further research is required to elucidate causality or long term prognostication.

TH-PO469

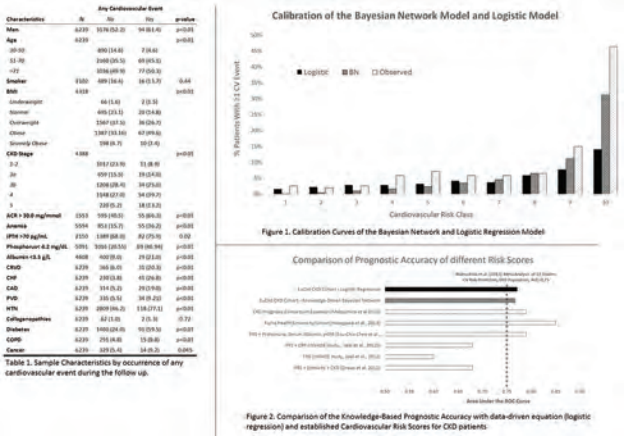
CALIBRA: A Cardiovascular, Literature-Based Risk Algorithm for CKD Patients Luca Neri, Francesco Bellocchio, Carlo Barbieri, Flavio Mari, Ulrich Tschulena, Stefano Stuard. *Fresenius Medical Care, Bad Homburg, Germany*.

Background: Current cardiovascular (CV) risk scores may have limited generizability; do not implement patient-specific prognostic reasoning; require large datasets for derivation and cannot be easily updated as new evidence emerge. CALIBRA is a Knowledge-Driven Bayesian Network risk algorithm overcoming such limitations. We compared CALIBRA predictions against established risk scores and a data-driven model.

Methods: CALIBRA is a Bayesian Network (BN) based on several meta-analyses of original cohort studies on CV risk among CKD patients. For each potential risk factor, all effect sizes were pooled with a fixed effect method and then converted to BN weights using epidemiologic data (incidence of CV events in the population; prevalence of risk factors). CALIBRA implements personalized prognostic reasoning by yielding a summary risk score, by ranking the most impacting risk factors for each patient, by suggesting further diagnostic testing maximizing prognostic accuracy. We evaluated CALIBRA accuracy (AUC) in the EuCliD CKD stage 3-5 cohort (2011-2015) and compared it to a data-driven model (logistic regression derived in the same data).

Results: We included 32 variables from high quality studies in the final model (e.g.: socio-demographic, life-style, antropometry, comorbidities, bipochemistry tests). We used the knowledge-driven model to predict CV occurrence in the validation cohort (n=6239). There were 153 CV hospitalizations in 12 months (0,025 events/100 person*year) in the validation sample, Due to incomplete clinical records, predictions were based on 16.9±2.0 variables per patient. CALIBRA accuracy was similar to the data-driven model (AUC=0.77 for both) (fig.1)

Conclusions: CALIBRA provides unique features of prognostic reasoning along with accurate risk prediction. It represents a valid tool for risk stratification and clinical evaluation. The tool is easily and promptly updatable with the most recent scientific knowledge.



TH-PO470

Design of a Clinical Risk Calculator for Atherosclerotic Renovascular Disease Diana Vassallo,[1] Robert N. Foley,[2] Philip A. Kalra.[1] *[1]Salford Royal Hospital NHS Foundation Trust, Salford, United Kingdom; [2]University of Minnesota, Minneapolis, MN.*

Background: Risk stratification in atherosclerotic renovascular disease (ARVD) can influence treatment decisions and facilitate patient selection for revascularization. In this study, we aim to use variables with the best predictive value to design a risk calculator that can assist clinicians with risk stratification and outcome prediction.

Methods: Patients with a radiological diagnosis of ARVD were recruited into a single-center prospective cohort study between 1986 and 2014. Primary clinical end-points included: death, end-stage kidney disease (ESKD) and cardiovascular events (CVE). A stepwise regression model was used to select variables with the most significant hazard ratio for each end-point. The risk calculator was designed using HyperText Markup language (HTML). Survival and CVE-free survival were estimated at 1, 5 and 10 years.

Results: In total 872 patients were recruited into this study with a median follow-up of 54.9 months (20.2-96.0). Only models predicting death and CVE showed good performance (c-index >0.80). The risk calculator (figure 1) showed that while all patients with ARVD had poor longterm survival, revascularization may improve outcomes in patients with better preserved eGFR and lower baseline proteinuria (table 1).

Conclusions: Although this risk calculator requires further independent validation in other ARVD cohorts, this study shows that a small number of easily obtained variables can help predict clinical outcomes and encourage a patient-specific therapeutic approach.

Table 1 Predicted survival probabilities for patients with different clinical phenotypes.

Overall Survival	Patient A-non-revascularized	Patient A-revascularized	Patient B-non-revascularized	Patient B-revascularized
1-year	0.75	0.89	0.75	0.75
5-year	0.36	0.48	0.36	0.36
10-year	0.08	0.17	0.08	0.08

Patient A – 70 years old, eGFR 30ml/min/1.73m2, proteinuria 0.5g/day, previous myocardial infarction, congestive heart failure and peripheral vascular disease.

Patient B – 70 years old, eGFR 20ml/min/1.73m2, proteinuria 1.0g/day, previous myocardial infarction, congestive heart failure and peripheral vascular disease.

Risk Calculator

TH-PO471

Insulin Resistance Index from OGTT Predicts Outcomes of Ischemic Stroke in Non-Diabetic Patients with Renal Dysfunction Yi-Lun Zhou, Yin Zhang, Yuesong Pan, Yilong Wang, Yongjun Wang. *Beijing Tiantan hospital, Capital Medical University, Beijing, China. Group/Team: On behalf of ACROSS-China group*.

Background: Insulin resistance is associated with increased stroke risk and poor stroke outcomes. Renal dysfunction contributes substantially to both insulin resistance

and adverse outcomes of ischemic stroke. However, the impact of impaired renal function on the associations of insulin resistance with stroke outcomes is unknown. Therefore, we sought to investigate the associations of both fasting and post-glucose load insulin resistance indices with ischemic stroke prognosis in non-diabetic patients with impaired renal function.

Methods: Patients with ischemic stroke without a history of diabetes mellitus in the Abnormal Glucose Regulation in Patients with Acute Stroke across China (ACROSS-China) registry were included. Fasting and oral glucose tolerance test (OGTT) derived measures of insulin resistance,the homeostatic model assessment of insulin resistance (HOMA-IR) and the insulin sensitivity index (ISI) were calculated. The highest quartile of HOMA-IR (Q4) or the lowest quartile of ISI (Q1) in the overall population was defined as insulin resistance. The associations between insulin resistance and stroke outcomes were investigated according to estimated glomerular filtration rate (eGFR) strata.

Results: Among 1196 patients, HOMA-IR Q4 vs.Q1-3 was associated with increased 1-year mortality (adjusted hazard ratio [95% confidence interval], 1.75 [1.03-3.00]) and poor outcome (adjusted odds ratio 2.23 [1.43-3.46]) only in participants with eGFR≥90ml/min/1.73m^2. In comparison, ISI Q1 vs. Q2-4 was associated with higher risks of mortality (adjusted hazard ratios: 3.69 [0.95-14.40]; 2.21 [1.02-4.78]; and 1.81 [1.05-3.11]) and poor outcome (adjusted odds ratios: 3.96 [1.02-15.28]; 1.96 [1.00-3.82]; and 2.25 [1.42-3.57]) in all three subgroups with eGFR<60, 60-89, and ≥90 ml/min/1.73m^2, respectively.

Conclusions: OGTT derived estimate of insulin resistance with ISI was associated with increased risks of 1-year mortality and poor outcome in non-diabetic ischemic stroke patients with impaired renal function. While the predictive value of HOMA-IR was compromised in the context of renal dysfunction.

Funding: Government Support - Non-U.S.

TH-PO472

Left Ventricular Geometry in Type 2 Diabetic Patients with Kidney Disease: Predictive Factors Klotho and FGF23 Ana P. Silva,[3,2] Filipa B. Mendes,[1] Pedro L. Neves.[3,4] *[1]Centro Hospitalar do Algarve, Faro, Portugal; [2]Department of Biomedical Sciences and Medicine, University of Algarve, Faro, Portugal; [3]Nephrology, CHA, Faro, Portugal; [4]Department of Biomedical Sciences and Medicine, University of Algarve, Faro, Portugal.*

Background: Chronic Kidney Disease (CKD) is known to induce a cardiac overload that reconfigures the architecture and physiology of the myocardium, inducing hypertrophy and fibrosis. Those alterations begin in the early stages of the disease and aggravate as renal functions declines. The this work we evaluated a population of CKD patients to ascertain the potential use of plasmatic Klotho, FGF23 or both as markers for CKD-induced cardiac disease.

Methods: This prospective cohort study was conducted in our outpatient diabetic nephropathy (DN) clinic from 2012 to 2016. For this study we included one hundred and seven (107) patients with stage 2-3 CKD. The mean age was 57.2±7.1 years and the mean LVMI level was 99.31±23.45 g/m2. LVH and RWT were used to categorize LV geometry: normal (no LVH and normal RWT), eccentric hypertrophy (LVH and normal RWT), and concentric hypertrophy (LVH and increased RWT). Patients were classified as having LVH if they had LVMI 100 g/m2 in women and 131 g/m2 in men, and RWT was considered to be increased if .0.45.

Results: Multinomial regression analysis demonstrated that diminished eGFR (OR=0.959; 95% IC;0.921 – 0.999;p=0.043)and elevated P (OR=2.859;95%IC; 2.238 – 5.693; p=0.003) levels were associated with a greater risk of Eccentric Hypertrophy but not with Concentric Hypertrophy. On contrary, low Klotho (OR=0.737; 95% IC; 0.603 – 0.972;p=0.031) and higher FGF-23 (OR= 1.031; 95% IC 1.008 – 1.055; p=0.009) levels were associated with a greater risk of Concentric Hypertrophy. Using the Kaplan-Meier analysis, it was observed that patients' survival at 60 months was 90.2 % in patients without Hypertrophy, 76.3 % in patients with Eccentric Hypertrophy and 53.6 % in patients with Concentric Hypertrophy (log rank=9.422; p = 0.009).

Conclusions: In conclusion, both Klotho and FGF23 serum levels represent good biomarkers of CVD in CKD patients they might be used along with imaging techniques, as diagnostic parameters biomarkers of the CVD.

TH-PO473

Gut Microbiome Derived Short Chain Fatty Acids Alter with Advancing CKD and Improve Prediction of Associated Cardiovascular Disease Adil Jadoon, Anna V. Mathew, Jaeman Byun, Farsad Afshinnia, Subramaniam Pennathur. *University of Michigan, Ann Arbor, MI.*

Background: Short chain free fatty acids (SCFA) are products of dietary complex carbohydrate fermentation by the intestinal microbiota and exert multiple effects on mammalian energy metabolism. However, reports of alterations in SCFAs by CKD and association with CVD are lacking. In this study, utilizing targeted metabolomics by liquid-chromatography mass-spectrometry (LC/MS), we quantified SCFAs at different stages of CKD and analyzed their association with CVD.

Methods: This is a cross sectional observational study of the population in Clinical Phenotyping Resource and Biobank Core. Inclusion criteria are patients with CKD, aged older than 18. Clinical and demographic data at the time of enrolment were gathered. Secondary outcomes were history of CAD, CHF and peripheral artery disease (PAD). SCFAs were measured by LC/MS using the plasma at enrolment. We used analysis of variance to compare means by CKD stages, and applied Receiver Operating Characteristics Curve to compare c-statistic of different models.

Results: Overall we enrolled 214 patients, including 36, 99, 61, and 18 patients from stages 2 to 5 of CKD. Mean age was 60 years (SD=16), and 51.4% were males (n=110). We found a significant graded decrease in level of acetate from 14.3±2.8 ug/L in stage 2 to 12.2±1.9 ug/L in stage 5 (p=0.011), but a significant increase in mean level of butyrate, valerate, and caproate from stage 2 to stage 5 (p≤0.018). Specifically, level of valerate increased from 1.8±0.1 ug/L in CKD stage 2 to 1.9±0.3 ug/L in stage 5 (p=0.006), and caproate increased from 1.6±0.1 ug/L to 2.0±1.4 ug/L from CKD stage 2 to 5. Mean±SD of valerate in patients with and without CAD was 1.79±0.08 ug/L and 1.62±0.09 ug/L, respectively (P<0.0001). Similarly, this value was 1.80±0.08 ug/L and 1.84±0.09ug/L in patients with and without CHF, respectively (p=0.037). Compared to a model consisting of age, diabetes, and stages of CKD to predict CAD, addition of valerate significantly improved c-statistic from 0.74 to 0.78 (p=0.029).

Conclusions: This study provides evidence for alterations in gut-microbiome derived SCFAs with advancing CKD and links SCFAs to CVD, suggesting possible contribution of gut microbiome to CKD and its complications.

TH-PO474

Urinary Biomarkers of Tubular Damage and Risk of Cardiovascular Disease and Mortality in Elders Vasantha Jotwani,[7] Ronit Katz,[5] Joachim H. Ix,[4] Orlando M. Gutierrez,[3] Chirag R. Parikh,[6] Mark J. Sarnak,[2] Michael Shlipak.[1] *[1]San Francisco VA Medical Center, San Francisco, CA; [2]Tufts Medical Center, Boston, MA; [3]UAB School of Medicine, Birmingham, AL; [4]UCSD, San Diego, CA; [5]University of Washington, Seattle, WA; [6]Yale University and VAMC, New Haven, CT; [7]UCSF, San Francisco, CA.*

Background: Novel urinary biomarkers have enabled earlier detection of kidney tubular damage, but their prognostic value for adverse cardiovascular outcomes is uncertain. We hypothesized that tubular damage, measured by urine α1-microglobulin (α1m), pro-collagen type III N-terminal pro-peptide (PIIINP), and neutrophil gelatinase-associated lipocalin (NGAL), would be associated with higher risks for cardiovascular events and mortality among elders.

Methods: In this case-cohort study of participants enrolled in the Health, Aging, and Body Composition Study, we measured urine concentrations of α1m, PIIINP, and NGAL among randomly selected CVD cases (n=245), heart failure cases (n=220), and a subcohort (n=502). We used Cox proportional hazards models to evaluate biomarker associations with incident CVD, heart failure, and all-cause mortality.

Results: At baseline, the mean age was 74 years and eGFR was 73 ml/min/1.73m^2. There were 248 deaths in the subcohort over a median follow-up of 12.4 years. After multivariable adjustment, urine α1m, PIIINP and NGAL were each associated with higher risks for CVD (**Table**). Urine α1m and NGAL were also associated with higher mortality risk. The biomarkers did not have statistically significant associations with heart failure.

Conclusions: Kidney tubular damage is an independent risk factor for CVD and death among elders. Future studies should investigate mechanisms by which renal tubular damage may adversely impact cardiovascular risk.

Funding: NIDDK Support, Other NIH Support - NIA funding of Health, Aging, and Body Composition Study (N01-AG-6-2101, N01-AG-6-2103, N01-AG-6-2106, R01-AG028050)

Associations of individual urine biomarkers with incident CVD, heart failure, and mortality

Biomarker	Incident CVD HR (95% CI)	Heart failure HR (95% CI)	All-cause mortality HR (95% CI)
α1-microglobulin	1.44 (1.11, 1.87)	1.18 (0.94, 1.48)	1.26 (1.07, 1.47)
PIIINP	1.20 (1.00, 1.44)	0.90 (0.77, 1.05)	1.06 (0.94, 1.18)
NGAL	1.12 (1.04, 1.20)	0.96 (0.88, 1.04)	1.07 (1.02, 1.12)

Hazard ratios per doubling in biomarker. Models adjust for demographics, cardiovascular risk factors, eGFR, urine albumin, and urine creatinine.

TH-PO475

Growth Differentiation Factor-15, Galectin-3, and Soluble ST-2 and Risk of Mortality and Cardiovascular Disease in CKD Courtney Tuegel,[2] Ronit Katz,[2] Zeenat Y. Bhat,[1] Keith A. Bellovich,[1] Ian H. de Boer,[2] Frank C. Brosius,[1] Crystal A. Gadegbeku,[1] Debbie S. Gipson,[1] Jennifer J. Hawkins,[1] Jonathan Himmelfarb,[2] Wenjun Ju,[1] Bryan R. Kestenbaum,[2] Matthias Kretzler,[1] Cassianne Robinson-Cohen,[2] Susan P. Steigerwalt,[1] Nisha Bansal.[2] *[1]University of Michigan, Ann Arbor, MI; [2]University of Washington, Seattle, WA.*

Background: Novel pathways may explain the excess risk of cardiovascular disease (CVD) in the chronic kidney disease (CKD) population. Growth differentiation factor-15 (GDF-15), galectin-3 (gal-3), and soluble ST-2 (sST-2) are biomarkers of inflammation, cardiac remodeling, and fibrosis that may reflect pathways promoting CVD in CKD.

Methods: We pooled CKD participants in the cohorts Seattle Kidney Study and Clinical Phenotyping and Resource Biobank Study. GDF-15, gal-3 and sST-2 were measured at baseline. Outcomes were physician-adjudicated heart failure (HF) events, atherosclerotic CVD events (myocardial infarction or cerebrovascular accident), and mortality. Cox proportional hazards were used to test associations of biomarker levels with each outcome, adjusting for demographics, CVD risk factors, and renal function.

Results: Among 883 participants, the mean eGFR was 49 mL/min per 1.73 m^2. Over median follow up of 3.10 years, there were 98 deaths (3.3%/year), 41 HF events (1.42%/year), and 29 atherosclerotic CVD events (1%/year). After adjusting for confounders, higher GDF-15, gal-3, and sST-2 levels were all independently associated with increased mortality (**Table**). Higher GDF-15 also associated with increased risk for HF and there was a trend for a similar association with sST-2. There were no statistically significant associations between GDF-15, gal-3, or sST-2 and risk of atherosclerotic CVD.

Conclusions: In adults with CKD, higher GDF-15, gal-3, and sST-2 are associated with increased risk of mortality. Elevated GDF-15 and sST-2 are also associated with increased risk of HF. The pathways of inflammation, cardiac remodeling, and fibrosis represented by these biomarkers may be important in the pathogenesis of CVD in those with CKD.

Funding: NIDDK Support

Table:

Associations of GDF-15, Gal-3 and sST2 with risks of all-cause mortality, heart failure, and atherosclerotic cardiovascular disease events

Biomarker	*Mortality* HR (95% CI)	*Heart Failure* HR (95% CI)	*Atherosclerotic CVD* HR (95% CI)
GDF-15	1.84 (1.49, 2.28)	1.74 (1.24, 2.44)	1.18 (0.77, 1.82)
Gal-3	1.57 (1.32, 1.86)	1.09 (0.76, 1.57)	1.18 (0.79, 1.59)
sST-2	1.36 (1.16, 1.58)	1.29 (0.99, 1.68)	0.77 (0.41, 1.45)

- Hazard ratios are reported per standard deviation increase in biomarker level. Standard deviation for GDF-15 (1607 pg/mL), Gal-3 (7.87 ng/mL), and sST-2 (17.49ng/mL).
- Data adjusted for demographics, CVD risk factors, and kidney function measures

TH-PO476

Syndecan-4 Is Associated with eGFR and the Incidence of Myocardial Infarction in a General Population: The Tromsø Study Marit D. Solbu,[2,4] Trine M. Reine,[5] Svein O. Kolset,[3] Trond G. Jenssen.[1,4] *[1]Oslo University Hospital, Oslo, Norway; [2]University Hospital of North Norway, Tromsø, Norway; [3]University of Oslo, Oslo, Norway; [4]Metabolic and Renal Research Group, UiT The Arctic University of Norway, Tromsø, Norway; [5]Univrsity of Oslo, Oslo, Norway.*

Background: Cardiovascular disease (CVD) is a common cause of morbidity and mortality. A link between chronic kidney disease (CKD) and CVD exists, but mechanisms are poorly understood. The endothelial glycocalyx is essential in maintaining vascular integrity. Disruption and shedding of the glycocalyx may be a common pathway in CVD and CKD. Syndecans are components of the glycocalyx. Increased serum levels of syndecan-4 is a marker of glycocalyx change or damage. We studied the cross-sectional association between syndecan-4 and kidney function, and the longitudinal association of these markers with myocardial infarction.

Methods: We used a case-cohort design and included participants from the Tromsø 5 Study (2001-02). Syndecan-4 was measured in frozen serum specimens with ELISA-assays. Baseline variables also included age, sex, cardiovascular risk factors, estimated GFR (eGFR) and urinary albumin-creatinine ratio (ACR). We used Spearman correlation, linear regression, and in Cox regression models we applied Borgan II weights.

Results: Among the 1496 men and women included, 328 experienced a fatal or non-fatal myocardial infarction between inclusion and the end of 2007. In the subcohort (n=831), mean age was 63.8 (±10.0) years, and 60.3% were women. Mean syndecan-4 was 18.7 (±5.6) ng/mL, mean eGFR was 87.7 (±13.7) ml/min/1.73 m² and median ACR (IQR) was 0.43 (0.30, 0.77) mg/mmol. In the entire cohort, syndecan-4 was significantly correlated with eGFR (r=0.15; p<0.001), but only borderline significantly with ACR (r=0.05; p=0.045). In multiple linear regression analyses adjusted for age, sex, systolic blood pressure and waist circimference, syndecan-4 was positively associated with eGFR, but not significantly associated with ACR. Adjusted for the same variables plus smoking, glycosylated hemoglobin A1c, eGFR and ACR, syndecan-4 was an independent predictor of myocardial infarction (per 1 ng/mL: HR 1.24 (1.01, 1.52; P=0.04)), but eGFR and ACR were not.

Conclusions: In a general population serum syndecan-4 was positively associated with baseline eGFR and an independent predictor of myocardial infarction. Whether this association partly may be mediated through kidney function, remains to be studied.

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TH-PO477

Decreased Serum Sulfatide Level and Hepatic Sulfatide Synthesis Ability in 5/6 Nephrectomy CKD Model Mice Yosuke Yamada,[1] Kosuke Yamaka,[1] Keita Inui,[1] Yuji Kamijo.[2] *[1]Shinshu University, Matsumoto, Japan; [2]Shinshu University School of Medicine, Matsumoto, Japan.*

Background: Chronic kidney disease (CKD) is increasing worldwide. As CKD is an independent risk factor of critical cardiovascular disease, its pathological clarification has become imperative. We earlier reported that the serum level of sulfatide, a glycosphingolipid, was decreased in CKD patients and that the risk of cardiovascular disease was higher in end-stage renal disease patients with diminished serum sulfatide. Accordingly, we have hypothesized that CKD impairs the ability to synthesize sulfatide and lowers serum sulfatide concentration to adversely affect peripheral circulation and contribute to cardiovascular disease onset. However, patients with CKD often possess comorbidities, such as hypertension and diabetes, which may act as confounders. It is therefore challenging to determine whether or not CKD influences sulfatide synthesis and serum level. To address this issue, CKD model mice whose renal function was impaired by 5/6 nephrectomy were produced for evaluation of serum sulfatide level and sulfatide synthesis ability in the liver, which is the major origin of sulfatide in the serum.

Methods: Of 14 C57B6J mice, 6 underwent 5/6 nephrectomy in which two thirds of the right kidney was removed at 11 weeks of age and the whole left kidney was removed at 12 weeks of age. The remaining 8 mice were used as controls and underwent sham operations of skin incisions only at 11 and 12 weeks of age, respectively. Both groups were maintained under identical circumstances post-operatively. The animals were sacrificed 12 weeks after the final operation and sulfatide concentrations in the serum and liver tissue were measured by Matrix-assisted laser desorption/ionization-time of flight mass spectrometry.

Results: The 5/6 nephrectomy mice developed CKD with elevated serum creatinine, urea nitrogen, and urine volume as compared with control mice. There were no significant differences in blood pressure or pulse rate between the groups. Serum sulfatide level and liver sulfatide concentration were significantly decreased in test mice versus controls (both P<0.01).

Conclusions: CKD is a cause of decreased serum sulfatide and diminished sulfatide-synthesizing ability in the liver. Further research is needed to investigate whether serum sulfatide level abnormalities contribute to the development of cardiovascular disease.

TH-PO478

Uric Acid-Lowering and Markers of CKD-Associated Mineral and Bone Disorder, Vascular Calcification, and Atherosclerosis Emily Andrews,[4] Loni J. Perrenoud,[3] Kristen L. Nowak,[7] Zhiying You,[1] Andreas Pasch,[2] Michel Chonchol,[3] Jessica B. Kendrick,[6] Diana I. Jalal.[5] *[1]UC Denver, Aurora, CO; [2]University Hospital Bern, Bern, Switzerland; [3]University of Colorado, Aurora, CO; [4]University of Colorado Denver, Aurora, CO; [5]University of Colorado Denver Health Science Center, Aurora, CO; [6]University of Colorado Denver and Denver Health Medical Center, Denver, CO; [7]University of Colorado Denver: Anschutz Medical Campus, Aurora, CO.*

Background: Chronic kidney disease (CKD)-associated mineral and bone disorder (MBD) is associated with vascular calcification and accelerated atherosclerosis. Higher uric acid reportedly suppresses 1,25-dihydroxyvitamin D (1,25(OH)2D). It is unknown if lowering serum uric acid improves markers of CKD-MBD, vascular calcification, or atherosclerosis in CKD.

Methods: Post-hoc analysis of a clinical trial randomizing 80 patients with stage 3 CKD and hyperuricemia to placebo vs allopurinol. Serum markers of CKD-MBD were measured. Protein expression of extra-renal 1α-hydroxylase was evaluated from participants' vascular endothelial cells. T_{50} and carotid intima-media thickness (CIMT) were measured as markers of serum calcification and vascular atherosclerosis, respectively. The Wilcoxon two-sample T-test was applied.

Results: Baseline characteristics between both study groups were similar except for significantly higher FGF-23 levels in the placebo group vs allopurinol. Allopurinol lowered serum uric acid levels significantly vs placebo (Table). We found no significant change in vitamin D metabolites or iPTH. Median FGF-23 levels increased slightly with allopurinol vs placebo (4.1(-10.2, 16.7) vs -1.83(-27.8, 19.1)), but this was not statistically significant. There was not a significant change in the expression of endothelial 1α-hydroxylase, serum T_{50}, or CIMT.

Conclusions: These data suggest that factors other than uric acid play a more important role in the regulation of CKD-MBD including vitamin D metabolism and the progression of vascular calcification and atherosclerosis in patients with CKD.

Funding: NIDDK Support

Changes in CKD-MBD markers, CIMT, and T50 from baseline to the end of study visit (week 12)

Variable	Placebo (n=34)	Allopurinol (n=29)	p value
Serum urate (mg/dL)	0.09±1.58	-3.28±1.42	<0.0001
Calcium (mg/dL)	-0.11±0.33	-0.04±0.48	0.45
Phosphorus (mg/dL)	-0.13±0.65	0.08±0.66	0.46
25 vitamin D (ng/mL)	2.41±6.15	0.29±5.13	0.46
1,25 vitamin D (pg/mL)	0.94±8.71	-1.53±9.98	0.63
24,25 vitamin D (pg/mL)	0.15±0.79	-0.14±0.74	0.42
iPTH (pg/mL)	1.99±31.81	2.27±29.28	0.77
FGF-23 (RU/mL) - median (IQR)	-1.83(-27.8, 19.1)	4.1(-10.2, 16.7)	0.35
Serum T50 (min)	-2.5±41.3	-13.9±57.8	0.42
CIMT (mm)	0.011±0.10	-0.01±0.07	0.40

Values are expressed as means ± SD or median (IQR)

TH-PO479

Impact of Renal Function on Association between Uric Acid and All-Cause Mortality in Patients with Chronic Heart Failure Viera Stubnva,[1,5] Ingrid Os,[3] Morten Grundtvig,[2] Bård Waldum-Grevbo.[4] *[1]Finnmark Hospital Trust, Kirkenes, Norway; [2]Innlandet Hospital Trust Lillehammer, Lillehammer, Norway; [3]Oslo University Hospital, Oslo, Norway; [4]Oslo University Hospital, Ullevål and University of Oslo, Oslo, Norway; [5]Institute of Clinical Medicine, University of Oslo, Oslo, Norway.*

Background: Serum uric acid (SUA) is associated with poor prognosis in patients with heart failure (HF). It is still unclear whether there is a causal inference between SUA and increased mortality. We investigated if SUA was an independent predictor of all-cause mortality in HF outpatients using a propensity score matching model to correct for

possible confounding variables. As SUA is closely related to renal function, we examined if renal function affected the relationship between SUA and all-cause mortality.

Methods: Patients from the Norwegian Heart Failure Registry with available baseline SUA were eligible for the study. Individuals in the highest SUA quartile were propensity score matched 1:1 with patients in the three lowest quartiles. The propensity score matching procedure was based on 16 measured baseline characteristics. Univariate Cox regression analyses were used to investigate the independent effect of SUA on all-cause mortality.

Results: A total of 4698 patients (70.4%) had valid registrations of SUA and were included in the study. Propensity score matching identified 886 pairs of patients (SUA quartile 4 compared to SUA quartiles 1 to 3). The groups were well matched, mean age was 71.1± 11.6 years, 74% were males, and mean eGFR was 50.0±20.8 ml/min/1.73 m^2. SUA was an independent predictor of all-cause mortality in HF outpatients (hazard ratio (HR) 1.21, 95% confidence interval (CI) 1.05-1.39). Renal function was found to interact the relationship between SUA and all-cause mortality (p=0.011). In patients with normal renal function (eGFR > 60 ml/min/1.73 m^2), SUA remained an independent predictor for all-cause mortality (HR1.67, 95% CI 1.25-2.24). In contrast, high SUA levels did not predict outcome in HF outpatients with renal dysfunction (HR 1.09, 95% CI 0.93-1.28).

Conclusions: Elevated SUA was an independent predictor of all-cause mortality in HF outpatients in this propensity matched study. However, SUA was associated with poor outcome only in patients with normal renal function, but not in patients with renal dysfunction.

TH-PO480

Identifying Sudden Cardiac Death using Electronic Health Records Melissa Makar,[2] Patrick H. Pun.[1] [1]*Duke University, Durham, NC;* [2]*Duke University, Durham, NC.*

Background: Sudden cardiac death (SCD) is a leading cause of mortality in the US, and disproportionally affects CKD patients. Ascertaining SCD events in electronic health records (EHRs) allows for a better understanding of modifiable risk factors and prevention; however, the complexity of the SCD phenotype makes accurate identification difficult using ICD-9 data alone. By comparing the identification of SCD using a non-machine algorithm versus physician adjudication, we aim to standardize the process of identifying cases of sudden cardiac death in large cohorts as the first step in ultimately reducing SCD incidence among CKD patients.

Methods: An automated search for ICD-9 code 427.5 (cardiac arrest) was applied to the Duke Databank for Cardiovascular Disease, a cohort of over 36,000 patients at a single institution that have undergone cardiac catheterization over the past twenty years. Non-physician, trained staff then applied an algorithm to review the EHRs of detected cases. This algorithm used questions about location, timing, and patient details to guide reviewers to pinpoint SCD cases. This was compared to the gold standard of adjudication by physicians using death certificate data, discharge summaries, and eye witness accounts.

Results: The ICD-9 search identified 1,334 potential events. Of these, 617 unique cases remained after excluding duplicate and missing records. Applying the algorithm then narrowed this to 209 cases of true sudden cardiac arrest events. A total of 88 of the 209 cardiac arrests (42%) resulted in death within 24 hours and qualified as SCD. In comparison, only 63 of the 88 cases (72%) were identified as SCD by the physician adjudication method. Additional information gathered identified the type of arrhythmia (43% VF/VT; 45% PEA or asystole; 12% other) and the type of death (75% witnessed/resuscitation attempted, 25% unobserved).

Conclusions: On its own, ICD-9 data mining to identify SCD is fraught with false positives. Adding an algorithm, based on a precise definition of sudden cardiac death, improves detection of SCD cases. This systematic approach compares favorably to the gold standard of physician adjudication. By following a standard approach to isolate cases of SCD in large cohorts, we hope to delineate a clear phenotype that can then be studied further to eventually lead to reduced SCD incidence among CKD patients.

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TH-PO481

Utility of Screening for Albuminuria among US Hispanic Adults with Preserved eGFR Harini Sarathy,[7] Rebecca Scherzer,[2] Michael Shlipak,[1] James P. Lash,[5] Donglin Zeng,[3] Neil Schneiderman,[6] Carmen A. Peralta.[4] [1]*San Francisco VA Medical Center, San Francisco, CA;* [2]*UCSF, San Francisco, CA;* [3]*University of North Carolina, Chapel Hill, NC;* [4]*University of California San Francisco/SFVAMC, San Francisco, CA;* [5]*University of Illinois at Chicago, Chicago, IL;* [6]*University of Miami, Coral Gables, FL;* [7]*UC San Francisco, San Francisco, CA.*

Background: In the U.S., Hispanics have higher prevalence of albuminuria and faster rates of CKD progression, compared to non-Hispanic whites. The yield of screening for albuminuria among Hispanics without a current indication to screen i.e. without diabetes, cardiovascular disease (CVD), or CKD is unknown. Current rates of blood pressure control and use of angiotensin converting enzyme inhibitors/ angiotensin II receptor blockers (ACEI/ARB) in those with albuminuria are not known.

Methods: Among 9510 participants in the Hispanic Communities Health Study/ Study of Latinos (HCHS/SOL) with eGFR≥60ml/min/1.73m^2 and without diabetes or CVD, we determined prevalence of albuminuria (albumin to creatinine ratio ≥30mg/g) and calculated number needed to screen (NNS), overall, and within predefined subgroups. Among those identified with albuminuria, we determined rates of blood pressure (BP)≥140/90, and use of ACEI/ARB.

Results: The median age and eGFR were 34 years (IQR 25-45) and 113 ml/min/1.73m^2 (IQR 100- 123) respectively. Prevalence of albuminuria was 5.7% (95% CI 5.2%- 6.4%) resulting in NNS of 17.0 (95% CI 16.0-19.0), and NNS was lowest among those with BP≥140/90 mmHg, followed by those with BP≥130/80 mmHg. (Figure). Among Hispanics with albuminuria, rates of BP≥140/90mmHg was 23% and ranged from 8.5 to 53% with increasing age. Only 29.5% of persons with albuminuria and BP≥140/90 were on ACEI/ARB.

Conclusions: Among Hispanics without a current indication for albuminuria testing, screening for albuminuria identified opportunities to initiate and/or intensify CVD and CKD risk reduction therapies, especially persons with hypertension.

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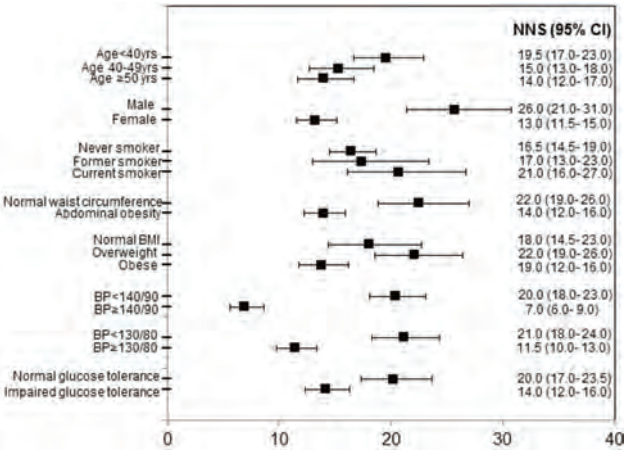


Fig 1: Number needed to screen [NNS (95%CI] to detect one case of albuminuria among Hispanic adults without diabetes or CVD and with *preserved eGFR*

TH-PO482

Moderate Impairment in Kidney Function Is Correlated to Changes in Cardiac Function and Structure Anders Christensson. *Skåne University Hospital, Malmö, Sweden.*

Background: Patients with chronic kidney disease (CKD) have an increased risk of cardiovascular diseseas and in severe renal dysfunction changes in the structure and function of the heart is common. Previous reports show that also early renal dysfunction is a risk factor for cardiovascular death, but it is not fully known if the changes in cardiac structure and function already exist in early impairment of renal function. Cystatin C is a stronger predictor for the risk of cardiovascular morbidity compared with creatinine. This study aims to investigate if there is an early link between kidney disease and cardiac structural and/or functional changes

Methods: We used a population based cohort, Malmö Preventive Project Re-examination-study (MPP-RES). 1792 participants with mean age 67 ± 6 were examined in 2002-2006. Echocardiography with tissue doppler imaging (TDI) is a method that provides a precise measure of left ventricular (LV) wall motion. Cystatin C was measured in plasma and used in the CKD-EPI formula to estimate glomerular filtration rate (eGFR). General linear regression was used for statistical analyses. We included 1504 of the participants with no prior history of heart failure (HF), EF =>40% and eGFR based >15 mL/min/1,73m2. Patients were divided in 8 groups based on e-GFR levels =>90 mL/min/1.73m2; 80-89; 70-79; 60-69; 50-59; 40-49; 30-39 ;and <30. Number of participants in these groups were 167, 221, 376, 322, 238, 121, 51 and 8, respectivley. 29,9% of the participants were women and 70,1% were men. We studied associations between e-GFR groups and echocardiography parameters.

Results: Significant correlations were found between eGFR groups and Mean é latsept and Mean E/é in the total cohort (p=0,001 and p=0.022, respectively). These correlations remain significant among men but not among women. We also dichotomized the cohort in those with eGFR <40 and >40 mL/min/1.73m2 and those with eGFR <50 and >50 mL/min/1.73m2. This demonstrated that the association was found in partcipants with eGFR <40 mL/min/1.73m2.

Conclusions: Moderate impairment of renal function correlated significantly with functional and structual echocardiographic markers of early diastolic dysfunction.

TH-PO483

CKD Increases Risk for HFpEF Admission Independent of Cardiac Function Thomas Mavrakanas,[3,4] Aisha Khattak,[2,3] Wei Wang,[1] Karandeep Singh,[3,5] David M. Charytan.[3] [1]*Department of Medicine, Brigham & Women's Hospital, Boston, MA;* [2]*University of Texas Health Science Center of Huston, Houston, TX;* [3]*Renal Division, Brigham and Women's Hospital, Boston, MA;* [4]*Division of General Internal Medicine, Geneva University Hospitals, Geneva, Switzerland;* [5]*Departments of Learning Health Sciences and Internal Medicine, University of Michigan Medical School, Ann Arbor, MI.*

Background: Chronic kidney disease (CKD) is common among patients with heart failure with preserved ejection fraction (HFpEF) and is associated with worse clinical outcomes. Whether the association of CKD with HFpEF is independent of underlying echocardiographic abnormalities is uncertain.

Methods: This retrospective cohort study included adult patients without prevalent heart failure referred for echocardiography. Patients with serial echocardiograms, left ventricular ejection fraction (LVEF) ≥50% on baseline echocardiogram and estimated glomerular filtration rate (eGFR) ≥90 ml/min/1.73m2 were matched 1:1 with patients with eGFR<60 for age (±5 years), sex, history of hypertension or diabetes, use of renin-angiotensin inhibitors, and LVEF (±5%). A secondary analysis included patients with preserved LVEF and normal left ventricular mass index matched for the same parameters except for use of renin-angiotensin inhibitors.

Results: Among 685 matched pairs, those with CKD had higher prevalence of coronary disease and higher left atrial diameter compared with controls, as well as biochemical abnormalities associated with CKD. 256 admissions for HFpEF were observed. Patients with CKD were at increased risk for HFpEF admission: crude hazard ratio (HR) 1.79 [95% CI (confidence interval) 1.38-2.33, p<0.001] and adjusted HR (for coronary disease and left atrial diameter) 1.66 (95% CI 1.23-2.24, p=0.001). LVEF and left ventricular diameter decreased over time in both groups (p<0.001 and p<0.001 respectively) but no difference was observed in rate of dropping (p=0.39 and p=0.83 respectively). Results were similar in the secondary analysis that included 289 pairs with preserved LVEF and normal left ventricular mass index (crude HR 1.99, 95% CI 1.07-3.71, p=0.03 and HR adjusted for left atrial diameter 1.98, 95% CI 1.05-3.75, p=0.04). Rate of change was similar for LVEF, pulmonary artery pressure, and left ventricular mass index in both groups (p=0.80, p=0.38, and p=0.63 respectively).

Conclusions: The increased risk of HFpEF admission in CKD is independent of baseline cardiac function and occurs despite a similar change in relevant echocardiographic parameters over time in patients with or without CKD.

Funding: NIDDK Support

TH-PO484

Renal and Overall Survival (OS) in Type 5 Cardiorenal Syndrome in Systemic AL Amyloidosis Is Dictated by Cardiac Response at 12 Months Tamer Rezk,[1,2] Helen J. Lachmann,[2] Carol Whelan,[3] Ashutosh Wechalekar,[2] Philip N. Hawkins,[2] Julian D. Gillmore.[2] *[1]Center for Nephrology, UCL Division of Medicine, London, United Kingdom; [2]National Amyloidosis Centre, London, United Kingdom; [3]National Amyloidosis centre, UCL, London, United Kingdom.*

Background: Systemic AL amyloidosis is a progressive, fatal disease that is a cause of Type 5 cardiorenal syndrome. Renal involvement leading to ESRD is the main determinant of morbidity and cardiac involvement the main determinant of mortality. Current consensus is that renal progression (reduction in eGFR>25%) is the main determinant of renal survival. We hypothesize that in patients with systemic AL amyloidosis and type 5 cardiorenal syndrome both OS and renal survival is primarily dictated by cardiac organ response as defined by current consensus criteria.

Methods: 1000 patients were prospectively enrolled into the UK ALCHEMY study from 2009-2016; 318 patients were diagnosed with cardiorenal syndrome. We report OS, renal survival and time to the composite endpoint of death and dialysis. Organ outcomes were defined according to consensus criteria, NTproBNP increase/decrease of >30% (cardiac progression/regression) and reduction in eGFR >25% (renal progression).

Results: Median age was 66yr, eGFR 55ml/min and NTproBNP 655ng/L. Median systolic BP was 112mmHg. 199 patients died and 50 required RRT with an overall survival of 18.5 months by Kaplan Meier analysis. Factors predictive at baseline of OS, renal survival and composite endpoint were NTproBNP (p<0.001, p<0.008, 0<0.001), systolic BP (p<0.001, p<0.03, p<0.007) and eGFR (p<0.001, p<0.001, p<0.001). Cardiac progression (NTproBNP increase >30%) compared to renal progression (eGFR reduction of >25%) at 12 months was more predictive of death (HR 5.0 vs 1.3, p<0.001), dialysis (HR 3.7 vs 2.7, p=0.017) and composite endpoint (HR 3.8 vs 1.7, p<0.001). Cardiac response (NT-proBNP reduction of >30%) compared to renal response (reduction in proteinuria by 30% without >25% reduction in eGFR) at 12 months was also more predictive of OS (HR 0.3 vs 0.8, p<0.001), renal survival (HR 0.3 vs 0.6, p=0.008) and composite endpoint (HR 0.3 vs 1.0, p<0.001).

Conclusions: OS, renal survival and the composite endpoint of death or dialysis in patients with type 5 cardiorenal syndrome in systemic AL amyloidosis are strongly associated with baseline eGFR, systolic BP and NTproBNP. Cardiac organ response at 12 months, as defined by consensus criteria, is more predictive of both patient and renal survival in this cohort of patients than renal organ response.

TH-PO485

Associations of Cardio-Renal Biomarkers in CKD Patients with Non-Alcoholic Fatty Liver Disease Rajkumar Chinnadurai,[1] Helen Alderson,[1] Philip A. Kalra.[2] *[1]SALFORD ROYAL NHS FOUNDATION TRUST, Manchester, United Kingdom; [2]Salford Royal Hospital NHS Trust, Salford, United Kingdom.*

Background: Non-Alcoholic Fatty Liver Disease (NAFLD) and Chronic Kidney Disease (CKD) are both associated with increased risk of cardiovascular disease(CVD). Novel biomarkers may aid early diagnosis and guide prognosis. We studied the associations of Cardio-Renal biomarkers in a cohort of non-dialysis dependent CKD (NDD-CKD) patients with NAFLD.

Methods: Patients with and without ultrasound characteristics of NAFLD were identified within the Salford Kidney Study(SKS), a large single-centre NDD-CKD cohort study. Associations of important biomarkers (KIM-1, NGAL, MPO, Anti ApoA1, NTproBNP and HsTNT) with NAFLD and major outcomes (MACE, mortality and ESKD) were studied using Cox-Regression analysis.

Results: Of the 3061 patients registered in SKS, 630 patients (NAFLD-137, Normal-493) had had liver US, complete datasets and analysis of baseline CRBM. Demographics and median values (with IQR) of biomarkers are expressed in the Table. In a Multivariable Cox-Regression Model adjusted for age, gender, NAFLD Status and baseline history of cardiovascular risk factors, TropT (HR:1.008, P=0.021), NGAL (HR:1.003, P<0.001) and KIM-1(HR-1.001, P=0.005) showed associations with MACE. All biomarkers except Anti Apo-A1 showed a positive association with mortality with Trop T showing a strong association HR 1.012, P<0.001. Higher KIM-1 and NGAL were associated with progression to ESKD.

Conclusions: The biomarker associations were very much reflective of the renal and cardiac status of the patient group. A strong independent association of biomarkers was observed with outcomes in this cohort, but NAFLD was not independently associated with any particular pattern.

VARIABLE	NAFLD(n=137)	NORMAL(n=493)	pValue (NAFLD vs Normal)
Age (Years:range)	65(59-72)	67(54-74)	0.237
Gender(Male)	84(61.3%)	294(59.6%)	0.723
Anti-Apo-A1(OD)	0.51(0.31-0.74)	0.48(0.30-0.77)	0.814
KIM-1(pg/ml)	364.4(254.7-561.7)	338.6(220.5-527.9)	0.137
MPO(ng/ml)	28.7(21.5-52.9)	36.5(20.9-59.7)	0.055
NGAL(ng/ml)	191.9(142.8-262.1)	214.6(136-323.8)	0.054
NTproBNP(pg/ml)	179.7(78-544)	299.7(116.6-958.9)	0.005
HsTrop(ng/ml)	14.9(7.8-23.7)	15.7(7.9-28.7)	0.541
Creatinine(umol/L)	143(110-191)	174(131-236)	0.000
eGFR(CKD-EPI) ml/min/1.73sqm	39.6(28.6-58.2)	31.2(20.4-44.1)	0.000

TH-PO486

Iron Therapy Modifies Oxidative Stress in Uraemic Cardiomyopathy Faisal Nuhu,[3] Roger G. Sturmey,[1] Anne-Marie L. Seymour,[3] Sunil Bhandari.[2] *[1]Hull York Medical School, Hull, United Kingdom; [2]Hull and East Yorkshire Hospitals NHS Trust and Hull York Medical School, East Yorkshire, United Kingdom; [3]University of Hull, HULL, United Kingdom.*

Background: Uraemic cardiomyopathy (UCM) is characterised by cardiac hypertrophy (LVH), metabolic remodelling and mitochondrial dysfunction, key factors in the development of heart failure (HF). Anaemia and oxidative stress are closely associated with LVH. Thus, the co-existence of both factors in chronic kidney disease (CKD) may aggravate progression to HF and increase the risk of sudden cardiac death. The aim of this study was to characterise oxidant status and iron deficiency (ID) anaemia in animal model of UCM; and determine the impact of intravenous (IV) iron therapy.

Methods: Experimental uraemia was induced in male Sprague-Dawley rats via a subtotal nephrectomy, parenteral iron injected intravenously at week 6 (10mg/Kg body weight) and studies conducted 12 weeks post-surgery. Oxidative stress was evaluated through pro-oxidant enzyme activities and anti-oxidant capacities and levels of thiobarbituric acid-reactive substances (TBARS) in UCM. The extent of uraemia, anaemia and iron status was determined by serum biochemistry. Cardiac, renal and skeletal iron content was measured by inductively coupled plasma atomic emission spectroscopy.

Results: The induction of uraemia resulted in LVH (HW/TL ratio (g/cm): 0.38 ± 0.01 vs 0.34 ± 0.01; p < 0.05); ID (serum iron (μM): 31.11 ± 1.80 vs 46.38 ± 1.44; p < 0.01), low total iron binding capacity (TIBC (μM): 26.43 ± 0.72 vs 29.46 ± 0.83; p < 0.05) and anaemia (haematocrit (%): 42.5 ± 3 vs 55.0 ± 3; p < 0.05); reduced systemic glutathione peroxidase (GPx) activity ((U/ml): 1.12 ± 0.11 vs 1.48 ± 0.12; p < 0.05). Oxidative stress in UCM was further evidenced by elevated cardiac GSSG/GSH ratio, TBARS and activities of pro-oxidant enzymes. IV iron therapy had little effect on LVH but caused repletion of hepatic iron stores, improved anaemia and systemic GPx activity. In turn, iron supplementation ameliorated oxidative stress in the heart by enhancing anti-oxidant defence system without any significant impact on the kidney. Therapy also improved oxidant status in both skeletal and hepatic tissues.

Conclusions: Iron therapy improved the anti-oxidant defence system and consequently oxidant status of cardiac and skeletal muscles. These data highlighted the benefits of managing ID anaemia in the early stages of CKD to reduce vulnerability to oxidative stress and may lessen associated adverse cardiovascular outcomes.

Funding: Commercial Support - Takeda UK Ltd; Hull and East Riding Cardiac Trust Fund and the Hull and East Yorkshire Hospitals NHS Trust R&D; Renal Research Fund (Hull and East Yorkshire), Clinical Revenue Support

TH-PO487

Iron Status and the Risk for Heart Failure Hospitalization in Veterans with CKD Monique E. Cho,[1,2] Jared Hansen,[1] Celena B. Peters,[1] Brian C. Sauer.[1,2] *[1]Veterans Health Administration, Salt Lake City, UT; [2]University of Utah, Salt Lake City, UT.*

Background: The risk for heart failure (HF) hospitalization associated with abnormal iron balance has not been evaluated in a large pre-dialysis CKD population.

Methods: We performed a historical cohort study using the national data from the Veterans Affairs Informatics and Computing Infrastructure. We identified a pre-dialysis CKD cohort (MDRD eGFR <60 mL/min/1.73m^2) with at least one set of iron indices between 2006-2015. The clinical characteristics were determined from the ICD-9 codes and laboratory data during the *baseline period*, defined as the year preceding the first available iron indices (index date). Patients with ESRD, genetic and chronic disorders affecting iron metabolism were excluded. The cohort was divided into 4 iron groups based on the joint quartiles (Q) of transferrin saturation (Tsat) and ferritin: functional iron deficiency (FID), 1st Tsat Q + 3rd–4th ferritin Qs; Low Iron (LI), reflecting absolute iron deficiency, 1st Tsat+ferritin Qs; High Iron (HI), 4th Tsat+ferritin Qs; and Reference

(R), 2nd–3rd Tsat+ferritin Qs. First hospitalization for HF following the index date was determined by ICD-9 codes. Matching weights were used to determine the effect of FID, HI, and LI on HF hospitalization risk, using R as the reference. Diabetes was examined as a potential effect modifier.

Results: Of the 1,159,371 Veterans with CKD, 148,611 met the inclusion criteria. The mean±SD for age and eGFR were 72±11 years and 43±11 mL/min/1.73 m^2, respectively. The median (IQR) Tsat and ferritin values were 20 (14, 26)% and 119 (64, 196) ng/mL. Of the study cohort, 42% could not be categorized into any of the 4 iron groups. In the remaining 83,439 Veterans, the prevalence for FID, HI, LI, and R were 13%, 17%, 20%, and 50%, respectively. After matching weights were implemented, the clinical covariates were evenly distributed among the iron groups. During the mean±SD follow-up period of 4.0±2.7 years, FID and LI groups exhibited similarly increased risk for HF hospitalization [risk ratio (95% CI): 1.14 (1.08, 1.21) and 1.13 (1.08, 1.19), respectively]. HI was associated with lower risk for HF hospitalization, 0.86 (0.81, 0.92). The association between iron status and HF hospitalization risk was not modified by the diabetes status.

Conclusions: Iron deficiency, both functional and absolute, is associated with an increased risk for HF in CKD, regardless of the diabetes status.

Funding: Veterans Affairs Support, Private Foundation Support

TH-PO488

Extracellular Vesicles (EV) Plus Swimming Exercise Training (EXE) Improve Creatinine Clearance (CrCl), Proteinuria, and Glomerulosclerosis and Decrease Mortality in Rats with CKD Rafael Luiz,[1] Rodolfo R. Rampaso,[1] Edson A. Pessoa,[1] Maria A. Gloria,[1] Luciana Jorge,[1] Kleiton A. Silva,[2] Mario luis R. Cesaretti,[1] Nestor Schor.[1] *[1]Universidade Federal de São Paulo, São Paulo, Brazil; [2]University of Missouri, Columbia, AL.*

Background: The aim of this study was to evaluate the EV and EXE on renal function and glomerulosclerosis in rats with by 5/6 Nephrectomy (5/6Nx).

Methods: Adult Wistar rats were divided in groups (n=8): Control (C), Exercise (E), Sedentary 5/6Nx (NS), Exercise 5/6Nx (NE), NS + EV (VSD) and NE + EV (VEX). The protocol was employed in 5/6Nx rats after 7 days from the surgical procedures. EXE periods were 60min/day, 5 days a week during 8 weeks and EV (100 μg) was induced into the tail vein. It was evaluated creatinine *clearance* (CrCl), proteinuria (uProt), glomerulosclerosis (%), mortality rate as well mean arterial pressure (MAP) and maximal exercise test (MEtest).

Results: The EV and EXE improve the CrCl vs NS group 0.96±0.20 ml/min, ($p<0.05$). Proteinuria was significantly different in VSE and VEX vs NE and NS groups. Glomerulosclerosis was higher in NS vs VSE and VEX ($p<0.05$). A higher mortality rate was observed in NS and VSE, but not in NE and VEX groups. BUN was normalized in NE, VSE and VEX vs NS. There is an increment in MAP but prevent, at least in part, a lower decline in the MEtest caused by 5/6Nx.

Conclusions: Results suggested that EV plus 8 weeks of EXE minimize the impact of 5/6Nx by decreasing of proteinuria, glomerulosclerosis and reduce the impact on CrCl. Finally, the decreasing mortality rate in NE and VEX vs NS and VSE indicate that exercise, at least swimming in this protocol, induced protection on renal function. Thus, it is reasonable to suggest that EV plus EXE could be an additional strategy to be employed in Chronic Kidney Disease.

	C	E	NS	NE	VSE	VEX
MAP (mmHg)	125±1	128±2	220±16*#	210±6*#	231±20*#	212±11*#
MEtest (m/min)	26±2	36±1*	16±2"	29±1#	26±1#	36±1*@
CrCL/ (ml/min/BW)	1.8±0.2	1.5±0.2	0.9±0.2"#	2.3±0.3&	1.1±0.1$	1.2±0.0$
BUN (mg/dL)	46.67±5.10	44.90±5.18	180.60±49.22"	43.62±7.30	57.8±10.8	51.1±4.2
uProt (mg/24h)	12.00±1.12	18.92±1.74	40.13±2.35*#	37.78±3.12"#	30.2±3.5%	30.9±2.6%
Glomerulosclerosis (%)	0	0	5.8±2	2.8±0.6	1.5±0.3	1.2±2.2
Mortality Rate (%)	0	0	70	39	39	12

* vs C; # vs E; & vs NxS; @ vs C, NS, NE and VSE; % vs NS and NE; " vs

TH-PO489

The Association between Neutrophil to Lymphocyte Ratio and Severity of Coronary Artery Disease in Patients with CKD Il Young Kim,[2] In seong Park,[1] Min Jeong Kim,[2] Miyeun Han,[1] Harin Rhee,[1] Sang Heon Song,[1] Eun Young Seong,[1] Dong Won Lee,[2] Soo Bong Lee,[2] Ihm Soo Kwak.[1] *[1]Pusan National University Hospital, Busan, Busan, Republic of Korea; [2]Pusan National University Yangsan Hospital, Yangsan, Republic of Korea.*

Background: Chronic inflammation is associated with increased cardiovascular mortality in patients with chronic kidney disease (CKD). Neutrophil to lymphocyte ratio (NLR) was introduced as a potential marker of inflammation in cardiac disorder. Emerging evidence have suggested that NLR might be a useful marker of cardiovascular disease. This study aimed to investigate the association between NLR and severity of coronary artery disease (CAD) in patients with CKD.

Methods: A total of 952 pre-dialysis CKD patients [estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2] who underwent elective coronary angiography (CAG) were studied. Depending on eGFR, study subjects were categorized into 3 groups (stage 3: n = 617, stage 4: n = 240, stage 5: n = 95). NLR values were calculated from complete blood count before CAG. The severity of CAD was evaluated by Gensini score according to the degree of luminal narrowing and location(s) of obstruction in the involved main coronary artery. A significant CAD was defined as lumen narrowing of one or more main coronary artery ≥ 50%.

Results: In univariate analysis, Gensini score correlated with NLR ($r = 0.542$, $P < 0.001$), age ($r = 0.123$, $P < 0.001$), diabetes mellitus (DM) ($r = 0.124$, $P < 0.001$), hypertension ($r = 0.133$, $P < 0.001$), smoking ($r = 0.088$, $P = 0.007$), eGFR ($r = -0.343$, $P < 0.001$), uric acid ($r = 0.390$, $P = 0.001$), calcium ($r = -0.097$, $P = 0.003$), phosphate ($r = 0.107$, $P = 0.001$), total cholesterol ($r = 0.115$, $P < 0.001$), CRP ($r = 0.292$, $P < 0.001$), and hemoglobin ($r = -0.225$, $P < 0.001$). In multiple regression analysis, NLR ($\beta = 0.468$, $P < 0.001$), age ($\beta = 0.064$, $P = 0.013$), DM ($\beta = 0.07$, $P = 0.007$), hypertension ($\beta = 0.068$, $P = 0.009$), eGFR ($\beta = -0.227$, $P < 0.001$), total cholesterol ($\beta = 0.063$, $P = 0.015$), and CRP ($\beta = 0.095$, $P = 0.001$) were independent predictors of Gensini score. In ROC analysis (AUC: 0.741, 95% CI: 0.710-0.772), the best cut-off value of NLR for identifying the significant CAD was 2.26 with associated sensitivity of 70.2% and specificity of 67.2%.

Conclusions: A higher NLR was an independent predictor of the severity of CAD in CKD patients. NLR could be a valuable measure for CAD risk stratification in CKD patients.

TH-PO490

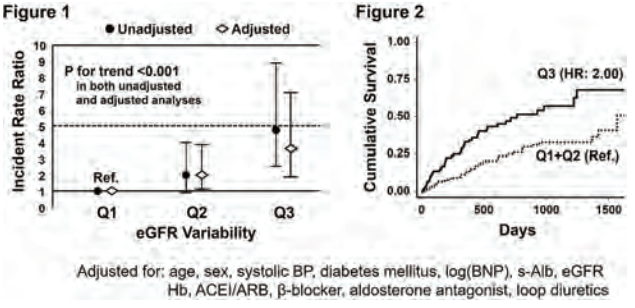
Estimated GFR Variability: A Novel Predictor of Cardiac Outcome in Outpatients with Congestive Heart Failure Tatsufumi Oka,[1] Takayuki Hamano,[2] Satoshi Yamaguchi,[1] Keiichi Kubota,[1] Masamitsu Senda,[1] Sayoko Yonemoto,[1] Yusuke Sakaguchi,[2] Isao Matsui,[1] Yoshitaka Isaka.[1] *[1]Nephrology, Osaka University Graduate School of Medicine, Suita, Japan; [2]Comprehensive Kidney Disease Research, Osaka University Graduate School of Medicine, Suita, Japan.*

Background: Reportedly, variability in renal function is associated with mortality and CKD progression in predialysis patients with CKD. However, its clinical relevance in patients with congestive heart failure (CHF) is uncertain.

Methods: In this retrospective cohort study, we enrolled CHF patients who were discharged from an educational hospital. Using 6-month data just after discharge, we linearly regressed each patient's eGFR on time and calculated eGFR variability (EGV) as "mean sqrt(residuals of eGFR)^2 / mean eGFR ×100(%)". Exposure of this study was EGV, and outcome was death or hospitalization rates over the follow-up period starting 6 months after discharge. For main analyses, we employed negative binomial regression models. As sensitivity analyses, we used Cox proportional hazards models to estimate the hazard risk of mortality or readmission whichever occurred first. Additionally, we calculated the net reclassification index (NRI) and the integrated discrimination index (IDI) of EGV.

Results: Among the 351 outpatients, median left ventricular ejection fraction, eGFR, EGV, and follow-up period were 54%, 57.5 mL/min/1.73m^2, 4.4%, and 23.6 months, respectively. Multivariate negative binomial regression analyses showed that higher EGV was associated with an increased incidence rate ratio for the outcome (Figure 1). Excluding the patients with their eGFR measured only 3 times during 6 months after discharge didn't change the results substantially. Cox regression analyses also showed that EGV of Q3 had significantly higher hazard ratio (HR) than the combined group of Q1 and Q2 (HR, 2.00; 95%CI, 1.27 to 3.15) (Figure 2). The NRI and IDI were 0.283 (P=0.014) and 0.013 (P=0.038), respectively.

Conclusions: Higher eGFR variability predicts worse cardiac outcome in outpatients with CHF.



TH-PO491

Assessment of Comorbidities and Pre-Dialysis Adverse Outcomes among Incident Renal Replacement Therapy Patients MinJeong Lee,[1,2] Inwhee Park,[1] Heungsoo Kim,[1] Gyu Tae Shin,[1] Jong Cheol Jeong.[1] *[1]Nephrology, Ajou University School of Medicine, Suwon, Republic of Korea; [2]Emergency Medicine, Ajou University School of Medicine, Suwon, Republic of Korea.*

Background: Several observational studies have shown that initiation of RRT at high estimated glomerular filtration rate(eGFR) was associated with poorer post-RRT patient survival. But, most of previous studies have been based on registry data by patients who survived to initiate RRT. Therefore, we investigated pre-dialysis morbidity and adverse outcome preceding initiation of dialysis as clinical outcomes and the association of pre-dialysis clinical outcomes with eGFR at RRT initiation.

Methods: EMR of incident dialysis patients who started maintenance dialysis between Jan 2010 and Dec 2015 were reviewed. Patients with eGFR≤20ml/min were enrolled. Comorbidity indices were calculated for each patient based on the comorbidity at the enrolled time. Patients were classified as 'safe RRT' group vs 'urgent RRT' group, defined as the patients who started RRT from urgent indication such as uremic encephalopathy, uremic pericarditis, pulmonary edema, or serum potassium≥7.0mEq/L.

Results: Among total 1,044 patients, mean eGFR at RRT initiation was 6.7±4.3ml/min/1.73m^2. Mean eGFR at RRT initiation was higher in larger comorbidity burdens(Fig1). Urgent RRT group had higher modified Charlson score than safe RRT group(4.9±2.1 vs 3.5±2.3, p< 0.001). During pre-dialysis period from enroll time to RRT initiation, patients with higher comorbidities experienced more cardiovascular adverse outcome such as MI or angina, and more infection event requiring hospitalization(Fig2).

Conclusions: Patients with larger comorbidities experienced more adverse events during pre-RRT period. Timing of RRT initiation should be individualized considering burden of comorbidities.

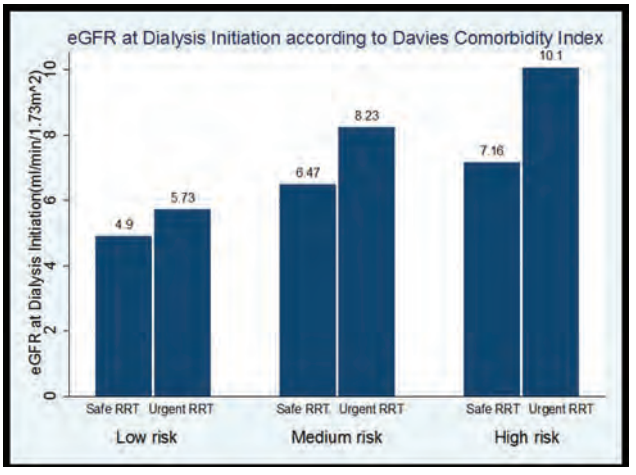


Fig1. eGFR at Dialysis Initiation

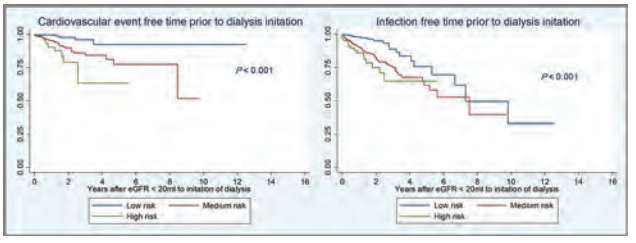


Figure 2. Pre-Dialysis Adverse Outcomes

TH-PO492

The Association between Cardiac Troponin T and Left Ventricular Structure in CKD: Result from the Korean Cohort Study for Outcomes in Patients with Chronic Kidney Disease (KNOW-CKD) Eunjeong Kang,[1] Hyo Jin Kim,[2] Hyunjin Ryu,[1] Miyeun Han,[3] Hyun suk Kim,[4] Curie Ahn,[1] Kook-Hwan Oh.[1] *[1]Seoul National University Hospital, Seoul, Republic of Korea; [2]Internal medicine, Dongguk University Gyeongju Hospital, Gyeongju, Republic of Korea; [3]Internal medicine, Busan National University Hospital, Busan, Republic of Korea; [4]Internal Medicine, Chuncheon Sacred Heart Hospital, Chuncheon, Republic of Korea.*

Background: Serum cardiac troponin T (cTnT) is a useful marker for cardiovascular disease risk in several population settings. We investigated the association between cTnT and cardiac structure and function in chronic kidney disease (CKD) patients in Korea.

Methods: Data were collected from the KNOW-CKD cohort. cTnT was measured using the highly sensitive assay and was categorized into 4 groups by quartiles (≤6.0, >6.0-10.0, >10.0-16.0, >16.0 pg/mL). Left ventricular hypertrophy (LVH) was defined as LV mass/height$^{2.7}$ ≥47g/m$^{2.7}$ in female and ≥50g/ m$^{2.7}$ in male. LV geometry was categorized into 4groups using left ventricular (LV) mass index and relative wall thickness. Systolic dysfunction was defined as ejection fraction <50% and diastolic dysfunction as E/E' >15. Demographic and clinical characteristics including age, sex, CKD stage, history of myocardial infarction, body mass index, hemoglobin, and lipid profile were included as covariates. We carried out subgroup analysis dividing into 2 groups based on estimated glomerular filtration rate (eGFR) 60mL/min/1.73m^2.

Results: Total 2,061 patients were included and the mean age was 53.5±12.3 years old. The highest 2 quartiles of cTnT were related to more than 2-fold odds ratio(OR) of LVH in the fully adjusted model. The highest quartile of cTnT was significantly associated with concentric remodeling, eccentric and concentric LVH, although such associations were not evident with the 2nd or 3rd quartile groups. Systolic and diastolic dysfunction had independent association with increment of cTnT. After the analysis according to eGFR, LVH, diastolic dysfunction, concentric and eccentric LVH were associated with cTnT independently, but not with systolic dysfunction and concentric remodeling. In ROC analysis, area under the curve for both LVH and diastolic dysfunction are above 0.7, regardless of eGFR subgroups.

Conclusions: cTnT was associated strongly with alterations of LV structure and functional abnormalities including systolic and diastolic dysfunction. These tendencies were still observed in subgroup analysis according to the eGFR, except systolic dysfunction. In ROC analysis, cTnT concentration is a reliable screening test for LVH, diastolic dysfunction, regardless of renal function.

Funding: Government Support - Non-U.S.

TH-PO493

The Efficacy of Febuxostat in CKD Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials Daqing Hong,[2] Ying Wang.[1] *[1]None, Epping, NSW, Australia; [2]Sichuan Provincial People's Hospital, CHENGDU, China.*

Background: Uric acid is considered as an independent risk factor for kidney disease. Hyperuricemia is associated with progression of renal dysfunction. Febuxostat, a xanthine oxidase (XO) inhibitor, is used to treat hyperuricemia in patients with gout. However, its effects on renal functions remain unclear. We aimed to systematically evaluate the efficacy and safety of febuxostat in patients with chronic kidney disease (CKD).

Methods: Cochrane library, MEDLINE, EMBASE and trial register system were searched for randomized controlled trials to May 18, 2017 with the terms of "febuxostat" and "chronic kidney disease". The primary outcomes were serum creatinine level, while secondary outcomes included serum uric acid level, eGFR, hsCRP, HDL-C, LDL-C, SBP and DBP. Fixed effects model analysis was used to explore the effect size of febuxostat versus control.

Results: Eight studies involving 981 participants were eventually included in this review. All studies were high quality studies. Compared with the control group, febuxostat significantly reduced the serum uric acid levels (WMD=-2.71, 95%CI: -3.68, -1.73, P<0.01, I^2=96%), with a nonsignificant effect on renal functions (a reduction in serum creatinine levels by 0.07mg/dl (WMD, 95%CI: -0.34, 0.20, P=0.60, I^2=90%), and an increase in the level of eGFR by 3.15ml/min/1.73 m^2 (WMD, 95%CI: -1.40, 7.71, P=0.17, I^2=83%)). Subgroup analysis show that febuxostat significantly increase in the level of eGFR by 6.58ml/min/1.73 m^2 compared with placebo (WMD, 95%CI: 5.04, 8.13, P<0.01, I^2=0%). Fixed effect model analysis showed that febuxostat can significantly reduce hsCRP levels by 0.24mg/L (WMD, 95%CI: -0.38, -0.09, P=0.001, I^2=31%), reduce HDL-C levels by 0.77mg/dl (WMD, 95%CI: -4.52, 2.98, P=0.69, I^2=0%) and reduce LDL-C levels by 5.95mg/dl (WMD, 95%CI: -11.89, -0.01, P=0.05, I^2=18%). There was no significant difference in the blood pressure between the febuxostat group and the control group.

Conclusions: Conclusions: Febuxostat can significantly reduce serum uric acid levels in patients with CKD with hyperuricemia with potential beneficial impact on renal function as compare to placebo. Further large RCTs are needed to assess the effect of febuxostat on renal outcomes as compared to other active uric acid lowering treatment.

TH-PO494

The Effect of Uric Acid Lowering on Albuminuria and Renal Function in Type 1 Diabetes: A Randomized Clinical Trial Sascha Pilemann-lyberg,[2,3] Frederik Persson,[1] Jan Frystyk,[3] Peter Rossing.[2] *[1]Steno Diabetes Center, Gentofte, Denmark; [2]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [3]Aarhus University, Aarhus, Denmark.*

Background: Epidemiological studies indicate that uric acid (UA) is a risk factor for development and progression of CKD. Whether UA lowering with allopurinol changes urinary albumin excretion rate (UAER) or GFR in patients with type 1 diabetes (T1D) suffering from diabetic nephropathy is not known.

Methods: We conducted a randomized, placebo-controlled, double-blinded, cross-over trial enrolling patients with T1D and a plasma uric acid ≥ 4.4 mg/dL, persistent albuminuria (urinary albumin creatinine ration) ≥30 mg/g and an eGFR ≥ 40 ml/min/1.73m^2 on stable RAS blocking intervention. The participants were randomized to: (1) Allopurinol (400 mg daily) + standard therapy; or (2) placebo + standard therapy for 60 days. Participants underwent a 4 week washout period prior to cross-over. Primary end-point was change in UAER (3*24h collections), secondary endpoint was change in GFR (^{51}Cr-EDTA-plasma clearance) measured at the end of each treatment period. The effect of UA lowering was tested using a paired t-test, after testing for carryover effects.

Results: We enrolled 30 patients, blood pressure 133(3)/75(2) mmHg and HbA1c 67(3) mmol/mol. UA decreased to 3.6 (1.2) mg/dl with allopurinol compared to 5.8 (1.5) with placebo (p<0.001). The 24h UAER (geometric mean (IQR)) was 221 (131-367) mg/24h after treatment with allopurinol and 228 (151-344) mg/24h with placebo (p=0.83). Mean (SD) GFR (^{51}Cr-EDTA) was 74 (20) ml/min/1.73m^2 after allopurinol treatment compared with 73 (20) ml/min/1.73m^2 after placebo (p=0.51). Glycemic control 24h-blood pressure and RAS blockade was stable. We found no significant association (p=0.45) between uric acid and UAER. In an unadjusted linear model, UA was significantly associated with the level of GFR (^{51}Cr-EDTA) in the placebo treatment period (R^2=0.2, p=0.017).

Conclusions: Short term UA lowering by allopurinol did not improve UAER or GFR in patients with T1D and nephropathy. The clinical significance of long-term UA lowering is currently investigated in a large multicentre clinical trial (the PERL Study), investigating the effect of 3 years of allopurinol treatment on albuminuria and slopes of measured GFR.

Funding: Private Foundation Support

TH-PO495

Effect of Losartan on Uric Acid in Patients with CKD Komal Patel,[2] Jordan L. Rosenstock.[1] *[1]None, New York, NY; [2]Northwell Health Lenox Hill Hospital, Paramus, NJ.*

Background: Increased serum uric acid (UA) is a risk factor for end-stage renal disease and agents that lower it such as allopurinol may decrease renal disease progression. Losartan inhibits URAT1 mediated renal tubule urate reabsorption by the proximal tubule, which results in an increase in urate excretion. This appears to be an effect that is unique to losartan of all the angiotensin receptor blockers. Losartan has previously been shown to increase UA excretion and decrease serum UA levels in patients without kidney disease. However, the effects of losartan on serum and urine UA in patients with kidney disease is unknown. The purpose of this study was to evaluate the change in serum and urine UA levels among individuals with stage 3 chronic kidney disease (CKD3).

Methods: The study enrolled 15 individual outpatients with CKD 3 that were to be started on losartan as part of standard clinical care indications such as proteinuria or hypertension. Baseline serum UA and 24 hour urine for fractional excretion of uric acid (FeUA) were collected prior to starting losartan and after 30 days. Patients were excluded if they had started other medications affecting UA levels within 30 days or during study period.

Results: Mean baseline GFR was 42.07 ± 6.05, and 60% were males. We found that serum UA 30 days post treatment was significantly lower than baseline (7.39 ± 1.47 to 6.85 ± 1.70) (p = 0.009). The median serum UA percent decrease from pre to post was 6% (p=0.008). However, the FE UA 30 days post treatment was not significantly different from baseline(p = 0.89).

Conclusions: This study did show a statistically significant change in serum UA levels in CKD 3 patients after the initiation of losartan. Though statistically sigfnicant, the small change in UA level may not be clinically meaningful. In patients without kidney disease levels may fall by as much as 20% and the difference suggests that renal disease may compromise the ability to respond to the uricosuric effect of losartan. Furthermore, we did not find a significant change in the FeUA. It has been suggested that the uricosuric effect with losartan is short lived as a new steady state is reached quickly, so 30 days may have been to long to recheck FeUA. This study involved a small cohort of patients, and a larger study is warranted to confirm our finding.

TH-PO496

The Effect of Uric Acid-Lowering via Allopurinol on Markers of Kidney Function and Damage in Stage III CKD Loni J. Perrenoud,[2] Emily Andrews,[3] Zhiying You,[1] Michel Chonchol,[2] Richard J. Johnson,[3] Diana I. Jalal.[4] *[1]UC Denver, Aurora, CO; [2]University of Colorado, Aurora, CO; [3]University of Colorado Denver, Aurora, CO; [4]University of Colorado Denver Health Science Center, Aurora, CO.*

Background: Hyperuricemia associates with kidney disease progression and pilot data suggest that lowering serum uric acid may slow kidney disease progression. It remains unknown if lowering serum uric acid levels improves markers of kidney damage in CKD.

Methods: Post-hoc analysis of a double-blind randomized placebo-controlled clinical study utilizing allopurinol to lower serum uric acid in 80 subjects with stage III CKD. The following markers of kidney damage were evaluated: urinary albumin/creatinine ratio (ACR), urinary neutrophil gelatinase-associated lipocalin (NGAL), urinary kidney injury molecule-1 (KIM-1), and urinary transforming growth factor (TGF)-β1. Urinary NGAL, KIM-1, and TGF-β1 were normalized to urinary creatinine. The Wilcoxon Two-Sample Test was applied.

Results: No significant differences existed between both groups at baseline. Specifically, serum uric acid levels, CKD-EPI estimated glomerular filtration rate (eGFR), and urinary ACR were similar in the placebo and allopruinol groups. After 12 weeks, allopurinol lowered serum uric acid significantly. CKD-EPI eGFR increased by 1.79 (8.08) mL/min/1.72m^2 with allopurinol group vs declined by 0.83 (5.2) mL/min/1.72m^2 in the placebo arm, but this did not achieve statistical significance (p=0.07). There was no significant difference between study groups regarding changes in serum cystatin C, cystatin C-eGFR, urinary ACR, or urinary NGAL, KIM-1, or TGF-β1 (Table).

Conclusions: Allopurinol significantly lowers serum uric acid levels in adults with stage III CKD and may increase CKD-EPI eGFR. The mechanism behind the increased eGFR is unclear as uric acid-lowering was not associated with significant change in markers of kidney damage.

Funding: NIDDK Support

Changes in markers of kidney function and kidney damage from baseline to the end of study visit (week 12)

Variable	Placebo (n=41)	Allopurinol (n=39)	P value
Serum uric acid (mg/dL)	0.05±1.54	-3.24±1.35	<0.0001
CKD EPI eGFR (mL/min/1.73m^2)	-0.83±5.2	1.79±8.08	0.07
Cystatin C (mg/L)	0.01±0.18	0.02±0.32	0.83
Cystatin C- eGFR (mL/min)	-0.18±5.44	0.32±6.10	0.93
Urinary ACR (mg/g)	-64(-3064, 52)	-0.20(-213, 414)	0.17
Urinary NGAL/Creatinine (ng/mL)	-68.9(-406, 165)	-123.3(-609, 207)	0.72
Urinary KIM-1/Creatinine (pg/mL)	4767(-19842, 20016)	3876(-17818, 36270)	0.49
Urinary TGF-β1/Creatinine (pg/mL)	0(-1253, 1857)	454(-675, 1996)	0.59

Values are expressed as means ± SD or median (IQR)

TH-PO497

Reduction in Uric Acid Correlates with Better eGFR in Patients with Hyperuricemia and CKD Treated with XOIs – A Systematic Meta-Analysis Fredrik Erlandsson, Eva K. Johnsson, Anna Hellsten kronander, Magnus K. Bjursell, Magnus Andersson. *AstraZeneca R&D, Gothenburg, Sweden.*

Background: Hyperuricemia may contribute to worsening of renal function in patients with chronic kidney disease (CKD). Uric acid (UA) lowering xanthine oxidase inhibitors (XOIs) may therefore preserve GFR.

Methods: TrialTrove was queried for studies with results using the terms "+Uricosuric agent or xanthine oxidase inhibitor". Of 660 trials 8 were published randomized clinical trials in patients with hyperuricemia and CKD treated with XOI. The effect of XOI treatment relative to control on eGFR and the impact of reduction in serum uric acid on eGFR was assessed in a random effects meta-analysis model.

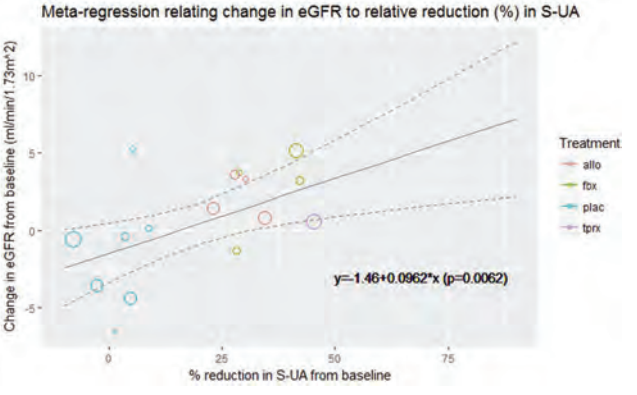
Results: Estimated GFR at end of treatment was significantly higher in the XOI arms (p<0.035) without significant heterogeneity in effect (p-value=0.075, I2- index: 45.7%). Greater reduction in UA correlated with better eGFR at the end of treatment (p<0.0062).

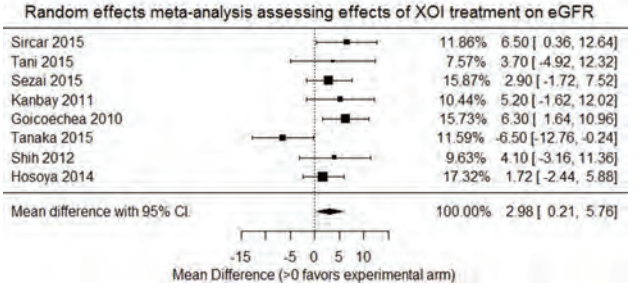
Conclusions: Renal function may benefit from intensive UA lowering therapy in CKD. Prospective studies of intensive UA lowering in CKD are warranted.

Funding: Commercial Support - AstraZeneca

Included studies

	Follow up	Experimental Arm		Control Arm	
Reference	Months	Intervention	N	Intervention	N
Sircar 2015	6	febuxostat	45	placebo	48
Tani 2015	6	febuxostat	30	placebo	30
Sezai 2015	6	febuxostat	56	allopurinol	53
Kanbay 2010	4	allopurinol	30	placebo	37
Goicoechea 2010	24	allopurinol	56	placebo	57
Tanaka 2015	3	febuxostat	21	placebo	19
Shih 2012	6	allopurinol	21	placebo	19
Hosoya 2014	5.5	topiroxostat	60	placebo	60
		Total	319	Total	323





TH-PO498

Prospective Comparative Pilot Study of the Short Term Efficacy and Oxidative Stress Effects of Various IV Iron Therapies in Iron Deficient CKD Patients Ahmed Zeidan.[1,2] *[1]Academic Renal Department, Hull & East Yorkshire Hospitals, NHS Trust, Hull, United Kingdom; [2]Research, Hull & York Medical School, Hul/York, United Kingdom.*

Background: Iron deficiency is common in chronic kidney disease (CKD) and usually leads to anaemia which is associated with fatigue, reduced quality of life and poorer clinical outcomes. Treatment with oral iron is often insufficient and guidelines recommend intravenous (i.v.) iron as an option for the treatment of iron deficiency anaemia in certain clinical situations. Reports have raised safety concerns regarding the potential increase in oxidative stress reactions and effects on cardiovascular events related to changes in endothelial function. In this study we hypothesized that CKD patients who receive intravenous iron, although efficacy may be similar, there may be differences in the

effects of iron preparation on the acute generation of oxidative stress markers and clinical effects on endothelial function.

Methods: Patients were randomised in a 1:1:1:1 ratio to intervention with one of 3 iron preparations (Cosmofer, Venofer at 200mg single dose or Monofer at 200mg or high single dose 1000mg). All patients underwent baseline assessments and following iron infusion, at 1 day, 1 week, 1 month and 3 monthly intervals. At each visit a SF-36, Pulse Wave Velocity (PWV) and blood samples for the assessment of renal function, changes in haemoglobin, iron markers, and markers of oxidative stress and endothelial function were collected.

Results: I.V. iron led to a rise in storage iron within the first 24 hours of administration and by one week a maximal rise with all iron preparations. Monofer 1000mg produced the most significant rise and reduced over the subsequent period. There was a rise in TS% within hours to levels within a toxic range (>80% for some irons). Venofer produced the greatest rise, while with Monofer this rise was more gradual in the first 24 hours. The most significant improvement in SF-36 score over the 3 month follow-up period was seen in patients who received Monofer. Acutely i.v. iron did not affect measures of endothelial function, but there was a trend in the reduction in PWV over the 3 month period.

Conclusions: All studied parenteral iron preparations led to a rise in storage and circulating iron. Those producing a saturation approaching 100% may cause an increase in catalytic iron which may lead to increased oxidative stress (under evaluation). Paradoxically there was a fall in PWV suggesting benefit in endothelial function.

Funding: Commercial Support - Pharmacosmos

TH-PO499

On Top of Standard Treatment Selective Endothelin-A Receptor Antagonism Improves Lipid Profile in CKD Neeraj Dhaun. *Cardiovascular Sciences, University of Edinburgh, Edinburgh, United Kingdom.*

Background: CKD patients have an increased risk of cardiovascular disease (CVD) that is partly explained by conventional CVD risk factors. Current guidelines recommend the use of HMG-CoA reductase inhibitors (statins) to improve lipid profile in patients with pre-dialysis CKD. Despite their use many patients continue to have elevated lipids and remain at increased CVD risk. Endothelin-A (ET_A) receptor antagonism is currently being investigated as a novel therapeutic approach to reduce proteinuria and blood pressure (BP), and to improve outcomes in pre-dialysis CKD. Here, we investigated the effects of ET_A antagonism on circulating lipids in these patients.

Methods: In a randomized double-blind, 3-way crossover study, 27 subjects with proteinuric, pre-dialysis CKD received 6 weeks treatment with placebo, sitaxentan 100mg, an ET_A antagonist, and nifedipine 30mg. Those with nephrotic syndrome were excluded. Serum total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides were measured at baseline and week 6 of each treatment period, alongside the primary endpoints of proteinuria, BP, and arterial stiffness.

Results: 18 of 27 subjects were prescribed statin therapy. Baseline lipid profile was similar in the 3 phases of the study (mean±SEM – total cholesterol: 4.9±0.1mmol/L; HDL: 0.9±0.1mmol/L; LDL: 2.8±0.2mmol/L; triglycerides: 1.7±0.3mmol/L). Whereas placebo and nifedipine did not affect total cholesterol, LDL or triglycerides, treatment with the ET_A antagonist reduced all three – baseline *vs.* week 6 – cholesterol: -11% (95% CI 8.7-13.2%, p <0.001); LDL: -21% (95% CI 17.8-27.3%, p <0.001); triglycerides: -26% (95% CI 15.1-36.5%, p <0.001). These effects were independent of the reductions seen in proteinuria, BP and arterial stiffness and were greatest in those receiving statin treatment. HDL was unaffected by all treatments.

Conclusions: In addition to currently recognized effects on proteinuria and BP, ET_A antagonism may modify lipid profile and so have broader cardioprotective effects in CKD. Larger and longer-term trials with this specific endpoint are now warranted.

TH-PO500

Phase I Evaluation of AZD9977, a First in Class Mineralocorticoid Receptor (MR) Modulator Fredrik Erlandsson,[1] Muna Albayaty,[2] Ligia E. Chialda,[2] Hans I. Ericsson,[1] Carl Amilon,[1] Karin Nelander,[1] Krister Bamberg,[1] Rasmus Jansson-Lofmark,[1] Linda C. Wernevik,[1] Magnus B. Kjaer,[1] Judith Hartleib-Geschwindner.[1] *[1]AstraZeneca R&D, Gothenburg, Sweden; [2]PAREXEL International, Berlin, Germany.*

Background: MR antagonists may improve outcomes in patients with chronic kidney disease, but are associated with hyperkalemia. Pre-clinical data indicate AZD9977 could be a first in class MR modulator with similar organ protection as eplerenone, but associated with minimal urinary electrolyte effects.

Methods: Phase I development began with a single dose escalation trial from 5mg to 1200mg, followed by a randomized placebo controlled cross-over four period clinical trial in 23 healthy volunteers. The treatments administered were fludrocortisone (A), 200mg AZD9977 + fludrocortisone (B), 100mg eplerenone + fludrocortisone (C), and 200mg AZD9977 + 100mg eplerenone + fludrocortisone (D). Treatment D was administered to assess if AZD9977 could attenuate the natriuresis induced by eplerenone as observed in rodent studies. A baseline session without treatment was performed. Food and fluid intake was controlled and urine collected in 2h intervals. The primary endpoint was log[Na]/[K] in urine collected from 2 to 8h.

Results: In the single dose escalation trial all doses were well tolerated. Pharmacokinetic and safety results were compatible with further development. In the cross-over trial 200mg AZD9977 (B) exhibited similar effects on diuresis and urinary electrolytes as 100mg eplerenone (C), and the combination (D) had an additive effect on urinary electrolytes. Fludrocortisone exposure was similar across treatments, and there was no significant pharmacokinetic interaction between eplerenone and AZD9977.

Conclusions: The results in man contradict the results in rodent models driven by aldosterone, in which AZD9977 had minimal electrolyte effects, but aligned with studies in rodent models driven by fludrocortisone. The effect of MR modulators on electrolyte excretion may depend on the MR agonist. Clinical studies of how AZD9977 or other MR modulators affect urinary electrolytes in the presence of aldosterone are needed.

Funding: Commercial Support - AstraZeneca

Cross-over trial results

Endpoint	Baseline	A	B	C	D
Log [Na]/[K] 2-8h	2.4	-4.1	-0.69	-0.54	0.69
Diuresis 2-8h (ml)	782	668	749	766	774
U-Na 2-8h (mmol)	47	11	25	28	38
U-K 2-8h (mmol)	20	36	31	32	30

TH-PO501

A Phase 2a Trial of DMX-200: Synergistic Blockade of AT1R and CCR2 in Patients with CKD David A. Power,[1] Stephen G. Holt,[4] Paul J. Champion de Crespigny,[5] Matthew A. Roberts,[3] James H. Williams,[6] Kathryn M. Harrison,[2] David K. Packham.[7] *[1]Austin Health, Heidelberg, VIC, Australia; [2]Dimerix Bioscience Limited, Melbourne, NSW, Australia; [3]Eastern Health, Blackburn, VIC, Australia; [4]Royal Melbourne Hospital, Melbourne, NSW, Australia; [5]The Royal Melbourne Hospital, Parkville, NSW, Australia; [6]Dimerix Bioscience Pty Ltd, Nedlands, WA, Australia; [7]Melbourne Renal Research Group, Melbourne, VIC, Australia.*

Background: The angiotensin II receptor type 1 (AT1R) and chemokine receptor 2 (CCR2), both G protein-coupled receptors, form functional heteromers. Simultaneous antagonism of these receptors had a beneficial effect on proteinuria, podocyte viability and recruitment of inflammatory monocytes to the kidney in the sub-total nephrectomy rat model of nephrotic syndrome.

Methods: Patients (n=27) were enrolled in an open label, Phase 2a, dose escalation study at 4 sites in Australia. The primary objective was to determine the safety and tolerability of the CCR2 antagonist organic germanium added to stable treatment of the AT1R antagonist irbesartan in patients with proteinuria. The secondary objective was to evaluate the effects of organic germanium on various biomarkers including proteinuria. All patients were on a stable dose of irbesartan for ≥ 3-months prior to enrolment and throughout the study. Patients received escalating doses of organic germanium (10, 20, 30, 50, 80mg TID) at 4-week intervals unless proteinuria was within normal limits. Participants remained on their maximum dose for a further 2 intervals

Results: No serious safety concerns were observed in patients on irbesartan when treated with 10-80 mg TID organic germanium. The average age of patients was 61±13 (SD) years. Primary diagnoses were diabetic nephropathy (n=7), IgA nephropathy (n=5), and other proteinuric diseases (n=15). The baseline eGFR was 32±12 (range 15-59), PCR 255±174 mg/mmol (range 70-700), and irbesartan dose 75-300 mg (81% on 300 mg). Three patients withdrew from the study for reasons unlikely to be related to the study drug. There were no clinically relevant changes in blood pressure, eGFR and serum potassium. Of the 24 patients that completed dosing, 6 achieved ≥ 50% reduction in proteinuria during at least one dose level of organic germanium.

Conclusions: No safety concerns were observed in patients on irbesartan when treated with 10-80 mg TID organic germanium. The additive reduction in proteinuria over and above AT1R blockade in some patients warrants additional clinical investigation of DMX-200 for proteinuric CKD.

Funding: Commercial Support - Dimerix Limited

TH-PO502

Stanniocalcin-1 Inhibits ER Stress and Renal Fibrosis via an AMP-Activated Protein Kinase-Dependent Pathway in HK2 Cells Eun mi Yang,[1,2] Eun Hui Bae,[1,2] Seong Kwon Ma,[1,2] Soo Wan Kim.[1,2] *[1]Chonnam National University Hospital, Gwangju, Republic of Korea; [2]Chonnam National University Medical School, Gwangju, Republic of Korea.*

Background: The role of endoplasmic reticulum (ER) stress in the development of renal disease is a relatively recently described, and has been suggested as a cause for the fibrotic remodeling. Therefore, modulation of ER stress could be one of the possible therapeutic approaches to renal fibrosis. Stanniocalcin-1 (STC-1) is a multifunctional glycoprotein with antioxidant and anti-inflammatory properties and regulates AMP-activated protein kinase (AMPK) activity in the kidney. Activation of AMPK may reduce ER stress. The present study aimed to investigate the effects of STC-1 in ER stress and renal fibrosis in human renal proximal tubular (HK-2) cells

Methods: HK2 cells pretreated with STC-1 (200 ng/ml) for 1 hours followed by treatment with TGF-β (10 ng/ml) for 16 hours. To determine whether effect of STC-1 mediated by AMPK activation, pharmacological inhibitor (compound C, 5 uM) pretreated with STC-1. The protein expression of ER stress markers and fibrosis markers was determined by semiquantitative immunoblotting. The level of reactive oxygen species (ROS) was determined by fluorescent microscopy immunofluorescence.

Results: TGF-β treatment induced upregulation of glucose-related protein (GRP)78 and C/EBP homologous protein (CHOP) and STC-1 pretreatment attenuated the rise in the GRP 79 and CHOP. TGF-β treatment also induced upregulation of fibronectin and alpha-smooth muscle actin (α-SMA) and STC-1 pretreatment attenuated the TGF-β induced upregulation of fibronectin and α-SMA. STC-1 pretreatment significantly blocked TGF-β induced downregulation of AMPK and decreased level of ROS via upregulate the uncoupling protein (UCP2). On the other hand, compound C pretreatment with STC-1

before TGF-β treatment abolished the activation of AMPK, diminished the upregulation of UCP2, and aggravated ER stress and fibrosis but did not affect STC-1 expression.

Conclusions: STC-1 Inhibits ER stress and renal fibrosis via an AMPK Pathway and STC-1 may be a therapeutic target through reducing ER stress and renal fibrosis.

Funding: Government Support - Non-U.S.

TH-PO503

Tubulointerstitial Nephritis with IgM-Positive Plasma Cells Naoki Takahashi,[1] Takako Saeki,[2] Atsushi Komatsuda,[3] Ken-ichi Samejima,[4] Yudai Nishikawa,[1] Kazuhisa Nishimori,[1] Sayu Morita,[1] Mamiko Kobayashi,[1] Yukie Morikawa,[1] Sachiko Fukushima,[1] Seiji Yokoi,[1] Daisuke Mikami,[1] Hideki Kimura,[1] Kenji Kasuno,[1] Ichiei Narita,[5] Masayuki Iwano.[1] *[1]Department of Nephrology, University of Fukui, Fukui, Japan; [2]Department of Internal Medicine, Nagaoka Red Cross Hospital, Nagaoka, Japan; [3]Department of Hematology, Nephrology and Rheumatology, Akita University School of Medicine, Akita, Japan; [4]First Department of Internal Medicine, Nara Medical University, Kashihara, Japan; [5]Division of Clinical Nephrology and Rheumatology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan.*

Background: Infiltration by IgG-positive plasma cells is a common finding in tubulointerstitial nephritis (TIN). Routine immunofluorescence of frozen sections is currently considered the gold standard for detection of immune deposits; however, the immunoenzyme method with formalin-fixed, paraffin-embedded sections is superior for detecting IgM- or IgG-positive cells within the renal interstitium. It was thought that CD138-positive mature plasma cells secrete IgG, and the occurrence of TIN with CD138-positive plasma cells secreting IgM has rarely been reported. We recently discovered a case of TIN showing IgM-positive plasma cell (IgMPC) accumulation within the interstitium (*Clin Nephrol* 74: 74-80, 2010).

Methods: To further explore the morphological and clinical features of such cases, we performed a nationwide search for patients with biopsy-proven TIN and high serum IgM levels.

Results: In 13 of those patients, the pathologic findings were interstitial nephritis with diffusely distributed CD3-positive T lymphocytes and co-localized IgMPCs as well as tubulitis in the proximal tubules and collecting ducts with CD3-positive T lymphocytes. The number of infiltrating IgMPCs per high-power field from 13 patients was significantly higher than from control patients with other forms of TIN chosen as controls for staining (n=44) ($p<0.001$). Receiver operating characteristic (ROC) curve analysis revealed that optimal predictive cutoff number for infiltrating IgMPCs was 13 per high-power field, with an area under the ROC curve of 0.99 ($p<0.0001$). The sensitivity and specificity were 100% and 93.2%, respectively. In addition, levels of H^+-ATPase, H^+, K^+-ATPase and HCO_3^--Cl^- anion exchanger in the collecting ducts were significantly lower in 13 patients than in control patients with TIN. The clinical findings with these patients were a high prevalence of distal RTA (100%), Fanconi syndrome (92%) and anti-mitochondrial antibodies (82%).

Conclusions: We propose to designate this group of cases, which have a common histological and clinical form, as "IgM-positive plasma cell-tubulointerstitial nephritis" (IgMPC-TIN).

Funding: Government Support - Non-U.S.

TH-PO504

Clinicopathologic Characteristics, Treatment, and Outcome of Tubulointerstitial Nephritis and Uveitis Syndrome in Children Asako Hayashi, Takayuki Okamoto, Toshiyuki Takahashi, Yasuyuki Sato. *Hokkaido University Graduate School of Medicine, Hokkaido, Japan.*

Background: Tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare disease, presenting as a combination of tubulointerstitial nephritis and uveitis. A few case-series previously reported good renal prognosis of this syndrome, but long-term prognosis is not known enough in children. To further investigate this syndrome, we report here the clinical features and outcome. All patients followed up at least 24 months (median, 47months; range 24-179).

Methods: Retrospective study of the case records of all patients diagnosed with the TINU syndrome in the Departments of Pediatrics and Medicine of the Hokkaido University Hospital (Sapporo, Japan) from February 1990 through April 2017.

Results: We report here the clinical features and outcome of 20 patients (female 12, F/M ratio: 3:2), aged 9 to 14 years at diagnosis (median, 13.0) with TINU syndrome. The initial symptoms were visual impairment in sixteen patients (80%) and deterioration of health status in six patients (30%). The median estimated glomerular filtration rate (eGFR) at diagnosis was 99.8 mL/min per 1.73m^2 (range 59.7-117.4) and deteriorated renal function (eGFR <90 mL/min per 1.73m^2) was observed in 9 patients (30%). An increase in urinary β_2-microglobulin levels was noticed at the initial checkup in all patients. Topical and oral corticosteroids were prescribed to 15patients (75%) and Mizoribine or Methotrexate therapy was required in 2 patients (10%). After 24 months follow-up, the median eGFR was 111.4mL/min per 1.73m^2 (range 80.1-127.9). In three patients (15%) decreased eGFR<90 mL/min per 1.73m^2 after 24 months but the renal function of all patients was normalized at the latest checkup. Urinary β_2-microglobulin excretion gradually declined but was slightly elevated in 11 patients (55%) at 24 months. Recurrent or exacerbating uveitis was seen in ten patients (50%). On the other hand, TIN is not recurrence.

Conclusions: The TINU syndrome should be considered in the differential diagnosis of patients presenting with visual and renal manifestations. The presence of increase in urinary β_2-microglobulin levels may be of some help for the early discovery of recognition of TINU syndrome. In children and adolescents with this syndrome, the long-term prognosis of TIN is good, but uveitis often relapse.

TH-PO505

Clinical Advantage of Renal Arterial Doppler Ultrasonography for the Assessment of Tubulo-Interstitial Nephropathy Minoru Hatano,[2] Kaori Takayanagi,[2] Hiroaki Hara,[2] Masaaki Terao,[2] Yuichiro Kawai,[2] Saeko Sato,[2] Takatsugu Iwashita,[2] Taisuke Shimizu,[2] Tomonari Ogawa,[3] Koichi Kanozawa,[1] Hajime Hasegawa.[4] *[1]Saitama Medical Center, Saitama Medical University, Kawagoe, Japan; [2]Nephrology, Hypertension, Blood Purification, Saitama Medical Center, Saitama Medical University, Kawagoe, Japan; [3]Saitama Medical Center, Saitama Medical University, Kawagoe, Japan; [4]School of Medicine, Saitama Medical University, Kawagoe, Japan.*

Background: At present, potential clinical parameters for the assessment of tubulo-interstitial nephropathy (TIN) are poorly available. Here, we focused on the resistive index (RI) measured by renal arterial doppler ultrasonography (RAUS), and studied its efficacy for the assessment of TIN by comparative analysis with the conventional TIN parameter, urine N-acetylglusaminidase-to-creatinine ratio (NAG index) in patients with clinically suspected TIN.

Methods: Patients who have received RAUS under the clinical suspicion of renal artery disorders were retrospectively analyzed (n=33). Clinical diagnosis was renal artery stenosis, (n=13), diabetic nephropathy (n=4) and the others (n=16). We focused on RI measured at two different points independently, with the main trunk of the renal artery (RA) and intra-renal branch of the renal artery (IRA) corresponding to the inter-lobular artery.

Results: An analysis stratified by the median NAG index value for the estimation of TIN revealed a significant difference in the estimated glomerular filtration rate (eGFR), urine protein-to-creatinine ratio (uPCR) and RA/IRA-RI, although the correlation was not significant between the NAG index and the RI. Next, we focused the cases showing NAG index less than 20 U/mgCr because higher NAG index indicates advanced renal damage and the assessment of TIN is not required in those patients. When the patients showing higher NAG index are excluded, IRA-RI showed a significant correlation with NAG index ($R=0.59$, $p<0.01$), but RA-RI did not. A multivariate analysis for the NAG index as a response variable revealed that IRA-RI was a significant predictor variable ($\beta=0.59$, $P=0.02$), but RA-RI did not. A ROC analysis showed that the cut-off value of IRA-RI was 0.645 (AUC 0.80, sensitivity 72%, specificity 82%).

Conclusions: Resistive index by RA-US would be a useful clinical parameter for the assessment of TIN. For this purpose, RI should be measured at the intra-renal artery, not the main trunk of renal artery. In addition, threshold of NAG index value indicating the presence of TIN might be lower than the value corresponding the renal artery stenosis (0.8 U/mgCr).

TH-PO506

Blood Oxygen Level Dependent Imaging of CKD in Children Fenglan Luo, Yuhong Tao. *West China Second University hospital, Sichuan University, Chengdu, China.*

Background: Renal chronic hypoxia plays a vital role in the development of end-stage renal disease. Blood oxygen level dependent(BOLD) imaging can assess the oxygenation of kidney. Although BOLD-MRI is used for studying chronic kidney disease(CKD) in adults, BOLD has fewer applications in children with CKD. This study aims to investigate the values of BOLD-MRI in evaluating oxygenation of kidney and renal function of CKD in children.

Methods: All of these subjects underwent studies BOLD images on 1.5T MRI scanner as follows: scanning sequence FFE, FOV=200mm×282mm×70mm, slice thickness=5mm, slice number=12, TR=400ms, voxel size=3mm×3mm, flip angle =45°, echo train length=16. R2* value of cortex and medulla were obtained. The cortical and medullary R2* value were compared between the groups. The correlation of serum creatinine level(Scr) and eGFR with R2* value was also discussed. With the ROC curve, the diagnostic effectiveness of R2* value for severity of CKD was evaluated.

Results: The images of 6 healthy volunteers and 21 minor/moderate CKD children(CKD stage1-3), 16 severe CKD children(CKD stage4-5) were finally analyzed. Both in the CKD groups and control group, the R2* value in cortex was significantly lower than that in medulla. Cortical R2* value(11.61051±0.42012) of CKD stage1-3 was significantly higher than that of control group(10.74787±0.17737). Both cortical R2* value(12.99746±1.35398) and medullary R2* value(21.13990±1.90089) of CKD stage 4-5 were significantly higher than those of CKD stage1-3. In CKD patients, negative correlations were found between cortical R2* value with Scr level($r=0.800$,$P<0.001$), and also between medullary R2* value with Scr level($r=0.898$,$P<0.001$). Positive correlations were found between cortical R2* value($r=-0.586$,$P<0.001$) and medullary R2* value($r=-0.838$,$P<0.001$) with eGFR. The area under ROC curve for cortical R2* value in differentiating between minor/moderate CKD kidneys and normal kidneys, and between minor/moderate CKD kidneys and severe CKD kidneys were 1.00 and 0.89, respectively. With the threshold from ROC curve, the sensitivity and specificity of differentiating CKD stage1-3 and controls were all 100%.

Conclusions: BOLD-MRI is valuable in diagnosis and severity of CKD in children. Renal R2* value presents the level of oxygenation of kidney and reflects the change of

renal function. BOLD-MRI provides a novel technique to evaluate the severity of CKD in children.

TH-PO507

The Nephropathy Studied in the African American Study of Kidney Disease (AASK) May Be an Atypical Tubulopathy Salem Almaani,[2] Daniel J. Birmingham,[1] Brad H. Rovin,[1] Lee A. Hebert.[1] *[1]Ohio State University, Columbus, OH; [2]University Hospital Network - The University of Toronto, Toronto, ON, Canada.*

Background: It has been suggested that the nephropathy associated with patients enrolled in the AASK (AASK-N) may be a primary tubulopathy (and not a glomerulopathy or a vasculopathy related to hypertension) because it progresses at levels of proteinuria below that of progressive glomerulopathy. However, studying this in AASK-N urine samples has been hampered due to protein degradation because of the presence of acetic acid as a preservative. This report addresses this question by studying urine samples from patients enrolled in the Chronic Renal Insufficiency Cohort (CRIC) who met criteria for AASK enrollment.

Methods: Urine samples were obtained from 43 African American CRIC patients with urine protein-to-creatinine ratios (uPCRs) of 0.2 to 1.1 and eGFRs ranging from 65 to 20. Six kidney injury markers were measured in these samples by a multiplex platform (Meso Scale Discovery, MSD) that uses a capture and detection antibody pair for each analyte. For comparison, urine samples from 20 lupus nephritis (LN) patients with the same uPCR range were also tested.

Results: There were no differences in albumin-to-protein ratios (uAPR) between the CRIC cohort (mean 0.59) and the LN cohort (0.54). The results of the MSD analysis are shown in the table. Notably, levels of B2M, a classic marker of proximal tubule injury/dysfunction, were 8-fold higher in CRIC, while levels of cystatin C, another marker of proximal tubule dysfunction, were no different between the two cohorts. Decreased EGF levels in the CRIC cohort reflect their lower GFRs.

Conclusions: The 8-fold increase in urine B2M levels in the CRIC cohort compared to the LN cohort in the face of similar levels of uAPRs and other indicators of proximal tubular injury suggest that AASK-N is not a typical tubulopathy, but may involve unique proximal tubular damage.

Funding: NIDDK Support

Analyte	CRIC (N=43)	LN (N=20)	P value
Beta-2 -microglobulin (B2M)	768	94	0.013
Cystatin C	53	66	0.364
Epidermal growth factor (EGF)	1.4	6.5	<0.001
Neutrophil gelatinase-associated lipocalin (NGAL)	50	46	0.746
Osteopontin (OPN)	420	628	0.154
Uromodulin (UMOD)	7,440	10,750	0.032

Analyte levels = median ng/mg urine creatinine

TH-PO508

Successful Use of Renal Denervation (RDN) in Patients with Loin Pain Hematuria Syndrome (LPHS): The Prairie LPHS Study Bhanu Prasad,[3] Shelley Giebel,[2] Michelle C. McCarron.[1] *[1]Regina Qu'Appelle Health Region, Regina, SK, Canada; [2]Regina QuAppelle Health Region, Regina, SK, Canada; [3]Nephrology, Regina Qu'Appele Health Regiona, Regina, SK, Canada.*

Background: Loin Pain Hematuria Syndrome (LPHS) is a rare disease with a reported prevalence of 0.012%. Its characterized by painful unilateral or bilateral loin pain that suggests a renal origin but occurs in the absence of identifiable or relevant urinary tract disease. Hematuria can be either microscopic or macroscopic, and the renal abnormalities responsible for the hematuria are often unexplained. Debilitating pain refractory to conventional medications lead to multiple trips to the emergency rooms and is the main cause of morbidity. Treatment options include opiates, autotransplantation and autonephrectomy.

Methods: We conducted a single centre, single arm study. Twelve patients between the ages of 21-62 years (eleven females) with LPHS underwent RDN between July 2015 and November 2016 using the Vessix renal denervation system. Secondary causes were excluded by triphasic CT scan of the abdomen and pelvis and MAG3 split function renogram. The primary objective was a 30% reduction in self reported pain using the McGill pain questionnaire (MPQ). The secondary objectives were: changes in self reported diabilitity using Oswestry disability index (ODI), changes in quality of life using the EQ5D, Short Form Health Survey (SF-36), changes in mood using the Geriatric depression score (GDS) at 3 and 6 months as compared to the baseline.

Results: 11/12 patients had a >30% reduction in MPQ at 6 months. MPQ score median (IQR) at baseline was 38.5 (34.3-63.8), and 2.0 (0.018.5) at 6 months (p=0.001). ODI (%) mean (IQR) at baseline was 43.5% (20.8-59.3), and 4.4% (0.0-43.0) at 6 months (p=0.003). GDS was 3 (1.3-5) at baseline), and 1(1.0-4.5) at 6 months) (p=0.002). The visual analogus score (VAS) on EQ5D mean (IQR) improved from 50 (33.8-60.0) at baseline to 75.0 (55.2-88.3) at 6 months (p=0.022). There was consistent improvement across the spectrum of quality of life measures in both EQ5D and SF-36.

Conclusions: This is the first reported study that shows succesful pain relief post RDN in patients with LPHS. There was also considerable improvement in mood, functionality and quality of life post procedure. In a clinical condition, where autrotransplantation and autonephrectomy are considered to be reasonable therapeutic optons, this rapid, safe, minimlly invasive procedure should be considered in all patients with LPHS.

TH-PO509

Efficacy and Safety of Initial Pulse Methylprednisolone Treatment in Renal Sarcoidosis: A Randomized Trial Jean-Jacques Boffa,[7,11] Matthieu Mahevas,[8] Eric Daugas,[9] Dominique Guerrot,[5] Michel Delahousse,[2] Tabassome Simon,[6] Laurence Vrigneaud,[10] Evguenia Krastinova,[12,13] Evangeline Pillebout,[3] Vincent Audard,[14] David Verhelst,[4] Dominique Valeyre.[1] *[1]Avicenne Hospital AP-HP, Bobigny, France; [2]FOCH Hospital, Suresnes, France; [3]Hopital Saint-Louis, Paris, France; [4]None, PARIS, France; [5]Rouen University Hospital, Rouen, France; [6]Assistance Publique -Hôpitaux de Paris, Paris, France; [7]Tenon Hospital, AP-HP, Paris, France; [8]AP-HP, UPEC UNIVERSITY, Paris, France; [9]Bichat hospital, AP-HP, Paris, France; [10]hospital, Valenciennes, France; [11]INSERM U1155 / UPMC, Paris, France; [12]Creteil Hospital, Créteil, France; [13]URC-EST, AP-HP, Paris, France; [14]Mondor Hospital, AP-HP, Paris, France. Group/Team: Corticoïdose Group.*

Background: Sarcoidosis tubulo-interstitial nephritis (STIN) induces severe renal insufficiency with poor outcome. Despite treatment with steroids, most patients develop chronic kidney disease. Pulse methylprednisolone treatment has been used to improve renal function but this therapeutic strategy has never been evaluated. We assessed whether initial pulse methylprednisolone is effective and safe at improving renal function compared to oral steroids at 3 months of follow-up.

Methods: In a multicenter randomized open control trial, in patients with proven acute sarcoidosis tubulo-interstitial nephritis, we randomly assigned forty patients with STIN to receive pulse methylprednisolone 15 mg/kg/day for three days and per os steroids afterwards (group A) or per os 1 mg/kg/d steroids from the start (group B). The primary outcome was CKD-EPI estimated glomerular filtration rate (eGFR) during the follow-up. The primary efficacy end point was the percentage of patients having a positive response at 3 months of follow-up, defined by an improvement of more than 100% of eGFR compared to eGFR before treatment or eGFR ≥ 60 ml/min/1.73m². Secondary end points included side effects of steroids.

Results: The mean age of the trial participants was 59 (45-68) years and 70% were men. Among 40 participants, only one patient was excluded for a misdiagnosis of tuberculosis. Baseline eGFR before treatment were 25(22-37) ml/min/1.73m² for group A and 22(17-40) ml/min/1.73m² for group B, p=0.3. In the intent-to-treat population, the median eGFR was 45(39-64) ml/min/1.73m² for group A and 45(34-73) ml/min/1.73m² for group B at 3 months. Patients randomized to pulse methylprednisolone were significantly less likely to achieve the primary efficacy end point: 10 of 20 (50%) vs 16 of 20 (80%), p=0.047. eGFR were similar between groups after 1 month of treatment. No participants presented cardiac arrhythmia or conduction disorder during pulse methylprednisolone. Number of adverse effects was similar between groups: 15 in group A and 14 in group B.

Conclusions: Among patients with acute STIN, pulse methylprednisolone treatment was not significantly different from oral steroids in improving renal function at three months follow-up.

Funding: Government Support - Non-U.S.

TH-PO510

A Novel I-Body AD-114 Suppressed TGFβ1-Induced Fibronectin and Collagen 4 in Renal Proximal Tubular Cells via Smad and p38 Pathways Qinghua Cao,[1] Chunling Huang,[4] Hao Yi,[1] Stefanie Stangenberg,[3] Carol A. Pollock,[2] Xinming Chen.[4] *[1]Kolling Institute, Sydney, NSW, Australia; [2]The University of Sydney, Sydney, NSW, Australia; [3]None, Naremburn, NSW, Australia; [4]University of Sydney, Sydney, NSW, Australia.*

Background: Fibrosis is the final common pathway of chronic kidney disease (CKD). CXCR4 has been demonstrated to be a central player in the development of tissue fibrosis. However, the only approved CXCR4 antagonist was terminated due to its off-target cardiotoxicity. Our collaborator (Adalta Limited, Australia) has developed a fully human single-domain antibody-like scaffold termed i-body AD-114 with specific high binding affinity to CXCR4. AD-114 selectively blocks CXCR4 signaling and has shown anti-fibrotic effects in lung, liver and eye fibrosis. However, the role of AD-114 in renal fibrosis has not been studied.

Methods: To detect CXCR4 expression in the kidney, biopsies from patients with diabetic nephropathy (DN) and kidneys from three mouse models of CKD were collected and CXCR4 expression was detected using immunohistochemistry. To determine the role of TGFβ1 in AD-114 binding with CXCR4 in human renal proximal tubular cells (PTCs), PTCs were incubated with/without TGFβ1 (2ng/ml) in absence or presence of AD-114 for 48 hours, and then AD-114 binding with PTC was detected using immunocytochemistry. To examine whether AD-114 blocks TGFβ1-induced fibrotic responses in PTCs, PTCs were incubated with/without TGFβ1 (2ng/ml) in absence or presence of AD-114 (1mM or 3mM) for 48 hours and the supernatant and cell lysis protein were collected for Western blot analysis. Fibronectin (FN) and collagen 4 (Col 4) in the supernatant and phosphorylation of Smad2/3, p38 and NF-κB(p65) in cell lysis were measured by Western blot.

Results: CXCR4 expression was significantly upregulated in patients with DN and fibrotic kidneys of three mouse models of CKD compared to control groups (P<0.001, n=6). TGFβ1 significantly increased AD-114 binding to renal PTCs compared to negative control i-body and normal controls (P<0.001, n=4). AD-114 (3μM) suppressed TGFβ1-induced overexpression of FN and Col 4 via decreasing Smad2/3 and p38 phosphorylation compared to a lower concentration of AD-114 (1μM) and negative control i-body (P<0.001, n=4). However, AD-114 did not change the phosphorylation of NF-κB (p65).

Conclusions: Blocking CXCR4 using the i-body AD-114 is a promising therapeutic strategy to prevent the development of CKD.

Funding: Government Support - Non-U.S.

TH-PO511

Effect of Addition of Silybin and N-Acetylcysteine to Renin-Angiotensin System Inhibitors on Albuminuria in Type 2 Diabetic Patients with Overt Nephropathy: A Randomized Controlled Trial

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Background: A large proportion of patients with type 2 diabetes mellitus have diabetic nephropathy. Despite current therapies including hypertension control and renin-angiotensin system inhibitors, diabetic nephropathy progresses to end-stage renal disease in many of these patients. The aim of this study was to evaluate the efficacy of silybin and N-acetylcysteine (NAC), natural supplements with antioxidant and anti-inflammatory properties, in preventing the progression of diabetic nephropathy.

Methods: After institutional IRB and VA R&D approval, we conducted a randomized, double-blind, placebo-controlled, 5-arm parallel trial where subjects with diabetic nephropathy with albumin-creatinine ratio (ACR) of =/>150 mg/g and eGFR of 15-60 ml/min on the background of angiotensin inhibition after 1 month run-in period received either A) double placebo BID (n=16); or B) silybin placebo + NAC 600 mg BID (n=12); or C) silybin 480 mg + NAC placebo BID (n=16); or D) silybin 480 mg + NAC 600 mg BID (n=16); or E) silybin 960 mg + NAC 600 mg BID (n=15) for 3 months. Primary outcome was absolute change in urinary ACR from baseline to the end of the treatment phase.

Results: Overall, the study population was 62.97±7.48 years old, 89% male, 65% Hispanic, 27% non-Hispanic white and 7% non-Hispanic blacks, had BMI of 35.02±8.54 kg/m^2, eGFR of 36.4±13.3 ml/min, and ACR of 702.8±608.5 mg/g at baseline. The baseline characteristics were similar across the treatment arms except for systolic and diastolic BP and fasting glucose. There was no difference in change in Urinary ACR in different arms (ΔUACR in B=-156±604.8, C=10.9±542.9, D=96.6±422.4 and E=353.7±732.7 mg/g) compared to placebo (ΔUACR in A=50.5±291.2, Anova p=ns). Moreover, the change in eGFR was not different in 4 treatment arms compared to placebo arm. Small sample size and short duration of the treatment phase were the major limitation of the study.

Conclusions: 3-month intervention with dietary supplements silybin and NAC did not reduce urinary excretion of albumin in diabetic nephropathy patients in our study cohort.

Funding: Other NIH Support - NIH-NCCAM AT004490, Clinical Revenue Support

TH-PO512

Multiple Determinants of Early Renal Decline in Type 2 Diabetes

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Background: There has been a significant effort to identify the mechanisms for progressive renal decline in diabetic patients with chronic kidney disease (late progressive renal decline). Much less is known about the mechanisms, determinants and markers of early progressive renal decline. We aimed to evaluate several markers as determinants of early renal decline in 1032 patients with Type 2 diabetes (T2D), enrolled into the 2nd Joslin Kidney Study. With these data, we aimed to develop a multi-marker index to improve the identification of patients with incipient renal decline.

Methods: At enrollment, all patients had preserved GFR (median of 98 mL/min (1st and 3rd quartile; 85 -110), 58% had normoalbuminuria (urinary ACR median of 4 μg/mg) and 42% had albuminuria (ACR median of 44 μg/mg). Early renal decline (defined as GFR loss from baseline of 30% per < 5 years) occurred in 38 (6%) normoalbuminurics and in 76 (18%) albuminurics. As predictors of the decline we examined: (1) baseline clinical characteristics, (2) several blood markers proposed by previous targeted studies, (2) new urinary biomarkers.

Results: When analyzed jointly with other markers/predictors, baseline systolic BP, plasma TNFR1, KIM-1 as well as urinary ACR predicted early renal decline; a strongest, negative association with the risk of early renal decline was found for the urinary EGF normalized to MCP1, expressed as EGF/MCP1 ratio (Nowak et al, submitted). Integration of the independent biomarkers into multi-marker index resulted in significant improvement of the accuracy of prediction, compared with a model with ACR and systolic BP alone (c-statistics=0.81 vs c-statistics=0.73; p<0.001).

Conclusions: Our study underscores the power of examining multiple pathways in plasma and urine for understanding the mechanisms of early renal decline in T2D. Two novel markers of tubular injury, KIM-1 and EGF/MCP ratio in urine, had independent effects on risk of early renal decline in T2D.

Funding: NIDDK Support, Commercial Support - Lilly Inc., Pfizer Inc., Private Foundation Support

TH-PO513

Effect of Baseline Serum Calcium on Responses to Extended-Release Calcifediol (ERC) in Stage 3-4 CKD

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Background: Calcitriol and its 1α-hydroxylated analogs frequently increase serum calcium (Ca) and the risk of vascular calcification in patients with stage 3-4 CKD. For this reason, the revised KDIGO guideline for CKD-Mineral and Bone Disorder suggests that these agents not be routinely used in this population. Randomized clinical trials (RCTs) with ERC, a new FDA-approved therapy for secondary hyperparathyroidism (SHPT), demonstrated effective control of iPTH with minimal changes in serum Ca in stage 3-4 CKD. Data from these RCTs were examined post-hoc to assess the potential impact of baseline serum Ca on end-of-treatment (EOT) serum Ca, phosphorus (P), total 25-hydroxyvitamin D (25D) and total 1,25-dihydroxyvitamin D (1,25D), and on plasma intact parathyroid hormone (iPTH) in ERC-treated and placebo (PL)-treated subjects.

Methods: Two identical, double-blind trials were conducted in 429 subjects with stage 3-4 CKD, SHPT (iPTH >85 pg/mL) and vitamin D insufficiency (25D of 10-29 ng/mL). Subjects were randomized 2:1 to receive ERC (30 or 60 mcg/day) or PL for 26 weeks. Per-protocol data were pooled and analyzed by baseline serum Ca tertile.

Results: The table below shows mean baseline values at left and EOT values at right for ERC tertiles (n= 78 each) and for PL tertiles (n=40-41 each). ERC and PL had similar effects on mean serum Ca and P irrespective of baseline serum Ca tertile. ERC increased mean serum 25D and 1,25D and decreased mean plasma iPTH to similar levels in all tertiles, with the greatest observed changes occurring in the lowest tertile (T1). PL treatment produced increases in iPTH and no changes in 25D and 1,25D.

Conclusions: Baseline serum Ca affected serum 1,25D and plasma iPTH responses to ERC treatment. ERC-induced increases in 1,25D and decreases in iPTH were greatest in subjects with the lowest baseline Ca.

Funding: Commercial Support - OPKO Health

Table 1

	Serum Ca (mg/dL)		Serum P (mg/dL)		25D (ng/mL)		1.25D (pg/mL)		iPTH (pg/mL)	
	ERC	PL	ERC	PL	ERC	PL	ERC	PL	ERC	PL
T1	8.9/9.1	8.9/9.0	3.8/4.0	3.7/3.9	20/68	19/19	32/47	37/38	157/115	147/152
T2	9.2/9.4	9.3/9.4	3.7/3.9	3.7/3.9	19/68	20/18	34/47	34/38	138/109	149/161
T3	9.5/9.6	9.5/9.5	3.7/3.9	3.7/3.7	20/65	18/18	37/46	36/37	136/112	141/144

TH-PO514

Ferric Citrate Lowered Serum Phosphate Only When Elevated in Patients with Nondialysis-Dependent (NDD) CKD and Iron Deficiency Anemia (IDA)

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Background: Ferric citrate (FC), an oral iron-based phosphate (P) binder approved for control of serum P in patients (pts) with CKD on dialysis, has also shown improvement in hemoglobin (Hb) and iron parameters in pts with NDD-CKD with IDA. Here, in a post-hoc analysis of a phase 3 study, we examine effects of FC on serum P in pts by different baseline (BL) P levels and stages of CKD.

Methods: 233 pts with NDD-CKD and IDA were randomized 1:1 to receive FC (n=117) or placebo (n=116) for 16 weeks. FC was initiated at 3 1-g tablets/day and titrated to achieve a Hb increase ≥1 g/dL from BL (max 12 g/day). FC effects on P were examined by BL strata of P, CKD stage (per eGFR), and FGF23 (grouped by BL quartile [Q]).

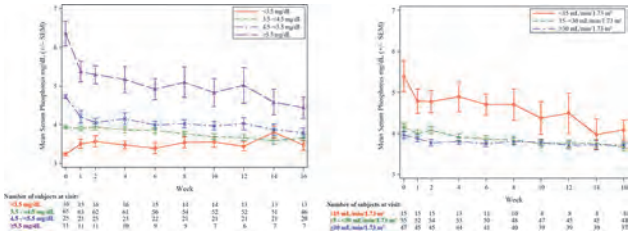
Results: Decreases in P with FC treatment were greater in pts with higher BL P levels. P remained stable in pts in the lowest BL P group even with increased FC dose. Likewise, P decrease was greatest in pts with lower BL eGFR (which correlated to higher BL P) [Figure]. Similar results were seen when pts were stratified by BL FGF23 [Table]. At 16 wks, the FC dose was similar across sub-groups, suggesting BL P did not affect dosing for treatment of IDA. Multivariate linear regression analysis confirmed BL P as a strong independent predictor of change in P (p<0.0001) after adjusting for treatment, BL eGFR and BL albumin.

Conclusions: In NDD-CKD pts with IDA, the effect of FC on P reduction is dependent on the BL P, with the greatest reduction in pts with the highest serum P. These results support the use of FC in NDD-CKD pts with IDA regardless of BL P.

Funding: Commercial Support - Keryx Pharmaceuticals

Mean Serum P (mg/dL) Levels Stratified by BL FGF23

i-FGF23 (pg/mL)	Q1 (<87)	Q2 (87 – <134.8)	Q3 (134.8 – <211.3)	Q4 (≥211.3)
BL±SE (n)	3.87±0.13 (28)	3.96±0.09 (31)	4.20±0.13 (25)	4.83±.21 (33)
16 wks±SE (n)	3.68±0.13 (22)	3.58±0.11 (26)	3.86±0.19 (16)	3.84±0.10 (22)
Mean Δ (SE)	-0.24 (0.13)	-0.37 (0.16)	-0.33 (0.13)	-0.92 (0.26)



TH-PO515

PTH Suppression with Extended-Release Calcifediol (ERC) Is Directly Proportional to Severity of Secondary Hyperparathyroidism (SHPT) Stuart M. Sprague,[1] Stephen A. Strugnell,[2] Akhtar Ashfaq,[2] Martin P. Petkovich,[4] Charles W. Bishop.[3] *[1]NorthShore University HealthSystem University of Chicago Pritzker School of Medicine, Chicago, IL; [2]OPKO Health, Miami, FL; [3]Opko Health, Miami, FL; [4]Queen's University, Kingston, ON, Canada.*

Background: Oversuppression of parathyroid hormone (PTH) is a significant concern in patients with stage 3-4 CKD treated with calcitriol or its 1α-hydroxylated analogs since iatrogenic induction of a low PTH concentration is an independent strong risk factor for adynamic bone disease, fractures and cardiovascular death. Randomized controlled trials have shown that ERC gradually but effectively reduces PTH without oversuppression. These data have been further examined post-hoc to determine the impact of baseline PTH levels on end-of-treatment (EOT) levels.

Methods: Two identical, randomized, double-blind, placebo-controlled trials were conducted in 429 adult subjects with stage 3-4 CKD, SHPT (>85 pg/mL) and vitamin D insufficiency. Subjects were randomized 2:1 to receive ERC (30 or 60 mcg/day) or placebo (PL) for 26 weeks. Per-protocol data for plasma intact (i) PTH, serum calcium (Ca) and phosphorus (P), serum total 1,25-dihydroxyvitamin D (1,25D), and serum total 25-hydroxyvitamin D (25D) were pooled and analyzed by baseline plasma iPTH tertile. Mean baseline iPTH in each tertile was 98, 130 and 203 pg/mL for ERC and 102, 133, and 201 for PL.

Results: The table shows the mean changes from baseline to EOT in iPTH, Ca, P, 1,25D and 25D with ERC (n=78 in each tertile) and PL (n=40-41 in each tertile). Significant differences from the corresponding placebo groups are as marked. ERC and PL had similar, minor effects on mean serum Ca and P. ERC increased serum 25D and 1,25D significantly and to comparable levels irrespective of baseline iPTH tertile. However, decreases in mean iPTH with ERC differed between tertiles and were directly proportional to baseline levels, with EOT suppression increasing from 19 to 26% of baseline from T1 to T3. Oversuppression was not observed.

Conclusions: ERC produced mean absolute iPTH reductions that were proportional to baseline iPTH levels, consistent with a mechanism of action involving physiological regulation of iPTH modulated by SHPT severity.

Funding: Commercial Support - OPKO Health

	Plasma iPTH (pg/mL)		Serum Ca (mg/dL)		Serum P (mg/dL)		1,25D (pg/mL)		25D (ng/mL)	
	ERC	PL	ERC	PL	ERC	PL	ERC	PL	ERC	PL
T1	-18[b]	4	0.2	0.1	0.2	0.1	11[b]	1	48[b]	-2
T2	-28[b]	2	0.1[a]	0.0	0.3[a]	0.1	13[b]	2	46[b]	-1
T3	-50[b]	15	0.3[b]	0.1	0.2	0.1	12[b]	2	47[b]	-1

[a]P<0.05 [b]P<0.001

TH-PO516

Effect of Sodium Bicarbonate Treatment on a Novel Marker of Serum Calcification Propensity Jessica B. Kendrick,[5] Emily Andrews,[4] Andreas Pasch,[2] Zhiying You,[1] Michel Chonchol.[3] *[1]UC Denver, Aurora, CO; [2]University Hospital Bern, Bern, Switzerland; [3]University of Colorado, Aurora, CO; [4]University of Colorado Denver, Aurora, CO; [5]University of Colorado Denver and Denver Health Medical Center, Denver, CO.*

Background: Acid retention in patients with chronic kidney disease (CKD) results in increased production of inflammatory markers and activation of the renin-angiotensin-aldosterone system, all of which can induce vascular calcification. We examined the effect of treatment of metabolic acidosis with oral sodium bicarbonate therapy on a novel test that measures the overall calcification propensity of serum, T50, in patients with CKD stage 3-4.

Methods: We performed a prospective, randomized, open-label, 14-week crossover study of 20 patients with CKD stage 3-4 and metabolic acidosis (serum bicarbonate level of ≥ 16 and <22 mEq/L). Subjects were randomly assigned to start with either treatment or control. Each period was 6 weeks in duration with a 2-week washout period in between. Patients were treated with oral sodium bicarbonate tablets for goal bicarbonate of ≥ 22 mEq/L. Serum T50 was measured at the beginning and end of each treatment period. T_{50} measures the transformation time of amorphous calcium phosphate-containing primary calciprotein particles (CPP) to crystalline hydroxyapatite-containing secondary CPP. A higher T_{50} represents lower calcification propensity. Mixed effect models were used to examine changes in T50 during treatment and control conditions.

Results: The mean (SD) age and eGFR was 58.5 ± 12.8 years and 24.6 ± 8.1 ml/min/1.73m², respectively. The mean (SD) serum bicarbonate level and T50 level at baseline was 19.7 ± 2.3 mEq/L and 256.4 ± 56.2 minutes, respectively. Serum bicarbonate levels increased significantly with sodium bicarbonate therapy. There was no significant change in serum T50 during treatment or control conditions. Serum phosphate increased significantly with bicarbonate therapy.

Conclusions: In our study, treatment of metabolic acidosis with oral sodium bicarbonate therapy did not decrease serum calcification propensity in patients with CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI

	Control Baseline	Control 6 weeks	P-value	Treatment Baseline	Treatment 6 weeks	P-value	Between group P-value
Bicarbonate (mEq/L)	19.7 ± 2.3	19.6 ± 3.2	0.93	19.3 ± 2.9	22.0 ± 3.1	<0.001	0.005
T50 (minutes)	279.9 ± 44.5	275.1 ± 33.5	0.64	233.0 ± 57.9	225.2 ± 94.3	0.77	0.90
Calcium (mg/dL)	9.4 ± 0.5	9.2 ± 0.5	0.13	9.2 ± 0.5	9.3 ± 0.5	0.39	0.03
Phosphorus (mg/dL)	4.2 ± 0.8	4.2 ± 1.1	0.85	4.1 ± 0.6	4.5 ± 1.1	0.02	0.04

TH-PO517

Dietary Acid Reduction with Fruits and Vegetables Better Prevents Transition of Stage 3 CKD to Stage 4 Than Oral NaHCO3 Nimrit Goraya,[4,5] Jan Simoni,[3] Yolanda Munoz Maldonado,[2] Donald E. Wesson.[1,6] *[1]Diabetes Health and Wellness Institute, Dallas, TX; [2]Biostatistics, Baylor Scott & White Health, Temple, TX; [3]Surgery, Texas Tech University Health Sciences Center, Lubbock, TX; [4]Internal Medicine, Baylor Scott and White Health, Temple, TX; [5]Internal Medicine, Texas A and M School of Medicine, Temple, TX; [6]Internal Medicine, Baylor Scott and White Health, Temple, TX.*

Background: The USRDS most recently reported a net increased prevalence of individuals with chronic kidney disease (CKD) stage 3 (eGFR=30-59 ml/min/m²). The CKD 3 to CKD 4 transition yields the greatest net increase in morbidity and care cost in the CKD 1 to CKD 4 progression, supporting need for kidney-protective interventions. Because dietary acid reduction added to pharmacologic anti-angiotensin II therapy appears to provide adjunctive kidney protection, we tested the hypothesis that oral $NaHCO_3$ (HCO_3) or base-producing fruits and vegetables (F+V) reduce the proportion of CKD 3 subjects who transition to CKD 4.

Methods: One hundred eight macroalbuminuric, non-diabetic CKD 3 subjects with metabolic acidosis but with serum [HCO_3] between 22 -24 meq/L were randomized to receive F+V (n=36) in amounts to reduce dietary potential renal acid load by half, oral $NaHCO_3$ (HCO_3, n=36) 0.3 meq/Kg bw/day to approximate the base-producing potential of F+V, or to Usual Care (UC, n=36). All had a systolic blood pressure (SBP) goal < 130 mm Hg using drug regimens including ACE inhibition. Cystatin C-based eGFR and SBP were followed at baseline and annually for five years.

Results: Baseline eGFR among UC, HCO_3, and F+V (39.5 ± 6.9, 39.6 ± 6.6, and 39.4 ± 6.4 ml/min/m², respectively, p=0.99) was not different but baseline SBP for UC (159 ± 11 mm Hg) was lower (p=0.04) than HCO_3 and F+V (165 ± 10, and 163 ± 12 mm Hg, respectively). At five years, the % of patients (%, 95% confidence interval or CI) that maintained eGFR> 30 ml/min/m² was higher in F+V (40%, CI=24-58) than UC (6%, CI=0.7 - 20) but that for HCO_3 (34%, CI=19 – 52) was not higher than UC. Although the five-year increase in plasma [HCO_3] was not different between F+V (0.89 mM, CI=0.68-1.09) and HCO_3 (0.87 mM, CI=0.67-1.08) supporting similar dietary acid reduction, a greater % of F+V (89%, CI= 73-97) than HCO_3 (17%, CI=7-34) achieved SBP goal of < 130 mm Hg, possibly contributing to better eGFR preservation in F+V.

Conclusions: Adjunctive dietary acid reduction with F+V but not $NaHCO_3$ yielded a significantly greater proportion of CKD 3 patients who did not progress to CKD 4, possibly due to a greater proportion of F+V achieving blood pressure goal. The data support that dietary acid reduction with F+V better prevents the CKD 3 to CKD 4 transition than NaHCO3.

TH-PO518

Randomized, Placebo-Controlled Trial of Rifaximin Therapy for Lowering Gut-Derived Cardiovascular Toxins in CKD Cassandra A. Kimber,[1] Cassandra R. Johnson,[1] Alexander J. Prokopienko,[3] Kerri A. McGreal,[1] Thomas D. Nolin,[3] Jason R. Stubbs.[2] *[1]University of Kansas, Kansas City, KS; [2]University of Kansas Medical Center, FAIRWAY, KS; [3]University of Pittsburgh, Pittsburgh, PA.*

Background: Accumulating evidence suggests that byproducts of gut bacteria contribute to cardiovascular morbidity in CKD patients. One example is trimethylamine-N-oxide (TMAO), a pro-atherosclerotic compound generated from metabolites produced by intestinal bacteria. Rifaximin is a minimally absorbed, oral antibiotic that targets intestinal pathogens and can chronically suppress circulating levels of gut-derived bacterial toxins that contribute to disease comorbidities in other patient populations.

Methods: We conducted a randomized, double-blinded, placebo-controlled trial to determine the impact of a 10-day course of oral rifaximin 550 mg BID vs. placebo on serum TMAO and fecal bacterial composition in patients with stage III-V CKD (*n*=38). Fasting serum, urine and stool samples were collected at baseline and immediately post-therapy. Our primary outcomes of interest were change in serum TMAO and relative abundance of fecal bacterial communities. Secondary analyses of interest included change in serum p-cresol, indoxyl sulfate, and pro-inflammatory cytokines.

Results: Rifaximin therapy decreased the relative abundance of bacterial families known to generate TMAO precursors; mean relative abundance of Clostridiaceae decreased from 0.6 to 0.1% (p<0.01) and Peptostreptococcaceae decreased from 2.2 to 1.4% (p=0.17) in the rifaximin group vs. a change from 0.5 to 0.6% (p=0.21) and 1.3

to 1.9% (p=0.57), respectively, in the placebo group. Despite an apparent reduction in these bacterial populations, we observed only a minor, non-significant reduction in serum TMAO with rifaximin; mean TMAO changed from 18.8 ± 18.7 μM at baseline to 14.8 ± 10.2 μM post-therapy (p=0.31) in the rifaximin group vs. a mean TMAO change from 15.6 ± 11.6 at baseline to 16.1 ± 13.4 μM post-therapy (p=0.84) in the placebo group. Analysis of the stated secondary outcomes is currently ongoing.

Conclusions: Short-term rifaximin therapy effectively suppresses bacteria that generate TMAO precursors; however, these changes in gut flora do not translate to significantly lower serum TMAO in CKD patients.

Funding: Other NIH Support - NIH R21 DK108093

TH-PO519

Acute and Chronic Effects of Different Exercise Modalities on Hepcidin Levels in Non-Dialysis CKD Soteris Xenophontos,[1] Douglas W. Gould,[1] Thomas J. Wilkinson,[1] Emma L. Watson,[1] Joao L. Viana,[2] Alice C. Smith.[1] *[1]University of Leicester, Leicester, United Kingdom; [2]University Institute of Maia, Maia, Portugal.*

Background: Functional iron deficiency (FID) is common in chronic kidney disease (CKD). Iron is essential for many cellular processes including energy generation. FID has negative effects on skeletal and cardiac muscle as well as haemoglobin (Hb) production, and contributes to anaemia, functional deficits, fatigue and cardiovascular (CV) risk. Hepcidin, which is upregulated by inflammatory cytokines and inhibits release of iron stores, is implicated in CKD FID due to chronic inflammation and reduced renal clearance. We have previously shown that regular exercise exerts anti-inflammatory effects in CKD. In this study, we investigated the effects of different exercise modalities on hepcidin levels in non-dialysis CKD.

Methods: 36 CKD patients (14 male, mean±SD age 61±12 years, eGFR 26±8 ml.min-1.1.73m-2, Hb 119±15 g/l) were randomised to 12 weeks thrice weekly aerobic exercise (AE, n=18) or combined aerobic and resistance exercise (CE, n=18). Plasma was collected to assess the chronic effects of exercise (resting samples at baseline and end of study) and the acute effects (collected 24h following the first and last exercise sessions). Hepcidin was measured by ELISA.

Results: Following 12 weeks training, resting hepcidin decreased by 21±35% (p=.037) in the CE group, but was unchanged in the AE group (1±50%, p=.976). Acutely, 24h after the first exercise session hepcidin decreased by 34±27% (p=.008) in the CE group and by 18±24% (p=.101) in the AE group. 24h after the final exercise session hepcidin decreased by 3±42% (p=.438) in the CE group and by 0±27% (p=.651) in the AE group, compared to resting levels.

Conclusions: CE training reduced resting plasma hepcidin, but there was no change with AE alone. An acute reduction in hepcidin was observed 24h after the first CE session, but not after the first AE session or in either group after the last session, indicating an adaptation effect of regular CE. Hepatic hepcidin release is stimulated by IL-6, which peaks after unaccustomed exertion but is reduced by regular exercise. Therefore, our results likely mirror the effects of exercise on circulating inflammatory cytokines. CE may ameliorate FID in CKD, thereby helping to reduce CV and anaemia risk, and improve muscle function and fatigue.

Funding: Private Foundation Support

TH-PO520

Supervised Exercise Intervention and Overall Physical Activity in Individuals with Moderate to Severe CKD Jacob M. Taylor,[1] Aseel Alsouqi,[1] Cassianne Robinson-Cohen,[2] Charles D. Ellis,[1] Sam A. Headley,[3] Katherine R. Tuttle,[2] Elizabeth E. Evans,[3] Michael J. Germain,[4] Chutatip Limkunakul,[5] Aihua Bian,[6] Thomas G. Stewart,[6] Jonathan Himmelfarb,[2] Talat Alp Ikizler.[1] *[1]Medicine, Vanderbilt University Medical Center, Nashville, TN; [2]University of Washington, Seattle, WA; [3]Springfield College, Wilbraham, MA; [4]Renal and Transplant Assoc of New England, Hampden, MA; [5]Srinakharinwirot University, Nonthaburi, Thailand; [6]Biostatistics, Vanderbilt University, Nashville, TN.*

Background: Patients are often instructed to engage in multiple weekly sessions of exercise to increase physical activity; however, whether this increases overall physical activity in individuals with chronic kidney disease (CKD) remains unknown.

Methods: We performed a post-hoc analysis of a pilot randomized 4-arm trial examining the effects of diet and exercise (dietary restriction of 10%-15% reduction in caloric intake, exercise three times/week, combined diet and exercise and control) (NCT01150851). A total of 122 participants were consented, 111 were randomized, 104 started intervention and 92 completed the study. Activity was measured as counts, which are proportional to the muscular force producing motion detected by the accelerometer (ie. higher counts = more activity). For the exercise arm, counts data were only collected on non-exercise days. The primary outcome was a change from baseline in counts/minute between individuals in the exercise arms and the control group. A t-test was used to assess differences with p<0.05 being considered statistically significant.

Results: We examined all individuals who had completed at least four days wearing an accelerometer device at baseline and at the four month follow-up (n=70, n=36 in exercise arms and n=34 controls). Most participants were male (57%), white (66%), hypertensive (89%) and small portion with diabetes (29%). Mean (SD) for age was 56 (11) years, for estimated glomerular filtration rate was 43 (17) mL/min/1.73m². Mean (SD) counts per min at baseline were 294 (257) and at month four were 288 (270). No differences were observed in change in counts/min between the exercise and control groups at month 4 (p=0.83). The results were similar in a sensitivity analysis including only those who were compliant with the exercise prescription in the exercise arm (n=11, >75% compliance at month four).

Conclusions: Our findings indicate that engaging in supervised exercise program does not necessarily increase overall physical activity in individuals with Stages 3 and 4 CKD.

Funding: Other NIH Support - National Heart, Lung, and Blood Institute

TH-PO521

Body Fat and Phase Angle, Rather Than Lean Mass, Show the Strongest Correlations with VO2 Peak in Stage 3 and 4 CKD Patients Jacob M. Taylor,[1] Aseel Alsouqi,[1] Cassianne Robinson-Cohen,[2] Charles D. Ellis,[1] Sam A. Headley,[3] Katherine R. Tuttle,[2] Elizabeth E. Evans,[3] Michael J. Germain,[4] Chutatip Limkunakul,[5] Aihua Bian,[6] Thomas G. Stewart,[6] Jonathan Himmelfarb,[2] Talat Alp Ikizler.[1] *[1]Medicine, Vanderbilt University Medical Center, Nashville, TN; [2]University of Washington, Seattle, WA; [3]Springfield College, Wilbraham, MA; [4]Renal and Transplant Assoc of New England, Hampden, MA; [5]Srinakharinwirot University, Nonthaburi, Thailand; [6]Biostatistics, Vanderbilt University Medical Center, Nashville, TN.*

Background: VO_2 peak is a measure of aerobic fitness and is a good indicator of cardiovascular health. Understanding how body composition measures are correlated with VO_2 peak is important for developing targeted interventions aimed at improving health.

Methods: We performed a post-hoc analysis of a pilot randomized 4-arm trial examining the effects of diet and exercise (dietary restriction of 10%-15% reduction in caloric intake, exercise three times/week, combined diet and exercise and control) (NCT01150851). A total of 122 participants were consented, 111 were randomized, and 108 completed baseline VO_2 peak testing. Body composition metrics were measured via dual energy x-ray absorptiometry, including total mass, fat mass, lean mass, and fat free mass, body fat percentage (including android and gynoid fat percentage), body mass index, weight, and waist to hip ratio. In addition, body cell mass and phase angle were measured by bioelectrical impedance analysis. The primary outcome was to determine whether body composition measurements were correlated with VO_2 peak at baseline. Correlations were adjusted for age, gender, diabetes status, and site of study visits in the model.

Results: Most participants were male (57%), white (68%), and had 24% diabetes. Median (IQR) for age was 57 (49-63) years, with baseline VO_2 peak 19.6 (16.2-22.6) mL/kg/min. At baseline, body fat percentage (rs=-0.38), android (rs=-0.336) and gynoid fat percentage (rs=-0.313), body mass index (rs=-0.372), weight (rs=-0.282), and phase angle (rs=0.278) were all significantly correlated with VO_2 peak after adjustment (p<0.03 for each individual variable). Holding other covariates at the mean, the difference in VO_2 peak between the 25th and 75th percentiles of lean mass was 1.9 (-0.5,4.2) mL/kg/min, whereas the same difference comparing the 25th and 75th percentiles of fat mass was -3.6 (-5.5,-1.3) mL/kg/min.

Conclusions: Our findings indicated that body fat composition and phase angle, rather than lean mass, show the strongest correlations to VO_2 peak. An intervention aimed at reducing body fat or improving phase angle may prove effective at improving VO_2 peak in future research.

Funding: Other NIH Support - National Heart, Lung, and Blood Institute

TH-PO522

Food Insecurity and Longitudinal Risk of Rapid Kidney Function Decline Deidra C. Crews,[2] Caroline Kwon,[5] Dingfen Han,[8] Yang Liu,[2] Tanushree Banerjee,[7] Michele K. Evans,[3] Alan B. Zonderman,[1] Neil R. Powe,[6] Marie Kuczmarski.[4] *[1]Intramural Research Program, NIA, NIH, Baltimore, MD; [2]Johns Hopkins University, Baltimore, MD; [3]National Institutes of Health/National Institute on Aging, Baltimore, MD; [4]University of Delaware, Newark, DE; [5]None, Washington, DC; [6]Priscilla Chan & Mark Zuckerberg San Francisco General Hospital & University of California SF, San Francisco, CA; [7]University of CA, San Francisco, San Francisco, CA; [8]Johns Hopkins University, Baltimore, MD.*

Background: Food insecurity, defined as limited or uncertain ability to acquire food, has been associated with prevalent CKD and CKD progression to ESRD. Whether food insecurity is associated with loss of kidney function among persons with preserved kidney function is not known.

Methods: We conducted a longitudinal analysis of the Healthy Aging in Neighborhoods of Diversity Across the Life Span (HANDLS) Study (Baltimore MD) to determine whether food insecurity was associated with rapid kidney function decline (KFD). Participants with eGFR≧60 ml/min per 1.73m² were included (n=1471). Food insecurity was defined as an affirmative response to, 'In the last 12 months, did you or your household ever cut the size of your meals or skip meals because there wasn't enough money for food?' KFD was defined over an average of 5-years' follow-up as: follow-up eGFR decreased by more than 3% per yr from baseline; or full follow-up eGFR decreased by more than 25%. Multivariable logistic regression models assessed the relation of food insecurity and KFD.

Results: At baseline, 24.8% of participants were food insecure. These persons were younger, more likely to be female, African American, living in poverty, with fewer yrs of education, uninsured and current smokers than were food secure persons (p<0.05 for all). Food insecure persons had lower Healthy Eating Index (HEI) 2010 scores and were more likely to be obese, but equally as likely to have diabetes and hypertension as food secure

persons. Overall, 13.3% had >3% per yr eGFR decline, while 4.2% had ≥25% eGFR decline over full follow-up. Food insecurity was not associated with >3% per yr eGFR decline, but was associated with ≥25% eGFR decline (**Table**). Clinical factors explained little of this association. Among 1,164 participants with HEI data, the magnitude of the association of food insecurity with ≥25% eGFR decline was similar, though not statistically significant (1.87, 95% CI 0.9, 3.9).

Conclusions: For persons free of CKD, food insecurity may be a risk factor for rapid loss of kidney function over time.

Funding: NIDDK Support, Other NIH Support - National Institute on Aging, Private Foundation Support

Association of Food Insecurity (vs. Security) and Rapid Kidney Function Decline

Model	>3% eGFR decline per year Odds Ratio (95% CI)	≥25% eGFR decline over full follow up Odds Ratio (95% CI)
1-Unadjusted	1.18 (0.78, 1.79)	1.84 (1.11, 3.06)
2-Adjusted for age, race, sex, poverty status and baseline eGFR	1.13 (0.72, 1.79)	1.86 (1.05, 3.29)
3-Adjusted for age, race, sex, poverty status, baseline eGFR, diabetes, hypertension and obesity	1.10 (0.66, 1.84)	1.83 (0.94, 3.58)

TH-PO523

Mortality and Co-Morbidities in South Asian Individuals with CKD Compared to White Ethnicities Rupert Major,[1,2] Gang Xu,[1,3] Laura Gray,[2] Nigel J. Brunskill.[1,3] *[1]University Hospitals of Leicester, Leicester, United Kingdom; [2]Department of Health Sciences, University of Leicester, Leicester, United Kingdom; [3]Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, United Kingdom. Group/Team: LCC-CKD Cohort.*

Background: The epidemiology of CKD in South Asian (SA) populations in high-income countries is poorly studied. The Leicester City and County Chronic Kidney Disease (LCC-CKD) cohort has been developed to study this population in comparison to other ethnic groups. To our knowledge no study has compared all-cause mortality in SA subpopulations with CKD compared to other ethnicities.

Methods: Data was collected for LCC-CKD from primary care electronic records. The cohort has 5 years of completed follow-up from 2011 to 2016. Comparison was made between individuals of SA and Whites ethnicities. The groups' baseline characteristics were compared using t-tests and Chi^2. Unadjusted and adjusted Cox proportional hazards models were used for comparison of all-cause mortality.

Results: 3,887 of 6,133 (63.4%) individuals in the LCC-CKD cohort have an ethnicity code of whom 268 are of SA ethnicity (6.9%). Gender proportions were similar, but mean age and EPI eGFR were lower and ACR higher for SA compared to White ethnicities. diabetes mellitus was more common in SA but clinical cardiovascular disease was less common (see table). Unadjusted all-cause survival analysis suggested all-causes mortality was 39% lower (HR 0.61, 95% CI 0.46-0.80, p<0.0001) in SA. However, in an adjusted model using the variables listed in the table, SA had similar risk to the White population (HR 0.97, 95% CI 0.71-1.33, p=0.85).

Conclusions: Compared to the White population, SA with CKD are younger with more advanced CKD and more likely to have diabetes. Adjusted all-cause mortality was similar between ethnicity groups. These factors may explain why SA individuals are more likely to progress to endstage renal disease.

Comparison of Cohort Characteristics in South Asian and White Ethncities

Variable	South Asian	White	p-value
n	268	3,552	
Female	60.8%	57.1%	0.23
Age	76.3 (12.0)	84.2 (9.1)	<0.001
EPI eGFR	46.8 (11.8)	48.8 (9.9)	0.001
ACR (mg/mmol)	19.9 (52.4)	10.0 (29.9)	<0.001
Hypertension	86.3%	90.3%	0.07
Diabetes Mellitus	55.2%	33.6%	<0.001
Cardiovascular Disease	36.2%	44.5%	0.008

p-values are for comparisons between South Asian and White ethnicities. For continuous variables, mean values are presented with standard deviations in parentheses.

TH-PO524

Improving Implementation of Evidence-Based CKD Care for an Underserved Population: An IT-Enhanced Collaborative Care Model Miguel A. Vazquez,[7] George Oliver,[4] Adeola O. Jaiyeola,[3] Beverley Adams-Huet,[7] Nitin Budhwar,[7] Blake R. Barker,[7] Brett Moran,[3] Noel O. Santini,[6] Ying Ma,[2] Javier A. Velazquez,[5] Vibin Roy,[1] Xilong Li,[7] Robert D. Toto.[7] *[1]PCCI, Dallas, TX; [2]Parkland Center for Clinical Innovation, Dallas, TX; [3]Parkland Health & Hospital System, Dallas, TX; [4]Parkland Health and Hospital System, Dallas, TX; [5]Pieces Technologies, Dallas, TX; [6]UT Southwestern/PHHS, Dallas, TX; [7]University of Texas Southwestern Medical Center, Dallas, TX.*

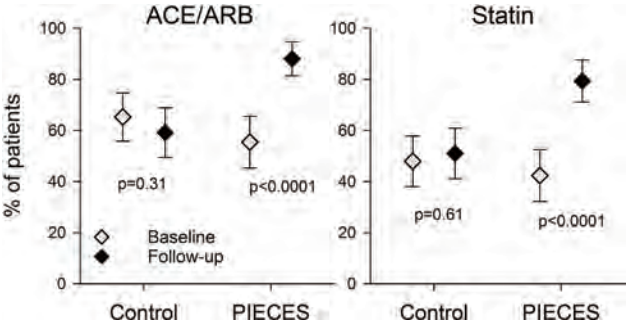
Background: There is a gap between knowledge and implementation of evidence-based guidelines (EBG) for treating CKD. Developed at Parkland Health System (PHHS), a safety net hospital serving a predominantly minority population in Dallas County, PIECES is a novel health information technology (IT) that can be embedded in the electronic health record to detect patients with conditions of interest and monitor outcomes. We hypothesized that using PIECES in a collaborative model of primary and nephrology care for patients newly diagnosed with CKD or referred to a CKD clinic at PHHS would improve implementation of EBG.

Methods: PIECES was used to identify patients with previously undiagnosed CKD or newly referred to a CKD kidney clinic and to monitor clinical measures and improve adherence to EBG for CKD care. The main study outcomes were blood pressure (BP) control, use of renin-angiotensin-aldosterone system blockers (RAAS-ACE inhibitors or ARBs) and statins for patients receiving care enhanced by PIECES (implementation group) compared to control patients receiving usual care.

Results: Demographics and baseline (BL) characteristics were similar for patients in implementation (n=92) and control (n=127) groups. After a follow-up (FU) of 6-24 months the use of RAAS (88% vs 59.2%, p<0.0001) and statins (79.4 vs 51%, p<0.0001) was significantly higher in the implementation than in the control group (Figure). In the implementation group, BP of <140/90 at BL and FU was achieved by 50% and 59% (p=0.2) and BP of <130/80 was met by 22% and 28% (p=0.2) respectively; the BP responses were not statistically different from controls.

Conclusions: In this study of collaborative care in primary and nephrology practices use of an IT-embedded program improved implementation of CKD EBGs including use of RAAS and statins. This model can lead to better care, and has the potential to improve outcomes, in underserved populations with CKD.

Funding: NIDDK Support



TH-PO525

Primary Care Providers' Dietary Counseling of Their Low Income African American (AA) Patients with CKD Deidra C. Crews,[6] Debra L. Roter,[2] Raquel C. Greer,[4] Stella Park,[2] Patti Ephraim,[5] Jessica Ameling,[7] Lapricia L. Boyer,[5] Michael C. Albert,[3] Lisa A. Cooper,[6] L. Ebony Boulware.[1] *[1]Duke University School of Medicine, Durham, NC; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [3]Johns Hopkins Health System, Baltimore, MD; [4]Johns Hopkins Medical Institutions, Baltimore, MD; [5]Johns Hopkins University, Baltimore, AL; [6]Johns Hopkins University School of Medicine, Baltimore, MD; [7]University of Michigan, Ann Arbor, MI.*

Background: Diet influences outcomes in CKD, but little is known about how patients with CKD are counseled about their diet. We examined primary care providers' (PCPs) use of the 5A's (*Assess, Advise, Agree, Assist, and Arrange*) counseling strategy in diet discussions with AA patients with CKD, and explored their use of a *6th* 'A' "*Awareness*", reflecting recognition and discussion of the home and community food environment within which the patient resides--especially relevant for patients living with food insecurity.

Methods: In a trial of urban AAs with uncontrolled hypertension, we audio-recorded patients' routine visits with their PCPs at the first visit after enrollment. Among 44 patients with CKD [eGFR<60 (33%) and/or ACR ≥30mg/g (88%)], we assessed presence of diet discussions and use of the 6A's in the discussions. Using linear regression, we examined predictors of number of A's used.

Results: Mean age was 59.5 years, 37% were male and 31% had annual income <$10K; 63% were obese, 70% had diabetes and mean systolic BP was 147 mmHg. A majority (67%) were either at risk for or with food insecurity (inability to afford nutritionally adequate foods). Most (88%) visits included dietary counseling, most commonly in the context of *Assess* (68%) and *Advise* (61%); *Agree* (14%), *Assist* (14%) and *Arrange* (9%) were infrequent. Only one visit included reference to *Awareness*. Median number of A's was 2 (IQR 1-2.5). No visit included all A's. Representative quotes are in the **Table**. Visits attended by patients earning <$10K included fewer A's than those of patients with higher incomes, though not statistically significant (-0.5, 95% CI -1.4, 0.4).

Conclusions: Among urban AAs with CKD, dietary counseling by their PCP primarily included assessing or advising on diet. PCPs may struggle to cover all A's in the context of visits with high risk patients. Multidisciplinary approaches to dietary counseling of high risk CKD patients warrants investigation.

Funding: NIDDK Support, Other NIH Support - NHLBI

6A's Framework and Representative Quotes

Assesses diet or weight	"How are you doing with the salt in your diet?"
Advises on topics of diet or weight	"Try to stay away from bananas. If you eat a banana, eat a half. Because of the diabetes."
Agrees on a specific plan	Physician: "Our plan for now is for you to continue all this dietary stuff you"
Assists in identifying barriers/supports for behavior change	Physician asks about eating out and the patient says they can seldom afford to, so doctor responds "But of course, that also makes it tough to afford the fresh stuff."
Arranges a specific plan for follow up	"I would like to see you back in a month. By then you should have seen the nutritionist."
Awareness, recognition and discussion of food environment	Physician suggests adding apricots to patient's diet, but patient does not know what they are. Physician recognizes that "Those aren't common. I wouldn't find them in a store around here."

TH-PO526

Sex Differences in Progression and Resource Utilization in CKD Pradeep Arora,[3] Edwin J. Anand,[3] Joseph A. Eberle,[1] Kabir Jalal,[2] Rocco C. Venuto.[3,1] *[1]Intelligent Care Management, East Amherst, NY; [2]University at Buffalo, Hamburg, NY; [3]Medicine, University at Buffalo, Buffalo, NY.*

Background: Prevalence of CKD in early stages is higher among females than males, in contrast more males develop ESRD. Resource utilization between sexes is not well studied. We hypothesized that resource utilization is greater among males when compared to females.

Methods: Data from a large third party payer, with an enrollment of 1.4 million, from 2007-14. CKD was defined as GFR less than 60 ml/min/1.73 BSA for more than three months. Data analyzed included demographics, comorbid conditions (CAD, CHF, PVD, COPD, depression, cancer, diabetes, and hypertension), hospitalization and cost of care. Univariate and multivariate analyses of the predictive variables were undertaken. Chi squared test was used to compare the proportions of clinical variables among the sexes.

Results: 33,328 CKD cases were identified. There were 18,146 females, 13, 257 males, 1,925 sex non specified. The proportion of CKD was higher in females compared to males (54 % vs 40 %, 6% unknown). CKD stages 3, 4 and 5 were found in respectively 51%, 54%, and 50% compared to 47%, 45%, and 48% in males. Female CKD patients had higher prevalence of comorbidities. Annual hospitalization rates were 2.26 for females and 2.35 for males. Cost/patient-year was higher in males $12,000 vs $10,426, which was statistically significant. Progression to renal replacement therapy revealed a shift to a male dominance (57% vs 43%). More males received renal transplantation (56% vs 42%)

Conclusions: The total per patient cost was higher for males in CKD 3-5. Males more often progressed to ESRD. The results of predictive modeling will be included.

Funding: Private Foundation Support

	Unknown Gender	Female	Male	Total
Number of patients	1,925	18,146	13,257	33,328
Total costs	$ 17,087,129	$ 189,196,152	$ 159,167,515	$ 365,450,797
Total drug costs	$ 5,353,367	$ 36,042,849	$ 30,295,035	$ 71,691,251
Professional Fees	$ 4,608,269	$ 49,624,616	$ 38,755,082	$ 92,987,967
Hospital Costs	$ 6,426,096	$ 77,916,991	$ 73,052,148	$ 157,395,236
Hospice	$ 2,784	$179,365	$ 137,650	$ 319,799
Outpatient costs	$ 104,303	$ 5,464,626	$ 6,488,736	$ 12,057,665
Home health costs	$ 254	$ 20,421	$ 11,316	$ 31,992
Skilled nursing facility	$ 222,472	$ 10,217,411	$ 5,030,576	$ 15,470,459
Specialty facility	$ 133,033	$ 1,283,666	$ 885,179	$ 2,301,878
Miscellaneous	$ 236,550	$ 8,445,722	$ 4,511,655	$ 13,193,927
Reserved amount	$0	$ 485	$ 138	$ 623
Religious non med amount	$0	$0	$0	$0
Total Medical Amount	$11,733,762	$ 153,153,303	$ 128,872,481	$293,759,546

TH-PO527

Health Literacy and Blood Pressure Control in Individuals with CKD Rekha Kambhampati,[3] Marie Kuczmarski,[5] Mara McAdams-DeMarco,[2] Dingfen Han,[2] Alan B. Zonderman,[1] Michele K. Evans,[4] Deidra C. Crews.[6] *[1]Intramural Research Program, NIA, NIH, Baltimore, MD; [2]Johns Hopkins, Baltimore, MD; [3]Johns Hopkins University School of Medicine, Baltimore, MD; [4]National Institutes of Health/National Institute on Aging, Baltimore, MD; [5]University of Delaware, Newark, DE; [6]Johns Hopkins University School of Medicine, Baltimore, MD.*

Background: Low health literacy is associated with poor clinical outcomes, including worse blood pressure (BP) control. The relation between health literacy and BP control among those with CKD is unknown. We examined this relation among participants in the Baltimore-based Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study.

Methods: Cross-sectional analyses were conducted of 276 HANDLS participants with CKD (eGFR <60 mL/min/1.73m^2 and/or urine albumin:creatinine ratio (ACR) of ≥30 mg/gm). Health literacy was defined by a Rapid Estimate of Adult Literacy in Medicine (REALM) score of ≤60 (lower) versus >60 (high). Multivariable logistic regression was used to assess the association of health literacy with BP control (systolic BP <140 mm Hg and diastolic BP <90 mm Hg) and linear regression was used to assess health literacy and systolic BP level among persons with self-reported hypertension.

Results: Participants' mean age was 56.4 years. At baseline, 134 (48.6%) had lower health literacy. Those with lower health literacy were more likely to be female (54.5%), African American (81.3%), and living in poverty (56.0%) than those with high health literacy (p <0.05 for all). Both literacy groups had similar levels of education, smoking status, eGFR, and self-reported hypertension and diabetes. A total of 105 (33.5%) had uncontrolled BP. Results of the multivariable regression models are found in the **table**.

Conclusions: Lower health literacy is associated with uncontrolled BP among persons with CKD. Addressing health literacy to improve risk factor control among CKD patients is worthy of further investigation.

Funding: Other NIH Support - Grant Numbers T32 DK007732 and K23 DK097184

Association of Lower Health Literacy (versus High Health Literacy) and BP Control

Model	Odds of BP control (OR (95% CI))	SBP continuous (B coefficient (95% CI))
1- Unadjusted	2.02 (1.26, 3.24)	9.70 mm Hg (1.97, 17.44)
2 – Adjustment for age, sex, race, poverty status, education	2.07 (1.26, 3.41)	9.48 mm Hg (1.23, 17.72)
3 – Model 2 + adjustment for diabetes and smoking status	2.15 (1.24, 3.73)	11.59 mm Hg (2.28, 20.91)
4 – Model 3 + adjustment for eGFR and ACR category*	2.19 (1.24, 3.87)	9.17 mm Hg (0.25-18.09)

*ACR categories (mg/gm): <30, ≥30-≤300, >300

TH-PO528

Sociodemographic Trends in CKD Prevalence in the US Priya Vart,[2] Neil R. Powe,[5] Charles E. McCulloch,[3] Rajiv Saran,[6] Brenda W. Gillespie,[6] Sharon Saydah,[1] Sundar Shrestha,[1] Deidra C. Crews.[4] *[1]Centers for Disease Control and Prevention, Hyattsville, AL; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [3]University of California San Francisco, San Francisco, CA; [4]Johns Hopkins University School of Medicine, Baltimore, MD; [5]Priscilla Chan and Mark Zuckerberg San Francisco General Hospital & University of California SF, San Francisco, CA; [6]University of Michigan, Ann Arbor, MI. Group/Team: CDC CKD Surveillance Team.*

Background: Overall prevalence of CKD in the U.S. has stabilized in recent years, however, whether this is true across sociodemographic groups is unknown. We examined trends in CKD prevalence by race/ethnicity, income (defined by poverty income ratio) and education using data from the population-based, cross-sectional National Health and Nutrition Examination Surveys (NHANES).

Methods: Participants >20 years with available creatinine were included. CKD prevalence was defined as eGFR 15 to <60 ml/min/1.73 m^2 (CKD-EPI). NHANES data included for every 2 years from 2009-2014 (n range 4,869 to 5,662 per period). Unadjusted CKD prevalence was calculated for each sociodemographic group in each period. Interactions were tested between each sociodemographic group and survey period to assess trends. Adjusted [for age, sex, race/ethnicity (when not being examined)] relative risks were obtained comparing most vs. least disadvantaged category in each sociodemographic group for all periods 2009-2014.

Results: Adjusted CKD prevalence was higher in the most recent time period (2013-2014) for non-Hispanic whites (8.0%), Mexican-Americans (5.8%), poor (10.1%), high income (7.5%), 9-11th grade (8.4%) and some college/equivalent -educated persons (8.6%), as compared to earlier time periods for each specific group. Adjusted CKD prevalence among persons with <9th grade education fell to 7.9% in 2013-2014 (from 9.2% in 2011-2012). A statistically significant trend was only present for income (P for 6 year time trend of CKD prevalence was 0.2 for race, 0.03 for income and 0.3 for education). Adjusted relative risks for CKD prevalence are presented in the **Table**.

Conclusions: In recent years, CKD prevalence has increased in some sociodemographic groups, while decreasing in others.

Funding: NIDDK Support, Other U.S. Government Support

Adjusted Relative Risk of CKD (95% CI) by Sociodemographic Group and Year

Group	2009-2010	2011-2012	2013-2014
Non-Hispanic black vs. Non-Hispanic white	1.3 (1.0-1.6)	1.2 (0.9-1.5)	0.9 (0.7-1.1)
Mexican American vs. Non-Hispanic white	0.7 (0.4-0.9)	0.7 (0.3-1.1)	0.7 (0.4-1.1)
Poor vs. high income	1.2 (0.7-1.6)	1.3 (0.9-1.7)	1.4 (0.7-2.0)
<9th grade vs. college education	1.7 (1.2-2.2)	1.4 (0.7-2.2)	1.2 (0.6-1.8)

TH-PO529

Racial/Ethnic Differences in CKD and Its Risk Factors in Hawaii Connie Rhee,[2] Victoria Page,[1] Glen Hayashida,[1] Merle R. Kataoka-Yahiro,[5] James Davis,[5] Linda L. Wong,[5] Krupa Gandhi,[5] Amy S. You,[2] Kamyar Kalantar-Zadeh.[2] *[1]National Kidney Foundation of Hawaii, Honolulu, AL; [2]University of California Irvine, Huntington Beach, CA; [5]University of Hawaii, Honolulu, HI.*

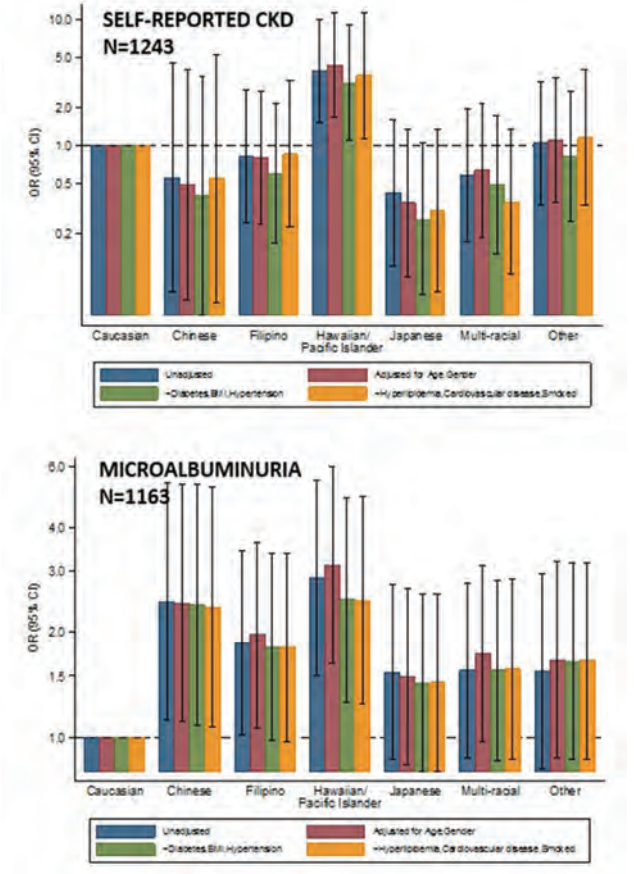
Background: While traditional risk factors for chronic kidney disease (CKD) are highly prevalent in Hawaii, there is limited data on the risk of early CKD among the racially/ethnically diverse population of this state. To address this knowledge gap, the National Kidney Foundation of Hawaii developed the Kidney Early Detection Screening (KEDS) Program to promote early CKD screening among its residents.

Methods: Among participants from the KEDS Waves 1 (2006-9) screening events, we examined the association between race/ethnicity and markers of early CKD, defined as 1) microalbuminuria (albumin-creatinine ratio ≥30mg/g) and 2) self-reported CKD using case-mix logistic regression models (adjusted for age, gender, diabetes, hypertension, body mass index, hyperlipidemia, cardiovascular disease, and smoking status).

Results: Among 1254 participants, the most predominant racial/ethnic groups were participants of Caucasian (22%), multi-race (19%), Japanese (19%), Filipino (16%), Hawaiian/Pacific Islander (8%), and Chinese (5%) background. Compared to Caucasian

participants, those of native Hawaiian/Pacific Islanders race/ethnicity had a higher likelihood of self-reported CKD: adjusted OR (aOR) 3.60 (1.14-11.40). Native Hawaiian/ Pacific Islander and Chinese participants also had a higher likelihood of microalbuminuria: aORs 2.37 (1.07-5.27) and 2.48 (1.25-4.91), respectively. Examination of CKD risk factors showed that Native Hawaiian/Pacific Islanders had higher risk of hypertension (aOR 1.86 [1.07-3.25]) and obesity (aOR 4.01 [2.42-6.67]).

Conclusions: These data suggest Hawaiian/Pacific Islanders have a higher risk of CKD markers compared to other racial/ethnic subgroups in the KEDS Program. Further studies are needed to determine the effectiveness of CKD interventions in this population.



TH-PO530

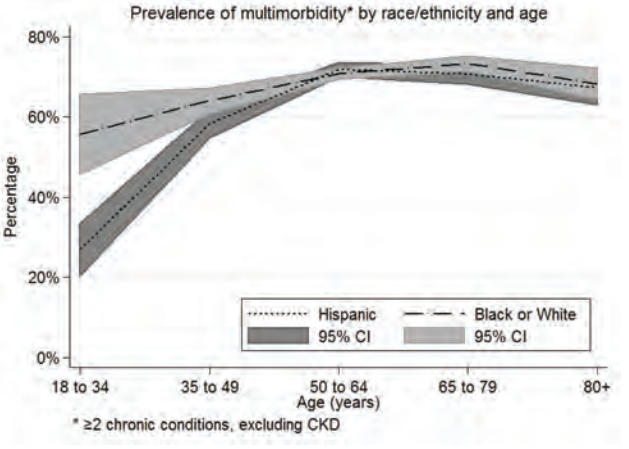
Multimorbidity and Race/Ethnicity in CKD Carl P. Walther, Jingbo Niu, Jingyin Yan, Wolfgang C. Winkelmayer, Sankar D. Navaneethan. *Baylor College of Medicine, Houston, TX.*

Background: Multimorbidity is common in CKD. It increases treatment burden and complexity, can result in conflicting therapies, and is associated with adverse outcomes. This may be especially important in socioeconomically disadvantaged populations. We examined the demographics of multimorbidity in a diverse, disadvantaged, non-dialysis CKD cohort.

Methods: We identified adults with eGFR <60 ml/min/1.73 m^2 for ≥90 days who received care through an urban safety-net health care system from 2006-16. ICD codes for chronic conditions (excluding CKD) prior to or within two weeks of cohort entry were identified and categorized into 21 groups. The relationships of comorbidity patterns with demographics and CKD stage (3A, 3B, 4, and 5) were studied. Multimorbidity was defined as 2 or more chronic conditions in addition to CKD. Race/ethnicity was recorded in 5 mutually-exclusive categories. We used proportions with binomial confidence intervals in stratified analyses, and multivariate logistic regression, to study relationships.

Results: We identified 13,678 patients, of whom 39.4% were Hispanic, 40.9% black, 11.5% white, 5.9% Asian/Pacific Islander, and 2.2% other/unknown. Comorbidity count (excluding CKD) ranged from 0 to 10, with median [interquartile range] of 2 [1,3]. Multimorbidity varied markedly by race/ethnicity and age (Figure). The logistic regression model (adjusted for gender, CKD stage, and year of cohort entry) corroborated this interaction (likelihood ratio test: $p < 0.001$). Among those aged 18-34, blacks or whites had slightly higher diabetes and HTN prevalences than Hispanics, compared with 10-fold higher HIV prevalence, and 4-fold higher depression and CHF.

Conclusions: Multimorbidity among young adults with non-dialysis CKD varies markedly by race/ethnicity, with lower prevalence among Hispanics than blacks or whites. This may be due to differences in CKD etiology, disparities in access to care, and other factors which warrant further investigation.



TH-PO531

Does Vitamin D Level Explain the Racial Disparity in Albuminuria? Marcelo B. Lopes,[4,5] Jennifer L. Bragg-Gresham,[5] Hal Morgenstern,[5] Nilka Rios Burrows,[1] Deidra C. Crews,[2] Neil R. Powe,[3] Rajiv Saran.[5] *[1]Centers for Disease Control and Prevention, Atlanta, GA; [2]Johns Hopkins University School of Medicine, Baltimore, MD; [3]Priscilla Chan and Mark Zuckerberg San Francisco General Hospital & University of California SF, San Francisco, CA; [4]Universidade Federal da Bahia, Salvador, BA, Brazil; [5]University of Michigan, Ann Arbor, MI.*

Background: Results from observational studies have shown that African Americans (AA) are more likely to have albuminuria than are whites and that 25-OH vitamin D3 (VitD) level is inversely associated with albuminuria. We hypothesized that VitD may partly explain the racial disparity in albuminuria risk by acting as a mediator in the causal pathway. Thus, the aim of this study was to estimate the direct and indirect (through VitD) effects of race on albuminuria in US adults.

Methods: Using cross-sectional data from 2007–2010 datasets from the National Health and Nutrition Examination Survey we applied the approach to mediation analysis of VanderWeele & Vansteelandt (2010) to estimate the direct and indirect effects of race on albuminuria prevalence, where VitD was treated as a continuous mediator. Estimated odds ratios (ORs with 95% CIs) were derived from: (1) a logistic model, where albuminuria prevalence was regressed on race, VitD, their product, and two potential confounders, age and sex; and (2) a linear model, where VitD was regressed on race, age, and sex. A secondary analysis adjusted for 6 additional risk factors for VitD or albuminuria. The total effect of race on albuminuria was estimated as the product of the direct and indirect effects.

Results: AA individuals had a higher prevalence of VitD<50nmol/L (72.4% vs. 20.5%. p<0.001) and albuminuria (11.2% vs. 8.6%. p=0.025) compared to Whites. The OR for the direct effect of race on albuminuria was 1.42 (95% CI: 1.10, 1.94), and the OR for the indirect effect was 1.29 (1.14, 1.46). The OR for the total race effect was 1.83, and the proportion of the race effect mediated by VitD was 42%. Additional adjustment for 6 other potential confounders yielded weaker direct and indirect effects but increased the proportion mediated to 51%.

Conclusions: The effect of VitD may explain nearly half the racial disparity in albuminuria prevalence in the United States; however, causal inference is limited by the cross-sectional design and possible residual confounding. Future research may address these limitations and consider other possible mediators of the race effect.

Funding: Other U.S. Government Support

TH-PO532

Disadvantaged Childhood Socioeconomic Position Represents a Critical Period for the Embedding of Kidney Disease Risk in Women Mark Canney,[1,2] Siobhan Leahy,[1] Siobhan Scarlett,[1] Rose Anne M. Kenny,[1] Mark A. Little,[2] Conall M. O'Seaghdha,[3] Cathal McCrory.[1] *[1]The Irish Longitudinal Study on Ageing, Trinity College Dublin, Dublin, Ireland; [2]Trinity Health Kidney Centre, Trinity College Dublin, Dublin, Ireland; [3]Department of Nephrology and Transplantation, Beaumont Hospital, Dublin, Ireland.*

Background: Socioeconomic position (SEP) is an important determinant of health but is dynamic across the lifespan. This study examines the relationship between life course SEP and chronic kidney disease (CKD) using three conceptual life course models: critical period, pathway and accumulation. We test each model in a population of Irish adults who experienced dramatic social mobility during their lifetime, as Ireland transitioned rapidly from a primarily agricultural to post-industrial society.

Methods: Cross-sectional analysis of data from 4996 participants from The Irish Longitudinal Study on Ageing, a nationally representative sample of community-dwelling adults aged ≥50 years. We defined CKD as a glomerular filtration rate <60mL/min/1.73m^2 estimated from the combination of creatinine and cystatin C using the CKD-EPI formula. We defined childhood and adulthood SEP according to father's and respondent's

occupation respectively, and categorised SEP as high (reference), intermediate, low or never worked. We tested the critical period and pathway models by examining the age-adjusted relationship between SEP and CKD using logistic regression separately in men and women. We tested the accumulation model by fitting an interaction between childhood and adulthood SEP, and assessed social mobility trajectories arising from that interaction.

Results: Low childhood SEP was strongly associated with CKD in women, even after adjusting for adulthood SEP (odds ratio 1.90 [95% confidence interval 1.24, 2.92]), supporting the critical period over the pathway hypothesis. This association was not explained by traditional CKD risk factors including central obesity, diabetes, smoking or hypertension. Women who experienced low childhood SEP and whose circumstances improved in adulthood also had increased odds of CKD, further supporting a critical period effect in childhood. The interaction between childhood and adulthood SEP was not statistically significant in either sex. We did not observe any substantive association between SEP and CKD in men.

Conclusions: Our findings suggest that women exposed to disadvantaged SEP in childhood represent an at-risk group in whom there may be opportunities for identification of CKD and facilitation of health-promoting behaviours from an early age.

Funding: Government Support - Non-U.S.

TH-PO533

Consideration of Living Donor Kidney Transplantation across the Continuum of Care in CKD Helene Vilme,[2] Clementina A. Davenport,[1] Jane F. Pendergast,[1] L. Ebony Boulware.[1] *[1]Duke University School of Medicine, Durham, NC; [2]Duke University, School of Medicine, Durham, NC.*

Background: African Americans (AA) have had persistent disparities in achieving live donor kidney transplants (LDKT). It is unclear whether patients' interest and pursuit of LDKT varies based on their exposures to kidney disease treatments (pre-dialysis, dialysis, and transplant waitlist) and what knowledge or attitudinal factors might affect interest and pursuit among different groups.

Methods: We conducted separate secondary cross-sectional analyses of baseline data collected among AA with advanced kidney disease or kidney failure in three randomized clinical trials studying access to LDKT. Patients were either (1) not previously exposed to renal replacement therapies ('pre-dialysis'), (2) on hemodialysis, or (3) on the transplant waiting list. We measured participants' interest in LDKT on a 10-point scale ranging from 0-7 (not interested) to >7(highly interested). We measured patients' pursuit (present versus absent) of LDKT based on their self-reported discussion of LDKT with their families or physicians, or their completion of an LDKT evaluation. We quantified the association of knowledge, health literacy, and trust with medical care with interest and pursuit in separate multivariable logistic regression models adjusting for age, sex, marital status, and education.

Results: A majority of participants (total N=62 pre-dialysis, N=92 dialysis, N=156 transplant waitlist) in all three cohorts reported having high interest in LDKT (pre-dialysis, 62.9%; dialysis, 67.4%; transplant waitlist, 74.2%). Compared to pre-dialysis patients, those with exposure to dialysis and those on the waiting list more frequently pursued LDKT (pre-dialysis, 45.0%; dialysis, 72.7%; transplant waitlist, 92.2%). No significant association was observed between interest in LDKT, knowledge, health literacy, or the three trust factors for pre-dialysis, dialysis, and transplant waitlist, respectively ($p>.05$). Similarly, we found no significant association with LDKT pursuit in either of the study cohorts ($p>.05$).

Conclusions: Progress has been made in assisting African Americans to pursue LDKT. Our study showed that interest in LDKT is high at all stages of treatment, but pursuit is lower at early stages. Efforts are needed to assist individuals with interest in LDKT move towards LDKT pursuant behaviors.

Funding: NIDDK Support

TH-PO534

Cost of Potentially Preventable Hospitalizations among Patients with CKD: A Population-Based Analysis Paul E. Ronksley,[2] James Wick,[2] Scott Klarenbach,[1] Braden J. Manns.[2] *[1]University of Alberta, Edmonton, AB, Canada; [2]University of Calgary, Calgary, AB, Canada. Group/Team: Alberta Kidney Disease Network.*

Background: Prior studies have observed high rates of hospitalization among patients with chronic kidney disease (CKD). We conducted a population-based analysis to determine the proportion and cost of hospitalizations that are potentially preventable and whether this varies by CKD severity.

Methods: We identified all adults (≥18 years) with an outpatient serum creatinine measurement between January 1 and December 31, 2013 in Alberta, Canada. We used KDIGO guidelines to categorize CKD severity (including dialysis-dependent patients) based on measures of albuminuria and eGFR. Patients were then linked to administrative data to capture frequency and cost of hospital encounters, and followed until death or end of study (December 31, 2014). Within each CKD category we calculated the rate, proportion, and cost attributable to potentially preventable hospitalizations as defined by six CKD-related ambulatory care sensitive conditions (ACSCs); heart failure or volume overload, hyperkalemia, malignant hypertension, and diabetes with hyperosmolarity or ketoacidosis.

Results: Of the 1,007,051 adults with eGFR and albuminuria measurements, 157,465 had CKD of which 1.1% were dialysis-dependent. During a median follow-up of 1 year, there were 56,372 hospitalizations among CKD patients resulting in a total cost of $873 million CAD. Adjusted rates of all-cause hospitalization increased linearly with CKD severity with dialysis-dependent patients having 416 hospitalizations per 1,000 person-years and the highest average cost per inpatient encounter ($26,507 [95% CI: $23,504-$29,510]). Overall 3,769 (6.9%) of hospitalizations were for CKD-related ACSCs, with the majority being for heart failure. Adjusted rates of CKD-related ACSCs also increased with CKD severity and were highest among patients with non dialysis-dependent severe CKD (21 hospitalizations per 1,000 person-years). The total cost of potentially preventable hospitalizations was $54 million (6.1% of total cost), with an average cost per encounter of $13,734 (95% CI: $12,956-$14,511).

Conclusions: While only a small proportion of hospital costs among patients with CKD are for potentially preventable hospitalizations, these findings suggest that effective strategies that reduce preventable admissions among CKD patients may lead to significant cost savings.

TH-PO535

Clinical Profile and Outcomes of Young Adult Patients with CKD at Philippine General Hospital under the Pediatric to Adult Transition Program Lipat Kalinga Dianne V. Vieja. *Department of Medicine, UP-Philippine General Hospital, Manila, Philippines.*

Background: Advances in the care of patients with CKD resulted in substantial improvement in survival. More patients transfer from pediatric to adult medicine department, instigating the need for proper transition programs- a purposeful, planned movement from child-centered to adult-oriented health services. ISN-PNA in 2011 recommended development of locally appropriate practices for transferring patients. This study describes the transition experience of a pioneer transition program in a low-resources environment.

Methods: A retrospective chart review of 48 transitioned patients from 2011- 2016 was conducted. General data and laboratory parameters before transition and 2 years later were obtained. The no.of hospitalizations, ER consults, OPD followup and the rate of renal function decline after 2 years were also noted.

Results: One hundred thirteen patients were enrolled in the transition program from 2011- 2016. Sixtyfive (58%) patients were not transitioned, 31% were lost to follow-up before transfer. Fortyeight patients completed the transition process, but more than half disengaged from care. Nineteen patients (42%) were actively following up. Mean transition score was 81.18% and it was not associated with the no. of followup, hospital admissions and ER consults. Majority of patients missed their first scheduled adult followup. Mean no. of followup per year was 2 at an average of 1 consult in 6 months. Five patients were admitted post transition with 5 days mean hospital stay. Four patients had ER consults with a mean of 1 ER and 1 hospital admission per year. Fourteen of the patients had a higher BMI 2 years after with mean increase of 1.05 points. There was no significant difference between the baseline and the posttransfer laboratories (electrolytes, albumin, hemoglobin, proteinuria, creatinine and BUN). Mean decline in renal function was 1 ml/min/1.7 per year. There was no significant change in the eGFR of patients before and 2 years after transition.

Conclusions: To improve outcomes of young patients with CKD as they transfer to adult-focused services, transition preparation is critical. In this pioneer group, follow-up rate was only 42%. Obvious difficulties encountered suggest developing more standardized transition methods and strenghtening adult Nephrology participation in the pre-transfer period.

TH-PO536

A Business Case for New CKD Payment Models Harry Liu,[2] Sophia Zhao.[1] *[1]Massachusetts General Hospital, Brookline, MA; [2]RAND Corporation, Boston, MA.*

Background: Various interventions have been demonstrated to effectively slow down the progression of chronic kidney disease (CKD), smooth the transition to renal replacement therapy (RRT), and improve patient outcomes. Such interventions, however, are rarely adopted due to misaligned incentives in the current healthcare system. This study aims to quantify the savings from CKD interventions and design associated new payment models.

Methods: We constructed a simulation model that identifies and quantifies savings opportunities during the CKD progression and transition to RRT, and extracted the model's parameters from the published literature. Simulation model sensitivity analyses were conducted to account for the uncertainty in input parameters. Assumptions were made only when published data were lacking. New payment models were proposed to materialize such savings opportunities.

Results: The simulation includes the following interventions: increasing the use of pre-dialysis nephrology care to slow down disease progression; smoothing transition to dialysis initiation to decrease the use of inpatient services and increase the adoption of arteriovenous fistula and peritoneal dialysis; and decreasing the use of dialysis among patients with an eGFR of 15 or greater or among patients with advanced age and multiple conditions, for whom the benefits of dialysis is very limited or nonexistent. The simulation model results in an annual savings of $1.0 billion for Medicare [range: $0.5 - $1.8 billion] and $1.8 billion for all payers [range: $0.7 - $2.1 billion]. Increased use of pre-dialysis nephrology care and decreased use of inpatients services at dialysis initiation each contributes to about one third of savings, respectively. The simulation model also suggests that new payment models should focus on Stage 3 and 4 patients and the transition from CKD to RRT. Within Medicare, new payment models can be designed around ESRD Seamless Care Organizations, Special Needs Plans, or Medicare Advantage Plans to streamline incentives and optimize care efficiency. A joint program between Medicare and other payers should be set up so that Medicare and other payers can share savings from CKD interventions.

Conclusions: Tremendous savings opportunities exist in slowing CKD progression and smoothing the transition to RRT, and new payment models should be designed and implemented to reap the benefits.

TH-PO537

Limitations of ICD Codes in Detection, Staging, and Assessing Progression of CKD Kabir Jalal,[4] Edwin J. Anand,[3] Rocco C. Venuto,[1] Pradeep Arora,[5] Joseph A. Eberle.[2] *[1]Erie County Medical Center, Buffalo, NY; [2]Intelligent Care Management, East Amherst, NY; [3]None, Getzville, NY; [4]University at Buffalo, Hamburg, NY; [5]Nephrology, VAMC, Buffalo, NY.*

Background: The International Classification of Diseases (ICD) coding system is the industry standard tool for disease classification and epidemiology purposes. However, ICD codes in practice unreliably reflect the true diagnosis for a given disease/patient. This study seeks to quantify that inaccuracy among patients with Chronic Kidney disease (CKD).

Methods: Using insurance data consisting of 222,664 insured individuals with serum creatinine measurements over seven years, diagnoses based on a set of CKD-related ICD codes were compared against gold standard Kidney Disease Outcomes Quality Initiative (KDOQI) clinical guidelines to evaluate accuracy of ICD codes to detect CKD-positive patients. Patient serum creatinine levels were used to estimate progression of disease course using a longitudinal mixed model to identify advanced progressors, or those patients with loss of eGFR (estimated glomerular filtration rate) greater than 1 ml/year, and to assess accuracy of ICD codes in detecting advanced progressors.

Results: ICD codes correctly identified only 10,101 of 33,159 individuals as CKD, for a sensitivity of 30.46% with positive predictive value (PPV) of 65.05%; codes correctly identified 184,078 individuals as CKD-negative, for a specificity of 97.14% with negative predictive value (NPV) of 88.87%. In identifying rapid progressors, ICD codes achieved a sensitivity of 11.95% with PPV of 8.46%, and a specificity of 94.73% with NPV of 96.35%.

Conclusions: The use of ICD codes alone is insufficient in identifying patients with CKD. This study is the first to attempt the use of ICD codes in identifying rapidly progressing patients, revealing poor coding performance when compared to gold standard KDOQI guidelines. Use of ICD codes to identify CKD patients, assess disease severity, or to evaluate disease progression for either clinical or epidemiological purposes is not recommended.

Funding: Other U.S. Government Support

Progression Performance Measures

Measure	Mean	Lower 95%	Upper 95%
Sensitvity	11.95	8.020	16.90
Specificity	94.73	94.11	95.30
Positive Predictive Value	8.460	5.410	11.52
Negative Predictive Value	96.35	95.85	96.84

TH-PO538

Lab Vigilance in Patients with CKD on Renin Aldosterone Inhibitors and Diuretics: Are We Monitoring Appropriately? Katherine Garlo,[2] Diane Seger,[4] Julie Fiskio,[1] David W. Bates,[3] David M. Charytan.[2] *[1]Brigham & Womens Hospital, Boston, MA; [2]Renal Division, Brigham and Women's Hospital, Boston, MA; [3]Brigham and Women's Hospital/Harvard Medical School, Brookline, MA; [4]Partners Healthcare System, Somerville, MA.*

Background: Renin Aldosterone Inhibitors (RASi) are first line agents for hypertension. Their efficacy has been shown in reducing blood pressure, slowing progression of chronic kidney disease (CKD), and cardiovascular protection. Grade A level 1 evidence supports their use in CKD with or without proteinuria. However, ideal lab monitoring during initiation of RASi is uncertain and guidelines are opinion based if present at all. We assessed outpatient lab monitoring in a large cohort of patients with CKD prescribed a new RASi or diuretic.

Methods: We evaluated adults with pre-dialysis CKD stage 3-5 who received a new outpatient RASi or diuretic prescription during 2009-2011. Lab data was collected electronically and analyzed for baseline and follow-up labs creatinine and potassium.

Results: A total of 8,272 individuals (mean age 72±13.5 years, 44% male, 86% white) with CKD (90% stage 3) were included. The average interval following baseline labs to first prescription was 41±79 days. Fewer individuals in the RASi group received baseline labs within two weeks 61% compared to the diuretic group 59%, P =0.02. Mean time to follow up labs was 78 days and was longer in the RAS inhibitor group 86±103 days compared to the diuretic group 69 days ±90.4 days, P<0.01. Follow up labs were checked within 2 weeks in 28% (RASi: 24%, diuretic: 31%, P<0.01). Nearly half of individuals did not receive labs for >6 weeks (overall:45%, RASi: 48%, diuretic: 41%). Male sex, black race, CKD stage, cardiovascular disease, and diabetes were associated with lab monitoring within 14 days. Age >65 years and RASi were associated with a lower risk of having baseline labs within 14 days (OR 0.69, 95% CI 0.63-0.76, P <0.01, OR 0.91, 95% CI 0.83-0.98, P =0.02) and follow up (OR 0.74, 95% CI 0.66-0.82, P <0.01, OR 0.69, 95% CI 0.63-0.76, P <0.01).

Conclusions: Many patients with CKD do not receive lab monitoring with 2 weeks of initiating a RASi or diuretics. Elderly individuals and women may be at higher risk. The results suggest that advancements in electronic prescription ordering or automated reminders may improve safety of RASi and diuretic use in patients with CKD.

TH-PO539

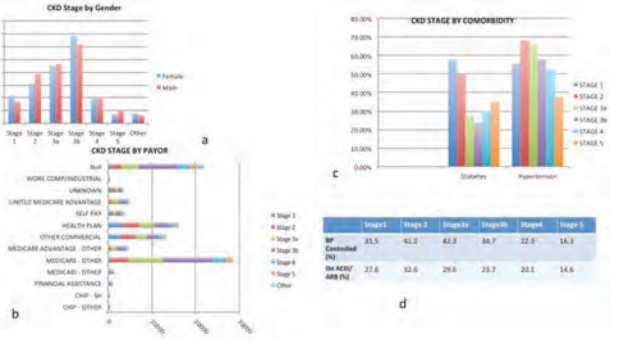
Electronic Health Record (EHR) Based Pre-ESRD Chronic Kidney (CKD) Registry in the Intermountain West as a Clinical Tool Titte Srinivas,[2] Denney Edgel,[2] Sharon Hamilton,[2] Mark R. Greenwood,[2] Steve Hadley,[2] Katie Larson,[2] Ray Morales.[1] *[1]Intermountain Healthcare, Murray, UT; [2]Intermountain Medical Center, Murray, UT.*

Background: The field of kidney disease is richly endowed with data sources. However, data are lacking on pre-End-Stage Renal Disease (ESRD) CKD especially at a granular level in the context of clinical care. Such data can be used to drive optimal care delivery in the clinic. We report on an EHR based CKD registry built at a large integrated health system in the Intermountain West that captures longitudinal patient level data as well as payer information from diverse sources. The scope of this registry encompasses 5 states, 179 clinics, 22 hospitals and 800,000 lives under a private payer and 2 million lives overall.

Methods: Patients were acccrued to this pre-ESRD CKD registry based on estimated GFR (eGFR), ICD 10 codes, CPT codes, EHR comorbidity data, prescription data, drug names and doses, laboratory data and claims data. Results were cross validated by eGFR and claims data. The registry was built off an Enterprise Data Warehouse that has been extant since 1990. A subset of patients recieved birth to death care within this Integrated Health System. Data from this registry are use to track quality and care delivery in real time with EHR advisories to drive care in the clinic as well as serving as vehicles to update care process modules based on accrued outcomes.

Results: Results are depicted in Figure 1. A total of 97877 patients with pre-ESRD CKD are included with a White predominance; 96.4 percent of patients in Stages 1 through 5 and CKD 2-4 comprising 81.6 %. Early stage CKD showed a male preponderance. The Registry was able to provide classification by demographics (a)and comorbidity (b), as well as by CKD Stage and Payer type (c) and BP control/ ACEI/ARB use (d) on a real time basis. Overall, BP was deemed controlled in 34.6 % and ACEI/ARBs were used in 25.5%.

Conclusions: We demonstrate the utility of an EHR based CKD Registry with Longitudinal Real Time Follow up as way to optimize pre-ESRD CKD care in a Large Integrated Health System.



TH-PO540

Use of Analgesics among Older Patients with CKD in the United States (2006-2015) Yun Han,[3] Rajesh Balkrishnan,[2] Kevin He,[1] David W. Hutton,[1] Diane Steffick,[3] Richard A. Hirth,[1] Rajiv Saran.[3] *[1]Kidney Epidemiology and Cost Center, University of Michgian, Ann Arbor, MI; [2]University of Virginia School of Medicine, Charlottesville, VA; [3]Internal Medicine - Nephrology, University of Michigan, Ann Arbor, MI.*

Background: Pain is common among patients with kidney disease yet few studies examine this, especially among older patients with non-dialysis CKD. We investigated US national trends in the use of nonsteroidal anti-inflammatory agents (NSAIDs) and opioid analgesics by older CKD patients over the past decade.

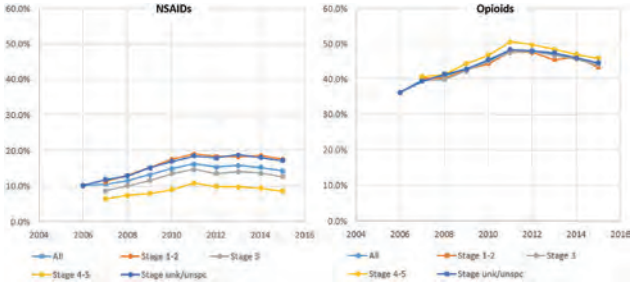
Methods: We identified eligible CKD patients enrolled in Medicare Part D through claims data (5% Medicare sample, 2006-2015). Demographics, CKD stages and comorbidities were assessed over a one-year entry period. Analgesic use by year was measured as the proportion of patients prescribed non-steroidal and opiate analgesics. The days-prescribed-per-user (DPPU) during a given calendar year were computed from medication claims. Logistic regression was used to explore factors associated with use of specific analgesics.

Results: There was a notable increase in use of NSAIDs among Medicare CKD patients in the past decade, from 10.5% in 2007 to a peak of 16.3% in 2011, with a decline to 14.3% in 2015 (Figure). DPPU were relatively stable, ranging from 104-109 days. NSAID use was consistently lower at higher stages of CKD. Opiates were prescribed to 39.4% of CKD patients in 2007, peaking at 48.3% in 2011 before declining to 44.6% in 2015 (Figure). Unlike NSAIDs, opioid use was highest in Stage 4-5 CKD. There was a significant increase in days prescribed in all CKD stages (30%-33%), from 89-104 to 116-138 per year. Younger age, female sex, not receiving the Part D subsidy, comorbid hypertension and diabetes were predictors of analgesic use in CKD patients. Opioids were more likely to be used by CKD patients who were white, or had higher stages of CKD, cancer or coronary artery disease.

Conclusions: Use of analgesics, particularly opioids, is very high in the Medicare CKD population, and rose substantially between 2007 and 2011. This study suggests both

a high burden of pain in this vulnerable population, and the potential for suboptimal pain management and dangerous adverse effects, including narcotic dependence.

Funding: NIDDK Support



Proportion of Analgesic Use in Medicare Patients by CKD Stages

TH-PO541

CKD Patient Characteristics and Attitudes Towards Kidney Disease Education Devasmita Choudhury,[1,2] Urbi Dev,[1] Lesley Mcneil,[1] Suzanne T. West.[1] *[1]Salem Veterans Affair Medical Center, Salem, VA; [2]University of Virgnia, Salem, VA.*

Background: CKD education (CKD-Ed) is crucial to managing and improving CKD health outcomes. Patients (pts) often defer or miss CKD –Ed appointments. We compare characteristics and attitudes of pts who opt to receive education (R-Ed) to pts who decline (D-Ed).

Methods: A web-based CKD-Ed (VA-ekidneyclinic) education program designed at the 5th grade level was offered consecutively to 179 known CKD patients and their family members during CKD clinic appointments at Salem VAMC from 7/2016 to 5/2017 with continuing web-based home education as part of a study.

Results: R-Ed: 61/179 (34%); D-Ed: 118/179 (66%) patients. Reasons for declining education: 46% - no interest, 36% -no home web access, 12%- too busy, 5% live too far, 3% confused. See data table for age, ethnicity, CKD stage, number or medical problems, differences in education level between groups. 76% of "non-interested", 82% of "no computer", 100% "live too far" pts were from counties and cities with < 88% HS and higher education; 70% "too busy" pts came from >88% HS education counties and cities. 62% pts despite computer access declined both clinic and home CKD-Ed.

Conclusions: CKD patients who decline CKD education are more like to be older, male, from lower educated surroundings and interestingly fewer medical problems than those that opt to receive CKD education. Creative education tools and practices (eg: games, comics, jingles) need to be explored to motivate and educate a majority of CKD patient in order improve CKD health outcomes.

Funding: Private Foundation Support

Demographics Data: Opting to Receive (R-Ed) vs Decline (D-Ed) CKD Education

Grp/total number of patients in group/%	R-Ed/61/34	D-Ed/118/66	p
Age (years) (mean±SD)	65 ±9	80±9	0.000
Education (Ed) level	89% ≥HS^ Ed	75% reside in cty&cntyS that report+ <89 % HS Ed level[3] 65% are in cnty&cty < US avg HS Ed level of 87%#^	
Gender (M:F)%	78:22	99:1	
Ethnicity (%)	71C 23AA.6 other	71C, 23AA,6 other	No difference
CKD stage – 2/3/4/5 (%)	2.5/85/12.5/0	8/62/23/6	
No. of Medical Problems (mean±SD)	23±8	21±8	0.000
^HS = high school No = number	SCnty =county SCty = city	* VA state avg Ed level 89% ** US avg 87% + https://literacyfacts.wordpress.com/	C = Caucasian AA= African American

TH-PO542

Cost-Effectiveness of a Multiple Intervention Model for Management of CKD in Primary Health-Care Rafael A. Ayala cortes,[2] Laura Cortes-Sanabria,[1] Alfonso M. Cueto-Manzano,[1] Enrique Rojas-Campos.[1] *[1]Unidad de Investigación Medica en Enfermedades Renales, IMSS, Guadalajara, Jalisco, Mexico; [2]Unidad de Investigación Médica en Enfermedades Renales, Guadalajara, Jalisco, Mexico.*

Background: Strategies to prevent and delay progression of early CKD are urgently needed; however, there is little information about costs and outcomes at the primary health-care. **Objective:** To evaluate cost-effectiveness of multiple intervention model (MIM) *vs* conventional health-care model (CHCM) for CKD diagnosis and treatment.

Methods: Prospective evaluation from the health-care provider perspective, performed in 2 Family Medicine Units of Guadalajara, Mexico: MIM and CHCM were evaluated in one unit each. Three phases evaluated: Educative intervention for health professionals, Screening of CKD, and Management/Follow-up of CKD patients. All resources were identified, quantified and recorded; official lists for drugs, medical materials and services, and laboratory/image tests were employed for costs calculation. Only direct medical costs (in USD) were considered. *Main outcome and measures:* Total cost, average cost per person, and incremental cost-effectiveness ratio (ICER) with bootstrap analysis were determined in each phase. Clinical competence of health professionals was measured with a validated questionnaire, and CKD progression was defined as decline in GFR category.

Results: Clinical competence was not different between models neither at baseline (MIM 63±21 *vs* CHCM 60±19, p=0.52) nor at final (MIM 94±14 *vs* CHCM 89±17, p=0.76) evaluations. Average cost per health professional receiving educative intervention in MIM was $833 (CI95% 762-899) *vs* $901 (819-976) in CHCM ($p$=0.26). ICER was $22.6 favoring MIM. CKD stages 1-3 were present in 30% of patients from MIM (N 336) and 32% from CHCM (N 454). Average cost per person of CKD screening was $45 (CI95% 41-47) in MIM and $42 (CI95% 37-45) in CHCM (p=0.60). ICER was $2.3 favoring CHCM. For Management/Follow-up phase, 57 patients with CKD stages 1-3 were studied during 12-month in MIM and 58 patients in CHCM. CKD progression was observed in 16% of patients in MIM *vs* 28% in CHCM (p=0.09). Average cost per patient was $826 (CI95% 760-900) in MIM *vs* $701 (CI95% 632-777) in CHCM. ICER was dominant in MIM.

Conclusions: MIM are more cost-effective than CHCM to delay kidney disease progression when strategies combining educative interventions for health professionals, screening and adequate management of early CKD are employed at the primary health care.

TH-PO543

Applying Lean Tools to Optimize Delivery of Patient CKD Education in Primary Care Julie A. Wright Nunes,[4] Emily P. Chen,[2] Eve Kerr,[3] Audrey Fan,[1] Tejpreet Nakai,[6] Gunjan Garg,[3] Angela Fagerlin.[5] *[1]Univ of Mich, Northville, MI; [2]University of Michgan, Ann Arbor, MI; [3]University of Michigan, Ann Arbor, MI; [4]University of Michigan Health System, Ann Arbor, MI; [5]University of Utah, Salt Lake City, UT; [6]Univeristy of Michigan, Ann Arbor, MI.*

Background: Eighty percent of patients with CKD do not have the knowledge necessary to be fully activated in CKD management. Efficient and sustainable programs are needed to address patient education needs early in the CKD care continuum.

Methods: Applying Lean Tools (cause/effect analysis, process mapping / re-engineering), we created an efficient and sustainable way to integrate CKD patient education seamlessly into primary care practice. Utilizing a multi-disciplinary team (including primary care and nephrology physicians, patients, medical assistants, nursing, check-out staff, Health IT, and Lean coaches) a current-state process map of patient care and education was created for a large primary care practice. Lean coaches facilitated the multi-disciplinary team to create an improved future-state process that incorporated a CKD education module (a patient education worksheet) into current practice, using existing staff and resources. Content of the worksheet was optimized using quality improvement techniques. Health IT staff created an electronic version to use in the electronic medical record (EMR). This electronic patient education worksheet auto-populates with each patient's eGFR, blood pressure, and urine protein values. Medical assistants enter the worksheet into the EMR for patients with CKD stages 3-5 during patient check-in for routine visits. Providers review this worksheet in the EMR with patients during clinic encounters. Providers may enter 1-2 tailored messages about shared care goals. The worksheet prints automatically upon check-out and is given to the patient.

Results: Pilot testing shows the process is efficient and feasible to integrate into busy clinical settings. It takes seconds (two key-strokes) to enter into the EMR and approximately ~2 minutes for providers to review. Next steps will examine the impact of the electronic education worksheet and future state process on patient, clinic and provider related outcomes.

Conclusions: We provide a model of a future state process that incorporates patient CKD education seamlessly into practice, leveraging IT resources and existing clinic staff. The ultimate aim of this project is to improve patient CKD knowledge by addressing the unmet need of providing disease-specific education to patients early in the care continuum.

Funding: NIDDK Support

TH-PO544

Primary Care-Nephrology Multidisciplinary Partnership Improves CKD Care Paula Haberman,[1] Denney Edgel,[3] Sharon Hamilton,[3] Arasu Gopinath,[4] Ray Morales,[2] Mark R. Greenwood,[3] Titte Srinivas.[3] *[1]Family Practice, Park City, UT; [2]Intermountain Healthcare, Murray, UT; [3]Intermountain Medical Center, Murray, UT; [4]Nephrology Associates, Salt Lake City, UT.*

Background: Resources for CKD care are often clustered around late stage CKD with poor medical care in early stages leading to increased costs of care. Patients with realy stage stage CKD may overburden alaredy stretched nephrology resources and are cared for by primary care providers (PCPs) who may not be fully empowered to render appropriate CKD Care. Structured partnerships between PCPs, health systems, payers and nephrologist could be used to improve early stage CKD care. We report on a process improvement and care delivery redesign in a large integrated health system serving 5 states in the Intermountain West that demonstrates initial success of a PCP centered multidisciplinary approach to CKD care.

Methods: As a first step, we aimed to increase the numbers of urine albumin creatinine ratios (ACR) obtained on patients in CKD stage 3a/ 3b from 15% to 25% over a year. Engagement of frontline staff in primary care practices was identified as a key driver to ensure success. EMR advisories werefollowed by academic detailing through care process modules to Drive change. Key Process Drivers and Change Implementation methods are shown in Figure 1, a, b.

Results: A robust and sustained increase in rates of ordering albumin creatinine ratios is shown in Figure 1, c. Marked improvement in adherence to ACR ordering followed academic detailing.

Conclusions: A multidisciplinary primary care-nephrology-health system partnership in care redesign can produce robust sustained improvements in Early Stage CKD evaluation. This approach will be extended to CKD treatment

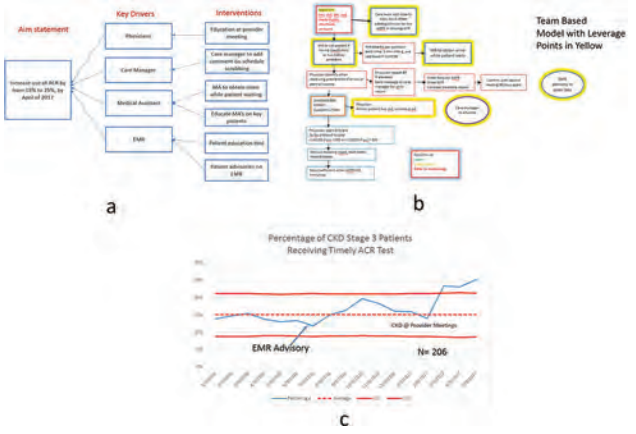


Figure 1 Process Drivers, Leverage Points, Results; a) Key Drivers, b) Leverage for change c) Change in Behaviour

TH-PO545

CKD Phenotype Validation Using Electronic Health Records (EHR): A Pilot Study John W. Stanifer,[1] C. Blake Cameron,[2] Cherry M. Beasley,[4] Daphne W. Wang,[1] Nrupen A. Bhavsar,[3] L. Ebony Boulware,[3] Clarissa J. Diamantidis.[3] *[1]Duke University, Durham, NC; [2]Duke University Medical Center, Durham, NC; [3]Duke University School of Medicine, Durham, NC; [4]The University of North Carolina at Pembroke, Pembroke, NC.*

Background: Few studies have assessed the accuracy of EHR-based methods for detecting CKD, and phenotypes validated from EHR data abstraction alone are inadequate.

Methods: In a rural healthcare system we piloted a novel EHR-based CKD detection phenotype. Individuals were assigned to one of six mutually exclusive groups according to expected likelihood of CKD from available EHR data. Group 1 had individuals with persistently (≥90 days) reduced eGFR (<60ml/min/1.73m^2) or albuminuria (≥30mg/g) or an ICD diagnosis of ESRD or kidney replaced by transplant; (2) individuals with 1 reduced eGFR or albuminuria and a comorbidity index ≥4, adopted from the Screening for Occult Renal Disease prediction tool; (3) individuals with 1 reduced eGFR value or albuminuria and comorbidity index <4; (4) individuals with no kidney function measurements and comorbidity index ≥4; (5) individuals with no kidney function measurements and comorbidity index <4; (6) individuals with normal eGFR and no albuminuria. As a reference standard for validation, we randomly sampled individuals from each group and assessed for CKD through measured assessments, with CKD defined by KDIGO 2012 criteria or self-reported transplant or dialysis. We calculated sensitivity and specificity and used ROC curves to assess performance of the CKD phenotype.

Results: Of 59,848 adults in the EHR, 4036 (7%) were classified group 1; 1690 (3%) group 2; 3007 (5%) group 3; 4726 (8%) group 4; 39,349 group 5 (66%); and 7040 (12%) group 6. For validation, we enrolled 110 individuals, of whom 75 (68%) had CKD based on the reference standard. The CKD phenotype showed a range of sensitivity and specificity corresponding with the CKD phenotype groups (**table**). The ROC curve area was 0.82 (95% CI 0.74-0.90).

Conclusions: Our CKD phenotype showed ability to detect CKD in a small sample identified from the EHR. Additional studies are needed to validate the CKD detection phenotype in other settings and larger samples.

Funding: Private Foundation Support

CKD phenotype performance

Group	Sensitivity	Specificity	Likelihood Ratio
≤6	100%	0%	1.0
≤5	100%	9%	1.1
≤4	99%	17%	1.2
≤3	96%	37%	1.5
≤2	84%	54%	1.8
1	79%	83%	4.6

TH-PO546

Using Kidney Failure Risk Scores to Identify Veterans Needing CKD Care C. Blake Cameron,[1,2] Joel Boggan,[2,1] Susan B. Gurley,[1,2] Richard M. Atkins.[2,1] *[1]Duke University Medical Center, Durham, NC; [2]Durham VA Health Care System, Durham, NC.*

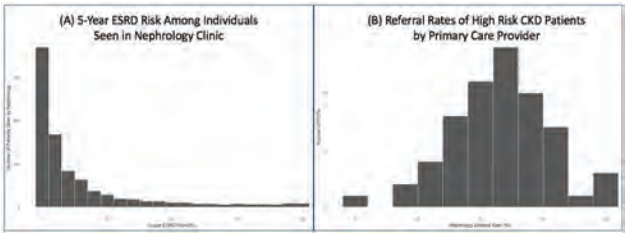
Background: Both over- and under-referral to nephrology threaten the quality and efficiency of CKD care. Optimizing veterans' nephrology referrals may improve their outcomes. Few studies have evaluated patterns of nephrology referral among veterans as a function of CKD progression risk.

Methods: Using the Veterans Health Administration Clinical Data Warehouse, we identified all non-ESRD individuals who received primary care at the Durham VA Health Care System between Dec 2014 and Jun 2017 and had ≥1 outpatient serum creatinine measurement during that time. For each individual, we identified the assigned primary care provider (PCP); tabulated nephrology/CKD clinic visits; and calculated the Kidney Failure Risk Equation (KFRE), an internationally validated predictor of 5-year ESRD risk utilizing age, sex, CKD-EPI eGFR, and optionally, urine albumin-to-creatinine ratio. We stratified the population by KFRE risk (low <5%, intermediate 5-15%, and high >15%), by nephrology referral status and by assigned PCP. We performed descriptive analyses.

Results: Overall, 48,700 unique, non-ESRD individuals with at least one creatinine measurement received care from 139 PCPs. Only 32% (n=359/1,116) and 58% (n=503/865) of individuals at intermediate and high risk for CKD progression respectively had been seen in nephrology clinic. Conversely, among the 1,816 individuals seen in nephrology clinic, 53% (n=957) were at low risk [Figure 1A]. Nephrology referral rates for high-risk patients varied widely across PCPs (mean 58% [s.d. 20%]) [Figure 1B].

Conclusions: Within a single integrated medical center, nephrology referral rates were not aligned with clinical risk. More than 40% of individuals with high-risk CKD had not received nephrology care. Conversely, approximately half of individuals seen in nephrology/CKD clinic were at low risk of progression to ESRD and potentially could have avoided referral. Substantial provider-to-provider variation in nephrology referral rates exists. Identifying the sources of variation will be critical to developing decision support tools and models of care that better align the provision of CKD care with clinical risk.

Funding: Veterans Affairs Support



TH-PO547

Cause-Specific Hospitalization among Older Adults with CKD in the US (2006-2015) Yun Han,[3] Kevin He,[1] Diane Steffick,[3] Rajesh Balkrishnan,[4] Brahmajee K. Nallamothu,[2] Rajiv Saran.[3] *[1]Kidney Epidemiology and Cost Center, University of Michgian, Ann Arbor, MI; [2]University of Michigan, Ann Arbor, MI; [3]Internal Medicine - Nephrology, University of Michigan, Ann Arbor, MI; [4]University of Virginia School of Medicine, Charlottesville, VA.*

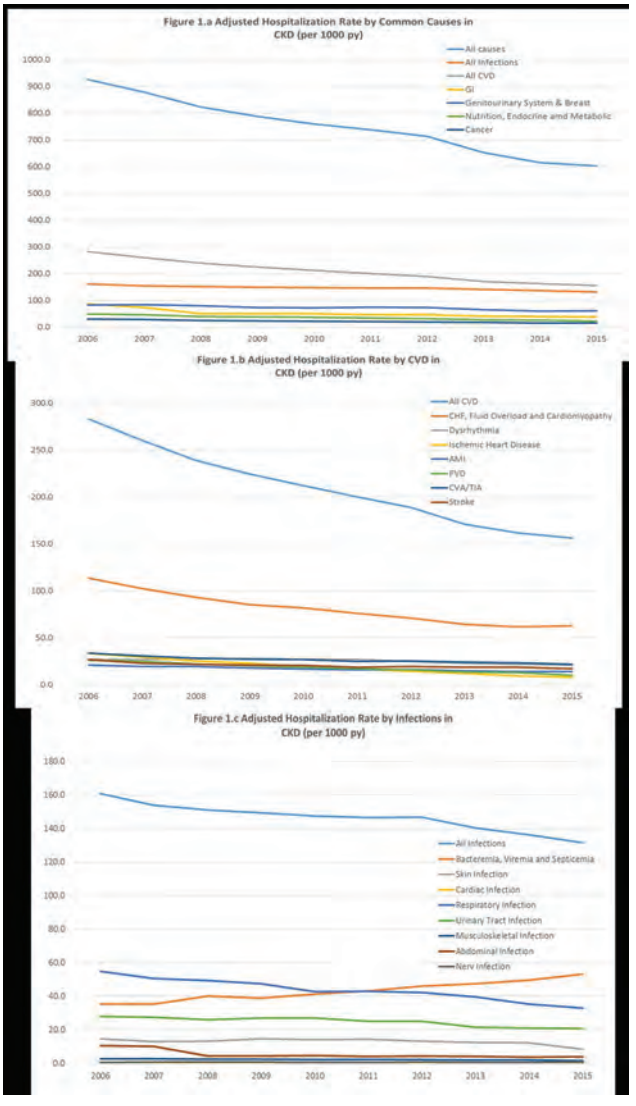
Background: Patients with CKD are at high risk of hospitalization, but there are few long-term studies of cause-specific hospitalizations in this vulnerable patient population. We examined these and long-term trends in hospitalization rates among older adults with CKD in the US.

Methods: We identified eligible CKD patients through claims (5% Medicare sample, 2006-2015). Patients were censored at the earliest of death, start of ESRD, disenrollment from Medicare Parts A&B or the last day of each calendar year. The cause of hospitalization was determined by principal ICD-9-CM diagnosis code. Adjusted hospitalization rates were calculated using a GLM with adjustment for age, gender and race.

Results: There was a notable decrease in the adjusted all-cause hospitalization rates among older CKD patients over the past decade, from 926.9/1000 patient years in 2006 to 739.0/1000 in 2011, with a steeper slope thereafter to 602.9/1000 in 2015 (Fig.1.a). Cardiovascular diseases (CVDs) and infections were the leading causes of hospitalization in CKD, accounting for 26% and 22% of all-cause admissions in 2015 (156.3/1,000 and 131.4/1,000). Congestive heart failure-related admissions were the most common CVD cause in CKD (Fig.1.b). Although overall infection-related hospitalization decreased over time, admissions resulting from bacteremia, septicemia and viremia increased by 51% and admissions due to nervous system infections increased by 42% (Fig.1.c).

Conclusions: While all-cause hospitalization rates among CKD patients gradually decreased in the past decade, CVD (especially heart failure related) and certain specific infections remained the leading causes. Future research will focus on preventable hospitalizations (e.g., septicemia, heart failure), disparities, geographic variation, costs, and care coordination.

Funding: NIDDK Support



TH-PO548

Effect of Exercise Intensity on Renal Blood Flow in Patients with CKD Stage 2 Kazuko Koutoku,[2,6] Tetsuhiko Yasuno,[7] Syotaro Kawakami,[4] Takao Saito,[3] Takuro Matsuda,[8] Kanta Fujimi,[8] Yoshinari Uehara,[5,1] Yasuki Higaki,[5,1] Hiroaki Tanaka.[1,5] *[1]Fukuoka University Institute for Physical Activity, Fukuoka, Japan; [2]Graduate School of Sports and Health Science, Fukuoka University, Fukuoka, Japan; [3]Sanko Clinic, Fukuoka, Japan; [4]Rehabilitation, Fukuoka University Chikusa Hospital, Fukuoka, Japan; [5]Laboratory of Exercise Physiology, Faculty of Health and Sports Science, Fukuoka University, Fukuoka, Japan; [6]Nursing, Ube Frontier University, Yamaguchi, Japan; [7]Division of Nephrology and Rheumatology, Department of Internal Medicine, Fukuoka University School of Medicine, Fukuoka, Japan; [8]Rehabilitation, Fukuoka University Hospital, Fukuoka, Japan.*

Background: The 2014 American College of Sports Medicine (ACSM) guidelines recommend that patients with chronic kidney disease (CKD) perform moderate intensity aerobic exercise for 20-60 min per day, 3-5 days per week. Several studies have shown that aerobic and resistance exercise improve exercise capacity, muscular strength, left ventricular function, blood pressure, and cardiovascular function in patients with CKD. However, few studies have specifically assesed the risks of exercise specific to CKD patients. In particular, exercise causes a decrease in renal blood flow (RBF), as well as a less marked and more variable decrease in glomerular filtration rate (GFR). The purpose of this study was to determine the association of RBF with intensity of exercise in patients with CKD stage 2.

Methods: Eight males with CKD stage 2 (eGFRcys : 60-89/min/1.73m^2) participated in the study, consisting of three separate experiments using a cycle ergometer. In the first experiment, participants performed a maximal graded exercise test. In the second, they performed a multi-stage exercise test to determine their lactate threshold (LT). In the third, they performed a multi-stage exercise test (4 minutes/stage) at intensities of 60%, 80%, 100%, 120%, and 140% of LT. RBF was assessed by Duplex ultrasound (Aplio 300, TOSHIBA, Japan).

Results: The maximal graded exercise test resulted in a 53% reduction in RBF and a significant increase in the filtration fraction (FF) after strenuous exercise (100% of VO_{2peak}). RBF did not significantly decrease until 100%LT was attained, and showed significant decreases of 64% at 120%LT and 62% at 140%LT relative to its resting value ($p<0.01$). FF also did not change until the LT was reached. In addition, LT corresponded with anaerobic threshold, 40% heart rate reserve, and 55%VO_{2peak}.

Conclusions: Our results demonstrate that RBF and FF do not change during exercise until the LT is attained. These findings may assist in making appropriate exercise intensity recommendations to patients with CKD stage 2.

Funding: Private Foundation Support

TH-PO549

Impacts of Pre-Dialysis Options Education on Albumin Levels and Catheter Use in Patients Starting Dialysis John W. Larkin, Yue Jiao, Marta Reviriego-Mendoza, Rob Lynch, Len A. Usvyat, Jeffrey L. Hymes, Franklin W. Maddux. *Fresenius Medical Care North America, Waltham, MA.*

Background: Options education before progression to end stage renal disease (ESRD) teaches patients about optimal ways to prepare for dialysis (e.g. early access placement, nutritional requirements, renal replacement therapy options). We aimed to understand whether patients receiving options education prior to initiating dialysis exhibited improvements in their albumin (Alb) levels and rates of catheter use.

Methods: We analyzed data from incident Fresenius Kidney Care (FKC) patients who initiated dialysis between 2009 and 2016. Patients were grouped by enrollment in FKC options education prior to initiating dialysis or not, as well as whether patients started dialysis as an outpatient or inpatient. In these groups, we calculated the annual mean Alb levels in all dialysis patients and percent catheter use during the first 120 days of dialysis in hemodialysis patients.

Results: We studied data from a total of 300,818 patients, of which 68,721 patients received options education prior to initiating dialysis. Throughout 2009-2016, patients who received options education generally exhibited higher mean Alb levels and there was a lower proportion of patients with a catheter, as compared to those who did not receive education. These observations were similar, yet less pronounced for catheter use in patients starting dialysis as an inpatient versus outpatient. In 2016 specifically, we observed that patients who started as an outpatient and received options education had higher Alb levels (3.5 mg/dL options education versus 3.4 mg/dL no education); for those starting dialysis as inpatients, Alb levels were 3.3 mg/dL and did not differ with options education or not. Concurrently, we observed that catheter use in patients starting dialysis as an outpatient was 13.8 percentage points lower in those with options education versus patients without education; in those starting dialysis as inpatients, the catheter use was 4.9 percentage points lower in with options education, compared to patients without education.

Conclusions: These findings indicate that options education before progression to ESRD is associated with dialysis patients achieving higher Alb levels and hemodialysis patients having lower catheter use in the incident dialysis period. Further analyses are warranted to confirm these results.

Funding: Commercial Support - Fresenius Medical Care North America

TH-PO550

Abstract Withdrawn

TH-PO551

Factors Associated with Non-Conservative Treatment of Stage 5 CKD Robert N. Foley, Scott Reule. *University of Minnesota, Minneapolis, MN.*

Background: Quality of death and patient autonomy are prominent public health issues. In this regard, the decision to institute dialysis in patients with non-dialysis Stage 5 chronic kidney disease (CKD_5, GFR ≤ 15) is often difficult, because comorbid illnesses are the rule, and survival and quality of life with maintenance dialysis are often poor. Hence, we set out to examine factors associated with choosing to institute maintenance dialysis, as opposed to conservative management, in older adults.

Methods: We used the (US) Medicare 5% CKD random sample to identify 15,884 patients with diagnostic claims for CKD_5 between 2006 and 2011, with at least 6 months of prior Parts A and B Medicare insurance. Hospital admission codes in the prior 6 months were used to characterize comorbidity. Time to renal replacement therapy (RRT) was the primary outcome.

Results: The mean age of the study population at diagnosis of CKD_5 was 76 years. Mean follow-up was 2.8 years and 51.3% opted to begin RRT. In models that adjusted for age, demography and comorbid illnesses, adjusted hazards ratios (AHR) for RRT were > 1 ($P < 0.05$) for African American race (AHR 1.25 Vs. white), Native American race (AHR 1.38) and cardiac failure (AHR 1.38). RRT was less likely with older age (AHR 0.73 for 70-79, 0.63 for 80-89 and 0.44 for ≥ 90 [Vs. < 70 years]), female sex (AHR 0.89) and malignancy (AHR 0.92).

Conclusions: These findings suggest that a substantial proportion of Medicare patients with GFR ≤ 15 decline the option of RRT. Age, sex, race and comorbidity profiles influence this choice.

TH-PO552

Effect of N-Acetyl Cysteine in Patients with CKD: The Longer, the Better? A Nationwide Population-Based Retrospective Cohort Study Chen-Yi Liao, Chia-chao Wu. *Division of Nephrology, Department of Internal Medicine, Tri-Service General Hospital, Taipei, Taiwan.*

Background: This study aimed to evaluate the potential benefits of N-acetylcysteine (NAC) on the risk for chronic kidney disease (CKD) progression to dialysis-requiring end-stage renal disease (ESRD)

Methods: In a population-based cohort study of 145,062 individuals, a total of 123,608 CKD patients who were followed up for 10 years were compared with patients who were prescribed NAC after been diagnosed as CKD (ICD-9-CM). Using propensity score matching, we analyzed the predictors of CKD progression to ESRDd by Cox proportional hazards regression with adjustment for sex, age, and comorbidities and evaluated the effect of NAC using cumulative defined daily dose (cDDD).

Results: NAC use was associated with reduced risk for progression to ESRDd (HR 0.819, 95% CI 0.781-0.965, p = 0.017). Risk reduction was accentuated by an increase in cDDD in patients on NAC compared with non-NAC users (HR was 0.8350, 0.811, and 0.799 for cDDDs 91-180, 180-360, and ≥360, respectively; P for trend =0.018). Risk reduction was apparent in women (P = 0.001); younger age at 18-29 years (P = 0.021) and 30–39 years (P = 0.033); the presence of hypertension (P = 0.003); the absence of diabetes mellitus (P = 0.042); and the absence of congestive heart failure (P = 0.036).

Conclusions: NAC administration was associated with a lower risk of subsequent ESRD. Further studies are warranted to confirm these findings.

TH-PO553

Metformin Prescription in a Contemporary Cohort of Patients with Stage 3a CKD Rocco Ferrandino, Tielman T. Van Vleck, Jeremy S. Leventhal, Bart Ferket, Jaime Uribarri, Steven G. Coca, Girish N. Nadkarni. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Eligibility criteria for metformin have shifted from serum creatinine (SCr) to estimated glomerular filtration rate (eGFR) based guidelines. In 2009, the American Diabetes Association endorsed metformin use in type 2 diabetes (T2D) patients with stage 3a chronic kidney disease (CKD3a). We evaluated contemporary prescribing patterns in patients with CKD3a with as well as patient/process of care factors associated with non-prescription of metformin in a large multiethnic cohort.

Methods: We identified T2D patients with CKD3a from Mount Sinai CKD registry and calculated proportion of eligible patients actually receiving metformin. We then used nearest neighbor propensity matching to compare adjusted odds ratios (aOR) for non-prescription in user: non-user pairs. We also used natural language processing (NLP) tools to query clinical documentation for process of care factors.

Results: We identified 5213 metformin-eligible patients in 2015-16 based on eGFR criteria. Of these, only 1992 (38.2%) received metformin. We identified 1820 user: non-user matched pairs. Patient-specific factors associated with non-prescription included male sex (aOR 1.67, 95% CI 1.12-2.47) and black race (aOR 1.79, 95% CI 1.09-2.91). Interestingly, 21.7% of male and 20.3% of black patients eligible by eGFR guidelines were ineligible by SCr guidelines. Patients in whom other preventative T2D guidelines were adhered to (identified by NLP) had lower non-prescription odds. (Figure)

Conclusions: Despite a shift to eGFR-based guidelines and eGFR threshold lowering, a substantial proportion of eligible patients do not receive metformin. Factors responsible may be continued adherence to outdated guidelines, and patient/process of care specific factors, which should be explored in greater detail.

Funding: Other NIH Support - RF was supported by 1TL1TR001434

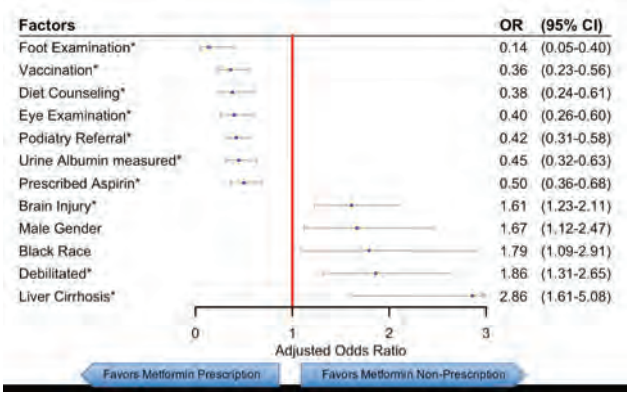


Figure. Factors associated with metformin non-prescription identified by analysis of structured and unstructured data. Asterisks(*) denote factors identified by NLP.

TH-PO554

Low Utilization of Statins in US Veterans with Non-Dialysis Dependent CKD David J. Leehey,[1,3] Talar Markossian,[2] Nicholas Burge,[1] Kevin Stroupe,[1] Ivan Pacold,[1] Julia Schneider,[1,3] Benjamin Ling,[1,3] Holly J. Kramer.[3,1] *[1]Hines VA Medical Center, Hines, IL; [2]Loyola University Chicago, Maywood, IL; [3]Loyola University Medical Center, Maywood, IL.*

Background: Cardiovascular disease is the major cause of morbidity and mortality among adults with non-dialysis dependent chronic kidney disease (CKD). Statin medications, especially when combined with ezetimibe, significantly reduce atherosclerotic cardiovascular disease (ASCVD) risk in this population. Renal guidelines therefore recommend statin use for all patients with non-dialysis dependent CKD age 50 years or older regardless of lipid profile. However, the recent AHA/ACC recommendations for statin use for adults (including those with CKD) in the absence of ASCVD or diabetes is based on the predicted 10-year ASCVD risk derived from the pooled risk cohort equation. The objective of this study was to examine statin utilization in a national sample of U.S. Veterans with non-dialysis dependent CKD, defined as an eGFR < 60 ml/min/1.73 m2, and to calculate the predicted ASCVD risk by diabetes status using the pooled risk cohort equation.

Methods: The design was a retrospective review of statin use and clinical and demographic factors associated with statin use. Statin use was ascertained from pharmacy dispensing records during fiscal years 2012 and 2013. The study included 581,344 Veterans age ≥ 50 years with non-dialysis dependent CKD stages 3-5 with no history of kidney transplantation or dialysis receiving care at VA healthcare facilities.

Results: 97% of patients were male and 58% were older than 70 years. Statin use ranged from as high as 76% in those with ASCVD or diabetes to as low as 22% in those without these conditions (p<0.001). Overall, 94% of Veterans without diabetes and 97% of Veterans with diabetes had a ASCVD risk score >7.5%, of whom 42% were not using statins. Strikingly, even in patients in whom the ASCVD risk score was very high (>= 20%), only 52% of non-diabetic CKD patients and 75% of diabetic patients were using statins.

Conclusions: Utilization of statins is low in Veterans with non-dialysis dependent CKD in the absence of well-known indications for statin use (i.e., ASCVD or diabetes) despite high-predicted ASCVD risk. We conclude that whether one follows renal or cardiovascular guidelines, statin utlization is suboptimal in CKD patients. National education efforts will be needed to increase statin use in CKD, especially in patients without established ASCVD or diabetes.

TH-PO555

Nephrology Practices and Patient Perspectives in regards to Conservative Care for ESKD: The Chronic Kidney Disease-Renal Epidemiology and Information Network Study (CKD-REIN) Elodie Speyer,[1] Luc Frimat,[2] Carole Ayav,[2] Christian Combe,[3] Denis Fouque,[4] Christian Jacquelinet,[5] Maurice Laville,[6] Ziad Massy,[7] Bruce M. Robinson,[8] Benedicte Stengel.[1] *[1]INSERM-CESP, UPSud, UVSQ, Villejuif, France; [2]CHU de Nancy, Vandoeuvre les Nancy, France; [3]CHU de Bordeaux, Bordeaux, France; [4]Université Claude Bernard, Pierre Benite, France; [5]Agence de la biomedecine, Saint-Denis La Plaine, France; [6]Université de Lyon, Pierre-Bénite, France; [7]Ambroise Pare University Hospital and Inserm U1018 Eq5, Boulogne Billancourt/ Paris cedex, France; [8]Arbor Research Collaborative for Health, Ann Arbor, MI. Group/ Team: CKD-REIN Investigators.*

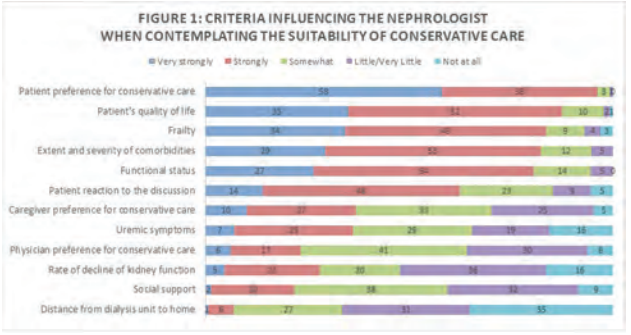
Background: Current KDIGO guidelines indicate that patients with advanced CKD should receive information on all renal replacement therapy (RRT) options, including conservative care (CC), but little is known about nephrologist practices and patient perspectives in regards to CC.

Methods: CKD-REIN is a prospective cohort study that enrolled 3,033 adult patient with CKD stage 3-5 (45% in stage 4-5) from a national representative sample of 40 nephrology clinics in France. Nephrologists were surveyed about practices regarding information, whether they offer, and clinic organization about CC. Patients completed a self-administered questionnaire (PQ) including their understanding of, education on, and preferences for RRT options, including CC.

Results: Among 31 clinics with data, 33% had a guideline (implemented or in preparation) for managing ESRD by CC. Eighty-two percent of the 131 respondent-nephrologists (mean age=44±10; 53% men) reported to be fairly or extremely comfortable with discussing CC with patients, but only 29% reported discussing it with all patients aged 75+. Patient's quality of life and preference for CC were more likely to influence nephrologists when contemplating the suitability of CC than medical or social conditions (figure 1). Among the 1,363 patients with CKD stage 4-5 (88% PQ respondents; 70% men; 35% aged ≥75), 5% of 75+ year-old patients reported to have been informed by their doctor about the "no treatment" option; and 2.3% stated they would choose the "no treatment" option if their kidneys failed.

Conclusions: Despite guidelines and that nephrologists declare that patients with advanced CKD receive information about all RRT options, patients report limited knowledge about CC, especially in elderly. In-depth studies about discrepancies between current practices and the CKD patient perception as they approach kidney failure are requested.

Funding: Commercial Support - Amgen, Baxter, Fresenius Medical Care, MSD, Lilly, Otsuka, GSK, Government Support - Non-U.S.



TH-PO556

Does Longer Duration of Predialysis Care Improve Survival in People Treated with Dialysis? Ping Liu,[1] Robert R. Quinn,[1] Matthew J. Oliver,[2] Paul E. Ronksley,[1] Brenda Hemmelgarn,[1] Hude Quan,[1] Swapnil Hiremath,[3] Aminu K. Bello,[4] Peter G. Blake,[5] Amit X. Garg,[5] John F. Johnson,[5] Mauro Verrelli,[6] James M. Zacharias,[6] Samar Abd elhafeez,[7] Marcello Tonelli,[1] Pietro Ravani.[1] *[1]University of Calgary, Calgary, AB, Canada; [2]Sunnybrook Health Sciences Center, Toronto, ON, Canada; [3]University of Ottawa, Ottawa, ON, Canada; [4]UNIVERSITY OF ALBERTA, Edmonton, AB, Canada; [5]London Health Sciences Centre, London, ON, Canada; [6]University of Manitoba, Winnipeg, MB, Canada; [7]High Institute of Public Health, Alexandria, Egypt.*

Background: Guidelines recommend early referral to nephrology care for people with chronic kidney disease, based on observational studies showing that longer nephrology care before dialysis start (predialysis care, PDC) is associated with lower mortality after dialysis start. This association may be observed because PDC truly improves patient outcomes, or because healthier people with an uncomplicated course of disease will have both longer PDC and better outcomes. We designed this study to assess whether the survival benefit of longer PDC exists after accounting for the potential confounding effect of acute events (markers of disease course) that may also be affected by prior PDC.

Methods: We did a retrospective cohort study in adults with kidney failure who initiated dialysis not following a failed kidney transplant between 2004 and 2014 in five Canadian programs. Data were collected from medical records and double-reviewed by two investigators.

Results: Of the 3152 participants: 23% had no PDC; 8%, 10%, and 59% received 1-119, 120-364, and ≥365 days of PDC, respectively. When we ignored markers of acute events (including unplanned dialysis start and higher residual kidney function around dialysis start) as in prior studies, longer PDC was associated with lower mortality (Hazard Ratio$_{120\text{-}364 \text{ vs. } 0\text{-}119 \text{ d}}$ 0.60, 95% CI 0.46-0.78; HR$_{\geq 365 \text{ vs. } 0\text{-}119 \text{ d}}$ 0.60 (0.51-0.71), standard Cox model adjusted for demographics, laboratory and clinical characteristics). When we accounted for markers of acute events, this association was weaker and no longer significant (HR$_{120\text{-}364 \text{ vs. } 0\text{-}119 \text{ d}}$ 0.84 (0.60-1.18); HR$_{\geq 365 \text{ vs. } 0\text{-}119 \text{ d}}$ 0.88 (0.69-1.13), marginal structural Cox model).

Conclusions: Current guidelines on early nephrology referral are based on studies that may have overestimated the survival benefit of longer PDC, because they may have inadequately addressed confounding by occurrence of acute events.

TH-PO557

Perspectives of Healthcare Professionals on Access to Emergency-Only Hemodialysis for Undocumented Immigrants with ESKD Lilia Cervantes,[1] Sara Richardson,[2] Rajeev Raghavan,[6] Nova Hou,[5] Allison Tong,[3] Romana Hasnain,[1] Michel Chonchol.[4] *[1]Denver Health, Denver, CO; [2]Denver Health Hospital, Denver, CO; [3]The University of Sydney, Sydney, NSW, Australia; [4]University of Colorado, Aurora, CO; [5]University of Texas at Houston Medical School, Houston, TX; [6]Baylor College of Medicine, Houston, TX.*

Background: Providing emergency-only hemodialysis for undocumented immigrants with end-stage kidney disease (ESKD) is challenging for healthcare providers as access is variable across the United States, can be legally and ethically complex, and is highly distressing for patients. We aimed to describe the perspectives of healthcare professionals on providing healthcare (emergency-only hemodialysis) to undocumented immigrants with ESKD.

Methods: We conducted face-to-face, semi-structured interviews with 50 healthcare professionals (nurses [N=16], physicians [N=27], physician assistants [N=3], social workers [1], and dieticians [1], certified nurse assistants [2]) at Denver Health (Denver, CO) and Harris Health (Houston, Texas). Interviews were transcribed and analyzed using thematic analysis.

Results: We identified five themes: Frustrated with hospital operations and care delivery (impersonal rationing of healthcare, struggle to provide primary care in the inpatient setting, inefficiencies lead to unnecessary labs and imaging, and lower priority for undocumented patients); overwhelmed by intense patient and family burden (advocating for a palliative care focus, anger seeing patients suffer when their friends die and receive cardiopulmonary resuscitation, disheartened when patients appear depressed and tired from the weekly accumulation of symptoms leading up to admission, and empathy for their families who struggle when patients require higher level of care); distressed by severity of patient condition (conflicted when patients take desperate measures to meet critically ill criteria, higher acuity care is commonplace, and frustrated by limited care options); and sense of uncertainty from the complex political and financial influence (lacking clarity about cost-benefit, sense that immigration status should not limit access to hemodialysis because other states provide routine dialysis, and desire to change current model of care because this care is more expensive and cruel).

Conclusions: Healthcare professionals are burdened by their patient's suffering and advocate for routine hemodialysis care.

Funding: Private Foundation Support

TH-PO558

Racial Disparities in Mortality in CKD versus ESRD: Results from the CRIC Study Elaine Ku,[1] Wei Yang,[2] Alan S. Go,[2] Nisha Bansal,[2] Harold I. Feldman,[2] Jiang He,[2] Edward J. Horwitz,[2] James P. Lash,[2] Ana C. Ricardo,[2] Tariq Shafi,[2] James H. Sondheimer,[2] Raymond R. Townsend,[2] Sushrut S. Waikar,[2] Chi-yuan Hsu.[1] *[1]University of California San Francisco, San Francisco, CA; [2]CRIC Study, Philadelphia, PA. Group/Team: CRIC Study.*

Background: Black individuals on maintenance dialysis have lower mortality rates than their white counterparts, but the reasons for this observation remain unexplained.

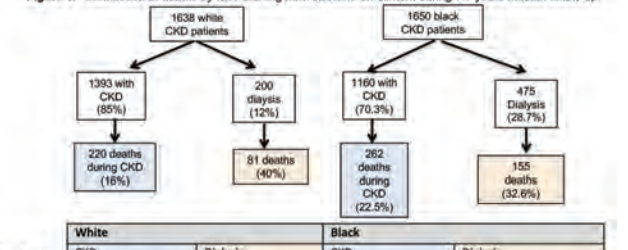
Methods: We examined risk of death among 3288 (non-Hispanic) white and black participants of a national CKD cohort, the Chronic Renal Insufficiency Cohort (CRIC) Study. We included deaths occurring *before and after dialysis* using Cox models. We also examined the evolution of comorbidities at baseline CRIC enrollment (prior to dialysis) vs. at dialysis initiation by race.

Results: Consistent with prior studies, risk of death was lower among blacks (Cox model HR 0.67 [95% CI 0.51- 0.88]) vs. whites when analysis began at incident dialysis. However, starting analysis at CKD/CRIC enrollment (mean eGFR 45±15 mL/min/1.73m^2), risk of death was higher (HR 1.41 [95% CI 1.22-1.64]) for blacks vs. whites counting deaths both before and after ESRD [Figure]. Longitudinal analyses of the evolution of comorbidities suggest that the relative prevalence of co-morbidities at baseline vs. at incident dialysis worsens for whites vs. blacks [Table].

Conclusions: Overall, risk of death was higher for blacks vs. whites when accounting for events occurring before and after ESRD. The apparent survival advantage among blacks on dialysis may be because the subset of whites who transition from CKD to dialysis are persons with a heavier burden of co-morbidities.

Funding: Other NIH Support - NHLBI

Figure 1. Distribution of deaths by race starting from baseline enrollment during 7.7 years median follow-up.*



	White		Black	
Death rate (per 100 P-Y)	CKD	Dialysis	CKD	Dialysis
	2.0	14.6	2.6	9.9

RR death (blacks vs whites) after dialysis =(155/475$_{blacks}$)/(81/200$_{whites}$) =0.83 → (survival paradox)
RR death (blacks vs whites) from CKD through dialysis= ((155+262)/1650$_{blacks}$)/((81+220)/1638$_{whites}$) =1.38 (no survival paradox)
*Preemptive transplants not shown.
P-Y = person-years

Table. Evolution of co-morbidities by race over time in Chronic Renal Insufficiency Cohort (CRIC) Study.

Characteristic N (%)	At time of CRIC enrollment			At time of dialysis initiation		
	White N=1638	Black N=1650	P-value	White N=200	Black N=466	P-value
Myocardial infarction	376 (23.0)	360 (21.8)	<0.001	101 (50.5)	153 (32.8)	<0.001
Peripheral vascular disease	105 (6.4)	117 (7.1)	0.43	46 (23.0)	80 (17.2)	0.08
Congestive heart failure	117 (7.1)	217 (13.2)	<0.001	67 (33.3)	162 (34.8)	0.75
Diabetes	649 (39.6)	848 (51.4)	<0.001	140 (70.0)	327 (70.2)	0.97

TH-PO559

Racial Differences in Nephron Number, Role of Body Size, Kidney Weight, and Cortical Volume in Adult Subjects among Five Populations Go Kanzaki,[1,5] Victor G. Puelles,[3] Luise A. Cullen-McEwen,[1] Wendy E. Hoy,[4] Yusuke Okabayashi,[5] Nobuo Tsuboi,[5] Akira Shimizu,[2] Takashi Yokoo,[5] John F. Bertram.[1] *[1]Department of Anatomy and Developmental Biology, Monash University, Melbourne, VIC, Australia; [2]Department of Analytic Human Pathology, Nippion Medical School, Tokyo, Japan; [3]Department of Nephrology and Clinical Immunology, University Hospital RWTH Aachen, Aachen, Germany; [4]Centre for Chronic Disease, The University of Queensland, Brisbane, QLD, Australia; [5]Division of Nephrology and Hypertension, The Jikei University School of Medicine, Tokyo, Japan.*

Background: Nephron number in normal adult kidneys varies widely and is influenced by birth weight, age and race. Our recent studies have shown that Aboriginal and Japanese subjects have fewer nephrons than most populations studied to date and they are at high-risk for CKD. However, the cause of these racial differences in nephron number is not fully elucidated. In this study, we examined the effects of body size, kidney weight, and cortical volume on nephron number among races.

Methods: We analysed kidneys at autopsy from subjects aged 20-65 years without overt kidney disease in Aboriginal Australians (n=16), Japanese (n=12), Caucasian Americans (n=79), African Americans (n=65), and Senegalese (n=36). Total nephron number (Nglom) was estimated by design-based stereology. Cortical volume was calculated by Cavalieri Principle.

Results: Nglom per kidney in Aboriginal Australians (730,523±224,460; mean±SD) and Japanese subjects (716,236±185,767) was significantly lower than in Caucasian Americans (974,940±304,731), African Americans (943,446±276,017) and Senegalese (982,450±276,210). Although this difference was still present after adjustment for height or kidney weight, Nglom after adjustment for BMI, BSA, or cortical volume was similar in the five populations.

Conclusions: This study shows there is no difference in nephron number among the five races after adjustment for body size or cortical volume. It indicates that while Aboriginal and Japanese subjects with smaller body size have fewer nephrons than the other races, further nephron loss and/or increased body size would likely increase the risk of CKD.

Nephron number in 20-65 years old subjects among five populations

	Aboriginal	Japanese	Caucasian Americans	African Americans	Senegalese	ANOVA (P value)
N	16	12	79	65	36	
Nglom	730,523±224,460	716,236±185,767	974,940±304,731	953,446±276,017	982,450±276,210	0.0016
Nglom/Ht (/m)	437,159±136,925	427,795±111,339	579,028±178,574	555,577±154,286	583,028±165,931	0.0018
Nglom (/m^2)	454,593±148,486	440,301±130,080	580,791±167,970	476,932±134,520	544,714±165,881	0.1305
Nglom/BMI (/kg/m^2)	36,795±13,022	33,819±11,843	35,085±13,686	34,609±12,747	40,691±13,229	0.2016
Nglom/Kwt (/g)	4,798±1,754	4,141±1,497	5,826±2,178	6,132±2,001	7,266±2,210	<0.0001
Nglom/Vcort (/cm^3)	6,417±1,506	6,963±1,902	7,650±2,342	7,777±2,209	8,152±2,117	0.0889

mean±SD

TH-PO560

Angiomotin Is a Novel Interaction Partner of the Polycystin-1 C-Terminal Tail Kavita Mistry, Nikolay P. Gresko, Michael J. Caplan. *Yale University School of Medicine, New Haven, CT.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the fourth leading cause of adult end-stage renal disease. The majority of ADPKD cases are caused by mutations in the PKD1 gene, which codes for the membrane protein polycystin-1 (pc1). Pc1 is thought to play both direct and indirect roles in modulating gene expression; specifically, portions of the C- terminal tail of pc1, including a ~200 residue fragment ("p200"), are cleaved and may translocate to the nucleus, where they are hypothesized to regulate gene transcription. Previous work in our lab has focused on the transcriptional co-activator TAZ, and demonstrated that p200 stimulates the transcription of TAZ-target genes.

Methods: Using a mass spectrometry-based approach in HEK cells, we have identified angiomotin (AMOT) and Merlin (NF2) as novel interaction partners of the polycystin-1 C-terminal tail. AMOT and NF2 are critical upstream regulators of the Hippo pathway, and they exert their effects via direct binding to the downstream transcriptional co-activators YAP and TAZ, as well as to the inhibitory upstream Hippo kinases.

Results: We have shown using co-immunoprecipitation that AMOT and p200 interact with each other in the nucleus, and that deletion of the p200 nuclear localization sequence, which prevents nuclear trafficking of p200, abrogates the p200-AMOT interaction. In addition, we have shown using CRISPR/Cas9 knockout that AMOT is involved in the biochemical interaction between p200 and TAZ. Furthermore, the expression of several putative transcriptional targets of p200 is altered in AMOT knockout HEK cells. We have shown using co-immunoprecipitation that NF2 and p200 interact, and that NF2 phosphorylation status is altered in the setting of p200 overexpression.

Conclusions: In summary, our data show that the C-terminal tail of pc1 binds to AMOT and NF2, forming a nuclear protein complex that may facilitate target gene transcription.

Funding: NIDDK Support, Other NIH Support - NHLBI

TH-PO561

Discovery of Novel Treatments for Ciliopathies and Cystic Kidney Disease Elisa Molinari,[2] Jacquelyn Bond,[1] Julie Higgins,[1] Shalabh Srivastava,[2] Simon Ramsbottom,[2] Colin A. Johnson,[1] John Sayer.[2] *[1]University of Leeds, Leeds, United Kingdom; [2]University of Newcastle, Newcastle upon Tyne, United Kingdom.*

Background: Nephronophthisis (NPHP) is an autosomal recessive cystic kidney disease that represents one of the most frequent genetic causes of end-stage kidney disease during childhood and adolescence. NPHP is a genetically heterogeneous disorder with 20 identified causative genes all encoding for proteins with a function in the primary cilium. NPHP is part of a spectrum of disease phenotypes associated with ciliopathies. We have previously generated a *Cep290*$^{LacZ/LacZ}$ viable mouse model for NPHP. These animals exhibit renal cysts that originate from collecting duct epithelium from which we derived an immortalised cell culture. In recent work, we have shown that the Hedgehog (Hh) agonist Purmorphamine can rescue the cellular and ciliary phenotype in these cells, indicating that ciliopathies are both reversible and treatable. However, the carcinogenic effects of Hh agonism make it unsuitable as a means of treatment, especially of paediatric patients. We set forth to identify existing compounds which can be repurposed for the treatment of NPHP.

Methods: A PerkinElmer "Operetta" High Content Imager, with an "Harmony' and "Columbus" analysis and data storage system, was used to test 1120 biologically active compounds from the Tocriscreen Mini drug library on ciliated monolayers of immortalised murine *Cep290*$^{LacZ/LacZ}$ collecting duct epithelial cells. Measured parameters were cell number, cilia incidence and cell junction integrity.

Results: Through a high-throughput screening approach, we have tested 1120 existing drugs for their efficacy in ameliorating the cellular and ciliary defect of NPHP cells and we identified 33 hits in a primary screen. A secondary screen validated the efficacy of 5 compounds.

Conclusions: Our high-throughput screening revealed that the ciliary phenotype of NPHP cells can be rescued by treatment with selected drugs. Positive hits from our high-throughput screening will be further validated on murine and human NPHP 2D and 3D cell models.

Funding: Private Foundation Support

TH-PO562

Suppressive Effect of RXR Ligand and MEK Inhibitor on RXR Expression and Cellular Proliferation in Immortalized Polycystic Kidney Cells Masanori Kugita,[5] Tamio Yamaguchi,[2] Kazuhiro Nishii,[3] Mai Sasaki,[5] Noboru Ogiso,[1] Harold M. Aukema,[4] Shizuko Nagao.[5] *[1]Laboratory of Experimental animals, National Center for Geriatrics and Gerontology, Obu-city, Aichi, Japan; [2]Department of Clinical Nutrition, Suzuka University of Medical Science, Suzuka, Mie, Japan; [3]Faculty of Rehabilitation, Fujita Health University, Toyoake, Aichi, Japan; [4]Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, MB, Canada; [5]Education and Research Facility of Animal Models for Human Diseases, Fujita Health University, Toyoake, Aichi, Japan.*

Background: We previously reported that expression of renal retinoid X receptor (RXR) was increased in three animal models of cystic kidney disease (Kugita et al AJP Renal 2011), and presented that treatment with bexaroten, a RXR agonist, significantly decreased renal RXR expression and kidney weight to body weight ratios in Han:SPRD-Cy/+ rats (Kugita et al ASN 2015). In hepatocellular carcinoma, phosphorylated RXR is related to aberrant cell proliferation accompanied by MEK-ERK phosphorylation to inhibit its degradation. RXR ligands may have suppressive effects on cell proliferation by dephosphorylation and degradation of RXR (Adachi et al Hepatology 2002). In the current study, we determined the phosphorylation sites of RXR, and elucidated the effects of a RXR ligand and a MEK inhibitor on expression of RXR and ERK, and proliferation of immortalized PKD cells.

Methods: An immortalized PKD cell line, WT9-12 was obtained from ATCC and was maintained in DMEM with 10% FBS. Phosphorylation of RXR was analyzed by Phos-tag SDS-PAGE. To elucidate the effect of RXR ligand and MEK inhibitor, starved WT9-12 cells were treated with 10mM 9-*cis* retinoic acid (9cRA) and/or 100mM U0126. The expression levels of RXR and phospho-ERK (pERK) were analyzed by western blotting. Cell proliferation activity was measured by the MTT assay.

Results: In WT9-12 cells, RXR was phosphorylated on Ser and Thr residues. Treatment with 9cAR alone, U0126 alone and the combination of these two reduced the expression of RXR by 20%, 8% and 23%, of pERK by 40%, 22% and 42%, and cell proliferation by 9%, 14% and 26%, respectively, when compared with vehicle treated cells.

Conclusions: The RXR ligand had a suppressive effect on proliferation of immortalized PKD cells, possibly by reducing expression of RXR and pERK. RXR ligands may have therapeutic potential either alone or in combination with MEK inhibitors to ameliorate PKD progression.

Funding: Government Support - Non-U.S.

TH-PO563

TRPP2-Dependent Cellular Metabolism and Transcription Alexis Hofherr, Hannah Müller, Sebastian Keller, Michael Kottgen. *Medical Center - University of Freiburg, Freiburg im Breisgau, Germany*.

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenetic cause of chronic kidney disease, accounting for 7–10 % of patients with end-stage renal disease. ADPKD is caused by loss of function mutations in *PKD1* or *PKD2*. The gene products of *PKD1* and *PKD2*, Polycystin-1 (PC1) and Transient Receptor Potential ion channel Polycystin-2 (TRPP2), form a receptor-ion channel complex of unknown molecular function. In an unbiased forward genetic screen we have previously identified a Short Ca^{2+}-binding Mitochondrial metabolite Carrier (SCaMC) as a downstream effector of TRPP2. Here we investigate, whether TRPP2-SCaMC-associated metabolite fluctuations regulate cellular gene expression – translating transient TRPP2 ion channel activity into lasting cellular responses.

Methods: To correlate changes in metabolite levels with cellular gene expression, we performed broad-coverage discovery metabolomics and whole transcriptome shotgun sequencing in differentiated wild-type, *PKD2*$^{-/-}$, and *SCaMC*$^{-/-}$ renal epithelial cell lines.

Results: The quantitative measurement of the dynamic multiparametric metabolic response to the pathophysiological loss of TRPP2 and SCaMC identified significantly changed metabolites in both systems. We found that these metabolites are associated with amino acid metabolism including branched chain amino acids (BCAA) in mitochondria. Similarly, the expression of a large number of genes is affected by loss of TRPP2 and SCaMC. We are now correlating concordant changes in cellular metabolism and gene expression to identify novel molecular entities in the polycystin signaling cascade.

Conclusions: We have shown previously that loss of the metabolite carrier SCaMC phenocopies loss of TRPP2 in invertebrate and vertebrate model systems. Emerging evidence suggests that metabolite fluctuations regulate cellular signal transduction. We have tested this hypothesis and discovered a significant number of metabolites and genes indeed regulated by TRPP2 and SCaMC. It is tempting to speculate that concordantly changed molecular entities may provide mechanistic links between the polycystin receptor-ion channel complex and the diverse morphological changes observed in ADPKD.

TH-PO564

Truncating PKHD1 Mutations Alter Energy Metabolism Phillip H. Chumley,[1] Sylvie Mrug,[1] Juling Zhou,[1] Bradley K. Yoder,[1] Michal Mrug.[1,2] [1]*University of Alabama at Birmingham, Birmingham, AL;* [2]*Department of Veterans Affairs Medical Center, Birmingham, AL*.

Background: Polycystin 1 deficiency triggers specific changes in energy metabolism. However, it remained uncertain whether similar changes are caused by relevant defects in other human cystoproteins. As our initial step addressing this question, we studied *in vitro* metabolism effects of engineered *PKHD1* gene disruption along sites of truncating mutations found in patients with autosomal recessive polycystic kidney disease (ARPKD).

Methods: We prioritized *PKHD1* mutations for targeting based on their reported frequency in the Aachen University Mutational Database for ARPKD. We used CRISPR/Cas9 technology to generate multiple clones of HEK293 cell lines with *PKHD1* truncating mutations. Clones without mutation in this gene (WT) served as controls.

Results: *PKHD1* gene mutations had no overall effect on proliferation rate estimated by MTT proliferation assay in this model, and neither did the position of the truncation. However, these mutations resulted in progressively increased extracellular media acidification. For example, when the acidity data for each of the six consecutive days (day in culture 3-8; D3-D8) were used for trajectory analyses, the trajectories of clones with *PKHD1* gene mutations did not differ from WT initially on D3 (b=-0.017, p=0.2436) but had greater increase in cell culture media acidity over time (i.e., steeper increase in acidity between D3 and D8; per day: b=-0.02, p<0.0001). Likewise, specific truncating *PKHD1* mutations did not differ from WT at D3 (b=-0.011 to -0.036, all p>0.2189) but each showed greater increase in acidity over time (per day: b=-0.018 to -0.029, all p<0.0001). These studies were done in aliquots of 10^4 cells plated in six replicates from each clone; replication with 2 x 10^4 cells yielded similar results. Our follow up analyses of the multiple clones point to several phenotypes that distinguish *PKHD1* mutant from WT effects; they include changes in non-glycolytic acidification rate (1.19 vs 1.03; p=0.002), basal oxygen consumption rate (7.59 vs 5.42; p=0.015) and ATP-linked oxygen consumption rate (4.55 vs 2.98, p=0.004).

Conclusions: Together, these data suggest that defects in the major ARPKD gene are associated with abnormal energy metabolism. Future validation of these initial observations in more relevant *in vivo* models would point to a potential benefit of energy metabolism targeting in ARPKD.

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TH-PO565

Preferential Utilization of Histidine as a Glucogenic Amino Acid for PKD Cyst Growth Peili Chen,[2] Chunyu Ma,[1] Arlene B. Chapman.[2] [1]*Emory University, Atlanta, GA;* [2]*University of Chicago, Chicago, IL*.

Background: Autosomal dominant polycystic kidney disease (PKD) is a proliferative disorder characterized by progressive development of renal cysts and renal failure. Alterations in metabolism in patients with PKD have been identified with increased representation of the histidine pathway with increasing disease severity. Histidine has multiple roles, regulating intracellular pH, entry into the Krebs cycle via glutamate/α-ketoglutarate, shared pathways with purine metabolism and generation of histamine for host defense purposes. To understand the role of histidine in PKD epithelial cell proliferation, non-targeted metabolomic analysis of cystic and non-cystic tubular epithelial cells were evaluated.

Methods: Primary human PKD cyst epithelial and human proximal and distal tubular cell lines were established. Conditioned media (8 replicates/sample) were harvested after 24h-incubation and subjected to high-resolution liquid chromatography mass spectrometry (LC-MS). Histidine decarboxylase inhibitor, α-fluromethylhistidine (α -FMH) in increasing doses (0-10uM) was administered and cell proliferation rates measured over 48 hrs with XTT assays. Data were analyzed using xMSanalyzer to identify metabolic features after normalization for protein content. Significant features were subjected to metabolic pathway analysis and enrichment with Mummichog.

Results: Metabolites were differentially expressed between PKD cells and controls. Histidine, histamine and methylimidazole acetaldehyde were decreased (P<0.05) in cystic cells vs. control media. Terminal histamine pathways not leading to further energy metabolism were decreased in cystic vs non-cystic cells (p<0.05). Aspartate and glutamate (entry points to the Krebs cycle) were increased in cystic vs. non-cystic cells (P<0.05). Cystic cells demonstrated an up to 21% increase in proliferation with α-FMH compared to baseline (P<0.05), and greater than non-cystic cells (P<0.001).

Conclusions: Histidine metabolism is abnormal PKD cystic epithelia demonstrating increased generation of aspartate and glutamate, precursors for energy generation. Inhibition of histidine decarboxylase reduced histamine generation, and thereby increased cell proliferation, consistent with increased energy substrate availability.

Funding: NIDDK Support

TH-PO566

Prostaglandin E2 Stimulates Cyst Expansion and Induces Cyst Formation in ADPKD Morgane Lannoy,[1] Lijun Chang,[1] Fatma Abdela-Ali,[1] Dorien J. Peters,[2] Andrew J. Streets,[1] Albert C. Ong.[1] [1]*University of Sheffield, Sheffield, United Kingdom;* [2]*Leiden University Medical Center, Leiden, Netherlands*.

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a major cause of kidney failure in man. Although multiple signalling pathways have been implicated in ADPKD pathogenesis, there is a general consensus that cyclic AMP (cAMP) signalling plays a central role in disease progression. Clinical trials lowering renal cAMP levels with a vasopressin 2 receptor antagonist, or a somatostatin agonist, have shown positive effects in slowing disease progression. Here, we report that selective blockade of prostaglandin E_2 (PGE_2) action, could be an alternative or adjunctive therapeutic strategy in ADPKD, through reducing cAMP.

Methods: cAMP, PGE_2 and its receptors (EP1-4) were analysed by qPCR, ELISA, immunoblotting and immunohistochemistry (IHC) on human cystic cell lines, human ADPKD kidney tissue and two mouse models of ADPKD. The functional effects of selective PGE_2 receptor agonists and antagonists on cyst growth were studied using 3D cyst assays in three cellular models.

Results: EP2 and EP4 mRNA were significantly elevated in cystic kidneys from two murine models of ADPKD (*Pkd1*$^{nl/nl}$, *Pkd1*-iKspCre). PGE_2 and cAMP were also found upregulated in *Pkd1*$^{nl/nl}$ at the peak of the disease. The overexpression of EP2 and EP4 were confirmed in human ADPKD kidney tissue by IHC. There was differential upregulation of EP2 in a panel of human cystic lines. PGE_2 stimulated a significant increase in cyst growth in dog (MDCKII), human (OX161) and mouse (F1/CRE) cells in a dose-dependent manner. This effect was mediated by EP2 and EP4 since its action was blocked by selective antagonists and reproduced by selective agonists in the absence of PGE_2. The effects of PGE_2, EP2 and EP4 agonists on cyst growth were closely correlated with increased proliferation and decreased apoptosis. Strikingly, PGE_2 was able to transform tubular structures formed by a non-cystic human kidney cell line (UCL93) in 3D culture to a predominant cystic phenotype. Current work is investigating the effect of EP2 and EP4 antagonists on cyst initiation and disease progression *in vivo*.

Conclusions:

Funding: Private Foundation Support

TH-PO567

Diminished TRPV4 Activity and Glycosylation Contributes to Compromised [Ca2+]i Homeostasis in Human ADPKD Cells Viktor N. Tomilin,[2] Oleg L. Zaika,[2] Gail Reif,[1] Darren P. Wallace,[1] Oleh Pochynyuk.[2] [1]*University of Kansas Medical Center, Kansas City, KS;* [2]*University of Texas Health Science Center-Houston, Houston, TX*.

Background: PKD is a devastating clinical pathology leading to a decline in kidney function due to development of fluid-filled cysts. No effective pharmacological treatments exist for PKD patients. Defective flow-mediated $[Ca^{2+}]_i$ responses and disrupted $[Ca^{2+}]_i$ homeostasis have been repeatedly associated with the development of PKD. Our previous work in rodents demonstrated that the activity of the Ca2+-permeable TRPV4 channel is imperative for flow-mediated [Ca2+]i responses in the distal renal tubule. TRPV4 function is dramatically decreased in isolated cystic cell monolayers and systemic stimulation of TRPV4 interferes with PKD progression in PCK 453 rats, an ARPKD model.

Methods:

Results: Here, we determined the role of TRPV4 in Ca2+ signaling in human ADPKD and normal human kidney (NHK) cells. ADPKD cells failed to respond to flow and had significantly lower basal [Ca2+]i levels compared to NHK cells, consistent with our previous work (*Yamaguchi et al. J. Am. Soc. Nephrol. 17, 2006*). Application of TRPV4 antagonist, HC-067047 significantly reduced basal [Ca2+]i levels in NHK cells but had no measurable effect in ADPKD cells. TRPV4 activator, GSK1016790A elicited more than two times higher [Ca2+]i response in NHK than in ADPKD cells. GSK1016790A-

mediated responses were precluded by HC-067047 or a Ca2+-free media. Patch clamp analysis revealed significantly lower basal TRPV4 single channel activity and diminished responses to GSK101670A in ADPKD cells. Consistent with our previous results in an ARPKD rat model, we detected a marked decrease in TRPV4 glycosylation in human ADPKD cells pointing to the common mechanism of compromised mechanosensitive [Ca2+]i responses for both PKD forms. TRPV4 glycosylation and activity were dramatically reduced in cultured distal tubule cells upon silencing of polycystin 1 expression. Moreover, blockade of glycosylation with tunicamycin significantly inhibited TRPV4 activity pointing to a mechanism of reduced TRPV4 function in ADPKD cells.

Conclusions: Taken together, TRPV4 glycosylation and function are greatly diminished in human ADPKD cells, contributing importantly to aberrant [Ca2+]i signaling and deficient responses to flow. We speculate that TRPV4 stimulation might be beneficial in restoring [Ca2+]i homeostasis in cyst cells thereby counteracting ADPKD progression in humans.

Funding: Private Foundation Support

TH-PO568

Overexpression of Activated TGFβ1 in Collecting Ducts Induces Cyst-Like Tubule Dilations and Renal Fibrosis in Wildtype Mice and Accelerates the Decline in Renal Function in ADPKD Mice

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Background: Transforming growth factor β1 (TGFβ1), a master regulator of extracellular matrix production, is elevated in autosomal dominant polycystic kidney disease (ADPKD). TGFβ1 is also elevated in Marfan Syndrome (MFS), a genetic disorder leading to abnormal connective tissue development, defects in multiple organs, and formation of renal cysts in approximately 60% of patients. Currently, the role of activated TGFβ1 in renal cyst formation in MFS and the effect of TGFβ1 on cyst growth and disease progression in ADPKD remain unclear.

Methods: To determine if activated TGFβ1 is sufficient to induce renal cyst formation and fibrosis, we crossed $\beta 1^{glo}$ (TGFβ1) mice, which conditionally express TGFβ1, with *Pkhd1-Cre* mice to express activated TGFβ1 selectively in collecting ducts (CD; $TGF\beta 1^{CD}$). We also overexpressed activated TGFβ1 in CDs of $Pkd1^{RC/RC}$ mice, a slowly progressive model of ADPKD.

Results: CD overexpression of TGFβ1 caused cyst-like tubule dilations and increased kidney weight (% body weight; KW%BW) by 5 wk of age. However, by 10 wk, the kidneys developed focal area of fibrosis and pitting of the surface that was indicative of scarring, and there was a significant reduction in KW%BW of $TGF\beta 1^{CD}$ mice compared to wildtype (WT) mice. There were increased renal levels of periostin, a marker for PKD progression, phosphorylated SMAD3, α-smooth muscle actin (α-SMA) and vimentin, markers for myofibroblasts. Blood urea nitrogen (BUN) was slightly increased in $TGF\beta 1^{CD}$ mice compared to WT mice at 20 wk, but this difference was not statistically significant. Similar results were obtained in $Pkd1^{RC/+}$ mice, which have one hypomorphic *Pkd1* allele. Overexpression of TGFβ1 in $Pkd1^{RC/RC}$ mice did not increase cystic index, but rather caused extensive fibrosis and contraction of the kidneys, leading to decreased KW%BW. This was accompanied by increased levels of periostin, α-SMA and vimentin, and a decline in renal function, evidenced by an elevation of BUN compared to $Pkd1^{RC/RC}$ mice.

Conclusions: Our results demonstrate that expression of activated TGFβ1 is sufficient to induce cyst-like tubule dilations and renal fibrosis in normal mice, and accelerate the decline in kidney function in ADPKD mice. .

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TH-PO569

Increased Wnt/β-Catenin Signaling in Postnatal Mouse Model of ADPKD

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Background: The Wnt signaling pathway has an important role for nephron development and elevated expression of β-Catenin, master regulator of the Wnt pathway, is shown to correlate with cystogenesis in autosomal dominant polycystic kidney disease (ADPKD). We previously demonstrated increased expression of *Wnt7a* and *7b* in an embryonic mouse model of ADPKD. Here we provide further evidence that β-catenin is elevated in a postnatal model of ADPKD using *Hoxb7-Cre-IRES-eGFP;*$Pkd1^{flox/flox}$ mice.

Methods: To understand the contribution of Wnt signaling in ADPKD, we measured β-Catenin expression, *in vivo* and *in vitro*, using cystic kidneys of *Hoxb7-Cre-IRES-eGFP;*$Pkd1^{flox/flox}$ mice and *Hoxb7-Cre-IRES-eGFP;*$Pkd1^{flox/+}$ controls and then used immunofluorescence and nuclear/cytoplasmic fractionation to quantify levels of β-Catenin with Western blotting at relevant subcellular locations. The use of two small molecules targeted the interaction of β-Catenin with p300 and CBP (Creb binding protein) and allowed us to measure, *in vitro*, the effect on the expression of Fibronectin and alpha smooth muscle actin (αSMA).

Results: Kidneys from *Hoxb7-Cre-IRES-eGFP;*$Pkd1^{flox/flox}$ develop cysts beginning at postnatal day 3 and have overwhelming cystogenesis by postnatal day 21. Nuclear b-catenin was evident in cyst lining cells of cystic kidneys at postnatal day 7. The expression of *Tcf-1*, a b-catenin target gene, was elevated in postnatal kidneys as further evidence of hyperactivation of the canonical Wnt pathway. Fibronectin and αSMA expression were also increased in cystic kidneys. Inhibition of the β-catenin-CBP with ICG-001 decreased expression of fibronectin and αSMA, suggesting that they are expressed downstream of the Wnt/b-catenin pathway.

Conclusions: The canonical Wnt pathway appears to be hyperactivated in mouse models of ADPKD and may serve as a therapeutic target to decrease cyst formation.

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TH-PO570

The Role of ATMIN in Autosomal Recessive Polycystic Kidney Disease (ARPKD)

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Background: ARPKD is a genetic disorder with an incidence of ~1:20,000 that can lead to perinatal mortality. In the ~60% of ARPKD patients who survive the neonatal period, there is a range of disease severity, however, little is known about the genetic mechanisms that regulate ARPKD. ARPKD is caused by mutations in *PKHD1* which encodes the large membrane protein, fibrocystin, required for normal branching morphogenesis of the ureteric bud during embryonic renal development. The range of disease severity observed in ARPKD suggests that besides *PKHD1* that when mutated causes ARPKD, other genes might also play a role in ARPKD, acting as modifiers of disease severity. Our previous work on ATMIN has shown that it plays a role in kidney morphogenesis by modulating Planar Cell Polarity (PCP) signalling.

Methods: Quantitative Real-time PCR and immunohistochemistry was employed in age-matched normal and ARPKD human kidneys, to investigate causal (fibrocystin) and PCP (Daam2, ATMIN, NPHP2/Inversin) effects. *Atmin* and *Pkhd1* siRNA-mediated knockdowns and Atmin-Green Fluorescent Protein (GFP) overexpression studies were conducted in mouse inner medullary collecting duct (IMCD3) cells, to study the mechanistic relationship between Atmin and Fibrocystin.

Results: A 2-fold increase in *ATMIN* was observed in human ARPKD vs normal kidneys; no significant differences were seen in *DAAM2* or *NPHP2*. In normal human kidneys ATMIN, Inversin and Fibrocystin were expressed in ureteric bud-derived collecting tubules, whereas in age-matched ARPKD tissue, strong ATMIN and Inversin expression was observed in cyst-lining epithelia. An association was observed between Atmin and Fibrocystin in IMCD3 cells, as siRNA-mediated knockdown of *Atmin* dramatically reduced *Pkhd1* expression; siRNA-mediated knockdown of *Pkhd1* almost completely depleted *Atmin* expression. Atmin-GFP overexpression in IMCD3 cells caused a 6-fold increase in *Pkhd1* expression. No significant change in other Wnt signalling (*Dvl1, Nphp2*) or polycystin (*Pkd1, Pkd2*) levels was observed. We are currently investigating whether ATMIN and Fibrocystin are in the same protein complex, with preliminary data in normal mouse kidney suggesting that this is the case.

Conclusions: This work suggests that ATMIN interacts with Fibrocystin, proposing *ATMIN* as a modifier of ARPKD that could in the long term be used as a biomarker of ARPKD severity and progression.

TH-PO571

Activation of CD8+ T-Cells Inhibits Cyst Growth in a Murine Model of ADPKD

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Background: Phenotypic heterogeneity observed in Autosomal Dominant Polycystic Kidney Disease (ADPKD) cannot be explained solely by genic effects. As in other disorders, changes in the microenvironment likely contribute to disease variability. In ADPKD, the role of the adaptive immune system, a critical microenvironmental component, is largely unknown. The goal of this study was to determine the function of T-cells in ADPKD progression.

Methods: Using flow cytometry, immunofluorescence, qPCR, histopathology, and antibody depletion, we evaluated the role of T-cells in the ADPKD *Pkd1* p.R3277C (RC) model. In the C57BL/6 strain this model progresses slowly, while in the BALB/c strain disease advances rapidly.

Results: By flow cytometry, $Pkd1^{RC/RC}$ mice showed an increase in both $CD4^+$ and $CD8^+$ T-cells, correlating with disease severity (fold change RC vs wildtype (WT) (3mo, 9mo), C57BL/6: 1.9, 8.8; BALB/c: 6.0, 12.3). Importantly, by immunofluorescence, even at mild/moderate disease and modest overall increases in T-cell number, the majority of T-cells localized to cysts ($Pkd1^{RC/RC}$ 3mo; C57BL/6: 87.5%; BALB/c: 85.7%). This was associated with increased *Cxcl9* and *Cxcl10* expression, both implicated in T-cell recruitment ($Pkd1^{RC/RC}$ 3mo (fold change RC vs WT *Cxcl9*, *Cxcl10*); C57BL/6: 2.7, 2.8; BALB/c: 6.6, 17.6). We further observed increases in $CD44^+/CD69^+$ $CD8^+$ T-cells but not $CD4^+$ T-cells, and noted that WT animals of the more severe strain (BALB/c) have a lower $CD8^+$ to $CD4^+$ T-cell ratio (1:4 vs C57BL/6 1:1), suggesting selective activation of $CD8^+$ T-cells in our model and a potential correlation of $CD8^+$ T-cell numbers to disease severity. In concordance, antibody depletion of $CD8^+$ T-cells from 1-3 months in C57BL/6 $Pkd1^{RC/RC}$ mice versus IgG control significantly increased %kidney weight/body weight (2.3 vs 2.1), average cyst size (18.6 vs 14.2 $x10^3 \mu m^2$), and %fibrotic area (2.6 vs 1.7). However, cyst number did not change (8.4 vs 8.6 per mm^2), indicating that $CD8^+$ T-cells slow cyst progression/fibrosis, but not initiation.

Conclusions: These data indicate that T-cells are upregulated in ADPKD and are specifically recruited to cystic lesions. Further, $CD8^+$ T-cells play a crucial role in attenuating cyst growth, suggesting that therapeutic compounds designed to activate $CD8^+$ T-cells may be promising ADPKD treatment options.

Funding: Private Foundation Support

TH-PO572

Effectiveness of MTT in Liver Phenotype in a Model of Autosomal Recessive Polycystic Kidney Disease (ARPKD) Adrian Cordido,[3] Olaya Lamas-Gonzalez,[2] Ana Barcia de la Iglesia,[3] Jesus Bañales,[1] Candido Diaz-Rodriguez,[4] Miguel A. Garcia-Gonzalez.[2] *[1]Biodonostia Health Research Institute, San Sebastián, Spain; [2]Health Research Institute of Santiago de Compostela (IDIS)., Santiago de Compostela, Spain; [3]Instituto de Investigacion Sanitaria (IDIS) de Santiago de Compostela, Santiago de Compostela, Spain; [4]University Clinical Hospital of Santiago de Compostela (CHUS), Santiago de Compostela, Spain.*

Background: Polycystic liver disease (PLD) are genetic disorders characterized by progressive bile duct dilatation and cyst development in hepatic parenchyma. PLD are inherited in a dominant or recessive form and can develop alone or in association with polycystic kidney disease (PKD). A number of different mechanisms have been related to the pathogenesis of Polycystic Disease, which we focused on alteration in the extracellular matrix (ECM). MTT is a Metalloproteinases inhibitor. In previous work (ASN2016), we have shown the effectiveness of MTT in models of Autosomal Dominant PKD (ADPKD), both in renal and hepatic phenotype.

Methods: Here, we focused our work testing MTT as a potential therapy for PLD associated to Autosomal Recessive PKD (ARPKD). In this regard, we use a model of ARPKD, Pkhd1$^{del3-4/del3-4}$ (Pkhd1-KO), to test the effectiveness of MTT in hepatic cystogenesis.

Results: In our previous work, we showed the benefit effect of MTT in Autosomal Dominant Polycystic Kidney Disease (ADPKD) inhibiting the hepatic cystogeneis and collecting duct cyst (DBA+ cyst). Now, we have deeply characterized the liver phenotype in our ARPKD model, identifying a time depending gender effect of disease progression. We have also tested MTT, alone and in combination with Tolvaptan, in different points resulting in a significant inhibition of hepatic cystic progression in ARPKD.

Conclusions: In ASN 2016, our group showed the effect of MTT in Autosomal Dominant Polycystic Kidney Disease (ADPKD) inhibiting the hepatic cystogeneis and collecting duct cyst (DBA+ cyst). With this work, we have demonstrated the effectiveness of MTT in the inhibition of hepatic phenotype of ARPKD.

TH-PO573

Cytokine TWEAK Promotes Cystogenesis in Autosomal Dominant Polycystic Kidney Disease (ADPKD) in a Time Dependent Manner Adrian Cordido,[2] Ana B. Sanz,[3] Ana Barcia de la Iglesia,[2] Candido Diaz-Rodriguez,[4] Alberto Ortiz,[1] Miguel A. Garcia-Gonzalez.[2] *[1]Fundacion Jimenez Diaz, Madrid, Spain; [2]Instituto de Investigacion Sanitaria (IDIS) de Santiago de Compostela, Santiago de Compostela, Spain; [3]Instituto de Investigacion Sanitaria Fundacion Jimenez Diaz, Madrid, Spain; [4]University Clinical Hospital of Santiago de Compostela (CHUS), Santiago de Compostela, Spain.*

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common monogenic disorder in which kidneys develop fluid-filled cyst derived from the tubule epithelial cells. Several mechanisms are associated with cyst initiation and cyst progression, recent findings aim inflammation as one the most important molecular mechanism in the progression of ADPKD. TWEAK (tumor necrosis factor TNF-like weak inducer of apoptosis) is a TNF-like cytokine and member of the TNF superfamily. TWEAK promotes inflammation, proliferation, cell death and angiogenesis. However, the role of TWEAK in ADPKD is unknown.

Methods: We have studied the effect of TWEAK in our ADPKD animal model, *Pkd1*$^{cko/cko}$Tam-Cre. This model presents a cystogenesis developmental switch, because the inactivation of Pkd1 gene in different points of life determines cystic phenotype.

Results: We tested TWEAK in different developmental windows of our animal model (*Pkd1*$^{cko/cko}$Tam-Cre) we show that proinflammatory cytokines can be accelerates the progression of ADPKD. The mice that received TWEAK presented higher levels of BUN and worst survival rate than the group of control mice. In addition, TWEAK promotes the progression of hepatic cystic phenotype (PLD associated to ADPKD). These results suggest that TWEAK not online acts at the kidney level.

Conclusions: Doing use of *Pkd1*$^{cko/cko}$Tam-Cre animal model, we demonstrated that TWEAK promotes the progression of ADPKD in a time dependent manner. We results show how inflammation may modulate the severity of ADPKD and the possibility of a treatment with anti-inflammatory therapy.

TH-PO574

Effects of a Novel Vasopressin V2 Receptor Antagonist on Cystic Disease Progression in the PCK Rat Lorenzo Pellegrini,[2] Megan M. Constans,[1] Peter C. Harris,[1] Vicente E. Torres.[1] *[1]Mayo Clinic, Rochester, MN; [2]Palladio Biosciences, Newtown, PA.*

Background: Vasopressin V2 receptor inhibition is a clinically validated mechanism of action for Autosomal Dominant Polycystic Kidney Disease (ADPKD), a progressive genetic disease characterized by the formation and enlargement of fluid-filled cysts in the kidneys. However, safe and effective disease-modifying therapies for ADPKD are still lacking. Here we report the first evidence that lixivaptan, a promising, selective vasopressin V2 antagonist, could have utility for the treatment of ADPKD.

Methods: We examined the effects of lixivaptan in PCK rats, an orthologous animal model of Autosomal Recessive PKD that develops a phenotype reminiscent of ADPKD. 4-week old PCK rats were randomly assigned to vehicle control, standard dose of lixivaptan or two alternative lixivaptan dosing protocols and subsequently treated for 8 weeks. At the end of treatment, a comprehensive panel of biochemical and histomorphometric endpoints was evaluated to assess the effect of lixivaptan on disease progression.

Results: PCK rats in the control group showed enlarged kidneys and extensive cyst formation, consistent with the development of a polycystic kidney phenotype. Compared to control animals, PCK rats treated with the standard dose of lixivaptan showed a 27% reduction in kidney weight as a percentage of body weight (p=0.006), a 23% reduction in kidney cAMP levels (p=0.014), a small but statistically significant reduction in liver weight as a percentage of body weight (6%; p=0.03) and a reduction in cyst burden. As expected, these reductions were associated with statistically significant increases in 24h urine output (179%; p<0.0001) and serum sodium (1.7%; p=0.02). Pharmacological efficacy on disease manifestations was also observed in animals treated with the two alternative dosing regimens of lixivaptan, however the difference with the control group did not reach statistical significance.

Conclusions: The beneficial effect of lixivaptan in the PCK rat model of PKD adds to the body of evidence implicating vasopressin V2 receptors in the pathology of ADPKD. These results pave the way to the potential demonstration of a disease-modifying effect of lixivaptan in upcoming clinical trials in ADPKD patients.

Funding: Commercial Support - Palladio Biosciences, Inc.

TH-PO575

Targeting Epithelial Innate Immunity Improves Inflammation and Fibrosis in a Mouse Model of Nephronophthisis Heng Jin,[2] Shanshan Wang,[1] Qiong Ding,[2] Dongmei Lu,[1] Massimo Attanasio.[2] *[1]UT Southwestern Medical Center, Dallas, TX; [2]University of Iowa, Iowa City, IA.*

Background: Inactivation of the gene *GLIS2* causes nephronophthisis type 7 (NPHP7), a kidney disease characterized by progressive interstitial inflammatory infiltration and fibrosis. Recently, we have shown that cell senescence of kidney epithelial cells is a central pathogenic event in this disease. Senescent cells are known to secrete an array of molecules, referred to as senescence associated secretory phenotype (SASP), that is controlled by the NF-κB pathway and sustain organ inflammation and fibrosis. Toll-like receptors (TLRs) are 'surveillance' receptors that recognize microbial particles and endogenous molecules. TLR2 and TLR4 are abundantly expressed on the surface of kidney epithelial cell and, when stimulated, induce activation of the NF-κB pathway through the shared adaptor myeloid differenziation protein 88 (MyD88).

Methods: We found that multiple NF-κB genes are overexpressed in *Glis2* defective kidney tubular cells, including *Tlr2*, which is at the same time a target and an activator of NF-κB, and hypothesized that activation of epithelial innate immunity may affect inflammation and fibrosis in *Glis2* knockout kidneys. We tested this hypothesis by generating *Glis2*$^{mut/mut}$;*Tlr2*$^{-/-}$ and kidney epithelial specific *Glis2*$^{mut/mut}$;$^{Ksp\text{-}cre}$*Myd88*$^{f/f}$ double knockouts. We measured cystic area, tubular cells proliferation, apoptosis, DNA damage and senescence, interstitial inflammatory cells, fibrosis and kidney function in single and double knockout mice.

Results: No differences were detected in these parameters between *Glis2*$^{mut/mut}$;*Tlr2*$^{-/-}$ and *Glis2*$^{mut/mut}$ mice at 3, 6 and 9 months of age. On the other hand, proliferation, DNA damage, cystic index, interstitial inflammation and fibrosis was decreased in kidneys of *Glis2*$^{mut/mut}$;$^{Ksp\text{-}cre}$*Myd88*$^{f/f}$, comapred to *Glis2*$^{mut/mut}$ mice at 3 months of age. No differences of kidney function and tubular cell senescence were detected.

Conclusions: Our results indicate that epithelial innate immunity signaling concurs in maintaining inflammation and fibrosis in the mouse model of NPHP7.

Funding: NIDDK Support

TH-PO576

Tissue Mass Spectrometry Analysis of Glycosphingolipid Distribution in Murine Polycystic Kidney Disease Cristina I. Silvescu,[1] Lilu Guo,[2] Laurie A. Smith,[5] Mandy Cromwell,[1] Dinesh Bangari,[5] Susan Ryan,[4] Petra Oliva,[5] Alla Kloss,[1] Thomas J. O'Shea,[1] Walter Korfmacher,[1] Oxana Beskrovnaya,[5] Thomas A. Natoli.[3] *[1]Sanofi, Waltham, MA; [2]Sanofi, Waltham, MA; [3]Rare Disease Research, Sanofi, Framingham, MA; [4]Sanofi Corporation, Framingham, AL; [5]Sanofi Genzyme, Framingham, MA.*

Background: Elevated glucosylceramide synthase (GCS) activity is a hallmark of polycystic kidney disease (PKD), and pharmacologic or genetic reduction of glycosphingolipid (GSL) accumulation slows cyst growth and preserves kidney function in multiple models of murine PKD. To better understand the role of GSL accumulation in PKD progression, we sought to characterize spatial tissue distribution of GSLs in cystic kidneys of juvenile cystic kidney (jck) mice.

Methods: Liquid chromatography coupled to tandem mass spectrometry (LC/MS/MS) and tissue MALDI/TOF mass spectrometry imaging (MSI) were used to quantify GSL species in kidney tissue isolated from wild-type mice, jck mice, or jck mice treated with a GCS inhibitor.

Results: LC/MS/MS analysis demonstrates roughly 3- to 6-fold accumulation of Gb3, globoside, GM2, and GD3 in jck mouse kidneys compared to wild-type kidneys; these levels are all reduced following GCS inhibition. GM3 was detectable by tissue MSI in a diffuse pattern consistent with epithelial accumulation throughout the jck mouse kidney. A hydroxylated form of GM3 accumulates in blood vessels of the jck mouse kidneys. Elevated levels of GM1 species were detected in jck mouse kidneys in a patchy pattern that was distinguishable from that seen with GM3. Several sulfatide species could be detected in discrete patterns localizing to the cortex, medulla, and papilla; the C20

isoform was excluded from the papilla, while the C24 isoform was highly enriched in the papilla, and clear epithelial localization could be observed.

Conclusions: Accumulation of complex glycosphingolipids downstream of glucosylceramide is evident in cystic kidneys compared to normal kidneys, and tissue distribution of multiple GSL species can be assessed using mass spectrometry imaging. Differences in either the carbohydrate composition of the GSL or the chain length of the lipid moiety can result in localization to distinct cell types. Tissue MSI therefore provides a unique approach to better understand the role of glycosphingolipids in kidney disease.

Funding: Commercial Support - Sanofi

TH-PO577

Phosphorylation Insensitive 4E-BP1 Reduces Hyperproliferative Phenotype In Vitro Sara Holditch,[1] Carolyn N. Brown,[1] Kameswaran Ravichandran,[1,3] Charles L. Edelstein.[2] *[1]UC Denver Anschutz Medical Campus, Aurora, CO; [2]University of Colorado Denver, Aurora, CO; [3]Hera BioLabs, Lexington, KY.*

Background: Unchecked proliferation of cystic epithelial cells is a major contributor to cyst growth in PKD. The 4E-BP1 pathway is a crucial checkpoint in protein translation initiation and cellular proliferation. Evidence from oncology supports the malignant potential of 4E-BP1. A recognized oncotarget, 4E-BP1 is associated with worsening progression, metastasis, and morbidity in oncology. The aim of this study was to determine 1) whether PKD patient and animal model kidney tissues have dysregulated phospho 4E-BP1 species and 2) the effect of a phosphorylation insensitive 4E-BP1 (F113A) on phospho 4E-BP1 species distribution, cap dependent protein translation, and proliferation in renal epithelial cells.

Methods: Immunofluorescence staining of phospho 4E-BP1 species (T70, T37/47, S65) was performed on human ADPKD and Han:SPRD rat (Cy) kidneys. Western blot analysis, Cyquant cellular proliferation, and Firefly-renilla assays were performed on human primary epithelial cells from normal renal cortical tubular epithelium ($PKD1^{+/+}$) and ADPKD cyst-lining epithelium ($PKD1^{-/-}$) transfected with control or pCAG-F113A or transduced with control or F113A lentivectors.

Results: Phospho 4E-BP1 species were present in cyst lining cells of human ADPKD and Cy renal tissues. F113A resulted in substantially reduced phospho 4E-BP1 T37/46(0.89±0.08 vs 0.012±0.004DU, $p<0.01$) and S65 (0.63±0.04 vs 0.003±0.001DU, $p<0.01$), reduced cap-dependent protein translation (37%, $p<0.01$), and reduced 72hr proliferation (250±4 vs 180±5 480/528nm O.D, $p<0.0001$) in $PKD1^{-/-}$ cells. Surprisingly, in $PKD1^{+/+}$ cells, F113A resulted in no phospho 4E-BP1 reduction, reduced cap-dependent protein translation (32%, $p<0.01$), and marginally reduced proliferation (375±5 vs 314±4 480/528nm O.D, $p<0.0001$). Acute stimulation with insulin resulted in maintained S65 suppression with F113A transfection in $PKD1^{-/-}$ (2.1±0.3 vs 0.2±0.1AU, $^*p<0.0001$).

Conclusions: F113A results in a shift towards hypophosphorylated 4E-BP1 species, reduced cap dependent protein translation, and reduced proliferation, with more aggressive effects in $PKD1^{-/-}$ vs $PKD1^{+/+}$. Utilizing F113A gene therapy to counter the loss of the translationally repressive 4E-BP1 pathway in a murine model of PKD, is the next step in addressing a pathway seemingly integral to the pathobiology of PKD.

Funding: Other U.S. Government Support

TH-PO578

Altered Liver Bioactive Lipid (Oxylipin) Profiles in PCK Rats with Polycystic Kidney and Liver Disease Tamio Yamaguchi,[1] Jessay G. Devassy,[2] Aruni Jha,[3] Andrew J. Halayko,[3] Masanori Kugita,[4] Shizuko Nagao,[4] Amir Ravandi,[5] Harold M. Aukema.[2] *[1]Department of Clinical Nutrition, Suzuka University of Medical Science, Suzuka, Mie, Japan; [2]Department of Human Nutritional Sciences, University of Manitoba, Winnipeg, MB, Canada; [3]Children's Hospital Research Institute of Manitoba, University of Manitoba, Winnipeg, MB, Canada; [4]Education and Research Facility of Animal Models for Human Diseases, Fujita Health University, Toyoake, Aichi, Japan; [5]Institute of Cardiovascular Sciences, St. Boniface Hospital Research Centre, Winnipeg, MB, Canada.*

Background: Oxylipins are bioactive lipids derived from polyunsaturated fatty acids formed via cyclooxygenase (COX), cytochrome P450 (CYP) and lipoxygenase activities. Previously, we reported that renal COX oxylipins were elevated in diverse animal models of renal cystic kidney disease, suggesting that COX inhibition may be a viable approach to treating these types of renal disorders. Since liver cystic disease also commonly occurs in several types of renal cystic disease, we determined kidney and liver oxylipin profiles in the PCK rat, an orthologous model of autosomal recessive polycystic kidney disease (ARPKD) with cystic kidney and liver disease.

Methods: Liver oxylipin profiles of 16-week PCK and normal rats were determined by targeted lipidomic analyses using HPLC-tandem mass spectrometry. Correlations of oxylipins with disease were analyzed using supervised and unsupervised multivariate models.

Results: Both kidney and liver weight/body weight and lumen or cyst area/tissue section, as well as liver fibrosis were higher in PCK compared to normal rats. Based on the profile of the 61 oxylipins detected in liver, diseased rats clustered distinctly from normals. Consistent with previous findings in which higher levels of renal oxylipins derived via the COX pathway were associated with disease, the strongest predictor of diseased liver was elevated COX derived 6-keto-prostaglandin $F_{1\alpha}$, the main metabolite of prostacyclin. In addition, all 7 of the dihydroxy fatty acid oxylipins formed via CYP and soluble epoxide hydrolase (sEH) that were detected were reduced in diseased livers, also consistent with kidney findings. The unsupervised multivariate model also indicated the correlation of diseased livers with at least 9 lipoxygenase derived oxylipins.

Conclusions: Oxylipins from all three biosynthetic pathways are associated with diseased livers in the PCK rat model of ARPKD. The COX derived oxylipin 6-keto-prostaglandin $F_{1\alpha}$ is higher and CYP/sEH derived oxylipins are lower in PCK livers compared to normals. The potential effects of prostacyclin synthase inhibitors and the role of the novel CYP/sEH derived oxylipins in the development of cystic kidneys and livers remains to be elucidated.

Funding: Government Support - Non-U.S.

TH-PO579

Palmitoylation of Polycystin 1 Occurs in the Carboxylterminus and May Regulate Polycystin 1 Localization and Expression Levels Kasturi Roy, Lindsey K. Stavola, Michael J. Caplan, Ethan P. Marin. *Yale School of Medicine, New Haven, CT.*

Background: Polycystin 1 (PC1) is a polytopic membrane protein that localizes to primary cilia. Genetic mutations that lead to reduced PC1 expression levels and/or trafficking to cilia cause cystic disease of the kidney and/or liver. Such mutations may occur in the PC1 gene (*Pkd1*), or in genes encoding endoplasmic reticuluum proteins involved in the maturation and trafficking of PC1. Cysteine palmitoylation is the post-translational attachment of the 16-carbon lipid palmitic acid to a cysteine sidechain, and is known the affect trafficking and stability of numerous proteins.

Methods: Palmitoylation of PC1 was assessed using a variety of biochemical approaches including incorporation of a clickable palmitate analog as well as acyl exchange methods. Effects of palmitoylation were gauged using chemical inhibitors of palmitoylation and depalmitoylation, coupled with immunofluorescence to assess PC1 localization and semi-quantitative Western blotting to assess PC1 expression levels.

Results: PC1 is palmitoylated on at least one cysteine in the ~140kDa carboxylterminal domain. Experiments using inhibitors of enzymatic palmitoylation and de-palmitoylation suggest that the modification facilitates trafficking of PC1 from the plasma membrane into the cilia membrane. Pharmacological inhibition of palmitoylation or depalmitoylation also alters PC1 expression levels in reciprocal directions

Conclusions: Collectively, these data identify palmitoylation as a novel post-translational modification on PC1 which may affect its trafficking and stability. Both factors are relevant to the development of cystic kidney and liver disease. Consequently, a more detailed understanding of the palmitoylation of PC1 may identify targets to pharmacologically manipulate its expression level and localization, and potentially reverse the effects of disease-causing mutations.

Funding: Private Foundation Support

TH-PO580

Pkd1-Deficient Mice Show Increased Susceptibility to Induction of Endoplasmic Reticulum Stress Following Mild Renal Ischemia/Reperfusion Andressa G. Amaral,[1] Andre F. Pires,[2] Elieser H. Watanabe,[1] Luiz F. Onuchic.[1] *[1]Nephrology and Molecular Medicine, University of São Paulo, Sao Paulo, Brazil; [2]Sirio Libanes Hospital, Sao Paulo, Brazil.*

Background: *Pkd1* haploinsufficiency has been shown to increase susceptibility to renal ischemia-reperfusion (IR) in mice. IR is a classical cause of endoplasmic reticulum stress (RS) and RS can aggravate renal injury induced by IR. Inactivation of *Xbp1*, in turn, has been proposed to amplify the cystic phenotype of $Sec63^{flox/flox}$:Ksp-Cre mice by decreasing polycystin-1 activity. To investigate the effect of mild renal IR on RS in *Pkd1* deficiency, we analyzed RS and inflammation markers in $Pkd1^{+/-}$ (HT) and $Pkd1^{+/+}$ (WT) mice submitted to mild renal IR.

Methods: HT and WT male mice were submitted to 32-min bilateral renal IR or sham intervention (SI). Serum urea nitrogen (SUN) was measured 24h prior to and 48h after these procedures. Kidneys were harvested 48h post-IR or SI to evaluate IL1β, IL6, IL10, MCP1, TNFα and RANTES by multiplex assay; GRP78 and XBP1s by western blot; *Hif1α*, *Hspa5* and *Ddit3* by real time RT-PCR; and *Xbp1*s/*Xbp1*u transcript ratio by end-point RT-PCR.

Results: SUN did not differ between WT and HT mice after IR and SI. *Hif1α* expression did not significantly increase following renal IR in mice with either genotype, indicating that the induced insult was mild. The levels of IL1β, IL6, IL10, MCP1, TNFα and RANTES did not differ between HT and WT kidneys in response to IR and SI. Renal expression of XBP1s protein was higher in HT than WT animals after IR [0.67 (0.55-0.72) *vs* 0.48 (0.34-0.53), $p<0.01$)] while HT kidneys presented lower *Xbp1s/Xbp1*u than WT following this insult [6.59 (5.85-7.05) *vs* 10.29 (9.48-12.18); $p<0.001$). Notably, renal IR decreased this ratio in HT mice [*vs* 9.00 (8.24-9.14), $p<0.01$] whereas slightly increased it in WT animals [*vs* 8.22 (6.48-9.54), $p<0.05$]. No differences in *Hspa5* gene and GRP78 protein expression were detected between kidneys of both genotypes in response to IR and SI. *Ddit3* gene expression, in addition, did not differ between HT and WT kidneys after IR and SI.

Conclusions: Our findings support that *Pkd1* haploinsufficiency increases the level of RS following mild renal IR in mice, by favoring the activation of the IRE1α-XBP1 branch of UPR. Our data suggest that this effect may possibly modulate polycystin-1 functional activity and attenuate renal injury in mild IR, potentially limiting the increased susceptibility associated with *Pkd1* haploinsufficiency.

Funding: Government Support - Non-U.S.

TH-PO581

Induced Inactivation of Pkd2 Results in Progressive Tubule Reduction and Loss in New, 3D Model of ADPKD Cystogenesis Eryn E. Dixon, Owen M. Woodward. *University of Maryland School of Medicine, Baltimore, MD.*

Background: The role of *PKD1/PKD2* loss in renal cytogenesis remains both unequivocal and undefined. Many disparate pathways are known to be altered in ADPKD without a definitive mechanistic pathway connecting back to the loss of either polycystin protein. A long standing roadblock has been the inability to model cystogenesis resulting from the spontaneous loss of *PKD1/PKD2* as postulated by the two-hit ADPKD hypothesis.

Methods: To better understand the local effects of *Pkd2* inactivation on cystogenesis, signaling, and organization of differentiated, E-cadherin positive, structures, a new, three-dimensional (3D) *in vitro* model has been developed that employs primary renal cells from an inducible Cre (*Pkd2 Pax8 rtTA TetOCre+mTmG*) mouse line. This 3D culture system combines a unique "sandwich" plating technique with a glial-derived neurotrophic factor (GDNF) growth factor cocktail to increase the yield of differentiated and complex epithelial structures, including spheroids and tubules. In addition, this new model system allows tracking of gross morphological changes of 3D structures and cellular components before and after the inactivation of *Pkd2*.

Results: Characterization of the differentiated tubule structures reveals that the cells of the organoids demonstrate typical apicobasolateral polarization and primary cilium as defined by basolateral Na+/K+-ATPase and lumenal acetylated tubulin, respectively. Interestingly, the differentiated organoids are positive for collecting duct markers, *Dolichos biflorous agluttinin* (DBA), and the apical water channel, aquaporin-2 (AQP2), while negative for proximal tubule markers, *Lotus tetrogonobulus lectin* (LTL) and ATP-binding cassette sub-family G member 2 (ABCG2). Addition of doxycycline induces Cre and mosaic inactivation of *Pkd2* with an approximately 50% decrease in the abundance of total polycystin-2 (PC2). The loss of PC2 protein results in a progressive reduction and eventual loss of tracked tubule structures when compared to control organoids.

Conclusions: Changes in morphology of differentiated structures following inactivation of *Pkd2* in this novel cystogenesis culture system suggest a defect in the 3D organization of epithelial structures that is dependent on PC2 and the study of cystogenesis in 3D organoid culture systems may provide novel insights into the pathogenesis of ADPKD.

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TH-PO582

Anks3 and Anks6 Expression Pattern and Co-Localization in the Kidney Is Tightly Regulated during Development and Disturbed by the Anks6pR823W Mutation in Rats with ADPKD Euan Clark,[2] Stamatia Matina Papagiannarou,[4] James Bowie,[3] Sigrid C. Hoffmann.[1] *[1]Medical Research Centre, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany; [2]Medical Research Centre, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany; [3]University of California, Los Angeles, Los Angeles, CA; [4]Medical Research Centre, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) in rats is caused by a missense mutation in Anks6 (Anks6^{pR823W}). The Anks6^{pR823W} mutation disrupts the interaction between the SAM domains of Anks6 and Anks3, a novel protein. The function of this interaction is unknown. Co-localization of Anks6 and Anks3 is a precondition that interaction can occur. Thus, this study aimed to analyze the spatial and developmental renal expression pattern of Anks6 and Anks3 in WT and Anks6^{pR823W} cy/cy rats.

Methods: Anks3 and Anks6 expression were studied during renal development (0- and 10-days of life) and in the mature kidney at the age of 4 weeks in normal wild type (WT) and homozygous Anks6^{pR823W} cy/cy rats by in situ hybridization, immunohistochemistry and confocal microscopy.

Results: In kidneys of 0d -10d old WT rats both, Anks6 and Anks3, were expressed only in the cortex, not in the medulla and do not co-localize. In contrast, in the mature WT kidney both, Anks3 and Anks6, are strikingly expressed in the medullary collecting ducts and co-localizes with aquaporin 2 (Aqp2). In the renal cortex they co-localizes in distal tubules, however, only Anks6 but not Anks3 expression was noted in the S3 segment of the proximal tubule; the tubular segment in which cysts originate in Anks6^{pR823W} cy/cy rats. Unlike WT kidneys, Anks6^{pR823W} cy/cy rats already show during kidney development a strong expression and co-localization of Anks6 and Anks3 in the medullary collecting ducts and the cortical tubules. The Aqp2 expression is significantly less in both, 0d -10d old and mature kidneys, of cy/cy rats when compared with WT rats indicating a reduced water retention.

Conclusions: A developmental regulated spatial expression pattern of Anks6 and Anks3 exist in the WT kidney, which is disturbed in Anks6^{pR823W} cy/cy rats. Since we have previously shown that Anks3 knockout in rats decreases urine production and increases Aqp2 expression, data suggests that Anks3 is overactive in Anks6^{pR823W} and suppresses Aqp2 expression. In WT kidneys, Anks6 and Anks3 interaction via their SAM domain might block this Anks3 effect. Further studies are required to relate these findings to the cystogenesis. *This study was supported by the grant of the NIH (5RO1DK100482) to JB and SH*

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TH-PO583

Kidney Glycosphingolipidomics and Metabolomics Reveal Metabolic Crosstalk between Elevated Glycosphingolipids and Glucose Metabolisms in PKD Progression Kazuki Nakajima,[1] Kazuo Takahashi,[3] Masanori Kugita,[2] Shizuko Nagao,[2] Yukio Yuzawa.[4] *[1]Fujita Academy, Fujita health university, Toyoake, Aichi, Japan; [2]Fujita Health University, Toyoake, Aichi, Japan; [3]Fujita Health University School of Medicine, Toyoake, Japan; [4]Fujita Health University School of Medicine, Toyoake, Japan.*

Background: Polycystic kidney diseases (PKDs) are characterized by abnormal proliferation and cyst formation in renal epithelial cells. Particularly, abnormal glucose and lipid metabolism are known therapeutic targets of PKD. We previously reported that a crucial cellular energy sensor, AMP-activated protein kinase, tightly regulates glycosphingolipid (GSL) biosynthesis by reducing nucleotide sugars, suggesting a metabolic crosstalk between GSLs and glucose metabolism (Ishibashi. Y et al. *J.Biol. Chem.* 2015). Herein, we investigated whether this crosstalk leads to cooperative effects in PKD progression by using lipidomics and metabolomics.

Methods: Glycosphingolipidomics and metabolomics in 10-week-old male juvenile cystic kidney (*JCK*) mice and control mice were performed by four newly developed methods using liquid chromatography electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS). This study included the (1) global analysis of abundant sphingolipids, (2) quantification of glucosylceramides using an isometric separation system, and (3) acidic GSLs-focused analysis. Moreover, (4) metabolomics included the quantification of nucleotide sugars, the substrate of GSLs. The involvement of the crosstalk in PKD progression was demonstrated by analyzing changes in cell lines treated with several inhibitors.

Results: Global analysis of sphingolipids revealed no significant changes in more than 100 species of abundant ceramides and sphingomyelins. However, the second method showed higher levels of major GlcCer species in the PKD mouse kidney. Further, acidic GSL-focused analysis showed a remarkable increase in GM3 gangliosides, but not sulfatides. Metabolomics revealed that the UDP-glucose level was up-regulated in PKD. The elevated GSL levels were abrogated by treatment with 2-deoxy-glucose, an inhibitor of glucose metabolism. Conversely, treatment with Genz-123346, an inhibitor of GSL synthesis, suppressed UDP-glucose levels in a PKD model cell line.

Conclusions: The metabolic crosstalk between GSL and glucose metabolism may play a role in PKD progression. Our workflow provides valuable information regarding the molecular mechanisms studied during the search of novel therapeutic targets of PKD.

TH-PO584

ADAM10-MMP14 Complex Regulates Renal Cystogenesis in Autosomal Dominant Polycystic Kidney Disease Frank Xu,[1] Li-lun Ho,[1] Bradley M. Denker,[2] Tianqing Kong,[1] Joseph V. Bonventre,[1] Tzongshi Lu.[1] *[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is associated with mutations in polycystins, alterations in cell-cell junctions and focal adhesions in renal epithelial cells. Polycystin 1 (PC1) forms a large protein complex that includes E-cadherin and Gα12 binding proteins that play key roles to maintain cell-cell junctions and cell polarity. We previously reported that deletion of PC1-regulated protein, Gα12, protected kidneys from kidney cystogenesis induced by Pkd1 inactivation, and activation of Gα12 increased the shedding of E-cadherin. However, signaling pathways of PC1 induced ADPKD are not fully understood.

Methods: We used Madin-Darby canine kidney (MDCK) cells, Pkd1 deletion renal cells and Pkd1 knockout mice kidney tissue. Inducible Pkd1 knockout mice were generated by flanking exons 2 through 6 with two LoxP sites (Mx1Cre+; Pkd1flox/flox). Double knockout of Pkd1 and Gα12 mice were obtained by crossing Mx1Cre^{+}Pkd1$^{flox/flox}$ mice with Gα12$^{-/-}$ mice (Pkd1-/-Gα12-/-). MDCK Tet-off inducible Gα12 and Gα12QL cell lines were used in 3D cell culture.

Results: The conditional deletion of Pkd1 (Pkd1$^{-/-}$) resulted in multiple kidney cysts forming within 9 weeks, but Pkd1-/-Gα12-/- mice had no structural and functional abnormalities in the kidneys. Pkd1 deletion promoted increased E-cadherin fragments in renal cystic fluid. No change in cyst E-cadherin fragments in Gα12$^{-/-}$ mice. Gα12 increased the active form of ADAM10, and knockdown of ADAM10 blocked the Gα12 mediated E-cadherin shedding. Our data indicate that ADAM10 is the major sheddase for cleavage of E-cadherin caused by Gα12 activation. Increased ADAM10/MMP14 complex promotes cystogenesis in renal epithelial cells. ADAM10 activity is dependent on the catalytic and hemopexin domains of MMP14. Inhibition of ADAM10 and MMP14 activity blocks cystogenesis induced by Gα12 activation. The deletion of Pkd1 increases the activation of Gα12, which subsequently decreases cell-matrix and cell-cell adhesion by affecting focal adhesion and E-cadherin cleavage.

Conclusions: Gα12 is an essential downstream signaling molecule for PC1, and Gα12 activation increases ADAM10 activity promoting the ectodomain shedding of E-cadherin that plays a key role in renal cystogenesis in Pkd1 deletion induced ADPKD. The ADAM10-MMP14-Ecadherin axis is a potential therapeutic target for ADPKD.

Funding: Private Foundation Support

TH-PO585

Recessive Mutations of MAP7D3 Cause a Renal Ciliopathy Tilman Jobst-Schwan,[1] Joao Goncalves,[2] Einat Lahav,[3] Deborah R. Stein,[1] Benjamin Dekel,[3] Laurence Pelletier,[2] Friedhelm Hildebrandt.[1] *[1]Division of Nephrology, Boston Children's Hospital, Boston, MA; [2]Lunenfeld-Tanenbaum Research Institute, Toronto, ON, Canada; [3]Sheba Medical Center, Safra Children's Hospital, Division of Pediatric Nephrology, Pediatric Stem Cell Research Institute, Ramat Gan, Israel.*

Background: Renal ciliopathies are characterized by dysfunction of the primary cilium and centrosomes. Mutations in one of 95 genes have been discovered to cause these single gene-disorders in ~65% of patients with renal ciliopathies.

Methods: To identify novel ciliopathy genes, we analyzed whole exome sequencing (WES) data in individuals with ciliopathies, who had no mutations in any known ciliopathy genes. We examined the subcellular localization of *MAP7D3* using confocal immunofluorescence (IF) analysis in and performed co-immunoprecipitation (co-IP) to test the interactions with other known ciliopathy genes.

Results: The male index patient from a non-consanguineous family presented with polyuria, enuresis, tubular proteinuria, impaired kidney function (GFR 30ml/min) and acidosis. Renal ultrasound (US) showed small, echogenic kidneys. By WES trio analysis, we identified the hemizygous truncating mutation c.1284_1285insC (p.Ser429Glnfs) in the X-chromosomal *MAP7D3* gene in this patient. In a second unrelated non-consanguineous family, the male patient presented with severe hyperkalemia, small echogenic kidneys upon US and end stage renal disease. Renal biopsy of this patient showed nephronophthisis-like features with additional glomerulosclerosis. By WES, we identified the hemizygous missense mutation c.65G>C, p.Arg22Pro in *MAP7D3* introducing a proline residue in a coiled-coil domain that is known to interact with microtubules. By IF, we show that wild type Flag-BirA-MAP7D3 localizes to the mitotic spindle. By co-IP, we show that wild type MAP7D3 interacts with CEP120, mutated in the ciliopathy Jeune asphyxiating thoracic dystrophy, and with SPICE1 as well as CP110, which are all centrosomal proteins.

Conclusions: We here identify mutations of *MAP7D3* as a novel monogenic cause of a renal ciliopathy in humans and demonstrate that the protein interacts with other ciliopathy associated or centrosomal proteins. Further studies will elucidate allele specific expression and pathogenic pathways involved.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-PO586

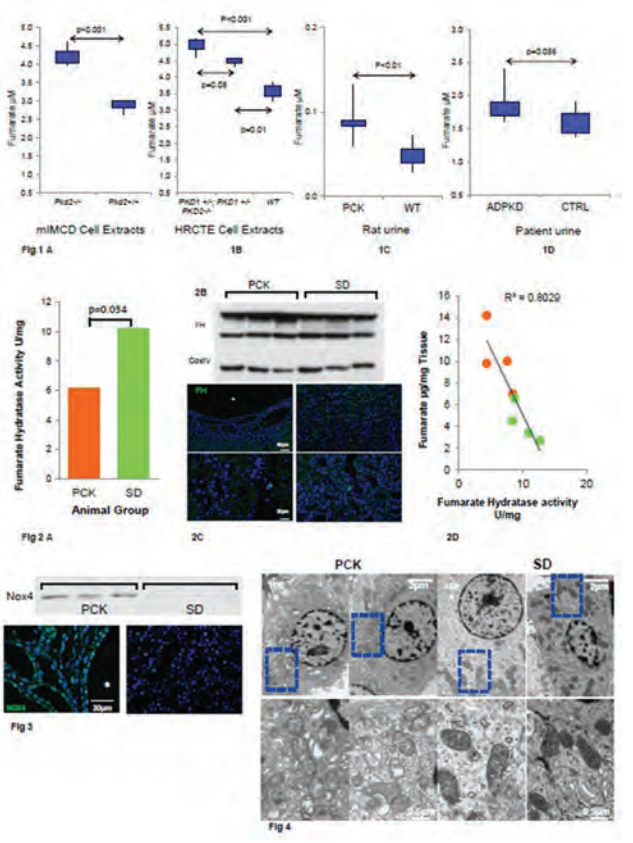
Possible Role of Nox4 in Cystogenesis through Its Effects on Fumarate Hydratase in Experimental PKD Ivan Vuckovic, Jennifer Arroyo, Fouad T. Chebib, Peter C. Harris, Slobodan Macura, Vicente E. Torres, Maria V. Irazabal. *Mayo Clinic, Rochester, MN.*

Background: Autosomal Dominant Polycystic Kidney Disease (PKD) is the most frequent hereditary renal disease, but the exact mechanisms of cystogenesis remain to be elucidated. Deficiency in fumarate hydratase (FH) is accompanied by increases in fumarate and is associated with the development of kidney cysts. Studies in diabetic nephropathy showed that NADPH oxidase (NOX)-4 (Nox4) can inhibit FH leading to accumulation of fumarate. No studies have explored the role of Nox4 in PKD.

Methods: Metabolomics analysis of cell extracts, urine, plasma & kidney of PCK (n=32) and wildtype (WT; n=24) rats, and human samples (ADPKD n=10; ctrl n=10) was performed by HNMR & confirmed by MS. Immunoreactivity and protein expression of FH & Nox4 were assessed by staining & western blotting, FH activity by a colorimetric method and mitochondria by electron microscopy.

Results: Fumarate was consistently increased in PKD-deficient cells, PCK rats & human samples (Fig1A-D). Mitochondrial FH activity was significantly lower in PCK rats (2A), but protein expression and immunoreactivity did not differ (fig2B-C). Furthermore, FH activity highly correlated with tissue fumarate (fig2D). Decreased FH activity was associated with significantly increased protein expression and immunoreactivity of Nox4 in PCK compared to WT rats (fig3). These findings were associated with disruption of mitochondria cristae, swelling, and decreased matrix density exclusively in tubular cells from CD lining microcysts in PCK rats (fig4).

Conclusions: Metabolomic analysis identified fumarate as a potential mediator of cystogenesis in PKD. Accumulation of fumarate in PKD may be due to FH inhibition through upregulation of Nox4. Further experiments are needed to investigate the role of Nox4, FH and fumarate in PKD.



TH-PO587

Suppressing Interferon Regulatory Factor-5 Synthesis Attenuates Kidney Macrophages and Cytokines in Polycystic Kidney Disease Kurt Zimmerman,[3] Lan He,[1] Bradley K. Yoder,[3] Alexey Revenko,[2] Adam E. Mullick,[2] P. Darwin Bell,[1] Takamitsu Saigusa.[1] *[1]Division of Nephrology, University of Alabama at Birmingham, Birmingham, AL; [2]Ionis Pharmaceuticals, Carlsbad, CA; [3]Cell Developmental and Integrative Biology, University of Alabama at Birmingham, Birmingham, AL.*

Background: Inflammatory cells are increased in both human and mouse models of polycystic kidney diseases (PKD). Interestingly, macrophages in the kidney may appear before significant cystic development and deleting phagocytic macrophages with liposomal clodronate has been reported to slow cyst formation. Interferon regulatory factor-5 (IRF5) is a transcription factor involved in activation of macrophage and cytokine release and maybe an effective target for therapeutic intervention. To determine the significance of IRF5 and macrophages in PKD, we tested an antisense oligonucleotide (ASO) that inhibits IRF5 in adult *Pkd1* mice.

Methods: Four week old adult *Pkd1* conditional floxed allele mice with or without cre were administered tamoxifen to induce cre. Two weeks after tamoxifen injection, mice underwent unilateral nephrectomy to accelerate cyst formation. After nephrectomy, mice were treated with weekly injection of either IRF5 ASO (40mg/kg/wk) or scrambled ASO for a total of 3 weeks. Kidneys were harvested for analysis at the end of the treatment.

Results: Three weeks following nephrectomy, *Pkd1*$^{-/-}$ mice showed early focal cyst formation/dilated tubules in the kidney. *Pkd1*$^{-/-}$mice treated with IRF5 ASO demonstrated significant reduction in level of kidney IRF5 mRNA compared to scrambled ASO treatment. Flow cytometry analysis of kidneys suggest that treatment with IRF5 ASO specifically reduces the number of infiltrating and resident macrophages but the level of neutrophils and T cells was unaffected by IRF5 ASO. IRF5 ASO compared to control ASO reduced kidney mRNA levels of pro-inflammatory cytokines.

Conclusions: These results suggest that suppressing IRF5 reduced both resident and infiltrating macrophages in early stage of PKD and may potentially become a novel therapeutic target in PKD.

Funding: NIDDK Support

TH-PO588

Cardiac Valvulogenesis Is Cilia Dependent and Exocyst-Mediated Ciliogenic Programs Are Conserved across Species and Organs Diana B. Fulmer,[1] Ben Fogelgren,[2] Katelynn A. Toomer,[1] Russell A. Norris,[1] Joshua H. Lipschutz.[1] *[1]Medical University of South Carolina, Charleston, SC; [2]University of Hawaii, Honolulu, HI.*

Background: Polycystic kidney diseases such as ADPKD, Joubert, and Meckel's syndromes are associated with cardiac valve abnormalities. Our recent data show that primary cilia are expressed on developing, but not adult, cardiac valves and are required for normal valvulogenesis. Mutations in the highly-conserved, octameric exocyst complex disrupt ciliogenesis, and result in Joubert and Meckel's syndromes. Exoc5 is a central component of the exocyst, and shRNA-induced knockdown in Madin Darby canine kidney cells inhibits ciliogenesis, increases cell proliferation, and results in low intracellular calcium levels that do not increase in response to fluid flow, all without grossly affecting cell polarity. Conversely, Exoc5 overexpression, results in longer cilia with normal intracellular calcium levels and enhanced response to fluid flow. The exocyst participates in cilogenesis by trafficking vesicles carrying ciliogenic cargo proteins, such as polycystin-2, from the Trans-Golgi network to the membrane. The exocyst and its cargo are localized to the nascent cilium by interactions with Cdc42 and other docking proteins. We have shown altered cilogenesis and nephrogenesis, in both exoc5 zebrafish morphants and *Exoc5*$^{fl/fl}$ mice bred with a kidney-specific Cre. *Cdc42*$^{fl/fl}$ kidney-specific Cre mice also displayed a cystic phenotype.

Methods: Exoc5 zebrafish mutants, along with cardiac-valve specific knockout in mice were used.

Results: Zebrafish morphants and two distinct lines of *exoc5*$^{-/-}$ mutant zebrafish have cardiac edema and severe outflow tract stenosis, and we demonstrate rescue of these phenotypes with human *EXOC5* mRNA. We also found significant activation of the Hippo pathway in the *exoc5* mutant zebrafish, which has been previously linked by us and others to PKD. Furthermore, *Exoc5*$^{fl/fl}$ mice bred with cardiac valve-specific *NfatC1* Cre, have highly penetrant bicuspid aortic valve disease.

Conclusions: These data show that ciliogenic programs are conserved across species and organs, which helps to explain the association of cardiac valve abnormalities and PKD, and offer new animal models for future testing of therapeutic compounds.

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TH-PO589

Neutralization of Programmed Death Ligand 1 Delays Cyst Growth in ADPKD Jacqueline D. Peda, Ekaterina Marilovtseva, Xiaoyan Li, James P. Calvet, Xiaogang Li. *Kidney Institute at the University of Kansas Medical Center, Kansas City, KS.*

Background: Interstitial inflammation plays a significant role in polycystic kidney disease (PKD). This inflammation features macrophages and other inflammatory cells, and cytokines released by these cells can be found in cyst fluid and urine. The Programmed Death 1 (PD1)/PD Ligand 1 (PDL1) pathway is a recent target for the treatment of multiple cancers. The upregulation of PDL1 on the surface of tumor cells due to immune infiltrates acts as a natural 'balance' to limit tissue-specific responses to inflammation, limiting T-cell mediated destruction. However, the roles and mechanisms of T-cells and PDL1 in underlying inflammation of ADPKD remain unknown

Methods: To evaluate a potential role of T-cells and PDL1 in cyst immunopathology, we investigated the presence of T-cells in cystic kidneys from *Pkd1*$^{flox/flox}$*:Pkhd1-Cre* knockout mice using FACS sorting and immunostaining. The expression of PDL1 in cystic renal epithelial cells and tissues was evaluated via immunostaining, protein and RNA expression. A PDL1 neutralizing antibody was used to evaluate its effects on cyst growth *in vivo*.

Results: We found that T-cells were present in higher levels in cystic kidneys and that they were localized to the interstitium surrounding cystic tissue. We also found that the expression of PDL1 mRNA and protein was increased in *Pkd1* mutant renal epithelial cells compared to control cells. Additionally, we detected PDL1 in kidneys of *Pkd1* conditional knockout mice, where it was primarily expressed in the cyst-lining epithelia derived from collecting ducts. The expression of PDL1 could be epigenetically regulated and enhanced in response to inflammatory cytokines in cystic renal epithelial cells. We further found that neutralizing PDL1 with a monoclonal antibody, which is well tolerated and currently being studied in late phase cancer trials, delayed cyst growth. This was reflected by decreased cystic index and kidney weight (KW)/body weight (BW) ratios in *Pkd1* conditional knockout mice compared to untreated mice. Effects on disease progression is likely due to blocking the PDL1 interaction with PD1 on T-cells.

Conclusions: This is the first report that T-cells are present in higher numbers in cystic kidneys when compared to controls, and that PDL1 is uniquely expressed in non-cancerous renal epithelial cells. Blockade of PDL1 interaction with T-cells may prove therapeutic in ADPKD.

Funding: NIDDK Support, Private Foundation Support

TH-PO590

Macrophage Depletion Leads to Temporal and Spatial Changes in miRNA Profiles That Drive Fibrosis in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Ameya P. Patil,[1,2] William E. Sweeney,[1] Cynthia G. Pan,[1,2] Ellis D. Avner.[1] *[1]Medical College of Wisconsin, Wauwatosa, WI; [2]Childrens Hospital of Wisconsin, Wauwatosa, WI.*

Background: In ADPKD, the decline in kidney function correlates with onset of fibrosis. Such fibrosis begins in peri-cystic areas (PA) between multiple cysts. Key factors involved in process of fibrosis include macrophages (Ø) at a cellular level and miRNAs at a molecular level. We hypothesize that localized changes in miRNA's and Ø phenotypes drive fibrosis in ADPKD, and provide potential targets for future therapeutic intervention.

Methods: Cystic kidneys from mcwPkd1$^{(nl/nl)}$ mice and age matched controls at postnatal days (PN) 21, 28, 42 and 56 were evaluated. These stages encompasses the disease process from maximum cyst growth and total kidney volume (TKV) at PN28 to dramatically reduced TKV due to fibrosis at PN56. Clodronate, which eliminates Ø, was administered from PN14 to PN56. FFPE fixed cystic kidneys at PN 56 following clodronate treatment were analyzed with serial sections for miRNA, mRNA analysis and trichrome (TriC) and compared to age-matched untreated cystic kidneys. Øs and Ø phenotypes were analyzed by flow cytometry, IHC and IF in serial sections and following clodronate treatment.

Results: Flow cytometry reveals significant increase in Øs from PN21 to PN28. At PN21, Øs located in PAs express predominantly INOS, a marker for M1 Øs. Between PN28 and PN56, Øs predominantly express arginase, a marker of M2 Øs. These findings correlate directly with increasing TriC staining in PAs and the decline in renal function. As expected, clodronate treatment :1) depleted Øs in both spleen and kidney; 2) resulted in significantly less TriC positivity; and 3) inhibited the decrease in TKV. miRNA analysis of serial sections in both treated and untreated cystic kidney showed a total of 158 miRNA's that were differentially expressed with 85 upregulated in treated kidneys. mRNA analysis on the same section was significant for differentially expressed AKT1 and EGF, 11 and 6.4-fold respectively.

Conclusions: (1) In this unique model of ADPKD; changes in Ø number and phenotype play a key role in fibrosis; (2) Changes in miRNA profiles after macrophage elimination with clodronate provide unique miRNA targets that may guide future therapeutic intervention; (3) This profile correlates with change in EGF and AKT which play critical roles in ADPKD.

TH-PO591

Gli1 Rescues the Angiogenic Potential of Polycystic Kidney Disease-Derived Endothelial Cells Federico Franchi, Karen M. Peterson, Ezequiel J. Tolosa, Peter C. Harris, Martin E. Fernandez-Zapico, Martin G. Rodriguez- Porcel. *Mayo Clinic, Rochester, MN.*

Background: We showed that Polycystic Kidney Disease (PKD)-derived Endothelial Cells (ECs) have a diminished response to the ligand-dependent activation of the Hedgehog (Hh) pathway, leading to an impaired angiogenic potential of these cells. We then hypothesized that restoring the activity of the Hh signaling by overexpressing GLI1, a central effector of this pathway, will ameliorate the vascular defects in PKD-ECs.

Methods: To assess the role of Gli1 in ECs, we knocked-down the expression of Gli1 (using siRNA) in WT-ECs and study their angiogenic profile. To restore function, we overexpressed Gli1 in PKD-ECs and measured the expression levels of pro-angiogenic markers (phenotype) and the capacity to form vascular structures (function).

Results: A 50% decrease in Gli1 mRNA expression was associated with a decrease in vascular endothelial growth factor A (VEGFA) expression, similar to that seen in PKD-ECs (Fig. 1A). Chromatin immunoprecipitation shows that the pro-angiogenic factors VEGFA and fibroblast growth factor 2 (FGF2) are direct targets of GLI1 in ECs. The overexpression of Gli1 in PKD-ECs led to a 740-fold increase in Gli1 mRNA expression. Importantly, exogenous Gli1 substantially restored the expression levels of the pro-angiogenic molecules VEGFA, VEGF receptor 1 (FLK1) and FGF2 (Fig. 1B), as well as the ability of PKD-ECs to form angiogenic tubes (Fig. 1C).

Conclusions: Our data suggest that a dysregulation in Hh signaling, and particularly of GLI1, may be responsible for the abnormal angiogenic profile seen in PKD-ECs. Furthermore, we provide evidence that Gli1 overexpression rescues the vascular deficiencies in PKD. These studies can be useful for the development of novel therapeutic strategies that focus on the vascular aspects of PKD.

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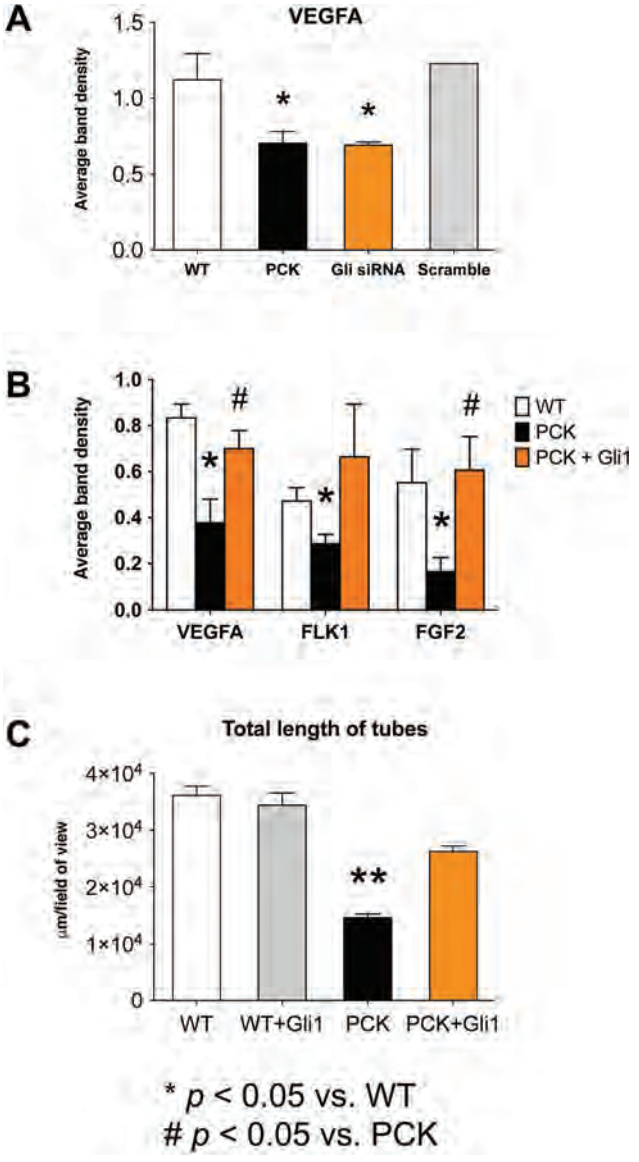

TH-PO592

Autophagy Induction in Mouse Kidneys Carolyn N. Brown, Sara Holditch, Charles L. Edelstein. *UC Denver Anschutz Medical Campus, Aurora, CO.*

Background: Autophagy occurs in all eukaryotic cells in order to adapt under stressful conditions. Damaged organelles and proteins are sequestered into autophagosomes, which subsequently fuse with lysosomes where cargo is degraded and recycled. The aim of the current study was to determine the effects of autophagy inducers metformin (MET), 2-deoxyglusoce (DOG), and trehalose (TRE) on autophagy in wild type (WT) and RC/RC (PKD) mouse kidneys *in vivo*.

Methods: WT and PKD mice were treated with MET (250mg/kg IP), DOG (100mg/kg IP), or TRE (2% P.O.) for 6-12 days. At the end of the study, mice received wither vehicle (VEH) or bafilomycin (BAF) (1.75mg/kg IP) to block autophagic flux. P62, an autophagy-specific tag for degradation and a marker of autophagy inhibition, and LC3-II, a marker of autophagome formation, were measured by immunoblot.

Results: WT Kidneys: Significantly reduced LC3-II was detected in the kidneys of MET and DOG mice compared to VEH, suggesting an increase in autophagosome turnover by the lysosome. This was supported by increased LC3-II in MET+BAF vs MET, and DOG+BAF vs DOG, which were notably larger than VEH+BAF vs VEH. TRE had modest effects on LC3-II. PKD Kidneys: LC3-II was increased after BAF treatment in both TRE and MET, but not DOG. Most importantly, in PKD kidneys, MET, DOG, and TRE cleared most p62 protein aggregates, which are characteristic of defective autophagy. Further studies will be performed in PKD kidneys to achieve statistical significance. ImageJ software was used for densitometry (Table 1).

Conclusions: In summary, MET and DOG were both able to successfully induce autophagy in WT and PKD kidneys. Autophagy plays an important role in maintaining kidney homeostasis, and PKD has been described as a case of suppressed autophagy. The effect of autophagy inducers on PKD progression merits further study.

Funding: Other U.S. Government Support

Table 1

Group/Genotype	LC3-II/B-actin WT	LC3-II/B-actin PKD	p62/B-actin PKD
VEH	3.3±0.7	1.8±0	3.9±0.8
VEH+BAF	9.6±2.0	5.0±0	
MET	1.4±0.1 *	5.4±0.1	0.7±0.1†
MET+BAF	8.8±4.3 **	6.7±1.0	
DOG	1.2±0.2 *	4.1±0.4	0.6±0.03†
DOG+BAF	11.4±3.1 ***	3.8±0.3	
TRE	9.7±2.5	4.8±0.8	0.6±0.1†
TRE+BAF	13.2±3.7	6.9±0.7	

*p<0.05 vs VEH, **p<0.05 vs MET, ***p<0.06 vs DOG, †p<0.06 vs VEH

TH-PO593

Lack of Alpha-Intercalated Cells Links Autosomal Dominant Polycystic Kidney Disease to Urinary Tract Infection in Mice and Humans Chao Gao,[3] Long Zhang,[3] Lihe Chen,[4] Ye Zhang,[1] Enuo Chen,[2] Darren P. Wallace,[5] Qiaoling Zhou,[6] Paul J. Higgins,[2] Wenzheng Zhang.[2] *[1]AMC, Albany, NY; [2]Albany Medical College, Albany, NY; [3]Albany medical college, Albany, NY; [4]NIH, Bethesda, MD; [5]University of Kansas Medical Center, Kansas City, KS; [6]Xiangya Hospital, Changsha, China.*

Background: Urinary tract infection (UTI) is a common feature of autosomal dominant polycystic kidney disease (ADPKD) with ~30-50% of ADPKD patients having at least one UTI during their lifetime. However, the underlying cellular and molecular mechanisms linking ADPKD to UTI remain unaddressed.

Methods: Hence, *Pkd2$^{f/f}$ Aqp2Cre* mice were generated to disrupt *Pkd2* in Aqp2$^+$ progenitor cells, which give rise to all known cell types of the connecting tubule/collecting duct (CNT/CD).

Results: *Pkd2$^{f/f}$ Aqp2Cre* mice developed severe PKD and died by P17. Double and triple immunofluorescence (IF) staining for various segment- and/or cell-specific markers were conducted. At least 1000 CNT/CD cells from 3 *Pkd2$^{f/f}$ Aqp2Cre* and 3 WT mice for each IF combination were categorized and counted based on the marker expression. Using Aqp2, V-ATPase B1B2 and AE1 as markers for principal cells (PC), intercalated cells (IC) and a-IC, respectively, we found that *Pkd2$^{f/f}$ Aqp2Cre* mice had a reduced IC/PC ratio from 37.61±1.23% in WT to 7.45±1.08% and completely lost a-IC at P17. Neutralized urine from *Pkd2$^{f/f}$ Aqp2Cre* mice is significantly less inhibitory for bacterial growth than that from WT mice. In P6 *Pkd2$^{f/f}$ Aqp2Cre* mice, cysts began to be detectable with occasional presence of a-IC. TUNEL assay showed that IC, particular a-IC, were more apoptotic than PC. We conducted the same IF with kidneys from ADPKD patients (n=27) and minimal change disease patients (MCD) as normal control (n=5). While all PC and IC markers were readily detectable in each of MCD samples, cysts containing AQP2$^+$ cells were found only in 13 ADPKD samples. Among these 13 ADPKD samples, we counted >4000 CNT/CD cells and found that ADPKD diminished the IC/PC ratio from 26.07±6.19% in MCD to 10.12±6.53%. None of the ADPKD kidneys had AE1$^+$ cells in Aqp2$^+$ labeled cystic structure. Seldom AE1$^+$ cells were observed in apparently normal CNT/CD of some ADPKD kidneys.

Conclusions: Our data suggest that *Pkd2* deletion in Aqp2$^+$ progenitor cells is sufficient for PKD development, and a-IC are selectively depleted with the disease development in both mice and human. The lack of a-IC to acidify urine and secret neutrophil gelatinase-associated lipocalin (NGAL) that chelates siderophore-containing iron may link ADPKD to UTI.

Funding: NIDDK Support

TH-PO594

A Mouse Model of Tsc Renal Cystic Disease John J. Bissler,[2] Kamyar A. Zahedi,[1] Sharon L. Barone,[1] Manoocher Soleimani.[1] *[1]University of Cincinnati, Cincinnati, OH; [2]University of Tennessee, Le Bonheur Children's Hospital and St. Jude Children's Research Hospital, Memphis, TN.*

Background: Tuberous sclerosis complex (TSC) renal cystic disease affects over 500,000 patients world-wide. There are five patterns of TSC-associated renal cystic disease, and they are the macrocystic diseases including polycystic, cortical cystic, multicystic, focal cystic diseases, and microcystic disease. The cysts can have a simple single cellular layer, have a multiply layer or even papillary histology. Although the basic histology has been described, the cystogenic mechanism in TSC is poorly understood.

Methods: To begin to better understand this cystic disease process, we created a mouse model of TSC renal cystic disease by targeting principle cells by using aquaporin 2-driven Cre recombinase expression to delete the floxed *Tsc2* gene. Double immunofluorescence labeling was performed to determine the identity of cyst epithelium.

Results: In this cell specific model, we identify the similar histological characteristics of the renal cystic epithelium as occurs in the human. Interestingly, the cyst epithelium was predominantly comprised of intercalated cells as determined by intense and uniform apical expression of H+-ATPase in both mouse and human. There was no expression of AQP-2, NHE-3, NBC-e1, NCC or Na-K-ATPase, indicating the absence of principal, proximal tubule, distal convoluted and thick ascending limb epithelial cells in the cyst wall. The cysts in human and mouse also exhibited a significant decrease in cilia expression.

Conclusions: We have developed a mouse model that resembles human TSC-associated renal cystic disease. This TSC renal cystic disease in both the mouse model and human exhibits significant histolopathological differences compared to other renal cystic

diseases. These differences raise the possibility that therapies like V_2 receptor antagonism may not have similar efficacy.

Funding: Other U.S. Government Support

TH-PO595

Lessons from Pkd1 Therapeutic Targeting Strategies in a Loss-of-Function Mouse Model Camila Parrot, Almira Kurbegovic, Jennifer Lake, Guanhan Yao, Marie Trudel. *Institut de Recherches Cliniques de Montréal, Montréal, QC, Canada.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) causes renal and extrarenal phenotypes. The PKD1 gene responsible for most cases of ADPKD has a developmentally and temporally regulated expression pattern. While CRISPR-Cas as a therapeutic strategy for PKD is attractive, the high frequency of off-targets preclude clinical application. Because microscopic cysts below clinical detection are likely formed *in utero* in ADPKD kidneys (Grantham et al CJASN 2010,2012), we targeted *Pkd1* at early stage in mouse model to assess for long-term treatment. *Pkd1* null mouse model that display severe renal cysts and die by birth, were used to assess whether wild type Pc1 from 2 series of transgenic lines prevent cyst formation.

Methods: One mating overexpressing Pc1 was generated with 2 systemic $Pkd1_{TAG}$ mouse lines and the second with 2 renal-specific $SBPkd1_{TAG}$ mice. RNA and proteins in kidneys and pancreas were assessed along with histomorphologic and cellular longitudinal analysis.

Results: $Pkd1^{-/-}$ mice crossed into each of the $Pkd1_{TAG}$ transgenic lines escaped perinatal lethality. These mice exhibit no renal or pancreatic phenotypes in the first few months of age. Thus, the $Pkd1_{TAG}$ transgene produced a functional protein with proper transgene regulation. $Pkd1_{TAG}$;$Pkd1^{-/-}$ mice at >8mo developed however renal cysts but milder than the parental transgenic line consistent with their Pkd1 overexpression and a gene-dosage pathogenic mechanism. $Pkd1^{-/-}$ mice mated to $SBPkd1_{TAG}$ renal specific expressors avoided neonatal death but consistently, developed renal (kidney/body weight 2.3 fold that of normal mice) and pancreatic cysts. Despite Pc1 ~7 and 15-fold overexpression, deaths occur at P10-P15 with the mild Pc1 expressor and ~3 mo in the high expressor, indicating that renal cysts likely result from differential tubular response: insufficient expression and/or overexpression of Pc1. Collectively, these results demonstrate that early Pc1 expression can delay cystogenesis and extend mouse lifespan, and revealed that Pc1 re-expression requires highly controlled spatiotemporal regulation.

Conclusions: Maintenance of tightly regulated PKD1/PC1 expression will be a major clinical challenge as PC1 expression varies between renal cell types and age. Presently, targeting PC1 in ADPKD is a double-edge sword and cannot practically serve as a useful therapeutic target.

Funding: Government Support - Non-U.S.

TH-PO596

Compound-Homozygous Pkd1 and Pkd2 Inactivation Has No Additive Effect on Cyst Formation Xin Tian, Yiqiang Cai, Ming Ma, Chao Zhang, Whitney E. Besse, Ashima Gulati, Stefan Somlo. *Yale University School of Medicine, New Haven, CT.*

Background: Autosomal dominant polycystic kidney disease results from mutations in PKD1 or PKD2. The two genes work together in a common signaling pathway in which PKD1 is the rate limiting step. We previously showed an extra-additive increase in cystogenic events in Pkd1+/-;Pkd2+/- mice that may result from a modified threshold effect. In the current study, we examined whether there is a similar effect with conditional homozygous inactivation of both genes in mouse kidney collecting ducts.

Methods: We generated Pkd1fl/fl;Pkd2fl/fl;Pkhd1Cre mice which inactivate both genes in collecting ducts by postnatal day 7 (P7). Pkd1fl/fl;Pkd2fl/fl;Pkhd1Cre mice (n=7), Pkd1fl/fl;Pkhd1Cre mice (n=8) and Pkd2fl/fl;Pkhd1Cre mice (n=7) were examined at P14, P24 and P48.

Results: Histological and functional examination of kidneys from Pkd1fl/fl;Pkd2fl/fl;Pkhd1Cre mice at P14 and P24 showed no significant difference in kidney-body weight ratio (KW/BW), cystic index (CI) and BUN when compared with Pkd1fl/fl;Pkhd1Cre mice. When compared with Pkd2fl/fl;Pkhd1Cre mice, both groups had statistically significant increase in KW/BW ($P<0.05$), CI ($P<0.05$) and BUN ($P<0.05$) at both time points. At P48, multiple comparison showed no significant differences in any parameter among the three groups. We also documented normal appearance of cilia by immunofluorescence microscopy in the cyst lining cells of Pkd1fl/fl;Pkd2fl/fl;Pkhd1Cre mice. There was no significant difference in cyst cell proliferation by BrdU incorporation and apoptotic activity by TUNEL between Pkd1fl/fl;Pkd2fl/fl;Pkhd1Cre mice and Pkd1fl/fl;Pkhd1Cre mice at P14, P24 and P48. However, both these groups had significantly higher cell proliferation rates when compare to Pkd2fl/fl;Pkhd1Cre mice at P14 ($P<0.05$). Notably, all three groups has significantly increased apoptosis at P48 when compared to P24 and P14.

Conclusions: Dual inactivation of Pkd1 and Pkd2 shows no additive effect on cyst formation but early stage inactivation of Pkd1 results in more rapid cyst growth than inactivation of Pkd2, likely due to longer persistence of the Pkd2 protein. Late stage models show genotype-independent increase in apoptosis.

Funding: NIDDK Support

TH-PO597

Disruption of Ca2+-Binding in the EF-Hand Domain of Polycystin-2 Does Not Result in a Cystic Phenotype Matteus Krappitz, Ke Dong, Sorin V. Fedeles, Rachel Gallagher, Yiqiang Cai, Stefan Somlo. *Yale University School of Medicine, New Haven, CT.*

Background: Polycystin-2 (PC2/TRPP2), the product of one of the genes mutated in ADPKD, is expressed in the endoplasmic reticulum (ER) and ciliary membranes. The COOH-terminal tail of PC2 contains 2 potential Ca^{2+} binding EF hand motifs, an ER retention domain and a coiled-coiled domain. Only the second EF hand motif can bind Ca^{2+}. It has been proposed that a mutation in this EF hand abrogates Ca^{2+} binding which leads to a substantial reduction of channel function resulting in decreased inward Ca^{2+} currents conducted by PC2. This study investigates the relevance of abolishing the Ca^{2+} binding properties of the EF-hand domain in PC2 by generating a mouse model mutated at critical residues.

Methods: CRISPR/Cas9 methodology was used to generate a mouse model termed $Pkd2^{TEAA}$, in which critical residues at the EF hand *–z, –x* coordination vertices were substituted with alanine (T769A, E772A) to eliminate Ca^{2+} binding. Mutant alleles were further modified by insertion of a V5 epitope tag in-frame at the C-terminus.

Results: The animals were aged up to 18 months. All organs were extracted and analyzed. The kidney and livers were examined by measuring kidney weight (KW) and liver weight (LW) as a fraction of body weight (BW) and by detailed histological examination. Expression of the mutated protein in the kidney was confirmed by immunoblot analysis with anti-V5. Homozygous $Pkd2^{TEAA/TEAA}$ animals survive up to and past 18 months of age with no histological signs of cystic disease in either kidney or liver. There was no significant difference in BW, KW or LW between wild type, $Pkd2^{TEAA/TEAA}$ or $Pkd2^{+/-}$ animals at the same age. The $Pkd2^{TEAA/+}$ mice were crossed with $Pkd2^{+/-}$ animals to generate $Pkd2^{TEAA/-}$ mice. These mice also did not display a kidney or liver cystic phenotype at 9 months of age.

Conclusions: Inactivation of the Ca^{2+}-binding properties of PC2-EF hand does not result in a significant loss of PC2 function as evidenced by the lack of cystic disease phenotype in the kidney and livers of the $Pkd2^{TEAA/TEAA}$ and $Pkd2^{TEAA/-}$ animals. This suggests that the PC2 channel does not require EF-hand Ca^{2+} binding in order to function in vivo.

Funding: NIDDK Support, Government Support - Non-U.S.

TH-PO598

mTORC2 (Rictor) Knockout Decreases the Cystic Phenotype in Pkd1-/- Mice Sara Holditch,[1] Carolyn N. Brown,[1] Kameswaran Ravichandran,[2,1] Charles L. Edelstein.[1] *[1]UC Denver Anschutz Medical Campus, Aurora, CO; [2]Hera BioLabs, Lexington, KY.*

Background: mTOR exists in two distinct structural and functional complexes mTORC1 (Raptor) and mTORC2 (Rictor-Rapamycin-independent companion of mTOR). We have shown that mTOR kinase inhibition, capable of inhibiting both Raptor and Rictor, reduces cyst growth. However, the effect of mTORC2 (Rictor) inhibition alone on PKD is not known. The aim of our study was to determine the effect of $Rictor^{-/-}$ on the cystic phenotype of $Pkd1^{-/-}$ mice.

Methods: Expression of kidney specific Cre recombinase, with Tamoxifen administration on days 19-21, in Pkd1 fl/fl mice results in $Pkd1^{-/-}$ mice that have a slow onset of cystic disease with severe PKD and renal failure at 130 days post tamoxifen injection. To determine if the effect of $Rictor^{-/-}$ on the cystic phenotype of $Pkd1^{-/-}$mice, Rictor fl/fl mice were bred with the Pkd1 fl/fl; KspCad-CreERT2 mice to develop Rictor fl/fl, Pkd1 fl/fl; KspCad-CreERT2 mice treated with tamoxifen to develop kidney-specific $Rictor^{-/-}Pkd1^{-/-}$ mice and aged to 150 days post Tamoxifen. Non-invasive quantitative assessment of cyst development per kidney at 90 days, a time when nascent cysts are forming, was performed by T2-weighted and FISP-MRI at 4.7 Tesla.

Results: Genetic deletion of mTORC2 (Rictor) in $Pkd1^{-/-}$mice results in significantly lower kidney weight, cyst volume, number of cysts and SCr. (See Table)

Conclusions: Study of signaling pathways downstream of mTORC2 (pAkt, SGK1, PKCα) and a head to head study of sirolimus (Raptor inhibitor) VS. new generation mTOR kinase inhibitors (inhibit both Raptor and Rictor) is warranted to better understand the pathways responsible for PKD cyst expansion.

Funding: Other U.S. Government Support

	Wild type (n=8)	Pkd1-/- (n=9)	Pkd1-/- Rictor-/- (n=6)
Body wt (g)	30	27	32
2K (g)	0.35	0.53	0.36*
2K/TBW (%)	1.1	2.0	1.2*
Cyst volume (%)	0	40.1	14.6*
No of cysts/kidney	0	5.3	0.8*
Heart wt (g)	0.3	0.15	0.17
BUN (mg/dL)	24	29	25
SCr (mg/dL)	0.22	0.33	0.2*

2K/TBW (%) Two kidney/total body weight, *p<0.05 vs. Pkd1-/-

TH-PO599

Anks6-/- Mice Have Laterality Defects and Develop Renal Cystic Disease Rannar Airik,[2,3] Merlin Airik,[1] Nathan A. Herdman.[1] *[1]University of Pittsburgh, Pittsburgh, PA; [2]Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA; [3]Developmental Biology, University of Pittsburg, Pittsburgh, PA.*

Background: Nephronophthisis-related ciliopathies (NPHP-RC) are a group of heterogeneous recessive kidney diseases, that are frequently associated with extra-renal organ malformations. Recently mutations in the ankyrin repeat and sterile alpha motif domain containing 6 (ANKS6) gene were identified, as causing nephronophthisis with extrarenal manifestations in humans (1). Anks6 localizes to the inversin compartment (INVS, NEK8, NPHP3) in the primary cilium, where it regulates the activity of NEK8 kinase (2). In order to study the function of Anks6 in mouse we generated an Anks6 transgenic mouse model.

Methods: Targeted Anks6 ES cells were obtained from KOMP and injected into blastocysts to generate the *Anks6*$^{-/-}$ mice. Loss of Anks6 expression in the mutant animals was confirmed by immunoblotting. Anks6 tissue expression in the kidneys was studied using X-gal staining and in situ hybridization. Gross morphological characterization and tissue histological analysis of the mutant mice was performed at E15.5, E18.5 and P0.

Results: Inactivation of Anks6 causes perinatal lethality in mice due to multiorgan abnormalities. Homozygous Anks6 mutant mice displayed situs inversus, with morphogenesis defects of the heart, lungs, liver and kidneys. Histological and molecular analysis of the kidneys revealed a defect in nephrogenesis that we localized to the glomerulus and proximal tubles in the mutant animals. In kidneys the mutant mice developed glomerular cystic disease.

Conclusions: Our data demonstrate that abrogation of Anks6 in mice leads to laterality and developmental defects in multiple organs, which resemble the phenotypes of mouse models for other inversin compartment components. Homozygous mutant mice recapitulate the major features of loss of ANKS6 function in humans, including liver fibrosis, cystic kidney disease and situs inversus. Together, Anks6$^{-/-}$ mouse represents a novel genetic model of NPHP-RC.

Funding: NIDDK Support

TH-PO600

A Systems Biology Approach Identifies Reciprocal Changes in mir-193b-3p and PIK3R1 as Drivers of Cyst Growth in ADPKD Laura Vergoz,[2] Andrew J. Streets,[2] Tareq B. Malas,[1] Morgane Lannoy,[2] Peter A. 't Hoen,[1] Dorien J. Peters,[1] Albert C. Ong.[2] *[1]Leiden University Medical Center, Leiden, Netherlands; [2]University of Sheffield, Sheffield, United Kingdom.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited cause of end-stage renal disease worldwide. *PKD1* and *PKD2* mutations are present in most patients with clear genotype-phenotype correlations. However, the intra-familial phenotypic variability in some pedigrees suggests the influence of non-allelic factors. Non-coding RNAs e.g. microRNAs are known to play a major role in health and disease (including PKD) via control of mRNA stability or translation. We recently conducted a parallel mRNA/miRNA array study which found mir-193b-3p, among others, downregulated in human ADPKD cells (Streets et al, 2017), associated with dysregulation of the ErbB4/EGF pathway.

Methods: To select other relevant genes regulated by mir-193b-3p, we compared our human mRNA dataset with mRNA expression data from *Pkd1* mutant mice (Malas et al, 2017). Dual-reporter luciferase assays with native and mutant seed sequences and immunoblotting were used to demonstrate functional binding of mir-193b-3p to the 3'UTR of *PIK3R1* mRNA. IGF-1 stimulation of human ADPKD cystic cells in 2D and 3D cultures characterized the role of *PIK3R1* in Akt or ERK signaling and on cyst growth.

Results: *PIK3R1* was selected as a strong candidate gene and shown to be upregulated ~3-fold in human cells and mouse *Pkd1* kidney tissue. In parallel, the catalytic subunit *PIK3CA* was also overexpressed suggesting the most common PI3K enzyme combination is upregulated in ADPKD cells. A functional interaction between *PIK3R1* and mir-193b-3p was confirmed by luciferase assays and immunoblotting. Knockdown of *PIK3R1* or PI3K chemical inhibitors significantly reduced cyst growth in ADPKD cells and influenced Akt and ERK activation by IGF-1.

Conclusions: We report that *PIK3R1* and one of its catalytic subunits are upregulated in ADPKD and confirm that it is a target for mir-193b-3p. The role of *PIK3R1*/*PIK3CA* in driving cyst growth in ADPKD was functionally linked to hyperactivation of Akt and ERK. Co-regulation of *PIK3R1* and *ErbB4* by mir-193b-3p supports the development of PI3K and ErbB4 inhibitors or mir-193b-3p activators for the treatment of ADPKD.

Funding: Government Support - Non-U.S.

TH-PO601

Anks3 Knockout in Rats Causes Prenatal Lethality Due to Major Disturbances in Organ Patterning Euan Clark,[3] Stamatia Matina Papagiannarou,[1] Christian Gosmann,[8] Hermann-Josef Groene,[4] Gergana D. Dobreva,[7] Brigitte Lelongt,[5] Dominique Gauguier,[6] James Bowie,[2] Sigrid C. Hoffmann.[3] *[1]Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany; [2]University of California, Los Angeles, Los Angeles, CA; [3]Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany; [4]German Cancer Research Center, Heidelberg, Germany; [5]UMR_S1155, PARIS, France; [6]INSERM, Paris, France; [7]Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany; [8]Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany.*

Background: Anks3 was first discovered as a novel interacting partner of Anks6. The Anks6^{R823W} mutation disrupts binding to Anks3 and causes dominant polycystic kidney disease (ADPKD) in rats. Though its function remains obscure, Anks3 involvement in nephronophthisis was suggested. The present study aimed to study the consequences of a total Anks3 knockout (Anks3KO) in rats.

Methods: Anks3KO rats were generated by injection of a gRNA targeting the second exon of Anks3 (aa5-12) and Cas9 mRNA into fertilized Sprague Dawley rat zygotes. Rats were genotyped by sequencing the amplified targeted region. RT-PCR and Western blotting were used to prove loss of Anks3. We determines clinical parameters in 24-hr urine and blood plasma to evaluate renal function Histological analysis was performed by standard techniques.

Results: Founders were obtained carrying either a 5bp or an 8bp deletion at the targeted position, which resulted in a premature translational stop at positions aa46 and aa45 respectively, and were used for breeding. Among 82 progenies, 39% were genotyped as wildtype and 61% as heterozygotes. Homozygous Anks3KO rats frequently died in mid-gestation and never survived birth. They exhibited a complex pattern of disturbances in organ patterning including defects in cortex and midbrain development, craniofacial defects, focal hemorrhages and complex structural heart defects. Kidney size was often recduced and associated with abnormal glomerulogenesis and tubulogenesis. Heterozygous Anks3 +/- rats survived and developed mild kidney abnormalities when aged, including small medullary cysts and fibrosis in the cortico-medullary renal border. Urine production was significantly less in Anks3 +/- rats compared to WT littermates. However, Anks3KO rats never developed an ADPKD-like phenotype, as seen in Anks6^{R823W} rats.

Conclusions: Conclusion: Here we provide the first evidence that Anks3KO in mammals causes major, lethal developmental disturbances in organ patterning, similarly to heterotaxy mutants with cilia defects, and a nephronophthisis like phenotype in heterozygous adults. We conclude that Anks3 might be a major factor in regulating ciliary function and controls urine concentration. *This study was supported by the grant of the NIH (5RO1DK100482) to JB and SH*

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TH-PO602

Effects of Moderate and High Intensity Chronic Exercise on Renal Function in PCK Rats of Polycystic Kidney Disease Jiahe Qiu,[1] Takahiro Miura,[1] Sato Yoichi,[1] Masahiro Kohzuki,[1] Osamu Ito.[2] *[1]Department of Internal Medicine and Rehabilitation Science, Tohoku University Graduate School of Medicine, Sendai, Japan; [2]Division of General Medicine and Rehabilitation Faculty of Medicine, Tohoku Medical and Pharmaceutical University, Sendai, Japan.*

Background: Polycystic Kidney Disease (PKD) is a genetic disorder characterized by progressive enlargement of epithelial cysts, leading to destruction of renal function and which is a major cause of chronic kidney disease. We have previously shown that chronic exercise exerts beneficial effects including renal protection in hypertensive, diabetic and 5/6-nephrectomized rats. Therefore, we assessed the effects of moderate and high intensity chronic exercise on renal function in the PCK rat model of PKD.

Methods: Six-week-old, male PCK rats were divided into three groups: sedentary group (Sed, n=10), moderate exercise group (Exm, n=9) and high intensity exercise group (Exi, n=10). Exm and Exi underwent forced treadmill exercise for 12 weeks with the following protocols: 20m/min and 28m/min respectively for 60 min/day, 5 days/week. At the end of experiment, the blood and urine was collected and the kidney were removed. Cyst Area/Total Kidney Area ratio and podocyte injury index were examined.

Results: The present research showed the body weight (504.1±8.4 vs.431.8±7.9 and 433.6±4.3g) and total kidney weight (5.34±0.27 vs.4.22±0.41 and 4.20±0.06g) was significantly lower in both Exm and Exi compared with Sed after 12-week protocol of exercise. The kidney/body weight ratio had a declining tendency but not significant different between the groups. The urine volume(18.0±1.2 vs.13.1±0.9 and 13.0±0.8ml/day), urinary protein excretion (1426±120 vs.537±50 and 452±77mg/day) and blood urea nitrogen (18.2±0.9 vs.15.4±0.4 and 15.9±0.3mg/dL) also had remarkable decrease in both Exm and Exi compared with Sed. The result of serum creatinine had a declining tendency in both exercise groups. As demonstrated by the data, exercise alleviated cyst formation in PCK rats. The Cyst Area/Total Kidney Area ratio had significant decrease in the both exercise groups (30.2±3.4% vs.14.5±1.0% and 17.3±1.3%). The staining of desmin positive staining area in glomeruli as a marker of podocyte injury also had a descending tendency after the chronic exercise.

Conclusions: Both moderate and high intensity chronic exercise significantly decreased cystic area in PCK rats, which also have beneficial effects on attenuating the urinary protein excretion and preventing podocyte injury in this model of PKD.

TH-PO603

Inhibition of PLK1 Delays Cyst Growth in Autosomal Dominant Polycystic Kidney Disease Xia Zhou, Guangqiang Ma, Xiaoyan Li, James P. Calvet, Xiaogang Li. *University of Kansas Medical Center, Kansas City, KS.*

Background: The G2/M DNA damage checkpoint serves to prevent the cell from entering mitosis with genomic DNA damage. G2-phase transition is dependent on the activity of the Cyclin B-cdc2 complex which is regulated by CDC25 phosphatases, CDC25B and CDC25C. Polo-Like Kinase 1 (PLK1) is a major kinase with pivotal roles in multiple aspects of cell division (mitosis) by activating CDC25. However, the roles of PLK1 and CDC25B/C in cystogenesis in ADPKD remain elusive.

Methods: To understand dysregulated signaling pathways in cystic kidneys, we performed RNA-seq and Ingenuity Pathway Analysis (IPA). To explore the roles of PLK1 and CDC25B in regulating cyst growth, we targeted PLK1 in *Pkd1* mutant cells and mice with a PLK1 inhibitor volasertib.

Results: We found that DNA damage response was increased in *Pkd1* mutant PN24 cells and kidneys of *Pkd1*$^{flox/flox}$*:Tamoxifen-Cre* mice by phospho-H2AX staining. Our RNA-seq and IPA analysis indicated that the genes related to the cell cycle G2/M DNA damage checkpoint regulation pathway, including PLK1, CDC25B and CDC25C, were upregulated and activated in cystic kidneys compared to those in wild type kidneys. The upregulation of PLK1, CDC25B and CDC25C was confirmed by qRT-PCR, western blot and immunohistochemistry (IHC) staining in cystic kidneys versus controls. Treatment with the PLK1 inhibitor volasertib and the CDC25 inhibitor NSC663284 decreased cystic renal epithelial cell proliferation as examined by MTT assay. We also found that volasertib treatment increased the expression of p21, phospho-CDK2, active caspase 3, and cleaved PARP expression, and decreased the phosphorylation of ERK, S6 and Rb in PN24 cells. Furthermore, treatment with volasertib delayed cyst growth in *Pkd1* conditional knockout mice. Volasertib treatment decreased cyst lining epithelial cell proliferation as examined by PCNA and Ki67 staining, decreased the phosphorylation of ERK, S6, STAT3 and Rb, but increased cyst lining epithelial cell apoptosis as examined by TUNEL assay in cystic kidneys.

Conclusions: The cell cycle G2/M DNA damage signaling pathway is dysregulated in ADPKD. Inhibition of PLK1 produces a potent anti-proliferative and pro-apoptotic effect, regulates the known PKD associated pathways in cystic renal epithelia, and delays cyst growth *in vivo*, which suggests that targeting PLK1 may be a potential therapeutic strategy for ADPKD treatment.

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TH-PO604

Effects of Smoking on Pkd1-Deficient Cystic Mice: An Extended Study on the Renal and Cardiac Phenotypes Marciana V. Sousa,[1] Andressa G. Amaral,[1] Bruno E. Balbo,[1] Fernanda S. Messias,[1] Marcelo D. Melo,[2] Renato A. Hortegal,[2] Isac D. Castro,[1] Vera M. Salemi,[2] Luiz F. Onuchic.[1] *[1]Nephrology and Molecular Medicine, University of Sao Paulo, Sao Paulo, Brazil; [2]Cardiopneumology, University of Sao Paulo, Sao Paulo, Brazil.*

Background: Previous studies have shown that heavy smoking increases the risk of advanced chronic kidney disease and that smoking raises the risk of progression to ESKD in men with ADPKD.

Methods: Cystic *Pkd1*$^{flox/flox}$*:Nestin*^{cre} and noncystic *Pkd1*$^{flox/flox}$ mice were exposed to cigarette smoking (CYS and NCS, respectively) from conception to 18 weeks of life, twice a day, 30-min periods. Control groups also included cystic and noncystic mice not submitted to smoking (CY and NC, respectively). Renal function, cystic index and cell proliferation; cardiac function, including deformation (strain); body weight (BW); and kidney and heart apoptosis, fibrosis and weight were analyzed at 16-18 weeks.

Results: We showed in a 2016 ASN abstract that BUN was higher in CYS mice than CY and NC, and in NCS than NC, while no difference was detected between CYS and NCS. CYS kidneys developed increased cystic index, cell proliferation in cyst epithelium and fibrosis compared to CY. Higher tubular cell proliferation and fibrosis were found in NCS kidneys than NC. CYS animals had lower BW than CY and NC. In the present work we show increased apoptosis in CYS kidneys compared to NCS and NC, and in CY and NCS compared to NC. Renal weight/BW was higher in CYS mice than NCS and NC but not than CY. Cardiac apoptosis and heart weight/BW did not differ among the groups. Increased fibrosis was found in CYS hearts compared to NCS [1.10% (0.79-2.95) *vs* 0.26% (0.15-0.45), $p<0.05$] and NC ($p<0.01$), and in CY hearts compared to NC [0.82% (0.64-1.60) *vs* 0.21% (0.09-0.38), $p<0.05$]. Left ventricle ejection fraction was lower in CYS mice than NCS (35.6±15.1% *vs* 49.5±11.1%, $p<0.05$) and NC (*vs* 52.3±9.5%, $p<0.01$). CYS animals showed decreased circumferential strain and strain rate compared to CY, NCS and NC; lower values were also found in CY compared to NC. CYS and CY mice presented lower radial strain on the short axis than NC. Radial strain rate on the short axis and longitudinal strain were decreased in CYS and NCS animals in comparison to NC.

Conclusions: Our findings show that smoking worsened the renal and cardiac phenotypes of *Pkd1*-deficient cystic mice. Detrimental effects also affected noncystic animals. Our results suggest that smoking aggravates the kidney and heart phenotypes associated with ADPKD.

Funding: Government Support - Non-U.S.

TH-PO605

CMV Infection as a Trigger for APOL1-Associated Collapsing FSGS in Renal Allograft Leigh-Anne Dale,[3] Syed A. Husain,[3] Jae Hyung Chang,[3] Russell J. Crew,[1] David J. Cohen,[2] Mariana C. Chiles,[3] Yifu Li,[2] Ali G. Gharavi,[2] Sumit Mohan.[2] *[1]Columbia University, New York, NY; [2]Columbia University, New York, NY; [3]Columbia University Medical Center, New York, NY.*

Background: Apolipoprotein L1 gene (APOL1) risk alleles are associated with increased risk of focal segmental glomerulosclerosis (FSGS) in patients with 2 risk alleles (G1 or G2) compared to those with at least 1 wild type allele (G0). The mechanisms of APOL1-mediated renal disease remain unclear. While 13% of African Americans (AA) carry two APOL1 risk alleles and only a minority of these individuals develop kidney disease, this appears to contribute to inferior allograft outcomes with kidneys transplanted from AA donors. We present 2 cases of FSGS in transplanted kidneys from a donor with 2 APOL1 risk alleles.

Methods: The donor was a 57-year-old AA man with a history of hypertension who died from a stroke. Recipient 1 was a 47-year-old AA woman with diabetes-associated end stage renal disease (ESRD). Post-reperfusion biopsy was notable for mild focal global glomerulosclerosis. Post-operative course was notable for delayed graft function (DGF), and a nadir creatinine (SCr) of 1.6mg/dL. She subsequently developed proteinuria (6.7g/g) and elevated SCr (3.7) 7 months post-transplant in the setting of a diarrheal illness secondary to cytomegalovirus (CMV) infection. Viremia cleared with reduced immunosuppression. Repeat biopsy for persistent proteinuria showed tubular injury, and collapsing FSGS that led to allograft failure 18 months post-transplant. Recipient 2 was a 64-year-old Caucasian woman with ESRD from polycystic kidney disease. Post-operative course was notable for DGF, with a nadir SCr of 1.3mg/dL. She developed CMV viremia and colitis 12 months post-transplant that was followed by SCr rising to 2.9mg/dl with 7.6g/g proteinuria. Renal biopsy showed acute tubular injury and collapsing FSGS. Viremia cleared after mycophenolic acid was discontinued and ganciclovir was initiated. Allograft failed 14 months after transplant. While both the donor (G1/G1) and recipient 1 (G1/G1) had 2 APOL1 risk variants, recipient 2 (G0/G0) did not have any risk alleles.

Results:

Conclusions: This suggests that the genetic susceptibility for APOL1-related lesions is linked to the presence of donor risk alleles. Additionally, CMV infection appears to be a second hit resulting in the development of collapsing FSGS after transplant in kidneys with 2 risk alleles.

TH-PO606

A Girl with a Mutation of the Ciliary Gene CC2D2A Presenting with FSGS and Nephronophthisis Kazuya Matsumura,[1] Nariaki Asada,[1] Akinori Hashiguchi,[2] Kenjiro Kosaki,[3] Midori Awazu.[1] *[1]Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan; [2]Department of Pathology, Keio University School of Medicine, Tokyo, Japan; [3]Center for Medical Genetics, Keio University School of Medicine, Tokyo, Japan.*

Background: It has been reported that mutations in the ciliary gene *TTC21B* and *NPHP4* cause familial FSGS. We report a girl with a mutation of the ciliary gene *CC2D2A* presenting with FSGS and nephronophthisis.

Methods: The patient is a 6-year-old girl with mental retardation, postaxial polydactyly, and ataxic breathing. She was diagnosed as having compound heterozygous *CC2D2A* missense mutation at age 5. In retrospect, azotemia at 1 year and proteinuria at 5 years were recorded but unnoticed at local hospitals. At age 6, she was referred to pediatric nephrology service. Height was 106 cm (-1.5 SD), weight 12.6 kg (-2.3 SD), and BP 116/53 mmHg (>95th percentile). She had pretibial pitting edema. Urinalysis showed protein 3+, blood 2+, granular cast +, protein to creatinine ratio (pro/Cr) 6.6 g/gCr, ß2 microglobulin 112 μg/l, NAG/Cr 33 U/gCr, and selectivity index 0.09. Blood test revealed Hb 13.2 g/dl, UN 23.2 mg/dl, Cr 0.56 mg/dl (eGFR 66 ml/min/1.73 m^2), cystatin C 1.34 mg/l, total protein 5.3 g/dl, albumin 2.4 g/dl, cholesterol 317 mg/dl, and uric acid 7.5 mg/dl. Serologic tests for glomerulonephritis were negative. Ultrasonography showed normal-sized kidneys with a cyst in the right. Losartan was started for hypertension and proteinuria. Open renal biopsy was performed. On light microscopy, 8 out of 24 glomeruli were globally sclerosed, and 3 showed segmental sclerosis or hyalinosis. Mild tubular dilatation, tubular atrophy, and interstitial fibrosis were observed. No immune deposits were seen. On electron microscopy, glomeruli showed foot process effacement with no electron dense deposits. Since losartan did not exert an obvious effect, treatment with prednisolone was tried. Urine pro/Cr decreased to 3.7 g/gCr, but prednisolone was discontinued after 10 days because she developed duodenal ulcer perforation that necessitated omentoplasty. CT scan performed then showed bilateral multiple cysts in the kidney. Since then she had been treated with losartan and dipyridamole. Her renal function rapidly deteriorated. Current serum creatinine is 2.6 mg/dl with urine pro/Cr 13 g/gCr.

Results:

Conclusions: Based on the clinically overt nephrotic syndrome and foot process effacement, FSGS in this patient was thought to be due to podocytopathy associated with *CC2D2A* mutation, rather than subsequent to chronic injuries secondary to nephronophthisis.

TH-PO607

Not Just Sickle Nephropathy: Hematuria and Proteinuria in a Child with Hemoglobin SS Disease and Alport Syndrome Stephanie Lynch,[1] Elizabeth Yang,[3] Haresh Mani,[2] Patricia Seo-Mayer.[4,1] *[1]Inova Children's Hospital, Alexandria, VA; [2]Inova Fairfax Hospital, Falls Church, VA; [3]Pediatric Specialists of Virginia, Falls Church, VA; [4]Pediatric Specialists of Virginia (Inova-CNMC) and Georgetown University School of Medicine, Fairfax, VA.*

Background: Nephropathy is known complication of sickle cell disease but is seldom observed in young children. We report the case of a 9-year-old boy with Hemoglobin SS Disease, hematuria and proteinuria, who had concurrent Alport Syndrome. This case illustrates the value of targeted investigation in patients with primary conditions with known renal sequelae who demonstrate atypical presentation or progression. For our patient, this approach uncovered a second unrelated diagnosis.

Methods: A 4 month old African boy presented with fever, anemia, hematuria and proteinuria. He was diagnosed with urosepsis and Hemoglobin SS disease. Over time, hematuria and mild proteinuria persisted. He had normal blood pressure, albumin, creatinine, complements, and RBUS. Family history was negative for CKD. Sickle nephropathy was considered, and ACE-inhibitor was initiated for renoprotection. He later developed gross hematuria and worsened proteinuria in the context of fever and abdominal pain. Papillary necrosis and pyelonephritis were ruled out. Revised family history revealed a maternal male cousin with new hematuria, and a deaf maternal uncle who died in the Congo at an early age of kidney disease, raising suspicion for Alport Syndrome. Genetic testing revealed COL4A5 mutation (Exon 5, c.305_306dupGG), confirming X-linked Alports. Renal biopsy revealed abnormal GBMs with variable areas of thinning and thickening, and retained α1 but lack of staining for α3/α5 chains of type IV collagen.

Results:

Conclusions: This is an unusual case of a boy with two concurrent genetic diseases, both with known renal sequelae. Sickle nephropathy usually manifests in the 3rd decade of life, but our patient had early and persistent hematuria and proteinuria, resulting in diagnosis of Alports. Future management will be challenging. Alports will inevitably lead to ESRD, and ongoing vaso-occlusive crises and ischemia reperfusion injury will hasten progression. ACE-inhibitors are key, as they have shown benefit for both conditions, and hydroxyurea may reduce progression of sickle nephropathy. Stem cell transplantation may prove useful to mitigate CKD progression, but risks exist due to lack of a sibling-matched donor. In summary, this case describes a child with two indepedent and unrelated genetic causes of CKD, illustrating an exception to the rule of Occam's razor.

TH-PO608

Digenic Heterozygous Mutations in CEP164 and ALMS1 May Cause Nephronophthisis Haris F. Murad, Neera K. Dahl. *Yale School of Medicine, New Haven, CT.*

Background: Nephronophthisis is a cystic kidney disease that is the most common genetic cause of End Stage Renal Disease (ESRD) in the first three decades of life. It is a genetically heterogeneous disorder associated with extra renal manifestations (eyes, liver, bones, and central nervous system) in 15% of cases. Renal histology shows tubular basement membrane disruption and tubulointerstitial nephropathy. The cysts are usually in the corticomedullary junction and kidney size is normal or slightly reduced in contrast to polycystic kidney disease. Here we describe two cases with Nephronophthisis from novel genetic mutations.

Methods: A 51-year old lady presents with a gradually rising serum Creatinine up to 2.7mg/dL. Renal biopsy showed interstitial nephritis, and her ultrasound showed several scattered subcentimeter cysts and a 1.6 cm cyst. Whole exome sequencing showed heterozygous mutations in both the CEP164 and ALMS1 genes. Both mutations, CEP164, pL248fs, and ALMS1 pY1713X, resulted in the creation of a premature stop codon and are known to be pathogenic. MUC1 and UMOD were normal. The patient's sister has a history of cerebral palsy developed ESRD at the age of 30. Her CT abdomen shows innumerable bilateral renal cysts. Biopsy revealed interstitial nephritis as well. Whole exome sequencing is currently in process.

Results:

Conclusions: Nephronophthisis is a disorder in the normal functioning of primary cilia, which are sensory organelles detecting flow, osmotic, chemo and other stimuli and link them to cellular processes. A homozygous or compound heterozygous mutation in the CEP164 gene is known to cause NPHP15 which causes an alteration in DNA damage response signaling pathway. A mutation in ALMS1 gene causes abnormal ciliary structure in knockout mice. A homozygous or compound heterozygous mutation in this gene causes Alstrom syndrome which is a rare cause of renal failure associated with blindness, hearing loss, systemic fibrosis as well as hepatic, urologic and pulmonary dysfunction. To our knowledge, this is the first case of a clinical nephronophthisis phenotype caused by digenic pathogenic alleles rather than by a homozygous or compound heterozygous mutations in the above genes. It is possible that ALMS and CEP164 mutations have a complementary effect in exerting this phenotype.

TH-PO609

Functional Splicing Analysis in an Infantile Case of Atypical Hemolytic Uremic Syndrome Caused by Digenic Mutations in C3 and MCP Genes Tomohiko Yamamura,[2] Kandai Nozu,[2] Keita Nakanishi,[2] Junya Fujimura,[2] Shogo Minamikawa,[2] Hiroaki Ueda,[3] Rika Fujimaru,[3] Yuko Shima,[4] Koichi Nakanishi,[1] Hiroshi Kaito,[2] Kazumoto Iijima.[2] *[1]Graduate School of Medicine, University of the Ryukyus, Nishihara-cho, Japan; [2]Kobe University Graduate School of Medicine, Kobe, Japan; [3]Osaka City General Hospital, Osaka, Japan; [4]Wakayama Medical University, Wakayama City, Japan.*

Background: Atypical hemolytic uremic syndrome (aHUS) is a heterogeneous disease that is caused by defective complement regulation as reported in over 50% of cases. Up to now, pathogenic variants have been identified in various compliment related genes. Some reports also indicated that patients of aHUS with digenic inheritance of these genes might present more severe phenotype than monogenic inheritance. In addition, generally, transcript analysis is necessary for variants located outside of the splicing consensus sequence to assess the biological effect. However, this technique is often difficult for the influence of nonsense-mediated mRNA decay (NMD) for the products of truncating variants and quantity of mRNA of sample.

Methods: Here we report an infantile case with aHUS from unrelated parents. Targeted resequencing detected a reported variant of *C3* gene and a novel intronic variant of *MCP* gene (c.97 + 5 G>A, IVS1 + 5 G>A), on maternal and paternal alleles respectively. These variants were thought to be working digenically since there was early onset in this patient although the parents were asymptomatic. However, the pathogenicity of a variant in *MCP* gene was unknown because this is a novel variant and located outside apparent splice consensus sequence. To assess the pathogenicity of a novel intronic variant of *MCP* gene, we tried to detect abnormal splicing variant by standard transcriptional analysis using mRNA extracted from peripheral blood. However, we obtained only normal splicing variant from maternal allele and transcript from paternal allele was missing. Then, we conducted functional splicing assay using minigene construction to detect abnormal splicing caused by c.97 + 5 G>A variant and quantitative mRNA PCR to confirm the result. As a result, it was revealed that the paternal allele of *MCP* gene with c.97 + 5 G>A variant did not produce any transcript as confirmed by qPCR and minigene splicing assay. These results lead us to conclude *MCP* gene c.97 + 5 G>A was pathogenic.

Results:

Conclusions: A combination of minigene assay and quantitative analysis is non-invasive and useful as methods for functional splicing assay of inherited diseases even if standard transcriptional analysis could not detect abnormal splicing.

TH-PO610

Upshaw–Schulman Syndrome Muhammad Afzal,[2] Krishna M. Baradhi.[1] *[1]None, TULSA, OK; [2]OU Tulsa, Tulsa, OK.*

Background: Hereditary Thrombotic Thrombocytopenic Purpura (TTP) is an extremely rare life threatening disorder characterized by thrombotic microangiopathy caused by severely reduced activity of the von-Willebrand factor-cleaving protease ADAMTS13. It is characterized by small-vessel platelet-rich thrombi that cause thrombocytopenia and microangiopathic hemolytic anemia.

Methods: A male infant who was cyanotic at birth was found to have thrombocytopenia of 18000/microliter presumed to be from sepsis as it improved with platelet transfusion and antibiotics. This was followed by recurrent hospitalizations every few years either for diarrhea or anemia or renal failure in the context of severe thrombocytopenia. However, each time, he was misdiagnosed as Evan's syndrome or Hemolytic uremic syndrome(HUS) until he succumbed to stroke at the age of 18 years. This time, as he had classical features of TTP in the form of stroke, anemia, renal failure and thrombocytopenia, an evaluation for TTP was initiated. His ADAMTS 13 activity came back as < 10% without the inhibitor. Genetic testing showed biallelic mutations in the *ADAMTS13* gene. Both parents were carriers. He was diagnosed with Hereditary TTP and was started on monthly plasma infusions. His renal function eventually deteriorated by the age of 31 years requiring dialysis. He continues to have monthly plasma infusion and is relatively doing well.

Results:

Conclusions: Hereditary TTP also known as Upshaw–Schulman Syndrome is an autosomal recessive condition caused by biallelic mutations in *ADAMTS13*. It represents <5 percent of all TTP cases. Clinical features are similar to acquired TTP or other thrombotic microangiopathies often leading to patients being misdiagnosed as having ITP, HUS, HELLP, or Evan's syndrome. Hereditary TTP should be considered in any one who presents with microangiopathic hemolytic anemia and thrombocytopenia in infancy, childhood or pregnancy. The diagnosis is made by demonstration of severe ADAMTS13 deficiency without an inhibitor and confirmed by demonstration of *ADAMTS13* gene mutation(s). Without appropriate diagnosis and treatment, it can be life threatening. Treatment of an acute episode with plasma infusion should not be delayed while confirming the diagnosis. Plasma infusion is the treatment of choice rather plasma exchange. Recombinant ADAMTS13 is under development. All siblings of an individual with hereditary TTP should be tested.

TH-PO611

A Case of Lesch-Nyhan Syndrome in an Adult Presenting with AKI

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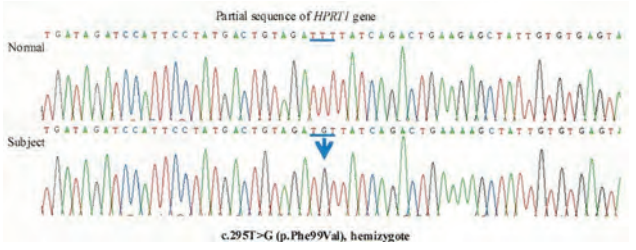
Background: Lesch-Nyhan syndrome (LNS) is a rare X-linked disorder caused by a deficiency of the enzyme hypoxanthine-guanine phosphoribosyl transferase (HPRT) and underlying HPRT gene mutations. When the enzyme HPRT is nonfunctional, substrates accumulate and are converted to uric acid by the action of xanthine-oxidase. LNS diagnosis is based on clinical symptoms and hyperuricemia, together with neurological evaluation of mental function, molecular testing for pathogenic mutations, and enzymatic analysis for HPRT function.

Methods: We report a case of LNS in a 26-year-old man, who presented with acute kidney injury and excessive hyperuricemia. He had a 7-year history of gout. He had tophectomy for gouty arthritis on left ankle 3 months ago and was taking aceclofenac (NSAID) from then on. He had a 3-year history of dystonia. Mutation analysis and enzyme assay revealed a mutation of exon 3 of the HPRT gene (c.295T>G (p.Phe99Val)) and total deficient HPRT confirming the diagnosis of LNS. His renal function and serum uric acid level improved after hydration and allopurinol treatment.

Results:

Conclusions: The diagnosis of LNS in adults is extremely rare. We report a case of LNS in a 26-year old man, who presented with acute kidney injury and excessive hyperuricemia, with molecular diagnosis.



TH-PO612

Proteinuric Renal Injury in an Adolescent with a Distal Partial Trisomy Chromosome 1

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Background: Distal partial trisomy 1q is a rare disease, with no previous case reports of renal insufficiency occurring in relation to this chromosomal disorder. We report a case of distal partial trisomy 1q that showed proteinuric renal injury.

Methods: We treated a 17-year-old adolescent with clinical features of low birth weight, mild mental retardation, and mild deafness. When he was 13 years old, he was diagnosed as having a partial trisomy of chromosome 1 from q32.1 to 41 using chromosomal and microarray tests. He showed persistent proteinuria since age 16 and underwent medical check-up at our hospital. Proteinuria was estimated to be approximately 1-2 g/day, although serological examination revealed no abnormal findings. Computed tomography detected no morphological abnormalities of the kidneys other than their slightly small size. Renal biopsy showed no evidence of immune-mediated glomerular diseases, but revealed a very low glomerular density and glomerulomegaly, as evidenced by a marked increase in the estimated mean glomerular volume (10.3×10^6 μm^3). Combination therapy with dietary sodium restriction, body weight reduction, and the administration of losartan potassium markedly reduced his proteinuria to 0.3 g/day.

Results:

Conclusions: The section of partial trisomy found in this case does not include podocyte-related genes that have been related to proteinuric renal injuries. Thus, in this case, the mismatch between congenital reduction in the number of nephrons due to low birth weight and catch-up growth of whole body size may have resulted in glomerular hyperfiltration and renal injury. Renal prognosis is poor in patients with a history of low birth weight, which is sometimes complicated in patients with genetic comorbidities. In such patients, where the renal prognosis has not been studied well, continuous follow-up is necessary to evaluate renal complications and inhibit progression of renal disease.

TH-PO613

Headache and Diplopia in a Patient with Nephropathic Cystinosis

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Background: Nephropathic cystinosis is a lysosomal storage disease resulting in the accumulation of cystine, development of Fanconi syndrome, and progression to end-stage renal disease. Extrarenal manifestations of cystinosis affecting the endocrine, muscular, and ophthalmologic systems have been well described. However, idiopathic intracranial hypertension (IIH) is a rare and poorly understood condition associated with cystinosis.

Methods: A 33 year old female with nephropathic cystinosis three years status post living donor kidney transplant on immunosuppressive therapy had been experiencing one month of headache, diplopia, and nausea. Approximately one and a half years prior to presentation, she had switched from cysteamine bitartrate (Cystagon) to extended release cysteamine bitartrate (Procysbi), both of which are cystine depleting agents. Four months prior to presentation, her WBC cystine level was subtherapeutic, and her Procysbi dose was increased. Dilated retinal exam revealed bilateral optic disc swelling and right optic disc hemorrhage. Additional workup revealed an elevated lumbar CSF opening pressure with unremarkable MRI and MRV consistent with IIH. Her symptoms and papilledema improved with acetazolamide, discontinuation of Procysbi, and resumption of Cystagon.

Results:

Conclusions: There is a known increased incidence of IIH in individuals with cystinosis; although, the underlying cause is unknown. Potential etiologies include decreased CSF reabsorption secondary to crystal deposition or increased thrombotic risk secondary to renal disease. Additional risk factors such as immunosuppressive therapy, growth hormone supplementation, and renal transplant have been associated with IIH, but no study has correlated a specific risk factor with development of IIH in patients with cystinosis. Procysbi is reported to have a more favorable side effect profile and less medication noncompliance compared to Cystagon due to twice rather than four times daily dosing. However, in the setting of subtherapeutic WBC cystine levels with Procysbi, the patient developed IIH. This case highlights the rare, but known, association between cystinosis and IIH, and encourages clinicians to consider this diagnosis in patients with cystinosis presenting with headache and vision changes.

TH-PO614

Moyamoya Disease – A Rare Association of Autosomal Dominant Polycystic Kidney Disease

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Background: Moyamoya disease is an idiopathic progressive vaso-occlusive disorder of the intracranial arteries located at the base of the brain that can predispose to stroke. Although cerebral aneurysms and other vascular abnormalities are well described in autosomal dominant polycystic kidney disease (ADPKD), co-incident Moyamoya syndrome and ADPKD has only previously been reported on two occasions.

Methods: A 29-year old Romanian woman presented with a 3 days of headache and right hemiparesis. She was a smoker with a history of untreated hypertension. Her mother, sister and maternal uncle also had ADPKD. No family member had a history of intracranial aneurysms. MRI Brain with contrast revealed a left middle cerebral artery (MCA) territory subcortical infarct, with established infarcts in the right caudate nucleus, left internal capsule and left parietal lobe. Digital Subtraction Angiography confirmed no flow in the MCAs bilaterally with good flow in distal ICAs, ACAs and PCAs bilaterally, multiple collateral vessels consistent with Moyamoya disease. She had a renal ultrasound as part of her work up for hypertension and this revealed bilateral cystic changes consistent with polycystic kidney disease.

Results:

Conclusions: The coexistence of these malformations suggests a common genetic background predisposing to these structural abnormalities. Although the genetic contribution in Moyamoya is indisputable, its cause remains uncertain. In this case, alterations in the arterial wall may be linked to the PKD1 or PKD2 genes, expanding the phenotypic variability of ADPKD and providing insight into the pathogenesis of Moyamoya.

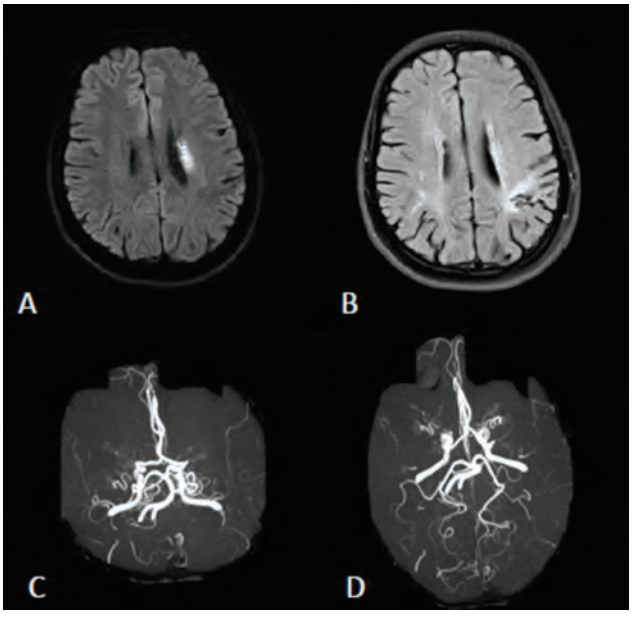


Figure 1: A: MRI DWI shows acute left MCA subcortical infarct. B: Flair sequences reveal MCA-PCA watershed infarcts C+D: Bilateral proximal M1 MCA occlusions with collateralization

TH-PO615

Painful Cyst Hemorrhage with Trivial Trauma in Tuberous Sclerosis Complex with Angiomyolipomas without Nephromegaly – A Case Report Jaime A. Baynes-Fields, Myriam C. Vela-Ortiz, Sandeep Aggarwal. *Drexel University College of Medicine, Philadelphia, PA.*

Background: Tuberous sclerosis complex (TSC) is characterized by renal angiomyolipomas and cysts which have the potential to be complicated by hemorrhagic and malignant conversion. Cyst hemorrhage in such cases may happen spontaneously or by trivial trauma due to their highly vascular nature.

Methods: We present a case of a 25 year old male with TSC with subependymal giant cell astrocytoma, seizure disorder, ash leaf spots, bicuspid aortic valve with cardiac rhabdomyoma, multiple renal angiomyolipomas and cysts, hypertension, and CKD stage 1. On a follow up visit, patient presented with right flank pain of one week duration. Patient's symptoms were preceded by a motor vehicle accident, characterized by sudden deceleration of his vehicle without bodily impact. Patient denied hematuria, lower urinary tract symptoms, or change in urine output. Pertinent physical examination –blood pressure 126/72 mmHg, pulse 85 per minute, right flank tenderness, remainder of physical exam at baseline. Work up – gadolinium enhanced MRI: hemorrhagic conversion of large cystic lesion (1.4cm) as well as increasing angiomyolipomas with stable renal size (right 11.33cm, left 11.2cm). Patient's renal function remained stable with baseline creatinine 0.66mg/dL, trace proteinuria, no hematuria on dipstick, and 5mcg/mg microalbumin to creatinine ratio. Conservative treatment was provided with pain control and oral hydration given hemodynamic and laboratory stability. Patient improved clinically in follow up.

Results:

Conclusions: Cystic nephropathies with nephromegaly present a high risk of hemorrhagic conversion due to fragility and lack of protection by our thoracic cage. TSC with angiomyolipomas present a higher risk due to pathological vascular aneurysms even without nephromegaly, which is emphasized in this case. Hemorrhagic risk of angiomyolipomas are approximately 25-50% and may lead to circulatory shock. Frequent assessment of patient's symptoms and history, especially related to physical trauma should be sought during each visit. Emphasis should be laid on seizure control, preventative measures and patient education of avoidable injury with immediate follow up after such an event which could be life threatening.

TH-PO616

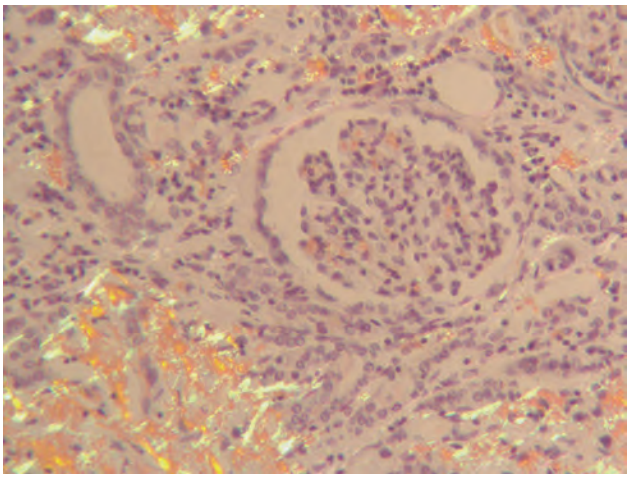
LECT2 Amyloidosis – An Entity in Elderly Hispanics with Distinct Pathologic Features Nilin Raj, William L. Whittier, David J. Cimbaluk. *Rush University Medical Center, Chicago, IL.*

Background: Leukocyte chemotactic factor 2 amyloidosis (ALECT2), discovered in 2008, is characterized by renal and liver involvement. It mainly affects elderly Hispanics and typically presents with a bland urine, subnephrotic proteinuria, and progressive CKD. Histologically, ALECT2 has a preferential interstitial involvment. Diagnosis is made by liquid chromotagraphy mass spectrometry (LC/MS) of affected tissue.

Methods: A 71 y/o Mexican man presented with a 2 month history of gross hematuria. PMHx includes recently diagnosed DM II. His vitals and exam were unremarkable. Creatinine (SCr) 3.8 mg/dl, K+ 5.4 mmol/L, Hgb 6.3 g/dl. UA grossly red, 1+ protein, large blood, and >300 RBCs. Renal U/S: left renal mass with adjacent lymphadenopathy and blood clots in the bladder. Left radical nephrectomy was consistent with sarcomatoid renal cell carcinoma but the renal cortex revealed tubulointerstitial amyloidosis. Amyloid A stain (-). Immunofluorescence without light chain restriction. EM with characteristic fibrils. Serum/urine immunofixation nl. Serum free κ 8.6, λ 4.5 mg/dl (ratio of 1.9), consistent with CKD. Echo and bone scan were nl. LC/MS confirmed LECT2 type amyloidosis. Following curative surgery, his hematuria resolved and his SCr stabilized at 1.8 mg/dl. Urine p/c ratio 593 mg/g. He was placed empirically on colchicine and at one year follow up his SCr is 1.8 mg/dl.

Results:

Conclusions: ALECT2 is an emerging disease that predominantly affects pts of Hispanic ethinicity. Its characteristic demographic predilection and tubulointerstitial involvement should raise suspicion of this disease and alert one to perform LC/MS. Our pt's diagnosis was discovered by examination of a nephrectomy specimen and confirmed by LC/MS. Althouth there are no known treatments, colchicine impairs chemotaxis of leukocytes and on this therapy his SCr remains stable at one year.



Congo red stain: apple green birefringence under polarized light in the interstitium, sparing the glomerulus.

TH-PO617

Predominantly Vascular AL Amyloidosis Mimicking Vascular Hyalinosis on Renal Biopsy – A Diagnostic Pitfall Anthony F. Iluyomade,[1] Niti Madan,[2] Kuang-Yu Jen.[2] *[1]University of California Davis Medical Center, Sacramento, CA; [2]University of California, Davis, Sacramento, CA.*

Background: Vascular-limited renal amyloidosis accounts for ~5% of AL amyloidosis cases. In this form, patients often present with minimal proteinuria, making the diagnosis clinically challenging. Histologically, vascular hyalinosis mimics vascular amyloidosis and may lead to errors in diagnosis, especially in elderly patients with a history of hypertension where chronic vascular disease is expected on biopsy.

Methods: An unusual case of predominantly vascular AL amyloidosis with nephrotic range proteinuria and histologic appearance indistinguishable from vascular hyalinosis is presented. A 75-year-old male was noted to have normal serum creatinine but nephrotic range proteinuria. Physical examination was significant for anasarca. Further work-up showed elevated serum free light chains with lambda predominance. A kidney biopsy was performed to characterize renal involvement. The biopsy contained 12 glomeruli, 2 of which were globally sclerotic. All the non-sclerotic glomeruli showed normal histology with no evidence of amyloid deposition. Severe chronic vascular disease was noted with prominent arteriosclerosis in larger caliber vessels. Smaller caliber vessels including small arteries and arterioles exhibited mural deposition of hyaline-like material that stained strongly for PAS but showed minimal silver staining. Congo red stain revealed that this material within the vessels was positive, confirming vascular amyloid deposition. No Congo red staining was seen in any of the glomeruli. Ultrastructural examination confirmed the widespread presence of amyloid within the vessels. Rare and minimal amyloid deposition was noted in the glomerular capillary loops and mesangium. He was started on CYBORD (Cyclophosphamide, Bortezomib and Dexamethasone), a repeat serum immunofixation showed undetectable overt evidence of monoclonal protein.

Results:

Conclusions: This case of predominantly vascular renal amyloidosis was indistinguishable from vascular hyalinosis based on routine light microscopic stains for renal biopsy, showing similar intense PAS positivity in the amyloid as normally seen in hyaline arterio- and arteriolosclerosis. However, Congo red stain and electron microscopy confirmed the presence of amyloid. Vascular-limited or predominantly vascular renal amyloidosis can be mistaken for vascular hyalinosis in such instances, resulting in a diagnostic pitfall.

TH-PO618

Gelsolin Amyloidosis (Familial Amyloidosis of Finnish Type) in a North American Kindred Hassan A. Salameh,[1] Aneel A. Ashrani,[2] Matthew Howard,[1] Lynn D. Cornell,[1] Marie C. Hogan.[1] *[1]Mayo Clinic, Rochester, MN; [2]Mayo Clinic, Rochester, MN.*

Background: Gelsolin amyloidosis is a rare form of systemic amyloidosis characterized by lattice corneal dystrophy, cranial nerve neuropathies and elastolysis. Renal involvement with nephrotic syndrome is rare. Early onset severe kidney disease has been reported in homozygotes and late onset slowly progressive forms in heterozygotes. It is usually caused by a gelsolin gene defect, namely a G640A previously known as G654A or G654T mutation.

Methods: We report a 74-year-old man presenting with CKD3 and nephrotic syndrome (NS). Medical history was significant for hypertension and lattice corneal dystrophy type II (LCD II) and family history of LCD II (son, mother, two maternal uncles and maternal aunts, (all of Lithuanian-Finnish heritage)) and no family history of kidney disease. Exam showed periorbital and ankle edema. Serum creatinine was 2.1 mg/dL with eGFR 33 mL/min/1.73 m2 and 5.6 g proteinuria/24h. SPEP and UPEP were negative. Free light chains were mildly elevated. Kidney biopsy (KB) showed minimal Congo red positivity along

with immunofluorescence findings revealed amyloidosis of undetermined type. Electron microscopy showed 10.8 nm fibrils focally replacing the glomerular basement membrane. No additional KB material was available for laser microdissection (LMD) and mass spectroscopy (MS). MS proteomics of fat aspirate material (with equivocal Congo red stain) typed the most abundant peptides were from GELS_HUMAN with p.D214N AA change identified. A heterozygous pathogenic variant c.640G>A (g.124073097; p.D214N also known as p.D187N) in the GSN gene was confirmed by Sanger sequencing consistent with familial amyloidosis Finnish type.

Results:

Conclusions: Our patient had an unusual presentation with renal and ophthalmic involvement and no neurologic or dermatologic manifestations. This report highlights (1) importance of MS evaluation in atypical amyloidosis cases (2) implications for management (therapies are now in pre-clinical studies) (3) genetic counseling implications for families; heterozygous cases have late onset slowly progressive disease and (4) in cases where there is insufficient KB tissue for MS analysis, fat aspirate material (a relatively minimally invasive procedure) permitted confirmation.

TH-PO619

Renal-Limited Fabry Disease with Negative Genetic Screening

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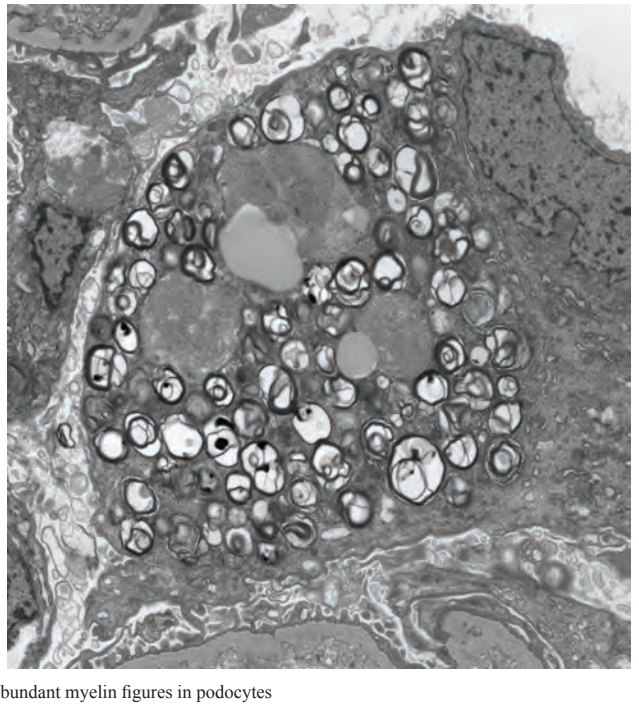
Background: Fabry disease(FD) is an X-linked lysosomal storage disorder caused by deficient α-galactosidase A(α-GLA) activity. Female carriers disease severity is substantially dependent on random inactivation of X chromosome.

Methods: A 65year old female with history of hypertension was evaluated for lower extremity edema, proteinuria and serum creatinine (SCr) of 1.2mg/dL. Kidney biopsy showed mild mesangial hypercellularity and myelin figures in few podocytes. Genetic testing for FD was negative. No history of supplement use, exposure to silica or amiodarone. Her mother was diagnosed with focal segmental glomerulosclerosis(FSGS) at age 69 and started dialysis 2 years later. Despite treatment with antihypertensive over 4 years her SCr increased to 1.7 mg/dL. She was referred to Mayo Clinic for further evaluation. On exam she had trace edema, no neuropathy or skin changes and normal ophthalmology evaluation. Proteinuria was 6.1g/24h. Second kidney biopsy showed FSGS pattern of injury, severe hypertensive arteriosclerosis and abundant myelin figures in podocytes(PC). Repeat FD genetic testing was negative. Magnetic resonance cardiac and brain imaging showed no FD features. Serum α-GLA was normal 35(>23.1nmol/h/mg). Urine Globotriaosylceramide(GL3) was 0.019 mg/mmol Creatinine(control <0.030). However urine globotriaosylsphingosine(Lyso-GL3) was elevated at 12.3 ng/mmol Creatinine(Fabry range 0.4-356.6).

Results:

Conclusions: This is a case of a renal-limited FD in a female patient apparently superimposed on familial FSGS. Myelin inclusions in some but not all PC is consistent with finding in females with FD. Genetic testing was negative as has been reported in, especially in females. It highlights the importance of measurement of Lyso-GL3/Gb3 in cases where genetic mutation can't be found.



Abundant myelin figures in podocytes

TH-PO620

An Unusual Case of Presumed Lecithin-Cholesterol Acyltransferase Inhibitor

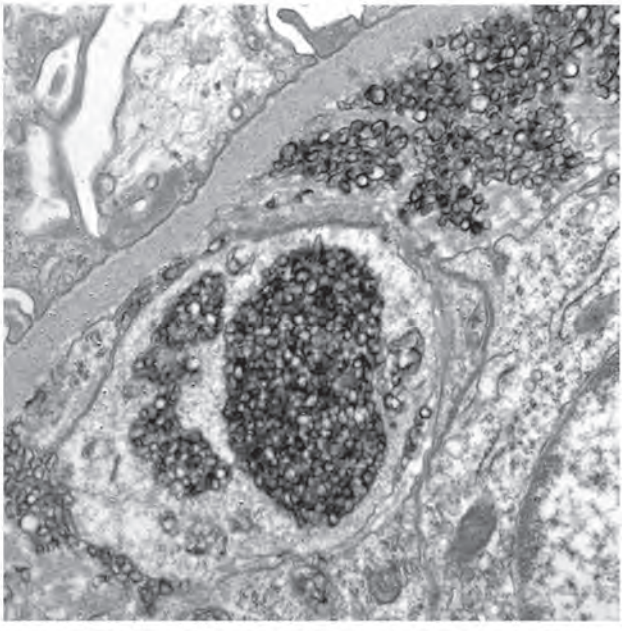
Mohammad Katout,[3] Lynn A. Fussner,[5] Sergey V. Brodsky,[2] Tibor Nadasdy,[4] Isabelle Ayoub.[1] *[1]None, Columbus, OH; [2]OSU, Columbus, OH; [3]OSU Nephrology, Columbus, OH; [4]Ohio State University, Columbus, OH; [5]The Ohio State University Wexner Medical Center, Columbus, OH.*

Background: Lecithin-cholesterol acyltransferase (LCAT) is a glycoprotein produced predominantly by the liver. LCAT binds mainly to HDL particles and contributes to HDL maturation and cholesterol homeostasis. LCAT deficiency is a rare autosomal recessive disease, however an immune-mediated, acquired form has been reported. In both situations lipoprotein deposition in the glomeruli may lead to end stage kidney disease. This case illustrates the challenge of managing acquired LCAT deficiency when the underlying etiology is unclear.

Methods:

Results: A 27 *y* old woman transferred to our center for worsening shortness of breath over 2 months. She already received 1g of rituximab and was on prednisone for concerns of an underlying auto-immune disease. Diagnostic work up was significant for AKI, hemolytic anemia, thrombocytopenia, hyperbilirubinemia, high ferritin, low HDL (3mg/dl), + ANA,+ SSA and bilateral pulmonary infiltrates. Kidney biopsy showed lipoprotein deposits in the widened sub-endothelial space with some mesangial and intracellular deposits(see figure). Some features of TMA were noted. Lung biopsy showed NSIP and isolated intravascular foreign material. LCAT activity was checked, but after rituximab infusion and having been on prednisone for 2 weeks, and it was normal. LCAT genetic testing didn't show sequence variants. The patient was continued on high dose prednisone. Cytopenia and hyperbilirubinemia resolved. Her HDL level began normalizing (up to 20 mg/dl) and AKI resolved. She had a mild improvement in respiratory symptoms.

Conclusions: Immune-mediated acquired LCAT deficiency may be difficult to diagnose. In this case clues to the presence of an inhibitor of LCAT included response to steroids and negative genetic testing. Confirming an underlying auto-immune disease remains a challenge for future decisions regarding immunosuppressive therapy to prevent further organ damage.



Mesangial lipoprotein deposits

TH-PO621

An Unusual Cause of Nephrotic Syndrome: LCAT Deficiency

Melissa Makar,[2] Eugene C. Kovalik.[1] *[1]Duke University Medical Center, Durham, NC; [2]Duke University Medical Center, Durham, NC.*

Background: Lecithin-cholesterol acyltransferase (LCAT) deficiency is an autosomal recessive disorder in which cholesterol cannot be esterified on high-density lipoprotein (HDL). The subsequent accumulation of unesterified cholesterol leads to kidney failure. Although it mainly affects those of European decent, we present two cases in African-Americans.

Methods: In Case 1, a 30 year old African-American female was evaluated for proteinuria and hematuria seen on routine urinalysis during a pre-operative evaluation. She had lower extremity edema; an estimated glomerular filtration rate (eGFR) of 115 ml/min/1.73m^2; and 9 grams of proteinuria on 24 hour urine collection. Her serologies were negative; and on kidney biopsy, her light microscopy showed vacuolization of her capillary loop basement membranes while her electron microscopy showed subendothelial, intermembranous, and mesangial deposits of lamellated, myelin-figure lipid material along with mesangial and endocapillary foam cells. In support of LCAT deficiency, her HDL and serum cholesteryl levels were very low at 8 mg/dl and 13%, respectively.

Unfortunately, as expected with LCAT deficiency, she progressed to end-stage kidney disease at age 36 despite blood pressure control with an angiotensin-converting enzyme inhibitor (ACEI). Two years later, she underwent a deceased donor kidney transplant and was doing well at last check. In Case 2, a 69 year old African-American female with a longstanding history of dyslipidemia was seen for a HDL of less than 5 mg/dl. A low serum cholesteryl ester level of 15% confirmed her diagnosis. At the time, her eGFR was 102 ml/min/1.73m^2 and she had no proteinuria while on three anti-hypertensive agents including an ACEI. Over the past seven years, her eGFR has fallen to 52 ml/min/1.73m^2 and she has developed proteinuria of 4 grams on spot check. A subsequent full evaluation was otherwise negative, and she is followed closely as an outpatient.

Results:

Conclusions: Although rare, LCAT deficiency should be included in the differential for nephrotic syndrome in all persons with a low HDL. The diagnosis can be made by low serum cholesteryl ester levels; kidney biopsy shows diffuse foam cells and lipid deposits. Current treatment is supportive care.

TH-PO622

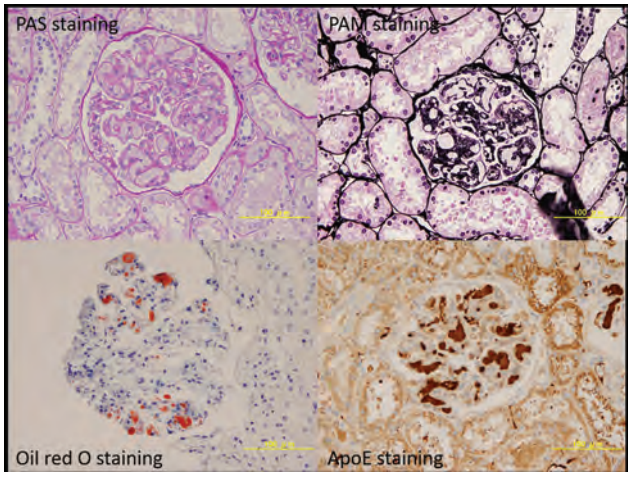
A Case of Lipoprotein Glomerulopathy Which Achieved Remission by Bezafibrate Monotherapy Manabu Kanda,[5] Mitsuhiro Sato,[1] Satoru Sanada,[4] Hiroshi Sato,[2] Toshinobu Sato,[1] Yoshio Taguma.[3] *[1]Japan Community Health care Organization Sendai Hospital, Sendai, Japan; [2]Clinical Pharamacology and Therapeutics, Graduate School of pharmaceutical Sciences, Tohoku University, Sendai, Japan; [3]Japan Community Health care Organization Sendai Hospital, Sendai, Miyagi, Japan; [4]Japan Community Health Care Organization Sendai Hospital, Sendai, Japan; [5]Japan Community Health care Organization Sendai Hospital, Sendai, Japan.*

Background: Lipoprotein glomerulopathy (LPG) is a rare hereditary renal disease with a relatively rapid progression to renal failure, accompany with proteinuria, hyperlipidemia, and lipoprotein thrombi in glomeruli. The first LPG case was reported in 1989, then our facility firstly reported efficacy of intensive therapy with combination of three lipid-lowering agents, which decreased proteinuria by removal of lipoprotein thrombi in 2000. In this report, we show that even fibrate monotherapy could ameliorate proteinuria in patients with LPG.

Methods: A 38-year-old Japanese man was admitted with a 10-year history of proteinuria. None of his family has renal disease or dyslipidemia. His body mass index was 17.8, and blood pressure was 140/90 mmHg. He has no corneal opacity, xanthoma nor leg edema. Laboratory tests showed urine protein 1.30 g/day, serum creatinine 0.80 mg/dL, total cholesterol 155 mg/dL, and the triglyceride 142mg/dL. Apolipoprotein profiles revealed B 66 mg/dL, normal range 73 to 109, and E 11.9 mg/dL, 2.7 to 4.3. Heterozygous ApoE-Sendai mutation was detected by DNA sequencing analysis. Renal Biopsy showed distinct dilatation of glomerular capillary lumina filled with lipoprotein thrombi which was positive for oil red O and apoE staining (figure). Bezafibrate monotherapy decreased proteinuria to less than 0.3 g/day in five months. Clinical remission has been lasted for 2 years, though the ApoE level was still high.

Results:

Conclusions: We experienced a LPG case without dyslipidemia and family history. The previous reports have shown the effectiveness of combination therapy multiple lipid-lowering agents, however, in our case even monotherapy with fibrate could decrease proteinuria and prevent disease progression.



TH-PO623

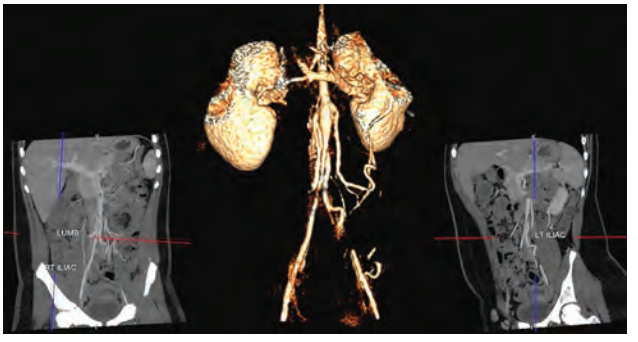
Hemihypertrophy versus Hemiatrophy: A Unique Presentation of Midaortic Syndrome Rachel Herdes, Nikita R. Patel, Cullen Clark, Isa Ashoor. *Pediatrics, Louisiana State University Health Sciences Center, New Orleans, LA.*

Background: Midaortic syndrome is the acquired or congenital narrowing of the abdominal aorta and associated branches. Patients often present prior to adolescence with severe hypertension (HTN), headaches, claudication, or abdominal angina. Treatment consists of multiple antihypertensive medications and often requires surgical intervention for adequate control. Left untreated, patients usually die in their 40s from malignant HTN.

Methods: Case report

Results: A previously healthy 10-year-old girl was referred to genetics for right-lower extremity (RLE) hemihypertrophy. She was incidentally noted to have severe HTN (180/100 mmHg) in clinic and was admitted to the ICU for BP control. She denied headaches, vision changes, or abdominal discomfort. Exam was notable for coarse facies, enlarged RLE compared to left lower extremity (LLE), and a paraumbilical bruit. ECHO demonstrated mild LVH. CRP, serum aldosterone, plasma renin activity, creatinine, and metanephrines were normal. Renal ultrasound showed elevated bilateral peak systolic velocities. Abdominal CT angiogram revealed significant vasculopathy with abdominal aorta narrowing and multiple stenotic areas along the main branches, including complete left common iliac artery occlusion with collateral flow (Figure 1). She was diagnosed with idiopathic midaortic syndrome and treated with amlodipine, atenolol and chlorthalidone. Genetics evaluation of vascular anomalies is pending.

Conclusions: We present an unusual case of unilateral anatomic asymmetry. While the patient had been given a diagnosis of RLE hemihypertrophy, it is more likely that she suffered from LLE hemiatrophy due to ischemia from midaortic syndrome. This case demonstrates the importance of pediatric HTN evaluation including thorough examination to identify abdominal bruits, extremity size discrepancy, or end-organ damage from severe HTN.



TH-PO624

Inconceivable! A Case of Hydralazine Induced ANCA Vasculitis and Alport's Syndrome Derian Lai, Natasha N. Dave, Rajeev Raghavan. *Baylor College of Medicine, Houston, TX.*

Background: Hydralazine induced ANCA associated vasculitis (AAV) is one of the earliest described drug induced vasculitides. The diagnosis is challenging due to the variety of clinical presentations. We present a patient who developed acute kidney injury due to Hydralazine induced AAV superimposed on Alport's syndrome.

Methods: A 53 year-old woman with atrial fibrillation, hypertension and a baseline creatinine of 2.3mg/dl (unknown etiology) presented to the hospital with 2 weeks of malaise, intractable vomiting and diarrhea. She was started on hydralazine 7 months ago. Her brother was on dialysis (unknown etiology). On admission she was afebrile with a blood pressure of 130/92. Her BUN was 189 mg/dl and creatinine was 16.6 mg/dl. Urinalysis had 600mg/dL of protein and >182 RBCs. Urine drug screen was negative. Immunologic serologies revealed: ANA titers of 1:2560 (homogenous pattern), complement levels (C3 71, C4 23), Anti –MPO antibody titers > 800AI (n<1), Anti-Proteinase 3 antibody titers 2.7 AI (n<1), and Anti-histone antibodies 7.1 U (n<1). On renal biopsy, the histology revealed characteristic findings of Alport's syndrome: loss of staining of alpha 3 and 5 chains of type 4 collagen; splitting of the lamina densa in the basement membrane. There was 60% interstitial fibrosis and tubular atrophy. No crescents or glomerular necrosis identified. ANCA serologies 1 week later showed persistently elevated titers (Anti PR3 1.2AI, Anti MPO >800AI). Despite lack of clear evidence of vasculitis on renal biopsy, we concluded patient had hydralazine induced AAV based on her clinical presentation and immunologic lab values. The patient's kidney function never recovered despite cessation of Hydralazine and immunosuppressive therapy.

Results:

Conclusions: We present a rare case of double glomerulonephropathy (DGN): Alport's and hydralazine induced AAV. DGNs are defined as pathologic confirmation of 2 coexisting glomerular diseases or superimposition of a second glomerulopathy onto an original glomerulopathy. One center reported Alport's as the original disease in 6 of 9 patients with DGN. There is no known association between Alport's and Hydralazine induced AAV.

Funding: Government Support - Non-U.S.

TH-PO625

Geller Syndrome: Two Cases of Hypertension and Hypokalemia in Pregnancy Vinay Mulkanoor, Sharon E. Maynard. *Lehigh Valley Health Network, Emmaus, PA.*

Background: In 2000, Geller et al described a familial syndrome of hypertension (HTN) and hypokalemia, exacerbated by pregnancy, caused by an activating mutation of the mineralocorticoid receptor (MR). Since this description, no further cases have been reported. Here we describe 2 patients with features consistent with Geller syndrome.

Methods: Case 1: A 38 yo woman was admitted at 32 weeks gestation for HTN and hypokalemia. She had a history of HTN prior to pregnancy but was on no medications. At 22 weeks, she developed weakness and hypokalemia (K 2.8 mg/dl). The BP was 130/99. She received IV and PO KCl replacement. At 30 weeks, the BP was 150/80 and she was prescribed methyldopa. One week later, the BP was 160/100 and labetalol was started. On the day of admission, 32 weeks gestation, the BP was 163/89 and the K was 3.0 mg/dl. She denied nausea, vomiting, or diarrhea. There was a family history of HTN in the patient's mother and father, but no family history of hypokalemia. Physical examination showed 1+ bilateral lower extremity edema. There was no proteinuria. Urine K was 23.2 mmol/L, urine Cr 44.5 mg/dl, plasma Aldosterone <3.0 ng/dL, and renin activity 2.1 ng/ml/h **Case 2:** A 36 yo woman was admitted at 26 weeks gestation for HTN and hypokalemia. She had a history of gestational HTN in two prior pregnancies, and chronic HTN diagnosed 2 years prior. Her BP was normal off medications for the first half of pregnancy. At 24 weeks, the BP was 151/91. At 26 weeks, she reported weakness and her K was 2.6 mg/dl; she was admitted. Physical exam showed BP 179/80 and peripheral edema. There was no proteinuria. Urine K was 20.3 mmol/L, urine Cr 43.7 mg/dl, plasma aldosterone 1 ng/dl, renin activity 1.9 ng/ml/h

Results:

Conclusions: Normally the MR is activated by aldosterone, but inhibited by progesterone. The novel MR S810L, described by Geller et al, is activated by both aldosterone and progesterone. In the initial description, two MR L810 carriers had a pregnancy-induced exacerbation of HTN and hypokalemia in 5 pregnancies, with low aldosterone levels. High progesterone in pregnancy was implicated. Our patients experienced worsening HTN and new hypokalemia in pregnancy, with renal potassium wasting and low renin and aldosterone levels, consistent with Geller syndrome. Both patients responded to amiloride. Geller syndrome should be considered in women with HTN and hypokalemia in pregnancy.

TH-PO626

HUStling for HELLP: A Case of Pregnancy Induced Atypical HUS (aHUS) and HELLP Syndrome Huda N. Khan,[2] Roberto L. Collazo-Maldonado,[2,1] Lisa M. Sebastian.[2,1] *[1]Dallas Nephrology Associates, Dallas, TX; [2]Methodist Dallas Medical Center, Dallas, TX.*

Background: Atypical or complement mediated Hemolytic uremic syndrome (aHUS) is a rare disorder mostly associated to gene mutations of complement factors and/or antibodies to complement factors. In rare cases it may be triggered by the stress of pregnancy. This is a case of a pregnant woman with aHUS that initially presented with HELLP Syndrome which made the diagnosis of aHUS challenging.

Methods: A 32 y/o AA woman G6P4A1 with no known past medical history presented to the ER at 25 weeks of gestation with acute onset of lower abdominal pain that started 48 hours prior to admission. On her physical exam, she was very hypertensive at 180/100 mmHg. Labs revealed new onset of proteinuria (urine prot/creat 9.5 g), elevated AST 226/ALT 48, thrombocytopenia 83,000, anemia Hgb 8.5/ Hct 24.9. She was admitted with initial diagnosis of pre-eclampsia with HELLP. She was taken to L&D due to abruptio placenta and intrauterine fetal demise. D&C was performed which was complicated with massive blood loss requiring multiple blood transfusions. She developed anuric AKI that required CRRT. Her condition stabilized, but remained anuric and was still dependent on intermittent dialysis. She continued to be hypertensive and developed anemia with schistocytes on the peripheral smear. Renal biopsy revealed thrombotic microangiopathy and classic findings of aHUS. ADAMTS13 level was normal. Patient was treated with plasmapheresis for 7 days followed by Eculizumab. Once treatment was initiated, the patient's condition improved with resolution of AKI and hemolysis, and normalization of platelet count. She was discharged to continue indefinite treatment with Eculizimab as outpatient.

Results:

Conclusions: Complement mediated HUS may present as a complication from pregnancy. The diagnosis of aHUS during pregnancy may be challenging because the clinical presentation may resemble that of HELLP syndrome as both conditions can coexist and may present with similar laboratory findings. Nephrologists should have high level of suspicion for aHUS in a pregnant woman who presents with HELLP Syndrome. Renal biopsy is valuable in making appropriate diagnosis.

TH-PO627

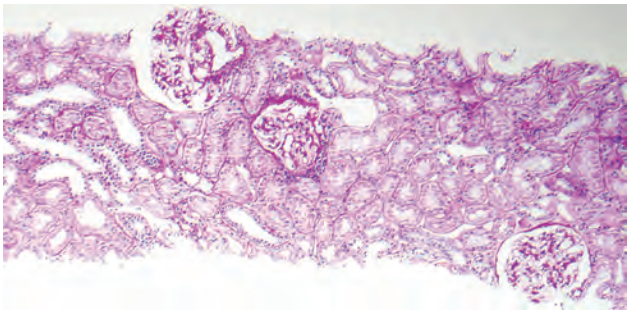
Successful Twin Pregnancy in a Patient with IgA Nephropathy and Nephrotic Range Proteinuria Robert S. Niznik, Andrea G. Kattah, Vesna D. Garovic. *Mayo Clinic, Rochester, MN.*

Background: There is literature for using tacrolimus in patients with IgA nephropathy for anti-proteinuric effect in those that cannot tolerate ACE inhibitors due to hypotension. We present a case of tacrolimus use in pregnancy primarily for anti-proteinuric effects.

Methods: This is a 29 year old female with a history of IgA nephropathy diagnosed in 2003. A renal biopsy at the time showed a small fibrocellular crescent. She was initially treated with steroids; however, she experienced significant side effects and this was discontinued after 3 days. Subsequently, she was treated with lisinopril, irbesartan and omega-3 fatty acid with improvement of her 24 hr urine protein, blood pressure and 24 hour creatinine clearance. She then had a recurrence of subnephrotic proteinuria in May of 2012 and was treated with Myfortic with improvement in proteinuria. In 2015, she desired pregnancy and so a repeat biopsy was done, showing focal glomerulosclerosis and minimal mesangial changes (M1 E0 S0 T0). She had 1.3g/24 hr of proteinuria and a creatinine of 1.0. Her Myfortic and lisinopril were stopped and nifedipine was initiated for hypertension. Unfortunately, she had rapid worsening of her proteinuria off of the ACE inhibitor up to 5.9g/24 hrs and refused steroids. She had decreased levels of TPMT and so was started on a low dose of azathioprine for immunosuppression. She continued to have worsening disease activity with 10g of proteinuria and dysmorphic hematuria and so low-dose tacrolimus (trough 2-4) was started with improvement in proteinuria to 4g/24 hrs. She then naturally conceived a twin pregnancy and had a full term delivery without complications.

Results:

Conclusions: Intolerance to steroids and contraindication to mycophenolate in addition to low TPMPT limited the therapeutic options in this case. Using tacrolimus for its antiproteinuric effects at low dose can be beneficial.



Light microscopy with PAS stain showing IgA nephropathy with mild mesangial proliferative changes and focal global glomerulosclerosis

TH-PO628

Normal GFR to ESRD after Pregnancy with Diabetic Nephropathy Hassan B. Attique, Anika Lucas, Ibrahim Elali. *University of Connecticut Health Center, Farmington, CT.*

Background: While pregnancy associated incidence of complications in Type 1 diabetic (T1D) patients with nephropathy is well established, the rate of progression of the nephropathy is yet to be adequately studied.

Methods: 36 year old female with history of uncontrolled HTN and T1D, complicated with diabetic nephropathy, presented at 12 weeks of gestation with nephrotic range proteinuria of 7.6 g, creatinine clearance (Ccr) of 104 ml/min on 24- hour urine collection and a serum creatinine (SCr) of 0.8mg/dl. Prior to her pregnancy, her baseline SCr was 0.61mg/dl with estimated glomerular filtration rate (eGFR) of 118 ml/min/1.73m^2, and reported urinalysis with 2$^+$- 3$^+$ proteinuria or sub-nephrotic range. During pregnancy, diabetes remained uncontrolled despite intensive insulin regimen. Blood pressure ranged from 116-167 mmHg systolic and 68-101 mmHg diastolic. Peak SCr was 1.2 mg/dl and protein-creatinine ratio (PCR) of 17 g/g. She developed preeclampsia at 35 weeks of gestation resulting in preterm delivery of 2095 g newborn via caesarean section. Post-delivery SCr at one month was 1.1 mg/dl with eGFR of 60 ml/min/1.73m^2, and albumin-creatinine ratio of 9 g/g. Over the course of eight months postpartum, renal function continued to decline, and progressed to ESRD, requiring chronic renal replacement therapy support. Peak SCr was 4.3 mg/dl, and 24-hour urine collection revealed Ccr of 12.4 ml/min with 20 grams proteinuria. Serological workup was negative. Renal biopsy was consistent with diabetic nephropathy and showed diffuse nodular global sclerosis.

Results:

Conclusions: Although preclampsia, caesarean section, and preterm delivery are known complications in diabetic nephropathy, nephrotic range proteinuria with preserved GFR progressing to ESRD post pregnancy is not well documented. Previous studies showed no increased risk of overt nephropathy or ESRD in women with preserved GFR at conception, and proteinuria generally returns to baseline postpartum. We observed an accelerated decline in renal function as well as worsening proteinuria leading to ESRD post partum, requiring chronic hemodialysis support. Pre-existing Proteinuria seems to be a stronger factor than preserved GFR pre-pregnancy in predicting future progression and disease outcome. Aggressive preconception counseling should be considered to avoid preventable fetal and maternal morbidity, including the possibility of disease progression to ESRD.

TH-PO629

Thrombotic Thrombocytopenic Purpura in Early Second Trimester Pregnancy Successfully Treated with Membrane Therapeutic Plasma Exchange Charissa Marie R. Carag, Casey N. Gashti, William L. Whittier. *Rush University Medical Center, Chicago, IL.*

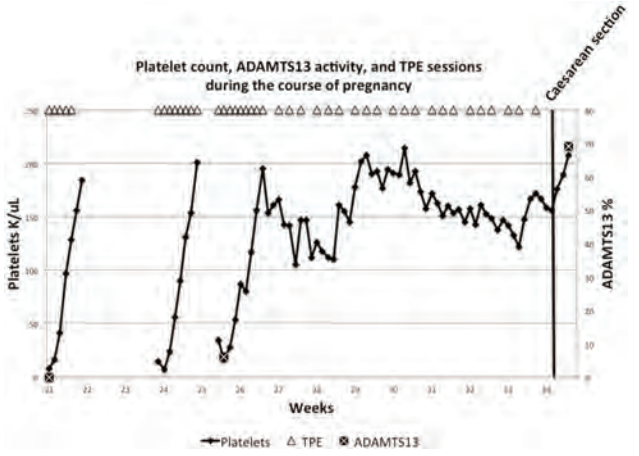
Background: Thrombotic thrombocytopenic purpura (TTP) is a life-threatening thrombotic microangiopathy which presents with hemolytic anemia, thrombocytopenia, and an ADAMTS13 activity <10%. Although rare, it can flare in pregnancy, and should be considered in the differential diagnosis of thrombocytopenia in pregnancy. In the general population, acquired TTP is more common, although recently, more studies have demonstrated that hereditary TTP makes up a greater number of pregnancy-associated TTP. We report a case of acquired TTP in pregnancy successfully managed by membrane-based therapeutic plasma exchange (mTPE) leading to delivery of a healthy child 13 weeks after diagnosis.

Methods: The patient was a 34-year-old G4P2012 woman with severe thrombocytopenia (platelets 8 K/uL) and anemia (Hgb 4.9 g/dl) in the 21st week of gestation. Her ADAMTS13 activity was <10% on two occasions with the presence of

an inhibitor. She was started on daily mTPE and high-dose steroids, followed by thrice-weekly mTPE to maintain a platelet count of at least 150 K/uL. The patient received 43 mTPE sessions during pregnancy without any complications. She delivered a healthy child at 34 weeks of gestation. After delivery, her platelets normalized without mTPE or steroids. An ADAMTS13 activity after delivery was 69%. (Fig 1)

Results:

Conclusions: TPE should be initiated immediately in cases of TTP, and can be performed safely in pregnancy. This case highlights the unique pathophysiology of TTP in pregnancy, as the mother did not require TPE once the placenta was delivered and her ADAMTS13 activity normalized. It has been theorized that certain proteins in the placental circulation induce antigen-triggering antibody production against ADAMTS13. Our case is the first report of using mTPE in pregnancy and demonstrates its efficacy and safety with 43 sessions over 13 weeks.



TH-PO630

Eculizumab, a Novel Treatment for Acute Kidney Failure Associated with Severe Preeclampsia Hatem Elabd, Rushi K. Nayak, Belinda Jim, Kisra Anis, Anjali Acharya. *Jacobi Medical Center/Albert Einstein College of Medicine, Bronx, NY.*

Background: Preeclampsia is a leading cause of maternal and neonatal morbidity and mortality. It is the most common cause of AKI during pregnancy. Preeclampsia complicates approximately 5% of all pregnancies, making it perhaps the most common glomerular disease in the world. The complement system is a key mediator of systemic inflammation and is excessively activated in preeclampsia. As alloantibodies commonly develop against the semi-allogeneic fetal tissues, the placenta is potentially a target for complement-mediated immune attack.

Methods: A 29-year-old female multiparous at 40 weeks of gestation admitted to surgical ICU post emergent cesarean section for severe preeclampsia complicated with rupture membrane and fetal heart deceleration. Peri-operatively course complicated with bleeding, shock and acute kidney injury, for which patient needed resuscitation, and mechanical ventilation. She remained anuric with progressive kidney failure and continuous renal replacement therapy was started. We performed extensive workup to rule out acute fatty liver of pregnancy, TTP, atypical HUS, SLE, or antiphospholipid syndrome. Also complement gene mutation studies associated with atypical HUS were checked, which later turned out to be negative. Therefore, she was diagnosed with severe preeclampsia with multi-organ dysfunction. We decided to give Eculizumab 900mg/dose, a C5 inibitor, on day 4 post admission. One week later, patient had marked clinical improvement, and dialysis was discontinued. Furthermore, there was complete normalization of all laboratory abnormalities and complement activation markers.

Results:

Conclusions: To our knowledge this is the first case describing the use of Eculizumab in acute kidney injury (AKI) in setting of severe preeclampsia. The use of Eculizumab was previously described in a women with HELLP syndrome which led to improved liver function tests and pregnancy prolongation for 17 days. As opposed to our case, Eculizumab was given intrapartum and their patient had no evidence of kidney failure. The use of Eculizumab in this report supports a possible benefit of C5 inhibition for the treatment of severe preeclampsia and AKI. Its use may be particularly helpful among women with mutations in complement regulatory proteins. Further research is warranted to validate our findings.

TH-PO631

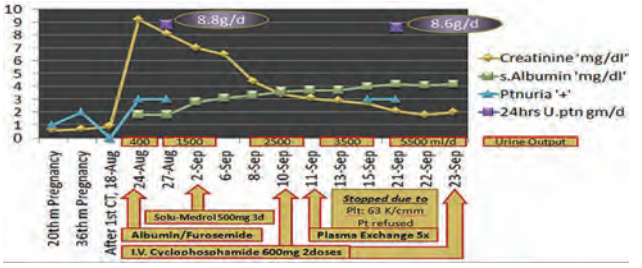
New-Onset Crescentic Glomerulonephritis Following Preeclampsia: A Diagnostic Dilemma Karim M. Soliman,[1,2] Mohammed Z. Mohialdeen,[1] David W. Ploth.[1] *[1]Medical University of South Carolina, Charleston, SC; [2]Nephrology, Cairo University, Cairo, Egypt.*

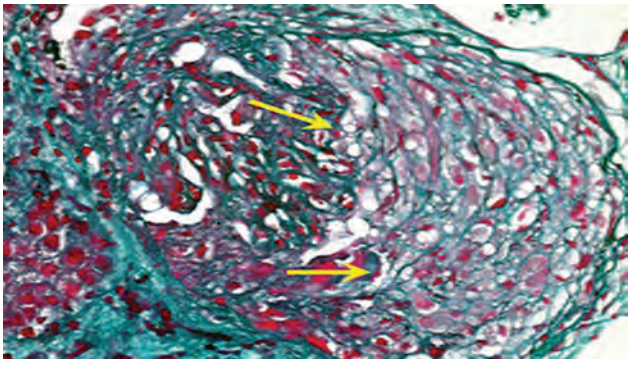
Background: New-onset crescentic Glomerulonephritis (GN) in the postpartum period following preeclampsia with normal GFR after delivery has not been reported. AKI 2 days post CT with contrast complicates making this diagnosis.

Methods: A 28 year old female G3P2 with no significant past medical history presented during her 36th week of pregnancy with preeclampsia and urine protein excretion of 4 gm/24hr. C-section delivered a viable fetus. She was discharged with serum creatinine (Cr) 0.8 mg/dl. She returned with fatigue and abdominal tenderness 2 weeks later. CT imaging with contrast revealed a supra-uterine hematoma prompting surgical evacuation. Two days later she developed progressive increase in lower extremity edema, puffiness of eyelids, oliguria and microscopic hematuria. Hemoglobin was 7.6 gm/dl, platelets 220 K/cmm, Cr 9.2 mg/dl, albumin 1.8 gm/dL and urine protein excretion 8.8 gm/24hr (clinical course in Fig.1). Viral markers (Hepatitis B, C and HIV), C3, C4 and immune profile, were all negative. Renal biopsy revealed twenty glomeruli, all showed cellular crescents (arrows in Fig.2) and collapsing of capillary loops with moderate endocapillary proliferation. Immunoperoxidase staining was negative for IgA, IgG with weak focal positive staining for IgM within the crescents.

Results:

Conclusions: The patient did not require dialysis and renal functions responded favourably to plasma exchange, steroids and cyclophosphamide. Three months later Cr was 2 mg/dl and urine protein 4 gm/24 hr. At this time, further therapy options are being discussed. Educational objectives include; always confirm the clinical suspicion of glomerular disease with biopsy whenever possible. Hidden triggering elements for crescentic GN merit consideration.





TH-PO632

Microscopic Polyangiitis with Pulmonary Renal Syndrome in a Pregnant Woman: Management Challenges Ramprasad Kandavar,[2] Sandhya L. Kommana,[1] Anuja P. Shah.[3] *[1]Harbor ULCA MEDICAL CENTER, Harbor City, CA; [2]Harbor-UCLA Medical Center, Torrance, CA; [3]Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, CA.*

Background: Introduction Microscopic Polyangiitis occurring either de novo or relapse during pregnancy has significant maternal and fetal morbidity and mortality. Here we report a case of pregnant woman developing de novo MPA manifesting as pulmonary renal syndrome posing considerable management challenges

Methods: Case Description A 21year-old pregnant woman (G1P0) presented to the Emergency department at 21 weeks gestation with uncontrolled blood pressure, pulmonary edema and acute renal failure. Laboratory data significant for Hemoglobin of 6.4, BUN 49 and Serum Creatinine 7.15 mg/dl. UA showed 3+protein, 3+ blood with numerous Acanthocytes. Further studies revealed P- ANCA 1:160 and Anti MPO: 24. Renal US was revealed normal sized kidneys. Early clinical course also complicated by hemoptysis suggestive of pulmonary hemorrhage. A diagnosis of RPGN secondary to Microscopic Polyangiitis was made. She was started on pulse steroids followed by oral Prednisone, IV cyclophosphamide, Hemodialysis 6 times/week and Plasmapheresis. Over the course of several days patient made significant clinical stabilization, hemoptysis resolved and ANCA and anti-MPO titers became negative. Patient was managed in close consultation with Obstetrics Service and underwent Cesarean section at 27.2 weeks. Patient received monthly infusion of Cyclophosphamide with no signs of renal recovery and currently is dependent on hemodialysis. Renal biopsy was done after delivery, showed immune complex mediated glomerulonephritis, chronic/inactive crescentic glomerulonephritis involving 85% of glomeruli with moderate to severe scarring.

Results:

Conclusions: Discussion: The data on MPA in pregnancy and its outcomes is very limited and is thought to have a more aggressive course. A systematic review of 48 pregnancies with small vessel vasculitis showed 33 % prematurity, 8% miscarriage, pre-eclampsia 17% and maternal death 4%. Many of the immunosuppression drugs including Cyclophosphamide are contraindicated in pregnancy because of teratogenicity, ovarian

failure, and fetal prematurity. However, there are anecdotal reports of Cyclophosphamide use in pregnant women with malignancies like leukemia, lymphoma and breast cancer confirming safety of the drug in pregnancy. In our case we faced similar treatment dilemmas though in the end we were able to deliver a viable fetus.

Funding: Other U.S. Government Support

TH-PO633

Transient Hypertension in a Preterm Infant after the Administration of Indomethacin for Patent Ductus Arteriosus Takahiro Tominaga,[2] Sayu Omori,[2] Midori Awazu.[1] *[1]Keio University School of Medicine, Tokyo, Japan; [2]Saitama Municipal Hospital, Saitama, Japan.*

Background: While hypertension is a known complication of non-steroidal anti-inflammatory drugs (NSAIDs) in adults, it has not been reported in children. We report a preterm infant who developed hypertension after the administration of indomethacin for patent ductus arteriosus (PDA).

Methods: A preterm boy was delivered at 31 weeks' gestation *via* caesarean section for placenta previa. Birth weight was 1676 g. PDA was detected on day 2. Indomethacin 0.2 mg/g/dose was given intravenously from day 2 to day 4. On day 5, the ductus arteriosus was still patent. Although serum creatinine increased from 0.62 mg/dL to 1.05 mg/dL, urine output was normal (2.4 ml/kg/hr) and indomethacin was readministered on day 5 and 6. On day 7, the ductus arteriosus was closed. On day 8, urine output decreased to 0.8 ml/kg/hr, and fluid was restricted to 60 ml/kg/day. FE_{Na} was 2.2% which could be normal for preterm infants. Urine output gradually increased. Blood pressure (BP) had been normal until day 12. On day 13, BP increased to 82/41 mmHg and became 90/58 mmHg (99th percentile for postconceptional age 34 weeks) on day 14. Body weight did not change from day 7 to day 14. Physical examination was unremarkable with heart rate of 140 beates/min with no edema. Blood urea nitrogen was 2.5 mg/dL, serum creatinine 0.41 mg/dL, calcium 9.2 mg/dL, phosphorus 3.8 mg/dL, sodium 130 mmol/L, potassium 4.3 mmol/L, chloride 101 mmol/L, bicarbonate 16.3 mmol/l, uric acid 1.0 mg/dL, TP 4.7 mg/dL, albumin 3.0 mg/dL, NT-pro BNP 18210 pg/dL, plasma renin activity 1.1 ng/mL/hr, and aldosterone 382 pg/mL. Cardiac ultrasonography showed mean velocity of circumferential fiber shortening (mVcfc) of 0.6 circ/s and end-systolic wall stress (ESWS) of 119.3 g/cm^2 suggesting afterload mismatch, which occurs in response to an acute increase in vascular resistance. Nitroglycerin infusion was started. On day 15, BP decreased to 78/44 mmHg. Cardiac ultrasonography showed improvement of after load mismatch.

Results:

Conclusions: NSAID-induced hypertension has been ascribed to sodium retention due to COX-2 inhibition in the kidney. The major mechanism of the increased blood pressure of this patient, however, is thought to be high afterload due to increased peripheral vascular resistance presumably by indomethacin.

TH-PO634

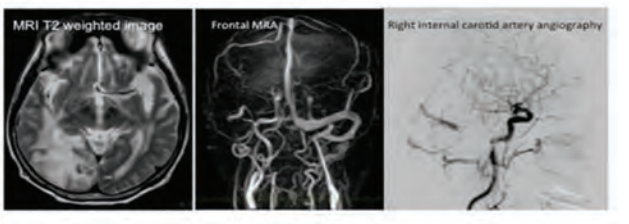
A Case of Dural Arteriovenous Fistula Caused by Dural Venous Sinus Thrombosis Complicated by Minimal Change Nephrotic Syndrome (MCNS) Risa Yamashita, Shoko Ochiai, Akihiro Minakawa, Takashi Iwakiri, Ryuzoh Nishizono, Masao Kikuchi, Hideto Nakagawa, Yuji Sato, Shouichi Fujimoto. *Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan.*

Background: Venous thrombosis is an important complication of nephrotic syndrome (NS). Dural sinus venous thrombosis is uncommon, but it is a major risk of dural arteriovenous fistula (DAF). We present a case of DAF due to dural venous thrombosis that was successfully treated by an intravascular approach.

Methods: A 78-year-old man was admitted to our hospital with a 1-week history of edema, weight gain, exertional dyspnea, and new-onset of disorientation. On admission, a urinary examination showed microscopic hematuria and heavy proteinuria (protein/creatinine ratio of 9.5 g/g creatinine). A blood examination showed an elevated blood urea nitrogen level of 24.3 mg/dL, creatinine level of 1.38 mg/dL, fibrinogen level of 352 mg/dL, D-dimer level of 21.6 μg/mL, and antithrombin-III was 57%. Additionally, serum albumin was reduced to 1.49 g/dL. His renal biopsy findings showed minor glomerular abnormalities. These findings were compatible with MCNS. Deep vein thrombosis of the right leg was found by echogram. Prednisolone, cyclosporine, and oral anticoagulant were administered. Despite proteinuria being reduced, his disorientation became worse daily. Head computed tomography showed a low-density area in his occipital lobes. Magnetic resonance imaging showed DAF with sigmoid sinus thrombosis in addition to cerebral venous reflux, micro-hemorrhages, and venous blood stasis. Thereafter, transcatheter embolization was performed on the 29th hospital day, and then his disorientation improved. He was discharged on the 42nd hospital day. At an 8-month follow-up, MCNS and DAF had not relapsed.

Results:

Conclusions: Hypoalbuminemia and reduced anticoagulant activity are considered as major risk factors for thrombosis in NS. When thrombus in the cranial sinus occurs, increased venous pressure may cause DAF, dural hypertension, or arterial steal, followed by neurological deficits. We describe the first case of NS that was complicated by disorientation due to DAF in association with dural sinus thrombosis.



TH-PO635

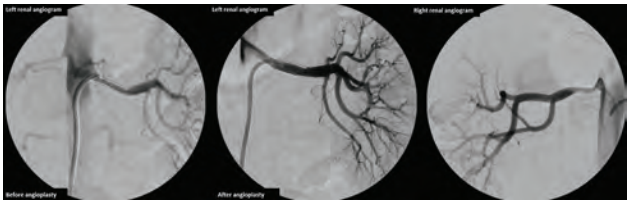
Renovascular Hypertension: A Diagnostic and Therapeutic Conundrum Abhilash Koratala,[2] Freddy R. Malpartida,[2] Siddharth Wayangankar,[1] Rajesh Mohandas.[2] *[1]University of Florida, Gainesville, FL; [2]University of Florida, Gainesville, FL.*

Background: The commonest causes of renal artery stenosis (RAS) are atherosclerosis and fibromuscular dysplasia (FMD). Despite the availability of advanced imaging modalities, there are substantial challenges to accurately distinguishing between the two. Since treatment options and benefits of revascularization are different in FMD and atherosclerosis, it is essential to make an accurate diagnosis. Herein, we present the case of a young patient with hypertension (HTN) and RAS who was mistakenly labelled as FMD and later diagnosed with atherosclerotic RAS.

Methods: A 46-year-old woman with a diagnosis of FMD was referred to us for evaluation of resistant HTN. Uncontrolled HTN was confirmed by ambulatory blood pressure monitoring. 3 months prior to presentation, she had undergone angioplasty and stenting of the left renal artery for imaging suggestive of FMD. We optimized her anti-hypertensive regimen and recommended life-style modifications. At follow up, her clinic BP was 258/130 mmHg. She was on lisinopril 10mg, amlodipine 10mg, Chlorthalidone 25mg and spironolactone 25mg/ day. Renal angiography confirmed in-stent restenosis (90%) of the left renal artery and 80% diffuse stenosis of the ostial and proximal segments of the right renal artery. Intvascular ultrasound (IVUS) demonstrated atherosclerotic plaques. The proximal and ostial nature of the disease, absence of beading, and presence of plaques in a patient with diabetes and history of irradiation suggested atherosclerotic RAS. The restenosis was successfully treated with IVUS guided angioplasty [Figure]. Her blood pressures improved immediately after the procedure and she was weaned off all antihypertensive medications other than Lisinopril and chlorthalidone.

Results:

Conclusions: Accurately distinguishing between FMD and atherosclerotic RAS is critical. FMD is usually treated with angioplasty while most patients with atherosclerotic RAS do not benefit from revascularization. Patients who have stents placed should undergo periodic surveillance for restenosis with Doppler ultrasound.



TH-PO636

Labetalol or Amphetamine? : That Is the Question Shimontini Mitra,[2,3] Nikhil Agrawal.[1] *[1]Beth Israel Deaconess Medical Center, Brookline, MA; [2]Nephrology, Beth Israel Deaconess Medical Center, Boston, MA; [3]Harvard Medical School, Boston, MA.*

Background: Uncontrolled hypertension is a frequent cause of hospitalizations. Evaluation for causes of accelerated hypertension includes urine analysis for ingested substances like amphetamine. Interpretation of urine amphetamine testing becomes difficult when patients are administered high doses of labetalol. Understanding the chemical structures of amphetamines and their breakdown products can help distinguish true amphetamine use from labetalol effect. In this case, mass spectroscopy proved helpful in interpreting a positive urine amphetamine test.

Methods: A forty-two year old male with ESRD and Type I Diabetes status post pancreas and kidney transplant in October 2015 and hypertension presented with elevated blood pressures and acute kidney injury. The patient was noted to have uncontrolled blood pressures for the past month. His blood pressure on admission was 211/113 and throughout most of his stay ranged 160-190/90-110mm Hg. His admission physical exam was notable for a chronic systolic murmur, no abdominal or carotid bruits, non-tenderness over kidney and pancreatic graft sites, no papilledema, and no edema. His admission creatinine was 1.8 mg/dL from a baseline of 1.4 mg/dL. Cardiac enzymes and EKG were unrevealing. His blood pressure regimen in-house consisted of labetalol 800mg TID, hydralazine 75mg QID and clonidine patch 0.3mg QD. A urine toxicology screen was also performed which returned positive for amphetamine. The patient denied the use of illicit substances prompting further analysis. Mass spectroscopy of the sample was negative for amphetamine but demonstrated a breakdown compound of labetalol, 3-amino-1-phenylbutane (APB). His blood pressures were eventually controlled with the addition

of isosorbide mononitrate 120mg QD and furosemide 40mg QD orally. His creatinine returned back to baseline and patient was discharged.

Results:

Conclusions: Labetalol breaks down into multiple compounds. One of these metabolites is APB. Urine amphetamine assays work by competitive inhibition between glucose-6-phosphate dehydrogenase (G6PDH)-labeled amphetamine and urinary amphetamine for a fixed number of reagent antibody binding sites. APB is structurally similar to amphetamine and can bind to reagent antibody in this assay resulting in false positivity. Therefore, for patients with uncontrolled hypertension who are also on high doses of labetalol, mass spectroscopy is a means of correctly interpreting a positive test.

TH-PO637

Systemic Sclerosis Sine Syndrome: Another Cardio Renal Collusion! Panpan Chen, Anum Bilal, Loay H. Salman, Mauricio Monrroy, Rafia I. Chaudhry. *Albany Medical College, Albany, NY.*

Background: SSc is a diffuse connective tissue disorder with cutaneous and visceral involvement, presenting with characteristic skin sclerosis. Systemic Sclerosis sine scleroderma (ssSSC) is a rare (<10%) subset of SSc with visceral and immunologic features of SSc without skin involvement. Additionally, hypocomplementemia can be found in 20% cases of SSc, and may represent an "Overlap Syndrome", i.e. second autoimmune condition. Scleroderma renal crisis occurs in 5-20% of SSc, and diagnosis can be missed without the characteristic sclerotic skin findings of SSc.

Methods: A 26 yr-old female with a PMHx of HTN and CKD III, presented with sub-sternal chest pain, palpitations, headaches and malignant hypertension. Exam was significant for BP 211/136 mm Hg, HR 84/m and trace LE edema. Laboratory data: Hb 10.6 g/dL, Sr Cr 2.5 mg/dL, and troponin, b-hCG and urine toxicology screen were negative. Urine microscopy did not reveal RBC casts; spot urine protein/Cr ratio was 1.14. TTE showed moderate pericardial effusion, and a pericardial window drained 100 mL of transudative fluid with benign mesothelial cells, and benign pericardial tissue on biopsy. An ANA titer of 160 and low C4 < 8.0 mg/dL (C3 normal 93.9 mg/dL) increased suspicion for lupus nephritis. However, renal pathology revealed thrombotic microangiopathy, moderate to severe chronic sclerosing nephropathy, severe arteriolar hyalinosis, myxoid intimal hyperplasia, fibrin thrombi, suggestive of chronic thrombotic microangiopathy. IF did not show "full house" staining. While the patient had no history of Raynaud's phenomenon, or hallmark sclerotic skin changes of Systemic sclerosis (SSc), diagnosis of SSc was confirmed with positive scleroderma Ab (6.0); antiphospholipid Ab, and serum cryoglobulin were also positive. Beta blockers were discontinued to prevent vasospasm; ACE inhibitor and calcium channel blocker were initiated.

Results:

Conclusions: Prompt diagnosis is needed for timely initiation of ACE inhibition, which has dramatically improved renal outcomes. Hence it is crucial to recognize atypical clinical features of SSc such as pericardial effusion due to primary cardiac involvement, or secondary to pulmonary hypertension. Pericardial effusion may also be a surrogate for active or severe disease, signifying poor prognosis in cases with primary cardiac involvement.

TH-PO638

Renovascular Hypertension Due to a Bcr-Abl Tyrosine Kinase Inhibitor and Response to Revascularization Syed O. Amin,[3] Marcel Ruzicka,[2] Swapnil Hiremath.[1] *[1]University of Ottawa, Ottawa, ON, Canada; [2]None, Ottawa, ON, Canada; [3]Windsor Regional Kidney Care and Hypertension Clinic, WINDSOR, ON, Canada.*

Background: Bcr-Abl tyrosine kinase inhibitors (TKI) are first line agents for management of chronic myelogenous leukemia (CML). Amongst the second generation TKIs, which have less resistance and improved side effect profile, nilotinib and ponatinib have also been reported to be associated with vascular adverse events (VAEs), including systemic and peripheral arterial stenosis.

Methods: We report on a patient with CML treated with ponatinib, who developed bilateral renal artery stenoses, difficult to control hypertension, and responded to revascularization.

Results: Case: A 55 year old man, with CML due to a Bcr-Abl truncating mutation diagnosed in 2007, was treated with ponatinib 45 mg daily starting in 2011, which induced a complete remission. He subsequently developed hypertension. Hypertension appeared angiotensin II-dependent as BP normalized on combination of candesartan 32 mg once daily and hydrochlorothiazide 25 mg once daily. This treatment was however associated with an increase in serum creatinine from 1.4 to 2.6 mg/dL. Consistent with our clinical suspicion, a computed tomography angiogram revealed bilateral renal artery stenosis. He eventually required bilateral renal artery angioplasty and stenting as the BP could not be controlled without renin-angiotensin system blockers despite using up 5 classes of BP lowering drugs. Furthermore, follow up imaging of renal arteries showed progressive renal artery stenosis bilaterally. He underwent angioplasty and stenting in the left renal artery and angioplasty of both the branches of the right main renal artery, which could not be stented because of the early branching. After 6 months, BP is within target with 8 mg candesartan, amlodipine 10 mg and bisoprolol 2.5 mg daily, and the renal function is stable (creatinine 1.1 mg/dL). Overall, in this case, renal artery angioplasty and stenting stabilized renal function and improved control of hypertension.

Conclusions: Second generation TKIs are associated with VAEs, including renal artery stenosis. Renal artery angioplasty and stenting stabilized renal function and improved control of hypertension in this case. Future research should clarify the mechanisms of VAEs with TKIs, natural history, and long term response to revascularization in this setting.

TH-PO639

Nephrotic Syndrome as First Presentation of Waldenstrom's Macroglobulinemia Ayushi Chauhan. *University of Connecticut, Hartford, CT.*

Background: Waldenstrom's macroglobulinemia (WM) is a disorder characterized by bone marrow (BM) infiltration by a lymphoplasmacytic lymphoma and a serum immunoglobulin M (IgM) paraprotein. In contrast to multiple myeloma, renal involvement is uncommon in WM with nephrotic syndrome (NS) being rare. Here we describe a case of NS as a first presentation of WM.

Methods: 83-year-old male with a history of hemorrhagic stroke and hypertension presented for evaluation of anasarca. He reported worsening bilateral lower extremity, scrotal and penile edema over 4 weeks. He also felt "slowed down" and noted vision changes and gait instability. Lab values yielded the following: Hemoglobin 9.5, hematocrit 28.2, WBC 6.9 and platelets 282. BUN/creatinine (Cr) was 29/0.8. ESR was markedly elevated at 101. Urinalysis showed a bland sediment and more than 300 mg/dL protein without casts. Urine protein excretion was 5188 mg/g Cr. Serum protein electrophoresis showed significant hypoalbuminemia with a gamma region spike consistent with the presence of a monoclonal protein: IgM >3150, IgA 32 and IgG <108. Serum and urine immunofixation showed monoclonal IgM lambda (λ) and Bence-Jones proteinuria, respectively. λ free light chains were elevated at 13.10 with the Kappa/ λ ratio 0.19. β-2 microglobulin was 4.1. Serum viscosity and complement (C3 and C4) levels were within normal limits and cryoglobulins were negative. A subsequent BM biopsy revealed near effacement of marrow by diffuse interstitial B-Cell infiltrate and a positive MYD88 mutation indicative of WM. A kidney biopsy was not performed and no cancer-targeted therapy was initiated as the patient elected comfort focused care.

Results:

Conclusions: Diagnosis of WM-associated nephropathy is of immense clinical import due to its prognostic impact. Biopsy-proven WM nephropathy is associated with shortened overall survival especially in those with renal function decline despite treatment. Pathology can be variable however light-chain amyloidosis usually causes NS in WM. Despite presence of Bence-Jones proteinuria, as in our case, cast nephropathy is less culpable due to low quantity of the light chains. Reports are also emerging on minimal change disease as a paraneoplastic manifestation of WM with resultant NS. Regardless of mechanism of nephropathy, treatment of the underlying WM with chemoimmunotherapy, especially Rituximab, has largely shown to result in NS resolution.

TH-PO640

Lambda Light Chain Tubulopathy in Waldenstrom's Macroglobulinemia Joseph De Leon,[2] Sandhya L. Kommana,[1] Ramanath B. Dukkipati.[2] *[1]Harbor ULCA MEDICAL CENTER, Harbor City, CA; [2]Harbor-UCLA Medical Center, Torrance, CA.*

Background: Light Chain Tubulopathy is typically seen in Plasma cell dyscrasias such as Multiple Myeloma, however it has been reported in Waldenstrom's Macroglobulinemia. The vast majority of cases involve the Kappa Light Chains, with Lambda Light Chains being exceedingly rare.

Methods: A 63 year old female with untreated Waldenstrom's Macroglobulinemia was admitted for decreased oral intake resulting into acute kidney injury(AKI). She has not had definitive treatment due to absence of absolute indications such as cytopenias, organomegaly, hyperviscosity symptoms and nephropathy until 2 months prior to admission, when she had a rising creatinine of 1.6 mg/dl (baseline 1.3) and opted not to get the treatment of Rituximab. She presented on admission with AKI with creatinine of 3.9 mg/dl, trace proteinuria, 2-3RBC/HPF and FeNa<1%. She was volume repleted to manage the pre renal state although the possibility of plasmacytoma related kidney injury remained high. Unexpectedly, her kidney function did not have robust improvement and she eventually underwent kidney biopsy, the strongest suspicion being immune mediated MPGN. Pathology revealed renal involvement by atypical lymphoplasmacytic infiltrate with λ-light chain restriction with inclusions within proximal tubular epithelial cells with crystalloid appearance consistent with λ-light chain tubulopathy.

Results:

Conclusions: Waldenstrom's Macroglobulinemia have circulating monoclonal IgM proteins in association with a B cell lymphoproliferative disorder. Renal involvement occurs in < 5% of patients with varied pathology including direct invasion of renal parenchyma by neoplastic lymphoplasmacytic cells, intraglomerular occlusive thrombi of the IgM paraprotein and in some, development of MPGN with associated type I or type II cryoglobulinemia. Light chain proximal tubulopathy (LCPT) is characterized by cytoplasmic inclusions of monoclonal light chains within proximal tubular cells. One study focused on pathologic features of 40 cases of crystalline LCPT from 2000-2014 all of which showed κ-restriction. The incidence of LCPT is typically seen in Multiple Myeloma and has been reported in Waldenstrom's Macroglobulinemia. The vast majority of reported cases of LCPT are κ-restricted. The finding of LCPT, from Waldenstrom's Macroglobulinemia, with λ-light chain restriction makes this case exceedingly rare and to our knowledge, never been reported.

TH-PO641

Renal Heavy/Light-Chain Amyloidosis Diagnosed by Immunostaining and Liquid Chromatography-Tandem Mass Spectrometry in a Patient with Non-Ischemic Cardiomyopathy Mami Sugimoto,[5] Hideki Inoue,[2] Mikiko Fukagawa,[5] Tomoko Yamasaki,[5] Yutaka Kakizoe,[2] Yuichiro Izumi,[3] Takashige Kuwabara,[4] Masataka Adachi,[1] Yushi Nakayama,[2] Masashi Mukoyama.[4] *[1]Department of Nephrology, Kumamoto University, Kumamoto, Japan; [2]Department of Nephrology, Kumamoto university graduate school of medical sciences, Kumamoto, Japan; [3]Kumamoto University, Kumamoto, Japan; [4]Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan; [5]Kumamoto University Hospital, Kumamoto, Japan.*

Background: Heavy- and light-chain amyloidosis (AHL) is a rare type of amyloidosis caused by deposition of monoclonal immunoglobulin heavy and light chain. Compared with patients with renal light-chain amyloidosis (AL), those with renal AHL are reported to be rarely complicated with cardiac amyloidosis, resulting in relatively better survival. We here report a rare case of renal AHL diagnosed by immunofluorescent staining and liquid chromatography-tandem mass spectrometry (LC-MS/MS) in a patient with non-ischemic cardiomyopathy.

Methods: A 73-year-old woman was referred to our hospital due to proteinuria and hematuria. Non-ischemic cardiomyopathy had been diagnosed 6 years before. Cardiac amyloidosis was suspected, but only slightly delayed gadolinium enhancement by cardiac MRI, which was confined to the inferolateral wall, did not meet the criteria for cardiac amyloidosis. She had received implantable cardioverter defibrillator because of ventricular arrhythmia. Approximately 1 year before the referral, she had experienced hematuria with no proteinuria when her serum creatinine level was 0.7 mg/dL. Upon admission, she exhibited an increased serum creatinine level to 1.89 mg/dL and significant proteinuria of 2.83 g/g creatinine. Plasma electrophoresis showed the presence of IgG-κ monoclonal protein. The ratio of κ:λ free light chain levels in serum was increased. Renal AL was first suspected on the basis of diagnosis by kidney biopsy. However, monoclonal immunoglobulin heavy-chain deposition was revealed by immunofluorescent staining and LC-MS/MS. Therefore, we finally diagnosed her as having renal AHL. We started to treat her with low doses of dexamethasone and lenalidomide, but the treatment was abandoned due to acute exacerbation of chronic heart failure. Echocardiogram exhibited concentric left ventricular hypertrophy. Further scrutiny and close follow-up are crucial to demonstrate that she suffered from cardiac amyloidosis complicated with AHL.

Results:

Conclusions: We here report a rare case of renal AHL diagnosed with LC-MS/MS, who could be probably complicated with morbid cardiac amyloidosis. Accurate diagnosis is extremely important to give insight into prognostic implication in patients with AHL.

TH-PO642

Light Chain Cast Nephropathy and Vascular Limited Renal Amyloidosis Occurring Simultaneously in a Patient Krishna Sury,[1] Gilbert W. Moeckel,[2] Jeffrey M. Turner.[1] *[1]Section of Nephrology, Yale University School of Medicine, New Haven, CT; [2]Department of Renal Pathology, Yale University School of Medicine, New Haven, CT.*

Background: Bence Jones proteins can lead to renal injury by multiple mechanisms; the biochemical properties of the immunoglobulin light chain play a central role in determining which type of kidney insult occurs. We present a case in which a patient simultaneously had vascular limited AL amyloidosis and light chain cast nephropathy. This sparked our interest in the molecular characteristics that, when present, might allow an immunoglobulin light chain to concurrently cause two distinct types of injury in separate compartments of the kidney.

Methods: A 53-year-old man presented with acute kidney injury (AKI) in the setting of six months of dizziness and progressively worsening pain from lower extremity claudication. Imaging revealed lucent lesions in the vertebrae, prompting a bone marrow biopsy that was diagnostic for multiple myeloma. The Congo red stain was negative for amyloid. Treatment of myeloma was delayed by onset of severe, symptomatic orthostatic hypotension. Workup including echocardiogram and cosyntropin stimulation test was unrevealing, and administration of intravenous fluids, fludrocortisone and midodrine was ineffective. His AKI progressed and he required dialysis but could not tolerate treatment due to severe hypotension. We attributed his renal decline to untreated myeloma, but this did not explain the orthostasis. Kidney biopsy revealed both light chain cast nephropathy and vascular-limited AL amyloidosis. Sadly, shortly thereafter the patient developed bradyarrhythmias and died of bradycardic arrest.

Results:

Conclusions: Multiple myeloma can present with a variety of renal manifestations; the type of injury depends upon the biochemical properties of the causative immunoglobulin light chain. AL amyloidosis occurs when the specific amino acid sequences and charge properties present promote the conformational change of light chains into amyloid fibrils. Alternatively, cast nephropathy occurs when there is an amino acid segment that stimulates light chain binding to uromodulin within the tubules. Rarely, these two distinct lesions occur simultaneously, as seen in our patient. We speculate that this occurs when a single species of monoclonal light chain possesses biochemical properties encompassing characteristics of both AL amyloidosis and cast nephropathy.

TH-PO643

A Case of Rapidly Progressive Glomerulonephritis Secondary to Monoclonal Gammopathy Diego A. Beltran Melgarejo, Ahmed Al-Sheyyab, Neil S. Sanghani. *Division of Nephrology, Vanderbilt University Medical Center, Nashville, TN.*

Background: Proliferative glomerulonephritis with monoclonal IgG deposition (PGNMID) is characterized by monoclonal glomerular deposits staining for a single light-chain isotype and a single heavy-chain subclass. It is more common in white female adults and usually presents with hematuria, nephrotic range proteinuria, and renal failure. Evidence of dysproteinemia is seen in only ~30% of the cases.

Methods: A 74 y/o Caucasian man with history of hypertension presented with a rash and rapidly progressive glomerulonephritis (RPGN). Physical exam revealed severe hypertension, trace lower extremity edema, and a non-blanching purpuric rash in all 4 extremities. The rest of his exam was normal. Lab results showed a serum creatinine (SCr) of 4.5 mg/dl (baseline 1 mg/dl), hematuria, and nephrotic range proteinuria. C3 and C4 were normal. There was no hemolysis or thrombocytopenia. ANA, AntiDNA, ANCA, antiGBMAb, cryoglobulins, and HCV/HBV/HIV serologies, were negative. Immunofixation electrophoresis did not show a monoclonal protein in the serum or urine. Kappa (κ) and lambda (λ) serum light chains were mildly elevated but κ/λ ratio was normal. Skin biopsy demonstrated superficial perivascular dermatitis suggestive of a drug eruption or urticaria. Renal biopsy revealed endocapillary proliferation, cellular crescents, and fibrinoid necrosis. There was granular mesangial and pseudo-linear capillary loop staining by IF with monoclonal IgG λ (2-3+), C3 (3+) and C1q (1-2+), IgG3 (3+) and IgG4 (1-2+), with trace IgG1 and IgG2. Subendothelial and mesangial deposits without specific substructure were seen on EM. Pulse steroids resulted in stabilization of SCr and resolution of skin rash, but were discontinued due to delirium. Rituximab was started with further improvement in SCr to 3.7mg/dl.

Results:

Conclusions: PGNMID is a monoclonal gammopathy that resembles an immune-complex GN. This case highlights RPGN and possibly skin involvement as atypical presentations of this condition. Renal biopsy with particular attention to light chain and IgG subclass restriction is key to confirm the diagnosis. Though no treatment guidelines are available, the severity of renal involvement might guide immunosuppressive choice. Pulse steroids and rituximab could be a potential effective treatment for this pathology.

TH-PO644

Proliferative Glomerulonephritis with Monoclonal IgG Deposits in a Heart Transplant Patient with Hypogammaglobulinemia Jennifer Scott, Mira T. Keddis. *Mayo Clinic, Phoenix, AZ.*

Background: We report a case of proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) in a heart transplant recipient with hypogammaglobulinemia.

Methods: A 70 year-old man status post heart transplantation 4 years prior presented with peripheral edema, new onset hypertension, rising creatinine(creatinine 2.7 mg/dL), hypoalbuminemia (3.1 g/dL), hematuria and nephrotic proteinuria (7.7 g/24Hr). Baseline chronic kidney disease (creatinine 1.5-1.9 mg/dL) was attributed to immunosuppression with calcineurin inhibition. Kidney biopsy revealed membranoproliferative glomerulonephritis with monoclonal IgG3 kappa deposit. Despite persistent absolute hypogammaglobulinemia, serum IgG3 levels were normal. Bone marrow biopsies at diagnosis, and 4 years later were both negative. No monoclonal spike was detected on serum or urine protein electrophoresis with immunofixation and free light chain ratio was normal during follow-up. He was initially treated with 6 months course of cyclophosphamide and tapering prednisone and mycophenolate mofetil was held during that time. He achieved partial remission with resolution of hematuria, normalizaton of serum albumin and reduction in proteinuria by ≥50% (2.9 g/24Hr) and creatinine nadir was 1.6 mg/dL. Four months after cessation of treatment, he suffered renal relapse with creatinine peak at 3.8 mg/dL and 7g/24 Hr proteinuria. He was treated with two doses of rituximab and tapering dose of prednisone and IgG3 levels nadired to 28.6 mg/dL (normal reference 18.4-106 mg/dL). Creatinine plateaued at 3.0 mg/dL with mimal improvement to proteinuria. Progressive renal failure developed and he was commenced on dialysis 31 months after diagnosis.

Results:

Conclusions: We describe the first case of PGNMID post heart transplant, despite immunosuppression and chronic hypogammaglobulinemia. We hypothesize that treatment failure was due to persistently normal IgG3 serum levels and absence of an identified clone for targeted therapy.

TH-PO645

A Case Report of Proliferative Glomerulonephritis with Monoclonal Immunoglobulin G Kappa Deposits in the Setting of Propionibacterium granulosum Infection Sara Syeda, Sairah Sharif. *Div of Kidney Diseases and Hypertension, Brown University, Providence, RI.*

Background: Proliferative glomerulonephritis with monoclonal immunoglobulin deposition disease (PGNMID) is a rare disease that is caused by monoclonal IgG deposition. On light and electron microscopy it mimics immune complex glomerulonephritis (GN). Here we report a patient with Propionibacterium granulosum (P. granulosum) joint infection who developed acute nephrotic-nephritic syndrome, without detectable paraprotein, eventually found to have PGNMID.

Methods: An 80-year-old Hispanic male with history of insulin dependent diabetes who was being treated with penicillin for left hip P. granulosum prosthetic infection,

presented with sudden onset anasarca and serum creatinine (SCr) of 2.8mg/dL (baseline SCr was 0.7mg/dL). Workup showed nephrotic syndrome with microscopic hematuria. Over the span of next two weeks he developed anuric failure requiring dialysis. He underwent a renal biopsy which showed PGNMID on a background of diabetic nephropathy. Immunofluorescence showed 3+ granular staining for IgG, C3 and kappa light chain. Electron microscopy showed diffuse sub-epithelial "humps" and diffuse podocyte foot process effacement. Few mesangial deposits were present, but no sub-endothelial deposits seen. Serology was non-revealing, hepatitis and HIV screens were negative, complement levels (C3, C4) were normal and no paraprotein could be detected in serum or urine. He was started on steroids and given rituximab therapy (4 doses) but he remains dialysis dependent to date.

Results:

Conclusions: We report a case of PGNMID in a patient with P. granulosum infection. PGNMID typically presents with nephrotic range proteinuria, hematuria, and renal failure. Approximately one fifth patients progress to end stage renal disease. The pathogenesis is elusive, but one hypothesis is that there is hyper secretion of IgG by plasma cells or a clonal B cell population leading to its glomerular deposition. Only about 30% cases have a monoclonal spike. We speculate that an immune reaction against bacterial antigen may have triggered the process in our case. This may explain widespread sub-epithelial deposits seen on his biopsy, contrary to the literature reports of the deposits being primarily sub-endothelial and mesangial. Overall, PGNMID remains a poorly understood disease and there is no validated optimum therapy for it.

Funding: Clinical Revenue Support

TH-PO646

Natural History of Proliferative Glomerulonephritis with Monoclonal IgG Deposits: A Unique Case with 3 Renal Biopsies Obtained over 46 Years of Follow-Up Omar A. Aleter, Marjan Afrouzian, John Badalamenti, Hania Kassem. *University of Texas Medical Branch, Galveston, TX.*

Background: Introduction: Proliferative Glomerulonephritis (GN) with Monoclonal IgG deposits (PGNMID) is a rare entity first described in 2004 by Nasr et al. Since then, only 49 cases have been reported. We present a case of PGNMID with recurrent hematuria and nephrotic range proteinuria with almost half a century of follow-up.

Methods: Case Description: 79 year old Caucasian female presents with a history of two separate episodes of biopsy-proven recurrent GN over a course of 46 years. Both biopsies from 1974, and 1987 were reported as Membranoproliferative GN. The patient presented in 2016 for the third time with symptoms of fluid overload, a slight worsening in renal function (creatinine increased from 1 to 1.3), 7grams of proteinuria along with glomerular hematuria. Serological work up including serum cryoglobulins, Hepatitis B and C, ANA, Anti DNA, Complement levels, and rheumatoid factor was negative. Serum and urine protein electrophoresis showed no M spike. The third kidney biopsy was performed.

Results: Pathology: Light microscopy revealed the following glomerular findings in 9 glomeruli: global sclerosis (1/9), segmental sclerosis (3/9), endocapillary proliferation (6/9) and double contours. Other findings included mild tubular atrophy, moderate interstitial inflammation and fibrosis, and mild arteriolar hyalinosis. By immunofluorescence microscopy (IF), 12 glomeruli showed severe (+++) staining with IgG (IgG3), C3 and Kappa, only. Electron microscopy (EM) showed intramembranous and mesangial electron dense deposits, spikes and massive subepithelial humps. None of the findings fit the diagnostic criteria for any glomerular disease caused by monoclonal deposits. The final diagnosis was PGNMID with monotypic IgG/Kappa deposits

Conclusions: Discussion: With 3 renal biopsies obtained over 46 years of follow-up, our case opens a unique window into the natural history, and most importantly the pathogenesis of PGNMID. The biopsies show the immunologic/morphologic evolution of PGNMID in the kidney, confirming the benign course of the entity and its slow progression as our patient did not develop any hematological malignancy and was treated only with ACE inhibitors.

TH-PO647

Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits in Adolescent Patient Successfully Treated with Daratumumab Maria E. Drosou, Hassan A. Salameh, Fernando C. Fervenza, Nelson Leung. *Mayo Clinic, Rochester, MN.*

Background: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a renal complication of monoclonal gammopathy of renal significance (MGRS). Treatment with renin-angiotensin system blockade and immunosuppressive therapy with steroids, cyclosporine, cyclophosphamide, mycophenolate mofetil, and clone directed with rituximab and bortezomib have produced varying results. Daratumumab is a monoclonal antibody that targets the CD38 antigen on the surface of plasma cells. Since 50% of the clones in PGNMID are plasma cell in origin, this makes daratumumab a reasonable treatment option.

Methods: A 17 year old previously healthy female patient presented with nephrotic syndrome and hematuria without renal function impairment. Laboratory findings included serum albumin of 2.4 g/dl, serum creatinine (Scr) of 0.8mg/dl and proteinuria of 9 g/d. Renal biopsy revealed a PGNMID with IgG3 lambda deposits. Serum and urine monoclonal studies were negative and serum free light chains were normal.

Results: Initial treatment included steroids, mycophenolic acid and rituximab transiently reduced proteinuria to below the nephrotic range. In the next 7 months, multiple doses of intravenous steroids was administered for recurrent proteinuria and hematuria. Twelve months after initial presentation, proteinuria was back up to 5 g/d and bortezomib dexamethasone was started. Proteinuria initially improved to 2 g/d but was increasing to 3 g/d. The decision was made to add daratumumab to bortezomib dexamethasone. After 2 cycles, proteinuria was reduced by 80% to 0.7 g/d and the hematuria resolved. Scr was stable at 0.8 mg/dl.

Conclusions: To our knowledge, this is the first case of PGNMID treated with daratumumab. The young age of this patient made the treatment options more limited as preservation of her future fertility was a concern and little data exist on the long term effects of immunomodulatory drugs (IMiDs) on teratogenicity of future pregnancy. Daratumumab was chosen in order to avoid some of these complications. In combination with bortezomib and dexamethasone, it was very effective at reducing proteinuria and resolving her hematuria. With its high activity against plasma cells and its safety profile, daratumumab could be an excellent choice in the treatment of MGRS patients.

TH-PO648

De Novo Proliferative Glomerulonephritis with Monoclonal IgG in Renal Allograft Brad Long, Catreena Marji, Faris Ahmed, Mazdak A. Khalighi, Fuad S. Shihab, Laith Al-Rabadi. *University of Utah Hospital, Salt lake, UT.*

Background: Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) has recently been recognized as a unique type of glomerular injury with a wide spectrum of pathologic and clinical manifestations. It is characterized by deposition of monotypic IgG in glomeruli and is often accompanied by C3 and C1q deposition. We have previously reported a series of three cases of recurrent PGNMID in renal allografts, all of which were associated with IgG3-Kappa deposition. De novo PGNMID in renal allografts has only been reported in three cases.

Methods:

Results: Herein, we present a fourth case of de novo disease that occurred in the renal allograft of a 32 year old man with primary disease of renal dysplasia since birth and prior allograft failure due to chonic antibody-mediated rejection. The patient presented to the hospital with 10 day history of dark urine. He was found to have acute kidney injury with Cr up to 2.5 mg/dl from 1.4 mg/dl. Urine microscopy showed many RBCs and several WBCs. Urine protein to Creatinine ratio was 1.5 g/g. Serum protein electrophoresis and immunofixation were normal. Serum kappa lambda ratio was 1.3. Cryoglobulins were negative. Biopsy showed mild mesangial hypercellularity without evidence of allograft rejection. Immunofluorescence microscopy revealed mesangial deposits staining for IgG, C3, C1q and kappa light chain without staining for lambda light chain. IgG subtype staining revealed IgG1-restriction. Electron microscopy showed mesangial electron dense deposits without substructural organisation.

Conclusions: Similar to native cases of PGNMID, recurrent disease in the allograft is most often related to deposition of IgG3-kappa. However, of the four reported cases of de novo PGNMID, three were IgG1-Kappa and only one was IgG3-kappa. IgG1-kappa in renal allografts has so far been described only in de novo cases, not in recurrent cases. Ours is the fourth de novo case but is the only one that occured in the second allograft. Patients with renal transplants are on immunosuppressive therapy that may alter the disease course. Deposition of IgG1-kappa in renal allografts may represent a distinict entity which is more resistant to IS therapy. More studies are needed to investigate the impact of different immunoglobulin subclasses on disease phenotype.

TH-PO649

Acute Interstitial Nephritis in the Setting of Fibrillary Glomerulonephritis: Case Report and Review of Literature Khetisuda Suvarnasuddhi, Sairah Sharif. *Brown University, Providence, RI.*

Background: Fibrillary glomerulonephritis (FGN) is a rare primary glomerular disease that presents with hypertension, proteinuria, microscopic hematuria and variable renal failure. It is often associated with hepatitis C virus (HCV). We report a case of FGN along with acute interstitial nephritis (AIN) in patient with HCV who had response to therapy.

Methods: A 61 year old Caucasian male with past history HCV (viral load PCR 979330IU/ml), HTN, chronic kidney disease (baseline creatinine (Cr) 1.2 mg/dL), and hemorrhagic stroke presented for evaluation of hypotension and fatigue. He was found to have urinary tract infection secondary to Proteus and Enterococcus started on piperacillin/tazobactam; later de-escalated to amoxicillin/clavulanate. Course complicated by acute kidney injury (AKI). Initial etiology of AKI thought to be pre-renal azotemia from poor oral intake and ischemia from hypotension. Urine sediment revealed few muddy brown casts, WBCs> 100/HPF, RBCs >100/HPF, and few dysmorphic RBCs. Serologies were negative for autoimmune diseases, and C3 and C4 were normal. Renal ultrasound showed increased echogenicity of renal cortex; and no hydronephrosis. AKI worsened and Cr peaked at 4.3mg/dL. Due to worsening AKI renal biopsy was performed that showed on light microscopy (LM) mesangial expansion, interstitial nephritis, mild interstitial fibrosis and tubular atrophy, electron microscopy (EM) demonstrated numerous random fibrils average 15nm identified as FGN. Patient was started on steroids for interstitial nephritis, and plan to start outpatient HCV therapy. His SCr improved to 1.7 in about 2 weeks from steroid initiation.

Results:

Conclusions: FGN is found in about 1% renal biopsies. It typically presents in the fifth to sixth decade. There maybe background of HCV, polyclonal gammopathy, and/ or lymphoproliferative disorders. The LM is heterogenous usually membranoproliferative, or mesangioproliferative, or diffuse proliferative GN. EM (EM) shows randomly oriented fibrils about 20nm in diameter. Optimal therapy is not known but corticosteroids and immunosuppressants have been tried with little success. About half of patients progress to dialysis. To the best of our knowledge this is the first case of FGN with AIN reported that showed response to corticosteroids.

TH-PO650

The Uroplakin Plaque Promotes Renal Structural Integrity During Congenital and Acquired Urinary Tract Obstruction Ashley R. Jackson,[1,2] Birong Li,[1] Sudipti Gupta,[1] Shira H. Cohen,[1] Rachel Millner,[1,2] Christina B. Ching,[1,3] Kirk M. McHugh,[1,4] Brian Becknell.[1,2] *[1]Center for Clinical and Translational Research, The Research Institute at Nationwide Children's Hospital, Columbus, OH; [2]Nephrology Section, Nationwide Children's Hospital, Columbus, OH; [3]Division of Pediatric Urology, Department of Surgery, Nationwide Children's Hospital, Columbus, OH; [4]Department of Anatomy, The Ohio State University College of Medicine, Columbus, OH.*

Background: Congenital urinary tract obstruction (UTO) is the leading cause of chronic kidney disease and end stage renal disease in children. Yet many children with congenital ureteropelvic junction obstruction (UPJO) can be managed nonoperatively, with spontaneous improvement or resolution of hydronephrosis on postnatal imaging. This implies the existence of renal adaptations during UTO that preserve parenchymal integrity and function. We hypothesized that uroplakin (Upk) expression by renal urothelial cells initiates a protective adaptation during congenital and acquired UTO, serving as a gatekeeper to progressive renal injury.

Methods: The Upk plaque was destabilized in a congenital model of functional lower UTO by generating *Mgb*$^{-/-}$;*Upk1b*$^{-/-}$ mice. Diphtheria toxin (DT)-mediated depletion of Upk(+) cells was induced following unilateral ureteral obstruction (UUO) in *Upk2*$^{CreERT2/+}$;*R26*$^{DTR/+}$ mice (acute UTO model). Urine UPK2 and UPK3A levels were measured by ELISA in children undergoing pyeloplasty for UPJO versus nonobstructed controls.

Results: In *Mgb*$^{-/-}$ mice with congenital hydronephrosis, the renal urothelium acquires a bladder-like cellular composition and ultrastructure. The extent of hydronephrosis positively correlates with *Upk* mRNA content in *Mgb*$^{-/-}$ kidneys. Likewise, urinary UPK3A and UPK2 levels increase in children with UPJO, when compared to nonobstructed controls. *Mgb*$^{-/-}$; *Upk1b*$^{-/-}$ mice display disrupted renal urothelial ultrastructure; rapid onset of bilateral hydronephrosis; and adolescent mortality due to renal failure, compared to single gene deficient or wild type control mice. DT-depletion of Upk(+) cells in *Upk2*$^{CreERT2/+}$;*R26*$^{DTR/+}$ mice accelerates the progression of hydronephrosis following UUO. Absence of the Upk plaque leads to increased interstitial fibrosis in both congenital and acute UTO models, respectively, compared to Upk intact controls.

Conclusions: These studies provide the first experimental evidence that the renal Upk plaque confers an essential, protective adaptation during congenital and acquired UTO. Conversely, loss of the Upk plaque leaves the kidney vulnerable to obstructive hydronephrosis and may identify patients in need of surveillance or more immediate surgical intervention for renal deterioration.

Funding: NIDDK Support

TH-PO651

The Renal Urothelial Plaque Protects the Kidney Following Obstructive Injury Birong Li,[1] Ashley R. Jackson,[1,4] Hanna H. Cortado,[1] Sudipti Gupta,[1] Christina B. Ching,[1,2] Kirk M. McHugh,[1,3] Brian Becknell.[1,4] *[1]Center for Clinical and Translational Research, The Research Institute at Nationwide Children's Hospital, Columbus, OH; [2]Division of Pediatric Urology, Department of Surgery, Nationwide Children's Hospital, Columbus, OH; [3]Department of Anatomy, The Ohio State University College of Medicine, Columbus, OH; [4]Nephrology Section, Nationwide Children's Hospital, Columbus, OH.*

Background: The urothelial plaque, comprised of Uroplakin (Upk) proteins, establishes the urine permeability barrier and promotes structural integrity of the urinary tract. The role of the plaque in obstructive nephropathy remains incompletely understood. We tested the hypothesis that the plaque serves a critical role in limiting hydronephrosis and parenchymal injury following obstruction.

Methods: Unilateral ureteral obstruction (UUO) was induced in three week old *Upk1b*$^{-/-}$ and wild type (WT) mice. Hydronephrosis was measured by serial ultrasound. Kidneys were analyzed by standard histologic stains and immunohistochemistry (IHC). The plaque was visualized by transmission electron microscopy (TEM). Upk protein levels in total kidney extracts were evaluated by Western blotting. Urothelium from children undergoing pyeloplasty for ureteropelvic junction obstruction (UPJO) was subject to IHC, TEM, and FITC-Dextran permeability studies.

Results: UUO leads to increased Upk protein levels; urothelial stratification and uniform apical Upk expression; and ultrastructural evidence of mature, bladder-like plaque formation in WT mice. In contrast, *Upk1b*$^{-/-}$ UUO renal urothelium lacks Upk expression and urothelial plaque, and displays hyperplasia of Krt5/Krt14 cells. *Upk1b*$^{-/-}$ UUO kidneys displayed accelerated progression of hydronephrosis and increased parenchymal injury, compared to WT UUO. Urothelium from the renal pelvis and ureteropelvic junction of children with UPJO displayed Krt5/Krt14 hyperplasia, disrupted plaque and tight junctions, and increased permeability to FITC-Dextran, compared to distal urothelium.

Conclusions: Renal urothelium undergoes extensive remodeling following obstructive injury, acquiring the appearance of lower tract urothelium with increased stratification and a mature plaque. The rapid progression of hydronephrosis and parenchymal injury in *Upk1b*$^{-/-}$ mice with UUO supports the hypothesis that the plaque serves a key role in protecting the obstructed kidney. Chronic obstructive injury in children with UPJO leads to disruption of the plaque and compromised barrier function. Strategies to augment or stabilize the renal uroplakin plaque may offer a formidable therapeutic approach to preventing acute and chronic obstructive renal injury.

Funding: NIDDK Support

TH-PO652

Urothelial Injury Markers Are Elevated in Neurogenic Bladder Patients and Correlate with the Presence of Hydronephrosis Rachel Millner, Janae Preece, Sudipti Gupta, Brian Becknell, Christina B. Ching. *Nationwide Children's Hospital, Columbus, OH.*

Background: Neurogenic bladder (NGB) leads to varying bladder dysfunction and poses a high risk for chronic kidney disease. Urinary markers of urothelial injury are an intriguing approach to monitor NGB and associated urinary tract abnormalities. We hypothesize that urinary markers of urothelial integrity and injury are significantly altered in NGB vs non NGB patients and that these markers correlate with renal injury and degree of bladder dysfunction. We measured Uroplakin 3a (Upk3a), a structural urothelial protein, as a marker of urothelial integrity; and HIP/PAP, an antimicrobial peptide expressed solely by damaged urothelium, as a marker of urothelial injury.

Methods: We recruited 87 NGB patients for urine collection. Mean age was 8.7y (0.2-33y). Healthy controls consisted of 18 patients with a mean age of 13y (7-18y). Urine Upk3a and HIP/PAP were measured by ELISA. We estimated GFR using age appropriate equations and obtained urodynamics (UDS), VCUG, and renal ultrasound results by chart review. In NGB, we correlated UPK3a and HIP/PAP levels with GFR; presence of VUR, hydronephrosis, or scarring; and bladder dysfunction based on UDS classification. UDS classification was based on CDC protocol. Statistical analysis was performed by Mann Whitney U test, Spearman Correlation, and logistic regression; $p<0.05$ was considered statistically significant.

Results: Urinary HIP/PAP and UPK3a levels were significantly higher in NGB vs controls ($p<0.005$ and <0.0001, respectively) regardless of age, sex, or race. HIP/PAP was significantly associated with hydronephrosis ($p=0.02$) but not VUR, scarring, GFR, or UDS classification. Upk3a expression correlated only with presence of NGB. Type of bladder management (catheterization vs free voiding) did not impact UPk3a or HIP/PAP level. There was a negative correlation between presence of hydronephrosis and GFR ($p=0.03$).

Conclusions: NGB may be associated with urothelial exfoliation. HIP/PAP and UPK3a are potential, noninvasive biomarkers of NGB. Elevated levels of UPK3a and HIP/PAP in NGB are independent of renal function and may reflect alterations in urothelial remodeling or mechanical shedding of urothelium in response to bladder dysfunction. Furthermore, HIP/PAP may serve as an early, noninvasive marker of hydronephrosis in NGB, which is associated with reduced renal function.

TH-PO653

Identification of Novel Urinary Proteins to Distinguish Urinary Tract Infection from Colonization in Catheterization-Dependent Children Catherine Forster,[3] Stuart Goldstein,[3] Ken Greis,[2] Prasad Devarajan.[1] *[1]Cincinnati Children's Hospital, Cincinnati, OH; [2]University of Cincinnati, Cincinnati, OH; [3]Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

Background: Children with neurogenic bladders who require clean intermittent catheterization (CIC) often have bacteriuria. Distinguishing urinary tract infection (UTI) from urinary tract colonization (UTC) is difficult. Our objective was to identify urinary proteins to distinguish UTI from UTC in CIC-dependent children.

Methods: 10 CIC-dependent children were included (UTI=5, UTC=5). UTI was defined as: 1) ≥ 50,000 cfu/ mL of a uropathogen, 2) ≥ 10 urinary white blood cells, and 3) ≥2 of the following: fever, abdominal or back pain, worsened incontinence, pain with CIC, or cloudy or malodorous urine. UTC was defined as a bacteriuria in an asymptomatic patient. Medical records of patients who met UTI criteria were reviewed to select those with clear UTI symptomatology. 5 UTC patients were matched on age and uropathogen. Quantitative profiling of urine proteins with isobaric protein labeling was performed using tandem mass spectrometry. Candidate markers were normalized using a collective mixture of proteins from all samples. Relative quantitative abundance of proteins across all samples were compared. Proteins with a significant fold-change across either UTI or UTC, with ≥50% change in the average abundance across groups were identified as proteins of interest.

Results: Eight proteins were differentially expressed. These included: haptoglobin and liver fatty-acid binding protein (LFABP) overexpressed in UTI; and apolipoprotein D, α-amylase 2B, inter-α-trypsin inhibitor heavy chain H4, non-secretory ribonuclease, CD44 antigen, and prosaposin overexpressed in UTC. Protein functions include antimicrobial activity (haptoglobin), inflammation (LFABP, apolipoprotein D, inter-α-trypsin inhibitor heavy chain H4, non-secretory ribonuclease, prosaposin, and CD44 antigen), and metal binding (α-amylase 2B).

Conclusions: These urinary proteins have potential to distinguish UTI from UTC in CIC-dependent children.

Figure 1

Protein of Interest	Mean log UTC	p-value for UTC	Mean log UTI	p-value for UTI	Log ratio UTI/UTC
Haptoglobin	-0.06	0.60	0.17	0.02	0.23
Apolipoprotein D	0.20	0.01	-0.001	0.99	-0.20
a-amylase 2B	0.22	0.02	0.004	0.93	-0.22
Inter-a-trypsin inhibitor heavy chain H4	0.11	0.12	-0.11	0.04	-0.23
Non-secretory ribonuclease	0.22	0.08	-0.12	0.04	-0.34
CD44 antigen	0.22	<0.01	-0.09	0.35	-0.31
LFABP	-0.46	0.01	-0.12	0.60	0.34
Prosaposin	0.38	<0.01	0.13	0.21	-0.26

Red: increase in relative abundance of protein: Blue; decrease in relative abundance of protein: Green; statistical significance.

TH-PO654

Tubular Epithelial Cell Function in Polycystic Kidney Disease (PKD): Analysis of Cells from Children with ARPKD and NPH Wolfgang H. Ziegler, Birga Soetje, Kathrin Swolana, Arne Mertens, Amrit Khera, Dieter Haffner. *Hannover Medical School, Hannover, Germany.*

Background: PKD-related cellular defects are best understood genetically or in epithelial (cell) models analysing cell proliferation and signalling. Use of primary patient-derived renal epithelial cells provides a unique opportunity to study and quantify cell properties in epithelial function-related assays. Apart from the analysis of differences due to specific mutation, it appears interesting to correlate the severity of the renal disease i.e. GFR or organ size / morphology with alterations in epithelial cell function determined *ex vivo*.

Methods: We culture urine-derived renal epithelial cells (URECs) of patients with genetically confirmed causes of PKD, autosomal recessive polycystic kidney disease (ARPKD) and nephronophtisis (NPH), and of age-matched healthy controls. Populations of primary cells obtained within 14 days of culture are tested with respect to their proliferation rates, formation of cell-cell junctions in monolayer and barrier function (impedance) in 2D culture. In addition, their capacity to build spheroids and form cilia is addressed in 3D culture conditions using matrigel and micro-patterned adhesion chips.

Results: URECs from cohorts of patients (5-6 each) with ARPKD or NPH (mostly NPHP-1 mutation), and controls are compared in cell culture to measure quantitative characteristics that can be correlated to clinical parameters and progress of PKD. We observe a much higher success rate of epithelial cell cultivation from urine of PKD patients. Cells are mostly of collecting duct origin as determined by aquaporin 2- positive staining. MTS-based assessment of cell proliferation shows relatively stable rates between days 10 and 15 (20) of culture, which are moderately higher in patient cells. Analysis of spheroid formation in matrigel (6 days) reveals on average bigger clusters of patient cells and an individual tendency of defective lumen formation. Barrier function of UREC monolayers is increased in a patient-specific manner.

Conclusions: Determination of genotype and / or disease state specific renal epithelial cell properties in URECs is expected to provide a better understanding of the mechanism and progression of disease processes in renal epithelium and may provide options for testing of pharmaceutical intervention.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO655

Early Proteinuria Lowering by ACE Inhibition Predicts Renal Survival in Children with CKD Sophie Van den Belt,[1] Hiddo J. Lambers Heerspink,[1] Valentina Gracchi,[1] Dick de Zeeuw,[1] Elke Wuehl,[2] Franz S. Schaefer.[2] *[1]University Medical Center Groningen, Groningen, Netherlands; [2]University of Heidelberg, Heidelberg, Germany.*

Background: Proteinuria predicts renal disease progression in adults and children with chronic kidney disease (CKD). While lowering of proteinuria by various interventional strategies has been demonstrated to be nephroprotective in adults, pediatric data are scarce. Here, we present a post-hoc analysis of the ESCAPE Trial regarding the relationship between the initial antiproteinuric effect of standardized ACE inhibition and renal disease progression in children with CKD.

Methods: All children were started on a fixed dose of ramipril (6 mg/m^2/day) and subsequently randomized to aim for conventional (<95th percentile) or intensified (<50th percentile) blood pressure control. The initial log-transformed change in proteinuria was assessed from baseline to first measurement after starting ramipril (at 2.6 ± 1.4 months). Cox proportional hazard models were used to estimate the association between initial proteinuria change and risk of reaching the renal end point (composite of 50% decline in eGFR or progression to end-stage-renal disease), adjusted for age, gender, renal diagnosis, baseline proteinuria, blood pressure, eGFR and change in blood pressure.

Results: Of 285 eligible children (60% male, age 11.5±3.9 years), 81 reached the composite endpoint within 5 years of follow-up. Proteinuria was reduced following start of ramipril treatment by a median of 39% (interquartile range 7-64%). The initial proteinuria reduction was associated with a reduction in the renal composite endpoint: hazard ratio 0.71 (CI 0.41-1.23) and 0.44 (CI 0.23-0.82) for the 30-60% and >60% proteinuria reduction groups respectively compared to the <30% reduction group. This association was independent of all the above mentioned tested covariates.

Conclusions: The degree of early anti-proteinuric effect of ACE inhibition is independently predictive of long-term preservation of renal function in children with CKD. This finding lends support to the notion that proteinuria lowering should be considered an important target in the management of pediatric CKD.

TH-PO656

Association between Routine Newborn Metabolic Profiles, CKD, and the Need for Dialysis in Infants and Children Manish M. Sood. *Ottawa Hospital Research Institute, Ottawa, ON, Canada. Group/Team: Ottawa Newborn Metabolomics Project.*

Background: Metabolomics offers considerable promise in early disease detection. We set out to test the hypothesis that routine newborn metabolic profiles at birth, obtained as screening for inborn errors of metabolism, would be associated with kidney disease and add incremental information to known clinical risk factors.

Methods: We conducted a population-level cohort study in Ontario, Canada including metabolic profiles from 1, 288, 905 newborns from 2006 to 2015. The primary outcome was CKD or dialysis. Individual metabolites and their ratio combinations were examined in logistic regression models after adjustment for established risk factors for kidney disease and incremental risk prediction measured.

Results: : CKD occurred in 2,086(0.16%, median time 612 days) and dialysis in 641(0.05%, median time 99 days) infants and children. Individual metabolites consisted of amino acids, acyl-carnitines, markers of fatty acid oxidation and others. Base models incorporating clinical risk factors only provided C-statistics of 0.61 for CKD and 0.70 for dialysis. The addition of identified metabolites to the models composed of clinical risk factors resulted in significant incremental improvement in the performance of both models (CKD model: c-statistic 0.66 NRI 0.36 IDI 0.04, dialysis model: c-statistic 0.77 NRI 0.57 IDI 0.09). This was consistent after internal validation using bootstrapping and a sensitivity analysis excluding outcomes within the first 30 days.

Conclusions: Routinely collected screening metabolites at birth are associated with chronic kidney disease and the need for dialytic therapies in infants and children and add incremental information to traditional clinical risk factors.

TH-PO657

Proteomic Study Revealed the Elevation of Urinary Alpha-1-Microglobulin/Bikunin Excretion in Nephrolithiasis Familial Members Thasinas Dissayabutra, Trairak Pisitkun, Piyaratana Tosukhowong. *Chulalongkorn University, Pathumwan, Bangkok, Thailand. Group/Team: Biochemistry and Molecular Disease Research Unit.*

Background: Several literatures demonstrated higher incidence of urinary tract stone formation in familial members of nephrolithiasis (NL), although no responsible gene was established. Our previous studies revealed elevated urinary excretion rate of calcium, phosphate, albumin and protein as well as diminished urinary citrate and sulfated glycosaminoglycan excretion in non-stone-forming children of NL patients compare with normal children. These disorders were similarly observed in NL patients comparing with general population but in the greater severity pattern. Hence, to indicate which proteins were over-excreted in children with NL parents, we investigated proteomic profile in the susceptible children comparing with stone patients and general population.

Methods: Fourteen NL patients (N) and 29 of their children (NC), 26 healthy volunteers (V) and 28 of their children (VC) were enrolled. The 24-hour urine were collected. Except for NL, participants were screened for hematuria by urine strip test. Then, urine of NC and VC (children group) were used for proteomic study by mass spectrophotometry (LC-MS). Alpha-1-microglobulin/bikunin [AMBP] was subsequently measured in all participants using ELISA.

Results: According to proteomic profiles, the urinary excretion rate of 29 proteins were higher in non-stone-forming NC than VC. Among these, many proteins were previously reported to be associated with NL, such as AMBP, α_1-antitrypsin, serotransferrin, trefoil factor, prothrombin, vitronectin, etc. Our study observed the elevation of AMBP excretion in both NL patients (28.3±41.2 *vs* 10.2±20.1 mg/day, p=0.048) and their children (25.2±27.8 *vs* 10.2±10.6 mg/day, p=0.011.)

Conclusions: Urinary excretion rate of several stone-related proteins, including AMBP, appeared to be elevated in NL family even in members who yet to develop stone. Our results indicated that these abnormal urinary proteins may be the risks for high incidence of NL in familial members, and may be heritable. Further study aims to validate other susceptible urinary proteins, the pathogenesis and inherited pattern.

Funding: Government Support - Non-U.S.

TH-PO658

A Novel SLC12A1 Compound Heterozygous Mutation in Antenatal Bartter Syndrome Type 1 Showing Benign Clinical Course Zentaro Kiuchi,[2] Kandai Nozu,[1] Kunimasa Yan.[2] *[1]Kobe University, Kobe, Japan; [2]Kyorin University School of Medicine, Tokyo, Japan.*

Background: [Introduction]Antenatal Bartter syndrome (BS) type 1 is an autosomal recessive kidney disorder that shows severe renal dysfunction caused by loss-of-function mutations in the solute carrier family 12 member 1 (*SLC12A1*) gene.

Methods: [Case Description]This case is currently a 2 year-old girl. At 24 weeks of gestation, she had polyhydramnios in utero. She was born by vaginal delivery at 33 weeks 3 days. Polyuria (5-7ml/kg/hr) was observed from at the age of 1 day, accompanied by hyponatremia and hypokalemia and mild metabolic alkalosis. Urine osmotic pressure was always under 200mOsm/L. She had high reninemia and hyperaldosteronism. There was no morphological abnormality in kidney ultrasonography. Abdominal CT did not show kidney calcification. She had no hypertension or edema, but she suffered from failure to thrive (body length –2.1SD, body weight -2.7SD). Her psychomotor development is

currently normal and growth is becoming to be within normal range. Analysis of the *SLC12A1* gene demonstrated heterozygous mutation consisting of 2 novel mutations: c.2094delG in exon16 from father and c.1094T>C (p.I365T) in exon8 from mother, which led to the final diagnosis as BS type 1. Currently she receives treatment with oral medications including NaCl, KCl, Spironolactone and Alfacalcidol.

Results:

Conclusions: [Discussion]We here present an antenatal BS type 1 caused by novel heterozygous mutations of the *SLC12A1* gene. c.2094delG leads to the final formation of the protein mass of 75 kDa compared to the mature mass of 120 kDa. This immature mass is predicted to interfere homo-oligomer formation. On the other hand, the functional influence of p.I365T is not able to speculate so far. However, this report clearly indicates that a combination of heterozygous mutation found in our case would not severely impact on the renal tubular function after birth even in the cases with antenatal Bartter syndrome type1.

TH-PO659

Combination of Different Urinary Omics Traits Improves the Prediction of Postnatal Renal Outcome in Fetuses with Posterior Urethral Valves (PUV) Benedicte Buffin-Meyer, Julie Klein, Francoise Muller, Benjamin Breuil, Panagiotis Moulos, Lounis Nadia, Jean-loup Bascands, Stéphane Decramer, Joost Schanstra. *Inserm U1048, Toulouse, France.*

Background: Urinary omics-based strategies are promising tools in medicine as they have already led to the design of multimarker models for the assessment of complex diseases. Nevertheless, advances still need to be made since most models using single omics traits are unable to reach a 100% accuracy and display a so-called "gray zone" defined by the uncertainty of the prediction. Here we verified the hypothesis whether a combination of urinary fetal peptides and metabolites provides an improved prediction of postnatal renal function in fetuses with PUV compared to the individual omics traits.

Methods: Using capillary electrophoresis coupled to mass spectrometry, we explored the urinary metabolome from 13 PUV fetuses with early ESRD and 12 PUV fetuses without postnatal ESRD at 2 years.

Results: This allowed the identification of 24 differentially abundant fetal urinary metabolites which were modelled into a svm classifier, alone or in combination with 12 peptides predictive of disease progression (Klein et al, PMID:23946195). The predictive capacities of models composed of metabolites (24m model), peptides (12p model) or association of both (24m_12p model) were compared in a separate independent validation cohort of 35 fetuses with PUV. The gray zone was generated as the range of svm scores for which the negative likelihood ratio (LR) was >0.05 and the positive LR was <20. Sensitivity, specificity (excluding patients in gray zone) as well as area under the ROC curve (AUC) and net reclassification improvements (NRI) of PUV patients were evaluated (Table 1).

Conclusions: While the individual metabolome- and peptidome-based models already display high accuracy for identification of the disease classes, the discriminative power can be significantly improved by combination of omics traits. This supports the general concept that multi-omics approaches can improve the clinical assessment of disease.

Funding: Private Foundation Support, Government Support - Non-U.S.

Table 1

Model	24m	12p	24m_12p
Sensitivity (%)	50.0 [25 - 74]	81.3 [62 - 100]	87.5 [71 - 100]*
Specificity (%)	68.4 [47 - 89]	78.9 [61 - 97]	84.2 [68 - 100]
AUC	0.90 [0.79-1]	0.97 [0.91-1]	0.99 [0.96-1]
NRI versus 24m (%)			36.5 [4-69]§
NRI versus 12p (%)			11.5 [0-39]

*p<0.05 vs 24m, §p<0.05 vs 0.

TH-PO660

Comparison of Different Urine Collection Techniques to Establish and Monitor Albuminuria in Healthy Toddlers Sophie Van den Belt, Valentina Gracchi, Dick de Zeeuw, Hiddo J. Lambers Heerspink. *UMC Groningen, Groningen, Netherlands.*

Background: For measurement of albuminuria, guidelines in adults recommend to measure urinary albumin creatinine ratio (U_{ACR}) in first morning void (FMV) urine samples collected over three consecutive days. Since such a guideline is absent in toddlers, we compared several urine collection strategies.

Methods: Both a FMV and a random daytime urine sample were collected on three consecutive days at week 0 (visit 1), week 4 (visit 2) and week 8 (visit 3) in toddlers aged 12 to 48 months. Urinary albumin (U_{AC}), urinary creatinine (U_{CR}) and U_{ACR} were assessed. Intra-individual coefficients of variation (CV) of U_{AC} and U_{ACR} were determined using only the first U_{AC} or U_{ACR} measurement of each visit and using all three U_{AC} or U_{ACR} measurements per visit, and were compared with published CV of adults (Witte et al. JASN 2009).

Results: 80 toddlers (mean age 26.6 months, 53% male) were included. Geometric Mean (GM) U_{AC} was 5.7 mg/L (SD 1.9) in FMV and 5.5 mg/L (SD 2.0) in random samples. GM U_{ACR} was 17.6 mg/g (SD 2.6) in FMV and 21.7 mg/g (SD 2.3) in random samples. The variation in GM U_{AC} or U_{ACR} between toddlers derived from three FMV or random samples at visit 1 was smaller compared to single samples. The lowest intra-individual CV was observed when U_{AC} was measured in FMV over three consecutive days (table). CV's of U_{AC} and U_{CR} were similar to adults. However, U_{ACR} CV was considerably higher in toddlers.

Conclusions: These data confirm that FMV samples are preferred over random samples to establish and monitor (micro)albuminuria in toddlers, just like in adults. Surprisingly, unlike adults, within-individual CV was smaller for U_{AC} compared to U_{ACR} in toddlers. This appears not to be explained by a higher U_{CR} variability in toddlers. Further studies, particularly into variations in other renal functions that cause the mismatch between albumin and creatinine variation, are needed to explain these differences between children and adults.

Intra-individual CV, median (25th-75th percentile)

	Toddlers				Adults (Witte et al. JASN 2009)	
	Single urine sample per visit		Three urine samples per visit		Three urine samples	
	FMV sample	Random sample	FMV sample	Random sample	FMV sample	Random sample
UAC	47.5% (20.4-99.8)*‡	44.7% (11.8-85.6)	38.3% (22.1-56.7)	41.7% (24.4-64.1)	30.9% (19.4-47.8)	40.9% (27.8-70.2)
UACR	54.3% (27.5-114.6)*†	81.6% (39.5-144.3)*†	44.5% (28.2-74.2)*	61.7% (34.1-90.4)*†	19.1% (11.6-28.4)*	35.8% (17.6-55.6)
UCR	42.3% (20.4-77.6)	58.4% (35.6-87.7)	27.8% (15.8-57.3)	46.4% (23.9-69.5)	23.5% (13.8-66.7)	31.3% (19.1-56.1)

*p<0.05 vs UAC three FMV samples; †p<0.05 vs UACR three FMV samples

TH-PO661

Effect of Growth Hormone Therapy on Renal Function in Children Born Small for Gestational Age Kazuya Matsumura, Hironori Shibata, Tomohiro Ishii, Tomonobu Hasegawa, Midori Awazu. *Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan.*

Background: Low birth weight infants, especially those born small for gestational age (SGA), are known to have fewer nephrons. Growth hormone (GH) induces catch-up growth in short children born SGA, which is a risk factor for chronic kidney disease (CKD). GH also causes hyperfiltration, which may lead to glomerulosclerosis. We retrospectively examined the effect of GH therapy on renal function in children born SGA.

Methods: Nineteen subjects born SGA (age 3 to 25 years) were studied. Ten were treated with GH and 9 served as controls. Blood pressure, serum creatinine, uric acid, urine microalbumin to creatinine ratio (malb/Cr), and the trajectory of eGFR, calculated by quantic equation for Japanese children (2 to 18 years) or formulas for Japanese adults (≥19 years), were compared.

Results: GH was started at the median age of 4 years (range 3-5). The median dose and duration was 0.25 mg/kg/week (range 0.2-0.3) and 66 months (range 23-95). There were no significant differences in the background characteristics between GH group and controls including age (11 vs 10 years), birth weight (1109 vs 804 g), gestational age (32.3 vs 28.5 weeks), sex, and initial eGFR (107 vs 98 ml/min/1.73 m^2). Only one child in each group did not show catch-up growth. eGFR declined in 6 (60%) in GH group and in 1 (11%) in controls (P<0.05). Of 6 GH-treated children whose eGFR declined (107 to 89 ml/min/1.73 m^2, P=0.09), eGFR before GH was stable in 2, increasing in 2, and declining in 2. In the remaining children who received GH, eGFR trajectory before and after the start of GH was decline followed by increasing (2), decline followed by stable (1), and continuously increasing (1), suggesting GH-induced hyperfiltration. There was no change in eGFR trajectory in control children; 2 increasing, 6 stable, and 1 decline. Urine malb/Cr (9.7 vs 9.6 mg/g) and the number of children with elevated malb/Cr (6 vs 4) were not different between GH group and controls. One child, however, developed microalbuminuria after GH was started. Hypertension or hyperuricemia was not observed in either group throughout the observation period.

Conclusions: eGFR decline was more frequent in SGA children with GH therapy compared with those not on GH. Initially stable or increasing eGFR followed by decline after the initiation of GH suggests that GH may promote progression of CKD in SGA children.

TH-PO662

Identifying Important Outcomes for Children with CKD and Their Caregivers: Focus Groups with Nominal Group Technique Camilla S. Hanson,[2,3] Gayathri Raman,[3] Yifan Zhang,[3] Angelique F. Ralph,[2,3] Angela Ju,[2,3] Laura J. James,[2,3] Andrea K. Viecelli,[1] Jonathan C. Craig,[2,3] Allison Tong.[2,3] *[1]Sir Charles Gairdner Hospital, Perth, NSW, Australia; [2]University of Sydney, Sydney School of Public Health, Faculty of Medicine, Westmead, NSW, Australia; [3]Centre for Kidney Research, The Children's Hospital at Westmead, Sydney, NSW, Australia. Group/Team: SONG Kids Investigators and Steering Committee.*

Background: Chronic kidney disease has a devastating impact on the lives of children and their families, due to delayed development, debilitating symptoms and life-threatening complications. Trials frequently report surrogate outcomes, rather than clinical and patient-centered outcomes, and children and caregivers are rarely involved in determining what outcomes should be reported. We aimed to identify outcomes that are important to children with CKD and their caregivers, and ultimately to inform clinical care and a patient-focussed research agenda.

Methods: Children and adolescents with CKD (stage 1-5, dialysis, transplant) and caregivers were purposively sampled from 4 centers across Australia, the United States and Canada. Participants identified and ranked outcomes, and discussed the reasons for their priorities. The mean rank score was determined, and qualitative data were analyzed thematically.

Results: Twenty-six patients (aged 10 – 21 years, mean 14 years) and 45 caregivers participated in 12 groups, and identified 32 outcomes. The five highest ranked outcomes for patients were: physical activity (7.6/10), kidney function (7.6), fatigue (6.9), infection (6.8) and survival (6.8). Caregiver's five highest ranked outcomes were: kidney function (8.5), weight gain (8.2), survival (7.5), infection/immunity (7.4), and graft survival (7.2). The themes underpinning their choices were gaining independence and realizing potential; upheaval and intrusion on daily living; preserving health and kidney function; seeking control; and certainty of future.

Conclusions: Children prioritized their kidney health and survival, appearance, and social, sport, and school participation. Caregivers were most concerned about their child's kidney function, graft survival, infection, survival, and gaining weight. Trials that include outcomes important to children with CKD and their caregivers can better inform shared decision-making.

TH-PO663

Renal Function and Blood Pressure in Adolescents Born Preterm with Very Low Birth Weight Andrew M. South,[5,6] Patricia A. Nixon,[4,5] Mark C. Chappell,[6,3] Debra I. Diz,[6,3] Gregory B. Russell,[2] Elizabeth T. Jensen,[1] Hossam A. Shaltout,[6] Lisa Washburn.[5,6] *[1]Wake Forest School of Medicine, Winston-Salem, NC; [2]Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, NC; [3]Surgery-Hypertension and Vascular Research, Wake Forest School of Medicine, Winston-Salem, NC; [4]Health and Exercise Science, Wake Forest University, Winston Salem, NC; [5]Pediatrics, Wake Forest School of Medicine, Winston Salem, NC; [6]Cardiovascular Sciences Center, Wake Forest School of Medicine, Winston Salem, NC.*

Background: Survival of children born prematurely has improved, but preterm birth as well as low birth weight may increase the risk of developing kidney disease in adulthood. However, the timing of the development of renal dysfunction and its progression is unclear. We hypothesize that worse kidney function will be present in early adolescence in children born preterm with very low birth weight (VLBW) as compared to term controls.

Methods: We measured systolic and diastolic blood pressure (BP), serum creatinine, and urine albumin at age 14 years in 96 subjects born preterm with VLBW (mean birth weight 1048 g) and 43 term controls. We calculated the glomerular filtration rate (GFR) by the Schwartz equation and urine albumin-to-creatinine ratio (ACR). We used generalized linear models to estimate the association between preterm birth and renal function, adjusting for maternal hypertensive pregnancy and socioeconomic status.

Results: In addition to higher mean systolic and diastolic BP (p<0.01 and p=0.03, respectively), adolescents born preterm had significantly-decreased GFR (β: -8.17 mL/min/1.73 m^2, 95% CI -15.93 to -0.4) as compared to term controls. Adjustment for covariates attenuated this relationship (β: -6.34 mL/min/1.73 m^2, -15.04 to 2.36). While subjects born preterm had higher median ACR, adjustment for potential confounders attenuated this relationship (ln ACR β: 0.34, -0.04 to 0.72).

Conclusions: Higher BP and reduced renal function were present in adolescents born preterm with VLBW compared to term peers, though the association between preterm birth and GFR was weakened after adjusting for confounders. While other factors should be considered, our study provides evidence of an early divergence of renal function during adolescence as a consequence of prematurity.

Funding: Other NIH Support - NICHD PO1 HD047584

TH-PO664

Assessing the Hydration Status of Children with CKD and On Dialysis: A Comparison of Techniques Caroline S. Eng,[1] Rukshana Shroff.[2] *[1]Hospital Tuanku Jaafar Seremban, SEREMBAN, Malaysia; [2]Department of Paediatric Nephrology, Great Ormond Street Hospital for Children, London, United Kingdom.*

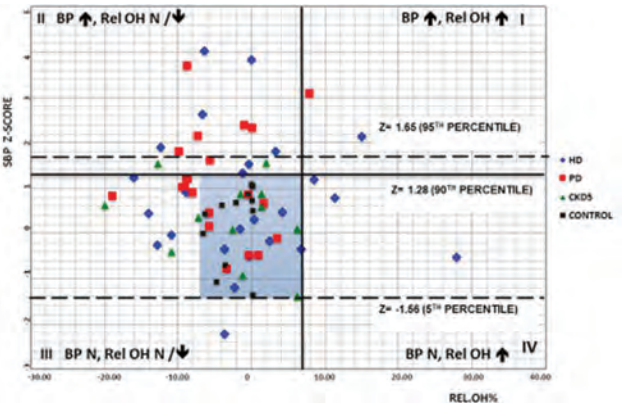
Background: Fluid balance is pivotal in the management of children with chronic kidney disease (CKD) and on dialysis. Although many techniques are available to assess fluid status, there are few studies in children, and none of the techniques have been compared against each other or against cardiovascular outcome measures.

Methods: We performed a longitudinal study in 30 CKD children and 13 age-matched healthy controls (71 measurements) to determine a correlation between optimal weight by bioimpedance spectroscopy (Wt-BIS) and clinical assessment (Wt-CA). The accuracy of Wt-BIS (relative overhydration [Rel-OH]) was compared against indicators of fluid status and cardiovascular measures.

Results: There was poor agreement between Wt-CA and Wt-BIS in children on dialysis when compared to CKD5 or control subjects (p=0.01). We developed a modified chart to plot Rel-OH against systolic BP z-score for the appropriate representation of volume status and BP in children. 25% of measurements showed systolic BP >90th percentile but not with concurrent overhydration. Rel-OH correlated with peripheral pulse pressure (p=0.03; R=0.3), higher NT-proBNP (p=0.02; R=0.33) and left ventricular end-diastolic diameter (p=0.05;R=0.38). Central aortic mean and pulse pressure significantly associated with the left ventricular end-diastolic diameter (p=0.03;R=0.47 and p=0.01;R=0.50 respectively), but not with Rel-OH. Systolic BP was positively associated with PWV z-score (p=0.04). 40% of children on HD and 30% on PD had increased LVMI.

Conclusions: BIS provides an objective method for the assessment of hydration status in children on dialysis. We noted a marked discrepancy between BP and hydration status in children on dialysis that warrants further investigation.

Funding: Clinical Revenue Support



Relative overhydration (Rel-OH) against systolic blood pressure (SBP) Z-score.

TH-PO665

Effect of Glomerulus Endocapillary Proliferation Lesion on the Heavy Proteinuria in Children with HSPN Yanjie Huang, Xia Liu. *The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, Zhengzhou, China.*

Background: To analyse whether glomerulus endocapillary proliferation lesion is one of important pathologic factors in HSPN and its influence on high and medium molecular weight proteins in urine.

Methods: The pathological features of 148 children HSPN with heavy proteinuria were investigated retrospectively. The means of 24h proteinuria and urinary IgG, transferrin and albumin were detected using immunonephelometry method. The correlation between endocapillary proliferation lesion and 24h proteinuria, urinary IgG, transferrin and albumin were analyzed respectively.

Results: Of 581 cases of HSPN who underwent renal biopsy, 148 cases of HSPN accompanied by heavy proteinuria accounted for 25.47%. Pathological types of HSPN accompanied by heavy proteinuria included IIb, IIIb, IIIb and endocapillary proliferation, IVb, and pure endocapillary proliferation type. Among these types, pure endocapillary proliferation type accounted for 7.43%. The value of 24h proteinuria and urine albumin quantitation in endocapillary proliferation type HSPN were higher than other pathological types, and the percentage of endocapillary proliferation is correlated positively with 24h proteinuria and urine albumin quantitation.

Conclusions: The pathological type of HSPN with heavy proteinuria is diversity. Glomerulus endocapillary proliferation is one of the important pathological factor of HSPN heavy proteinuria, and albumin is major urine protein composition.

Funding: Government Support - Non-U.S.

TH-PO666

Polycythemia in Subjects Born with a History of Preterm Birth and Extremely Low Birth Weight Nariaki Asada,[2] Kazuya Matsumura,[2] Yohei Matsuzaki,[1] Midori Awazu.[2] *[1]Keio University, Tokyo, Japan; [2]Keio University School of Medicine, Tokyo, Japan.*

Background: Low birth weight (LBW) infants have reduced number of nephrons and are at risk of chronic kidney disease (CKD). While capillary rarefaction has been reported in other organs, it had been unknown whether LBW affects peritubular capillary (PTC) development. We recently reported 2 subjects with a history of preterm birth and extremely LBW (ELBW) who showed PTC rarefaction and erythropoietin (EPO)-induced polycythemia in adolescence (Asada N. Pediatr Nephrol 2017). In the present study, we examined the frequency and risk factors of polycythemia in subjects born with preterm and ELBW.

Methods: Thirty-six patients with a history of ELBW whose hemoglobin, eGFR, and urinalysis had been measured were analyzed retrospectively (17 male, 19 female; age at analysis 4-19 years; birth weight 316-998 g; gestational age 22-32 weeks). Polycythemia was defined as hemoglobin levels more than 2 SD above the mean for age and gender for at least 2 consecutive years (>13.5 g/dL under 6 years, >15.5 g/dL from 6 to 12 years, and >16.0 g/dL above 12 years. Expected EPO levels were calculated from hemoglobin levels using an equation of "Log (EPO) = 3.436 – 0.1675 × Hb".

Results: Twelve patients (33.3%) showed polycythemia (7 male, 5 female; age at finding 2-16 years). Serum EPO, evaluated in 4 patients, were higher than expected levels. Birth weight was significantly smaller in polycythemia group (618 g vs 802 g). Gestational age, intrauterine growth restriction, and sex were not associated with polycythemia. In polycythemia group, eGFR was significantly smaller (72.7 vs 106.8 ml/min/1.73 m^2), and eGFR less than 90 ml/min/1.73 m^2 and proteinuria were found in 9 (75%) and 3 (25%), respectively. In non-polycythemia group, on the other hand, only 5 (21%, P=0.06) and 1 (4%, P<0.05) had reduced eGFR and proteinuria, respectively. Thus CKD was more prevalent in polycythemia group (75% vs 25%, P<0.05). Among perinatal complications, chronic lung disease was significantly associated with polycythemia, while retinopathy of prematurity and acute kidney injury were not.

Conclusions: Polycythemia was observed in one third of subjects born preterm with ELBW, and was associated with CKD.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO667

Role of Endothelial Leptin Receptor in the Development of Renal Injury Induced by a High Fat Diet Hidenori Urai, Takeshi Kanda, Arata Kurokochi, Rina Kitahama, Shu Wakino, Hiroshi Itoh. *Keio University School of Medicine, Tokyo, Japan.*

Background: Obesity and type 2 diabetes promotes endothelial dysfunction, which contributes to the progression of chronic kidney disease. Leptin is secreted from adipocyte and decreases body weight by controlling energy expenditure and food intake. Leptin-deficient ob/ob mice and leptin receptor (ObR)-deficient db/db mice are prone to glomerulosclerosis. However, the effect of leptin on renal injury is controversial and the site target of leptin action in the kidney has not been fully elucidated. In this study, we examined the role of ObR in the endothelium on glomerulosclerosis on high fat diet.

Methods: Using the Cre/loxP system, vascular endothelial (VE)-cadherin-Cre transgenic mice were crossed with $ObR^{flox/flox}$ mice to generate vascular endothelial ObR deficient mice (EC-KO mice). EC-KO mice and control $ObR^{flox/flox}$ without Cre (EC-WT) mice were fed on standard diet or 45% high-fat diet for 24 weeks. Urinary albumin, blood pressure and pathological findings were examined. The We evaluated gene expressions in isolated microvascular endothelial cells from EC-WT and EC-KO mice were also evaluated.

Results: The expression of ObR was detected in glomerulus and peritubular capillaries in EC-WT mice while its expression was not detected in EC-KO mice. When comparing EC-WT with EC-KO on high fat diet, Tthere was no significant difference in body weight, kidney weight, blood pressure and serum parameters between EC-WT and EC-KO on high fat diet,. However, high fat diet-induced increase in urinary albumin excretion was significantly lower in EC-KO mice (0.453 ± 0.064 g/gCr) compared with EC-WT mice (0.656 ± 0.052 g/gCr). High fat diet-induced glomerular hypertrophy was also ameliorated in EC-KO mice compared with EC-WT mice (2874 ± 110 μm^2 vs. 3269 ± 129 μm^2, n=6). Glomerular sclerosis, evaluated by masson's trichrome staining, was significantly reduced in EC-KO mice. The tissue fibrosis was also reduced in EC-KO mice. In addition, The expression of TGFβ1 and PAI-1, which are known for promoting fibrosis and downstream target of leptin, were significantly decreased in primary endothelial cells from EC-KO mice.

Conclusions: These data suggest that leptin exacerbates renal injury through the development of glomerular hyperfiltration and endothelial induction of TGFβ1 and PAI-1 genes.

TH-PO668

Evaluation of the Reno-Protective Effects of Empagliflozin in Diabetic Nephropathy Using In Vivo Imaging Kengo Kidokoro,[2] Atsushi Uchida,[1] Yuji Sogawa,[1] Hajime Nagasu,[1] Minoru Satoh,[1] Tamaki Sasaki,[3] Naoki Kashihara.[1] *[1]Kawasaki Medical School, Kurashiki, Japan; [2]Kawasaki Medical school, Kurashiki Okayama, Japan; [3]None, Kurashiki, Japan.*

Background: Diabetic nephropathy (DN) is one of the most common vascular complications associated with diabetes mellitus. In the EMPA-REG outcome trial, Empagliflozin (Empa), a sodium–glucose cotransporter 2 inhibitor, not only reduced the risk of cardiovascular events but also slowed the progression of DN in patients with type 2 diabetes. Improvement of glomerular hyperfiltraion via the tubulo-glomerular feedback (TGF) mechanism is considered one of the possible reasons for renal protection by Empa in DN. However, the theory remains a matter of speculation. In this study, the in vivo multiphoton microscope (MPM) imaging technique was used to investigate the glomerular protective effects of Empa and whether Empa regulated the vascular tonus of the glomerular afferent artery via the TGF mechanism.

Methods: We used C57BL/6 mice and spontaneously diabetic Ins2Akita mice (Akita). In the first experiment, mice were treated with Empa (20mg/kg/day; gavage) and insulin (0.1U/body; i.s.) for four weeks. Glomerular reactive oxygen species (ROS) and nitric oxide (NO) production were evaluated in an ex vivo study. Next, we measured a single nephron GFR (SNGFR) using MPM in each group. Furthermore, the change of the SNGFRs in the same glomeruli before and two hours after medication were also studied to evaluate the acute effect of Empa. Finally, an nNOS inhibitor and a COX2 inhibitor were administered to these groups to inhibit vasodilator factors delivered from the macula densa. The SNGFR was then evaluated.

Results: Increased ROS and decreased NO productions in the glomeruli were observed in the Akita, but they were improved with the Empa treatment. The SNGFR in the Akita was significantly higher than in the control, however, Empa improved that alteration. In the acute study using Akita, the SNGFR in the same glomeruli were significantly reduced by Empa with blood glucose level lowering. Moreover, the diameter of the afferent artery was significantly decreased after the Empa treatment. An nNOS inhibitor and a COX2 inhibitor reduced the SNGFR in the Akita, and no additional effect regarding Empa was observed. These data indicate that Empa can reduce glomerular hyperfiltration in DN via TGF.

Conclusions: Empagliflozin improved glomerular hyperfiltration in DN via the TGF mechanism and contributed to glomerular protection.

Funding: Commercial Support - Boehringer Ingelheim

TH-PO669

PBI-4050 Prevents Diabetic Nephropathy and Protects β-Cells in NOD Mice: A Model of Type 1 Diabetes Lyne Gagnon, Kathy Hince, François Sarra-Bournet, Mikaël Tremblay, Marie-Pier Cloutier, Sylvie Létourneau, Pierre Laurin, Brigitte Grouix, Francois A. Leblond. *Prometic BioSciences Inc., Laval, QC, Canada.*

Background: PBI-4050, a novel first-in-class orally active antifibrotic compound, which is currently in a phase II clinical trial, significantly reduced glycated hemoglobin (HbA1c) after 12 and 24 weeks of treatment in patients with type 2 diabetes and metabolic syndrome with elevated HbA1c despite anti-hyperglycemic treatment. PBI-4050 also reduced biomarkers associated to kidney injury. In the present study, we examined whether PBI-4050 may prevent diabetic nephropathy in NOD mice, a model of type 1 diabetes.

Methods: NOD/ShiLtJ female mice (8 weeks of age) received vehicle (water) or PBI-4050 (200 mg/kg/day) by daily gastric gavage for 23 weeks.

Results: In kidney, PBI-4050 protects against lesions by reducing glomerular volume and mesangial cross sectional area. Furthermore, tubular lesions were absent in PBI-4050-treated mice. Tubular dystrophy as PAS granular accumulation was constantly present in proximal tubules of NOD control mice and was completely abrogated by treatment with PBI-4050. Mice treated with PBI-4050 did not develop diabetes. OGTT was also normalized in PBI-4050 treated mice. Despite a reduced number of islets compared to non-diabetic mice, NOD mice treated with PBI-4050 maintained normoglycemia and showed a 30% reduction in the number of islets with grade 4 lesions.

Conclusions: This data suggests that PBI-4050 prevents diabetic nephropathy and complete destruction of β-cells and islets in type 1 diabetes model.

Funding: Commercial Support - Prometic Life Sciences Inc.

TH-PO670

Inhibiting Inflammasome Activation with Suramin Protects against Progression of Diabetic Kidney Disease in KK-Ay Mice Kaori Oda,[1] Satoshi Miyamoto,[2] Ryo Kodera,[2,3] Jun Wada,[1] Kenichi Shikata.[2] *[1]Graduate School of Medicine Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan; [2]Center for Innovative Clinical Medicine, Okayama University Hospital, Okayama, Japan; [3]Osafune Clinic, Setouchi, Japan.*

Background: Recent reports have suggested that innate inflammation via inflammasome activation is involved in the pathogenesis of diabetic kidney disease (DKD). Inflammasome, a protein complex, is activated in various diseases, leading to production of IL-1β and IL-18 through activation of caspase-1. In addition, danger-associated molecular patterns (DAMPs) are the crucial triggers for inflammasome activation via its receptors including P2X and P2Y receptors. We have demonstrated that both serum and urinary IL-18 levels are elevated in patients with DKD (Nakamura A et al. Diabetes Care, 2005), and that ATP, one of the important DAMPs, is increased in the glomeruli of diabetic mice by mass spectrometry imaging (Miyamoto S et al. EBioMedicine, 2016). The aim of this study was to determine if suramin, a non-selective P2X and P2Y antagonist, protects against DKD in KK-Ay mice.

Methods: Four weeks-aged male nondiabetic C57BL/6 mice and diabetic KK-Ay mice ($KK\text{-}A^y$/TaJcl) were randomly assigned to four groups: C57BL/6+vehicle (Control), C57BL/6+suramin, KK-Ay+vehicle (KK-Ay), KK-Ay+suramin, n=6-12/group. Vehicle or suramin (1 mg/kgBW) were injected intraperitoneally once every two weeks over an 8-week period. Glomerular size and mesangial matrix area were assessed by morphometric analysis. Expression of inflammasome-related genes in renal cortex were examined by quantitative real-time PCR.

Results: Urinary albumin/creatinine ratio, elevated in KK-Ay (280.0 ± 29.3 mg/gCr, p<0.001) vs. Control (1.7 ± 0.3 mg/gCr) mice, was significantly reduced with suramin (160.6 ± 27.3 mg/gCr, p<0.01), whereas there were no significant differences in body weight or HbA1c between both diabetic groups. The increases in both glomerular size and glomerular mesangial matrix area in KK-Ay group, were significantly reduced with suramin (p<0.001). In addition, the increase in inflammasome-related gene expressions including IL-18, P2X4 and P2X7 in KK-Ay group were significantly suppressed with suramin (p<0.001).

Conclusions: Our results suggest that inflammasome is activated in the diabetic kidney and the inhibition of inflammasome with suramin protects against progression of DKD. Suramin may be beneficial for the treatment of DKD.

Funding: Commercial Support - Eli Lilly Japan K.K.

TH-PO671

The Effect of GSTK1 on the MAM Related Apoptosis in Diabetic Nephropathy Li Zhao, Chun Hu, Xianghui Chen, Yachun Han, Xiaofen Xiong, Li Li, Ming Yang, Peng Gao, Li Xiao, Jun Li, Fuyou Liu, Lin Sun. *Department of Nephrology, 2nd Xiangya Hospital, Central South University, Changsha, China.*

Background: Mitochondria-associated ER Membrane (MAM)is a platform between mitochondria and ER, which involved in mitochondrial dynamic, calcium signaling, autophagy, apoptosis and so on. GSTK1 has glutathione peroxidase activity, which as an important antioxidant enzyme can blocking ROS damage. We found by first time GSTK1 locates on MAM of the mouse kidney, but its function in MAM is nuclear. Here we

hypothesize that GSTK1 in MAM modulates cell apoptosis may paly an important role in the kidney damagy of DN.

Methods: Morphological change of MAM was measured by EM in db/db and db/m mice. The protein of mitochondria, MAM and ER were extracted from the kdieny of diabetic mouse. The expression of GSTK1, Mfn-2, cytochrome C, caspase-3 and Bax were measured by Western blot analyse. In vitro study: MAM morphology was detected by confocal scanning in HK-2 cells. The mitochondria and MAM were also isolated from HK-2 cells induced by high glucose transfection with or without GSTK1 plasmid. The expression and distribution of GSTK1,Mfn-2,cytochrome C and Bax in MAM were detected by Western blot. Further, the interaction between GSTK1 and cytochrome C was observed by physical conformation, Confocal scanning and co-immunoprecipitation.

Results: Compared with db/m mice, the morphology of MAM was abnormal with the distance widen in the kidney of db/db mice. The expression of GSTK1 and Mfn-2 in mitochondria and MAM subdomain were down-regulated in db/db mices kidney. Conversely, the expression of Bax, Caspase-3 and cytochrome C were up-regulated. In addition, mitochondria was less adjacent to ER in HK-2 cells treated with high glucose(HG), while the expression of Mfn-2 was increased in mitochondria and MAM. all of altered were reversed in that transfection of GSTK1. Furthermore, a increased GSTK1 binding to cytochrome C was obsvered in HK-2 cells treated by HG. Overexpression of GSTK1 in HK-2 cells inhibited the release of mito.cytochrome C into the cytosol and Bax translocation to mitochondria, and reduced mitochondria modulate cells apoptosis.

Conclusions: The integrity of MAM were damaged and the distance between mitochondria and ER was increased in diabetic kidney or HG induced HK-2 cells. Overexpression of GSTK1 up-regulated the expression of Mfn-2 and then enhanced the interaction of MAM, which could inhibits apoptosis in DN.

Funding: Government Support - Non-U.S.

TH-PO672

Amelioration of Kidney Injury by Inhibition of Sodium Glucose Cotransporter 2 with Canagliflozin in Mice with Type 2 Diabetes Mellitus L. Gabriel Navar,[1] Ryousuke Satou,[2] Kayoko Miyata,[2] Akemi Katsurada,[1] Courtney M. Dugas,[1] Daniel J. Lightell, jr.,[1] T C. Woods.[1] *[1]Tulane University, New Orleans, LA; [2]Tulane University Health Science Center, New Orleans, LA.*

Background: Type 2 diabetes mellitus (T2DM) is associated with progressively declining renal function resulting from hyperglycemia, oxidative stress and activated intrarenal renin-angiotensin system. The sodium glucose co-transporter 2 (SGLT2) is responsible for most of the glucose reabsorption by renal tubules. SGLT2 inhibitors increase glucose excretion and lower blood glucose levels, thus serving as a new therapy for T2DM. However, their effects on the developing renal injury in T2DM remain unclear.

Methods: Accordingly, we evaluated the ability of canagliflozin (CANA), an SGLT2 inhibitor, to ameliorate kidney injury in T2DM. Intrarenal angiotensinogen (AGT) and oxidative stress were also evaluated as contributing factors to diabetic nephropathy. Male New Zealand Obese mice were fed a regular fat diet (RFD, 4% fat) or a high fat diet (HFD, 40% fat) to induce diabetes. When the mice fed with the HFD exhibited >350 mg/dl blood glucose levels, both RFD and HFD fed mice were treated with 10 mg/kg/day CANA or vehicle for 6 weeks by daily oral gavage.

Results: CANA treatment decreased blood glucose levels and suppressed body weight gain in HFD mice, which remained suppressed for the duration of the study. Systolic blood pressure in HFD groups (134.7±3.6 mmHg) was also normalized by CANA (110.0±6.0 mmHg). The augmented cortical AGT mRNA and protein levels and elevated urinary 8-isoprostane levels caused by the HFD were ameliorated by CANA treatment. Histological analysis revealed the development of renal tubular fibrosis in HFD group (3.4±0.9-fold, fibrotic score, ratio to RFD) that was suppressed by CANA (0.9±0.3-fold). Furthermore, elevated macrophage infiltration into the interstitium caused by HFD was attenuated by CANA (RFD: 0.35±0.07, HFD: 0.99±0.09 and HFD+CANA: 0.49±0.07, positive area %). In contrast, CANA did not improve glomerular matrix expansion and albuminuria observed in the HFD group.

Conclusions: These results demonstrate that CANA mitigates renal tubular fibrosis and renal inflammation accompanied by suppression of renal oxidative stress and AGT expression in T2DM.

Funding: Other NIH Support - CoBRE Grant on Translational Research in Hypertension and Renal Biology, Commercial Support - Janssen Pharmaceuticals

TH-PO673

Contribution of Myo-Inositol Oxygenase in Age: Rage Mediated Renal Tubulo-Interstitial Injury Isha Sharma,[1] Rashmi S. Tupe,[2] Yashpal S. Kanwar.[3] *[1]NORTHWESTERN UNIVERSITY, CHICAGO, IL; [2]Northwestern University, Chicago, IL; [3]Northwestern University Medical School, Chicago, IL.*

Background: Advanced glycation end products (AGEs) have been postulated to play a critical role in pathogenesis of diabetic nephropathy (DN). Myo-inositol Oxygenase (MIOX), a proximal tubular enzyme, which has been implicated in tubulo-interstitial injury in the context of DN.

Methods: Aim of the present study was to investigate the effect of AGEs on MIOX expression and to delineate the mechanisms that lead to tubulo-interstitial injury. To test this we examined the status of MIOX, RAGE and relevant cellular signaling pathway activated following AGE:RAGE interaction in cultured tubular cells and kidneys of AGE-BSA treated mice.

Results: Using solid phase binding assay an enhanced binding of RAGE with AGE-BSA, -laminin and -collagen IV was observed compared to non-glycated proteins. AGE-BSA treatment led to an increased MIOX activity and its expression in a time- and dose-dependent manner. AGE-BSA also increased MIOX promoter activity. This was associated with activation of various signaling kinases of PI3K-AKT pathway and increased expression of NF-κB, TGF-β and fibronectin. Treatment with MIOX- and RAGE-siRNA negatively impacted the activation of PI3K-AKT signaling cascade and expression of fibronectin, NF-κB and TGF-β. Interestingly, concomitant with the up-regulation of MIOX there was an increased generation of reactive oxygen species (ROS), which could be abrogated with the MIOX- or RAGE-siRNA treatment. *In vivo* the kidneys of mice treated with AGE-BSA for 2 weeks had significantly high urinary AC ratio, up-regulation of MIOX, RAGE and NF-κB along with influx of monocytes in the tubulo-interstitium, increased expression of MCP-1, IL-6 and fibronectin, and generation of ROS. These molecular derangements were abrogated with the concomitant treatment of inhibitors MIOX or RAGE (D-glucarate & FPS-ZM1).

Conclusions: These *in vivo* and *in vitro* studies support a critical role of AGE:RAGE interaction in the activation of PI3K-AKT pathway and up-regulation of MIOX; as a result of which there is an excessive generation of ROS, increased expression of NF-κB, inflammatory cytokines, TGF-β and fibronectin. Collectively, these observations highlight the importance of MIOX in the contribution towards tubulo-interstitial injury in DN.

Funding: NIDDK Support

TH-PO674

Dyslipidemia Worsens Diabetic Kidney Disease in a Novel Type 2 Diabetes Mouse Model of Combined Kidney Disease and Atherosclerosis – A Possible Role for ApoC-III Jenny E. Kanter,[3] Farah Kramer,[3] Anna Batorsky,[4] Baohai Shao,[4] Jinkuk Choi,[1] Kelly L. Hudkins,[2] Karin Bornfeldt,[3] Charles E. Alpers.[5] *[1]UCLA, Los Angeles, CA; [2]University of WA, Seattle, WA; [3]University of Washington, Seattle, WA; [4]University of Washington, Seattle, WA; [5]University of Washington Medical Center, Seattle, WA.*

Background: Diabetic kidney disease and atherosclerotic disease are major causes of morbidity and mortality associated with type 2 diabetes (T2D), and diabetic kidney disease is a major cardiovascular risk factor. The BTBR mouse strain with leptin-deficiency (*Lep*^{ob}) has emerged as one of the best mouse models of human diabetic kidney disease. However, no T2D mouse model of combined diabetic kidney disease and atherosclerosis exists. Our goal was to generate such a model.

Methods: To this end, the LDL receptor was targeted for degradation via IDOL (inducible degrader of the LDL receptor) overexpression, using a liver-targeted adeno-associated virus (AAV-DJ/8) in BTBR wildtype (WT) and BTBR *Lep*^{ob} (OB) mice.

Results: Liver-targeted IDOL-AAV-DJ/8 increased plasma LDL cholesterol, as compared with the control eGFP-AAV-DJ/8 (OB eGFP 194 ± 15 vs OB IDOL 250 ± 10 mg/dl LDL cholesterol). IDOL-induced dyslipidemia caused formation of atherosclerotic lesions of an intermediate stage, which contained both macrophages and smooth muscle cells. BTBR OB mice exhibited diabetic kidney disease. IDOL-induced dyslipidemia worsened albumin/creatinine ratio (885 ± 96 μg/mg in OB eGFP vs 1681 ± 391μg/mg in OB IDOL) and glomerular macrophage accumulation (1.9 ± 0.4 Mac-2 positive cells/glomerulus in OB eGFP vs 3.5 ± 0.7 in OB IDOL) and cortex inflammation (increased expression of *Ccl2, Il1b* and *Vcam1* comparing OB IDOL to OB eGFP), but had no effect on mesangial expansion or podocyte numbers. Furthermore, HDL-associated apolipoprotein C-III (apoC-III) was elevated in OB mice compared with WT mice and this was further increased by IDOL-induced dyslipidemia. ApoC-III in turn correlated positively with both atherosclerosis and albuminuria.

Conclusions: Thus, by inducing hepatic degradation of the LDL receptor, we generated a T2D model of combined kidney disease and atherosclerosis in which dyslipidemia may worsen the kidney disease, potentially through elevated apoC-III. This model provides a new tool to study mechanisms, interactions, and treatment strategies of diabetic kidney disease and atherosclerosis.

Funding: NIDDK Support, Other NIH Support - NHLBI, Private Foundation Support

TH-PO675

NADPH-Oxidase NOX5 Aggravates Renal Injury in Human Diabetic Nephropathy Jay C. Jha,[4] Melinda T. Coughlan,[3] David A. Power,[1] Chris R. Kennedy,[2] Mark E. Cooper,[3] Karin Jandeleit-Dahm.[3] *[1]Austin Health, Heidelberg, NSW, Australia; [2]Kidney Research Centre, Ottawa, ON, Canada; [3]Monash University, Melbourne, VIC, Australia; [4]Department of Diabetes, Monash University, Melbourne, VIC, Australia.*

Background: Renal oxidative stress plays an important role in mediating kidney injury in diabetes. There is increasing evidences that recently discovered pro-oxidant enzyme, Nox5 plays a significant role in human diabetic nephropathy (DN). Nox5 is present in humans and rabbits but not in mice or rats. Thus, there is a paucity of information about Nox5 in conventional animal models of DN. We examined the role of Nox5 in human diabetic nephropathy, in human renal cell populations as well as in a high fat fed rabbit model of kidney disease.

Methods: Protein expression of Nox5 and its localization in glomerular cells (podocytes and mesangial cells) and tubular cells were examined by immunostaining in human kidney biopsies obtained from non-diabetic and diabetic individuals. In vitro, human mesangial cells, podocytes and proximal tubules were exposed to high glucose, TGF-β and AngII and Nox5 was knockdown in these renal cells. Cell morphology, gene and protein expression of markers of fibrosis and inflammation as well as putative signalling pathways and the level of ROS were assessed in these human renal cells. We

also examined expression of pro-fibrotic gene in high fat fed rabbits by next generation sequencing (NGS) and RT-PCR and renal injury by histochemistry.

Results: Expression of Nox5 was increased in both glomerular and tubular compartments of kidney biopsies obtained from diabetic individuals when compared to non-diabetic individuals. In addition, silencing of Nox5 in human renal cells resulted in reduced ROS production and decreased expression of pro-fibrotic and pro-inflammatory markers as well as putative elements that are implicated in DN. Moreover, increased expression of Nox5 in high fat fed rabbits versus normal diet fed rabbits was associated with increased expression of fibronectin, CTGF, collagen IV and VCAM-1 as well as increased mesangial expansion in the kidney.

Conclusions: These findings suggest that Nox5 accelerates renal injury in diabetes and provide proof of principle for the development of a new renoprotective agent in diabetes.

TH-PO676

Function of NADPH Oxidase in Diabetic Nephropathy and Development of Its Inhibitor as a Therapeutic Candidate Sae rom Lee, Eunjung An, Yun soo Bae. *Ewha Womans University, Seoul, Republic of Korea.*

Background: Substantial evidence has indicated that transient reactive oxygen species (ROS) can be produced by receptor-mediated biochemical processes, although ROS including superoxide anion and hydrogen peroxide (H2O2) are thought to be by-products of aerobic respiration damaging effects on DNA, protein, and lipid. ROS generation in cell signaling has been extensively studied in terms of NADPH oxidase (gp91phox) in phagocytic cells. However, after identification of the homologs of gp91phox (Nox1, Nox3-5, Duox1-2) from non-phagocytic cells, the function of the generated ROS has been extended into an understanding of various cellular events, including cell growth, differentiation, apoptosis, and inflammation responses. We show the effect of a novel pan-NOX-inhibitor, EWHA-18278, on diabetic nephropathy in type 2 diabetic mice.

Methods: Six-week-old male diabetic db/db mice was treated with EWHA-18278(60mpk) per day and sacrificed after 12 weeks. The effect of EHWA-18278 on oxidative markers such as 8-isoprostane in plasma or urine was measured. Furthermore, EHWA-18278 effect on renal function was investigated by urinary albumin excretion and creatinine clearance and PAS-staining, alpha-SMA histologically.

Results: EWHA-18278 significantly improved insulin resistance in diabetic mice, similar to GKT137831. Oxidative stress as measured by plasma 8-isoprostane level was decreased in the EWHA-18278 group compared to diabetic controls. All lipid profiles, both in plasma and tissues improved with Nox inhibition. EWHA-18278 decreased urinary albumin excretion and preserved creatinine clearance. In diabetic kidneys, EWHA-18278 significantly improved mesangial expansion, but GKT137831 did not. Additionally, F4/80 infiltration in the adipose tissue and kidney decreased with EWHA-18278 treatment.

Conclusions: In conclusion, our findings provide evidence that pan-Nox inhibition by EWHA-18278 may have greater renoprotective potential than does GKT137831 in diabetic nephropathy. These findings suggest that EWHA-18278 may be a useful new therapeutic agent in treating type II diabetes and diabetic nephropathy.

TH-PO677

Calorie Intake Reduction May Prevent Progression of Diabetic Nephropathy by Suppressing Podocyte Hypertrophic Injury via mTORC1 Pathway Activation Akihiro Minakawa,[1] Akihiro Fukuda,[2] Masao Kikuchi,[1] Yuji Sato,[1] Shouichi Fujimoto.[1] *[1]Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, University of Miyazaki, Miyazaki, Japan; [2]Department of Endocrinology, Metabolism, Rheumatology and Nephrology, Faculty of Medicine, Oita University, Yufu, Japan.*

Background: Glomerular hypertrophy is a well-established component of diabetic nephropathy. We have previously shown that a mismatch between glomerular volume and podocyte mass (reduced podocyte density) was associated with development of albuminuria and accelerated podocyte hypertrophic stress in a rat model of type 2 diabetes. Here, we tested whether calorie intake reduction prevents progression of diabetic nephropathy by suppressing podocyte hypertrophic injury.

Methods: Using the leptin-deficient Zucker diabetic fatty rat model of type 2 diabetes with *ad libitum* feeding, we have found increased glomerular volume and decreased podocyte density at 15 weeks. At 15 weeks, we thus divided the rats into an *ad libitum* diet group (n=5) and a 40% calorie intake reduction group (n=6). Urine samples were collected every 4 weeks and the rats were sacrificed at 30 weeks. We measured the urinary excretion of podocyte mRNA, urine albumin/creatinine ratio, glomerular volume, podocyte number per glomerular tuft, podocyte density, and P-S6 expression of podocytes.

Results: In the calorie intake reduction group, urine volume and blood glucose were significantly decreased by 18 weeks, albuminuria was significantly decreased by 22 weeks and urinary excretion of podocyte mRNA was decreased by 26 weeks, compared with the *ad libitum* diet group. At 30 weeks, in the calorie intake reduction group, podocyte number per glomerular tuft was not decreased ($p=0.30$), while glomerular volume tended to be decreased (12% decrease, $p=0.052$), podocyte density was significantly preserved ($p=0.02$), and P-S6 expression of podocytes was significantly decreased ($p<0.01$), compared to the *ad libitum* diet group.

Conclusions: Our results suggest that calorie intake reduction prevented the progression of diabetic nephropathy in a rat model of type 2 diabetes by suppressing podocyte hypertrophic injury via mTORC1 pathway activation. Calorie intake reduction could thus be a useful tool for slowing the progression of diabetic nephropathy.

TH-PO678

Elevated Prorenin Accelerates the Development of Diabetic Nephropathy in STZ-Induced Cyp1a1-Prorenin Transgenic Rats Chunyan Gu,[1] Alfred K. Cheung,[1] Yufeng Huang.[1,2] *[1]Division of Nephrology, University of Utah, Salt Lake City, UT; [2]Dept. of Pathophysiology, University of Nantong School of Medicine, Nantong, China.*

Background: Elevated plasma prorenin levels are commonly found in diabetic patients and appear to predict the development of diabetic nephropathy (DN). However, the potential pathological role of prorenin in diabetes is unclear. In this study, a transgenic, inducible, hepatic prorenin-overexpressing rat model (cyp1a1-prorenin transgenic rat, TG) was generated and then a model of STZ-induced diabetic cyp1a1-prorenin transgenic rat was established to mimic diabetic patients with elevated plasma prorenin.

Methods: Four transgenic groups (5 rats per group): TG controls, STZ-induced diabetic TG rats, and STZ-induced diabetic TG rats treated with either amlodipine (AM, 10mg/kg/d by daily gavage) or enalapril (Ena, 200mg/L in drinking water), were assigned to receive a diet containing 0.15% of the gene activator indole-3-carbinonl (I3C) started at 2wks after diabetes was confirmed (BG>250 mg/dl). Four corresponding groups of 5 wild-type (WT) rats receiving same treatments served as WT controls. Treatments were given at the same as I3C was given for 6 wks. Animals in all groups were sacrificed at 8 wks after induction of diabetes.

Results: Diabetic WT rats had normal blood pressure but developed microalbuminuria and had kidney hypertrophy and mildly increased glomerular ECM accumulation. Diabetic TG rats with elevated plasma prorenin levels showed hypertension and much worsen features of DN when compared with the diabetic WT animals or non-diabetic transgenic rats, including worsen albuminuria, kidney hypertrophy, enhanced podocyte foot effacement and glomerulosclerosis. Furthermore, increased prorenin in diabetes further stimulated renal cellular signals of Nox2, p47phox and NF-kB-p65, which have been shown to contribute to the development of DN. Treatment with either amlodipine or enalapril had no effect on blood glucose levels, but prevented the development of hypertension and ameliorated, but did not prevented, the development of renal fibrosis, related pro-fibrotic signals and podocyte injury.

Conclusions: These results indicate that prorenin accelerates the development of DN, which is only partially dependent on prorenin-induced hypertension and angiotensin II's action. These results may suggest the involvement of additional angiotensin II-independent effects of prorenin in DN.

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TH-PO679

Transcriptomic Profile in Early versus Late Stages of Murine Diabetic Nephropathy Haichun Yang,[4] Anette E. Ericsson,[3] Anna Reznichenko,[3] José Sanchez,[2] Lena William-Olsson,[3] Magnus Soderberg,[1] Anna Granqvist,[3] Raymond C. Harris,[4] Kasey C. Vickers,[4] Agnes B. Fogo.[4] *[1]Drug, Safety and Metabolism, AstraZeneca, Molndal, Sweden; [2]Discovery Sciences, AstraZeneca, Molndal, Sweden; [3]Innovative Medicines and Early Development, Cardiovascular and Metabolic Diseases, AstraZeneca R&D Molndal, Molndal, Sweden; [4]Vanderbilt University Medical Center, Nashville, TN.*

Background: Diabetic nephropathy (DN) has both glomerular and tubular injury. As a DN model, db/db/eNOS$^{-/-}$ mice develop albuminuria and glomerular hypertrophy by age 10 weeks, and progress to nodular glomerular injury and reduced GFR by week 18. By RNA sequencing of isolated glomeruli and kidney cortex at different time points, we aimed to determine the transcriptional profiles critical for glomeruli vs tubular injury in DN.

Methods: db/db/eNOS$^{-/-}$ (DN) and nondiabetic control db/eNOS$^{-/-}$ mice (C) were sacrificed at week 10 and 18. The left kidney was harvested for isolating glomerular RNA, while the right kidney was used for extracting cortex RNA.

Results: 86 genes from the glomerular extract showed different expression levels in DN vs C at week 10 (49 upregulated and 37 downregulated), and 5248 genes differed at week 18 (3599 up and 1649 down). 528 transcripts from cortical extracts were different in DN and C at week 10 (213 up and 315 down), and 684 transcripts differed) at week 18 (456 up and 228 down, but with overlap of only 116 genes in early vs late cortical samples. Metabolic processes, such as calcium, urea and P450 pathways, differed mostly in tubular vs glomerular analysis. Genes expressed at week 10 but not week 18 suggest a role in early but not progressive DN. We detected 118 upregulated and 188 downregulated genes at week 10, which did not differ at week 18 in DN. Among them, only 10 genes (7 up and 3 down) were present only in glomerular but not cortical samples, and include genes that modulate matrix, cell proliferation and tissue-specific differentiation.

Conclusions: In summary, by comparing db/db/eNOS$^{-/-}$ vs db/eNOS$^{-/-}$ mice, early vs late stage diabetics, and glomeruli vs cortex, we determined that there were marked increases in differentially modulated glomerular genes at later stages of disease, with different gene expression patterns in the tubulointerstitial compartment over time. These data indicate that glomerular and tubular mechanisms of DN injury are not identical, and also evolve over time.

Funding: Commercial Support - AstraZeneca PLC

TH-PO680

Comparison of Glomerular Endothelial Cell Gene Expression Profiles in Diabetic Mice with or without eNOS Deficiency Jia Fu,[1,3] Chengguo Wei,[3] Weijia Zhang,[3] Detlef O. Schlondorff,[3] Peter Y. Chuang,[2,3] Zhihong Liu,[1] John C. He,[3] Kyung Lee.[3] *[1]National Clinical Research Center of Kidney Diseases, Nanjing, China; [2]Connecticut Kidney Center, LLC, Orange, CT; [3]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Glomerular endothelial cell (GEC) injury is a key early event in DN, but the underlining mechanisms remain unclear. In order to assess the key molecular changes in GECs in early DN, we performed a transcriptomic analysis of GECs isolated from diabetic and nondiabetic mice. Two diabetic models were used: 1) streptozotocin (STZ)-induced diabetic mice and 2) STZ-induced diabetic eNOS$^{-/-}$ mice to take advantage of the accelerated DN development with eNOS-deficiency.

Methods: GECs were isolated from transgenic mice expressing histone H2B-fused enhanced yellow fluorescent protein (EYFP) under the Flk-1 promoter. Flk1-EYFP mice were crossed with wildypte or eNOS$^{-/-}$ mice, and diabetes was induced with STZ. Vehicle-injected mice served as controls. All mice were sacrificed at 10 weeks post-injection, and GECs were sorted for mRNA sequencing. Differentially expressed genes (DEGs) from GECs of diabetic mice were analyzed. Key altered pathways were validated by qPCR and immunostaining in second set of experimental mice, and kidney biopsies were performed over time in diabetic and control mice to determine GEC numbers.

Results: DEGs in both diabetic models showed significant alterations in genes related to apoptosis, oxidative stress, cell migration, and proliferation. GECs from diabetic eNOS$^{-/-}$ mice further exhibited altered expressions in genes related to vascular endothelial cell function and epigenetic regulation. We confirmed by immunostaining that GECs indeed exhibited increased oxidative stress and apoptosis in diabetic wildtype mice, which were further exacerbated in diabetic eNOS$^{-/-}$ mice. We also confirmed that epigenetic regulation was altered specifically in diabetic eNOS$^{-/-}$ GECs. Interestingly, we observed a biphasic change in GECs of diabetic eNOS$^{-/-}$ mice that was characterized by an increase at 6-weeks post-diabetes induction, followed by a significant loss by 10-weeks post-induction, suggesting that an early angiogenic process precedes increased apoptosis and failure of regeneration at the subsequent phase of DN injury.

Conclusions: Our results reveal several novel mechanisms of GEC injury in early DN, which can serve as a basis for further exploration into the mechanism of early diabetic GEC injury and for potential new therapeutic intervention to prevent GEC injury in early DN.

Funding: NIDDK Support

TH-PO681

Gene Expression Profiles of Glomeruli from BTBR ob/ob Mice Treated with Prolyl Hydroxylase Inhibitor Suggest Involvement of Extracellular Matrix Modulators in Pathogenesis of Diabetic Kidney Disease Mai Sugahara,[1] Tetsuhiro Tanaka,[1] Shinji Tanaka,[1] Kenji Fukui,[1,2] Akira Shimizu,[3] Yu Ishimoto,[1] Reiko Inagi,[1] Masaomi Nangaku.[1] *[1]University of Tokyo, Tokyo, Japan; [2]JT CPRI, Osaka, Japan; [3]Nippion Medical School, Tokyo, Japan.*

Background: We have previously shown that administration of prolyl hydroxylase (PHD) inhibitor, JTZ-951 (Japan Tobacco Inc.), improved glucose/lipid metabolism and decreased albuminuria in BTBR ob/ob mice (TH-PO450, ASN Kidney Week 2016). In order to elucidate the mechanism, we performed microarray gene expression analysis using isolated glomeruli.

Methods: Four-week-old male BTBR ob/ob mice were divided into the vehicle and JTZ-951 groups. JTZ-951 (0.005%; in feed) was administered from 4 weeks of age until euthanasia at 22 weeks. cDNA samples from isolated glomeruli were hybridized using Agilent SurePrint G3 Mouse GE Microarray 8x60K ver. 2.0.

Results: During the study period, mice in the JTZ-951 group tended to exhibit lower blood glucose levels (HbA1c: 8.9±0.3 vs 8.2±0.2%) and significantly lower total cholesterol levels (260±26 vs 164±19 mg/dL) with comparable food intake. JTZ-951 significantly decreased urinary albumin at 16 and 22 weeks (4.8±0.7 vs 1.9±0.4 and 5.9±1.3 vs 2.3±0.5 mg/mgCr, respectively) without affecting GFR. Podocyte and endothelial damages were markedly ameliorated in the JTZ-951 group. In gene expression analysis, 315 transcripts were upregulated and 150 were downregulated more than 3-fold in BTBR ob/ob mice compared to the wild type (WT). Among the 315 diabetes-upregulated genes, 102 revealed smaller increases in the JTZ-951 group (JTZ-951/WT<3). Similarly, the expression of 103 of the 150 diabetes-downregulated genes were restored in the JTZ-951 group (JTZ-951/WT>1/3). Pathway analysis of these 205 genes using Reactome database indicated that 5 out of the 25 top-ranked enriched pathways were related to extracellular matrix (ECM) organization and cell-matrix interactions; the corresponding entities included lysyl oxidase-like 2, thrombospondin 1, collagen type VIII alpha 1, bone morphogenetic protein 2, and CD44.

Conclusions: Long-term administration of JTZ-951 decreased albuminuria and ameliorated podocyte and endothelial damage, along with improvement in glucose/lipid metabolism. Microarray analysis revealed changes in the expression of genes associated with ECM, suggesting that ECM modulation within the glomerulus may play a role in the pathogenesis of diabetic kidney disease.

Funding: Commercial Support - Japan Tobacco Inc.

TH-PO682

Reduced C/EBP-α Expression Aggravates the Podocyte Impairment and Renal Injury in Experimental Diabetes Liwen Zhang, Fangfang Zhou, Jian Liu, Ji Ying, Weiming Wang, Nan Chen. *Department of Nephrology, Ruijin Hospoital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.*

Background: CCAAT/enhancer binding protein-α (C/EBP-α) is one of the critical transcription factors involved in inflammation, cell proliferation and lipid metabolism. We have previously showed that C/EBP-α expression was suppressed in glomerular cells in focal segmental glomerulosclerosis. However, its specific role in diabetic nephropathy (DN) is unclear. We developed a podocyte-specific C/EBP-α-null mouse model to study the function of C/EBP-α in DN progression.

Methods: By crossing floxed C/EBP-α mice with Pod-Cre mice, we generated podocyte specific C/EBP-α knockout mice. The transgenic mice and their wild-type littermates underwent either high-fat diet for 6 months with a single injection of streptozotocin as diabetic models or general diet as control.

Results: We confirmed that C/EBP-α expression was significantly reduced in the renal cortex in podocyte-specific knockout mice by western blotting. Genetic ablation of C/EBP-α in podocytes led to more serious deterioration of diabetic kidney injuries, characterized by increased urinary albumin-to-creatinine ratio, increased mesangial matrix expansion, glomerulosclerosis and tubulointerstitial fibrosis (determined by Mason's trichrome and Picrosirius Red stains). Diabetes induced down-regulation in the expression of podocyte and epithelial markers such as nephrin, podocin and E-cadherin, and these markers were further reduced in C/EBP-α knockout diabetic mice. In addition, a further increased expression of markers of fibrosis (vimentin, fibronectin) and inflammation (MCP-1, TNF-α) were found in diabetic C/EBP-α knockout mice when compared to diabetic WT mice. Mechanistically, we identified that conditional deletion of C/EBP-α in podocytes resulted in significantly decreased p-AMPK and PGC-1α expression in diabetic mice.

Conclusions: These findings suggest that knockdown of C/EBP-α expression in podocytes aggravates the podocyte impairment and the progressing of DN, and point to C/EBP-α as a potential therapeutic target in DN.

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TH-PO683

Intestine Can Modulate Diabetes in Renal Failure (RF) in Animals Siddhartha S. Ghosh,[2] Austin J. Gonzalez,[3] Daniel E. Carl,[2] Richard Krieg,[1] Todd W. Gehr,[3] Shobha Ghosh.[1] *[1]VCU, Richmond, VA; [2]VCU Medical Ctr, Richmond, VA; [3]Virginia Commonwealth University, Fredericksburg, VA.*

Background: Intestine and gut microbiota play a major role in various diseases including diabetic nephropathy. Changes in gut microbiota influences glucagon like peptide (GLP-1) secretion. Drugs that modulate GLP-1 has been known to ameliorate not only diabetes but also improve renal function. Butyrate commonly secreted by commensal bacteria has be shown to stimulate GLP-1 release. We hypothesized that sodium butyrate (BU) might improve diabetes and renal function in animals with renal failure.

Methods: 5/6 nephrectomy was done in ten Sprague dawley rats to induce RF and divided into 2 groups, untreated (RF) and butyrate treated (RF+BU). Na Butyrate (250 mg/100ml) was given in drinking water for 6 weeks. Oral Glucose tolerance test GTT and insulin tolerance test (ITT) were done by oral 2 g/kg glucose and pyruvate tolerance test (PTT) were done by giving sodium pyruvate (1.5 g/Kg) ip. Tail blood glucose was measured by at baseline and at 15, 30, 60, and 120 mins after administration to measure area under the curve (AUC). Duodenal AMPK and colon calmodulin-dependent protein kinase II (CAMKII) were measured by western blots

Results: Results in the table show that both renal failure and diabetes were ameliorated by butyrate. AMPK and CAMKII play a major role in the secretion of GLP-1. Both proteins are downregulated in RF and were restored by butyrate.

Conclusions: In a recent study it has been shown that metformin activates duodenal AMPK dependent pathway to lower hepatic glucose production. PTT, a measure hepato-gluconeogenesis suggests that butyrate may act by similar mechanism. In addition recent clinical trials have shown GLP- 1 agonist improves GFR in renal failure. By improving GLP-1 secretion butyrate may improve diabetes and renal function in renal failure.

	Control	RF	RF+BU
Creatinine (mg/dl)	0.42±0.1	0.93±0.2*	0.63±0.2#
Urinary protein/creatinine	138.5±2.2	241.5±31.4*	154.9±26.6#
GTT AUC (mg.min/dl)	18735±943	29954±7577*	18590±1242#
PTT AUC (mg.min/dl)	16770±683	21950±665*	18123±1348#
ITT (AUC) (mg.min/dl)	12558±919	16633±698*	12555±812#
Plasma GLP (pg/ml)	219.5±25.4	151.9±19.1*	222.5±15.4#
pAMPK/AMPK Duodenum (Fold Change)	1.0±0.2	0.49±0.06*	0.89±0.26#
Calmodulin Kinase II (CamkII) Fold change	1.0±0.2	0.42±0.06*	0.74±0.09#

*P<0.05 compared to control; #p<0.05 compared to RF

TH-PO684

Insulin Resistance Suppresses Intercalated Cell Antibacterial Defenses Matthew J. Murtha,[2] Tad Eichler,[4] Birong Li,[1] Brian Becknell,[1] John D. Spencer.[3] *[1]Nationwide Children's Hospital, Columbus, OH; [2]The Research Institute at Nationwide Children's Hospital, Columbus Ohio, Pickerington, OH; [3]The Research Institute at Nationwide Children's, Columbus, OH; [4]The Research Institute at Nationwide Childrens Hospital, COLUMBUS, OH.*

Background: Urinary tract infection (UTI) is prevalent in people with diabetes mellitus. New evidence suggests antimicrobial peptides (AMP) play a role in maintaining urine sterility. Data from our lab shows that the kidney's intercalated cells (IC) secrete AMPs into the urine. Our data also show that insulin induces AMPs to shield the host from uropathogenic *E. coli* (UPEC). To investigate the impact of insulin resistance on renal antibacterial defense and AMP production, we selectively deleted the insulin receptor (IR) in murine ICs.

Methods: Using a Cre-loxP approach, mice homozygous for the floxed IR gene were crossed with mice expressing Cre recombinase under the ATP6V1B1 promoter (IC-specific isoform of VATPaseB1) to create IC-specific IR knockout mice (IRKO). A Cre-dependent tdTomato fluorescent reporter was incorporated to isolate ICs by fluorescent activated cell sorting (FACS). IRKO mice and Cre-negative littermates (IRflox) were subjected to experimental UTI with UPEC. 24 and 48 hrs post infection, UPEC burden was enumerated. The effects of IR deletion on host defense were confirmed *in vitro* using siRNA and *ex vivo* with urine neutralization assays.

Results: Compared to IRflox mice, IRKO mice exhibit a normal phenotype with normal serum insulin/glucose levels and serum/urine pH. qRT-PCR and Western blot confirmed IR mRNA and protein deletion in FACs-isolated ICs. qRT-PCR on FACS-isolated ICs shows that IRKO mice have decreased transcript expression of several AMPs, including RNase 4 and Lipocalin 2. ELISA confirmed lower urinary AMP peptide concentrations in IRKO mice compared to controls. Following experimental UTI, IRKO mice had 2-3 fold greater UPEC burden in urine, bladder, and kidneys. To confirm that suppressed AMP production increases UPEC susceptibility, RNase 4 was silenced in medullary cells *in vitro.* Cells were challenged with UPEC. With RNase 4 knock-down, UPEC invasion increased. When anti-RNase 4 blocking antibodies were added to mouse urine, UPEC survival increased.

Conclusions: This data suggest that intact IC insulin signaling is critical for UTI defense. Also, they indicate that the hyperglycemic environment alone does not explain diabetes-associated UTI risk. In part, increased UTI risk may be due to decreased expression of AMPs. Studies are needed to develop agents that target IC-specific insulin signaling or AMP production to reduce UTI risk.

Funding: Other NIH Support - Diabetes Complications Consortium, Private Foundation Support

TH-PO685

Lysosomal Enzymes Dominate the Urinary Proteome of Adolescents with Early Type 1 Diabetes Julie Anh Dung Van,[5] Anne-Christin Hauschild,[3] Ihor Batruch,[1] Eleftherios P. Diamandis,[2] James W. Scholey,[5] Ana Konvalinka.[4] *[1]Mount Sinai Hospital, Toronto, ON, Canada; [2]Mount Sinai Hospital and University Health Network, Toronto, AB, Canada; [3]Princes Margaret Cancer Center, Toronto, Ontario, ON, Canada; [4]University Health Network, University of Toronto, Toronto, ON, Canada; [5]University of Toronto, Toronto, ON, Canada.*

Background: Diabetes is the leading cause of kidney disease worldwide. Microalbuminuria has been recognized as one of the earliest indicators of renal damage in diabetes. However, maladaptive changes have been described in the diabetic kidney long before the onset of microalbuminuria, in the form of renal hyperfiltration and hypertrophy. Our aim is to examine the urinary proteome of adolescents with early type 1 diabetes and to examine the biological processes and pathways underlying early changes in the diabetic kidney.

Methods: We collected second-morning, midstream urines from 15 cases with type 1 diabetes and 15 age- and sex-matched controls. Urine volumes normalized to creatinine were subjected to 10kDa ultrafiltration to isolate proteins. Proteins (200 ug) were digested with trypsin, fractionated, and analyzed on Q-Exactive mass spectrometer. MaxQuant software was used for peptide/protein identification and label-free quantification. Pathway Data Integration Portal (pathDIP), an annotated database of signaling cascades and core pathways, was used to examine the significantly altered pathways in early type 1 diabetes.

Results: A total of 576 proteins were consistently detected across all thirty urine samples, representing roughly 25% of our total urinary proteome (n = 2313). Of these, 34 were differentially excreted between groups (Benjamini-Hochberg FDR, $q < 0.05$): seven were decreased in diabetes (e.g., ACY1, TIMP1, FSTL1), and 27 were increased (e.g., LRG1, MAN2B1, NAGA). More than half of these differentially excreted proteins were lysosomal enzymes, and the dominant pathways and processes associated with these lysosomal enzymes include "hydrolase activity", "glycosaminoglycan degradation", and "spingolipid metabolism".

Conclusions: Differences in the urinary proteome can be detected prior to the onset of microalbuminuria in adolescents with type 1 diabetes, compared to healthy controls. Enzymes from lysosomal compartment were overrepresented in diabetes, suggesting that lysosomal protease activity is an early response of the kidney to hyperglycemia.

TH-PO686

Diabetes-Induced Impairments in Robo Signalling Augment Glomerular Angiogenesis Johnny Y. Zhang,[1,2] Ahmad M. Sidiqi,[1,2] Xiaolin He,[1] Feng Gao,[1] Darren A. Yuen.[1,2] *[1]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada; [2]Faculty of Medicine, University of Toronto, Toronto, ON, Canada.*

Background: Diabetic glomerular angiogenesis represents an early form of diabetic kidney injury, and is classically thought of as being driven by increased podocyte VEGF production. Robo1 and Robo4 are cell surface receptors that can regulate VEGF-mediated endothelial angiogenic activity. We have shown previously that glomerular endothelial Robo4 expression is downregulated by high glucose exposure, whereas Robo1 expression is unchanged, and that Robo1 is essential for VEGF-induced angiogenic activity. Our objective is to determine whether high glucose-induced alterations in Robo4 levels regulate VEGF-induced glomerular angiogenesis in diabetes.

Methods: Glomerular endothelial cell (GEC) responsiveness to VEGF in angiogenesis assays was examined in both normal glucose (NG) and high glucose (HG) conditions, and following Robo4 knockdown. Using Robo4 knockout (KO) mice, the effect of Robo4 deficiency on diabetic glomerular angiogenesis was also analyzed using fluorescence microangiography (FMA) and PECAM-1 immunohistochemistry, while kidney functional output was measured by creatinine clearance.

Results: As compared to GEC grown in NG medium, GEC grown in HG medium expressed lower levels of the anti-angiogenic Robo4 receptor, but not the pro-angiogenic Robo1 receptor, and exhibited greater VEGF responsiveness. Robo4 deficiency was associated with augmented migration in vitro and increased PECAM-1 density, glomerular capillary length, and creatinine clearance in Robo4 KO mice (compared to their WT littermates) after 5 weeks of STZ-induced diabetes.

Conclusions: Our observations suggest that diabetic glomerular angiogenesis is driven not only by enhanced VEGF production, but also by enhanced glomerular endothelial VEGF responsiveness. This increased responsiveness appears to be promoted by a shift in glomerular endothelial Robo signalling, favouring more pro-angiogenic Robo1, and less anti-angiogenic Robo4 activity.

TH-PO687

Deficiency of Ketohexokinase-A Exacerbates Renal Tubular Injury in Streptozotocin-Induced Diabetic Mice Tomohito Doke,[1] Takuji Ishimoto,[1] Takahiro Hayasaki,[1] Miguel A. Lanaspa,[2] Richard J. Johnson,[2] Shoichi Maruyama.[1] *[1]Nagoya University Graduate School of Medicine, Nagoya, Japan; [2]University of Colorado Denver, Aurora, CO.*

Background: Ketohexokinase (KHK), a primary enzyme for fructose, exists as two isoforms, KHK-C and KHK-A. Recently, we have reported that the metabolism of fructose endogenously produced by polyol pathway activation in diabetes may have a deleterious role in the pathogenesis of diabetic nephropathy using mice lacking both KHK-A and KHK-C (KHK-A/C KO). Although both isoforms express in proximal tubule, the role of KHK-A is not yet elucidated. The aim of this study is to determine the role of KHK-A in the development of diabetic nephropathy.

Methods: Male wild-type mice (WT), KHK-A knockout mice (KHK-A KO), and KHK-A/C KO were used. Diabetes was induced with i.p. injections of streptozotocin (5 days). At 18 weeks, urine, blood, and kidney tissues were collected from diabetic (D) and control mice. Renal injuries, inflammation, hypoxia, oxidative stress, and polyol pathway enzymes were analyzed. Metabolomic analysis including polyol pathway, fructose metabolism, nucleotides, glycolysis, and TCA cycle in kidney and urine was done.

Results: The levels of blood glucose were equally elevated, and polyol pathway in kidney was similarly activated among all mice induced diabetes. However, D-WT and D-KHK-A KO showed increases of urinary NGAL, glomerular hypertrophy, and tubular injuries with increased oxidative stress and renal XO activity compared to D- KHK-A/C KO. Urinary NGAL was significantly associated with renal AMP and urinary allantoin. Moreover, those renal injuries were more severe in D-KHK-A KO accompanied by significant renal dysfunction, increases of renal inflammatory cytokines and HIF1alpha expressions. Metabolomic analysis revealed elevations of renal fructose and fructose-1-phosphate contents in D-WT and D-KHK-A KO compared with respective controls. Furthermore, downstream metabolites of fructose, renal DHAP (Dihydroxyacetone phosphate) and TCA cycle were significantly increased in D-KHK-A KO compared with D-WT and D-KHK-A/C KO.

Conclusions: Kidney injury in streptozotocin-induced diabetes was exacerbated in mice lacking KHK-A with increased endogenous fructose metabolism than WT, while that was prevented in mice lacking both isoforms. These results suggest that KHK-C has a deleterious role, and KHK-A might has an opposite role in endogenous fructose-related kidney injury in diabetic mice.

TH-PO688

Proteomics and Systems Biology Analysis of Human Kidney Cells Reveals a Link between Androgen-Induced Alterations in Renal Metabolism and Circulating Metabolite Levels in CKD Sergi Clotet freixas,[1,3] Maria Jose Soler,[1] Marta Riera,[1] Julio Pascual,[1] Ihor Batruch,[2] Stella K. Vasiliou,[2] Apostolos Dimitromanolakis,[2] Eleftherios P. Diamandis,[2] James W. Scholey,[3] Ana Konvalinka.[2,3] *[1]Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain; [2]Mount Sinai Hospital, Toronto, Canada, Toronto, ON, Canada; [3]University Health Network, University of Toronto, Toronto, ON, Canada*.

Background: Male sex predisposes to chronic kidney disease (CKD) progression. We hypothesized that dihydrotestosterone (DHT) would affect renal cells by altering the proteome.

Methods: We used isotope labeling to quantify the proteome in human proximal tubular epithelial cells (PTEC) exposed to DHT or estradiol. Top proteins were verified in vitro and in vivo. Renal oxidative stress (OS) was assessed by N-Tyr staining. Systems biology of sex hormone-protein signatures was studied in Cytoscape.

Results: Of 5043 quantified proteins, 76 were regulated by sex hormones. Processes related to metabolism were significantly enriched in proteins regulated by DHT. Proteins representing glucose, glucosamine and fatty acid metabolism, namely glucose-P-isomerase (GPI), glucosamine-P-N-acetyltransferase (GNPNAT1), and mitochondrial trifunctional protein subunit alpha(HADHA), were validated in vitro and in vivo. Renal expression of GPI, GNPNAT1 and HADHA was significantly higher in males compared to females, in 2 models of diabetes. OS was enriched in our proteins and genes highly expressed in diabetic kidneys. We demonstrated increased OS in diabetic and control male mice kidneys. We asked whether dysregulated metabolic enzymes in male kidneys may be responsible for changes in circulating metabolites. Using data from the human KORA F4 study, we found that serum metabolites related to TCA cycle and aminoacid metabolism (e.g.malate, glutamine and proline) were increased in CKD men and also associated with our DHT-proteins.

Conclusions: Androgen-induced perturbations in renal metabolism may be responsible for the more rapid kidney disease progression ascribed to men. Metabolic alterations in the male kidney may be reflected in circulating levels of malate, glutamine, and proline metabolites in CKD.

Candidate proteins for validation	Median SILAC ratio (n=3-4)		In vitro validation studies (n=3-4)		
	DHT/CONT	EST/CONT	CONT	DHT	EST
GPI	12.1±9.1*	1.2±3.2	0.32±0.2	1.30±0.2*	0.78±0.4
GNPNAT1	5.6±1.6*	2.2*±0.0	0.22±0.1	1.58±0.2*	0.40±0.4
HADHA	8.0±1.1*	0.9±0.7	0.96±0.3	2.02±0.5	1.33±0.1
	*q<0.05 according to significance A		*p<0.05 vs CONT (Mann–Whitney U test)		
	In vivo validation studies (n=5-7)				
	Female-CONT	Male-CONT	Female-STZ	Male-STZ	Female-Akita	Male-Akita
Renal GPI	0.59±0.0	0.90±0.1*	0.85±0.1	1.16±0.2	0.67±0.1	1.22±0.3
Renal GNPNAT1	0.98±0.1	0.66±0.1	0.76±0.1	0.88±0.1	0.55±0.1	1.01±0.1*
Renal HADHA	0.48±0.0	0.87±0.1*	0.65±0.1	0.97±0.1*	0.65±0.1	1.25±0.2*
Renal nitrotyrosine (% positive area)	8239±2.0	22262±4.2*	13917±1.6	22038±2.3*	N.A	N.A
	*p<0.05 vs Female (Mann–Whitney U test)					

TH-PO689

MDM2 Contributes to High Glucose-Induced Glomerular Mesangial Cell Proliferation and Extracellular Matrix Accumulation via Notch1 Signaling Chun-Tao Lei, Hua Su, Chun Zhang. *Union Hospital, Huazhong University of Science and Technology, Wuhan Hubei Provicne, China*.

Background: Murine double minute 2 (MDM2), an E3-ubiquitin ligase, is critical for various biological functions and its dysregulation is involved in tumorigenesis. Previous data have documented an indispensable role of MDM2 in kidney homeostasis and disorders. However, its role in glomerular mesangial cell (GMC) proliferation and extracellular matrix (ECM) accumulation under hyperglycemia remains unclear.

Methods: In vitro study, rat mesangial cell line was employed, and subjected to different treatments. RNA interfere and Nutlin-3a treatment were utilized to knockdown MDM2 expression and block MDM2-p53 interaction respectively. Diabetic mice model was established by intraperitoneal injection of streptozotocin (STZ) and intraperitoneal administration of Nutlin-3a was adopted to disrupt the in vivo binding between MDM2 and p53.

Results: In the present study, we found MDM2 protein level is upregulated in high glucose-cultured GMCs. Knocking down MDM2 by siRNA attenuates high glucose-induced ECM accumulation and cell proliferation. However, MDM2-p53 interaction blocker Nutlin-3a, cannot protect diabetic mice from renal impairment not only in vivo but also has no benefit on high glucose-induced ECM accumulation in vitro. Intriguingly, we found Notch1 signaling is activated in GMCs with high glucose exposure which is obviously attenuated by MDM2 depletion. However, Numb, another substrate of MDM2 which suppresses Notch1 signaling, is not involved in the MDM2 mediated Notch1 regulation. Lastly, our findings revealed that MDM2 binds with and ubiquitinates Notch1 intracellular domain (NICD1), however the ubiquitination status of NICD1 does not lead it to degradation but activates its downstream gene expression.

Conclusions: Collectively, our data propose a pivotal role of MDM2 in high glucose-induced GMC proliferation and ECM accumulation, through modulating the activation of Notch1 signaling in an ubiquitination-dependent but p53-independent way.

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TH-PO690

FcgRIIb-Deficience and FcgRIII-Deficience Exacerbate Renal Injury Respectively in Diabetic Mice Rui Zhang. *Division of Nephrology, West China Hospital, Sichuan university, Chengdu, China*.

Background: Fcg receptors are key immune receptors responsible for both humoral and innate immunity. FcgRI, FcgRIIb and FcgRIII are the members of Fcg receptors superfamily. We aimed to investigate the involvement of Fcg receptors respectively in diabetic mice.

Methods: Eight week-old C57BL/6 mice, FcgRIIb knockout mice and FcgRIII knockout mice were subdivided into three groups: the normal diet group, high fat diet group, type 2 diabetes group induced by high fat diet combined with streptozotocin. The levels of blood glucose, serum creatinine, urineprotein were tested. The expressions of TGF-β, TNF-α, pNK-κB, oxLDL were detected by real-time PCR or westernblot in isolated glomeruli. In vitro studies were performed in mice renal glomerular mesangial cell (GMCs) tranfected with lentivirus vectors carrying siRNA targeting FcgRIII, FcgRII and FcgRI gene respectively. GMCs were cultured with normal glucose, high glucose, oxLDL, high glucose combined with oxLDL.

Results: FcgRIII-/- diabetic mice and FcgRIIb-/- diabetic mice had elevated levels of fasting blood glucose, creatinine, urine protein compared with WT diabetic mice. Renal histology showed mesangial expansion, westernblot and real-time PCR indicated higher expression of TGF-β, TNF-α and pNK-κB, immunofluorescence or immunohistochemistry showed expressing in glomeruli, in diabetic FcgRIII knockout and FcgRIIb knockout than wild type and HFD respectively. The HFD group exist more severely biochemical dates, renal injury factors than control group and appeared most oxLDL deposition. To further examine the mechanism that which fc gamma receptor exacerbated renal injury for the most part, in vitro we observed that high glucose, high glucose combined with oxLDL activated expression of TGF-β, TNF-α, pNF-κB in mice renal glomerular mesangial cells, the transfection of FcgRIIb or FcgRIII siRNA had upregulated TGF-β, TNF-α, pNF-κB expression, whereas the transfection of FcgRI siRNA had appeared to attenuate the level of TGF-β, TNF-α, pNF-κB expression.

Conclusions: FcgRI deficience downregulated inflammation, fibrosis. FcgRIIb deficience accelarated inflammation, fibrosis and anomalous deposition of oxLDL. FcgRIII deficience failed to delay renal injury. These observations suggest that FcgRs represent a novel target in the therapeutic interventions for diabetic nephropathy. Funding: The National Natural Science Foundation of China

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TH-PO691

MAD2B-Numb Interaction Is Involved in High Glucose Induced Podocyte Injury by Regulating Cell Polarity Hua Su,[1] Hui Tang,[2] Chun Zhang.[3] *[1]Huazhong Science and Technology University, Wuhan, China; [2]Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [3]Union Hospital, Huazhong University of Science and Technology, Wuhan Hubei Provicne, China*.

Background: The loss of podocyte is a critical event in the pathogenesis of diabetic nephropathy (DN). Recent studies have demonstrated the importance of cell polarity in the maintenance of podocyte architecture. Previously, our group found the mitotic arrest deficient protein MAD2B is implicated in high glucose (HG) induced podocyte injury. However, the exact mechanism of MAD2B in podocyte injury still remains to be established.

Methods: Patients diagnosed with DN were enrolled in this study, and DN model was constructed on C57BL/6 mice by a single intra-peritoneal injection of STZ. In vitro study, immortalized human podocyte cell line was employed, and exposed to different treatments after differentiation. The expression of MAD2B and Numb was suppressed by recombinant lentivirus infection.

Results: Previously we have demonstrated the enhancement of MAD2B in DN mice and HG treated podocytes. Using a yeast two-hybrid interaction trap we identified Numb as a novel MAD2B binding protein in human kidney. Through confocal laser scanning microscopy we confirmed the co-localization of MAD2B and Numb in podocyte in vivo and in vitro. Subsequent endogenous co-immunoprecipitation established the direct interaction between MAD2B and Numb. HG exposure upregulated MAD2B expression and Numb phosphorylation in podocyte. Interestingly, HG also induced Numb translocation from podocyte basolateral membrane to cytoplasm, which accompanied by podocyte cytoskeleton re-organization. MAD2B genetic deletion partly reversed Numb phosphorylation and cytoplasm translocation as well as cytoskeleton re-organization in podocyte. In addition, Numb bound to integrin-β1 and correlated with its basolateral membrane distribution. But this binding was greatly disrupted by HG or phosphatase inhibitor calyculin-A or Numb depletion.

Conclusions: Upregulated MAD2B expression accelerates Numb phosphorylation and its translocation from podocyte basolateral membrane to cytoplasm in HG condition. Phosphorylated Numb has a reduced binding affinity to integrin-β1 which diminishes integrin-β1 distribution on podocyte basolateral membrane and ultimately leads to the loss of cell polarity and podocyte injury.

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TH-PO692

Insulin Prevents Bcl2 Modifying Factor-Induced Renal Proximal Tubular Cell Apoptosis via Stimulation of Heterogeneous Nuclear Ribonucleoprotein F and Sirtuin-1 Expression in Diabetic Akita Mice Anindya Ghosh,[3] Chao-Sheng Lo,[2] Isabelle Chenier,[1] Shaaban Abdo,[3] Janos G. Filep,[5] Julie R. Ingelfinger,[7] Shao-Ling Zhang,[6] John S. Chan.[4] *[1]CHUM-Hotel Dieu Hosp, Montreal, QC, Canada; [2]CRCHUM, Universite de Montreal, Montreal, QC, Canada; [3]CRCHUM, University of Montreal, Montreal, QC, Canada; [4]CRCHUM, University of Montreal, Montreal, QC, Canada; [5]Maisonneuve-Rosemont Hosp., Montreal, QC, Canada; [6]Research Center of Centre Hospitalier de l Universite de Montreal (CRCHUM), Montreal, QC, Canada; [7]The New England Journal of Medicine, Boston, MA.*

Background: Tubular atrophy and tubulointerstitial fibrosis are closely associated with loss of renal function in diabetes. However, the underlying mechanisms are not fully understood. Here we investigated the role of the pro-apoptotic BH3-only protein, BCL2-modifying factor (Bmf), in renal proximal tubular cell (RPTC) apoptosis in mice and studied the effects of insulin on Bmf in rat immortalized RPTCs (IRPTCs) in vitro.

Methods: Non-transgenic (Tg) and Tg mice specifically overexpressing human Bmf in RPTCs were studied at 10 to 20 weeks of age. Non-Akita littermates and Akita mice (a type 1 diabetes model) +/- insulin implant from the age of 12 weeks were also studied until week 16. Blood glucose, systolic blood pressure (SBP), and urinary albumin creatinine ratio (ACR) were measured bi-weekly. Kidneys were processed for histology. RPTC apoptosis was evaluated by TUNEL assay. Freshly isolated RPTs were assessed for gene and protein expression by qPCR and Western blotting, respectively. Urinary cells were assessed by flow cytometry and then qunatified by qPCR for human Bmf transgene expression. Rat IRPTC stably transfected with a plasmid containing the full length Bmf promoter fused to luciferase reporter (pGL4.20 N-1370/+102) were cultured in normal glucose (5mM) or high glucose (HG, 25mM) medium +/- insulin.

Results: Bmf-Tg mice exhibited higher systolic blood pressure, ACR, RPTC apoptosis and more urinary RPTCs than non-Tg mice. Insulin treatment suppressed Bmf expression and tubular apoptosis and reduced urinary RPTCs in Akita mice. In vitro, insulin stimulated hnRNP F and sirtuin-1 expression and inhibited Bmf promoter activity in HG medium. Promoter DNA analysis identified putative responsive elements for hnRNP F, p53 and Foxo3 in rat Bmf promoter. Transfection of small interference RNA of hnRNP F or sirtuin-1 abrogated insulin inhibition of Bmf promoter activity.

Conclusions: Overexpression of Bmf in RPTCs induces RPTC apoptosis. Insulin prevents RPTC apoptosis via stimulation of hnRNP F and sirtuin-1 expression to inhibit Bmf gene expression in the diabetic kidney.

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TH-PO693

Nuclear Factor Erythroid 2-Related Factor 2 Deficiency Attenuates Hypertension and Nephropathy via Up-Regulation of Renal Angiotensin Converting Enzyme-2 and Mas Receptor Expression in Diabetic Mice Shuiling Zhao,[2] Anindya Ghosh,[4] Chao-Sheng Lo,[3] Isabelle Chenier,[1] Janos G. Filep,[6] Julie R. Ingelfinger,[8] Shao-Ling Zhang,[7] John S. Chan.[5] *[1]CHUM-Hotel Dieu Hosp, Montreal, QC, Canada; [2]CRCHUM, MONTREAL, QC, Canada; [3]CRCHUM, Universite de Montreal, Montreal, QC, Canada; [4]CRCHUM, University of Montreal, Montreal, QC, Canada; [5]CRCHUM, University of Montreal, Montreal, QC, Canada; [6]Maisonneuve-Rosemont Hosp., Montreal, QC, Canada; [7]Research Center of Centre Hospitalier de l Universite de Montreal (CRCHUM), Montreal, QC, Canada; [8]The New England Journal of Medicine, Boston, MA.*

Background: We investigated the impact of nuclear factor erythroid 2-related factor 2 (Nrf2) deficiency on *hypertension, kidney injury and* renin-angiotensin system (RAS) *gene expression* in renal proximal tubule cells (RPTCs) *in diabetic* Akita (type 1 diabetes model) Nrf2 knockout (KO) mice and Akita mice treated with trigonelline (a Nrf2 inhibitor).

Methods: Male wild type (WT), Akita and Akita Nrf2 KO mice at 12 to 20 weeks were studied. Akita mice receiving trigonelline from weeks 12-18 +/- oltipraz (a Nrf2 activator) from weeks 16-18 were also studied. Blood glucose and systolic blood pressure were monitored weekly. Urinary albumin/creatinine ratio (ACR), angiotensin II (Ang II) and angiotensin 1-7 (Ang 1-7) levels were measured by ELISA. Kidneys were processed for histology. RAS mRNA and protein expression in renal proximal tubules (RPTs) were evaluated by RT-qPCR and Western blotting, respectively. We also performed Nrf2 knockdown in rat immortalized RPTCs (IRPTCs) stably transfected with plasmid containing rat angiotensinogen (Agt), angiotensin converting enzyme (ACE), angiotensin converting enzyme-2 (Ace2) or angiotensin 1-7 receptor (MasR) gene promoter.

Results: Nrf2 deficiency attenuated hypertension, renal hypertrophy, tubulointerstitial fibrosis, urinary ACR and Ang II, down-regulated RPTC Agt, ACE and pro-fibrotic gene expression and up-regulated Ace2 and MasR expression and urinary Ang 1-7 levels in Akita Nrf2 KO mice, compared to Akita mice. Similar changes were observed in Akita mice treated with trigonelline +/- oltipraz. Transfection of siRNA of Nrf2 prevented high glucose (HG, 25 mM)-stimulation of Agt and ACE expression and enhanced Ace2 and MasR expression in IRPTCs in vitro. Trigonelline decreased Agt/ACE and up-regulated Ace2/MasR mRNA expression in HG and these actions were reversed by oltipraz.

Conclusions: Nrf2 deficiency attenuates hypertension and kidney injury, via decreasing renal Agt/ACE expression and increasing Ace2/MasR expression. These results identify Nrf2 as a novel target for the prevention of hypertension and kidney injury in diabetes.

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TH-PO694

High Fat Diet Increases Plasma Soluble Prorenin Receptor (sPRR), Ang II, Systolic Blood Pressure (SBP), and Arterial Stiffness in Type 2 Diabetic (T2D) Male but Not in Female Mice Bruna Visniauskas, Virginia Reverte, Carla B. Rosales, Michelle Galeas-Pena, Caleb M. Abshire, Sarah Lindsey, Minolfa C. Prieto. *Physiology and Pharmacology, Tulane University School of Medicine, New Orleans, LA.*

Background: Activation of the renin angiotensin system (RAS) leads to complications during T2D; however, whether these outcomes exhibit sex differences remains unknown. Plasma prorenin levels are high in T2D patients and associated to microvascular complications. The sPRR activates prorenin in the extracellular compartments. In this study, we determined if plasma sPRR contributes to sex differences in the RAS and complications in a murine model of high fat diet (HFD)-induced T2D.

Methods: Male and female C57BL/6 mice were subjected to normal diet (NFD; Protein: 25% Kcal/ Fat: 13%/ Carbohydrate: 62%) or HFD (Protein: 18% Kcal/ Fat: 45%/ Carbohydrate: 36%) for 28 weeks to assess temporal changes in plasma sPRR and Ang II quantified by ELISA, and SBP measured by telemetry. Phenotype of T2D was established based on changes in body weight, glucose tolerance test, and plasma insulin and lipid levels. Vascular stiffness was measured in carotid arteries by pressure myography.

Results: By Week 16, a T2D phenotype was evident in HFD mice with greater exacerbation in males than in females. After Week 20, plasma sPRR started to increase in HFD male mice (4±3 vs. 3±1 ng/day; $P<0.05$) and remained elevated until Week 28 (5±3 vs. 3±.1 ng/day; $P<0.05$). No significant changes were observed in females. These changes paralleled increases in Ang II and SBP only in males [Ang II (HFD: 131±20 vs. NFD: 59±12 pg/day; $P<0.05$), SBP (HFD: 135 ±7 vs. NFD: 115± 2mmHg; $P<0.001$)] but not in females. Males on HFD also showed significant decreases in carotid compliance and distensibility. After Week 20, urinary angiotensinogen excretion (uAGT) started to increase only in HFD males compared to NFD; and by the end of the study, it was 4X higher, even in the absence of overt microalbuminuria.

Conclusions: In conclusion, in mice with HFD-induced T2D, plasma sPRR contributes to marked sex differences in systemic Ang II, SBP, and vascular stiffness. Concomitant uAGT differences support the concept of sexual dimorphism of intrarenal RAS activation. Plasma sPRR may reflect the status of systemic RAS and anticipate vascular complications during T2D.

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TH-PO695

Prolonged Exposure of Podocytes to Insulin Induces Insulin Resistance through Lysosomal and Proteasomal Degradation of the Insulin Receptor Abigail C. Lay,[2] Jenny Hurcombe,[2] Mette V. Østergaard,[2] Fern Barrington,[2] Rachel Lennon,[3] Gavin I. Welsh,[2] Richard Coward.[2] *[2]University of Bristol, Bristol, United Kingdom; [3]University of Manchester, Manchester, United Kingdom.*

Background: Podocytes are insulin responsive cells of the glomerular filtration barrier and are key in preventing albuminuria, a hallmark feature of diabetic nephropathy. While there is evidence that a loss of insulin signalling to podocytes is detrimental, the molecular mechanisms underpinning the development of podocyte insulin resistance in diabetes remain unclear. Thus, we aimed to further investigate podocyte insulin responses early in the context of diabetic nephropathy.

Methods: Conditionally immortalised human and mouse podocyte cell lines and glomeruli isolated from db/db DBA2J mice were studied. Podocyte insulin responses were investigated with western blotting, cellular glucose uptake assays and automated fluorescent imaging of the actin cytoskeleton. Q-PCR was employed to investigate changes in mRNA. Human cell lines stably overexpressing the IR and nephrin were also generated, using lentiviral constructs.

Results: Podocytes exposed to a diabetic environment (high glucose, high insulin and the pro-inflammatory cytokines TNF-α and IL-6) become insulin resistant with respect to glucose uptake and activation of PI3K and MAPK signalling. These podocytes lose expression of the insulin receptor (IR) as a direct consequence of prolonged exposure to high insulin concentrations, which causes an increase in IR protein degradation via a proteasome-dependent and bafilomycin-sensitive pathway. Reintroducing the IR into insulin resistant human podocytes rescues upstream phosphorylation events, but not glucose uptake. Stable expression of nephrin is also required for the insulin-stimulated glucose uptake response in podocytes and for efficient insulin-stimulated remodelling of the actin cytoskeleton.

Conclusions: Together these results suggest that IR degradation, caused by high levels of insulin, drives early podocyte insulin resistance and that both the IR and nephrin are required for full insulin sensitivity of this cell. This could be highly relevant for the development of nephropathy in diabetic patients and patients with the metabolic syndrome who are commonly hyperinsulinaemic in the early phases of their disease.

Funding: Government Support - Non-U.S.

TH-PO696

Inactivation of the SPAK Kinase Generates an Obesity-Resistant Phenotype in Mice Braulio A. Marfil,[1] Ivan Torre-Villalvazo,[1] Luz G. Cervantes-perez,[1] Lilia G. Noriega,[1] Maria Chavez-Canales,[2] Jose V. Jimenez,[1] Norma O. Uribe-uribe,[1] Nimbe Torres,[1] Norma Bobadilla,[1,2] Armando R. Tovar,[1] Gerardo Gamba.[1,2] *[1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [2]Instituto de Investigaciones Biomédicas, UNAM, Mexico City, Mexico.*

Background: The WNK (with-no-lysine)/SPAK (Ste20-related proline/alanine rich kinase) pathway has a well-known role in hypertension through its predominant effect on renal salt reabsorption. Recent evidence suggests this pathway could also be involved in the pathophysiology of obesity, which could link both diseases intrinsically. In humans the STK39 gene, which encodes SPAK, has been suggested as a susceptibility gene for arterial hypertension and for obesity. In this regard, the lack of SPAK activity in a knockin mice model (SPAK-T243A/T243A) leads to a reduction in blood pressure, but the effect of SPAK inactivation on body weight balance has not been evaluated.

Methods: To characterize the role of SPAK in energy balance, we fed wild-type and SPAK-knockin mice (SPAK-T243A/T243A) a high-fat diet (HFD) for 17 weeks and evaluated body composition, energy expenditure, thermogenesis, lipid metabolism, leptin levels, glucose metabolism and end-organ damage such as hepatic lipid content and pancreatic islet hypertrophy.

Results: Our results reveal that in contrast to wild type mice fed with HFD, the SPAK-T243A/T243A mice fed a HFD exhibit a significantly lower weight gain (15.1 ± 0.8 vs 10.2 ± 2.0 g; $p<0.001$) and decreased adiposity along the study, exhibiting at the end a better glucose tolerance, lower cholesterol, triglyceride and leptin levels, less hepatic steatosis and less pancreatic islet hypertrophy. The HFD intake was similar in both groups along the study. Calorimetric studies showed in the SPAK-T243A/T243A mice an increased thermogenic activity in brown adipose tissue, increased UCP1 expression, and white adipose tissue browning.

Conclusions: Our data suggest that SPAK-T243A/T243A mice are partially resistant to obesity induced with a HFD due to an increase in energy expenditure and thermogenesis, suggesting that the WNK/SPAK pathway could play a role in the pathophysiology of obesity and energy balance. Our results also suggest that inhibition of SPAK activity could have a therapeutic value in obesity. Supported by "Fronteras de la Ciencia" grant No. 23 from Conacyt, Mexico to GG.

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TH-PO697

Effect of ACE2 Deletion on Glucose Homeostasis, Renin Angiotensin System, and Necrosis Vanesa Palau,[1] Marta Riera,[1] Heleia Roca Ho,[1] David Benito,[1] Julio Pascual,[2] Maria Jose Soler.[2] *[1]Hospital del Mar Medical Research Institute (IMIM), Barcelona, Spain; [2]Hospital del Mar, Parc de Salut Mar, Barcelona, Spain.*

Background: Angiotensin converting enzyme 2 (ACE2) acts as a negative regulator of renin angiotensin system (RAS). Downregulation of ACE2 either by gene deletion or by pharmacological inhibition worsens renal injury and hypertension. Indiabetes, ACE2 activity is increased in pancreas from non-obese diabetic (NOD) mice. ACE2 deletion on pancreas from NOD mice has not been previously studied. We propose to study the effect of ACE2 deletion in NOD mice in an early pre-diabetic stage on glucose homeostasis, insulin secretion, RAS, oxidative stress and necroptosis.

Methods: Female NOD-ACE2$^{-/-}$ mice were studied at 12 weeks of age and compared to NOD-ACE2$^{+/+}$ mice. Glucose tolerance tests were performed by intraperitoneal administration of D-glucose bolus. Circulating glucose levels were determined at 0, 15, 30 and 60 minutes after injection. Insulin secretion was determined by ELISA technique from serum samples collected at 0, 2 and 5 minutes after glucose bolus injection. Immunohistochemistry studies for insulin, ACE, angiotensin II receptor 1 (AT1R), nitrotyrosine and RIP-1 were performed in paraffin-embedded pancreas.

Results: NOD-ACE2$^{-/-}$ mice had less tolerance to glucose bolus, lower insulin secretion after glucose administration, less insulin production and smaller islet area. Regarding RAS, NOD-ACE2$^{-/-}$ mice presented higher levels of ACE and AT1R staining as compared to NOD-ACE2$^{+/+}$ mice. NOD-ACE2$^{-/-}$ mice had higher levels of nitrotyrosine and RIP-1 as markers of oxidative stress and necroptosis, respectively (Table).

Conclusions: NOD mice with ACE2 deletion present altered glucose tolerance, functional and morphological alterations at a pancreatic level due to insulin synthesis and secretion as well as decreased islet area. ACE2 deletion leads to a worsening glucose homeostasis in NOD mice accompanied to higher levels of oxidative stress and necroptosis and RAS stimulation by increasing ACE and AT1R expression.

	Glucose bolus tolerance (AUC) (mg/dl60min)	Insulin secretion (ng/mL5min)	Insulin/renin pancreatic islet (µm²)	Pancreatic islet area (µm²)	Pancreatic islet ACE staining (MGV)	Pancreatic islet AT1R staining (MGV)	Pancreatic islet Nitrotyrosine staining (Scale 0-4)	Pancreatic islet Rip-1 staining (MGV)
NOD-ACE2$^{+/+}$	11026.0±246.26	4.18±0.56	9667.29±942.93	22902.13±3125.39	2.68±0.54	2.03±0.48	1.60±0.40	4.19±1.01
NOD-ACE2$^{-/-}$	12343.9±308.50*	3.90±0.44	6493.16±877.51*	14602.49±2084.70*	5.26±0.70*	4.31±0.49*	3.20±0.20*	10.74±1.78*

*p≤0.05 NOD-ACE2$^{-/-}$ vs NOD-ACE2$^{+/+}$

TH-PO698

Urinary Ubiquitinated Factor XII and Beta-2-Glycoprotein-1 May Identify Different Histological Patterns of Diabetic Kidney Disease Massimo Papale,[2] Chiara Divella,[2] Francesca Conserva,[2] Giuseppe Castellano,[2] Paola Pontrelli,[2] Antonella Di Franco,[2] Mariagrazia Barozzino,[2] Francesco Pesce,[2] Annarita Oranger,[2] Francesco Giorgino,[2] Luigi Laviola,[2] Simona Simone,[2] Vincenzo Trischitta,[1] Salvatore De Cosmo,[1] Giuseppe Grandaliano,[3] Loreto Gesualdo.[2] *[1]Casa Sollievo della Sofferenza Hospital, San Giovanni Rotondo (Fg), Italy; [2]University of Bari-Dept. of Emergency and Organ Transplantation, Bari, Italy; [3]University of Foggia, Foggia, Italy.*

Background: Diabetic Kidney Disease (DKD) is a heterogeneous disease with distinct histopathological phenotypes spanning from the typical nodular Kimmelstiel-Wilson lesions (DN) observed in ≈ 40% of the cases to the arteriolosclerotic changes and other primitive glomerulonephropathies (non DN-CKD) reported in the remaining cases. Recent studies (PMID: 20671095; 27881486) suggest a role of protein ubiquitination in DKD thus we tested the usefulness of urinary ubiquitinated proteins (ubi-prot) as novel biomarkers for DKD.

Methods: Sixty-four Type 2 Diabetes Mellitus patients (pts) with normoalbuminuria (NORMO), microalbuminuria (MICRO), and micro or macroalbuminuria with biopsy-proven DN or non DN-CKD were enrolled. Urinary ubi-prot were purified by Immunoprecipitation with specific anti-ubiquitin antibody and identified by LTQ Orbitrap XL™ Mass Spectrometry (MS) analysis. Protein Pattern Analysis (PPA) allowed the recognition of specific molecular patterns in each group and the most confident biomarkers were then validated by IF and ELISA or immunoblotting in tissue and urine samples, respectively.

Results: MS analysis identified 79 ubi-prot in NORMO, 111 in MICRO, 135 in non DN-CKD and 116 in DN, respectively. PPA analysis associated differentially excreted ubi-prot to the activation of the classical pathway of complement system in DKD. Urinary C5b9, measured in an independent set of pts, was significantly more excreted ($P < 0.01$) in DKD Vs. non proteinuric T2DM and pts with Lupus Nephritis and correlated, in the DN subset, with an increased deposition in proximal tubuli. Furthermore, 5 unique ubi-prot namely Factor XII, Ig K and Lambda chains, Beta-2-glycoprotein-1 (B2GP-1) and C6 were excreted in DN group only. Independent validation in 8 DN Vs 8 non DN-CKD pts confirmed that urinary ubiquitinated Factor XII and B2GP-1 were significantly more excreted in DN Vs. non DN-CKD ($P< 0.001$ and $P < 0.0001$, respectively).

Conclusions: Combined evaluation of urinary C5b9, ubiquitinated Factor XII and B2GP-1 may allow noninvasive stratification of pts with DKD

Funding: Government Support - Non-U.S.

TH-PO699

Neuropeptide Y Is a Novel Modulator of Podocyte Function and Its Loss Is Protective in Several Models of Albuminuric Renal Disease Abigail C. Lay, Jenny Hurcombe, Eleanor W. Ross, Fern Barrington, Gavin I. Welsh, Richard Coward. *University of Bristol, Bristol, United Kingdom.*

Background: Neuropeptide Y (NPY) is one of the most abundant peptides of the central and peripheral nervous systems, with a key role in energy homeostasis. However its function in the glomerulus has not previously been reported. Using a non-biased transcriptomic approach we discovered that NPY was highly significantly down-regulated in both human and mouse conditionally immoralised podocytes when rendered insulin resistant mimicking a diabetic environment (25-fold down regulated $p=10^{-125}$). Data from the nephromine database, comparing diabetic nephropathy (DN) patient groups, suggests this also occurs in human glomeruli. We therefore went on to study the biological importance of NPY on podocyte and glomerular biology.

Methods: Conditionally immortalized human and mouse podocytes were studied *in vitro* to determine NPY receptor signalling. For our *in vivo* investigations we studied wild-type (WT) 129Sv and NPY-deficient (NPY-/-) 129Sv mice, comparing two models of albuminuric renal injury; adriamycin nephropathy and streptozotocin (STZ)-induced diabetic nephropathy (DN).

Results: NPY rapidly signals to human and mouse podocytes through the PI3K and MAPK pathways and this is blocked in the presence of the Y2 receptor antagonist BIIE0246, indicating these responses are NPY2R-dependent. NPY also causes a rapid increase in intracellular calcium, which in turn promotes the nuclear translocation of NFAT. Interestingly, in contrast to WT controls, NPY-/- mice are protected from albuminuria 6 months after the induction of STZ-DN (a 4-fold increase in albuminuria is observed in WT mice, $p=0.036$ WT citrate vs STZ. No significant increase in albuminuria is observed in NPY-/- mice, $p=0.6828$ NPY-/- citrate vs STZ). Similarly, 14 days after the induction of adriamycin nephropathy, NPY-/- mice had a significantly ($p=0.0172$) lower level of albuminuria than WT controls.

Conclusions: NPY has a novel role in regulating podocyte and glomerular biology. Our data suggests that in diabetic nephropathy and insulin resistant states its glomerular secretion is supressed to protect against disease progression.

TH-PO700

Modulation of Epigenetics Led to a Decrease in Proteinuria in a Mouse Model of Diabetic Podocytopathy Himanshu Vashistha,[3] Abheepsa Mishra,[1] Ashwani Malhotra,[5] Leonard G. Meggs,[4] Pravin C. Singhal.[2] *[1]Feinstein Institute of Medical Research, Northwell Health, MANHASSET, NY; [2]North Shore LIJ Health System, Great Neck, NY; [3]Ochsner Health System, New Orleans, LA; [4]Ochsnher Health Foundation, New Orleans, LA; [5]Immunolgy and Inflammation, Feinstein Inst.Med research and NSLIJ, Manhasset, NY.*

Background: Modulation of renin angiotensin system has been reported to slow down the progression of diabetic podocytopathy by alterations of hemodynamic factors. Recent reports suggest that epigenetic factors also contribute to the development and progression of diabetic podocytopathy. We evaluated blockade effect of Angiotensin II (Ang II) on reversal of epigenetic alterations in diabetic podocytopathy. We hypothesize that demethylation by a low-dose hydralazine (HYDZ, non-hypertensive dose) would further augment the effect of Ang II blockade on reversal of epigenetic factors and decrease proteinuria in diabetic mice

Methods: Protein blots of renal tissues/cortical sections of 2, 4, and 6 months old control and Akita mice (diabetic, n=3) were probed for methylation at histone (H)3 lysine (K)4 residues, acetylation at H3 lysine (K)9 residues, SNAIL, vitamin D receptor (VDR), and nephrin. *In vitro* studies, protein blots of control (glucose, 5 mM) and high glucose (30 mM, HG)-treated human podocytes (HPs) were probed for SNAIL, VDR, nephrin, H3K4me3, H3K9ac and actin. Podocyte VDR and nephrin gene methylation status (Bisulphite pyrosequencing) and SNAIL binding to VDR and nephrin promoters (ChIP assay) were determined. Control and Akita mice (n=4) were treated with losartan (an Ang II receptor blocker, 10 mg/Kg/day) with/without HYDZ (10 mg/kg/day, 4 weeks) followed by evaluation of proteinuria and renal epigenetic alterations.

Results: Protein blots of renal tissues/cortical sections of Akita mice and HG/HPs displayed enhanced expression of SNAIL and H3K4me3 but down regulation of VDR, nephrin and H3K9ac. Losartan not only decreased proteinuria but also partially reversed epigenetic alterations and associated SNAIL, VDR and nephrin expressions; HYDZ alone has similar effects on proteinuria and epigenetic markers and further augmented these effects when combined with losartan. Both nephrin and VDR displayed more than 70% cytosine methylation (CpG islands). HG/HP displayed deacetylation of nephrin and degradation via ubiquitation. ChIP assays revealed binding of SNAIL at VDR and nephrin promoters.

Conclusions: Reversal of epigenetic alterations in renal tissues contributed to decrease in proteinuria in diabetic mice.

Funding: NIDDK Support

TH-PO701

Absence of Inner Medullary Urea Transporters Attenuates Fibrosis in Diabetic Nephropathy Fitra Rianto,[3] Mitsi A. Blount,[3] Faten Hasounah,[1] Joseph A. Ruiz,[1] Jeff M. Sands,[2] Janet D. Klein.[1] *[1]Emory University, Atlanta, GA; [2]Emory University Renal Division, Atlanta, GA; [3]Emory University School of Medicine, Atlanta, GA.*

Background: Kidney fibrosis is commonly observed in diabetic nephropathy. Animal studies show that a low protein diet reduces the incidence of diabetic nephropathy and kidney fibrosis, suggesting that kidney urea levels may contribute to nephropathy. Benefits of low protein diets in patients are controversial. We investigated diabetes (DM)-related kidney fibrosis under conditions of minimal urea reabsorption and maximal urea load.

Methods: C57Bl6 mice +/- genetic ablation of UT-A1 and UT-A3 urea transporters (A1/A3 KO mice) were given daily doses of streptozotocin (55mg/kg/day) until blood glucose >200mg/dl. After 4 weeks mice were given low (14%) or high (40%) protein diets for 2 weeks (group 1) or 5 weeks (group 2). Kidneys were collected for protein and histochemical analysis.

Results: Mice required between 4 to 7 days injection of STZ to produce blood glucose levels >200 mg/dl. Body weights of non-DM mice remained stable while DM WT mice lost ~2% and A1/A3 KO mice lost ~14% body weight prior to termination. Urine values for 40%-fed DM mice: urine urea: 2.5±03 mmol/Uv WT vs 2.9±0.3 mmol/Uv KO; in mEq/L: Na: 147±6.8 WT /132±2.2 KO; Cl: 102±0.7 WT/97±0.7 KO; K: 6.3±0.5 WT/5.8±0.8 KO. Urine volume in both WT and UT-A1/A3 mice was increased by diabetes, but UT-A1/A3 KO mice still produced more urine than WT. Smooth muscle actin (SMA), vimentin were used as markers of fibrosis. In the 2 week high protein fed mice, diabetic WT mice showed 56% increased SMA vs diabetic WT mice fed a 14% protein diet whereas the A1/A3 KO mice showed a 26% increase with 40% protein feeding. Vimentin was 70% increased in high protein fed animals vs 12% increase in comparably fed A1/A3 KO mice. Trichrome staining of histological sections revealed higher collagen levels in 40%-fed WT mice vs A1/A3 KO mice.

Conclusions: These data show that fibrosis that characterizes diabetic nephropathy is attenuated by the absence of urea transporters. This suggests that urea reabsorption mediated by urea transporters in the inner medulla contributes to the development of diabetic renal fibrosis and is aggravated by high protein diet. If urea transport inhibitors replicate the effects of genetic knock out, they may represent a promising future therapy.

Funding: Private Foundation Support

TH-PO702

Nicotine Enhances Renal Mesangial Cell Proliferation and Fibronectin Production in High Glucose Milieu via Activation of Wnt/β-Catenin Pathway Xiqian Lan,[1] Rukhsana Aslam,[2] Seyedeh Shadafarin Marashi Shoshtari,[6] Abheepsa Mishra,[3] Ashwani Malhotra,[4] Pravin C. Singhal.[5] *[1]Feinstein Institute for Medical Research, Great Neck, NY; [2]Feinstein Institute for medical research, Glenoaks, NY; [3]Feinstein Institute of Medical Research, Northwell Health, MANHASSET, NY; [4]Feinstein Inst.Med research, Manhasset, NY; [5]North Shore LIJ Health System, Great Neck, NY; [6]The Feinstein Institute for Medical Research, Manhasset, NY.*

Background: Diabetic nephropathy (DN) is a major complication of diabetes mellitus, and the commonest cause of end-stage renal disease (ESRD) in developed countries, including USA. Clinical reports have demonstrated that cigarette smoking is an independent risk factor for chronic kidney disease including DN; however, the underlying molecular mechanisms are still not clear. Recent studies have demonstrated that nicotine, one of the highly active compounds in cigarette smoke, is required for cigarette smoking-accelerated chronic kidney disease. DN is characterized by mesangial expansion, a precursor of glomerulosclerosis. In this study, we examine the role of Wnt/β-catenin pathway in nicotine-mediated mesangial cell phenotype in high glucose milieu.

Methods: We treated human mesangial cells (HRMC) with both normal/high glucose (5 mM and 25 mM) and nicotine (0.1, 1, and 10 uM), and then examined their phenotype. To evaluatet proliferation, we counted the total cell numbers (in a hemocytometer), or calculated the Ki-67 positive cell ratio by using immunofluorescent staining. We also performed real-time PCR to detect the expression of Wnts, β -catenin, and fibronectin. In addition, we used β-catenin inhibitor FH535 to examine a causal relationship between nicotine and high glucose treatment-mediated mesangial cell proliferation and fibronectin production.

Results: In 5 mM glucose medium, nicotine increased the total cell count and Ki-67 positive cell ratio in a dose-dependent manner, indicating that nicotine enhanced mesangial cell proliferation in normal glucose milieu, only moderately; 25 mM glucose further exacerbated nicotine-mediated mesangial cell proliferation. Similarly, nicotine increased the expression of Wnts, β-catenin, and fibronectin in normal glucose milieu, however, high glucose further increased these expressions. Addition of FH535 significantly inhibited the cell proliferation and fibronectin production.

Conclusions: Nicotine enhansces renal mesangial cell proliferation and fibornectin production in high glucose milieu, and Wnt/ β-catenin pathway plays an important role to regulate these effects. The present study provides insight into molecular mechanisms involved in diabetic nephropathy.

Funding: NIDDK Support

TH-PO703

Endothelial Dysfunction in High Fat Diet Fed Diabetic Mice Is Dependent on Ketohexokinase Tomohito Doke,[1] Takuji Ishimoto,[1] Takahiro Hayasaki,[1] Mayumi Kawabe,[3] Miguel A. Lanaspa,[2] Richard J. Johnson,[2] Shoichi Maruyama.[1] *[1]Nagoya University Graduate School of Medicine, Nagoya, Japan; [2]University of Colorado Denver, Aurora, CO; [3]Nagoya City University, Nagoya, Japan.*

Background: The metabolism of both dietary and endogenously produced fructose via activated polyol pathway by ketohexokinase (KHK) has been reported to induce metabolic syndrome, a cluster of hyperglycemia, hypertension, and obesity, and also hyperuricemia attributed to ATP depletion and activation of nucleotide degradation pathway in human and rodents. Metabolic syndrome is associated with vascular dysfunctions. KHK have two splicing variant, KHK-C and KHK-A. The aim of this study is to determine the role of KHK in the development of vascular dysfunction in diabetes.

Methods: Diabetes was induced by low-dose streptozotocin in male wild-type (WT), KHK-A knockout mice (KHK-A KO), and both KHK-C and KHK-A knockout mice (KHK-A/C KO). Then they were fed high fat diet (45% fat). At 24 weeks, blood, urine, and tissue samples including aorta were collected. Biochemical analysis, urinary nitrate/nitrite measurement, and metabolomic analysis of urine was done. The relaxing effects of acetylcholine (ACh) and effects of NO synthase inhibitors, N-nitro-L-arginine (LNA), on the contractions by phenylephrine (PE) were measured in endothelium-intact aortas.

Results: The level of blood glucose, body weight and blood pressure was similar among diabetic mice. However, urinary nitrate/nitrite concentration was significantly lower in diabetic WT and diabetic KHK-A KO compared with diabetic KHK-A/C KO. Whereas ACh-induced relaxation in the aortas did not show significant difference among diabetic mice, PE-induced contractions with pretreatment of LNA (LNA/PE ratio) was significantly decreased in both diabetic WT and diabetic KHK-A KO compared to A/C KO mice, indicating endothelial dysfunction was alleviated in diabetic KHK-A/C KO mice. Metabolomic analysis revealed the significant correlations between LNA/PE ratio and urinary metabolites. Especially, urinary uric acid was inversely correlated with LNA/PE ratio in diabetic mice.

Conclusions: Vascular dysfunction was attenuated in diabetic KHK-A/C KO compared with WT and KHK-A KO. These results suggest that endothelial dysfunction in high fat fed diabetic mice might be due to fructose metabolism dependent on KHK-C.

TH-PO704

Effects of Clinically Validated Renal Therapies in the Renin AAV db/db Uninephrectomized (uNx) Mouse Model Shannon M. Harlan, Josef G. Heuer, Matthew D. Breyer, Kevin L. Duffin, Tao Wei, Hana Baker. *Eli Lilly and Company, Indianapolis, IN.*

Background: The recently developed ReninAAV *db/db* uNx mouse model, exhibits key hallmarks of advanced human diabetic kidney disease (DKD), including progressive elevations in albuminuria, increased serum creatinine, loss of glomerular filtration rate and pathological changes similar to human DKD. The renal transcriptome changes in this model were demonstrated to be more similar to human DKD when compared to the *db/db* eNOS$^{-/-}$ model. Recent clinical studies have demonstrated inhibiting the JAK/STAT pathway or SGLT2 inhibition improves renal function on top of ACEi or ARB. To further explore similarities of this model to human DKD we tested the response of Renin AAV db/db uNx to clinically validated therapeutics.

Methods: Four weeks after ReninAAV, mice were randomized and treated with vehicle, lisinopril (ACEi), losartan (ARB), Canagliflozin (SGLT2i) or Ruxolotinib (JAK/STATi). At 48 hours or 2 weeks post treatment urine was collected for measurement of albumin to creatinine ratio (ACR) and serum collected for measurement of clinical parameters and kidney collected for gene expression.

Results: Vehicle treated ReninAAV mice exhibited significant ($p<0.02$) elevations in ACR compared to baseline at 48 hour (+53,776ug/mg) and 2 weeks (+12,842ug/mg). Lisinopril and losartan reduced ACR ($p<0.01$) as compared to baseline at both 48 hour (-15,973ug/mg and -17,655ug/mg respectively) and 2 week time points (-15,622ug/mg and -7,774ug/mg respectively. Treatment with Canagliflozin led to significant ($p<0.01$) reductions in ACR at 48 hours (-12,238ug/mg) as compared to baseline, with no reductions ($p=0.5$) in ACR at 2 weeks (+257ug/mg). Ruxolotinib treated mice did not exhibit a significant lowering of ACR at 48 hours, with only a trend ($p=0.07$) at 2 weeks post treatment (-6,569ug/mg). However, significant ($p<0.01$) reductions from vehicle treated mice were observed in both Canagliflozin and Ruxolotinib treated mice (-5,791ug/mg and -9,103ug/mg, respectively) indicating a halting of disease progression. Effects of the inhibitors on gene expression in the model were compared.

Conclusions: The results support further clinical validation of this mouse model of DKD and provide further insights into disease pathophysiology allowing for a better understanding of human disease progression and identification of potential new targets.

Funding: Commercial Support - Eli Lilly and Company

TH-PO705

Insulin Suppresses Gluconeogenesis in Renal Proximal Tubules via the IRS1/Akt2/mTORC Pathway Motonobu Nakamura,[1] Masashi Suzuki,[2] Nobuhiko Satoh,[1] Atsushi Suzuki,[1] Hiroyuki Tsukada,[1] George Seki,[3] Yusuke Sato,[4] Yukio Homma,[5] Shoko Horita,[1] Masaomi Nangaku.[1] *[1]Division of Nephrology and Endocrinology, The University of Tokyo, Graduate School of Medicine, Bunkyo, Tokyo, Japan; [2]Tokyo Gakugei University, Koganei, Tokyo, Japan; [3]Yaizu City Hospital, Yaizu, Shizuoka, Japan; [4]Department of Urology, The University of Tokyo, Graduate School of Medicine, Bunkyo, Tokyo, Japan; [5]Japanese Red Cross Medical Center, Shibuya, Tokyo, Japan.*

Background: Previously, we found that the stimulatory effect of insulin on sodium transport in proximal tubules (PTs) is dependent on insulin receptor substrate (IRS)2/Akt2/mammalian target of rapamycin complex (mTORC) 2 and preserved even in insulin resistance and diabetes mellitus (Kidney Int 87:535,2015, ASN Kidney Week 2016). In addition to liver, kidney also significantly contributes to whole body gluconeogenesis particularly after prolonged fasting. Insulin is known to suppress gluconeogenesis in PTs, the only nephron segment where gluconeogenesis takes place. However, little is known about the signaling mechanism underlying this insulin action.

Methods: PTs freshly isolated from rat kidneys were incubated overnight in DMEM with or without 0.2 mM cAMP, and 10^{-8}M insulin was subsequently added for 4-hr. Total RNA was extracted from the PTs, and quantitative PCR was performed to determine the relative mRNA expression levels of glucogenic enzymes phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6P). To uncover the signaling mechanism, PTs were incubated in the presence of Akt1/2 inhibitor VIII or an mTORC1 inhibitor rapamycin. PTs were also incubated with siRNAs against IRS1, IRS2, Akt1, Akt2, raptor (a component of mTORC1), or rictor (a component of mTORC2) in the presence of lipofectamine.

Results: cAMP increased the expression levels of PEPCK and G6P 19 and 7-fold, respectively. Insulin decreased both of the cAMP-stimulated expression levels of PEPCK and G6P by more than 80% (n = 12-13). Akt1/2 inhibitor VIII and rapamycin completely abolished this inhibitory effect of insulin on gluconeogenesis. siRNAs against IRS1, Akt2, raptor and rictor also completely abolished the inhibitory effect of insulin. By contrast, siRNAs against IRS2 or Akt1 failed to affect the insulin effect.

Conclusions: Our results, for the first time to our knowledge, revealed that insulin suppresses gluconeogenesis in PTs via IRS1/Akt2/mTORC pathway. In insulin resistance and diabetes mellitus, the reduced expression of IRS1 in PTs that we reported (Kidney Int 87:535,2015, BBRC 461:154,2015) is expected to selectively attenuate the IRS1-dependent insulin action. The resultant enhancement in renal gluconeogenesis may at least partially contribute to hyperglycemia in these conditions.

Funding: Government Support - Non-U.S.

TH-PO706

Glomerulosclerosis Attenuated by Retinoic Acid through Bone Morphogenetic Protein 4 Suppression in Mice with Streptozotocin-Induced Diabetes Masanori Tamaki, Tatsuya Tominaga, Yui Fujita, Seiji Kishi, Taichi Murakami, Kojiro Nagai, Hideharu Abe, Toshio Doi. *Department of Nephrology, Graduate School of Biomedical Sciences, Tokushima University, Tokushima, Japan.*

Background: Mesangial matrix expansion, leading to glomerulosclerosis and renal dysfunction, is an important histologic change in diabetic nephropathy. A major component of mesangial matrix is collagen IV (COL4), which increases by bone morphogenetic protein 4 (BMP4)/mothers against decapentaplegic (Smad1) signaling. Retinoic acid (RA) attenuates glomerulosclerosis, although details are unclear. In general, RA receptor (RAR) combines directly with RA response element (RARE), although RARE is not determined around *BMP4* gene. In the present study, we investigated the effect of RA on diabetic nephropathy, focusing on the regulatory mechanism of BMP4.

Methods: Male CD-1 mice were given streptozotocin at 12 weeks of age, followed a month later by intraperitoneal all-*trans* RA (atRA, 15 μg/gBW) or corn oil, each given thrice weekly. Animals' kidneys were harvested after sacrifice at 24 weeks of age. atRA or specific agonists for each subtype of RAR were added to cultured CD-1 mice derived mesangial cells for 24 hours (from 1 nM to 10 μM). RAR binding capacity to RARE, suggested by genome analysis, was confirmed by ChIP analysis.

Results: Serum creatinine levels and urinary protein excretion increased in diabetic mice. Renal BMP4 and COL4 expression levels increased in diabetic mice. Glomerulosclerosis worsened in diabetic mice, and glomeruli phosphorylated Smad1 and COL4 levels increased. These findings were attenuated after atRA administration. In cultured mice mesangial cells, BMP4 and COL4 expression levels decreased after atRA addition or a low concentration addition of AM580, a specific agonist for RARα, but did not after a low concentration addition of either RARβ or RARγ agonist. ChIP analysis showed that a suggested RARE around mice *Bmp4* gene combined with RARα after atRA addition.

Conclusions: atRA administration attenuated glomerulosclerosis and decreased BMP4 and COL4 expression levels in diabetic mice. Our study suggests that RARα combined with a novel RARE around the *Bmp4* gene, plays an important role for regulating BMP4 expression, although further study is needed. These findings indicate that RA may provide a novel therapeutic mechanism for diabetic nephropathy.

Funding: Government Support - Non-U.S.

TH-PO707

Stem-Cell Derived Nano-Extracellular Vesicles Promote Recovery of Diabetic Nephropathy Damaged Kidneys in Mice Cristina Grange,[1] Benedetta Bussolati,[1] Marta Reviriego-Mendoza,[2] Ciro Tetta,[2] Franklin W. Maddux.[2] *[1]Molecular Biotechnology & Health Science, University of Turin, Turin, Italy; [2]Fresenius Medical Care North America, Waltham, MA.*

Background: Nano-Extracellular Vesicles (nEVs) released by stem cells carry transcriptional regulators and secreted RNAs that could be transferred to target cells and induce phenotypic changes. nEVs can reprogram injured cells by activating regenerative processes in acute tissue injury. The aim of this study was to evaluate whether nEVs inhibit chronic kidney injury in a mouse model of diabetic nephropathy (DN).

Methods: To develop ND, NSG mice were injected with 35 mg/Kg of streptozotocin for 4 consecutive days. All treated mice developed diabetes (glycaemia > 250 mg/ml) within 10 days, and DN within 1 month. Mice were intravenously treated with n-EVs derived from human bone marrow stromal cells (MSCs), adipose derived stem cells or liver stem cells (HLSCs) once a week for 5 weeks. Empty n-EVs were used as control[MMRM1]. Kidney function and morphology were evaluated a week later by histological analyses. A comparative bioinformatics analysis of n-EVs-associated miRNAs and proteins was used to identify common anti-fibrotic and pro-regenerative pathways from different kidney cells. The anti-fibrotic effect of n-EVs was analysed by treating mouse kidney fibroblasts *in-vitro* with TGF-β1 and collagen, and a-sma production.

Results: n-EV treatment resulted in reductions of albumin/creatinine excretion ratio and plasma creatinine, and restoration of urinary acidification when compared to control animals. Histological analyses showed a significant reduction of glomerular and interstitial fibrosis, vascular injury and of Bowman's space enlargement. Using specific markers, we found significant reduction of cell death and enhanced proliferation in the tubules. All MSC and HLSC stem cell derived n-EVs, but not n-EVs derived from fibroblasts, displayed similar positive effects on reducing DN development. Comparative analyses showed that HLSC and, to a lesser extent MSC n-EVs interfered with the expression of pro-fibrotic miRNAs and inhibited collagen/a-sma production.

Conclusions: We show that n-EVs prevent development of DN in mice by inhibiting fibrosis and promoting regeneration.

Funding: Commercial Support - Fresenius Medical Care, North America

TH-PO708

Abstract Withdrawn

TH-PO709

VEPTP Inhibition as a Vasculoprotective Strategy to Treat Diabetic Kidney Disease Isabel A. Carota,[3,7] Christina S. Bartlett,[8] Tuncer Onay,[2] Rizaldy P. Scott,[4] Yael Kenig-Kozlovsky,[1] Sunday S. Oladipupo,[6] Matthew D. Breyer,[5] Susan E. Quaggin.[2] *[1]Feinberg cardiovascular Research Inst, Northwestern University, Chicago, IL; [2]Northwestern University, Chicago, IL; [3]FCVRI and Division of Nephrology, Northwestern University, Chicago, IL; [4]Northwestern University, Feinberg School of Medicine, Chicago, IL; [5]Lilly Research Laboratories, Indianapolis, IN; [6]Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN; [7]BioTDR, Eli Lilly & Company, Indianapolis, IN; [8]Boehringer Ingelheim, Ridgefield, CT.*

Background: With a growing number of patients suffering from diabetic kidney disease new treatments to halt progression of DKD are urgently needed. Silenced Tie2 signaling following dysregulated expression of its ligands Angpt1 and 2 found in diabetic patients has been linked to increased mesangial expansion and glomerular scarring. Here we show that the endothelial specific phosphatase VEPTP is upregulated in kidney tissue of diabetic, hypertensive rodents, suggesting VEPTP as effector of reduced Tie2 activity in diabetes. Following this finding we investigated VEPTP inhibition as target to prevent deterioration of renal function and glomerular endothelium under diabetic conditions.

Methods: To test the impact of VEPTP blockade on the progression of DKD we postnatally deleted VEPTP in a model of diabetic hypertension (Akita/ReninAAV+) and followed the mice until 24 weeks of age, before evaluating renal function, blood pressure, ACR and renal histology as measurement for the degree of DKD.

Results: Genetic deletion of VEPTP in non-diabetic mice promotes Tie2 phosphorylation and eNOS signaling resulting in elevated glomerular filtration rates and decreased systolic blood pressure. At 24 weeks of age GFRs of Ak/Ren mice declined significantly compared to their start values, whereas GFRs from diabetic VEPTP iKOs maintained their baseline GFR values (Ak/Ren=242.6, Ak/Ren VEPTP iKO=480.3 ul/min). The prevention of decline in GFR over time correlated with lower elevation of urine albumin/creatinine ratios in diabetic VEPTP iKO compared to diabetic controls (Ak/Ren=1549.4, Ak/Ren/VEPTP iKO=741.2 ul/min). Additional histological analysis revealed that diabetic/hypertensive VEPTP deficient mice presented less glomerular scarring, mesangial expansion as well as a lower number of aSMA positive glomeruli. Analysis of kidney lysates from Ak/Ren/VEPTP iKO mice showed rescue of Tie2 phosphorylation levels compared to Ak/Ren mice, demonstrating that blockade of VEPTP slows the progression of renal complications under diabetic and hypertensive conditions by stabilizing Tie2 signaling.

Conclusions: Genetic loss of VEPTP causes increased TIE2 activity in diabetic hypertension, slowing the development of DKD in mice. In sum, we identify VEPTP as a candidate therapeutic target to protect the kidney from diabetic injury.

Funding: Commercial Support - Eli Lilly & Company

TH-PO710

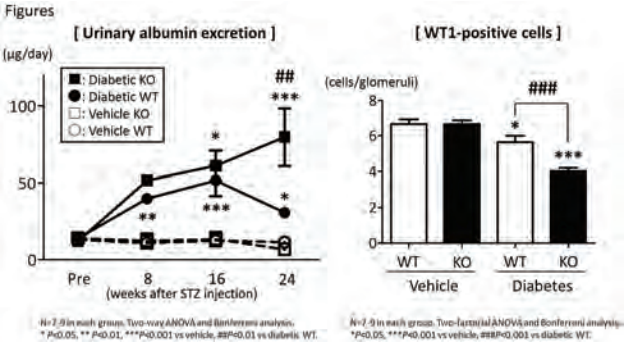
Angiotensin II Type 1 Receptor-Associated Protein Ameliorates Streptozotocin-Induced Diabetic Nephropathy in Mice Kotaro Haruhara,[1,4] Hiromichi Wakui,[1] Ryu Kobayashi,[1] Kenichi Ohashi,[2] Daisuke Kurotaki,[3] Nobuo Tsuboi,[4] Takashi Yokoo,[4] Kouichi Tamura.[1] *[1]Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan; [2]Department of Pathology, Yokohama City University Graduate School of Medicine, Yokohama, Japan; [3]Department of Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan; [4]Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan.*

Background: Over-activation of renin-angiotensin system and enhanced infiltration of immune cells are critical factors in the development and progression of diabetic nephropathy (DN). AT1 receptor-associated protein (ATRAP) binds specifically to the AT1 receptor, and suppresses the over-activation of AT1 receptor signals. We have previously shown that ATRAP inhibits hypertension and cardiovascular disease in the animal models of renin-angiotensin system over-activation. Our aim was to determine the protective role of ATRAP in a mouse model of DN.

Methods: Diabetes was induced in wild-type mice (WT) and systemic ATRAP knock-out mice (KO) on a C57BL/6J background by the intraperitoneal injection of streptozotocin (55 mg/kg, daily for 5 consecutive days).

Results: The glycemic and blood pressure status of the diabetic WT and KO were comparable throughout the study period. The urinary albumin excretion was increased and the podocyte number, as estimated by immunohistochemical staining for WT-1, was decreased in the diabetic KO in comparison to the diabetic WT at 24 weeks after the streptozotocin injection (**Figure**). Furthermore, the renal expression of alternatively activated macrophage-related genes, including *Chil3*, *Arg1*, *Il4*, and *Il-13*, were suppressed in diabetic KO in comparison to diabetic WT; these macrophages are known to be factors associated with anti-inflammation and tissue repair.

Conclusions: These results suggested that ATRAP plays protective roles in the progression of DN via the maintenance of the renal expression of alternatively activated macrophages, indicating that ATRAP is therefore a novel therapeutic target of DN.



TH-PO711

Renal Inflammation, Insulin Resistance, and Enhanced Renal Gluconeogenesis in Type 2 Diabetic Nephropathy: The Missing Links Qianling Liu, Liangyan Zhang, Wei Qiu, Wei Zhang, Yubing Wen, Haiyun Wang, Xuemei Li. *Department of Nephrology, Peking Union Medical College Hospital, Chinese Academy of Medicine Sciences & Peking Union Medical College, Beijing, China.*

Background: Renal gluconeogenesis is substantially stimulated in patients with type 2 diabetes, but the mechanism remains unknown. Renal gluconeogenesis is negatively regulated by insulin. Since inflammation is activated in diabetic nephropathy (DN), however, inflammation is well known to induce insulin resistance, we wondered whether enhanced renal gluconeogenesis in DN was partially resulted from renal inflammation-mediated insulin resistance. If so, whether inflammation inhibitor could partially reverse this change.

Methods: Eight-week-old male diabetic db/db (C57BLKS/J-LepR^{db}/LepR^{db}) mice and their non-diabetic littermates db/m (C57BLKS/J-LepR$^{db/+}$) mice were used in this study. Diabetic db/db mice were treated with 1 mg/kg NF-κB inhibitor parthenolide (PTN) or saline as control intraperitoneal every other day. After 12 weeks of treatment, blood, urine and kidney samples were collected for measurement.

Results: Expression of inflammatory factors and the gluconeogenic rate-limiting enzyme phosphoenolpyruvate carboxykinase (PEPCK) were increased in the renal cortex of both type 2 DN human patients and db/db mice. Moreover, reduced insulin signaling as demonstrated by downregulated phosphorylation of AKT and increased expression of downstream gene FOXO1 were detected in db/db+saline mice compaired with db/m mice. Consistant with our hypothesis, NF-κB inhibitor PTN significantly reduced renal expression of NF-κB, TNF-a, ICAM-1, MIP-1α and macrophage infiltration in db/db+PTN mice compaired with db/db+saline mice. Moreover, it partially alleviated renal insulin resistance and reduced the expression of gluconeogenic enzyme PEPCK (1.62±0.47 VS 0.89 ±0.14, $p<0.05$), indicating that inflammation could be one of the triggers for insulin resistance and enhanced renal gluconeogenesis.

Conclusions: Our study demonstrated for the first time that renal gluconeogenesis is upregulated in db/db mice, and this was associated with renal inflammation-mediated insulin resistance. PTN partially reversed this change by promoting renal insulin sensitivity. This work shed light on the role of inflammation in enhanced renal gluconeogenesis and may yield a novel target for hyperglycemia.

TH-PO712

Agonistic Anti-CD148 Monoclonal Antibody Attenuates Diabetic Nephropathy in Mice Keiko Takahashi, Rachel H. Kim, Shinya Nagasaka, Daisuke Katagiri, Ray Mernaugh, Takamune Takahashi. *Vanderbilt University, Nashville, TN.*

Background: CD148 is a transmembrane protein tyrosine phosphatase (PTP) that is expressed in renal vasculature, including glomerular endothelial cells and podocytes. Previous studies have shown that CD148 suppresses multiple growth factor signaling pathways (e.g. VEGF, EGF) and prominently inhibits endothelial or epithelial cell proliferation. Here, we have generated an agonistic anti-CD148 monoclonal antibody (18E1) and evaluated its effects in murine diabetic nephropathy.

Methods: Monoclonal antibodies (mAbs) against mouse CD148 ectodomain (CD148ecto) were produced by immunizing CD148 -/- mice with CD148ecto-Fc fusion protein. The mAbs that specifically bind to CD148 and increase its catalytic activity and inhibit the proliferation of CD148 stably- transfected cells were selected by a series of biochemical (Western blot, PTP activity) and biological (proliferation) assays. The specificity of the effects was evaluated by CD148 knockdown or knockout. The mAb (18E1) that showed strong agonistic activity was injected (10 mg/kg, i.p., three times per week) into wild-type (WT) and CD148 -/- (KO) diabetic mice (DBA2 strain, 8 week-old, N=6 per group) for 6 weeks, then renal phenotype was assessed. Diabetes was induced by low-dose STZ injections and mouse IgG was used as a control. Furthermore, the effects of 18E1 mAb in glomerular endothelial cell and podocyte cell proliferation were also assessed in culture.

Results: As compared with control Ab, the 18E1 mAb significantly decreased albuminuria (~50%) and mesangial expansion (~30%) without altering hyperglycemia and blood pressure in WT diabetic mice. Immunohistochemical evaluation showed that the 18E1 mAb significantly prevents the reduction of podocyte number and nephrin

expression and decreases glomerular macrophage (F4/80) infiltration (~40%) and matrix expansion (fibronectin) (~30%). The 18E1 mAb showed no effects in CD148KO diabetic mice. In addition, the 18E1 mAb significantly (~50%) inhibited proliferation of glomerular endothelial cells and podocytes in culture concomitant with reduction of VEGFR2 or EGFR phosphorylation. These inhibitory effects were largely abolished by CD148 knockdown.

Conclusions: Agonistic anti-CD148 antibody attenuates diabetic nephropathy in mice. Anti-CD148 antibody may be used as a new therapeutic agent for the treatment of early phase diabetic nephropathy.

Funding: NIDDK Support

TH-PO713

NO and SIRT1 Protect Glomerular Endothelial Cells with TERC Deletion from Hyperglycemia-Induced Senescence Huifang Cheng,[2] Raymond C. Harris.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Medicine/Nephrology, Vanderbilt University Medical Center, Nashville, TN.*

Background: Endothelial dysfunction plays an important role in the development of diabetic nephropathy (DN). We have previously reported that telomerase deficiency may predispose to diabetic renal injury.

Methods: To investigate the role of nitric oxide (NO) and SIRT1 in mediation of telomerase-dependent vulnerability to DN, we used streptozotocin (STZ) to induce diabetes in fourth generation (G4) TerC /T KO mice and compared their response with wild type (Wt) in response to treatment with NO precursor, L-arginine (L-arg). We also used primary cultured glomerular endothelial cells (GEnCs) for *in vitro* studies to explore the interaction of NO and SIRT1.

Results: STZ induced similar hyperglycemia, but TERC/T KO mice had increased renal involvement, which was alleviated by L-arg administration, with decreased albuminuria and less GBM thickening. Increased cell senescence and more severe oxidative stress was seen in diabetic mice with TERC/T deficiency, indicated by higher urinary F2-isoprostane and accumulation of renal nitrotyrosine. L-arg treatment partially ameliorated those alterations. In addition, L-arg limited the reduction in SIRT1 expression, associated with decreased senescence in the diabetic kidney, especially with telomerase deficiency. Ex vivo study with freshly isolated de-capsulated glomeruli demonstrated that high glucose (HG, 30 mM) incubation stimulated endothelial cell detachment from GBM in glomeruli with TERC deletion, which could be prevented by co-incubation with a SIRT activator, SRT1720. Primary cultured GEnCs exhibited reduced NO and cellular senescence after incubation for 96 hours in HG medium, with a marked increase in cells with TERC deletion. HG also decreased SIRT 1 expression and activity to a greater extent in the TERC deficient GEnCs. SRT1720 partially restored NO expression, and co-incubation with either SRT1720 or L-arg attenuated HG induced senescence in TERC deleted GEnCs.

Conclusions: These results suggested that both NO and the SIRT1 pathway are involved in the telomerase dependent susceptibility to DN progression and GEnCs senescence.

Funding: NIDDK Support

TH-PO714

pNaKtide Targeted to Adipocytes Inhibits Na/K-ATPase Reactive Oxygen Species, Systemic Inflammation, and Obesity Development in Mice Fed a Western Diet Rebecca Martin,[4] Cameron Brickman,[3] Jiang Liu,[2] Komal Sodhi,[1] Joseph I. Shapiro.[4] *[1]Marsha, Huntington, WV; [2]Marshall University JCE School of Medicine, Huntington, WV; [3]Marshall University JCESOM, Huntington, WV; [4]Marshall University School of Medicine, Huntington, WV.*

Background: Obesity is a worldwide epidemic with many comorbidities. It has been demonstrated that oxidative stress can exacerbate obesity development. We have previously published that systemic administration of pNaKtide, a Na/K-ATPase signaling antagonist, decreased oxidative stress and adipogenesis by blocking Na/K-ATPase signaling mediated amplification of oxidative stress. Adipocyte dysfunction may be prevented by lentiviral mediated adipocyte-specific delivery of pNaKtide.

Methods: C57Bl6 mice were randomly divided into five groups: 1) normal chow 2) normal chow+lenti-adipo-pNaKtide 3) WD 4) WD+lenti-adipo-GFP and 5) WD+lenti-adipo-pNaKtide (n=6-8/group). Lentiviral constructs with pNaKtide driven by an adiponectin promoter were used to achieve pNaKtide expression specifically in adipose tissue. Groups 2 and 5 were given an intraperitoneal injection of lenti-adipo-pNaKtide and group 4 was given an intraperitoneal injection of lenti-adipo-GFP at beginning of the experiment and again at week 2; total time 12 weeks. Body weight was measured weekly. Glucose clearance was determined using an intraperitoneal glucose tolerance test before termination of the experiment. At sacrifice body weight, visceral and subcutaneous fat content of all mice were measured. Blood samples were collected for determination of inflammatory cytokines. Tissues were flash frozen and maintained at -80°C.

Results: Lenti-adipo-pNaKtide significantly reduced WD-induced weight gain, and visceral and subcutaneous fat content. Lenti-adipo-pNaKtide reduced WD-induced changes in glucose tolerance and inflammatory markers TNFα, IL-6 and MCP-1 ($p<0.05$). An increase in cardiac hypertrophy in WD animals was attenuated ($p<0.05$). Visceral fat of WD mice expressed higher levels of adipogenic markers PPARγ, FAS, and C/EBP. WD-induced Na/K-ATPase signaling was decreased. Renal function was not significantly impacted; slight decreases in function are evident, suggesting a potential decrease in renal function with chronic obesity.

Conclusions: Collectively this study introduces the novel idea that adipocytes may have a systemic effect. Specifically targeting pNaKtide to the adipocytes with lenti-adipo-pNaKtide ameliorates this systemic effect. This new information is important in the development of new therapeutic targets for obesity.

TH-PO715

Effect of Dietary Fat/Carbohydrate Ratio on Renal Lipid Deposition in Rats with Diabetic Nephropathy Miho Sugimoto,[1] Takuya Yoshida,[1] Naoki Ikegaya,[2] Hiromichi Kumagai.[1] *[1]Dept. of Clinical Nutrition, Univ. of Shizuoka, Shizuoka, Japan; [2]Dept. of Medicine, Yaizu City Hospital, Yaizu, Japan.*

Background: High-fat/low-carbohydrate diet (HFD) has been used to achieve glycemic control among diabetic patients. However, HFD may be harmful to those with diabetic nephropathy. This study aimed to examine the effect of HFD on diabetic nephropathy.

Methods: Twelve-week-old male Hos:ZFDM-*Lepr*$^{fa/fa}$ (a novel diabetic rat strain) rats were maintained under a calorie-restrictive (60%–70% *ad libitum*) and isoenergetic condition with either HFD (14% protein, 40% fat, and 46% carbohydrate) or pair-fed control diet (14% protein, 15% fat, and 71% carbohydrate) for 7 weeks. Oral glucose tolerance test (OGTT), urinary protein excretion, creatinine clearance (Ccr), and renal triglyceride (TG) content were assessed at the end of the experiment. The renal histology and lipid deposition were also evaluated.

Results: The HFD rats had lower plasma glucose levels at 60 and 120 min OGTT than the control rats (at 120 min OGTT: 524±24 and 648±38 mg/dl for HFD and control rats, respectively; $p<0.001$). However, although the HFD rats had better glycemic control than the control rats, the former showed significantly lower Ccr (HFD and control rats: 1.63±0.13 and 3.86±0.34 L/day, respectively: $p<0.001$) and higher proteinuria than the latter. Furthermore, the HFD rats displayed significantly higher plasma and renal TG concentrations than the control rats. Glomerular mesangial expansion and lipid deposition in the proximal tubular cells were observed in the HFD rats. The renal TG content was correlated with the urinary liver-type fatty acid-binding protein excretion.

Conclusions: These results indicated that HFD may accelerate the progression of diabetic nephropathy, even under caloric restriction.

Funding: Government Support - Non-U.S.

TH-PO716

Study of mTORC2 Pathway on CD4+CD25+Treg in Diabetic Nephropathy Qiu yue Li,[1] Jing Zhou.[2] *[1]The First Affiliated Hospital of Nan Chang University, Nanchang, China; [2]The first affiliated hospital of Nanchang University, Nanchang, China.*

Background: To investigate the effect of mTORC2 pathway blocker on $CD4^+CD25^+$Treg in diabetic nephropathy (DN) rats, and to explore the possible mechanism of Treg in DN podocyte injury.

Methods: Thirty SD rats were randomly divided into DN group, DN + FK506 group and DN + ku0063794 group. Treantment groups were respectively given FK506 1mg/kg/d, ku0063794 1mg/kg/d orally every day. Blood glucose, Creatinine clearance (Ccr) and urinary protein were measured at 0, 4, 8 weeks. The expression of mTOR, Raptor, Rictor in renal tissue was detected at 4, 8 weeks. The levels of IL-17 and TGF-β1 in peripheral blood were detected by ELISA, and the percentage of $CD4^+CD25^+$Treg was detected by flow cytometry at 4, 8 weeks.

Results: Urinary protein of model group was higher than control group($P<0.05$), intervention groups were lower than model group ($P<0.05$); Ccr of model group compared with control group significantly decreased ($P<0.05$), intervention groups compared with model group significantly increased ($P<0.05$); mTOR, Raptor, Rictor increased significantly in the model group and decreased in the intervention groups ($P<0.05$); $CD4^+CD25^+$Treg of the model group was significantly lower than control group ($P<0.05$), and intervention groups were higher than model group ($P<0.05$); it of intervention groups at 8 week were higher than at 4 week ($P<0.05$); Pathological score of intervention groups compared with model group significantly decreased($P<0.05$); TGF-β1 and IL-17 of the model group were significantly higher than control group ($P<0.05$), and the intervention groups were lower than model group ($P<0.05$); TGF-β1 of FK506 intervention group was lower than that of ku0063794 intervention group ($P<0.05$); Correlation analysis: In model group at 8 weeks, Rictor was negative correlation with $CD4^+$ $CD25^-$Treg and Ccr ($P<0.05$), positive correlation with TGF-β1, IL-17, urinary protein, pathological score ($P<0.05$); Raptor was positively correlated with urinary protein and pathological score ($P<0.05$), negative correlation with Ccr ($P<0.05$), no correlation with $CD4^+CD25^+$ Treg, TGF-β1, IL-17.

Conclusions: $CD4^+CD25^+$Treg may be regulated by the mTORC2 pathway in DN rats, and involved in the pathogenesis of DN.

Funding: Government Support - Non-U.S.

TH-PO717

ESRD and Mortality after VA NEPHRON-D Linda F. Fried,[6] Yuan Huang,[7] Jane H. Zhang,[8] Paul M. Palevsky,[4] Gary R. Johnson,[8] Stephen L. Seliger,[3] Peter A. McCullough,[1] Todd A. Conner,[8] Mary Brophy,[5] Nicholas Emanuele.[2] *[1]Baylor University Medical Center, Dallas, TX; [2]Hines VA, Hines, IL; [3]University of Maryland School of Medicine, Baltimore, MD; [4]University of Pittsburgh, Pittsburgh, PA; [5]VA Boston Healthcare System, Boston, MA; [6]VA Pittsburgh Healthcare System, Pittsburgh, PA; [7]Yale University, New Haven, CT; [8]VA CSP, Albuquerque, NM.*

Background: VA NEPHRON-D, a trial of ACEI+ARB vs. ARB alone in type 2 diabetes, eGFR 30-89.9 ml/min/1.73m^2 and ACR ≥ 300mg/g, was stopped for safety; questions of benefit remained.

Methods: At the end of the study, participants were asked to join passive follow-up with electronic data abstraction through 9/30/14. ESRD was defined during study as eGFR < 15 or chronic dialysis; and during follow-up by USRDS linkage of ICD9 and CPT coding. AKI was a study safety event; during follow-up it was defined by ICD9 code or 50% rise in creatinine. All-cause mortality was obtained from VHA Vital Status File.

Results: Of the 1448 randomized, 895 (61.8%, 445 in the ARB alone and 450 in the ARB+ACEI) consented to follow-up. Over the entire study, 75 (10.4%) in the monotherapy arm developed ESRD and 157 (21.7%) died vs. 63 (8.7%) and 146 (20.2%) respectively in the ACEI + ARB arm, which was not statistically significant. There was a significant decline in eGFR slope over time, but the slope was similar in both treatment groups (p= 0.13); eGFR at start of study and end of followup was 59.0 and 38.2 in ARB alone vs. 57.6 and 37.1 in ACEI + ARB. There was a significant AKI*treatment interaction for ESRD (p=0.013) (table). Combination therapy was associated with a decreased risk of ESRD in those without AKI (HR=0.61), but with a higher risk in those with AKI (HR=1.3). AKI predicted mortality, but there was no AKI*treatment interaction.

Conclusions: Overall, there was not an apparent long-term benefit or harm for combination therapy. Further research into the AKI * treatment interaction to determine whether it is unmasking a higher risk of ESRD or could be used to identify sub-populations that may benefit from combination therapy is needed

Funding: Veterans Affairs Support

Number of ESRD events by AKI and Treatment

	no AKI	AKI
ARB alone	10.0%	11.5%
ACEI + ARB	5.8%	19.1%

TH-PO718

Baseline Characteristics in PRIORITY Study: Proteomics and Mineralocorticoid Receptor Antagonism for Prevention of Diabetic Nephropathy in Type 2 Diabetes Nete Tofte. *Steno Diabetes Center, Copenhagen, Denmark. Group/Team: On behalf of PRIORITY study group.*

Background: In PRIORITY (Proteomic prediction and Renin angiotensin aldosterone system Inhibition prevention Of early diabetic nephRopathy In TYpe 2 diabetic patients with normoalbuminuria) the aim is to test if the urinary proteomics based classifier CKD273 can predict microalbuminuria prospectively, and to test whether mineralocorticoid receptor antagonism (MRA) delays progression to microalbuminuria.

Methods: Prospective, randomized, double-blind, placebo-controlled multicentre clinical trial and observational study in normoalbuminuric type 2 diabetic patients. Patients are stratified into high- or low risk groups based on CKD273. Patients in the high risk group are assigned to spironolactone 25 mg once daily or placebo, the low-risk group is followed on standard care. Patients are followed for up to 4.5 years. Primary endpoint is development of microalbuminuria.

Results: From 15 sites we have included 1811 patients. The high- and low-risk populations differ in terms of gender, age, diabetes duration, UACR and eGFR (table). Univariate regression analyses of CKD273 vs each baseline variable demonstrated weak associations (R^2 of 0.03, p <0.0001) for the strongest correlations with UACR and eGFR. In a logistic regression model predicting CKD273 risk strata, including all baseline variables, eGFR and UACR remain statistically significant (p < 0.0003) with an AUC of 0.70 (95 % CI: 0.65, 0.74).

Conclusions: Classical risk factors for diabetic kidney disease differ only slightly, and overlap to a great extent, between high and low risk patients based on the urinary proteomics based risk classifier CKD273 in type 2 diabetes, suggesting it provides additional information to the measures already available in the clinic. The potential added value will be tested in this prospective study. Funding received from European Union Seventh Framework Programme (FP7/2007-2013) grant agreement no. 279277.

Baseline characteristics of the overall study cohort and by subgroup

Variable	Included N=1811	Low-risk N=1587	High-risk N=224	P-value (high vs. low)
Gender, male, n (%)	1132 (62)	976 (61)	156 (69)	0.03
Age, years	62 (8)	61 (8)	63 (7)	0.0014
Diabetes duration	11 (8)	11 (8)	13 (8)	0.0010
Systolic blood pressure, mmHg	134 (14)	133 (12)	134 (13)	0.07
eGFR, ml/min/1.73 m2	87 (15)	88 (15)	81 (17)	<0.0001
UACR, Median (IQR), mg/g	7 (3-9)	5 (3-8)	7 (4-12)	<0.0001

Mean (SD)

TH-PO719

Non Albuminuric Chronic Kidney Disease (NA-CKD) Phenotype in Patients (Pts) with Type 2 Diabetes (DM2): Results from a Population Based Study Stefano Bianchi, Elisa Poderelli, Chiara Bilanceri, Sara Samoni, Eva D'Aurizio, Andrea Grillo, Roberto Bigazzi. *ASL Toscana Nordovest, Livorno, Italy.*

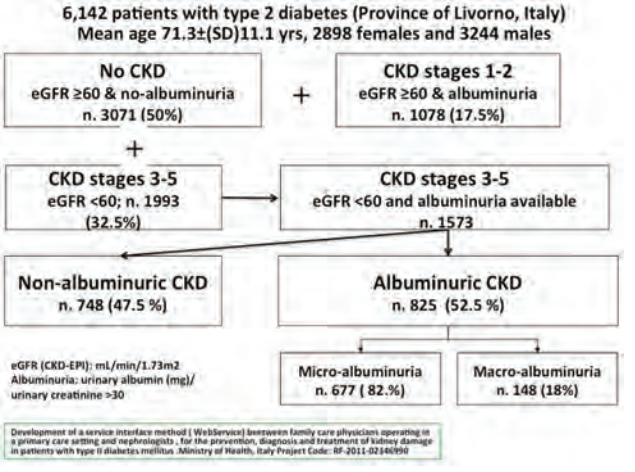
Background: Albuminuria (A) is considered the first clinical sign of renal involvment and it is widely used as the most useful screening test for CKD in pts with DM2. However, in the last years increasing evidences have shown that a significant number of pts with DM2 has stage 3-5 CKD without significant A, a condition known as NA-CKD. The aim of this study was to determine the prevalence of NA-CKD in pts with DM2, living in the Province of Livorno, Italy.

Methods: Pts with DM2 living in the Province of Livorno, Italy are routinely screened for the presence of CKD, as a part of a three years project financed by the Italian Ministry of Health Care (Italian HC system RF-2011-02346990). We have screened 6,142 pts (2,898 F and 3,244 M, mean age 71.3±(SD)11.1 yrs), measuring the estimated glomerular filtration rate (eGFR, CKD-EPI) and A (Ualb,mg/Ucreat,g).

Results: 3,071 pts (50%) presented CKD in different stage (222 Stage 1,13.6%; 856 Stage 2,13.9%;1,227 Stage 3a, 20%; 579 Stage 3b, 9.4%; 147 Stage 4, 2.4% and 40 Stage 5, 0.6%). 1,573 pts with stage 3-5 CKD and measured A were classified as non albuminuric (748, 47.5%, 399 M and 409 F, mean age 77.1±(SD) 8.8 yrs) or albuminuric (825, 52.5%, 460 M and 365 F, mean age 76.9±(SD)9.4 yrs). 677 albuminuric pts had A >30<300 (82%) while148 (18%) had A >300. The albuminuric CKD phenotype was more prevalent in M than in F.

Conclusions: In our study half of pts with DM2 and stage 3-5 CKD shows NA-CKD and most of albuminuric pts have A in microalbuminuric range. Our population is under active investigation (blood pressure and lipis control, duration and metabolic control of diabetes etc) to evaluate which clinical pathways could be involved in the development of different CKD phenotypes in DM2. We are also following up these patients to investigate the renal and cardiovascular outcomes of the different phenotypes.

Funding: Government Support - Non-U.S.



TH-PO720

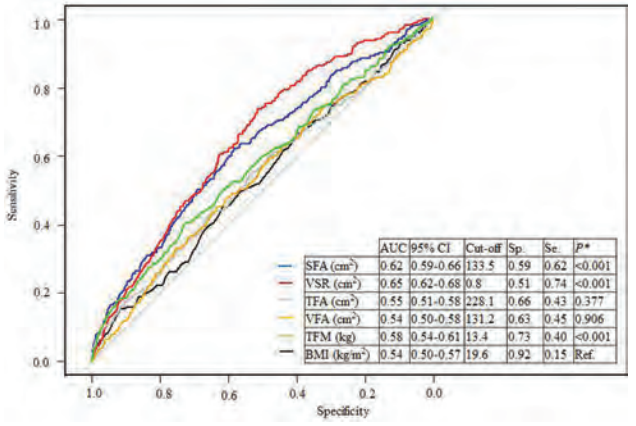
Body Fat Distribution Is More Predictive of All-Cause Mortality Than Overall Adiposity Sung Woo Lee,[1] Nam ju Heo.[2] *[1]Eulji General Hospital, Seoul, Republic of Korea; [2]Seoul National University Hospital, Seoul, Republic of Korea.*

Background: The relationship between directly measured body fat and all-cause mortality has been rarely studied. The aim of this study was to evaluate the predictive significance of computed tomography (CT)-measured body fat, including both visceral fat area (VFA) and subcutaneous fat area (SFA), for mortality.

Methods: The study included 36,656 participants who underwent abdominal CT as part of a health check-up at a single university-affiliated healthcare centre in 2007–2015. Of those, 32,593 participants with data regarding vital status as of May 2016 were included in the final analysis. The main factors evaluated were VFA, SFA and visceral-to-subcutaneous fat area ratio (VSR), and the primary outcome was all-cause mortality.

Results: There were 253 deaths during a mean follow-up of 5.7 years. Increased SFA was associated with decreased all-cause mortality, whereas an increased VFA and VSR were related to increased all-cause mortality. Compared with the predictive power of body mass index (BMI), SFA and VSR showed a larger area under the curve than did BMI. In Kaplan-Meier survival curve analysis, increased SFA and VSR were associated with decreased and increased hazard of all-cause death, respectively. However, in multivariate Cox proportional hazard regression analysis, only VSR was independently associated with all-cause mortality. Moreover, this relationship was paralleled by the harmful impact of increased VSR on metabolic profiles.

Conclusions: Increased VSR was an independent predictor of all-cause mortality. This suggests that the location of fat deposits may be more important than the actual amount of body fat.



	AUC	95% CI	Cut-off	Sp.	Se.	P*
SFA (cm²)	0.62	0.59-0.66	133.5	0.59	0.62	<0.001
VSR (cm²)	0.65	0.62-0.68	0.8	0.51	0.74	<0.001
TFA (cm²)	0.55	0.51-0.58	228.1	0.66	0.43	0.377
VFA (cm²)	0.54	0.50-0.58	131.2	0.63	0.45	0.906
TFM (kg)	0.58	0.54-0.61	13.4	0.73	0.40	<0.001
BMI (kg/m²)	0.54	0.50-0.57	19.6	0.92	0.15	Ref.

TH-PO721

Glycemic Status and Mortality in CKD According to Transition versus Non-Transition to Dialysis Connie Rhee,[3] Csaba P. Kovesdy,[7] Vanessa A. Ravel,[2] Elani Streja,[1] Melissa Soohoo,[5] Gregory Brent,[8] Danh V. Nguyen,[6] Kamyar Kalantar-Zadeh.[4] *[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [2]Harold Simmons Center, University of California at Irvine, Orange, CA; [3]University of California Irvine, Huntington Beach, CA; [4]University of California Irvine, School of Medicine, Orange, CA; [5]University of California at Irvine, Orange, CA; [6]University of California, Irvine, Irvine, CA; [7]University of Tennessee Health Science Center, Memphis, TN; [8]VA Greater Los Angeles Healthcare, Los Angeles, CA.*

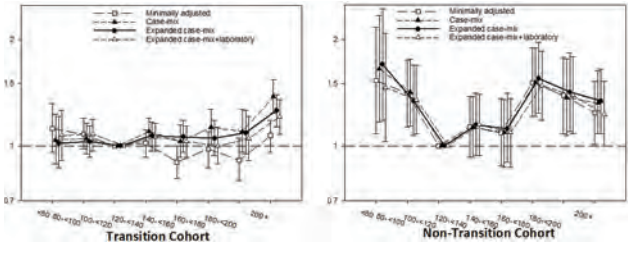
Background: The optimal glycemic target in diabetic non-dialysis dependent chronic kidney disease (NDD-CKD) patients remains uncertain, as most trials of glycemic control excluded advanced kidney disease patients. We examined pre-ESRD glycemic status, defined by random blood glucose and hemoglobin A1c (HbA1c), with *early* post-ESRD mortality among diabetic NDD-CKD patients transitioning to dialysis. In parallel, we examined glycemic status and mortality in a matched cohort of NDD-CKD patients who did not transition to dialysis.

Methods: Among US veterans with diabetic NDD-CKD transitioning to dialysis from 2007-11 (Transition Cohort), we examined 1-year pre-ESRD averaged random glucose and HbA1c with 1-year all-cause mortality using expanded case-mix Cox models. Analogous analyses were conducted among CKD patients who did not transition to dialysis within 1-year (Non-Transition Cohort) matched on the basis of age, sex, race, ethnicity, and baseline CKD stage.

Results: Among 17,121 patients in the Transition Cohort, averaged random glucose ≥200mg/dl was associated with higher mortality (ref: 100-<120mg/dl), and HbA1c ≥8% was associated with higher mortality (reference: 6-<8%). Among 8711 patients in the Non-Transition Cohort, lower glucose <100mg/dl and higher glucose ≥160mg/dl were associated with higher mortality, whereas HbA1c was not associated with death.

Conclusions: In diabetic NDD-CKD patients transitioning to dialysis, higher averaged random glucose and HbA1c were associated with early dialysis mortality. In patients who did not transition, there was a U-shaped association between glucose and mortality. These data suggest liberal glycemic status is associated with long-term mortality risk, whereas intensive glycemic status is associated with short-term risk.

Funding: NIDDK Support



TH-PO722

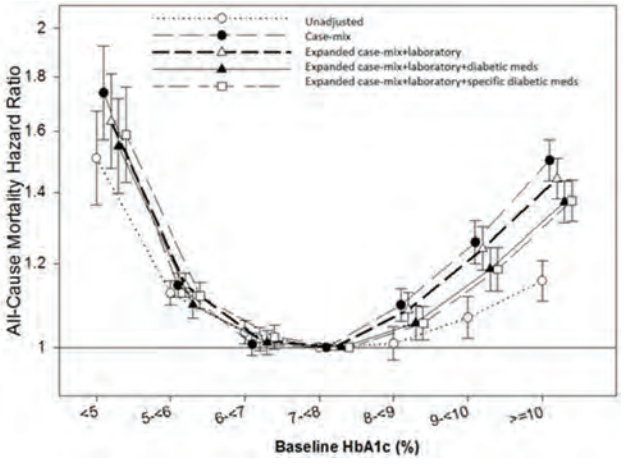
Glycemic Status and Mortality Among Patients with CKD Connie Rhee,[3] Kamyar Kalantar-Zadeh,[4] Vanessa A. Ravel,[2] Gregory Brent,[7] Danh V. Nguyen,[5] Elani Streja,[1] Csaba P. Kovesdy.[6] *[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [2]Harold Simmons Center, University of California at Irvine, Orange, CA; [3]University of California Irvine, Huntington Beach, CA; [4]University of California Irvine, School of Medicine, Orange, CA; [5]University of California, Irvine, Irvine, CA; [6]University of Tennessee Health Science Center, Memphis, TN; [7]VA Greater Los Angeles Healthcare, Los Angeles, CA.*

Background: There is uncertainty with regards to the optimal, precise glycemic level in diabetic non-dialysis dependent chronic kidney disease (NDD-CKD) patients. Whereas multiple studies show both lower and higher hemoglobin A1c (HbA1c) levels are associated with worse survival in diabetic dialysis patients, there are sparse data in NDD-CKD patients showing conflicting findings.

Methods: We examined the association of glycemic status, defined by baseline HbA1c, with all-cause mortality among US veterans with diabetes and Stage 3-5 NDD-CKD who underwent ≥1 HbA1c measure(s) over 2004-12 using expanded case-mix+laboratory Cox models. Sensitivity analyses incrementally adjusted for broad categories of anti-diabetic medications (insulin, oral medications) as well as specific categories (biguanides, thiazolidinediones, alpha-glucosidase inhibitors, insulin, insulin secretors, other oral medications).

Results: Among 213,123 patients who met eligibility criteria, both lower HbA1c <6% and higher HbA1c ≥8% were associated with higher mortality (ref: 7-<8%): adjusted HRs (95% CI) 1.63 (1.47-1.81), 1.15 (1.12-1.18), 1.02 (0.99-1.04), 1.09 (1.05-1.13), 1.24 (1.18-1.30), 1.44 (1.38-1.51) for HbA1c <5, 5-<6, 6-<7, 8-<9, 9-<10, and ≥10%, respectively. This pattern of association was robust across analyses incrementally adjusted for broad and specific categories of anti-diabetic medications.

Conclusions: Among diabetic US veterans with NDD-CKD, there was a U-shaped association between HbA1c levels and mortality. Further studies are needed to determine whether treatment to a HbA1c target of 6-<8% improves survival in this population.



TH-PO723

Hemoglobin A1c Levels and Infection Risk Among Dialysis Patients Connie Rhee,[3] Kamyar Kalantar-Zadeh,[4] Amy S. You,[5] Elani Streja,[2] Steven M. Brunelli,[1] Gregory Brent,[7] Csaba P. Kovesdy,[6] Danh V. Nguyen.[5] *[1]DaVita Clinical Research, Needham, MA; [2]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [3]University of California Irvine, Huntington Beach, CA; [4]University of California Irvine, School of Medicine, Orange, CA; [5]University of California, Irvine, Orange, CA; [6]University of Tennessee Health Science Center, Memphis, TN; [7]VA Greater Los Angeles Healthcare, Los Angeles, CA.*

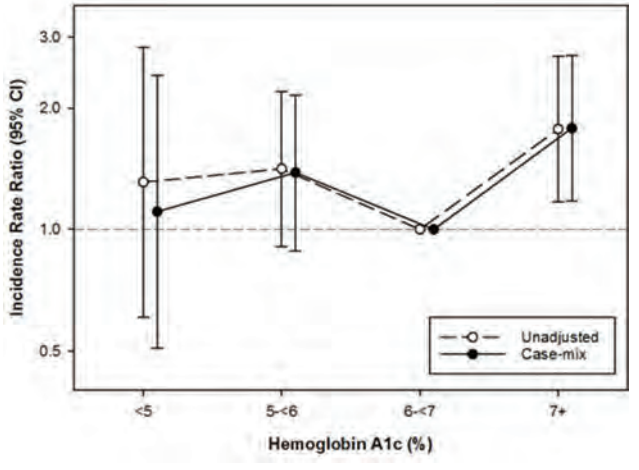
Background: Diabetic patients are at heightened risk of infection due to the immune dysfunction (i.e., impaired neutrophil function, antioxidant system, and humoral immunity) ensuing from hyperglycemia. While infections are the second leading cause of death in end-stage renal disease patients, little is known about the relationship between average glucose control defined by hemoglobin A1c (HbA1c) and infection risk in the dialysis population.

Methods: Among 642 dialysis patients from the national Biospecimen Registry Grant Program (BioReG) who underwent HbA1c testing over 1/2008-12/2014, we examined the relationship between average glucose control, as reflected in the HbA1c, and risk of bacteremia using case-mix adjusted Poisson regression models adjusted for age, sex, and race/ethnicity.

Results: In the overall cohort, the mean±SD and minimum-maximum HbA1c values were 6.7±1.5% and 3.8-16.0%, respectively; approximately 16% of patients experienced one or more bacteremia events during the follow-up period. Compared to a HbA1c level 6-<7%, patients with HbA1c levels ≥7% had a higher incident rate of bacteremia in case-

mix models: adjusted IRRs [aIRRs] 1.11 (0.51-2.41), 1.38 (0.89-2.16), and 1.79 (1.18-2.71) for HbA1c levels <5, 5-<6, and ≥7%, respectively.

Conclusions: Higher HbA1c levels were associated with higher incident rates of bacteremia in dialysis patients. While clinical practice guidelines advise against tight glycemic control in diabetic ESRD patients due to risk of hypoglycemia, liberal glycemic status may also contribute to adverse outcomes due to heightened infection risk. Further studies are needed to more granularly define the upper threshold for heightened infection risk within specific populations.



TH-PO724

Coronary Artery Calcification Scores and Intrarenal Hemodynamic Function in Adults with Type 1 Diabetes of ≥50 Years' Duration: Results from Canadian Study for Longevity in Type 1 Diabetes Julie A. Lovshin,[4] Petter Bjornstad,[2] Leif E. Lovblom,[1] Yuliya Lytvyn,[4] Genevieve Boulet,[1] Mohammed A. Farooqi,[1] Johnny-Wei Bai,[1] Vesta S. Lai,[4] Leslie Cham,[4] Josephine Tse,[4] Andrej Orszag,[1] Daniel Scarr,[1] Alanna Weisman,[1] Hillary A. Keenan,[3] Michael Brent,[4] Narinder Paul,[4] Vera Bril,[4] Bruce A. Perkins,[4] David Cherney.[4] *[1]Lunenfeld-Tanenbaum Research Institute, Toronto, ON, Canada; [2]Children's Hospital Colorado, Aurora, CO; [3]Joslin Diabetes Center, Boston, MA; [4]University of Toronto, Toronto, ON, Canada.*

Background: Diabetic nephropathy (DN) carries a significant risk for premature cardiovascular (CV) mortality. It is unclear whether atherosclerosis associates with intrarenal hemodynamic dysfunction in type 1 diabetes (T1D).

Methods: T1D (n=69) and age/sex-matched controls without diabetes (n=73) underwent CAC volume scoring by electron beam CT [mean age 65±8 years, 81(57%) female]. Gold standard measures of glomerular filtration rate [GFR_{INULIN}] and effective renal plasma flow [$ERPF_{PAH}$] were used, and renal blood flow [RBF], renal vascular resistance [RVR], and afferent (R_A) and efferent (R_E) arteriole resistances were derived from Gomez' equations. The cohort was dichotomized to high (≥300 AU) or low (<300 AU) CAC and stratified by T1D status. Additionally, linear regression was used to examine relationships between CAC (transformed) and intrarenal hemodynamic function, adjusting for age, sex, and HbA1c.

Results: Compared to controls, T1D subjects had higher prevalence of high CAC (68 vs. 14%, p<0.001) and median CAC volumes (1000[222,2373] AU vs. 1[0,75] AU, p<0.001). Mean baseline GFR_{INULIN} was 103±17 mL/min/1.73m^2 in T1D and 106±19 mL/min/1.73m^2 in controls (p=0.34). In T1D, high CAC was associated with higher HbA1c, presence of neuropathy, and a history of macrovascular disease. In T1D and in controls, no parameter of intrarenal hemodynamic function including GFR

Conclusions: Despite the strong epidemiologic relationships between DN and CV disease, the presence of atherosclerosis did not impact intrarenal hemodynamic function to RAAS activation in older adults with longstanding T1D.

TH-PO725

Kidney Disease and Risk of Incident Diabetes Mellitus Yan Xie,[1] Benjamin C. Bowe,[1] Tingting Li,[2] Hong Xian,[3] Yan Yan,[2] Ziyad Al-Aly.[1] *[1]Clinical Epidemiology Center, Research and Development Service, Veterans Affairs St Louis Health Care System, St. Louis, MO; [2]Washington University School of Medicine, Saint Louis, MO; [3]Saint Louis University College for Public Health & Social Justice, St. Louis, MO.*

Background: Kidney disease is associated with disturbances in glucose and insulin homeostasis. Experimental evidence suggests that urea causes a state of insulin resistance and may also suppress insulin secretion. However, whether higher levels of Blood Urea Nitrogen (BUN) are associated with increased risk of incident diabetes mellitus in humans is not known.

Methods: We built a national cohort of 1,337,452 United States Veterans without diabetes to characterize the association of BUN and risk of incident diabetes. Cause specific survival analyses with time-varying variables were conducted.

Results: Over a median follow-up of 4.93 years, in joint risk models of eGFR and BUN; there was no association between eGFR and the risk of incident diabetes in those with BUN ≤25 mg/dl, the risk was significantly increased in those with BUN>25 mg/dl at all eGFR levels even in those with eGFR≥60 ml/min/1.73m^2 (HR=1.27;CI=1.24-1.31). The risk of incident diabetes was highest in those with BUN >25 mg/dL and eGFR<15 ml/min/1.73m^2 (HR=1.68;CI=1.51-1.87). Spline analyses of the relationship between BUN and risk of incident diabetes showed that risk was progressively higher as BUN increased. In models where eGFR was included as a continuous covariate; compared to BUN≤25 mg/dl, BUN>25 mg/dl was associated with increased risk of incident diabetes (HR=1.23;CI=1.21-1.25); every 10 ml/min/1.73m^2 increase in eGFR was not associated with risk of incident diabetes (HR=1.00;CI=1.00-1.01). Two-stage residual inclusion analyses showed that independent of the impact of eGFR, every 10 mg/dL increase in BUN concentration was associated with increased risk of incident diabetes (HR=1.15;CI=1.14-1.16).

Conclusions: Our results suggest that higher levels of BUN are associated with increased risk of incident diabetes mellitus. A bidirectional nexus (between diabetes and kidney disease) likely exists, in that diabetes causes kidney disease, and elevated levels of urea-often present in the context of advanced kidney disease-are associated with increased risk of incident diabetes.

Funding: Veterans Affairs Support

TH-PO726

Mortality in Diabetic Adults with Low eGFR in the Absence of Increased Urine Albumin Excretion Is Increasing Holly J. Kramer,[1] R. E. Boucher,[2] Guo Wei,[2] Tom Greene,[2] David J. Leehey,[1] Linda F. Fried,[4] Sylvia E. Rosas,[5] Srini Beddhu.[3] *[1]Loyola University Medical Center, Maywood, IL; [2]University of Utah, Salt Lake City, UT; [3]University of Utah School of Medicine, Salt Lake City, UT; [4]VA Pittsburgh Healthcare System, Pittsburgh, PA; [5]Joslin Diabetes Center, Boston, MA.*

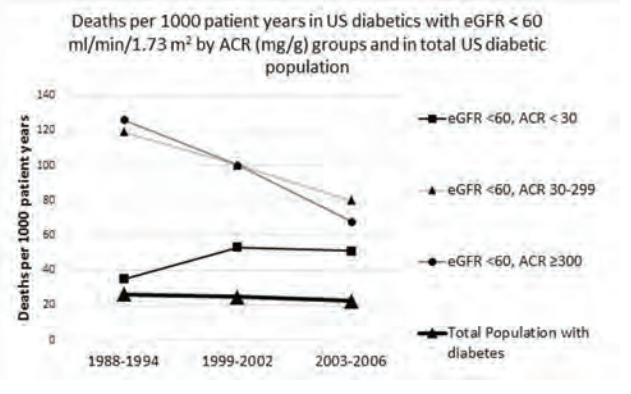
Background: Due to improvements in diabetes management, the prevalence of low estimated glomerular filtration rate (eGFR) has increased while prevalence of increased urine albumin excretion (albumin-to-creatinine ratio [ACR] ≥ 30 mg/g) has decreased. These trends may influence mortality due to the heterogeneity of risk across chronic kidney disease (CKD) phenotypes.

Methods: We used data from the National Health and Nutrition Examination Surveys 1988-2006 linked with the National Death Index through December 31, 2011 to examine temporal trends in mortality and total number of deaths by CKD phenotype in the U.S. diabetic population by CKD phenotype. Diabetes was defined as presence of a fasting glucose ≥ 126 mg/dl, hemoglobin A1c > 6.5% or use of glucose lowering medications. The analyses accounted for the complex survey design.

Results: From 1988 to 2006, diabetic adults with low eGFR and ACR < 30 mg/g increased from approximately 0.9 (95% CI 0.7, 1.1) million during years 1988-1994 to 2.0 (95% CI 1.5, 2.6) million during years 2007-2010. During years 1988-2006, mortality rates generally trended downward for all groups with ACR ≥ 30 mg/g but increased in adults with low eGFR and ACR < 30 mg/g from 35 deaths per 1000 person-years (95% CI 22,55) during years 1988-1994 to 51 deaths per 1000 person-years (95% CI 33, 83) during years 2003-2006 (Figure). The proportion of deaths in the total U.S. population with diabetes occurring in the setting of low eGFR and ACR < 30 mg/g increased from 8.7% during years 1988-1994 to 21.9% during years 2003-2006. Findings did not change substantially after standardizing for the age distribution of the populations.

Conclusions: These findings demonstrate an urgent need to determine optimal management strategies to reduce mortality in diabetics with low eGFR in the absence of increased urine albumin excretion.

Funding: NIDDK Support



TH-PO727

Greater Insulin Use with More Advanced Stages of DKD Christine K. Raj,[1] Vishwa Srinivasan,[2] Arianna N. Jensen,[2] R. E. Boucher,[2] Guo Wei,[2] Srini Beddhu.[2] *[1]UC Berkeley, Saratoga, CA; [2]Univ. of Utah, SLC, UT.*

Background: Those with more advanced CKD are assumed to require less insulin because of decreased renal metabolism of insulin. On the other hand, uremia might result in insulin resistance and/or pancreatic islet cell failure which can ↑ the need for insulin.

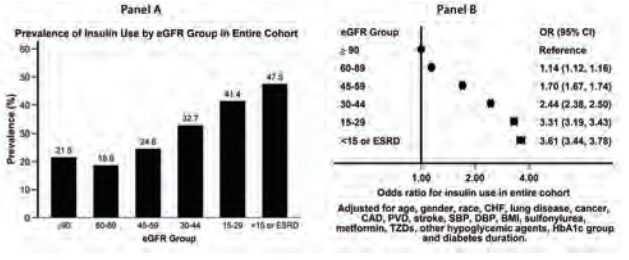
Methods: Veterans in the national VA data with a diagnosis of type 2 DM (defined by ICD-9 codes) from January 1, 2008 to December 31, 2010 and non-missing data for variables of interest were included (N = 943,995). CKD stages defined by CKD-EPI eGFR was related to insulin use in multivariate logistic regression models.

Results: Mean age was 66.0 ± 10.7, 96.8% were men, and 16.3% were black. Clinical characteristics by insulin usage are summarized in the table. Prevalence of insulin use was higher with more advanced CKD (Figure 1 panel A). In multivariate logistic regression model adjusted for demographics, comorbidity, duration of DM, BMI, HBA1C and medications use, the odds of insulin use was significantly higher with more advanced CKD (panel B).

Conclusions: Contrary to the commonly held belief that insulin use is lower in more advanced CKD, insulin use is indeed higher in this population.

Funding: NIDDK Support

	Not on Insulin (N = 735,446)	On Insulin (N = 208,549)
Age (years)	67 ± 11	65 ± 11
Male (%)	96.7	97.1
Black (%)	16.4	20.5
DM duration (years)	3.8 ± 3.0	5.6 ± 3.3
CHF (%)	8.3	15.8
CAD (%)	32.0	40.0
Stroke (%)	10.3	12.9
PVD (%)	11.0	15.4
BMI (kg/m^2)	31.4 ± 6.3	32.8 ± 6.9
ACE-I or ARB use (%)	65.2	77.5
Statin Use (%)	70.1	77.1
Sulfonylurea (%)	42.1	36.7
Metformin (%)	49.7	44.4
TZD (%)	5.2	6.6
Other Hypoglycemic Agents (%)	1.3	2.0
eGFR (mL/min/1.73 m^2)	74.2 ± 20.8	70.1 ± 24.3
HbA1c (%)	7.0 ± 1.4	8.4 ± 2.0
Urine Albumin Creatinine Ration (µg/mg)**	12 (6,35)	23 (9, 85)



TH-PO728

Higher Concentrations of Urea Are Associated with Increased Risk of Failure of Oral Hypoglycemic among Diabetic Patients with CKD Yan Xie,[1] Benjamin C. Bowe,[1] Tingting Li,[1,2] Hong Xian,[1,3] Yan Yan,[1,4] Ziyad Al-Aly.[1,5] *[1]Clinical Epidemiology Center, Research and Education Service, VA Saint Louis Health Care System, Saint Louis, MO; [2]Department of Medicine, Washington University School of Medicine, Saint Louis, MO; [3]Department of Biostatistics, College for Public Health and Social Justice, Saint Louis University, Saint Louis, MO; [4]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, Saint Louis, MO; [5]Renal Section, Medicine Service, VA Saint Louis Health Care System, Saint Louis, MO.*

Background: Kidney disease is associated with disturbances in glucose and insulin homeostasis. Experimental evidence suggests that urea suppresses insulin secretion and increases insulin resistance. However, whether elevated concentrations of urea are associated with increased risk of failure of oral hypoglycemic agents, and increased risk of insulin requirement among diabetic patients with kidney disease is unknown.

Methods: We built a national cohort of 158,099 United States Veterans with incident diabetes and used time-varying survival model to estimate the cause-specific hazards of requiring treatment with insulin.

Results: Over a follow-up period of 4.93 years, compared to those with BUN <=25 mg/dl, the risk of requiring insulin was significantly increased among those with BUN>25 mg/dl (HR=2.55; CI=2.38-2.72). An analysis which considered BUN categorized in quintiles suggested a graded association in that risk of insulin treatment was gradually increased with increased BUN concentrations. An Analysis which only included those with incident diabetes who were on diabetes medications (N=56,702) yielded consistent results; compared to BUN<=25 mg/dl, risk of transitioning from oral hypoglycemic agents to insulin was increased in those with BUN>25 mg/dl (HR=2.52; CI=2.36-2.70). The results were consistent in analyses considering BUN in quintiles.

Conclusions: Our results suggest that higher levels of BUN are associated with increased risk of requiring insulin within patients with diabetes. Further studies are required to examine whether interventions to reduce urea will ameliorate glycemic control or reduce the need for insulin treatment among patients with diabetes.

Funding: Veterans Affairs Support

TH-PO729

Improvement of Glycaemic Control in Patients with Diabetes and CKD through a "One-Stop" Joint Diabetes Kidney Clinic Jayna Patel,[3] Niyati Sodani,[1] Mona Wahba.[2] *[1]St. George's, University of London, London, United Kingdom; [2]st Helier Hospital NHS Trust, London, United Kingdom; [3]St HELIER HOSPITAL, LONDON, United Kingdom.*

Background: Diabetic nephropathy is a significant complication of diabetes mellitus and is associated with increased cardiovascular morbidity and mortality. There is substantial evidence to show that optimal glycaemic control has a significant impact on the progression of diabetic nephropathy. There is no consensus regarding the best model for following up patients with diabetes and CKD in the outpatient setting.

Methods: We conducted a single centre, retrospective observational analysis of patients that attended a monthly 'one stop' joint diabetic and nephrology clinic between 2013 and 2016. This newly established service is run by a consultant nephrologist, endocrinologist and diabetic specialist nurse. Reasons for referral were suboptimal diabetic control, hypoglycaemic episodes in the context of CKD, or where renal function had deteriorated to a point necessitating a change in diabetic medications (e.g. a switch to insulin). They were also referred for further management of weight gain and new onset diabetes after transplantation (NODAT).

Results: A total of 93 patients were reviewed in the clinic. Mean age was 65 years [39-92years]. 57 patients were male and 36 were female. Mean HbA1c of patients at referral was 73 [35-151]. Mean eGFR at referral was 33.6 ml/min [9-90ml/min]. 69.9% of patients were type 2 diabetics and 45% of these patients were switched to an insulin based regimen. 16 patients were started on liraglutide and their mean eGFR at referral was 52.7mls/min [24-90 ml/min]; 13 of these patients were followed up at 1 year and 92% of these patients had lost weight and had a stable eGFR, mean 51.6mls/min [23-90ml/min]. At 1 year follow up, 71% saw an improvement in HbA1c ($p<0.05$, paired t test).

Conclusions: This study showed that this model of care for patients with diabetes and CKD may be used to help improve diabetic control. Liraglutide, a glucagon-like peptide-1 receptor agonist, seems to be an effective agent to promote weight reduction in patients without causing deterioration in renal function.

TH-PO730

Use of Fundus Photography in the Dialysis Facility to Screen for Diabetic Retinopathy Greg S. Garza,[2] Michael P. Martin,[1] Chris Richmond,[1] Andrew Aronson,[1] Maria Radonova,[1] Marta Reviriego-Mendoza,[2] John W. Larkin,[2] Len A. Usvyat,[2] Terry L. Ketchersid,[2] Franklin W. Maddux.[2] *[1]Fresenius Health Partners, Austin, TX; [2]Fresenius Medical Care North America, Waltham, MA.*

Background: Diabetic retinopathy is a leading cause of vision loss in the United States and 2 times more prevalent in kidney disease patients (Varma 2014; Ricardo 2014). Through the Comprehensive ESRD Care (CEC) Model, Fresenius Medical Care North America has partnered with CMS to identify, test, and evaluate new ways to improve care for Medicare beneficiaries with ESRD. We aimed to increase preventative retinal exams that diabetic end stage renal disease (ESRD) patients receive. We are obligated to disclose that the statements contained in this document are solely those of the authors and do not necessarily reflect the views or policies of CMS. The authors assume responsibility for the accuracy and completeness of the information contained in this document.

Methods: We implemented a preventative retinal exam initiative at one Fresenius Kidney Care (FKC) dialysis clinic. Claims data was utilized to identify patients diagnosed with diabetes (Type 1 or Type 2). Eligible patients were invited to have fundal eye examinations performed in the dialysis facility. The exam was ordered by the nephrologist and administered by nurses in the Care Navigation Unit. Photography results were transmitted in a HIPAA compliant fashion to be reviewed and interpreted by a board certified ophthalmologist. The interpretation of the retinal exam was uploaded into FKC's electronic medical records for nephrologist review.

Results: We identified 27 diabetic patients who were eligible for retinal screening. 22% had successful images captured without the need for pupil dilation. For those who did not obtain a successful eye exam, reasons were: Presence of cataracts (<30%), anxiety (<10%) or small pupils (<25%). Ophthalmologists reported the interpreted results within 90 minutes.

Conclusions: Introduction of this device may yield favorable retinal exam screenings in greater than 20% of the eligible diabetic population without pupil dilation. Counseling to reduce anxiety and the use of mydriatics may improve the proportion of successful retinal exam screenings.

Funding: Commercial Support - Fresenius Medical Care North America

TH-PO731

The Magnitude of Obesity and Metabolic Syndrome among the Diabetic CKD Population: A Nationwide Study Piyawan Kittiskulnam,[2] Nintita S. Thokanit,[4] Pisut Katavetin,[3] Paweena Susantitaphong,[1] Kearkiat Praditpornsilpa,[1] Somchai Eiam-Ong.[1] *[1]Chulalongkorn University, Bangkok, Thailand; [2]Chulalongkorn university, Bangkok, Thailand; [3]King Chulalongkorn Memorial Hospital, Thai Red Cross Society and Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [4]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.*

Background: Although the prevalence of obesity among dialysis patients has been exceeding than that of in general population, little is known regarding obesity in non-

dialysis CKD. We aimed to find the magnitude of obesity and metabolic syndrome (MetS) and their associations with the development of CKD among diabetic patients.

Methods: A national survey of type 2 diabetes mellitus (T2DM) patients was collected in the Thai National Health Security Office database during 2014-5. The sampling frame was designated as distinct geographic regions throughout the country. A stratified two-stage cluster sampling was used to select study population. Anthropometry and 12-hour fasting blood samples were obtained by trained personnel. BMI of ≥25 kg/m^2 was classified as obesity. MetS was defined as having elevated waist circumference (>90 cm in men and >80 cm in women) plus any 2 of the followings: triglyceride>150 mg/dL, HDL<40 in men or <50 mg/dL in women, BP≥130/85 mmHg, and blood sugar ≥100 mg/dL. CKD was defined as eGFR <60 ml/min according to the CKD-EPI equation. Logistic regression analysis was performed to examine the relationship between obesity and MetS with the development of CKD.

Results: A total of 32,616 patients were finally recruited from 997 hospitals. The mean age was 61.5±10.9 years and eGFR 70.9±26.6 ml/min with 32% men. Of the participants, 35% were CKD patients (n=10,672). The prevalence of obesity was 46.5% in CKD and 54.1% in non-CKD patients with T2DM. In contrast, the prevalence of MetS in CKD was higher than non-CKD patients (58.5 vs 57.2, p=0.03). There was a trend association between the prevalence of MetS with CKD stage from 3 to 5 (58.1, 61.6, and 63.2%, respectively, p=0.01). When stratified by sex in diabetic CKD group, the presence of MetS was significantly higher among female compared to male (68.6% vs 38.0%, p<0.001). MetS, but not obesity, had a significant higher risk prediction for developing of CKD among T2DM patients after adjusting for age, sex, and comorbidities [OR 1.11; 95%CI 1.03-1.21, p=0.01].

Conclusions: The relatively high prevalence of both obesity and MetS were observed in diabetic CKD community. Identification of obesity-related metabolic phenotypes is necessary to determine risk for the development of CKD among T2DM patients.

Funding: Government Support - Non-U.S.

TH-PO732

Association of Anthropometric Obesity Measures with CKD in Chinese Individuals with Type 2 Diabetes Dongsheng Cheng, Niansong Wang. *Department of Nephrology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China.*

Background: Obesity is associated with both type 2 diabetes and chronic kidney disease (CKD). It remains controversial whether anthropometric obesity measures are related to the risk of CKD in type 2 diabetic patients.

Methods: We investigated the association between anthropometric obesity measures including body mass index (BMI), waist circumference (WC), and waist-to-hip ratio (WHR) with chronic kidney disease in Chinese individuals with type 2 diabetes. CKD was defined as eGFR < 60ml/min/1.73m^2, the presence of albuminuria or both. Logistic regression was used to examine associations of obesity and CKD.

Results: A total of 4701 patients were included in the final analysis. The mean age was 55.7 years, and 59.7% was male. Of these patients, 1362 (29.0%) had CKD. Obesity (BMI≥28 kg/m^2) was found in 18.2%, and overweight (BMI 24–28kg/m^2) was 43.0%. The highest quartile of BMI (odds ratio [OR] 2.55 [95% CI 2.05-3.17]), WC (OR 1.86 [95% CI 1.50-2.30]) and WHR (OR 1.88 [95% CI 1.52-2.32]) was significantly associated with CKD compared with the lowest quartile after adjustment for multiple confounding factors. Interestingly, in the normal weight patients (BMI<24 kg/m^2), no associations were found between quartiles of WC and CKD, whereas increased WHR were associated with CKD.

Conclusions: This study has highlighted a strong association between obesity and CKD in type 2 diabetes. In selected population, such as normal weight patients with type 2 diabetes, larger waist-to-hip ratio but not waist circumference is associated with CKD.

TH-PO733

Effect of GSTK1 on Ectopic Fat Deposition in the Kidney of Patients with Diabetic Nephropathy Xianghui Chen, Chun Hu, Li Zhao, Yachun Han, Xiaofen Xiong, Li Li, Ming Yang, Peng Gao, Li Xiao, Fuyou Liu, Lin Sun. *Departments of nephrology, Second Xiangya Hospital Central South University, Changsha, China.*

Background: Ectopic fat deposition in kidney is closely related to the progression of diabetic nephropathy(DN). GSTK1 is a kind of protein involved in adiponectin secretion and multimerization. This study to observe by first time the relationship between the expression of GSTK1 and ectopic fat deposition(EFD) induced kidney injury in DN patients.

Methods: 36 DN patients diagnosed by renal biopsy were enrolled. 30 patients with mild glomerular lesions were selected as controls. ADRP expression was used as a marker of EFD in the kidney. The expression of GSTK1 and ADRP were detected by immunohistochemistry staining. RT-PCR was used to test the GSTK1mRNA expression in PBMCs. ROS was measured by DHE staining. Lipid accumulation in kidney and cells were observed by Oil Red O staining. HK-2 cells were treated with different concentrations of glucose for 24 hours. The expression of GSTK1 and ADRP was tested by Western blot or immunofluorescence in HK-2 cell transfected with or without GSTK1 plasmid, or treated with MitoQ respectively. Mitochondrial ROS production was detected by Mitosox staining.

Results: Compared with the control group, the levels of TG, CHOL, LDL-C, BUN, SCr, UA and 24h urine protein in DN patients were incresed (p <0.05), while the HDL-C, ALB were decreased (p <0.05). The expression of GSTK1 mRNA in PBMCs was down-regulated(p<0. 01). In addition, the protein expression of GSTK1 in kidneys were decreased, while ADRP, ROS level and the deposition of lipids were significantly increased (p<0.01), which assocaited with different stages of DN. Moreover,the expression of ADRP was positively correlated with UACR, URBP and tubulointerstitial injury score, while GSTK1 was negatively correlated with ROS level and EFD as detected by the ADRP expression and Oil red O staining in DN kidneys. In vitro study showed a notablely increased of ADRP expression, mitochondrial ROS level and intracellular lipid accumulation in HK-2 cells treated by HG or H_2O2 were seen, while downregulated expression of GSTK1 protein was found. All changes above could be bloacked partially by overexpression of GSTK1 or mito Q,a target mitochondrial antioxidants, but failure to co-treatment with H_2O_2.

Conclusions: This data suggested that the decreased expression of GSTK1 in the kidney was significantly correlated with EFD induced renal injury in DN patients.

Funding: Private Foundation Support

TH-PO734

Differences in the Prevalence of Metabolic Syndrome and Its Components among Ethnic Minorities with CKD Robert Lorch, Jingbo Niu, Carl P. Walther, Rajeev Raghavan, Wolfgang C. Winkelmayer, Sankar D. Navaneethan. *Baylor College of Medicine, Houston, TX.*

Background: Metabolic syndrome (MetS) and chronic kidney disease (CKD) are common among ethnic minorities. Whether clustering of various metabolic risk factors occurs irrespective of race is unclear. Herein, we studied whether the prevalence of MetS and its components differed between African Americans (AAs) and Hispanics with CKD.

Methods: We identified patients with stage 3 and 4 CKD (based on 15≤ eGFR <60 ml/min/1.73 m^2) who were followed during 2006-2016 in the Harris Health System, a safety-net health system in Houston, TX. Demographics, comorbid conditions, and laboratory data were extracted from electronic medical records. MetS was defined as the presence of three or more of the following components: body mass index (BMI) ≥30 kg/m^2, serum triglyceride level≥150 mg/dl, HDL≤50 mg/dl in women and ≤40 mg/dl in men, hypertension (BP>130/85 mmHg or on antihypertensive medications), and impaired glucose metabolism (presence of diabetes, use of oral hypoglycemics, or blood glucose level≥200 mg/dl). Age- and sex-adjusted prevalence ratios were calculated using modified Poisson regression with robust variance.

Results: Of 8664 patients with CKD Stage 3 or 4, 6954 (80%) had MetS. The prevalence of MetS was highest among Hispanics (87%), followed by non-Hispanic whites (85%), AA (74%), and Asian Americans (71%). While comparing MetS and its components between AAs and Hispanics, we noted higher prevalence for high triglycerides, low HDL levels, and diabetes, but lower prevalence of obesity among Hispanics than AAs (Table 1).

Conclusions: MetS and its components were highly prevalent in patients with CKD receiving care in a Texan safety-net system, particularly among Hispanics and non-Hispanic Whites. Differences in the prevalences of MetS-defining components between AAs and Hispanics suggest that interventions targeting MetS might need to be tailored based on race.

Funding: NIDDK Support

Table 1. Prevalence of metabolic syndrome and its components among Hispanics and African American patients with CKD stage 3-4

Variable	Race/ ethnicity	Crude prevalence, N (%)	Age and sex-adjusted Prevalence (95% CI)	Prevalence ratio* (95% CI)
MetS	African American	2720 (74.4)	0.713 (0.696, 0.730)	1.0(referent)
	Hispanic	2820 (87.1)	0.844 (0.828, 0.859)	**1.18 (1.15, 1.20)**
Obesity	African American	2772 (75.8)	0.713 (0.694, 0.731)	1.0(referent)
	Hispanic	2340 (72.3)	0.683 (0.664, 0.703)	0.96 (0.93, 0.99)
Low HDL	African American	1981 (54.2)	0.518 (0.498, 0.538)	1.0(referent)
	Hispanic	2229 (68.8)	0.667 (0.647, 0.686)	**1.28 (1.23, 1.32)**
High triglycerides	African American	1297 (35.5)	0.361 (0.341, 0.380)	1.0(referent)
	Hispanic	2004 (61.9)	0.624 (0.604, 0.643)	**1.74 (1.65, 1.83)**
Hypertension	African American	3648 (99.8)	0.998 (0.995, 1.000)	1.0(referent)
	Hispanic	3216 (99.3)	0.993 (0.990, 0.996)	1.00 (0.99, 1.00)
Diabetes	African American	2316 (63.4)	0.589 (0.569, 0.609)	1.0(referent)
	Hispanic	2481 (76.6)	0.725 (0.707, 0.744)	**1.22 (1.18, 1.25)**

*Adjusting for age and sex

TH-PO735

Altered Functional Characteristics of Adipose-Derived Mesenchymal Stem/Stromal Cells (MSC) in Diabetic Kidney Disease (DKD) LaTonya J. Hickson, Ahmed Saad, Alfonso Eirin, James L. Kirkland, Tamara Tchkonia, Travis Mckenzie, Andrew D. Rule, Allyson Palmer, Stephen C. Textor, Lilach O. Lerman. *Mayo Clinic, Rochester, MN.*

Background: Novel interventions such as MSC to delay the progression of DKD are needed. However, the origin of MSC may affect the regenerative capacity of autologous cell-based therapy. We hypothesized that functional capacity and senescent cell burden of MSC from DKD subjects would be impaired compared to healthy volunteers (HV).

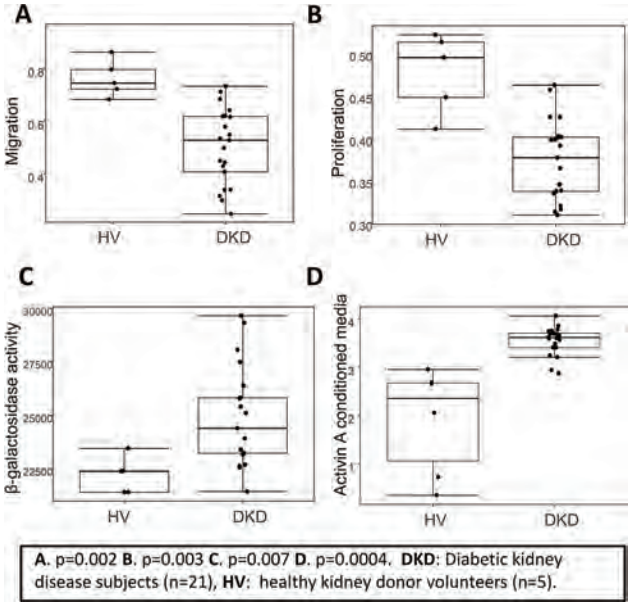
Methods: MSC were cultured from subcutaneous abdominal adipose tissue from 21 subjects with DKD and 5 HV (kidney donors). MSC proliferation, migration, senescence-associated β-galactosidase activity, Activin A, and Annexin V (apoptosis marker) were studied.

Results: DKD subjects were older (65±8 vs 35±16 years; p<0.001), with higher body mass index (37±5 vs 31±4 kg/m^2; p=0.03) and lower eGFR [median 40 (IQR: 31, 54) vs 87 (IQR: 76, 114); p<0.001] compared to HV. Race (76% vs 100% white) and sex (43% vs 60% female) were not different. MSC migration and proliferation were decreased in DKD-MSC compared to HV-MSC. Senescence was increased in DKD-MSC, but

apoptosis was similar between groups. Similarly, markers of senescence (Activin A) measured in the MSC-cultured media were higher in DKD. [Figure]

Conclusions: DKD-MSC exhibit altered functional characteristics and increased senescence, possibly due to aging and diabetic microenvironments. Diabetes and uremia may alter the function of MSC, potentially limiting the effectiveness of autologous-based therapy.

Funding: NIDDK Support, Private Foundation Support



MSC Function and Senescence Studies - DKD and HV Subjects

TH-PO736

Ectopic Lipid Accumulation and Its Clinic Relevance in Type 2 Diabetic Kidney Disease Patients Li Xiao,[1] Ying Luo,[1] Wenxia Yang,[1] Hang Liang,[1] Fan Zhang,[1] Yiming Zhou,[2] Mengru Zeng,[1] Lin Sun,[1] Fuyou Liu.[1] *[1]Department of Nephrology, The Second Xiangya Hospital, Central South University, Changsha, China; [2]Renal Division, Department of Medicine and Glom-NExT Center for Glomerular Kidney Disease and Novel Experimental Therapeutics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA.*

Background: Growing evidence suggests that ectopic lipid accumulation may contribute to organ injury in the context of metabolic diseases, including diabetes. However, the ectopic lipid accumulation in the kidney and its clinic relevance in the patients with Diabetic kidney disease (DKD) remains unknown.

Methods: Twelve patients of type 2 DKD (stage II-III) were enrolled and kidney tissue biopsy were stained with Oil red and immunohistochemistry assay for key lipid droplet marker and regulator protein, including adipose differentiation-related protein (ADRP), sterol regulatory element binding protein-1 (SREBP-1) and PPAR-α, while 8 patients of MCD and 10 patients of primary FSGS served as the control. At the same time, the expression of serum and urine ADRP, β-NG and inflammation marker (IL-1, TNF-α) were also detected in 15 DM patients and 35 DKD patients (including 12 patients of stage III, 13 patients of stage IV and 10 patients of stage V) with ELISA. qPCR and western blot assay were used to detect the expression of SREBP-1 mRNA and protein from peripheral blood mononuclear cells (PBMC). The correlation of ADRP, SREBP-1 and the clinic parameter, inflammation and tubular damage were evaluated with Pearson (SPSS) analysis.

Results: We observed heavy lipid deposition and increased intracellular lipid droplets in the kidney, especially in proximal tubule of DKD patients, as compared to that of MCD and FSGS. In accordance with lipid accumulation, intensity of ADRP and SREBP expression in the kidney sections obviously increased, while PPAR-α expression decreased. Moreover, compared to DM patients, the expression of ADRP both in serum and urine were unregulated in DKD patients. Similarly, both mRNA and protein expression of SREBP1 from PBMC in DKD patients also increased. Notably, the urine ADRP level and the expression of SREBP showed a parallel change with that of serum creatinine, proteinuria, β-NG, IL-1and TNF-α expression and tubular-interstitial damage.

Conclusions: Aberrant lipid regulation and ecotopic kidney lipid accumulation were observed in the DKD patients, which correlated to the inflammation and disease progression. Suggesting that amelioration of ecotopic lipid deposit may provide a new approach for prevention of DKD.

TH-PO737

Proteinuria and Cholesterol Reduction Are Independently Associated with Less Renal Function Decline in Statin Treated Patients: A Post-Hoc Analysis of the PLANET Trials Nienke Idzerda,[2] Michelle Pena,[2] Hans-Henrik Parving,[1] Dick de Zeeuw,[2] Hiddo J. Lambers Heerspink.[2] *[1]Rigshospitalet, Copenhagen, Denmark; [2]University Medical Center Groningen, Groningen, Netherlands.*

Background: Statins have shown multiple effects on different renal risk factors such as lowering of cholesterol (TC) and lowering of proteinuria (U_{PCR}). These effects seem to vary between individuals. We questioned whether the changes in U_{PCR} and TC run in parallel within one individual, and secondly, how this contributes to renal outcome (eGFR decline).

Methods: The PLANET studies studied the effects of a 52-week treatment with atorvastatin and rosuvastatin on U_{PCR} and renal function (eGFR) in proteinuric patients. In this post-hoc analysis, we first assessed the individual variability in U_{PCR} and TC response (0-14 weeks). U_{PCR} response was defined as a decrease in U_{PCR} of >0% and TC response as decrease in TC of >100 mg/dl (2.59 mmol/l) from baseline. Second, we determined whether these responses were predictive of eGFR decline during subsequent 9 months follow-up.

Results: U_{PCR} and TC response varied between patients: mean U_{PCR} response was -1.3% (5^{th} – 95^{th} percentile -59.9, 141.8), mean TC response was -93.9 mg/dl (-169.1, -26.9). Out of 471 patients, 123 (26.1%) showed a response in U_{PCR} but not in TC, and 96 (20.4%) showed a response in TC but not in U_{PCR}. eGFR (ml/min/1.73m²) decreased non-significantly from baseline in both U_{PCR} responders (0.4; 95%CI [-1.6, 0.8]; p=0.54) and TC responders (0.4; [-1.8, 1.1]; p=0.62), whereas U_{PCR} and TC non-responders showed a significant decline in eGFR (1.8; [0.6, 3.0]; p=0.004 and 1.7; [0.5, 2.9]; p=0.006, respectively). A lack of response in both parameters resulted in the fastest rate of eGFR decline (2.1; [0.5, 3.7]; p=0.01). These findings were not different for rosuvastatin or atorvastatin.

Conclusions: TC and U_{PCR} response to statins vary between individuals and do not run in parallel within an individual. The initial fall in cholesterol and proteinuria are independently associated with a reduction in the long term eGFR decline. This highlights the importance of both monitoring TC and U_{PCR} after initiating statin therapy.

Funding: Commercial Support - AstraZeneca

TH-PO738

Impact of Gender on the Pattern of Glucose-Lowering Treatment and Hypoglycaemia in Patients with Type 2 Diabetes and Advanced CKD: The French CKD-REIN Study Marie Metzger,[1] Beverley Balkau,[1] Luc Frimat,[2] Christian Combe,[3] Maurice Laville,[4,5] Christian Jacquelinet,[6,1] Ziad Massy,[1,7] Benedicte Stengel,[1] Denis Fouque.[4,5] *[1]CESP U1018, INSERM, UPS-UVSQ, Villejuif, France; [2]Nancy University Hospital, Vandoeuvre les Nancy, France; [3]CHU de Bordeaux, Bordeaux, France; [4]Claude Bernard University Lyon 1, Lyon, France; [5]Hospices Civils de Lyon - Centre Hospitalier Lyon-Sud, Pierre Bénite, France; [6]Agence de la biomedecine, Saint-Denis La Plaine, France; [7]Ambroise Pare University Hospital, Boulogne Billancourt/ Paris cedex, France. Group/Team: On behalf of CKD Rein and CKDopps investigators.*

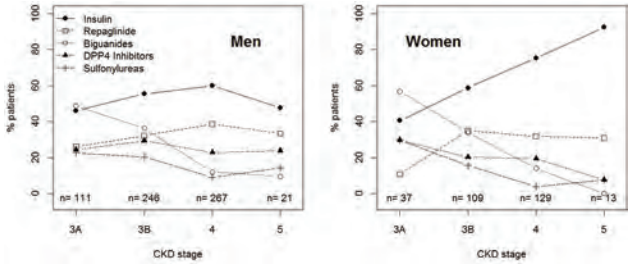
Background: Recommendations for glucose lowering treatments differ according to CKD stage, but not by gender, despite possible differences in efficacy; in consequence, glucose control and hypoglycaemia may differ.

Methods: Of the 3033 patients recruited with CKD stages 3 to 5, 645 men and 288 women were treated by glucose lowering drugs. Uncontrolled glucose was defined by HbA1c ≥ 7%, hypoglycaemia by self-report.

Results: Treatment with insulin (55% men, 65% women) was more frequent in the later stages of CKD (see Figure) with fewer women than men treated with insulin at lower CKD stages, more at higher stages (P_{inter}=0.008); overall, 31% were treated only with insulin, 28% with combinations: insulin and another drug, 42% by non-insulin glucose lowering drugs. The prevalence of uncontrolled glucose was 57%; in a multivariable model, only insulin treatment, longer diabetes duration and higher BMI were associated with uncontrolled glucose, not gender, age, nor eGFR. Hypoglycaemia were reported by 40% of men and 59% of women; they were not related with eGFR, nor to HbA1c, but were more frequent in people treated with insulin, after adjustment for age, sex, BMI, diabetes duration.

Conclusions: In people with diabetes and CKD, HbA1c, CKD stage and reported hypoglycaemia were not associated. However, glucose–lowering treatment, hypoglycaemia but not glucose control were gender dependent; this seems to be related to insulin treatment which may need to be adapted to avoid hypoglycaemia, especially in women.

Funding: Commercial Support - Amgen, Baxter, Fresenius Medical Care, MSD, Lilly, Otsuka, GSK



Glucose lowering medications by CKD stage and gender

TH-PO739

AdipoRon Ameliorates Diabetic Nephropathy through Activation of Intracellular Ca++-AMPK-PPARα in Type 2 Diabetes Yaeni Kim, Ji Hee Lim, Min Young Kim, Eun Nim Kim, Hye Eun Yoon, Seok Joon Shin, Bumsoon Choi, Yong-Soo Kim, Cheol Whee Park. *The Catholic University of Korea College of Medicine, Seoul, Republic of Korea.*

Background: In diabetic nephropathy (DN), adiponectin's renoprotective effects are related to the activation of AMP protein kinase (AMPK)-peroxisome proliferative-activated receptor (PPAR)α pathway by binding to adiponectin receptors, AdipoR1/R2, respectively

Methods: We investigated the expression of AdipoRs and their relevant intracellular pathway in twenty-seven type 2 diabetic patients and found the role of AdipoRon on DN in male C57BLKS/J *db/db mice* and glomerular endothelial cell (GEC) and podocyte.

Results: While the degree and extent of glomerulosclerosis and tubulointerstitial fibrosis correlated with renal functional deterioration, the expression of AdipoR1/R2 and Ca^{++}/calmodulin-dependent protein kinase kinase (CaMKK)b and number of phosphorylated liver-kinase B (LKB)-1and AMPK-positive cells in the glomerulus was significantly decreased even in earlier stages of human DN. Diabetes-induced alterations shown in human DN were relieved by AdipoRon in *db/db* mice. The protective role of AdipoRon occurred through a direct activation of intrarenal AdipoR1/R2, which in turn increased expression of CaMKKb-phospho-Ser^{431}LKB1-phospho-Thr^{172}AMPK-PPARα pathway independently of systemic effects of adiponectin. Subsequent their relevant intracellular pathways related to lipid accumulation and endothelial dysfunction were reduced by improving diabetes-induced oxidative stress and apoptosis in the kidney. In human GECs and murine podocytes exposed to high glucose, AdipoRon increased the expression of intracellular Ca^{++}, which subsequently activated CaMKKb-phospho-Ser^{431}LKB1-phospho-Thr^{172}AMPK-PPARα and their downstream signals and resulted in decreased high glucose-induced oxidative stress, apoptosis, and endothelial dysfunction.

Conclusions: Our study suggests AdipoRon may be an effective therapeutic strategy for type 2 DN via ameliorating GEC and podocyte injury by the activation of intracellular Ca^{++}-AMPK-PPARα pathway.

Funding: Private Foundation Support

TH-PO740

Development of a Differential Diagnostic Model of Diabetic Kidney Disease and Non-Diabetic Kidney Disease in Patients with Type 2 Diabetes Mellitus Hui Zhuan Tan,[2,1] Jia Liang Kwek,[2] Stephanie C. Fook,[2] Chan Choong Meng,[2] Jason Choo Chon Jun.[2] *[1]Ministry of Health Holdings, Singapore, Singapore, Singapore; [2]Singapore General Hospital, Singapore, Singapore.*

Background: Renal biopsy is the gold standard for distinguishing diabetic kidney disease (DKD) from non-diabetic kidney disease (NDKD) but is invasive. We aimed to identify predictive factors of DKD in diabetic patients with kidney disease in our population and develop a quantitative differential diagnostic model to guide decision for kidney biopsy.

Methods: Clinical and laboratory data from 102 patients with Type 2 Diabetes Mellitus (T2DM) who underwent kidney biopsy from 2007 to 2016 in our tertiary hospital were analyzed. Univariate analysis and multivariate logistic regression were performed to identify independent predictors of DKD and generate a differential diagnostic model. Model discrimination and calibration were evaluated using the area under the receiver operating characteristic curve (AUROC) and Hosmer-Lemeshow goodness-of-fit test respectively.

Results: The cohort included 64 males (62.7%), mean age 55.7 years (±11.0) and duration of T2DM 10.4 years (±7.2). Mean serum creatinine at time of biopsy was 121.7 μmol/L (±46.4) with mean estimated glomerular filtration rate (eGFR) (MDRD) of 61.7 ml/min/1.73m^2 (±30.8). Sixty-five patients (63.7%) were diagnosed with diabetic nephropathy (DN) on kidney biopsy. In multivariate analysis, presence of diabetic retinopathy (Dr), higher Hba1c (Gh), absence of hematuria defined as urinary red blood cells <10 per high power field (Hu), and absence of positive systemic markers were revealed to be independent predictors of DN. A differential diagnostic model was constructed as follows: exp (-4.857 + 0.623 Gh – 1.208 Hu + 2.742 Dr -1.402 SM) / [1 + exp ((-4.857 + 0.623 Gh – 1.208 Hu + 2.742 Dr -1.402 SM)]. The model showed excellent discrimination (AUC=0.886; 95% CI 0.815-0.956) and calibration (Hosmer-Lemeshow p=0.242, good calibration plot of observed vs predicted probability, close to equality line).

Conclusions: The differential diagnostic model may be useful in the clinical differentiation of DKD and NDKD in patients with T2DM. Further validation of the model is required to determine its clinical utility.

TH-PO741

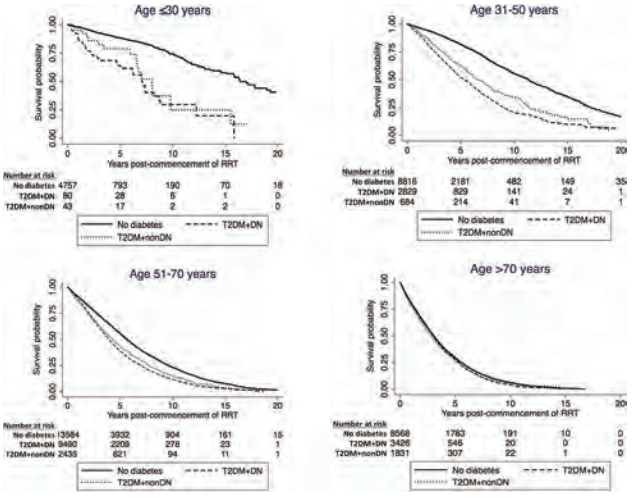
Impact of Type 2 Diabetes Mellitus (T2DM) with or without Diabetic Nephropathy (DN) on Long-Term Outcomes in ESKD Patients Initiated on Dialysis Wai H. Lim,[4] David W. Johnson,[3] Kevan Polkinghorne,[1] Carmel M. Hawley,[3] Charmaine E. Lok,[5] Germaine Wong.[2] *[1]Monash Medical Centre and Monash University, Melbourne, VIC, Australia; [2]None, Auambie, NSW, Australia; [3]Princess Alexandra Hospital, Brisbane, QLD, Australia; [4]Sir Charles Gairdner Hospital, Perth, NSW, Australia; [5]Toronto General Hospital, Toronto, ON, Canada.*

Background: DN is the most common cause of ESKD among patients with T2DM, however there is growing evidence that T2DM patients with non-DN as a cause of ESKD form a distinct clinical entity with differential prognostic significance

Methods: All incident ESKD patients initiated on hemodialysis/peritoneal dialysis in Australia and New Zealand between 1980-2014 were included, using data from the ANZDATA Registry. The association between diabetes status at dialysis initiation (i.e. no diabetes, T2DM+DN or T2DM+non-DN) and mortality were examined using Cox regression and competing risk analyses, with transplantation censored or considered as competing risk, respectively

Results: Of 56,552 incident dialysis patients followed for a median of 2.5 years, 15,829 (28%) and 4993 (9%) had T2DM+DN and T2DM+non-DN, respectively. Patients with T2DM were significantly older and a greater proportion had vascular comorbidities. Compared to patients with no diabetes, the adjusted HR (95%CI) for mortality in those with T2DM+DN and T2DM+non-DN were 1.39 (1.35-1.43) and 1.24 (1.29-1.29) in the Cox regression model, and the adjusted subdistribution HR were 1.52 (1.47-1.56) and 1.32 (1.27-1.38), respectively in the competing risk model. There was a significant interaction (p<0.001) between age and diabetes status, with the hazard for mortality greater in younger compared to older patients. Cardiovascular disease as a cause of mortality was more common in patients with T2DM compared to no diabetes (43% vs. 34%, p<0.001). Kaplan Meier survival curves for mortality stratified by age categories are shown below

Conclusions: Younger ESKD diabetic patients with or without DN experienced substantially poorer survival compared to non-diabetic patients. A vigilant approach to CVD prevention and monitoring is critical to improve clinical outcomes in diabetic patients with ESKD



TH-PO742

Risk Factors for Anemia in Diabetic Kidney Disease Andreea Andronesi, Bogdan M. Sorohan, Cristina Robe, Danut Andronesi, Bogdan Obrisca, Gener Ismail. *Fundeni Clinical Institute, Bucharest, Romania.*

Background: Anemia is a frequent complication of diabetic kidney disease (DKD). It is diagnosed at earlier stages and is associated with important morbidity and mortality. The aim of our study was to identify risk factors for the presence and severity of anemia in chronic kidney disease (CKD) due to DKD not under renal replacement therapy (RRT).

Methods: We performed a case-control study in which we included 156 patients with type 2 diabetes mellitus: study group with 72 patients with DKD-associated CKD and anemia, control group with 84 patients with DKD-associated CKD without anemia. We excluded patients in RRT, other causes of anemia, recent history of malignancy, blood transfusions and recent treatment with erythropoietin / immunosuppressive agents. Independent risk factors for anemia were identified by logistic regression using *IBM SPSS ver. 20.0.*

Results: Patients from study group had significantly lower body mass index (BMI) (27.4±3.5 *vs.* 30.4±4.9 kg/m^2, p=0.01) and albuminemia (3.4±0.5 g/dl *vs* 4.1±0.7 g/dl, p<0.001). We found strong positive correlations between Hb and albuminemia (R=0.515, p<0.001), Hb and eGFR (R=0.465, p<0.001) and weak negative correlation between Hb

and phosphatemia (R=-0.307, p=0.02). Time from CKD diagnosis (5.7±2.6 *vs* 3.5±1.5 years, p=0.003) and time from DM diagnosis (15.8±7.3 *vs* 13.1±6.3 years, p=0.04) were significantly longer in study group. Prevalence of anemia was higher with advancing CKD stage (p<0.001). Anemia was diagnosed even in patients with stage 2 CKD. Abnormal proteinuria was risk factor for anemia (OR 3.13, 95%CI 1.5-7.6, p=0.01). Calcemia was significantly lower (9.2±0.6 mg/dl *vs* 9.5±0.5 mg/dl, p=0.006) and phosphatemia significantly higher (4.7±0.9 mg/dl *vs* 3.8±0.7 mg/dl, p<0.001) in the study group. After adjustment for confounders, independent risk factors for anemia were abnormal proteinuria (adjusted OR 5.9, 95%CI 1.5-22.9) and treatment with renin-angiotensin-aldosteron system (RAAS) blockers (adjusted OR 6.2, 95%CI 1.3-30.1).

Conclusions: We found an increased prevalence of anemia in CKD due to DKD, even in patients with mild CKD. Anemia was associated with malnutrition (low BMI and albuminemia) and abnormal calcium-phosphate metabolism (low calcemia and high phosphatemia), mechanisms involved in the pathogenesis of anemia in these patients. Independent risk factors for anemia were proteinuria and RAAS blockers.

TH-PO743

Burnt-Out Diabetes Phenomenon and Association between Glycemic Control and Cardiovascular Comorbidity Rate in Hemodialysis Patients Masanori Abe,[3] Takayuki Hamano,[4] Junichi Hoshino,[5] Shigeru Nakai,[1] Ikuto Masakane.[2] *[1]Fujita Health University School of Health Scieneces, Toyoake, Aichi, Japan; [2]Honcho-Yabuki Clinic, Yamagata, Japan; [3]Nihon University School of Medicine, Tokyo, Japan; [4]Osaka University Graduate School of Medicine, Suita, Japan; [5]Toranomon Hospital, Tokyo, Japan. Group/Team: Committee of Japanese Renal Data Registry, Japanese Society for Dialysis Therapy.*

Background: In patients with diabetes on hemodialysis (HD), glycemic control improves spontaneously, leading to normal glycated hemoglobin (HbA1c) levels; this phenomenon is known as "burnt-out diabetes." However, glycated albumin (GA) might be a better indicator of glycemic control than HbA1c in HD patients. Therefore, the aim of this study was to identify how many patients experience "burnt-out diabetes" using HbA1c and GA levels and to examine the association between glycemic control and cardiovascular comorbidity risk in patients on HD.

Methods: The data were obtained from the annual nationwide surveys of dialysis patients conducted by the Japanese Society for Dialysis Therapy (JSDT) in 2013. Patients with diabetes on HD whose HbA1c and GA levels were measured and whose antidiabetic therapy was recorded were included. The "burnt-out diabetes" phenomenon was investigated in patients who were assessed for both HbA1c and GA levels. The association between cardiovascular comorbidity risk and HbA1c and GA levels were assessed using multivariable logistic regression models.

Results: In this cohort study, 23,668 patients were included. When "burnt-out diabetes" was defined as HbA1c <6.0% without treatment with antidiabetic medication, it was noted in 4,899 patients (20.7%). However, when "burnt-out diabetes" was defined as HbA1c <6.0% and GA <16.0% without treatment with antidiabetic medication, it was found in 1,286 patients (5.4%). Higher HbA1c levels were associated with the comorbidity rate of all cardiovascular diseases. However, higher GA levels were associated with comorbidities of all cardiovascular diseases except cerebral hemorrhage. The odds ratio (OR) of the cardiovascular comorbidity rate based on the GA category, with GA 16.0 to <18.0% treated as the reference group. The OR of cardiovascular comorbidity risk were significantly associated with GA >18%. After adjustment for confounders, the OR of the GA <16.0% group was significantly decreased as compared to the reference group.

Conclusions: Although the "burnt-out diabetes" phenomenon might be present in 20.7% of patients with diabetes on HD in terms of HbA1c, the rate was significantly decreased to 5.4% in terms of GA. The risk of cardiovascular comorbidity was higher in patients with GA > 18%.

TH-PO744

Absolute versus Percentage Renal Functional Losses in Patients with Diabetes and CKD William P. Martin,[1,2] Tomas P. Griffin,[1,2] David W. Lappin,[2] Damian G. Griffin,[2] John P. Ferguson,[3] Timothy O'Brien,[1,2] Matthew D. Griffin.[1,2] *[1]Regenerative Medicine Institute, National University of Ireland, Galway, Ireland; [2]Endocrinology and Nephrology Services, Saolta University Health Care Group, Galway, Ireland; [3]HRB Clinical Research Facility, Galway, Ireland.*

Background: Chronic kidney disease (CKD) management focuses on minimizing the rate of renal functional loss, usually expressed in absolute terms of mL/min/BSA lost per annum. We evaluated the impact of expressing renal functional loss as a percentage of existing renal function on the interpretation of renal functional trends of patients with diabetes before and after attending a Diabetes Renal Clinic (DRC).

Methods: All patients attending a DRC at a tertiary referral center from 2008 to 2012 were reviewed. Serial laboratory indices were recorded from 2004 to 2014. Linear mixed effects models fitted using the R-package ImerTest were used to calculate absolute eGFR slopes. In a second analysis, similar mixed effects models were fitted with log-transformed eGFR as the response, to estimate annual percentage decline in eGFR. Renal function was estimated using both MDRD and CKD-EPI equations.

Results: 147 subjects with ≥3 available eGFR values for ≥1 year before and after first DRC attendance were categorized based on presumptive CKD etiology. Rates of renal functional loss were calculated with similar results being obtained using both MDRD and CKD-EPI estimating equations (Table).

Conclusions: Following DRC consultation, absolute rate of eGFR decline was similar for T1D but slower for T2D and additional CKD etiology groups. Expressed as a percentage of prior eGFR, renal function declined more rapidly in T1D, similarly in T2D, and more slowly in those with additional CKD etiologies. Thus, interpretation of the impact of a CKD intervention is influenced by the initial eGFR and by the approach used to calculate renal functional decline.

Funding: Government Support - Non-U.S.

Baseline characteristics at first DRC attendance and renal functional losses before and after first DRC attendance stratified by CKD etiology (n = 147).

	Type 1 Diabetes (T1D) (n = 32)			Type 2 Diabetes (T2D) (n = 91)			Diabetes with Additional CKD Etiology (n = 24)		
Age [mean ± SD; years]	43.8 ± 16.2			69.1 ± 10.0			69.5 ± 10.5		
Male [n (%)]	19 (59.4)			60 (65.9)			17 (70.8)		
Diabetes duration [median (IQR); years]	21.0 (16.7)			10.1 (11.7)			9.3 (4.8)		
CKD-EPI eGFR [mean ± SD; mL/min/BSA]	59.4 ± 30.8			44.5 ± 17.8			40.3 ± 14.7		
MDRD eGFR [mean ± SD; mL/min/BSA]	56.5 ± 29.5			45.0 ± 17.5			40.9 ± 14.5		
Urine ACR [median (IQR); mg/g]	508.9 (1900.0)			176.1 (779.1)			38.1 (512.4)		
	Type 1 Diabetes (T1D) (n = 32)			Type 2 Diabetes (T2D) (n = 91)			Diabetes with Additional CKD Etiology (n = 24)		
Absolute loss of renal function (mL/min/BSA/year)	Before DRC	After DRC	p	Before DRC	After DRC	p	Before DRC	After DRC	p
CKD-EPI eGFR	-3.78	-4.58	.430	-4.04	-2.34	.005	-4.19	-0.73	.003
MDRD eGFR	-3.14	-4.66	.133	-3.82	-2.50	.035	-3.87	-0.87	.008
Percentage loss of renal function (%/year)	Before DRC	After DRC	p	Before DRC	After DRC	p	Before DRC	After DRC	p
CKD-EPI eGFR	5.20%	14.49%	.002	8.01%	7.49%	.770	8.82%	2.12%	.057
MDRD eGFR	4.80%	14.51%	.001	7.57%	7.54%	.986	8.16%	2.30%	.084

TH-PO745

Comparison of Clinicopathological Features of Biopsy-Proven Diabetic Nephropathy between CKD Heat Map Classification and the Japanese Classification of Diabetic Nephropathy Kengo Furuichi,[2] Miho Shimizu,[2] Tadashi Toyama,[2] Yasunori Iwata,[2] Norihiko Sakai,[2] Takashi Wada.[1] *[1]Dept of Nephrology and Labo Med, Kanazawa University, Kanazawa, Japan; [2]Division of Nephrology, Kanazawa University Hospital, Kanazawa, Japan.*

Background: CKD heat map classification and the Japanese classification of diabetic nephropathy reflects the risks of mortality, cardiovascular events and kidney prognosis and is clinically useful. Furthermore, pathological findings of diabetic nephropathy are also known to be useful for predicting prognoses. In this study, we evaluated the characteristics of clinicopathological features between the two clinical classification of diabetic nephropathy.

Methods: The clinical data of 600 biopsy-confirmed diabetic nephropathy patients were collected retrospectively from 13 centres across Japan. Pthologica features and decreasing rate of estimated GFR (eGFR) were evaluated, and compared between CKD heat map classification and the Japanese classification of diabetic nephropathy.

Results: The median observation period was 70.4 (IQR; 20.9-101.0) months. Each stage had specific characteristic pathological features. Diffuse lesions, interstitial fibrosis and/or tubular atrophy (IFTA), interstitial cell infiltration, arteriolar hyalinosis and atherosclerosis were detected in more than half the cases, even in Green and Yellow in CKD heat map and Stage 1 in the Japanese classification of diabetic nephropathy. Median declining speed of eGFR in all cases was 5.61 mL/min/1.73m^2/year, and the median rate of declining kidney function within 2 years after kidney biopsy was 24.0%. Declining rate of eGFR within 2 years after kidney biopsy increased as CKD heat map classification and the stage of Japanese classification of diabetic nephropathy increased; and Green and Yellow, Orange, Red; 3.7, 17.9, 34.3 %, respectively, Stage 1, 2, 3, 4; -0.9, 10.7, 26.5, 38.8 %, respectively. Sensitivity of 30% reduction of the eGFR in two years as a surrogate end point of kidney death was 56.7% (Green and Yellow, Orange, Red; 0, 80.0, 56.5 %, and Stage 1, 2, 3, 4; 0, 0, 84.2, 11.1 %, respectively).

Conclusions: This study indicated that there were characteristic pathological features in each clinical classification. Moreover, decreasing rate of eGFR increased in advanced stages of diabetic nephropathy, and sensitivity of surrogate end point (30% reduction of the eGFR in two years) was relatively high in Stage 3 Japanese classification of diabetic nephropathy, and Orange in CKD heat map.

TH-PO746

Endothelial Cell Transfusion Inhibits Venous Neointima Formation in Arteriovenous Fistulae of Rats with CKD Dongqi Xing, Li Li, Yuanyuan Guo, Yiu-Fai Chen, Yasin Oduk, Suzanne Oparil, Fadi G. Hage. *University of Alabama at Birmingham, Birmingham, AL.*

Background: The arteriovenous fistula (AVF) is the preferred choice of vascular access for hemodialysis patients with chronic kidney disease (CKD). However, AVF fail to mature in ~ 40% of cases due to early neointimal hyperplasia (neointimal formation) in AVF vein and persistent inadequate outward remodeling (expansion) of the AVF vein. We have shown that intravenous (i.v.) transfusion of rat aortic endothelial cells (RAECs) ameliorates endothelial dysfunction in a rat model of CKD. In this study, we tested the hypothesis that i.v. transfusion of RAECs inhibits venous neointima formation in AVF of CKD rats.

Methods: Female ovariectomized Sprague-Dawley rats underwent 5/6th nephrectomy (Nx). After 4 wks, an AVF was created by anastomosing the right femoral vein to the right femoral artery in an end-to-side manner, and rats received i.v. transfusion of 3.0x10^6 RAECs in 2 ml saline or saline vehicle control. Rats were sacrificed and perfused with

formalin 4 wks later. Fistulae were fixed, sectioned and stained with hematoxylin and eosin (HE). The ligation site was identified and the vein was sectioned a 400, 600, 800, 1000 and 1200 μm proximal to the ligation site. To calculate the neointima area to vessel size (cross-sectional area) ratio, the circumferential profiles of the lumen and the external lamina of the vein were delineated, and the areas encompassed by these boundaries were determined by ImageJ software.

Results: Serum creatinine level increased from 4.6±0.5 μg/ml to 8.5±1.1 μg/ml after 5/6 Nx (n=11). EC transfusion significantly inhibited neointima formation in femoral vein at 4 wks after AVF (Figure).

Conclusions: EC transfusion inhibited venous neointima formation in AVF, suggesting that EC therapy after AVF may provide a novel strategy for the maintenance of vascular access in hemodialysis patients.

Funding: Other NIH Support - R56 HL128285-01A1,RO1HL116727, Veterans Affairs Support

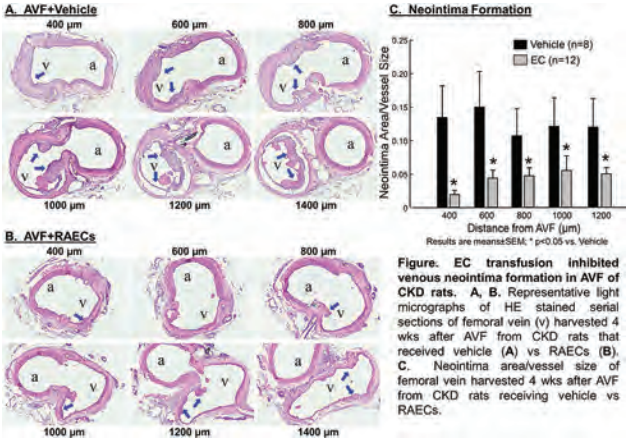


Figure. EC transfusion inhibited venous neointima formation in AVF of CKD rats. A, B. Representative light micrographs of HE stained serial sections of femoral vein (v) harvested 4 wks after AVF from CKD rats that received vehicle (**A**) vs RAECs (**B**). **C.** Neointima area/vessel size of femoral vein harvested 4 wks after AVF from CKD rats receiving vehicle vs RAECs.

TH-PO747

Reduced Endothelium-Dependent Vasodilation and Impaired Arteriovenous Fistula (AVF) Development in a Rat Model with CKD Yan-Ting Shiu,[3] Yuxia He,[3] Daniel R. Machin,[5] CS Jason Tey,[3] Jack Z. Fan,[3] Zhen Chen,[1] Miriam E. Leary,[2] Hirofumi Tanaka,[4] Tony J. Donato,[3] Alfred K. Cheung.[3] *[1]Beckman Research institute, City of Hope, Duarte, CA; [2]University of Texas at Austin, Austin, TX; [3]University of Utah, SALT LAKE CITY, UT; [4]University of Texas at Austin, Austin, TX; [5]University of Utah, SALT LAKE CITY, UT.*

Background: AVF maturation failure results from neointimal hyperplasia (NH) and insufficient dilation of lumen, but the latter remains largely unexplored. We investigated endothelium-dependent vasodilation (EDV) and AVF development in a clinically relevant CKD-AVF model.

Methods: CKD was induced in 10-week-old Wistar male rats fed a 0.25% adenine-containing diet (AD) for 10 wk. EDV of femoral arteries was non-invasively assessed at baseline, 10 wk on AD, and 4 wk after returning to normal diet (ND). Gene expression of key endothelial regulators, including transcription factors Krüppel-like factor 2 (KLF2) and KLF4 and their target endothelial nitric oxide synthase (eNOS), was assessed in the aorta of CKD and normal rats. Femoral AVFs were created in CKD and normal rats. AVF lumen diameter was measured by ultrasound, and animals were euthanized for histology.

Results: In CKD rats, plasma creatinine and BUN increased 3-fold after 10 wk on AD, and the elevated levels persisted after return to ND for 4 wk. EDV was lower after AD (5.6±2.2%) than baseline (16.3±1.7%)($p<0.05$; n=8) and remained impaired after CKD rats returned to ND (6.0±2.8%, n=4). Aortic eNOS expression was lower in CKD rats than in control rats (0.77±0.25 vs. 2.84±0.71; $p<0.05$; n=4 each), and the expression of KLF2/4 was also lower in CKD. At 4 wk after AVF creation, while NH was observed in both groups, AVF lumen was significantly smaller in CKD than in control rats **(Fig. 1)**.

Conclusions: CKD decreased the expression of KLF2/4 and eNOS, which may decrease the NO availability and NO-mediated dilation. CKD may impair AVF dilation via decreased EDV.

Funding: NIDDK Support

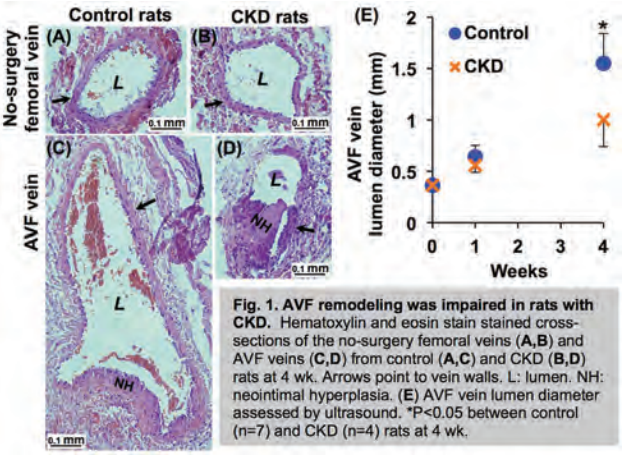


Fig. 1. AVF remodeling was impaired in rats with CKD. Hematoxylin and eosin stain stained cross-sections of the no-surgery femoral veins (**A,B**) and AVF veins (**C,D**) from control (**A,C**) and CKD (**B,D**) rats at 4 wk. Arrows point to vein walls. L: lumen. NH: neointimal hyperplasia. (**E**) AVF vein lumen diameter assessed by ultrasound. *P<0.05 between control (n=7) and CKD (n=4) rats at 4 wk.

TH-PO748

Decreased Collagen Cross-Linking Improves the Biomechanical Performance of Experimental Arteriovenous Fistulas Diana R. Hernandez,[2] Yuntao Wei,[2] Fotios M. Andreopoulos,[3] Laisel Martinez,[2] Loay H. Salman,[1] Roberto I. Vazquez-Padron.[2] *[1]Albany Medical College, Albany, NY; [2]University of Miami Miller School of Medicine, Miami, FL; [3]University of Miami, Miami, FL.*

Background: The role of lysyl oxidase (LOX) in arteriovenous fistula (AVF) remodeling has never been studied. As the enzyme that catalyzes the cross-linking of collagen and elastin precursors in the vascular wall, a deficiency in LOX activity may impair wall integrity while excessive activity may lead to stiffness and favor occlusive stenosis. This study hypothesizes that local or systemic inhibition of LOX with β-aminopropionitrile (BAPN) prevents excessive cross-linking of collagen and other extracellular matrix (ECM) proteins and improves the biomechanical performance of experimental AVFs.

Methods: Surrogate indicators of vascular remodeling included fibrosis (% area of collagen) by Masson's trichrome staining, and gene expression of ECM proteins by RT-PCR. Biomechanical properties were evaluated by pressure myography.

Results: We first demonstrated that gene expression of LOX, but not of LOX-like enzymes (LOXL1-4), was significantly upregulated in a rat AVF model created by anastomosing the left epigastric vein to the nearby femoral artery. Systemic administration of BAPN (100 mg/kg, ip) decreased collagen deposition in treated versus control AVFs ($p=0.013$). In addition, BAPN treatment upregulated the elastin and fibronectin genes in the fistula wall. Next, we electro-spun a PLGA/BAPN (15:1.5) scaffold to locally deliver the drug around the juxta-anastomotic area of experimental AVFs for 21 days post-op. In vitro, BAPN release from the scaffold was almost complete within 7 days, while it took 60 days at 37°C for the scaffold to be fully degraded. Local delivery of BAPN to experimental AVFs improved vascular remodeling by decreasing fibrosis, compared to AVFs wrapped with scaffold alone (n=6 per group, $p=0.043$). Furthermore, local delivery of BAPN increased distensibility and decreased the incremental elastic modulus (E_{inc}) (4.93 ± 0.85 vs. 2.22 ± 0.39 x 10^6 dynes cm^{-2}, $p=0.019$) as determined by pressure myography.

Conclusions: In conclusion, we have demonstrated that inhibition of LOX mediated cross-linking with BAPN significantly improved vascular compliance and the biomechanical properties of experimental AVFs.

Funding: NIDDK Support

TH-PO749

Altered Molecular Profiles in Hemodynamically Vulnerable Segments of Arteriovenous Fistulae (AVF) in a Uremic Pig Model Jaroslav Janda,[2] Begoña Campos,[4] Aous Jarrouj,[1] Frank C. Brosius,[2] Lindsay N. Kohler,[2] Prabir Roy-Chaudhury,[2] Diego Celdran-Bonafonte.[3,5] *[1]Banner-University of Arizona, Tucson, AZ; [2]University of Arizona, Tucson, AZ; [3]University of Arizona / BIO 5 Institute, Tucson, AZ; [4]University of Cincinnati, Cincinnati, OH; [5]Southern Arizona VA Healthcare System, Tucson, AZ.*

Background: Arteriovenous fistulae (AVF) are the preferred vascular access for hemodialysis patients but are subject to stenosis, disrupted flow and failure. The uremic pig serves as a useful model for studying the pathogenesis of AVF dysfunction in humans. Previously, we reported properties of vascular structure and flow in pig AVF that mimicked changes in human AVF. In the current project, we determine whether known differences in AVF hemodynamics between the inner and outer curves of the venous segment of an AVF and between the anastomotic and more proximal segments, were associated with altered gene expression for 8 candidate genes in adjacent AVF segments.

Methods: Renal insufficiency in 4 Yorkshire pigs was surgically induced by 5/6 nephrectomy, and 2 weeks later bilateral AVFs were created between femoral arteries and veins. The inner and outer curves of each AVF were harvested 6 wk later. Four sequential samples from the anastomosis to the more proximal venous segment were collected

for each AVF. cDNA was generated from total RNA from these individual segments. Quantitative real time-PCR reactions were performed for ICAM, VCAM, NOS3, NOX4, KLF2, CCL2, MMP2, and MMP9.

Results: MMP9 levels (average of all four venous segments) were consistently and significantly higher in the outer curve of the AVF than the inner curve ($p < 0.05$). ICAM and VCAM mRNA levels also showed similar trends. eNOS levels trended towards being lower at the anastomosis (both inner and outer curves) as compared to the most proximal venous segment.

Conclusions: Our findings suggest that differences in fluid hemodynamics especially wall shear stress (we have previously demonstrated differences in wall shear stress [WSS] between the inner and outer curves of an AVF, and also between the anastomosis and more proximal segment), could be important determinants of the molecular profile (and subsequent stenosis or lack thereof) in AVFs. Future studies will aim to assess whether manipulation of both upstream WSS and downstream molecular biology (as identified in this work) could reduce AVF stenosis in our uremic pig model.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO750

MRI Modeling of Arteriovenous Fistula (AVF) Stenosis in a Pig Model: Creating a Test Bed for Mechanistic and Therapeutic Innovation

Diego Celdran-Bonafonte,[1] Begoña Campos,[2] Aous Jarrouj,[1] Keith L. Saum,[2] Jaroslav Janda,[1] Lindsay N. Kohler,[1] Frank C. Brosius,[1] Prabir Roy-Chaudhury.[1,3] *[1]University of Arizona, Tucson, AZ; [2]University of Cincinnati, Cincinnati, OH; [3]SAVAHCS, Tucson, AZ.*

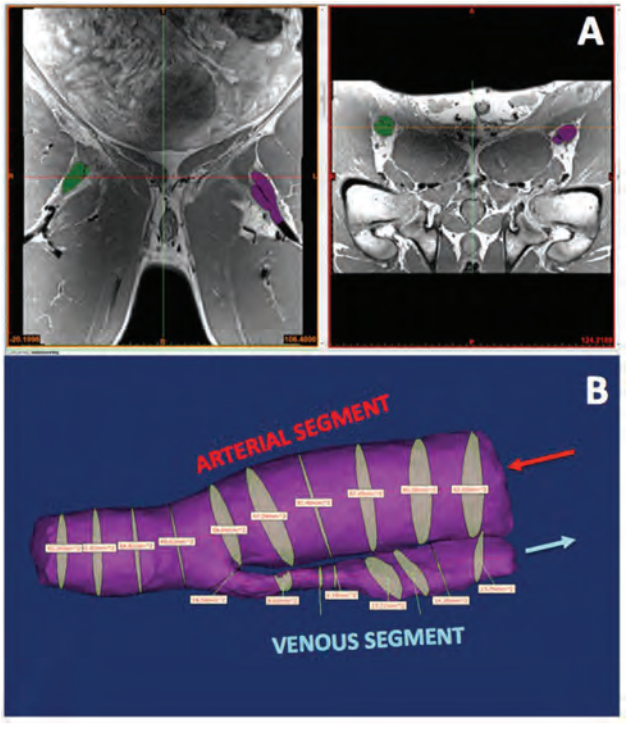
Background: Arteriovenous fistula (AVF) stenosis (resulting in the use dialysis catheters) is an important cause of morbidity and mortality in hemodialysis patients. We have previously described a pig model of AVF stenosis. We now describe the use of MRI imaging in this model to enhance its capabilities for mechanistic and therapeutic innovation.

Methods: AVFs were created in the groin in 6 male Yorkshire Cross pigs. Black blood contrast-free MRIs were performed at days 28 and 56 (Figure A). MIMICS software was used for segmentation and 3D processing. 3-D reconstructions were analyzed along the first 35 mm of the venous segment. Centerline software was used to identify regions of maximal and minimal stenosis and to create a model for average stenosis, using cross sectional images at 5mm intervals (Figure B). Flow data was collected and is currently being analyzed.

Results: MRI imaging described a peri-anastomotic stenosis very similar to the human lesion (Figure B). The mean maximal stenosis area was 10.042 and 13.037mm^2 at 28 and 56 days respectively. Mean minimal stenosis (maximal dilation) was 34.175 and 69.290mm^2 at 28 and 56 days respectively. The average sectional area of the entire venous segment increased from 28.863 mm^2 at 28 days to 32.626 mm^2 at 56 days.

Conclusions: The use of sophisticated 3D MRI technology to obtain standardized end points for AVF stenosis (both anatomy and flow) significantly reduces the subjectivity associated with the evaluation of novel therapies in this test bed. We hope that the use of these sophisticated technologies in a reproducible and validated large animal model, will incentivize much needed innovation in this area, both at a mechanistic and therapeutic level.

Funding: NIDDK Support



TH-PO751

Study of Vascular Intimal Thickness around Different Locations of Catheter Tips in Dog Model

Li H. Wang,[1] Lan Jia,[2] Hai B. Yu,[3] Fang Wei,[4] Ai L. Jiang.[5] *[1]Department of Kidney Disease and Blood Purification Centre, nstitute of Urology & Key Laboratory of Tianjin, Tianjin, China; [2]Department of Kidney Disease and Blood Purification Centre, 2nd Hospital of Tianjin Medical University, Tianjin, China; [3]Department of Kidney Disease and Blood Purification Centre, 2nd Hospital of Tianjin Medical University, Tianjin, China; [4]Department of Kidney Disease and Blood Purification Centre, 2nd Hospital of Tianjin Medical University, Tianjin, China; [5]Department of Kidney Disease and Blood Purification Centre, 2nd Hospital of Tianjin Medical University, Tianjin, China.*

Background: Many studies have found intimal thickness around catheter tip after catheterization. Meanwhile Caveolin-1 is a shear sensor that may transmit mechanical change into biochemical signals resulting in vascualr remodeling.

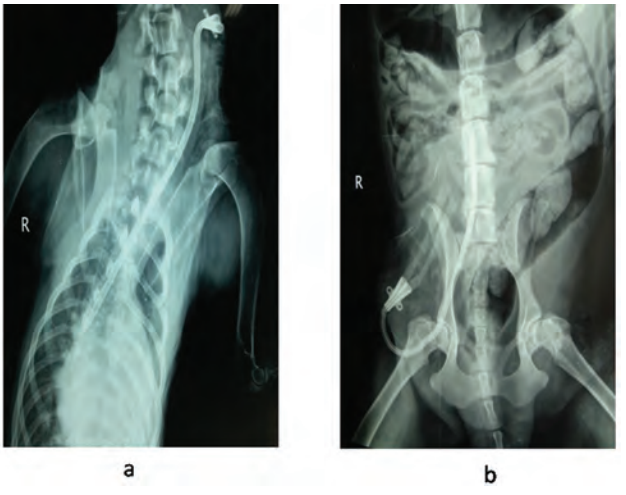
Methods: TDCs were inserted into the left jugular vein and right femoral vein in eight dogs for 28 days. Histological and immunohistochemistry were performed to confirm specific cell populations after extracorporeal circulation.

Results: There were higher catheter dysfunction rates and low blood flow rates in the femoral vein group compared to left jugular vein group. There was intimal hyperplasia around the catheter tip in both group with no significant difference. There were also caveolin-1 expression between the different groups.

Conclusions: After catheter placement, focal areas of intimal thickening were seen in the venous wall adjacent to the catheter tip with a high expression of caveolin-1. These findings indicate that different catheter tip locations may influence catheter function and targeting of specific caveonlin-1 could be possible future novel therapies for haemodialysis vascular access stenosis.

Comparison of catheter function of study groups

Parameter	Left internal jugular vein catheter group	Right Femoral vein catheter group	P value
Blood flow(ml/min)	236±21	197±13	0.001
Episode of catheter dysfunction	1(12.5%)	5(62.5%)	0.035
Episode of catheter infection	3(37.5%)	4(50%)	0.614



TH-PO752

AFE System Treatment Rapidly Dilates Ovine Cephalic Veins before AVF Surgery

F. Nicholas Franano,[1] Howard M. Loree,[1] J. S. Richardson,[1] Dale M. Groth,[2] Maneesh Taneja,[3] Lesley A. Szenay,[3] Barrett S. Hutto,[4] Bradley S. Dixon.[5] *[1]Flow Forward Medical, Inc., Olathe, KS; [2]Dale Groth Preclinical Consulting, LLC, Forest Lake, MN; [3]Surpass, Inc., Osceola, WI; [4]CIRTEC Medical Systems LLC, Los Gatos, CA; [5]University of Iowa Hospital and Clinics, Iowa City, IA.*

Background: Suboptimal wall shear stress (WSS) and cyclic stretching may slow AVF outflow vein dilation and lead to maturation failure. The AFE System™ is a medical device that delivers non-pulsatile blood flow to a peripheral vein, stimulating vein dilation prior to AVF surgery. During treatment, blood flow can be adjusted to maintain a mean WSS dose of 4 Pa in the vein. Use of larger veins to make AVFs may result in greater eligibility for AVF surgery, faster maturation, reduced maturation failure, and better primary and secondary patency rates.

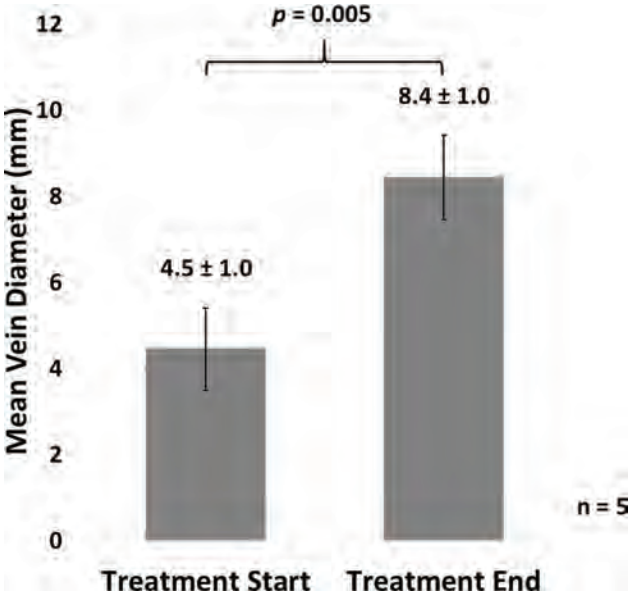
Methods: AFE System prototypes were used to treat five sheep (54-68 kg). The devices comprised an extracorporeal centrifugal blood pump, heparin-coated and cuffed inflow and outflow conduits, and a benchtop controller. The inflow conduit was inserted into an external jugular vein and the tip was positioned in the superior vena cava. The outflow conduit was connected to a cephalic vein. Three sheep were treated using a duckbill tip inflow conduit and an outflow conduit with a distal ePTFE segment sutured to the vein. Two sheep were treated using an inflow conduit with a duckbill tip surrounded

by a nitinol cage to prevent vein wall suction and an outflow conduit with an intravascular connector inserted into the vein lumen.

Results: Mean vein diameter increased significantly from 4.5 to 8.4 mm with 6-11 days of treatment (n=5, *p*=0.005). Variation in conduit designs had no effect on final vein diameter. The average rate of vein dilation was 0.51 mm/day. The intravascular connector simplified placement of the outflow conduit and the inflow conduit tip-protecting nitinol cage prevented low flow events. AVFs were made with the dilated veins in all animals.

Conclusions: This pilot study shows the feasibility of dilating peripheral veins with the AFE System prior to AVF surgery.

Funding: NIDDK Support, Commercial Support - Flow Forward Medical, Inc.



TH-PO753

Vonapanitase Increases Fistula Use for Hemodialysis Using a Robust and Clinically Relevant Definition Anthony J. Bleyer,[5] Bradley S. Dixon,[4] Timmy C. Lee,[3] Steven K. Burke,[2] Rick E. Mishler.[1] *[1]Arizona Kidney Disease and Hypertension Center, Ltd., Phoenix, AZ; [2]Proteon Therapeutics, Inc., Waltham, MA; [3]Univ of Alabama at Birmingham, Birmingham, AL; [4]University of Iowa Hospital and Clinics, Iowa City, IA; [5]Wake Forest University School of Medicine, Winston-Salem, NC.*

Background: Vonapanitase is an investigational recombinant human elastase applied to the external surface of the fistula at the time of surgical creation. A recently reported randomized double-blind trial (NCT02110901) showed vonapanitase increased radiocephalic fistula survival and use for hemodialysis (HD) compared with placebo in 311 pre-HD (56%) and HD (44%) patients over 1 year. In other trials, varying definitions of use have been employed that required shorter durations of use but detailed information on individual HD session blood flow or urea clearance. The current trial employed a pragmatic definition based on continued 2-needle hemodialysis for ≧ 90 days.

Methods: Successful use was defined as (1) ≥90 days or (2) ≥30 days and in use at the final study visit for those pre-HD patients initiating HD late in the follow-up period. Non-use was defined as insufficient duration of use or fistula abandonment prior to use. Those not defined as having use or non-use were considered indeterminate (eg, a pre-HD patient who never initiated HD) and excluded from analysis. Of those with use, 82% had at least one Kt/V or URR recorded. Adequate HD was defined as Kt/V≥1.2 or URR≥65%.

Results: More vonapanitase than placebo patients successfully used the fistula for HD (n=230, 64% vs 44%, p=0.006). Use was established by the 90-day rule in 92% and the 30-day rule in 8%. Only 3 patients abandoned the fistula following successful use (2 placebo, 1 vonapanitase) the others continued use in a follow-on registry. Non-use was defined by fistula abandonment prior to use in 91% and by insufficient duration of use in 9%. Fistula abandonment was due to thrombosis (occlusion) in 64% of cases and a mix of intractable stenosis, non-maturation, inadequate HD, inability to cannulate, and steal syndrome in the remaining. The percentages of those with successful use who had adequate HD were vonapanitase 99% and placebo 97%. In those on HD at baseline, median duration from surgical creation to first use was 103 days for vonapanitase and 135 days for placebo patients.

Conclusions: Vonapanitase increased successful use of the fistula for HD employing a robust and pragmatic definition of use that is clinically relevant and associated with adequate hemodialysis. These results are being confirmed in a larger ongoing trial (NCT02414841).

Funding: Commercial Support - Proteon Therapeutics, Inc.

TH-PO754

Six Month AV Fistulae Outcomes Following Local Perianastomotic Delivery of Sirolimus – Preliminary Report from a US Phase 3 Clinical Trial (ACCESS Trial) Sriram Iyer,[1] Nelson P. Kopyt,[2] Joseph J. Lee,[3] Osman S. Khawar,[4] Thomas D. Wooldridge,[5] Nirav Gandhi,[6] Robert I. Lynn,[7] William D. Paulson,[8] Maria V. DeVita.[9] *[1]Vascular Therapies Inc;, Cresskill, NJ; [2]Lehigh Valley Hospital, Allentown, PA; [3]Nephrology Associates Medical Group, Riverside, CA; [4]Balboa Nephrology Medical Group, Escondido, CA; [5]Nephrology & Hypertension Associates, LTD, Tupelo, MS; [6]Nephrology Medical Group of Orange County, Anaheim, CA; [7]Kidney Medical Associates, Bronx, NY; [8]Augusta University, Augusta, GA; [9]Lenox Hill Hospital- Northwell Health System, New York, NY. Group/Team: On behalf of ACCESS Trial investigators.*

Background: AV Fistula (AVF) maturation delay impacts its functional patency and prolongs catheter dependence. USRDS (2015) reports median time to first cannulation of 112 days and only 45% of AVF are suitable for dialysis at 6 months [Range 38% (DAC) - 65% (HFM)]. A prior single arm Phase 2 study (Table) tested the value of perivascular Sirolimus delivered intraoperatively at and around the AVF anastomosis from a collagen membrane (drug product; Vascular Therapies, Cresskill, NJ), for improving AVF outcomes.

Methods: Incident ESRD patients undergoing hemodialysis via catheter at time of AVF creation (Radiocephalic RCF or Brachiocephalic BCF) are eligible for enrollment in this ongoing US Phase 3 multicenter, randomized controlled clinical trial (NCT02513303). The first subject enrolled at each site received the drug product ["Open-label" subject (OL)]. Baseline vascular mapping (Cephalic vein ≥ 2.5mm; Artery ≥ 2mm; vein depth ≤5mm) was performed to ensure suitability.

Results: There were no product related serious adverse events. Table lists key demographic and outcome metrics. Time to First Dialysis (TTFD): Time from AVF creation, to the time when the fistula can support three consecutive 2-needle dialysis sessions with a mean dialysis pump flow of ≥300 mL/min (2N/300). Fistula Suitability for Dialysis at 6 months (FSD6): Ability to use the fistula (2N/300) for two-thirds of the dialysis sessions during a 30 day suitability ascertainment period commencing on day150. Excluding the 2 AVF that thrombosed early, TTFD was <90 days for 11/16 (69%) subjects.

Conclusions: 1. Time to maturation and AVF suitability for dialysis at 6 months in the open label Phase 3 subjects are similar to Phase 2 results and signal an improvement in comparison to historical controls. 2. Results are promising and may suggest that prophylactic local treatment with Sirolimus at time of AVF creation could *predictably* reduce catheter dependence to less than 90 days with durable AV fistula functionality. Enrollment is ongoing in the ACCESS trial.

Funding: Commercial Support - Vascular Therapies, Inc

Phase	N	Age (years) Mean(Range)	Male	Diabetes	RCF	BCF	Thrombosis*	TTFD (Median Days)	FSD6
Phase 2	30	51 (25-77)	60%	20%	22	08	4/30 (13%)	45	76%
Phase 3 (OL)	18	61 (38-91)	89%	61%	10	08	2/18 (11%)	67	15/17 (88%)**

* Within 2 weeks of surgery

** Currently17 are eligible for this analysis

TH-PO755

Vascular Histology of Upper Extremities in Patients with CKD and Normal Controls Yan-Ting Shiu,[2] Silvio H. Litovsky,[1] CS Jason Tey,[2] Chad A. Sundberg,[2] Y. Zhang,[2] Alfred K. Cheung,[2] Michael Allon.[1] *[1]University of Alabama at Birmingham, Birmingham, AL; [2]University of Utah, SALT LAKE CITY, UT.*

Background: Several studies have documented histologic features in the peripheral arteries and veins of patients with chronic kidney disease (CKD), but few have compared them to the vascular histology observed in control subjects.

Methods: We obtained upper extremity arterial and venous specimens used to create arteriovenous fistulas from 125 CKD patients, and from 15 cadavers with no CKD. Intimal hyperplasia was quantified using elastic stains as well as hematoxylin and eosin stains, medial fibrosis using Masson's trichrome stains, and micro-calcification using von Kossa stains. Second-harmonic-generation microscopy was used to quantify the anisotropy index (measure of randomness of fiber orientation, ranging from 0 for completely random to 1 for completely aligned) and the dominant direction of the medial collagen fibers (measure of the angle of the fibers relative of the vascular lumen, ranging from 0° (parallel with lumen) to 90° (perpendicular to lumen)).

Results: The CKD patients were significantly younger (53±14 vs 76±11 yr; p<0.001). As compared to the control subjects, the CKD patients had greater arterial medial fibrosis (69±14 vs 51±10%, p<0.001), greater arterial micro-calcification (3.03±5.17 vs 0.01±0.03%, p<0.001), and greater venous intimal thickness 37±40 vs 14±6 um, p<0.001), but less arterial intimal thickness (30±25 vs 63±25 um, p<0.001). The anisotropy index of the collagen fibers was lower in both arteries (0.24±0.10 vs 0.44±0.04, p<0.001) and veins (0.28±0.09 vs 0.53±0.10, p<0.001) obtained from CKD patients. The dominant medial direction of the collagen fibers in CKD patients was greater in the arteries (49.3±23.6 vs 4.0±2.0, p<0.001) and the veins (30.0±19.6 vs 3.9±2.1, p<0.001).

Conclusions: CKD is associated with greater arterial medial fibrosis, arterial micro-calcification and venous intimal hyperplasia, but less arterial intimal hyperplasia than that present in control subjects. In addition, the collagen fibers in the arteries and veins of CKD patients are oriented more randomly and more perpendicular to the vascular

lumen. The vascular histology in CKD patients may affect the maturation outcomes of arteriovenous fistulas.

Funding: NIDDK Support

TH-PO756

Differences in Vascular Fibrosis Explain Sex Disparities in AVF Maturation Outcomes Laisel Martinez,[2] Juan C. Duque Ballesteros,[2] Angela Paez,[2] Marwan Tabbara,[2] Diana R. Hernandez,[2] Guillermo Selman,[1] Loay H. Salman,[1] Omaida C. Velazquez,[2] Roberto I. Vazquez-Padron.[2] *[1]Albany Medical College, Albany, NY; [2]University of Miami, Miller School of Medicine, Miami, FL.*

Background: Women have a higher risk of arteriovenous fistula (AVF) maturation failure than men, and the reason for this propensity is still unknown. Several studies have excluded sex-related differences in the diameter of native vessels as the explanation for this disparity, which suggests that the remodeling process in women is inferior. The purpose of this study was to compare two surrogate indicators of venous remodeling in females and males undergoing surgeries for two-stage AVF creation.

Methods: We measured intimal hyperplasia (IH) and medial fibrosis in native veins and AVF venous samples obtained during AVF creation (first-stage) and transposition (second-stage) surgeries, respectively. The analysis of native veins allowed the assessment of pre-existing sex-related differences in IH and medial fibrosis, whereas evaluation of AVFs allowed the comparison of postoperative remodeling between both sexes.

Results: Anatomical maturation failure (an AVF that never achieved an internal luminal diameter ≥ 6mm) occurred in 22/64 (34.4%) females and 18/97 (18.6%) males (p=0.027). The internal luminal diameter of the native basilic vein was similar between females and males (median 4.0 mm, interquartile range 4.0-4.0 in both, p=0.7). There were no significant sex-related differences in pre-existing IH and medial fibrosis between AVFs with successful maturation and maturation failure. Postoperative IH was also similar in AVFs with distinct maturation outcomes in both sexes. Interestingly, there was a significant increase in postoperative medial fibrosis in AVFs with maturation failure vs. successful maturation in females (55.0±2.7% vs. 44.0±2.2 [mean ± SEM], p=0.003), but not in males (51.2±2.9% vs. 48.0±1.6, p=0.4). Accordingly, logistic regression analyses demonstrated that the degree of medial fibrosis was associated with maturation failure in women (odds ratio [OR] 1.80 per 10% increase in medial fibrosis, p=0.034) but not in men (OR 1.03, p=0.4).

Conclusions: This study demonstrates for the first time the existence of sex-related differences in vascular remodeling after AVF creation, and that medial fibrosis is a major contributing factor to the increased risk of maturation failure in females.

Funding: NIDDK Support

TH-PO757

Extracellular Vesicles as Novel Markers in Hemodialysis Access Complications Tushar Chopra,[1] Sabrina La salvia,[2] Luca Musante,[2] Kambiz Kalantari,[2] Nicolas Intagliata,[2] Thu H. Le,[1] Uta Erdbruegger.[3] *[1]None, Nashville, TN; [2]University of Virginia, Charlottesville, WV; [3]University of Virginia Health System, Charlottesville, VA.*

Background: Failure of hemodialysis vascular access (HVA) is the most common cause of hospitalization and morbidity among end stage renal disease (ESRD) patients. Circulating extracellular vesicles (EVs) are potential candidate biomarkers to identify patients at risk for these HVA complications and failure. We hypothesize that these circulating EVs reflect endothelial damage in patients with vascular access complications, are pro-coagulant and predict VA longterm outcome.

Methods: EVs were isolated from platelet free plasma from citrated blood of 19 patients with recurrent HVA complications (mean age 64, HD vintage 2.8 years) and 16 patients without (mean age 61, HD vintage 5.7 years). Enumeration and phenotyping of EVs was performed using imaging flow cytometry. CD42 positive, CD31, S-Endoglin (CD105), E-Selectin (CD62E) and Annexin V (AnV) positive EVs were used as surface markers for circulating EVs. The size and concentration of EVs was measured with tunable resistive pulse sensing by qNano (Izon). A thrombin generation assay (TGA) (Stago) was performed and compared between groups. All patients were followed prospectively up to 4 years and assessed for total failure of their HVA.

Results: Endothelial derived EVs (activated (CD62E+), and non-activated (CD105+)) were significantly higher in patients with vascular access stenosis and thrombosis (CD62E: median 141,596/µl plasma, CD105: 114,983/µl plasma) compared to patients without VA complications (CD62E: median 63411/µl plasma, CD105 86505/µl plasma, CD62E p=0.014, CD105 p=0.004). Out of the 35 patients 19 (80%) had a functioning graft at time of follow up. Higher CD31+/CD41- EV levels correlated with a functioning access up to 5 years (CD31+/CD41- EVs: functioning 406,514/µl plasma, failed 161,000/µl plasma, p=0.02). However, EV concentration, EV size profile and endogenous thrombin potential were not statistically different between patients with and without HVA complications.

Conclusions: Activated and non-activated endothelial derived EVs are elevated in HD patients with vascular access complications, independent of HD vintage. These EVs might reflect endothelial pathology in HVA and have the potential to guide surveillance and treatment. A larger cohort of patients needs to be examined to confirm this finding.

Funding: Other NIH Support - K award 1K23HL126101

TH-PO758

Isolation of High-Quality RNA from Human Veins and Arteriovenous Fistulas Guillermo Selman,[1] Nieves Santos,[2] Laisel Martinez,[2] Juan C. Duque Ballesteros,[2] Marwan Tabbara,[2] Loay H. Salman,[1] Roberto I. Vazquez-Padron.[2] *[1]Albany Medical College, Albany, NY; [2]University of Miami, Miller School of Medicine, Miami, FL.*

Background: Functional genomics and transcriptome analysis of pre-access veins and arteriovenous fistulas (AVF) require RNA of high quality and integrity. However, the vast majority of intraoperative vascular biopsies have a small size, are low in cell density, and rich in collagen and other extracellular matrix components that hinder the complete disruption of the tissue by guanidine isothiocyanate-based RNA extraction buffers. The application of current extraction protocols to AVF samples typically results in low RNA yields with poor quality. In this work, we developed a standard operating procedure that combines a pulverizing method that keeps the tissue completely frozen for RNA extraction with commercial reagents for purification.

Methods: We optimized this method using RNA-later (Qiagen) preserved veins (n=63) and AVFs (n=30) that were obtained intraoperatively during the creation of two-stage brachiobasilic fistulas in consented patients at the University of Miami. Briefly, 50-60 mg of tissue was cut in small pieces and ground to a fine powder in a Spex/Mill 6770 (15 min pre-cooling; 30 sec run; 2 min cycle cooling; 15 cycles total, 10 Hz rate) in the presence of 100 uL of Trizol. The homogenate was collected with 700 uL Trizol, transferred to 2-mL RNase-free microcentrifuge tubes, and further homogenized using an Ultra-Turrax T8 instrument for 30-45 seconds. After removing cellular debris by centrifugation (12,000 x g, 5 min, RT), the clear homogenate was extracted with chloroform according to the standard Trizol protocol, and 0.55 volumes of ethanol were added prior to loading onto an Omega EZNA column for further purification (Omega Bio-tek). On-column DNase digestion was applied as desired. Total RNA was eluted with 40 uL of RNAse-free water.

Results: The total RNA yield had a median of 44.5 ng/ul (interquartile range [IQR] 32.1 – 68.0) in veins and 124.0 ng/ul (IQR 85.2 – 220.0) in AVFs. High-quality RNA (RIN > 5) was obtained in 79.4% of veins and 86.7% of AVFs as demonstrated using an Agilent 2100 Bioanalyzer.

Conclusions: In conclusion, we have developed a new protocol for isolation of high-quality RNA from small vascular biopsies. We have successfully used these RNAs for RT-PCR and highly sensitive techniques for transcriptome analysis (RNA-seq).

Funding: NIDDK Support

TH-PO759

Percutaneous AV Fistula Creation for Vascular Access Randy I. Cooper,[2] Rajeev Narayan,[1] Matthew E. Schaefer,[1] Umar Waheed.[2] *[1]San Antonio Kidney Disease Center, San Antonio, TX; [2]Southwest Kidney Institute, PLC, Phoenix, AZ.*

Background: In the era of Fistula First, nephrologists are well versed on the pitfalls of arterio-venous fistula (AVF) failure rates and surgical issues related to AVF creation. USRDS 2016 reports a primary fistula failure rate of 35.9%. Few innovations have evolved in AVF creation but recently several novel devices have been developed that can create AVF percutaneously.

Methods: Two nephrology groups with vascular centers were among 5 centers in a U.S. IDE pivotal study using a percutaneous device (Ellipsys; Avenu Medical, San Juan Capistrano, CA) to create AVF. Patients were selected based upon suitable anatomy as determined by ultrasound mapping. All procedures were performed in the physician's centers. The primary outcome is maturation rate, defined as percentage of fistula suitable to allow successful cannulation for dialysis within 90 days including vein size and flow. The device is a single catheter that engages the walls of a perforating vein and proximal radial artery in the forearm. The AVF is created using thermal energy to "heat weld" the vessels together and cut the anastomosis.

Results: The Interventional Nephrologists (INs) in the study reported an average procedure time of 23 minutes. In addition, available 12 month follow-up data indicate a high patency rate of 96% and no significant clinical sequelae such as mega-fistulas or steal syndrome have been reported. One year data will be provided at the meeting.

Conclusions: Despite the advances from Fistula First, 80% of incident patients still initiate HD without a functioning AV access and 30% are still dialyzing with a catheter at 1 year. Our study demonstrates that PAVF offers a minimally invasive option for AVF creation that can be safely performed in an office-based setting by INs. The 90 day and 1 year data demonstrate technical and clinical success as well as a reduction in the maturation period in comparison to surgically created AVF. It is estimated, with the process under the control of the nephrologist, that catheter contact time (CCT) can be reduced by 90 days or more.

Funding: Commercial Support - Avenu Medical

RESULTS

Fistula Type	Technical Success	Time to Maturation*	Serious Adverse Events
Ellipsys pAVF n=69	91.3%	68 days	1 (related to anesthesia)
Surgical creation	64.1%	136 days	Ranges 2%-11%

*Access had flow suitable for dialysis (>4 mm vein/ >500 ml flow)

Ave. Flow @ 90 days-1092 ml/min (cephalic) 1269 ml/min (basilic)

Ave. Vessel diameter @ 90 days- 6.7 mm (cephalic) 6.2 mm (basilic)

TH-PO760

Real-World Experience Utilizing Endovascular Arteriovenous Fistula (endoAVF) to Deliver Hemodialysis Treatment Frank Dellanna,[1] Christoph Radosa,[2] Ralf Hoffmann,[2] Linda Nuth,[3] Robert Shahverdyan,[3] Tobias Steinke.[3] *[1]MVZ DaVita Rhein-Ruhr GmbH, Duesseldorf, Germany; [2]Universitätsklinikum Carl Gustav Carus, Dresden, Dresden, Germany; [3]Schön Klinik Düsseldorf, Düsseldorf, Germany.*

Background: The arteriovenous fistula (AVF) is the primary option for end stage renal disease patients to receive hemodialysis treatment. However, the surgical trauma of dissecting, mobilizing and suturing the vein to the artery can lead to early AVF failure rates as high as 60% [1-4]. A novel endovascular approach to create AVFs has been developed to avoid this surgical trauma. This report describes the initial real-world experience with the endoAVF at two European vascular centers.

Methods: Consecutive dialysis and pre-dialysis patients who underwent the endoAVF procedure were followed to assess the ability to create a functional vascular access. Eligible patients were traditional surgical candidates for upper arm AVFs. Patients did not receive an endoAVF if they were ideally suited for a radiocephalic fistula (healthy arteries with a >2.5 mm forearm cephalic vein) or had a previously failed upper arm vascular access. Patients were followed to assess the technical success of the procedure, functional usability via two-needle cannulation, interventions necessary to mature and maintain the endoAVF and maturation time.

Results: An endoAVF was attempted in 23 patients between 07/2015 and 05/2017. The median age was 60 (25-84) with 65% male 61% pre-dialysis, 9% having a failed forearm fistula and typical comorbidities of the German dialysis patient population. Technical success was reported at 100%. Dialysis was successfully administered via 2-needle cannulation in 72% (13/18) of the patients; three patients were still pre-dialysis, one patient had less than 2 months follow-up and one was lost to follow-up. Three pre-planned vein elevations as well as three interventions to augment flow were performed. The median maturation time was 56 days (range: 10 – 86 days) at one center and 63 days (range: 26 – 137) at the other with the longest maturation times associated with elevation procedures.

Conclusions: The endoAVF procedure produced usable AVFs with high technical success. These real-world results are consistent with the results demonstrated in previous endoAVF clinical studies, FLEX [5] and NEAT [6]. 1. J Vasc Surg 2012;55:274-80. 2. Kidney International, 2003;64:1487–1494 3. J Nephrol 2007;20:150-163. 4. JAMA 2008; 299:2164–2171 5. J Vasc Interv Radiol. 2015;26(4):484-490. 6. J Am Soc Nephrol 2016; 27:31A.

TH-PO761

Long-Term Outcomes of Arteriovenous Fistulas and Grafts in a Large European Cohort Bram M. Voorzaat,[2] Koen E. van der Bogt,[1,2] Cynthia J. Janmaat,[2] Friedo W. Dekker,[2] Joris I. Rotmans.[2] *[1]Haaglanden Medisch Centrum, Den Haag, Netherlands; [2]Leiden University Medical Center, Leiden, Netherlands. Group/Team: Dutch Vascular Access Study Group.*

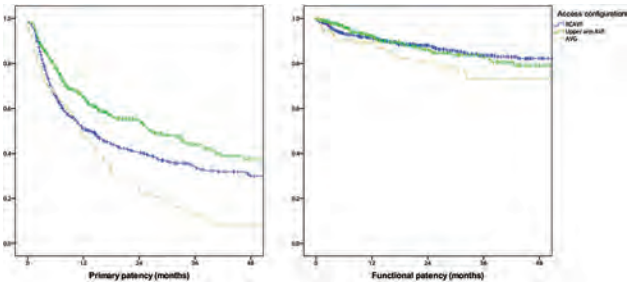
Background: For hemodialysis (HD), arteriovenous fistulas (AVF) are the preferred type of vascular access (VA). Most data on VA durability originate from North America. As practice patterns and patient characteristics differ between Europe and the US, we evaluated outcomes of radiocephalic (RCAVF) and upper arm AVFs and arteriovenous grafts (AVG) in a large retrospective cohort of Dutch HD patients.

Methods: This Dutch Vascular Access Study cohort consists of 1,656 VAs in 1,221 patients in 8 hospitals. To obtain independent observations, only the first matured VA per patient was included. Primary patency started at VA creation and ended at the first intervention or abandonment. Functional patency started at the first cannulation and ended at abandonment. Patency was censored at death or transplant. Patency is presented as median VA survival and analysed using Kaplan-Meier analysis. Hazard ratios for patency loss are calculated using Cox regression analysis using RCAVFs as the reference. Procedure rates are presented per year of functional patency.

Results: 863 VAs (420 RCAVF, 341 upper arm AVF, 102 AVG) were analysed. The median primary patency for RCAVFs was 13.8 ± 1.8 months, for upper arm AVFs 26.6 ± 4.5 months and for AVGs 11.4 ± 1.8 months. The hazard ratio for loss of primary patency was higher for AVGs than RCAVFs (HR 1.52, 95% confidence interval: 1.18 – 1.96), and lower for upper arm AVFs (HR 0.74, 0.60 – 0.90). The median of functional patency was not met during the follow-up (fig 1). At 48 months 82% of RCAVFs, 79% of upper arm AVFs and 73% of AVGs were still functionally patent (death-censored). The number of procedures was lowest for RCAVFs (0.8 ± 2.1/year) versus upper arm AVFs (1.4 ± 8.7/year) and AVGs (2.5 ± 5.8/year).

Conclusions: In the Dutch Vascular Access Study cohort, long-term functional patency was comparable between the 3 groups of arteriovenous access configurations. However, the number of procedures required to maintain AVG patency is 3-fold higher compared to RCAVFs.

Funding: Commercial Support - Proteon Therapeutics



Death/transplant-censored primary and functional patency

TH-PO762

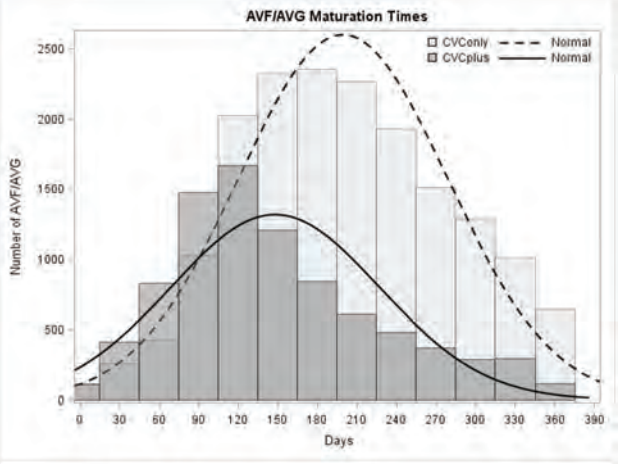
The Significance of a Maturing Fistula or Graft at HD Initiation Rita L. McGill,[2] Eduardo K. Lacson.[1] *[1]Tufts University School of Medicine, Boston, MA; [2]University of Chicago Medicine, Chicago, IL.*

Background: Increasing use of fistulas (AVF) and grafts (AVG) is a national priority, especially for incident hemodialysis (HD) patients. One-quarter of patients who initiated HD with catheters (CVC) have an accompanying 'maturing' AVF or AVG. We examined the characteristics and one-year outcomes of these patients.

Methods: All patients initiating HD from 7/2010 – 12/2011 were assessed. Medical Evidence forms were used to determine baseline characteristics and vascular access at 1st outpatient HD. HD claims were used to assess changes in vascular access, and treatment history files were used to identify deaths during the first year of HD.

Results: Among 52,573 patients initiating HD with CVCs, 12,201 (23.2%) had a maturing AVF/G. Compared to patients with CVC-only, patients with maturing AVF/G were more likely to be black (30.6 vs. 27.3%, P<0.01) and diabetic (61.7 vs 55.6%, P<0.01), but similar in age, sex, and body mass index. Patients with pre-HD nephrology care were twice as likely to have maturing AVF/G (31.1 vs. 15.6%, *P*<0.001). Over the first year, 10.9% of patients with maturing AVF/G died, 71.6% converted to AVF/G use, and 14.1% had CVC at one year. Among patients with CVC-alone, 23.0% died, 42.7% converted to AVF/G, and 23.8% had CVC at 1 year. Among patients who transitioned to AVF/G, median catheter-days were 131 (IQR=94-194) for patients with maturing access versus 195 (IQR=95-252) for those with CVC-only. The distributions of maturation times were unimodal for both groups.

Conclusions: HD initiation with a maturing AVF/AVG is associated with improved first-year outcomes relative to CVC as sole access, suggesting that vigorous efforts to secure access may be beneficial even in advanced CKD. Although a maturing AVF/AVG was associated with fewer catheter days, CVC use was prolonged in both groups. The reasons for prolonged CVC use merit further investigation.



TH-PO763

Comparison of FTM Risk Score versus Surgical Opinion for Primary and Secondary AV-Fistula Creations Eliot J. Winkler,[3] Sami Suleiman,[2] Prakash Gudsoorkar,[1] Charmaine E. Lok.[2] *[1]None, Toronto, ON, Canada; [2]Toronto General Hospital, Toronto, ON, Canada; [3]University Health Network, Toronto, ON, Canada.*

Background: Arteriovenous fistulas (AVF) continue to have high failure-to mature (FTM) rates. A validated FTM Risk Score may help stratify patients by FTM risk to improve VA decision making. It is unclear how well the FTM Risk Score correlates with surgical opinion. We aimed to describe the FTM risks of primary and secondary AVFs and elucidate the relationship between the FTM Risk Score and surigcial opinion for these two subgroups.

Methods: Data was propsectively collected between 2006-2014 during VA clinics where 5 surgeons assessed patients for potential VA creation at an academic hospital. The FTM Score was determined for each patient ("FTM Score") while surgeons independently evaluated the patient's likelhood of AVF maturation as: Excellent, Good, Marginal, or Poor ("Surgeon Score"), which corrleated to the FTM Risk Score e.g. FTM Risk of "low" corresponded to Surgeon Score "Excellent". Descriptive statistics categorized the surgeon and clinician risk scores as low, moderate, high, or very high risk;overall Fleiss Kappa statistics were calculated (SPSS, V. 23).

Results: There were 355 primary AVF, 42 secondary AVF with both Scores collected and verified. Overall, the Risk Scores were: low risk-26%; moderate risk-41.5%; high risk-30.3%; very high risk-2.2%. The Risk Score had a Kappa agreement of 0.78 with the Surgeon Score ($p<0.001$). The categories of risks were similar (Table 1). The FTM Score and Surgeon Score had Kappas of 0.72 (primary) and 0.75 (secondary). Mean FTM Risk Score was 3.11 (primary) and 3.45 (secondary); mean Surgeon Score was 3.22 (primary and 3.64 (secondary).

Conclusions: The distribution of AVF failure risk was similar between the FTM Risk Score and Surgeon's clinical evaluation. However, the agreeement improved with secondary AVFs, suggesting that more clinical information from prior AVF outcomes improve clinical predication. The AVF outcomes according to FTM Risk Score and Surgeon Score are the focus of ongoing research.

Funding: Clinical Revenue Support

Primary AVF Access Risk of FTM (%)	% (n=355)	Surgeon Evaluation	% (n=355)	Secondary AVF Access Risk of FTM (%)	% (n=42)	Surgeon Evaluation	% (n=42)
Low	23.1	Excellent	23.9	Low	16.7	Excellent	19
Moderate	43.1	Good	41.1	Moderate	38.1	Good	38.1
High	30.4	Marginal	31.8	High	45.2	Marginal	42.9
Very High	3.4	Poor	3.1	Very High	0	Poor	0
Overall Kappa	0.72*			Overall Kappa	0.75*		
*p<0.001							

TH-PO764

Prediction for Maturation of Arteriovenous Fistula by Vascular Ultrasonography Jae seok Kim,[5] Jun young Lee,[3] Byoung Geun Han,[1] Seung-Ok Choi,[4] Jae Won Yang.[2] *[1]None, Wonju, Republic of Korea; [2]Wonju Christian Hospital, Wonju, GANGWON-DO, Republic of Korea; [3]Wonju christian severance hospital, Wonju, Kangwon do, Republic of Korea; [4]Yonsei University Wonju College of Medicine, Wonju, Kangwon, Republic of Korea; [5]Yonsei wonju college of medicine, Won-ju, Republic of Korea.*

Background: Vascular access formation is an important step in starting hemodialysis therapy. However, because most patients with end stage renal disease have poor vascular condition, the rate of success in maturation of arteriovenous fistula (AVF) is lower than expected. We aim to investigate the predictors for successful AVF maturation through the ultrasound examination which was performed at pre and post AVF surgery.

Methods: We collected the data of vascular sonography from the seventy patients undergoing AVF formation surgery at Wonju Severance Christian Hospital in South Korea. We performed ultrasound vascular mapping as a pre-evaluation searching appropriate vessels for AVF, and followed it at around one-month after the surgery to evaluate whether the AVF is maturated possible to use for hemodialysis. In the ultrasonography, we measured the diameter of artery (A1) and vein (V1) before surgery, and feeding artery (A2) and AVF (V2) after AVF formation. Additionally, we evaluated blood flow (Bf) of AVF and calculated the change of diameter in artery (A2-A1, delta A) and vein (V2-V1, delta V).

Results: Thirty-seven men and thirty-three women comprised of the subjects. The mean age was fifty-nine years old. We defined the cases with Bf<600 mL/min as a poor maturation group and the other cases with Bf>600 mL/min as a good maturation group. The independent T-test showed that there were significant differences in the parameters of A2 (poor vs. good; 4.0±1.1 vs. 5.1±1.2 mm, $p=0.003$), delta A (0.7±0.6 vs. 1.2±0.7 mm, $p=0.025$), V2 (4.5±0.9 vs. 5.7±1.3 mm, $p<0.001$) and delta V (1.3±0.7 vs. 2.1±1.2 mm, $p=0.001$) between the poor and good maturation groups. ROC analysis demonstrated that 4.0 mm of A2, 0.6 mm of delta A, 4.9 mm of V2 and 4.2 mm of delta V were suggested to predict good AVF maturation. In pearson's correlation analysis, Bf of AVF had the positive relationships with A1 ($p=0.005$), A2 ($p<0.001$), delta A ($p<0.001$), V1 (0.002) and V2 ($p<0.001$). In regression test, the results demonstrated that delta A best predict the success in the AVF maturation.

Conclusions: In conclusion, the change of the arterial diameter between before and after the AVF formation is the most important factor for AVF maturation.

TH-PO765

Influence of Arterial Dilatation on Fistula Maturation with Adequate Blood Flow: Supports Concept That Arterial Elasticity Has Key Role William D. Paulson,[1] Sulav Bastola,[3] Steven A. Jones.[2] *[1]Augusta University, Augusta, GA; [2]Louisiana Tech University, Ruston, LA; [3]Charu Polyclinic and Diagnostic Center, Kathmandu, Nepal.*

Background: Fistula maturation success is strongly dependent on adequate dilatation of the inflow artery and outflow vein. The Rule of 6s emphasizes an adequate vein luminal diameter is needed to allow successful cannulation. However, poor arterial elasticity is associated with maturation failure, probably because of failure of the inflow artery to dilate adequately. We further explored this issue by applying a mathematical model of the fistula in which the outflow vein dilates but the artery dilates minimally or not at all.

Methods: Mathematical model was a brachiocephalic fistula that included cephalic vein anastomosed end to side to the brachial artery; ulnar artery; palmar arch; and vein that drains the hand and connects to the cephalic vein. We set mean arterial pressure = 93 mmHg, central venous pressure = 5 mmHg. We predicted fistula blood flow at dilated vein luminal diameters ranging from 4 to 8 mm, and arterial diameters ranging from 2 to 6 mm. We also evaluated influence of stenosis at arteriovenous anastomosis on blood flow.

Results: A fistula with an arterial diameter of 2 mm is predicted to have a blood flow ranging from only 232 to 241 ml/min despite widely accepted adequate venous diameters ranging from 4 to 8 mm. Even arterial dilatation to 3 mm diameter will provide only marginal blood flows ranging from 581 to 665 ml/min. Flows in the range of 1,000 ml/min or more require an arterial diameter of at least approximately 4 mm. Development of stenosis at the arteriovenous anastomosis will significantly impair flow and thereby require even larger arterial diameters if blood flow is to be adequate.

Conclusions: These results support the concept that dilatation of the inflow artery is a key step in fistula maturation. Arterial properties are as important as venous in assessing suitability of vessels for fistula formation. Poor arterial elasticity may result in a high resistance fistula circuit despite adequate dilatation of the outflow vein. An arterial diameter of 2 mm is widely accepted as a minimally acceptable preoperative diameter, but such an artery cannot support adequate blood flow unless it is able to dilate.

Funding: Clinical Revenue Support

	Fistula blood flow (ml/min) at inflow artery luminal diameters ranging from 2 to 6 mm				
Vein diameter	2 mm	3 mm	4 mm	5 mm	6 mm
4 mm	232	581	971	1221	1352
6 mm	240	652	1344	2097	2715
8 mm	241	665	1445	2493	3626

TH-PO766

CKD-Mineral Bone Disorder and Risk of Maturation Failure in Hemodialysis Arteriovenous Fistula Chung-te Liu.[1,2] *[1]Division of Nephrology, Department of Internal Medicine, Wanfang Hospital, Taipei Medical University, Taipei, Taiwan; [2]Graduate Institute of Clinical Medicine, Collage of Medicine, Taipei Medical University, Taipei, Taiwan.*

Background: Arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis. However, instant usability of this vascular access type is limited by high rates of maturation failure. Chronic kidney disease-mineral bone disorder (CKD-MBD) is associated systemic vascular calcification and increased mortality in dialysis patients. While CKD-MBD correlates with cardiovascular disease in dialysis patients, the association between CKD-MBD and maturation failure of AVF remains to be elucidated.

Methods: A retrospective cohort study was conducted to enroll patients receiving AVF creation and maintenance hemodialysis in Wanfang Hospital, Taipei Medical University from January, 2004 to February, 2017. The outcome of the study was maturation failure of AVF, which was defined as non-usage of the AVF for hemodialysis from its creation to the establishment of another hemodialysis vascular access. Predictors included baseline demographic profiles and laboratory data. Categorical and continuous variables were compared using chi square test and two-tailed t-test for unpaired samples, respectively. The association of predictors to outcome was tested using logistic regression.

Results: During the study period, 408 patients receiving AVF creation and maintenance hemodialysis were included. Among the included patients, the mean age was 56.6±13.7 years. In addition, 56.4% were male and 49.3% had diabetes. Fifty-nine (14.5%) patients had maturation failure. Compared with patients with mature AVF, the maturation failure patients had significantly more diabetes, higher serum glucose and parathyroid hormone (PTH) levels. Serum calcium, phosphorus and other laboratory tests were not significantly different between the two groups. Univariate logistic regression showed that diabetes and serum PTH were significantly associated with maturation failure. In multivariate logistic regression, only PTH remained significantly associated with maturation failure. The above findings showed that higher PTH level was associated higher risk of AVF maturation failure.

Conclusions: This study preliminarily showed the association between higher PTH level and AVF maturation failure. This finding indicate that secondary hyperparathyroidism may have detrimental effect on successful rate of AVF creation.

TH-PO767

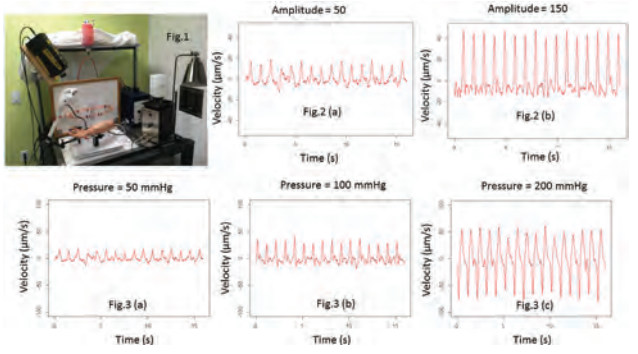
Feasibility of Laser Doppler Vibrometry to Quantitate Arterio-Venous Fistula Thrill Israel Campos,[1] Schantel Williams,[1] Laura Rosales,[1] Fansan Zhu,[1] Peter Kotanko.[1,2] *[1]Renal Research Institute, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Clinical examination is the corner stone of identifying arterio-venous fistula (AVF) pathologies and recognizing changes in AVF thrill carries important information. While currently subjective, quantitating AVF thrill objectively may improve the diagnosis of AVF pathologies. AVF thrill is vibrational in nature and depends on AVF pressure and flow rate. The aims of this study was to evaluate how pressure and flow rate affect the vibrational characteristics.

Methods: In this bench study we used a 3D printed AVF cannulation simulator (Phacon, Germany) with artificial "skin" above the AVF and a pumping system to provide flow. In this study, the pump rate was set to 60 per minute. Two series of experiments were conducted. In one series the pressures varied and the flow was set constant. In a second series of experiments the pressure was set constant and the pumping amplitude varied. The motion characteristics (amplitude, velocity) of the artificial "skin" above the AVF were measured by laser Doppler vibrometry (PDV100, Polytec, Germany). The set-up is shown in Fig. 1.

Results: The laser Doppler vibrometry provided excellent high-resolution measurements of the "skin" movements. The "skin" movements clearly depended on both AVF pressure and stroke volume (Fig.2a, b and Fig.3a-c).

Conclusions: Our in vitro study demonstrates that, first, laser Doppler vibrometry can determine regional "skin" vibrations above AVF with high accuracy and precision. Second, vibration characteristics ("thrill") of the "skin" above the AVF depend on both flow and pressure. Clinical studies are required to extend these findings to hemodialysis patients with AVF as vascular access.



TH-PO768

Postoperative Vascularization of the Arteriovenous Fistula Is Not Associated with Maturation: A Pilot Study Juan C. Duque Ballesteros,[2] Laisel Martinez,[2] Angela Paez,[2] Marwan Tabbara,[2] Guillermo Selman,[1] Loay H. Salman,[1] Roberto I. Vazquez-Padron.[2] *[1]Albany Medical College, Albany, NY; [2]University of Miami, Miller School of Medicine, Miami, FL.*

Background: The venous vasa vasorum provides oxygen and nutrients to the walls of native veins and arteriovenous fistulas (AVF). Nonetheless, whether expansion or growth of the AVF microvasculature has an effect on clinical outcomes remains undetermined. The purpose of this study was to evaluate the association of AVF vascularization with maturation and with the development of medial fibrosis and intimal hyperplasia (IH).

Methods: We assessed pre-existing and postoperative vascularization in both native veins and AVF venous samples (*i.e.*, tissue pairs) from 19 patients undergoing two-stage AVF creation. Patients with successful maturation (N=9) and maturation failure (N=10) were matched with respect to age, demographics, and comorbidities. Vasa vasorum density (VVD; microvessel count/wall area) and area (VVA; microvessel luminal area/wall area) were quantified in the vascular layers of CD31-stained cross-sections. Change in vascularization after AVF creation was calculated by subtracting pre-existing VVD and VVA from the postoperative values in tissue pairs.

Results: Total VVD in native veins was 6/mm^2 (interquartile range [IQR] 2-10), with no significant change in AVFs as determined by pairwise comparisons (p=0.3). Total VVA increased during remodeling, from 956 um^2/mm^2 (IQR 509-1466) in native veins to 1879 um^2/mm^2 in AVFs (IQR 766-2578; p=0.046), with the most significant increase observed in the adventitia (1751 vs. 4798, respectively; p=0.004). AVF vascularization was not associated with baseline factors (age, ethnicity, sex, diabetes), nor with the time interval between AVF creation (first-stage) and transposition (second-stage) surgeries. Interestingly, although IH increased significantly in AVFs compared to veins (p=0.0003), microvessels were detected in the intima of only four AVFs and not in veins, and neither VVD nor VVA was associated with the degree of IH. Similarly, none of the vascularization parameters measured were associated with medial fibrosis. Lastly, there were no significant differences in VVD or VVA between AVFs with distinct maturation outcomes.

Conclusions: This study indicates that AVF vascularization is not a major contributing factor in remodeling after access creation, and it does not determine maturation.

Funding: NIDDK Support

TH-PO769

Outcome of Endovascular Salvage of Immature Hemodialysis (HD) Arteriovenous Fistulae (AVF) Hye Eun Yoon, Yaeni Kim, Byung ha Chung, Bumsoon Choi, Cheol Whee Park, Chul Woo Yang, Yong-Soo Kim. *The Catholic University of Korea College of Medicine, Seoul, Republic of Korea.*

Background: To assess the anatomical causes of immature AVF and the outcome of endovascular salvage.

Methods: Anatomical causes, clinical characteristics, and the success rate of endovascular salvage of 110 immature AVF were analyzed.

Results: A total of 110 patients included 52 females and 64 diabetics. The mean age was 63±13 years old. The access types were radiocephalic (n=62), brachiocephalic (n=45), and transposed brachiobasilic (n=3) fistulae. At the time of angiography, 75 patients were maintained on HD using catheters. Mean interval between AVF creation and referral to angiography was 94±69 days. Angiography revealed stenoses (n=49; 26 inflow, 9 outflow, and 14 mixed), accessory veins (n=16), and inadequate selection of vessels (n=2) in 62 patients with radiocephalic fistulae. It revealed stenoses (n=41; 14 inflow, 17 outflow, and 10 mixed), accessory veins (n=11), deeply located cephalic veins (n=2), and inadequate selection of vessels (n=4) in 48 patients with upper arm fistulae. Endovascular procedures performed in 107 patients included percutaneous transluminal angioplasty (PTA) (n=95) and accessory vein obliteration (n=27; 1 percutaneous, 12 surgical ligations, 14 coil insertions). The number of procedures was once in 83, twice in 17, and three times in 7 patients. The overall technical and clinical success rates were 95.2% and 92.3%. Mean interval between endovascular procedure and the first successful cannulation of the fistula was 26±17 days in patients on maintenance HD At 3, 6, 12, and 24 months following the first successful cannulation, the primary patency rates were 84.7%, 71.0%, 57.4%, and 39.7%, respectively. Assisted patency rates of 97.7%, 95.2%, 91.0%, and 79.0% and secondary patency rates of 98.9%, 97.5%, 96.1% and 91.4% at 3, 6, 12, and 24 months, respectively. Multivatiate Cox regression analyses revealed mixed stenosis to be the only determinant that affects secondary patency rate of immature AVF. Consistently, immature AVF with mixed stenosis showed poorer access outcome in terms of secondary patency rate compared with that of no mixed stenosis. ($p < 0.001$)

Conclusions: Immature AVF can be salvaged by aggressive and timely intervention. Endovascular procedures can salvage the majority of cases with high success and patency rates. The presence of mixed stenosis is associated with poor access outcome.

TH-PO770

Tailored Selection of Elevation Transposition and Lipectomy for Superficialization of Cephalic Arteriovenous Fistula Veins Shouwen Wang. *Arizona Kidney Disease and Hypertension Center, Phoenix, AZ.*

Background: Cephalic vein arteriovenous fistulas are the most commonly used vascular accesses for hemodialysis. However, as high as 34% of these fistulas are situated too deep under the skin and require superficialization before use. Various superficialization techniques have been employed, such as tunnel transposition, elevation, elevation transposition, and lipectomy. Each of these techniques may have advantages and disadvantages, and there have been few reports comparing their outcomes. This report compares the clinical outcomes of cephalic elevation transposition (CET) vs lipectomy and discusses tailored selection of these techniques.

Methods: The clinical data of patients who underwent second-stage cephalic vein elevation transposition or lipectomy at an ambulatory surgery center were collected and analyzed. The patients who underwent basilic elevation transposition (BET) were included for comparison with CET.

Results: A total of 240 patients were included. Comparing the CET group (n=118) vs the lipectomy group (n=28) vs the BET group (n=94): males were 28% vs 32% vs 59%; the mean age was 58.0±14.1 vs 56.3±12.1 vs 60.0±15.0; the mean body mass index was 36.9±7.8 vs 38.1±7.2 vs 26.8±6.9; the percentages of upper arm fistulas were 84% vs 61% vs 100% and of the forearm fistulas were 16% vs 39% vs 0%; and the mean follow-up was 18.8±17.6 vs 37.1±24.4 vs 24.6±20.0 months. For the CET vs the lipectomy vs the BET groups, the primary patency rates of the whole fistula conduit were 40% vs 49% vs 44% at one year and 17% vs 37% vs 37% at three years; the assisted primary patency rates were 93% vs 96% vs 97% at one year and 78% vs 96% vs 88% at three years; the secondary patency rates were 99% vs 100% vs 100% at one year and 92% vs 100% vs 98% at three years; the primary patency rates of the superficialized fistula vein segments were 72% vs 67% vs 65% at one year and 57% vs 51% vs 53% at three years; and the mean numbers of percutaneous interventions required for the superficialized fistula vein segments were 0.55±1.10 vs 0.43±0.71 vs 0.60±1.02 per access-year.

Conclusions: CET and lipectomy are reliable approaches for superficialization of cephalic fistula veins that yield high cumulative fistula survival rates, which are comparable to that of BET for basilic fistula veins. The selection of CET or lipectomy is mainly based on the location and depth of a fistula vein.

TH-PO771

Changes in Blood Pressures, Adequacy, and Blood and Dialysate Flow Rates before and after Arteriovenous Access Angioplasty Hao Han,[1] Tommy C. Blanchard,[1] Hanjie Zhang,[3] Murat Sor,[2] Elsie Koh,[2] Yue Jiao,[1] Sheetal Chaudhuri,[1] Marta Reviriego-Mendoza,[1] John W. Larkin,[1] Len A. Usvyat,[1] Peter Kotanko,[3] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Fresenius Vascular Care, Malvern, PA; [3]Renal Research Institute, New York, NY.*

Background: Stenosis is a common complication in arteriovenous fistulas and grafts (AVFs/AVGs), and is a major cause of hospitalizations and dialysis access failure. Clinical predictors for early detection of severe stenosis in AVFs/AVGs are sparse. To determine predictors of stenosis, we investigated trends in levels of predialysis systolic and diastolic blood pressures (preSBP/preDBP), dialysis adequacy, blood flow rate (Qb), and dialysate flow rate (Qd) before and after angioplasties in hemodialysis (HD) patients.

Methods: We analyzed data from 7,910 Fresenius Kidney Care HD patients who had an AVF/AVG angioplasty in 2015 and 2016. The preSBP, preDBP, Kt/V, Qb, and Qd were tracked in HD patients for 90 days before and after an angioplasty, and plotted using a penalized B-spline to fit the mean with 95% confidence limits.

Results: During the 90 days prior to an angioplasty, HD patients exhibited a slight decline of approximately 1.5 mmHg in both mean preSBP and preDBP. The most precipitous decline for both preSBP and preDBP was in the final 2 weeks prior to angioplasty. About a week after an angioplasty, mean preSBP and preDBP increased by approximately 1.0 mmHg and 0.5 mmHg, respectively. The preSBP blood pressures at 90 days after an angioplasty were found to decrease by about 0.5 mmHg below the levels seen 2 weeks before an angioplasty. We also observed similar findings for all parameters; specifically, the following changes occurred after angioplasty compared to before angioplasty: i) average Kt/V increased by about 1%; ii) average Qb increased by about 1%; and iii) average Qd increased by approximately 0.5%.

Conclusions: These findings indicate that blood pressures, Kt/V, Qb and Qd decline before and increase after an AVF/AVG stenosis requiring an angioplasty. While

individually these are small changes in patient parameters, they can be useful for creation of comprehensive AVF/AVG stenosis prediction models. Nonetheless, further analyses are needed to confirm these observations and assess their usefulness.

Funding: Commercial Support - Fresenius Medical Care North America

TH-PO772

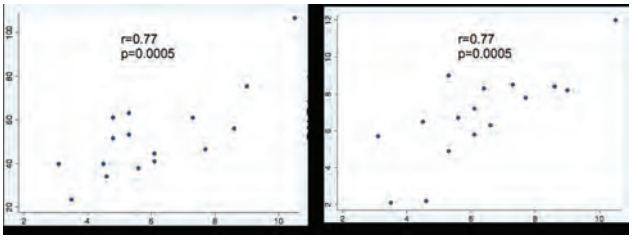
Arterial Diameter Following AVF Creation May Predict Aneurysmal Formation Alexis M. Cahalane, Vivek G. Sahani, Zubin Irani, Jie Cui. *Massachusetts General Hospital, Boston, MA.*

Background: Aneurysmal formation in arteriovenous fistulae (AVF), which is the preferred vascular access for hemodialysis in end-stage renal disease, can lead to insufficient hemodialysis, risk of rupture and access abandonment.

Methods: This retrospective chart review study looked at patients with AVF aneurysmal dilatation requiring surgical correction between 01/01/2014 and 07/30/2016. All fistulogram images were reviewed and the diameter of the feeding artery, venous outflow, maximum aneurysmal segment (AnS), and length of AnS were measured. Location of any stenotic lesions were also recorded.

Results: 10 female and 17 male patients were identified. 21 patients (77.78%) had brachiocephalic fistula and 6 had radiocephalic fistula (22.22%). Mean interval between surgical creation of the AVF and access revision was 1411± 955days. On the first fistulogram, there was a significant correlation between diameter of feeding artery and diameter of fistula (r=0.51, p=0.02), the maximum diameter of the aneurysm (r=0.67, p=0.03) and the length of the AnS (r=0.92, p=0.0001). The most common venous outflow lesion was cephalic arch stenosis (64.7%), while 7 patients had no outflow stenosis. Interval between first recorded fistulogram and surgical revision was 818 days. On the presurigical fistulagram the diameter of the artery was strongly correlated with the diameter of the artery in the first fistulogram (Figure 1A, p<0.05). Furthermore, the length of the AnS on the last fistulogram also correlated with the diameter of the artery in the first fistulogram (Figure 1B).

Conclusions: Aneurysm formation is a long-term complication of AVF. In AVF created using the cephalic vein, cephalic arch stenosis was the most common stenotic lesion. The diameter of the feeding artery at time of the first fistulogram can predict the likelihood of aneurysm formation and its calibre. AVF with relative larger arterial diameter should be closely monitored for aneurysm formation and early intervention may avoid loss of the access.



TH-PO773

Vein Grafting – A Novel Approach for Forearm Dialysis Arteriovenous Fistula Creation Jian Chen, Jie Tang. *University Medicine, Brown University, Providence, RI.*

Background: With the growing need for reliable and durable forearm hemodialysis access, here we describe a novel "autologous vein grafting" technique for the creation of forearm arteriovenous fistula (AVF).

Methods: All study participants failed to have native distal cephalic or basilic veins large enough for forearm AVF creation. Therefore, we harvested a segment of contralateral forearm mid-basilic vein or leg great saphenous vein from the same patient, and performed an end-to-side anastomosis to the radial artery and an end-to-end anastomosis to the mid-cephalic or basilic vein to create a forearm AVF. We identified patients who underwent this procedure between January 2014 and January 2016, and report measurements of fistula diameter (at 1 cm from the arterial anastomosis) and doppler flow at 6 weeks and 3 months after surgery, as well as 1-year primary unassisted patency, cumulative patency, and complications.

Results: We identified a total of 7 study participants. 6 underwent surgeries for radiobasilic AVF and 1 for radiocephalic AVF. Among the 6 who had radiobasilic AVF, 5 used contralateral forearm basilic vein segments, 1 used great saphenous vein segment. The one with the radiocephalic AVF used great saphenous vein. The diameters of their native forearm distal cephalic or basilic veins were <1.5mm, and the mean diameter of harvested vein graft segments was 2.4 mm (range 2.1-3.9 mm). 6 weeks after surgery, the mean diameter of AVF was 5.1 mm (range 4.6-5.3 mm), the mean fistula flow was 684 ml/min (range 521-772 ml/min). 3 months after surgery, the mean diameter of AVF was 5.2 mm (range 4.8-5.5 mm), the mean fistula flow was 756 ml/min (range 627-820 ml/min). The 1-year primary unassisted patency was 86%, and cumulative patency was 100%. There have been no complications reported.

Conclusions: Autologous vein grafting appeared to be an effective way to create a forearm AVF.

Funding: Clinical Revenue Support

Vascular Characteristics of Study Participants

Age	Gender	AVF	Graft	Graft Length	Radial Artery Diameter	Graft Diameter	Native Distal Vein Diameter	6-week AVF Diameter	6-week AVF Flow	3-month AVF Diameter	3-month AVF Flow	Complications & Patency
65	Male	Radiobasilic	Contralateral basilic vein	5.5 cm	2.2 mm	2.2 mm	<1.5 mm	5.2 mm	760 ml/min	5.5 mm	820 ml/min	Thrombosis at 4 months*, patent at 12 months
58	Male	Radiobasilic	Contralateral basilic vein	6.0 cm	1.8 mm	2.1 mm	<1.5 mm	5.0 mm	710 ml/min	5.0 mm	730 ml/min	Patent at 12 months
68	Male	Radiobasilic	Contralateral basilic vein	7.0 cm	1.8 mm	2.1 mm	<1.5 mm	4.6 mm	521 ml/min	4.8 mm	627 ml/min	Patent at 12 months
53	Male	Radiobasilic	Contralateral basilic vein	5.2 cm	2.3 mm	2.2 mm	<1.5 mm	5.2 mm	628 ml/min	5.4 mm	783 ml/min	Patent at 12 months
36	Male	Radiobasilic	Contralateral basilic vein	6.6 cm	2.1 mm	2.2 mm	<1.5 mm	5.2 mm	651 ml/min	5.3 mm	784 ml/min	Patent at 12 months
52	Male	Radiobasilic	Great saphenous vein	22 cm	1.8 mm	2.3 mm	<1.5 mm	5.3 mm	748 ml/min	5.3 mm	768 ml/min	Patent at 12 months
67	Male	Radiocephalic	Great saphenous vein	25 cm	2.1 mm	3.9 mm	<1.5 mm	5.0 mm	772 ml/min	5.0 mm	782 ml/min	Patent at 12 months

* status post angioplasty

TH-PO774

Racial and Gender Disparities in Initial Hemodialysis Access among Medicare Beneficiaries Silvi Shah, Anthony C. Leonard, Charuhas V. Thakar. *University of Cincinnati, Cincinnati, OH.*

Background: Arteriovenous (AV) access confers survival and economic benefits over catheters in incident hemodialysis (HD) patients. However, after considering the influence of pre-dialysis health status (defined as nephrology care and acute care hospitalizations), the effects of race and gender in the utilization of HD access is not known.

Methods: We evaluated 47,602 adult incident HD patients (1/1/2008 to 12/31/2008) from the United States Renal Data System (USRDS) with linked Medicare data for at least 2 years prior to HD initiation. Information on pre-dialysis health status was obtained from form 2728 and linked Medicare claims. Using case-mix adjusted logistic regression models; we examined the effects of race and gender on type of vascular access (arteriovenous [AV] access vs. catheter) at HD initiation.

Results: The majority of patients were male (55%) and White (62%). Catheter was the dominant access method used to initiate HD (82% vs. 18% AV access). A higher rate of Blacks (19%) and Asians (19%) initiated HD with AV access than did Whites (17%), Native Americans (16%) or Hispanics (15%) (unadjusted p<0.001). Pre-dialysis nephrology care was received by 58% of patients; and was associated with higher rate of AV access for initial HD than those without pre-dialysis nephrology care (27% vs. 4%, p<0.001). Acute hospitalization during the 2 years prior to HD initiation occurred in 89% of patients; and was associated with lower rate of AV access than those without pre-dialysis acute hospitalization (15% vs. 40%, p<0.001). In adjusted analyses, Blacks were more likely than Whites (odds ratio [OR], 1.10; 95% confidence interval [CI], 1.03-1.17) and Hispanics were less likely than Whites (OR, 0.82; CI, 0.74-0.90) to initiate HD with AV access. Similarly, females were less likely to initiate HD with AV access than were males (OR, 0.83; CI, 0.72-0.87).

Conclusions: Among Medicare beneficiaries', Blacks are more likely than Whites to use AV access for first outpatient HD; whereas Hispanics are less likely than Whites and females are less likely than males to initiate HD with AV access. These differences across race and gender are independent of pre-dialysis health status, among other factors. Further investigation of biological and process of care factors is warranted to reduce these disparities.

TH-PO775

Effects of Denosumab in Osteoporotic Hemodialysis (HD) Patients with Secondary Hyperparathyroidism (SHPT) Satoshi Funakoshi,[2] Naoto Taguchi,[2] Jyunichiro Hashiguchi,[2] Makiko Yamashita,[2] Tayo Kawazu,[2] Osamu Sasaki,[2] Hiroshi Ichinose,[2] Kenji Sawase,[2] Yoko Obata,[1] Tomoya Nishino,[1] Takashi Harada.[2] *[1]Nagasaki University School of Medicine, Nagasaki, Japan; [2]Nagasaki Kidney Center, Nagasaski, Japan.*

Background: Denosumab, a human monoclonal antibody which binds to RANKL, inhibits osteoclast differentiation/activation and exerts primarily anti-resorptive action. Denosumab also inhibits bone formation and hence may correct high bone turnover observed in HD patients. Meanwhile serum markers for bone metabolism are reported to correlate with PTH but not with circulating fibroblast growth factor 23 (FGF23), which decreases bone mineralization and is markedly increased in HD patients.

Methods: Among HD patients with secondary hyperparathyroidism (SHPT) who received intravenous pulse therapy with vitamin D (VD) analogues, those with bone mineral density < 70% YAM were enrolled in this study after their informed consent was obtained. Serum calcium, phosphate, PTH, bone metabolism markers and FGF23 were measured before and 4 weeks after subcutaneous administration of 60mg of denosumab.

Results: A steep decline in serum calcium levels was observed in all 16 subjects (5 males and 11 females; mean age, 66.7±7.4 years old; mean HD duration, 11.4±7.6 years), and calcium-based phosphate binders and VD analogues were started to adjust their calcium levels. After 4 weeks of denosumab administration, significant decreases were seen in the bone resorption markers TRCP-5B and NTX, and the bone formation markers BAP and P1NP as well as in PTH; furthermore, FGF23 was significantly decreased (table).

Conclusions: Study results suggest that denosumab may potentially correct bone turnover in osteoporotic HD patients with SHPT. A possible explanations for decreased FGF 23 could be that the addition of calcium-based phosphate binders lowered the phosphate burden in HD patients and that VD signaling resulted in a negative feedback loop within FGF family.

Funding: Private Foundation Support

Change of Serum Bone Metabolism Markers and FGF 23 after Denosumab Administration

	baseline (mean±SD)	week 4 (mean±SD)	p-value
calcium (mg/dL)	9.4±0.5	8.3±1.4	p<0.001
phosphorus (mg/dL)	5.6±0.7	4.1±1.3	p<0.001
i PTH (pg/mL)	118.6±87.1	375.6±332.6	p<0.001
TRACP-5b (mU/dL)	672.6±306.2	132.5±68.6	p<0.001
NTX (nM BCE/L)	171.0±96.0	20.7±4.0	p<0.001
BAP (μ g/L)	16.6±6.4	14.4±6.7	0.007
PINP (ng/mL)	333.0±168.0	205.3±125.3	0.002
FGF 23 (pg/mL)	12954.6±16395.0	7646.4±14726.0	0.029

TH-PO776

Hemodialysis (HD) Treatment Can Improve Taste Sensitivity to Salt – Assessment by the Filter Paper Disc (FPD) Method Satoshi Funakoshi,[1] Kenta Torigoe,[2] Miki Torigoe,[2] Asami Nakamura,[1] Makiko Yamashita,[1] Osamu Sasaki,[1] Hiroshi Ichinose,[1] Kenji Sawase,[1] Takashi Harada,[1] Yoko Obata,[2] Tomoya Nishino,[2] Jyunichiro Hashiguchi.[1] *[1]Nagasaki Kidney Center, Nagasaki, Japan; [2]Nagasaki University Hospital, Nagasaki, Japan.*

Background: Several studies in chronic uremic and HD patients indicate decreased taste sensitivity. However, whether a single HD session can improve their sensitivity or not warrants investigation. The aim of this study was to determine if the taste sensitivity to salt is affected by HD treatment in maintenance HD patients by using FPD method, a reliable method to measure taste with a high degree of reproducibility.

Methods: All subjects were assessed for their taste sensitivity to salt by the FPD method before and after HD sessions. Filter paper discs prepared with different concentrations of sodium chloride from 0.6 mg/cm^2 (level 1) to1.6 mg/cm^2 (level 6) for scoring, and the lowest level at which taste was identified was defined as the taste threshold to salt. Relevant clinical parameters were determined in each patient, and the correlation to the taste sensitivity was analyzed.

Results: At our Facility, 122 HD patients (mean age, 66.5±28.2 years old; mean HD duration, 12.0±9.5 years) were assessed for taste sensitivity by FPD method. According to the taste threshold subjects were diagnosed as normal (score <2), moderately impaired (score 3-4) and severely impaired (score >5). As shown in table, a significant decrease in taste threshold to salt was observed in the moderately - severely impaired group, but not in the group with normal taste sensitivity to salt. There was no correlation between altered taste sensitivity and various parameters including age, gender, HD vintage, serum zinc and prescribed medications.

Conclusions: Our findings suggest that HD treatment favorably affects tasting function by improving uremia. It remains to be seen whether taste sensitivity is correlated with various clinical factors in HD patients.

Funding: Private Foundation Support

Average Taste Threshold to Salt Before and After HD (mg/cm2)

	before HD (mean ±SD)	after HD (mean ±SD)	p-value
normal group (n=63)	0.68±0.08	0.74±0.11	0.09
moderately impaired group (n=11)	1.11±0.22	0.87±0.19	0.019
severely impaired group (n=48)	1.73±0.27	1.50±0.18	0.0003

TH-PO777

Factors Associated with Gastrointestinal Bleeding in ESRD Patients Tommy C. Blanchard, Teresa A. Nash-Hampton, Ashish Goulatia, Jay Ray, Len A. Usvyat, Dugan Maddux, Franklin W. Maddux. *Fresenius Medical Care North America, Waltham, MA.*

Background: Gastrointestinal (GI) bleeding is a serious problem among patients with End Stage Renal Disease (ESRD), affecting this population at rates almost two orders of magnitude higher than in the general population (Yang et al., 2012). We aimed to characterize the demographic, treatment, and laboratory parameters in dialysis patients with GI bleeds and build prediction models that could identify patients at a higher risk of experiencing a GI bleed.

Methods: We analyzed data on all dialysis patients treated at Fresenius Medical Care North America dialysis clinics as of December 2016. We used a logistic regression with 40 variables including demographics, comorbidities, treatment parameters and laboratories to identify factors highly associated with GI bleeds and measured the effect size. Variables on treatment and laboratory parameters were determined from mean values at 90 to 183 days prior to December 2016.

Results: We studied data from 141,973 dialysis patients, of which 0.7% were diagnosed with a GI bleed. We found that lower hemoglobin, calcium, and transferrin saturation (TSAT) values were associated with GI bleeds. Variability in calcium and hemoglobin (using standard deviation) was also associated with GI bleeds. Further, GI bleeds were more common among those diagnosed with ulcers and with older patients. When tested on a held-out set of 50% of the data, the model was able to accurately predict which patients have a GI bleed with a receiver operating characteristic area under the curve of 0.81.

Conclusions: Our analysis identifies several factors associated with GI bleeds in dialysis patients, which may be useful for predicting patients who are likely to experience a GI bleed. Further research validating the accuracy of the prediction of patients with GI bleed is needed to confirm these findings.

Funding: Commercial Support - Fresenius Medical Care North America

Parameter	Odds Ratio	p-value
Calcium (mg/dL)	0.87	0.034
Calcium variance	1.64	0.001
Hemoglobin (g/dL)	0.75	< 0.001
Hemoglobin variance	2.98	< 0.001
Tsat (%)	0.98	< 0.001
Demographic Values	**Odds Ratio**	**p-value**
Age (years)	1.02	< 0.001
Comorbidities (ulcers)	**Odds Ratio**	**p-value**
Duodenal	127.6	< 0.001
Esophagus	219.4	< 0.001
Gastric	145.2	< 0.001
Gastrojejunal	239.3	< 0.001
Peptic	30.0	< 0.001

TH-PO778

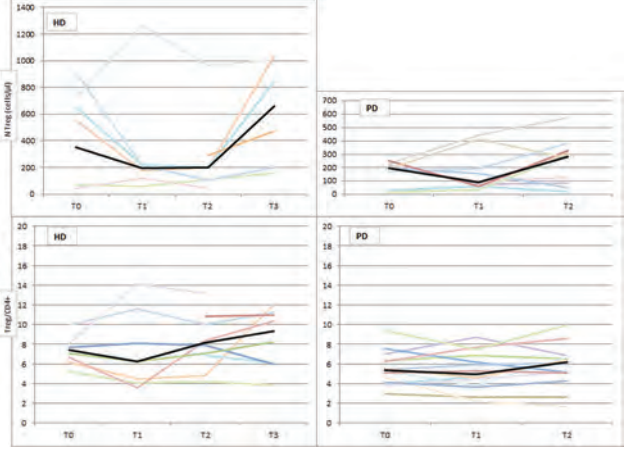
T Regulatory Cells in Uremia: Effect of the First Dialysis Session Carlotta Caprara,[2] Elisa Scalzotto,[2] Anna chiara Frigo,[3] Francesca Paderi,[2] Fiorenza Ferrari,[2] Valentina Corradi,[1,2] Claudio Ronco.[1,2] *[1]Hospital, San Bortolo Vicenza, Vicenza, Italy; [2]IRRIV, Vicenza----, Italy; [3]University of Padova, Padova, Italy.*

Background: In the literature, contrasting results have been reported about the influence of dialysis on Treg cells in chronic kidney disease stage G5 patients (CKD G5) that show activated but impaired immune system. Moreover the influence of dialysis on T cells needs further investigation.

Methods: A total of 22 CKD G5 patients that have to start dialysis (8 HD and 14 PD) were enrolled. Treg were studied by flow cytometry with: CD3(PerCP); CD4(FITC); CD25(PECy7); CD127(PE) and FOXP3(APC) antibodies. Time point: T0 (before the first dialysis treatment) for HD and PD; T1 (after the first dialysis); T2 (after 48 hours) and T3 (after 1 month) for HD; T1 (after 48 hours) and T2 (after 1 month) for PD.

Results: Medians for Treg/CD4+ ratio (%) in HD pts are: 7.405 (5.220; 18.940)(T0); 6.26 (3.55; 14.12)(T1), 8.140 (4.190; 17.210)(T2); 9.305 (3.840; 12.050)(T3); in PD are: 5.36 (2.96; 9.37)(T0); 4.98 (2.22; 8.69)(T1); 6.17 (1.65; 9.97)(T2). The ratio Treg/CD4 didn't change during time of the study (HD: p= 0.6310; PD: p= 0.4191). While, as showed in Fig.1, we observed a trend in increase Treg number, more evident in HD, between T0 and after 1 month of treatment. Medians for Treg absolute number (cells/μl) in HD are: 349.895 (42.910; 912.240)(T0); 194.595 (57.150; 1266.850)(T1); 199.905 (43.700; 961.160)(T2); 659.60 (160.04; 1039.86)(T3); in PD are: 194.970 (16.420; 250.880)(T0); 90.535 (34.530; 444.640)(T1); 281.63 (19.75; 575.51)(T2). This difference didn't reach significativity (HD: p= 0.16; PD: p=0.3995).

Conclusions: For the first time the same patient was analyzed during time before and after the first dialysis treatment. It seems that heamodialysis treatment improve T cells status, increasing Treg absolute number, while it does not interfere with Treg/CD4 ratio. Due to extreme variability of Treg values and poor number of patients we need further analysis.



TH-PO779

Outcomes in ESRD Patients on Hemodialysis Taking Patiromer for Hyperkalemia Dinesh K. Chatoth,[1] Peter M. Wahl,[2] Viatcheslav Rakov,[3] Carly R. Van Zandt,[4] Kathryn P. Anastassopoulos,[2] Sam Colman,[2] Tyler Knight,[2] Nina Oestreicher,[5,6] Ann Mooney,[4] David M. Spiegel,[5] Matthew R. Weir.[7]
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Background: Real-world data on hyperkalemia (HK) treatment with patiromer in dialysis patients in the United States (US) are limited. We sought to examine outcomes of end-stage renal disease (ESRD) patients on hemodialysis (HD) and treated with patiromer for HK at US Fresenius Kidney Care (FKC) centers.

Methods: We identified adult patients who initiated patiromer between 10/1/2015 and 7/31/2016; were prescribed permanent in-center HD ≥3 times per week; and had ≥1 serum potassium (sK) lab value in the 91 days prior to patiromer initiation (baseline). We examined changes from baseline in sK values and potassium (1K) baths over 6 months.

Results: Among 268 patients included in the analysis, mean age was 57.5 years, 55.2% male, and 77.2% white, with a mean of 4.9 years on dialysis. Median patiromer daily dose was 8.4 g/day. Overall, sK decreased by 0.5 mEq/L (decrease of 0.8 and 1.7 among those with baseline sK >5.5 and sK >6.5, respectively) (Table 1). Unobserved events may have prompted treatment in patients with baseline sK <5.5 mEq/L. The percentage of patients treated with 1K baths decreased by 2.2%.

Conclusions: These results demonstrate that treatment with patiromer lowers sK levels in real-world settings, with the greatest effect among patients with sK >6.5 mEq/L. The predominant use of the recommended starting dose (8.4 g/day) supports the feasibility of this dose for long-term (≥6 months) sK control.

Funding: Commercial Support - Vifor Pharma

Table 1. Change in Serum Potassium Over 6 Months Following Patiromer Initiation

Baseline sK (mEq/L)	Baseline	Follow-Up Period After Patiromer Initiation								
		Week 1	Week 2	Week 3	Week 4	Month 2	Month 3	Month 4	Month 5	Month 6
Overall (N=268)										
n (%)	268 (100.0)	181 (67.5)	187 (69.8)	191 (71.3)	187 (69.8)	240 (89.6)	211 (78.7)	181 (67.5)	172 (64.2)	156 (58.2)
Mean (SD)	5.8 (0.81)	5.5 (0.64)	5.5 (0.65)	5.5 (0.74)	5.4 (0.74)	5.4 (0.70)	5.4 (0.70)	5.3 (0.72)	5.3 (0.65)	5.3 (0.69)
Mean Δ (SD)	-	-0.3 (0.81)	-0.3 (0.89)	-0.3 (0.92)	-0.4 (0.98)	-0.4 (0.94)	-0.4 (0.88)	-0.4 (0.97)	-0.5 (0.95)	-0.5 (0.96)
≤5.5 mEq/L (N=89)										
n (%)	89 (100.0)	63 (70.8)	65 (73.0)	69 (77.5)	69 (77.5)	81 (91.0)	75 (84.3)	70 (78.7)	65 (73.0)	60 (67.4)
Mean (SD)	4.9 (0.47)	5.1 (0.52)	5.3 (0.61)	5.3 (0.75)	5.3 (0.71)	5.3 (0.64)	5.2 (0.61)	5.2 (0.64)	5.2 (0.69)	5.1 (0.75)
Mean Δ (SD)	-	0.2 (0.60)	0.3 (0.68)	0.3 (0.76)	0.3 (0.79)	0.3 (0.78)	0.2 (0.71)	0.2 (0.73)	0.2 (0.77)	0.1 (0.86)
>5.5 mEq/L (N=179)										
n (%)	179 (100.0)	118 (65.9)	122 (68.2)	122 (68.2)	118 (65.9)	159 (88.8)	136 (76.0)	111 (62.0)	107 (59.8)	96 (53.6)
Mean (SD)	6.2 (0.56)	5.7 (0.60)	5.6 (0.64)	5.6 (0.72)	5.5 (0.74)	5.5 (0.72)	5.5 (0.72)	5.4 (0.76)	5.4 (0.62)	5.4 (0.63)
Mean Δ (SD)	-	-0.6 (0.77)	-0.7 (0.82)	-0.7 (0.82)	-0.7 (0.87)	-0.7 (0.83)	-0.7 (0.80)	-0.9 (0.86)	-0.9 (0.80)	-0.8 (0.83)
>6.5 mEq/L (N=39)										
n (%)	39 (100.0)	34 (87.2)	26 (66.7)	27 (69.2)	25 (64.1)	35 (89.7)	31 (79.5)	30 (76.9)	28 (71.8)	23 (59.0)
Mean (SD)	7.1 (0.55)	5.8 (0.65)	5.7 (0.70)	5.9 (0.67)	5.7 (0.80)	5.8 (0.84)	5.7 (0.84)	5.7 (0.79)	5.6 (0.70)	5.4 (0.73)
Mean Δ (SD)	-	-1.3 (0.70)	-1.5 (0.88)	-1.2 (0.76)	-1.4 (0.88)	-1.2 (0.99)	-1.3 (0.92)	-1.3 (0.86)	-1.4 (0.99)	-1.7 (0.84)

Abbreviations: Δ, change; SD, standard deviation; sK, serum potassium.

TH-PO780

Patient Characteristics and Correlates of Patiromer Initiation for Hyperkalemia in Hemodialysis Christopher G. Rowan,[1] Wolfgang C. Winkelmayer,[2] Nina Oestreicher,[3,4] Viatcheslav Rakov,[5] Jeffrey J. Connaire,[6] David M. Spiegel,[3] Csaba P. Kovesdy.[7]
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Background: Patiromer is a novel potassium-binding polymer for treatment of chronic hyperkalemia. We retrospectively compared U.S. hemodialysis (HD) patients (pts) who initiated patiromer *vs* sodium polystyrene sulfate (SPS) in typical practice.

Methods: We identified new users of patiromer or SPS between 12/2015-12/2016 from a large U.S. dialysis provider. Baseline characteristics were obtained in the year prior to the 1st patiromer or SPS order. We identified correlates of patiromer *vs* SPS using multivariable logistic regression.

Results: Pts initiating patiromer *vs* SPS were less likely to be black, more likely to use a dialysate K^+<2 mEq/L; had higher serum K^+, and more electrolyte-related hospitalizations (Table). Having ≥3 serum K^+ tests ≥5.0 was associated with 5x the odds of initiating patiromer *vs* SPS (Figure).

Conclusions: Multiple hyperkalemia episodes and a recent SPS order were associated with patiromer initiation. Patiromer may be used predominantly in HD pts with more severe hyperkalemia who failed SPS. Studies are needed to determine the clinical impact of patiromer.

Funding: Commercial Support - Relypsa, Inc., a Vifor Pharma Company

Table. Baseline Characteristics

Baseline Characteristics	Patiromer (N=527)	SPS (N=852)	Baseline Characteristics	Patiromer (N=527)	SPS (N=852)
Age: Mean (SD)	59 (14)	61 (14)	SPS order 91 days b/f index date	10.80%	5.30%
Female	43.1%	47.1%	Insulin order 1 year b/f index date	23.90%	30.00%
Race: Black	17.1%	29.9%	K+ mEq/L: Mean (SD)	5.8 (0.7)	5.4 (1.0)
Primary Payer: Medicare	79.5%	80.0%	# K+ tests ≥5.0 mEq/L: 91 days b/f index date	8.4 (4.1)	4.8 (4.3)
Dialysis Vintage (years): Mean (SD)	5.7 (4)	5.4 (4.4)	Kt/V: Mean (SD)	1.6 (0.3)	1.6 (0.3)
# HD treatments 91 days b/f index date	37.8 (3.6)	37.2 (4.2)	nPCR: Mean (SD)	1.2 (0.3)	1.1 (0.3)
K+ dialysate <2 mEq/L	32.3%	19.2%	Hospitalization: 1 year b/f index date	60.30%	67.70%
Peripheral Vascular Disease	10.2%	4.8%	Electrolyte Related Hospitalization	14.40%	8.50%

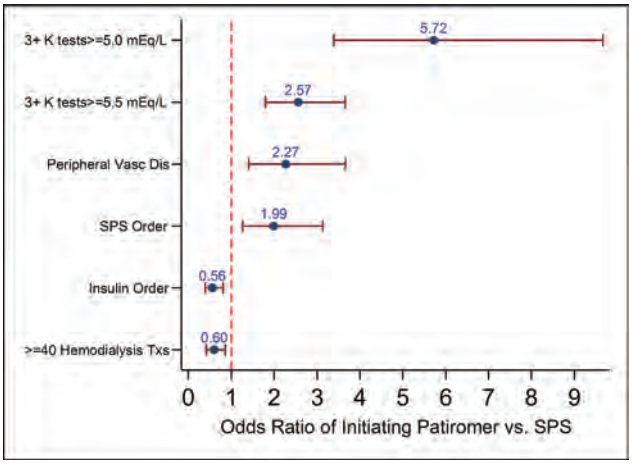


Figure. BaselineCorrelates of Patiromer Initiation

TH-PO781

Association of Continuation of Loop Diuretics at Hemodialysis Initiation with Clinical Outcomes Steven M. Brunelli,[1] Scott Sibbel,[1] Adam G. Walker,[1] Carey Colson,[1] Francesca Tentori,[1] Jennifer E. Flythe.[2]
[1]DaVita Clinical Research, Minneapolis, MN; [2]University of North Carolina Kidney Center, Chapel Hill, NC.

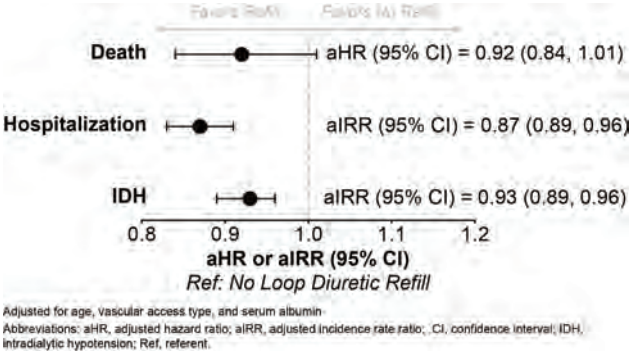
Background: Loop diuretics are commonly utilized in the management of non-dialysis dependent chronic kidney disease. Despite potential benefits of augmented urine output, loop diuretics are often discontinued after hemodialysis initiation. In the present study, we assessed the association of the early decision to continue vs discontinue loop diuretics at dialysis start with clinical outcomes during the first year of dialysis.

Methods: This analysis considered all patients who initiated in-center hemodialysis at a large dialysis organization (2007-2013) with Medicare part A & D benefits who had an active supply of loop diuretic at the time of dialysis initiation (N = 11,297). Exposure status was based on whether loop diuretic prescription was refilled after dialysis initiation and within 30 days of exhaustion of prior supply. Patients were followed under an intention-to-treat paradigm for up to 12 months for death, hospitalization, and intradialytic hypotension (IDH).

Results: We identified 5219 patients who refilled a loop diuretic prescription and 6078 eligible controls who did not. After adjustments for case mix and clinical differences, continuation of loop diuretics (vs not) was associated with lower hospitalization (P < 0.001) and IDH (P < 0.001) rates, and a lower death rate which did not achieve statistical significance (P =0.07).

Conclusions: Among incident hemodialysis patients, continuation of loop diuretics in the immediate post-transition period was associated with lower rates of hospitalization and IDH over the first year of dialysis. The practice of discontinuing loop diuretics should be re-evaluated.

Funding: Commercial Support - DaVita, Inc



Adjusted for age, vascular access type, and serum albumin

Abbreviations: aHR, adjusted hazard ratio; aIRR, adjusted incidence rate ratio; CI, confidence interval; IDH, intradialytic hypotension; Ref, referent.

TH-PO782

The Influence of Frailty and Body Composition on Risk of Mortality in Incident Hemodialysis Patients Jessica Fitzpatrick,[1] Stephen M. Sozio,[2] Bernard G. Jaar,[2] Michelle M. Estrella,[3] Jose M. Monroy-Trujillo,[2] Dorry L. Segev,[2] Rulan S. Parekh,[1] Mara McAdams-DeMarco.[2] *[1]University of Toronto, Toronto, ON, Canada; [2]Johns Hopkins University, Baltimore, MD; [3]UCSF/San Francisco VA Medical Center, San Francisco, CA.*

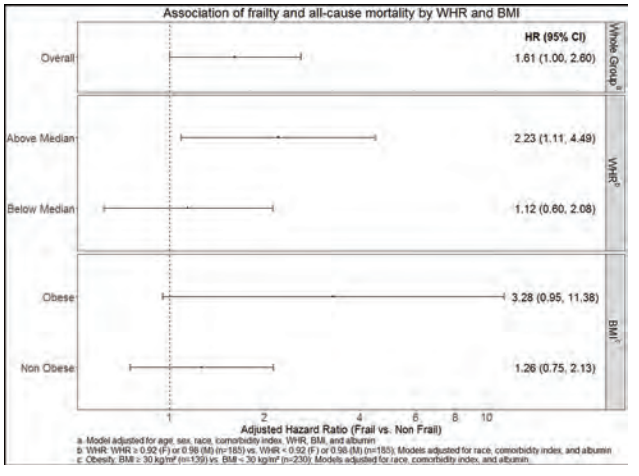
Background: Increased body mass index (BMI) is associated with lower risk of mortality in end stage renal disease (ESRD). Frailty is a phenotype of decreased physiologic reserve common among hemodialysis (HD) patients and associated with sarcopenia in this population. We sought to understand the role of body composition on mortality among frail and non-frail incident HD patients.

Methods: This study included 370 incident HD patients enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in ESRD (PACE) Study. Frailty was defined as presence of ≥ 3 of the following: shrinkage, weakness, reduced gait speed, exhaustion, and low physical activity. General and abdominal adiposity were assessed with BMI and waist-to-hip ratio (WHR), respectively. Proportional hazards regression was used to estimate the association of frailty and WHR with all-cause mortality.

Results: The mean age was 55 years, 42% were female, 73% were African American, 57% had diabetes, the mean comorbidity index was 5.2, and 52% were frail. BMI, but not WHR, was higher (P<0.05) among frail vs. non-frail participants. There were 81 deaths over a mean of 2.5 years of follow-up. Frailty, but not WHR, was associated with higher mortality risk. There was no evidence of an interaction between frailty and BMI (P=0.33) or WHR (P=0.88). There was, however, a trend for stronger association between frailty and mortality among those above the median WHR.[Figure]

Conclusions: Frailty was associated with higher risk of mortality independently of WHR and BMI. These results suggest that general and central adiposity do not mitigate the influence of frailty on mortality among HD patients.

Funding: NIDDK Support



a. Model adjusted for age, sex, race, comorbidity index, WHR, BMI, and albumin
b. WHR: WHR ≥ 0.92 (F) or 0.98 (M) (n=165) vs. WHR < 0.92 (F) or 0.98 (M) (n=185); Models adjusted for race, comorbidity index, and albumin
c. Obesity: BMI ≥ 30 kg/m² (n=139) vs. BMI < 30 kg/m² (n=230); Models adjusted for race, comorbidity index, and albumin

TH-PO783

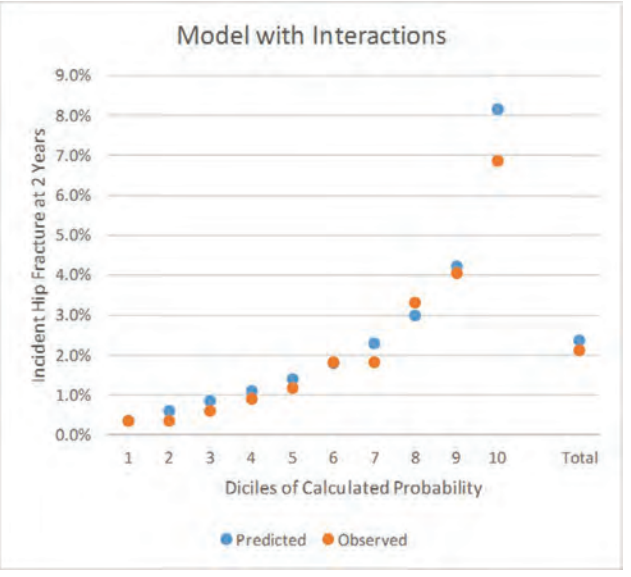
FRAX-HD: A Two-Year Incident Hip Fracture Risk Assessment Tool for Japanese Hemodialysis Patients Naohiko Fujii,[2] Takayuki Hamano,[3] Ikuto Masakane.[1] *[1]Honcho-Yabuki Clinic, Yamagata, Japan; [2]Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Japan; [3]Osaka University Graduate School of Medicine, Suita, Japan. Group/Team: Committee of Japanese Renal Data Registry, Japanese Society for Dialysis Therapy.*

Background: Dialysis patients are at 5-to-6-fold higher risk of hip fracture than general population. FRAX® is a useful tool for assessing future fracture risk; however, it is not optimized for hemodialysis (HD) patients. Our aim was to create a 2-year risk assessment tool for hip fracture among Japanese HD patients (FRAX_HD).

Methods: We extracted patients on facility-based HD, aged 20-100, with ≥1 yr of vintage at the end of 2007 using the Japanese nation-wide dialysis registry (JRDR-08102). Hip fractures were detected annually up to 2 years by questionnaire. We excluded patients who later received cinacalcet during the follow-up period, and randomly-selected 60%, 20%, and 20% of the eligible subjects to generate TRAIN, VALIDATE, and TEST sets, respectively. Multivariable Poisson regression analyses with interaction terms were performed to create prediction models, and validation was done later.

Results: TRAIN, VALIDATE, and TEST sets included 73999, 24667, and 24665 patients and 1574, 525, and 524 hip fractures, respectively. The subjects, aged 65.2 ± 12.3, included 39% of female and 34% of diabetes, with median vintage of 5.6 yrs. In TRAIN set, there were significant interactions between sex and age, sex and prior PTX/PEIT, and diabetes and vintage. Incidence rate ratio (IRR) elevated with age more prominently in female than in male (IRR 5.62 [95%CI: 3.32, 7.91]; females aged ≥80 vs. males aged <50). Prior history of PTX/PEIT was associated with lower risk only in female (IRR 0.58 [0.36, 0.81]). The model including these interactions demonstrated best performance and was selected as final model, which also achieved similar results in TEST set (AUC 0.739).

Conclusions: We successfully generated a 2-year risk assessment tool for hip fracture among HD patients. Further refinement and sensitivity analyses are required before its clinical application.



TH-PO784

Fracture Rates and Post-Discharge Outcomes Among Patients Undergoing Hemodialysis Across Etiologies of Kidney Diseases Berenice Y. Gitomer,[1] Lorien S. Dalrymple,[5] Zhiying You,[8] Norma J. Ofsthun,[6] Franklin W. Maddux,[4] Tamara Isakova,[3] Isidro B. Salusky,[7] Myles S. Wolf,[2] Michel Chonchol.[9] *[1]Div. Renal Diseases and Hypertension, Aurora, CO; [2]Duke University, Durham, NC; [3]Feinberg School of Medicine, Northwestern University, Chicago, IL; [4]Fresenius Medical Care, Waltham, MA; [5]Fresenius Medical Care NA, Waltham, MA; [6]Fresenius Medical Care North America, Waltham, MA; [7]Mattel Children's Hospital, Los Angeles, CA; [8]UC Denver, Aurora, CO; [9]University of Colorado, Aurora, CO.*

Background: We have previously identified a low bone turnover state in patients with autosomal dominant polycystic kidney disease (ADPKD) and normal kidney function based on histomorphometric measurements. This is indicated by both decreased indices of bone formation and resorption measured in trabecular bone. However, the rates and risk of fracture have not been characterized in ADPKD patients compared to other etiologies of kidney disease among hemodialysis patients.

Methods: The cohort included incident in-center hemodialysis patients aged 18–100 years with kidney disease secondary to diabetes, hypertension, glomerulonephritis (GN) or ADPKD starting hemodialysis at Fresenius Medical Care Norh America 2000-2013. Cohort was followed through 2014 for the first fracture-related hospitalization and up to one additional year for post-fracture mortality. Fractures were identified using ICD-9-CM diagnosis codes. Fracture rates were calculated within strata of etiology of kidney disease. Among patients with complete data, one year mortality following hospital discharge was examined using Cox regression models.

Results: A total of 10,131 fracture-related hospitalizations were observed during follow-up. Age, gender, and race adjusted fracture rates per 1,000 person-years (PYs) varied across etiology of kidney disease: patients with ADPKD had the lowest rate (8.1, 95% CI 6.6-10.0) and patients with diabetes had the highest rate (12.3, 95% CI 11.4-13.4). Patients with hypertension and GN had fracture rates of 8.8 (95% CI 8.1-9.6) and 8.9 (95% 7.9-9.9), respectively. Patients with ADPKD had a significantly lower adjusted incident rate ratio (aIRR) of fractures compared with patients with diabetes [aIRR: 0.66 (053, 0.82); p=0.0002]. After adjustment for demographics, vintage, comorbidities, albumin and measures of mineral metabolism, the mortality in the first year post-discharge for a

fracture-related hospitalization was lower in patients with ADPKD compared to patients with diabetes (HR 0.65 95% CI 0.46-0.92; p=0.01).

Conclusions: The decrease in bone formation rate observed in patients with early ADPKD does not appear to increase the risk of fracture or portend a worse prognosis among those who survive hospitalization when compared to other etiologies of kidney disease.

Funding: NIDDK Support

TH-PO785

Changes in Serum Phosphorus, Pill Burden, and Medication Possession Ratio among Chronic Hemodialysis Patients Who Converted to Sucroferric Oxyhydroxide as Part of Routine Care

Kathryn S. Gray,[1] Linda H. Ficociello,[2] Abigail Hunt,[1] Claudy Mullon,[2] Steven M. Brunelli.[1] *[1]DaVita Clinical Research, Minneapolis, MN; [2]Fresenius Medical Care - North America, Waltham, MA.*

Background: The large pill burden associated with many phosphate binders (PB) may decrease adherence to PB therapy. The current analysis examines the changes in serum phosphorus, PB pills/day, and medication possession ratio (MPR; estimate of adherence) among patients who converted from a baseline PB to sucroferric oxyhydroxide (SO) as part of routine care.

Methods: Patients eligible for analysis were ≥18 years, received chronic hemodialysis at a large dialysis organization (LDO), and received benefits through the LDO's pharmacy program. Patients converting to SO use were those who had supply of another PB, received a first prescription fill for SO as part of routine care, and subsequently did not refill a non-SO PB. Baseline (BL) was considered as the 6-month period leading up to first SO fill and SO follow-up (SO-F) the 6-month period following the first SO fill. Patients were censored from the analysis upon loss to follow-up, dialysis modality change, discontinuation of SO, or fill of a prescription for another PB after SO initiation. MPR is the proportion of time that a patient had enough medicine to take as prescribed and was assessed among patients not enrolled in the LDO pharmacy automated refill management service.

Results: There were 490 patients who converted to SO. The majority of patients (66%) were using sevelamer at time of SO initiation, followed by calcium acetate (19%). There was an improvement in serum phosphorus (sP): mean (95% CI) sP was 6.9 mg/dL (6.8, 7.1) at BL and 6.8 mg/dL (6.6, 6.9) at SO-F (P=0.02). The percent of patients achieving sP ≤5.5 mg/dL increased from 21.7% at BL to 28.8% at SO-F (P<0.001). The mean total PB pill burden at BL was 10.8 pills/day and this decreased by 49% to 5.5 pills/day at SO-F (P<0.001). Among patients who were not using the LDO refill management service (n=30), mean total PB MPR was 0.68 at BL and 0.80 at SO-F.

Conclusions: In a cohort of hemodialysis patients prescribed SO through a renal pharmacy service as part of routine care, improvements in sP were observed along with a 49% decrease in prescribed PB pills/day and, among the subset of patients not using the LDO pharmacy refill management service, an increase in MPR from 0.68 to 0.80.

Funding: Commercial Support - Fresenius Medical Care

TH-PO786

Phosphate Removal in Maintenance Hemodialysis with Different Dialysis Modality and Different Dialyzer

Jing Luo,[1] Li Fang,[1] Hong Ye,[2] Junwei Yang.[2] *[1]Nanjing Medical University, Nanjing, China; [2]Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.*

Background: Hyperphosphatemia is one of the most common complications of maintenance hemodialysis (MHD) patients, and the association with an increased risk of mortality has been demonstrated. The normalization of phosphate plasma levels is therefore an important goal in the treatment of MHD patients. Accordingly, to assess phosphate removal by hemodialysis (HD) is important to improve phosphate control in patients on maintenance HD.

Methods: 48 MHD patients enrolled in this study underwent three period: one week HD with B3-1.6a (Toray, 1.6m^2, low-flux) (period 1), then one week HD with TS-1.6SL (Toray, 1.6m^2, high-flux) (period 2) and switched to another week hemodiafiltration (HDF) with TS-1.6SL (period 3). Each study period was separated by a washout of 2 weeks. Blood samples were collected at 0 min, 30 min, 60 min, 120 min, 180 min, 240 min after the start of dialysis and 60 min postdialysis. Effluent dialysate samples were collected every 15 min during the 4-hour HD treatment to measure the phosphate removal. Predialysis levels of serum phosphate, potassium, hematocrit, intact parathyroid hormone, alkaline phosphatase Echocardiogram, clinical and dialysis characteristics were obtained.

Results: The reduction of phosphate concentration of blood in dialysis process were 34.74%±6.01%, 48.10%±6.62%, 60.76%±6.98%, 63.81%±7.35%, 63.07%±7.93% at 30 min, 60 min, 120 min, 180 min, 240 min point respectively and returned to 52.41%±9.18% at 60 min postdialysis. There were statistical differences in the period 1, period 2 and period 3 at 30min point (29,79%±3.79%, 36.79%±6.82% and 36.64%±3.95%, P=0.000), 60min point (43.36%±4.94%, 49.86%±6.87% and 51.07%±5.44%, P=0.002), 120 min point (56.14%±6.36%, 62.86%±6.27% and 63.29%±6.28%, P=0.007). Total amount of phosphate removal within the 4-hour HD was mostly 25.54±5.77 mmol during per four-hour treatment. The first hour of treatment removed 39.85%±3.99% of the total mass, and 24.41%±1.67%, 18.34%±1.94%, 17.32%±3.00% at the second, the third and the forth hour respectively. However, no statistical differences were found in the three periods.

Conclusions: The maximum reduction of blood phosphate concentration was about 60% at 120 min point, and rised again postdialysis. The reduction of blood phosphate concentration was higher with HDF or with high-flux dialyzer.

Funding: Government Support - Non-U.S.

TH-PO787

FGF23 and Mortality in a Large Cohort of Prevalent Hemodialysis Patients: Results from the J-DOPPS

Hirotaka Komaba,[1] Douglas S. Fuller,[2] Masatomo Taniguchi,[3] Suguru Yamamoto,[4] Takanobu Nomura,[5] Brian Bieber,[2] Bruce M. Robinson,[2] Ronald L. Pisoni,[2] Masafumi Fukagawa.[1] *[1]Tokai University School of Medicine, Isehara, Japan; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]Kyushu University, Fukukoka, Japan; [4]Niigata University, Niigata, Japan; [5]Kyowa Hakko Kirin Co Ltd, Tokyo, Japan.*

Background: Elevated levels of fibroblast growth factor 23 (FGF23) have been associated with mortality in the pre-dialysis and incident hemodialysis population, but few studies have examined this relationship in a large cohort of maintenance hemodialysis patients. We analyzed the Japan Dialysis Outcomes and Practice Patterns Study (J-DOPPS) data to explore the association between FGF23 levels and all-cause mortality among maintenance hemodialysis patients.

Methods: We included 1,122 maintenance hemodialysis patients from the J-DOPPS phase 5 (2012-2015) who had FGF23 measurements. We evaluated the association between FGF23 levels and all-cause mortality using Cox regression adjusted for potential confounders.

Results: At study enrollment, the median FGF23 level was 2,113 (IQR, 583-6,880) pg/ml. These levels remained essentially unchanged among patients with repeated measurements. During 3-year follow-up, 154 of the 1,122 participants died. FGF23 was associated with younger age and fewer comorbidities. After adjustment for these plus dialysis vintage, albumin, and creatinine, FGF23 was positively associated with death (HR per unit increase in log-transformed FGF23, 1.17; 95% CI, 1.04-1.32). Although median FGF23 was higher in patients with longer dialysis vintage, the adjusted association between FGF23 and mortality was less pronounced as the duration of dialysis increased.

Conclusions: FGF23 was positively associated with mortality in chronic hemodialysis patients. However, this association was less pronounced in patients with longer dialysis vintage. These results suggest that long-term hemodialysis patients may be less susceptible to the toxic effects of FGF23, or correlated biological processes.

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TH-PO788

Phase 2 Open Label Single Arm Repeat Dose Study to Assess the Effect of SNF472 on Wound Healing in Uraemic Calciphylaxis Patients

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Background: SNF472, an intravenous (i.v.) formulation of myo-inositol hexaphosphate, is being developed for treating calciphylaxis (CUA) in patients with end-stage renal disease on hemodialysis (HD). It selectively inhibits the final common pathway in the etiology of vascular calcification, the formation and growth of hydroxyapatite crystals.

Methods: An open label, single arm trial investigating the effect of SNF472 on top of standard of care in the treatment of CUA in HD patients. Inclusion criteria was a new diagnosis of CUA or a recurrence of CUA after a period of at least 90 days without evidence of active CUA-related skin lesions. Patients are treated for 12 weeks with i.v. 6-9 mg/kg of SNF472 three times per week during each dialysis session. The endpoints are lesion score based on the Bates-Jensen Wound Assessment tool (BWAT; primary endpoint), pain assessed by Visual Analog Pain Scale (VAS) and a validated wound-associated quality of life (QoL) questionnaire. The BWAT and VAS are assessed every 2 weeks; wound-QoL is assessed at baseline, week 6 and week 12.

Results: The study has enrolled 12 patients with 9 completing the 12-week treatment, and 2 discontinued early due to death (not related to study drug) and 1 withdrew consent. Data from 9 completers shows a statistically significant reduction in BWAT score by week 10 which continued to week 12. Similarly, there was a statistically significant reduction in mean pain VAS score by week 8 and week 12. An increase in pain is noted one week after ending SNF472 treatment, strengthening the likelihood of a causal impact on pain. SNF472 has a statistically significant improvement on global wound-QoL, by week 12. Similarly, the 3 subscales of the global wound QoL scale all show improvements by week 12. There were 14 serious adverse events and 2 deaths, and none were related to SNF472 as per investigator.

Conclusions: These results suggest that SNF472 has a consistent benefit across multiple parameters and is well tolerated in patients with CUA. Thus, SNF472 has the potential to treat CUA, a rare and serious disease with a high mortality rate and no approved treatment.

Funding: Commercial Support - Laboratoris Sanifit

TH-PO789

Low Parathyroid Hormone Levels Predict Infection-Related Mortality in Incident Dialysis Patients Yu ah Hong,[2] Su Hyun Kim,[3] Yong-Lim Kim,[4] Yon Su Kim,[5] Shin-Wook Kang,[6] Seong il Jo,[1] Yoon-Kyung Chang,[1] Suk young Kim,[1] Yong Kyun Kim.[1] *[1]The Catholic University of Korea, Daejeon, Republic of Korea; [2]College of Medicine, The Catholic University of Korea, Daejeon, Republic of Korea; [3]Chung-Ang University Hospital, Seoul, Republic of Korea; [4]Kyungpook National University Hospital, Daegu, Republic of Korea; [5]Seoul National University College of Medicine, Seoul, Republic of Korea; [6]College of Medicine, BK21, Yonsei Univ., Seoul, Republic of Korea.*

Background: Background/Aims: Dialysis patients have increased susceptibility to infection, and infection related mortality is considerably high in dialysis patients. Parathyroid hormone (PTH) receptors were located in most immunologic cells, and has been known as an immunoregulatory factor. We evaluated the impact of intact PTH (iPTH) levels on infection related outcomes in incident dialysis patients.

Methods: Methods: Incident dialysis patients were selected from the Clinical Research Center registry a prospective Cohort study on dialysis patients in Korea. Serum iPTH levels were divided into three groups (iPTH <150 pg/mL, 150 ≤iPTH< 300 pg/mL, and iPTH ≥300 pg/mL). The primary outcome was all cause and infection-related mortality and the secondary outcome was infection-related hospitalization.

Results: Results: A total of 1,260 hemodialysis and 511 peritoneal dialysis patients were included. The median follow-up period was 24 months. During follow up period, 175/1,771 (9.9 %) was died and 35/1,771 (2.0 %) was died of infection related cause. Kaplan-Meier analysis showed that the all-cause mortality rates ($P < 0.001$, Log-rank) as well as infection-related mortality rates ($P = 0.003$, Log-rank) were significantly higher in patients with lower iPTH levels than in patients with higher iPTH levels. There were no significant differences among groups in rates of infection-related hospitalization. Serum iPTH levels were independently correlated with age, albumin, corrected calcium, alkaline phosphatase and phosphate by multiple logistic regression. The multivariate Cox regression analysis showed that patients with serum iPTH <150 pg/mL remained at higher risk for infection-related mortality than those with target range of iPTH levels by KDIGO guideline, 150 ≤iPTH< 300 pg/mL, after adjusting for confounding variables (Hazard Ratio = 2.439 [1.027-5.793], $P = 0.043$). However, there was no significant risk for all-cause mortality after adjusting for confounding variables.

Conclusions: Conclusion: Low iPTH levels was an independent predictor marker of infection related mortality after adjustment of multiple confounders in incident dialysis patients.

TH-PO790

HCV Viraemia in Anti-HCV-Negative Haemodialysis Patients: A Myth? Ioannis Griveas.[1,2] *[1]401 General Military Hospital of Athens, Athens, Greece; [2]PRIVATE DIALYSIS UNIT "NEFROIATRIKI", ATHENS, Greece.*

Background: Hepatitis C virus (HCV) infection is still common among dialysis patients. The Centers for Disease Control and Prevention (CDC) recommends that chronic hemodialysis (HD) patients should be screened for HCV antibody upon admission to the dialysis clinic and every six months thereafter if susceptible to HCV infection. However, previous studies have shown the presence of HCV viraemia in anti-HCV negative HD patients as up to 22%. **Aim:** To evaluate the presence of HCV viraemia using HCV-RNA detection among anti-HCV-negative HD patients from a tertiary dialysis unit in Athens.

Methods: We enrolled 41 anti-HCV negative HD patients [M/F: 31/10, median age: 55 years (range: 18-88), median hemodialysis duration: 29 months (range: 2-345)] diagnosed with third generation enzyme immunoassay. One patient was HBsAg positive. HCV viraemia was evaluated using a sensitive (cut-off 12IU/ml) reverse transcriptase polymerase chain reaction (COBAS AmpliPrep/TaqMan system) test for HCV-RNA.

Results: None of the 41 anti-HCV-negative HD patients were shown to be viraemic.

Conclusions: Routine HCV RNA testing appears not to be necessary in HCV antibody negative HD patients.

TH-PO791

Direct-Acting Antiviral Agents Therapy Reduce Beta2 Microglobulin Levels of Hemodialysis Patients with Hepatitis C Virus Infection Minoru Ito. *Yabuki Hospital, Yamagata City, Japan.*

Background: Hepatitis C virus (HCV) infection is still major comorbidity in patients receiving hemodialysis. Recently, the direct-acting antiviral agents (DAAs) against HCV has been allowed to use for end-stage renal disease patients in Japan. Moreover, a prior study reported that HCV infection was related to serum beta2 microglobulin (ß2MG) elevation. ß2MG is known as a causative substance of dialysis-related amyloidosis (DRA). In this study, we evaluated the ß2MG lowering effect of the DAAs therapy to hemodialysis patients with HCV infection.

Methods: We treated sixteen HCV (Serotype 1)-infected hemodialysis patients with DAAs between October 2015 and April 2017. We prescribed daclatasvir and asunaprevir combination for twelve patients, and elbasvir and grazoprevir combination for four patients. We evaluated the sustained virologic response (SVR) and the serum ß2MG level before and after DAAs therapy.

Results: 16 patients were enrolled in this study (age: 62.2 years old, dialysis vintage: 20.4 years, male 12, female 4). All the 16 patients completed the DAAs therapy without remarkable side effects. At the end of treatments, all patients had undetectable HCV RNA levels. However, one patient had a virological failure a month after. The serum ß2MG levels before the treatment were higher than the target level that several clinical guidelines recommend. Just after the treatments, the ß2MG levels decreased significantly (30.4 mg/L v.s. 24.8 mg/L, p=0.0016). ß2MG levels of 15 patients with satisfactory results remained lower after several weeks (observational periods) of treatment. A patient with virological failure showed ß2MG level increased again immediately.

Conclusions: ß2MG-removal therapies have developed dramatically. Online-hemodiafiltration, hemodialysis with high-flux membrane and ß2MG apheresis column show high ß2MG removal performance. However, these treatments were insufficient for the patients with HCV infection. In this study, we found the ß2MG lowering effect of DAAs therapy. DAAs therapy is highly likely to prevent DRA for dialysis patients with HCV infection.

TH-PO792

Association of Hepatitis B Vaccination Response and Sleep in Chronic Hemodialysis Patients Maggie Han,[1] Xiaoling Ye,[1] Sharon Rao,[1] Stephan Thijssen,[1] Marcee Bonner,[2] Candace Young,[2] Daniel Marsh,[2] Jeffrey L. Hymes,[3] Peter Kotanko.[1,4] *[1]Renal Research Institute, NYC, NY; [2]Renal Associates of Baton Rouge, Baton Rouge, LA; [3]Fresenius Medical Care North America, Franklin, TN; [4]Icahn School of Medicine, NYC, NY.*

Background: While hepatitis B vaccination (HBVacc) is standard of care in chronic hemodialysis (HD) patients, seroconversion (SC) rate is only 58%, and poor SC has been linked to age, dialysis vintage, albumin level, and diabetes [Lacson, HDI 2005]. In healthy subjects, poor sleep in the night after HBVacc results in a significantly lower SC rate [Lang, J Immnol 2011]. Recent work revealed that patients who start HD early in the day have disturbed sleep-wake patterns [Han, Blood Purif 2016]. We hypothesize that sleep duration in the night after HD (post-HD) impacts HBVacc SC.

Methods: We conducted two studies. First, HD patients in Fresenius Medical Care North America (FMCNA) clinics were followed between 01/2010-12/2015. HBVacc was administered concurrent to HD treatment. Patients who completed the prescribed HBVacc series were included. SC was recorded if a hepatitis B antibody titer of ≥10 IU/mL was detected up to a year after HBVacc. Patients were stratified into early and late groups if 90% of treatments started before or after 8:30am, respectively. In the 2nd study, nightly sleep duration of HD patients were collected over a 5-week period using the Fitbit Flex. Mean post-HD sleep was calculated for shift 1(HD start before 8:30am) and shifts 2, 3, and 4 combined(HD start after 8:30am).

Results: Descriptive statistics of the vaccination and sleep study cohort are listed in **Table 1**. HBVacc SC rates in early vs. late group were 74% vs 72% (Δ=2%;95% C.I. 0.7 to 3.3;p=0.003). Mean post-HD sleep of those patients scheduled for HD in shift 1 vs. shifts 2,3, and 4 combined were 417 minutes vs 380 minutes(Δ=38 minutes;95% CI -3.2 to 78.6;p=0.069).

Conclusions: Patients who started HD before 8:30am had a significantly higher SC rate than those who started later. A previously unrecognized, yet plausible, explanation is that patients in shift 1 slept more on the post-HD night. This finding may add to the many effects sleep, or lack thereof, exerts on HD patients' health. Further work looking at the sleep following HD in a bigger cohort is required to confirm or reject these initial findings. If confirmed, sleep hygiene intervention in non-seroconverting patients could be considered.

Funding: Commercial Support - Renal Research Institute

Table 1.

	Vaccination Cohort (FMCNA)				Sleep study cohort			
Parameter	Early shift (n=6,613)	Later shifts (n=13,356)	Δ	95% C.I.	Shift 1 (n=30)	Shift 2,3,4 (n=28)	Δ	95% C.I.
Vaccine type: Engerix B %	94.8%	95.2%	-0.40%	(-1.06, 0.26)				
Age [years]	63.0 (13.4)	65.8 (14.2)	-2.79	(-3.20, -2.38)	55.02 (11.78)	49.60 (13.35)	5.42	(-1.08,11.92)
Race: White %	66.84%	70.69%	-3.85%	(-5.23, -2.46)	23.33%	28.57%	-5.24%	(-0.28,0.17)
Sex: Male %	61.15%	55.69%	5.46%	(4.0, 6.91)	46.67%	50.00%	-3.33%	(-0.29,0.22)
Diabetes mellitus %	61.94%	61.24%	0.70%	(-0.7, 2.15)	53.33%	21.43%	31.90%	(0.08,0.55)
BMI [kg/m^2]	30.5 (10.3)	29.1 (9.3)	1.42	(1.12, 1.72)	31.26 (7.42)	28.32 (9.25)	2.94	(-1.39,7.27)
Albumin [g/L]	3.9 (0.3)	3.8 (0.4)	0.04	(0.03, 0.05)	4.00 (0.27)	4.01 (0.33)	-0.01	(-0.16,0.14)
Hemoglobin [g/dL]	11.3 (0.8)	11.2 (0.8)	0.07	(0.05, 0.09)	11.00 (1.27)	11.35 (1.52)	-0.34	(-1.06,0.37)

TH-PO793

Effects of Access to Vascular Surgeons on Catheter Rates in Hemodialysis Patients Hao Han,[1] Tommy C. Blanchard,[1] Sheetal Chaudhuri,[1] Sophia Rosen,[1] Marta Reviriego-Mendoza,[1] John W. Larkin,[1] Len A. Usvyat,[1] Walead Latif,[2] Elsie Koh,[2] Murat Sor,[2] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Fresenius Vascular Care, Malvern, PA.*

Background: The rates of central venous catheter (CVC) use in hemodialysis (HD) patients have been relatively unaltered over the last decade. In 2016, the United States Renal Data System estimated that 68% of incident HD patients utilize a CVC 90 days after starting HD, and approximately 20% of patients never transition to a permanent vascular access (VA). We aimed to investigate if availability of surgeons at outpatient VA centers proximal to the patients' residence is associated with lower CVC rates in incident and prevalent HD patient populations.

Methods: We analyzed data from incident and prevalent patients treated by Fresenius Medical Care North America between January 1, 2016 and December 31, 2016. We selected patients who resided in a zip code that was within 5 miles of a Fresenius Vascular Care (FVC) VA center. Patients were stratified into groups based on whether they resided near a VA clinic with or without a vascular surgeon on site. We analyzed the percentage of catheters in incident patients and prevalent patients within these two groups.

Results: We observed that incident HD patients who lived proximal to a VA center without a surgeon were more likely to have a CVC (72% with a CVC) when compared to incident patients who resided near a VA center with a surgeon (66% with a CVC). Likewise, when analyzing all HD patients (incident and prevalent), 29% of patients who

were living near a VA center without a surgeon used a CVC, as compared to 27% who lived close to a VA facility with a surgeon.

Conclusions: Our findings suggest that incident and prevalent HD patients residing in the proximities of an outpatient VA center with a surgeon on site are more likely to have a permanent access, possibly due to better access to care. Additional studies are necessary to confirm this observation and assess longitudinal trends for VA utilization.

Funding: Commercial Support - Fresenius Medical Care North America

TH-PO794

Attitudes of Dialysis Patients to Information Technology: Disinterest or Overload? Anthony F. Iluyomade,[2] Andrew I. Chin.[1] *[1]University of California Davis, Sacramento, CA; [2]University of California Davis Medical Center, Sacramento, CA.*

Background: The utilization of information technology in enhancing the delivery of healthcare is becoming ubiquitous. Dialysis patients tend to have access to a number of technologies (smart phones, computers e.t.c) and utilize these as an essential part of their daily lives. The question is whether these patients would be interested in incorporating their devices in their overall dialysis and medical care.

Methods: This is an English-language, 1 page questionnaire-based study, of prevalent in-center adult HD patients from 5 clinics in an urban Northern California city. The questionnaires were answered by the patients or read to them and filled out by a nurse. All questionnaires were completed within a one-month period. The questionnaire consisted of 7 "yes or no" questions related to: 1) access to text messages; 2) access to "smart phone" and computer technologies; and 3) willingness to use or receive information on these devices.

Results: Out of a population of 355 in-center HD patients, 245 (69%) completed the questionnaire. In total, 194 patients (79%) could potentially receive text messages; 160 patients (65%) had a phone that could receive text messages. An additional 34 patients had a caregiver who could receive texts. When asked if they would like to receive text message about upcoming medical appointments or dietary reminders such as to take oral phosphate binders, only 90 patients who had access to texts (46%) would be willing to participate. When asked about access to a "smart device" or computer for viewing educational materials, 106 patients (43%) had a "smart phone", 38 patients (16%) had a caregiver with a smart phone, and 22 (9%) had access to only a computer. Therefore, 166 (68%) had potential to view educational materials related to diet and overall health on HD, if they brought their device into the clinic. However, when asked if willing to view such videos, only 80 (48% of those with access) indicated a desire to do so.

Conclusions: Most of our in-center HD patients (or through their caregivers) were able to receive text messages for appointment, medication or dietary reminders. However, more than half of the patients who had access to these technologies desire not to participate. This attenuates the main goal of integrating technology platform in dialysis patients care and more research is needed in this regard to fully understand their perceptions of such integration.

TH-PO795

Burden of ESKD in Latin America Maria C. Gonzalez-Bedat,[1] Guillermo Rosa Diez,[1,2] Alejandro Ferreiro,[1] Rosario Luxardo.[1,2] *[1]Latinoamerican Registry of Dialysis and Trasplantation, Montevideo, Uruguay; [2]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina. Group/Team: RLADTR Delegates.*

Background: End Stage Renal Disease (ESKD) represents a major challenge for Latin America (LA). The strategic plan from the Panamerican Health Association (PAHO) has proposed goal for ESKD in LA: Renal Replacement Therapy (RRT) prevalence of at least 700 patients pmp by 2019. Then, epidemiological information is needed to assist in the development of ESKD care in the region.

Methods: Participant countries completed an annual survey to provide data on incident and prevalent cases of patients undergoing RRT by means of all modalities: Hemodialysis (HD), Peritoneal Dialysis (PD), and trasplantation as well as other relevant parameters. Analyses of these variables were performed to determine correlations with GNI and life expectancy at birth as well as other socioeconomic indexes. For the statistical analysis, the Pearson (r) coefficient was applied, and a p-value < 0.05 was considered significant. The incidence and prevalence of LA RRT rate was compared with USA and Europe.

Results: 20 countries participated in the survey, more than 90% of the LA countries. The prevalence of RRT in LA increased from 119 patients pmp in 1991 to 709 pmp in 2014, but only 6 countries have a prevalence above of goal of PAHO. HD continues to be the choice of treatment (90%). The RRT prevalence correlated positively with GNI (r 0.81; $p < 0.001$) and life expectancy at birth (r 0.56; $p < 0.01$). A wide incidence rate variation was observed, from 420.9 pmp in Jalisco to 22.6 in Paraguay. When compared with the United States data from 2014, incidence in LA, was substantially lower (157.6 vs 370 respectively), but when compared to the European ERA/EDTA registry (133 pmp) the rate is higher in most LA countries. Diabetes remained the leading cause of ESRD in the region. The most frequent cause of death was cardiovascular. There is a wide rate variation of nephrologists by country.

Conclusions: The heterogeneity or even the absence of registries in some LA countries is congruent with the inequities in access to RRT in such countries, as well as the availability of qualified personnel. The SLANH in cooperation with PAHO, is currently running training programs as well as cooperation programs between LA countries to support less developed ESKD programs. In this spirit, RLADTR is training personnel to carry out dialysis and transplant registries in LA.

TH-PO796

Outcomes of Chronic Dialysis in Infants under Two Years Natasha Jawa,[1] Claire M. Gallibois,[1] Damien G. Noone.[1,2] *[1]The Hospital for Sick Children, Toronto, ON, Canada; [2]Paediatrics, University of Toronto, Toronto, ON, Canada.*

Background: Infants with end-stage renal disease require renal replacement therapy in the form of dialysis, until of sufficient weight to be transplanted; typically by age two. Infant dialysis is associated with significant morbidity and mortality. Peritoneal dialysis (PD) has historically been the preferred choice for infant dialysis, due to technical complexities and risk for complications associated with hemodialysis (HD). Management of very young patients on HD has improved in recent years, but outcomes have yet to be assessed. This study retrospectively reviewed long-term patient- and dialysis-specific outcomes of chronic PD and HD in a contemporary cohort of infants less than two years of age and weighing <10 kg at The Hospital for Sick Children, Toronto.

Methods: Infants <2 years of age and <10 kg undergoing chronic dialysis from 2005-2015 were included. Demographic, dialysis-related and outcome data were extracted from patient's electronic medical records. Summary statistics were analyzed using STATA v.14. Median with interquartile range is provided.

Results: A total of 28 infants (64.3% male) were included. 20 (71.4%) were diagnosed antenatally. Time from birth to dialysis initiation was 13.5 (10, 67) days. 14 (50%) were initiated on PD and 14 (50%) on HD. 8 infants switched modalities a median of 3 (2, 11) times. In patients on PD, the rate of peritonitis was 1 episode/22 patient months. In patients on HD, 11 (64.7%) required a central line change and the central line associated blood stream infection (CLABSI) rate was 1.48 per 1000 central line days. Median time in hospital from dialysis initiation until death/transplant was 8.5 (3.6, 16.7) months. 6 (21.4%) infants died, 17 (61%) were transplanted and 5 (17.9%) remain on dialysis at study end. In those receiving a transplant, median time to transplantation was 2.1 (1.8, 2.7) years.

Conclusions: There has been an increase in the use of HD in recent years. Survival and transplantation rates have improved over time as compared to previously reported rates; however this is associated with prolonged hospital stays and multiple switches between dialysis modalities.

TH-PO797

An International Multicenter Analysis of Incident Patients on Hemodialysis – Practice Patterns, Vascular Access, Demographics and Laboratory Profiles Stefan H. Jacobson,[6,4] Maciej B. Drozdz,[1,4] Andre L. Weigert,[2] Werner Kleophas,[5] Szymon Brzosko,[1] Abdulkareem Alsuwaida.[3,2] *[1]DaVita Poland, Bialystok, Poland; [2]Nephrology, Davita, Lisbon, Portugal; [3]King Saud University, Riyadh, Saudi Arabia; [4]DaVita, Washington, DC; [5]DaVita Deutschland, Dusseldorf, Germany; [6]Nephrology, Danderyd Hospital, Stockholm, Sweden.*

Background: Mortality rates are particularly high in the first few months following initiation of hemodialysis. The risk is associated with characteristics of predialysis care including delayed nephrology referral, type of vascular access and failure to attain guideline-based targets. In this study we analyzed the clinical characteristics in a large international cohort of incident hemodialysis patients.

Methods: We analyzed patient demographics, practice patterns, and laboratory data (February 2017) from 2592 patients (median age: 62 years; 46% female) receiving hemodialysis at 25 DaVita centers in Poland (8 centers, 529 patients), Portugal (5 centers, 529 patients), and Saudi Arabia (12 centers, 1306 patients) with the objective of comparing incident and prevalent patients. We considered the 10th percentile of time on hemodialysis (4.7 months) and compared practices and laboratory data between incident patients (<4.7 months on dialysis; mean 2 months) and prevalent patients (>4.7; mean 44 months).

Results: Incident patients (n=259) were younger ($p<0.001$) than prevalent patients (n=2333), and had lower Charlson comorbidity index ($p<0.001$) and BMI ($p<0.001$). There were significant differences in renal anemia, nutrition, and mineral bone disease variables (Table). Incident patients were more often treated using a central dialysis catheter (CDC, $p<0.001$). The proportion of patients within treatment targets for Kt/V (>1.3), Hb (10-12 g/dL), phosphate (<5.5 mg/dL), albumin (>35 g/L) and treated blood volume (>1 L/kg bw) were all lower in incident patients compared to prevalent patients (all comparisons $p<0.001$).

Conclusions: This large, international, multicenter analysis of incident hemodialysis patients indicates that there is opportunity to improve predialysis management, especially in terms of earlier placement of a permanent vascular access prior to start of hemodialysis. Since mortality is high after initiation of dialysis, such efforts may contribute to improved treatment results.

Comparison of 259 incident vs 2333 prevalent patients on hemodialysis (mean values)

	Age	CDC %	BMI	Charlson median	Albumin	Hb	TSAT	Ferritin	Ca	P	PTH
Incident	57	64	24.3	0	37	10.8	28.4	343	8.6	5.3	412
Prevalent	62	24	25.2	2	39	11.1	29.0	507	8.8	4.8	465
p	<0.001	<0.001	<0.05	<0.001	<0.001	<0.001	<0.001	<0.001	<0.05	<0.001	NS

TH-PO798

Chronic Pain Poses a Significant Burden on Lives of Dialysis Patients Nancy Culkin,[2] Kathryn M. Aebel-Groesch,[2] Duane V. Dunn,[2] Sean Mayes,[2] Deborah A. Benner,[2] Francesca Tentori.[1] *[1]DaVita Clinical Research, Minneapolis, MN; [2]DaVita, Inc, Denver, CO.*

Background: Chronic pain is common in end-stage renal disease (ESRD) due both to multiple comorbidities as well as the dialysis treatment itself. Given differences in dialysis treatment and underlying health status, it is possible that pain perception and burden may differ for in-center hemodialysis (ICHD) and peritoneal dialysis (PD) patients. We characterized the impact of pain on the daily life among patients treated in a large dialysis organization (LDO).

Methods: Pain was assessed monthly by LDO nurses using the Wong-Baker 0-10 scale (May 2016-April 2017). For those patients indicating the presence of pain (rating ≥ 2), a follow-up survey was administered further assessing pain characteristics and burden.

Results: There were a total of 1,094,897 pain assessments performed for ICHD patients (6.5 screenings per patient on average) and 173,739 for PD patients (7.2 screenings per patient on average). Of these, 161,800 (14.8%) ICHD and 23,101 (13.3%) PD assessments had ratings ≥ 2. Back pain was the most common location for both modalities. ICHD patients were more likely to report dialysis-related pain (8.5% responses, 5.7% in PD) and pain of duration ≥ 3 weeks (73.8% vs. 67.0%). Chronic pain had a great impact on lives of both ICHD and PD patients. Use of pain medications was more common in ICHD (74.8%) vs PD (65.1%). For both modalities, acetaminophen was the most common pain medication (~ 30% responses) followed by hydrocodone/acetaminophen (ICHD 15.4%, PD 13.5%).

Conclusions: Our results indicate that pain poses a great burden on lives of dialysis patients, affecting many everyday activities and likely contributing to depressive symptoms. Interestingly, perception of pain and its impact were largely similar between ICHD and PD patients, suggesting that the dialysis treatment process may only play a marginal role. There is a need to integrate pain management in the care of dialysis patients in order to optimize quality of life.

Funding: Commercial Support - DaVita, Inc

Impact of Pain on Quality of Life in ICHD and PD Patients

	ICHD	PD
Affects activities of daily life	55.9%	53.7%
Affects ability to sleep	43.8%	42.8%
Affects appetite	18.8%	20.6%
Affects ability to concentrate	25.7%	26.4%
Has negative effects on relationships	12.8%	15.5%
Symptoms of depression [a]	4.0%	3.8%

[a] Defined as receiving a score ≥ 2 using the PHQ-2 scale (range 0-6).

Data presented as the percentage responding "yes" to the respective question in the follow-up survey administered to those with an overall Wong-Baker score ≥ 2.

Abbreviations: ICHD, in-center hemodialysis; PD, peritoneal dialysis.

TH-PO799

Internet-Based Positive Psychological Intervention for Hemodialysis Patients with Comorbid Depression: Design and Feasibility Brett Burrows,[1] Ken Wilund,[1] Michael A. Cohn,[2] Judith T. Moskowitz,[3] Shuo Xu,[1] Rosalba Hernandez.[1] *[1]University of Illinois at Urbana-Champaign, Urbana, IL; [2]University of California San Francisco, San Francisco, CA; [3]Northwestern University, Chicago, IL.*

Background: Depression is the most pervasive psychological issue facing hemodialysis (HD) patients and treatment strategies have mainly concentrated on the use of pharmacotherapy. Alternative treatment strategies that circumvent drug-related side effects and poor medication adherence (i.e., psychosocial interventions) have not been the focus for therapy and few published studies exist. The aim of the current trial was to determine the feasibility and acceptability of a 5-week Internet-based positive psychological intervention in HD patients with comorbid depression.

Methods: HD patients (n=14) with elevated symptoms of depression were enrolled in a single-arm pre-post pilot trial with clinical assessments at baseline and immediately post intervention. Chairside during regularly scheduled HD treatment, patients completed on-line modules promoting skills for increasing positive emotion over a 5-week period using an Apple IPad. Targeted skills included noting of daily positive events, cultivation of gratitude, practicing positive reappraisal, partaking in acts of kindness, and engagement in mindfulness/meditation.

Results: Mean age was 57.4 years; 50% female; 50% non-Hispanic White; mean duration on dialysis was 3.6 years. Twelve of 14 patients completed the program for an 85.7% retention rate. Participants felt satisfied overall with each session and offered consistently positive feedback. At the end of the intervention, significant improvements were evident for depressive symptoms (15.3 vs. 10.9; p=0.04) as measured by the Center for Epidemiological Studies Depression Scale. Statistical trends indicated clinically meaningful improvement in emotional well-being, kidney disease burden, and quality of social interactions as per the Kidney Disease Quality of Life Instrument.

Conclusions: Results indicate that an innovative and low-cost Internet-based positive psychological intervention represents a feasible and useful therapeutic option for HD patients with comorbid depression. This psychosocial strategy can be a valuable self-guided tool that reduces costly face-time with clinical staff.

TH-PO800

Hospitalization and Missed Dialysis Treatments Are More Common in Hemodialysis Patients with Depressive Symptoms Kathryn M. Aebel-Groesch,[2] Duane V. Dunn,[2] Angie Major,[2] Sean Mayes,[2] Deborah A. Benner,[2] Francesca Tentori.[1] *[1]DaVita Clinical Research, Minneapolis, MN; [2]DaVita, Inc, Denver, CO.*

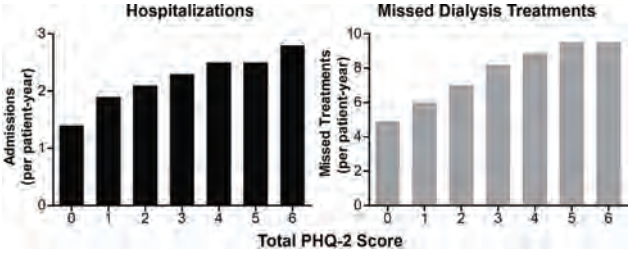
Background: Depression is common in end-stage renal disease and is likely to have a negative impact on patient engagement in self-care and clinical outcomes. Here we characterized incidence of hospitalization and missed dialysis treatments among in-center hemodialysis patients who screened positive for depressive symptoms.

Methods: We analyzed data from a large dialysis organization electronic health record database. Depression screenings were performed biannually (May 2016-April 2017) with the PHQ-2 scale (range 0-6). Patients with active diagnosis of depression, bipolar disorder, cognitive impairment, language barriers, or who were hospitalized were not screened. Rates of hospitalization and of missed dialysis treatments due to non-adherence in the 3 months after screening were compared in patients with depressive symptoms (PHQ-2 score ≥ 2) and those without.

Results: A total of 54,441 (17.3%) screenings were positive for depression. The hospitalization rate was higher among those with depressive symptoms compared to those without (2.2 vs 1.5 admissions per patient-year). Patients who screened positive for depression were also more likely to miss dialysis treatments (7.7 vs 5.1 missed HD session per patient-year). Overall, patients with higher PHQ-2 scores were more likely to have higher hospitalization and missed treatment rates.

Conclusions: These findings indicate that hemodialysis patients who screen positive for depression are more likely to be hospitalized and be non-adherent to dialysis treatment schedules. Since the PHQ-2 may underestimate actual depression rates, our results represent conservative estimates of the possible impact of depression on clinical outcomes. Clinical initiatives should be designed to specifically target high-risk patients who screen positive for depression.

Funding: Commercial Support - DaVita, Inc



TH-PO801

Impact of Baseline Scores on the Responsiveness of Quality of Life (QOL) Tools to Interventions: An ACTIVE Dialysis Trial Secondary Analysis Meg J. Jardine,[1,2] Brendan Smyth,[1,3] Oliver van den Broek-Best,[1,3] Li Zuo,[1] Nicholas A. Gray,[4] Christopher T. Chan,[5] Janak R. de Zoysa,[6] Kirsten Howard,[7] Kris Rogers,[1] Vlado Perkovic.[1] *[1]The George Institute for Global Health, UNSW, Sydney, NSW, Australia; [2]Nephrology, Concord Repatriation General Hospital, Sydney, NSW, Australia; [3]University of Sydney, Sydney, NSW, Australia; [4]Sunshine Coast University Hospital, Birtinya, NSW, Australia; [5]Toronto General Hospital, Toronto, ON, Canada; [6]Waitemata District Health Board, AUCKLAND, New Zealand; [7]School of Public Health, University of Sydney, Sydney, NSW, Australia. Group/Team: ACTIVE Dialysis Steering Committee.*

Background: There is little clarity on the relative validity, reproducibility and generalisability of available tools for measuring the patient experience in the trial context. The ACTIVE Dialysis trial found no benefit from extended hemodialysis (HD) hours for the utility-based QOL measure, EQ-5D, with small but significant benefits for generic health-related SF-36 QOL. Participants in extended hours trials have better average health than patients overall raising the possibility EQ-5D responsiveness may be limited by a 'ceiling' effect. **Aim:** To explore whether the impact of extended hours HD on QOL scores is dependent on baseline scores.

Methods: The ACTIVE Dialysis trial randomized 200 HD patients to standard (median 12) or extended (median 24) weekly HD hours for 12 months. Dialysis population-validated QOL assessments including the EQ-5D utility instrument and SF-36 Physical (PCS) and Mental (MCS) Composite Scores were administered by blinded interviewers during the trial. After confirming the absence of an interaction of the score with time, the average intervention effect was determined using mixed linear regression and analysed in subgroups defined by tertiles of the relevant baseline score.

Results: Overall extended weekly HD hours had no impact on EQ-5D (mean difference 0.03, CI -0.03, 0.09; p=0.30) with small but significant improvements in PCS and MCS (mean difference PCS 2.30, 95%CI 0.52-4.07; MCS 2.54, 95%CI 0.42-4.65). The lack of impact on EQ-5D results were consistent across all tertiles (lowest third 0.01 [CI -0.12-0.14, p=0.89], middle third 0.05 [CI -0.03-0.13, p=0.26], highest third 0.02 [CI -0.07-0.12, p=0.60], p-interaction 0.80). The benefits for PCS and MCS were similarly consistent across tertiles (p-interaction: PCS 0.96; MCS 0.34).

Conclusions: The impact of extended dialysis hours on EQ-5D, PCS and MCS QOL was not dependent on baseline scores. The scores appear to be at least internally robust to variation in baseline QOL. NCT00649298

Funding: Commercial Support - Baxter, Government Support - Non-U.S.

TH-PO802

Identifying the Critical Dimensions of Fatigue for a Core Outcome Measure for Trials in Haemodialysis: An International Survey Angela Ju,[3] Mark L. Unruh,[2] Jonathan C. Craig,[4] Allison Tong.[1] *[1]The University of Sydney, Sydney, NSW, Australia; [2]University of New Mexico, Los Ranchos, NM; [3]University of Sydney, Sydney, NSW, Australia; [4]University of Sydney/ Children's Hospital, Sydney, NSW, Australia.*

Background: Measures of fatigue used for research in patients on haemodialysis have differing dimensions, length, and scales. The extent to which of the dimensions of fatigue are valued by patients and health professionals are unknown.

Methods: An online survey was conducted among patients/caregivers and health professionals in English and Spanish. The survey consisted of 11 content dimensions of fatigue such as 'life participation' and 'muscle weakness', and 4 modes of assessment such as 'severity' and 'frequency', identified in existing measures. A 9-point Likert scale was used to assess absolute importance and relative importance obtained from a best-worst scale (BWS) task. Multivariate regression analysis was used to examine the Likert scores and mixed-multinominal regression for the BWS scores.

Results: In total, 342 (60%) health professionals and 227 (40%) patients/caregivers from 60 countries participated in the two surveys. Among all participants, the top rated dimension was 'life participation' (impact of fatigue on life participation) with a mean Likert score of 7.55 (95%CI: 7.42-7.68) for the English survey and 5.50 (95% CI: 4.90-6.10) for the Spanish survey. Severity was more important than frequency, duration or change in fatigue in both the English (7.20: 7.06-7.34) and Spanish survey (5.13: 4.52-5.74). English-speaking patients placed highest relative importance on 'life participation' (BWS score 9.0:7.8-10.4), compared with Spanish-speaking patients for whom 'post-dialysis fatigue' was most important (9.0:7.0-11.0).

Conclusions: Impact of fatigue on life participation was identified as a critical dimension of fatigue, and severity the most important metric. Differences in relative importance of fatigue dimensions suggest cultural differences in priorities. The core outcome measure for fatigue should include severity of impact upon life participation with consideration of cultural validity.

Funding: Government Support - Non-U.S.

TH-PO803

The Association of RAAS Blockade and the Progression of Residual Kidney Function Decline: A Nationwide Prospective Cohort Study Yunmi Kim,[4] Kyung Don Yoo,[4] Clara T. Kim,[6] Yun Kyu Oh,[3] Shin-Wook Kang,[1] Chul Woo Yang,[2] Yong-Lim Kim,[5] Yon Su Kim,[8] Chun Soo Lim,[7] Jung Pyo Lee.[7] *[1]College of Medicine, BK21, Yonsei Univ., Seoul, Republic of Korea; [2]Seoul St. Mary's Hospital, Seoul, Republic of Korea; [3]Department of Internal Medicine, Boramae Medical Center, Seoul, Republic of Korea; [4]Dongguk University Gyeongju Hospital, Gyeongsangbuk-do, Republic of Korea; [5]Kyungpook National University Hospital, Daegu, Republic of Korea; [6]School of Public Health, Seoul National University, Seoul, Republic of Korea; [7]Seoul National University Boramae Medical Center, Seoul, Republic of Korea; [8]Seoul National University College of Medicine, Seoul, Republic of Korea.*

Background: Our aim was to evaluate the clinical effects of renin angiotensin aldosterone system (RAAS) blockade on residual renal function (RRF) in newly diagnosed patients with end-stage renal disease (ESRD) undergoing hemodialysis in Korea.

Methods: Total of 1,571 patients were enrolled in the Clinical Research Center for ESRD prospective observation cohort. RAAS treatment was defined as the use of angiotensin converting enzyme inhibitor or angiotensin receptor blocker for at least 3 months. RRF was defined using 24-hour urine volume and Creatinine Clearance measured at 0, 3 and 12 months after dialysis initiation.

Results: The 671 patients (43%) were in the RAAS group. The RAAS and control groups were comparable in terms of age, sex, primary renal disease, comorbidities, and dialysis dose including Kt/V, ultrafiltration volume per session. The development of total anuria at 12 months was similar in both groups (39.3% vs. 41.1%, RAAS group vs. control group). The RRF in both group decreased over a 12-month period. After adjustment for age, sex, diabetes history, blood pressure and ultrafiltration volume, use of RAAS did not provide a significant protective effect on RRF preservation (Odds ratio 0.57 95% CI 0.31-1.04, p=0.069). Mixed effect linear regression revealed no significant difference in the course of residual renal function between RAAS group and control group (p value=0.127). In subgroup analysis for patients with completely followed-up cases, patients using RAAS over 12 months did not significantly lower the RRF than other patients(p value=0.388).

Conclusions: In Korean patients with ESRD, RAAS blockade failed to clarify the protective effect for RRF. Further research is needed to provide optimal treatment for preservation of RRF, especially in Korean patients with incident dialysis.

Funding: Government Support - Non-U.S.

TH-PO804

Validation of a New Physical Activity Instrument against Pedometers among Dialysis Patients Piyawan Kittiskulnam,[1] Anoop Sheshadri,[2] Kirsten L. Johansen.[3] *[1]Chulalongkorn university, Bangkok, Thailand; [2]None, San Francisco, CA; [3]University of California, San Franicsco, San Francisco, CA.*

Background: The newly developed Low Physical Activity Questionnaire (LoPAQ) was designed to capture the low activity level among physically inactive patients undergoing dialysis and correlated well with physical activity questionnaires used in general population. However, this instrument has not been validated against a more objective measure.

Methods: We performed a cross-sectional study and recruited 55 ambulatory patients receiving HD or PD for ≥3 months from 3 dialysis facilities in San Francisco during 2016-7. Spontaneous walking activity was measured by pedometers over 7 days including a dialysis-free weekend and used as the reference. Patients were instructed to record their activities and step count readings. Study coordinators administered the LoPAQ and recorded participants' responses during a dialysis session (HD) or clinic visit (PD). We used measures in the LoPAQ that can be compared with available metrics, including minutes of walking in the past week and time expended from light to vigorous, and total physical activity. We also asked about the average time spent in sitting activities over 1 week. Spearman correlation was used to determine whether the LoPAQ results correlate with step counts.

Results: Fifty-two dialysis patients (HD=45, PD=7) completed the LoPAQ. Mean age was 57±12 years with 80% men. Median dialysis vintage was 39 (IQR, 17-708) months. Total kilocalories per week (kcal/wk) of physical activity reported on the LoPAQ were 630 (420-2,222). Participants reported an average of 5.7±3.2 sedentary hours per day. Most patients (83%) reported walking activity around the neighborhood, for transportation, and/or for fitness or pleasure, with a median of 560 (52-1,225) kcal/wk. The patients had average step counts of 18,578 (9,701-37,029) steps/week (2,630 [1,360-5,176] steps/day). The activity reported on the LoPAQ correlated with that reported on weekly pedometer readings (r=0.37, p=0.006). In addition, energy expenditure in walking between the LoPAQ and weekly step counts was highly correlated (r=0.59, p<0.001), particularly among PD patients (r=0.82, p=0.01).

Conclusions: The LoPAQ was easier and less time-consuming than previously validated physical activity questionnaires. LoPAQ demonstrated a good correlation, similar to other widely used physical activity instruments, with objective pedometer step counts among dialysis patients.

Funding: NIDDK Support

TH-PO805

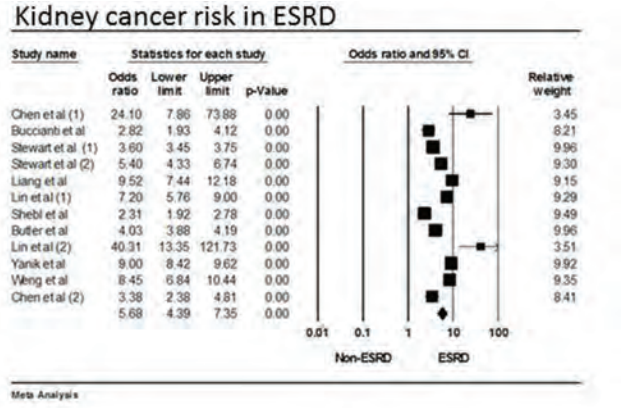
Incidence and Association of Urologic Malignancies with ESRD: A Meta-Analysis Panagiotis Kompotiatis,[3] Charat Thongprayoon,[1] Sandhya Manohar,[2] Wisit Cheungpasitporn,[2] Sandra Herrmann.[2] *[1]Bassett Medical Center, Cooperstown, NY; [2]Mayo Clinic, Rochester, MN; [3]Nephrology, Mayo Clinic, Rochester, MN.*

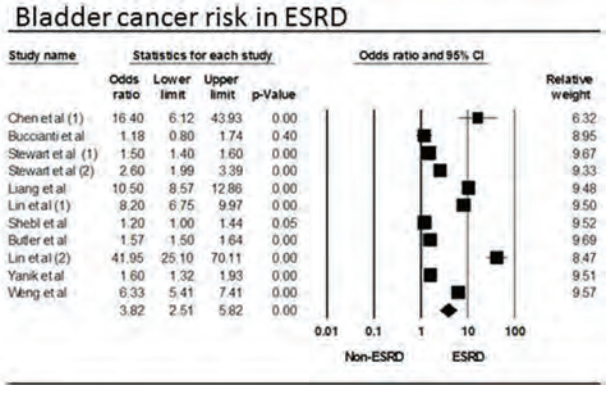
Background: Previous studies have suggested higher incidence of urologic malignancies in patients with end-stage renal disease (ESRD). However, incidence trends of urologic malignancies in ESRD patients remain unclear. The study's aims were 1) to investigate the pooled incidence/incidence trends 2) to assess the risks of urologic malignancies in ESRD patients.

Methods: A literature search was performed using MEDLINE, EMBASE and Cochrane Database from inception through April 2017. Studies that reported incidence or odd ratios (OR) of urologic malignancies among ESRD patients were included. Pooled OR and 95%CI were calculated using a random-effect model. The protocol for this study is registered with PROSPERO (International Prospective Register of Systematic Reviews; no. CRD42017067687).

Results: Eighteen observational studies with 1,872,952 ESRD patients were included. The pooled estimated incidence of kidney cancer and bladder cancer in ESRD patients were 0.4% (95%CI: 0.3%-0.6%) and 0.5% (95%CI: 0.3%-0.7%), respectively. Meta-regression showed significant positive correlation between incidence of urologic malignancies in ESRD patients and year of study (slopes=+0.06, p<0.001 for both kidney and bladder cancers). Compared to non-ESRD status, ESRD was significantly associated with both kidney cancer (pooled OR 5.68; 95% CI 4.39-7.35) and bladder cancer (pooled OR 3.82; 95% CI 2.51-5.82).

Conclusions: Our study demonstrates a significant association between ESRD and urologic malignancies. The overall estimated incidence rates of kidney cancer and bladder cancer are 0.4% and 0.5%, respectively. There is also a significant positive correlation between the incidence of urologic malignancies and year of study.





TH-PO806

Time between Predicted versus Actual Time to RRT Initiation: Just How Early Are We Starting? Elaine Ku, Charles E. McCulloch, Kirsten L. Johansen. *University of California San Francisco, San Francisco, CA.*

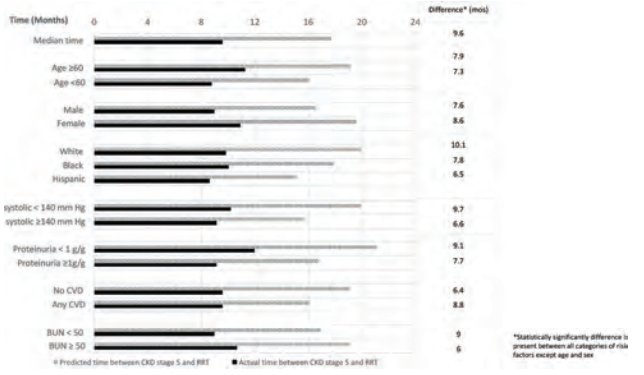
Background: Prior studies have defined "early" vs. "late" renal replacement therapy (RRT) initiation based on eGFR at the time of RRT. Few studies have described timing of RRT based on *time spent in CKD stage 5*. Our goal was to compare time that could be spent in CKD stage 5 if RRT were initiated after a fall in eGFR to below 5mL/min/1.73 m^2 (a conservative threshold for RRT) vs. actual observed time spent in CKD stage 5.

Methods: We used mixed models to estimate the person-specific trajectory of renal function decline (using all eGFRs prior to RRT) among 736 Chronic Renal Insufficiency Cohort (CRIC) participants followed longitudinally for 9.6 years who eventually began RRT. We used these trajectories to estimate the expected amount of time in CKD stage 5 (between eGFR of 15 and 5 mL/min/1.73 m^2), which we compared to the observed time spent in CKD stage 5 (until actual receipt of RRT). We then tested for differences between predicted and actual times in stage 5 according to known risk factors for CKD progression.

Results: Overall, the median difference between the predicted and actual time spent in CKD stage 5 was 9.6 months (i.e., patients started RRT 9.6 months before they were predicted to reach an eGFR of 5 mL/min/1.73 m^2). Variations in the predicted time in CKD stage 5 were observed by race and ethnicity, co-morbidities, and laboratory parameters, but not by age or sex [figure]. In general, patients at lower risk of progression were started earlier than those at higher risk [Figure], with the time difference being largest among white patients (10.1 months), those with SBP <140 mmHg (9.7 months) and proteinuria <1 g/g (9.1 months).

Conclusions: We found marked differences in the actual vs. predicted amount of time spent in CKD stage 5 based on various risk factors of interest. RRT initiation occurred 10 months earlier than would be expected based on projected time to eGFR of <5 mL/min/1.73 m^2. Given the lack of mortality benefit to early RRT initiation, we have identified subgroups that may especially benefit from more a concerted effort to delay RRT.

Funding: Other NIH Support - NHLBI



TH-PO807

Association between Low-Molecular-Weight Heparin and Risk of Bleeding among Hemodialysis Patients: A Retrospective Cohort Study Hind H. Lazrak,[1] Emilie Rene,[1] Naoual Elftouh,[1] Annie-Claire Nadeau-Fredette,[1,2] Louis-Philippe Laurin,[1,2] Jean-Philippe Lafrance.[1,2] *[1]Research center, Maisonneuve-Rosemont hospital, Montreal, QC, Canada; [2]Division of nephrology, Maisonneuve-Rosemont hospital, Montreal, QC, Canada.*

Background: Low molecular weight heparins (LMWH) replaced unfractionated heparin (UFH) in multiple indications. While their efficacy in hemodialysis was proved through multiple studies, their safety remains controversial. The potential bioaccumulation in patients undergoing chronic hemodialysis raised the question of bleeding risk among this population. The aim of this study was to evaluate bleeding risk among patients with chronic hemodialysis receiving LMWH or UFH for the extracorporeal circuit anticoagulation.

Methods: We conducted a retrospective cohort study of patients undergoing chronic hemodialysis in 22 participating centers using data extracted from administrative databases in Quebec, Canada, from January 2007 to March 2013. Minor, major and total bleeding risk for a first event with LMWH compared to UFH was estimated using a proportional Cox model with time-dependent exposure using demographics, comorbidities and drug use as covariates.

Results: We identified 5322 prevalent and incident chronic hemodialysis patients. The incidence rate for minor, major and total bleeding was 9.5 events /1000 patient-year (95%CI: 7.6-11.0), 24.2 events /1000 patient-year (95%CI: 21.5-27.1) and 32.9 events /1000 patient-year (95%CI: 29.8-36.3) respectively. We found similar risks of minor (adjusted hazard ratio (HR)=1.04; 95%CI: 0.67-1.61), major (HR=0.84; 95%CI: 0.64-1.10) and total bleeding (HR=0.91; 95%CI: 0.72-1.15) when comparing LMWH to UFH.

Conclusions: LMWH was not associated with a higher minor, major or total bleeding risk compared to UFH in a large cohort of chronic hemodialysis patients. LMWH is a suitable alternative to UFH in hemodialysis.

TH-PO808

Survival in Patients on Hemodialysis: Effect of Sex According to Body Mass Index and Creatinine Jong-Hak Lee,[1] Jeong hoon Lim,[3] Man-hoon Han,[3] Hee-Yeon Jung,[3] Ji-Young Choi,[4] Sun-Hee Park,[3] Chan-Duck Kim,[2] Jang-Hee Cho,[3] Yong-Lim Kim.[3] *[1]Daegu Fatima Hospital, Daegu, Republic of Korea; [2]Kyungpook University Hospital, Daegu, Republic of Korea; [3]Kyungpook National University Hospital, Daegu, Republic of Korea; [4]Kyungpook National University School of Medicine, Daegu, Republic of Korea.*

Background: The association of a higher body mass index (BMI) with better survival is a well-known "obesity paradox" in patients on hemodialysis (HD). However, men and women have different body compositions, which could impact the effect of BMI on mortality. We investigated the effect of sex on the obesity-mortality relationship in Korean patients on HD.

Methods: This study included 2,833 maintenance patients on HD from a multicenter prospective cohort study in Korea (NCT00931970). The relationship between categorized BMI and sex-specific all-cause mortality was analyzed by an adjusted Cox proportional hazard model with restricted cubic spline analyses. We also investigated the effect of changes in BMI over 12 months and serum creatinine level on survival in male and female patients on HD.

Results: The mean BMI was 22.6 ± 3.3 kg/m2 and the mean follow up duration was 24.2 ± 3.4 months. The patients with the highest quintile of BMI (≥25.1 kg/m2) showed lower mortality (Hazard ratio [HR]=0.63, 95% confidence interval [CI]=0.42-0.95, P=0.026) compared with those with the reference BMI quintile. When analyzed by sex, male patients with a BMI over 25.1 kg/m2 had lower mortality risk (HR=0.43, 95% CI=0.25-0.75, P=0.003); however, no significant difference was found in female patients. Increased BMI after 12 months and high serum creatinine were associated with better survival only in male patients on HD.

Conclusions: BMI could be used as a risk factor for mortality in male patients on HD. However, the mortality of female patients on HD was not related with baseline

and follow-up BMI. This suggests that BMI is a good surrogate marker of lean body composition, especially in male patients on HD.

Funding: Government Support - Non-U.S.

TH-PO809

Pre- and Post-ESRD Trajectories of Serum Albumin among Incident ESRD Patients: A Transition of Care in CKD Study Patricia W. Lieu,[1] Melissa Soohoo,[2] Christina Park,[2] Connie Rhee,[2] Csaba P. Kovesdy,[3] Kamyar Kalantar-Zadeh,[2] Elani Streja.[2] *[1]UCLA, Los Angeles, CA; [2]UC Irvine, Orange, CA; [3]University of Tennessee Health Science Center, Memphis, TN.*

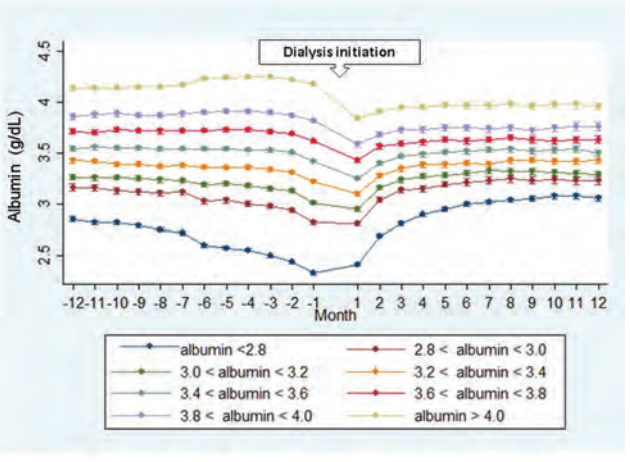
Background: Hypoalbuminemia is a strong predictor of mortality in chronic kidney disease patients, however the extent of change in serum albumin (Alb) in the year surrounding transition to end-stage renal disease (ESRD) is relatively unknown.

Methods: We examined serum Alb trajectories in the 1-year pre- and post-ESRD initiation among 31,053 patients who transitioned to ESRD from 2007-2014 using a mixed-effects regression model. Trajectories were stratified by baseline Alb levels in the 6-month pre-ESRD (prelude) period. Finally, we examined the association of 1-year pre-ESRD Alb slope with early mortality using Cox models adjusted for demographics and lab variables.

Results: The mean±SD age of the cohort was 68±11 years and included 2% females and 30% blacks. The median[IQR] of 1-year prelude Alb slope was -0.22[-0.48,0.23] g/dL/year. Among baseline Alb ≥2.8 g/dL, there was a sharp decline at initiation and a slow rise then plateau towards a normal range in the year after initiation. In patients with Alb <2.8 g/dL, there was a steep drop and a sudden increase in Alb in the few months surrounding transition. Moreover, a steep drop in pre-ESRD Alb of greater than -0.5 g/dL/year was associated with the highest risk of early 12-month post-ESRD mortality compared to no change in Alb slope [HR[95%CI]: 1.07[1.01, 1.13].

Conclusions: Across baseline albumin levels, pre-ESRD serum albumin tends to drop and then rise in the months around ESRD transition, while distinctions are observed for low baseline Alb. Also, a drop in Alb was associated with a higher risk of early mortality. Screening for rapid drops in Alb in the prelude period may identify those at greatest risk of early ESRD mortality. Further studies are required to determine if dietary and medication intervention to maintain elevated Alb impacts early ESRD outcomes.

Funding: NIDDK Support



TH-PO810

Employment among Patients Starting Dialysis in the United States Kevin F. Erickson,[2,1] Bo Zhao,[2] Vivian Ho,[1] Wolfgang C. Winkelmayer.[2] *[1]Baker Institute for Public Policy, Houston, TX; [2]Baylor College of Medicine, Bellaire, TX.*

Background: Patients with end-stage renal disease (ESRD) face significant challenges to remaining employed, and the rate of employment among the prevalent population of patients receiving dialysis is low. It is unknown when in the course of their kidney disease patients stop working. We examined employment trends among patients in the United States who are initiating dialysis and in the six months prior to ESRD.

Methods: We selected patients aged 18-54 who initiated dialysis between 1996 and 2013 from a U.S. registry of patients with ESRD. We compared unadjusted trends in employment at the start of dialysis and six months prior to ESRD, and used linear probability models to estimate changes in employment over time after adjusting for patient health, demographic and socioeconomic characteristics along with local unemployment rates in the general population. We also examined employment among selected vulnerable patient populations.

Results: Employment was low among patients starting dialysis throughout the study period at 22%-23%. However, after adjusting for observed characteristics, the probability of employment increased over time; patients starting dialysis between 2008 and 2013 had a 3.6% (95% CI 3.2%-4.0%) increase in the absolute probability of employment at the start of dialysis compared to patients starting dialysis between 1996 and 2001. More than 30% of patients who were employed six months prior to ESRD stopped working by dialysis initiation, but the adjusted probabilities of employment six months prior to ESRD and of remaining employed among those employed six months prior increased during the study period by 5.5% (95% CI 5.1%-5.9%) and 4.6% (95% CI 3.9%-5.3%), respectively. Black and Hispanic patients were less likely to be employed than other patients starting dialysis, but this gap narrowed during the study period.

Conclusions: Although working-aged patients starting dialysis between 1996 and 2013 experienced increases in the adjusted probability of employment over time, rates of employment remained low. Efforts to help patients with ESRD remain employed should target patients approaching ESRD as well as those already on dialysis.

Funding: NIDDK Support

TH-PO811

Impact of Employment Status or Insurance Type on Outcomes Among Patients with ESRD Jiacong Luo, Dena E. Cohen, Steven M. Brunelli. *DaVita Clinical Research, Minneapolis, MN.*

Background: It is widely thought that patients with end-stage renal disease who remain employed and/or commercially insured following dialysis initiation have better clinical outcomes and higher quality of life than those who do not. However, scientifically robust data are lacking.

Methods: This retrospective (2015-2016) study considered incident patients at a large US dialysis organization. Exposures of interest were insurance status (commercial, N=4858; Medicare/self-pay, N=13,329) and employment status (employed, N=1848; unemployed, N=10,001). Clinical outcomes and Kidney Disease Quality of Life (KDQoL) scores were determined from electronic health records. Comparisons were made using intention-to-treat principles and generalized linear models adjusted for imbalanced patient characteristics, including sociodemographic variables.

Results: Compared to commercial insurance, Medicare/self-pay was independently associated with higher rates of mortality and hospitalization, lower rates of transplant, and lower KDQoL scores in 4 of 5 domains. Similarly, unemployment (vs. employment) was independently associated with higher rates of mortality and hospitalization, lower rates of transplant, and lower KDQoL scores in 4 of 5 domains. Among patients who initiated dialysis while unemployed, those who resumed work by dialysis day 180 had lower rates of hospitalization (adjusted rate ratio 0.46, 95% confidence interval 0.25-0.84) than those who remained unemployed.

Conclusions: Commercial insurance, and separately, employment, were independently associated with better clinical and quality of life outcomes compared to other insurance and employment categories. These findings may inform patient and physician education, and guide advocacy efforts.

Funding: Commercial Support - DaVita, Inc

TH-PO812

Association of Hemodialysis Quality Measures with Patients Dialysis Facility Rating Ziad M. Ashkar. *Lafayette, LA.*

Background: The ICH-CAHPS In-Center Hemodialysis Survey is designed to measure the experiences of people receiving in-center hemodialysis care. Studies of Hospital HCAHPS have shown a significant positive associations between quality measures and patient satisfaction scores. Non profit hospitals and smaller hospitals also scored more favorably. The purpose of this study is to look into the association ICH-CAHPS global patient dialysis facility rating (GDR) with dialysis quality measures.

Methods: An observational retrospective, cross-sectional design. Data are obtained and matched from CMS Dialysis Facility Compare, release date April 2017. From ICH CAHPS, percent of patients who gave their dialysis facility a rating of 9 or 10 over 10 are divided into deciles and used as outcome variables. Ordinal logistic regression with cluster by state is then done with averages of % hemodialysis patients with hemoglobin < 10 g/dl, % KT/V>= 1.2, % with AV Fistula use, % with catheters more than 90 days, phosphorus < 3.5 mg/dl and > 7mg/dl, average mortality rate, readmission rate, hospitalization rate, standardized infection ratio, number of dialysis stations, for-profit status, and chain ownership.

Results: For each unit increase in number of dialysis stations, there was 3% decrease in odds of a decile improvement in global facility rating(GDR). For each unit increase in percent patients with KT/V>=1.2 there was 10% increase in odds of a decile improvement in GDR. % AV fistula in use was only associated with 2% increase. Each unit change in phosphorus of <3.5 and > 7.0 was associated with 11% and 7% decrease odds of a decile change in facility rating. Readmission rate was associated with 2% decrease and for-profit status was associated with 67% decrease odds of GDR. There were no significant relationship with other variables.

Conclusions: Using data from dialysis facility compare, there is significant positive association between higher KT/V, AV fistula use and GDR. Hospital readmission rate, low and high serum phosphorus were negatively related to GDR. Units with more stations, and for-profit units are negatively associated with GDR. More studies are needed to

understand deteminants for dialysis clearance and mineral bone disease with patients satisfaction. More is also needed to understand factors behind relationship of for-profit status and dialysis unit size with patients satisfaction.

TH-PO813

Trends in Insurance Coverage among ESRD Medicare Beneficiaries Claudia Dahlerus, John Wheeler, J. M. Messana, John Stephen, Tempie H. Shearon, Yi Li. *University of Michigan, Kidney Epidemiology and Cost Center, Ann Arbor, MI.*

Background: The 2010 Patient Protection Affordable Care Act (ACA) reduced the number of uninsured in the U.S. general population. Most ESRD patients are eligible for and covered by Medicare; however, it is unclear how implementation of the ACA impacted insurance status for ESRD Medicare beneficiaries. The ACA increased access to Medicaid for more people and made it possible for more people to purchase private health insurance. This potentially resulted in an increase in patients with Medicare/Medicaid Dual Eligibility (DE) coverage. Our objective is to examine whether there were changes in insurance status of ESRD dialysis patients in the initial period following ACA implementation.

Methods: Administrative data (Medicare claims files and Medicare Enrollment Data Base for 2012-2015) were used to classify ESRD dialysis patients by whether they were covered by both Medicare and Medicaid (Medicare/Medicaid DE). Trends were examined for coverage changes.

Results: From 2012-2015, there was an increase of 9.7% in the number of patients with ESRD eligible for Medicare. Over this period, the number of DE patients increased by 14.9%. Therefore, the percentage of Medicare ESRD patients with DE rose steadily from 39% to 41%.

Conclusions: The ACA extended Medicaid eligibility to more people in states choosing to participate in the Medicaid expansion. As a result, the trend in growth of persons with Medicare-Medicaid dual eligibility exceeded that of the overall Medicare ESRD population. This aspect of the ACA may therefore have improved access to dialysis care for more relatively low income people, by enabling them to afford the coinsurance and deductibles of the Medicare ESRD Program.

Funding: Other U.S. Government Support

Number of ESRD Beneficiaries by Insurance Coverage and Year

					% Change
Insurance Coverage	2012	2013	2014	2015	2012-2015
Medicare/Medicaid Dual Eligible	165,796	168,770	182,949	190,549	14.9%
All Medicare	422,609	436,358	449,611	463,568	9.7%

TH-PO814

Utilization of Benchmarks to Reduce Transportation Costs for Dialysis Patients Terry L. Ketchersid,[2] Michael P. Martin,[1] Chris Richmond,[1] Greg S. Garza,[1] Daniel E. Geary,[1] John W. Larkin,[2] Marta Reviriego-Mendoza,[2] Len A. Usvyat,[2] Franklin W. Maddux.[2] *[1]Fresenius Health Partners, Austin, TX; [2]Fresenius Medical Care North America, Waltham, MA.*

Background: End stage renal disease (ESRD) patients have high costs for transportation services. We examined if using benchmark data to identify outliers was associated with reductions in transportation costs. Through the Comprehensive ESRD Care (CEC) Model, Fresenius Medical Care, North America (FMCNA) has partnered with CMS to identify, test, and evaluate new ways to improve care for Medicare beneficiaries with ESRD. We are obligated to disclose that the statements contained in this document are solely those of the authors and do not necessarily reflect the views or policies of CMS. The authors assume responsibility for the accuracy and completeness of the information contained in this document.

Methods: We analyzed annual transportation costs and monthly treatment rates during 2015 to 2016 at 6 FMCNA ESRD Seamless Care Organizations (ESCOs). Two ESCOs with persistent historically high utilization of transportation costs (ESCO "A" & ESCO "B") were provided with benchmarking metrics and a root cause analysis. Quality improvement (QI) initiatives with enhanced education on medical necessity documentation were implemented.

Results: Mean transportation cost was $174 per member per month (PMPM) at the six ESCOs in 2015. ESCO "A" and "B" were identified as outliers with a transportation cost of $681 PMPM, and $263 PMPM, respectively. After implementation of the QI initiatives, ESCO "A" and "B" showed decreased transportation cost PMPM of 25% and 30%, respectively. As % of total PMPM, there was a decrease of 19% in transportation cost PMPM for ESCO "A", and a 30% decrease for ESCO "B". Associated with these QI initiatives, ESCO "A" and "B" recognized year-over-year reductions in transportation costs equal to $1,798,940 and $791,185, respectively. We found no differences in dialysis treatment rates before and after the implementation of the initiatives.

Conclusions: Our findings suggest that benchmarking transportation costs in ESCOs may help to identify outliers and lead providers to implement QI initiatives to reduce healthcare costs.

Funding: Commercial Support - Fresenius Medical Care North America

TH-PO815

Effects of the Affordable Care Act (ACA) and Medicaid Expansion on Incident ESRD Patients Richard A. Hirth,[3] Diane Steffick,[4] Jeffrey Pearson,[1] David W. Hutton,[3] William H. Herman,[2] Vahakn B. Shahinian,[4] John Z. Ayanian,[2] Rajiv Saran.[4] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]University of Michigan, Ann Arbor, MI; [3]Kidney Epidemiology and Cost Center, University of Michigan, Ann Arbor, MI; [4]Internal Medicine - Nephrology, University of Michigan, Ann Arbor, MI.*

Background: The expansion of insurance coverage under the ACA may have improved access to pre-ESRD care in the United States through the health insurance exchanges and the expansion of the Medicaid program. We assessed whether changes in insurance status at onset of ESRD were accompanied by changes in markers of pre-ESRD care.

Methods: Data were from the CMS Medical Evidence Form 2728. Patients whose first dialysis treatment occurred before the ACA's insurance expansions (10/1/11-12/31/13) were compared to patients incident after the ACA (1/1/14-3/31/16). A difference-in-difference approach was utilized to control for background trends in populations not likely to be affected by the ACA. The primary pre- vs. post-ACA comparisons were: 1) patients <65 years old with no Medicare coverage vs. patients 66+ with coverage, and 2) patients <65 in states expanding Medicaid on 1/1/14 vs. patients <65 in states that did not expand.

Results: Overall, the percent of patients <65 uninsured at incidence fell from 17.6% pre-ACA to 11.3% post-ACA [Figure]. Relative to trends for patients 66+, among patients <65, 6.2% saw gain in insurance coverage, 1.6% had gain in pre-ESRD nephrology care, 1.7% increased to use of home dialysis, and 1.4% showed a slower decline in use of EPO, but no improvement in vascular access type. Relative to trends for patients <65 in non-Medicaid expansion states, those in expansion states had a 3.4% gain in insurance, 1.1% gain in pre-ESRD nephrology care, 1.7% gain in fistula-in-use or maturing, but no change in EPO or home dialysis.

Conclusions: The ACA improved insurance coverage for patients initiating dialysis in the US, and increased many but not all markers of pre-ESRD care.

Funding: NIDDK Support

Impact of the Affordable Care Act (ACA) on Incident ESRD Patients

A. Comparing those <65 & not on Medicare at incidence to those 66+ on Medicare at incidence

	Under 65, not on Medicare			Age 66+ and on Medicare			(Under 65
	Pre-Period	Post-Period	Δ under 65	Pre-Period	Post-Period	Δ 66+	- Age 66+)
Total	N=80,114	N=89,912		N=112,423	N=119,276		
No insurance at incidence	17.58%	11.34%	-6.24%	0.21%	0.15%	-0.06%	-6.18%
Had "other" insurance at incidence	11.49%	14.87%	3.38%	27.14%	24.38%	-2.76%	6.14%
Had Medicaid at incidence	32.51%	36.36%	3.85%	17.85%	16.58%	-1.27%	5.12%
Had Medicare at incidence	–	–	–	–	–	–	–
Any use of EPO before ESRD	13.26%	11.48%	-1.78%	18.83%	15.69%	-3.14%	1.36%
Any nephrology care before ESRD	54.56%	57.68%	3.12%	64.04%	65.55%	1.51%	1.61%
Any renal dietician care before ESRD	8.13%	7.61%	-0.52%	7.57%	7.19%	-0.38%	-0.14%
First access type							
Fistula	13.59%	13.34%	-0.25%	16.21%	16.51%	0.30%	-0.55%
Graft	1.92%	1.95%	0.03%	3.05%	3.11%	0.06%	-0.03%
Catheter	75.35%	73.24%	-2.11%	73.34%	72.28%	-1.06%	-1.05%
Other	0.15%	0.15%	0.00%	0.16%	0.17%	0.01%	-0.01%
Unknown	8.99%	11.31%	2.32%	7.24%	7.92%	0.68%	1.64%
Had maturing fistula in place at incid	16.77%	15.46%	-1.31%	16.08%	14.57%	-1.51%	0.20%
Initial dialysis setting: home	7.06%	9.62%	2.56%	6.65%	7.48%	0.83%	1.73%
Initial dialysis type: peritoneal	6.79%	9.31%	2.52%	6.41%	7.18%	0.77%	1.75%

B. Comparing patients living in states that expanded Medicaid to those in states that did not

	Immediate Expansion and Age<65			No expansion and Age<65			(Immed
	Pre-Period	Post-Period	Δ Immed	Pre-Period	Post-Period	Δ Never	- Never)
Total	N=64,929	N=66,121		N=55,922	N=58,938		
No insurance at incidence	9.34%	3.68%	-5.66%	16.76%	14.49%	-2.27%	-3.39%
Had "other" insurance at incidence	13.74%	14.99%	1.25%	8.19%	12.11%	3.92%	-2.67%
Had Medicaid at incidence	35.68%	42.02%	6.34%	28.73%	27.21%	-1.52%	7.86%
Had Medicare at incidence	30.66%	29.63%	-1.03%	36.24%	34.20%	-2.04%	1.01%
Any use of EPO before ESRD	15.72%	13.44%	-2.28%	13.16%	10.87%	-2.29%	0.01%
Any nephrology care before ESRD	59.41%	61.52%	2.11%	58.78%	59.78%	1.00%	1.11%
Any renal dietician care before ESRD	10.40%	9.52%	-0.88%	6.94%	6.36%	-0.58%	-0.30%
First access type							
Fistula	14.49%	14.58%	0.09%	12.79%	12.26%	-0.53%	0.62%
Graft	2.00%	2.07%	0.07%	2.21%	2.14%	-0.07%	0.14%
Catheter	68.65%	67.91%	-0.74%	70.60%	70.29%	-0.31%	-0.43%
Other	0.17%	0.12%	-0.05%	0.15%	0.16%	0.01%	-0.06%
Unknown	14.69%	15.32%	0.63%	14.26%	15.14%	0.88%	-0.25%
Had maturing fistula in place at incid	16.22%	15.66%	-0.56%	16.34%	14.66%	-1.68%	1.12%
Initial dialysis setting: home	10.88%	11.91%	1.03%	11.72%	13.04%	1.32%	-0.29%
Initial dialysis type: peritoneal	10.58%	11.69%	1.11%	11.35%	12.49%	1.14%	-0.03%

Data source: USRDS ESRD database, Medical Evidence form (CMS 2728). Exclusions: (1) patients not living in the 50 states or DC; (2) patients without a 2728 form; (3) patients missing residence at incidence. Patients aged 65 at incidence are excluded from Panel A as they would likely have received Medicare only a short time before incidence. Pre-Period: 10/1/2011 - 12/31/2013 (27m Post-period: 1/1/2014 to 3/31/2016 (27m). States expanding Medicaid immediately (N=25) are: AZ, AR, CA, CO, CT, DE, DC, HI, IL, IA, KY, MD, MA, MN, NV, NJ, NM, NY, ND, OH, OR, RI, VT, WA, WV. States that did not expand Medicaid (N=20 are: AL, FL, GA, ID, KS, LA, ME, MS, MO, NE, NC, OK, SC, SD, TN, TX, UT, VA, WI, WY.

Impact of the Affordable Care Act (ACA) on Incident ESRD Patients

TH-PO816

Socioeconomic Status and Dialysis Quality of Care Rathika Krishnasamy,[1] Dev K. Jegatheesan,[2] Paul D. Lawton,[3] Nicholas A. Gray.[1] *[1]Sunshine Coast University Hospital, Birtinya, QLD, Australia; [2]University of Queensland School of Medicine, Brisbane, QLD, Australia; [3]Menzies School of Health Research, Casuarina, NT, Australia.*

Background: Lower socioeconomic status (SES) has been associated with increased mortality in end stage kidney disease (ESKD) populations across USA, South America, Europe and Australasia. However, less is known about the association between SES and the quality of care (QOC) delivered to dialysis patients.

Methods: This study included all non-Indigenous adults commencing hemodialysis (HD) or peritoneal dialysis (PD) registered with Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry between 2002 and 2012 (n=16867). Each patient's location at dialysis start was classified into SES quartiles of advantaged through to disadvantaged using Australian Bureau of Statistics socio-economic indexes for areas. National and international guidelines were used to set limits for QOC attainment. The association between area-level SES and attainment of QOC indicators at 6-18 months and 18-24 months after dialysis start were assessed using logistic regression models. QOC measures included pre-dialysis phosphate, calcium, hemoglobin, transferrin saturation and ferritin. HD-related parameters included single pool Kt/V and percentage with functioning arteriovenous fistula/graft. PD-related parameters included weekly Kt/V and percentage lost to HD.

Results: The median age was 65 years (interquartile range 53-74), 62.2% were male and 85.1% were Caucasian. There were no significant differences in attainment of biochemical targets, PD or HD adequacy between the SES quartiles at 6-18 months after dialysis commencement. The least advantaged quartile were less likely to achieve hemoglobin target [Odds Ratio (OR) 0.89, 0.79-0.99, p=0.03] or to have a functioning fistula or graft (OR 0.75, 0.61-0.94, p=0.01] compared with the most advantaged group at 18-24 months.

Conclusions: Area-level SES has minimal impact on QOC attainment among non-Indigenous dialysis patients in Australia, where all residents have equal access to government funded healthcare. Increased mortality in lower SES groups is therefore likely due to pre-dialysis, other area-level and individual patient factors such as health-related behaviors, lifestyle and literacy, rather than disparities in QOC.

Funding: Government Support - Non-U.S.

TH-PO817

CAHPS Domains as Predictors of Dialysis Facility Star Ratings and QIP Abhijit V. Kshirsagar,[1] Amir Alishahitabriz,[1] Heejung Bang,[2] Shoou-Yih D. Lee.[1] *[1]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]UC-Davis, Davis, CA.*

Background: Recent national initiatives have focused on differing aspects of dialysis care quality in the United States. The Dialysis Facilities Compare (DFC) star rating & the Quality Incentive Program (QIP) generate distinct scores from clinical measures to quantify care quality. The Consumer Assessment of Healthcare Providers and Systems (CAHPS) survey evaluates the patient experience to assess the perceived quality of care in separate domains related to dialysis facility & staff, nephrologists, and peer-to-peer counseling. Knowing how the patient experience relates to star ratings & QIP may help providers develop strategies to improve dialysis care delivery.

Methods: We linked the star ratings and QIP scores with CAHPS survey results for each dialysis clinic by its unique identifier (available at the DFC website) for calendar year 2016. With the CAHPS domains as independent variables, we calculated odds ratio from an ordered Logit model for star ratings, and calculated the linear strength of association for QIP. We adjusted for facility size, profit status, and home dialysis status. Peer-to-peer counseling was not analyzed due to a large proportion of non-reported data.

Results: From a total of 6750 dialysis facilities nationally, 6027 had star ratings (1 - low to 5 - high), 6229 facilities had QIP score and 3354 facilities had CAHPS survey results. CAHPS domains related to preceived facility delivery of care (staff and operations) were consistently stronger predictors of a 5-star rating or high QIP than domains related to perceived delivery of care by nephrologists, Table.

Conclusions: Patient's perception of care delivery, captured by CAHPS, is directly related to the known quality measures-- star ratings and QIP. Interestingly the facility staff and environment are stronger predictors of quality than nephrologists. Understanding patients' perception of care may help with their engagement to ultimately reach important quality goals.

Funding: NIDDK Support, Clinical Revenue Support

CAHPS	5 Star (Odds Ratio)*	QIP (β-coefficient)*
Nephrologist-Related Domains		
Patients rating nephrologists' communication and caring	1.46	12.79
Patients rating of the nephrologist	1.34	11.79
Facility-Related Domains		
Patients rating of quality of dialysis center care and operations	1.98	32.86
Patients rating of the dialysis center staff	1.70	24.71
Patients rating of the dialysis facility	1.76	26.28

* $p < 0.001$

TH-PO818

Patient Reported Clinical Symptoms Are Associated with Patient Outcomes Dugan Maddux,[1] Hao Han,[1] John W. Larkin,[1] Len A. Usvyat,[1] Frank van der Sande,[2] Jeroen Kooman,[2] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Maastricht University Medical Centre, Maastricht, Netherlands.*

Background: Traditional outcomes-related research on dialysis patients typically focuses on biomarkers such as blood pressure, body size, albumin (alb) and hemoglobin. During dialysis treatment, however, nurse-documented "chairside" patient information is also collected, and majorly includes patients' symptoms that may have an effect on patients' clinical outcomes. The association of chairside data with patient outcomes has not been well described. We aim to understand the relationship of "shortness of breath" (SOB), a nurse-reported patient symptom, to patient outcomes.

Methods: We included all patients who initiated dialysis treatment in the network of Fresenius Medical Care North America clinics between Jan 1, 2013 and June 30, 2015. Only patients who survived the first 365 days on dialysis were included. Patient laboratory and treatment parameters including The Kidney Disease Quality of Life (KDQOL) survey were computed as averages of the first year on dialysis. Patient hospitalization outcomes were assessed in year 2 on dialysis. We computed percent of treatments where patients experienced SOB symptoms as determined by either nursing notes or checkbox-based assessment in the electronic health record. A Poisson model using hospital admissions as an outcome was utilized to calculate the association of SOB to hospital admissions.

Results: We analyzed data on 39,594 dialysis patients. In a univariate analysis, we noted that the strongest correlation with percent of treatments with SOB were hospital admission rate (r=0.14, p<0.001), alb level (r=-0.09, p<0.001), KDQOL physical composite score (r=-0.12, p<0.001), and KDQOL symptom problem score (r=-0.11, p<0.001). We also observed that the percent of treatments with SOB was clearly significantly associated with more hospital admissions.

Conclusions: Chairside observation and clinician documentation of patient-reported symptoms may be an important predictor of outcomes in dialysis patients. Additional analyses are needed to understand the association of SOB and other symptoms to patient outcomes.

Funding: Commercial Support - Fresenius Medical Care North America

TH-PO819

Transplantation as a Competing Risk in Dialysis RCTs Christos Argyropoulos,[5] Maria-Eleni Roumelioti,[4] Mark L. Unruh,[5] V. Shane Pankratz,[3] Francesco Locatelli,[1] Adelheid Gauly.[2] *[1]Azienda Ospedaliera Della Provincia di Lecco-Ospedale Alessandro Manzoni, Lecco, Italy; [2]Fresenius Medical Care, Bad Homburg, Germany; [3]UNM Health Sciences Center, Albuquerque, NM; [4]University of New Mexico, Albuquerque, NM; [5]University of New Mexico, Albuquerque, NM.*

Background: Transplantation is a competing risk and potential confounder in the analysis of outcomes in ESRD RCTs. We examined whether results of RCTs are affected by the method to account for these informative censoring events.

Methods: We analyzed patient level data from the NIDDK sponsored HEMO and the European MPO RCTs of high flux (HF) membranes. Together these two studies contribute 96% of the evidence for the use of HF in clinical practice. We compared conventional Cox proportional hazards (CPH) models and methods for competing risk events (cumulative incidence functions, CIF) and relevant regressions models.

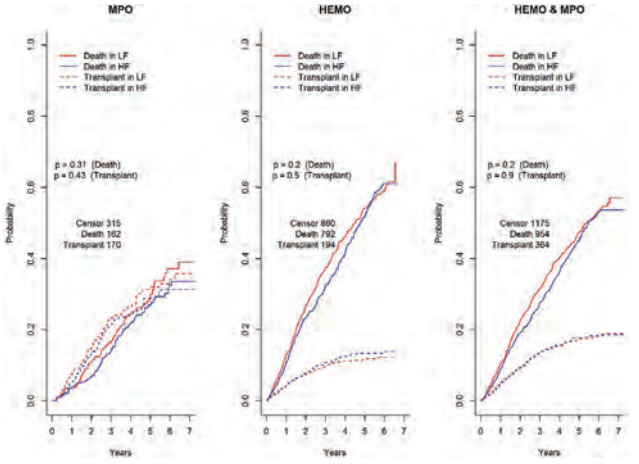
Results: In HEMO there were 194 transplantation out of 1846 patients; 170 out of 647 participants were transplanted during MPO. In unadjusted analyses of CIF[figure], HF dialysis was not associated with improved survival (p=0.20). In adjusted CPH analyses, treatment effects differed in both studies (HR 0.82 in MPO, but 0.95 in HEMO). In analyses that accounted for the competing risks of transplant, treatment effects were similar in magnitude [table]. Furthermore, when the studies were analyzed together HF was associated with 16% reduction in the incidence of death (p=0.022).

Conclusions: Effect sizes, and perceived congruency of interventions in RCTs in ESRD, may depend on the methods for handling censoring due to transplantation. Our findings mirror recent reports in hemodiafiltration (HDF) RCTs [Nephrol Dial Transplant (2017) 32: ii31–ii39], raising the question whether many negative (e.g. statins) and/or discrepant results in nephrology (HF or HDF) are due to the statistical methods employed to analyze trials.

Funding: Clinical Revenue Support

	CPH	Competing Risk Model	
	Death	Death	Transplant
	HR[95%CI]	HR[95%CI]	HR[95%CI]
HEMO	0.92 [0.80,1.06]	0.84 [0.72,0.99]	0.89 [0.64,1.22]
MPO	0.82 [0.59,1.12]	0.80 [0.56,1.15]	0.84 [0.58,1.22]
Both	0.92 [0.81,1.04]	0.84 [0.73,0.98]	0.96 [0.77,1.20]

Adjusted for age, gender, black race, albumin, diabetic status and country



TH-PO820

Early Mortality Comparison between Hemodialysis and Peritoneal Dialysis Patients Who Transition with an Optimal Outpatient Start John J. Sim,[1] Hui Zhou,[1] Jiaxiao Shi,[1] Sally F. Shaw,[1] Scott A. Rasgon,[1] Csaba P. Kovesdy,[3] Kamyar Kalantar-Zadeh,[2] Steven J. Jacobsen.[1] *[1]Kaiser Permanente Southern California, Pasadena, CA; [2]University of California Irvine, School of Medicine, Orange, CA; [3]University of Tennessee Health Science Center, Memphis, TN.*

Background: Lower early mortality observed in peritoneal dialysis (PD) compared to hemodialysis (HD) may be due to differential pre- end stage renal disease (ESRD) care and the stable setting of transition to dialysis. Specifically, PD starts occur more frequently in an outpatient setting rather than during a hospitalization. To account for these circumstances, we sought to compare early mortality among PD and HD patients who had optimal ESRD starts and first transitioned to dialysis on an outpatient basis.

Methods: A retrospective cohort study (1/1/2002-12/31/2013) within Kaiser Permanente Southern California (an integrated health system) was performed on chronic kideny disease patients who had optimal start transition to ESRD in an outpatient setting. Optimal start was defined as 1) initiation of HD with an arteriovenous fistula or graft or 2) initiation with PD. Propensity score modeling factoring sex, race, age, co morbidities, eGFR level, and change in eGFR prior to ESRD was used to create a matched cohort of HD and PD patients. All-cause mortality odds ratio (OR)'s were estimated for 6 months, 1 yr, and 2yr post transition to ESRD.

Results: A total of 2,094 (1398 HD and 696 PD) patients had an optimal outpatient transition to ESRD. The mean age was 62 yrs with 40% females, 39% Hispanics, 26% whites, and 21% blacks. In the 2 year observation window, 20% PD patients switched to HD while only 2% of HD patients switched to PD. 547 HD patients were matched to 547 PD patients on the propensity score with caliper distance <=0.001. All-cause mortality OR in HD compared to PD patients were 1.09 (0.47-2.57), 1.64 (0.92-2.93), and 0.90 (0.61-1.33) for 6 months, 1yr, and 2yrs, respectively. White race and age >/=60 yrs were associated with higher mortality.

Conclusions: There were no differences in early mortality between PD and HD patients who transitioned to ESRD with an optimal start in an outpatient setting. While prior observations have suggested an early survival advantage with PD, our finding suggest that the pre-ESRD care and the stable transition to dialysis likely account for lower early mortality among the ESRD population.

Funding: NIDDK Support

TH-PO821

KDOQI Nutrition Guideline 21 Associates with Overfeeding in Critically Ill ESRD Patients Eli McKenna-Weiss, Daniel L. Landry, Patrick Mailloux, Young hee Kim, Gregory L. Braden. *Medicine, U Mass Medical School/ Baystate, Springfield, MA.*

Background: KDOQI nutrition guideline 21 states that critically ill ESRD patients(pts) less than 60 yr old receive at least 35 kcal/kg/day of total parenteral nutrition(TPN) & pts over 60 should receive 30-35 kcal/kg/day TPN. U.S. guidelines for ICU nutrition suggest 22-24 kcal/kg/d for critically ill non ESRD pts.

Methods: We studied 11 intubated ESRD pts (4W/7M) in the ICU with the Puritan Bennett indirect calorimeter on 3 different non dialysis days while NPO and during TPN with 28 or 38 kcal/kg/d. 4 pts were under age 60 & 7 pts were over age 60. Only 1 pt had diabetes mellitus. Causes for the ICU: sepsis 4, respiratory failure 5, cva 1 & chf 1. Mean time on hemodialysis was 1.5 years and mean serum albumin pre study was only 2.4+/- 0.2 gm/dl. Pts were studied from 5 am to 1 pm & the results of resting energy expenditure (REE), VO2 (ml/min), VCO2 (ml/min) and respiratory quotient(RQ) were calculated by the continuous machine averages for all parameters. Time averaged glucose levels q 4 hours were calculated. TPN intake ratios for both the 28 and 38 kcal studies were: 20% protein, 30% fat & 50% carbohydrates.

Results: Baseline REE for age under 60 was 26.0 +/- 4 kcal/kg/d and for over 60 was 22.0 +/- 2 kcal/kg/d despite sepsis in 2 pts in each group (p NS). REE for all NPO pts was only 23.5 +/- 4 kcal/kg/d & only 24.5 +/- 4 & 26.0 +/- 3 for TPN days with 28 or 38 kcal/kg/d (p NS). The mean +/- SE for indirect calorimetry are shown in the table:

Conclusions: We conclude: 1) The REE in critically ill ESRD pts is similar to non ESRD pts with a mean REE of 23.5 kcal/kg/d. 2) There are no differences in REE in ESRD pts less than or over age 60. 3) Early feeding TPN in ICU ESRD pts at 28 or 38 ckal/kg/d signicantly increaed VO2, VCO2, RQ and glucose levels which indicates excessive carbohydrate metabolism &/or increased lipogenesis which may be harmful to these pts. 4) KDOQI nutrition guideline 21 needs to be modified based on our study.

	VO2 (ml/min)	VCO2 (ml/min)	RQ	Glucose
NPO	208+/- 19	166 +/- 12	0.80	106 +/- 15
28 Kcal/kg	204 +/- 20	192 +/- 13#	0.95#	162 +/- 30#
38 Kcal/kg	239 +/- 32#	214 +/- 24#	0.95#	159 +/- 25#

# $p < 0.05$ compared to NPO. The increased VCO2, RQ & glucose levels suggest carbohydrate overfeeding and increased lipogenesis in the TPN groups. No differences found between 28 and 38 kcal groups in any parameter.

TH-PO822

Limitations of the KDQoL for Assessing Quality of Life Among Patients with ESRD Andrew Lee,[1] Dena E. Cohen,[1] Scott Sibbel,[1] Deborah A. Benner,[2] Steven M. Brunelli,[1] Francesca Tentori.[1] *[1]DaVita Clinical Research, Minneapolis, MN; [2]DaVita, Inc, Denver, CO.*

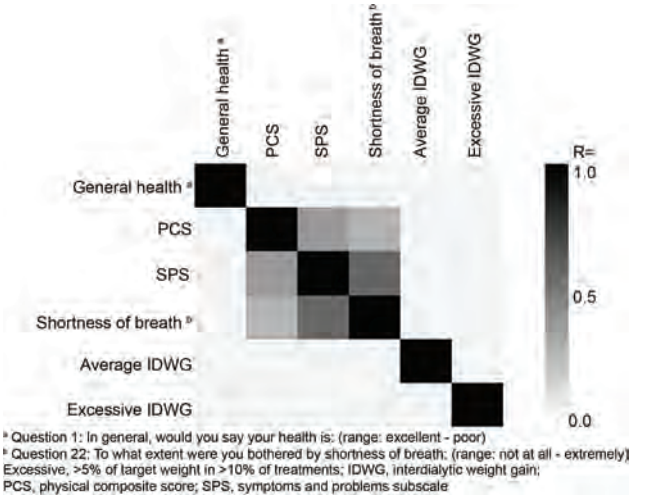
Background: Achieving the best possible quality of life (QoL) is a key goal for patients with end-stage renal disease (ESRD). The Centers for Medicaid and Medicare Services mandate regular assessment using the Kidney Disease Quality of Life (KDQoL) survey. Given concerns that the KDQoL may not adequately capture QoL among contemporary ESRD patients, we examined its construct validity.

Methods: We considered 282,895 KDQoL surveys completed by 175,826 adult patients receiving in-center hemodialysis at a large US dialysis organization (2014-2016). Correlations between item responses, domain scores, and interdialytic weight gain (IDWG) were calculated using Pearson correlations computed with pairwise complete observations.

Results: Patient perceptions of general health were not correlated (R<0.05) with any other question in the physical composite score (PCS) or the symptoms and problems subscale (SPS). Mean SPS (77.9 ± 16.9) exceeded mean PCS (36.3 ± 12.2); correlation between the two was modest (R=0.42). Many items in the SPS showed ceiling effects: for all 12 items, <10% of patients were "extremely bothered," while >65% of patients reported being "not at all" or only "somewhat bothered;" for 3 items, >85% of patients gave these two responses. IDWG was not correlated with patient-reported shortness of breath, PCS, or SPS.

Conclusions: We identified possible limitations in the mandated tool that is used for assessment of QoL in ESRD patients. New measures of QoL that focus on factors that affect a considerable proportion of contemporary dialysis patients, particularly those that can be addressed by modifiable clinical practices, are needed.

Funding: Commercial Support - DaVita, Inc



TH-PO823

Adverse Drug Effects in Patients with ESRD Who Present to the Emergency Department Lili Chan,[1] Priti Poojary,[1] Aparna Saha,[1] Kinsuk Chauhan,[1] Steven G. Coca,[1] Pranav S. Garimella,[2] Girish N. Nadkarni.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]University of California San Diego, San Diego, CA.*

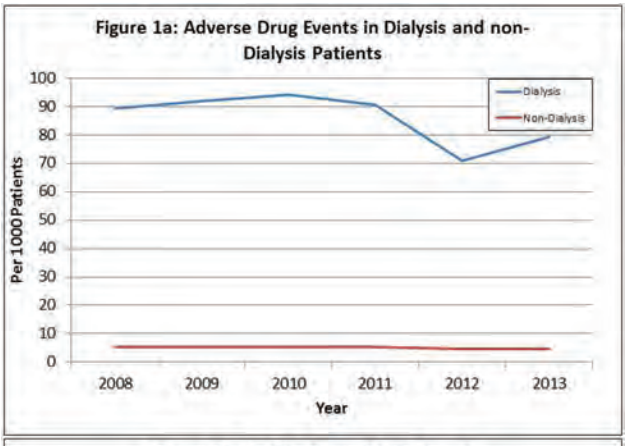
Background: Patients on dialysis are at high risk for adverse drug effects (ADEs) due to impaired renal clearance of medications and polypharmacy. We aimed to explore trends and outcomes of ADEs in dialysis patients.

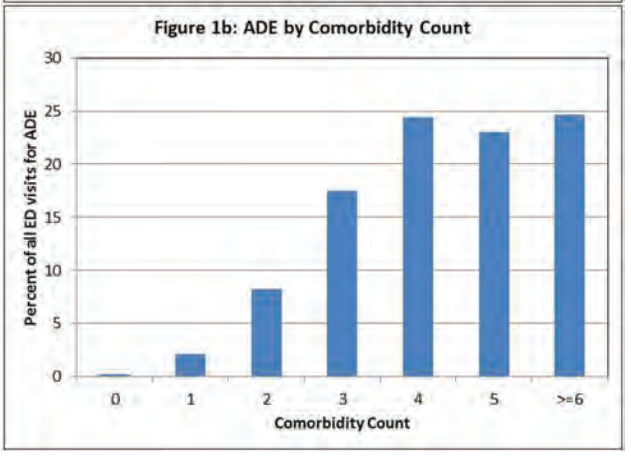
Methods: We utilized a nationally representative database, the Nationwide Emergency Department Sample, to identify dialysis patients who present to the emergency

department (ED) for an ADE. We excluded illicit drug toxicities, intentional poisoning, renal transplantation, pregnancy and age <18. Incidence was calculated using the United States Renal Data System and the United States Census Bureau data.

Results: From 2008 to 2013, there were 9,734,821 ED visits for ADEs. ED visits for ADEs were consistently higher in dialysis patients compared to non-dialysis patients, 70-94/1000 patients vs. 4-5/1000 patients (Figure 1a). In dialysis patients, ADEs were more common in females, age ≥ 65 years, and hemodialysis vs. peritoneal dialysis patients. Incidence of ED visits for ADEs increased with increasing number of co-morbidities (Figure 1b). In-patient admission was more common in dialysis patients, 88% vs. 58%, P <0.001. Mortality of ESRD patients who were admitted was 3 times that of non-dialysis patients.

Conclusions: ED visits for ADEs are common in dialysis patients, and substantially higher than in non-dialysis patients. Nearly 90% of all ER visits for ADEs in dialysis patients results in an inpatient hospital admission which contributes to great financial burden on the health care system.





TH-PO824

Impact of Pre-Dialysis Acute Hospitalizations on Post-Dialysis Outcomes in Incident Dialysis Patients Silvi Shah, Anthony C. Leonard, Charuhas V. Thakar. *University of Cincinnati, Cincinnati, OH.*

Background: Mortality in end stage renal disease (ESRD) patients is highest during the first year of dialysis. Although survival is similar in hemodialysis (HD) and peritoneal dialysis (PD), overall costs of care are lower in PD. In spite of the increasing burden of cardiovascular (CV) disease and infections with kidney disease progression, the impact of pre-dialysis acute hospitalizations on dialysis modality and on mortality in dialysis patients is not known.

Methods: We evaluated 49,645 adult incident dialysis patients (1/1/2008 to 12/31/2008) from the United States Renal Data System (USRDS) with linked Medicare data for at least 2 years prior to dialysis initiation. Using case-mix adjusted logistic regression models (16 variables), we examined the impact of pre-dialysis acute hospitalizations on type of dialysis modality (PD vs. HD) and one-year all-cause mortality. We evaluated 4 groups of patients by cause of hospitalizations: CV related, infection related [INF], both CV and INF [CV+INF]; and neither CV nor INF related.

Results: The sample was 55% male, 63% White with a mean age of 72±11 years. Only 4% of patients received PD as initial modality. Among the study cohort, 89% had at least one pre-dialysis hospitalization [CV-34%; INF-11%; CV + INF-12%; and 33%-neither CV nor INF]. In adjusted analyses, as compared with no pre-dialysis hospitalizations, patients with INF, CV, CV+INF and neither CV nor INF hospitalizations were more likely to be started on HD (odds ratio [OR] 2.7, 95% confidence interval [CI] 2.24-3.26; OR 2.7, CI 2.37-3.08; OR 3.3, CI 2.68-4.08; OR 2.6, CI 2.3-2.93 respectively). In adjusted analyses, one-year mortality was higher with pre-dialysis INF hospitalizations (OR, 1.41; CI 1.28-1.54), CV hospitalizations (OR, 1.47; CI 1.35-1.59) and INF+CV hospitalizations (OR, 1.87; CI 1.7-2.05), compared with no pre-dialysis hospitalizations.

Conclusions: Pre-dialysis hospitalizations are frequent; infection or cardiovascular related hospitalization independently increases the odds of HD vs. PD; and is an independent predictor of one-year mortality in incident dialysis patients. Effects of pre-ESRD hospitalization should be considered while comparing mortality as quality of dialysis care. Reducing pre-ESRD hospitalizations may improve survival and costs of care after initiating dialysis.

TH-PO825

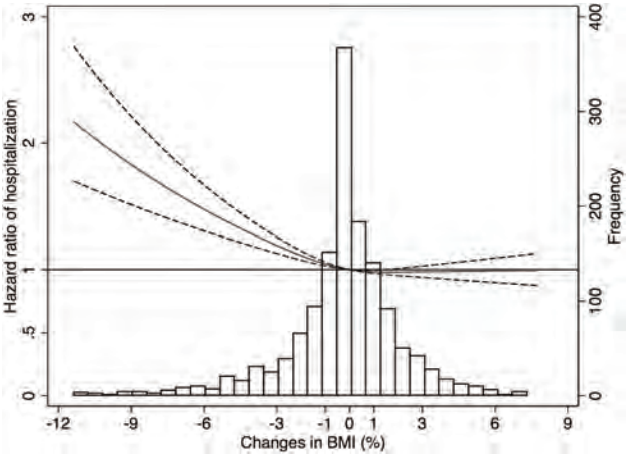
Change in Body Mass Index and Subsequent Risk of Hospitalization in Elderly Hemodialysis Patients: The Japanese Dialysis Outcome and Practice Patterns Study (J-DOPPS) Keiichi Sumida,[1] Shungo Yamamoto,[2] Tadao Akizawa,[3] Shunichi Fukuhara,[2] Shingo Fukuma.[2] *[1]Toranomon Hospital Kajigaya, Kawasaki, Japan; [2]Kyoto University, KYOTO, Japan; [3]Showa University School of Medicine, Tokyo, Japan.*

Background: Short-term weight gains and losses are associated with lower and higher mortality risk, respectively, in patients on hemodialysis (HD). However, little is known about their association with the risk of subsequent hospitalization.

Methods: In a prospective cohort of 1,804 HD patients aged ≥65 years enrolled in the J-DOPPS phases 3 (2005–2008) and 4 (2009–2011), we examined the associations of changes in body mass index (BMI) over a 4-month baseline period (<-3, -3-<-1, -1-<1 [reference], 1-<3, and ≥3%) with subsequent risk of all-cause, cardiovascular (CV), and non-CV hospitalizations, respectively, using Cox models with adjustment for potential confounders.

Results: During a median follow-up of 1.2 years, there were 1,027 incident hospitalizations for any cause. There was an L-shaped association between BMI change and all-cause hospitalization (Figure). The adjusted HRs (95% CI) of all-cause hospitalization associated with BMI changes of <-3, -3-<-1, 1-<3, and ≥3% (vs. -1-<1%) were 1.30 (1.04-1.63), 1.23 (0.99-1.52), 1.04 (0.84-1.30), and 1.13 (0.86-1.49), respectively. Qualitatively similar associations were present for non-CV hospitalization (corresponding HRs [95% CI] were 1.33 [1.04-1.69], 1.24 [0.98-1.56], 1.07 [0.85-1.35], and 1.14 [0.84-1.56], respectively), but not for CV hospitalization (corresponding HRs [95% CI] were 1.23 [0.65-2.33], 1.10 [0.69-1.75], 0.87 [0.51-1.49], and 1.03 [0.46-2.33], respectively).

Conclusions: Decreases in BMI over a relatively short-term period were independently associated with higher risk of subsequent hospitalization, particularly non-CV hospitalization, among elderly HD patients.



TH-PO826

Weekend versus Weekday Admission in Dialysis Dependent Patients Requiring Hospitalization – A Nationwide Analysis Yumeng Wen,[1,2] Di Pan,[1,2] David Mariuma,[1,2] Michael Gramuglia,[3] Ira S. Meisels.[1,2] *[1]Division of Nephrology, Department of Medicine, Mount Sinai St. Luke's and Mount Sinai West Hospitals, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]Department of Medicine, Montefiore Medical Center, Scarsdale, NY.*

Background: End Stage Renal Disease (ESRD) is a major cause of worldwide mortality and morbidity. ESRD requiring chronic dialysis is associated with high mortality and morbidity, requiring frequent hospitalization for complications from dialysis and comorbidities. The aim of this study is to determine the differences in outcomes and resource utilization of dialysis dependent patients hospitalized on weekends compared to weekdays.

Methods: This is a retrospective cohort study using the 2014 National Inpatient Sample, the largest publically available inpatient database in the United States. The inclusion criteria were age above 18 and an ICD-9 CM code for diagnosis of ESRD on chronic dialysis. Patients hospitalized for elective procedures were excluded. The primary outcome was in-hospital mortality. The secondary outcomes were morbidities, as measured

by the development of shock and acute respiratory failure, as well as resource utilization including length of hospital stay (LOS) and total hospitalization charges. Analysis is performed by using Stata, version 14.2. Odds ratio (OR) and means were adjusted for the following confounders using multivariate regression models: demographics, Charlson Comorbidity Index, early dialysis in hospital (defined as receiving dialysis within 1 day of admission), primary insurance, hospital bedsize, hospital region and household income.

Results: 934,575 patients with ESRD on chronic dialysis were included in the study. Patients admitted on weekends were associated with significantly higher in-hospital mortality rates (5.45% versus 4.87%, p=0.02) and higher rate of acute respiratory failure (3.89% versus 3.32%, OR 1.11, p=0.001). The development of shock was not significantly different (OR 0.97, p=0.69). Weekend admission was associated with greater length of stay (6.90 versus 6.89, p<0.001), however the total hospital charges were not significantly different (p=0.07). Patients admitted on weekends had lower rate of receiving early dialysis (43.72% versus 52.72%, p<0.001).

Conclusions: Compared to weekday admission, weekend admission in patients with ESRD on chronic dialysis was associated with higher rates of mortality and acute respiratory failure, as well as greater length of stay even after controlling for early dialysis. Patients admitted on weekends were less likely to receive early dialysis.

TH-PO827

Urgent Start Dialysis: Peritoneal Dialysis versus Hemodialysis via a Central Venous Catheter Neelam M. Bhalla,[3] Neiha Arora,[2] Jeanne A. Darbinian,[1] Sijie Zheng.[2] *[1]Kaiser Permanente, Oakland, CA; [2]The Permanente Medical Group, Oakland, CA; [3]nephrology, kaiser permanente, Hayward, CA.*

Background: Though underutilised in the US, PD is a safe and effective home modality of renal replacement therapy. One reason for under use of PD is the practice of initiating patients on HD via a central venous catheter (CVC) if they do not have a functional AVF/AVG. When compared with AVF/AVG, CVC use is associated with increased mortality. Recently, use of urgent start PD has gained interest since it decreases use of CVCs, while affording a mechanism of increased PD utilization. In this retrospective cohort study, we compared complications and outcomes between the two urgent start dialysis modalities.

Methods: We identified a subpopulation of KPNC members who met clinical criteria for being in urgent need of beginning PD or HD between 1/1/2011 and 12/31/2014. Urgent start HD patients were matched 3:1 with PD urgent starts on selected characteristics. Medical records of all cohort members were reviewed by three nephrologists. Complications and outcomes occurring after initiation of dialysis were compared between the modalities using Chi-square or Fisher exact tests.

Results: We compared 335 HD starts with 84 PD starts. There were no modality switches in the PD cohort; in HD start cases one changed to home HD and four to PD. Transferring to hospice accounted for 92% of modality terminations in HD; reasons in PD were psychosocial (43%); medical (28.6%); peritonitis (14.3%) and others (14.3%). Major complications were low in both groups (<5%), though rate of catheter malfunction was higher in HD (12.8% vs. 6.0%, p=0.09). There was a statistically significant difference in overall infectious complications between PD (20%: peritonitis -13%; exit site - 7%) and HD (9%: bacteremia - 7.2%; exit site - 1.8%, p<0.01). There were more deaths in the HD group (19.7% vs 7%, p=0.015). Furthermore a higher proportion of deaths was observed in patients with bacteremia compared with those who had peritonitis (25 vs. 16.7%). Pericatheter leaks developed in 7% of PD cases and in no HD patients.

Conclusions: Urgent PD start is a viable alternative to urgent HD start via CVC. Although infectious complications were higher in PD, peritonitis was associated with less mortality than bacteremia. Notably there is a high patient retention rate, leading to increased utilization of PD.

Funding: Private Foundation Support

TH-PO828

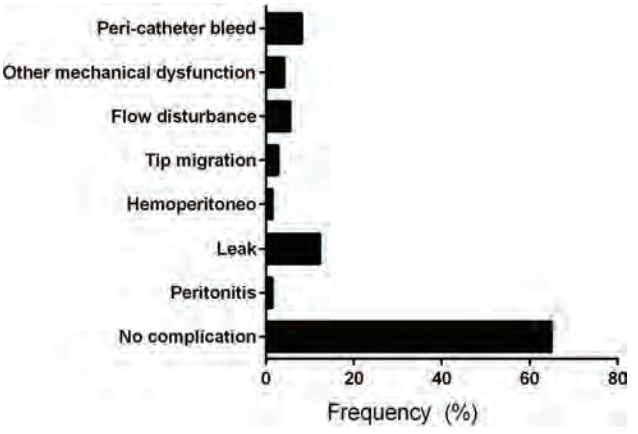
Urgent-Start Peritoneal Dialysis by the Nephrologist Javier Soto-Vargas,[3] Heriberto R. López,[3] Martín D. Vargas ezquivel,[3] Carlos Daniel Jiménez Mejía,[3] Ana L. Garc?a-Vera,[3] Rodolfo A. Cortina,[2] Alfonso Ramos,[1] Renato Parra,[3] Mario A. Garc?a C?rdenas.[3] *[1]Baxter Mexico, San Jer?nimo Chicahualco, Mexico; [2]ISSSTE, MEXICO CITY, Mexico; [3]Regional General Hosptial 46, Mexican Institute of Social Security, Guadalajara, Mexico, Guadalajara, Mexico.*

Background: Urgent-start peritoneal dialysis is an alternative to initiation of renal support in patients with end-stage renal disease. The objective is to describe our experience with an urgent-start PD program.

Methods: In this prospective observational study, we report on our experience in a single academic center. All patients treated with urgent-start PD, defined as PD therapy initiated within 1 week after catheter insertion, and from September 2016 to April 2017 were included. Peritoneal dialysis catheters were inserted percutaneously by punction. Dialysis was initiated in an inpatient setting whit a fix dose of 60 liters in fast cycles.

Results: Seventy three patients were started on urgent PD during our study period. Follow-up of 30.5 days (IQR 25-55.5). Dialysis was initiated with a median of 1 day (IQR, 0.6-2.0). The major indications for treatment were acidosis and uremic syndrome. The median hemoglobin was 8 g/dL (IQR 6.9-8.9), urea 224.5 mg/dL (194-293), potassium 4.8 mEq/dL (IQR 4.1-5.4), pH 7.32 (IQR 7.2-7.38) and HCO3 12.8 mEq (IQR 9.5-16.1). Twenty-five patients (34%) developed a mechanical complication of which: nine (12.2%) were peri-catheter leak, flow dysfunction in 7 (9.5%) patients and 6 (8.1%) cases of peri-catheter bleed. Eight (10.8%) patients required catheter removal and reinsertion, and only one (1.4%) patient required modality switch. No demographic or biochemical characteristic was associated with the development of any complication.

Conclusions: Urgent-start PD is an acceptable and safe alternative compared to hemodialysis for initiation of renal support in patients with end-stage renal disease.



TH-PO829

Abstract Withdrawn

TH-PO830

The Gastrointestinal Symptoms in Peritoneal Dialysis Patients I-kuan Wang,[2] Chin-Chi Kuo,[1] Chiu-Ching Huang.[2] *[1]None, Taichung, Taiwan; [2]China Medical University Hospital, Taichung, Taiwan.*

Background: Gastrointestinal (GI) symptoms such as gastrointestinal reflux, constipation, indigestion, abdominal pain and diarrhea are common in peritoneal dialysis (PD) patients. Constipation is a risk factor of PD-related peritonitis. The aim of this study is to evaluate the prevalence of GI symptoms in PD patients.

Methods: Patients undergoing PD more than one month in China Medical University hospital was enrolled from July 2011 to March 2013. To evaluate the presence of GI symptoms, PD patients were asked to complete the gastrointestinal symptom rating scale (GSRS). The GSRS, a questionnaire, include 15 items, which could be classified into abdominal pain, reflux, diarrhea, indigestion, and constipation. Each item was rated as 0, 1, 2, and 3 according to severity.

Results: A total of 40 patients completed the questionnaire. The mean age was 49.58 ± 11.49 years. The duration of PD was 43.26 ± 31.47 months. 21 (52.5%) patients were female. The etiology of ESRD includes chronic glomerulonephritis (19 patients, 46.3%), diabetes (8 patients, 20%), hypertension (6 patients, 15%), chronic tubulointerstitial nephritis (4 patients, 10%) and polycystic kidney disease (3 patients, 7.5%). Only 3 patients (7.5%) have no GI symptoms. The prevalence of abdominal pain, reflux, diarrhea, indigestion, and constipation was 40% (16 of 40), 35% (14 of 40), 37.5% (15 of 40), 77.5% (31 of 40), and 62.5% (25 of 40). The prevalence of 0, 1, 2, 3, 4, 5 GI symptoms was 7.5% (3 of 40), 15% (6 of 40), 30% (12 of 40), 20% (8 of 40), 20% (8 of 40), and 7.5% (3 of 40), respectively.

Conclusions: GI symptoms are highly prevalent in PD patients. Medical staffs have to pay attention to and take good care of these GI problems

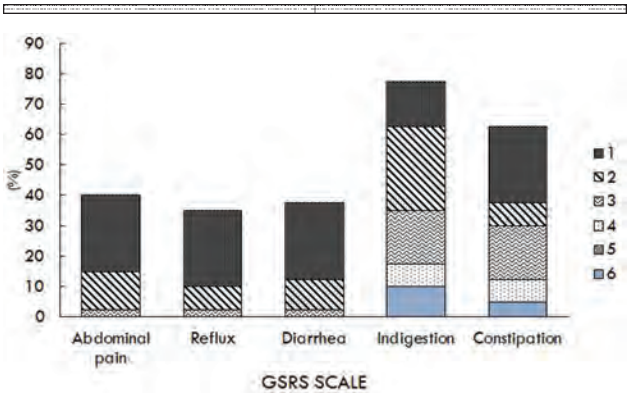


Figure 1. The prevalence and grading of gastrointestinal symptoms in peritoneal dialysis patients according to the gastrointestinal symptom rating scale.

TH-PO831

Allopurinol Does Not Protect Renal Function in Patients on Peritoneal Dialysis Antonio A. Portela Neto,[4] Rosilene M. Elias,[5] Rosa M. Moyses,[2] Hugo Abensur,[3] Benedito J. Pereira,[6] Lilian Cordeiro.[1] *[1]None, Sao Paulo, Brazil; [2]Universidade Nove de Julho, São Paulo, Brazil; [3]Universidade de Sao Paulo, Sao Paulo, Brazil; [4]University State of São Paulo, São Paulo, Brazil; [5]University of Sao Paulo, Sao Paulo, Brazil; [6]University of Sao Paulo School of Medicine, Sao Paulo, Brazil.*

Background: Preservation of renal function in peritoneal dialysis (PD) patients is essential, since it is directly associated with increased survival in this method. Although there is evidence that allopurinol protects residual renal function (RRF) in patients with chronic renal disease not yet on dialysis, whether there is still benefit after these patients started PD is unknown. We therefore examined a cross-section of incident patients on PD to test the association between uric acid (UA) and the use of allopurinol with preservation of RRF.

Methods: Patients starting PD between January 2009 and December 2016 in an academic center, with demographic, clinical and laboratorial data were included. The outcome of interest was renal Kt/V, obtained in two moments: within the first 6 months of PD and at the end of the follow-up period. The difference between final and initial Kt/V was defined as Kt/V delta.

Results: Sixty-nine patients (age 47±18 years, 47% male, 79% hypertensive and 25% diabetic) were included. The UA was 7.2±1.8, ranging from 3.2 to 12.8 mg/dl. More than half of the patients (53.6%) presented UA higher than 7.0 mg/dl, with no difference in Kt/V delta [-0.33 (-0.55, -0.05 vs. -0.19 (-0.44, -0.01) in patients with UA higher and lower than 7.0 mg/dl, respectively; p = 0.382]. Delta Kt/V correlated with UA delta (r=-0.390, p=0.001), but it was not different between patients with and without allopurinol [-0.17 (-0.45; -0.01) vs. -0.29 (-0.66, 0.93; -0.02, respectively; p = 0.443]. Multiple regression analysis showed that neither UA nor UA delta (adjusted for allopurinol use) were independently associated with Kt/V delta.

Conclusions: The use of allopurinol had no impact on the preservation of RRF in patients on PD. In view of possible harm associated with allopurinol, prospective and interventional studies are required prior to recommendation of a regular prescription of such a drug for the PD population, as an attempt for renal preservation.

TH-PO832

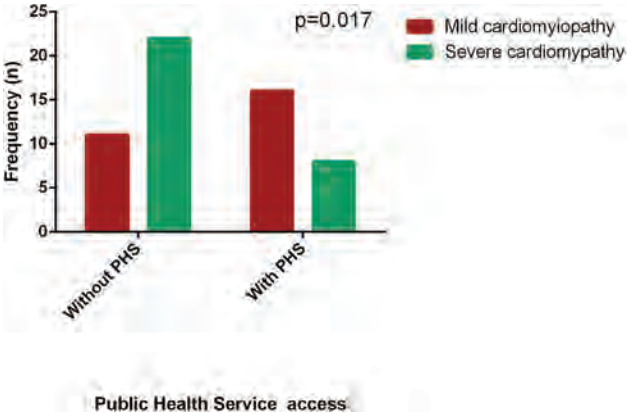
Uremic Cardiomyopathy in Young Incident Peritoneal Dialysis Patients According to the Access of Public Health Services Perla T. Figueroa-Gonzalez,[1] Javier Soto-Vargas,[1] Ana S. Espinoza,[1] Julio A. Gutierrez,[1] Osvaldo Rafael Medina Zepeda,[2] Leonardo Pazarin-Villaseñor.[1] *[1]Nephrology, Regional General Hospital 46, Mexican Institute of Social Security, Guadalajara, Mexico, Guadalajara, Mexico; [2]Cardiology, Regional General Hospital 46, Mexican Institute of Social Security, Guadalajara, Mexico.*

Background: Uremic cardiomyopathy is responsible for high morbidity and mortality rates among patients with end-stage renal disease. Our objective was to describe and compare the echocardiography characteristics of young incident peritoneal dialysis (PD) patients with and without access to Public Health Services (PHS).

Methods: Seventy-two incidents PD patients under 35 years old and with no history of cardiovascular disease underwent Doppler echocardiography evaluation. The results were reported according to the American Society of Echocardiography and the European Association of Cardiovascular Imaging.

Results: Thirty-six patients with universal medical care access and 36 without it were evaluated. Fifty-seven (79.2%) of the total cohort had at least one alteration on Doppler echocardiography evaluation. Thirteen (18.1%) had systolic dysfunction, and the median VEF was 60% (IQR, 51-63.7), in 9 (12.5%) patients diastolic dysfunction was present and 21 (11.1%) had a degree of pulmonary hypertension. The patients without access to PHS were younger (median 20 years, IQR 19-24, p=0.005), had higher left ventricular mass (median 238 grams, IQR 200-270, p <0.000), greater systolic dysfunction, VEF (median 55.5, IQR 42.25-60, p = 0.003), higher pulmonary arterial pressure (median 30 mmHg, IQR 28 -49, p <0.000), had more frequency of cardiomyopathy (91.7% vs 66.7%, p=0.018), and severity of the cardiomyopathy (66.7% vs 33.3% p=0.017).

Conclusions: The uremic cardiomyopathy is highly prevalent in young incident peritoneal dialysis patients. There is a difference according to the social security status, in the frequency of echocardiographic alterations and their severity.



PHS, Public Health Services. Fisher's Exact test.

TH-PO833

Functional Status among Patients Receiving Peritoneal Dialysis: Results from the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) Karthik K. Tennankore,[1] Junhui Zhao,[2] Angelo Karaboyas,[2] Hal Morgenstern,[3] Fredric O. Finkelstein,[4] Areewan Cheawchanwattana,[5] Ronald L. Pisoni,[2] Jenny I. Shen,[6] Jeffrey Perl.[7] *[1]Dalhousie/Nova Scotia Health, Halifax, NS, Canada; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]University of Michigan, Ann Arbor, MI; [4]Yale University, New Haven, CT; [5]Khon Kaen University, Khon Kaen, Thailand; [6]LaBiomed at Harbor-UCLA, Torrance, CA; [7]St. Michael's Hospital, Toronto, ON, Canada. Group/Team: On behalf of PDOPPS patient support working group.*

Background: We have shown that high functional dependence among hemodialysis (HD) patients is associated with mortality. Little is known about functional status in peritoneal dialysis (PD) patients and its variation by country.

Methods: In our cross-sectional study of PD patients (PDOPPS 2014-17), functional status (FS) was assessed by self-reported patient questionnaire. Numerical scores were assigned to 8 instrumental and 5 basic activities of daily living, based on one's ability to perform each activity with or without assistance. A summed FS score (range: 1.25-13) was calculated for each patient and categorized as <8 (functionally dependent), 8-<11, 11-<13, or 13 (independent).

Results: To date, 2405 enrolled patients have complete data on FS. The distribution of FS scores varied across countries; scores were lowest in Thailand and highest in Japan (Fig 1). Among patients with FS=13 (48%), mean age was 58 and 35% had diabetes. The 20% of patients with FS <11 were older and have more comorbidities; 68-97% were receiving some assistance with PD, compared to 11% with FS=13. Only 6% of PD patients but 14% of HD patients (Am J Kidney Dis. 2016;67(2):283-92) had FS scores <8; 48% of PD patients but only 36% of HD patients had scores of 13.

Conclusions: Differences in FS scores were observed across countries in the PDOPPS. These differences may have been influenced by regional differences in PD utilization (i.e. availability of PD assistance) or measurement error. FS scores are higher in PD patients than in previously studied HD patients, but future work will need to address the sources of these differences, how interventions for improving functional status might benefit PD patients and assess the outcomes of functionally dependent patients with the use of assisted PD.

Funding: Commercial Support - Amgen, AstraZeneca, Baxter Healthcare, Kyowa Hakko Kirin, Hexal AG, Janssen, Keryx, Proteon, Relypsa, Roche, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, Association of German Nephrology Centres, Societies for Nephrology in Germany, Italy, & Spain., Private Foundation Support, Government Support - Non-U.S.

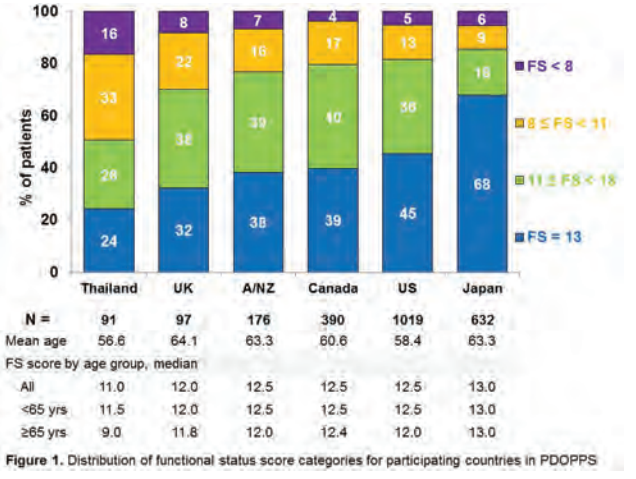


Figure 1. Distribution of functional status score categories for participating countries in PDOPPS

TH-PO834

The Effect of Combined Therapy with Peritoneal Dialysis and Hemodialysis on Patient Survival: A Prospective Multicenter Study in Japan Yukio Maruyama,[5,10] Keitaro Yokoyama,[5,10] Masaaki Nakayama,[5,4] Chieko Higuchi,[5,1] Tsutomu Sanaka,[5,7] Yoshihide Tanaka,[5,2] Ken Sakai,[5,2] Yoshihiko Kanno,[5,6] Munekazu Ryuzaki,[5,3] Tsutomu Sakurada,[5,8] Tatsuo Hosoya.[5,9] *[1]Division of Internal Medicine, Tokyo Women's Medical University Medical Center East, Tokyo, Japan; [2]Department of Nephrology, Toho University School of Medicine, Tokyo, Japan; [3]Division of Nephrology, Tokyo Saiseikai Central Hospital, Tokyo, Japan; [4]Center for Advanced Integrated Renal Science, Tohoku University Graduate School of Medicine, Sendai, Japan; [5]EARTH (Evaluation on the Adequacy of Renal Replacement Therapy) Study Group, Tokyo, Japan; [6]Department of Nephrology, Tokyo Medical University, Tokyo, Japan; [7]Center of CKD and Lifestyle Related Diseases, Edogwa Hospital, Medical Center, Tokyo, Japan; [8]Division of Nephrology and Hypertension, Department of Internal Medicine, St. Marianna University School of Medicine, Kawasaki, Japan; [9]Department of Pathophysiology and Therapy in Chronic Kidney Disease, The Jikei University School of Medicine, Tokyo, Japan; [10]Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan. Group/Team: EARTH Study Group.*

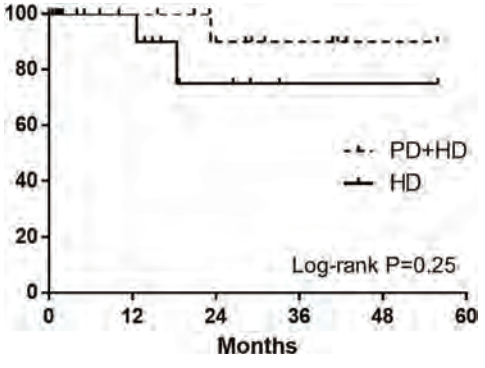
Background: Combined therapy with peritoneal dialysis (PD) and hemodialysis (HD) was widely performed to correct underdialysis and/or overhydration in Japan. However, its clinical result was only reported in retrospective observational studies, and the effect on patient survival is unknown. Hence, we conducted a prospective study to investigate its clinical efficacy in Japan.

Methods: In this prospective multicenter study, we recruited 164 patients started PD from January 1, 2011 to December 31, 2016 (59±16 years, 118 males, and 61 diabetes), and collected clinical information on an annual basis until March 31, 2017.

Results: Median follow-up period was 35 months (range, 0-71 months). During follow-up, 21 patients were switched to the combined therapy with PD and HD, and 15 were switched to HD alone 30±16 and 23±13 months after PD initiation, respectively. The reasons for switching therapy were underdialysis in 8 (22%), overhydration in 12 (33%), both in 1 (3%), and others or unknown in 15 patients (42%). Nineteen patients (11.6%) died of all causes, including 6 (3.7%) died of CVD. Sixteen patients on PD alone, 1 patient on HD alone, and 2 patients on combined therapy were dead. Mortality after switching therapy was no significantly difference between patients on HD alone and those on combined therapy (Log-rank p=0.25, Figure 1).

Conclusions: The effect of switching combined therapy with PD and HD from PD alone on patient survival could not be inferior to switching HD directly. Long-term observation is needed to prove survival advantage of combined therapy.

Funding: Commercial Support - TERUMO, Private Foundation Support



TH-PO835

Patient-Reported Advantages and Disadvantages of Peritoneal Dialysis: Results from the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) Jeffrey Perl,[1] Junhui Zhao,[2] Douglas S. Fuller,[2] Brian Bieber,[2] James A. Sloand,[3] Lalita Subramanian,[2] David W. Johnson,[4] Matthew J. Oliver,[5] Kriang Tungsanga,[6] Tadashi Tomo,[7] Rachael L. Morton,[8] Bruce M. Robinson.[2] *[1]St. Michael's Hospital, Toronto, ON, Canada; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]Baxter Healthcare Corporation, Deer ield, IL; [4]Princess Alexandra Hospital, Brisbane, QLD, Australia; [5]Sunnybrook Health Sciences Center, Toronto, ON, Canada; [6]King Chulalong Memorial lHospital, Bangkok, Thailand; [7]Oita University Hospital, Yufu, Japan; [8]The University of Sydney, Sydney, NSW, Australia. Group/Team: On behalf of clinical application of PD therapy working group.*

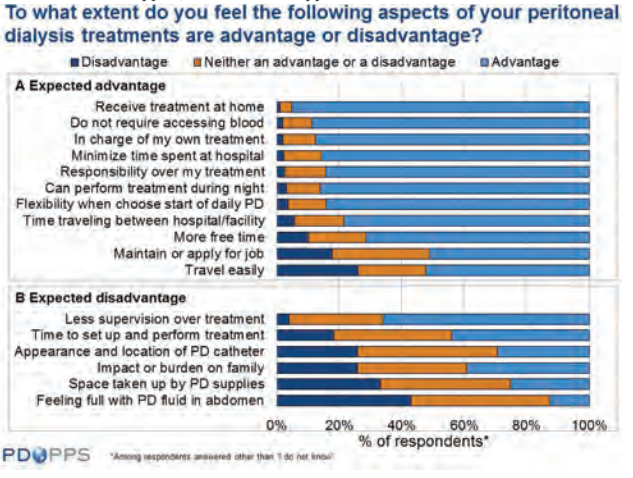
Background: Compared to facility-based hemodialysis, home-based peritoneal dialysis (PD) may offer patients advantages and disadvantages. We sought to better understand patient-reported perceptions of the advantages and disadvantages of PD treatment.

Methods: PDOPPS is a prospective cohort study of PD treatment and outcomes in Australia, Canada, Japan, New Zealand, Thailand, the United Kingdom (UK) and the United States (US). Opinions on how PD treatment impacts 17 aspects of daily life were assessed using the self-reported PDOPPS patient questionnaire (PQ).

Results: Between 2014 and 2017, 2641 patients returned a PQ; item-level response rates ranged from 88% to 96%. Among the 11 factors of expected advantages (Figure 1A), "receive treatment at home" was most commonly perceived as an advantage (95%), followed by "do not require accessing of blood" (89%). The most commonly cited disadvantages of PD treatments were "feeling full with PD fluid in abdomen" (43%) and "space taken up by PD supplies" (overall 33%, Figure 1B), which was particularly regarded as a disadvantage by patients in UK (53%), Canada (40%), US (36%), vs. 16-32% elsewhere. Fewer patients in Japan and Thailand (28% and 43%, respectively, compared to over 57-67% elsewhere) perceived "able to travel more easily" as an advantage of PD.

Conclusions: Abdominal fullness and space taken up by PD supplies appear to be concerns for a substantial minority of patients receiving PD, while treatment receipt at home obviating the need for accessing blood appear to be the predominant advantages. Better understanding of the patient, treatment and regional variation associated with these concerns may provide insights into improving the patient experience of PD and allow for more informed dialysis modality education.

Funding: Commercial Support - Amgen, AstraZeneca, Baxter Healthcare, Kyowa Hakko Kirin, Hexal AG, Janssen, Keryx, Proteon, Relypsa, Roche, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, Association of German Nephrology Centres, Societies for Nephrology in Germany, Italy, & Spain., Private Foundation Support, Government Support - Non-U.S.



TH-PO836

Transitions from Peritoneal Dialysis (PD) to In-Center Hemodialysis or Death: Trends in the United States Renal Data System from 1996-2011 Nidhi Sukul,[2] Purna Mukhopadhyay,[1] Jeffrey Pearson,[1] Douglas E. Schaubel,[2] Marc Turenne,[1] Rajiv Saran,[2] Bruce M. Robinson,[1] Ronald L. Pisoni.[1] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]University of Michigan, Ann Arbor, MI.*

Background: Transitioning from PD to in-center hemodialysis (ICHD) is disruptive to care. To understand changes in rates of mortality and transition from PD to ICHD among incident PD patients, we examined trends in the US Renal Data System from 1996-2011.

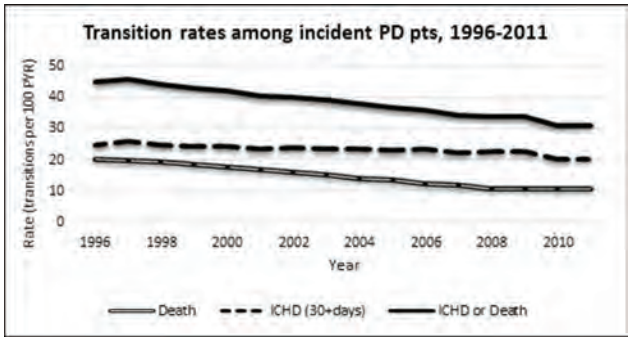
Methods: Annual cohorts of incident PD patients were followed for up to 3 years (Fig.1) for the outcomes of death, transition to ICHD, or the combined outcome of the two. Time at risk (expressed per 100 patient years [PY]) was calculated as days from PD incidence until date of transplant, death, 30 days after switching to ICHD or home hemodialysis, recovery of renal function, loss to follow-up, discontinuation of dialysis, or

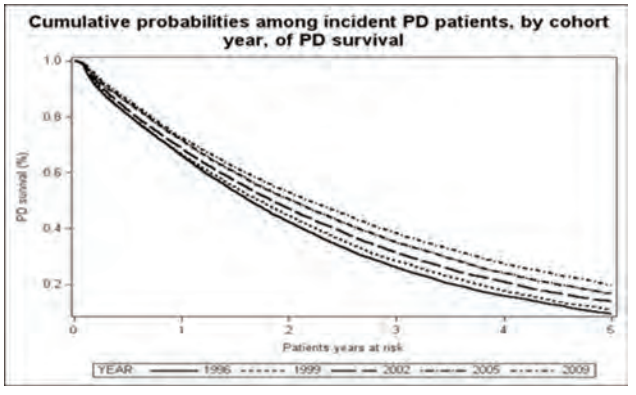
end of follow-up. Kaplan-Meier curves for 5-year survival on PD, adjusted for age, sex, race, ethnicity, and primary cause of ESRD, are shown for 5 annual cohorts (Figure 2).

Results: Trends in transition rates per 100 PY from 1996-2011 were: 20.2 to 10.7 for death, 24.7 to 20.7 for ICHD, 44.9 to 31.3 for death/ICHD (Fig.1). The Kaplan-Meier curves demonstrate that 50% of patients died or transitioned to ICHD by 1.63, 1.72, 1.83, 2.02, and 2.18 PY for 1996, 2002, 2005, and 2009 (Fig.2).

Conclusions: While rates of mortality and transition to ICHD have both declined, this was greater among mortality rates. Overall longer PD survival seen in recent years could potentially be due to better PD education, treatment, and/or patient selection. Further investigation is needed to better understand patient- and center-level predictors of these outcomes to further extend survival time on PD and the experiences of patients selecting this modality.

Funding: NIDDK Support





TH-PO837

The Superiority of Combination Therapy with Peritoneal Dialysis and Hemodialysis over Conventional Hemodialysis Hironori Nakamura, Anayama Mariko, Yasushi Makino, Masaki Nagasawa. *Nephrology, Shinonoi General Hospital, Nagano, Japan.*

Background: Combination therapy consisting of peritoneal dialysis (PD) and hemodialysis (HD) is a type of renal replacement therapy that possesses the advantages of both types of dialysis. In Japan, approximately 20% of all PD patients receive this unique combination of PD and HD (PD+HD) therapy, which consists of 6 days of PD and 1 session of HD a week. However, little is known about the differences in clinical characteristics or QOL between PD+HD and HD patients.

Methods: The aim of this study was to verify the superiority of PD+HD over HD in the clinical characteristics and Kidney Disease Quality of Life Short Form (KDQOL-SF36) score in dialysis patients. One single-center cross-sectional comparative study was conducted. Seven PD+HD patients and 11 control patients were included; age- (±3 years) and dialysis duration- (±5 months) matched controls were selected from HD patients who were undergoing HD thrice a week in our dialysis center.

Results: The mean age of the patients was 73.1 ± 5.7 years, and dialysis duration was 66.7 ± 42.3 months. Laboratory data showed that the values for blood urea nitrogen (44.0 ± 9.2 vs. 58.6 ± 13.4 mg/dL, p = 0.015), potassium (4.1 ± 0.70 vs. 5.0 ± 0.88 mEq/L, p = 0.028), iron (72.5 ± 17.0 vs. 42.3 ± 15.5 mg/dL, p = 0.005), transferrin saturation (27.0% ± 7.8% vs. 17.9% ± 6.4%, p = 0.039), pH (7.40 ± 0.02 vs. 7.34 ± 0.04, p = 0.005), and HCO_3 (23.6 ± 2.8 vs. 19.7 ± 1.7 mEq/L, p = 0.018) were significantly better in PD+HD than HD patients. Total protein (5.5 ± 0.48 vs. 6.2 ± 0.39 mg/dL, p = 0.01) and albumin (2.7 ± 0.48 vs. 3.3 ± 0.38, p = 0.019) levels were lower in PD+HD than HD patients. Regarding the KDQOL questionnaire results, the score for the item indicating patient satisfaction to dialysis care was significantly higher in PD+HD than HD (90.4 ± 8.9 vs. 66.6 ± 19.2 points, p = 0.004). No significant items were observed for the superiority of HD over PD+HD.

Conclusions: Our results suggested that PD+HD may have meaningful advantages in terms of iron metabolism, acid–base balance, and patient satisfaction compared with those in conventional HD in this study population.

TH-PO838

Evaluation of Healthcare Resource Consumption in Simulated Patients on Automated Peritoneal Dialysis (APD) Using a Remote Monitoring System Kiyotaka Uchiyama,[5] Naoki Washida,[7] Nobuyuki Yube,[1] Takahiro Kasai,[3] Kohkichi Morimoto,[6] Shu Wakino,[3] Souzana S. Deenitchina,[2] Hiroshi Itoh.[4] *[1]Baxter, Tokyo, Japan; [2]Baxter Limited Japan, Tokyo, Japan; [3]Keio University, Tokyo-to, Japan; [4]Keio University School of Medicine, Tokyo, Japan; [5]Keio University, School of Medicine, Tokyo, Japan; [6]School of Medicine, Keio University, Tokyo, Japan; [7]keio university, school of medicine, Tokyo, Japan.*

Background: Studies are in progress to evaluate the usefulness of remote monitoring (RM) in chronic disease patients. For patients undergoing peritoneal dialysis (PD), who also have chronic disease (e.g., end-stage renal failure) and are basically on home care, RM is highly likely to contribute to better prognosis and improved quality of life (QOL). However, evidence is scarce in this area. Automated peritoneal dialysis (APD) involves the use of a device to enable automated PD while the patient is asleep, and has greatly contributed to the improved QOL of PD patients. However, no APD device with RM function is available in Japan. In this preliminary study, we evaluated the usefulness of RM in APD patients employing a simulated patient approach.

Methods: We prepared two clinical scenarios with RM (RM+) and without RM (RM-), consisting of 12 simulated patients with PD-related problems commonly experienced in daily clinical practice, with modifications from the original US Baxter's scenarios to reflect the actual clinical situation in Japan. Each scenario was evaluated by two teams consisting of one nephrologist and one nurse each, or by two nephrologists for the frequency of healthcare resource consumption, such as "hospitalizations" and "emergency room visits", for comparison between the RM+ and RM- groups.

Results: The RM+ group showed a significantly reduced total healthcare resource consumption (36.8 vs. 107.5 times, $p = 0.002$), as compared to the RM- group. More specifically, the RM+ group showed significantly lower frequency of the following resource consumption: "unplanned hospital visits" ($p = 0.005$), "emergency room visits"gency room visits ($p = 0.003$), "home visits" ($p = 0.020$), "exchanges over the telephone" ($p = 0.002$)," change to hemodialysis" ($p = 0.003$) and "other" ($p = 0.004$).

Conclusions: The present results indirectly demonstrate the usefulness of RM in reducing the frequency of healthcare resource consumption in APD patients. This is the first time this evidence has been found in Japan.

Funding: Commercial Support - Baxter Ltd.

TH-PO839

Peritoneal Dialysis Annual Drop Out Monitoring Increases Patient and Technique Survival Belen Marron,[1] Delia Timofte,[2] Michael Roesch,[3] Janusz Ostrowski,[4] Marietta Török,[5] Dan Munteanu,[6] Pawel Kochman,[4] Attila Orosz,[7] Gustavo L. Moretta,[8] Paul Stroumza,[9] Elisabeth Fabricius,[10] Jorgen B. Hegbrant.[11] *[1]Medical Office, Diaverum, Madrid, Spain; [2]Sema Clinic, Diaverum, Bucharest, Romania; [3]Schlankreye Clinic, Diaverum, Hamburg, Germany; [4]Wloclawek Clinic, Diaverum, Wloclawek, Poland; [5]Rokus Clinic, Diaverum Hungary Ltd., Budapest, Hungary; [6]Fundeni Clinic, Diaverum, Bucharest, Romania; [7]Bajcsy Clinic, Diaverum, Budapest, Hungary; [8]LATAM Medical Office, Diaverum, Buenos Aires, Argentina; [9]Marseille Clinic, Diaverum, Marseille, France; [10]Visby Clinic, Diaverum, Visby, Sweden; [11]Medical Office, Diaverum, Lund, Sweden.*

Background: PD drop out (DO) is often not routinely measured and seldom reported in the literature.

Methods: Observational, prospective registry in 9 countries (FR, DE, HU, PL, RO, SE, AR, CL, UR) during 2 years. Only EU countries with ≥ 100 prevalent PD patients (pts) [RO, DE, PL, HU] are presented here. All PD pts were tracked on a monthly basis for DO due to: TX, RRF recovery, transfer to HD (due to peritonitis, exit site or catheter issues, UFF, low adequacy, burn out or others), transferred to other centers, death or others. Total DO, controllable DO (transfer to HD and to other centers) and underlying causes are provided as percentage of pts at risk.

Results: 565 pts (372 prevalent, 193 incident) in 47 clinics, 2015 and 813 (623 prevalent, 190 incident) in 61 clinics, 2016. DO results (2016 vs. 2015) was as follows: total annual DO (41 vs. 49%), controllable DO (18.3 vs. 19.1%), TX (5.9 vs. 9.3%), RRF recovery (0.3 vs. 0.5%), transfer to other centers (1.2 vs. 2.9%), death (14.9 vs. 18.3%) and HD (14.8 vs. 15.4%). Cardiac events deaths decreased from 50 to 47.6% (n=42 pts) and fatal peritonitis from 6 to 4.6% (n=4 pts). Causes of HD transfer in 2016 were: peritonitis 5%, low adequacy 2.4%, UF failure 2%, catheter issues 1.7%, burn out 0.3% and other reasons 3%. Results improved in all countries, in terms of total and controllable DO, death and transfer to HD. By contrast, RRF recovery and TX rate decreased in all countries. Country specific data not shown here.

Conclusions: Annual DO monitoring increased quality in PD, comparisons across countries and resulted in a decreased mortality and HD transfer DO rate.

TH-PO840

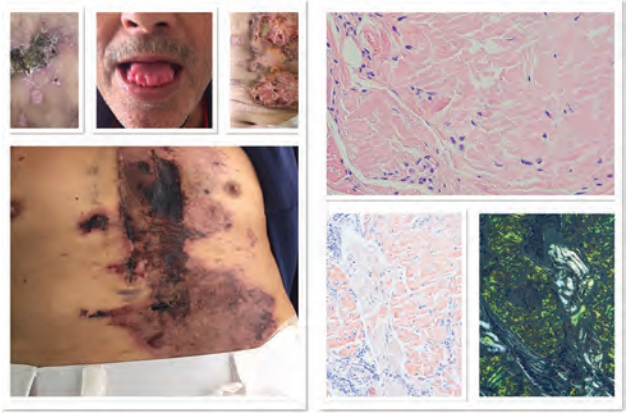
Amyloidosis Mimicking Calciphylaxis in a Peritoneal Dialysis Patient Mabel H. Aoun,[1,2] Christelle Riachi,[3] Dania Chelala.[2] *[1]Saint-Georges Hospital Ajaltoun, Beirut, Lebanon; [2]Saint-Joseph University, Beirut, Lebanon; [3]Holy Spirit University, Kaslik, Lebanon.*

Background: Skin lesions in ESRD patients on dialysis are frequent mostly benign related to itching. More severe necrotic lesions usually point out to calciphylaxis. However the diagnosis is not so easy to establish in some cases and appears to be a real challenge.

Methods: We report the case of a 60-year-old Caucasian male who presented to our clinic in October 2013 for advanced chronic kidney disease. He had hypertension and several episodes of malaria 10 years ago treated with chloroquine. He was known to have focal and segmental glomerulosclerosis confirmed by a kidney biopsy in 2008 and was put on ARB. He was started on peritoneal dialysis in July 2014. Six months later during the pre-transplant work-up he was diagnosed with triple coronary artery disease and he underwent coronary artery bypass graft. Following the surgery, he developed severe oral aphtosis and necrotic lesion of the sternotomy that took 6 months to heal. He was treated with colchicine for his presumed cutaneous Behçet disease. His ANA were negative. After the thoracic healing he presented with ulcerative lesions of the legs that raised the suspicion of calciphylaxis. The PTH level was 88 pg/ml, serum phosphorus 6 mg/dl and serum calcium 10.1 mg/dl. He was put on lanthanum instead of calcium carbonate. He developed later chronic hypotension and macroglossia. Serum protein electrophoresis was normal. A salivary gland and skin biopsies revealed amyloidosis AA (Congo-red positive staining, permanganate sensitive). His cutaneous lesions worsened dramatically and got infected. He died from septic shock.

Results:

Conclusions: This is the first report showing secondary amyloidosis presenting as necrotic skin lesions in a peritoneal dialysis patient. This case highlights the importance of an early skin biopsy to confirm the diagnosis and lead the treatment.



Clinical and pathology

TH-PO841

Epimorphin Expression in the Repair Process of Experimental Peritoneal Fibrosis in Mice Muneharu Yamada,[2] Shuuhei Komatsu,[2] Aki Kojima,[2] Taito Oshima,[2] Go Hirose,[2] Tadasu Kojima,[2] Kentaro Sugisaki,[1] Tomohiro Tomiyasu,[2] Noriko Yoshikawa,[2] Takashi Oda.[2] *[1]Hachioji Medical Center, Tokyo, Japan; [2]Tokyo Medical University Hachioji Medical Center, Tokyo, Japan.*

Background: Epimorphin is a mesenchymal cell surface-associated protein that is essential for epithelial morphogenesis in embryonic organs. However, recent studies indicate important roles of epimorphin in the repair process from pathologic organ damages, such as pulmonary fibrosis and liver injury. We previously reported that epimorphin was involved in the repair of fibrosis in UUO release mice (*Lab Invest 2010)*. In the previous Meeting, we presented the increased epimorphin expressions in the submethothelial area corresponding to the fibrotic area in mice model of peritoneal fibrosis. In the present study, we evaluated the expression of epimorphin in the repair of peritoneal fibrosis.

Methods: Peritoneal fibrosis was induced by the injection of 0.1% chlorhexidine gluconate in 15% ethanol and 85% normal saline (CG-injected mice) into peritoneal cavity of 10 week-old male C57/Bl6 mice every other day for three weeks. As the repair phase of peritoneal fibrosis mice model, we used peritoneal tissues of the CG-injected mice which were harvested at 1,2,3,7 and 14 days after the last CG injection. Morphologic peritoneal changes were assessed by Masson's Trichrome staining. Epimorphin expressions were assessed by immunohistochemically and real-time RT-PCR.

Results: In the repair of CG-injected mice, the thickening of the submesothelial compact zone was decreased over time in Masson's trichrome staining. However epimorphin expression was increased at 2 days rather than at 1 day after the last CG injection, and significantly decreased at 3, 7 and 14 days compared to 2days after the last CG injection by real-time RT-PCR.

Conclusions: These findings suggest that epimorphin may have important role in the repair of peritoneal fibrosis similar to that of UUO release model in mice as reported previously.

TH-PO842

A Way to Woman's Heart Is through Her Stomach: A Case of a Pericardial-Peritoneal Fistula Natasha N. Dave,[1] Jingyin Yan.[2] *[1]Baylor College of Medicine, Houston, TX; [2]None, Houston, TX.*

Background: An exceedingly rare and potentially life-threatening complication of peritoneal dialysis (PD) is the development of a pericardial-peritoneal fistula (PPF). Typically this communication can occur in cases of pericardiocentesis or an embryological defect in diaphragmatic closure. We report a case of a young female who developed PPF after history of multiple pericardial windows.

Methods: A 26 year-old female with a history of end stage renal disease (ESRD) on PD presented to cardiology clinic for kidney transplant clearance. She was diagnosed with ESRD secondary to focal segmental glomerulosclerosis (FSGS) 6 months ago. At that time, she had a large pericardial effusion deemed uremic pericarditis warranting a sub-xiphoid pericardial window. She was initiated on hemodialysis (HD) then transitioned to PD and has since been compliant with a Kt/V above 2.0. In clinic, an echocardiogram showed a large circumferential pericardial effusion and early right ventricular diastolic collapse. She was taken to surgery for drainage of pericardial effusion with pericardial biopsy and creation of pericardial window into the left pleural cavity. The biopsy showed fibrosis and mild chronic inflammation. Immediately after the surgery, she resumed PD. Two weeks later, she developed shortness of breath (SOB) with exertion and orthopnea during dialysis. A chest X-ray revealed an enlarged cardiomediastinal silhouette and large left sided pleural effusion; she was taken to surgery. Intra-operatively the previous upper midline incision was dissected down to the subxiphoid matter. The surgeon was able to identify the defect in the pericardium that communicated with the abdominal cavity above the caudate lobe of the liver. A second window was made through the left thoracotomy and the defective area was sutured closed. About 2L of serous pleural fluid was drained as well. Post-operatively, she tolerated low volumes of CCPD and was discharged with a prescription to advance dialysis as tolerated. One month later, she developed recurrent episode of SOB secondary to a left sided pleural effusion. A CT peritoneography was negative for peritoneal leakage. She transitioned to HD and her symptoms have since resolved.

Results:

Conclusions: This case of recurrent pericardial effusions in patient on PD emphasizes the need for the clinician to suspect a PPF especially with a history of multiple pericardial interventions.

TH-PO843

Inhibition of H3K4 Methyltransferase SET7/9 Ameliorates Peritoneal Fibrosis Ryo Tamura, Shigehiro Doi, Ayumu Nakashima, Kensuke Sasaki, Toshinori Ueno, Takao Masaki. *Hiroshima University Hospital, Hiroshima, Japan.*

Background: Transforming growth factor-β1 (TGF-β1) is widely recognized as a major mediator of peritoneal fibrosis. TGF-β1 is reportedly responsible for the expression of the H3K4 methyltransferase, SET7/9. SET7/9-induced H3K4 monomethylation (H3K4me1) has a critical function in transcriptional activation of fibrotic genes. In this study, we examined the inhibitory effects of SET7/9 on peritoneal fibrosis in mice and human peritoneal mesothelial cells (HPMCs). We also investigated SET7/9 expression in nonadherent cells isolated from peritoneal dialysis (PD) effluent from actual PD patients.

Methods: Peritoneal fibrosis was induced by intraperitoneal injection of methylglyoxal (MGO) in male C57/B6 mice for 21 days. Sinefungin, a SET7/9 inhibitor, was administered subcutaneously just before MGO injections at 10 mg/kg. In *in vitro* experiments, HPMCs were pre-incubated with 3 or 10 μL/mL sinefungin 1 hour before stimulation with 5 ng/ml of TGF-β1.

Results: SET7/9 expression increased in both MGO-injected mice and nonadherent cells isolated from effluent of PD patients, and was positively correlated with dialysate-to-plasma ratio of creatinine. Immunohistochemical staining showed that sinefungin suppressed expression of mesenchymal cells and collagen deposition, which was accompanied by decreased H3K4me1 expression. A peritoneal equilibration test showed that sinefungin attenuated the transport rate of blood urea nitrogen from plasma and the absorption rate of glucose from dialysate. In *in vitro* experiments, sinefungin suppressed TGF-β1-induced expression of fibrotic markers while inhibiting H3K4me1.

Conclusions: These findings suggest that inhibition of H3K4 methyltransferase SET7/9 ameliorates peritoneal fibrosis by inhibiting H3K4me1.

TH-PO844

Abstract Withdrawn

TH-PO845

Mortality after Switching from Peritoneal Dialysis to In-Center Hemodialysis: Trends in the United States Renal Data System from 1996-2013 Nidhi Sukul,[2] Purna Mukhopadhyay,[1] Jeffrey Pearson,[1] Douglas E. Schaubel,[2] Marc Turenne,[1] Rajiv Saran,[2] Bruce M. Robinson,[1] Ronald L. Pisoni.[1] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]University of Michigan, Ann Arbor, MI.*

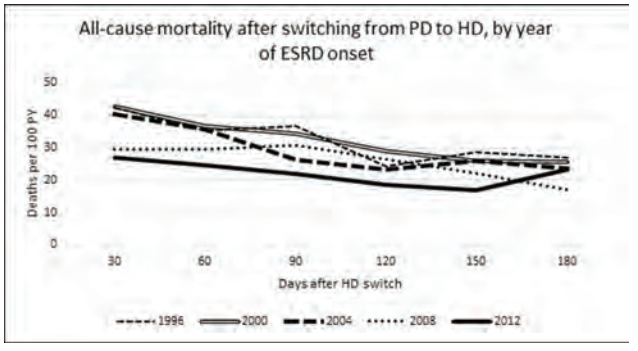
Background: Switching from peritoneal dialysis (PD) to in-center hemodialysis (ICHD) is disruptive to patients' care, and transitioning from PD to ICHD has been associated with higher mortality risk when transitions are unplanned. To understand how mortality rates after a switch from PD to ICHD have changed over time, we examined trends in the United States Renal Data System from 1996-2013.

Methods: Five annual cohorts of incident PD patients who initiated PD within 180 days of ESRD designation and switched from PD to ICHD for ≥1 day were followed for death events for up to 180 days after switch. This 180-day risk period was divided into six consecutive 30-day segments. Death and time at risk were determined in each time segment, censoring for transplantation, return to PD, recovery of renal function, or loss to follow-up. Death rates are expressed per 100 patient years (PY).

Results: In each cohort, mortality was highest in the first 30 days post-switch, thereafter gradually declining (Figure). Death rates during the first 30 day period following switch to ICHD were 42.4 and 31.2 deaths/100 PY for the 1996 and 2013 cohorts, and decreased to 27.1 and 23.2 deaths/100 PY for the 151-180 days post-switch period. The percentage of patients in the first 30-day risk set who died decreased from 3.4% to 2.2% from 1996 to 2013, and in the 151-180-day risk set decreased from 2.2% to 1.6%. The summary death rate (combining the six time periods) was 33.2 deaths/100 PY for 1996 and 22.6 deaths/100 PY for 2013.

Conclusions: The initial 30 days post-switch from PD to ICHD is a high risk period, though there is an extended period of elevated risk after transition. The lower mortality rate for more recent cohorts may reflect improved peri-transition care in more recent years. Next steps will include adjusted analyses, and defining patient and center-level predictors to help inform means to improve mortality rates during this high-risk period.

Funding: NIDDK Support



TH-PO846

Apoptosis Inhibitor of Macrophage Ameliorates Fungus-Induced Peritoneal Injury Model in Mice Yasuhiko Ito,[1,2] Takako Tomita,[2] Masashi Mizuno,[2] Yasuhiro Suzuki,[2] Fumiko Sakata,[2] Yoshifumi Takei,[3] Shoichi Maruyama.[2] *[1]Aichi Medical University, Nagakute, Japan; [2]Nagoya Univeristy Graduate School of Medicine, Nagoya, Japan; [3]Aichi Gakuin University, Nagoya, Japan.*

Background: Fungal peritonitis is not common, but carries a most serious and poor prognosis due to severe inflammation. In addition, a single episode of fungal peritonitis can reportedly induce encapsulating peritoneal sclerosis. A decrease in the clearance of debris, such as that of apoptotic or necrotic cells, has been reported to prevent resolution of inflammation and tissue remodeling, leading to fibrosis and organ dysfunction. Recently, apoptosis inhibitor of macrophage (AIM/CD5L) was reported to enhance the phagocytic removal of debris by epithelial cells, contributing to kidney tissue repair. In this study, we investigated the roles of AIM in zymosan-induced fungal peritonitis models (zymosan models) that we previously reported (J Immunol 2009).

Methods: We studied zymosan models in wild and AIM deficient mice and evaluated the effects of recombinant AIM (rAIM) in AIM deficient zymosan models. We investigated whether rAIM enhances engulfment of cell debris by cultured macrophages and mesothelial cells.

Results: Inflammation with necrosis was much more severe in the AIM deficient mice at 4 weeks. M1 macrophages and neutrophils were predominant on days 7 and 14. M2 macrophages were higher in wild mice than in AIM deficient mice on days 21 and 28. IL-6, TNF-a, iNOS, and CD86 mRNA expression was significantly higher on day 28 in AIM deficient mice compared with wild mice. AIM levels in serum increased and peaked on day 14, and AIM was strongly detected in the necrotic area in zymosan models of wild mice on day 14. Inflammation with necrosis was suppressed by administration of rAIM in AIM deficient mice on day 28. In vitro, AIM enhanced the engulfment of necrotic debris by macrophages derived from zymosan-induced peritonitis, M1- and M2a-like bone marrow derived macrophages, as well as by mesothelial cells.

Conclusions: AIM was found to play a role in the reduction of inflammation by clearance of necrotic debris in zymosan-induced peritonitis models. Enhancement of engulfment could be a novel therapeutic strategy for improving fungal peritonitis-induced peritoneal membrane injury and prognosis.

Funding: Government Support - Non-U.S.

TH-PO847

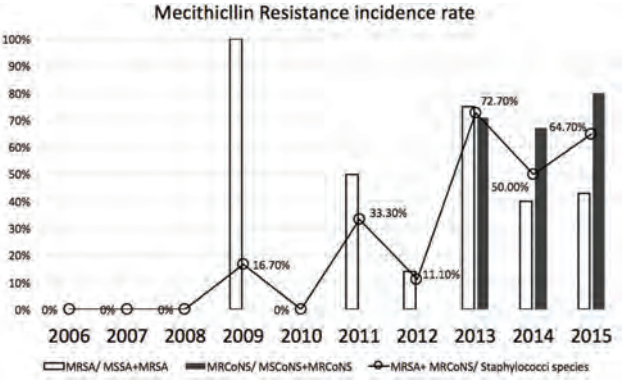
Increasing Staphylococcus Species Resistance in Peritoneal Dialysis-Related Peritonitis over 10 Years in Southern Taiwan Hoching Chen. *E-Da hospital, Kaohsiung City, Taiwan.*

Background: Peritonitis remains the major complication of peritoneal dialysis. Staphylococcus species are the most associated gram-positive peritoneal peritonitis. The increasing antimicrobial resistance rate has become a very important burden when considering the initial choice of antibiotics. The aim of this investigation was to exam the trends of Staphylococcus species, resistance rate and the clinical outcomes from 2006 to 2015 in southern Taiwan.

Methods: We retrospectively investigated all peritoneal dialysis-related peritonitis episodes in southern Taiwan between January 2006 and December 2015. We also evaluated the clinical characteristics, microbiology prevalence, resistance incidence of Staphylococcus species, and outcomes.

Results: Out of 244 episodes of peritonitis, Staphylococcus species accounted for around 30% gram positive bacteria. Methicillin resistance rate among staphylococcus species infection has greatly increased to 64% in 2015 both in Staphylococcus aureus and Coagulase-negative Staphylococci in southern Taiwan. Importantly, Methicillin resistance Staphylococcus species (59.1%) has significant higher hospitalization rate compare to Methicillin-sensitive Staphylococcus species(34.6%) ($p<0.01$). However, the catheter removal rate and transfer to hemodialysis didn't have a difference between two groups.

Conclusions: Peritonitis is the most serious complication in peritoneal dialysis patients and microbiological trends have changed during the past 10 years at a single center in southern Taiwan. Methicillin resistance Staphylococcus species has increased significantly. Empirical initial antibiotics therapy should take in consideration according to growing resistance of microbiology.



Methicillin resistance incidence rate in Staphylococcus aureus, CoNS and Staphylococci species

TH-PO848

Astragalus Inhibits Epithelial-to-Mesenchymal Transition of Peritoneal Mesothelial Cells via Suppressing Wnt/β-Catenin Signaling and Promoting Smad7 Jun Shi,[1,2] Manshu Yu,[1,2] Kun Gao,[3] Lu Zhang,[3] Meixiao Sheng.[3] *[1]First Clinical Medical College, Nanjing University of Chinese Medicine, Nanjing, China; [2]Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, China; [3]Department of nephrology, the affiliated hospital of Nanjing University of Chinese Medicine, Nanjing, China.*

Background: Epithelial-to-mesenchymal transition (EMT) of peritoneal mesothelial cells (PMCs) is a crucial event inducing peritoneal fibrosis (PF), in which Wnt/β-catenin signaling participates. Smads signaling is reported to interact with β-catenin and synergistically regulates EMT. This study was aimed to reveal the effect of *Astragalus*(a famous Chinese herbal)on Wnt/β-catenin signaling in PMCs with EMT, as well as on the crosstalk between β-catenin and Smads.

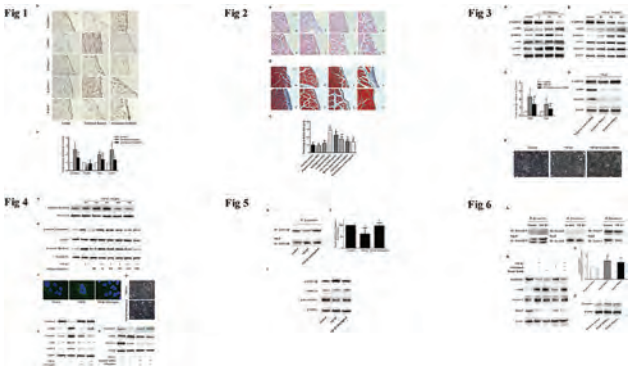
Methods: Rats with peritoneal fibrosis and the human HMrSV5 peritoneal mesothelial cell line were used to explore the effects of *Astragalus* on EMT. EMT markers or signaling pathway-related indicators were detected by Western blotting, immunofluorescence, immunohistochemistry, immunoprecipitation and rt-PCR.

Results: β-Catenin knockdown inhibited EMT of PMCs. *Astragalus* not only relieved EMT and peritoneal fibrosis in rats but also inhibited β-catenin-mediated EMT in the HMrSV5 cell line, resulting from increased E-cadherin and decreased α-SMA.

The nuclear translocation of β-catenin was suppressed by *Astragalus* as a result of the stabilization of GSK-3β promoting dissociative β-catenin degradation. Smad7, which was associated with β-catenin, was enhanced by *Astragalus* during EMT. The knockdown of Smad7 induced an increase in β-catenin and EMT.

Conclusions: *Astragalus* promotes Smad7 expression and effectively inhibits the Wnt/β-catenin signaling pathway during EMT of PMCs, indicating its potential therapeutic effect for PF.

Funding: Government Support - Non-U.S.



TH-PO849

Prediction of Peritoneal Membrane Function in Pre-Dialysis ESRD Patients

Hui Xu. *Nephrology Department, Xiangya Hospital, Central South University, Changsha, Hunan, China, Changsha, China.*

Background: Background: Peritoneal membrane function decides the efficiency of peritoneal dialysis (PD). However, an effective method is still lack to value the peritoneal membrane function discrimination for pre-dialysis patient is. As a valid classification and prediction tool, random forest using clmay serve efficiently for predicting pre-dialysis peritoneal membrane function in ESRD patients.

Methods: Firstly, random forest method was used to build discrimination model for predicting peritoneal membrane function. The clinical data of 247 patients was used as the training set and the other 50 was used as the validation set. Secondly, random forest-based algorithm was applied in training set for model development and validation set.

Results: The discrimination model performed well for the primary objective. 10-fold cross validation was considered to be internal validation, the evaluation for this model showed that its accuracy rate, sensitivity and specificity respectively reached 0.862, 0.877, and 0.795. The coefficient of martensite (MCC) was turned out to be 0.60 and AUC (area under the receiver operating characteristics curve) was 0.840 (Fig.1a). For external validation, test was conducted on validation set. And the results showed that the accuracy rate, sensitivity, and specificity were respectively 0.78, 0.765, and 0.812. MCC was 0.546, AUC was 0.731(Figure.1b). Of the 28 variables considered, 7 were selected by the model for peritoneal membrane function prediction, among which thrombin time and urine volume reveal evident significance(Figure1c).

Conclusions: Conclusion: Random forest based model provides a robust tool to predict the peritoneal membrane function in non-dialysis ESRD patients.

Funding: Government Support - Non-U.S.

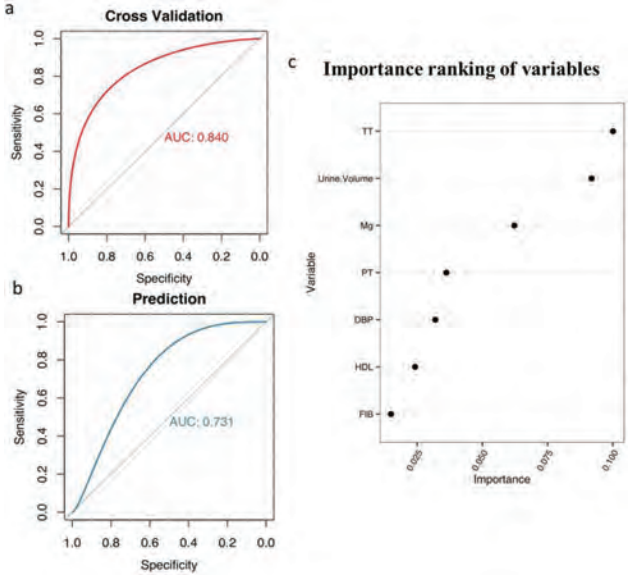


Figure 1

TH-PO850

Percutaneous Re-Positioning of PD Catheter Accidentally Placed in the Subcutaneous Space Leaving the Tunnel and Exit-Site Intact – A Novel Idea

Santosh Varughese. *Christian Medical College, Vellore, India.*

Background: Peritoneal dialysis (PD) catheter insertion by blind bedside percutaneous technique is a simple procedure. Rarely, the intra-abdominal portion of the catheter may accidentally be placed in the subcutaneous space if the introducer needle does not enter the peritoneal cavity during the initial part of the procedure. If this happens, the catheter insertion has to be redone either percutaneously or surgcially. The catheter often has to be replaced as part of it has been externalized and the external portion is unsterile.

Methods: A 70 year old man with end stage renal disease underwent PD catheter insertion by blind bedside percutaneous technique. Unfortunately, the cathteter was accidentally placed in the subcutaneous space. There was inflow and outflow of PD fluid as the subcutaneous space had expanded with the PD fluid infused during the procedure, but the outflow rate was slow. On CT scan, the intra-abdominal portion of catheter was seen to be lying in the subcutaneous space. A novel technique of repositioning was attempted in which the exit site and tunnel were untouched. The abdomen was scrubbed and cleaned. The skin sutures and subcutanous sutures at the original insertion site were removed. The deep cuff of the catheter was dissected free of the surrounding tissue. The intra-abdominal part of the cathteter was exteriorized. A Veress needle was advanced till it reached the peritoneal space. The track was dilated using a peel-away sheath-dilator assembly. The dilator was removed and the intra-abdominal portion of the catheter (that had just been exteriorized) was slid in and the peel-away sheath was removed. The wound was closed in layers after ensuring good inflow and outflow. Peritoneal dialysis exchanges were begun the same day and was the patient was continued on continuous ambulatory peritoneal dialysis successfully.

Results:

Conclusions: This novel technique allows for a simple bedside repositioning technique of a PD catheter accidentally placed in the subcutanous space without change of catheter or disruption of the tunnel or exit-site. Compared to a repeat PD catheter insertion, this procedure has the advantages of saving operating room time, reducing costs, reducing duration of hospital stay and possibly avoiding unnecessary hemodialysis.

TH-PO851

Fat Mass Monitoring in the Follow-Up of Peritoneal Dialysis Patients: Prognostic Value of Excessive Fat Gain

Jwa-kyung Kim,[2] Hyung jik Kim.[1] *[1]Hallym Univ. Sacred Heart Hospital, Anyang, Republic of Korea; [2]Hallym University, Seoul, Republic of Korea.*

Background: Visceral obesity caused by fat accumulation is an important change in body composition among patients undergoing peritoneal dialysis (PD). Although a significant portion of patients become obese, its long-term effect is not clear and associated changes in peritoneal characteristics are also unknown.

Methods: In this prospective observational study, the prognostic value of excessive fat accumulation on technical failure rate and death was tested. Body composition monitoring was performed twice, 18.0 ± 6.0 months apart, and increment of percentage of body fat (delta_PBF, %) were used to predict long-term outcomes during the following 28.1 ± 8.5 months. Also, accompanying changes of peritoneal characterises with fat accumulation were evaluated by modified peritoneal equilibration test. Technical failure was defined as a transfer from PD to haemodialysis (HD).

Results: Among the 205 patients, 66.8% (N=137) and 59.5% (N=122) experienced BMI increase and PBF gain during the 18 months. The mean PBF was 24.5% and 35.3% at first test, and 25.9% and 37.0% at second test in men and women respectively. Excessive fat gain was defined as a delta_PBF over the gender-specific highest quartile (4.8% for men and 5.7% for women). However, lean mass was not significantly changed. Patients with excessive fat gain was more diabetic and had higher systolic blood pressure. Interestingly, they exprienced significantly higher rate of technical failure than those without excessive fat accumulation (90.5 cases vs. 22.4 cases per 1000 patient-year, p=0.002), but mortality was not affected. Even after adjusting the volume status and other comorbidities, excessive fat gain increased the risk of technical failure by 4.86-fold. Furthermore, with excessive fat gain, the peritoneal characteristics showed a tendency to change to a low transporter (p=0.013). However, mortality was not affected by the excessive fat gain.

Conclusions: Excessive fat gain during PD have an independent prognostic value for technical failure. Concomitant peritoneal membrane changes, decreased solute clearance in low transporter, may affect the higher rate of technical failure.

Funding: Private Foundation Support

TH-PO852

Itraconazole Ameliorates Chlorhexidine Gluconate-Induced Peritoneal Fibrosis in Mice through Regulating Hedgehog Signaling Pathway

Jin sug Kim,[2] Yu ho Lee,[1] Eun ji Park,[2] Su Woong Jung,[2] Chun-Gyoo Ihm,[2] Tae won Lee,[2] Yang gyun Kim,[1] Ju young Moon,[1] Sang-Ho Lee,[1] Kyung-hwan Jeong.[2] *[1]Kyung Hee University Hospital at Gangdong, Seoul, Korea, Seoul, Republic of Korea; [2]Kyung Hee University Medical Center, Seoul, Republic of Korea.*

Background: Peritoneal fibrosis is a devastating complication of peritoneal dialysis (PD). However, the precise mechanism is unclear and specific treatment has not yet been established. Recent evidence suggests that Sonic hedgehog (Shh) signaling pathway is

involved in fibrogenesis, and drugs that inhibit this pathway are emerging in the treatment of fibrosis. Itraconazole, an anti-fungal agent, is recently also reported as an inhibitor of Shh signaling pathway. In this study, we investigated whether itraconazole suppressed chlorhexidine gluconate (CG)-induced peritoneal fibrosis in mice.

Methods: Peritoneal fibrosis was induced by intraperitoneal (IP) injection of 0.1% CG every other day for 4 weeks, with or without itraconazole treatment (20mg/kg, IP injection on a daily basis). Saline was administered intraperitoneally to the control groups. Male C57BL/6 mice were divided into four groups: saline injection (group 1), saline injection plus itraconazole (group 2), CG injection (group 3), CG injection plus itraconazole (group 4). The effects of itraconazole were evaluated based on peritoneal thickness, immunohistochemical staining, and real-time polymerase chain reaction. The peritoneal thickness was identified by Masson's trichrome staining.

Results: Peritoneal thickening was evident in group 3 (CG injection), and the thickening was markedly decreased in group 4 (CG injection plus itraconazole) (59.9±34.9 μm vs. 16.8±9.0 μm, $p<0.001$). The mRNA expression of markers for fibrosis, including transforming growth factor-β1 (TGF-β1), fibronectin, and α-smooth muscle actin (α-SMA), were increased in the group 3 and were downregulated in the group 4. Similar results were shown in the markers for Shh signaling pathway. Itraconazole suppressed mRNA expression of Shh, Patched 1 (PTCH1), Smoothened (SMO), and Gli in peritoneal tissues. Immunohistochemistry analysis revealed that the expression of Hedgehog pathway components were increased in group 3, and decreased by using Itraconaozle in peritoneal tissues.

Conclusions: Our results suggest that itraconazole ameliorates the peritoneal fibrosis by regulating Shh signaling pathway. Itraconazole can be a potential therapeutic strategy for peritoneal fibrosis.

TH-PO853

Hemophagocytic Lymphohistiocytosis Secondary to Tubercular CAPD Peritonitis Manisha Dassi,[1] Garima Aggarwal.[2] *[1]Max Super Speciality Hospital, Vaishali, Ghaziabad, India; [2]Amrita Insitiute Of Medical Sciences, New Delhi, India.*

Background: Tubercular CAPD peritontis, though infrequent, has been reported to have a higher incidence in developing countries. HLH, seen in both inherited and secondary forms, is a rare & lethal disorder of the immune system. We report a case of HLH secondary to tubercular CAPD peritonitis.

Methods: A 49 years old male ESRD, on CAPD since 01 year presented with CAPD peritonitis. He required CAPD catheter explantation & shift to HD in view of refractory peritonitis. Though fever resolved, he continued to have clear watery discharge from the poorly healed surgical wound. He was lost to follow up & presented again 03 months later with complaints of fever, weight loss, fatigability and copious amount of yellowish discharge from the surgical wound. Clinically, he was hemodynamically stable, febrile, had pallor, multiple cutaneous ecchymotic spots, hepatosplenomegaly, reduced air entry at right lung base and a 5 cm infra-umbilical midline horizontal poorly healed discharging surgical scar mark with surrounding skin inflammation. Relevant clinical & lab parameters are shown in Table 1. NCCT abdomen revealed hepatosplenomegaly, moderate ascites & loculated fluid collection in the right subphrenic space extending inferiorly into the abdominal & pelvic cavity. Subphrenic fluid aspirate revealed a yellow turbid fluid which was sterile on pyogenic and fungal culture, negative on gram's, fungal and ZN stains, positive for *M tuberculosis* on PCR & positive on tubercular culture. Bone marrow asp + biopsy revealed marked degree of histiocytic hemophagocytosis. Patient fulfilled 6/8 criteria for diagnosis of HLH. He was managed with Dexamethasone (6 wks) & ATT (HRZE → HR). He gradually became afebrile with resolution of the infra-umbilical wound discharge, improvement in pancytopenia (Inv at 6 mnths: Hb 11.3 gm%, TLC 4000, Plts 95000/uL) along with improvement in general condition.

Results:

Conclusions: HLH should be considered in ESRD patients with tubercular peritonitis in presence of pertinent clinical and lab findings. It has been reported in association with tuberculosis especially extrapulmonary forms. A high index of suspicion is necessary for timely diagnosis & management.

Clinical and Lab Parameters for diagnosis of HLH

HLH Diagnostic Criteria	Criteria fulfilled by Index Patient
1.Fever	
2.Splenomegaly	1.Fever
3.Cytopenias (affecting ≥ 2/3 on PBS)	2.Splenomegaly
4.Fasting TG ≥ 265 mg/dl and/or fibrinogen ≤ 150 mg/dl	3.Hb 5.0 gm/dl, TLC 1800/uL, Plts 45000/uL
5.Hemophagocytosis in BM or LN or Spleen	4.TG 350 mg/dl
6.Ferritin ≥ 500 μg/L	5.Hemophagocytosis (BM)
7.Low or absent NK cell activity	6.Ferritin 1053 ug/L
8.Soluble CD25 ≥ 2400 U/ml	

HLH Diagnosis based on fulfilment of 5/8 criteria

TH-PO854

Blunting Toll-Like Receptor Activity with Soluble TLR2 Inhibits PD Solution-Induced Fibrosis Anne-Catherine Raby,[2] Guadalupe T. Gonz?lez-Mateo,[4] Donald Fraser,[1] Manuel Lopez-Cabrera,[3] Mario O. Labéta.[1] *[1]Cardiff University, Cardiff, United Kingdom; [2]Welsh Kidney Research Unit, Cardiff University, Cardiff, United Kingdom; [3]Consejo Superior de Investigaciones Cientificas (CSIC). Spain, Madrid, Spain; [4]Molecular Biology Research Centre Severo Ochoa, Spanish Research Council, Madrid, Spain.*

Background: Membrane failure due to fibrosis limits the use of peritoneal dialysis (PD). Fibrosis results from peritoneal inflammation caused by infections or by ongoing cellular stress induced by PD (sterile inflammation). The immune mechanisms involved in sterile peritoneal inflammation leading to fibrosis are still poorly defined. Toll-like receptors (TLRs) mediate sterile inflammation by recognising endogenous components released by cellular stress (DAMPs). We hypothesise that TLRs play a crucial role in sterile inflammation and fibrosis by recognising DAMPs released during PD and, thus, are major therapeutic targets for fibrosis prevention.

Methods:

Results: A range of PD solutions (PDS) underwent comprehensive *in vivo* and *ex vivo* characterisation of TLR-mediated inflammatory and fibrotic mediator production (genes and proteins). All PDS elicited proinflammatory and fibrotic responses from primary human uremic peritoneal leukocytes and mesothelial cells. TLR2/4 blockade inhibited these effects. PDS did not induce rapid ERK phosphorylation, suggesting that they do not contain components capable of direct TLR activation. However, PDS increased the release of Hsp70 and HA from a panel of DAMPs tested, and their blockade repressed PDS-driven inflammation. The peritoneal response to Hsp70 and HA was mediated mainly by TLR4 and to a lesser extent TLR2. Soluble TLR2 (sTLR2), an inhibitor of DAMP-TLR interaction, was found to inhibit Hsp70-, HA- and PDS-induced peritoneal proinflammatory cytokine release. PDS exposure also increased peritoneal Hsp70 and HA in mice, and the use of TLRKO mice confirmed a major role of TLR2/4 in PD solution-induced fibrotic responses. The therapeutic potential of sTLR2 was examined in a mouse model of PDS-induced sterile peritoneal fibrosis. Daily catheter infusion of PDS led to robust peritoneal fibrosis by day 40. Co-administration of sTLR2 prevented peritoneal fibrosis development by suppressing profibrotic gene expression, proinflammatory cytokine production and reducing leukocyte recruitment.

Conclusions: The study reveals a major role of TLR2 and TLR4 in PD solution-associated peritoneal inflammation and fibrosis, identifies Hsp70 and HA as main DAMPs and demonstrates the therapeutic potential of blunting TLR activity to prevent PD solution-induced fibrosis by using a TLR modulator, sTLR2.

TH-PO855

Peritoneal Inflammation Increases over Time, with an Associated Increase in Plasma IL-6 Predicting Worse Survival: Results From the Global Fluid Study Emma H. Elphick,[1] Vasileios Zavvos,[2] Simon J. Davies,[1] Nicholas Topley,[2] Donald Fraser,[2] Mark Lambie.[1] *[1]Keele University, Stoke on Trent, United Kingdom; [2]Cardiff University, Cardiff, United Kingdom.*

Background: Local peritoneal inflammation is a feature of peritoneal dialysis (PD) treatment and high concentrations of dialysate IL-6 (dIL6) are a strong determinant of solute transport. Solute transport increases during long term PD but it is unknown whether dialysate IL-6 rises. Plasma IL-6 (pIL6) is an independent predictor of patient survival but whether dialysate IL-6 contributes to plasma levels is unknown.

Methods: We conducted a longitudinal analysis of the Global Fluid study, a multinational cohort study from UK, Canada and Korea. All incident patients with 3 or more paired dialysate/plasma samples were assayed for IL-6 by electrochemiluminescence. A linear mixed model with random intercept/slopes was used, including time on PD, centre, dIL6, gender, baseline age, comorbidity score and urine volume with backwards selection, for log transformed pIL6. An unadjusted joint longitudinal survival model (JLSM) assessed pIL6 values and changes over time on survival.

Results: There were 217 patients with 1274 measurements, with a median follow up time of 2.2 years from 6 centres. Over time there is a significant increase in dIL6 (1.17 pg/ml/year 95% CI 1.11 to 1.24) and pIL6 (1.08 pg/ml/year per year 95% CI 1.02 to 2.24). In the multivariate model pIL6 was significantly positively associated with dIL6 (β =0.099 95% CI 0.063 to 0.135) and negatively associated with urine volume (coeff=-0.0058 95% CI 0.0020 to 0.010 p=0.005, time interaction coeff=-0.019 95% CI -0.032 to -0.005 p=0.006). In adjusted Cox models, time varying pIL6 was negatively associated with survival (HR 4.51 per $\log_{10}$ order, 95% CI 1.85 to 11.0). In a JLSM there was a significant negative effect on survival of pIL6 values (β=4.31 95% CI 2.73 to 5.90) and trajectories over time (β=-23398 95% CI -31313 to -15483). pIL6 trajectories were a better predictor of survival than raw values (AIC 1283 vs AIC 1333 respectively) or combined raw values with trajectories (AIC 1331).

Conclusions: There is a rise in pIL6 over time, associated with increasing dIL6 and decreasing urine volume. pIL6 is a strong predictor of mortality, and the rate of increase in pIL6 is a stronger predictor of mortality than the absolute value.

TH-PO856

Inhibition of NLRP3 Inflammasome Blocks Peritoneal Dialysis Solution-Induced Mesothelial-to-Mesenchymal Transition Lu Zhang,[2] Min Zheng,[2] Dong Zhou,[1] Kun Gao,[2] Weiming He,[2] Qing Li,[2] Zhenghong Li,[2] Meixiao Sheng,[2] Wei Sun.[2] *[1]University of Pittsburgh, Pittsburgh, PA; [2]nephrology, the affiliated hospital of Nanjing University of Chinese Medicine, Nanjing, China.*

Background: To investigate the role of activated Nod-like Receptor Protein 3 (NLRP3) inflammasome in peritoneal dialysis (PD) solution-induced mesothelial-mesenchymal transition (MMT) in peritoneal mesothelial cells (PMC).

Methods: 1. Human peritoneal mesothelial cells (HMrSV5) were incubated with different concentrations of PD solution (1.5%,2.5%,4.25%) for 24h or 4.25% PD solution for various periods of time at 0, 6, 12, 24, 48 hours, respectively. The supernatant was collected for ELISA assay and cells were lysed using RIPA buffer for a western blot assay.2. After stable transfection of siRNA plasmid targeting NLRP3, HMrSV5 were incubated with 4.25% PD solution for 24h, cells were then harvested for western blot assay.3. HMrSV5 were treated with 4.25% PD solution for 24h in the absence or presence

of different doses of Astragaloside IV (As-IV), which is a cycloartane triterpene saponin with a clear formula($C_{41}H_{68}O_{14}$).

Results: 1. The PD solution promotes IL-18 secretion in the condition medium of cultured PMCs as dose- and time-dependent manner. Accordingly, it significantly induced NLRP3, pro-IL-1β, IL-1β, pro-casepase-1, and caspase-1 expression in vitro. 2. The PD solution induces MMT which is featured with decreased E-cadherin and increased vimentin, α-SMA. 3. Knockdown NLRP3 partially preserve PMCs from MMT by inhibited IL-18 secretion and NLRP3, caspase-1, pro-IL-1β, IL-1β expression in cultured PMC. 4. Therapeutic inhibition of NLRP3 inflammasome with a novel small molecule inhibitor, As-IV, preserves mesothelial phenotypes in the established model in vitro.

Conclusions: The activated NLRP3 inflammasome mediates PD solution-induced MMT in PMCs. Targeting NLRP3 inflammasome activity by small molecule inhibitor AS-IV abolishes inflammatory factors and blocks mesenchymal conversion of mesothelium.

Funding: Government Support - Non-U.S.

TH-PO857

The Effects of Peritoneal Dialysis and Intraperitoneal Amino Acids on Protein Carbamylation Sahir Kalim,[1] Jeffrey Perl,[2] Megan J. Freeman,[2] Caitlin A. Trottier,[1] Anders H. Berg.[3] *[1]Massachusetts General Hospital, Boston, MA; [2]St. Michael's Hospital, Toronto, ON, Canada; [3]Beth Israel Deaconess Medical Center, Boston, MA.*

Background: Protein carbamylation is a urea-driven post translational protein modification associated with mortality in hemodialysis (HD) patients. Free amino acids (AA) competitively inhibit protein carbamylation and parenteral AA therapy reduces carbamylation in HD patients. Peritoneal dialysis (PD) yields differences in urea clearance and AA balance compared to HD, but its effects on carbamylation are unclear. We assessed carbamylation burden in PD patients and determined the effects of AA enriched PD solutions on carbamylation.

Methods: We measured carbamylated albumin levels (C-Alb; a marker of total body carbamylation load) in 100 diabetic HD subjects, matched by age, sex, and race to 98 PD subjects with available plasma samples from the IMPENDIA trial. The IMPENDIA randomized trial (n=180) examined whether low-glucose PD solutions (combination of dextrose, icodextrin, and amino acids) improved metabolic control in diabetic PD patients compared to a control group (dextrose only solutions; 48 treated and 50 control subjects had samples available). C-Alb was compared between HD and PD groups and within IMPENDIA by treatment allocation.

Results: PD patients had a higher baseline C-Alb level compared to HD patients (Table). There were no major differences in basic clinical parameters between the complete IMPENDIA group and the subset with available samples. Among the IMPENDIA participants analyzed, there was no significant difference in C-Alb change from baseline to 6 months in either arm, but treated subjects showed a trend to increased carbamylation (Table). The intervention arm demonstrated a greater change in blood urea nitrogen, possibly explaining the trend for increased carbamylation (Table).

Conclusions: For the first time, we show that carbamylation levels in PD patients run higher than matched HD patients. Incorporating intraperitoneal AA solutions was associated with an increase in urea levels and a marginal increase in C-Alb. PD outcomes may improve if carbamylation burden can be reduced. However, unlike HD where parenteral AA therapy reduces carbamylation, AA-based intraperitoneal solutions as part of the IMPENDIA treatment arm were not effective at reducing carbamylation.

Funding: NIDDK Support, Commercial Support - Baxter Healthcare funded the parent study

Table

Variable	Hemodialysis baseline (n=100)	All peritoneal dialysis baseline (n=98)	P-value	Control peritoneal dialysis baseline (n= 50)	Control peritoneal dialysis 6 months (n=50)	Intervention peritoneal dialysis baseline (n=48)	Intervention peritoneal dialysis 6 months (n=48)	P-value for treatment difference (control – intervention)
Carbamylated albumin (mmol/mol, mean±SD)	11.5±4.5	10.1±4.2	0.03	11.8±4.6	11.3±3.7	11.1±4.2	12.3±4.8	0.09
Blood urea nitrogen (mg/dL, mean±SD)	47.7±14.7	59.2±16.7	<0.01	59.1±16.8	61.6±16.8	56.3±14.0	69.7±16.8	<0.01

TH-PO858

Peritoneal Membrane Morphology Following Peritonitis in Low GDP Peritoneal Dialysis Betti Schaefer,[1] Maria Bartosova,[1] Akos Ujszaszi,[1] Bruno Ranchin,[3] Karel Vondrak,[6] Gema Ariceta,[2] Ariane Zaloszyc,[4] Franz S. Schaefer,[7] Bradley A. Warady,[5] Claus P. Schmitt.[1] *[1]Center for Pediatric and Adolescent Medicine, Heidelberg, Germany; [2]Hospital Universitari Vall d' Hebron, Barcelona, Spain; [3]Pediatrics, Lyon, France; [4]Strasbourg's Hospital University, Strasbourg, France; [5]The Children's Mercy Hospital, Kansas City, MO; [6]University Hospital Prague-Motol, Prague 5, Czech Republic; [7]University of Heidelberg, Heidelberg, Germany. Group/Team: International Pediatric Peritoneal Biopsy Study Group.*

Background: Long term impact of peritonitis on peritoneal membrane integrity and function is incompletely understood. Whereas experimental studies suggest a major impact of peritonitis, respective human data is scant. Children are uniquely suited for analyses of specific PD related effects, since they are devoid of preexisting tissue changes.

Methods: Within the scope of the International Pediatric Peritoneal Biopsy Study we obtained 94 standardized peritoneal specimens from children on low GDP PD for automated quantitative morphometric and molecular tissue analyses. Ten patients who had acute peritonitis less than 4 weeks before biopsy sampling were excluded from the analysis.

Results: 37/84 children had a history of peritonitis and 16/37 had 2 or more episodes of peritonitis. Median age at biopsy was 6.2 (2.6, 13.2) years, 46% girls, and median PD vintage was 15.0 (8.5, 32.9) months. The 37 patients who previously suffered from peritonitis did not differ in anthropometrical parameters from those without peritonitis. Patients with peritonitis were on PD longer (21.0 (12.0, 36.0) v. 12.8 (7.3, 27.0) months; p=0.053). The mesothelial cell layer integrity and the submesothelial zone thickness were similar in both groups. There was no difference in median capillary density, lymphatic capillary density or in the endothelial surface area. Lymphatic vessel density remained low in both groups. Lumen / Vessel ratio as a marker of vasculopathy was also comparable in both groups. $ASMA^+$ activated fibroblasts (59% v. 47%; p=0.27), CD45+ lymphocytes (65% v. 66%; p=0.97) and CD68+ macrophages (60% v. 70%; p=0.18) had a similar prevalence. There were no alterations in fibrin deposits or the degree of Epithelial-Mesenchymal Transition (EMT). In a sensitivity analysis where 24 (total 48) patients were matched for age and PD duration, we did not find any significant differences.

Conclusions: Peritonitis is a common complication of PD. The impact on peritoneal membrane integrity, however, is low. Non-acute post peritonitis peritoneal membrane morphology does not differ with regard to inflammation, EMT, fibrosis and vessel density as compared to children without a history of peritonitis.

TH-PO859

Help of Remote Patient Monitoring in the Assessment of Changes in Ultrafiltration before, during, and after a Peritonitis Episode in Patients on Automated Peritoneal Dialysis Mario R. ---,[2] Alfonso Ramos.[1] *[1]Baxter Mexico, San Jer?nimo Chicahualco, Mexico; [2]Hospital Especialidades Dr Belisario Dominguez SEDESA, Mexico, Mexico.*

Background: Peritonitis is a common complication in patients on peritoneal dialysis and it has become the single most important cause of failure of the technique. The aim of this study is to assess if remote patient monitoring (RPM) allow to detect changes in ultrafiltration (UF) before, during and after a peritonitis episode.

Methods: This report is a retrospective review of a series of cases involving the use of RPM to evaluate UF in Automated Peritoneal Dialysis (APD) patients before, during and after a peritonitis episode. The day of clinical diagnosis of peritonitis was considered day zero. UF volumes from day 7 prior to diagnosis to day 10 after the diagnosis were collected from electronic records of RPM device. For analysis purpose, data were categorized in four groups: Group one: 7 days before the onset of peritonitis; Group 2: One day before the episode; Group 3: Two days after the diagnosis; and Group 4: Days 3-7 after the diagnosis. Group comparison was performed using the Wilcoxon test.

Results: Ten patients were studied, 5 female and 5 male, median age of 48 ± 6 years, with a median length of stay in the program of 18 months. The analysis showed a difference in UF between the values measured 1) 7 days before (194 ml) vs the day before the event (-302 ml) (P<0.04); 2) 7 days before (194 ml) vs during the event (-1,062 ml) (p<0.009); and 3) during the peritonitis (-1,062 ml) vs after the peritonitis episode (-319 ml) (p< 0.01)

Conclusions: This is the first report documenting the use of RMP for the detection of minor changes in UF in a group of APD patients, which will allow us to suspect the presence of peritonitis and monitor its progress over time before conventional clinical data are available.

TH-PO860

Relation between BCM and Echocardiographic Parameters to Reflect Volume Status in Peritoneal Dialysis Min ji Kim,[1] Sunwoo Kang,[2] Tae Hee Kim,[4] Yeong Hoon Kim.[3] *[1]Nephrology, Busan Paik Hospital, Busan, Republic of Korea; [2]Inje University, Busan, BUSAN, Republic of Korea; [3]Inje University Medical School, Busan, Republic of Korea; [4]None, Busan, Republic of Korea.*

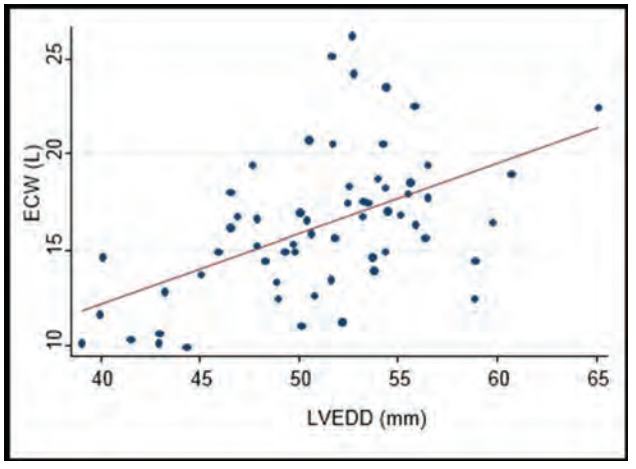
Background: Fluid imbalance is a frequent condition in peritoneal dialysis (PD) patients. Fluid overloading is one of causes to lead to cardiovascular instability. Even though there are no accurate methods to determine volume status in PD, body composition monitor (BCM) is used as an objective measurement. The aim of this study was to find echocardiographic parameters associated with volume status compared to BCM parameters in PD patients.

Methods: This study was conducted on 74 PD patients in Busan Paik Hospital during 2014 – 2015. We used BCM to assess volume status, echocardiography to evaluate heart function and structure, and collected epidemiologic data. To account for the relation between BCM and echocardiographic parameters, we conducted regression analysis.

Results: Patients were 46±12 years old, 55% female, and 39% diabetic. A total of 6 (8%) all-deaths were reported. 10 (13%) among 74 patients received kidney transplantation, 10 patients transferred from PD to hemodialysis. Median dialysis vintage was 25.3 months (IQR 1.6, 127.2 months). Relative overhydration had positive correlation with systolic blood pressure ((r^2=0.12, p=0.003), diastolic blood pressure (r^2=0.07, p=0.03), and extracellular water (ECW) (r^2=0.27, p<0.001). Conversely relative OH had negative correlation with intracellular water (r^2=0.08, p=0.02) and lean tissue index (r^2=0.17, p=0.003). ECW had positive correlation with left ventricular end diastolic dimension (LVEDD) (r^2=0.27, p<0.001) (Figure 1) and left ventricular diastolic posterior wall thickness (LVDPWT) (r^2*=0.14, p=0.003)*.

Conclusions: Fluid overload in PD patients was associated with rise in ECW, which increased according as LVEDD enlargement. Echocardiographic parameters of

Left ventricle were good markers of volume status in PD patients. Further studies to understand the change in volume status over time are needed.



TH-PO861

APD Could Alleviate Acute Left-Heart Failure via Increasing Peritoneal Dialysis Ultra-Filtration: A Single Center Observation Clinical Research Jun Ai. *Nanfang Hospital, Southern Medical University, Guangzhou, China.*

Background: Ultrafiltration failure (UFF) is a major reason which causing water retension, acute left-heart failure (LHF), and peritoneal dialysis (PD) failure for PD patients. Automated peritoneal dialysis (APD) might have better ultra-filtration than CAPD. We had observed whether short time APD could increase UF and alleviate LHF.

Methods: Patients had been collected since December 1, 2015 to Jan 1, 2017 in Renal Department, Nanfang Hosipital of Southern Medical University. All patients had been treated with CAPD (mean dialysate glucose concentration 2.0±0.3%, total dialysate volume 8.3±1.1L) before came to our center and were treated with APD in the hosipital (mean dialysate glucose concentration 2.0±0.2%, 4 cycles per night, total treatment volume 9.6±1.2L, total treatment time 12.0±2.0h). Fluid state, peritoneal ultra-filtration volume, 24h urine volume, body weight, blood pressure were collected and compared between the last three days before receiving short-time APD and in those when receiving short-time APD. Serum creatinine, BUN, albumin, potassium, hemoglobin and glucose were collected and compared before and after receiving APD, respectively. Manifestation and grades of left heart failure were collected and comparted before and 3 days after receiving APD.

Results: A total of 47 patients (31 men, mean age 46.8±16.2yr) were enrolled in this study. The mean duration of CAPD was 26 months (2-195months). Of the 47 patients, peritoneal dialysis UF was significantly increased when receiving short-time APD than that of CAPD (1261.9±329.6ml vs 706.2±222.3ml, p<0.001), and body wights had significantly decreased 3 days after treated with APD (57.73±10.5 Vs 59.81±10.8, p<0.001). The grades of LHF were significantly decreased 3 days after receiving APD (1.7±0.8 vs 2.4±1.0, p<0.001), also manifestation of LHF had been significant improved 3 days after receiving APD (40% vs 70%, p= 0.007). Blood pressre were well controled 3 days after treated with APD (146.6±14.4 vs 162.5±23.8 of SBP, p= 0.0007, and 85.6±11.1 vs 95.6±14.7 of DBP, p=0.001). There were no changed in serum creatinine, albumin, potassium, nor hemoglobin.

Conclusions: In conclusion, short-time APD could significantly increase ultrafiltration, alleviate edema and acute left heart failure, which might be an effective method to treat UFF and acute left heart failure in PD patients.

TH-PO862

Left Ventricular Mass Index at Peritoneal Dialysis Initiation Is Possible Risk of Cardiovascular Disease and Death in Peritoneal Dialysis Patients Using Biocompatible Solution Yoshifumi Hamasaki, Teruhiko Yoshida, Ryo Matsuura, Kent Doi, Eisei Noiri, Masaomi Nangaku. *The University of Tokyo, Tokyo, Japan.*

Background: Left ventricular hypertrophy (LVH) is recognized as a predictor of cardiovascular disease (CVD) and risk of mortality in patients undergoing maintenance peritoneal dialysis (PD). It is not well known whether LVH at PD initiation is associated with the mortality or CVD in patients even when they are treated using biocompatible PD solution (BPDS). We investigated the relationship between clinical parameters including left ventricular mass index (LVMI) at PD initiation and prognosis of patients using BPDS.

Methods: The data from patients who started PD from 2001 to 2015 at The University of Tokyo Hospital were collected retrospectively. To identify the predictors of death and major cardiovascular adverse event (MACE), we analyzed data including clinical parameters measured within 6 months after starting PD using BPDS. LVMI was also evaluated using the data of echocardiography performed at the same period. MACE is defined as cardiovascular death or CVD (cerebrovascular disease, ischemic heart disease or heart failure, and peripheral arterial disease), occurred until April 2017.

Results: 121 patients who started PD as their first dialysis modality were included. The mortality rate was 10.7% (13/121), and MACE were occurred in 31 patients. Logistic regression analysis found that LVMI and age were independent risk factors of mortality (odds ratio, 1.04 and 1.19; 95% confidence interval (CI), 1.01 to 1.07 and 1.08 to 1.32; p <0.01 and p <0.01; respectively). When patients were divided into two groups according to LVMI, Kaplan-Meier analysis revealed that higher LVMI group had significant higher mortality, higher incidence of MACE, and lower persistence rate of PD (Log rank: p = 0.003, 0.005 and 0.011, respectively). On ROC analysis, LVMI predicted mortality with statistical significance (AUC [95%CI] =0.87 [0.76-0.98]). The result of Cox proportional hazards model on mortality demonstrated that LVMI and age were independent predictor of mortality (hazard ration, 1.02 and 1.08; 95%CI, 1.00 to 1.05 and 1.02 to 1.15; p = 0.02 and <0.01; respectively).

Conclusions: LVMI at PD initiation may be a predictor of mortality and CVD in patients using BPDS.

TH-PO863

Therapeutic Experiences of Peritoneal Dialysis Therapy for Patients with Severe Heart Failure and/or Liver Cirrhosis Eiichi Sato,[1,2] Tsukasa Nakamura,[2] Takao Ono,[2] Manaka Degawa,[2] Hongmei Lu,[2] Daisuke Matsumura,[2] Mayumi Nomura,[2] Mayuko Amaha,[2] Akiko Fujii,[1] Yuko Ono,[1] Yoshihiko Ueda.[1] *[1]Dokkyo Medical University, Koshigaya Hospital, Koshigaya, Saitama prefecture, Japan; [2]Shinmatsudo Central General Hospital, Matsudo city, Japan.*

Background: Peritoneal Dialysis (PD) is one type of renal replacement therapy for end-stage renal failure, however, some reports have described the application of PD for severe heart failure and liver cirrhosis using the slight change in hemodynamics caused by the gradual dehydration effect. We describe our experience of introducing PD to patients with severe heart failure or refractory ascites with liver cirrhosis.

Methods: The study included 6 out of 11 patients for whom PD was introduced at our department over the past year. Three patients had severe heart failure and difficulty in weaning off extracorporeal circulation, one patient had refractory ascites caused by liver cirrhosis, and two patients had both conditions.

Results: The subject sample consisted of four male and two female patients, aged 78.3 ± 5.0 years (mean ± standard deviation), and the underlying disease was dilated cardiomyopathy concurrent with diabetes, with ischemic heart disease in four patients, non-alcoholic steatohepatitis in one patient, and hypoalbuminemia in one patient. The mean estimated glomerular filtration rate was 21.8 ± 2.8 ml/min/1.73m2. The mean survival period was 60.7 ± 14.5 days, with two fatal cases at 65 days and 45 days, respectively, both of which were caused by sepsis unrelated to PD. In five patients weaning off extracorporeal circulation was possible, and in one patient, who was unsuited to extracorporeal circulation, heart failure was managed by PD alone and the patient was successfully weaned off the mechanical ventilator. Brain natriuretic peptide was 516.0 ± 172.9 pg/mL prior to PD introduction, and 316.7 ± 82.3 pg/mL following PD introduction, with a significant decrease (p = 0.01).

Conclusions: In patients with chronic heart failure or renal failure concurrent with liver cirrhosis, dehydration management is often performed by extracorporeal circulation, however in many instances, hemodynamics become unstable, making dehydration difficult. At our department, in such cases, it is expected that PD will achieve gradual dehydration, and we experienced cases in which PD enabled CHDF weaning and the control of heart failure and refractory ascites. The effectiveness of PD was suggested as a means of fluid management in severe heart failure and refractory ascites.

TH-PO864

Bioimpedance Monitoring and Blood Pressure in Peritoneal Dialysis Patients Malik Touam,[2] Marielle L. Cottereau,[2] Didier Biroteau,[2] Dominique A. Joly.[1] *[1]Assistance Publique Hôpitaux de Paris, Paris, France; [2]Necker Hospital, Paris, France.*

Background: We used bioelectrical impedance analysis (BIA) to determine body composition parameters in peritoneal dialysis patients (PD), and we compared the relationships of hydratation status with home blood pressure (HBP) and office blood pressure (OBP).

Methods: This single center study enrolled all prevalent PD from 2014 to 2016. Patients recently started on PD (<3 m) or with recent peritonitis (<2 m) were not included. A bioimpedance monitor (BCM®, Fresenius Medical Care, Germany) was used to assess body composition. Demographic data, blood, 24-h dialysate and urine samples were collected. HBP and OBP measurements were collected the same day. Multivariate analysis was used to determine the relationship between HBP, OBP and extracellular fluid volume/total body water ratio (ECV/TBW). Potential cofounders included age, diabetes, Charlson comorbidity index, PD method (CAPD, APD), and residual renal function (RRF) were identified.

Results: 63 PD were included (59.7 ± 13.4 y; average follow-up 13.6 ± 5.2 m). Systolic OBP (sOBP) and systolic HBP (sHBP) were correlated with ECV/TBW. It was a very strong relationship between sHBP and ECV/TBW (p<0.001) with sHBP, RRF and serum BNP being the independent predictors (table 1)

Conclusions: Systolic HBP, decreased RRF and serum BNP were major independent predictors of expanded ECV. In daily practice, expanded ECV should prompt to check home blood pressure.

Funding: Government Support - Non-U.S.

Table 1. Predictors of % ECV/TBW

	Slope (95% CI)	p
sHBP	-0.07 (-0.12 to -0.03)	<0.001
RRF	-0.28 (-0.45 to -0.12)	<0.001
Serum BNP	-0.23 (-0.36 to -0.09)	<0.001
Hemoglobin	-0.04 (-0.12 to 0.03)	0.250
CRP	0.10 (0.02 to 0.18)	0.016
Age at onset PD	-0.24 (-1.12 to 0.93)	0.250
Male gender	-0.77 (-2.41 to 0.88)	0.357
Diabetes	1.49 (-0.13 to 3.12)	0.072
Charlson index	0.40 (-1.32 to 2.12)	0.649
sOBP	0.02 (-0.02 to 0.07)	0.376
OBP (diastolic)	-0.70 (-0.32 to 1.56)	0.429
HBP(diastolic)	-0.55 (-0.37 to 1.28)	0.312
CAPD vs APD	0.71 (-0.42 to 1.76)	0.234
Albumin	0.22 (-0.34 to 0.77)	0.439

TH-PO865

PD Patients Undergoing CABG: Modality Change and Complications Matthew J. Diamond,[1,2] Jennifer L. Waller,[1] Mufaddal F. Kheda,[1] Stephanie L. Baer,[2] Rhonda E. Colombo,[1] Lu Huber,[1] John J. White,[1,2] Matt Day,[1] Troy J. Plumb,[4] N. Stanley Nahman.[3] *[1]Augusta University, Augusta, GA; [2]Augusta VA Medical Center, Augusta, GA; [3]Medical College of Georgia at Augusta University, Augusta, GA; [4]University of Nebraska Medical Center, Omaha, NE.*

Background: Efforts to continue PD when patients undergo CABG may minimize infectious and thoracic complications of temporary HD, alleviate interruptions in therapy, and be more cost effective. To investigate patterns of modality change and post-op complications in PD patients undergoing CABG, we queried the USRDS.

Methods: Incident PD patients from 2004 – 2011 (n=56,192) who underwent CABG were studied. Groups included: no interruption of PD (PD); planned temporary (PT) HD then back to PD ($_{PT}$HD-->PD); permanent switch (PS) to HD ($_{PS}$HD); urgent temporary (UT) HD then back to PD ($_{UT}$HD-->PD); or urgent (U) HD with PS to HD ($_{U}$HD-->$_{PS}$HD). Demographics and outcomes were determined. The relative risk (RR) of complications of interruption of PD vs. no interruption of PD up to 90 days post-op were estimated.

Results: 1259 PD patients had CABG, 63% men, 79% White, with mean±SD age 61±2 years, and time on dialysis of 24.1±2.7 months. Readmissions 90 days post-op (Re-adm90, number), and group comparisons by complication, are shown in the table. Continuing PD, and planned temporary HD ($_{PT}$HD-->PD), were the most common forms of dialysis in PD patients with CABG. However, planned or urgent HD that returns to PD had the most readmissions, and when compared to those staying on PD, had the greatest risk of complications.

Conclusions: Continuing PD during CABG appears safe. A planned permanent switch to HD had the fewest readmissions and a non-significant tendency toward lower complication rates. Restarting PD after planned or urgent HD has a high complication rate. Risk stratification my help identify the best candidates for returning to PD post-CABG.

Funding: Clinical Revenue Support

Variable	$_{PT}$HD-->PD	$_{PS}$HD	$_{UT}$HD-->PD	$_{U}$HD-->$_{PS}$HD	PD	p value
N (%)	427 (34)	135 (11)	72 (6)	145 (12)	480 (38)	NA
Re-adm90 (SD)	2.0 (1.2)	1.4 (1.0)	2.7 (1.3)	1.5 (1.0)	1.5 (1.0)	<0.0001
Complications (RR, 95% CI)						
Level	Peritonitis		Bacteremia		Wound infection	
$_{PT}$HD-->PD vs PD	0.59 (0.23 – 1.47)		1.91 (1.24 - 2.96)*		2.05 (1.21 - 3.49)*	
$_{PS}$HD vs PD	0.54 (0.12 – 2.42)		0.77 (0.36 - 1.64)		0.39 (0.12 -1.35)	
$_{U}$HD-->PD vs PD	2.56 (0.89 – 7.35)		3.13 (1.60 – 6.10)*		4.64 (2.24 - 9.65)*	
$_{U}$HD-->$_{P}$HD vs PD	1.36 (0.51 – 3.62)		1.55 (0.84 – 2.82)		1.60 (0.75 – 3.38)	
* significantly different from staying on PD						

Readmission data, dialysis modality, and Relative Risk (RR) of complications amongst incident PD patients receiving CABG (2004-11)

TH-PO866

Burkholderia Cepacia: An Outbreak in the Peritoneal Dialysis Unit Sarah Gleeson, Hari M. Talreja. *Middlemore hospital, Auckland, New Zealand.*

Background: Introduction *Burkholderia cepacia* is a, gram negative, opportunistic, environmental bacillus which commonly affects cystic fibrosis and immunocompromised patients. Rarely, it can cause peritoneal dialysis exit site infection (ESI). Data on predisposing factors, clinical course and treatment options is limited. Although a common cause of nosocomial infections, no nosocomial outbreaks in peritoneal dialysis (PD) patients have previously been reported. A recent outbreak of *B. cepacia* ESIs in our PD unit provided a unique opportunity to gain more information on *B. cepacia* ESIs and to outline an approach to investigating an outbreak in the PD unit. Eight such cases were identified.

Methods: Case description Following the identification of *B. Cepacia* as the causative organism in PD catheter exit site infection in three patients over an eleven week period, we began screening our PD population for *B. cepacia* exit site colonisation. Over the following sixteen weeks, a further three patients were identified as having asymptomatic colonisation, and a further two patients suffered symptomatic *B. cepacia* ESI. Of the five symptomatic ESIs, three developed tunnel infections requiring multiple courses of antibiotic treatment and eventual catheter removal. Isolated ESIs were treated with oral and topical antibiotics with full resolution. Five of eight patients were female, three had proud flesh at the exit site, three were diabetic (all of the asymptomatic infections were in non-diabetics; two of the three tunnel infections developed in diabetic patients). A thorough investigation into the likely source of the outbreak implicated the 4% chlorhexidine handwash used by the patients. However, samples from the manufacturer did not contain *B. cepacia* suggesting mishandling of the product by the patients may have contributed

Results:

Conclusions: Discussion This is the first reported outbreak of *B. cepacia* PD exit site infections. A number of interesting observations were made. Firstly, diabetes may potentially be a risk factor for refractory or more extensive infection. Secondly, treatment should be individualised according to the extent of the infection; our cohort suggests that an isolated ESI can be treated successfully with oral antibiotics whereas tunnel infections generally require catheter removal.

TH-PO867

The Lower Left Quadrant Incision Significantly Reduced Catheter Tip Migration in Peritoneal Dialysis – A Single Center Retrospective Analysis Yaohui Chen, Lin Yang, Chunyan Lang, Lili Yang, Zhenhua Liu, Yun Li. *Jiangxi Provincial People's Hospital, Nanchang, China.*

Background: The reported rate of catheter tip migration in peritoneal dialysis(PD) is 5-35%. In order to reduce it, a modified catheter implantation incision was studied.

Methods: One hundred and seventy-six of Han Chinese end stage renal disease(ESRD) patients were implanted with Tenckhoff double cuff straight catheter to carry out PD from November 2010 to September 2016. The patients were divided into two groups, 40 in the conventional group and 136 in the modified group. In the conventional group, the incision for the catheter implantation was at 9-13cm above pubic symphysis, left or right paramedian. In the modified group, the incision was at 6-9cm above pubic symphysis and about 2cm left paramedian in the lower left quadrant. It was also the position for catheter pouch. All operations were performed by one physician. The dialysate inflow and outflow times, ultrafiltration volume, urine volume, body weight and edema changes, leakage, infection, bleeding, intestinal obstruction, and catheter tip migration were observed.

Results: Within six months of implantation, 6(15%) patients in the conventional group *vs* 4(2.94%) patients in the modified group had catheter tip migration. Compared with the conventional group, the incidence of catheter tip migration was significantly lower in the modified group (p=0.01). In addition, in the conventional group, all 6 patients who had catheter tip migration needed surgical repositioning after conservative treatment to restore the catheter function. In the modified group, non-surgical repositioning in 1 of the 4 patients with catheter tip migration was achieved while the rest needed surgical repositioning. There were no significant differences in the dialysate inflow and outflow times, ultrafiltration volume, urine volume, body weight between two groups. There were no obvious leakage, infection, bleeding, intestinal obstruction and other complications.

Conclusions: The modified incision at 6-9cm above pubic symphysis and about 2cm left paramedian in lower left quadrant significantly reduced catheter tip migration in peritoneal dialysis in Han Chinese.

TH-PO868

Feasibility of Urgent-Start Peritoneal Dialysis in Older Patients with ESRD: A Single-Center Experience Haijiao Jin,[1] Zhaohui Ni.[2] *[1]Department of Nephrology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; [2]None, Shanghai, China.*

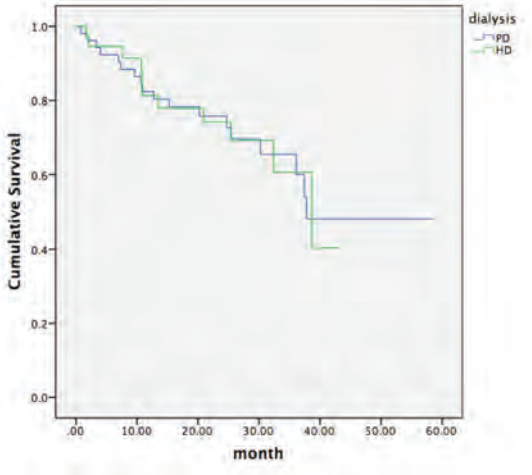
Background: Patients with end-stage renal disease (ESRD) frequently require urgent-start dialysis. Recent evidence suggests that peritoneal dialysis (PD) might be a feasible alternative method of urgent dialysis, including in older patients.

Methods: This retrospective study enrolled patients aged >65 years with ESRD who underwent urgent dialysis without functional vascular access or PD catheter at a single-center, from January 2011 to December 2014. Patients were grouped based on their dialysis modality (PD or hemodialysis [HD]). Patients unable to tolerate PD-catheter insertion or wait for PD were excluded. Each patient was followed for at least 30 days after catheter insertion. Short-term (30-day) dialysis-related complications and patient survival were compared between the two groups.

Results: A total of 94 patients were enrolled, including 53 (56.4%) who underwent PD. The incidence of dialysis-related complications during the first 30 days was significantly lower in PD compared with HD patients (3 [5.7%] vs. 10 [24.4%], P=0.009). Logistic regression identified urgent-start HD as an independent risk factor for dialysis-related complications compared with urgent-start PD (odds ratio 4.760 [1.183–19.147], P=0.028). The 6-, 12-, 24-, and 36-month survival rates in the PD and HD groups were 92.3% vs. 94.6%, 82.4% vs. 81.3%, 75.7% vs. 74.2%, and 69.5% vs. 60.6%, respectively, with no significant differences between the groups (log-rank=0.011, P=0.915).

Conclusions: Urgent-start PD was associated with fewer short-term dialysis-related complications without affecting survival compared with urgent-start HD in older patients with ESRD. PD may thus be a safe and effective dialysis modality for older ESRD patients requiring urgent dialysis.

Funding: Government Support - Non-U.S.



TH-PO869

Poor Early Exit Site Condition Was Associated with Subsequent Exit Site Infection and Catheter Loss of Peritoneal Dialysis Masaki Uehara, Takafumi Yamakawa, Takehiko Kawaguchi, Toshiyuki Imasawa, Moritoshi Kadomura. *Department of Nephrology, National Hospital Organization Chiba-East Hospital, Chiba, Japan.*

Background: Exit site infection (ESI) is a common complication for peritoneal dialysis (PD) patients. A previous study reported that the first ESI before eight month post-implant period was a higher risk of PD related infections. However, it is unclear whether an early condition of exit site after PD initiation is associated with subsequent ESI and PD catheter loss.

Methods: We retrospectively examined 46 patients who started PD from 2010 to 2015 at Chiba East Hospital in Japan. The patients were divided into two groups, good or poor exit site condition group (G or P group), according to ISPD exit site scoring system. We defined the poor exit site as the score more than 2 points on the first outpatient visit after PD initiation, or the worse score on the second visit. We compared episodes of ESI more than twice (E), peritonitis (P) and catheter loss (L) between the groups. Cox regression was used to estimate hazard ratios (HRs) adjusting for age and diabetes as primary disease.

Results: The patients were mostly male (69.6%), with a mean age of 61.0 years, and 50% of patients had diabetes. There were no statistical differences in baseline characteristics between the two groups. During the median follow-up of 719 days, we observed 13 of Es, 15 of Ps, and 13 of Ls. In unadjusted analyses, we found no statistical difference in P free survival rates, but E and L free survival rates were significantly lower in P group than in G group (Figure). In multivariable analyses, the adjusted HRs (95% CI) for E, P, and L in P group were 29.5 (2.62-331.61), 1.90 (0.61-5.94), and 3.00 (1.01-8.95), respectively.

Conclusions: Poor early exit site conditions were associated with subsequent ESIs and PD catheter losses. It may be crucial to keep good exit conditions after PD initiation. Further studies are needed to verify that early screening and interventions for poor exit sites can improve the outcomes.

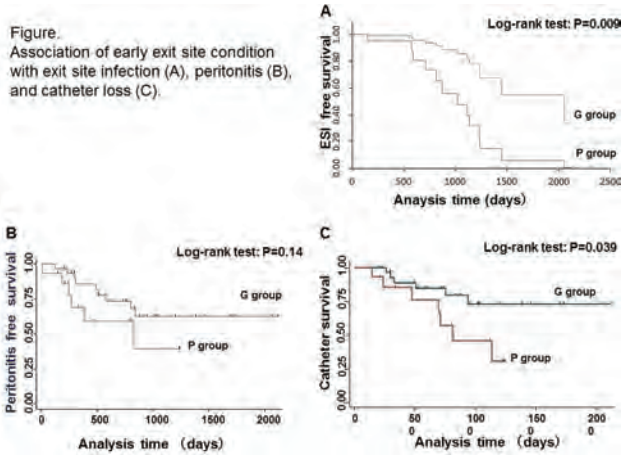


Figure.
Association of early exit site condition with exit site infection (A), peritonitis (B), and catheter loss (C).

TH-PO870

Evaluating Bacterial Flush Efficiency and Touch Contamination Across 3 Different Twinbag Systems Paul Straka, James A. Sloand. *Baxter Healthcare Corporation, Deerfield, IL.*

Background: Peritonitis is a significant complication of peritoneal dialysis (PD). PD system design to reduce touch contamination by at-home PD patients is critical in reducing peritonitis risk. Impact of connection-design differences on contaminant flush efficiency among three different Twinbag CAPD system was assessed by examining differences in the amount of bacteria entering the fluid path under worse case touch contamination.

Methods: 3 studies were performed: A1, A2, and B, with details as follows: A1) Touch contamination at the transfer set connector adapter (TSCA) and the patient connector adapter (PCA) ends, each connector quantified. A2) Touch contamination simulated as in A1, connected and flushed to quantify the bacteria transferred into the fluid path. B) Known levels of bacterial contamination were inoculated into the fluid path, performed CAPD procedure and quantified the patient infusion fluid. Three different commercially available PD delivery systems (System 1, 2, 3) were tested using the above (27 times over a 4 day period) that differed in location of the frangible, the Y-configuration and the size of the shrouds (short: Camex; long: Hytrel) on the PCA.

Results: For touch contamination evaluation (A1), the TSCA had a significant (p-values <0.0001) lower mean bacterial level compared to the PCA. For touch contamination evaluation (A2), system 2 had a significantly higher mean count than systems 1 and 3 (p-value <0.001). For the flush efficiency evaluation (B), the three systems were compared within each day. There were no significant differences in the mean log base 10 values among the three systems within days 1, 3 and 4 (p-values ≥0.05). For day 2, system 3 mean was significantly higher than system 2 mean (p-value = 0.0031).

Conclusions: Touch contamination studies show that when contaminated, the smaller surface area of the TSCA when compared to the PCA resulted in lower bacterial counts. Despite what would appear as a more protective design, the deeply recessed Hytrel shroud resulted in significantly higher bacterial transfer into the fluid path than the shallow recessed Camex shroud. These differences are immaterial given no difference between "Flush before Fill" efficiency of the 3 systems, irrespective of frangible location or asymmetric Y position. This highlights the importance of redundancy in connection design features to reduce PD touch contamination.

TH-PO871

Peritoneal Membrane Transport Characteristics in Uni-Peritoneal Equilibration Test (PET) with Preceding Icodextrin Dwell as Compared to Classic PET with Preceding Glucose Dwell: A Pilot Study Harbir S. Kohli,[1] Gaurav Vohra,[1] Vivek Kumar,[3] Krishan Lal L. Gupta.[2] *[1]Post Graduate Institute of Medical Education and Research (PGIMER), CHANDIGARH, India; [2]Postgraduate Institute of Medical Education & Research, Chandigarh, India; [3]Postgraduate Institute of Medical Education and Research, Chandigarh, India.*

Background: In subjects on CAPD who use icodextrin for long night dwell, it has been recommended that nocturnal icodextrin exchange be replaced by dextrose dwell whenever PET is to be performed. This is because it has been thought that preceding exchange with icodextrin temporarily increases peritoneal membrane permeability and therefore, gives high dialysate/plasma creatinine (D/P cr) and low dialysate glucose at end of PET/dialyste glucose in fresh solution (D/D0) value. Whether this temporary change is also seen with use of Uni-PET (which involves one hour dwell of 1.5% dextrose followed by 4-hour dwell of 4.25% dextrose) is not known.

Methods: In this self, controlled study, subjects on CAPD, who were using icodextrin for long nocturnal dwell for at least 3 months, were screened for enrolment. Pregnancy or lactation, history of any PD related infectious complication in the past one month, present or past malignancy, and poor functional status were exclusion criteria. On day 1 enrolled subjects underwent classic PET with preceding 2.5% dextrose long nocturnal dwell and on day 2 Uni-PET was done with preceding 7.5% icodextrin long nocturnal dwell. Difference in D/P cr and D/D0 glucose between the two PETs were primary objectives. The study was approved by Institute Ethics Committee.

Results: Of 26 screened subjects 15 were enrolled over a period of 18 months (July 2015-December 2016). The mean (±SD) age of study population was 60.8±9.1 years. Majority were males and diabetes was the most common cause of CKD. Mean D/P cr were 0.68 ± 0.11 and 0.64 ± 0.08 in classic PET and Uni-PET, respectively. The difference between the two values was not significant [mean difference between D/P cr (classic PET-Uni-PET): 0.040 ± 0.86; 95% CI (-0.007 to 0.088); p=0.09]. Similarly, D/D0 glucose between classic PET and Uni-PET were also similar [mean difference between D/D0 glucose (classic PET-Uni-PET): -0.02 ± 0.09; 95% CI (-0.06 to 0.03); p = 0.448].

Conclusions: Peritoneal membrane small solute transport characteristics in Uni-PET with preceding icodextrin dwell are similar to classic PET with preceding glucose dwell. If Uni-PET is used, it is not necessary to replace preceding nocturnal exchange of icodextrin with that of dextrose

TH-PO872

Increasing Peritoneal Inflammation Over Time Drives Increasing Peritoneal Solute Transport: Results from the Global Fluid Study Vasileios Zavvos,[1] Emma H. Elphick,[2] Simon J. Davies,[2] Nicholas Topley,[1] Mark Lambie,[2] Donald Fraser.[1] *[1]Cardiff University, Cardiff, United Kingdom; [2]Keele University, Crewe, United Kingdom.*

Background: Local peritoneal inflammation is a feature of peritoneal dialysis (PD) treatment and high concentrations of dialysate IL-6 (dIL6) are a strong determinant of solute transport (PSTR). PSTR is associated with patient survival and increases during long term PD but it is not known to what extent the rise is driven by dIL-6.

Methods: We conducted a longitudinal analysis of the Global Fluid study, a multinational cohort study from UK, Canada and Korea. All incident patients with 3 or more paired dialysate/plasma samples were assayed for IL-6 by electrochemiluminescence. A linear mixed model with random intercept/slopes assessed associations with pIL6. Covariates included time on PD, centre, glucose exposure, icodextrin use, dIL6, gender, baseline age, comorbidity and urine volume in an adjusted model with backwards selection. pIL6 and dIL6 were log transformed. PSTR was assessed by modified peritoneal equilibration testing to calculate the dialysate to plasma creatinine ratio.

Results: There were 217 patients with 1274 measurements, with a median follow up time of 2.2 years from 6 centres. PSTR increased from a mean value of 0.715 within the first 6 months to 0.741 after 3.5 years, whilst dIL6 increased from 6.0 pg/ml to 12.0 pg/ml over the same period. When adjusted for centre, icodextrin use, urine volume and dIL6 were significant predictors of PSTR (β=0.069 95% CI 0.056 to 0.083 p<0.001). Time varying dIL6 was a better predictor than baseline dIL6 (AIC -1377 vs. AIC -1342). Time became insignificant with both varying and baseline dIL6. The effect of urine volume and icodextrin was reduced over time. Random slopes were significant for time (LRT 19 d.f.=2 p=<0.0005).

Conclusions: Both dIL6 and PSTR increase with duration of PD. The increase in PSTR over time is mostly accounted for by changes in dIL6 and urine volume.

Predictors of PSTR over time

	Coefficient	p value/95% Confidence Intervals
Time on PD	0.0091	0.000040 to 0.018
Centre	χ 2 = 44.5, d.f. = 5	p =<0.001
Urine Volume (L)	-0.040	0.0025 to 0.055
Urine Volume Time Interaction	-0.010	-0.017 to -0.003
Use of Icodextrin	0.023	0.0031 to 0.041
Icodextrin Time Interaction	-0.011	-0.021 to 0.002
Time varying dIL6 (log transformed pg/ml)	0.064	0.047 to 0.083

Table showing adjusted multilevel model for PSTR

TH-PO873

Transversus Abdominis Plane Block Relieves Perioperative Pain on Peritoneal Dialysis Catheter Insertion Kenji Harada. *Division of nephrology, Kokura memorial hospital, Kitakyusyu city, Japan.*

Background: The effectiveness of Transversus Abdominis Plain (TAP) block has been reported in the pain control at abdominal operation. However, its usefulness in pain management remains unclear in peritoneal dialysis (PD) patients undergoing catheter insertion. We investigated the effectiveness and safety of TAP block for perioperative on PD catheter insertion.

Methods: The present study is a single-centred, prospective, randomised study of initiated PD patients between from April 2016 to March 2017. VAS (Visual Analogue Scale), which is often used around anesthesiology and pain management field, was measured as pain assessment. VAS was measured at two points, right after and 24 hours after operation, using t-test with P values.

Results: Overall, 66 PD patients were included (mean age; 67.2 year old, male/female; 42/24, average eGFR 7.63±2.81). Patients were divided into two groups TAP block (n=31) and non-TAP block(n=35). There were significant low VAS in TAP block group right after operation (1.06 vs 3.47, p<0.0001). Furthermore, even at 24 hours after operation VAS in TAP block was lower (1.55 vs 2.59, p=0.041). There were no cases needed for ventilation and anesthetic drug such as morphine. TAP block-related adverse events were not found.

Conclusions: TAP block technique was significantly associated with relief from post-operative pain in PD catheter insertion. This treatment procedure might be a minimally invasive and effective therapeutic option for perioperative pain management on PD catheter insertion.

TH-PO874

Peritoneal Dialysis Is Associated with Lower Mortality Compared to Hemodialysis in Patients with Low Serum Albumin Sana Waheed,[3] Brad C. Astor,[2] Tripti Singh.[1] *[1]None, Madison, WI; [2]University of Wisconsin, Madison, WI; [3]Medicine, University of Wisconsin School Of Medicine and Public Health, Madison, WI.*

Background: Low serum albumin is associated with high mortality in patients on chronic dialysis. Clinicians are reluctant to offer peritoneal dialysis (PD) as an option for dialysis for patients with low serum albumin due to concerns of loss of albumin with PD. We evaluated mortality based on dialysis modality in patients with low serum albumin (<2.5 gm/dL)

Methods: We analyzed USRDS data from 2010-2015 to assess mortality by modality type adjusted for age, sex, race, employment, comorbidities and the year of dialysis initiation.

Results: Low serum albumin (<2.5 gm/dL) was present in 78,625 (19.9%) of 395,656 patients. Those with low serum albumin were less likely to use PD as their first modality than those with higher albumin (3.1% vs. 10.9%; p<0.001). Use of PD was associated with lower mortality compared to HD (hazard ratio [HR]= 0.86, 95% CI 0.80-0.93, p< 0.05) in patients with low serum albumin. This difference was more pronounced in patients who had glomerulonephritis (HR= 0.70) or hypertension (HR=0.79) than in those with end-stage renal disease (ESRD) due to diabetes mellitus or other causes [Table 1].

Conclusions: PD is associated with lower mortality than HD in patients with low serum albumin. Therefore, it is of concern that the rate of PD utilization is lower in these patients. We recommend advocating the use of PD in patients with low serum albumin as is associated with a lower mortality rate.

Table 1: Hazard ratio for mortality associated with PD compared to HD in patients with low serum albumin, by cause of ESRD

Cause of ESRD	HR (PD/HD)	CI (95%)	P-interaction
Glomerulonephritis	0.70	0.54-0.92	Reference
Hypertension	0.79	0.64-0.97	0.53
Diabetes Mellitus	0.92	0.83-1.02	0.04
Others	1.03	0.85-1.25	0.01
Overall	0.86	0.8-0.93	

TH-PO875

Race-Ethnicity and Mortality Associated with Serum Potassium in Peritoneal Dialysis Patients Rieko Eriguchi,[1] Yoshitsugu Obi,[2] Elani Streja,[2] Melissa Soohoo,[2] Connie Rhee,[2] Csaba P. Kovesdy,[3] Kamyar Kalantar-Zadeh.[2] *[1]Kaizuka Hospital, Fukuoka, Japan; [2]UC Irvine, Orange, CA; [3]University of Tennessee Health Science Center, Memphis, TN.*

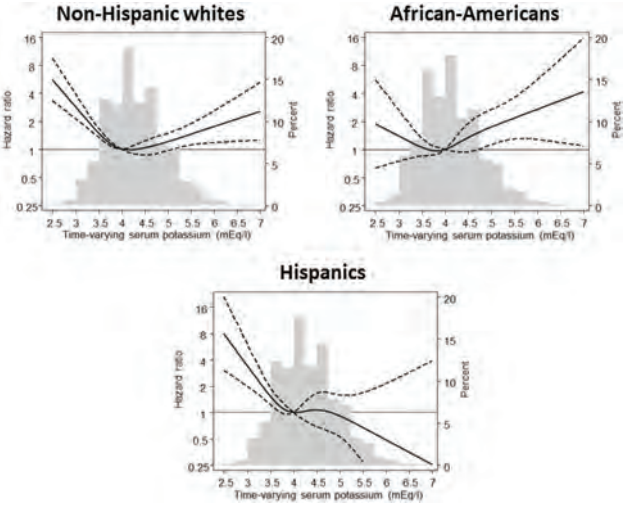
Background: Abnormalities in serum potassium are risk factors for sudden cardiac death and arrhythmias among dialysis patients. A previous study showed that lower potassium is associated with mortality in peritoneal dialysis (PD) patients. However, it remains unknown whether the impact of serum potassium levels on mortality may be different according to race-ethnicity in PD patients.

Methods: We retrospectively examined 19,131 PD patients with available serum potassium data during treatment in a large dialysis organization from January 1, 2007 and December 31, 2011. Using a time-dependent Cox model and splines, we explored the association between monthly-averaged serum potassium level and cause-specific deaths potentially caused by dyskalemias (defined as deaths attributed to hypokalemia, hyperkalemia, cardiac arrhythmia, or cardiac arrest) across race-ethnicity with adjustments for case-mix variables (demographics and comorbidities).

Results: Mean age was 56±16 years, 44% were women, 57% were non-Hispanic white, 23% were African-American, and 12% were Hispanic. Compared to non-Hispanic white patients, African-Americans had lower serum potassium levels, and Hispanics had higher serum potassium levels at baseline. In the total cohort, serum potassium levels less than 3.5 mEq/L were significantly associated with higher cause-specific deaths. In regards to potential potassium-related deaths, hypokalemia was associated with mortality in both non-Hispanic whites and Hispanics. Hyperkalemia was not associated with mortality in Hispanics, only in non-Hispanic whites and African-Americans.

Conclusions: Among PD patients, lower serum potassium levels were associated with cause-specific deaths. The impact of serum potassium levels on potential potassium-related deaths varied according to race-ethnicity.

Funding: NIDDK Support



TH-PO876

Barriers to Peritoneal Dialysis in Kenya Ahmed P. Sokwala. *Aga Khan University Hospital, Nairobi, Kenya.*

Background: Peritoneal dialysis (PD) is not commonly practiced in Kenya. Kenya has approximately 4000 patients on hemodialysis (HD) with less than 20 patients on PD. The perception and attitude of both the patient and the doctor on the modality of chronic renal replacement therapy determines what type of dialysis the patient will be started on. Increase in PD in developing countries with poor infrastructure for HD, will increase the number of patients who can access renal replacement therapy for both acute kidney injury and end stage renal disease.

Methods: A questionnaire was formulated and mailed to the nephrologists to determine their attitude towards PD and to bring out the reasons why they are reluctant to start peritoneal dialysis. A total of 22 questions were formulated and the questionaires mailed to the 25 nephrologists in the region. Questions were about the nephrologists' opinions on reasons that limited patients and doctors selection of peritoneal dialsis as initial therapy. After analyzing the reasons, interventions can be put into place to improve the numbers of patients on peritoneal dialysis.

Results: Twenty three out of twenty five (93%) nephrologists responded to the questions. Only 38% of the nephrologists took care of patients on peritoneal dialysis and out of those 55% of the nephrologists had less than 2 patients on PD. Despite that 70% of the nephrologist thought that more than 20% of end stage renal disease patients should be on PD. Most of the doctors said they had adequate training and exposure to peritoneal dialysis in their training. Lack of nursing expertise was one of the main reasons stated by the nephrologist as being the main chalenge of starting peritoneal dialysis. Lower physcian reimbursement for peritoneal dialysis vis a vis haemodialysis was another point brought out, the Government had started paying for hemodialysis rather than peritoneal dialsysis The other major hinderance was insertion and care of the peritoneal dialysis catheter. Most nephrologists thought patients do well on peritoneal dialysis with no mortality difference between PD and HD.

Conclusions: There is positive attitude about PD amongst the nephrologist. Training more nurses on peritoneal dialysis and training doctors on bedside insertion of peritoneal dialysis catheres will probably increase the uptake of peritoneal dialysis in our country. Nephrologists should be equally reimbursed for PD as for HD or even better.

TH-PO877

Burden on Caregiver and Risks of Patients in Peritoneal Dialysis Marica Mulè,[3] Valerio Vizzardi,[2] Anna Bertoni,[4] Sara Molgora,[5] Massimo Sandrini.[1] *[1]Spedali Civili, Brescia, Italy; [2]University and Spedali Civili, Brescia (BS), Italy; [3]Università Cattolica, Milano, Italy; [4]Università Cattolica, Milano, Italy; [5]Università Cattolica, Milano, Italy.*

Background: This qualitative research aims to assess the psychological aspects about the caregivers of patients with Chronic Kidney Disease (CKD) in Peritoneal Dialysis (PD). This study has two goals: to observe the role of caregiver in PD; to compare fatigues, resources of dialysis team, patients and partners.

Methods: Two Focus Groups have been conducted: The first one with PD team and the second one with patients and their caregivers. Focus Groups were videotaped and transcribed. The transcripts were analyzed using the textual analysis software T-LAB. It has been performed a thematic analysis of elementary contexts.

Results: The thematic analysis implemented overall corpus of interviews showed a four-cluster solution. Clusters identify four thematic areas about PD team, patients and caregivers perceptions. We labeled these cluster respectively: "The relationship: the best possible support"; "Burden caregiver"; "Patient and Caregiver engagement" and "Quality of life in CKD". Clusters explain respectively 32,3%, 27,3%, 25% and 15,4% of the data variance. For the first aim the analysis showed as the caregiver is the best resource for the PD team and for the patients. In addition, the analysis shows as one of the possible risks of peritoneal dialysis that the caregiver feels more responsibility and fatigues than the patient does. This could bring the caregiver towards the burnout and dehumanizing behavior. In fact the CKD seems removing the patient freedom and looks like a cage for the caregiver. Regarding the second aim the clusters evidence as strength the relationship as the best chance in process of care in CKD. The greatest difficulty for PD team is recognizing when the caregiver becomes a "patient" and when the caregiver is a resource. In the same way the most fatigue for the caregivers is to recognize their role and their limits in patient caring. Last but not least the most difficult challenge for patients is going beyond their demotivation to be engaged in the care process.

Conclusions: The study shows as the CKD is a couple matter and a daily challenge for PD team. All clusters concern the burden caregiver may be one possible factor contributing to poor quality of life and depression in both family and patients.

TH-PO878

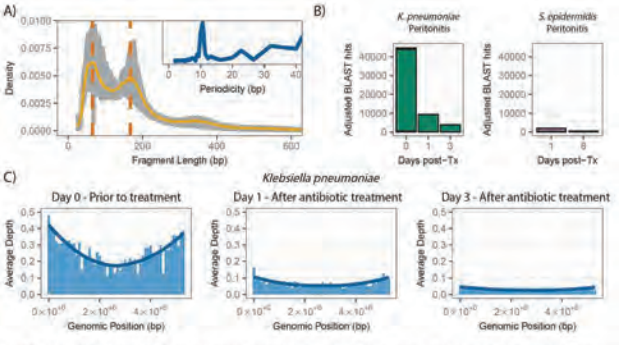
Metagenomic Sequencing of Cell-Free DNA in Peritoneal Fluid: A Novel Strategy to Identify Pathogens and Characterize Bacterial Growth Dynamics and Antibiotic Resistomes in Peritonitis John R. Lee,[3] Philip Burnham,[1] Amanda D. Renaghan,[3] Jeffrey I. Silberzweig,[2] Vesh Srivatana,[2] Darshana Dadhania,[3] Thangamani Muthukumar,[3] Manikkam Suthanthiran,[3] Iwijn De Vlaminck.[1] *[1]Cornell University, Ithaca, NY; [2]The Rogosin Institute, New York, NY; [3]Weill Cornell Medicine-, New York, NY.*

Background: Peritonitis is a devastating complication in peritoneal dialysis (PD) patients. Newer techniques are needed to predict peritonitis development and to characterize pathogen dynamics.

Methods: In this first-in-kind study, we recruited 4 ESRD PD patients; 2 subjects had peritonitis at the time of recruitment and the remaining 2 did not. We collected serial peritoneal fluid (PF) specimens from these subjects. We performed metagenomic sequencing on PF under single-stranded DNA library preparation using an Illumina NextSeq platform (2x75 bp).

Results: A mean of 3.6 million cfDNA fragments was obtained per specimen (N=7 specimens) and these fragments had peaks at 65 bp and 167 bp (Fig A). cfDNA profiling confirmed 2 cases of peritonitis (*Klebsiella pneumoniae, Staphylococcus epidermis*). Serial profiling showed decreasing adjusted BLAST hits after antibiotic treatment (Fig. B). Alignment of cfDNA fragments to the reference genome of *K. pneumoniae* revealed disproportionate coverage over the replication origin, highlighting active growth of *K. pneumoniae*, and subsequent decrease in growth activity after antibiotic treatment (Fig. C). Antibiotic resistance determination revealed the presence of PmrE, PmrF, oqxB, mfd, FosA5, cpxAR, PatA-PatB, and msbA, which provide resistance to colistin, novobiocin, ciprofloxacin, and norfloxacin.

Conclusions: Our first-in-kind study demonstrates that cfDNA profiling of peritoneal fluid is an all-inclusive approach to comprehensively identify pathogens, bacterial growth dynamics, and antibiotic resistomes, which may be useful in culture-negative peritonitis and recurrent peritonitis.



A) Cell free DNA fragments in PD fluid with fragment length on the x axis and density on the y axis. Peaks are noted at 65 bp and 167 bp, resembling patterns in the urine and plasma. The upper box represents peaks at 10 bp (representing breakpoints between nucleosomal wrapping). B) Microbial profiling of the 2 subjects with peritonitis after treatment. On the left is the subject diagnosed with *Klebsiella pneumoniae* peritonitis (green) and on the right the subject diagnosed with *Staphylococcus epidermis* (purple). Days after treatment are on the x axis and adjusted blast hits are on the Y axis. C) Disproportionate coverage over the origin site of replication (a parabola shape) is correlated with active bacterial growth rate based on Korem et al., Science 349(6252):1101, 2015. We applied this principle to the cfDNA metagenomic sequences prior to treatment (left) and after treatment (center and right panel). The genome position with 0 as site of origin is on the x axis and the depth of coverage is on the y axis. As shown, there is increasingly more even coverage over the origin site which is correlated with a non-dividing bacterial population.

TH-PO879

The Involvement of p38MAPK in Impaired Neutrophil Bactericidal Activity of Hemodialysis Patients Yasutaka Kamikawa,[1] Norihiko Sakai,[1] Yasuyuki Shinozaki,[1] Shinji Kitajima,[1] Tadashi Toyama,[1] Akinori Hara,[1] Yasunori Iwata,[1] Miho Shimizu,[1] Kengo Furuichi,[1] Takashi Wada.[1,2] *[1]Division of Nephrology, Kanazawa University Hospital, Kanazawa, Japan; [2]Department of Nephrology and Laboratory Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan.*

Background: Mortality from infections has been reported to be higher in hemodialysis (HD) patients than that in healthy subjects. Previous studies reported that vascular access was the main route of bacterial infection in HD patients and also pointed that the most common micro-organism were staphylococcus aureus (*S. aureus*). To protect the host from bacterial infection, neutrophils have been thought to play central roles in the pathogenesis of the infection. This far, the dysfunction of neutrophils against bacterial infection in HD patients was reported. However the precise mechanism of neutrophil dysfunction in HD patients against bacteria remains unclear. In this study, we investigated the impacts of neutrophil inflammatory signaling against bacterial infection in HD patients.

Methods: Comprehensive analyses of intracellular signalings were performed in whole blood of HD patients and hypertensive (HT) patients as control using microarray system. None of patients had diabetes, cardiovascular disease and cancer. To confirm the contribution of the signaling to bactericidal activity in neutrophils, we examined the

phosphorylation, bacterial killing function, reactive oxygen species (ROS) production and myeloperoxidase (MPO) release in neutrophils against *S. aureus*.

Results: There were no difference at age and nutrition states such as serum albumin levels, cholesterol profile between HD and HT patients. RNA microarray analysis showed the suppression of p38 mitogen activated protein kinase (MAPK) signaling in HD patients. Neutrophils in HD patients showed the impairment of bactericidal activity against *S. aureus* compared to healthy subjects. Phosphorylation rate of p38MAPK of neutrophils in response to *S. aureus* was lower in HD patients than healthy subjects. The levels of ROS produced by neutrophils after co-culture with *S. aureus* were lower in HD patients, on the other hand, there was no difference of MPO release between HD patients and healthy subjects. A selective pharmacological inhibitor of p38MAPK suppressed bacterial killing function as well as ROS production in neutrophils of healthy subjects.

Conclusions: Impairment of p38MAPK signaling pathway might contribute to the suppression of neutrophil bactericidal activity in HD patients through the less production of ROS.

TH-PO880

Seasonal Variations in Blood Stream Infections in Hemodialysis Patients in the Midwest Marta Reviriego-Mendoza,[1] Sophia Rosen,[1] Hao Han,[1] Tommy C. Blanchard,[1] Jerry W. Jackson,[2] Julia I. Brennan,[4] John W. Larkin,[1] Len A. Usvyat,[1] Peter Kotanko,[3] Jeffrey L. Hymes,[1] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]FMC Patient Safety Council, Mountain Brk, AL; [3]Renal Research Institute, New York, NY; [4]Spectra Laboratories, Rockleigh, NJ.*

Background: Blood stream Infections (BSIs) are the most common cause of morbidity and second leading cause of mortality in hemodialysis patients (HD). Environmental variations, particularly heat and humidity, are known to promote pathogenic growth and be associated with the incidence of BSIs and the worsening of clinical conditions. We aimed to study whether seasonal changes in the Midwestern area of the United States are associated with the variations in BSI rates in hemodialysis patients.

Methods: We collected data from HD patients treated at Fresenius Kidney Care clinics in the Midwest region from Jan-2014 through Dec-2016. This region was selected due to its more demarcated seasonal changes. Clinics included were those from the following states: Illinois, Indiana, Iowa, Kansas, Michigan, Minnesota, Missouri, Nebraska, North Dakota, Ohio, South Dakota, and Wisconsin. The average monthly BSIs were calculated for HD patients and the association between the mean BSI rate and season was analyzed and plotted using a seasonally varying function that was optimized to the data using a least-squared method (Figure 1).

Results: We observed a distinct seasonal variations in BSI rates with a mean fluctuation of 9.25% below and above during July versus February of 2014-2016, respectively. Although BSI rates appeared to increase during warmer months, we observed a 34.3% decrease in BSI rates in the Midwest from 2014 to 2016.

Conclusions: Our findings suggest that seasonal variability is associated with alterations in BSI rates. In the Midwest, the highest BSI rates were observed during warmer months. The downward trends in BSI rates may be representative of improvements in infection control in HD facilities. Further analyses are warranted to confirm these results.

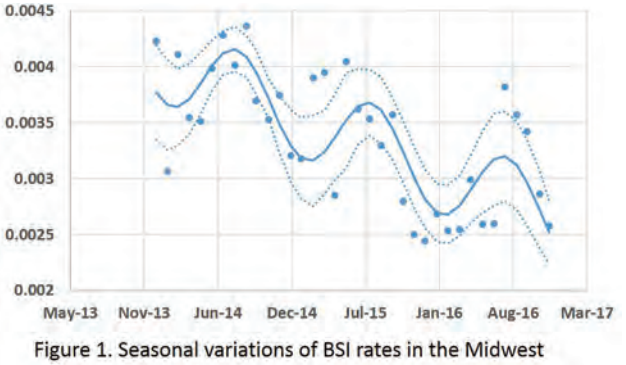


Figure 1. Seasonal variations of BSI rates in the Midwest

TH-PO881

Sex-Specific Differences in Blood Stream Infection and Hospitalization Rates in Hemodialysis Patients Marta Reviriego-Mendoza, Sophia Rosen, Dugan Maddux, John W. Larkin, Len A. Usvyat, Franklin W. Maddux. *Fresenius Medical Care, Waltham, MA.*

Background: It is known that men and women have physiological, hormonal, and genetic differences that can impact treatment regimens and clinical outcomes. Investigations on sex-specific differences in patients undergoing hemodialysis (HD) are limited. We performed a cross-sectional analysis to investigate if there are sex specific differences in systolic blood pressure (SBP) levels, blood stream infection (BSI) rates and hospitalization rates.

Methods: We analyzed data from all Fresenius Medical Care North America HD patients in 2016. Patients were grouped in 17-age categories from 18 years to 95 based on their age at initiation of dialysis. Yearly average SBP was calculated for each patient and averaged for each age-group. Hospitalization rates per patient year (ppy) and rate of admissions ppy were calculated for each age-group. We identified patients who had 1 or more BSIs during 2016 and calculated the percent of patients with at least 1 infection in that particular age group.

Results: Overall, we studied data from 230,091 patients; 43% were female. We used linear and quadratic regressions with an interaction term for Sex to study the sex-specific differences. From our analysis we noted: i) SBP remained stable for women at 139 (+/- 1) mmHg in all age groups, while males showed a steady decline from 143 mmHg to 130 mmHg from the age of 25 to 90 ($p<.0001$). ii) For both genders, BSIs are most common at a young age (between 25 and 40) and decline later in life. However, women exhibited a significantly higher percentage of BSIs compared to men with 9.2% vs 7.5% at age 25-30 ($p<.0001$). iii) Hospital admission rates ppy were significantly higher for women when compared to men, peaking at age 25 with nearly a 2 fold higher admission rates than men (3.0 vs 1.7 admissions ppy). Admission rates for women declined with age and equaled those of men by the age of 90 ($p<.0001$).

Conclusions: Our analysis shows that women, in particular those of a younger age, are at a significantly higher risk of BSIs and hospitalization than men. The characterization of these health disparities between the sexes may aid in identifying patients at risk of poorer outcomes.

Funding: Commercial Support - Fresenius

TH-PO882

Association of Low Molecular Weight Heparin Compared to Unfractionated Heparin and the Risk of Dialysis-Related Infection and Septicemia among Hemodialysis Patients Hind H. Lazrak,[1] Emilie Rene,[1] Naoual Elftouh,[1] Annie-Claire Nadeau-Fredette,[1,2] Louis-Philippe Laurin,[1,2] Jean-Philippe Lafrance.[1,2] *[1]Research center, Maisonneuve-Rosemont Hospital, Montreal, QC, Canada; [2]Division of nephrology, Maisonneuve-Rosemont Hospital, Montreal, QC, Canada.*

Background: Hemodialysis patients have a higher risk of infection compared to the general population. The administration of low molecular weight heparin (LMWH) for the extracorporeal circuit anticoagulation requires less manipulation in comparison with unfractionated heparin (UFH), which may result in a reduced bacterial contamination. The aim of this study is to evaluate the association between the use of LMWH and dialysis-related infection and septicemia compared to UFH among chronic hemodialysis patients.

Methods: We conducted a retrospective cohort study of 6012 adult chronic hemodialysis patients (prevalent and incident) using an administrative database in Quebec, Canada. Hospitalizations due to dialysis-related infections or septicemia were identified using ICD-10 codes. Patients' exposure to LMWH or UFH was determined at the facility level. Infection rates were calculated as person-year and risk of infection was estimated using Cox proportional hazard ratios (HR) and 95% confidence interval adjusting for demographics, prior hospitalizations, comorbidities and steroids use.

Results: The incidence rate of hospitalizations for dialysis-related infections and septicemia was 0.044 patient-year. From the total cohort, 37% of patients were exposed to LMWH. Compared to UFH, LMWH was associated with a statistically significant decrease of infection risk (HR=0.79, 95%CI: 0.64-0.96). Moreover, younger age (HR=0.99, 95%CI: 0.98-1.00), hospitalization in prior year (HR=1.26, 95%CI: 1.00-1.58), chronic pulmonary disease (HR=1.36, 95%CI: 1.09-1.70) and diabetes (HR=1.26, 95%CI: 1.03-1.54) increased the infection risk among chronic hemodialysis patients.

Conclusions: Among hemodialysis patients, LMWH use decreased the risk of hospitalization for dialysis-related infection and septicemia compared to UFH.

TH-PO883

An Outbreak of Catheter-Related Bacteremia on Hemodialysis Patients Caused by Serratia marcescens Omar I. Delgado, Javier Soto-Vargas, Heriberto R. López, Jorge fernando Topete reyes, Ma anabel Salazar lopez, Oscar C. Martinez Garcia, Leonardo Pazarin-Villase?or. *Nephrology, Regional General Hosptial 46, Mexican Institute of Social Security, Guadalajara, Mexico, Guadalajara, Mexico.*

Background: Catheter related infections in hemodialysis patients are associated with a great morbidity, hospitalization, and death. *Serratia marcescens* it has been reported to cause nosocomial infection due to their ability to colonize antiseptic soaps. Our objective was to present an outbreak of S. marcescens in HD patients.

Methods: In our HD unit there are 27 HD machines, with a total of 945 treatments at week, we have 370 maintenance HD patients with 2 or more sessions per week. During the period of April to May 2015 ninety-five HD patients reported a bacteremia episode during, of which 56 cases were positive to *S. marcescens*. An epidemiologic search was conducted finding positive cultures on antiseptic soap used by medical personal.

Results: There were 95 cases of bacteremia, of which *S. marcescens* represented the 58.9% (56) of the cases, 14 (16.1%) we were unable to localize and agent, and other pathogens had a frequency no bigger than 2%. The median age was 35 years (IQR 25-53), 62 (65.33%) were male, 65 (68.4%) patients had HD thrice weekly, and 30 (31.6%) had twice or less HD sessions per week, 46 (48.4%) patients received their treatment on nocturnal hours, 27 (28.4%) on the morning hours and 12 (12.6%) on the evening and there were no association between the time of the HD sessions and the need for hospitalization and catheter removal. Seventy-one percent of the patients had a non-tunneled catheter, 29% had a tunneled catheter, and there were no cases in patients who had FAV as theirs venous access. The antibiotic treatment was standardized according to sensibility analysis of the cultures consisting of amikacin in lock therapy and systemic ciprofloxacin. There were no fatal cases, but the infection results in the need of hospitalization and access removal in four cases (4.2%).

Conclusions: The appearance of S. marcescens in blood cultures of HD patients units should alert the possibility of an outbreak, given its ability to colonize antiseptic substances. Early and targeted antibiotic treatment as well as rutinary microbiology screening is recommended for the prevention of outbreaks.

TH-PO884

Epidemiology and Outcomes of Infective Spondylodiscitis in Hemodialysis Patients Yuehan Lu, George Kuo, Chao-Yu Chen, Hsiang-Hao Hsu. *Kidney Research Center, Department of Nephrology, Linkou Chang Gung Memorial Hospital; College and School of Medicine, Chang Gung University, Taiwan, Taoyuan, Taiwan.*

Background: Infective spondylodiscitis, defined as the pathogenic invasion of vertebra and intervertebral disc, is an uncommon but serious disease. As the disease progresses, patients develop neurological deficits, sepsis, and even mortality. Microorganisms reach vertebra and intervertebral discs in different ways, including antegrade bacteremia from the blood stream, retrograde infection from the urinary tract and direct invasion from contiguous tissue or a surgical procedure. Patients on maintenance hemodialysis (HD) have additional risk factors that contribute to blood stream infection because of the repeated vascular puncturing, long-term catheter or Gore-Tex graft indwelling, and contamination of dialysis water purification system. The characteristics and outcomes of infective spondylodiscitis in HD patients may be different from those in the general population.

Methods: The cases of 1,402 patients who were hospitalized for infective spondylodiscitis in a 13 year period in a tertiary hospital were retrospectively reviewed. Of these, 102 patients on maintenance HD were enrolled in this study. Cox's proportional hazard model was used to evaluate the risk factors of mortality and recurrence.

Results: The 102 enrolled patients had an average age 63.3±11.2 years old and male-to-female ratio of 1:1.04. Back pain was present in 75.5% of patients and the most commonly infected site was the lumbosacral spine. Infection associated with vascular access was identified in 31.4% of patients and the use of dialysis via central venous catheters was three times higher than in outpatient cohort. Methicillin-resistant *S. aureus* was the most common pathogen, followed coagulase-negative staphylococci. The patients' in-hospital survival rate was 82.4%; their vascular access survival was 75.5% their one-year survival was 78.4% and their one-year recurrence rate was 20.2%. Congestive heart failure was associated with an increased one-year mortality. Other variables exhibited no significant relationship with patients' in-hospital mortality, one-year mortality or recurrence.

Conclusions: The characteristics and outcomes of infective spondylodiscitis in HD patients were elucidated. Most of the demographic and clinical variables, evaluated upon admission, did not predict mortality or recurrence. An algorithm for the diagnosis and treatment of infective spondylodiscitis in an HD cohort is provided.

TH-PO885

Epidemiology and Outcomes of Endophthalmitis in Chronic Dialysis Patients: A 13-Year Experience in a Tertiary Referral Center in Taiwan George Kuo,[1] Hsiang-Hao Hsu.[2] *[1]Chang-Gung Memorial Hospital, Taiwan, Taoyuan City, Taiwan; [2]Kidney Research Center, Department of Nephrology, Linkou Chang Gung Memorial Hospital; College and School of Medicine, Chang Gung University, Taiwan, Taoyuan, Taiwan.*

Background: Endophthalmitis is a severe eye infection leading to disabling outcome. we would like to investigate the epidemiology and clinical features of endophthalmitis in chronic dialysis patient in a tertiary referral center.

Methods: We perfoemed chart review and searched discharge diagnosis with ICD9 encoding endophthalmitis during Jan. 2002 to Dec. 2015.

Results: In total 32 patients, 25 were endogenous and another 7 were exogenous endophthalmitis. Most patients presented with ophthalmalgia and periocular swelling, whereas half of the patients suffered blurred vision (n=16, 50%). *S. aureus, K. pneumoniae,* and *P. aeruginosa* were the most frequent causative pathogens. Dialysis vascular infection was an important focus. The final visual outcomes in both groups were worse in the chronic dialysis patients compared with previous studies of general population

Conclusions: This is the first and the largest case series focusing on endophthalmitis in chronic dialysis patients. Our study showed different pathogen spectrum, an unique bacterial origin and worse visual outcome in these group of patients. Prompt referral to ophthalmologists is important.

Funding: Government Support - Non-U.S.

Characteristic of dialysis patient with endophthalmitis

	Endogenous (N = 25)	Exogenous (N = 7)
Days from symptoms onset to ophthalmoogist visit	1-30 (median: 2)	1-7 (median: 2)
Recent trauma or surgery	0 (0%)	7 (100%)
Days post trauma or surgery		3-20 (median: 4)
Blurred vision	14 (56%)	2 (28.5%)
Ophthalmalgia	25 (100%)	7 (100%)
Periocular swelling	25 (100%)	6 (85.7%)
Fever	8 (32%)	0 (0%)
Septic shock	2 (8%)	0 (0%)
Respiratory failure	2 (8%)	0 (0%)
Dialysis access infection	4 (14.8%)	0 (0%)
White blood cell counts	11 (+/- 5)	10 (+/- 6)
CRP level	71 (+/- 75)	16 (+/- 10)
Bacteremia	8 (32%)	0 (0%)
Fungemia	0 (0%)	0 (0%)
Positive vitreous culture	13 (52%)	4 (57.1%)
Treatment		
Intravitreous antibiotic injection (IVI)	12 (48%)	7 (100%)
Trans pars plana vitrectomy (TPPV)	2 (8%)	3 (42.9%)
Enucleation	5 (20%)	0 (0%)
Parenteral antibiotic alone	8 (32%)	0 (0%)

TH-PO886

Reduction in Rates of Blood Stream Infection Associated with Adoption of TeamSTEPPS as a Framework for Improved Hemodialysis Facility Workflows Jerry W. Jackson,[1,3] Norma J. Ofsthun,[3] Carol Meredith,[2] Marcy E. Goldberg,[3] Uddar Onta,[3] Franklin W. Maddux.[3] *[1]FMC Patient Safety Council, Mountain Brk, AL; [2]Fresenius Kidney Care, Downers Grove, IL; [3]Fresenius Medical Care North America, Waltham, MA.*

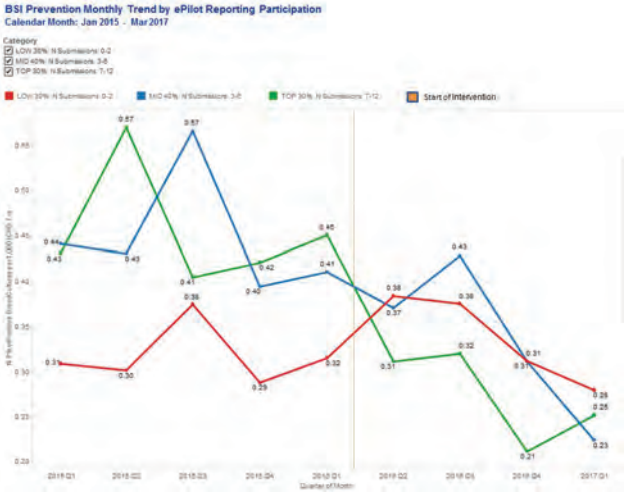
Background: Blood Stream Infection (BSI) remains one of the most serious adverse events affecting end stage renal disease (ESRD) patients. Multiple barriers and situational factors impede infection control in ambulatory hemodialysis (HD) facilities. We implemented a Quality Improvement Project (QIP) and analyzed its impact on BSI rates in HD facilities.

Methods: We deployed the QIP in 97 Fresenius Kidney Care facilities from January 2016 through March 2017. After performing a Failure Mode and Effects Analysis, we identified 55 HD workflow steps (distributed throughout the HD treatment) with high-risk for infection. The QIP design included training and observational auditing for the high-risk steps, use of TeamSTEPPS training to instill team-oriented care and to reduce barriers to infection control, ongoing coaching and feedback for caregivers in the use of TeamSTEPPS tools, incorporation of an infection control data set for analysis and action-planning during QAPI, and closed-loop communication pathways. The facilities were divided into Low, Mid and Top participatory subgroups based on monthly reported process metrics. Mean BSI rate by subgroup during 2015 was used for baseline. Implementation BSI rates by subgroup were followed Q1 2016 through Q1 2017.

Results: We studied data from a mean census of 10,988 patients. Mean baseline BSI rates (expressed as BSI episodes/1,000 HD treatments) by subgroup were: Low, 0.32; Mid, 0.46; Top, 0.46. Data collected at the end of the QIP showed changes in mean BSI rates of (+) 4.6%, (-) 23.7%, and (-) 32.2% for the Low, Mid and Top subgroups, respectively (Figure 1).

Conclusions: These findings suggest the use of TeamSTEPPS combined with the other interventions of this QIP might be associated with a reduction in dialysis associated blood stream infections.

Funding: Commercial Support - Fresenius Medical Care North America



TH-PO887

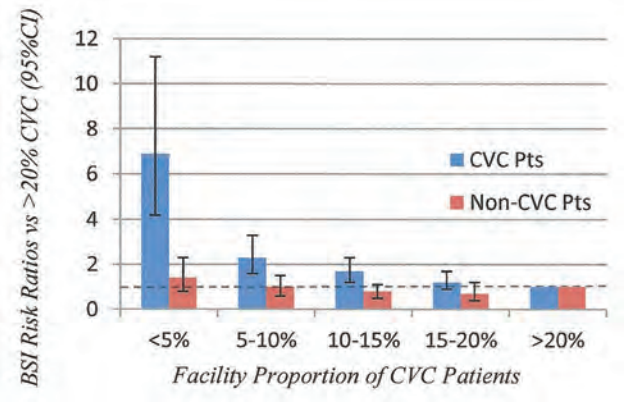
Bloodstream Infection (BSI) Rates in Catheter Patients Are Markedly Higher in Hemodialysis Facilities with Lower Proportions of Catheters Robert S. Brown,[1] Kristin M. Brickel,[2] Roger B. Davis.[1] *[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]DaVita, Naugatuck, CT.*

Background: BSI rates of HD patients with catheters (CVC) are greater than with other accesses. Medicare assesses financial penalties and lower Five-Star ratings to high CVC facilities, prompting a study of BSI rates in CVC patients relative to facility CVC percentages.

Methods: CROWNWeb and NHSN data from all 171 Medicare facilities providing adult outpatient HD in the IPRO ESRD Network of New England throughout 2015 (mean, 12,626 patients/mo) compared BSI rates of CVC and non-CVC patients based upon facility proportion of CVCs, patient census, batch submitting organization and season.

Results: There were an average of 74±40 HD patients with 9±6 (13%) having CVC accesses per facility. Mean BSI/100 pt-mo was 0.50±1.0 for all accesses, 3.0±8.7 for CVC, and 0.21±0.72 for non-CVC patients (relative risk of BSI for CVC vs non-CVC patient, 10.7, 95%CI 8.7, 13.2, P=<0.0001). Surprisingly, annual BSI rates in CVC patients were negatively correlated with the facility's proportion of CVCs (–0.247, P=0.001) but positively correlated in non-CVC patients (0.147, P=0.056). Facilities with <5%, 5-10%, 10-15%, 15-20%, >20% CVCs have BSI rates of 11.7, 3.5, 2.5, 1.8, 1.6 per 100 pt-mo, respectively, in CVC patients (P=<0.0001). This striking difference was not seen in non-CVC patients (P=0.07, risk ratios in figure). Smaller providers have 1.3-2.6 times the BSI rates of the 4 large dialysis organizations (4.6 vs 1.8-3.6 BSI/100pt-mo, P=0.01) despite similar CVC proportions. There was no effect of facility census or season.

Conclusions: HD facilities with the lowest proportion of CVCs have significantly higher BSI rates (up to 6.9 times) in their CVC patients. This large difference may be explained by "dilution" of CVC patients with those in the lower risk non-CVC pool and by better training and experience in facilities with higher CVC proportions and the larger dialysis organizations. BSI rates in CVC patients may be a better quality parameter than CVC percentage.



TH-PO888

Tunnelled Hemodialysis Catheter Care Practices and Blood Stream Infection Rate in Children: Results from the SCOPE Collaborative Olivera Marsenic Couloures,[4] Jonathan Rodean,[1] Troy Richardson,[1] Bradley A. Warady,[3] Alicia Neu.[2] *[1]Children's Hospital Association, Overland Park, KS; [2]Johns Hopkins University School of Medicine, Baltimore, MD; [3]The Children's Mercy Hospital, Kansas City, MO; [4]Pediatric Nephrology, Yale University, New Haven, CT.*

Background: The Standardizing Care to Improve Outcomes in Pediatric End-stage renal disease (SCOPE) collaborative seeks to reduce hemodialysis (HD) catheter associated blood stream infections (CA-BSI) by increasing implementation of standardized HD catheter care bundles. We report on HD catheter care practices and HD CA-BSI rates from SCOPE.

Methods: Catheter care practices and HD CA-BSI reported between 6/2013 and 3/2017 are included. Catheter care bundle compliance is monitored across the reporting period on a sample of patients at each center. Compliance with each element in the care bundle is evaluated as is overall compliance, which is scored as "all or none", ie each element must be performed to be compliant. For catheters with multiple observations compliance is reported as a percent compliance across observations. Only observations prior to the CA-BSI are included for catheters with infections. Results are reported as median and interquartile range (IQR) and compared by CA-BSI status with Wilcoxon Rank Sum tests. Associations between CA-BSI status and categorical characteristics are compared with chi-square tests.

Results: 427 catheters in 424 children [median (IQR) age 12.5 years (6,16), M: 54%, F: 46%] at 27 centers were included. 3569 catheter care observations were submitted with median (IQR) 4 (1,12) observations per catheter. 111 CA-BSI from 66 catheters were reported, yielding a rate of 2.0 infections/100 catheter months. Bundle compliance [%, median (IQR)] in catheters with and without CA-BSI and their comparisons are presented in the Table.

Conclusions: Compliance with an HD catheter care bundle was relatively high among SCOPE centers, and the overall CA-BSI rate is low. The low number of CA-BSI limits the ability to detect significant associations between compliance with care practices and CA-BSI. A comparison of CA-BSI rates before and after implementation of care practices is required to evaluate the impact of SCOPE on CA-BSI rates.

Care practice	No CA-BSI	CA-BSI	P
Dressing/site assessment	100 (100,100)	100 (90,100)	0.068
Connection/entry	100 (94.4,100)	100 (90,100)	0.221
Disconnection	100 (100,100)	100 (100,100)	0.806
Cap care	100 (100,100)	100 (100,100)	0.082
Dressing change and exit site care	87.5 (50,100)	100 (40,100)	0.483
Overall	87.5 (57.1,100)	75 (33.3,100)	0.062

TH-PO889

Infection Rates in ESRD and Renal Transplant Patients Using Real World Claims Data Katherine Belenduik,[1] Richa Rajwanshi,[1] Yingjie Ding,[2] Kelly Kwon,[1] Dominic Borie,[1] Matthew Cascino,[1] Jay P. Garg,[1] Thomas Schindler,[3] Ha N. Tran.[1] *[1]Genentech, Inc., South San Francisco, CA; [2]Genesis Research, Hoboken, NJ; [3]F. Hoffmann - La Roche Ltd., Basel, Switzerland.*

Background: End stage renal disease (ESRD) patients (pts) are at increased risk of infections due to immune dysregulation, malnutrition, and indwelling dialysis access. After transplant (tx), pts are at further risk due to immunosuppressive therapy. Characterization of infections in large, real world samples will allow clinicians to better evaluate and understand infection risks in their patients. The objective of this study was to characterize the rates of serious and opportunistic infections in ESRD and renal tx pts.

Methods: We conducted a retrospective cohort study using the Truven Healthcare MarketScan® Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits database between 2000 and 2014. The ESRD cohort index date was the first of either an ESRD or dialysis claim, separated by ≥7 days. The tx cohort index date was the first of ≥2 claims related to kidney tx, separated by ≥7 days.

Results: 23,433 ESRD pts on dialysis and 18,660 renal tx pts were identified. One year following the index date, the rates of serious infections were higher in ESRD than tx pts. Most serious infections required hospitalization in both groups and opportunistic infection rates were comparable (Table 1).

Conclusions: ESRD and post-tx pts experience serious infections with high rates of hospitalization indicating high burden of illness. Physicians should carefully evaluate infection risks when considering pre- and post-tx immunosuppressive regimens.

Funding: Commercial Support - Genentech, Inc./F. Hoffmann-La Roche

Table 1.

	ESRD					Post-Tx				
	Event	PY	Incidence per 100 PY	95% CI		Event	PY	Incidence per 100 PY	95% CI	
Serious infections	11,757	15,252	77.1	75.7	78.5	6,254	14,438	43.3	42.2	44.4
Hospitalization required	7,885	18,132	43.5	42.5	44.5	4,028	16,006	25.2	24.4	26.0
IV antibiotics required	4,719	20,585	22.9	22.3	23.6	1,965	17,478	11.2	10.8	11.6
Opportunistic infections	4,837	20,375	23.7	23.1	24.4	4,106	16,147	25.4	24.7	26.2
Sepsis	1,970	22,224	8.9	8.5	9.3	481	18,391	2.6	2.4	2.9
Peritonitis	1,199	22,230	5.4	5.1	5.7	220	4,189	5.3	4.6	6.0

TH-PO890

Advocating for a Unique ICD-10 Code for ESRD Tunneled Catheter Bacteremia Taurino N. Avelar, Katya Corado calvo, Sharon G. Adler. *Harbor-UCLA Medical Center, Torrance, CA.*

Background: In ESRD, infections account for 8% of cause-specific mortality. Hospitalizations are frequent, prolonged, and impair quality of life. Inpatient cost is ~$2.7 billion/yr. ICD-10 coding is intended to specifically characterize hospitalization clinical events. We tested whether ICD-10 coding accurately captures and distinguishes bloodstream infections (BSI) in ESRD patients with tunneled HD catheters from BSI in patients with other implanted devices.

Methods: This is a single-center retrospective chart review in patients with BSI from 10/1/15–12/31/16. Subjects were grouped: (Gp1) ESRD BSI from tunneled dialysis catheter infection; (Gp2) ESRD BSI with AV fistula (AVF) or graft (AVG); and (Gp3) Non-ESRD BSI from an implanted device (PICC lines, ICD/pacer leads, bioprosthetic/mechanical heart valves, orthopedic hardware, and non-HD grafts/stents (vascular, ureteral). Groupings were based on: (Gp1) Infectious Diseases Society of America Guidelines for Intravascular Catheter-Related Infection (CID 2009:49); (Gp2) Positive blood cultures in ESRD with AVF or AVG; and (Gp3) Positive blood/wound cultures, physical exam, radiological assessments, and biopsy results. We descriptively compared the use of ICD-10 codes among the clinical groups.

Results: Table shows ICD-10 codes used to classify the BSI events in these 3 groups. For some, >1 ICD-10 code was used. In 12, no code was used. There is substantial overlap in the ICD-10 codes used to describe BSI in patients with ESRD tunneled catheters, AVFs, and AVGs, and non-ESRD BSIs associated with other implantable devices.

Conclusions: In this "Discovery" cohort, the lack of a unique ICD-10 identifier for BSI due to tunneled dialysis catheters makes it difficult or impossible to distinguish these clinical events from other BSIs. "Validation" cohorts at other centers is in progress. A unique code is needed to quantify the burden of this devastating clinical entity.

ICD-10 codes in patients with BSIs

ICD-10 diagnosis	ICD-10 code	Gp1, n=19	Gp2, n=7	Gp3, n=17
BSI due to central venous catheter	T80.211A	0	0	1
Bacteremia/Sepsis	A41.01, A41.02, A41.89, A41.9, R65.20, R65.21, R78.81	18	5	5
Infection, inflammation, or other reaction/complication of vascular or cardiac valvular devices, implants, grafts	T82.898S, T82.6XXS	0	0	2
Infection, inflammation, from other complication of vascular or cardiac valvular devices, implants, grafts	T82.7XXA, T82.7XXS	0	0	0
Acute or subacute endocarditis	I33.9, I38	2	0	1
Abscess, discitis	K65.1, L02.91, M46.46	2	1	0
Cellulitis, UTI, pyelonephritis, aneurysm, unspecified	L03.90, N39.0, N12, R89.9, I71.2	2	1	2
No code for infection	-	4	1	7

TH-PO891

Comparison of National Healthcare Safety Network Dialysis Event Validation in Georgia and Tennessee Gianna S. Peralta,[1,3] Ashley Fell,[2] Elizabeth N. Smith,[1] Jeanne Negley,[1] Marion Kainer.[2] *[1]Georgia Department of Public Health, Atlanta, GA; [2]Tennessee Department of Health, Nashville, TN; [3]CDC/CSTE Applied Epidemiology Fellowship, Atlanta, GA.*

Background: 370,000 people in the United States rely on hemodialysis and are at risk for developing serious infections. Outpatient hemodialysis (OHD) facilities are required to report dialysis event (DE) data to the National Healthcare Safety Network (NHSN) including intravenous antimicrobial starts (AMX), positive blood cultures (PBC), and pus, redness, or increased swelling at the vascular access site (PRS). The Georgia Department of Public Health (GDPH) and Tennessee Department of Health (TDH) validated NHSN DE data to assess data quality and identify common reporting errors.

Methods: Sixty OHD facilities were selected for data validation (30 each in TN and GA). Facilities were selected due to having few reported PBCs, or at random. TDH validated data from January-June 2014, while GDPH validated DE data from January-June 2015. Both states followed the CDC DE Data Quality Evaluation Guide to select up to 30 patients per facility for medical record review to identify DEs, conduct a concordance check, and survey staff members responsible for NHSN DE data collection and reporting.

Results: Record review TDH reviewed a total of 790 patient records; GDPH reviewed 876. TDH identified 272 (34%) patients with at least one DE for a total of 497 events; GDH identified 201 (23%) patients with least one DE for a total of 332 events. Under-reporting of DEs was common (TN: 28%; GA: 39%). Over-reporting of DEs was more frequent in GA (12%) than TN (5%). **Survey** Compared to TN, a higher proportion of facility administrators in GA had read the CDC NHSN DE reporting protocol (79% vs. 51%). In TN, 55% of facility administers could not correctly describe how to count patients for the denominator, compared to 35% in GA. A majority of facility administrators in both states did not know how to correctly assign vascular access category (59% in TN; 78% in GA).

Conclusions: Validation of NHSN DE data provided valuable insight about data quality and common reporting errors that can be addressed through education and training. Reporting deficiencies were identified among all types of DEs. All facilities should have a strong working knowledge of the CDC DE Protocol. Consistent and accurate documentation of DEs can help facilities detect problems, identify trends, evaluate infection prevention activities, and engage staff in quality improvement.

Funding: Other U.S. Government Support

TH-PO892

National Healthcare Safety Network Dialysis Bloodstream Infection Data—2016 Duc B. Nguyen,[1] Shunte Moon,[1] Taylor Guffey,[1] Christi Lines,[1] Preeti Rvindhran,[2] Jonathan Edwards,[1] Priti R. Patel.[2] *[1]Centers for Disease Control and Prevention, Atlanta, GA; [2]Centers for Disese Control and Prevention, Atlanta, GA.*

Background: Among hemodialysis (HD) patients, bloodstream infections (BSIs) are often severe adverse events. The Centers for Disease Control and Prevention (CDC) conducts surveillance for these events through the National Healthcare Safety Network (NHSN). We summarized 2016 BSI data submitted to NHSN Dialysis Event Surveillance and compared to data from previous years.

Methods: A BSI is defined in the NHSN surveillance protocol as a positive blood culture collected in an HD outpatient or within 1 calendar day of a hospitalization. Access-related BSIs (ARBSI) are positive blood cultures with either a suspected vascular access source or uncertain source as indicated on the event reporting form. Denominator data consist of the number of HD outpatients treated at the facility during the first two working days of each month. BSI rates were stratified by vascular access type (e.g., arteriovenous fistula [AVF], arteriovenous graft [AVG], central venous catheter [CVC]). We compared BSI rates during 2014–2016 controlling for access type using generalized linear models.

Results: In 2016, 6,437 outpatient HD facilities reported 151,943 dialysis events to NHSN, including 27,108 BSIs, of which 20,375 (75.2%) were ARBSI. Most BSIs (62.7%) and ARBSIs (70.2%) occurred in patients with a CVC. Hospitalization and death associated with events occurred among 52.9% and 2.8% of BSI, respectively. The rate of BSI per 100 patient-months was 0.56 (0.22 for AVF, 0.37 for AVG and 1.84 for CVC) with 25th and 75th percentile of 0.2 and 0.79, respectively. During 2014–2016, the yearly reduction in rates controlling for access type was 7.1% (95% confidence interval [CI]: 5.9–8.2) for BSI and 8.3% (95% CI: 7.0–9.6) for ARBSI.

Conclusions: Rates of BSI were highest among patients with CVC. BSI and ARBSI appeared to have decreased during 2014–2016, possibly due to nationwide prevention efforts. Our results suggest that even though progress towards BSI prevention has been achieved, opportunities exist to reduce rates of BSIs and ARBSIs among HD patients.

Funding: Other U.S. Government Support

Pooled mean rate per 100 patient-months, stratified by access type

	2014	2015	2016
BSI	0.64	0.60	0.56
AVF	0.26	0.24	0.22
AVG	0.39	0.39	0.37
CVC	2.16	2.02	1.86
ARBSI	0.49	0.45	0.42
AVF	0.16	0.13	0.13
AVG	0.27	0.26	0.25
CVC	1.83	1.68	1.56

TH-PO893

Bloodstream Infections in Pediatric Hemodialysis Outpatients: National Healthcare Safety Network, 2013-2015 Mark K. Weng,[1] Duc B. Nguyen,[1] Alicia Neu,[2] Ibironke W. Apata,[1] Bradley A. Warady,[3] Priti R. Patel.[1] *[1]Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, GA; [2]Johns Hopkins University School of Medicine, Baltimore, MD; [3]University of Missouri, Kansas City School of Medicine, Children's Mercy Kansas City, Kansas City, MO.*

Background: Compared to adults, children on chronic hemodialysis (HD) are more often dialyzed via a central venous catheter (CVC), which poses a high risk of infection. However, data on bloodstream infections (BSIs) in the outpatient pediatric HD population are sparse. To characterize these infections, we analyzed 2013-2015 BSI data that outpatient HD centers reported to the Centers for Disease Control and Prevention's (CDC's) National Healthcare Safety Network (NHSN), a widely used healthcare-associated infection surveillance system.

Methods: The NHSN dialysis event surveillance protocol defines a BSI as a positive blood culture collected as an outpatient or within 1 calendar day of a hospitalization. Access-related BSIs are positive blood cultures with a suspected vascular access source or uncertain source. Up to 3 organisms per BSI can be reported. Pediatric BSIs were defined as those occurring in patients < 18 years of age at the time of event, and these BSIs could be reported by any participating HD center (adult or pediatric). Events in patients with a calculated age < 1 year were excluded due to data quality concerns. We categorized BSI by highest-risk vascular access type present (CVC > graft > fistula).

Results: During 2013 to 2015, 634 BSIs occurred in pediatric patients > 1 year of age. Of the 634 BSIs, 588 (93%) occurred in patients with CVC; 542 (85%) of the BSIs were classified as access-related. A total of 384 (61%) BSIs resulted in hospitalization, and 10 (2%) resulted in death. The most common pathogens identified were *Staphylococcus aureus* (30%), coagulase-negative Staphylococci (23%), and Enterococci (8%).

Conclusions: Catheters account for the majority of pediatric HD BSIs reported to NHSN, demonstrating the importance of interventions targeting catheter care and use of permanent vascular access, when possible. Further characterization of the incidence of BSIs in the pediatric outpatient HD population may yield additional opportunities for prevention. A limitation of the analysis is reliance upon calculated age, which may be subject to data entry error.

Funding: Other U.S. Government Support

		AGE: 1y to < 5y [n (%)]	AGE: 5y to < 12y [n (%)]	AGE: 12y to <18y [n (%)]
GENDER	Female	56 (32)	84 (36)	115 (51)
HIGHEST-RISK VASCULAR ACCESS TYPE	CVC	157 (90)	221 (95)	210 (93)
	Graft	6 (3)	5 (2)	1 (0)
	Fistula	12 (7)	6 (3)	16 (7)
BSI SOURCE	Vascular access	105 (60)	164 (71)	161 (71)
	Other	24 (14)	19 (8)	13 (6)
	Contamination	12 (7)	15 (6)	9 (4)
	Uncertain	34 (19)	34 (15)	44 (19)
TOTAL BSI		175	232	227

TH-PO894

Age-Dependent Production of Highly Apoptosis-Resistant CD31 – Memory-Tresps May Cause Chronic Inflammatory Conditions in Dialysis Patients Matthias Schaier,[1] Angèle Leick,[1] Florian Kälble,[1] Christian Morath,[1] Claudia Sommerer,[1] Martin G. Zeier,[1] Andrea Steinborn-Kroehl.[2] *[1]Nephrology, University of Heidelberg, Heidelberg, Germany; [2]Gynecology, University of Heidelberg, Heidelberg, Germany.*

Background: Dialysis patients have an increased susceptibility for chronic inflammation. In addition, an increased risk for virus-associated cancers and atherosclerotic diseases are documented.

Methods: We analyzed whether age-related differences in the differentiation of both recent-thymic-emigrant-(RTE)- regulatory (Tregs) and RTE-responder T cells (Tresps) into CD31--memory Tregs/Tresps led to differences in the suppressive activity of naïve and memory Tregs on autologous Tresps between healthy volunteers (n= 89) and dialysis patients (n=80).

Results: Our findings suggest, that the thymic release of RTE-Tregs decreases with age and thereby causes their enhanced differentiation via $CD31^+$-memory Tregs into $CD31^-$-memory Tregs, so that the suppressive activity of both naïve and memory-Tregs is maintained with age in healthy controls. In addition, the decreasing thymic release

of RTE-Tresps may cause their enhanced differentiation via MN-Tresps into CD31$^-$-memory-Tresps. Thus, the reactivity of the total Tresp pool may be weakened with age, as the resulting CD31$^-$-memory- Tresps may be much more sensitive to apoptosis. Presumably, both effects contribute to the fact that the functional activity of Tregs increases with age in healthy volunteers. Dialysis patients exhibit an increased RTE-Treg differentiation via CD31$^+$-memory Tregs which may enhance the suppressive activity of both naïve CD45RA$^+$- and CD45RA$^-$-memory-Tregs, especially in young individuals. However, the differentiation of RTE-Tresps via MN-Tresps, seen in healthy volunteers, could not be detected in dialysis patients. Instead, there was an age-dependent increase in the differentiation via CD31$^+$-memory Tresps into CD31$^-$-memory Tresps in dialysis patients. This effect may strengthen the functionality of Tresps with age and explain why Tregs of elderly dialysis patients show difficulties suppressing autologous Tresps, but preserve the ability to suppress non-autologous Tresps of healthy volunteers.

Conclusions: The aging immune system sustainably suppresses autoimmunity, but favors the incidence of inflammation. In contrast, the increased age-dependent production of highly apoptosis-resistant CD31$^-$-memory-Tresps in dialysis patients may cause chronic inflammatory conditions in these patients.

TH-PO895

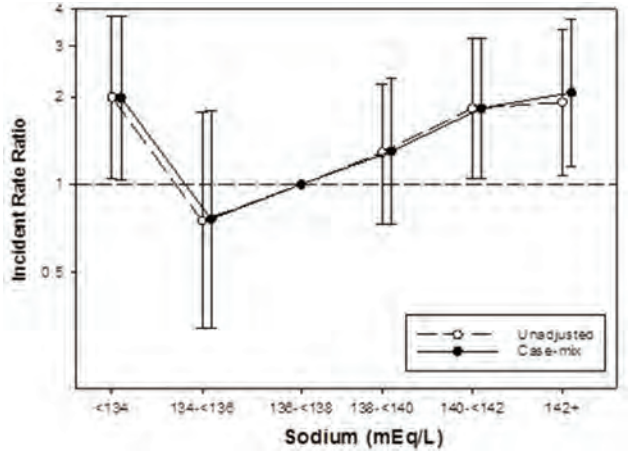
Serum Sodium and Bacteremia Risk in Dialysis Patients Connie Rhee,[4] Amy S. You,[6] Elani Streja,[2] Juan Carlos Ayus,[3] Hamid Moradi,[6] Steven M. Brunelli,[1] Csaba P. Kovesdy,[7] Danh V. Nguyen,[6] Kamyar Kalantar-Zadeh.[5] *[1]DaVita Clinical Research, Needham, MA; [2]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [3]Renal Consultants of Houston, Houston, TX; [4]University of California Irvine, Huntington Beach, CA; [5]University of California Irvine, School of Medicine, Orange, CA; [6]University of California, Irvine, Orange, CA; [7]University of Tennessee Health Science Center, Memphis, TN.*

Background: Hyponatremia is a potential risk factor for infection, which may be due to impairment of IL-17 producing helper T cells that function in host immunity, and concomitant mucosal membrane and cellular edema leading to breakdown of microbial barrier function. While dysnatremia and infection-related mortality are common in dialysis patients, little is known about the association between serum sodium levels and bacteremia in this population.

Methods: Among 823 dialysis patients from the national Biospecimen Registry Grant Program (BioReG) who underwent serum sodium testing over 1/2008-12/2014, we examined the relationship between sodium level and risk of bacteremia using case-mix adjusted Poisson regression models adjusted for age, sex, and race/ethnicity.

Results: In the overall cohort, the mean±SD and minimum-maximum serum sodium values were 138±3mEq/L and 115-154mEq/L, respectively; approximately 10% of all patients experienced one or more bacteremia events during the follow-up period. Patients with both lower sodium <134mEq/L and higher sodium ≥140mEq/L had higher incident rates of bacteremia in case-mix models (ref: 136-<138mEq/L): adjusted IRR [aIRR] 1.99 (1.04-3.81), 0.76 (0.32-1.80), 1.30 (0.73-2.31), 1.83 (1.05-3.18), and 2.07 (1.15-3.72) for sodium levels <134, 134-<136, 138-<140, 140-<142, ≥142mEq/L, respectively.

Conclusions: Both lower and higher serum sodium levels were associated with higher incident rates of bacteremia in dialysis patients. Further studies are needed to determine whether correction of dysnatremia ameliorates infection risk in this population.



TH-PO896

Impact of Pre-ESRD Nephrology Care on Early Post-Dialysis Sepsis-Related Hospitalizations Robert Nee,[2,3] Christina M. Yuan,[2,3] Lawrence Agodoa,[1] Kevin C. Abbott.[1] *[1]NIDDK, National Institutes of Health, Bethesda, MD; [2]Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; [3]Medicine, Uniformed Services University, Bethesda, MD.*

Background: Pre-end-stage renal disease (ESRD) nephrology care has been reported to improve morbidity and mortality in dialysis patients. However, its impact on infectious complications in dialysis patients has not been studied. Herein we assessed the association between pre-ESRD nephrology care and hospitalizations for sepsis within 12 months after initiation of dialysis.

Methods: Using the US Renal Data System database, we identified 282, 571 Medicare primary patients initiated on maintenance dialysis from 1 January 2009 through 1 June 2013, and followed until 31 December 2013. We abstracted Medicare hospital claims for "septicemia" as primary discharge diagnosis, using the International Classification of Diseases, Ninth revision, Clinical Modification (ICD-9-CM) codes 038. xx (x = 0 to 9 inclusive). We conducted Cox regression analyses for sepsis, adjusted for demographic characteristics, cause of ESRD, dialysis modality, comorbidities, vascular access and other clinical variables.

Results: 11,614 (5.4%) patients were hospitalized for sepsis within 12 months after start of dialysis, 33% of whom had more than one hospitalization. Patients with pre-ESRD care had a lower incidence rate of early sepsis compared to those without pre-ESRD care (78.4 per 1,000 patient-years (PY) vs. 111.3 per 1,000 PY, respectively; p<0.001). Hospital length of stay was shorter in patients with pre-ESRD care compared to those without pre-ESRD care (13.7 days vs. 17.6 days, p<0.001). In fully adjusted Cox models, pre-ESRD care was associated with significantly lower likelihood for early sepsis (adjusted hazard ratio [aHR] 0.86, 95% CI 0.80-0.91). Compared to patients without pre-ESRD care, those with > 12 months of pre-ESRD care were significantly less likely to be hospitalized for early sepsis (aHR 0.78, 95% CI 0.71-0.86) but the association with those who had 6-12 months of pre-ESRD care was nonsignificant (aHR 0.95, 95% CI 0.86-1.05).

Conclusions: Pre-ESRD nephrology care was associated with lower risk of sepsis-related hospitalizations within 12 months of dialysis initiation. *Disclaimer: The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of the Army/Navy/Air Force, the Department of Defense, National Institutes of Health, or the United States government.*

TH-PO897

Incidence, Risk Factors, and Distribution of Syphilis in the ESRD Population in the United States Erena Weathers,[2] Jennifer L. Waller,[2] N. Stanley Nahman,[2,1] Rhonda E. Colombo,[2] Jake E. Turrentine,[2] Mufaddal F. Kheda,[2] Stephanie L. Baer.[1,2] *[1]Augusta VA Medical Center, Augusta, GA; [2]Augusta University, Augusta, GA.*

Background: The incidence of syphilis has increased 67% in 4 years to 7.5 per 100,000 in the US, but is undefined in the end stage renal disease (ESRD) population. This study examined diagnoses of syphilis and associated risk factors in ESRD patients to identify opportunities for improving screening and risk modification.

Methods: All incident ESRD patients from 2004-2010 in the USRDS were queried. ICD-9 codes were used to determine syphilis diagnosis and related comorbidities. Neurosyphilis (NS) was defined with both an ICD-9 code and an associated lumbar puncture CPT code. The geographical distribution was determined by number of cases per 100,000 ESRD patients in each state. A 5% random sample of patients without syphilis was used for analysis. Statistical analysis was performed using SAS 9.4 and a generalized linear model was used to examine the adjusted relative risk (aRR).

Results: Of 773,600 patients, 585,072 had complete data for analysis. 383 diagnoses of syphilis were identified. The incidence of syphilis diagnosis increased yearly from 2004-2011, with a peak incidence in 2011 of 54 per 100,000. The syphilis diagnoses were: 59% other unspecified, 22% NS and other types 1% or less. Associated risk factors included: hepatitis B (aRR=1.75 95% confidence interval (CI) 1.12-2.71), hepatitis C (aRR=3.60 95% CI 1.99-6.51), herpes simplex virus (aRR=2.05 95% CI 1.46-2.87), and HIV (aRR=7.55 95% CI 5.42-10.52). Demographic risk factors included black (aRR=4.96 95% CI 3.85-6.40) and other (non-white) race (aRR=1.99 95% CI 1.14-3.47). The highest rates were in the southeast followed by the northeast and west coast.

Conclusions: In the ESRD population, the incidence of syphilis was over 3 fold greater than in the general population in 2011, with the majority coded as unspecified syphilis followed by NS. The trend of rising incidence from 2004-2011, associated risk factors, and the geographic spread of syphilis in ESRD reflects the general population. These data suggest that routine screening for syphilis in the ESRD population may be beneficial.

TH-PO898

A Case of Leclercia Adecarboxylata Hemodialysis Catheter-Related Bacteremia Yasir Alfi, Ashte K. Collins. *Division of Renal Diseases & Hypertension, George Washington University, Washington, DC.*

Background: *Leclercia adecarboxylata*, formerly known as *Escherichia adecarboxylata*, was first identified by Lecrerc in 1962. It is a motile Gram-negative rod that is considered an uncommon opportunistic human pathogen. Here we describe a case of *L. adecarboxylata* bacteremia as part of a polymicrobial infection in a dialysis patient with a tunneled catheter.

Methods: A 50 year-old male with ESRD on HD for 7 months via left internal jugular tunneled catheter, HTN, and DM type II, who was admitted to the hospital with 1 day of subjective fever, chills, and malaise, all of which exacerbated by his dialysis treatment. He reported taking showers while the dialysis catheter is in place, but stated he only lets the water land below his chest. On admission, he was afebrile and hemodynamically stable. Lab results were remarkable for WBC of 19.6 x 10^3/µl. Vancomycin and piperacillin-tazobactam were started. Blood cultures grew *Staphylococcus epidermidis* (oxacillin-resistant), methicillin-sensitive *Staphylococcus aureus, Pseudomonas floures* (resistant to trimethoprim-sulfamethoxazole), *Escherichia coli* (pansensitive), *Serratia marcescens* (resistant to ampicillin and first generation cephalosporins) and *Leclercia adecarboxylata* (pan-sensitive). Antibiotic regimen was changed to vancomycin, gentamicin and levofloxacin. The tunneled catheter was removed and a new right internal jugular tunneled

catheter was placed 4 days later, after clearance of blood cultures. He was maintained on the above antibiotics for another 14 days, and recovered without long-term sequelae.

Results:

Conclusions: *L. adecarboxylata* is a ubiquitous organism and has been isolated from water sources including drinking water in the US. Water exposure is a possible source of infection in the patient presented above. Although there are several case reports of clinically significant infections with *L. adecarboxylata* in immunocompromised patients, it has been mostly isolated from post-traumatic flora in immunocompetent individuals. ESRD patients may be susceptible to *L. adecarboxylata* infection as they are relatively immunosuppressed. Only four previous reports were found on a PubMed literature search of tunneled hemodialysis catheter-related bacteremia with *L. adecarboxylata*. This infection can be treated successfully with catheter removal and a course of appropriate IV antibiotics. Most isolates are susceptible to all available antimicrobial agents.

TH-PO899

Mortality Risk and Cause of Death Following Staphylococcus aureus Endocarditis in a Danish Hemodialysis Population Mavish Chaudry,[6] Gunnar Gislason,[9] Anne-Lise Kamper,[1] Marianne Rix,[2] Anders Dahl,[7] Trine K. Lauridsen,[5] Louise B. Oestergaard,[3] Christian Hassager,[2] Christian Torp-Pedersen,[4] Niels E. Bruun.[8] *[1]Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark; [2]Rigshospitalet, Copenhagen, Denmark; [3]Aalborg University, Aalborg, Denmark; [4]Aalborg University Hospital, Aalborg, Denmark; [5]Copenhagen University Hospital, Charlottenlund, Denmark; [6]Department of Cardiology, Copenhagen, Denmark; [7]Gentote University Hospital, Hellerup, Denmark; [8]Herlev-Gentofte Hospital, Hellerup, Denmark; [9]Gentofte Hospital, Copenhagen, Denmark.*

Background: Staphylococcus aureus endocarditis has increased over the past decades and is a contributing factor to high mortality and morbidity. Outcome data are sparse. The study aimed to investigate causes and risk factors of mortality subsequent to staphylococcus aureus (S. aureus) IE in a hemodialysis- and a non-hemodialysis population.

Methods: S. aureus IE in hemodialysis patients was identified in The Danish National Registry on Regular Dialysis and Transplantation and The Danish National Patient Registry, and in non-hemodialysis patients in The East Danish Database on Endocarditis which contains data on consecutive patients with S. aureus IE from tertiary centres in the eastern part of Denmark. Independent risk factors of outcome were identified in multivariable Cox regression models.

Results: The cohorts of S. aureus IE included 121 hemodialysis patients and 197 non-hemodialysis patients from the period 1996-2012 and 2002-2012, respectively. The all-cause in-hospital mortality was 22.3% in hemodialysis- and 24.8% in non-hemodialysis patients. At one-year follow-up the all-cause mortality, excluding in-hospital mortality, was higher in hemodialysis patients 26.4% compared to non-hemodialysis patients 15.2% (p=0.017). In hemodialysis- and non-hemodialysis patients, the cardiovascular in-hospital mortality was 20.7% and 21.7% and one-year mortality, excluding in-hospital mortality, was 21.5% and 12.2% (p=0.030), respectively. In patients with S. aureus IE, hemodialysis was associated with an increased risk of all-cause mortality at >74 days after admission with S. aureus IE with a hazard ratio of 2.71 (95% CI 1.78-4.16). Age and diabetes mellitus were identified as independent risk factors of all-cause mortality. Hemodialysis treatment was also associated with an increased risk of cardiovascular death at >56 days after admission with a hazard ratio of 2.76 (95% CI 1.74-4.40).

Conclusions: In hemodialysis patients, the short-term in-hospital mortality rates are similar to the non-hemodialysis population whereas the long-term mortality rates are markedly increased in the hemodialysis population. Further investigations are needed to identify direct IE related reasons for these findings.

TH-PO900

Dialysis Access and Risk of Staphylococcus aureus Bacteremia – A Nationwide Study Mavish Chaudry,[3] Gunnar Gislason,[8] Anne-Lise Kamper,[2] Marianne Rix,[6] Paal S. Andersen,[7] Henrik Westh,[5] Henrik C. Schønheyder,[1] Christian Torp-Pedersen,[1] Niels E. Bruun.[4] *[1]Aalborg University Hospital, Aalborg, Denmark; [2]Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark; [3]Department of Cardiology, Copenhagen, Denmark; [4]Herlev-Gentofte Hospital, Hellerup, Denmark; [5]Hvidovre hospital, Hvidovre, Denmark; [6]Rigshospitalet, Copenhagen, Denmark; [7]Statens Serum Institut, Copenhagen S, Denmark; [8]Gentofte Hospital, Copenhagen, Denmark.*

Background: Staphylococcus aureus bacteremia (SAB) is a high-risk infection. This study aimed to investigate incidence and risk factors of SAB with various modalities of dialysis.

Methods: The end-stage renal disease population was retrieved from The National Registry on Regular Dialysis and Transplantation, in the period from January 1st 1996 to December 31st 2011. Information on SAB was obtained from the nationwide SAB Database. Patients were followed until death, the first episode of SAB, end of study (December 31st 2011), or a maximum of 16 years of follow-up. Independent risk factors were assessed by multivariable Cox regression.

Results: In the study period, 9997 patients commenced renal replacement therapy. The initial modality was hemodialysis in 6826, peritoneal dialysis in 2882 and 289 patients had a pre-emptive kidney transplantation. Changes in renal replacement therapy modality and vascular access was identified and entered time-updated during follow-up, allowing for time-updated exposure. SAB was found in 1278 patients (12.8%). The incidence rate of SAB was highest in uncuffed central venous catheter (CVC) (10.20/100 person-years) followed by cuffed CVC (9/100 person-years), arteriovenous graft (4.98/100 person-years) and arteriovenous fistula (4.93/100 person-years). The adjusted hazard ratio for SAB was: in cuffed CVC, 5.77 (95% CI 4.45-7.49), in uncuffed CVC, 7.13 (95% CI 5.39-9.42), in arteriovenous graft, 4.54 (95% CI 2.11-9.77) and in arteriovenous fistula, 3.40 (95% CI 2.78-4.14) compared to peritoneal dialysis. There was no difference in risk of SAB between uncuffed- and cuffed CVC. The first 1.5 months in renal replacement therapy in particular in CVC, diabetes mellitus and male gender were additional risk factors of SAB.

Conclusions: Patients in hemodialysis have a high incidence of SAB, in particular with CVC. In this study, the risk of SAB was similar in cuffed- and uncuffed CVC. The first 1.5 months in renal replacement therapy in particular in CVC, diabetes mellitus and male gender were independent risk factors of SAB.

TH-PO901

Latent Tuberculosis in Dialysis Patients: Prevalence, Risk Factors, and Inflammatory Markers Randah A. Dahlan, Mahmoud M. Shaheen, Mostafa A. Abd_elkhalek, Abdulkareem Alsuwaida. *Davita KSA, Jeddah, Saudi Arabia.*

Background: Dialysis patients are more susceptible to infections than the general population as they have a dysfunctional immune system. Therefore, various prevention and screening strategies must be implemented in dialysis units to decrease the rate of infection. Screening for latent tuberculosis (LTB), is an important preventative strategy in countries with moderate or high disease burden. We conducted this continuous quality improvement project to ensure the process of screening for LTB is being appropriately implemented as per our dialysis unit policy, to know the prevalence of LTB using interferon—γ release assay (IGRA), and to determine if certain patients' variables may play a role as a risk factor or as a disease marker.

Methods: We reviewed the clinical data of all patients dialyzing at DaVita dialysis units in Jeddah, SA to abstract data about IGRA test, patients demographic, laboratory, radiological and clinical status.

Results: 302 dialysis patients were screened for LTB using the IGRA, and 92 patients (30.5%) were positive. All positive patients were assessed for presence or absence of suspicious symptoms and a chest X-ray (CXR) was obtained to rule out active disease. Active TB was thought to be unlikely in all patients. When patients with positive test were compared to those who tested negative, they were older (54.74 ± 16.05 versus 50.4 ± 16.2 years,*p* value = 0.033), more likely to have had a previous history of TB (*p* value = 0.0014), less likely they had received the BCG vaccine in the past (*p* value = 0.0003), and had a higher ferritin (*p* value = 0.45). There was no difference between the 2 groups in terms of sex, dialysis vintage, the background rate of DM, HCV, or HBV, lymphocytes count, neuropils, platelets, neutrophil to lymphocyte ratio, platelets to lymphocytes ratio, transferrin saturation, or albumin level.

Conclusions: Elderly, those with a past history of TB, and those who have no past history of BCG vaccination are all potentially at risk of LTB. Although many inflammatory markers are not characteristically high in patients with LTB, high ferritin level is commonly seen. This is the first study to describe simple inflammatory markers in dialysis patients with LTB. Screening dialysis patients who have persistent unexplained high ferritin level for LTB should be considered in appropriate settings.

TH-PO902

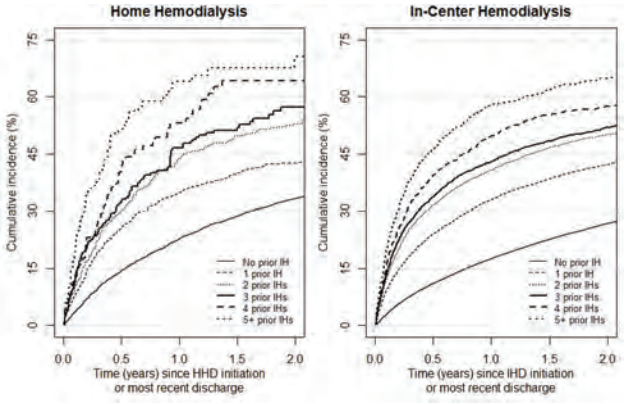
First and Recurrent Hospitalized Infections in Home and In-Center Hemodialysis Patients Eric D. Weinhandl,[1,2] Allan J. Collins.[1,2] *[1]NxStage Medical, Inc., Victoria, MN; [2]University of Minnesota, Minneapolis, MN.*

Background: Compared to thrice-weekly in-center hemodialysis (IHD), daily home hemodialysis (HHD) is associated with higher risk of infection-related hospitalization (IH). Strategies to reduce risk of infectious complications on HHD are needed to improve clinical and economic outcomes. We aimed to estimate the incidence of first and recurrent IHs in HHD and IHD patients with a fistula.

Methods: We analyzed data from the United States Renal Data System. The HHD cohort comprised patients who completed HHD training with the NxStage System One in 2006-2012 and who carried Medicare as primary payer (MPP). The IHD cohort comprised patients who initiated IHD in 2006-2012 and who carried MPP. We followed patients until the earliest of modality change, death, or December 31, 2012. We ascertained IHs from principal discharge diagnoses on Medicare claims. We estimated the cumulative incidence of IH, stratified by the cumulative number of prior IHs on HHD or IHD, and the hazard ratio of IH for HHD versus IHD, with adjustment for age, race, sex, ESRD duration, and primary cause of ESRD.

Results: We identified 4304 HHD and 46,988 IHD patients. On both HHD and IHD, the cumulative incidence of IH increased with each additional IH discharge (figure). For HHD versus IHD, the adjusted hazard ratio (AHR) of first IH was 1.24 (95% confidence interval, 1.07-1.44); the AHR of second IH, following discharge from the first IH, was 1.01 (0.86-1.19); and the AHR of each subsequent IH, following discharge from the preceding IH, was 0.92 (0.78-1.09).

Conclusions: Compared to IHD patients with a fistula, HHD patients with a fistula had higher risk of a first IH, but similar or slightly lower risk of recurrent IHs. However, in both dialytic settings, each additional IH discharge increased the risk of another IH. Less time to first IH in HHD patients prematurely sets in motion the cycle of increasing risk, ultimately manifesting as a higher IH rate on HHD versus IHD. Attention should be devoted to prevention of the first infection on HHD.



TH-PO903

Circulating Interferon-λ3, HBV Vaccination, and HBV/HCV Infections in Hemodialysis Patients Alicja E. Grzegorzewska,[4] Monika K. Swiderska,[3] Adrianna Mostowska,[2] Pawel P. Jagodzinski.[1] *[1]PUMS, Poznan, Poland; [2]PUMS, Poznan, Poland; [3]PUMS, Poznan, Poland; [4]Poznan University of Medical Sciences (PUMS), Poznan, Poland.*

Background: Interferon (IFN)-λ3 gene (*IFNL3*) is known from its crucial role in HCV clearance. Our aim was to investigate circulating IFN-λ3 and single nucleotide polymorphisms (SNPs) of *IFNL3* in hemodialysis (HD) patients who differed in response to HBV vaccination and status of HBV/HCV infections.

Methods: In 201 HD patients and 28 controls, plasma IFN-λ3 (ng/L) was determined using ELISA. *IFNL3* SNPs (rs12979860, rs8099917) were genotyped using HRM analysis.

Results: HBV vaccine responders among HD patients showed higher IFN-λ3 than healthy responders (120, 36–233 vs 62, 12.3–280, P=0.0004). In HD group, significant differences in circulating IFN-λ3 were shown between responders and non-responders to HBV vaccination (120, 36–233 vs 43, 15.9–77.4, P=1.0E-7) as well as between HBsAg positive patients and those who developed anti-HBs and became HBsAg negative after HBV infection (39.1, 10–83.4 vs 125, 35–215, P=0.010). Responders to HBV vaccination, who resolved HCV infection, did not differ in circulating IFN-λ3 from non-infected responders (133, 14.8–400 vs 120, 36–233, P=0.714), whereas responders to HBV vaccination, who did not show spontaneous HCV resolution, revealed lower IFN-λ3 than non-infected responders (74, 4.9–275 vs 120, 36–233, P=0.013). In patients with both infections, HBsAg positive/HCV RNA positive subjects showed lower IFN-λ3 (13.3, 9–21.6) than only HCV RNA positive patients (57.5, 13.7–203, P=0.031) and lower compared with patients who resolved both infections (88.5, 16.0–300, P=0.020). Circulating IFN-λ3 showed independent positive association with anti-HBs titer (β±SE 8.4±1.1, P=4.0E-13) and negative associations with HCV RNA (β±SE -32.5±11.4, P=0.005) and HBsAg (β±SE -45.3±22.9, P=0.049) positivity. Non-responders to HBV vaccination, patients HBsAg positive, and subjects replicating HCV composed a group with unfavorable outcomes. The remaining patients were analyzed as having favorable outcomes. The latter showed higher IFN-λ3 (120, 14.8–400 vs 50.7, 4.9–275, P=1.0E-11), but did not differ in distribution of *IFNL3* SNPs compared with subjects with unfavorable outcomes.

Conclusions: Higher IFN-λ3 concentrations are associated with response to HBV vaccination, self-limited HBV infection, and spontaneous HCV resolution.

TH-PO904

High Dose and Quadrivalent Influenza Vaccine Safety and Efficacy in Dialysis Patients: Interim 2016-17 Flu Season Analysis Harold J. Manley,[2] Eduardo K. Lacson,[1] Hocine Tighiouart,[3] Daniel E. Weiner,[3] Dana Miskulin,[3] Klemens B. Meyer.[3] *[1]Dialysis Clinic Inc, Boston, MA; [2]Dialysis Clinic Inc, Albany, NY; [3]Tufts Medical Center, Boston, MA.*

Background: Dialysis patients have high morbidity and mortality risk from influenza. During the 2016-17 flu season, Dialysis Clinic, Inc. administered Quadrivalent (Quad) and High Dose (High) flu vaccines. We compared safety and efficacy associated with each vaccine type.

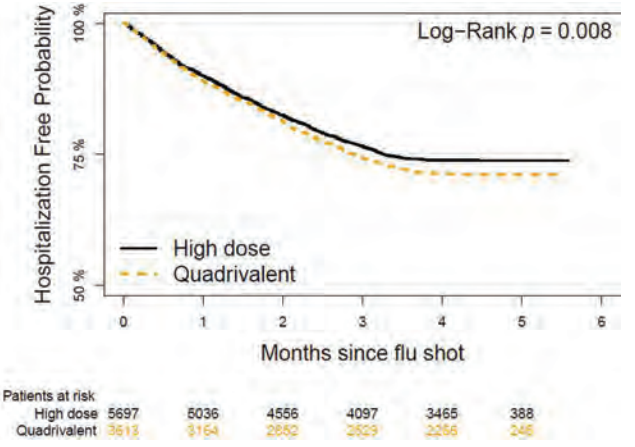
Methods: All patients administered vaccine in clinic between 8/1/2016 and 12/31/2016 were followed thru 3/13/2017. Safety signal events were death, hospitalization, urgent care/ED visit or practitioner visit within 3 days of vaccination. Efficacy measures were death, hospitalization, and urgent care/ED visits ≥14 days post dose. Cox models were constructed for the entire population and within age subgroups (<65, ≥65 yrs old).

Results: There were 9393 patients vaccinated, 3646 (39%) with Quad and 5747 (61%) with High. Older patients were more likely to receive High flu vaccine (p<0.001). Hemodialysis was principal modality (90.2%). Safety signals were insignificant between vaccine type except for practitioner visit (1.6% v 0.5% in Quad and High patients, respectively (p<0.001). Vaccine hazard ratio (95% CI) and p-values regarding long term outcomes are shown in table. Kaplan-Meir survival curve for hospitalization is shown in figure.

Conclusions: Interim 2016-17 flu season analysis demonstrated that dialysis patients tolerated High and Quad vaccines similarly. High was associated with fewer hospitalizations in patients overall and ≥65 yrs old. High vaccine use also trended towards fewer hospitalizations in patients < 65 yrs old. No differences were noted in mortality rates. Dialysis providers should consider High flu vaccine in patients ≥65 yrs old.

Outcome	Age <65 group		Age≥ 65 group		Overall	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
HOSP	0.93 (0.82, 1.06)	0.30	0.83 (0.73, 0.95)	0.01	0.90 (0.82, 0.98)	0.02
Death	0.98 (0.73, 1.31)	0.87	1.06 (0.82, 1.37)	0.64	1.04 (0.86, 1.25)	0.69
HOSP + Death	0.95 (0.83, 1.07)	0.37	0.86 (0.77, 0.97)	0.02	0.92 (0.84, 1.00)	0.06

HOSP = hospitalization



TH-PO905

Accelerated Vaccination Schedule against HBV with Combined Hepatitis A and B Vaccine among Hemodialysis Patients: Does It Work? Mahmoud H. Imam. *Internal medicine Department, Faculty of Medicine Benha University, Benha, Egypt.*

Background: Hemodialysis patient possesses particular attributes which increase susceptibility to HBV infections. HBV vaccination significantly decreased the number of new HBV-infected patients. Using the conventional dosage schedule requires six months of vaccination. The aim of this study is to examine the result of seroprotection using the accelerated vaccination schedule in vaccination of hemodialysis patient through using combined hepatitis A and B vaccine.

Methods: In this study, 114 consecutive hemodialysis patients at New Jeddah hospital were enrolled. Their age ranged from 18 to 71 years. The inclusion criteria were [1] Age was above 18 years, [2] All patients had undetectable HBV surface antigen and antibody. Exclusion criteria included [1] A positive serum HBV surface antigen and antibody; [2] patient received a previous course of HBV vaccine, [3] patient positive for HBV surface Ag. Patients were sequentially randomized to receive either Hepatitis B recombinant DNA vaccine or to receive combined hepatitis A and B vaccine injection. Testing for HBV surface antibodies was done one and three months after completion of the mentioned dosage schedule. The primary outcome was the detection of seroprotection using serum HBV surface antibodies ≥ 10 mIU/mL. Adverse reactions were evaluated regarding both fever and post-injection pain scale.

Results: After one and three months of completion of the vaccination schedule, there were no statistically different proportion of positive seroprotected patients among both groups.

Conclusions: Accelerated vaccination schedule using combined hepatitis A and B vaccine may be equivalent to the conventional dosage of Hepatitis B.

TH-PO906

Hepatitis B Prevention in Dialysis – Needs Reconsideration Sonalika Agarwal. *Hnery Ford Hospital, Detroit, MI.*

Background: Hepatitis B virus (HBV) infection is a significant cause of morbidity in end stage renal disease (ESRD) patients undergoing hemodialysis (HD). A significant reduction in the incidence of HBV has occurred by segregating patients with the disease from those who are at risk for contracting it. We report a case of a patient on HD who developed seroconversion to hepatitis B surface antigen (HBsAg) positivity with viremia despite presumed natural immunity to HBV.

Methods: Our patient is a xx-year-old female who was started on HD in 2012. At that time, her serum HBsAg was negative, hepatitis core antibody (HBcAb) was positive and hepatitis b surface antibody titer >150 mIU/ml implying a prior history of infection with natural immunity. She lacked risk factors for contracting the HBV infection and was dialyzed with the general population in our dialysis unit. Routine annual screening yielded a positive HBsAg despite having negative levels in the past; however, she maintained a high titer of HBsAb. Additional testing revealed a negative IgM HBcAb, positive HBeAb and normal transaminase levels reflecting the absence of a new infection. Given low-grade viremia (1,489 IU/ml), the decision was made to relocate her to a dedicated dialysis machine in the unit isolation area. Hepatology diagnosed her with a

chronic inactivated form of hepatitis infection. A month later her repeat hepatitis panel showed seroconversion back to HBSAg negativity.

Results:

Conclusions: HBeAg negative patients with normal serum transaminases and low (<2000 IU/mL) or undetectable HBV DNA are considered to be in an inactive carrier state. According to Center for Disease Control (CDC) guidelines updated in 2016, patients who are HBsAg negative and HBsAb positive are not considered infectious. Annual HBsAb testing confirms that immunity is not lost in this population. The CDC does not recommend rechecking HBSAg on HD patients once antibody screen establishes immunity. This case highlights the importance of recognizing the chronic inactive hepatitis B infection state in HD patients. Given potential for transmission of infection during transient viremia, these patients should be isolated from the general population during HD. Although current guidelines do not recommend routine testing for HBsAg in HD patients with known immunity, addition of antigen testing to routine surveillance may be warranted to reduce the risk of HBV transmission in this population.

TH-PO907

Extreme Duration of Positive Hepatitis B Surface Antigen (HBsAg) after Vaccination in a Hemodialysis Patient Robert H. Barth,[1,2] Amar V. Patel.[2,1]
[1]Medicine, VA NY Harbor Healthcare System, Brooklyn, NY; [2]Medicine, SUNY Downstate College of Medicine, Brooklyn, NY.

Background: Patients with end stage renal disease (ESRD) without immunity to hepatitis B virus (HBV) frequently receive vaccines containing purified non-infectious subunits of HBsAg. The two vaccines available in the U.S., Engerix-B (ENG) and Recombivax HB (REC), are both produced by cloning HBV DNA into the yeast Saccharomyces cerevisae and harvesting and purifying the resultant HBsAg expressed by the yeast. There have been many reports of transient positivity of HBsAg assays in patients who have received these vaccines, almost always lasting less than 14 days, with several case reports of HBsAg positivity of 28 to 48 days' duration.

Methods: We report a case of extremely long-term HBsAg positivity apparently induced by vaccination. The patient was a man with ESRD secondary to diabetes. After beginning hemodialysis he received 3 doses of ENG in 2003-2004, and within one month developed a positive assay for antibodies (Ab) to HBV (HBsAb). HBsAg was never positive, but the assays were obtained 15-40 days after the vaccinations. He continued to have positive assays for HBsAb for 33 months, after which the Ab gradually became undetectable, and in 2007 a new series of vaccinations, this time with REC, was begun. 30 days after the first vaccination HBsAg and HBsAb had simultaneously become weakly positive, and 32 days after the second dose both antigen (Ag) and Ab assays were fully positive. The patient was clinically stable, LFTs were entirely normal, and HBV DNA, core antibody, e antibody and e antigen were repeatedly negative. No further vaccinations were given. Concurrent HBsAg and HBsAb positivity persisted for 4.3 years, with reduction of HBsAg titers after 1.5 years, but with weak positivity persisting until the patient's death from an unrelated cause in 2011.

Results:

Conclusions: The mechanism for this persistent Ag positivity is not clear, but was almost certainly not active HBV infection, and was temporally very closely correlated with REC vaccination. The sequential use of two different vaccines may have played a role through differences in their antigenic structure, but this is not certain. Explanation of this phenomenon will require further study, but this case illustrates the extreme variability of HBV Ag/Ab assay results after HBV vaccination in patients on hemodialysis.

TH-PO908

Comparison of Outpatient Antibiotic Use in Dialysis Units of NY State Ilay Rakhman,[4] Aaron S. Stern,[4] Tina Adjei-Bosompem,[4] George N. Coritsidis,[2,4] Teresa Lubowski,[3] Ti-Kuang Lee,[3] Carol Lyden.[1]
[1]ESRD Network 2, Lake Success, NY; [2]Elmhurst Hospital Center, Elmhurst, NY; [3]IPRO, Lake Success, NY; [4]Mount Sinai Hospital, Elmhurst, NY.

Background: Little information is available regarding oral antibiotic use in outpatient clinical dialysis settings. Our study compares different prescribing practices in end stage renal disease (ESRD) patients and non-ESRD patients in both rural and urban areas.

Methods: 2015 IPRO Medicare part D data from all 62 New York State (NYS) counties were reviewed to obtain oral antibiotic (ABX) prescription information for the ESRD and non-ESRD populations. The average number of prescribed ABX per patient and average number of prescription days were compared between rural and urban areas as well as ESRD and non-ESRD populations.

Results: We found that ESRD patients were prescribed significantly more ABXs than non-ESRD patients in NYS regardless of urban or rural setting. The average number of ABX prescription days was greater with ESRD patients compared to non-ESRD patients, primarily in urban areas. Urban patients were prescribed Ampicillin (p=0.0295), Cefeclor (p=0.464), Cefadroxil (p=0.003), Dicloxacillin (p=0.018), and Metronidazole (p=0.0078) more often. Rural patients were prescribed Cefpodoxime 3.5 times more often than urban ESRD patients.

Conclusions: ESRD patients are prescribed more antibiotics for a longer duration when compared to the general population. Differences in prescribing patterns could be explained by more judicious prescription practices, less diversity of prescribers, fewer individual prescribers or the clinical status of ESRD patients. We cannot yet answer the question of appropriateness of antibiotic prescriptions, but these data can help establish prescription patterns, which can then be applied more broadly. Ultimately the data can be used to modify prescribing practices using evidence based recommendations to decrease inappropriate antibiotic use and promote antibiotic stewardship.

Table 1. Comparison of Antibiotics Prescribing Patterns Between ESRD Non-ESRD Patients

	Non-ESRD	ESRD	p
Avg ABX prescribed per patient	0.89 ± 0.02	1.66 ± 0.06	<0.001
Rural	0.87 ± 0.04	1.79 ± 0.25	0.003
Urban	0.89 ± 0.02	1.63 ± 0.04	<0.001
Avg days ABX prescribed per patient	10.27 ± 0.92	13.30 ± 0.41	<0.001
Rural	10.61 ± 0.18	12.70 ± 1.43	0.171
Urban	10.17 ± 0.10	13.46 ± 0.37	<0.001

TH-PO909

Sustained Low Central Venous Catheter-Related Bloodstream Infection Rates in HD Patients with an Antibiotic Lock over a 3-Year Period Sumi J. Sun,[1] Norma Gomez,[1] Fang Yang,[1] Graham E. Abra,[1,2] Brigitte Schiller.[1,2] *[1]Satellite Healthcare, San Jose, CA; [2]Stanford University, Palo Alto, CA.*

Background: CVCs are associated with catheter-related bloodstream infection (BSI) resulting in increased morbidity and mortality. Following our report of significantly reduced infection when 320 μg/mL gentamicin in 4% citrate is used as the CVC locking solution (Moran AJKD 2012), this has remained the standard of care in patients dialyzing with a CVC, unless physician order requested otherwise. The infection rates were monitored through an internal QC program developed for National Healthcare Safety Network (NHSN) reporting.

Methods: This study evaluated NHSN data with self-reported infection rates from January 2014 to December 2016 in a non-profit dialysis provider with a total of 57 free-standing dialysis facilities serving more than 5000 HD patients. BSI was reported according to NHSN criteria. Data were audited through comparison to an internal infection control report and discrepancies reconciled prior to final NHSN submission. Blood cultures were mandated before any antibiotic administration for suspected BSI, and 85% or more are sent to one internal lab (Ascend).

Results: The rate of catheter-related bloodstream infection over the three years was 1.00 episodes/100 patient months, 54% lower than the national average of 2.16 for CVC-related BSI (2014 NHSN BSI Pooled Mean Rate/100 patient-months). Monthly BSI rates showed minor fluctuations, however none exceeded the national average in any given month.

Conclusions: Gentamicin 320 μg/mL in 4% sodium citrate as a routine catheter lock demonstrated sustained low CVC-related BSI rates in HD patients, with approximately half the infection rate compared with the national average. Gentamicin-citrate lock should be considered the standard of care in patients with CVC access.

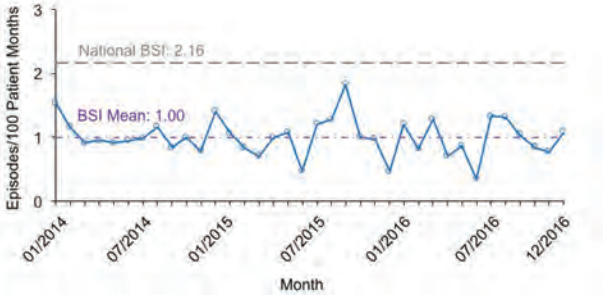


Figure 1: Monthly Bloodstream Infection Rates for Patients with Any CVC Access from 01/2014 to 12/2016

TH-PO910

First Treatment of Human Bacteremia during Dialysis Using a Biomimetic Sorbent Hemoperfusion Device Jan T. Kielstein,[2] Kathleen A. White,[1] Keith McCrea,[1] Robert S. Ward.[1] *[1]ExThera Medical, Martinez, CA; [2]Academic Teaching Hospital Braunschweig, Braunschweig, Germany.*

Background: Blood stream infections are the 2nd leading cause of mortality among CKD5D patients. To subvert the host immune response many pathogens bind to heparan sulfate, a key receptor on cell surfaces. The Seraph® 100 Blood Filter (Seraph) uses this affinity to bind and remove pathogens, toxins, and cytokines from flowing blood.

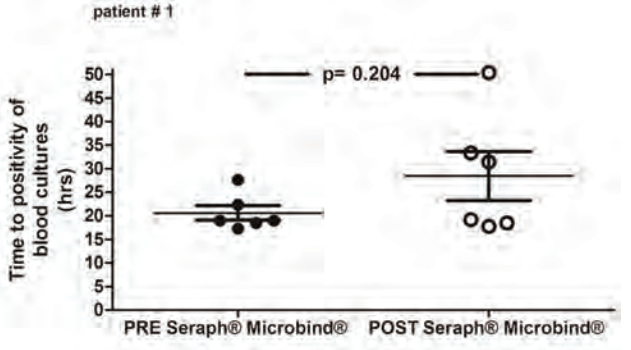
Methods: The first patients treated with the Seraph as part of an ongoing first-in-man study (www.clinicaltrials.gov. NCT02914132) are presented. The Seraph was placed in series, upstream from a FX80 high-flux dialyser (FMC), during a regular hemodialysis procdure with a 5008H dialysis machine (FMC) (Qb 300 mL/min; Qd 500 mL/min).

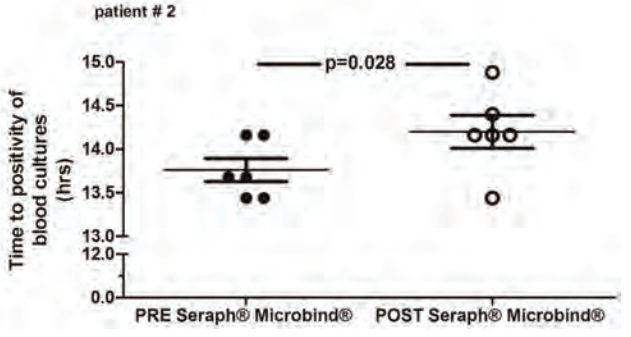
Results: Two male hemodialysis patients 57 and 82 years of age presented with S. aureus bacteremia. In adjunction to antibiotic therapy they were treated with Seraph concurrent with hemodialysis. As measured by automated blood culture, post-Seraph/pre-dialyzer blood samples had increased time to positivity (TTP) relative to contemporaneous pre-Seraph samples, indicating reduced concentration of bacteria. As estimated from TTP, mean incoming blood-borne bacteria decreased by 99% and 47% respectively per pass through the Seraph cartridge. During the 4-hour in-series treatment with Seraph and a dialyzer both patients remained hemodynamically stable and showed no adverse reactions.

Heart rate, blood pressure, and cardiac output were stable and reproducible. No clinically significant post treatment-changes in hematology or clinical chemistry occurred.

Conclusions: Seraph appears to be well tolerated by patients, and is capable of quickly removing pathogens from blood. It's rapid, broad-spectrum binding and inherent blood compatibility suggest future use as a prophylactic, or at the first sign of bloodstream infection, even before pathogen identification.

Funding: Commercial Support - ExThera Medical Corporation





TH-PO911

Effectiveness of Direct-Acting Antiviral Regimens in the Treatment of Hepatitis C Virus Infection in a Diverse Dialysis Population Michelle T. Martin,[2,1] Ignatius Y. Tang,[2] Todd Lee.[1] [1]*University of Illinois at Chicago, Chicago, IL;* [2]*University of Illinois Hospital and Health Sciences System, Chicago, IL.*

Background: Direct-acting antiviral (DAA) regimens offer high sustained virologic response (SVR) in patients infected with the hepatitis C virus (HCV). However, clinical trial data in dialysis patients and real-world data in a multi-ethnic dialysis population are limited.

Methods: All HCV-infected dialysis patients who received DAA therapy at an urban academic medical center from 1/1/2014 to 12/1/2016 and had SVR data available were included in this single center retrospective review. Data collection included demographics, comorbidities, treatment regimen, and laboratory data. Descriptive statistics, Fisher's exact test, and Pearson's chi-square test were used for analysis.

Results: A total of 17 patients started treatment; SVR data were not available for 2 patients. Among the remaining 15 patients, the mean age was 63.1 (±6.9) years and BMI was 26.3 (±4.7) kg/m^2, 80% were male, 60% African American, 67% cirrhotic, 80% treatment-naive, 27% had diabetes, and 20% had psychiatric illness. The HCV genotype mix was 67% 1a, 27% 1b, and 6% 2b. Forty percent had received organ transplants: 33% liver and 7% liver + kidney; 83% of transplant patients received tacrolimus for immunosuppression. Sixty-seven percent of patients received elbasvir/grazoprevir, 20% elbasvir/grazoprevir + ribavirin, and 13% ledipasvir/sofosbuvir. SVR was achieved in all 15 patients (100%). Fatigue was reported by 20% of patients. All 3 patients who received ribavirin experienced anemia. One patient received additional erythropoietin during dialysis and had a ribavirin dose reduction. The SVR rates did not differ by genotype, regimen, cirrhosis, treatment history, ethnicity, gender, age, BMI, diabetes, psychiatric history, or transplant status. The SVR rates also did not differ by adherence; 13% of patients reported missing 1 dose of HCV medication during treatment.

Conclusions: Despite a high proportion of cirrhotic patients, all patients achieved SVR in this diverse dialysis patient population. While ledipasvir/sofosbuvir is not recommended for HCV-infected dialysis patients, both patients treated with this regimen achieved SVR. The SVR rates did not differ by treatment or demographics due to the 100% cure rate, and conclusions across groups are limited due to the small numbers. DAA regimens were well tolerated except for anemia in patients receiving ribavirin.

TH-PO912

Incidence of Dialysis-Related Infections in the Automated Peritoneal Dialysis Population in the United States Eric D. Weinhandl,[1,2] Allan J. Collins.[1,2] [1]*NxStage Medical, Inc., Victoria, MN;* [2]*University of Minnesota, Minneapolis, MN.*

Background: Infection increases risks of peritoneal dialysis technique failure and death. However, data about the magnitude of and trends in the incidence of all-setting peritoneal dialysis-related infection (DI) in the US are lacking. We estimated incidence of both hospitalized and non-hospitalized DI in the automated peritoneal dialysis (APD) population.

Methods: We analyzed United States Renal Data System records. From 2006 to 2013, we collected cohorts of end-stage renal disease patients on APD. We identified hospitalized and non-hospitalized cases of DI from Medicare claims with ICD-9-CM diagnosis codes [a] 567.x (peritonitis), [b] 996.68 (infection due to peritoneal dialysis catheter), and [c] 038.x (septicemia). We estimated incidence rates with definitions of diagnosis code [a], codes [a]-[b], and codes [a]-[c], and with only principal or with both principal and secondary diagnosis codes.

Results: In 2013, the incidence rate was 11.2 (annualized rate of change between 2006 and 2013, -6.3%), 25.1 (-4.7%), and 35.1 (-3.1%) events per 100 patient-years with diagnosis code [a], codes [a]-[b], and codes [a]-[c], respectively, as a function of only principal diagnosis codes. In contrast, as a function of both principal and secondary diagnosis codes, corresponding rates were 45.7 (-3.3%), 55.1 (-2.7%), and 66.3 (-2.1%) events per 100 patient-years. These rates corresponded to one DI case per 26, 22, and 18 patient-months, respectively. With DI defined by both principal and secondary diagnosis codes, hospitalized cases comprised between 53% and 61% of all cases.

Conclusions: Between 2006 and 2013, the incidence of DI decreased among APD patients in the US. However, the absolute magnitude of the incidence of DI was uncertain, as rates defined by an array of diagnosis code sets and diagnosis code positions varied by a factor of nearly 6 in 2013. The incidence rate associated with broader claims-based definitions indicated that DI remains a common complication in 2013; for frame of reference, the incidence of all-setting peritonitis ranged from 35 to 40 events per 100 patient-years in Australia between 2012 and 2015. In addition, more than half of DI cases involved hospitalization, a possible marker of inadequate monitoring in the outpatient setting. With continued growth of PD utilization in the US, novel tools to reduce risk of DI on APD are needed.

TH-PO913

Comparison of CAPD and APD Peritonitis in a Nephrology Reference Center in Mexico City Ruben Garrido,[2] Julio C. Arriaga,[2] Bernardo Moguel,[1] Francisco Rodriguez.[2] [1]*Instituto Nacional de Cardiologia, Mexico City, Mexico;* [2]*Instituto Nacional de Cardiologia Ignacio Chavez, Tlalpan, Mexico.*

Background: Peritonitis is a major cause of morbidity, mortality and increase health care cost in patients on peritoneal dialysis (PD). PD infection is associated with peritoneal membrane loss, technique failure and mortality. Following an episode of peritonitis, the risk of more peritonitis episodes, hemodialysis switch and death increased during the first month and during the next 6 months.

Methods: We evaluated retrospectively all patients with peritonitis episode from October 2014 to December 2016 in the "National Institute of Cardiology Ignacio Chávez" in Mexico City on different PD modalities: Continuous Ambulatory Peritoneal Dialysis (CAPD) and automated peritoneal dialysis (APD).

Results: 71 patients were evaluated, 36 (50.7%) of female sex with a median age of 50 years. 54 (76.1%) on CAPD and 17 (23.9%) on APD. The main cause of renal failure were diabetic nephropathy in 34 patients (45.1%). On 28 patients (39.4%)no history of peritonitis and the comorbidities were chronic hypertension (47.9%), ischemic heart disease (16.9%) and chronic heart failure (8.5%). The most frequent organism identified on cultures were S aureus in 23 (32.4%) patients, E coli in 7 (9.9%), S marcescens in 5 (7%), S epidermidis with 5 (7%) cases and Candida in 5 patients (7%).

Conclusions: The CAPD group presented more frequently peritonitis episodes. Most frequent infection was gram positive organisms: S. aureus in 39.4%. Mechanical dysfunction presented only in 1 patient of APD patients, and also only 1 patient died in this group. The level of albumin and BUN demonstrated a statistical significance and are associated with worst outcome in all patients.

Table. Clinical and biochemical outcomes APD and CAPD patients

Mechanical dysfunction	n	%
Yes	10	14.1
No	61	85.9
Final outcome	**n**	**%**
Live	63	88.7
Death	5	7
Lost to follow up	3	4.2

Outcome	n	%
Repeat	12	16.1
Refractory	5	7
Relapsing	3	4.2
Recurrent	1	1.4
Catheter related peritonitis	5	7
Mycotic	5	7
Remission	40	56.3

	Outcome (Live/death)	Median	P value
Albumin	Yes	3.11	0.012
	No	2.3	
BUN	Yes	65.88	0.02
	No	36.92	
Leucocytes	Yes	8.47	0.05
	No	21.16	
Lymphocytes	Yes	1.21	0.36
	No	0.97	
Age	Yes	49.27	0.62
	No	57.80	
Cell count #	Yes	2567	0.83
	No	2262	

TH-PO914

Effects of Prospective Improvement Trail to Reduce the Incidence of Peritonitis in a Peritoneal Dialysis Population in Qatar Mohamed amin Khalil elesnawi,[1] Fadwa S. Al-Ali,[1] Abdullah Hamad,[1] Vimala K. Lonappan,[1] Sahar Aly,[2] Rania A. Ibrahim,[1] Ahlam Ali,[3] Tarek A. Fouda,[4] Hanaa Ahamed.[1] *[1]Hamad Medical Corporation, Doha, Qatar; [2]Hamad medical corporation, Doha, Qatar; [3]hamad medical corpartion, Doha, Qatar; [4]Hamad medical cooperation, Doha, Qatar.*

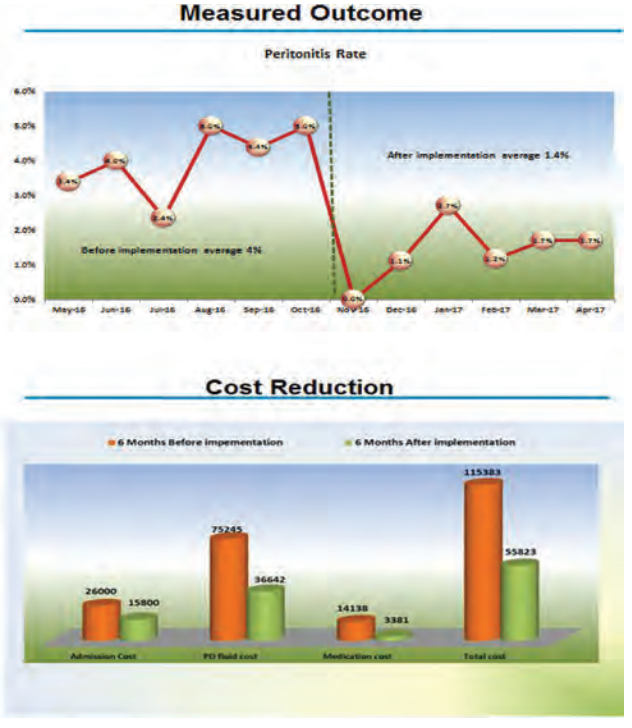
Background: Peritonitis is the major complication in patients on peritoneal dialysis (PD). Peritonitis carries high morbidity and mortality. In addition it carries an economic burden of increasing hospitalization. We have 180 PD patients and over the period of 6 months in 2016 the peritonitis was average 4%. With this high incidence we decided to run a prospective improvement trial to reduce the incidence

Methods: We conducted a random survey for 60% of patients to determine daily practice. Root cause analysis for each case in the 6 months trial to identify risk factors. Based on the data, procedure check list created during monthly visits and re-training at same time. Regular home visit assessment and questionnaire taking for environmental evaluation and daily practice. All aspects of the trial were planned and drawn by Multidisciplinary team (MDT).

Results: 110 Patients took part in the survey and after analysis of the data using pareto chart, 24% had poor hand hygiene, 22% not using mask, 20% had constipation, 14% had an unsuitable environment at home, 8% had poor personal hygiene, 7% traveled abroad and 5% did not have adequate time to undertake the procedure properly. The incidence of peritonitis in the 6 months of the trial has fallen from average 4% to 1.4% which presents a 65% reduction of peritonitis. Furthermore there was 51.6% reduction in the overall medical cost

Conclusions: In this prospective trial we have demonstrated that peritonitis can be significantly reduced by MDT approach and monthly retraining of patients. Although there is medical and economical benefit, there is some cost implication for the monthly retraining. More work is needed to establish what would be the most effective frequency of training

Funding: Government Support - Non-U.S.



TH-PO915

Microbiologic Surveys and Resistance Profiles in Mexican PD Patients Martín D. Vargas ezquivel,[2] Javier Soto-Vargas,[2] Heriberto R. López,[2] Ana L. Garc?a-Vera,[2] Carlos Daniel Jiménez Mejía,[2] Alfonso Ramos,[1] Mario A. Garc?a C?rdenas.[2] *[1]Baxter Mexico, San Jer?nimo Chicahualco, Mexico; [2]Regional General Hospital 46, Mexican Institute of Social Security, Guadalajara, Mexico.*

Background: Guidelines that recommend specific antibiotics for empiric treatment of peritonitis are not specific to populations and time variable microbiology. Our objective was to present the microbiologic change and antibiotic resistance in a reference center in México.

Methods: We recorded the cultures from PD patients with peritonitis from 2008-2015, an analysis was performed of resistance profile to different antibiotics according to their Gram stain and species.

Results: A total of 1814 samples were obtained, the more prevalent bacteria were *Staphylococcus* coagulasa negative (ConN) (23.7%), *S. aureus* (16.5%), *Escherichia coli* (12.2%) and *Enterococcus* spp (9.2%). The distribution of agents according to Gram stain between the years studied were no different (p=0.214), being Gram positive responsible of 70 to 64% of the cases of peritonitis. It was observed an increase of cases due to *S. aureus* and *Klebsiella* spp, as well to *E. coli* without a specific patron. The majority of the cases were in the ambulatory setting (73.5%). 60.3% of the infections caused by *Staphylococcus* were methicillin resistant. Of importance, 76% of CoNS had methicillin resistance and only 28.1% of *S. aureus*. The prevalence of Vancomycin resistant *Enterococcus* was 18%, with no difference between acquisitions on community or nosocomial setting. In the Gram negative bacilli group, 72.5% of the *E. coli* and 35.1% of the *Klebsiella* spp were BLEE-producing, but the susceptibility to carbapenems reached 98%. In respect to fluoroquinolones, *E. coli* resistance reached 77.8% of the cases, and *Klebsiella* spp only 20.9%. Surprisingly there were no differences between the resistance and the ambulatory or hospital setting of the infection.

Conclusions: The agents responsible of peritonitis during this 8 year study were primarily Gram positive coccus, with a high prevalence of methicillin resistance in both ambulatory and nosocomial setting. The presence of BLEE-producing Gram negative bacilli was high as well as the resistance to quinolones and aminoglycosides with a little variation over time.

TH-PO916

Services Associated with Increased Cost of Hospitalization for Peritonitis in Pediatric Patients Receiving Chronic Peritoneal Dialysis Allison C. Redpath,[4] Troy Richardson,[1] Alicia Neu,[2] Bradley A. Warady.[3] *[1]Children's Hospital Association, Overland Park, KS; [2]Johns Hopkins University School of Medicine, Baltimore, MD; [3]The Children's Mercy Hospital, Kansas City, MO; [4]University of Wisconsin School of Medicine & Public Health, Madison, WI. Group/Team: SCOPE Collaborative.*

Background: Peritonitis is a leading cause of hospitalization in children on chronic peritoneal dialysis. The Standardizing Care to improve Outcomes in Pediatric ESRD (SCOPE) Collaborative has demonstrated a reduction in peritonitis rates and associated hospitalizations resulting in over $7million in cost-savings. Prior investigation has demonstrated that ICU stay and fungal peritonitis are associated with high-cost hospitalizations. The objective of this analysis is to describe service-line utilization associated with high-cost hospitalizations for peritonitis.

Methods: Peritonitis episodes reported by 24/29 SCOPE centers between 10/2011 and 9/2015 were linked with data in the Pediatric Health Information System (PHIS) database. Linkage was performed on the basis of sex, birth month and year, and date of peritonitis episode and hospitalization. Charges in PHIS were adjusted for cost-of-living differences and converted to costs. Detailed billing information was used to compare service-line utilization among the top 25 % of infection episodes by cost with bottom 75% and to compare fungal infection episodes to other types of infections.

Results: During the first 48 months of SCOPE, 266 peritonitis episodes were linked to 278 hospitalizations in PHIS. Detailed billing data was available for 246 hospitalizations and 238 peritonitis episodes. The proportions of hospitalization costs were similar between the top 25% of peritonitis episodes (N=66) and the lower 75% (N=180) for pharmacy (p=0.63), lab (p=0.30), imaging (p=0.85), supply (p=0.98), clinical (0.33) and other (p=0.18) service lines. Cost per case was significantly higher (p<0.001) for all service lines in the top 25% group. Compared with other types of infections (N=215), fungal peritonitis episodes (N=23) had elevated costs per episode (p<0.001) in lab, imaging, supply, room and board costs (including ICU costs) and costs associated with hemodialysis (HD).

Conclusions: The increase costs attributed to the top 25% of peritonitis hospitalizations can be attributed to all service lines. Increased hospitalization cost per case among fungal peritonitis infections is driven by increased room and board costs associated with prolonged length of stay, costs associated with HD, and lab costs.

TH-PO917

Comparison in Mortality in Dialysis Requiring AKI (AKI-D) in Native versus Kidney Transplant Recipients Tripti Singh,[1] Sana Waheed,[1] Arjang Djamali,[1] Neetika Garg,[1] Kristen Sipsma.[2] *[1]School of Medicine and Public Health, University of Wisconsin, Madison, WI; [2]UW Health, Madison, WI.*

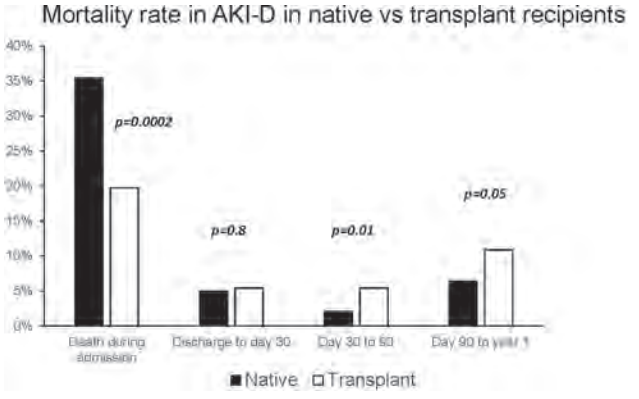
Background: There is limited information on mortality rates in patients with native versus transplant kidneys requiring renal replacement therapy (RRT) for acute kidney injury (AKI).

Methods: We compared one-year patient outcomes in a retrospective single center analysis of all adult patients with acute kidney injury requiring dialysis (AKI-D) admitted between February 2012- June 2016.

Results: 962 patients with native kidney (AKI-N) and 147 patients with kidney transplant (AKI-T) with AKI-D were admitted during the study period. Mean age was 57.6 years for AKI-N and 52.6 years for AKI-T patients (p=0.0001). 63% were males and 88% were Caucasians (p=ns). Serum creatinine at admission was significantly higher in AKI-T compared to AKI-N kidney patients (4.4 vs 3.2 mg/dL, p<0.0001). Length of stay was similar for both groups (21.6 vs 21.2 days). Continuous renal replacement therapy (CRRT) was utilized in 65% of AKI-N compared to 36.7% of AKI-T (p<0.0001).

Mortality at discharge was significantly higher for AKI-N compared to AKI-T (35% vs 19.8%, p = 0.0002). However, 1 year mortality for AKI-D was not different between native and kidney transplant recipients (49% vs 41%, p=0.09) because of poor late outcomes in transplant recipients (Fig 1). Logistic regression analyses determined CRRT (HR 3.6, 95% CI 2.8-4.7, p<0.0001), serum creatinine (HR 0.87 CI .82-.92, p<0.0001), LOS (HR 0.98 CI .98-.99, p<0.0001), and age (HR 1.01 CI 1.00-1.02, p<0.005), as significant predictors of one year mortality.

Conclusions: In patients with AKI requiring RRT early mortality is higher in native kidney disease while late mortality is greater in kidney transplant recipients. Overall, AKI requiring RRT is associated with nearly 40-50% mortality at one year, regardless of transplant status.



TH-PO918

A Multi-Platform Approach for the Noninvasive Differential Diagnosis of Acute Dysfunction of the Kidney Allograft Thangamani Muthukumar,[6] Carol Y. Li,[2] Catherine Snopkowski,[4] Hua Yang,[5] Liana S. Perry,[6] Steven Salvatore,[2] John R. Lee,[3] Surya V. Seshan,[1] Darshana Dadhania,[2] Manikkam Suthanthiran.[2] *[1]Weill Cornell Medical Center, New York, NY; [2]Weill Cornell Medical College, New York, NY; [3]Weill Cornell Medicine-, New York, NY; [4]Weill Medical College of Cornell University, New York, NY; [5]Weill-Cornell, New York, NY; [6]Weill Cornell Medicine, New York, NY.*

Background: We tested a multi-platform approach for the noninvasive differential diagnosis of acute dysfunction of the kidney allograft.

Methods: We studied 118 kidney transplant recipients with acute kidney allograft dysfunction. All had kidney allograft biopsy done that were studied by light, immuno and electron microscopy and were stained for C4d and SV40 large T antigen. Serum samples were obtained at the time of biopsy for detecting donor-specific anti-HLA antibodies by Luminex single antigen bead assay (DSA). Urine specimen was obtained at the time of biopsy for urinary cell mRNA profiling. Using preamplification enhanced real-time quantitative PCR assays, we quantified CXCL10 mRNA, and CD3e mRNA levels as well as 18S rRNA levels and expressed their abundance as copies/ug total RNA. Using these three transcript levels, we derived our 3-gene molecular signature (Suthanthiran et al. N Engl J Med 2013). We also quantified BK virus VP1 mRNA levels (Ding et al. Transplantation 2002) in the biopsy matched urinary cells.

Results: Among the 118 kidney transplant recipients, biopsy revealed acute cell-mediated rejection (ACR) in 22 biopsies, acute antibody-mediated rejection (AMR) in 10 biopsies, acute tubular injury (ATI) in 49 biopsies, or polyomavirus nephropathy (PVAN) in 37 biopsies. All biopsies classified as ACR, AMR and ATI were negative for SV40. The first step in the differential diagnosis was the identification of the patients based on DSA. This identified the 10 patients with AMR. The next step in the differential diagnosis was the measurement of urinary cell VP1 mRNA. Based on our previously published cutoff value of 6.5 x 10^8 BKV VP1 mRNA copy number, 77 of the 81 patients who did not have PVAN were identified and excluded, with a negative predictive value (NPV) of 95%. In the final step, ACR and ATI were distinguished based on our previously published cutoff value of -1.213 of the 3-gene signature. Based on this cutoff value, the NPV was 83%.

Conclusions: A multi-platform approach, which involves testing DSA in the serum, BK virus VP1mRNA in urinary cells and the 3-gene signature in the urinary cells, offers a noninvasive method for the differential diagnosis of acute dysfunction of the kidney allograft with a high degree of accuracy.

Funding: Other NIH Support - NIAID

TH-PO919

Delayed Graft Function in Living Donor Kidney Transplantation – Risk Factors and Outcomes Manohar Reddy Mogulla, Philip A. Clayton. *Central and Northern Adelaide Renal and Transplantation services, Adelaide, SA, Australia.*

Background: Delayed graft function (DGF) is associated with poorer outcomes in deceased donor renal transplantation recipients. The association of DGF in living donor kidney transplantation has not been well studied. This study reviews the risk factors for DGF in Australia and New Zealand living donor kidney transplant recipients and its association with short and long term outcomes.

Methods: Data that had been prospectively collected in the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry was reviewed. The inclusion criteria were all adult living donor kidney transplants performed between 2004 and 2015. Data from pediatric recipients (<18 years) and donors with pre-existing renal pathology (n=404), with incomplete data (n=46) and those with early graft loss (graft loss within 1 week of implantation) (n=38) were excluded. The variables studied included multivariable logistic regression to identify the risk factors for DGF and the association between DGF and rejection at 6 months; linear regression model to examine the association with eGFR at 1 year; and Cox proportional hazards models to examine the relationships between DGF and patient and graft survival.

Results: We observed DGF in 77 (2.3%) of 3358 transplants. Risk factors for DGF included right-sided kidney (odds ratio [OR] 2.00 [95% CI 1.18-3.40]); donor BMI (OR 1.06 [95% CI 1.01 - 1.12]); increasing time on dialysis and total ischemia time (OR 1.09 per hour [1.00-1.17]). DGF was associated with increased risk of rejection, worse patient and graft survival, and lower renal function at 1 year (Table).

Conclusions: In living donor kidney transplants DGF is uncommon but associated with significantly worse outcomes. The only modifiable risk factor identified was total ischemia time. Attention towards minimization of ischemia time in high-risk patients is recommended.

outcomes

Outcome	Estimate type	Estimate	95% CI	p-value
Rejection	Odds Ratio	2.37	1.41 - 3.97	0.001
Patient survival	Hazard ratio	2.14	1.21 - 3.10	0.009
Graft survival	Hazard ratio	1.98	1.27 - 3.10	0.003
eGFR at 1 year	Coefficient	-9.57	-13.5 - -5.64	<0.001

TH-PO920

Comparison between Delayed Graft Function and Slow Graft Function in Predicting Outcomes amongst Kidney Transplant Recipients Brittany L. Schreiber, Rohan Patankar, Vishy Chaudhary, Sujan P. Shah, Muhammad A. Mujtaba. *University of Texas Medical Branch, Galveston, TX.*

Background: Allograft dysfunction in the immediate post transplant period, commonly referred to as delayed graft function (DGF), has been associated with poor outcomes including acute rejection and decreased allograft longevity. Defining DGF continues to remain controversial with multiple definitions in literature. The United Network for Organ Sharing (UNOS) defines DGF as dialysis within the first week of transplantation (UNOS-DGF), leaving other measures of allograft dysfunction under the umbrella of slow graft function (SGF). Initiation of dialysis remains subjective and varies in different institutions. We aim to compare UNOS-DGF with SGF in predicting poor patient outcomes and long-term allograft dysfunction.

Methods: Our study was a single center, retrospective study that included 154 renal transplant recipients from January 1, 2015 - May 1, 2017. The patients were divided into 4 groups based on graft function: i) DGF, ii). SGF (creatinine reduction ratio <0.3 in the first 48 hours post transplant), iii). combined group and iv). immediate graft function (IGF). Chart review was performed and data collected including patient demographics, length of stay (LOS), 30-day-readmission rates, incidence of graft loss, and creatinine at 1 month post transplant.

Results: Of the 154 patients, 34 were included in the DGF group, 71 in the SGF group, 23 in the combined group, and 72 in the IGF group. Patients in the DGF and combined groups were noted to have significantly increased LOS by more than 200% and higher 30 day readmission rates compared to the IGF group with a relative risk increase of 1.68 and 1.57 respectively. Creatinine at 1 month post-transplant was significantly higher amongst the DGF, SGF and combined groups, with the greatest statistical difference in the SGF. Graft loss was seen in 13% of patients in the combined group as compared to 9%, 6%, and 3% in the DGF, SGF, and IGF groups respectively.

Conclusions: We observed that while the UNOS-DGF definition correlated with worse patient outcomes and impaired allograft function at 1 month post-transplantation, the SGF criteria identified patients at risk that were not defined by UNOS-DGF and therefore may better predict poor patient outcomes and long-term allograft dysfunction.

TH-PO921

Acute Kidney Dysfunction with No Rejection (ADNR) Is Associated with Poor Outcomes in Kidney Transplant Recipients François Paquot,[1] Hans Pottel,[2] Catherine Bonvoisin,[1] Laurent E. Weekers,[1] Francois Jouret.[1] *[1]University of Liege Hospital (ULg CHU), Liege, Belgium; [2]KULeuven, Kortrijk, Belgium.*

Background: The entity "acute kidney dysfunction with no rejection (ADNR)" has been proposed for kidney transplant recipients (KTR) presenting with acute elevation of serum creatinine without histological evidence of acute rejection (AR). The prognosis of ADNR has not been studied thus far.

Methods: From 2007 to 2015, we retrospectively categorized all KTRs with a *for-cause* kidney biopsy within 12 months post-kidney transplantation (KTx) into 2 groups: ADNR and biopsy-proven AR. Control group (C) included KTR with no ADNR or AR within 24 months post-KTx. BK virus nephropathy and primary nonfunction were excluded. Estimated glomerular filtration rate (eGFR) was determined using the Modification of Diet in Renal Disease (MDRD) equation. Linear mixed models established intercepts and slopes of eGFR decline from 6 to 24 months post-KTx. Cubic

spline analysis calculated the percentage of patients with a ≥30% reduction of eGFR from 6 to 24 months post-KTx.

Results: The mean age (years) at KTx was 50.2±14.2, 47.9±17.8 and 53.6±12.4 for ADNR (n=93), AR (n=22) and C (n=135), respectively. The female/male ratio was 39.8% (ADNR), 45.5% (AR) et 34.1 (C). The rate of delayed graft function was not significantly different among groups, and reached 26.9% (ADNR), 22.7% (AR) and 14.1% (C). The median time for *for-cause* graft biopsy was 22 [10-70] and 13 [7-43] days post-KTx for ADNR and AR, respectively. Of note, ADNR included 21 (22.6%) patients with "borderline" histology. At 6 months post-KTx, eGFR was higher in C (55.2±1.6 mL/min) *vs.* ADNR (45.5±1.9 mL/min; *p<0.05*) and *vs.* AR (48.6±3.9 mL/min; *p, 0.13*). The eGFR slope from 6 to 24 months post-Tx was positive in C (0.16±0.06mL/min/month) compared to negative slopes in ADNR (-0.04±0.08mL/min/month, *p<0.05*) and in AR (-0,04±0.16mL/min/month, *p, 0.26*). The proportion of KTR presenting with a ≥30% reduction of eGFR from 6 to 24 months post-KTx reached 7.4% in C *vs.* 25.8% in ADNR (*p<0.05)* and 19.1% in AR (*p<0.05)*.

Conclusions: In the present monocentric cohort, ADNR occurs frequently and early *post* KTx, and is associated with a significantly lower eGFR at 6 months and a significantly faster eGFR decline from 6 to 24 months post-KTx, in comparison to controls.

Funding: Clinical Revenue Support

TH-PO922

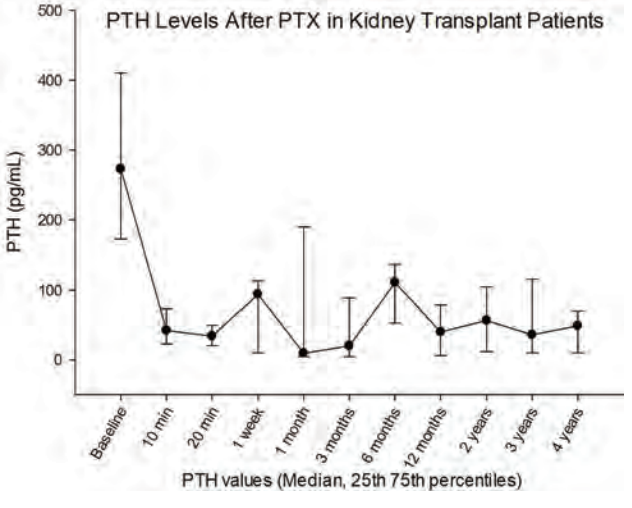
Value of Intra-Operative PTH Assay during Parathyroidectomy in Renal Transplant Recipients with Secondary and Tertiary Hyperparathyroidism Kevin Wang, Adeleye A. Edon, David Saxon, Florence Lima, David Sloan, B. Peter E. Sawaya, Amr E. Mohamed. *University of Kentucky, LEXINGTON, KY.*

Background: In renal transplant patients with secondary and tertiary hyperparathyroidism (HPT), the association between intra-operative parathyroid hormone (ioPTH) levels during parathyroidectomy (PTX) and long-term PTH is unknown. The present study aims at evaluating the value of ioPTH measurements on long-term outcome of PTX in renal transplant recipients in a single center study.

Methods: The ioPTH was measured in 18 renal transplant recipients (12 males and 6 females) who underwent PTX from 2005 to 2015 because of persistent hyperparathyroidism post-transplant. Near-total PTX was performed in 13 patients and total PTX in 5 patients. The ioPTH monitoring included 3 samples: pre-intubation (pre-ioPTH), 10- and 20-minute post parathyroid gland excision (10-ioPTH and 20-ioPTH). Patients were followed for up to 5 years (mean ± SD: 2.5 ± 1.6 years).

Results: The median (25^{th}-75^{th} percentile) pre-, 10- and 20-ioPTH levels were: 273 pg/ml (173-411), 42 pg/ml (22-73) and 34 pg/ml (20-50), respectively. All patients had a functional kidney transplant at time of surgery with a median serum creatinine of 1.3 mg/dl (1.2-1.7) and eGFR of 55 ml/min (40-60). The median time between renal transplant and PTX surgeries was 22 months (7-81). The median last follow-up PTH level was 59 pg/ml (17-83). There was no significant difference between 20-ioPTH and follow-up PTH measurements (*P*=0.6). The pre- PTX and follow-up PTH levels are shown in the Figure. Three patients (17%) were readmitted within 90 days because of hypocalcemia. Apart from easily treated hypocalcemia, the PTX surgeries were uneventful. No patient required repeat PTX because of recurrent HPT.

Conclusions: The 20-ioPTH is a good indicator of long-term PTH measurements. There were minimal complications associated with the procedure.



TH-PO923

A Prospective and Randomized Trial of Zoledronic Acid to Prevent Bone Loss in the First Year after Kidney Transplantation Igor Marques,[9] Maria Julia C. Araujo,[2] Fabiana Graciolli,[6] Luciene dos Reis,[7] Rosa M. Pereira,[1] Melani Custodio,[5] Vanda Jorgetti,[4] Rosilene M. Elias,[4] Rosa M. Moyses,[3] Elias David-Neto.[8] *[1]Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil; [2]None, Sao Paulo, Brazil; [3]Universidade Nove de Julho, São Paulo, Brazil; [4]Universidade de Sao Paulo, Sao Paulo, Brazil; [5]Universidade de São Paulo, São Paulo, Brazil; [6]University of Sao Paulo, Sao Paulo, Brazil; [7]University of Sao Paulo - Medical School - Nephrology Division, Sao Paulo, Brazil; [8]University of São Paulo School of Medicine, São Paulo, Brazil; [9]Unidade do Sistema Urinario, Hospital Universitario da UFPI, Teresina, Brazil.*

Background: Bone and mineral disorders occur frequently in kidney transplant (Ktx) recipients and have been associated with a high risk of fracture, morbidity, and mortality. Bisphosphonates may prevent or treat the bone loss promoted by the immunosuppressive regimens used in Ktx.

Methods: We conducted an open-label, prospective, randomized trial to assess the efficacy and safety of zoledronate to prevent the bone loss in the first year after Ktx. Ktx recipients were randomized 1:1 to receive zoledronate (5 mg at baseline) or no treatment (control group). Both groups received vitamin D supplementation. We evaluated bone mineral density (BMD) and microarchitecture with dual-energy X-ray absorptiometry (DXA) and with high-resolution peripheral quantitative computed tomography (HR-pQCT). Bone histomorphometric analyses were done at the time of Ktx and after 12 months of therapy.

Results: Differing from previous studies, after Ktx, neither zoledronate nor control group presented bone loss. Ktx has promoted an increase of BMD in both lumbar spine and total femur ($p<0.0001$). The late was more pronounced in the zoledronate group ($p<0.05$). Out of 34 patients, 29 had baseline and follow-up bone biopsies. On histomorphometry, we found that Ktx, but not zoledronate, suppressed bone activity without causing adynamic bone disease. Bone trabecular volume decreased only in zoledronate group ($p<0.05$). There was an improvement in cortical bone, as depicted by an increase in cortical thickness and a decrease in cortical porosity, in both groups.

Conclusions: In conclusion, we have confirmed that Ktx is not associated with significant bone loss, based on histomorphometric data. Therefore, although zoledronate had a beneficial effect in total femur BMD, the inclusion of bisphosphonates to prevent bone loss should be reconsidered in face of a contemporary immunosuppressive therapy.

Funding: Government Support - Non-U.S.

TH-PO924

Efficacy and Safety of Different Bisphosphonates for Bone Loss Prevention in Kidney Transplant Patients: A Systematic Review and Network Meta-Analysis Yan Yang,[1] Shi Qiu,[4] Xi Tang,[3] Ping Fu.[2] *[1]Kidney Research Institute, Division of Nephrology, West China Hospital, Sichuan University, Chengdu, China; [2]West China Hospital of Sichuan University, Chengdu, China; [3]west china hospital, sichuan university, Chengdu, China; [4]Department of Urology, Institute of Urology, West China Hospital, Sichuan University, Chengdu, Sichuan, P.R. China, Chengdu, China.*

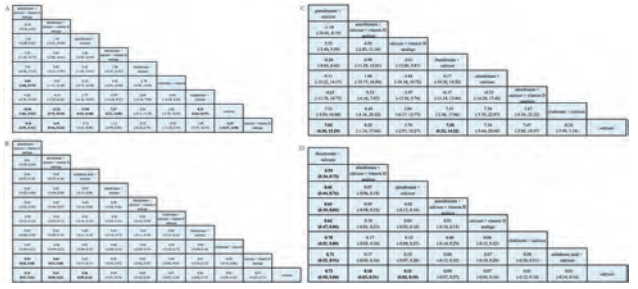
Background: Because the preferred bisphosphonate regimen for kidney transplantation (KT) patients is still controversial, we aimed to compare different bisphosphonate treatments.

Methods: We searched PubMed, Embase, CENTRAL and reference lists of relevant articles up to April 1, 2017. We included RCTs comparing bisphosphonates in adult KT patients. The primary outcome was BMD change at the lumber spine and femoral neck. We performed pairwise meta-analyses by random effect model and network meta-analysis (NMA) by Bayesian model. We used the GRADE framework to assess the quality of evidence.

Results: A total of 21 RCTs involving 1332 patients with 6 bisphosphonate regimens were included in the NMA. At the lumber spine (Figure 1A), calcium alone showed significantly lower percent change in BMD compared to combination with vitamin D analogs or other bisphosphonates except clodronate. Pamidronate with calcium and vitamin D analogs showed improvemed BMD in comparison to clodronate with calcium. The combination of calcium and vitamin D analogs had a significantly lower influence than adding pamidronate or alendronate. Considering absolute terms (Figure 1B), zoledronic acid and calcium outperformed calcium alone. In terms of percent change in BMD at femoral neck (Figure 1C), both pamidronate and ibandronate combined with calcium revealed a remarkable gain compared with calcium. In absolue terms (Figure 1D), alendronate with or without vitamin D analogs, displayed a significant increase compared to calcium alone. Ibandronate with calcium demonstrated advantages than any other treatments.

Conclusions: New generation bisphosphonates were more favorable in KT patients to improve BMD. Bisphosphonate therapy was well-tolerated without increasing the frequency of adverse events and graft loss.

Funding: Government Support - Non-U.S.



Summary MD and 95%CrI from NMA of BMD change. The results are read from top to bottom and left to right. Significant results are in bold. A. Percent change at lumber spine; B. Absolute change at lumber spine; C. Percent change at femoral neck; D. Absolute change at femoral neck.

TH-PO925

Prevalence of Vitamin D Deficiency after Kidney Transplantation and Its Association with Clinical Outcomes Puneet Bedi,[1] Nicole A. Hayde,[1] Maria Ajaimy,[1] Enver Akalin.[2] *[1]Montefiore Medical Center, Bronx, NY; [2]Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY.*

Background: Kidney transplant recipients usually have low vitamin D levels, especially in the early posttransplantation period. Vitamin D deficiency is recognized as a risk factor for progression of kidney disease in general population. However, its association with graft outcomes in renal transplant patients is not well established.

Methods: We measured 25-hydroxyvitamin (OH) D levels and intact-Parathyroid hormone (i-PTH) levels at 6, 12, 24 and 36 months post-transplant in patients transplanted at our center between Jan 2009 and Dec 2014 and measured the association between 6 month post-transplant 25-OH-vit D and i-PTH levels and clinical outcomes.

Results: Prevalence of 25-OH-vit D levels <15, 15-19.9, 20-29.9, and > 30 ng/ml, was (29.2%, 22.2%, 34.7%, 13.3%) at 6 months, (21.4%, 23.7%, 35.0%, and 19.7%) at 1 year, (14.9%, 21.9%, 41.3%, 21.8%) at 2 years, and (16.8%, 18.5%, 38.5%, 26.2%) at 3 years, respectively. A total of 383 patients were followed up for 3.8 (2.4-5.3) years. There was no difference between the 4 groups in terms of age, sex, race, type of transplant, donor age, donor final creatinine, KDPI score, PRA levels, pretransplant DSA, and type of induction. A negative correlation between 25-OH-vit D and i-PTH levels at 6 months was found to be statistically significant (P<0.0001). Lower 25-OH-vit D levels did not increase risk of graft loss. Patient survival, incidence of acute antibody or T cell mediated rejection, transplant glomerulopathy, development of de novo DSA, incidence of opportunistic viral (CMV and BKV) and fungal infections, malignancy, proteinuria and serum creatinine levels at 1,2 and 3 years post-transplant were found to be similar in the 4 groups.

Conclusions: 25-OH-vit D deficiency is common after kidney transplantation and has a negative correlation with post-transplant i-PTH levels. Low 6 months post renal transplant 25-OH-vit D levels are not associated with decreased allograft survival or function or with increased risk for opportunistic infections/malignancy.

TH-PO926

Validation of Body Composition by Dual-Energy X-Ray Absorptiometry and Bioelectrical Impedance Analysis in Renal Transplant Recipients Thomas J. Wilkinson,[3] Danielle Richler-Potts,[2] Jill Neale,[2] Alice C. Smith.[1] *[1]John Walls Renal Unit, Leicester General Hospital, Leicester, United Kingdom; [2]Leicester Kidney Exercise Team, Leicestershire, United Kingdom; [3]University of Leicester, Leicester, United Kingdom.*

Background: Renal transplant recipients (RTR) experience adverse body composition (BC) changes including obesity and muscle wasting. Aberrant BC is associated with poor physical function and graft recovery, and increased mortality. Measuring BC is vital to understanding health status and comorbidity prognosis. Whilst dual-energy x-ray absorptiometry (DXA) is seen as the gold-standard, bioelectrical impedance analysis (BIA) may be an accessible and cheaper alternative. Formulas using anthropometric data that estimate BC may provide an alternative where DXA or BIA is not available. However, due to fluid and metabolic disturbances as a result of renal impairment, these methods need to be validated. We aimed to assess the validity of BIA and the Hume formula against DXA in RTR.

Methods: 36 RTR (12 females; 52±12 years; eGFR 54±21ml/min/1.73m^2) were measured using DXA and BIA. Estimated lean mass (LM), fat mass (FM), and FM% were compared using regression and Bland-Altman plots. Using only age, sex, height and weight, BC was estimated using the Hume (1966) formula.

Results: BIA showed 'excellent' agreement against DXA (LM *r*=.98, FM .95, FM% .92). Bland-Altman bias showed that BIA tended to marginally overestimate LM (+2.1kg 95% limits of agreement -3.9-8.1), and underestimate FM (-2.1kg -8.6-4.3) and FM% (-3.8% -11.7-4.0). The Hume formula performed exceedingly well against DXA. Regression revealed 'good' to 'excellent' agreement for LM (*r*=.94), FM (.92), and FM% (.79). Like BIA, the Hume formula overestimated LM (+3.5kg -4.7-11.6) and underestimate FM% (-3.8% -11.7-4.0). Remarkably, FM from the Hume was nearly identical to DXA.

Conclusions: Compared to DXA, BIA is a valid and accurate measure of BC. Interestingly, BC (in particular, FM) can be accurately estimated using just age, sex, height and weight. Due to its ease, the Hume formula may provide another method using routinely collected data. As unfavourable BC is associated with adverse outcomes in RTR, it should be routinely measured. In the absence of DXA, BIA or the Hume formula are valid alternatives to estimate BC. Research should investigate the sensitivity of these methods following interventions.

Funding: Private Foundation Support

TH-PO927

Restless Legs Syndrome (RLS): An Unresolved Uremic Disorder after Successful Renal Transplantation (TXR) Secundino Cigarran,[2] Jesus Calvino,[3] Lourdes Gonzalez tabares,[3] Monica Guijarro,[4] Nicolas Menendez,[2] Carmen R. Cobelo casas,[3] Beatriz Millan,[3] Ana maria Sanjurjo amado,[2] Sonia Cillero,[3] Juan Latorre,[2] maria-jesus Sobrido.[1] *[1]IDIS. Sergas, Santiago Compostela, Spain; [2]Nephrology, Eoxi Cervo-Lugo-Monforte, Burela, Spain; [3]Nephrology, Eoxi Cervo-Lugo-Monforte, Lugo, Spain; [4]Neurology, Eoxi Cervo-Lugo-Monforte, Lugo, Spain.*

Background: RLS is a common disorder of uremia that may improve after TXR. However, RLS frequency might not be as low as expected as some uremic disturbances related with RLS may continue even after a successful graft. The **aim** of this study was to assess the prevalence and related conditions for RLS in TXR.

Methods: A validated questionnaire for RLS study group diagnostic criteria was self-administered by 129 TXR, 82 men and 47 women, aged 57 ± 12.8 years followed in the nephrology clinic for more than one year and with stable renal function (creatinine 1.5 ± 0.54 mg/dL). Patients classified as probable RLS according to the questionnaire underwent a systematic neurological examination in order to exclude RLS mimics.

Results: The frequency of probable RLS according to the questionnaire results was 29.5% (18 men and 20 women). After thorough neurological examination, the diagnosis of RLS was confirmed in 18 patients providing an overall definitive RLS frequency of 14.5% (above the average prevalence reported for the general population). Therefore, RLS diagnosis was established for six men (7.5%) and 12 women (27. 3%). These results rendered a positive predictive value for the self-administered questionnaire remarkably higher for women (60%) than for men (33%) pinpointing a higher rate of RLS mimics among men. Besides gender differences, confirmed RLS cases showed no differences regarding age, diabetes, comorbid disorders, BMI, anticalcineurin therapy, renal function, anemia and time from transplantation. Neither blood pressure nor number of antihypertensive drugs was statistically different though RAAS blockade was significantly less frequent among the confirmed RLS cases (22.2% versus 47.2%). Because of the clear-cut preponderance of women, we performed a separate analysis for females. A poorer renal function estimated by CKD-EPI (52 ± 17.5 vs 42 ± 13.9 ml/min) and a lower phosphate tubular reabsorption rate (75 ± 10.5 vs 65 ± 9.2) characterized women with RLS.

Conclusions: RLS prevalence after transplantation (14.5%) remains high. This condition is twice more prevalent for females. Contribution of RAAS, graft function impairment and phosphate overload for this remarkable prevalence requires further investigation.

Funding: Other NIH Support - SERGAS

TH-PO928

Chymase and Neprilysin: Key Regulators of the Renin-Angiotensin System (RAS) in Kidney Allografts Johannes J. Kovarik,[2,5] Christopher Kaltenecker,[2] Chantal M. Kopecky,[3] Oliver Domenig,[6] Marlies Antlanger,[2] Johannes Werzowa,[2] Farsad A. Eskandary,[1] Renate Kain,[2] Marko Poglitsch,[6] Georg Bohmig,[1] Marcus Saemann.[4] *[1]Medical University Vienna, Vienna, Austria; [2]Medical University of Vienna, Vienna, Austria; [3]University of New South Wales, Sydney, NSW, Australia; [4]Wilhelminen Hospital, Vienna, Austria; [5]Division of Clinical Pharmacology, Vanderbilt University, Nashville, TN; [6]Attoquant Diagnostics, Vienna, Austria.*

Background: Angiotensin-converting enzyme inhibitors (ACEis) are well established to be beneficial in patients with heart failure and chronic kidney disease (CKD). Their role after kidney transplantation (KTx), however, remains ambiguous, and the effects of ACEis on plasma and intrarenal metabolites of the 'classical' and 'alternative' renin-angiotensin-system (RAS) in KTx recipients have not yet been studied.

Methods: This prospective study, which was designed to investigate allograft-specific RAS metabolism, included 48 kidney transplant recipients subjected to allograft biopsy for graft dysfunction, progression of proteinuria, and/or DSA detection early (0-24 months; n=14), intermediate (24-144 months; n=18) or late post-KTx (>144 months; n=16).

Results: Patients on ACEi therapy (n=24) had lower plasma levels of angiotensin (Ang) II (p<0.01), but higher levels of Ang I (p<0.05) and Ang-(1-7) (p<0.01) than patients without RAS blockade (n=24). Mass spectrometry-based renal biopsy analysis displayed a 2.8-fold increase in renal Ang II formation, with a stepwise increase from the early to the late biopsy group (p<0.005), paralleled by enhanced chymase activity (early group: 34±29%; late: 54±32%, p<0.005). Renal Ang-(1-7) formation via neprilysin (NEP) was dominant (59±13%) over Ang II-mediated Ang-(1-7) formation (15±10%).

Conclusions: Our study reveals a profound tissue-specific distortion of the RAS within renal allografts in a time-dependent fashion, with chymase and neprilysin being the predominant regulators of the RAS in kidney allografts. While the clinical significance

of these results remains to be determined, a conspicuous role of chymase and neprilysin determining allograft survival may be hypothesized.

TH-PO929

Cardiovascular Risk Prediction in Renal Transplant: Post-Hoc FAVORIT Trial Analyses Theresa I. Shireman,[2] Basma O. Merhi,[1] Jessica A. Ogarek,[2] Andrew Bostom.[3] *[1]Nephrology, Rhode Island Hospital, East Greenwich, RI; [2]Center for Gerontology and Health Care Research, Brown University, Providence, RI; [3]Memorial Hospital of Rhode Island, Chepachet, RI.*

Background: Cardiovascular disease (CVD) is the leading cause of mortality and kidney graft failure in renal transplant recipients (KTR), but predictive risk algorithms consistently underestimate the incidence of arteriosclerotic outcomes.

Methods: We conducted a secondary analysis of data from the Folic Acid for Vascular Outcome Reduction in Transplantation (FAVORIT) randomized clinical trial. Measures included traditional CVD risk factors along with an expanded list of variables clinically important for KTRs, such as baseline phosphorus, cholesterol (HDL, LDL, remnant), triglycerides, graft vintage, donor type, glomerular filtration rate (eGFR), albumin-to-creatinine ratio (ACR), and diastolic (DBP) and systolic blood pressure (SBP). The cohort was split into training (2/3) and validation (1/3) samples after excluding individuals with pre-existing CVD. After deriving the most parsimonious risk calculator for the clinically adjudicated CV endpoint (CVE) in the training sample, we then applied the risk score to the validation sample and assessed model fit with area under the curve (c-statistic). Secondary outcomes, all-cause mortality (ACM) and graft failure, were also modeled using the CV risk score.

Results: From the training sample (n=1,892), key variables associated with CVD endpoint were age, smoking status, diabetes, living donor, eGFR ≥ 45, ln(ACR), DBP (<70) and SBP (>140). Combined with race and gender, the c-statistics for the training model was 0.754 for CVD endpoint, 0.762 for all-cause mortality, and 0.83 for graft failure. The model results from the validation sample generated c-statistics of 0.666 (CVE), 0.682 (ACM), and 0.643 (graft failure).

Conclusions: Important kidney transplant related risk factors (donor type, eGFR, and ACR) add significantly to cardiovascular risk prediction that include more typical measures. Further testing in other cohorts is needed to validate our findings and strengthen the model.

Funding: NIDDK Support, Private Foundation Support

TH-PO930

Hospital Readmissions in Kidney Transplant Recipients with Peripheral Vascular Disease Michelle L. Lubetzky,[3] Layla Kamal,[4] Maria Ajaimy,[4] Puneet Bedi,[1] Enver Akalin.[2] *[1]Brookdale University Hospital Medical Center, Brooklyn, NY; [2]Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY; [3]Medicine, Montefiore Medical Center, New York, NY; [4]Montefiore Medical Center, Bronx, NY.*

Background: The benefits of kidney transplantation (KTx) in diabetic patients with peripheral vascular disease (PVD) are unclear. While patients may have improved survival compared to dialysis, the burden of care post KTx has not been assessed.

Methods: We performed a review of diabetic patients with and without PVD transplanted from January 2012 to June 30, 2015. Data on readmissions, re-operations and length of stay was collected. Patient and graft survival was assessed.

Results: Of 203 diabetic patients reviewed 56 (27.6%) had PVD and 147 no PVD. There was no difference in age, sex, race, or type of KTx between the two groups. At a median of 3.14 years follow up (range 30, 1947) there was no difference in 30 or 90 day readmissions between the groups, however significantly more PVD patients were admitted at 1 year (p=0.03), Figure 1. Additionally, PVD patients spent significantly more time in hospital at 1 year (p=0.03). More patients with PVD had re-operations at 90 days and 1 year (p<0.01, p<0.01). Overall graft survival was worse in diabetic patients with PVD although this was not significant (93.2% versus 85.7% p=0.1). Patients with PVD who were re-admitted had significantly worse graft survival than patients with PVD who were not readmitted (100% vs 78.9% p=0.04, Figure 2).

Conclusions: Diabetic patients with PVD have worse graft survival than those without PVD and utilize more resources after KTx with significantly longer length of stays and more re-operations. Readmission in KTx patients with PVD portends poor graft survival.

Table 1

	NO PVD	PVD	P value
Time to first readmission (days, mean±SD)	192±272	217±268	0.59
30-day readmission (%)	33.3%	26.8%	0.40
90-day readmission (%)	37.4 %	35.7%	0.87
1-year readmission (%)	**61.9%**	**78.6%**	**0.03**
Total length of stay at 1 year			
0 days	38.9%	32.1%	0.51
1-9 days	34.7%	23.2%	0.13
10 or more days	**27.9%**	**44.6%**	**0.03**
Readmission cause			
Graft complications	14.3%	14.2%	1.0
Infection	33.9%	**50% (of which 23.5% PVD related)**	**0.09**
Re-operation at 1 year (%)	**8.7% (11/12 were graft related)**	**28.6% (5 graft related, 6 PVD related, 5 other operations)**	**0.0004**
90 day re-operation (%)	**4.7%**	**12.5% (4 graft related, 3 non graft related)**	**0.008**
1 year acute rejection (%)	8.1%	10.7%	0.56
Graft survival (%)	93.2%	85.7%	0.10
Patient survival (%)	93.9%	92.9%	0.76

Patient and Graft Survival in Patient with a History of Readmissions

	No PVD		
	No 1 year readmission	1-year readmission	P value
Last creatinine	**1.30±0.41**	**1.58±0.73**	**0.01**
Graft Survival	**100%**	**87.9%**	**0.07**
Patient Survival	96.4%	92.3%	0.44
	PVD		
Last creatinine	1.48±0.42	1.61±0.80	0.52
Graft Survival	**100%**	**78.9%**	**0.04**
Patient survival	100%	89.5%	0.29

TH-PO931

De Novo Heart Failure after Kidney Transplantation: Trends in Incidence and Outcomes Colin R. Lenihan,[3] Sai Liu,[2] Anita Deswal,[1] Maria E. Montez-Rath,[3] Wolfgang C. Winkelmayer.[1] *[1]Baylor College of Medicine, Houston, TX; [2]Stanford University, Santa Clara, CA; [3]Stanford University School of Medicine, Palo Alto, CA.*

Background: Older US data indicate that heart failure (HF) occurs in 18% of patients in the 3-years following kidney transplant. Herein, we sought to explore secular trends in the incidence of de novo post-kidney transplant HF and its associated mortality.

Methods: We identified adult patients who underwent their first kidney transplant in the US between 1998 and 2010. We required that patients had ≥6 months of continuous Medicare parts A and B coverage prior to transplant. HF diagnosis was ascertained using ICD-9 diagnosis codes. Patients with a diagnosis of HF prior to transplant were excluded from the cohort. Cox models were employed to examine secular trends in 1) de novo post-kidney transplant HF and 2) mortality following de novo post-transplant HF diagnosis. Calendar year of transplant was the primary exposure of interest.

Results: 48,771 patients met the study inclusion criteria. Age at transplant, BMI, dialysis vintage and the prevalence of several baseline comorbidities increased between 1998 and 2010. 7269 patients developed HF within 3 years of kidney transplantation with a median time to HF of 0.76 years and an incidence rate of 6.2 per 100 person-years. When adjusted for demographic, comorbid, and transplant-related characteristics the incidence of de novo post-transplant HF was 31% lower for patients transplanted in the year 2010 compared to those transplanted in 1998 (HR 0.69; CI 0.60-0.79; **Figure 1**). However, we observed no temporal trend in adjusted mortality following de novo post-transplant HF diagnosis.

Conclusions: When adjusted for demographic and clinical characteristics, the incidence of de novo post-kidney transplant heart failure has declined significantly during the period from 1998 to 2010, with no apparent change in subsequent mortality.

Funding: NIDDK Support, Private Foundation Support

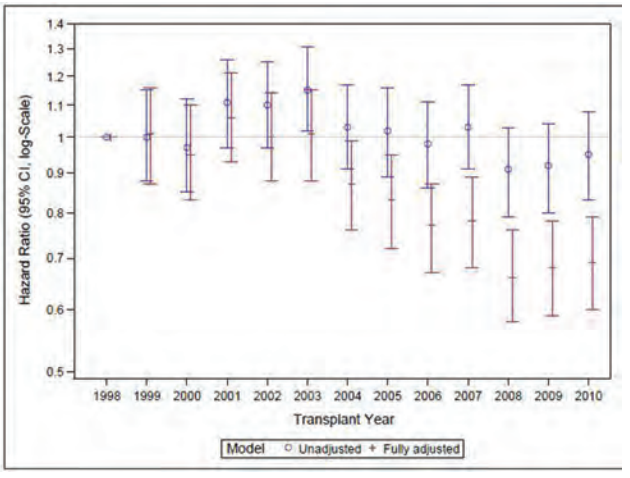


Figure 1. Unadjusted and adjusted relative hazards of *de novo* post-kidney transplant heart failure by calendar year of transplant

TH-PO932

NT-proBNP as a Predictor of Major Cardiac Events in Renal Recipient Patients Carola-Ellen Kleine,[3] Roxana Werberich,[4] Louisa Werberich,[5] Dominik Boes,[6] Felix Hundt,[2] Rainer Woitas.[1] *[1]Nephrology, University Hospital of Bonn, Bonn, Germany; [2]Nephrology, University Hospital of Bonn, Bonn, Germany; [3]Nephrology, University Hospital of Bonn, Bonn, Germany; [4]Nephrology, University Hospital of Bonn, Bonn, Germany; [5]Nephrology, University Hospital of Bonn, Bonn, Germany; [6]Nephrology, University Hospital of Bonn, Bonn, Germany.*

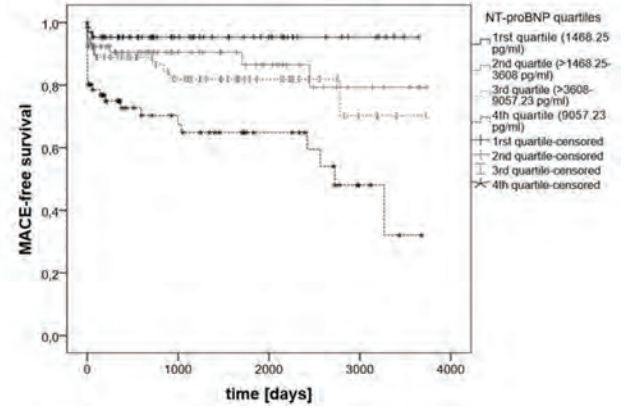
Background: Patients on renal replacement therapy have an increased cardiovascular risk. NT-proBNP is an established marker for cardiovascular risk and mortality in the general population. In a small cohort of kidney transplant patient NT-proBNP was significantly higher in patients suffering from major cardiac events (MACE). We aimed to further investigate NT-proBNP as a predictor of MACE in renal transplantation.

Methods: The study cohort consisted of 264 patients that were kidney transplanted between 01/2005-05/2015. MACE was defined as myocardial infarction (ST-segment elevation (STEMI) or non ST-segment elevation (NSTEMI)), stroke, intervention requiring coronary artery disease (CAD) or cardiovascular death. Blood samples were drawn prior to the kidney transplantation. Mann-Whitney *U* tests, multivariate Cox regression and Kaplan-Meier survival analysis were performed. Before, age, NT-proBNP, creatinine and C-reactive protein (CRP) were logarithmic transformed.

Results: The cohort consisted of 60.6% male patients, median age was 54 years. Mean observation time lasted for 3.2 years. 17.4 % of the patients suffered of MACE: 74% NSTEMI, each 11% STEMI and CAD and 2% cardiovascular death. Recipients with preoperative NT-proBNP greater 9057.3 pg/ml (4th quartile) had a significant greater risk to develop MACE (p<0.05) (Figure 1). After adjustment to age, sex, diabetes mellitus, preexisting CAD, hypertriglyceridemia, cholesterolemia, peripheral occlusive disease, atrial fibrillation, arterial hypertension, creatinine and CRP, NT-proBNP remained an independent risk factor (HR 3.81, 95% CI 2.04-7.12, p=0.000).

Conclusions: In our cohort of renal transplant recipients NT-proBNP proved to be an independent predictor of MACE. NT-proBNP level at the time of transplantation may identify patients at greater risk for cardiovascular complications.

Figure 1. MACE-free survival according to NT-proBNP quartiles



TH-PO933

Early Initiation of ACE Inhibitors in the Post Renal Transplant Period: A Study from a State Run Tertiary Care Centre Umesh L. *NEPHROLOGY, INSTITUTE OF NEPHROUROLGY, BANGALORE, India.*

Background: Angiotensin converting enzyme inhibitors (ACEI) comprise drug class, which inhibit the effects of angiotensin II by blocking the synthesis of same. Angiotensin converting enzyme inhibitors (ACEI) are well documented to be potent anti-hypertensives with renoprotective effects but are grossly underutilized in renal transplant recipients. However, these drugs have been reported to cause elevated potassium and creatinine levels in some renal transplant patients. There have been no reports of prospective studies of ACEI in renal transplant patients in the early posttransplant period. The purpose of this study is to assess the safety of an ACEI class, when started in early posttransplant period.

Methods: This study is a Prospective observational study. We reviewed 78 kidney transplant patients during the period of January 2012 to march 2017 at our institution. 64 patients were initiated on ACEI therapy within a month of post- transplant. Patients were considered to be enrolled when they met the following criteria: Declining serum creatinine, improving urine output and serum potassium < 5.5 mEq/L. Exclusion criteria: anaphylaxis to ACEI, use of ACE or ARB for treatment of posttransplant erythrocytosis and serum potassium >5.5 mEq/L.

Results: 64 Patients were studied, 53(83%) were male and 11(17%) were females. Mean age was 32±15 years (12-56). Minimum duration of follow up was 6 months. For each patient haemoglobin, serum creatinine and potassium levels were analyzed at the beginning of ACE inhibitors and at the end of the first, third, sixth month. Average potassium levels, hemoglobin levels did not differ significantly between groups and were in normal clinical ranges. While incidence of graft failure did not differ, death with functioning graft was lower in the ACEI group.

Conclusions: ACEI can be used successfully in post-renal transplant with beneficial long term impact on renal function. There is need for further randomized controlled studies to see the effect of ACEI on Graft function and its survival.

Funding: Government Support - Non-U.S.

TH-PO934

Changes in Renal Function in Patients Bridged to Heart Transplantation with a Continuous-Flow Left Ventricular Assist Device (LVAD): Analysis of 2480 Patients Nissreen Elfadawy,[1] Sadeer Al-Kindi,[2] Anne M. Huml,[1] Guilherme H. Oliveira.[2] *[1]Division of Nephrology, Department of Medicine, University Hospitals Cleveland Medical Center, Cleveland, OH; [2]Harrington Heart and Vascular Institute, University Hospitals Cleveland Medical Center, Cleveland, OH.*

Background: Left ventricular assist devices (LVADs) have become an established option for patients with end-stage heart failure. The impact of LVAD on renal function is not widely studied and remain controversial. **Objectives:** The aim of this study was to determine the impact of LVAD implantation on renal function in patients with end-stage heart failure and discover risk factors associated with renal dysfunction in these patients

Methods: We used the United Network Of Organ Sharing registry (UNOS) to identify adult patients who are bridged to heart transplantation with HeartMate II or Heartware continuous-flow LVADs from 2007-2015. We excluded patient on dialysis, intra-aortic balloon pumps, extra-corporeal membrane oxygenation, or inotropes. Calculated glomerular filtration rate (GFR) using CKD-EPI formula was assessed at listing and prior to heart transplantation. Significant change in GFR at time of transplantation was defined ≥10 ml/min/1.73 m2 change from baseline. Predictors for worsening in GFR were examined by multivariable logistic regression model.

Results: A total of 2480 patients were included, mean age 54±12 years, 80% were male, 36% were status 1A, and 45% had ischemic cardiomyopathy. Mean time on wait-list was 192 days. Mean baseline GFR was 76±26, mean GFR at time of HTx was 72±26 (p<0.001). Overall, 31% (n=788) showed significant worsening in GFR. Risk factors for worsening GFR were older age (1.03 [1.02-1.04] per year, P<0.001), longer time on wait-list (1.001 [1.000-1.001] per day, P=0.001), higher PCWP (1.02 [1.01-1.03] per 1 mmHg, P<0.001), and higher baseline GFR (1.04 [1.03-1.04] per 1 ml/min/1.73 m2, P<0.001)

Conclusions: Approximately one third of candidates for heart transplantation experience significant GFR worsening after LVAD implantation. Older age, longer wait time, and higher baseline GFR are significant risk factors

TH-PO935

The Change in Carotid Arterial Inflammation in De Novo Renal Transplant Recipients as Assessed by 18F-FDG PET/CT Hye Eun Yoon,[1,3] Yaeni Kim,[1,3] Chul Woo Yang,[2,3] Yong-Soo Kim,[2,3] Seok Joon Shin.[1,3] *[1]Incheon St. Mary's Hospital, The Catholic University of Korea, Incheon, INCHEON, Republic of Korea; [2]Seoul St. Mary's Hospital, Seoul, Republic of Korea; [3]The Catholic University of Korea College of Medicine, Seoul, Republic of Korea.*

Background: Chronic kidney disease (CKD) is associated with an increased risk of cardiovascular disease, and characterized by increased inflammation. Inflammatory activity of the arterial wall can be assessed by measuring ^{18}F-fluorodeoxyglucose (^{18}F-FDG) uptake with positron emission tomography computed tomography (PET/CT). Data on change in arterial inflammation in CKD patients after renal transplantation are not available to date. This study investigated the change in the inflammatory activity in carotid artery after renal transplantation in CKD patients.

Methods: We assessed ^{18}F-FDG uptake, quantified as target-to-background ratio (TBR), in the right and left carotid arterial walls in 10 CKD patients. ^{18}F-FDG PET/CT was performed before transplantation and at post-transplantation 4 months. TBR was evaluated in the whole carotid artery (WH) and most diseased segment (MDS). Most diseased segment (MDS) was defined as the 1.5-cm arterial segment, centered on the slice of artery demonstrating the highest ^{18}F-FDG uptake at baseline. WH-TBRmax was calculated as the mean of maximum TBR values for all of the whole carotid artery segments, and WH-TBRmean was calculated as the mean of averaged TBR values of the whole carotid artery segments. MDS-TBRmax was calculated as the mean of maximum TBR values derived from 3 contiguous axial segments of the MDS, and MDS-TBRmean was calculated as the mean of averaged TBR values of the MDS segment.

Results: Eight patients showed a reduction in right Whole-TBRmax and WH-TBRmean, and left MDS-TBRmean, WH-TBRmax, and WH-TBRmean. Seven patients showed a reduction in right MDS-TBRmax and MDS-TBRmean, and left MDS-TBRmax. There was a tendency of reduction in right WH-TBRmax MDS-TBRmax, and MDS-TBRmean (% reduction [95% CI]: -6.50% [-12.81, 1.54]; -4.06% [-13.42, 9.38]; -4.47% [-13.64, 7.29]) and in left WH-TBRmax, WH-TBRmean, MDS-TBRmax, and MDS-TBRmean, (% reduction [95% CI]: -6.13% [-15.17, 8.32]; -8.37% [-17.62, 6.56]; -6.14% [-14.53, 7.01]; -7.29% [-17.91, 4.18]). The right Whole-TBRmean was significantly reduced from baseline (% reduction [95% CI]: -5.74% [-15.37, -0.02], P = 0.047).

Conclusions: The ^{18}F-FDG uptake of WH and MDS were reduced after renal transplantation. Renal transplantation may confer an anti-inflammatory effect on carotid atherosclerosis in CKD patients.

Funding: Government Support - Non-U.S.

TH-PO936

Extracellular Fluid Excess Is Significantly Associated with Coronary Artery Calcification in Kidney Transplant Recipients Seohyun Park,[2] Arum Choi,[1] Heebyung Koh,[2] Jaeyeol Kwon,[2] Tae-Hyun Yoo.[2] *[1]Department of Internal Medicine, College of Medicine, Severance Biomedical Science Institute, Brain Korea 23 PLUS, Yonsei University, Seoul, Republic of Korea; [2]Department of Internal Medicin, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea.*

Background: Coronary artery calcification (CAC) is associated with increased mortality in CKD patients and does not regress after kidney transplantation. Extracellular fluid excess measured by bio-impedance analysis (BIA) is also associated with adverse clinical outcomes in kidney transplant recipients (KTR). Present study is aimed to identify the relationship between extracellular volume status and CAC in KTR.

Methods: We evaluated 123 KTR of CMERC-HI (Cardiovascular and Metabolic Disease Etiology Research Center-High Risk, NCT02003781), a prospective observational cohort study of high risk patients with cardiovascular disease. Extracellular volume status was assessed by BIA and extracellular fluid excess (EFE) was defined if the ratio of extracellular water and total body water (ECW/TBW) was more than 0.390. CAC was measured by multi-detector CT and CAC ≥400 was considered as a calcified coronary artery.

Results: In this study, fifty-four (43.9%) patients showed excess with body fluid. Compared with non-EFE group, EFE group was older and had a longer time on KT, a longer duration of previous dialysis, and a lower estimated glomerular filtration rate (eGFR). The CACS and the proportion of calcified coronary artery were significantly higher in the EFE group. In logistic regression analysis, EFE was significantly associated with calcified coronary artery. Moreover, EFE was found to be independently associated with calcified coronary artery after adjustment for multiple confounders (Odds ratio; 4.327, 95% confidence interval; 1.309 – 14.298, P = 0.016).

Conclusions: Our study demonstrated that extracellular volume excess was significantly associated with CAC in KTR. Present study suggests that EFE might be a risk factor for cardiovascular disease in KTR.

TH-PO937

Hypertension, Renal Function, and Histologic Changes in Living Kidney Transplant Recipients from Hypertensive Donors Thomas Dienemann,[4] Jana Schellenberg,[2] Kerstin U. Amann,[5] Christoph Daniel,[3] Katharina M. Heller.[1] *[1]Friedrich - Alexander University Erlangen - N?rnberg, Erlangen, Germany; [2]Uniklinikum Erlangen, Nürnberg, Germany; [3]University Erlangen-Nürnberg, Erlangen, Germany; [4]Nephrology and Hypertension, University of Erlangen, Erlangen, Germany; [5]Department of Pathology, University of Erlangen, Erlangen, Germany.*

Background: Due to the ever-increasing organ shortage, centers increasingly accept living kidney donors with preexisting hypertension despite concerns over donor safety for over two decades. Data on outcomes in recipients of such kidneys of hypertensive living donors is very limited. In the present study, we examined we examined whether use of hypertensive living kidney donors associates with kidney function, blood pressure and histologic changes at transplantation and one year after transplantation in living kidney transplant recipients

Methods: Retrospective single center analysis of 182 living kidney transplant recipients (age>18; transplant date 2008-2015). Hypertension in donors was defined as ABPM above 135/85 or ≥1 BP medication. Recipients eGFR was measured at 1 year using the MDRD equation. All renal biopsies were examined by a blinded pathologist using the recently advocated total renal chronicity score (TRCS). Logistic regression models adjusted for multiple potential confounders were used to examine the relationship of hypertensive donor on blood pressure and renal function in recipients.

Results: One year follow up was complete in 180 patients including a biopsy at transplant, in 131 patients a protocol biopsy 12 months after transplant was also available. 138 recipients had normotensive donors (dNT), 42 recipients had hypertensive donors (dHT). There were no differences in age, sex, BMI, and eGFR between recipients from dNT and dHT. Average systolic and diastolic blood pressure in dHT was significantly higher (131/76 vs 119/72 mmHg in dNT, p < 0.001 for both). Adjusted for multiple confounders there was no difference in blood pressure, number of antihypertensive drugs, and eGFR in recipients at 1 year. The TRCS showed no difference at time of transplant and at 1 year after transplantation

Conclusions: In our cohort, recipients of a living kidney transplant from hypertensive donors showed no differences in blood pressure, renal function or the TRCS after a 1 year follow up. Prudent selection in terms of accepting hypertensive donors remains mandatory. However longer follow up data is needed to assess potential long term effects which might affect the commonly superior results of living kidney transplantation in recipients of such kidneys.

TH-PO938

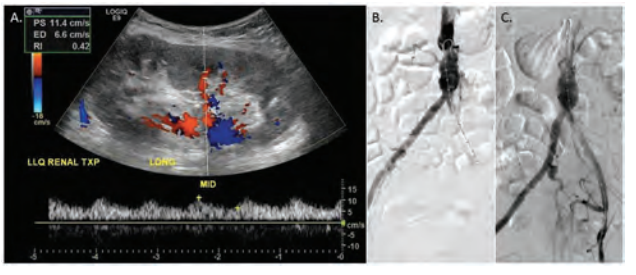
Allograft Rescued from Pseudo Transplant Renal Artery Stenosis Gunjan Garg, Laura H. Mariani, Milagros D. Samaniego-Picota. *University of Michigan, Ann Arbor, MI.*

Background: Transplant renal artery stenosis (TRAS) is a common vascular complication typically occurring 3-24mos post-transplant and may be due to surgical technique or size discrepancy between donor and recipient arteries. As the transplant population ages, there is increasing recognition of pseudo-transplant renal artery stenosis, in which vascular disease proximal to the arterial anastomosis results in graft failure. Here we present a rare case of late acute allograft failure secondary to pseudo-TRAS.

Methods: A 53 yo woman with diabetes, hypertension, smoking, without known peripheral vascular disease, who underwent a living unrelated kidney transplant 5yrs ago for PKD, presented with 4 days of graft tenderness and decreased urine output. Physical exam showed BP of 183/94 and tenderness over the left lower quadrant allograft. UA was negative for blood, protein or leukocytes. Serum Creatinine was 7.1 mg/dL (baseline 1.2 mg/dL). She reported compliance with immunosuppressants. A transplant ultrasound with Doppler showed 11.4cm kidney without hydronephrosis, although a parvus tardus waveform (Fig) was seen in the transplant renal artery with low resistive indices. A CO2 angiogram showed complete left common iliac (CIA) and proximal external iliac artery (EIA) occlusion with almost no flow to the transplant renal artery. Left CIA was stented with improved flow to the graft without any pressure gradient. Within 72 hrs, creatinine was 1.8 mg/dL and 1.2 mg/dL in 2 wks.

Results:

Conclusions: TRAS is a potentially reversible cause of graft dysfunction in early post transplant period, but patients with CVD risk factors can develop pseudo-TRAS in the iliac vessels as a late complication. Early detection can prevent complete graft loss. Transplant renal artery Doppler can show parvus tardus waveform, prolonged systolic acceleration with small amplitudes and blunting of the systolic peak suggesting poor arterial inflow to the kidney. Prompt intervention within 24 hrs of initial presentation, in our case, successfully rescued the allograft.



A.Parvus tardus waveform B.Aortoiliac angiogram showing complete occlusion of left CIA C.Post intervention angiogram

TH-PO939

Sodium/Glucose Cotransporter 2 (SGLT2) Inhibitor for Diabetic Kidney Transplant (KT) Patients Hyuk yong Kwon, Jin M. Kong. *Nephrology, BHS-Hanseo hospital, Busan, Republic of Korea.*

Background: SGLT2 inhibitor is a newly introduced hypoglycemic drug that inhibits glucose reabsorption at proximal tubule. A recent RCT in diabetic CKD patients showed a long-term renoprotective effect, by a decrease in hyperfiltration as a consequence of increased distal sodium delivery with tubuloglomerular feedback. This result seems relevant to KT patients where reduced nephron mass may suffer from hyperfiltration that jeopardizes long term graft survival. But the experience of this drug in KT patients is limited and there are concerns of lower urinary tract infection and acute graft dysfunction due to volume depletion by osmotic diuresis as well as reduction in intraglomerular pressure. The aim of this study is to evaluate the safety and efficacy of SGLT2 inhibitor in KT patients.

Methods: Twenty-five KT patients were treated with dapagliflozin 5mg/d. Three patients had type 1 DM and 7 had NODAT. Sixteen patients were on insulin with or without oral agents. Median posttransplant months were 72(9-262). Diuretics were stopped before the initiation of study drug.

Results: Baseline HbA1c was 7.9±1.3%, decreased significantly at 3(7.4±1.1%, p=0.01) and 6(7.4±1.0%) months(M). Body weight decreased significantly from 72.2±22.1 to 68.1±22.0(p=0.001)kg at 12M. Two patients could stop insulin and another 4 patients could reduce ≥20% dose of insulin. eGFR did not change significantly (71.1±20.1ml/min at baseline, 71.5±25.8 at 12M). Clinically apparent acute graft dysfunction was not observed. Office blood pressure also was not changed significantly but 10 of 24 patients had a decrease in number and/or dose of anti-hypertensives. No significant change in urine albumin-creatinine ratio at 1 year. Six patients discontinued study drug due to acute cystitis in 2, weight loss in 1 and lack of efficacy in 3.

Conclusions: SGLT2 inhibitor seems to be beneficial in glucose control of KT patients, with acceptable safety profile. Further studies are clearly needed to determine the possible long-term renoprotective effect in this patient population.

TH-PO940

Diabetes Weighted Genetic Risk Scores and Prediction of New Onset Diabetes after Kidney Transplantation Kelly A. Birdwell,[1] M. Lee Sanders,[2] Digna R. Velez edwards,[1] Talat Alp Ikizler,[1] Ayush Giri.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]University of Iowa Hospitals and Clinics, Iowa City, IA.*

Background: New onset diabetes after transplantation (NODAT) is associated with increased cardiovascular events and mortality, but the underlying pathogenesis is not well understood. We examined the genetics of NODAT in kidney transplant recipients using genetic risk scores constructed from previously identified single nucleotide polymorphisms (SNPs) for type 1 and type 2 diabetes in the general population to observe if NODAT overlaps with these disorders genetically.

Methods: Our study cohort included 54 cases and 248 controls, all European American, identified through our prior genome-wide association study completed using Illumina OMNI1 or OMNI5 platforms. Genetic risk scores (GRS) for type 1 and type 2 diabetes were created using SNPs published in the literature. GRS are used as a tool to summarize risk-associated SNPs across the genome to improve prediction of polygenic diseases. For type 1 diabetes, 3 GRS were created: 1) Full, with 25 type 1 SNPs and 3 HLA SNPs 2) Non-HLA, with 25 type 1 SNPs 3) HLA-only, with 3 HLA SNPs. For type 2 diabetes, 65 SNPs were used. All SNPs were from independent loci. Both non-weighted and weighted GRS were created. Logistic regression models were run using NODAT as the dependent variable and GRS as independent variables, with and without adjustment for covariates (sex, BMI, steroid use, and CMV infection).

Results: The cohort mean age was 42.4 years and 59.9% female. Weighted type 1 GRS, both Full and HLA-only, were significantly associated with NODAT in unadjusted and adjusted analyses. The odds of having NODAT was 1.25 times higher (OR 1.25, 95% CI 1.03-1.53, p = 0.03) in the weighted adjusted Full model, and similarly was 1.25 times higher (OR 1.25, 95% CI 1.01-1.534 p = 0.04) in the weighted adjusted HLA-only model, for each unit increase in weighted GRS score. Noteworthy associations were not observed using the type 1 Non-HLA GRS or the type 2 GRS.

Conclusions: Kidney transplant recipients with NODAT have genetic variants that are associated with those SNPs that predict type 1 diabetes but not type 2. This suggests the underlying pathogenesis might reflect more of a type 1 mechanism.

Funding: Other NIH Support - NIGMS, UL1TR000445 from the National Center for Advancing Translational Sciences

TH-PO941

Advanced Glycation End Products (AGEs) by Skin Autofluorescence (SAF) in Renal Transplant (TxR): Risk and Influence in Clinical Practice Secundino Cigarran,[1] Lourdes Gonzalez tabares,[2] Nicolas Menendez,[1] Juan Latorre,[1] Carmen R. Cobelo casas,[2] Beatriz Millan,[2] Nuria C. López,[1] Sonia Cillero,[2] Ana maria Sanjurjo amado,[1] Jesus Calvino.[2] *[1]Nephrology, Eoxi Cervo-Lugo-Monforte, Burela, Spain; [2]Nephrology, Eoxi Cervo-Lugo-Monforte, Lugo, Spain.*

Background: AGEs accumulation constitute a vascular pathogenic mechanism involved in aging, diabetes and chronic kidney disease (CKD) moreover of being a measure of cumulative metabolic stress. Despite removal of uremic toxins&AGEs after a succesful TxR, cardiovascular disease (CVD) remains the leading cause of mortality. Our aim was to evaluate AGEs by SAF in TxR and its relation with markers associated to CV risk.

Methods: 191 stable TxR were analyzed (38.7% women, aged 56±13.1 years). All were on CKD stages1-4 and > 12 months of transplantation. Variables assessed: diabetes, CVD history, subclinical atheromatosis by arm-ankle-index and allograft resistivity index, 24-h ABPM, anthropometric and nutritional markers (including dynamometry), biochemical (hemoglobin, albumin, transferrin, CKD-EPI, Ca, P, iPTH, vitamin D and C reactive protein). Urinalysis included ACR (mg/gr) and phosphorus tubular reabsortion (RTP,%). AGEs were measured by SAF. Vascular age was estimated by Koetsier formula (AFD-0.83/0.024) and estimated 10-years cardiovascular death risk by REGICOR formula.

Results: Mean SAF was 2.99±0.83 UA and estimated vascular age was 90±34.6 years (30 years above biological). After univariable analysis, SAF was higher in men (3.1±0.90 vs 2.8±0.67, p<.001), diabetic (3.2±0.86 vs 2.9±0.81, p<.001) and steroids use (3.1±0.91vs2.7±0.71 p<.001). A positive correlation with night SBP (r=0.240 p<.005), iPTH (r=0.210 p<.001), P (r=0.300 p<.005) and negative with hemoglobin (r=-0.310 p<.005), CKD-EPI (r=-0.350 p<.005) & RTP (r=-0.263 p<.005). Nutritional parameters&AGEs showed a negative correlation with albumin, transferrin, arm circumference & dynamometry (r=-0.200 p<.005). AGEs also showed correlation with subclinical vascular atheromatosis as well as with REGICOR scale (r=0.400 p<.001). After multivariate analysis significant variables were:age, male, steroid use, P and dynamometry.

Conclusions: SAF is a validated, economic, and non-invasive tool to assess cardiovascular risk in TxR.Besides age and male gender, our results suggest that P overload, steroid use and nutritional status are the main significant determinants that promote AGEs accumulation. Further longitudinal studies are required in order to confirm this hypothesis.

Funding: Other NIH Support - SERGAS

TH-PO942

The Impact of Hyperuricemia in Transplanted Kidney in Women Yasuyuki Nakada,[1] Izumi Yamamoto,[1] Haruki Katsumata,[1] Kohei Unagami,[2] Masayoshi Okumi,[2] Hideki Ishida,[2] Takashi Yokoo,[1] Kazunari Tanabe.[2] *[1]Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan; [2]Department of Urology, Tokyo Women's Medical University, Tokyo, Japan.*

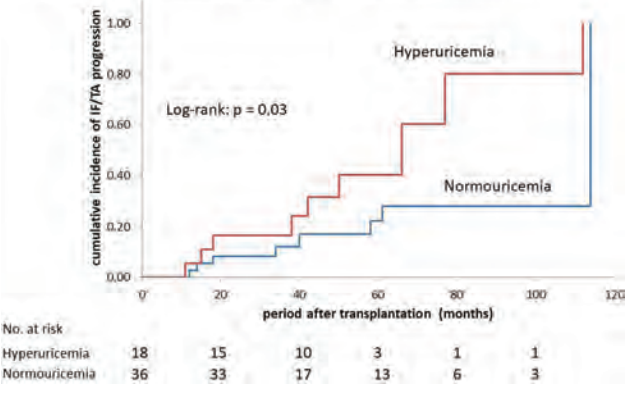
Background: The progression of arteriolar hyalinosis (AH) and interstitial fibrosis / tubular atrophy (IF/TA) is closely associated with graft failure in patients with kidney transplantation. Several clinical factors (aging, hypertension, diabetes, calcineurin inhibitor) influence this mechanism but the significance of hyperuricemia (HUA) was not fully understood. We here postulated that the HUA could influence AH and IF/TA progression in kidney allograft recipients.

Methods: We evaluated 126 recipients who received kidney transplants from January 2005 to December 2009 at the Department of Urology, Tokyo Women's Medical University. Patients with diabetes mellitus were excluded. AH and IF/TA progression were defined if Banff scores inceased more than one. HUA was defined as serum UA >7.0 mg/dL in males and >6.0 mg/dL in females. Survival analysis methods including Kaplan-Meier and Cox Proportional Hazard Model were used to evaluate the independent association of the UA burden over time (the average annual level of s-UA) with pathological progression, after adjustment for baseline covariates (age, gender, BMI, blood pressure, serum CNI concentration, baseline UA in serum).

Results: Hyperuricemic recipients were shown to have a higher cumulative progression of IF/TA (log-rank: $p = 0.01$) but not AH (log-rank: $p = 0.76$). HUA was found to be a significant predictor for the progression of IF/TA (HR: 1.71, p = 0.01). These trends were observed only in females (log-rank: $p = 0.03$) but not in males (log-rank: $p = 0.19$).

Conclusions: The impact of HUA on pathological deterioration is greater in females than males, suggesting the importance of more cautious management of HUA in females.

Figure. 1 The cumulative incidence of IF/TA progression in females



TH-PO943

Physical Frailty and Cognitive Change Among Kidney Transplant Recipients Nadia M. Chu,[1] Alden L. Gross,[1] Qianli Xue,[2] Karen J. Bandeen-roche,[1] Richey Sharrett,[2] Michelle C. Carlson,[1] Dorry L. Segev,[2] Mara McAdams-DeMarco.[2] *[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [2]Johns Hopkins University, Baltimore, MD.*

Background: With restoration of kidney function, kidney transplant (KT) recipients may experience preserved or improved cognitive function. However, KT recipients have a higher burden of frailty at the time of KT, and frail recipients may not experience this potential benefit. The goal of this prospective study was to assess post-KT cognitive trajectories by frailty status (12/2008 – 12/2016).

Methods: Participants completed a physical frailty exam (five Fried criteria) and global cognitive testing (3MS) at time of KT-admission, as well as at least one cognitive test during post-KT. We used a mixed effects model adjusted for follow-up time, age, sex, race, donor type, and 3MS score at time of KT with a random slope (time) and intercept (person) to describe multiple 3MS scores post-KT by frailty status.

Results: Of 665 KT recipients (mean age 52 years) followed for a mean of 2.2 years (3.7 visits), 15.2% were frail, and the mean 3MS score was 92.5 at time of KT. In the first month post-KT, non-frail recipients experienced a significantly greater rate of cognitive improvement (0.53 points-per-week, 95% CI: 0.33, 0.73), however there was no evidence

of such an improvement among frail recipients (0.20 points-per-week, 95% CI: -0.35, 0.75). Rates of cognitive change among non-frail KT recipients continued to increase 1-3 months post-KT, and plateaued thereafter through 1 year post-KT. Frail individuals did not significantly improve anytime during the year post-KT.

Conclusions: In conclusion, frailty is associated with mitigated improvement in global cognition post-KT. Frail recipients may benefit from interventions to improve cognitive function after KT.

Funding: NIDDK Support

Rates of Change in Global Cognition Overall and By Physical Frailty Status within Specified Time Intervals post-KT (95% Confidence Intervals) in 3MS points per week

	<= 4 weeks	4 - 12 weeks	12 - 24 weeks	24 - 52 weeks
Overall	0.48 (0.29, 0.68)*	0.26 (0.050, 0.46)*	-0.021 (-0.16, 0.12)	0.035 (-0.013, 0.082)
Non-Frail	0.53 (0.33, 0.73)*	0.25 (0.031, 0.47)*	-0.011 (-0.16, 0.14)	0.021 (-0.031, 0.073)
Frail	0.20 (-0.35, 0.75)	0.30 (-0.31, 0.91)	-0.085 (-0.49, 0.31)	0.11 (-0.0031, 0.22)

* Statistically significant at a cut-off p=0.05.

All models adjusted for baseline age (centered at 55), race, education, self-reported quality of life, donor type (live or dead), and the Charlson Comorbidity Index adapted for ESRD patients.

TH-PO944

High Hemoglobin Levels Maintain Graft Function in Japanese Kidney Transplant Recipients Makoto Tsujita. *Nagoya Daini Red Cross Hospital, Nagoya, Japan.*

Background: Post transplant anemia is an important factor for graft survival in kidney transplant recipients. But how we should manage hemoglobin (Hb) values for better graft survival in Japanese recipients, remains unknown.

Methods: This was an open-label, randomized controlled trial to demonstrate high Hb values on graft function. One hundred twenty six stable recipients were randomized into two groups - Hb normal group (12.5-13.5 g/dL, n=65) and Hb subnormal group (10.5-11.5 g/dL, n=61). Either Darbepoetin alfa or Epoetin beta were included in the study from January 2012 to March 2014 at Nagoya Daini Red Cross Hospital and Masuko Memorial Hospital. Primary endpoint was the difference between both groups rate of decline in kidney function.

Results: During the course of this study, 12 patients dropped out. At baseline, the mean age was 49.7 and 49.6 years old, eGFR was 35.4 and 35.9 ml/min/1.73m2, and Hb 11.3 and 11.2 g/dL in Hb normal group (n=59) and subnormal groups (n=55), respectively. After 24 months(M), the mean Hb was 12.6 and 11.2 g/dL(p<0.001), the eGFR was 34.8 and 32.7 ml/min/1.73m^2 (p=0.27). Figure1 showed a change of eGFR from baseline eGFR (ΔeGFR). From baseline to 24M, the eGFR decreased by a mean 0.1 and 3.7 ml/min/1.73m2(p=0.02). Patients who doubled their serum creatinine levels and reached end stage renal disease were not found. Also no cardiovascular event and acute rejection occurred in both groups.

Conclusions: This study shows that high Hb values might be more impactful on graft function in Japanese kidney transplant recipients.

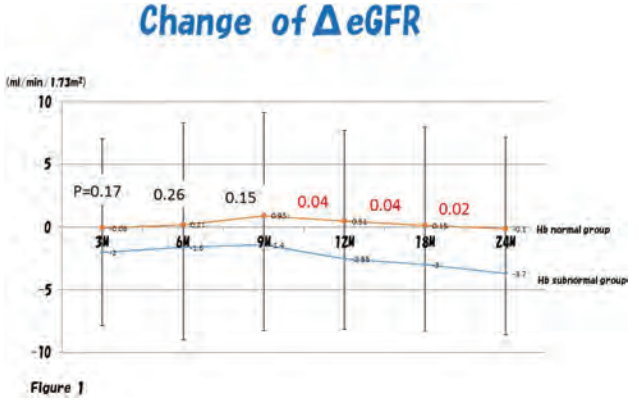


Figure 1

TH-PO945

Relationship of Magnesium and Insulin Resistance in Living Donor Kidney Transplant Recipients Joy V. Nolte,[2] Biruh Workeneh,[3] Linda W. Moore,[2] Marie C. Gabour,[4] Ahmed O. Gaber,[2] William E. Mitch.[1] *[1]Baylor College of Medicine, Houston, TX; [2]Houston Methodist Hospital, Houston, TX; [3]MD Anderson Cancer Center, Houston, TX; [4]UMASS Boston, Lexington, MA.*

Background: Magnesium (Mg) is an important cofactor for blood glucose control and energy metabolism. Decreased Mg stores have been correlated with increased insulin resistance (IR) in diabetes and chronic kidney disease. It is difficult to assess total magnesium stores because serum Mg does not necessarily correlate with total body magnesium. Dietary intake of Mg before and after kidney transplant (KT) has not been heretofore described.

Methods: We sought to determine differences in Mg intake before and after KT. We analyzed 31 subjects who completed the ASA24 24hr dietary recall and oral glucose tolerance tests (OGTT) <1 month prior to transplant and 3 months post-transplant. Subjects were noninsulin dependent at KT, mostly male (84%) and an average age of 48yo. IR was indicated by Matsuda Index (MI). Spearman's correlation (ρ) and mixed model statistics were used.

Results: Dietary recalls revealed most subjects consumed inadequate Mg pre- and post-KT(Table 1); however, serum Mg (SMg) remained within range for 83% pre-KT and 90% post-KT. Mean SMg decreased 0.23mg/dL despite increased dietary intake. Neither calcinuerin dose nor trough correlated with SMg post-KT. SMg, but not dietary Mg, correlated with fasting insulin and MI at baseline but did not reach significance (ρ= -0.346, P=0.056 and ρ=0.332, P=0.068). IR significantly correlated with weight (PE= -0.087, P=0.0003), waist circumference (PE= -0.096, P<0.0001), and BMI (PE= -0.119, P=0.032) over time but not serum or dietary Mg intake (ρ=0.001, P=0.61).

Conclusions: We found that pre-KT patients do not consume sufficient dietary Mg and a significant number were insulin resistant. Post-KT insulin resistance worsened despite increased Mg intake, but we speculate that treatment with calcinuerin inhibitors and other undetermined mechanisms could be depleting total Mg stores and potentially contributing to the insulin resistance observed post-KT. More accurate biomarkers for total body Mg and overall dietary Mg intake are needed to further examine magnesium's role in IR.

	Pre-KT	Post-KT	p-value†
Met Recommended Dietary Allowance, n (%)	3 (10%)	9 (34%)	--
Serum Mg, mg/dL (SD)	2.0 (0.43)	1.77 (0.17)	0.004
Total Mg intake*, mg (SD)	321 (238)	501 (433)	0.006
Matsuda Index, (SD)	4.35 (3)	3.54 (2.5)	0.09

*Total Mg intake includes prescription Mg dose. †Wilcoxon

TH-PO946

Proton Pump Inhibitors versus Histamine 2 Receptor Antagonists in Transplant Patients Julio L. Chevarria, Hannah M. O'Keeffe, Ecaterina Berzan, Neil L. Thompson, Maura Looney, George S. Mellotte, Catherine A. Wall, Peter J. Lavin. *Trinity Health Kidney Centre, Tallaght Hospital, Dublin, Ireland.*

Background: Proton pump inhibitors (PPIs) are among the most commonly prescribed drugs. It has been estimated that two-thirds of those on PPIs do not have a verified indication. Recent literature has related their use with acute and chronic renal impairment. Therefore it is important to determine if PPIs are being used appropriately. The purpose of this work was to evaluate the appropriateness of PPI use in prevalent kidney transplant patients.

Methods: We performed a cross-sectional study in prevalent transplant patients from January to December 2016. We reviewed their records during that timeframe. We recorded demographic characteristics, principal comorbidities, creatinine and CKD-EPI, PPIs or H2RAs, indication, time of use, steroid dose. For the statistical analysis we used SPSS19. We carried out descriptive and inferential analysis, accepting a p<0.05 as significant.

Results: 282 patients were included. 57(20%) were on steroid free regimens and 210(69.7%) were on 5mg or less. The mean dose was 3.9mg(SD 2.1). A total of 120(42.6%) were on PPIs, 87(30.9%) on Ranitidine and 75(26.6%) on neither. The most common was Omeprazole(43.3%) followed by Lansoprazole(25.8%), and 99.03% for more than 90 days. Only 14(6.7%) had a clearly documented indication for their use. The use of PPIs was greater in hypertensive patients(p:0.02, OR 2.05, CI 95% 1.11-3.77), older patients(56.3 vs 51.8 years, p:0.023). The use of PPIs compared to ranitidine was greater in patients with diabetes(p:0,03, OR 2.30, CI95% 1.08-4.90), older patients(56.3 vs 52.3years, p:0.04) and longer transplant vintage(11.9 vs 7.3years, p:0.01) and there was no difference in the creatinine or CKD-EPI (p:0.24) at the time of review. The use of Ranitidine over PPIs was more frequent in heavier patients(79.0 vs 73.1 Kg, p:0.04).

Conclusions: A large number of patients are being treated with PPIs or Ranitidine without a documented indication. These findings highlight the importance of evaluating appropriate therapy and recommending discontinuation if a clear indication does not exist. Reducing inappropriate prescribing of PPIs in kidney transplant patients can minimize potential for adverse events, and foster controllable cost expenditure.

TH-PO947

Higher Risk of Mortality Among Girls with ESRD Is Mediated by Lower Access to Transplant Patrick Ahearn, Kirsten L. Johansen, Barbara A. Grimes, Elaine Ku. *UCSF, San Francisco, CA.*

Background: Although women live longer than men in the general population, survival in the adult ESRD population does not appear to differ by sex. Few studies have focused on differences in survival by sex among children with ESRD.

Methods: Using data from the United States Renal Database Service (USRDS) we performed a retrospective cohort study of children between the ages of 2 and 19 years who required their first RRT between January 1, 1995 and December 31, 2011. We examined the association between sex and mortality using a Cox proportion hazards model adjusted for demographic characteristics, cause of ESRD, socioeconomic status, calendar year of ESRD onset, and BMI.

Results: We included 13,087 children, of whom 1694 died during 7.4 years of mean follow-up. In unadjusted analysis, risk of death was 45% higher for girls than boys (95% CI 1.32-1.60). In fully adjusted analyses, risk of death remained 35% higher for girls (95% CI 1.22-1.48). This higher risk of death was present regardless of initial RRT modality but was more marked in older girls (≥13 years, p<0.05 for interaction). The risk

of death for girls was higher both on dialysis and after transplant (p>0.05 for interaction by treatment modality). Girls were also less likely to receive kidney transplant than boys (adjusted HR 0.93 [95% CI 0.90-0.97]). In mediation analysis, when we further adjusted for transplant as a time-dependent covariate in our models for mortality risk, the risk of death in girls was partially attenuated [HR 1.28, Table].

Conclusions: Mortality risk is substantially higher for girls with ESRD than for boys. This risk of death is partially attributable to lower access to transplant among girls. However, even after adjustment for transplant access, risk of death remains higher for girls treated with either dialysis or transplant. Further investigation is needed to determine reasons for these observations.

Funding: NIDDK Support, Other NIH Support - NHLBI

Risk of death comparing girls versus boys in unadjusted and adjusted analyses.

Overall cohort (N=13,087)	Girls N= 5,951 Hazard ratio (95% CI)	Boys N=7,136 Hazard ratio (95% CI)
Total follow-up time, person-years	43,323	53,513
Follow-up time attributable to dialysis	18,177	20,021
Unadjusted model	1.45 (1.32-1.60)	1.0 (Ref)
Adjusted model	1.35 (1.22-1.48)	1.0
Adjusted model with transplant as time-dependent covariate	1.28 (1.16-1.41)	1.0
Risk of death during follow-up time attributed to dialysis	1.30 (1.16-1.44)	1.0
Risk of death during follow-up time attributed to transplant	1.28 (1.03-1.60)	1.0

TH-PO948

Hospitalisations Following Kidney Transplantation in Children Siah Kim,[2,4] Rebecca A. Spicer,[1] Hugh J. Mccarthy,[3] Fiona Mackie,[2] Sean E. Kennedy.[2] *[1]None, Sydney, NSW, Australia; [2]Sydney Children's Hospital, Newtown, NSW, Australia; [3]Syndey Children's Hospital Network, Westmead, NSW, NSW, Australia; [4]School of Women's and Children's Health, University of NSW, Randwick, NSW, Australia.*

Background: Although there is extensive published information about graft survival and acute rejection among paediatric kidney transplant recipients, there a paucity of published data on hospitalisations within the first twelve months post kidney transplant.

Methods: We performed a retrospective review of children who received kidney transplants at Sydney Children's Hospital from 2009 to 2015. We collected data on length of stay (LOS) in hospital immediate post-transplant, LOS in intensive care, elective and non-elective readmissions over the first twelve months following kidney transplant.

Results: 35 children received kidney transplants over 2009 to 2015, 20 female (57%) and 15 male (43%). 20 received deceased donor grafts, 15 living related including one ABO incompatible and one paired kidney exchange. Mean age of the kidney transplant recipients was 10 years (sd 5 years). Median length of stay was 15 days (IQR 11 to 22 days), with median intensive care LOS 4 days (IQR 3 to 6 days). There were 136 admissions to hospital within the first twelve months with 80 (59%) elective and 56 (41%) non-elective. 22 (63%) of children had non-elective admissions post transplant. Planned admission was due to biopsy (40 admissions) and stent removal (25 admissions). The most common cause for unplanned admission was AKI (14 admissions), UTI (13 admission) and infective illness (23 admissions). Median cumulative days of hospital admission over the first twelve months was 5 days (IQR 1 day to 16 days) for patients.

Conclusions: Hospitalisation within the first year post kidney transplant is common, however cumulative inpatient days in hospital in the first year post-transplant is relatively short for most children. Our data shows that kidney transplantation is associated with low levels of hospitalisation within the first twelve months and will help counsel children and their families about their post-transplant course.

TH-PO949

Results of a Pediatric Transplant Program in a Low Income Country: 10 years of Guatemalan Experience Angie L. Aguilar,[2] Sindy Soveranis,[2] Edgar E. Reyes,[1] Randall M. Lou-Meda.[2] *[1]Hospital Roosevelt, Guatemala, Guatemala; [2]FUNDANIER, Guatemala, Guatemala.*

Background: ESRD rates appear to be increasing for many developing countries, becoming more challenging to get access to Renal Replacement Therapy and transplant in particular. Guatemala, situated in Central America, has an incidence of ESRD in children of 4.6 pmarp and a transplant rate of 6.9 pmp including children and adults. FUNDANIER (Foundation for Children with Kidney Diseases) has become the only center that provides free access to RRT to Guatemalan Children and during the last decade has performed and follow up close to 80 transplants. Hereby we analyzed our program database

Methods: We retrospectively described the results of all transplanted patients between 2007 and 2017. Data including demographic characteristics of recipients and donors were obtained from FUNDANIER data base. Variables like immunosuppression, reasons for discharge of the program, graft loss causes, No. of rejections, acute complications, patient and graft survival at 1 year were analyzed

Results: 78 patients were transplanted. The mean age was 12.6ys(SD3.12),54% were male and the etiology of ESRD was unknown in 65%, followed by CAKUT in 21% of patients. Regarding donors, the mean age was 33ys(SD7.62) and 37% were male. Most of the donations were from living donors (88%). The maintenance immunosuppression used in 91%(n=71) of the patients was Tacrolimus, Mycophenolate and Prednisone. The most common acute complication after transplant was infections (19%). In total 26% of patients (18/70) experience at least 1episode of rejection after 12mo post transplant. Of 43 episodes of rejection reported, 53%(23/43) were after 1year post transplant. The mean time of follow up was 3.5 years (SD1.97).8(23%) patients discharged from the program were moved to other type of RRT due to graft loss. The patient and graft survival at 1 year was 89% and 88%. When divided by type of donation, the 1year graft survival for living and deceased donor was 89% and 70%

Conclusions: After the first decade of the program this is the 1st analysis. Most of the transplants are from young and living donors. Increasing the number of deceased donor is mandatory in order to improve the transplant rate in a country with a high rate of ESRD with unknown etiology. The overall graft survival is 88% at 1 year. The main cause of graft loss is rejection due to poor compliance and acute vascular complications

TH-PO950

Time to Second Kidney Transplantation after Failed Pediatric Kidney Transplant: A Retrospective Cohort Analysis Korntip Phonphok,[2] Yong W. Cho,[1] Suphamai Bunnapradist.[2] *[1]Mendez National Institution of Transplantation, Los Angeles, CA; [2]UCLA, Los Angeles, CA.*

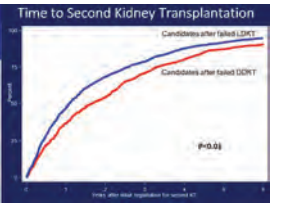
Background: With the prioritization of age ≤ 18 years old at time of registration on the kidney transplant waiting list, deceased donor rates have increased. Majority of these patients require subsequent transplantation at later time. Waiting periods before re-transplantation may vary in length, depend on donor type, PRA, and HLA mismatch. We hypothesized that candidates of those after failed first pediatric DDKT would have greater time to subsequent KT than those after failed first living donor KT (LDKT).

Methods: We used data from the Organ Procurement Transplant Network (OPTN/UNOS) as of December 8, 2016. A retrospective cohort analysis was created to examine time to second KT in 1,935 candidates listed at age 18-30 from January 1, 2000 to September 30, 2015 with previous KT at age ≤ 18. Those with > 2 KT episodes or multiorgan transplant were excluded. Patients were divided into 2 groups according to donor type of first KT; 1) those with failed first DDKT and 2) those with failed first LDKT.

Results: Median time to second KT were 646.5 days and 412.0 days in those candidates with failed first DDKT and those with failed first LDKT, respectively. (p<0.01) First LDKT recipients were more likely to have subsequent LDKT than those with failed DDKT. Median PRA were 85% and 68% (p<0.01), and high PRA (PRA≥98%) were found 26.0% and 16.0% (p<0.01) in recipients of second KT after failed first DDKT and those after failed first LDKT, respectively.

Conclusions: Candidates with previously failed pediatric DDKT had significant greater time to subsequent KT than those with failed first LDKT as well as higher PRA value. Pediatric KT recipients prioritize DDKT in the past could face a challenge with greater waiting time and PRA before re-transplantation.

	Group1 First DDKT (n=796; 41.14%)	Group2 First LDKT (n=1139; 58.86%)	P value
Second Donor type			<0.01
DDKT	625 (78.51%)	655 (57.50%)	
LDKT	171 (21.48 %)	484 (42.49%)	
Time to second KT (days) median (min-max)	646.5 (1-4762)	412 (1-5128)	<0.01
PRA median (min-max)	85 (0-100)	68 (0-100)	<0.01
PRA=0	120 (15.07%)	243 (21.33%)	0.01
PRA>=98%	207 (26.00%)	182 (15.98%)	<0.01



TH-PO951

The Incidence of Chronic Changes in Protocol Biopsies in Asymptomatic Young Pediatric Renal Transplant Recipients Sunee Panombualert, Patricia L. Weng, Robert B. Ettenger. *Mattel Children's Hospital at UCLA, Los Angeles, CA.*

Background: Previous studies of protocol biopsies (Bx) in stable pediatric kidney transplant (KTx) patients have found a high incidence of interstitial fibrosis (ci) and tubular atrophy (ct), but the effect of recipient age as a continuous variable is unclear.

Methods: We examined the relationships between recipient age (1-10 yrs vs 11-20 yrs) at Bx and the results of protocol Bxs at 6 months, 1 and 2 years in stable pediatric KTx patients from 2005-2016. Bxs were evaluated for subclinical rejection and ci/ct by Banff 2013 criteria.

Results: A total of 506 protocol Bxs were performed. Subclinical rejection was found in 5.5%, 3.8%, and 2.5% at 6 months, 1 and 2 years, respectively of all Bxs and did not differ significantly by time post-Tx or by patient age. In all Bxs, ci ≥ 1 was detected in 15.1% and ct ≥ 1 was found in 16.3% at 6 months. There was no relationship between time after transplant or subclinical rejection and the incidence of ci or ct. However, in the 6 months Bxs, the frequency of ci score was 26.8% in patients 1-10 yrs and only greater than 9.5% those 10-20 yrs (p=0.003). Similarly, ct scores were 28.6% vs 10.3% (p=0.002) at 6 months. By 1 year, ci and ct had increased in both age groups but continued to be significantly higher in patients 1-10 yrs (Table).

Conclusions: Young age as a continuous variable is significantly associated with a higher incidence of chronic tubulointerstitial damage in early protocol biopsies, and this is unrelated to subclinical rejection.

Histology scores	ci score ≥ 1			ct score ≥ 1		
	6 mo Bx	1 yr Bx	2 yr Bx	6 mo Bx	1 yr Bx	2 yr Bx
Age 1-10	15(n=56) 26.8%	23(n=51) 45.1%	19(n=41) 46.3%	16(n=56) 28.6%	24(n=51) 47.1%	18(n=41) 43.9%
Age 11-20	11(n=116) 9.5%	24(n=100) 24%	17(n=56) 30.4%	12(n=116) 10.3%	25(n=100) 25%	16(n=56) 28.6%
p-value	0.003	0.008	0.107	0.002	0.006	0.118

TH-PO952

Effect of Pregnancy Post-Transplant on Rejection and HLA-DSA Development Nadeen J. Khoury, Andrea G. Kattah, Fernando G. Cosio. *Mayo Clinic, Rochester, MN.*

Background: Pregnancy is known to be a sensitizing event; however, most studies have suggested that allograft function is not impaired. We looked at our transplant cohort to assess for rejection post-pregnancy and development of de Novo donor specific antibodies (DSA).

Methods: We used our transplant database to identify the female patient population who were 16-46 years old at the time of transplant. We included transplants which occurred between 1996 to 2014. Patients with a functioning graft for at least 2 years post-transplant were included in our data analysis. We then used pregnancy codes to select those who had a pregnancy or pregnancy-related event.

Results: We identified 47 patients with pregnancy-specific codes from an initial cohort of 412 patients. After excluding patients who had pregnancies prior to transplant and multiorgan transplants, we were left with 11 patients with appropriate pathology and DSA data. These patients were all Caucasian and received living kidney transplants. Thymoglobulin and alemtuzumab were used for induction. Triple immunosuppression was used initially with mycophenolate mofetil switched to azathioprine prior to pregnancy. Age at the time of pregnancy was between 27 and 38 and primary kidney disease included: HTN nephrosclerosis, reflux disease, IgA and anti-GBM disease. Serum creatinine at the time of transplant was 0.9-2.1 with proteinuria ranging between 31 to 157 mg/24h. 8 had a single pregnancy post-transplant and 3 had two pregnancies. Post-pregnancy biopsies were performed at 2-12 months post delivery. None of the patients had evidence of acute rejection, 8 had mild to moderate arteriosclerosis and arteriolar hyalinosis and 3 had features of chronic antibody mediated rejection, including transplant arteriopathy and glomerulopathy. The women with chronic antibody mediated rejection all had de novo DSA and were the ones with 2 pregnancies.

Conclusions: Most pregnancies post-transplant carry a benign course; it does appear however, that multiple pregnancies might trigger de novo DSA and chronic antibody mediated rejection. It would be important to have larger studies to further delineate this phenomenon and help counsel women who desire to conceive after transplant.

TH-PO953

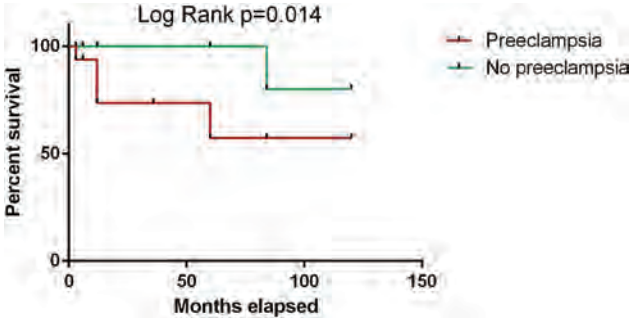
Preeclampsia Predicts Chronic Dysfunction in Kidney Transplantation Javier Soto-Vargas,[2] Karla L. Lemus,[2] Efrain CHAVARRIA-AVILA,[1] Renato Parra.[2] *[1]UNIVERSIDAD DE GUADALAJARA, GUADALAJARA, Mexico; [2]Nephrology, Regional General Hospital 46, Mexican Institute of Social Security, Guadalajara, Mexico.*

Background: The goal was to evaluate the renal and obstetric outcomes in pregnancy after kidney transplantation in a Mexican center

Methods: Kidney transplant recipients who underwent pregnancy after transplantation at Regional General Hospital of the IMSS between January 1997 and January 2016 were identified. Data on demographics, comorbidities and clinical and graft outcomes were collected with a median follow up of 61.3 months post-partum.

Results: There were 41 pregnancies identified in 34 recipients. The median age of recipient at childbearing was 26.5 years (IQR, 22.7-30.5) and the median interval from transplantation to conception was 84.4 months (IQR, 43-106). There was a difference between the median pre-pregnancy estimated glomerular filtration rate (eGFR) (91.0 mL/min/1.73 m(2); IQR, 71.0-106.0) and median eGFR at time of last post-partum follow up (66.0 mL/min/1.73 m(2); IQR, 37.0-87.5, P<0.001). 31 (75.6%) pregnancies ended in singleton live births. Pre-eclampsia occurred in 16 pregnancies (39.0%). There were 7 (17.1%) patients with chronic dysfunction during the follow up, 4 (9.8%) lost their graft, and only one death was recorded, attributed to histoplasmosis. Only the occurrence of preeclampsia was associated with the development of chronic dysfunction and loss of graft (p=0.009 and p=0.018 respectively) independent of the presence of rejections.

Conclusions: Post-transplantation pregnancies with preeclampsia are associated with the development of chronic dysfunction and loss of graft.



TH-PO954

Endothelin-1 Type A Receptor Antibodies Are Associated with Arteritis and Functional Decline in Pediatric Renal Transplantation Meghan Pearl,[1] Jonathan Grotts,[1] Maura Rossetti,[1] Qiuheng J. Zhang,[1] Patricia L. Weng,[1] Elaine F. Reed,[1] Eileen W. Tsai.[2] *[1]UCLA, Los Angeles, CA; [2]Duke University, Durham, NC.*

Background: We recently found that the non HLA antibody, Angiotensin II Type 1 Receptor Antibody (AT_1R-Ab) is associated with poor outcomes in pediatric kidney transplant recipients (KTRs); however, the role and clinical impact of other non-HLA antibodies such as endothelin-1 Type A receptor Antibody (ETAR-Ab) remains unknown.

Methods: 65 pediatric patients were monitored for 2 years after transplantation from August 2005 to November 2014. ETAR-Ab (ELISA), AT_1R-Ab (ELISA), and HLA DSA (Luminex bead assay) were measured pre-transplant, 6 months (m), 12m, 24m post-transplant and during episodes of rejection. Based on a receiver operating curve analysis, > 10 and >17 units/ml was considered positive for ETAR-Ab and AT_1R-Ab respectively while MFI cut off ≥1000 was considered positive for HLA DSA. Biopsies were performed at 6m, 12m, 24m post-transplant per protocol and for clinical suspicion of rejection and evaluated by 2013 Banff criteria. Clinical risk factors and renal function (MDRD for >18 and updated Schwartz Equation for <18 years old) were assessed.

Results: The prevalence of ETAR-Ab was 32%. Risk factors for ETAR-Ab included younger age (p=0.038), steroid free immunosuppression (p=0.038), and AT_1R-Ab (p<0.001), but not HLA DSA (Figure 1a). ETAR-Ab was associated with greater median declines in renal function (p=0.034, Figure 1b) and arteritis on biopsy (p=0.011), but not acute rejection (data not shown).

Conclusions: In pediatric KTRs, ETAR-Ab is highly prevalent and associated with AT_1R- Ab, vascular inflammation, and worsening renal function. This suggests that ETAR-Ab and AT_1R-Ab monitoring may be warranted in children, especially those on steroid-free immunosuppression. Dual blockade may attenuate allograft injury and improve renal function.

Funding: NIDDK Support, Private Foundation Support

Variable	ETAR-Ab Positive (n = 21)	ETAR-Ab Negative (n = 44)	p-value
Age at Transplant, median (IQR)	14 (12.8-15.7)	16.9 (13.4-18.2)	0.038
Sex (Male)	15 (71.4%)	24 (54.5%)	0.280
Race			0.057
White	18 (85.7%)	29 (65.9%)	
Asian	1 (4.8%)	3 (6.8%)	
Black	2 (9.5%)	2 (4.5%)	
Other	0 (0%)	10 (22.7%)	
Hispanic Ethnicity	8 (38.1%)	28 (63.6%)	0.066
Etiology of ESRD			0.577
Dysplasia	1 (4.8%)	8 (18.2%)	
FSGS	3 (14.3%)	6 (13.6%)	
Glomerulosephritis	1 (4.8%)	7 (15.9%)	
IgA nephropathy	0 (0%)	1 (2.3%)	
Obstructive Uropathy	7 (33.3%)	9 (20.5%)	
Polycystic Kidney Disease	1 (4.8%)	1 (2.3%)	
other	4 (19%)	6 (13.6%)	
Unknown	4 (19%)	6 (13.6%)	
Primary Transplant	18 (85.7%)	41 (93.2%)	0.379
Donor Type (Deceased)	11 (52.4%)	29 (65.9%)	0.418
Delayed Graft Function	1 (4.8%)	3 (6.8%)	>0.99
Physician Assessed Nonadherence	8 (38.1%)	8 (18.2%)	0.123
ATG Induction (vs IL-2)	3 (14.3%)	3 (6.8%)	0.379
Steroid Free Immunosuppression	15 (71.4%)	19 (43.2%)	0.038
HLA Mismatch, mean (SD)	1.1 (0.7)	1.3 (0.4)	0.170
Baseline PRA I > 20%	1 (4.8%)	3 (6.8%)	>0.99
Baseline PRA II > 20%	1 (4.8%)	6 (13.6%)	0.413
HLA DSA			>0.99
Negative	15 (71.4%)	31 (70.5%)	
Class 1 only	2 (9.5%)	3 (6.8%)	
Class 2 only	4 (19%)	8 (18.2%)	
Class 1 and 2	0 (0%)	2 (4.5%)	
AT_1R-Ab > 17	21 (100%)	17 (38.6%)	<0.001

Figure 1a: Demographic and Clinical Risk Factors for ETAR-Ab. ETAR-Ab; endothelin-1type A receptor antibody, ESRD; end stage renal disease, FSGS; focal segmental glomerulo-sclerosis, HLA; human leukocyte antigen, PRA; panel reactive antibody, ATG; anti-thymocyte globulin, DSA; donor specific antibody, AT_1R-Ab; angiotensin II type 1 receptor antibody

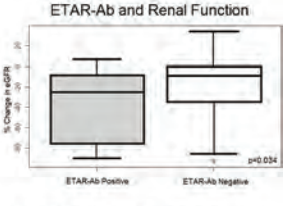


Figure 1b: ETAR-Ab and Renal Function. ETAR-Ab positivity was associated with more severe declines in eGFR. Percent change in eGFR taken from baseline (hospital discharge) to minimum during the 2 year follow-up period. p=0.034. eGFR; estimated glomerular filtration rate

TH-PO955

Creatinine Monitoring by Remote Blood Spot Testing in Pediatric Kidney Transplant Recipients Marian Sinkey,[2] Jane Dickerson,[3] Jodi M. Smith.[1] *[1]Children's Hospital & Regional Medical Center, Seattle, WA; [2]Seattle Children's, Seattle, WA; [3]Seattle Children's Hospital, Seattle, WA.*

Background: Pediatric kidney transplant patients are monitored frequently with laboratory testing to assess kidney transplant function and optimize therapeutic drug doses. Dried blood spots could reduce the number of lab trips, benefiting those who are remote, elderly, working, or unable to travel.

Methods: We collected 35 samples via phlebotomy from 30 participants for simultaneously paired venous and finger-poke (capillary) to assess the correlation of venous plasma creatinine with capillary dried blood spot creatinine (DBS had already been validated for immunosuppression levels (1)). This method uses creatinine-d3 as the calibrators, and creatinine-13C3-d3 as internal standard measured with a SCIEX QTRAP 6500. Limits of detection and quantitation were determined on the equivalent of 3 μL dried blood spot extractions.

Results: We demonstrate a strong correlation between venous and capillary (DBS) creatinine values when the creatinine was less than 1.5 mg/dl. There was a small negative bias of -0.1 mg/dL for samples less than 1.5 mg/dL. When the Cr was greater than 1.5 mg/dl we observed a larger negative bias of -0.7 mg/dL in capillary specimens (DBS).

Conclusions: The study established that remote (home) dried blood spot testing (DBS) is a logistically possible method of monitoring both creatinine and immunosuppression levels on the same card when the expected creatinine concentration is less than 1.5 mg/dL. Detecting sudden increases in creatinine may result in more immediate actions prolonging the life of the graft. Eliminating barriers to timely lab draws may improve adherence, decrease costs, and improve overall quality of life. Results greater than 1.5 mg/dl should be confirmed with venous plasma method. Further investigation is on-going to improve the method's accuracy at high creatinine concentrations. 1. Dickerson, J.A.; Sinkey, M.; Jacot, K.; Stack, J.; Sadilkova, K.; Law, Y.M.; Jack, R.M. Tacrolimus and sirolimus in capillary dried blood spots allows for remote monitoring. Ped Trans. 2015, 19(1): 101-6.

TH-PO956

PACT Score Identifies Nonadherence and Acute Rejection in Pediatric Renal Transplantation Kyle Freischlag,[2] Vivian M. Chen,[1] Shashi K. Nagaraj,[1] Annabelle N. Chua,[1] Eileen W. Tsai.[1] *[1]Duke University, Durham, NC; [2]Duke University School of Medicine, Durham, NC.*

Background: In this pilot study, we examined the utility of a pre-transplant Psychosocial Assessment of Candidates for Transplantation (PACT) score to identify at-risk pediatric patients.

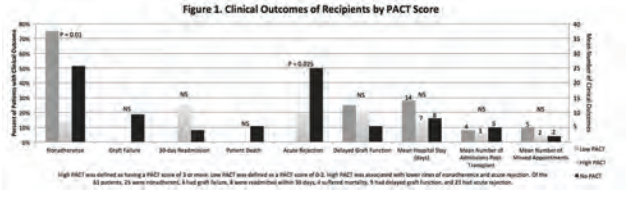
Methods: Patients were <21 year-old renal transplant recipients at our institution between 2005 and 2017. Pre-transplant psychosocial evaluation was standardized in 2011 utilizing PACT scores to assesses candidates (0-5) on social support, psychological health, lifestyle factors, and understanding. Demographics and clinical outcomes were analyzed by low PACT score (≤2), high PACT score (≥3), and no PACT score.

Results: 61 pediatric patients were identified: 7% low PACT score, 33% high PACT score, and 61% no PACT score (Table 1). High PACT scores were associated with lower rates of medical non-adherence (Low 75% vs High 15% vs No 51.4%, p=0.01) and acute rejection (0% vs 20% vs 50.0%, p=0.025) (Figure 1). Controlling for HLA mismatch, PACT score reduced (OR 0.15 95% CI 0.03-0.83) while non-adherence increased (OR 5.72 95% CI 1.35-24.28) the chances of acute allograft rejection.

Conclusions: PACT was associated with less medical non-adherence and fewer incidences of acute rejection. Our study highlights PACT score in risk stratifying candidates, which warrants prospective validation.

Patient Demographics by PACT Score

	Low PACT (N=4)	High PACT (N=20)	No PACT (N=37)	P-value
Transplant Age	12.17 (8.19, 15.97)	14.74 (8.47, 16.98)	13.53 (9.11, 16.69)	0.866
Male	25.0% (1)	70.0% (14)	67.6% (25)	0.206
Female	75.0% (3)	30.0% (6)	32.4% (12)	
African American	25.0% (1)	44.4% (8)	44.8% (13)	0.115
Caucasian	25.0% (1)	38.9% (7)	48.3% (14)	
Hispanic	50.0% (2)	5.6% (1)	3.4% (1)	
Other	0.0% (0)	11.2% (2)	3.4% (1)	
BMI	25.00 (13.75, 33.25)	22.50 (12.75, 37.25)	28.00 (15.00, 42.00)	0.7
HLA Mismatch	2.0 (2.0, 2.5)	2.0 (2.0, 3.5)	4.0 (2.5, 5.5)	0.004
Cyclosporine	0.0% (0)	0.0% (0)	8.1% (3)	0.359
Steroids	100.0% (4)	100.0% (20)	91.9% (34)	0.359
Cellcept/Myfortic	50.0% (4)	47.5% (19)	41.9% (31)	0.8
Tacrolimus	100.0% (4)	100.0% (20)	75.7% (28)	0.033
Azathioprine	0.0% (0)	10.0% (2)	8.1% (3)	0.801



Clinical Outcomes by PACT Score

TH-PO957

A Modified "Teach Back" Method to Improve Self-Management in Youth with Kidney Transplants Jayanthi Chandar, Adela D. Mattiazzi, Malgorzata N. Bielecka, Marissa J. Defreitas, Alan M. Delamater. *University of Miami Miller School of Medicine, Miami, FL.*

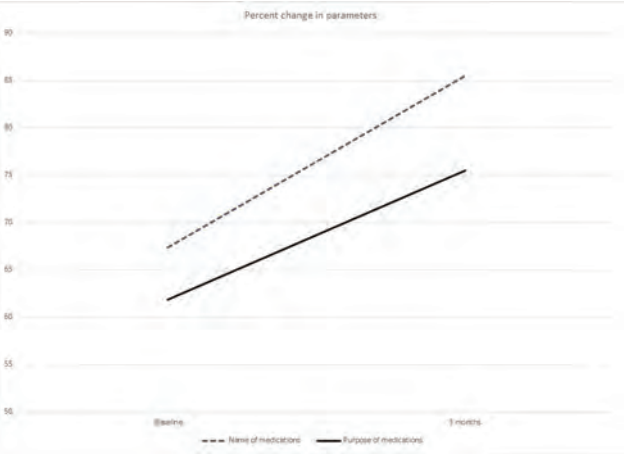
Background: Kidney transplant recipients require adherence to a strict medical regimen. Higher rates of non-adherence are reported among adolescents, often resulting in transplant loss. Inadequate functional health literacy is one of the factors affecting adherence. Teach Back' is a verbal literacy tool that facilitates patient understanding and knowledge retention.

Methods: We performed a quasi-experimental pilot study using a modification of the 'Teach Back' method, in which the patient used digital media to answer basic questions regarding their health and medication regimen while waiting to be seen by the health care provider (HCP) in clinic. The HCP then created a corrected version during the encounter and gave it to the patient. Rapid assessment of literacy-TEEN score was assessed at baseline. Knowledge of names and purpose of medications used were assessed by digital capture and by questionnaire, at baseline, upon introduction of the program with access to the patient for 1 month, and after taking away the program for one month. Knowledge was scored as 0-100% with 0 indicating no answers were correct and 100 indicating all were correct.

Results: Sixteen patients (10 male, 6 female) were recruited to the study. Mean age was 17.3± 2.4 years and 94% were ethnic minority (Black or Hispanic). Seven of 16 patients (43.75%) had an academic achievement below grade level. REALM-TEEN score was < 65% in 3/16 (18.75%) patients. At the end of the study period, there was a trend towards improvement in knowledge of medications (see figure). Only one patient used the program at home.

Conclusions: A significant proportion of adolescent transplant recipients are disadvantaged by low academic achievement. Digital technology used during clinic visits appears to be useful in improving knowledge and purpose of medications in adolescents with kidney transplants. This is an important self-management tool for transitioning adolescents to adult HCPs.

Funding: Private Foundation Support, Clinical Revenue Support



TH-PO958

Impact of Immediate Post-Transplant Parenteral Iron Therapy on Prevalence of Anemia and Short-Term Allograft Function in a Cohort of Pediatric Renal Transplant Recipients Oluwatoyin F. Bamgbola,[2] Diego H. Aviles,[3] Franca M. Iorember.[1] *[1]Phoenix Children's Hospital, Scottsdale, AZ; [2]SUNY Downstate Medical Center, Brooklyn, NY; [3]Dept of Pediatrics, Louisiana State University Health Science Center, New Orleans, LA.*

Background: Anemia is common but under-diagnosed and is often inadequately treated in renal transplant {KTX} recipients. Due to high turn over rate during chronic dialysis and blood loss during KTX surgery, iron deficiency (ID) is the major determinant of early-onset (< 6 mo) post-transplant anemia (PTA). We sought to examine the clinical benefit of routine use of parenteral (IV) iron in patients who had KTX surgery.

Methods: Subjects aged 2 -18 yrs who had KTX between 2011 & 2015 received 1-2 mg/kg of diluted iron sucrose over 1 hr in the first week of surgery. Historical control was their counterparts between 2005 & 2010. We determined i) the prevalence rate (PR) and predictors of early- (6 mo) and late-onset (12 mo) anemia, ii) relationship between IV iron therapy and anemia; and iii) association of IV iron treatment with the rates of acute rejection (ARE), allograft dysfunction, infection, erythropoietin (EPO) use and hospitalization (HOS).

Results: Prevalence rate of anemia for the cohort (n = 79): 85% at 1 mo, 74% at 3 mo, 55% at 6 mo, 60% at 12 mo & 47% at 24 mo. There was greater PR of anemia at 3 (p = 0.01), 6 (p = 0.03) and 12 mos. (p = 0.03) in the Controls (n = 42). The best set of predictors in multiple regression analysis for early anemia were poor donor quality and no IV iron treatment; $R^2 = 0.13$; p = 0.01. Predictors for late-anemia at 12 mo: anemia at 6 mo, steroid use, allograft, previous KTX, and no IV iron treatment (p = 0.001). Although not significant, there was greater frequency of allograft dysfunction, ARE, and hospitalization in the Controls. There was greater number of anemia treated with EPO rescue in the Controls (p = 0.03).

Conclusions: - Post-surgery treatment with IV iron reduces the rate of anemia up to 12 mo after KTX - Post-surgery IV iron use reduced the need for later EPO rescue treatment for anemia - Early anemia is predominantly due to iron deficiency and poor donor quality - Late anemia is due to pre-existing anemia, steroid use, previous KTX and allograft dysfunction - Literatures support association of early and late anemia with lower graft and patient survival - Randomized controlled trials are needed to determine the scope of evaluation for PTA and cost benefit analysis of therapeutic options including EPO, oral iron and/ or IV iron

TH-PO959

Malignancies after Pediatric Kidney Transplantation: A Long Term Single-Center Experience in Japan Tomoo Yabuuchi,[1] Ken-ichiro Miura,[1] Shoichiro Kanda,[1,2] Yohei Taniguchi,[1] Takeshi Nagasawa,[1] Ryutaro Hisatomi,[1] Hideki Ban,[1] Yoko Shirai,[1] Yoko Takagi,[1] Naoto Kaneko,[1] Kiyonobu Ishizuka,[1] Hiroko Chikamoto,[1] Yuko Akioka,[1] Motoshi Hattori.[1] *[1]Department of Pediatric Nephrology, Tokyo Women's Medical University, Tokyo, Japan; [2]Department of Pediatrics, University of Tokyo, Tokyo, Japan.*

Background: Kidney transplantation (KTx) is the preferred treatment option for children with end-stage renal disease. Today, approximately 11.3% of all deaths after pediatric KTx are related to cancer. With improved graft survival and overall survival, this proportion is likely to rise. Increased cancer risks are well documented in adult KTx recipients. However, the spectrum of malignancies and risk in the pediatric KTx population, particularly in Asia, are less well described.

Methods: We retrospectively reviewed medical charts of all consecutive pediatric KTx patients aged less than 20 years in our center between April 1983 and December 2016.

Results: During maximum 31 years of follow-up, 13 out of 363 patients (3.6%) developed malignancy, which included 3 EBV-associated posttransplant lymphoproliferative disorder (PTLD), 1 EBV-associated post-transplant smooth muscle tumor (PTSMT), 2 brain tumors, 1 B-cell lymphoma, 1 renal cell carcinoma, 1 thyroid carcinoma, 1 lung cancer, 1 bladder cancer, 1 breast cancer, and 1 Wilms tumor. Patients diagnosed with EBV-associated PTLD, EBV-associated PTSMT, and Wilms tumor were mostly transplanted at younger ages and the median age at diagnosis of malignancy was 6.6 years (range 5.5-11.5), with a median time to diagnosis of 1.2 years (range 0.6-1.2). In contrast, the median age at diagnosis of other malignancies was 27.6 years (range 20.4-31.8), and the median time from KTx to diagnosis of malignancy was 15.2 years (range 10.6-17.1). No EBV-associated PTLD has occurred since 2005, when we started regular screening of EBV-DNA load in children at risk for developing PTLD.

Conclusions: This is the first study which investigated occurrence of malignancies in pediatric KTx recipients in Asian populations. EBV-associated PTLD and PTSMT occurred during early periods from KTx. Regular screening of EBV-DNA load might be helpful to prevent EBV-associated PTLD. Other malignancies were diagnosed during early adulthood, emphasizing the need for long term surveillance of these patients.

TH-PO960

Pubertal and Growth Development of Children and Adolescents Following Renal Transplantation Rainer Büscher, Deniz Serdar, Cordula Kiewert, Peter F. Hoyer, Anja K. Büscher. *University of Duisburg-Essen, Pediatrics 2, Essen, Germany.*

Background: Children with chonic kidney disease often show a delayed pubertal development and growth restriction, which is an enormous psycho-social stress factor. The improvement of renal function following RTx seems to positively influence some of the involved mechanisms. We analyzed pubertal development and growth in children following RTx in order to identify potential risk factors.

Methods: Data of 90 children (0-18 years, 32 ♀) from our center who underwent RTx between 2000-2015 have been retrospectively analyzed. Mean observation time was 6.7 years. We studied the influence of gender, age, underlying disease, mode and duration of dialysis, glucocorticoid and growth hormone therapy prior to RTx, renal function and immunosuppression on the annual course of weight and growth, bone age, testicle volume, estradiol/testosterone levels, age at onset of menarche and change of pubertal Tanner-stage.

Results: Mean age at RTx was 6.8 years (±4.7 years). Length (-1.6SD) and weight (-0.9SD) were reduced prior to RTx and we found a pronounced dissociation between skeletal and chronological age. While all patients gained weight ($p=0.007$) following RTx, length and dissociation of bone age showed no improvement ($p=0.032$). On the contrary, the dissociation was more pronounced in the group of patients between 7-12 years ($p<0.05$). Patients receiving growth hormone therapy prior to RTx showed a negative dissociation and reduced length at time of RTx and presentd an accelerated catch-up-growth with no further significant differences after RTx. Living kidney donation was associated with a significantly enhanced length (-0.9SD vs. -1.7SD, $p=0.025$). Age at onset of menarche (12.98±1.64 years, normal range 11.2-15.6 years) and change from Tanner-stage P1 to P2 (11.2±15.6, normal range 8-12.6 years) were in the upper normal range. Boys were 12.3±1.5 years old (normal range 9.2-15.2 years) at transition to P2. No dependancy on gender, disease, duration and mode of dialysis, immunosuppression or prior glucocorticoid therapy could be observed.

Conclusions: The majority of our patients showed a timely pubertal development following RTx. Despite a improved renal function, growth and bone age remained retarded.

TH-PO961

Donor and Recipient Size Mismatch Is Associated with Graft Survival in Pediatric Living Donor Kidney Transplantation Heather L. Wasik, Rebecca Ruebner, Cozumel S. Pruette, Dorry L. Segev, Allan Massie. *Johns Hopkins University, Baltimore, MD.*

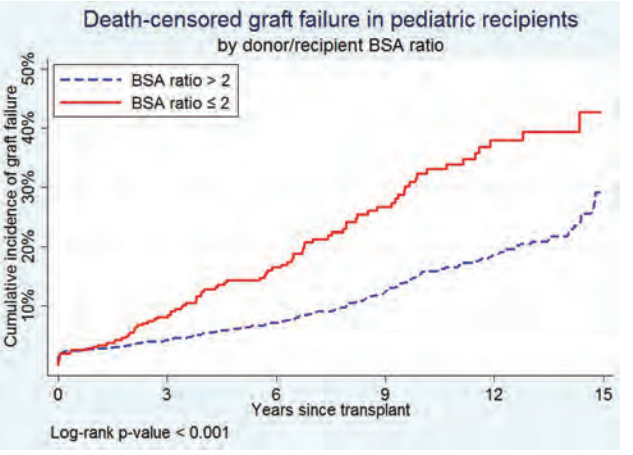
Background: Studies in adults and adolescents have shown that a small donor body size in relation to recipient body size is associated with increased risk of graft loss following kidney transplantation. Little is known about this relationship in young children undergoing living donor kidney transplantation (LDKT) in whom greater size mismatch is possible.

Methods: We studied first-time LDKT recipients 1995-2015 aged <11y at transplant using SRTR data. Patients were divided into two groups based on donor/recipient body surface area ratio (D/R BSA ratio): BSA ratio ≤ 2 and BSA ratio > 2. Multivariable Cox models were used to compare time to death-censored graft failure (DCGF) between patients in the two BSA ratio groups, adjusting for recipient, donor, and clinical characteristics including recipient age at transplant, recipient BSA, sex, race, cause of ESRD, years of dialysis prior to transplant, donor age, donor/recipient sex mismatch, number of HLA mismatches, and year of transplant.

Results: Of 1,948 pediatric patients undergoing LDKT, 352 (18%) had a D/R BSA ratio ≤ 2. Patients with BSA ratio ≤ 2 had a higher incidence of DCGF compared to those with a BSA ratio > 2 (32.3% at 10 years vs. 15.4%, logrank p <0.001). After adjustment, D/R BSA ratio ≤ 2 remained associated with an increased risk of DCGF (aHR (95% CI)=1.62 (1.10-2.39), p=0.01).

Conclusions: Low D/R BSA ratio is associated with increased risk of DCGF in children undergoing LDKT. Donor size may be an important factor to consider when selecting organs for pediatric LDKT.

Funding: Other NIH Support - NIH T32 Renal Epidemiology Training Grant



TH-PO962

Long-Term Neurodevelopmental and Anthropometrical Outcome of Children Born to Female Kidney Transplant Recipients Natalja Haninger,[1] Apostolos Vacariu,[2] Alice Schmidt,[1] Gere Sunder-Plassmann.[1] *[1]Department of Medicine III, Division of Nephrology and Dialysis, Medical University of Vienna, Vienna, Austria; [2]Medical University of Vienna, Vienna, Austria.*

Background: Pregnancy rates have increased during the last years among kidney transplant recipients and live birth rate is high. These pregnancies are deemed high risk, with many obstetric complications and negative delivery outcomes. No long-term data of neurodevelopmental and anthropometrical outcome in this high risk population are available.

Methods: We retrospectively analyzed neurodevelopmental and anthropometrical long-term outcome data of 36 children born to 29 female kidney transplant recipients between 1989 and 2017. Data were collected from chart reviews (including Bayley Scales of Infant Development, percentile lines by WHO growth charts adjusted to expected height), personal interviews of the mother, and the Austrian Mother Child Booklet.

Results: We evaluated a total of 51 pregnancies. Pre-eclampsia was observed in 5 pregnancies (10%). Live birth rate was 71% (n=36), rate of abortion 29% (n=15), including 2 stillbirths. 34 singletons and one set of twins were born after organ transplantation (19 females, 17 males; 2 singletons after IVF). 83% required C-section, 16 infants were born term, 20 (56%) premature; 16 of them had low birth weight, including 6 with very low and 4 with extremely low birth weight. 11 (31%) were small for gestational age. Mean gestational week at delivery was 35±4. 14 children required neonatal intensive care treatment. One child was born with renal pelvic dilatation (4%). Mean age of children was 11,3±8,2 years at assessment for physical, social, and psychomotor skills. Growth retardation was seen in 9 children (25%); 5 (14%) were above normal range; 22 (61%) as expected. Hyperactivity disorder (n=2), poor fine motor skills (n=3), delayed speech development or speech abnormalities (n=3), and cognitive developmental disorder (n=1) were diagnosed.

Conclusions: We observed an enhanced rate of neurodevelopmental delay and anthropometrical abnormalities in this high risk population. Obstetric and delivery complications might influence neurodevelopmental and anthropometrical outcome in children born to female kidney transplant recipients.

TH-PO963

Improving Identification and Documentation of Urinary Tract Infection Risk after Renal Transplantation in Children Marie-Michele Gaudreault-Tremblay,[2] Damien G. Noone,[2] Rory F. McQuillan,[3] Diane Hebert,[2] Rulan S. Parekh.[1] *[1]The Hospital For Sick Children, Toronto, ON, Canada; [2]The Hospital for Sick Children, Toronto, ON, Canada; [3]University of Toronto, Toronto, ON, Canada.*

Background: Urinary tract infection (UTI) is the most frequent infectious complication after kidney transplantation in children. Trimethoprim-Sulfamethoxazole is standard UTI prophylaxis in all transplant recipients, irrespective of pre-transplant diagnosis or post-transplantation UTI risk factors. Identification and documentation of patient's risk of post-transplantation UTI is often lacking, which complicates the choice of appropriate prophylaxis. The aim of this quality improvement project is to improve documentation and categorization of post-transplantation UTI risk for transplant recipients, with a target screening rate of 90%.

Methods: In our Centre, the model for improvement (Plan-Do-Study-Act) was used to sequentially implement an educational initiative and a checklist to facilitate systematic review of UTI history and risk factors. The purpose of the intervention was to allow clinicians to categorize children's post-transplantation UTI risk. Documentation in patients' medical records was assessed at each clinic visit. Parameters analyzed were:

appropriate identification/documentation of post-transplantation UTI risk, UTI history and risk factors. The medical team satisfaction regarding the intervention and the supplementary time used to document was also assessed. A *u* chart was used for analysis.

Results: A total of 14 renal transplant outpatient clinics (77 patients; 126 medical visits) were reviewed from February to May 2017. The baseline documentation of UTI history in the patient's medical record was 45% and of UTI risk factors 25%. After the medical team educational session, an increase of the documentation of UTI risk factors was observed (47% of documentation following educational session) but no significant change in documentation of UTI history (41%). Following implementation of the checklist, documentation of UTI history and risk factors improved by 21% and 17% respectively. However, categorization of patient's post-transplantation UTI risk was almost always missing.

Conclusions: UTI is a major clinically significant complication following pediatric kidney transplantation. Implementation of a checklist significantly improved documentation of UTI history and risk factors in children after renal transplantation.

TH-PO964

CMV Viraemia Is Associated with Decline in Graft Function in Paediatric Renal Transplant Recipients Shazia Adalat, Martin Garcia-Nicoletti, Nabil Z. Melhem, Grainne M. Walsh, Helen E. Jones, Jelena Stojanovic. *Evelina London Children's Hospital, London, United Kingdom.*

Background: Little is documented about impact of post-transplant CMV viraemia on graft function in paediatric renal transplant recipients.

Methods: A retrospective analysis of CMV viral loads, graft outcomes, amendments in immunosuppression (IS) and rejection episodes in renal allografts in a large paediatric transplant centre. CMV donor/recipient status, timing of CMV viraemia, duration of any antiviral therapy and time to CMV seroconversion were analysed. Rejection episodes were noted with correlation to IS changes and decline in GFR was calculated annually using the Schwartz formula.

Results: Of 101 paediatric renal transplants performed over a 5 year period (2010-15), data was analysed for 76 followed-up patients. Follow up ranged 1.3-7.3 years at time of review (mean 4.2 years). Two thirds of all transplants came from living donors and two thirds followed a standard IS protocol of basiliximab, tacrolimus, azathioprine and tapering prednisolone. In 43% both donor and recipient were CMV naive; both were CMV seropositive in 23% and in 25% the donor was positive while recipient was naive. In 9% recipient positive only. Of CMV naïve recipients with CMV positive donor(n=19), all received 3 months of prophylactic valganciclovir. Despite prophylaxis, 52% developed CMV viraemia at a median of 4.3mo (range 1.4-7mo). 3 of these developed CMV disease (1 hepatitis, 1 enteritis and 1 fever with neutropenia). Of the remaining 7, who had viraemia with no systemic features, 6 were on standard IS. Median time to seroconversion was 3.3 (range 0.6-54) months. Decline in graft function was 2-66 ml/min/1.73m^2 (median 21). Of those who didn't develop viraemia, two grafts were lost. Of CMV seropositive recipients, 59% (n=10/17) developed CMV viraemia 0-26 (median 1.9) months post-transplant. 9 patients were on standard IS. Decline in graft function ranged from -8 to 42 (median 8) ml/min/1.73m^2 from first to last follow up, compared to median decline in GFR in those without viraemia of 2(range-27 to 42) ml/min/1.73m^2. No primary infection in CMV-/- or reactivation of latent infection in CMV -/+allografts was found.

Conclusions: There is a greater decline in graft function in CMV naive patients who develop viraemia regardless of seroconversion. There is no evidence that this is related to changes in immunosuppression at the time of the CMV viraemia.

TH-PO965

Tubular Cell Senescence in the Donated Kidney Predicts Allograft Functions, but Not Donor Remnant Kidney Functions, in Living Donor Kidney Transplantation Tadashi Sofue,[1] Yoshio Kushida,[2] Taro Ozaki,[1] Masahiro Moritoki,[1] Yoko Nishijima,[1] Akira Nishiyama,[3] Tetsuo Minamino.[1] *[1]Department of CardioRenal and Cerebrovascular Medicine, Kagawa University, Kagawa, Japan; [2]Department of Pathology, Kagawa University, Kagawa, Japan; [3]Department of Pharmacology, Kagawa University, Kagawa, Japan.*

Background: It is uncertain whether kidneys from marginal donors are suitable for living kidney transplantation. In deceased donor kidneys, tubular cell senescence in the donated kidney is reported to affect allograft functions. However, the degree of cell senescence in a living donor kidney with marginal factors has not been reported so far. In this study, we assessed the association of tubular senescence with allograft and remnant kidney functions in living donor kidney transplantation by a prospective observational clinical study.

Methods: Thirty-eight living donor kidney transplantations were analyzed prospectively. Tissue sections obtained from pre-implantation kidney biopsies were immunostained for p16^{INK4a} to indicate tubular senescence. Various kidney biomarkers were analyzed in urine and blood samples. The protocols and informed consent forms were reviewed and approved by the Ethics Committee of Kagawa University (#H22-056) and registered in the UMIN Clinical Trials Registry (UMIN000004905).

Results: Of the 38 donors, 21 had marginal factors. Severe tubular senescence was found in living donors with overlapping marginal criteria. Tubular senescence in living donor kidneys was significantly related to donor age and lower recipient kidney functions at 1 year after transplantation independently of donor age (β = -0.281; P = 0.050), but did not affect remnant kidney functions after donation. Pre-transplant donor factors, such as pre-eGFR, hypertension, systolic blood pressure, and albuminuria, did not show any significant AUC for prediction of high tubular cell senescence. High plasma soluble αKlotho levels were associated with a higher predictive value for low tubular cell senescence with an area under the curve of 0.78 (95% confidence interval 0.62–0.93; P < 0.01).

Conclusions: The nuclear p16-staining rate in donated kidney tubules is a predictor for allograft kidney functions, but not donor remnant kidney functions in living donor kidney transplantation. Detection of tubular cell senescence may facilitate selection of appropriate living donor candidates.

Funding: Government Support - Non-U.S.

TH-PO966

Validation of Living Donor Nephrectomy Codes Ngan Lam,[7] Krista L. Lentine,[5] Scott Klarenbach,[7] Manish M. Sood,[4] John Paul Kuwornu,[8] Kyla L. Naylor,[1] Greg A. Knoll,[3] Joseph Kim,[6] Amit X. Garg.[2] *[1]Institute for Clinical Evaluative Sciences, University of Toronto, London, ON, Canada; [2]London Health Sciences Centre, London, ON, Canada; [3]Ottawa Hospital, Ottawa, ON, Canada; [4]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [5]Saint Louis University, St. Louis, MO; [6]Toronto General Hospital, University Health Network, Toronto, ON, Canada; [7]University of Alberta, Edmonton, AB, Canada; [8]Institute for Clinical Evaluative Sciences, London, ON, Canada.*

Background: Use of administrative data for outcomes assessment in living kidney donors is increasing given the rarity of post-donation complications and challenges with loss to follow-up.

Methods: Using linked healthcare administrative databases in Ontario, Canada, we conducted a retrospective cohort study to determine the validity of diagnostic and procedural codes for living donor nephrectomies. The reference standard was living kidney donation events identified through the province's tissue and organ procurement agency, with verification by manual chart review. All living kidney donors from 2003 to 2010 who had donated at one of five major transplantation centers in Ontario were included. Operating characteristics (sensitivity and positive predictive value, PPV) of various algorithms using diagnostic, procedural, and physician billing codes were calculated.

Results: During the study period, there were a total of 1199 living donor nephrectomies performed. Overall, the best algorithm for identifying living kidney donors was the presence of one diagnostic code for kidney donor (ICD-10 Z52.4) and one procedural code for kidney procurement or excision during a hospital admission (1PC58, 1PC89, 1PC91). Compared to the reference standard, this algorithm had a sensitivity of 97.4% and a PPV of 90.1%. The diagnostic and procedural codes performed better than the physician billing codes (sensitivity 60.1%, PPV 78.3%).

Conclusions: An algorithm consisting of one diagnostic and one procedural code accurately identified living kidney donors in administrative databases. This algorithm can be used to identify and follow living kidney donors for post-donation outcomes.

TH-PO967

Nephrosclerosis beyond That Expected for Age Is Predictive of Early New-Onset Hypertension in Living Kidney Donors Naim S. Issa,[2] Lisa E. Vaughan,[2] Aleksandar Denic,[2] Venkata vamsi Nagineni,[2] Harini A. Chakkera,[3] John C. Lieske,[2] Lilach O. Lerman,[2] Sandra J. Taler,[2] Mark D. Stegall,[2] Emilio D. Poggio,[1] Andrew D. Rule.[2] *[1]Cleveland Clinic, Cleveland, OH; [2]Mayo Clinic, Rochester, MN; [3]Mayo Clinic Arizona, Scottsdale, AZ.*

Background: Nephrosclerosis on kidney biopsy of living donors is known to associate with older age and hypertension (HTN). Whether nephrosclerosis is also predictive of adverse kidney function changes early after donation is unclear.

Methods: We retrospectively studied living kidney donors who had an implantation renal biopsy as part of the Aging Kidney Anatomy study. Age-based thresholds (95th percentile for 18-75 yo) were defined for glomerulosclerosis percentage (8-30%), cortical fibrosis (1-10%), number of fibrosis foci (1-6) and arteriosclerosis (60-76%). A Nephrosclerosis Index was defined assigning a value of 1 for each parameter that was abnormal. The Nephrosclerosis Index was assessed as a predictor of residual eGFR, eGFR<60 ml/min/1.73 m^2, elevated 24-hour albumin excretion, and new onset HTN (defined as SBP>140 or DBP>90 mm Hg or use of anti-hypertensive medications) after donation.

Results: There were 1409 donors available to define age-based thresholds of which 741 returned for a follow-up visit 2-24 months after donation (mean and median # months). The Nephrosclerosis Index was 0 in 65.3%, 1 in 26.2%, 2 in 6.3%, and 3 or higher in 2.2%. After adjusting for clinical predictors, baseline characteristics that associated with Nephrosclerosis Index were age (p<0.001) and HTN (p=0.003). After adjusting for age at donation, pre-donation HTN, and follow-up time, the Nephrosclerosis Index was not predictive of change in eGFR (p=0.89) at follow-up, a follow-up eGFR<60 ml/min/1.73 m^2 (p=0.56), or change in urine albumin (p=0.70). After excluding baseline HTN and adjusting for age and follow-up time, the Nephrosclerosis Index per level increase associated with new-onset HTN at follow-up (OR=1.9, p=0.021). A Nephrosclerosis Index of 2 or higher was also associated with new-onset HTN at follow-up (OR=4.2, p=0.017). An alternative analysis using single-thresholds rather than age-based thresholds for Nephrosclerosis Index found no association with new-onset HTN at follow-up.

Conclusions: Although uncommon, nephrosclerosis beyond that expected for age in a living kidney donor is associated with both prevalent HTN at donation and new-onset HTN at short-term follow-up.

Funding: NIDDK Support

TH-PO968

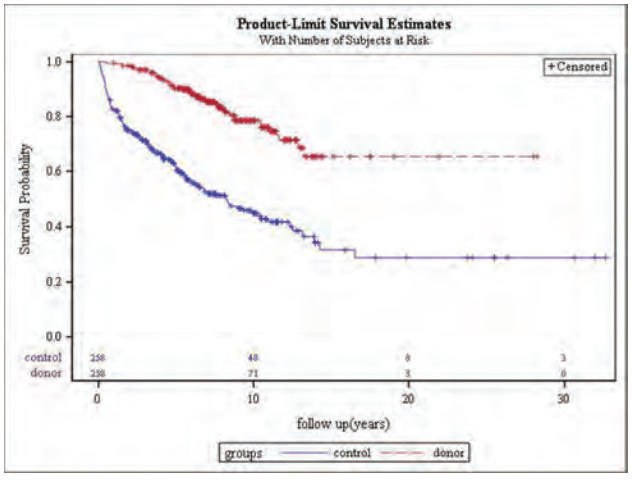
Mortality in Living Kidney Donors with ESRD: A Propensity Score Analysis Using the United States Renal Data System Robert Nee,[3,4] Amarpali Brar,[1] Dimitre Stefanov,[1] Rahul M. Jindal,[2] Madhu R. Joshi,[1] Bair Cadet,[1] Moro O. Salifu.[1] *[1]SUNY Downstate Medical Center, Brooklyn, NY; [2]USU-Walter Reed Department of Surgery, Uniformed Services University, Bethesda, MD; [3]Nephrology, Walter Reed National Military Medical Center, Bethesda, MD; [4]Medicine, Uniformed Services University, Bethesda, MD.*

Background: Living kidney donation has been performed with the premise of acceptable safety of kidney donors. Although a very small percentage of living donors progress to end-stage renal disease (ESRD) after donor nephrectomy, evidence suggest that the rate of ESRD is comparable to that in the general population. However, for those donors who develop ESRD, their survival on dialysis has not been systematically assessed.

Methods: We used the United States Renal Data System (USRDS), and abstracted 274 prior living kidney donors (cases) between 1995 to 2009. There were 609,398 on dialysis without kidney donation (controls). Univariate analysis was used to test differences between the unmatched groups. We used propensity score matching to identify 258 cases and 258 controls. Time-dependent Cox proportional hazards model, adjusted for demographic factors and comorbidities, was used to compare survival between the two matched cohorts.

Results: In the propensity score-matched cohort, mortality was lower in cases compared with controls (19% vs 49%, p<0.0001). Cox model results demonstrated that cases had significantly lower mortality compared with controls (adjusted hazard ratio [AHR] 0.20, 95% CI 0.14-0.28, p<0.0001). Time-segmented analyses showed cases with significantly lower mortality 0-5 years (AHR 0.15; 95% CI 0.10-0.24; p<0.0001), and 5-10 years since start of dialysis (AHR 0.26; 95% CI 0.14-0.48; p<0.0001). After 10 years, the difference in survival was nonsignificant (AHR 0.48; 95% CI 0.17-1.32; p=0.15), likely due to the small sample size of patients in this time interval.

Conclusions: We observed a lower mortality rate in living donors with ESRD compared to matched non-donors. This data will guide clinicians in the informed consent process with prospective donors.



Survival curves of donors vs. matched non-donors with ESRD

TH-PO969

Dynamic Contrast Computed Tomography as a Separate Renal Function Test for Living Renal Transplantation Donors Midori Hasegawa, Jin Iwasaki, Kazuo Takahashi, Hiroki Hayashi, Shigehisa Koide, Daijo Inaguma, Yukio Yuzawa. *Fujita Health University School of Medicine, Toyoake, Japan.*

Background: Non-ionic contrast agent is stable in vivo and is eliminated without being metabolized, exclusively by glomerular filtration. The purpose of this study is to establish the method of measurement of glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) by dynamic computed tomography (CT), for use in accurate separate renal function evaluation.

Methods: When preoperative abdominal contrast-enhanced CT of renal transplant donor candidates was performed, low level radiation (8 mSv) dynamic CT images were added every 2 for 30 seconds. The region of interest (ROI) was set at the right and left renal artery just before branching, and the CT value in the ROI was obtained. A time-density curve was derived from the CT value and photographing time. ERPF was calculated using the Patlak plot method. GFR was calculated using a 3-compartment model (intra-arterial, extracellular space, glomerulus) analytic method. CT based GFR was compared with inulin clearance results.

Results: Table 1 shows the results in 5 renal transplant donors. CT-based GFR closely coincided with inulin clearance. The filtration fraction (GFR/ERPF) was 0.22±0.03. Figure 1 shows the images of ERPF and GFR.

Conclusions: This method can be clinically applied for separate renal function evaluation.

Gender		Female	Female	Female	Male	Male
Age (year)		45	43	49	60	73
Height (cm)		160	162	155	160	153
Body Weight(kg)		70	58	60	58	53
ERPF (mL/min)	Right	275.4	299.8	201.7	152.3	198.9
	Left	242.5	254.7	176.4	146.3	78.0
	Both	517.9	554.5	378.1	298.6	276.8
CT based GFR (mL/min)	Right	67.1	48.5	43.6	43.0	45.9
	Left	55.5	49.9	35.3	33.5	21.4
	Both	122.6	98.4	78.9	76.5	67.3
Inulin clearance(mL/min)		115.9	93.3	87.7	79.9	60.0

Table 1. The results of 5 renal transplant donors

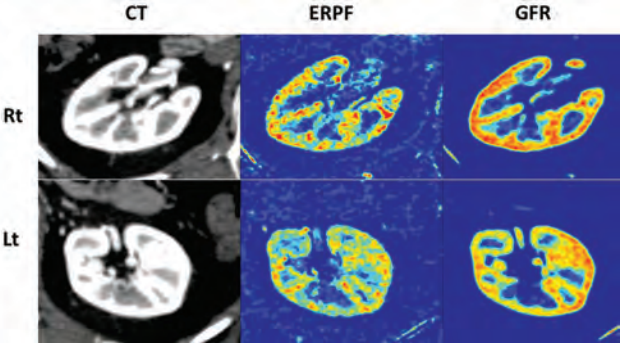


Figure1 The images of ERPF and GFR

TH-PO970

A Multivariate Model to Predict Post-Donation Kidney Function and Outcomes in Living Kidney Donors Sophie Limou,[2,3] Lola Jacquemont,[1] Edouard Gardan,[1] Simon Nusinovici,[1] Matthieu Hanf,[1] Maryvonne Hourmant.[1] *[1]CHU de Nantes, Nantes, France; [2]Inserm UMR1064, Center for Research in Transplantation and Immunology, Nantes, France; [3]Ecole Centrale de Nantes, Nantes, France.*

Background: Predicting kidney function after donation is a major challenge in living kidney donors. The aim of this study was to assess a wide range of demographics and clinical variables as non-invasive preoperative markers of post-donation kidney function.

Methods: 110 French living kidney donors who had a 51Cr-EDTA scintigraphy and a measured glomerular filtration rate (mGFR) pre- (D0) and one-year post-donation (Y1) were included. Over 15 characteristics were collected for each subject before and after nephrectomy (*e.g.* sex, age, hypertension, creatinine and lipids levels). Kidney volume was quantified using three methods: total parenchymal three-dimensional renal volume (3DRV), total parenchymal renal volume contouring (RVCt), and renal cortical volume (RCoV). We tested each variable for association with Y1 mGFR using univariate and multivariate regression models. Finally, we produced receiver operating characteristic (ROC) curves to assess the performance of our model in discriminating chronic kidney disease (mGFR<60mL/min) at Y1.

Results: The mean mGFR was 105.2±17.7 mL/min at D0 and 68.1±12.8 mL/min at Y1. Total parenchymal volume measurements exhibited a high correlation with RCoV (R2=0.92 for 3DRV and 0.84 for RVCt). In univariate models, the correlation between kidney volume and mGFR was the highest for the RCoV measures with R2=0.44 ($P=2x10^{-6}$) at D0 and R2=0.59 ($P=3x10^{-11}$) at Y1. Y1 mGFR was also strongly associated with age (R2=-0.62, $P=7x10^{-13}$) and D0 mGFR (R2=0.68, $P=4x10^{-16}$). Using stepwise regressions, we developed a model integrating 5 non-invasive preoperative markers (D0 mGFR, age, RCoV, triglycerides level and birth weight) predicting Y1 mGFR with a R2=0.68. Finally, the ROC curve analysis showed that this multivariate model could reliably predict chronic kidney disease at 1-year post donation (area under the curve [AUC]=0.92).

Conclusions: The integration of non-invasive preoperative characteristics in one statistical model can accurately predict post-donation kidney function and outcomes in French living kidney donors. These results warrant validation in an independent population. Our report therefore opens the way for developing a predictive risk score that would be easily implemented in clinics.

TH-PO971

Liberalization of Living Kidney Donor Selection Criteria and Long-Term Outcomes Marco van Londen, Anthony B. Wijninga, Maarten A. de Jong, Stefan P. Berger, Gerjan Navis, Martin H. De Borst. *University Medical Center Groningen, Groningen, Netherlands.*

Background: To meet the increasing demand for donor organs, selection criteria for living kidney donors have been liberalized. The impact of this liberalization is largely unknown. We compared long-term outcomes of living kidney donors over different time periods.

Methods: In this single-center prospective cohort study, we divided 323 living kidney donors into two groups according to the year of donation (1987-2004, n=81 vs. 2005-2012, n=242). We analyzed differences in age, sex, measured GFR (mGFR, continuous iothalamate), systolic blood pressure, proteinuria, BMI, and number of antihypertensives among the two groups (1987-2004 vs. 2005-2012) at baseline and at 5 years post-donation, using Student's t-test and Pearson's Chi-square test.

Results: At donation, sex (41% vs. 50%, p=0.13) and mGFR (105±14 vs. 103±16 ml/min/1.73m^2, p=0.23) were similar among both groups. However, donors who donated after 2004 were older (46±10 vs. 53±10, p<0.001), had a higher systolic blood pressure (122±11 vs. 129±14 mmHg, p<0.001), and BMI (25±4 vs. 27±4 kg/m^2, p=0.002), and more often used antihypertensives (5% vs. 15%, p=0.04). At 5 years post-donation, individuals who donated after 2004 had a lower mGFR (72±11 vs. 68±12 ml/min/1.73m2, p=0.01) and a more pronounced mGFR reduction compared with pre-donation (-35±12 vs. -39±15 ml/min, p=0.01). There were no differences in systolic blood pressure (126±13 vs. 128±14 mmHg, p=0.44), proteinuria (1.1±2.0 vs. 0.8±1.0 g/24h, p=0.34), BMI (27±4 vs. 27±4 kg/m^2, p=0.19) or number of antihypertensives at 5 years post-donation.

Conclusions: Our study confirms a trend in the liberalization of living kidney donors, at least regarding age and blood pressure at donation. Moreover, we observed a small but significant reduction in long-term renal function in living kidney donors who donated more recently. Future studies with longer follow-up should address the impact of donor liberalization on outcomes.

Funding: Government Support - Non-U.S.

TH-PO972

Long-Term Renal and Non-Renal Morbidities in Living Kidney Donor Yaerim Kim, Hyunjin Ryu, Young Lee Jung, Jae shin Choi, Cheolgu Hwang, Mi-yeon Yu, Yon Su Kim, Hajeong Lee. *Seoul National University Hospital, Seoul, Republic of Korea.*

Background: Kidney transplantation (KT) is the best treatment option for end-stage renal disease (ESRD). Safety of kidney donor has become an overarching theme according to increase of KT from living donor. However, risk factors for renal and non-renal morbidities were not clearly identified.

Methods: We observed 1,238 living kidney donors who underwent nephrectomy from January 1986 to February 2016 in a single tertiary hospital retrospectively. We estimated overall incidences of renal morbidities including ESRD and non-renal morbidities: hypertension (HTN), prediabetes, diabetes and malignancy. In addition, we analyzed significant risk factors for renal and non-renal morbidities.

Results: A total of 901 donors who were followed up more than 1 month were finally included. Median age was 42 (IQR, 18-65) years and 47.2% was women. Preexisting HTN was found in 47 (5.2%) donors. Only three donors had impaired glucose tolerance or diabetes at the time of donation. After 27 months of follow-up, final estimated glomerular filtration rate (eGFR) was 71.3 ± 14.36 ml/min/1.73m^2. One donor progressed to ESRD. Total 20.3% of donors failed to recover up to eGFR ≥ 60 ml/min/1.73m^2. Seventy eight (8.7%) of 901 donors presented new onset HTN, 43 (4.8%) prediabetes or diabetes, and 17 (1.9%) malignancy after donation. Interestingly, donors with preexisting HTN or diabetes did not show increased inadequate renal recovery. In the multivariate analysis, women, higher BMI and lower initial eGFR contributed to new onset hypertension independently. In addition, older age, higher BMI and inadequate renal recovery elevated new onset diabetes. Malignancy after donation was affected by older age, lower serum uric acid and albumin levels. Finally, inadequate renal recovery was associated with older age, higher BMI and lower initial eGFR.

Conclusions: Post-donation renal and non-renal morbidities are not rare. In our study, donors with older age, higher BMI and lower initial GFR should be monitored meticulously for developing renal and non-renal complications after donation. It is important to control adjustable risk factors strictly such as BMI and uric acid before and after donation to maintain their residual kidney function well.

TH-PO973

Hemodialysis Patient Social Networks Promote Living Donor Transplant Discussions Avrum Gillespie,[1] Swati Rao,[3] Sarah E. Dawson,[2] Heather M. Traino,[2] Peter P. Reese,[4] Zoran Obradovic,[2] Crystal A. Gadegbeku,[3] Edward L. Fink.[2] *[1]None, Philadelphia, PA; [2]Temple University, Levittown, PA; [3]Temple University School of Medicine, Philadelphia, PA; [4]University of Pennsylvania, Philadelphia, PA.*

Background: Social contagion theory posits that ideas, attitudes, and behaviors spread within social networks. However, little is known about the structure and influence of social networks within the unique setting of hemodialysis (HD) clinics. We examine the role of patient HD social networks and discussing living donor kidney transplantation (LDKT), a well-known barrier to renal patients' access to transplantation.

Methods: Survey and observational data collected between 8/2012 and 2/2015 were used to characterize the social network of 46 hemodialysis patients in a newly opened clinic.

Results: The mean age of participants was 54yrs, 58% were male, 39% Hispanic and 30% African Americans and 65% had discussed transplant with clinic nephrologist. Thirty-two (70%) patients interacted with others to form a social network, with 44% discussing transplantation with other patients. Patients who discussed transplant with others in their network were 19 times more likely (OR 18.7; 95% C.I. 3.4-101.5; p = 0.001) to request consideration of living donation from family/friends than those who were not connected through the clinic network. Patients who discussed transplant with HD staff were also more likely to discuss the possibility of live donation (OR 5.1 C.I. 1.5-18.1, p = 0.01). Patient demographic characteristics were not associated with discussions about living donation with individuals outside the clinic setting.

Conclusions: This study found that patients who discuss transplant with other patients and staff in the hemodialysis clinic are more likely to request consideration of living donation from member of their extra-clinic networks. These findings suggest HD patient social networks are potential target for social network interventions. This research also challenges the current ecological approach to barriers to transplantation which attributes only a small role to the HD clinic and often neglects the role of patient interactions.

Funding: Other U.S. Government Support, Private Foundation Support

TH-PO974

Racial/Ethnic Differences in Barriers to Kidney Transplant Evaluation among Hemodialysis Patients Derek R. Jones,[3] Zhiying You,[1] Jessica B. Kendrick.[2] *[1]UC Denver, Aurora, CO; [2]University of Colorado Denver and Denver Health Medical Center, Denver, CO; [3]University of Colorado School of Medicine, Denver, CO.*

Background: Only a small percentage of patients with end stage renal disease receive a transplant and this is particularly the case for racial/ethnic minorities. Our objective was to identify barriers to transplant evaluation in our dialysis centers.

Methods: We conducted a survey of adult hemodialysis patients in the Denver Metro area. Participants completed an 11-item survey with demographic information and questions regarding time on dialysis, if a provider ever spoke to them about a transplant and whether they had been evaluated for a transplant. Reasons for not having an evaluation were explored. Descriptive statistics were used to provide summaries of the responses.

Results: 167 patients completed the survey (response rate 63.9%). The majority of participants were male between the ages of 50-79 years and were Hispanic (49%) or Non-Hispanic Black (31.7%). 140 patients (84.0%) reported having a discussion about kidney transplantation with their doctor but only 53% (N=89) reported having a transplant evaluation. Fewer Non-Hispanic Blacks reported having a transplant evaluation than Non-Hispanic whites or Hispanics (43.4% vs. 57.7% (Whites) and 59.7% (Hispanics)) which trended towards statistical significance, p=0.07. The most frequent responses of the patients who had not been evaluated were: not referred by their provider (46%), did not know how to proceed (43.4%) or did not understand the benefits (39.5%) or transplant process (38.2%). Additionally, compared to Non-Hispanic whites, Blacks and Hispanics reported less understanding of the benefits and/or process of transplant.

Conclusions: Improved patient-provider communication and kidney transplantation education may reduce disparities in access to kidney transplantation.

Funding: NIDDK Support

TH-PO975

Care and Outcome of Refugees Kidney Transplant Patients in Jordan Kamel Hatahet,[3] Mohamed A. Sekkarie,[2] Sami Alasfar.[1] *[1]John Hopkins University Hospital, Baltimore, MD; [2]Nephrology and Hypertension Associates, Bluefield, WV; [3]Syrian American Medical Society, Waldorf, MD.*

Background: Taking care of displaced Kidney Transplant recipients (KTRs) is a big challenge and requires having a sustainable infrastructure. The Syrian American Medical Society (SAMS) shares its experience in managing these patients who are refugees camps in Jordan.

Methods: The screening process started by organizing medical missions to Jordan through SAMS established mobile clinic. SAMS medical missions were held every 3 months. The mission included one nephrologist from the US assigned to examine all KTRs, evaluate their recent labs, and to modify their immunosuppressants (IS) regimen. Others aims of the missions are to assure access and coverage for IS medications and to assess barriers for care.

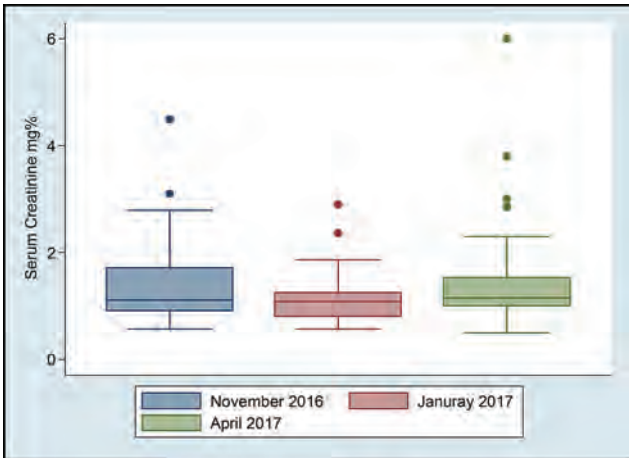
Results: In July 2016, missions started providing care and medications for 17 KTRs and the number of patients has increased up to 41 patients April 2017. IS were provided and shipped from the U.S and given to the KTRs without charges with 3 months' worth of IS with each medical mission. No graft loss was noted throughout this period. There was one death due to pancreatic cancer. Figure 1 shows that serum Creatinine measurements have remained stable since mission started. Patients' characteristics is shown in table 1 Barriers included lack of a dedicated local nephrologist to address urgent medical problems, lack of affiliation with a nearby hospital to provide additional care such as renal biopsies, and costs of the IS and their shipments.

Conclusions: Medical missions to Syrian refugees' camps in Jordan seem to achieve a good outcome in KTRs. More work is needed to reach out to patients in other camps and countries and to overcome barriers. Future steps may include hiring a local nephrologist or developing affiliations with local hospitals.

Funding: Private Foundation Support

Table1

Gender	23 M, 18 F
Age range	6-73 years
Patients on mycophenolate	39
Patients on calcineurin inhibitor	30 on tacrolimus and 11 on cyclosporine
Year of transplant	2000-2016



TH-PO976

Kidney Donor Risk Index Is a Good Prognostic Tool for Prediction of Early Post-Transplant Kidney Function and Graft Survival in a Korean Population Han Ro,[3] Miyeun Han,[4] Jong Cheol Jeong,[1] Ji Yong Jung,[3] Wookyung Chung,[2] Curie Ahn.[5] *[1]Ajou University Hospital, Suwon, Republic of Korea; [2]Gachon University Gil Hospital Nephrology, Incheon, Republic of Korea; [3]Gachon University Gil Medical Center, Incheon, Republic of Korea; [4]SEOUL NATIONAL UNIVERSITY HOSPITAL, SEOUL, Republic of Korea; [5]Seoul National University Hospital, Seoul, Republic of Korea.*

Background: Kidney donor risk index (KDRI) is used in the United States to estimate the deceased donor kidney. However, KDRI is not yet used in Asian population. We tried to validate KDRI in assessment of deceased donor kidney in a large number of Korean population group.

Methods: The data of Korean Organ Transplantation Registry (KOTRY) between 2009 to 2012 was used in the analysis. Among 1924 deceased donor kidney transplantation, 1582 cases in which KDRI score could be calculated were included in this study. We investigate the impact of KDRI on the graft function and graft survival.

Results: We divided the donors by KDRI tertile (T1: range, 0.6432~1.17025, T2: range, 1.17057~1.48566, T3: range, 1.48630~3.80629). The recipients of T1 were younger and had less diabetes. Mean estimated glomerular filtration rate at post transplant 1 year of each group was 76.1 ±21.0, 64.7 ±20.3, 55.5 ± 21.0 ml/min/1.73m^2 respectively. In the Cox regression analysis, KDRI showed good association with death censored graft survival, of which median follow up duration was 24.6 months (hazard ratio 1.778, 95% confidence interval 1.087-2.906, p=0.022).

Conclusions: KDRI is a good tool for estimation of early posttransplant outcomes in Korean population.

Funding: Government Support - Non-U.S.

TH-PO977

Defining the Delays to Kidney Transplant among American Indian Patients with Kidney Disease Mira T. Keddis,[1] Muneeb Ilyas,[1] Nan Zhang,[2] Raymond L. Heilman,[3] Amit Sharma.[1] *[1]Mayo Clinic, Phoenix, AZ; [2]Mayo Clinic Arizona, Scottsdale, AZ; [3]None, Phoenix, AZ.*

Background: The purpose of this study is to examine differences in the time from kidney transplant (KTx) evaluation to wait-listing and KTx rates in a cohort of American Indian (AI) patients compared to whites from 2012 to 2016 at a single center.

Methods: All AI patients presenting for KTx evaluation at Mayo Clinic Arizona from 2012 to 2016 were included (n=300). A random sample of non-Hispanic white controls matched for year of KTx evaluation was included (n=300).

Results: Compared to white controls, AI patients were younger (mean age 53±12.2 vs 57.2±13.4 years, p=0.0001), more likely to have diabetes (79 vs 41%, p<0.0001) and diabetic kidney disease (66.3 vs 35.7%, p<0.0001) and require dialysis at the time of evaluation (88 vs 58.3%, p<0.0001). They were more likely to have limited functional capacity at the time of KTx evaluation compared to white controls (55.3 vs 26.6%, p<0.0001). Several socioeconomic variables differed between the two groups with AI patients more likely to have the following associations: less than high school education (24.9 vs 7.3%, p<0.0001), single or widowed (32.6 vs. 17.8, p=0.008), and unemployed (81.7 vs 68.7%, p=0.001), There was no difference in the rate of prior history of cardiovascular disease between the two groups. AI patients had significantly lower rates of cancer diagnoses compared to white controls (3.3 vs 20.1%, p<0.0001). The time from initial KTx evaluation to selection conference decision regarding candidacy was delayed by 38 days for AI patients (mean 83 vs 45 days, p=0.0001) and they were more likely to be denied KTx compared to white controls (28.7 vs 19.2%, p=0.04). Reasons for denial did not differ between the two groups. Among patients deemed acceptable for KTx, AI patients were less likely to be listed on UNOS (84.2 vs 92.1 %, p=0.019), experienced longer delays from the time of approval for KTx to UNOS listing (median 42 vs 16 days, p<0.0001), and had longer waiting time from UNOS listing to receiving KTx (median 499 vs 380, p<0.0001) compared to whites. Transplant rates were significantly lower among AI compared to whites (25.5 vs 62%, p<0.0001).

Conclusions: Our study confirms that AI patients presenting for KTx suffer from significant delays in all steps of KTx evaluation and KTx rates in current times and highlights several clinical and socio-economic differences that may explain this disparity.

TH-PO1000

High Levels of Parathyroid Hormone after One Month of Renal Transplantation Are Related to Long Term Graft Loss Carlo M. Alfieri, Maria Teresa Gandolfo, Valentina Binda, Donata Cresseri, Mariarosaria Campise, Anna Regalia, Maria Meneghini, Piergiorgio Messa. *Fondazione IRCCS Ca' Granda Ospedale Policlinico Milan, Milan, Italy.*

Background: Renal transplantation (RTx) only partially corrects certain metabolic alterations, especially in mineral metabolism (MM). Our aim was to examine the effect of RTx during the 1styear of RTx on MM parameters and to evaluate the factors mostly related to long term graft outcome.

Methods: In 531 RTx pts (age:48[39;58]yrs–303males), transplanted in our unit between 2004 and 2014, clinical parameters, blood and urinary samples were collected before RTx and at 1, 6, 12 mths after RTx. Median follow up was 7[2-12]yrs.

Results: 84% of pts received a RTx from a deceased donor; 72% and 20% of pts were treated with haemodialysis and peritoneal dialysis before RTx. Time of dialysis was 48[30-71]mths. In the overall cohort MM parameters before RTx were: Ca 9.3[8.8-9.8] mg/dL, P 5.0[4.05-5.85] mg/dL, iPTH 205[123-443]pg/mL, ALP 106[66-170] U/L. Cold ischemia time (CT) was 13[11-16]h. In 13% of pts DGF was reported, and 13% of pts had a rejection during the 1st year of RTx. During the 1st year of RTx, 6% of pts received cinacalcet. Thirty-five% of pts were treated with active vitamin D, whereas in 11 % were supplemented with natural vitamin D alone. In the 1st year of RTx, a reduction of iPTH levels was observed(p=0.005). During follow up time, 66 pts restarted dialysis (D+). Compared to pts with a functioning graft (D-), D+ had longer CT(p=0.01) and at the 3-timepoints considered, worst renal function, higher urinary protein excretion and of iPTH. A difference in 1st year rejection prevalence was found (p=0.001) between the two groups. In multivariate analysis only iPTH at 1st mth and not iPTH at 12th mth resulted independently related with graft loss(p=0.03). Using ROC curve, the the discriminatory power in predicting graft outcome was tested for: 1st mth eGFR (AUC 0.37±0.04 – p=0.003), 1st mth Prot-U(AUC 0.62±0.04 – p=0.002) and 1st mth iPTH (AUC 0.62±0.05 – p=0.01 – cut-off value 75 pg/mL). The inclusion of iPTH to eGFR and Prot-U provided an increase in discriminatory power which was +30% for eGFR + iPTH (AUC from 0.37 to 0.67 –p<0.001) and +3% for Prot-U + iPTH (AUC from 0.62 to 0.65 –p=0.002).

Conclusions: Our data confirm that RTx is able to influence MM from the beginning, and that early elevated iPTH levels at 1st month of RTx may play a role on long-term graft outcome.

TH-PO1001

Impact of Elevated PSA on Time to Kidney Transplant and Mortality in ESRD Patients Nagaraju Sarabu,[2] Nicholas K. Schiltz,[1] Donald E. Hricik.[2] *[1]Case Western Reserve University, Cleveland, OH; [2]University Hospitals Case Medical Center, Rocky River, OH.*

Background: Conflicting opinions and practices exist about screening for prostate cancer prior to kidney transplant with a PSA because of the concern that it might delay transplant causing more harm than benefit.

Methods: This study included incident male ESRD patients over 45 years from the 1999-2012 United States Renal Data System, linked with Medicare claims data. Our main study variable of interest was elevated prostate specific antigen (PSA) as indicated through an ICD-9-CM diagnosis code. Primary outcomes of interest were time to kidney transplant and mortality. We used propensity score matching to control for selection bias, and Cox proportional hazards models and Kaplan Meier curves to compare the risk between men with elevated and non-elevated PSA.

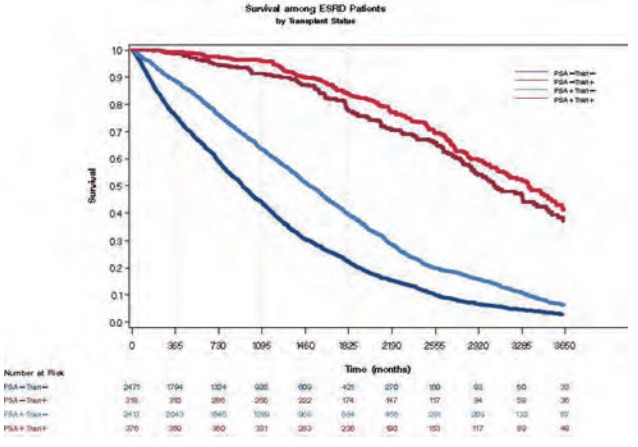
Results: 2789 of 64307 (4.3%) of the patients had elevated PSA. Figure 1 shows the baseline characteristics of 2789 patients with elevated PSA and 2789 propensity based matched controls. Elevated PSA was associated with lesser mortality (HR:0.66; CI: 0.62-0.70), and did not significantly increase time to transplant (HR: 0.80; CI: 0.80-1.06). Kidney transplant significantly improved survival regardless of the PSA status prior to transplant.

Conclusions: Elevated PSA is not a contraindication for kidney transplant, and therefore should not be delayed.

Characteristic	No Elevated PSA (2789)		Elevated PSA (2789)		p-value
Age group					<.001
40-44	70	3%	37	1%	
45-49	99	4%	88	3%	
50-54	181	6%	183	7%	
55-59	254	9%	242	9%	
60-64	386	14%	403	14%	
65-69	573	21%	685	25%	
70-74	592	21%	666	24%	
75-79	634	23%	485	17%	
Race					0.370
Black	760	27%	795	29%	
White	1,919	69%	1,899	68%	
Other	110	4%	95	3%	
Hispanic ethnicity	231	8%	258	9%	0.218
Dialysis Type					0.879
CAPD	151	5%	161	6%	
CCPD	69	2%	71	3%	
Hemo	2,563	92%	2,549	91%	
Inability to ambulate	56	2%	61	2%	0.709
Inabilty to transfer	21	1%	22	1%	0.999
Comorbidities					
Atherosclerotic heart disease	343	12%	332	12%	0.681
Alcohol dependence	41	1%	45	2%	0.745
Cancer	284	10%	283	10%	0.999
Congestive heart failure	699	25%	700	25%	0.999
COPD	267	10%	246	9%	0.354
Cerebrovascular disease	254	9%	233	8%	0.343
Diabetes	932	33%	967	35%	0.337
Hypertension	2,359	85%	2,375	85%	0.575
Needs assistance with ADL	79	3%	89	3%	0.481
Peripheral vascular disease	367	13%	350	13%	0.522
Current tobacco user	158	6%	172	6%	0.461
Employment Status					0.925
Employed	292	10%	282	10%	
Retired	2,088	75%	2,110	76%	
Unemployed	361	13%	351	13%	
Other	48	2%	46	2%	
Insurance					
Medicare Advantage	32	1%	27	1%	0.601
Employer Group Plan	584	21%	557	20%	0.388
VA	19	1%	27	1%	0.300
Medicaid	480	17%	472	17%	0.803
Medicare	2,085	75%	2,116	76%	0.352
None	165	6%	182	7%	0.375
Other	960	34%	980	35%	0.593
Dead at end of study period	2,221	80%	1,969	71%	<.001
Received a transplant	318	11%	2,789	100%	0.021

All cells reflect counts. For binary variable comparisons, p values obtained by Fisher's Exact Test. For multicategorical variables, p values from Likehood Ratio Chi-Square Test.

Baseline characteristics of propensity matched groups



Kidney Transplant Improves Survival regardless of PSA status

TH-PO1002

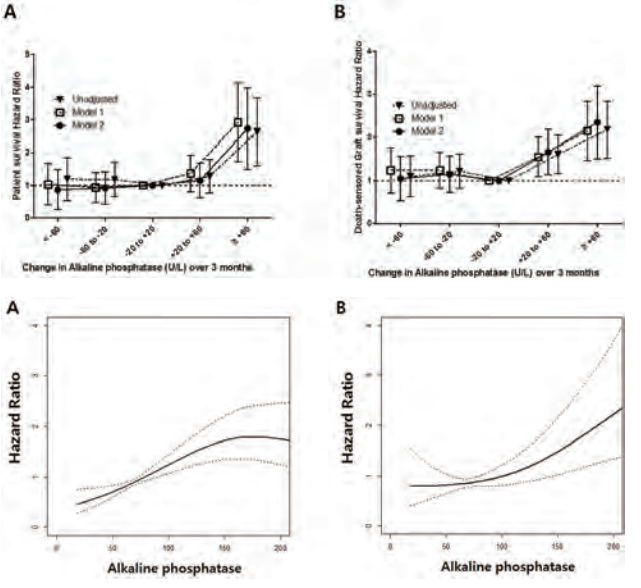
Pre- and Post-Transplant Serum Alkaline Phosphatase Predicts Graft Failure and Mortality in Kidney Transplant Recipients Yong Chul Kim,[1] Seokwoo Park,[1] Hajeong Lee,[1,2] Chun Soo Lim,[2,3] Yon Su Kim,[1,2] Jung Pyo Lee.[2,3] *[1]Seoul National University Hospital, Seoul, Republic of Korea; [2]Seoul National University College of Medicine, Seoul, Republic of Korea; [3]Seoul National University Boramae Medical Center, Seoul, Republic of Korea.*

Background: Recent studies showed that high levels of serum alkaline phosphatase (AlkPhos) are associated with all-cause or cardiovascular death in chronic kidney diseases. However, there are apparently no data on the effect of AlkPhos in kidney transplant recipients (KTRs). The aim of this study was to evaluate whether serum AlkPhos is associated with graft failure and mortality after kidney transplantation.

Methods: Among the 3029 kidney transplant recipients (KTRs) who were enrolled in a multicenter cohort, we examined the association of pre- and post-transplant serum AlkPhos levels and long-term outcomes in KTRs.

Results: Pre-transplant serum AlkPhos ≥ 80 IU/L was associated with a hazard ratio (HR) for graft failure of 1.571 (95% CI 1.146-2.152, P = 0.005) in a fully adjusted model. Death-censored graft failure (DCGF) rate in kidney recipients gradually increased along the increments of AlkPhos. Also, a rise in serum AlkPhos by 40 IU/L during the first 3 months after kidney transplantation was associated with higher rates of DCGF (HR 2.353, 95% CI 1.506-3.676) and higher rates of mortality (HR: 2.733, 95% CI 1.479-5.050). Cox regression models using time-varying AlkPhos for initial 3 months after transplantation demonstrated significant relationships between AlkPhos and DCGF (HR 1.39, 95% CI 1.04-1.84) or mortality (HR 2.14, 95% CI 1.39-3.27).

Conclusions: Increased pre- and post-transplant serum AlkPhos and a rise of serum AlkPhos during early period after kidney transplantation is associated with graft failure and mortality in kidney transplant recipients.



TH-PO1003

High-Resolution Digital Analysis of Leukocyte Densities in Early Surveillance Biopsies Significantly Improves Prediction of Kidney Transplant Function after Four Years of Follow-Up Sibylle Von Vietinghoff,[1] Jan H. Braesen,[3] Abedalrazag A. Khalifa,[3] Jessica Schmitz,[1] Gunilla Einecke,[2] Bernhard M. Schmidt,[1] Anke Schwarz,[1] Hans H. Kreipe,[1] Hermann G. Haller.[1] *[1]Hannover Medical School, Hannover, Germany; [2]Medical School Hannover, Hannover, Germany; [3]Medizinische Hochschule Hannover, Hannover, Germany.*

Background: Minor histopathological changes are difficult to quantify by eye. The impact of inflammation on renal allograft survival has been demonstrated in grafts with rejection, and, on a molecular level, also in early surveillance biopsies. We assessed leukocyte abundance in early surveillance biopsies by digital image analysis and analyzed impact on outcome.

Methods: In 67 surveillance biopsies six weeks after transplantation a full Banff classification was performed. T cell (CD3), B cell (CD20), macrophage (CD68) and dendritic cell (CD209) densities and CD206 and HLA-DR markers were assessed by digital image analysis (Definiens system).

Results: An average surface area of 4.7±2.4 mm^2 renal cortex was assessed, with average 1.7%CD3, 0.5%CD20, 0.3%CD68, 0.2% CD209. CD3, CD20 and CD68% were significantly higher in grafts with histological rejection. High CD68 density associated with lower combined patient and graft survival after four years. CD20 and CD68 densities inversely correlated with eGFR. CD68 correlated with eGFR loss. $CD68^+$ macrophages were localized mainly in the interstitium. Tubular macrophages increased in grafts with rejection. HLA-DR and CD206 were assessed for M1 and M2 polarization with more M1 positivity in the cortex, and more M2 in the medulla. Among histological measurements including a complete Banff classification, only CD68 density was a significant predictor of CKD IV after four years. It also significantly contributed to the best eGFR prediction set in multivariable linear regression analysis of clinical and pathological parameters. The original CD68 median maintained its discriminative power for survival and eGFR in a second independent cohort.

Conclusions: In comparison to other histopathological markers and as an addition to known clinical risk factors, $CD68^+$ macrophage density measurement significantly improves prognostic value of early surveillance biopsies.

Funding: Government Support - Non-U.S.

TH-PO1004

Renal Parenchymal Calcifications in a Cohort of Renal Transplanted Patients and Their Correlations with Long Term Graft Outcome Carlo M. Alfieri, Gabriella Moroni, Donata Cresseri, Anna Regalia, Francesca Zanoni, Valentina Binda, Maria Teresa Gandolfo, Mariarosaria Campise, Paola Simonini, Masami Ikehata, Maria Meneghini, Piergiorgio Messa. *Fondazione IRCCS Ca' Granda Ospedale Policlinico Milan, Milan, Italy*.

Background: Renal calcifications(RC) have been described in kidney transplantation(KTx), but the aetiology and significance of this finding are still unclear. Our aim is to evaluate the prevalence an the clinical impact on long term graft prognosis of RC.

Methods: 95 KTx pts, submitted to renal biopsy(RBx) on clinical indication from 2009 to 2012 were followed up until 2016 (FU time:(5[4-6]yrs). Clinical and biochemical data were collected at the time of RBx(TBX),12mth before(T-12) and after(T+12) the RBx. Exposition to Ca, P and PTH during the year before RBx was calculated by averages of the observed values. In yrs after T+12(Tfu), creatinine, Ca, P, PTH, ALP, Prot-U were recorded annually and analyzed as averages of observed values. RBx were studied for general histology and for RC by Von Kossa(VK) staining. In pts with more than one RBx, only the 1st one was considered. Pts in which VK was negative or slight positive were defined as group1(VK-1:n 68;46 slightly positive), while pts with moderate or severe VK positivity were included in group2(VK-2:n=27;8 high VK positive).

Results: The pts were 51 males and 44 females, age 50±12 yrs. VK groups did not differ for gender, age, type of KTx, VK-2 had longer time of KTx(p= 0.03). At T-12, TBX and T+12, renal function was similar between the groups. No differences were found in mineral metabolism(MM) at TBX, while VK-2 had a lower exposition to PTH during the year before RBx(p<0.001). VK-2 had higher glomerulosclerosis(GS;p=0.04). During Tfu, VK-2 pts had worst sCr(p=0.04) higher PTH and ALP(p=0.03;p=0.002). 33 pts have lost their graft during the F-U time, with a higher prevalence in VK-2(p=0.0006). By means of Cox regression and Kaplan Meier analysis belonging to VK-2 was the stronger independent parameter related to graft loss (HR=3.49–p=0.001;K-M p<0.0001).

Conclusions: The prevalence of RC in RBx is quite high. RC correlated with PTH exposition during the year before RBx, but not with Ca and P levels. Time of KTx and GS also were related to RC, assigning to RC a significance of chronic damage rather than a simply result of MM imbalance, at least in the RBX performed on clinical indication. A relation between VK positivity at TBX and long term graft loss was also found.

TH-PO1005

Dynamics of DNA Methylation in Renal Allograft: From Early Ischemia/Reperfusion Injury to Late Fibrosis Response Sai Vineela Bontha, Valeria Mas. *University of Virginia, Charlottesville, VA.*

Background: The mechanisms of development of fibrosis post-transplantation are not completely understood. Early graft insults like ischemia/reperfusion injury followed by course of its response/repair could involve changes in molecular determinants including DNA methylation (DNAm) which influence long term allograft function. In the current study we assessed the dynamics of DNAm across 1) pre-implant biopsies post-ischemic injury (PI) 2) post-reperfusion (PR) and 3) >24 months post kidney transplantation (KT).

Methods: Infinium 450K methylation (n = 96) and gene expression (n = 182) arrays were performed in PI, PR and KT renal allograft biopsies and analyzed. Genome runner was used to assess distribution and enrichment of Dme CpG sites along regulatory features. Integrative analyses of differentially methylated (Dme) CpGs and corresponding differential gene expression were performed at each matched time points.

Results: PI allografts classified based on progression to allograft dysfunction showed 1,188 Dme CpGs mapped to genes involved in inflammation and metabolism. When paired PI and PR allografts were compared there was apparent change in DNAm of genes involved in pathways like *NRF2* mediated oxidative stress response and functions like cellular assembly and organization, cell death and survival. Integration analysis showed Dme and expression of genes involved in energy metabolism, transporters and transcription factors important in regulation of immune response. Further, comparison of post-KT allografts with differential outcomes revealed 21,351 Dme CpG sites. The Dme CpGs observed at early time points were mostly hypomethylated and promoter associated. However, a shift in the pattern was observed in later stages. Dme CpGs were interestingly located in gene bodies and in evolutionarily conserved tissue specific regions. Integration analysis corroborated with findings as gene expression changes in kidney tissue specific regions like tubular epithelium was observed.

Conclusions: Shift in DNAm pattern over time in renal allograft is evident with corresponding change in gene expression pattern. It is important to study closely the sequential changes to evaluate timely therapeutic intervention based on the pathways dysregulated at different molecular levels.

Funding: NIDDK Support

TH-PO1006

Investigating Angiotensin II-Regulated Proteins as Biomarkers of Fibrosis in Kidney Transplant Recipients Zahraa Mohammed-Ali,[4] Shelby Reid,[2] Tomas Tokar,[6] Paul M. Yip,[4] Alexandre Tavares-Brum,[1] Heloise Cardinal,[1] Joseph Kim,[3] Ana Konvalinka.[5] *[1]Centre Hospitalier de l'Université de Montréal, Montral, QC, Canada; [2]Institute of Medical Science, University of Toronto, Toronto, ON, Canada; [3]Toronto General Hospital, University Health Network, Toronto, ON, Canada; [4]University Health Network, Toronto, ON, Canada; [5]University Health Network, University of Toronto, Toronto, ON, Canada; [6]Princess Margareth Cancer Center, Toronto, ON, Canada*.

Background: AngiotensinII, the main effector of the renin-angiotensin system (RAS), causes kidney interstitial fibrosis/tubular atrophy (IFTA). However, specific markers of kidney AngII activity remain unknown. Here we report on the urine excretion of 6 AngII-regulated proteins (BST1, GLNA, LAMB2, LYPLA1, RHOB and TSP1), and show that 1) they reflect IFTA in kidney transplant recipients; 2) they are modified by RAS inhibition.

Methods: A previously developed mass spectrometry-based assay was used to quantify 6 AngII-regulated proteins in urine of 2 cohorts of kidney transplant recipients from a single Canadian centre: 1) 19 patients with IFTA and 19 stable controls with concomitant urine and biopsy samples; 2) 20 patients with urine and biopsy samples before and after RAS inhibition. Differences in creatinine-adjusted urine levels of AngII-regulated proteins between IFTA and control patients were assessed using two-tailed t-test. Correlations between AngII-regulated proteins and traditional markers of kidney graft function were evaluated using Spearman's rank correlation. Fixed-effects model was used to assess changes in AngII-regulated proteins following RAS therapy.

Results: Urine excretion of all AngII-regulated proteins was significantly higher in IFTA compared to control (ln fmol/µmol of creatinine ± SD, BST1: 17.46±0.65 vs 9.76±0.20, p=0.01; GLNA: 9.73±0.52 vs 1.62±0.17, p=0.009; LAMB2: 90.22±2.99 vs 54.05±1.55, p=0.03; LYPLA1: 6.61±0.77 vs 2.13±0.05, p=0.0002; RHOB: 9.02±3.42 vs 1.10±0.13, p=0.004; TSP1: 8.05±0.81 vs 3.47±0.16; p=0.002). These proteins correctly separated IFTA and control patients in unsupervised hierarchical clustering analysis. Urine excretion of all AngII-regulated proteins correlated with each other, but not with serum creatinine and total urine protein. All AngII-regulated proteins negatively correlated with RAS inhibitor use over time (fixed effects coefficient<0); however, GLNA and TSP-1 were most significantly decreased (p<0.05).

Conclusions: Urine excretion of AngII-regulated proteins was significantly increased in patients with IFTA and was modified by RAS inhibition. These proteins may represent coveted markers of kidney fibrosis, and may be valuable in guiding therapy with RAS inhibitors.

Funding: Government Support - Non-U.S.

TH-PO1007

Clinical and Histologic Review of Transplant Nephrectomy Cases in a Single Center Soo Ya Bae,[1] Chung Hee Baek,[2] Su-Kil Park.[2] *[1]Asan Medical Center, Seoul, Republic of Korea; [2]Asan Medical Center, Songpa-gu, SEoul, Republic of Korea*.

Background: Despite advancement in the management of kidney allograft, several indications for transplant nephrectomy still exists. Chronic allograft intolerance syndrome is the most common reason of transplant nephrectomy (TN). Recent studies reported antibody mediated rejection (ABMR) plays an important role in chronic allograft injury and subsequent graft failure. There is few studies about histopathology of TN, resulting lack of knowledge about predominant type of rejection resulting chronic allograft intolerance syndrome. We investigated clinical indications and histologic diagnosis of TN cases, especially the type of rejection.

Methods: From January 1995 to March 2016, 96 cases of TN were done in Asan Medical Center. We reviewed 88 cases of TN for baseline clinical characteristics, clinical indication of TN and histologic diagnosis after TN.

Results: Most common cause of end stage renal disease (ESRD) were primary glomerular nephritis (23.9 %) and hypertension (23.9 %). Most common clinical indication of TN was chronic allograft intolerance syndrome (43.3%). Rejection was the most common histologic diagnosis of TN (73.1%), of chronic allograft intolerance syndrome cases either (92.1%). Among 24 rejection cases diagnosed by Banff 2007, 13 cases were T cell mediated rejection (TCMR), and 10 cases were mixed rejection. Among 10 rejection cases by Banff 2013, 2 cases were TCMR, and 8 cases were mixed rejection. Among 14 cases of chronic allograft intolerance syndrome by Banff 2007 and 2013 classifications, 6 cases were TCMR, and 8 cases were mixed rejection. 9 cases showed discrepancies between clinical indication and histologic diagnosis (10.2 %), 7 cases showed discrepancies in the type of rejection (8.0 %).

Conclusions: Chronic allograft intolerance syndrome was the leading clinical indication for TN, and rejection was the most common histologic diagnosis. By Banff 2007 and 2013 classification, pure TCMR and mixed rejection cases were predominant. Some discrepancies between clinical indication and histologic diagnosis existed, with discrepancies in the type of rejection as well.

TH-PO1008

Uncovering the Association between Early Histological Features of Diabetic Kidney Disease and Renal Allograft Outcomes Jacob Cho, Chelsea C. Estrada, Sandeep K. Mallipattu. *Stony Brook Medicine, Stony Brook, NY.*

Background: Diabetes Mellitus is a risk factor for worse renal allograft survival, but patients typically do not lose their allograft due to diabetic kidney disease (DKD). However, it remains unclear whether early diabetic changes in the transplanted kidney are associated with worse outcomes. The objective of this pilot study is to determine whether histological features consistent with early DKD are predictive of subsequent graft loss.

Methods: We reviewed consecutive, clinically indicated, renal allograft biopsies performed at Stony Brook University Hospital from 2010 to 2015. Biopsies with either mesangial matrix expansion (MME) or thickened basement membrane (TBM) were classified as early DKD (eDKD). Patients with a final diagnosis of transplant glomerulopathy (TG) or overt DKD were excluded. Graft failure, creatinine, and eGFR were also collected at 6 months, 1 year and 2 years post biopsy. All data was assessed for normality, and then parametric or non-parametric tests were employed for data analysis.

Results: In total, 247 renal transplant biopsies were reviewed. Biopsies were performed at a mean of 3.98 ± 0.93 years post-transplantation. In total, 83 were excluded for either overt DKD or TG. Of the remaining 164 biopsies, 89 (54.2%) were classified as eDKD and the rest (45.7%) as non-diabetic kidney disease (NDKD). Baseline demographics for the two groups are in **Table 1**. Mean HbA1C was 6.0 ± 0.1% in the eDKD group and 6.2 ± 0.2% in the NDKD group. In all, 25/89 (28.1%) patients in the eDKD had graft failure at a mean of 0.9 years post biopsy, as compared with 16/75 (21.3%) patients in the NDKD group (p= 0.368).

Conclusions: In this small cohort, these data suggest there is a trend towards worse renal allograft outcomes in patients with early histological features of DKD. Further analysis of eGFR trends and a larger sample size are required to determine the significance of early DKD changes on allograft outcomes.

	eDKD	NDKD	
N	89	75	*p value*
Age (years)			
at time of transplant	45.8 ± 1.8	44.7 ± 2.1	*0.687*
at time of biopsy	49.4 ± 1.7	46.6 ± 2.1	*0.297*
Gender			*0.422*
Male	48.5%	34.7%	
Female	51.5%	41.6%	
Race			*0.251*
Caucasian	57.3%	46.7%	
Black	19.1%	22.7%	
Hispanic	11.2%	8.0%	
Other	12.3%	22.7%	
Average HbA1c	6.0 ± 0.1%	6.2 ± 0.2%	*0.426*
Allograft Failure	28.1%	21.3%	*0.368*

Table 1

TH-PO1009

The Association of Calcium Oxalate Deposition in Kidney Allografts with Graft and Patient Survival Ragnar Palsson,[1,2] Anil K. Chandraker,[1,2] Gary C. Curhan,[1,2] Gearoid M. McMahon,[1,2] Sushrut S. Waikar.[1,2] *[1]Brigham and Women's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA.*

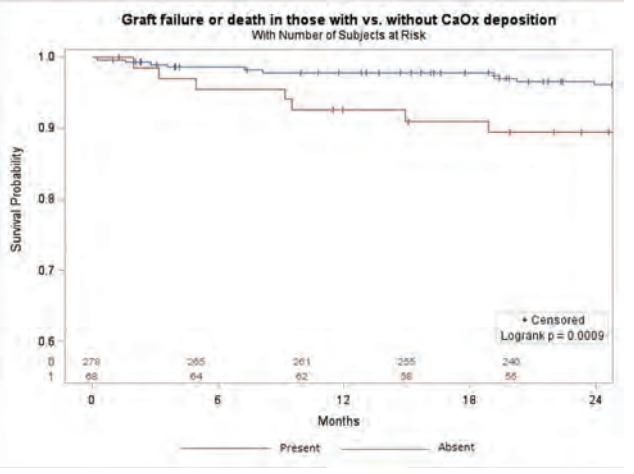
Background: Oxalate is a dicarboxylic anion that can precipitate with calcium and cause kidney injury. Patients with end-stage renal disease (ESRD) have elevated plasma levels of oxalate. After kidney transplant (Tx), hyperoxaluria ensues, increasing risk of calcium oxalate deposition (CaOxD) in the allograft. Few studies have examined risk factors for CaOxD in this setting and its association with patient outcomes.

Methods: We performed a retrospective cohort study of patients who had allograft biopsies at our hospital within 3 months of Tx, from 10/1999–2/2015. The presence or absence of CaOxD was extracted from biopsy reports. We determined risk factors for CaOxD and evaluated its association with the composite outcome of graft failure or death at 2 years.

Results: 68 of 346 patients had CaOxD in allograft biopsies. Factors associated with CaOxD in multivariable models adjusting for serum calcium, black race and donor type (living vs. deceased) were: dialysis vintage (odds ratio (OR) 1.15, 95% CI 1.01-1.30 per additional year), diabetes as a cause of ESRD (OR 2.67, 95% CI 1.26-5.63) and elevated serum creatinine at the time of biopsy (OR 1.31, 95% CI 1.16-1.48 per additional mg/dL). After further adjusting for delayed graft function (DGF), these associations became non-significant with only DGF remaining a significant predictor of CaOxD. CaOxD was associated with 2.56-fold (95% CI 1.20-5.45) increased odds of graft failure or death at 2 years in a multivariable model adjusted for black race, donor type, dialysis vintage and acute rejection. After adjusting for DGF, the association between CaOxD and graft failure or mortality became non-significant (OR 1.56, 95% CI 0.68-3.57).

Conclusions: CaOxD is common in patients with early graft dysfunction after Tx, and is strongly associated with DGF and poor graft and patient survival. Whether CaOxD in the allograft contributes to poor outcomes through DGF or other mechanisms is a possibility that could be tested in trials involving oxalate lowering therapies prior to Tx.

Funding: NIDDK Support



TH-PO1010

Urinary Microvesicles in Kidney Transplantation: A Source for Novel Early Biomarkers for Delayed Graft Function and Overall Outcome Fabian Braun,[1] Markus M. Rinschen,[1] Corinna Klein,[2] Denise Buchner,[3] Roger Wahba,[3] Dirk L. Stippel,[3] Christine E. Kurschat,[1,2] Bernhard Schermer,[1] Andreas Beyer,[2,4] Thomas Benzing,[1,2] Roman-Ulrich Mueller.[1,2] *[1]Department II of Internal Medicine and Center for Molecular Medicine Cologne, University Hospital Cologne, Cologne, Germany; [2]Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases, University of Cologne, Cologne, Germany; [3]Department of General, Visceral and Cancer Surgery, Division of Transplantation Surgery, Transplant Center Cologne, University Hospital of Cologne, Cologne, Germany; [4]Systems Biology of Ageing Cologne, SyBaCol, University of Cologne, Cologne, Germany.*

Background: Microvesicles (MVs) are a promising source for cellular material comprising specific proteins and nucleic acids that can be isolated easily from most body fluids. This is especially true for urinary microvesicles, yet their implementation in routine diagnostics is still subject to investigation. We hypothesize that the diagnosis of kidney transplant failure by kidney biopsy could in particular benefit from the addition of novel noninvasive biomarkers for the prediction of graft survival.

Methods: We established a protocol of differential centrifugation, to isolate MVs from urine collected from living kidney transplant recipients and their corresponding donors over the course of 20 kidney transplantations. We collected whole urine samples on day -1 (donor sample), 0, 1 and 3 months after transplantation (recipient sample). MV pellets were analyzed using quantitative mass spectrometry based proteomics. We used linear regression models to find proteins which linearly change their abundance in correspondence to clinical parameters, e.g. GFR measured at 6 and 12 Months after transplantation.

Results: With our approach we were able to identify >1500 proteins present in at least 50% of the collected samples. Strikingly, using hierarchical cluster analysis we detected a clear clustering of the sample proteomes by time point of urine collection. Furthermore we detected specific proteomic time course patterns over the course of transplantation, with complement and serum-bourne proteins peaking shortly after transplantation. Also, MV proteins of glomerular or tubular origin were regulated distinctly over the course of transplantation. We chose 64 candidate proteins that showed low statistical error and high stability in the leave-one-out cross-validation of the linear models with GFR values measured after 6 and 12 months or that were either only or not detected in samples depicting delayed graft function.

Conclusions: Our analysis represents the first concise data set depicting the changes in the human urinary MV proteome over the course of kidney transplantation. Ongoing experiments will focus on the validation of candidate proteins correlating with long term outcomes and the analysis of their clinical implementation.

Funding: Government Support - Non-U.S.

TH-PO1011

Dynamic Creatinine Clearance Calculation Enables Early Assessment of Kidney Function and Advances Detection of Functional Decline After Renal Transplantation Paul Beele, Arjan D. Van Zuilen, Maarten B. Rookmaaker. *UMCU, Utrecht, Netherlands.*

Background: Immediately after renal transplantation (RTX), graft function can be compromised for which early intervention can be crucial. However, the rapid fall

in plasma creatinine concentration immediately after RTX can conceal graft function decline. We present a strategy to estimate creatinine clearance (C_{Cr}) immediately after RTX and advance detection of functional decline.

Methods: C_{Cr} was derived from 2 subsequent plasma creatinine levels over time using a newly developed method for Dynamic Creatinine Clearance Calculation (D3C) (Fig1A). We estimated C_{Cr} one day (T1) after RTX by D3C and correlated this to the estimated C_{Cr} using CG at T12 in 154 uncomplicated RTX patients. We also investigated whether monitoring of D3C could advance detection of functional decline in patients with early rejection.

Results: Average plasma creatinine at T1 was 350±204μM and 155±75μM at T12. D3C at T1 was 50±22ml/min whereas CG estimated C_{Cr} was 59±21ml/min at T12. D3C at T1 correlated to GC estimated C_{Cr} at T12 (R=0.741, R^2=54,9%, p=0.000) (Fig1B), improving upon plasma creatinine correlation at T1 and T12 (R=0.661, R^2=43.7%, p=0.000). Detection of functional decline was advanced by identifying a decreasing D3C over time as compared to an increase in plasma creatinine concentration over time. This is illustrated by 2 patients with biopsy proven rejection (Fig1C,D) and 2 uncomplicated transplantations (Fig1E,F).

Conclusions: One day after RTX D3C significantly correlates to CG estimated C_{Cr} at T12 in uncomplicated RTX patients. Moreover, monitoring of renal function using D3C after RTX advances detection of functional decline on average by 2 days, expediting therapeutic intervention and conceivably improving clinical outcome.

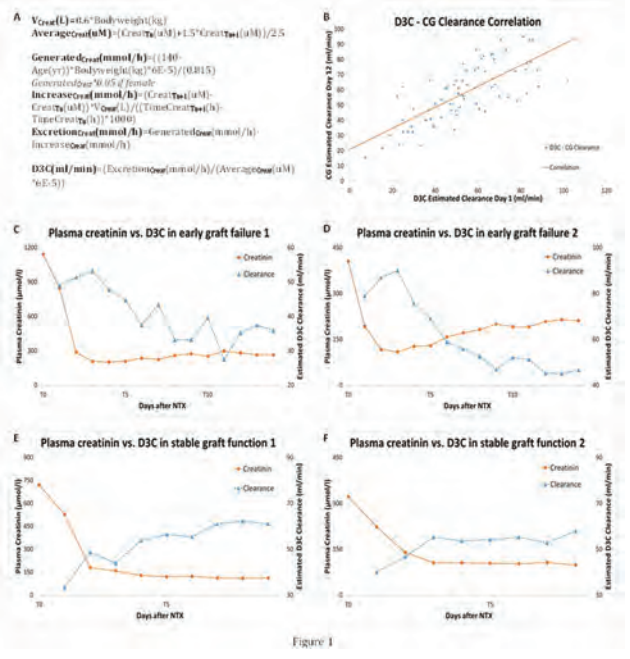


Figure 1A-F

TH-PO1012

Proposal of Score to Predict Outcome of Deceased Donor Renal Transplantation Carlos rafael A. Felipe,[3] Andre S. Alvarenga,[3] Silvana Maria C. Miranda,[1] Gerson M. Pereira jr,[3] Pedro Augusto M. Souza,[2] Izabela L. Piana,[4] Ana elisa S. Jorge.[3] *[1]Hospital Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; [2]None, Belo Horizonte, Brazil; [3]Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; [4]Faculdade de Minas Faminas BH, Belo Horizonte, Brazil.*

Background: Kidney Donor Profile Index (KPDI) correlated with graft loss and death. However, patients who received kidneys with the same KDPI may have different outcomes.

Methods: We developed a score system based on data of 113 deceased donor renal transplants (DDRT) from 01/2013 to 02/2016: mean age 50.7 years; mean cold ischemia time was 13.4 hours; 62% presented delayed graft function; the median of the KDPI was 53.5%. The score was calculated assigning one point for KDPI ≥ 70%, donor serum creatinine ≥ 2.0mg/dL and donor age ≥ 50 years (table 1). Patients were divided in 4 groups according to the sum of points (0, 1, 2, 3 points) and graft survival was evaluated for each group.

Results: Distribution of patients by points categories: 0 points - 47.8%; 1 point - 27.4%; 2 points - 19.5%; 3 points - 5.3%. One year graft survival was 88.4% for 0 points, 73.6% for 1 point (p = 0.0735 vs 0 pts), 61.5% for 2 points (P = 0.0076 vs 0 pts) and 0% for 3 points (p <0.0001 vs 0 pts). Combining kidneys with a score of 0 and 1 point, 1-year graft survival was 82.9%, significantly higher than kidneys with 2 points (p = 0.0368) and 3 points (p <0.0001) [figure 1].

Conclusions: Kidneys with 0 or 1 point had better survival, being acceptable for most transplant candidates. Kidneys with 2 points presented intermediate survival, and may be more suitable for candidates with a low expectation of obtaining a better graft in a timely manner. None of the 6 recipients who received 3-point kidneys had a functioning graft after 1 year, raising serious concerns about the acceptability of these organs.

Scoring points system

Criteria	Points
KDPI > 70%	1
Final Donor creatinine > 2.0mg/dL	1
Donor age > 50 years	1
Total	

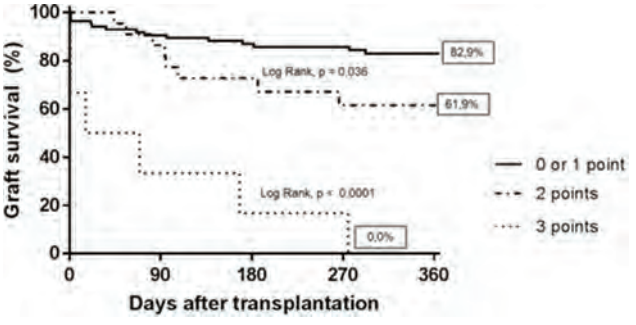


Figure 1. Graft survival according to scoring points groups

TH-PO1013

Development of a New Prediction Model for Graft Function in Living Donor Kidney Transplantation Yuta Matsukuma,[1] Kosuke Masutani,[1] Shigeru Tanaka,[2] Akihiro Tsuchimoto,[1] Kohei Unagami,[3] Masayoshi Okumi,[3] Kazunari Tanabe,[3] Kazuhiko Tsuruya,[1] Takanari Kitazono.[1] *[1]Department of Medicine and Clinical Science, Fukuoka, Japan; [2]Fukuoka Dental College, Fukuoka, Japan; [3]Tokyo Women's Medical University, Tokyo, Japan.*

Background: In recent years, there has been an increase in usage of grafts from marginal donors in living donor kidney transplantation. Such donors have several co-existing atherosclerotic factors such as aging, hypertension, dyslipidemia, and relatively low renal function. A simple prediction model for post-operative graft function may help to determine whether marginal donors are suitable in clinical settings of living donor kidney transplantation.

Methods: We conducted a single-center retrospective cohort study using clinical and laboratory measurements to construct a prediction model for graft function at 1 year. Low graft function was defined as estimated glomerular filtration rate (eGFR) ≤ 45 mL/min/1.73m^2 at 1 year. A risk prediction model for low graft function was developed using multivariable logistic regression model with a stepwise backward elimination method.

Results: A total of 343 living donor kidney transplantation procedures were performed between January 2006 and May 2016. 123 patients had eGFR ≤ 45 mL/min/1.73m^2 at 1 year after transplantation. Risk prediction model for low graft function was developed using donor age, pre-operative eGFR, hypertension, and donor/recipient body weight mismatch. The incidence of low graft function increased linearly with increase in total risk scores (p for trend <0.01). This model demonstrated modest discrimination (c-statistics = 0.75) and good calibration (Hosmer–Lemeshow test: p=0.77).

Conclusions: A new prediction model computed from four pre-operative variables created in this study is simple and useful system in clinical settings for prediction of graft function at 1 year in living donor kidney transplantation.

TH-PO1014

Patients with ESRD Secondary to a Plasma Cell Dyscrasia: The Combined Transplantation Is a Good Option Beatriz Redondo navarro, Candela Moliz, Maria Molina, Enrique Morales, Manuel Praga, Esther Gonzalez monte, Amado Andres. *Nephrology Department, Hospital 12 de Octubre, Madrid, Spain.*

Background: Plasma cell dyscrasias (PCD) are due to an abnormal proliferation of a single clone of plasma or lymphoplasmacytic cells leading to secretion of immunoglobulin (Ig) or an Ig fragment and are a known cause of end stage renal disease (ESRD). Traditionally, renal transplantation (RT) has been avoided in these patients due to the poor patient survival, the risk of recurrence in renal allograft and the high incidence of life threatening infections. However, the improving result of stem cell transplantation (SCT) in combination with the new drug in PCD patients with ESRD has encouraged to considerer in them a RT therapy.

Methods: We performed a retrospective study that included all patients with PCD who have received both SCT and RT in our hospital. We reviewed renal and haematological evolution, infections complications and recipient and RT survival after 3 year of follow-up.

Results: We included 6 patients: 4 (67%) males, median age 55 years old (49-57). The causes of ESRD were: 2 cast myeloma, 2 light-chain diseases, 1 primary amyloidosis and 1 focal segmental glomerulosclerosis. The causes of PCD were: 5 multiple myeloma and 1 primary amyloidosis. 4 (67%) of the patients received SCT 4 before RT and 2 (33%) after RT. The median creatinine at 1 and 3 year were 1.6 (1.1-1.9) and 1.3 (1.1-1.9) mg/dl, respectively. After 3 years of follow-up, renal graft survival non-death censored was

83 %. 5 episodes of infections that need admission occurred in 3 patients: 2 Aspergillus, 2 viral infections and 1 urinary infection. 3 patients developed a recurrence of their PCD: 2 had a remission after treatment with lenalidomide (one partial and the other one complete remission) and 1 patient finally died 15 months. Patient survival at the end of follow-up was 83%.

Conclusions: Sequential SCT and RT could be a suitable option for patients with PCD and ESRD. The patient and renal graft survival arte conditioned to the relapse of hematological disease and infections complications. The high incidence of fungal infection will require special prophylaxis measure. These results highlight the importance of declaring more number of patients in this situation and with longer follow-up to elucidate the best management of PCD with ESRD.

TH-PO1015

Assessment of a Dedicated Transplant Low Clearance Clinic and Patient Outcomes on Dialysis after Graft Loss at Two UK Transplant Centres Rhys D. Evans,[3] Soliana Bekele,[2] Sarah G. Clark,[2] Lauren Harris,[4] Samantha M. Campbell,[4] Alice Thomas,[2] Gareth L. Jones,[4] Raj Thuraisingham.[1] *[1]Barts Health NHS Trust, London, United Kingdom; [2]Barts Health NHS trust, London, United Kingdom; [3]UCL Centre for Nephrology, London, United Kingdom; [4]Royal Free Hospital, London, United Kingdom.*

Background: Recipients with a failing kidney transplant (RFKT) receive worse care than those with native disease and outcomes on dialysis after graft loss (DAGL) are poor. Dedicated low clearance transplant clinics (LCTC) are recommended for the management of RFKT but data to support their use is limited. We assessed the management of RFKT at two London transplant centres, one with a dedicated LCTC (Centre A) and one without (Centre B).

Methods: Transplant patients at Bart's Health (Centre A) and the Royal Free Hospital (Centre B) who transitioned to an alternative form of renal replacement therapy (RRT) between 01/01/2012-30/11/2016 were included. Patients with graft failure within a year of transplantation or due to an unpredictable acute event were excluded. Data were recorded after review of medical records.

Results: 179 patients were included; mean age at dialysis restart was 48.6 (+/- 13.4) years, 99 (55.3%) were male, and mean transplant duration was 3678 (+/- 2851) days. Pre-dialysis counseling was documented in 79 (91%) and 68 (74%) patients at Centre A and B respectively (p=0.003). Listing for re-transplantation at restart occurred in 61 (34.1%) patients across both groups. Table 1 outlines clinical parameters at restart and modes of RRT restarted. Outcomes at 1 year after initiation of DAGL were determined in 136 patients; 1-year mortality was 6.6% overall.

Conclusions: A dedicated LCTC improved pre dialysis care. Rates of pre-emptive re-transplantation were low, but 1-year mortality across both centres was better than published estimates.

Clinical parameters at restart and modes of RRT restarted

Parameter at restart (mean; SD)	Centre A (n=87)	Centre B (n=92)	p-value
Haemoglobin (g/L)	89.4 (15.3)	96.1 (17.1)	0.007
Phosphate (mmol/L)	1.69 (0.46)	1.77 (0.52)	0.28
PTH (pmol/L)	52.2 (44.6)	41.8 (36.7)	0.09
Bicarbonate (mmol/L)	19.5 (3.5)	19.8 (4.6)	0.64
Creatinine (µmol/L)	626 (225)	675 (302)	0.22
Urea (mmol/L)	30 (9)	30 (11)	0.63
Systolic Blood Pressure (mmHg)	147 (27)	146 (22)	0.68
Diastolic Blood Pressure (mmHg)	81 (15)	86 (13)	0.019
Mode of RRT restarted (n; %)			
Haemodialysis	70 (80.5)	70 (76.1)	0.35
Peritoneal Dialysis	11 (12.6)	17 (18.5)	
Transplant (pre-emptive)	4 (4.6)	5 (5.4)	
Supportive care	2 (2.3)	0 (0.0)	

TH-PO978

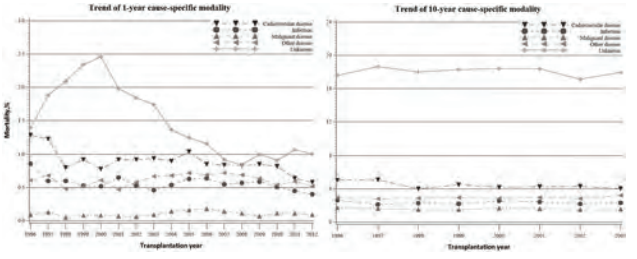
Causes of Death among Kidney Transplant Recipients in the United States Sankar D. Navaneethan,[1,3] Jingbo Niu,[1] Sreedhar A. Mandayam,[2] Saed Shawar,[1] Jenny S. Pan,[1] Kevin F. Erickson,[1] Wolfgang C. Winkelmayer,[1] Venkat Ramanathan.[1] *[1]Baylor College of Medicine, Houston, TX; [2]None, Bellaire, TX; [3]Michael E.DeBakey VA Medical Center, Houston, TX.*

Background: Mortality rate among kidney transplant recipients is lower than the dialysis population. However, except for single center studies, comprehensive examination of reasons for death among those with functioning allograft is lacking. Herein, we studied the causes of death among those who underwent kidney transplantation in the United States.

Methods: We examined United States Renal Data System (USRDS) database to identify patients (age ≥18 years) who received their first kidney transplantation between 1996 and 2012, and subsequently died with functioning graft. Deaths were classified into: a) cardiovascular, b) infectious, c) malignancy, d) others and e) unknown reasons. We examined the trends for 1-year and 10-year risk of death due to above mentioned causes for the study population. We also used competing risk models to assess the associations between transplantation year and each cause-specific mortality during 10-year follow-up.

Results: We included 196,748 transplant recipients and among them, 40,742 died with functioning allograft. Of these, cause of death was reported as unknown for 64% of patients. For those with reported cause of death, cardiovascular deaths accounted for 37%, malignancy: 14%, infection: 21% and other causes: 28% of deaths. One and 10-year trends for these various causes of deaths are shown in Figure 1. Patients who underwent transplantation in later years had lower hazards of death (for various causes) compared to patients who underwent transplantation in 1996 (Figure 2).

Conclusions: In this national registry of kidney transplant population, cause of death is unknown for substantial proportion of patients dying with functioning allografts. Risk for deaths due to cardiovascular disease and other causes have decreased over time.



Transplantation year and 10-year cause-specific mortality (adjusted for age, sex and race)

	Cause-specific mortality, sub-hazard ratio (95% CI)				
Year	Cardiovascular	Infection	Malignancy	Other	Unknown
1996	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)	1.0 (referent)
1997	0.93 (0.81, 1.06)	0.71 (0.58, 0.87)	0.90 (0.70, 1.15)	0.86 (0.72, 1.03)	1.00 (0.94, 1.07)
1998	0.69 (0.60, 0.80)	0.82 (0.67, 1.00)	0.87 (0.68, 1.11)	0.86 (0.72, 1.03)	0.96 (0.90, 1.01)
1999	0.77 (0.67, 0.89)	0.74 (0.61, 0.90)	0.86 (0.68, 1.10)	0.83 (0.70, 0.99)	0.89 (0.84, 0.95)
2000	0.70 (0.61, 0.80)	0.72 (0.59, 0.87)	0.81 (0.64, 1.03)	0.76 (0.64, 0.91)	0.85 (0.80, 0.91)
2001	0.65 (0.57, 0.75)	0.71 (0.59, 0.86)	0.79 (0.62, 1.00)	0.77 (0.65, 0.91)	0.76 (0.72, 0.81)
2002	0.64 (0.56, 0.73)	0.62 (0.51, 0.76)	0.69 (0.54, 0.88)	0.68 (0.57, 0.81)	0.67 (0.63, 0.71)
2003	0.57 (0.50, 0.66)	0.62 (0.51, 0.75)	0.66 (0.52, 0.85)	0.75 (0.63, 0.88)	0.63 (0.59, 0.67)

TH-PO979

Correlation of Pre Kidney Transplant Psychosocial Factors with Post-Transplant Kidney Graft Survival Brittany L. Schreiber, Ramon Noriega, Ann Kathleen N. Gamilla-Crudo, Sujan P. Shah, Flor Espinoza, Rohan Patankar, Wayne G. Fischer, Muhammad A. Mujtaba. *University of Texas Medical Branch, Galveston, TX.*

Background: Pretransplant psychosocial and nutritional factors are important aspects of kidney transplant evaluation as they may be associated with post-transplant outcomes; however there is scant data on this topic. The aim of the study was to determine the correlations between pretransplant, nonclinical and psychosocial factors to post-transplant kidney allograft survival.

Methods: We selected the following pre-transplant factors: race, gender, food stamp, marital relationship, family support, income status, insurer, education, Karnofsky score, history of depression, active clinical follow up, dialysis compliance, serum albumin level, history of substance abuse, distance from transplant center etc. One year kidney allograf survivalwas selected as an outcome. The study involved retrospective analysis of 131 kidney transplant patients. There were 56 female patients and 75 male patients. There were 56 female patients and 75 male patients. We had 72 Hispanics (53%), 33 African Americans (24%), 22 Whites (16%), 9 Asians (7%). Patients age ranged from 25 years to 77 years. Nominal logistic regression analysis and multinominal logistic regression analysis were used to identify the significant relationship between one dependent nominal variable and one or more continuous-level independent variables. A p-value of ≤ 0.05 was considered significant

Results: Female gender (p .02), active pre listing clinic follow up (p=0.04), stronger immediate family support(p=0.06), proximity to primary transplant center (p 0.0012), pre transplant nutrional status as evidenced by serum albumin >3.5 gm/dl, was associated with a better one year graft survival, however food stamps status (p 0.004), repeat transplant status (p 0.05) was associated with poor allograft survival. Remaining variable's did not show a significant relationship.

Conclusions: Pretransplant psychosocial assessment is an important component of kidney transplant work up as it is associated with one year kidney allograft survival. More studies are needed to confirm our findings.

TH-PO980

Health Literacy and Inequity in Access to Transplantation: Results from the ATTOM Study Dominic Taylor.[1,2] *[1]University of Southampton, Southampton, United Kingdom; [2]North Bristol NHS Trust, Bristol, United Kingdom. Group/Team: On behalf of ATTOM investigators.*

Background: Access to kidney transplantation is reduced among people with low socioeconomic status, a component of which is low educational level. Transplant preparation requires patients to understand complex concepts, demanding adequate health literacy (HL). In the Access to Transplant and Transplant Outcome Measures (ATTOM) study, low HL was associated with low educational level and was more common in incident dialysis patients compared to wait-listed or transplanted patients. We hypothesised that HL mediates the association between low educational level and reduced access to transplantation.

Methods: ATTOM recruited UK incident dialysis patients, 2011-13. Data collected included the exposure (no educational qualifications vs any), outcomes (time to transplant wait listing/time to live donor transplant censored at 2 years), the mediator (HL, defined by 'Single Item Literacy Screener' on a five-point scale, 5 indicating lowest HL), and covariates (age, ethnicity, comorbidity by Charlson index). Structural Equation Modelling was used to calculate effect sizes for the exposure on the mediator, the mediator on the outcome and the exposure on the outcome, adjusted for the covariates. From these, the *total effect* of education on access to transplant and the *indirect effect* mediated by HL were calculated. Weibull AFT models were used and effect size expressed as time-to-event ratio (TR). $p<0.05$ was deemed significant.

Results: 2463 of 2621 recruited patients responded to the SILS, and were included. A 1-point increase in HL score was independently associated with 15% increased time to wait listing (TR 1.15;95% CI 1.07-1.25) and 25% increased time to live donor transplant (TR 1.25;95% CI 1.06-1.47). In the mediation model, the *total effect* of low educational level was to increase time to wait listing by 22% (TR 1.22;95% CI 1.02-1.48) and time to live donor transplant by 47% (TR 1.47;95% CI 1.04-2.08). The *indirect effect* mediated by HL accounted for 35% of the increase in time to wait listing and 30% of the increase in time to live donor transplant.

Conclusions: In this large UK cohort study, HL mediated a substantial proportion of the effect of low educational level on reduced access to deceased-donor transplant wait listing and live donor transplantation. Interventions to improve patients' understanding of the transplantation process have potential to reduce socioeconomic inequity in access to transplantation.

Funding: Other NIH Support - National Institute for Health Research (UK) Programme Grants for Applied Research (RP-PG-0109-10116)

TH-PO981

Effectiveness of iChoose Kidney Decision Aid on Kidney Transplant Knowledge Rachel E. Patzer,[2] Laura J. McPherson,[2] Mohua Basu,[3] Sumit Mohan,[1] Stephen O. Pastan.[2] *[1]Columbia University, New York, NY; [2]Emory University, Atlanta, GA; [3]None, Peachtree City, GA.*

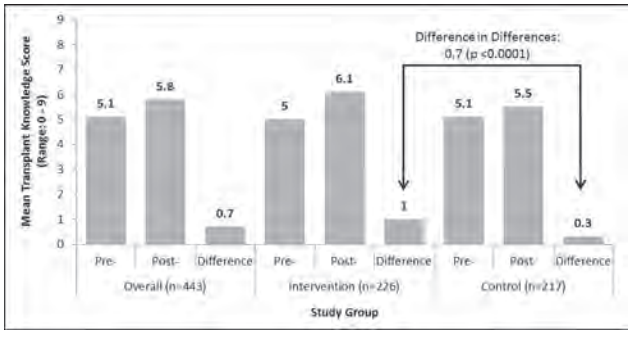
Background: We developed a shared mobile decision aid (iChoose Kidney) that displays individualized risk estimates of survival and mortality for dialysis vs. kidney transplant for patients with end-stage renal disease (ESRD). We examined whether use of iChoose Kidney was associated with improved gains in transplant knowledge.

Methods: In a randomized controlled trial, 470 patients at 3 centers were randomized to receive education with (intervention) or without (standard of care) iChoose Kidney during their transplant evaluation. Patients completed surveys immediately before and after evaluation and gain in transplant knowledge (9 item scale) from pre- to post-evaluation was calculated by subtracting mean pre-survey from post-survey scores. Knowledge gains were assessed by study group and by race, health literacy and numeracy levels.

Results: Among 443 patients completing both surveys, mean age was 51 years, with 63% male, and 48% black. The mean pre- and post-evaluation transplant knowledge scores were 5.1 ± 2.1 and 5.8 ± 1.9, respectively, with a mean difference of 0.7 ± 1.7 points. Change in knowledge during the visit was significantly greater among iChoose (1.0 ± 1.8) vs. control (0.3 ± 1.4) for all patients ($p<0.0001$) (Figure 1) as well as for black (1.1 ± 1.7 vs. 0.4 ± 1.4; $p=0.04$) and white (1.5 ± 1.8 vs. 0.2 ± 1.9; $p=0.003$) patients. Intervention (vs. control) patients with moderate (1.2 ± 1.7 vs. 0.4 ± 1.1; $p=0.02$) and high (1.0 ± 1.8 vs. 0.2 ± 1.5; $p=0.001$) literacy and moderate (1.3 ± 1.9 vs. 0.2 ± 1.4; $p=0.0001$) and high numeracy (0.8 ± 1.4 vs. 0.2 ± 1.1; $p=0.02$) benefited most from the tool; while patients with low literacy (1.0 ± 1.9 vs. 0.7 ± 1.4; $p=0.41$) and low numeracy (1.0 ± 1.9 vs. 0.7 ± 1.6; $p=0.39$) had non-significant improvements.

Conclusions: The iChoose Kidney decision aid was effective in improving ESRD patient transplant knowledge among patients undergoing transplant evaluation. Similar shared decision aids could help clinicians better inform patients about transplant.

Funding: Private Foundation Support



TH-PO982

Impacts of Options Education on Modality Choice in Incident ESRD Patients Yue Jiao, Marta Reviriego-Mendoza, John W. Larkin, Rob Lynch, Len A. Usvyat, Jeffrey L. Hymes, Franklin W. Maddux. *Fresenius Medical Care North America, Waltham, MA.*

Background: Dialysis education programs that teach chronic kidney disease (CKD) patients about their renal replacement therapy (RRT) options may help patients to make informed decisions. The impact of educational programs on kidney modality choice is unknown. We analyzed the impacts of an options educational program on incident modality choice for hemodialysis (HD), peritoneal dialysis (PD), or transplant in patients who progressed to ESRD.

Methods: For this analysis, we collected data from Fresenius Kidney Care (FKC) patients who progressed to ESRD and started RRT between 2009 and 2016. Patients were categorized into groups depending on whether they received options education and if they started dialysis as outpatient or inpatient. We determined the annual percentage of ESRD patients who initiated RRT by modality choice (HD, PD, or transplant) in the first 120 days of RRT.

Results: A total of 300,818 patients who progressed to ESRD and initiated a RRT were included in the study; 68,721 patients received options education. In 2016, education prior starting RRT was associated with more patients (1 percentage point) receiving a transplant in the first 120 days of RRT, as compared to those without options education. Concurrently, in patients who received options education and started with outpatient dialysis for RRT, there were 16 percentage points more who utilized PD and 17 percentage points less treated by HD when compared to patients without options education. In patients who received options education and started dialysis as an inpatient in 2016, there were 3 percentage points more who were treated with PD and 2 percentage points less treated by HD when compared to patients without options education. Similar findings were observed in during every year in the study period.

Conclusions: These findings suggest that options education prior starting RRT may lead to a higher proportion of patients choosing a transplant or home dialysis when progressing to ESRD. Further analysis are needed to confirm these findings.

Funding: Commercial Support - Fresenius Medical Care North America

TH-PO983

Experiences of Kidney Transplant Recipients as Patient Navigators Anne M. Huml,[6] Catherine M. Sullivan,[3] Adam T. Perzynski,[3] Kitty V. Barnswell,[4] Kate A. Greenway,[1] Cindy Kamps,[5] Marquisha Marbury,[3] Julie A. Pencak,[3] Derrick L. Wilson,[2] Jacqueline Dolata,[3] Ashwini R. Sehgal.[6] *[1]Comprehensive Transplant Center, The Ohio State University Wexner Medical Center, Salem, VA; [2]Luthren Hospital Kidney Transplant Center, Fort Wayne, IN; [3]MetroHealth Medical Center, Cleveland, OH; [4]University Of Louisville, Louisville, KY; [5]University of Kentucky, Richmond, KY; [6]Center for Reducing Health Disparities, Division of Nephrology, Case Western Reserve University, Cleveland, OH.*

Background: The use of trained kidney transplant recipients as patient navigators resulted in increased completion in steps in the transplant process by dialysis patients (1). We sought to understand the experiences of these patient navigators.

Methods: Six kidney transplant recipients were hired and employed by transplant centers in Cleveland, OH, Columbus, OH, Fort Wayne, IN, Lexington, KY, and Louisville, KY. The transplant navigators received formal training as peer educators, met with dialysis patients on a regular basis, and provided tailored education and assistance about transplantation to each patient. In addition, they worked closely with the pre-transplant coordinators and social workers to learn the details of each patient's transplant work-up. We queried navigators using open-ended questions delivered by email to learn about their experiences. We used qualitative analyses to compile and code navigator responses and identify and categorize common themes. A thematic auditor reviewed and refined the coding.

Results: Two primary categories of themes emerged from the data about the navigator experience: 1) practical comments that supported programmatic or implementation observations of the navigators, and 2) affective comments that reflected a shared experience among the navigators and patients. The navigators were able to fill voids in the transplantation and dialysis care process that were not fulfilled by other dialysis caregivers. This was accomplished by a natural bond based upon a shared experience (of dialysis and kidney failure) between the navigator and the patient. The patient and navigator effectively were experiential partners.

Conclusions: Kidney transplant recipients trained as patient navigators fill the role of a non-traditional medical provider, offer support during the transplant process, and from the navigator perspective, provide an added-benefit to complement routine dialysis and nephrology care. References: 1. Sullivan C, Leon JB, Sayre S, et al. Impact of navigators on completion of steps in the kidney transplant process: a randomized, controlled trial. Clin J Am Soc Nephrol. 2012 Oct 5; 7(10): 1639–1645.

Funding: NIDDK Support, Other NIH Support - NIMHD P60MD002265, NIDDK K23DK101492

TH-PO984

Patient and Provider Perceptions of Medication Safety Issues in Adult Kidney Transplant Recipients Bashir Hamidi, David J. Taber. *Medical University of South Carolina, Charleston, SC.*

Background: Medication safety adverse events (AEs), which include non-adherence to drug regimens and adverse drug events, are associated with graft loss following transplantation. Although kidney transplant recipients are considered high-risk for developing these issues, there are limited studies analyzing long-term patient and provider perceptions of medication safety issues in this population.

Methods: This was a prospective, cross-sectional study of 176 stable kidney transplant recipients which assessed patient self-reported medication adherence and adverse drug events through surveys and compared these to blinded provider assessments occurring during a coinciding routine clinic visit.

Results: In the 176 patients, self-reported medication adherence was 38%, 45%, and 17% for high, medium, and low categories, as measured by a validated survey. AEs were common, with 96% of patients reporting at least one and a mean of 5.9 AEs per patient-visit across the entire study population. Self-reported AE burden was significantly correlated with medication non-adherence with a one unit increase in self-reported patient AE burden (measured by the validated Memphis score) increasing the odds of patients being in a lower adherence category by a factor of 1.35 (CI 1.13 to 1.62, P<0.001). The analysis of clinic assessments revealed that providers only assessed 49% of participants to have at least one AE, with a mean count of 0.8 per patient-visit. Patient self-reported AE burden had a weak positive correlation (Kendall tau= 0.15, P=0.008) with providers' assessment of patient AEs during routine visits.

Conclusions: These results indicate a significant relationship between between AE burden and medication adherence in kidney transplantation. Further, providers tended to under-assess medication AEs during routine clinic visits, when compared to patient assessments. Improving recognition and management of AEs in kidney transplant recipients may impact medication adherence.

Funding: NIDDK Support

TH-PO985

Knowledge and Attitude of Medical Students towards Organ Transplantation Alicja Rydzewska-Rosolowska,[3] Milena Jamiolkowska,[2] Tomasz Hryszko,[3] Szymon Brzosko,[1,3] Beata Naumnik.[3] *[1]DaVita Poland, Bialystok, Poland; [2]Medical University of Bialystok, Bialystok, Poland; [3]I Department of Nephrology and Transplantation with Dialysis Unit, Medical University of Bialystok, Bialystok, Poland.*

Background: In modern era transplantation has become an important mean of treatment. Although it is widespread and medically accepted, certain controversies still exist. The aim of this study was to evaluate attitudes toward organ transplantation among students from Medical University of Bialystok.

Methods: The anonymous survey was conducted among 273 students (medicine, dentistry, nursing and physiotherapy). The questionnaire was self-designed and contained 15 dichotomous questions regarding the attitude towards transplantation from deceased donors, living donors, the definition of brain death and whether the family was made aware of students' beliefs.

Results: 99.6% of students accepted organ transplantation as a therapeutic method. Living transplantation was accepted by 98.9% of students and transplantation from unrelated donors by 92.6% and 87.6% (respectively depending on the existence of an emotional bond between the donor and the recipient). Interestingly 12.8% of students approved selling of organs as a means of expanding the donor pool with significant differences between different divisions (medicine 18.4%, dentistry 6.1%, nursing 7.4% and physiotherapy 19.2%, p<0.05). On average 90.1% of students declared that they know the definition of brain death and again there were statistically significant differences between groups (medicine 96.5%, dentistry 74.2%, nursing 95.6% and physiotherapy 84.6%, p<0.01). Unfortunately, only 81.3% of students accepted the concept of brain death (medicine 91.2%, dentistry 66.1%, nursing 77.9% and physiotherapy 79.2%, p<0.01). Noteworthy 98.5% of students would accept an organ if needed but only 93.8% declared willingness to donate organs after death. Interestingly 26.4% of subjects stated that family should decide whether organs can be retrieved (medicine 17.5%, dentistry 37.9%, nursing 27.9% and physiotherapy 30.8%, p<0.01). Only 69.2% of respondents talked to their family about their attitudes concerning transplantation.

Conclusions: Although organ transplantation is widely accepted by medical students from different faculties and divisions there are still certain areas were controversies exist (e.g. definition of brain-death and the subject of organ selling). A structured, well-planned educational program should be implemented to improve the awareness and attitude, especially among medical students.

TH-PO986

The Effects of Marriage Duration after Transplantation on Graft Outcomes in Spousal Donor Kidney Transplantation Mi-yeon Yu,[3] Ji In Park,[2] Hyunjeong Cho,[1] Yon Su Kim,[1] Hajeong Lee.[1] *[1]Seoul National University College of Medicine, Seoul, Republic of Korea; [2]Kangwon National University Hospital, Chuncheon-si, Republic of Korea; [3]Seoul national university hospital, Seoul, Republic of Korea.*

Background: It is well known that graft survival rate in spousal donor kidney transplantation (SKT) is similar to that of living related donor kidney transplantation (LRKT) despite poor histocompatibility and older age. Marriage is a distinctive feature of spousal kidney donation and other living unrelated kidney donation. Although married people live longer and healthier than singles due to their closest environmental and habitual relationship, the effect of marriage on graft outcome has not been evaluated.

Methods: In a retrospective cohort study, we recruited patients undergone living donor kidney transplantation at Seoul National University Hospital between January 2000 and February 2016. We divided patients into three groups as follows: SKT, LRKT and other living unrelated kidney donor transplantation (LURKT). For spousal donors, the marriage duration after transplantation (MDAT) was surveyed by both personal interview and telephone questionnaire. Outcome was biopsy proven acute rejection (BPAR), graft survival (GS) and patient survival (PS).

Results: A total of 824 living donor kidney transplantation recipients were included. Among them, LRKT was most common with 68.8 %, followed by SKT with 22.3 %, and LURKT with 8.9 %. SKT group received their allografts from donors with older age (median age 46.0), more female sex (65.8%), more ABO incompatibilities and higher HLA mismatches than LRKT or LURKT groups. They tended to receive more preemptive transplantation. In[S1] the Kaplan-Meier curve, SKT revealed lower BPAR free survival rate than LRKT, whereas GS and PS were not different. Among SKT, longer MDAT was demonstrated as a novel protective factor for BPAR even after adjustment (adjusted HR 0.244, 95% CI 0.121-0.493, P<0.001), although it did not affect GS or PS.

Conclusions: We demonstrated that graft and patient survival rate of SKT was not inferior to LRKT, despite their immunologic risk. Moreover, we found that longer MDAT was a novel protective factor for BPAR free survival rate. Not only immunologic similarity but also habitual similarity between donor and recipient may influence on graft outcome after kidney transplantation.

TH-PO987

Cannabis Dependence or Abuse before and after Kidney Transplantation: Implications for Post-Transplant Outcomes Krista L. Lentine,[6] Tarek Alhamad,[9] Ngan Lam,[7] Abhijit S. Naik,[3] Farrukh M. Koraishy,[5] David A. Axelrod,[2] Dorry L. Segev,[1] Vikas R. Dharnidharka,[8] Daniel C. Brennan,[9] Mark Schnitzler.[4] *[1]Johns Hopkins University, Baltimore, MD; [2]Lahey Hospital and Clinic, Burlington, MA; [3]None, Ann Arbor, MI; [4]Saint Louis Univ, St Louis, MO; [5]Saint Louis University, Saint Louis, MO; [6]Saint Louis University, St. Louis, MO; [7]University of Alberta, Edmonton, AB, Canada; [8]Washington University School of Medicine, St Louis, MO; [9]Washington University in St. Louis, St. Louis, MO.*

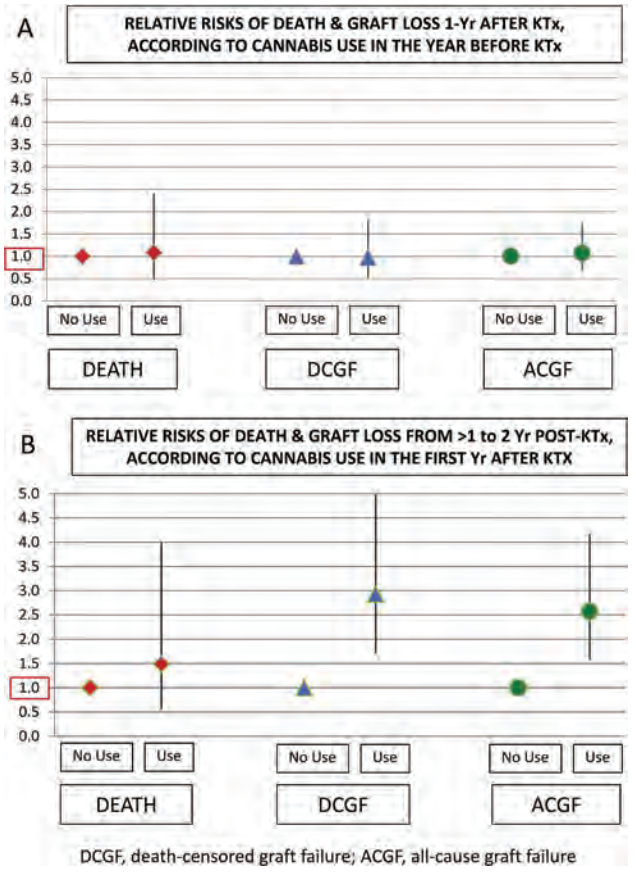
Background: Currently, transplant centers vary in screening practices for marijuana use and requirements for abstinence in kidney transplant (KTx) recipients.

Methods: We examined billing claims for 52,689 Medicare-insured KTx recipients to identify diagnoses of cannabis dependence or abuse (CDOA, International Classification of Diseases-9 diagnosis codes 304.3, 305.2) in the year before and after KTx. Associations of CDOA with post-KTx death and graft failure (adjusted hazard ratio, 95% $_{LCL}$ aHR 95% $_{UCL}$) were quantified by multivariate Cox regression including adjustment for recipient, donor and transplant factors, and propensity for CDOA.

Results: CDOA diagnoses were uncommon, found in 0.5% and 0.3% in the year before and after KTx, respectively. The likelihood of CDOA diagnosis before and after KTx declined with older recipient age, and was increased in men, African Americans, those with less than a college education and unemployed patients. After multivariate and propensity adjustment, CDOA in the year before KTx was not associated with increased risk of death or graft survival in the year after KTx (**Fig 1A**). However, CDOA in the first year post-KTx was associated with three-times the risk of death-censored graft failure (aHR $_{1.72}2.93_{4.99}$) and 2.5-times the risk of all-cause graft loss (aHR $_{1.59}2.57_{4.17}$) in the subsequent year (**Fig 1B**).

Conclusions: Diagnoses of CDOA are uncommon among KTX recipients, and likely reflect a select subgroup of cannabis users who reach clinical attention. While associations likely in part reflect associated conditions or behaviors, clinical diagnosis of CDOA in the year after transplant appears to have prognostic importance for subsequent allograft survival.

Funding: NIDDK Support



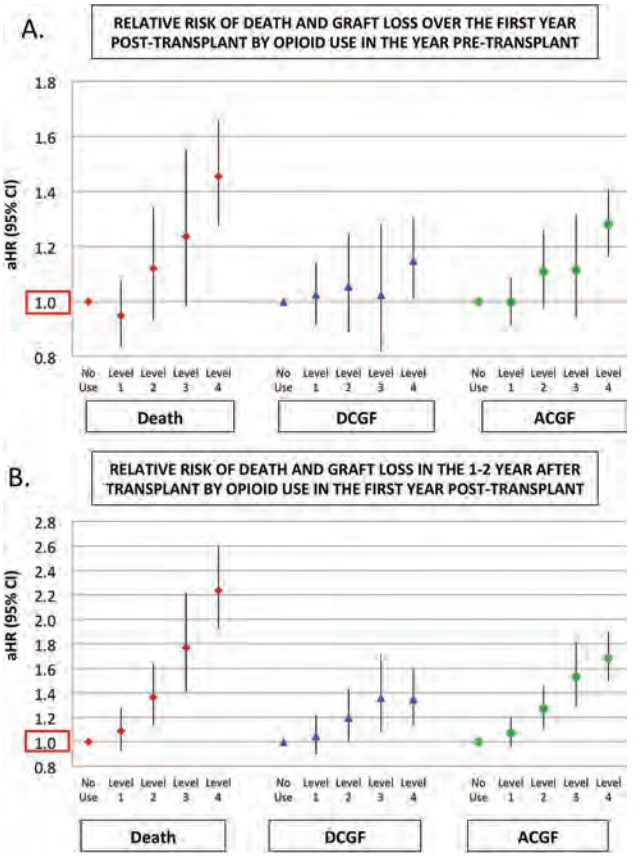


Figure. Adjusted associations of Level 1-4 prescription opioid use before and after transplant and death and graft failure (referent=no use). Abbreviations: ACGF, all-cause graft failure; CI, confidence interval; DCGF, death-censored graft failure.

TH-PO988

Prescription Opioid before and after Kidney Transplant Ngan Lam,[7] Krista L. Lentine,[5] Zidong Zhang,[5] Dorry L. Segev,[2] Vikas R. Dharnidharka,[8] Gregory P. Hess,[3] Radhika Devraj,[6] Bertram L. Kasiske,[1] Daniel C. Brennan,[9] Mark Schnitzler.[4] *[1]Hennepin County Medical Center, Minneapolis, MN; [2]Johns Hopkins University, Baltimore, MD; [3]LDI University of Pennsylvania/ IMS, Plymouth Meeting, PA; [4]Saint Louis Univ, St Louis, MO; [5]Saint Louis University, St. Louis, MO; [6]Southern Illinois University Edwardsville, Edwardsville, IL; [7]University of Alberta, Edmonton, AB, Canada; [8]Washington University School of Medicine, St Louis, MO; [9]Washington University in St. Louis, St. Louis, MO.*

Background: An evolving body of literature suggests the epidemic of prescription opioid use has impacted the transplant population.

Methods: We examined a novel database wherein national U.S. transplant registry identifiers were linked to records from a large pharmaceutical claims warehouse (2008 to 2015) to characterize antidepressant use before and after kidney transplantation, and associations (adjusted hazard ratio, $_{95\%\ LCL}aHR_{95\%\ UCL}$) with death and graft failure.

Results: Among 75,430 eligible patients, 43.1% filled opioids in the year before kidney transplantation, and use was more common among recipients who were women, white, unemployed, publicly insured, and those with longer pre-transplant dialysis. The majority of recipients (60%) with the highest level of pre-transplant opioid use continued high-level usage post-transplant. Pre-transplant opioid use bore graded associations with 1-year post-transplant outcomes, with the highest level use predicting 45% increased risk of death (aHR $_{1.28}1.45_{1.66}$) and 28% increased risk of all-cause graft failure (aHR $_{1.17}1.28_{1.41}$). High-level opioid use in the first year after transplant was associated with twice the risk of death (aHR $_{1.93}2.24_{2.60}$) and 68% higher risk of all-cause graft failure (aHR $_{1.50}1.68_{1.89}$) over the subsequent year.

Conclusions: While associations may, in part, reflect underlying conditions or behaviors, opioid use history appears relevant in assessing and providing care to transplant candidates and recipients.

Funding: NIDDK Support

TH-PO989

Provision of Highly Specialized Aftercare by the Transplant Center Strongly Improves Patient and Allograft Survival in Long-Term Follow-Up After Kidney Transplantation Thomas Schachtner,[1] Natalie M. Otto,[2] Petra Reinke.[3] *[1]Charite Campus Virchow Clinic, Berlin, Germany; [2]Charité Berlin, Berlin, Germany; [3]Charité, Campus Virchow Klinikum, Berlin, Germany.*

Background: Despite rapid medical advancements in the field of transplantation, mean kidney allograft survival remained at a standstill. If and to what extent a highly specialized and experienced aftercare of kidney transplant recipients (KTRs) impacts patient and allograft outcomes in long-term follow-up, however, remains mostly unknown.

Methods: We retrospectively analyzed 1328 KTRs between 1998 and 2015 with respect to patient and allograft survival. KTRs treated regularly in our transplant center in long-term follow-up were compared with KTRs followed by local nephrologists and general practitioners. KTRs that make no use of the transplant center provided aftercare, were assessed by a questionnaire-based survey with respect to allograft survival and their reasons not to make use of it.

Results: In total 824 KTRs (62.0%) were followed in our transplant center and 504 KTRs (38.0%) were followed by local nephrologists. Multivariate analysis identified shorter distance to the transplant center (p<0.001), living donation (p<0.001), early registration to the waiting list (p=0.009), and shorter initial hospital stay (p=0.004) as independet factors for strong adherence to the transplant center. KTRs followed in our transplant center showed significantly better patient (72.7% vs. 50.4% after 15 years; p=0.001) and death-censored allograft survival (85.0% vs. 64.4% after 15 years; p<0.001) compared to KTRs followed by local nephrologists. These differences were equally observed in deceased and living donation. Reasons not to make use of the transplant center provided aftercare included distance (47%), prohibitively expensive costs (37%), no identifiable advantages (34%), and negative experiences (7%).

Conclusions: Our data strongly indicate that provision of aftercare by the transplant center is highly associated with superior patient and allograft survival. The observed wide differences may be attributed to highly specialized screening protocols, careful and critical guidance of immunosuppression, and more comprehensive medical care. Despite long distances, transplant centers, local nephrologists, and health insurances must encourage patients to make use of transplant center provided aftercare.

TH-PO990

The Impact of Donor BMI on Outcomes after Deceased Kidney Transplantation Adam Arshad,[4] Imogen Chappelow,[4] James Hodson,[5] Andrew Ready,[2] Jay Nath,[3] Adnan Sharif.[1] *[1]Queen Elizabeth Hospital, Birmingham, Birmingham, United Kingdom; [2]University Hospital BIrmingham, Birmingham, United Kingdom; [3]University Hospital Birmingham, Birmingham, United Kingdom; [4]University of Birmingham, Stoke on Trent, United Kingdom; [5]University Hospital Birmingham NHS Trust, Biostatistics, Birmingham, United Kingdom.*

Background: The shortage of available donor organs means we must reconsider our current policies on donor selection. There is variation in practice between centers as to the acceptable limit to donor BMI in deceased kidney transplantation, with no recommendations in American or UK guidelines.

Methods: Data from the UK National Health Service Blood and Transplantation register was analysed for all patients receiving deceased donor kidney transplants (Jan 2003 - Jan 2015). Transplants were separated into 5 categories depending on the donor's body mass index (BMI) (kg/m^2): < 18.50 (underweight), 18.50 – 25.00 (normal), 25.01 – 30.00 (overweight), 30.01 – 35.00 (obese) and > 35.00 (morbidly obese). Risk-adjusted outcomes were assessed by multivariable analysis, adjusting for donor, recipient and peri-operative characteristics.

Results: Data for 17,590 transplants were assessed (donor BMI < 18.50 kg/m^2 in 380, 18.50 kg/m^2 – 25.00 kg/m^2 in 6890, 25.01 kg/m^2 – 30.00 kg/m^2 in 6692, 30.01 kg/m^2 – 35.00 kg/m^2 in 2503 and > 35.00 kg/m^2 in 1148). On multivariable analyses, increasing donor BMI was found to be an independent risk factor for delayed graft function (p<0.001), with rates of 27.8%, 31.4% and 32.8% for normal, obese and morbidly obese patients, respectively. However, no evidence of significant differences in longer term outcomes such as patient survival (p= 0.109), graft survival (p= 0.093) or 12-month creatinine values (p= 0.550) were detected between donor BMI groups. A subgroup analysis of DCD recipients was performed (n = 3593). Whilst increasing donor BMI was found to be associated with an increase the functional warm ischaemia time (WIT) and standard WIT by an average 1.80 (p = 0.030) and 2.19 minutes (p = 0.015) respectively, this was not found to have a significant impact on the incidence of delayed graft function (p= 0.464, p= 0.520) or graft survival (p= 0.760, p = 0.423) on multivariable analysis.

Conclusions: In this large national cohort study, we found that there was no evidence of significant differences in long-term outcomes between deceased donor kidneys from different BMI groups. Rejection of kidneys based upon donor BMI alone does not appear to be justified.

TH-PO991

The Impact of Recipient BMI on Outcomes after Kidney Transplantation Adam Arshad,[3] Imogen Chappelow,[3] James Hodson,[4] Jay Nath,[2] Adnan Sharif.[1] *[1]Queen Elizabeth Hospital, Birmingham, Birmingham, United Kingdom; [2]University Hospital Birmingham, Birmingham, United Kingdom; [3]University of Birmingham, Stoke on Trent, United Kingdom; [4]University Hospital Birmingham NHS Trust., Biostatistics, Birmingham, United Kingdom.*

Background: A high recipient BMI is still considered a contraindication for transplantation across many centres. However, there is inconsistent evidence as to the influence of recipient BMI on post-transplant outcomes.

Methods: Data from National Health Service blood and transplantation was analysed for all patients receiving deceased donor kidney transplantations between January 2003 to January 2015. Transplants were separated into 5 categories depending on the recipient's body mass index (BMI) (kg/m^2): < 18.50 (underweight), 18.50 – 25.00 (normal), 25.01 – 30.00 kg/m^2 (overweight), 30.01 – 35.00 (obese) and > 35.00 (morbidly obese).

Results: Data for 11,916 transplants were analysed (recipient BMI < 18.50 kg/m^2 in 300, 18.50 kg/m^2 – 25.00 kg/m^2 in 4730, 25.01 kg/m^2 – 30.00 kg/m^2 in 4270, 30.01 kg/m^2 – 35.00 kg/m^2 in 2132 and > 35.00 kg/m^2 in 480). In multivariable analysis, obese and morbidly obese recipients were seen to have impaired graft outcomes, with risk-adjusted rates of delayed graft function of 33.0% and 33.1%, relative to 25.3% in normal BMI recipients (p < 0.001). Obese and morbidly obese BMI were also found to be at increased risk of graft failure (death-censored), with adjusted rates of 1-year and 5-year (in brackets) graft survival of 92.8% (86.0%) and 91.6% (84.4%), relative to 94.4% (88.2%) in normal BMI recipients (p < 0.001). Interestingly, the only group found to be at increased risk of death were the underweight recipients, with adjusted 1- and 5- year survival of 95.1% and 83.5%, compared to 97.0% and 90.6% in normal BMI recipients and 97.2% and 89.7% for morbidly obese recipients (p = 0.005).

Conclusions: Raised recipient BMI increases the risk of graft failure in long-term. Overall, methods to reduce this increased risk of graft failure should be explored.

TH-PO992

Alteration in Body Mass Index and Estimated Glomerular Filtration Rate after Kidney Transplantation Ekamol Tantisattamo,[1] Possawat Vutthikraivit.[2] *[1]Multi-Organ Transplant Center, Division of Nephrology, Department of Internal Medicine, Oakland University William Beaumont School of Medicine, Royal Oak, MI; [2]PHRAMONGKUTKLAO COLLEGE OF MEDICINE, BANGKOK, Thailand.*

Background: The pattern of post-transplant weight change and renal allograft function is unclear. We aim to determine this association.

Methods: A retrospective cohort study of 70 renal transplant recipients was divided into 3 groups (BMI <25, 25 to <30, and ≥30 kg/m2). Changes in the mean BMI compared to pre-transplant BMI (ΔBMI) every 3-month follow-up periods up to 96 weeks post-transplant were correlated with post-transplant eGFR and changes in mean eGFR (ΔeGFR) during the corresponding 3-month follow-up.

Results: Compared to pre-transplant BMI, BMI at the time of discharge from the transplant admission increased in 3 groups (p=0.003, 0.000, and 0.514). In normal and overweight groups, BMI was lower during the first 4- and 12-week post-transplant compared to BMI at the time of transplant, respectively (p=0.236 and p=0.012-0.069) and then became persistently higher through 96 weeks post-transplant (p=0.001-0.122 and p=0.004-0.299). Mean eGFR continued trending up post-transplant until 24-week post-transplant and appeared to be plateau among all 3 BMI groups (Figure). By comparing mean eGFR every 12-week interval during post-transplant, there was no difference among 3 groups. In addition, ΔBMI between consecutive 3-month follow-up period did not associate with ΔeGFR at the corresponding 3-month follow-up period (p=0.104-0.922). The probability of developing worsening CKD stage was higher in overweight and obese groups compared to normal weight group, but there was no statistical significance (HR 0.697 (CI 0.296 to 1.641) for overweight and HR 0.695 (CI 0.279-1.728) for obese compared to normal weight group - Figure).

Conclusions: eGFR appears to increase with weight loss during the first 24-month post-transplantation in all BMI strata; however, it does not significantly change and not associated with BMI alteration thereafter. Pre-transplant obesity may not be the main determinant for post-transplant renal allograft function during early and late post-transplant periods.

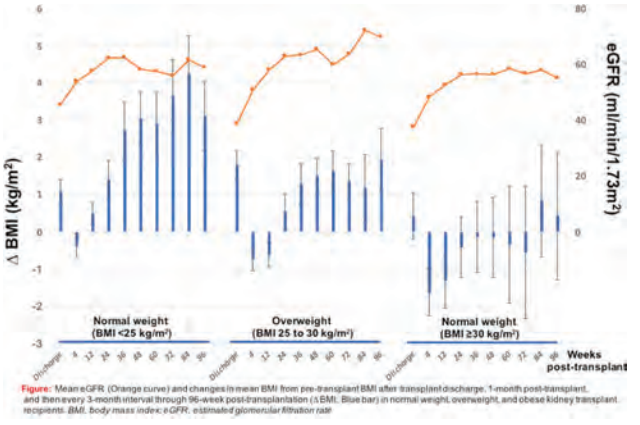


Figure: Mean eGFR (Orange curve) and changes in mean BMI from pre-transplant BMI after transplant discharge, 1-month post-transplant, and then every 3-month interval through 96-week post-transplantation (Δ BMI, Blue bar) in normal weight, overweight, and obese kidney transplant recipients. *BMI, body mass index; eGFR, estimated glomerular filtration rate*

TH-PO993

Is Body Mass Index a Significant Independent Risk Factor for Graft Failure and Patient Death in the Modern Immunosuppressive Era? Ho Sik Shin,[2,1] Anil K. Chandraker.[2] *[1]Kosin University College of Medicine, Gospel Hospital, Busan, Republic of Korea; [2]Harvard Medical School, BWH, Transplantation Research Center, Boston, MA.*

Background: In previous studies, kidney transplant recipients with high body mass index (BMI) had inferior or superior outcomes compared to patients with lower BMI, and thus it remains unclear whether BMI is a significant independent risk factor for graft failure and patient death in the modern immunosuppressive era. We used United Network for Organ Sharing (UNOS) data to determine whether obesity affects patient and graft outcome following kidney transplantation.

Methods: From the UNOS database, we identified patients who underwent primary kidney-only transplantation between 1987 and 2016. The study sample consisted of 69,749 from 1987-1999 and 197,986 from 2000-2016. We correlated BMI with graft and patient survival, and created multivariate models to evaluate the independent effect of BMI on graft and patient outcomes, adjusting for factors known to affect graft success and patient survival.

Results: Mean BMI shifted from 25 kg/m^2 in 1987-1999 to 27 kg/m^2 in 2000-2016. Higher BMI was associated with significantly worse graft, patient and patient with functioning graft survival from 1987-1999. Lower and higher BMI were also associated with significantly worse graft, patient and patient with functioning graft survival from 2000-2016. In the same BMI group, graft and patient survival rates from 2000-2016 were higher than in 1987-1999. Cox regression modeling hazard ratios showed that obesity also increased the risk of graft failure and patient death.

Conclusions: BMI is a significant independent risk factor for graft failure and patient death in the modern immunosuppressive era.

Table 1. Patient characteristics according to era.

Characteristics	Year 1987-1999 (n = 69,749)	Year 2000-2016 (n = 197,986)
Recipient age (years)*	45.6 ± 12.7	51.2 ± 13.4
BMI (kg/m²)*	25.4 ± 4.6	27.7 ± 5.1
Donor age (years)*	34.6 ± 16.4	39.6 ± 15.2
Cold ischemic time (hours)*	19.4 ± 11.5	13.5 ± 10.8
Ethnicity (number/%)		
White	41,312/59.2	99,909/50.5
African American	17,316/24.8	52,899/26.7
Hispanic	7,171/10.3	29,706/15.0
Asian	2,627/3.8	11,495/5.8
Native American	631/0.9	1,901/1.0
Other	692/1.0	2076/1.0
Donor type (number/%)*		
Living	10,407/14.9	65,795/33.2
Deceased	69,342/85.1	132,191/66.8
Donor hypertension (number/%)*	6,211/7.9	37,356/18.8
Donor DM (number/%)*	990/1.4	9,069/4.5
Recipient gender (M/F %)	61.1/38.9	61.2/38.8
HLA full match (number/%)	5,196/7.4	16,234/8.1
Donor gender (M/F %)	58.1/41.9	52.9/47.1
Acute rejection within 6 months (number/%)*	16,962/24.3	12,969/6.5
Age > 65 years (number/%)*	4,816/6.9	34,707/17.5
Comorbidity, no. (%)		
Peripheral vascular disease*	3,208 (4.6)	10,097 (5.1)
Diabetes Mellitus*	9,563 (13.7)	65,426 (33.0)
Hypertension*	8,068 (11.5)	45,928 (23.1)
Recipient died with functioning graft*, no.(%)	18,479 (26.4)	26,336 (13.3)
Delayed graft function, no. (%)*	14,832 (21.2)	36,168 (18.2)

*P value < 0.05

BMI: Body Mass Index; DM: Diabetes Mellitus; HLA: Human Leukocyte Antigen.

TH-PO994

Obesity: A Risk Factor for Hypertension after Kidney Transplantation Ekamol Tantisattamo,[1] Possawat Vutthikraivit.[2] *[1]Multi-Organ Transplant Center, Division of Nephrology, Department of Internal Medicine, Oakland University William Beaumont School of Medicine, Royal Oak, MI; [2]PHRAMONGKUTKLAO COLLEGE OF MEDICINE, BANGKOK, Thailand.*

Background: Hypertension (HTN) after kidney transplantation is common. Underweight leads to unfavorable outcomes in ESRD. The magnitude of risk factors including obesity after kidney transplantation is unclear.

Methods: Seventy kidney transplant recipients were enrolled in a retrospective closed cohort study. Post-transplant HTN is defined as SBP ≥ 140 mmHg first detected after 1-month post-transplantation. The incidence of HTN and the association between potential risk factors and post-transplant HTN were determined.

Results: Mean age was 52.66±1.43 years old and 41 patients (58.6%) was male. There were 49 patients (70%) diagnosed with post-transplant HTN, which was an account of the incidence of post-transplant HTN was 48.67 person-year. Mean SBP and DBP at the time of diagnosis were 151 mmHg; whereas, SBP and DBP of the remaining 21 patients (30%) without post-transplant HTN were 119 mmHg, respectively (p= 0.0167, mean difference 31.79, CI 5.9367 to 57.6433). Several traditional risk factors for HTN were examined and pre-transplant obesity (BMI ≥30 kg/m^2) and old age (≥ 65 years old) were significantly associated with post-transplant HTN (RR 1.382 (CI 1.050 to 1.819) and RR 1.6 (1.306 to 1.96); Table)). By using binary logistic regression analysis, post-transplant HTN was 1.140 times greater in obese than in non-obese patients after adjusted for age, gender, race, pre-transplant BMI, and eGFR at transplant discharge (CI 1.006 – 1.291, p=0.040).

Conclusions: Although the reverse epidemiology of non-obesity leading to potential harmful effect in ESRD patients, pre-transplant obesity can lead to poor post-transplant cardiovascular outcomes. Since obesity continues carrying and remains one of the traditional risk factors of HTN after successful kidney transplantation, pre-transplant weight control is still warranted.

Association between systolic hypertension beyond 1-month post-kidney transplantation and its potential risk factors

	RR	CI
Pre-transplant BMI	1.382	1.050 to 1.819
Age ≥65 years old	1.600	1.306 to 1.960
Male	1.218	0.873 to 1.700
African American	1.214	0.904 to 1.629
eGFR ≥ stage 3 CKD	1.064	0.716 to 1.580

BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate (ml/min/1.73m2); RR, relative risk

TH-PO995

Metabolic Responses to Kidney Transplantation: Is Early Weight Gain Benign? Biruh Workeneh,[3] Joy V. Nolte,[2] Linda W. Moore,[2] Roman Shypailo,[1] Ahmed O. Gaber,[2] William E. Mitch.[1] *[1]Baylor College of Medicine, Houston, TX; [2]Houston Methodist Hospital, Houston, TX; [3]MD Anderson Cancer Center, Houston, TX.*

Background: It is widely assumed that modest weight gain following kidney transplantation (KT) is advantageous to patients. However, there is no consensus about what constitutes appropriate degree of weight gain nor has there been rigorous explorations about the nature and metabolic implications of changes in body composition.

Methods: We analyzed 31 living kidney transplant (KT) recipients. Subjects were 18-65yrs old, noninsulin dependent, and received tacrolimus-based immunosuppression. All measurements were obtained <1mo prior to and 3mo post-KT. DXA and BodPod were used to measure body mass and define body compartments. Resting energy expenditure (REE) was obtained by indirect calorimetry and physical activity was assessed by accelerometory. Insulin resistance (IR) was determined by HOMA-IR and dietary intake determined ASA24 dietary recall.

Results: We observed significant increases in body weight and fat (Table1). DXA revealed fat accumulation primarily in the truncal region. Visceral and subcutaneous fat volumes increased significantly, and visceral fat volume positively correlated with IR (r=0.452, p=0.012). REE did not change significantly and there was no relationship with fat or muscle mass. Accelerometry showed subjects were more ambulatory post-KT, 5201 vs 6515 average daily steps(p=0.034). Vector magnitude (total axis activity) also increased. Food recalls showed more calories comprised of fat and protein are consumed post-KT(42% and 17% of total kcals).

Conclusions: We conclude that only 3 months after KT there are small but significant increases in adipose deposition and have reported adverse responses including insulin resistance. Even at this early stage, patients accumulate total body fat and importantly, visceral fat. The changes we observed could not be attributed to changes in other body compartments, decreased metabolic rate, or physical activity but dietary factors may influence orexigenic factors and adipose tissue accumulation.

Funding: Private Foundation Support

	Pre-KT (mean, (SD))	Post-KT (mean, (SD))	p-value
Weight, kg (SD)	83.8 (16.6)	85.3 (16.7)	0.032
DXA fat, kg	25 (10.7)	27 (10)	0.004
Trunk fat mass, kg	13.4 (6.5)	14.9 (6.3)	000.1
Visceral fat volume, cm3	839 (780)	916 (482)	0.006
Subcutaneous fat volume, cm3	1539 (689)	1703 (602)	0.002
Total daily calories	1954 (978)	2260 (776)	0.240)
HOMA-IR	2.92 (1.98)	4.47 (3.6)	0.012

TH-PO996

Android Obesity and NT-ProBNP in Kidney Transplant Patients Magdalena B. Kaziuk. *Chair and Department of Nephrology, Jagiellonian University Medical College, Kraków, Poland.*

Background: Adipose tissue is a typical location for storage of water-insoluble toxins in a body. An excess of adipose tissue may be either systemic or local. According to a pattern of fat distribution in the body, we distinguish two types of obesity: android (visceral, abdominal) and gynoid (around bottom and tights, peripheral). The obesity increases a risk of the kidney failure and cardiovascular complications in a group of kidney transplant patients (KTx). An attempt was made to evaluate a relationship between the amount of adipose tissue, obesity type, and NT- proBNP level in KTx patients.

Methods: The study covered 128 patients (60 women and 68 men, average age 49.5 ± 10.8 years) with a functioning renal transplant more than 3 months after the transplant. The amount of adipose tissue was determined using the bioelectrical impedance analysis (BIA) and anthropometric measurements, nutrition status and the obesity type were established by Waist to Height Ratio (WHtR) and Waist to Hip Ratio (WHR), the function of the transplanted kidney was evaluated by calculation of the estimated glomerular filtration rate (eGFR) using the MDRD formula, and their relation with the N-terminal pro-brain natriuretic peptide (NT- proBNP) was studied.

Results: In the study group, 22.7% of patients were classified as having a correct body weight, while 56.7% and 20.6% of participants had an android and gynoid type, respectively. In the logistic regression analysis, an increase by 0.2% in a risk of abdominal obesity in KTx patients (OR=1.002 95% CI: 1.001–1.003; p< 0.001) was associated with an increase in NT- proBNP by 100 pg/ml. An increase in eGFR by 1ml/min/1,73m2 was associated with a reduction in the androidal obesity risk by 4.5% (OR= 0.955 95% CI: 0.923–0.984; p=0.005). The higher the NT-proBNP value, the higher the percentage content of adipose tissue (Spearman rank correlation coefficient: 0.473; p<0.001) in KTx patients.

Conclusions: A large amount of adipose tissue, particularly in a case of androidal obesity, may be a predictor of kidney or cardiovascular system. Furthermore, high NT-proBNP levels may be associated with an increased risk of obesity in KTx patients; therefore, correct diet and pharmacological management, and physical activity adapted to the physical fitness level of a patient are necessary.

TH-PO997

Waist to Hip Ratio (WHR) as a Predictor of Increased Length of Stay Post Kidney Transplantation Flor Espinoza, Rohan Patankar, Ramon Noriega, Brittany L. Schreiber, Vishy Chaudhary, Muhammad A. Mujtaba. *University of Texas Medical Branch, Galveston, TX.*

Background: Objective: To determine if WHR vs body mass index (BMI) could be used as a reliable predictor of increased length of stay from transplant to first discharge, defined as 7 days or more, in a group of first time kidney transplant recipients. Background: Prolonged hospitalizations in renal transplant patients continues to be a concern due to its potential effect on health care costs and patient satisfaction scores. Various factors including BMI are considered while establishing suitability for kidney transplantation. However, BMI has its limitations as it does not take into account body fat distribution. WHR may provide an alternative tool for pre-transplant candidate selection. We aimed to assess if WHR could to be used to predict increased length of stay (LOS) post kidney transplantation.

Methods: This is a single center retrospective analysis of deceased and living donor kidney transplants performed through the period of May 2015 to March 2017. Increased LOS was defined as 7 days or more. A multivariate linear regression analysis was performed comparing BMI and WHR, and results were reviewed. A p-value of ≤ 0.05 was considered significant.

Results: A total of 69 patients were included, 60 of which received deceased donor kidney transplants and 9 received living donor kidneys. All patients were first time kidney transplant recipients. Patients WHR ranged from 0.78 – 1.07. The LOS ranged from 5 to 22 days. Increased WHR was significantly assocated with LOS (P-value = 0.04), whereas BMI was not (P-value = 0.84).

Conclusions: Our results suggest that WHR can be used as an accurate tool to predict increased length of stay in first time kidney transplant recipients. Further collaborative efforts and research are needed to fully elucidate the relationships between WHR and increased length of stay with respect to cost, patient satisfaction and graft outcomes

TH-PO998

Genome Wide Non HLA Alloimmunity Contributes to Graft Loss after Kidney Transplantation Rainer Oberbauer,[3] Roman Reindl-Schwaighofer,[3] Alexander Kainz,[1] Andreas Heinzel,[4] Kira Jelencsics,[2] Petra Hruba,[6] Ondrej Viklicky,[1] Georg Bohmig,[2] Gottfried Fischer,[3] Brendan Keating.[1] *[1]Department of Nephrology, Vienna, Austria; [2]Medical University Vienna, Vienna, Austria; [3]Medical University of Vienna, Vienna, Austria; [4]Medical University of Vienna, Vienna, Vienna, Austria; [6]Institute for Clinical and Experimental Medicine, Prague, Czech Republic.*

Background: HLA alloimmunity is the main cause of renal transplant loss but the contribution of nonHLA donor recipient mismatches on a genome wide basis has not been elucidated thoroughly yet.

Methods: We made use of the iGeneTrain consortium and genotyped 753 donors and 863 corresponding recipients using the Affymetrix Axiom Tx GWAS Array (Affymetrix). Raw genotypes were after an initial quality control phased and imputed with impute2 using GoNL and 1KG data as reference panels. The ensemble Variant Effect Predictor and ANNOVAR were used for SNP annotation. The number of recipients with a median follow up of 6.5 years were obtained from the Vienna and Prague transplant cohort study. The main available outcomes are death censored graft loss and eGFR slope after transplantation. HLA incompatibility and other clinical variables known to influence these outcomes are available. In a first preliminary analysis elucidating the effect of donor recipient non-synonymous SNP (nsSNP) mismatches (MM) on graft survival a Cox model was employed to analyze the association of nsSNP MM with graft survival. For this preliminary analysis 180 donor recipient pairs with 36 events were available.

Results: The association of nsSNP MM with graft survival showed a trend towards elevated risk for death censored graft loss (table). Table: Multivariable Cox model relating the time of graft survival to donor recipient HLA MM and nsSNP MM. A follow up study utilizing the full cohort and imputation results will be performed in the next months prior to the meeting. Further custom peptide arrays (NimbleGen/Roche) holding 172,943 features will be employed to uncover the formation of antibodies in case of donor recipient LoF and nsSNP MM.

Conclusions: NonHLA alloimmunity independently contributes to graft loss after kidney transplantation.

Cox model

Parameter	HR	95CI lower	95CI higher	p-value
HLA MM	1.29	1.05	1.60	0.017
SNP a 100	1.58	0.78	3.21	0.201

TH-PO999

Effect of Human Leukocyte Antigen Mismatching on the Outcomes of Kidney Transplantation: A Systematic Review and Meta-Analysis Xinmiao Shi,[1] Rui Liu,[3] Jicheng Lv,[2] Xinfang Xie,[2] Xuhui Zhong,[1] Jie Ding.[1] *[1]Peking University First Hospital, Beijing, China; [2]Renal Division, Peking University First Hospital, Beijing, China; [3]The First Hospital of Tsinghua University, Beiijng, China.*

Background: The impact of HLA mismatching on kidney transplantation(KT) remains controversial. We aimed to evaluate the effect of HLA mismatching on KT.

Methods: We systematically searched PubMed, EMBASE, and the Cochrane Library for relevant studies.

Results: For adults, every HLA mismatch(mm) increase was associated with increased risk of overall graft failure (HR=1.06;95%CI,1.05-1.07), death-censored graft failure (HR=1.09;95%CI,1.06-1.11) and mortality (HR=1.05;95%CI,1.02-1.07). Moreover, HLA-DR mismatching was associated with significantly inferior graft survival(HR=1.08; 95%CI,1.05-1.11), but not HLA-A (HR=1.06;95% CI,0.98-1.14) or HLA-B (HR=1.01;95%CI,0.89-1.14). For children, compared with 0–1 HLA-DR mm, 2 mm significantly increased the risk of graft failure at 1 year (RR=1.41,95%CI:1.11–1.80),3 years (RR=1.28,95%CI:1.08–1.52),5 years(RR=1.21,95%CI:1.04–1.41), and 10 years (RR=1.30,95%CI:1.02–1.67). For HLA-A+B, the 5-year graft failure risk was higher for 2–4 compared with 0–1 mm (RR=3.17,95%CI:1.20–8.36), but not for 3–4 compared with 0–2 mm (RR=1.49,95%CI:0.79–2.80).

Conclusions: For adults, HLA mismatching is an independent factor affecting graft failure and mortality. HLA-DR appears to be more essential than HLA-A or -B. For children, HLA-DR and HLA-A+B are important factors affecting graft failure.

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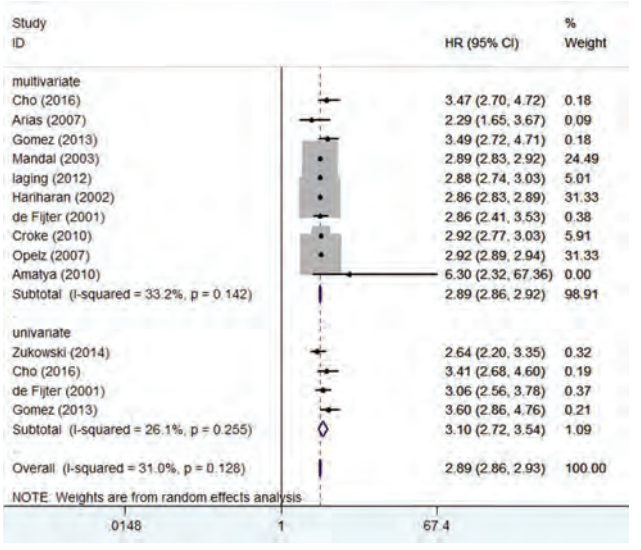
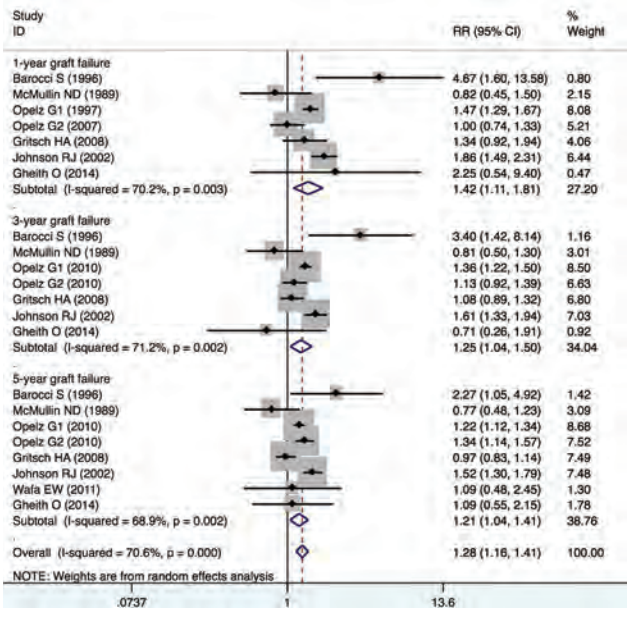




TH-PO1016

Effect of Hyperkalemia on Renal Ammonia Metabolism Autumn N. Harris,[1] P. R. Grimm,[2] Hyun-Wook Lee,[1] Eric J. Delpire,[3] Paul A. Welling,[2] Jill W. Verlander,[1] I. D. Weiner.[1,4] *[1]Nephrology, University of Florida, Gainesville, FL; [2]University of Maryland School of Medicine, Baltimore, MD; [3]Vanderbilt University Medical Center, Nashville, TN; [4]Nephrology, NF/SGVHS, Gainesville, FL.*

Background: Type IV Renal Tubular Acidosis (RTA) is characterized by metabolic acidosis and hyperkalemia, but the mechanism(s) through which the metabolic acidosis

develops remains in question. In particular, hyperkalemia's role in the pathogenesis of the metabolic acidosis has been unclear. This is because in vivo models testing the effects of hyperkalemia are difficult to perform because of robust renal K excretory mechanisms that limit development of chronic hyperkalemia. To obviate this limitation, we used a genetic model of hyperkalemia that does not target the proximal tubule (PT) or collecting duct, does not directly target proteins involved in ammonia metabolism and does not involve altered K intake to determine hyperkalemia's effect on acid-base homeostasis and ammonia metabolism.

Methods: We used a recently reported DCT-specific constitutively active SPAK (DCT-CA-SPAK) mouse model and compared it with wild type (WT) littermates. We used thiazide administration to block the NCC over-activity and correct the hyperkalemia.

Results: Under basal conditions DCT-CA-SPAK mice exhibited hyperkalemia and metabolic acidosis. Despite the metabolic acidosis, they had decreased urine ammonia excretion compared to WT mice. Titratable acid excretion was not altered. Thiazide administration, to reverse the effect of DCT-CA-SPAK on NCC, corrected the hyperkalemia and increased ammonia excretion, but had neither effect in WT mice. Phosphoenolypyruvate and phosphate-dependent glutaminase, key ammonia generating proteins, expression was significantly less in DCT-CA-SPAK PT. Glutamine synthetase, which recycles ammonia, was significantly greater in DCT-CA-SPAK cortical PT. NKCC2 and Rhbg expression were unchanged. Thus, hyperkalemia in a genetic model that does not alter K intake, does not directly involve the PT and does not directly alter proteins involved in ammonia metabolism, alters expression of multiple proximal tubule proteins involved in ammonia generation, leading to decreased ammonia excretion, which is reversible with correction of the hyperkalemia.

Conclusions: Hyperkalemia can directly inhibit proximal tubule ammonia metabolism, decreasing ammonia and net acid excretion, and leading to metabolic acidosis. Moreover, the effects of hyperkalemia on ammonia metabolism to suppress ammonia excretion are greater than those of metabolic acidosis to stimulate it.

Funding: NIDDK Support, Private Foundation Support

TH-PO1017

Diabetes-Induced Ammoniagenesis and Kidney Growth Are Independent of Acidosis and Increased Filtered Load of Glutamine Hassane Amlal,[1] Cara E. Molulon,[2] Sritej Devineni.[1] *[1]University of Cincinnati, Cincinnati, OH; [2]University of Cincinnati College of Medicine, Cincinanti, OH.*

Background: Studies have shown that total ammonia ($NH_4^+ + NH_3$) causes renal cell hypertrophy. We have previously demonstrated that diabetes-induced kidney growth occurs early during the onset of hyperglycemia and is associated with the stimulation of ammonia synthesis in the proximal tubule (*J Am Soc Nephrol* 27: 652A, 2016). However, whether the stimulation of ammoniagenesis is secondary to the development of acidosis and/or increased filtered load of glutamine remain unknown.

Methods: The inhibition of carbonic anhydrases by acetazolamide (ACTZ) in the proximal tubule activates the tubulo-glomerular feedback and induces metabolic acidosis by increasing NaCl delivery to macula densa and by increasing bicarbonate wasting in the urine, respectively. Rats were housed in metabolic cages with free access to food and water for water balance studies and urine collections. After acclimation, rats were divided into 4 groups, and treated with vehicle, ACTZ, Streptozotocin (STZ) to induce type 1 diabetes or STZ + ACTZ for 7 days. Blood chemistry and urinary NH_4^+ excretion were analyzed and kidney mass (kidney weight/body weight) was measured.

Results: As indicated by serum [HCO3-], significant metabolic acidosis was developed in rats treated with ACTZ or ACTZ + STZ but not in STZ-treated rats as compared to vehicle group. NH4+ excretion increased by 3-fold, 10-fold and 15-fold in ACTZ, STZ alone and ACTZ+STZ animals, respectively vs. Control group. Kidney mass increased slightly in ACTZ group (15%) and sharply in STZ alone (42%) and ACTZ+STZ (60%) groups, as compared to Controls. ACTZ did not alter food intake but significantly reduced body weight loss in ACTZ+STZ rats (-3g) vs. STZ alone (-20g). This correlated with improved levels of blood volume markers (BUN, Hct and Hb) and reduced urine output in ACTZ + STZ, indicating a reduction in glomerular filtration rate by ACTZ vs. STZ alone.

Conclusions: The stimulation of ammoniagenesis and increased renal mass are more profound in STZ-induced diabetes than in ACTZ-induced metabolic acidosis. Moreover, acidosis and diabetes exert an additive effect on both parameters, indicating that the signaling mechanism mediating the effects of acidosis and diabetes are different. Lastly, the stimulation of ammonia synthesis in diabetes is independent of increased filtered load of glutamine.

Funding: NIDDK Support, Clinical Revenue Support

TH-PO1018

Sex Differences in Renal Ammonia Metabolism Autumn N. Harris,[1] Gunars Osis,[1] Hyun-Wook Lee,[1] Kierstin L. Webster,[1] Jill W. Verlander,[1] I. D. Weiner.[1,2] *[1]Nephrology, University of Florida, Gainesville, FL; [2]Nephrology, NF/SGVHS, Gainesville, FL.*

Background: Renal ammonia excretion is an important component of acid-base homeostasis. Previous studies indicate that sex impacts multiple aspects of renal function. This study's purpose was to investigate gender differences in renal ammonia metabolism.

Methods: We compared 4-month-old male (M) and female (F) C57Bl/6 mice, with measurement of plasma electrolytes, urinary ammonia excretion, and evaluation of changes in key proteins involved in ammonia metabolism using immunoblot analysis and immunohistochemistry.

Results: Under basal conditions, female mice excreted significantly more urine ammonia than male mice (F, 71.9±22.9; M, 46.1±18.6 μmol/day; $P \leq 0.02$) and had significantly lower plasma bicarbonate concentrations than male mice (F, 18.1±1.6; M, 19.9±1.5 mmol/L; $P \leq 0.02$). Titratable acid excretion (F, 63±42; M, 78±17 μmol/day), urine pH (F, 6.40±0.18; M, 6.36±0.14), plasma Na^+ and K^+ concentrations, and food intake (F, 8.9±0.9; M, 9.6±1.2 g/day) did not differ significantly. Total expression of key ammonia generating proteins, phosphoenolypyruvate and phosphate-dependent glutaminase were significantly greater in the cortex of female than male mice. Expression of glutamine synthetase, which recycles ammonia, was significantly greater in the cortical proximal tubules (PT) of female mice. Expression of NBCe1, a basolateral PT bicarbonate transporter, recently shown to regulate PT ammonia metabolism, did not differ significantly between sexes. Expression of the ammonia transporter family member, Rhbg, was significantly greater in connecting segment cells and intercalated and principal cells in the collecting duct in the cortex and inner stripe of the outer medulla (ISOM) in female mice. Expression of Rhcg was significantly greater in female mice in connecting segment cells and in the basolateral membrane of intercalated and principal cells in the collecting duct in the ISOM.

Conclusions: Despite similar levels of food intake and thus protein intake, which is the primary determinant of endogenous acid production, female mice excreted higher amounts of basal ammonia, but not titratable acid. This increase in ammonia excretion was associated with differences in the expression of several proteins involved in ammonia generation and transport. Thus, there are sex-dependent differences in basal ammonia metabolism and acid-base homeostasis.

Funding: NIDDK Support, Private Foundation Support

TH-PO1019

Hypercapnia Increases Urinary Ammonium Excretion and Upregulates Expression of the NH3/NH4+ Transporters Rh Glycoproteins Nazih L. Nakhoul,[1] L. Lee Hamm,[1] Kathleen S. Hering-Smith,[1] Mohammed T. Islam,[1] Solange Abdulnour-Nakhoul.[1,2] *[1]Tulane Medical School, New Orleans, LA; [2]SLVHCS, New Orleans, LA.*

Background: Hypercapnia and subsequent respiratory acidosis is a serious complication observed in patients with respiratory disorders such as chronic obstructive pulmonary disorder (COPD) and acute respiratory distress syndrome. A recent study shows that the presence of COPD in patients with CKD greatly increases the risk of death. The acute response to hypercapnia is buffering of H^+ by hemoglobin and other cellular proteins but this effect is limited. The chronic response (usually complete in 3-5 days) is renal compensation that increases HCO_3^- reabsorption, mostly in the proximal tubule, and stimulates urinary excretion of titratable acids (TA) and NH_4^+. However, the main effective pathway is the excretion of NH_4^+ in the collecting duct. Our hypothesis is that the renal NH_3/NH_4^+ transporters Rhbg and Rhcg in the collecting duct mediate this response. The effect of hypercapnia on these transporters is unknown.

Methods: We conducted *in-vivo* experiments on mice subjected to induced respiratory acidosis. We placed two groups of mice in special chambers where breathing gas mixtures can be controlled. One group breathed 8% CO_2 (21% O_2 & 71% N2) to induce respiratory acidosis and the other breathed normal air as control. After 5 days, the mice were euthanized and kidneys, blood and urine samples were collected. We used immuno-histochemistry, Western analysis and qRT-PCR to determine how breathing high CO_2 levels affects localization, abundance and gene expression of the Rh proteins.

Results: Western analysis showed a significant increase in expression of Rhbg (by 43% ± 3.3) and Rhcg (by 12.6% ± 3.0) in animals that breathed 8% CO_2, ($P<0.01$, n=10). In addition, carbonic anhydrase (CA-IV) expression was increased significantly in hypercapnia (by 51% ± 14, $P<0.005$). In hypercapnic animals, there was a significant increase in urinary NH_4^+ excretion (by 50% ± 3.2, $P<0.01$) but the change in TA was not statistically significant.

Conclusions: These data suggest that hypercapnia (for 5 days) leads to compensatory upregulation of Rhbg & Rhcg proteins that contributes to excretion of NH_3/NH_4^+ in the kidney. These studies are the first to show a link between hypercapnia, NH_4^+ excretion and Rh expression.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO1020

The A-Splice Variant of NBCe1 Is Necessary for Basal and Acidosis-Stimulated Renal Ammonia Metabolism Hyun-Wook Lee,[1] Gunars Osis,[1] Autumn N. Harris,[1] Lijuan Fang,[1] Heather L. Holmes,[2] Adam J. Rossano,[2] Michael F. Romero,[2] Jill W. Verlander,[1] I. D. Weiner.[1,3] *[1]Nephrology, University of Florida, Gainesville, FL; [2]Mayo Clinic, Rochester, MN; [3]Nephrology, NF/SGVHS, Gainesville, FL.*

Background: Renal ammonia excretion is the largest component of net acid excretion during both basal conditions and metabolic acidosis. Proximal tubule (PT) ammonia generation is critical for normal renal ammonia excretion, but the mechanisms through which external stimuli alter PT ammonia metabolism are incompletely understood. This study's purpose was to determine the role of the predominant proximal tubule NBCe1 (SLC4A4) splice variant, NBCe1-A, in ammonia metabolism under basal conditions and in response to metabolic acidosis.

Methods: We used mice with specific deletion of the NBCe1-A splice variant generated using TALEN gene editing. Mice were fed normal diet or were acid-loaded by adding HCl to chow. All studies compared homozygous deletion (KO) mice with wild-type (WT) littermates.

Results: Under basal conditions, KO mice had spontaneous metabolic acidosis, consistent with proximal RTA from impaired proximal tubule bicarbonate reabsorption. Despite this acidosis, urinary ammonia excretion was not elevated in KO mice. Urine pH was lower in KO than WT mice, indicating that the failure of basal acidosis-stimulated

ammonia excretion was not due to impaired urine acidification. Immunoblots and immunohistochemistry (IHC) showed KO mice, despite their acidosis, expressed less phosphate-dependent glutaminase (PDG) and phosphoenolpyruvate carboxykinase (PEPCK), key ammonia generating enzymes, throughout the entire PT, and expressed more glutamine synthetase (GS) in cortical PT segments than did WT. After acid-loading, the ability to increase ammonia excretion was impaired significantly, by ~70%, in KO mice. Immunoblots and IHC showed less change in PEPCK, PDG and GS in the proximal convoluted tubule (PCT) of KO than WT mice. However, in the proximal straight tubule (PST) in the outer medulla, where in the normal mouse NBCe1-A expression is less than in the PCT, PDG and PEPCK upregulation and GS downregulation were greater in KO than in WT mice.

Conclusions: (1) NBCe1-A is a key protein in the signaling pathway through which PCT ammonia metabolism is regulated during basal conditions and metabolic acidosis; and, (2) In the PST, one or more additional mechanisms enable responsiveness to exogenous acid-loading, but not to the spontaneous metabolic acidosis, in KO mice.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

TH-PO1021

The A-Splice Variant of NBCe1 (NBCe1-A) Regulates Citrate Excretion and NaDC1 Expression Gunars Osis,[1] Kierstin L. Webster,[1] Heather L. Holmes,[2] Adam J. Rossano,[2] Michael F. Romero,[2] Jill W. Verlander,[1] I. D. Weiner.[1,3] *[1]Nephrology, University of Florida, Gainesville, FL; [2]Mayo Clinic College of Medicine, Rochester, MN; [3]Nephrology, NF/SGVHS, Gainesville, FL.*

Background: Urinary citrate affects several critical kidney functions, including acid-base homeostasis and prevention of calcium nephrolithiasis. Proximal tubule (PT) NaDC1 is believed to be the major regulator of urinary citrate excretion. These studies examined the role of the A-splice variant of NBCe1 (NBCe1-A) in basal and acidosis-stimulated citrate excretion and NaDC1 expression.

Methods: We used recently developed NBCe1-A-specific deletion (KO) mice and their wild-type (WT) littermates. We performed exogenous acid-loading with dietary HCl loading for 7 days. We used quantitative immunohistochemistry (qIHC) to examine NaDC1 expression in proximal convoluted tubule in the cortical labyrinth (PCT), proximal straight tubule (PST) in the medullary ray (PST-MR) and PST in the outer medulla (PST-OM). Urinary citrate was measured using ^{1}H-NMR.

Results: In WT mice under basal conditions, NaDC1 immunolabel intensity exhibited significant axial heterogeneity, PCT < PST-MR < PST-OM. Under basal conditions, NBCe1-A deletion induces spontaneous metabolic acidosis. Despite the acidosis, which in normal conditions decreases citrate excretion, citrate excretion was significantly greater in KO than WT mice (~3x-fold). Quantitative IHC showed NaDC1 expression was significantly less in KO than WT mice in all PT sites. Exogenous acid-loading decreased urinary citrate excretion >98% in both genotypes such that final urinary citrate did not differ significantly between WT and KO mice. Exogenous acid-loading increased NaDC1 expression in WT mice in the PCT and PST-MR, but not the PST-OM. In KO mice, in contrast, exogenous acid-loading did not alter PCT NaDC1 expression significantly, but did increase expression significantly in both PST-MR and PST-OM.

Conclusions: 1) Under basal conditions NBCe1-A expression is critical to the normal regulation of citrate excretion and NaDC1 expression; 2) in WT mice, there is significant axial heterogeneity of both basal NaDC1 expression and its response to acid-loading; and, 3) during exogenous acid-loading alternative signaling pathways in NBCe1-A KO mice increase NaDC1 expression with a different axial pattern than in WT mice. We conclude that NBCe1-A is critical for citrate metabolism through its regulation of normal NaDC1 expression under basal conditions and in response to acid-loading.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

TH-PO1022

Exploring the Exchangeability of Transmembrane Segments between Na/HCO3 Cotransporter NBCe1-A and Cl-HCO3 Exchanger AE1 Seong-Ki Lee, Walter F. Boron. *Physiology and Biophysics, Case Western Reserve University, Cleveland, OH.*

Background: The SLC superfamily of transport proteins comprises >300 genes in 52 families. Here we study 2 SLC4 family members: electrogenic NBCe1 (SLC4A4) and electroneutral Cl-HCO_3 exchanger AE1 (SLC4A1). NBCe1-A is predominantly expressed in the renal proximal tubule basolateral membrane, where it reabsorbs HCO_3^- into the blood. The erythrocyte variant of AE1 is important for CO_2 carriage in blood. Recently, Arakawa et al. published the crystal structure of human AE1, which has 14 transmembrane segments (TMs). They classified the TMs into a core domain (CD; 8 TMs) and a gate domain (GD; 6 TMs). They proposed that conformational changes of the GD allow transport of substrate, whereas the CD provides substrate specificity.

Methods: Guided by this new AE1 structure, we defined NBCe1's TMs (~25-30% amino-acid identity to AE1). We hypothesized that NBCe1-A will work when implanting gate TMs of AE1 into NBCe1-A, whereas NBCe1-A will not work when implanting core TMs of AE1 into NBCe1-A. We generated 14 NBCe1-A chimeras, 1 for each TM. We assessed NBCe1-A's electrogenic activity by two-electrode voltage-clamping *Xenopus* oocytes expressing each mutant. We checked surface expression (SExp) by biotinylation.

Results: Data is summarized in Table. We found that, in general, implanting gate TMs induces SExp, whereas implanting core TMs does not. We also found that some mutants show robust electrogenic activity (I_{NBC}, NBCe1-A current, or ΔV_m upon HCO_3^- addition).

Conclusions: Our findings suggest that the CD of NBCe1-A cannot tolerate swapping of individual TMs because of coordination with substrates, whereas the GD of NBCe1-A generally expresses after such swaps, and even shows robust electrogenic activity in some cases presumably because the swapped TM still works as a structural component.

ΔTM	1st	2nd	3rd	4st	8st	9st	10st	11st	5st	6st	7st	12st	13st	14st
CD/GD	core	core	core	core	core	core	core	core	gate	gate	gate	gate	gate	gate
SExp	-	+	+	-	-	-	-	+++	+++	+++	+++	-	+++	+++
ΔV_m	-	-	-	-	-	-	-	++	+	++	+++	-	+++	+
I_{NBC}	-	-	-	-	-	-	-	++	-	++	+++	-	+++	-

TH-PO1023

Novel Point Mutation in NBCe1/SLC4A4 Displays Dominant-Negative Inhibition of Wild-Type NBCe1A Activity in Mammalian Cells and Xenopus Oocytes Adam J. Rossano, Heather L. Holmes, Michael F. Romero. *Mayo Clinic College of Medicine, Rochester, MN.*

Background: NBCe1 (electrogenic Na^+/HCO_3^- cotransporter 1; SLC4A4) is present at the proximal tubule basolateral membrane where it controls systemic pH by reclaiming HCO_3^-. Human recessive NBCe1 mutations cause proximal renal tubular acidosis, cataracts, and glaucoma. A recently discovered novel point mutation (NBCe1-Mut) produces similar clinical findings, but its biophysical characterization is lacking.

Methods: NBCe1A activity was assessed by voltage clamp in *Xenopus* oocytes. Membrane trafficking was followed using HA-tagged constructs. NBCe1A activity was also assayed in human trabecular meshwork cells (NTM-5) and retinal pigment epithelia (RPE) by co-transfecting GFP-tagged NBCe1 constructs with pHire (RFP-based pH indicator) to monitor intracellular pH.

Results: In oocytes, CO_2/HCO_3^- (CB) addition elicited strong inward currents with NBCe1A-WT (WT). Currents in E91R (low-function) and Mut injected oocytes were indistinguishable from water controls. WT/E91R coinjections produced currents similar to WT, but co-injection of WT/Mut reduced maximum current to ~35% of WT-alone. HA tracking revealed that Mut trafficking to the plasma membrane was impaired compared to WT/E91R, and co-injection of WT/Mut constructs decreased successful trafficking to ~50% of WT-alone. Exposure of human cells expressing pHire to CB solutions produced a characteristic fall in pH followed by a gradual Na^+-sensitive pH increase (HCO_3^- entry) via endogenous NBCe1. Cells transfected with WT displayed more rapid HCO_3^- entry than neighboring untransfected cells as well as dramatic acidification upon Na^+ removal. pH transients in E91R transfected cells were indistinguishable from those in untransfected neighbors while expression of Mut slowed HCO_3^- entry and diminished the rate of acidification upon Na^+ removal in both cell types studied.

Conclusions: NBCe1A-Mut displays poor transport and trafficking to the plasma membrane. Surprisingly, Mut can impair WT function and localization when co-expressed in amphibian and human cells. These results suggest a unique dominant-negative phenotype which requires further mechanistic analysis.

Funding: NIDDK Support

TH-PO1024

Expression of Phosphate-Dependent Glutaminase (PDG) in Normal and Neoplastic Human Kidney Hyun-Wook Lee,[1] William L. Clapp,[2] Dara N. Wakefield,[2,3] Jill W. Verlander,[1] I. D. Weiner.[1,4] *[1]Nephrology, University of Florida, Gainesville, FL; [2]Pathology, University of Florida, Gainesville, FL; [3]Pathology, NF/SGVHS, Gainesville, FL; [4]Nephrology, NF/SGVHS, Gainesville, FL.*

Background: Phosphate-dependent glutaminase (PDG) is a mitochondrial protein that has a critical role in renal ammonia metabolism, catalyzing the initial step in ammoniagenesis, and may have a role in glutamine-derived ATP generation. The cellular distribution of PDG in the human kidney is currently unknown. This study's purpose was to determine PDG's cellular expression in normal and neoplastic human kidney.

Methods: We used human kidney tissues from unused portions of nephrectomy specimens removed during routine treatment of renal cell carcinoma for immunohistochemistry studies. Three separate PDG antibodies were used; all gave similar results. Normal human kidney protein lysates were obtained from commercial sources.

Results: Immunoblot analysis of both human whole kidney and cortical protein revealed an ~63 kDa protein. Immunohistochemistry showed PDG immunolabel throughout the nephron and in arterial walls in a granular pattern consistent with mitochondrial expression. Glomerular label was punctate and weak compared to tubules. Tubule distribution of PDG was verified using H^+-ATPase and NKCC2 as markers. Strong PDG expression was present in proximal tubule, descending and ascending thin limb, thick ascending limb, distal convoluted tubule, connecting segment (CNT), and throughout the collecting duct (CD). Cellular heterogeneity in label intensity was evident in CNT and CD profiles. PDG expression in kidney neoplasms varied among tumor types. In tumors of presumed proximal tubule origin, clear cell and papillary renal cell carcinoma (RCC), weak, 1+, PDG immunolabel was present. In tumors of presumed intercalated cell tubule origin, oncocytoma and chromophobe RCC, PDG immunolabel was substantially more intense, 2-3+, and immunolabel intensity was greater in oncocytoma than in chromophobe RCC.

Conclusions: 1) PDG is widely expressed in epithelial and non-epithelial cells in the human kidney. 2) PDG expression in RCC varies with tumor type; it is weakly expressed in clear cell and papillary RCC, whereas in oncocytoma and chromophobe RCC it is expressed more strongly. 3) This wide-spread expression suggests PDG may have critical roles both in ammoniagenesis and glutamine-derived ATP generation.

Funding: NIDDK Support, Private Foundation Support

TH-PO1025

Axial Heterogeneity of Phosphate-Dependent Glutaminase Expression and Response to Metabolic Acidosis Hyun-Wook Lee,[1] Gunars Osis,[1] Autumn N. Harris,[1] Lijuan Fang,[1] Jill W. Verlander,[1] I. D. Weiner.[1,2] *[1]Nephrology, University of Florida, Gainesville, FL; [2]Nephrology, NF/SGVHS, Gainesville, FL.*

Background: Phosphate-dependent glutaminase (PDG) is critically important in renal ammoniagenesis and may also contribute to 2-oxoglutarate generation used for TCA-derived ATP generation. Although increased proximal tubule (PT) PDG expression during metabolic acidosis is well-recognized, its expression and regulation in other renal tubule cells is not well-characterized. This study's purpose was to determine PDG's cellular expression in the kidney and the cell-specific response to metabolic acidosis.

Methods: C57Bl/6 mice were fed normal diet or were acid-loaded by adding HCl to chow for 7 days. Three separate PDG antibodies were used; all gave similar results.

Results: Under basal conditions, immunohistochemistry (IHC) showed PDG immunolabel throughout the renal nephron, collecting duct and papillary surface epithelium. Immunogold electron microscopy confirmed mitochondrial localization; gold label density was generally greater in mitochondria in distal tubule and collecting duct cells than in PT cells. The cellular distribution of PDG expression was verified using double-immunolabel IHC with NHE3, AQP1, NKCC2, and H^+-ATPase. Cells with strong PDG expression were present in the proximal convoluted tubule, proximal straight tubule, descending and ascending thin limbs, thick ascending limb, distal convoluted tubule, connecting segment, and throughout the collecting duct. In the PT, label intensity was heterogeneous, with interspersed intensely- and weakly-labeled cells. In medullary collecting ducts, intercalated cells had greater expression than principal cells. In addition, intercalated cell expression was heterogeneous in CCD and CNT. Acid-loading increased the number of strongly PDG-positive PT cells, did not alter expression in cortical and medullary thick ascending limb (mTAL) in the OSOM or the entire collecting duct and decreased expression in mTAL in the ISOM.

Conclusions: (1) The finding of cellular heterogeneity in PT PDG expression, with acid-loading increasing the number of PT cells with intense PDG expression, identifies a new ammoniagenic regulatory mechanism. (2) The wide-spread expression of PDG in non-PT cells, which was not altered by acidosis, suggests PDG may contribute to glutamine-derived ATP generation via the TCA cycle.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

TH-PO1026

Monophosphoryl Lipid A Prevents Sepsis-Induced Inhibition of HCO3- Absorption in Medullary Thick Ascending Limb Bruns A. Watts,[1] Thampi George,[1] Edward R. Sherwood,[2] David W. Good.[1] *[1]U TX Med Branch, Galveston, TX; [2]Vanderbilt U Med Center, Nashville, TN.*

Background: Sepsis impairs HCO_3^- absorption in the MTAL through two distinct mechanisms: 1) by decreasing the intrinsic HCO_3^- absorptive capacity, and 2) by enhancing inhibition of HCO_3^- absorption by LPS through upregulation of basolateral TLR4 signaling. Both effects depend on ERK activation. Monophosphoryl lipid A (MPLA) is a detoxified derivative of LPS that enhances innate host resistance to infection and improves survival following endotoxemia or sepsis. Recently we showed that pretreatment of MTALs with MPLA in vitro prevents LPS inhibition of HCO_3^- absorption by activating a TLR4-TRIF-PI3K-Akt pathway that prevents LPS-induced ERK activation. Here we examined whether pretreatment with MPLA in vivo would protect the MTAL against sepsis.

Methods: Mice were treated with vehicle or MPLA 48 h before sham or cecal ligation and puncture (CLP) surgery. MTALs were studied in vitro 18 h post-surgery.

Results: As shown previously, CLP decreased basal HCO_3^- absorption rate by 22% and increased inhibition by LPS from 21 to 41% vs sham controls ($P<0.05$). Pretreatment with MPLA prevented both the effects of sepsis to decrease the basal HCO_3^- absorption rate and to enhance inhibition by LPS. MPLA treatment increased Akt phosphorylation and prevented the CLP-induced activation of ERK that reduces basal HCO_3^- absorption rate in the MTAL. These effects of MPLA on Akt and ERK were eliminated in MTALs from CLP mice treated with a PI3K inhibitor and in MTALs from TRIF-deficient mice. Treatment of MTALs from CLP mice with MPLA in vitro reduced ERK activity through activation of PI3K. In addition, treatment with a PI3K inhibitor in vitro enhanced the ability of LPS to inhibit HCO_3^- absorption through ERK activation in MTALs from MPLA-treated CLP mice. MPLA attenuated the decrease in plasma [HCO_3^-] in CLP mice.

Conclusions: MPLA treatment prevents the effects of sepsis to impair MTAL HCO_3^- absorption. These protective effects are mediated through MPLA stimulation of a TRIF-PI3K-Akt pathway that downregulates ERK activation in the MTAL. These results identify TLR4-based immunomodulators such as MPLA as novel agents to treat or prevent sepsis-induced renal tubule dysfunction and identify pathways that can be targeted to preserve MTAL HCO_3^- absorption during bacterial infection.

Funding: NIDDK Support

TH-PO1027

Metabolic Acidosis Inhibits AMPK Function in Kidney Cells Nuria M. Pastor-Soler,[1] Hui Li,[1] Kazuhiro Omi,[2] Kenneth R. Hallows.[1] *[1]Keck School of Medicine of USC, Los Angeles, CA; [2]University of Southern California, Los Angeles, CA.*

Background: AMP-activated protein kinase (AMPK) is stimulated by cellular metabolic depletion. We have shown that AMPK activation inhibits kidney membrane transport proteins, thus protecting cells from further metabolic depletion and damage. AMPK is tightly regulated, and when pharmacologically activated, can protect kidneys from superimposed injury. Conversely, AMPK is inhibited in chronic kidney disease (CKD) and pharmacologic AMPK activators are proposed as therapies to slow CKD progression. However, the mechanisms by which AMPK may promote kidney survival are unclear. CKD results in systemic metabolic acidosis (MA) due to the inability of the kidney to excrete non-volatile acid. MA often goes undetected and, if untreated, MA has severe health sequelae such as worsening glomerular filtration rate (GFR). We hypothesized is that there is cross-talk between acid-base status and AMPK signaling, and that dysregulation of AMPK function by MA disrupts kidney regeneration.

Methods: We used kidney epithelial cell lines in culture and adult male C57BL/6 mice for our experiments. Cells were exposed to media at either pH 7.3-7.4 (control) or 6.9-7.0 (acidic) for 3 d ± an AMPK activator for the last 16 h. Mice were given 1.5% saccharin ± 0.28 M NH_4Cl in the drinking water for 2 months. Mice also underwent uninephrectomy (UNX) as a model for CKD vs. sham surgery. To evaluate the AMPK pathway in tissue, we examined levels of phosphorylation of acetyl CoA carboxylase (pACC) by immunoblot.

Results: We found that as compared to cells grown at pH 7.4, kidney cells grown in acidic media have reduced baseline AMPK activity and blunted pharmacologic AMPK activation. Mice on the acidogenic diet developed MA without significant weight loss compared to mice on the control diet (blood pH 7.2 vs 7.3 ± 0.01). In mice after UNX, the superimposed MA induced a statistically significant decrease in pACC, compared to mice with UNX in a control diet.

Conclusions: Our results point to a direct inhibition of the AMPK pathway in the setting of combined CKD and MA. This AMPK inhibition may be detrimental to kidney regeneration in the setting of CKD and MA.

Funding: NIDDK Support, Other U.S. Government Support, Private Foundation Support

TH-PO1028

Acute Secretin-Induced Urinary HCO3- Excretion: A Function of Pendrin Peder Berg,[1] Casper K. Larsen,[1] Inês Cabrita,[2] Karl Kunzelmann,[3] Jens G. Leipziger.[1] *[1]Aarhus University, Aarhus, Denmark; [2]Physiology, University of Regensburg, Germany, Regensburg, Germany; [3]University of Regensburg, Regensburg, Germany.*

Background: The gastro-intestinal hormone secretin is able to acutely increase the amount of HCO_3^- in the urine by a currently unknown mechanism. The actions of secretin are well understood in gastro-intestinal physiology; among many functions it acts as an important activator of pancreatic HCO_3^- secretion. The secretin receptor (SCTR) is also expressed in kidney collecting ducts (CD), the function here is not well defined. The present study investigated the acute effects of bolus injections of secretin (i.p., 10μg) on urinary pH in Pendrin knockout (KO) and wildtype (WT) mice.

Methods: Real time monitoring of urine flow and urinary pH was performed by bladder catheterization and insertion of micro pH-electrodes in the outflow of the catheter in i.v. anaesthetized mice. Two different protocols were used to assess the functional effects of secretin on urinary pH: **1.** Mice were under a continuous i.v. infusion through a tail vein catheter. After 30 minutes the animals were injected with either secretin or vehicle. **2.** After a gavage load, mice were injected with furosemide (0.2μg/g BW, i.p.) and subsequently treated with secretin or vehicle.

Results: 1. WT secretin treated animals had a significant transient urinary alkalization, peak difference: 0.41 pH units (n=6, p=0.014), whereas no alkalization was observed in the secretin treated KO mice and neither in sham injected WT and KO mice. **2.** WT secretin treated animals had a significant transient urinary alkalization, peak difference: 0.64 pH units (n=6, p=0.002), whereas no alkalization was observed in the secretin treated KO mice and neither in sham injected WT and KO mice. Furthermore, SCTR mRNA was specifically localized only in isolated connecting tubules and collecting ducts. In IHC results the SCTR (basolateral) co-localized with Pendrin (apical).

Conclusions: Secretin is a potent activator of renal HCO_3^- excretion. Its mechanism requires functional Pendrin (SLC26A4) and is likely mediated via the SCTR in β-intercalated cells of the collecting duct.

Funding: Government Support - Non-U.S.

TH-PO1029

Hydrochlorothiazide and Acute Urinary Acidification: The Voltage Hypothesis of ENaC-Dependent H+ Secretion Refuted Niklas Ayasse, Jens G. Leipziger. *Aarhus University, Aarhus, Denmark.*

Background: It has been assumed that furosemide-induced urinary acidification is due to the coupling between increased electrogenic sodium transport via the epithelial sodium channel (ENaC) in the collecting duct (CD) and a subsequent increased activity of the vacuolar H^+-ATPase, localized in the α-intercalated cells of the CD. However, we recently showed that urine acidification by furosemide occurs apparently independent of ENaC activity. We demonstrated that furosemide directly stimulates H^+ secretion in the thick ascending limb (TAL) via the Na^+/H^+ exchanger NHE3. Under the assumption that urinary acidification takes place in the TAL we expect that the administration of hydrochlorothiazide (HCT) does not cause an acute change in urinary pH. We investigated the effect of HCT both under conditions of low and high ENaC expression.

Methods: Mice having been subjected to either a control diet or a low-Na^+ diet were anesthetized and infused (0.5 ml/h) with a control solution. The urinary bladder was catheterized and urine pH was measured directly in the outflow of the catheter with an electrode. Mice received either HCT (30mg/kg/h) or a vehicle solution. Diuresis was simultaneously quantified. Urinary Na^+ and K^+ excretions were measured using flame

photometry. The kidneys were harvested to quantify ENaC expression by Western Blotting.

Results: (1) Mice having been fed a low-Na^+ diet showed a significant upregulation of ENaC. **(2)** After the administration of HCT urine output was increased in both groups. **(3)** HCT caused an increase in Na^+ excretion that did not reach significance. **(4)** K^+ excretion rates increased markedly after HCT administration from 18.55±3.83 to 31.67±7.62 in the control diet group and from 22.95±3.68 to 48.71±8.36 µmol/h in the low-Na^+ diet group. **(5)** Importantly, no changes in urine pH were observed after the administration of HCT in both groups.

Conclusions: Despite the induction of acute kaliuresis by HCT, indicating an increased electrogenic transport of Na^+ via ENaC, an acute increased H^+ secretion was not observed, neither under control conditions nor under conditions of marked ENaC upregulation. Thus, this study supports our previous finding that H^+ secretion by furosemide takes place in the TAL.

Funding: Government Support - Non-U.S.

TH-PO1030

Two Year Follow Up on Chronic Hemodialysis (HD) Patients Prescribed Sucroferric Oxyhydroxide as Part of Routine Care

Stuart M. Sprague,[1] Vidhya Parameswaran,[3] Linda H. Ficociello,[3] Norma J. Ofsthun,[3] Claudy Mullon,[3] Robert J. Kossmann,[3] Daniel W. Coyne.[2] *[1]NorthShore University HealthSystem University of Chicago Pritzker School of Medicine, Chicago, IL; [2]Washington University School of Medicine, St. Louis, MO; [3]Fresenius Medical Care North America, Waltham, MA.*

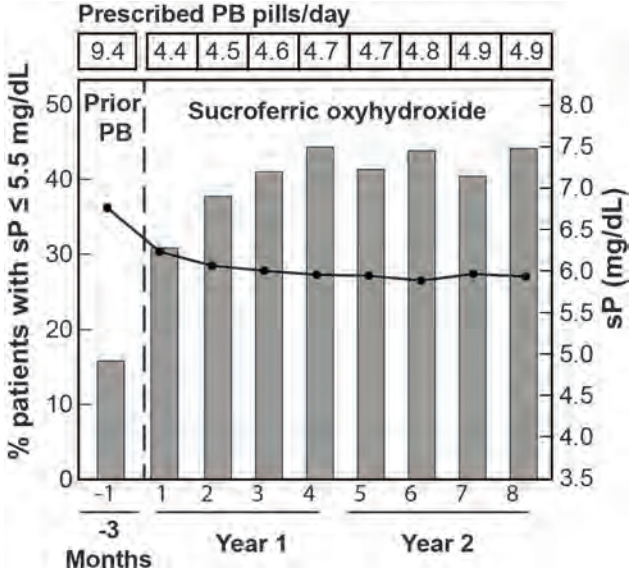
Background: Controlling serum phosphorus (sP) in HD patients is challenging, in part, due to lack of compliance with the high pill burden typically associated with phosphate binder (PB) therapy. Sucroferric oxyhydroxide (SO) is a PB with a starting dose of 3 pills per day. The current analysis aimed to assess the long-term effectiveness of SO in lowering sP and PB pill burden.

Methods: Adult Fresenius Kidney Care HD patients switched during 1/1/14 -3/31/15 from PB monotherapy to SO monotherapy and continued on SO for two years were included (n=241). Baseline was defined as the 3 months before SO, when prior PB was used. Mean prescribed PB pills/day and sP levels were calculated using mixed effects linear regression. In-range sP was defined as sP ≤ 5.5 mg/dl.

Results: Patients had a mean age of 54 years and dialysis vintage of 57 months at baseline. The majority of patients (67%) were on sevelamer before switching to SO. Mean pill burden decreased by 48-53% from baseline (9.4 pills/day) to SO follow-up (4.4-4.9 pills/day). Prior to switching to SO, 15.8% of patients had a sP ≤ 5.5 mg/dl, after switch this increased to 30.8% at Q1 (a 95% increase or 1.9x from baseline) to 44.1% at 2 years (a 179% increase or 2.7x from baseline) [Figure].

Conclusions: During two year follow-up after switching PB to sucroferric oxyhydroxide, patients were 1.9x to 2.7x more likely to have sP ≤ 5.5 mg/dl (95%-179% increase from baseline) while being prescribed 50% less PB pills/day compared to baseline.

Funding: Commercial Support - Fresenius Medical Care North America



TH-PO1031

Effectiveness of Sucroferric Oxyhydroxide (SO) in Lowering Serum Phosphorus (sP) in 4,925 Chronic Hemodialysis (HD) Patients Prescribed SO as Part of Routine Care

Daniel W. Coyne,[1] Linda H. Ficociello,[2] Vidhya Parameswaran,[2] Norma J. Ofsthun,[2] Claudy Mullon,[2] Robert J. Kossmann,[2] Stuart M. Sprague.[3] *[1]Washington University School of Medicine, St. Louis, MO; [2]Fresenius Medical Care North America, Waltham, MA; [3]NorthShore University HealthSystem University of Chicago Pritzker School of Medicine, Chicago, IL.*

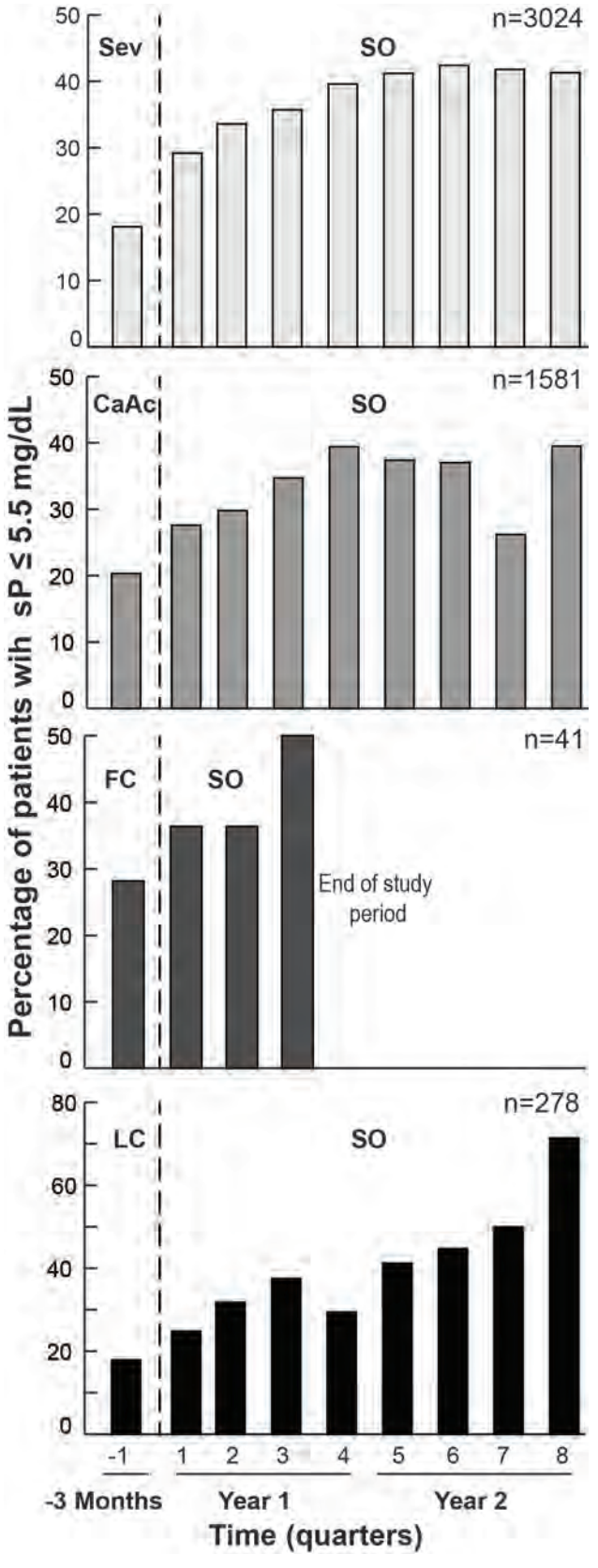
Background: Although the majority of HD patients are prescribed phosphate binders (PB), hyperphosphatemia is highly prevalent. A barrier to phosphorus control can be the high pill burden of most PB. The current analysis aimed to assess the effectiveness of SO in lowering sP and PB pill burden in a large patient population.

Methods: Patients included in the analysis were all Fresenius Kidney Care (FKC) patients switched during 1/1/14 -12/31/16 from PB monotherapy to SO monotherapy for at least three months. Baseline was defined as the 3 months before SO, when prior PB was used. Patients were followed until end of analysis period, end of monotherapy SO, or discharge from FKC. Mean prescribed PB pills/day and sP levels were calculated using mixed effects linear regression. In-range sP was defined as sP ≤ 5.5 mg/dl.

Results: Patients (n=4925) had a mean age of 55 years and dialysis vintage of 53 months. During baseline the majority of patients were hyperphosphatemic (only 18.9% had sP ≤ 5.5 mg/dl). Achievement of sP ≤ 5.5 mg/dl improved over SO from 28.5% at Q1 to 41% at Q8. Patients were prescribed, on average, 9.5 pills/day and this was reduced by >50% (4.2 to 4.7 pills/day) during SO follow-up. At baseline, patients were treated with sevelamer (Sev), calcium acetate (CaAc), ferric citrate (FC), or lanthanum carbonate (LC). Figures demonstrate the increases in patients achieving sP ≤ 5.5 mg/dl by the 4 baseline PB.

Conclusions: In a large cohort of patients switching to SO, improvements in achieving sP ≤ 5.5 mg/dl were observed across all baseline PB.

Funding: Commercial Support - Fresenius Medical Care North America



TH-PO1032

Changes in Mineral Bone Disease (MBD) Markers in Hemodialysis (HD) Patients Switched to Sucroferric Oxyhydroxide (SO) Sandeep Shori,[1] Vidhya Parameswaran,[2] Linda H. Ficociello,[2] Claudy Mullon,[2] Robert J. Kossmann.[2] *[1]None, Westlake, TX; [2]Fresenius Medical Care North America, Waltham, MA.*

Background: Elevated levels of MBD markers (sP, PTH, Ca) increase patient's risk of morbidity and mortality. This current analysis assesses the changes in MBD markers in patients who lower sP to ≤ 5.5 mg/dl when switching to SO.

Methods: Adult, baseline (BL) hyperphosphatemic (sP> 5.5 mg/dl) Fresenius Kidney Care HD patients switched to SO as part of routine clinical care during 1/1/14 -12/31/16 and maintaining sP ≤ 5.5 mg/dl for 2 quarters (Q1, Q2) after the switch were eligible. BL was defined as the 3 months before SO, when prior phosphate binders (PB) was used. Mean prescribed PB pills/day, sP, Ca, and PTH levels were calculated using mixed effects linear regression.

Results: At baseline the majority of patients were treated with sevelamer (66%), followed by calcium acetate (28%), lanthanum carbonate (5%) and ferric citrate (1%). MBD markers and number of phosphate binder pills/day at BL, Q1 and Q2 for 394 patients who achieved sP ≤ 5.5 mg/dl during Q1 and Q2 are presented in the table.

Conclusions: In a cohort of hyperphosphatemic HD patients switching to SO, improvements in achieving sP ≤ 5.5 mg/dl were accompanied by improvements in Ca and PTH and a 46% reduction in number of phosphate binder pills/day.

Funding: Commercial Support - Fresenius Medical Care North America

	Baseline (Prior PB)	SO follow-up Q1	SO follow-up Q2	p-value
Serum Phosphorus (sP, mg/dl)	6.3	4.8	4.6	<0.0001
Serum Calcium (Ca, mg/dl)	9.2	9.2	9.1	0.002
Intact Parathyroid Hormone (PTH, pg/ml)	540	448	470	<0.0001
Phosphate Binder pills/day	7.9	4.2	4.3	<0.0001

TH-PO1033

Serum Albumin and Serum Phosphorus among Hemodialysis Patients after Initiating Sucroferric Oxyhydroxide (SO) Kamyar Kalantar-Zadeh,[1] Linda H. Ficociello,[2] Vidhya Parameswaran,[2] Hasi Mondal,[2] Nicolaos V. Athienites,[3] Claudy Mullon,[2] Robert J. Kossmann.[2] *[1]University of California Irvine, School of Medicine, Orange, CA; [2]Fresenius Medical Care North America, Waltham, MA; [3]Renal Medical Care PC, Abington, MA.*

Background: Dietary protein intake may result in higher phosphorus burden and increases in serum phosphorus (sP) in hemodialysis (HD) patient, whereas restricting high-protein diet to control phosphorus may lead to hypoalbuminemia. This presents a challenge as both low serum albumin (sAlb) and high sP increase mortality risk. We hypothesized that under routine clinical care scenario, SO can lead to increase in sAlb, while lowering sP and pill burden.

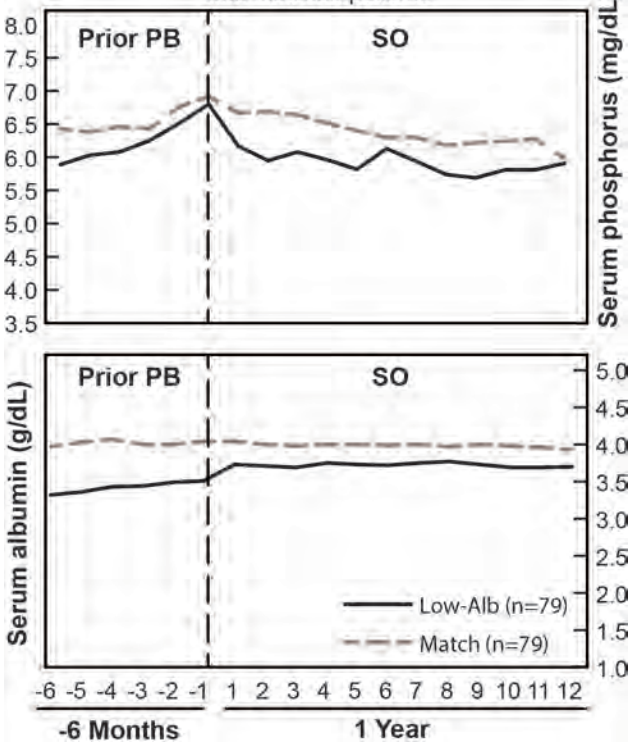
Methods: All adult patients who completed 1 year of uninterrupted SO treatment (Q1-Q4) with sP and sAlb measurements were eligible for the analysis. Hypoalbuminemic patients (Low-Alb) had sAlb ≤ 3.5g/dl during at least one 3 month baseline interval and were matched on gender, race, diabetes status, and age (+/-5 years) to patients with normal sAlb during baseline (Match). 79 matched pairs were created.

Results: The two groups did not differ on matched baseline factors or BMI (31.1 vs 31.2 kg/m^2) but Low-Alb patients had a shorter dialysis vintage (32 vs 60 months) at baseline. Comparing baseline to Q4 of SO follow-up, PB pills/day decreased by 44.9 and 45.1% (both p<0.0001) and sP decreased by 0.7 and 0.5 mg/dl (both p<0.0001), for Low-Alb and Match, respectively. Mean sAlb stayed stable in Match, but increased significantly (p<0.0001) in the low sAlb group from 3.49 mg/dl at baseline to 3.71, 3.73, 3.74, and 3.69 mg/dl during Q1-Q4, respectively. Figure 1 shows monthly changes for sP and sAlb.

Conclusions: Lowering of sP and PB pills/day was observed in Low-Alb and Match patients after switch to SO. Low-Alb patients who received SO also experienced significant increases in sAlb.

Funding: Commercial Support - Fresenius Medical Care North America

Figure 1:Changes in serum phosphorus and serum albumin before and after the switch to SO among Low-Alb and matched patients



TH-PO1034

Diet Induced Iron Deficiency Inhibits Intestinal Phosphate Absorption by a NaPi-IIb-Independent Mechanism Evans O. Asowata,[2] Surjit K. Srai,[3] Robert J. Unwin,[1] Joanne Marks.[2] *[1]Centre for Nephrology, University College London, London, United Kingdom; [2]Department of Neuroscience Physiology & Pharmacology, University College London, London, United Kingdom; [3]Department of Structural and Molecular Biology, University College London, London, United Kingdom.*

Background: Recent evidence suggests that iron-deficiency influences phosphate (Pi) homeostasis through altered transcription and processing of FGF-23 in osteocytes. In addition, older studies have provided conflicting data as to whether diet induced iron-deficiency impacts intestinal Pi absorption. We aimed to confirm if iron-deficiency alters intestinal Pi absorption, and if so, to investigate the underlying mechanisms.

Methods: Six-week old male Sprague-Dawley rats and C57Bl/6 mice were fed an iron-deficient (ID) diet (2-6 ppm iron) or control (C) diet (48 ppm iron) for 2-weeks, with both diets including 0.6% Pi. *In vivo* and *in vitro* Pi uptake experiments using a physiological Pi concentration (10mM) were used to examine changes in intestinal Pi absorption in these models. Western blotting, qPCR, and ELISAs were employed to understand the underlying mechanisms.

Results: Diet induced iron-deficiency inhibited Pi absorption in the rat duodenum *in vivo* (C: 6.0±0.6 *vs.* ID: 2.5±0.6 nmoles Pi in 1ml plasma/5cm, n=7, P<0.01), while FGF-23 and 1, 25$(OH)_2D_3$ levels were unaffected. In contrast, *in vivo* Pi absorption in the mouse ileum, which is known to be mediated predominantly by NaPi-IIb, was unaffected by iron-deficiency (C: 92.2±9.9 *vs.* ID: 98.3±8.5 nmoles Pi in 1ml plasma/5cm, n=6). In addition, the NaPi-IIb inhibitor, PFA (10mM), did not inhibit *in vitro* Pi absorption in the duodenum of control rats (C: 32.80±2.95 *vs.* C + PFA: 32.03±1.32 nmoles Pi/100mg, n=6), while iron-deficiency caused a significant reduction (ID: 10.04±1.21, P<0.0001, n=6), suggesting that this response is not dependent on NaPi-IIb. Interestingly, Western blotting showed that iron-deficiency significantly increased the expression of claudin 3 (C: 0.18±0.01 *vs.* ID: 0.37±0.07; P<0.05, n=6), as well as the apical membrane iron transporter, DMT1 (C: 0.10±0.02 *vs.* ID: 0.51±0.01; P<0.05, n=3).

Conclusions: We hypothesise that increased DMT1 expression may locally impact intestinal Pi absorption by a mechanism involving DMT1-induced accumulation of intracellular H^+ in the enterocyte resulting in increased claudin 3 levels, and subsequent sealing of the tight junction to reduce paracellular Pi absorption. Understanding how diet induced iron-deficiency affects intestinal Pi absorption may identify a novel target for the management of hyperphosphataemia in CKD patients.

TH-PO1035

Incidence, Predictors, and Therapeutic Consequences of Hypocalcemia in Patients Treated with Cinacalcet: The EVOLVE Trial Jürgen Floege,[5] Kate Tsirtsonis,[2] Jan Iles,[1] Tilman B. Drueke,[3] Glenn M. Chertow,[6] Patrick S. Parfrey.[4] *[1]Amgen Inc, Thousand Oaks, CO; [2]Amgen ltd, Uxbridge, United Kingdom; [3]Inserm UMR 1018, CESP, Université Paris-Sud, France; [4]Memorial University, St. John's, NL, Canada; [5]RWTH University of Aachen, Aachen, Germany; [6]Stanford University School of Medicine, Palo Alto, CA.*

Background: The calcimimetic cinacalcet is used to treat secondary hyperparathyroidism in patients receiving dialysis. Asymptomatic hypocalcemia is often observed following its initiation. Here we investigated the incidence, predictors and therapeutic consequences of hypocalcemia.

Methods: This was a post-hoc analysis of the randomized, double-blind, placebo-controlled EValuation Of Cinacalcet Hydrochloride Therapy to Lower CardioVascular Events (EVOLVE) trial. Hypocalcemia was classified as mild (total serum calcium 8.0 – 8.39 mg/dL), moderate (7.5 – 7.99 mg/dL) or severe (<7.5 mg/dL).

Results: At least one episode of hypocalcemia developed within 16 weeks after the first administered dose among 58.3% (1130/1938) patients randomized to cinacalcet versus 14.9% (286/1923) with placebo. Hypocalcemia in the cinacalcet group was severe in 18.4% of the patients versus 4.4% in the placebo group. Severe hypocalcemia following administration of cinacalcet was associated with geographic region (patients with Latin America and Russia had a higher risk relative to US), higher body mass index, higher baseline plasma PTH, lower corrected total serum calcium and higher serum alkaline phosphatase. Median cinacalcet dose immediately prior to the first hypocalcemia episode was 54-58 mg/day and similar in the three hypocalcemia categories. In the majority of patients, hypocalcemia resolved spontaneously within 14 days without modification of background therapy. Among patients who received an intervention, the most common was an increase in active vitamin D sterol dose.

Conclusions: The occurrence of hypocalcemia is a frequent effect following initiation of cinacalcet. The likelihood of developing hypocalcemia was related to the severity of secondary hyperparathyroidism. Hypocalcemia was generally asymptomatic and self-limited.

Funding: Commercial Support - Amgen

TH-PO1036

Intradialytic Change in Serum Calcium Concentration, but Not Dialysate Calcium Concentration, Is Associated with Cardiovascular Events in Hemodialysis Patients Miho Tagawa,[1] Takayuki Hamano,[2] Shinichi Sueta,[3] Satoshi Ogata,[2] Yoshihiko Saito.[1] *[1]Nara Medical University, Nara, Japan; [2]Committee of Renal Data Registry, Japanese Society for Dialysis Therapy, Tokyo, Japan; [3]Kyoto University, Kyoto, Japan.*

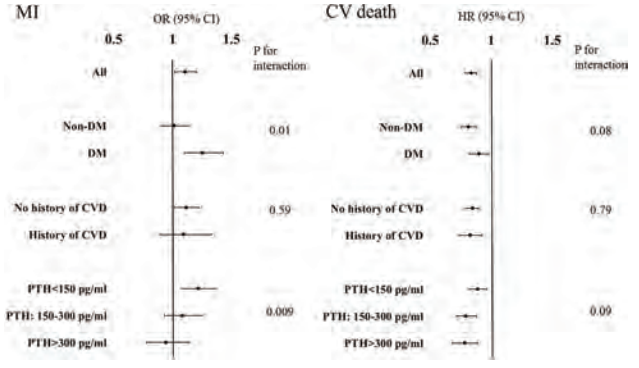
Background: Association of dialysate calcium (Ca) concentration and cardiovascular (CV) events has been studied but intradialytic change in serum Ca concentration has not been studied in detail.

Methods: This was a longitudinal study based on the Japan Renal Data Registry from 2008 to 2009. Predictor variable was deltaCa (postdialysis - predialysis serum Ca concentration). Outcome variable was CV events during 1-year observation period. Statistical analyses were performed using multivariate logistic regression or Cox regression model, adjusted for potential confounders.

Results: Among 301,649 patients on the database, data for 44,700 patients were available after excluding missing data. There were 844, 1,450, and 1,815 events of myocardial infarction (MI), ischemic stroke, and CV death, respectively. Delta Ca was associated with higher incidence of MI and lower incidence of CV death (Table). Additional adjustment for dialysate Ca yielded similar results. Delta Ca was not associated with ischemic stroke. Delta Ca was associated with MI especially among diabetics and patients with low PTH (Figure).

Conclusions: Intradialytic increase in serum Ca concentration was associated with higher incidence of MI and lower incidence of CV death and it was not mediated through dialysate Ca concentration. It is suggested that not only predialysis but also postdialysis serum Ca concentration should be evaluated carefully and both large increase and decrease in intradialytic serum Ca concentration should be avoided not to increase MI and CV death, respectively.

	MI (OR)	CV death (HR)
Intradialytic change in serum Ca concentration (per mg/dL)	1.11 (1.02-1.20)	0.83 (0.79-0.88)



TH-PO1037

Hidden Hypocalcemia at the Initiation of Dialysis Satoshi Yamaguchi,[1] Takayuki Hamano,[2] Karin Shimada,[1] Ayumi Matsumoto,[1] Nobuhiro Hashimoto,[1] Tatsufumi Oka,[1] Daisuke Mori,[1] Yusuke Sakaguchi,[2] Isao Matsui,[1] Yoshitaka Isaka.[1] *[1]Nephrology, Osaka Univ Graduate School of Medicine, Suita, Japan; [2]Comprehensive Kidney Disease Research, Osaka Univ Graduate School of Medicine, Suita, Japan.*

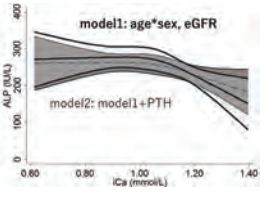
Background: Hypocalcemia (HypoCa) often leads to arrhythmia and heart failure. Our aims of this study are to reveal serum calcium abnormalities in incident hemodialysis (HD) patients and its clinical significance.

Methods: We performed a retrospective cohort study of incident HD patients. We collected the latest data just before the initiation of HD. We used logistic regression models to examine the factors associated with true HypoCa defined as ionized Ca (iCa) <1.15 mmol/L. We performed analyses to explore the association between the iCa levels and QTc prolongation in electrocardiogram, which was reported to be a predictor of cardiovascular death in CKD. Restricted cubic spline analyses were employed to explore potential nonlinear relationships between iCa and ALP or intact PTH (iPTH) levels.

Results: Among the enrolled 336 patients, the mean (SD) eGFR was 5.1 (1.9) mL/min/1.73m2. Eighty-one % of the patients showed true HypoCa, 60 % of whom showed normal corrected Ca (cCa), in other words, hidden HypoCa. Among patients with normal cCa levels, the ALP levels greater than upper normal limit were significantly associated with hidden HypoCa (Odds ratio; 8.4, 95%CI 1.1~64), accounting for 75% of normal cCa. Multivariate analysis showed the significant factors associated with true HypoCa were male, lower eGFR and serum albumin levels, higher serum phosphate levels, non-use of active vitamin D in pre-dialysis CKD, polycystic kidney disease, and high BNP levels (Fig.1). Moreover, lower iCa levels were associated with higher prevalence of QTc prolongation. A negative association between iCa and ALP were observed. Additional adjustment for iPTH did not change the relationship between iCa and ALP substantially (Fig.1), implying that osteomalacia induced by low iCa levels might explain high ALP levels.

Conclusions: Hidden HypoCa was prevalent just before the start of HD and associated with high ALP and BNP levels accompanied by QTc prolongation. High ALP levels despite normal cCa imply the presence of hidden HypoCa. The impact of pre-dialysis HypoCa on hard outcomes after HD initiation remains to be elucidated.

Variables	Odds Ratio	95 % CI
male	4.61	1.56-13.6
eGFR(per ml/min/1.73m²)	0.75	0.60-0.94
Alb (per g/dL)	0.23	0.07-0.70
Phosphate (per mg/dL)	1.84	1.20-2.84
active D user	0.32	0.12-0.88
ADPKD	19.3	1.20-311
BNP (per unit of logBNP)	1.55	1.01-2.38



TH-PO1038

Effect of an Individualized Therapy for Hyperphosphatemia in Hemodialysis Patients – A Single-Center, Open-Label Randomized Clinical Trial Xinyu Dong, Mengjing Wang, Qian Zhang, Jiaying Zhang, Minmin Zhang, Li Ni, Jing Chen. *Huashan Hosopital, Fudan Univeristy, Shanghai, China.*

Background: We hypothesized that estimation of phosphorus balance would improve the efficiency of treatment of hyperphosphatemia. Thus we compared individualized therapy with traditional therapy of hyperphosphatemia in maintenance hemodialysis (MHD) patients.

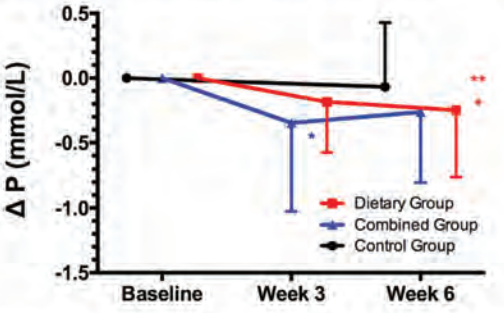
Methods: 67 eligible MHD patients with serum phosphate >1.45mmol/L were randomized into Control Group (n=20) and Individualized group (Dietary Group, n=23 and Combined Group, n=24) for 6 weeks. Phosphorus balance was achieved in Individualized group by the following equation: Diet Pi×60% = Pi removed by hemodialysis and phosphate binders. Patients in Dietary Group were assigned diet education and individualized diet for 6 weeks, while patients in Combined Group were assigned individualized diet for 3 weeks following correction of phosphate retention by increased hemodialysis sessions. No estimation of phosphorus balance was assessed in Control Group and patients were assigned conventional HD regimen and phosphate binders according to serum calcium and phosphate. Analysis was done among patients with good compliance.

Results: Mean age of the participants was 57.7±9.0 years old. Baseline serum phosphate was 1.96±0.38 mmol/L, 2.08±0.41 mmol/L and 2.13±0.47 mmol/L in Control, Dietary and Combined Group, respectively. Serum phosphate decreased significantly at Week 3 and Week 6 compared to Baseline in Dietary Group (Week 3: -0.18±0.39, *P*=0.113; Week 6: -0.41±0.42, *P*=0.004), and in Combined Group (Week 3: -0.35±0.68, *P*=0.045; Week 6: -0.26±0.54, *P*=0.056), but not in Control Group (Week 6: -0.09±0.50, *P*=0.556). No significant change was found in albumin, creatinine, calcium, iPTH, AKP, and nPCR during the follow-up period.

Conclusions: Individualized therapy was effective and safe in correcting hyperphosphatemia without inducing malnutrition. Current study provided a new and applicable approach in treating hyperphosphatemia in MHD patients.

Funding: Government Support - Non-U.S.

Change of serum phosphate level during 6-week follow-up in the Dietary Group, Combined Group, and Control Group.



* $P < 0.05$ compared with Baseline, ** $P < 0.05$ compared with Week 3. ΔP = Serum phosphate level (at Week 3 or Week 6) – Baseline phosphate level. Results are mean ± SD

TH-PO1039

Can CKD Patients Estimate Phosphate Content (PC) in the Food Correctly? Petr Taborsky. *Fresenius Medical Care, Praha, Czech Republic.*

Background: Hyperphosphatemia has been identified as a risk factor for survival of CKD patients. Food is the main source of increased serum phosphate in CKD. Patients are advised to control the amount of absorbed phosphate by phosphate binders. Reasonable PC estimate is a prerequisite for successful treatment with phosphate binders and for their adequate dosing.

Methods: Phosphate and protein content of 53 popular food items available on the market in Czech Republic were measured using standard chemical methods. Five typical Czech meals were prepared by nutritional specialist using recipes recommended for dialysis patients. The identical meals were purchased fresh in restaurant or frozen in supermarket and phosphate and protein content of all meals were measured. Virtual menu consisting of meal photos and short descriptions including information on the meal origin was compiled, nutrition facts were blinded. 23 predialysis patients CKD stage 3-5 were asked during their regular visit in nephrology clinic to go over the menu and put together the three days diet corresponding to their kidney function. Importance of low PC in the diet was repeatedly stressed. All patients were previously instructed in renal diet by nutrition specialist using the standard protocol. The optimal diet and the "worst" choice (the lowest and the highest possible content of phosphate) were calculated for comparison.

Results: Calculated PC in dietary regimens ranged from 730 to 1780 mg per day, all diets contained at least 60 g of protein per day. Phosphate to protein ratio in food varies much widely: from 9 mg/g in non-processed beef to 85 mg/g in some brands of spread cheese. PC in home-made meals was 1.2 to 2 times lower than in ready-to-eat meals. Food products labeled as "for children" contained less phosphate. Mean PC in diet chosen by patients was 1420 mg per day ranging from 920 to 1690 mg of phosphate per day. Difference in PC was done mainly by individual preferences of some sorts of dairy products and manufactured pastries.

Conclusions: PC is extremely variable, even within the same sort of food. For ordinary patient without special training the correct estimation of PC in food is very difficult even impossible. Traditional education based on close correlation between protein and PC in food should be changed because of widespread use of phosphate-containing additives.

TH-PO1040

Phosphate and Phosphate Changes Are Associated with Mortality in Dutch Dialysis Patients: A Registry Based Analysis Tiny Hoekstra,[1,2] Frans J. van Ittersum,[1] Marc H. Hemmelder,[2] Marc G. Vervloet.[1] *[1]VU University Medical Center, Amsterdam, Netherlands; [2]Nefrovisie Foundation, Utrecht, Netherlands.*

Background: Observational data suggest that an improvement over time of hyperphosphatemia in dialysis patients is associated with improved mortality. However it is unknown if an absolute or relative decline is optimal. This knowledge could have

clinical implications. Our aim is to associate the magnitude of changes in phosphate concentration with survival taking into account its initial value.

Methods: At quarterly intervals data on phosphate are available in a subset (N=5,487) of the Dutch renal replacement registry. Patients were followed from the date of the first available measurement until death or censoring (transplantation, recovery of renal function, lost to follow-up, end of study period). Time-updated cox regression analysis was performed with phosphate as well as changes in phosphate between subsequent measurements as continuous exposure variables. To allow for non-linear associations penalized splines smoothing was used. The analyses with changes were also performed stratified for categories of initial phosphate level. Adjustments were performed for age, sex, primary kidney disease, vintage, year of baseline, dialysis modality, previous transplantation.

Results: Both phosphate levels and phosphate changes showed a non-linear, U-shaped association with mortality. Lowest mortality was found for phosphate levels around 1.25 mmol/L. A gradually increase in benefit of phosphate decrease was observed across strata of initial phosphate level (from < 1.5 mmol/L to > 2.00 mmol/L), suggesting that a phosphate target of about 1.40 mmol/L is optimal. (Figure 1).

Conclusions: Patients with higher baseline phosphate concentrations appear to benefit form a greater absolute decline. Our data reinforce current clinical practice aiming at a target range for dialysis patients with hyperphosphatemia, instead of a fixed absolute decline.

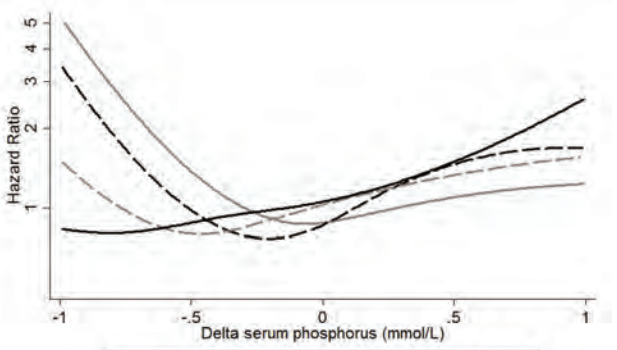


Figure 1. Changes in phosphate and mortality, stratified for categories of initial phosphate levels. The curves are adjusted for confounding factors.

TH-PO1041

Effects of Mineral Bone Disorder Medication Non-Adherence on Dialysis Patient Outcomes Yue Jiao,[1] Michelle Dias,[2] Savannah R. Clary,[2] Diane M. Rondeau,[1] Marta Reviriego-Mendoza,[1] John W. Larkin,[1] Len A. Usvyat,[1] Terry L. Ketchersid,[1] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Fresenius Rx, Franklin, TN.*

Background: Patients on dialysis are known to have a high medication burden, taking about 10 to 12 different medications. This burden has been associated with increased rates of medication non-adherence, especially for mineral bone disorder (MBD) therapies. It has been estimated that >50% of dialysis patients do not take their phosphate binders as prescribed (Ghimire et al. 2015). We aimed to characterize the outcomes of dialysis patients based on their MBD medication adherence levels.

Methods: In this retrospective cohort analysis, we included all patients dialyzed at Fresenius Kidney Care clinics between 2006 and 2016. Patients were characterized based on their MBD medication adherence levels per dietician assessment and categorized as: 1) "taking the medication as prescribed", and 2) "taking the medication inconsistently or not at all." The most recent MBD medication adherence assessment per patient was utilized for categorization. Rates of hospital admissions and mortality were calculated during the entire study period per patient basis.

Results: We analyzed data on 135,340 dialysis patients and identified that 9,929 (8%) took MBD medications inconsistently or not at all. Overall, we found lower rates of hospitalizations and mortality in patients who were determined to be adherent to their MBD medications versus those who were non-adherent. The hospitalization rate was 2.1 admissions per patient year (ppy) for the non-adherent group and 1.7 ppy for the patients taking MBD medication as prescribed ($p<0.001$ using Poisson regression). There were 9.3 deaths per 100 patient years (p100py) in the non-adherent group, and 8.8 p100py in the adherent group ($p=0.0013$ using a Kaplan Meier analysis).

Conclusions: In dialysis patients with bone disorders, MBD medication adherence appears to be associated with hospitalization and mortality outcomes. Importantly, these results are only reflective of patients with bone disorders and not the overall dialysis population. Further analyses are needed to understand root causes for dialysis patient medication non-adherence.

Funding: Commercial Support - Fresenius Medical Care North America

TH-PO1042

Coordination of Pharmaceutical Care in Dialysis Patients Is Associated with Lower Mortality and Hospital Admission Rates Sophia Rosen,[1] Marta Reviriego-Mendoza,[1] Savannah R. Clary,[2] Sheetal Chaudhuri,[1] Michelle Dias,[2] John W. Larkin,[1] Len A. Usvyat,[1] Terry L. Ketchersid,[1] Franklin W. Maddux.[1] *[1]Fresenius Medical Care, Waltham, MA; [2]FreseniusRx, Franklin, TN.*

Background: It is estimated in the literature that >50% of ESRD patients do not take their phosphate binders as prescribed. The renal pharmacy FreseniusRx provides coordinated mineral and bone disorder (MBD) medication delivery and adherence support for enrolled patients. We investigated whether coordinated MBD pharmaceutical care is associated with improvements in hospital admission and mortality rates in dialysis patients.

Methods: We included data from hemodialysis patients in the network of Fresenius Medical Care North America clinics who were first enrolled into FreseniusRx pharmacy in January-February of 2016. This analysis utilized data on patients before and up to 9 months after pharmacy enrollment. We identified control patients not enrolled in the pharmacy by nearest neighbor 1:1 matching on the logit of the propensity score for demographics, comorbidities, state, insurance type, as well as, baseline lab values, vintage, access, hospitalization rates and other parameters. We compared hospital admission and mortality rates in 3, 6, and 9 months after enrollment.

Results: We analyzed data on 7116 patients (3558 in Rx and 3558 matched patients not in Rx). Rx patients had lower hospital admission rates per patient year (Rx vs non-Rx at 3, 6, and 9 months: 1.41 vs 1.54, 1.52 vs 1.62, 1.49 vs 1.60; $p=0.03$, $p=0.09$ and $p=0.065$ based on Poisson model). Mortality rates were also lower (HR for Rx vs non-Rx at 3, 6, and 9 months: 1.4, 1.4 and 1.3; $p=0.03$, $p=0.004$ and $p=0.003$ based on Cox model).

Conclusions: Coordinated pharmaceutical care is associated with lower hospital admission and mortality rates in the hemodialysis patient population. Further analyses are needed to understand what elements of this coordinated care are associated with improvements.

Funding: Commercial Support - Fresenius

TH-PO1043

Four Times Daily versus Three Times Daily Dosing of Phosphorus Binders Does Not Improve Serum Phosphorus in Dialysis Patients Richard S. Muther.[1,2] *[1]Kidney Associates of Kansas City, Kansas City, MO; [2]Dialysis Clinics Inc., Kanssa City, MO.*

Background: Hyperphosphatemia associates with poor outcomes in ESRD patients. Dietary phosphorus restriction and phosphorus binding compounds taken with meals are the primary (though often ineffective) treatments to limit intestinal phosphorus absorption and lower serum phosphorus. Because phosphorus is known to undergo enterohepatic recirculation, a quality improvement project was conducted to determine whether bedtime administration of phosphate binder could favorably impact serum phosphorus.

Methods: Twenty-nine (29) dialysis patients with hyperphosphatemia received their daily phosphorus binding dose either 3 times a day with meals or 4 times a day with meals and at bedtime for 3 months, crossing over to the alternate dosing schedule for an additional 3 months. The type and total daily dose of binder was not changed and patients continued their usual phosphorus restricted diet.

Results: Standard of care data over the project period was available on 23 patients (3 expired, 2 withdrew, 1 transfer). Serum phosphorus did not change over the 3 month course of treatment, regardless of a 3 times daily with meals (5.63 ± 1.4 to 5.72 ± 1.49) or 4 times daily with meals and at bedtime (5.71 ± 1.01 to 5.95 ± 1.47) dosing schedule. The results were not influenced by baseline serum phosphorus (greater or less than 6.0 mg/dL) or the type of phosphorus binder.

Conclusions: If enterohepatic recirculation of dietary phosphorus affects serum phosphorus in dialysis patients, it does not appear to respond to increasing the frequency of administration of phosphorus binding compounds.

TH-PO1044

Association between Use of Phosphate-Binders and the Risk of Infection-Related Mortality in Hemodialysis Patients: The Q-Cohort Study Shunsuke Yamada,[1] Masanori Tokumoto,[2] Masatomo Taniguchi,[3] Hideki N. Hirakata,[3] Takanari Kitazono,[1] Kazuhiko Tsuruya.[4] *[1]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [2]Department of Medicine, Fukuoka Dental College, Fukuoka, Japan; [3]Fukuoka Renal Clinic, Fukuoka, Japan; [4]Department of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.*

Background: Use of phosphate (P)-binders enables hemodialysis patients to take more protein, stay in a better nutritional status, and maintain serum P level in a recommended range. By contrast, dietary protein restriction often leads to protein-energy-malnutrition, which is closely related to the increased risk of infection-related deaths. However, it still remains unknown whether the risk of infection-related deaths is decreased in patients with P-binders compared with those without P-binders.

Methods: The present study was a prospective multicenter observational study consisting of 2926 hemodialysis patients registered to the Q-Cohort Study. The main exposure was use of P-binders and the main outcome was infection-related deaths. Patients' information was collected only at baseline. Propensity score (PS) for P-binder

use was created by multivariable logistic regression analysis. Multivariable-adjusted Cox proportional hazards models with or without PS-based approaches were used to estimate the risk of infection-related mortality.

Results: During the 3.9 years of median follow-up period, 106 patients died of infection. Patients with P-binders showed a higher body mass index and normalized protein catabolic rate and higher serum levels of creatinine and albumin compared with those without P-binders. Even after adjustment for confounding factors including serum levels of P, albumin, and creatinine, protein catabolic rate, and body mass index, the incidence of infection-relate deaths was significantly lower in patients with P-binders than those without P-binders; hazard ratio [95% confidence interval] for infection-related deaths was 0.63 [0.40–0.99]. The associations remained significant even after applying four different propensity score (PS) based adjustments; PS matching, PS stratification, PS covariate adjustment, and inverse probability weighting treatment.

Conclusions: Our results suggest that use of P-binders was significantly associated with a lower incidence of infection-related deaths in hemodialysis patients, even after accounting the nutritional factors and confounding by indication. Further studies are necessary to determine why P-binder users have the advantage of having a lower risk of infection-related deaths in hemodialysis patients.

TH-PO1045

Gastrointestinal Tolerability of Tenapanor to Treat Hyperphosphatemia in Patients on Hemodialysis Geoffrey A. Block,[2] David P. Rosenbaum,[1] Paul Korner,[1] Zhiwu Yan,[1] Glenn M. Chertow.[3] *[1]Ardelyx, Inc., Fremont, CA; [2]Denver Nephrology, Denver, CO; [3]Stanford University School of Medicine, Palo Alto, CA.*

Background: Hyperphosphatemia (HP) is common in ESRD and associated with morbidity and mortality. Phosphate binders are commonly associated with gastrointestinal (GI) side effects including diarrhea, nausea, vomiting, dyspepsia, constipation, abdominal pain, and abdominal bloating. Tenapanor (TEN) is a minimally absorbed small molecule NHE3 inhibitor that reduces GI sodium and phosphate absorption.

Methods: 8-week, double-blind, randomized treatment period (RT) with a 4-week placebo-controlled randomized withdrawal period (RW). Patients on hemodialysis (HD) with serum phosphate (sP) ≥6.0 mg/dL and a 1.5 mg/dL increase from baseline were randomized 1:1:1 to receive 3, 10 or 30 mg TEN twice daily. The 30 mg cohort was allowed to down-titrate weekly (30 to 20 to 15 to 10 to 3 mg twice daily) during the first 4 weeks of RT based on GI tolerability. At the end of RT, all patients were re-randomized 1:1 to either remain on TEN or placebo for RW. Patient reporting of loosened stool or increased frequency in bowel movements (BMs), regardless of magnitude, was classified as "diarrhea." Patients recorded daily BM frequency and form [Bristol Stool Form Score (BSFS)] using an eDiary.

Results: 219 patients were randomized to RT, 164 entered RW, and 152 completed the study. There was only one TEAE observed in >5% of patients during RT (diarrhea, 39%) and no TEAE >5% during RW. During RT, 7.8% (n=17) of patients discontinued due to diarrhea; one (3 mg TEN) with SAE; during RW there were no discontinuations due to diarrhea. During RW, diarrhea was reported by 1.2% of the TEN group vs 2.4% on placebo and there were no discontinuations. Mean BM frequency increased by 0.4/day (baseline of 1.5/day) during RT, and BM frequency was 0.3/day higher with TEN than with placebo during RW. Mean BM frequency was within the normal range in all groups. Mean BSFS scores increased by 0.9 (baseline 4.2) during RT, and there was a 0.7-point difference between placebo (4.4) and TEN treatment (5.1) during RW.

Conclusions: TEN was well-tolerated in HD patients; the only TEAE >5% was diarrhea, reflecting the pharmacodynamic mechanism of action of TEN, resulting in softer more frequent BMs that, on average, remained within the normal range with regard to both frequency and form.

Funding: Commercial Support - Ardelyx, Inc.

TH-PO1046

Efficacy of Tenapanor to Treat Hyperphosphatemia in Patients on Hemodialysis Geoffrey A. Block,[2] David P. Rosenbaum,[1] Paul Korner,[1] Zhiwu Yan,[1] Glenn M. Chertow.[3] *[1]Ardelyx, Inc., Fremont, CA; [2]Denver Nephrology, Denver, CO; [3]Stanford University School of Medicine, Palo Alto, CA.*

Background: Tenapanor (TEN) is a minimally absorbed oral small molecule that blocks the sodium-hydrogen type 3 exchanger (NHE3) in the gastrointestinal (GI) tract inhibiting the absorption of dietary sodium and has been demonstrated to alter paracellular phosphate transport and reduce serum phosphate (sP) concentration in patients receiving hemodialysis (HD).

Methods: 8-week, double-blind, randomized treatment period (RT) with a 4-week placebo-controlled randomized withdrawal period (RW). Patients on HD with sP ≥6.0 mg/dL and a 1.5 mg/dL increase from baseline were randomized 1:1:1 to receive 3, 10 or 30 mg TEN twice daily. The 30 mg cohort was allowed to down-titrate weekly (30 to 20 to 15 to 10 to 3 mg twice daily) during the first 4 weeks of RT based on GI tolerability. At the end of RT all patients were re-randomized 1:1 to either remain on TEN or placebo for RW. The primary endpoint, based on the responder population (defined as patients demonstrating a ≥1.2 mg/dL decrease in sP during RT), was the difference in change in sP between pooled TEN and placebo from the end of RT to the end of RW.

Results: 219 patients receiving HD were randomized and 164 patients (75%) completed RT, of which 152 (93%) completed RW. Principal reasons for discontinuation included adverse events (8%), and hyperphosphatemia (5%). 80 patients were responders in whom the mean decrease in sP as compared to baseline during RT was 2.6 mg/dL. During RW, mean sP increased by 1.5 mg/dL in placebo treated patients and 0.5 mg/dL in TEN treated patients, resulting in a LS mean difference of –0.8 (95% CI: –1.4, –0.2, p=0.01). For the intent to treat (ITT) group (all 164 patients in RW), mean sP increased by 0.8 mg/dL in placebo treated patients and 0.1 mg/dL in those receiving TEN resulting in a LS mean difference of –0.7 (95% CI: –1.2, –0.3, p=0.003). TEN resulted in statistically significant reductions in sP during RT in all 3 TEN groups.

Conclusions: TEN, an oral small molecule NHE3 inhibitor that reduces intestinal phosphate transport, significantly lowers sP in patients receiving HD with hyperphosphatemia.

Funding: Commercial Support - Ardelyx, Inc.

TH-PO1047

A Novel, Selective, and Non-Systemic Na+/H+ Exchanger 3 Inhibitor, TP0469711, Potently Enhances Phosphate Excretion with a Favorable Gastrointestinal Tolerability in Rats Eiji Munetomo, Tomohiro Abe, Hideki Tomoike, Hiromitsu Kajiyama, Saori Koyasu, Lisa Okumura, Shoichi Kuroda, Haruyuki Mori, Yasunobu Ushiki, Teisuke Takahashi, Koji Yamamoto. *Taisho Pharmaceutical Co., Ltd., Saitama, Japan.*

Background: Na^+/H^+ Exchanger 3 (NHE3) inhibitor is known to enhance the excretion of phosphate and expected as a new candidate for anti-hyperphosphatemia drug. However, NHE3 inhibitor also causes diarrhea frequently because of the excessive enhancement of Na excretion.

Methods: NHE1, NHE2 and NHE3 activities of TP0469711 (TP) were evaluated by measuring intracellular pH recovery in each NHE over-expressing cells. Na-dependent phosphate transporter 2b (NaPi2b) activity was evaluated by uptake of ^{33}P phosphate in NaPi2b over-expressing cells. To examine the effect of TP on the phosphate absorption and excretion, the radioactivity of ^{32}P phosphate in the blood and feces were measured after oral administration of TP. Inhibitory effects of NHE3 by TP were evaluated by measuring pH and luminal Na content in the intestinal tract. Na excretion and water content in feces up to 24 hours were evaluated after oral dosing of TP in rats.

Results: TP inhibited human and rat NHE3 activities with IC_{50} values of 2.2 and 2.1 nM, respectively. However, TP (3 μM) had no effects on human NHE1, NHE2 and NaPi2b activities. Oral administration of TP increased pH of luminal content in the upper intestine in a dose-dependent manner in rats. TP (0.1 mg/kg, p.o.) significantly decreased the area under the curve of plasma ^{32}P phosphate radioactivity by 40.7 ± 4.7 % (n=5, $P < 0.001$). TP (0.1 mg/kg, p.o.) significantly increased the fecal excretion of phosphate by 62 % (n=6, $P < 0.05$), without affecting Na excretion and water content in feces. TP significantly enhanced the excretion of Na and increased water content at a higher dose of 1 mg/kg (n=7, $P < 0.01$). Over dose of TP (30 mg/kg, p.o.) did not raise plasma concentration (< 1 ng/ml), which means TP is a non-systemic NHE3 inhibitor.

Conclusions: We discovered a novel, selective and non-systemic NHE3 inhibitor, TP0469711, which potently excreted phosphate into feces with a favorable gastrointestinal tolerability in rats. TP is suitable for a new therapeutic agent for the treatment of hyperphosphatemia in patients with end-stage renal disease.

Funding: Commercial Support - Taisho Pharmaceutical Co., Ltd.

TH-PO1048

VS-505: A Novel Phosphate Binder: First Clinical Experience in Haemodialysis Patients Johan Rosman,[1,4] Testuji Asao,[3] Mark A. Thomas,[4] Shitotomo Yamauchi.[2] *[1]School of Medicine, Curtin University, Perth, WA, Australia; [2]Ethic Co., Ltd., Chiyoda, Japan; [3]KDL Inc., Tokyo, Japan; [4]Royal Perth Hospital, Perth, NSW, Australia.*

Background: Phosphate binders (PB) side effects lead to non-compliance. Recently, iron-based PB were introduced, but absorption leads to high iron levels. VS-505 is a novel class PB where the iron ion (as ferric chloride) is bound to inert Arabic Gum. Animal studies showed superior efficacy and better tolerance without change in serum iron levels. This is the first study in haemodialysis patients to test safety, efficacy and tolerability.

Methods: This single arm, open label, dose escalation study used VS-505 in haemodialysis patients, stable on treatment for over 12 weeks. Plasma phosphate (Pi) level had to be between 6 - 10 mg/dl after a 2 weeks wash out from current PB. Other treatment, and dialysis modality remained unchanged. Treatment with VS-505 was 8 weeks with 2-weekly dose escalations, guided by Pi levels, from 1.5 g/day to 9.0 g/day. From screening to treatment day 22, lab parameters were followed weekly, then fortnightly. Primary Efficacy Endpoint was the Pi change during treatment. Secondary Efficacy Endpoints were Time Course of Pi to end of treatment and Plasma Calcium (Ca) change. Other criteria were trajectory of Iron Parameters, standard dialysis bloodtests, and Electro-Cardiograms. Tolerability was evaluated with questionnaires. Endpoints analysis by Intention to Treat/Full Analysis Set and a Per Protocol Set. A last Observation Carried Forward was applied for patients not completing the study.

Results: Sixteen patients were enrolled. 11 withdrew consent: 3 for diarrhea after dose escalation, 8 for medication-unrelated AE's. 30% of all patients reported black stools (iron). Only one subject received full dose escalation to 9 g/day, 4 reported abdominal dyscomfort after the escalation to 4.5 g/day. No changes of iron parameters were found. Routine parameters remained unchanged. Plasma Pi was significantly reduced in the treatment group, median Pi change -2.40 mg/dl (-30.9%), ($p<0.0001$). Significant lowering of Pi levels were already observed at the lowest given dose of VS-505. There was no change of Ca levels, but a significant reduction in iPTH over the treatment period.

Conclusions: VS-505 is a promising, effective, safe and well-tolerated PB for the treatment of hyperphosphatemia with advantages over current drugs. Further studies in larger numbers of patients are warranted to find its exact place in routine treatment.

Funding: Commercial Support - KDL Inc, Japan

TH-PO1049

Impact of Admission Serum Phosphate Levels on Mortality in Hospitalized Patients Michael A. Mao,[2] Wisit Cheungpasitporn,[2] Charat Thongprayoon,[1] Wonngarm Kittanamongkolchai,[2] Ankit Sakhuja,[3] Stephen B. Erickson.[2] *[1]Bassett Medical Center, Cooperstown, NY; [2]Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [3]Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN.*

Background: The aim of this study was to assess the relationship between admission serum phosphate levels and in-hospital mortality in all hospitalized patients.

Methods: All adult hospitalized patients who had admission serum phosphate available between years 2009 and 2013 were enrolled. Admission serum phosphate was categorized based on its distribution into six groups (<2.5, 2.5-3.0, 3.1-3.6, 3.7-4.2, 4.3-4.8 and ≥4.9 mg/dL). The odds ratio (OR) of in-hospital mortality by admission serum phosphate, using the phosphate category of 3.1-3.6 mg/dL as the reference group, was obtained by logistic regression analysis. Pre-specified subgroup analysis stratified by chronic kidney disease (CKD) and cardiovascular disease (CVD) status was performed.

Results: 42,336 patients were studied. The lowest incidence of in-hospital mortality was associated with a serum phosphate within 3.1-4.2 mg/dL. A U-shaped curve emerged demonstrating higher in-hospital mortality associated with both serum phosphate <3.1 and >4.2 mg/dL. After adjusting for potential confounders, both serum phosphate <2.5 and >4.2 mg/dL were associated with an increased risk of in-hospital mortality with ORs of 1.60 (95% CI 1.25-2.05), 1.60 (95% CI 1.29-1.97) and 3.89 (95% CI 3.20-4.74) when serum phosphate were within <2.5, 4.3-4.8 and ≥4.9 mg/dL, respectively. Among subgroups of patients with CKD and CVD, the highest mortality was associated with a serum phosphate ≥4.9 mg/dL with ORs of 4.11 (95% CI 3.16-5.39) in patients with CKD and 5.11 (95% CI 3.33-7.95) in patients with CVD. While serum phosphate <2.5 mg/dL was associated with increased in-hospital mortality in patients with CVD (OR 3.24, 95% CI 1.82-5.58), the risk was not significantly increased among CKD patients with serum phosphate <2.5 mg/dL.

Conclusions: Hospitalized patients with admission serum phosphate <2.5 and >4.2 mg/dL are associated with an increased risk of in-hospital mortality. In addition, CKD and CVD patients with hyperphosphatemia at admission (≥4.9 mg/dL) carry the highest mortality risk.

TH-PO1050

Mineral Bone Disease after Kidney Transplantation Silvana Maria C. Miranda,[1] Ana elisa S. Jorge,[2] Gerson M. Pereira jr,[2] Pedro Augusto M. Souza,[1] Andre S. Alvarenga,[2] Carlos rafael A. Felipe,[2] Izabela L. Piana.[3] *[1]Hospital Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; [2]Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; [3]Faculdade de Minas Faminas BH, Belo Horizonte, Brazil.*

Background: Mineral bone disease (MBD) after kidney transplant (KT) is frequent and associated with pre-existing MBD, immunosuppressive therapy and graft function.

Methods: We analyzed the evolution of serum calcium (Ca), phosphorus (P) and parathyroid hormone (PTH) before and after KT from a retropective cohort of 39 KT patients in a Brazilian KT center.

Results: There was a significant reduction of P and PTH after KT, whereas Ca increased significantly (Table 1). At 1 year of KT, 17.9% of patients had hypercalcemia and 17.1%, hypophosphatemia. PTH above the normal range was observed in 68% of patients. Pre-transplant PTH was positively correlated with post-transplant PTH (r = 0.519, p = 0.001) and negatively correlated with post-transplant P (r = -0.450, p = 0.004). There was no correlation between pre-transplant PTH and post-transplant Ca (r = 0.174, p = 0.296) or eGFR (r = -0.035, p = 0.840). Figure 1 shows the positive correlation between post-transplant PTH and Ca; the negative correlation between post-transplant PTH and P. Interestingly, the only variable associated with post-transplant eGFR was pre-transplant P, with a negative correlation (r = -0.326, p = 0.042).

Conclusions: After KT, there were a significant increase in Ca and reduction of PTH and P levels. Post-transplant hyperparathyroidism, hypercalcemia and hypophosphatemia were frequent, and post-KT PTH correlated with Ca and P. Pre-transplant P correlated negatively with eGFR post-trasnplant.

Table 1: Evolution of mineral parameters after kidney transplant

Variable	Pre-transplant (n=39)	Post-transplant (n=39)	p
PTH (pg/mL) – median	340.8	91.6	<0.0001
P (mg/dL) - mean	5.27	3.02	<0.0001
Ca (mg/dL) – median	8.68	9.37	<0.0001

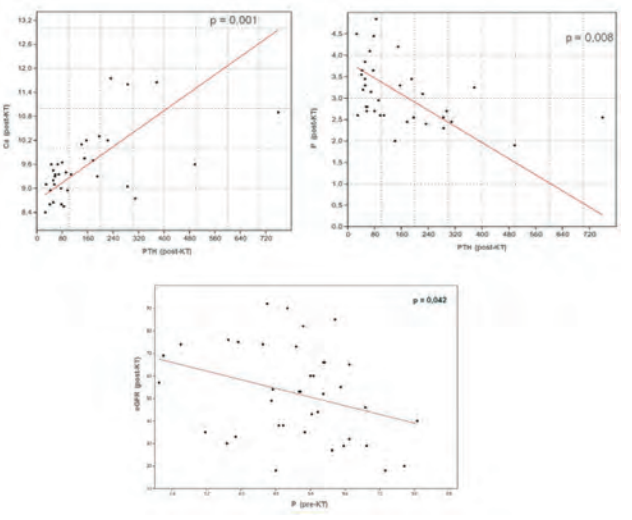


Figure1: Linear Regression for mineral parameters

TH-PO1051

Influence of Dialysis Vintage on Mineral and Bone Disorders after Kidney Transplantation Keiji Kono,[1] Hideki Fujii,[1] Kentaro Nakai,[2] Nozomi Hosokawa,[1] Shunsuke Goto,[1] Shinichi Nishi.[1] *[1]Kobe University Graduate School of Medicine, Kobe, Japan; [2]Fukuoka Red Cross Hospital, Fukuoka, Japan.*

Background: Mineral and bone disorder (MBD), such as hypercalcemia and hypophosphatemia, frequently occurs after kidney transplantation (KT), and its evidence has accumulated. However, the relationship between pre-KT dialysis vintage and post-KT MBD has not been evaluated in the detail.

Methods: Ninety-six patients who underwent KT were included. Patients with parathyroidectomy during pre-KT and the 12 months post-KT were excluded. We compared the natural history of post-KT MBD between pre-emptive KT (PKT) and non-PKT. Furthermore, non-PKT group was divided into 3 groups according to the dialysis vintage; <3years, 3-6years, >6years. Parameters of MBDs and kidney function were followed at pre-KT, 1 and 2 weeks, and 1, 2, 3, 6 and 12 months post-KT. We also checked pre-KT parathyroid enlargement by ultrasound evaluation.

Results: Serum calcium levels increased and reached a plateau at the 2 months post-KT in all the groups. Patients with longer dialysis vintage had higher serum calcium levels from the 1 week post-KT, and particularly the group with dialysis vintage > 6 years had persistent hypercalcemia, which was significantly higher serum calcium levels from the 1 month to 12 months post-KT compared to the other groups. Serum phosphate levels substantially decreased until the 1 week post-KT, after which it gradually increased in all the groups. The non-PKT group had significantly lower serum phosphate levels compared to the PKT group from the 1 week to 3 months post-KT, but there was no significant difference depending on dialysis vintage. PTH levels were significantly higher in the PKT group compared to the non-PKT group at pre-KT, but substantially decreased in the PKT group to almost the same levels as the other groups until the 1 month post-KT. The group with dialysis vintage > 6 years had higher prevalence of pre-KT parathyroid enlargement and persistent higher PTH levels during the 12 months post-KT, and its levels were significantly higher at the 12 months post-KT compared to the other groups. Kidney function was comparable among all the groups during the 12 months post-KT.

Conclusions: Our findings suggest that patients with longer dialysis vintage have persistent higher serum calcium levels just after KT, and its levels are significantly higher especially in dialysis vintage > 6 years probably due to persistent hyperparathyroidism.

TH-PO1052

Serum Lithium (Li) Values within Recommended Range May Induce Changes in Renal Tubular Function and Calcium Homeostasis in Patients with Bipolar Disorder (BD) Lucas D. Hortêncio,[2] Karla M. DE ALMEIDA,[2] Michelle Silva,[2] Beny Lafer,[2] Claudia Helou.[1] *[1]Lab Pesquisa Basica LIM12 Fac Medicina Univ Sao Paulo, SP, Brazil, Sao Paulo, Brazil; [2]Institute of Psychiatry of University of Sao Paulo, Sao Paulo, Brazil.*

Background: Li is the first choice for maintenance treatment of patients with BD. However, Li can induce nephrogenic insipidus diabetes and some patients may develop asymptomatic hypercalcemia because Li may cause primary hyperparathyroidism.

Methods: Thus, we studied 76 patients with BD treated with or without Li by a cross-sectional analysis. We collected blood (B) and 24-hour urine (U) samples to evaluate renal function, electrolyte homeostasis and serum (S) hormone levels.

Results: As shown in the Table, we studied more women than men, but they had similar age, eGFR, and S Li values were within recommended range. Both women and men treated with Li had higher U pH and lower U density than Non-Li-treated patients. Li-treated-women had also higher levels of S PTH, S ionized Ca (S iCa) than that of other

groups. Moreover, Li-treated-women showed a positive correlation between high levels of S iCa and increases of S PTH, diuresis and U pH and low U density when we plotted levels of S iCa≥5.47 mg/dL. On the other hand, only Non-Li-treated women showed low levels of S PTH, diuresis and U pH and high U density when we plotted levels of S iCa≤4.88 mg/dl. No patient showed any symptom and other ionic homeostasis disorder.

Conclusions: Li induced changes in both parathyroid and renal tubular function without clinical manifestations justifying a periodically monitored surveillance especially in women patients.

Funding: Government Support - Non-U.S.

	WOMEN		MEN	
	Li	Non-Li	Li	Non-Li
n	20	32	17	7
Age, years	45±2	45±2	45±2	49±5
eGFR, ml/min	91±5	97±3	92±5	101±3
S Li, mEq/l	0.71±0.05		0.66±0.05	
S iCa, mg/dl	5.25±0.07*$	4.96±0.03	5.07±0.05	5.03±0.09
S PTH, pg/ml	58±7*	42±3	46±3	44±4
25 OH vitamin D, ng/ml	18±2	19±2	18±1	19±2
Free T4, ng/dl	1.14±0.04	1.15±0.04	1.22±0.05	1.14±0.04
U output, ml/day	1998±228	1469±105	2388±303	1430±170
U pH	6.73±0.18*##	6.10±0.16	6.44±0.17#	5.50±0.33
U density	1010±1**###	1017±1##	1013±1##	1025±2
UV Ca, mg/day	138±15	141±22	189±55	162±45

eGFR, estimated glomerular filtration rate calculated by CKD-EPI formula. *P<0.05, **P<0.01, ***P<0.001 vs Non-Li-treated women; #P<0.05, ##P<0.01,###P<0.001 vs Non-Li-treated men derived from ANOVA followed by Newman-Keuls test

TH-PO1053

Association between Mineral Metabolism Parameters and Carotid Intima Media Thickness in a Cardiovascular Risk Population (CORDIOPREV Study) Maria Encarnacion Rodriguez Ortiz,[1] Francisco Gómez-Delgado,[2] Antonio Arenas-Larriva,[2] Antonio Canalejo,[3] Purificación Gómez-Luna,[2] Carmen maria Herencia,[1] Javier López-Moreno,[2] Mariano Rodriguez,[4] José López-Miranda,[2] Yolanda Almaden peña.[2] *[1]Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC). Reina Sofia University Hospital/University of Córdoba, Córdoba, Spain; [2]Lipid and Atherosclerosis Unit. IMIBIC/Reina Sofia University Hospital/University of Cordoba, and CIBER Fisiopatologia Obesidad y Nutricion (CIBEROBN), Instituto de Salud Carlos III, Córdoba, Spain; [3]Department of Integrated Sciences, University of Huelva, Huelva, Spain; [4]Nephrology Service. Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC). Reina Sofía University Hospital/University of Córdoba, Córdoba, Spain.*

Background: Cardiovascular diseases (CVD) are the main cause of mortality in patients with Mineral Metabolism (MM) alterations, as those with CKD. Thus, factors related to MM may play a key role in the onset and development of CVD. Carotid intima media thickness (IMT-CC) has shown strong associations with well-recognized risk factors of CVD and it is a predictor of coronary artery disease. The aim of this study was to assess whether there is an association between some key parameters of MM and the IMT-CC in a cardiovascular risk population.

Methods: This work was carried out in the setting of the CORDIOPREV study (Clinical Trials 128 Registry NCT0092493741), a prospective, randomized, controlled trial including 1,002 patients aged 20-75 years with coronary heart disease. Carotid arteries were examined bilaterally using a Doppler ultrasound high-resolution B-mode. IMT-CC was calculated as the mean of three measurements. Basal plasma levels of FGF23, Ca, P, creatinine (Cr), Mg, 25-OH and calcitriol (CTR) were measured.

Results: As shown in the table (mean±SE), a significant inverse relationship was observed between IMT-CC and eGFR and Mg, while Cr and FGF23 were directly associated with IMT-CC.

Conclusions: Even within the normal range, there was an association between some MM parameters and the IMT-CC in a cardiovascular risk population. Thus, these factors might be useful for the monitoring of CVD. Grant ISCIII (PI14/00872)

Table

	IMT-CC (mm)				
	Q1 (0.43-0.61)	Q2 (0.62-0.70)	Q3 (0.71-0.80)	Q4 (0.81-1.27)	P-value
eGFR (ml/min)	95.4±1.3	95.9±1.4	90.9±1.4	89.5±1.4	0.001
Cr (mg/dl)	0.87±0.01	0.85±0.01	0.91±0.01	0.93±0.01	0.001
P (mg/dl)	3.57±0.05	3.58±0.05	3.62±0.05	3.60±0.05	0.883
Mg (mg/dl)	1.89±0.03	1.90±0.03	1.76±0.03	1.62±0.03	<0.001
Ca (mg/dl)	9.56±0.03	9.51±0.03	9.59±0.03	9.59±0.03	0.195
FGF23 (pg/ml)	40.3±1.4	39.9±1.5	45.3±1.5	50.4±1.5	<0.001
25OH (ng/ml)	16.0±2.7	16.6±0.5	16.4±0.5	16.7±0.5	0.814
CTR (pg/ml)	64.4±2.7	62.6±2.8	61.4±2.7	60.7±2.8	0.791

TH-PO1054

Functional Analysis of Gcm2 in Adult Gcm2 Conditional Knockout Mice Yamada Taku,[1] Norifumi Tatsumi,[3] Sahoko Kamejima,[3] Taketo Uchiyama,[2] Ichiro Ohkido,[2] Masataka Okabe,[4] Takashi Yokoo.[4] *[1]Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan; [2]Division of Nephrology and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan; [3]Jikei University School of Medicine, Tokyo, Japan; [4]The Jikei University School of Medicine, Tokyo, Japan.*

Background: *Glial cells missing-2* (*Gcm2*) is exclusively expressed in the parathyroid gland (PTG). The specific role of mice *Gcm2* in the development of PTG from the third pharyngeal pouch has been further investigated, although its function in adult mice remains largely unknown. *Gcm2* directly regulates *calcium-sensing receptor* (*CaSR*) and transactivates it through *Gcm2* response elements in the *CaSR* promoter, which has important implications for the exacerbation of CKD-MBD. Accordingly, it is possible that *Gcm2* plays a crucial role in CKD-MBD and particularly, in secondary hyperparathyroidism (SHPT).

Methods: We generated *Gcm2* conditional knockout mice in which loxP sites flanked exons 2 and 3 in the *Gcm2* allele. We then crossed these mice with tamoxifen-inducible Cre strain. Next, we intraperitoneally injected 40 mg/kg of tamoxifen into 8-week-old mice for five days. The mice were sacrificed one (1KOmice) and seven (7KOmice) months after tamoxifen administration. We then investigated their serum biochemistry and performed histological analysis.

Results: Serum biochemical parameters of 1KOmice were not significantly different when compared with those of control mice. However, compared with control mice, a significant increase in the serum phosphate level and significant decrease in calcium and parathyroid hormone levels were confirmed in the 1KOmice. Staining of PTG with HE showed that normal structure was generally conserved in 1KOmice, except for the presence of a few follicles, whereas normal structure was not conserved in 7KO mice and their PTGs showed many follicles.

Conclusions: 7KOmice showed hypocalcemia, hyperphosphatemia, low parathyroid hormone level, and many follicles in PTG. In addition, normal PTG structure was not observed in these mice. These results suggest that the loss of function of *Gcm2* at an adult age leads to hypoparathyroidism, as observed in congenital *Gcm2* knockout mice. This animal model is useful to study distinct roles of *Gcm2* at different ages and the relationship between *Gcm2* and CKD-MBD, particularly SHPT.

Funding: Private Foundation Support

TH-PO1055

3'UTR Regulates the Baseline Protein Abundance and Activity of Mouse NaPi-IIa Hassane Amlal, Sulaiman Sheriff, Perwez Alam. *University of Cincinnati, Cincinnati, OH.*

Background: The apical sodium-phosphate cotransporter NaPi-IIa plays an important role in the control of phosphate balance by regulating the rate of inorganic phosphate reabsorption in the kidney proximal tubule. We have previously shown that the 3'-untranslated region (3'UTR) of NaPi-IIa mRNA transcript plays an important role in the post-transcriptional regulation of NaPi-IIa in response to estrogen. However, whether 3'UTR regulates the baseline expression of NaPi-IIa has not been studied.

Methods: We have studied the role of 3'UTR in mNaPi-IIa expression and activity using OK cells transfected with mammalian expression plasmids containing the open-reading frame (ORF) 3'-UTR or 5'-UTR ORF or the full-length (FL) mouse NaPi-IIa transcript. Immunoblotting, Real-time PCR and ^{32}P uptake studies were performed. Further, the role of microRNAs (miRNA) in the function of mNaPi-IIa-3'UTR was examined by luciferase assay using the miRNA target expression vector. Full-length mNaPi-IIa 3'UTR or 4 overlapping (~250bp) fragments (F1-F4 from stop codon) were generated by PCR and individually sub-cloned into the miRNA target expression vector. Subsequently, chimeras of 5'UTR-ORF-(F1 to F4) were generated in mammalian expression vector and used to examine the expression of mNaPi-IIa protein in OK cells by immunoblotting.

Results: The protein abundance of mNaPi-IIa is increased by 3-fold in OK cells transfected with 3'UTR-free plasmid (i.e. 5'-ORF), as compared to FL or ORF-3'UTR. This correlates with 50% increase in Pi transport activity, as shown by a sharp increase in Na^+-dependent ^{32}P uptake in cells expressing 5'-ORF vs. ORF-3'UTR. Real-time PCR data showed no difference in the mRNA expression levels between the 3 plasmid constructs. Normalized luciferase activity was increase by 36%, 74%, 54% and 27% for F1 to F4 fragments, respectively, compared to 3'UTR. Interestingly, the protein abundance of NaPi-IIa was significantly reduced in cell transfected with all F1 to F4 chimeras, with a more profound reduction in chimera 5'UTR-ORF-F4, as compared to 5'UTR-ORF construct.

Conclusions: 3'UTR regulates the baseline expression of mouse NaPi-IIa protein abundance and activity in OK cells. This phenomenon is mediated through a sequence specific post-transcriptional mechanism involving microRNAs, which interact with *cis*-acting elements distributed throughout the 3'UTR.

Funding: NIDDK Support, Clinical Revenue Support

TH-PO1056

Transition from Low to High Dietary Phosphate Reduces Serum Calcium but Increases Vascular Calcification in Experimental CKD Cynthia M. Pruss, Kimberly J. Laverty, Emilie C. Ward, Bruno A. Svajger, Paul S. Jeronimo, Mandy E. Turner, Martin P. Petkovich, Rachel M. Holden, Michael A. Adams. *Queen's University, Kingston, ON, Canada.*

Background: Chronic kidney disease (CKD) impairs phosphate (PO_4) homeostasis resulting in hyperphosphatemia, which is associated with cardiovascular events and vascular calcification (VC). Animal models of CKD demonstrate pathologies and outcomes similar to those of CKD patients. We examined the impact of dietary phosphate loading on markers of mineral metabolism in controlled adenine-induced CKD.

Methods: Sprague Dawley rats were fed a 0.25% adenine, 0.5% PO_4 diet for 4-5 weeks to induce stable CKD (creatinine >250 uM), then fed 0.5% PO_4 diet without adenine. At 5.5 weeks, rats were fed either s 0.5%, 1% or 1.5% PO_4 diet, N=9, 10, 6, while another group (N=21) was fed increasing dietary PO_4 every 4 days (0.5%→0.75%→1%→1.5%). Controls were fed 0.5% PO_4 diet (N=8). Serum calcium (Ca), PO_4, FGF-23, PTH, and tissue Ca and PO_4 were determined.

Results: At 5 weeks, CKD rats vs control had 3.2±0.6 vs 2.5±0.3 mM PO_4 and 2.8±0.2 vs 2.4±0.1 mM Ca. Off adenine, the 0.5% group was at control PO_4 levels but had elevated Ca at 6.5 weeks. At 7 weeks, the 1.0 and 1.5% groups had marked increases in PO_4, PTH, and FGF-23, while serum Ca dropped (table 1). VC was observed in 80% of high PO_4 rats (1 or 1.5%). In the increasing dietary PO_4 group, serum PO_4 (mM) increased with dietary PO_4: baseline(2.1±.3), 0.5%(2.7±0.7), 1%(4.2±0.5), 1.5%(4.8±1.3) PO_4. Fasting serum Ca (mM) increased in CKD rats given 0.5% PO_4 (2.1±0.2→3.1±0.3), but significantly declined when fed 1%(2.4±0.7) and 1.5%(2.2±0.9) dietary PO_4. PTH and FGF-23 both increased (4x, 2x) with the increased dietary PO_4 and VC was observed in all rats.

Conclusions: In our CKD model, 0.5% PO_4 diet increased serum Ca but did not induce VC. In contrast, dietary PO_4 of 1% or more led to significant decreases in serum Ca, but generated high serum PO_4, FGF-23, PTH and VC. These findings uncover a new link between dietary PO_4 and serum Ca.

Funding: Commercial Support - OPKO Health, Inc. Renal Division, Government Support - Non-U.S.

Rat Serum Levels at 7 Weeks

PO_4 Diet	PO_4 (mM)	Ca (mM)	PTH (ng/ml)	FGF23 (ng/ml)
0.5	2.2±0.3	2.6±0.3	0.41±0.18	3.1±2.7
1.0	5.0 ±1.0	2.2±0.1	2.4 ±1.3	47±18
1.5	5.8 ±1.4	2.0±.1	3.1 ±0.6	35 ±17

TH-PO1057

Regulation of Intestinal Phosphate Transport in a Rat Model of CKD Komuraiah Myakala,[2] Evgenia Dobrinskikh,[4] Eileen M. Sutherland,[1] Moshe Levi.[3] *[1]Uniiversity of Colorado, Denver, CO; [2]University of Colorado, Aurora, CO; [3]University of Colorado Denver, Aurora, CO; [4]University of Colorado, Denver, Aurora, CO.*

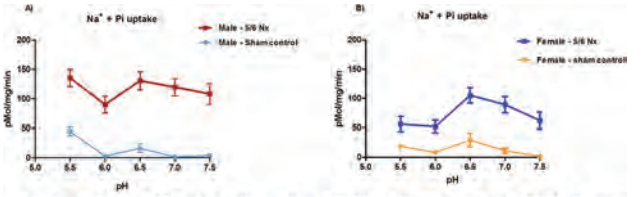
Background: In chronic kidney disease (CKD) hyperphosphatemia is a common occurrence and plays important roles in cardiovascular and bone disease. The mechanisms however still remain unknown and the role of intestinal phosphate (Pi) transport is subject of ongoing debate.

Methods: We studied regulation of intestinal phosphate transport in a model of 5/6 nephrectomy (Nx) induced CKD in the rat fed a relatively high Pi diet (1.5% Pi, 0.6% Ca).

Results: Male rats with 5/6 Nx had a marked increase in serum BUN (37.7 ± 2.0 vs. 150.5 ± 29.8 mg/dl in sham control, p<0.02), serum creatinine (0.5 ± 0.06 vs. 1.65 ± 0.23 mg/dl in sham control, p<0.008), and serum Pi (7.48 ± 0.85 vs. 18.19 ± 1.84 mg/dl in sham control, p<0.001). We isolated apical brush border membrane vesicles (BBMV) from the duodenum and the jejunum and studied sodium gradient dependent Pi (Na^+/Pi) cotransport as a function of pH. Across every single pH studied, including 5.5, 6.0, 6.5, 7.0, and 7.5 Na^+/Pi transport activity was increased in BBM from 5/6 Nx rats. This was associated with a 2-fold increase in NaPi-2b protein abundance in the duodenum and a1.4-fold increase in NaPi-2b protein abundance in the jejunum. To determine if there are sex-dependent differences in CKD and intestinal Na^+/Pi transport, we also studied in parallel female rats with 5/6 Nx. We found that female rats with 5/6 Nx also had a marked increase in serum Pi (4.75 ± 0.39 vs. 10.7 ± 1.24 mg/dl in sham control, p<0.003). In addition, there were marked increases in intestinal Na^+/Pi transport activity paralleled by increases in NaPi-2b protein abundance.

Conclusions: Our study therefore indicates that in both male and female rats with CKD, the hyperphosphatemia is mediated by increased intestinal Na//Pi transport activity and increased NaPi-2b protein expression.

Funding: NIDDK Support



pH dependent Na+/Pi uptake into isolated BBMV of sham control and 5/6 NX A) male and B) female rats.

TH-PO1058

The Role of Gut Microbiota in Phosphorus Metabolism in Maintenance Hemodialysis Patients Yuanyi Miao,[1] Min Xia,[2] Yuqing Chen.[2] *[1]Peking University First Hospital, Beijing, China; [2]Renal Division, Peking University First Hospital, Beijing, China.*

Background: Disturbance of phosphorus metabolism is a risk factor associated with mortality in hemodialysis patients. Gut absorption is the major source of phosphorus. Recent studies indicated that the intestinal flora of uremic patients changed a lot. And phosphorus is an essential element of bacterial survival and reproduction. The purpose of the study was to explore the role of intestinal microbiota in the control of serum phosphorus.

Methods: Microbial DNA was isolated from the stools of 20 healthy controls and 21 maintenance hemodialysis patients from one hemodialysis center. 14 out of the 21 patients were treated with Lanthanum carbonate for 12 weeks, thus stools were also collected before and after the treatment. The bacterial composition was analyzed by 16S ribosomal RNA pyrosequencing. Bioinformatics tools, including abundance profiling, taxonomic diversity and correlation analyses were used in microbiome data analyses.

Results: Clinical biochemical traits were compared before and after the use of Lanthanum carbonate in MHD patients. The serum phosphorus decreased after using Lanthanum carbonate for 12 weeks (P<0.001). There was no difference in other traits. 13 genera were closely correlated with serum phosphorus and the correlation coefficient was above 0.4 (P<0.05). And 11 genera were positively related to serum phosphorus, suggesting that survival of the 11 genera were related to phosphorus. We also found that 2 genera were negatively related to serum phosphorus, indicating that the 2 bacteria may be involved in the absorption process of phosphorus. 58 bacterial operational taxonomic units (OTUs) were different before and after the use of phosphorus binder. More decreased OTUs were identified after using phosphorus binder. 7 genera were obviously reduced, including Centipeda, Chryseobacterium, Gemella, unclassified_ Rhodocyclaceae, Pelomonas, Curvibacter and Parvimonas. Furthermore, the microbial richness and diversity decreased in hemodialysis patients and declined further after phosphorus reduction.

Conclusions: Gut flora is related to phosphorus metabolism in hemodialysis patients, and improving intestinal microbiota may regulate the absorption of phosphorus in the intestine. The use of phosphorus reduction drugs lead to decreased microbial richness and diversity.

Funding: Government Support - Non-U.S.

TH-PO1059

Vessels Are an Important Depot for Phosphate in Response to an Oral Load in an Experimental Model of CKD Mandy E. Turner, Paul S. Jeronimo, Emilie C. Ward, Kimberly J. Laverty, Rachel M. Holden, Michael A. Adams. *Queen's University, Kingston, ON, Canada.*

Background: Dysregulated phosphate (PO_4) homeostasis contributes to increased cardiovascular risk in CKD patients, in part due to vascular calcification. We sought to determine if tissue deposition of PO_4 following an oral PO_4 load was altered by level of kidney function and changes in dietary PO_4.

Methods: CKD was induced in rats using dietary adenine (0.25%, 0.5% PO_4). At 6 weeks, adenine was stopped and animals were fed either low phosphate (LP) (0.5%, N=48) or high phosphate (HP) (1.0%, N=24) diet for 2 weeks. Non-CKD animals followed a parallel protocol (0.5%, N=12 and 1.0%, N=12). Prior to sacrifice, 6 hr fasted animals consumed 0.1g of PO_4 spiked with ~5mil CPM of $^{33}PO_4$. Blood samples were drawn at 20 min up to 6 hrs after the PO_4 load for measurement of $^{33}PO_4$ and phosphate. Animals were sacrificed at 0, 2, and 6 hrs post-oral load. Various tissues were collected for radioactivity and PO_4 measurement.

Results: The pattern of tissue disposition of PO_4 was altered by kidney function and pre-existing level of dietary PO_4. An HP diet produced a greater increase in serum PO_4, parathyroid hormone and fibroblast growth factor 23 than the LP diet. Serum $^{33}PO_4$ was detectable within 20 min following the oral load. In control animals, vascular tissue levels of $^{33}PO_4$ fell between 2 hrs and 6 hrs indicating lack of retention. In contrast, in CKD rats, vascular tissue levels of $^{33}PO_4$ were markedly higher at 6 hrs compared to 2 hrs, indicating substantial accrual and retention of phosphate. Although both bone and blood vessels had greater phosphate accrual in CKD, only the HP diet induced a vascular-selective deposition. That is, the vascular tissue:bone ratio was more than twice that found in either controls or LP CKD (bone:vessel CPM, 2hr: 1.7±0.8 vs. 0.6±0.2, p=0.003; 6hr: 1.2±0.9 vs. 0.4±0.1, p=0.008). CKD rats exposed to the HP diet had higher levels of phosphate in arteries compared to the LP diet (74±176 v. 715±624 nmol/mg of tissue, p<0.0001) consistent with more severe vascular calcification.

Conclusions: Changing from an LP to a HP diet in experimental CKD produces maladaptive responses in vascular tissue resulting in preferential and sustained vascular deposition of phosphate that likely associates with the vascular calcification phenotype.

Funding: Government Support - Non-U.S.

TH-PO1060

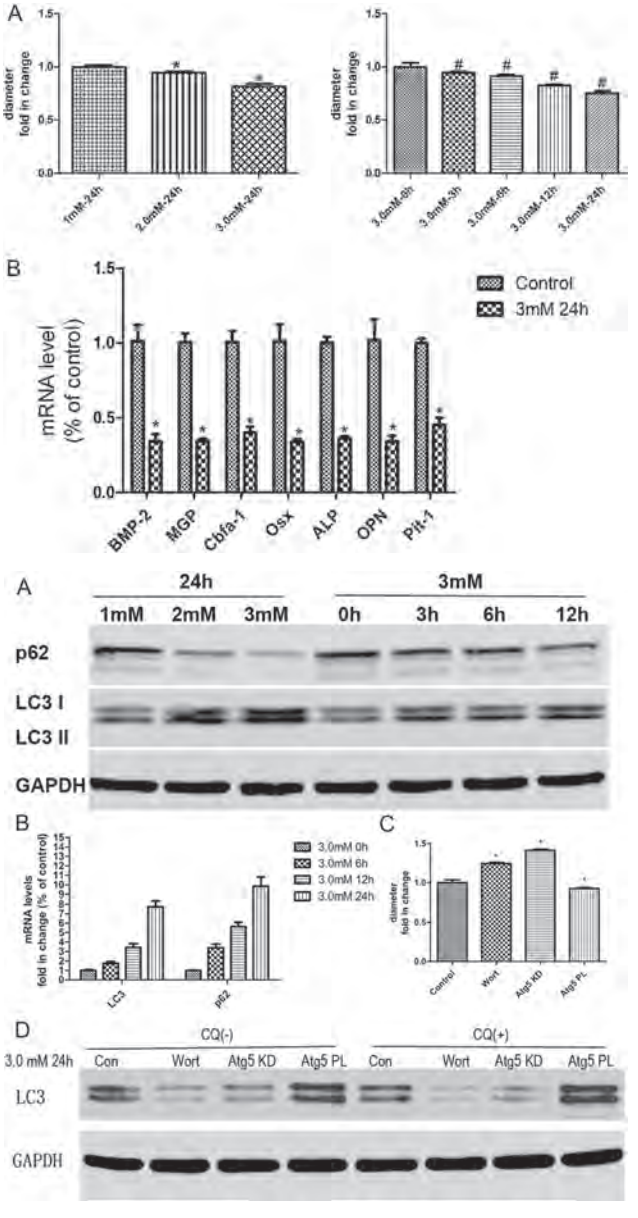
Phosphate Stimulates Myotube Atrophy through Autophagy Activation – Evidence That Hyperphosphatemia Contributes to Skeletal Muscle Wasting in CKD yue yue Zhang, Wei jie Yuan. *Shanghai General Hospital, Shanghai Jiaotong University School of Medcine, Shanghai, China.*

Background: Although evidence indicates that autophagy is involved in the maintenance of muscle homeostasis, it is unidentified if high phosphate could stimulate the activation of autophagy leading to muscle protein loss.

Methods: Immortalized rat L6 myotubes were exposed to a high concentration of phosphate with or without autophagy inhibition. Myotube atrophy was examined by phase contrast microscope. The autophagy activity was assessed by the expression of microtubule associated protein 1 light chain 3 (LC3) and p62 using quantitative real-time PCR and western blot.

Results: Phosphate induced cell atrophy in L6 myotubes with a dose- and time-dependent fashion and these response were not associate with the development of calcification or osteogenesis. Phosphate also dose- and time-dependently increased the ratio of LC3-II/LC3-I. Inhibition of autophagy with wormannin or knockdown of Atg5 significantly suppressed myotube atrophy caused by high concentration of phosphate.

Conclusions: High concentration of phosphate induces muscle cell atrophy through the activation of autophagy. Targeting autophagy could be a therapeutic strategy for muscle wasting caused by hyperphosphatemia.



TH-PO1061

Phosphate Retention Induces Growth Retardation in Adolescent Mice Marina Kohara,[1] Kazuhiro Shiizaki,[1] Yoshitaka Iwazu,[1] Yutaka Miura,[1] Kenichi Akiyama,[2] Toshihiro Nakano,[2] Ruri Kaneda,[1] Hiroshi Kurosu,[1] Makoto Kuro-o.[1] *[1]Jichi Medical University, Shitsuke, Japan; [2]Tokyo Women's Medical University, Tokyo, Japan.*

Background: Growth retardation is a major problem of chronic kidney disease (CKD) in adolescence. It is well known that the effect of supplementation of growth hormone (GH) is not sufficient, so more effective treatments have been requiring. CKD causes the phosphate retention and this control is very difficult due to the nutritional concern. We hypothesized that phosphate retention might be one of pathogenesis of growth retardation in adolescence with CKD.

Methods: Female C57BL/J6 mice were fed the regulated diets consists of various amount of phosphate from four to eight weeks old. Body weight, femur length and serum phosphate and insulin-like growth factor-1 (IGF-1) levels were measured. The target genes of GH including IGF-1, acid-labile subunit (ALS), major urinary proteins (MUP) 1 and 3, solute carrier organic anion transporter family member 1a1 (SLCO1A1), and hydroxysteroid dehydrogenase 3β5 (HSD3B5) mRNA, IGF-1 binding protein-1 (IGFBP-1) mRNA as an inhibitory marker of IGF-1 signaling and signal transducers and activators of transcription (STAT) 5 protein levels were evaluated in liver.

Results: The remarkable growth retardation with significantly high phosphate and low IGF-1 levels in serum were confirmed in mice fed the highest phosphate diet. The significantly lower expression levels in all of target genes of GH and STAT5 protein, and higher expression level in IGFBP-1 mRNA were also observed. The mice fed the middle phosphate diets showed the significantly lower levels in serum IGF-1 and in target gene expressions of GH compared with those fed the normal phosphate diet but not growth retardation.

Conclusions: The phosphate retention induces the growth retardation resulting from the inhibitions of both GH and IGF-1 signaling. Its moderate restriction might improve the growth retardation resulting from the improvement of the resistance to IGF-1 even though serum IGF-1 level was low. These findings suggest that the controlling phosphate retention using the phosphate binders and dietary restriction should be considered in adolescent CKD patients who require the supplementation of GH.

TH-PO1062

Alteration of Renal Claudins in Rats with Hypercalciuria Gheun-Ho Kim, Il hwan Oh. *Hanyang University College of Medicine, Seoul, Republic of Korea.*

Background: Ninety-eight to 99% of the filtered load of calcium is reabsorbed by the renal tubules. Whereas most of the calcium reabsorption passively occurs in the proximal tubule through tight junctions, the distal nephron has been known as the major site for regulation of calcium excretion. Claudins form the conductive and selective part of the tight junctions along the nephron and may be involved in regulatory events in the control of calcium transport. This study was undertaken to test if the renal expression of claudins are altered in the different settings of hypercalciuria.

Methods: Male Sprague-Dawley rats were used for three different animal protocols: $CaCO_3$, NaCl, and NH_4Cl loading. The rats were randomly divided into control (n=6) and treated (n=6) group in each experiment, and a daily fixed amount of food flurry was given to each rat. The control diet contained 0.8% calcium and 0.3% NaCl, and the treated diet had additional $CaCO_3$ (6%), NaCl (7%), or NH_4Cl (7.2 mmol/220 g BW) for 7 days. Plasma and urine data were followed, and kidneys were harvested for immunoblotting and qPCR analysis at the end of our animal experiment.

Results: Hypercalciuria was successfully induced by $CaCO_3$, NaCl, and NH_4Cl loading, and fractional excretion of calcium was significantly increased by the loading of $CaCO_3$ (5.00 ± 0.92 vs. 0.27 ± 0.08%, $P < 0.05$), NaCl (2.07 ± 0.57 vs. 0.25 ± 0.27%, $P < 0.05$), and NH_4Cl (0.90 ± 0.36 vs. 0.27 ± 0.12%, $P < 0.05$). The abundance of claudin-2 protein was not significantly altered by $CaCO_3$ or NaCl loading, but both claudin-2 protein (85 ± 9 vs. 100 ± 11%, $P < 0.05$) and mRNA (49 ± 23 vs. 100 ± 17%, $P < 0.05$) expression were significantly decreased by NH_4Cl loading. In response to $CaCO_3$ loading, the protein abundance of claudin-4 (47 ± 17 vs. 100 ± 12 %, $P<0.05$) and occludin (59 ± 17 vs. 100 ± 25%, $P<0.05$) were decreased, suggestive of changes in distal nephron. Interestingly, claudin-7 protein was decreased by NaCl loading (29 ± 14 vs. 100 ± 34%, $P<0.05$).

Conclusions: We confirmed that hypercalciuria in metabolic acidosis is associated with claudin-2 down-regulation in the proximal tubule. However, hypercalciuria induced by high calcium or salt intake was not accompanied by claudin-2 dysregulation. Further studies are required to investigate the regulatory role of paracellular calcium transport in the distal nephron.

TH-PO1063

Green Tea (GT) Increases Urinary Excretion of Calcium and Phosphorus, but These Effects Were Not Due to Caffeine (CAF) Claudia Helou,[1] Igor O. Da silva,[1] Talita R. Sanches,[2] Mirela Santinho,[1] Lucia Andrade.[2] *[1]Lab Pesquisa Basica LIM12 Fac Medicina Univ Sao Paulo, SP, Brazil, Sao Paulo, Brazil; [2]University of Sao Paulo School of Medicine, Sao Paulo, Brazil.*

Background: The consumption of industrialized (i) or natural (n) GT increases worldwide because this beverage is rich in antioxidant. However, there is a lack of studies about GT effect on the renal tubular function and a possible role exerted by the presence of CAF.

Methods: Thus, we housed Male Wistar rats in individual cages and randomly assigned them to have ad libitum access to tap water (W), iGT (Feel Good©), nGT or 8 mg% CAF dissolved in tap water. On day 8, we moved them to metabolic cages and collected 24-h urine samples. The rats were then anesthetized, and we placed a catheter in abdominal aorta to measure blood pressure (BP) and collect blood samples. We quantified creatinine and electrolytes in urine and plasma samples. We removed the kidneys to quantify protein expression (PE) of ion transporters in the cortex (C) and outer medulla (OM), by Western blot. We used ANOVA followed by Newman-Keuls test for statiscal analysis.

Results: All groups showed all ion plasma concentration values within normal range. As shown in the Table, nGT decreased BP and increased liquid intake and urine output. However, both i and n GT increased urinary excretion (UV) of calcium (Ca), phosphorus (P) and magnesium (Mg) and CAF increased only UVMg. With regard to PE of ion transporters, we only evaluated PE of TRPM6 and Na-Pi type IIa in C and PE of NKCC2 and Na-Pi type IIa in OM, and we only found decrease in PE of TRPM6 in iGT when compared with nGT, $p<0.05$, until now.

Conclusions: Even though we have not yet identified the mechanism for which GT induced Ca and P urinary losses we suggest to add GT in the list of risks for lithiasis.

Funding: Government Support - Non-U.S.

	W	iGT	nGT	CAF
n	15	13	12	12
Body weight (b.w.),g	332±9	343±7	337±7	319±7
BP, mmHg	105±2	101±3	90±3**	108±4
Creatinine clearance, ml/min/100g b.w.	0.48±0.04	0.47±0.04	0.41±0.02	0.41±0.03
Liquid intake,ml/day	24±3	34±3	45±4##	36±5
Urine output,ml/day	21±2	30±3	36±3##	27±4
UVNa,µmol/day	0.98±0.07	1.20±0.10	0.98±0.13	0.82±0.09
UVK,µmol/day	2.4±0.1	2.6±0.1	2.5±0.2	2.4±0.2
UVCl,µmol/day	0.71±0.08	0.82±0.10	0.44±0.07	0.53±0.06
UVCa,µmol/day	27±2	42±5#	39±4#	34±3
UVP,µmol/day	476±43	686±58##	655±43#	529±32
UVMg,µmol/day	106±14	178±24##	192±16##	157±12#

**p<0.01 vs other groups;#p<0.05 and ##p<0.01 vs W

TH-PO1064

Determinants of Reduced Urinary Calcium Excretion in Patients with CKD: The Role for 1.25-VitD Janaina d. Ramalho,[1] Estela M. Duarte,[1] Ana P. Takeichi,[1] Alisson D. Machado,[1] Paulo Lotufo,[2] Isabela M. Bensenor,[2] Rosa M. Moyses,[1] Silvia M. Titan.[1] *[1]Nephrology Division, Faculty of Medicine, University of São Paulo, São Paulo, Brazil; [2]Clinical Research Center, Universitary Hospital, University of São Paulo, São Paulo, Brazil.*

Background: A positive calcium balance may contribute to the pathogenesis of vascular calcification, which is highly prevalent in CKD. Recent studies have shown that CKD is associated with a reduction in urinary calcium excretion (UCE), but determinants are not fully known. Our aim was to evaluate mineral metabolism biomarkers associated with UCE in a CKD population.

Methods: Clinical data, CKD-MBD biomarkers and 24h urinary calcium excretion from 412 participants in the Progredir Study were evaluated. Univariable and multivariable linear regression models were used to explore determinants of UCE expressed in mg/kg – log transformed.

Results: Median UCE was 0.48 mg/kg (IQR 0.28 – 0.82 mg/kg). In the descriptive analysis, calciuria was negatively related to age, serum phosphorus, serum potassium, PTH, FGF23, and acidosis, whereas positively associated to eGFR, serum calcium, and 1,25-vit D. In linear regression models, even after adjustment for age, sex and eGFR, only 1,25-vit D, serum calcium, serum potassium and acidosis remained significantly related to UCE. However, in the multivariable model (Table1), only age, eGFR, 1.25-VitD and serum calcium were independently related to UCE.

Conclusions: Our results show that eGFR decline is associated with a dramatic decrease in UCE. Age, 1.25-VitD and serum calcium are independently associated to this effect in this CKD population. Therapeutic measures on 1.25-VitD reduced levels could have an impact on UCE.

Funding: Government Support - Non-U.S.

Table 1. Multivariable linear regression model on UCE(log)

	B	95% CI B	p value
Age	-0.003	-0.006	0.05
eGFR-CKDEPI	0.006	0.003	<0.0001
Bicarbonate	0.008	-0.004	0.20
K	-0.05	-0.12	0.11
Total Calcium	0.13	0.07	<0.0001
1.25-VitD	0.004	0.001	0.009

TH-PO1065

The Plant 3,4,5-Tri-O-Galloyl Quinic Acid Methyl Ester Inhibits Calcium Oxalate Crystals Growth in a Drosophila Model and Decreases Renal Cell Annexin A1 Surface Expression and Crystal Adhesion Mohamed A. Abd El-Salam,[2,3] Jairo Bastos,[3] Jing jing Han,[5] Daniel Previdi,[4] Paulo Donate,[4] Michael F. Romero,[1] John C. Lieske.[2] *[1]Mayo Clinic College of Medicine, Rochester, MN; [2]Department of Internal Medicine, Division of Nephrology and Hypertension, Mayo Clinic College of Medicine, Rochester, MN; [3]Department of Pharmaceutical Sciences, School of Pharmaceutical Sciences of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Brazil; [4]Department of Chemistry, Faculty of Philosophy, Arts and Sciences, University of Sao Paulo, Ribeirão Preto, Brazil; [5]Department of Internal Medicine, Division of Nephrology and Hypertension, Mayo Clinic College of Medicince, Rochester, MN.*

Background: The design of more effective therapies for urinary stone prevention depends on identifying critical pathogenic steps. Adherence and retention of crystals is one potential early event. Many studies have identified crystal-binding proteins (e.g. annexin A1, heat shock protein 90 (HSP90) and α-enolase) on the apical membranes of renal tubular epithelial cells. Agents that affect expression of these molecules could ameliorate crystal retention.

Methods: The plant metabolite 3,4,5-tri-*O*-galloyl quinic acid methyl ester (QAME) was prepared by total synthesis and its potential effect on calcium oxalate monohydrate (COM) crystal binding to the surface of Madin-Darby Canine Kidney Cells type I (MDCK I) and crystal growth in a *Drosophila melanogaster* (fruit fly) Malpighian tubule model were studied. Membrane, cytosolic, and total α-enolase, Annexin A1 and HSP90 levels were evaluated by subcellular fractionation followed by Western blot. Immunofluorescence staining and confocal microscopy were also performed on cultured cells.

Results: Pretreatment of MDCK 1 cells with QAME for up to 6 h significantly diminished crystal-binding in a concentration-dependent manner. QAME significantly reduced surface expression of Annexin A1 by immunofluorescence microscopy, whereas the intracellular level increased. Western blot analysis confirmed these changes in membrane and cytosolic fractions of QAME-treated cells, whereas total cell QAME remained unchanged. The compound also significantly decreased the size and growth of COM crystals induced *ex vivo* in the *Drosophila melanogaster* Malpighian tubule model.

Conclusions: These data indicate that QAME decreased binding of COM crystals to cells by decreasing the surface expression of Annexin A1 via changing localization of Annexin A1 from the plasma membrane to the cytosol. Thus, QAME may be useful for the prevention and modulation of stone formation. Further pre-clinical and clinical studies should be done for the use of this compound in urolithiasis.

TH-PO1066

Establishing a Drosophila Model System to Study the Molecular Function of Human Genes Identified from Patients with Nephrolithiasis/ Nephrocalcinosis Fujian Zhang, Qiuxia Fan, Xizhen Hong, Xiaoming Feng, Fan Fan Hou. *Division of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China.*

Background: Nephrolithiasis/nephrocalcinosis is a frequent condition that affects 15% of adults, causing a huge burden on health care systems globally. Calcium oxalate stones account for more than 75% of renal stone diseases. In recent years, more than 30 genes have been identified as novel monogenic causes of kidney stone disease by using whole exome sequencing. However, the pathological function of the majority of these novel genes have not been validated *in vivo*.

Methods: First, we established the principal cell-specific gene knock-down method using UAS-RNAi/Gal4 system and examined its effect on calcium oxalate stone formation. Then, we investigated the effect of fly homology of 30 human genes identified from patients with kidney stone disease on calcium oxalate stone formation. We also examined the effect of calcium oxalate stone formation on lifespan. Furthermore, we examined the effect of these genes on the metabolism of oxalate in malpighian tubule cells.

Results: In this study, we found that knockdown of genes encoding v-ATPase protein complex in malpighian tubule principal cells led to the formation of large calcium oxalate stones. We also found that defects in 80% (24 of 30) fly homology of 30 known nephrocalcinosis/nephrolithiasis genes led to the accumulation of calcium oxalate stone in malpighian tubule. We also observed that the formation of large kidney stones significantly shortened the lifespan in adult flies. Furthermore, we found that RNAi knockdown of these nephrolithiasis genes led to the accumulation of oxalate in malpighian tubules, suggesting that these nephrolithiasis genes in principal cells may affect the secrection of oxalate from malpighian tubule.

Conclusions: In this study, we present the first *Drosophila* model system to study the molecular function of human genes identified from patients with nephrolithiasis/ nephrocalcinosis. These results suggest that *Drosophila* malpighian tubules could be a very powerful system to screen genes involved in the formation of calcium oxalate stone *in vivo*, and small molecules that could be used to dissolve calcium oxalate stones in patients with nephrolithiasis/nephrocalcinosis.

Funding: Government Support - Non-U.S.

TH-PO1067

Development of a Humanized Murine Model for Study of O. formigenes Intestinal Colonization Amanda Pebenito,[1] Lama Nazzal,[1] Menghan Liu,[1] Martin J. Blaser.[1,2] *[1]New York University School of Medicine, New York, NY; [2]New York Harbor V.A. Medical Center, New York, NY.*

Background: *Oxalobacter formigenes* (*O.f.*) are symbiotic bacteria in the human gut that degrade oxalate, a component of most kidney stones. Observational studies suggest that *O.f.* colonization reduces the risk for kidney stones. Given the importance of dietary oxalate and calcium levels, studies in mice are more practical than in humans; however, *O.f.* do not naturally colonize laboratory rodents. Our objective was to develop a humanized murine model to investigate the therapeutic potential of *O. formigenes* in its native microbiome.

Methods: To humanize mice, we transplanted feces from a pool of healthy human donors who were *O.f.*-negative (confirmed by PCR, qPCR, and oxalate degradation assay), supplemented with a human *O.f.* strain: OXCC13 (10^8 CFU/mL). The inoculum was introduced to C57BL/6J mice via esophageal gavage three times over six days. We compared two methods of humanization, transplanting inocula into mice that were (i) germ free; or (ii) treated with high-dose, broad-spectrum antibiotics (0.5g/L vancomycin, 1g/L ampicillin, 1g/L neomycin, 1g/L metronidazole in drinking water for 6 days) to suppress their native microbiome. As controls, one group received humanization with no pre-treatment and another received a sham gavage.

Results: Based on *oxc* qPCR and 16S rRNA sequencing, all humanized groups were stably colonized with *O.f.* through 8 weeks post-gavage, whereas mice that received sham gavage remained uncolonized ($p<0.001$). Humanization significantly changed microbial community structure as measured by unweighted UniFrac distances ($p<0.001$) and humanized germ-free and antibiotic-treated groups were highly similar in β-diversity. We also assessed humanization by the number of shared OTUs between treatment groups and donor inoculum over time. Both germ-free and antibiotic-treated mice had a significant increase in shared OTUs compared to sham ($p=0.024$, $p=0.036$). The number of shared OTUs was stable in each group through 8 weeks post-gavage without significant difference between germ-free and antibiotic-treated mice.

Conclusions: Our method of transplanting human feces and *O.f.* conferred a new microbial phenotype in mice that resembled a human microbiome and was stable over time. Antibiotic pre-treatment, a simpler alternative to germ-free mice, provided comparable results. This model may allow insights to *O.f.*'s role in preventing calcium oxalate stones.

Funding: Other NIH Support - U01 AI22285

TH-PO1068

Activation of the PKA Signaling Pathway Stimulates Oxalate Transport by Human Intestinal Caco2-BBE Cells Hatim A. Hassan, Donna L. Arvans, Altayeb Alshaikh, Mohamed Bashir. *University of Chicago, Chicago, IL.*

Background: Most kidney stones are composed of calcium oxalate, and small increases in urine oxalate affect the stone risk. The mammalian intestine plays a crucial role in oxalate homeostasis and we had recently reported that *oxalobacter*-derived factors stimulate oxalate transport by human intestinal Caco2-BBE (C2) cells through mechanisms including PKA activation. We therefore evaluated whether intestinal oxalate transport is directly regulated by activation of the PKA signaling pathway. To this end, PKA is activated with forskolin and IBMX (F/I). F/I significantly stimulated (4-fold) ^{14}C-oxalate transport by C2 cells (≥ 49% of which is mediated by the oxalate transporter SLC26A6 [A6]), an effect completely blocked by the PKA inhibitor H89, indicating that it is PKA-dependent. Utilizing selective pharmacological inhibitors in preliminary studies, we found that the PKC, ERK1/2, PI3K, P38, and Src kinases are not involved in the observed stimulation. Evaluating A6 total and surface (using brush border membrane vesicles) protein expression revealed that the observed stimulation is not due to changes in A6 total and surface protein expression. Assessing ^{14}C-oxalate transport as a function of increasing ^{14}C-oxalate concentration in the flux medium showed that the observed stimulation is due to F/I-induced increase (1.8-fold) in V_{max} (the maximal velocity) and reduction (2-fold) in K_m (the apparent affinity for oxalate) in preliminary studies. siRNA knockdown studies showed that significant components of the observed stimulation are mediated by the A6 and SLC26A2 (A2) oxalate transporters. Since F/I did not affect A6 total and surface protein expression, and in view of the reduced K_m (reflecting greater A6 affinity for oxalate upon PKA activation), it is likely possible that the observed stimulation is due to mechanisms including F/I-induced enhanced A6 transport activity resulting from an increase in the intrinsic activity of the preexisting A6 membrane transporters. We conclude that activation of the PKA signaling pathway significantly stimulates intestinal oxalate transport by C2 cells through mechanisms including increased intrinsic activity of preexisting A6 membrane transporters, as well as enhanced A2 transport activity (resulting from more A2 membrane transporters and/or increased intrinsic activity).

Methods:

Results:

Conclusions:

Funding: NIDDK Support, Other NIH Support - ARRA

TH-PO1069

P2X7 Receptor Stimulation Is Not Required for Oxalate Crystal-Induced Kidney Injury Hannah L. Luz,[3] Martin Reichel,[3] Kai-Uwe Eckardt,[1] Robert J. Unwin,[4] Frederick W. Tam,[2] Felix Knauf.[1] *[1]Dept of Nephrology and Medical Intensive Care, University Hospital Charite Berlin, Berlin, Germany; [2]Renal and Vascular Inflammation Section, Hammersmith Hospital, Imperial College Kidney and Transplant Institute, London, United Kingdom; [3]Dept of Nephrology and Hypertension, University of Erlangen-Nuremberg, Erlangen, Germany; [4]Centre for Nephrology, Royal Free Hospital, University College London Medical School, London, United Kingdom.*

Background: Oxalate crystal-induced renal inflammation is associated with progressive kidney failure due to activation of the NLRP3/CASP-1 inflammasome. It has been suggested previously that purinergic P2X7 receptor signaling is critical for crystal-induced inflammasome activation and kidney injury. Therefore, we investigated the role of the P2X7 receptor in response to crystal-induced cytokine release, inflammation, and kidney failure using *in vitro* and *in vivo* models.

Methods: Bone marrow-derived dendritic cells (BMDC) from C57BL/6 (wild-type), Casp1$^{-/-}$ and P2X7$^{-/-}$ mice were stimulated with calcium-oxalate crystals, monosodium urate crystals or ATP. Interleukin-1beta (IL-1ß) release was measured using ELISA and western blot analysis. For studies *in vivo*, age- and gender-matched wild-type, Casp1$^{-/-}$ and P2X7$^{-/-}$ mice were placed on a high oxalate diet to induce oxalate nephropathy. Kidney sections were analyzed for crystal deposition, tubular damage, and macrophage infiltration using F4/80 staining. Renal function was monitored by changes in plasma creatinine sampled retro-orbitally.

Results: Stimulation of BMDC from wild-type mice with oxalate crystals, urate crystals or ATP induced a robust release of IL-1ß. Treatment with the P2X7 inhibitor A740003 selectively abrogated ATP-induced, but not oxalate and urate crystal-induced IL-1ß release. In line with this finding, BMDC from P2X7$^{-/-}$ mice released reduced amounts of IL-1ß following stimulation with ATP, while oxalate and urate crystal-induced IL-1ß release was unaffected. In sharp contrast, BMDC from Casp1$^{-/-}$ mice exhibited reduced IL-1ß release following either of the three stimulants. In addition, while Casp1$^{-/-}$ mice were protected from crystal-induced renal failure, P2X7$^{-/-}$ mice demonstrated similar degrees of crystal deposition, tubular damage and inflammation when compared with WT mice. In line with these findings, increases in plasma creatinine were no different between WT and P2X7$^{-/-}$ mice.

Conclusions: In contrast to previous findings, our results indicate that P2X7 receptor is not required for crystal-induced CKD and it is unlikely to be a suitable therapeutic target for crystal-induced progressive kidney disease.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO1070

Structural Alteration of Urinary Tamm Horsfall Protein under Hyperoxaluric Conditions in Rats: Role of Calnexin, a Glycoprotein Chaperone Rishi Bhardwaj,[1] Ankita Bhardwaj,[1] Chanderdeep Tandon,[2] Devinder K. Dhawan,[1] Tanzeer Kaur.[1] *[1]Department of Biophysics, Panjab University, Chandigarh, India; [2]Amity Institute of Biotechnology, Amity University, Noida, India.*

Background: Tamm Horsfall Protein (THP), a urinary glycoprotein has been studied extensively for its involvement in the progression or regression of renal stone formation. Also, some studies have pointed out the abnormality in structural conformation and glycosylation as the root cause for the altered nature of THP. Calnexin, an ER resident chaperone, deals with the proper folding of glycoproteins in order to ensure their structural and functional entity. Therefore, study was carried out to decipher the role of calnexin and THP under hyperoxaluric environment in rat model mimicing renal stone condition, if any.

Methods: Rats were randomly divided into four groups: control, hyperoxaluric groups i.e. ethylene glycol alone, ethylene glycol with ammonium chlroide and hydroxy-l-proline, respectively. After hyperoxaluric induction, urine from the rats was collected for THP isolation. Rats were then sacrificed and kidneys were removed for further investigations. Methods employed to carry out the investigations included protein expression analysis via Western Blot and Immunohistochemistry and gene expression analysis by mRNA studies. Fourier Tranform Infrared Spectroscopy and hydrophobicity analysis of isolated THP were carried out in order to demonstrate any structural changes. Sialic acid content was estimated both in renal tissues and isolated THP.

Results: Studies revealed a significant increase in the expression of calnexin as well as THP in the renal tissue of all the hyperoxaluric groups at both protein and gene level. Moreover, absence of peak at 1462 cm^{-1} in the FTIR spectrum of THP was also demonstrated by the hyperoxaluric animals with significant alteration in the extent of hydrophobicity. Also, sialic acid content of renal tissues and isolated THP was found to be significantly lowered in the animals subjected to hyperoxaluric insult.

Conclusions: Above mentioned finding suggests a possiblity that alteration in the working environment of glycoprotein chaperone, calnexin can greatly modulate the role of THP by regulating its structural, conformational and functional aspects. This could pave a path towards the development of novel therapeutic approaches targeting chaperone activity as well as stress thus generated under renal stone ailment.

Funding: Government Support - Non-U.S.

TH-PO1071

ALLN-177, a Novel Oral Enzyme Therapy, Reduces Urinary Oxalate Excretion and Plasma Oxalate in Porcine Dietary Model of Severe Hyperoxaluria Danica Grujic,[1] Paulina Szczurek,[2] Nadia Mosiichuk,[2] Liudmyla Lozinska,[2] Stefan Pierzynowski.[2] *[1]Allena, Newton, MA; [2]Lund University, Lund, Sweden.*

Background: Hyperoxaluria (HO) is a chronic metabolic disorder and a major risk factor for nephrolithiasis and oxalate nephropathy. Secondary HO is caused by increased intestinal oxalate absorption from the diet due to enteric disorders or unexplained causes. There are no pharmacologic therapies approved for HO. ALLN-177 is an oral oxalate-specific enzyme therapy (Rx) that degrades oxalate in the gastrointestinal (GI) tract, decreasing oxalate absorption and thereby reducing urine oxalate. ALLN-177's ability to decrease oxalate burden as assessed by urine and plasma oxalate was tested in a porcine model of HO induced with high oxalate diet (HOD). Pigs were chosen due to physiological similarities to humans in GI and renal function.

Methods: To induce severe HO, 12 pigs were fed HOD for 7 days, followed by a 7-day treatment period continuing on HOD during which a daily oral dose of 22,500 units (u) ALLN-177 was given with feed 3x/day, 7,500 u/meal. HOD was a mix of a regular chow with 2.2 g/kg of Ca, 20% fat and frozen rhubarb (2:1 w/w). The primary endpoint was the within-pig difference in 24h urine oxalate (UOx) on HOD plus ALLN-177 compared to HOD alone, expressed as mg oxalate/g creatinine/24h (mg/gCr/d). Change in plasma oxalate was analyzed, and *Oxalobacter* colonization was assessed using PCR on fecal samples collected the last day of study treatment with primers designed to detect multiple species of Oxalobacter.

Results: Daily oral ALLN-177 with meals significantly reduced UOx by mean of 38.7 mg/gCr/d (39%) when compared to pre-treatment UOx on HOD (100.1±20.1 vs.: 61.5±14.3 mg/gCr/d on HOD+ALLN-177; $p<0.001$), returning UOx to the range recorded prior to HOD (61.3 ± 14.5 mg/gCr/d). In addition, mild hyperoxalemia while on HOD (plasma oxalate 13.9±0.9 umol/L) was significantly reduced with Rx to 9.9±2.3 umol/L, $p<0.001$. PCR of fecal samples was negative for Oxalobacter indicating absence of colonization. Therapy was well tolerated without adverse effects observed.

Conclusions: Orally administered ALLN-177 with meals was well tolerated and normalized UOx and plasma oxalate in a pig model of secondary HO.

Funding: Commercial Support - Allena Pharmaceuticals

TH-PO1072

Crystalluria and Monocyte Responses in Healthy Subjects Following a Single Dietary Oxalate Load Tanecia Mitchell, Mikita Patel, Vidhush Yarlagadda, Adam D. Ambrosetti, John Knight, Dean G. Assimos, Ross P. Holmes. *University of Alabama at Birmingham, Birmingham, AL.*

Background: Dietary oxalate has been suggested to play an important role in the risk and progression of stone formation in patients with calcium oxalate (CaOx) kidney stone disease. Oxalate has also been associated with crystal formation and inflammation in renal cells. We have previously determined that monocyte mitochondrial function is altered in patients with CaOx kidney stone disease. The purpose of this study was to determine whether dietary oxalate causes crystal formation in the urine and alters monocyte mitochondrial responses in the circulation of healthy subjects.

Methods: Twenty healthy subjects (29.1 ± 1.7 years old) with an average BMI of 25.5 ± 0.8 kg/m^2 were enrolled in the study. Participants consumed a low oxalate diet for 3 days prior to consuming a single high dietary oxalate load (spinach smoothie; 8 mmoles). Urine and peripheral blood was collected prior to the load and five hours later. Crystalluria was quantified by measuring oxalate levels using ion-chromatography mass spectrometry (IC/MS) and a Nanosight nanoparticle counter. Monocyte mitochondrial responses were assessed using the Seahorse XF96 Analyzer.

Results: A single high dietary oxalate load in healthy subjects significantly increased total urinary oxalate levels (pre-oxalate 2.36 ± 0.6 vs. post-oxalate 35.35 ± 4.8 mg; $p<0.0001$). In addition, urinary crystals were observed following the load and determined to be approximately 180 nm in diameter via the Nanosight nanoparticle counter. The effect of the high dietary oxalate load on monocyte mitochondrial responses was variable among participants. Eleven of the healthy subjects (55%) had decreased monocyte mitochondrial function; whereas, 3 (15%) were not affected by the load and 6 (30%) had increased mitochondrial function following the load compared to pre-oxalate samples.

Conclusions: These findings suggest that a single high dietary oxalate load causes crystal formation and changes in monocyte mitochondrial responses in healthy subjects. Understanding these mechanisms further may aid in designing dietary recommendations to mitigate crystal formation in patients with CaOx kidney stone disease.

Funding: NIDDK Support

TH-PO1073

Results of a Phase 2 RCT of ALLN-177 in Patients with Secondary Hyperoxaluria Sagar U. Nigwekar,[2] James E. Lingeman,[1] James A. Bolognese,[3] Annamaria T. Kausz.[4] *[1]IU Health Physicians Urology, Indianapolis, IN; [2]Massachusetts General Hospital, Boston, MA; [3]Cytel inc, Cambridge, MA; [4]Allena Pharmaceuticals, Newton, MA.*

Background: Hyperoxaluria (HOx) is a metabolic disorder associated with increased risk of nephrolithiasis and other sequelae including oxalate nephropathy. Secondary HOx is caused by excess oxalate absorption from diet due to enteric disorders (enteric HOx, EH) or is unexplained (idiopathic). There are no approved pharmacotherapies for HOx. To address this unmet need, ALLN-177 was developed as a novel oral formulation of crystalline oxalate decarboxylase, an oxalate-specific enzyme that degrades oxalate in the gastrointestinal (GI) tract, thereby reducing urine oxalate (UOx).

Methods: This double-blind, placebo-controlled RCT randomized adult subjects with secondary HOx and UOx ≥50 mg/d 1:1 to ALLN-177 (7500 u/meal) or placebo taken orally with meals 3x/day for 28 days. Multiple 24-hr urine collections were obtained to determine change in UOx, and the primary analysis used a mixed effects repeated measures analysis of variance model.

Results: 67 subjects were randomized and treated (32 ALLN-177, 35 placebo); 18 had EH. The primary endpoint (EP) 24-hr UOx change from baseline to Week (Wk) 4 showed a trend favoring ALLN-177 (-5.4 mg/d; see Table). Key secondary EP were statistically significant, and a substantially greater, clinically meaningful treatment effect was seen in post-hoc analyses in the predefined EH subset, including the time-weighted average (TWA) assessing the aggregate effect across the study duration. Adverse events were reported by 50% of ALLN-177 subjects vs. 63% placebo, and GI AEs were the most frequently reported, 16% ALLN-177 vs 40% placebo. No subjects discontinued ALLN-177 for any reason.

Conclusions: ALLN-177 was well-tolerated and has potential to meaningfully reduce UOx in patients with EH, who have a substantially increased risk for renal complications and thus an unmet need for an effective therapy to reduce UOx.

Funding: Commercial Support - Allena Pharmaceuticals

Endpoints	All Comparison vs. Placebo mean (90% CI)	Enteric Comparison vs. Placebo mean (90% CI)
Least squares mean change in UOx to Wk4 – mg/d	-5.4 (-14.05, 3.16)	-15.4 (-46.31, 15.62)
Change in TWA UOx (Wks1-4) – mg/d	-6.7 (-13.03, -0.30)	-23.1 (-43.95, -2.15)
% change in UOx to Wk4	-13.18% (-24.66, -1.71)	-35.3% (-70.19, -0.41)

TH-PO1074

SLC26A6 Is the Principal Oxalate Transporter in Macrophages Teresa R. Wagner,[1,2] Louise M. Tonner,[3,1] Zhirong Jiang,[1] Robert B. Thomson,[1] Felix Knauf,[4,1] Peter S. Aronson.[1] *[1]Yale School of Medicine, New Haven, CT; [2]University Tübingen, Tübingen, Germany; [3]FAU Erlangen, Erlangen, Germany; [4]University Hospital Charite, Berlin, Germany.*

Background: Macrophages are able to phagocytose calcium oxalate crystals, dissolve the crystals into their molecular components, and discharge accumulated oxalate. The goal of this study was to identify the transporter(s) responsible for oxalate transport across the plasma membrane of macrophages. We specifically evaluated the potential role of SLC26A6 because of its known activity as a Cl^--oxalate exchanger in kidney and intestine.

Methods: Oxalate transport in macrophages was assessed by using the human monocytic THP-1 cell line and bone marrow-derived macrophages from mice in ^{14}C-oxalate transport assays. Immunoblotting and qPCR were used to detect expression of SLC26A6. The functional role of SLC26A6 in mediating oxalate transport was studied by siRNA knockdown in THP-1 cells and isolation of macrophages from Slc26a6$^{-/-}$ mice. Macrophage viability was measured by WST-1 assays.

Results: DIDS-sensitive Cl^- gradient-stimulated oxalate transport was detected in both THP-1 cells and mouse macrophages, consistent with Cl^--oxalate exchange activity. Expression of SLC26A6 in THP-1 cells and mouse macrophages was detected by qPCR and immunoblotting. Partial knockdown of SLC26A6 expression by siRNA in THP-1 cells caused significant reduction of Cl^--oxalate exchange activity. There was complete loss of Cl^--oxalate exchange activity in macrophages isolated from Slc26a6$^{-/-}$ mice. Prolonged incubation with ^{14}C-oxalate revealed significantly higher accumulation of oxalate in macrophages from Slc26a6$^{-/-}$ mice compared to wild-type mice, indicating that SLC26A6 plays a major role in mediating oxalate efflux under physiological conditions. Moreover, incubation in high oxalate media was found to cause significantly greater loss of viability of macrophages from Slc26a6$^{-/-}$ mice compared to wild-type mice.

Conclusions: We conclude that SLC26A6 is the principal oxalate transporter in macrophages and likely plays a role in mediating oxalate efflux and reducing cellular oxalate toxicity.

Funding: NIDDK Support

TH-PO1075

Urinary Stone Events Are Predicted by Urinary Oxalate Excretion in Enteric Hyperoxaluria Matthew R. D'Costa,[1] Annamaria T. Kausz,[2] Felicity T. Enders,[1] Kristin C. Mara,[1] Ramila A. Mehta,[1] John C. Lieske.[1] *[1]Mayo Clinic, Rochester, MN; [2]Allena Pharmaceuticals, Newton, MA.*

Background: Elevated urinary oxalate (UOx) excretion is considered an important pathologic contributor towards the development of renal complications of enteric hyperoxaluria (EH). Since there are limited outcomes data we assessed the relationship between UOx and kidney stone events in an EH cohort.

Methods: In all, 589 patients from Olmsted County, MN were identified who had 24h urine supersaturation test results and a diagnosis of malabsorption or bariatric surgery (defined as EH). "Baseline" was the date of the first available 24h urine. Urologic procedures and emergency department visits with diagnostic codes consistent with kidney stones ≥1 month after baseline were considered a stone event. Multivariate logistic regression was performed to predict a first stone event >6 months after index date.

Results: Median follow-up time was 4.2 yrs. Mean age was 50.2 yrs and 74% were female. Baseline UOx was associated with a first stone event in models adjusted for baseline urine calcium and citrate (Table). For each 10 mg/24h increase in UOx, odds of a

stone event was 1.15 (p=0.012). Similarly, among EH patients with baseline urine oxalate of 60 mg/24h or greater, odds of a stone event after six months was 2.75 times greater than for EH patients whose baseline urine oxalate was below 40 mg/24h (p=0.030); for baseline urine oxalate between 40 and <60 mg/24h this odds ratio was 2.69 (p=0.008).

Conclusions: Baseline UOx predicts risk of future stone events in a cohort of EH patients. This risk persists even after adjustment for other urinary stone risk factors, including calcium and citrate excretion. Thus strategies to reduce UOx in EH patients should also reduce kidney stone risk.

Predictors of first stone event six months or more after baseline

Model 1*	Odds Ratio	Lower 95% CL	Upper 95% CL	p-value
Baseline UOxalate (per 10 mg/24h)	1.15	1.03	1.28	0.012
Baseline UCalcium (per 10 mg/24h)	0.99	0.96	1.04	0.71
Baseline UCitrate (per 10 mg/24h)	0.99	0.98	1.01	0.38
Model 2**				
Baseline UOxalate				0.045
Baseline UOxalate 40 - < 60 vs < 40	2.69	1.08	6.72	0.008
Basline UOxalate 60+ vs < 40	2.75	0.98	7.69	0.30
Baseline UCalcium (per 10 mg/24h)	0.98	0.94	1.03	0.53
Baseline UCitrate (per 10 mg/24h)	0.99	0.98	1.01	0.37

*AIC: 211.89; AUC: 0.645

**AIC: 213.30; AUC: 0.649

TH-PO1076

Relative Supersaturation of 24-Hour Urine and Likelihood of Kidney Stones Megan Prochaska,[4] Eric N. Taylor,[3] Pietro Manuel Ferraro,[2] Gary C. Curhan.[1] *[1]Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA; [2]Fondazione Policlinico Universitario A. Gemelli, Rome, Italy; [3]Maine Medical Center, Portland, ME; [4]Renal, Brigham and Women's Hospital, Boston, MA.*

Background: Relative supersaturations of calcium oxalate, calcium phosphate, and uric acid are used clinically in kidney stone prevention. However, the magnitudes of association between levels of relative supersaturation and stone risk require further quantification.

Methods: We performed a cross-sectional study using 24-hour urine collections from 2,505 stone formers and 1,267 controls from the Nurses' Health Study I (NHS I), Nurses' Health Study II (NHS II), and Health Professional Follow-up Study (HPFS) cohorts to quantify the association between level of calcium oxalate, calcium phosphate, and uric acid relative supersaturations and the likelihood of being a stone former.

Results: The relative risks (RR) for being a stone former were 5.85 (3.40 to 10.04) in NHS I and 6.38 (3.72 to 11.0) in NHS II for calcium oxalate relative supersaturation of 3.0 or greater compared with <1.0, and the RR was 6.95 (3.56 to 13.6) in HPFS for calcium oxalate relative supersaturation of 4.0 or greater compared with <1.0. The RR for being a stone former were 1.86 (0.92 to 3.71) for NHS I, 4.37 (2.68 to 7.10) for NHS II, and 3.59 (2.04 to 6.31) for HPFS for calcium phosphate relative supersaturation category of 4.0 or greater compared with <1.0. For uric acid relative supersaturation, the relative risks for being a stone former were 4.30 (2.34 to 7.90) for NHS I and 2.74 (1.71 to 4.40) for NHS II for the highest relative supersaturation category of 4.0 or greater compared with <1.0. In HPFS, uric acid relative supersaturation was not significantly associated with likelihood of stone formation.

Conclusions: The likelihood of being a stone former increases with higher calcium oxalate and calcium phosphate relative supersaturation levels in men and women, and higher relative supersaturation levels of uric acid in women. This increase begins at levels below the currently accepted 'normal' values.

Funding: NIDDK Support

TH-PO1077

Absolute Compared with Percentage Differences in 24-Hour Urine Oxalate and Likelihood of Being a Kidney Stone Former Gary C. Curhan,[1] Eric N. Taylor,[3] Pietro Manuel Ferraro.[2] *[1]Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, MA; [2]Fondazione Policlinico Universitario A. Gemelli, Rome, Italy; [3]Maine Medical Center, Portland, ME.*

Background: Higher absolute differences in 24-hour urine oxalate have been demonstrated to be associated with risk of kidney stone formation, but there are no published data about the magnitude and shape of the associations per 20% increase. For the latter, the change is dependent on the starting value, which has implications for intervention studies.

Methods: In three large cohort studies (Nurses' Health Study (NHS) I, NHS II and Health Professionals Follow-Up Study (HPFS)), we obtained 24-hr urine collections from individuals with and without a history of kidney stones. We calculated the likelihood of being a stone former per 10 mg/d and also per 20% higher 24-hour urine oxalate. For the former, logistic regression was used to calculate odds ratios of being a stone former. For the latter, we used a logarithmic approach such that the interpretation of the coefficient was the increase in risk per 20% higher urine oxalate (on a non-linear, continuous scale). The analyses adjusted simultaneously for age and all 24-hr urinary factors. The initial analysis used a single 24-hr urine (N=3775). A secondary analysis used the subset of participants who had completed two 24-hr urine collections (N=2426).

Results: Spline plots showed that the relation was not linear so the 'per 10 mg/d' results were biased. Using a non-linear model, the per 20% higher urine oxalate multivariable adjusted relative risk (MVRR) for the single urine collection was 1.15 (0.85, 1.57), p =0.37 for NHS I, 1.10 (0.81, 1.48), p=0.54 for NHS II, and 1.17 (1.00, 1.36), p =0.04 for HPFS. The per 20% higher urine oxalate MVRR for the average of two urine collections was 1.37 (1.23, 1.53), p <0.001 for NHS I, 1.22 (1.11, 1.33), p <0.001 for NHS II, and 1.17 (1.07, 1.29), p =0.001 for HPFS. When we pooled the estimates for the non-linear model, the MVRR using the single collection, was 1.15 (1.02, 1.31), p=0.02 and for the average of two collections was 1.25 (1.14, 1.36), p<0.001.

Conclusions: These data strongly support an independent non-linear association between higher 24-hr urine oxalate and likelihood of stone formation, which must be taken into consideration when designing oxalate reduction trials.

Funding: NIDDK Support, Commercial Support - Allena Pharmaceuticals

TH-PO1078

Determinants of Urine Chemistry in the Rare Kidney Stone Consortium (RKSC) Cystinuria Registry Frank Modersitzki,[2] David S. Goldfarb.[1,3] *[1]Nephrology Section, New York Harbor VAMC, New York, NY; [2]New York University School of Medicine, New York, AL; [3]Nephrology, NYU Langone Medical Center, New York, NY.*

Background: Urine chemistry is a determinant of stone formation in cystinuria. We previously showed that positive cystine capacity (CysCap), a measure of higher cystine solubility, led to fewer stone events. We queried the RKSC Cystinuria Registry to determine urinary and medication variables associated with positive (CysCap+), rather than negative (CysCap-) values.

Methods: This is the 1st report from the Cystinuria Registry, with data on 300 people with cystinuria (142 males, 158 females; age at enrollment 38 ± 17 years). 112 participants had 306 determinations of CysCap, measured by Litholink (Chicago, IL). In this cross-sectional study we compared variables associated with CysCap+ vs CysCap-.

Results: Lower urine Na (r=0.48; Fig 1A) and creatinine (r=0.62, not shown) were associated with lower 24h urine cystine (UC; P<0.001). Increasing CysCap values were seen with increasing urine pH (r_s=0.45, Fig 1B), volume (r_s=0.44) and decreasing UC (r_s=-0.44 Fig 1C; all P<0.001). Dividing Cyscap determinations into CysCap+ and CysCap- groups (Table), only higher urine volume and greater daily citrate doses were different. Relatively few participants were taking citrate or tiopronin.

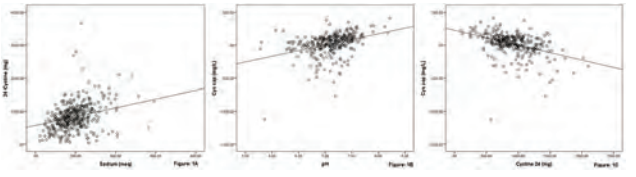
Conclusions: Higher urine pH and volume and lower UC were associated with less lithogenic urine; lower UC was seen with less Na and creatinine. Higher volume and citrate doses distinguished patients with less lithogenic urine. Many patients with cystinuria may be undertreated and would benefit from better dietary adherence.

Funding: NIDDK Support, Other NIH Support - NCATS

24h Urine Chemistry and Medications for CysCap- vs CysCap+

Values are mean (± SD)	CysCap-	CysCap+
24h Urine Volume (L): n:102,205	2.5 (0.9)	3.8 (1.6) P<0.001
Urine pH: n:100,199	6.96 (0.33)	7.18 (0.36)
24h Urine Sodium (meq): n:93,193	195.8 (79.4)	191.3 (101.0)
24h Urine Cystine (mg): n:101,206	1078.3 (324.7)	824.0 (269.9)
24h Urine Creatinine (mg): n:95,204	1700.8 (656.6)	1620.4 (683.1)
Citrate dose (meq/day): n:28,61	42.3 (22.4)	69.3 (32.9) P<0.05
Tiopronin dose (mg/day): n:22,41	963.6 (410.0)	1026.8 (502.5)

n was variable due to incomplete data



See results for figure legend

TH-PO1079

Urinary Cystine Excretion in an Adult Kidney Stone Cohort William E. Haley,[1] Felicity T. Enders,[1] Ramila A. Mehta,[3] David S. Goldfarb,[2] John C. Lieske.[1] *[1]Mayo Clinic, Jacksonville, FL; [2]New York Harbor VAMC, Hastings on Hudson, NY; [3]Mayo Clinic, Rochester, MN, Rochester, MN.*

Background: Cystinuria is caused by mutations in the amino acid transporter coded by *SLC3A1* and *SLC7A9*. Heterozygotes are not well defined or characterized. This study determined the distribution of urinary cystine (Ucys) in adult kidney stone formers and defined the prevalence of moderate to severe cystinuria.

Methods: Ucys, ornithine, lysine, and arginine (OLA) were analyzed by quantitative liquid chromatography – tandem mass spectrometry in all new adult patients in a tertiary stone clinic (2000 – 2014; N=1173; median follow up 1.4 yrs (IQR 2, 12)).

Results: Ucys excretion was abnormal in 15% (176/1173) of adult kidney stone formers. The majority were moderate, and 1% were severe (consistent with homozygous cystinuria). Patients with moderate Ucys differed from normal being more likely male with a greater percentage uric acid (UA) stones. Higher urinary levels of OAL were present with moderate and severe Ucys, suggesting the moderate group contains a subset of heterozygous cystinuria carriers. Non-cystine stones were present with moderate Ucys including a higher proportion UA stones compared to the normal Ucys group. Only a

minority with severe Ucys excretion had a family history of cystinuria. In univariate models, predictors of moderate Ucys (>115 µmol/24h) and severe cystinuria (>1000 µmol/24h) were higher UNa, sulfate and OAL (P<0.001). In multivariate models, Usulfate, Ulysine, Uornithine remained significant.

Conclusions: A high index of suspicion and low threshold for screening are necessary since cystinuria requires specialized treatment for best outcomes. Moderate cystinuria may confer UA stone risk and requires further study.

Funding: NIDDK Support, Other NIH Support - U54-KD083908 Rare Diseases Clinical Research Network, Private Foundation Support

Laboratory values and demographics (Median; Q1,Q3)

Cystine group (µmol/24h)	< 115	115-1000	> 1000
N	997	164	12
Male %	49	79	42
FH Cystine stones (n (%))	0	0	3 (25)
FH any kidney stone (n (%))	277 (46)	69 (44)	6 (50)
U Cys (µmol/24h)	51.0 (37, 71)	151.0 (128, 192)	2810 (2186, 3747)
U Ornithine (µmol/24h)	13 (9, 18)	32 (23, 44)	2262 (1625, 3050)
U Lysine (µmol/24h)	100 (57, 169)	457 (302, 747)	9955 (6595, 11551)
U Arginine (µmol/24h)	24 (14, 49)	42 (26, 88)	4110 (2328, 4971)
U Ca (mg/24h)	169 (108, 245)	239 (165, 325)	176 (145, 214)
Documented Cystine stone (n (%))	0	1 (0.01)	9 (75)
Documented CaOx stone (n (%))	261 (72)	50 (65)	0
Documented CaP stone (n (%))	67 (18)	14 (18)	0
Documented uric acid stone (n (%))	29 (8)	13 (17)	0

TH-PO1080

Interference of Tiopronin with Urine Cystine Measurement Is Assay-Dependent Callen D. Giesen,[1] Robin S. Chirackal,[1] Clayton Brady,[2] Nick Voskoboev,[1] Ryan M. Flanagan,[1] John C. Lieske.[1] *[1]Mayo Clinic, Rochester, MN; [2]None, Fairport, NY.*

Background: Patients with cystinuria often suffer frequent stone events, require multiple surgical interventions, and even develop CKD. When conservative measures fail (fluids and alkali), thiol drugs including tiopronin that reduce cystine to create tiopronin-cysteine dimers (and thus increase cystine solubility) are the next option. Urine cystine is often measured using a cyanide-nitroprusside colorimetric assay. Quantitation by liquid chromatography tandem mass spectrometry (LC-MSMS) is specific but not readily available. The present study compared urine cystine measurement by both methods to determine the relative effect of tiopronin.

Methods: Waste urine samples (n=16) from the Mayo Clinic Renal Testing Laboratory were spiked to expected therapeutic (0.1 mg/L) and super-therapeutic (1 mg/L) urine levels of tiopronin and a synthetically prepared tiopronin-cysteine complex. Neat and spiked samples were assayed by the cyanide-nitroprusside assay (modified for microplate settings) and by LC-MSMS.

Results: Tiopronin increased urinary cystine by the colorimetric assay but appropriately decreased it by LC-MSMS (Table). Tiopronin-cysteine complexes also increased values in the colorimetric assay, but had no effect on the LC-MSMS assay.

Conclusions: Tiopronin caused significant interference with the colorimetric assay, even when added as a tiopronin-cysteine complex. The underlying chemistry of the method, which effectively measures reduced cysteine monomers, is the likely reason. Conversely, LC-MSMS accurately detects a fall in intact cystine when tiopronin is added to urine, and is not affected by the resulting cysteine-tiopronin complexes. Thus patients on tiopronin should ideally be monitored using an MS-based assay of intact urinary cystine to ensure proper drug dosing and disease monitoring.

Spike Material	Level (mg/L)	Assay	Mean Difference (mg/L; %)		95%CI (mg/L; %)	
Tiopronin	0.1	Colorimetric	24	80%	0 to 48	26% to 135%
		LC-MSMS	-83	-32%	-154 to -12	-55% to -8%
	1	Colorimetric	323	906%	290 to 356	654% to 1158%
		LC-MSMS	-218	-96%	-350 to -86	-98% to -95%
Tiopronin + Cysteine	0.1	Colorimetric	28	62%	7 to 48	31% to 93%
		LC-MSMS	-34	8%	-87 to 19	-22% to 39%
	1	Colorimetric	234	645%	181 to 286	475% to 815%
		LC-MSMS	-19	11%	-61 to 22	-31% to 54%

TH-PO1081

ROKS II Nomogram: Predicting Future Symptomatic Stone Episodes Lisa E. Vaughan,[1] Felicity T. Enders,[1] John C. Lieske,[1] Terri J. Vrtiska,[1] Ramila A. Mehta,[2] Andrew D. Rule.[1] *[1]Mayo Clinic, Rochester, MN; [2]Mayo Clinic, Rochester, MN, Rochester, MN.*

Background: We previously developed a prediction tool for symptomatic recurrence after the first stone event (ROKS nomogram). A more generalizable prediction tool is needed that can also be applied in stone formers with more than one prior stone episode.

Methods: We performed a population-based cohort study of validated incident kidney stone formers in Olmsted County, Minnesota, from 1984-2012 and followed them for all subsequent episodes through 2017. Predictors for symptomatic recurrence were identified from clinical characteristics at each stone episode. A nomogram was developed from a multivariable cox proportional hazards model using robust standard errors.

Results: There were 3,364 validated first-time kidney stone formers with 4,951 stone episodes. The stone recurrence rates per 100 person-years were 3 after the first stone episode, 7 after the second episode, 12 after the third episode, and 18 after the fourth episode or higher. A parsimonious model included the following risk factors for recurrence: younger age per 10 years (HR=0.88, p<0.001), male sex (HR=1.25, p=0.002), higher body mass index per 5 kg/m² (HR=1.07, p=0.004), family history of stones (HR=1.36, p<0.001), pregnancy during last episode (HR=1.82, p=0.005), asymptomatic stone prior to the first validated episode (HR=1.35, p=0.008), suspected stone episode prior to the first validated episode (HR=1.75, p<0.001), brushite, struvite or uric acid stone ever (HR=1.24, p=0.16), no known calcium oxalate monohydrate stone ever (HR=0.89, p=0.08), pelvic or lower pole stone (HR=1.39, p<0.001), no ureterovesicular junction stone on imaging (HR=0.84, p=0.01), number of kidney stones on imaging (0 ref.; 1 HR=1.30, p<0.001; 2+ HR=2.03, p<0.001), and diameter of largest kidney stone on imaging (<3 mm or none ref.; 3-6 mm HR=1.25, p=0.021, >6 mm HR=0.96, p=0.79). The risk of recurrence also increases with number of past episodes (p<0.001). The final model had a C-index of 0.653; with bootstrapping, the C-index corrected for optimism was 0.643.

Conclusions: The ROKS II nomogram was developed to aid physicians in identifying patients at high versus low risk for symptomatic stone recurrence and is more generalizable than the current ROKS nomogram. With an estimate of the risk of recurrence, physicians and patients can make informed decisions on dietary and medical interventions.

Funding: NIDDK Support

TH-PO1082

Recurrent but Not First-Time Symptomatic Kidney Stone Formers Are at Higher Risk for ESRD and Death Tsering Dhondup, Wonngarm Kittanamongkolchai, Ramila A. Mehta, LaTonya J. Hickson, Felicity T. Enders, John C. Lieske, Andrew D. Rule. *Mayo Clinic, Rochester, MN.*

Background: Prior studies reporting an increased risk of ESRD in kidney stone formers (SFs) are limited by the use of codes, lack of diagnosis validation, and short follow-up time. In this study we determined the incidence of ESRD and mortality in a cohort of carefully characterized SFs.

Methods: Coded SFs (ICD-9: 592, 594 & 274.11) in Olmsted County, Minnesota between1984-2012 were categorized after chart review into mutually exclusive groups: incident (first-time) symptomatic SF, recurrent symptomatic SF (first stone event prior to study period), asymptomatic SF, bladder SF, and miscoded (not a SF). Age and sex-matched controls were randomly sampled from the Olmsted County population (4:1 ratio). Cox proportional hazards models were used to determine the risk of ESRD (identified using the United States Renal Data System) and mortality (National Death Index) after adjustment for baseline comorbidities.

Results: The cohort of 7036 SFs and 28,136 controls (mean age 48 years and 58% male) had 94 and 183 ESRD events and had 1139 and 3923 deaths, respectively, over a mean follow-up of 9.4 years. After adjusting for baseline CKD, diabetes mellitus, hypertension, dyslipidemia, obesity and gout, recurrent SFs but not incident SFs were at higher risk of ESRD and mortality (Table). Asymptomatic SFs were also at higher risk of ESRD and mortality, while bladder SF were at higher risk of mortality and miscoded SF were at higher risk of ESRD.

Conclusions: The risk of ESRD and mortality may be higher in recurrent than incident symptomatic SFs due to more substantial renal injury from more severe stone disease. Thus efforts to reduce kidney stone recurrence may have beneficial impact on ESRD and mortality risk. Other disease that leads to kidney imaging (incidental detection of asymptomatic stones) or is miscoded as kidney stones can bias the risk of ESRD or mortality in code based studies that lack chart validation.

Funding: NIDDK Support

Risk of ESRD and death by SF groups compared to controls : HR with (95% CI)

Outcome	Incident SF	Recurrent SF	Asymptomatic SF	Miscoded	Bladder SF
ESRD	1.38 (0.87, 2.16)	3.32 (1.55, 6.99)	3.79 (1.66, 8.68)	6.52 (2.46, 19.08)	1.26 (0.28, 4.11)
Death	1.07 (0.96, 1.18)	1.21 (1.03, 1.41)	1.41 (1.18, 1.67)	1.07 (0.87, 1.3)	1.37 (1.11, 1.68)

TH-PO1083

Lower Than Normal Urine pH in Calcium Oxalate (CaOx) Stone Forming (SF) Women Is Due to Reduced Gastrointestinal (GI) Alkali Absorption Kristin J. Bergsland, Fredric L. Coe, Elaine M. Worcester. *University of Chicago, Chicago, IL.*

Background: We have previously found that in normal (N) men (M) and women (W) fed identical diets in a General Clinical Research Center (GCRC), the urine pH (UpH) of W exceeds that of M due to greater absorption of alkali from the GI tract. Since calcium (Ca) SF is often accompanied by altered UpH that reduces the solubility of SF salts in urine, we have similarly studied idiopathic hypercalciuric CaOx and CaP stone formers in the GCRC to identify whether differences in UpH regulation are associated with stone type within sex and if so, what components of acid-base metabolism are responsible for the differences.

Methods: We measured UpH and determinants of acid-base regulation in 25 N (13 M), 17 CaOx SF (11 M) and 15 CaP SF (8 M). We collected 15 urines and 20 blood samples over a 15 hour day in the GCRC; diet was fixed. GI anion excretion (GIAE) = [(Na + K + Ca+ Mg) - (Cl + P)] in urine (mEq/hr).

Results: W CaOx SF had lower UpH than other W during the fed period (Table). Lower UpH in CaOx W was accompanied by higher net acid excretion (NAE) and urine titratable acid (TA), and reduced urine CO_2 excretion and GIAE. In M CaP SF, GIAE was higher vs M N. Sulfate excretion (Sul) was reduced in all SF vs N.

Conclusions: The pathophysiology of Ca stone formation differs by sex. In the presence of hypercalciuria, normally high GIAE and UpH of W predisposes to CaP SF while higher TA and NAE and lower UpH in M favors CaOx SF. Exceptions are M CaP, with increased GIAE that correlates with a trend to higher UpH, and W CaOx, with lower than normal GIAE and higher NAE which translates into reduced urine CO_2 and lower UpH. These differences may have clinical implications for use of stone therapies that affect UpH.

Funding: NIDDK Support

ANOVA by Sex and Subject Type

	WOMEN			MEN		
	NONE	CAOX	CAP	NONE	CAOX	CAP
UpH	6.49 ± 0.05	6.12 ± 0.07*	6.58 ± 0.06	6.19 ± 0.05#	6.29 ± 0.05	6.39 ± 0.06
U CO2	1.19 ± 0.09	0.49 ± 0.13*	1.10 ± 0.12	0.89 ± 0.09	0.68 ± 0.10	1.14 ± 0.11†
U TA	0.42 ± 0.03	0.59 ± 0.04*	0.34 ± 0.04	0.64 ± 0.03#	0.61 ± 0.03	0.56 ± 0.04#
U NH4	1.07 ± 0.05	1.18 ± 0.07	0.97 ± 0.06	1.21 ± 0.05	1.17 ± 0.05	1.26 ± 0.06#
U NAE	0.30 ± 0.13	1.29 ± 0.18*	0.22 ± 0.17	0.96 ± 0.13#	1.10 ± 0.14	0.68 ± 0.16
U SUL	1.64 ± 0.05*	1.36 ± 0.07	1.22 ± 0.07	1.77 ± 0.05*	1.55 ± 0.06	1.56 ± 0.06#
GIAE	3.11 ± 0.18	1.50 ± 0.25*	2.95 ± 0.23	1.87 ± 0.17#	1.99 ± 0.19	2.77 ± 0.22$

Mean ± SE. *p<0.01 vs other subject types, same sex; #p<0.05 vs WOMEN, same subject type; †p<0.05 vs CAOX, same sex; $p<0.05 vs NONE, same sex. Excretions are in mmol/hr and adjusted for body surface area.

TH-PO1084

An Association between the Genetic Hypercalciuric Stone-Forming Rat and the Gut Microbiome Joshua M. Stern,[2] Nancy S. Krieger,[3] Matthew K. Abramowitz,[1] David A. Bushinsky.[4] *[1]Albert Einstein College of Medicine, New York, NY; [2]Albert Einstein College of Medicine, Bronx, NY; [3]Univ. of Rochester, Rochester, NY; [4]University of Rochester Medical Center, Rochester, NY.*

Background: The Genetic Hypercalciuric Stone-forming (GHS) rat has been an established model of kidney stone disease. The rats have been selectively inbred for hypercalciuria for over 100 generations, originally from standard Sprague Dawley (SD) rats. All GHS rats make stones by 18 weeks of age. The model has been extensively studied and phenotyped. However, no study has previously examined differences in the rat's microbiome. In this study we characterize the gut microbiome (GMB) from GHS rats compared to age and sex matched SD controls.

Methods: 4 male GHS rats and 2 male SD rats were housed separately and fed similar diets of rat chow in the same animal room. Fresh fecal pellets were collected at one single time point, stored at -80ºC and sent to the Albert Einstein Department of Urology where the pellets were prepared for analysis by DNA extraction, amplification of the 16S rRNA V4 region using barcoded primers on an Illumina platform. QIIME was used for analyses.

Results: 16S rRNA analysis between the 2 groups found significant differences. *Bacteriodes genus* was 39% more abundant in the GHS. *Firmicutes Phylum* was 17.2% more abundant in the SD rats as compared to 5.7% in the GHS rats, a 67% increase in the SD rats. The alpha diversity of the GHS rats' GMB cluster well and are widely separated from SD. The GHS rats have a lower Shannon score diversity. *Roseburia genus*, known to contain species that produce beneficial short chain fatty acids was 70% more abundant in the SD group. Similarly *Faecalibacterium genus*, with known butyrate producers, was increased 35% in the SD rats.

Conclusions: We, for the first time, demonstrate that age and sex matched GHS rats carry a GMB that is distinct from its SD ancestors. Of particular interest is the decreased bacterial diversity seen in these rats at just 12 weeks of age. *Bacteroides genera* is significantly up-regulated in the GHS rats and similar to findings seen in human stone formers (Stern et al., Urolithiasis 44:399, 2016). Future studies to determine causality and directionality of this effect are warranted.

Funding: Private Foundation Support

TH-PO1085

Tubular Crosstalk in Renal Calcium Handling Olivier Bonny,[1,2] Fanny Durussel,[1] Suresh Krishna Ramakrishnan.[1] *[1]Dpt Pharmacology and Toxicology, University of Lausanne, Lausanne, Switzerland; [2]Service of Nephrology, Lausanne University Hospital, Lausanne, Switzerland.*

Background: Calciuria is one of the main risk factors for kidney stone and the understanding of its regulation is essential for stone prevention. In the kidney, calcium tubular reabsorption is complex, starting in the proximal tubule (PT) with paracellular reabsorption, continuing in the ascending limb (TAL) with transepithelial paracellular transport through the claudin system and regulation by the basolateral calcium sensing receptor and ending by transcellular calcium reabsorption in the distal convoluted tubule (DCT). When calcium reabsorption is challenged in one specific part of the nephron, reaction in other segments of the nephron has been observed, but not studied systematically. We hypothesized that challenge in one segment is affecting calcium reabsorption in other segments through tubular crosstalk.

Methods: We used mice and challenged renal calcium reabsorption by furosemide (acutely at 4 hours and chronically at 7 days) and thiazide injections or by feeding them with cinacalcet. We microdissected tubular segments and studied the most relevant genes and proteins involved in calcium transport in each segment.

Results: We found that upon acute challenge with furosemide, Nhe3 was downregulated in the proximal tubule, while Cldn16 and 19 were upregulated in the TAL and Trpv5, Ncx1, Pmca4 and calbindin 28 and 9 were upregulated in the DCT. On chronic furosemide treatment, we observed a shift toward increased proximal and TAL calcium reabsorption, with higher levels of Nhe3, Nkcc2 and CaSR in addition to high levels of Cldn 16 and 19. Interestingly, chronic cinacalcet treatment was increasing NHE3 and CaSR expression. In the DCT, NCC was upregulated, but Trpv5 and other more distal genes involved in calcium transport were not changed. Thiazide challenge did not modify expression of the tested genes acutely (4 hours), but chronically was increasing NHE3 (protein level) and some distal genes.

Conclusions: Altogether, this data show that tubular crosstalk is part of the intrarenal regulation of calciuria. The precise mechanisms leading to tubular adaptation to a segment-specific calcium reabsorption challenge still need further studies.

Funding: Government Support - Non-U.S.

TH-PO1086

Differential Expression of miRNAs from Urinary Extracellular Vesicles Identify Pathogenesis of Kidney Stones and Randall's Plaque in Humans Suchitra Sutthimethakorn,[1] Xiangling Wang,[2] Robin S. Chirackal,[1] Felicity T. Enders,[2] Andrew D. Rule,[2] Pritha Chanana,[2] Muthuvel Jayachandran,[2] John C. Lieske.[2] *[1]Mayo Clinic, Rochester, MN; [2]Mayo Clinic, Rochester, MN.*

Background: Kidney stone disease is a complex disease associating with various types of kidney cells. Activation of the kidney cells could influence the sorting of specific cargo, especially miRNAs into urinary extracellular vesicles (EVs) as well as the release of these EVs into urine, linking the patho- and physiological process of the kidney. However, the roles of miRNAs within urinary EVs of kidney stone disease remain largely unknown. The current study thus aimed to extensively define the changes of miRNAs in urinary EVs between varying degrees of stone formers and controls.

Methods: Bio-banked cells-free urine samples from kidney stone formers with low plaque (LP, n=4; < 5% papillary surface area coverage) and high plaque (HP, n=4; > 5% papillary surface area coverage), first-time stone formers (SF, n=4), and non-stone forming controls (n=4) were used in this study. Urinary EVs-derived miRNAs were extracted and analyzed by XRNA Exosome RNA-Seq Library Kit. Differentially expressed miRNAs (p-value < 0.05) between first-time stone formers and controls, and between HP and LP stone formers were validated by RT-qPCR method and submitted to DIANA-miRPath Bioinformatics tool for biological pathway prediction.

Results: Exosome RNA-Seq analysis revealed a total of 17 and 10 differentially expressed miRNAs between SF and controls, and between LP and HP stone formers, respectively. Pathway analysis demonstrated the involvement of these altered miRNAs in various cellular processes and signaling pathways such as endocytosis, TGF-beta signaling pathway, MAPK signaling pathway and focal adhesion. Interestingly, several altered miRNAs have been related to numerous kidney-related diseases, including kidney fibrosis, chronic kidney disease, and acute kidney injury. Thus far, RT-qPCR data confirmed the increased expression level of hsa-miR-1299 in the SF group, as compared to the controls.

Conclusions: These findings revealed the changes in miRNAs profile within urinary EVs and their possible roles in kidney stone pathogenesis as well as the formation of Randall's plaque. Further investigations of these potential miRNAs may lead to better understanding of pathogenic mechanism underlying calcium-based kidney stone disease.

TH-PO1087

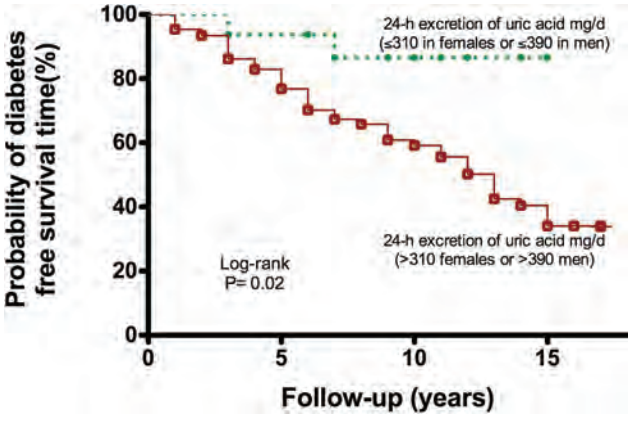
Association of Hyperuricemia and Higher Uricosuria and the Development of Prediabetes or Diabetes in Kidney Stone Formers Bernardo A. Martinez-Guerra,[1] Juan Carlos Ramirez-Sandoval,[1] María F. Castilla-Peón,[2] Alfonso Gulias-Herrero,[1] Cynthia Garcia,[1] Ricardo Correa-Rotter.[1] *[1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [2]Hospital Infantil de Mexico Federico Gomez, Ciudad de México, Mexico.*

Background: Nephrolithiasis (NL) isassociated withinsulin resistance and may be a sentinel event before the diagnosis of diabetes mellitus (DM).

Methods: Demographics, associated medical conditions, laboratory data, including 24-h urine analysis, and treatment were obtained at least annually from records. We excluded from analysis KSF who were taking the following drugs that alter uric acid serum levels and excretion (thiazide diuretics, losartan, allopurinol).

Results: From 266 patients of the NL clinic, 118 non-diabetic KSF that fulfilled inclusion criteria were included, 73 (62%) were female, mean age 44±13 yrs, median baseline BMI 26 kg/m^2(IQR 23-31) and 12 (10%) were hypertensive. Median follow-up was 8.6 years (range 1.4-19.3). During follow-up, preDMwas diagnosed in 27(23%) and DM in 24 (20%). Median time to DM diagnosis was 6.4 yrs (IQR 3.8-13). Bivariate analysis showed thatage, serum uric acid (≥5.5 in females and ≥7 mg/dL in males), and total excretion of uric acid (>310 mg/day in females and >390 mg/day in males in 3 or more 24-h urine analysis; see figure)were risk factors for development of preDMor DM. Other variables such as baseline BMI, eGFR, triglycerides, cholesterol, blood pressure or other 24-h urine profile determinations were not associated with the occurrence of the event. After adjusting for age, sex, and hyperuricemia (HR:2.2;95%CI:1.3-3.8), higher uric acid excretion (HR:8.7; 95%CI:1.2-65) was a strongprognostic factor for DM developmentin KSF patients.

Conclusions: The present study is the largest known report exploring the effect of 24-h urine analysis characteristics of KSDand the risk of development preDM andDM. Older age and hyperuricemia, predicted development of preDM and DMyet a higher 24-h urine uricosuriawas thestrongest predictor for this outcome even several years before the diagnosis of preDM or DM.



TH-PO1088

Epidemiological Insight into Nephrolithiasis in Pakistan Ali Amar,[1,2] Amar J. Majmundar,[1] Ayesha Afzal,[2] Mumtaz Ahmad,[3] Shagufta Khaliq,[2] Friedhelm Hildebrandt.[1] *[1]Medicine, Div Nephrology, Boston Children's Hospital, Boston, MA; [2]University of Health Sciences, Lahore, Pakistan; [3]Fatima Jinnah Medical University & Sir Ganga Ram Hospital, Lahore, Pakistan.*

Background: Nephrolithiasis (NL) affects 1 in 11 individuals worldwide and causes high patient morbidity, frequent hospitalizations and surgical interventions. Pakistan resides within the Afro-Asian stone belt with a high NL prevalence of 12-15% (Rizvi *BJU Int* 89: S62, 2002). We have shown that a genetic cause in NL can be identified in about 11% of adult and 16-20% of pediatric stone formers (Halbritter *JASN* 26: 543, 2015; Braun *cJASN* 11: 664, 2016).

Methods: From 07/2014 to 12/2016, we recruited 242 families with NL, based on ultrasound finding of at least one renal stone, from 5 different tertiary care hospitals in Punjab, Pakistan, administrating a clinical survey that characterized age of onset, stone recurrence, and family history confirmed by their urologist and/or medical records. In 33 NL families, additional recruitments were made who had an average of 4 family members with at least one stone (range 1-28) and pedigrees were constructed.

Results: Our NL cohort consisted of 438 individuals (348 affected). The median age of onset of probands was 28 years (1-76 years, n = 123). 26% (32/123) presented at <18 years of age. There were 148 male and 94 female stone formers (M:F is 1.57:1). 50% (110/220) had >1 stone episode in their lifetime. Multiple stones at presentation were observed in 60.4% (134/222) of subjects. The family history of NL was positive in 48.6% (108/222) of cases. 50% (79/158) of subjects were born of consanguineous unions. 78.8% (26/33) of large multigenerational families for whom pedigrees were generated, exhibited multiple affected individuals in each generation, suggesting a strong genetic pattern of inheritance that is dominant or recessive with multiple consanguinity.

Conclusions: Here we describe a large cohort of Pakistani NL subjects with a high frequency of stone recurrence and familial cases. Pedigree analysis suggests a genetic causation. Whole exome sequencing to identify causative mutations in known or novel NL genes is underway.

Funding: Government Support - Non-U.S.

TH-PO1089

Increasing Prevalence of Nephrolithiasis Correlating with an Increase in BMI – A Population Based Study of Israeli Children Hadas Alfandary,[4,5] Orly Haskin,[4] Miriam Davidovits,[3] Oren Pleniceanu,[2] Adi Leiba,[1] Amit Dagan.[4,5] *[1]None, Ramat Gan, Israel; [2]Pediatric stem cell research institute, Sheba medical center, Petach Tqiwa, Israel; [3]Schneider Children's Medical Center of Israel, Petah Tiqva, Israel; [4]Schneider Children's medical center of Israel, Petah Tiqva, Israel; [5]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.*

Background: Studies of adult and pediatric populations have shown a significant rise in nephrolithiasis incidence in recent decades. In adults, a clear association has been demonstrated between increasing BMI and a higher risk of kidney stone formation. Evidence is less conclusive for the pediatric population. This study examined the epidemiology of nephrolithiasis in the Israeli pediatric population during a 30-year period

Methods: We accessed data from the compulsory medical evaluations of 17 year olds in Israel, prior to enlistment for military service during 1980-2013. Candidates for the army with a history of stone disease were compared to those without such history.

Results: Of 1,908,893 candidates, 1691 reported a history of nephrolithiasis before the age of 18 years; this yields an average incidence rate of 88.6 in 100.000. During 1980-1995 the average reported incidence of nephrolithiasis was 69 cases per 100,000 candidates. From 1995, reported incidence increased by an average of 6% per year, and reached 120 per 100,000 during 2010-2012. This increased incidence was observed for both males and females, but was more prominent among males. The mean BMI of stone formers was higher than that of the control group (22.7±3.5 vs. 22.1±3.9 kg/m2 p<0.001). The odds ratio for nephrolithiasis in candidates with BMI 25-30 kg/m2 was 1.3 (1.1-1.5) and for BMI>30 kg/m2, it reached 1.7 (1.4-2.1) compared to the control group (table 1). The trend of increasing BMI among male candidates during 1995 to 2012 parallels the trend of increasing reports of nephrolithiasis during these years, r=0.71 p<0.01

Conclusions: In conclusion, our study is the largest population based epidemiological analysis on nephrolithiasis in children. We were able to show that in the last 20 years the incidence of nephrolithiasis in children has risen significantly. In our study population males had higher rates of nephrolithiasis than did females, with no change in the difference between the genders in the last 20 years. We report a correlation between increasing BMI and increasing prevalence of nephrolithiasis in children. More prospective observational and intervention studies are needed to examine a pathophysiological explanation linking high BMI with nephrolithiasis

TH-PO1090

Inflammatory Markers in Pediatric Nephrolithiasis Kirsten Kusumi,[1,4] John Ketz,[2,3] Andrew L. Schwaderer.[2,3] *[1]Akron Children's Hospital, Akron, OH; [2]Nationwide Children's Hospital, Columbus, OH; [3]The Ohio State University, Westerville, OH; [4]Northeastern medical university, Rootstown, OH.*

Background: Kidney stones associate with higher rates of heart attack/stroke and low bone mineral density/fractures. The mechanism of this association remains unknown; inflammation may be key. Our objective is to determine if pediatric stone formers have inflammation.

Methods: Urine was collected from 11 stone formers and 16 controls; 12-17 years old with radiographic evidence of stones. Exclusion criteria: metabolic acidosis, CKD II or >, immobilization, hyperlipidemia, hypertension, diabetes, inflammatory bowel disease, rheumatoid arthritis, or lupus. Urine was tested via a Mesoscale V-Plex Human Cytokine panel inflammation array. Levels were normalized to creatinine to control for concentration. Statistics by paired T-Test; p value <0.05 was significant.

Results: Five inflammatory markers were significantly increased in stone children: Il-13, Il-1B, MIP-1B, Il-12/Il-23p40 and Il-16.

Conclusions: This is the first evidence of inflammation in pediatric stone formers; this population is free of confounding diseases that are common in adults. Identification of inflammation in pediatric stone formers may be the first step in delineating the molecular mechanisms linking stone, bone and cardiovascular disease.

Table 1

Inflammatory Marker	Control (pg/mg)	Stone former (pg/mg)	P value
IL-12/IL-23P40	0.167	0.403	0.017
IFNY	0	0	0.407
Il-10	0	0	0.999
Il-12p70	0	0	0.056
Il-13	0	0.08	0.003
Il-1B	0.011	0.294	0.01
Il-2	0	0	0.937
Il-4	0	0	0.067
Il-6	0.255	0.366	0.394
Il-8	17.4	50.15	0.162
TNFA	0	0	0.157
Eotaxin	5.158	8.273	0.107
Eotaxin-3	1.045	0.886	0.514
IP-10	7.888	8.932	0.544
MCP-4	9.593	14.22	0.568
MCP-1	95.37	119.7	0.301
MCD	1.519	1.957	0.438
MIP-1A	0	0	0.371
MIP-1B	2.582	5.829	0.0004
GM-CSF	0.047	0.114	0.441
TARC	0	0.004	0.396
Il-15	0.241	0.134	0.394
Il-16	0	0.2863	0.013
Il-17	0	0	0.183
Il-1A	1.587	4.549	0.365
IL-7	0.49	0.506	0.862
TNFB	0	0	0.688
VEGFA	152.5	171.5	0.08
IL-5	none detected	none detected	NA

MW: Mann–Whitney test

TH-PO1091

Hidden Sources of Sodium: The Role of Water Purification and Hypernatriuria in Kidney Stone Formation Adedeji O. Sodeinde, Samir A. Brahmbhatt, Juan C. Calle. *Cleveland Clinic Foundation, Cleveland, Ohio, Beachwood, OH.*

Background: One of the mainstays of dietary modification for prevention of calcium-containing stone formation is salt intake restriction. This is usually achieved by reducing dietary intake of high salt containing foods like smoked, cured or salted foods and canned goods. However the purity of water consumed is usually not addressed. The case presented here highlights the difference of well water, which is purified by reverse osmosis, compared to bottled water, which is purified by distillation, and their effect on urinary sodium levels.

Methods: A 49 year old male with a history that is significant for recurrent urinary tract infections due to uric acid and calcium oxalate stones was being followed up in the outpatient setting for stone prevention. Initial 24-hour urine studies were positive for

hypercalcemia, hyperphosphatemia and hypernatruria, all while consuming well water purified by reverse osmosis. He was advised to drink and cook with bottled water which is purified by distillation. After the change, his initial urine sodium of 305 mmol/d decreased to 208 mmol/d. As a confirmation, it increased to 241 mmol/d when he asked to use well water again and back down to 177 mmol/d once back on bottled water.

Results:

Conclusions: As sodium restriction is one of the main therapies in preventing calcium-containing stones, there should be increased awareness about the routes with which it can be consumed. Reverse osmosis, though an efficient and economical method of water purification, may leave more sodium content in the water than distillation which is the purest form of water purification. If hypernatriuria remains an issue in a patient with persistent stone formation and well controlled dietary sodium ingestion, there might be benefits to assessing the water consumed and its purification process.

TH-PO1092

Longitudinal Assessment of Health-Related Quality of Life (HRQoL) in Rare Kidney Stone Formers (RKSF) Frank Modersitzki,[3,2] Mary I. McIntosh,[1] David S. Goldfarb.[2] *[1]Mayo Clinic, Rochester, MN; [2]New York Harbor VAMC, New York, NY; [3]New York University School of Medicine, New York, AL. Group/Team: Rare Kidney Stone Consortium.*

Background: The assessment of HRQoL in RKSF is important for following disease course and evaluating treatment. Previously, using a non-disease specific instrument we showed that RKSF present differently, with the worst domain scores in cystinuria. These are the first follow-up data based on summary scores for adults in a cross-sectional comparison.

Methods: RKSF were enrolled from 4 RKSC registries: primary hyperoxaluria, cystinuria, Dent disease and APRTd. HRQoL is measured with the generic non-disease specific SF-36v2. Results are norm-based scores (NBS) based on US Standard Population (Domain score mean = 50). Group means < 47 indicate the presence of impaired functioning in associated dimension.

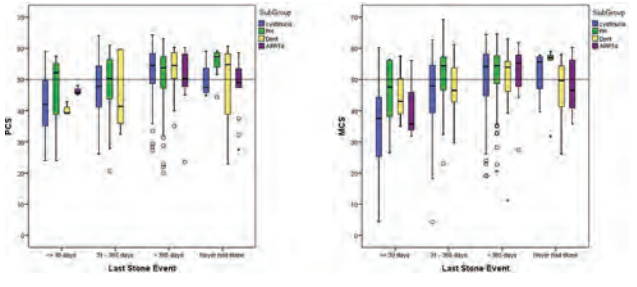
Results: We scored 545 surveys of the adult population at different time points, adjusted for the last stone event and compared the Physical and Mental Component Scores (PCS and MCS). We found the lowest PCS in Dent, and the highest in PH. The lowest MCS was found in cystinuria, the highest was found in PH. Low PCS indicate restrictions in self-care, physical, social and role activities; bodily pain, tiredness and poor rated health. Low MCS are associated with frequent psychological distress, social and role disability due to emotional problems, and poor rated health. Participants with cystinuria reported more stone events with related procedures than other RKSF (X^2 (9) 23.375, p=.005).

Conclusions: HRQoL in RKSF is influenced by stone events and can be assessed with a non-disease specific SF-36v2. Adjusting for time between the survey and last event allows for the interpretation of more meaningful HRQoL profiles. The time from the last stone event and related procedures affect HRQOL in RKSF significantly.

Funding: NIDDK Support

		Stone Event Groups			
		< 30 days	31 - 365 days	> 366 days	never
Cystinuria	PCS	42 (9.2), 60*	47 (8.8), 89	53 (8.0), 105	50 (8.0), 4
	MCS	36 (13), 60	36 (13), 60	51 (10.6), 105	52 (8.5), 5
PH	PCS	47 (13.0), 6	49 (8.5), 53	51 (8.7), 135	55 (5.0), 8
	MCS	45 (12.3), 6	51 (8.6), 53	52 (8.3), 135	54 (8.5), 8
Dent	PCS	41 (2.7), 2	46 (12.2), 5	53 (7.4), 26	48 (12.5), 16
	MCS	46 (16.0), 2	47 (12.0), 5	50 (10.4), 26	47 (8.9), 16
APRTd	PCS	46 (1.5), 3		51 (9.1), 16	49 (8.8), 14
	MCS	41 (13.0), 3		52 (8.7), 16	49 (9.3), 14

*mean (SD), N



TH-PO1093

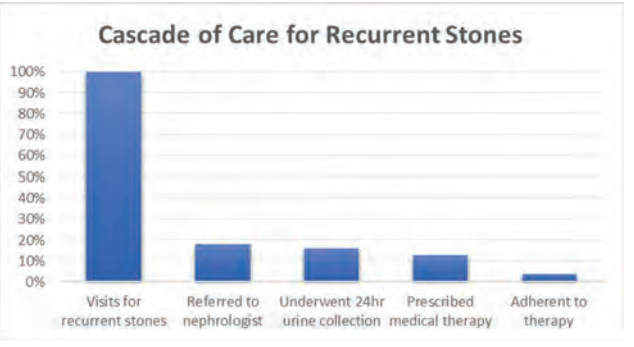
A Cascade of Care for Urinary Stone Disease (USD) Mansi Mehta, David S. Goldfarb. *Nephrology, NYU Medical Center, New York, NY.*

Background: USD is a preventable disease characterized by significant risk of recurrence. A "cascade of care" shows how many patients are lost to follow-up at diagnosis, referral, and treatment and is a useful tool in delivering HIV care. We can analyze our success, or failure, in the secondary prevention of kidney stones and retention of patients by constructing a cascade of care.

Methods: We abstracted data from observational studies to identify impediments to care of patients with USD

Results: In the US there are about 1.2 million ER visits per year. 37% of patients diagnosed with stones receive a follow-up consultation with a urologist and fewer see a nephrologist. Although 24h urine collection results may decrease stone recurrence rate, only 7.4% do them. 50% of patients experience a recurrent 2nd episode within 5 years. Of these 24% undergo a complete evaluation, 18% are referred to a nephrologist and 13.8% are prescribed medical therapy. 30% remain adherent to this pharmacotherapy. Of patients that are adherent 27% have lower odds of an ER visit than non-adherent patients. The cascade of care demonstrates that a low prevalence of patients receive proper follow-up. The impediments to the care of patients with kidney stones are (1) the unrecognized comorbidities of stones (2) disconnect between the ER and stone experts and (3) the low prevalence of 24h urine collections and prescribed medical therapy.

Conclusions: It is important to identify loci in the cascade of care that could represent opportunities to change practice. Prescription of appropriate fluid therapy and dietary changes and a referral to an expert should 1st be initiated by the ER. The low prevalence of 24h urine collections may reflect that the data are intimidating for some. Empiric therapy for calcium stones with fluids, diet, thiazides and potassium citrate may be a rational therapy to achieve significant supersaturation reductions and could be compared with targeted medical therapy in a randomized controlled trial. A greater effort needs to be devoted to develp a comprehensive flow of participants to retain patients in the cascade of care for USD.



TH-PO1094

Raman Chemical Imaging in Kidney Stone Analysis Vincent Castiglione, Pierre-Yves Sacré, Eric M. Ziemons, Etienne Cavalier, Philippe Hubert, Romy Gadisseur. *University of Liege, CHU Sart-Tilman, Liege, Belgium.*

Background: The structure of kidney stones might provide clinical useful information in addition to the stone composition. The Raman chemical imaging (RCI) is a new technology used for the production of two-dimensions maps of the constituents' distribution in samples. We aimed at determining the use of RCI in urinary stone analysis.

Methods: Twelve calculi were analyzed by RCI using a confocal Raman microspectrophotometer. They were selected according to their heterogeneous composition and morphology. Prior to the analysis, samples were sliced and milled in order to detect the nucleus of the stones and having a smooth surface. RCI was performed on the whole section of stones. Once acquired, the data were baseline corrected and analyzed by MCR-ALS. Results were then compared to the spectra obtained by Fourier Transform Infrared spectroscopy, the gold standard method for the determination of urolithiasis composition.

Results: RCI succeeded in identifying all the chemical components contained in each sample, including monohydrate and dihydrate calcium oxalate, anhydrous and dihydrate uric acid, apatite, struvite, brushite, whitlockite and ammonium urate. However, proteins couldn't be detected because of the huge autofluorescence background and the small concentration of these poor Raman scatterers. Carbapatite and calcium oxalate were correctly detected even when they represented less than 5 percent of the whole stones, allowing the detection of very small structures like Randall's plaques. Moreover, RCI provided the distribution of components within the stones. The nuclei were accurately identified, as well as thin layers of other components. Conversion of dihydrate to monohydrate calcium oxalate was correctly observed in the center of one sample.

Conclusions: RCI showed a good accuracy in comparison with infrared spectroscopy in identifying components of kidney stones. In addition, RCI is nondestructive enabling the storage of samples. This analysis was also useful in determining the organization of components within stones, which help locating constituents in low quantity, such as nuclei. However, this analysis is time-consuming, which makes it more suitable for research studies rather than routine analysis.

TH-PO1095

Unique Case Renal Failure with Severe Metabolic Alkalosis and Hypermagnesaemia Requiring Hemodialysis Ravi K. Thimmisetty,[1] Omer Alrawi,[1] Yahya M. Osman Malik,[2] Zeenat Y. Bhat.[1] *[1]Wayne State University, Detroit, MI; [2]Wayne State University Medical School, Detroit, MI.*

Background: We are presenting an interesting case of renal failure, severe metabolic alkalosis and symptomatic hypermagnesemia that required dialysis for correction.

Methods: 60-year-old African American male with history of metastatic sigmoid colon cancer s/p resection with end-colostomy and Hartmann's stump admitted with abdominal pain, vomiting and dyspnea. Other medical problems were hypertension

and left ureteral obstruction from colonic mass s/p left percutaneous nephrostomy tube. Home medications include flomax, protonix, over the counter Alka-seltzer. Admission vitals were -temperature 97.5 fahreinheit, blood pressure of 95/77, heart rate 98 beats per minute, respiratory rate 16 per minute and saturating 97% on 40% fiO2. On exam, he was cachectic, mild somnolent and dry. There was no edema. Laboratory values on admission revealed sodium 135, K is 4.7, chloride 80, bicarbonate >45, creatinine is 5.5 mg/dl (baseline Cr is of 1.5), calcium 9, magnesium 5.6 and phosphorus 9.9. ABG results showed pH is 7.59, pCO2 is 71, pO2 183, bicarb is 59.9. After volume resuscitation, patient became bradypnea, more somnolent and further worsening of respiratory status requiring intubation. Immediately hemodialysis was started for treating symptomatic hypermagnesemia and severe metabolic alkalosis in the setting of acute renal failure. Urine output started increasing. With 2 sessions of renal replacement therapy, patient improved significantly interims of mental status and biochemically. Creatinine down to 2.4 and pH is 7.37. All other electrolytes were normalized and patient was extubation. Severe alkalosis could have been multifactorial oral alkali intake and vomiting in setting of renal failure and week ago, had gastrograffin for small bowel obstruction which can sometime result in metabolic alkalosis.

Results:

Conclusions: Gastrograffin sometimes prepared with solutions containing alkali. Caution should be taken while giving these solutions containing alkali especially in the setting of renal failure. Concomitant severe metabolic alkalosis and hypermagnesemia can contribute to high mortality and poses a therapeutic challenge especially in the setting of renal failure. Renal replacement therapy is required in these cases.

TH-PO1096

A Case Report of Severe Hypokalemia Induced by Posaconazole Sreelatha Katari,[1] Daniel W. Coyne.[2] *[1]Barnes Jewish Hospital, St Louis, MO; [2]Washington University School of Medicine, St. Louis, MO.*

Background: Hypokalemia is not a very common electrolyte abnormality that has been recognized with azole antifungals.

Methods: A 66 year old man with history of Acute Myeloid Leukemia (AML) status post stem cell transplant in 6/2016 and chemotherapy presented with weakness, loss of appetite and failure to thrive on 1/2017. His current outpatient medications are tacrolimus, atovaquone, fluconazole, valacyclovir and budesonide. His blood pressure was 137/76 mm Hg, pulse 118, and BMI 24. Serum sodium 137 mmol/L, potassium (K) 4.1 mmol/L, chloride 107 mmol/L, urea nitrogen 9 mg/dL, and creatinine 0.85mg/dL. Chest and abdominal CT showed recurrence of AML, so he was started on dasatinib. On day 3 he developed neutropenic fever so he was started on vancomycin, meropenem and posaconazole. On day#11 he developed polyuria of more than 4L and profound hypokalemia. Serum K was 2.1 mmol/L, bicarbonate of 24 mmol/L, phosphorus 1.8 mg/dl and magnesium of 1.9 mmol/L. Urine analysis showed no glycosuria with a PH of 5. Urine K 42 mmol/L, sodium 105mmol/L, osmolality of 393 mOsm/kg, serum osmolality of 297mOsm/Kg, calculated potassium deficit daily was nearly 440meq. His workup showed renal wasting of potassium with no evidence of renal tubular acidosis. Given the timeline of events the electrolyte abnormalities were attributed to posaconazole, so it was discontinued and switched with micafungin. Over next 10 days his serum potassium promptly normalized and did not require further supplementation.

Results: Posaconazole has been increasingly used in the treatment of zygomycetes and asperillus infections in hematological malignancies. It works by inhibiting enzyme lanosterol 14α-demethylase leading to defective fungal cell wall and its death. Exact mechanism of hypokalemia is not clear but animal studies have shown inhibition of 11β-hydroxysteroid dehydrogenase type 2 dependent cortisol inactivation by posaconazole leads to excessive cortisol byproducts like cortisone, leading to apparent mineralocorticoid excess causing urine potassium losses and hypokalemia.

Conclusions: Posaconazole induced profound Hypokalemia is rare complication with only two other published cases in literature. So we suggest serum potassium be closely monitored in patient treated with posaconazole and the treatment is its prompt discontinuation

TH-PO1097

Severe, Symptomatic Hyponatremia in Patient Started on New Anti-VEGF Therapy Priyanka Jethwani,[2] Ari B. Geller.[1] *[1]None, West Hartford, CT; [2]Department of Medicine, University of Connecticut Health Center, Hartford, CT.*

Background: Hyponatremia is described as a side-effect of various chemotherapeutic agents. However severe, symptomatic hyponatremia can often limit use of those agents despite good overall outcomes.

Methods: This is the case of a 62-year-old Caucasian male with history of metastatic renal cell carcinoma with sarcomatoid features who presented to ED with one week of progressive fatigue, decreased energy levels, unsteadiness, lightheadedness and poor oral intake. Three weeks prior, he was started on Carbozantinib (new anti-VEGF agent) after failure of prior therapy. Fluid intake was at baseline and he was euvolemic on physical examination. Complete neurologic exam was normal despite known brain metastases. Labs revealed sodium 112 (131 two weeks ago), K 4.1, BUN 16, Cr 0.6, serum osm 229, urine osm 645, urine Na 125, TSH 2.42, AM cortisol 6.8, based on which he was thought to have SIADH. He was on long-term SSRI at a stable dose. Head imaging showed known metastatic brain lesions that had decreased in size. Despite fluid restriction, sodium dropped to 110. 3% hypertonic saline infusion was started, followed by torsemide and salt tablets. He underwent a co-syntropin stimulation test with inadequate response. However, he had been normotensive and did not receive corticoid therapy during hospitalization or at discharge. Despite this, sodium levels improved. Sodium was 133 at discharge and 137 two days later. He was challenged with dose-reduced Carbozantinib as outpatient, however, sodium dropped to 128 again within two weeks. Consequently, therapy was discontinued.

Results:

Conclusions: Carbozantinib was FDA approved in April 2016 for use in patients with advanced renal cell carcinoma who have failed prior anti-VEGF therapy. It improves progression-free survival in patients with advanced renal cell cancer with failure of prior therapy ($p<0.005$) when compared to Everolimus, which is standard of care. In the phase I trial of the drug, 2 out of 25 participants developed hyponatremia. In the phase II and phase III trials, hyponatremia was not reported. The most commonly seen adverse effects were diarrhea, fatigue, nausea, decreased appetite, palmar-plantar erythrodysesthesia syndrome, hypertension, vomiting, weight loss, and constipation. This is the first known reported case of severe, symptomatic hyponatremia secondary to SIADH attributed to carbozantinib therapy.

TH-PO1098

Ibuprofen Abuse – A Case of Rhabdomyolysis, Hypokalemia, and Hypophosphatemia with Drug Induced Mixed Renal Tubular Acidosis Shakuntala S. Patil,[1] Swathi Subramany,[3] Manisha Singh,[2] Michelle W. Krause.[3] *[1]UAMS, LITTLE ROCK, AR; [2]University of Arkansas For Medical Sciences, Little Rock, AR; [3]University of Arkansas for Medical Sciences, Little Rock, AR.*

Background: Drug induced renal tubular acidosis (RTA) can pose an uncommon, but important cause of severe potassium wasting and hypokalemia. We report a case of mixed RTA presentation causing severe hypokalemia and unexplained hypophosphatemia in a patient who consumed large amounts of Ibuprofen

Methods: A 48-year old previously healthy African American woman was admitted to the Medical intensive care unit with complaints of diffuse myalgias and severe generalized weakness for past few days. She was urinating a large volume (more than 2 liters) of dark colored urine with dysuria. Past history was significant for a distal tibio-fibular stress fracture 5 months ago complicated by delayed union. Her admission labs revealed severe hypokalemia, a non-anion gap metabolic acidosis with a positive urine anion gap (UAG) and a urine pH of 6.5 consistent with distal (Type I) RTA. She had spontaneous, non-traumatic rhabdomyolysis secondary to severe hypokalemia, but with hypophosphatemia resembling proximal RTA (Type 2). She had low 25-OH Vitamin D, mild transaminitis and E. coli cystitis. 24 hour urine potassium was 104 mmol(normal <30 mmol). Upon further questioning, the patient revealed that she had been taking about 20 tablets of Ibuprofen tablets daily (about 4 grams/day) for the past 3 months to control her ankle pain. She tested negative for Sjogren's disease, other autoimmune disorders and paraproteinemia. With continued aggressive fluid and electrolyte replacement, Vitamin D therapy and cessation of ibuprofen, her biochemistries normalized within 5 days. Repeat serum chemistries were noted to be normal in 1 week follow up in clinic.

Results:

Conclusions: Our patient developed severe but reversible hypokalemia with a mixed proximal and distal RTA like picture, most likely due to Ibuprofen use. A few cases have been reported of Ibuprofen preparations causing either proximal or distal type RTA. This is thought to be related to its inhibitory effect on Carbonic Anhydrase II. This case highlights the potential of Ibuprofen to cause type 3 RTA like picture, or a mixed type 1 and 2 RTA with life threatening hypokalemia to the extent of causing rhabdomyolysis.

TH-PO1099

Transient Hyporeninemic Hypoaldosteronism with Renal Salt Wasting: An Unusual Presentation Huda Arif,[1] David J. Leehey.[2] *[1]Loyola University, Chicago, IL; [2]Loyola University Medical Center, Oak Park, IL.*

Background: We are presenting a case of transient hypoaldosteronism with hyporeninemia presenting with orthostatic hypotension and renal salt wasting without cerebral disease. Adrenal insufficiency was ruled out by normal ACTH and cortisol levels

Methods: A 61-year-old gentleman with no significant medical history except for mild essential hypertension was referred to the renal clinic after multiple visits to the emergency room for symptomatic orthostatic hypotension requiring isotonic saline infusion. Evaluation in clinic showed orthostatic hypotension with an intact autonomic response. He reported polyuria with approximately 3-4L daily urine output. Laboratory evaluation revealed persistent hypoaldosteronism with plasma aldosterone levels <1 ng/dL, low plasma renin activity (0.23-1.10 ng/mL/h), and normal ACTH and cortisol levels. He had normal renal function and normal plasma potassium and total carbon dioxide levels. His plasma sodium levels were generally normal with occasional mild hyponatremia noted. He had persistently elevated urinary sodium concentrations (> 20 mmol/L) in the face of hypotension, and 24h urine sodium and aldosterone excretions were 164 mg and < 1 mcg, respectively. He was treated with fludrocortisone 0.1 mg daily with marked improvement in orthostatic symptoms. Over the course of years, his renin and aldosterone normalized and fludrocortisone was tapered to minimal dose. Attempts to stop fludrocortisone resulted in recurrence of symptoms.

Results:

Conclusions: Aldosterone causes reabsorption of sodium and chloride and excretion of potassium and hydrogen ions in the distal convulated tubule. Selective or isolated aldosterone deficiency can result from a deficiency in renin secretion or decreased adrenal synthesis. Hyporeninemic hypoaldosteronism is most common in patient with mild to moderate renal insufficiency due to diabetic nephropathy or chronic interstitial nephritis. It can also occur with acute GN and in patients taking NSAID and CNI. The characteristic electrolyte findings of this disorder are hyperkalemic hyperchloremic acidosis and occasionally mild hyponatremia, usually in the setting of impaired renal function. This

case illustrates the importance of considering the diagnosis of hypoaldosteronism in adult patients with symptoms and signs of renal salt wasting in the absence of hyperkalemic hyperchloremic acidosis.

TH-PO1100

Hyperkalemia and Megestrol Acetate: Related? Nikhil Agrawal,[1] Ilka A. Netravali,[1] Shimontini Mitra,[2] Stewart H. Lecker,[1] Melanie P. Hoenig.[1] *[1]Beth Israel Deaconess Medical Center, Brookline, MA; [2]None, Brookline, MA.*

Background: Megestrol acetate (MGA) is a synthetic progestin widely used as an appetite stimulant for patients with cancer. MGA binds to the glucocorticoid receptor with nearly twice the affinity as cortisol and can cause symptoms of glucocorticoid excess while suppressing endogenous glucocorticoid production. We report a case of concomitant mineralocorticoid deficiency in a patient taking MGA with evidence of glucocorticoid deficiency.

Methods: A 51-year-old woman with allogenic stem cell transplant 2 years prior for AML and subsequent relapse was admitted for a line infection. She was noted to have a refractory hyperkalemia a week after admission that required repeated interventions with insulin, dextrose, IV fluids, furosemide, and sodium polystyrene. She reported 3 cups of tomato juice daily and a history of hypokalemia. Medications: atovaquone, ciprofloxacin, daptomycin, famotidine, folic acid, ondansetron, posaconazole, valacyclovir, cefepime and allopurinol. Two days prior to admission, her MGA was increased from 400 to 800mg daily. She denied fatigue, weakness, or hyperpigmentation. She was normotensive and her examination was unremarkable. She had pancytopenia without evidence of tumor lysis. Serum chemistry showed Na 139, K 6.2, Chloride 110, Bicarb 21, BUN 21, Cr 0.8 Early am cortisol: 0.8 mg/dl (increased to 8.8mg/dl at one hour with high dose ACTH stimulation). ACTH <5 pg/mL (6-50). Renin 2.79 ng/mL/hr (0.25-5.82), Aldosterone 1.0 ng/dL (supine 3-16). A low potassium diet was begun but potassium remained high. Urine potassium excretion was low. MGA discontinued, and fludrocortisone and hydrocortisone were begun. Potassium normalized within 24 hr. Within 5 days, she became hypokalemic, and fludrocortisone was discontinued.

Results:

Conclusions: This is the first reported case of hyperkalemia in association with MGA. Although MGA is a well-known cause of adrenal insufficiency, this is usually restricted to the glucocorticoid axis. Here low ACTH level suggests secondary adrenal insufficiency which is typically not associated with defects in the mineralocorticoid axis. Yet low aldosterone level in the setting of hyperkalemia without suppression of renin and with reduced renal potassium excretion is consistent with mineralocorticoid deficiency. Since this resolved with discontinuation of MGA, this suggests that MGA may have an additional effect on the mineralocorticoid axis.

TH-PO1101

An Unusual Case of Peripheral Edema Due to Suspected Liddle's Syndrome Sadeem Ali,[1] Sri jegan Radhakrishnan,[1] Reginald I. Obi.[2] *[1]ECU, Greenville, NC; [2]ECU Physicians Nephrology, Greenville, NC.*

Background: Liddle's syndrome is a rare autosomal dominant disease affecting epithelial sodium channels in which there is a primary increase in collecting tubule sodium reabsorption and usually associated potassium wasting. Patient usually presents with hypertension, hypokalemia, and metabolic alkalosis, with an overall clinical picture mimicking mineralocorticoid excess. However, its presentation with a chief complaint of peripheral edema has not been reported to our knowledge.

Methods: We present a 47 years old female who has been hypertensive since the mid thirties of her age. She came for management of hard to control generalized edema, mostly in her lower extremities, for the last three years. No cardiac or liver etiology identified. She had tried several diuretics including hydrochlorothiazide, furosemide, spironolactone and was then on chlorthalidone 50 milligrams daily. She had been profoundly hypokalemic while on diuretics and requiring 80 milli equivalents daily replacement of potassium chloride. Her labs also showed metabolic alkalosis and relatively high sodium levels. We suspected a potassium wasting syndrome. After holding chlorthalidone for three days, with continued potassium replacement, her trans tubular potassium gradient was calculated at 7.9 confirming urinary potassium wasting. Her plasma aldosterone to renin activity ratio was 13.2, making primary hyperaldosteronism unlikely. We started her on amiloride as 5 mg twice a day due to clinical suspicion of Liddle's syndrome. After three weeks, her swelling has completely resolved and blood pressure also normalized. Her potassium supplementation and all antihypertensive medications were discontinued except for a reduced dose of amiloride. Her labs now show normal potassium and bicarbonate levels. Genetic testing for Liddle's syndrome has not been done in this patient because it will not change management.

Results:

Conclusions: Refractory peripheral edema could be an unusual presentation of this rare but treatable condition. Paying close attention for pathophysiologic clues of Liddle's syndrome will result in more specific management for subsets of patients presenting with edema, refractory to the commonly used loop and thiazide diuretics.

TH-PO1102

Relationship between Serum Potassium and Dose Modification and Discontinuation of Renin-Angiotensin-Aldosterone System Inhibitors in UK Patients with Heart Failure Lei Qin,[4] Philip McEwan,[2] Marc L. Evans,[3] Laura Horne,[1] Susan Grandy.[4] *[1]Global Medical Affairs, AstraZeneca, Gaithersburg, MD; [2]Centre for Health Economics, Swansea University, Singleton Park, United Kingdom; [3]Department of Medicine, University Hospital Llandough, Cardiff, United Kingdom; [4]Health Economics and Outcomes Research, AstraZeneca, Gaithersburg, MD.*

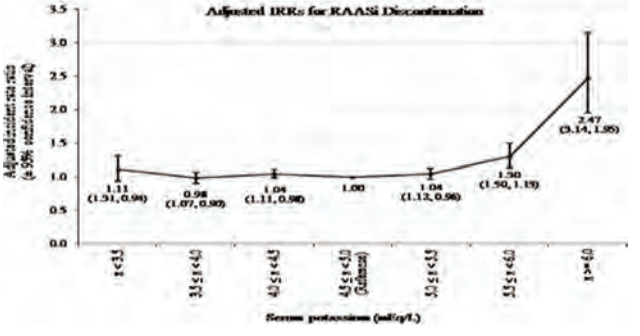
Background: Renin-angiotensin-aldosterone system inhibitors (RAASi) may be prescribed to heart failure (HF) patients, but discontinued due to concerns over hyperkalemia (HK). The real-world usage of RAASi in primary care was evaluated in UK HF patients with a range of serum potassium (K+) levels.

Methods: A retrospective observational study was conducted using primary care data from the Clinical Practice Research Datalink from Jan 2006 to Dec 2015. Patients (≥18 years) were included if they had a first diagnosis of HF during the study period. RAASi discontinuation was defined as a ≥90-day gap without a prescription using the medicines possession ratio, and dose reduction as a decrease to prescribed daily dose between successive prescriptions. Incidence rate ratios (IRRs) for discontinuation and odds of dose reduction were tested for association with time-updated serum K+ using Poisson and Logistic Generalized Estimating Equations respectively after adjustment for demographic and clinical covariates.

Results: Of the total HF population at baseline (n=23,541), 60.9%, 15.1%, 23.4% and 0.04% were taking angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, mineralocorticoid receptor antagonists and renin inhibitors, respectively. A total of 7,527 RAASi discontinuations were estimated in 68,133 patient-years of follow-up, a reference rate of 110 discontinuations per thousand patient-years. A J-shaped association between adjusted IRRs and serum K+ was observed, with high serum K+ (≥6.0 mEq/L) being strongly associated ($p<0.001$) with incidence of discontinuation (Figure). Serum K+ ≥5.5 mEq/L was associated with an increased odds of dose reduction (OR=1.33, p=0.035) versus Serum K+ < 5.5 mEq/L.

Conclusions: Physicians were more likely to discontinue RAASi or reduce dose in HF patients with HK. Further research is warranted to determine the clinical impact of RAASi dose modification and discontinuation in the treatment of HK in the UK.

Funding: Commercial Support - AstraZeneca



TH-PO1103

Relationship between Serum Potassium and Dose Modification and Discontinuation of Renin-Angiotensin-Aldosterone System Inhibitors in UK Patients with CKD Lei Qin,[4] Philip McEwan,[2] Marc L. Evans,[3] Eirini Palaka,[1] Susan Grandy.[4] *[1]Health Economics and Outcomes Research, AstraZeneca, Cambridge, United Kingdom; [2]Centre for Health Economics, Swansea University, Singleton Park, United Kingdom; [3]Department of Medicine, University Hospital Llandough, Cardiff, United Kingdom; [4]Health Economics and Outcomes Research, AstraZeneca, Gaithersburg, MD.*

Background: Renin-angiotensin-aldosterone system inhibitors (RAASi) may be prescribed to CKD patients, but discontinued or dose reduced due to concerns about hyperkalemia (HK). The real-world usage of RAASi was evaluated in UK CKD patients with a range of serum potassium (K^+) levels and severities of renal dysfunction.

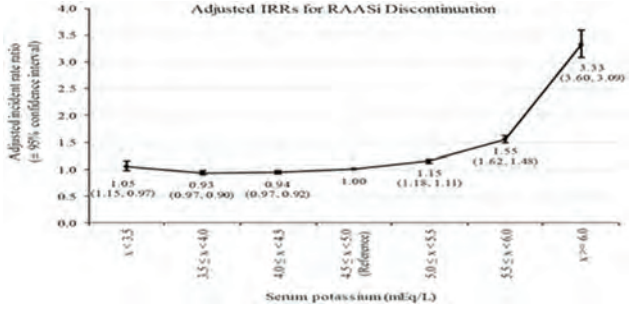
Methods: A retrospective observational study was conducted using primary care data from the Clinical Practice Research Datalink from Jan 2006 to Dec 2015. Patients (≥18 years) were included if they had a first diagnosis of CKD stage 3 or higher during the study period. RAASi discontinuation was defined as a ≥90-day gap without a prescription using the medicines possession ratio, and dose reduction as a decrease to daily dose between successive prescriptions. Incidence rate ratios (IRRs) for discontinuation and odds of dose reduction were tested for association with time-updated serum K^+ using Poisson and Logistic Generalized Estimating Equations respectively adjusting for demographic and clinical covariates, including eGFR.

Results: Of the total CKD population at baseline (n=144,388), 37.6% were taking angiotensin-converting enzyme inhibitors, 14.7% were taking angiotensin-II receptor blockers, 2.4% were taking mineralocorticoid receptor antagonists, and 0.04% were taking renin inhibitors. A total of 53,587 RAASi discontinuations were estimated in 704,830 patient-years of follow-up. A J-shaped association between adjusted IRRs and serum K^+ was observed, with high serum K^+ (≥6.0 mEq/L) being strongly associated with

incidence of discontinuation (Figure). This pattern was consistent across eGFR strata. Serum K^+ ≥5.5 mEq/L was associated with increased odds of dose reduction (OR=2.24, p<0.001) versus Serum K^+ < 5.5 mEq/L.

Conclusions: Physicians were more likely to discontinue RAASi or reduce dose in CKD patients with HK. Further research is warranted to determine the clinical consequences of RAASi dose modification and discontinuation in the management of HK in the UK.

Funding: Commercial Support - AstraZeneca



TH-PO1104

Metformin-Associated Lactic Acidosis in a Patient with Normal Renal Function Naushaba Mohiuddin,[2] Jian Li.[1] *[1]None, Detroit, MI; [2]Nephrology and Hypertension, Henry Ford Hospital, Detroit, MI.*

Background: INTRODUCTION Metformin -associated lactic acidosis (MALA) in patients without renal impairment is an infrequent serious complication. In patients in whom development of renal dysfunction is anticipated, monitoring renal function more frequently and discontinuing Metformin at early renal impairment is crucial. We present a case of severe lactic acidosis in a patient who had no contraindication to Metformin prescription.

Methods: Case: Patient is a 58 year old female presented with abdominal pain and diarrhea. She has history of Diabetes, HTN, with prior normal renal function on Metformin, Lisinopril and Lasix. In Emergency department patient was hypotensive. She was started on Vasopressors and given IV fluids. ABGs showed severe high an ion gap acidosis, acute renal failure and Lactate level of 11. Despite aggressive IV hydration, her Lactate trended up to 17. Braod spectrum antibiotics started. She was admitted to ICU. Acute abdomen, septic and cardiogenic shock were ruled out. On further review, was noted, patient was admitted at outside hospital 3 weeks ago, with diarrhea, had negative work up. At that time she had CT abdomen with IV contrast. Metformin was held prior and 4 days after. Metformin was resumed on discharge. A week later, she had CTA of abdomen. Baseline creatinine was around 0.7mg/dl and GFR 88ml/min/1.73m2. Patient was started on sustained low-efficiency dialysis with regional citrate anticoagulation (SLED RCA), for MALA. A progressive recovery was observed, with initially weaning off pressors, lactate level improving and later complete recovery of her renal function.

Results:

Conclusions: Conclusion: 1. Identifying patients who are on metformin, at risk to develop Prerenal azotemia, or alteration in renal function can potentially prevent this life threatening condition.2. Presence of elevated lactic acidosis in a diabetic patient on metformin, even with baseline normal renal function, should trigger to consider MALA.

TH-PO1105

Low K, Not OK: Distal Renal Tubular Acidosis Associated with Autoimmune Thyroiditis Timothy Yen,[1] Roberto L. Collazo-Maldonado.[2] *[1]Internal Medicine, Methodist Dallas Medical Center, Dallas, TX; [2]Division of Nephrology, Methodist Dallas Medical Center, Dallas, TX.*

Background: Profound hypokalemia can present with hypokalemic paralysis. This is a rare but potentially fatal condition. Potassium wasting secondary to renal tubular acidosis (RTA) is a common cause of severe hypokalemia. RTAs are associated with multiple systemic diseases including autoimmune disorders and endocrinopathies.

Methods: A 43 year old Hispanic woman with a previous history of calcium phosphate renal stones presented to the ED after she awoke with generalized limb paralysis and inability to rise from bed. She denied having similar symptoms in the past, and review of symptoms was negative. She denied having a history of family illness, or using alcohol, tobacco or drugs. The patient did not take any medications or herbal supplements. Vital signs were normal on admission except for sinus bradycardia of 49 BPM. On examination, she had 3/5 strength in all extremities but normal sensation and reflexes. Her blood and urine investigations were suggestive of a distal RTA. The patient had a normal anion gap metabolic acidosis (pH 7.236, HCO3 15 mmol/L), severe hypokalemia (K 1.8 mmol/L), with normal serum calcium and magnesium levels. Urine studies revealed a urine pH of 7.5 and anion gap of 31 (Cl 90 mmol/L; K 15 mmol/L; Na 106 mmol/L). The patient was given IV and oral potassium replacement before being started on a bicarbonate infusion. By morning, her serum potassium level had risen to 3.6 mmol/L and her weakness had completely resolved. Investigations into the etiology of her RTA were performed. ESR and CRP levels were normal, and screening for ANA and Anti-SSA/SSB was negative. Thyroid function tests ordered to investigate her sinus bradycardia revealed subclinical hypothyroidism (TSH 14.0 uIU/L, free T4 1.10 ng/dL) with an elevated anti-thyroid peroxidase antibody (2729 IU/mL). The patient was discharged in stable condition and placed on a regimen of 1.6 mcg/kg/day of levothyroxine with oral bicarbonate and potassium supplements.

Results:

Conclusions: This is a case of a previously healthy middle aged woman who presented with hypokalemic paralysis caused by a distal RTA. The patient lacks any classical risk factors for acquired RTA except for elevated anti-thyroid peroxidase antibody. Internists and nephrologists must be aware of this rare but documented association between autoimmune thyroiditis and distal RTA.

TH-PO1106

Associations between Serum Potassium and Clinical Outcomes in Patients with CKD in a Real World Setting Philip McEwan,[2] Lei Qin,[4] Marc L. Evans,[3] Laura Horne,[5] Eirini Palaka,[1] Susan Grandy.[4] *[1]Health Economics and Outcomes Research, AstraZeneca, Cambridge, United Kingdom; [2]Swansea Centre for Health Economics, Swansea University, Singleton Park, United Kingdom; [3]Department of Medicine, University Hospital Llandough, Cardiff, United Kingdom; [4]Health Economics and Outcomes Research, AstraZeneca, Gaithersburg, MD; [5]Global Medical Affairs, AstraZeneca, Gaithersburg, MD.*

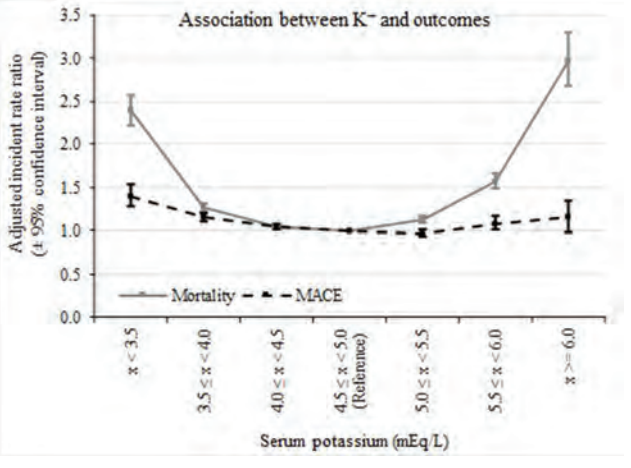
Background: The associations between serum potassium (K^+) and rates of mortality and serum K+ and rates of major adverse cardiovascular events (MACE) have previously been characterised using US healthcare data. This study assessed the generalisability of this finding and developed risk equations using UK real-world data on a cohort of chronic kidney disease (CKD) patients.

Methods: A retrospective observational study was conducted using the Clinical Practice Research Datalink from Jan 2006 to Dec 2015. Patients (≥18 years) with a first diagnosis of CKD stage 3 or higher during the study period were analysed with clinical outcomes of interest included all-cause mortality and MACE (arrhythmia, heart failure, myocardial infarction, stroke). Incidence rate ratios (IRRs) associated with time-updated serum K^+ were estimated using Generalized Estimating Equations adjusted for a broad range of demographic and clinical covariates.

Results: Analysis included 144,388 CKD patients with a mean follow-up of 4.9 years. Patients were predominantly female (60.4%) with a mean age of 73.7 years and mean eGFR of 49.7 mL/min/1.73m^2. Baseline ischemic heart disease, stroke, myocardial infarction and peripheral vascular disease were present in 11.5%, 6.6%, 3.4% and 2.6% of patients, respectively. There were 34,602 deaths and 71,607 MACE during the study period. U-shaped associations were observed between serum K^+ and IRRs for mortality and MACE (Figure), with low (<4.5 mEq/L) and high (≥5.5 mEq/L) K^+ concentrations being positively associated with incidence.

Conclusions: A real-world analysis of UK patients with CKD indicated associations between hypo- and hyperkalemia with risk of mortality and MACE. The observed U-shaped trends were consistent with previously reported US real-world studies.

Funding: Commercial Support - AstraZeneca



TH-PO1107

Prevalence of Hyperkalemia in Patients with ESRD Undergoing Hemodialysis Saravanan Balamuthusamy, Alagarsamy l Reddi, Sankarapandian Ponnaih, Ranjit K. Dhelaria, Balamurugan Sankarapandian. *Texas Research Institute and PPG Healthcare PA, Fort Worth, TX.*

Background: Adverse cardiovascular events are the most common reason for mortality and morbidity in patient with ESRD. Hyperkalemia is a well-known etiology of cardiac arrhythmias in ESRD and non-ESRD patients. We have analyzed the prevalence of hyperkalemia in prevalent hemodialysis patients dialyzed 3 times a week in an outpatient dialysis clinic.

Methods: Retrospective analysis of serum potassium levels in ESRD patients undergoing hemodialysis in 9 dialysis clinics. pre-dialysis Potassium levels were measured as per dialysis protocol. Based on serum potassium levels, patients divided into four groups i) Hypokalemia (Serum K level less than 3.5) ii) normokalemia (Serum K level between 3.6 to 5.4 mmol/lit), iii} moderate hyperkalemia (Serum K level between

5.5 to 5.9 mmol/lit), and iv) severe Hyperkalemia (Serum K level more than 6.0 mmol/lit). Institutional approval was obtained to review charts.

Results: 1022 ESRD patients undergoing hemodialysis were included in the analysis. 2.25% of these patients had severe and 6.75% had moderate hyperkalemia; 2.5% had hypokalemia and the remaining 88.5% had normokalemia.

Conclusions: We have estimated that 9% of HD patients either had moderate or severe hyperkalemia and 2.5% had hypokalemia. The risk of adverse cardiac events is greater when there are rapid fluctuations in serum K which is more likely to occur in hyperkalemic patients dialyzed with 2K baths. Ability to auto-titrate dialysis baths based on serum potassium levels might help mitigate the rapid fluctuations in serum potassium in hyperkalemic dialysis patients.

TH-PO1108

A Cause for Concern: RAAS Inhibitors Are Associated with Significant Risk of Hyperkalemia in Patients with Chronic Heart Failure: A Meta-Analysis Ankur Jain, Abhilash Koratala, Hesham Nasser, Amir Kazory. *University of Florida, Gainesville, FL.*

Background: Inhibitors of renin-angiotensin-aldosterone system (RAAS) are widely used in patients with chronic heart failure (HF). We previously reported that the impact of angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) on renal function is distinct from that of downstream blockers of the RAAS (i.e. mineralocorticoid receptor antagonists [MRA]). In this study, we sought to evaluate the effect of these agents on the incidence of hyperkalemia in HF.

Methods: Articles cited in PubMed, EMBASE, and Cochrane database from 1987 to 2017 using key words: "heart failure", "angiotensin-converting enzyme", "angiotensin receptor blocker", and "mineralocorticoid receptor antagonist" were searched and those randomized controlled trials (RCTs) that addressed the impact of RAAS inhibition in HF were identified. Hyperkalemia, defined as serum potassium level >5.5 mmol/L, was considered the primary endpoint. A meta-analysis was performed. Mantel-Haenszel random-effects model was used to calculate risk ratios (RRs) with 95% confidence intervals (CIs).

Results: A total of 3389 studies were selected after extensive database search. After excluding duplicate and non-randomized trials, 14 RCTs with 29,433 participants were found eligible for analysis. Compared to placebo, ACE-I/ARB significantly increased the risk of hyperkalemia (RR 2.31 CI 1.77-3.02, p≤0.01). Addition of MRA to ACE-I/ARB further increased the risk (RR 2.19 CI 1.51-3.16, p≤0.01). When evaluated for severe hyperkalemia (i.e. serum potassium levels > 6 mmol/L), ACE-I/ARB increased the risk compared to placebo (RR 1.59, CI 1.13-2.25, p=0.01), and addition of MRA to ACE-I/ARB further increased it (RR 1.63 CI 1.13-2.35, p=0.01).

Conclusions: In patients with HF, ACE/ARB therapy increases the risk of hyperkalemia by more than two folds and downstream addition of MRA increases the risk further. RAAS inhibitors have been shown to improve outcomes including mortality in this patient population. Future studies are needed to evaluate therapeutic strategies (e.g. newer potassium binders) for prevention of hyperkalemia to avoid underutilization of RAAS inhibition.

TH-PO1109

Workup of Unexplained Renal Hypophosphatemia Anneke Bech,[3] Ewout J. Hoorn,[1] Robert Zietse,[1] Jack F. Wetzels,[2] Tom Nijenhuis.[4] *[1]Erasmus Medical Center, Rotterdam, Netherlands; [2]Radboud University Medical Center, Nijmegen, Netherlands; [3]Radboud University Nijmegen Medical Center, Nijmegen, Nijmegen, Netherlands; [4]Radboud university medical center, Lent, Netherlands.*

Background: Hypophosphatemia can be caused by renal phosphate loss. Increased renal phosphate loss can be inherited or acquired. The most common causes of acquired renal hypophosphatemia are medication, Fanconi syndrome, hyperparathyroidism and tumor induced osteomalacia (TIO). The clinical picture of these disorders varies widely and is non-specific. An increasing number of patients with unexplained renal hypophosphatemia is being referred to our clinics.

Methods: We retrospectively evaluated all patients who were referred in the period of 2013-2017 because of unexplained renal hypophosphatemia in two university hospitals in the Netherlands (N=13).

Results: The median age was 51 years and ten patients were male. They did not show any other signs of tubulopathy and did not use drugs known to be associated with hypophosphatemia. Baseline characteristic are shown in table 1. We performed an ^{111}Indium-pentetreotide SPECT/CT in 5 patients and a ^{68}Ga-DOTA-TOC PET/CT scan in 3 patients. One of these scans showed an increased uptake suggestive of TIO. Genetic testing, performed in all patients, did not show a mutation in genes that are known to be associated with renal phosphate wasting (*DMP1, FGF23, FGFR1, GALNT3, PHEX, SLC34A1, SLC34A3, SLC9A3R1*).

Conclusions: We have evaluated a group of patients with unexplained renal hypophosphatemuia. Despite extensive and expensive additional investigations, the cause of renal phosphate loss remained unexplained in the majority of patients. The pretest probability of finding a phosphaturic hormone producing tumor on a scan with radiolabeled somatostatin analogs or to find a mutation with genetic analysis in a patient with aspecific complaints and an (inappropriately) normal FGF23 level is low. We therefore advise not to perform scans and genetic analyses as a standard workup in these patients.

Table 1 Baseline characteristics

	Median	Range	Reference value
Serum phosphate (mmol/l)	0.61	0.36-0.77	0.80-1.40
TmP/GFR (mmol/l)	0.50	0.38-0.55	0.80-1.40
Serum creatinine (µmol/l)	81	53-142	60-110
PTH (pmol/l)	5.2	3.2-8.7	1.0-6.5
25OHD (nmol/l)	71	40-135	>50
cFGF23 (RU/ml)	92	53-202	<125

TH-PO1110

Correcting Serum Potassium ([K]) in Critical Care Philip Goldwasser,[2] Andrea Roche-Recinos,[1] Robert H. Barth.[2] *[1]SUNY Downstate, Brooklyn, NY; [2]VA NY Harbor Healthcare System, Brooklyn, NY.*

Background: High platelet counts (PLT) positively bias serum [K] in chemistry panels (C_K). Because the C_K assay uses indirect potentiometry, it should also be positively biased by low total protein (TP), common in critical care, but this is unproved. Neither bias should affect [K] measured in gas panels (G_K) in whole blood anticoagulated with electrolyte-balanced heparin. Since even a subtle bias in C_K might be important at a decision limit, we sought to derive a practical correction for commonly seen values of PLT on C_K - G_K (ΔK), as well as to confirm TP bias.

Methods: In our critical care database (Clin Biochem 2017), we found 710 patients who had C_K, G_K, TP, and PLT obtained < 20 min. apart (median: 4 min). We excluded 17 cases with PLT ≥500 (units:10^9/L), as such values (i) are already known to bias C_K, and, (ii) being extreme, might skew the estimated effect of more usual PLT values. The independent effects of PLT and TP upon ΔK were estimated with multivariate methods.

Results: Mean values (±SE) were: PLT, 209±3.5 [range: 4-497]; TP, 6.5 ±0.04 g/dL [2.1-10.1]; ΔK, 0.27± 0.01 mEq/L [-1.8 to +2.5; 21% of values ≥ 0.5]. PLT correlated with both ΔK (r=0.13 $p<10^{-3}$) and TP (r= 0.19 $p<10^{-6}$). TP and ΔK didn't correlate (r=-0.06 p=0.11), possibly the result of confounding by PLT. No nonlinear effects of PLT category (TABLE) on ΔK were detected by ANOVA with polynomial contrast. By multiple linear regression, ΔK rose 0.053±0.014 mEq/L with each PLT rise of 100 ($p=10^{-4}$) and by 0.026±0.011 (p=0.02) with each 1 g/dL fall in TP (model adj. R^2=.024).

Conclusions: The accuracy of C_K can be improved simply with a 0.05 mEq/L reduction per 100 PLT rise. The effect of TP on C_K is minor, but, proportionally, the same as its effect on serum [Na]. Much of the variation in C_K relative to G_K is unexplained.

Funding: Veterans Affairs Support

Mean Values by PLT Category

PLT Category (mean)	N	CK	GK	ΔK (% cases ≥ 0.5)	TP
0-99 (65)	65	4.24	4.00	.238 ± .031 (17%)	5.9
100-199 (156)	284	4.30	4.05	.245 ± .019 (19%)	6.4
200-299 (242)	232	4.44	4.16	.278 ± .021 (21%)	6.7
300-399 (337)	70	4.49	4.14	.346 ± .045 (28%)	6.8
400-499 (443)	29	4.53	4.15	.383 ± .091 (38%)	6.4

TH-PO1111

Post-Hyperkalemia Prescription Patterns for Renin–Angiotensin–Aldosterone System Inhibitors (RAASis) in England Laura Horne,[1] Robert J. LoCasale,[1] Sharon Maclachlan,[2] Marvin V. Sinsakul,[1] James B. Wetmore.[3] *[1]AstraZeneca, Gaithersburg, MD; [2]Evidera, London, United Kingdom; [3]Hennepin County Medical Center, Minneapolis, MN.*

Background: It is unclear how physicians may adjust RAASi prescriptions for patients with hyperkalemia (HiK; elevated serum potassium [K^+]). We evaluated whether RAASi use is modified after incident HiK in England.

Methods: A retrospective cohort analysis of the linked Clinical Practice Research Datalink (CPRD) and Hospital Episode Statistics (HES) databases identified RAASi prescription changes after HiK. Patients (≥18 years) with an incident HiK event (first measurement of K^+ ≥5.0 mmol/L or HiK diagnosis code) using RAASis from 2009–2013 were included. Change in next RAASi prescription was defined as dose increase, augmentation with diuretic, no change, switch to other RAASi, dose decrease, or interruption. HiK severity was defined as K 5.0–≤5.5 (K^+ 5.0–≤5.5 mmol/L or CPRD diagnosis code with no lab results); K 5.5–≤6.0 (K^+ >5.5–≤6.0 mmol/L); or K >6.0 (K^+ >6.0 mmol/L or HES diagnosis code, regardless of K^+). Frequencies of post-HiK RAASi use were calculated overall, by clinical comorbidities, and by HiK severity.

Results: An HiK event was experienced by 59,465 RAASi users. Most patients (74.6%), including most with CKD (72.2%), continued the same RAASi drug/dose after HiK, even after K 5.5–≤6.0 (67.9%) and K >6.0 (45.6%). Augmentation with diuretics was uncommon, occurring in only 4.8% of the overall cohort, 10.4% of patients with heart failure (HF) and 13.0% of patients with K >6.0. Patients with HF more often switched RAASi and patients with K >6.0 more often interrupted treatment (**Table**).

Conclusions: Most patients continued the same RAASi drug and dose after incident HiK, even with K >6.0 and when renal function was likely reduced; addition of diuretics was uncommon. Whether this represents an optimal HiK treatment strategy needs further study.

Funding: Veterans Affairs Support, Commercial Support - AstraZeneca

	Overall	Chronic Kidney Disease	Diabetes	Hypertension	Heart Failure	K 5.0–≤5.5	K 5.5–≤6.0	K >6.0
N (%)	59,465 (100.0)	20,659 (34.7)	13,902 (23.4)	54,874 (92.3)	3344 (5.6)	54,532 (91.7)	4004 (6.7)	929 (1.6)
Dose increase, %	4.5	2.8	2.8	4.6	2.6	4.5	4.3	2.9
Augmentation, %	4.8	6.9	5.1	4.9	10.4	4.6	6.9	13.0
Continued, %	74.6	72.2	75.7	74.7	51.9	75.6	67.9	45.6
Switched, %	5.1	7.2	5.9	4.9	23.6	4.9	6.7	7.4
Dose decrease, %	1.0	1.3	0.9	1.0	1.4	0.9	1.9	2.0
Interruption, %	10.0	9.6	9.6	9.8	10.0	9.5	12.3	29.0

TH-PO1112

Maintained Efficacy and Safety of Sodium Zirconium Cyclosilicate for Hyperkalemia: 12-Month, Open-Label, Phase 3 Study Steven Fishbane,[8] Pablo E. Pergola,[15] David K. Packham,[6] Simon D. Roger,[9] Edgar V. Lerma,[2] Javed Butler,[11] Stephan Von haehling,[12] Bruce S. Spinowitz,[1] Geoffrey A. Block,[5] Scott H. Adler,[13] Bhupinder Singh,[7,14] Philip T. Lavin,[4] Peter A. McCullough,[3] Mikhail Kosiborod.[10] *[1]New York-Presbyterian/Queens and Weill Medical College of Cornell University, Flushing, NY; [2]UIC/ Advocate Christ, Oak Lawn, IL; [3]Baylor University Medical Center, Dallas, TX; [4]Boston Biostatistics Research Foundation, Framingham, MA; [5]Denver Nephrology, Denver, CO; [6]University of Melbourne, Melbourne, NSW, Australia; [7]ZS Pharma Inc., part of AstraZeneca, San Mateo, CA; [8]Hofstra Northwell Health School of Medicine, Great Neck, NY; [9]Renal Research, Gosford, NSW, Australia; [10]Saint Luke's Mid America Heart Institute, Kansas City, MO; [11]Stony Brook University, Stony Brook, NY; [12]University of Göttingen Medical Centre, Göttingen, Germany; [13]AstraZeneca, Gaithersburg, MD; [14]University of California, Irvine, Irvine, CA; [15]Renal Associates PA, San Antonio, TX.*

Background: We evaluated sodium zirconium cyclosilicate (ZS), an oral, highly selective potassium (K) binder for hyperkalemia over 12 mo.

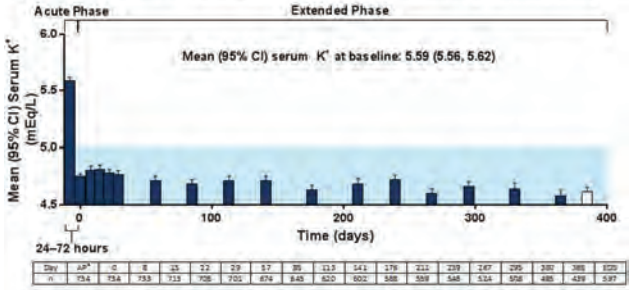
Methods: This international, multicenter, open-label, single-arm phase 3 trial enrolled 751 outpatients (≥18y) with K≥5.1mEq/L. In acute phase (AP), patients (pts) received 10g ZS TID for 24–72h until K ≤5.0mEq/L by point-of-care device (iSTAT). 746 pts with K 3.5-5.0mEq/L by iSTAT entered an extended phase (EP) and received ZS titrated to K ≤5.0mEq/L (5g to start, min 5g every other day, max 15g daily) for ≤12mo without diet or RAASi restrictions. Primary endpoints were measured by central laboratory: % with normal K acutely; % with K≤5.1 or ≤5.5mEq/L during 3-12mo; mean K; adverse events (AE).

Results: Pts had a median age of 64y, 74% had eGFR <60, 38% had heart failure and 70% were on RAASi. During AP, baseline mean K decreased from 5.6 to 4.8 mEq/L; K 3.5-5.0mEq/L was achieved in 99% and 78% of pts when assessed by i-STAT and central lab, respectively; K 3.5-5.5mEq/L was achieved in 99% (central lab). Overall, 466 (62.5%) completed EP. Mean daily ZS dose was 7.2g. Normokalemia was maintained up to 12 mo [Figure]. During EP, mean K ≤5.1 or ≤5.5mEq/L was achieved in 88% and 99% of pts over 3-12 mo, respectively; 489 (65.5%) pts experienced an AE and 21.6% a serious AE. There were 8 (1.1%) deaths. Common AEs (>5%) were hypertension, peripheral edema, urinary tract infection, constipation, and anemia. Laboratory-determined hypokalemia (<3.5mEq/L) occurred in 5.8% (1.2% with K 2.5-<3.0).

Conclusions: ZS treatment rapidly reduced K in pts with hyperkalemia and maintained normokalemia for up to 12 mo; safety profile was consistent with prior studies and acceptable for this patient population.

Funding: Commercial Support - AstraZeneca

Figure. Mean serum K⁺ over time in the acute and extended phases of study



White bar represents represents off-drug value (EOS [occurring 7 (± 1) days after the last administration of ZS])
AP, acute phase; CI, confidence interval; EOS, end of study.

TH-PO1113

Acute Efficacy of Sodium Zirconium Cyclosilicate for Hyperkalemia in Outpatients with Potassium ≥6.0 mEq/L: Post-Hoc Subgroup Analysis of a Phase 3 Trial David K. Packham,[3] Simon D. Roger,[6] Pablo E. Pergola,[9] Edgar V. Lerma,[1] Scott H. Adler,[8] Bhupinder Singh,[4,10] Philip T. Lavin,[2] Steven Fishbane,[5] Mikhail Kosiborod.[7] *[1]UIC/ Advocate Christ, Oak Lawn, IL; [2]Boston Biostatistics Research Foundation, Framingham, MA; [3]University of Melbourne, Melbourne, NSW, Australia; [4]ZS Pharma Inc., member of the AstraZeneca Group, San Mateo, CA; [5]Hofstra Northwell Health School of Medicine, Great Neck, NY; [6]Renal Research, Gosford, NSW, Australia; [7]Saint Luke's Mid America Heart Institute, Kansas City, MO; [8]AstraZeneca, Gaithersburg, MD; [9]Renal Associates PA, San Antonio, TX; [10]University of California, Irvine, Irvine, CA.*

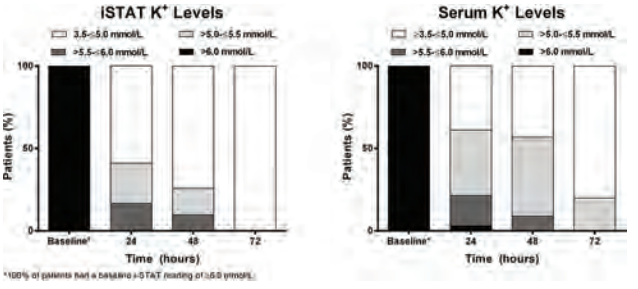
Background: Treatment for patients (pts) with potassium (K) ≥6.0 mEq/L is often hospital-based. Sodium zirconium cyclosilicate (ZS) is an investigational, oral, highly selective K-binder shown to restore normokalemia in hyperkalemic pts. We report subgroup results for outpatients with K ≥6.0 mEq/L during acute treatment in a 12 mo Phase 3 study.

Methods: We performed a post-hoc analysis of an international, multicenter, open-label, single-arm trial that enrolled 751 pts (≥18y) with point-of-care (iSTAT) K ≥5.1mEq/L. Immediate treatment decisions were based on iSTAT K data, and confirmed by central laboratory serum K. During acute phase, pts received 10g ZS TID (24–72h) until K 3.5–5.0 was achieved by iSTAT K. Post-hoc endpoints were: final K, change in K from baseline, achievement of K 3.5–5.0 and adverse events (AE) during acute phase. Proportions were calculated using last observation carried forward.

Results: At baseline, 126 (17%) of pts had serum K ≥6.0mEq/L. 99% completed the acute phase. Most pts (71%) had CKD and 74% used RAASi with no discontinuations observed. Median acute phase treatment duration was 1 day; median ZS dose was 30g. Mean (95% CI) baseline serum K was 6.2 (6.2, 6.3), final K was 4.6 (4.5, 4.7), with mean K change of -1.6 (-1.7, -1.5). The majority of pts achieved normokalemia; no patients had K >6.0 at 24h (Figure). Serum K values were higher than i-STAT K values. AEs were observed in 11 of 126 pts including 3 gastrointestinal disorders, 3 infections, 2 musculoskeletal disorders, 1 peripheral edema. No AEs were serious. There was 1 report of hypokalemia (3.0–<3.5 mEq/L) in the acute phase.

Conclusions: Oral outpatient treatment with ZS rapidly normalized K in pts with baseline K ≥6.0mEq/L with few adverse events and may be a viable therapy for this high-risk pt population.

Funding: Commercial Support - AstraZeneca



*100% of patients had a baseline i-STAT reading of ≥6.0 mmol/L

TH-PO1114

Risk Factors and Outcomes of Rapid Correction of Severe Hyponatremia Jason C. George,[2] Ion D. Bucaloiu,[2] Waleed Zafar,[1] Alex R. Chang.[2] *[1]Geisinger, Dnville, PA; [2]Geisinger Medical Center, Danville, PA.*

Background: Rapid correction of serum sodium is a concern in patients with severe hyponatremia and can have serious clinical consequences, including central pontine myelinolysis (CPM). Clinical risk factors of rapid correction and incidence of CPM has not been well-studied among patients with severe hyponatremia.

Methods: Using data from 1,352 inpatients in Geisinger Health System from 2001-2016 with serum sodium ≤120 mEq/L on admission, we examined possible predictors of overcorrection (demographics, comorbidity, medication, lab, and physical measurement data). Rapid correction of sodium (≥10mEq/L) was determined using sodium values closest to the 24 hour timepoint. CPM was determined by diagnostic codes and chart review of all brain MRIs.

Results: Mean age was 65.2 (SD 15.5) years, 54.9% were female, and 65.1% had a history of chronic hyponatremia (last outpatient sodium <135 mEq/L). The median change in sodium at 24 hours was 7.1 mEq/L (IQR 3.6–11.0), and 396 (29.3%) patients had rapid sodium correction. After multivariate adjustment, risk factors for overcorrection included female gender, schizophrenia, hypo- and hyperkalemia on presentation, and repletion of other electrolytes **(Table)**. History of chronic hyponatremia, outpatient loop diuretic use, and treatment at an academic center were associated with lower risk for rapid sodium correction. A total of 357 (26.4%) patients had brain MRIs completed during follow-up with 10 patients showing evidence of CPM (7 had documented rapid correction).

Conclusions: Consideration of various contributing factors, including age, gender, medications and co-morbidities could provide useful risk stratification for preventing rapid sodium correction and CPM.

	Model 1	Model 2
Academic center	0.57 (0.42 – 0.78)	0.59 (0.43 – 0.80)
Female	1.32 (0.97 – 1.80)	1.31 (0.96 – 1.79)
Age (per 1-y)	0.97 (0.96 – 0.98)	0.97 (0.96 – 0.98)
White	0.69 (0.25 – 1.92)	0.64 (0.22 – 1.84)
Schizophrenia	3.16 (1.33 – 7.48)	3.08 (1.28 – 7.41)
CCI	1.01 (0.95 – 1.07)	1.00 (0.94 – 1.06)
BMI >= 30 kg/m2	0.88 (0.64 – 1.21)	0.92 (0.66 – 1.26)
Baseline Na < 135	0.57 (0.42 – 0.76)	0.59 (0.44 – 0.79)
K >5 mEq/L	1.75 (1.22 – 2.53)	1.84 (1.27 – 2.66)
K < 3.5 mEq/L	1.52 (1.06 – 2.16)	1.08 (0.73 – 1.61)
Albumin (per 1 mg/dL)	1.53 (1.22 – 1.90)	1.50 (1.20 – 1.87)
OP loop diuretic	0.49 (0.31 – 0.75)	0.48 (0.31 – 0.74)
OP thiazide diuretic	0.89 (0.46 – 1.71)	0.87 (0.45 – 1.68)
IP hypertonic saline		1.52 (0.99 – 2.33)
IP electrolyte repletion		1.88 (1.35 – 2.62)
IP tolvaptan		1.36 (0.43 – 4.30)
Abbreviations: CCI (charlson comorbidity index), BMI (body mass index), OP (outpatient), IP (inpatient)		

TH-PO1115

Treatment of dRTA with an Innovative Combination Product as Compared to Current Standards of Care Aurélia Bertholet-Thomas,[1] Catherine Guittet,[2] Maria A. Manso,[2] Luc andre Granier.[2] [1]*Centre de référence des maladies rénales rares, Bron, France;* [2]*Advicenne, Nîmes, France. Group/Team: B21CS study investigators*.

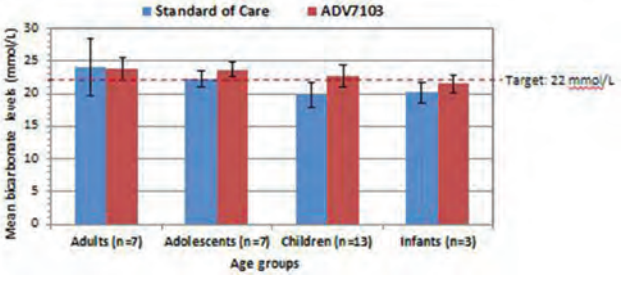
Background: Patients suffering from distal renal tubular acidosis (dRTA) require long-term treatment in order to restore and maintain physiological blood pH values. Products currently used as standards of care (SoC) require several daily administrations and are characterised by gastro-intestinal (GI) tolerability issues and bitter taste. A new innovative age-adaptable prolonged-release granule combination product (ADV7103), achieving adequate bicarbonataemia (blood bicarbonate ≥22 mM) with only two daily doses, together with improved tolerability and palatability, is proposed as an alternative. The objective of this work is to discuss the ability to restore bicarbonataemia with ADV7103 in comparison with SoC in dRTA patients.

Methods: A multicentre (N=13), open-label, non-inferiority, sequential study was performed. Adult and paediatric dRTA patients (N=37, 30 evaluable for bicarbonataemia) received their SoC and then ADV7103 at the most appropriate doses, both during 5-day periods. The alkali doses administered and the blood bicarbonate levels at steady state treatment conditions were compared. GI tolerability, palatability, easiness of administration and swallowing, were evaluated using visual analogue scales or 5-point facial hedonic scales.

Results: Blood bicarbonate levels were suboptimal in children and infants with the SoC and improved with two daily administrations of ADV7103. Less variability was observed with ADV7103 in adults and similar results were obtained with both treatments in adolescents. Improved GI tolerability, palatability and easiness of administration were observed in all age groups with ADV7103 compared to SoC. The improved ability to correct metabolic acidosis of ADV7103 was associated to the possibility of optimising dosing, while poor tolerability and acceptability appeared to limit further dosing increases with SoC.

Conclusions: ADV7103 is the first prolonged-release alcalinizing product improving bicarbonataemia control in dRTA patients compared with SoC, with less GI side effects and very good acceptability.

Funding: Commercial Support - Advicenne



TH-PO1116

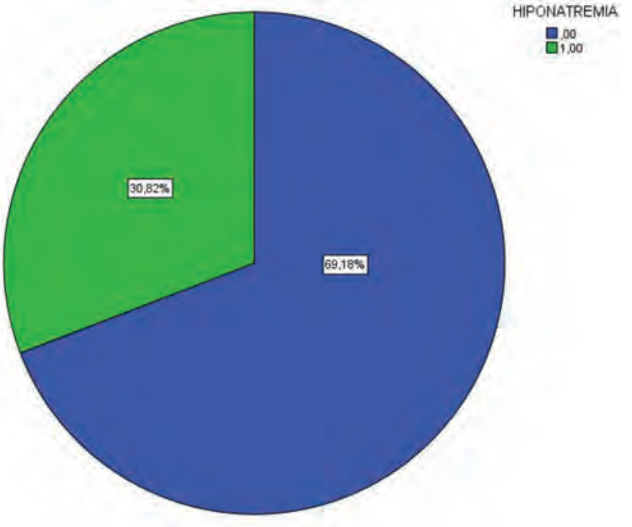
Prevalence of Hyponatremia in Dengue Infected Patients Daniel Caputo,[1] Armando L. Negri,[3] Juan Carlos Ayus,[4] Carlos Eghi,[2] Graciela E. Cabral,[2] Ydania Fernandez carreño.[2] [1]*Hospital Nacional Alejandro Posadas, El Palomar. Buenos Aires, Argentina;* [2]*Hospital Posadas, Buenos Aires, Argentina;* [3]*Instituto de Investigaciones Metabólicas, Buenos Aires, Argentina;* [4]*Renal Consultants of Houston, Houston, TX*.

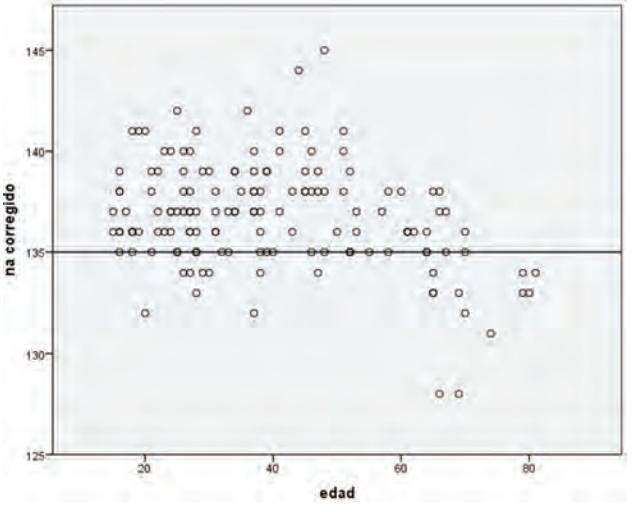
Background: PHO-WHO (Dengue guidelines 2016), and CDC recommended high water intake in patients with dengue. However, no information exists about the prevalence of hyponatremia in newly infected patients.

Methods: Cross-sectional study in patients with newly diagnosed dengue infection in Argentina from January 2016 to April 2016. Hyponatremia was defined as serum sodium concentration <=135 mEq/L. Natremia was corrected in patients with hyperglycemia. Patients with creatinine greater a 1,6 mg/dl were excluded.

Results: We evaluated 146 patients with dengue diagnosis confirmed by IgM serology or PCR. Hyponatremia was present in 30.8% of the patients **Figure 1**. In the multivariate logistic regression model, the OR of hiponatremia adjusting for age and sex was significant in the group of over 65 years; OR 9.2 (IC95 2.9-28.9) p= 0,001. **Figure 2**

Conclusions: The prevalence of hyponatremia in newly infected patients with dengue, especially in older patients is high. Electrolyte evaluation should be done at admission in all patients with dengue and routine use of hypotonic fluids should be avoided in these patients.





TH-PO1117

Safety and Efficacy of ADV7103, an Innovative Prolonged-Release Oral Alkalising Combination Product, after 6-Months of Treatment in Distal Renal Tubular Acidosis (dRTA) Patients Aurélia Bertholet-Thomas,[1] Catherine Guittet,[2] Maria A. Manso,[2] Luc andre Granier.[2] [1]*Centre de référence des maladies rénales rares, Bron, France;* [2]*Advicenne, Nîmes, France. Group/Team: B21CS study investigators*.

Background: A new innovative age-adapted prolonged-release granule combination of potassium citrate and potassium bicarbonate, ADV7103, has been developed in order

to achieve sustained physiological blood pH values in dRTA patients with a simplified dosing regimen. The current standards of care (SoC) require multiple administrations and are not always well tolerated. The objective of this clinical study was to assess safety of ADV7103 after treatment for 6 months as well as to follow-up bicarbonate levels and evaluate patient's satisfaction.

Methods: Adult and pediatric dRTA patients (N=30) were included in a multicentre (N=12), open-label, 24-month study. They received ADV7103 twice a day at appropriate doses. Preliminary data after 6 months of treatment were analysed, including adverse events and bicarbonataemia. Improvement of quality of life was evaluated at by patients and/or their parents using a 100-mm visual analogue scale.

Results: A total of 17 patients presented adverse events. Among the 45 adverse events observed, 40 were unrelated, 1 (abdominal pain) was unlikely related, 3 (alopecia, dyspepsia and abdominal pain) were possibly related, and 1 (diarrhea) was probably related to the treatment. The 5 latter adverse events were all of mild intensity. There was only one serious adverse event unrelated to the product (wisdom teeth removal). Efficacy was maintained after 6 months treatment, with blood bicarbonate levels above 21 mM in 79% of the patients. Only three patients presented bicarbonatemia levels below 20 mM. ADV7103 doses ranged from 1.3 to 7.2 mEq/kg/day. Patients and/or their parents were extremely satisfied with ADV7103. The change of alkalising treatment from the their SoC to ADV7103 allowed an average improvement of their quality of life of 80.5%, ranging from 76 to 98% depending of the age group considered.

Conclusions: The present preliminary results confirm the excellent safety and efficacy of ADV7103, a combination product allowing treatment with only 2-daily doses. The level of satisfaction of the patients is very high and clinicians are expecting registration of the product for first-line treatment of dRTA.

Funding: Private Foundation Support

TH-PO1118

Prognostic Factors in Sepsis Patients Who Have Undergone Direct Hemoperfusion with Polymyxin B-Immobilized Fibers Aiko Okubo, Ayumu Nakashima, Shigehiro Doi, Toshinori Ueno, Takao Masaki. *Hiroshima University Hospital, Hiroshima, Japan.*

Background: In 2016, the definitions of sepsis and septic shock were reviewed by the Society of Critical Care Medicine and Sequential Organ Failure Assessment (SOFA) and a quick SOFA score was added to those definitions. Direct hemoperfusion therapy with polymyxin B-immobilized fiber cartridge (PMX-DHP) has been widely used to treat sepsis and septic shock. However, prognostic factors are not well understood. We retrospectively assessed the prognostic factors of patients who had received PMX-DHP for sepsis and septic shock.

Methods: Data on 71 patients with severe infection who had undergone PMX-DHP from January 2006 to August 2015 were included in this study. Participants were re-evaluated according to the criteria of the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) and all were confirmed to satisfy the new definition of sepsis. The patients were divided into groups based on having survived (n=59) or not survived (n=12) for 28 days after PMX-DHP. Clinical data before and after PMX-DHP were compared between the two groups.

Results: In the non-survivor group, the Glasgow Coma Scale score before PMX-DHP was significantly lower than in the survivor group (12 [6 to 14] vs 14 [12 to 15], P<0.01). Furthermore, pH after the first PMX-DHP session was significantly lower in non-survivors than in survivors (7.28±0.23 vs 7.39±0.06, P=0.03). The only factor identified by multivariate analysis as significantly associated with 28-day mortality was pH after the first PMX-DHP session (odds ratio, 0.93; 95% CI, 0.83–0.99; P=0.02).

Conclusions: pH after the first PMX-DHP session is an independent risk factor for mortality in patients receiving PMX-DHP for sepsis and septic shock.

TH-PO1119

Urinary Acid Excretion in Overweight Patients with CKD Yuichiro Izumi,[3] Koji Eguchi,[5] Yushi Nakayama,[3] Hideki Inoue,[6] Hiroshi Nonoguchi,[2] Yutaka Kakizoe,[1] Takashige Kuwabara,[4] Masashi Mukoyama.[4] *[1]Department of Nephrology, Kumamoto university graduate school of medical sciences, Kumamoto, Japan; [2]Kitasato University Medical Center, Kitamoto, Japan; [3]Kumamoto University, Kumamoto, Japan; [4]Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan; [5]Kumamoto University Graduate School of Medicine, Kumamoto, Japan; [6]Kumamoto University School of Medicine, Kumamoto, Japan.*

Background: Urinary ammonium excretion, which reflects acid excretion by the kidney, has been suggested as a predictor for the chronic kidney disease (CKD) outcome. Overweight is one of the risk factors for progression of CKD. We examined urinary acid excretion in overweight CKD patients.

Methods: 25 Japanese out-patients with CKD who were treated with diet and medical therapy in our hospital were enrolled to evaluate acid excretion by the kidney. A 24-h urine collection was performed one day before visiting our hospital to determine excretion of creatinine, protein, urea, ammonium, pH, titratable acid (TA) and other electrolytes. Blood test was performed at visiting day. Their creatinine clearance (Ccr) corrected by body surface area was from 10 to 120 ml/min. For further analysis, patients, whose Ccr was > 30 ml/min, were divided into two groups: 11 normal (BMI 21 ± 2 kg/m^2) and 10 overweight (28 ± 3 kg/m^2) patients. Acid excretion between two groups was compared.

Results: Both ammonium (Figure 1) and TA excretions decreased with the decrease of Ccr (r^2 = 0.31, P = 0.0036 and r^2 = 0.20, P = 0.028). Between two groups, ammonium excretion was significantly decreased in overweight patients compared to that in normal weight patients (Figure 2). TA excretion tended to be increased in overweight group, resulting in no difference of total acid excretion (calculated by ammonium + TA) between the two groups. While protein and sodium chloride intakes were greater in overweight, net endogenous acid production (NEAP) and Ccr were not different between the two groups.

Conclusions: There might be a modulation of acid excretion mechanism in overweight patients with CKD.

Funding: Government Support - Non-U.S.

Figure 1

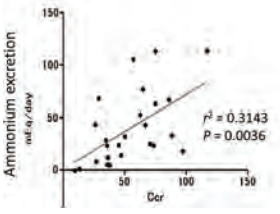
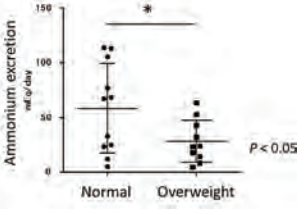


Figure 2



TH-PO1120

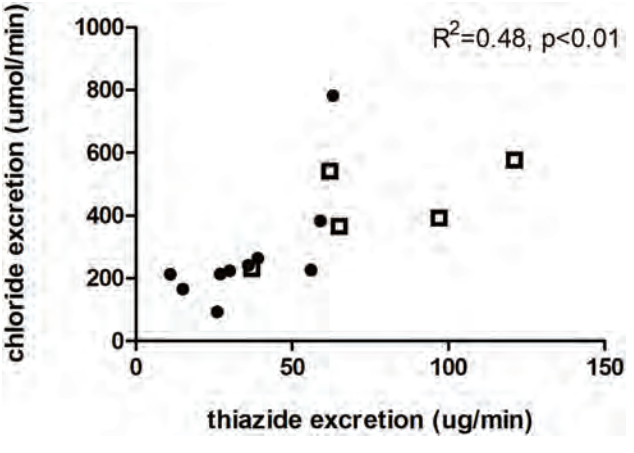
Thiazide Test in CKD: Variable Test Results Due to Differences in Thiazide Excretion Anneke Bech,[2] Tom Nijenhuis,[3] Jack F. Wetzels.[1] *[1]Radboud University Medical Center, Nijmegen, Netherlands; [2]Radboud University Nijmegen Medical Center, Nijmegen, Nijmegen, Netherlands; [3]Radboud university medical center, Lent, Netherlands.*

Background: The thiazide test is used to test the functionality of the sodium-chloride co-transporter (NCC). The test is used in the diagnostic work-up of patients with suspected Gitelman syndrome. Reference values for the thiazide test are based on small studies in young healthy volunteers. Patients presenting with tubular disorders however frequently are older and/or have a compromised kidney function. We observed a lower increase in fractional chloride excretion (delta FeCl) in patients with CKD and a remarkable variation in this parameter. In this study, we evaluated urinary thiazide excretion as an explanatory variable.

Methods: We performed thiazide tests in 10 individuals with CKD. Mean age was 65 years, mean serum creatinine was 124 μmol/l and seven individuals were male. Hydrochlorothiazide was measured in urine samples by LCMS.

Results: The median delta FeCl was 2.1% (range 0.0-3.9%). In 7 patients with CKD, the delta FeCl was below our threshold of 2.5% in healthy volunteers. CKD patients had a lower median thiazide excretion than young healthy individuals (33 μg/min vs 65 μg/min, p=0.01). There was a correlation between thiazide excretion and chloride excretion (Figure).

Conclusions: The standard thiazide test cannot be used in patients with CKD to evaluate the function of NCC. Our study indicates that invalid test results are likely explained by reduced tubular secretion of hydrochlorothiazide. Additional studies are needed to see if e.g. chloride excretion factored for thiazide excretion is a useful alternative parameter. Figure**:** urine hydrochlorothiazide concentration at maximal FeCl (closed circles CKD subjects, open squares young healthy individuals)



TH-PO1121

Proximal Tubular Function in Patients with Multiple Sclerosis Andrew S. Allegretti,[3] Nydjie Payas,[1] Scott Krinsky,[2] Ravi I. Thadhani,[3] Ishir Bhan.[4] *[1]Biogen, Cambridge, MA; [2]Mass General Hospital, Boston, MA; [3]Massachusetts General Hospital, Boston, MA; [4]Biogen, Inc, Cambridge, MA.*

Background: A recent database study revealed evidence of a higher than expected prevalence of Fanconi syndrome diagnosed in patients with multiple sclerosis (MS) relative to the general population. Proximal tubular function, which is altered in Fanconi

syndrome, has not been evaluated in patients with MS. Our objective was to compare the patterns of urinary electrolyte and amino acid excretion between MS and age- and gender-matched non-MS controls.

Methods: Subjects aged 18 or older with a diagnosis of MS were eligible to participate as cases; controls were age- and gender-matched individuals without MS. Exclusion criteria included known chronic kidney disease or kidney transplantation, use of a drug known to inhibit renal carbonic anhydrase, or use of a drug known to cause Fanconi syndrome. A blood sample was collected for a basic metabolic panel plus phosphorus. Urinalysis was performed and urine was assayed for electrolytes, glucose, creatinine and a panel of 28 amino acids. Univariate analysis was performed using Chi square and Wilcoxon testing.

Results: 11 MS patients (10 females, 1 male) participated, age and gender matched to 20 non-MS controls (17 females, 3 males). 10/11 MS patients were on disease-modifying therapy, including dimethyl fumarate (4/11), glatiramer (2/11), fingolimod (2/11), interferon (1/11), and natalizumab (1/11). Median age among MS patients and controls was 45 [IQR 32, 59] and 53 [IQR 31, 63] years, respectively. Race, ethnicity and gender were similar between groups. Mean levels of 17 /28 (61%) urinary amino acids were higher in MS patients than controls ($p < 0.05$ for carnosine, glutamate, hydroxyproline, and proline). Urinary amino acids were generally in the normal range, but abnormal levels were more common in MS patients for 8 amino acids and normal in all individuals for the remainder. Increased urinary amino acids were not associated with a particular MS treatment. MS patients had greater urine sodium levels (97 [IQR 73, 125] vs. 55 [IQR 29, 75] mmol/L; $p = 0.03$) and similar levels of urine potassium, chloride and phosphorus.

Conclusions: MS patients with normal kidney function may be at higher risk of urinary amino acid wasting. Future studies are needed to verify these findings and to elucidate whether MS or its treatment predispose to previously unrecognized proximal tubular dysfunction.

Funding: Commercial Support - Biogen, Inc

TH-PO1122

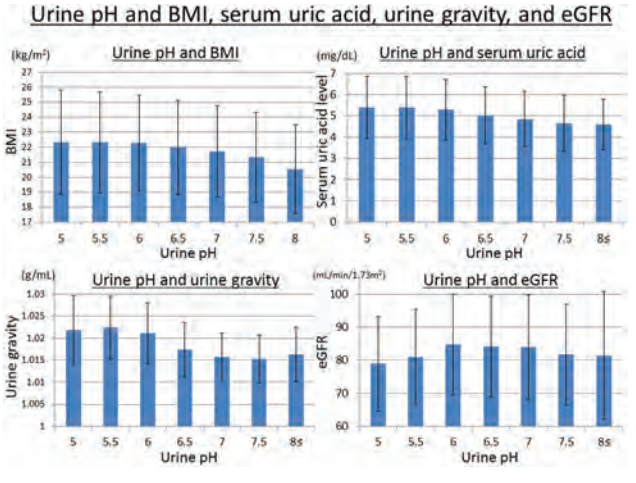
Associations between Urine pH and Body Mass Index, Serum Uric Acid, Urine Gravity, and Kidney Function Masanari Kuwabara,[2] Carlos A. Roncal-jimenez,[1] Ana Andres-hernando,[2] Yuka Sato,[1] Thomas Jensen,[1] Gabriela E. Garcia,[2] Miguel A. Lanaspa,[2] Richard J. Johnson.[2] *[1]University of Colorado, Aurora, CO; [2]University of Colorado Denver, Aurora, CO.*

Background: Obesity and metabolic syndrome are increasing in decades. Obesity usually decreases urine pH, and low urine pH is a good marked for metabolic diseases. Serum uric acid is also a good marker for metabolic syndrome. Uric acid is crystallized in low pH, which induces renal dysfunctions. This study is to clarify the association between urine pH and body mass index, serum uric acid, and kidney function.

Methods: This study is a large-scale cross-sectional study. We retrospectively analyzed the database from 90,143 Japanese people (men, 49.1%; age, 46.3 ± 12.0 years) undergoing annual medical examination at the Center for Preventive Medicine, St. Luke's International Hospital, Tokyo between January 2004 and June 2010. The subjects with any current medication were excluded. We tested the association between body mass index and urine pH. Furthermore, we analyzed the association between urine pH and body mass index (BMI), serum uric acid, urine gravity, and estimated glomerulus filtration rate (eGFR) levels in a healthy population.

Results: Of 90,143 subjects, 21,574 subjects with current medication and 595 subjects without urine data were excluded, and finally 67,974 subjects were enrolled in the study. Urine pH had significantly inverse correlation with BMI ($r=-0.1$, $p<0.001$), serum uric acid ($r=-0.12$, $p<0.001$), and urine gravity ($r=-0.28$, $p<0.001$). Moreover, low urine pH (less than 6.0, eGFR=80.9±14.4) and high urine pH (more than 7, eGFR=81.7±15.9) showed significantly lower eGFR compared to normal urine pH (from 6 to 7, eGFR=84.5±15.3) ($p<0.001$). **Figure** showed the mean level of BMI, serum uric acid, urine gravity and eGFR in each urine pH.

Conclusions: Low urine pH (less than 6) becomes a good marker for high BMI, high serum uric acid, and dehydration status (high urine gravity), which is associated with low eGFR.



TH-PO1123

A Low Initial Serum Sodium Level Is Associated with an Increased Risk of Overcorrection in Patients with Chronic Profound Hyponatremia: A Retrospective Cohort Analysis Sae Aratani,[1,8] Masahiko Hara,[4] Masahiko Nagahama,[5] Fumika Taki,[6] Miyuki Futatsuyama,[7] Shuichi Tsuruoka,[3] Yasuhiro Komatsu.[2] *[1]Nephrology, Nippon Medical School Hospital, Tokyo, Japan; [2]St. Lukes International Hospital, Tokyo, Japan; [3]Nephrology, Nippon Medical School, Tokyo, Japan; [4]Osaka City University Graduate School of Medicine, Osaka, Japan; [5]St. Luke's international hospital, Tokyo, Japan; [6]Nephrology, St. Lukes' International Hospital, Tokyo, Japan; [7]Nephrology, st.luke's international hospial, Tokyo, Japan; [8]Nephrology, St. Luke's International Hospital, Tokyo, Japan.*

Background: Even with abundant evidence for osmotic demyelination in patients with hyponatremia, the risk factors for overcorrection have not been fully investigated. Therefore the purpose of this study is to clarify the risks for overcorrection during the treatment of chronic profound hyponatremia.

Methods: This is a single-center retrospective observational study. We enrolled 56 adult patients with a serum sodium (SNa) concentration of ≤125 mEq/L treated by nephrologists in an intensive care between February 2012 and April 2014. The impact of patient parameters on the incidence of overcorrection was estimated using univariable and multivariable logistic regression models. Overcorrection was defined as an increase of SNa by >10 mEq/L and >18 mEq/L during the first 24 and 48 hours, respectively.

Results: The median age was 78 years, 48.2% were male, and 94.6% of the patients presented with symptoms associated with hyponatremia. The initial median SNa was 115 mEq/L (quartile, 111–119 mEq/L). A total of 11 (19.6%) patients met the criteria for overcorrection with 9 (16.0%) occurring in 24 hours, 6 (10.7%) in 48 hours, and 4 (7.1%) in both 24 and 48 hours. Primary polydipsia, initial SNa, and early urine output were the significant risk factors for overcorrection on univariable analysis. Multivariable analysis revealed that the initial SNa had a statistically significant impact on the incidence of overcorrection with an adjusted odds ratio of 0.84 (95% confidence interval, 0.70–0.98; $p=0.037$) for every 1 mEq/L increase. Additionaly, the increase in SNa during the first 4 hours and early urine output were significantly higher in patients with overcorrection than in those without ($p=0.001$ and 0.005, respectively).

Conclusions: An initial low level of SNa was associated with an increased risk of overcorrection in patients with profound hyponatremia. In this regard, the rapid increase in SNa during the first 4 hours may play an important role.

TH-PO1124

New Sodium Equation with Built-In Rate of Correction to Simplify Therapeutic Orders for Hyponatremia or Hypernatremia Sheldon Chen. *MD Anderson, Houston, TX.*

Background: Both hyponatremia and hypernatremia occur frequently in hospitalized patients. To understand these disorders, investigators have mathematically modeled the serum sodium concentration in humans. Edelman published the seminal equation (*J Clin Invest* 37: 1236-56, 1958), and others have refined it for clinical use.

Methods: The model has been expanded to incorporate time, and then a term explicitly appears for a rate of sodium correction, a key consideration to avoid treatment complications like osmotic demyelination. The equation is solved for the fluid administration rate to assist the clinician with the hospital order in the management of dysnatremia. To handle the calculations, we programmed the equation into a spreadsheet that aggregates the relevant data, *e.g.*, urine [Na+K], and provides immediate results to facilitate patient care on rounds.

Results: Entering baseline data on the inputs and outputs of Na/K/water along with the patient's body weight, a clinician can use the new sodium equation to aim for a desired serum [sodium] over a safe timeframe. The formula returns the infusion rate for any treatment fluid such as normal saline, hypertonic saline, or 5% dextrose in water. The formula can also calculate treatment in terms of the dosage of salt tablets. With a slight modification, it can handle an abrupt water diuresis and appropriately decrease the IV fluid rate so that hyponatremia is not overcorrected. Demonstrating efficacy, the new sodium equation has performed well in real-life cases of hyponatremia and hypernatremia.

Conclusions: The proposed equation improves upon existing sodium equations by accounting for all inputs and outputs, if known, and incorporating a rate of correction. The quantitative approach provides a rational and effective basis for prescribing intravenous fluids and salt tablets in the hospital.

TH-PO1125

Diagnostic Accuracy of a Central Venous Blood Gas in the Diagnosis of Acid-Base Disorders in the Medical Intensive Care Unit Sarah J. Schrauben, Dan Negoianu, Raphael M. Cohen, Jeffrey S. Berns. *University of Pennsylvania, Philadelphia, PA.*

Background: Acid-base disturbances are frequently encountered in critically ill patients. Arterial blood gas (ABG) is the gold standard in the diagnosis but has potential hazards to the patient. For patients with a central venous catheter, venous blood gas (VBG) sampling may be an alternative, less-invasive diagnostic tool. However, little is known about the central VBG diagnostic accuracy. The primary objective of this study was to assess the accuracy of a central VBG for the diagnosis of acid-base disorders in critically ill adult patients.

Methods: This was a cross-sectional single blinded study at two university-based urban hospitals. Study participants were adults in a medical intensive care unit (MICU) that had simultaneously drawn ABG and central VBG samples. Expert acid-base diagnosticians, all nephrologists, were blinded to the clinical data and blood gas origin to interpret the acid-base disorder(s) from each sample. Blood gas samples were classified as: no disorder, metabolic acidosis, metabolic alkalosis, respiratory acidosis, respiratory acidosis, or as a mixed disorder. Diagnostic accuracy of central VBG-based diagnoses were compared to ABG-based diagnoses by assessing percent clinical agreement, sensitivity and specificity.

Results: The study involved 23 participants. The most common underlying primary diagnoses were respiratory-related (45.5%) and sepsis-related (40.9%). Overall, the central VBG had 100% sensitivity for metabolic acidosis, metabolic alkalosis, and respiratory acidosis, and 71% for respiratory alkalosis, and high percent clinical agreement, ranging from 75-94%, with a lower agreement of 57% for respiratory alkalosis. VBG-based diagnoses in vasopressor dependent patients (n=13, 56.5%) performed very similarly.

Conclusions: In critically ill adult patients, central VBG detects acid-base disturbances with good diagnostic accuracy, even in shock states. This study supports the use of central VBG for diagnosis of acid-base disturbances in MICU patients.

Funding: NIDDK Support

Diagnostic Accuracy of VBG-based Diagnosis compared to ABG-based Diagnosis.

Disorder	Sensitivity	Specificity	% Clinical Agreement
Metabolic Acidosis	100%	64%	87.5%
Metabolic Alkalosis	100%	100%	75%
Respiratory Acidosis	100%	60%	94%
Respiratory Alkalosis	71%	100%	57%

TH-PO1126

Primary Aldosteronism Associated with a Mutation of CACNA1H Kendra E. Wulczyn,[4] Robert L. Nussbaum,[1] Lowell J. Lo,[2] Edward Perez-Reyes,[5] Meyeon Park.[3] *[1]Invitae Corp, San Francisco, CA; [2]None, San Francisco, CA; [3]UCSF, San Francisco, CA; [4]University of California San Francisco, San Francisco, CA; [5]University of Virginia, Charlottesville, VA.*

Background: Several genetic mutations have been described in rare forms of primary aldosteronism (PA). We report a case of aldosteronism with hypokalemia and hypotension, found to have a mutation of CACNA1H, encoding a voltage-gated calcium channel ($Ca_v3.2$) expressed in adrenal glomerulosa.

Methods: A 31 year old female with type III Ehlers-Danlos syndrome and postural orthostatic tachycardia syndrome (POTS) presented for evaluation of chronic hypokalemia. The patient was receiving infusions of potassium every 2-4 weeks (baseline K 2.6-3.6 mmol/L) for profound weakness. Prior evaluation had revealed elevated plasma aldosterone level (38 ng/dL) and suppressed renin (0.17 pg/dl), and MRI demonstrated normal appearing adrenal glands. Low-dose spironolactone was initiated, which improved the hypokalemia, yet the patient still required monthly potassium infusions for symptoms. A laboratory assessment was made pre- and post-hydration with 2L IVF, supplemented with 25 mEq K and 2.5g Mg (shown in table below). Results demonstrated persistently elevated aldosterone level despite volume repletion (of note, patient was unable to stop spironolactone for the testing). During this course, results of whole exome sequencing (Personalis, Inc.) revealed a de novo loss-of-function missense mutation, R890H, in the voltage-sensing domain of the CACNA1H gene.

Results:

Conclusions: POTS has been associated with both increased and decreased activity of the RAAS system; however, in this patient, laboratory testing pre- and post-fluid resuscitation suggest aldosterone secretion was independent of volume status. Therefore, the mutation of CACNA1H, not previously described, is the likely cause of pathologic aldosterone secretion. $Ca_v3.2$ has been implicated in genetic forms of PA in which a mutation to CACNA1H results in increased intracellular Ca^{2+}, the signal for cholesterol transport into mitochondria and induction of steroidogenesis. Unique to our case is the absence of hypertension experienced by this patient, expanding our understanding of the different phenotypes associated with mutations of CACNA1H.

	Pre-Hydration	Post-Hydration
Aldosterone (ng/dl)	17	45
Plasma Renin Activity (pg/dl)	0.23	0.27
Potassium, serum (mmol/L)	3.8	4.1
Potassium, 24-hr urine (mmol/d)	38.5	61.4
Sodium, 24-hr urine (mmol/d)	94	99

TH-PO1127

Relationship between Central Venous, Peripheral Venous, and Arterial Potassium in the ICU Richard M. Treger,[1,2] Caleb Hsieh,[3,2] Tristan Grogan,[4,2] Nader Kamangar.[3,2] *[1]Nephrology, VA Greater Los Angeles Healthcare System, Los Angeles, CA; [2]David Geffen School of Medicine at UCLA, Los Angeles, CA; [3]Critical Care, Olive View-UCLA Medical Center, Sylmar, CA; [4]Medicine and Biostatistics, UCLA, Los Angeles, CA.*

Background: As shown in small studies evaluating regional hypoperfusion, venous potassium concentration (K^+) may better reflect interstitial and tissue K^+ than arterial values, and thus better predict serious cardiac manifestations of hyperkalemia. Moreover, because central veins drain a much greater tissue mass (muscle and splanchnic) than peripheral veins, discrepancies between peripheral venous (PV), central venous (CV), and arterial (Art) K^+ may exist, especially in states of global hypoperfusion such as sepsis. No prior study has examined this relationship.

Methods: Art, CV, and PV samples were prospectively obtained within 10 minutes of each other from single-center adult medical ICU patients.

Results: 51 paired samples from 23 patients were included. The correlations between Art-PV K^+, Art-CV K^+ and CV lactate (Figure) were not statistically significant ($p = 0.60$ and 0.99, respectively). The correlations between PV and Art K^+, as well as CV and Art K^+ yielded an R^2 of 0.83 and 0.83, respectively. Bland-Altman plots of Art K^+ and PV K^+, as well as Art K^+ and CV K^+ showed 95% limits of agreement of -0.42 to 0.35 and -0.43 to 0.51, respectively.

Conclusions: In medical ICU patients with global hypoperfusion, CV K^+ was not different from that of Art and PV K^+ and did not correlate with serum lactate. This disproved our hypothesis that in global hypoperfusion CV blood would demonstrate higher K^+ and better reflect tissue K^+ compared with Art blood. In fact, CV and PV K^+ showed high correlation and strong agreement with Art K^+ and can be used interchangeably. This contrasts with prior studies of regional hypoperfusion that demonstrated a higher K^+ in venous blood relative to arterial blood, reflective of local interstitial and tissue K^+ levels. Our results likely did not demonstrate this because of augmented intracellular K^+ shifting and CV system dilution of K^+ in global hypoperfusion.

Funding: Veterans Affairs Support

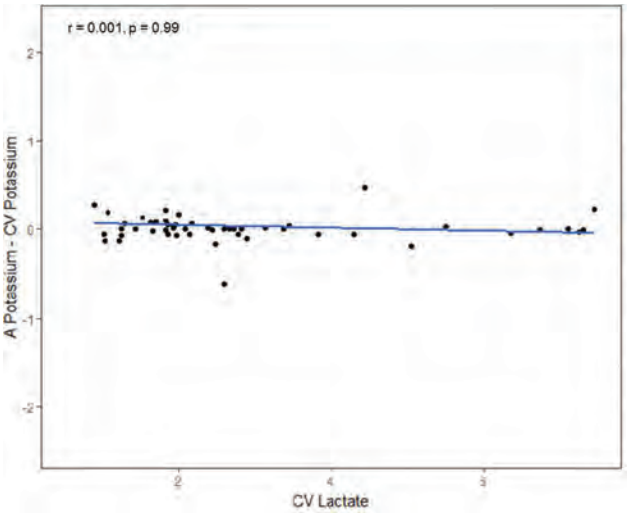


Figure: Correlation between CV Lactate and Art-CV Potassium

TH-PO1128

Rate of Cisplatin Salt Wasting (CSW) Sheron Latcha.[1,2] *[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Weill Cornell, New York, NY.*

Background: CSW likely results from cisplatin injury to the proximal renal tubules, the major site of sodium and water reabsorption. Up to 10% of patients developed CSW in early clinical studies with cisplatin. Subsequently, CSW has only been rarely reported. The rate of CSW may have declined due to agressive hydration with normal saline (NS), which is renoprotective, or it may be due to under recognition and therefore under reporting of CSW.

Methods: We obtained retrospective data on adult patients who received cisplatin from 1/1/2014-12/34-2015 who met the following criteria: sodium ≤135mEq/l, received IV normal saline (NS) ≥24H after cisplatin administration, and diagnosis codes for hypotension, polyuria, dehydration, hypovolemia or shock. A nephrologist randomly reviewed the medical record of 35% of episodes, and determined if the patient had SIADH, dehyration, CHF, CSW or other cause for to explain the criterion outlined above. The diagnosis of CSW was based on the findings of hypotension, nocturia, polyuria with the absence of other causes of dehydration (decreased oral intake, infection, diarrhea).

Results: 652 patients and 829 hyponatremic episodes were identified; 300 episodes in 230 patients were reviewed; 48 episodes were removed from analysis (record incomplete, duplicates)/ 252 episodes were analyzed. CSW was identified in 8 (3.2%) epispodes, dehydration in 111 (44%), SIADH in 86 (34.1%) and CHF 11 (4.4%). Urine sodium and osmolarity were checked in 41 (16%) and renal consults in 5 (2%) episodes. With the exception of episodes of CHF, hyponatremia was empirically treated with IV NS, even when patients were normotensive, and had no tachycardia or edema. Patients were not asked for symptoms of polyuria, nocturia or thirst.

Conclusions: CSW is likely underdiagnosed and underreported. Nausea is most often interpreted as a cause of dehydration as opposed to a symptom of hyponatremia itself and patients complaining of dizziness and lightheadness are assumed to have dehydration from decreased oral intake. Patients were not specifically questioned about symptoms of CSW, specifically polyuria, nocturia or thirst. Orthostatic blood pressure reading, and urine and serum sodium and osmolarity are rarely used to evaluate hyponatremia. Consequently, patients with CSW may remain hyponatremic because they are not receiving adequate hydration, and patients with SIADH are inappropriately receiving IVF.

TH-PO1129

Occurrence of Proton-Pump Inhibitor-Induced Severe Hypocalcemic Hypomagnesemia Only after Thiazide Withdrawal: A Case Report Yohei Kita, Atsuko Uehara, Tsutomu Sakurada, Yugo Shibagaki. *Division of Nephrology and Hypertension, Department of Internal Medicine, St. Marianna University School of Medicine., Kawasaki-shi, Kanagawa, Japan.*

Background: Although relatively common, hypomagnesemia is often undiagnosed because its clinical significance is underrated and therefore magnesium levels are not routinely checked. Symptomatic hypocalcemia is a key indicator for a diagnosis of hypomagnesemia; however, if patients are administered thiazide, hypocalcemia is masked, which may disguise hypomagnesemia. We describe a case of symptomatic hypocalcemic hypomagnesemia after thiazide withdrawal. The patient was a 79-year-old woman with a medical history of asthma, chronic heart failure, diabetes mellitus, and hypothyroidism. Five weeks prior to admission, she developed thiazide-induced hyponatremia and thiazide was discontinued. Two weeks before admission, she experienced hand tremors and found it difficult to hold chopsticks. Two days before admission, she vomited and was admitted to our hospital. A physical examination revealed Trousseau's sign and her albumin-corrected calcium and magnesium levels were 5.8 mg/dL and 0.4 mg/dL, respectively, revealing hypocalcemia and hypomagnesemia. Urine magnesium was low, which indicated increased gastrointestinal magnesium excretion. We reviewed the medical charts and discovered that 4 years earlier, her serum magnesium was 2.2 mg/dL; but 2 years earlier, it had already decreased to 0.4 mg/dL, which indicated that her hypomagnesemia had been present for at least 2 years. As the patient had started proton-pump inhibitor therapy approximately 2 years previously, proton-pump inhibitor-induced hypomagnesemia was strongly suspected. Hypocalcemia was thought to result from decreased parathyroid hormone secretion and increased parathyroid hormone resistance induced by hypomagnesemia. We hypothesized that symptomatic and profound hypocalcemia had not developed over the previous 2 years because the concomitant use of thiazide contributed to calcium reabsorption; thus, the thiazide withdrawal 5 weeks earlier had triggered progressive hypocalcemia. We withdrew the proton-pump inhibitor and prescribed a calcium and magnesium supplement, which normalized serum calcium and magnesium with symptomatic improvements. Our findings indicated that even severe hypomagnesemia may be overlooked in patients with concomitant use of a proton-pump inhibitor and thiazide.

Methods:

Results:

Conclusions:

TH-PO1130

Narrow Upper Airway Due to Fluid Overload Affects Severity of Asymptomatic Sleep Apnea Syndrome in ESRD Toshiki Kano, Hitoshi Suzuki, Ryotaro Shioda, Yusuke Suzuki. *Nephrology, Juntendo University Faculty of Medicine, Tokyo, Japan.*

Background: Sleep apnea syndrome (SAS) has been reported in 50% of patients with end-stage renal disease (ESRD). It is hypothesized that SAS in ESRD patients is caused by narrow upper airway due to fluid overload. SAS is considered as an independent risk factor for hypertension, congestive heart failure, acute coronary syndrome, pulmonary hypertension, arrhythmia and cerebrovascular event. The aim of present study is to clarify involvement of SAS in ESRD patients and to evaluate the association between severity of SAS and body fluid condition in ESRD patients.

Methods: The apnea-hypopnea index (AHI) and its severity were measured in twenty-five patients with ESRD using a portable sleep monitoring device. Body weight (BW), cardio thoracic ratio (CTR), serum levels of BNP, AHI were measured during the therapeutic course of hemodialysis. The association of AHI with age, gender, body mass index (BMI), history of smoking and complication of ESRD were analyzed.

Results: In twenty-five patients with ESRD, 96.0 % patients were diagnosed as asymptomatic SAS. Those ESRD patients with SAS were divided according to AHI scores into mild (AHI 5-14.9, 20.8%), moderate (AHI 15-29.9, 29.2%) and severe SAS (AHI ≥30, 50.0%) groups. Patients with hypoalbuminemia showed severe SAS ($P<0.05$). Moreover, there was a trend that patients with diabetes showed severe SAS. Asymptomatic SAS was improved by treatment of fluid overload ($P<0.01$). Changes of AHI by intervention of fluid overload was associated with decrease of BNP ($P<0.05$) and CTR ($P<0.05$).

Conclusions: Asymptomatic SAS is a major complication in patients with ESRD. Present findings suggested that fluid overload induced edema of upper airway resulted in asymptomatic SAS. Diagnosis and appropriate management of SAS is important to improve the mortality of ESRD patients.

TH-PO1131

Prevalence and Predictors of Hypomagnesemia in CKD Monika Aggarwal (Gupta), George M. Feldman. *Medicine, Hunter Holmes McGuire VAMC, Richmond, VA.*

Background: Hypomagnesemia has been reported in patients with chronic kidney disease (CKD), and shown to be associated with progression of CKD and increased mortality. We studied the prevalence and predictors of hypomagnesemia in patients with CKD.

Methods: We reviewed charts of all patients (n=891) seen in our outpatient CKD clinic in the year 2014, at Hunter Holmes McGuire Veterans Affairs Medical Center. We collected five most recent serum values for magnesium, creatinine, estimated glomerular filtration rate (EGFR), calcium, phosphorus, parathyroid hormone intact (PTH) and 25(OH) Vitamin D, presence of diabetes, and use of diuretics, proton pump inhibitors (PPI), phosphate binders, and magnesium supplementation in past 5 years. Hypomagnesemia was defined as serum magnesium less than 1.8 mg/dl or a serum magnesium ≥1.8 mg/dl on magnesium supplement. We then determined possible associations of plasma magnesium with age, presence of diabetes, use of PPI, diuretics, and phosphate binders, and mean values of serum calcium, phosphorus, eGFR, PTH, and 25(OH)Vitamin D.

Results: Mean age was 70.01±10.87 years. All patients were male, with 60.36% (N=536) with diabetes. 53% (N=471) had stage 3 CKD. 57.9 % (N=514) were on a PPI. 32% (N=286) were on magnesium supplement. 33.67% (N=299) had a mean serum magnesium <1.8 mg/dl. While 66.33% (N=589) had a mean serum magnesium ≥ 1.8 mg/dl, 121 of those patients were on magnesium supplement. Hence, 47.29% (N=420) had hypomagnesemia. Presence of diabetes mellitus, use of potassium supplement, thiazide diuretics, and PPI increased odds of having hypomagnesemia (Table 1).

Conclusions: Hypomagnesemia is common in patients with CKD. Use of PPI and presence of diabetes have the highest odds of developing hypomagnesemia.

Funding: Clinical Revenue Support

Table 1.

	coeff b	s.e.	Wald	p-value	exp(b)	lower	upper
Intercept	-0.02893	0.56849	0.00259	0.959413	0.971484		
Age(Years)	-0.02309	0.006616	12.17748	0.000484	0.977178	0.964589	0.989931
EGFR	0.005358	0.003327	2.593387	0.107311	1.005372	0.998838	1.011949
Diabetes	0.47146	0.145743	10.46443	0.001217	1.602332	1.204193	2.132107
PPI	0.589063	0.143496	16.8517	4.04E-05	1.802299	1.360451	2.387651
Potassium Supplement	0.315967	0.156103	4.096938	0.042961	1.371584	1.01006	1.862506
Thiazide Diuretics	0.390187	0.148757	6.88003	0.008716	1.477257	1.103656	1.977327

TH-PO1132

Case of Amphotericin Induced Refractory Hypokalemia Mark Kozicky,[2] Maya K. Rao,[1] Jacob Stevens.[3] *[1]Columbia University, New York, NY; [2]Nephrology, Columbia University, New York, NY; [3]NYP Columbia - Nephrology Fellowship, New York, NY.*

Background: Amphotericin (AmB) B is often used to treat severe fungal infections. It increases membrane permability of the renal tubular cell potentially leading to hypomagnesemia, hypokalemia and renal tubular acidosis. It also causes resistance to anti-diuretic hormone leading to polyuria that can potentiate hypokalemia by increasing distal urinary flow.

Methods: A 29 yr old male with sinonasal & intracranial aspergilloma infection was admitted to NICU in septic shock and respiratory failure requiring intubation. Despite anti-fungal treatment with micafungin, voriconazole, imaging showed growth of the fungal mass and treatment with AmB was initiated. Within 2 days of starting amphotericin the patient developed new onset hypokalemia ranging from 2.3 to 3.4mmol/L with U waves seen on EKG. Hypokalemia remained refractory to supplementation over a week despite intravenous potassium repletion of ~ 200meq/ day plus an additional 40-100meq of oral KCl. Pt had some polyuria during this time with urine output(UOP) ranging from 1.5 - 5L daily in part driven by high input of ~ 5-6L/day, though UOP remained elevated over 2L/day even once IV hydration was reduced. While polyuria continued urine osmolarity ranged from 380 to 472 mOsm/kg demonstrating some persistent tubular concentrating function. Pt had no diarrhea noted and magnesium was supplemented to maintain adequate levels. Diagnostic studies for hypokalemia including a cortisol level of 21.5ug/dL, renin & aldosterone levels of 0.38 ng/mL/h and 4.7ng/dL respectively were unremarkable upon evaluation of alternative causes of hypokalemia. 24 hour urinary potassium was elevated at 292 mmol/day while coincident serum potassium was 2.8mmol/L. Due to refractory hypokalemia despite aggressive repletion and evidence of urinary potassium wasting, the patient started amiloride with slight improvement of potassium to ~3- 3.5mmol/L though not until AmB was discontinued after nearly 1 month of therapy did potassium levels normalize consistently to > 3.5mmol/L without further need of repletion and amiloride.

Results:

Conclusions: This case demonstrated amphotericin induced urinary potassium wasting via increased excretion along with polyuria refractory to high dose supplementation showing the potential harm & limitations in using AmB. It also demonstrates benefit of early initiation of potassium sparing diuretics to achieve potassium stabilization in patients requiring this medication.

TH-PO1133

Recurrent SIADH: A Rare Complication of Intrathecal Interleukin-2 Treatment for Melanoma with Brain Metastases Ali Ziaolhagh,[2] Chinonye C. Ogbonnaya-Odor,[2] Jade M. Teakell,[2] Amit Lahoti.[1] *[1]M D Anderson Cancer Center, Houston, TX; [2]Univ of Texas Medical School at Houston, Houston, TX.*

Background: The 10- year survival rate for patients with metastatic melanoma is less than 10%. Systemic therapy is the mainstay of treatment for most patients, and immunotherapeutic agents have been associated with durable response in some patients. High dose Interleukin-2 (IL-2), which activates T-cells and NK cells, was approved by FDA in 1998 for treatment of metastatic melanoma. Common adverse effects include fever, chills, hypotension, cardiac arrhythmias, oliguria, volume overload, delirium, and rash. Hyponatremia has not been commonly reported. We present an unusual case of recurrent SIADH with each cycle of intrathecal IL-2.

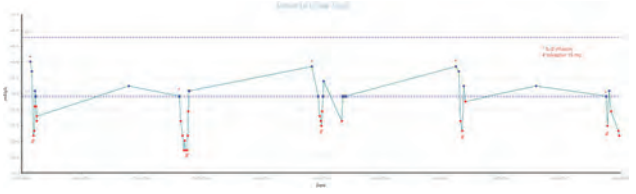
Methods: A 65 year old man with Stage IV melanoma with left parietotemporal hemorrhagic metastases, underwent stereotactic radiosurgery of a left temporal lesion. He was subsequently treated with intrathecal IL-2 every 3 months for 4 years. After every infusion, he developed symptomatic hyponatremia (gait instability and confusion). Elevated urine osmolality and urine sodium were consistent with SIADH (Table). The patient did not complain of pain or nausea with treatment. During each cycle of IL-2, hyponatremia improved with a single dose of oral tolvaptan 15 mg (Figure).

Results:

Conclusions: To our knowledge, this is the first reported case of recurrent SIADH with long-term intrathecal IL-2 administration. While this does not appear to be a common side effect, physicians should be aware of this potential complication. Hyponatremia in this situation appears to respond well to single dose of tolvaptan 15 mg orally.

Recurrent SIADH with Intrathecal IL-2 Administration

Aldesleukin (IL-2)	Serum Na on Admission	Serum Na Nadir	Serum OsM	Urine OsM	Urine Na
3/28/16	141	125	265	496	87
5/23/16	142	127	271	682	114
8/23/16	135	124		683	110
11/15/16	141	129			
2/8/17	141	128	268	651	178
5/10/17	135	129			40



Temporal Relationship of Hyponatremia with IL-2 and Improvement with Tolvaptan.

TH-PO1134

Pseudohypernatremia in Patients with Hemodialysis Catheters Locked with Trisodium Citrate Szymon Brzosko,[1,4] Maciej B. Drozdz,[2] Alicja Rydzewska-Rosolowska,[4] Stefan H. Jacobson.[3] *[1]DaVita, Bialystok, Poland; [2]DaVita, Krakow, Poland; [3]Danderyd Hospital, Stockholm, Sweden; [4]Medical University of Bialystok, BIALYSTOK, Poland.*

Background: International guidelines recommend arterio-venous fistula (AVF) as the preferred type of vascular access (VA) for hemodialysis (HD). Infections and patency-related complications of central venous catheters (CVC) pose a potential risk for patients. Trisodium citrate (TSC) locking solution is a promising alternative to unfractionated heparin (UFH) for prevention of CVC dysfunction. Pseudohypernatremia secondary to TSC contamination of blood specimens obtained from the CVC may potentially lead to profound but unnecessary diagnostic interventions. The aim of the study was to analyze pre-dialysis Na concentration and the prevalence of hypernatremia in relation to the type of locking solution (TSC vs UFH) and VA in a large cohort of HD patients (DaVita Poland).

Methods: The population studied consisted of 543 prevalent hemodialysis patients (45% female), mean age 67±14 years treated in a standard HD program (100% High Flux, 94% HD time>12h/week, 94% spKt/V>1.3, 18.5% CVC). We analyzed laboratory results from February & March 2017. Pre-dialysis Na concentration was compared between patients with CVC locked with 30%TSC, UFH (5000 IU/ml) and non-CVC types of VA (AVF, AVG). The proportion of patients with pre-dialysis Na ≥145 mEq/l (hypernatremia) was analyzed in both groups and from both months separately. Descriptive statistics was used together with ANOVA, t and X^2 tests as appropriate.

Results: The mean plasma concentration of Na was significantly higher in patients with TSC locking solution (141±3 mEq/l n=26, 142±3 mEq/l n=35) when compared to UFH (138±3 mEq/l n=76, 138±4 mEq/l n=75) and non-CVC VA (138±2 mEq/l n=430, 138±3 mEq/l n=440; ANOVA p<0.001 for February & March respectively). The proportion of patients with Na≥145 mEq/l was significantly higher in patients with CVCs with TSC (n=11/61) as a locking solution than in patients with UFH (n=4/152; 18.0% vs 2.6%; X^2 p<0.001). The highest plasma concentration of Na was 171 mEq/l, obtained from a patient with uneventful follow up. Repeated analysis from a peripheral vein showed a Na concentration of 138 mEq/l.

Conclusions: Pseudohypernatremia is may occur in HD patients when 30% TSC is used as a locking solution. Need for diagnostic laboratory investigations may be lowered by strictly following procedures for blood sample collection from CVC (including discarding proper volume of blood).

TH-PO1135

Sorafenib Induced Resistant Hypocalcemia in a Patient with Chronic Mild Hypocalcemia from Possible Lysozyme Induced Nephropathy: A Nightmare to Treat Sanjeev Gupta, Anastasios Papanagnou, Yorg Al Azzi, Maureen E. Brogan. *Westchester Medical Center, Valhalla, NY.*

Background: Sorafenib is a multikinase inhibitor; approved for treatment of multiple cancers. A lesser-known side effect of this drug is hypocalcemia (hypoCa). Diarrhea and Vit D malabsorption due to exocrine pancreatic dysfunction are proposed causes for hypoCa from Sorafenib. We present a case of Sorafenib induced severe hypoCa in a patient with chronic mild asymptomatic hypoCa.

Methods: A 67-year-old man with a history of CMML, MDS and hypoCa with c/o joint pain and weakness admitted for management of possible AML. Work-up showed anemia, thrombocytopenia, and leukocytosis. Bone marrow aspiration confirmed AML. A single dose of Cytarabine and Sorafenib was administered. His serum calcium (S.Ca) dropped to 6.2 from 7.9 (at admission). IV and oral calcium with Vit D were initiated. The patient, however, became symptomatic with oral numbness due to a further drop in S.Ca to 5.8. IV calcium drip was added to oral calcium and Vit D. His S.Ca was difficult to maintain above 7, even on an IV calcium drip with Vit D. High-dose IV calcitriol was added to the treatment plan. His PTH and 25-Vit D levels were 576 and 20 respectively. Given his history of CMML, lysozyme-induced proximal RTA was considered as an underlying etiology of chronic hypoCa supported by glycosuria, high fractional excretion of phosphate, elevated trans-tubular potassium gradient and increased urinary level of alpha-aminobutyric acid, alanine, arginine, and asparagine. His urinary Ca/Cr ratio was low (<7). The patient finally responded to treatment and was subsequently switched to oral calcium and calcitriol and discharged home with S.Ca of 7.9.

Results:

Conclusions: Lysozyme-induced nephropathy is an under-recognized complication of CMML. A persistently elevated level of lysozyme exceeds the reabsorption capacity of tubules leading to tubular injury. The exact mechanism of action of Sorafenib induced hypoCa is still unknown attributing to challenges in managing such patients. Our patient's S.Ca level did not respond well to Vit D as suggested by few case reports and required heavy doses of calcitriol along with IV calcium and Vit D analogues. This case highlights that it is essential to consider underlying history of hypoCa before starting a patient on Sorafenib, as it can lead to severe hypoCa, which can be difficult to manage.

TH-PO1136

Fluid Overload Is a Risk Factor for AKI and Mortality in Influenza Patients Luis I. Bonilla,[1,2] Raymundo Vera,[1] Raymundo A. Sánchez,[1] Israel A. Villegas-Gasson,[1] Sara Samoni,[2] Claudio Ronco,[2] Lilia M. Rizo Topete.[1,2] *[1]Nephrology, University Hospital "Dr. José Eleuterio González", Monterrey, Mexico; [2]International Renal Research Institute of Vicenza, Vicenza, Italy.*

Background: Influenza virus, especially A(H1N1) has been consistently associated with high mortality in the subset of critically ill patients who develop Acute Distress Respiratory Syndrome (ADRS). Risk factors for this association have not been well described. Fluid overload (FO) is now a recognized condition which increases the incidence of acute kidney injury (AKI) and its association with mortality in critically ill patients has been well documented. Nevertheless the impact of FO in mortality of ARDS influenza patients has not been yet described.

Methods: This is a retrospective analysis of 30 records of patients who were admitted to the ICU with the diagnosis of ARDS and suspicion of influenza infection during the Influenza season 2016-2017. Demographic, laboratory, and clinical data were obtained. We calculated FO as the algebraic sum of the inputs and outputs recorded every day during the whole ICU stay divided by the patient's weight at admission and expressed as a %. We divided patients into 2 groups: A) < 5% FO and B) > 10% FO and compared mortality among both groups.

Results: Mean age in our cohort was 46.4yrs, 66.6% were male and 46.6% were obese. Influenza was confirmed in 12 patients; 41.6% with A(H1N1). Mortality among A(H1N1) patients was 100%. AKI was diagnosed in 20 patients (66.6%) with 16.6%, 10% and 36.6% of KDIGO stages 1-3 respectively. RRT was initiated in 10 (50%) of AKI patients. Among groups A and B AKI was diagnosed in 50% and 75% of patients respectively p=0.23. ICU mortality was 60% among the whole cohort. Median fluid balance (FB) among survivors was +3,885.8ml (2,108.7-7,525.5) and among non-survivors +8,036.5ml (5,283-18,863) p=0.043. Mortality in group A was 35.7% and in group B 63.3% p=0.22. The OR for mortality and AKI in group A was 0.58 (CI95% 0.22-1.54) and in group B 3.0 (CI 95% 0.49-18.1) p=0.22.

Conclusions: In our cohort of ARDS patients, FO >10% was associated with increasing incidence of AKI and mortality. Also, the presence of a confirmatory diagnosis influenza A(H1N1) conferred a 100% mortality. With these findings, we can strongly recommend a conservative fluid strategy in the treatment of this kind of patients. More studies with bigger cohorts are needed to obtain statistical significance and clearly demonstrate these associations.

TH-PO1137

Prediction of Hyponatremia from Electronic Medical Records Using an Deep Learning Approach with an Artificial Neural Network Algorithm Young-Il Jo,[1] Sug kyun Shin.[2] *[1]Nephrology, Konkuk University Medical Center, Seoul, Republic of Korea; [2]Ilsan Hospital NHIS, , GOYANG-SI, GYEONGGI-DO, Republic of Korea.*

Background: Hyponatremia is associated with increased morbidity and mortality in both hospitalized and ambulatory patients. In the era of big data, analysis of electronic medical records (EMR) may have a significant impact on patient's outcomes by identifying high-risk patients or supporting clinical decision making. The aim of this study was to predict hyponatremia from EMR using an deep learning approach with artificial neural network (ANN) algorithm.

Methods: A total 182,181 patients who measured serum sodium concentrations from 2010 to 2016 in a tertiary referral hospital were enrolled. Clinical, biochemical and medication data were obtained from EMR data warehouse. A total of 853 columns were presented along with basic patient information. For training, 500 random number trees

were given to the random forest algorithm. The medication dataset was based on a neural network based on Dense Matrix. Learning and modeling have attempted to construct a combined dataset by using Ensemble model. The predictive value and diagnostic accuracy were calculated for the dataset based on serum sodium concentration less than 134 mEq/L.

Results: Using the confusion matrix and statistics for clinical and laboratory data set, the predicted value was 0.9104 (95% CI, 0.9040-0.9157). In the medication data set, he predicted value was 0.7515. Deep learning predictive approaches using the Ensemble model, the prediction probability for hyponatremia was 92.05% (Table).

Conclusions: Using an deep learning approach with the ensemble model, an artificial neural network can accurately predict hyponatremia from the laboratory dataset and the medication dataset of EMR.

Confusion matrix and statistics (Prediction/Real) for prediction of hyponatremia in the Ensemble model

	0	1	2
0	3199	64	69
1	170	3351	281
2	91	150	3014

TH-PO1138

The Association between Serum Sodium and Potassium Concentration and the Risk of Cardiovascular Disease: A Large Community-Based Cohort Study Nicholas I. Cole,[1] Pauline A. Swift,[1] Feng J. He,[2] William Hinton,[3] Filipa I. Ferreira,[3] Simon De lusignan,[3] Rebecca Suckling.[1] *[1]Epsom and St Helier NHS Trust, London, United Kingdom; [2]Queen Mary University of London, London, United Kingdom; [3]University of Surrey, Guildford, United Kingdom.*

Background: Observational and randomised studies have shown that reduced dietary sodium (Na) and higher potassium (K) are associated with lower blood pressure and cardiovascular (CV) disease. Changes in dietary intake may alter the serum concentration of these electrolytes, but few studies have investigated if there is a relationship between serum Na, K and CV risk.

Methods: This was a retrospective cohort study using data from the Royal College of General Practitioners Research and Surveillance Centre, a database of routinely-collected primary care data in the UK. Data were extracted using Read V2 and EMIS codes. Only individuals with both a serum Na and K value were included, with the most recent data prior to April 2010 used to define baseline levels. Exclusion criteria were: age less than 40 years; diabetes mellitus; prior CV event; end-stage renal disease; liver cirrhosis. The primary outcome was incident CV disease (acute coronary syndrome; coronary revascularisation; stroke; new diagnosis of heart failure) over 5 years.

Results: 235,676 individuals met the criteria for inclusion in the study. The median age was 59 years (IQR 49-68), 57% were female, and 5% were known to be of non-white ethnicity. The median serum Na was 140 mmol/L (IQR 139-142), and the median serum K was 4.4 mmol/L (IQR 4.1-4.6). 21% were prescribed at least one diuretic medication, and 23% were prescribed a renin angiotensin system (RAS) inhibitor. There were 9,464 (4.0%) incident CV events during the follow-up period. After multivariate adjustment for confounding factors, there were significant associations between the primary outcome and serum Na (≤ 140 and ≥ 144 mmol/L) and serum K (≥ 4.5 mmol/L) – see *Figure*. No relationship with blood pressure was demonstrated.

Conclusions: There is a significant association between serum Na, serum K and primary CV events. This relationship is unexplained but could be associated with activation of the RAS.

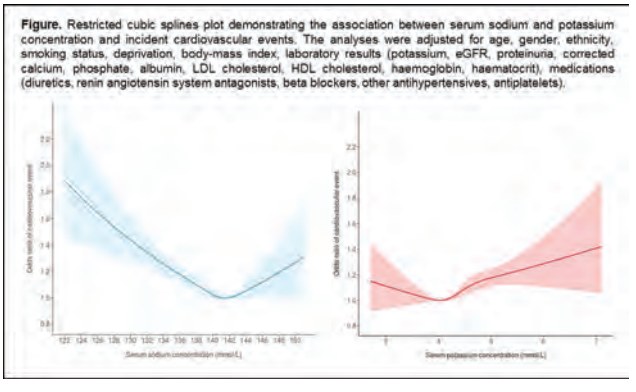


Figure. Restricted cubic splines plot demonstrating the association between serum sodium and potassium concentration and incident cardiovascular events. The analyses were adjusted for age, gender, ethnicity, smoking status, deprivation, body-mass index, laboratory results (potassium, eGFR, proteinuria, corrected calcium, phosphate, albumin, LDL cholesterol, HDL cholesterol, haemoglobin, haematocrit), medications (diuretics, renin angiotensin system antagonists, beta blockers, other antihypertensives, antiplatelets).

TH-PO1139

Quantitative Urine Proteomics by SWATH-MS Reflects Intricate Metabolic Processing in Cirrhosis Patients Bo Xu, Yoshitoshi Hirao, Keiko Yamamoto, Ichiei Narita, Tadashi Yamamoto. *Niigata University, Niigata, Japan.*

Background: Cirrhosis of the liver often has no signs or symptoms until damages is extensive, 3-4 million people are suffered from cirrhosis in the world. However, early diagnosis and treatment are difficult due to cirrhosis could be leaded by a wide range of disease. The aim of this study is to reveal sophisticated metabolic processing pathway in cirrhosis patients by comparison of quantitative analysis of urine proteins between health volunteers and cirrhosis patients.

Methods: Urine proteins were purified by precipitation method from patients and health volunteers individually. After digestion, purified urine peptides were analyzed by optimized Sequential window acquisition of all theoretical mass spectra (SWATH-MS). ProteinPilot™ and PeakView™ were used for protein identification and SWATH data analysis respectively. Differentially expressed molecules were further analyzed by Gene Ontology (GO) and KEGG pathway analysis using DAVID.

Results: In total 2047 proteins were identified. 1425 proteins were reliably quantified in both groups. 861 proteins were observed with more than 2 times fold change (FC),415 proteins with over 5 times FC between cirrhosis and health control (HV) groups. We focused on these 415 molecules that were regulated in cirrhosis, since they will be supposed as potential molecules involved in the onset of cirrhosis. GO analysis indicated 282 of these 415 genes were clustered in extracellular exosome, and enrichment analysis revealed serine-type endopeptidase activity was the most significant over-represented molecular function for the 282 molecules. KEGG pathway analysis showed 38 proteins related to metabolic pathway. Glycolysis / Gluconeogenesis pathway is most significantly enriched. Low abundance proteins revealed that protein expression of cell adhesion, immune response, and proteolysis in cirrhosis patients.

Conclusions: Quantitative proteomic results of urine proteins from cirrhosis patients show significant increase of proteins related to the complement and coagulation cascades, regulation of actin cytoskeleton pathway, and decrease of proteins in the cell adhesion molecules (CAMs), endocytosis, PI3K/Akt signaling and phagosome pathways. Our pilot studies of cirrhosis patient urinary proteomes may promote to discover urine biomarkers of cirrhosis in the early stage of liver dysfunction.

Funding: Private Foundation Support

TH-PO1140

Dietary Acid Load Is Associated with Greater Urinary Nitrogen and Muscle Mass Loss in CKD Patients Larissa R. Angeloco,[1] Tanushree Banerjee,[3] Lynda A. Frassetto.[2] *[1]University Of São Paulo, Ribeirao Preto, Brazil; [2]University of California San Francisco, San Francisco, CA; [3]University of California, San Francisco, San Francisco, CA.*

Background: In chronic kidney disease (CKD), high dietary acid loads may promote metabolic acidosis, which in turn may contribute to adverse clinical health outcomes. We hypothesize that high diet acid load plus higher acid body content in CKD leads to greater muscle breakdown and greater urine nitrogen loss. We examined associations between dietary acid load, serum bicarbonate, 24- hour urine urea nitrogen (UUN), arm muscle area (AMA), and diet protein/potassium (K) ratio in pre-dialysis CKD subjects.

Methods: 100 subjects with CKD stage 3 and 4 and 29 healthy control subjects were enrolled in this cross-sectional study. Potential renal acid load (PRAL) and net acid excretion (NAE) were determined by the average of 3-day food records using the equations by Remer, Frassetto, and Lemann. PRAL and NAE were divided into quintiles. Pearson correlation and multivariable regression analysis were used to evaluate the associations of dietary acid measurements (PRAL and NAE) with serum bicarbonate, UUN, AMA, and diet protein/K ratio. The regression models were adjusted for demographics, body mass index, diabetes, systolic and diastolic blood pressure, urine pH, and creatinine clearance.

Results: Mean age of the population was 57 yrs (range 28-69) with 53% females. Median eGFR was 30 ml/min for the CKD subjects, and 100 ml/min for the controls. The correlation coefficients (p value) in CKD subjects in the highest quintile of diet acid load are presented (see table). PRAL correlated significantly with UUN in the control subjects (r=0.9). In adjusted analysis, compared to the lowest quintile, no significant association was observed between the higher quintiles of PRAL with serum bicarbonate in CKD patients (β[95% CI]: -0.4[-2.5-1.7] in quintile 5, -0.4[-2.4-1.6] in quintile 4, -0.05[-1.9-1.8] in quintile 3, 1.3[-0.5-3.2] in quintile 2).

Conclusions: We found a significant association of higher body acid balance with urinary nitrogen loss, but not with serum bicarbonate. In patients with CKD, limiting diet acid load may improve metabolic acidosis and its long-term adverse health effects.

Funding: Private Foundation Support

	24 hr UUN	diet protein/K ratio	AMA
NAE (Frassetto)	0.5 (0.04)	0.5 (0.02)	0.5 (0.03)
NAE (Remer)	0.5 (0.01)	0.6 (0.005)	0.02 (0.3)
NAE (Lemann)	0.5 (0.02)	0.05 (0.8)	0.1 (0.6)

correlation coeffient (p value)

TH-PO1141

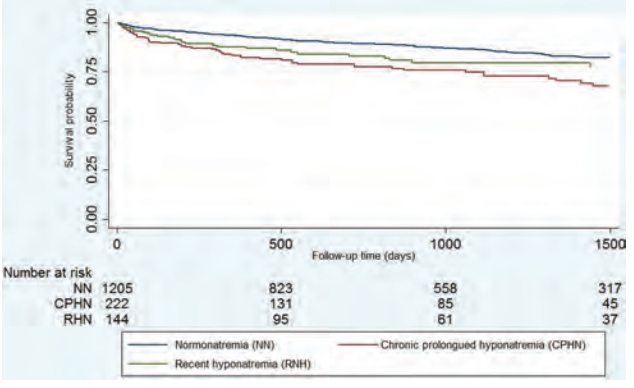
Mild Chronic Prolonged Hyponatremia at Admission Is Associated with Long Term Mortality in Patients with Hip Fracture Repair Juan Carlos Ayus,[4] Nora Fuentes,[5] Michael L. Moritz,[1] Alan S. Go,[2] Armando L. Negri.[3] *[1]Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA; [2]Kaiser Permanente Northern California, Oakland, CA; [3]Instituto de Investigaciones Metabólicas, Buenos Aires, Argentina; [4]Renal Consultants of Houston, Houston, TX; [5]Hospital Italiano de Buenos Aires, Buenos Aires, Argentina.*

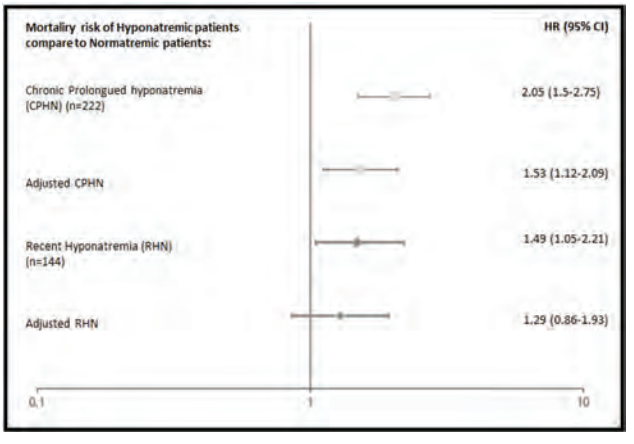
Background: A recent study indicates that chronic prolonged hyponatremia is a significant risk factor for hip fracture in the elderly (Ayus JC; NDT 2016; 31(10):1662-9). No information exists with respect the chronicity of the hyponatremia prior to admission and its effects on long term mortality.

Methods: We designed a cohort study in adults admitted for traumatic hip fracture who had at least one serum Na performed at admission. Hyponatremic patients (HN) were divided in those with chronic prolonged (hyponatremia for 90 days or more, CPHN), and those with recent hyponatremia (hyponatremia for 30 days or less, RHN) prior to admission.

Results: 1205 (76.7%) patients were normonatremic (NN) and 366 (23.3%) were HN at admission (138 ± 3 vs 132 ± 4 mmol/L Na; p <0,001). Of these, 222 (14%) had CPHN and 144 (9.1%) had RHN. Overall mortality rate was higher in CPHN 25% (56/222), followed by RHN 20% (29/144) and finally NN 14% (169/1205). Five year survival in patients with CPHN and RHN was lower than those with NN: 0.83 and 0.87 compared to 0.93 (p <0.001) **figure 1**. Unadjusted HR for long term mortality > in CPHN and RHN vs NN but adjusted HR was only significant for CPHN **figure 2**.

Conclusions: Mild chronic prolonged hyponatremia at admissionin in patients with hip fracture repair is associated with increased long term mortality.





TH-PO1142

Villous Adenoma: A Rare Cause of Hypokalemia and Metabolic Alkalosis

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Background: The differential diagnosis of hypokalemia and metabolic alkalosis is large and includes fluid loss without HCO3- wasting (vomiting/diuretics), mineralocorticoid excess, and hereditary conditions such as Bartter syndrome. We present an unusual case of hypokalemia and metabolic alkalosis.

Methods: A 58 year-old previously healthy male was admitted to the ICU after 15 days of weakness, muscle cramps, orthostatis and blood streaked stools. He had hyponatremia and acute kidney injury, and was fluid resuscitated. Two months later his physician saw him for rectal pain, diagnosing hemorrhoids, and noted a potassium of 2.4. He was given KCl without work up. He had two more ICU admissions for severe volume depletion in 4 weeks. Representative labs: serum Na 131, K 2.9, Cl 88, CO2 34, Cr 1.5, aldosterone 78 and plasma renin activity 39.5. He was believed to have Bartter's syndrome, given amiloride and ibuprofen, and referred to our facility for nephrology consultation. A history of rectal mucoid discharge prompted a suspicion of villous adenoma, confirmed by colonoscopy. The 11 cm distal rectal lesion was resected transrectally. All symptoms resolved.

Results:

Conclusions: The mistaken initial diagnosis of Bartter Syndrome was based on the elevated aldosterone, hypokalemia, metabolic alkalosis, and lack of hypertension. However inadequate resuscitation of his fluid and electrolyte loss from the villous adenoma explains the hormonal and electrolyte abnormalities. Villous adenoma depletion syndrome (McCrittrick Wheelock) is rare, resulting from a mucous secreting villous adenoma in the distal colon causing volume depletion, hypokalemia, and usually metabolic acidosis. Up to 3% of villous adenomas are secretory. Hypersecretion of bicarbonate and electrolytes from abnormal enterocytes is likely the cause. We describe a rare case of villous adenoma with metabolic alkalosis. Literature review identified 58 cases of villous adenoma depletion syndrome; 7 had metabolic alkalosis. The cause of the metabolic alkalosis variant may be over expression or activation of apical chloride channels in adenoma goblet cells. Increased cAMP or cGMP production in goblet cells could also lead to over activity of CFTR channels causing chloride secretion. Finally, decreased expression of the Downregulated in Adenoma (DRA) gene may decrease expression of Cl/Na exchangers reducing chloride absorption.

FR-PO001

Serious Breakdown: A Rare Case of Spontaneous Tumor Lysis Syndrome from Aggressive Diffuse Large B-Cell Lymphoma

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Background: Introduction: Tumor Lysis Syndrome (TLS) is a well-known cause of AKI classically seen in patients with high grade tumors treated with chemotherapy. However, spontaneous TLS is a rare presentation that has been described mostly in Diffuse High Grade B-cell Lymphomas.

Methods: Case Description: This is a 67 year old woman with PMH of hypertension, hypothyroidism, and marginal cell lymphoma in remission after receiving treatment with rituximab 6 months prior to admission. She was admitted with non-oliguric Stage 3 AKI after her routine outpatient labs revealed an elevated serum creatinine of 3.5 mg/dL from a baseline of 1.0 mg/dL. She was normotensive, euvolemic, and physical exam revealed some wasting, but otherwise unremarkable. Her renal ultrasound showed bilateral hydronephrosis, but renal scan showed no obstruction. Labs were significant for WBC 20,600, Hgb 10.3 g/dL, platelets 470,000 /mm3., K 4.4 mmol/L, phosphate 4.8 mg/dL, calcium 10.8 mg/dL, uric acid 14.9 mg/dL, LDH 1,458 U/L, CPK was normal. A PET scan showed multiple enhancing pelvic lymph nodes as well as supra- and infra-diaphragmatic tracer uptake. Biopsy of left axillary lymph nodes revealed diffuse large B cell lymphoma (DLBCL). Patient was started on IVFs, rasburicase, and allopurinol. After tissue diagnosis was obtained, she initiated chemotherapy with R-CHOP for her aggressive DLBCL. With therapy, her creatinine improved to her baseline 1.01 mg/dL, uric acid level decreased to 1.2 mg/dL, and calcium normalized to 9.8 mg/dL by discharge.

Results:

Conclusions: Discussion: While rare, spontaneous TLS occurring in the absence of current or prior chemotherapy have been reported mostly occurring in the context of B-cell lymphomas. Nephrologists should consider an occult malignancy in the differential diagnosis of a patient presenting with AKI and hyperuricemia. With high level of suspicion, early initiation of therapy may result in renal improvement and avoid potential complications which may increase morbidity and mortality.

FR-PO002

Spontaneous Tumor Lysis Syndrome Presenting as Acute Renal Failure from Numerous Bilateral Obstructing Uric Acid Stones

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Background: Tumor lysis syndrome (TLS) causes a recognized collection of metabolic abnormalities including hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia. TLS can result in acute renal failure (ARF) from multiple mechanisms including intra-renal precipitation of uric acid, xanthine, or calcium phosphate crystals resulting in obstruction and inflammation. It is an anticipated complication after initiation of chemotherapy for lymphoproliferative malignancies or in patients with high tumor burden; it can also occur spontaneously. We report an unusual case of a B-cell lymphoma presenting as ARF from extensive obstructing bilateral uric acid nephrolithiasis from spontaneous TLS.

Methods: A 36-year-old male with HIV was admitted to the hospital with oliguric ARF after presenting with 2 weeks of weight loss and dysphagia. He had started Bactrim and Atripla one month prior to presentation. Admission plasma lab values: creatinine 17.44 mg/dl, BUN 158 mg/dl, potassium 7.7 mEq/l, LDH 2097 u/l, phosphorous 11.7 mg/dl, and calcium 9.1 mg/dl. Urine studies were notable for 130 RBC/hpf and spot urine protein to creatinine ratio of 12. He underwent emergent hemodialysis for his hyperkalemia and work up of his ARF was initiated. A peripheral blood smear demonstrated the presence of lymphoma cells. Uric acid was found to be 24.5 mg/dL. Renal ultrasound demonstrated bilateral enlarged and echogenic kidneys with mild hydronephrosis of the left kidney and multiple bilateral renal calculi. A cystoscopy revealed heavy stone burden bilaterally with numerous calculi requiring placement of double J-stents for bilateral obstructive nephrolithiasis. Bone marrow biopsy and PET scan showed an aggressive B-cell lymphoma and he was started on rasburicase and chemotherapy while on renal replacement therapy. He ultimately regained kidney function and was able to stop dialysis 3 weeks after presentation.

Results:

Conclusions: To our knowledge, there is only one other case report of a patient with HIV and lymphoma who presented with spontaneous TLS. Despite multiple case reports discussing ARF due to spontaneous TLS, there are limited reports of nephrolithiasis as the etiology for renal failure. This case demonstrates the importance of including TLS in the differential when a patient presents in new ARF with significant bilateral nephrolithiasis despite no known malignancy.

FR-PO003

Tumor Lysis Syndrome in Multiple Myeloma Treated with Carfilzomib Nupur N. Uppal,[1] Rimda Wanchoo,[1] Jamil Ibrahim,[1] Anna T. Levy,[2] Kenar D. Jhaveri.[1] *[1]Nephrology, Hofstra Northwell School of Medicine, Great Neck, NY; [2]Hematology/Oncology, Hofstra Northwell School of Medicine, Lake Success, NY.*

Background: Tumor lysis syndrome(TLS) is extremely uncommon in patients with multiple myeloma(MM) because of low rate of proliferation of the plasma cells. Carfilzomib is a proteasome inhibitor that has been recently used for treatment of relapsed/refractory MM. Only a few cases of MM associated TLS have been reported in the literature. These cases include spontaneous TLS, drug induced TLS, or TLS due to plasmablastic transformation of MM. While acute kidney injury(AKI) has been seen with carfilzomib treatment, TLS has been rarely reported. We describe a case of TLS in patient with MM on carfilzomib therapy.

Methods: A 58-year-old female with known IgG kappa MM, with poor and complex cytogenetics and a plasma cell pleural mass, who had failed treatment with standard MM therapy, followed by lenalidomide, presented with shortness of breath and hypotension, and was noted to have AKI [serum creatinine (Scr) of 1.7mg/dL) on admission. She was started on carfilzomib treatment 4 weeks prior to presentation. Lab work also revealed elevated levels of LDH (1700U/L), phosphorus (9.1mg/dl), potassium (5.1mmol/L) and uric acid (22mg/dl). A diagnosis of TLS was made. Besides usual therapy with hydration, and rasburicase, she also required continuous renal replacement therapy (CRRT), followed by hemodialysis (once hemodynamically stable) for management of TLS. After a week of RRT, renal function improved and TLS labs stabilized. However, her kappa/lambda free light chain ratio increased from 144 to 344. Patient opted for end of treatment and hospice care. Her Scr stabilized ~2mg/dl upon discharge.

Results:

Conclusions: TLS has been seen in 1% of patients treated with high-dose chemotherapy following autologous stem cell transplant, and ~1.4% in patients receiving bortezomib. Although rare in patients with MM, TLS can occur in this population, especially in patients with poor prognostic features including high tumor mass, immature morphology, high proliferative activity, and poor cytogenetics. To our knowledge, our case is the second reported case of TLS following carfilzomib treatment. While risk of TLS is small in patients with MM, physicians should be aware of this potential adverse effect in patients receiving carfilzomib therapy.

FR-PO004

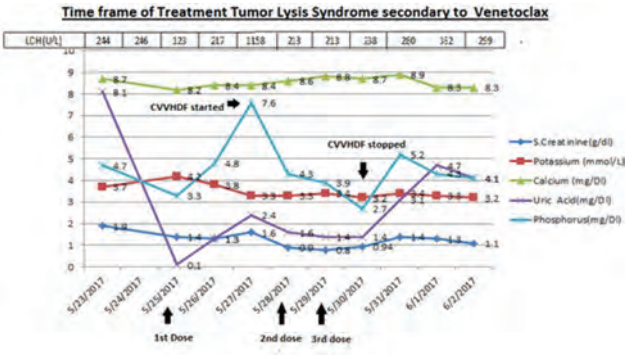
Tumor Lysis Syndrome with Venetoclax Nishita Parikh,[1] Jacqueline Barrientos,[2] Richard L. Barnett,[1] John F. Katsetos,[2] Massini Merzkani,[3] Anna Mathew,[1] Kenar D. Jhaveri.[1] *[1]Nephrology, Hofstra Northwell School of Medicine, Great neck, NY; [2]Hofstra Northwell School of Medicine, CLL Research and Treatment Center, Lake Success, NY; [3]Nephrology, Hofstra Northwell School of Medicine, Great Neck, NY.*

Background: Venetoclax is a BCL2 inhibitor approved for CLL treatment. A low dose of this drug has led to fatal cases of tumor lysis syndrome (TLS) in the initial trials.

Methods: A 64 year old female with CLL was admitted for worsening lymphadenopathy. After failing all therapy, she was planned to start on venetoclax (BCL2 inhibitor). Given her admission serum creatinine(Scr) of 1.9mg/dl, uric acid level of 8.1mg/dl, and serum phosphorus was 4.8mg/dl, she was started on crystalloid fluid resusitation and received one dose of rasburicase(0.2mg/kg). Pt. Scr improved to 1.3mg/dl. Given high tumor burden, nephrology was consulted early for TLS prevention. The patient was initiated at 20mg dose of venetoclax and TLS labs were monitored every four hours. Three hours after the initial dose, the patient had a sudden rise in the LDH to 1158u/dl, Scr was 1.6mg/dl and serum phosphorus was 7.6 g/dL, despite urine output of 100 cc of urine per hour. An early transfer to intensive care unit and initiation of continuous renal replacement therapy (CRRT) allowed for ongoing dosing of venetoclax with controlled clearance of phosphate, potassium and uric acid. She received a modified dosing of this drug and ultimately was given 50mg of the dose before CRRT was discontinued. LDH was followed serially as a marker for ongoing TLS. Following resolution of TLS lab markers, CRRT was stopped, the patient received 100mg of venetoclax, with stable renal function and no abnormal TLS markers. Figure below summarizes the lab data supporting early successful prevention of fatal TLS reported with this agent.

Results:

Conclusions: This case illustrates that early involvement of nephrology in high risk TLS associated with venetoclax can improve patient outcomes. Early initiation of CRRT even without significant renal injury along with modified dose escalation can prevent fatal TLS outcomes as described in the initial trials of this agent. Nephrologists need to be aware of this toxicity with this agent as it becomes commonly used.



FR-PO005

Hypothyroidism with Rhabdomyolysis Causing AKI Antonio M. Villegas, Macgivenny A. Goris felix, Alberto Flores, Freddy Mejia, Guillermo Alvarez. *CEDIMAT., Santo Domingo, Dominican Republic.*

Background: Muscle complaints is frequent in adult onset hypothyroidism, accompanied by mild elevation of serum creatine kinase, but few cases have reported extremely high elevations of serum creatine kinase and rhabdomyolysis and acute renal failure. We report a case of acute kidney injury (AKI) associated with rhabdomyolysis secondary to severe hypothyroidism in a 57 year old female. The patient had general weakness, without muscle tenderness, elevated muscle enzymes and thyroid stimulating hormone (TSH), which normalized with thyroid replacement therapy.

Methods: A 57 year old female admitted to the general ward with complaints of general weakness, fatigue and body swelling, prominently on both legs. She denied any neither physical activity nor trauma, all beginning 1 week prior admission. She was pale, afebrile, had leg pitting edema, no goiter with no muscle weakness or tenderness. Investigation revealed: hemoglobin 10.2 g/dL, white blood cells 3.9 x 10^9L, blood urea nitrogen 53 mg/dL, creatinin 7.24 mg/dL, aspartate aminotransferase 257 IU/L. Serum muscle enzymes were elevated; creatinin phosphokinase (CPK) >1600 U/L (upper normal limit (UNL) of 135), lactate dehydrogenase 1430 U/L (UNL of 618), and a negative antinuclear antibody. Urine analysis showed mild blood with dipstick with no erythrocytes, and a 24 hour urine collection with 0.36 g/day of protein. She reported fluctuation in mood, and weight gain in the last 6 months, TSH >100 μUI/mL, free T4 0.08 ng/dL, free T3 0.26 pg/mL and a extremely elevated anti-thyroid peroxidase (236.4 IU/mL). A thyroid scintigraphy revealed a low Tc-99m uptake. Hydration and replacement therapy with thyroxine was started at a dose of 50 μg/day for 1 week, increased to 100 μg/day for 3 more weeks, TSH in 10.7 μUI/mL in 2 weeks, with normalization at week 8, creatinin 4.1 mg/dL and CPK 610 U/L after 2 weeks of treatment, also patient reporting the disappearing of the legs edema and the weakness after 1 week of treatment. At 3 month follow up all clinical and laboratory findings were normalized, with a creatinin 0.8 mg/dL.

Results:

Conclusions: Hypothyroidism associated rhabdomyolysis is quite rare, depending on its severity, may be complicated with acute renal failure, hypothyroidism should be suspected in patients presenting with AKI in the absence of common causes of AKI, and in patients with vague muscular symptoms.

FR-PO006

AKI Secondary to Trabectedin Induced Rhabdomyolysis Deepa Amberker, Sreelatha Katari, Anitha Vijayan. *Washington University in St. Louis, St. Louis, MO.*

Background: Onconephrology is a growing field with nephrologists being consulted for various renal issues. Chemotherapy(chemotx) is associated with multiple renal complications including TMA, AIN, electrolyte abnormalities and CKD. Rhabdomyolysis (rhabdo) secondary to chemotx is extremely rare. We report a case of severe AKI secondary to rhabdo from trabectidin, an alkylating agent approved for soft tissue sarcomas in 2015.

Methods: A 46 year old Caucasian male with relapse of retroperitoneal liposarcoma was started on trabectedin 4wk prior to admission. He presented with 10d history of n/v, diarrhea, chest pain and sob, starting a week after his 2nd cycle of trabectedin given 1wk before admission. Initial labs showed pancytopenia, Trop-I of 0.15 and SCr of 1.4 (baseline 1.1). On day 9, SCr started increasing and peaked at 5.61. Creatinine kinase (CK) was obtained and noted to be elevated and peaked at 93300. He was treated with bicarbonate drip with subsequent improvement in renal function.(Table1)

Results:

Conclusions: Trabectedin has been associated with pancytopenia, myocarditis, transaminitis and GI side effects. In the company drug data base, rhabdo has only been reported in 0.7% of cases, but had a high mortality of 41%. CK elevation is typically reported after the 2nd cycle and rare after the 4th cycle. Median time to CK elevation was 2mo post chemotx. Trabectidin undergoes hepatic metabolism and inhibitors of CYP3A4 increase risk for adverse events. Our patient was not on any medications which is known to inhibit this pathway. With increasing use of trabectedin in soft tissue sarcomas, it is critical that physicians be aware of this devastating complication and monitor patients closely during chemotx. Early, adequate hydration, frequent lab checks including SCr and CK is crucial in preventing AKI and its complications.

Lab Trend

Labs	1 week before admission	Day 1 of admission	Day 9 of admission	Day 18 of admission (peak values	At Discharge (day 35)
SCr (mg/dl)	1.10	1.40	1.95	5.61	0.9
K (mmol/l)	3.5	4.1	3.7	3.5	3.5
Ca (mg/dl)	8.8	7.8	7.2	<5	8.2
Phos (mg/dl)	2.3	-	-	7.5	3
Trop(ngml)	-	0.15	8.3	16	-
CK (units/l)	55	177	8154	93300	161
AST (units/l)	48	198	1203	1665	119
ALT (units/l)	96	340	422	862	73
ALP (units/l)	83	207	178	264	77
Uric acid (mg/dl)	5	-	-	16.8	7

FR-PO007

A Case of AKI due to Rhabdomyolysis in Association with Exposure to Daptomycin Eldrid Baez, Juan Carlos Q. Velez. *Ochsner Clinic Foundation, Kenner, LA.*

Background: Rhabdomyolysis has been reported in association with exposure to the cyclic lipopeptide daptomycin. However, reports of acute kidney injury (AKI) resulting from daptomycin-associated rhabdomyloysis are sparse in the medical litearature.

Methods: A 35 year-old Caucasian man presented to the hospital with a 3-day history of fever and worsening delirium after a recent reduction and fixation of a motor vehicle accident-related wrist fracture which had been performed 2 weeks prior to presentation. Past medical and family history were unremarkable. Vital signs were significant for temperature of 38ºC and blood pressure of 99/56 mmHg. Physical examination disclosed confusion and an erythematous, inflamed right wrist. Laboratrory data on admission revealed a serum creatinine (sCr) of 1.3 mg/dL. Blood cultures revealed growth of methicillin-resistant *Staphyloccous aureus.* He was initiated on empiric antibiotic therapy with vancomycin, tobramycin and aztreonam. The patient remained febrile and blood cultures failed to clear after 3 days of therapy. The wrist hardware was then surgically removed. Antibiotic coveraged was broadened with the addition of daptomycin. Three days after the addition of daptomycin, sCr began to increase progressively, reaching a peak level of 7.1 mg/dL 4 days later. Serum creatinine kinase (CK) was found to be 29,000 U/L. Urine microscopy revealed muddy brown granular casts, no red blood cells and 1+ blood by urine disptick. As a result, daptomycin was discontinued in light of suspected toxic acute tubular necrosis (ATN) due to rhabdomyolysis. He transiently required renal replacement therapy. One week later, sCr and CK began to normalize.

Results:

Conclusions: While rhabdomyolysis was reported in up to 3% of patients receiving daptomycin in pre-marketing clinical trials, AKI due to rhabdomyolysis was not reported until the post-marketing era. To date, only 3 probable cases are found in the literature. By the Naranjo criteria, our case is also classified as probable. This case demonstrates that awareness should be raised about the risk of severe AKI due to toxic ATN from daptomycin-associated rhabdomyolysis.

FR-PO008

Recurrent Exercise Associated AKI: An Unusual Presentation of Malignant Hyperthermia Megha R. Joshi,[2] Sarah M. Gordon.[1] *[1]WRNMMC, Rockville, MD; [2]Walter Reed, Bethesda, MD.*

Background: We present a healthy soldier with recurrent exercise associated acute kidney injury (AKI) and hematuria. After extensive testing, muscle biopsy was diagnostic of malignant hyperthermia (MH). This case suggests myopathic disorders should be discussed in exercise-associated AKI.

Methods: A thirty-five year old white male was referred for recurrent painless dark urine after running. He had no medical or surgical history, and no family history of renal disease. He denied new medications, substance or supplement use. There was no history of nephrolithiasis or urinary tract infection.

Results: He was normotensive with an unremarkable physical exam. Pre-exercise renal function, proteinuria quantification, urine dipstick and microscopy, sickle cell screen, drug screen, and creatinine kinase (CK) were normal. Serum creatinine was 0.9 mg/dL. Post exercise serum creatinine rose to 1.5mg/dL. Testing demonstrated elevated serum and urine myoglobin (111ng/mL and 29ng/mL respectively) and mildly elevated CK (309 U/L). Repeat urine sediment showed muddy brown casts consistent with acute tubular necrosis (ATN) and 20 isomorphic red cells per field. Labs normalized within one week of rest. He was evaluated by Hematology and Rheumatology for muscular and red blood cell abnormalities; no etiology was identified. Cystoscopy and contrasted tomography urogram were normal. Pre- and post-exercise renal artery dopplers were normal. He was referred to a neuromuscular specialist, and a muscle biopsy was diagnostic for malignant hyperthermia. We recommended avoidance of strenuous exercise and anesthetic agents. Renal function is normal without symptom recurrence following de-escalation of his exercise regimen.

Conclusions: The classic presentation of MH is characterized by acute hyperthermia, muscle rigidity, and rhabdomyolysis with AKI. There are also case reports of subclinical rhabdomyolysis in MH, however none document evidence of ATN. Exercise-induced AKI is a rare clinical presentation of MH, and should be considered in the differential. Avoidance of AKI precipitants is important, as the risk for CKD among individuals with recurrent AKI is well documented.

FR-PO009

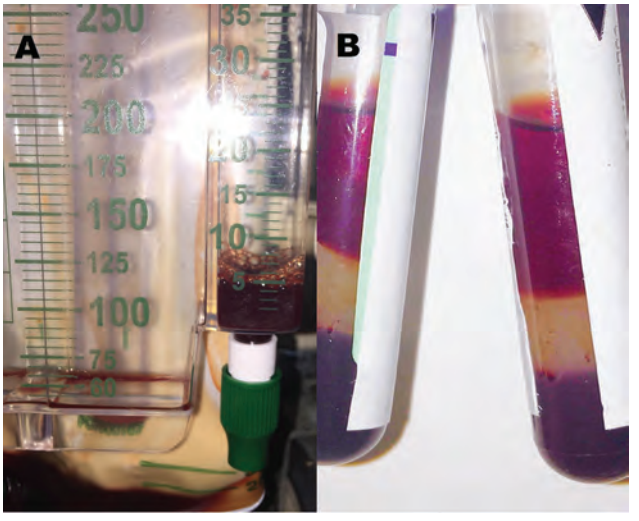
Acute Intravascular Hemolysis and Kidney Injury from an Amplatzer Device: Complication of an Innovative Cardiac Procedure and the Challenge of Dialysis Kevin D. Marquez, Andrew I. Chin. *University of California Davis Medical Center, Sacramento, CA.*

Background: The Amplatzer septal occluder is a transcatheter device used as a treatment option for ostium secundum atrial septal defects. It has also been used to treat residual mitral regurgitation (MR) in patients with a high open surgical risk. We describe a rare complication of rapid mechanical hemolysis leading to acute kidney injury, and describe the challenge of hemodialysis (HD) in this setting.

Methods: A 68 yo man with persistent MR despite 2 prior procedures had an elective 3rd MitraClip with placement of the Amplatzer septal occluder device in the lateral mitral commissure. The procedure went well. The following morning, his serum creatinine doubled from 1.33 to 2.62 mg/dL, his urine turned dark in color (Figure A), and he became oliguric. Labs at that time: potassium 5.9 mEq/L, lactate dehydrogenase 2200 U/L, haptoglobin 4 mg/dL, and peripheral smear with schistocytes. Notably, plasma was red in color (Figure B). Rapid mechanical hemolysis due to the Amplatzer device was suspected. The device was immediately removed. HD was initiated. However, within a minute, the dialysate blood leak detector alarm was triggered. No blood was visualized in the dialysate, which tested positive using hemoglobin test strips. Blood was not returned and a new circuit and machine were set up. Using low blood flow of 100 cc/min and high dialysate flow of 800 cc/min, HD was resumed with minimal alarms. Subsequent HD treatments did not activate the blood leak alarms.

Results:

Conclusions: While intravascular hemolysis with the Amplarzer device has been reported, this is the second reported case of hemolysis when this device is used to treat residual mitral regurgitation. This case demonstrates the sensitivity of the dialysate blood leak detector to being triggered by the diffusion of free hemoglobin into dialysate due to intravascular hemolysis.



FR-PO010

Renal Hemosiderosis as a Complication of Total Artificial Heart Therapy Mirza S. Baig,[2] Gaurav Gupta,[1] Dhiren Kumar.[1] *[1]Medical College of Virginia/Virginia Commonwealth University, Richmond, VA; [2]VCU Medical Centre, Richmond, VA.*

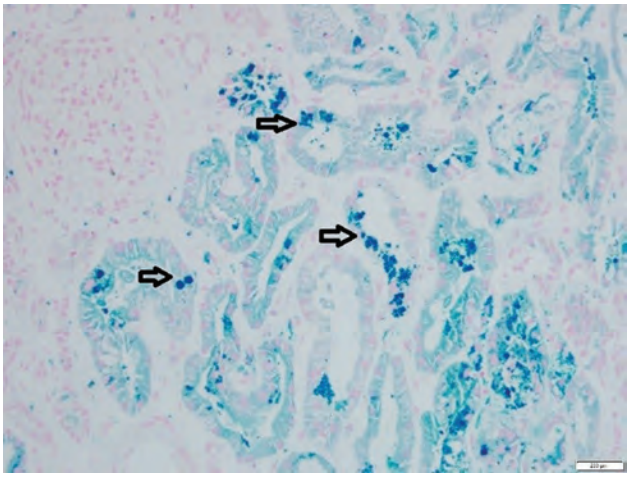
Background: Mechanical circulatory support with a total artificial heart (TAH) is approved as a bridge to heart transplantation. Hemolysis is a common complication after implantation of a TAH. The incidence of renal failure requiring dialysis after TAH has been estimated at 12-15%. Kidney biopsy findings in patients with TAH and chronic hemolysis with renal failure have not been described.

Methods: A 57-year-old male with a history of non-ischemic cardiomyopathy underwent implantation of TAH. Post-TAH he developed progressive renal dysfunction (GFR decline= 70ml/min to 40 ml/min) presumed secondary to cardio-renal syndrome. He was also noted to have chronic hemolysis confirmed by evidence of fragmented RBC's on smear, elevated LDH and undetectable haptoglobin concentration. Due to this, he required blood transfusions for the next seven months till the time he underwent an orthotopic heart transplant (OHT). Post-OHT he developed worsening acute kidney injury requiring hemodialysis (HD). After being maintained on HD for 8 weeks, a kidney biopsy was performed. In addition to moderate interstitial fibrosis, his biopsy was remarkable for extensive intracytoplasmic and luminal iron deposition in tubular epithelial cells. His renal function recovered partially over the next 4 weeks with a most recent recorded GFR of 20 and dialysis was withdrawn. He was listed pre-emptively for a kidney transplant.

Results:

Conclusions: We posit that the TAH-induced hemolysis and subsequent hemosiderosis contributed to the renal dysfunction seen in this patient. This pre-transplant injury could predispose OHT patients to further acute kidney injury in the setting of hemodynamic peri-operative insults and calcineurin inhibitor therapy. We propose that

assessment of renal histology might shed further light on the etiopathogenesis of renal failure and to assess the potential for renal recovery in patients with artificial heart devices and/or heart transplant.



Prussian Blue

FR-PO011

A Stitch in Time Saves Nine: Renal Infarction Secondary to Forgotten Prophylaxis Muhannad Leghrouz, Volodymyr Chornyy, Abhilash Koratala. *University of Florida, Gainesville, FL.*

Background: Antibiotic prophylaxis against bacterial endocarditis is indicated prior to invasive procedures in patients with certain high-risk cardiac conditions and thorough history needs to be elicited prior to performing such procedures. We present a case of spleno-renal infarction secondary to septic emboli in a patient with prosthetic aortic valve who underwent a dental procedure without endocarditis prophylaxis.

Methods: A 42-year-old white man with history of bioprosthetic aortic valve presented with intermittent fevers for a week and bilateral flank pain for 2 days. He saw a dentist 2 weeks ago for toothache and underwent a dental procedure involving manipulation of gingival tissue. Exam was significant for systolic murmur in the aortic area and tenderness in bilateral flanks. Serum LDH was elevated. A CT scan of the abdomen with contrast demonstrated areas of non-enhancement involving more than 50% of the right kidney predominantly involving the lower pole and also most of the spleen consistent with renal and splenic infarction [Figure 1a]. Interestingly, the patient was noted to have an accessory right renal artery providing flow to the upper part and probably accounts for relative sparing of this portion of the kidney [Figure 1b]. Subsequently, patient's blood cultures grew Streptococcus mitis and oralis; trans-esophageal echo revealed infective endocarditis, which supports the diagnosis of renal and splenic infarction from septic emboli. Patient improved with antibiotic therapy and renal function remained stable.

Results:

Conclusions: The learning point from our case is that thorough history taking before invasive procedures might prevent potentially life-threatening complications. Our patient had prosthetic valve, and appropriate antibiotic prophylaxis prior to the dental procedure could have evaded the complications he developed.

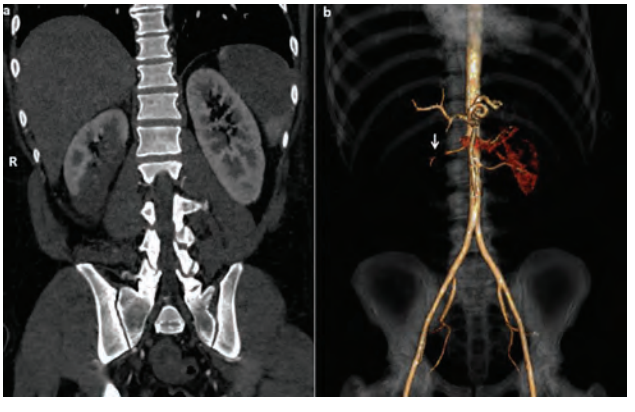


Figure 1a and 1b

FR-PO012

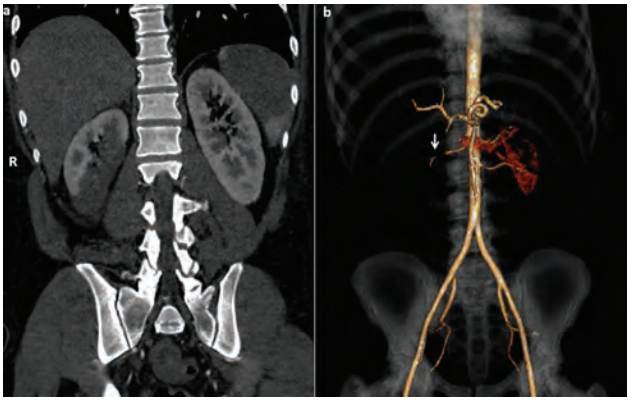
Idiopathic Renal Infarction Volodymyr Chornyy, Abhilash Koratala. *University of Florida, Gainesville, FL.*

Background: Renal infarction is a rare condition that typically presents with back pain, flank or abdominal pain, hematuria and laboratory abnormalities such as leukocytosis, high CRP and elevated LDH. Most common causes of renal infarction are cardiac conditions such as atrial fibrillation, ischemic or valvular heart disease followed by other etiologies including hypercoagulable states and renal artery dissection. Interestingly no cause can be found in about a third of patient. Herein, we present a case of idiopathic renal infarction, which presented without the classic laboratory abnormalities.

Methods: A 42-year-old man with a history of hypertension has presented with nausea and abdominal pain for 2 days. Approximately 6 months prior to presentation, he was diagnosed with deep venous thrombosis of the right leg and was treated with warfarin for 3 months. Notably, he had similar pain at that time but of lesser intensity and no abdominal imaging was done. He was afebrile and urinalysis was negative for blood or WBC. Serum creatinine was 0.7 mg/dL and LDH, CRP normal. CT scan of the abdomen without contrast showed possible bilateral renal infarcts. MRA of the abdomen was performed which showed subacute bilateral focal infarcts in both the kidneys with a new wedge-shaped infarct in the right kidney (Figure 1A). Aorta and branch vessels demonstrated normal vascular enhancement without evidence for wall thickness, aneurysm or stenosis (Figure 1B). EKG showed sinus rhythm and telemetry monitoring during his inpatient stay did not show any arrhythmia. ANA, ANCA, viral hepatitis panel, HIV test were negative. Hypercoagulability work up was essentially negative. He was discharged on oral anti-coagulation.

Results:

Conclusions: Our case emphasizes the fact that high index of suspicion is required to diagnose renal infarction in patients presenting with abdominal pain. Early recognition is important because it may have long-term implications on kidney health.



FR-PO013

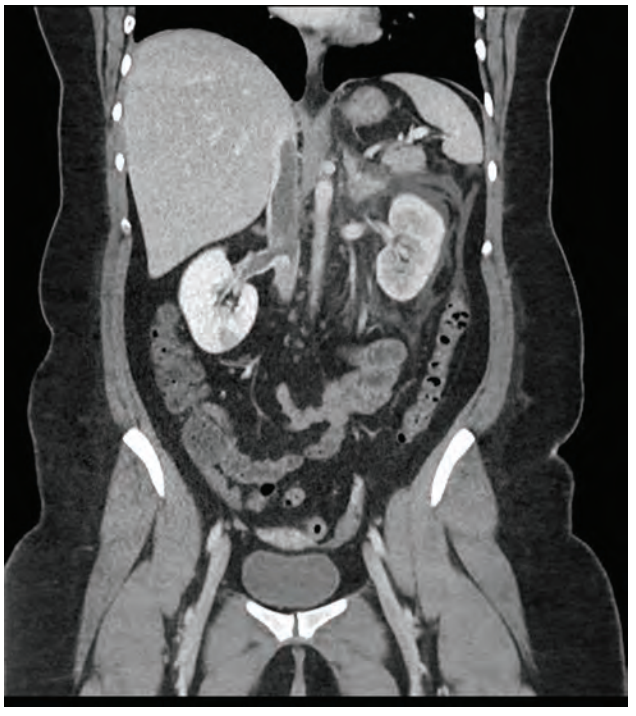
Acute Spontaneous Bilateral Renal Vein Thrombosis in a Healthy Young Woman Yuzana K. Zaw, Mira T. Keddis. *Mayo Clinic, Chandler, AZ.*

Background: Introduction: Acute spontaneous bilateral renal vein thrombosis in native kidneys is extremely rare. We report the first case of acute spontaneous bilateral renal vein thrombosis in a healthy young woman.

Methods: Case Description: A 26 year old Caucasian female non-smoker presented to Mayo Clinic with a chief complaint of 24hr history of acute left flank pain. She has asthma, dyslipidemia and polycystic ovarian syndrome for which she was on oral contraceptives, Azurette for 9 years and then switched to Ashlyna 4 months ago. She experienced dyspnea two weeks before which was initially attributed to her underlying asthma. CT scan of abdomen and pelvis showed acute bilateral renal vein thrombosis with extension of thrombus to involve a long segment of IVC with associated segmental ischemia to lower pole of right kidney. CT chest showed bilateral acute pulmonary emboli. She had transient microscopic hematuria, low grade proteinuria (2grams) and acute kidney injury with serum creatinine of 1.3 mg/dL from baseline 1 mg/dL. She was initiated on intravenous Heparin drip and transitioned to Apixaban therapy. Hypercoagulable workup was negative. She had Minera intrauterine contraceptive device placed during admission and she was advised not to use estrogen containing contraception or supplements in the future due to her history of massive thrombosis while taking oral contraceptives.

Results:

Conclusions: Discussion: We report the first case of spontaneous bilateral renal vein thrombosis (RVT) and acute bilateral pulmonary emboli in an otherwise healthy young woman with long term contraceptive use. This case illustrates the importance of high clinical suspicion for RVT in the differential diagnosis of acute flank pain particularly, in patients with oral contraceptive use. Early recognition and prompt treatment is the corner stone of management.



FR-PO014

Managing Bilateral Renal Artery Stenosis (RAS) Franklin Lam,[2] Rafia I. Chaudhry,[2] Loay H. Salman,[1] Mauricio Monrroy.[2] *[1]Albany Medical College, Albany, NY; [2]None, Providence, RI.*

Background: Renal artery stenosis (RAS) accounts for 2-4% cases of HTN in the US. Etiology of RAS includes age related atherosclerosis, and fibromuscular dysplasia in young females.

Methods: 79-year-old Caucasian female, with PMHx of well controlled HTN, HLD, DM 2 and CKD (baseline Cr 1.7 mg/dL) presented with HTNsive urgency (BP 220/90 mm Hg), AKI (Cr 2 mg/dL), pulmonary edema and severe LE edema. Cr notably worsened over 6 months. Abdominal CTA revealed severe bilateral RAS. Renal artery stenting was held due to AKI with Cr rising to 3 mg/dL. After prolonged hospitalization, pt was discharged on medical therapy (Bumetanide, Doxazosin, Clonidine, Metoprolol, and Nifedipine). Cr remained elevated at 3.1 mg/dL on follow-up. Pt underwent left renal artery stenting at this time. Right renal artery was not amenable to stenting due to complete occlusion. Renal function improved, Cr stabilized at 1.4 mg/dL at five months later. BP and volume status well controlled.

Results:

Conclusions: RAS results in decreased renal perfusion and activation of renin-angiotensin-aldosterone system (RAAS), resulting in systemic vasoconstriction, Na retention and HTN. Significant reduction of renal blood flow occurs at greater than 70% narrowing of the artery. As the stenosis worsens global renal ischemia leads to shrinking of the affected kidney, and AKI or CKD. While medical therapy is initially indicated, failure of medical therapy i.e. worsening renal function, poorly-controlled BP, recurrent pulmonary edema and hypervolemia are indications for revascularization that is performed with percutaneous transluminal renal angioplasty (PRTA). Despite multiple studies showing the effectiveness of medical therapy, there is still a role for targeted endovascular therapy in cases of RAS resistant to conventional therapy.

FR-PO015

Pseudo-AKI Due to "Reverse Autodialysis": A Case of Spontaneous Rupture of the Urinary Bladder Connor Deal, Xixi Zhao, Casey N. Gashti, Stephen M. Korbet. *Rush University Medical Center, Chicago, IL.*

Background: Spontaneous rupture of the urinary bladder (SRUB) is rare and can appear to present as AKI. This "Pseudo" AKI results from reabsorption of Cr and urea across the peritoneal membrane, referred to as "reverse autodialysis". We describe a case of SRUB following an alcohol binge.

Methods: A 46 yo WM p/w abdominal distention, anuria and AKI following a 2-day alcohol binge. On exam his abdomen was distended with urgency upon suprapubic palpation. Labs: BUN- 63 mg/dl, SCr- 6.4 mg/dl and SAlb-4.4 g/dl, LFTs were nml. A non-con abd CT showed large "ascites" and no urinary obstruction. Paracentesis yielded 5L of clear fluid with a Cr level elevated at 27 mg/dl indicating the presence of urine in the peritoneal cavity. A Foley catheter was placed with 12L of UOP over 1-hour. CT cystography demonstrated extravasation of contrast into the peritoneal space(Fig 1). At laparoscopy a 1cm defect at the superior dome of the bladder was repaired. Renal function normalized within two days.

Results:

Conclusions: SRUB in the setting of alcohol intoxication is thought to be due to altered sensorium and decreased urge to urinate. The volume of ingested alcohol and its diuretic effect further increase bladder filling. The pt's elevation in BUN and Cr are the result of reabsorption of urine across the peritoneal membrane ("reverse autodialysis"). This gives the appearance of AKI when in fact GFR is normal. The rarity of SRUB as well as the nonspecific presenting symptoms of abdominal distention with ascites and AKI presents a diagnostic challenge. Analysis of the ascitic fluid for Cr to establish a urine leak is a critical diagnostic step. Treatment is immediate surgical repair of the bladder with good prognosis.

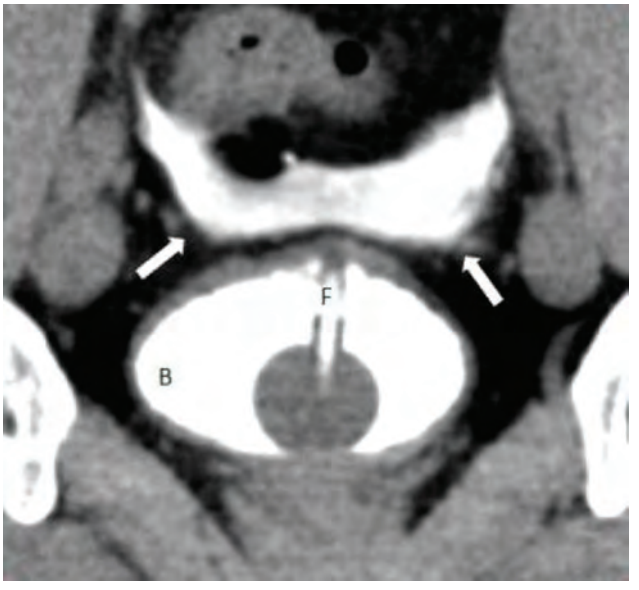


Fig 1. Foley catheter (F) penetration through the bladder (B) wall with contrast extravasation in the peritoneal cavity (white arrows).

FR-PO016

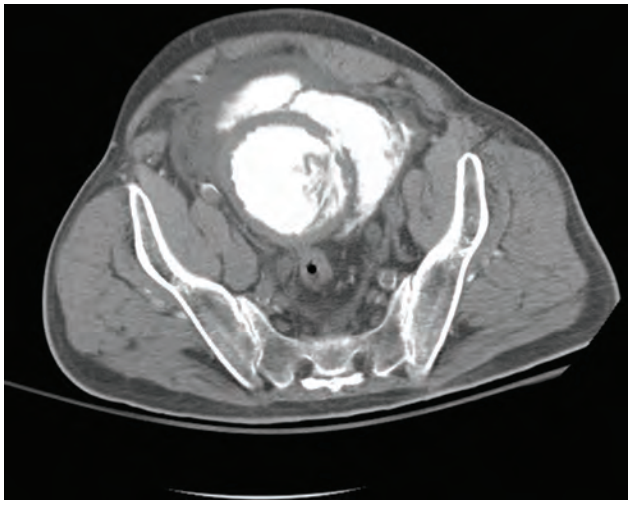
AKI Due to Bladder Rupture After a Fall Brad Long, Josephine Abraham. *University of Utah, Salt Lake City, UT.*

Background: Urinary bladder rupture is usually associated with high impact trauma and is rarely seen in milder trauma. We present a case in which a patient sustained a ground level fall leading to bladder rupture and acute kidney injury.

Methods: A 68 year old male with CKD stage III due to diabetic nephropathy with baseline creatinine of 2.5-2.9mg/dL presented to the emergency department after falling onto his walker after having cocktails with friends. The fall resulted in brief loss of consciousness and right wrist injury. On presentation he had exquisitely tender abdomen and nausea and emesis. Foley catheter was placed resulting in drainage of gross hematuria. Initial labs showed acute kidney injury with creatinine of 6.3mg/dL, serum potassium 7.2meq/L, and serum bicarbonate of 16mmol/L. He had no elevation in anion gap or serum lactate. The hyperkalemia and acidosis were not improved with boluses of IV sodium bicarbonate and furosemide. CT abdomen/pelvis revealed extraperitoneal bladder rupture that was further characterized on CT cystography.

Results: The patient was taken emergently to the operating room emergently by the consulting urology service for exploratory laparotomy and repair of the bladder. He did require a single treatment of hemodialysis for hyperkalemia. Following repair of the bladder, his renal function rapidly returned to baseline and the hyperkalemia and metabolic acidosis resolved.

Conclusions: Traumatic bladder injury resulting in obstructive uropathy is a cause of AKI that should be excluded in patients suffering even mild trauma. A full bladder is more susceptible to rupture than an empty bladder. In this setting, a low-impact event can produce dramatic internal injury. CT cystography provides accurate and rapid identification of bladder injuries. Prompt surgical management is crucial.



CT cystogram demonstrating extraperitoneal bladder rupture

FR-PO017

Wunderlich Syndrome Bilal Ahmed, Muhammad Afzal, Krishna M. Baradhi. *University of Oklahoma, Tulsa, OK.*

Background: Wunderlich syndrome is spontaneous, nontraumatic renal hematoma confined to perirenal and subcapsular space and is often due to underlying renal pathology. We herein present a rare case of wunderlich syndrome secondary to acute pyelonephritis.

Methods: 55-year-old woman presented with fever, acute abdominal pain, nausea, vomiting and dizziness. Examination was pertinent for orthostatic hypotension and mild right flank tenderness. Initial labs showed acute kidney injury with creatinine of 4.8 mg/dl and Bun of 50 mg /dl along with anemia and leukocytosis. Urine sediment showed muddy-brown granular casts as well as pyuria with bacteriuria. She was diagnosed with acute pyelonephritis and acute tubular necrosis, which gradually improved with antibiotics and fluid resuscitation. However CT scan revealed a large right subcapsular perinephric hematoma concerning for renal cancer. A follow up contrast enhanced MRI, a week after her renal function improved showed much smaller and a more organized evolving right subcapsular renal hematoma making a diagnosis of wunderlich syndrome, which is indeed a rare complication of pyelonephritis. Patient was managed conservatively with eventual resolution of hematoma.

Results:

Conclusions: Spontaneous perinephric hematoma (SPH) also called wunderlich syndrome, first described by wunderlich in 1856, is characterized by lenk's triad of abdominal pain, flank mass and hypovolemic shock. Most common etiologies are renal cell carcinoma, angiomyolipoma and vascular diseases. Amongst the rare causes include infectious and inflammatory renal diseases. Pyelonephritis complicating SPH is exceedingly rare and should be considered with intractable symptoms despite antibiotics or concurrent anemia without identified cause. Etiology and clinical severity dictates treatment, varying from close monitoring to nephrectomy. SPH requires high index of suspicion and careful investigation to rule out renal tumors and vascular disorders

FR-PO018

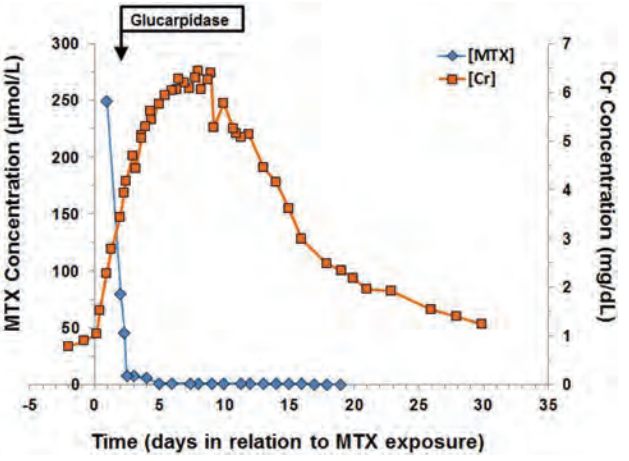
Use of Glucarpidase in AKI from Methotrexate Toxicity and Delayed Methotrexate Clearance from Levetiracetam Jacob Stevens, Andrew S. Bomback. *Columbia University, New York, NY.*

Background: Methotrexate (MTX) is the backbone of many chemotherapeutic regimens, and the management of subsequent toxicity from delayed elimination is challenging. We describe a case of MTX toxicity and delayed MTX elimination and demonstrate the successful use of glucarpidase, a recombinant bacterial enzyme carboxypeptidease G2 that rapidly metabolizes MTX into glutamate and the inactive 2,4-diamino-N-methylpteroic acid.

Methods: A 67-year-old woman with hypothyroidism and CKD-3 presented with a 2-week history of progressive right hemiparesis. A R-thalamic lesion with vasogenic edema was found on imaging and dexamethasone and levetiracetam were started. A brain biopsy showed diffuse large B-cell lymphoma and temozolomide 150mg/m2, rituximab 500mg/m2, and high dose MTX (4271mg/m2 adjusted as a ~50% reduction based on a 24h CrCl of 47mL/min) were initiated, with leucovorin (LV) rescue 50mg q6h initiated at 24h. She developed delayed early MTX elimination and acute kidney injury (AKI) attributed to MTX crystal nephropathy despite urinary alkalinization (urine pH 8.0-9.0). She was supported with LV and isotonic bicarbonate with furosemide; despite these measures her MTX level remained elevated at 80μmol/L at 48h and a single dose of glucarpidase (3600units, 50units/kg) was given 53h after MTX exposure (LV held for 2h before and after) resulting in a rapid and precipitous fall in her MTX levels. She developed a mild transaminitis but no mucositis or severe myelosuppression. Her Cr peaked 10 days after MTX exposure, and returned to baseline before discharge.

Results:

Conclusions: This case of delayed early MTX elimination and AKI illustrates the importance of dose adjustment in the setting of co-administration of MTX and levetiracetam, which has been reported to delay MTX clearance, and highlights the successful use of glucarpidase for rapid metabolism of MTX in challenging cases when levels remain toxic despite LV and IVF supportive management.



FR-PO019

Everolimus-Associated Acute Tubular Necrosis Nupur N. Uppal,[1] Rimda Wanchoo,[1] James M. Pullman,[3] Anna T. Levy,[1] Kenar D. Jhaveri.[2] *[1]Hofstra Northwell School of Medicine, Great Neck, NY; [2]Hofstra Northwell School of Medicine- Northwell health system, Great neck, NY; [3]Montefiore Medical Center, Bronx, NY.*

Background: Everolimus is a mTOR inhibitor used in treatment of renal cell cancer (RCC). Acute kidney injury (AKI) is a rarely seen adverse event of everolimus treatment. We report a case of biopsy-proven acute tubular necrosis(ATN) with everolimus treatment.

Methods: A 43 year old male with history of nephrectomy for RCC 7 months prior to admission presented with AKI and a serum creatinine(Scr) of 3.7mg/dl (baseline of 1.2mg/dl). He had begun everolimus treatment for metastatic RCC to the liver 4 weeks prior to admission and also received radiation. On admission his urinalysis revealed 150 mg/dl/day protein, granular casts, and moderate blood (10-15 RBCS and 20-25 WBCs). ANA was 1:360 but all other serologies were negative. A renal sonogram with Doppler ruled out hydronephrosis and renal vein thrombosis. When sCr rose to 7.5mg/dl, hemodialysis was initiated. A biopsy of the solitary kidney showed toxic ATN with vacuolization, minimal interstitial fibrosis and tubular atrophy, all likely related to everolimus treatment. There was no glomerular disease. He required dialysis for 6 weeks and his ATN recovered and his most recent Scr is 1.4mg/dl, supporting the pathology diagnosis of ATN. A pulmonary embolism requiring anticoagulation was the only complication. He is being considered for treatment with a tyrosine kinase inhibitor for his metastatic RCC.

Results:

Conclusions: We describe the second published case of ATN secondary to everolimus treatment. This toxic kidney injury from anti-neoplastic use of of an mTOR inhibitor is more severe than the more common form seen when used in transplants, proteinuria. A dose dependent effect might explain this difference since toxicity might be enhanced when there is a solitary kidney, as in this case. Although this risk of nephrotoxicity is still small, physicians should be aware of it and renal function should be closely monitored during everolimus therapy.

FR-PO020

Rapid Progression of CKD to ESRD after Tyrosine Kinase Inhibitor Use for Chronic Phase CML Sandhya L. Kommana,[2] Cynthia C. Nast,[1] Sharon G. Adler.[3] *[1]Cedars-Sinai Medical Center, Los Angeles, CA; [2]Harbor ULCA MEDICAL CENTER, Harbor City, CA; [3]Harbor-UCLA Medical Center, Torrance, CA.*

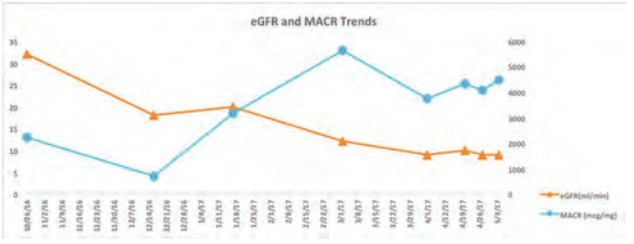
Background: Long-term tyrosine kinase inhibitor (TKI) use may cause AKI, CKD, proteinuria and/or hypertension, but case reports document that these are transient and reversibile with drug discontinuation. We report a case of rapid progression of CKD to ESRD with no improvement despite discontinuation of TKIs.

Methods: A 39-year-old woman with presumed diabetic kidney disease (DKD), eGFR 28 ml/min/1.73m^2 and UACR 700 mcg/ml, was diagnosed with chronic myelogenous leukemia (CML). She was started on Imatinib 100 mg QD with dose escalation to 400 mg QD. Her eGFR rapidly declined in 3 weeks and remained low despite dose reduction, and then discontinuation. She was changed to dasatinib but she developed shortness of breath, fatigue and pleural effusions, which prompted switching to nilotinib. During follow-up, her eGFR fell further, and nilotinib was discontinued. During this 4-month period, hypertension and proteinuria worsened. Her UACR increased to 5000 mcg/mg. A renal biopsy performed when her eGFR was 10 ml/min/1.73 m^2 showed focal moderate interstitial nephritis containing mononuclear leukocytes, neutrophils, and few eosinophils with ATN on underlying nodular diabetic glomerulosclerosis. Urine culture was negative. Arterioles showed arteriolosclerosis and thrombotic microangioapthy. Her

renal function continued to worsen despite discontinuation of TKIs and she was initiated on hemodialysis.

Results:

Conclusions: In this patient with underlying DKD, sequential impairment of eGFR, worsening proteinuria, and HTN exacerbation occurred with serial introduction of imatinib, dasatinib, and nilotinib, contributing to rapid progression to ESRD. To our knowledge, this is the first reported case in which progression of CKD to ESRD was associated with TKI use. Our case suggests that in patients with underlying advanced CKD, irreversible renal injury may occur and patients should be informed of this possibility. Further studies are warranted to understand the effects of TKIs on renal function.



FR-PO021

Tyrosine Kinase Inhibitors: Need Not Be TMA! Franklin Lam,[4] Apryl Jacobs,[5] Llewellyn A. Foulke,[5] Anum Bilal,[1] Swati Mehta,[3] Loay H. Salman,[2] Krishnakumar D. Hongalgi.[4] *[1]AMC, Albany, NY; [2]Albany Medical College, Albany, NY; [3]Icahn school of medicine at Mount Sinai, Rensselaer, NY; [4]None, Providence, RI; [5]Albany Medical Center, Albany, NY.*

Background: Multi-targeted receptor tyrosine kinase inhibitors (TKIs) are considered the standard of care for renal cell carcinoma (RCC). Few reports have raised concern for nephrotoxicity (NT) with TKIs. We report a case of biopsy-proven acute interstitial nephritis (AIN) after sunitinib use.

Methods: A 69-year-old male with stage IV left clear cell RCC began sunitinib 50 mg daily with baseline SCr of 1.0 mg/dL and BUN of 18 mg/dL. On day 18 of the sunitinib dosing cycle, the patient presented with a three-day history of hematuria, non-oliguric AKI with SCr of 2.7 mg/dL and BUN of 39 mg/dL, and other electrolytes within normal limits. Sunitinib was held upon admission but the patient subsequently required renal replacement therapy (RRT) for worsening acute renal failure (ARF). Thrombocytopenia developed, but hematuria occurred intermittently.

Results: Renal biopsy was performed on hospital day six, which confirmed AIN with extensive interstitial inflammation, frequent eosinophils and interstitial edema. No endothelial swelling, loss of endothelial fenestration, subendothelial widening, abnormal glomerular basement membrane thickness, or evidence of thrombotic microangiopathy (TMA) was seen. Renal function partially improved with prednisone and intermittent hemodialysis (HD) and he was discharged 32 days later on weekly HD.

Conclusions: AIN is a common cause of renal failure and is seen in as many as 15% of renal biopsies performed as part of the work up for ARF. Sunitinib is rarely associated with NT, although there are multiple reports of sunitinib-induced TMA. There are only few case reports of TKI-associated, biopsy-proven AIN to our knowledge to date. Our patient's AIN was consistent with sunitinib use and other causes were ruled out. This report highlights the importance of recognizing AIN as one of the differential diagnoses in a patient receiving sunitinib who develops AKI and thus vigilant renal monitoring is required during TKI use.

FR-PO022

Nephrotoxicity of Immune Checkpoint Inhibitors: MD Anderson Cancer Center's Experience Umut Selamet,[1] Ali Ziaolhagh,[2] Laila S. Lakhani,[2] Amit Lahoti,[1] Biruh Workeneh,[1] Amanda Tchakarov,[2] William F. Glass,[2] Ala Abudayyeh.[1] *[1]MD Anderson Cancer Center, Houston, TX; [2]UT Houston, Houston, TX.*

Background: Immune checkpoint (ICP) inhibitors, anti-CTLA-4 (Ipilimumab) and anti-PD-1 (Nivolumab and Pembrolizumab) have revolutionized treatment options for many types of cancers. Adverse events associated with ICP inhibitors are mainly due to uninhibited immune system causing autoimmune diseases. Literature on nephrotoxicity of these novel agents is limited. Acute tubulointerstitial nephritis (ATIN) is the most commonly described kidney injury secondary to ICP inhibitors. Few case reports also identified glomerulonephritis (GN) induced by ICP inhibitors.

Methods: We present 7 cases of biopsy proven nephrotoxicity during treatment with ICP inhibitors. Malignancies asscoiated with the cases were as following: Renal cell carcinoma (n=1), smoldering myeloma (n=2), melanoma (n=1), chondroma (n=1), bladder cancer (n=1) and lung cancer (n=1). Six out of 7 cases showed features of ATIN at kidney biopsy specimens. Several types of GNs were also observed: membranous GN, IgA nephropathy, and pauci immune GN. One patient had AA type amyloidosis. ICP inhibitors discontinued in all cases, and 5 cases were also treated with steroid. Steroid treatment resulted in either partial or full renal recovery in 4 out of 5 cases. Cases are summarized at Tables 1 and 2.

Results:

Conclusions: Early recognition of nephrotoxicity, utilization of kidney biopsy and steroid treatment for both ATIN and GN are the hallmarks of management of nephrotoxicities induced by ICP inhibitors.

Funding: Clinical Revenue Support

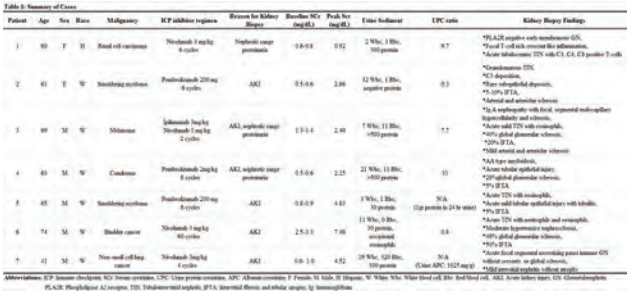


Table 2: Management of Nephrotoxicity and Renal Outcomes

Patient	Nephrotoxicity Management	Renal Outcome	Cancer/Patient Status
1	ICP inhibitor discontinued, Prednisone 80 mg/day tapered off in 6 months	Full recovery	Started on Axitinib, regression of metastasis
2	ICP inhibitor discontinued, Prednisone 80 mg/day tapered off in 5 months	Partial recovery	No progression on observation
3	ICP inhibitor discontinued, Prednisone 60 mg/day tapered off in 2 months	Full recovery followed by recurrence of AKI and nephrotic range proteinuria after prednisone tapered off. Restarted on Prednisone 60 mg/day with plans of slow taper	No evidence of disease on observation
4	ICP inhibitor discontinued	No recovery	Patient deceased due to bowel perforation and sepsis
5	ICP inhibitor discontinued	Full recovery	Progression to multiple myeloma, started on Cyclophosphamide/Bortezomib/Dexamethasone
6	ICP inhibitor discontinued, Prednisone 60 mg/day tapered off in 6 weeks due to infections	No recovery	Minimal residual disease
7	ICP inhibitor discontinued, Rituximab 1gr iv given for one dose, Prednisone 60 mg/day tapered off in 3 months	Full recovery	Patient deceased due to progression of cancer

FR-PO023

Using Steroids in Acute Interstitial Nephritis Secondary to Immune Checkpoint Inhibitors Sean Verma, Kayla Shirley, Claude Bassil. *University of South Florida, Tampa, FL.*

Background: Immune checkpoint inhibitors (ICI), both anti programmed death ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies, are novel immunotherapies that have transformed the treatment of non-small cell lung cancer, renal cell cancer, and metastatic melanoma. Renal toxicities associated with ICI are a rare side effect that must be elucidated.

Methods: A 78 year old man with metastatic lung adenocarcinoma on PD-L1 antibody durvalumab and anti-CTLA-4 antibody tremelimumab had acute kidney injury (AKI) with creatinine of 3.2 mg/dL (baseline 1.4 mg/dL) on routine labs. He completed 4 cycles of therapy and his last cycle finished 1 month ago. Labs were notable for bicarbonate 12 meq/L and phosphorus 4.7 mg/dL. Urinalysis revealed pH 7, specific gravity 1.008, and hyaline casts. Urine eosinophils were positive and he was started on intravenous methylprednisolone at 1mg/kg BID (80 mg BID) for acute interstitial nephritis (AIN). With 4 days of methylprednisolone 80 mg BID, creatinine improved to 2.3 mg/dL. He was transitioned to 80 mg PO prednisone daily for 2 days with creatinine improving to 1.9 mg/dL. He was discharged on 60 mg prednisone daily with instructions to decrease prednisone by 10 mg every 5 days. One week later creatinine was 1.4 mg/dL and his creatinine continues to be at baseline 2 months later.

Results:

Conclusions: ICI upregulate the patient's innate anti-tumor T cell response to the tumor and have been shown to significantly decrease tumor progression in comparison to standard treatment options previously available. Renal injury has seldomly been described in cases of both CTLA-4 and PD-L1 antibodies alone or in combination, though combination increases the risk of AKI. A variety of renal injury may occur, though AIN appears most reported. Hematuria, eosinophilia, worsening or new hypertension, and nephrotic syndrome have occurred in a few cases. The pathogenesis of AIN with ICI is unclear but it is thought to be due to uncontrolled increased T regulatory cell activity in which auto-reactive T cells infiltrate the kidney and cause cytotoxic injury. PD-L1 knockout mice have shown to spontaneously develop granulomatous AIN. Treatment is based on case reports and anecdotal data with prednisone 1 mg/kg over a taper of 1-2 months. A renal biopsy can be considered in cases with unclear etiology of AKI or if steroids aren't effective.

FR-PO024

Acute Tubulointerstitial Nephritis Induced by Anti-PD-1 Antibody: An Analysis of Infiltrating Cells in the Kidney Akifumi Tabei,[1,2] Hidekazu Ikeuchi,[1] Masao Nakasatomi,[1] Toru Sakairi,[1] Yoriaki Kaneko,[1] Akito Maeshima,[1] Yoshihisa Nojima,[3] Keiju Hiromura.[1] *[1]Department of Nephrology and Rheumatology, Gunma University Graduate School of Medicine, Maebashi, Japan; [2]Department of Nephrology and Rheumatology, Gunma Prefecture Saiseikai-Maebashi Hospital, Maebashi, Japan; [3]Department of Rheumatology and Nephrology, Japan Red Cross Maebashi Hospital, Maebashi, Japan.*

Background: Nivolumab, an anti-PD-1 antibody, is one of the immune checkpoint inhibitors (ICIs), which are increasingly used as anti-cancer agents. It has been known to induce various autoimmune diseases in some patients, such as thyroiditis, pneumonitis and pancreatitis, via disruption of immune tolerance. As for kidneys, acute interstitial nephritis has recently been reported. However, the precise renal pathology has not been well understood yet.

Methods: A 57-year-old man was admitted to our department due to an acute increase of serum creatinine (SCr). He had been treated with nivolumab for stage IV lung cancer for 2 months with 2 weeks interval. On the 5th scheduled administration day, he was found to have an elevated SCr level from 0.80 mg/dL to 1.57 mg/dL. Nivolumab was stopped and he was referred to our department and admitted 8 days later. Renal biopsy was performed immediately. A marked infiltration of inflammatory and immune cells was observed in tubulointerstitial area. Immunohistochemical staining revealed that infiltrating cells were positive for CD3 (T cell), CD20 (B cell), CD68 (macrophage), CD163 (M2 macrophage), BDCA-1 (dendritic cell) and DC-SIGN (dendritic cell). Among these cells, CD68 and CD163 were predominant, followed by CD3. Proton pump inhibitor (PPI), rabeprazole, was discontinued, because previous reports showed a possible association between PPI and tubulointerstitial nephritis under the treatment of ICIs. By the treatment with 50 mg/day of prednisolone, the peaked SCr of 3.48 mg/dL retuned to baseline level within 2 months.

Results:

Conclusions: Just recently, several reports showed increased T cells accumulation in ICIs-induced acute tubulointerstitial nephritis. Our case highlights a potential role of macrophage, as well as T cells, in the pathogenesis of interstitial nephritis caused by anti-PD-1 antibody.

FR-PO025

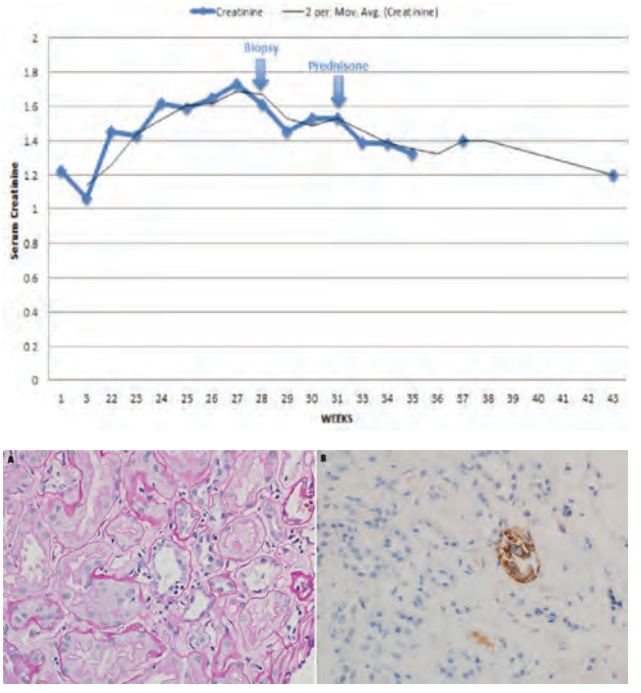
Tubulitis in a Patient Treated with Nivolumab: Case Report and Literature Review Viral Vakil, Mark Birkenbach, Katti Woerner, Safwan Muhammad, Lihong Bu. *University of Minnesota, Minneapolis, MN.*

Background: Immune checkpoint inhibitors are monoclonal antibodies that are increasingly approved by FDA for treatment of solid organ and hematologic malignancies by enhancing anti-tumor T cell immune response. Nivolumab is a monoclonal antibody targeting programmed death-1 (PD1), an inhibitory molecule expressed on cell surface of activated effector T cells. PD1 has two ligands programmed death ligand-1 (PD-L1) and programmed death ligand-2 (PD-L2), located on antigen presenting cells and hematopoietic cells respectively. Nivolumab prevents interaction of PD1 and PD-L1, allowing T cells to continue to attack tumor cells expressing PD-L1. Immune related adverse events (IRAEs), the effect of activated cytotoxic T cells on non-neoplastic antigens, are commonly seen across various organ systems. Renal toxicities associated with PD1 inhibitors are thought to be very low (0.9%), however some reports are more frequent and as high as 29%. Kidney injury associated with PD1 inhibitors commonly manifests as acute tubulointerstitial nephritis on kidney biopsy, with a late onset ranging from 3 to 10 months. Steroids appear to be effective in treating such IRAEs. Here we describe a patient with metastatic urothelial carcinoma treated with Nivolumab who develops acute kidney injury at 6 months after initiation of treatment. A renal biopsy showed focal moderate to severe tubulitis without evident interstitial inflammation. PD-L1 immunopositivity was detected only in tubules with lymphocytic tubulitis. The patient's renal function improved to baseline after withholding Nivolumab followed by prednisone treatment.

Methods:

Results:

Conclusions:



Kidney Biopsy under light microscopy (A) and immunohistochemical staining for PDL1 (B)

FR-PO026

Hemodialysis in the Management of Ifosfamide-Induced Fanconi Syndrome Priyamvada Singh,[1] Hanni Menn-Josephy,[1] Craig E. Gordon.[2] *[1]Renal, Boston University, Boston, MA; [2]None, Newton, MA.*

Background: Chemotherapy-induced nephrotoxicity is an emerging problem.

Methods: A 32-year-old man with CKD stage 4 secondary to biopsy-proven hypertension, and metastatic stage 3c mixed non-seminomatous germ-cell testicular cancer was admitted for the first of four planned chemotherapy cycles. Each cycle was comprised of five days of cisplatin/etoposide/ifosfamide and mesna. Based on case reports showing the benefit of HD in preventing ifosfamide-induced encephalopathy, HD was performed 10-12 hours following ifosfamide therapy. On day 2 of cycle #1, testing revealed urine pH of 8, 2+ glucosuria (with normal blood sugar), hypophosphatemia (1.0 mg/dL), and normal anion gap metabolic acidosis, consistent with Fanconi syndrome (FS). Baseline studies were normal the day prior to chemotherapy. FS resolved shortly after cessation of treatment but recurred during treatment for all 4 cycles. Upon completion of chemotherapy, there was no evidence of FS.

Results:

Conclusions: Ifosfamide-induced nephrotoxicity is characterized by proximal tubulopathy. Chloroacetaldehyde, a metabolite of ifosfamide, is toxic to renal tubules and depletes the antioxidant glutathione and adenosine triphosphate while inhibiting the activity of NA+/K+-ATPase. Risk factors for ifosfamide nephrotoxicity include cumulative dose, underlying CKD, and concomitant cisplatin therapy. This case highlights that FS can occur rapidly following a single dose of ifosfamide and in spite of HD performed to remove chloroacetaldehyde. Another noteworthy feature was the rapid reversibility of FS, which resolved within 3-5 days of the last dose of any chemotherapy cycle. Often, it takes few years for Ifosfamide-induced FS to resolve following completion of chemotherapy. The rapid resolution in our patient could be secondary to HD treatment and clearance of chloroacetaldehyde which is thought to be the cause of both neurotoxicity and proximal tubulopathy. This case highlights the role of HD to prevent tubular and neurotoxicity in ifosfamide-treated patients with advanced CKD.

FR-PO027

6-Mercaptopurine (6-MP)-Associated Acute Interstitial Nephritis (AIN) Brian C. Y'Barbo, John M. Childs, James D. Oliver. *Walter Reed Natl Mil Medical Center, Bethesda, MD.*

Background: AIN is an uncommon complication of Inflammatory Bowel Disease (IBD) which occurs from medications such as 5-aminosalicylate (5-ASA) or as an extra-intestinal manifestation of IBD (granulomatous interstital nephritis). We present the first reported implication of 6-MP as a cause of AIN.

Methods: A 38 yo M was admitted for cough, cytopenias, and acute kidney injury. Seven months prior to admission (PTA) he was diagnosed with ulcerative colitis and initially treated with prednisone+5-ASA. Ten weeks PTA therapy was switched to prednisone+6-MP for better symptom control. Two weeks PTA he developed cough which prompted evaluation and admission. IBD activity was mild. Labs were significant for leukopenia, anemia, and AKI (see Table). Urine sediment showed numerous WBCs

and WBC casts. Workup for infection was negative, and 6-MP metabolite levels were not supertherapeutic. Renal biopsy showed patchy interstitial inflammation with eosinophils, normal glomeruli, and no evidence of granulomas or viral cytopathic effect. 6-MP was held and sCr and cytopenias improved over a week. 15 weeks post-discharge sCr was near baseline and the patient was doing well on methotrexate+adalimumab.

Results:

Conclusions: A PUBMED search resulted in no previous reports of AIN from 6-MP. Azathioprine (AZA, the inactive prodrug of 6-MP) has known associations with AIN and delayed hypersensitivity reactions in the treatment of vasculitis. In such patients, it has been reported that 6-MP can safely be used in place of AZA. This case shows that AIN may result from 6-MP therapy as well, though it cannot be determined if this is a cross-sensitivity with AZA or a separate mechanism. In this patient, AIN did not occur with 5-ASA (a common culprit) and occurred despite concomitant treatment with steroids, which likely ameliorated the degree of injury. 6-MP should be included in the differential diagnosis of medications associated with AIN. The views expressed in this abstract are those of the authors and do not reflect the official policy of the Departments of Army or Navy, Department of Defense, or U.S. Government.

Funding: Other U.S. Government Support

Day	11w PTA	Admit	Biopsy	Discharge	6d Post-d/c	15w Post-d/c
Meds	CS + 5-ASA	CS + 6-MP	CS + 6-MP	CS	CS	MTX + ADAL
sCr (mg/dL)	0.9	1.83	2.0	1.87	1.4	1.2
WBC (K/μL)	11.4	3.7	5.4	7.2	9.6	5.2
Hgb (g/dL)	12.4	8.2	8.8	9.9	11.5	13.5

CS = corticosteroids, MTX=methotrexate, ADAL=adalimumab

FR-PO028

A Friend on Marijuana Is a Friend in Need: A Report of Acute Interstitial Nephritis (AIN) after Marijuana Use Mario J. Robles-Franceschini, Michael M. Strauss, Roberto L. Collazo-Maldonado. *Nephrology Division, Methodist Dallas Medical Center, Dallas, TX.*

Background: Acute kidney injury from synthetic Marijuana use has been reported, but until now no reports are available involving the non-synthetic variety. This is a rare case of Acute Interstitial Nephritis caused by non-synthetic Marijuana smoking.

Methods: A 20 y/o AA man with PMH of asthma, presents to the ER complaining of excruciating bilateral flank pain with associated nausea for 1 day prior to admission. His only medication was PRN albuterol inhaler. He denied OTC drugs or NSAIDS use. Three days prior to the symptoms, he smoked marijuana, but denied other illicit drugs. Physical examination was remarkable for obesity (BMI 37), hypertension 168/92mmhg and unilateral subconjunctival hemorrhage. On admission his creatinine was 1.75 mg/dL, urinalysis revealed protein 300mg/dl, RBCs 10-20/HPF, WBC's 0-5 /HPF, with no casts or eosinophils. Urine toxicology was positive for tetrahydrocannabinol. Serology studies were normal, including ANA panel, anti GBM, ANCA, ASO titers, HIV, Hepatitis B/C complements, ESR, IgG 4, SSA/B/ and ACE levels. His renal ultrasound with Doppler was normal. An abdominal CT scan showed perinephric stranding surrounding both kidneys with no stones. Initial management included blood pressure control, volume expansion and he was started empirically on IV steroids due to active sediment and worsening creatinine that peaked at 5mg/dL. Kidney biopsy was performed and showed AIN with marked interstitial lymphocytic infiltrate with eosinophils, interstitial and tubular edema, with normal glomeruli. His kidney function improved with steroids and he was discharged with a creatinine of 2.1 mg/dL.

Results:

Conclusions: Acute interstitial Nephritis from smoking non-synthetic marijuana has not been reported. The presentation of this young man with hypertension, active sediment, worsening renal function suggested possibility of Rapidly Progressive Glomerulonephritis and it prompted early treatment with steroids. The finding of AIN on the renal biopsy was crucial in establishing the association to the use of marijuana. It is important to consider AIN in the differential diagnosis of marijuana users that present with AKI, particularly in light of its increasing legalization.

FR-PO029

Azithromycin-Induced Severe Acute Interstitial Nephritis: Role of Corticosteroids Nupur N. Uppal, Nishita Parikh, Hitesh H. Shah. *Hofstra Northwell School of Medicine, Great Neck, NY.*

Background: Acute interstitial nephritis (AIN) is characterized by deterioration of renal function with inflammatory infiltration of the renal interstitium. B-lactam antibiotics, NSAIDs and proton pump inhibitors have been recognized as the leading causes of drug induced AIN, however any drug can potentially cause AIN. We present a very rare case of AIN following treatment with oral azithromycin that was successfully treated with use of corticosteroids.

Methods: 73-year-old Caucasian female with history of hyperlipidemia was sent to the hospital for evaluation of elevated serum creatinine (Scr) of 6.8 mg/dL. Patient had a normal Scr of 0.7 mg/dL, 6 months prior to this presentation. Patient was asymptomatic at the time of presentation. Patient however completed a course of oral azithromycin therapy (first time use) for upper respiratory tract infection, 5 weeks prior to her presentation. Her only home medication was rosuvastatin. Her BP was elevated at 160/75 and physical examination was unremarkable. Renal ultrasound ruled out obstructive uropathy, however showed bilateral enlarged kidneys. Urinalysis showed trace blood and 5-10 white blood cells. Spot urine total protein to creatinine ratio was elevated at 1.1. Serological work up for proteinuria was negative. Scr peaked to 7.6 mg/dL, however patient remained non-oliguric and did not require hemodialysis. A kidney biopsy was subsequently performed which revealed findings of AIN that was thought to be secondary to previous azithromycin use. Patient received intravenous pulse dose corticosteroid therapy for 3 days, followed by transition to oral prednisone taper over the following 8 weeks. AKI resolved and Scr decreased to 1.1 mg/dL, a week after completion of prednisone therapy.

Results:

Conclusions: Azithromycin is a readily available and widely used macrolide antibiotic all over the world. This drug is considered generally well tolerated. To our knowledge, only four cases of kidney biopsy proven AIN associated with azithromycin use have been reported in the literature. Although rare, physicians should be aware of this potential serious nephrotoxic effect of this agent. Our patient responded well to a prolonged course of oral corticosteroid therapy with significant improvement in renal function.

FR-PO030

Tubulointerstitial Nephritis with Uveitis Syndrome: A Case Report of a Rare Syndrome Adam W. Scott,[1,3] Matthew M. Hand,[2] Lisa Teot,[1] Deborah R. Stein.[1] *[1]Boston Children's Hospital, Boston, MA; [2]Elliot Hospital, Manchester, NH; [3]Nephrology, Brigham & Women's/Harvard Medical School, Boston, MA.*

Background: Tubulointerstitial nephritis with uveitis (TINU) syndrome is a rare disorder characterized by acute interstitial nephritis (AIN) along with concurrent development of uveitis. First described in 1975, there have been few case reports in both the ophthalmology and nephrology literature since. The underlying pathogenesis and etiology remains poorly understood. We present a case of a young adolescent male with an antecedent Epstein-Barr virus (EBV) infection who presented with severe AIN who later developed uveitis. This case highlights the importance of considering TINU in the evaluation of patients with AIN, and provides a framework for the evaluation and follow-up of such patients.

Methods: A 13 year old previously healthy Caucasian male, diagnosed with EBV via positive heterophile antibody test 2 months prior, presented to the hospital with severe fatigue and unintentional weight loss. His examination revealed a non-toxic, pale-appearing young man with a normal blood pressure. Ophthalmologic examination was unremarkable on presentation. Initial evaluation revealed severe acute kidney injury, with a peak serum creatinine of 6.8 mg/dL. His urine sediment was significantly active, with abundant white blood cell casts. He had evidence of proximal tubular dysfunction with low-molecular weight proteinuria, renal glycosuria, and renal tubular acidosis. A renal biopsy demonstrated typical findings of AIN, with only minimal fibrosis, no vascular changes, and unremarkable immunofluorescence and electron microscopy. He was started on pulse-dose steroids, followed by oral steroids. After a prolonged steroid taper over about 3 months, his creatinine improved to a nadir of 1.0 mg/dL. Shortly after discontinuing steroids, he developed bilateral eye pain and conjunctivitis. Repeat ophthalmology evaluation revealed active uveitis. The patient was placed on topical steroid therapy, with little response, and then started back on oral steroids. His renal function remained acceptable, and his urinalysis quiescent.

Results:

Conclusions: This case highlights the importance of considering TINU in patients with AIN, and the need for ongoing monitoring for the development of uveitis following resolution of AIN, as uveitis may occur sequentially and remotely from the initial presentation. The case also implicates antecedent EBV infection as a possible etiology for TINU.

FR-PO031

Sarcoidosis Associated AKI: The Path Less Traveled Haris F. Murad, Valerie Jorge Cabrera, Mamta Shah. *Yale School of Medicine, New Haven, CT.*

Background: Mechanisms of kidney injury in sarcoidosis include interstitial nephritis with or without granuloma formation and/or abnormal calcium metabolism with nephrolithiasis and nephrocalcinosis. Calcium phosphate deposition on biopsy is uncommon and prior case reports have speculated its association with the more common calcium oxalate crystals, representing an underreported finding in sarcoid related kidney injury.

Methods: A 43 year-old Caucasian man presented with worsening wrist pain and swelling following a traumatic injury. He had noticed recent fatigue and weight loss. Further questioning revealed excessive milk and calcium carbonate intake. His examination was remarkable for a palpable tender mass on his right wrist. He was noted to have an elevated serum creatinine of 4.3mg/dL and serum calcium of 14mg/dL. Other investigations included parathyroid hormone of 9.3 pg/mL, ionized calcium of 6.02 mg/dL and 1,25-OH vitamin D (vit D) level of 112 pg/mL. Imaging of the wrist was suspicious for secondary tumoral calcinosis and computed tomography (CT) of the chest showed ground glass opacities and hilar lymphadenopathy. Ultrasound demonstrated bilateral non obstructing renal calculi. Kidney biopsy revealed non necrotizing granulomas and calcium phosphate crystals with surrounding giant cell formation. The diagnosis of sarcoidosis was established. In addition to management of hypercalcemia, he was started on oral prednisone. Serum creatinine improved to 2.2mg/dL along with normalization of 1,25-OH vitamin D and serum calcium in the following weeks.

Results:

Conclusions: Although the most common pathological lesion in renal sarcoidosis is non caseating granuloma formation, nephrocalcinosis with calcium oxalate deposition may be seen. Calcium phosphate deposition with surrounding giant cell formation is less common and has been pathologically associated with kidney injury in sarcoid. Although our patient had granulomas, the proximity of the giant cell formation to the calcium phosphate crystals suggests a localized reaction and may potentially be a significant

contributor to kidney injury. This case highlights the importance of renal biopsy in patients with sarcoidosis. Findings are important to help clarify the pathology, prognosis and guide treatment.

FR-PO032

Recurrent Acute Interstitial Nephritis Secondary to Crohn's Disease Dina Abdelwahab, Mira T. Keddis. *Mayo Clinic, Scottsdale, AZ.*

Background: Immune mediated tubulointerstitial nephritis secondary to Crohn's disease is uncommon. We report a case of recurrent episodes of acute kidney injury (AKI) due to acute interstitial nephritis (AIN) coinciding with Crohn's flare-up in an otherwise healthy man

Methods: A 37 year old male with 7 year history of Crohn's disease was found to have an increased creatinine to 1.7 mg/dL from a normal baseline of 1.3 mg/dL. He was treated with mesalamine for 18 months prior to the increase in creatinine. Kidney biopsy showed acute eosinophilic interstitial nephritis suspicious for mesalamine associated AIN. Mesalamine was discontinued and he was treated with a 6 months course of tapering dose of prednisone. His creatinine peaked as high as 2.2 mg/dl and ranged between 1.7-1.9 mg/dl during treatment. 4 months after discontinuation of prednisone, he developed a flare up of his Crohn's disease with diarrhea and hematochezia. Laboratory results showed an increase in creatinine to 2.4 mg/dl in absence of any medications. Urinalysis was performed and showed 1-3 white blood cells. Repeat kidney biopsy was performed and showed acute on chronic tubulointerstitial nephritis with eosinophils with moderate background fibrosis and tubular atrophy. The findings of acute on chronic interstitial nephritis in the context of active Crohn's flare and absence of nephrotoxic medications confirmed suspicion for Crohn's associated AIN. He was treated with prednisone for 8 weeks and started on adalimumab for treatment of his Crohn's disease.

Results:

Conclusions: This case highlights the uncommon presentation of AIN as a primary extra-intestinal complication of Crohn's disease. We hypothesize that treatment of Crohn's disease will improve renal outcome.

FR-PO033

Vancomycin: New Player in the World of Cast Nephropathy Srikanth Thiruvarudsothy,[3] Samantha Pettigrew,[4] Ryan Butzko,[3] Mary elizabeth Swift-Taylor,[7] Neeraj Sharma,[6] Aravindan V. Jeyarajasingam,[1] Sushma Munugoti,[5] Anuradha Konkesa,[2] Jennine Michaud,[1] Michelle Dallapiazza,[3] Alluru S. Reddi,[4] Surya V. Seshan.[8] *[1]None, Swedesboro, NJ; [2]Rutgers, Morrisplains, NJ; [3]Rutgers NJMS, Belleville, NJ; [4]Rutgers New Jersey Medical School, Kearny, NJ; [5]Rutgers UNIVERSITY, Montclair, NJ; [6]Rutgers University, Bloomfield, NJ; [7]Rutgers-NJMS, Newark, NJ; [8]Weill Cornell Medical Center, New York, NY.*

Background: Vancomycin associated cast nephropathy (VACN) is a rare entity that has only recently been described in literature, is an additional mechanism by which vancomycin can induce renal injury.

Methods: A 20-year-old African American man, presented with bilateral pneumonia complicated by a large loculated pleural effusion. He was treated with vancomycin, piperacillin-tazobactam, azithromycin and oseltamivir. Urinalysis showed an isolated proteinuria. His renal function worsened with an increase in creatinine from 0.9 mg/dL to 3.2 mg/dL with oliguria. Vancomycin trough at that time was 43.3 mg/L. Creatinine peaked at 10.6 mg/dL despite adequate hydration. Work-up for acute kidney injury was unrevealing. He was started on hemodialysis, and subsequently underwent a renal biopsy. The biopsy showed diffuse acute tubular injury with focal eosinophilic tubular casts containing tubular protein and nanospheric vancomycin, consistent with VACN. Patient required three sessions of hemodialysis with recovery of renal function. At a 4- month follow-up, his creatinine was 0.7 mg/dL.

Results:

Conclusions: Vancomycin is known to cause acute kidney injury due to acute tubular injury (ATI) and acute interstitial nephritis (AIN). VACN was first described by Luque et al. in Feb. 2017. They reported a patient with severe acute tubular necrosis on renal biopsy that also had proteinaceous casts with nano-to-microspherical formations that corresponded with vancomycin spectral signature. They also retrospectively reviewed biopsies on patients who had vancomycin toxicity and found similar casts. Vancomycin nanospheres are incorporated into Tamm–Horsfall protein and then cause tubular obstruction. Presence of vancomycin in the casts was confirmed by infrared spectroscopy and immunohistochemistry. Our report confirms the findings of Luque and associates, and suggests that VACN is another mechanism for vancomycin-induced nephrotoxicity.

FR-PO034

Acute Oxalate Nephropathy from Vegetable Juicing and Lower Dose Vitamin C Supplementation Youngjun Park, Daniil Shimonov, Shayan Shirazian, James Drakakis, Nobuyuki (Bill) Miyawaki. *NYU Winthrop Hospital, Mineola, NY.*

Background: High dose intravenous and oral ascorbic acid are associated with acute kidney injury (AKI) with oxalate nephropathy. We report a case of oxalate nephropathy at a lower than often described doses in combination with high oxalate juicing.

Methods: A 47-year-old male with newly diagnosed Diffuse Large B Cell Lymphoma with consistently normal creatinine of 0.8mg/dL had deferred chemotherapy and instead started kale, spinach and berry juicing with daily apricot kernels plus 2 grams/day of Vitamin C supplement. This continued for 2 months, at which point his creatinine was noted to be 5.3mg/dL on routine labs prompting an admission. Additional labs indicated calcium level of 13.3mg/dL, Vitamin D-25-OH of 75ng/mL, serum bicarbonate level of 32mEq/L and K of 3.9mEq/L. Phosphate and uric acid level from that admission is unfortunately not available. AKI with microscopic hematuria and 1-2+ proteinuria led to a kidney biopsy which revealed acute tubular injury with dilated lumina, cytoplasmic vacuolization and abundant intratubular calcium oxalate crystals. Scattered large calcium phosphate crystals were also seen. Additional workup did not reveal hydronephrosis. Without recovery, he was initiated on hemodialysis.

Results:

Conclusions: Even in the absence of known primary hyperoxaluria, AKI from oxalate nephropathy is associated with varying Vitamin C doses. Typical descriptions of oxalate nephropathy from IV ascorbic acid have referenced doses of 45 grams to as much as 224 grams per day. Oral ingestions of more than 4 grams/day consecutively over 30 days have been implicated in AKI yet high oral doses of 10 grams/day also have been documented to not induce AKI in others. This patient sustained AKI with far less Vitamin C intake than typically-described toxic doses, but the combined impact of high oxalate foods (spinach, kale, berries, kernels) along with 2 grams of daily oral Vitamin C and hypercalcemia possibly from lymphoma contributed to oxalate nephropathy. While the patient denies knowingly using significant calcium carbonate, high dose Vitamin D or other associated agents to induce milk-alkali syndrome, rather ample Vitamin D level, metabolic alkalosis and high calcium suggest its contribution to the calcium phosphate crystals noted on the biopsy as well. Extra caution may be needed on diet and modest dose supplements.

FR-PO035

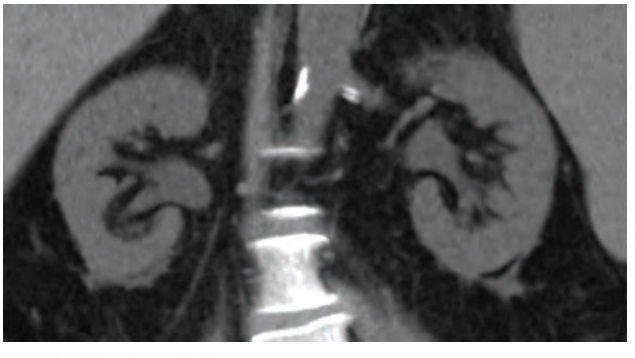
An Uncommon Presentation of Acute Uric Acid Nephropathy Anna J. Lee-Mulay,[1] Gauri Bhutani.[2] *[1]University of Wiconsin, Madison, WI; [2]University of Wisconsin, Madison, WI.*

Background: Secondary hyperuricemia from ineffective erythropoiesis can be seen in myeloproliferative disorders. Uric acid (UA) crystal precipitation may cause acute tubular injury and urinary obstruction in this rare disease group but is not commonly described in myelofibrosis (MF).

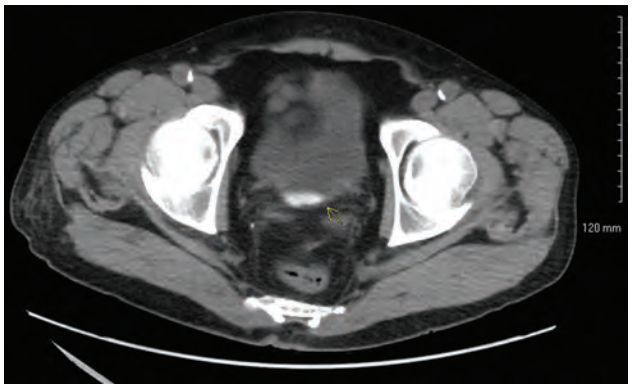
Methods: A 68-year-old male with essential thrombocythemia & secondary MF diagnosed 6 years ago, who has been on ruxolitinib for 2 years with a dose increase within the last 3 months, presented with a few hours of nausea and vomiting following a fall 1 day prior. Serum creatinine (S.Cr) was 2.71 mg/dL (baseline 1.1 mg/dL). A CT abdomen pelvis showed gravel layers within bladder & distal ureters with resultant bilateral hydroureter & pelviectesis. Serum UA was 19.4 mg/dL. Cystoscopy showed stone debris (100% UA) & bilateral ureteral stents were placed. S.Cr increased to 4.5 mg/dL over next 2 days with UA still >15 mg/dL despite intravenous hydration, urinary alkalinization & initiation of allopurinol. Rasburicase (2 doses of 3 mg IV) was started next with prompt renal recovery & normalization of UA levels. Now, 6 months later, S.Cr is 1.06 mg/dL, UA 7.1 mg/dL, on allopurinol 300 mg daily.

Results:

Conclusions: Acute UA nephropathy is only rarely described in MF, especially in secondary MF. Hyperuricemia has not been described with use of JAK2 inhibitor ruxolitinib, although it is not clear if & how much this medication contributed to the above presentation. Our case highlights that UA related renal diseases should be an important consideration in all myeloproliferative disorders. Timely intervention with rapid uric acid lowering is needed for renal recovery.



UA gravel within urinary bladder



bilateral hydronephrosis from UA debris in urinary collecting system

FR-PO036

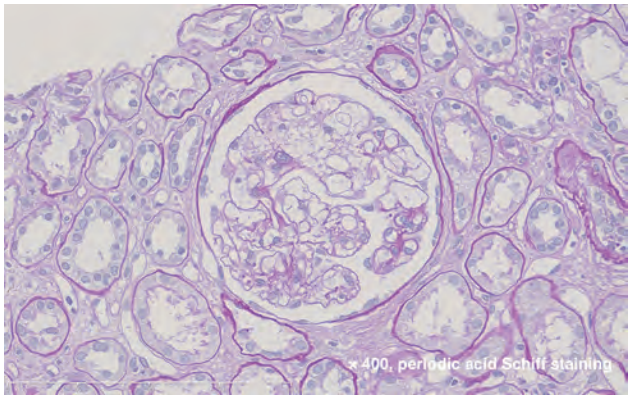
A Case of Radiation Nephropathy Presented with Delayed Massive Proteinuria and Renal Dysfunction Following Hematopoietic Stem Cell Transplantation Norisuke Shimamura,[1] Yosuke Nakagawa,[1] Chiaki Kawabata,[1] Naoto Hamano,[1] Masahiro Koizumi,[1] Go Ogura,[2] Takehiko Wada,[1] Masafumi Fukagawa.[1] *[1]Division of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, Isehara, Japan; [2]Department of Pathology, Tokai University School of Medicine, Isehara, Japan.*

Background: Hematopoietic stem cell transplantation (HSCT)-associated nephropathy can progress to end stage renal disease and can also increase mortality risk. Its etiologies are often multifactorial, including medication such as calcineurin inhibitors and antineoplastic agents including molecular targeted drugs, transplantation-associated thrombotic microangiopathy, graft-versus-host disease (GVHD), and radiation. Because therapeutic approaches vary depending on the diagnoses, renal biopsy should be considered to determine the cause. Here, we report a case of radiation nephropathy with delayed massive proteinuria and renal dysfunction following HSCT.

Methods: A 33-year-old Japanese woman had been diagnosed with Philadelphia chromosome-positive acute lymphoblastic leukemia two years prior to this episode. Complete remission was achieved by cytarabine and daunorubicin followed by dasatinib, a tyrosine kinase inhibitor. She underwent allogeneic HSCT from matched unrelated donor. She had received total body irradiation and intravenous cyclophosphamide as myeloablative conditioning and methotrexate plus tacrolimus as acute GVHD prophylaxis. At one month after HSCT her serum creatinine level (sCr) was 0.9 mg/dL and her urinalysis was normal. However, her sCr elevated to 1.2 mg/dL and proteinuria developed at 4 months after HSCT. SCr did not decrease even after tacrolimus was discontinued, and proteinuria gradually got worse to 2-3 g/gCr. Renal biopsy at 15 months after HSCT demonstrated prominent mesangiolysis with formation of capillary mircroaneurysms. Under the diagnosis of radiation nephropathy, an angiotensin receptor blocker was started to mitigate proteinuria.

Results:

Conclusions: Radiation nephropathy often develops with a latent period of 6-12 months after radiation exposure. We should take radiation nephropathy into account if renal dysfunction and proteinuria exacerbate in a late phase.



FR-PO037

Focal and Segmental Glomerulosclerosis (FSGS) in Association with Carfilzomib Therapy Roshni Radhakrishna,[2] Volker Nickeleit,[1] Gerald A. Hladik.[3] *[1]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]University of North Carolina, Carrboro, NC; [3]University of North Carolina at Chapel Hill Kidney Center, Chapel Hill, NC.*

Background: Carfilzomib is a proteasome inhibitor widely used for treatment of multiple myeloma and monoclonal gammopathies of renal significance (MGRS). Herein, we report a case of new onset FSGS in association with carfilzomib therapy.

Methods: A 63-year-old man with stage G3b chronic kidney disease secondary to biopsy proven monoclonal immunoglobulin deposition disease (MIDD) secondary to monoclonal kappa light chains developed nephrotic range proteinuria during therapy with carfilzomib and dexamethasone. He was initially diagnosed with biopsy-proven MIDD 10 years ago. He was treated with bortezomib and dexamethasone followed by melphalan/prednisone with achievement of a sustained remission over the next 10 years. Over that interval, his proteinuria ranged between 200 to 400 mg/d, decreased from 800 mg/d prior to therapy. His serum free light chain-kappa (SFLC-kappa) level was subsequently found to rise from 7 to 110 mg/dl, prompting therapy with 2 cycles of carfilzomib and dexamethasone. He had an excellent clinical response with a decline in the SFLC-kappa level to 29 mg/dl. Despite this response, he developed increased leg edema with a rise in proteinuria from 400 mg/d to 3700 mg/d (72% albumin). Urine immunoelectrophoresis showed no monoclonal spike. His serum creatinine level increased from 2 to 2.4 mg/dl. He did not have evidence of infection. A kidney biopsy showed focal and segmental glomerulosclerosis with collapsing features without evidence of light chain deposition disease. His proteinuria fell to 1.7 g/d over the next 5 months.

Results:

Conclusions: Proteasome inhibitors have had proven efficacy in relapsed/refractory multiple myeloma and MGRS. Carfilzomib is a second generation proteasome inhibitor that previously has been reported to cause thrombotic microangiopathy. The temporal onset of this lesion coincident with carfilzomib therapy raises the possibility of carfilzomib-induced FSGS. Worsening proteinuria despite improvement in SFLCs during carfilzomib therapy should raise suspicion for this lesion. This is the first reported case of carfilzomib-associated FSGS and highlights the importance of ongoing surveillance for renal toxicity of novel therapeutic agents

FR-PO038

Dysregulated Neutrophil Extracellular Traps in a Patient with Propylthiouracil-Induced Microscopic Polyangiitis Kanako Watanabe, Daigo Nakazawa, Saori Nishio, Tatsuya Atsumi. *Internal Medicine II, Hokkaido University Hospital, Sapporo, Japan.*

Background: Neutrophil extracellular traps (NETs) are one of the immune defense system, which spread out DNA fibers with histons and myeloperoxidase (MPO) after phagocytosis in order to trap and kill microbes effectively. However, when NETs are not properly regulated, they could possibly become autoantigens, which result in the production of myeloperoxidase-anti-neutrophil cytoplasmic antibodies (MPO-ANCA), developing Microscopic polyangiitis (MPA). Propylthiouracil (PTU) is an antithyroid drug, clinically known to produce MPO-ANCA and develop MPA. A recent study showed that in vitro experiment neutrophils with PTU were induced to morphologically-abnormal NETs, which were hardly degraded by DNaseI. In Rat model, dysregulated NETs led to the production of MPO-ANCA, causing pulmonary capillaritis and glomerulonephritis. In this report, we examined whether neutrophils of a patient with PTU-induced MPA show the similar characterization during NETs formation.

Methods: A 19-year-old woman who had been treated with PTU for Graves' disease showed the presence of high fever and arthritis. Increased levels of proteinuria, hematuria, and C-reactive protein were found. In immunological examination, MPO-ANCAs were detected. Computed tomography revealed pulmonary infiltrates. Based on these findings, the patient was diagnosed with PTU-induced MPA. For evaluating NETs formation, we analyzed neutrophils of this patient. The fluorescence microscopy revealed NETs formation in unstimulated neutrophils of the patient, which was more massive in phorbol myristate acetate-stimulated neutrophils. Furthermore, they were not degraded by DNaseI, which can degrade the NET-DNA. On the other hand, the healthy NETs were degraded by DNaseI.

Results:

Conclusions: This is the first case report showing that abnormal and dysregulated NETs persisted in a PTU-induced MPA patient. These results indicate that dysregulated NETs can lead to the breakdown of immunological tolerance for NETs components and result in the production of autoantibody for NETs, developing autoimmune vasculitis.

FR-PO039

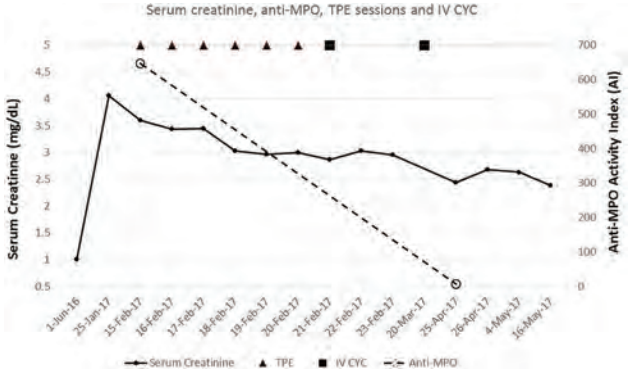
A Case of Life-Threatening Pulmonary-Renal Syndrome from Hydralazine Ranadheer Dande,[1] Pravir V. Baxi,[1] Sejal K. Kalawadia,[2] Casey N. Gashti.[1] *[1]Rush University Medical Center, Chicago, IL; [2]NANI (Nephrology Associates of Northern Illinois), Blue Island, IL.*

Background: Drug-induced lupus (DIL) from hydralazine is well described but renal involvement is uncommon. Hydralazine induced vasculitis presenting with pulmonary-renal syndrome is exceedingly rare, despite the widespread use of the drug. We describe an unusual case of hydralazine-induced, ANCA+, immune complex (IC) mediated GN with pulmonary involvement that exhibits features of both DIL and vasculitis.

Methods: A 60 yo male p/w dyspnea and fatigue. He was noted to have a HgB of 5.7 g/dl, b/l pulmonary opacities on CXR, AKI and microhematuria. His meds included hydralazine. Exam was significant for respiratory distress. His SCr was 4.06 mg/dL from a nl prior bsl. UA showed 2+ protein and 3+ blood. His ANA was 1:160, p-ANCA was 1:640, anti-MPO Ab of 647 AI (>1 pos), neg anti-PR3, and nl C3+C4. Renal biopsy showed crescentic GN on LM. There was a full house pattern of IC deposition in the subendothelial and mesangial space on IF. Bronchoscopy was c/w diffuse alveolar hemorrhage (DAH). His hydralazine was discontinued. He was started on IV steroids, IV cyclophosphamide (CYC) and daily membrane based therapeutic plasma exchange (TPE). After 3 days, his respiratory status improved. On 2 month follow up, anti-MPO was 6.7 AI and SCr was 2.4 mg/dL (Graph 1). CXR showed resolution of opacities.

Results:

Conclusions: Drug induced syndromes can often be overlooked as features mimic idiopathic disease. A positive p-ANCA with exceedingly high anti-MPO titers are highly suggestive of a drug-induced vasculitis. We postulate that our pt's severe clinical manifestations are a result of hydralazine-induced ANCA vasculitis. The presence of subendothelial IC desposits on the renal biopsy also suggest coexisting DIL from hydralazine, leading to an unusual overlap syndrome. Prompt cessation of the drug is the initial step in management. In cases with severe clinical symptoms, treatment is identical to idiopathic disease with immunosuppressive therapy. Pts who present with DAH require immediate initiation of TPE due to their high risk of mortality.



Graph 1

FR-PO040

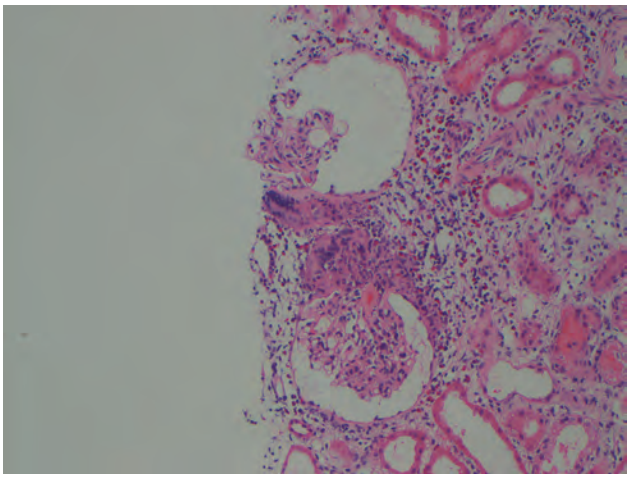
Alemtuzumab Induced Anti-Glomerular Basement Membrane Disease with Histological Evidence of Perihilar Giant Cell Vasculitis Ryan P. Gately,[4] Aye San,[2] Tegan Stevenson,[1] Sonu Nigam,[3] Jagadeesh Kurtkoti,[2] Dakshinamurthy Divi.[2] *[1]Gold Coast Hospital, Ashmore, NSW, Australia; [2]Gold Coast University Hospital, Southport, QLD, Australia; [3]Pathology Queensland, Gold Coast, QLD, NSW, Australia; [4]Nephrology, Gold Coast University Hospital, City of Gold Coast, QLD, Australia.*

Background: To our knowledge there have been three published cases of alemtuzumab induced anti-glomerular basement membrane(GBM) disease to date. Here we report a case of fulminant anti-GBM disease that was exceptional given its unusual histological features

Methods: A 34 year-old Caucasian female presented with a one-week history of malaise and painless, frank hematuria. She had a background of relapsing-remitting multiple sclerosis(RRMS) previously treated with two courses of alemtuzumab(anti-CD52 monoclonal antibody) the most recent course completed six months prior. On admission creatinine was 2.26mg/dL and imaging did not reveal any nephrolithiasis or masses. Renal biopsy showed granulomatous vasculitis in a perihilar distribution with evidence of arteriolitis and glomerulitis with giant cells(figure 1). Immunofluorescence confirmed linear IGG staining along the GBM.ANCA titers were negative however anti-GBM antibodies were markedly elevated at 855 CU(<20). Plasma exchange, methylprednisolone and cyclophosphamide failed to prevent worsening of the patient's renal function and six days after admission haemodialysis was initiated. Cyclophosphamide was ceased due to intolerable side effects however two days subsequent to this the patient developed severe hemoptysis. Chest X-ray was suggestive of pulmonary hemorrhage. Daily plasma exchange and pulse methylprednisone were reinitiated resulting in attenuation of haemoptysis without improvement in renal function. The patient remains dialysis dependent with slowly falling antibody titers and it is hoped that she will ultimately be eligible for renal transplantation

Results:

Conclusions: Anti-GBM disease is an extremely rare but catastrophic complication of alemtuzumab therapy. With increasing use of alemtuzumab in RRMS we believe it is imperative to consider this condition in those exposed to this medication with worsening renal function or hematuria



FR-PO041

Nintedanib-Induced Nephrotic Syndrome: First Case Report Reio Sekine,[6] Masataka Hasegawa,[5] Tomo Suzuki,[5] Masahiko Yazawa,[1] Daisuke Ichikawa,[3] Junki Koike,[4] Yugo Shibagaki.[2] *[1]Division of Nephrology and Hypertension, Department of Internal Medicine, St.Marianna University School of Medicine, Kawasaki, Japan; [2]Division of Nephrology and Hypertension, St Marianna University Hospital, Kawasaki, Japan; [3]St Marianna University of Medical School, Yokohama City, Japan; [4]St.Marianna University, Kawasaki, Kanagawa, Japan; [5]St.Marianna university school of medicine, Tokyo, Japan; [6]St.Marianna university school of medicine, Kawasaki, Kanagawa, Japan.*

Background: Nintedanib, a triple kinase inhibitor of platelet derived growth factor receptor, fibroblast growth factor receptor and vascular endothelial growth factor receptor (VEGF), has been used in non-small cell lung cancer and idiopathic pulmonary fibrosis offering substantial benefit. We report a very rare case of nephrotic syndrome caused by nintedanib.

Methods: A 68-year old man after partial lung resection for cancer was treated with nintedanib as the adjuvant therapy. At the initiation of nintedanib, his serum creatinine was 0.78 mg/dl and neither hematuria nor proteinuria was evident before. One week after the initiation of nintedanib, his dipstick urine showed 2+ proteinuria. Since proteinuria had persisted afterwards, he was referred to us for evaluation of heavy proteinuria in January 2017 (8 months after nintedanib initiation). On physical examination, he had developed lower extremity edema. Urinalysis showed proteinuria of 4 g/day with mild glomerular hematuria with cast. Though his serum creatinine was normal, he was diagnosed nephrotic syndrome for concomitant hypoalbuminemia. Renal biopsy at 10 months after the onset of proteinuria showed mild mesangial proliferation and widely expanded subendothelial area occupied by hyaline-like materials with some huge subendothelial deposition. Mesangiolysis and double contour were also observed focally in some glomeruli. Immunofluorescence (IF) staining showed only moderate IgM deposition in huge subendothelial depositions without any other positive staining. Electron microscopy showed electron dense deposits in subendothelial areas and mesangial areas. Foot process effacement was not noticeable. Histologic diagnosis was intracapillary deposition disease with severe endothelial injury. After renal biopsy, nintedanib was withdrawn and the patient underwent follow-up with unremarkable therapy. Proteinuria and hematuria very gradually but substantially decreased to 1.0 gram/gram creatinine.

Results:

Conclusions: To our knowledge, this is the first case report of nephrotic syndrome highly suspected to be due to nintedanib. Recently Anti-VEGF antibody therapy was often used for the various kinds of cancer. Paramesangial and subendothelial deposits caused by Anti-VEGF antibody therapy was reported and histology of our case was very similar.

FR-PO042

Can a Patient with Membranoproliferative Glomerulonephritis (MPGN) Following Anabolic Testosterone and Supplement Abuse Benefit from Glucocorticoid Treatment? Olumide O. Rowaiye,[1] Piotr Donizy,[2] Mariusz Kusztal,[1] Jozef Penar,[1] Agnieszka Halon,[2] Magdalena Krajewska,[1] Marian Klinger.[1] *[1]Nephrology and Transplantation Medicine, Wroclaw Medical University, Wroclaw, Poland; [2]Pathomorphology, Wroclaw Medical University, Wroclaw, Poland.*

Background: The use of anabolic androgenic steroids (AAS) have been associated with a number of adverse effects; however, the occurrence of MPGN is uncommon. We describe a rare case of MPGN following anabolic testosterone and supplement abuse.

Methods: a 22-yr-old man with no significant past medical history presents with high serum creatinine (3.62 mg/dl), edema and gross hematuria. He admits that 8 months prior to presentation, he started a regimen of regular intensive physical workouts and OTC supplements (7 kg/month of a product containing 60.7 g of protein and 177.8 g of complex carbs). He used i.m. injections of testosterone enanthate (250 mg every 5 days

for 3 months). Last testosterone dose was 3 months prior to presentation. On examination, he was found to have BP 150/80 mmHg and lower extremity edema. Urinalysis revealed 2+ blood, active urinary sediments. Urine protein excretion was 4.6 g/day while serum albumin was 2.8 g/dl. Serological studies were negative for ANA, anti-dsDNA, ANCA, anti-GBM, HBV, HCV and HIV. CRP was normal. Serum C3 factor was low (0.17 g/l) while C4 was normal. Ultrasound showed enlarged kidneys: right -12.9 cm, left - 13.1 cm. Renal biopsy was performed which revealed active MPGN with segmental fibrinoid necrosis in 5 glomeruli but no crescents (fig 1). Also moderate tubulo-interstitial nephritis (TIN I/II°) (fig 2) was seen. Immunohistochemistry showed moderately intense mesangial IgG deposits in most glomeruli with a few mesangial IgM deposits; C3 was negative. Patient was treated with i.v. pulse methylprednisolone and i.v. diuretics which resulted in serum creatinine level of 1.77 mg/dl and disappearance of the edema. On follow-up visit 4 weeks later, serum creatinine was 1.38 mg/dl and patient continued to further improve.

Results:

Conclusions: Patients with MPGN following AAS and supplement abuse, with features of rapidly progressive glomerulonephritis may benefit from glucocorticoid treatment.

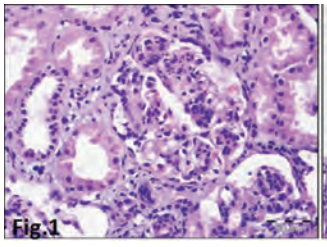


Fig.1

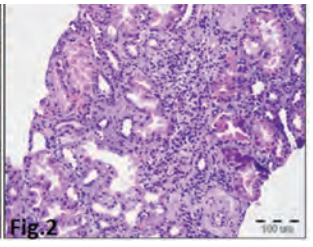


Fig.2

FR-PO043

Nephrotic Syndrome in Dasatinib-Treated Patients with Chronic Myeloid Leukemia Takeo Koshida, Hitoshi Suzuki, Masao Kihara, Chieko Nogi, Yusuke Suzuki. *Nephrology, Juntendo University Faculty of Medicine, Tokyo, Japan.*

Background: Chronic myeloid leukemia (CML) is now a manageable disease with the tyrosine kinase inhibitors (TKI). Dasatinib, a second-generation of TKI, has proven to be effective for the long-term treatment of CML, both as initial and subsequent lines of therapy. Off-target effects of these medications can have beneficial or adverse effects on the kidney. We present a case of CML who developed nephrotic-range proteinuria after initiation on Dasatinib therapy that resolved after changing therapy to Imatinib.

Methods: A 70-year-old woman was detected leukocytosis at a medical check-up, and diagnosed with CML by bone marrow examination. Treatment with Dasatinib was initiated and was effective for CML resulted in clinical remission. After one year from the initiation of medication with Dasatinib, proteinuria was detected. Finally, she was consulted to the nephrologist and had a thorough examination. Nephrotic-range proteinuria (5.2 g/gCr) and hypoalbuminemia (2.6 g/dL) was detected and then kidney biopsy was performed. Pathological findings of kidney biopsy specimen showed edematous thickening of basement membrane, duplicated glomerular capillary wall and reticuloendothelial cells. Those pathological findings are compatible as the kidney injuries induced by Dasatinib. After switchover from Dasatinib to Imatinib, levels of proteinuria significantly decreased.

Results:

Conclusions: We present a case of nephrotic syndrome during the course of medication with Dasatinib for CML. Pathological findings indicated thrombotic microangiopathy with endothelial cell injuries and the proteinuria resolved after changing therapy from Dasatinib to Imatinib. Therefore, it is suggested that those kidney injuries was caused by Dasatinib. We should concern that off-target effects of Dasatinib can have adverse effects on the kidney.

FR-PO044

Successful Treatment of Hashimoto Encephalopathy with Therapeutic Plasma Exchange Hassan B. Attique, Arundati Rao, Lalarukh Haider, Ruchir D. Trivedi. *University of CT Health Center, West Hartford, CT.*

Background: Hashimoto's encephalopathy (HE) is a rare neuropsychiatric syndrome characterized by encephalopathy of unknown etiology associated with the high titers of antithyroid antibodies in the absence of alternative diagnoses. HE with robust clinical response to therapeutic plasma exchange (TPE) in the setting of end stage renal disease (ESRD) has not been published. We present steroid-resistant HE with reliable reduction in antithyroid peroxidase antibodies (anti-TPO), after 5 sessions of TPE along with linear improvement in clinical status.

Methods: 72 year old lady with ESRD on maintenance hemodialysis (HD) presented with altered mental status. Investigations including CT scan did not suggest central nervous system (CNS) infection, tumor or stroke. There were no signs of uremia or underdialysis as well. Further investigations revealed status epilepticus controlled with propofol infusion apart from maximal dose of three anti-epileptic agents. As part of resistant status epilepticus work up, free thyroxine was 0.52 ng/dl, thyroglobulin antibody level of 2299 IU/ml and anti-TPO antibody level was 4886 IU/ml. Her cerebrospinal fluid (CSF) anti-TPO antibody was 36.4 IU/ml and CSF protein of 50 mg/dl. This led to diagnosis of HE and treatment with pulse dose IV Methylprednisone 500mg every day was initiated for five days. She remained clinically refractory for which 1.5 plasma volume TPE was initiated using 5% albumin as replacement fluid on alternate days in an attempt to remove detectable antibodies and provide immunomodulation. She continued to receive daily HD to optimize fluid electrolyte status during entire course. Clinical condition improved with reduction in anti-TPO antibody. She was continued on maintenance steroids and rituximab.

Results:

Conclusions: HE is presumably autoimmune in origin. Proposed etiology includes autoimmune reaction between antibodies and cerebral vascular and brain cells and perivascular lymphocytic inflammation. Available literature is unclear about pathogenic role of antithyroid antibodies. Our case did not improve with steroid but showed remarkable clinical improvement with TPE. This suggests possible immunomodulatory role of TPE in select case of acute HE. Our case is in line with considerable variance that exists in ESRD and non-ESRD population. ESRD may represent a distinct subgroup in which HE may respond favourably to TPE.

FR-PO045

Denosumab: Is It Safe to Use in CKD? Eimear Mckenna,[1] Girish H. Shivashankar,[3,1] Francis Mccarroll.[2] *[1]Altnagelvin Area Hospital, Coleraine, United Kingdom; [2]Western Health and Social Care Trust, Derry, United Kingdom; [3]Western Health and social care Trust, Londonderry, United Kingdom.*

Background: Denosumab is a monoclonal antibody directed against receptor activator of RANK ligand used to treat osteoporosis. It has been promoted as safe to use in Chronic Kidney Disease (CKD) as it does not appear to accumulate in kidney failure and because of the experience in a small number of patients with CKD stages 3 and 4 in RCTs. There is no evidence for use in CKD stage 5. Published case reports suggest patients with severe CKD are at higher risk of developing hypocalcemia following Denosumab which may be due to hyperparathyroidism and vitamin D deficiency. In this case series we have examined the incidence of hypocalcemia following Denosumab to identify risk factors for hypocalcemia.

Methods: Retrospective data was collected using an electronic patient database on patients with CKD stages 3-5 attending our service who received Denosumab in the last 5 years. We examined Corrected calcium levels prior to and after each dose, Vitamin D and Parathormone (PTH) levels prior to each dose.

Results: 14 patients were identified; 9 had a functioning renal transplant and 1 patient was on hemodialysis. 4 patients were male and 10 female. Mean duration of treatment was 2.2 years. Average eGFR was 27 ml/min/1.73m2. Mean patient age was 60 years. Mean BMI was 25. 11 patients were on oral steroids. The average calcium prior to dosing was 2.35 mmol/l, falling to 1.98mmol/l after dosing. 9 patients achieved their lowest calcium at 1 week, 2 at 4 weeks and 3 at 8 weeks. Average PTH level prior to dosing was 153ng/l and after was 888ng/l. 5 patients developed severe hypocalcemia (corrected calcium less than1.9mmol/l), the average prior calcium in this group was 2.39mmol/l, falling to 1.77mmol/l. The average prior PTH was 206ng/l, rising to 1171ng/l. Four patients did not have Vitamin D status checked before dosing.

Conclusions: Denosumab will cause a small but not clinically significant reduction in serum Calcium in most patients with CKD. Severe hypocalcaemia can result if Vitamin D levels are unknown or in higher PTH levels. eGFR does not seem to correlate with the risk of hypocalcaemia. Biochemical abnormalities associated with CKD should be corrected, specifically, calcium, phosphate, PTH and vitamin D. Densoumab is the preferred treatment in CKD 4/5 however its use should be avoided in severe hyperparathyroidism and vitamin D deficiency.

FR-PO046

Native BK Nephropathy: A Case Series Ankur Shah,[1] Matthew Palmer,[2] Jonathan J. Hogan,[1] Deirdre L. Sawinski.[1] *[1]Division of Nephrology, University of Pennsylvania, Philadelphia, PA; [2]Pathology, University of Pennsylvania, Philadelphia, PA.*

Background: BK Polyoma Virus is highly seroprevalent but rarely pathologic in humans. Genitourinary BK disease is most commonly seen after kidney transplantation. Here we present two cases of native kidney BK nephropathy.

Methods: The first patient was a 70 yo man with ischemic cardiomyopathy s/p OHT in 2011 and was on tacrolimus, mycophenolate mofetil, and prednisone maintenance immunosuppression. His pre-transplant SCr was 1.5-1.7 mg/dL which remained stable after OHT. In 2013 he experienced a rapid rise in SCr over 5 months to 3.8 mg/dL. His urinalysis was negative for blood and albumin, microscopy showed no cells, and UProt:Cr ratio was 200 mg/g. A kidney biopsy showed tubular epithelial cells with focal glassy nuclear inclusions, and positive nuclear staining for SV40 and Pab597. Serum BK PCR was positive (296075 copies/ml). MMF was stopped. His serum BK viral load decreased and SCr stabilized at 3.5 for approximately 3 years before beginning to rise again and his progressing to ESRD. The second patient was a 34 yo man who was treated for non-Hodgkin's lymphoma at age 18 with chemotherapy (CHOP regimen). He was hospitalized for weakness, diarrhea and volume depletion and found to have AKI (Cr 4.0 mg/dL, baseline 1.2 mg/dL) and transaminitis (AST 134, ALT 61 IU/L) Urinalysis showed 500+ mg/dl protein and small blood with 1-2 rbc/hpf on microscopy and UProt:Cr was 13 g/g. A kidney biopsy revealed tubular epithelial cells with widespread degenerative and regenerative epithelial changes, frequent epithelial mitoses and intranuclear inclusions. IHC staining for polyoma virus showed positive nuclear staining in tubular epithelial cells. He was subsequently diagnosed with hemophagocytic syndrome and died of multi-organ system failure.

Results:

Conclusions: BK Virus infection has long been described as a cause of renal disease after renal transplantation but has been described in 41 cases to date in non-kidney transplant patients. These patients included HIV, bone marrow transplant, heart transplant, and other solid organ transplant recipients. BK nephropathy in the native kidney should be considered as a cause of renal injury in immunocompromised patients.

FR-PO047

Hello, Goodbye Proteinuria Jeremy J. Sorkin,[4] Patrick H. Nachman,[5] Vimal K. Derebail,[2] Roshni Radhakrishna,[4] Volker Nickeleit,[1] Alexei V. Mikhailov.[3] *[1]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]University North Carolina at Chapel Hill, Chapel Hill, NC; [3]University of North Carolina, Chapel Hill, NC; [4]University of North Carolina, Chapel Hill, NC; [5]University of North Carolina School of Medicine, Chapel Hill, NC.*

Background: Tyrosine kinase inhibitors (TKIs) have been associated with proteinuria and even overt nephrotic syndrome with variable renal histopathology (thrombotic microangiopathy (TMA), FSGS, or minimal change disease (MCD)). These agents have been thought to indirectly inhibit vascular endothelial growth factor (VEGF) receptors on glomerular endothelial cells. Sorafenib has been reported to cause proteinuria in several cases and discontinuation may result in resolution of proteinuria, although typically over several months. We present a case of severe nephrotic syndrome after starting sorafenib in a patient with a history of graft-versus-host disease (GVHD) whose history suggested several potential etiologies.

Methods: A 61-year-old man was evaluated for acute onset severe edema. He had acute myeloid leukemia (AML) and had received allogeneic-stem cell transplantation from his sister, complicated by steroid-induced diabetes and prior GVHD. Immunosuppression included tacrolimus and daily prednisone. He was started on sorafenib 400mg daily three months prior to admission. He was found to have a serum albumin to 2.1 mg/dl and new nephrotic range proteinuria with urine albumin/creatinine ratio (UACR) 9.0g/g. Baseline serum creatinine was <1mg/dl. Hgb and platelets were at baseline. Tacrolimus troughs were <2ng/ml. Bone marrow biopsy was negative for active GVHD. Renal biopsy was pursued to differentiate between GVHD-associated immune complex-mediated disease versus proteinuria related to VEGF inhibition by sorafenib. Pathology revealed a podocytopathy consistent with MCD and arteriolopathy indicative of early calcineurin inhibitor toxicity. Sorafenib was discontinued and no additional corticosteroids were administered. After two weeks, the patient had complete resolution of proteinuria, and increase in serum albumin to 2.9 mg/dl.

Results:

Conclusions: TKIs can lead to proteinuria, overt nephrotic syndrome, and TMA. In this case, no clinical signs suggestive of TMA were present and pathology showed only MCD. Discontinuation of sorafenib led to surprisingly fast resolution of nephrotic syndrome, more rapid than typically reported. This case highlights the variable etiologies and timing to proteinuria resolution related to nephrotic syndrome and TKIs.

FR-PO048

Idiopathic Diffuse Global Hypertrophic Podocytopathy without Proteinuria with AKI in a Patient with a Solitary Kidney Jaime A. Baynes-Fields,[1] Sandeep Aggarwal,[2] Myriam C. Vela-Ortiz.[1] *[1]Drexel University, Philadelphia, PA; [2]Drexel University College of Medicine, Philadelphia, PA.*

Background: Podocytopathies in adults usually present as significant proteinuria but can be associated with AKI, especially in elderly patients. We present a case with AKI without proteinuria with predominant finding of diffuse podocytopathy on renal biopsy.

Methods: A 35 year old black male with history of Wilms tumor and left nephrectomy (age 2 years) presented with 2 day history of progressive anasarca, and muscle soreness. Patient denied arthralgia, upper respiratory infections, rashes, joint pain, or new prescription medications. **Pertinent initial physical examination:** blood pressure 140/78 mmHg, HR 106 per minute and generalized anasarca, no lymphadenopathy appreciated, and otherwise normal examination. **Laboratory workup:** serum creatinine (cr) 6.28mg/dl, with baseline cr 1.4 mg/dL. CPK 350 IU/L. Albumin 2.6g/dL. Paraproteinemia workup, rheumatological serologies, HIV, and Hepatitis panel were negative. Urine drug screen was positive for opiates and THC. Urinalysis specific gravity 1.019, negative for protein and blood. Urine protein/cr ratio 0.12mg/g of cr. **Imaging:** renal ultrasound, with enlarged right solitary kidney (17.9cm), otherwise normal. Chest xray was normal. Renal biopsy was performed with; **light microscopy:** diffuse global glomerulomegaly with severe glomeruli hyper cellularity without inflammatory cells, capillary lumens and glomerular space were globally obliterated without crescents. There was no glomerular sclerosis seen. No evidence of tubulitis, interstitial nephritis or vasculitis/capillaritis. Proximal tubular cells showed luminal obliteration with occasional mitotic bodies. **Electron microscopy**: diffuse global podocyte hypertrophy with >80% foot process effacement and microvillus changes, proximal tubular showed protein reabsorption bodies, no immune complexes were identified. **Immunofluorescence:** no immune deposits and negative parvovirus. Given predominant podocytopathy with otherwise preserved renal histology, patient was treated with total 3g IV methylprednisolone and transitioned to oral prednisone taper with improvement in serum creatinine.

Results:

Conclusions: In the emerging field of biomarkers, our case emphasizes the role of renal biopsy in diagnosing the otherwise unidentifiable causes of AKI. An atypical presentation of podocytopathy with non-proteinuric AKI was revealed by biopsy in this case.

FR-PO049

Blast from the Past: Methysergide Induced Retroperitoneal Fibrosis Ayushi Chauhan,[2] Shehryar H. Ashraf,[2] Sankar N. Niranjan.[1] *[1]Greater Hartford Nephrology, Bloomfield, CT; [2]University of Connecticut, Hartford, CT.*

Background: Methysergide induced retroperitoneal fibrosis (RPF) lapsed into relative obscurity at culmination of the ergot era in migraine prophylaxis. Consequently, our collective vigilance has diminished regarding this entity. We describe an uncommon case of methysergide induced RPF causing acute kidney injury (AKI).

Methods: 34-year-old woman with history of intractable migraines requiring multiple hospitalizations for parenteral pain management, bipolar disorder on chronic lithium therapy, and hypertension presented with a 3-week history of abdominal pain, associated with nausea, and daily episodes of non-bloody emesis. She also reported decreased urine output, difficulty voiding and new bilateral lower extremity edema. Review of systems was positive for constipation due to increased use of previously prescribed opiates for analgesia. She used Ketorolac for pain and also was treated with trimethoprim/sulfamethoxazole for a presumed UTI. Laboratory data revealed mild leukocytosis (14.4), acute on chronic anemia (hemoglobin and hematocrit 9.0/26.9) and AKI with BUN/ serum creatinine (SCr) at 22/2.7 mg/dl. BUN/SCr was 13/0.7 mg/dl a year prior. Urinalysis as well as an abdominal X-ray did not exhibit any abnormalities. Lithium levels were normal. CT abdomen/pelvis showed bilateral hydronephrosis with prominence of the left ureter and associated perinephric stranding. Urology performed cystoscopy, bilateral retrograde pyelography and left ureteroscopy. During the procedure, bilateral symmetric narrowing of mid to distal ureters was noted with medial deviation suggestive of RPF. On specifically questioning the patient, she disclosed surreptitious use of Methysergide which was deemed the culprit agent. She was treated with bilateral ureteric stenting with improvement in SCr levels.

Results:

Conclusions: RPF is a chronic, predominantly idiopathic, fibroinflammatory disorder. Only one-third of cases are secondary with Methysergide being an established etiologic agent. Pathogenesis is thought to involve drug-related pro-fibrotic haptenic role or a feedback rebound serotonin release resulting in TGF-β/Smads cascade-mediated myoblast proliferation. This case highlights the importance of careful history-taking especially in cases of AKI where multiple intersecting nephrotoxins might play a role and brings to the forefront a now rare disease.

FR-PO050

Timing of AKI after Urgent Percutaneous Coronary Intervention and Adverse Outcomes: The PATTERN Study Thida C. Tan,[2] Thomas Leong,[2] Robert J. Lundstrom,[2] Jamal S. Rana,[2] Douglas J. Watson,[1] Alan S. Go.[2] *[1]CSL Behring, King of Prussia, PA; [2]Kaiser Permanente Northern California, Oakland, CA.*

Background: Conflicting evidence exists about the frequency and outcomes associated with acute kidney injury (AKI) after percutaneous coronary interventions (PCI). Limited insights also exist about whether the timing of AKI influences outcomes after PCI in contemporary populations. We examined the association between AKI at 12 and 24 hours post-PCI with subsequent renal and mortality outcomes.

Methods: We identified all adult members within Kaiser Permanente Northern California undergoing urgent PCI from 2008-2013 who had both pre- and post-PCI serum creatinine data. Patients with prior dialysis, renal transplant or estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m^2 were excluded. AKI was defined as a ≥50% relative increase or ≥0.3 mg/dL increase in post- vs. pre-PCI serum creatinine measures at 12 (±6) and 24 (±6) hours post-PCI. We ascertained post-discharge significant loss of renal function (defined as a 50% decrease from baseline eGFR or development of ESRD) and all-cause death up to 1 year post-PCI based on data from electronic health records. We used Cox regression to evaluate the independent association between timing of AKI and outcomes after adjustment for a high-dimensional propensity score for developing AKI and pre-PCI eGFR and proteinuria.

Results: Among 8522 urgent PCI patients, mean age was 67 years, with 29% were women, and 21% minorities. AKI was documented in 1.8% of patients at 12 hours and 1.6% at 24 hours post-PCI. In multivariable Cox models, the risk of all-cause death up to 1 year was similarly high for AKI at 12 hours (adjusted hazard ratio [HR] 3.35, 95%CI:2.08-5.40) and 24 hours (HR 3.68, 2.18-6.21) post-PCI. In contrast, AKI at 24 hours post-PCI (HR 4.56, 2.37-8.79) was more strongly associated with significant loss of kidney function at 1-year than was AKI at 12 hours (HR 2.27, 1.19-4.32) post-PCI.

Conclusions: In a large, community-based population undergoing urgent PCI, AKI at 12 and 24 hours post-PCI were independently associated with high excess mortality at 1-year to a similar degree, while AKI at 24 hours was more strongly associated with subsequent significant loss of kidney function at 1 year compared with AKI at 12 hours. Studies are needed to determine whether prevention or treatment of AKI after PCI can mitigate the excess risks of death and renal function loss.

Funding: Commercial Support - CSL Behring

FR-PO051

Slope-Based Staging Outperforms KDIGO Staging for Assessing Inpatient Mortality Risk with AKI David G. Warnock,[3] Mirela Bojan,[2] Christoph Wanner,[5] Anupam Agarwal,[4] Marc Froissart.[1] *[1]CHUV / UNIL, Lausanne, Switzerland; [2]Necker-Enfants Malades University Hospital, Paris, France; [3]UAB, Birmingham, AL; [4]University of Alabama at Birmingham, Birmingham, AL; [5]University Hospital, Wuerzburg, Germany.*

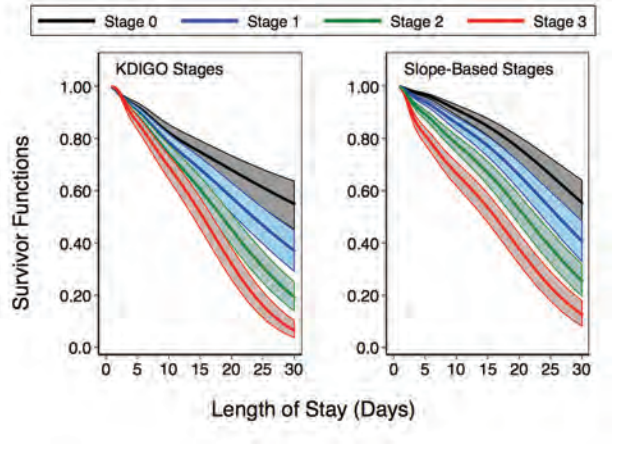
Background: The association between AKI severity and mortality is well described, but current staging criteria have not be optimized for risk assessment or developing prognostic models for specific outcomes

Methods: Confidence limits (CI) for individual patient serum creatinine (sCr) trajectories were developed using an adaptive Bayesian approach. AKI episodes were defined by sCr excursions above the CI, with a) ≥3 sCr values between baseline and peak; b) ≥6 hours between peak and baseline; and c) sCr increase ≥0.3 mg/dL. Specific baseline sCr values were defined for each as the minimal sCr value immediately preceding each AKI episode. Survivor functions, and relative Integrated Discrimination Improvement (rIDI) were done with Stata version 14.1.

Results: All adult 1st admissions were reviewed for FY2010-2013 at UAB Hospital, for patients with ≥3 sCr determinations, length of stay ≥1 & <31 days, excluding patients with ESRD before admission; 35, 079 patients with 1,544 inpatient deaths. AKI staging was done with KDIGO criteria, and slope-based staging for patients with AKI episodes. Survivor functions (Figure) show better discrimination between AKI stages with slope-based criteria compared to KDIGO criteria: rIDI=15.5% (95% CI: 13.5%–17.6%, P<0.001); C-statistics of 0.7694 vs. 0.7226, and AUC/ROC 0.8616 vs. 0.8551 (P=0.012).

Conclusions: Slope-based AKI staging outperforms KDIGO staging criteria for describing the association of AKI severity with inpatient mortality at UAB Hospital. Sloped-based staging is compatible with real-time, dynamic risk assessment than KDIGO staging, and also recognizes multiple AKI episodes during a single admission, with baseline sCr defined for each AKI episode. KDIGO staging is based on the absolute inclrease in sCr with reference to a prior baseline sCr, and does not recognize multiple AKI episodes.

Funding: NIDDK Support, Clinical Revenue Support



Survivor Functions for AKI Staging by a) KDIGO criteria and b) Slope-Based criteria

FR-PO052

Thrombocytopenia Predicts Mortality in Patients with AKI Requiring Renal Replacement Therapy (RRT) Benjamin Griffin,[2] Zhiying You,[1] Paul M. Palevsky,[5] Sarah Faubel,[3] Diana I. Jalal.[4] *[1]UC Denver, Aurora, CO; [2]University of Colorado, Aurora, CO; [3]University of Colorado Denver, Denver, CO; [4]University of Colorado Denver Health Science Center, Aurora, CO; [5]University of Pittsburgh, Pittsburgh, PA.*

Background: Thrombocytopenia is common in critically ill patients and is associated with increased mortality. The impact of thrombocytopenia in patients requiring RRT for AKI is unknown. In this study we assessed the prognostic value of thrombocytopenia at RRT initiation in a large database of critically patients with AKI requiring RRT.

Methods: We conducted a secondary analysis of the Acute Renal Failure Trial Network (ATN) database. The ATN study compared intensive to less-intensive RRT dosing strategies in patients with AKI. In this analysis, patients were categorized based on pre-RRT platelet levels, which were classified as normal (> 100 x 10^3/μL), moderate (50-100 x 10^3/μL) and severe (<50 x 10^3/μL) thrombocytopenia. 60-day mortality was compared using chi-squared test. Logistic regression was used to adjust for age, race, and gender in the initial model, and body mass index (BMI) and SOFA score in the final model.

Results: 62% of patients had at least moderate thrombocytopenia prior to initiation, and 14% had severe thrombocytopenia. Thrombocytopenia was highly associated with 60-day mortality even after adjustments for demographics and illness severity (Table 1). In patients who survived >72 hours, the platelet decrease at day 3 as a continuous variable did not have a clinically relevant association with 60-day mortality, with an OR of 0.996 (0.993 - 0 .999, p = 0.02).

Conclusions: Thrombocytopenia is present > 60% of patients with at the initiation of RRT and is independently and significantly associated with increased mortality even after adjusting for illness severity. The role of thrombocytopenia in outcomes of patients with AKI requiring RRT merits future study.

Table 1. Final multivariate model for 60-day ICU mortality. Platelet levels are compared to <50 x10^3/μL

Variable	OR (95% CI)	P value
Platelet Level 50-100 x10^3/μL	0.46 (0.27 -0 .79)	.0047
Platelet Level >100 x10^3/μL	0.34 (0.20 – 0.55)	<0.0001
SOFA Score	1.30 (1.18 – 1.42)	<0.0001
Female Gender	0.91 (0.64 – 1.28)	0.57
African-American Race	1.21 (0.78 – 1.86)	0.38
Age (years)	1.03 (1.02 – 1.04)	<0.0001
BMI (kg/m^2)	0.98 (.095 – 1.00)	0.06

FR-PO053

Renal Recovery and Progression of CKD Following Postoperative AKI Thorir E. Long,[3,2] Sólveig Helgadóttir,[1] Dadi Helgason,[3,2] Runolfur Palsson,[2,3] Tomas Gudbjartsson,[2,3] Gisli H. Sigurdsson,[2,3] Martin I. Sigurdsson,[4] Olafur S. Indridason.[2] *[1]Akademiska Hospital Uppsala University, Uppsala, Sweden; [2]Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland; [3]Faculty of Medicine, University of Iceland, Reykjavik, Iceland; [4]Duke University Medical Center, Durham, NC.*

Background: Acute kidney injury (AKI) is a known risk factor for chronic kidney disease (CKD). The aim of this study was to examine how renal recovery associates with the development or progression of CKD among individuals with AKI following surgical procedures.

Methods: This was a retrospective study of all adult patients undergoing abdominal, cardiothoracic, vascular or orthopedic surgery at the University Hospital in Reykjavik in 1998-2015. AKI was defined according to the KDIGO serum creatinine (SCr) criteria. CKD was defined as eGFR <60 ml/min/1.73m^2 persistent for ≥90 days, and development and progression of CKD as increase to a higher stage, present for ≥90 days. Association between incident CKD or CKD progression and renal recovery of varying degree (SCr reduction to <1.5, <1.25 and <1.1 x baseline SCr) at 30 days following AKI was compared with a non-AKI control group using propensity score matching (1:1).

Results: Following a total of 43,876 surgeries, 2,497 (5.7%) patients developed AKI. In the AKI group, 1,071 (42.9%) had baseline eGFR <60 ml/min/1.73 m^2, compared with 8,562 (20.7%) among those who did not develop AKI. Median follow-up time was 4.4 (range 0.1-18.1) years and 36,563 (83%) patients had two or more SCr measurements available at least 90 days apart. Development or progression of CKD was observed during follow-up in 585 (23.4%) patients with AKI compared with 3.181 (7.7%) of those without AKI (<0.001). Progression of CKD was observed in 19.8%, 25.1%, 36.2% and 27.8% of individuals with renal recovery to <1.10, <1.10-1.25, <1.25-1.5 x baseline SCr and no recovery (SCr >1.5 x baseline SCr) at 30-days, respectively. In comparison, 11% of a propensity score-matched control group without AKI experienced CKD progression during follow-up (p<0.001).

Conclusions: Postoperative AKI increases the risk of development of incident CKD and/or progression of existing CKD, even in patients who experience apparent good renal recovery.

Funding: Government Support - Non-U.S.

FR-PO054

Early Renal Replacement Therapy Improves Outcome of Burned Patients with AKI Zhong hong Liew,[1] Manish Kaushik,[1] Han K. Tan,[1] Andrew Cheah,[2] Si jack Chong,[1] Bien keem Tan.[1] *[1]Singapore General Hospital, Singapore, Singapore; [2]Singhealth, Singapore, Singapore.*

Background: Burned patients with acute kidney injury (AKI) require renal replacement therapy (RRT) have exceedingly high mortality rates of 73-100%. Since January 2011, we have been adopting early RRT approach in managing burned patients with AKI. Our hypothesis was that early initiation of RRT leads to improved outcome and survival among burned patients with AKI by allowing better management of fluid, electrolytes and acid-base balance

Methods: We conducted a retrospective analysis of Burns Database from January 2011 to February 2016. Indications for dialysis included serum creatinine > 1.5 times baseline or urine output < 0.5 ml/kg/h for at least 2 consecutive hours. Patients with similar parameters from January 2006 to December 2010 were recruited for comparison.

Results: A total of 27 patients with burns and AKI were recruited from January 2011 to February 2016. Mean age was 45.4 years and 88.9% were male. Mean TBSA was 54.8%. Total volume of fluid resuscitation was 2.7 ml/kg/TBSA. Time from onset of burn to RRT was 6.4 days. Majority of patients presented with stage 1 AKI (51.9%); while 22.2% and 25.9% had stage 2 and stage 3 AKI respectively. Most patients (74.1%) received CRRT and 18.5% received SLED. The mortality rate was 37.0% with majority (70%) were due to sepsis/multiorgan failure. Only 1 patient required long-term RRT after discharge and there was no occurrence of abdominal compartment syndrome. Mean age of 15 patients from 2006 to 2010 was 47.8 years. Mean TBSA was 49.5%. Only 26.7% of patients were started on RRT. The mortality rate was 66.7%, which was higher than that of subjects from 2011 to 2016 (37.0%).

Conclusions: We compared our findings with 5 studies published in recent 10 years on burned patients with AKI started on RRT and found that early RRT approach reduced mortality of burned patients with AKI. Optimal timing of RRT for burned patients with AKI has not been established and further large clinical trials are required.

	Steinvall 2008 (n=4)	Chung 2009 (n= 29)	Soltani 2009 (n= 33)	Mariano 2010 (n=70)	Gille (2014) (n=14)
Age (year)	NA	27 (mean)	49 (mean)	57.5 (median)	64 (median)
TBSA (%)	NA	64% (mean)	36% (mean)	40% (median)	42.5% (median)
Criteria to start RRT	Creatinine > 300 µmol/L, together with oliguria or anuria	AKIN 2 + shock, AKIN 3	Severe fluid overload refractory to diuretics Refractory hyperkalemia Severe metabolic acidosis Azotemia	NA	Oxygenation index (PaO2/FiO2) < 200 mmHg Serum potassium > 6 mmol/L Increase of serum creatinine > 200% Reduction of glomerular filtration rate > 50% Urea > 25 mmol/L Diuresis ≤ 0.5 ml kg/hour for 6 hours Rhabdomyolysis
Time to RRT (days from admission)	Started on day 5 to 19	9 (median)	14 (mean)	16.8 (mean)	6 (median)
Duration of RRT (days)	Ranging from 10 to 15 days	5.6 (mean)	10.5 (mean)	9.5 (mean)	7 (median)
Abdominal compartment syndrome	NA	NA	7	NA	NA
Mortality rate	3 (75%)	18 (62%)	23 (69.7%)	50 (71.4%)	2 (11.1%)

FR-PO055

AKI and Remission of Proteinuria in Adult-Onset Minimal Change Disease: A Multicenter Retrospective Cohort Study Maki Shinzawa,[4] Yasuyuki Nagasawa,[4] Ryohei Yamamoto,[4] Atsushi Yamauchi,[3] Megumu Fukunaga,[5] Terumasa Hayashi,[2] Masaaki Izumi,[1] Yoshitaka Isaka.[4] *[1]Kansai Rosai Hospital, Amagasaki, Hyogo, Japan; [2]Osaka General Medical Center, Osaka, Japan; [3]Osaka Rosai Hospital, Sakai-city, Japan; [4]Osaka University Graduate School of Medicine, Suita, Osaka, Japan; [5]Toyonaka Municipal Hospital, Toyonaka, Japan. Group/Team: STOP-MCD.*

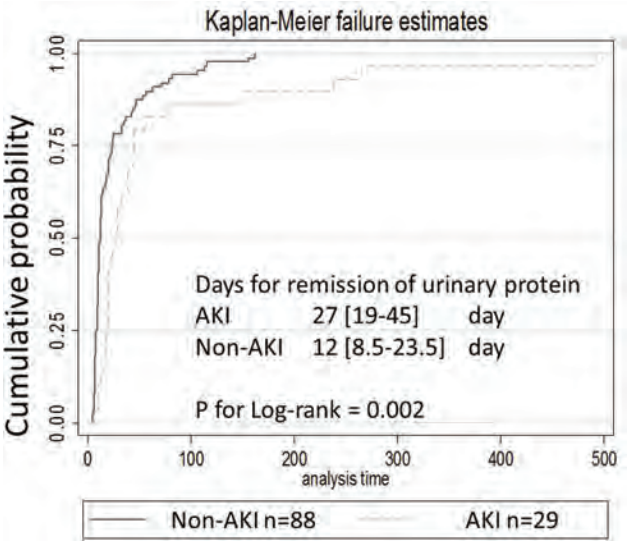
Background: Acute kidney injury (AKI) is common (20% to 50%) in adult-onset minimal change disease (MCD). However, its effect on remission of proteinuria is unknown.

Methods: Design: a multicenter retrospective cohort study, the STudy of Outcomes and Practice patterns of Minimal-Change Disease (STOP-MCD). Patients: 117 nephrotic patients aged ≥15 years with histological diagnosis of primary MCD between 2000 and 2009 in 5 hospitals in Japan. Outcome: First remission of proteinuria defined as urinary protein < 0.3 g/day, urinary protein / creatinine ratio < 0.3, and/or negative/trace result of dipstick test. Exposure: AKI defined as ≥0.3mg/dL of an increase of creatinine (Cre) at initiating immunosuppressive therapy. Statistics: Multivariable Cox proportional hazards (CPH) model.

Results: Baseline characteristics at initiating of immunosuppressive therapy.of AKI group (n=29) and non-AKI group (n=88) were as follows; age, median 53 [interquantile range 28, 63] vs. 37 [22, 58] yr (P=0.135); male, 66 vs. 61 % (P=0.689); Cre, 1.6 [1.3, 2.0] vs. 0.8 [0.7, 0.9] mg/dL (P<0.001); serum albumin, mean 1.8 ± SD 0.6 vs. 1.8 ± 0.6 g/L (P=0.950); urinary protein, 11.6 [7.9, 14.7] vs. 7.2 [3.3, 14.4]) g/day (P=0.021); initial dose of prednisolone, 0.7 ± 0.1vs. 0.7 ± 0.2 mg/Kg (P=0.449). During 4.2 [2.2-7.2] year of the observational period, all patient achieved remission. Maximum Cre after initial treatment was 2.5 [2.0-3.6] mg./dL in AKI group and 0.9 [0.8-1.2] mg/dL in non-AKI group. Remission was delayed in AKI group (27 [19, 45] vs. 12 [9, 24] day, P=0.002) (Figure). AKI was identified as a significant predictor of remission in the multivariable CPH model (AKI vs. non-AKI, hazard ratio 0.48 [95% confidence interval 0.29–0.79, P=0.004]).

Conclusions: AKI before immunosuppressive therapy delayed remission of proteinuria in adult-onset MCD.

Funding: NIDDK Support



FR-PO056

Subclinical AKI Is Associated with Poor Patient Outcomes in Critically Ill Children Natalja Stanski,[1] Shina Menon,[2] Stuart Goldstein,[1] Rajit K. Basu.[1] *[1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [2]Seattle Children's Hospital, University of Washington, Seattle, WA.*

Background: The diagnosis of acute kidney injury (AKI) depends on the detection of increases in serum creatinine (SCr), which can result in delayed recognition. Neutrophil gelatinase-associated lipocalin (NGAL) is a biomarker of renal tubular injury that rises early and can be used to detect AKI sooner. Subclinical AKI, a state defined by biomarker positivity in the absence of SCr elevation, has not been well studied in children thus far.

Methods: We conducted a single center, prospective study of children admitted to the ICU with urinary NGAL and SCr samples collected in the first day of admission. NGAL elevation (NGAL+) was defined as >500 ng/ml and SCr elevation (SCr+) was defined as KDIGO stage 1 AKI or greater. Patients were separated into 4 groups: NGAL+/SCr+, NGAL+/SCr-, NGAL-/SCr+ and NGAL-/SCr-. Groups were compared across a variety of outcomes: in-hospital mortality, need for renal replacement therapy (RRT) (primary outcomes), incidence and duration of mechanical ventilation, ICU and hospital length of stay (LOS), organ failure days and incidence of late onset-AKI (day 3-7). Particular attention was paid to the comparison of the NGAL-/SCr- and NGAL+/SCr- groups.

Results: 178 patients (51.6% male, median age 6.7 years) were included. 115 (64.6%) were NGAL-/SCr-, 12 (6.7%) were NGAL+/SCr-, 26 (14.6%) were NGAL-/SCr+ and 25 (14.1%) were NGAL+/SCr+. Compared to NGAL-/SCr- patients, NGAL+/SCr- patients had higher odds of in-hospital mortality [OR 1.64 (95% CI: 0.18,14.8) p=0.66], need for mechanical ventilation [OR 2.92 (95% CI: 0.61,13.9) p=0.18], and late-onset AKI [OR 2.5 (95% CI: 0.68,9.1) p=0.16]. This group also had longer mean duration of mechanical ventilation, more organ failure days, and longer LOS (both ICU and hospital). There was no difference in need for RRT initiation as no patients in either group required RRT use.

Conclusions: Elevated urine NGAL on ICU admission is associated with increased morbidity and mortality in pediatric patients, even in the absence of elevated SCr, and may represent a state of subclinical AKI.

FR-PO057

Analysis of Morbidity and Mortality in Patients with Biliary Obstruction and AKI Di Pan,[1,3] Yumeng Wen,[1,3] David Mariuma,[1,3] Michael Gramuglia,[4] Ira S. Meisels.[2,3] *[1]Mount Sinai St. Luke's and Mount Sinai West Hospitals, New York, NY; [2]Division of Nephrology, Mount Sinai St. Lukes and Mount Sinai West Hospitals, New York, NY; [3]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; [4]Montefiore Health System, New York, NY.*

Background: Acute kidney injury has been shown to be a negative prognostic factor for a variety of diseases. Patients with biliary obstruction are unique in the fact that they may develop acute kidney injury through the nephrotoxic effects of hyperbilirubinemia in addition to the conventional mechanisms of renal failure. The goal of this study is to analyze the impact and burden of acute kidney injury on patients with biliary obstruction.

Methods: This is a retrospective cohort study using the 2014 National Inpatient Sample (NIS), which is the largest inpatient database in the United States. A total cohort of 59,500 patients over the age of 18 admitted with either a primary or secondary diagnosis of biliary obstruction were identified using ICD-9 codes. 8,760 (17%) individuals had a concurrent diagnosis of acute kidney injury. The primary outcome was overall in-hospital mortality. Secondary outcomes included length of stay (LOS), total hospital charge, and incidence of receiving renal replacement therapy. Multivariate regression analyses were performed to test for independent associations between AKI and outcomes of interest adjusting for age, gender, race and comorbidities. Independent t-tests were performed

for continuous variables, and chi-squared and fisher's exact tests were performed for categorical variables. Analysis was performed using Stata 14.2.

Results: The presence of acute kidney injury was independently associated with increased overall in-hospital mortality in patients with biliary obstruction (adjusted OR 2.93 p<0.0001, 95% CI 2.34-3.65). LOS was 2.08 days longer (P<0.0001, 95% CI 1.43 -2.73) in patients with acute kidney injury, and total hospital charges were $24832.04 more than in patients without acute kidney injury (p<0.0001 95% CI 14673.35 - 34990.74). 3.2% of patients received renal-replacement therapy.

Conclusions: The presence of acute kidney injury poses significant burden on patients with biliary obstruction. It is associated with increased mortality, with increased length of stay and hospital charge. We should pay close attention and be aggressive in the monitoring and treatment of AKI in this population.

FR-PO058

Definition of Baseline Serum Creatinine Levels Which Are the Best to Predict Clinical Prognosis in Acute Kidney Injury Patients Jeonghwan Lee,[2] Dong Ho Shin,[1] Ho Jun Chin,[3] Ki Young Na,[3] Sejoong Kim.[3] *[1]College of Medicine, Hallym University, Seoul, Republic of Korea; [2]Hallym University Hangang Sacred Heart Hospital, Seoul, Republic of Korea; [3]Seoul National University Bundang Hospital, Seong nam, Republic of Korea.*

Background: The classification of acute kidney injury (AKI) may be different depending on how the baseline serum creatinine is defined. The authors aimed to determine the best way to define the baseline serum creatinine according to the patients' kidney function.

Methods: A total of 19656 adult patients were enrolled at one university hospital during the year 2013. The baseline serum creatinine levels were defined by 4 different methods (the lowest value of serum creatinine levels during 14 days, 92 days, or 184 days before admission; and the serum creatinine levels inversely calculated from the MDRD GFR 75 ml/min/1.73m^2 values). Using the Receiver Operating Characteristic curve analysis, the area under the curve (AUC) was measured to compare the diagnostic performance of AKI for clinical outcomes according to the definition of baseline serum creatinine levels.

Results: In patients with a baseline GFR above 60 ml/min/1.73m^2, the AUCs for in-hospital mortality were similar for the four definitions of baseline creatinine levels. The AUC for ESRD was significantly superior when the baseline serum creatinine values were calculated from the GFR 75 value. In patients with a baseline GFR below 60 ml/min/1.73m^2, when the baseline serum creatinine values calculated from the GFR 75 value, the AUC for in-hospital mortality was poor and the AUC for ESRD was significantly lower.

Conclusions: In patients with normal GFR, serum creatinine levels, which were back-calculated from the GFR 75 values, can be used as the baseline creatinine levels to define AKI. However, in patients with impaired kidney function, baseline serum creatinine levels obtained directly from the 6-month serum creatinine levels before admission can predict the prognosis of AKI more accurately.

C-statistics for ROC curve for in-hospital mortality and end-stage renal disease according to the AKI with 4 different baseline creatinine definitions

		In-hospital mortality		ESRD	
Basal GFR	Baseline Creatinine (Cr) Definition	AUC	95% confidence interval	AUC	95% confidence interval
GFR ≥ 60 ml/min/1.73m^2	Cr from GFR 75	0.569	0.556-0.582	0.920	0.877-0.962
	Lowest Cr 14 days before admission	0.558	0.545-0.571	0.775	0.702-0.848
	Lowest Cr 92 days before admission	0.570	0.557-0.583	0.778	0.707-0.849
	Lowest Cr 184 days before admission	0.574	0.561-0.587	0.775	0.704-0.846
GFR < 60 ml/min/1.73m^2	Cr from GFR 75	0.639	0.579-0.699	0.638	0.593-0.684
	Lowest Cr 14 days before admission	0.741	0.672-0.810	0.730	0.677-0.783
	Lowest Cr 92 days before admission	0.735	0.669-0.800	0.770	0.725-0.814
	Lowest Cr 184 days before admission	0.735	0.673-0.797	0.782	0.744-0.821

FR-PO059

A 10-Year National Trend in AKI among Hospitalized Adults Undergoing Invasive Cardiac Electrophysiology Studies Yumeng Wen,[1,2] Di Pan,[1,2] David Mariuma,[1,2] Fernando Vazquez de lara,[1,2] Yiming Luo,[1,2] Michael Gramuglia,[3] Ira S. Meisels.[1,2] *[1]Division of Nephrology, Department of Medicine, Mount Sinai St. Luke's and Mount Sinai West Hospitals, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]Department of Medicine, Montefiore Medical Center, Scarsdale, NY.*

Background: Invasive cardiac electrophysiology (EP) study is a collection of clinical techniques for investigation and treatment of cardiac rhythm disorders. Limited literature has addressed the risk of acute kidney injury (AKI) following invasive EP procedures. The aim of this study is to analyze the temporal trend of AKI among patients undergoing invasive cardiac EP studies, as well as in-hospital mortality and other outcomes among those developed AKI between 2005 and 2014.

Methods: This is a retrospective study using the 2005-2014 National Inpatient Sample, which is the largest publically available inpatient database in the United States. A cohort of 962,394 patients over the age of 18 undergoing invasive cardiac EP studies based on ICD-9 CM codes was included in the study. There were no exclusion criteria. In the primary analysis, we examined the temporal trend in the incidence of AKI and dialysis-requiring AKI. In the secondary analysis, we examined temporal changes in in-hospital mortality, length of stay (LOS), and total charges in hospitalizations complicated by AKI over the study time period. Odds ratios (OR) were calculated based on multivariate logistic analyses, adjusted for demographics and comorbidities. Analysis was performed using Stata, version 14.2.

Results: Our results showed that from 2005 to 2014 there was a significant increase in the incidence of AKI (3.26% in 2005 vs. 13.03% in 2014, p<0.001), as well as in dialysis-requiring AKI (0.22% in 2005 vs. 0.61% in 2014, p<0.001). Among those who developed AKI, the in-hospital mortality rate remained stable over time (OR 0.96, p=0.071). The LOS decreased significantly (15.85 days in 2005 vs. 11.22 days in in 2014, p<0.001), along with an increase in total hospital charges over time ($151,369 in 2005 vs. $193,384 in 2014, p<0.001). Hospitalizations complicated by AKI compared to those that were not were associated with significant higher in-hospital mortality (OR 3.77, p<0.001).

Conclusions: Our study demonstrated a significant increase in the incidence of AKI and dialysis-requiring AKI among patients undergoing invasive cardiac EP studies, however in-hospital mortality remained the same over time. Development of AKI after invasive cardiac EP studies was associated with higher hospital mortality rate and financial burden.

FR-PO060

A 10-Year National Trend in Dialysis-Requiring AKI among Hospitalized Adults with HIV Infection Yumeng Wen,[1,2] Di Pan,[1,2] David Mariuma,[1,2] Marcelo X. Hernandez cuchillas,[1,2] Yiming Luo,[1,2] Michael Gramuglia,[3] Ira S. Meisels.[1,2] *[1]Division of Nephrology, Department of Medicine, Mount Sinai St. Luke's and Mount Sinai West Hospitals, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]Department of Medicine, Montefiore Medical Center, Scarsdale, NY.*

Background: Patients with HIV are at risk for both acute kidney injury (AKI) and chronic kidney disease (CKD). Previous studies demonstrated an increasing incidence of AKI among HIV population. The aim of this study is to observe beyond the time frame of the previous studies and to explore the in-hospital mortality and other outcomes among hospitalized HIV patients who developed dialysis-requiring AKI between 2005 and 2014.

Methods: This is a retrospective study using the 2005-2014 National Inpatient Sample, the largest inpatient database in the US. A cohort of 2,133,610 patients over the age of 18 diagnosed with HIV based on ICD-9 CM codes was included in this study. Patients hospitalized for elective procedures were excluded. In the primary analysis, we examined the temporal trend in the incidence of dialysis-requiring AKI. In the secondary analysis, we examined temporal changes in in-hospital mortality, length of stay, and total charges in hospitalizations complicated by dialysis-requiring AKI. Odds ratios (OR) were calculated based on multivariate logistic analyses, adjusted for demographics, related comorbidities and procedures. Analysis was performed using Stata 14.2.

Results: There was an increasing incidence of dialysis-requiring AKI among the HIV population over time (1.03% in 2005 vs 1.49% in 2014). Among HIV patients developing dialysis-requiring AKI, the in-hospital mortality rates decreased over time (25.35% in 2005 vs 18.79% in 2014, OR 0.93, p<0.001). The length of hospital stay had a increasing trend after initial decline (18.62 days in 2005 vs 15.62 days in 2011 vs 17.03 days in 2014, p=0.016). There was also a increase in total hospital charges ($122,273 in 2005 vs. $188,613 in 2014, p<0.001). Hospitalizations complicated by dialysis-requiring AKI compared to those that were not were associated with higher in-hospital mortality (OR 1.64, p<0.001)

Conclusions: This study demonstrates that despite an increase in incidence of dialysis-requiring AKI among patients with HIV, the in-hospital mortality of these patients has improved over time. The development of dialysis-requiring AKI continues to have significant life-altering impact and financial burden on HIV patients within our health-care system.

FR-PO061

Prospective Cohort Study Assessing the Role of Urine Microscopy in Diagnosis and Management of AKI Arani D. Nanavati, James F. Simon. *Cleveland Clinic, Cleveland, OH.*

Background: Nephrologist-performed urine microscopy is a competency taught during training and encouraged in practice when working up acute kidney injury (AKI). Despite this its use in clinical practice has waned for multiple reasons. Available data showing that nephrologist-performed microscopy(NPM) positively impacts the diagnosis and management of AKI patients is limited to differentiating prerenal azotemia from ATN. We conducted a prospective cohort study at a tertiary care center to identify to what extent NPM aids in identifying the etiology and proposed management of AKI when all cases are considered.

Methods: Fresh urine samples were obtained from 113 patients with AKI on inpatient Nephrology consult service between September and December 2016. AKI was defined by at least stage 1 AKI as per the Kidney Disease Improving Global Outcomes definition [an increase of serum creatinine (SCr) by ≥0.3 mg/dl and/or increase ≥50%-100% from baseline]. Only cases reviewed by staff nephrologists were included. Nephrologists were provided with questionnaires before inspecting the urine sediment. They were asked to provide the proposed etiology of AKI and planned management prior to and after performing urine microscopy. A logistic regression model was created to investigate how often the etiology and proposed management changed based on urine sediment review and what variables may have increased the likelihood of either change.

Results: Presumptive etiology of AKI was changed with urine microscopy in 24%(n=27) of patients. Proposed management of AKI was changed in 12% of patients.

Management remained unchanged in 98% of patients in whom diagnosis was unchanged after microscopy. But of 27 patients in whom the etiology was changed after urine microscopy, management was changed in 44% of cases (n=12) (p<0.001) (Fischer's exact test). In a multivariable logistic regression model sepsis on presentation was found to be associated with higher odds of change in diagnosis of AKI after urine microscopy after adjusting for baseline and consult SCr (Odds ratio 4.19, 95% CI- 1.59-11.47, p= 0.004).

Conclusions: Nephrologist-performed urine microscopy plays a significant role in identifying the etiology and in management of patients with AKI in hospital. The likelihood was found to be higher in patients who were septic on presentation in our study.

FR-PO062

Use of a Serum Creatinine Point of Care Test in Low Resource Settings: Correlation and Agreement with Hospital Based Assessment Etienne Macedo,[5] Ulla Hemmila,[3] Sanjib K. Sharma,[2] Rolando Claure-Del Granado,[4] Emmanuel A. Burdmann,[6] Michael V. Rocco,[7] Jorge Cerda,[1] Ravindra L. Mehta.[5] *[1]Albany Medical College, Albany, NY; [2]B P Koirala Institute of Health Sciences, Dharan, Nepal; [3]College of Medicine, Malawi, Kokemäki, Finland; [4]Universidad Mayor de San Simon, School of Medicine, Cochabamba, Bolivia, Plurinational State of; [5]University of California San Diego Medical Center, San Diego, CA; [6]University of Sao Paulo Medical School, Sao Paulo, Brazil; [7]Wake Forest School of Medicine, Winston-Salem, NC.*

Background: The ISN0by25Pilot Project was designed to evaluate an education and training program coupled with a point of care (POC) serum creatinine (sCR) test and teleconsultation to improve detection and management of AKI in low resource settings. We evaluated in paired samples the correlation between the POC sCR test applied in the health center to the hospital lab sCR results.

Methods: Paired results of sCR POC test and hospital lab values were compared in adults and childre with and without CKD in the 3 clusters (Bolivia, Nepal and Malawi) participating in the project. sCR was measured by Jaffe reaction and the sCR POC test was performed using the StatSensor® Cr Xpress™ Meter. Correlation between lab and POC test was evaluated by Spearman's test and Bland Altman tests.

Results: We assessed 58 samples collected during clinical care obtained at the same time as the POC test. None of the pts were receiving renal support. Lab sCR values ranged from 0.5-25.9 mg/dl in adults and 0.4-13 mg/dl in children. Overall, correlation between hospital lab assessment and POC test was 0.872, (adults 0.879 and children 0.962) and similar for pts with and without CKD (no CKD 0.817, CKD 0.857); p<0.001. Bland Altman plot (Figure 1) showed a good agreement between the two measurements through the middle range of CR values.

Conclusions: The sCR POC test performed well in adult and children and can be utilized to assess kidney function in health care centers in low resource settings. The good correlation and agreement between the two measurements, suggests that POC test values are probably valuable for pt follow up through their course of illness and to assess kidney function recovery.

Funding: Private Foundation Support

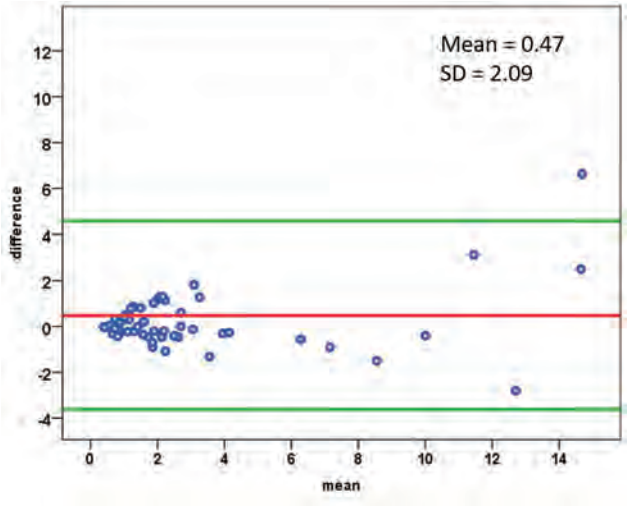


Figure 1 – Bland Altman plot showing the differences between laboratory and Xpress values and *vs*. the mean of the two measurements.

FR-PO063

Prevention of AKI in a Tertiary Pediatric Hospital by Real Time Risk Surveillance and Curated Alerts Abhay N. Vats, Sheena Sharma, Franca M. Iorember, Martin A. Turman, Brittany Wold, Melinda Loya, Nina Farhoudi, David F. Carpentieri, Jamie Librizzi, Vinay Vaidya, Kanwal K. Kher. *Phoenix Children's Hospital, Phoenix, AZ.*

Background: Hospital acquired acute kidney injury (HA-AKI) can significantly increase morbidity, mortality and health care costs in children. We developed a novel electronic health record (EHR) based real-time surveillance system for AKI detection & generation of curated alerts.

Methods: A software designed to provide enterprise-wide data analysis based on algorithms utilizing AKIN criteria for staging was developed. It queries EHR every 6 hours for AKI risks including: baseline serum creatinine (SC), % change, rate of rise in SC, nephrotoxic medications (NTM), therapeutic drug levels (TDM), and renal replacement therapy /nephrology intervention. Quick links to the patient charts are available. The analytic output is automated and made available on a self-updating dashboard which is utilized to generate curated alerts by the enterprise nephrologists.

Results: The dashboard (Fig) generates color coded signals for stage I to III AKI, plots weekly change in SC, NTM exposure, TDM listing, day(s) since last SC & documented nephrology intervention. It detects both NTM & non NTM associated AKI & risk factors. It is even programmed to detect AKI where the absolute SC is <0.5 mg/dl. An AKI surveillance team (pharmacist & nephrologist) reviews the dashboard daily to direct AKI prevention and treatment strategies through curated alerts to the responsible healthcare providers through "two way" integrated Vocera® secure messaging system. This avoids "alert fatigue" and has led to a proactive change in provider's approach to HA-AKI prevention. The dashboard access progressively increased from 45% to 87% over a short period of 6 weeks.

Conclusions: This novel EHR dashboard and AKI alert system serves as an early warning tool for enterprise wide application. The alerts are traceable, auditable & are HIPAA compliant. AKI biomarkers will be incorporated in the dashboard in near future. This tool allows the HA-AKI prevention team to track at risk patients, provide early detection & prevention of HA-AKI.

AKI Dashboard Screen Shot

FR-PO064

Initial Application of Electronic Alert for AKI among High-Risk Wards Yanhua Wu, Yuanhan Chen, Wei Dong, Xinling Liang. *Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China. Group/Team: China collaborative study on AKI.*

Background: The effectiveness of acute kidney injury alert might differ in different care settings. We aimed to investigate the value of electronic alert for acute kidney injury among high-risk wards.

Methods: A prospective, randomized, controlled study was conducted. We developed an electronic alert for AKI and ran the system in intensive care units and cardiovascular departments. Eligible participants were adults aged 18 years or older who were in hospital with acute kidney injury as defined by Kidney Disease Improving Global Outcomes creatinine-based criteria. Exclusion criteria were initial hospital creatinine 353.6μmol/L or greater, end-stage renal disease, renal replacement therapy before randomization, kidney transplantation and amputation. The primary outcomes were AKI and expanded AKI diagnosis rates, nephrology consultation, dialysis, recovery of renal function and death. Patients were randomly assigned to alert group and non-alert group. Alert group could receive popup messages. This study is registered with ClinicalTrials.gov, number NCT02793167.

Results: Between Mar.1 2016 and Jul.31 2016, 5535 patients were screened.318 eligible participants were assigned to the alert group and 623 were assigned to the non-alert group. The diagnosis rate of AKI in alert group was higher than non-alert group(5.6% vs. 2.1%,P=0.004). The expanded AKI (AKI and multiple organ dysfunction syndrome) diagnosis rate was also higher in alert group (11.2% vs. 4.5%,P<0.001). Patients were stratified according to the severity of AKI and different wards. At AKI stage 1, the AKI and expanded AKI diagnosis rates in alert group were higher than non-alert group (AKI: 2.8% vs. 0.8%,P=0.037; expanded AKI: 4.7% and 1.3%, P=0.011). There was no difference at AKI stage 2 and stage 3. Among the different wards, the AKI alert had greater impact on AKI and expanded AKI diagnosis rates in cardiovascular surgery wards(AKI:3.9% vs. 1.2%,P=0.077; expanded AKI:9.0% vs. 2.9%, P=0.003). There was not significantly different in nephrology consultation, dialysis, recovery of renal function or death in the two groups.

Conclusions: Electronic warning system could reduce the misdiagnosis rates of AKI and expanded AKI in high-risk wards. Standard diagnosis rate of AKI was still very low. The electronic alert system for AKI did not improve clinical outcomes in these wards.

Funding: Government Support - Non-U.S.

FR-PO065

Assessment of the Renal Angina Index for Prediction of Severe AKI Prediction in Critically Ill Children

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Background: Acute kidney injury (AKI) occurs in one in four children admitted to the intensive care unit (ICU) and escalating AKI severity is independently associated with increased risk of patient morbidity and mortality. Early prediction of AKI has the potential to improve outcomes.

Methods: We conducted a multi-national, multi-center, prospective study of children admitted to the intensive care unit (ICU) between January-December 2014 with an expected length of stay ≥ 48 hours (NCT01987921). Our primary aim was to assess the performance of fulfillment of renal angina (RA+), a context-driven risk stratification system, on the day of ICU admission (Day_0) for prediction of severe AKI occurrence 3 days after ICU admission (Day_3). The primary outcome was the performance of renal angina for prediction of severe AKI three days after ICU admission (Day_3-severe AKI) by Stage 2-3 AKI KDIGO AKI guidelines. Renal angina was determined at 12 hours into Day_0 using the renal angina index (RAI); RA+ was defined as a RAI ≥ 8. The predictive performance of the Day_0-RAI was compared to changes in serum creatinine (SCr) (measured in the first 12 hours of ICU admission) relative to baseline (Day_0-SCr/Base).

Results: 1590 patients studied were 55% male and median age of 54.5 months. 286 patients (17.9%) were Day_0-RA+, 121 (42.3%) of whom developed Day_3-severe AKI (versus 247 (18.9%) of Day_0-RA- patients, relative risk (RR) 2.23; 95% confidence interval (CI): 1.87-2.66, p<0.001). Patients with Day_3-severe AKI (368, 23.1%) had increased utilization of renal replacement therapy (10.9% vs. 1.5%, p<0.001), and higher rate of Day_{28} mortality (7.6% vs. 4.3%, p=0.01) versus patients without Day_3-severe AKI. Day_0-RA+ demonstrated superior prediction for Day_3-severe AKI than SCr>Base (RR: 1.61; (1.33-1.93), p<0.001) and maintained this superiority with Day3-severe AKI on multivariate regression (independent odds ratio (OR): RA+ 3.21; 95% CI (2.20-4.67) vs. SCr>Base 0.68; 95% CI (0.49-4.94)).

Conclusions: Compared to isolated context-free changes in SCr, the RAI demonstrates improved accuracy for prediction of severe AKI in critically ill children and young adults. Earlier, more accurate prediction of severe AKI has the potential to improve AKI associated patient outcomes.

FR-PO066

Spectrum of AKI in Patients from Low Income Countries Participating in the ISN0by25 Initiative

Etienne Macedo,[4] Sanjib K. Sharma,[3] Ulla Hemmila,[2] Rolando Claure-Del Granado,[5] Jorge Cerda,[1] Emmanuel A. Burdmann,[7] Michael V. Rocco,[8] Ravindra L. Mehta.[6] *[1]Albany Medical College, Albany, NY; [2]College of Medicine, Malawi, Kokemäki, Finland; [3]B P Koirala Institute of Health Sciences, Dharan, Nepal; [4]UCSD, San Diego, CA; [5]Universidad Mayor de San Simon, School of Medicine, Cochabamba, Bolivia, Plurinational State of; [6]University of California San Diego Medical Center, San Diego, CA; [7]University of Sao Paulo Medical School, Sao Paulo, Brazil; [8]Wake Forest School of Medicine, Winston-Salem, NC.*

Background: The ISN0by25 Pilot Project is designed to evaluate the effects of an education and training program, point of care (POC) test and teleconsultation on the detection and management of AKI in low resource settings with the goal of reduce preventable deaths from AKI.

Methods: Study consist of 3 phases: observation, education, training and intervention over 1year. In the observation phase, patients presenting at a health care center (HCC) or hospital ER with signs and symptoms associated with moderate/high AKI risk underwent a serum creatinine (sCR) POC test and a urine dipstick. We assessed progression of AKI, need for RRT, hospitalization, mortality and kidney recovery at 7days, 1, 3 and 6 mo, and compared patient characteristics, management and outcomes.

Results: Of 851 adults enrolled, pt characteristics were different within the 3 countries (Table 1). Dehydration as an AKI risk factor was present in>85% of pts enrolled in Bolivia and Nepal, but only in 38% in Malawi. AKI was diagnosed at enrollment in 48%: 42% KDIGO AKI stage1, 20% stage2 and 38% stage3. Of 778 pts with discharge information, 35% were admitted to the hospital and 55% were observed in a HCC for a maximum of 24 hrs. 58% of patients received PO fluids, 62% IV fluids, 10% diuretics, and 2.7% were dialyzed. Mortality at discharge was 4.3% and increased to 10% at 3 mo. AKI pts had higher mortality rate at discharge (AKI 6% vs. non-AKI 2.5%, p=0.02) and at 3 mo (AKI 13% vs non-AKI 6%, p<0.001).

Conclusions: Risk factors for AKI varied according to the region and local health care delivery. Frequency of AKI and hospitalization were high in patients with high AKI risk across these low resource settings. sCR POC test helped to identify patients with higher risk for worse outcomes. This ongoing study will help to understand the profile of preventable deaths from AKI around the globe.

Funding: Private Foundation Support

Patient characteristics.

	Bolivia (157)	Malawi (316)	Nepal (378)
Age (y)	60(43-74)	38(30-52)	53(35-65)
Comorbidities (%)			
Hypertension	36(23)	38(12)	125(33)
DM	31(20)	24(7)	62(16)
HIV	0	140(44)	2(0.5)
Anemia	15(10)	49(15)	29(8)
CKD	18(11)	1(0.3)	6(1.6)

Values represent median (interquartile range) or number (proportion)

FR-PO067

AKI in Patients Treated for Cancer: A Population-Based Cohort Study

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Background: Patients undergoing treatment for cancer are at increased risk of acute kidney injury (AKI). There are few data on AKI incidence and risk factors in the current era of treatment.

Methods: Using linked administrative datasets, we conducted a population-level cohort study of all patients initiating systemic therapy (inclusive of chemotherapy and targeted agents) for a new cancer diagnosis in Ontario, Canada from 2007 to 2014. The primary outcome was hospitalization with AKI or acute dialysis. We estimated the cumulative incidence of AKI and fitted Cox proportional hazards models (accounting for the competing risk of death), adjusting for demographics, cancer characteristics, comorbidities and co-prescriptions. We modeled exposure to systemic therapy (the 90-day period following each treatment) as a time-varying covariate. We also assessed secular trends in annual AKI incidence according to year of systemic therapy initiation.

Results: We identified 163,071 patients initiating systemic therapy, of whom 10,880 were hospitalized with AKI. The rate of AKI was 27 per 1000 person-years (PY), with 1-, 5-year and overall cumulative incidences of 3.9, 7.8 and 9.3%, respectively. Cancers with the highest 5-year AKI incidence were myeloma (26%), bladder (19%), and leukemia (15%). Advanced stage, pre-existing chronic kidney disease (CKD), and diabetes mellitus (DM) were associated with increased risk of AKI [adjusted hazard ratios (aHR) 1.41 (95%CI 1.28, 1.45), 1.80 (95%CI 1.67, 1.93) and 1.43 (95%CI 1.37, 1.50), respectively]. In patients age ≥66 years, use of diuretics and angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers (ACEi/ARBs) were associated with increased risk [aHR 1.20 (95%CI 1.14, 1.28) and 1.30 (95%CI 1.23, 1.38)]. AKI risk was significantly elevated in the 90 day period following systemic therapy exposure [aHR 2.34 (95%CI 2.24, 2.45)]. The annual incidence of AKI increased over time (from 18 to 52 per 1000-PY between 2007 and 2014).

Conclusions: Cancer-related AKI is common and associated with more advanced stage, CKD, DM and the concomitant receipt of diuretics or ACEi/ARBs. Risk is heightened in the 90 days after systemic therapy. Preventive strategies are needed to address the increasing burden of AKI in this population.

FR-PO068

Assessment of the Pathophysiology of AKI Using Magnetic Resonance Imaging

Huda Mahmoud,[1] Charlotte E. Buchanan,[2] Eleanor Cox,[2] Benjamin L. Prestwich,[2] Maarten W. Taal,[1] Susan Francis,[2] Nicholas M. Selby.[1] *[1]Center for Kidney Research and Innovation, Derby, United Kingdom; [2]Sir Peter Mansfield Imaging Centre, Nottingham, United Kingdom.*

Background: The pathophysiology of Acute Kidney Injury(AKI) in humans is not well delineated, in part due to limitations in current methods of renal imaging. Recent advances in Magnetic Resonance Imaging(MR) allow assessment of structural and functional changes relevant to kidney disease. We performed a multiparametric MR study to assess its utility and reproducibility in patients with AKI.

Methods: We studied 9 patients with AKI stage2/3(with no pre-existing CKD) and 13 healthy volunteers(HV). Patients underwent multiparametric renal MR scans at the time of AKI and 90d later. MR scans were performed on a 3T Philips Ingenia scanner. Structural assessments included renal volume, longitudinal-relaxation time(T_1) and Diffusion-Weighted Imaging(DWI) as markers of fibrosis and/or inflammation. Functional assessments included Arterial Spin Labelling(ASL) to measure renal perfusion and Blood Oxygenation Level Dependant Imaging(BOLD) as an indicator of renal oxygenation.

Results: AKI patients: mean 47±19yrs, baseline creatinine 78±14μmol/L, peak creatinine 467±254μmol/L. All achieved complete biochemical recovery(creatinine 88±17μmol/L) and 5 have had repeat scans at 90d. Renal volumes were significantly increased at time of AKI as compared to HVs(270±92ml vs 189±25ml respectively p=0.001). BOLD T_2*, cortical and medullary T_1 values were significantly increased in AKI patients at the time of injury compared to HVs. 90d post AKI renal volumes had reduced(210±75ml p=0.04), as had T_2*, cortical and medullary T_1 values. T_1 values at 90d remained significantly higher than the HVs(p<0.001).

Conclusions: This is the first study to use multiparametric MR in patients with AKI, assessing kidney function and structure at time of AKI and during recovery. The

increase in renal volumes and T_1 values at time of AKI may be indicate inflammation or oedema. The persistent increase in T_1 at 90d may represent persistent inflammation or fibrosis development. Importantly, persistent MR abnormalities at 90d despite complete biochemical normalisation show the potential of MR to better characterise recovery. Further studies are required to build on this initial pilot work, and determine how best multiparametric MR can be used to characterise the nature of renal injury in AKI and its recovery.

Funding: Private Foundation Support

FR-PO069

Does the Ultrasound Intrarenal Resistive Index Have a Diagnostic and Prognostic Value in Acute Graft Dysfunction? Juan Carlos Ramirez-Sandoval,[2] Monica Chapa,[2] Tábata Cano-Gámez,[3] Elena López-Sosa,[5] Mariana Oria-y-Anaya,[4] E G. Ramírez-Gutiérrez,[3] Luis E. Morales-Buenrostro,[2] Ricardo Correa-Rotter.[1] *[1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, México city, Mexico; [2]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, MEXICO, Mexico; [3]Escuela de Medicina, Universidad Panamericana., Mexico, Mexico; [4]Escuela de Medicina, Universidad Panamericana, Mexico, Mexico; [5]Escuela de Medicina, Universidad Panamericana, México City, Mexico.*

Background: The intrarenal resistive index is commonly employed in kidney transplant recipients (KTR) with acute kidney injury (AKI) yet its clinical usefulness remains controversial. Our objective was to evaluate the prognostic performance of the resistive index in KTR with AKI after 1 year of follow-up. We also analyzed the relation between the index and graft histologic features.

Methods: Retrospective analysis of the resistive index measured at the time of renal graft biopsies performed due to AKI (rise in serum creatinine [SCr] ≥0.3mg/dL from baseline). We excluded KTR with shock, significant renal-artery stenosis, hydronephrosis, and perigraft-fluid collections with marked compression. All KTR were followed for at least 1 year after the AKI event.

Results: 91 KTR with AKI were included: 46 (51%) females, median age 36 yr (IQR 27-48), median time post kidney transplant 5.1 yr (IQR 2.1-9.2), median SCr at AKI 2.5 mg/dl (IQR 2.0-4.3), and 22 (24%) with a severe AKI (AKIN 3). The resistive index of arcuate arteries was higher in 13 (14%) KTR with graft loss caused by AKI as compared to 78 (76%) of KTR without graft loss (0.69± 0.11 Vs. 0.63±0.09 respectively, p=0.047) yet no differences were observed in the resistive index of interlobar or segmental arteries. SCr at AKI diagnosis and age of KTR were associated with a higher resistive index in segmental and arcuate arteries (p=0.002). The resistive index of all measured arteries was not useful to differentiate causes of AKI (Table) and was also not useful to predict graft outcomes (graft survival, requirement of dialysis during AKI episode or eGFR after AKI episode).

Conclusions: The resistive index is time consuming and not useful to define etiology or graft outcomes in KTR with AKI. Our results support that it should not be employed to evaluate acute kidney-graft dysfunction.

Area under the curve in ROC curve for resistive index and AKI etiology

Resistive index	Immunological rejection (n=41)	Acute tubular necrosis (n=8)	Calcineurin toxicity (n=8)
Interlobar	0.57	0.58	0.50
Arcuate	0.50	0.60	0.62
Segmental	0.49	0.53	0.51

*Other causes of aki were mixed [immunological+calcineurin toxicity or BK virus] (n=29), parvovirus (n=1), and prerenal with normal biopsy (n=4).

FR-PO070

AKI Following CABG versus PCI in Advanced CKD Patients Abduzhappar Gaipov,[4] Miklos Z. Molnar,[4] Praveen Kumar Potukuchi,[4] Keiichi Sumida,[2] Oguz Akbilgic,[4] Elani Streja,[1] Connie Rhee,[3] Robert B. Canada,[4] Kamyar Kalantar-Zadeh,[3] Csaba P. Kovesdy.[4] *[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [2]Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; [3]University of California Irvine, School of Medicine, Orange, CA; [4]University of Tennessee Health Science Center, Memphis, TN.*

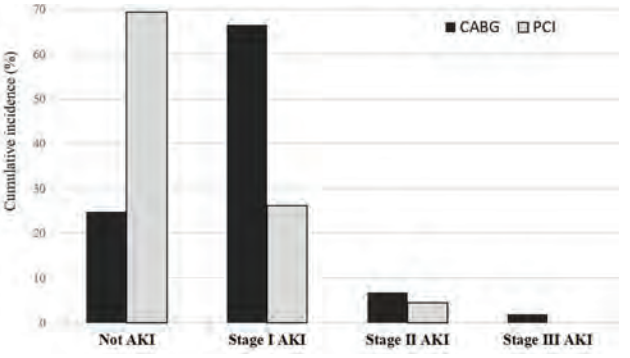
Background: Previous studies reported that GABG is associated with reduced risk of mortality and repeat revascularization in mild-to-moderate CKD, ESRD, and in diabetics. However, the relative risk of acute kidney injury (AKI) associated with CABG vs. PCI in patients with advanced CKD is not clear.

Methods: We examined 655 US veterans with incident ESRD who underwent a first CABG or PCI up to 5 years prior to dialysis initiation. Stages of AKI following the procedures were classified according to the Acute Kidney Injury Network classification. The association of CABG vs. PCI with AKI was examined in multivariable adjusted logistic regression analyses.

Results: 472 patients underwent CABG and 183 patients underwent PCI. Mean age was 63.7 (SD=8.1) years, 99% were male, 76.5% were white, and 21.8% were African Americans. The pre-procedure eGFR and the incidence of AKI in the CABG vs PCI group were 36.4 (IQR=23.5–58.2) vs. 33.2 (IQR=20.6–48.6) ml/min/1.73m^2 and 75.2% vs 30.6%, respectively. The incidence of all stages of AKI were higher after CABG compared to PCI (Figure). CABG was associated with a 5.1-fold higher crude risk of AKI (odds ratio and 95%CI: 5.1, 2.9–8.8; p<0.001), which remained significant after multivariable adjustments (5.2, 2.9–9.2; p<0.001).

Conclusions: CABG was associated with a 5-fold higher risk of AKI compared to PCI in patients with advanced CKD. Despite other benefits of CABG over the PCI, the extremely high risk of AKI associated with GABG should be considered in this vulnerable population when deciding on the optimal revascularization strategy.

Funding: NIDDK Support



FR-PO071

IgG4-Related Disease as a Cause of Urinary Tract Obstruction and AKI: A Case Report Suhaib A. Andrabi,[2] Beenish Noor,[2] Melissa C. Fajardo,[2] Olurntobi Rahaman,[1] Sudhanshu Jain,[2] Jeffrey D. Wallach.[2] *[1]Harlem Hospital Center, New York, NY; [2]Nephrology, Harlem hospital Center, New York, NY.*

Background: IgG4-related disease (IgG4-RD) is a fibroinflammatory condition with multisystem involvement. We report the case of a male admitted for with chronic abdominal pain who was found to have acute kidney injury, retroperitoneal fibrosis and hydroureteronephrosis.

Methods: A 61 year old male presented with a 4-month history of persistent lower abdominal pain, unintentional weight loss of ~15 kg over last year but no urinary complaints. Medical history significant for Hypertension, cerebrovascular accident and chronic kidney disease. Examination findings included a BP 163/101, lower abdomen tenderness and hyper pigmented skin macules on both shins. Initial investigations revealed BUN/Creatinine of 51 /7.9 (previous Creatinine 1.6 one year ago), leukocytosis, severe anemia, and thrombocytosis. Urinalysis was bland. Initial non-contrast Abdominal CT showed bilateral hydroureteronephrosis, perinephric stranding and mid-ureter compression by a soft tissue mass. Also noted was a tissue mass, suspicious for an acute hemorrhage from a aneurysmal infrarenal aorta and retroperitoneal fibrosis. A contrast CT scan ruled out a ruptured aneurysm. The patient underwent IR-guided nephrostomy tubes/stents with subsequent internalization. There was rapid improvement in renal function and Cr stabilized at ~2. The focus then shifted to evaluation of retroperitoneal fibrosis(RPF). Serum IgG4 levels were elevated [258, normal <121]. Flow cytometry showed no evidence oflymphoproliferative disorder or presence of blasts. Steroid therapy was initated. Biopsy of the retroperitoneal mass revealed extensively hyalinized and fibrotic soft tissue without evidence of fibromatosis or malignancy. Immunohistochemical analyses revealed plasma cells including IgG4 positive plasma cells. A renal biopsy was not performed due to hydronephrosis. Given patient's prompt response to treatment, he was discharged to follow up as outpatient.

Results:

Conclusions: IgG4-RD is now recognized as a link between many clinical entities that were previously regarded as organ-specific disorders. Obstructive uropathy occurs in about 45%-65% of reported patients with IgG4-related RPF. Management involves relieving the obstruction, halting progression of the fibrotic process and preventing recurrence. Obstructive uropathy with RPF should prompt a work up for IgG4-RD.

FR-PO072

Biomarkers for the Prediction of AKI Progression after Pediatric Cardiac Surgery Jason H. Greenberg,[4] Michael Zappitelli,[3] Yaqi Jia,[4] Heather Thiessen Philbrook,[4] Christina A. de Fontnouvelle,[4] Francis P. Wilson,[4] Steven G. Coca,[2] Prasad Devarajan,[1] Chirag R. Parikh.[5] *[1]Cincinnati Children's Hospital, Cincinnati, OH; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]McGill University Health Centre, Montreal Children's Hospital, Montreal, QC, Canada; [4]Yale University, New Haven, CT; [5]Yale University and VAMC, New Haven, CT.*

Background: The risk for adverse outcomes dramatically increase as children progress to higher stages of AKI. No reliable methods currently exist to predict AKI progression in hospitalized children.

Methods: The TRIBE-AKI pediatric study is a three-center prospective cohort of children, 1 month to 18 years old, undergoing cardiopulmonary bypass. Urine biomarkers of injury (neutrophil gelatinase–associated lipocalin (NGAL), interleukin (IL) 18 (IL-18), kidney injury molecule 1 (KIM-1), liver fatty acid binding protein (LFABP), albumin) and plasma biomarkers of inflammation (interferon (INF), IL-1, IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, tumor necrosis factor alpha (TNF)) were measured on the first day of serum

creatinine defined AKI. AKI progression was defined as a worsening of AKIN stage; from stage I to stage II or III, from stage II to III, or stage III at any time.

Results: 408 children were enrolled, of which 176 (43%) were diagnosed with AKI. On the first day of AKI, Stage I, Stage II, and Stage III AKI was diagnosed in 145 (36%), 25 (6%), and 6 (1.4%) children, respectively. 28 (7%) children had AKI progression. On the first day of serum creatinine diagnosed AKI, 11/17 biomarkers were significantly higher in patients with AKI progression *vs* without (Table). Urine LFABP among injury biomarkers and plasma IL-8 among inflammatory biomarkers had the highest discrimination for AKI progression [optimism adjusted AUC 0.70 (95% CI:0.58-0.81) and 0.80 (95% CI:0.67-0.90), respectively].

Conclusions: Urine and plasma biomarkers predict AKI progression in children after cardiac surgery. If validated, these biomarkers could be used to improve clinical care and guide enrollment in therapeutic trials of AKI.

Funding: NIDDK Support, Veterans Affairs Support

Table: Biomarkers of AKI Progression

Biomarker	AKI Without Progression (N=148)	AKI With Progression (N=28)	P-value♦	Optimism Adjusted AUC (95% CI)*
Traditional Biomarkers				
Serum Cr Rise (%)	0.67 (0.5, 1)	0.8 (0.58, 1.33)	0.05	0.62 (0.49, 0.74)
Urine Albuminuria (mg/g)	33.2 (13.7, 96.8)	76.3 (32.1, 142.6)	0.05	0.63 (0.48, 0.81)
Kidney Injury Biomarkers				
Urine IL-18 (pg/ml)	40.67 (12.45, 131.05)	79.2 (43.2, 492.9)	0.01	0.67 (0.29, 0.81)
Urine NGAL (ng/ml)	10.36 (4.95, 30.11)	34.13 (12.49, 240.89)	0.02	0.66 (0.43, 0.83)
Urine KIM-1 (ng/ml)	0.63 (0.27, 2.28)	0.95 (0.53, 2.3)	0.27	0.54 (0.40, 0.68)
Urine L-FABP (ng/ml)	32.05 (7.77, 151.53)	257.29 (15.81, 591.98)	0.001	0.70 (0.58, 0.81)
Inflammatory Biomarkers				
Plasma IFN (pg/ml)	2.07 (1.02, 3.69)	1.98 (1.28, 3.96)	0.79	0.51 (0.38, 0.67)
Plasma IL-1 (pg/ml)	0.18 (0.18, 0.18)	0.18 (0.18, 0.22)	0.01	0.56 (0.47, 0.69)
Plasma IL-2 (pg/ml)	0.25 (0.13, 0.48)	0.54 (0.26, 1.05)	0.02	0.66 (0.38, 0.80)
Plasma IL-4 (pg/ml)	0.05 (0.03, 0.12)	0.07 (0.05, 0.17)	0.23	0.57 (0.45, 0.72)
Plasma IL-6 (pg/ml)	18.92 (9.28, 38.79)	33.18 (22.75, 81.44)	0.009	0.69 (0.55, 0.83)
Plasma IL-8 (pg/ml)	22.68 (12.11, 43.23)	63.81 (44.03, 159.9)	<0.001	0.80 (0.67, 0.90)
Plasma IL-10 (pg/ml)	33.66 (5.82, 88.09)	94.3 (34.44, 163.39)	0.03	0.65 (0.50, 0.80)
Plasma IL-12 (pg/ml)	0.1 (0.07, 0.14)	0.15 (0.07, 0.21)	0.07	0.60 (0.39, 0.76)
Plasma IL-13 (pg/ml)	0.44 (0.26, 1.04)	0.55 (0.44, 1.77)	0.02	0.66 (0.49, 0.79)
Plasma TNF (pg/ml)	3.93 (2.85, 5.46)	4.88 (3.89, 6.83)	0.09	0.60 (0.43, 0.76)

♦ p-values obtained by the Kruskal-Wallace test. AUC, area under the curve. SE, standard error. * The optimism corrected AUC was estimated using a bootstrap procedure with 1000 replicates. The model fitted using the bootstrap dataset was applied to the original dataset as well as the bootstrap dataset. The average difference in predictive abilities is the optimism. The average optimism in AUCs was subtracted from the apparent AUC to get the optimism adjusted AUC.

FR-PO073

Evaluation of the Clinical Utility of Urinary Sediment in Predicting Prognosis of AKI Mingfeng Lee,[2] Masahiko Nagahama,[3] Yasuhiro Komatsu.[1]
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Background: Urinary sediment is helpful for differential diagnosis of acute kidney injury (AKI), but evidence is lacking whether urinary sediment findings are related to prognosis of AKI. In this study, we evaluate the relationship between urinary cast and prognosis of AKI.

Methods: We retrospectively collected the data from the patients who developed AKI during hospitalization at our hospital between April 2011 and March 2016. AKI was defined by KDIGO definition (either increase in S-Cr of ≥0.3 mg/dl within 48 hours or ≥50% within 7 days). Known risk factors for AKI, such as baseline CKD stage and comorbidities as well as urinalysis at the time of AKI were obtained. Patients with CKD stage 5, including on maintenance dialysis, received kidney transplantation, or age<18yr were excluded. We set our primary endpoint as "long term prognosis of AKI: recovery of renal function 3 months after AKI", and secondary endpoint as "short term prognosis of AKI: the receipt of renal replacement therapy (RRT) during the hospitalization". Baseline S-Cr level was defined as the lowest outpatient value within 6 months before admission. Risk factors for AKI were sought using univariate and multivariate logistic regression.

Results: We identified 833 patients for the study. The mean age of the patients was 68.4±16 (mean+/-S.D.) yr, the male ratio was 60.6%. Among them, 292 patients (35.1%) showed granular cast at the time of AKI, 51 patients (6.1%) needed RRT during hospitalization and 146 patients (17.5%) showed worsened renal function 3 months after AKI. On multivariate logistic regression analysis, baseline CKD stage was associated with both "long term prognosis of AKI" (OR=2.01, P=0.04) and "short term prognosis of AKI" (OR=8.95, P<0.001). In contrast, the presence of granular cast was associated with "short term prognosis of AKI" (OR=2.9, P=0.001), but was not with "long term prognosis of AKI" (P=0.26).

Conclusions: The presence of granular cast at the time of AKI can predict the need for RRT during hospitalization, but cannot predict recovery of renal function 3 months after AKI. Our study underscores the importance of urinalysis not only for diagnosis but also for "short term prognosis". Baseline renal function affects renal function recovery.

FR-PO074

Urine Injury Biomarker Level before and after AKI: Results from the CRIC Study and CKD Biomarker Consortium Chi-yuan Hsu,[8] Dawei Xie,[15] Xiaoming Zhang,[14] Joseph V. Bonventre,[1] Jing Chen,[7] Paul E. Drawz,[12] Harold I. Feldman,[13] Alan S. Go,[4] Edward J. Horwitz,[6] Paul L. Kimmel,[5] Mitchell R. Lunn,[10] Theodore E. Mifflin,[13] Ana C. Ricardo,[11] Sushrut S. Waikar,[2] Jingrong Yang,[3] Kathleen D. Liu.[9]
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Background: Change in serum creatinine (SCr) estimated glomerular filtration rate (GFR) may underestimate the renal sequelae of AKI since SCr rise after AKI may be blunted due to loss of muscle mass, decreased creatinine production, compensatory increase in single nephron GFR and other factors. Changes in levels of sensitive tubular injury biomarkers may capture more subtle persistent damage to the kidneys following an episode of mild-moderate AKI.

Methods: We studied a subset of Chronic Renal Insufficiency (CRIC) participants enrolled from Kaiser Permanente Northern California (KPNC) who had urine specimen banked as part of annual research study visits. We used data gathered as part of clinical care and captured in the KPNC electronic medical record to define episodes of AKI (peak/nadir inpatient SCr ≥1.5). We measured level of kidney injury molecule-1 (KIM-1) in urine samples collected at the annual CRIC study visit before the AKI episode and urine samples collected at the annual CRIC study visit after the AKI episode. We compared 29 participants with documented AKI (69% with KDIGO severity stage 1; 10% stage 2; 21% stage 3) with 157 participants who did not (matched for calendar year and time gap between first and second measurement [overall mean 419 days]).

Results: Overall, 70% of participants were female; 48% were white/39% black and 70% had diabetes mellitus; mean age was 63 yrs, eGFR 49 ml/min/1.73m^2 and urine albumin/Cr ratio (ACR) 21 mg/mg. Although there were no change in eGFR or ACR from pre-AKI to post-AKI (Table), rise in urine KIM-1/Cr was greater for patients who had AKI vs. those who did not (median delta 381 vs. 46 ng/g; p<0.002)(Table).

Conclusions: These data suggests there is persistent tubular injury months after an episode of mild to moderate AKI.

Funding: NIDDK Support

	Non-AKI	AKI	p-value
Change in eGFR, ml/min/1.73m2, median [IQR]	0 [-4, 5]	-1 [-5, 4]	0.417
Change in ACR, mg/gm, median [IQR]	2 [-5, 14]	2 [-9, 87]	0.650
KIM-1/Cr pre-AKI, ng/g, median [IQR]	524 [311, 952]	804 [452, 1463]	0.026
KIM-1/Cr post-AKI, ng/g, median [IQR]	581 [365, 1009]	1053 [555, 2864]	0.002
Change in KIM-1/Cr, ng/g, median [IQR]	46 [-246, 293]	381 [-107, 1264]	0.019

FR-PO075

Persistent Elevation of Biomarkers of Dysregulated Mineral Metabolism and Inflammation after AKI: The ASSESS-AKI Study Kathleen D. Liu,[6] Chi-yuan Hsu,[6] Thida C. Tan,[2] Valerie Arends,[8] Amy Saenger,[8] Chirag R. Parikh,[11] Talat Alp Ikizler,[10] Jonathan Himmelfarb,[3] Mark M. Wurfel,[12] Vernon M. Chinchilli,[5] Paul L. Kimmel,[4] James S. Kaufman,[9] Alan S. Go.[2]
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Background: AKI is associated with dysregulated mineral metabolism and inflammation. However, it is unknown if these abnormalities persist after AKI.

Methods: ASSESS-AKI is a parallel cohort study of hospitalized patients with and without AKI enrolled in 2009-2015, with matching based on center, age, baseline chronic kidney disease status, diabetes mellitus, prior cardiovascular disease, baseline eGFR, and ICU/non-ICU status during the index admission. Plasma biospecimens were collected at the index hospitalization (V0) and at the first outpatient 3-month study visit (V3).

Results: Mean age of the 1,484 participants analyzed was 55 yr and 48% were women. Baseline eGFR (from prior to the index hospitalization) was 69 mL/min/1.73m^2. Compared to non-AKI patients, levels of parathyroid hormone (PTH), phosphorus, fibroblast growth factor-23 (FGF-23) and C-reactive protein (CRP) and were higher in AKI patients at both V0 and V3 (and higher among those with more severe AKI) (p< 0.001 for all comparisons). At V3, FGF-23 and phosphorus levels increased in both AKI and non-AKI participants, whereas CRP fell markedly (Table). In those with AKI,

PTH levels fell modestly from V0 to V3, whereas there was no difference in non-AKI participants.

Conclusions: Markers of dysregulated mineral metabolism and inflammation are elevated during an episode of AKI; among these biomarkers, FGF-23 remains elevated months later. These raise the possibility that persistently dysregulated mineral metabolism may link AKI to adverse outcomes after hospital discharge.

Funding: NIDDK Support

	V0 : AKI	V3: AKI	P value	V0: No AKI	V3: No AKI	P value
PTH	65 (41-103)	54 (38.5-81)	< 0.0001	48 (35-68.5)	47 (36-62)	0.17
Phosphorus	3.1 (2.5-3.9)	3.6 (3.2-4)	< 0.0001	2.8 (2.4-3.4)	3.5 (3.1-3.9)	< 0.0001
FGF-23	42.2 (20.7-88.7)	66.5 (48.9-97.6)	< 0.0001	30.8 (18.6-48.7)	57.6 (45.6-78.5)	< 0.0001
CRP	118 (40-213)	4.3 (1.8-10.5)	< 0.0001	84.9 (18.5-173)	3.0 (1.3-6.3)	< 0.0001

FR-PO076

A Novel Biomarker for Detecting Both AKI and CKD Andrea Sanchez-Navarro,[3] Rosalba Pérez-villalva,[2] Juan M. Mejia-Vilet,[1] Nadyeli Linares,[2] Norma Bobadilla.[3] *[1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico; [2]Molecular Physiology Unit, México, Mexico; [3]Molecular Physology Unit, MEXICO, DF, Mexico.*

Background: The early diagnosis of AKI and CKD undoubtedly will have a potential impact on the treatment of these pathologies and on the kidney health. This study was designed to provide a suitable method for overcoming the limitations of the procedures or methods previously used for the AKI and CKD diagnosis.

Methods: Abnormal presence of serpinA3K in urine samples from animals with CKD was identified by mass spectrometry. We evaluated the urinary serpinA3K in rats and in patients with AKI, as well as, the temporal course of serpinA3K presence during the AKI to CKD transition and in urines from patients previously diagnosed with CKD by renal biopsy and without renal dysfunction. For AKI model, 44 Wistar rats were divided in different periods of reperfusion: 3, 6, 9, 12, 18, 24, 48, 72, 96, or 120 h after renal bilateral ischemia (45 min) and compared to sham-operated rats; in addition, 20 rats were studied to evaluate different renal injury severity induced by 15, 30, 45 or 60 min of ischemia. For CKD model, 36 rats were divided in: sham operated (S) or nephrectomy plus left renal ischemia of 45 min (UNx+IR) groups; these rats were studied 1, 2, 3, or 4 months. Mean arterial pressure, creatinine clearance, and renal blood flow were determined. Urinary serpinA3K was evaluated in all these rats and in the urines from patients diagnosed with AKI or CKD.

Results: SerpinA3K was not detected in the urines from sham rats or healthy volunteers. In contrast, serpinA3K appeared in the rat urines and it increased proportionally to the AKI severity. This protein was detected since 3 h post-ischemia. Accordingly, abnormal urinary serpinA3K was found in patients with AKI. After 4 months, the UNx+IR rats developed CKD characterized by a progressive proteinuria, renal dysfunction and tubulointerstitial fibrosis. Interestingly, urinary serpinA3K, was detected since the 1st-month and progressively increased in the follow-up and correlated with the tubulointerstitial fibrosis. In CKD patients, urinary serpinA3K was significantly elevated without changes in serum creatinine.

Conclusions: We demonstrated that urinary serpinA3K is a promising and early biomarker to detect AKI, AKI to CKD transition and CKD from different etiologies. In addition, this biomarker could detect renal injury before renal dysfunction.

Funding: Government Support - Non-U.S.

FR-PO077

A Mechanism for Interstitial Nephritis Associated with "Checkpoint" Blockade: Unleashing Renal Microvascular Endothelial Cell (RMEC) Secondary Signals for T Cell Activation Kimberly A. Muczynski, Bairbre A. McNicholas, Susan K. Anderson, Maria E. Danoviz. *Medicine-Nephrology, University of Washington, Seattle, WA.*

Background: T cell activation is a two-step process: 1) T cell receptor recognition of an antigenic peptide presented by a HLA molecule; and 2) engagement of activating secondary signal molecules. The second step is actually more complex because antigen presenting cells may have both stimulatory and inhibitory molecules for T cell activation. A new approach for treating metastatic cancer is to block inhibitory second signals such as the programmed death-1 (PD-1) pathway, allowing T cells greater activation and killing of a tumor. We and others have identified cases of interstitial nephritis in patients treated with the new "checkpoint" blockers (eg nivolumab, pembrolizumab). Other work in the lab identified high levels of HLA class II molecules on RMEC of normal kidneys without inflammation. We have been puzzled by this due to the potential exposure of RMEC to circulating peptides; and we found that isolated RMEC activate T cells in a class II-peptide dependent manner. We hypothesize that RMEC express inhibitory second signals which limit their ability to activate T cells.

Methods: Ex-vivo renal T cells and RMEC from normal human kidneys were evaluated by flow cytometry for expression of inhibitory and stimulatory second signal molecules. An assay was developed using CD3-activated T cells with isolated RMEC to assess the role of second signal molecules.

Results: RMEC express activating secondary signal molecules CD58 and CD275; and inhibitory molecules CD274 (PDL1), CD273 (PDL2), CD276 (B7-H3) and B7-H4. Intrarenal T cells in normal human kidney express CD28, CD2, CD274 (PDL1) and CD279 (PD1). Blockade of PD-1 or its ligands, or B7-H4 enhance T cell activation measured as cytokine release and expression of CD69. Blockade of CD58 or CD2 decreases T cell activation.

Conclusions: A unifying interpretation of results is that RMEC, while capable of activating T cells when the appropriate peptide is presented, limit the strength of the response by the PD-1 pathway. Blocking the PD-1 pathway with checkpoint agents unleashes RMEC's stimulatory second signal molecules creating the potential for inflammation when there is an appropriate signal 1. We suggest interstitial nephritis develops when a RMEC-T cell signal 1 is engaged in the presence of checkpoint blockade.

Funding: Private Foundation Support

FR-PO078

Knockout of Interleukin-36 Receptor Protects Against Renal Ischemia-Reperfusion Injury through Reduction of Proinflammatory Cytokines Hirofumi Nishikawa, Tomohiro Eguchi, Masami Ogasawara, Tatsuki Matsumoto, Kazu H. Ode, Yoshiko Shimamura, Kosuke Inoue, Yoshinori Taniguchi, Taro Horino, Yoshio Terada. *Kochi University, Nankoku, Japan.*

Background: IL-36, a newly named member of the IL-1 cytokine family, includes 3 isoforms, IL-36α, IL-36β, and IL-36γ, all of which bind to a heterodimer containing IL-36 receptor (IL-36R). Little is known about the role of the IL-36 axis in acute kidney injury (AKI) pathogenesis. We examined IL-36 function using mice AKI model and clinical samples.

Methods: We evaluated IL-36 function in the bilateral renal ischemia-reperfusion injury (IRI) AKI model by using IL-36R knockout (KO) and wild-type (WT) mice. We at first evaluate the localization of IL-36R in WT mice kidney by confocal microscopy. The effects of IL-36α on NF-kB and Erk activities were examined in primary cultured renal tubular cells. In clinical study, we measured urine IL-36α in AKI patients, and immunohistological examination of IL-36α in AKI and minimal change renal biopsy sample.

Results: IL-36R was found to be expressed in the kidney mainly in proximal tubules. IL-36R KO mice had significantly lower PCr (0.41+0.12 versus 1.08 + 0.21 mg/dl), BUN (65.3+14.8 versus 158+31.5 mg/dl) and IL-6 (24.3 + 5.7 versus 39.6+7.9 pg/ml) at 24h after IRI compared to WT mice. Immunohistological examination showed mild tubular injury in IL-36R KO mice. IL-36α/β/γ levels were increased after IRI, and IL-36α was expressed in lymphocytes and renal tubular cells, but post-IRI mRNA levels of IL-6 and TNF-α were low in IL-36R KO mice. We found that IL-36R expression in radioresistant renal tubule-resident cells, but not hematopoietic bone marrow-derived cells, was essential for IRI pathology by bone marrow chimeras experiments. In primary cultures of renal tubular epithelial cells, IL-36α treatment upregulated NF-κB activity and Erk phosphorylation. Notably, in AKI patients, urine IL-36α levels were increased, and IL-36α staining in renal-biopsy samples was enhanced.

Conclusions: Our results demonstrate that IL-36α is upregulated in renal tissues in both mouse and human AKI, and that IL-36α stimulates NF-κB and Erk pathways and might induce cytokines such as IL-6 and TNF-α in AKI. Thus, IL-36α/IL-36R blockage could serve as a potential therapeutic target in AKI.

FR-PO079

Treatment with PD-1 Inhibitor Associated with AKI and Hypocalcemia: A Meta-Analysis of Clinical Trials Sandhya Manohar,[2] Panagiotis Kompotiatis,[2] Charat Thongprayoon,[1] Wisit Cheungpasitporn,[2] Sandra Herrmann.[2] *[1]Bassett Medical Center, Cooperstown, NY; [2]Mayo Clinic, Rochester, MN.*

Background: Programmed cell death protein 1 (PD-1) inhibitors, Nivolumab and Pembrolizumab, are novel agents approved for use in many cancers. However, their renal safety profiles have not yet been systematically studied. The objective of this meta-analysis was to assess the risks of electrolyte abnormalities and nephrotoxicity in patients treated with PD-1 inhibitors.

Methods: A literature search was performed using MEDLINE, EMBASE and Cochrane Database from inception through April 2017. We included clinical trials that monitored electrolyte levels and kidney functions during treatment with PD-1 inhibitors. Pooled risk ratio (RR) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method. The protocol for this study is registered with PROSPERO (CRD42017060579).

Results: 48 clinical trials (with a total of 11,482 patients), which had electrolytes and/or serum creatinine monitored, were enrolled. The overall pooled RRs of acute kidney injury (AKI) and electrolyte abnormalities in patients treated with PD-1 inhibitors were 1.86 (95% CI, 0.95-3.64) and 1.67 (95% CI, 0.89-3.12), respectively. Compared with non-nephrotoxic controls, the pooled RR of AKI in patients treated with PD-1 inhibitors was 4.19 (95% CI, 1.57-11.18). Pre-specified subgroup analysis demonstrated a significant association between PD-1 inhibitors and hypocalcemia with pooled RR of 10.87 (1.40-84.16). The pooled estimated incidence rates of AKI and hypocalcemia in patients treated with PD-1 inhibitors were 2.2% (95%CI: 1.5%-3.0%) and 1.0% (95%CI: 0.6%-1.8%). Among patients who developed AKI with PD-1 inhibitors, the pooled estimated rate of interstitial nephritis was 16.6% (95%CI: 10.2%-26.0%). When hypocalcemia occurred after treatment with PD-1 inhibitors, the pooled estimated rate of severe hypocalcemia was 13.0% (95%CI: 3.3%-39.4%).

Conclusions: Based on the findings of our meta-analysis, treatment with PD-1 inhibitors is associated with higher risk of AKI compared with non-nephrotoxic agents. Interstitial nephritis can occur 16.6% in patients with AKI following treatment with PD-1 inhibitors. In addition, treatment with PD-1 inhibitors is also associated with hypocalcemia.

FR-PO080

Vancomycin-Associated AKI Geeta G. Gyamlani,[3] Praveen Kumar Potukuchi,[3] Oguz Akbilgic,[3] Melissa Soohoo,[2] Elani Streja,[2] Keiichi Sumida,[1] Kamyar Kalantar-Zadeh,[2] Miklos Z. Molnar,[3] Csaba P. Kovesdy.[3] *[1]Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; [2]University of California Irvine, School of Medicine, Orange, CA; [3]University of Tennessee Health Science Center, Memphis, TN.*

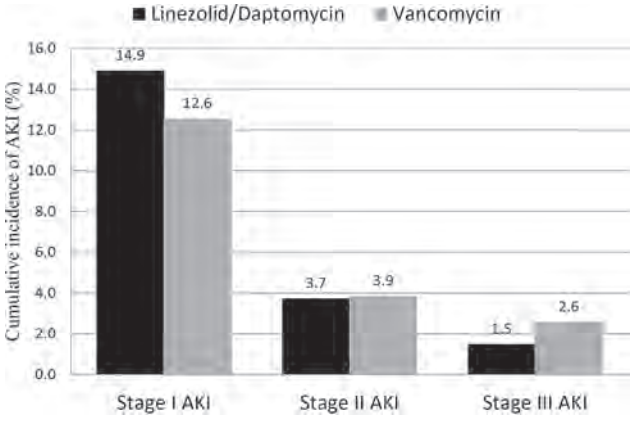
Background: Vancomycin is a tricyclic glycopeptide antibiotic that is currently the mainstay of therapy for serious infections due to methicillin-resistant staph aureus. Data on the nephrotoxic potential of this agent is still highly controversial and based on small studies and meta-analyses.

Methods: From a nationally representative cohort of >3.5 million US veterans with baseline eGFR ≥60 ml/min/1.73m², we identified 40,059 patients who received either intravenous vancomycin (N=24,461) or nonglycopeptide antibiotics (linezolid/daptomycin, N=15,598). We matched patients in the two groups by propensity scores calculated from patient demographics, comorbidities, baseline eGFR and mean arterial pressure, and nephrotoxic medication exposure. Associations of vancomycin vs. nonglycopeptides with the risk of incident AKI by AKIN stages was assessed in logistic regressions.

Results: Among 27,964 propensity-matched patients (13,982 in both groups), the mean age was 66±11 years and the mean baseline eGFR was 72 ml/min/1.73m², 97% were male, 20% African-American, 51% diabetic, 27% had CHF and 8% received vasopressors. Baseline characteristics were identical in patients receiving vancomycin and nonglycopeptides. There were a total of 2,656 (19%) AKI events in the vancomycin group and 2,814 (20%) in the nonglycopeptide group. AKI stage 1 was less common, but stage 3 was more common among patients on vancomycin (Figure). The odds ratios of AKI stages 1, 2 and 3 in patients on vancomycin vs. nonglycopeptides were 0.83 (0.78-0.89), 1.02 (0.90-1.15) and 1.71 (1.44-2.03), respectively.

Conclusions: Vancomycin use is associated with a higher risk of severe AKI.

Funding: NIDDK Support



FR-PO081

Preoperative Renin-Angiotensin System Inhibitors Increased AKI after Noncardiac Major Surgery Hyunjeong Cho,[3] Seokwoo Park,[3] Sejoong Kim,[1] Dong Ki Kim,[3] Kook-Hwan Oh,[3] Kwon Wook Joo,[3] Yon Su Kim,[2] Hajeong Lee.[2] *[1]Seoul National University Bundang Hospital, Seongnam, GYEONGGI-DO, Republic of Korea; [2]Seoul National University College of Medicine, Seoul, Republic of Korea; [3]Seoul National University Hospital, Jongno- gu, SEOUL, Republic of Korea.*

Background: Many conflicting results have been reported on the association between preoperative renin-angiotensin system (RAS) inhibitors and postoperative acute kidney injury (AKI). In this study, we evaluated the impact of RAS inhibitors on postoperative AKI and mortality after noncardiac major surgery.

Methods: We analyzed a retrospective cohort of 50,897 adult patients (age≥18) underwent noncardiac major surgery from 2004 to 2013. Major surgery was defined as surgery duration more than 1 hour. Patients with chronic kidney disease (CKD) 5, nephrectomy and kidney transplantation were excluded. The primary outcome was postoperative AKI defined by the KDIGO creatinine criteria and initiation of dialysis within 14 days of surgery. The secondary outcomes were all-cause mortality within 30 days of surgery and length of hospital stay. Propensity scores matching and multivariable logistic regression analyses were performed.

Results: The patient mean age was 54.3 years, 44.5% were males. In overall, 2,686 (5.3%) patients developed AKI events after operation. RAS inhibitors were used in 1,486 patients. After propensity score matching, 2,955 patients were divided into two groups: using (n=1,469) or not using (n=1,486) preoperative RAS inhibitors. There were no differences in baseline parameters, including age, sex, body mass index, CKD stage, history of diabetes and the American Society of Anesthesiologists physical status. Preoperative RAS inhibitor use was associated with 50% higher risk of postoperative AKI (adjusted relative risk (RR): 1.501; 95% confidence interval (CI): 1.103-2.044; P = 0.01) after adjusting for potential confounders. In addition, RAS inhibitor use was related to prolonged hospitalization (P = 0.000). The 30-day mortality rate was 0.6%, with no significant difference between RAS inhibitor use and non-use (P = 0.149).

Conclusions: This large cohort study demonstrates that preoperative RAS inhibitors were associated with a higher risk of AKI, but not mortality. Withholding preoperative RAS inhibitors should be considered in the perioperative setting.

FR-PO082

Factors Associated with the Development of AKI in Patients Treated with Tenofovir Disoproxil Fumarate – The AKIT Study Adrian Liew,[1,2] Ru S. Lim,[1] See Cheng Yeo.[1] *[1]Renal Medicine, Tan Tock Seng Hospital, Singapore, Singapore; [2]Lee Kong Chian School of Medicine, Nanyang Technological University-Imperial College London, Singapore, Singapore.*

Background: Acute kidney injury (AKI) from renal tubular mitochondrial toxicity had been reported with Tenofovir Disoproxil Fumarate (TDF) treatment. Whilst impaired baseline renal function had been consistently found to be associated with TDF-related AKI, studies looking at other predictors for renal dysfunction had demonstrated conflicting results. The current study aims to determine the risk factors for the development of AKI in the largest known cohort of Asian patients undergoing TDF treatment for HIV and/or Hepatitis B (HBV).

Methods: This is a retrospective cohort study of 1700 patients treated with TDF from 2006-2015. AKI was identified using KDIGO definition, and time to AKI was defined as time from TDF initiation to renal dysfunction or when censored. Risk factors for AKI were compared using Cox regression, between patients who developed AKI and in whom renal function remained stable.

Results: Of the 1700 patients in the study population (87% Males, 75% Chinese, Age 44.5±12.6 years), TDF was initiated for treatment of HBV (n=185; 10.8%), HIV (n=1412; 83.1%) or HBV-HIV co-infection (n=103; 6.1%). AKI occurred in 226 (13.3%) patients, with a median time to AKI of 23.5 months. Risk factors for AKI included older age (HR=1.028, 95%CI [1.016, 1.039], p<0.0001), lower weight (HR=0.984, 95%CI [0.974, 0.995], p=0.004), diabetes (HR=2.000, 95%CI [1.405, 2.849], p<0.0001), hypertension (HR=1.823, 95%CI [1.349, 2.464], p<0.0001), Charlson score (HR=1.217, 95%CI [1.104, 1.342], p<0.0001), use of ACE-inhibitors (HR=2.125, 95%CI [1.420, 3.180], p<0.0001) and diuretics (HR=2.894, 95%CI [1.484, 5.643], p=0.002), and lower CD4 counts (HR=0.997, 95%CI [0.996, 0.998], p<0.0001). A lower baseline serum creatinine below 75umol/L appears to be protective (HR=0.936, 95%CI [0.924, 0.949], p<0.0001) whilst creatinine levels above 75umol/L increases the risk of AKI (HR=1.012, 95%CI [1.006, 1.018], p<0.0001).

Conclusions: AKI is not uncommon with TDF use. The incidence and association with impaired baseline renal function are consistent with published literature, though the threshold creatinine level of 75umol/L is a new finding. Predictors of a frail health state and factors that may affect baseline renal function appears to increase the risk of AKI. The use of ACE inhibitors and diuretics with TDF-associated AKI requires further investigation.

FR-PO083

Utility of a Vascularized Microphysiological 3D Model of Human Kidney Proximal Tubule for Predictive Tenofovir Toxicity Testing Ranita S. Patel,[3] Jonathan Himmelfarb,[1] Edward J. Kelly.[2] *[1]Kidney Research Institute, Seattle, WA; [2]University of Washington, Seattle, WA; [3]Seattle Children's Hospital, Seattle, WA.*

Background: Tenofovir is a nucleotide reverse transcriptase inhibitor indicated for the treatment of HIV/AIDS and chronic hepatitis B and used worldwide. Despite its widespread use, nephrotoxic side effects of tenofovir remain a concern. Following exposure to tenofovir in animal and human subjects, clinical markers of kidney injury are increased and associated pathophysiological changes in the kidney proximal tubule are observed. Since tenofovir enters proximal tubule cells via organic anion transporters (OAT) localized to the basolateral membrane and because cells in 2-dimensional cultures often fail to polarize, *in vitro* cellular toxicity studies have been unsuccessful.

Methods: Primary human proximal tubule cells (PTECs) and human umbilical vein endothelial cells (HUVECs) were cultured in dual channel 3-dimensional microphysiological systems (MPS) to simulate a vascularized proximal tubule for evaluation of tenofovir-induced toxicity. Probenecid, an OAT competitive inhibitor, was added to the HUVEC (vascular) channel in select MPS to assess its role in attenuating tenofovir influx and toxicity. Renal injury biomarkers were used to determine the severity of cellular damage: heme oxygenase-1 (HO-1) signal intensity was quantified following immunocytochemistry and kidney injury molecule-1 (KIM-1) effluent concentrations were measured by ELISA.

Results: Exposure of MPS cultured PTECs from three different tissue donors to 10μM tenofovir for 48 hours induced a 0.9-fold, 4-fold, and 7-fold rise in KIM-1 expression. When 2mM probenecid is concurrently added to the MPS vascular channel, only a 0.5-fold and 2-fold rise in KIM-1 expression is observed. Exposure of MPS cultured PTECs to 100μM tenofovir for 5 days resulted in HO-1 signal intensity 1.8 times that of controls.

Conclusions: These results suggest that our dual channel MPS can function as an ideal *ex vivo* model to investigate transporter-dependent toxicity. Future efforts include directly inhibiting tenofovir toxicity with the OAT-1 inhibitor probenecid in both HUVEC and PTEC channels to affect both basolateral membrane OATs and apical membrane MRP transporters. Additionally, measurement of drug concentration differentials across HUVEC and PTEC channels can confirm active tubular transport since the HUVEC channel acts as a surrogate capillary for tenofovir infusion.

Funding: Other NIH Support - UH3TR000504

FR-PO084

Supratherapeutic Vancomycin Levels: Risk Factors and Outcomes Reza Zonozi,[1] Aozhou Wu,[2] Jung-Im Shin,[2] Alex M. Secora,[2] Josef Coresh,[2] Alex R. Chang,[3] Morgan Grams.[1,2] *[1]Department of Medicine, The Johns Hopkins University, Baltimore, MD; [2]Department of Epidemiology, The Johns Hopkins University, Baltimore, MD; [3]Geisinger Medical Center, Danville, PA.*

Background: Vancomycin is a commonly administered intravenous (IV) antibiotic, and supratherapeutic levels of vancomycin may be an avoidable cause of nephrotoxicity. The objective of this study was to investigate the frequency of, risk factors for, and outcomes after elevated levels of vancomycin.

Methods: There were 31,316 hospitalizations in which IV vancomycin was given between 2008 and 2014 among 21,166 people in the Geisinger Health System, a large, integrated, tertiary, rural health care system.

Results: There were 12,713 hospitalizations with vancomycin monitoring, and 1.24% of these hospitalizations had a vancomycin level >50 mg/L. Among hospitalizations with >7 days duration of therapy, 2.65% had a vancomycin level >50 mg/L. The risk of vancomycin levels >50 mg/L was higher with younger age, female sex, black race, pre-hospitalization diuretic use, an ICU stay, sepsis, concurrent use of piperacillin-tazobactam, and higher doses of vancomycin (Table). Neither BMI nor eGFR was associated with vancomycin levels >50 mg/dL in adjusted analysis. Length of stay, acute kidney injury (AKI), and in-hospital mortality were all higher among persons with vancomycin levels >50 mg/L.

Conclusions: We identified modifiable risk factors for Vancomycin levels >50 mg/L, which were associated with greater in-hospital mortality, AKI, and length of stay.

Funding: NIDDK Support

Adjusted Incidence Rate Ratio (IRR) of High Vancomycin Levels (>50 mg/L)

Predictor	IRR (95% confidence interval)	P-value
Age, per 10 years	0.76 (0.68 to 0.84)	<0.001
Sex (female)	1.40 (1.00 to 1.94)	0.049
Race (Black)	2.04 (1.00 to 4.15)	0.049
eGFR		
Spline < 60	1.02 (0.86 to 1.21)	0.85
Spline ≥ 60	1.09 (0.94 to 1.27)	0.243
ICU	1.90 (1.33 to 2.71)	<0.001
Sepsis	1.75 (1.26 to 2.42)	0.001
Use of pre-hospitalization diuretics	1.48 (1.00 to 2.19)	0.048
Concurrent use of piperacillin-tazobactam	1.44 (1.04 to 2.00)	0.029
Vancomycin dose (mg)		
≤1000	1 (ref)	-
1000-1500	2.83 (1.74 to 4.59)	<0.001
1500-2000	3.02 (1.76 to 5.18)	<0.001
>2000	3.08 (1.75 to 5.44)	<0.001

FR-PO085

Proton Pump Inhibitor Use and Risk of AKI: A Meta-Analysis of Observational Studies Yi Yang,[3] Gang Xu,[2] Shuwang Ge.[1] *[1]Tongji Hospital, Huazhong University of Science and Technology, WUHAN, China; [2]Tongji Hospital, Tongji Medical College, Huazhong Univ of Science and Technology, WUHAN, China; [3]Tongji hospital affiliated to Tongji medical college, Huazhong University of Science and Technology, Wuhan, Hubei, China, Wuhan, China.*

Background: Recent studies have suggested a potential increased risk of acute kidney injury (AKI) among proton pump inhibitor (PPI) users. However, the present results are conflicting. Thus, we performed a meta-analysis to investigate the association between PPI therapy and the risk of AKI.

Methods: EMBASE, PubMed, Web of Science and Cochrane Library databases (up to September 23, 2016) were systematically searched for any studies assessing the relation between PPI use and risk of AKI. Studies that reported relevant relative risks (RRs), odds ratios or hazard ratios were included. We calculated the pooled relative risks with 95% confidence intervals (CI) using a random effects model of the meta- analysis. Subgroup analysis was conducted to explore the source of heterogeneity.

Results: Seven observational studies (five cohort studies, two case-control studies) were identified and included, and a total of 513,696 cases of PPI use among 2,404,236 participants were included in the meta-analysis. The pooled adjusted RR of AKI in patients with PPIs use was 1.61 (95% CI, 1.16–2.22; I^2=98.1%). Furthermore, higher risks of AKI were found in several subgroups of cohort studies, participant's average age < 60 years, participants with and without baseline PPI excluded, sample size < 300,000, and number of adjustments ≥ 11. Subgroup analyses revealed that participants with or without baseline PPI excluded might be a source of heterogeneity.

Conclusions: PPI use could be a risk factor for AKI and should be administered carefully. Nevertheless some confounding factors might impact the outcomes. More well-designed prospective studies are needed to clarify the association.

Funding: Government Support - Non-U.S.

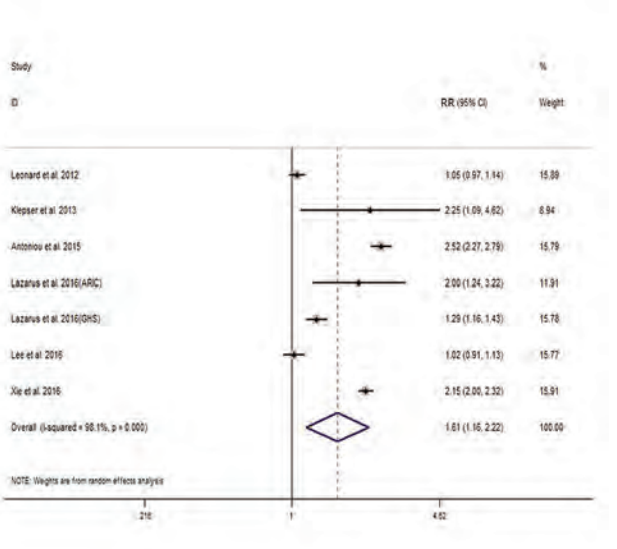


Figure 2 association between proton-pump inhibitors use and risk of acute kidney injury

FR-PO086

Renal Toxicities of Agents Used for CLL Rimda Wanchoo,[2] Vipulbhai Sakhiya,[2] John F. Katsetos,[3] Nishita Parikh,[2] Carolina Bernabe,[3] Jacqueline Barrientos,[1] Kenar D. Jhaveri.[2] *[1]CLL Research and Treatment Center, Lake Success, NY; [2]Nephrology, Hofstra Northwell School of Medicine, GREAT NECK, NY; [3]Heme/Onc, Hofstra Northwell School of Medicine, Lake Success, NY.*

Background: Drugs with novel mechanisms of action and targeted therapies are being explored in both the pre-clinical and clinical settings for chronic lymphocytic leukemia (CLL). A possible limiting complication for these agents could be their nephrotoxic potential.

Methods: We reviewed the FDA adverse event reporting system (FAERS) quarterly legacy data file 3rd quarter of 2014 to 2nd quarter of 2017 for all recently approved targeted agents for CLL. Well established chemotherapy agents used in CLL such as cyclophosphamide and fludarabine were excluded. The adverse event terms queried were: hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, hypocalcemia, hypercalcemia, hyperkalemia, hypernatremia, hyperphosphatemia, proteinuria, renal failure acute, acute kidney injury, tumor lysis syndrome(TLS), hypertension, and nephritis. We reviewed the literature using pubmed, case series and the registrational studies of these agents for any reported nephrotoxicity. We compared renal toxicities of the newer agents such as ibrutinib, idelalisib, obinutuzumab, and venetoclax(to older targeted agents such as alemtuzumab and ofatumumab).

Results: The table here summarizes the drugs studied and results found. Ofatumumab, alemtuzumab and ibrutinib were the top three offenders with AKI as the most common finding reported followed by TLS and hyponatremia. The newer agents used to treat CLL had fewer renal toxicities than the older agents. The mechanism of AKI is likely related to TLS in most of these agents. The literature reviewed in the FAERS reported additional toxicities of the newer agents such as TLS with venetoclax that was fatal leading to early trial modifications.

Conclusions: Novel targeted agents are changing the CLL treatment paradigm with ensuing reports of nephrotoxic events such as AKI and TLS. As these drugs become more widely used, knowledge of novel agents used in CLL and their possible renal toxicities is important for the practicing nephrologists and the hematologists.

Table

Name	Renal injury	Hyponatremia	Hypokalemia	Hypophosphatemia	Hypomagnesemia	Hyperkalemia	Proteinuria	Tumor Lysis Syndrome	Grand Total
Alemtuzumab	25	4	0	0	0	0	3	1	33
Ofatumumab	29	7	6	0	0	3	0	16	61
Ibrutinib	9	9	5	4	1	3	0	6	37
Idelalisib	4	1	2	0	0	3	0	8	18
Obinutuzumab	10	0	0	1	0	1	0	8	20
Venetoclax	0	4	0	0	0	0	0	2	6

FR-PO087

AKI in Heart Failure Hospitalizations – National Trends and Outcomes Ankit Sakhuja, Kianoush Banaei-Kashani, Robert C. Albright. *Mayo Clinic, Rochester, MN.*

Background: Heart failure (HF) is an important cause of morbidity and mortality. Dialysis requiring acute kidney injury (AKI-D) is associated with worse outcomes in HF, however, longitudinal trends of AKI-D and its impact on mortality are unclear.

Methods: Using Nationwide/National Inpatient Sample from years 2000-2014, we identified patients with primary discharge diagnosis of HF and those with AKI-D by ICD-9-CM codes. We used linear regression to assess trends of AKI-D and multivariable regression models to estimate adjusted odds of AKI-D and mortality over time. Model for AKI-D was adjusted for patient age, sex, race, payer, admission day, history of peripheral vascular disease, coronary artery disease, hyperlipidemia, stroke, diabetes, chronic kidney disease, hypertension, presence of cardiogenic shock, use of balloon pump, mechanical ventilation, hospital location, teaching status, volume, bed-size and region. Model for mortality was also adjusted for AKI-D and interaction between year and AKI-D.

Results: Of 15,092,707 HF hospitalizations, 149,468 (0.99%) had AKI-D. Patients with AKI-D were <80 years old (77% vs 60.5%; p<0.001), males (55.6% vs 47.8%; p<0.001) and whites (70.5% vs 60.0%; p<0.001). Incidence of AKI-D increased from 0.5% in 2000 to 1.5% in 2014 (p<0.001 for trend). Odds of developing AKI-D steadily increased to nearly 4 times by year 2014 (Fig 1a). Though, odds of mortality due to AKI-D decreased steadily, AKI-D continued to be independently associated with 3.67 times higher mortality even by year 2014 (Fig 1b).

Conclusions: AKI-D is seen in about 1% HF hospitalizations, however, the risk of AKI-D in these admissions on the rise. Though the impact of AKI-D on mortality is decreasing, it is still a significant risk factor for mortality in HF admissions.

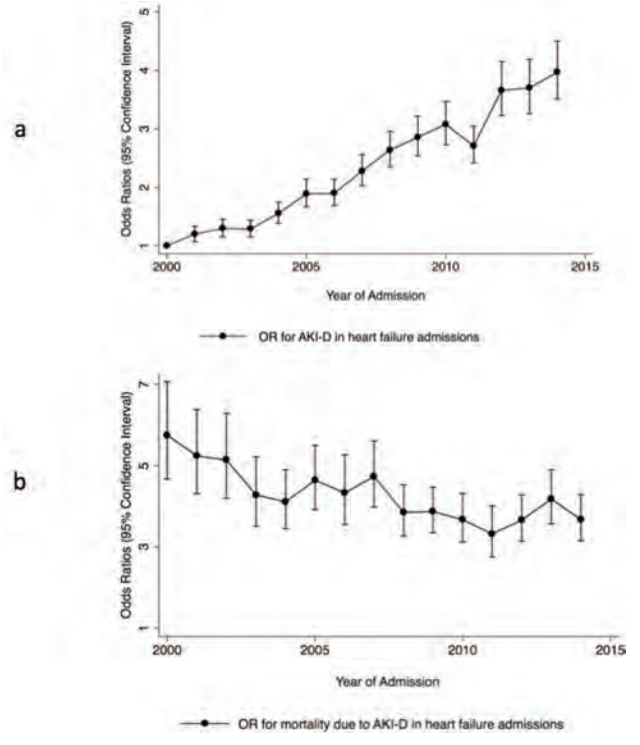


Fig1: OR for AKI-D(a) & its impact on mortality(b)

FR-PO088

Pre-Admission Proteinuria Increases Risk of Non-Recovery after Dialysis-Requiring AKI Benjamin J. Lee,[3] Alan S. Go,[4] Rishi V. Parikh,[4] Thomas Leong,[1] Thida C. Tan,[4] Sophia Walia,[2] Raymond K. Hsu,[3] Kathleen D. Liu,[6] Chi-yuan Hsu.[5] *[1]KPNC, Oakland, CA; [2]KPNC, Oakland, CA; [3]UCSF, San Francisco, CA; [4]KPNC, Oakland, CA; [5]UCSF, San Francisco, CA; [6]UCSF, San Francisco, CA.*

Background: Renal recovery after dialysis-requiring acute kidney injury (AKI-D) is an important clinical and patient-centered outcome. We examined whether pre-AKI-D proteinuria level is an independent risk factor for non-recovery within a diverse, community-based population.

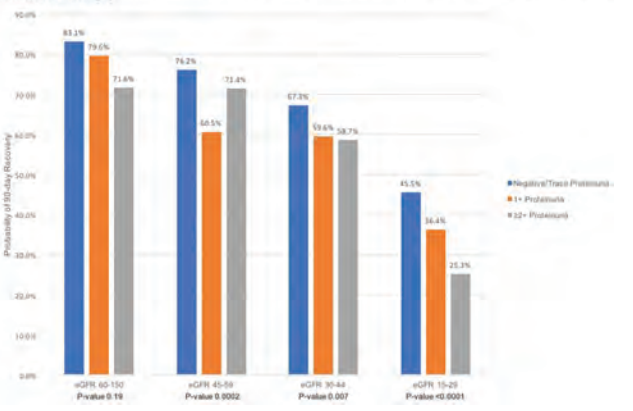
Methods: We evaluated all adult members of Kaiser Permanente Northern California who experienced an episode of AKI-D between 1/1/2009 and 9/30/2015. Pre-admission dipstick proteinuria level was identified ≤4 years before hospitalization. Renal recovery was defined as alive and dialysis-independent ≥4 weeks at 90 days after starting renal replacement therapy. Baseline estimated glomerular filtration rate (eGFR), age, gender, race, short-term predicted risk of death, relevant comorbidities, and medication use were identified from electronic health records.

Results: Among 5,347 adults with AKI-D, mean age was 66 years, 59% were men, and 50% were white. In multivariable logistic regression, compared with negative/trace proteinuria, adjusted odds ratios for non-recovery were 1.47 (95%CI 1.19-1.82) for 1+ proteinuria and 1.92 (1.54-2.38) for ≥2+ proteinuria. Among survivors, crude probability of recovery ranged from 83% for negative/trace proteinuria with baseline eGFR >60 mL/min/1.73m^2 to 25% for ≥2+ proteinuria with eGFR 15-29 mL/min/1.73m^2 (Figure).

Conclusions: Dipstick proteinuria was a graded, independent risk factor for non-recovery after AKI-D and contributes to short-term risk stratification and prognostication in combination with baseline eGFR. Pre-AKI-D proteinuria information is important for appropriately counseling patients and planning follow-up care.

Funding: NIDDK Support

Figure. Crude probability of recovery conditional on survival, by baseline eGFR and proteinuria level. χ^2 tests compared the 3 proteinuria levels within each eGFR category.



FR-PO089

Multicenter Evaluation of the Selective Cytopheretic Device (SCD) in Critically Ill Children Requiring CRRT: Report from the First 4 Patients Stuart Goldstein,[1] David T. Selewski,[1] David J. Askenazi,[1] Patrick D. Brophy,[1] Theresa A. Mottes,[1] Tara C. Terrell,[1] Matthew L. Paden,[1] H. David Humes.[2] *[1]Prospective Pediatric AKI Research Group, Cincinnati, OH; [2]University of Michigan Medical School, Ann Arbor, MI.*

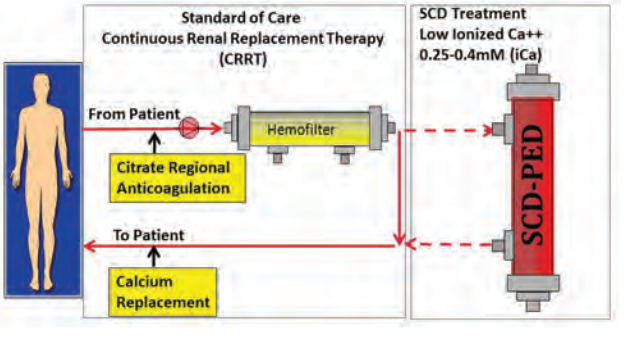
Background: Critically ill children and adults who develop AKI requiring CRRT are at increased risk of death. In a randomized trial, adult pts on CRRT treated with the SCD, who maintained CRRT-SCD circuit ionized Ca (iCa) <0.4 mmol/L, had improved survival/dialysis independence. An CRRT-SCD circuit iCa< 0.4 mmol/L promotes an immunomodulatory effect in animal models of inflammation. We are conducting an FDA grant sponsored safety evaluation of the SCD in 16 critically ill children and report our experience with the first 4 treated patients.

Methods: 5 center US study of the SCD in children (>20 kg, ≤22 years) with AKI and multi-organ failure receiving CRRT as part of standard of care. The SCD is integrated into the CRRT circuit post CRRT membrane (Figure), changed daily, and CRRT-SCD circuit iCa is maintained <0.4 mmol/L. Pts receive SCD treatment for up to 7 days or CRRT discontinuation, whichever comes first.

Results: 4 pts (2F/2M) were enrolled since 12/2016 and completed SCD therapy. Age range = 12.5-17.5 years, PRISM-2 Score range = 2-14. Admission diagnoses were severe rhabdomyolysis(1), septic shock(1) STEC HUS(1) and pneumonia(1). Pts received 3 (1), 4 (1) and 7 (2) days of SCD therapy. Circuit iCa has been maintained at <0.4 mmol/L in 95% of assessments. All pts survived and were off RRT at hospital discharge. No SCD-related serious adverse events occurred. Evidence of hemolysis (increased LDH, thrombocytopenia) reversed within 24 hours of SCD therapy in the 2 pts with hemolysis at SCD initiation.

Conclusions: Our initial data suggest the SCD is safe in children. While we cannot make any efficacy claims, the unepxected early reversal of hemolysis in 2 pts may suggest a role for the SCD in mitigating leukocyte related endothelial damage.

Funding: Other NIH Support - FDA Orphan Device Grant



Schematic of SCD filter intergration in the a CRRT Circuit

FR-PO090

Low-Density Lipoprotein Receptor-Related 2 (Megalin) as Target Antigen in Human Kidney Anti-Brush Border Antibody Disease Claire Trivin-Avillach,[1] Christopher P. Larsen,[2] Paige A. Coles,[1] A. Bernard Collins,[3] Michael Merchant,[4] Hong Ma,[1] Daniel W. Wilkey,[4] Josephine M. Ambruzs,[2] Nidia C. Messias,[6] Nicholas Cossey,[2] Ivy A. Rosales,[3] Thomas D. Wooldridge,[5] Patrick D. Walker,[2] Robert B. Colvin,[3] Jon B. Klein,[4] David J. Salant,[1] Laurence H. Beck.[1] *[1]Boston University Medical Center, Boston, MA; [2]Arkana Laboratories, Little Rock, AR; [3]Massachusetts General Hospital, Boston, MA; [4]University of Louisville Medicine, Louisville, KY; [5]Nephrology & Hypertension Associates, LTD, Tupelo, MS; [6]Nephrology Associates, PLC, Little Rock, AR.*

Background: Acute kidney injury (AKI) has a broad differential diagnosis. Autoimmune diseases against glomerular antigens are well recognized but tubular injury as a result of direct immunologic insult is not part of the routine evaluation. We report a cohort of patients with a distinct, underappreciated kidney disease characterized by kidney anti-brush border antibodies and renal failure (ABBA disease).

Methods: Ten cases of ABBA disease were identified that had a combination of proximal tubule damage, IgG-positive immune deposits in the tubular basement membrane, and circulating antibodies reactive with normal human kidney proximal tubular brush border. Immunoblotting of a protein extract from human tubular cells was performed with serum from cases and controls, and immunoprecipitation followed by mass spectrometry was used to identify the protein targeted by the anti-brush border antibodies. Cell expression of recombinant protein followed by immunoblotting and immunoprecipitation was used to confirm the identity of the antigen.

Results: Patients with ABBA disease were elderly (mean age 72.9 years), presented with acute kidney injury (median serum creatinine 4.0 mg/dl) and moderate proteinuria. The kidney biopsy showed acute tubular injury with apical cytoplasmic blebbing, loss of brush border, regenerative changes and granular IgG and C3 deposits along tubular basement membranes. All patient sera were reactive to the proximal tubular brush border on sections of normal human kidney. Serum from all patients but not controls recognized a high molecular weight protein in renal tubular protein extracts that was identified as low-density lipoprotein receptor-related 2 (LRP2) by immunoprecipitation and mass spectrometry. Recombinant expression of an N-terminal recombinant fragment of LRP2 was used to confirm this finding by Western blot and immunoprecipitation. LRP2 specifically co-localized with IgG in the tubular immune deposits.

Conclusions: We present the first case series detailing the clinicopathologic findings of patients with ABBA disease and show that the antigenic target of these autoantibodies is LRP2.

Funding: NIDDK Support

FR-PO091

AKI in Pregnancy and the Puerperium Catherine Brumby, Graeme Duke, Elizabeth Low, Lawrence P. McMahon. *Eastern Health Clinical School, Monash University, Melbourne, VIC, Australia.*

Background: Acute kidney injury (AKI) either during pregnancy or postpartum is associated with significant maternal and neonatal morbidity. Past population-based studies (1999-2011) in US and Canada suggest the incidence may be increasing, with contributing factors including increasing rates of hypertensive disorders of pregnancy (HDP) and CKD. We aim to determine recent developments in this apparent trend.

Methods: All public hospital admissions with pregnancy >20 weeks gestation in Victoria, Australia (2006-2016) were identified by ICD-10 diagnostic codes from a validated administrative database. Analysis included 560,778 antenatal and postpartum admissions, of which 533,876 included delivery. Trends in AKI incidence and associated risk factors were examined, and multivariate logistic regression determined whether changes in risk factors explained observed temporal changes.

Results: The incidence of AKI per 10,000 deliveries rose from 2.37 in 2006 to 11.59 in 2016, p<0.001. Of the 499 AKI cases, 228(45.6%) also had CKD, 22(4.4%) required renal replacement therapy, and 3(0.6%) died. The strongest risks factors associated with AKI were CKD, HDP, diabetes, and critical care admission. After adjustment, the temporal relationship for AKI risk was maintained, with risk factors being CKD, HDP, and sepsis.

Conclusions: The incidence of obstetric-related AKI continues to rise. This trend persists after adjusting for factors such as HDP, CKD and maternal age. Other, as yet unidentified or unmeasured factors may be implicated, such as greater awareness and reporting of AKI and increasing complexity of maternal comorbidities. Longterm risks of obstetric-related AKI remain to be determined.

Risk Factors Assocated with Obstetric AKI: Logistic Regression Analysis

Risk Factor associated with AKI	Deliveries, number	AKI rate per 10,000 deliveries	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Year of admission	560,778	n/a	1.16 (1.10-1.24)	1.11 (1.07-1.14)
Maternal age per 5yr	560,778	n/a	1.33 (1.18-1.50)	1.15 (1.04-1.28)
CKD	228	1842.1	473.9 (318.1-578.3)	37.5 (23.6-59.6)
Chronic HT	3,123	124.9	49.8 (28.17-88.03)	ns
Pre-existing diabetes	1,376	174.4	43.38 (29.23-64.41)	1.69 (1.21-2.36)
GH/Pre-eclampsia (HDP)	36,309	74.6	16.05 (4.69-12.27)	12.32 (9.63-15.76)
Sepsis	22,631	40.7	7.59 (4.69-12.27)	7.32 (5.32-10.08)
Postpartum haemorrhage	73,589	20.1	2.76 (2.01-3.8)	2.33 (1.86-2.92)
Caesarean delivery	155,734	18.2	3.22 (2.15-4.83)	2.02 (1.54-2.64)
Prematurity <33 weeks	13,491	54.84	7.27 (5.68-9.31)	not entered
Critical Care admission	1,412	687.0	153.4 (95.9-245.4)	not entered

*All covariates adjusted for. OR p<0.005 for all variables

FR-PO092

MA-0204 Modulation of PPARδ Promotes Recovery after AKI in Normal and Aged Proteinuric Diabetic CKD Zsf1 Rats by Enhancing Fatty Acid Oxidation in Proximal Tubular Epithelial Cells Christina Bracken,[2] Katelyn Pulito,[2] Jeff H. Stanwix,[2] Hien G. Hoang,[2] Silvia B. Campos-bilderback,[1] Ruben M. Sandoval,[1] Bruce A. Molitoris,[1] Effie Tozzo.[2] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Mitobridge, Cambridge, AL.*

Background: Ischemic acute kidney injury (AKI) is characterized by persistent proximal tubule mitochondrial dysfunction. Due to their highly oxidative metabolism, proximal tubule cells utilize fatty acids to generate the energy required for their specialized function. We hypothesized that enhancing fatty acid oxidation (FAO) with a PPARδ modulator will restore mitochondrial function and offer a potential therapeutic treatment for AKI.

Methods: Human hTERT RPTECs were treated with MA-0204 and analyzed for PPARδ target gene expression and their ability to utilize palmitate. Sprague-Dawley (SD) rats underwent ischemia-reperfusion (IR) AKI and were treated orally with 30 mg/kg of selective PPARδ modulator MA-0204 for 2 days. EPO served as positive control and was dosed IV at 1000 U/kg 30 minutes prior to ischemia. We also tested this hypothesis in aged (18 week old), diabetic and proteinuric CKD Zsf1 rats, a preclinical model that presents with similar comorbidities as diabetic-chronic kidney disease (CKD) patients.

Results: MA-0204 significantly increased expression of PPARδ-target genes associated with mitochondrial FAO (such as *Cpt1a)* and increased palmitate oxidation in RPTECs. In rats, MA-0204 treatment significantly reduced plasma creatinine (69%), BUN (62%), fractional excretion of Na^+ (82%) and restored creatinine clearance (800%) 24 and 48 hours post AKI. MA-0204 treated rats had significantly improved histopathology scores, normalized expression of kidney injury related genes (KIM-1, NGAL), and reduced urinary injury biomarker levels ([TIMP2]*[IGFBP7], FABP-1). Importantly MA-0204 attenuated AKI in diabetic proteinuric CKD Zsf1 rats, resulted in a decrease of plasma creatinine levels (33%), accelerated recovery of creatinine clearance and reduced urinary TNFR1, an indicator of CKD progression.

Conclusions: Our data demonstrates that enhancing fatty acid oxidation and improving mitochondrial function, through PPARδ modulation, following ischemic kidney injury is sufficient to recover renal function, reduce tubular injury and promote recovery in SD as well as in aged, diabetic, proteinuric CKD Zsf1 rats.

Funding: Veterans Affairs Support

FR-PO093

AKI after Severe Burn Audra T. Clark,[4] Rohan Kulangara,[7] Xilong Li,[1] Tarik D. Madni,[6] Jonathan Imran,[5] Steven E. Wolf,[3] Javier A. Neyra.[2] *[1]UT Southwestern Medical Center, Dallas, TX; [2]University of Kentucky Medical Center, Lexington, KY; [3]University of Texas - Southwestern Medical Center, Dallas, TX; [4]University of Texas Southwestern, Dallas, TX; [5]University of Texas Southwestern Medical Center, Dallas, TX; [6]University of Texas Soutwestern, Dallas, TX; [7]Ut Southwestern medical center, Dallas, TX.*

Background: Acute kidney injury (AKI) is a common and morbid complication in patients with severe burn. We aim to examine the incidence, onset, severity, and mortality of AKI after thermal injury.

Methods: A retrospective cohort study of adults with thermal injury admitted to the Burn ICU from 2008-2015 was conducted. Patients with preexisting ESRD, kidney transplant, eGFR<15, or absent serum creatinine (SCr) data were excluded. AKI was defined by SCr-KDIGO criteria. The onset of AKI ≤7 days vs >7 days from ICU admission were used to define early vs late AKI, respectively. Patient- and burn-specific characteristics among those with or without AKI were compared. Multivariable logistic regression with AKI as the independent variable and hospital mortality as the dependent variable was utilized.

Results: 1040 patients with thermal injury were included in the study. Mean (SD) age was 48.9 (18.9), 70.5% were men and 16.4% black. The median total body surface area (TBSA) of burn was 16% (IQR: 6-29%). AKI was present in 617 (59%) patients, KDIGO stages: 1, 59.3%, 2, 20.3%, 3, 11.3%, 3D, 9.1%. Early AKI was present in 551/617 (89%) of patients. Patients with AKI had larger TBSA burn (median 20.5% vs 11.0%, p<0.001), received more mechanical ventilation days (median 2.0 vs 0.0, p<0.001), and stayed longer in the hospital (median 21.0 vs 10.0 days, p<0.001). Hospital mortality was higher in those with AKI vs those without AKI: 19.7% vs 4% (p<0.001) and increased by each KDIGO stage (p trend<0.001). AKI was independently associated with hospital mortality

(early AKI vs. no AKI adjusted OR 8.69, 95% CI 4.20–18.0; late AKI vs. no AKI adjusted 4.78, 1.61–14.15; early AKI vs. late AKI 1.82, 0.74–4.46). Other independent predictors of hospital mortality were age, TBSA, black race, mechanical ventilation, and inhalational injury.

Conclusions: AKI occurs frequently in patients after thermal injury and portends increased mortality. Further investigation is indicated to develop risk-stratification tools and examine AKI recovery patterns in this susceptible population.

FR-PO094

TissueFAXS Analysis as an Experimental Tool for Assessing the Degree of Intrarenal Lymphocytes Infiltration Minjung Kim,[1] Su Hyun Kim,[2] Junseok Jeon,[1] Jung eun Lee,[1] Wooseong Huh,[1] Yoon-Goo Kim,[1] Dae Joong Kim,[1] Ha Young Oh,[1] Hye Ryoun Jang.[1] *[1]Samsung medical center, Seoul, Republic of Korea; [2]samsung medical center, Seoul, Republic of Korea.*

Background: Intrarenal infiltration of immune cells is an established pathogenic mechanism in various inflammatory kidney diseases. Quantitative analyses of intrarenal immune cells, especially intrarenal lymphocytes, using flow cytometry analysis of kidney mononuclear cells (KMNCs) have been used as a precise and useful diagnostic method in a murine model of ischemic acute kidney injury (AKI). However, flow cytometry analysis of KMNCs is not feasible in patients because sufficient amount of renal tissue required for this method cannot be obtained with kidney biopsy. In this study, we investigated the diagnostic potential of tissueFAXS as a tool assessing the degree of intrarenal lymphocytes infiltration.

Methods: A total of 10 cynomolgus monkeys with various renal function were included. Kidney samples for flow cytometry analysis of KMNCs and immunohistochemistry were collected simultaneously. Flow cytometry analysis of KMNCs were performed using FACS verse. Immunohistochemistry of CD3, CD20, and CD45 on formalin-fixed kidney tissues were performed and followed by tissueFAXS analysis. The proportion of lymphocytes positive for each CD marker was acquired using different denominators as follows: kidney mononuclear cells isolated with percoll in flow cytometry vs. all nucleated cells stained with hematoxylin in tissueFAXS. Linear regression analysis was used to compare the association of CD3, CD20, and CD45 (+) lymphocytes evaluated with two different methods.

Results: Flow cytometry and tissueFAXS analyses showed positive correlation with CD45 (+) lymphocytes (R^2 =0.5378, P=0.0245). There was a positive correlation between the proportion of both CD3 (+) T cells (R^2 =0.8120, P=0.0002) and CD20 (+) B cells (R^2 =0.4587, P=0.0650). The ratio of CD3 (+) T cells and CD20 (+) B cells measured with both methods also showed positive correlation (R^2 =0.5144, P=0.0296).

Conclusions: Our study showed significant positive correlation of intrarenal CD3, CD20, and CD45 (+) lymphocytes measured with flow cytometry and tissueFAXS in cynomolgus monkeys. These results suggest that immunohistochemistry followed by tissueFAXS analysis may be used as a diagnostic tool performing semiquantitative evaluation of intrarenal lymphocytes in patients.

FR-PO095

AKI Detection Using a Novel 5-Plex Panel Candace M. Adamo,[1] Timothy H. Carlson,[1] Eibhlin M. Mccole,[2] Marie Mcgarvey,[2] Ciaran Richardson,[2] Peter Fitzgerald,[3] John Lamont,[3] Amar Sethi.[1] *[1]Pacific Biomarkers, Seattle, WA; [2]Randox Teoranta, Dungloe, Ireland; [3]Randox Laboratories Limited, Crumlin, United Kingdom.*

Background: Acute kidney injury (AKI) is classified using serum creatinine and urine output. However, since creatinine is a lagging index of impending AKI, studies are now underway to qualify a set of biomarkers for detecting drug-induced kidney injury (DIKI) in clinical trials. Since assessment of renal injury using multiple biomarkers is more clinically discriminating than single biomarker analysis, we report here the development and optimization of the first human multiplex for determining early and robust diagnosis of AKI.

Methods: Randox Biochip Array technology was used to develop a multiplex immunoassay panel for the below biomarkers. Performance goals for the multiplex were established by testing >1000 subjects using the predicate ELISA methods for KIM-1, NGAL, cystatin C, clusterin, and osteopontin (OPN). Functional sensitivity, cross reactivity, and interference were assessed, along with a sample correlation in 30 subjects.

Results: The 1000 patient samples provided dynamic ranges of 31.3-4000pg/mL; 1-100ng/mL; 1.5-150ng/mL; 10-1000ng/mL; 80-8000ng/mL for KIM-1, NGAL, cystatin C, clusterin, and OPN, respectively. The functional sensitivity was confirmed for all analytes at the low end of the dynamic range as the precision of the lowest non-zero standard was <20%CV for all five biomarkers (n=6). The effective upper limits of measurement, determined by calculating precision of the highest standard were <10%CV. There was no significant cross reactivity (<1% cross reactivity or <10% interference) for any of the analytes when spiked with x10 concentration of the highest standard of the other panel antigens. Cross reactivity from non-panel proteins were tested for cystatin C, clusterin and KIM-1 showing no significant cross-reactivity. Method comparison between the two methods provided correlations (r^2) of 0.927; 0.962; 0.872; 0.812; 0.899 for KIM-1, NGAL, cystatin C, clusterin and OPN, respectively. Slopes were 0.994, 0.544, 0.636, 1.67, and 0.685, respectively.

Conclusions: The AKI multiplex panel simultaneously detects KIM-1, NGAL, cystatin C, clusterin, and OPN with a solid performance and improved dynamic ranges compared to the predicate ELISA methods. This multiplex panel provides a robust and cost-effective solution for detecting DIKI in, not only, clinical trials, but potentially also in kidney patients for future diagnostic use.

Funding: Commercial Support - Pacific Biomarkers, Randox Laboratories

FR-PO096

Clinical Factors Associated with Progression from Acute Mesoamerican Nephropathy to CKD Rebecca S. Fischer. *Baylor College of Medicine, Houston, TX.*

Background: Greater than 20,000 deaths in Central America have been attributed to the epidemic of Mesoamerican nephropathy (MeN). Men is a mysterious kidney disease of unknown etiology that disproportionately affects young agricultural workers without traditional risk factors for kidney disease. MeN had been characterized as a chronic kidney disease (CKD) until we recently documented an acute clinical scenario, characterized by acute kidney injury (AKI) with interstitial nephritis and markers of systemic inflammation, namely neutrophilic leukocytosis and leukocyturia. We also observed that some patients, but not all, later progressed to CKD.

Methods: We conducted an analysis to identify clinical characteristics of acute MeN that predict progression to CKD. Using univariate analysis, we compared patients with acute MeN who developed CKD to those who did not to identify clinical risk factors for CKD. Physicians at a private hospital in Nicaragua completed case reports detailing acute clinical encounters on cases of MeN and provided follow-up data on subsequent CKD diagnoses.

Results: From Feb 2015-Jan 2017, 468 cases of acute MeN were reported, mostly male (91%) and young (median age 27 yrs). Most (92%) had acute kidney injury (AKI). Frequent acute symptoms were fever (62%), nausea/vomiting (72%), back pain (61%), and headache (52%). Leukocytosis (80%), neutrophilia (84%), lymphopenia (53%), elevated C-reactive protein (76%), and anemia (59%) were common, along with leukocytes (99%) and leukocyte casts (30.2%) in urine. 30 patients (6%) progressed rapidly (median 90 days) to CKD, with half (51%) progressing to ≥Stage 3 CKD. We found that age >25 years (Prevalence Ratio [PR] 2.90 [1.03, 8.19], p=0.045), hyperuricemia (2.56 [1.26, 5.21], p=0.010), anemia (3.37 [1.31, 8.67], p=0.012) and hyponatremia (PR 3.20 [1.46, 7.02], p=0.004) were associated with CKD. Leukocytosis (PR 0.39 [95%CI 0.19, 0.81], p=0.012) and leukocyturia (PR 0.36 [0.17, 0.75], p=0.006) during the acute phase of MeN were negatively associated with CKD.

Conclusions: Our data suggest that acute systemic inflammation during acute MeN may mediate progression to CKD. Our ongoing longitudinal analysis will enhance our understanding of clinical events during disease progression and shed light on the mechanism of injury. This is the first of clinical factors associated with CKD and with recovery in MeN.

Funding: Private Foundation Support

FR-PO097

Impact of AKI on Urine Protein Excretion Chi-yuan Hsu,[12] Raymond K. Hsu,[14] Kathleen D. Liu,[13] Amanda H. Anderson,[16] Jing Chen,[9] Vernon M. Chinchilli,[8] Harold I. Feldman,[16] Amit X. Garg,[4] L. Lee Hamm,[10] James S. Kaufman,[17] Paul L. Kimmel,[7] John W. Kusek,[6] Chirag R. Parikh,[19] Ana C. Ricardo,[15] Sylvia E. Rosas,[2] Georges Saab,[5] Daohang Sha,[11] James H. Sondheimer,[18] Jonathan J. Taliercio,[1] Wei Yang,[16] Alan S. Go.[3] *[1]Glickman Urological and Kidney Institute, Cleveland, OH; [2]Joslin Diabetes Center, Boston, MA; [3]Kaiser Permanente Northern California, Oakland, CA; [4]London Health Sciences Centre, London, ON, Canada; [5]MetroHealth Medical Center, Rocky River, OH; [6]NIDDK, Bethesda, MD; [7]National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; [8]Penn State College of Medicine, Hershey, PA; [9]Tulane School of Medicine, New Orleans, LA; [10]Tulane University School of Medicine, New Orleans, LA; [11]Uiversity of Pennsylvania, Philadelphia, PA; [12]University of California San Francisco, San Francisco, CA; [13]University of California at San Francisco School of Medicine, San Francisco, CA; [14]University of California, San Francisco, San Francisco, CA; [15]University of Illinois at Chicago, Chicago, IL; [16]University of Pennsylvania, Philadelphia, PA; [17]VA New York Harbor Healthcare System, New York, NY; [18]Wayne State University School of Medicine, Detroit, MI; [19]Yale University and VAMC, New Haven, CT.*

Background: Little is known about the impact of AKI on proteinuria as existing studies of the adverse long-term renal consequences of AKI have almost exclusively focused on estimated glomerular filtration rate (eGFR). Some recent interventional studies suggest that mild-moderate severity AKI actually only lead to small loss of eGFR. However, examining changes in eGFR alone may underestimate the renal sequelae of AKI.

Methods: To increase sample size and generalizability, we combined data from participants of two prospective NIH cohort studies: all enrollees from ASsessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI)(2003-16)(N=1599) and the subset of Chronic Renal Insufficiency Cohort (CRIC) study enrollees recruited from Kaiser Permanente Northern California (KPNC), a large integrated healthcare delivery system (2003-15)(N=455). Urine protein-creatinine ratio (PCR) was measured centrally once a year per ASSESS-AKI and CRIC research protocols. For study participants who were hospitalized, inpatient serum creatinine (SCr) measurements obtained as part of clinical care were abstracted from medical records and AKI defined as peak/nadir inpatient SCr≥1.5. Mixed effects regression was used to examine the impact of AKI on PCR, adjusting for demographics, co-morbidities and time-updated estimated GFR, sysotlic blood pressure (BP), number of BP medications and use of renin-angiotensin-system (RAS) blockers.

Results: Baseline eGFR was 66 (±25) ml/min/1.73m^2 and median PCR 0.12 [IQR 0.07-0.25] (g/g), There were 275 episodes of AKI during follow-up, of which 58% were KDIGO stage 1 in severity, 23% stage 2 and 18% stage 3 (including 22 cases requiring

dialyais). We found that an episode of AKI was independently associated with an increase in PCR of 0.17 g/g (P<0.0001). This increase in proteinuria is independent of changes in eGFR and does not appear to explained by higher BP or withdraw of BP medications (including RAS blockers) after AKI.

Conclusions: AKI is an independent risk factor for worsening of proteinuria among CKD patients.

Funding: NIDDK Support

FR-PO098

Impact of AKI and Source of Serum Creatinine Measurements on Subsequent Kidney Function Decline

Raymond K. Hsu,[5] Chi-yuan Hsu,[5] Charles E. McCulloch,[5] Jingrong Yang,[3] Amanda H. Anderson,[6] Jing Chen,[4] Harold I. Feldman,[6] Jiang He,[4] Kathleen D. Liu,[5] Sankar D. Navaneethan,[1] Anna C. Porter,[8] Mahboob Rahman,[2] Thida C. Tan,[3] Francis P. Wilson,[7] Dawei Xie,[6] Xiaoming Zhang,[6] Alan S. Go.[3] *[1]Baylor College of Medicine, Houston, TX; [2]Case Western Reserve University, Cleveland, OH; [3]Kaiser Permanente Northern California, Oakland, CA; [4]Tulane School of Medicine, New Orleans, LA; [5]University of California San Francisco, San Francisco, CA; [6]University of Pennsylvania, Philadelphia, PA; [7]Yale School of Medicine, New Haven, CT; [8]University of Illinois, Chicago, Chicago, IL.*

Background: Acute kidney injury (AKI) is linked to chronic kidney disease (CKD) progression, but this epidemiological association may be susceptible to ascertainment bias in studies using clinical data, as patients may be more likely to undergo kidney function testing post-AKI.

Methods: We evaluated whether impact of AKI on kidney function trajectory varied using clinical vs. research protocol-driven data in 444 adult CKD participants of the Chronic Renal Insufficiency Cohort (CRIC) Study who were also members of a large integrated healthcare system. We estimated separate eGFR trajectories using (1) serum creatinine (SCr) measurements performed annually through CRIC research protocol, or (2) SCr measurements performed in clinical care. We used linear mixed models to test the associations of AKI with absolute change in eGFR and post-AKI eGFR slope and whether these associations varied by source of serum creatinine (clinical vs. research), adjusting for demographics, baseline albuminuria and diabetes.

Results: During mean follow-up of 7.5 years, mean rate of eGFR loss was 0.31 ml/min/1.73m^2 per year overall (in the referent group with mean age of 60, male, non-black, and without albuminuria or diabetes); 74 individuals experienced AKI (54% Stage 1). An AKI episode was not significantly associated with an acute change in absolute eGFR level after discharge, but was significantly associated with a faster rate of eGFR decline (mean additional loss of 0.67 ml/min/1.73m^2 per year, P<0.0001). However, the latter association was attenuated and no longer significant when using only research measurements (Table1).

Conclusions: The impact of AKI on subsequent rate of kidney function loss is influenced by source of SCr, and may be modest after accounting for other risk factors.

Funding: NIDDK Support

Table1: Multivariable mixed effects model showing association of AKI and kidney function trajectory

Predictors	Coefficient	P
Impact of AKI episode on acute change in level of eGFR (overall)	2.01	0.59
Impact of AKI episode on acute change in level of eGFR (using research SCr only)	-0.35	0.69
Impact of AKI episode on subsequent rate of eGFR decline (overall)	-0.67	<0.0001
Impact of AKI episode on subsequent rate of eGFR decline (using research SCr only)	-0.029	0.9

FR-PO099

Late Onset Glutaric Acidemia Type 2 Caused by a Novel ETFDH Gene Mutation Presenting with Fulminant Hepatic and Acute Renal Failure

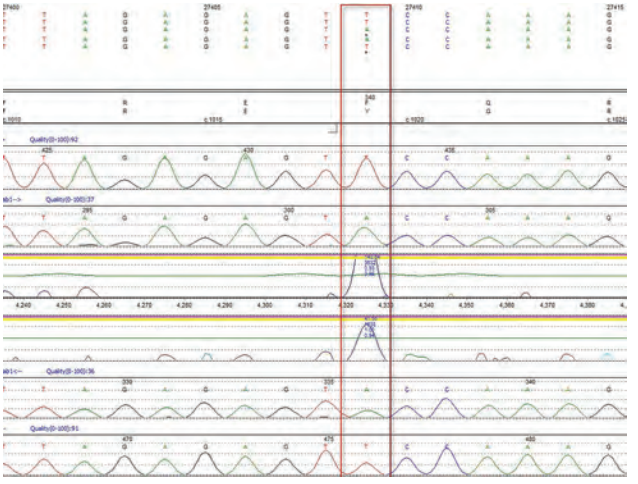
Xiangling Wang, Bekir Tanriover, Christopher Y. Lu, Mythili Ghanta. *University Texas Southwestern Medical Center, Dallas, TX.*

Background: Glutaric acidemia type 2 (GA 2) is an autosomal recessive disorder caused by deficiency of electron transfer flavoprotein. A vast majority of cases were diagnosed in early childhood and late onset cases were thought to present with mild clinical symptoms. Here we report one late onset case with novel ETFDH missense mutation presenting with metabolic decompensation requiring liver transplant and hemodialysis.

Methods: A 30-year-old African American female presented with fatigue, nausea, vomitings and abdominal pain. Hospital course was complicated by severe hypoglycemia, acute cardiopulmonary failure requiring mechanical ventilation, acute liver failure with biopsy findings of diffuse micro steatosis, rhabdomyolysis and acute renal failure requiring continuous renal replacement therapy. She emergently received a liver transplant (LT). Pretransplant plasma, concentrations of fatty acids C6-C16 were elevated suggestive of GA 2. Sanger sequencing disclosed homozygous missense mutation in ETFDH gene (c.1019 T>A; p.Phe340Tyr). This mutation has never been reported as pathogenic or benign variant in population database. Silico analysis revealed this novel mutation as likely pathogenic. One month after LT she was transferred to rehab facility with good allograft function tolerating 1-2 hours of moderate physical activity and recovered renal function to remain off dialysis.

Results:

Conclusions: Elevated fatty acids along with identification of this novel mutation support the diagnosis of late onset GA 2. In addition, inborn errors of metabolism should be suspected even in adults who present with unexplained rhabdomyolysis and acute renal failure.



FR-PO100

Therapeutic Plasma Exchange as Rescue Therapy in Refractory Septic Shock

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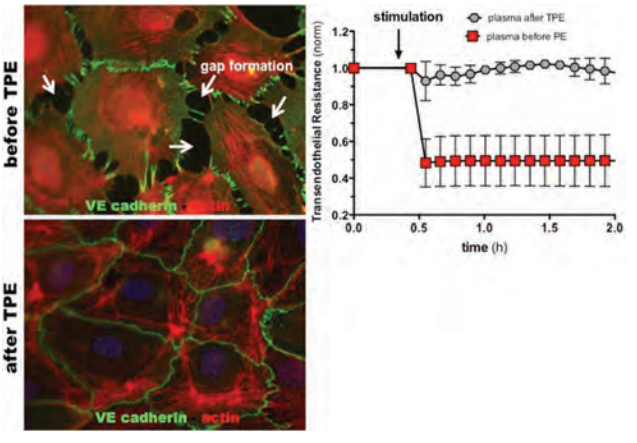
Background: Sepsis is a life-threatening dysregulated host response to infection. Given the injurious role of 1) the overwhelming immune response and 2) the consumption of protective plasmatic factors (vWF cleaving proteases etc.) we hypothesize that early therapeutic plasma exchange (TPE) in severely ill individuals might be beneficial. TPE combines 2 aspects in 1 procedure: Removal of harmful circulating molecules and replacement of protective plasma proteins.

Methods: We have included 14 septic shock patients (onset < 12 h) requiring high doses of noradrenaline (> 0.4 ug/kg/min). TPE (against FFP) was performed within 4 hrs. Clinical and chemical data were obtained longitudinally besides the evaluation of 28-day mortality. Plasma samples before and after TPE were obtained for stimulation of human umbilical vein endothelial cells (HUVECs) to analyze their phenotype with regard to permeability *in vitro* (fluorescent immunocytochemistry & transendothelial electrical resistance (TER)).

Results: The 28-day mortality in this study was found 20% lower (69.2%) as the predicted mortality (88.95%) by APACHE II score (37.6±4). TPE resulted in hemodynamic stabilization as indicated by mean arterial pressure (63±11 vs. 70±9 mmHg, p=0.002) and lower vasopressor requirement (NA 0.93±0.5 vs. 0.6±0.3 ug/kg/min, p<0.001). Fluid balance was also positively affected probably by reduced capillary leakage. This is supported by *ex vivo* stimulation of HUVECs with septic plasma where plasma before TPE induced severe alteration of cellular architecture including a disassembly of adherens junction (VE-cadherin IF) and a dramatic increase in permeability (TER, **Figure**). The same patients' plasma after TPE did not induce this typical septic phenotype.

Conclusions: This pilot study supports our hypothesis that early TPE in highly unstable patients might be beneficial with regard to hemodynamic stability, microcirculatory perfusion and overall outcome. A multicenter randomized trial powered for mortality is highly desirable.



FR-PO101

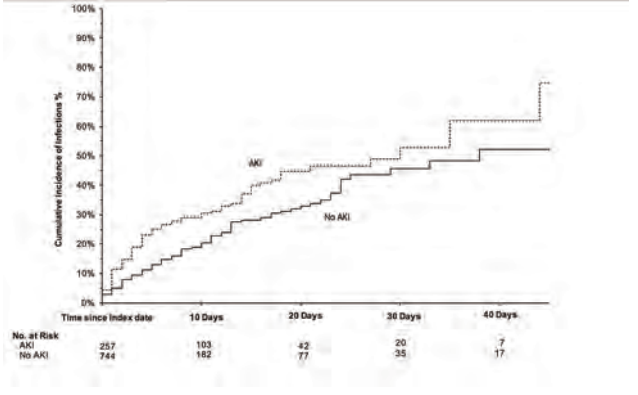
Risk of Infections Following AKI Amelie Bernier-Jean, William Beaubien-Souligny, Josee Bouchard. *Université de Montreal, Montreal, QC, Canada.*

Background: Recent studies suggest that AKI can affect distant organ function and increase non-renal complications. We aimed to determine whether AKI is independently associated with an increased risk of infectious complications in ICU patients.

Methods: We conducted a single-center retrospective cohort study of ICU patients over a year. We excluded readmission, patients on chronic dialysis, with a kidney transplant or an ICU stay less than 24 hours. The primary outcome was the development of de novo infections, analyzed with a time-dependent multivariate Cox regression model.

Results: We enrolled 1001 patients. Mean age was 64±15 years, 61% were male, 26% suffered from diabetes, 12% from CKD, 17% from COPD, and 6% were immunosuppressed. The SOFA score at ICU admission was 5 (2-8). During their stay, 51% of patients received vasopressors, 56% received mechanical ventilation (MV), and 68% underwent surgery. Twenty-six percent developed AKI and 44% had at least one infection. Patients with vs. without AKI were more likely to suffer from infections (62% vs 37%, p<0.001) (Figure 1). Pneumonia, intra-abdominal infections, and lower urinary tract infections were most common. In a time-dependent Cox-regression model, AKI (HR 1.57 95%CI 1.20-2.06) and MV (HR 1.88 95%CI 1.43-2.47) were predictors of incident infections. Patients who remained AKI and infection-free had the lowest mortality rate (2.6%), followed by those with infection alone (16.2%), infection after AKI (16.7%), AKI alone (20.4%) and infection before AKI (34.2%) (p<0.001 between groups;p=0.03 for infection after vs before AKI;p=0.03 for infection before AKI vs AKI alone;p=0.60 for infection after AKI vs AKI alone).

Conclusions: In a multivariate model, AKI was significantly associated with the development of incident infections. However, the occurrence of infection after AKI was not associated with increased mortality rate compared to infection-free AKI in our study. Patients with AKI should still be considered at higher risk for infections and targeted for infection prevention and rapid management of infections.



FR-PO102

Distinct Morphological Features of Acute Tubular Injury in Renal Allografts Correlate with Clinical Outcome Andrea Schumann-Bischoff,[1] Jessica Schmitz,[1] Irina Scheffner,[2] Roland Schmitt,[3] Verena Broecker,[4] Hermann G. Haller,[1] Jan H. Braesen,[3] Wilfried Gwinner.[1] *[1]Hannover Medical School, Hannover, Germany; [2]Medical School Hannover, Nephrology, Hannover, Germany; [3]Medizinische Hochschule Hannover, Hannover, Germany; [4]Sahlgrenska University Hospital, Gothenburg, Sweden.*

Background: Acute tubular injury (ATI) is common in renal allografts and is related to inferior long-term allograft function. However, it is unknown which of the morphological features of ATI can predict outcome and how they should be graded. Here, we examine features of ATI systematically in protocol biopsies and biopsies for cause to define the most predictive features for allograft outcome.

Methods: Analyses included 521 protocol biopsies taken at 6 weeks, 3 and 6 months after transplantation and 141 biopsies for cause from 204 patients. Features of ATI included brush border loss, tubular epithelial lucency, flattening, pyknosis, nuclei loss and luminal debris, each graded semi-quantitatively. Additional immunohistochemical stainings were performed for markers of cell injury (NGAL), cell death (cleaved caspase-3, FACL4) and proliferation (Ki-67).

Results: Inter-observer reproducibility was good for pyknosis, flattening, brush border loss, fair for lucency and poor for nuclei loss and luminal debris. In protocol biopsies between 6 weeks and 6 months, the degree of ATI remained virtually unchanged. Biopsies for cause had generally higher injury scores. Deceased donor source, delayed graft function, ganciclovir/valganciclovir treatment and urinary tract infection correlated with ATI. The degree of brush border loss, lucency, pyknosis, and FACL4 expression correlated best with impaired allograft function. Only in patients with tubular Ki-67 expression long-term allograft function improved.

Conclusions: Reliable assessment of ATI is possible by semi-quantitative grading of tubular epithelial cell brush border loss, lucency and pyknosis, and the novel ferroptosis marker FACL4. Examination of Ki-67 expression can help determine the potential for recovery from this damage.

FR-PO103

AKI in the Tertiary Care Setting in Rwanda: Three Month and One Year Outcomes after Hospital Discharge Marla D. McKnight,[1,3] Fredric O. Finkelstein,[2] Grace Igiraneza.[4] *[1]Brigham and Women's Hospital, Renal Division and Division of Global Health Equity, Harvard Medical School, Boston, MA; [2]Yale University, New Haven, CT; [3]Human Resources for Health Program, Ministry of Health, Kigali, Rwanda; [4]Department of Medicine, University of Rwanda, Kigali, Rwanda.*

Background: Despite a burgeoning body of literature regarding the epidemiology and outcomes of acute kidney injury (AKI) in low-income settings, there remains limited data regarding the medium to long-term outcomes of patients presenting with or sustaining AKI in hospital.

Methods: In this observational, multicenter study in Rwanda, all patients > age 15 who met KDIGO definition of AKI, based on changes in serum creatinine, while admitted at one of the four national tertiary care hospitals between September 1, 2014 and January 31, 2015 had demographic and clinical information collected and were followed up post hospital discharge at 3 months (+/- 30 days) and at one year (+/- 3 months) for decline in estimated glomerular filtration rate (GFR) by 30% from baseline and mortality. Logistic regression models were performed to determine predictors of progression and mortality at 3 months.

Results: Of the 427 patients having met criteria for AKI in hospital, 291 survived to discharge. At 3 months post hospitalization, 241 were accounted for and 199 had creatinine measured. 63 (31.7%) demonstrated a GFR decline of >30%. Patients with exposure to traditional medicines prior to hospitalization were at higher risk of progression to CKD at 3 months (OR 3.02, p=0.08), whereas those who recovered baseline kidney function in hospital were significantly less likely to experience a drop in GFR at 3 months (OR 0.31, p=0.001). Patients that underwent dialysis uniformly experienced a >30% decline in GFR at 3 months. All-cause mortality at 3 months was 14.9% and having TB (OR 3.52, p=0.05), cancer (OR 3.82, p=0.03) and receiving dialysis (OR 9.01, p=0.003) were significantly associated with death. At one year, 120 patients were followed up and 102 had creatinine measured. 33 (32.3%) had a decline of GFR >30% at 12 months--10 additional patients had a decline of GFR >30% who had not at 3 months and 7 recovered renal function to within 30% of baseline. At one year there were 13 additional deaths, 9 of which had a decline of GFR>30 at 3 months.

Conclusions: Patients who experience AKI in hospital are at high risk for progression to CKD at three months and at one year. The study underscores the importance of careful follow-up of patients with AKI after hospital discharge and reflects the difficulty of capturing longterm outcome data in low-resource settings.

Funding: Private Foundation Support

FR-PO104

Effectiveness of AKI E-Alerts in Primary Care James Tollitt,[1] Lauren Emmett,[1] Samantha C. Glynn-Atkins,[2] Denise Darby,[1] Brandon Bennett,[3] Sheila Mccorkindale,[2] Smeeta Sinha,[1] Dimitrios J. Poulikakos.[1] *[1]Salford Royal NHS Foundation Trust, Salford, United Kingdom; [2]NHS Salford Clinical Commissioning Group, Salford, United Kingdom; [3]Improvement Science Consulting Inc., Washington, DC.*

Background: AKI e-alerts in secondary care are well researched but the impact of e-alerts in primary care is unknown. The NHS AKI alert algorithm, based on KDIGO AKI classification, was implemented across primary care in UK in 2016. This project analyzed the impact of the e-alert and AKI educational outreach sessions on primary care AKI 2&3.

Methods: GP practices were randomised into 4 groups. A 2x2 factorial design exposed each group to different combinations of the 2 interventions. The study population was 258,729. Time to repeat test or hospitalisation was measured. Age <18years and dialysis patients were excluded. Repeat tests within 48hrs were considered to be the same AKI event. When analysing time to response, AKI events were excluded if no repeat test had occurred within 14 days to avoid infinite time bias. Baseline data were collected between Jan 2015-Oct 2015. The study was undertaken from Oct 2015 to Aug 2016. The follow up period was Aug 2016-Apr 2017. All groups had e-alerts after August 2016. Yates algorithm analyzed the impact of each intervention during the study period. Time to response and mortality pre and post the intervention period was analyzed using Mann U Whitney and Chi Square respectively.

Results: 1807 (0.8%) primary care blood tests demonstrated AKI1-3 (78.4% AKI1, 14.8% AKI2, 6.9% AKI3). There were 391 AKI 2 & 3 from 251 patients. A total of 234 AKI events met all inclusion criteria. E-alerts demonstrated a marked reduction in mean response time (-29.2hrs) and educational outreach had a modest impact (-3.5hrs). Median response to AKI 2 & 3 pre and post interventions was 27 hours v 16 hours respectively (p=0.037). AKI event related 30-day mortality was significantly less (18.4% v 4.1% p=0.036).

Conclusions: AKI e-alerts in primary care hastens response to AKI and may reduce mortality. Educational outreach sessions further improve response time.

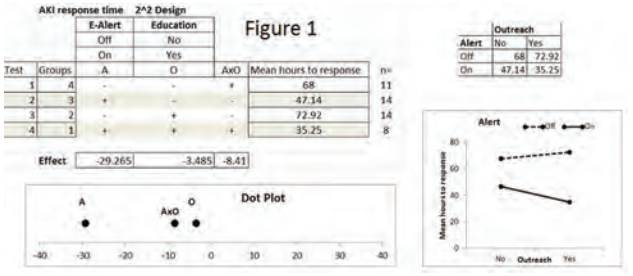


Figure 1: Yates algoirthm (left), response plot (right)

FR-PO105

AKI and CKD after Allogeneic Hematopoietic Stem Cell Transplantation (HSCT) – A Retrospective Analysis Elena K. Kirilova,[1] Jan Kowald,[3] Friedrich Stölzel,[1] Martin Bornhauser,[2] Christian Hugo.[4] *[1]Uniklinik Dresden, Dresden, Germany; [2]University Hospital, Dresden, Germany; [3]University Hospital of Dresden, Dresden, Germany; [4]University of Dresden, Dresden, Germany, Dresden, Germany.*

Background: Acute kidney injury is a common complication after HSCT and the procedure-related mortality rate increases with the stage of acute kidney injury. In the present study we assessed incidence and risk factors for acute kidney injury, chronic kidney disease and delta eGFR after HSCT.

Methods: In this retrospective study we included 312 patients which received allogeneic HSCT at our center between Jan. 2012 and Dec. 2014. The patients have been followed up until December 2016. We assessed Kidney function through documentated serum creatinine values. We evaluated the following risk factors before transplantation: age, co-morbidity index, previous CKD, diabetes mellitus, arterial hypertension, previous chemotherapy, conditioning regimens, stem cell source, HLA compatibility and relationship between donor and patient. Among the evaluated risk factors after transplantation were the complications: acute and chronic graft versus host disease, sepsis, cytomegalovirus reactivation, sinusoidal occlusive disease, immunosuppressive therapy, nephrotoxic medications and contrast medium.

Results: The incidence of acute kidney injury (AKI) amounts to 63.5 % (AKI stage 1: 27.8 %, AKI stage 2: 39.9 % and AKI stage 3: 32.3 %). Chronic kidney disease was found in 203 patients (65.1 %). 109 Patients (34.9%) did not show any signs of CKD. 127 patients (40.7%) from 203 patients with CKD after HSCT have developed CKD for the first time after HSCT. Multivariate analysis showed that CKD before HSCT and sepsis, contrast media and duration of the stay in an intensive care unit after HSCT were risk factors for AKI. Age, duration of the therapy with CsA and the count of acute kidney injuries were risk factors for chronic kidney disease in the multivariate analysis. Risk factors in the multivariate analysis for eGFR ≥ 15 ml/min/ 1.73 m^2 one year after HSCT were acute graft versus host disease and sepsis. Sepsis was the only risk factor in the multivariate analysis associated with mortality after HSCT.

Conclusions: AKI and CKD are common complications after HSCT. Sepsis was a universal risk factor in the multivariate analysis which was associated not only with kidney injury but also with excess mortality. The mortality rate after HSCT is high mostly in the first 6 months.

FR-PO106

The Epidemiology and Impact of Fluid Balance on Outcomes in Critically Ill Near-Term/Term Neonates: A Report from the AWAKEN Study David T. Selewski,[14] Ayse Akcan Arikan,[1] Elizabeth Bonachea,[8] Katja M. Gist,[12] Stuart Goldstein,[5] Mina Hanna,[13] Catherine Joseph,[15] John D. Mahan,[9] Arwa Nada,[6] Amy Nathan,[4] Kimberly J. Reidy,[3] Amy Staples,[15] Pia Wintermark,[7] Louis J. Boohaker,[2] Russell Griffin,[10] David J. Askenazi,[11] Ronnie Guillet.[16] *[1]Baylor College of Medicine, Houston, TX; [2]Children's of Alabama, Hoover, AL; [3]Children's Hospital at Monte iore/ Albert Einstein College of Medicine, Bronxville, NY; [4]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [5]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [6]LeBonheur Children's Hospital, Memphis, TN; [7]McGill University, Montreal, QC, Canada; [8]Nationwide Children's hospital, Columbus, OH; [9]Nationwide Children's Hospital, Columbus, OH; [10]University of Alabama at Birmingham, Birmingham, AL; [11]University of Alabama at Birmingham, Birmingham, AL; [12]University of Colorado, Children's Hospital Colorado, Aurora, CO; [13]University of Kentucky, Lexington, KY; [14]University of Michigan, Ann Arbor, MI; [15]University of New Mexico, Albuquerque, NM; [16]University of Rochester, Rochester, NY. Group/Team: On behalf of Neonatal Kidney Collaborative.*

Background: Neonates in the neonatal intensive care unit(NICU) are at increased risk of AKI and disorders of fluid balance(FB). Although normal term neonates are expected to lose weight (5-10%) over the first week of life, a paucity of data exists on FB in critically ill neonates. We aim to evaluate FB in the first week of life in a multi-center cohort of critically ill near-term/term neonates and the impact of FB on outcomes.

Methods: The Assessment of Worldwide Acute Kidney injury Epidemiology in Neonates (AWAKEN) study included NICU admissions at 24 institutions (4 countries) from 01/14-03/14. Inclusion criteria: intravenous fluids for ≥48 hrs. Exclusion criteria: congenital heart disease repair at ≤7 days of life(DOL), lethal anomaly or death at ≤48 hrs. This analysis includes infants ≥36 wks gestational age admitted by DOL 7. FB was defined by percentage change in weight from birthweight(BW). Outcomes: Mechanical ventilation(MV) at DOL 7, NICU mortality

Results: 749 neonates were included, median peak FB was 0.6%(-0.8, 4.3) and occurred at a median DOL 2(IQR 1,5). Peak FB over the first week was: <0%(<BW) in 231(30.5%), 0-5% in 345(45.4%), 5-10% in 90(11.9%), 10-15% in 39(5.1%), and >15% in 44(5.9%). 67(9%) were on MV on DOL 7 and 17(2.3%) died. Table 1 describes the association of variables, including FB, with MV at DOL 7. FB was not associated with mortality.

Conclusions: The AWAKEN study describes for the first time, the epidemiology and impact of FB in critically ill near-term/term neonates. Over half of the cohort had a positive peak FB in the first week of life. Peak FB during the first week of life was associated with the need for MV at DOL 7.

	MV at 7 days (N=67)	No MV at 7 days (N=682)	p
Birthweight ≥ 2501 gm	55 (82.1%)	560 (82.5%)	0.83
Apgar 1 Minute*	5 (2, 8)	8 (5, 9)	<0.001
Apgar 5 Minutes*	8 (6, 9)	9 (7, 9)	<0.001
Acute Kidney Injury	21 (31.3%)	151 (22.1%)	0.09
Diagnosis			
Respiratory failure	38 (56.7%)	185 (27.1%)	<0.001
Sepsis evaluation	30 (44.8%)	296 (43.4%)	0.83
Hypoxic Ischemic Encephalopathy	12 (17.9%)	73 (10.7%)	0.08
Congenital heart disease	10 (14.9%)	52 (7.6%)	0.04
Fluid Balance			
Peak Fluid Balance*	5.2%(0, 11.9)	0.3%(-0.9, 3.9)	<0.0001
Fluid Balance DOL 3*	0%(-2.0, 2.7)	-1.4%(-3.6, 0.6)	0.01
Fluid Balance DOL 7*	3.6%(-0.3, 11.0)	-1.3%(-4.7, 2.4)	<0.0001

*Median(IQR)

Table 1: Association of variables with Mechanical Ventilation at day of life 7

FR-PO107

Epidemiology of AKI among Hospitalized Children in China Sheng Nie,[2] Fan Fan Hou,[1] Xin Xu.[3] *[1]Nanfang Hospital, Guangzhou, China; [2]National Clinical Research Center for Kidney Disease of China, State Key Laboratory of Organ Failure Research, Nanfang Hospital, Southern Medical University, Guangzhou, China; [3]Renal Division, Nanfang Hospital, Southern Medical University; National Clinical Research Center for Kidney Disease, Guangzhou, China.*

Background: High quality epidemiological data on acute kidney injury (AKI) in children are particularly lacking in Asian countries.

Methods: We performed a nationwide, multicenter study in a cohort of hospitalized children aged 1 month to 18 years from 25 general and children's hospitals in China during 2013-2015. We obtained patient-level data from the electronic hospitalization information system and laboratory databases of all inpatients who had at least two serum creatinine tests within any 7-day window during their first 30 days of hospitalization. We identified AKI events according to the creatinine criteria of Kidney Disease Improving Global Outcomes.

Results: A total of 20 006 (19.6%) AKI cases were identified among 102 107 pediatric inpatients analyzed, of which 7283 (7.1%) were community acquired and 12 723 (12.5%) hospital acquired. Up to 96% of these AKI events were not diagnosed on the discharge records. The cumulative incidence of AKI in infants (27.6%) doubled that in adolescents (11.9%). The profiles of risk factors differed between CA- and HA-AKI and varied with age. Diarrhea and sepsis were the top risk factors for CA-AKI, contributing to 5.7% and 5.5% of the risk, respectively. Congenital heart disease/cardiac surgery was the major risk factor for HA-AKI, contributing to 18.7% of the risk. Exposure to nephrotoxic drugs, mostly non-steroidal anti-inflammatory drugs and proton pump inhibitors, was common in hospitalized children and associated with an increased risk of AKI. Death occurred in 845 of 20 006 patients (4.2%) with AKI *versus* 451 of 82 101 children (0.5%) without AKI. The risk of in-hospital death was higher among children with severe AKI, shock and respiratory failure. Pediatric AKI was associated with longer hospital stay and higher daily cost, even after adjustment for covariates.

Conclusions: Pediatric AKI is common with substantial under-diagnosis in China.

Funding: Government Support - Non-U.S.

FR-PO108

Variation in Community-Based AKI Trends Using Administrative Codes versus Serum Creatinine Values Among >5 Million Adults Between 2004-2014 Alan S. Go,[1] Chi-yuan Hsu,[2] Thida C. Tan,[1] Kathleen D. Liu,[2] Sijie Zheng,[1] Jingrong Yang.[1] *[1]Kaiser Permanente Northern California, Oakland, CA; [2]University of California San Francisco, San Francisco, CA.*

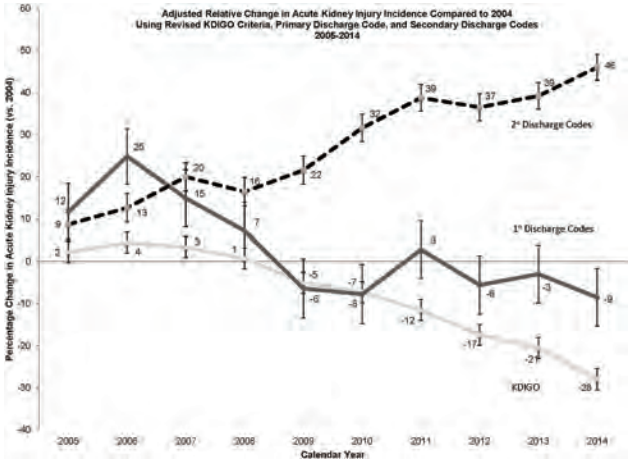
Background: We evaluated potential variation in community-based temporal trends in acute kidney injury (AKI) incidence using administrative codes vs. serum creatinine (SCr)-based changes.

Methods: In Kaiser Permanente Northern California, a large integrated healthcare delivery system, we identified all hospitalized AKI episodes between 2004-2014 using revised KDIGO criteria (≥50% relative rise in SCr from baseline, ≥0.3 mg/dL SCr increase within 48 hours or receipt of acute dialysis) (KDIGO-AKI) vs. primary or secondary discharge ICD-9 diagnostic codes (DIAG-AKI). We examined age-sex-adjusted incidence and multivariable-adjusted incidence of AKI per year using each AKI definition.

Results: Among 5,253,185 adults, mean age was 48 years, 53% were women and 45% were minorities. Age-sex-adjusted incidence (per 100,000 person-years) of KDIGO-AKI rose from 587 in 2004 to 645 in 2006 but then decreased progressively to 471 by 2014. In contrast, age-sex-adjusted incidence of primary DIAG-AKI remained stable over time, while secondary DIAG-AKI consistently increased from 297 in 2004 to 484 in 2014. After adjustment for potential confounders using Poisson regression, compared with 2004, the relative incidences of KDIGO-AKI and primary DIAG-AKI peaked in 2006 but decreased through 2014; however, the relative incidence of secondary DIAG-AKI steadily increased throughout the study period (Figure).

Conclusions: These data extend prior studies which have reported suboptimal operating characteristics of administrative AKI codes, with increased sensitivity for detecting AKI in later calendar years. Importantly, however, estimates of population-based temporal trends in AKI that rely solely on administrative codes to define AKI are likely to be biased compared with using SCr-based definitions.

Funding: NIDDK Support



FR-PO109

Hyperpolarized Carbon-13 MRI to Assess AKI David D. Aufhauser,[1] Mehrdad Pourfathi,[1] Douglas R. Murken,[1] Zhonglin Wang,[1] Guanghui Ge,[1] Seth Concors,[1] Wayne W. Hancock,[1,2] Matthew H. Levine.[1,2] *[1]University of Pennsylvania, Philadelphia, PA; [2]Children's Hospital of Philadelphia, Philadelphia, PA.*

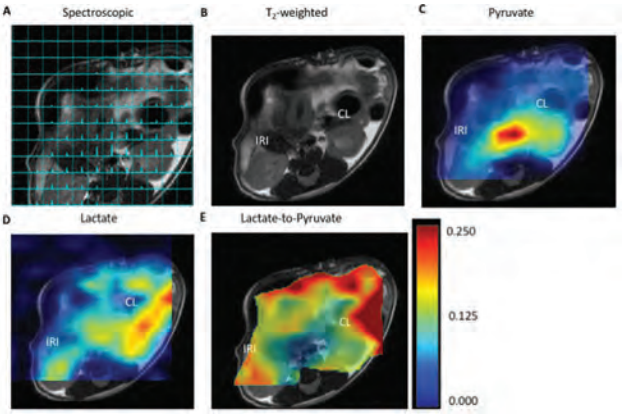
Background: Assessing the severity of renal disease often requires extended periods of observation and data collection. Hyperpolarized MRI (HP-MRI) offers a novel, noninvasive tool to probe metabolic pathways regionally with exceptional signal to noise, both in research and preclinical settings. Here we demonstrate its feasibility to assess changes in renal metabolism early after ischemia-reperfusion injury (IRI).

Methods: C57BL/6 mice were subjected to standardized unilateral warm renal IRI. 1 hour post-operatively, mice with placed in a 9.4T micro-imaging MRI system. Images were acquired using 30-mm H/^{13}C dual-tuned coils. Anatomical scans were obtained using a respiratory-gate multi-slice fast spin-echo pulse sequence. Proton T_2-weighted images were acquired using a multi-slice RARE sequence. [1-^{13}C]-pyruvate was polarized using a HyperSense DNP polarizer and injected via internal jugular venous cannula. A single-slice axial ^{13}C chemical shift image was acquired using FID-CSI sequence.

Results: Raw spectroscopic imaging data (Fig 1A) show tall peaks in each voxel indicating pyruvate signals and small peaks indicating lactate. Injured kidneys (IRI) had loss of structure on T2-weighted imaging (Fig 1B). Pyruvate intensity was higher in the control (CL) kidney (Fig 1C), and lactate-to-pyruvate ratio was elevated in the IRI kidney compared to CL (Fig 1D-E).

Conclusions: These data show that hyperpolarized [1-^{13}C]-pyruvate MRI is a promising technique to assess rapidly regional metabolic derangements associated with kidney disease, including renal IRI.

Funding: NIDDK Support, Other NIH Support - NIBIB and NHLBI



FR-PO110

Using the Kinetic eGFR (KeGFR) Formula for Estimating GFR and Detecting AKI: A Pilot Study Manohar Bairy,[1] Faith H. See,[2] Ru S. Lim.[1] *[1]TTSH Singapore, Singapore, Singapore; [2]Yong Loo Lin School of Medicine, Singapore, Singapore.*

Background: Estimating GFR when the Creatinine(Cr) is rapidly changing as in AKI has been a challenge. The KeGFR formula by S.Chen estimates GFR by factoring in the time interval between rising Cr values and the Volume of distribution(Vd). It has the added advantage of providing the clinician with a eGFR value for each non steady state Cr value. We employed the KeGFR formula to detect AKI in an adult non ICU inpatient setting. We then compared KeGFR with the current standard (AKIN and RIFLE) and newer criteria (Waikar-Bonventre, Delta Check) for AKI detection.

Methods: 250 consecutive adult patients admitted to the Medical wards were screened. Patients with a change in Cr of >4.3 % (Biological Variation) were included in the study(n=80). The KeGFR formula was applied to this cohort after calculating the Vd individually after estimating the initial GFR by MDRD. A fall in eGFR of 25% or more was considered as AKI. The AKIN, Waikar-Bonventre, RIFLE and Delta Check criterion were also applied to this cohort and compared with the KeGFR criterion.

Results: Forty nine patients had AKI by AKIN classification. All but one patient (30) found to have AKI by KeGFR criterion fulfilled the AKI definition by AKIN(Table 1). AKIN diagnosed an additional 19 patients to have AKI. However, all of these had an elevated creatinine level on admission hence requiring the incorporation of baseline creatinine(BCr) by AKIN which is not part of the KeGFR formula. Moreover, the latest Cr value in the preceeding 3 months was assumed to be the BCr. 5 of these 19 patients were deemed not to have AKI by clinical adjudication. All patients with in-hospital AKI and progressive AKIwere detected by both the criteria.

Conclusions: The KeGFR formula can be readily applied to estimate GFR in the non-steady state. A KeGFR based criterion successfully detected progressive and in hospital AKI in this study.

Table 1Comparison of KeGFR against other AKI Criteria

Criteria	Kinetic eGFR No AKI	Kinetic eGFR With AKI	Total
AKIN			
No AKI	30	1	31
With AKI	19	30	49
Total	49	31	80
RIFLE			
No AKI	26	1	27
With AKI	23	30	43
Total	49	31	80
Waikar-Bonventre Criteria			
No AKI	48	7	55
With AKI	1	24	25
Total	49	31	80
Delta Check			
No AKI	31	12	43
With AKI	18	19	37
Total	49	31	80

FR-PO111

Low Serum Bicarbonate Levels at Admission Predict the Development of Hospital Acquired AKI: A Retrospective Cohort Study Soojin Lee,[4] Sung Yoon Lim,[1] Anna Lee,[2] Ho Jun Chin,[3] Ki Young Na,[3] Sejoong Kim.[3] *[1]Korea University Medical Center, Sungbuk-Gu, SEoul, Republic of Korea; [2]SNUBH, Gyeonggi-do, Democratic People's Republic of Korea; [3]Seoul National University Bundang Hospital, Seong nam, Republic of Korea; [4]Seoul national university hospital, Seoul, Republic of Korea.*

Background: Acute kidney injury(AKI) is a common complication and is strongly related to increase in mortality. Low serum bicarbonate levels are associated with adverse renal outcomes and increased mortality in patients with chronic kidney injury. Nevertheless, it is unknown whether lower than normal serum bicarbonate levels can predict the development of AKI in hospitalized patients. The purpose of the study was to determine whether serum bicarbonate levels at admission could be a predictor for the AKI development and mortality in hospitalized patients.

Methods: 17706 adult patients who were admitted to Seoul National University, Bundang Hospital from January 2013 to December 2013 were enrolled, retrospectively. The patients were divided into 3 groups based on serum bicarbonate levels on the first measurement of their admission. The group 1 presented below normal levels, (<23 mEq/L); group 2 presented normal levels, (23 to 27 mEq/L); and group 3 presented elevated levels, (>27 mEq/L). AKI was defined as an increase in the serum creatinine level by ≥ 0.3 mg/dL or ≥ 1.5 times of the baseline value during the hospital stay.

Results: During the median 6.0 days of hospital stay, the incidence rates of AKI and in-hospital mortality were 5.1% and 0.9%, respectively. The incidence of AKI was higher in group 1 (8.1%) than in group 2 (4.1%) and group 3 (3.6%) ($P < 0.001$). Low serum bicarbonate levels at admission were significantly associated with AKI even after the adjustment for age, sex, hypertension, diabetes mellitus, and estimated glomerular filtration rate (adjusted odds ratio [OR] 2.181, $P < 0.001$). In addition, low serum bicarbonate levels also independently predicted in-hospital mortality (adjusted hazard ratio [HR] 1.864, $P < 0.001$). Pre-existing low bicarbonate levels and subsequent development of AKI increased in-hospital mortality by 15 times, compared to the in-hospital mortality of the patients with normal bicarbonate levels and absence of AKI.

Conclusions: Low serum bicarbonate levels may be associated with the development of AKI and increase in in-hospital-mortality. Clinical trials are needed to clarify the protective role of bicarbonate replacement therapy in preventing further AKI development.

FR-PO112

Incidence and Risk Factors of AKI in the General Population Arnar J. Jonsson,[1,2] Olafur S. Indridason,[1] Sigrun H. Lund,[2] Runolfur Palsson.[1,2] *[1]Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland; [2]University of Iceland, Reykjavík, Iceland.*

Background: Acute kidney injury (AKI) in the setting of acute illness or major surgery is well described. Little is known about the burden of AKI in the general population. The purpose of this study was to estimate the incidence and risk factors for AKI in the Icelandic general population.

Methods: In this retrospective study, we obtained all serum creatinine (SCr) values from all clinical laboratories in Iceland for the years, 2008-2013. Data on age, gender, diagnoses of comorbid conditions and HbA1c values were retrieved from electronic medical records. Using computerized algorithms, we identified episodes of AKI defined according to the KDIGO criteria as a rise in SCr of ≥0.3 mg/dL over 48 hours and/or ≥50% from baseline over 7 days. CKD was defined and staged according to the KDIGO classification system. Chi-squared test and Students T-test were used to compare groups. Age-adjusted incidence was calculated for men and women and stratified by age groups and standardized to the EU27 population.

Results: We obtained 1,230,563 SCr values for 183,931 individuals aged ≥18 years. The median age was 62 years and 47.5% were men. For individuals with AKI, 19.1% had hypertension, 14.8% had diabetes, 19.5% had coronary artery disease and 10.5% had CKD compared with 6.7%, 5.3%, 5.8% and 1.2% for individuals without AKI, respectively ($p<0.001$ all variables). For men, the annual age-adjusted incidence of AKI was 1124/100,000 for stage 1, 57.7/100,000 for stage 2 and 18.1/100,000 for stage 3 AKI. In women, the annual age-adjusted incidence was 1349/100,000 for AKI stage 1, 62/100,000 for stage 2 and 21/100,000 for stage 3 AKI with significant difference between sexes ($p<0.05$). The incidence of AKI stages 1-3 rose with advancing age; it was 111/100.000, 329/100.000, 1076/100.000, 1984/100.000 and 3470/100.000 for the age groups 20-44 years, 45-64 years, 65-74 years, 74-85 years, and ≥85 years, respectively. Age-adjusted incidence of AKI stages 1-3 increased during the study period with RR of 1.026 (95%CI, 1.017-1.035) for each year.

Conclusions: This nationwide study shows a steep rise in the incidence of AKI with advancing age. Individuals who developed AKI had an increased prevalence of comorbid conditions, suggesting the need for caution in these groups of patients.

Funding: Government Support - Non-U.S.

FR-PO113

Pre-Operative Plasma TNFR1, TNFR2, and KIM-1 Are Associated with AKI and One Year Mortality in Cardiac Surgery Patients Steven G. Coca,[1] Dennis G. Moledina,[5] Yaqi Jia,[5] Sherry Mansour,[5] Heather Thiessen Philbrook,[5] Michael Shlipak,[3] Jay L. Koyner,[4] Amit X. Garg,[2] Chirag R. Parikh.[6] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]London Health Sciences Centre, London, ON, Canada; [3]San Francisco VA Medical Center, San Francisco, CA; [4]University of Chicago, Chicago, IL; [5]Yale School of Medicine, New Haven, CT; [6]Yale University and VAMC, New Haven, CT. Group/Team: TRIBE-AKI Consortium.*

Background: Plasma tumor necrosis factor receptor (TNFR)1, TNFR2, and kidney injury molecule (KIM)1 provide prognostic information in ambulatory patients with diabetes for incident or progressive kidney disease. However, their utility is not well described in settings of acute kidney injury (AKI) post cardiac surgery.

Methods: In a prospective cohort study of 1444 high-risk adults undergoing cardiac surgery (CABG, valve, or both), we sought to assess the association of pre- and post-operative (peak days 1-3) concentrations of TNFR1, TNFR2, and KIM-1 with post-operative AKI (AKIN stage 1) and 1-year all-cause mortality after cardiac surgery. Plasma TNFR1, TNFR2 and KIM-1 were measured *via* MesoScale Discovery multiplex assay.

Results: Pre-operative concentrations of TNFR1, TNFR2, and KIM-1 were higher in those who developed post-operative AKI (n=492, 34%) and those who died (n= 68, 6.2%) by one-year. Each log-increase of pre-operative biomarker was independently associated with a 2-3 fold higher odds of both AKI and one-year mortality [Table]. TNFR1, TNFR2, and KIM-1 concentrations increased by 136, 65, and 36%, respectively, after surgery, and differed minimally by AKI status. After adjustment for pre-operative biomarker value, peak change in serum creatinine and 13 other covariates, peak post-operative levels of TNFR1 and TNFR2, but not KIM-1, were associated with one-year mortality [Table].

Conclusions: The panel of three pre-operative biomarkers, TNFR1, TNFR2, and KIM1, provided strong prognostic information about AKI and mortality in patients undergoing cardiac surgery. Post-operative concentrations of TNFR1 and TNFR2 also provided additional prognostic information for death.

Funding: NIDDK Support

Biomarker	Adjusted Odds Ratio Per Doubling in Biomarker Concentration (95% Confidence Interval)	
	AKI*	One-year all-cause mortality‡
Pre-operative		
TNFR1	2.9 (2.0-4.1)	2.4 (1.2-5.0)
TNFR2	1.9 (1.4-2.5)	2.0 (1.1-3.7)
KIM1	2.1 (1.6-2.7)	2.5 (1.4-4.5)
Peak Post-operative		
TNFR1	NA	3.0 (1.4-6.4)
TNFR2	NA	4.8 (2.0-11.4)
KIM1	NA	1.1 (0.5-2.8)

*Adjusted for recipient Age (per year), recipient gender, white race (Yes/No), CPB time >120 Mins (Yes/No), non-elective surgery, surgery type, pre-op eGFR, diabetes, hypertension, CHF, history of MI, pre-op urine albumin to creatinine ratio, clinical site

‡Adjusted for above variables plus pre-operative biomarker concentration, change in serum creatinine from baseline to peak post-operative

NA- not applicable

FR-PO114

Serum and Urine FGF23 and IGFBP-7 for the Prediction of AKI in Critically Ill Children Yanhong Li. *children hospital of Soochow University, SuZhou, China.*

Background: Fibroblast growth factor 23 (FGF23) and insulin-like growth factor binding protein 7 (IGFBP-7) are novel biomarkers of acute kidney injury (AKI). We compared them with proposed AKI biomarker of cystatin C (CysC), and aimed (1) to examine whether concentrations of these biomarkers vary with age, body weight, illness severity assessed by pediatric risk of mortality III score, and kidney function assessed by estimated glomerular filtration rate (eGFR), (2) to determine the association between these biomarkers and AKI, and (3) to evaluate whether these biomarkers could serve as early independent predictors of AKI in critically ill children.

Methods: Serum and spot urine samples were collected from 144 patients during the first 24 hours after pediatric intensive care unit admission. The diagnosis of AKI developed within 120 hours of sample collection was based on the AKI network (AKIN) criteria. AKIN stage 1 was defined as mild AKI, and AKIN stages 2 and 3 were defined as severe AKI.

Results: Of the 144 patients, 21 developed AKI within 120 hours of sample collection, including 11 with severe AKI defined as AKI Network stages 2 and 3. All the serum levels of FGF23, IGFBP-7, and CysC and urinary level of FGF23 were highest among children with lowest eGFR. However, only serum FGF23 levels were independently associated with eGFR after adjustment in a multivariate linear analysis (B =-0.557, $P <0.001$). Urinary IGFBP-7 (AOR =2.94 per 1,000 ng/mg increase, $P =0.035$), serum CysC (AOR =5.28, $P=0.005$), and urinary CysC (AOR =1.13 per 1,000 ng/mg increase, $P =0.022$) remained significantly associated with severe AKI after adjustment for body weight and illness severity. Urinary IGFBP-7 level was predictive of severe AKI and achieved the AUC of 0.79 ($P =0.001$), but was not better than serum CysC(AUC =0.89, $P <0.001$) or

urinary (AUC =088, P <0.001) CysC in predicting severe AKI. However, the difference between the two AUCs of either urinary IGFBP-7 (AUC =0.79) and serum CysC (AUC =0.89) (P =0.103) or urinary IGFBP-7 and urinary CysC (AUC =0.88) (P =0.225) did not reach statistically significant.

Conclusions: Serum FGF23 levels were inversely related to measures of eGFR, and an increased urinary IGFBP-7 level was independently associated with the increased risk of severe AKI, but not superior to serum or urinary CysC in predicting severe AKI in critically ill children.

FR-PO115

Early Increase in Renal Injury Urinary Biomarkers Is Associated with AKI Development in Major Elective Non-Vascular Abdominal Surgeries Lia J. Marçal,[1] Graziela R. Souza,[1] Veronica T. Costa e Silva,[1] Dirce M. Zanetta,[2] Luis Yu,[1] Leila Antonangelo,[1] Emmanuel A. Burdmann.[1] *[1]University of Sao Paulo Medical School, Sao Paulo, Brazil; [2]University of São Paulo, S Paulo, Brazil.*

Background: There are few data on the incidence of acute kidney injury (AKI) diagnosed by KDIGO criteria and the role of renal injury urinary biomarkers (BMs) for predicting AKI in patients (pts) submitted to major elective non-vascular abdominal surgeries (MENVAS).

Methods: A total of 171 pts submitted to MENVAS were prospectively assessed peri-operatively and from the ICU admission up to 7 d. Analyzed outcomes were AKI development, ICU and hospital length of stay (LoS) and mortality. AKI was diagnosed by serum creatinine increase or urinary output decrease (KDIGO criteria). Urine was collected 1 day before surgery (baseline), 30 min, 12 and 24 h after ICU admission. Five urinary BMs were assessed: NGAL, KIM-1, monocyte chemotactic protein 1 (MCP1), microalbuminuria (μalb) and interleukin-18 (IL-18) by Luminex x-MAP method. Data are mean (± SD), frequency or median (first and third quartiles). Statistical significance was set at p<0.05.

Results: Overall, age was 54±16 y, 59% were female, hospital LoS was 17.0±16.6 d, ICU LoS was 3.0±1.7 d and mortality was 7%. A total of 102 pts (59.6%) developed AKI and most were KDIGO I (81.4%). AKI pts were older (57±13 vs. 50±17 y, p=0.006), had longer hospital (20±20 vs. 12±8 d, p=0.001) and ICU LoS (3.3±2.0 vs. 2.5±0.8 d, p=0.02) and higher mortality (9.8 vs. 2.3%, NS), compared to non-AKI. Those developing AKI KDIGO II and III had significantly higher BMs values compared to pts KDIGO I or non-AKI in all studied times (Table).

Conclusions: We found a strikingly high incidence of MENVAS-associated AKI diagnosed by KDIGO criteria in patients admitted to the ICU. AKI was associated with significantly higher ICU and hospital LoS. Those who developed more severe AKI showed significantly higher BMs in all times studied, including the preoperative period.

Funding: Government Support - Non-U.S.

	baseline			30 minutes - ICU			12h - ICU			24h - ICU		
	non-AKI	KDIGO I	KDIGO II/III	non-AKI	KDIGO I	KDIGO II/III	non-AKI	KDIGO I	KDIGO II/III	non-AKI	KDIGO I	KDIGO II/III
MCP-1 ng/mg	0.1 (0.1-0.2)**	0.1 (0.1 – 0.2)###	0.4 (0.2 - 0.9)	0.4 (0.2 - 1.6)°	0.5 (0.3 – 1.0)#	1.6 (0.8 - 5.1)	0.8 (0.4 - 1.4) *	0.6 (0.2- 1.3) ##	2.1 (1.1 - 4.1)	0.5 (0.3 - 1.5)*	0.7 (0.3 - 1.7)#	1.7 (0.8-4.1)
IL-18 pg/mg	19 (9 - 41)	16 (8 - 33)#	36 (13 - 300)	35 (12 - 125)	25 (10 - 62)	88 (16 - 281)	19 (9 - 41)	16 (8 - 33)##	36 (13 - 300)	34 (10 - 115)	18 (10 -65)#	76 (20 - 261)
KIM-1 ng/mg	0.2 (0.1-0.3)$**	0.2 (0.1 - 0.5)###	0.6 (0.3 - 1.2)	0.3 (0.2 -0.8)**	0.4 (0.2 - 0.8)##	1.0 (0.5 - 1.8)	0.7 (0.3 - 1.6) *	0.7 (0.2 - 1.6) ##	2.0 (0.8 - 3.5)	1.0 (0.4 - 1.8)*	1.0 (0.4-1.8)#	2.0 (1.3 - 5.1)
μAlb μg/mg	6 (2 - 20)***	6 (2 - 14)###	44 (13 - 76)	25 (11 - 68)*	27 (16-49)#	69 (29 - 83)	27 (9-53)	16 (9 - 31) #	31 (29 - 83)	27 (11 - 50)	22 (10 - 40)	33 (15-69)
NGAL μg/mg	26 (13 - 63)**	27(13 - 60)##	60 (43 - 369)	46 (17 - 97)**	42 (20 - 134)##	191 (52 - 447)	40 (17 - 87) **	28 (11 - 76) ###	173 (59-615)	48 (25-134)*	57 (25 - 139)	243 (37 - 1518)

KDIGO II/III vs non-AKI: * p<0.05; ** p<0.01; *** p<0.001

KDIGO II/III vs KDIGO I: # p<0.05; ## p<0.01; ### p<0.001

FR-PO116

The iTRAQ Technology Identifies Biomarkers for the Early Diagnosis of Contrast-Induced AKI Lina Han,[2,3] Qun Luo,[2,3] Fangfang Zhou,[2,3] Gen Shen,[4,3] Honghua Ye,[4,3] Zemin Wang,[1] Yumei Li.[1] *[1]Ningbo NO.2 Hospital, Ningbo, China; [2]Department of Nephrology, Ningbo NO.2 Hospital, Ningbo City, China; [3]School of Medicine, Ningbo University, Ningbo, China; [4]Department of Cardiology, Ningbo NO.2 Hospital, Ningbo, China.*

Background: This study was to detect differentially expressed urine proteins in contrast-induced acute kidney injury (CI-AKI) patients after percutaneous coronary intervention(PCI) by Isobaric Tags for Relative and Absolute Quantitation (iTRAQ) technology, and to find new biomarkers for early diagnosis of CI-AKI.

Methods: We collected urine samples of older patients(>60yrs) before PCI and at 6hrs after PCI. And the samples were collected between July 1st 2015 and Jan 31st 2016 in Ningbo No.2 Hospital. Blood collected for biochemical analyses. iTRAQ technique was used to screen differentially expressed proteins, and to identify potential biomarkers by analysis of the biological process, cellular components, molecular functions, Kyoto Encyclopedia of Genes and Genomes(KEGG) pathways and protein-protein interactions(PPI).

Results: 48 older patients admitted for elective PCI were included in the study. Among these patients, 6 (4 male cases and 2 female cases) developed CI-AKI. In our study, the mean Scr levels were measured at 24h (121.80 ±54.31umol/L vs 94.43±33.56umol/L, P=0.059) and 48h (133.1±41.21umol/L vs 94.43 ±33.56umol/L, P=0.009) after PCI in the CI-AKI patients. Comparing to patients before PCI, a total of 151 proteins were identified in the CI-AKI group (6hrs after PCI). 74 proteins were up-regulated and 77 proteins were down-regulated. We identified 20 biological process, 20 cellular components, 20 molecular functions and 10 significant KEGG pathways. Combined with the PPI results, mannan-binding lectin (MBL)-associated serine protease 2 (MASP2), angiotensinogen (AGT) and apolipoproteins A-I(apoA-I) might play a role in the pathogenesis of CI-AKI.

Conclusions: 1. The quantitative iTRAQ technology provided an accurate and effective assessment of identifying and profiling potential urine biomarkers for early diagnosis of CI-AKI in this study.2. Our research showed that MASP2, AGT, and apoA-I were significantly up-regulated at 6hr after PCI. And they were earlier than Scr for diagnosis of CI-AKI. They were potential urine biomarkers and played key roles in the pathogenesis of CI-AKI.

Funding: Government Support - Non-U.S.

FR-PO117

Relationship of Cardiac Biomarkers and AKI: The ASSESS-AKI Study Kathleen D. Liu,[6] Chi-yuan Hsu,[6] Thida C. Tan,[2] Valerie Arends,[8] Amy Saenger,[8] Chirag R. Parikh,[11] Talat Alp Ikizler,[10] Jonathan Himmelfarb,[3] Mark M. Wurfel,[12] Vernon M. Chinchilli,[5] Paul L. Kimmel,[4] James S. Kaufman,[9] Alan S. Go.[2] *[2]Kaiser Permanente Northern California, Oakland, CA; [3]Kidney Research Institute, Seattle, WA; [4]National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; [5]Penn State College of Medicine, Hershey, PA; [6]University of California San Francisco, San Francisco, CA; [8]University of Minnesota, Minneapolis, MN; [9]VA New York Harbor Healthcare System, New York, NY; [10]Vanderbilt University Medical Center, Nashville, TN; [11]Yale University and VAMC, New Haven, CT; [12]University of Washington, Seattle, WA. Group/Team: For ASSESS-AKI Study Investigators.*

Background: Several studies have reported AKI is associated with an increased risk of cardiovascular events after hospital discharge, especially heart failure. However, little is known about whether AKI impacts heart failure biomarker levels.

Methods: ASSESS-AKI study is a parallel cohort study of hospitalized AKI and matched non-AKI patients enrolled in 2009-2015. Plasma biospecimens were collected during the index hospitalization (V0) and at the first outpatient study visit 3 months later (V3) and tested for levels of Suppression of tumorigenicity 2 (ST-2) and galectin-3 (GAL-3) using clinical grade ELISA assays (Critical Diagnostics and BG Medicine, respectively).

Results: Mean age of the 1,484 participants analyzed was 55 yr, 48% were women, and baseline (pre-index admission) eGFR was 69 mL/min/1.73m^2. Compared to non-AKI patients, ST-2 and GAL-3 levels were higher in AKI patients during the index hospitalization and at V3 (Table), and both duration and severity of AKI were associated with biomarker levels (p< 0.001 for all comparisons). Of note, ST-2 levels fell markedly from V0 to V3 in both groups, to median ST-2 levels that are typically associated with a lower risk of heart failure (< 35 ng/mL).

Conclusions: ST-2 and GAL-3 are elevated during an episode of AKI, with GAL-3 remaining elevated but ST-2 declining at 3 months post-discharge. Future studies should determine whether patients with persistently elevated biomarker levels after AKI are at increased cardiovascular risk.

Funding: NIDDK Support

	V0: AKI	V3: AKI	P value	V0: No AKI	V3: No AKI	P value
ST-2 (ng/mL)	105.5 (51.5-306)	28.3 (22.8-37.9)	<0.0001	64.5 (33.4-184)	25.2 (20.5-31.4)	<0.0001
Galectin-3 (ng/mL)	18.5 (13.2-26.1)	17.5 (13.1-22.9)	<0.0001	13.3 (10.5-17.1)	15.1 (12.1-19.3)	<0.0001

* Comparing V0 to V3 levels, by AKI status

FR-PO118

Measurements of Volatile Organic Compounds by Proton-Transfer-Reaction Mass Spectrometry for the Diagnosis of AKI in the Intensive Care Unit Michael G. Janech,[1] Mohammed Z. Mohialdeen,[1] Anand Achanti,[1] Milos N. Budisavljevic,[1] Juan Carlos Q. Velez,[2] Nithin Karakala,[3] John M. Arthur,[3] Peter A. Lee.[4] *[1]Department of Medicine, Division of Nephrology, Medical University of South Carolina, Charleston, SC; [2]Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA; [3]Division of Nephrology, Department of Medicine, University of Arkansas for Medical Sciences, Little Rock, AR; [4]Department of Biology, College of Charleston, Charleston, SC.*

Background: Current biomarkers for acute kidney injury (AKI) in the intensive care unit (ICU) do not offer real-time detection capability, are based on serum creatinine or urine proteins, and diagnostic levels significantly lag behind the injury. A lesser explored area of AKI biomarker research is the volatile organic compound (VOC) space. The goal of this pilot study was to assess whether detection of VOCs using a mass spectrometer conducive to near real-time detection capability could detect urine VOCs and classify or characterize patients with AKI in the ICU.

Methods: Urine specimens (40 mL) from 32 ICU subjects with or without AKI (AKIN criteria) were collected at bedside and transferred to an adjacent laboratory for Proton-Transfer-Reaction Mass Spectrometry (PTR-MS)-based analysis. VOCs were detected in positive hydronium ion mode and spectra were background subtracted and aligned. Individual VOCs were assessed for ability to classify AKI or no AKI using

area under ROC (AUC) curves. Parametric statistics were utilized for individual VOC comparisons between AKI and non-AKI groups.

Results: 105 VOC masses were detected in urine from 32 ICU patients. Mean serum creatinine values were 3.3 ± 3.0 mg/dL for the AKI group (n=14) and 0.9 ± 0.3 mg/dL for the non-AKI (n=18) group. Ten masses comprised 98% of the signal intensity and were less than 63 m/z suggesting that more volatile components were better detected. Eighteen masses were significantly lower in AKI subjects (1.2 to 13 fold lower, P<0.05). A single VOC, putatively identified by molecular weight as formic acid or ethanol (47.2 m/z), was elevated 2-fold in AKI patients compared to non-AKI patients (AUC = 0.70; p=0.03). When the ratio of 47.2 and 70.9 m/z was calculated, this resulted in a better classifier (AUC = 0.78) than 47.2 m/z alone.

Conclusions: PTR-MS has the capability to detect urine VOCs. Elevated urinary formic acid/ethanol combined with a reduction in several VOCs may provide value for early real-time detection of AKI in the ICU. This platform may provide diagnostic and prognostic information during AKI.

Funding: Other NIH Support - NIH/NCATS CTSA/SCTR

FR-PO119

Pre-Operative Level of Fibroblast Growth Factor 23 Is Associated with the Risk of Developing Severe AKI after Heart Surgery Stuart Goldstein,[2] Oded Volovelsky.[1] *[1]Center for Acute Care Nephrology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [2]Center for Acute Care Nephrology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

Background: Fibroblast growth factor 23 (FGF23) has been assessed as an early AKI biomarker after renal ischemia in animals and humans. FGF23 is an early marker of chronic kidney disease in humans. We assessed the ability of pre-operative FGF23 to predict severe AKI after cardiac surgery in children.

Methods: Blood and urine samples were collected in a prospective observational study from 83 children with congenital heart disease. Serum creatinine, cystatin C, FGF23 and urine levels of NGAL, IL18, KIM-1, L-FABP were assessed pre-operatively. Severe AKI (sAKI; KDIGO stages II-III) was the primary outcome. Non-parametric multivariable linear regression and ROC analyses were used to evaluate the association between pre-operative FGF23, urine markers and the development of sAKI in the first week after CS.

Results: Median age [IQR] was 7 (2.2, 61) months and median bypass time was 135 [89,205] minutes. Surgical severity level, Cystatin C and urinary biomarkers did not differ between pts with vs. without sAKI. Pre-operative FGF23 was higher in pts who developed sAKI (Table) The AUC-ROC for preoperative FGF23 level to predict sAKI was 0.75 (0.56-0.95). Logistic regression of FGF23 had superior odd ratio for severe AKI (4.96).

Conclusions: Pre-operative FGF23 levels were associated with developing sAKI after CS. Current biomarker strategies focus on early postoperative diagnosis and treatment of AKI. Preoperative identification of children with higher risk of AKI after CS may help in developing AKI prevention strategies and risk stratification scores.

Preoperative parameters	Severe AKI		Without severe AKI		p-value
	Median	IQR	Median	IQR	
Age (days)	0.4	0.34, 9.1	0.8	0.02, 2.3	0.08
RACHS score	3	2, 4	2	2, 3	0.09
FGF23 level	572	275, 1294	498	226, 928	0.0008
Cystatin C GFR	88.5	66.5, 126	96	67, 122	0.81
NGAL	3.06	2.7, 29.2	3.48	2, 6.9	0.60
IL18	97.76	16.61, 108.2	28.6	12.7, 63.2	0.27
KIM1	273	194, 390	534	239, 831	0.08
LFABP	2.5	0.7, 4.4	2.2	0.7, 4	0.89

IQR = Interquartile range

FR-PO120

Glyco-iELISA: A Novel Assay to Detect STEC-HUS Kioa L. Wijnsma,[1] Susan Veissi,[1] Juan E. Ugalde,[3] Diego J. Comerci,[3] Nicole Van De Kar,[1] Bert Van den heuvel.[2,4] *[1]Pediatrics, Radboud medical center, Nijmegen, Netherlands; [2]Radboudumc, Nijmegen, Netherlands; [3]Universidad Nacional de San Martin, San Martin, Argentina; [4]Pediatrics, University Hospital Leuven, Leuven, Belgium.*

Background: Differentiation between hemolytic uremic syndrome (HUS) caused by Shiga toxin-producing *E. coli* (STEC-HUS) or a dysregulated complement system (atypical HUS; aHUS) is a clinical conundrum. As aHUS, whose treatment requires the highly expensive orphan drug eculizumab, is a diagnoses *per exclusionem*, a method to reliably detect STEC infection is warranted. Since the current golden standard (fecal diagnostics; FD) for the detection of STEC infection has important drawbacks, serological detection of antibodies against STEC-associated lipopolysaccharides by ELISA (LPS-ELISA) has proven its value. However, LPS-ELISA have important limitations. Therefore, we have developed and evaluated the diagnostic value of ELISA employing recombinant glycoproteins of STEC-associated LPS (glyco-iELISA).

Methods: In this retrospective study, patients (n=61) who presented with clinical STEC-HUS in the Radboudumc, Nijmegen, Netherlands, between 1990-2014 were included. Clinical, diagnostic and follow up data were gathered. Both LPS-ELISA and glyco-iELISA were employed to detect IgM antibodies against the most common serotype of STEC (*O157*).

Results: FD, LPS-ELISA, and glyco-iELISA identified STEC infection in respectively, 53%, 64%, and 75% of patients. Glyco-iELISA provided evidence of STEC infection in 7 (11%) and 20 (33%) additional patients when compared to LPS-ELISA or FD, respectively. Combining the glyco-iELISA with FD identified STEC infection in 89% of patients. The glyco-iELISA appeared highly reproducible and reliable, as the intra- and inter-assay variability was low.

Conclusions: The glyco-iELISA is a highly sensitive and accurate serological method to detect STEC in HUS patients. Combined with FD, the glyco-iELISA improves STEC detection by 36%. Thus, the glyco-iELISA may drastically limit the unnecessary use of eculizumab in STEC-HUS.

FR-PO121

Raised Serum Creatinine and Decrease in Renal Cyp2c11 Gene Expression in Bile Duct Ligated Rats Is Attenuated by the Adsorbent of Gut Bio-Toxins: YAQ001 Amin Oomatia,[1] Francesco Chiara,[2] Jane Macnaughtan,[2] Rajiv Jalan.[2] *[1]Centre for Nephrology, University College London, London, United Kingdom; [2]Institute for Liver and Digestive Health, University College London, London, United Kingdom.*

Background: Renal dysfunction confers a poor prognosis in patients suffering from acute-on-chronic liver failure. Bile duct ligation (BDL), an established model for cholestatic liver injury, potentiates LPS mediated acute kidney injury (AKI) in rats. Gut decontamination using antibiotics attenuates this, suggesting translocation of gut flora products in cirrhosis may prime the kidney for exaggerated inflammatory responses. Yaq001 (YQ) is a non-absorbable, ingested carbon polymer, which adsorbs and reduces translocation of biotoxins. We investigated the effect it has on BDL rats.

Methods: Sprague-Dawley rats underwent either BDL or sham laparotomy and were then randomised to normal or YQ supplemented chow for 2-weeks. At four weeks, LPS or saline was injected intraperitoneally. Rats were sacrificed two hours later. Serum and tissue were collected. Next generation sequencing of RNA expression in rat kidney (sham vs BDL vs BDL+YQ, n=2 vs 3 vs 3) was performed for 17,327 and then analysed using DESeq2 workflow.

Results: Serum creatinine (SC) of groups of interest are shown in table 1. A difference in SC in BDL+LPS+YQ vs BDL+LPS rats was seen (32vs41 μmol/L), and tended towards statistical significance (p=0.086). Differential gene expression was significant (q<0.05) for a 107 genes in the BDL vs Sham groups, and 886 in the BDL vs BDL+YQ groups. Shrunken log2 fold change of expression for Cyp2c11, a CYP450 enzyme, was decreased in Sham vs BDL (8.66 vs 6.64, q=0), only to return to normal levels with treatment Yaq001 (5.87 vs 8.11, q=0.001).

Conclusions: BDL predisposes rats to AKI when faced with a septic insult, which is attenuated by Yaq001. Decrease in Cyp2c11 expression in BDL animals, which is normalised by Yaq001, suggests that disruption of cellular responses to oxidative stress may account for why kidneys in BDL rats and possibly cirrhotic patients are more susceptible to septic injury. Further research is needed to determine the effects of Cyp2C11 dysregulation and its effects on kidneys in cirrhosis.

Funding: Commercial Support - Yaqrit, Government Support - Non-U.S.

Table 1

	Sham	BDL	BDL+YQ	Sham+LPS	BDL+LPS	BDL+LPS +YQ
(n)	22	29	27	8	12	8
Median SC (μmol/L)	28.1	32	31	24.5	41	32
Range (μmol/L)	21.2-39	23-40	18.8-44.2	19.8-32.6	22.4-60	25.3-38
	p=0.024			p=0.004		

FR-PO122

Plasma Cytokines Are Associated with Increased AKI and 1-Year Mortality after Cardiac Surgery Dennis G. Moledina,[6] Sherry Mansour,[6] Yaqi Jia,[6] Heather Thiessen Philbrook,[6] Jay L. Koyner,[5] Eric McArthur,[2] Amit X. Garg,[3] Francis P. Wilson,[6] Michael Shlipak,[4] Steven G. Coca,[1] Chirag R. Parikh.[7] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Institute for Clinical Evaluative Sciences, London, ON, Canada; [3]London Health Sciences Centre, London, ON, Canada; [4]San Francisco VA Medical Center, San Francisco, CA; [5]University of Chicago, Chicago, IL; [6]Yale School of Medicine, New Haven, CT; [7]Yale University and VAMC, New Haven, CT. Group/Team: TRIBE-AKI.*

Background: Inflammatory pathways are activated in ischemia reperfusion injury (IRI) and their decreases IRI-related acute kidney injury (AKI) and improves survival in animal models. However, the significance of these pathways in humans is unknown

Methods: In the TRIBE-AKI cohort of high-risk adults who underwent cardiac surgery (n=1444), we measured 10 inflammatory cytokines [interferon (IFN)-γ, tumor necrosis factor(TNF)-α, interleukin (IL)-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12p70, and IL-13] from plasma samples collected after cardiac surgery using Mesoscale multiplex assay. We tested the association of peak postoperative cytokine values with postoperative AKI Network stage 1 AKI and 1-year mortality

Results: AKI occurred in 492 and 1-year mortality in 81 participants. Higher cytokine levels were independently associated with increased odds of AKI and 1-year mortality for 10 cytokines in the model adjusted for 14 key variables (**Figure**). After further adjustment for IL-6, only IL-2, IL-8 and IL-10 remained significantly associated with 1-year mortality, and IL-10 with AKI. Given that cytokines in the multiplex were highly collinear, we performed principal component analysis to combine these cytokines. Adding the principal components to the clinical model consisting of the above 14

variables improved the AUC by 0.01 (P<0.001) for AKI and 0.04 (P<0.001) for 1-year mortality resulting in final AUCs of 0.77 (0.75, 0.80) and 0.76 (0.70, 0.82), respectively

Conclusions: Combination of inflammatory cytokines measured using a multiplex assay after cardiac surgery provided higher discrimination for AKI and 1-year mortality as compared with the clinical model

Funding: NIDDK Support, Private Foundation Support

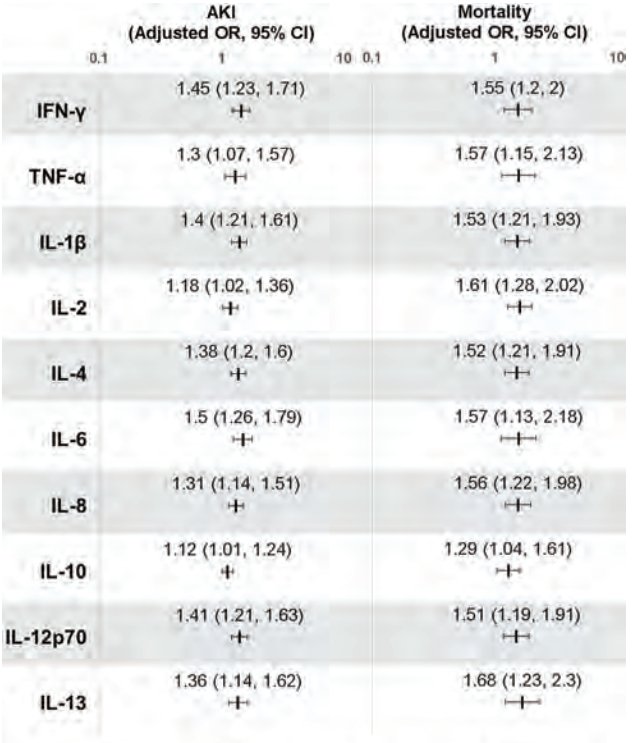


Figure. Association of plasma cytokine levels with 1-year mortality. Odds ratio (OR) per log increase in cytokine. Adjusted for age, sex, race, CPB time, non-elective surgery, surgery type, pre-op eGFR, diabetes, hypertension, congestive heart failure, myocardial infarction, pre-op urine albumin to creatinine ratio, site, corresponding pre-operation biomarker, and change in serum creatinine from pre-op

FR-PO123

Low-Dose Atrial Natriuretic Peptide for Preventing and Treating AKI: Systematic Review and Meta-Analysis Hiroyuki Yamada,[1] Kent Doi,[2] Tatsuo Tsukamoto,[3] Kazuto Yamashita,[4] Hideyasu Kiyomoto,[5] Motoko Yanagita,[1] Yoshio Terada,[6] Kiyoshi Mori.[7] *[1]Department of Nephrology, Kyoto University Graduate School of Medicine, Kyoto, Japan; [2]Department of Acute medicine, University of Tokyo, Tokyo, Japan; [3]Department of Nephrology & Dialysis, Kitano Hospital, Tazuke Kofukai Medical Research Institute, Osaka, Japan; [4]Department of Healthcare Economics and Quality Management, Kyoto University Graduate School of Medicine, Kyoto, Japan; [5]Division of Integrated Nephrology and Telemedicine, Department of Community Support, Tohoku Medical Megabank Organization, Tohoku University, Sendai, Japan; [6]Department of Endocrinology, Metabolism and Nephrology, Kochi Medical University, Kochi, Japan; [7]Department of Nephrology and Kidney Research, Shizuoka General Hospital, Shizuoka, Japan.*

Background: Low-dose atrial natriuretic peptide (ANP) could theoretically bring about beneficial effect for acute kidney injury (AKI) as a pharmacological intervention. We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) comparing low-dose ANP with placebo or conventional therapy for the prevention or treatment of AKI.

Methods: Low dose of ANP was defined as 50 ng/kg/min or smaller according to KDIGO AKI Guideline 2012. EMBASE, PubMed and Cochrane CENTRAL databases were searched for RCTs comparing low-dose ANP with placebo or conventional therapy for patients with high risk of AKI or with AKI. Two reviewers independently collected data assessed outcomes. The primary outcome was hospital mortality. Secondary outcomes were requirement of renal replacement therapy (RRT), length of intensive care unit (ICU) stay and incidence of hypotension. The risk of bias was evaluated using Cochrane risk of bias tool. Trial sequential analysis was used for the main outcome of interest. The publication bias of the included studies was assessed by funnel plot. All the statistical analyses were performed using Review Manager Version 5.3 and TSA version 0.9 version software.

Results: A total of 18 RCTs (16 prevention, 2 treatment) fulfilled our inclusion criteria. Most of them had a high or unclear risk of bias in more than two domains. Low-dose ANP showed a significantly beneficial effect to reduce RRT both in the prevention trials (RR 0.20; 95%CI 0.07–0.59; p=0.003) and treatment trials (RR 0.43; 95%CI 0.20–0.93; p=0.03). Regarding RRT, however, TSA indicated that the number of patients included was below the information size required for a definitive conclusion. On the other hand, no significant difference was observed on hospital mortality, length of ICU stay and induction of hypotension. The shape of the funnel plots in each outcome did not show an obvious asymmetry.

Conclusions: These results indicated that low-dose ANP could be potentially effective for the prevention and treatment of AKI. However, the quality and sample sizes of these RCTs were not sufficient to demonstrate the effects of low-dose ANP. It showed the necessity for RCTs with high-quality and large sample size.

FR-PO124

AKI after Cytoreductive Surgery and Intraoperative Cisplatin Exposure for Malignant Pleural Mesothelioma Tamar Hod, Katherine J. Freedberg, Margaret E. Chen, Joseph V. Bonventre, Sushrut S. Waikar. *Brigham and Women's Hospital, Boston, MA.*

Background: Cytoreductive surgery with or without intraoperative administration of intrathoracic cisplatin is a treatment for certain cases of malignant pleural mesothelioma. The combinations of surgery-induced inflammation, ischemia, and nephrotoxin administration increase the risk of acute kidney injury (AKI), but has not been thoroughly investigated in this unique patient population exposed to multiple kidney insults.

Methods: We assembled a retrospective cohort of patients undergoing cytoreductive surgery with or without intraoperative cisplatin for malignant pleural mesothelioma at Brigham and Women's Hospital between 2006-2015. We defined AKI according to the KDIGO criteria. Pre-operative characteristics, intra-operative blood loss, and post-operative outcomes of mortality and length of stay were compared in those who did versus did not develop post-operative AKI.

Results: Post-operative AKI occurred in over three quarters of the 504 patients studied (379 of 504, 75.2%); 261 (51.8%) had stage 1 AKI; 85 (16.9%) had stage 2 AKI, and 33 (6.5%) had stage 3 AKI. 16 patients required dialysis. 391 patients (77.6%) received intraoperative cisplatin. The following variables were found to be associated with an increased odds for postoperative AKI: baseline estimated glomerular filtration rate (odds ratio (OR) 0.97; 95% CI 0.96-0.99), male sex (OR 3.44; 95% CI 1.95-6.09), estimated blood loss during surgery (OR 1.47; 95% CI 1.07-2.02) and exposure to intraoperative cisplatin (OR 3.51; 95% CI 1.47-8.39). Higher stages of AKI were associated with longer length of stay (14.8 vs. 16.3 vs. 18.4 vs 30.2 days) and with increased risk of death at 1 year (30.4% vs. 26.4% vs. 41.2% vs 60.6%) for no AKI, stage 1 AKI, stage 2 AKI, and stage 3 AKI, respectively; P < 0.001).

Conclusions: Cytoreductive surgery with intraoperative cisplatin for the treatment of malignant pleural mesothelioma is associated with a substantially higher risk of post-operative AKI than other surgical procedures such as cardiac surgery. The high rate of AKI in this unique patient population makes it a suitable setting for investigation into ischemic and nephrotoxic AKI in humans.

FR-PO125

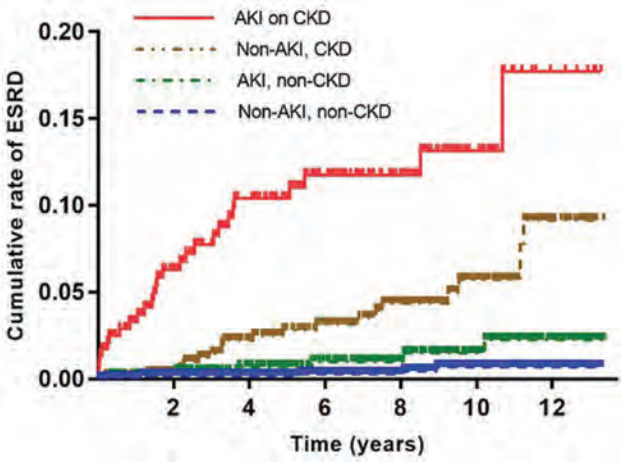
Synergistic Effects of AKI and CKD on the Development of ESRD after Coronary Artery Bypass Grafting Yeonhee Lee,[3] Hongran Moon,[3] Jung Pyo Lee,[1] Sejoong Kim,[2] Dong Ki Kim,[3] Yun Kyu Oh,[1] Ho Jun Chin,[2] Chun Soo Lim,[1] Yon Su Kim,[3] Ki Young Na,[2] Seung Seok Han.[3] *[1]Seoul National University Boramae Medical Center, Seoul, Republic of Korea; [2]Seoul National University Bundang Hospital, Seongnam, GYEONGGI-DO, Republic of Korea; [3]Seoul National University Hospital, Seoul, Republic of Korea.*

Background: Because end-stage renal disease (ESRD) affects patient outcomes in several diseases, exploring risk factors for ESRD is a critical issue in clinical practice. This study firstly addressed to evaluate the synergistic effects of acute kidney injury (AKI) and chronic kidney disease (CKD) on the development of ESRD in patients with coronary artery bypass grafting (CABG).

Methods: This study included 1,899 patients (aged ≥18 years) underwent CABG between 2004 and 2015 in two tertiary referral centers. Patients were classified as groups with postoperative AKI, preoperative CKD, or both according to the KDIGO guidelines. We performed the Kaplan-Meier method and the multivariable Cox regression model to calculate the cumulative incidence of ESRD and to estimate the hazard ratio of ESRD. Patients were followed for 74±44 months (maximum 13 years).

Results: Postoperative AKI occurred in 799 patients (26.5%), including 23.8% in stage 1 and 2.7% in stages 2 and 3. CKD was identified in 890 patients (29.5%). ESRD occurred in 60 patients (1.4%) as following subject numbers and proportions: the group without AKI and CKD, 6 (0.4%); the AKI group, 6 (1.2%); the CKD group, 20 (3.4%); and the group with both AKI and CKD, 28 (9.2%). The cumulative rate of ESRD increased in the following order, the group without AKI and CKD, the AKI group, the CKD group, and the group with both AKI and CKD (Figure). In multivariate analyses, both AKI [HR, 3.2 (1.01-10.13)] and CKD [HR, 9.2 (3.46-24.43)] were independently associated with the risk of ESRD (all Ps<0.05). Particularly, in the CKD patients, the presence of AKI significantly increased the risk of ESRD compared with the counterpart group without AKI, as follows: HR, 3.4 (1.91-6.04); P<0.05.

Conclusions: The presences of AKI and CKD synergistically increase the risk of ESRD in CABG patients.



FR-PO126

Dialysis-Requiring AKI in CKD Patients Receiving Radiocontrast Di Pan,[1,3] David Mariuma,[1,3] Yumeng Wen,[1,3] Michael Gramuglia,[4] Ira S. Meisels.[2,3] *[1]Mount Sinai St. Lukes and Mount Sinai West Hospitals, New York, NY; [2]Division of Nephrology, Mount Sinai St. Luke's and West Hospitals, New York, NY; [3]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; [4]Montefiore Health System, New York, NY.*

Background: Contrast-induced nephropathy has been a widely recognized and long-accepted complication of radiocontrast administration. However, there have been recent studies that call into question whether a link between acute kidney injury (AKI) and radiocontrast truly exists in the setting of iso-osmolar or low-osmolar contrast use in imaging and vascular procedures. The goal of this study is to evaluate the relationship between dialysis-requiring AKI and contrast administration in patients with different stages of chronic kidney disease (CKD).

Methods: This is a retrospective analysis utilizing the 2014 Nationwide Inpatient Sample, the largest publically available inpatient database in the United States. A total of 3,367,411 patients over age 18 with CKD were included. End-stage renal disease patients on chronic dialysis were excluded. Multivariate logistic regression was performed to test for indepedent associations between dialysis-requiring AKI and exposure to either intravenous contrast (IV; n=8170), arteriography/angiogram (AG; n=160,110), or arterial catheterization with intervention (ACI; n=86,715), specifically coronary, peripheral vascular, or neurovascular interventions. Further subgroup analysis was performed for CKD stages 3 to 5. Procedures and diagnoses were identified using ICD-9-CM codes. Analysis was performed using Stata 14.2.

Results: All CKD patients regardless of stage, who received either IV (OR 2.4, p<0.0001), AG (OR 1.28, p<0.0001), or ACI (OR 1.24, p=0.005), had increased associations with dialysis-requiring AKI. Similar results were observed in the subgroup analyses. CKD 5 subgroup: IV (OR 3.15, p=0.007), AG (OR 2.34, p<0.0001), ACI (OR 1.24, p=0.005). CKD 4 subgroup: IV (OR 5.0, p<0.0001), AG (OR 2.13, p<0.0001), ACI (OR 1.66, p=0.022). CKD 3 subgroup: IV (OR 1.98, p=0.045), AG (OR 1.28, p=0.013), ACI (OR 1.81, p<0.0001).

Conclusions: Our results demonstrate that there are strong associations between dialysis-requiring AKI and radiocontrast exposure among patients with CKD. Despite conflicting data that challenge this relationship, clinicians should continue to exercise caution when administering radiocontrast in this patient population. Further prospective cohort and randomized controlled studies should be performed before definitive conclusions can be made.

FR-PO127

Factors Associated with Dialysis-Requiring AKI in Patients with Septic Shock Di Pan,[1,3] David Mariuma,[1,3] Yumeng Wen,[1,3] Fernando Vazquez de lara,[1,3] Marcelo X. Hernandez cuchillas,[1,3] Michael Gramuglia,[4] Ira S. Meisels.[2,3] *[1]Mount Sinai St. Lukes and Mount Sinai West Hospitals, New York, NY; [2]Division of Nephrology, Mount Sinai St. Luke's and Mount Sinai West Hospitals, New York, NY; [3]Department of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; [4]Montefiore Health System, New York, NY.*

Background: Acute kidney injury (AKI) poses significant burden on patients with septic shock, especially for those who ultimately require renal replacement therapy (RRT). The aim of this study is to identify potential risk factors and patient characteristics associated with receiving RRT in patients with septic shock.

Methods: This is a retrospective analysis based on the 2014 Nationwide Inpatient Sample. A total of 435,835 patients over age 18 with either a primary or secondary diagnosis of septic shock were included. Patients on chronic RRT were excluded. The outcome of interest was dialysis-requiring AKI. Multivariate logistic regression adjusting for age, gender, hospital characteristics, insurance, and comorbidities was performed to test for independent associations between variables of interest (which included 29 AHRQ comorbidity measures), and dialysis-requiring AKI. Diagnoses and procedures were identified using ICD-9-CM codes. Analysis was performed using STATA 14.2.

Results: Our study revealed that male gender (OR 1.24, p<0.0001), African-American (OR 1.34, p<0.0001), and Hispanic (OR 1.14, p=0.03) race have increased odds of having AKI-requiring dialysis in septic shock. Pre-existing comorbidities and other factors found to have increased association with AKI-requiring dialysis were: chronic alcohol abuse (OR 1.20, P=0.005), chronic anemia (OR 1.16, p<0.0001), congestive heart failure (OR 1.13, p=0.001), coagulopathy (OR 2.07, p<0.0001), diabetes with complications (1.27, p<0.0001), history of hypertension (OR 1.14, P<0.0001), chronic liver disease (OR 1.45, p<0.0001), obesity (OR 1.67, p<0.0001), pulmonary circulation disorders (OR 1.21, p=0.001), and the presence of bacteremia (OR 1.97, p=0.005).

Conclusions: Clinical and microbiological characteristics, as well as pre-existing comorbidities should be considered in the prognostication and risk stratification of patients with septic shock, and the development of dialysis-requiring AKI. Future prospective studies can be considered for further evaluation.

FR-PO128

Non-Recovery After Dialysis-Requiring AKI Is Associated with Increased Short-Term Mortality and Cardiovascular Events in Incident ESRD Patients Benjamin J. Lee,[1] Chi-yuan Hsu,[1] Rishi V. Parikh,[2] Thomas Leong,[2] Thida C. Tan,[2] Sophia Walia,[2] Raymond K. Hsu,[1] Kathleen D. Liu,[1] Alan S. Go.[2,1] *[1]University of California, San Francisco, San Francisco, CA; [2]Kaiser Permanente Northern California, Oakland, CA.*

Background: There is a high burden of early mortality and cardiovascular disease (CVD) in ESRD patients. We hypothesized that patients with ESRD precipitated by non-recovery after dialysis-requiring acute kidney injury (AKI-D) are at higher risk for short-term death and CVD events compared to incident ESRD patients who did not experience AKI-D.

Methods: We evaluated adult members of Kaiser Permanente Northern California who initiated renal replacement therapy between January 2009 and September 2015. Outcomes were all-cause death, heart failure hospitalization, acute coronary syndrome (ACS), and acute ischemic stroke or transient ischemic attack (TIA) within 1 year of dialysis initiation. Baseline demographics, eGFR, dipstick proteinuria, other labs, comorbidities, and medication use were identified from electronic health records and used for multivariable adjustment.

Results: Patients with ESRD due to AKI-D (n=1,865) were older, more likely to be white, and had more baseline CVD than incident ESRD patients without AKI-D (n=3,772). Preceding AKI-D was associated with higher crude risks of death and CVD events (**Table**). In multivariable Cox regression, patients with ESRD due to AKI-D were at statistically significantly higher risk for death (adjusted hazard ratio [aHR] 1.79, 95% CI 1.49-2.13) and heart failure hospitalization (aHR 2.22, 1.43-3.33). Trends for ACS (aHR 1.25, 0.88-1.75) and acute ischemic stroke/TIA (aHR 1.27, 0.85-1.89) were not statistically significant.

Conclusions: Patients who transition to ESRD via AKI-D are a high-risk subgroup that may benefit from aggressive monitoring and medical management, particularly for heart failure.

Funding: NIDDK Support

Crude rates of death and CVD outcomes at 1 year after dialysis initiation, stratified by whether ESRD was precipitated by AKI-D.

Outcome	Subgroup	Rate per 100 person-years (95% Confidence Interval)	P-value
All-Cause Death	ESRD not due to AKI-D	9.51 (8.50-10.65)	**<0.0001**
	ESRD due to AKI-D	23.58 (18.06-30.78)	
Heart Failure Hospitalization	ESRD not due to AKI-D	3.00 (2.45-3.67)	**<0.0001**
	ESRD due to AKI-D	8.17 (5.09-13.11)	
Acute Coronary Syndrome	ESRD not due to AKI-D	3.45 (2.86-4.17)	**0.0081**
	ESRD due to AKI-D	5.14 (3.17-8.33)	
Acute Ischemic Stroke or TIA	ESRD not due to AKI-D	2.68 (2.16-3.32)	0.1168
	ESRD due to AKI-D	3.53 (2.02-6.18)	

FR-PO129

High Incidence of Transition to ESRD in Patients Discharged with Dialysis Dependent AKI: The Cleveland Clinic Experience Samir A. Brahmbhatt,[3] Sherif Armanyous,[2] Michael Lioudis,[1] Robert J. Heyka,[3] Leslie P. Wong,[1] Sevag Demirjian.[1] *[1]Cleveland Clinic, Solon, OH; [2]Cleveland Clinic Foundation, Cleveland Heights, OH; [3]Cleveland Clinic Foundation, Cleveland, Ohio, Beachwood, OH.*

Background: Acute kidney injury in hospitalized patients has been reported in 20-67% of patients and is a known cause of significant morbidity and mortality. Many of them continue to require dialysis support after discharge as an out-patient, while being monitored for renal recovery. Recent approval of financial reimbursement by the Centers for Medicare & Medicaid Services (CMS) for this group of patients, labelled as Acute Kidney Injury-requiring dialysis (AKI-D) in an out-patient dialysis center, even if not declared end-stage renal disease (ESRD), will change practice patterns and shift dialysis care to chronic units. Our goal is to describe the incidence of non-recovering AKI-D and associated risk factors.

Methods: A retrospective observational cohort study of patients with AKI-D discharged from Cleveland Clinic and received outpatient dialysis at Cleveland Clinic, Cleveland, OHIO from 2010 to 2016. Data were extracted from Cleveland Clinic Acute Renal Registry.

Results: The study included 390 patients discharged from index hospitalization with AKI-D. The median age was 62 years (52, 70); 62% were male and 65% white. Two thirds of patients were critically ill requiring intensive care and most had multifactorial etiology for kidney injury with acute tubular necrosis being the clinical diagnosis in 2/3. Comorbidities included baseline chronic kidney disease (CKD) in 38%, hypertension 62%, diabetes 42%, heart failure 23%, and liver disease 20%. Baseline serum creatinine was 1.4 mg/dL (1,2); serum creatinine and urine output at dialysis initiation were 5.8 mg/dL (4.2,8), and 290 mL/day (100,660). 221 patients (56%) were transitioned to ESRD, the primary endpoint of the study. Univariate analysis showed male gender, CKD, hypertension, diabetes mellitus and heart failure to be associated with transition to ESRD.

Conclusions: In a single center study of large cohort of patients with AKI-D, the presence of baseline kidney disease, diabetes mellitus, hypertension and heart failure were associated with higher incidence of transition to ESRD.

FR-PO130

Serum Troponin-T Levels and Intensity of Pulmonary Liquid Removal Can Indicate Myocardial Injury during Intermittent Hemodialysis Session in Patients with AKI Lygia Lussim, Fernanda D. Martins, Carolina Brianez, Isabella C. Ribeiro, Marco antonio D. Carvalho filho, Thiago Santos, Rodrigo B. de Oliveira. *School of Medical Sciences of the University of Campinas, Campinas, Brazil*.

Background: Intermittent hemodialysis (IHD) is a modality of renal replacement therapy used in critical patients with acute kidney injury (AKI), in which one of the most common complications is hemodynamic instability, assessed either by clinical, laboratory and point of care ultrasound parameters (POCUS). In this clinical study we evaluated the relationship between serum high sensitivity cardiac troponin-T levels (hs-cTnT) and clinical, POCUS and laboratorial parameters in critical ill patients with AKI over IHD session.

Methods: Clinical and observational study where critical ill patients with AKI were submitted to IHD sessions. Every hour over IHD session we evaluated POCUS parameters [inferior vena cava diameter (IVC) and distensibility (dIVC), extravascular lung water (SLESS score)], mean arterial blood pressure (ABP), heart rate, vasopressors dose, hs-cTnT (reference range: < 14 ng/L), lactate, bicarbonate levels and venous and arterial oxygen saturation.

Results: Six patients (mean SOFA and APACHE II scores of 13±4 and 25±4, respectively), four men (66%), aged 45±15 years, with AKIN III [3 (50%) due to sepsis] were enrolled during 11 IHD sessions. Urea reduction ratio (URR) and ultrafiltration rate (UF) were 43±12 % and 5.1±2.3 mL/kg/h, respectively. At the end of IHD sessions a significant increase of hs-cTnT was detected (186±157 *vs.* 229±195 ng/L; p=0.02). The magnitude of this variation was not correlated with hemodynamic instability, ABP variation, heart rate, vasopressors dose, UF, POCUS parameters or serum lactate levels. In contrast, a positive correlation was detected between the increase of hs-cTnT and the decrease of SLESS score variation (R=0.74; p=0.02), suggesting impairment of fluid removal from lungs.

Conclusions: Serum hs-cTnT levels as well as the range of variation of pulmonary fluid removal may signal worsening of myocardial injury in critically ill patients with severe AKI and under IHD.

Funding: Private Foundation Support

FR-PO131

Vitamin D Deficiency Prevalent in Pediatric Patients with Severe AKI on Prolonged Continuous Renal Replacement Therapy Ayse Akcan Arikan,[1] Naile Tufan Pekkucuksen,[5] Molly R. Vega,[3] Peace D. Imani,[4] Eileen D. Brewer,[2] Poyyapakkam Srivaths.[4,1] *[1]Baylor College of Medicine, Houston, TX; [2]Baylor College of Medicine and Texas Children's Hospital, Houston, TX; [3]Texas Children's Hospital/Baylor College of Medicine, Houston, TX; [4]Texas Children's Hospital, Houston, TX; [5]texas childrens hospial, Houston, TX*.

Background: Vitamin D deficiency is reported in critically ill children and pediatric chronic kidney disease (CKD) patients (pts) with associated with adverse outcomes. Children on continuous renal replacement therapy(CRRT) are at risk of micronutrient deficiencies; however, serum vitamin D profiles in children with severe acute kidney injury on CRRT are unreported. We aimed to describe vitamin D levels and frequency of vitamin D deficiency in pediatric pts requiring prolonged CRRT(>28days).

Methods: Our center utilizes continuous venovenous hemodiafiltration with regional citrate anticoagulation per institutional protocol for CRRT. Calcium is infused postfilter to keep serum ionized calcium levels in the normal range. All prolonged CRRT pts are assumed to be at risk of CKD and undergo monthly monitoring for CKD labs, including vitD(25;1,25) and parathyroid hormone(PTH) levels. All pts receiving prolonged CRRT during 2015-2017 were included in this study.

Results: 16 patients, 56% male received prolonged CRRT for acute kidney injury; CRRT duration was 60±34 days. First vitD levels were obtained after 28 days on CRRT; 4 pts (25%) were vitD deficient (<20), 7(44%) were insufficient (<30). Mean vitD25 level was 25.4 ± 7.5 ng/ml, mean vitD1,25 level was 47 ± 55 pg/ml; total calcium was10 ±1.5 mg/dl, ionized calcium was 1.23(1.16-1.28) mmol/L, phosphorus was 4.2 ±1.3 mg/dl. Despite routine vitD supplementation in total parenteral nutrition and additional oral supplementation when needed, all 4 patients with normal vitD25 levels became insufficient over time, 6 deficient or insufficient pts never had vitD25 levels>30. There was a negative correlation between vitD25 and PTH levels which did not reach statistical significance (Spearman r=-0.28, p=0.08). Despite strict control of serum ionized calcium and phosphorus levels in the normal range, 4/6 patients who became vitD deficient/ insufficient developed rising PTH levels(from 52 (45-176) to 434 (348-656) pg/ml, p=0.06).

Conclusions: Vit D deficiency/insufficiency is prevalent in pediatric prolonged CRRT, and might worsen despite usual pharmacological supplementation. Our preliminary data suggesting vitamin D abnormalities might be related to developing bone mineral disease in prolonged CRRT require confirmation through further studies.

FR-PO132

Successful Treatment of Severe AKI Caused by Catastrophic Anti-Phospholipid Syndrome (CAPS) Associated Thrombotic Microangiopathy (TMA) by Anti-C5 Monoclonal Antibody Sanjeev Gupta,[1] Praveen N. Chander,[2] Anastasios Papanagnou,[1] Tasleem Katchi,[1] Savneek S. Chugh.[2] *[1]Westchester Medical Center, Valhalla, NY; [2]New York Medical College, Valhalla, NY*.

Background: CAPS is a severe form of the anti-phospholipid syndrome, characterized by arterial and/or venous thrombosis leading to multi-organ failure, occurring over a short period of time. Steroids, IVIG, and plasmapheresis have long been the standard of care. Recently, the role of complement inhibition in CAPS has been explored. We present a very rare case of refractory CAPS successfully treated with Eculizumab (Ecu) which is a monoclonal antibody against complement protein C5.

Methods: A 65 years old male with a history of positive antiphospholipid antibodies (APA) presented with intermittent abdominal pain for 5 months and altered mentation. Physical examination highlighted a malar rash and bluish discoloration of the left 5th toe. Laboratory workup revealed anemia (Hgb-7.5g/DL), thrombocytopenia (platelet-106,000) and AKI (SCr 7.53), positive ANA, anti-dsDNA Ab, elevated lupus anticoagulant (LA- 1.69:1), anti-cardiolipin IgM (33), anti-β2-glycoprotein (22), low C3 & C4 (52, <5) and schistocytes on peripheral blood smear. Renal biopsy showed typical findings of TMA. ADAMTS13 activity was 25 which ruled out thrombotic thrombocytopenic purpura. Given multiple organ involvements within a week, TMA on renal biopsy and positive APA, a diagnosis of CAPS was made and the patient was started on steroids, plasmapheresis, IVIG and hemodialysis (HD). Despite adequate immunosuppression, LA titers remained elevated, and Rituximab was started. The patient subsequently failed treatment and remained on HD for 3 months. Because of ongoing TMA, Ecu was started which resulted in improvement of thrombocytopenia and urine output. The patient subsequently recovered his renal function and HD was discontinued 2 months after Ecu initiation.

Results:

Conclusions: Therapeutic options for refractory cases are limited. Rituximab is the next line treatment but, our patient failed that as well. Based on few case reports patient was started on Ecu and responded well. Ecu is a potent terminal complement blockade, which appears to be equally effective in CAPS induced TMA as in aHUS. In conclusion, complement blockade can be a useful mode of therapy in CAPS even in cases that have failed standard treatment and after months of organ failure.

FR-PO133

Multisystem Manifestations of Haemolytic Uremic Syndrome: A Pictorial Case Series Louise J. Hartley, Sandra Butler, Emily J. Stenhouse, Ben C. Reynolds. *NHS Greater Glasgow and Clyde, Glasgow, United Kingdom*.

Background: We present a comprehensive pictorial case series illustrating the diverse multisystem radiological manifestations of Shiga toxin-producing Escherichia coli Haemolytic Uremic Syndrome (STEC-HUS). STEC-HUS is characterised by haemolytic anaemia, thrombocytopenia and acute renal dysfunction with significant morbidity and mortality.

Methods: We retrospectively reviewed the imaging findings of 148 cases of STEC-HUS in a national paediatric nephrology centre over a 13 year period. The average presenting age was 5.5 years (52% female; 48% male).

Results: Renal: Renal ultrasound was performed in 18.2% of cases, of which a hyperechoic renal cortex was the most common finding (19/27). Three cases of renal cortical necrosis and one case of acquired cystic kidney disease were diagnosed on serial ultrasound and MRI imaging. **Gastrointestinal:** Abdominal radiography (AXR) was performed in 14.2% of cases, of which colonic wall thickening was the most common finding (14/21). On abdominal ultrasound colonic thickening (12/27) and free fluid (10/27) were the most common findings. One case of bowel ischaemia was diagnosed on MRI. **Neurological:** Neuroimaging was performed in 8.1% of cases, of which bilateral lentiform nuclei and/or thalamic infarctions were the most common abnormality (5/12). Two patients had multi-territorial infarcts including the first reported case of large vessel arterial thrombosis in HUS on imaging. **Hepatobiliary:** Two cases of hepatomegaly were seen on abdominal ultrasound. On AXR biliary excretion of contrast media due to renal failure was reported in one case. Haemodialysis-related secondary haemochromatosis was diagnosed on follow-up MRI in two cases. **Respiratory:** Chest radiography was performed in 21.6% of cases, of which pulmonary oedema was the most common abnormality (7/32). **Ocular:** Eye ultrasound demonstrated severe vitreous haemorrhages in one case.

Conclusions: This pictorial case series illustrates the imaging findings of common, rare and previously unreported multisystem manifestations of STEC-HUS. Awareness of the role of radiology will aid early diagnosis and subsequent management in this complex disease.

FR-PO134

Clinical Presentation and Outcome in a Series of 258 Japanese Pediatric Patients with Thrombotic Microangiopathy: A Nationwide Survey during 2012-2015 Akira Ashida,[1] Hideki Matsumura,[1] Toshihiro Sawai,[2] Rika Fujimaru,[3] Yuko Fujii,[1] Akihiko Shirasu,[1] Hyogo Nakakura,[1] Kazumoto Iijima.[4] *[1]Pediatrics, Osaka Medical College, Takatsuki, Japan; [2]Pediatrics, Shiga university of medical science, Shiga, Japan; [3]Pediatrics, Osaka City General Hospital, Osaka, Japan; [4]Dept. of Pediatrics, Kobe Univ. Graduate School of Medicine, Kobe, Japan.*

Background: Thrombotic microangiopathy (TMA) includes hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP). As recent studies have shown that HUS has various pathogenesis, we conducted the present study to clarify in detail the epidemiological characteristics of pediatric patients with TMA classified according to etiology.

Methods: This survey evaluated 258 Japanese pediatric patients who were diagnosed as having TMA and followed up between 2012 and 2015.

Results: The primary diseases responsible for TMA were categorized as TTP, Shiga toxin-producing *Escherichia coli* associated HUS (STEC-HUS), atypical HUS, and secondary TMA. In these four categories, the most frequent primary disease was STEC-HUS which was present in 64.3% of the patients, followed in order by atypical HUS (15.5%), secondary TMA (10.1%), and TTP (5.8%). About 40% of patients with TMA required renal replacement therapy during the acute phase. The final outcomes in terms of renal functions were normal renal function with normal urinalysis parameters in 95 patients, and CKD stage I in 62. However, in 31 patients chronic renal insufficiency (CKD stage II to V) persisted, including 4 patients with end-stage kidney disease (CKD stage V). Seventeen patients suffered recurrence of TMA, and 8 patients died. Among extrarenal complications at the final outcome point, hypertension and neuro-psychological complications were most frequent.

Conclusions: This study of epidemiological and demographic information for Japanese pediatric patients with TMA over the period 2012-2015 has confirmed the relative proportions of the primary underlying diseases reported previously. Pediatric patients with TMA should be followed up with monitoring of laboratory data including urinalysis, as in this series various symptoms remained at the end of the observation period.

FR-PO135

Acquired Thrombotic Thrombocytopenic Purpura Secondary to Hereditary Autoimmunity: A Model for a New Pathogenic Mechanism? Sofia H. Marques,[2] Rute Carmo,[2] Ana R. Freitas,[1] Pedro S. Rodrigues,[2] Patricia Martinho,[3] Teresa Fidalgo,[3] Manuel Pestana.[2] *[1]Centro Hospitalar de Entre o Douro e Vouga, Vale de Cambra, Portugal; [2]Centro Hospitalar de São João, Porto, Portugal; [3]Centro Hospitalar Universitário de Coimbra, Coimbra, Portugal.*

Background: Thrombotic thrombocytopenic purpura (TTP) may result from mutations of the ADAMTS13 gene (congenital TTP) or inactivating autoantibodies against the enzyme (acquired TTP).

Methods: We present the case of a 21-year-old male admitted for TTP with a suppressed ADAMTS13 enzyme activity (0%) and high titers of anti-ADAMTS13 antibody (99AU/mL) who was treated with plasmapheresis and rituximab. The patient's mother had an episode of thrombotic microangiopathy in 1998 without major health issues since then. After her son's disease, her blood tests were performed and revealed absent ADAMTS13 enzyme activity (0%) and positive anti-ADAMTS13 antibody (46AU/mL). Molecular studies were performed by a next generation sequencing - based gene panel (ADAMTS13, CFH, CFHR1, CFHR3, CFHR4, CFHR5, CFI, CFB, C3, THBD and DGKE), and no molecular abnormalities were detected. Results of HLA genotyping for both patients are displayed on Table 1.

Results:

Conclusions: As far as we know, this is the second report of an acquired TTP due to autoantibodies inactivating ADAMTS13 in two relatives. Our patients did not have any of the alleles which were associated by other authors with increased disease susceptibility. We discuss possible mechanisms behind hereditary antibody-mediated autoimmune diseases such as post-translational protein changes or epigenetic inherited processes. We also reflect on the fact that severe enzyme deficiency does not seem sufficient to express clinically as TTP and an environmental trigger may be required to precipitate an acute episode.

Table 1: HLA genotyping for patients 1 and 2

HLA	Patient 1	Patient 2
A*	01:01/11:01	11:01/30:02
B*	37:01/55:01	44:03/55:01
Cw*	03:03/06:02	03:03/04:01
DRB1	*03/*10	*03/*11
DQB1	*02:01/*05:01	*02:01/*03:01

FR-PO136

Ongoing Eculizumab (ECU) Prevents Thrombotic Microangiopathy (TMA) in Patients (Pts) with Atypical Hemolytic Uremic Syndrome (aHUS): Final Long-Term Observational Study Data Jan Menne,[1] Yahsou Delmas,[2] John F. Kincaid,[3] Christoph Licht,[4] Enrico E. Minetti,[5] Chris Mix,[3] Francois Provot,[6] Eric Rondeau,[7] Neil S. Sheerin,[8] Bradley Dain,[3] Laurent E. Weekers,[9] Larry A. Greenbaum.[10] *[1]Medical School Hannover, Hannover, Germany; [2]CHU Bordeaux, Bordeaux, France; [3]Alexion Pharmaceuticals, Inc., New Haven, CT; [4]The Hospital for Sick Children, Toronto, ON, Canada; [5]Careggi University Hospital - Florence, Firenze, Italy; [6]CHU de Lille, Lille, France; [7]APHP; University Paris 6, PARIS, France; [8]Newcastle University, Newcastle upon Tyne, United Kingdom; [9]CHU ULg, Esneux, Belgium; [10]Emory University, Atlanta, GA.*

Background: Pts from previous ECU trials in aHUS could enroll in this observational long-term follow-up study (NCT01522170; enrollment/follow-up concluded), regardless of ongoing ECU use. The objective was to evaluate TMA rates and safety off and on ECU.

Methods: Endpoints included TMA event rate (primary) and targeted serious adverse events (TSAEs).

Results: In 93 pts (42 with off-, 82 with on-treatment periods), the TMA event rate was 3-fold higher off vs on ECU. Rates were stratified by baseline characteristics (**Table**). TSAE rates were higher off vs on ECU. Four pts had meningococcal infections on ECU in the current study; all recovered with treatment and remained on ECU without dosing changes.

Conclusions: Final data from the largest prospective cohort with aHUS, with some pts receiving ECU for >5 yrs, demonstrate clinical benefits with ongoing ECU.
Acknowledgment: Medical writing support provided by Peloton Advantage with funding from Alexion.

Funding: Commercial Support - Alexion Pharmaceuticals, Inc.

Table. Outcomes Off and On ECU (N=93)[a]

TMA Events[b]	Off Treatment[c] (n=42)	On Treatment[c] (n=82)
TMA event rate overall, per 100 PY (number of events)	18.3 (19)	6.8 (20)
TMA event rate by ECU regimen,[d] per 100 PY (number of events)		
Labeled	—	6.1 (13) [n=73][f]
Non-labeled	—	9.0 (7) [n=34][f]
TMA event rate by complement abnormality, per 100 PY (number of events)		
Identified abnormality	26.0 (13) [n=24]	8.5 (16) [n=51]
No identified abnormality	11.2 (6) [n=18]	3.8 (4) [n=31]
TMA event rate by TMA manifestation[e] history, per 100 PY (number of events)		
Single	15.6 (11) [n=29]	8.3 (16) [n=51]
Multiple	24.0 (8) [n=13]	4.0 (4) [n=31]
TMA event rate by age at first ECU infusion, per 100 PY (number of events)		
Adult (≥18 years of age)	14.2 (10) [n=25]	5.1 (8) [n=47]
Pediatric (<18 years of age)	27.1 (9) [n=17]	8.8 (12) [n=35]
Safety Endpoints	**Off Treatment (n=42)**	**On Treatment (n=82)**
TSAEs[f] per 100 PY (number of events)	27.9 (29)	21.5 (63)
Renal impairment	11.6 (12)	6.8 (20)
Infection, other	10.6 (11)	11.3 (33)
TMA	4.8 (5)	1.4 (4)
Malignant neoplasm	1.0 (1)	0 (0)
Infection, meningitis/meningococcal	0 (0)	1.4 (4)
Infection, aspergillus	0 (0)	0.3 (1)
Leukopenia	0 (0)	0.3 (1)

Three pts died during the current study. An adult pt discontinued non-labeled dosing of ECU and died due to severe intensive care complications and multi-organ dysfunction secondary to a gastrointestinal hemorrhage, lithiasic cholecystitis, and severe sepsis. A 2-year-old pt with history of infection, fatigue, hypotension, pulmonary hemorrhage, dialysis, and blood transfusion, suffered a seizure and died after ~10 months of labeled-dose ECU. Another pt <1 year of age was on long-term dialysis and received ECU for 2 months but discontinued due to lack of efficacy; subsequently, the pt had a TMA manifestation with multi-organ failure and died of sepsis after being off treatment for 7 months. [b]Median (range) total exposure to ECU was 61.0 (1.3–94.1) months. Pts had a median (range) follow-up of 31.2 (0.7–95.1) months off treatment. [c]TMA was defined as ≥1 of the following: changes in ≥1 laboratory parameter (decreases in platelet counts or increases in lactate dehydrogenase or serum creatinine levels), clinical signs and symptoms of TMA, or required intervention due to TMA. [d]Pt groups were not mutually exclusive; individual pts could be represented in both groups. [e]After completion of the parent study and entry into the current study, the labeled dosing regimen of ECU was defined as that specified in the prescribing information approved by regulatory authorities and other dosing schedules were permitted and classified as non-labeled regimens. [f]All unique TMA manifestations occurring in all on- or off-treatment periods in the current study were included. [g]Defined as serious infections, meningococcal infection, sepsis, renal impairment, and malignancy occurring during the current observational study. ECU, eculizumab; pts, patients; PY, patient-years; TMA, thrombotic microangiopathy; TSAEs, targeted serious adverse events.

FR-PO137

Atypical Hemolytic Uremic Syndrome (aHUS) Presenting as Acute Heart Failure: A Rare Presentation Diagnosed on Skin Biopsy Sanjeev Gupta,[1] Savneek S. Chugh,[2] Anastasios Papanagnou,[1] Tasleem Katchi,[1] Praveen N. Chander.[2] *[1]Westchester Medical Center, Valhalla, NY; [2]New York Medical College, Valhalla, NY.*

Background: aHUS is associated with Complement over-activation secondary to regulatory gene mutations. Kidney is the most commonly involved organ due to unique characteristics of glomerular endothelium. Cardiac involvement occurs in about 3-10% cases with aHUS, can be severe with the acute presentation but, a diagnosis of aHUS remains unrecognized in many such cases. Cardiac manifestations include myocardial infarction, cardiomyopathy and heart failure (HF). Treatment of aHUS includes blockade of the terminal Complement pathway (C5b-9) however, spontaneous recovery can occur. We present a unique case of aHUS with primary cardiac involvement that affected kidney as well but, was diagnosed with specific manifestations on the skin biopsy.

Methods: A 24-year-old man presented with acute onset of shortness of breath. Initial workup revealed cardiogenic shock, acute kidney injury (serum creatinine 2.54 mg/dl) and thrombocytopenia (platelet count 69,000). Right heart catheterization showed an ejection fraction (EF) of 10% requiring intra-aortic balloon pump. Laboratory

investigations revealed new onset hematuria with RBC casts, proteinuria (0.7gm), low hemoglobin (11.5 g/dl) and Haptoglobin (< 8), low C3, C4 and CH-50 and ADAMTS13 activity- 84%. ANA, p and c-ANCA, hepatitis panel and antiphospholipid Ab tested negative. The patient also developed a skin rash on the arm, which on biopsy showed features consistent with thrombotic microangiopathy (TMA) with positive staining for C3 and C4d. He underwent spontaneous clinical remission before initiation of complement blockade therapy. The patient was discharged following significant improvement of renal function, cardiac output (EF 35%) and normalization of platelet count.

Results:

Conclusions: aHUS is a rare disease with diagnosis resting on clinical, laboratory and pathological features. In a clinical setting of aHUS, performing kidney biopsy at times may not be feasible in the presence of thrombocytopenia and hence, a skin biopsy may provide diagnostic findings of TMA associated with microvascular staining of Complement and its metabolic products (C4d). HF is a grave complication of aHUS requiring a prompt diagnosis for initiation of treatment and resultant good long-term prognosis. A skin biopsy can show specific changes of TMA and be of diagnostic value.

FR-PO138

The Burden of Kidney Dysfunction in Hospitalized Patients with Hepatorenal Syndrome in the United States (US): 2009-2015 An T. Pham,[1,2] Khurram Jamil,[3] Kunal Lodaya,[5] David K. Hayashida,[4] Belinda Lovelace,[3] Xingyue Huang.[3] *[1]Health Economics and Outcomes Research, Mallinckrodt Pharmaceuticals, Hampton, NJ; [2]University of California San Francisco, San Francisco, CA; [3]Mallinckrodt Pharmaceuticals, Hampton, NJ; [4]Boston Strategic Partners, Inc., BOSTON, MA; [5]Boston Strategic Partners, Boston, MA.*

Background: Hepatorenal Syndrome (HRS), the development of functional renal failure in patients with advanced chronic liver disease, is associated with high morbidity and mortality. The objective of this study was to assess the clinical sequelae, cost burden, and cost drivers of HRS from US hospital perspective.

Methods: A retrospective, longitudinal analysis of the CERNER Health Facts® electronic health record (EHR) database from a large network of US hospitals was performed. Adult patients diagnosed with HRS based on ICD-9 code (572.4) between 2009 and 2015 were included in the analysis. Clinical staging and laboratory data were used to assess the health impact of these patients.

Results: We identified 1,571 male (61.8%) and 971 female (38.2%) patients (mean age: 57.9). Overall, the average length of stay was 34.6 days and hospitalized cost was $91,504. Using Kidney Diseases Improving Global Outcomes Acute Kidney Injury (KDIGO®-AKI) staging classification, the average hospitalization cost for patients without AKI was $62,563, in comparison to $143,620 for patients with stage 2 AKI. In addition, when changes in serum creatinine were examined over the duration of the HRS hospitalization, 44.1% had either no change or <20% improvements in serum creatinine from the time of hospital admissions. During the first HRS hospitalization, 36.8% of patients died and average cost of hospitalization was $108,497 for deceased versus $82,048 for a surviving patient. The HRS hospital readmission rate was 33.1%, which was comprised of 13.5% unplanned readmissions and 19.6% planned readmissions. Patients with unplanned readmissions had an average total cost of care of $97,590 in comparison to $76,803 for patients with planned readmissions.

Conclusions: From a hospital perspective, results from this analysis of a large network of US hospital database indicate that HRS is associated with high cost burden along with high rate of readmission and mortality. More importantly, many patients had either limited or no serum creatinine improvement during their hospital stays. Higher disease severity and unplanned re-admissions may be associated with higher cost of care. Together, these results point to a significant unmet medical need in this patient population and the need for additional treatment options to improve patient outcomes.

Funding: Commercial Support - Mallinckrodt Pharmaceuticals

FR-PO139

Vitamin C Therapy Attenuates the Severity of AKI in Mice Model of Hepatorenal Syndrome Nadia Yousef,[2] Siddhartha S. Ghosh,[3] Daniel E. Carl.[1] *[1]None, Richmond, VA; [2]VCU Medical Center, GLEN ALLEN, VA; [3]VCU Medical Ctr, Richmond, VA.*

Background: Hepatorenal syndrome (HRS) type 1 is a life threatening complication of cirrhosis with limited therapeutic options and it manifests when an acute insult leads to renal vasoconstriction and secondary impairment of glomerular filtration in the setting of liver disease. There are unfortunately few therapeutic options to offer. A significant limitation in HRS research is the lack of animal models investigating the pathophysiology of HRS as well as potential beneficial therapies. We hypothesized that Vit C has a protective effect in HRS. We tested this hypothesis in murine model of HRS.

Methods: C57BL6 mice received 1ml/kg of carbon tetrachloride (CCl4) biweekly for 12 weeks to induce cirrhosis. A 6 mg/Kg of Lipopolysaccharide (LPS) was given intraperitoneally to induce acute kidney injury by simulating the inflammatory stressor caused by acute infection. Vit C 200 mg/kg was given 15 min prior to LPS. Four mice populations were studied: 1. Control mice (received Vit C only) 2. CCl4 treated mice 3. CCl4 + LPS mice 4. CCl4+LPS+Vit C mice (N=4-6 per group). Serum BUN, creatinine, urine output and urinary Na+ were measured in all 4 groups. MCP-1 and NFkB proteins expression were determined by western blot. Plasma IL-6 was measured by ELISA

Results: Control group 1 received Vit C only and showed the ideal BUN, SrCr and urine output. CCl4+LPS treated mice had renal phenotype suggestive of HRS, including a higher SCr, lower UNa and UOP compared to CCl4 mice ($p<0.05$). Vit C treated mice in group 4 showed significant improvement in renal function, as CCl4+LPS+Vit C mice had a significant improvement SCr and UNa+ ($p<0.05$) compared with CCl4+LPS mice, and there was a trend towards an improvement in UOP (p 0.07). MCP-1 protein expression was significantly higher ($p<0.05$) in CCl4+ LPS group compared with control and with the CCl4+LPS+Vit C group. Moreover, NFkB protein expression was significantly higher ($p<0.05$) in CCl4+LPS compared to the control group and CCl4+LPS+Vit C

Conclusions: Vit C administration has a protective role in severity of HRS, manifested by improved SCr, UOP, and UNa+ in this model of HRS. One potential etiology is via inflammation, as pre-treatment with Vit C down-regulates both inflammatory markers.

FR-PO140

Achieved Mean Arterial Pressure Target and Renal Recovery during Treatment of Hepatorenal AKI Juan Carlos Q. Velez, Ana Belen Rivera de Rosales, Edgar Hernandez- Montalvo, Bronwyn Leblanc, Jason R. Ledoux, Ivo Lukitsch. *Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA.*

Background: We previously reported that a rise in mean arterial pressure (MAP) during treatment of hepatorenal (HR) acute kidney injury (AKI) with vasoconstrictors is associated with improvement in kidney function. However, it remains unclear whether the treatment target should be a specific absolute MAP value or a defined increment in MAP respect to baseline.

Methods: Records from hospitalized adult patients with HR-AKI treated with vasoconstrictors without shock were reviewed. We selected those who achieved ≥ 5-mmHg rise in MAP within 48 hours. The relationship between the mean MAP achieved during the first 72 hours of therapy and the change in kidney function at the end of therapy as determined by serum creatinine (sCr) was examined by analyses of variance for trend and multiple comparisons.

Results: Ninety-two patients with HR-AKI treated for up to 3-7 days with either midodrine/octreotide (M/O, n=73) or norepinephrine (NE, n=19) were identified. Forty-three (47%) of the patients (mean age 52 years, 44% women, mean sCr 3.7 ± 1.3 mg/dL and MELD 33.5) achieved ≥ 5 mmHg rise in MAP by 48 hours [24 (33%) with M/O, 18 (95%) with NE]. When analyzed based on tertiles of absolute value of achieved MAP (65-74, 75-84, ≥ 85 mmHg), there was a significant trend for greater reduction in sCr with higher achieved MAP (p=0.002). Furthermore, those who achieved a MAP of ≥ 85 mmHg had a greater reduction in sCr [-1.76 ± 0.6 mg/dL] compared to those who reached a MAP of 65-74 or 75-84 mmHg [-0.03 ± 0.5 mg/dL (p=0.019) and -0.25 ± 0.6 mg/dL (p=0.02), respectively]. When analyzed based on tertiles of magnitude of MAP increment from baseline (5-9, 10-14, ≥ 15 mmHg), there was a significant trend for greater reduction in sCr with greater rise in MAP (p=0.005). Moreover, those who achieved a MAP increase ≥ 15 mmHg had a greater reduction in sCr [-1.95 ± 0.5 mg/dL] compared to those with either a 5-9 or 10-14 mmHg increment in MAP from baseline [+0.17 ± 0.4 mg/dL (p=0.0004) and -0.58 ± 0.5 mg/dL (p=0.04), respectively].

Conclusions: Achievement of either a target MAP ≥ 85 mmHg or an increment in MAP ≥ 15 mmHg from baseline within the first 3 days of vasoconstrictor therapy is associated with greater reduction in sCr in HR-AKI. These data support the notion of a shift in the renal autoregulatory curve in HR-AKI.

FR-PO141

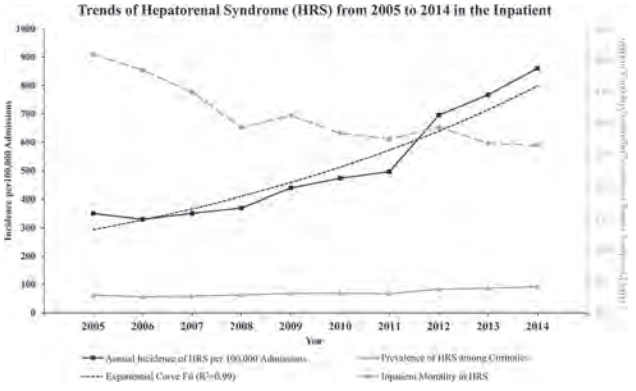
National Trends in Hospitalization and Resource Utilization in the Hepatorenal Syndrome Population: 2005-2014 Paris Charilaou,[3] Kalpit Devani,[1] Ayan De,[2] Alvaro Cornejo cobo,[6] Romela Petrosyan,[5] Pablo Garcia.[4] *[1]Division of Gastroenterology, East Tennessee State University, Johnson City, TN; [2]Internal Medicine, Saint Peter's University Hospital, New Brunswick, NJ; [3]Internal Medicine, Saint Peter's University Hospital, New Brunswick, NJ; [4]Internal Medicine, Saint Peter's University Hospital, New Brunswick, NJ; [5]Internal Medicine, Greenville Memorial Hospital, Greenville, SC; [6]Internal Medicine, Saint Peter's University Hospital, New Brunswick, NJ.*

Background: Recent changes in guidelines for diagnosis and treatment of Hepatorenal Syndrome (HRS) could have potentially affected hospital outcomes in these patients. We analyzed hospitalization and outcome trends of HRS cases, as well as outcome predictors, in the US inpatient population from 2005 to 2014.

Methods: We included all adults from the National Inpatient Sample (2005-2014), excluding cases with missing data on age/gender/inpatient mortality, who had documented liver cirrhosis (571.2, 571.5, 571.6) and HRS (572.4) as any discharge diagnosis, using the International Classification of Diseases Revision 9 – Clinical Modification (ICD-9-CM) codes. Multivariable mixed-effects regression was used to assess hospitalization trends as well as predictors of mortality, length of stay (LOS), and hospitalization costs. National estimates were calculated.

Results: We identified 158,306 HRS discharges, with males (65.4%) and white race (66.4%) being the majority. HRS annual prevalence increased exponentially (adjusted-R^2=0.99). Mean age was 57.6±0.08 years (increasing;p-trend<0.001). Mean mortality rate was 30.2% with decreasing trend (41% to 26.5%, $p<0.001$). Mean costs were unchanged at $31,061, as well as LOS (10.3 days), while aggregated costs increased by 2.5 times ($310.8 million in 2005 to $762.8 million in 2014). Significant (all $p<0.001$) mortality predictors included variceal bleed (aOR=1.90), hepatic encephalopathy (aOR=1.37), spontaneous bacterial peritonitis (aOR=1.42) and hepatocellular carcinoma (aOR=1.20). Urban and Midwest hospitals carried lower mortality risk ($p<0.001$). Urban and teaching hospitals exhibited longer LOS and higher costs. Midwest hospitals had 27% shorter LOS and 21% lower costs than the Northeast.

Conclusions: HRS hospitalizations are exponentially increasing, with an ever-growing financial burden to healthcare. While overall mortality is decreasing, there are disparities in hospitalization outcomes among regions.



FR-PO142

Renal Hypertrophy in End-Stage Liver Disease Marc M. Saad, Carla L. Ellis, W. Charles O'Neill. *Emory University, Atlanta, GA.*

Background: Renal failure has been extensively studied in liver disease but the normal physiologic responses to liver dysfunction remain unknown. We hypothesized that decreased clearance of metabolic products by the liver increases metabolic demand on the kidneys, leading to hypertrophy.

Methods: Renal parenchymal volume (RPV) was measured on outpatient CT scans performed in 29 patients with end-stage liver disease (ESLD) and 30 controls without liver disease. Cross-sectional kidney areas (excluding the renal sinus, vessels, collecting system, and cysts) from sequential transverse images were summed and muliplied by the slice thickness to derive RPV, which was normalized to body height. Renal histology was evaluated in 5 autopsies that were suitable for analysis and compared to 8 autopsies in patients without liver disease. Glomerular size was estimated from the area of Bowman's capsule measured at maximal cross-section (7-29 glomeruli/patient, mean 22). Subjects with diabetes, kidney stones, serum creatinine > 1.2 mg/dl, or proteinuria > 100 mg/dl by dipstick were excluded.

Results: The characteristics of the patients in whom RPV was measured are shown in the table. There were no significant differences between the groups. RPV/height was 21% greater in ESLD than in controls: 230 ± 7 ml/m vs 190 ± 7 ml/m (mean ± SE; p= 0.0002). This difference remained significant (p<0.001) in a multivariate analysis that included age, gender, serum creatinine, and degree of ascites. Glomerular volume was 24% greater in ESLD than in controls (3.68 ± 0.46 vs. 2.96 ± 0.41 $\mu m^3 x 10^6$) but significance was limited by the small sample size. No edema or vascular congestion was noted in any ESLD kidney.

Conclusions: Renal parenchymal volume is increased in patients with ESLD without evidence of renal disease. This cannot be explained by interstitial edema, vascular congestion, or ascites. There appears to be a similar increase in glomerular volume consistent with renal hypertrophy. This enlargement needs to be considered when evaluating kidney size in ESLD, and the hypertrophy could contribute to the increased risk of acute renal failure in ESLD.

Funding: Clinical Revenue Support

	ESLD	Control
Age	50.3 ± 2.9	53.3 ± 2.6
Gender (% male)	45	47
Height (cm)	170 ± 2	170 ± 2
Weight (kg)	85.5 ± 6.0	82.7 ± 3.4
Serum creatinine (mg/dl)	0.83 ± 0.04	0.90 ± 0.3

FR-PO143

Outcome of Decompensated Liver Cirrhosis Patients with AKI Treated with Renal Replacement Therapy Jian Li,[1] Lenar T. Yessayan,[2] Sandeep S. Soman.[1] *[1]Henry Ford Hospital, Detroit, MI; [2]University of Michigan, Ann Arbor, MI.*

Background: Acute kindey injury(AKI) is a common complication in patients with cirrhosis and is associated with high mortality, renal repalcement therapy(RRT) is considered futile in hepatorenal syndrome if patient is not liver transplant candidate. The over survival and predictive factors has not been well established in those patients.

Methods: We retrospectively identified 123 patients with decompensated Liver cirrhosis receiving RRT for AKI between Nov. 1, 2013 and Dec. 31, 20015 in our hospital. Diagnosis of decompensated liver cirrhosis was based on previous histology findings or on various associations of clinical, biological, endoscopic, and/or imaging findings; AKI and HRS diagnosis were based on KDIGO and International Ascites Club 2007 criteria. The initiation of RRT was determined by nephrologist based on routine practice indications with assent of intensivist or hepatologist involved the care. RRT modality includes SLED-RCA, CVVH or IHD. Death served as outcome. 1, 3 and 6 month's mortality and selected clinical characteristics were examined. Chi-square two-sided tests were used to compare categorical variables, t test used for numerical data, P<0.05 is statistical significant.

Results: In this cohort, 52.8% was male; age 53.3 ±11.6; AKI causes: HRS 65; ATN 54, others 4. in 123 patients, Cirrhosis causes: alcohol 79, NSAH 18, hepatitis C and B: 10 and 1, others 15. 121 patients had outcome data, 2 patients lost follow up. In the death group, 1, 3 and 6 month's mortality rate was: 84.9%; 97.2% and 100%, average time on RRT were 20 ±30 days. In the 15 patients who survived till the time of transplanted, remained or off RRT, their average time on dialysis was 114 ± 106 days; 7 had simultaneous liver and kidney, 2 had liver transplant and off RRT, other 5 patients recovered or with CKD3, one was HD dependent. ICU admission, sepsis, infection and ventilator support were much higher in non-survival patients vs survival patients (P<0.0007-0.03). MELD score no difference in two groups, but all patients had higher score at time of RRT than at admission (P<0.01).

Conclusions: Patients with RRT dependent AKI in decompensated liver cirrhosis had very high short and long term mortality if they were not a liver transplant candidate. ICU admission, sepsis, infection and ventilator support rates were much higher in non-survival group than survived group.

FR-PO144

Hepatorenal Syndrome in Teaching versus Non Teaching Hospitals: A Nationwide Analysis Yumeng Wen,[1,2] Di Pan,[1,2] David Mariuma,[1,2] Marcelo X. Hernandez cuchillas,[1,2] Fernando Vazquez de lara,[1,2] Michael Gramuglia,[3] Ira S. Meisels.[1,2] *[1]Division of Nephrology, Department of Medicine, Mount Sinai St. Luke's and Mount Sinai West Hospitals, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]Department of Medicine, Montefiore Medical Center, Scarsdale, NY.*

Background: Decompensated cirrhosis is a major cause of mortality and morbidity in the United States. Hepatorenal syndrome (HRS) is one of the potential causes of acute kidney injury (AKI) in patients with cirrhosis. The aim of our study is to determine the differences in outcomes and resource utilization in patients with HRS admitted to teaching hospitals as compared to nonteaching hospitals.

Methods: This is a retrospective cohort study using the 2014 National Inpatient Sample, the largest inpatient database in the United States. A corhort of 32,980 patients over the age of 18 diagnosed with HRS based on ICD-9 CM code was included in the study. Patients admitted for elective procedures were excluded. Hospitals were identified as teaching or nonteaching hospitals based on the American Hospital Association annual survey of hospitals. The primary outcome was in-hospital mortality. The secondary outcomes were morbidity, as measured by the development of shock, acute respiratory failure, variceal bleed, requirement for dialysis and resource utilization, as measured by the length of hospital stay (LOS) and total hospital charges. Odds ratios (OR) were estimated based on multivariate regression model adjusted for demographics, hepatitis C status, hospital region, primary insurance and household income. Analysis was performed using Stata, Version 14.2. Group 1: HRS admission to teaching hospital. Group 2: HRS admission to nonteaching hospital.

Results: Among patients with HRS, the in-hospital mortality rates were not significantly different between the two groups (OR 1.06, p=0.38). However patients in teaching hospital had significantly higher rates of shock (OR 2.33, p<0.001), acute respiratory failure (OR 1.44, p<0.001), variceal bleeding (OR 1.54, p<0.05) and requirement for dialysis (OR 1.34, p<0.001). In teaching hospitals the total charges were $57711.91 more (p<0.001), and the length of stay was also greater (12.02 days vs. 8.07 days, p<0.001).

Conclusions: Patients with HRS admitted to teaching hospitals had significant increase in morbidities as compared to those admitted to non-teaching hospitals. The development of shock, acute respiratory failure, variceal bleed, the requirements for dialysis and resource utilizations were greater in teaching hospitals despite similar rates of mortality.

FR-PO145

Different Effects of Aerobic and Combined Exercise on Mitochondrial OXPHOS Proteins in Skeletal Muscle of CKD Patients Douglas W. Gould,[2] Emma L. Watson,[2] Scott Mcguire,[1] Soteris Xenophontos,[2] Thomas J. Wilkinson,[2] Matthew P. Graham-Brown,[2] Joao L. Viana,[3] Alice C. Smith.[2] *[1]Coventry university, Coventry, United Kingdom; [2]University of Leicester, Leicester, United Kingdom; [3]University Institute of Maia, Porto, Portugal.*

Background: Patients with CKD exhibit skeletal muscle wasting and dysfunction. Mitochondrial dysfunction is observed in non-dialysis (ND) CKD, resulting in abnormal oxidative phosphorylation (OXPHOS) and reduced exercise capacity. Exercise is a potent stimulus for mitochondrial adaptations, however the effects in CKD are under investigated.

Methods: 17 ND-CKD patients (63±14 years; 11 female; eGFR: 28±8ml/min/kg/1.73m^2) completed 12-weeks aerobic exercise (AE) (n=9), or combined aerobic and resistance exercise (CE) (n=8) 3x/wk. Muscle biopsies were obtained from the vastus lateralis at baseline (B1) and 24h (B2) post the first and final exercise sessions (B3). Mitochondrial OXPHOS proteins were analysed by Western blotting and reported as %change (90% CI) from baseline. Data was analysed using Cohens effect size (*d*) and magnitude-based inferences (MBI) that calculates quantitative and qualitative probabilities of a true effect based on effect and 90%CI.

Results: CE showed moderate effects on total OXPHOS protein expression with mean increases of 27% (-11 – 80) *d*=0.39 and 34% (-3 – 80) *d*=0.47 at B2 and B3 respectively. In comparison, the effects of AE were negligible with mean changes of +2% (-28 – 50) *d*=0.03 at B2 and -3% (-70 – 150) *d*=0.04 at B3. Figure 1 shows the results

for the individual complexes along with MBI, where probability is the likelihood of a meaningful difference between time points in direction of change.

Conclusions: We report preliminary evidence of differential effects of AE and CE on OXPHOS complex protein expression in the muscle of ND-CKD. Mean % changes tended to be higher following CE, supported by larger effect sizes and MBI indicating beneficial effects for a number of respiratory chain complexes. This may suggest CE is more effective at modulating oxidative capacity of skeletal muscle in ND-CKD.

		Aerobic					Combined				
		%Change [90%CI]	p	d	Probability	Inference	%Change [90%CI]	p	d	Probability	Inference
OXPHOS	B2	↑2 [-28 - 50]	.882	0.03	12%	*Unclear*	↑27 [-11 - 80]	.241	0.39	62%	*Possibly ↑*
	B3	↓3 [-70 - 150]	.812	0.04	59%	*Unclear*	↑34 [-3 - 80]	.129	0.47	73%	*Possibly ↑*
I	B2	↑4 [-2 - 10]	.282	0.03	20%	*Unclear*	↓18 [-41 - 10]	.235	0.31	83%	*Unclear*
	B3	↑14 [-41 - 110]	.705	0.01	38%	*Trivial*	↓6 [-6 - 9]	.139	0.34	64%	*Unclear*
II	B2	↓7 [-72 - 200]	.912	0.08	8%	*Trivial*	↑12 [-3 - 30]	.179	0.17	68%	*Possibly ↑*
	B3	↓6 [-18 - 10]	.415	0.07	0.1%	*Trivial*	↑34 [-6 - 90]	.165	0.55	71%	*Possibly ↑*
III	B2	↑50 [10 - 100]	.039	0.49	89%	*Likely ↑*	↑31 [10 - 70]	.101	0.54	72%	*Possibly ↑*
	B3	↓7 [-12 - 10]	.565	0.04	72%	*Trivial*	↑31 [10 - 60]	.043	0.54	77%	*Likely ↑*
IV	B2	↑13 [-19 - 6]	.514	0.19	37%	*Unclear*	↑27 [-7 - 100]	.168	0.46	73%	*Possibly ↑*
	B3	↓4 [-26 - 20]	.773	0.07	17%	*Unclear*	↑39 [-9 - 110]	.189	0.44	73%	*Possibly ↑*
V	B2	↑15 [-7 - 40]	.246	0.14	36%	*Trivial*	↓13 [-42 - 30]	.531	0.18	42%	*Unclear*
	B3	↑115 [20 - 300]	.051	1.04	95%	*Likely ↑*	↓13 [-45 - 40]	.590	0.10	41%	*Unclear*

Magnitude based inference analysis for total OXPHOS and respiratory chain complexes (I-V)

FR-PO146

ABCA1 Mediated Mitochondrial Remodeling in Podocyte Injury and Diabetic Kidney Disease Gloria Michelle Ducasa,[1] Alexis J. Sloan,[1] Christopher E. Pedigo,[1] Mayrin Correa,[1] Matthias Kretzler,[2] Armando Mendez,[3] Robert G. Nelson,[4] Flavia Fontanesi,[5] Sandra M. Merscher,[1] Alessia Fornoni.[1] *[1]Katz Family Center/ Div of Nephrology, Univ of Miami, Miami, FL; [2]U. Michigan, Ann Arbor, MI; [3]Diabetes Research Inst, Univ of Miami, Miami, FL; [4]NIDDK, Phoenix, AZ; [5]Biochem. and Molec. Bio., Univ of Miami, Miami, FL.*

Background: Diabetic kidney disease (DKD) is the most common cause of ESKD. Decreased podocyte number and glomerular lipid accumulation occurs in clinical and experimental DKD. It has been suggested that podocyte injury in DKD may result from impaired ATP Binding Cassette A1 (ABCA1) mediated cholesterol efflux, mitochondrial dysfunction or increased reactive oxygen species (ROS). However, if impaired ABCA1 function confers susceptibility to DKD by contributing to mitochondrial dysfunction or ROS remains to be established.

Methods: Patients enrolled in the *"Renoprotection in Early Diabetic Nephropathy in Pima Indians trial"* were separated into progressors and non-progressors (dGFR -97.39±8.2, n=15 and +40.62±8.6, n=16, respectively) based on the change in glomerular filtration rate (dGFR) between enrollment and last examination (10±1.7 years). Human podocytes were treated with patient sera. ABCA1 expression and cholesterol efflux were measured. SiRNA *ABCA1* (siABCA1p) and scrambled control (siCO) podocytes were treated with progressor sera and analyzed for caspase 3 activity. Mitochondrial respiratory chain complexes and ROS production were measured in siABCA1p. Podocyte specific Abca1 fl/fl mice were injected with streptozotocin (STZ) or bred to BTBR ob/ob (DKO) mice. Proteinuria was measured.

Results: Podocytes treated with progressor sera showed reduced ABCA1 mRNA expression ($p<0.05$) and cholesterol efflux ($p<0.01$) compared to non-progressors. siABCA1p treated with progressor sera have increased caspase 3 activity ($p<0.05$) compared to siCO. siABCA1p have increased mitochondrial respirasome formation ($p<0.01$), complex I activity ($p<0.05$) and ROS production ($p<0.001$). STZ injected Abca1 fl/fl ($p<0.05$) and DKO mice ($p<0.01$) have increased albuminuria compared to diabetic controls.

Conclusions: Our in vitro and in vivo studies show that reduced *ABCA1* expression confers susceptibility to DKD progression possibly by contributing to mitochondrial remodeling. Treatment strategies aimed at restoring ABCA1 function or mitochondrial dysfunction may be beneficial to prevent podocyte injury in DKD.

Funding: NIDDK Support

FR-PO147

Kidney Injury Molecule-1 (KIM-1) Mediates the Proximal Tubule Uptake of Free Fatty Acids (FFA) Resulting in Mitochondrial Injury and the DNA Damage Response (DDR) Yutaro Mori, Pierre Galichon, Craig R. Brooks, Takaharu Ichimura, Joseph V. Bonventre. *Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.*

Background: KIM-1 is the most upregulated proximal tubule protein in kidney injury. KIM-1 mediates the uptake of apoptotic cells and oxidized low-density lipoproteins (oxLDL). Deregulation of lipid metabolism during diabetes causes disturbed FFA metabolism which is implicated in injurious effects on the kidney in diabetic nephropathy (DN).

Methods: Renal epithelial cells expressing KIM-1 (KIM-1-PK1) were exposed to the FFA palmitic acid, and FFA uptake, necrotic cell death, accumulation of lipids and the DDR were assessed *in vitro*. Mitochondrial status and lysosomal activation were measured using the MitoTracker and LysoSenser dyes, respectively. Pro-fibrotic factor(s) production by FFA-treated KIM-1-PK1 cells were determined with a fibrosis bioassay using mouse primary baby kidney fibroblasts. Functional knockout of KIM-1 (KIM-$1^{\Delta mucin}$) and control mice were used for electron micrographic assessment of the effects of KIM-1 on mitochondrial fragmentation in diabetic nephropathy.

Results: FFA were taken up in the KIM-1-PK1 cells but not in control pcDNA-PK1 cells. Necrosis was increased after FFA treatment with FFA in KIM-1-PK1 cells when compared to controls. Lipid droplets were formed in the KIM-1 cells. FFA-treated KIM-1-PK1 cells had an increased number of fragmented mitochondria at 48 hr. These mitochondria co-localized with activated lysosomes suggesting mitophagy. Nuclear p-ATM and p-H2AX were increased in FFA-treated KIM-1-PK1 cells but not in the control cells. Conditioned media, harvested from KIM-1-PK1 cells treated with FFA, increased α-smooth muscle actin expression of mouse fibroblasts. oxLDL uptake also induced mitochondrial fragmentation and nuclear p-ATM and p-H2AX in a KIM-1 dependent way. Mitochondrial fragmentation occurred in a streptozotocin model of diabetic nephropathy in wild-type mice but not in KIM-$1^{\Delta mucin}$ mice.

Conclusions: KIM-1 mediates the epithelial uptake of FFA, which leads to cell death, lipid accumulation, activation of mitochondrial fragmentation and mitophagy, DDR and fibrosis. Our findings suggest that KIM-1-mediated FFA uptake may play an important role in pathophysiology of the DN.

Funding: NIDDK Support

FR-PO148

The Iron Chelator Deferasirox Causes Kidney Disease via Mitochondrial Dysfunction Esther M. Gottwald, Claus D. Schuh, Dominik Haenni, Susan Ghazi, Milica Bugarski, Michael Duss, Ehud M. Landau, Andrew Hall. *University of Zurich, Zurich, Switzerland.*

Background: Deferasirox (DFX) is an oral iron chelator widely used in individuals at high risk of iron overload. It frequently causes kidney disease, by previously unknown mechanisms. Toxicity is localized to the proximal tubule (PT) and manifests clinically as the renal Fanconi syndrome (FS). PT cells are densely packed with mitochondria, which require iron for normal metabolism. We hypothesized that DFX causes kidney disease via mitochondrial toxicity.

Methods: Experimental models: PT-derived cell line, ex vivo mouse kidney cortex, in vivo mouse kidney. Techniques: confocal/multiphoton live imaging, electron microscopy, oxygen consumption measurements.

Results: In PT-derived cells and fresh slices of mouse kidney cortex we discovered that DFX induces rapid swelling of mitochondria, leading ultimately to rupture of the inner mitochondrial membrane (IMM). Other iron chelators did not have the same effect. Mitochondria remained polarized during the swelling process, which was not prevented by inhibition of the permeability transition pore, but was rapidly reversed by the addition of iron. Of note, DFX did not inhibit oxygen consumption or cause oxidative stress, and targeted anti-oxidants did not prevent the phenotype. Interestingly, DFX-induced mitochondrial swelling and rupture was accelerated by stimulation of respiratory chain (RC) activity, whilst RC inhibition had the opposite effect, suggesting that swelling is an active process. Moreover, DFX did not induce rupture in an artificial lipid vesicle model of the IMM, implying that toxicity requires proteins normally expressed within mitochondria. Using EM and intravital multiphoton microscopy, we observed that mice given DFX for 10 days showed evidence of mitochondrial swelling and dysfunction in vivo, exclusively in the PT, as well as impaired solute transport (consistent with FS). DFX is mainly albumin bound in blood, and we found that albumin binding reduced its toxicity in vitro, which might explain why the drug is tolerated by patients. Furthermore, since albumin is actively taken up by the PT, this could also explain the localization of DFX toxicity to this nephron segment.

Conclusions: In summary, we have found that DFX induces swelling and rupture of mitochondria in the PT, which most likely explains why it causes kidney disease in humans

Funding: Government Support - Non-U.S.

FR-PO149

Bisphenol A Is an exogenous Toxin That Promotes Mitochondrial Injury and Death in Tubular Cells Enrique Bosch,[1] Alberto Ruiz,[1] Esther Civantos,[1] Alberto Ortiz,[2] Emilio E. Gonzalez-parra,[2] Sebastian Mas.[1] *[1]IIS- FJD, Madrid, Spain; [2]Fundacion Jimenez Diaz, Madrid, Spain.*

Background: Protein-bound uremix toxins, such a p-Cresol (pC) and metabolites, are harmful chemicals difficult to remove by hemodialysis. Bisphenol A is a ubiquitous environmental toxin, structurally related with pC, that accumulates in CKD, but is not currently considered a uremic toxin. Our aim was to characterize the nephrotoxic potential of BPA. Specifically, we addressed whether it disrupts mitochondrial function and causes cell death in energy demanding cells as tubular cells.

Methods: Experiments were performed on HK-2 human proximal tubular epithelial cells. Cell death and oxidative stress were evaluated by flow cytometry and confocal microscopy in HK-2 human proximal tubular epithelial cells. Functional assays tested ATP, intracellular Ca2+, mitochondrial function (TMRM), oxygen consumption, Nrf2-binding and NAPDH oxidase activity. Gene expression was assessed by qRT-PCR.

Results: Following acute exposure (24h), proximal tubulo-epithelial cell viability is only affected by BPA or pC at concentrations higher than 100 μM. The observed mechanisms are similar for both toxins, since they both promote mitochondrial dysfunction leading to energy depletion, mitochondrial and cytoplasmic oxidative stress (MitoSOX and NAPDH oxidase) and apoptosis in a concentration-dependent manner. An antioxidant response was observed consisting of Nrf2 translocation and increased expression of the Nrf2 target genes Heme oxygenase 1 (HO-1) and NAD(P)H dehydrogenase [quinone] 1 (NQO-1).

Conclusions: This study demonstrates for the first time that BPA causes mitochondrial injury, oxidative stress and apoptotic death in tubular cells. These results characterize BPA as an exogenous toxin that, similar to uremic toxins, may contribute to CKD progression.

FR-PO150

Elastica Masson's Trichrome (EMT) Staining Is Useful for the Visualization of Podocyte Foot Process and Tubular Mitochondria in the Kidney Ayumi Matsumoto, Isao Matsui, Karin Shimada, Nobuhiro Hashimoto, Daisuke Mori, Satoshi Yamaguchi, Keiichi Kubota, Tatsufumi Oka, Sayoko Yonemoto, Yusuke Sakaguchi, Tomoko Namba, Masayuki Mizui, Takayuki Hamano, Yoshitaka Isaka. *Osaka University Graduate School of Medicine, Suita, Japan.*

Background: Changes in microstructures of renal cells, such as foot process effacement in podocytes and mitochondrial fission in tubular cells, are tightly correlated with the development and the progression of kidney disease. Because the sizes of these structures are less than the diffraction limit of visible light, electron microscopy is usually required for their observation. Super-resolution microscopy (SRM) is also available, but the common technique for SRM requires time-consuming immunofluorescent staining for specific molecules.

Methods: To visualize the microstructures more easily, we analyzed paraffin-embedded human renal biopsy sections stained with EMT, Hematoxylin Eosin (HE), Periodic Acid-Schiff (PAS), or Periodic Acid Methenamine Silver (PAM) using structured illumination microscopy. Sections of animal kidney disease models were also analyzed.

Results: EMT-stained paraffin-embedded sections excited by 457 or 561 nm laser were useful for the visualization of podocyte foot process. We could observe foot process in the sections from minor glomerular abnormalities but not from minimal change disease. Foot process was also observable in EMT-stained normal rat kidney but not in puromycin aminonucleoside injected kidney. The other staining methods — HE, PAS, and PAM — were not applicable to the evaluation of foot process. In the tubulointerstitial area of the human kidney, EMT-stained sections excited by 561 nm laser were useful for the evaluation of mitochondria. In some patients with kidney disease, we observed short mitochondria, which suggested the progression of mitochondrial fission. We confirmed the usefulness of EMT staining for the evaluation of mitochondria by observing mitochondrial fission in endotoxin-induced kidney injury and mitochondrial swelling in ischemia reperfusion kidney injury in mice. Tubular mitochondria were also observable in HE or PAS-stained sections, but the images obtained by these staining were less clear.

Conclusions: Paraffin-embedded kidney sections stained with EMT were useful for the visualization of foot process and mitochondria in the kidney.

Funding: Private Foundation Support

FR-PO151

Advanced Oxidation Protein Products Aggravate Tubulointerstitial Fibrosis through PKC-Dependent Mitochondrial Injury in Early Diabetic Nephropathy Xiaoyan Bai,[2] Xiao Li,[1] Jianwei Tian,[2] Wan Jiao.[3] *[1]Emergency, Nanfang Hospital, Southern Medical University, Guangzhou, China; [2]Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China; [3]Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China.*

Background: The accumulation of advanced oxidation protein products (AOPPs) has been regarded as an initiating factor in podocyte injuries via the protein kinase C (PKC) signaling in diabetes. Yet, mechanisms of PKC signaling activation in renal tubular cell injuries and tubulointerstitial fibrosis (TIF) remain unclear. It has been established that PKC signaling plays a critical role in triggering oxidative stress and mitochondrial injuries in multiple diseases. Herein, we hypothesized that the accumulation of AOPPs in diabetes incurs mitochondrial dysfunction and oxidative stress causing renal TIF through the PKC signaling pathway.

Methods: The functional relevance of AOPP and PKC signaling in relation to mitochondrial injury, oxidative stress and fibrosis were investigated in high glucose (HG) cultured HK-2 cells and renal tubules from diabetic rats and patients using *in vitro* and *in vivo* approaches. Biological parameters were analyzed using enzyme linked immunosorbent assay (ELISA).

Results: *In vitro*, HG stimulated AOPP expression and augmented PKC-mediated oxidative stress and fibrosis in proximal tubular epithelial cells (PTECs). Further, we provide mechanistic evidences that inhibition of PKCη isoform alleviated mitochondrial injuries and function, attenuated apoptosis and renal fibrosis in HG cultured AOPPs-induced PTECs. *In vivo*, AOPPs-induced mitochondrial injuries, apoptosis and TIF were significantly decreased by PKCη inhibition in diabetic rats. Intrarenal AOPPs accumulation correlated with oxidative stress and fibrosis in renal biopsy samples from DN patients. AOPP and PKCη expression correlate with elevated proteinuria and declined renal function in diabetic rats and DN patients.

Conclusions: We propose a novel mechanism that AOPPs trigger mitochondrial dysfunction and oxidative stress causing TIF in diabetic nephropathy through activation of the PKCη isoform of the PKC signaling.

Funding: Government Support - Non-U.S.

FR-PO152

Urinary Mitochondrial DNA Level as a Biomarker of Diabetic Nephropathy Zhongping Wei. *Department of Medicine & Therapeutics, The Chinese University of Hong Kong, Hong Kong, China.*

Background: Diabetic nephropathy (DN) is the most common cause of end stage renal disease (ESRD). However, there is no reliable non-invasive biomarker for the diagnose or risk stratification of DN. Since mitochondrial dysfunction is involved in the progression of many kidney disease, we study the relation between urinary supernatant cell-free mitochondrial DNA (mtDNA) level and renal dysfunction in DN.

Methods: We recruited 92 patients with biopsy-proven DN. Urinary supernatant mtDNA level was measured by digital polymerase chain reaction, and compared to clinical, biochemical, histological data, as well as renal function decline in the subsequent 24 months.

Results: Mitochondrial DNA could be detected in all urine supernatant and renal biopsy specimens, with average levels 1421.0 ± 1827.5, and 286114.4 ± 193481.0 copies/μL, respectively. There was a modest but statistically significant inverse correlation between urinary supernatant and intra-renal mtDNA levels ($r = -0.453$, $p = 0.012$). Urinary supernatant mtDNA level had modest but statistically significant correlations, inversely with estimated glomerular filtration rate (GFR) ($r = -0.214$, $p = 0.04$), and positively with the severity of interstitial fibrosis ($r = 0.300$, $p = 0.005$). However, there was also no significant correlation between the rate of GFR decline in 2 years and urinary supernatant mtDNA level ($r = -0.070$, $p = 0.5$).

Conclusions: Urinary supernatant mtDNA level may reflect the severity of kidney damage and intra-renal mitochondrial depletion in DN. Further studies are needed to confirm its role as biomarker of diabetic nephropathy.

Funding: Government Support - Non-U.S.

FR-PO153

Metabolic Reprogramming in Diabetic Kidney Disease Can Be Restored via SGLT2 Inhibition Manjula Darshi,[1,2] Akira Onishi,[2] Jiwan J. Kim,[1] Jessica Pham,[1] Benjamin F. Van espen,[1] Anne Murphy,[3] Hiddo J. Lambers Heerspink,[4] Volker Vallon,[2] Kumar Sharma.[1,2] *[1]Department of Medicine, University of California, San Diego, Irvine, CA; [2]Division of Nephrology-Hypertension, Veterans Affairs, San Diego, La Jolla, CA; [3]Department of Pharmacology, UCSD, La Jolla, CA; [4]Department of Clinical Pharmacy and Pharmacology, University of Groningen, University Medical Center, Groningen, Netherlands.*

Background: Recent studies indicate mitochondrial dysfunction as a dominant pathway in diabetic kidney disease (DKD), however underlying mechanisms are unclear. In this study we used metabolomic and biochemical assays in the type 1 Akita DKD mouse model and in patients with DKD to decipher the consequences of high glucose on metabolic reprogramming leading to proximal tubule damage. Furthermore, we analyzed a therapeutic potential of the proximal tubule glucose transporter, SGLT2, responsible for reabsorption of the majority of the filtered glucose.

Methods: Metabolomic analysis was performed by GC-MS/MS from control and type 1 diabetic mice (Akita, n=6 each) in the presence and absence of SGLT2 inhibitor empagliflozin (~45mg kg^{-1} day^{-1}). Urinary lactate and pyruvate concentrations were measured using biochemical assays in patients with type 2 diabetes and albumin:creatinine ratio>100mg/g, enrolled in a cross-over study with the SGLT2 inhibitor dapagliflozin or placebo (6 weeks, 10mg/day, n=33 total). Mitochondrial functional changes in human kidney proximal tubule (HK2) cells were analyzed using Seahorse XF technology.

Results: Metabolomic analysis in Akita mice indicated a marked increase in glycolysis with an increase in the lactate/pyruvate ratio in urine ($p=0.0002$, 95% CI), plasma ($p=0.02$) and kidney tissue ($p=0.06$) as compared with non-diabetic controls. The urinary lactate/pyruvate levels in Akita mice were reduced upon treatment with empagliflozin ($p=0.002$) and in the urine of SGLT2 knockout mice vs wild type controls despite similar blood glucose levels ($p=0.03$). Furthermore, in T2D patients, dapagliflozin decreased the urine lactate /pyruvate ratio by 34% ($p=0.03$) compared to placebo and this decrease correlated with the decline in eGFR ($r-0.042$, $p=0.04$). Studies in HK2 cells further identified that acute glucose treatment can significantly inhibit rate of oxygen consumption and enhance lactate production suggesting a 'Crabtree' effect indicative of glucose suppression of mitochondrial respiration.

Conclusions: High glucose suppresses mitochondrial function with a shift to glycolysis and may be linked to proximal tubule injury. Our studies suggest ta protective role of SGLT2 inhibition, may be via reduction of the lactate/pyruvate ratio resulting in improved mitochondrial function.

Funding: NIDDK Support, Veterans Affairs Support, Government Support - Non-U.S.

FR-PO154

Mitochondria-Targeted Antioxidant Peptide SS-31 Attenuates Renal Tubulointerstitial Injury via Regulating Mitochondrial Dynamics in DN Hao Zhang,[1] Shi-kun Yang,[3] Jianwen Wang.[2] *[1]The Third Xiangya Hospital of Central South University, Changsha, China; [2]The third Xiangya Hospital of Central South University, Changsha, China; [3]The third Xiangya Hospital, Central South University, Changsha, China.*

Background: Accumulating studies indicate that mitochondrial dysfunction is central to the pathogenesis of DN. We investigate the effects and mechanisms of mitochondria-targeted peptide SS-31 therapy on tubulointerstitial injury in DN.

Methods: 40 C57BL/6 mices were randomly divided into control, DN group, STZ+SS-31 group, STZ+ normal saline group. The DN model was induced by injection intraperitoneally with 40mg/kg body weight STZ for four times. SS-31 was intraperitoneally injected to the mice every other day for 24 weeks. Renal lesions and the expression of Drp1, P66Shc, Bcl-2, Bax, Caspase-1, IL-1, FN were detected by HE, Masson staining, TUNEL, DHE, immunohistochemistry and western-blot. In vitro, HK-2 cells were incubated with different concentrations of D-glucose (5, 30mM) or high glucose (30mM) combimed with SS-31(100nM) or Drp1 inhibitor Midivi1 for indicated time (0-

72h). The expression of Drp1, P66Shc, Bcl-2, Bax, Caspase-1, IL-1, FN were detected by Western-blot and immunoflurescence. Mitochondrial functional and morphology analysis were carried out by measuring ROS, TMRE, mitochondrial morphology.

Results: Extracellular matrix deposition and apoptosis of tubular cells were found in DN mices, The expressions of Drp1, P66Shc, Bax, Caspase-1, IL-1, FN were increased in the kidney of DN mices, while treatment with SS-31 could partially reverse such abnormalities, in addition, SS-31 treatment could attenuate renal pathological changes, serum creatinine, microalbuminuria, renal ROS and apoptosis levels. On the other side, the tubular mitochondrion of DN mice exhibiting deformations, such as swelling and fragmentation, while SS-31 treatment could reduce mitochondria fragmentation. In vitro, HG induced mitochondrial dysfunction, including altered membrane potential and increased overproduction of mitochondrial superoxide. Furthermore, HG increased the expression of Drp1 and P66Shc, Bax, Caspase-1, IL-1, FN. However, pretreatment with SS-31could partially reverse such abnormalities. Pretreatment with Drp1 inhibitor Midivi1 could also ameliorate HG-induced mitochondrial dysfunction, while SS-31 used in combination with Midivi1 could enhance the effects of antioxidant and anti-apoptosis.

Conclusions: These data indicate that SS-31 ameliorates tubulointerstitial injury via inhibiting mitochondrial fragmentation in DN.

FR-PO155

Re-Routing of Mutant Protein from Mitochondria to Peroxisome: A Therapeutic Approach for Primary Hyperoxaluria Type I Ruth Belostotsky,[2] Roman Lyakhovetsky,[3] Bodo B. Beck,[5] Björn Reusch,[4] Fanny Shkedy,[1] Yaacov Frishberg.[1] *[1]Shaare Zedek Medical Center, Jerusalem, Israel; [2]Shaarey Zedek Medical Center, Jerusalem, Israel; [3]Teva Pharmaceuticals, Maale Adumim, Israel; [4]University of Cologne, Cologne, Germany; [5]University of Cologne Medical Center, Cologne, Germany.*

Background: Primary hyperoxaluria type I (PH1) is caused by deficiency of the liver specific peroxisomal (Px) alanine-glyoxylate aminotransferase (AGT). Due to low solubility of calcium oxalate, PH1 results in progressive nephrocalcinosis and decline in kidney function to ESRD. The most frequent AGT mutation G170R results in aberrant mitochondrial localization with preserved catalytic activity. Thus, molecules that stimulate Px localization of the mutated protein may prevent oxalate production. To identify such molecules we developed the split GFP system in which only peroxisomal AGT sub-population produces a fluorescent signal. This sensitive and specific tool allows precise monitoring of Px sub-population of AGT: confocal microscopy confirms that GFP signal of both WT and G170R AGT is localized exclusively in Px and is substantially stronger in the WT-AGT. Using split GFP, we demonstrated that localization of G170R-AGT can be corrected by mild translation inhibition using the inhibitors emetine (a known antiprotozoal agent) and GC7. 7 days incubation of G170R-AGT-GFP transfected CHO cells with 40 nM emetine resulted in 70-80% increase in the number of GFP positive cells as quantified by FACS analysis. Under these conditions, total protein synthesis decreased by less than 25%. We also measured the effect of mitochondrial transport inhibitors: DECA and monensin, recently indicated to correct G170R-AGT localization. Both compounds, but not GC7, presented synergistic effect with emetine. We assume that DECA and monensin assist AGT relocation by mitochondrial transport interference while emetine and GC7 interfere with protein synthesis. The functional competence of peroxisomal retargeted AGT-LRM was confirmed in cultured human hepatocytes bearing G170R mutation. Augmented oxalate level in culture media was substantially reduced. In summary, we demonstrate that mild translation inhibition can re-route nascent AGT molecules into the Px. We suggest that this approach may be applicable not only for treating PH1 but also for other diseases caused by protein misfolding. The split-AGT system can be a useful tool in developing new treatments for PH1.

Methods:

Results:

Conclusions:

Funding: Government Support - Non-U.S.

FR-PO156

Clearance of Damaged Mitochondria via Mitophagy Plays an Important Role in the Protective Effect of Renal Ischemic Preconditioning Man J. Livingston, Zheng Dong. *Augusta University Medical College of Georgia, Augusta, GA.*

Background: Ischemic preconditioning (IPC) affords tissue protective effects in organs including the kidney; however, the underlying mechanism remains unclear. Autophagy is induced in renal tubular cells during acute kidney injury (AKI) and plays a protective role, but whether autophagy contributes to the protective effect of IPC is unknown.

Methods: This study has examined the role of autophagy in the renoprotection of IPC using both in vivo and in vitro ischemic AKI models. IPC was induced in mice by mild (15 minutes) renal ischemia followed by 1-hour reperfusion. The mice were then subjected to more severe (27 minutes) renal ischemia to examine kidney injury. In in vitro, IPC was induced in proximal tubular cells (RPTC) by 30 minutes of "chemical ischemia" with CCCP followed by 40-minute recovery. The cells were then incubated with CCCP for 3 hours followed by 2-hour recovery (CCCP3h/R2h) to examine injury.

Results: IPC suppressed subsequent ischemic AKI. Autophagy was induced in kidneys by IPC. Notably, the renoprotective effect of IPC was abolished by autophagy inhibitors and also in kidney proximal tubule-specific Atg7 knockout mice, suggesting the dependence of IPC renoprotection on autophagy. Along with autophagy induction, the mitophagy regulator Pink1 was activated and there was a remarkable loss of mitochondrial proteins following ischemic AKI, suggesting that autophagy may protect kidneys by activating mitophagy. Consistent with in vivo observations, IPC in RPTC cells showed protective effects, which were abrogated by autophagy inhibition. Interestingly, IPC in RPTC cells induced a significant increase in the colocalization of autophagosomes with mitochondria, suggesting mitophagy induction. Moreover, IPC increased the delivery of mitochondria to lysosomes as shown by Cox8-EGFP-mCherry mitophagy reporter assay. Consistently, IPC induced higher levels of mitochondrial loss or clearance during subsequent CCCP treatment that was suppressed by autophagy inhibitors. IPC-induced clearance of mitochondria was associated with the reduction of ROS generation during subsequent CCCP treatment.

Conclusions: Together, these results suggest that autophagy, especially mitophagy, plays an important role in the protective effect of IPC.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO157

PKC-a Inhibition Normalizes Nephrotoxic Serum Induced Disruption of Mitochondrial Membrane Potential and Morphology in Glomerular Endothelial Cells Nino Kvirkvelia,[1] Malgorzata McMenamin,[1] Marie Warren,[1] Raghavan Raju,[1] Rudolf Lucas,[2] Michael P. Madaio.[1] *[1]Augusta University, Augusta, GA; [2]Medical College of Georgia, Augusta University, Augusta, GA.*

Background: Nephrotoxic serum nephritis (NTN), an inflammatory model of antibody mediated nephritis caused by single injection of nephrotoxic serum (NTS), proceeds to end stage kidney disease. Earlier studies have shown that NTS treatment damages cultured glomerular endothelial cells by disrupting mitochondrial respiration, and that PKC-a Inhibition normalized these perturbations. The goal of this study was to determine the mitochronical pathways involved in this process.

Methods: Murine glomerular endothelial cell (GEC) viability was evaluated by LDH release following NTS exposure. PKC-α was pharmacologically inhibited with Ro-320432 (EMD Millipore, Billerica, MA). Changes in mitochondrial membrane potential ($\Delta\psi_m$) were measured using cationic carbocyanine dye, which changes fluorescence spectrum depending on mitochondrial potential status. Mitochondrial morphology and distribution were examined using Mitotracker–mitochondrion selective probes.

Results: Following NTS exposure, LDH release, measured as per cent of LDH cytotoxicity, was dramatically increased in GEC up to 50%, whereas PKC-α inhibition (50 nM Ro-320432) reduced cytotoxicity significantly (12%), indicating that PKC-α is involved in NTS-induced endothelial cell cytotoxicity. NTS treatment of GEC resulted in reduction of $\Delta\psi$ and in an increase of cells with depolarized mitochondria by 73%, PKC-α inhibition of NTS-treated cells reduced the number of cells with depolarized mitochondria to 15%. Furthermore, NTS reduced the fraction of cells with healthy mitochondria by 34%, whereas PKC-α inhibition increased that fraction to 79%. Severe mitochondrial swelling, documented by the appearance or large and round shaped mitochondria, was observed in endothelial cells after NTS treatment using Mitotracker–mitochondrion selective probes, which coincided with a loss of $\Delta\psi_m$. PKC-α inhibition in NTS-treated GEC restored the rod-type appearance in the majority of mitochondria.

Conclusions: PKC-α participates in NTS induced mitochondrial dysfunction in GEC cells and inhibition of PKC-α significantly improves endothelial cell viability by normalizing mitochondrial membrane potential and morphology. These results may foster the design of novel therapeutic approaches that preserve mitochondrial function during kidney injury.

Funding: NIDDK Support

FR-PO158

Mitochondrial Protection Regulates Expression of Senescent Cell Regulators p16 and p21 in Parietal Epithelial Cells (PECs) of Aged Kidneys Mariya T. Sweetwyne, Peter S. Rabinovitch, Stuart J. Shankland. *University of Washington, Seattle, WA.*

Background: Mitochondrial dysfunction increases with age and can induce cellular senescence. Kidneys are a mitochondrial rich tissue and show predictable pathological changes with age. We have previously demonstrated that systemic late-age treatment with the mitochondrial protective peptide SS-31 reduced age-induced glomerulosclerosis in mice of 24-28 months of age (~70-85 yr old human). Additionally, mitochondria-protected aged kidneys showed reduced podocyte injury, preservation of endothelial cell number and increased parietal epithelial cell density. Concomitant to these changes was a significant reduction in senescence-associated-β-galactosidase (SA-β-gal) expression across all compartments of the renal cortex. Staining for cell-cycle senescence regulator, p16 increased with age, but with SS-31 treatment was reduced in both PECs and the glomerular tuft of aged mice relative to aged baseline.

Methods:

Results: In our current studies we further characterized PEC senescence by staining for expression of p21. Expression of p21 in PECs demonstrated an inverse relationship to that of p16 (p21 young =57.48% vs. aged vehicle =20.08% vs. aged SS-31 =31.46%; p16 young =11.9% vs. aged vehicle =55.0% vs. aged SS-31 =29.6%). Furthermore, expression of p21 in tuft cells did not change with either age or treatment. Close examination of glomeruli in serial sections showed a differential expression of p16 and p21 in PECs along Bowman's capsule, with individual PECs expressing either p16 or p21, but not both. To determine if senescence in PECs could be directly regulated by mitochondrial damage, we exposed immortalized mouse PECs (mPEC) to mitochondrial insult via low doses (5,15, 20 nM) of Rotenone, Oligomycin A and Antimycin A. After 3d exposure, mitochondrial injury and oxidative stress increased in cells with mid and high doses of all treatments, as detected by MitoTrackerFR and CellRox green respectively. At 2 weeks of culture, 20 nM

Rotenone increased expression of SA-β-gal in mPECs. In the treated cells, p16 but not p21 nuclear expression increased by immunocytochemistry.

Conclusions: Late-age SS-31 intervention amelorates renal mitochondrial damage and senecence. In the glomeruli of aged mice and in cell culture, mitochondrial dysfunction corresponds to PEC senescence with increased expression of p16 but not p21.

Funding: NIDDK Support, Other NIH Support - NIA

FR-PO159

Alterations of Mitochondrial Oxidative Metabolism in an Aging Model of Cisplatin Induced AKI Kranti A. Mapuskar,[1] Hsiang M. Wen,[2] Michael L. Mccormick,[1] Gilbert V. Schaeffer,[3] Amy L. Sindler,[3] Danniele G. Holanda,[4] Prerna Rastogi,[4] Douglas R. Spitz,[1] Bryan Allen,[1] Diana Zepeda-Orozco.[2] *[1]Free Radical and Radiation Biology Program, Department of Radiation Oncology, University of Iowa, Iowa City, IA; [2]Stead Family Department of Pediatrics, Universiy of Iowa, Iowa City, IA; [3]College of Liberal Arts and Sciences, Department of Health and Human Physiology, University of Iowa, Iowa City, IA; [4]Department of Pathology, University of Iowa Health Care, Iowa City, IA.*

Background: Elderly patients have increased susceptibility to acute kidney injury (AKI). Increased oxidative stress and decreased antioxidant response may play a role in age associated AKI. The electron transport chain (ETC) complexes are a major metabolic site of reactive oxygen species (ROS) production in mammalian cells. In this study we hypothesized that aging is accompanied by abnormal mitochondrial oxidative metabolism that increases susceptibility to cisplatin induced AKI.

Methods: Young (4 months) and old (18 months) C57BL/6J mice received 10mg/kg intraperitoneal cisplatin injection *vs.* vehicle control. Blood urea nitrogen (BUN) and creatinine (Cr) measurements were obtained at baseline, 3, and 6 days post injection. Kidneys were harvested at 6 days to assess histological changes, mitochondrial oxidative metabolism, and antioxidant response

Results: Baseline renal function was not significantly different in young *vs.* old mice. Cisplatin caused significant renal function decline at 3 days in both groups. However, old cisplatin mice had less than 50% survival rate at 6 days compared to 100% survival in young mice. Control old mice demonstrated significant increased steady state levels of O_2^- and %GSH/GSSG, downregulation of mitochondrial ETC complex I, II, citrate synthase, and aconitase activities compared to young control mice. In both cisplatin groups, there was significant upregulation of complex I activity, with no significant change in complexes II-IV activity or citrate synthase activity compared to their respective vehicle controls suggesting that reverse electron transport (RET) may be a source of ROS production in cisplatin induced AKI. In cisplatin treated groups young mice had a significant upregulation of aconitase activity, which was not observed in old mice. Finally, in cisplatin treated old mice increased steady state levels of O_2^- were observed which was not seen in young mice

Conclusions: Our results support the hypothesis that aging is accompanied by alterations in oxidative mitochondrial metabolism that can be exacerbated by cisplatin injury. We hypothesize that RET through complex I may contribute to increased ROS production and enhanced kidney injury seen in older mice treated with cisplatin

Funding: Other NIH Support - NIH K12 Child Health and Research Development Award, and the Research Program of Excellence in Redox Biology and Medicine as well as the Department of Radiation Oncology, Commercial Support - Galera Therapeutics

FR-PO160

Sulfotransferase 1C2 (SULT1C2) Post-Translationally Increases Mitochondria Respiration Alexander L. Kolb,[2] Zechariah Pfaffenberger,[4] Seth Winfree,[3] Simon J. Atkinson,[1] David P. Basile,[3] Robert L. Bacallao.[3] *[1]Indiana University - Purdue University Indianapolis, Indianapolis, IN; [2]Biology, Indiana University Purdue University Indianapolis, Indianapolis, IN; [3]Indiana University School of Medicine, Indianapolis, IN; [4]Indiana Wesleyan University, Mishawaka, IN.*

Background: Sulfotransferases are enzymes responsible for xenobiotic detoxification. Mechanistically, these enzymes add a sulfate group to xenobiotics which increases their water solubility and urinary excretion. We identified SULT1C2 in a proteomic screen of mitochondria isolated from ischemic preconditioned kidneys. Using hydrodynamic gene delivery, we show that SULT1C2 protects against subsequent ischemia one week after gene delivery.

Methods: To determine SULT1C2's mechanism of action, we assayed mitochondria function with and without human recombinant SULT1C2 and its substrate, 3' Phosophoadenosine-5'-phosophosulfate (PAPS). Mitochondria respiration was assayed using an Oroboros Oxygraph O2K.

Results: We found that that PAPS and SULT1C2 incubated with mitochondria increase mitochondria state 3 respiration (from 139.4 ±36 to 370.7 ±32 pmol/min/mg), following succinate and rotenone addition, 2.7-fold compared to mitochondria ($P<0.05$). The increase in SULT1C2/PAPS dependent respiration was inhibitable with antimycin A but not rotenone.

Conclusions: In conclusion SULT1C2 and PAPS increase the efficiency of complex II respiration indicating a potential change in the movement if electrons through the complex culminating in increased oxidative phosphorylation. This is a novel new function for an enzyme that heretofore was considered to be solely involved in detoxifying xenobiotics.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO161

Megalin-Mediated Shuttling of Angiotensin II, TGF-ß, and Stanniocalcin-1 to the Mitochondria Qingtian Li,[1] Fan Lei,[3] Yi Tang,[2] Jenny S. Pan,[1] Qiang Tong,[1] David Sheikh-Hamad.[1] *[1]Baylor College of Medicine, Houston, TX; [2]West China Hospital of Sichuan University, Chengdu, China; [3]Baylor College of Medcine, Houston, TX.*

Background: Some extracellular signaling molecules are detected in the mitochondria, including angiotensin II, insulin, stanniocalcin-1 (STC1), TGF-ß and erythropoietin; these are known as mitochondrial intracrines. The mechanism of mitochondrial targeting of these proteins is unknown. Megalin/LRP2 is highly expressed on the apical surface of kidney proximal tubule cells, where it is involved in the uptake/reclamation of filtered vitamins, uptake and lysosomal degradation of filtered proteins, uptake of hormones including angiotensin II and angiotensin 1-7. Megalin mutations are linked to the pathogenesis of Donnai-Barrow and Lowe syndromes, characterized by developmental brain abnormalities and kidney dysfunction. Megalin has not been shown to reside in the mitochondria.

Methods:

Results: Mass spectroscopy analysis of mitochondrial acetyl proteome from kidneys of stanniocalcin-1 transgenic mice identified megalin as a resident mitochondrial protein. Megalin is also present in the mitochondria of a number of cell lines, including 293T, C2C12 and Raw267.4 cells, and associates stanniocalcin-1 and the mitochondrial longevity protein SIRT3. These observations were validated using immunoprecipitation, confocal immunofluorescence, electron microscopy and co-expression experiments. Because megalin, stanniocalcin-1, angiotensin II and TGF-ß are found at the plasma membrane and mitochondria, we hypothesized that megalin serves as a shuttle for mitochondrial intracrines from the cell surface to the mitochondria. CRISPR-Cas9-mediated knockdown of megalin in C2C12 cells diminishes whole-cell and mitochondrial content of megalin. Upon the addition of recombinant hSTC1-FLAG, hSTC1-FITC, angiotensin II-FITC or TGF-ß-FITC to the medium of WT C2C12 cells, we detect the corresponding FLAG or FITC within the mitochondria; however, we observe diminished presence of STC1-FLAG, STC1-FITC, angiotensin II-FITC or TGF-ß-FITC in the mitochondria of megalin knockdown cells.

Conclusions: The data suggest that megalin is present in the mitochondria and exists in complex with proteins involved in anti-oxidant defenses. Megalin serves as a shuttle for signaling molecules from the cell surface to the mitochondria, including angiotensin II, TGF-ß and stanniocalcin-1.

Funding: Veterans Affairs Support

FR-PO162

Muscle Mitochondrial Energetics, Objective Muscle Fatigability, and Symptoms of Fatigue in CKD Baback Roshanravan,[1] Sophia Liu,[2] Amir S. Ali,[2] Jorge Gamboa,[3] Ian H. de Boer,[1] Jonathan Himmelfarb,[1] Bryan R. Kestenbaum,[1] Kevin Conley.[2] *[1]Division of Nephrology and Kidney Research Institute, University of Washington, Seattle, WA; [2]University of Washington, Seattle, WA; [3]Vanderbilt University, Nashville, TN.*

Background: People with chronic kidney disease (CKD) often report symptoms of fatigue. Impaired skeletal muscle mitochondrial function due to the abnormal uremic milieu of CKD may contribute to muscle fatigability and symptoms of fatigue.

Methods: We performed a cross-sectional analysis of 30 participants from the Muscle Mitochondrial ENergetics and Dysfunction (MEND) study. Persons were excluded from MEND if they used medications effecting mitochondrial metabolism, had mobility disability, or weighed >300 pounds. We measured mitochondrial capacity of the tibialis anterior muscle as ATPmax using ^{31}P magnetic resonance spectroscopy. We determined the force time integral (an objective measure of muscle fatigability) and assessed fatigue symptoms using the FACIT-F questionnaire.

Results: Mean GFR was 35 ±15 ml/min; mean age was 61 ±14yr; 53% were female, and 23% had diabetes. Lower muscle ATPmax was associated with lower force time integral (indicating greater fatigability) (figure 1; $P=0.007$) and greater symptoms of fatigue after adjustment (figure 2; $P=0.013$).

Conclusions: Muscle mitochondrial capacity measured by ATPmax is associated with objective fatigability and subjective symptoms of fatigue in CKD patients. These findings are the first connecting impaired human skeletal muscle mitochondrial energetics in CKD with functional and clinical measures.

Funding: NIDDK Support

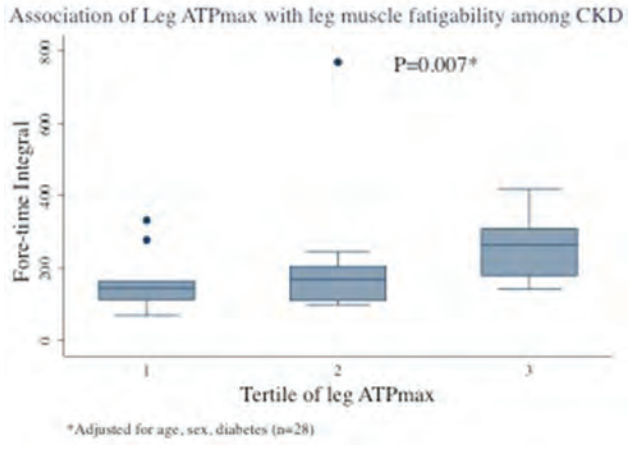


Figure 1. Association of ATPmax with muscle fatigability.

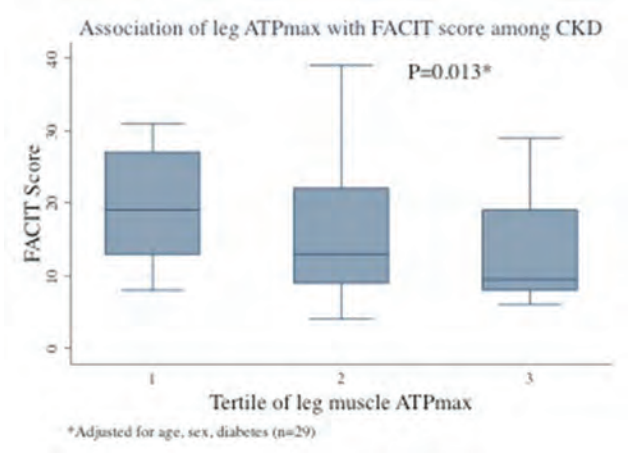


Figure 2. Association of ATPmax with self-reported fatigue.

FR-PO163

Protease Inhibition Improves Renal Mitochondrial Function during Cold Storage and Transplantation Lee Ann MacMillan-Crow, Nirmala Parajuli, Julia Tobacyk, Stephen A. Shrum. *University of Arkansas for Medical Sciences, Little Rock, AR.*

Background: Kidneys were the first successfully transplanted organs and are the most common organ transplant today. Cold storage (CS) of deceased donors is required for successful renal transplantation, but it also leads to renal and mitochondrial damage. During stressful conditions such as CS, mitochondrial fusion allows compensatory mixing of functional mitochondrial content with damaged mitochondria. Thus, impaired fusion can limit acute damage control and ultimately lead to loss of respiratory capacity and cell death. OPA1 is a key mitochondrial fusion protein and is regulated by the mitochondrial protease OMA1. The goal of this study was to evaluate how CS alters mitochondrial fusion machinery and to evaluate the therapeutic benefit of OMA1 inhibition.

Methods: Male rodent (Lewis) kidneys were isolated and cold stored for 0 or 18 hr and then transplanted (CS/Tx) in a naïve Lewis rat followed by right nephrectomy. Mitochondrial function was assessed via high resolution respirometry and ATP measurement. Mitochondrial fusion and fission pathways were monitored using western blot. A novel method was developed to measure OMA1 activity. Renal injury was assessed by serum creatinine and PAS staining.

Results: Data clearly revealed that CS worsens mitochondrial function when compared to transplantation without CS. Combined CS/Tx lead to OPA1 inhibition and increased OMA1 activity along with an altered protein expression of OMA1. Inhibition of OMA1 using phenanthroline during CS lead to increased OPA1 expression and improved mitochondrial function. Further studies will characterize the benefit of mitochondrial targeted phenanthroline as a novel therapy to improve mitochondrial and renal function during CS/Tx.

Conclusions: Our results suggest that CS/Tx alters the mitochondrial protease, OMA1, and that OMA1 inhibition improves mitochondrial function. These findings raise the possibility that impaired mitochondrial dynamics may be an unrecognized contributor to cold storage induced injury and compromised renal graft function after transplantation. Supported in part by and AHA 16SDG276000026 (NP) and AHA 16PRE30830010 (SS); as well as NIH T32GM106999 (SS), T32GM106999 (JT).

Funding: Other NIH Support - GM106999-training fellowship, Private Foundation Support

FR-PO164

Transfer of Exogenous Mitochondria Protects the Kidneys from Ischemia-Reperfusion Injury Amandeep Bajwa, Kailo H. Schlegel, Kyle J. Alexander, Elvira Kurmaeva. *University of Virginia, Charlottesville, VA.*

Background: Mitochondria, a critical player in acute kidney injury, have dual roles as primary source of energy (ATP) and as key regulators of cell death. Ischemia induces altered bioenergetics with increased mitochondrial swelling and reactive oxygen species and ultimately cell death. Ischemia followed by reperfusion (IRI) induces mitochondrial fragmentation in 30-40% of proximal tubule (PT) cells. Therapeutic interventions that target to improve mitochondrial health to repair, reprogram or replace mitochondria to restore respiratory functions are beneficial for prevention and/or treatment of disease.

Methods: Renal injury was assessed by plasma creatinine (PCr; mg/dl). 8-wk old C57BL/6 [WT or Rag1ko] mice were i.v. injected with exogenous mitochondria (Exo-Mito; 0-500mcg protein equivalent) 1d prior to 26 mins IRI. Exo-Mito was isolated from healthy non-ischemic mouse liver. Splnx was done 7d prior to IRI. Structure (sonicated) or function (Rot/Ant A) of Exo-Mito altered prior to injection. For *in vitro* studies, PT cells (TKPTS) were treated with 200 mcg of Exo-Mito 1d prior to analysis that included measurement of ATP levels, mitochondrial functions (Seahorse flux analyzer), cytokines (pcr), immunofluorescence microscopy (uptake efficiency) and flow cytometry (dyes [mitotracker or JC-1]).

Results: *In vivo* studies demonstrated mitochondria (200mcg, mouse or human) treated mice are significantly protected compared to vehicle treated mice after IRI [PCr (2.2±0.05 vs 0.62±0.2), $p<0.01$]. The protection by transferred Exo-Mito in IRI studies was partially abrogated in absence of a spleen but maintained in Rag1ko mice. Furthermore, structurally or functionally altered Exo-Mito no longer protected kidneys from IRI. Transfer of labeled Exo-Mito signal was found in spleen (in macrophages), kidney (in PT, identified with anti-CD13 antibody [labels brush border]), liver and lungs. *In vitro* studies demonstrate that Exo-Mitochondria are taken up by TKPTS in a dose dependent manner. TKPTS with Exo-Mito had significantly higher levels of extra- and intracellular ATP, higher basal oxygen consumption rate and spare respiratory capacity measured by Seahorse analyzer and lower cytokines after LPS stimulation.

Conclusions: Our current study demonstrates that up take of Exo-Mito by PT cells (*in vivo* and *in vitro*) helps maintain bioenergetics [ATP] to prevent injury.

Funding: NIDDK Support

FR-PO165

Megalin Shuttles Extracellular Angiotensin II and Stanniocalcin-1 to the Mitochondria via Retrograde Early Endosomes to the Golgi Pathway and Regulates Glycolytic and Respiratory Capacities Qingtian Li,[1] Fan Lei,[3] Yi Tang,[2] Jenny S. Pan,[1] Qiang Tong,[1] David Sheikh-Hamad.[1] *[1]Baylor College of Medicine, Houston, TX; [2]West China Hospital of Sichuan University, Chengdu, China; [3]Baylor College of Medcine, Houston, TX.*

Background: Some extracellular signaling molecules are detected in the mitochondria, including angiotensin II, insulin, stanniocalcin-1 (STC1), TGF-ß and erythropoietin; these are known as mitochondrial intracrines. The mechanism of mitochondrial intracrine targeting is unknown. Megalin/LRP2 is highly expressed on the apical surface of kidney proximal tubule cells, and is involved in the uptake of filtered vitamins and proteins. Megalin mutations are linked to the pathogenesis of Donnai-Barrow and Lowe syndromes, characterized by brain defects and kidney dysfunction. Megalin has not been shown to reside in the mitochondria.

Methods:

Results: Our data suggest that megalin is present in kidney mitochondria in vivo, and mitochondria of cultured 293T, C2C12 and Raw267.4 cells, and associates with stanniocalcin-1 and SIRT3. Megalin shuttles extracellular angiotensin II, TGF-ß and STC1 to the mitochondria (detailed in separate abstract). We sought to characterize the shuttling pathway for megalin and its cargo (angiotensin II and STC1) from the cell surface to the mitochondria. Using chemical inhibitors of vesicular trafficking, we identified the microtubules and Golgi as key mediators, consistent with involvement of the retrograde early endosome-to-Golgi pathway. This was confirmed using an inhibitor of PIKfyve phosphoinositide kinase, a critical kinase involved in early endosome fusion with the Golgi. These findings were validated using CellLight® Reagent BacMan 2 technology, to trace the intracellular movement of extracellularly-applied rSTC1-FITC or angiotensin II-FITC. CRISPR-Cas9 knockdown of megalin in C2C12 cells prevents the entry of rSTC1-FITC and angiotensin II-FITC to the early endosome compartment (identified by early endosome RFP), while PIKfyve inhibition prevents their entry to the Golgi (identified by Golgi-RFP). Moreover, seahorse analysis reveals diminished glycolytic and respiratory capacities in megalin knockout C2C12 cells.

Conclusions: Megalin shuttles extracellularly applied angiotensin II and STC1 to the mitochondria through retrograde early endosome-to-Golgi pathway. Megalin is critical for glycolysis and respiration. The data also suggest that Donnai-Barrow and Lowe syndromes may represent mitochondrial intracrine signaling defects.

Funding: Veterans Affairs Support

FR-PO166

PKA/CREB Signaling Prevents Adriamycin-Induced Podocyte Apoptosis via Upregulation of Mitochondrial Respiratory Chain Complexes Production Kewei Xie, Zhaohui Ni, Leyi Gu. *Renji Hospital, Shanghai, China*.

Background: The present study was designed to explore the role of cAMP response element binding protein (CREB) in the PKA-induced protection in podocytes.

Methods: Conditionally immortalized differentiated murine podocytes were used in the present experiments. Cell toxicity was examined by using a cell count kit-8. Annexin V/PI staining and flow cytometry were uesd to detect cell apoptosis. MitoSOX™ Red mitochondrial superoxide indicator was used for detecting mitochondrial ROS. We also used Agilent expression profile chip to screen the mRNA expression in differential podocytes treated with or without PKA agonist in the presence or absence ADR. The message RNAs of respiratory chain complexes subunits encoded by mitochondrial genes were detected by using real-time PCR. Luciferase chemiluminescence was used to detect the production of ATP. Western blot was used to detect protein expression.

Results: We found that pretreatment with pCPT-cAMP prevented podocytes against Adriamycin (ADR)-induced increase of cleaved caspase-3 and the loss of podocytes. ADR treatment strikingly enhanced both mitochondrial superoxide and index of ROS in podocyte, this increase was prevented by pCPT-cAMP pre-treatment. Pretreatment with pCPT-cAMP was unable to prevent ADR-induced increase of cleaved caspase 3 expression in CREB RNAi treated podocytes. Data of Agilent expression profile chip studies showed that ADR predominantly decreased the mRNA expression of respiratory chain complex I subunits encoded by mitochondrial genes in podocytes, which was prevented by pretreatment with pCPT-cAMP. Immunoblot experiments showed that activation of PKA prevented ADR-induced decrease of mitochondrial respiratory chain complexes I subunits ND1/3/4 protein expression. Inhibiting of CREB expression prevented pCPT-cAMP-induced ND3, but not ND1/4 protein overproduction in podocytes. CREB RNAi can also block pCPT-cAMP-induced increase of ATP and the expression of Peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1 a).

Conclusions: PKA signaling may upregulate expression of mitochondrial respiratory chain complexes, which reduced ROS production and increased ATP generation, thus prevented ADR-induced podocyte apoptosis. This was at least partially dependent on CREB activation.

Funding: Government Support - Non-U.S.

FR-PO167

Thioredoxin-Interacting Protein (TXNIP) Regulates Mitochondrial Function and Prognosis of Ischemia/Reperfusion Induced AKI Satoshi Inogtani,[3] Daisuke Hashimoto,[3] Masami Ogasawara,[3] Tomohiro Eguchi,[3] Hirofumi Nishikawa,[3] Tatsuki Matsumoto,[3] Kazu H. Ode,[3] Yoshiko Shimamura,[2] Kosuke Inoue,[4] Yoshinori Taniguchi,[3] Taro Horino,[1] Yoshio Terada.[5] *[1]Kochi Medical School, Kochi University, Kochi, Japan; [2]Kochi Medical School, Kochi University, Nankoku, Japan; [3]Kochi university, Nankokushi, Japan; [4]kochi medical school, Nankoku, Japan; [5]None, Nankoku-city, Japan*.

Background: Thioredoxin-interacting protein (TXNIP) has been found to regulate the cellular reduction-oxidation (redox) state by binding to and inhibiting thioredoxin in a redox-dependent fashion. However, little is known about the role of TXNIP in mitochondrial function and acute kidney injury (AKI) pathogenesis.

Methods: We evaluated the role of TXNIP in renal function in bilateral renal ischemia (27 min)/reperfusion injury (IRI) model using TXNIP knock-out (KO) and wild type (WT) mice. To elucidate the functional roles of TXNIP, we evaluated mitochondrial enzymes, morphology, and NLRP3 inflammasome in primary cultured renal tubular epithelial cells (TECs).

Results: TXNIP KO mice had significantly higher SCr (0.78±0.28 versus 0.45 ± 0.20 mg/dl) and significantly higher BUN (152.5±32.5 versus 75.3±18.2 mg/dl) at 24h post ischemia compared to WT mice. Immunohistological examination showed severer tubular injury in cortex and outer medulla in TXNIP KO mice. The number of TUNEL positive tubular cells and KIM-1 positive cells were increased in in TXNIP KO mice. Dysmorphic mitochondria were observed in proximal tubules of TXNIP KO mice compared to WT mice. The protein expressions of mitochondrial enzymes (ATP5a, UCP2 and complex IV) and ATP production were decreased in TXNIP KO mice at 24h post ischemia. In vitro experiments, protein and mRNA levels of ATP5a, complex IV, PGC-1a were significantly decreased by H2O2, and these reductions were more prominent in TECs of TXNIP KO mice. Moreover, NLRP3, IL-1β, and caspase 1 (p10) protein expressions were significantly increased by LPS in TECs of WT mice, but this effect was reduced in TECs of TXNIP KO mice.

Conclusions: These data demonstrate that TXNIP protects from IRI induced AKI. TXNIP regulates mitochondrial function and inflammasome in cytotoxic conditions. These results indicate that TXNIP plays a key role in the pathophysiology of AKI.

FR-PO168

Collecting Duct Cell Specific Mitochondrial Dysfunction Influence to Inflammation and Fibrosis in UUO Mice Jin young Jeong,[1] Chang hun Song,[2] Hong jin Bae,[2] Jiwon M. Lee,[3] Youngrok Ham,[2] Kiryang Na,[2] Kang Wook Lee,[2] Dae Eun Choi.[2] *[1]Department of Medical Science, Chungnam National University, Daejeon, Republic of Korea; [2]Nephrology, School of Medicine, Chungnam National University, Daejeon, Republic of Korea; [3]Pediatrics, School of Medicine, Chungnam National University, Deajeon, Republic of Korea*.

Background: Unilateral ureteral obstruction (UUO) induced mitochondrial dysfunction resulting in increase of oxidative stress and infammation in obstructed kidney. Although mitochondria play a role in UUO injury including tubulo-interstitial apoptosis, infammation and fbrosis, the role of collecting duct cells was not evaluated. We evaluated whether collecting duct specifc mitochondrial dysfunction affect the renal injury induced by UUO.

Methods: For generation collecting duct specifc mitochondrial injury mice, CRIF flox/flox mice were bred with Hoxb7-Cre mice. For evaluation of the phenotype of mice, we observed mitochondria using electron microscopy in mice. For evaluation of influence of CRIF1 deletion on mitochondrial function, we measured O2 consumption and membrane potential in control and silencing RNA treated mIMCD cells. For evaluation of effect on UUO induced renal injury, we divided mice into the following 4 groups: CRIF1flox/flox(WT) group; CRIF1 flox/flox-Hob7 Cre (CRIF1-KO) group; WT UUO group; and CRIF1-KO UUO group. I evaluated oxidative stress, inflammatory, and fibrosis marker in urine and kidney tissue.

Results: There are no significant difrenence in phenotype between CRIF1-KO and WT mice. Renal expression of MCP-1, osteopontin (OPN), Numbers of F4/80 positive cells, TGF-b, a-SMA, and Masson Trichrome stained area were significantly increased in CRIF1-KO-UUO kidneys compared with WT UUO kidneys., Urinary 8-OHDG was increased in CRIF1-KO-mice compared with WT mice. Also, Crif1-KO mice had significantly increase of 8-OHDG-positive cell recruitment compared to WT mice. CRIF1-KO-UUO-kidneys were shown more increase recruitment of 8-OHDG-positive cells compared to WT-UUO-kindneys

Conclusions: Collecting duct specific mitochondrial injury induced increase of oxidative stress, renal inflammation, and renal fibrosis in UUO mice

FR-PO169

Metabolic Syndrome Induces Transit Peptide Protein Import into the Mitochondria of Porcine Mesenchymal Stem Cells Arash Aghajani nargesi, LaTonya J. Hickson, Kyra L. Jordan, Lilach O. Lerman, Alfonso Eirin. *Mayo Clinic, Rochester, MN*.

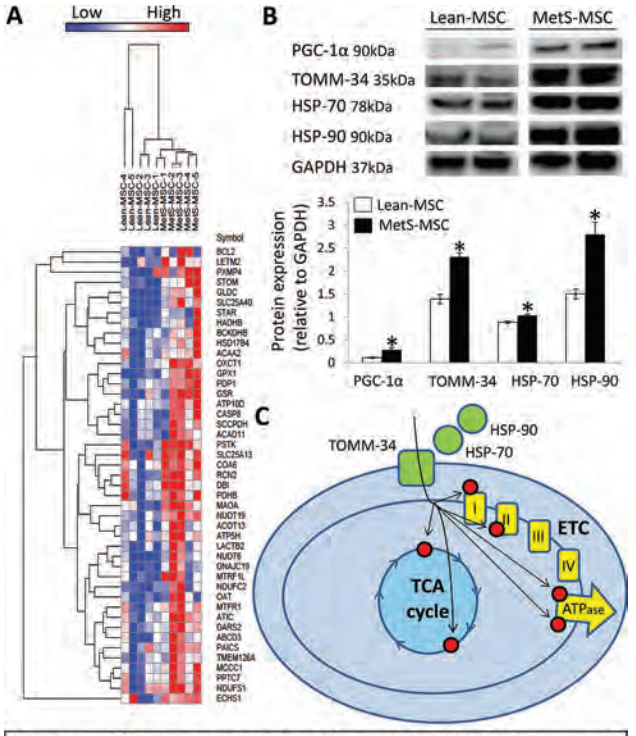
Background: Autologous transplantation of mesenchymal stem cells (MSC) is currently being tested in clinical trials for patients with renal disease. Mitochondrial aerobic respiration is essential for successful differentiation of MSC, but whether coexisting cardiovascular risk factors modulate MSC mitochondrial function remains unknown. We hypothesized that metabolic syndrome (MetS) alters expression of genes regulating mitochondrial biogenesis and metabolism.

Methods: MSC were isolated from swine abdominal adipose tissue after 16 weeks of Lean or Obese diet (n=5 each). Next-generation sequencing was performed to detect differentially expressed mRNA in MetS-MSC, and mitochondrial genes were identified (MitoCarta). Expression of the mitochondrial biogenesis regulator peroxisome proliferator-activated receptor gamma coactivator (PGC)-1α was measured by western blot. Finally, we assessed protein expression of transporters of mitochondrial transit peptides (MTP), including translocase of outer membrane (TOMM)-34, heat shock protein (HSP)-70, and HSP90.

Results: Out of 1,088 unique mitochondrial mRNA, 45 were upregulated in MetS- vs. Lean-MSC (fold change >1.4, $p<0.05$), of which MTP, primarily involved in oxidative phosphorylation and electron transport, comprised the top category. Protein expression of PGC-1α, TOMM34, HSP70, and HSP90 was upregulated in MetS-MSC.

Conclusions: MetS upregulates MSC mRNA expression of MTP, and protein expression of mitochondrial membrane transporters that import them into mitochondria. These might be linked to altered mitochondrial biogenesis and may impact aerobic metabolism. These observations provide a molecular framework for optimization of cell-based strategies as we move towards clinical applications of MSC for renal repair.

Funding: NIDDK Support



A. Heat map of 45 unique mitochondrial mRNA upregulated in MetS-MSC compared to Lean-MSC. **B:** Expression of PGC-1α, TOMM34, HSP70, and HSP90 was upregulated in MetS-MSC. **C:** Diagram showing that mitochondrial transit peptides upregulated in MetS-MSC are precursors of several subunits of the electron transport chain (ETC) and intermediates of the tricarboxylic acid (TCA) cycle. *p<0.05 vs. Lean-MSC.

FR-PO170

Downregulation of Akt Induces Mitochondrial Injury in Proteinuric States Elif Erkan,[1] Lu Lu.[2] *[1]Children's Hospital of Cincinnati, CIncinnati, OH; [2]Cincinnati Children's Hospital, Cincinnati, OH.*

Background: Nephrotic range proteinuria contributes to progression of glomerular diseases by causing tubulointerstitial injury. High concentrations of albumin in the glomerular filtrate triggers proximal tubular cell apoptosis, a precursor for tubular atrophy. We propose that downregulation of prosurvival serine/thereonine kinase, protein kinase B (Akt) induces apoptosis in proximal tubule epithelial cells by causing mitochondrial injury.

Methods: *In-vitro* albumin overload is induced by incubating human kidney proximal tubule epithelial (HKC-8) cells with 10mg/ml of human albumin for 24 hours. C57BL/6 B6 mouse with targeted deletion of Akt1/2 in proximal tubule epithelial cells(Akt1/2 $^{lox/lox}$ Sglt2 cre) is generated and subjected to intraperitoneal albumin injections (10 mg/g body weight) for 6 weeks. Intraperitoneal albumin and saline injected Sglt2 cre negative mice are utilized as negative controls. Apoptosis is evaluated by fluorogenic caspase-3 assay, caspase 9 staining and TUNEL assays. Mitochondrial and cytosolic translocation of cytochrome-c and Bax is assessed by Western Blotting.

Results: Albumin overload caused caspase-3 activation in association with downregulation in expression of pSer473 Akt and pThr 308 Akt and Akt substrate phospho Fork head box O1(FOXO 1) and fork head box O3 (FOXO 3) proteins in HKC-8 cells. Expression of FOXO target BIM is upregulated in association with albumin induced apoptosis. Furthermore overexpression of Akt by constitutively active Akt construct mitigates albumin induced-apoptosis where as treatment with pan Akt inhibitor MK-2206 potentiates the apoptotic response in HKSC-8 cells. In-vivo albumin overload results in cytochrome-c release in the cytoplasm of Akt1/2 $^{lox/lox}$ Sglt2 cre mice in association with tubular apoptosis. This response was associated with translocation of proapoptotic Bax to the mitochondria and increase in BIM expression.

Conclusions: We concluded that Akt plays an important role in protection of proximal tubule epithelial cells from apoptosis. We propose that in proteinuric states, inhibition of Akt phosphorylation causes nuclear translocation of FOXO 1 and FOXO 3 and an increase in transcription of BIM leading to cytochrome-c release to cytoplasm and apoptosis in proximal tubule epithelial cells. We postulate that therapeutic interventions that are targeted to increase tubular Akt expression can attenuate tubulointerstitial injury in proteinuric states.

FR-PO171

The Role of a Novel Mitochondrial Protease, OMA1, During Renal Cold Storage and Rewarming Julia Tobacyk, Lee Ann MacMillan-Crow, Nirmala Parajuli, Stephen A. Shrum. *University of Arkansas for Medical Sciences, Little Rock, AR.*

Background: Most kidney transplants come from deceased donors. These kidneys must undergo cold preservation before transplantation to maintain function of the organ during storage so that the graft will function at reperfusion. However, cold storage (CS) can result in renal and mitochondrial damage impairing overall graft outcome. OMA1 is a novel metallopeptidase in the mitochondria that plays a key role in mitochondrial dynamics. The goal of this study is to determine the role of OMA1 during renal CS in an *in vitro* model. Specifically, we will investigate the interaction of key proteins that regulate the fission and fusion machinery in the mitochondria such as OMA1, YME1L and OPA1.

Methods: Both rat and human normal proximal tubular kidney cells were exposed to 18 hr of CS followed by rewarming (CS/RW) for 6 hr. Expression of OMA1, YME1L, and OPA1 were assessed using western blot analysis. The interaction between these proteins was determined via OMA1 siRNA silencing techniques and OMA1 co-immunoprecipitation.

Results: In our studies we show that OMA1 expression is altered during CS both in rat and human normal proximal tubular kidney cells. Furthermore, expression of the long form of OPA1 is decreased in CS/RW suggesting compromised mitochondrial fusion. Our initial studies with OMA1 siRNA studies show successful knockdown, and further experiments will assess how OMA1 knockdown affects YME1L and OPA1.

Conclusions: Overall, CS initiates impairment of proteins related to mitochondrial fission and fusion. Our preliminary data suggest that OMA1 may be a promising therapeutic target for improving the function of kidneys transplanted after CS.

Funding: Other NIH Support - NIGMS for trainee fellowship, Private Foundation Support

FR-PO172

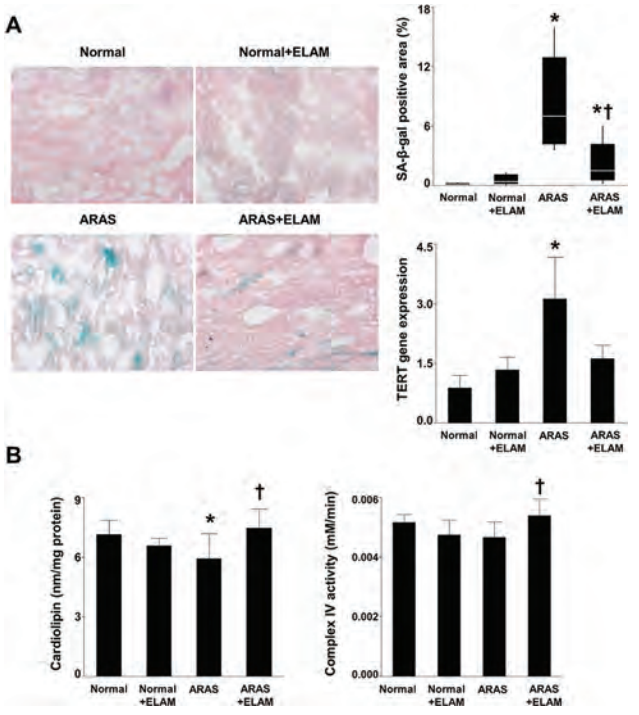
Mitochondrial Protection Restores Renal Function and Partly Mitigates Cellular Senescence in Swine Atherosclerotic Renal Artery Stenotic Kidney Seo Rin Kim, Xin Zhang, Alfonso Eirin, James Krier, Amir Lerman, Lilach O. Lerman. *Mayo Clinic, Rochester, MN.*

Background: Atherosclerotic renal artery stenosis (ARAS) may cause kidney injury and mitochondrial dysfunction, which might be linked to cellular senescence. Elamipretide (ELAM), a mitochondrial cardiolipin-targeting peptide, improves renal function and tissue damage in ARAS. We hypothesized that ELAM would also reduce senescence in the ARAS stenotic kidney (STK).

Methods: Domestic pigs were randomized to a 4-week treatment with ELAM (0.1 mg/kg sc q.d.) or vehicle starting after 6 weeks of unilateral ARAS or sham (n=6 each). Then, single kidney renal blood flow (RBF) and glomerular filtration rate (GFR) were measured in-vivo using CT. Renal senescence markers (activity of senescence-associated β-galactosidase (SA-β-Gal), *p*16, *p*21, and telomerase reverse transcriptase (TERT)), mitochondrial markers (total cardiolipin content and complex IV (COX-IV) activity), and tissue fibrosis were studied ex-vivo.

Results: Blood pressure and tissue scarring was elevated whereas RBF and GFR were decreased in ARAS STK compared to sham. Renal SA-β-Gal and TERT activity increased in ARAS, suggesting cellular senescence, and total cardiolipin content decreased (Fig. A, B), suggesting mitochondrial impairment. Renal cardiolipin content was restored and COX IV activity was elevated in ELAM-treated ARAS pigs. ELAM also normalized STK-RBF and GFR and improved renal fibrosis in ARAS. ELAM normalized TERT activity, and improved but not normalized SA-β-Gal activity, whereas *p*16 and *p*21 gene expression remained unchanged in all groups.

Conclusions: Mitochondrial protection with ELAM improved renal function, fibrosis and mitochondrial dysfunction in the ARAS STK, and partly alleviated cellular senescence. These observations support development of senolytic strategies in ARAS.



FR-PO173

The 5-HT1F Receptor as an In Vivo Regulator of Renal Mitochondrial Homeostasis Whitney S. Gibbs,[2,1] Justin B. Collier,[2,1] Rick G. Schnellmann.[1] *[1]Pharmacology and Toxicology, University of Arizona, Tucson, AZ; [2]Drug Discovery and Biomedical Sciences, Medical University of South Carolina, Charleston, SC.*

Background: Mitochondrial dysfunction limits repair mechanisms and restoration pathways required for the recovery of cellular functions following acute kidney injury. Stimulation of the 5-hydroxytryptamine 1F (5-HT_{1F}) receptor induces new, functional mitochondria through mitochondrial biogenesis (MB), resulting in accelerated renal recovery following ischemia/reperfusion (IR) induced acute kidney injury in mice. The goal of this study was to determine the contribution of the 5-HT_{1F} receptor in the regulation of renal mitochondrial homeostasis and renal function in healthy and injured mice.

Methods: Male 5-HT_{1F} receptor knockout (KO) mice and age-matched controls (WT) were euthanized at 10 and 26 weeks of age. In a second experiment, 10 week old male 5-HT_{1F} receptor WT and KO mice underwent renal IR injury and were euthanized at 24 hr. Renal mitochondrial homeostasis was assessed by RT- qPCR. Kidney function were assessed using serum creatinine and renal cortical KIM-1 and NGAL.

Results: In 5-HT_{1F} receptor KO mice, components of the electron transport chain, including ATP synthase β (ATSβ) and COX1 mRNA were elevated 1.3- and 1.6-fold at 10 weeks of age and these increases corresponded with elevated mitochondrial DNA (mtDNA) copy number. At 26 weeks of age, the master regulator of MB, peroxisome proliferator- activated receptor g coactivator- 1α, PGC-1α, ATPSβ, and mtDNA copy number were elevated 1.7-, 1.8- and 1.7-fold compared to WT mice. In addition, the mitochondrial fission protein Drp1 increased 1.7-fold at 10 weeks of age and remained elevated at 26 weeks of age in KO mice. The 5-HT_{1F} receptor KO mice did not exhibit basal renal injury. At 24 hr following renal IR, KO mice exhibited greater renal cortical levels KIM-1 and NGAL than WT mice. Serum creatinine was greater in KO mice compared to WT mice after IR. Finally, PGC-1α was decreased in IR KO mice but not in WT mice.

Conclusions: These findings reveal that mitochondrial homeostasis is disrupted in 5-HT_{1F} receptor KO mice, resulting in compensatory MB and mitochondrial fission. Moreover, the absence of the 5-HT_{1F} receptor potentiates tubular injury and suppresses MB in IR injury mice. These results demonstrate the 5-HT_{1F} receptor is a key mediator of MB and renal injury

Funding: NIDDK Support, Veterans Affairs Support

FR-PO174

Skeletal Muscle Mitochondrial Function and Dynamics in Patients on Maintenance Hemodialysis Jorge Gamboa,[1] Aaron M. Falck,[1] Chad A. Keller,[1] Baback Roshanravan,[2] Talat Alp Ikizler.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Kidnery Research Institute, University of Washington, Seattle, WA.*

Background: Patients on maintenance hemodialysis (MHD) commonly suffer of frailty and sarcopenia, which increase the risk of morbidity and mortality. The loss of muscle power is one of the components of the frailty phenotype, and poor muscle function is recognized as a major cause of frailty. Mitochondria are the main source of energy in skeletal muscle and are important for muscle function. Proper mitochondrial function depends on the balance between fission and fusion (mitochondrial dynamics). Thus, we evaluated changes in mitochondrial function and dynamics in skeletal muscle in patients on MHD.

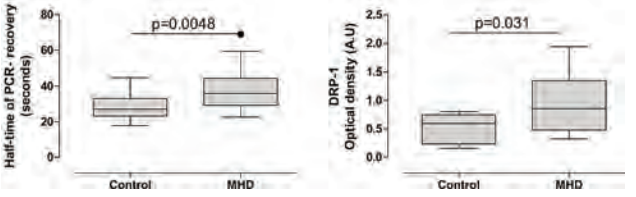
Methods: We evaluated 20 patients on MHD and 19 controls with no history of CKD that were matched by age, gender, history of diabetes, BMI, and race. We measured *in vivo* mitochondrial function by 31-phosphorus magnetic resonance spectroscopy (^{31}P-MRS) in the quadriceps muscle. We used the half time recovery of phosphocreatine (P-Cr) after a brief exercise as the measure of mitochondrial function. A faster recovery correlates with better mitochondrial function. We also measured markers of mitochondrial fusion and fission by western blot in skeletal muscle biopsies from the vastus lateralis.

Results: Controls and patients on MHD were similar in terms of age (47.0±9.5 *vs.* 47.7±12.3) and BMI (30.0±6.0 vs. 30.4±7.8). We found that the half time recovery of P-Cr was faster in controls compared to patients on MHD (**Figure 1A**). We found an increase in the abundance of dynamin related protein 1 (DRP-1), a marker of mitochondrial fission, in patients on MHD (**Figure 1B**). We did not find changes in other marker of mitochondrial dynamics.

Conclusions: Our data suggest that *in vivo* mitochondrial function is impaired in patients on MHD. The increase in mitochondrial fission marker DRP-1 in MHD patients could be a mechanism for segregation and elimination of damaged mitochondria.

Funding: NIDDK Support

Figure 1.



FR-PO175

Osteopontin Deficiency Ameliorates Alport Pathology by Preventing DNM3-Mediated Cholesterol Influx and Mitochondrial Energetic Deficit Wen Ding,[3] Keyvan Yousefi,[4] Stefania Goncalves,[3] Bradley J. Goldstein,[5] Alfonso L. Sabater,[1] Armando Mendez,[2] Lina Shehadeh.[5] *[1]Bascom Palmer Eye Institute, Miami, FL; [2]UM, Miami, FL; [3]University of Miami Miller School of Medicine, Miami, FL; [4]University of Miami-Miller School of Medicine, Miami, FL; [5]University of Miami, Miami, FL.*

Background: Clinical implications of Alport Syndrome consist of proteinuria, hypertension, progressive renal failure, high frequency sensorineural hearing loss and ocular anomalies. Osteopontin (OPN) has not been studied in Alport Syndrome. We elected to investigate the role of OPN in Alport pathology.

Methods: At 8-9 weeks of age, WT, OPN-/-, COL4A3-/-, COL4A3-/-OPN+/-, COL4A3-/-OPN-/-, and COL4A3-/-LDLR+/- mice (n=7-25/group) were studied. Renal OPN protein expression was studied by immunofluoresce. KIM-1 protein expression and EdU and TUNEL staining were analyzed by immunofluorescence. Blood pressure was recorded by a tail cuff. Basement membrane morphology in kidneys, cochleas, and retinas was analyzed by electron microscopy. Optical coherence tomography was used to study corneal dimensions. 100ug DiI-LDL was injected via tail vein in Alport and wild type mice and kidneys were studied after 2 hours. Bioenergetics assays were performed on DNM3-over-expressing human tubular epithelial HK2 cells (or their isolated mitochondria) using a flux analyzer.

Results: We found that OPN is highly expressed in the renal tubules (not glomeruli) of the Alport mouse and plays a causative pathological role. OPN genetic deletion ameliorated albuminuria, hypertension, tubulointerstitial proliferation, renal apoptosis, lenticonus, and cochlear and retinal structural deficits in the Alport mouse. We found extensive cholesterol accumulation and increased protein expression of DNM3 and LDLR in Alport renal tubules. Increased pathological cholesterol influx was confirmed by a remarkably increased 50 fold uptake of injected DiI-LDL cholesterol by Alport renal tubules, and by the extended lifespan of the Alport mice when crossed with the *LDLR*$^{-/-}$ mice with defective cholesterol influx. Over-expressing DNM3 in HK2 cells resulted in elevated LDLR protein expression and defective fatty acid based- mitochondrial respiration, and impaired phosphorylating respiration, resting respiration, and maximal uncoupling respiration relative to the scrambled groups. All results reported here were statistically significant (at least $p<0.05$).

Conclusions: Our results suggest a new pathway in Alport pathology where renal tubular OPN causes DNM3-mediated enhanced cholesterol influx and reduced mitochondrial respiration.

Funding: Other NIH Support - NHLBI, Private Foundation Support

FR-PO176

Inhibition of Mitochondrial Carnitine Palmitoyl Transferase 1 Prevents Renal Ischemia/Reperfusion Injury in Rats Mads V. Damgaard,[2] Rikke Norregaard,[2] Jorgen Frokiaer,[2] Søren Nielsen.[1] [1]*Aalborg University, Aalborg, Denmark;* [2]*Aarhus University, Aarhus C, Denmark.*

Background: Acute kidney injury is associated with high mortality and a lack of effective therapeutic treatment of the most common cause i.e., ischemia/reperfusion-injury (IR-I). Hypoxia leads to ATP depletion, apoptosis and necrosis, resulting in a marked inflammatory cascade causing further tissue damage. Inhibition of the inflammatory responses after IR-I is crucial for renal protection. Fatty acid β-oxidation is controlled by carnitine palmitoyl transferase 1 (CPT1). Etomoxir (ETO) inhibits CPT1 and block lipid metabolism. We hypothesize that CPT1 blockade can decrease the inflammatory response, induce an immune modulation, reduce mitochondrial dysfunction and hence alleviate renal IR-I.

Methods: Male Wistar rats (n = 10 animals per group) were subjected to either sham operation or renal ischemia/reperfusion (IR) by bilateral artery clamping for 40 min followed by ETO (5 mg/kg/day) or vehicle administrated at reperfusion. Clearance experiments were performed and renal tissue was removed and prepared for qPCR, immunohistochemistry and western blot analysis at sacrifice 48 hrs after reperfusion.

Results: IR-I resulted in polyuria *(ml/kg/day ± SEM, Sham: 36 ± 3, IR: 125 ± 5, IR+ETO: 62 ± 4),* increased fractional sodium excretion *(%, Sham: 0.3 ± 0.04, IR: 2 ± 0.3, IR+ETO: 0.3 ± 0.09),* plasma creatinine *(μmol/L/kg, Sham: 77 ± 3, IR: 649 ± 183, IR+ETO: 141 ± 19)* as well as BUN *(mmol/L/kg, Sham: 18 ± 1, IR: 102 ± 20, IR+ETO: 41 ± 8).* ETO treatment prevented these increases, improved creatinine clearance *(ml/min, Sham: 7.4 ± 0.6, IR: 1.9 ± 0.2, IR+ETO: 3.8 ± 0.4)* as well as attenuated downregulation of AQP1, Na/K-ATPase and AQP2 expression. All changes were significantly different between IR and IR+ETO. In addition, expression of (pro)inflammatory cytokines (IL-6, IL-1β, TNFα, MCP-1, IL-10) and key markers (ICAM-1) were significantly reduced including NGAL *(Sham: 1, IR: 49 ± 16, IR+ETO: 1 ± 0.1)* and KIM-1 *(Sham: 1, IR: 725 ± 101, IR+ETO: 218 ± 65)* in response to ETO administration. Expression of CPT1A increased following the ETO treatment *(Sham: 1, IR: 1.2 ± 0,1, IR+ETO: 1.6 ± 0.1*).

Conclusions: ETO treatment impaired development of renal dysfunction and attenuated tissue injury after renal IR-I. Decreasing the lipid metabolism attenuate the inflammatory response and may provide a novel potent pathway for treatment of renal IR-I.

Funding: Government Support - Non-U.S.

FR-PO177

The Role of Gβγ-Dependent Signaling in Formoterol-Induced Mitochondrial Biogenesis and Recovery of Renal Function in Mice Robert B. Cameron,[1,2] Justin B. Collier,[1,2] Rick G. Schnellmann.[2] [1]*Medical University of South Carolina, Charleston, SC;* [2]*University of Arizona, Tucson, AZ.*

Background: Acute kidney injury (AKI) is prevalent and has substantial morbidity and mortality with few effective therapies. AKI is associated with the activation of kinases, such as ERK1/2, that prolong injury and prevent recovery. Our laboratory has recently shown that ERK1/2 activation suppresses mitochondrial function and induces KIM-1 expression following AKI in mice. Formoterol, a β_2 adrenoceptor agonist, accelerates recovery of renal function in mouse models of AKI. However, the effects of formoterol on signaling in healthy and injured kidney are unknown.

Methods: Male C57BL/6 mice received DMSO or 0.3 mg/kg formoterol i.p. and were euthanized at 30 min or 24 h. For inhibitor studies, mice received gallein (an inhibitor of the G protein heterodimer Gβγ) 1 h prior to formoterol or diluent control. To model the effects of formoterol on AKI, mice were subjected to bilateral ischemia-reperfusion (IR) injury and received formoterol 24 h following surgery. Injured and sham mice were euthanized 30 min and 24 h following formoterol administration.

Results: Formoterol increased Akt phosphorylation and cGMP in the renal cortex at 30 min following treatment. At 24 h, formoterol increased expression of the mitochondrial protein ATP synthase beta (ATPSβ), a marker of mitochondrial biogenesis (MB). The increases in Akt phosphorylation and ATPSβ were blocked by pretreatment with gallein. Following IR injury, formoterol accelerated recovery of renal function as measured by blood urea nitrogen (BUN) and serum creatinine (SCr) at 24 h following formoterol administration. This was accompanied by a decrease in renal injury as measured by KIM-1 expression in the renal cortex. At 30 minutes following formoterol administration after I/R, the phosphorylation of ERK1/2 was reduced compared to mice treated with vehicle.

Conclusions: In the healthy kidney, formoterol activates Gβγ-Akt dependent signaling to upregulate mitochondrial proteins and biogenesis. Following injury, formoterol has rapid effects on renal recovery, in part through modulation of ERK1/2. Modulation of Gβγ-dependent signaling and MB by formoterol may provide novel therapeutics for AKI.

Funding: NIDDK Support, Other NIH Support - R01 GM084147, T32 GM008716, Veterans Affairs Support

FR-PO178

Gender Differences in Renal Mitochondrial Injury during Sepsis Lee Ann MacMillan-Crow, Philip R. Mayeux. *University of Arkansas for Medical Sciences, Little Rock, AR.*

Background: Acute kidney injury (AKI) is a frequently encountered complication of sepsis. Sepsis accounts for about 50% of AKI cases in intensive care units and patients with sepsis complicated by AKI have markedly worse prognosis and have a higher mortality rate. Numerous studies, including our own, have reported the involvement of mitochondrial damage and oxidant production during sepsis. The goal of this study was to evaluate whether gender differences exist in the extent of mitochondrial damage using a murine model of sepsis.

Methods: Cecal ligation and puncture (CLP) was performed in male and female CD1 mice to induce sepsis. Briefly, the cecum was punctured twice with a 21-gauge needle, followed by a right nephrectomy. Animals received antibiotics and fluid resuscitation at 6 h and every 12 h thereafter. Mitochondrial function was assessed via high resolution respirometry (HRR) and ATP measurement. Mitochondrial fusion and fission pathways were monitored using western blot.

Results: Male mice exposed to CLP (18 hr) showed a significant decline in complex I, II, and III activities compared to sham animals. However, only complex I was inactivated in female mice exposed to CLP (18 hr). Interestingly, baseline (sham) complex II and IV activities were significantly higher in female mice, compared to male mice. In addition, studies show that sepsis in our male model leads to loss of the long form of Optic Atrophy Protein (OPA1), which normally fuses the inner mitochondrial membrane between mitochondria, as an essential part of the overall fusion process. OPA1 is cleaved to the short form by two zinc metalloproteinases, OMA1 and YME1L. OMA1 is considered a stress-induced protease and appears to be activated in our male sepsis model, but not in female mice. Interestingly, sepsis in female mice induced protein expression of the mitofusions (MFN1/2) proteins which regulate outer mitochondrial membrane fusion, which was not observed in male mice. Survival studies showed that female mice exposed to CLP were more likely to die compared to male mice.

Conclusions: Our results suggest that sepsis induces gender dependent differences in mitochondrial damage and remodeling via fusion/fission processes. These findings raise the possibility that altered mitochondrial dynamics may be an unrecognized contributor to gender specific responses to sepsis induced AKI.

Funding: Other NIH Support - NIGMS RO1GM106419

FR-PO179

SIRT1/P53/Drp1-Dependent Mitochondrial Fission Mediates Aldosterone-Induced Podocyte Injury and Mitochondrial Dysfunction Yanggang Yuan,[1] Aihua Zhang,[1] Changying Xing.[2] [1]*Nanjing Medical University, Nanjing, China;* [2]*The First Affiliated Hospital of Nanjing Medical University, Nanjing, China.*

Background: Mitochondrial dysfunction is increasingly recognized as an important factor in glomerular diseases. Previous study showed that mitochondrial fission contributed mitochondrial dysfunction. However, the mechanism of mitochondrial fission on mitochondrial dysfunction in aldosterone-induced podocyte injury remains ambiguous. This study aimed to investigate the pathogenic effect of mitochondrial fission both in vivo and in vitro.

Methods: Aldosterone-infused mice were implanted subcutaneously with 14-day-release pellets containing aldosterone. Mitochondrial fission inhibitor mdivi-1 was given by peritoneal injection. The expression of mitochondrial fission protein Drp1 (dynamin-related protein 1) was determined by western blotting and immunofluorescence. Podocyte injury was measured by nephrin expression and labelled by TUNEL assay. In vitro, podocytes were treated with aldosterone at the concentration of 0, 25, 50, 100 nmol/L. The expressions of Drp1, p53 and SIRT1 were examined by real-time PCR and western blot. Then podocytes were transfected with Drp1 siRNA, p53 siRNA and SIRT1 plasmid, respectively. After aldosterone treatment, podocyte injury, mitochondrial morphology and mitochondrial function were detected.

Results: In an animal model of aldosterone-induced nephropathy, inhibition of Drp1 suppressed aldosterone-induced podocyte injury. In cultured podocytes, aldosterone dose-dependently induced Drp1 expression. Knockdown of Drp1 inhibited aldosterone-induced mitochondrial fission, mitochondrial dysfunction and podocyte apoptosis. In addition, aldosterone dose-dependently induced p53 expression. Knockdown of p53 inhibited aldosterone-induced Drp1 expression, mitochondrial dysfunction and podocyte apoptosis. Furthermore, aldosterone dose-dependently decreased SIRT1 expression. SIRT1 overexpression blocked aldosterone-induced p53 and Drp1 expression, mitochondrial dysfunction and podocyte injury.

Conclusions: These findings implicated that aldosterone-induced mitochondrial dysfunction and podocyte injury mediated by SIRT1/p53/Drp1-dependent mitochondrial fission, which may provide opportunities for therapeutic intervention for podocyte injury.

Funding: Government Support - Non-U.S.

FR-PO180

Super Resolution Imaging of Kidney Tissue Is a Novel Technique to Study Three Dimensional Mitochondrial Networks and Functional Correlates In Vivo Craig R. Brooks,[2] Kensei Taguchi.[1] [1]*Department of Nephrology and Hypertension, Nashville, TN;* [2]*Vanderbilt University Medical Center, Nashville, TN.*

Background: Mitochondria are essential for all eukaryotic life. Kidney proximal tubule cells (PTCs) have the highest content of mitochondria, by surface area, of any cell type in mammals. The large complement of mitochondria is necessary to support the tremendous amount of transport that occurs in the PTC during the reabsorption of sodium and other solutes from urine. Previous studies have demonstrated that mitochondrial morphology is important to maintain both the health and functionality of mitochondria.

Methods: Sham or ischemically injured kidneys from wild-type C57BL/6 mice were fixed and embedded in paraffin following standard protocols. Sections of the kidneys were mounted on (3-Aminopropyl)trimethoxysilane treated coverslips and stained for

mitochondrial and PTC markers, and then imaged by Structured Illumination Microscopy (SIM) or Zeiss Airyscan.

Results: Super resolution imaging enabled the resolution of not only individual mitochondria but also distinguished inner membrane space vs. outer membrane. SIM revealed that PTC mitochondria form a 3D network *in vivo*. Mitochondrial networks extend throughout the cell body and into the interdigitations of the PTCs. Co-staining of mitochondrial makers with Na^+-K^+-ATPase revealed a tight association of the mitochondria with interdigitations of the basolateral membrane in PTCs, in which mitochondria from one PTC often run parallel to the mitochondria of neighboring cells within Na^+-K^+-ATPase positive inholdings of the plasma membrane. Injury to the kidney led to reduced mitochondrial interconnectivity and rearrangement of the inner membrane space. Injury also resulted in retraction of the basolateral interdigitations of the plasma membrane.

Conclusions: Super resolution imaging provides a novel approach to analyze individual mitochondria and inner vs. outer membrane structure *in vivo* and provides a 3D morphological analysis of the cell and mitochondrial network. Individual mitochondria that extend through interdigitations of the PTCs are part of a larger network that extends through the cell body. Injury to the kidney leads to a breakdown of this network and disassociation of mitochondria from the basolateral membrane.

Funding: NIDDK Support

FR-PO181

Honokiol Decreases UUO-Induced Tubulointerstitial Inflammation and Fibrosis by Regulation of Mitochondrial Sirt3 and Its Dynamics Kyung Pyo Kang,[2] Woong Park,[2] Yi Quan,[2] Jin won Jang,[1] Sung K. Park,[2] Won Kim.[2] *[1]Chonbuk National University Hospital, Jeonju, Republic of Korea; [2]Chonbuk National University Medical School, Jeonju, Jeollabuk-Do, Republic of Korea.*

Background: Sirt3 is a NAD^+-dependent deacetylase in mitochondria, which has a role of maintain the mitochondrial function by deacetylation. Sirt3 might protect the cells from reactive oxygen species, apoptosis, and mitochondrial dynamics. In progressive renal disease, tubulointerstitial fibrosis is a final common feature, which is characterized by inflammation, excessive extracellular matrix deposition and organ dysfunction. Honokiol is a natural biphenolic compound derived from the bark of magnolia trees and known as an activator of sirt3 in murine cardiomyopathy model. In this study, we investigate the protective effect of honokiol on unilateral ureteral obstruction (UUO)-induced tubulointerstitial inflammation and fibrosis by regulation of mitochondrial Sirt3.

Methods: Renal fibrosis was induced by UUO in the six-week-old C57BL/6 mice for 10 days. Honokiol (5 mg/kg) was treated by intraperitoneal injection for 7 days before induction of renal fibrosis and continued for 10 days. Histologic examination and Western blot analysis for α-SMA, type I collagen were performed. We also evaluated cell adhesion molecule expression, mitochondrial dynamics and TGF-β1/Smad signaling pathway after ureteral obstruction.

Results: Renal tubular injury and fibrosis were increased after ureteral obstruction. After treatment of honokiol, renal tubular injury and fibrosis were significantly decreased. The number of α-SMA positive fibroblasts and F4/80 positive macrophages were significantly decreased after honokiol treatment in UUO kidney. In Western blot analysis, type I collagen and intercellular adhesion molecule (ICAM)-1 expression was decreased after honokiol treatment in UUO kidney. Sirt3 expression was significantly decreased after UUO surgery, however, honokiol treatment recovered Sirt3 expression in UUO kidney. Mitochondrial fission, as shown Drp1 expression, was increased afer ureteral obstruction, however, honokiol treatment decreased UUO-induced increases of Drp1 expression. In contrast, mitochondrial fusion, as shown OPA1 expression, was decreased after ureteral obstruction and honokiol treatment was recovered.

Conclusions: These results suggest that honokiol has a beneficial effect on UUO-induced tubulointersitial inflammation and fibrosis by regulation of mitochondrial sirt3 and its dynamics.

Funding: Government Support - Non-U.S.

FR-PO182

Impaired Cutaneous Wound Healing in a Rodent Model of Uremia Sai Krishna Duraisingham,[2,1] Julius E. Kieswich,[2] Steven M. Harwood,[2] Muhammad M. Yaqoob.[2,1] *[1]The Royal London Hospital, Barts Health NHS Trust, London, United Kingdom; [2]William Harvey Research Institute, Queen Mary University, London, United Kingdom.*

Background: Patients with CKD develop a multitude of skin changes associated with the duration and severity of renal failure. Additionally, causative comorbidities such as peripheral vascular disease and diabetes directly impact on wound healing. In clinical practice, poor healing contributes to prolonged hospital stays, a susceptibility to infective complications and significant morbidity, including a considerable negative psychological impact. For these reasons finding methods to assess wound healing in uremia will be valuable.

Methods: We developed a rodent model of excisional wound healing. Animals were maintained in a temperature controlled facility with a 12h light/dark cycle. After 2 weeks acclimatization, 6 week old male Wistar rats were fed a diet of standard rat chow supplemented with 0.75% adenine and given water *ad libitum* for 4 weeks to establish uremia. Healthy controls were fed standard chow. Survival, growth rate and well-being were monitored during the experimental period. Under inhaled 1.5% Isoflurane anesthesia a 30µl subcutaneous injection of Buprenorphine 0.3mg/ml was administered before creating bilateral 5mm full thickness dorsal punch biopsies with a Stiefel Biopsy Punch. Recovery from anesthesia was observed before returning animals to cages. Measurements of the wounds were taken on subsequent days. At day 3 and 7, half the animals were sacrificed under Ketamine and Xylazine anesthesia. Blood samples obtained by cardiac puncture were centrifuged for plasma and organs were harvested for histology or for protein and RNA analysis. Wounds were excised and bisected, one semicircle section was stored in formalin, the other snap frozen under liquid nitrogen. Experiments were conducted under our UK Home Office license after institutional approval.

Results: This model successfully established a uremic state with no premature deaths, excess bleeding or infected wounds observed. Serum urea was significantly higher in the uremic group at both day 3 and 7 ($p<0.01$) as was serum creatinine ($p<0.02$). Percentage of the wound area healed compared to day 0, was significantly greater in the control group at day 3 and day 7 ($p<0.02$ and $p<0.001$).

Conclusions: We have developed a novel rodent model with low complication rates to study factors contributing to delayed wound healing in uremia. Moreover, we have demonstrated a delay in healing in the uremic state.

FR-PO183

CD4 Lymphopenia Is Associated with Cardiovascular Disease in Patients with Non-Dialysis Dependent CKD Kenichiro Iio, Yutaka Ando. *National Hospital Organization, Osaka Minami Medical Center, Kawachinagano, Japan.*

Background: The role of T cells in the pathogenesis of atherosclerosis is complex. T-cell infiltration is thought to occur at atherosclerotic sites; CD4 lymphopenia in HIV patients is associated with atherosclerosis. Patients with chronic kidney disease (CKD) not only have a high prevalence of cardiovascular disease (CVD), but their circulating CD4 lymphocyte count is also decreased. The aim of this study was to assess the relationship between CVD and circulating T cell phenotype in patients with CKD.

Methods: We enrolled 97 patients with CKD stages 3-5 (mean age 68.4 ± 12.1 years; 65 males [67%]; CKD stage 3/4/5, 32/14/51) who were hospitalized between June 2013 and May 2017. We determined the numbers of immune cell phenotypes ($CD4^+$, $CD8^+$, $CD28^+CD8^+$) and the ratio of CD4/CD8 cells in peripheral blood or peripheral blood mononuclear cells using flow cytometry, to define their relationships with CVD, prospectively.

Results: Among 28 (29%) CVD patients, $CD4^+$ (678 vs. 473, $p = 0.004$) and $CD28^+CD8^+$ (147 vs. 97, $p = 0.012$) cell counts were significantly lower and this group was significantly older (age 67 vs. 72 y, $p = 0.09$) than non-CVD patients. Multivariate logistic analysis indicated a significant negative association between CVD and the number of $CD4^+$ T cells (odds ratio, 0.997; 95% confidence interval, 0.995 - 1.000, p=0.023).

Conclusions: Peripheral blood CD4 lymphopenia is associated with CVD in patients with non-dialysis CKD. CD4 lymphopenia may reflect atherosclerosis in CKD patients.

FR-PO184

CKD and Arterial Thrombosis: Role of the Receptor for Advanced Glycation End-Products (RAGE) Jeremy Ortillon,[8] Nathalie Hézard,[1] Karim Belmokhtar,[9] Kawecki Charlotte,[2] Christine Terryn,[5] Ann Marie Schmidt,[3] Pascal Maurice,[4] Philippe V. Nguyen,[6] Philippe Rieu,[7] Fatouma Toure.[7] *[1]EA 3801 HERVI, REIMS, France; [2]INSERM U1176, le Kremlin-Bicêtre, France; [3]NYU Medical Center, New York, NY; [4]UMR CNRS/URCA 7369, Reims, France; [5]Universite de Reims Champagne Ardenne, REIMS, France; [6]University of Reims, REIMS, France; [7]CHU and UMR CNRS URCA 7369, Reims, France; [8]CNRS UMR URCA 7369, Reims, France; [9]CNRS UMR URCA 7369, Reims, France.*

Background: Chronic kidney disease (CKD) is associated with extensive vascular wall remodelling and vasculopathy as well as accumulation of uremic toxins. Among these toxins, advanced glycation end-products (AGEs) interact with the receptor for advanced glycation end-products (RAGE). *In this study, we aimed to analyze the impact of CKD on* arterial thrombosis and the potential role of RAGE in this process.

Methods: *We used a mouse model of uremic vasculopathy consisting in a 2-step 5/6 nephrectomy. Four groups of animals were studied: $Apoe^{-/-}$ mice sham operated (n=12) or uremic (n=10) and $Apoe^{-/-}/Ager^{-/-}$ (= $Apoe^{-/-}RAGE^{-/-}$) mice sham operated (n=11) or uremic (n=15). Twelve weeks after surgery: 1) arterial thrombosis was induced by* ferric chloride application on the carotid artery and complete carotid occlusion time was measured, 2) platelet function was analysed in whole blood and in platelet rich plasma (PRP).

Results: *In-vivo*, uremia significantly accelerates the occlusion time in *$Apoe^{-/-}$ mice* (9.2 ±1,1min *vs* 11.1 ±0,6 min, $p<0.01$) compared to sham animals. IIn contrast, uremia had no effect on *$Apoe^{-/-}/Ager^{-/-}$ mice* carotid occlusion time (14,5 ±2,3 min, *vs* 13 ±1,5 min in sham, NS). Moreover occlusion time of the uremic *$Apoe^{-/-}$ mice was significantly accelerated compared to uremic $Apoe^{-/-}$ /$Ager^{-/-}$ mice ($p<0,0001$).* **Ex-vivo**, *agonist-induced platelet aggregation in whole blood was significantly increased in uremic condition in both $Apoe^{-/-}$ and $Apoe^{-/-}$ /$Ager^{-/-}$ mice. In PRP,* aggregation of uremic *$Apoe^{-/-}$ mice platelets was significantly increased compared to that of uremic $Apoe^{-/-}/Ager^{-/-}$ mice. In agreement, agonist induced expression of activated integrin* αIIbβ3 and P-selectin were both significantly increased at the surface of *$Apoe^{-/-}$ uremic platelets compared to 1) $Apoe^{-/-}$ sham platelets and to 2) $Apoe^{-/-}/Ager^{-/-}$ platelets (uremic & sham).*

Conclusions: In this murine model of thrombosis we report that uremia accelerates arterial thrombus formation and induces platelets hyperreactivity. We found that *Ager* deletion had a protective role on uremia-induced arterial thrombosis, and in uremia-induced platelet hyperreactivity. We suggest that RAGE signaling may be involved in CKD-induced atherothrombosis.

Funding: Government Support - Non-U.S.

FR-PO185

Renal Hemodynamic Effects of sGC Activation versus ACE Inhibition in Conscious Rats Karen A. Griffin,[6] Geoffrey A. Williamson,[3] Aaron J. Polichnowski,[2] Perriannan Sethupathi,[5] Agnes M. Benardeau,[1] Frank Eitner,[1] Anil K. Bidani.[4] *[1]Kidney Diseases Research, Bayer AG, Wuppertal, Germany; [2]East Tennessee State University, Johnson City, TN; [3]Illinois Institute of Technology, Chicago, AL; [4]Loyola University Med Ctr and Hines VA Hospital, Maywood, IL; [5]Loyola University Medical Center, Maywood, IL; [6]Loyola University Medical Center Hines VA Hospital, Maywood, IL.*

Background: Substantial evidence indicates that endothelial dysfunction and/or NO loss accelerates the progression of diabetic and non-diabetic chronic kidney disease (CKD). Therefore, soluble guanylate cyclase (sGC) modulators are being developed as potential novel therapeutic interventions in CKD, but only limited data are available as to their renal hemodynamic effects, particularly in the unanesthetized state.

Methods: Conscious chronically instrumented normal Sprague-Dawley rats (Charles River & Envigo) underwent repeated simultaneous 1-2 hr BP (radiotelemetry) and RBF (Transonic) recordings over 3 wks (2-4 x wk) while they were sequentially receiving: vehicle only by gavage (5 ml/kg), a low and a high dose of either the sGC activator (Bay-543) or enalapril (4 d/wk with a 3d washout). Effects on mean arterial pressure (MAP), RBF and the autoregulatory AR ability to buffer spontaneous BP fluctuations were assessed using a methodology recently developed in our lab (AR indices are calculated for ~500 adjacent pairs of short segments of 2.5 sec length/rat, which exhibit a difference in MAP of at least 5mmHg, SSARI). GFR was additionally measured during each wk using chronic FITC inulin infusion by osmotic pumps, and 24 hr urine collections. The data for both colonies of SD rats are combined as the results were similar.

Results: Table (mean ± SEM) GFR was not significantly or consistently altered by either agent. Thus, while both agents reduced BP comparably, significantly greater dose dependent renal vasodilation was observed with the sGC activator, while a more modest RBF increase was only seen with the higher dose of enalapril. Surprisingly, AR buffering of spontaneous BP fluctuations was moderately improved by the sGC activator but not enalapril.

Conclusions: Collectively, the BP and renal hemodynamic effects of sGC activation suggest that sGC modulators may have significant therapeutic utility in CKD states, meriting additional and more direct investigations in CKD models.

Funding: Commercial Support - Bayer AG, Kidney Diseases Research, Germany

	sGC activator, BAY-543 (n=24)			Enalapril (n=14)		
	Vehicle	3 mg/kg	10 mg/kg (n=18)	Vehicle	20 mg/kg	50 mg/kg (n=13)
MAP (mmHg)	114.3±2.1	110.2±1.8*	104.0±2.8*#	116.6±2.8	107.7±2.9*	104.8±2.5*#
RBF ml/min	7.1±0.3	8.0±0.4*	9.2±0.6*#	8.4±0.3	8.3±0.4	9.2±0.4*
SSARI	0.48±0.04	0.32±0.04*	0.29±0.03*	0.53±0.06	0.63±0.06	0.61±0.06

* p<0.05 minimum vs. vehicle; # p<0.05 minimum vs lower dose (repeated measures analysis of variance)

FR-PO186

Endothelial Dysfunction in ESRD Results from Advanced Glycation End-Products (AGE)-Mediated Suppression of Krüppel-Like Factor 2 Keith L. Saum,[3] Begoña Campos,[3] Diego Celdran-Bonafonte,[2] Albert P. Owens,[3] Prabir Roy-Chaudhury.[1] *[1]University of Arizona, Tucson, AZ; [2]University of Arizona / BIO 5 Institute, Tucson, AZ; [3]University of Cincinnati, Cincinnati, OH.*

Background: Cardiovascular disease is the leading cause of morbidity and mortality in patients with end-stage renal disease. The accumulation of uremic toxins in this patient population is associated with endothelial dysfunction and accelerated arteriosclerosis. We investigated the impact of protein-bound uremic toxins such as advanced glycation end products (AGEs) on the expression of Krüppel-like Factor 2 (KLF2), the key regulator of endothelial function and activation.

Methods: We used serum from a porcine model of chronic renal failure to assess the impact of uremia on endothelial KLF2 expression in vitro. Human umbilical vein endothelial cells (HUVEC) were treated with increasing concentrations of uremic or non-uremic porcine serum and analyzed for cell viability, apoptosis, and KLF2 expression. Similarly, cells were treated with individual protein-bound toxins at average uremic concentrations. Reactive oxygen species (ROS) production and monocyte adhesion were then assessed in treated cells with and without KLF2 overexpression. Finally, we investigated nuclear factor kappa-B (NF-KB) signaling as a mechanism underlying the AGE-mediated suppression of KLF2 and the potential of a RAGE antagonist, TTP488, to increase endothelial KLF2 expression and function.

Results: Treatment with uremic serum decreased HUVEC viability and increased apoptosis in a dose-dependent manner compared to non-uremic serum. Furthermore, uremic serum suppressed HUVEC KLF2 expression > 50%, which was reversed by dialysis and shear stress. Of the uremic toxins tested, carboxymethyl-lysine (CML) modified albumin, an AGE, resulted in the greatest suppression of KLF2 similar to uremic serum. Overexpression of KLF2 inhibited the production of ROS and leukocyte adhesion by uremic serum and CML. Inhibition of RAGE-mediated NF-KB signaling blocked the translocation of p65 to the nucleus and suppression of KLF2 by CML.

Conclusions: Suppression of KLF2 by uremic toxins such as AGEs is associated with increased endothelial dysfunction. This study, therefore, identifies suppression of KLF2 as a potential mechanism by which uremic toxins impair endothelial function in regions prone to arteriosclerosis. Future studies targeting this pathway could lead to novel therapies to decrease cardiovascular mortality in ESRD.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO187

Carotid Intima–Media Thickness Predicts Dialysis Vascular Access Failure in Hemodialysis Patients: A Prospective Study Hong joo Lee. *Seoul Red Cross Hospital, Seoul, Republic of Korea.*

Background: A well-functioning dialysis vascular access is a mainstay to perform an efficient hemodialysis. Dialysis vascular access dysfunction is a common cause of morbidity and mortality for the hemodialysis patients. Carotid intima–media thickness (cIMT) and carotid plaque are ultrasound imaging that measures carotid atherosclerosis and predicts potential stroke, myocardial infarction, and vascular death. Hence, we conducted our study to elucidate the predictive value of cIMT on dialysis vascular access failure from the patients with end-stage renal disease (ESRD) on hemodialysis.

Methods: All hemodialysis patients in Red Cross Hospital within a period of one year were included in the study. cIMT of the participants were measured at 6 points of the carotid artery including right and left common carotid artery, right and left bulb, and right and left internal carotid artery by using the carotid ultrasonography. Moreover, they were classified in 2 degrees of severity: more than 1.0 mm of maximal cIMT and less than 1.0mm of maximal cIMT. Dialysis vascular access dysfunction served as outcome variables over a median follow-up period of 12 months. Statistical analysis was carried out by using SPSS.

Results: Among the 58 cases, 19 of the patients and 29 events were having dialysis vascular access dysfunction for the 12 months follow-up period. The maximal cIMTs were 2.34±1.10. The patients with more than 1.0mm of maximal cIMT were older (66.08±11.92 versus 50.90±13.26) with lower protein and albumin and higher hemoglobin A1C than the patients with less than 1.0mm of maximal cIMT. However, maximal cIMT was not associated significantly with the level of lipid profiles, including total cholesterol, high and low density lipoprotein cholesterol, triglyceride, and phospholipid. We observed a positive correlation between weight, body mass index, triglyceride, and dialysis vascular access dysfunction. Dialysis vascular access dysfunction was significantly often occurred in the patients with more than 1mm of maximal cIMTs than the patients with less than 1mm of maximal cIMT.

Conclusions: Our results show that dialysis vascular access dysfunction may be associated with the maximal cIMT. Therefore, the measurement of cIMT may have an advantage for prediction of dialysis vascular access dysfunction in hemodialysis patients.

FR-PO188

Masked Uncontrolled Hypertension and Target Organ Damage in Patients with CKD Markus P. Schneider,[5] Ulrike Raff,[5] Rolf Janka,[5] Christoph Wanner,[2] Thorsten Klink,[2] Christian O. Ritter,[3] Turgay Saritas,[4] Georg Schlieper,[1] Jürgen Floege,[4] Roland E. Schmieder,[5] Kai-Uwe Eckardt,[5] Johannes B. Scheppach.[5] *[1]MVZ DaVita Karlstraße, Duesseldorf, Germany; [2]University Hospital Würzburg, Wuerzburg, Germany; [3]University Medicine of Goettingen, Goettingen, Germany; [4]RWTH University of Aachen, Aachen, Germany; [5]University of Erlangen-Nuremberg, Erlangen, Germany.*

Background: Masked uncontrolled hypertension (MUCH), i.e. normal blood pressure (BP) in the office but elevated ambulatory BP, has been associated with target organ damage and increased cardiovascular (CV) events in the general population. However, in patients with chronic kidney disease (CKD), who are exposed to a variety of additional CV risk factors, the role of MUCH for target organ damage is less clear.

Methods: In 305 CKD patients under treatment for arterial hypertension, we compared left ventricular mass (LVM, by magnetic resonance imaging), intima-media thickness (IMT), central augmentation index and pulse wave velocity (cAIx and PWV, Mobil-O-Graph®) between the four BP phenotypes: controlled hypertension (CH, normal office BP and normal ambulatory BP), white coat hypertension (WCH, elevated office BP but normal ambulatory BP), MUCH (normal office BP but elevated ambulatory BP) and sustained uncontrolled hypertension (SUCH, elevated office BP and elevated ambulatory BP).

Results: MUCH was present in 18% of patients (table). LVM, IMT, cAIx and PWV differed between BP phenotypes. LVM was greater in MUCH and SUCH versus CH (*P<0.05 for post-hoc comparisons). IMT was increased only in MUCH versus CH. Similarly, cAIx was increased only in MUCH versus CH. Finally, PWV was increased in WCH, MUCH and SUCH versus CH.

Conclusions: MUCH was found in 1 of 5 patients with mild to moderate CKD, and associated with several features of target organ damage. To identify CKD patients at high risk of subclinical target organ damage and future CV events, ambulatory BP monitoring should be used more frequently.

Funding: Commercial Support - Fresenius Medical Care

Target organ damage according to BP phenotype

	CH (n=124, 41%)	WCH (n=35, 12%)	MUCH (n=56, 18%)	SUCH (n=90, 30%)	P-Value trend
LVM (g)	111(61-218)	126(72-225)	130(79-206)*	134(72-216)*	<0.001
IMT (mm)	0.62(0.32-1.02)	0.65(0.37-1.29)	0.68(0.32-1.12)*	0.62(0.15-1.01)	0.017
cAIx (%)	22±8	25±7	26±6*	24±6	0.025
PWV (m/s)	8.1±1.7	9.0±1.4*	9.4±1.6*	8.9±1.7*	<0.05

FR-PO189

Biomarkers of Endothelial, Renal, and Platelet Dysfunction in Stage 5 CKD Hemodialysis (CKD5-HD) Patients with Heart Failure (HF) Vinod K. Bansal, Ryan Mcmillan, Debra Hoppensteadt, Jawed Fareed. *Loyola University Medical Center, Maywood, IL.*

Background: The aim of this study was to determine the role of endothelial, renal and inflammatory biomarkers in the pathogenesis of heart failure (HF) in patients with stage 5 chronic kidney disease (CKD5-HD) undergoing maintenance hemodialysis (HD).

Methods: Plasma levels of biomarkers: kidney injury molecule-1 (KIM-1), N terminal-pro brain natriuretic peptide (NT-proBNP), glycated hemoglobin (HgA1C), neutrophil gelatinase associated lipocalin (NGAL), interleukin-18 (IL-18), platelet derived growth factor (PDGF), platelet factor 4 (PF4), 25-OH vitamin D, parathyroid hormone (PTH), endothelin and endocan were measured in CKD5-HD patients at the Loyola University Ambulatory Dialysis facility. Normal plasma samples (n=50) were used as control.

Results: The HF (+) CKD5-HD patients, as compared to HF (-) CKD5-HD patients, exhibited significantly elevated NT-proBNP (P = 0.0194) and KIM-1 (P = 0.0485). The NT-proBNP in HF (+) CKD5-HD patients was found to correlate with the levels of serum potassium (P = 0.023 | R = -0.39), calcium (P = 0.029| R = -0.38) and PF4 (P = 0.045 | R = -0.35). The KIM-1 in HF (+) CKD5-HD patients was found to correlate with PTH (P = 0.043 | R = -0.36) and 25-OH vitamin D (P = 0.037 | R = 0.36). In comparison to the normal plasma samples the CKD5-HD patient plasma exhibited varying degrees of elevation in all of the parameters studied.

Conclusions: Elevated plasma NT-proBNP and KIM-1 in CKD5-HD and HF (+) CKD5-HD patients suggest that natriuretic peptides and KIM-1 may contribute to the pathogenesis of HF in CKD5-HD patients. Thus profiling of the biomarkers in CKD5-HD may be helpful in the risk stratification and identifying patients with heart failure.

FR-PO190

Renal Hemodynamic Effects of Sgc Activation Versus ACE Inhibition in Conscious Obese Diabetic ZSF1 Rats Anil K. Bidani,[4] Geoffrey A. Williamson,[3] Aaron J. Polichnowski,[2] Perriannan Sethupathi,[5] Agnes M. Benardeau,[1] Frank Eitner,[1] Karen A. Griffin.[4] *[1]Kidney Diseases Research, Bayer AG, Wuppertal, Germany; [2]East Tennessee State University, Johnson City, TN; [3]Illinois Institute of Technology, Chicago, AL; [4]Loyola University Med Ctr and Hines VA Hospital, Maywood, IL; [5]Loyola University Medical Center, Maywood, IL.*

Background: Substantial evidence indicates that endothelial dysfunction and/or NO loss accelerates the progression of diabetic and non-diabetic chronic kidney disease (CKD). Therefore, soluble guanylate cyclase (sGC) modulators are being developed as potential novel therapeutic interventions in CKD, but only limited data are available as to their renal hemodynamic effects and none in the unanesthetized rodent disease models.

Methods: Conscious chronically instrumented 12-14 wk old obese diabetic ZSF1 rats (body wt ~500g) underwent repeated simultaneous 1-2 hr BP (radiotelemetry) and RBF (Transonic) recordings over 3 wks (2-4 x wk) while they were sequentially receiving: vehicle only by gavage (5 ml/kg), a low and a high dose of either the sGC activator (Bay-543) or enalapril (3-4 days/wk with a ~3 day washout period). Effects on mean arterial pressure (MAP), RBF, renal vascular resistance (RVR) and the autoregulatory (AR) ability to buffer spontaneous BP fluctuations were assessed using a methodology recently developed in our lab (AR indices [fractional change in RBF / fractional change in MAP] are calculated for ~500 adjacent pairs of short segments of 2.5 sec length/rat, which exhibit a difference in MAP of at least 5mmHg, SSARI).

Results: Table (mean ± SEM) Similar to what we have observed in normal rats, at the dosages used, both agents reduced BP comparably. However, significantly greater dose-dependent renal vasodilation was observed with the sGC activator, but not enalapril. Although enalapril did reduce RVR at the higher dose, the increase in RBF did not reach statistical significance. AR buffering of spontaneous BP fluctuations was well preserved and not altered by either agent.

Conclusions: Collectively, the BP and renal hemodynamic effects of sGC activation in the conscious ZSF1 rat suggest that sGC modulators may have significant therapeutic utility in CKD states meriting additional investigations directly addressing CKD progression.

Funding: Commercial Support - Bayer AG, Renal Diseases Research, Germany

	sGC Activator, BAY-543 (n=9)			Enalapril (n=9)		
	Vehicle	3 mg/kg	10 mg/kg	Vehicle	20 mg/kg	50 mg/kg
MAP (mmHg)	130.8±2.2	123.3±3.0*	114.3±1.6*#	135.1±2.4	127.7±2.9*	118.8±3.3*#
RBF (ml/min)	9.3±0.9	11.1±0.9*	13.3±1.1*#	8.6±0.9	8.9±0.8	9.7±1.0
RVR (mmHg/ml.min)	15.5±1.6	12.0±1.2*	9.3±1.0*#	17.0±1.7	15.2±1.1	13.4±1.3*
SSARI	0.20±0.06	0.21±0.07	0.19±0.08	0.19±0.07	0.25±0.08	0.32±0.06

*p<0.05 minimum vs. vehicle; # p<0.05 minimum vs lower dose (repeated measures ANOVA)

FR-PO191

Lipoprotein-Apheresis (LA) Slows Down Artery Disease Progression by Modulating the Cytokine Network Involved in the Atherosclerosis Signaling Simona Simone,[1] Matteo Accetturo,[1] Paola Pontrelli,[1] Gianluigi Zaza,[2] F. Rascio,[1] Loreto Gesualdo,[1] Giuseppe Grandaliano,[3] Giovanni B. Pertosa.[1] *[1]University of Bari, BARI, Italy; [2]University of Verona, Verona, Italy; [3]UNIVERSITY OF FOGGIA, FOGGIA, Italy.*

Background: LA is a potentially valuable treatment applied to conventional therapy-resistant patients with familial hypercholesterolemia (FH). Several clinical studies report that LA is associated with a significantly greater reduction of cardiovascular events, but the molecular mechanisms underlying this effect are still unknown.

Methods: Aim of the study was to evaluate the progression of atherosclerosis lesions (by measuring intima-media thickness, IMT, and the brachial artery Flow-Mediated Dilation, FMD) in 8 pts treated with LA (HELP system, BBraun, Italy). Moreover, by using a high-throughput approach, was also evaluated the transcriptomic profile in PBMCs isolated before and after LA (Agilent Technologies). The results were evaluated by statistical (Genespring software) and functional pathway analysis (Ingenuity Pathway Analysis, IPA). The data were validated by real-time PCR and ELISA test in an independent testing-group (n=10).

Results: A significant reduction of IMT (p<.001) was observed after 36 months of LA along with an increase of FMD (p<.02). Using a fold-change (FC) ≥2, we demonstrated that LA modulates the expression of 84 genes. The top canonical pathways was atherosclerosis signaling (p=.0003). Many pro-inflammatory cytokines involved in the development and progression of the atherosclerotic process were significantly down-regulated: Interleukin 1 (IL-1b FC=-2.97), IL-6 (FC=-2.07), IL-8 (FC=-3.56) and MCP-1 (FC=-2.13). Real Time PCR showed a different gene expression before and after LA (IL-1 p<.0004; IL-6: .01; IL-8 p<.005; MCP1 p<.0002). Similarly, circulating protein level (ELISA) confirmed that IL-1β (Pre 2.77±0.4pg/ml, After 0.93±0.2, p=0.003), IL-6 (Pre 2.09±0.6, After: 1.02 ±0.5 pg/ml, p=0.01), IL-8 (Pre 141.53±45.0, After: 27.9±5.2 pg/ml, p=0.008) and MCP1 (Pre 485.5±38.0, After 330.2±51.0 pg/ml, p=.0001) were down-regulated after LA.

Conclusions: Our data suggest that LA may contribute to cardiovascular risk reduction through the modulation of different pathways involved in the progression of atherosclerotic disease and improvement of microcirculation. This observation might open new perspectives in the prevention of cardiovascular risk in patients with FH

Funding: Government Support - Non-U.S.

FR-PO192

Aerobic Exercise Improves Vascular Function in Non-Dialysis CKD Danielle L. Kirkman,[1] Meghan G. Ramick,[1] Bryce J. Muth,[1] Joseph M. Stock,[1] Raymond R. Townsend,[2] David G. Edwards.[1] *[1]University of Delaware, Newark, DE; [2]University of Pennsylvania School of Medicine, Villanova, PA.*

Background: Endothelial dysfunction is a cardiovascular disease risk factor (CVD) characteristic of chronic kidney disease (CKD). This study investigated the effect of aerobic exercise on vascular function in Stage 3-5 CKD.

Methods: In this randomized controlled trial, 36 patients (eGFR 44±2ml/min/1.73m^2) were randomized to an Exercise Training (EXT) or Control (CON) arm. EXT consisted of 3x45min of supervised exercise per week at 60-85%HRR for 12 weeks whereas CON received routine care. Outcomes were assessed at 0 and 12 weeks. VO_{2peak} was assessed by cardiopulmonary exercise testing. Conduit artery function was assessed via brachial artery flow mediated dilation (FMD). Microvascular function was assessed via cutaneous vasodilation during local heating coupled with intradermal microdialysis measured by laser Doppler flowmetry. Participants were instrumented with 3 microdialysis fibers for the delivery of 1) Ringer's solution; 2) superoxide scavenger Tempol; 3) NADPH oxidase inhibitor Apocynin. Cutanoues vascular conductance was calculated as a percent of maximum achieved with sodium nitroprusside infusion.

Results: A training response was indicated by an increase in VO_{2peak} following EXT (Week 0 *vs.* 12; EXT:17.9±1.2 *vs.* 19.9±1.60ml/kg/min, p=0.05; CON:18.2±1.7 *vs.* 17.4±1.6ml/kg/min, p=0.1). Brachial artery FMD was maintained and cutaneous microvascular function was improved following EXT compared to CON (Figure 1). At baseline, pharmacological delivery of Apocynin and Tempol improved microvascular function (Ringer's *vs.* Apocynin *vs.* Tempol:85±1% *vs.* 90±1% *vs.* 90±1%, p=0.02) but was no longer effective following EXT (91±2% *vs.* 87±2% *vs.* 87±2%, p=0.03), suggesting that reduced oxidative stress plays a role in vascular improvements following EXT.

Conclusions: Aerobic exercise improves vascular function and could be implemented as an adjunct therapy to reduce CVD risk in non-dialysis CKD patients.

Funding: Other NIH Support - National heart Lung and Blood Institute R01HL113514

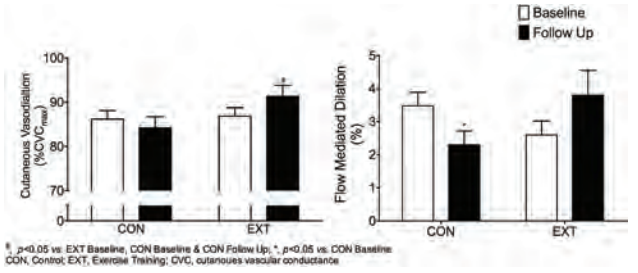


Figure 1 A Cutaneous vasodilation response to heating at the Ringer's microdialdysis site (interaction p=0.04) **B** Brachial artery flow mediated dilation (interaction p=0.02)

FR-PO193

Disruption of Angiopoietin-TIE2 Signaling Causes Loss of Ascending Vasa Recta and Cystic Kidney Disease Yael Kenig-Kozlovsky, Rizaldy P. Scott, Tuncer Onay, Isabel A. Carota, Benjamin R. Thomson, Susan E. Quaggin, Hyea Jin Gil. *Northwestern University, Feinberg School of Medicine, Chicago, IL.*

Background: The renal vasculature is a complex and highly specialized vascular network. Heterogeneous segments of the renal vasculature differ in their anatomical structure, expression of endothelial markers and their role in renal function. The specialized capillaries of the ascending and descending vasa recta form the vascular bundles of the outer medulla, which play a key role in countercurrent exchange and urine concentration. In this study we sought to determine how the angiopoietin-Tie2 signaling pathway, which is known to be important in development and remodeling of blood and lymphatic vessels, affects the complex renal vasculature.

Methods: Using a Cre-based inducible gene targeting strategy we deleted *Angpt1*, *Angpt2*, and *Tie2* at late gestational age in the mouse in order to overcome null mutant embryonic lethality.

Results: Compound deletion of Angpt1 and Angpt2 or Tie2 at late gestation age, leads to marked reduction in density of the vascular bundles and medullary capillary plexus, due largely to loss of the ascending vasa recta. Interestingly, we discovered that the ascending vasa recta (AVR) are "hybrid" vessels, which co-express blood (CD34, endomucin) and lymphatic markers (Prox1, VEGFR3). Loss of AVR in mutant animals leads to urine concentration defects with high urine output and low urine osmolality. As early as postnatal day P2 mutant animals develop renal cysts in the outer medulla. Cells lining the cysts do not express epithelial or vascular (blood and lymphatic) markers but do express several molecular markers of myofibroblasts including vimentin, calponin, SM-22α, and α –SMA.

Conclusions: Our results show for the first time the presence of "hybrid" vessels in the kidney that rely on Angpt-Tie2 signaling to develop. Furthermore, our data show that loss of AVR leads to dramatic cysts and renal insufficiency, underscoring the key functional role vasa recta play in draining interstitial fluid from the medulla that lacks classic lymphatic circulation.

Funding: Other NIH Support - HL124120

FR-PO194

Central Blood Pressure, Statins, and LDL-Cholesterol: A Mediation Analysis Florence Lamarche,[1] Francois Madore,[1] Mohsen Agharazii,[2] Remi Goupil.[1] *[1]Hopital du Sacre-Coeur, Montreal, QC, Canada; [2]CHUQ-HDQ, Quebec City, AB, Canada.*

Background: Central blood pressure (CBP) is a better predictor of cardiovascular burden than peripheral blood pressure (BP). While studies have suggested a reduction in peripheral BP with statins, it remains uncertain to what extent statins reduce CBP and whether this reduction is mediated through a decrease in LDL-cholesterol (LDL).

Methods: Of the 20,004 CARTaGENE participants, 17,011 had CBP and LDL measurements (n=3,133 with statins; n=13,439 without). Multivariate regression analyses were used to evaluate the association between CBP, LDL and statin use (after stratification for treatment indication for the latter). The impact of LDL on the association between statin use and CBP was determined by mediation analyses. All analyses were adjusted for age, sex, diabetes, cardiovascular disease, smoking, eGFR, BMI, uric acid, heart rate, anti-hypertensive agents and aspirin.

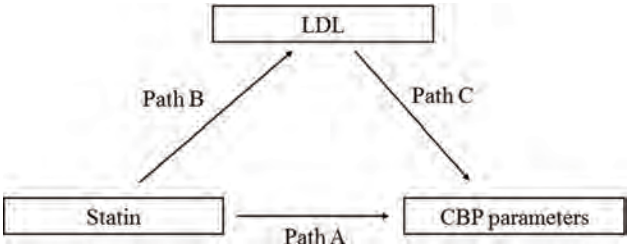
Results: Lower levels of LDL were associated with lower systolic and diastolic CBP in participants treated with (b=0.098 and 0.125; p<0.001) and without statins (b=0.089 and 0.105; p<0.001). Statin use as primary prevention (per ACC/AHA guidelines; n=8,865) was also associated with lower systolic CBP, diastolic CBP and central pulse pressure (b=-0.091, -0.073 and -0.055; p<0,001). Mediation analyses demonstrated that 15%, 46% and -22% of these effects were achieved through the concomitant changes in LDL (Table 1). In secondary prevention (n=995), statins use was not associated with lower CBP, although the small sample size may lack power.

Conclusions: In this populational cohort, statin use is associated with lower CBP when used as primary prevention. These changes are mediated directly by statin use but also indirectly through the effects on LDL.

Table 1: Mediation analyses

	Path A (total effect)	Path A (direct effect)	Path BC (indirect effect)	Percent mediation
Systolic CBP	-3.0 (-3.8, -2.3)	-2.6 (-3.4, -1.7)	-0.5 (-0.2, -0.0)	15%
Diastolic CBP	-1.7 (-2.2, -1.2)	-1.0 (-1.5, -0.4)	-0.8 (-1.0, -0.5)	44%
Central pulse pressure	-1.3 (-1.8, -0.9)	-1.6 (-2.2, -1.1)	0.3 (0.0, 0.6)	-22%

Effect represent change of CBP parameter per 1 standard deviation of LDL (95% CI).



Mediation analysis

FR-PO195

The Rapid Membrane Insertion of the Endothelial Sodium Channel Is Induced by Shear Stress and Stiffens the Cell Cortex Kristina Kusche-Vihrog. *University of Muenster, Muenster, Germany.*

Background: The endothelial Na^+ channel (EnNaC) determines endothelial nanomechanics in that an increased membrane abundance of EnNaC stiffens the endothelial cell cortex. Surface EnNaC expression is mainly regulated by aldosterone via the mineralocorticoid receptor (MR). Endothelial cells are constantly exposed to wall shear stress by blood flow, whereas disturbed blood flow causes and maintains atherosclerotic processes. Here, it is hypothesized that EnNaC serves as a flow sensor. Thus, we tested whether laminar shear stress (LSS) and non-laminar shear stress (NLSS) influence EnNaC membrane abundance and endothelial stiffness.

Methods: LSS (8 dyne/cm^2) was applied by a shear stress pump on HUVECs seeded on slides with and without branching regions in the presence of 1nM aldosterone to simulate blood flow. After applying shear stress (chronic 48h and acute 15min) HUVECs were fixed. EnNaC membrane abundance was quantified by a Quantum Dot-based immunofluorescence approach. Cortical stiffness was monitored using nanoindentation measurements via atomic force microscopy (AFM) in LSS and NLSS regions of the slides.

Results: Under chronic shear stress (48h) a significant increase of membrane EnNaC was found. Importantly, already after 15 min. LSS αEnNaC membrane abundance was increased by 58.5±4.5%. Both (i) inhibition of exocytosis with Brefeldin A and (ii) (ii) MR antagonism with Canrenone, could prevent the acute shear stress-induced EnNaC membrane insertion indicating a rapid MR-mediated effect of shear stress. EnNaC membrane abundance under NLSS in branching regions was also significantly increased compared to static controls (+24.9±4.3%). AFM measurements revealed that the shear stress-induced increase in EnNaC lead to stiffening of the cell cortex by 18.9±5.5% compared to static controls.

Conclusions: Our results suggest that EnNaC, besides being a mechano-sensor, is regulated by shear stress. Since both chronic and acute shear stress increase the membrane abundance we postulate genomic and non-genomic mechanisms leading to the MR-dependent membrane insertion of EnNaC and subsequent endothelial stiffening. These changes in nanomechanics and thus endothelial function might be a physiological response to changes in hemodynamics and further explain the atherogenic potential of disturbed blood flow.

Funding: Government Support - Non-U.S.

FR-PO196

Decreased Blood Pressure in Vascular Smooth Muscle Specific ATP2B1 Overexpressing Mice Yosuke Ehara,[1] Nobuhito Hirawa,[2] Akira Fujiwara,[2] Kouichi Tamura.[1] *[1]Yokohama City University Graduate School of Medicine, Yokohama-shi, Kanagawa, Japan; [2]Yokohama City University Medical Center, Yokohama, Japan.*

Background: We reported the association between high blood pressure and ATP2B1 gene polymorphisms in Japanese population through Millennium Genome Project. ATP2B1 is a gene encoding plasma membrane calcium ATPase 1 (PMCA1), which is known to be expressed throughout the body. PMCA1 plays a role of discharging Ca^{2+} from the inside of the cell to the outside of the cell, and strictly adjusts the intracellular Ca^{2+} concentration. In subsequent studies we reported that ATP2B1 vascular smooth muscle-specific knockout mice exhibit hypertension and are associated with elevated Ca^{2+} concentrations in vascular smooth muscle cells(VSMC). However, there were no data concerning the effects of ATP2B1 overexpressions. Thus, we generate the vascular smooth muscle-specific ATP2B1 overexpressing mice, and investigate the effects of ATP2B1 on blood pressure.

Methods: ATP2B1 vascular smooth muscle-specific overexpressing mice (Tg^{ATP2B1}) was prepared by microinjection method using transgelin (sm22) as a promoter. The expression level of ATP2B1 was confirmed in the aorta. Birth rate, body weight, organ weight, biochemical findings of Tg^{ATP2B1} were compared with the wild type mice. We

compared the blood pressure and heart rate by the tail cuff method and telemetry method in the two groups.

Results: There was no significant change in birth rate, body weight (Tg^{ATP2B1} versus WT : 27.1 ± 0.6 versus 28.1 ± 1.1 ; P:0.46), organ weight. Serum calcium concentrations (8.83 ± 0.13 versus 8.78 ± 0.12 ; P:0.78) of Tg^{ATP2B1} were also the same with those of wild mice. Although there was no difference in heart rate, a significant decrease in blood pressure was observed in Tg^{ATP2B1} mice using tail-cuff methods (99.4 ± 2.73 versus 108.4 ± 2.72 ; P:0.03). By radio-telemetry methods, the blood pressure of Tg^{ATP2B1} were decreased throughout 24hrs. The blood pressure variabilities were not altered by the over-expression of ATP2B1 in vascular smooth muscle cells.

Conclusions: Vascular smooth muscle-specific ATP2B1 overexpressing mice exhibited lower blood pressure compared to those of wild mice by the tail cuff method and the telemetry method. ATP2B1 over-expression in VSMC might decrease the intra-celular Ca^{2+} concentrations and decrease the contractilities in Tg^{ATP2B1} mice.

FR-PO197

Atherosclerosis Is Associated with a Reduction in the Density of Renal Microcirculation Miguel Hueso,[1] Angela I. Casas Parra,[1] Estanislao Navarro,[3] Nuria Bolanos,[3] Cristian Varela,[3] Elia Ripoll,[2] J. Grinyo,[1] Josep M. Cruzado,[1] Juan Torras.[1] *[1]Hospital Universitari de Bellvitge, Barcelona, Spain; [2]Laboratory of Experimental Nephrology, IDIBELL. Hospital Universitari de Bellvitge, Barcelona, Spain; [3]IDIBELL, L'Hospitalet, Spain.*

Background: Cardiovascular disease is increased in renal diseases but the role of renal microcirculation in the development of atherosclerosis is unknown. CD40/CD40L signaling has a critical role in atherosclerosis and CD40 silencing reduces their progression. In addition, CD40/CD40L signaling may lead to blood vessel dysfunction and occlusion. Thus, we used the CD40-silenced $ApoE^{-/-}$ model of atherosclerosis to study the interplay between atherosclerosis and renal microcirculation.

Methods: CD40 was silenced with a specific siRNA in the $ApoE^{-/-}$ mouse model during 16 weeks. We administrated scrambled siRNA (SC) or PBS (vehicle) as controls. Endothelium was identified by immunohistochemistry using PECAM-1 antibody (platelet endothelial cell adhesion molecule-1). Kidneys were isolated from 24 weeks-old mice. The density of peritubular capillaries was quantified using ImageJ v1.48 and expressed as a proportion. The extension of atherosclerotic lesions was quantified in HE staining from ascending aortas.

Results: SiRNA-CD40 treated $ApoE^{-/-}$ mice reduced the extension of atherosclerotic lesions in $ApoE^{-/-}$ mice. Furthermore, a decrease of renal microcirculation density was observed in this experimental model of atherosclerosis (siRNA-CD40, n=9, 4.5±2.2%; SC, n=4, 2.1±0.8 %; Vehicle, n=9, 2.0±1.4%, p<0.0001). No differences in serum creatinine was detected (siRNA-CD40: 0.6±0.18 mg/dL; SC: 0.54±0.2 mg/dL; Vehicle: 0.51±0.3 mg/dL, p=ns).

Conclusions: A reduction in peritubular capillaries was associated with severe atherosclerosis lesions. This data provide structural basis of renal disease in patients with atherosclerosis.

FR-PO198

Activin Receptor Activation in the Skeleton, Vasculature, Heart, and Kidney During CKD Toshifumi Sugatani,[2] Matthew J. Williams,[1] Olga A. Agapova,[3] Hartmut H. Malluche,[5] Keith A. Hruska.[4] *[1]None, Saint Louis, MO; [2]WASHINGTON UNIVERSITY IN ST. LOUIS SCHOOL OF MEDIC, St.Louis, MO; [3]Washington University School of Medicine, St. Louis, MO; [4]Washington University St. Louis, St. Louis, MO; [5]University of Kentucky, Lexington, KY.*

Background: To study whether factors stimulating renal fibrosis produce systemic disease, we examined activin receptor type IIA (ActRIIA) activation in CKD by signal analysis and inhibition in Alport syndrome mice, using a ActRIIA ligand trap (RAP-011) from 75 to 200 days of life.

Methods: We measured ActRIIA signaling and inhibited its activity with RAP-011.

Results: By 200 days, Alport mice had severe CKD and the CKD-MBD, consisting of osteodystrophy, vascular calcification, cardiac hypertrophy, hyperphosphatemia, hyperparathyroidism, and elevated FGF23 and reduced klotho levels. ActRIIA inhibition by RAP-011 reversed CKD-stimulated bone resorption and osteoblast dysfunction by inhibition of osteoclast function, while osteoblast function and bone formation were increased. ActRIIA inhibition prevented formation of calcium apatite deposits in aortic adventitia and tunica media and decreased aortic Ca levels from 0.59 mg/g in Alport mice to 0.36 in RAP-011 treated mice (p<.05). Aortic ActRIIA stimulation increased p-Smad2 levels and the transcriptional targets, sm22α and αSMA, in Alport mice. ActRIIA inhibition reversed aortic expression of Runx2 and osterix, markers of osteoblastic transition. Heart weight was 26% increased in Alport mice, but remained normal during RAP-011 treatment (p<.01). In 150 do Alport mice, GFR was reduced by 55%, p<0.05, but GFR was only 30% reduced in the RAP-011 treated group. At 200 do, the BUN was 100mg/dl in Alport mice compared to 60 in the treated group. In kidneys of 200 day old Alport mice, ActRIIA and p-Smad2 were induced and MCP-1, fibronectin and interstitial fibrosis were stimulated, but inhibited by RAP-011 treatment.

Conclusions: The results demonstrate CKD activation of ActRIIA signaling contributing to CKD-MBD components, osteodystrophy and cardiovascular disease, and to renal fibrosis. Inhibition of ActRIIA signaling may be efficacious in Alport syndrome.

Funding: NIDDK Support

FR-PO199

Endothelial Glucocorticoid Receptor (GR) Modulates Wnt Signaling in a Mouse Model of Atherosclerosis Han Zhou, Julie Goodwin. *Yale University School of Medicine, New Haven, CT.*

Background: Apo E KO/endothelial GR double knock-out (DKO) mice develop more severe atherosclerotic lesions compared to Apo E KO mice alone. Genomic data from ChIP-seq and RNA-seq experiments in endothelial cells indicate that endothelial GR binding to genes in the Wnt signaling pathway is enriched. The Wnt signaling pathway is a potentially important, yet understudied, mediator of vascular inflammation.

Methods: Male Apo E KO mice and Apo E KO/endothelial GR double knock-out mice (DKO) were bred to mice carrying the BAT GAL reporter to enable visualization of the activation of the canonical Wnt signaling pathway. Mice were fed a high-fat diet for 4-5 weeks and then sacrified for blood and tissue processing. Whole aortas and cross sections of brachiocephalics arteries were stained with X-gal. Brachiocephalics were also subjected to double immunofluorescent staining with antibodies to BAT GAL and CD31. Luciferase assay was used to invesigate modulation of canonical Wnt signaling by GR in vitro using mouse lung endothelial cells subjected to GR siRNA knockdown and treatment with Wnt3a, a canonical Wnt ligand.

Results: BAT GAL+ Cre+ mice had significantly more aortic area stained after X-gal than did BAT GAL+ Cre- mice (32% vs. 6%, p=.0061, n=5/group). Staining of BAT GAL- Cre- mice was used as a control. X gal staining in brachiocephalic arteries was also signficantly increased in BAT GAL+ Cre+ mice compared to BAT GAL+ Cre- littermate controls. TCF/LEF luciferase assay demonstrated a 3-fold higher induction in Wnt3a-treated GR knockdown cells compared to similarly treated GR replete cells.

Conclusions: We conclude from these results that: 1. Loss of endothelial GR augments canonical Wnt signaling both in vivo and in vitro 2. Modulation of the Wnt pathway may represent a novel therapeutic strategy for treatment of vascular disease

Funding: Other NIH Support - NHLBI

Representative images of whole aortas stained with X gal after 4-5 weeks of high fat diet feeding.

FR-PO200

Mineralocorticoid Antagonism and Vascular Oxidative Stress and Inflammation in Early Autosomal Dominant Polycystic Kidney Disease: A Randomized-Controlled Trial Kristen L. Nowak,[1] Wei Wang,[1] Berenice Y. Gitomer,[1] Anna J. Jovanovich,[1,2] Heather Farmer-Bailey,[1] Michel Chonchol.[1] *[1]University of Colorado Anschutz Medical Campus, Aurora, CO; [2]Denver VA Medical Center, Denver, CO.*

Background: Oxidative stress and inflammation are present in early autosomal dominant polycystic kidney disease (ADPKD) and contribute to reduced nitric oxide bioavailability and arterial dysfunction. Aldosterone may further exacerbate oxidative stress and inflammation. We hypothesized that aldosterone antagonism would reduce vascular oxidative stress and inflammation in patients with early-stage ADPKD.

Methods: In a randomized, controlled, double-blind trial, n=60 adults 30-55 years of age with ADPKD, normal kidney function (estimated glomerular filtration rate [eGFR] ≥60 mL/min/1.73 m^2), and receiving the maximum tolerable dose of an angiotensin converting enzyme inhibitor were randomized to receive either spironolactone (titrated to maximum dose of 50 mg/day) or placebo for 6 months. As secondary endpoints in this trial, we measured protein expression of NADPH oxidase, interleukin-6 (IL-6), nuclear factor k B (NFκB), and phosphorylated endothelial nitric oxide synthase (PeNOS) in vascular endothelial cells (ECs) collected from a peripheral vein of study participants, and change in brachial artery flow-mediated dilation (FMD_{BA}) in response to an acute infusion of ascorbic acid as an index of vascular endothelial oxidative stress.

Results: Participants were 34±10 (mean±s.d.) years of age, 53% female and 80% White, with an eGFR of 94+21ml/min/1.73m^2. Acute infusion of ascorbic acid improved FMD_{BA} at baseline (8.4±5.9 vs. 9.5±5.7%, p<0.05). After 6 months, ascorbic acid continued to improve FMD_{BA} in both the spironolactone and placebo group, indicating no reduction in vascular endothelial oxidative stress. Similarly, there was no change in EC protein expression of the oxidant enzyme NADPH oxidase. IL-6 and PeNOS EC expression were also unchanged. However, EC expression of the pro-inflammatory transcription factor NFκB was reduced in the spironolactone group (0.51±0.13 vs. 0.43±0.08 [immunofluorescence intensity relative to HUVEC control]; p<0.05) with no change in the placebo group (0.48±0.10 vs. 0.48±0.09).

Conclusions: Six months of aldosterone antagonism with spironolactone does not reduce ADPKD-associated vascular oxidative stress, but may attenuate vascular inflammation.

Funding: NIDDK Support

FR-PO201

Arteriolar Hyalinosis in Klotho Deficiency Rik Mencke,[1] Jakob Voelkl,[2] Geert Harms,[1] Marian L. Bulthuis - van der horst,[1] Anja Umbach,[3] Harry Van Goor,[1] Florian C. Lang,[3] Jan-luuk Hillebrands.[1] *[1]University Medical Center Gronigen, Groningen, Netherlands; [2]Charité University Medicine, Berlin, Germany; [3]University of Tübingen, Tübingen, Germany.*

Background: Hyalinosis is a vascular lesion affecting the renal vasculature in ageing, hypertension, and after transplantation. It is thought to contribute to renal function decline. We wanted to assess whether arteriolar hyalinosis is caused by Klotho deficiency – a state known to induce both renal and vascular ageing-related pathologies.

Methods: The presence of hyalinosis was assessed in kidneys from 7-week-old Klotho$^{-/-}$, Klotho$^{+/-}$, and WT mice. We used (immuno)histochemistry to investigate the composition of the lesions and the different layers of the vascular wall. Finally, using *kl/kl* mice (with a promoter disruption rather than the exon deletion of Klotho$^{-/-}$ mice and with more severe vascular calcification) we assessed the effect of spironolactone treatment (80 mg/L of drinking water, between 3 and 8 weeks of age) on the vascular lesions in the kidney as spironolactone inhibits vascular calcification.

Results: We detected marked arteriolar hyalinosis in Klotho$^{-/-}$ mice, present up to the afferent arterioles. Hyalinosis was accompanied by local loss of α-smooth muscle actin expression, while the endothelial lining was mostly intact. Hyalinous lesions were positive for IgM and iC3b/c/d, indicating subendothelial leakage of plasma proteins. The increased presence of extracellular matrix proteins suggests increased production by smooth muscle cells and the gain of S100A4 expression indicates smooth muscle cell de-differentiation towards a synthetic phenotype. In *kl/kl* mice, spironolactone treatment inhibited the development of calcification and resulted in the development of hyalinosis.

Conclusions: Klotho deficiency induces the development of hyalinosis: spontaneously in Klotho$^{-/-}$ mice and after inhibition of calcification in *kl/kl* mice, also attesting to the phenotypic variability of Klotho deficiency. Klotho deficiency potentiates both endothelial hyperpermeability and smooth muscle cell de-differentiation to a synthetic phenotype, likely in response to subendothelial leakage of plasma proteins. Klotho may play a role in preventing ageing-related or calcineurin inhibitor-induced arteriolar hyalinosis.

Funding: Private Foundation Support

FR-PO202

Nephrotic Syndrome Modulates Flow and Composition of Mesenteric Lymph Jianyong Zhong, Babak Banan, Vance L. Albaugh, Yohei Tsuchida, Patricia G. Yancey, Carrie B. Wiese, Kasey C. Vickers, Haichun Yang, Valentina Kon. *Vanderbilt University Medical Center, Nashville, TN.*

Background: Although hyperlipidemia and altered lipid/lipoprotein metabolism that characterize nephrotic syndrome (NS) are usually ascribed to functional changes in the liver, little is understood about how NS impacts another relevant organ system, i.e., gut. Small intestine functions not only to reabsorb dietary lipids but also contributes to lipoprotein synthesis, particularly apolipoprotein AI, the main protein in high density lipoprotein (HDL) that provides beneficial effects to many different tissues. All reabsorbed lipids and synthesized lipoproteins are taken-up and transported through the lymphatics. Since integral to NS is development of edema that reflects lymphatic inadequacy, we examined the lymphatic network in a model of NS.

Methods: NS was induced by puromycin aminonucleoside (PAN) in 12 Sprague Dawley rats, while 12 non-injected rats served as control (C). Eight days later, plasma, urine, mesenteric lymph, kidney and ileum were collected for further analysis.

Results: Along with massive proteinuria, PAN significantly increased plasma cholesterol and triglyceride that was accompanied by increased renal lymphatic vessel density (assessed by staining for podoplanin). Proteinuric injury caused a 6-fold increase in mesenteric lymph flow (PAN:10.7±1.3ml vs C:1.5±0.3 x 3h, p<0.001). Despite apparent dilution, the mass of cholesterol and triglycerides transported by mesenteric lymph over time was 3- and 5-fold higher in PAN than C (both p<0.05). PAN dramatically increased lymphatic transport of apoAI (PAN:108.3±13.0μg vs C:13.7±2.6 x 3 hours p<0.001). While plasma cytokines (IL-6, IL-10, IL-1, IL-17a) were not different, PAN significantly increased lymphatic concentration of IL-6 (>200%, p<0.05), IL-10 (>150%, p<0.05) and IL-17a (>200%, p<0.05). In addition, PAN raised the number of Th17 cells (>50%, p<0.05) and increased the level of VEGFA (>100%, p<0.05) compared to C.

Conclusions: Proteinuric kidney injury expands the renal lymphatic network and enhances mesenteric lymph flow which carries more fluid, lipids, lipoproteins, inflammatory cytokines and growth factors. These data suggest a potentially critical role for the intestinal lymphatic network in edema, inflammation and cardiovascular complications of NS and present a new target to lessen these complications.

Funding: Other NIH Support - 1P01HL116263-01A1 NHLBI HDL Function in Human Disease (Project PI)

FR-PO203

Chronic Kidney Dysfunction Impairs Experimental Arteriovenous Fistula Healing Makoto Orii,[1] Jie Cui,[2] Harkamal S. Jhajj,[2] Jason McCarthy,[2] Farouc A. Jaffer.[2] *[1]Massachusetts Genaral Hospital, Boston, MA; [2]Massachusetts General Hospital, Boston, MA.*

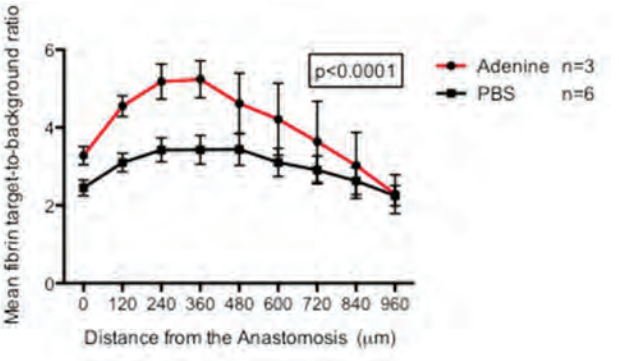
Background: Thrombosis and neointimal hyperplasia are major causes of arteriovenous fistula (AVF) failure in chronic kidney disease (CKD) patients. Here, we utilize in vivo molecular imaging characterize fibrin deposition after AVF creation in CKD mice.

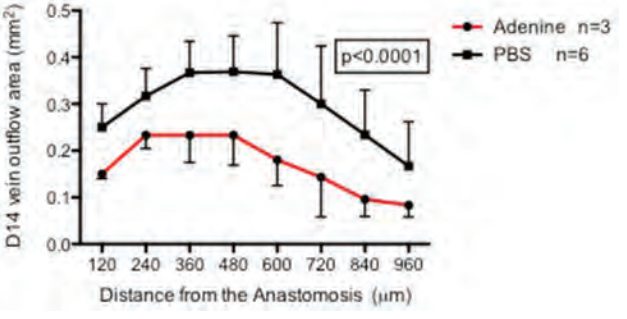
Methods: CKD was induced in C57BL/6 mice using daily adenine gavage(50mg/kg). Serial blood sampling was performed to measure the creatinine (Cr) and BUN. Fourteen days after adenine (n=3) or PBS gavage (n=6), AVF were created using an end-to-side internal jugular vein and carotid artery anastomosis. AVF blood flow was measured 15 minutes post-surgery (Transonic). Molecular imaging of fibrin deposition on AVF was enabled using fluorophore-labeled peptide (FTP11-Cym7). On day 7 after AVF creation, a 150 nmol/kg IV bolus of FTP11-Cym7 was administered. Forty-five minutes after FTP11 injection, fibrin deposition was imaged in vivo using epifluorescence microscopy. Mice were then sacrificed at day 14. AVF vein wall thickness area (WTA), vein outflow area (OA), and patent area (PA) were measured using picrosirius red staining. The fibrin target-to-background ratio (TBR) was calculated as mean signal intensity (MSI) of the fistula divided by the MSI of the control vein. Regions-of-interest were defined as areas between the anastomosis and 960μm away from the anastomosis.

Results: The BUN/Cr values on day 14 and 28 after adenine administration were 93±24/1.3±0.4 mg/dl and 94±6/0.6±0.1 mg/dl, respectively (p<0.001 vs. PBS). AVF blood flow immediately after AVF surgery were similar between CKD and PBS groups (1.44±0.25ml/min vs 1.22±0.19 ml/min, p=0.5). The in vivo day 7 fibrin deposition after AVF creation (FTP11-Cym7 TBR) was significantly higher in CKD mice (p<0.0001 vs. PBS mice). The vein WTA, OA, and PA was also significantly lower in CKD group (p<0.0001 vs. PBS).

Conclusions: Compared to non-CKD subjects, CKD impairs AVF healing, as indicated by greater fibrin deposition and reduced outward remodeling.

Funding: Other NIH Support - NHLBI R01 HL 122839





FR-PO204

An Impairment of the Coagulation-Fibrinolysis System Implicates Vascular Access Patency in Patients on Hemodialysis after Vascular Access Intervention Yukiko Hasuike, Naoto Kakita, Aritoshi Kida, Masayoshi Nanami, Takeshi Nakanishi. *Internal Medicine, Division of Kidney and Dialysis, Nishinomiya, Japan.*

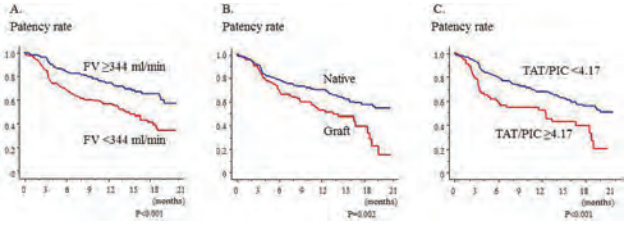
Background: Vascular access (VA) is essential for the HD patients. However, VA is often occluded even after the VA intervention therapy (VAIVT). There is increasing evidence indicating the importance of the coagulation-fibrinolysis system in the progression of vascular disease. We intended to clarify whether the imbalance of coagulation-fibrinolysis might be associated with VA failure after VAIVT.

Methods: Blood samples were taken from 462 HD patients at the VAIVT. Among them, 352 patients (76.2%) had native arteriovenous fistula (AVF). Thrombin/anti-thrombin (TAT) as a marker of coagulation, plasmin-α_2-plasmin inhibitor complex (PIC) as markers of fibrinolysis, and factors related to inflammation (CRP, interleukin-6, tumor necrosis factor-α, pentraxin-3), mineral-bone metabolism (calcium, phosphate, parathyroid hormone), and uremia were measured. Blood flow volume (FV) of VA was evaluated by Doppler ultrasonography before VAIVT. The end point was the re-vascularization or re-operation of VA during the observational period after VAIVT (mean follow-up periods 278.7±182.8 days). The results were analyzed using receiver operating characteristic curve, Kaplan-Meier methods, and Cox regression analyses.

Results: Age of patients was 69.9±10.6 years, and 225 female patients (48.7%). During follow-up period, re-VAIVT was performed in 82 patients and re-operation in 80

patients. The Kaplan-Meier analysis showed that the patients with lower FV (<344 ml/min), graft AVF, and higher TAT/PIC ratio (≥4.17) were associated with poor patency rates [figure A, B, C]. Cox regression analysis revealed that higher TAT/PIC ratio (adjusted HR 1.67, 95%CI 1.14 to 2.43, p=0.008) was linked to VA failure event.

Conclusions: The impaired coagulation-fibrinolysis system as well as lower FV and graft VA can affect VA failure after VAIVT.



FR-PO205

Transcriptomic Profiling of Tight Junction Dysfunction in CKD Jen Xu,[1,2] Kenneth Lim,[3] Li-lun Ho,[1] Thomas F. Hiemstra,[4] Tzongshi Lu.[1] *[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Harvard College, Cambridge, MA; [3]Massachusetts General Hospital, Boston, MA; [4]University of Cambridge, Cambridge, United Kingdom.*

Background: Tight junctions (TJ) are specialized membrane domains that play multiple functions in endothelium and epithelium to maintain cellular homeostasis. TJ dysfunction is an important pathogenic process in the development of uremic-related cardiovascular disease (CVD), cerebral small-vessel diseases (CSVD) and cystogenesis in polycystic kidney disease. The goal of the present study was to elucidate the transcriptomic profile of TJ dysfunction in CKD.

Methods: We performed transcriptome analysis by RNA sequencing in: 1) primary human aortic endothelial cells (HAECs) and human brain microvascular endothelial cells (HBMECs) that were treated in calcification medium (CM: 5mM β-glycerolphosphate+5mM $CaCl_2$) in time-course experiments (0-48 hours), *in vitro*; 2) human kidney proximal tubule epithelial cells (HK-2) treated with H_2O_2, *in vitro* and 3) human arteries, *ex vivo* from healthy and CKD patients; Gene selections were performed by the combinations of fold-changes on log 2 ratio, and p value < 0.05.

Results: In primary cells treated with CM: we found that heat-shock protein 70 (HSP70) co-chaperone, BAG1 (Bcl2 Associated Athanogene 1) was significantly increased at 6 hours prior to upregulation of antiapoptotic gene, Bcl2 at 12 hours in HAECs but not in HBMECs. DNAJB6 (HSP40) and HSPA5 (HSP70 member5) was significantly increased at 24 and 12 hours respectively in HAECs. The major transmembrane TJ protein-Occludin was upregulated at 6 hours and peaked at 24 hours (HAECs) and 48 hours (HBMECs) under CM treatment respectively, but cytoplasma TJ-ZO1 displayed similar patterns in HAECs only. Inflammation sensitive TJ, Claudin-5 increased at 1 hour followed by upregulation of downstream ZO-1 at 6 hours. In addition, ZO1, occludin and Claudin-5 were downregulated after H_2O_2 treated but preserved by HSP70 induction in HK2 cells. In human CKD arteries, we found that claudin-5 was down-regulated (Fold changes, FC, 2.16) while ZO-1 was upregulated (FC=2.17). Bcl2 (FC=4.52) and HSPA5 (FC=3.85) was preserved in healthy arteries alone with activated BAG1 (FC=7.44).

Conclusions: Complex differential gene regulation involving apoptosis, TJ dysfunction and upregulation of the HSP stress response occur in endothelial and epithelial cells in renal failure. Our findings may serve to inform the rational development of therapeutic strategies for arterial and epithelial cells dysfunction in CKD.

Funding: Private Foundation Support

FR-PO206

Effect of Spironolactone on a Transgenic Rat Model of Hypertension and Myocardial Infarction Catherine Leader, Ivan A. Sammut, Gerard T. Wilkins, Robert J. Walker. *University of Otago, Dunedin, New Zealand.*

Background: Hypertension contributes to heart disease and renal injury. However the impact of MI plus hypertension on renal injury is not clearly described. Spironolactone (SP) can reduce cardiac fibrosis and improve cardiac re-modelling post MI; its effects on the kidney are unknown. We examined the effects of SP on renal fibrosis in hypertensive rats post MI.

Methods: Ffive groups of adult male Cyp1a1Ren2 rats: normotensive (N), hypertensive (H), hypertensive fed SP daily (50 mg day^{-1}) (H-SP), hypertensive with MI (left anterior coronary ligation) (H-MI) and hypertensive with MI plus daily SP (H-MI-SP). Hypertension (>160 mmHg systolic) was induced by 0.167 % (w/w) indole-3-carbinol added to the rat chow. Systolic blood pressure (SBP) and echocardiograms were recorded at termination, 28 days after MI. Cardiac and renal tissue was harvested for analysis.

Results: SBP was only reduced in the H-MI group (p=0.05) compared with all the other H groups (155±24 and 173±11mmHg respectively). SBP was not significantly reduced by SP in either of the treated groups. Ejection fraction (EF) was significantly reduced in all animals with MI (42±10%), addition of SP had no effect (43±10%). The Glomerulosclerosis Index (GSI) in normals was 0.2±0.1 and was significantly higher in all hypertensive groups (p>0.001). The H-SP group (0.9±0.04) showed a significant decrease in GSI from H controls (1.2±0.07) (p=0.002). The GSI in H-MI-SP (1±0.1) was significantly decreased from the H-MI group (1.3±0.1) (p=0.04). The degree of cortical interstitial fibrosis in all hypertensive groups was not modified by SP. Figure 1: PAS cortex pictures of representatives from each experimental groups. Scale bar is 200μm.

Conclusions: Conclusion: Severe hypertension caused extensive renal glomerulosclerosis and interstitial fibrosis. SP showed no effect on SBP or EF, but significantly improved GSI scores in hypertensive animals and post MI. SP did not reduce renal interstitial fibrosisl. Further work will aim to define the relation between cardiac injury and renal damage.

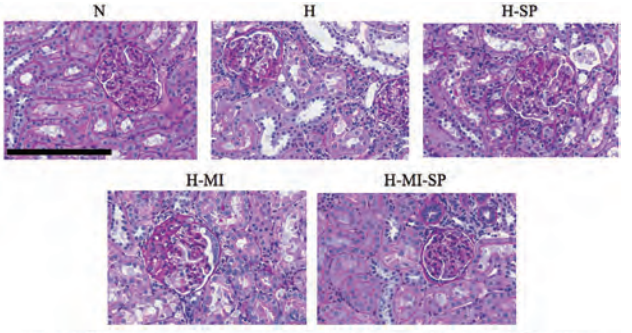


Figure 1: PAS cortex pictures of representatives from each experimental groups. Scale bar is 200μm.

FR-PO207

Patients with CKD Have Heightened Vascular α1-Adrenergic Receptor Sensitivity Doree G. Morison,[1,2] Ryan M. Downey,[1,2] Dana Dacosta,[1,2] Jeanie Park.[1,2] *[1]Renal Division, Department of Medicine, Emory University School of Medicine, Atlanta, GA; [2]Research Service Line, Atlanta VA Medical Center, Decatur, GA.*

Background: Patients with chronic kidney disease (CKD) have sympathetic overactivity and difficult-to-control hypertension. Our previous studies showed that CKD patients have augmented increases in blood pressure in response to the same degree of sympathetic nerve activation, suggesting heightened neurovascular transduction. We hypothesized that augmented vascular α_1-adrenergic receptor (α_1-AR) sensitivity contributes to the exaggerated vasoconstriction and blood pressure responses to sympathetic activation in CKD.

Methods: In 13 CKD (Stage IIIB and IV) patients and 5 Controls, we measured the degree of vasoconstriction of a dorsal hand vein in response to serial infusions of 10 doses (ranging 15-12,000 ng/min) of the selective α_1-AR agonist phenylephrine (PE) using a linear variable differential transformer with a movable central core to detect changes in vascular diameter. Vascular diameters were expressed as a % reduction from baseline maximum dilation, and plotted against PE dose rates in individual semilogarithmic dose-response graphs, and analyzed using a 4-variable sigmoid dose-response model. The natural log (ln) PE dose that produced a 50% maximal constriction (ED_{50}) reflects sensitivity to PE (i.e. α_1-AR sensitivity).

Results: CKD patients had a significantly lower PE ED_{50} compared to Controls (ln PE dose 5.1±0.5 vs 8.3±0.9 ng/min, p=0.0045), demonstrating that CKD patients have heightened vasoconstriction in response to PE.

Conclusions: Augmented vascular α_1-AR sensitivity could contribute to increased neurovascular transduction and hypertension in CKD patients.

Funding: Other NIH Support - NHLBI, Veterans Affairs Support

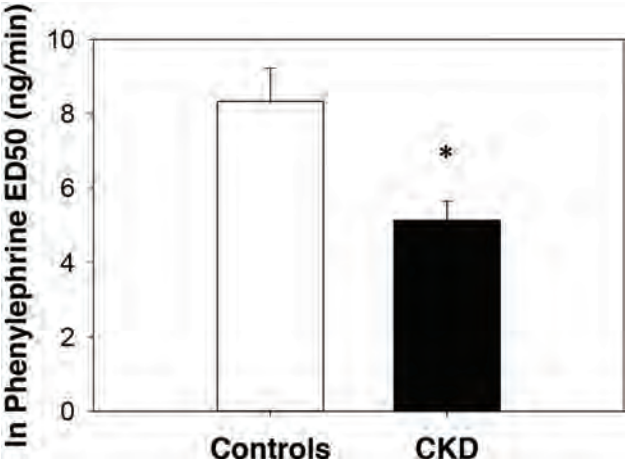


Figure. Vascular α_1-adrenergic receptor sensitivity is heightened in chronic kidney disease.

FR-PO208

Induction of Unique Scavenger Receptor Dysregulation Pattern in Advanced CKD Nobuyuki (Bill) Miyawaki, Nicolle M. Siegart, Farah Daccueil, Joshua De leon, Joseph Mattana, Lora Kasselman, Allison B. Reiss. *Medicine, NYU Winthrop Hospital, Mineola, NY.*

Background: In chronic kidney disease (CKD), scavenger receptors (SR) are the main cholesterol entry paths into macrophages, bypassing the regulated LDL receptors, to accelerate foam cell production in synergy with defective cholesterol efflux. Yet alteration patterns of SR in CKD remain poorly defined.

Methods: Following THP-1 human macrophage (10^6/ml) incubation for 24h with 10% plasma from 10 CKD Stage 4+5 patients (without diabetes, rheumatological illnesses or active infections) or plasma from 10 healthy control subjects, mRNA was isolated and reverse transcribed. The resulting cDNA was subjected to quantitative real-time PCR using specific primers for major cholesterol scavenger receptors CD36, LOX-1, SR-A1 as well as efflux proteins, ATP binding cassette transporter (ABC)A1 and G1.

Results: Exposure to CKD plasma decreased the expression of scavenger receptor CD36 with a 32% reduction (Fold change with CKD plasma exposure: 0.68, 95% CI [0.54, 0.87], p<0.01). SR-A1 expression with CKD plasma exposure was unaffected with a fold change of 0.80, 95% CI [0.52, 1.24], p<0.01). LOX-1 expression was not reduced; rather a very strong trend to LOX-1 enhancement with 1.54-fold increase with CKD plasma exposure (95% CI [1.01, 2.35], p=0.053). Downregulation of ABCA1 and ABCG1 were demonstrated, respectively, by 33% (0.67, 95% CI [0.04, 0.92], p=0.01) and by 30% (0.70, 95% CI [0.50, 0.98], p=0.03).

Conclusions: Prior studies of CKD populations have evaluated isolated SR and often without exclusion of other known inflammatory conditions which impact SR dysregulation patterns. Our demonstration of decreased CD36, unaffected SR-A1 and a very strong suggestion of increased LOX-1 in CKD differs from those previously described in rheumatoid arthritis or lupus and may provide future avenues for viable therapeutic targets. Additional studies on LOX-1 as well as impact of its inhibition may be helpful in further elucidation of SR mediated uptake mechanisms in CKD. Reduced ABC gene expression likely lowers defense against lipid overload and may be a target for therapeutic intervention.

Funding: Private Foundation Support

FR-PO209

CPAP Therapy Improves Central Arterial Stiffness and Decreases Arterial Renin Angiotensin System Activity in Humans with Obstructive Sleep Apnea David D. Nicholl,[2] Patrick Hanly,[2] Ann A. Zalucky,[2] Michelle C. Mann,[2] Jennifer M. MacRae,[2] Marc Poulin,[2] George Handley,[1] Darlene Y. Sola,[2] Sofia B. Ahmed.[2] *[1]Healthy Heart Sleep Company, Calgary, AB, Canada; [2]University of Calgary, Calgary, AB, Canada.*

Background: Chronic kidney disease (CKD) is associated with increased arterial stiffness, a marker of cardiovascular risk. Treatment of obstructive sleep apnea (OSA), common in CKD, reduces arterial stiffness, though the mechanism is not clear. Limited studies suggest a prominent role for the renin angiotensin system (RAS), activation of which is deleterious to kidney and cardiovascular function. We sought to determine the effect of CPAP therapy on arterial stiffness at baseline and in response to the physiological stressor, Angiotensin II (AngII), in humans with OSA.

Methods: Newly diagnosed OSA subjects (respiratory disturbance index [RDI]>15hr^{-1}) with nocturnal hypoxia (oxyhemoglobin saturation [SaO_2] <90% for >12% of night) who were otherwise healthy were studied in high-salt balance, at state of maximal RAS suppression, pre-CPAP and then after 4 weeks of effective CPAP therapy (>4h/night) in a second identical study day. Central (aortic augmentation index [AIx]) and peripheral (carotid-femoral pulse-wave velocity [PWV_{cf}]) arterial stiffness were measured by applanation tonometry. Arterial stiffness was measured at baseline and in response to a graded AngII infusion (3ng/kg/min x 30min, 6ng/kg/min x 30min, Recovery x 30min). The primary outcome was the effect of CPAP on the arterial stiffness responses to AngII.

Results: Twenty-six subjects (18 men, 8 women; 49±2y) completed the study. CPAP corrected OSA (RDI: 44.2±4.1 vs 3.5±0.5hr^{-1}, p<0.001; duration SaO_2<90%: 45.4±5.6 vs 6.7±2.1%, p<0.001; all values pre- vs post-CPAP). Treatment with CPAP was associated with increased sensitivity in central arterial stiffness (ΔAIx: AngII, 8.7±1.4 vs 11.6±1.6%, p=0.038; Recovery, 1.7±1.4 vs 1.0±2.0%, p=0.8), while no change in peripheral arterial stiffness (ΔPWV_{cf}: AngII, 1.0±0.3 vs 0.9±0.2 m/s, p=0.8; Recovery, 1.0±0.3 vs 0.2±0.4 m/s, p=0.13) was observed.

Conclusions: CPAP therapy was associated with increased central, but not peripheral, arterial stiffness sensitivity to AngII, consistent with downregulation of the vascular RAS. These findings may have important implications in mitigating cardiovascular risk in CKD patients with OSA.

FR-PO210

Mineralocorticoid Receptor Antagonists Augment Arginine Transport and Nitric Oxide Generation through Modulation of Cationic Amino Acid Transporter-1 in Human Umbilical Vein Endothelial Cell Doron Schwartz,[1] Moshe Shashar,[1] Idit F. Schwartz.[2] *[1]Sourasky Medican Center, Tel Aviv, Israel; [2]Tel Aviv Medical Sourasky Center, Tel Aviv, Israel.*

Background: Blockade of the mineralocorticoid receptor (MCR) has been shown to improve endothelial function far beyond blood pressure control. In the current studies we looked at the effect of MCR antagonists on the activity of cationic amino acid transporter-1 (CAT-1), a major modulator of endothelial nitric oxide (NO) generation.

Methods: Using radio-labeled arginine, {[3H] L-arginine} uptake was determined in Human umbilical vein endothelial cells (HUVEC) following incubation with either spironolactone or epleronone with or without silencing of the MCR. Western blotting for CAT-1, PKCα and their phosphorylated forms were performed. NO generation was measured by the Griess reaction.

Results: Both Spironolactone and epleronone significantly increased endothelial arginine transport, an effect which was augmented by co-incubation with aldosterone and blunted by either silencing of the MCR or Co-administration of amyloride. Following MCR blockade but not amyloride, we identified two bands for CAT-1. The addition of tunicamycin (a de-glycosylation agent) or silencing of the MCR resulted in disappearance of the extra band and prevented the increase in arginine transport. Spironolactone but not epleronone decreased CAT-1 phosphorylation through inhibition of PKCα (CAT-1 inhibitor). Subsequently, the concentration of NO2/NO3 (stable NO metabolites) following incubation with both MCR antagonists significantly increased. This was attenuated by silencing of MCR or tunicamycin. GO 6076 (PKCα inhibitor) augmented the increase of NO metabolites only in the epleronone treated cells.

Conclusions: Spironolactone and epleronone augment arginine transport and NO generation through modulation of CAT-1 in endothelial cells. Both MCR antagonists activate CAT-1 by facilitating its glycosylation while only spironolactone inhibits PKCα.

FR-PO211

Diabetes Mellitus Modulates Interaction of Inflammation with Asymmetric Dimethyl Arginine in Hemodialysis Marcelo C. Batista,[2,5] Mauro sergio M. Marrocos,[2,6] Beata M. Quinto,[2] Andrei A. Teixeira,[3] Maria Eugenia F. Canziani,[1] Silvia R. Manfredi,[4] Cassio J. Rodrigues.[1] *[1]Federal University of Sao Paulo, Sao Paulo, Brazil; [2]UNIFESP, São Paulo, Brazil; [3]UNIFESP / EPM, Pouso Alegre, Brazil; [4]Universidade Federal de São Paulo, Sao Paulo, Brazil; [5]Nephrology, Einstein Jewish Hospital, Nephrology, São Paulo, Brazil; [6]Nephrology, State Public Server Hospital of São Paulo, São Paulo, Brazil.*

Background: inflammation and Dimethyl Arginine Asymmetric (ADMA) are related to mortality in hemodialysis (HD). Study aims to analyze interaction between ADMA and CRP among DM- and + patients in HD.

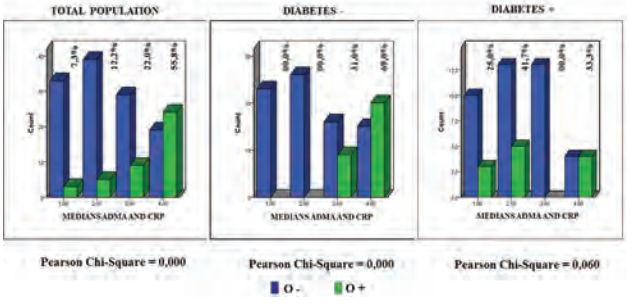
Methods: Pre-HD ADMA measured by HPLC in 202 adults prevalent in HD. CRP measured by ultra-sensitive immunoturbidimetry. Association with mortality in 4 years through SPSS 23.0.

Results: Forty individuals censored by transplantation. DM+ were older (57.1 ± 13.3 x 50.2 ± 15.1 years, P = .002), with higher BMI (25.9 ± 2.9 x 24.9 ± 2.4, P =, 017), and higher prevalence of coronary disease (36.9% x 15.0%, P = .001). ADMA and CRP were similar between DM+ and DM-. ADMA and CRP were similar between DM + and DM-. Only ADMA - median IQR μM - (0.88 0.60 - 1.37 and 1.71 1.34 - 2.17 P =, 000) and median CRP IQR mg / dL - (0.38-0.15 - 1.18 and 0.77 0.23 - 2.25 P = .034) differed between individuals with no evolution to death (O-) or with (O +). Only ADMA - median IQR μM - (1.03 0.81 - 1.55 and 1.95 1.75 - 2.54 P =, 000) differed between DM-, O- or O+. In binary logistic regression, ADMA remained as a variable related to mortality in DM- (OR 2,379 CI 1.36 - 3.68 P =, 000). DM + showed no differences between O- or O+. In 4 groups according to ADMA and CRP medians: I = lower ADMA and CRP, II = higher CRP and lower ADMA, III = lower CRP and higher ADMA and IV = higher ADMA and CRP - respective mortalities of 0.0%, 0, 0%, 31.0%, 69.0% among DM- (P =, 000). No differences in mortality between DM + (GRAPHIC).

Conclusions: ADMA has a significant relationship with mortality in prevalent DM- in HD and can improve evaluation of mortality risk in these patients. Other risk factors may overlap ADMA in DM +. Synergistic effect of ADMA and CRP; Mortality in group IV in DM- in HD higher than simple addition of mortality in group III with II or I. Previous work reported no differences between DM + and DM-, but DM + totaled 15% of the cohort (CJASN 6 1714 -21.2011).

Funding: Government Support - Non-U.S.

RELATION BETWEEN GROUPS MEDIANS ADMA AND CRP IN RELATION TO EVOLUTION



FR-PO212

Characterization of a Novel β-Common Receptor Inhibitory Peptide Cody Kilar,[3] Yanpeng Diao,[2] Shahar Keinan,[1] Yong Shen,[2] Jorg Bungert,[2] Rajesh Mohandas,[3,4] Mark S. Segal.[3,4] *[1]Cloud Pharmaceuticals, RTP, NC; [2]University of Florida, Gainesville, FL; [3]University of Florida, GAINESVILLE, FL; [4]North Florida/South Georgia Veterans Health System, Gainesville, FL.*

Background: In short term animal models of ischemia, erythropoietin (EPO) signaling through the heterodimeric EPO receptor/β-common receptor (βCR) is believed to elicit tissue protective effects. However, large randomized controlled trials demonstrate that administering high doses of EPO, which can activate the βCR, is associated with an increase in adverse cardiovascular events. Thus, inhibition of the βCR may have therapeutic implications. This study aimed to design and evaluate the efficacy of a novel computationally designed βCR inhibitory peptide (βIP).

Methods: The novel βIP was designed from the crystal structure of EPO consisting of 16-amino acids (VLERYLLEAKEAEKIT) from residues 11 to 26. Ultimately, the 16-amino acid peptide model comprising of *VLERYL**H**EAK**H**AEKIT,* was selected as a novel βIP. The efficacy of βIP to inhibit βCR-induced nitric oxide (NO) production and angiogenesis in human umbilical vein endothelial cells (HUVECs) was evaluated.

Results: We found that βIP completely abolished EPO-induced NO production, however could be overcome with super physiological doses of EPO. βCR-induced angiogenesis in HUVEC's was also abolished with treatment of βIP, but βIP did not inhibit vascular endothelial growth factor (VEGF)-induced angiogenesis. In addition, we show that the novel βIP does not increase erythropoiesis or inhibit EPO-induced erythropoiesis with use of peripheral blood mononuclear cells (PBMCs).

Conclusions: These results introduce, for the first time, a novel, potent βCR inhibitor that inhibit the actions of the βCR without affecting erythropoiesis. Experiments addressing the therapeutic use of this peptide will be discussed.

Funding: Other NIH Support - NIGMS

FR-PO213

Pathophysiological Analysis of Renal Congestion Using a Novel Rat Model Satoshi Shimada,[1] Takefumi Mori,[2] Yusuke Ohsaki,[1] Chika Takahashi,[1] Sadayoshi Ito.[1] *[1]Graduate School of Medicine, Tohoku University, Sendai, Japan; [2]TOHOKU MEDICAL AND PHARMACEUTICAL UNIVERSITY HOSPITAL, Sendai, Japan.*

Background: A physiological association between kidney and heart has been well known, however the mechanisms involved is remain unknown. Renal congestion (RC) has been shown to play a role in heart failure (HF), precise mechanism involved in the pathogenesis of cardio-renal injury and Na retention has not been well investigated. The present study designed to investigate the role of renal congestion on glomerular filtration rate (GFR), renal histology, volume and blood pressure (BP).

Methods: RC was made by occluding left renal vein in Sprague Dawley rats. First, RC was made in left kidney while right kidney remained intact in anesthetized rats. GFR, renal interstitial hydrostatic pressure (RIHP) and urinary Na excretion was monitored in each kidney. Next, renal histology was compared between RC left kidney and intact right kidney after 9 days of RC. Finally, BP was monitored in rats with left RC with the other kidney removed. Rats were fed either normal salt or high salt for 2 weeks in either RC rats or sham operated rats.

Results: GFR and renal medullary blood flow significantly decreased in RC kidney while those of contralateral intact kidney remained unchanged. RIHP was increased during RC. Tubulo-glomerular injury was observed in the RC left kidney compared to the contralateral intact right kidney. These renal injuries were improved by reducing RIHP with removing renal capsule. In one-kidney RC model, plasma renin activity (renal congestion group 5.6±0.7 ng/ml/h, n=13 vs sham group 10.1±0.8 ng/ml/h, n=9, p=0.011) and hematocrit (operation group 43.5±1.4 ng/ml/h, n=13 vs sham group 47.8±0.9 ng/ml/h, n=9, p=0.001) is significantly lower in RC group compared to those of sham group, which suggests the increase in volume of body fluid. High salt induced increase in systolic BP the one-kidney renal congestion rats (normal salt period 95.8±5.9mmHg vs high salt period 116.1±6.1 mmHg, n=7, p=0.013), while no significant changes in BP was observed in sham operated rats.

Conclusions: RC increases body fluid volume by Na retention and reduced GFR and renal circulation by increase in RIHP, thereby induce salt induced increase in BP and renal injury. These results indicate that renal congestion play a pathophysiological role in the pathogenesis of HF.

Funding: Government Support - Non-U.S.

FR-PO214

Diffusion-Weighted Magnetic Resonance Imaging (DWI) Correlates with the Response to Renal Revascularization in Patients with Atherosclerotic Renovascular Disease (ARVD) Ahmad F. Hedayat, Alfonso Eirin, Christopher M. Ferguson, James Glockner, Stephen C. Textor, Lilach O. Lerman. *Mayo Clinic, Rochester, MN.*

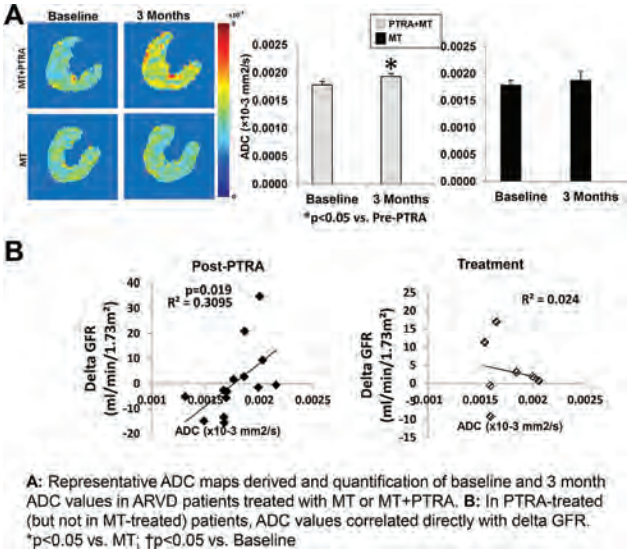
Background: Selecting patients with ARVD likely to improve glomerular filtration rate (GFR) after percutaneous transluminal renal angioplasty (PTRA) is challenging. DWI is an experimental tool to assess tissue morphology based on water molecule motion, and its index apparent diffusion coefficient (ADC) falls in damaged kidneys. We hypothesized that low basal ADC values would identify stenotic kidneys with subsequent diminished functional recovery after PTRA.

Methods: ADC was measured on 3T MRI in 20 patients with hemodynamically significant ARVD before and 3 months after standardized medical therapy (renin-angiotensin system inhibition) with or without PTRA. During protocol studies patients consumed a constant sodium intake, and eGFR was measured by CKD-EPI. Baseline ADC values were correlated with the change in eGFR after PTRA (delta eGFR).

Results: Baseline eGFR and ADC values were similar between groups (p>0.05). ADC values increased In patients 3 months after PTRA, and correlated directly with delta GFR, but remained unchanged in patients treated with medical therapy (MT) alone.

Conclusions: Low basal ADC value may serve as biomarker of kidney injury and predict benefit from revascularization in ARVD. This noninvasive imaging technique may be useful for identification of patients likely to improve renal function after revascularization.

Funding: NIDDK Support



A: Representative ADC maps derived and quantification of baseline and 3 month ADC values in ARVD patients treated with MT or MT+PTRA. **B:** In PTRA-treated (but not in MT-treated) patients, ADC values correlated directly with delta GFR. *p<0.05 vs. MT; †p<0.05 vs. Baseline

FR-PO215

Gene Expression Analysis of Active and Chronic Renal Lesions in IgA Nephropathy Diagnosed Using the MEST-C Classification: A Multicenter Study Sharon N. Cox,[2,1] Claudia Curci,[2,1] Grazia Serino,[3,2] M. Rossini,[4] Mario Bonomini,[5] Vittorio Sirolli,[7] Paolo Felaco,[6] Gianluigi Zaza,[8] Isabella Squarzoni,[9] Concetta Gangemi,[10] Francesco P. Schena.[2,1] *[1]Schena Foundation, Valenzano, Bari, Italy; [2]University of Bari, Bari, Italy; [3]IRCCS "S de Bellis", Castellana Grotte, Bari, Italy; [4]University of Bari, Department of Emergency and Organ Transplantation, Nephrology Unit, Bari, Italy; [5]University of Chieti, Chieti, Italy; [6]Clinical of Nephrology, University G.d'Annunzio Chieti, Francavilla al Mare, Italy; [7]clinical nephrology university of chieti, Chieti, Italy; [8]University of Verona, Verona, Italy; [9]Azienda Ospedaliera Universitaria Integrata Verona, Verona, Italy; [10]AOUI verona, Verona, Italy.*

Background: The diagnosis of idiopathic IgA Nephopathy (IgAN) is based on the "split system" where 4 types of renal lesions are scored: Mesangial hypercellularity (M 0-1), Endocapillary hypercellularity (E 0-1), Segmental glomerulosclerosis (S 0-1) and Tubular atrophy/interstitial fi brosis (T 0-2). Recently an extension of the MEST score has been suggested introducing crescents (C 0-2) in the split system because this lesion, together with E, are predictive of outcome (Trimarchi H et al KI, 2017). Aim of our study was to identify specific gene expression changes that characterize active renal lesions (E and C) that may be more responsive to immunosuppressive therapy and chronic lesions (S and T).

Methods: Total RNA was extracted from archival FFPE renal tissue samples of 52 IgAN patients, 24 non-IgAN patients (Minimal change 12, membranous nephropathy 12) and 7 kidney living donors (controls). Genome-wide gene expression profiles were generated and Oneway ANOVA with tukeyHSD post hoc testing was used to identify specific transcripts associated with active and chronic lesions in IgAN. Real Time PCR was used for validation of the identified transcripts.

Results: We identified 391 genes exclusively modulated in IgAN biopsies with active lesions, 35 were down regulated and 355 were up-regulated. Some genes were specifically involved in glomerular injury. These genes belonged to renal cellular damage and immune system regulatory pathways. Moreover, we identified 194 genes that were differentially modulated in IgAN characterized by chronic lesions, 78 were down regulated and 116 were up-regulated. Candidate transcripts were validated by qRT-PCR in an extended cohort of IgAN biopsies.

Conclusions: Transcriptomics on FFPE renal biopsies integrates histomorphologic renal lesions. Our study identifies specific gene expression changes involved in active and chronic lesions at the time of renal biopsy. We are using system pharmacology on these genes to identify targeted molecules able to revert aberrant expression networks characterizing active and chronic lesions.

Funding: Government Support - Non-U.S.

FR-PO216

Inhibiting Na/K-ATPase Oxidant Amplification Loop Regulates Aging in C57B16 Old Mice Rebecca L. Klug,[4] Alexandra Nichols,[1] Brian J. Snoad,[3] Hari Vishal Lakhani,[3] Joseph I. Shapiro,[2] Komal Sodhi.[4] *[1]MUSOM, Huntington, WV; [2]Marshall University School of Medicine, Huntington, WV; [3]Marshall University, Huntington, WV; [4]Marshall University, Joan C. Edwards School of Medicine, Huntington, WV.*

Background: Aging, the inevitable and progressive decline of physiological integrity, manifests as: loss of cell division, oxidative stress, DNA damage, and senescence gene overexpression. Oxidant stress plays a role in the aging process, presumably in cellular and DNA damage. This contributes to impaired physiological function, disease development, and life span reduction. As we identified, the Na/K-ATPase amplifies oxidant signaling; we speculate a peptide inhibiting this pathway, pNaKtide, may be effective to regulate cellular senescence, thus delaying and/or reversing aging by attenuating oxidative stress.

Methods: C57Bl6 mice, young (6-8 weeks old, male) and old (17 weeks old, male) were fed normal chow diet or Western Diet (WD). They were randomly divided into 6 groups: (1) Young Control, (2) Young+pNaKtide (3) Old+Control, (4) Old+pNaKtide (5) Old+WD, (6) Old+WD+pNaKtide. After 8 weeks of control or WD diet respectively, groups 2, 4 and 6 were injected with pNaKtide for 8 weeks, (intraperitoneal dose of 25-mg/kg-body weight every 7 days).

Results: Histological analysis of liver shows increased steatosis and fibrosis with age and more so with WD, this decreased with pNaKtide treatment. Histological analysis of kidney shows increased fat infiltration and sclerosis with age and WD, which decreased with pNaKtide treatment. TUNEL assay of liver and kidney indicated more DNA damage with age and WD, this significantly decreased with pNaKtide treatment ($p \leq 0.05$). Indicative of oxidative stress, carbonylation of the Na/K-ATPase α1-subunit, activation of p-Src and TBARS were significantly elevated in old and WD liver and kidney compared to those given pNaKtide treatment ($p \leq 0.05$). RT-PCR of senescence genes: p21, Apo lipoprotein J, Collagenase 1, fibronectin, and MMP-9 were significantly increased in hepatic and renal tissue with age and WD compared to those given pNaKtide treatment ($p \leq 0.05$).

Conclusions: Our study demonstrates that Na/K-ATPase regulates aging and pNaKtide significantly alleviates genetic and phenotypic attributes of aging. pNaKtide holds potential as a novel drug for treating cellular damage that contributes to manifestations of aging and WD.

Funding: Other NIH Support - This work was supported by National Institutes of Health Grants HL109015 (to J.I.S. and Z.X.), HL071556 and HL105649 (to J.I.S.), and HL55601 and HL34300 (to N.G.A.), Commercial Support - by the Brickstreet Foundation (to J.I.S. and N.G.A.) and by the Huntington Foundation, Inc.

FR-PO217

D-Serine, a Novel Uremic Toxin, Induces Senescence in Human Renal Tubular Cells via GCN2 Activation Akira Okada,[1] Tzu-Ming Jao,[2] Hiroshi Maekawa,[1] Yu Ishimoto,[1] Takahisa Kawakami,[1] Masaomi Nangaku,[1] Reiko Inagi.[2] *[1]Division of Nephrology and Endocrinology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan; [2]Division of CKD Pathophysiology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan.*

Background: A recent metabolomic analysis revealed the change in profile of metabolites, including uremic toxins, in plasma or urine from CKD patients. Accumulation of D-serine, an enantiomer of L-serine, in plasma is associated with faster progression of renal dysfunction in CKD patients. We investigated whether chirality of the amino acid plays a crucial role in the pathogenesis of CKD.

Methods: To address the effect of D-serine on tubules, human proximal tubular cell line, HK-2, and primary culture of human renal tubular cells, NHREC, were treated with D- or L-serine for 48 hr and the cell damages were evaluated by cell proliferation (MTS assay and cell count), cell cycle status (PI and Phospho-Histone H3 staining), senescence (p21, p16, γH2AX, and SA-βG), senescence-associated secretory phenotype [SASP: pro-inflammatory cytokines (IL-6 and IL-8)] and apoptosis (Annexin V staining and caspase 3/7 activity). To find out the molecular mechanism of the cell damages by D-serine, we assessed the status of amino acid-mediated signaling (integrated stress response: GCN2, ATF4, and CHOP) and L-serine synthesis pathway (PHGDH and PSAT1), To confirm signal transduction, siRNAs of integrated stress response molecules were used.

Results: D-serine, but not L-serine, markedly induced cellular senescence and apoptosis both in HK-2 and NHREC. Such tubular damage by D-serine was accompanied by G2/M cell cycle arrest and induction of SASP, including pro-inflammatory factors, contributing to tubulointerstitial fibrosis. Importantly, we found that integrated stress response mediated by GCN2-ATF4-CHOP pathway played a central role in D-serine-induced cell toxicity: knockdown of GCN2 ameliorated D-serine-induced tubular cell senescence, suggesting CKD progression and kidney aging by D-serine. Furthermore, D-serine upregulated the L-serine synthesis pathway, possibly as a counteracting mechanism, and D-serine-induced tubular toxicity is counteracted by L-serine, suggest that the proportion of D-/L-serine is critical for D-serine toxicity to tubular cells.

Conclusions: This study unveils a pathogenic role of the chiral amino acid and molecular mechanisms underlying D-serine-induced tubular damage, such as senescence with SASP, in CKD pathogenesis.

Funding: Government Support - Non-U.S.

FR-PO218

TAM Receptor TYRO3 Plays a Role in Pococyte Injury liwen ?. zhang, Zhao-hong Chen, Qing Hou, Ling Wang, Zhi Li, Wei-song Qin, Zhi-Hong Liu. *National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing China, Nanjing, China.*

Background: Podocyte injury plays a critical role in the development and progress of diabetic nephropathy (DN). Analyzing transcriptional profile of renal biopsy from diabetic nephropathy patients and control donors identified TYRO3, a member transmembrane receptor kinase receptor (TAM), as one of the main hub genes that are strongly associated with proteinuria in type 2 DN patients. TAM receptors have been shown to play roles in immune homeostasis, neuronal differentiation and survival.

Methods: Colocalization studies detected TYRO3 protein along with the podocyte marker synaptopodin in glomeruli.

Results: No colocalization was observed between TYRO3 and endothelial marker (CD31). IHC demonstrated TYRO3 and phosphorylated TYRO3 were downregulated in the glomeruli from DN patients and db/db mice. Knockdown of tyro3 by ATG or splicing morpholino-oligos (MO) in zebrafish larvae exhibited edema (36.23%) and foot-process effacement. Permeability studies in these zebrafish morphants demonstrated disruption of the selective glomerular permeability filter. Rescue experiment showed that zebrafish co-injected with synthetic zebrafish tyro3 mRNA and MO were morphologically normal in terms of edema and foot process. While, zebrafish injected with MO of mertk, another TAM member, didn't exhibit abnormal morphology. *in* vitro studies showed that podocyte express TYRO3 and its ligand GAS6. High-glucose downregulated TYRO3 mRNA and protein expression in podocytes. Moreover, depletion of TYRO3 expression with siRNAs induced and augmented high glucose induced podocytes apoptosis via PI3K/AKT /Bax/ Bcl-2 pathway.

Conclusions: Taken together, our findings demonstrated that TYRO3 is a novel protein that might play a crucial role in podocyte homeostasis via stabilizing PI3K-AKT signal pathway.

FR-PO219

Recognition of Apoptotic Cells by Viable Proximal Tubular Epithelial Cells (PTEC) Induces Death Receptor (DR)-Dependent PTEC Death: Dual Modes of PTEC Death Following Injury Michael E. Dietrich,[1,2] Lanfei Feng,[1,2] Joyce Rauch,[3] Jerrold S. Levine.[1,2] *[1]University of Illinois at Chicago, Chicago, IL; [2]Jesse Brown VAMC, Chicago, IL; [3]McGill University, Montreal, QC, Canada.*

Background: We have shown that mouse kidney PTEC have distinct non-competing receptors for apoptotic and necrotic targets. Recognition of apoptotic, but not necrotic, targets induces apoptotic death of PTEC responders. Here we study the role of DRs and their ligands (DR-L) in this process.

Methods: Responder cells were BU.MPT cells, a conditionally immortalized PTEC line. Target cells, induced to undergo apoptosis or necrosis, were homologous (BU.MPT) or heterologous (DO11.10 lymphocytes).

Results: Apoptotic target-induced death of PTEC responders is profound (~100% by 48-72 h) and, at least in part, DR-dependent, as shown by caspase-8 activation and augmented survival upon caspase-8 inhibition. To evaluate the role of DRs, we compared expression of DR3, DR5, and Fas in PTEC responders, exposed to dead targets. Expression fell into one of two patterns: (1) DR3: Responders at rest (i.e., not exposed to targets) lacked DR expression. 18 h after exposure to apoptotic (but not necrotic) targets, ~50% of responders newly expressed DR3. (2) Fas and DR5: Responders at rest expressed Fas and DR5 constitutively. 18 h after exposure to apoptotic (but not necrotic) targets, ~50% of responders had undetectable Fas and DR5. We next examined DR-shifted responders (i.e, with new DR3 expression, or lost Fas and DR5 expression). Consistent with apoptosis induction following exposure to apoptotic (but not necrotic) targets, DR-shifted PTEC responders of both patterns were smaller in size and positive for caspase-3 activation. Notably, quiescent PTEC do not express DR-L. However, after exposure to apoptotic (but not necrotic) targets, PTEC produced and secreted FasL and TRAIL. Pharmacologic inhibition of FasL and TRAIL augmented survival of apoptotic target-exposed PTEC.

Conclusions: Exposure of viable PTEC to apoptotic (but not necrotic) targets induces PTEC apoptosis via DR-dependent mechanisms. Expression of Fas and DR5 is constitutive, while expression of their ligands, FasL and TRAIL, is induced by apoptotic target recognition. We hypothesize that PTEC injury is characterized by two distinct waves of cell death. In the 1st wave, PTEC death is the direct result of injury. In the 2nd wave, PTEC death is independent of injury, and the result of receptor-mediated recognition of dead or dying PTEC.

FR-PO220

Activation of PPAR-γ Suppresses AngII Induced Proliferation of HBZY-1 Cell via the GPCR/Gαq/PLCβ4/TRPC Signaling Pathway Linting Wei,[2] Rongguo Fu,[1] Jiamei Lu.[3] *[1]Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; [2]Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; [3]Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.*

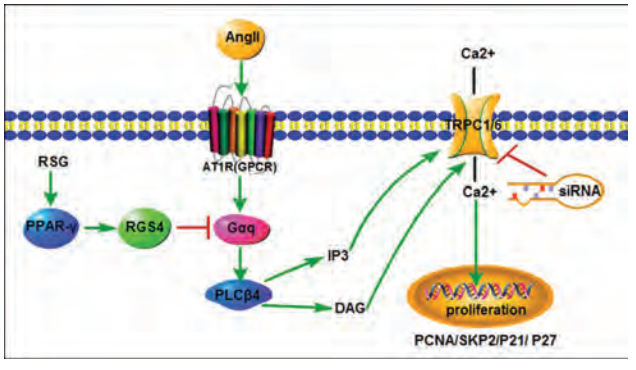
Background: Mesangial cell proliferation and ECM is the main pathological change commonly can be seen in CKD. TRPC and PPAR-γ can regulate cell proliferation and apoptosis. AngII can induce mesangial cell proliferation and affect TRPC expressions. However, the mechanism has not been well elucidated. This study was aimed to investigate the role of TRPC and effect of rosiglitazone (RSG) in the proliferation of HBZY-1 cell and its underlying mechanisms.

Methods: Immuofluoresence staining and qRT-PCR were performed to examine the expressions of TRPCs in HBZY-1. Gene expressions of TRPC, PPAR-γ, RGS4, GPCR/Gαq/PLCβ4/TRPC signaling pathway and downstream main proliferative molecules (PCNA, SKP2, P21 and P27) were detected by qRT-PCR and Western blotting. Additionally, changes in intracellular Ca^{2+} concentration were determined through Fluo-4 Ca^{2+} imaging and cell cycle conditions were examined by flow cytometry.

Results: Our results found that TRPC1and TRPC6 were at higher expression levels in HBZY-1. Following AngII stimulation, there were increasing expressions of TRPC1 and TRPC6, Ca^{2+} influx, elevated gene expressions of PCNA and SKP2, decresing expressions of P21 and P27 and declined G_0/G_1 percentage (NC vs AngII, $p<0.05$). While silencing the TRPC1and TRPC6 by RNA interference led to decreasing in Ca^{2+} influx, G_0/G_1 cell cycle arrest and attenuated cell proliferations ($p<0.05$). Notably, activated PPAR-γ by RSG up-regulated RGS4 (regulators of G protein signaling) expressions, which can interact with the Gαq family to inhibit Gαq-mediated signaling pathways. The results were similar to silencing the TRPC1and TRPC6 by RNA interference techniques ($p<0.05$). All these results indicate that RSG could inhibite HBZY-1 cell proliferation via AT1R/Gαq/PLCβ4/TRPC signaling pathways.

Conclusions: This study suggests that activation of PPAR-γ and down-regulation of TRPC might be promising therapeutic targets for the treatment of mesangial cell prolifrative glomerulonephritis.

Funding: Government Support - Non-U.S.



FR-PO221

Cytoprotective Role of Autophagy in Angiotensin II-Induced Podocyte Apoptosis Tae-Sun Ha. *Chungbuk National University College of Medicine, Cheongju-si, Republic of Korea.*

Background: Autophagy and apoptosis are two cellular processes through which injured and aging cells or organelles are eliminated. Angiotensin II (Ang II) induces podocyte injury resulting in apoptosis in vitro and in vivo. However, the relationship between autophagy and apoptosis in Ang II-induced podocyte injury is unknown and the role of Ang II-induced autophagy in podocyte survival or death remains unclear. We investigated the sequential relationship between autophagy and apoptosis in Ang II-induced podocytes as well as the role of PI3-kinase.

Methods: Mouse podocytes were incubated in media containing various concentrations of Ang II and at different incubation times. Cell survival/death-modifying reagents and Atg5 siRNA were applied. The changes of podocyte autophagy and apoptosis were observed by electron microscopy, confocal imaging, western blotting, TUNEL, and FACS assay according to the presence of Ang II.

Results: Ang II enhanced the podocyte expression of the autophagic proteins, LC3A/B-II and beclin-1, and also increased the number of autophagosomes compared with control cells at early phase of 12 hours in a dose-dependent manner. This pro-autophagic effect of Ang II was inhibited by pretreatment with 3-methyladenine (3-MA), a PI3-kinase class III inhibitor. Atg5 siRNA reduced LC3 puncta levels and increased the number of apoptotic podocytes over that observed with Ang II treatment at 12 hours. Thereafter, the Ang II-induced enhancement in autophagy decreased, whereas, podocyte apoptosis appeared later at 24 hours in concentration- and time-dependent manners in FACS and TUNEL assays. 3-MA and LY294002 further increased Ang II-induced podocyte apoptosis. Suppression of autophagy by Atg5 siRNA could induce podocyte apoptosis and further augment high-dose Ang II-induced podocyte apoptosis.

Conclusions: We suggest that Ang II induced autophagy in mouse podocytes prior to apoptosis as an early adaptive cytoprotective mechanism for podocyte survival after Ang II treatment and the imbalance between autophagy and apoptosis causes podocyte injury.

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FR-PO222

Forkhead Box O3 (FoxO3) Regulates Kidney Tubular Autophagy Following Urinary Tract Obstruction Ling Li, Ronald Zviti, Catherine Ha, Fangming Lin. *Department of Pediatrics, Columbia University College of Physicians & Surgeons, New York, NY.*

Background: Autophagy has been shown to be important for normal homeostasis and adaptation to stress in the kidney. Yet, molecular mechanisms regulating renal epithelial autophagy are not fully understood.

Methods: We explore the role of the stress-responsive transcription factor forkhead box O3 (FoxO3) in mediating injury-induced proximal tubular autophagy in mice with unilateral ureteral obstruction (UUO), which is a reproducible model of persistent tubular autophagy.

Results: We show that following UUO, FoxO3 is activated over basal level and displays nuclear expression in 34.0 ± 3.4% of proximal tubules at 3 days ($n=3$, $p<0.01$) and 45.5 ± 2.8% at 7 days ($n=3$, $p<0.05$) when the hypoxic tubules exhibit high levels of autophagy. Activation of FoxO3 by mutating its phosphorylation sites to enhance its nuclear expression induces profound autophagy in primary cultures of renal epithelial cells. Conversely, deleting FoxO3 in mice results in fewer numbers of autophagic cells in the proximal tubules and reduces the conversion of the key autophagy-associated protein LC3-I to LC3-II post-UUO. Interestingly, autophagic cells deficient in FoxO3 contain lower numbers of autophagic vesicles per cell upon stimulation with nutrient deprivation. Analysis of individual cells treated with various autophagic inhibitors to sequentially block the autophagic flux suggests that FoxO3 stimulates the formation of autophagosomes to increase autophagic capacity without significant effects on autophagosome-lysosome fusion or autolysosomal clearance. Furthermore, in kidneys with persistent UUO for 7 days, FoxO3 activation increases the expression of core autophagy-associated (Atg) proteins, including Ulk1, Beclin-1, Atg9A, Atg4B, and Bnip3, suggesting that FoxO3 may also function to replenish components of the autophagic machinery that would otherwise be consumed during sustained autophagy.

Conclusions: In summary, our findings indicate that FoxO3 activation can both induce and maintain autophagic activities in renal epithelial cells in mouse models of prolong tubular stress and injury.

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FR-PO223

The NRF2-Heme Oxygenase-1 System Modulates Autophagy and Inhibits High Glucose Induced Apoptosis in Renal Tubular Epithelial Cells Kyeong Min Kim, Young woong Song. *Eulji medical center, Daejeon, Republic of Korea.*

Background: Autophagy is a tightly regulated process in which endogenous cellular proteins aggregate is degraded by the lysosomal pathway. It's renoprotective role including those used for aging and acute kidney injury, has also been demonstrated. However, The role of autophagy in diabetic nephropathy remains a largely undetermined.

Methods: In present study, we evaluated the effects of high glucose concentrations on the induction of autophagy in the human renal tubular epithelial cell line, HK-2 cells. We also investigated the ability of Sulforaphane(SFN, nuclear factor E2-related factor 2 (Nrf2) inhibitor) to protect HK-2 cells against apoptosis induced by high glucose levels by targeting autophagy.

Results: The HK-2 cells stimulated with a high concentration of glucose for 72h exhibited an increased expression of the autophagic markers, LC3-II and Beclin 1. The level of LC3-II and Beclin 1 in cells treated with SFN was decreased compared to control cells. The level of Caspase-3 activated in tubule cells cultured in high glucose medium was also decreased. One important NRF2 target gene, Heme oxygenase-1(HO-1) is known as a key molecule of NRF2 protective function. To examine whether HO-1 can modulate autophagy and apoptosis in tubule cells like SFN, HK-2 cells cultured in 250 mM glucose medium for 1-2 days were treated with Adneovirus-HO-1 gene for 1 day. HO-1 transfection decreased the expression of Beclin1 and LC3-II associated with a decrease in the expression Caspase-3 with HG for 1-2days compared with mock-treated cells. Reactive Oxygen Species(ROS) are important inducers of autophagy and apoptosis. As expected, an increase of ROS was observed in HK-2 cells cultured in 250 mM glucose medium for 1-3 days. A decrease of ROS was observed in cells treated with SFN.

Conclusions: HO-1 and autophagy are induced after high glucose injury to overcome to oxidative stress and serve as adaptive responses to prevent cell death. NRF2-HO-1 overexpression is able to limit ROS generation and oxidative stress during high glucose injury and thereby significantly inhibiting autophagy and apoptosis. This study is the first study to show the effect of NRF2-HO-1 system on high glucose induced autophagy and apoptosis of tubule cells. Targeting NRF2-HO-1 as a modulator of autophagy may result in novel therapeutic intervention in diabetic nephropathy.

FR-PO224

Unfolded Protein Responses Potentiated Uremic Sarcopenia through Perturbation of Myoblast Differentiation Jia-Rong Jheng,[1,3] Yuan-Siao Chen,[1] Chih-Kang Chiang,[1,2] Shing-Hwa Liu.[1] *[1]Graduate Institute of Toxicology, National Taiwan University, College of Medicine, Taipei, Taiwan; [2]Department of Integrated Diagnostics & Therapeutics, National Taiwan University Hospital, Taipei, Taiwan; [3]Department of Internal Medicine, National Taiwan University, College of Medicine, Taipei, Taiwan.*

Background: Sarcopenia is the age-related degeneration characterized with the decline of skeletal muscle mass, strength, and mobility. The imbalance of protein synthesis and degradation which jeopardizes immune, hormone regulation, and muscle-motor neuron connection is the main cause of sarcopenia. There are limited knowledge regarding molecular mechanism of sarcopeia. As the endoplasmic reticulum (ER) is the control center of the protein syntheses and degradation, we hypothesized that ER stress and unfolded protein response (UPR) are important causes of sarcopenia. Understanding the sarcopenia molecular mechanisms may benefit the therapeutic diagnosis and treatment in the future.

Methods: Mouse myoblast C2C12 cells are exposed to designated time and concentration of indoxyl sulfate (IS). The proliferation, differentiation, and myotube atrophy are examined. The protein and mRNA expression of IS treated C2C12 cells are inspected to distinguish the role of ER stress and oxidative stress underlying the sarcopenia.

Results: IS inhibits myoblast differentiation. We demonstrate that number of multi-nuclei myotube decreased, the differentiation markers including myoD, myoG, and myosin heavy chain are also suppressed. IS inhibits myoblast proliferation and induces the myotubular atrophy marker atrogin 1 protein expression. IS stimulates eIF2α phosphorylation and XBP1 mRNA splicing in UPR. Interestingly, the oxidative stress is related to eIF2α phosphorylation but not XBP1 mRNA splicing. The eIF2α phosphorylation triggered by IS reduces myoD, myoG and myosin heavy chain protein expression, which is the antimyogenic modulation on the early differentiation event. The XBP1 mRNA splicing induced by IS, however, is considered the late differentiation event which is a promyogenic modulation— an adaptive response.

Conclusions: Our studies indicated that the ER stress and UPR modulation are critical both in sarcopenia and the CKD uremic toxin accumulation model. We believe that UPR-related molecules showed great potential in clinical application.

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FR-PO225

Darunavir Protects HIV-Transgenic Mice against Kidney Injury via HIV-Independent Mechanisms Xiaobo Gao, Alan Rosales, Heidi Karttunen, Michael J. Ross. *Albert Einstein College of Medicine/ Montefiore Medical Center, Hastings-on-Hudson, NY.*

Background: HIV-associated nephrology (HIVAN) is characterized by severe proteinuria and progressive CKD and is caused by infection of renal epithelial cells, though active viral replication is not necessary to induce disease in animal and in vitro models. Antiretroviral therapy (ART) markedly reduces the risk of progression to ESRD without eradicating HIV in the kidney and the mechanism(s) by which ART protects kidneys from HIVAN is poorly understood.

Methods: We studied HIV-transgenic mice, which develop a HIVAN phenotype. Since the transgene in these mice does not encode HIV Reverse Transcriptase (RT) or Protease we used these mice to determine if the HIV protease inhibitor darunavir (DRV) and/or RT inhibitor zidovidine (AZT) protect against HIVAN independent of effects on RT or HIV protease. Mice were treated for 4 weeks by daily oral gavage in 4 groups: DRV (100mg/kg), AZT (50mg/kg), DRV+AZT, or control.

Results: DRV and DRV+AZT, but not AZT alone reduced urinary albumin:creatinine ratio and histologic glomerular and tubulointerstitial injury. DRV and DRV+AZT, but not AZT also markedly reduced expression of the proliferation marker Ki67 in tubular cells, prevented loss of synaptopodin expression in podocytes, and reduced phosphorylation of ERK1,2, and Stat3, which are important mediators of HIV-induced kidney injury. To further examine the mechanism of DRV-induced protection, we studied the effects of DRV renal tubular epithelial cells (RTEC) transduced with gag/pol-deleted HIV lentivirus (lacking HIV protease and RT), HIV Vpr-expressing lentivirus, or control lentivirus. DRV significantly attenuated HIV and Vpr-induced activation of Stat3, ERK, and Src and decreased HIV and Vpr-induced expression of IL-6 and IL-8, which are key inflammatory mediators in HIVAN.

Conclusions: These data demonstrate that DRV but not AZT protects against HIV-induced renal injury via mechanisms that are at least partly independent of suppression of HIV replication and HIV Protease. Additional studies are needed to identify the non-HIV molecular targets of DRV which mediate these effects and to determine the efficacy in non-HIV related kidney diseases.

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FR-PO226

GLCCI1 as a Novel Therapeutic Target of Glucocorticoid-Resistant T-Cells Yukino Nishibori, Zentaro Kiuchi, Ichiro Hada, Kunimasa Yan. *Kyorin University School of Medicine, Tokyo, Japan.*

Background: Activation and dysfunction of T-cells underlie the pathogenesis of glomerular diseases including idiopathic nephrotic syndrome. Glucocorticoid (GC) is one of the major classes of drugs that target such T-cells; however, GC-dependence and resistance during the treatment are big issues to be solved. We previously reported that GC-induced transcript 1 (GLCCI1) of thymic T-cells is up-regulated through a GC-GC receptor cascade, bound to dynein-LC8, and phosphorylated by protein kinase-1, and its up-regulation is observed with the activation of a GC-induced apoptotic pathway (ASN meeting 2013). The aim of the present study is to determine the effect of GLCCI1 on T-cell apoptosis induced by GC.

Methods: Using a mouse thymocyte cell line, the GLCCI1 gene was knocked down by lentiviral sh-RNA delivery. Transgenic mice conditionally expressing human GLCCI1 were established using G57BL/6J mice and the tamoxifen-inducible CreER-LoxP system (*glcci1*-TG/Cre mice). Protein samples from thymocyte cell lines and thymi from mice were subjected to immunoblotting for caspases and Bim to compare the activation of apoptotic signaling. Thymi were analyzed to compare cell number, cell population and organ size between transgenic and non-transgenic mice (*glcci1*-TG mice).

Results: Immunoblotting for caspases and Bim in the samples from thymocyte cell lines revealed that knock-down of GLCCI1 activated the apoptotic pathway. The size of thymi was significantly larger in *glcci1*-TG/Cre mice compared to *glcci1*-TG mice. Cell number of thymi was increased in *glcci1*-TG/Cre mice compared to that in *glcci1*-TG mice, whereas there was no significant change in the ratio of T-cell subpopulations between these mice. Finally, immunoblotting for caspases and Bim revealed an apparent reduction of apoptotic signaling in thymi of *glcci1*-TG/Cre mice compared to *glcci1*-TG mice.

Conclusions: Although GC is known to cause T-cell death, the results of the present study indicate that GC-induced up-regulation of GLCCI1 limits apoptosis. Therefore, GLCCI1 may be a novel therapeutic target to overcome GC dependence and resistance.

FR-PO227

MicroRNA-21 Participates in IgA Nephropathy by Driving T Helper Cell Polarization Meng Sijun,[1] Hong Zhang,[2] Li Zhu.[3] *[1]Peking university first hospital, Beijing, China; [2]Peking University First Hospital, Beijing, China; [3]Renal Division, Peking University First Hospital, Beijing, China.*

Background: Previous studies revealed abnormal lymphocytes subsets in IgA nephropathy (IgAN). Recently, emerging studies indicate that miR-21 alters the balance of T helper cells differentiation and function. Here we explored the participation of miR-21 in IgAN, especially focused on T helper cell polarization.

Methods: Totally, 38 IgAN patients and 35 healthy controls (HC) were enrolled. Firstly, miRNAs and mRNA profiles in PBMC were determined by next-generation sequencing and gene expression array. Then, above identified miRNA were tested in both CD19+ B cells and CD3+ T cells. After the confirmation of differently expressed miRNA, expression of the miRNA target genes were further verified using real-time PCR. Meanwhile, T helper cells subgroups (Th1, Th2 and Th17), as well as plasma IgA1 and galactose deficient IgA1 (Gd-IgA1) levels were detected by FC and ELISA.

Results: MiR-21 showed highest level among 22 differently expressed miRNAs between IgANs and HCs. Through combined analysis of miRNA and mRNA profile data, SPRY1, SPRY2, FASLG were chosen as target genes for miR-21, for their negative correlation with miR-21 and bearing target sequence of miR-21. Next, we found that miR-21 levels in IgAN were only higher in CD3+ T cells (9.3±7.3 vs 4.0±3.4, p=0.02), but not CD19+ B cells. Accordingly, the mRNA levels of SPRY1, SPRY2, FASLG from CD3+ T cells were lower in IgAN than in HC (1.5±1. 3 vs 2.9±1.6, p<0.01; 1.2±1.2 vs 2.5±2.2, p<0.01; 0.9±0.6 vs 1.6±1.1, p<0.01). And miR-21 showed negative correlation with SPRY1 (r=-0.37, p<0. 01), while similar trend of correlation were observed to SPRY2 (r=-0.33, p=0.05) and FASLG (r=-0.31, p=0.07). FC analysis revealed elevated Th17 cells in IgAN than in HC (15.0±4.5 vs 12.6±1.8, p=0.04). Moreover, negative correlations were found between Th17 cells and SPRY1 (r=-0.33, p=0.04), SPRY2 (r=-0.36, p=0.03), FASLG;(r=-0.47, p<0.01). And in our recruited IgAN, the proportion of Th17 cells only showed a trend of positive correlation with plasma IgA1 (r=0.3, p=0.06), but not Gd-IgA1.

Conclusions: Our results showed higher miR-21 levels in IgAN, which inhibited the expression of *SPRY1, SPRY2, FASLG*, and thereby accelerated Th17 polarization.

Funding: Government Support - Non-U.S.

FR-PO228

Effect of Huaier on the Proliferation of Mesangial Cells in Anti-Thy-1 Nephritis Xiangmei Chen. *Department of Nephrology, Chinese PLA General Hospital, Beijing, China.*

Background: Mesangial proliferative glomerulonephritis (MsPGN) is one of the common kidney diseases. In this study, we investigated whether aqueous extract of Trametes robiniophila murr (Huaier) could suppress mesangial cell proliferation in rat cells treated with platelet-derived growth factor (PDGF)-BB and in rat model of anti-Thy-1 mesangial proliferative glomerulonephritis, and further explored the possible mechanisms of its antiproliferation effects.

Methods: In Vivo: Thirty Wistar rats were randomly divided into five groups: (1) Sham surgery (Sham); (2) anti-Thy-1 nephritis model (Thy-1); (3) anti-Thy-1 nephritis model + low-dose of Huaier (HRL); (4) anti-Thy-1 nephritis model + medium-dose of Huaier (HRM); (5) anti-Thy-1 nephritis model + high-dose of Huaier (HRH). Two weeks after drug treatment, urinary proteins were quantified and renal pathological changes were thoroughly examined. Meanwhile, the expression levels of Mxi-1 and PCNA in isolated glomeruli were also tested. In Vitro: Rat mesangial cell viability was measured by CCK8. DNA synthesis and cell proliferation evaluated by with 5-ethynyl-2'-deoxyuridine(Edu) Assay. The distribution of cell cycle, PI-Annexin-V staining was analyzed by flow cytometry, and western blot were used to test the cell cycle pathways.

Results: Huaier diminished the proliferative damages and urinary protein secretion in Thy-1 rats. PCNA was downregulated, whereas Mxi-1 was upregulated in the isolated glomeruli of Huaier-treated groups compared with the Thy-1 group. Huaier inhibited PDGF-BB–stimulated proliferation of rat mesangial cells in a time- and dose-dependent manner (50% inhibitory concentration = 6.19 mg/mL) and induced G2 cell-cycle arrest. Cell-cycle pathway proteins were downregulated, whereas Mxi-1 was upregulated in Huaier-treated mesangial cells compared with PDGF-BB–stimulated cells.

Conclusions: Huaier reduces urinary protein excretion and relieves hyperplasia in mesangial cells in anti-Thy-1 MsPGN as well as inhibits PDGF-BB–stimulated proliferation and DNA synthesis of rat mesangial cells *in vitro*, suggesting its novel therapeutic potential in MsPGN.

Funding: Government Support - Non-U.S.

FR-PO229

Kidney Organoids Generated from Bone Marrow-Derived Mesenchymal Stem Cells Xiangmei Chen. *Chinese PLA General Hospital, Beijing, China.*

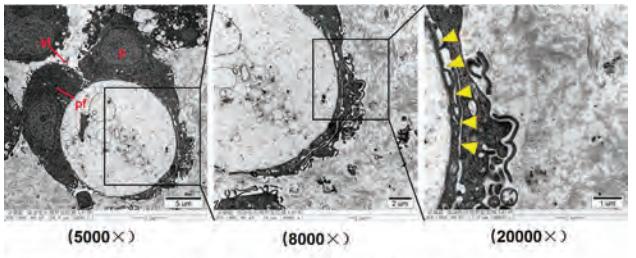
Background: Via the directed differentiation of stem cells, progenitors can be induced to both collecting duct and nephrons. The human kidney originates from intermediate mesoderm. Cells cephalad migrate from the primitive streak (presomitic mesoderm) to form the intermediated mesoderm. The intermediate mesoderm increases the number of key renal progenitor cells, as well as the ureteral epithelium and the metanephric mesenchyme, which respectively form the collecting ducts and nephrons. According to this theory, we have used bone marrow-derived mesenchymal stem cells (BM-MSCs) to differentiate into the kidney organoids by each other.

Methods: 1) By simulating the regulation of CHIR99021-FGF9 cytokines, and controlling the ratio of the formation of the ureteral epithelium and the metanephric mesenchyme, the kidney organoids were constructed by MSCs. 2) The kidney specific markers in the kidney organoids were detected by immunofluorescence staining. 3)The electron microscope was used to observe the structure of the organoids.

Results: 1) Using MSCs to differentiate into the kidney organoids through the regulation of cytokines. 2) Within these organoids, a single renal unit is divided into distal tubules, proximal tubules and glomeruli, which contains podocytes and blood vessels.

Conclusions: Such kidney organoids generated from MSCs represent powerful models of the human organ for future applications, including nephrotoxicity screening, disease modelling and as a source of cells for therapy.

Funding: Government Support - Non-U.S.



TEM images of avascular glomeruli showing podocytes surrounding a basement membrane (yellow arrowheads). Podocytes (p) with characteristic large nuclei and primary (pf) and secondary foot (sf) processes.

FR-PO230

CRISPR-Cas9-Induced Expression of Endogenous APOL1-G0 Reduced Cytotoxicity of Renal Risk Variant APOL1-G1 Opeyemi A. Olabisi,[3,4] Savannah Moore,[2,4] Martin R. Pollak.[1,4] *[1]Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA; [2]Massachusetts General Hospital, Brookline, MA; [3]Medicine, Massachusetts General Hospital, Boston, MA; [4]Harvard Medical School, Boston, MA.*

Background: Two protein coding mutations in the APOL1 gene account for much of the excess risk of non-diabetic end stage kidney disease (ESRD) among individuals of recent African Ancestry. These 2 common mutations (named G1- missense mutation, and G2- 2 amino acid deletion), collectively referred to as renal risk variant (RRV) APOL1 increase the risk of FSGS, HIVAN and hypertension-associated ESRD. The pattern of inheritance of APOL1-nephropathy is recessive--the disease is most consistently seen in African Americans with 2 copies of RRV APOL1 relative to those with zero or 1 copy of the risk allele. Yet, strong evidence suggests that cytoxicity of RRV APOL1 is due to gain of function. Expression of both G1 or G2 APOL1 result in toxicity in HEK-293 cells, human and mouse podocytes. We predict that induced cellular expression of wildtype APOL1 (G0) would compete with and reduce cytotoxicity of RRV APOL1 in HEK-293 cells.

Methods: We generated HEK-293 cell line that stably express APOL1-G1 in the presence of exogenous tetracycline. Transient transfection of these stable HEK-293 cells with CRISPR-transcription activator complex(dCas9-Vp64, p65-HSF1, and guide RNA specific for APOL1 promoter) induced robust expression of endogenous APOL1-G0. We then measured cytotoxicity of APOL1-G1 in the presence or abscence of these induced APOL1-G0.

Results: In the presence of APOL1-G0, the cytotoxicity of APOL1-G1 is significantly reduced up to 50%.

Conclusions: This result suggests that the cytoxicity of renal risk variants APOL1-G1 could be competitively be reduced by wild type APOL1-G0. This may explain in part why the risk of APOL1-nephropathy is negligible among individuals who carry at least one copy of wild type APOL1-G0, but high among individuals with 2 copies of RRV. Also, this finding suggests that differential upregulation of APOL1-G0 or downregulation of RRV APOL1 in podocytes may be a useful have therapeutic intervention.

Funding: Private Foundation Support

FR-PO231

Apolipoprotein L-1 and the Wound Healing Pathway: A Fight for Survival Joseph A. Giovinazzo,[1,2] Russell P. Thomson,[1,2] Anibelky Almanzar,[1,2] Simranjit Singh,[3] Ji Won Kang,[1,2] Jayne Raper.[1,2] *[1]City University of New york, New York, NY; [2]Hunter College, New York, NY; [3]NYU Medical Center, New York, NY.*

Background: APOL1 is an innate immunity protein that forms pores in trypanosomes. Variants of APOL1 have been linked to kidney disease, yet the mechanism responsible remains controversial. We tested the hypothesis that APOL1 toxicity is cell intrinsic and dependent upon secretion via the Golgi. Along the secretory pathway, APOL1 is acidified and then neutralized upon delivery to the plasma membrane, wherein the cation selective pore initiates wound repair via the influx of Ca^{2+}.

Methods: HEK293 cells were transfected with APOL1 and its variants, including deletion of the signal peptide. 24-48h later cell toxicity and viability were measured. Treatment with ammonium chloride was performed 2h prior to transfection. Recombinant APOL1 was purified from *E. coli* and reconstituted in planar lipid bilayers to measure ion channel conductivity and selectivity. HEK293 cells that stably express APOL1 were generated using the FlpIn recombinase system. The cells were transfected with the fluorescent calcium reporter gCAMP6f. Expression of APOL1 was induced at several timepoints and then read in a fluorescent plate reader. Activity of β-hexosaminidase (β-hex) was assayed in the supernatant of transfected cells at various timepoints after APOL1 expression.

Results: Deletion of the signal peptide led to a significant reduction of toxicity across all variants. Pre-treatment of cells with ammonium chloride reduced the toxicity of APOL1 by 50%. In planar lipid bilayers, rAPOL1 of all three major variants allowed for the passage of Ca^{2+}. In stably transfected cells, induction of APOL1 expression lead to an increase in cytoplasmic Ca^{2+}. In a cell, this would cause lysosomes to fuse with the plasma membrane to initiate removal of the wound and repair the membrane. Indeed, release of the lysosomal enzyme β-hexosaminidase, a marker of wound-healing, was detected prior to cell death.

Conclusions: These data support a model of APOL1 mediated cell death that requires acidic activation along the secretory pathway prior to forming pores at the plasma membrane. Increases in Ca^{2+} flux and the release of lysosomal enzymes prior to cell death indicate activation of the wound healing pathway by APOL1 pore-formation. Maintaining the balance between secretion and excessive pore-formation of APOL1 and the ability to remove and repair the wounds are key to cell survival.

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FR-PO232

APOL1 Preserves Podocyte Differentiation in High Glucose Milieu through Down-Regulation of MicroRNA193a Abheepsa Mishra,[4] Kamesh R. Ayasolla,[1] Xiqian Lan,[1] Vinod Kumar,[7] Rukhsana Aslam,[2] Ali Hussain,[3] Seyedeh Shadafarin Marashi Shoshtari,[6] Manali Bhooplapur,[2] Sheetal Chowdhary,[3] Ashwani Malhotra,[8] Pravin C. Singhal.[5] *[1]Feinstein Institute for Medical Research, Great Neck, NY; [2]Feinstein Institute for medical research, Glenoaks, NY; [3]Feinstein Institute of Medical Research, New York, NY; [4]Feinstein Institute of Medical Research, Northwell Health, MANHASSET, NY; [5]North Shore LIJ Health System, Great Neck, NY; [6]The Feinstein Institute for Medical Research, Manhasset, NY; [7]Immunolgy and Inflammation, Fienstine Institute for Medical Research, New York, NY; [8]Immunolgy and Inflammation, Feinstein Inst.Med research and NSLIJ, Manhasset, NY.*

Background: Dibetic podocytopathy is characterized by significant proteinuria an indication of loss of integrity of glomerular filatration barrier. High glucose milieu has been demonstrated to promote dedifferentiation of podocytes (PDs) contributing to the loss of integrity of glomerular filtration barrier; however, the involved mechanism is far from clear. APOL1 is expressed in kidneys of certain primates including humans. APOL1 risk alleles (G1 and G2) have been reported to be podocytotoxic, however, the role of APOL1G0 (wild-type) is far from clear. We hypothesize that APOL1 facilitates preservation of the molecular integrity of podocytes in adverse milieus such as high glucose through down-regulation of microRNA (miR) 193a.

Methods: To evaluate the effect of high glucose milieu, differentiated human podocytes (DIF-PDs, after incubation for 10 days at 37°C) were incubated in media containing different concentrations of glucose (5, 15, 25, 30, and 35 mM) for 48 hours. To evaluate the role of miR193a, DIF-PDs were incubated in media containing normal glucose (5mM, NGM), high glucose (30 mM) with/without miR193a inhibitor (25 nm) for 48 hours. To establish a causal relationship, DIF-PDs were transfected with either control or APOL1/miR193a siRNA followed by incubation in either normal (5 mM, NGM) or high glucose (HGM) media for 48 hours. To confirm a relationship, DIF-PDs were transfected with either vector or APOL1 lentivirus and then incubated in media containing either normal or high glucose for 48 hours. Proteins and RNA were extracted.

Protein blots were probed for APOL1, WT1, podocalyxin, nephrin and reprobed for actin. RNAs were assayed for miR193a.

Results: HGM down regulated WT1 and nephrin (2.5 fold) expressions but increased (3-fold) miR193a levels in PDs. HGM down regulated PD expression of APOL1 in a dose-dependent manner. PDs knocked down for APOL1 displayed enhanced (2.2 fold) levels of miR193a, whereas, PDs knocked down for miR193a displayed increased (2.5 fold) expression of APOL1. Over expression of APOL1 in PDs preserved podocyte molecular phenotype in HGM.

Conclusions: High glucose dedifferentiates PDs through down-regulation of APOL1; however, overexpression of APOL1 preserves PDs molecular integrity.

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FR-PO233

HIV and Interferon (IFN)-y Facilitate Parietal Epithelial Cell Transition through Induction of APOL1 Vinod Kumar,[4] Xiqian Lan,[1] Rukhsana Aslam,[2] Ali Hussain,[3] Seyedeh Shadafarin Marashi Shoshtari,[7] Manali Bhooplapur,[2] Sheetal Chowdhary,[3] Catherine Meyer-Schwesinger,[8] Ashwani Malhotra,[9] Karl Skorecki,[6] Pravin C. Singhal.[5] *[1]Feinstein Institute for Medical Research, Great Neck, NY; [2]Feinstein Institute for medical research, Glenoaks, NY; [3]Feinstein Institute of Medical Research, New York, NY; [4]Immunolgy and Inflammation, Fienstine Institute for Medical Research, New York, NY; [5]North Shore LIJ Health System, Great Neck, NY; [6]Rambam Health Care Campus, Haifa, Israel; [7]The Feinstein Institute for Medical Research, Manhasset, NY; [8]University of Hamburg, Hamburg, Germany; [9]Immunolgy and Inflammation, Feinstein Inst.Med research and NSLIJ, Manhasset, NY.*

Background: Genetic epidemiology indicated that HIV-infected patients carrying APOL1 risk alleles with African ancestry carry a risk of developing HIV-associated neprhopathy at 10 times higher rates when compared to patients carrying APOL1 (wild-type). Podocytes (PDs) express APOL1 constitutively and this expression is enhanced by HIV and IFN-y. However, parietal epithelial cells (PECs) do not express APOL1. Both PDs and PECs are evolved from the same mesenchymal cells during embryogenesis. Since APOL1 expression seems to be a differentiating phenotypic molecule between PECs and PDs, we wished to consider its potential role in distinct cellular phenotype determination. We hypothesize that HIV could be facilitating PECs transition to PDs through the induction of APOL1.

Methods: Immortalized PECs proliferate at 33°C and differentiate (transit) to podocytes at 37°C. PECs were transduced with either vector (PECV) or HIV (NL4-3, PECHIV) and incubated for 48 hours at 33°C (n=4). In another set of experiments, PECs were incubated in media containing different concentrations of IFN-Y (0, 5, 10, 15, 20 nM) for 48 hours at 33° (n=4). To establish a causal relationship, PECV and PECHIV were transfected with either control or APOL1 siRNA (n=4). To confirm the role in PECs transition, mouse (M) PDs, which do not express APOL1, were transduced with either vector or APOL1 lentivirus (n=4). Proteins and RNAs were extracted. Protein blots were probed for APOL1, markers of PECs (PAX2, and Claudin 1) and PDs (WT1, nephrin, podocalyxin, and podocin) and reprobed for GAPDH. cDNAs were amplified for APOL1, WT1, podocalyxin, nephrin, and podocin.

Results: HIV induced APOL1 expression in PECs. IFN-γ also induced APOL1 expression in PECs in a dose dependent manner. PECHIV/IFN-γ-treated PECs displayed induction of nephrin, enhanced expression of WT1 (2.5-fold) and podocalyxin (3-fold) but down regulation of PAX2 (2-fold). PECHIVs with knockout APOL1 displayed down regulation of WT1, podocalyxin, and podocin; on the other hand, mouse podocytes (MPDs) expressing APOL1 displayed enhanced expression of WT1, podocalyxin, and podocin when compared to MPDVector.

Conclusions: HIV and IFN-y stimulate PECs transition through induction of APOL1.

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FR-PO234

APOL1 Provides Podocyte Protection against Apoptosis through Down Regulation of MicroRNA (miR)193a in Adverse Milieus Vinod Kumar,[1] Xiqian Lan,[1] Rukhsana Aslam,[3] Ali Hussain,[4] Seyedeh Shadafarin Marashi Shoshtari,[5] Catherine Meyer-Schwesinger,[6] Ashwani Malhotra,[1] Karl Skorecki,[2] Pravin C. Singhal.[1] *[1]Feinstein Institute for Medical Research, Great Neck, NY; [2]Rambam Health Care Campus, Haifa, Israel; [3]Feinstein Institute for medical research, Glenoaks, NY; [4]Feinstein Institute of Medical Research, New York, NY; [5]The Feinstein Institute for Medical Research, Manhasset, NY; [6]University of Hamburg, Hamburg, Germany.*

Background: Adverse milieus such as high glucose and puromycin aminonucleoside (PAN) have been reported to induce podocyte (PD) injury both *in vitro* and *in vivo* studies. APOL1, expressed intracellularly is a minor component of circulating lipid-rich trypanolytic multiprotein complexes in certain primate species including humans. Genetic epidemiologic studies suggest that humans carrying APOL1 wild-type (G0) are less likely to develop chronic kidney disease when compared to humans carrying APOL1 risk alleles (APOL1G1 and G2). We hypothesize that PD expression of APOL1G0 provides protection against apoptosis in adverse milieus.

Methods: Human podocytes (PDs) were transduced with either vector (PDV) or APOL1G0 (wild- type, PDG0). PDVs and PDG0 were treated with different concentrations of glucose (5, 15, 30, and 35 mM) or PAN (0, 5, 10, 25, 50, and 100 nM) for 48 hours (n=4); in other set of experiments, PDs were incubated in media containing either buffer, high glucose (30 mM), PAN (50 nM) with or without interferon-γ (IFN-γ; 20 nM, an APOL1 inducer) for 48 hours (n=4); PDV were incubated in media containing, high glucose (30 mM), PAN (50 nM), with or without miR193a inhibitor (25 nM) for 48 hours (n=4). At the end of incubation periods, cells were evaluated for reactive oxygen species (ROS) generation and apoptosis. Proteins and RNAs were extracted from cells treated under similar conditions. Protein blots were probed for APOL1, and caspase-3; RNAs were assayed for miR193a.

Results: PDVs displayed higher generation of ROS and a greater number of apoptotic cells when compared to PDG0, both in high glucose and PAN milieus. PDG0 displayed enhanced expression of APOL1 but decreased miR193a levels when compared to PDVs. Both high glucose and PAN treated PDs displayed enhanced expression of caspase-3. IFN-γ increased APOL1 expression in PDs and attenuated induction of apoptosis as well as caspase-3 expression, both in high glucose and PAN milieus. MicroRNA193a inhibitor decreased miR193a levels, increased APOL1 expression and attenuated apoptosis, both in high glucose and PAN milieus.

Conclusions: APOL1G0 provides protection against apoptosis in adverse milieus through down regulation of miR193.

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FR-PO235

APOL1-microRNA193a Feedback Loop Facilitates Monocyte Macrophage Transition Vinod Kumar,[6] Xiqian Lan,[1] Seyedeh Shadafarin Marashi Shoshtari,[6] Sheetal Chowdhary,[3] Manali Bhooplapur,[2] Ashwani Malhotra,[7] Karl Skorecki,[5] Pravin C. Singhal.[4] *[1]Feinstein Institute for Medical Research, Great Neck, NY; [2]Feinstein Institute for medical research, Dix Hills, NY; [3]Feinstein Institute of Medical Research, New Hyde Park, NY; [4]North Shore LIJ Health System, Great Neck, NY; [5]Rambam Health Care Campus, Haifa, Israel; [6]The Feinstein Institute for Medical Research, Manhasset, NY; [7]Immunolgy and Inflammation, Feinstein Inst.Med research and NSLIJ, Manhasset, NY.*

Background: Macrophage influx in the mesangium has been considered to be a precursor of mesangial expansion, a feature of focal segmental glomerulosclerosis. APOL1 is expressed by macrophages but not by monocytes. Therefore, APOL1 expression is associated with monocyte transition. However, the role of APOL1 in the conversion of monocytes to macrophages (transition) has not been investigated to date. We have studied feedback loop relationship between APOL1 and microRNA193a in parietal epithelial cells (abstract submitted to ASN). We now hypothesize that APOL1-microRNA (miR)-193a feedback loop facilitates monocyte macrophage transition.

Methods: Peripheral blood mononuclear cells (PBMCs) were harvested and incubated in media containing either buffer or experimental agents including, PMA (100 ng/ml), vitamin D receptor (VDR) agonist (EB1089, 50 nM), IFN-y (10 nM), HIV (NL4-3, 100 GEU units X1000), and LPS (10 ng/ml) for adherence for 48 hours followed by assays for adherence and expression of APOL1 mRNA and protein. To examine a causal relationship APOL1 and miR193a, control human monocytes (THPs) were transfected with control and APOL1 siRNAs and incubated in media containing either buffer or PMA, VDR agonist, IFN-y, HIV, and LPS for 48 hours, followed by assays for adherence and miR193a. To confirm the role of feedback loop relationship, THPs were transfected with either control or miR193a plasmids followed treatment with PMA or VDA for 48 hours and assay for APOL1 expression.

Results: Experimental agents enhanced (PMA, 50 fold, VDA, 10 fold, IFN-y 15 fold, HIV 10 fold, and LPS 15 fold) adherence when compared to control PBMCs. All experimental agents induced protein expression of APOL1 in THPs and PBMCs. However, knockout of APOL1 in THPs partially inhibited (<0.01) adherence of PBMCs and THPs treated with PMA (90%), VDA (80%), IFN-y (90%), and LPS (80%). Experimental agents down regulated (P<0.01) THPs expression of miR193a whereas knockout APOL1 reversed this effect of experimental agents on THPs expression of miR193a. However, overexpression of miR193a inhibited PMA/VDA –induced expression of APOL1 in THPs.

Conclusions: These findings suggest that APOL1 through mi193a feedback loop facilitates monocyte macrophage transition

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FR-PO236

APOL1 Facilitates Transition of Parietal Epithelial Cells (PECs) via Down-Regulation of miR193a Vinod Kumar,[2] Xiqian Lan,[1] Seyedeh Shadafarin Marashi Shoshtari,[4] Catherine Meyer-Schwesinger,[5] Ashwani Malhotra,[6] Karl Skorecki,[3] Pravin C. Singhal.[2] *[1]Feinstein Institute for Medical Research, Great Neck, NY; [2]Immunolgy and Inflammation, Fienstine Institute for Medical Research, New York, NY; [3]Rambam Health Care Campus, Haifa, Israel; [4]The Feinstein Institute for Medical Research, Manhasset, NY; [5]University of Hamburg, Hamburg, Germany; [6]Immunolgy and Inflammation, Feinstein Inst.Med research and NSLIJ, Manhasset, NY.*

Background: Progenitor cells play an important role to maintain podocyte (PD) homeostasis during podocyte cytotoxic environment. A subset of pareital epithelial cells (PEC) has been reported to act as progenitor cells for the maintenance of podocyte homeostasis. Down- regulation of microRNA (miR) 193a has been demonstrated to facilitate transition (acquirement of podocyte differentiatin markers) of cultured PECs. APOL1 is expressed intracellularly in podocytes, however, PECs do not express APOL1. APOL1 risk alleles (G1 and G2) have been reported to PD cytotoxic, however, the role of PD expression of APOL1G0 is far from clear. We hypothesize that APOL1 expression emerges in PECs to facilitate PECs transition through down-regulation of miR193a.

Methods: Human immortalized cultured PECs proliferate at 33°C and differentiate at 37°C. PECs were differentiated for variable time periods (4, 8, 12 days; n=4). To examine a causal relationship, PECs were transfected with either control or APOL1 siRNA and followed by differentiation at 37◦C (n=4). To study the feedback relationship between APOL1 and miR193a, PECs and Hep G2 cells (+ve control) were treated with different concentrations of an inhibitor of miR193a (25, 50, and 100 nM) followed by differentiation at 37◦C. To confirm the relationship between APOL1 and miR193a, HEK (human embryonic kidney) cells /mouse (M) PDs (-ve control for APOL1) were transfected with either control or APOL1 plasmids. Protein blots were probed for APOL1, WT1, podocalyxin, podocin, and reprobed for actin. RNAs were assayed for miR193a levels. To confirm binding of miR193a to the *APOL1* gene, RIP-ChIP assay was carried out.

Results: PECs started displaying APOL1 on day 4 during their transition at 37°C. APOL1 expression was associated with down- regulation of miR193a and enhanced expression of WT1, podocalyxin, and podocin. Knockdown of APOL1 up regulated (2 fold) miR193a levels in PECs and Hep G2, whereas, expression of APOL1 in HEKs and mouse podocytes down-regulated (2.5 fold) miR193a expression. Since miR193a also inversely up-regulated APOL1 expression, this suggests a feedback loop relationship in PECs. RIP-ChIP assay confirmed binding of miR193a to APOL1 gene promoter.

Conclusions: APOL1 facilitates PEC transition through down-regulation of miR193a.

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FR-PO237

Modulation of Epigenetics Preserves Podocyte Phenotype in HIV Milieu Vinod Kumar,[2] Kamesh R. Ayasolla,[1] Xiqian Lan,[1] Seyedeh Shadafarin Marashi Shoshtari,[4] Ashwani Malhotra,[5] Pravin C. Singhal.[3] *[1]Feinstein Institute for Medical Research, Great Neck, NY; [2]Immunolgy and Inflammation, Fienstine Institute for Medical Research, New York, NY; [3]North Shore LIJ Health System, Great Neck, NY; [4]The Feinstein Institute for Medical Research, Manhasset, NY; [5]Immunolgy and Inflammation, Feinstein Inst.Med research and NSLIJ, Manhasset, NY.*

Background: Epgenetics have been reported to play an important role in the development of HIV-Associated Nephropathy (HIVAN). Recent report demonstrated that epigenetic alterations upregulated podocyte expression of SNAIL in HIVAN. We hypothesize that HIV-induced podocyte SNAIL expression compromises podocyte integrity (loss of podocyte markers such as nephrin and p-cadherin), however, vitamin D receptor agonist (VDA) has the potential to reverse this effect of SNAIL in HIV milieu. In this scenario, VDA would not only down regulate podocyte expression of SNAIL but would also preserve podocyte phenotype in HIV milieu.

Methods: Renal tissues of 6- week old control, HIVAN (Tg26), and VDR agonist (VDA)- treated Tg26 (2 weeks) mice (4 mice in each group) and vector/human podocytes (V/HP) or HIV (NL4-3)-transduced human podocytes (HIV/HPs) (n=4) were evaluated for expression SNAIL, VDR, nephrin, and p-cadherin. ChIP assays was carried to confirm binding of SNAIL to nephrin promoter. Immunoprecipitation (IP) studies were carried out to analyze composition of SNAIL repressor complexes. Genomic DNA was isolated and CpG island methylation was measured in V/HPs and HIV/HPs

Results: Protein blots of renal tissues from HIVAN mice and HIV/HPs displayed enhanced expression of SNAIL but down regulation of nephrin, p-cadherin, and VDR. VDA partially preserved expression of nephrin in renal tissues of Tg26 mice as well as in HIV/HPs. Genomic DNA methylation studies confirmed hypermethylated CpG islands at Nephrin promoter in HIV/HPs. ChIP assay suggested that enhanced SNAIL expression by HIV/HPs was the consequence of histone 3 methylation at lysine (K) 4 residues (H3K4me3) on SNAIL promoter, whereas, down regulation of nephrin could be due to consequence of histone 3 methylation at lysine 27 residues (H3K27me3). Co-immunoprecipitation studies in lysates of HIV/HPs revealed the association of histone deacetylase (HDAC) 4, DNMT3b and DNMT1, mSin3A and EZH2 with SNAIL; conversely, VDA treatment of HIV/HPs decreased the expression of HDAC4, DNMT3B, DNMT1, mSin3A, and EZH2 (disruption of SNAIL complex).

Conclusions: VDA preserves podocyte nephrin expression through down regulation of SNAIL transcription, disruption of SNAIL repressor complex, and attenuation of methylation at H3K27 residues at nephrin promoter.

Funding: NIDDK Support

FR-PO238

Exogenous ApoL1 Alters Acidification and Trafficking of Endocytic Compartments in Human Podocytes John C. Edwards. *St. Louis University, Saint Louis, MO.*

Background: Variants in ApoL1 confer increased risk of certain types of chronic kidney disease in people of African ancestry. We assessed effects of exogenous wild type ApoL1 on immortalized human podocytes.

Methods: 6 His/T7-tagged recombinant ApoL1 was prepared by Ni affinity and gel filtration. Immortalized human podocytes were differentiated by growth at restrictive temperature for 2 weeks. Purified protein was added to serum-free culture medium at 5 μg/ml. Localization of exogenous ApoL1 was determined with confocal microscopy. Rates of endocytosis were determined by uptake of fluorescently labeled dextran or transferrin as assessed by flow cytometry. Endosomal acidification was assayed using confocal ratiometric fluorescence microscopy of living podocytes that had been loaded with dual labeled FITC/TRITC dextran.

Results: UPTAKE: Endocytic compartments of podocytes exposed to ApoL1 were labeled with fluorescently-tagged dextran or transferrin, then stained for ApoL1. ApoL1 infrequently colocalized with both dextran and transferrin in small endosomes. Transferrin also accumulated in large peripheral structures that stained for ApoL1 and were not present in cells not exposed to ApoL1. **ENDOCYTIC KINETICS:** Differentiated podocytes were exposed to FITC-labeled dextran or transferrin in the presence or absence of ApoL1 and uptake/cell determined. Dextran uptake was not significantly altered by ApoL1, but uptake of transferrin was significantly increased (P<0.00001 at 80 minutes of uptake). **ENDOSOMAL ACIDIFICATION: C**ells were exposed to ApoL1 for 1 hour prior to pulse loading with dual-labeled dextran. 24 minutes after endocytic loading, the fraction of endosomes with pH above 7 was 11% in the control cells and 56% in the ApoL1-treated cells (P<0.0001).

Conclusions: Exogenous ApoL1 is endocytosed by podocytes and accumulates in structures that colocalize with a recycling pathway marker. ApoL1 has little effect on endocytic kinetics of the fluid phase pathway, but increases accumulation of a marker of the recycling pathway. Exogenous ApoL1 induces accumulation of endosomes which fail to acidify. Taken together, the data are consistent with the hypothesis that endocytosed ApoL1 alters endosomal trafficking and acidification with selective effects on kinetics of the recycling pathway. Whether these properties vary among the disease associated variants remains to be determined.

FR-PO239

Deubiquitinating Enzyme UCH-L1 Controls Dendritic Cell Cross Priming of the CD8+ T Cell Response Anna Reinicke,[4] Malte Mühlig,[6] Timo Lischke,[1] Christian Kurts,[3] Hans-willi Mittrücker,[2] Catherine Meyer-Schwesinger.[5] *[1]DRFZ, Berlin, Germany; [2]Institute for Immunology, Hamburg, Germany; [3]Institute of Experimental Immunology, Bonn, Germany; [4]University Clinic Eppendorf Hamburg, Hamburg, Germany; [5]University of Hamburg, Hamburg, Germany; [6]Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany.*

Background: The deubiquitinating enzyme Ubiquitin C-terminal Hydrolase-L1 (UCH-L1) is thought to regulate the intracellular pool of ubiquitin and is strictly required for the maintenance of axonal integrity in neurons. Within the kidney, UCH-L1 is *de novo* expressed in glomerular podocytes in human and rodent glomerulonephritis. Preliminary data demonstrate the expression of UCH-L1 in tubulo-interstitial cells of the kidney. Mice with constitutive UCH-L1-deficiency exhibit an exacerbated course of immune-complex nephritis suggesting that UCH-L1 affects the ability to mount an effective immune response in the kidney. Aims of this study were 1. To identify the origin of tubulo-interstitial UCH-L1-expressing cells in the kidney, 2. To analyze the immunologic phenotype of UCH-L1-deficient mice in response to a bacterial infection, 3. To analyze the role of UCH-L1 in dendritic cells for the degradation and cross-presentation of antigens by the ubiquitin proteasome system.

Methods: Mice with constitutive UCH-L1-deficiency were generated by Cre-Lox technology and back-crossed into the C57BL/6 background. The immunologic phenotype was investigated by challenging UCH-L1-deficient mice and dendritic cell-specific UCH-L1-deficient mice with *Listeria monocytogenes*. Cross presentation and cross priming assays were performed *in vitro* and *in vivo*. The dendritic cell (DC) phenotype and UCH-L1 expression was assessed in naïve and stimulated DCs by FACS, Western, proteasomal and deubiquitinase-based activity assays, and real-time PCR.

Results: In this study we show that UCH-L1 has an immunological function in DC antigen cross presentation. UCH-L1 is expressed in kidney, spleen, and bone-marrow derived DCs and its expression is regulated by the immune stimuli LPS and IFN-gamma. DCs from UCH-L1 knockout mice have reduced ability to cross present cell-associated antigens and mediate deficient CD8 T cell priming following Listeria infection while CD4 T cell priming is unaffected. Intriguingly, UCH-L1 colocalises with an ubiquitin selective segregase, VCP/p97 and in UCH-L1 knockout DCs, is strongly reduced suggesting a role for UCH-L1 in VCP/p97 dependent phagocytosis and sorting of ubiquitinated cargo in the endocytic pathway.

Conclusions: These results demonstrate a hitherto unrecognized role of UCH-L1 in DC-mediated immune responses.

FR-PO240

Loss of Methylthioadenosine Phosphorylase Confers Malignant Potential in Renal Cell Carcinoma Ching-Hsien Chen,[1] Matthew Kyoshi,[1] David Yang,[1] Burl R. Don,[1] Robert H. Weiss.[2] *[1]UC Davis, Davis, CA; [2]UC Davis, Nephrology, Davis, CA.*

Background: Renal cell carcinoma (RCC) has emerged as a metabolic disease characterized by dysregulated expression of metabolic enzymes. Given that patients with metastatic RCC have an unusually poor prognosis, there is an urgent need to discover metabolic molecules useful for predicting malignant changes which will lead to RCC.

Methods: The Cancer Genome Atlas (TCGA) datasets were first analyzed to discover the potential metabolic molecules associated with RCC progression. We confirmed gene expression by immunohistochemistry, qRT-PCR and Western blots. Genetic manipulations were achieved by siRNA silencing, CRISPR and ectopic expression approaches. RCC cell invasion, migration and proliferation were determined by Boyden chamber, scratch and MTT assays. In addition, signaling pathway activity in RCC cells was assessed and compared through utilizing phospho-receptor tyrosine kinase arrays.

Results: Through an integrated two-step analysis of RCC metabolic pathways, we identified that methylthioadenosine phosphorylase (MTAP) and its substrate methylthioadenosine (MTA) are dysregulated in aggressive RCC. A decrease of MTAP expression was observed in RCC tissues and was correlated with tumor grade. We found that MTAP gene deletion was significantly associated with worse overall survival in

RCC patients (n=538). Genetic manipulation of MTAP studies demonstrated that MTAP expression inhibits epithelial-mesenchymal transition, invasion and migration of RCC cells. Surprisingly, an increase of sphere-forming ability was noted in MTAP-knockout RCC cells. Loss of MTAP resulted in an activation of the IGF1R-Src-STAT3 axis in RCC cells.

Conclusions: Our results suggest a novel role of MTAP in kidney disease and contribute to a better understanding of metabolic enzymes involved in RCC oncogenesis.

Funding: Commercial Support - Dialysis Clinic, Inc

FR-PO241

Cardiotrophin-Like Cytokine Factor 1 (CLCF1), Proposed Permeability Factor in FSGS, Attenuates Autophagy and Maintains p-STAT3 (Ser727) via Upregulation of Mammalian Target of Rapamycin (mTOR) Mukut Sharma,[3] Jianping Zhou,[3] Maohui Chen,[3] Alok De,[5] Ram Sharma,[4] Tarak Srivastava,[1] Ellen T. McCarthy,[6] Jean-francois Gauchat,[7] Virginia J. Savin.[2] *[1]Childrens's Mercy Hospital, Kansas City, MO; [2]KC VA Medical Center, Kansas City, AL; [3]KCVA Medical Center, Kansas City, MO; [4]Kansas City VA Medical Center, Kansas City, MO; [5]MBRF, Kansas City VAMC, Kansas City, MO; [6]University of Kansas Medical Center, Kansas City, KS; [7]University of Montreal, Montreal, AB, Canada*.

Background: Autophagy, a critical mechanism for survival of podocytes, is downregulated in FSGS. We showed that an affinity purified fraction (Gal-FS) of plasma of patients with recurrent FSGS (recFSGS) or CLCF1, a cytokine of the IL-6 family that we identified in Gal-FS, increases glomerular albumin permeability (P_{alb}) and upregulates JAK/STAT signaling. These effects are blocked by the heterodimer cytokine receptor-like factor1 (CRLF1)-CLCF1 (Trans Res 2015;166:384-398). Mechanism of CLCF1-induced damage to podocytes is not known. We hypothesized that monomeric CLCF1 and FSGS plasma/serum attenuate autophagy through upregulation of mTOR.

Methods: Galactose affinity chromatography was used to obtain Gal-FS containing CLCF1 detected by proteomic analysis using LC-MS/MS. Immortalized mouse podocytes were incubated (to 48h) with Gal-FS (<5μg protein), monomeric recombinant human CLCF1 (CLCF1,100 ng/mL), heterodimer CRLF1-CLCF1 (100-400ng/mL), Rapamycin (RAPA, ≥0.1μM) and activators/inhibitors at indicated concentrations. Cell morphology and expression of mTOR, STAT3 and autophagy molecules LC3s and other ATGs were determined using light/fluorescence microscopy and Western blot analysis.

Results: Gal-FS or CLCF1 increased phospho-mTOR (15min+) and total mTOR in a dose and time-dependent manner that was blocked by CRLF-CLCF1. CLCF1 blocked the RAPA-induced decrease in total mTOR (P<.05) and phospho-mTOR levels (P<.001). Replenishing CLCF1 at 24h further increased mTOR levels at 48h (P<.005). CLCF1 w/wo RAPA, downregulated MAP1 LC3B (ATG8), a marker of autophagy-related processes (P<.005). ATGs 3, 5, 6 (beclin) and 7 were also modulated by CLCF1. Further work showed that CLCF1 blocked (P<.002) the RAPA-induced downregulation (P<.001) of p-STAT3(Ser727 but not Tyr705) suggesting specific regulation of STAT3 by mTOR kinase activity. Ongoing work indicates that CLCF1 also alters the phosphorylation of ERK and AKT- key cellular regulators that interact with mTOR.

Conclusions: Monomeric CLCF1 changes cellular homeostasis through attenuation of autophagy process via upregulation of mTOR which, in turn, also modulates STAT3 function. This may contribute to long-term podocyte loss and glomerular damage in recFSGS.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO242

Podocyte-Specific Loss of Huwe1 Causes Vacuolization and Glomerular Damage Linus A. Volker,[2] Sabine Bertsch,[2] Sebastian Dittrich,[2] Markus M. Rinschen,[2,1] Bernhard Schermer,[2,1] Thomas Benzing,[2,1] Martin Höhne.[2,1] *[1]CECAD, Cologne, Germany; [2]Department II of Internal Medicine and Center for Molecular Medicine Cologne, University of Cologne, Cologne, Germany*.

Background: As terminally differentiated cells, podocytes rely on precise regulation of homeostasis and specific responses to cellular stress to forego cell damage and loss, which would ultimately lead to glomerular scarring and kidney disease. In an attempt to characterize the networks that regulate cell stress responses, we identified the E3-ubiquitin ligase Huwe1 via interaction screening. In other cell types, Huwe1 has been shown to be a regulator of a wide spectrum of intracellular signaling cascasdes such as MAPK/ERK, Wnt, DNA-damage and cell cycle controll.

Methods: We generated a podocyte-specific Huwe1-knockout mouse and a Huwe1-knockdown podocyte cell line to characterize the role of Huwe1 in podocyte stress response and homeostasis *in vivo* and *in vitro*.

Results: Huwe1-knockout mice were born at expected ratios. They showed signs of kidney disease beginning at 4 weeks of age. Affected mice weighed less than littermates, developed heavy proteinuria, and died prematurely of uremic complications. At ultrastructural level, we saw significant foot process effacement, podocyte vacuolization, and cell loss. We employed biochemistry and mass spectrometry to elucidate the effect of Huwe1-knockdown on podocyte signaling. No direct interactors of Huwe1 could be identified, most likely due to the transient nature of interaction of E3-ubiquitin ligases. Mass spectrometry revealed a significant differential regulation of protein networks associated with lysosome function and DNA-damage signaling. Fittingly, podocyte vesicles stained positive for Lamp1 indicating a lysosomal origin. Biochemical analyses showed a marked downregulation of mTOR signaling as a putative effector of vesicle formation. Experiments to elucidate the role of Huwe1 in DNA-damage response in podocytes are in progress.

Conclusions: We identified the E3-ubiquitin ligase Huwe1 at the center of crucial signaling cascades as an indispensable regulator of podocyte homeostasis. Future research will be directed at identifying direct Huwe1-targets in podocytes and potential therapeutic exploitability

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FR-PO243

Inhibition of YAP Exacerbates Podocytes Apoptosis and Disease Progression in Adriamycin-Induced Focal Segmental Glomerulosclerosis Qiyuan Zhuang,[3] Fang Li,[1] Jianchun Chen,[4] Huijuan Wu.[2] *[1]AUGUSTA UNIVERSITY, AUGUSTA, GA; [2]Department of Pathology, School of Basic Medical Sciences, Fudan University, Shanghai, China; [3]Shanghai Medical College, Fudan University, Shanghai, China; [4]Vanderbilt University, Nashville, TN*.

Background: Focal Segmental Glomerulosclerosis (FSGS) is a common chronic glomerular disease with poor clinical outcomes, of which the main manifestation is nephrotic syndrome. Podocyte lost via apoptosis is one important mechanism underlying the pathogenesis of FSGS. Recently, Yes-associated-protein (YAP), one key downstream effector of Hippo pathway, was recognized as an activator for multiple gene transcriptional factors in nucleus to control cell proliferation, differentiation and apoptosis. However, the potential role of YAP activation in development and progression of FSGS remains unclear.

Methods: The localization, expression and phosphorylation of YAP were examined in kidney samples from patients with FSGS, adriamycin-induced FSGS mT/mG transgenic mouse model and the primary cultured podocytes treated with adriamycin.

Results: We first found that increases of podocyte apoptosis is closely correlated with the expression level of phospho-YAP at serine 397 which is associated with YAP degradation during the progression of FSGS. And then, we found that YAP distributed uniformly in the nucleus and cytoplasm in the podocytes of vehicle treated mouse kidney or in the primary cultured podocytes. Administration of adriamycin to the mice or exposure the primary cultures to adriamycin acutely induced YAP nuclear translocation, an indicator of YAP activation, followed by continuously exporting from the nucleus to the cytoplasm. Accordingly, our data also revealed that the expression of phospho-YAP at serine 127 in the podocytes was acutely decreased and then increased in response to Adriamycin treatment. In addition, administration of verteporfin, a YAP inhibitor, accelerated podocytes apoptosis and segmental glomerulosclerosis and deteriorated renal function in early phase after adriamycin treatment.

Conclusions: Our findings suggest that YAP activation in podocytes is an important endogenous anti-apoptotic mechanism during the progression of FSGS, and targeting YAP could be a potential therapeutic choice for treatment of FSGS.

Funding: Government Support - Non-U.S.

FR-PO244

The Role of TLR4 in Hepatitis B Virus X Protein Induced Immunity Disorder in Renal Tubular Epithelial Cells Xuan Wang. *Shanghai Jiaotong University Affiliated First People's Hospital, Shanghai, China*.

Background: Hepatitis B virus X protein could activate inflammatory immune response, which may contribute to the pathogenesis of HBV-GN. How HBx change the function of renal tubular epithelial cells(RTECs) was unknown. We want to explore the role of TLR4 in immunity disorder of RTECs mediated by HBx.

Methods: C57BL/6J-TgN mice(6 week old) were randomly divided into the experimental group and the intervention group. C57BL/6J mice were used as normal control group. Mice of the intervention group were injected TLR4 shRNA lenti virus from 8-week old, and injected every four weeks. Serum and urine were collected at 8, 12, 16, 20, 24-week old. Mice were sacrificed at 24 week old to observe the mice renal function and pathological changes. HBx and TLR4 expression in renal tissue were observed by immunohistochemistry, and macrophages and T cells were also detected by immunohistochemistry. We constructed a HBx-overexpression plasmid and a TLR4 shRNA plasmid and transfected them into human proximal tubular epithelial cell line(HK-2). Flow cytometry was used to investigate the expression of MHC-II, CD40 on HK-2 cells. Mixed lymphocyte reaction was used to ddetect the ability of stimulating T cells proliferation. IFN-gamma and IL-4 in supernatant were determined by ELISA.

Results: Proteinuria of C57BL/6J-TgN mice increased from 16-week old, and renal function deteriorated up to 24 week-old. HBx and TLR4 expression was observed in tubular epithelial cells of C57BL/6J-TgN mice, and they had significant interstitial CD4+ T cells and macrophages accumulation. Mice with TLR4 shRNA lenti virus intervention appeared reduced proteinuria and remission of renal function and fewer CD4+ T cells and macrophages infiltration. After transfection of HBx gene, the expressions of MHC-II and CD40 in HK-2 cells were up-regulated, and IFN-gamma/IL-4 ratio increased. TLR4 shRNA transfection down-reagulated expression of MHC-II and CD40 on renal tubular epithelial cells, decreased ability of stimulating T cell proliferation and lowered ratio of IFN-gamma/IL-4.

Conclusions: HBx could stimulate HK-2 cells MHC-II and CD40 expression, functioning as nonprofessional antigen-presenting cells, and activate inflammatory immune response, which may contribute to the pathogenesis of HBV-GN. Inhibiton of TLR4 can depress immune function of tubular epithelial cells and have prevention and treatment effect.

FR-PO245

Nrip2 Is Required for Endocytosis of Lrp6 and Wnt/β-Catenin Signaling Transduction in Zebrafish Pronephric Tubule Qing Hou,[1] Ling Wang,[2] Wei-bo Le,[5] Cai-hong Zeng,[5] Wei-song Qin,[4] Zhao-hong Chen,[5] Zhi-Hong Liu.[3] *[1]Jinling Hospital, Nanjing, China; [2]National Clinical Research Center of Kidney Disease, Jinling Hospital, Nanjing, China; [3]National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing China, Nanjing, China; [4]National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China; [5]Research Institute of Nephrology, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China.*

Background: Low-Density Lipoprotein Receptor-Related Protein 6 (LRP6) functions as a co-receptor for Wnt/β-catenin signaling and as a ligand receptor for endocytosis, which is implicated in pathogenesis of renal damage and transduction of Wnt/β-catenin signaling.

Methods: Here, we identified a nuclear receptor interacting protein 2 (nrip2) as being required for endocytosis of lrp6 in zebrafish. In zebrafish, nrip2 is dynamically and specifically localized in pronephric tubule.

Results: From 24 to 72hpf, nrip2 is dynamically expressed in distal tubule, proximal straight tubule and proximal convoluted tubule, which is examined by in situ hybridization. Global knockout of nrip2 in zebrafish by CRISPR/Cas9 genome editing approach leads to impaired low-molecular fluorescent dextran uptake in proximal tubule comparing with normal control, which is also companied by reduced amount of endocytic apparatus and cilia by Transmission Electron Microscope imaging, and decreased expression of EEA1, an early endosome antigen 1, by Immunoelectron Microscorpe. Interestingly, loss of nrip2 resulted in reduction of lrp6 expression, not lrp2a (megalin). Nrip2 knockdown in Tg(Tcf/Lef-mimiP:dGFP), expressing GFP under the control of β-catenin/TCF responsive elements, resulted in decreased GFP expression. Meanwhile, overexression of nrip2 in HK-2 cells activated total β-catenin and active β-catenin, which means nrip2 is required for activation of Wnt/β-catenin signaling.

Conclusions: Above all, we found that nrip2 is required for endocytosis of lrp6 and transduction of Wnt/β-catenin signaling. Next, we will investigate and demonstrate that Wnt/β-catenin signaling is activated by nrip2 through lrp6.

FR-PO246

Quantitative Proteomic Analysis of Induced Renal Tubular Epithelial Cells (iRECs) Sebastian Dittrich,[1] Thomas Benzing,[1] Soeren S. Lienkamp,[2] Michael Kaminski,[2] Markus M. Rinschen.[1] *[1]University Hospital Cologne, Cologne, Germany; [2]University Hospital Freiburg, Freiburg, Germany.*

Background: Reprogramming of differentiated cells into other cell types by forced expression of tissue specific transcription factors has been shown to be an effective tool to generate new cell models. iRECs are a renal epithelial cell line that has been reprogrammed from mouse embryonic fibroblasts (MEFs). While the cell line has been characterized at a genomic and transcriptomic level, proteomic studies still need to be performed to evaluate possible usage as an in vitro model.

Methods: We performed a proteomic mapping of proteins generated from iRECs and original MEFs. The method consists of protein solubilization, tryptic digestion and analysis of peptides by nLC-MS/MS on a quadrupole-orbitrap mass spectrometer.

Results: We mapped the iREC proteome and MEFs and quantified 5315 proteins using label-free quantification. The generated dataset was correlated with mRNA expression ("RNA-seq") data of microdissected rat kidney tubule segments. Consistent with previous transcriptome analysis, we found that iRECs expressed proteins from different segments of the tubule system, Henle loop and collecting ducts rather than resembling the expression profile of one specific segment. The iRECs had high abundance of mitochondrial proteins. In addition, the most strongly iREC-enriched proteins were the ligand- binding receptors Cubilin (Cubn) and Megalin (Lrp2) and its associated adaptor protein Disabled homolog 2 (Dab2), which mediate reuptake of albumin and other ligands. We furthermore found that iRECs expressed several soluble channels such as sodium bicarbonate transporter-like protein 11 (Slc4a11) which is highly expressed in the thin descending limb of Henle loop. Several subunits of V-type proton ATPase were highly expressed in iRECs as well as the transcription factors JunB and JunD.

Conclusions: Consistent with transcriptomic data, the iREC proteome does not resemble the protein expression profile of one single nephron segment. However, iRECs express several specialized segment specific proteins with high importance in physiological processes as well as for disease models. Especially the surprisingly high protein abundance of ligand-binding receptors Cubilin and Megalin could make this cell type a valuable new in vitro model for elucidating the yet unknown molecular signaling mechanisms of albumin reuptake in the proximal tubule of the nephron.

FR-PO247

Inhibition of Vasopressin Type 2 Receptor Signaling Suppresses Tumor Growth in Renal-Cell Carcinoma Sonali Sinha,[2] Nidhi Dwivedi,[1] Reena Rao.[1] *[1]University of Kansas Medical Center, Kansas City, KS; [2]university of kansas medical center, Kansas City, KS.*

Background: Renal cell carcinoma (RCC) accounts for 90% of all kidney cancers and is among the 10 most common cancers worldwide. Clear-cell and papillary-cell RCC represent 70-75% cases of all RCC. Clear cell RCC tumors originate from the renal proximal tubules that express vasopressin type 1 receptors (V_1R). However, in human clear cell RCC tumors we detected V_2R expression and V_2R mediated cell signaling. Since V_2R activity promotes cell proliferation in polycystic kidney disease, we hypothesized that V_2R activity is pathogenic in RCC, and V_2R inhibition can suppress tumor growth

Methods: In Caki-1 and 786-0 cells, we determined the effect of V_2R antagonist OPC31260 on cell viability, cell cycle, colonogenecity and cell migration. The effect of OPC31260 on tumor development was tested in female athymic nude mice. Mice were subcutaneously inoculated with a 100-µl suspension of Caki-1 cells. When tumor volume reached 80-100 mm^3 mice were randomized into groups (n=8) to receive vehicle or OPC31260, injected intraperitoneally daily for 28 days. Tumors volumes were measured and mice were weighed on alternate days. Tumors were harvested and weighed at the end of the study and portions were fixed in 10% formalin or snap frozen for protein and mRNA estimation.

Results: OPC31260 treatment dose dependently and significantly reduced cell viability, colony formation and cell migration. At higher doses of OPC31260, G2M cell cycle arrest was observed. In the mouse xenograft model, within 28 days of start of treatment, tumor volume increased by 9-folds in vehicle treated mice, while in the OPC31260 treated mice, less than 2-folds increase in tumor volume was observed. Tumor weights at sacrifice were 10- folds lesser in OPC31260 treated mice compared to vehicle treated mice. OPC31260 treatment significantly reduced pERK1/2 and pCREB levels compared to vehicle treated mice, suggesting suppression of V_2R signaling. Cell proliferation, detected by BRDU incorporation in the tumors was significantly reduced in OPC31260 treated mice and apoptosis detected by TUNEL assay was significantly high.

Conclusions: Vasopressin-V_2R signaling plays a pathogenic role in tumor progression in RCC and suppression of V_2R signaling by OPC31260 can suppress tumor growth in RCC. Hence V_2R is a novel target for therapy in RCC.

Funding: NIDDK Support

FR-PO248

Kidney Organoids Replicate Drug-Induced AKI in a Segment-Specific Manner Koichiro Susa,[1] Navin R. Gupta,[1,2] Joseph V. Bonventre,[1,2] Ryuji Morizane.[1,2] *[1]Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Harvard Stem Cell Inst, Cambridge, MA.*

Background: Drug-induced kidney injury is a serious problem in clinical settings and a major barrier to development of new drug candidates. Many nephrotoxicants are taken up into the cytoplasm through renal drug transporters such as organic cation/anion transporters (OCTs and OATs). These transporters, however, are generally not expressed in cell lines of immortalized human kidney tubules, a fact that markedly limits clinical translatability of drug screening systems *in vitro*. Recently, kidney organoids containing multi-segmented nephron epithelial cells have been generated from human pluripotent stem cells. These can to be used for drug screening as a novel technology using human cells.

Methods: Kidney organoids were differentiated from human ES and iPS cells by a previously established protocol. Organoids were exposed to various nephrotoxicants which induces segment specific injury: cisplatin, aristolochic acid (AA), tenofovir, puromycin aminonucleoside (PAN), adriamycin, and lithium. Drug transporter expression and kidney injury in organoids were evaluated by qRT-PCR and immunostaining and compared to a human kidney tubular cell line (HKC-8).

Results: qRT-PCR demonstrated marked expression of OCT2, OAT1 and 3, which are major renal drug transporters, in kidney organoids while HKC-8 cells showed much lower expression of these transporters. The organoids showed upregulated tubular injury markers such as KIM-1 and L-FABP after treatment with cisplatin, tenofovir, or AA, but not by PAN or lithium. Cimetidine and probenecid, which are inhibitors of OCT2 or OATs respectively, ameliorated the injury caused by cisplatin or tenofovir. Lithium caused significantly decreased expression of aquaporin 2 in kidney organoids. PAN and adriamycin induced severe morphological injury and decreased expression of nephrin in glomerulus-like structures of organoids, whereas cisplatin did not. On the other hand, HKC-8 treated with those nephrotoxicants did not exhibit significant change of tubular injury markers.

Conclusions: Kidney organoids faithfully mimic drug-induced tubular and glomerular injury, suggesting they will be useful for evaluation of nephrotoxicity of drugs and substantially superior to conventional nephrotoxicity screening method using cultured cells.

Funding: NIDDK Support, Commercial Support - Ajinomoto, TORAY, Government Support - Non-U.S.

FR-PO249

An ATP/ADP Biosensor as a Real-Time Toxicity Assay in Kidney Organoids Pierre Galichon,[1] Koichiro Susa,[1] Navin R. Gupta,[1,2] Joseph V. Bonventre,[1,2] Ryuji Morizane.[1,2] *[1]Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Harvard Stem Cell Institute, Cambridge, MA.*

Background: Renal toxicity is frequent and a major limitation to drug development. Renal organoids have been generated from human pluripotent stem cells (hPSCs), overcoming limitations related to the expense and translatability of cell culture and animal experiments. Here, we present a novel system to evaluate the toxicity of drugs with a real-time biosensor of ATP/ADP ratio in kidney organoids.

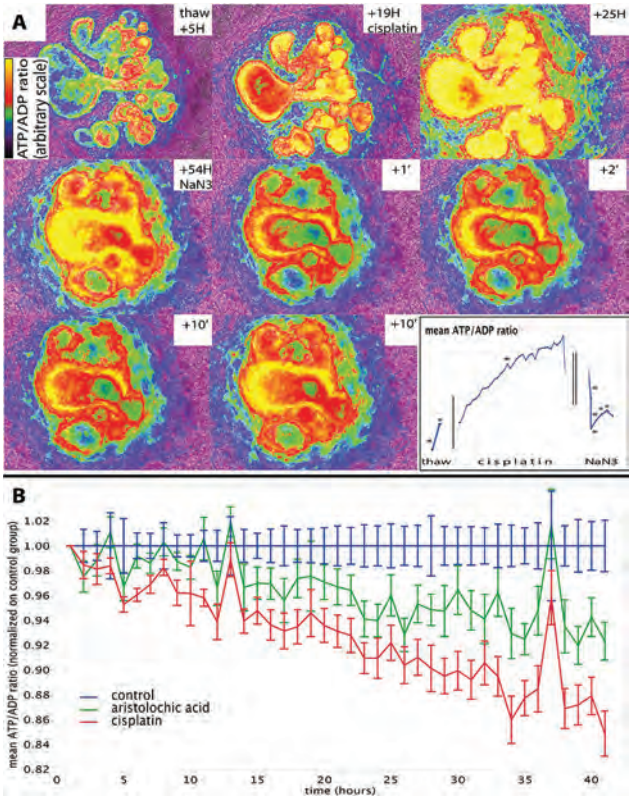
Methods: Stable hPSC lines, expressing the ATP/ADP ratio PercevalHR, were established with lentiviral transduction and differentiated in kidney organoids as previously described. Organoids were used fresh or after freeze/thaw. ATP and ADP signal were acquired via live fluorescence microscopy, and a ratio was quantified with

the ImageJ RatioPlus plugin. Organoids were exposed to various toxicants (10 or 50 μM cisplatin, 10 mg/ml aristolochic acid (AA), 5 mM sodium azide (NaN3) or vehicle.

Results: The ATP and ADP signals were greater in nephron epithelial structures than in the stromal compartment and NaN3 induced a rapid decrease in ATP/ADP ratio within one minute. Cisplatin and AA significantly reduced the ATP/ADP ratio as compared to control organoids after 15 hours. Reduction in ATP/ADP ratios preceded contraction of the organoids.

Conclusions: Reduction in ATP/ADP ratio in kidney organoids is a sensitive indicator of drug toxicity, offering a direct live readout in human tissues *in vitro*. The unlimited availability of hPSC-derived organoids and the ability to freeze them at the pre-analytical stage is well-suited to high-throughput screening and might facilitate the identification of lead candidates during drug discovery.

Funding: Private Foundation Support



A: ATP/ADP ratio imaging in a thawed organoidB: Mean ATP/ADP ratio in organoids exposed to nephrotoxicants (n=6/group)

FR-PO250

Laminar Flow Enhances Endothelial Differentiation from iPS Cells and Stabilizes Endothelial Cell Function Robin Bollin,[3] Yulia Kiyan,[1] Roman Kiyan,[2] Ulrich Martin,[3] Boris Chichkov,[2] Hermann G. Haller.[1] *[1]Hannover Medical School, Hannover, Germany; [2]Laser Zentrum Hannover e.V., Hannover, Germany; [3]Medical School Hannover, Hannover, Germany.*

Background: Endothelial cells (ECs) have essential roles in organ development and regeneration, and therefore they could be used for regenerative therapies. However, generation of abundant functional endothelium from pluripotent stem cells has been difficult because ECs have limited proliferative potential and display vascular instability. Since stimulation of functional properties may enhance EC differentiation we have tested the hypothesis that laminar flow enhances EC differentiation and analyzed the underlying molecular mechanisms.

Methods: iPSC have been cultured under feeder free conditions for 3 passages, and then seeded in the Geltrex-coated microfluidic chips. Chips contained 4 parallel channels allowing simultaneous analysis of several experimental conditions. Mesoderm differentiation was induced by Bone morphogenetic protein 4 (BMP4) 30 ng ml^{-1}; Activin A 25 ng ml^{-1}; small-molecule inhibitor of glycogen synthase kinase-3β (CHIR) 1.5 μM; Vascular endothelial growth factor (VEGF) 50 ng ml^{-1} for 4 days. At day 4 of mesoderm differentiation microfluidic chips have been attached to the medium flow and stimulated with VEGF 50 ng ml^{-1}; TGF-β pathway small-molecule inhibitor SB431542 10 μM to induce EC differentiation. Static control chips have been stimulated with the same medium. After 3 days cells were fixed by perfusion with 2% PFA solution, and stained for Sox17, VE-Cadherin, CD31, and heparin sulfate. Confocal microscopy of the cells was performed directly in the microfluidic chips.

Results: Characteristic flow-oriented morphological changes have been observed in the cells incubated under flow but not under static conditions. Control iPSC without flow displayed a low rate of <1% EC differentiation after 3 days of stimulation. In contrast, iPSC cultivated under medium flow conditions showed a more rapid (50.8 ± 4.1% after 3 days) and sustained differentiation to EC. Cells demonstrated expression of EC-markers CD31 and VE-Cadherin, and expressed heparin sulfates on the apical side of the cells indicating terminal differentiation.

Conclusions: Laminar shear stress may directly activate growth factor receptors on stem/progenitor cells, initiating signaling pathways leading toward endothelial cell differentiation. Our results suggest that laminar flow is an important factor in endothelial cell differentiation protocols.

FR-PO251

RAD51 Inhibition Exacerbates Injury in a Human Pluripotent Stem Cell-Derived Nephron Organoid Model in Which Repetitive DNA Damage Models Acute Injury and Transition to Fibrosis Navin R. Gupta,[1,2] Edgar Garcia,[1] Tomoya Miyoshi,[1] Koichiro Susa,[1] Ryuji Morizane,[1,2] Joseph V. Bonventre.[1,2] *[1]Brigham and Women's Hospital, Cambridge, MA; [2]Harvard Stem Cell Institute, Cambridge, MA.*

Background: Tubular DNA damage has been demonstrated to play a central role in tubulointerstitial crosstalk, implicated in the pathogenesis of kidney injury and fibrosis. Unlike traditional cell culture techniques, human pluripotent stem cell (hPSC)-derived nephron organoids contain multiple compartments representing glomeruli, proximal and distal tubules, and an interstitium. Following interstitial characterization, the organoid's response to cisplatin, a known nephrotoxicant that induces proximal tubular (PT) DNA damage, may enable the study of DNA damage response (DDR) and interactions between the tubular and interstitial compartments *in vitro.*

Methods: Nephron organoids were treated with twice weekly, 24 hour periods of cisplatin (5μM) for 5 treatments. Following each treatment, samples and controls were gathered for immunostaining and qRT-PCR. Flow cytometric gating on LTL-fluorescein determined the preponderance of PTs in nephron organoids. B02 was used at 5μM for continuous inhibition of RAD51, a DDR element for double strand break (DSB) repair.

Results: PDGFR-β^+ $desmin^+$ cells (pericytes) and PDGFR- β^+ $desmin^-$ cells (fibroblasts) comprise the interstitium of nephron organoids, in a similar distribution and ratio as in our human nephrectomy samples. Following acute injury with cisplatin, LTL^+ PT cells manifested preferential DSBs, entered the cell cycle, expressed luminal KIM-1, underwent mesenchymal dedifferentiation, and were associated with $PTEN^+NCAM^+$ peritubular interstitial cells. Following repeated cisplatin injury, LTL^+ cells had a reduced brush border, arrested at the G2/M DNA damage checkpoint, and pro-inflammatory cytokines were upregulated on organoid lysates. With further injury, peritubular interstitial cells transdifferentiated into myofibroblasts and fibronectin and collagen I accumulated in the interstitial space. B02, a RAD51 inhibitor, exacerbated proximal tubular G2/M arrest and interstitial fibrosis.

Conclusions: Inhibition of RAD51 augmented injury in nephron organoids treated with repetitive cisplatin, implicating DDR in the pathogenesis of kidney fibrosis. As an effective human model system *in vitro*, nephron organoids can be exploited to understand mechanisms of injury and repair and screen anti-fibrotic therapeutics.

Funding: Other NIH Support - T32

FR-PO252

FGFs Are Required for Stem Cell Recruitment to Nephrogenic Aggregates during Adult Zebrafish Kidney Regeneration Thomas F. Gallegos, Caramai N. Kamei, Iain A. Drummond. *Massachusetts General Hospital, Boston, MA.*

Background: In zebrafish, adult kidney injury (AKI) results in stem cell-mediated regeneration by the *de novo* production of new nephrons. This process occurs by progenitor cell aggregation and differentiation on kidney collecting ducts, leading to the insertion of new nephrons. Expression of *dusp6*, a transcriptional readout of FGF signaling, was induced upon AKI, suggesting a role for FGF signaling in new nephron formation. Early broad *dusp6* expression became restricted to single cells and ultimately to nephrogenic aggregates abutting mature collecting ducts. In addition to *dusp6*, nascent nephrons are marked by expression of *lhx1a*. After gentamicin-induced AKI, pharmacological or dominant-negative based genetic inhibition of FGFR signaling completely prevented recruitment of progenitor cells to *dusp6* and *lhx1a*-expressing nephrogenic aggregates. In juvenile *Tg(lhx1a:egfp)* zebrafish treated with FGFR inhibitor during developmental nephrogenesis, progenitor cells survive but fail to condense into organized aggregates. Upon kidney injury, expression of *fgf4*, *fgf8a*, *fgf10a*, and the receptors *fgfr1* and *fgfr4* were induced, suggesting multiple roles for FGF signaling in the formation of nephrogenic aggregates from single cell progenitors. By qPCR of fractionated kidneys, *fgf4* and *fgf10a* were found to be specifically expressed in the tubular fraction of the injured kidney, suggesting that these ligands may play a role in recruiting nephrogenic cells to injured tubules. *fgf8a* expression was restricted to the most distal end of the nephrogenic aggregate, suggesting a role in patterning the new nephron aggregate. Our results demonstrate essential roles for FGF in recruitment of progenitor cells and patterning of nephrogenic aggregates during kidney regeneration in the adult zebrafish.

Methods:

Results:

Conclusions:

Funding: NIDDK Support

FR-PO253

Effect of Integrin Signaling Blockade on Self-Renewal and Differentiation of Human Nephrogenic Progenitors In Vitro Astgik Petrosyan,[1] Sinem Karg?n,[1] Matthew E. Thornton,[2] Brendan Grubbs,[2] Roger E. De Filippo,[1] Laura Perin,[1] Stefano Da Sacco.[1] *[1]Children's Hospital Los Angeles, Los Angeles, CA; [2]University of Southern California, Los Angeles, CA.*

Background: Mammalian kidney development is controlled through the proliferation and differentiation of a specific population of nephron progenitors (NP) characterized by the expression of CITED1 and SIX2. The mechanisms regulating the balance between self-renewal and renal differentiation in NP are still elusive, impairing our ability to effectively expand NP in vitro for long term. In particular, the effects of extracellular matrix (ECM) composition and ECM-NP interaction are poorly understood.

Methods: We have investigated the relationship between ECM and self-renewal traits in NP isolated from human fetal kidneys (hFK). NP were isolated using our established RNA Smartflare protocol. Nephrogenic characteristics were confirmed by RNA-seq and nephrogenic potential by in vitro differentiation and dissociation/reaggregation assays. By immunofluorescence we have characterized the ECM present within the nephrogenic niche of hFK. Subsequently we have tested NP expansion on these ECM substrates and assessed effects on signaling cascade by PCR array.

Results: Among others, laminin alpha 5, collagen 16 and collagen 18 where found to be highly expressed within the cap mesenchyme of developing hFK. In vitro, laminin was confirmed to better preserve self-renewal properties in NP, as confirmed by maintenance of higher co-expression of SIX2 and CITED1 in cultured NP, both in short and long term experiments. Interestingly, blocking integrin mediated ECM-NP interaction with specific antibodies lead to an increase in SIX2 and CITED1 co-expression, suggesting an important role of integrin mediated signaling pathway on balance between renal specification vs self-renewal. Effect of integrin blocking in NP on downstream WNT signaling was further confirmed by PCR array, suggesting a direct role of ECM-NP interaction on self-renewal.

Conclusions: Our data indicate a strong link between ECM-NP during human renal development. NP-laminin interaction appears to play an essential role on nephron endowment by directly controlling self-renewal/differentiation balance. These results could provide not only a tool for the optimization of in vitro NP expansion but also a platform to advance our understanding of human renal development and nephron cell commitment.

Funding: Private Foundation Support

FR-PO254

A New Inducible Aqp2ECE System Reveals the Self-Renewal and Multipotentiality of Aqp2+ Progenitor Cells in Adult Mouse Kidneys Lihe Chen,[1] Ye Zhang,[2] Chao Gao,[2] Long Zhang,[2] Enuo Chen,[2] Wenzheng Zhang.[2] *[1]NIH, Bethesda, MD; [2]Albany Medical College, Albany, NY.*

Background: Stem cells are defined by unlimited self-renewal capacity and pluripotentiality. Progenitor cells have pluripotentiality, but no or limited self-renewal potential. Using *Aqp2Cre* driver, we previously showed that embryonic Aqp2$^+$ progenitor cells generate all known cell types in the connecting tubule/collecting duct. However, the constitutive *Aqp2Cre* driver cannot be used to assess adult Aqp2$^+$ progenitor cells.

Methods: Here, we report a new inducible *Aqp2ECE* knock-in mouse model, which allows us to demonstrate the self-renewal and multipotentiality of Aqp2$^+$ progenitor cells in adult kidneys. *Aqp2ECE* was created by inserting a cassette expressing a specific Cre fusion at the ATG of the endogenous *Aqp2* locus and used to generate *Aqp2ECE Rainbow* mice.

Results: Without Tamoxifen induction, no fluorescence proteins were detectable at P1, P23, and P42. In kidneys induced with Tamoxifen (4 mg/20g BW) at P42 and examined at P63, seldom and isolated individual cells expressing one of 4 fluorescence proteins (XFP$^+$, where X=G, R, C, or Y) were observed. Double and triple immunofluorescence (IF) staining revealed that all RFP$^+$ and GFP$^+$ cells were also Aqp2$^+$, with none of them having detectable expression of V-ATPase B1B2. In mice induced with Tamoxifen at P23 and P69, treated with dietary LiCl (40 mmol lithium/kg food) at P95 for 18 days, and examined at P113, there were clones of 2-5 cells expressing the same fluorescence protein without interruption by any single cell of another color. While the majority of the GFP$^+$ and RFP$^+$ cells remained Aqp2$^+$, some of them lost Aqp2 expression and gained expression of V-ATPase B1B2, AE1 or Pendrin, indicating conversion of "principal" cells to intercalated cells. Some GFP$^+$ and RFP$^+$ cells displayed an intermediate state and characterized by being positive for both a principal (Aqp2$^+$) and an intercalated cell marker (V-ATPase B1B2, AE1, or Pendrin).

Conclusions: We conclude that 1) *Aqp2ECE* has 0% leakiness (100% dependence of Cre recombinase activity on Tamoxifen), noticeable inducibility, and 100% fidelity in recapitulating the endogenous *Aqp2* expression; 2) Rare Aqp2$^+$ progenitor cells exist in adult mouse kidney, possess self-renewal and multipotentiality, and function in kidney maintenance and lithium-induced remodeling. Long-term chasing is underway to confirm and extend these findings.

Funding: NIDDK Support

FR-PO255

Adipose Tissue-Derived Stem Cells (ASC) Reverses Kidney Disease Progression in SHR Rats Induced to Metabolic Syndrome Marcelo C. Batista,[1] Renata Nakamichi,[2] Camila N. Oliveira,[1] Mario luis R. Cesaretti,[2] Maria Dalboni,[2,3] Beata M. Quinto.[1] *[1]UNIFESP, São Paulo, Brazil; [2]Universidade Federal de São Paulo, Santo André, Brazil; [3]Uninove, Sao Paulo, Brazil.*

Background: Visceral obesity, the physiopathological basis of Metabolic Syndrome (MS), determines a set of metabolic abnormalities linked to increased risk of kidney disease in the overall population. The excessive expansion of visceral adipose tissue, resulting in hypertrophied adipocytes is implicated in the development of hypoxic environment and increases inflammatory proteins. The adipose tissue is also considered an important source of stem cells which are able to proliferate and differentiate into multiple cell lines reducing the expression of inflammatory proteins. The aim of the study is to evaluate the treatment of the kidney disease progression in SHR rats induced to MS with ASCs.

Methods: SHR rats were induced to MS by hyperlipid/hypercaloric diet for 12 weeks, and then treated with injection of 2x10^5 ASC for 1 and 2 weeks, respectively. After this period, rats were sacrificed for analysis of albuminuria, as well as kidney function (serum concentration of creatinine and Cystatin C, and urinary NGAL) for comparison with baseline parameters. The characterization of ASC extracted from subcutaneous tissue of SHR control rats was performed through flow cytometry method.

Results: Previous analysis has shown that ASC expressed the cell surfaces markers: CD34, CD35, CD90 and CD105, confirming its characterization in adipocyte. Our results demonstrated a statistically significant deterioration of lipid profile, as shown by decrease in HDL-c and increase in triglycerides and total cholesterol, on those animals induced to MS when compared with the control group (CT). This adverse lipid profile was reversed on those MS-induced animals treated with stem cells. Parallel with the induction of MS, we observed the development of kidney disease as shown by the enhancement in albuminuria as well as an increase in creatinine, Cystatin C and Ngal concentrations among those rats induced to MS. Similarly with lipid profile, we could also evidence a reversion of kidney disease progression through the improvement in the above mentioned kidney disease parameters, among the MS-Induced rats treated with adipose tissue-derived stem cells.

Conclusions: Adipose tissue-derived stem cells reversed Metabolic Syndrome related kidney disease progression in SHR rats.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO256

Mesenchymal Stem Cells Cultured in Serum-Free Medium Ameliorate Experimental Renal Fibrosis by Their Strong Immunosuppressive Effects Ken Yoshida,[1] Ayumu Nakashima,[1,2] Shigehiro Doi,[1] Toshinori Ueno,[1] Yukio Kato,[2,3] Yukihito Higashi,[4] Takao Masaki.[1] *[1]Nephrology, Hiroshima University Hospital, Hiroshima, Japan; [2]Stem Cell Biology and Medicine, Graduate School of Biomedical & Sciences, Hiroshima University, Hiroshima, Japan; [3]TWOCELLS Company, Limited, Hiroshima, Japan; [4]Cardiovascular Regeneration and Medicine, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan.*

Background: The mechanism underlying the anti-inflammatory effect of mesenchymal stem cells (MSCs) has been elucidated. However, the anti-inflammatory effect of MSCs cultured in serum-free medium has not been clarified. Here we examined the effects of MSCs cultured in serum-free medium on infiltration of inflammatory cells and interstitial fibrosis induced by unilateral ureteral obstruction (UUO) operation in rats.

Methods:

Results: At 4 days post-UUO operation, we injected rat MSCs cultured in 10% fetal bovine serum containing DMEM (10%MSCs) or serum-free medium (SF-MSCs) or PBS only (control) through the tail vein. Although retention of MSCs collected from green fluorescent protein-positive rats was only observed for 3 days with no difference between 10%MSCs and SF-MSCs, immunohistochemistry revealed that SF-MSCs strongly ameliorated infiltration of macrophages and interstitial fibrosis. Next we examined whether serum-free culture conditions enhanced the anti-fibrotic and immunosuppressive effects by paracrine manners. Incubation of cultured human kidney-2 cells in human MSC-conditioned medium suppressed transforming growth factor-β1-induced phosphorylation of Smad2 and α-smooth muscle actin, but there was no significant difference in culture from 10%MSCs and SF-MSCs. Co-cultures of human MSCs and human monocytic THP-1 cell-derived pro-inflammatory phenotype (M1) macrophages using a transwell system showed significant increases in cells positive for CD163 and CD206, immunomodulatory phenotype (M2) macrophage markers, in SF-MSCs compared with 10%MSCs.

Conclusions: These results show that transplantation of MSCs cultured in serum-free medium ameliorated infiltration of inflammatory cells and renal fibrosis in UUO rats compared with MSCs cultured in serum containing medium, in part by enhancement of M2 macrophage polarization from MSCs cultured in serum-free medium. The replacement of serum containing medium of MSCs to serum-free medium is thought to reduce the risk of infections, and transplantation of MSCs cultured in serum-free medium may help alleviate renal diseases in which inflammation plays a critical role.

FR-PO257

Amniotic Fluid-Derived Mesenchymal Stem Cells (AFSCs) Are Renoprotective in Established Experimental CKD Rita de Cassia Cavaglieri,[1,2] Thalita Prado,[1] Luísa Albuquerque,[1] Marcelo Zugaib,[3] Sergio P. Bydlowski,[2] Irene L. Noronha.[1] *[1]Cellular and Molecular Nephrology Lab, University of São Paulo, São Paulo, Brazil; [2]Genetics and Molecular Hematology Lab, University of São Paulo, São Paulo, Brazil; [3]Obstetrics and Gynecology, University of São Paulo, São Paulo, Brazil.*

Background: AFSCs are a class of stem cells that present characteristics intermediate between embryonic stem cells (ESC) and adult mesenchymal stem cells (MSC). Given that the amniotic fluid consists of fetal urine, stem cell populations present in the amniotic fluid are likely derived from the fetal kidney. These characteristics have aroused great interest in the potential protective effects of AFSCs in renal diseases. The aim of this study was to analyze the effects of AFSCs in an experimental model of CKD, the 5/6 nephrectomy (Nx) model, after the disease has been established, in order to more closely resemble the clinical settings in humans.

Methods: Human AFSCs were isolated from second trimester amniocentesis samples by plastic adhesion and characterized as MSC. Male Wistar rats (n= 38) underwent 5/6 Nx or were Sham-operated. After 15 days, 14 rats were euthanized and renal disease was confirmed (**Nx-15d**). In subsequent experiments, the remaining 31 rats received $5x10^5$ AFSCs or saline, injected under the kidney capsule, and were followed for an additional 15 days. These rats were divided into 4 groups: **Sham 30d**, **Sham+AFSC 30d**, sham rats receiving AFSCs; **Nx,** 5/6 nephrectomy; and **Nx+AFSC**, Nx rats receiving AFSCs. The table shows the parameters analyzed.

Results: Nx rats with established CKD and treated with AFSCs displayed significant reductions in blood pressure, albuminuria and glomerulosclerosis. In addition, they showed lower expression of α-SMA and ED-1, as well as higher expression of WT-1, in comparison with untreated Nx rats.

Conclusions: These results demonstrate that inoculation of AFSCs ameliorate renal disease in established chronic kidney disease.

Funding: Government Support - Non-U.S.

	EXPERIMENTS AFTER ESTABLISHED CKD					
	15 DAYS		30 DAYS			
	Sham 15d (n=7)	Nx 15d (n=7)	Sham 30d (n=6)	Sham+AFSC 30d (n=6)	Nx 30d (n=10)	Nx+AFSC30d (n=9)
BP (mmHg)	131±2	159±3*	126±2	133±3[a]	188±2[a,b]	169±7[a,b,c]
uAlb (mg/24h)	2±1	27±8*	1±0	1±0	110±13[a,b]	43±9[c]
Glomerulosclerosis (%)	1.5±1	10.3±3	0.3±1	0.0±1	29.2±7[a,b]	3.5±1[c]
Interstitial Fibrosis (%)	2±0.3	6±0.5*	4±1.1	3±0.4	11±0.4[a,b]	11±0.6[a,b]
WT1 (cells/glom)	11±1	7±0*	11±1	11±0	6±0[a,b,d]	9±1
α-SMA (%)	0.7±0.2	3.2±0.6*	0.1±0.0	0.2±0.1	5.3±0.8[a,b]	1.3±0.4[c]
ED1+ (cells/mm^2)	18±4	38±11	15±1	7±2	59±13[a,b]	16±4[c]

Mean±SEM: *p<0.05 *vs* Sham 15d; [a]p<0.01 *vs* Sham 30d; [b]p<0.001 *vs* Sham+AFSC 30d; [c]p<0.01 *vs* Nx 30d

FR-PO258

Lithocholic Acid Increases Plasma Levels of FGF23 Nobuhiro Hashimoto, Isao Matsui, Daisuke Mori, Ayumi Matsumoto, Karin Shimada, Satoshi Yamaguchi, Keiichi Kubota, Tatsufumi Oka, Sayoko Yonemoto, Yusuke Sakaguchi, Takayuki Hamano, Yoshitaka Isaka. *Osaka University Graduate School of Medicine, Suita, Japan.*

Background: The phosphate sensing mechanisms remain unresolved. Oral phosphate load can increase fibroblast growth factor 23 (FGF23) without affecting serum levels of phosphate. Vitamin D receptor (VDR) plays important roles in the regulation of FGF23. In addition to active vitamin D, lithocholic acid (LCA), a secondary bile acid, can activate VDR. Therefore, we examined effects of LCA on FGF23.

Methods: Vitamin D receptor knockout (VDR-KO) mice and their wild type (WT) littermates were maintained on rescue diet (20% lactose, 2% Ca, 1.25% P). Mice fed with diet containing 0.2% cholic acid (CA), chenodeoxycholic acid (CDCA), deoxycholic acid (DCA), or lithocholic acid (LCA) were analyzed. Effects of bile acids *in vitro* were analyzed by using UMR106 cells. Gut flora of phosphate loaded mice were analyzed by PCR.

Results: Orally administered LCA elevated plasma intact FGF23 (WT-control 97 ± 35 vs. WT-LCA 204 ± 62 pg/mL, *P* <0.001). The other bile acids did not affect plasma iFGF23. LCA increased urinary phosphate, whereas serum phosphate was not changed. In VDR-KO mice, whose serum calcium levels were corrected to normal range by the rescue diet, the effects of LCA were completely abrogated. Real time PCR analyses of the WT mice demonstrated that LCA upregulated mRNA of FGF23 in the bone. We also found that LCA upregulates mRNA levels of FGF23 in cultured UMR 106 cells. Because serum 1,25-dihydroxyvitamin D was suppressed by LCA in the WT mice, it was indicated that LCA *per se* elevated FGF23 in a VDR-dependent manner. We examined serum creatinine and urinary N-acetyl-β-D-glucosaminidase levels because kidney function is a critical determinant of plasma FGF23. LCA did not worsen kidney function. Dietary phosphate load increased fecal Firmicutes XIVa, an intestinal bacteria that produces secondary bile acid.

Conclusions: Oral administration of LCA elevates FGF23 in a VDR-dependent manner. The change in gut microbiota may contribute to the phosphate sensing mechanism.

FR-PO259

Erythropoietin Is a Major Determinant of C-Terminal Fibroblast Growth Factor 23 Michele F. Eisenga, Martin H. De Borst, Maarten A. de Jong, Stephan J. Bakker, Carlo A. Gaillard. *University Medical Center Groningen, Groningen, Netherlands.*

Background: An increased plasma level of the phosphaturic hormone fibroblast growth factor 23 (FGF23) is an independent risk factor for mortality and allograft loss in renal transplant recipients (RTR). Similarly, high erythropoietin (EPO) levels increase the risk of adverse outcomes in RTR. Here, we investigated whether EPO modulates C-terminal FGF23 (cFGF23) and intact FGF23 (iFGF23) in RTR and chronic kidney disease (CKD) patients.

Methods: Plasma cFGF23 and iFGF23 were measured with ELISA in two single-center RTR cohorts. Serum EPO levels were measured on Immulite 2000 assay. Statistical analyses were performed using univariable linear regression followed by stepwise backward linear regression. Additionally, we assessed the effect of exogenous EPO on FGF23 in a post-hoc analysis of a randomized trial in CKD patients who received exogenous EPO (50 IU/kg/wk) for 52 weeks (EPOCARES, Eur J Heart Fail 2010;12:943-50) using linear mixed models.

Results: We included 680 stable RTR (age 53±13 years; 56% males at 5.4 (1.9-12.1 years after Tx). Median [IQR] cFGF23 was 140 (95-234) RU/ml, median iFGF23 was 61 (43-100) pg/mL, EPO was 6.9 (4.2-11.2) IU/L, and mean eGFR was 47±16 ml/min/1.73m2. In univariable analysis, EPO was a major determinant of cFGF23 (ß=0.24, *P*<0.001), but not of iFGF23 (ß=0.04, *P*=0.35). Upon multivariable analysis, EPO remained a major determinant of cFGF23 (ß=0.20, *P*<0.001), independent of known determinants including phosphate (ß=0.19, P<0.001), hemoglobin (ß=-0.13, P<0.001), and eGFR (ß =-0.35, P<0.001). In an independent replication cohort of 598 RTR, EPO was also a major determinant of cFGF23, independent of potential confounders (ß=0.22, *P*<0.001). Finally, in 56 CKD patients, exogenous EPO was significantly associated with an increase in cFGF23 (*P*=0.04), but not iFGF23 (*P*=0.21).

Conclusions: Serum EPO levels are a major, potentially modifiable independent determinant of serum cFGF23 in RTR, independently of known correlates including eGFR and phosphate. In CKD patients, exogenous EPO increased cFGF23 levels. We found no relationship between EPO and iFGF23 in either analysis. Our data suggest that EPO resistance, or an underlying mechanism, is related to FGF23 processing in CKD and after kidney transplantation.

FR-PO260

Acute Blood Loss Stimulates Fibroblast Growth Factor 23 Production Seham M. Rabadi,[2] Ikemesit Udo,[2] David E. Leaf,[1] Sushrut S. Waikar,[1] Marta Christov.[2] *[1]Harvard Medical School, Boston, MA; [2]New York Medical College, Valhalla, NY.*

Background: Fibroblast growth factor 23 (FGF23) production is upregulated by iron deficiency and hypoxia. The influence of acute blood loss and erythropoietin on FGF23 production is unknown.

Methods: Using wild-type C57BL/6 mice we determined the effect of acute loss of 10% total blood volume on Fgf23 mRNA expression in bone and circulating total FGF23 protein levels (measured by the c-terminal assay, cFGF23) and other markers of mineral metabolism. We also measured plasma cFGF23 levels in 131 critically ill patients admitted to the intensive care unit to assess the association with number of blood transfusions as an indicator of acute blood loss.

Results: We found that acute blood loss leads to an increase in plasma cFGF23 levels 3-5 fold within six hours, while plasma levels of intact FGF23, phosphate, calcium, parathyroid hormone, iron, and ferritin remain similar to control mice without acute blood loss. Volume resuscitation with PBS did not significantly alter these findings. The increase in plasma cFGF23 levels in bled animals was accompanied by increased plasma erythropoietin levels at 6 hours. Administration of erythropoietin led to an acute increase in plasma cFGF23 levels similar to that observed in acute blood loss. Fgf23 mRNA expression was increased 20-fold in bone marrow, but not in bone, of bled versus control mice, suggesting bone marrow as a key source of elevated plasma FGF23 levels following acute blood loss. To extend these findings to humans, we measured plasma cFGF23 levels in 131 critically ill patients. In univariate and multivariate models, we found a positive association between number of red blood cell transfusions, an indirect indicator of acute blood loss, and plasma cFGF23 levels.

Conclusions: We conclude that FGF23 production is rapidly increased after acute blood loss, and that erythropoietin may be the mediator of this increase. Thus, erythropoietin may represent a novel physiologic regulator of FGF23 production.

Funding: NIDDK Support, Private Foundation Support

FR-PO261

Ratios of Parathyroid Hormone, Fibroblast Growth Factor 23, and 1,25-Dihydroxylvitamin D and CKD Progression Adeera Levin,[2] Ognjenka Djurdjev,[1] Mila Tang,[5] Claudia Zierold,[3] Frank A. Blocki,[3] Fabrizio Bonelli,[3] Myles S. Wolf.[4] *[1]BC Renal Agency, Vancouver, AB, Canada; [2]UBC, Vancouver, BC, Canada; [3]DiaSorin, Stillwater, MN; [4]Duke University, Durham, NC; [5]St. Paul's Hospital, Vancouver, BC, Canada.*

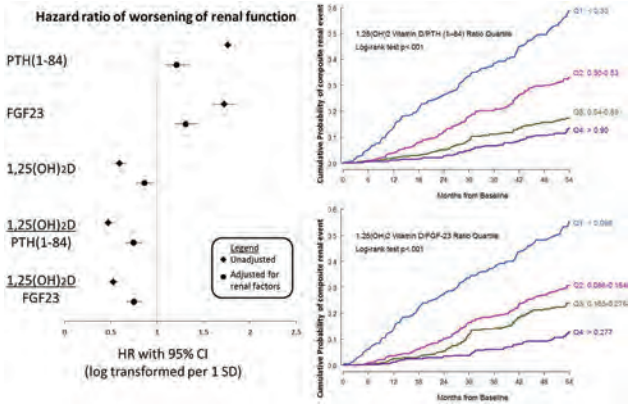
Background: Patients with CKD experience variable rates of progression. Ratios of parathyroid hormone (PTH(1-84)), fibroblast growth factor 23 (FGF23) and 1,25-dihydroxylvitamin D ($1,25(OH)_2D$) describing relative values of important hormonal systems and renal tubular function that provide insight into risk of CKD progression.

Methods: We examined data from CanPREDDICT, a prospective CKD pan-Canadian cohort from 2008-2013, followed biannually for 5yrs, with adjudicated outcomes. PTH(1-84), intact FGF23 and $1,25(OH)_2D$ were evaluated at baseline using precise new assays (Diasorin Inc), on the LIAISON XL analyzer. We used Cox proportional hazards to examine composite renal events (CRE) defined by need for renal replacement therapy or 50% decline of baseline eGFR, adjusted for age, sex, BP, weight, eGFR, ACR, Alb, PO_4, HCO_3, Ca, Hgb and K+ (base). Univariate and multivariate adjusted HRs were calculated per one standard deviation increments using natural log-transformed variables where appropriate.

Results: The study cohort included 1784 pts with a median follow-up of 41 months; mean age of 68yrs; 62% males; and mean eGFR of 28 ml/min/1.73m² (19% <20ml/min, 42% 20-29ml/min and 39% 30-45mil/min). There were 429 (24%) CRE. Higher PTH(1-84) and FGF23 levels, and lower $1,25(OH)_2D$ and ratios of $1,25(OH)_2D$/PTH(1-84) and $1,25(OH)_2D$/FGF23 precited significantly higher risk of CRE in unadjusted and adjusted analyses [p<0.01; Figure 1a]. The corresponding category-free net reclassification indices [95%CI] were 13.5%[-0.2 to 32.3%], 6.2%[-8.1 to 22.9%], 6.2%[-11.4 to 26.9%], 17.6%[-1.7 to 34.4%], and 2.8%[-13.6 to 20.0%] respectively.

Conclusions: High levels of PTH(1-84) and FGF23 predict higher risk of CRE; higher levels of $1,25(OH)_2D$ may be protective against CRE. The ratio of these may offer better insights than any one value alone. Further study of individual and combinations of biomarker levels is needed.

Funding: Commercial Support - DiaSorin Inc



FR-PO262

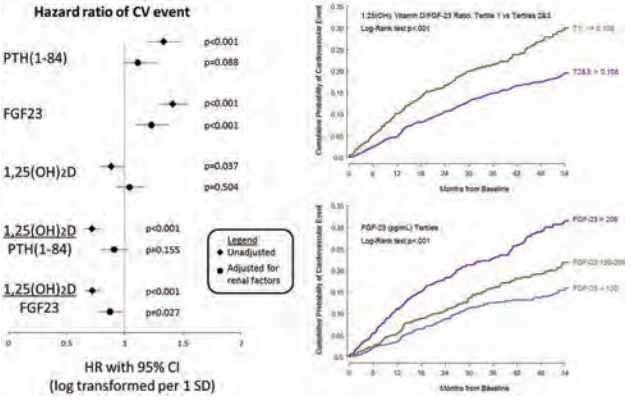
Ratios of Parathyroid Hormone, Fibroblast Growth Factor 23, and 1,25-Dihydroxylvitamin D and Cardiovascular Events Adeera Levin,[5] Ognjenka Djurdjev,[1] Mila Tang,[5] Claudia Zierold,[2] Frank A. Blocki,[3] Fabrizio Bonelli,[6] Myles S. Wolf.[4] *[1]BC Renal Agency, Vancouver, AB, Canada; [2]DiaSorin, Stillwater, MN; [3]DiaSorin INC, Stillwater, MN; [4]Duke University, Durham, NC; [5]St. Paul's Hospital and University of British Columbia, Vancouver, BC, Canada; [6]diasorin spa, Stillwater, MN.*

Background: Abnormal calcium homeostasis in patients with CKD may impact vascular health. Ratios of parathyroid hormone (PTH(1-84)), fibroblast growth factor 23 (FGF23) and 1,25-dihydroxylvitamin D ($1,25(OH)_2D$) may provide insight into imbalances in the system and its relation to cardiovascular events (CVE).

Methods: We examined data from CanPREDDICT, a prospective CKD pan-Canadian cohort from 2008-2013, followed biannually for 5yrs, with adjudicated outcomes. PTH(1-84), intact FGF23 and $1,25(OH)_2D$ were evaluated at baseline using precise new assays (Diasorin, Inc.). We used Cox proportional hazards to examine adjudicated CVE, adjusted for age, sex, diabetes and CVE history, BP, weight, eGFR, ACR, Alb, PO_4, HCO_3, Hgb, and ASA, ACEi, beta-blocker medications. Univariate and multivariate-adjusted HRs were calculated per 1 standard deviation increments using natural log-transformed variables where appropriate.

Results: The study cohort included 1789 pts with a median follow-up of 48 mo; mean age of 68yrs; 62% males; and mean eGFR of 28 ml/min/1.73m² (19% < 20ml/min, 42% 20-29ml/min and 39% 30-45ml/min). 44% of patients had history of CV disease and 46% had diabetes. 339 (19%) patients experienced CVE. Higher FGF23 levels, and lower $1,25(OH)_2D$ /FGF23 predicted significantly higher risk of CVE in unadjusted and adjusted analyses [p<0.01; Figure 1a]. The corresponding category-free net reclassification indices [95%CI] were 5%[-0.8 to 23.8%], and 7.7%[-6.4 to 20.2%] respectively.

Conclusions: High levels of FGF23 and lower $1,25(OH)_2D$/FGF23 predict higher risk of CVE. Further study of individual and combinations of biomarker levels is needed.



FR-PO263

Increased FGF23 Production in CKD Is Associated with Altered Osteocyte Development and Bone Mineralization Corey Dussold,[1] Samantha Neuburg,[1] Ying Liu,[2] Jian Feng,[2] Xueyan Wang,[1] Valentin David,[1] Myles S. Wolf,[3] Aline Martin.[1] *[1]Northwestern University, Chicago, IL; [2]Texas A&M-Baylor College of Dentistry, Dallas, TX; [3]Duke University, Durham, NC.*

Background: Fibroblast growth factor (FGF)-23 is a hormone produced by osteocytes that regulates phosphate (Pi) homeostasis. Chronic kidney disease mineral and bone disease (CKD-MBD) leads to alterations of mineral and bone metabolism, including elevation of circulating FGF23 levels that is associated with increased risk of cardiovascular mortality. The mechanism of increased FGF23 in CKD is poorly understood and the impact of CKD on osteocyte development and maturation has not been described. We tested the hypothesis that CKD induces changes in osteocyte morphology that result in altered osteocyte network, bone mineralization and mineral metabolism.

Methods: Using 3D-microtomography, acid-etched scanning electron microscopy, whole bone FITC staining and Imaris modelisation, we studied the bone and osteocyte phenotype of 9 week-old $Col4a3^{KO}$ mice with advanced CKD and wild-type (WT) littermates. We assessed in vitro matrix mineralization by alizarin red S (ARS) staining and osteoblast differentiation by alkaline phosphatase (ALP) staining of WT and $Col4a3^{KO}$ isolated primary osteoblasts (BMSCs). In parallel, we measured serum FGF23 and Pi levels, assessed renal function and measured FGF23 mRNA expression in vitro and in vivo.

Results: Renal function was dramatically impaired in $Col4a3^{KO}$ mice (BUN: 100±12 vs 18±1 mg/dL) and we observed a 15-fold increase in bone FGF23 mRNA expression, a 70-fold increase in serum FGF23 and a 50% increase in serum Pi levels (p<0.05 vs. WT for each). $Col4a3^{KO}$ mice displayed a 5% decrease in bone mineral density and a rounder, less polarized osteocyte morphology (osteocyte roundness index: 0.43±0.17 vs. 0.34±0.12) (p<0.05 vs. WT for each). The osteocyte network showed an 80% reduction in number and length of the dendritic processes (p<0.05 vs. WT). In vitro, $Col4a3^{KO}$ BMSCs maintained intrinsic abnormalities in activity and mineralization (-40% ALP activity and ARS; p<0.05 vs. WT).

Conclusions: Our data show that impaired osteocyte morphology and function is associated with defective bone mineralization and FGF23 overproduction in CKD. Whether altered osteocyte morphology is a cause of FGF23 overproduction and whether rescue of the bone mineralization and osteocyte morphology defects could prevent FGF23 elevation in CKD requires further investigation.

Funding: NIDDK Support

FR-PO264

Effects of Repeated Ferric Carboxymaltose on Phosphate and FGF23 Levels Rupal Mehta,[4] Alex Hodakowski,[3] Xuan Cai,[3] Myles S. Wolf,[1] Tamara Isakova.[2] *[1]Duke University, Durham, NC; [2]Feinberg School of Medicine, Northwestern University, Chicago, IL; [3]Northwestern University, Chicago, IL; [4]Northwestern Univesrsity, Feinberg School of Medicine, Chicago, IL.*

Background: Treatment of iron deficiency anemia (IDA) with a single dose of ferric carboxymaltose (FCM) reduces c-terminal FGF23 (cFGF23) levels, but paradoxically increases levels of biologically intact FGF23 (iFGF23), which results in hypophosphatemia. Although clinical trials of single doses of FCM reported high rates of reversible hypophosphatemia of unknown clinical significance, numerous reports have emerged of prolonged hypophosphatemia with severe skeletal complications in those who received repeated doses of FCM. No studies reported on the effects of repeated FCM dosing on phosphate and FGF23 levels.

Methods: We are conducting a longitudinal observational study of individuals who are receiving two doses of FCM for treatment of their IDA. We aim to test the following hypotheses: 1) repeated FCM dosing will be associated with prolonged increases in

iFGF23 levels and hypophosphatemia; 2) repeated FCM dosing will be associated with increased levels of markers of inflammation.

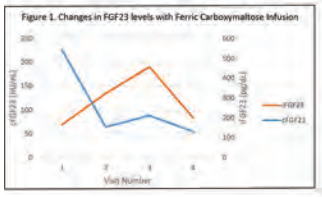
Results: We present data from 7 enrolled participants. Laboratory measurements (Table 1) were taken prior to each dose of FCM, 1 week after completion of therapy, and monthly until hypophosphatemia resolved. After a single FCM dose, ferritin markedly increased, cFGF23 decreased, but iFGF23 increased resulting in hypophosphatemia. After a second dose of FCM, iFGF23 further increased and hypophosphatemia persisted (Figure 1). During FCM treatment, serum phosphate decreased to ≤ 1.9 mg/dl in all 7 participants and ≤ 1.4 mg/dl n 5 of 7 participants, and criticlly low < 1.0 mg/dl in 2 patients (Figure 2). Two patients had persistent hypophosphatemia < 2.5 mg/dl at 90 days. Analyses of inflammatory marker are pending.

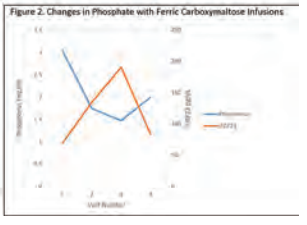
Conclusions: Administration of repeated doses of FCM treats ID and can lower cFGF23, but results in elevation of iFGF23 and prolonged hypophosphatemia. Given the increased utilization of FCM, the mechanisms and consequences of prolonged hypophosphatemia and elevated iFGF23 on bone and mineral metabolism markers necessitate further study.

Funding: Private Foundation Support

Table 1. Laboratory values of 7 participants before and after Ferric Carboxymaltose Infusions

	Pre-Infusion Visit 1	Post-Infusion Visit 1	Post-Infusion Visit 2	1 month Follow Up
Phosphorus (mg/dL)	3.0 ±0.3	1.7 ± 0.6	1.5 ± 0.5	2 ± 0.7
Tepi (%)	8.3 ± 1.2	18.4 ± 8.9	20.6 ± 4.7	26.0 ± 11.7
cFGF23 (RU/mL)	543 (484-684)	154 (130-211)	212 (140-224)	131 (96-162)
iFGF23 (pg/mL)	69 (53-81)	135 (106-152)	191 (122-217)	83 (70-98)
Ferritin (ng/mL)	13 (6-16)	369 (312-440)	717 (325-725)	262 (146-290)
TSAT (%)	8 ± 4	22 ± 7	29 ± 7	26 ± 7





FR-PO265

Effects of Iron Sucrose on Fibroblast Growth Factor 23 (FGF23) Levels in Iron-Deficient Patients with CKD and Heart Failure (HF) Rupal Mehta,[4] Alex Hodakowski,[3] Xuan Cai,[3] Myles S. Wolf,[1] Tamara Isakova.[2] *[1]Duke University, Durham, NC; [2]Feinberg School of Medicine, Northwestern University, Chicago, IL; [3]Northwestern University, Chicago, IL; [4]Northwestern Univesrsity, Feinberg School of Medicine, Chicago, IL.*

Background: Iron deficiency (ID) is a potent stimulus for increased FGF23 production. In healthy individuals with ID, upregulated FGF23 production is matched by FGF23 cleavage resulting in elevated c-terminal FGF23 (cFGF23) but normal intact FGF23 (iFGF23) levels. We hypothesize that FGF23 cleavage is impaired in CKD and HF and that the resultant imbalance between production and relatively decreased FGF23 cleavage contributes to the known elevation of iFGF23 levels in CKD and HF. Furthermore, if FGF23 cleavage is impaired in CKD and HF, we hypothesize that correction of ID in CKD and HF will lower both c- and iFGF23 levels unlike healthy individuals with normal cleavage in whom iron treatment only lowers cFGF23.

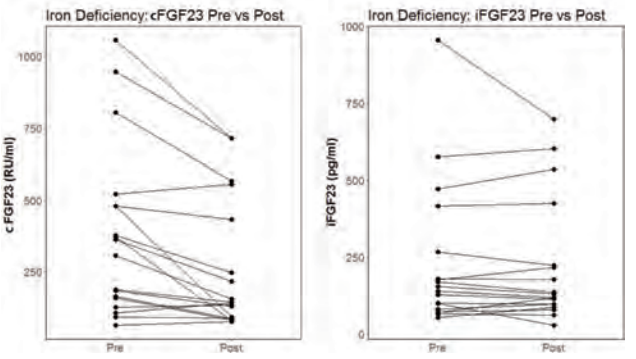
Methods: We recruited 18 individuals with ID anemia with CKD and HF to investigate the effects of 5 weekly doses of iron sucrose on c- and iFGF23 levels. ID anemia was defined as hemoglobin <12 g/dl and transferrin saturation (TSAT) <20%, or a hemoglobin <12 g/dl with a ferritin <100 mg/dl and TSAT <30%. Measurements were taken at baseline, prior to each iron dose, after 5 weeks, and 3 months later.

Results: Baseline laboratory values were as follows: mean eGFR was 36 ± 18 ml/min/1.73m^2, median ferritin was 44.0 (interquartile range [IQR] 22, 44 mg/dl), median TSAT 8% (IQR 8-19), median cFGF23 335 (IQR 158-480) RU/ml, and median iFGF23 147 (IQR 81-267) pg/dl. Baseline c- and iFGF23 strongly correlated (Spearman Correlation Coefficient 0.71, p value < 0.001). After 5 weeks, median cFGF23 was 142 (IQR 90-433) RU/ml with a mean decrease of -118 Ru/ml (-135 Ru/ml). Median iFGF23 was 125 (IQR 97-224) pg/dl, with a mean a decrease of 13 (± 70) pg/dl. No significant changes in eGFR or phosphate were appreciated.

Conclusions: ID patients with CKD and HF have elevated levels of c- and iFGF23. Treatment with iron sucrose lowers cFGF23 and may lower iFGF23 in states where FGF23 cleavage is impaired such as CKD and HF.

Funding: Private Foundation Support

Figure 1. Changes in c- and iFGF23 after Iron Sucrose administration



FR-PO266

Bone Content Is Related with Serum Fibroblast Growth Factor-23 (FGF23) in Patients on Maintenance Hemodialysis (MHD) Yukiko Hasuike, Wataru Fukao, Yuki Morikami, Tomoko Kimura, Yasuyuki Nagasawa, Takeshi Nakanishi. *Internal Medicine, Div Kidney and Dialysis, Nishinomiya, Japan.*

Background: FGF23 is a circulating factor that plays an critical role in the regulation of phosphate and vitamin D. In MHD patients, an increase in FGF23 can lead to the development of cardiovascular complications. FGF23 is produced by mature osteoblasts and osteocytes, however, the relationship between bone and FGF23 production remains poorly understood. We investigated whether bone content is related with FGF23 levels in MHD patients.

Methods: MHD patients with dialysis vintage at least 3 months (n=107) were enrolled in this study. Serum concentration of intact FGF23 (ELISA, Kainos) and the factors related to mineral bone disorders (calcium, phosphorus, bone-type ALP [BAP], 1,25(OH)$_2$vitamin D [calcitriol], 25(OH)vitamin D), inflammation (high-sensitivity CRP, interleukin-6, tumor necrosis factor-α), uremia (creatinine, p-crezol, indoxyl-sulfate, pentosidine) were measured. Walking speed, anthropometric parameters (body mass index, grip strength), bioelectrical impedance analysis (fat mass, body water volume) using inBody, and advanced body composition parameters (bone mineral content [BMC], bone mineral density [BMD], muscle mass) using Hologic QDR Discovery were assessed. The association between these factors and FGF23 were investigated.

Results: MHD patients recruited in this study showed mean age of 66.1±1.1 years, mean dialysis vintage 88.3±8.5 months, and median of serum FGF23 of 2100 (541 to 5825 pg/ml). Log-transformed FGF23 levels were associated with body weight, muscle mass, BMC, BMD, grip strength, serum calcium, phosphates, creatinine, and negatively linked with age, BAP, and walking speed. The stepwise regression analyses revealed that serum phosphorus, calcium, and BMC were the independent predictors of FGF23 (standardized regression coefficients were 0.620, 0.442, and 0.381, respectively, R^2=0.762, p<0.0001). There was no significant relationship between FGF23 and serum calcitriol.

Conclusions: FGF23 production can be independently associated with BMC as well as calcium and phosphate in MHD patients.

FR-PO267

Cardiac Fibroblast Growth Factor 23 Is Induced by Activated Renin-Angiotensin-Aldosterone System and Promotes the Pro-Fibrotic Crosstalk between Cardiac Myocytes and Fibroblasts Maren Leifheit-Nestler,[2] Felix Kirchhoff,[3] Julia Nespor,[1] Beatrice Richter,[4] Joerg Heineke,[1] Dieter Haffner.[1] *[1]Hannover Medical School, Hannover, Germany; [2]Hannover Medical School, Hannover, Germany; [3]Hannover Medical School, Hannover, Germany; [4]University of Alabama at Birmingham, Birmingham, AL.*

Background: FGF23 is discussed as a new biomarker associated with cardiac hypertrophy and mortality in patients with CKD, heart failure, and cardiogenic shock. We previously demonstrated that FGF23 is expressed by cardiac myocytes, enhanced in CKD, and induces cardiac hypertrophy via FGFR4-dependent activation of PLCγ/calcineurin/NFAT signaling independent of its co-receptor klotho. However, the impact of FGF23 on cardiac fibrosis is largely elusive.

Methods: By conducting a retrospective case-control study including myocardial autopsy samples from 24 patients with end-stage CKD and *in vitro* studies in cardiac fibroblasts and myocytes, we investigated the pro-fibrotic properties of FGF23.

Results: The accumulation of fibrillar collagens I and III was increased in myocardial tissue of CKD patients, and correlated with duration of dialysis, PTH, klotho deficiency, and enhanced angiotensinogen (*AGT*) expression. Using human fibrosis profiler PCR array analyzes, TGF-β and its related TGF-β receptor/Smad complexes, extracellular matrix remodeling enzymes, as well as pro-fibrotic growth factors were significantly upregulated in myocardial tissue of dialysis patients. In cultured cardiac fibroblasts, FGF23 stimulated pro-fibrotic TGF-β receptor/Smad complexes and collagen synthesis, whereas treatment of isolated cardiac myocytes with FGF23 resulted in enhanced collagen remodeling, expression of pro-inflammatory genes, pro-survival pathways, and induction of pro-hypertrophic genes. FGF23 enhanced the expression of *Agt* in cardiac fibroblasts and myocytes, and angiotensin II and aldosterone, as components of the renin-

angiotensin-aldosterone system (RAAS), strongly induced FGF23 in cardiac myocytes to directly promote fibrotic and hypertrophic response.

Conclusions: In conclusion, stimulation with active RAAS components induces FGF23 expression in cardiac myocytes, which in turn stimulates the pro-fibrotic crosstalk between cardiac myocytes and fibroblasts.

FR-PO268

Change in Fibroblast Growth Factor 23 during the Progression of Left Ventricular Hypertrophy in Hypertensive Model Rats Hideki Fujii, Kentaro Watanabe, Keiji Kono, Shunsuke Goto, Shuhei Watanabe, Shinichi Nishi. *Kobe University Graduate School of Medicine, Kobe, Japan.*

Background: Many clinical studies have demonstrated that serum fibroblast growth factor-23 (FGF23) levels are significantly associated with left ventricular hypertrophy (LVH). Although LVH is frequently observed in hypertensive patients, no experimental and clinical data have proved that FGF23 induces LVH in these patients. A previous study showed that subjects with high serum FGF23 levels may lead to hypertension in the future. Thus, the association between FGF23, hypertension, and LVH is very complexed and remains unknown. The purpose of our study was to examine the change in serum and intracardiac FGF23 during the progression of hypertension using spontaneously hypertensive rats (SHR).

Methods: We used male SHRs (HT group) and Wistar Kyoto rats (WKY) as a control group in the present study. At 10 weeks, urinary and blood biochemical analyses and blood pressure measurements were performed for these rats. At 18 weeks, the rats were sacrificed and urinary and blood biochemical analyses and real time PCR were performed in the two groups.

Results: At baseline, serum calcium, phosphate and FGF23 levels were comparable between the two groups. Although serum creatinine levels were also comparable, blood pressure, urinary excretion of albumin and serum NT-pro BNP levels were significantly elevated in the HT group compared to the control group. At 18 weeks, relative heart weight and serum NT-proBNP levels were significantly greater in the HT group. In addition, serum calcium and phosphate levels were significantly lower and serum FGF23 levels were significantly higher in the HT group than in the control group. Further analysis showed that mRNA expression of FGF23 in the heart was significantly increased in the HT group than in the control group. Both serum FGF23 levels ($r=0.63$, $p<0.05$) and intracardiac mRNA expression of FGF23 ($r=0.79$, $p<0.05$) were significantly correlated with relative heart weight.

Conclusions: During the progression of hypertension, serum FGF23 levels were elevated and LVH progressed. Although it is not known whether change in FGF23 is a cause or result of LVH, we suggest that FGF23 is associated with the development of LVH in hypertension.

FR-PO269

Effect of Dietary Sodium and Phosphorus Intake on Fibroblast Growth Factor-23 in Patients with Diabetic Nephropathy Manoj Bhattarai,[3,1] Jeet Gandhi,[3,1] Chakradhar Velagapudi,[3,1] Shuko Lee,[1] Sue E. Cunningham,[3] Subrata Debnath,[3] Shirley L. Hu,[2] Shweta Bansal.[3,1] *[1]South Texas Veterans Health Care System, San Antonio, TX; [2]UTHealth Houston, McALlen, TX; [3]University of Texas Health Science Center at San Anotonio, San Antonio, TX.*

Background: High FGF23 levels independently associate with cardiovascular and all-cause mortality in CKD patients. Higher dietary phosphorus intake increases FGF23 levels in healthy individuals. However, this association in CKD patients in unclear. FGF23 levels have been positively associated with markers of volume status in renal transplant patients suggesting possible role of dietary sodium intake. The relationship between dietary sodium and phosphorus and plasma FGF-23 levels is not well-studied in advance diabetic nephropathy patients. We hypothesize that high dietary sodium and phosphorus associate with high plasma FGF23 levels in patients with diabetic nephropathy.

Methods: We conducted a sub-analysis of a randomized-controlled trial where subjects with type 2 DM with albumin-creatinine ratio of >150 mg/g and eGFR 15-60 ml/min were recruited to test the anti-proteinuric effect of Silybin and N-acetylcysteine. Dietary phosphorus intake was assessed from 3-day diet record. Daily sodium intake was estimated by measuring 12-hour urinary sodium excretion. Plasma FGF23 was measured using a second generation C-terminal ELISA kit.

Results: The study population was 62.9±7.5 years old, 89% male, 65% Hispanic, and 27% non-Hispanic white, had BMI of 35±8.54 kg/m2, and eGFR of 36.4±13.3 ml/min. Mean dietary phosphorus intake and urinary sodium was 1418±438 mg/d and 3882±2486 mg/d, respectively with median plasma FGF23 78 [44, 127] RU/ml at baseline. On univariate analysis, plasma FGF23 correlated negatively with eGFR ($r=-0.6$, $p<0.001$) and positively with serum phosphorus ($r=0.5$, $p<0.001$) and NGAL ($r=0.7$, $p<0.001$). There was no correlation between plasma FGF23 and daily phosphorus or sodium intake. In multivariable regression model including age, eGFR, daily sodium and phosphorus intake, serum phosphorus and NGAL, only eGFR predicted the plasma FGF23 significantly ($\beta=-0.47$, $p=0.02$).

Conclusions: Daily sodium and phosphorus intake do not correlate with plasma FGF23 in patients with advance diabetic nephropathy. This observation is in contrast with healthy individuals where high phosphorus intake increases plasma FGF23 levels.

Funding: Other NIH Support - NIH-NCCAM AT004490, Veterans Affairs Support

FR-PO270

Effect of Treatment of Metabolic Acidosis on Fibroblast Growth Factor-23 in Patients with CKD Pratik B. Shah,[5] Emily Andrews,[3] Zhiying You,[1] Michel Chonchol,[2] Jessica B. Kendrick.[4] *[1]UC Denver, Aurora, CO; [2]University of Colorado, Aurora, CO; [3]University of Colorado Denver, Aurora, CO; [4]University of Colorado Denver and Denver Health Medical Center, Denver, CO; [5]University of Colorado at Denver and Health Sciences Center, Denver, CO.*

Background: The regulation of fibroblast growth factor-23 (FGF23) in patients with chronic kidney disease (CKD) is not understood. We conducted a study to test the hypothesis that treatment with oral sodium bicarbonate in patients with CKD and metabolic acidosis reduces intact FGF23 (iFGF23) levels.

Methods: We performed a prospective, randomized, open-label, 14 week crossover study of 20 subjects with stage 3B-4 CKD (eGFR 15-44 ml/min/1.73m^2) and metabolic acidosis (serum bicarbonate level of <22 and ≥16 mEq/L). Subjects were randomly assigned to start with treatment or control. Each period was 6 weeks in duration with a 2 week washout period in between. Patients were treated with oral sodium bicarbonate tablets for goal bicarbonate > 22 mEq/L. Outcome measures were repeated at the beginning and end of each period. Mixed effects models were employed in comparison of pre-post change in iFGF23 and phosphorus between treatment and control groups.

Results: The mean (SD) age and eGFR was 58.5 ± 12.8 years and 24.6 ± 8.1 ml/min/1.73m^2, respectively. iFGF23 increased significantly during the treatment period ($p=0.008$) and not during the control ($p=0.68$). When we compared iFGF23 between the treatment and the control periods, there was a trend towards significance ($p=0.065$). Serum phosphorus increased significantly during the treatment period but not in the control and the increase in phosphorus was significant between the groups ($p=0.038$). There was no significant change in serum parathyroid hormone or kidney function in either group.

Conclusions: Treatment of metabolic acidosis with sodium bicarbonate in CKD increases serum phosphorus and iFGF23. The mechanism of these observations is unexplained and further studies are needed to confirm these results.

Funding: NIDDK Support, Other NIH Support - NHLBI

	Control Baseline	Control 6 weeks	P-value	Treatment Baseline	Treatment 6 weeks	P-value	Between group P-value
Bicarbonate (mEq/L)	19.7 ± 2.3	19.6 ± 3.2	0.93	19.3 ± 2.9	22.0 ± 3.1	<0.001	0.005
iFGF23 (pg/mL) Median [IQR]	239.8 [142.3-465.4]	209.5 [171.4-677.6]	0.68	228.2 [149.6-362.6]	257.2 [176.2-832.3]	0.008	0.065
Calcium (mg/dL)	9.4 ± 0.5	9.2 ± 0.5	0.13	9.2 ± 0.5	9.3 ± 0.5	0.39	0.03
Phosphorus (mg/dL)	4.2 ± 0.8	4.2 ± 1.1	0.85	4.1 ± 0.6	4.5 ± 1.1	0.02	0.04
PTH (pg/mL) Median [IQR]	135 [72-266]	149 [68-251]	0.19	138 [86-251]	167 [101-385]	0.13	0.89

FR-PO271

Changes in FGF23 and Soluble Klotho Levels after Initiation of Hemodialysis Chiaki Kawabata,[1] Hirotaka Komaba,[1,2] Yosuke Nakagawa,[1] Naoto Hamano,[1] Masahiro Koizumi,[1] Genta Kanai,[1] Takehiko Wada,[1] Masafumi Fukagawa.[1] *[1]Tokai University School of Medicine, Isehara, Japan; [2]The Institute of Medical Sciences, Tokai University, Isehara, Japan.*

Background: FGF23 is markedly elevated in end stage of renal disease and these levels have been associated with increased risk of mortality. It has been suggested but not proved that long-term management of hyperphosphatemia is required to achieve sufficient reductions in FGF23 levels. Initiation of hemodialysis leads to a marked removal of phosphate from the body and resultant reductions in PTH levels, but the effect of hemodialysis initiation on FGF23 levels has not been explored.

Methods: We conducted a prospective observational study of twenty patients initiating hemodialysis. We follow upped over five days with four hemodialysis sessions. We did not change the prescription of vitamin D receptor activators, phosphate binders, or cinacalcet during the study period. We measured biochemical parameters of mineral metabolism including FGF23 pre and post each hemodialysis session, a total of 8 times. Serum full-length FGF23 levels were measured using a chemiluminescent enzyme immunoassay (Kyowa Medex, Co., Ltd) and soluble Klotho levels were measured using an enzyme linked immunosorbent assay (Immuno-Biological Laboratories, Co., Ltd).

Results: At baseline, serum levels were as follows; phosphorus, 5.6 ± 1.9 mg/dl; intact PTH, 299 (182-356) pg/ml; FGF23, 517 (300-919) pg/ml; and soluble Klotho, 297 ± 107 pg/ml. Initiation of hemodialysis led to a progressive reduction in serum phosphorus, intact PTH, and FGF23 levels (median percent changes from baseline to the start of the 4th hemodialysis session were -32%, -8%, and -43%, respectively). Prescription of vitamin D receptor activators did not modify the effect of hemodialysis initiation on FGF23 levels. There was no meaningful change in soluble Klotho levels.

Conclusions: FGF23 levels decrease drastically after initiation of hemodialysis. A marked removal of phosphorus by hemodialysis initiation could suppress the production of FGF23 by osteocytes. Our findings suggest a critical role of phosphorus retention in markedly elevated FGF23 and support the importance of serum phosphorus management for suppressing FGF23 production, which may have diverse toxic effects.

FR-PO272

Oxygen Consumption Is the Major Determinant of Klotho Release by the Kidney Daniela Picciotto,[1,3] Giacomo Garibotto,[1,3] Samantha Milanesi,[4] Abitha Murugavel,[6,3] Francesca Viazzi,[5,3] Daniela Verzola.[2] *[1]DIMI, Genoa University, Genoa, Italy; [2]University of Genoa Di.M.I. Nephrology, Genoa, Italy; [3]Clinica nefrologica, Dialisi, Trapianto, Ospedale Policlinico San Martino, Genoa, Italy; [4]University of Genoa, Genoa, Italy; [5]University of Genoa, Genoa, Italy; [6]University of Genoa, Genoa, Italy*.

Background: Plasma levels of soluble αKlotho (sKlotho), an anti-aging protein which serves as the co-factor for FGF23, progressively decline along with CKD progression. However, our knowledge of the sites and mechanisms which regulate circulating sKlotho is still incomplete.

Methods: To explore the role of the kidney and of the extra-renal sites on the metabolic handling of sKlotho, we measured sKlotho levels in venous effluents from different organs, including the kidney, the splanchnic organs and lung, as well as in arterial blood, in a cohort of patients (n=20,10M/10F, age 56-82 yr, BMI 25±1 Kg/m^2, eGFR 63±4 ml/min-range 23-98 ml/min), undergoing a right-sided cardiac catheterization.

Results: Mean arterial sKlotho was 202 ± 26 pg/ml. Renal vein αKlotho concentrations were remarkably higher (by ~8 %, $p < 0.05$) than the corresponding arterial values, indicating that plasma αKlotho increases substantially after a single pass across the kidney. The fractional enrichment (FE) of sKlotho across the kidney was similar (8±6 vs. 9±4%, respectively) in patients with normal renal function (n=11) and in patients with GFR< 60 ml/min (n=9, eGFR 39±3 ml/min). sKlotho level in the liver vein was lower (by 23±6 %, $p<0.05$) than the arterial one in patients with GFR< 60 ml/min. Arterial sKlotho levels were almost identical to pulmonary artery levels. In all subjects, at univariate analysis, fractional enrichment (FE) of sKlotho across the kidney was directly related to the fractional extraction of oxygen ($r=0.412$, $p< 0.05$), and inversely, to plasma sodium ($r=0.434$, $p< 0.05$) and uric acid ($r=0.357$, $p < 0.06$) but not to eGFR, hemoglobin and phosphate levels. At multivariate analysis, the fractional extraction of oxygen across the kidney was the only determinant of sKlotho FE.

Conclusions: Our data show that the human kidney is the only site for sKlotho production in the body, while splanchnic organs may participate to sKlotho removal. Oxygen uptake by the kidney is the major determinant of sKlotho production by the human kidney, suggesting a role for hypoxemia on reducing the availability of sKlotho to the systemic circulation. Besides providing a better understanding of physiology of αKlotho metabolism, the data reported in this study could be useful to understand the alterations in αKlotho that are observed in CKD and many systemic and organ diseases.

Funding: Government Support - Non-U.S.

FR-PO273

The Effect and Possible Mechanism of Klotho on the Expression of Fibroblastic Growth Factor 23(FGF23) Secreted by Osteoblast-Like UMR-106 Cells Huijuan Mao, Lulu Ma. *First Affiliated Hospital of Nanjing Medical University, Nanjing, China*.

Background: To investigate the effect and possible mechanism of Klotho on the expression of FGF23 in UMR- 106 cells.

Methods: UMR-106 cells were divided into 5 groups and cultured for 72 h: (1) control group;(2)β-glycerophosphate(β-GP) group;(3)β-GP+Klotho group;(4)β-GP+LiCl group;(5)β-GP+Klotho+LiCl group, and then the expression of FGF23, P-GSK-3β and GSK-3β protein was measured by Western blotting. The levels of mRNA of FGF23 and c-myc were determined by RT-PCR.

Results: 1.β-GP induced the increase of expression of FGF23 mRNA and protein. Compared with β-GP group, FGF23 mRNA and protein expression was downregulated after treating with Klotho(Figure 1).2.β-GP induced the increase of expression of P-GSK-3β/GSK-3β and c-myc mRNA.Compared with β-GP group, P-GSK-3β/GSK -3β and c-myc mRNA were downregulated after treating with Klotho(Figure 2). 3. The expression of FGF23, P-GSK-3β/GSK-3β and c-myc mRNA were upregulated when treated with LiCl(Figure 1 and 2).

Conclusions: Klotho down-regulates the expression of FGF23 induced by hyperphosphate in osteoblast-like UMR-106 cells via Wnt/β-catenin pathway.

Funding: Government Support - Non-U.S.

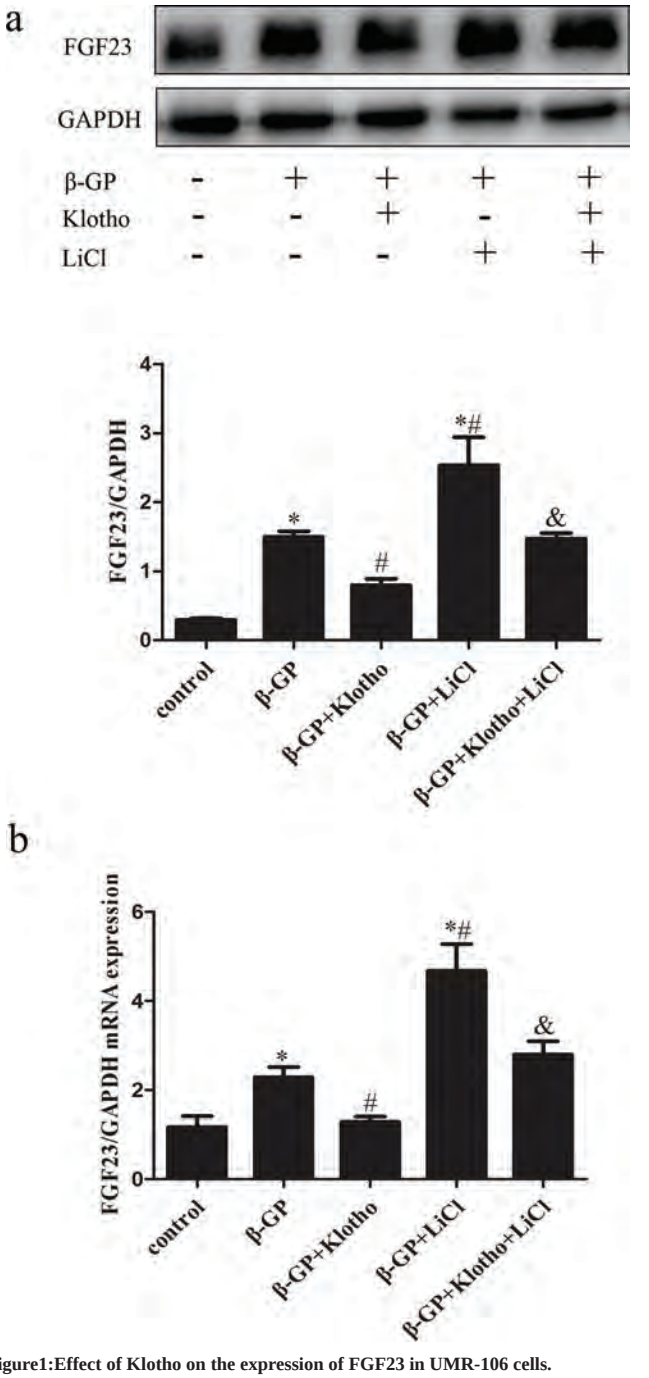


Figure1:Effect of Klotho on the expression of FGF23 in UMR-106 cells.

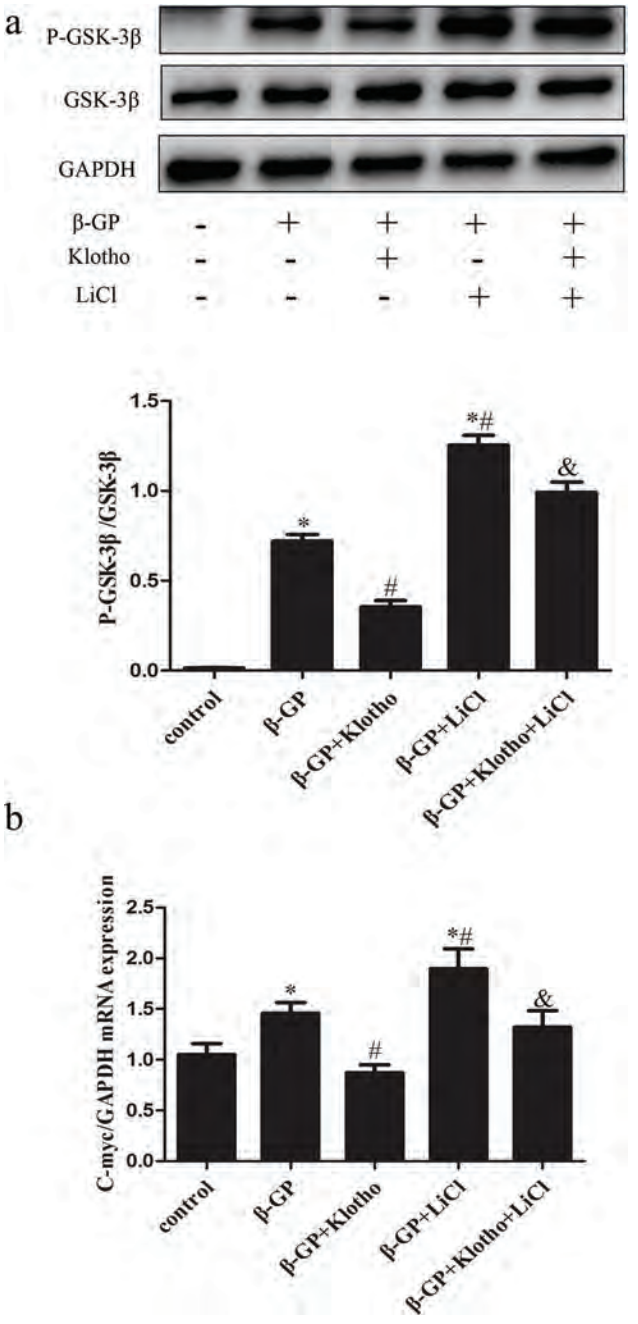


Figure2:Klotho regulated the expression of FGF23 through Wnt/β-catenin signaling pathway.

FR-PO274

Effects of Acute Administration of Ergocalciferol on Vitamin D Catabolism in Hemodialysis Patients Ornatcha Sirimongkolchaiyakul,[2] Anders H. Berg,[5] S. Ananth Karumanchi,[1] Katherine Wesseling-Perry,[2] Ravi I. Thadhani,[3] Isidro B. Salusky.[4] *[1]Beth Israel Deaconess Medical Ctr/ Harvard Medical School, Boston, MA; [2]David Geffen School of Medicine at UCLA, Los Angeles, CA; [3]Massachusetts General Hospital, Boston, MA; [4]Mattel Children's Hospital, Los Angeles, CA; [5]None, Boston, MA.*

Background: Vitamin D deficiency is highly prevalent in dialysis patients and D supplementation has been recommended. However, there is limited data of vitamin D catabolism in advanced CKD. Stimulation of 24-hydroxylase mediated catabolism of vitamin D metabolites may reduce serum 25(OH)D and 1, 25$(OH)_2$D levels. To test this possibility, we assessed vitamin D catabolism after a single ergocalciferol administration (D2) in hemodialysis patients (HD) and healthy volunteers (HV).

Methods: All subjects ingested a single oral dose of 50,000 IU ergocalciferol, HD patients aged 65.8 (20.6, 71.0) years (n = 35) and HV aged 41.0 (29.0, 62.0) years (n = 7). Biochemical determinations of 25D, 1,25D, 24,25 D and DBP were measured at baseline and 2-5 days after D_2 ingestion. Biochemical markers at baseline and post-therapy were compared.

Results: Concentrations of $25D_2$ increased after D_2 in both HD and HV (average increases of +14.5 ng/mL [95%CI 9.5-29.4] and +21.2 [95%CI 14.6-29.8], respectively). Although average pre-treatment $25D_3$ concentrations were significantly higher in HD compared to HV (21.2 ng/mL [95% CI 14.6-29.8] vs. 14.5 ng/mL [95%CI 9.5-29.4], $p<0.05$), concentrations of 24,25D3 were lower in HD (5.5 ng/mL [95% CI 3.5-15.6] vs. 14.5 ng/mL [95%CI 9.5-29.4], $p<0.05$). Average concentrations of $1,25D_3$ was also lower in HD (4.7 pg/mL [95% CI 2.8-8.4] vs. 54.1 pg/mL [95%CI 47.7-69.2], $p<0.05$). Amongst HV, concentrations of $25D_3$ decreased on average by -0.6 ng/mL [95%CI -3.9 to -0.2] after Vitamin D_2 administration, and $1,25D_3$ decreased by -10.6 pg/mL(95%CI -20.2 to -0.5), whereas there was no significant decrease in $24,25D_3$. Amongst HD, no significant changes in $25D_3$, $24,25D_3$, or $1,25D_3$ were seen. Amongst HV, concentrations of both $1,25D_3$ and $24,25D_3$ correlated strongly with $25D_3$ ($R^2 = 0.4558$ and $R^2 = 0.6993$, respectively). In contrast, the correlations between $25D_3$ and $1,25D_3$ and between $25D_3$ and $24,25D_3$ in HD were weaker ($R^2 = 0.1285$ and $R^2 = 0.4654$, respectively).

Conclusions: CKD is associated with higher $25D_3$ but lower 24,25D and 1,25D concentrations, and 1,25 levels are more closely associated with 24,25D than with 25D in ESKD. Feedback regulation of both 1,25D and 24,25D by PTH and/or FGF23 in HD warrants further investigation.

Funding: NIDDK Support, Private Foundation Support

FR-PO275

The Relation of the 24,25 to 25-Hydroxyvitamin D Ratio with Bone Density and Fracture Risk in Older Adults: The Cardiovascular Health Study Charles Ginsberg,[6] Ronit Katz,[2] Ian H. de Boer,[2] Bryan R. Kestenbaum,[2] Michel Chonchol,[1] Michael Shlipak,[3,7] Mark J. Sarnak,[4] Andrew N. Hoofnagle,[5] Dena E. Rifkin,[7] Pranav S. Garimella,[6] Joachim H. Ix.[6] *[1]University of Anschutz Medical Center, Aurora, CO; [2]University of Washington, Seattle, WA; [3]San Francisco VA Medical Center, San Francisco, CA; [4]Tufts Medical Center, Boston, MA; [5]University of Washington, Seattle, WA; [6]University of California, San Diego, San Diego, CA; [7]University of California, San Francisco, San Francisco, CA.*

Background: Serum 25-hydroxyvitamin D [25(OH)D] concentrations may not optimally indicate vitamin D receptor (VDR) activity. Catabolism of 25(OH)D to 24,25-dihydroxyvitmin D [$24,25(OH)_2$D] is stimulated by active 1,25-dihydroxyvitamin D. Thus, higher concentrations of $24,25(OH)_2$D and a higher ratio of $24,25(OH)_2$D to 25(OH)D (the vitamin D metabolite ratio [VMR]) may provide additional information on receptor activity. We compared the strength of associations of these markers with serum PTH concentrations, hip bone mineral density (BMD), and incident hip fracture among community-living older participants in the Cardiovascular Health Study (CHS).

Methods: We conducted a case-cohort study of 1116 CHS participants with over sampling for fracture outcomes. We used multiple linear regression to assess associations of 25(OH)D, $24,25(OH)_2$D, and VMR with PTH and hip BMD in the random cohort. We used a Cox proportional hazards model to estimate the association of each marker with incident fracture in the complete case-cohort population.

Results: Mean age was 78, 60% were female, and mean eGFR was 64 +/-16 ml/min/1.73m2. Serum 25(OH)D, $24,25(OH)_2$D, and VMR were each associated with PTH; the sizes of these associations were statistically indistinguishable. Higher serum $24,25(OH)_2$D concentrations, but not 25(OH)D or VMR, were associated with greater hip BMD. There were 289 hip fractures during 8.4 years mean follow-up. Serum concentrations of $24,25(OH)_2$D and VMR but not 25(OH)D were associated with incident fracture (Table).

Conclusions: Lower 24,25(OH)2D concentrations and VMR but not 25(OH)D concentrations were associated with hip fracture risk in community-living older adults.

Funding: NIDDK Support, Other NIH Support - NIH Loan Repayment Program, NHLBI, NINDS, National Institute on Aging, Private Foundation Support

Association of Vitamin D Measures with Incident Hip Fracture

	25-hydroxyvitamin D (ng/ml)	24,25-dihydroxyvitamin D (ng/ml)	VMR (ng/ml) / (ng/ml)
Hazard Ratio per SD higher (95% CI)	0.93 (0.79, 1.10)	0.73 (0.61, 0.87)	0.74 (0.61, 0.88)

Data for model adjusted for age, sex, race, season of measurements, site of measurement BMI, eGFR, serum calcium, phosphate and FGF-23.

FR-PO276

International Serum 25-OH-Vitamin D Measurement, Levels, and Treatment among Patients with CKD in Everyday Nephrology Practice: Results from CKDopps Sophie Liabeuf,[5] Keith McCullough,[4] Ronald L. Pisoni,[4] Yvonne Meier,[2] Jarcy Zee,[4] Helmut Reichel,[1] Roberto Pecoits-Filho,[6] Friedrich K. Port,[4] Bruce M. Robinson,[4] Ziad Massy.[3] *[1]Nephrological Center, Villingen-Schwenningen, Germany; [2]Vifor Pharma Ltd, Glattbrugg, Switzerland; [3]Ambroise Pare University Hospital, Boulogne Billancourt/ Paris cedex, France; [4]Arbor Research Collaborative for Health, Ann Arbor, AL; [5]CHU Amiens, Amiens, France; [6]Pontificia Universidade Catolica do Parana, Curitiba, Brazil.*

Background: CKD progression is linked to a decrease in 25 hydroxycholecalciferol (25[OH]D) with implications for secondary hyperparathyroidism. While the optimal

target for 25[OH]D has been defined in the general population as 30 ng/ml, the optimal target in CKD patients (pts) is under debate. We evaluate current international vitamin D (vit D) practices among CKD pts.

Methods: CKD pts with eGFR <60 ml/min/1.73m2 (N=3,360) from nephrology clinics in the prospective Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) (2013-2016) from Brazil (BR), Germany (GER) and the US were included. Serum 25[OH]D and prescribed vit D were each based on the first value reported in health records. Nephrologist preferences are from survey responses.

Results: 25[OH]D level was reported for 54% of pts, but this varied across clinics by country, being measured for >90% of pts in 70% of GER clinics and 43-44% of US & BR clinics. Among pts with measured 25[OH]D, 46-66% had 25[OH]D<30 ng/mL across the countries and CKD stages. Figure 1 shows for the pts with 25[OH]D data: (a) vit D (nutritional and/or active) prescription was similar for pts with 25[OH]D D<30 vs ≥30 ng/ml; (b) fewer than half of pts prescribed vit D are prescribed active vit D. More pts had active vit D prescriptions in stages 4/5 (28%) vs stage 3 (12%). Most US and BR nephrologists indicated a lower serum 25[OH]D target limit of 30 ng/mL. A few US, BR, and most GER nephrologists indicated 15-25 ng/mL. There was no consensus on the upper target limit. Neither limit differed by CKD stage.

Conclusions: Measurement of 25[OH]D levels is infrequent in many nephrology CKD clinics but common in others. Vit D prescription was similar for pts with 25[OH]D <30 v. ≥30. These findings raise questions regarding optimal approaches to incorporating serum 25[OH]D levels into broader MBD management in CKD practice.

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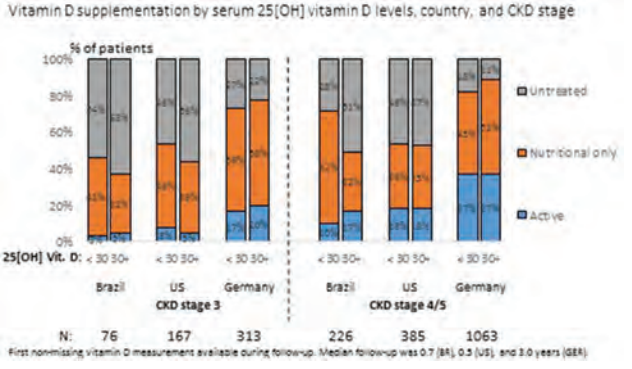


FR-PO277

The Impact of CKD on Analytical Performance of 25 Vitamin D Assays Hanna Karla A. Guapyass? Machado,[2] Carolina S. Martins,[2] Vanda Jorgetti,[2] Rosilene M. Elias,[2] Rosa M. Moyses.[2,1] [1]*Universidade Nove de Julho, São Paulo, Brazil;* [2]*Nephrology, Universidade de São Paulo, São Paulo, Brazil.*

Background: Current guidelines recommend evaluation of 25 vitamin D (25vitD) status and therapy when serum levels are below 30 ng/ml. Significant differences among some assays have been described. However, the impact of renal disease on these differences has never been assessed yet. In our service, the assay for 25vitD measurement was changed from Diasorin® to Beckman Coulter Unicel DXI 800®, which gave us the opportunity to evaluate the impact of the assay in the levels of 25vitD in CKD patients.

Methods: We obtained data from 540 patients [122 with eGFR > 90 ml/min (normal renal function); 138 with 30-60 ml/min (CKD3); 124 with 15-29 ml/min (CKD4) and 156 on dialysis (CKD5D)] in which serum 25vitD was measured with both assays with a time difference of 6 months.

Results: The median of serum 25vitD increased [23 (19-29) vs. 29 (22-37) ng/ml; p=0.0001], but could not be explained by seasonal differences, as the second measurement was done at wintertime. 25vitD increased in patients with CKD 3, 4 and 5D, but not in individuals with normal renal function. Indeed, the more advanced the CKD, the higher the median increase [-5 ng/ml (-9.3-4) in normal renal function; 3.5 ng/ml (-2.8-11) in CKD3; 3 ng/ml (-1.3-9) CKD4; and 8 ng/ml (1-15) in CKD5D; p<0.0001). The prevalence of 25vitD insufficiency increased from 49 to 62% in the entire population and from 44 to 57% only in CKD patients (p = 0.001 and 0.0001, respectively).

Conclusions: Our findings confirm the disagreement between 25vitD assays, showing higher levels with Beckman Coulter Unicel DXI 800®, which is more marked in CKD patients, suggesting that non-active fragments usually found in this population might be recognized as intact 25vitD. This technical problem will certainly affect hypovitaminosis D diagnosis and also therapy in CKD patients.

Funding: Government Support - Non-U.S.

FR-PO278

Free 25-OH Vitamin D, but Not Total 25-OH Vitamin D, Is Correlated with Gestational Age and Calcium in Normal Human Pregnancy Berthold Hocher,[2] Oleg Tsuprykov,[1] Claudia Buse,[1] Roman Skoblo.[1] [1]*Institute for Laboratory Medicine, IFLB, Berlin, Germany, Berlin, Germany;* [2]*University of Potsdam, Potsdam, Germany.*

Background: Basic science as well as epidemiological studies showed that vitamin D is causally involved in the pathogenesis of pregnancy-related diseases such as gestational diabetes as well as pregnancy-related hypertensive disorders, short- and long-term outcomes of the offspring. To translate this knowledge to clinical practice, suitable tools to determine the vitamin D status during pregnancy are mandatory. Since 25-OH vitamin D (25-OHD) is mainly bound to vitamin D binding protein (VDBP) in the circulating blood and female sex steroids regulate hepatic VDBP synthesis, it is doubtful whether the determination of total vitamin D, as it is currently clinical practice, does adequately reflect the vitamin D status of an individual pregnant women.

Methods: We compared the correlations of total serum 25-OHD, free serum 25-OHD, and 1,25-$(OH)_2$D in 475 healthy pregnant women with gestational age, calcium, phosphorus, bone alkaline phosphatase and PTH. Free 25-OHD was either measured directly using a novel assay system for direct measurements of free 25-OHD as well as calculated free 25-OHD based on measurements of VDBP, albumin and total 25(OH)D.

Results: Correlation of serum vitamin D isoforms with gestational age and selected serum parameters is shown in the Table.

Conclusions: Calculated and measured free 25-OHD provide comparable data and correlate much better with components of the endocrine vitamin D system and targets of vitamin D induced gene expression. Free 25-OHD concentrations decrease slightly during healthy pregnancy, whereas 1,25-$(OH)_2$D concentrations increases substantially. Given the impact of vitamin D on maternal and offspring's health outcomes, an adequate monitoring of the vitamin D status during pregnancy might require measurements of both free 25-OHD and 1,25-$(OH)_2$D at different time points of gestation.

Parameter	Total 25-OHD	Measured Free 25-OHD	Calculated Free 25-OHD	1,25-(OH)2D
Gestational Age	p=0.685, r=0.027	p=0.002, r=-0.206	p<0.001, r=-0.276	p<0.001, r=0.627
Calcium	p=0.065, r=0.085	p<0.001, r=0.161	p<0.001, r=0.223	p<0.001, r=-0.217
Phosphate	p=0.023, r=0.104	p=0.671, r=0.020	p=0.616, r=0.023	p=0.712, r=0.017
Parathyroid Hormone	p<0.001, r=-0.306	p<0.001, r=-0.239	p<0.001, r=-0.271	p<0.001, r=-0.186
Bone-Specific Alkaline Phosphatase	p<0.001, r=-0.163	p<0.001, r=-0.214	p<0.001, r=-0.230	p=0.012, r=0.108
Albumin	p=0.184, r=-0.061	p=0.007, r=0.123	p<0.001, r=0.180	p<0.001, r=-0.510
Low-Density Lipoproteins	p=0.301, r=0.048	p=0.007, r=-0.125	p=0.001, r=-0.155	p<0.001, r=0.399
Vitamin B6	p=0.156, r=0.067	p=0.004, r=0.138	p<0.001, r=0.192	p<0.001, r=-0.190

FR-PO279

Association between Urinary Full-Length Megalin and Serum Vitamin D Metabolites in CKD Norikazu Toi,[5] Shinsuke Yamada,[6] Eiji Ishimura,[4] Ayumi Nakatani,[5] Shinya Nakatani,[5] Yoshiaki Hirayama,[1] Naoko Tsugawa,[3] Akihiko Saito,[2] Masaaki Inaba.[5] [1]*Denka-seiken co., ltd., Gosen-shi, Japan;* [2]*Niigata University, Niigata, Japan;* [3]*Osaka Shoin Women's University, Higashi-osaka, Japan;* [4]*Meijibashi Hospital, Osaka, Japan;* [5]*Osaka City University Graduate School of Medicine, Osaka, Japan;* [6]*a. Department of Metabolism, Endocrinology, and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan.*

Background: 25-hydroxyvitamin D (25D) bound to vitamin D binding protein is reabsorbed by megalin, which is a membrane receptor highly expressed on proximal tubular epithelial cells. Increase in urinary megalin excretion due to tubular injury may affect vitamin D metabolism in chronic kidney disease (CKD) patients. The aim of the present study was to investigate whether increase in urinary excretion of megalin may have harmful effects on vitamin D metabolism in CKD patients.

Methods: One hundred fifty three CKD patients with eGFR less than 60 mL/min/1.73m^2 (101 males and 53 females, 64.7 ± 14.6 years) were recruited in this cross-sectional study. Urinary full-length megalin (C-megalin) and serum vitamin D metabolites (25D, 1α,25-dihydroxyvitamin D (1,25D), 24,25-dihydroxyvitamin D (24,25D) were measured.

Results: The mean levels of eGFR, serum levels of 25D, and urinary levels of C-megalin were 29.0 ± 15.8 mL/min/1.73m^2, 15.1 ± 6.2 ng/mL and 0.9 ± 1.1 pmol/gCr, respectively. In a simple regression analysis, 25D exhibited significant and negative correlation with urinary C-megalin (ρ = - 0.310, p = 0.0002), and urinary C-megalin had a significant and positive correlation with urinary protein (ρ = 0.603, p <0.0001), although both 25D and urinary C-megalin was not significantly correlated with eGFR. In a multiple regression analysis adjusted by age, gender, BMI, presence of diabetes, serum albumin, eGFR, serum PTH, serum FGF-23, and urinary C-megalin, urinary C-megalin was associated significantly with 25D in a negative manner (β = - 0.302, p = 0.0027). Furthermore, both 1,25D (β = 0.227, p = 0.0013) and 24,25D (β = 0.482, p <0.0001) were positively associated with 25D. The ratio of 1,25D/24,25D, which is a putative indicator of 1α-hydroxylase activity, was significantly, positively affected by urinary C-megalin independently to other clinical confounders.

Conclusions: This study demonstrated that serum 25D decreases with an increase in urinary C-megalin, and that serum 1,25D and 24,25D decrease with a decrease in 25D in CKD patients. Thus, decreased 25D induced by increased urinary C-megalin, which is a representative of tubular injury, affects decrease in 1,25D, suggesting the clinical importance of renal tubular dysfunction in vitamin D metabolism in CKD patients.

FR-PO280

VDR Deficiency Induces the Parathyroid Glands Lesions via NFκB Pathway Activation in Uremic Patients Jianping Mao, Minmin Zhang, Li Ni, Mengjing Wang, Jing Chen. *Huashan Hosopital, Fudan Univeristy, Shanghai, China.*

Background: Secondary hyperparathyroidism (SHPT) is one of the most common complications in CKD-MBD, but its pathogenesis remains unknown. Recent studies showed that 1,25D suppressed Nuclear Factor-κB (NFκB) activation to suppress tumor hyperplasia. Therefore, whether VDR deficiency induce the tumor-like hyperplasia of parathyroid gland(PTG) via the NFκB pathway activation in uremic patients.

Methods: PTG samples were collected from parathyroidectomy surgery of 10 uremic patients who failed to medical treatment with approval of the Ethics Committee on Human Research at Huashan Hospital. Immunohistochemistry and Western blot detected the expression of VDR, pp65 and PCNA in diffuse and nodular hyperplastic PTG. In vitro, freshly excised PTG tissues were minced into 1mm^3 fragments and incubated with 1,25D (0nM, 1nM, 10nM, 100nM, 1000nM) and PDTC (0uM, 2uM, 20uM, 200uM) for 24 hours. ELISA kit measured the levels of iPTH from supernatant. Real-time PCR measured the mRNA levels of preproPTH, PCNA, VDR and IκBα. Western blot measured the protein levels of VDR, p65, pp65 and PCNA.

Results: Compared with diffuse hyperplasia, immunohistochemistry results showed that VDR expression was down-regulated by 34.97% (P<0.01), while pp65 and PCNA were up-regulated by 86.51% (P<0.01) and 97.37% (P<0.01) in nodular hyperplastic glands. Western blot confirmed these above. In vitro, 1,25D up-regulated protein and mRNA levels of VDR by 150.62% (P<0.05) and 35.62% (P<0.05), down-regulated protein level of pp65 by 58.49% (P<0.01), up-regulated mRNA level of IκBα by 72.77% (P<0.01), and down-regulated protein and mRNA levels of PCNA by 42.48% (P<0.05) and 38.49% (P<0.01). These results suggested that 1,25D could activate VDR, inhibit cellular proliferation and inhibit NFκB activation. PDTC did not affect VDR expression, but down-regulated protein level of pp65 by 76.04% (P<0.01), down-regulated protein and mRNA levels of PCNA by 47.39% (P<0.05) and 26.95% (P<0.05). These results suggested that PDTC inhibit NFκB activation and inhibit cellular proliferation, while it had no effect on VDR expression. ELISA results showed that 1,25D and PDTC could both down-regulate iPTH levels by 61.16% (P<0.01) and 49.86% (P<0.05).

Conclusions: Deficiency of VDR and activation of NFκB pathway may be involved in the hyperplasia of PTG in uremic patients, the exact mechanism needs further study.

FR-PO281

Severe CKD Environment Affects CaSR Gene Expression and the Cascade of Genes in Parathyroid Glands Even without High Phosphorus Diets Taketo Uchiyama,[2] Ichiro Ohkido,[2] Sahoko Kamejima,[3] Akio Nakashima,[1] Takashi Yokoo.[4] *[1]Division of Kidney and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan; [2]Division of Nephrology and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan; [3]Jikei University School of Medicine, Tokyo, Japan; [4]The Jikei University School of Medicine, Tokyo, Japan.*

Background: Chronic kidney disease (CKD) disrupts mineral homeostasis and its representative pathosis is defined as secondary hyperparathyroidism (SHPT). SHPT occurs during the early course of progressive renal insufficiency, and is associated with mortality and cardiovascular events. Reduction of the calcium-sensing receptor (CaSR) occurs slowly and progressively throughout this process, although the underlying mechanism remains largely unknown.

Methods: CKD was induced by 0.75% adenine-containing diet. CKD rats and control rats were maintained for 2 weeks on diets containing 0.7% phosphorus or 1.3% phosphorus. In a gene expression analysis, TaqMan probes were used to do the quantitative real-time polymerase chain reactions. CaSR and glial cells missing-2 (Gcm2) protein expressions were analyzed using immunohistochemistry and western blotting. DNA methylation analysis was performed using a restriction digestion and quantitative PCR.

Results: CaSR mRNA was reduced in CKD rats fed the normal and high phosphorus diets (CKD NP and CKD HP, respetctively) (Figure 1), and the amount of CaSR protein was compatible with the gene expression assay. There is no significant difference in the DNA methylation status in the promoters of *CaSR* between the four groups. *Gcm2*, which has been shown to directly regulate *CaSR* and also to transactivate *CaSR* through *Gcm2* response elements in the *CaSR* promoter, was significantly decreased in CKD NP and CKD HP rats (Figure 2), and using western blotting the expression of Gcm2 was shown to be compatible.

Conclusions: A reduction of *CaSR* expression in parathyroid glands was observed in CKD NP and CKD HP rats; however, the DNA hypermethylaton was not demonstrated. We then analyzed the Gcm2 gene and its protein expression, as upstream transcription factor of *CaSR*, and we verified its depression in CKD NP and CKD HP rats. Consequently, our data suggest that *Gcm2* was responsible for the reduction in mRNA and protein levels of *CaSR* and *VDR* in PTGs of CKD HP rats.

Figure 1

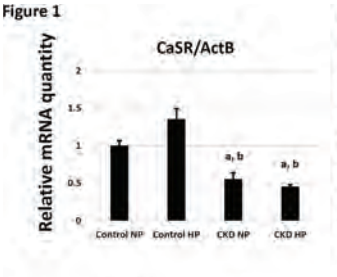
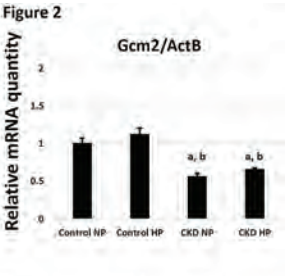


Figure 2



Number of animals: Control NP group, 6; Control HP group, 6; CKD NP group, 6; CKD HP group, 6
Results are mean ± SD.
a P<0.0083 vs. the Control NP group
B P<0.0083 vs. the Control HP group
c P<0.0083 vs. the CKD NP group
The mean difference is significant at the 0.0083 level for Bonferroni test.

FR-PO282

MicroRNA Analysis in Secondary Hyperparathyroidism Genta Kanai, Michio Nakamura, Masafumi Fukagawa. *Tokai University School of Medicine, Isehara, Japan.*

Background: Hyperparathyroidism is characterized by decreased calcium receptor expression and cell proliferation. However, the mechanism of progression is not clear. MicroRNA (miRNA) is a short RNA that is not translated into protein and has regulatory function of gene expression. To investigate the role of miRNA in cell proliferation of the parathyroid gland, we performed comprehensive miRNA analysis using the next generation sequence.

Methods: The parathyroid gland removed from patients with renal failure was used for the experiment. miRNAs extracted from the largest gland and the smallest gland in the same individual glands were examined. When analyzing the sequence of more than 1 million leads, about 25% of them corresponded to about 2,600 known miRNAs.

Results: There were 71 kinds of sequences detected in more than 10,000 leads in any glands, and 98 kinds of sequences with more than 1000 leads and less than 10,000 leads. The non-enlarged parathyroid gland was compared with the largest gland, and miRNAs that upregulated more than 2-fold were 11 and 10, respectively. Furthermore, miRNAs downregulated more than 2-fold were 14 and 24 kinds, respectively. Up to 31-fold expression difference was observed in these sequences.

Conclusions: The miRNA profile showed differential expression by parathyroid size. This suggests that miRNA may regulate parathyroid cell proliferation.

FR-PO283

A Mathematical Model of Parathyroid Gland Biology in Uremic Patients Gudrun Schappacher-Tilp,[3] Priscila Preciado,[2] Vaibhav Maheshwari,[1] Alhaji Cherif,[2] Doris H. Fuertinger,[2] Stephan Thijssen,[2] David A. Bushinsky,[4] Peter Kotanko.[2] *[1]Renal Research Insitute, New York, NY; [2]Renal Research Institute, New York, NY; [3]University of Graz, Graz, Austria; [4]University of Rochester Medical Center, Rochester, NY.*

Background: Chronic kidney disease-mineral bone disorder (CKD-MBD) affects the vast majority of CKD patients. A hallmark of CKD-MBD is an altered parathyroid gland biology with increased parathyroid hormone (PTH) secretion, reduced expression of calcium-sensing receptor (CaSR), and cell hyperplasia and hypertrophy. The aim of this study was to develop a mathematical model of the parathyroid gland enabling long-term simulations of parathyroid gland function in hemodialysis (HD) patients.

Methods: The mathematical model employs two PTH-producing cell populations, namely active secretory and quiescent cells that can proliferate or undergo apoptosis. PTH secretion can be modulated both on a cellular level and by increasing the number of secretory cells. The first mechanism involves the release of stored PTH, the decrease of intracellular degradation as well as increased biosynthesis. The second mechanism involves shorter secretory quiescence time as well as hyperplasia. All mechanisms are associated with different time constants implemented by positive or negative feedback loops on the CaSR and vitamin D receptor.

Results: We can successfully predict complex acute responses to changes in plasma calcium concentrations like different PTH values for the same serum calcium concentration during induction of and recovery from hypocalcemia. Moreover, we can predict a steady rising PTH release in hemodialysis patients due to high phosphate and low calcitriol levels. Long-term simulations allow the prediction of the effects of hyperplasia on PTH levels.

Conclusions: The *in silico* model of the parathyroid gland can be used to analyze pathophysiological alterations of the parathyroid gland in HD patients. It provides a useful tool to analyze long-term effects of dosing regimens of standard drugs like calcimimetics and vitamin D analogues on the parathyroid gland.

FR-PO284

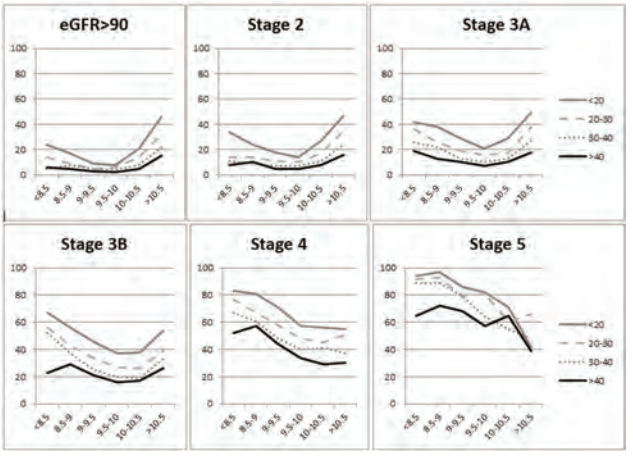
Interactions of Calcium, Vitamin D, and Kidney Function with Parathyroid Hormone Levels Rita L. McGill,[2] Elaine M. Worcester,[2] Jennifer L. Ennis,[1] Sangeet Dhillon-Jhattu,[2] Fredric L. Coe.[2] *[1]Litholink Corporation, Chicago, IL; [2]University of Chicago, Chicago, IL.*

Background: Parathyroid hormone (PTH) is a crucial factor in regulating calcium homeostasis and bone mineral deposition. Vitamin D and estimated glomerular filtration rate (eGFR) also interact with PTH, and we aimed to better characterize the interplay between these factors.

Methods: Laboratory results performed at LabCorp between April 2011 and February 2014 were assessed, if simultaneous PTH, calcium, vitamin D and eGFR were available. Calcium and vitamin D were categorized, and analyses were stratified for National Kidney Foundation stage of chronic kidney disease (CKD). Percentages of tests in which a PTH>65 was observed were calculated and plotted for each combination of calcium, vitamin D, and eGFR.

Results: Among 126,615 patients, 38% were male and mean age was 65.6 years. Compared to those withe GFR>90, PTH levels were more likely to be abnormal in CKD stages 2 and 3A. Higher vitamin D levels were associated with lower PTH in all patients, and this effect became more prominent with decreasing eGFR. The normal U-shaped relationships between calcium and PTH were distorted in CKD stages 4 and 5.

Conclusions: PTH levels become detectably abnormal even in very early CKD. Repletion of vitamin D to levels of 40 ng/mL or greater reduces PTH in patients with eGFR ≥ 15.



Percentage of Patients with PTH > 65, by Calcium, Vitamin D, and Chronic Kidney Disease Stage

FR-PO285

Kidney and Parathyroid Transplants for Hereditary Hypoparathyroidism Due to a Calcium Sensing Receptor (CaSR) Mutation Reduced Calciuria but Did Not Normalize Serum Calcium Kimberly A. Muczynski,[1] Michael O. Dorschner,[2] Nicolae Leca,[1] Ramasamy Bakthavatsalam,[3] Jorge D. Reyes,[3] David R. Byrd.[3] *[1]Medicine, University of Washington, Seattle, WA; [2]Pathology, University of Washington, Seattle, WA; [3]Surgery, University of Washington, Seattle, WA.*

Background: Parathyroid transplants have been reported for a couple cases of hereditary hypoparathyroidism using allografts from fetal and living donors. We now communicate success in transplantation of a living related kidney and deceased unrelated donor parathyroids into a patient with hereditary undetectable parathyroid hormone (PTH).

Methods: A father and daughter have had undetectable PTH levels since childhood. Calcium and vitamin D are essential to prevent symptomatic, life-threatening hypocalcemia. The father progressed to ESRD at age 52 due to nephrocalcinosis from his required calcium supplements. He received a kidney transplant pre-dialysis from an unaffected sister. The sister was felt not to be an appropriate parathyroid donor due to prior neck radiation for hyperthyroidism. Hence deceased donor parathyroids were transplanted into the father's forearm one week later, after institutional review board, hospital administration and organ procurement organization collaboration. Induction immunosuppression with ATG was used for the kidney and maintenance immunosuppression with tacrolimus, mycophenolate and prednisone were continued at the time of parathyroid transplant.

Results:

Conclusions: The father's kidney has functioned well, urine calcium excretion has been reduced by over 50%, and PTH levels are 13-15 pg/ml in the peripheral blood and 122 pg/ml from venous drainage of the parathyroid allograft seven months post-transplant. However, supplemental calcium and vitamin D are still required to prevent hypocalcemia. Perplexed by these findings, exome sequencing of genes that might account for hypoparathyroidism was performed by Precision Diagnostics at the University of Washington. PTH gene was normal but a mutation in the CaSR mapping to other gain of function mutations was identified. Having replaced the CaSR in the kidney and parathyroids with the combined allograft transplants we presume that renal calcium metabolism has been normalized and the new kidney will be protected from recurrent nephrocalcinosis. The need for supplemental calcium to prevent hypocalcemia suggests that CaSR in other organs (such as bone or gut), has a greater contribution in maintaining serum calcium levels than preventing calcium loss through the kidney.

Funding: Private Foundation Support, Clinical Revenue Support

FR-PO286

TRPC1 Gene Deletion Disturbs Homeostasis of Intracellular Free Ca ([Ca 2+]i), Produces Hyperparathyroidism, Hypercalcemia, Hyperphosphatemia, and Increased Bone Mass Due to Renal Ca and P Retention Bonnie Eby,[1] Marta Onopiuk,[2] Marybeth Humphrey,[3,4] Leonidas Tsiokas,[2] Kai Lau.[1,4] *[1]Nephrology, University of Oklahoma Health Sciences Center, Oklahoma City, OK; [2]Cell Biology, University of Oklahoma Health Sciences Center, Oklahoma City, OK; [3]Rheumatology, University of Oklahoma Health Sciences Center, Oklahoma City, OK; [4]Medicine, VA Hospital, Oklahoma City, OK.*

Background: Mice deleted of the gene for transient receptor potential canonical channel 1 (TRPC1) have higher PTH (313 vs 218 pg/ml), hypercalcemia (11.3 vs.10.2 mg %) & hypocalciuria (1.2 vs 2.2 mg/d), indicating TRPC1 deficiency mimics familial hypocalciuric hypercalcemia phenotypes from CaSR inactivating mutations. Micro-CT shows increased tibia bone volume:tissue volume (11 vs 6 %). Their hind limbs were heavier (189 vs.151 mg). We now studied the potential mechanisms.

Methods: We measured Ca & P balance & clearance by standard methods, calciotropic hormones by ELISA, and $[Ca^{2+}]_i$ in cultured cells by fura 2.

Results: In rat parathyroid (PT) cells, $[Ca^{2+}]_i$ stimulation by CaSR allosteric agonists was markedly blunted by TRPC1 siRNA, showing CaSR signaling pathway depends on this store-operated Ca entry (SOCE). Without TRPC1, $[Ca^{2+}]_i$ is down & PTH secretion is up. In contrast, high medium [Ca] raises $[Ca^{2+}]_i$ & reduces PTH secretion. Transfection with plasmid overexpressing TRPC1 also inhibits PTH. The null mouse phenotypes cannot be attributed to the comparable serum calcitriol (301 vs.308 pg/ml) & calcitonin (21.9 vs.22.3 pg/ml). Renal cells transfected with TRPC1 siRNA & osteocytes from null mice also have blunted $[Ca^{2+}]_i$ response to CaSR agonists, indicating a generalized signaling defect in TRPC1-deficient cells. Since FGF23 synthesis &/or secretion are known to change directionally with $[Ca^{2+}]_i$, we tested the thesis that P excretion is reduced in null mice, due to putatively low FGF23 from reduced $[Ca^{2+}]_i$ in osteocytes. At similar diet intake, 24 h urine P was similar (3.5 vs. 4.1 mg/d). Fasting serum P was elevated (7.4 vs. 6.3 mg %) due to concurrently decreased P clearance (48 vs. 67 µl/min).

Conclusions: Conclusions: 1. Our data support the model that, activated by upstream CaSR signaling, TRPC1 functions as a SOCE channel to control PT $[Ca^{2+}]_i$ and regulate PTH secretion. 2. Increased bone mineral accretion in TRPC1 deletion is mediated by greater renal Ca & P retention, the latter likely due to low FGF23 from reduced osteocyte $[Ca^{2+}]_i$. 3. The apparent skeletal PTH resistance is explicable by the hypercalcemia, hyperphosphatemia, &/or the known impaired osteoclast proliferation, differentiation & function due to loss of TRPC1 functions.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO287

Accuracy, Precision, and Stability of the LIAISON 1-84 PTH 3rd Generation Assay: Comparison to Existing Intact PTH Assays Andre Valcour,[2] Kevin J. Martin,[4] Sudhaker D. Rao,[1] Douglas M. Hawkins,[1] Frank A. Blocki,[3] Claudia Zierold,[3] Fabrizio Bonelli.[5] *[1]Henry Ford Health System, Detroit, MI; [2]LabCorp, Burlington, NC; [3]DiaSorin Inc., Stillwater, MN; [4]Saint Louis University Med Ctr, St. Louis, MO; [5]DiaSorin spa, Stillwater, MN.*

Background: Over the past few decades, PTH immunoassays have progressed through successive generations resulting in increased specificity and accuracy for detecting circulating PTH. With the introduction of 3rd generation assays, in which the biologically active PTH (1-84) is specifically targeted, the PTH (7-84) and other fragments are not detected. The specific recognition of PTH (1-84) whole molecule allows standardization and calibration with existing standards.

Methods: Samples from patients on hemodialysis, with primary hyperparathyroidism, and apparently healthy subjects were examined in different collection tubes (plasma, unspun plasma, and SST) stored for 0, 24, or 72h at room temperature to reflect the prevailing sample collection methods, shipping, and processing conditions of centralized labs in the US. Samples were analyzed by the LIAISON 1-84 PTH and the N-TACT assays, and three additional commercially available intact PTH methods.

Results: PTH is stable for up to 72 hours in plasma, but less stable in serum (SST) beyond 24h (% change from 0h in Table). Both the LIAISON assays (1-84 and N-TACT) demonstrated good precision. Furthermore, defined samples, prepared using two different standards (WHO 95/646 international standard and the synthetically synthesized Bachem PTH(1-84)), read accurately with the LIAISON 1-84 PTH assay, but not with the intact PTH assays (5-9% vs. 54-142% bias).

Conclusions: The FDA-approved LIAISON 1-84 PTH assay is accurate and precise and reliably measures the biologically active PTH molecule in serum or plasma stored at room temperature for up 72h in plasma, and 24h in serum.

Funding: Commercial Support - DiaSorin, LabCorp

% Change in PTH from T=0h

Method	Sample Type	24h	72h
LIAISON 1-84 PTH	plasma	1.1%	-1.3%
	SST	-0.9%	-18.5%
LIAISON N-TACT PTH	plasma	0.5%	-1.3%
	SST	0.9%	-18.3%
Method A iPTH	plasma	-0.9%	-2.1%
	SST	-0.6%	-13.7%
Method B iPTH	plasma	-2.6%	-5.1%
	SST	-11.0%	-28.6%
Method C iPTH	plasma	20.0%	27.3%
	SST	-17.8%	-21.6%

FR-PO288

Calcitriol at Therapeutic Doses for SHPT Promotes Vascular Calcification in Experimental CKD Bruno A. Svajger,[2] Cynthia M. Pruss,[2] Kimberly J. Laverty,[2] Jason Zelt,[1] Martin P. Petkovich,[1] Rachel M. Holden,[2] Michael A. Adams.[2] *[1]None, Kingston, ON, Canada; [2]Queen's University, Kingston, ON, Canada.*

Background: Vitamin D deficiency is common in CKD and leads to SHPT. Calcitriol (CAL) and active vitamin D analogs are often used to treat SHPT. CAL use has been associated with improved patient survival; however, it has also been linked with PTH over-suppression and increased risk of vascular calcification (VC). This study examined the effects of CAL dose frequency and magnitude on bone and mineral status (PTH, FGF23), endothelial function (von Willebrand Factor–VWF) and VC in experimental CKD.

Methods: CKD was induced by 0.25% dietary adenine in adult male Sprague-Dawley rats (n=42). At 4 weeks (W), CKD rats were divided into 4 groups and treated with CAL as follows: 0ng/kg (CKD control (Ctl), n=8), 5ng/kg QID (therapeutic dose divided, n=9), 20ng/kg SID (therapeutic dose, n=8), 20ng/kg QID (high dose divided, n=9), or 80ng/kg SID (high dose, n=8). After 3W treatment, rats were sacrificed, tissues and blood were collected and assessed for VC, PTH, FGF-23, and VWF.

Results: PTH therapeutic target levels (2-9x control) were achieved at some point during all CAL treatments. After 1W treatment, both 20 and 80ng/kg/day reduced PTH (-72%) relative to CKD Ctl ($p<0.05$). However, at 3W, CAL-induced PTH suppression was less effective (-41%). At 3W, PTH suppression (-55% vs -29%) and FGF-23 elevation (20x vs 10x) was greater in 80ng/kg/day compared to 20ng/kg/day ($p<0.05$). Increased serum calcium (+40%) and VC (94% vs 29%) was evident in all CAL treatments vs CKD Ctl ($p<0.05$), and VWF was significantly elevated in CAL treatment groups vs CKD Ctl at 1W (2x, $p<0.05$) and 3W(1.5x, $p<0.05$). Sub-analysis showed PTH suppression status (therapeutic, over-suppressed, no response) did not alter negative outcomes (FGF-23, VC).

Conclusions: CAL suppressed PTH as expected although the suppression effect was attenuated over time. All CAL treatment groups exhibited similar increases in FGF-23, VC, and endothelial dysfunction independent of dosing regimen. Importantly, mineral bone disorder occurrence was not corrected regardless of calcitriol treatment success (based on PTH response).

Funding: Commercial Support - OPKO Health Inc. Renal Division, Government Support - Non-U.S.

FR-PO289

Secondary Hyperparathyroidism in Hemodialysed Patients – Comparison of the Most Common Strategies of Treatment In a One-Year Observational Study Jacek P. Zawierucha,[1] Jolanta Malyszko,[3] Jacek S. Malyszko,[2] Wojciech Marcinkowski,[4] Grazyna Horowitz,[5] Tomasz R. Prystacki,[4] Teresa Dryl-Rydzynska.[1] *[1]Fresenius Medical Care Polska S.A., Poznan, Poland; [2]Medical University of Bialystok, Bialystok, Poland; [3]Medical University, Bialystok, Poland; [4]Fresenius Nephrocare Polska sp. z o.o., Poznan, Poland; [5]Gradatim, Tarnowo Podgorne, Poland.*

Background: Secondary hyperparathyroidism (sHPT) is one of the most common hormonal disorders in the course of chronic kidney disease (CKD). Associated with CKD hyperphosphatemia, hypocalcemia and active vitamin D deficiency are presumed the main causes of the sHPT. Two strategies of sHPT treatment are widely used – oral calcimimetics administration or intravenous paricalcitol administration during hemodialysis session. The third strategy is based on combination of both drugs – cinacalcet and paricalcitol administered in parallel. The aim of the study was to compare effectiveness of aforementioned therapeutic strategies.

Methods: 131 patients receiving hemodialysis and with inadequate parathyroid hormone level control were treated with iv paricalcitol – group of 60 patients (PAR) or cinalacet – group of 50 patients (CIN). Third group (21 patients) with unsatisfied results of the treatment with cinacalcet received also paricalcitol (PAR+CIN) and both drugs were administered simultaneously. Laboratory tests (iPTH, Ca, P, ALP) were performed on a monthly basis. The study duration was 12 months.

Results: In all groups significant decrease of iPTH level was observed. However, in group PAR iPTH level decrease was greater than in CIN and PAR+CIN groups. The highest change of iPTH level was noticed after three months of observation. After this period the iPTH level was stabilized and remained on similar level till the end of observation. The level of safety is similar for all the strategies. No severe hypercalcemia or hypocalcemia was observed during the whole period of observation.

Conclusions: The results of this study show significant advantage of intravenous treatment with paricalcitol. Adding paricalcitol to the therapy with cinacalcet does not improve outcomes of the treatment. In case of unsatisfactory results after 3-months treatment, a possible continuation should be considered carefully. Treatment with iv paricalcitol should be considered for all hemodialysed patients with inadequate serum PTH level control. sHPT treatment with cinacalcet should be considered for PD patients and when severe hypercalcemia occurs.

Funding: Commercial Support - Fresenius Medical Care

FR-PO290

The Novel Calcimimetic Agent Evocalcet (MT-4580/KHK7580) Has a Potential for the Treatment of Hyperparathyroidism with Less Effect on the Gastrointestinal Motility In Vivo Models Shin Tokunaga,[1] Hikaru Yoneda,[2] Masafumi Fukagawa,[3] Tadao Akizawa,[4] Kimihisa Ueno,[1] Ryutaro Shimazaki,[5] Takehisa Kawata.[1] *[1]Kyowa Hakko Kirin Co., Ltd., Shizuoka, Japan; [2]Mitsubishi Tanabe Pharma Corporation., Saitama, Japan; [3]Tokai University School of Medicine, Isehara, Japan; [4]Showa University School of Medicine, Tokyo, Japan; [5]Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan.*

Background: Cinacalcet is widely used for the management of secondary hyperparathyroidism (SHPT). Nevertheless, cinacalcet has adverse effects on the gastrointestinal (GI) tract, which sometimes causes poor compliance or discontinuation of the treatment. Evocalcet (MT-4580/KHK7580) is a novel oral calcimimetic compound developed for dialysis patients with SHPT and is expected to improve upon several issues associated with cinacalcet. The objective of present preclinical study was to confirm the characteristics of evocalcet as a calcimimetic agent and to evaluate its effects on GI tract.

Methods: *In vitro* and *in vivo* pharmacological studies (using HEK293 cells expressing human calcium receptor and 5/6 nephrectomized rats) were conducted. To compare the effects of evocalcet and cinacalcet on GI tract, the emetic responses by each compound in common marmosets and gastric emptying in rats were evaluated. In addition, the binding affinity of some vomiting-associated receptors was assessed.

Results: The pharmacodynamic properties of evocalcet were similar to those of calcimimetics. In marmosets, evocalcet achieved wider safety margin between dosages which induced emesis or PTH reduction compared to cinacalcet. Although cinacalcet caused significant delay in gastric emptying in rats, evocalcet had no marked effect on gastric emptying at doses that showed similar pharmacological activity to cinacalcet (Table 1). Evocalcet had lower binding affinities to vomiting-associated receptors, such as dopamine, cannabinoid, opioid, serotonin, and other receptors compared with cinacalcet.

Conclusions: Evocalcet has a potential as the novel oral calcimimetic agent with better safety profile and medication adherence than cinacalcet for the treatment of SHPT.

Table 1. The effects of evocalcet and cinacalcet on gastric emptying in rats

Treatment	Dosage (mg/kg)	Gastric emptying (%)
Vehicle	-	65.50 ± 5.01
Evocalcet	0.3	67.83 ± 5.44
	1	65.89 ± 4.71
	3	61.58 ± 4.58
Cinacalcet	10	55.17 ± 2.88
	30	35.72 ± 5.64 ***
	100	20.02 ± 5.52 ***

n=7~8, Mean ± SE.

***: $p<0.001$ compared with vehicle group.

FR-PO291

An Open-Label, Single-Arm Study to Assess the Safety, Tolerability, and Efficacy of Cinacalcet in Addition to Standard of Care in Pediatric Subjects Ages 28 Days to <6 Years William G. Goodman,[3] Jan Iles,[2] Jun Yang,[1] Bella Ertik,[1] Winnie Sohn,[1] Karel Vondrak,[6] Claus P. Schmitt,[4] Isidro B. Salusky.[5] *[1]Amgen, Thousand Oaks, CA; [2]Amgen Inc, Thousand Oaks, CO; [3]Amgen, Inc., CALABASAS, CA; [4]Center for Pediatric and Adolescent Medicine, Heidelberg, Germany; [5]Mattel Children's Hospital, Los Angeles, CA; [6]University Hospital Prague-Motol, Prague 5, Czech Republic.*

Background: Data are limited on the safety, tolerability, and efficacy of cinacalcet (CIN) in children with secondary hyperparathyroidism (SHPT) on dialysis. In this phase 2, multicenter, 26-week, single-arm, open-label study, we evaluated CIN+standard of care that includes vitamin D sterols in pediatric subjects with SHPT on dialysis.

Methods: Pediatric subjects ages 28d to <6yrs with SHPT on dialysis with parathyroid hormone (PTH) levels≥300pg/mL and serum corrected Ca≥9.4mg/dL (28d to <2yrs) or ≥8.8mg/dL (2 to <6yrs) were evaluated. The daily starting and maximum dose of CIN were changed during the study from 0.25mg/kg and 4.2mg/kg to 0.20mg/kg and 2.5mg/kg or 60mg maximum, whichever was lower. Primary endpoint: the proportion of subjects who developed cCa<9.0mg/dL (28d to <2yrs) and <8.4mg/dL (≥2 to <6yrs); secondary endpoints: percent change of plasma PTH from baseline, ≥30% reduction from baseline in PTH, PTH<300pg/mL, and cCa<8.8mg/dL. Nature, frequency, and severity of adverse events (AEs) were summarized.

Results: 17/18 enrolled subjects received ≥1dose of CIN; 66.7% were boys, 83.3% white, and mean age was 35.9mos. Mean CIN exposure time was 86.7days and the maximum daily dose of CIN was 30mg (2 subjects). Mean (SD) weight-adjusted daily starting dose and maximum dose during the study was 0.18(0.07)mg/kg and 0.73(0.66) mg/kg, respectively. No subject had cCa<9.0 or <8.4mg/dL for the 2 groups and 2 subjects (2 to <6yrs group) had cCa<8.8mg/dL. Overall, 70.6% of subjects showed

reductions in PTH≥30% and 52.9% subjects achieved PTH<300pg/mL during the study. All subjects received therapy with vitamin D sterols during the study. 94.1% of subjects had ≥1 treatment-emergent AE. The most common AEs were cough, hypertension, upper respiratory tract infection, and vomiting. There were no treatment-related serious AEs, fatal AEs nor AE leading to the discontinuation of CIN.

Conclusions: No subject had a Ca value below the threshold for the primary endpoint. Data show a downward trend in PTH from baseline after CIN administration. Safety data were consistent with the known safety profile.

Funding: Commercial Support - Amgen Inc

FR-PO292

A Phase 3, Multicenter, Randomized, Open-Label, Controlled Study to Assess the Efficacy, Safety, and Tolerability of Cinacalcet in Addition to Standard of Care in Pediatric Subjects Ages 6 to 17 Years

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Background: Standard of care (SoC) for secondary hyperparathyroidism for children on dialysis includes vitamin D sterols, calcium (Ca) supplementation, and phosphate (P) binders, while cinacalcet (CIN) has been shown to reduce parathyroid hormone (PTH), Ca, and P. Efficacy and safety data for CIN are limited in the pediatric chronic kidney disease population.

Methods: Pediatric subjects ages 6 to<18yrs were randomized 1:1 CIN+SoC:SoC stratified by age (6 to<12 & 12 to<18 yrs) to evaluate the efficacy of CIN+SoC for reducing mean plasma PTH by ≥30% from baseline during the efficacy assessment phase (EAP) wks 17-20. Eligible subjects had 2 consecutive PTH levels≥300pg/mL at entry and albumin corrected Ca (cCa) ≥8.8mg/dL. CIN was administered once daily starting at 0.20mg/kg/day and adjusted once monthly up to 2.5mg/kg/day or 180mg, whichever was lower, based on PTH, cCa, ionized Ca (iCa), and safety. CIN was held if cCa<8mg/dL or iCa<1mmol/L. Nature, frequency, and severity of adverse events (AEs) were assessed.

Results: 22/27 CIN+SoC (56% boys) and 25/28 SoC (46% boys) randomized subjects received ≥12wks of treatment. Mean age was 12.6yrs with more subjects in the 12 to<18yrs group. The proportion of subjects who achieved PTH reduction ≥30% was not significant: 22.2%(6/27) CIN; 32.1%(9/28) SoC (p=0.42 stratified by age). Mean(SD) duration of exposure to CIN was 112.8(41.0)days with average weight-adjusted daily dose of 0.398(0.467)mg/kg/day during EAP. 21(84.0%) CIN and 17(56.7%) SoC subjects had ≥1 AE during the study with most ≤grade 2 in severity. The most common CIN AEs were hypocalcemia(24.0%), muscle spasms(12.0%), nausea(12.0%) and headache(4.0%).

Conclusions: Efficacy of CIN was not demonstrated likely due to inadequate exposure. Safety data were consistent with the known safety profile.

Funding: Commercial Support - Amgen Inc

FR-PO293

Demographic Predictors of Mineral and Bone Disorders in the Pediatric Dialysis Population

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Background: Secondary Hyperparathyroidism in pediatric patients on dialysis results in bone and cardiovascular abnormalities that have major implications on morbidity and mortality in both childhood and adulthood. Therefore, it is important to understand the factors which contribute to and predict perturbations in the markers of mineral and bone disorders (MBD).

Methods: In a sample of 661 children with ESRD we explored predictors of abnormalities in Calcium (Ca), Phosphorous (P04), Alkaline Phosphatase (ALP) and Parathyroid Hormone (PTH) levels within the first 3 months of dialysis using linear regression models adjusted for age, sex, race and ethnicity, disease type, Ca, P04, AP, and medication use.

Results: The cohort characteristics are displayed in Table 1. Using age-adjusted norms and KDIGO-defined goals of PTH values 2-9 times the upper limit of normal, we found that Ca, ALP and PTH were most frequently within goal ranges, while P04 was most frequently above goal (Figure 1). Significant predictors of these markers included age which predicted higher PTH, lower ALP and lower Ca; Female gender which predicted lower P04 and lower ALP; Black race which predicted higher PTH, lower P04 and lower ALP and Hispanic ethnicity which predicted higher PTH and lower Ca and P04 (Table 2).

Conclusions: Non-modifiable demographic factors associate with the markers of MBD. In particular, Black and Hispanic children have higher PTH levels and, in addition, Black children have lower AP levels. While optimization of CKD-MBD management requires consideration of these observed differences, further studies are needed to assess potential racial/ethnic differences in PTH targets in children on dialysis.

Funding: NIDDK Support

Table 1.

N	661
Age, median (IQR)	19 (16-20)
Male Gender, n (%)	361 (54.6)
Race, n (%)	
Black	206 (32.2)
White	222 (33.6)
Hispanic	233 (35.2)
Modality, n (%)	
Hemodialysis	502 (76.3)
Peritoneal Dialysis	156 (23.7)

Figure 1.

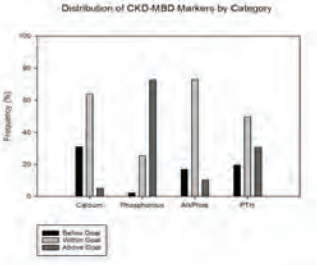

Table 2.

	log PTH	Calcium	Phosphorous	log AP
Age	0.02* (0.01, 0.03)	-0.03* (-0.05, -0.02)	-0.01 (-0.04, 0.02)	-0.03* (-0.04, -0.03)
Female Gender	0.04 (-0.01, 0.09)	0.08 (-0.02,0.17)	-0.52* (-0.72, -0.31)	-0.07* (-0.1, -0.03)
Black (ref=White)	0.08* (0.02, 0.14)	0.06 (-0.18, 0.06)	-0.44* (-0.69, -0.19)	-0.04* (-0.08, -0.0003)
Hispanic (ref=White)	0.07* (0.02, 0.13)	-0.21* (-0.33, -0.1)	-0.29* (-0.54, -0.05)	0.01 (-0.03, 0.04)

Regression Coefficients and 95% Confidence Intervals.
*p<0.05

FR-PO294

Mineral and Bone Disorder (MBD) Markers and Management over the First 5 Years after Dialysis Start: Results from the DOPPS

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Background: Abnormalities in MBD markers - including parathyroid hormone (PTH), serum phosphorus (P), calcium, and 25-hydroxy (OH) vitamin D - in the period immediately following hemodialysis (HD) initiation may increase short- and long-term risk of morbidity and mortality. International and racial variations in MBD markers and treatments have been well-described, but not their trajectories after transition to HD.

Methods: Locally weighted regression (LOESS) was used to smooth trends in mean MBD markers and drug prevalence over the first 5 years of HD using 472,930 patient-months from 34,105 patients in phases 4-5 (2009-2015) of the Dialysis Outcomes and Practice Patterns Study (DOPPS).

Results: PTH levels were high at HD initiation, especially among black patients in the US. PTH then declined during the first year of HD before increasing in the US and Europe but not in Japan. P levels increased sharply after HD initiation before subsequently declining in Europe but not in the US or Japan. Active vitamin D and cinacalcet prescription increased over 5 years, and was greatest in US black patients. Oral nutritional vitamin D was not prescribed in Japan, but was in Europe (27%) and the US (12%) despite infrequent measurement of 25-OH vitamin D.

Conclusions: Variation in PTH at HD initiation by region and race may reflect differences in patient characteristics, pre-HD care, and/or timing of HD initiation. After an initial decline, we observed a rise in PTH with time on HD in US patients, particularly black patients, despite greater prescription of vitamin D and cinacalcet than in other regions. The rapid rise in P immediately following HD initiation may be partially attributable to loss of residual renal function. Future research is needed to study how MBD management before, during, and after the transition to HD can be optimized to improve clinical outcomes.

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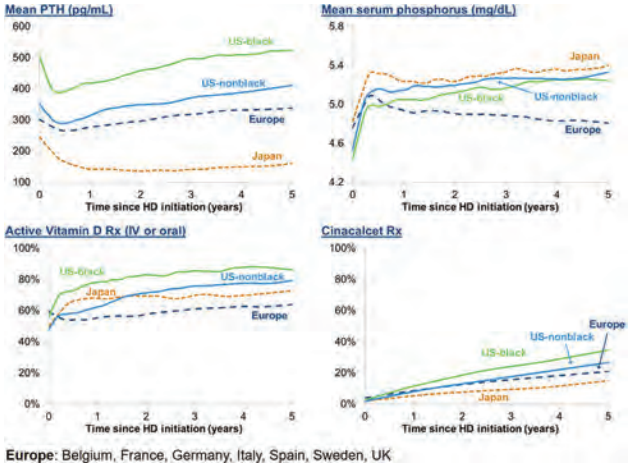


FR-PO295

Risk Factors for Hungry Bone Syndrome after Parathyroidectomy in CKD Patients on Dialysis Jorge I. Fonseca-Correa,[3] Juan Carlos Ramirez-Sandoval,[2] Luis Rojas-Concha,[6] Antonio Madrazo-Ibarra,[1] Pindaro S. Martínez-Delfín,[1] Paola Zinser-Peniche,[8] Juan Pablo Pantoja,[4] Mauricio Sierra-Salazar,[3] David VELAZQUEZ-FERNANDEZ,[5] Miguel Herrera-Hernández,[3] Ricardo Correa-Rotter.[7] *[1]Escuela de Medicina, Universidad Panamericana, Mexico City, Mexico; [2]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, México city, Mexico; [3]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, México City, Mexico; [4]Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubirán, Mexico, Mexico; [5]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [6]Instituto Nal Ciencias Med y Nutricion Salvador Zubiran, Puebla, Mexico; [7]Institutor Nacional de la Nutricion, Mexico City, Mexico; [8]Universidad Panamericana, CDMX, Mexico.*

Background: Hungry bone syndrome (HBS) is a frequent event after parathyroidectomy (PTx). While risk factors for HBS are well known in primary hyperparathyroidism (HPT), it is unclear whether these risk factors are similar in secondary or tertiary HPT.

Methods: We retrospectively analyzed the risk factors for HBS of a single-center cohort of 68 dialysis patients who underwent PTx. We defined HBS as persistent hypocalcemia (corrected calcium <7.5 mg/dL) lasting >3 days -with or without hypophosphatemia- requiring extended hospital stay for intravenous calcium supplementation. All patients were followed up for one year.

Results: HBS occurred in 36 (53%) patients. In the bivariate analysis, a higher preoperative intact parathyroid hormone (iPTH) (1984±777 vs. 940±581 pg/mL; p<0.001), a higher alkaline phosphatase (ALP) (706 [322-1155] vs. 132 [108-233] IU/L; p<0.001), and older dialysis vintage (4 [3-4] vs. 6 [4-11] years; p=0.049) independently predicted the development of HBS. Peritoneal dialysis (PD) treatment protected against HBS (68% Non-HBS vs. 47% HBS were on PD; p=0.02). Age, weight, preoperative phosphorus, and type of surgery did not predict HBS occurrence. Calcitriol prophylaxis for >2 days, prescribed in 91% of patients with HBS, was not effective to prevent HBS (median dose of 1.25 mcg/day [IQR 0.75-2.25]). When a multivariate analysis was performed only iPTH and ALP remained as predictors of HBS. During the year of follow-up, 4 (6%) patients died and 21 (31%) received a kidney transplant. At one year, patients who had HBS needed higher doses of calcium prescription (CaCO3 6.8 gr/day [IQR 4.5-14.8] vs. 1.5 gr/day [IQR 0-3.0]) and calcitriol (0.75 mcg/day [IQR 0.5-1.5] vs. 0.25 mcg/day [IQR 0-0.75].

Conclusions: HBS was a common complication after PTx and closely related to severity of HPT. At one year of follow up it was associated with continued prescription of higher doses of calcium and calcitriol. Consequences of this prolonged exposure to calcium and calcitriol could have deleterious systemic/vascular complications. Preoperative prophylactic calcitriol, prescribed in 91% of those who later developed HBS, was ineffective in preventing the appearance of this syndrome.

FR-PO296

Correlates and Outcomes Related to Parathyroidectomy in Veterans Who Transition to Maintenance Dialysis: A Transition of Care in CKD Study Vanessa A. Ravel,[1] Elani Streja,[1] Melissa Soohoo,[1] Yoshitsugu Obi,[1] Wei Ling Lau,[1] Connie Rhee,[1] Rajiv Saran,[2] Csaba P. Kovesdy,[3] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine, Orange, CA; [2]University of Michigan, Ann Arbor, MI; [3]University of Tennessee Health Science Center, Memphis, TN.*

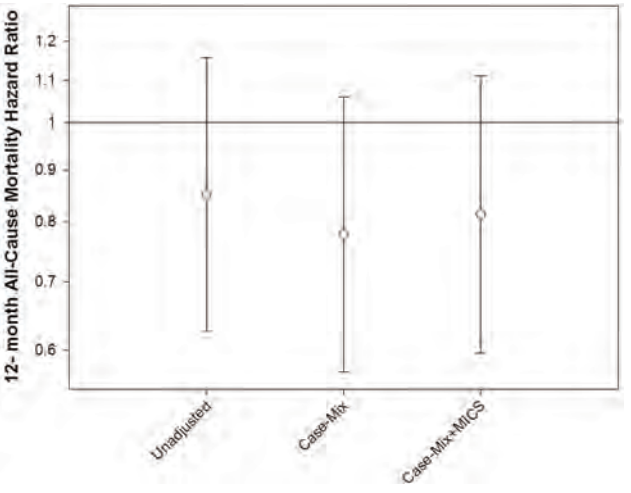
Background: Parathyroidectomy in the form of an elective, surgical resection of the parathyroid glands occurs less frequently since approved use of calcimimetics in 2004. Among patients who transition to ESRD, the correlates and consequences of parathyroidectomy are not known. We hypothesized that parathyroidectomy would be associated with better outcomes in incident dialysis patients.

Methods: Data of almost 80,000 US veterans who transitioned to dialysis between 10/2007 and 3/2014 were examined to identify those with documented parathyroidectomy prior to transition. The likelihood of parathyroidectomy was estimated via adjusted logistic regression odds ratios and the outcome of 1-year mortality via adjusted Cox regression hazard ratio.

Results: Out of 79,331 veterans who transitioned to dialysis, we identified 179 who had undergone parathyroidectomy prior to transition. Patients were 71±12 years old and included 11% women, 25% blacks and 7% Hispanics. Odds ratios (and 95% confidence intervals) of parathyroidectomy are shown in **Table 1**. The death hazard ratios (95% confidence interval bars) are shown in **Figure 1**. Case-mix adjustment included gender, race/ethnicity, comorbid states, and Malnutrition-Inflammation-Cachexia Syndrome (MICS) which includes additional laboratory variables and BMI.

Conclusions: Parathyroidectomy is performed more frequently among older veterans, women, and those with COPD, cancer, or hyperlipidemia, and those with higher serum levels of phosphorus, calcium or PTH. A consistent trend of 15-20% better survival was observed among those who underwent parathyroidectomy prior to transition.

Funding: NIDDK Support



	Unadjusted	Case-mix adjusted	Case-mix & MICS
Age (each 10 years older)	1.23 (1.08, 1.41)	1.27 (1.10, 1.46)	1.27 (1.10, 1.47)
Female (vs. male)	2.09 (1.30, 3.36)	2.26 (1.40, 3.66)	2.28 (1.41, 3.68)
COPD (vs. none)	1.60 (1.19, 2.15)	1.45 (1.06, 1.96)	1.46 (1.07, 1.98)
Cancer (vs. none)	2.40 (1.77, 3.25)	2.24 (1.63, 3.07)	2.20 (1.60, 3.02)
Hyperlipidemia (vs. none)	2.38 (1.56, 3.63)	2.27 (1.44, 3.59)	2.18 (1.38, 3.46)
Phosphorus (mg/dL)	1.02 (0.84, 1.25)	1.06 (0.87, 1.29)	1.28 (0.99, 1.65)
Calcium (mg/dL)	1.83 (1.26, 2.44)	1.76 (1.31, 2.38)	1.86 (1.23, 2.60)
PTH (100 pg/dL)	1.05 (0.96, 1.16)	1.07 (0.97, 1.17)	1.11 (1.03, 1.20)

FR-PO297

Effects of Parathyroidectomy on Plasma Different Parathyroid Hormone Fragments Levels in CKD Patients Ningning Wang,[1] Huimin Chen,[1] Xiaoming Zha,[2] Chang Ying Xing.[2] *[1]Department of Nephrology, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China; [2]First Affiliated Hospital of Nanjing Medical University, Nanjing, China.*

Background: Intact parathyroid hormone (iPTH) measured by the second generation assays include not only (1-84)PTH, but also (7-84)PTH. Now the third generation PTH assays have been shown specific test for (1-84)PTH. Here we investigated the levels of plasma iPTH, (1-84)PTH, (7-84)PTH in stage 5 chronic kidney disease (CKD) patients, and evaluate the effects of parathyroidectomy(PTX) on above parameters in severe secondary hyperparathyroidism(SHPT) subgroups.

Methods: We included 252 CKD patients divided by baseline plasma iPTH levels. Thirty-one PTX patients were followed up with median time of 7.1 months. Serum iPTH and (1-84)PTH were measured by electrochemiluminescence immunoassay. (7-84)PTH levels were calculated by subtracting the (1-84)PTH values from the iPTH values.

Results: Plasma iPTH, (1-84)PTH, (7-84)PTH levels were closely related with each other, while (1-84)PTH/iPTH gradually reduced with upregulated iPTH levels. For CKD subgroups with plasma iPTH level>800 pg/ml, (1-84)PTH/iPTH furtherly decreased to 0.5(Fig1). After PTX, plasma different PTH fragments levels were decreased obviously and (1-84)PTH/iPTH were increased in severe SHPT patients(Table 1).

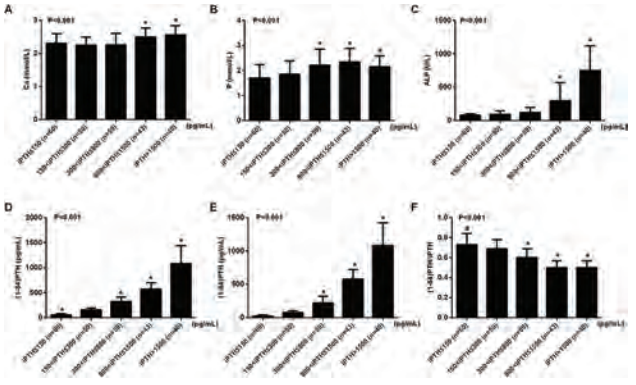
Conclusions: PTX can diminish abnormal increased iPTH, (1-84)PTH,(7-84)PTH levels and upregulate (1-84)PTH/iPTH for severe SHPT patients. Blood iPTH value may overestimate the severity of SHPT. Measurement of (1-84)PTH is suggested for accurate diagnosis and treatment in chronic kidney disease-mineral and bone disorder(CKD-MBD) patients.

Funding: Government Support - Non-U.S.

PTX can diminish blood PTH fragments levels and upregulate (1-84)PTH/iPTH in severe SHPT patients

Variable	Pre-PTX	Post-PTX
iPTH (pg/mL)	1662.0(965.7-2344.0)	67.9(44.0-125.9)*
(1-84)PTH (pg/mL)	773.0(495.4-1030.0)	53.6(35.9-90.5)*
(7-84)PTH (pg/mL)	749.0(591.8-1261.0)	12.9(5.1-41.5)*
(1-84)PTH/iPTH	0.5±0.1	0.8±0.2*

*,compared with Pre-PTX group, P<0.001



Characteristics of blood bone markers and different PTH fragments grouped by baseline plasma iPTH values

FR-PO298

High Prevalence of Aluminum Deposition in Bone and Osteoporosis in CKD Patients: Data from the Brazilian Registry of Bone Biopsy (REBRABO) Cinthia E. Carbonara,[1] Luciene dos Reis,[2] Renata A. Franca,[1] Kelcia R. Quadros,[1] André B. Esteves,[1] Noemi A. Roza,[1] Vanda Jorgetti,[2] Rodrigo B. de Oliveira.[1] *[1]School of Medical Sciences, Department of Internal Medicine, University of Campinas, Campinas, Brazil; [2]Medical School, Department of Nephrology, University of São Paulo, São Paulo, Brazil.*

Background: Mineral and bone disorder (MBD) due CKD is related with significant morbidity and mortality. REBRABO is a database wich contains information about Brazilian CKD patients with MDB.

Methods: Clinical, demographics, laboratorial, imaging, and bone histology data were collected from CKD patients between Aug/15-Apr/17. Diagnose of aluminum (Al) intoxication was when Al covered ≥30% of bone surface by solochrome-azurine; diagnose of osteoporosis was considered either by T *score* ≤2.5 S.D. or decreased bone volume detected by bone biopsy (BB).

Results: Data from 175 patients who were submitted to BB were analyzed. Patients aged 51±13 years, 89 (51%) men and 81(46%) white; 34 (19%) patients had history of bone fracture; symptoms of bone pain, weakness or myalgia were observed in 87 (51%) patients. Serum intact parathormone, alkaline phosphatase, calcium, and phosphate levels were 450 (58-500) pg/mL, 165 (73-250) IU/L, 9.2±1 mg/dL and 4.9±1.6 mg/dL, respectively. The main indication for BB was clinical protocol in 78 (45%) and suspected Al intoxication in 41 (23%) patients. Fibrous osteitis (FO) was detected in 67 (38%), mixed bone disease in 26 (15%), adynamic bone disease in 21 (12%) and osteomalacia in 6 (3,4%). Dialysis modality had no correlation with the type of renal osteodistrophy (ROD). Al intoxication was prevalent in 38 (22%); osteoporosis was present in 27 (15%) by bone densitometry and 54 (31%) by BB. Patients with osteoporosis diagnosed by BB presented higher prevalence of fracture (p=0.001).

Conclusions: FO was the main type of ROD in Brazil. A high prevalence of Al intoxication was detected. Osteoporosis when diagnoses by BB, but not by bone densitometry, was related with fractures. BB remains the gold standard for the differential diagnosis of ROD, as well as osteoporosis in CKD patients. Future studies are needed to clarify the clinical impact of Al intoxication in these patients.

FR-PO299

Bone Metabolism Markers, Epidemiological Profile, and Renal Function of HIV-Infected Patients before Initiating Antiretroviral Therapy Mariana G. Paula,[5] Unai Tupinambas,[1] Milena Guimarães,[3] Nathalia S. De,[1] Maria Goretti M. Penido,[4,2] Joao M. Penido.[6] *[1]Federal University of MInas Gerais, Belo Horioznte, Brazil; [2]Pediatric Nephrology Unit, Federal University of Minas Geraisl, Belo Horizonte, Brazil; [3]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; [4]Pediatric Nephrology Unit, Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; [5]Nephrology Center, Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; [6]Federal University of Ouro Preto, Ouro Preto, Brazil.*

Background: Data suggests that the HIV population is prone to changes in bone metabolism and renal function. The aim of this study was to describe the bone metabolism markers, epidemiological profile, and renal function of HIV-infected patients before initiating antiretroviral therapy (ART).

Methods: Transversal study with naive patients on ART, aged from 18 to 55 years of age, that underwent clinical evaluation, bone densitometry by DXA (lumbar spine L1-L4) and laboratory measurement: calcium, phosphorus, PTH, 25(OH)vitD, FGF23 and interleukin 1β (IL-1β) and 6 (IL-6) serum levels. The following statistic tests were used: Mann Whitney, Kruskal-Wallis, and the Spearman correlation test. The CKD-EPI formula was used to evaluate the glomerular filtration rate.

Results: We evaluated 70 patients (57M) with median age of 33.8 years. 93% had more than eight years of schooling, 84% were working, 77% were single, and sexual transmission was 93%. The time to diagnosis ranged from 0.13 to 300 months. 51 patients underwent DXA and 9 had reduced bone mineral density (BMD) at lumbar spine, 3 at femoral neck and 5 at total femur. 58% of the patients had altered 25(OH)vitD: 21% had deficient serum levels and 37% had insufficient levels. There was no change in serum calcium, phosphorus, and PTH. The FGF23 correlated positively with calcium (r=0.358; p=0.004) and with IL-1β (r=0.308; p=0.013). There was a significant difference in the FGF23 in relation to PTH, being higher in those who had normal PTH levels (p=0.025) and its relation to the femoral neck Z score, being higher in those with index ≤-2 (p=0.039). 9.4% had CKD II.

Conclusions: The majority of the patients were young, professionally active, singles, and had HIV sexual transmission. Although they were young and naive patients, 9.4% had compromised renal function and 8.5% of them had reduced BMD. There was a high prevalence of vitamin D deficiency/insufficiency, most likely because of early onset. The relationship between FGF23, PTH, BMD Z-score and the correlation between FGF23 and calcium and IL-1β suggests that this phosphatonin could be considered an early marker of bone metabolism. More studies are needed to improve the follow up of bone metabolism and renal function, which are crucial and important in HIV patients.

FR-PO300

Validating Whole Genome Sequencing (WGS) as a Diagnostic Technique for Autosomal Dominant Polycystic Kidney Disease (ADPKD) Amali Mallawaarachchi,[1] Yvonne Hort,[1] Sarah R. Senum,[2] Ben Lundie,[1] Jiang Tao,[1] Andre E. Minoche,[1] Mark J. Cowley,[1] John Shine,[1] Peter C. Harris,[2] Tim Furlong.[1] *[1]Garvan Institute of Medical Research, Sydney, NSW, Australia; [2]Mayo Clinic, Rochester, MN.*

Background: ADPKD is the most common monogenic renal disease. There are many benefits of genetic diagnosis (early diagnosis, family planning, cascade testing, living-donor selection and to predict disease severity). However genetic diagnostics is not routinely pursued. Diagnostic sequencing is challenged because 6 pseudogenes share 97% sequence homology with *PKD1* and confound standard sequencing techniques. WGS has the potential to overcome sequence homology, but has not been validated as a diagnostic test.

Methods: We studied 42 unrelated patients with an ADPKD phenotype. Thirty patients initially underwent long-range PCR/Sanger sequencing/MLPA (LR-PCR/SS/MLPA) of *PKD1* and *PKD2* in the Mayo Clinic (Grp1). Blinded WGS was then performed after PCR-free library preparation (Kappa Hyper kit, HiSeqX; 150bp paired-end sequencing) in the Garvan Institute. Concurrently, 12 patients were initially sequenced via WGS and then blinded LR-PCR/SS/MLPA of *PKD1* and *PKD2* (Grp2). Raw WGS data was analysed for single nucleotide and copy number variation via customized bioinformatics pipelines. WGS variant analysis was focussed on *PKD1* and *PKD2.*

Results: WGS provided uniform coverage (mean 36x; range 24-47), including in homologous and GC-rich regions. The same results as LR-PCR/SS/MLPA were obtained in 40/42 patients (37 disease-causing variants; 3 patients unknown with both methods). In 2/42 patients, using standard filters, WGS did not detect mosaic variants, however in 1 mosaic patient, reanalysis of WGS data showed the variant in 8% of reads. WGS defined the breakpoints of 2 multi-exon deletions, which was not possible with prior methods. On initial analysis of Grp1, the disease-causing variant was confirmed in 24/30 patients. After adjusting the variant filtering stringency, this was improved to 28/30. There were no false positive or false negative results with WGS.

Conclusions: WGS provides the basis of a new diagnostic test for ADPKD. It avoids laborious sample preparation and overcomes pseudogene homology. Unlike targeted sequencing, WGS allows scope for broadened genomic analysis if no *PKD1* or *PKD2* variants are identified. This study highlights the value of validating next generation sequencing against a gold-standard cohort prior to diagnostic application.

Funding: Private Foundation Support

FR-PO301

Evaluation of an Artificial Deep Neural Network for Fully Automated Segmentation of Individual Kidneys and Liver in Patients with Polycystic Kidney Disease Maatje D. van Gastel,[2,1] Marie E. Edwards,[1] Vicente E. Torres,[1] Ron T. Gansevoort,[2] Timothy L. Kline.[1] *[1]Mayo Clinic, Rochester, MN; [2]UMC Groningen, Groningen, Netherlands.*

Background: Polycystic kidney disease (PKD) leads to cyst formation in kidneys and often liver, with marked increase in total kidney volume (TKV) and total liver volume (TLV). TKV is recognized by the FDA and EMA as a biomarker that plays an important role in risk prediction in PKD. Thus far, there is no optimal alternative for the laborious and expensive measurement of manually tracing kidneys and liver in radiological imaging examinations. Therefore, we developed and validated a fully automated segmentation method for TKV and TLV measurement. This is the first study to propose a solution for measuring individual kidney volumes, and liver automatically in radiological examinations of patients with PKD.

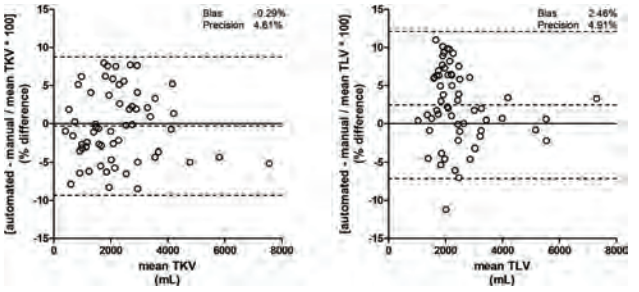
Methods: The automated approach that was developed was a deep learning network optimized to perform voxel-based classification. The network was first trained (80%) and

validated (20%) on a set of 100 abdominal MRIs (T2 weighted HASTE or TRUFI coronal sequences) of patients with PKD which had both kidneys and liver segmented manually. A test set of 60 patients was used to evaluate the performance of the developed automated method.

Results: TKV as well as TLV measured using the deep neural network correlated highly with manually traced TKV and TLV (ICC 0.996 and 0.994, resp.), with a bias and precision of -0.3%±4.6% for TKV and 2.5%±4.9% for TLV with maximal percentage differences observed being 8.5% and 11.2%, respectively. No proportional bias was observed, meaning that percentage differences between both methods are regardless of kidney or liver size.

Conclusions: This is the first fully automated segmentation method that measures individual kidney volumes, TKV and TLV almost as accurate as manual tracing, that has an inter-reader variability of 2.3%. The developed technique will facilitate future studies where automated and reproducible measurement of individual kidney volumes, TKV, and TLV are needed to assess (i) disease severity, (ii) progression of the disease, and (iii) treatment response.

Funding: Other NIH Support - This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases under NIH Grant/Award Number P30 DK090728 to the "Mayo Clinic Robert M. and Billie Kelley Pirnie Translational Polycystic Kidney Disease Center", and the PKD Foundation under grant 206g16a, Government Support - Non-U.S.



FR-PO302

Congenital Heart Disease (CHD) in Adult Patients with Autosomal Dominant Polycystic Kidney (ADPKD) Fouad T. Chebib, Maria V. Irazabal, Heidi M. Connolly, Emilie Cornec-Le Gall, Marie C. Hogan, Sarah R. Senum, Christina M. Heyer, Charles D. Madsen, Ziad El-Zoghby, Peter C. Harris, Vicente E. Torres. *Mayo Clinic, Rochester, MN.*

Background: Primary cilia and the polycystins have an important role in cardiac development. *Pkd1*$^{-/-}$ and *Pkd2*$^{-/-}$ mice have structural defects in cardiac septation including atrial and venticular septal defects (ASD,VSD). It is uncertain whether an association between ADPKD and CHD exists.

Methods: Clinical data was retrieved from medical records for patients with ADPKD and CHD evaluated at Mayo Clinic (1984-2015). Patent foramen ovale and isolated bicuspid aortic valve (BAV) were excluded from the prevalence analysis.

Results: Thirty of 667 patients with available echocardiograms had evidence of CHD:8 (1.2%) had a left-to-right shunt (4 ASD, 3 VSD, and 1 isolated PDA); 6 (0.9%) outflow obstruction (4 aortic coarctation, 1 aortic hypoplasia, and 1 pulmonic stenosis); 5 (0.75%) with cyanotic CHD (2 tetralogy of Fallot, 1 Ebstein's anomaly, 1 tricuspid atresia and 1 transposition of great arteries associated with double inlet left ventricle, pulmonic stenosis and ASD); and 14 (2.1%) BAV. Two additional patients had left coronary artery to pulmonary artery fistula and isolated persistent left superior vena cava. Genetic studies have revealed 18 patients with *PKD1* mutations (11 truncating and 4 non-truncating); none with *PKD2* mutations and no mutation was detected in 3 patients (Table 1).

Conclusions: Coexistence of ADPKD and CHD in our tertiary referral center cohort appears to be higher than expected by chance. The observed prevalence of CHD (excluding isolated BAV) in ADPKD patients seems higher than the general population (3.1 vs. 0.8%). We suggest that ADPKD mutations predispose to congenital heart malformations.

Funding: NIDDK Support

	Left-to-right shunts (n=8)	Outflow obstruction (n=6)	Cyanotic (n=5)	BAV (n=14)*
Male,%	37.5	50	60	78.5
Caucasian, %	87.5	100	100	100
Average age at diagnosis of CHD	28.6 ± 29.1	11.8 ± 12.3	3.4 ±5.2	39.3 ± 23.1
Surgery	2	5	5	9
Average age at first surgery	8.5 ± 9.2	14.2 ± 13.8	10.2 ± 15.6	38.4 ± 28.3
Age at ESRD, years	52.2 ± 7.1 (n=4)	43.5 ± 6.3 (n=2)	48 (n=1)	50.5 ± 6.6 (n=7)
Median TKV (IQR), ml	2599 (727 - 3609) N=7	1598 (544 – 4312) N=3	1546 (391 - 2745) N=4	1985 (810 – 3841) N=8
With PKD genetic testing (n)	5	5	3	7
PKD1 truncating mutations (n,%)	3, 60%	4, 80%	2, 66.7%	4, 57.1%
PKD1 non-truncating mutations (n,%)	2, 40%	0	0	2, 28.6%
PKD2 mutations (n,%)	0	0	0	0
No mutation detected (n,%)	0	1, 20%	1, 33.3%	1, 14.3%

*Three patients with BAV had another CHD condition; Abbreviations: ESRD : End Stage Renal Disease, TKV: Total Kidney Volume, BAV: Bicuspid Aortic valve; CHD: Congenital heart disease

FR-PO303

Association of Serum FGF23 and Klotho with Long-Term Renal Outcomes of Polycystic Kidney Disease (PKD) in the Consortium for Radiologic Imaging Studies of PKD (CRISP) Cohort Mireille El Ters,[1] Jason R. Stubbs,[3] Jonathan D. Mahnken,[2] Darren P. Wallace,[3] Alan S. Yu.[3] *[1]Mayo Clinic, Rochester, MN; [2]The University of Kansas Medical Center, Kansas City, AL; [3]University of Kansas Medical Center, Kansas City, KS.*

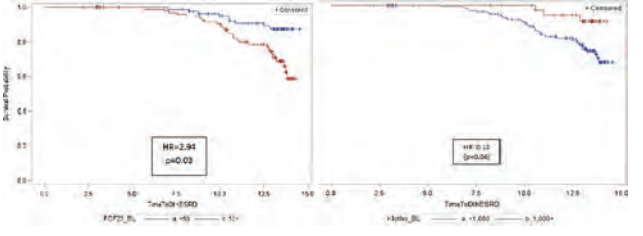
Background: PKD is a slowly progressive disease leading to end-stage renal disease (ESRD). Levels of FGF23 are elevated in PKD out of proportion to kidney function, and circulating levels of its receptor, Klotho, decreased. Whether these are associated with long term renal outcomes is unknown.

Methods: CRISP is an observational cohort study of 241 PKD patients. Kidney function was serially measured with iothomalate clearance(iGFR) and height-adjusted total kidney volume(htTKV) measured by MRI. Intact FGF23 and soluble Klotho were measured on 191 available baseline serum samples and dichotomized into high/low FGF23 groups (cutoff 50 pg/ml) and high/low Klotho groups (cutoff 1000 pg/ml). The association of baseline FGF23 and Klotho level with follow-up log-htTKV and iGFR was tested using linear mixed models with random intercepts and adjusted for age, gender and Irazabal class. The risk of combined endpoint of ESRD and death was evaluated using a multivariable adjusted Cox proportional hazards model.

Results: Baseline serum FGF23 was 58±29 pg/ml and Klotho 918±925 pg/ml (mean ± SD). High FGF23 and low Klotho were both associated with higher baseline htTKV and lower baseline iGFR. Median follow-up was 13 years, during which 37 patients died or reached ESRD. High FGF23 was associated with faster growth of htTKV over the follow-up period and faster decline in iGFR (adjusted mean slope -3.04 vs -2.21 ml/min/y, p= 0.0013). Low Klotho also was associated with faster increase in htTKV and faster decline in iGFR (adjusted mean slope -2.97 vs -1.70 ml/min/y, p<0.01). High serum FGF23 was associated with increased risk of ESRD/death (adjusted HR=2.4, p=0.04). Low Klotho was also associated with increased risk however not when adjusted for baseline iGFR (Adjusted HR=0.4, p = 0.14 for Klotho).

Conclusions: Higher serum FGF23 and lower serum Klotho are associated with faster kidney growth and decline in renal function. Higher FGF23 was associated with increased risk of ESRD or death after adjustments for age, gender, Irazabal class and baseline iGFR.

Funding: Other NIH Support - Frontier Grant (CTSA)



Time to Death/ESRD

FR-PO304

Mineralocorticoid Antagonism and Vascular Function in Early Autosomal Dominant Polycystic Kidney Disease: A Randomized-Controlled Trial Kristen L. Nowak, Berenice Y. Gitomer, Heather Farmer-Bailey, Wei Wang, Diana George, Michel Chonchol, Mikaela R. Malaczewski. *University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: Arterial dysfunction, featuring impaired vascular endothelial function and increased large-elastic artery stiffness, is evident early autosomal dominant polycystic kidney disease (ADPKD), and is an important predictor of cardiovascular events and mortality. Aldosterone excess has been implicated in the development of endothelial dysfunction are arterial stiffness. We hypothesized that aldosterone antagonism would reduce arterial dysfunction in patients with early-stage ADPKD.

Methods: In a randomized, controlled, double-blind trial, n=60 adults 30-55 years of age with ADPKD, normal kidney function (estimated glomerular filtration rate [eGFR] ≥60 mL/min/1.73 m^2), and receiving the maximum tolerable dose of an angiotensin converting enzyme inhibitor were randomized to receive either spironolactone (titrated to maximum dose of 50 mg/day) or placebo for 6 months. The primary endpoints were change in vascular endothelial function, measured as brachial artery flow-mediated dilation (FMD_{BA}) and arterial stiffness, measured as carotid-femoral pulse-wave velocity (CFPWV).

Results: Participants were 34±10 (mean±s.d.) years of age, 53% female and 80% White, with an eGFR of 94+21ml/min/1.73m^2. Spironolactone did not change FMD_{BA} (baseline: 8.0±5.5%, 6 months: 7.7±4.1%; placebo: baseline: 8.4±6.2%, 6 months: 7.9±4.3%; p≥0.63), but reduced CFPWV (baseline: 640±127 cm/sec, 6 months: 4: 603±101 cm/sec; p<0.05) with no change in the placebo group (baseline: 659+138 cm/sec, 6 months: 661±132 cm/sec; p=0.90). Brachial systolic blood pressure (SBP) was also reduced in the spironolactone group (baseline: 124±13 mmHg, 6 months: 117±11 mmHg; p<0.05) with no change in the placebo group (p=0.50). Spironolactone also reduced brachial and carotid pulse pressure, carotid SBP, and carotid augmentation index (p<0.05), with no changes in the placebo group.

Conclusions: Six months of aldosterone antagonism with spironolactone reduced arterial stiffness and SBP without changing vascular endothelial function in patients with early-stage ADPKD.

Funding: NIDDK Support

FR-PO305

Transplant Outcomes in Patients with Autosomal Dominant Tubulointerstitial Kidney Disease (AD-TKD) Sarah Cormican,[1] Dervla M. Connaughton,[3] Claire Kennedy,[1] Katherine A. Benson,[4] Gianpiero Cavalleri,[5] Brendan Doyle,[1] Anthony M. Dorman,[1] Mark A. Little,[6] Peter J. Lavin,[6] Kendrah O. Kidd,[7] Anthony J. Bleyer,[7] Peter J. Conlon.[2] *[1]Beaumont Hospital, Dublin 9, Ireland; [2]Beaumont Hospital, Dublin 9, Co Dublin, Ireland; [3]Boston Children's Hospital, Boston, MA; [4]Queen's University, Belfast, Belfast, United Kingdom; [5]RCSI, Dublin, Italy; [6]Trinity College Dublin, Dublin, Ireland; [7]Wake Forest University School of Medicine, Winston-Salem, NC.*

Background: ADTKD is a rare genetic cause of chronic kidney disease which causes progressive tubular atrophy and interstitial fibrosis with loss of renal function. Patients with ADTKD frequently progress to end stage renal disease (ESRD). Little is known about transplant outcomes in this group.

Methods: Patients with clinical characteristics consistent with ADTKD by the criteria outlined in the 2015 KDIGO consensus report were identified through the Irish Kidney Gene Project. Clinical and histology records were reviewed for patients who received a renal transplant during follow-up. We compared ADTKD transplant outcomes with those of 4004 non-ADTKD transplant recipients.

Results: 29 patients were identified; fifteen of whom had a known mutation (ADTKD-*MUC1* n=9, ADTKD-*UMOD* n=6). Fourteen patients met KDIGO criteria for diagnosis based on histology and family history without an identified mutation (ADTKD-NOS). Four patients received a second transplant during follow-up. In total 33 grafts (28 deceased donor, 5 living related donor) were included. 1-year, 5-year and 10-year graft survival for patients with ADTKD vs. non-ADTKD patients were: 100% vs. 90%, 96% vs. 77% and 72% vs. 60%. On log-rank test for equality of survival functions these differences were not statistically significant. Fifteen patients had at least one transplant biopsy performed during follow-up (26 transplant biopsies were performed in total). The most common findings were chronic allograft nephropathy (n=11) and acute rejection (n=10). Cyclosporin toxicity (n=2), polyoma virus nephropathy (n=1), acute tubular necrosis (n=1) and donor-related fibrosis (n=1) were also seen. Features sugestive of recurrent disease were not described Fourteen grafts were lost during follow-up due to patient death (n=7), chronic allograft nephropathy (n=6) and polyoma-virus nephropathy combined with acute rejection (n=1).

Conclusions: In patients with ESRD due to ADTKD we demonstrate that transplant outcomes are comparable with the general transplant population. Increasing our ability to identify the responsible genetic mutation in each patient will allow screening of relatives who wish to donate but are potentially affected.

FR-PO306

Efficacy and Safety of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease with Renal Insufficiency Masahiko Oguro,[3] Junichi Hoshino,[3] Masayuki Yamanouchi,[2] Yoshifumi Ubara.[1] *[1]None, Setagaya, Japan; [2]Okinaka Memorial Institute for Medical Research, Tokyo, Japan; [3]Toranomon Hospital, Kawasaki, Japan.*

Background: A recent study demonstrated that tolvaptan slowed kidney volume growth and kidney function decline in autosomal dominant polycystic kidney disease (ADPKD) patients with creatinine clearance ≧60 ml per minute. However, tolvaptan's efficacy in advanced chronic kidney disease (CKD) patients—especially those whose eGFR is <30ml per minute—has remained unknown.

Methods: In this prospective cohort study, 54 patients with ADPKD who had eGFR≧15 per minute and total kidney volume (TKV) ≧750 ml were treated with tolvaptan. The primary endpoint was a change in TKV and eGFR over 1 year treatment with tolvaptan across CKD stages G2-G4. The secondary endpoint was the final dose of tolvaptan and proportion of tolerance at each CKD stage.

Results: The rate of kidney growth during the 1-year treatment didn't differ significantly across CKD stages G2-G4. The median [IQR] of relative change in TKV in CKD stages G2, G3a, G3b, and G4 was, respectively, 5.70 [-0.67, 8.75], 6.66 [2.02, 17.66], 8.22 [5.97, 31.39], and 8.80 [4.12, 25.88] %/year (P=0.34). Nor did the rate of eGFR decline during the 1-year treatment differ significantly across CKD stages G2-G4. The relative annual change in eGFR—compared with the baseline eGFR—was, respectively, -4.15 [-11.78, 0.08], -7.28 [-11.17, -0.49], -7.02 [-16.74, -2.68], and -10.76 [-13.93, -18.6] %/year (P=0.59). Tolerance didn't differ significantly across CKD stages G2-G4.

Conclusions: This analysis suggests that patients with advanced CKD stages—including G4—might benefit from treatment with tolvaptan as do patients with preserved kidney function.

Funding: Government Support - Non-U.S.

FR-PO307

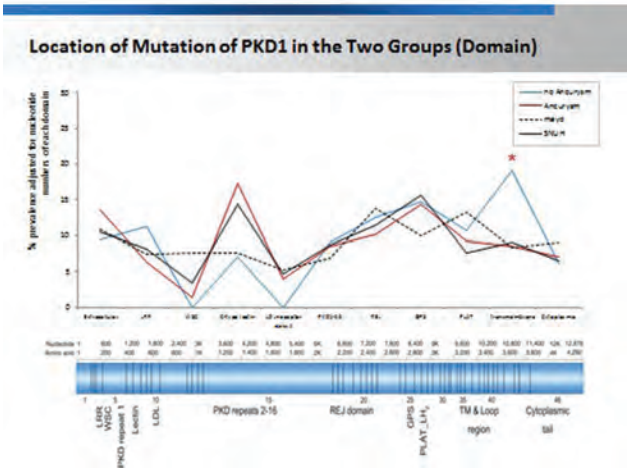
Cerebrovascular Phenotype and Genotype Correlation in ADPKD: A Study in HOPE-PKD Hyun suk Kim,[2] Hyunjin Ryu,[2] Chung Lee,[3] Jongho Heo,[4] Curie Ahn,[2] Yun Kyu Oh.[1] *[1]Department of Internal Medicine, Boramae Medical Center, Seoul, Republic of Korea; [2]Seoul National University Hospital, JongNo-Gu, SEOUL, Republic of Korea; [3]Samsung Genome Institute, Seoul, Republic of Korea; [4]JW LEE Center for Global Medicine, Seoul, Republic of Korea.*

Background: Cerebral aneurysm occurs in ADPKD (autosomal dominant polycystic kidney disease) by about 20% in the subjects older that 60years. The current study aimed to define phenotype characteristics of aneurysm, confirm the familial clustering effect and analyze the genetic differences in aneurysm vs. no aneurysm subjects in ADPKD.

Methods: Patients registered at the HOPE PKD cohort from October, 2009 to October, 2016 were included. Presence or absence of cerebral aneurysm and renal progression was reviewed, and PKD1/2 gene screening by targeted exome sequencing was performed. According to the presence or absence of cerebral aneurysm, the familial clustering effect was investigated and the proportions of PKD1 protein truncating (PT) mutations, PKD1 non-truncating (NT) mutations, PKD2, and no candidates (NC) were analyzed.

Results: A total of 398 families (n=538) were divided into aneurysm (n=131) or no-aneurysm group (n=407). In the aneurysm group, males were less prevalent (36.6 % vs. 49.9%, P=.010) and the mean age was significantly older (56.4 years vs. 50.2 years, P<.001). Similarly, females were prone to SAH events or intervention (n=21(72.4%)). The proportion of high risk group (Mayo classification 1C, 1D, and 1E) or ESRD, the median [IQR] of height adjusted kidney or liver were not different in age, and sex adjusted model. The family clustering effect adjusted for age and sex was significant in multilevel logistic regression model (P=0.012), However, the prevalence of genes (PT, NT, PKD2, NC) was not correlated with aneurysm. Four years later, aneurysm occurred in 16.1% (31/192, median follow up, 5.3 year) of the people who had not had it. The transmembrane domain was less related to occurrence of aneurysm.

Conclusions: Brain MRA is recommended at least every 4 years; every 3 years preferred for subjects with no aneurysm. The effect of PKD 1/2 gene type was not observed.



FR-PO308

Identifying ARPKD Patients at Risk for Dialysis in the First Year of Life – Data from the International Registry Study ARegPKD Kathrin Burgmaier,[3] Ismail Dursun,[7] Kevin Kunzmann,[4] Bruno Ranchin,[5] Rukshana Shroff,[1] Dorota Wicher,[2] Elke Wuehl,[4] Franz S. Schaefer,[4] Max Liebau.[3,6] *[1]Department of Nephrology, London, United Kingdom; [2]The Children's Memorial Health Institute, Department of Medical Genetics, Warsaw, Poland; [3]University Hospital Cologne, Cologne, Germany; [4]University of Heidelberg, Heidelberg, Germany; [5]Université de Lyon, Lyon, France; [6]Center for Molecular Medicine, University of Cologne, Cologne, Germany; [7]Erciyes University, Kayseri, Turkey. Group/Team: For ARegPKD consortium.*

Background: Autosomal recessive polycystic kidney disease (ARPKD) is a severe disease of early childhood and an important reason for renal replacement therapy in the first year of life. Yet, ARPKD shows pronounced phenotypic variability, making pre- and perinatal counseling challenging. Risk markers for the need of dialysis in the first year have not been established for ARPKD patients.

Methods: We studied the clinical courses of 385 patients from 18 countries included in the international ARPKD registry study ARegPKD using the time-to-event endpoint 'start of renal replacement therapy' and multivariate Cox regression.

Results: 36 patients started dialysis in the first year of life (median age at start of dialysis 0.14 years (0.00-0.91 years)). 30 children started peritoneal dialysis (PD), no patient underwent transplantation. Four patients deceased postnatally due to respiratory failure without onset of dialysis. Oligo/anhydramnios, enlarged prenatal kidney volume, high standardized birth weight and low 10-min APGAR score were associated with

an increased risk of dialysis need. Perinatal assisted breathing was associated with a markedly increased hazard ratio in the first 6 months of life but not thereafter.

Conclusions: The identification of indicators for the need of dialysis within the first year of life in ARPKD patients may allow predictive scoring to inform prenatal counseling.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO309

Relationship between Caffeine and Autosomal Dominant Polycystic Kidney Disease Progression Katelyn Mckenzie,[2] Mireille El Ters,[1] Alan S. Yu,[2] Jonathan D. Mahnken.[2] *[1]Mayo Clinic, Rochester, MN; [2]University of Kansas Medical Center, Kansas City, KS.*

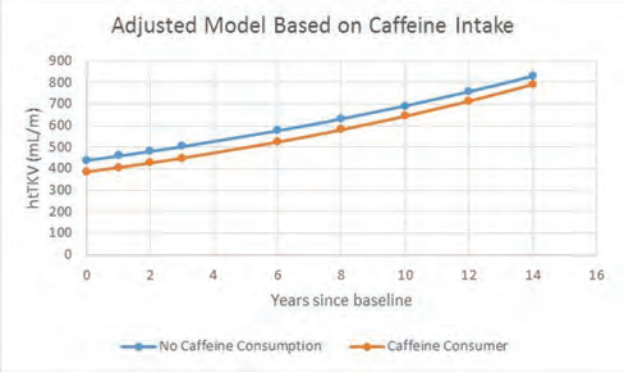
Background: Caffeine has been proposed, based on animal studies, to further progression of autosomal dominant polycystic kidney disease (ADPKD) by increasing cyst and kidney size. ADPKD patients are advised to minimize caffeine intake. We therefore investigated the effect of caffeine on kidney function in ADPKD.

Methods: Data from the Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease study included 239 patients (96 males, mean age = 32.3 ± 8.9 years, 188 caffeine consumers) from 2001-2015. Caffeine intake was dichotomized (any vs. none). Linear mixed models, unadjusted and adjusted for age, sex, race, hypertension, genetics and time, were used to model the outcomes of height adjusted total kidney volume (htTKV) and iothalamate clearance (mGFR). Cox Proportional Hazard Models and Kaplan-Meier plots examined the effect of caffeine on time until ESRD/death, along with corresponding log-rank tests. Sensitivity analyses were conducted.

Results: Known risk factors (age, hypertension and genetics) were statistically significant in all adjusted models. While caffeine-by-time was statistically significant in unadjusted and adjusted models ($p < 0.01$) indicating faster growth in kidney volume using ln(htTKV) as an outcome, total kidney volume remained smaller from baseline (0 years) through 14 years (e.g., $p = 0.60$ for caffeine vs. none at 14 years). No differences in time to ESRD/death by caffeine were detected ($p > 0.12$).

Conclusions: We found that caffeine consumption in ADPKD was associated with statistically faster kidney growth. However, our models indicated kidney volume was smaller among caffeine consumers despite the increased rate of growth. This phenomenon persisted over all years modeled. No association with GFR over time was detected. Caffeine does not appear to be associated with larger kidney volumes.

Funding: Other NIH Support - DK106912



FR-PO310

Circulating Interleukin-6 Level Predicts Decline in Kidney Function in Autosomal Dominant Polycystic Kidney Disease Berenice Y. Gitomer,[2] Wei Wang,[9] Kristen L. Nowak,[11] Katharina Hopp,[10] Zhiying You,[6] Godela M. Brosnahan,[4] Peter C. Harris,[3] Vicente E. Torres,[3] Arlene B. Chapman,[7] Ronald D. Perrone,[5] Theodore I. Steinman,[1] Alan S. Yu,[12] Kaleab Z. Abebe,[13] Kyongtae T. Bae,[13] Michel Chonchol.[8] *[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]Div. Renal Diseases and Hypertension, Aurora, CO; [3]Mayo Clinic, Rochester, MN; [4]None, Aurora, CO; [5]Tufts Medical Center, Boston, MA; [6]UC Denver, Aurora, CO; [7]University of Chicago, Chicago, IL; [8]University of Colorado, Aurora, CO; [9]University of Colorado Anschutz Medical Campus, Aurora, CO; [10]University of Colorado Denver, AMC, Aurora, CO; [11]University of Colorado Denver: Anschutz Medical Campus, Aurora, CO; [12]University of Kansas Medical Center, Kansas City, KS; [13]University of Pittsburgh, Pittsburgh, PA.*

Background: There is significant variability in the rate of kidney function decline among patients with autosomal dominant polycystic kidney disease (ADPKD). Resultant from the growth of cysts, several processes contribute to kidney injury including inflammation and consequent fibrosis. We hypothesized that the level of the circulating pro-inflammatory cytokine interleukin-6 (IL-6) may indicate kidney inflammation and predict the rate of kidney function decline.

Methods: Serum from 407 subjects who participated in the HALT clinical trial and had a *PKD1* mutation were utilized in the study. IL-6 level was measured by a high sensitivity ELISA assay in the 24 month samples which were treated as baseline. Kidney function was assessed by eGFR using the CKD-EPI equation. Due to skewed distribution IL-6 was log transformed for analysis. Linear regression and mixed effects models were used to assess the association between circulating IL-6 and subsequent kidney function decline. Analyses were adjusted for age, sex, race, randomization group, systolic blood pressure and urinary albumin excretion.

Results: The mean age of included subjects was 40 ± 10 years and eGFR was 62 ± 27 ml/min/1.73m^2. In cross-sectional analysis when stratified by the median level, higher Ln IL-6 was significantly negatively associated with lower eGFR in the fully adjusted model (β -6.315, 95%CI -10.517,-2.109; $p = 0.003$). In longitudinal analysis, higher circulating IL-6 measured at baseline was independently associated with a greater decrease in eGFR in the fully adjusted model (β -10.207, 95% CI -11.315,-9.10; $p = < 0.0001$).

Conclusions: Inflammation indicated by higher IL-6 level at baseline predicts kidney function decline. This suggests that measurement of serum IL-6 or other inflammatory mediators at baseline may represent a predictive biomarker of kidney disease progression in ADPKD. Future validation of IL-6 as a biomarker of ADPKD progression in additional cohorts will be necessary to confirm these results.

Funding: NIDDK Support, Private Foundation Support

FR-PO311

Clinical Diagnosis of Senior Loken Syndrome in a Patient with SDCCAG8 Mutation Genetically Diagnosed as Having Bardet-Biedle Syndrome Yuko Fujii,[1] Akira Ashida,[1] Hideki Matsumura,[1] Akihiko Shirasu,[1] Satoshi Yamazaki,[1] Hyogo Nakakura,[1] Naoya Morisada,[3] Kazumoto Iijima,[3] Motoshi Hattori,[2] Hiroshi Tamai.[1] *[1]Pediatrics, Osaka Medical College, Takatsuki, Japan; [2]Pediatric Nephrology, Tokyo Women's Medical University, Tokyo, Japan; [3]Pediatrics, Kobe Univ. Graduate School of Medicine, Kobe, Japan.*

Background: Both Senior Loken Syndrome (SLS) and Bardet-Biedle Syndrome (BBS) are ciliopathies. SLS is characterized by retinitis pigmentosa (RP) and familial nephronophthisis, leading to end-stage kidney disease. BBS is characterized by six major symptoms: RP, polydactyly, obesity, genital abnormalities, learning difficulties, and renal defects. So far, ciliopathy has been diagnosed according to phenotypes, but now it is often diagnosed by genetic testing using techniques such as next-generation sequencing. Here we describe a patient who was clinically diagnosed as having SLS but in whom genetic testing indicated BBS.

Methods: The patient was diagnosed as having RP at the age of six years. She had learning disability, preobesity and dyslipidemia, but no polydactyly. When she was eight years old, she was diagnosed as having chronic kidney disease, anemia, and liver dysfunction. Kidney and liver biopsy revealed renal tubule cysts, tubule membrane disruption, and liver fibrosis. Therefore, SLS was diagnosed but no mutation in *NPHP1* was detected. Peritoneal dialysis was started at the age of nine years, and the patient underwent kidney transplantation with a graft from her father at the age of fourteen years. At the age of twenty years, she again underwent genetic testing for most of the mutations associated with ciliopathy. This revealed that she had a homozygous mutation in intron 11 of the *SDCCAG8* gene which had caused a frameshift mutation.

Results:

Conclusions: *SDCCAG8* is known to be one of the causative genes related to SLS and BBS without polydactyly. The fact that the patient had learning disability, preobesity and dyslipidemia suggested a high probably of BBS. Although these symptoms are not specific, she did not have the typical symptom of BBS including polydactyly. Therefore, a definitive diagnosis of BBS was difficult without any information concerning genetic mutation. As only a few cases of *SDCCAG8* mutation have been reported previously, accumulation of further cases will help to clarify the characteristics of the phenotype of *SDCCAG8* mutation, thus contributing to the better management of patients with ciliopathy.

FR-PO312

Reversibility of Serum Creatinine Elevation Observed in ADPKD Subjects Receiving the Tyrosine Kinase Inhibitor Tesevatinib David A. Eiznhamer,[1] Anjay Rastogi,[2] Michel Chonchol,[3] Ashraf El-Meanawy,[4] Theodore I. Steinman,[5] Karin Herrera,[1] Olivier Schueller,[1] John L. Ryan,[1] Pablo E. Pergola.[6] *[1]Kadmon Corporation, LLC, Cambridge, MA; [2]UCLA Medical Center, Los Angeles, CA; [3]University of Colorado, Aurora, CO; [4]Medical College of Wisconsin, Milwaukee, WI; [5]Beth Israel Deaconess Medical Center, Boston, MA; [6]Renal Associates PA, San Antonio, TX.*

Background: The KD019-101 trial has evaluated the safety and preliminary efficacy of tesevatinib in patients with ADPKD. Preliminary data suggested that subjects with ADPKD receiving tesevatinib experienced elevations of serum creatinine without concomitant elevations of cystatin C. Pre-clinical laboratory investigations determined that tesevatinib inhibited the human multidrug and toxin extrusion transporters MATE1 and MATE2-K (IC_{50} = 80nM and 68nM, respectively). This inhibition could result in increased serum creatinine in the absence of decrease in kidney function, due to the reduced tubular secretion of creatinine.

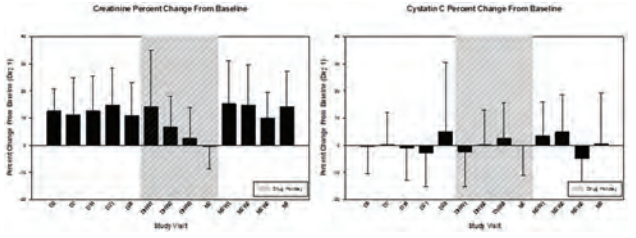
Methods: An additional cohort in Study KD019-101 enrolled subjects with eGFR ≥ 35 but ≤ 80 mL/min/1.73m^2 and htTKV ≥ 1000mL. These subjects had a mandatory 4-week drug holiday after the first 4 weeks of 50 mg QD tesevatinib treatment. During, and for 4 weeks after the drug holiday, subjects returned to the clinic weekly for serum creatinine and cystatin C measurement.

Results: 13 patients (6 males/7 females) were enrolled. Consistent with previous data, after an initial increase, serum creatinine stabilized. Creatinine levels begin to

decrease after 14 days of drug holiday and continued to decrease to baseline levels after 4 weeks of drug holiday. Resumption of drug resulted in similar increases as seen initially. Serum cystatin C levels were variable and did not show a pattern of increase before, during, or after the drug holiday period.

Conclusions: Serum creatinine elevations following tesevatinib dosing in patients with ADPKD are reversible upon cessation of dosing, and do not appear to result in a meaningful alteration in kidney function. This provides support for the hypothesis that serum creatinine elevation is a consequence of drug transporter inhibition resulting in the reduced tubular secretion of creatinine.

Funding: Commercial Support - Kadmon Corporation, LLC



FR-PO313

First Year Follow-Up Data from the German ADPKD Tolvaptan Treatment Registry – AD(H)PKD Roman-Ulrich Mueller,[1] Franziska Grundmann,[1] Polina Todorova,[1] Katharina Burkert,[1] Claudia Witte,[2] Volker R. Burst,[1] Thorsten Persigehl,[3] Bernhard Schermer,[1] Thomas Benzing.[1] *[1]Department 2 of Internal Medicine, Renal Division; University of Cologne, Cologne, Germany; [2]University of Cologne, Cologne, Germany; [3]Department of Radiology, University Hospital Cologne, Cologne, Germany.*

Background: Admission of Tolvaptan in Europe by the EMA as the first targeted therapy of autosomal-dominant polycystic kidney disease (ADPKD) based on the findings of the TEMPO 3:4 trial is a milestone in the treatment of this disease. After the significant benefit on eGFR in TEMPO 3:4 and 4:4 more data on this therapy regarding crucial questions in the real-life setting would be highly valuable. How do patients accept the treatment taking into account polyuria? Is the target dose reached? What side effects occur? How is the effect regarding kidney function and volume? Which patients are selected for treatment? How does Tolvaptan affect quality of life? How good is the adherence to the therapy?

Methods: In order to answer these questions we established the multicentric German AD(H)PKD registry. Patients that are generally eligible for Tolvaptan, independent of whether actually taking the drug or not, can be included in this observational study. Blood values, kidney volume from imaging data, indicators of quality of life, adherence to therapy, the actual dose administered, genotype and data regarding extrarenal manifestations, comorbidity, side effects and complications are documented. After enrolment patients are followed-up in yearly visits for ten years.

Results: We have been able to recruit more than 270 ADPKD patients so far and have started the first-year follow-up visits at the end of 2016. Consequently, analysis of this cohort allows for the first characterization of patients presented for evaluation regarding initiation of Tolvaptan on the one hand. On the other hand the first-year data provide an interesting insight into which patients were selected for treatment and sheds light on dosing strategies. Furthermore, adherence to therapy and the impact on quality of life are analyzed.

Conclusions: The AD(H)PKD-registry provides the first comprising dataset on the German cohort of ADPKD patients eligible for treatment with Tolvaptan and analyzes the selection criteria applied by German nephrologists as well as tolerability, side effects and impact on other kidney-related outcomes. Follow-up of this cohort will provide valuable data that can help in counseling patients and informing physicians dealing with this novel treatment opportunity.

Funding: Commercial Support - Otsuka Pharmaceuticals

FR-PO314

Diagnosis of Renal Cyst Infection in Adult Polycystic Kidney Disease (ADPKD) Using 67-Gallium Citrate SPECT/CT: A Case Series Ester Casillas,[2] Victor Burguera,[2] Haridian Sosa Barrios,[2] Maria Delgado yagüe,[2] María eugenia Rioja garcia,[1] Laura V. Blanco,[2] Maite Rivera.[2] *[1]Hospital Universitario Ramon y cajal, Madrid, Spain; [2]Nephrology, Hospital Universitario Ramón y Cajal, Madrid, Spain.*

Background: Renal cyst infection in ADPKD patients is challenging, as it can be the source of life-threatening sepsis and frequently lack localizing symptoms. Recent guidelines establish that intracystic material compatible with infection should be obtained for definite diagnosis. Gold standard imaging to do so is PET/CT, which is expensive and restrained to certain centers. We sought to determine whether 67-Gallium-citrate scintigraphy is a valuable and inexpensive alternative to orientate renal cyst infection in these patients.

Methods: Between January 2015 and January 2016 (both included), five patients with ADPKD diagnosis presented in our center with kidney cyst infection. 3 were female and 2 male with a mean age of 50.4 ±17 years (range 32-72 years). Two patients were on renal replacement therapy (one HD and one PD), one had a functioning renal transplant and the remaining two had CKD. The most frequent presenting symptoms of cyst infection were fever (n=5) and abdominal pain (n=4) (Table).

Results: Ultrasound (US) scanning of both kidneys was done in 4 patients (80%) and computed tomography (CT) in all of them. US was compatible with infected cyst in one patient (sensitivity of 33%) and CT in two patients. 67-Ga-citrate SPECT/CT was positive in 4 patients (80%) and true negative in 1, proving better sensitivity (100%) and specificity than US and CT. During follow-up, we used 67-Ga-citrate scintigraphy in those patients with initial positive results treated to assess resolution and decide whether antibiotics should be discontinued. Two patients (50%) showed persistent tracer uptake despite a complete course of appropriate antibiotics for 6 weeks.

Conclusions: 67-Ga-citrate SPECT/CT is a non invasive and inexpensive study available in most centers. It can be used in all ADPKD patients with suspected renal cyst infection regardless of kidney function, being more cost-effective than PET/CT. Due to demonstrated potential as a diagnostic tool in this setting, we think it could be considered as an alternative to the PET/CT.

N	GENDER	AGE	RRT	FEVER (C°)	ABD. PAIN	OTHER SYMPTOMS	CRP	US	CT	67-GA-C	DIAGNOSIS	ATB WEEKS	RELAPSE
1	F	72	TX	39	NO	DIARREA	105	COMPLEX CYST	INFECTED CYST HAEMORRHAGIC VS	POSITIVE	CYST INFECTION	8	YES
2	M	48	HD	38	YES	COUGH	240	NOT DONE	INFECTED CYST HAEMORRHAGIC	POSITIVE	CYST INFECTION HAEMORRHAGIC	6	NO
3	M	40	CKD	38	YES	HEMATURIA DYSURIA	123	COMPLEX CYST	CYST	NEGATIVE	CYST	1	NO
4	F	64	CKD	39	YES	COUGH	232	NEGATIVE	NEGATIVE	POSITIVE	CYST INFECTION	6	NO
5	F	38	PD	39	YES	DYSURIA	336	NEGATIVE	NEGATIVE	POSITIVE	CYST INFECTION	6	YES

FR-PO315

Urinary L-Type Fatty Acid-Binding Protein (L-FABP) Reflects the Progression of Autosomal Dominant Polycystic Kidney Disease Shiika Watanabe,[4] Atsuko Ikemori,[4] Takeshi Sugaya,[3] Daisuke Ichikawa,[2] Mikako Hisamichi,[5] Kenjiro Kimura,[6] Yugo Shibagaki.[1] *[1]Division of Nephrology and Hypertension, St Marianna University Hospital, Kawasaki, Japan; [2]St Marianna University of Medical School, Yokohama City, Japan; [3]St. Marianna Univ, Tokyo, Japan; [4]St. Marianna University School, Kawasaki, Kanagawa, Japan; [5]St.Marianna university school of medicine, Kawasaki, Japan; [6]Tokyo Takanawa Hospital, Tokyo, Japan.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is a common inherited progressive kidney disease. Although some imaging modalities, such as ultrasonography, CT or MRI, are useful for diagnosing and staging ADPKD, these modalities are not adequate for monitoring the severity of ADPKD because the modalities detect cyst formation, but not tubulointerstitial inflammation and fibrosis. The aim of this study is to elucidate that urinary L-type fatty acid binding protein (L-FABP) is associated with the severity of ADPKD.

Methods: Male PCK/CrljCrl-Pkhd1pck/Crl (PCK) rats (n=21), of which features are similar to human ADPKD, were used as the ADPKD model. Age and gender-matched Sprague-Dawley rats (n=21) were used as control. Serum, urine, kidneys were obtained at 8, 12 and 16 weeks of age. Serum creatinine, serum L-FABP, urinary L-FABP, urinary KIM-1, urinary NGAL and urinary creatinine were measured.

Results: Serum creatinine and serum L-FABP levels in PCK rats were similar to those in the control rats. Cystic enlargement and progression of both tubulointerstitial inflammation and fibrosis along with age were observed in the PCK rats. Urinary L-FABP levels increased along with the severity of renal pathology, and the levels at 12 and 16 weeks in the PCK rats were significantly higher than in the control rats. Although urinary KIM-1 and urinary NGAL levels at 8, 12 and 16 weeks in the PCK rats were significantly higher than in the control rats, these markers did not increase along with the progression of renal pathology including the degree of cystic enlargement in the PCK rats.

Conclusions: Urinary L-FABP reflects not only the degree of cystic enlargement, but also the progression of tubulointerstitial damage and, therefore, may be useful for monitoring the progression of ADPKD.

FR-PO316

Pharmacogenomics of Tolvaptan's Inhibitory Effect on Kidney Volume Increase in Patients with Autosomal Dominant Polycystic Kidney Disease Shigeo Horie,[1] Masatoshi Masuda,[2] Steffen Neuber,[3] Satoru Muto,[1] Tadashi Okada,[2] Carsten Bergmann.[3] *[1]Advanced Informatics for Genetic Disease, Juntendo University, Tokyo, Japan; [2]Otsuka Pharmaceutical Co., Ltd., Osaka, Japan; [3]Center for Human Genetics, Bioscientia, Ingelheim, Germany.*

Background: We investigated the influence of genetic factors on tolvaptan treatment efficacy in patients with approved autosomal dominant polycystic kidney disease (ADPKD).

Methods: In the extension study of TEMPO 3:4 in Japan, DNA was collected from 100 patients. Germline variants of 116 genes (including all genes known for cystic/polycystic kidney disease) were sequenced by targeted next generation sequencing and called with a custom variant analysis pipeline sensitive for variants in sequence homology regions. Genetic architecture of samples was modeled as binary factor, discriminating those samples carrying solely *PKD1* or *PKD2* pathogenic variants from samples that harbored additional likely pathogenic variants in any of the other 114 targeted genes. Kidney volume growth rate was used as a marker for tolvaptan efficacy. A two-way factorial ANOVA was applied to test for a correlation between genetic architecture, treatment / placebo group and treatment efficacy as outcome.

Results: Sixty percent of our samples demonstrated multiple likely pathogenic variants in non-*PKD* genes. Statistical analysis revealed a significant main effect of

treatment vs placebo group as expected (p<0.009), and a non-significant main effect when considering modifier variants only (p<0.29). The interaction term combining modifier cases with treatment group was non-significant as well (p<0.14). We carried out subgroup analysis assuming that low power is the cause for not reaching significance in the interaction model, and observed that the kidney growth rate in patients with modifier pathogenic variants was significantly lower in the tolvaptan group. This difference was not clear in patients with singleton *PKD1* or *PKD2* pathogenic variants. Therefore, we hypothesize that tolvaptan may be more effective in patients with modifier pathogenic variants.

Conclusions: Additional pathogenic variants in modifier genes other than *PKD1* or *PKD2* may potentially affect the efficacy of tolvaptan in patients with ADPKD.

FR-PO317

Assessing Rapid ADPKD Progression in Clinical Practice in the Era of Tolvaptan Monica Furlano,[4] Teresa Marti,[2] Irene Loscos giménez,[4] Gemma Bullich vilanova,[1] Jose Ballarin,[4,3] Elisabet Ars,[1] Roser Torra.[4,3] *[1]Molecular Biology, Fundacio Puigvert, Barcelona, Spain; [2]Radiology, Fundació Puigvert, Barcelona, Spain; [3]Universitat Autónoma de Barcelona, Barcelona, Spain; [4]Nephrology, Fundacio Puigvert, Barcelona, Spain.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most frequent inherited kidney disease. The progressive cyst growth, together with interstitial damage causes progressive kidney failure but the severity of the diseases varies a lot among affected individuals. The EMA has approved tolvaptan for adults with CKD stage 1-3 at baseline who are rapid progressors (RP). Being the mean age in Europe of onset of ESRD for ADPKD patients 58 years, the ERA-EDTA WGKID/EBPG recommended to consider RP those patients predicted to reach ESRD before 58 years of age.

Methods: 297 ADPKD patients followed up in an outpatient clinic for inherited kidney diseases were assessed for rapid progression according to the EDTA-ERA WGIKD/EBPG recommendations. Only patients between 18-50 years of age were considered. Assessment was only indicated when eGFR was over 45ml/min and eGFR for patients 30-40 years old was below 90ml/min and for those 40-50 years old was below 60 ml/min. If the patients met these eGFR according to age, retrospective eGFR decline was assessed; if it was > 5 ml/year or >2.5 ml/year for 3 consecutive years patients were considered RP. For those who didn't met the retrospective eGFR criteria ultrasound (US) diameter was assessed. Patients younger than 45 with a renal diameter >16.5 cm were considered RP. For those not fulfilling any of the above criteria total kidney volume (TKV) by MRI was measured and the Mayo ADPKD calculator was applied. Patients class 1C,D,E were considered RP. Finally for patients younger than 35 with hypertension or urinary symptoms than did not met the above criteria genetic testing was performed and the PROPKD score was applied.

Results: The step by step process of RP assessment based on the EDTA-ERA/EBPG recommendations proved to be cost-effective and sensitive to identify RP. RP was identified in 16.5% of patients with CKD stage 1, 29% in CKD2 and 34.3% in CKD3a. 53.8% of patients aged 18-30 were rapid progressors while this number decreased with age: 30.9% from 31-40 years and 13.5% from 41-50 years.

Conclusions: The multi step algorithm provided by the EDTA-ERA/EBPG is useful to identify RP that would benefit from tolvaptan treatment. The use of the algorithm is cost-effective and fairly easy to incorporate into clinical practice.

Funding: Government Support - Non-U.S.

FR-PO318

Total Kidney Volume (TKV) by Ellipsoid (EL) versus Manual Segmentation (MS) for Risk Classification in Autosomal Dominant Polycystic Kidney Disease (ADPKD): A Comparative Study Beili Shi,[1] Marina Pourafkari,[1,2] Ioan-Andrei Iliuta,[1] Elsa Guiard,[1] Crystal F. Quist,[1] Xuewen Song,[1] Korosh Khalili,[2] York P. Pei.[1] *[1]Division of Nephrology, University Health Network and University of Toronto, Toronto, ON, Canada; [2]Department of Medical Imaging, University Health Network and University of Toronto, Toronto, ON, Canada.*

Background: TKV derived by EL is technically simple, less laborous, and used in the Mayo Clinic Risk Classifcation (MCRC).[1] However, it is less accurate than MS ("gold standard") and can result in risk misclassification. Our study aims to define the disagreement in TKV measuremnt and its resultant risk misclassification by EL vs. MS. [1] JASN 26:160-72,2015

Methods: A single center study of 409 consecutive PKD patients who underwent standardized MRI and genetic testing between 4/2011 and 2/2017. TKV by EL and MS will be measured in all patients by a single radiologist. Bland-Atman plots are used to assess agreement.

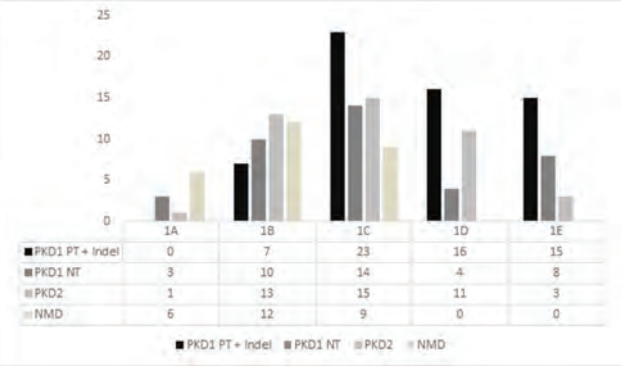
Results: Of 203 patients who completed analyses, 33 (16%) with atypical imaging patterns were excluded. The clinical characteristics of the remaining patients are shown in Table. The MC risk classes significantly correlated with distinct mutation classes (X2=48, P<0.001, Figure 1). We found >20% disagreement in 11.2% of individual kidney volume and 5.3% of TKV, resulting in misclassification of 24 (14.1%) patients. None of the misclassified cases spanned more than one risk category.

Conclusions: Our preliminary results suggest that TKV measured by EL in a standardized setting did not result in a high rate of risk misclassification of serious clinical consequence.

Funding: Government Support - Non-U.S.

Patient Characteristics

Total Number	170
Gender (M/F)	1:1
Age at MRI (y, mean ± SD)	44.3 ± 1.1
Serum Creatinine (μmol/L, median with IQR)	91.0 (69.3 – 121.2)
Estimated GFR (ml/min.1.73m2, mean ± SD)	77.1 ± 2.5
Mutation Class N (%)	
PKD1 truncating + in-frame deletion	61 (35.9)
PKD1 non-truncating	39 (23.0)
PKD2	43 (25.3)
No Mutation Detected	27 (15.8)



Significant difference between NMD vs. other mutation classes (P<0.001) and PKD1 PT+Indel vs. PKD2 (P=0.043).

FR-PO319

Elevated Circulating Homocysteine Levels Precede Hemodynamic Changes and Correlate with Disease Severity in Young Autosomal Dominant Polycystic Kidney Disease (ADPKD) Patients Madhuri Chengappa, Ali Kahveci, Marie E. Edwards, Fouad T. Chebib, Sandra Herrmann, Bernard F. King, Amir Lerman, Lilach O. Lerman, Vicente E. Torres, Maria V. Irazabal. *Mayo Clinic, Rochester, MN.*

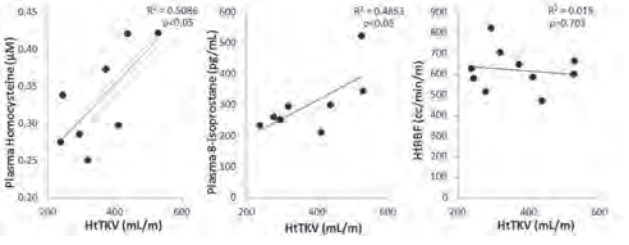
Background: Vascular manifestations are the most important non-cystic complications and the main cause of death in patients with ADPKD. Endothelial dysfunction and vascular remodeling are detectable early in ADPKD, and a decrease in magnetic resonance imaging (MRI)-derive renal blood flow (RBF) has been proposed as a marker of disease severity. Homocysteine (Hcy), a precursor of hydrogen sulfide, is an established biomarker for endothelial dysfunction and vascular disease and linked to increased oxidative stress. However, whether increased circulating Hcy levels correlate with disease severity and precede hemodynamic changes in early ADPKD has not been reported.

Methods: We prospectively measured circulating levels of Hcy (LC/MS/MS) and 8-isoprostane (ELISA) in early (18-30 years, eGFR>90 mL/min/1.73 m2) normotensive (<140/90 mmHg without BP medication) ADPKD patients, and in age-matched healthy volunteers (HV) (n=10, 6F/4M each). Total kidney volume (TKV) and RBF were evaluated with MRI.

Results: Mean age was 23 years old, but TKV twofold higher in ADPKD vs. HV (Table). BP tended to be elevated in ADPKD, but eGFR, RBF, and height adjusted RBF (HtRBF) were similar between the groups (Table). Circulating levels of Hcy and 8-isoprostanes were elevated in ADPKD vs. HV (Table, Fig, p<0.05). Furthermore, Hcy and isoprostane (but not RBF) levels directly correlated with TKV and HtTKV (Fig).

Conclusions: Early ADPKD is associated with elevation in circulating Hcy and isoprostane levels, which correlate with disease severity. These findings imply that oxidative stress and endothelial dysfunction might be present before overt hemodynamic changes, and possibly contribute to disease progression. Further experiments are needed to investigate the sources of oxidative stress in patients with ADPKD.

Baseline Parameter	ADPKD Patients	Healthy Volunteers	p value
Gender (M/F)	4/6	4/6	
Age	23 ± 3	23 ± 3	0.804
MAP (mmHg)	93 ± 9	85 ± 8	0.058
eGFR (mL/min/1.73m²)	110.6 ± 12.4	104.9 ± 19.3	0.436
TKV (mL)	641 (389 – 966)	304 (231 – 364)	<0.001
HtTKV (mL/m)	366 (239 – 529)	176 (144 – 198)	<0.001
RBF (cc/min)	1080 ± 147	1072 ± 137	0.903
HtRBF (cc/min/m)	621 ± 100	622 ± 78	0.993
Homocysteine (µM)	0.34 ± 0.07	0.03 ± 0.10	<0.001
8-isoprostanes (pg/mL)	303 ± 99	174 ± 84	0.036



FR-PO320

Decreased Urinary Citrate Excretion Associates with Disease Severity in Autosomal Dominant Polycystic Kidney Disease Arlene B. Chapman,[6] Bharathi V. Reddy,[6] Matthew Lanktree,[4] Chengli Shen,[8] Vicente E. Torres,[3] Michal Mrug,[5] Frederic F. Rahbari-Oskoui,[1] Alan S. Yu,[7] William M. Bennett,[2] Peter C. Harris,[3] Kyongtae T. Bae,[8] Doug Landsittel.[8] *[1]Emory University School of Medicine, Atlanta, GA; [2]Legacy Good Samaritan Medical Center, Portland, OR; [3]Mayo Clinic, Rochester, MN; [4]None, Dundas, ON, Canada; [5]University of Alabama at Birmingham, Birmingham, AL; [6]University of Chicago, Chicago, IL; [7]University of Kansas Medical Center, Kansas City, KS; [8]University of Pittsburgh, Pittsburgh, PA.*

Background: Autosomal dominant polycystic kidney disease (PKD) is characterized by increased cyst burden measured by total kidney volume (TKV) and loss of kidney function. Urinary citrate excretion (UCE), known to be decreased in PKD associates with complications of disease including nephrolithiasis and urinary acidification defects. In the observational longitudinal Consortium for Radiologic Studies in Polycystic Kidney Disease (CRISP), 24 hour UCE was measured annually during the first three years of study. We postulate that decreased UCE is an independent marker of disease severity in PKD and associates with genotype, increased TKV, decreased eGFR and decreases over time.

Methods: 224 of 241 participating CRISP subjects with baseline creatinine clearance >70 ml/min had 24 hr UCE as well as DNA, TKV and corrected iothalamate clearance (CIC) measurements completed in a Clinical Research Center setting.

Results: UCE correlated inversely with TKV (r=-0.26, P<0.001) and directly with CIC (r=0.16, P<0.02). Irazabal Class 1A subjects (n=14) had greater UCE (653±257 mg/day) than Class 1C (n=68, 449+241 mg/day, P<0.03), 1D (n=54, 452±295 mg/day, P<0.02) or 1E (n=35, 393±198 mg/day P<0.008). UCE was significantly lower in PKD1 vs. PKD2 patients (276 ±269 vs.682± 523 mg/day, P<0.01) No differences (P=NS) were seen in UCE between PKD1 truncating and non-truncating mutations (275±211 vs. 278±289 mg/day). UCE decreased 19.1 mg/day/year over 3 years (P<0.03), and significantly declined in PKD1 patients only. A forward linear regression selection method with an entry criteria of p=0.1 demonstrated that PKD1 genotype, urine volume, TKV and age, associated negatively with baseline UCE, while increasing sodium excretion, CIC and male gender associated with UCE. When baseline UCE was combined with TKV, area under the receiver operator characteristic curve for predicting CKD stage 3 in 8 years was 0.83.

Conclusions: TKV and CIC associate with decreased UCE early in PKD. Reductions in UCE in PKD1 patients showed no difference between truncating and non-truncating mutations. Decline in UCE occurred over three years and UCE may be a biomarker that associates with disease severity and progression in PKD.

Funding: NIDDK Support

FR-PO321

Patient-Reported Disease Burden in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Using the ADPKD Pain and Discomfort Scale (ADPKD-PDS) and ADPKD Impact Scale (ADPKD-IS) Dorothee Oberdhan,[1] Siddhesh Kamat,[1] Alexis Denny.[2] *[1]Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ; [2]PKD Foundation, Kansas City, MO.*

Background: ADPKD is an inherited disease leading to kidney enlargement, worsening of kidney function, and quality of life impacts. The objective of this research is to describe patient-reported pain, discomfort, and disease impact using two new questionnaires.

Methods: 2,353 ADPKD patients (age ≥18 years) were invited to participate in a survey. Assessments included: ADPKD-PDS measuring severity and impact of dull pain (chronic ache), sharp pain (acute), and discomfort (chronic fullness/pressure) over the last 7 days via 20 items, and ADPKD-IS measuring physical, emotional, and fatigue impact over the last 2 weeks via 18 items. Age, gender, ethnicity, chronic kidney disease (CKD) stage, and time since ADPKD diagnosis were collected.

Results: For 289 qualified respondents mean age was 48.8 years (SD ±12.3), 80.2% were female, and CKD stage broadly distributed: CKD Stage 1 (27.3%), CKD Stage 2 (21.1%), CKD Stage 3 (30.4%), CKD Stage 4 (11.4%), CKD Stage 5 (9.6%). Mean Scores for ADPKD-PDS and -IS are reported in the table below.

Conclusions: Patient burden starts early in disease with differentiation between CKD stages. Results follow clinically expected patterns where events triggering sharp pain (eg, cyst burst/infection) are rare and intermittent but chronic pain is more constant due to growing kidneys. Clinical significance of these scores needs further evaluation.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc.

Mean at Baseline (SD)		CKD 1 (n=79)	CKD 2 (n=61)	CKD 3 (n=88)	CKD 4 (n=33)	CKD 5 (n=28)	Total (N=289)
ADPKD-PDS 1=none/not at all - 5=extreme/completely							
Pain Severity	Overall	1.9 (0.8)	2.3 (0.9)	2.4 (0.9)	2.4 (0.9)	2.7 (0.9)	2.3 (0.9)
	Dull	2.1 (1.0)	2.6 (1.0)	2.6 (1.0)	2.6 (1.0)	2.8 (1.0)	2.5 (1.0)
	Sharp	1.5 (0.9)	1.9 (1.1)	1.9 (1.0)	2.0 (1.0)	2.1 (1.1)	1.8 (1.0)
	Discomfort	1.9 (1.1)	2.5 (1.1)	2.7 (1.1)	2.5 (1.1)	3.3 (0.9)	2.5 (1.2)
Pain Interference	Dull	1.4 (0.8)	1.9 (1.0)	2.0 (1.0)	2.2 (1.0)	2.4 (1.0)	1.9 (1.0)
	Sharp	1.3 (0.8)	1.6 (1.1)	1.7 (1.2)	1.7 (1.2)	1.9 (1.4)	1.6 (1.1)
	Discomfort	1.5 (0.9)	1.8 (0.8)	2.0 (0.8)	2.2 (1.1)	2.7 (0.9)	1.9 (1.0)
ADPKD-IS 1=not impacted/bothered - 5=extremely impacted/bothered							
Physical		1.7 (0.9)	2.2 (1.0)	2.4 (1.1)	2.6 (1.1)	3.2 (1.0)	2.2 (1.1)
Emotional		2.0 (0.8)	2.3 (1.1)	2.4 (1.0)	2.6 (1.0)	2.9 (1.0)	2.3 (1.0)
Fatigue		2.2 (1.1)	2.8 (1.3)	2.8 (1.2)	3.3 (1.3)	3.7 (1.1)	2.8 (1.3)

FR-PO322

Peritoneal Dialysis in Pediatric ARPKD Patients Aziz Akarkach,[1] Kathrin Ebner,[1] Anja C. Sander,[2] Franz S. Schaefer,[2] Max Liebau.[1,3] *[1]University Hospital Cologne, Cologne, Germany; [2]University of Heidelberg, Heidelberg, Germany; [3]Center for Molecular Medicine, University of Cologne, Cologne, Germany. Group/Team: For IPPN consortium.*

Background: Autosomal recessive polycystic kidney disease (ARPKD) is associated with dialysis-requiring end stage renal disease in about 40-50% of patients during childhood and adolescence. Many ARPKD patients receive peritoneal dialysis (PD) but structured data on PD in pediatric ARPKD patients is missing.

Methods: We identified ARPKD patients in the international pediatric peritoneal dialysis network (IPPN) registry and compared their clinical courses and PD-specific parameters to two control groups suffering from other renal disorders (CAKUT, Congenital Nephrotic Syndrome). Cohorts were matched for age and time on dialysis.

Results: 79 ARPKD patients were identified and matched to CNS (n=79) and CAKUT (n=158) patients. Mean age at inclusion into the IPPN registry was 4.38 years in the ARPKD group vs 4.33 years (CNS) and 4.40 years (CAKUT), respectively. Mean time on dialysis at inclusion was 1.01 years (ARPKD) vs. 0.77 years (CNS) and 1.00 years (CAKUT). Mean observation time within the frame of the registry was 14.6 months (ARPKD) vs. 11.2 months (CNS) and 13.2 months (CAKUT). There were no major differences in basic anthropometric data (height, weight, BMI) or general PD parameters (e.g. PD modality, applied PD fluids, fluid turnover per day, average glucose concentration), but ARPKD patients had regimes with lower overall fill volumes and more cycles than CNS- or CAKUT-patients. First longitudinal observations suggest that overall technique survival as well as the peritonitis rate in ARPKD children on PD do not show major differences compared to patients with other underlying disease entities.

Conclusions: Overall, children with ARPKD in this cohort do not show major dialysis-associated differences when compared to two age-matched pediatric PD control groups suggesting that PD can be applied in the same way as for children with other underlying renal disorders.

Funding: Private Foundation Support

FR-PO323

Frequent Genetic Variants in Autosomal Dominant Tubulointerstitial Kidney Disease Eric G. Olinger,[3] Celine Schaeffer,[1] Kendrah O. Kidd,[4] Daniel G. Fuster,[2] Andreas D. Kistler,[5] John Sayer,[6] Anthony J. Bleyer,[4] Luca Rampoldi,[1] Olivier Devuyst.[3] *[1]San Raffaele Scientific Institute, MILAN, Italy; [2]University Hospital of Bern, Bern, Switzerland; [3]University of Zurich, Zurich, Switzerland; [4]Wake Forest University School of Medicine, Winston-Salem, NC; [5]Cantonal Hospital Frauenfeld, Frauenfeld, Switzerland; [6]Institute of Genetic Medicine, Newcastle, United Kingdom.*

Background: An increasing number of purported pathogenic genetic variants are detected as relatively common in exome data from the general population, suggesting previous misclassification. Mutations in *UMOD* cause autosomal dominant tubulointerstitial kidney disease (ADTKD) that is rare (1-10/1'000'000), well indexed and has genetic features (private mutations, complete penetrance) making it paradigmatically suited to address the evolving distinction between normal genetic variation and pathogenic variants.

Methods: Reported *UMOD* mutations from our ADTKD registry were retrospectively compared to sequencing data from gnomAD (http://gnomad.broadinstitute.org). Matching variants were tested by cellular studies and segregation analysis.

Results: Based on then-available filtering strategies, 107 *UMOD* variants were reported as pathogenic in 181 families from our ADTKD registry. Two of them are reported in gnomAD: p.T62P (AF 0.00034) and p.T469M (0.00070). An allele frequency of ~$5x10^{-8}$ would be expected based on the disease prevalence and the number of reported mutations. The p.T62P and p.T469M variants have been previously linked to ADTKD and they were detected respectively in 9 and 2 unrelated patients with CKD, gout and positive family history in our registry. T62 lacks any evolutionary constraint and trained classifiers (eg. PolyPhen-2) predict a benign to possibly damaging phenotype for p.T62P. T469 is a conserved residue and p.T469M is predicted to be damaging. Expression studies in kidney cell lines reveal an extremely mild or no trafficking defect for p.T62P and p.T469M, as opposed to the well-established mutation p.C150S. Furthermore, the p.T62P variant does not segregate with disease, including several aged carriers with absent kidney disease.

Conclusions: The high frequency of 2 imputed variants in *UMOD* led us to reevaluate the genetic diagnosis of several ADTKD families in our registry and to definitively infirm the pathogenicity of *UMOD* p.T62P. With evolving sequencing data, careful curation of implausibly common variants in Mendelian diseases other than ADTKD is warranted.

FR-PO324

Clinical Assessment and Prediction of Efficacy of Tolvaptan in Autosomal Dominant Polycystic Kidney (ADPKD) Kaori Takayanagi, Yuta Kogure, Minoru Hatano, Hiroaki Hara, Kento Hirose, Koki Ogawa, Yuichiro Kawai, Ryo Yamamoto, Tomonari Ogawa, Koichi Kanozawa, Hajime Hasegawa. *Nephrol, Hypertens, and Blood Purification, Saitama Med Center, Saitama Med Univ, Kawagoe, Japan.*

Background: In Japan, more than 3000 patients with autosomal dominant polycystic kidney disease (ADPKD) have received Tolvaptan therapy at present, and its averaged clinical efficacy is suggested to be approximately 50%. Here, we report the clinical efficacy of Tolvaptan in our facility, and refer to the clinical features shown in the highly effective patients.

Methods: ADPKD patients with Tolvaptan therapy who have received follow up-CT scanning one year after beginning the therapy (n=23) were retrospectively analyzed.

Results: Mean age, number of male, median value of total kidney volume (TKV), median value of kidney growth rate (KGR) and mean eGFR at the start of the therapy were 45.4±14.7 years-old, 18 cases (78.8%), 1478.3 mL, 5.4%/year, and 50.9±20 mL/min, respectively. After one year Tolvaptan therapy, TKV and KGR were reduced to 1306.5 mL and -3.7%/year, and 17 of 23 cases (73.9%) showed reduced TKV (KGR<0%) by one year Tolvaptan therapy. When all cases were divided into four groups by the quartile value of KGR, and the 1st quartile group (1-QG, most effective, median KGR=-16.3%/year) was compared to 4-QG (worst effective, median KGR=8.1%/year) by the clinical parameters at the start of the therapy, mean age, mean BMI, mean systolic blood pressure, median TKV, median KGR, mean eGFR, mean serum Na and Mg, median urine osmolality were 49.6 vs 46.4 years-old, 20.0 vs 22.0, 125.0 vs 127.0 mmHg, 1514.4 vs 2511.5 mL, 6.4 vs 9.5%/year, 54.5 vs 48.5 mL/min, 139.7 vs 141.2 mmol/L, 1.87 vs 2.08 mg/dL, 247.2 vs 415.0 mOsm/kg, respectively. In comparison of two groups, significant difference was observed in urine osmolality and serum Mg.

Conclusions: In our facility, reduction of kidney volume was observed in 73.9% of cases, and 87.6% of cases showed KGR less than 5%/year, indicating that Tolvaptan therapy is significantly effective for the inhibition of cyst growth. It is also suggested that patients showing diluted urine by accelerated water intake and low serum Mg would be particularly expectable regarding the clinical efficacy of Tolvaptan.

FR-PO325

An Atypical Case of Fungal Cyst Infection in ADPKD Laura Onuchic,[1] Antonio A. Portela Neto,[1] Fernanda T. Ferreira,[1] Leonardo A. Testagrossa,[2] Elieser H. Watanabe,[1] Bruno E. Balbo,[1] Luiz F. Onuchic.[1] *[1]Nephrology and Molecular Medicine, University of Sao Paulo, Sao Paulo, Brazil; [2]Pathology, University of Sao Paulo, Sao Paulo, Brazil.*

Background: Cyst infection is a significant cause of mortality in autosomal dominant polycystic kidney disease (ADPKD). It is typically associated with gram-negative bacteria and is most often related to the ascending urinary tract route. Fungal etiology is rare, with very few reports. Positron emission tomography/computed tomography (PET-CT) has become the most sensitive imaging technique to diagnose cyst infection.

Methods: A 34-year-old female with ADPKD was referred for persistent fever and malaise. She reported vaginal candidiasis 2 months prior to admission. Following right kidney obstruction secondary to ureteral calculus, she was submitted to double-J stent placement. After 2 days she developed fever and abdominal pain. Urine and blood cultures were negative; WBC count and C-reactive protein, however, were elevated. Initial CT scan was inconclusive for cyst infection. At this point she received broad-spectrum antibiotics, including ciprofloxacin. Despite treatment, the patient presented no clinical improvement and developed acute kidney injury, with a rise in serum creatinine from 0.38 to 2.3 mg/dL. She was then transferred to our referral center. In this scenario, PET-CT revealed high 18F-glucose uptake in multiple right kidney cysts. Ultrasound-guided percutaneous drainage of the dominant suspected cyst and culture of its material led to the diagnosis of *Candida albicans* infection. Histopathology analysis confirmed this finding, showing cystic and pericystic hypha and pseudohypha invasion. She was then started on fluconazole, but this therapy was not effective. Given the refractoriness to this treatment, she was submitted to right nephrectomy, which led to initiation of hemodialysis. Prolonged hospitalization led to urinary infection by carbapenemase-resistant *Klebsiella pneumoniae* followed by sepsis. In this setting, the patient was submitted to left nephectomy, which resulted in clinical improvement and hospital discharge.

Results:

Conclusions: We report a case of ascendant fungal cyst infection, a very unusual form of this complication in ADPKD. Antibiotic treatment algorithms targeting cyst infection do not contemplate antifungal therapy as an initial approach. This case underscores, however, the importance of considering such an etiology and the need of culturing cyst material in refractory cyst infections.

Funding: Government Support - Non-U.S.

FR-PO326

Lixivaptan, a Novel Vasopressin V2 Receptor Antagonist in Development for the Treatment of Autosomal Dominant Polycystic Kidney Disease Lorenzo Pellegrini,[5] Jeffrey L. Woodhead,[3] Lisl Shoda,[1] Scott Q. Siler,[1] Brett A. Howell,[2] Cesare Orlandi.[4,6] *[1]DILIsym Services, Research Triangle Park, NC; [2]DILIsym Services Inc., Research Triangle Park, NC; [3]DILIsym Services, Inc., Research Triangle Park, NC; [4]Lantheus Medical Imaging, Boston, MA; [5]Palladio Biosciences, Newtown, PA; [6]Cardiokine, Inc., Philadelphia, PA.*

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is one of the most prevalent inherited genetic diseases in humans. Recent advances established vasopressin V2 receptor inhibition as a clinically validated mechanism of action for ADPKD, however safe and effective disease-modifying therapies for ADPKD are still lacking. Here we evaluated whether lixivaptan, a potent, selective vasopressin V2 antagonist, has characteristics that suggest a favorable benefit-risk profile for ADPKD.

Methods: Using the large body of existing preclinical and clinical data on lixivaptan encompassing 36 clinical studies and 1,673 independent patient exposures, we evaluated the projected efficacy and safety profile of lixivaptan for ADPKD. To explore efficacy, we compared the effect of lixivaptan with the related vasopressin V2 antagonist tolvaptan on accepted pharmacodynamic markers of efficacy in ADPKD. To explore safety, we conducted a multiscale computational model of drug-induced liver injury, a DILIsym evaluation, to determine lixivaptan's propensity to cause hepatocellular injury compared with the known hepatotoxin tolvaptan.

Results: Potent suppression of urine osmolality (U_{osm}) was seen with lixivaptan in healthy individuals and patients with hyponatremia of various etiologies, suggesting the potential for disease-modifying efficacy in ADPKD. In particular, 200mg BID doses of lixivaptan for 7 days resulted in uninterrupted U_{osm} below 300 mOsm/kg over 24 hours in 78% of healthy volunteers in study CK-0407. In contrast to tolvaptan, lixivaptan exposure was lower in patients with impaired renal function than in healthy individuals (32% and 31% lower for $AUC_{0-\infty}$ and C_{max}, respectively), without affecting lixivaptan's ability to attain target U_{osm} levels. Importantly, unlike tolvaptan, lixivaptan was not associated with hepatocellular toxicity at doses intended for ADPKD in the DILIsym evaluation.

Conclusions: Our analysis suggests that lixivaptan has the potential to become a safe and effective therapy for the treatment of ADPKD in a broad patient population, paving the way for upcoming clinical trials with lixivaptan for ADPKD.

Funding: Commercial Support - Palladio Biosciences, Inc.

FR-PO327

The Burden of Autosomal Dominant Tubulo-Interstitial Kidney Disease (ADTKD) in Ireland Sarah Cormican,[1] Dervla M. Connaughton,[3] Claire Kennedy,[4,1] Katherine A. Benson,[5] Gianpiero Cavalleri,[6] Brendan Doyle,[1] Anthony M. Dorman,[1] Mark A. Little,[7] Peter J. Lavin,[7] Kendrah O. Kidd,[8] Anthony J. Bleyer,[8] Peter J. Conlon.[2] *[1]Beaumont Hospital, Dublin 9, Ireland; [2]Beaumont Hospital, Dublin 9, Co Dublin, Ireland; [3]Boston Children's Hospital, Boston, MA; [4]None, Dublin 9, Ireland; [5]Queen's University, Belfast, Belfast, United Kingdom; [6]RCSI, Dublin, Italy; [7]Trinity College Dublin, Dublin, Ireland; [8]Wake Forest University School of Medicine, Winston-Salem, NC.*

Background: Hereditary mutations in the *MUC-1, UMOD, HNF* and *REN-1* genes cause renal tubular atrophy, interstitial inflammation and fibrosis with progressive renal impairment. A recent KDIGO consensus report advocated the unified term ADTKD (sub-classified by causative gene) for these conditions, replacing older terminology such as medullary cystic kidney disease.

Methods: Individuals with possible ADTKD were identified by the Irish Kidney Gene Project and invited to attend for DNA collection with the Rare Kidney Disease Registry and Biobank. Genetic analysis was undertaken in RCSI Renal Genetics Unit and the Nephrology Department in the Wake Forest School of Medicine. Patients were sub-categorised as ADTKD-*MUC1,* ADTKD-*UMOD* or ADTKD-*NOS* (not otherwise specified) based on the identification of a mutation in the patient or an affected relative.

Results: 64 individuals from 28 families were included. Genotyping results are available on 36 individuals from 22 families. Native kidney biopsy results were available for 32 patients. 19 patients from 3 families were categorised as ADTKD-*MUC,* 14 from 3 families were categorised as ADTKD-*UMOD*. 31 patients with clinical features of ADTKD met criteria for inclusion based on family history and renal biopsy findings. 18 have been tested without identified mutation, 4 have passed away and genetic material is not available. Details of genetic testing and clinical features are shown in Table 1. 40% of patients were hypertensive at presentation. Significant proteinuria occurred in 3/30 individuals with available. 26 patients with confirmed or suspected ADTKD have reached ESRD.

Conclusions: ADTKD accounts for approx. 0.06% of Irish cases of ESRD. Significant progress has been made in identifying causative mutations. Clinical awareness of ADTKD enables screening of relatives and early diagnosis.

Table 1

	UMOD (n=14)	MUC-1 (n=19)	ADTKD-NOS (n=31)	p-value
Confirmed Mutation (n) / Tested (n)	7/7	10/11	0/18	NA
Number of Families	3	3	22	NA
Mean Age at Presentation (years)	43	36	41	0.66
Mean Creatinine at Presentation	267	135	271	0.012
Mean Age at ESRD (years)	53	44	44	0.34
Gout (%)	86%	0%	31%	<0.0001
% Fibrosis on Biopsy (mean)	60%	74%	63%	Insufficient Data

FR-PO328

Identifying Genetic Modifiers in Severe Polycystic Liver Disease (PLD) by Whole Exome Sequencing Amirreza Haghighi,[1] Xuewen Song,[1] Marina Pourafkari,[2] Beili Shi,[1] Emilie Cornec-Le Gall,[4] Ning He,[1] Wybrich R. Cnossen,[3] Joost P. Drenth,[3] Peter C. Harris,[4] Vicente E. Torres,[4] York P. Pei.[1] *[1]Division of Nephrology, University Health Network and University of Toronto, Toronto, ON, Canada; [2]Department of Medical Imaging, University Health Network, Toronto, ON, Canada; [3]Radboud University Nijmegen Medical Center, Nijmegen, Netherlands; [4]Division of Nephrology, Mayo Clinic, Rochester, MN.*

Background: Severe PLD is a rare and poorly understood phenotype seen in both ADPKD and ADPLD. Mutations of *SEC61, SEC63, PRKCSH, GANAB,* and *ALG8* have been shown to cause PLD by imparing the maturation and transit of polycystin-1 (PC1) through the endoplasmic reticulum protein-processing (ER-PP) pathway. We hypothesize that rare mutations including ER-PP pathway genes that segregate in multiple families may modify PLD in patients with ADPKD and ADPLD.

Methods: We performed whole exome sequencing (WES) using Illumina HiSeq2000/2500 with SSV4/5 capture kit in 150 patients including 23 affected discordant sib-pairs and 10 affected concordant sib-pairs for sPLD from 33 families (matched by gender and age) and 83 sporadic cases. All patients with sPLD had a cystic liver of >4x normal volume. In addition to a focused analysis on 166 genes involved in ER-PP pathway, we also performed a genome-wide analysis. Standard algorithms for sequence alignment, base calling, and QC filtering were applied to identify rare (MAF ≤1%) deleterious variants of high and moderate impact as predicted by PolyPhen-2, Sift, Mutation Assessor, Mammalian and Vertebrate nucleotide-level conservation, and Combined Annotation Dependent Depletion (CADD).

Results: Overall, we achieved a mean target coverage of 108X with 90% of the targeted exomes having ≥30X read depth. In our preliminary analysis, we identified a total of 4,696 rare deleterious variants that segregated with PLD disease severity in at least one family. We found 8 ER-PP genes (i.e. *WFS1, UGGT1, UGGT2, SEC24D, SEC23B, EIF2AK4, ATF6B* and *RPN1*) with rare deleterious variants that segregated in at least one family and 3-4 sporadic sPLD cases. We also identified 7 non ER-PP genes (i.e. *TTN, DNAH10, DNAH14, HMCN2, NEB, OBSCN* and *ADAMTS8*) with rare deleterious variants that segregated in 4 to 6 families each.

Conclusions: Our preliminary results suggest extensive genetic heterogeneity with no one single gene accounting for a large proportion of severe PLD cases. Future *in-vitro* and/or *in-vivo* functional studies will be needed to define the potential pathogenicity of the most promising candidate genes. Identification of genetic modifiers of severe PLD has the potential to improve risk prediction and treatment of this unusual complication.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO329

Genomic Background of Adult Polycystic Kidney Disease Patients without a Family History Takuya Fujimaru,[1] Takayasu Mori,[1] Akinari Sekine,[2] Shintaro Mandai,[1] Motoko Chiga,[1] Hiroaki Kikuchi,[1] Fumiaki Ando,[1] Yutaro Mori,[1] Naohiro Nomura,[1] Shotaro Naito,[1] Tomokazu Okado,[1] Tatemitsu Rai,[1] Junichi Hoshino,[2] Yoshifumi Ubara,[2] Shinichi Uchida,[1] Eisei Sohara.[1] *[1]Nephrology, Tokyo Medical and Dental University, Tokyo, Japan; [2]Nephrology Center, Toranomon Hospital, Tokyo, Japan.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary kidney disease. Mutations in *PKD1* and *PKD2* are responsible for 85% and 15% of ADPKD patients, respectively. Diagnosis of ADPKD is usually based on positive family history and imaging findings. However, in the absence of a family history, there are no definitive imaging findings that provide an unequivocal diagnosis of ADPKD. Therefore, in the patients without a family history, it is required to distinguish ADPKD from other polycystic kidney diseases (PKDs), though it is difficult without genetic diagnosis in most of the cases.

Methods: We developed a custom panel for 69 genes that cause nine types of hereditary PKDs (ADPKD, autosomal recessive polycystic kidney disease, nephronophthisis, Joubert syndrome, Meckel syndrome, Senior-Loken syndrome, Bardet-Biedl syndrome, etc.) using next-generation sequencing. Comprehensive genetic screening approach was performed for the adult PKD patients without a family history. PKD was defined as more than 10 cysts in a kidney.

Results: Through the analysis for 35 patients (age 55±16, 68.6% of male), 19 patients (54.3%) had *PKD1*/*PKD2* mutations. Two patients (5.7%) identified compound heterozygous mutations in other genes, *PKHD1* and *NPHP4*, confirmed by trio analysis. De novo heterozygous frameshift mutation of *OFD1* was identified in one patient, which was likely to be causal. No obvious responsible mutations were detected in remaining 13 patients (37.1%).

Conclusions: In the adult PKD patients without a family history, other cystic kidney diseases than ADPKD may be overlooked, although it is hard to distinguish only by clinical data. Our custom panel appears to be useful to make genetic diagnosis of these patients.

Funding: Government Support - Non-U.S.

FR-PO330

Novel Semi-Automated Kidney Volume Measurements in Autosomal Dominant Polycystic Kidney Disease Satoru Muto,[2] Haruna Kawano,[3] Shigeo Horie.[1] *[1]Juntendo University, Tokyo, Japan; [2]Advanced Informatics for Genetic Disease, Juntendo University, Tokyo, Japan; [3]Juntendo university, Tokyo, Japan.*

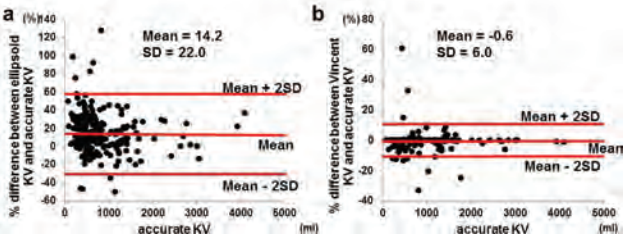
Background: We assessed the effectiveness and convenience of a novel semi-automatic kidney volume (KV) measuring high-speed 3D-image analysis system SYNAPSE VINCENT® (Fuji Medical Systems, Tokyo, Japan) for autosomal dominant polycystic kidney disease (ADPKD) patients.

Methods: We developed a novel semi-automated KV measurement software for patients with ADPKD to be included in the imaging analysis software SYNAPSE VINCENT®. The software extracts renal regions using image recognition software and measures KV (VINCENT KV). The algorithm was designed to work with the manual designation of a long axis of a kidney including cysts. After using the software to assess the predictive accuracy of the VINCENT method, we performed an external validation study and compared accurate KV and ellipsoid KV based on geometric modeling by linear regression analysis and Bland-Altman analysis.

Results: One hundred twenty four patients (male 62, female 62) participated in this study. The median eGFR was 46.9 ml/min/1.73m². Median accurate KV, Vincent KV and ellipsoid KV were 627.7 ml, 619.4 ml (IQR: 431.5–947.0) and 694.0 ml (IQR: 488.1–1107.4), respectively. Compared with ellipsoid KV (r = 0.9504), Vincent KV correlated strongly with accurate KV (r = 0.9968). Ellipsoid KV systematically under- or overestimate accurate KV, with a mean (± SD) percentage difference of 14.2% ± 22.0% (Figure 1a). Vincent KV did not systematically under- or overestimate accurate KV, with a mean (± SD) percentage difference of – 0.6% ± 6.0% (Figure 1b). There were no significant slice thickness-specific differences (p = 0.2980).

Conclusions: The VINCENT method is an accurate and convenient semi-automatic method to measure KV in patients with ADPKD compared with the conventional ellipsoid method.

Figure 1



FR-PO331

PRKCSH as a Genetic Modifier in Early-Onset Autosomal Dominant Polycystic Kidney Disease Ria Schönauer,[3] Anna Seidel,[3] Jana Hoepke,[3] Katalin Dittrich,[2] Steffen Neuber,[1] Carsten Bergmann,[1] Jan Halbritter.[3] *[1]BIOSCIENTIA, Ingelheim, Germany; [2]University Children Hospital, Leipzig, Leipzig, Germany; [3]University Clinic Leipzig, Leipzig, Germany.*

Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common hereditary renal disorder accounting for up to 10% of end-stage renal disease (ESRD). Germline mutations within the polycystin (PC) encoding genes *PKD1* and *PKD2* and accumulating somatic mutations continuously reduce the level of functional polycystins, which is a major determinant for cyst formation. Although most of the patients develop ESRD in the second half of life, a high intrafamilial clinical variability suggests that additional factors influence PC-levels in a disease relevant manner. We investigate the role of *PRKCSH* as a potential modifier in the family of a patient (index) who already developed ADPKD *in utero*.

Methods: Genomic mutations of the index patient were identified with an NGS-panel containing polycystic kidney and liver disease genes (*PKD1, PKD2, SEC63, PRKCSH, GANAB, HNF1B, LRP5, PKHD1)*. Analysis of cDNA transcribed from blood-derived mRNA was performed by PCR and Sanger sequencing. Functional impact of mutated *PRKCSH* and its influence on polycystins were characterized in vitro using transiently transfected cell culture systems.

Results: By NGS of a 2-year old male (index patient) with congenital PKD, we identified transheterozygous mutations in *PKD1 (*c.1723-1G>C) and *PRKCSH* (c.205G>A) that encodes the β-subunit of the glucosidase II (GlucII) and is involved in the development of polycystic liver disease. The *PKD1* mutation was found to affect the splice site donor of intron 8 and thus, the corresponding PC1 protein ([$(575\text{-}703)_{mut}$] $PC1_{1\text{-}703}$) is assumed to lose its function due to the lack of its transmembrane domains.

Additionally, the *PRKCSH* variant results in an amino acid exchange at the highly conserved position 69 of GlucIIβ (p.Ala69Thr), which abolishes its interaction with GlucIIα. Since GlucII participates in the maturation of polycystins in the endoplasmatic reticulum, its defect further reduces the level of functional polycystins.

Conclusions: In summary, while heterozygous loss-of-function mutation of *PKD1* resulted in adult onset of ADPKD, the presence of an additional deleterious *in-trans* variant in *PRKCSH* severely accelerated cystogenesis. Thus, we demonstrate that by interfering with polycystin maturation, *PRKCSH* plays a role as genetic modifier in ADPKD and contributes to the observed clinical variability.

FR-PO332

A Novel PKD1 Variant Demonstrates a Disease-Modifying Role in Trans with a Truncating PKD1 Mutation in Patients with ADPKD

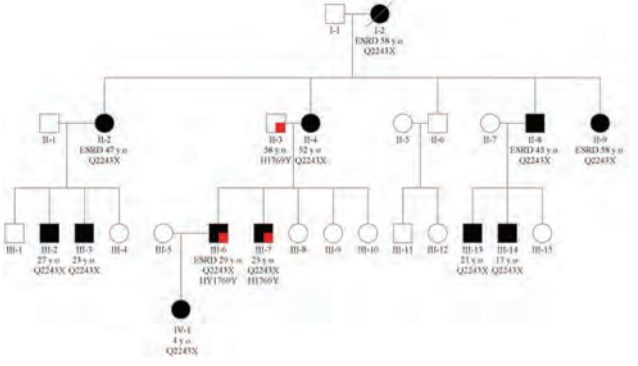
Medhat N. Ayoub. *Ministry of Health- Mubarak Hospital, KUWAIT, Kuwait.*

Background: Phenotypes associated with ADPKD in the terms of age of onset of end stage renal disease (ESRD), associated liver disease and other extrarenal manifestations showed high level of variability between patients. This phenotypic variability can be attributed to genic and allelic heterogeneity. Another element that adds to the complexity of phenotypic variability in ADPKD is the involvement of modifier genes which is suggested by the intrafamilial phenotypic variability observed in ADPKD families.

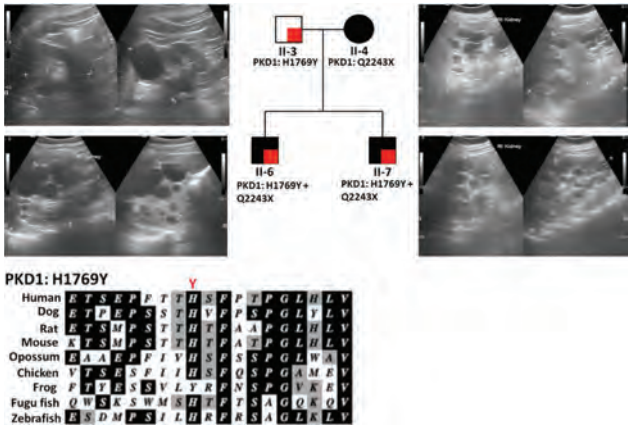
Methods: Patients were clinically evaluated using ultrasound and RFT. PKD1 was genotyped using next-generation sequencing by pooling long-range PCR amplicons and multiplexing bar-coded libraries. The significance of missense variants was assessed using the ADPKD Mutation Database, multisequence alignments and substitution assessment tools.

Results: In our case, we propose that the novel variant (p.H1769Y) aggravated the disease phenotype in patients resulting in early onset of ESRD and renal enlargement.

Conclusions: In summary, clinical evaluation of patients along with genetic prediction tools suggest that the novel PKD1 variant has a disease-modifying role, rather than disease causing role, in trans with the truncating PKD1 mutation in the studied family.



Pedigree of the ADPKD family showing the *PKD1* genotype of each member along with age and onset of ESRD.



Ultra soound of patients with the PKD1 novel variant and mutation.

FR-PO333

GPR124 Regulates Development of Kidney Medulla and Adult Kidney Fibrosis via Wnt7a/b Dependent and Independent Signaling

Yoichiro Ikeda,[4] Jing Liu,[2] Andrew P. McMahon,[1] Benjamin D. Humphreys.[3] *[1]Keck School of Medicine of the University of Southern California, Los Angeles, CA; [2]University of Southern California, Los Angeles, CA; [3]Washington University School of Medicine, Clayton, MO; [4]Washington University, School of Medicine, St. Louis, MO.*

Background: GPR124 is an orphan GPCR expressed in endothelial cells where it is a coreceptor for Wnt7a/b to activate canonical Wnt signaling. Wnt7b is required for the development of kidney medulla and cortico-medullary axis, and Wnt7a is associated with renal function and fibrosis. Pericyte-specific translational profiling revealed strong upregulation of GPR124 mRNA during kidney fibrosis. We investigated the role of GPR124 in pericytes and myofibroblasts during kidney development and fibrosis.

Methods: Models were developed for overexpression of GPR124 in fibroblasts (NRK-49F) and Crispr/Cas9-mediated knockout in myofibroblasts (10T1/2). Kidney stroma-specific deletion was accomplished with FoxD1-Cre;GPR124 floxed mice and conditional deletion with Gli1-CreER; GPR124 floxed; R26(tdTomato) mice.

Results: GPR124 mRNA was strongly upregulated in whole kidney during mouse UUO by qPCR, and specifically in the interstitium by in situ hybridization. GPR124 expression directly correlated with degree of fibrosis in human kidney. Lentiviral overexpression of GPR124 in NRK49f fibroblasts drove spontaneous myofibroblast differentiation even in the absence of Wnt ligand. By contrast, Crispr/Cas9 knockout of GPR124 in 10T1/2 mesenchymal cells, caused a strong reduction in fibrotic marker expression including aSMA and collagens. These knockout cells also failed to respond to Wnt7a and 7b ligand, confirming that GPR124 is a Wnt coreceptor in pericytes. Stromal specific GPR124 knockout mice resulted in a hypomorphic medulla phenotype and the loss of cortico-medullary axis, phenocopying the HoxB7-Cre; Wnt7b(f/f) phenotype. In addition, knockout mice showed microvascular hemorrhage in medulla. Conditional deletion of GPR124 in adult mouse kidney using Gli1-CreER; GPR124(f/f) ;tdTomato mice with tamoxifne administration resulted in reduced fibrosis in two fibrotic models also associated with reduced canonical Wnt-b-catenin signaling.

Conclusions: GPR124 is unexpectedly expressed in kidney pericytes and perivascular fibroblasts where it regulates Wnt7a/b signaling and drives myofibroblast differentiation. During development, stromal GPR124 is required for medullary development and in fibrosis GPR124 plays a critical role in regulating pericyte and fibroblast to myofibroblast transition.

Funding: NIDDK Support

FR-PO334

Tubular-Specific Krüppel-Like Factor 15 Mediates the Progression from Tubular Injury to Interstitial Fibrosis

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Background: Mechanisms by which tubular injury results in fibroblast to myofibroblast differentiation in the transition from AKI to CKD remains poorly understood. Renal stromal-specific Krüppel-Like Factor 15 (KLF15), a zinc-finger transcription factor, was recently shown as a potential mediator of kidney fibrosis. Here, we sought to determine the mechanism by which the tubular KLF15 serves a key mediator of AKI to CKD in the setting of proximal tubular (PT) injury.

Methods: PT-specific *Klf15* knockout mice ($Klf15^{\Delta Pepck}$) were generated by crossing $Klf15^{fl/fl}$ mice with *Pepck-Cre* mice. We utilized low-dose Aristolochic Acid I (AAI) to model PT injury and AKI to CKD, 3 mg/kg every three days for 3 weeks, followed by 3 weeks for remodeling (DMSO served as control). Full-length ORF cDNA of human KLF15 (*hKLF15*) was cloned into a TRE plasmid. Mice with *TRE-hKLF15* and *Pax8-rtTA* transgenes (Pax8-*hKLF15*) were generated for doxycycline (DOX) inducible tubule-specific *hKLF15* induction. Finally, mice with *TRE-hKLF15* and *CAG-rtTA* transgenes (*CAG-hKLF15*) were also generated for DOX-inducible global *hKLF15* induction.

Results: KLF15 mRNA and protein expression were reduced at 3 weeks post AAI treatment (AKI phase) and at 6 weeks (remodeling phase). $Klf15^{\Delta Pepck}$ mice exhibited an increase in pro-fibrotic markers (αSMA, Col1α1, fibronectin, vimentin) and myofibroblast proliferation (Ki67) as compared to AAI-treated wildtype mice. $Klf15^{\Delta Pepck}$ mice also demonstrated an increase in PT injury (AQP1 & lotus lectin redistribution and reduced expression) with activation of tubular Wnt/β-catenin signaling (nuclear phosho-β-catenin) and worsened renal function (elevated serum urea nitrogen and creatinine) compared to AAI-treated wildtype mice. Conversely, AAI-treated *Pax8-hKLF15* mice exhibited a reduction in these pro-fibrotic markers, myofibroblast proliferation, and Wnt/β-catenin signaling with an improvement in PT markers as compared to AAI-treated wildtype mice. Finally, AAI-treated *CAG-hKLF15* also validated this improvement in tubular injury, renal fibrosis, and renal function as compared to AAI-treated wildtype mice.

Conclusions: These data suggest that modulating the expression of tubular KLF15 is critical to the progression of AKI to CKD in the AAI-induced nephropathy, suggesting a potential target for therapy.

Funding: NIDDK Support

FR-PO335

Disruption of Genome Maintenance Mechanisms in Renal Proximal Tubular Epithelial Cells Exacerbates Human Kidney Fibrosis Seiji Kishi,[2,1] Kenji Nishimura,[2] Ryuji Morizane,[1] Takaharu Ichimura,[1] Joseph V. Bonventre,[1] Toshio Doi.[2] *[1]Brigham & Women's Hospital/Harvard Medical School, Boston, MA; [2]Nephrlogy, Tokushima University Hospital, TOKUSHIMA, Japan.*

Background: Renal proximal tubular epithelial cells (RPTECs) comprise the bulk of the renal parenchyma and are the primary target of a variety of insults to the kidney. While DNA damage and activation of the DNA damage response (DDR) play an important role in human disease, the role of DDR in the progression of human kidney disease remains unresolved. To investigate this mechanism, we evaluated the role of ataxia telangiectasia and Rad3-related (ATR) which is the key upstream regulator of cellular response to DNA damage.

Methods: We analyzed human kidney tissue from native kidney biopsy performed at Tokushima University Hospital. Of the 20 cases, 11 cases were kidneys with interstitial fibrosis and elevated serum creatinine, as well as 9 cases were with a pathologic diagnosis of minor glomerular abnormalities with normal serum creatinine and good preservation of tubules. An Active form of ATR (pATR) and the marker of DNA damage (γH2AX) were stained with KIM-1 to evaluate whether DDR correlates with eGFR or fibrosis. In vitro study, to examine whether the inhibition of the ATR affects the survival of a proximal tubular epithelial cell line (HKC-8) after toxic insult, we assessed the degree of DNA damage and cell viability with or without the ATR inhibitor; VE-821.

Results: In kidney tissue from humans with CKD, ATR was activated in chronically injured RPTECs. The number of pATR and KIM-1 double positive tubules was inversely correlated with eGFR and positively correlated with the degree of kidney fibrosis. The number of γH2AX and KIM-1 double positive tubules in each kidney section was markedly increased, inversely correlated with eGFR and positively correlated with the degree of kidney fibrosis. We found an inverse correlation between γH2AX/KIM-1 positive and pATR/KIM-1 positive cells in CKD kidney. DNA damage and decline of cell viability of HKC-8 cells were further exacerbated when exposed to cisplatin, aristolochic acid or hypoxia in the presence of VE-821. Furthermore, ATR inhibition upregulated p21 and CTGF expression in HKC-8 cells after aristolochic acid treatment.

Conclusions: We demonstrate that DDR is seen in human kidney disease and ATR plays a protective role against tubular cell injury, death and fibrotic response. Regulation of ATR may be a therapeutic target against human kidney disease.

Funding: Government Support - Non-U.S.

FR-PO336

Lineage Tracing Study Defines Erythropoietin-Producing Cells as the Distinct Subpopulation of Resident Fibroblasts with Unique Behaviors Keiichi Kaneko, Shuichiro Endo, Motoko Yanagita. *Kyoto University Graduate School of Medicine, Sakyo-ku, Japan.*

Background: We previously demonstrated that renal fibroblasts including erythropoeitin (Epo)-producing cells transdifferentiate into myofibroblasts with concomitant loss of Epo production during renal fibrosis. It has not been elucidated, however, whether Epo-producing cells, which account for less than 10 % of resident fibroblasts, are the distinct specialized population of resident fibroblasts. Lack of tools to label Epo-producing cells at desired time points has hindered our further understanding of the behavior of Epo-producing cells in adult kidneys.

Methods: We generated a novel mouse strain in which inducible Cre, Cre^{ERT2} was knocked-in at the locus of Epo gene (Epo-Cre^{ERT2} mice). Epo-Cre^{ERT2} mice were crossed with indicator mice, and tamoxifen was administered to the offspring to activate Cre^{ERT2}.

Results: Epo-Cre^{ERT2} labeled cells were located in the interstitium of the cortex and corticomedullary region of the kidney, and expressed PDGFRβ and CD73, indicating that these cells were resident fibroblasts. The labeled cells increased in parallel with the magnitude of anemia. Double in situ hybridization confirmed that around 50 % of the labeled cells expressed Epo mRNA, indicating that Epo-Cre^{ERT2} mice faithfully labeled the Epo-producing cells. Around 50 % of the labeled cells maintained Epo-producing ability even 16 weeks after the recombination, supporting the hypothesis that the labeled cells are the distinct population with Epo-producing ability. After unilateral ureteral obstruction (UUO), the labeled cells transdifferentiated into myofibroblasts, lost Epo-producing ability, and proliferated. The percentage of the labeled cells in resident fibroblasts increased 4.5 folds during fibrosis (1.9 % in healthy kidney and 9.2 % in UUO kidney, $p<0.01$), and Ki67 expression was more prevalent in the labeled cells than in other fibroblasts (12.7 % vs 8.3 %, $p<0.05$).

Conclusions: Utilizing the new mouse strain, Epo-Cre^{ERT2} mice, we, for the first time, analyzed the behavior of the Epo-producing cells. The maintenance of Epo-producing ability and faster proliferation during fibrosis indicate the possibility that Epo-producing cells are the distinct populations of renal fibroblasts. Detailed analysis of the population will provide us new therapeutic approach to renal anemia.

Funding: Government Support - Non-U.S.

FR-PO337

Pathologic Cross-Talk between Hippo-TAZ and CTGF Pathways during Renal Fibrosis Progression Rohan Samarakoon,[1] Alex Arnouk,[2] Jiaqi Tang,[2] Roel Goldschmeding,[3] Paul J. Higgins.[2] *[1]Albany Medical Center, Albany, NY; [2]Albany Medical College, Watervliet, NY; [3]None, Utrecht, Netherlands.*

Background: TAZ is a nuclear transducer of the Hippo pathway. We recently demonstrated that TAZ, upregulated in the tubulorinterstitium in multiple models of kidney injury, is a novel profibrotic effector of the TGF-beta1 pathway that promotes CKD. Ectopic expression of TAZ in HK-2 human renal epithelial cells induces expression of CTGF, a known fibrosis causative factor. It is unknown whether CTGF upregulation deregulates Hippo-TAZ signaling during kidney fibrosis and if TAZ promotes epithelial dysfunction via CTGF-dependent mechanisms.

Methods: A novel mouse model of global conditional CTGF knockout (created by crossing CTGF-flox and ROSA26-CreET2 mice and subsequent tamoxifen administration) was utilized to determine the role of CTGF silencing on TAZ activation and renal fibrosis driven by ureteral ligation (UUO). Various transgenic HK-2 cells with stable TAZ and CTGF expression or depletion were created to investigate the potential cross-talk between TAZ and CTGF in fibrogenesis.

Results: Fibrotic obstructed kidneys have elevated CTGF and TAZ expression relative to contralateral controls. CTGF knockout animals have attenuated renal fibrotic response and TAZ expression compared to control mice (receiving corn oil instead of tamoxifen) subjected to UUO. CTGF stable expression in HK-2 cells, furthermore, robustly induced TAZ expression and promoted fibrosis factor expression (i.e., fibronectin and collagen-1), epithelial dedifferentiation (marked by increased vimentin and decreased E-cadherin expression) and G_2M cell cycle arrest. TAZ gene silencing, indeed, attenuated CTGF-mediated fibronectin, collagen-1 and vimentin expression. Similarly, fibrotic gene upregulation (e.g., CTGF and fibronectin), dedifferentiation and growth inhibition induced by stable epithelial TAZ expression were abrogated by stable CTGF suppression (via shRNA approaches).

Conclusions: Conditional silencing of CTGF expression during obstructive nephropathy in mice leads to attenuated TAZ expression and kidney fibrosis. Epithelial fibrotic response induced by sustained CTGF signaling requires TAZ. Conversely, TAZ induced CTGF expression orchestrates epithelial maladaptive repair, demonstrating reciprocal regulation of TAZ and CTGF in promoting CKD progression.

Funding: Other NIH Support - NIH GM057242 and New York State Capital Region Medical Research Institute Grants, Private Foundation Support

FR-PO338

Perivascular Cell CD73 Modulates Macrophages in the Renal Microenvironment during Progressive Fibrosis Heather M. Perry,[2] Nicole Görldt,[2] Liping Huang,[2] Sun-sang J. Sung,[2] Diane L. Rosin,[1] Mark D. Okusa.[2] *[1]Pharmacology, University of Virginia, Charlottesville, VA; [2]Medicine, University of Virginia, Charlottesville, VA.*

Background: Progressive tubulointerstitial fibrosis can occur following an acute kidney insult such as ischemia-reperfusion injury (IRI). Mechanisms underlying these maladaptive repair processes are not well understood. Purinergic signaling by CD73, an enzyme that converts AMP to adenosine on the extracellular surface, via adenosine receptors can suppress inflammation and reduce IRI. As CD73 is expressed on renal perivascular cells (pericytes and/or fibroblasts of the Foxd1+ lineage), we hypothesized that perivascular cell expression of CD73 is necessary to suppress inflammation and prevent fibrosis.

Methods: *Foxd1CreCD73*$^{fl/fl}$ and littermate control *CD73* $^{fl/fl}$ mice were subjected to 20' unilateral IRI operation and after 14d, plasma was collected to quantify plasma creatinine (PCr). Also, kidneys were prepared for assessment of fibrosis by histology and inflammation and myofibroblast density by immunofluorescence. Kidney fibrosis and macrophage polarization markers were quantified by RT-qPCR. Soluble CD73 or macrophage depletion by liposome clodronate and controls were initiated 2d after IRI and kidney function and fibrosis were assessed at 14d.

Results: PCr levels were elevated in *Foxd1CreCD73*$^{fl/fl}$ ($n = 10$) compared to control mice ($n = 9$) (0.29 ± 0.07 vs. 1.1 ± 0.20 mg/dl respectively, $p < 0.001$). Fibrosis and myofibroblast marker expression was increased in kidneys of *Foxd1CreCD73*$^{fl/fl}$ mice compared to controls. Kidney macrophages and expression of pro-inflammatory, pro-fibrotic phenotypic markers were also increased in *Foxd1CreCD73*$^{fl/fl}$ mice compared to controls. Exogenous CD73 rescued the decline in kidney function and fibrotic phenotype in *Foxd1CreCD73*$^{fl/fl}$ mice. As macrophages switch from a pro-inflammatory to a wound healing phenotype on day 2, we sought to address this as a potential mechanism of increased fibrosis in *Foxd1CreCD73*$^{fl/fl}$ mice. Macrophage depletion in *Foxd1CreCD73*$^{fl/fl}$ mice resulted in protection against kidney dysfunction and fibrosis.

Conclusions: These results demonstrate that perivascular cell CD73 orchestrates the renal inflammatory microenvironment to promote a wound healing response after an acute event resulting in recovery of kidney function and prevention of progressive fibrosis.

Funding: NIDDK Support

FR-PO339

Endothelial Tie2 Deficiency Increases Tubulointerstitial Fibrosis Marie Jeansson. *Uppsala University, Uppsala, Sweden.*

Background: Renal tubulointerstitial fibrosis is predictive of progressive decline in kidney function, independent of underlying disease. It is characterized by an increase in aSMA+ fibroblasts, myofibroblasts, that produce collagen. We previously showed that loss of Angiopoietin-1 (Angpt1) in adult mice predisposes to fibrosis in wound healing, diabetic nephropathy, and the unilateral ureter obstruction (UUO) model. The tyrosine kinase receptor, Tie2, is expressed on endothelial cells and Angpt1 binding results in Tie2 signaling that is pro-survival and anti-inflammatory. Here, we test the hypothesis that loss of Tie2 signaling in endothelial cells results in capillary defects leading to an increased fibrotic response in kidney fibrosis.

Methods: Tie2 floxed mice were crossed with tamoxifen inducible endothelial specific Cadh5-Cre and a reporter line expressing TdTomato upon Cre-activation. This line enables both an endothelial specific KO of Tie2 and an endothelial lineage tracer.

To study the role of Tie2 signaling in renal fibrosis we utilized the unilateral ureter obstruction (UUO) model of kidney fibrosis.

Results: Endothelial specific KO of Tie2 resulted in an increase in fibrosis as seen by a 2-fold increased expression of SM22a and Col1a1 compared to controls 3 days after UUO. At the same time, there was a 4-fold increase in Kim1, suggesting more injury to tubular cells in Tie2 KO. Investigation of blood vessels before fibrotic onset 1 day after UUO, revealed less perfused capillary area and increased hypoxia in Tie2 KO mice. Ongoing work is designed to investigate blood vessel function in the early fibrotic process and to estimate the endothelial-mesenchymal contribution after UUO in controls and Tie2 knockout mice, utilizing the lineage tag of endothelial cells in the system.

Conclusions: Our results suggest that loss of Tie2 signaling destabilizes the endothelial cell and increases tubulointerstitial fibrosis. The mechanisms we are investigating are an early loss of endothelial cells due to endothelial-mesenchymal transition and/or apoptosis, resulting in less functional peritubular capillaries and more fibrosis.

Funding: Government Support - Non-U.S.

FR-PO340

ErbB4 Deletion Accelerates Renal Fibrosis Following Renal Injury Fenghua Zeng, Lance A. Kloepfer, Raymond C. Harris. *Vanderbilt University Medical Center, Nashville, TN.*

Background: Tubulointerstitial fibrosis (TIF) is a component of chronic kidney disease (CKD) of any etiology and is the best predictor of progression toward end stage kidney disease. Mechanisms underlying the development and progression of TIF are still incompletely understood. Increased ErbB4 expression were seen in the tubular epithelium of CKD kidneys. However, its role in the tubulointerstitial injuries remains to be determined.

Methods: ErbB4 expression was examined using immunohistochemistry in human biopsy fibrotic kidneys. Two mouse models of renal injury, unilateral ureteral obstruction (UUO) and ischemia reperfusion injury followed by uninephrectomy (IRI/UNx), were used to study the possible impact of ErbB4 deletion in renal fibrosis by comparing heart rescued ErbB4 deletion ($ErbB4^{del}ht^{+}$) and wild-type (WT) mice. Renal function and pathological changes were examined.

Results: In human fibrotic kidneys, ErbB4 expression levels were inversely correlated to renal fibrosis as indicated by double immunofluorescence staining of ErbB4 and colagen I. In both UUO and IRI/UNx mouse models, expression levels of ErbB4 were elevated in the early stage of renal injury in the wild-type mice. In mice with global ErbB4 deletion except for transgenic rescue in cardiac tissue (*ErbB4*$^{-/-}$*ht*$^{+}$), UUO induced similar injury in proximal tubules compared to wild-type mice but more severe injury in distal nephrons. TIF was apparent earlier and was more pronounced following both UUO and IRI-UNx injuries in *ErbB4*$^{-/-}$*ht*$^{+}$ mice. With ErbB4 deletion, UUO injury inhibited AKT phosphorylation and increased the percentage of cells in G2/M arrest. Meanwhile, increased levels of nuclear immunostaining of YAP and increased expression of p-Smad3, snail1 and vimentin were also detected in kidneys wiith ErbB4 deletion compared to the wild-type mice.

Conclusions: In conclusion, increased expression of ErbB4 was detected in the early stages of human renal injury, whereas its level decreased with severe renal fibrosis, which is consistent with the finding that ErbB4 deletion promoted renal fibrosis in mouse injury models. Therefore, the early increased ErbB4 expression may reflect a compensatory effect to lessen tubulointerstitial injury.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO341

Ablation of Transcription Factor HNF-1β Induces Epithelial-Mesenchymal Transition through Twist2 Derepression Siu Chiu Chan, Ying Zhang, Annie Shao, Sophia M. Vrba, Svetlana Avdulov, Jeremy Herrera, Shayan A. Farahani, Karam S. Aboudehen, Peter Igarashi. *University of Minnesota, Minneapolis, MN.*

Background: Hepatocyte nuclear factor-1β (HNF-1β) is a transcription factor that is essential for normal kidney development and function. Mutations of HNF-1β produce autosomal dominant tubulointerstitial kidney disease (ADTKD) characterized by tubular cysts, renal fibrosis, and progressive decline in kidney function. We have previously shown that HNF-1β regulates a network of cystic disease genes that are down-regulated in HNF-1β mutant kidneys.

Methods: To understand the mechanism whereby mutation of the epithelial-specific transcription factor HNF-1β leads to interstitial fibrosis, we used gene editing with CRISPR/Cas9 to ablate HNF-1β in mIMCD3 renal epithelial cells.

Results: HNF-1β mutant mIMCD3 cells exhibited loss of contact inhibition and adopted a spindle-shaped morphology. Compared with control cells, HNF-1β-deficient cells exhibited EMT features with increased cell migration and higher motility and produced a multilayered epithelium. RNA-seq analysis of HNF-1β-deficient cells and Ingenuity Pathway Analysis (IPA) revealed that fibrosis and epithelial-mesenchymal transition (EMT) pathways were highly activated in HNF-1β-deficient cells. Transcription factors involved in EMT, including TWIST2, SNAIL1, SNAIL2, and ZEB2, were upregulated in HNF-1β mutant cells. Mechanistically, we found that expression of *Twist2* was directly repressed by HNF-1β. Concomitant ablation of *Twist2* partially rescued the fibroblastic phenotype of HNF-1β mutant cells. Chromatin immunoprecipitation and qRT-PCR analysis of *Twist2* mutant cells showed that TWIST2 is an upstream transcriptional activator of *Snail2*. Immunohistochemistry and RNA in situ hybridization showed that the expression of TWIST and SNAIL, as well as downstream targets TGFβ2 and TGFβ3, was increased in the cyst epithelium of HNF-1β mutant kidneys.

Conclusions: We conclude that ablation of HNF-1β in renal epithelial cells leads to the activation of a transcriptional network that induces EMT and aberrant TGFβ signaling. Targeting this network may inhibit fibrosis in ADTKD and other chronic kidney diseases.

Funding: NIDDK Support

FR-PO342

Tubule-Derived Extracellular Vesicles Promotes Fibroblast Activation in Kidney Fibrosis Xi Liu,[1] Lili Zhou,[1] Youhua Liu.[2] *[1]Division of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China; [2]Department of Pathology, University of Pittsburgh, Pittsburgh, PA.*

Background: Kidney fibrogenesis is a complex process involving frequent cell-cell communication. Extracellular vesicles (EVs), consisting of exosomes and microvesicles, are increasingly recognized as an essential vehicle mediating cell-cell communication in both physiologic and pathologic conditions. Because tubular epithelium is the major constitute of kidney parenchyma and the epicenter of kidney injury, we hypothesized that tubular cells, in response to injury, may increase their production and release of EVs containing proteins, mRNAs and microRNAs, which act on interstitial fibroblasts, leading to their activation. In this study, we tested this hypothesis by in vitro and in vivo approaches.

Methods:

Results: In human kidney proximal tubular cells (HKC-8), TGF-β1 induced marked increase in the release of EVs. Conditioned media collected after TGF-β1 treatment promoted rat kidney interstitial fibroblast (NRK-49F) activation, proliferation and matrix production, compared with controls. However, depletion of EVs from TGF-β1-treated HKC-8 cell conditioned media abolished its action on NRK-49F cells, suggesting a predominant role of the EVs in mediating tubule-fibroblast communication. Interestingly, we found that Shh signal components were markedly induced in the EVs released by TGF-β1-treated HKC-8 cells. Knockdown of Shh in HKC-8 cells by RNAi abolished the tubular EVs-mediated induction of Gli1, Snail1, α-SMA, fibronectin, and collagen I in NRK-49F cells. In mouse model of kidney fibrosis induced by UUO, the secretion of EVs was dramatically increased, and blockade of EVs secretion with small molecule inhibitor DMA suppressed myofibroblast activation, inhibited fibronectin and collagen I expression and ameliorated renal fibrotic lesions.

Conclusions: These results indicate that tubule-derived EVs play a critical role in initiating fibroblast activation and development of renal fibrotic lesions. Our data also suggest that Shh signal components in the EVs may be responsible, at least partially, for mediating the tubule-fibroblast communication in renal fibrogenesis.

Funding: Government Support - Non-U.S.

FR-PO343

Nrf2 Deletion Promotes the Progression from Acute Tubular Damage to Chronic Renal Fibrosis Induced by Unilateral Ureteral Obstruction Weiwei Kong,[3] Jingqi Fu,[4] Congcong Jiao,[3] Guangying Guo,[3] Huihui Wang,[1] Lining Wang,[2] Jingbo Pi,[4] Hua Zhou.[3] *[1]China Medical University, Shenyang, China; [2]Department of Nephrology, First Affiliated Hospital of China Medical University, Shenyang, P. R. China, Shenyang, China; [3]The first hospital of China Medical University, Shenyang, China; [4]rogram of Environmental Toxicology, School of Public Health, China Medical University, Shenyang, China.*

Background: The role of Nrf2 (nuclear factor erythroid 2–related factor 2) in the progression from acute kidney damage to chronic renal fibrosis in obstructive nephropathy remains unclear. We aimed to verify whether Nrf2 deletion aggregates the progress of renal injury induced by unilateral ureteral obstruction (UUO) and further to investigate its mechanism in Nrf2-knockout mice ($Nrf2^{-/-}$ mice).

Methods: Renal injury was induced by UUO in 54 male $Nrf2^{+/+}$ mice and 36 male $Nrf2^{-/-}$ mice. The kidneys were collected at day 2, 5, and 14 after UUO and histological damage was evaluated by PAS or Masson staining. We compared tubular damage (cleaved caspase3 and PARP) on day 2, transdifferentiation (vimentin and PCNA) on day5, fibrosis (fibronectin and α-SMA), and inflammatory factors on day 14 after UUO in $Nrf2^{-/-}$ mice with $Nrf2^{+/+}$ mice on protein and mRNA levels. The temporal renal Nrf2 expression was examined in the mice with immunohitochemistry staining and western blotting. In addition, Nrf2 was also evaluated in renal biopsies from the patients with acute, sub-acute, or chronic tubulointerstitial nephritis.

Results: Tubular damage significantly occurred on day 2; vimentin, fibronectin, and α-SMA increased on day 5 and 14 in $Nrf2^{+/+}$ mice. Nrf2 downstream genes (Gclc and Ho-1) significantly increased from day 2 to 5, while Nrf2 protein remarkably rose on day 5 and 14 in $Nrf2^{+/+}$ mice. Renal Nrf2 positive staining was upregulated in patients with acute, sub-acute, and chronic tubulointerstitial nephritis conmared with normal huamn kidneys. Nrf2 deficiency significantly enhanced tubular damage, apoptotic cells evaluated by TUNEL staining, and levels of cleaved caspase3 and PARP on day 2. Nrf2 deletion markedly increased the cells co-expressed with vimentin and PCNA on double immunofluorecent staining on day 5. $Nrf2^{-/-}$ mice showed overproduction of fibronectin, α-SMA, and profibrotic inflammatory response genes (Tgfβ1, Tnfα, and IL6) on day 14 after UUO.

Conclusions: Nrf2 deficiency aggregated acute tubular damage, transdifferentiation, inflammation, and fibrosis under sustained UUO condition. The renalprotective role of Nrf2 in the development of tubulointerstitial fibrosis in UUO may be mediated by anti-apotosis and anti-inflammation. Nrf2 might be a potential therapeutic target for renal fibrosis.

Funding: Government Support - Non-U.S.

FR-PO344

Dickkopf-3 (Dkk-3) Overexpressed in Dysfunctional Endothelium Secretome Instructs Fibroblast-to-Myofibroblast Formation by Activating the Wnt Pathway Mark Lipphardt,[2,4] Sina Dadafarin,[2] Brian B. Ratliff,[2] Hassan Dihazi,[3] Gerhard A. Mueller,[1] Michael S. Goligorsky.[2] *[1]Georg-August University, Gottingen, Germany; [2]New York Medical College, Valhalla, NY; [3]University Medical Centre Goettingen, Goettingen, Germany; [4]Nephrology & Rheumatology, Universitätsmedizin Göttingen, Göttingen, Germany*.

Background: We have previously demonstrated that Sirt1^{endo}-/- mice with endothelial dysfunction show exaggerated renal fibrosis, whereas mice with silenced endothelial TGF-β signaling are resistant to fibrogenic signals. Collectively, this indicates that secreted substances regulate these contrasting responses. Thus, we sought to examine the differential secretome of those cells.

Methods: We performed unbiased proteomic analysis of the secretome of renal microvascular endothelial cells (RMVEC) isolated from these two mutants, discovered Dkk-3 (a putative ligand of Wnt/β-catenin pathway) expressed exclusively in fibrogenic secretome. Since Dkk-3 is an orphan member of the family of Wnt ligands, and its precise effects are poorly understood, we examined effects of Dkk-3 in renal fibroblasts (RF) isolated from α-SMA-GFP mouse kidneys using positive and negative selection with magnetic beads.

Results: Application of Dkk3 to RF showed that Dkk3 (10 ug/ml) alone induced myofibroblastic phenotype without altering responses to TGFβ. Dkk-1, a known antagonist of Wnt pathway, reduced activation of RF. When Dkk-3 was combined with Dkk-1, it antagonized its antimyofibroblastic effect. In RMVEC, Dkk-3 induced endothelial-mesenchymal transition (endo-MT) as judged by the appearance of α-SMA-GFP signal, and reduced capillary cords formation and their branching angiogenesis. In microfluidic RF-RMVEC co-cultures (kindly provided by NL Jeon, Seoul National University, Seoul, Korea) Dkk-3 was confirmed as an inducer of endo-MT and inhibitor of angiogenesis. Chronic administration of Sulindac, a potent Wnt pathway inhibitor, ameliorated UUO-induced renal fibrosis.

Conclusions: In conclusion, a prominent member of the secretome of dysfunctional RMVEC, Dkk-3, affords a Dkk-1 antagonistic paracrine effect on RF and induces myofibroblastic prenotype. Dkk-3 exerts a autocrine effect leading to endo-MT of RMVEC and reducing their angiogenic competence. These actions make Dkk-3 a potent pro-fibrogenic agonist.

FR-PO345

Lactic Acid Production from Glycolysis Activates TGF-b/Smad Signaling Pathway in Tubular Epithelial Cells Engaged in the Development of Renal Fibrosis Jing Xu,[2] Yan Shen,[1] Lei Jiang,[4] Junwei Yang.[3] *[1]Center for Kidney Disease, Second Affiliated Hospital, Nanjing Medical University, Nanjing, China; [2]Nanjing Medical University, Nanjing, China; [3]Second Affiliated Hospital, Nanjing Medical University, Nanjing, China; [4]Second Affliliated Hospital, Nanjing Medical University, Nanjing, China*.

Background: Renal proximal tubule is susceptible to hypoxic injury, because of the reliance on aerobic oxidative metabolism. Dysfunctional mitochondria participate the progression of chronic renal disease. In this paper, we investigate the profile of the energy metabolism of the proximal epithelial cell in fibrotic kidney, and evaluate the role of anaerobic metabolism in renal fibrosis.

Methods: 2-deoxyglucose (2-DG) was administered at a dose of 20mg/kg or 100mg/kg and Shikonin was oral performed at a dose of 1 or 5 mg/kg before unilateral ureter obstruction (UUO) surgery and administered for successive7 days. Human Recombinant TGF-β1 (5 ng/ml) and lactic acid (10mmol/L) were added to the serum-free medium for indicated time periods and concentration. 2-DG (0.2 or 1mM), dichloroacetic acid (DCA,2mM), BroPA (5nM) and oxamate (100nM) were added to the serum-free medium 30 minutes for indicated time periods and concentration before TGF-β1 treatment.

Results: The protein expression of key enzymes of glycolysis were markedly increased in a time depended in UUO induced renal interstitial fibrosis mice model. There was a similar result in primary renal tubular epithelial cells after disposed with TGF-β1. In addition, the fibrotic matrix was reduced and marks of collagen fibrils such as α-smooth muscle actin (α-SMA), fibronectin (FN) were down-regulated after mice or primary renal tubular epithelial cells (PTC) dealed with inhibitors of glycolytic pathway. At the same time, we found the expression of TGF-β1 receptor and p-smad3 were decreased. In the meantime, lactic acid, the production of glycolysis pathway, was involve in the activation of TGF-β1-smad pathway and changed renal tubular cells phenotype and contributed to the development of renal interstitial fibrosis.

Conclusions: Altered glucose metabolism of tubular epithelial cells is a hallmarks of renal fibrosis. Inhibition of aerobic glycolysis is effective to suppress renal fibrosis. Lactic acid production from glycolysis could further active TGFβ1/smad signaling and aggravate renal fibrosis.

Funding: Government Support - Non-U.S.

FR-PO346

ATF6 Knockout Mice Revealed That ER Stress Links Lipotoxicity and Kidney Fibrosis Tzu-Ming Jao,[1] Chia-Hsien Wu,[1] Mai Sugahara,[2] Hisako Saito,[2] Yu Ishimoto,[2] Akira Okada,[2] Hiroshi Maekawa,[2] Mari Aoe,[2] Tetsuhiro Tanaka,[2] Masaomi Nangaku,[2] Reiko Inagi.[1] *[1]The University of Tokyo Graduate School of Medicine, Tokyo, Japan; [2]the University of Tokyo School of Medicine, Tokyo, Japan*.

Background: Lipid accumulation in tubules is frequently observed in chronic kidney disease (CKD) patients. However, the molecular mechanism underlying lipotoxicity-induced tubulointerstitial fibrosis is still largely unknown. ATF6, a transcription factor of unfolded protein response (UPR), has been reported as an upstream regulator of lipid metabolism. In addition, fatty acid is the main energy source of proximal tubular cell because of its high energy demand. We thus hypothesized that ATF6 regulates tubular lipid metabolisms, and thereby contributes to lipotoxicity-induced renal fibrosis.

Methods: We employed ATF6+/+ and ATF6-/- mice or Sprague-Dawley rats with unilateral ureteral obstruction (UUO) or unilateral ischemia-reperfusion injury (uIRI) as tubulointerstitial fibrosis models. In *in vitro* study, human proximal tubular cell line, HK-2, expressing active ATF6 (nATF6) was used. Change in ATF6 activation, fatty acid synthetic factors (ACC and DGAT2), b-oxidation regulators (PPARα, CPT1, CPT2 and MCAD), pro-fibrogenic factor (CTGF) were assessed.

Results: ATF6 was significantly activated in associated with tubular lipid accumulation in rat fibrotic kidneys induced by UUO and uIRI. In contrast, ATF6 deficient mice exhibited amelioration of uIRI-induced tubulointerstitial fibrosis via reduction of collagen I and a-SMA expression. Intriguingly, tubular lipid accumulation was also attenuated by ATF6 deficiency, indicating the pivotal role of ATF6 in lipotoxicity-mediated tubulointerstitial fibrosis. To reveal the molecular mechanism underlying ATF6-mediated lipotoxicity and subsequent tubulointerstitial fibrosis, we overexpressed nATF6 in HK-2 and observed that nATF6 enhances fatty acid synthetic factors, as well as downregulates b-oxidation regulators, suggesting the exacerbation effect of nATF6 in lipid accumulation. Importantly, such nATF6-induced lipotoxicity causes depleted mitochondrial respiration and ATP production, and thereby decreased cell viability, inducing apoptotic signaling and elevating CTGF expression.

Conclusions: Collectively, we unveiled the role of ATF6 in the derangement of fatty acid metabolism in the tubular cells, leading to lipotoxicity-mediated tubular apoptosis and CTGF upregulation, both of which may accelerate tubulointerstitial fibrosis.

FR-PO347

Alteration of Fatty Acid Oxidation in Proximal Tubular Epithelial Cells during Renal Fibrosis Hao Ding,[1] Junwei Yang.[2] *[1]Nanjing Medical University, Nanjing, China; [2]Second Affiliated Hospital, Nanjing Medical University, Nanjing, China*.

Background: Chronic kidney diseases (CKD) generally lead to renal fibrosis and so far no effective therapeutic anti-fibrosis strategy is available. At the tubular cell scale, proximal tubular epithelial cells (PTCs) which prefer fatty acid as their energy source are the most energy-demanding cells in the body and involved in the process of interstitial fibrosis.

Methods: In this study, we employed mice with unilateral ureter obstruction (UUO) and TGFβ1-treated primary PTCs as two model systems. The Cre/loxP system was used to generate renal PTCs–specific CPT1α deletion mice (CPT1α^{KO}).

Results: Here we first demonstrated that a switch of metabolism from oxidative phosphorylation to aerobic glycolysis in mouse kidney with UUO surgery. We found rate-limiting enzymes and key transcription factors involved in FAO were reduced in fibrotic kidney and TGFβ1-treated primary PTCs. We uncovered that altered of FAO was associated with higher lipid accumulation in diseased renal and TGFβ1-treated primary PTCs. We also found that the enzymes and regulators of FAO were reduced in renal biopsy specimens of patients with CKD and was associated with the severity of renal interstitial fibrosis. PTCs-specific ablation of CPT1α resulted in a phenotype that body weight was lower compare with their control littermates. Kidney injury molecule-1, NAG enzyme in urine and blood urea nitrogen were increased within 4 months and recovery at 8 months. We noticed the expression of rate-limiting enzymes and key transcription factors involved in peroxisomal compartments pathway were up-regulated in kidneys of knockouts. In line with this, CPT1α^{KO} mice showed higher heat production compared to the controls which is indicative of proportion of energy expenditure derived from lipid oxidation in peroxisomal. Finally, inhibiting mitochondrial FAO of PTCs lead to up-regulation of peroxisomal FAO pathway.

Conclusions: In conclusion, our findings demonstrate altered of both mitochondrial and peroxisomal β-oxidation enzyme systems during the process of interstitial fibrosis. Furthermore, we found peroxisomal FAO pathway was compensatory up-regulated when mitochondrial FAO is shut down. Our results indicate that drugs that specifically restoring FAO may attenuate renal fibrosis.

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FR-PO348

Adiponectin Attenuates Kidney Injury and Fibrosis in Deoxycorticosterone Acetate-Salt and Angiotensin II Induced CKD Mice Mi Tian, Li Tang, Srini Beddhu, Yufeng Huang. *Division of Nephrology, University of Utah Health, Salt Lake City, UT*.

Background: Adiponectin (ApN) is a multifunctional adipokine with insulin-sensitizing, anti-inflammatory, and vasoprotective properties. However high, rather than

low, concentrations of ApN are unexpectedly found in patients with chronic kidney disease (CKD) via an as yet unknown mechanism and the role of ApN in CKD is unclear. We, herein, investigated the effect of ApN overexpression on the progression of renal injury resulted from deoxycorticosterone acetate-salt (DOCA) and angiotensin II (DOCA+AII) infusion using a transgenic, inducible, hepatic ApN-overexpressing mouse model.

Methods: Uninephrectomy was firstly performed on all experimental mice. Two weeks after uninephrectomy, three groups of male mice (wild type receiving no infusion and normal drinking water (WT), wild type and cyp1a1 ApN transgenic mice receiving DOCA+AII infusion (WT/DOCA+AII and ApN-Tg/DOCA+AII) and 1% NaCl in drinking water) (n=5/each group) were then assigned to receive a normal diet containing 0.15% of the transgene inducer indol-3-carbinol (I3C) for 3 weeks.

Results: The I3C-induced ApN-Tg/DOCA+AII mice, not the WT or WT/DOCA+AII mice, overexpressing ApN in liver resulted in 3.15-fold increases in circulating ApN levels than non-transgenic controls. Of note, these transgenic mice receiving DOCA+AII infusion were still hypertensive (SBP, 148±5.09 vs. 148.07±3.43 mmHg, P>0.05 vs. WT/DOCA+AII) but had much less albuminuria and glomerular and tubulointerstitial fibrosis (decreased by 67.3%, 76.6% and 67.3% respectively (P<0.001), when compared to WT/DOCA+AII), which were associated with reduced podocyte injury determined by ameliorated DOCA+AII-induced podocyte loss and foot process effacement; and alleviated tubular injury determined by ameliorated DOCA+AII-induced increases in renal KIM-1 and NGLA mRNA expression and decreases in renal cubilin and megalin mRNA expression. In addition, renal macrophage infiltration and productions of NF-kB-p65, Nox2 and p47phox, markers of inflammation and oxidative stress, which were induced by DOCA+AII infusion in WT mice, were markedly reduced in ApN-Tg mice.

Conclusions: These results indicate that elevated ApN in CKD mouse model is renal protective. Enhancing adiponectin production or signaling may have therapeutic potential for renal disease.

FR-PO349

Indoxyl Sulfate Disturbs Normal Iron Metabolism via Hepcidin Upregulation in CKD Hirofumi Hamano,[1] Yasumasa Ikeda,[1] Yuya Horinouchi,[1] Yuki Izawa-ishizawa,[1] Shoji Kagami,[2] Toshiaki Tamaki.[1] *[1]Department of Pharmacology, Tokushima University Graduate School, Tokushima City, Japan; [2]Department of Pediatrics, Tokushima University Hospital, Tokushima City, Japan.*

Background: Hepcidin, a secreted hormone derived from hepatocytes, is a key regulator of systemic iron metabolism to regulate iron efflux from intracellular iron by the internalization and degradation of ferroportin (FPN). Hepcidin concentration is increased in patients with chronic kidney disease (CKD), suggesting to the dysregulation of iron metabolism in CKD. Levels of indoxyl sulfate (IS), a uremic toxin, is elevated during the course of CKD progression, and its accumulation exacerbates the status of CKD. However, the role of IS accumulation on iron metabolism has remained unclear. In the present study, we investigated the involvement of IS on iron metabolism.

Methods: In *in vitro* experiments, HepG2 cells were used to examine the mechanism of IS on hepcidin regulation. We used a mouse model of adenine-induced CKD to analyze hepcidin action on body iron metabolism in *in vivo*. The CKD mice were divided into two groups: one was treated using AST-120 (uremic toxin adsorbent) and the other received no treatment. In addition, we tested mice with direct IS administration.

Results: In *in vitro* experiments using HepG2 cells, IS augmented hepcidin expression in a dose-dependent manner. IS-induced hepcidin upregulation was inhibited by silencing or pharmacological inhibition of aryl hydrocarbon receptor (AhR), a receptor of IS. IS also augmented oxidative stress and anti-oxidant drugs suppressed IS-induced hepcidin upregulation. Adenine-induced CKD mice showed the elevation of hepatic hepcidin mRNA expression and blood hepcidin concentration compared with control mice. In CKD mice, renal anemia, decreased blood iron concentration, increased blood ferritin levels, and increased splenic iron content were seen, and ferroportin was decreased in the duodenum and increased in the spleen. These changes were ameliorated by AST-120 treatment. CKD mice showed iron-deficient anemia, and this was slightly ameliorated by AST-120 treatment. Moreover, mice treated by direct IS administration showed hepatic hepcidin upregulation.

Conclusions: IS participates in the dysregulation of iron metabolism through hepcidin regulation via AhR and oxidative stress in CKD. Removal of IS might be a therapeutic strategy for abnormality of iron metabolism in CKD.

FR-PO350

Endothelial Sirtuin 1 Deficiency Is a Super-Inducer of Syndecan 4 (Synd4): Role of Its Ectodomain in Renal Fibrosis Mark Lipphardt,[2,5] Jong Wook Song,[4] Brian B. Ratliff,[2] Hassan Dihazi,[3] Gerhard A. Mueller,[1] Michael S. Goligorsky.[2] *[1]Georg-August University, Gottingen, Germany; [2]New York Medical College, Valhalla, NY; [3]University Medical Centre Goettingen, Goettingen, Germany; [4]Yonsei University College of Medicine, Millwood, NY; [5]Nephrology & Rheumatology, Universitätsmedizin Göttingen, Göttingen, Germany.*

Background: Syndecans comprise a family of membrane-spanning, glycocalyx-forming proteoglycans with glycosaminoglycans covalently bound to their ectodomain. There is evidence that Synd4 is required for integrin function and wound healing, but mice with the deletion of Synd4 appeared to be protected from renal fibrosis. Synd4 expression is regulated by NF-kB activity while degradation of the latter requires deacetylation by Sirtuin 1 (Sirt1).

Methods: To elucidate the role of Synd4 in fibrosis, we compared wild type and fibrosis-prone endothelial Sirt1-deleted Sirt1^{endo}-/- mice serving as a model of global endothelial dysfunction.

Results: Synd4 transcripts were dramatically increased in Sirt1^{endo}-/- kidneys. UUO further induced it in control but especially in Sirt1^{endo}-/- mouse kidneys. Synd4 ectodomain expression was significantly enhanced after UUO compared to contralateral kidneys, whereas there were no differences in expression of the intracellular domain. We next performed mass-spectrometry analysis of the secretome of renal microvascular endothelial cells (RMVEC) which revealed that Synd4 was highly enriched in TGFβ1-stimulated cells obtained from Sirt1^{endo}-/- mice; notably all detectable peptides were confined to the ectodomain of Synd4. Furthermore, hyperplasia of myofibroblasts accompanied by microvascular rarefaction and overexpression of Synd4 were detected in Sirt1^{endo}-/- mouse kidneys. The ectodomain of Synd4 acted as a chemoattractant for monocytes with higher levels of macrophages and higher expression level of Synd4 detected in the extracellular matrix of Sirt1^{endo}-/- mice. In vitro, ectodomain application resulted in generation of myofibroblasts from cultured renal fibroblasts, while in vivo, subcapsular injection of ectodomain induced interstitial fibrosis.

Conclusions: Based on our experimental results and the existing body of published work, we propose that it is the Synd4 ectodomain rather than Synd4 per se that is partially responsible for fibrosis in UUO and, especially, when it is combined with endothelial dysfunction.

FR-PO351

Class IIa Histone Deacetylase Inhibition Suppresses Renal Fibroblast Activation and Lessens Fibrosis Chongxiang Xiong,[1] Shougang Zhuang.[2,3] *[1]Rhode Island Hospital, Providence, RI; [2]Rhode Island Hospital, Alpert Medical School of Brown University, Providence, RI; [3]Department of Nephrology, Shanghai East Hospital, Tongji University, Shanghai, China.*

Background: Histone deacetylases (HDACs) are a family of enzymes involved in regulation of cellular functions, including proliferation, migration and survival. Class I and III HDACs are associated with renal fibrosis. The role of class II HDAC in this process is poorly understood.

Methods: We examined the role of class IIa HDACs (HDAC- 4, -5, -7, -9) in renal fibroblast activation and fibrosis using MC1568, a highly selective class IIa HDAC inhibitor, and the siRNA specifically targeting individual class IIa HDACs.

Results: Exposing cultured renal interstitial fibroblasts to MC1568, or silencing class IIa HDAC-4 and-7, significantly reduced activation as indicated by decreased a-smooth muscle actin, collagen 1 and fibronectin expression. In a murine model of renal fibrosis induced by unilateral ureteral obstruction (UUO), HDAC-4 was highly expressed whereas expression levels of HDAC-5, -7, -9 were only slightly elevated. MC1568 suppressed deposition of extracellular matrix proteins and renal fibroblast activation. This coincided with reduced numbers of renal epithelial cells arrested at G2/M cell cycle phase and restored expression of Klotho and BMP7 after UUO injury. MC1568 also abrogated UUO-induced phosphorylation of receptor tyrosine kinases (epidermal growth factor and platelet growth factor receptors) and several signaling molecules associated with renal fibrosis, including Smad-3, STAT3, and NF-κB and ERK1/2. Moreover, class IIa inhibition suppressed renal expression of HIF-1α, Notch-1 and -3 and preserved expression of PPAR-alpha and PPAR-gama following UUO.

Conclusions: Class IIa HDACs inhibition may attenuate renal fibrosis by inhibiting profibrotic signaling pathways and preserving expression of renoprotective factors.

Funding: NIDDK Support

FR-PO352

Lysyl Oxidase Like-2 Contributes to Alport Renal Disease Progression Dominic E. Cosgrove,[5] Daniel T. Meehan,[2] Brianna M. Dufek,[4] Duane C. Delimont,[1] Michael Hartnett,[1] Deidre Mackenna,[3] Gretchen Bain.[6] *[1]Boys Town National Research Hospital, Omaha, NE; [2]Boys Town National Research Hospital, Omaha, NE; [3]PharmAkea, San Diego, CA; [4]Boys Town National Research Hospital, Omaha, NE; [5]Boystown National Resident Hospital, Omaha, NE; [6]PharmAkea, Inc, San Diego, CA.*

Background: Lysyl oxidase like-2 (LOXL2) is thought to have both intracellular and extracellular functions. Extracellularly, LOXL2 performs the first step in the formation of crosslinks in collagen and elastin networks, resulting in increased stiffness which promotes the transition of fibroblasts to myofibroblasts. Intracellularly, LOXL2 modifies histones, stabilizes SNAIL, and reduces cell polarity which increases metastatic potential of tumors. LOXL2 promotes liver and lung fibrosis, but nothing is known regarding a role in the kidney. This study explored whether LOXL2 influences kidney disease in Col4a3(-/-) Alport mice.

Methods: LOXL2 protein and mRNA expression in WT versus Alport mice was examined. Alport mice were treated with a small molecule inhibitor (LOXL2i) or vehicle from 2 to 7 weeks of age. Both cortex and glomeruli were analyzed by real time PCR for genes associated with glomerular and interstitial disease, by immunofluorescence (IF) for collagen 1 and CD45 to assess interstitial fibrosis, by IF for fibronectin to score glomerulosclerosis, for mesangial filopodial invasion by IF for laminin α5 and integrin α8, and for albuminuria and BUN. TEM analysis was performed for ultrastructural analysis of the GBM. Lifespan was also assessed.

Results: LOXL2 protein and mRNA (>15-fold) are induced in Col4A3(-/-) Alport kidneys. LOXL2i-treatment significantly reduced interstitial fibrosis (by >50%) and mRNA expression for the fibrosis markers MMP-2, MMP-9, TBF-β1, and TNF-α in the interstitium. Additionally, LOXL2i treatment also reduced glomerulosclerosis (by

>75%) and mRNA expression of MMP-10, MMP-12, and MCP-1 in the glomeruli. Both albuminuria and BUN were significantly reduced in treated mice. Mesangial filopodial invasion of the capillary tufts was blunted, and the GBM ultrastructure was normalized. There was no effect on lifespan.

Conclusions: LOXL2 plays an important role in promoting both glomerular and interstitial pathogenesis associated with Alport syndrome in mice. LOXL2i may provide beneficial effects for treating human Alport syndrome and may extend to other etiologies of CKD given strong association between renal fibrosis and outcomes in end stage renal disease.

Funding: Commercial Support - PharmAkea Inc.

FR-PO353

Dysfunction of the Intestinal Carnitine/Organic Cation Transporter 1 in CKD Impairs an Antioxidant Effect of Ergothioneine Yasuyuki Shinozaki, Kengo Furuichi, Tadashi Toyama, Shinji Kitajima, Akinori Hara, Yasunori Iwata, Norihiko Sakai, Miho Shimizu, Takashi Wada. *Kanazawa University, Ishikawa, Japan.*

Background: Carnitine/organic cation transporter 1 (OCTN1) is a specific transporter of the food-derived antioxidant, ergothioneine (ERGO). ERGO absorbed by intestinal OCTN1 is distributed systemically through the bloodstream and incorporated into each organ by OCTN1. The OCTN1–ERGO axis is an adaptive antioxidant system that protects against further damage caused by oxidative stress. However, the role of OCTN1–ERGO axis in chronic kidney disease (CKD) progression remains unclear.

Methods: The ability of the intestine to absorb ERGO and OCTN1 expression were evaluated in CKD mice using the everted sac method, RT-PCR, western blot and immunohistochemistry. To identify the role of the OCTN1–ERGO axis in CKD, we evaluated kidney damage and oxidative stress in OCTN1-knockout CKD mice. To assess the protective effects of ERGO in CKD, we checked the antioxidant effect of ERGO using mProx24 cells. Moreover, we measured ERGO levels in the blood of CKD patients.

Results: Although the mRNA and protein expression of OCTN1 did not change as CKD progressed, the localization of OCTN1 to the apical cellular membrane was reduced in the intestines of CKD mice. OCTN1-knockout CKD mice showed enhanced kidney damage, interstitial fibrosis, and oxidative stress. An *in vitro* study using mProx24 cells treated with indoxyl sulfate, which was pretreated with ERGO, revealed a dose-dependent attenuation of oxidative stress. In CKD patients, ERGO levels decreased as CKD progressed and that there was a positive correlation between ERGO and eGFR levels. ERGO levels were restored 10 months after kidney transplants in three patients.

Conclusions: CKD attenuated the function of the OCTN1–ERGO axis because of the dysfunction of intestinal OCTN1. These results suggested that a novel inter-organ interaction mediated by transporters is associated with CKD progression.

FR-PO354

Myeloid TGFβ Receptor Promotes Fibrosis after AKI Ming-Zhi Zhang, Jessica M. Overstreet, Yinqiu Wang, Aolei Niu, Suwan Wang, Leslie S. Gewin, Raymond C. Harris. *Vanderbilt University Medical Center, Nashville, TN.*

Background: Transforming growth factor-β (TGF-β) is a central mediator of fibrosis. TGF-β signals through a receptor complex composed of two type I and two type II transmembrane subunits. Renal macrophages are major producers of TGF-β1 and play important roles in the development of fibrosis after acute kidney injury (AKI). However, a previous study found that deletion of myeloid TGF-β1 did not prevent fibrosis after severe renal ischemia/reperfusion (I/R) or obstructive injury. In the present study we examined whether deletion of myeloid type II TGF-ß receptors (Tgfbr2) affected development of fibrosis after AKI.

Methods: Wild type ($Tgfbr2^{f/f}$) or KO (CD11b-Cre;$Tgfbr2^{f/f}$ or LysM-Cre;$Tgfbr2^{f/f}$) mice (male, 3 months old, C57BL/6) were used. For a severe I/R AKI model, the animals were uninephrectomized, immediately followed by unilateral I/R with renal pedicle clamping for 29 min. Mice were sacrificed after 3 weeks. For an AKI-chronic kidney disease (CKD) model, unilateral I/R with renal pedicle clamping for 31 min was performed, with contralateral uninephrectomy on the 8th day, and animal sacrifice on day 28.

Results: Deletion of macrophage/dendritic cell Tgfbr2 did not affect functional recovery from AKI, as indicated by similar rates of BUN and creatinine recovery. However, deletion of Tgfbr2 in macrophages/dendritic cells led to dramatic decreases in development of fibrosis at 3 weeks in the severe AKI model, as indicated by quantitative picro-sirius red staining and Masson's trichrome staining. Deletion of Tgfbr2 in macrophages/dendritic cells was associated with decreased expression levels of profibrotic and fibrotic components, including CTGF, α-SMA and collagen I. In addition, macrophage/dendritic cell Tgfbr2 deletion led to marked decreases in macrophage and T cell infiltration and oxidative stress. Macrophage/dendritic cell Tgfbr2 deletion also markedly reduced development of fibrosis in the AKI-CKD model. In renal macrophages/dendritic cells isolated with CD11b microbeads, Tgfbr2 deletion led to decreased expression levels of M2 markers and increased M1 markers.

Conclusions: These studies indicate that myeloid Tgfbr2 promotes fibrosis after severe AKI at least in part by promotion of M2 polarization and suggest that activation of myeloid TGF-β receptors by TGF-β produced by non-myeloid cell types plays an important role in this process.

Funding: NIDDK Support

FR-PO355

Protective Effect of Vascular Endothelial Growth Factor-C on Renal Interstitial Fibrosis through Lymphangiogenesis in Mouse Unilateral Ureteral Obstruction Shoko Hasegawa,[2] Toshiaki Nakano,[2] Kumiko Torisu,[3] Akihiro Tsuchimoto,[2] Masahiro Eriguchi,[2] Kosuke Masutani,[2] Kazuhiko Tsuruya,[4] Takanari Kitazono.[1] *[1]Department of Medicine and Clinical Science, Fukuoka, Japan; [2]Kyushu University, Higashi-ku, Japan; [3]Kyushu University Hospital, Fukuoka, Japan; [4]None, Fukuoka, Japan.*

Background: Renal fibrosis is the final common pathway of chronic kidney diseases. Lymphatic vessel (LV) proliferation is found in human renal diseases and other fibrotic diseases, suggesting that lymphangiogenesis is associated with the progression or suppression of kidney diseases. However, the purpose of LV proliferation is not completely understood. We have previously reported the effect of vascular endothelial growth factor (VEGF)-C on lymphangiogenesis and fibrosis in the mouse kidney using the unilateral ureteral obstruction (UUO) model. At this time, we additionally investigated the effect of VEGF-C on inflammation and M1 and M2 macrophages. Furthermore, we investigated the effect of VEGF-C in vitro using lymphatic endothelial cells (LECs) by VEGF-C administration.

Methods: We continuously administered recombinant human VEGF-C to UUO model mice using an osmotic pump (UUO+VEGF-C group) for 14 days. We investigated the lymphangiogenesis (LYVE-1 staining, western blotting of VEGFR-3), inflammation (F4/80 staining, MCP-1 staining, ym-1 staining, western blotting of TGF-β1) and fibrosis (Sirius-red staining, western blotting of collagen 1). Additionally, we investigated the proliferation and adhesion molecules (ICAM-1, VCAM-1, E-selectin) of cultured LECs by administration of VEGF-C.

Results: Lymphangiogenesis was significantly induced in the UUO+VEGF-C group compared with the vehicle group, despite similar numbers of capillaries in both groups. The number of infiltrating macrophages (especially M1 macrophages) and levels of inflammatory cytokines and transforming growth factor-β1 were reduced in the UUO+VEGF-C group compared with the vehicle group. Renal fibrosis was consequently attenuated in the UUO+VEGF-C group. In cultured LECs, administration of VEGF-C increased the proliferation of LECs and expression of adhesion molecules.

Conclusions: These findings suggest that induction of lymphangiogenesis ameliorates inflammation and fibrosis in the renal interstitium. Enhancement of the VEGF-C signaling pathway in LECs may be a therapeutic strategy for renal fibrosis.

FR-PO356

Xanthine Oxidoreductase Inhibitor, Topiroxostat, Had a Renoprotective Role under Decreased Angiotensin II Type 1a Receptor Expression Atsuko Ikemori,[3,1] Takeshi Sugaya,[2] Mikako Hisamichi,[4] Kenjiro Kimura,[5] Yugo Shibagaki.[1] *[1]Division of Nephrology and Hypertension, St Marianna University Hospital, Kawasaki, Japan; [2]St. Marianna Univ, Tokyo, Japan; [3]Anatomy, St. Marianna University School, Kawasaki, Kanagawa, Japan; [4]St.Marianna university school of medicine, Kawasaki, Japan; [5]Tokyo Takanawa Hospital, Tokyo, Japan.*

Background: Xanthine oxidoreductase (XOR) inhibitors may function as renoprotective agents as well as antioxidants via decrease in oxidative stress produced by renal xanthine oxidase converted from XOR. The aim of this study was to confirm the renoprotective effect of the XOR inhibitor, topiroxostat (Top) under decreased angiotensin II type 1a (AT1a) receptor expression in the model of renal injury caused by adenine.

Methods: To evaluate the degree of tubular damage using urinary liver-type fatty acid-binding protein (L-FABP) under decreased AT1a expression, we used AT1a receptor knockdown hetero and human L-FABP chromosomal transgenic (Tg) mice ($AT1a^{+/-}$L-$FABP^{+/-}$). Male $AT1a^{+/-}$L-$FABP^{+/-}$ mice were divided into two groups: the adenine diet group (n=24) was given a diet containing only 0.2% w/w adenine, and the normal diet group (n=5) was given a normal diet. When renal dysfunction was confirmed in the adenine diet group 4 weeks after starting the diet, the adenine diet group was further divided into three groups. The adenine diet group (n=8) was continuously given only the adenine diet. Each group receiving high-dose (3mg/kg) or low-dose (1mg/kg) Top (Top-H, n=8, Top-L, n=8) was given the adenine diet including the drug for another 4 weeks.

Results: The levels of renal XOR, renal dysfunction, urinary L-FABP, tubulointerstitial damage, hypoxia, and oxidative stress were decreased or attenuated after treatment with Top compared with the adenine diet group.

Conclusions: In conclusion, Top attenuated renal damage under decreased AT1a expression in the adenine-induced renal injury model. Combination treatment with an XOR inhibitor and an RAS inhibitor might be a useful strategy for prevention of the progression of CKD.

Funding: Commercial Support - Sanwa Kagaku Kenkyusho Co., Ltd., Tokyo, Japan.

FR-PO357

Febuxostat Attenuates ER Stress Mediated Kidney Injury in a Rat Model of Hyperuricemic Nephropathy Ying Fan,[1] Li He,[1] Wenzhen Xiao,[2] Jiejun Wen,[1] Yang Dong,[1] John C. He,[2] Niansong Wang.[1] *[1]Nephrology, Shanghai 6th People's Hospital affiliated to Shanghai Jiaotong University, Shanghai, China; [2]Mount Sinai School of Medicine, New York, NY.*

Background: Hyperuricemia contributes to the renal tubular injury and kidney fibrosis. Febuxostat, a novel inhibitor of xanthine oxidase, has been widely used for

the treatment of hyperuricemia and prevention of gout. Recent studies suggested that Urate-lowering therapy (ULT) by Febuxostat might also have cardiovascular and renal benefits, yet the the mechanism of this protective effect is unknown. Endoplasmic reticulum (ER) stress has been well recognized as one of the important mechanisms in the onset and progression of many kidney diseases. In recent studies, we identified a novel ER-associated gene, reticulon-1A (RTN1A), which is associated with the progression of kidney diseases. However, the exact role of RTN1A and ER stress in hyperuricemia induced kidney disease hasn't been fully studied.

Methods: In the present study, we studied the expression of RTN1A and other ER Stress markers in kidney biopsies of patients with hyperuricemia-related kidney injury. We determined the role of RTN1A and ER stress in uric acid induced renal tubular cell injury *in vitro* as well as in a rat model of hyperuricemic nephropathy (HN). We also examined whether treatment of Febuxostat diminished ER stress and apoptosis of renal tubular cells and attenuated kidney injury in HN rat model.

Results: We found the expression of RTN1A and ER stress markers was significantly increased in kidney biopsies of patients with hyperuricemia-related kidney injury. In HN rat model established by oral administration of a mixture of adenine and potassium oxonate, increased expression of RTN1A and ER stress were shown in tubular and interstitial compartment of rat kidneys. Treatment of Febuxostat not only attenuated ER stress mediated renal tubular injury and tubulointerstitial fibrosis, but also reduced uric acid crystals deposition in HN rat kidneys. *In vitro*, Febuxostat also suppressed uric acid-induced ER stress and apoptosis in cultured tubular cells.

Conclusions: In conclusion, RTN1A and ER stress mediate tubular cell injury and kidney fibrosis in hyperuricemia induced nephropathy. ULT with Febuxostat attenuates uric-acid induced ER stress in renal tubular cells and the progression of HN. This study suggests a therapeutic role of Febuxostat in hyperuricemia-related CKD.

Funding: Government Support - Non-U.S.

FR-PO358

SOX9 Is a Critical Regulator of Extracellular Matrix Deposition during Kidney Fibrosis Sayyid M. Raza,[1] James P. Pritchett,[3] Neil Hanley,[1] Philip A. Kalra,[2] Karen Piper hanley.[1] *[1]University of Manchester, Manchester, United Kingdom; [2]Salford Royal Hospital NHS Trust, Salford, United Kingdom; [3]Manchester Metropolitan University, Manchester, United Kingdom.*

Background: Renal fibrosis is a major cause of morbidity and mortality and a common feature of most chronic kidney disease (CKD). It is characterised by extracellular matrix (ECM) secretion from effector cells (myofibroblasts) resulting in tissue dysfunction and scarring. Discovering how to block scar production represents a very attractive therapeutic avenue for much needed antifibrotic drug development.

Methods: Primary pericytes were extracted from wild type mice. Cells were analysed by immunohistochemistry, western blotting and qPCR. Kidney fibrosis was induced in vivo by 2 week unilateral ureteric obstruction (UUO). SOX9-loss was achieved through tamoxifen injections of Sox9fl/fl; RosaCreERT2 mice. Fibrosis was assessed histologically in mice and human kidney fibrotic tissue.

Results: In wild type fibrotic kidneys SOX9 was increased and detected in α-SMA positive cells, demarcating activated myofibroblasts, along with collagen type 1 (COL1) rich fibrotic tracts disrupting normal tissue. In vitro, primary mouse pericytes expressed nuclear SOX9 surrounded by α-SMA. SOX9 knockdown in activated pericytes using RNA interference caused a commensurate reduction in COL1 protein expression (~60%), whereas the pro-fibrotic cytokine transforming growth factor-beta (TGF-β) induced expression of SOX9 by 2.5 fold in pericytes and 2.3 fold in the rat fibroblast cell line, NRK-49F. To model the stiffening environment of fibrotic kidneys we cultured pericytes on 1, 4 and 12 KPa hydrogels where α-SMA, SOX9 and the mechanosensitive factor YAP1 became robustly expressed at 12KPa. Moreover, YAP1 was also increased in UUO kidneys. To support a role for SOX9 in kidney fibrosis, following UUO-fibrosis mice lacking SOX9 had significantly reduced fibrosis by picrosrius red quantification (35% reduction) and α-SMA positive myofibroblasts were reduced by 45%. Importantly, in various human kidney diseases (Membranous nephropathy, Diabetic nephropathy, IgA nephropathy) fibrotic areas were associated with SOX9 positivity histologically.

Conclusions: These data support a pro-fibrotic role for SOX9 (similar to other organs) in kidney fibrosis where it is regulated by TGF-β and the mechnosignalling factor YAP1. Moreover, this provides an interesting opportunity for inhibiting SOX9 or its dependent pathways for anti-fibrotic therapy.

FR-PO359

Lymphocytes and PD-1 in Aristolochic Acid Nephropathy Gilbert R. Kinsey, Brian K. Stevens, Mana Yang. *Division of Nephrology; Center for Immunity, Inflammation and Regenerative Medicine, Univerisity of Virginia, Charlottesville, VA.*

Background: Aristolochic acid is a nephrotoxic agent previously used in traditional Chinese medicine and found as an adulterant in some herbal supplements. Clinical studies have revealed extensive inflammation in kidneys of patients with aristolochic acid nephropathy (AAN). AAN involves an acute toxic injury to tubular epithelial cells that leads to immune cell infiltration and progressive fibrosis over time. Programmed death 1 (PD-1) is a co-stimulatory molecule that limits the activation of T cells and lymphocytes have important roles in other forms of kidney injury, but their mechanistic role in AAN has not been previously reported.

Methods: Male wild-type (WT), PD-1 KO and lymphocyte-deficient RAG-1 KO mice (all on C57Bl/6 background) were treated with AA 5 mg/kg by i.p. injection. Five and 14 days after initiating AA treatment renal function, injury and inflammation were assessed.

Results: Over time, a marked infiltration of CD45+ immune cells, especially T lymphocytes was observed in kidneys of WT mice after AA treatment (For example: CD4 T cells/g: Vehicle: 77,000 ± 11,000 vs. AA: 1,860,000 ± 250,000 at day 14). CD8 T cell, mononuclear phagocyte and PMN cell numbers were also elevated at day 14. Five days after AA treatment there were no differences in renal function between WT, PD-1 KO or RAG-1 KO mice as measured by creatinine or BUN levels. At day 14, RAG-1 KO mice had significantly higher BUN levels, while PD-1 KO mice had lower BUN levels compared to WT AA-treated mice (BUN in (mg/dl) in WT: 38 ± 7 vs. RAG-1 KO: 87 ± 11 vs. PD-1 KO: 16 ± 1). At day 14, RAG-1 KO kidneys exhibited higher innate leukocyte accumulation compared to WT mice. Conversely, PD-1 KO kidneys had lower innate leukocytes and dramatically reduced CD3+CD4+ T cell infiltration.

Conclusions: These results suggest that lymphocytes are protective in this intermediate-length exposure of mice to AA. Unexpectedly, PD-1 deficiency ameliorated renal dysfunction and inflammation, suggesting a pro-inflammatory role for this co-stimulatory molecule in AAN.

Funding: NIDDK Support

FR-PO360

Sonic Hedgehog Promotes Kidney Injury by Activating Renin-Angiotensin System via a Non-Canonical Pathway Songzhao Wu,[1] Lili Zhou,[1] Chunhong Wang,[1] Youhua Liu.[2] *[1]Division of Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China; [2]Department of Pathology, University of Pittsburgh, Pittsburgh, PA.*

Background: Sonic hedgehog (Shh) is a lipid-modified glycoprotein that plays a crucial role in embryonic development. Earlier studies indicate that Shh is a tubule-derived growth factor that specifically targets interstitial fibroblasts via a paracrine mechanism after various kidney injuries. Using hedgehog-responding reporter mice, studies show that kidney tubular epithelial cells are not responsive to hedgehog ligands via Gli-dependent canonical pathway. Whether Shh can target tubular epithelium via other mechanisms, however, remains to be defined.

Methods:

Results: In this study, we investigated this issue using both in vitro and in vivo approaches. We found that in cultured kidney proximal tubule cells (HKC-8), recombinant Shh protein induced multiple components of renin-angiotensin stystem (RAS), including renin, angiotensin-converting enzyme, and angiotensin II type 1 receptor (AT1). Shh also activated MAPK by inducing ERK, JNK and p38 phosphorylation, as well as its upstream PLC phosphorylation and activation. This cascade of events was dependent on Smo receptor, as either cyclopamine (CPN), a small molecule Smo inhibitor, or MAPK inhibitors abolished the Shh-mediated activation of MAPK and induction of RAS components, suggesting that Shh activates RAS via Gli-independent, MAPK-dependent non-canonical pathway. In vivo, overexpression of Shh aggravated the glomerular injury, interstitial matrix proteins expression and deposition, and renal fibrosis at 6 weeks after 5/6 nephrectomy. Shh also promoted the activation of PLC and MAPK and induction of multiple RAS proteins, and elevated blood pressure. However, CPN therapy attenuated glomerular lesions, reduced renal fibrosis. CPN also inhibited renal MAPK activation, repressed RAS protein expression and normalized blood pressure.

Conclusions: Collectively, these studies demonstrate that tubule-derived Shh can target tubular epithelium by inducing RAS protein expression via PLC/MAPK-dependent non-canonical pathway. Our results indicate that blockade of Shh signaling can repress multiple RAS genes, thereby leading to amelioration of kidney injury.

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FR-PO361

STAT3 Regulates Fibrogenic Signaling in Pericytes and Activates Migration, Differentiation, and Secretion of Pro-Fibrotic Cytokines Amrendra K. Ajay,[1,3] Shruti Vig,[2] Akinwande A. Akinfolarin,[1,3] Venkata Sabbisetti,[1,3] Joseph V. Bonventre.[1,3] *[1]Brigham and Women's Hospital, Boston, MA; [2]Brigham and women's hospital, Boston, MA; [3]Medicine, Harvard Medical School, Boston, MA.*

Background: STAT3 is a key transcription factor, which plays an important role in cell proliferation, cellular pluripotency, and differentiation. Here, we investigated the pathophysiological role of STAT3 signaling in kidney fibrosis.

Methods: Stromal cell-specific STAT3 deletion was performed by breeding STAT3 floxed mice with FoxD1 Cre mice. Kidney fibrosis was induced by injecting a single dose of 300 mg/kg body weight folic acid (FA) or 5 mg/kg body weight aristolochic acid (AA). Immunostaining for STAT3 phosphorylations (Ser727 and Tyr705) was performed on mice kidneys and 10T1/2 cells. We developed two activation mutants and one-inactivation mutant of STAT3 using CRISPR-Cas9 technology in pericytes-like (10T1/2) cells. Cell migration was evaluated with Boyden chambers and wound scratch assays. Cell proliferation was measured by MTT assay. RT-PCR and western blotting were used to measure STAT3 dependent genes and luminex-based assay of cytokines (CTGF, TGF-β and IL-6) were performed to quantitate pro-fibrotic cytokines.

Results: STAT3 phosphorylation was increased in tubular epithelial cells and pericytes of 5 human subjects with chronic kidney disease. Deletion of STAT3 in pericytes protects against FA or AA-induced kidney fibrosis at 7 and 14 days post-treatment. Fibrotic markers, including fibronectin, collagen1a1 and α-smooth muscle actin (α-SMA), were reduced in STAT3 knockout mice. *In vitro*, CRISPR-Cas9 mediated activation of STAT3 caused increased cell migration whereas the inhibition of STAT3 was associated with decreased migration of 10T1/2 cells. Treatment of cells with TGF-β increased the production of profibrotic cytokines and differentiation of 10T1/2 cells to

myofibroblasts. Pretreatment with stattic, a small molecule inhibitor of STAT3 inhibited both cytokines production and cell differentiation.

Conclusions: Inhibition of STAT3 in pericytes protects mice from kidney fibrosis and the specific inhibition of STAT3 signaling in pericytes prevents their differentiation into myofibroblasts.

Funding: NIDDK Support

FR-PO362

FHL2 Promotes Fibroblast Activation and Kidney Fibrosis Involving the Activation of β-Catenin Signaling Ying Duan,[3] Ting Cai,[1] Junwei Yang,[4] Weichun He.[2] *[1]Nanjing Medical University, NANJING, China; [2]Nanjing Medical University, 2nd Affiliated Hospital, Nanjing, China; [3]Nanjing medical university, Nanjing, China; [4]Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.*

Background: Four-and-a-half LIM domains protein 2 (FHL2) is an adaptor protein and has been implicated in β-catenin signaling. Previously, we found that FHL2 may mediate TGF-β1-induced tubular epithelial-to-mesenchymal transition through activating β-catenin signaling. The FHL2-positive cells were observed both in renal tubule and interstitium in mice with obstructive nephropathy. However, the potential role and mechanisms for FHL2 in fibroblast activation and kidney fibrosis remains to be clarified.

Methods: The regulation and function of FHL2 in TGF-β1-stimulated fibroblast activation were examined in cultured NRK-49F cells. Mice with fibroblast-specific deletion of FHL2 were generated by mating FHL2-floxed mice with S100a4-Cre transgenic mice. Mouse model of kidney fibrosis was established by unilateral ureteral obstruction (UUO).

Results: TGF-β1 induced FHL2 mRNA and protein expression in a time- or dose-dependent manner in cultured cells. Ectopic expression of FHL2 increased α-smooth muscle actin (α-SMA), type I collagen and fibronectin expression, whereas knockdown of FHL2 *via* small interfering RNA partially suppressed TGF-β1-induced expression of α-SMA, type I collagen and fibronectin. Overexpression of FHL2 led to activation of β-catenin signaling, which is evidenced by an increase in β-catenin nuclear translocation, β-catenin-mediated gene transcription, and expression of β-catenin target genes such as Snail and c-Myc. Treatment with TGF-β1 induced a physical interaction between FHL2 and β-catenin. *In vivo*, FHL2 was induced and β-catenin was activated in renal interstitial myofibroblasts from mice with obstructive nephropathy. Compared with wild-type littermates, the kidneys with fibroblast-specific ablation of FHL2 exhibited less interstitial extracellular matrix deposition at 2 weeks after UUO.

Conclusions: Our results suggest that FHL2, through activating β-catenin signaling, plays a critical role in mediating TGF-β1-induced fibroblast activation and contributes to the development and progression of kidney fibrosis, and FHL2 could be a potential future therapeutic target for chronic kidney disease.

Funding: Government Support - Non-U.S.

FR-PO363

Fibroblast-Specific p90RSK Promotes Kidney Fibrosis Ling Lin, Chaowen Shi, Kebin Hu. *Penn State University College of Medicine, Hershey, PA.*

Background: The 90 kDa ribosomal s6 kinases (RSKs) are a group of serine/threonine kinases that regulate diverse cellular process, such as cell growth, cell motility, and cell survival. There are 4 RSK isoforms (RSK1-4), of which RSK1 is also designated as p90RSK and predominantly expressed in the kidney. p90RSK is recently shown to promote diabetic endothelial dysfunction and atherosclerosis, however, the role of p90RSK in the development and progression of chronic kidney disease has never been investigated *in vivo*.

Methods: We generated a novel fibroblast-specific p90RSK trangenic mouse strain and investigated the role of p90RSK in kidney fibrosis.

Results: We examined the expression of phospho-specific and total p90RSK during the course of chronic kidney injury in the classic unilateral ureter obstruction (UUO) model. It's found that p90RSK is dramatically activated, as indicated by phosphorylation of p90RSK, in the obstructed kidneys as early as 3 days after UUO; and the activation continued increasing until 14 days after UUO when the mice were sacrificed. Whereas, there is little difference in the level of total p90RSK between the obstructed and control kidneys. Intriguingly, double immune staining analysis found that the activation of p90RSK in the interstitium is largely induced in the FSP-1-positive fibroblasts. We generated fibroblast-specific p90RSK transgenic mouse, p90RSK-Tg, and found that this mouse has normal phenotype as the littermate control. However, when UUO was induced in the p90RSK-Tg mice, it was found that p90RSK-Tg mice display significantly worse tubular damage, and dramatically increased deposition of extracellular matrix components such as collagen and fibronectin than that of their littermates. Western blot analysis also showed that p90RSK-Tg mice had decreased E-cadherin expression and *de novo* activation of alpha-SMA comparing to their littermates.

Conclusions: It is clear that fibroblast-specific p90RSK activation promotes kidney fibrosis, possibly, through the epithelial-to-mesenchymal transition mechanism.

Funding: NIDDK Support

FR-PO364

A Novel, Highly Specific TGFβ1 Inhibiting Antibody Demonstrates Antifibrotic Activity without Cardiotoxicity Stefan Wawersik, Thomas Schurpf, Abhishek Datta, Christopher Littlefield, Christopher Chapron, Kathy Y. Morgan, Constance Martin, Kimberly Long, Allan Capili, Kaleigh Pavlik, Justin W. Jackson, Gregory Carven, Alan Buckler. *Scholar Rock Inc, Cambridge, MA.*

Background: Transforming growth factor-β1 (TGFβ1) has diverse biological functions, including regulation of immune response and tissue homeostasis. TGFβ1 activation has been associated with diseases including kidney fibrosis, where chronic activation is a key driver. Because of high homology between the TGFβ1 growth factor and its close relatives TGFβ2 and TGFβ3, truly TGFβ1-specific inhibitors have remained elusive. Pan-TGFβ inhibition, on the other hand, can cause dose-limiting heart valvulopathies, leading to concerns with long-term dosing. TGFβs are expressed as pro-proteins that are proteolytically cleaved into a C-terminal growth factor and an N-terminal prodomain that remains noncovalently associated with the growth factor, preventing receptor binding. This latent TGFβ complex resides on cells or in the extracellular matrix until it is activated by integrins, freeing the growth factor and allowing receptor binding.

Methods: To identify TGFβ1-specific antibodies, we targeted the prodomain, which shares much lower homology to TGFβ2 and TGFβ3 than the growth factor.

Results: We identified SR-AB1, a monoclonal antibody that binds latent TGFβ1 with no detectable binding to latent TGFβ2 or TGFβ3. SR-AB1 blocks latent TGFβ1 activation by αVβ6 or αVβ8 integrins, providing specificity unachieved by biologics that target the TGFβ1 growth factor/receptor interaction. SR-AB1 further inhibits latent TGFβ1 complexed with all four known TGFβ-presenting molecules, allowing targeting of TGFβ1 in multiple tissues. SR-AB1 blocks activation of endogenous TGFβ1 in a number of primary cells, including dermal myofibroblasts and hepatic stellate cells. Critically, while pan-TGFβ inhibitors show evidence of valvulopathy or other cardiotoxicity, SR-AB1 is free of such toxicities in 1 and 4 week rat studies. Finally, we tested the *in vivo* efficacy of TGFβ1 inhibition via this novel mechanism in the UUO model of kidney fibrosis, showing that SR-AB1 suppresses fibrosis to levels similar to those achieved by pan-TGFβ inhibition.

Conclusions: Our data show that isoform-specific inhibition of latent TGFβ1 is efficacious in a preclinical fibrosis model and has a superior safety profile compared to pan-TGFβ inhibition.

Funding: Commercial Support - Scholar Rock, Inc.

FR-PO365

Transplantation of Amniotic Fluid-Derived Stem Cells Preconditioned with Glial Cell Line–Derived Neurotrophic Factor Alleviates Renal Interstitial Fibrosis Dong Sun,[1] Shulin Li,[1] yuan Zhao,[2] Zhuojun Wang,[1] Jia Wang,[1] Caixia Liu.[1] *[1]Affiliated Hospital of Xuzhou Medical University, Xuzhou, China; [2]Xuzhou Medical University, Xuzhou, China.*

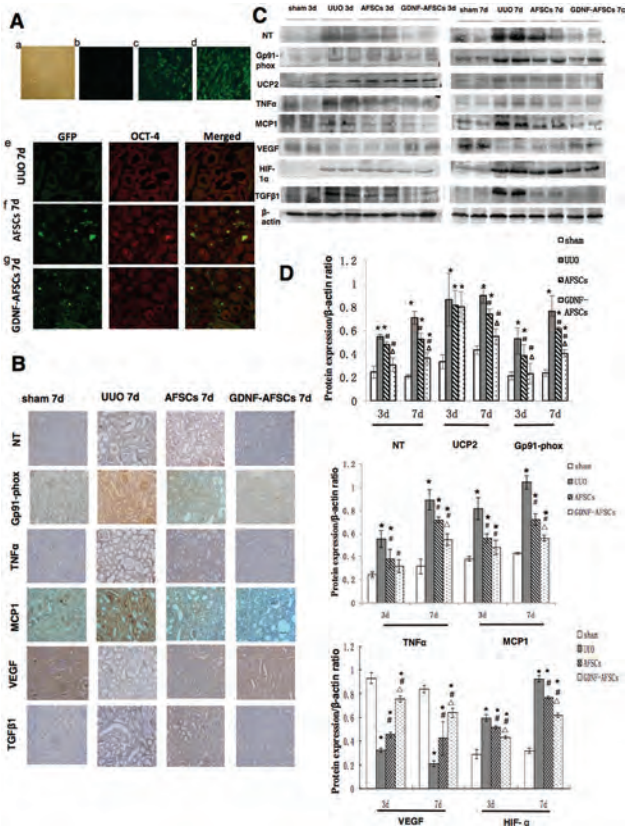
Background: The aim of the present study was to determine whether transplantation of glial cell line–derived neurotrophic factor (GDNF)–modified AFSCs is more useful than transplantation of unmodified AFSCs for the treatment of renal interstitial fibrosis.

Methods: A unilateral ureteral obstruction (UUO) model was established in mice. Either GDNF-AFSCs or AFSCs were transplanted into nu/nu mice via their caudal veins. The 48 mice (12 each group) were randomly assigned to sham-operation group (sham), UUO-saline solution group (UUO), AFSCs transplantation group (AFSCs) and GDNF-modified AFSCs transplantation group (GDNF-AFSCs). GFP fluorescent staining was used for the frozen sections in order to track the transplated AFSCs in the kidney under a fluorescence microscope. The oxidative, inflammatory, endothelial and mitochondrial makers were measured after 3 and 7 days transplantation.

Results: GDNF-AFSCs noticeably suppressed oxidative stress and inflammation; additionally, GDNF-AFSCs positively regulated peritubular capillaries (PTCs), vascular endothelial growth factor (VEGF), hypoxia inducible factor-1α (HIF-1α), transforming growth factor-β1 (TGF-β1) protein levels and mitochondrial factors.

Conclusions: GDNF promotes the abilities of AFSCs to inhibit inflammatory and oxidative stress effects, repair renal microvessels, relieve tissue hypoxia and mitochondrial damage and alleviate renal interstitial fibrosis.

Funding: Government Support - Non-U.S.



A. Culture of AFSCs, lentivirus vector transfection and immunofluorescent localization of frozen section in AFSC transplanted kidney.(B-D). Immunohistochemical staining (40×) and Western blot analysis of oxidative, inflammatory and endothelial markers.

FR-PO366

The Role of β-Catenin/Foxo in Renal Fibrosis Padmashree Rao,[1] Min Pang,[3] Xi Qiao,[3] Hong Yu,[1] Hailong Wang,[3] Min Hu,[1] Qi Cao,[1] Yiping Wang,[1] Chow H. P'ng,[5] Brian J. Nankivell,[4] Vincent W. Lee,[4] Stephen I. Alexander,[2] Guoping Zheng,[1] David C. Harris.[1,4] *[1]Centre for Transplant and Renal Research, Westmead Institute for Medical Research, University of Sydney, Sydney, NSW, Australia; [2]Centre for Kidney Research, Children's Hospital at Westmead., Sydney, NSW, Australia; [3]Shanxi Medical University, Taiyuan, China; [4]Westmead Hospital, Westmead, NSW, Australia; [5]Department of Tissue Pathology and Diagnostic Oncology, ICPMR, Westmead Hospital, Westmead, NSW, Australia.*

Background: TGF-β causes fibrosis by cross-talk with major profibrotic pathways. β-catenin is a common co-factor in different TGF-β signalling pathways. β-catenin binds to TCF to activate profibrotic genes, while β-catenin also binds to Foxo in competition with TCF. We propose that promoting β-catenin/Foxo will protect against β-catenin/TCF mediated profibrotic changes and kidney fibrosis.

Methods: Human kidney biopsies from kidney transplant and diabetic nephropathy patients were assessed for β-catenin/Foxo and β-catenin/TCF interactions in relation to kidney fibrosis. Mouse tubular epithelial C1.1 cells were treated with TGF-β1 with or without ICG-001 (5μM), an inhibitor of β-catenin/TCF. Foxo1 and TCF1 were knocked out by CRISPR/Cas9-mediated gene knockout. We evaluated kidney fibrosis in vivo in the unilateral ureteric obstruction (UUO) model. Profibrotic changes were examined by Western blot and immunofluorescence. Duolink - Proximity Ligation Assay (PLA) and co-immunoprecipitation assays (co-IP) were used to examine β-catenin/Foxo and β-catenin/TCF interactions.

Results: PLA of human kidney biopsies showed that β-catenin/Foxo correlated negatively (r=-0.785) whilst β-catenin/TCF correlated positively (r=0.679) with kidney fibrosis score (P<0.01). co-IP and PLA showed that ICG-001 promoted β-catenin/Foxo interaction by inhibiting β-catenin/TCF binding in TGF-β1-treated C1.1 cells. TGF-β1-induced β-catenin/TCF activity and expression of fibrotic genes (vimentin, N-cadherin, collagen I, III & IV) were reduced by ICG-001 and TCF1 knockout, while Foxo1 knockout prevented the reduction of the fibrotic gene expression. Kidney fibrosis was significantly reduced in UUO mice treated with TGF-β1 and ICG-001, which redirected TGF-β1 signalling from β-catenin/TCF to β-catenin/Foxo1 as shown by PLA.

Conclusions: These results indicate that β-catenin/Foxo plays a protective role against TGF-β's profibrotic activity by inhibiting β-catenin/TCF interaction and thereby preventing kidney fibrosis.

Funding: Government Support - Non-U.S.

FR-PO367

Inhibition of p300/CBP-Associated Factor Attenuates Renal Tubulointerstitial Fibrosis through Modulation of NF-kB and Nrf2 Sungjin Chung,[1,2] Zhilian Li,[1,3] Soojeong Kim,[4] Seok Joon Shin,[2] Cheol Whee Park,[2] Chul Woo Yang,[2] Yong-Soo Kim,[2] Eun Sil Koh.[2] *[1]Division of Nephrology, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN; [2]Department of Internal Medicine, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea; [3]Department of Nephrology, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China; [4]Department of Biochemistry, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea.*

Background: p300/CBP-associated factor (PCAF), a histone acetyltransferase, is involved in many cellular processes such as differentiation, proliferation, apoptosis and reaction to cell damage by modulating the activities of several genes and proteins through acetylation of either histones or transcription factors. Here, we examined a pathogenic role of PCAF and its potential as a novel therapeutic target in the progression of renal tubulointerstitial fibrosis induced by unilateral ureteral obstruction.

Methods: After UUO surgery, male C57BL/6 mice were administered either the PCAF inhibitor garcinol or a vehicle by intraperitoneal injection once a day for 3 or 7 days. Renal tubular epithelial cells (HK-2) were transfected with siRNA-PCAF and analyzed for expression of pro-fibrotic factors.

Results: Administration of garcinol reversed an increase in renal expression of total PCAF and histone 3 lysine 9 acetylation, and it reduced positive areas of trichrome and α-smooth muscle actin and collagen content in UUO kidneys. The increased mRNA levels of transforming growth factor-β1, matrix metalloproteinase (MMP) 2, MMP9 and fibronectin in obstructed kidneys was significantly reduced by garcinol treatment. Furthermore, garcinol suppressed nuclear factor-κB (NF-κB) and pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6 whereas it elevated nuclear expression of nuclear factor erythroid-derived 2-like factor 2 (Nrf2) and levels of Nrf2-dependent antioxidants including heme oxygense-1, catalase, superoxide dismutase 1 and NAD(P)H:quinone oxidoreductase-1. In addition, garcinol treatment resulted in reduction of TUNEL-positive cells and increased ratio of Bcl-2 to Bax in obstructed kidneys. PCAF siRNA in HK-2 cells inhibited the expression of type IV collagen and fibronectin when stimulated with TNF-α.

Conclusions: Our results suggest that inhibition of the inordinately enhanced PCAF could mitigate renal fibrosis by redressing the aberrant balance between inflammatory signaling and antioxidant response through modulation of NF-κB and Nrf2.

Funding: Government Support - Non-U.S.

FR-PO368

The Lysine Methyltransferase SETDB1 Inhibits Renal Myofibroblast Differentiation Victoria G. Shuttleworth,[2] Neil S. Sheerin,[1] Ian Logan.[3] *[1]Newcastle University, Newcastle upon Tyne, United Kingdom; [2]Newcastle University, UK, Newcastle Upon Tyne, United Kingdom; [3]newcastle hospitals, Newcastle----, United Kingdom.*

Background: Renal fibrosis is characterised by accumulation of myofibroblasts expressing alpha-SMA. These cells deposit extracellular matrix that replaces normal kidney tissue, leading to chronic kidney disease and organ failure. TGF β-1 is critical to myofibroblast transdifferentiation, signalling through transmembrane receptors, resulting in SMAD3 phosphorylation. Phosphorylated SMAD3 undergoes nuclear translocation to regulate transcription of transdifferentiation genes, such as alpha-SMA. Regulatory mechanisms governing these events are unknown, but SMAD3 may utilise co-regulators from other pathways. For this reason, we screened for methyltransferases involved in TGF β-1 signaling. We identify SETDB1 as a new repressor of SMAD3 and TGF β-1 induced transdifferentiation.

Methods: siRNA Screen. siRNAs targeting 48 human methyltransferases were transfected into cells harboring a TGF β-1-responsive pCAGA12-luc reporter gene. These were treated with TGF β-1, prior to reporter gene assay. **Immunoprecipitation.** HKC-8 cells were starved in serum-free medium and treated with TGF β-1. SETDB1 immunoprecipitation was performed on nuclear fractions. **Immunofluorescence.** HKC-8 cells starved in serum-free medium were treated with TGF β-1 prior to immunofluorescence with SMAD3 and SETDB1 antibodies. Human primary renal fibroblasts were transfected with either control or SETDB1 siRNA then treated with TGF β-1 and subjected to immunofluorescence for alpha-SMA, or light microscopy to evaluate morphology.

Results: 1 siRNA screening identified SETDB1 as a strong corepressor of SMAD3, even in the presence of TGF β-1 2 Immunoprecipitation showed an interaction between SETDB1 and SMAD3 in nuclear fractions. No interaction was observed without TGF β-1 or control immunoglobulins 3 TGF β-1 promoted both SMAD3 and SETDB1 nuclear translocation, demonstrating co-localisation 4 Primary renal fibroblasts transfected with SETDB1 siRNA exhibited markedly more alpha-SMA expression and myofibroblastic changes in morphology, compared to control cells

Conclusions: 1 SETDB1 is a new SMAD3 co-repressor 2 TGF β-1 treatment promotes a specific interaction between with SMAD3 and SETDB1, in the nucleus 3 SETDB1 inhibits myofibroblast differentiation in human renal fibroblasts The conclusions are explained by SETDB1 acting as a brake on TGF β-1, preventing myofibroblast transdifferentiation, which may prevent progressive CKD.

FR-PO369

Calcineurin A-Alpha regulation of Nox2 via NFκB Is Involved in Cyclosporine-Induced Nephrotoxicity Aswathy Miriam Cheriyan,[1] Robert S. Hoover,[1,2] Clintoria R. Williams.[1,2] *[1]Emory University, Atlanta, GA; [2]Atlanta VA Medical Center, Atlanta, GA.*

Background: The calcineurin inhibitor cyclosporine (CsA) is an effective immunosuppressant and dramatically improved the outcomes of transplant patients. However, one long-term consequence of CsA and other calcineurin inhibitor treatments is nephrotoxicity attributed to oxidative damage. Calcineurin has two primary isoforms of the catalytic subunit - CnAα and CnAβ. The renal phenotype of $CnA\alpha^{-/-}$ mice substantially mirrors CsA nephrotoxicity whereas $CnA\beta^{-/-}$ mice do not. However, mechanisms downstream of CnAα that are involved in nephrotoxicity are poorly understood. Since NADPH oxidase-2 (Nox2) derived oxidative stress has been implicated in CsA nephrotoxicity, we hypothesized that inhibition of CnAα by CsA stimulates Nox2 upregulation and promotes oxidative stress.

Methods: To test this hypothesis, WT mice were administered CsA or vehicle alone daily for 6 weeks. Kidneys were then collected for analysis of CnAα isoform activity, Nox2 expression and ROS generation. In addition, Nox2 regulation was investigated in kidneys from $CnA\alpha^{-/-}$, $CnA\beta^{-/-}$ and WT mice. Since Nox2 may be transcriptionally regulated via the NFκB pathway, fibroblasts derived from $CnA\alpha^{-/-}$, $CnA\beta^{-/-}$ and WT mouse kidneys were treated with the NFκB inhibitor, caffeic acid phenethyl ester (CAPE).

Results: In WT mice, CnAα was the predominant isoform bound to calmodulin, consistent with previous in vitro findings showing that CnAα is the basally active isoform. CnAα-calmodulin association was disrupted with CsA treatment and was accompanied by enhanced Nox2 upregulation. Consistent with CsA inhibition of CnAα, Nox2 upregulation and ROS generation occurred only in $CnA\alpha^{-/-}$ mice. Interestingly, NFκB but not NFAT activation was observed. In $CnA\alpha^{-/-}$ renal fibroblasts, NFκB inhibition prevented Nox2 and ROS upregulation.

Conclusions: Our findings demonstrate that CnAα plays a key role in Nox2 regulation and ROS generation. Additionally, loss of CnAα activity, such as with CsA, promotes Nox2-mediated oxidative stress via an NFκB-dependent mechanism. These novel findings provide additional evidence of divergent CnA isoform signaling pathways. Therefore, selective targeting of CnAα and not CnAβ could improve the long-term outcomes of transplant patients.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

FR-PO370

Inhibition of NLRP3 Inflammasome Attenuates Renal Injury in Adriamycin Nephropathy Viviane D. Faustino, Leonardo L. Tavares, Sara C. Ribeiro, Victor F. Avila, Orestes Foresto-Neto, Fernanda F. Zambom, Simone C. Arias, Flavia G. Machado, Claudia R. Sena, Camilla Fanelli, Vivian L. Viana, Denise M. Malheiros, Niels O. Camara, Roberto Zatz, Clarice K. Fujihara. *University of Sao Paulo, Sao Paulo, Brazil.*

Background: Innate immunity is activated in proteinuric models, and may contribute to long term interstitial fibrosis. We investigated whether the NLRP3 inflammasome pathway is involved in the pathogenesis of CKD in the adriamycin (ADR) model.

Methods: Adult male Munich-Wistar rats were given ADR (5 mg/kg iv) and either no therapy or Allopurinol (Allo), used as a NLRP3 inhibitor, 36 mg/kg/day (ADR+Allo). Control rats (C) received saline only. After 4 weeks, we assessed body weight (BW, g), albuminuria (ALB, mg/day), serum creatinine concentration (SCr, mg/dL), glomerulosclerosis (GS, %) and interstitial collagen (COLL, %), as well as infiltration by macrophages (MΦ) and by NLRP3+ cells (/mm²). The renal content (x C) of CASP1 and superoxide dismutase (SOD2), as well as that of uric acid (rUA, mg/g) and IL1β (pg/mg), were also measured.

Results: As expected, ADR promoted massive ALB, intense MΦ, GS and COLL deposition, along with increased rUA, activation of CASP1 and NLRP3, as well as evidence of oxidative stress. Allo normalized rUA and attenuated renal inflammation/fibrosis, despite the persistence of massive ALB. Likewise, Allo prevented the upregulation of NLRP3, CASP1 and IL1β. These findings were associated with an increase of the renal abundance of SOD2, suggesting an antioxidant action of Allo.

Conclusions: NLRP3/CASP1/IL1β upregulation may be a mechanism by which massive protein filtration promotes interstitial fibrosis. Inhibition of this pathway with Allo prevented the activation of this innate immunity pathway and attenuated renal injury even in the face of unabated massive proteinuria. Amelioration of rUA and oxidative stress may contribute to this beneficial effect. Allo may help to prevent or limit the progression of CKD. FAPESP/CNPq

Funding: Government Support - Non-U.S.

	BW	ALB	SCr	GS	COLL	MΦ	rUA	NLRP3	Casp1	IL1β	SOD2
C	273±7	2±1	0.5±0.1	0±0	3±1	7±1	1±1	1±1	1.0±0.2	1±1	1.0±0.1
ADR	213±9[a]	391±34[a]	0.6±0.1[a]	3±1[a]	14±1[a]	218±33[a]	3±1[a]	4±1[a]	2.4±0.5[a]	3±1[a]	0.6±0.1
ADR+Allo	231±9[a]	404±35[a]	0.7±0.1[a]	1±1[a]	8±1[ab]	42±6[ab]	1±1[b]	1±1[b]	1.1±0.2[b]	2±1[ab]	1.7±0.4[b]

Mean±SE, [a]p<0.05 vs C, [b]p<0.05 vs. ADR

FR-PO371

Oleanolic Acid Alleviates Renal Fibrosis through Regulating the Expression of miR-141 Minggang Wei, Jiaqi Yin. *The First Affiliated Hospital of Soochow University, Suzhou, China.*

Background: Renal fibrosis is characterized by the abnormal metabolism of extracellular matrix (ECM). However, ECM's abnormal metabolism mechanism has not been understood clearly. Recent studies suggested that metabolic regulation of ECM may be associated with some miRNA, such as miR-141, miR-21, miR-136 and so on. MiR-141 is the most important of them which control the ECM's metabolism. Both the cell signal pathway of TGF-β_1/Smads and the ECM's metabolism enzyme MMP-9 play important roles in renal fibrosis through effecting ECM's metabolism. So we hypothesize that miR-141 regulation the ECM's metabolism via both TGF-β_1/Smads and MMP-9. Oleanolic acid (OA) is the main extract of Achyranthes bidentate, which could reduce the symptoms of chronic kidney disease and improve the renal function. We have proved that OA can decrease the degree of renal fibrosis through regulating the metabolism of ECM. Therefore, we speculated that OA could lessen the excessive accumulation of ECM by enhancing the expression of miR-141.

Methods: Thirty-two healthy Balb/c male mice performed unilateral ureteral obstruction (UUO) surgery to induce ECM accumulation. Mice were randomly divided into 4 groups: sham-operated group (n=8), UUO group (n=8), OA (25mL/kg) group (n=8), Lotensin (25mL/kg) group (n=8). Daily OA and Lotensin was applied to mice by oral gavage for 10 days after surgery. Then all mice were killed and renal tissue were obtained for further analysis.

Results: We showed that OA group revealed obviously pathological injury including renal interstitial fibrosis compared with the model group by HE staining. And the expression of TGF-β1, Smad2/3, ColIV, FN were downregulated and the expression of MMP-9 was upregulated compared with the model group by immunohistochemistry ($P < 0.05$). Real-time quantitative PCR demonstrated that OA group increased significantly the expression of miR-141 and MMP-9, while obviously decreased the expression of TGF-β1, Smad2/3, ColIV and FN, compared with the model group ($P < 0.05$).

Conclusions: In summary, our study provides that OA could regulate the expression of miR-141 to release the abnormal accumulation of ECM through impacting TGF-β_1/Smads. On the other hand, OA could increase the expression of miR-141 to inhibit the excessive accumulation of ECM via upregulating the expression of MMP-9. OA may have beneficial effects on inhibiting the development of renal fibrosis.

Funding: Government Support - Non-U.S.

FR-PO372

RIPK3 Inhibition Alleviates Folic Acid-Induced Kidney Fibrosis of C57BL/6 Mouse Ying Shi,[2] Yongli Zhao,[1] Chunling Huang,[2] Xinming Chen,[2] Carol A. Pollock.[2] *[1]The Second Hospital of Dalian Medical University, Dalian, China; [2]kolling institute, the University of Sydney, Sydney, NSW, Australia.*

Background: Current therapies for renal fibrosis are largely ineffective. Therefore, identification of novel therapeutic targets is essential. RIPK3 is identified as a crucial regulator of necrosis, apoptosis and inflammation, which have been well recognised to be involved in renal fibrogenesis. To date, the role of RIPK3 in renal fibrosis has not been reported.

Methods: C57BL/6 wild-type and RIPK3 gene knock out (RIPK3-/-) mice and two interventional strategies were used in the study. 1. Folic acid was administrated i.p. to induce kidney injury in both WT and RIPK3-/- mice for 28 days; 2. C57BL/6 WT mice injected with folic acid were treated with Dabrafenib (RIPK3 inhibitor) or vehicle respectively for 28 days. Kidneys were harvested from above experiments and kidney function was assessed by measuring 24 hour of urinary albumin excretion and urinary albumin creatinine ratio (UACR) by ELISAs. Kidney histological change and ECM deposition was assessed by PAS, Masson's trichrome, picrosirius red staining and immunohistochemistry. MCP-1, TGF-β and a-SMA RNA expression level were detected by quantitative RT-PCR analysis.

Results: RIPK3 blockade reversed folic acid increased 24 hour urinary albumin excretion and decreased UACR compared to WT or vehicle control groups treated with folic acid. Histological analysis has shown that folic acid resulted in increased collagen accumulation and ECM deposition, whereas, RIPK3 inhibition attenuated ECM deposition and renal fibrosis. Similar results were also elucidated by immunohistochemistry on ECM components type I, III, IV Collagens and Fibronectin expression in renal interstitium. In addition, quantitative RT-PCR demonstrated Dabrafenib treated mice and RIPK3-/- mice inhibited RNA expression of MCP-1, TGF-β and a-SMA.

Conclusions: These results suggest that RIPK3 blockade may be a potential novel target in renal fibrosis.

Funding: Government Support - Non-U.S.

FR-PO373

Nuclear Localization of Phosphatase and Tensin Homolog (PTEN) Causes Cell Cycle Arrest and Is Associated with Kidney Fibrosis Amrendra K. Ajay, Akinwande A. Akinfolarin, Joseph V. Bonventre, Venkata Sabbisetti. *Brigham and Women's Hospital, Boston, MA.*

Background: PTEN is a lipid/tyrosine phosphatase that modulates various cellular processes including growth, survival and metabolism. Though the antagonistic effects of cytoplasmic PTEN on phosphatidylinositol-3-kinase (PI3K) is well defined, the function of nuclear PTEN is not known. Some studies have demonstrated that nuclear PTEN regulates DNA damage response followed by genotoxic stress and maintains genomic

stability. In this study, we investigated the function of nuclear PTEN in renal epithelial cells followed by DNA damage *in vitro* and *in vivo*.

Methods: HK2 cells were treated with aristolochic acid (AA) for 48 hrs and cell cycle and nuclear PTEN was assessed. HEK293 cells stably expressing wild-type-GFP-PTEN, NLS-GFP-PTEN, mutant (NLS-GFP-C124S-PTEN) were developed and treated with 5 mg/ml AA and 10 μM cisplatin for 48 hour and cell cycle analysis was performed. Bilateral ischemia/reperfusion (IR: 20 min) was performed in C57B6 mice and mice were sacrificed at 21 days post IR. Kidney fibrosis was evaluated by Masson's Trichrome and alpha-smooth muscle actin (α-SMA) staining. Immunostaining of PTEN was performed.

Results: HK2 cells displayed elevated nuclear PTEN localization following AA treatment. Cells stably expressing cytoplasmic PTEN exhibited G2/M arrest, while cells expressing nuclear PTEN rather displayed G1/S arrest. In mice, proximal tubular cells in fibrotic kidneys displayed elevated levels of nuclear PTEN staining.

Conclusions: Nuclear PTEN induces cell cycle arrest and is elevated after DNA damage in tubular epithelial cells *in vitro* and *in vivo*.

FR-PO374

Thymosin β4 Has Cell-Specific Effects on Renal Fibrosis Jianyong Zhong,[1] Jae Won Yang,[2] Haichun Yang,[1] Agnes B. Fogo.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Wonju Christian Hospital, Wonju, GangWon-Do, Republic of Korea*.

Background: Thymosin β4 (Tβ4) is a G-actin sequestering protein with effects on angiogenesis, cell migration and matrix. We previously showed that Tβ4 is increased in sclerotic glomeruli after 5/6 nephrectomy, but exogenous Tβ4 treatment ameliorated interstitial fibrosis after unilateral ureteral obstruction (UUO). In this study, we investigated the impact on renal fibrosis of Tβ4 knockdown in different cell types.

Methods: Endothelial cell Tβ4 knockdown mice (Tβ4 endo-KD) were generated by mating Tβ4 shRNA loxp mice with SCL Cre mice, with SCL Cre negative mice as control (endo-Cont). We also generated inducible macrophage Tβ4 knockdown mouse (Tβ4 mac-KD) by mating Tβ4 shRNA loxp mice with Lys Cre mice, inducing Tβ4 KD by tamoxifen, with Lys Cre negative mice as control (mac-Cont). Injury was induced by UUO and/or folic acid (FA), with in vitro study of primary macrophages.

Results: In UUO and FA models, Tβ4 endo-KD mice had significantly decreased peritubular capillary density vs control. After UUO at day 14, vascular permeability and interstitial fibrosis were significantly decreased in Tβ4 endo-KD. Endothelial-mesenchymal transition was also decreased in Tβ4 endo-KD vs control. In contrast, in the FA model, Tβ4 endo-KD mice had significantly increased collagen I mRNA, and slower recovery rate of tubular injury, measured by urinary KIM-1/Cr and NGAL/Cr, vs control. The hypoxia markers, HIF1 and HIF2 mRNA levels, were significantly higher in Tβ4 endo-KD mice vs control. Knockdown of Tβ4 in cultured macrophages reduced P-cJun and enhanced Ym-1, although in vivo in UUO, interstitial fibrosis and macrophage infiltration were not different in Tβ4 mac-KD vs control.

Conclusions: We conclude that endothelial cell Tβ4 affects peritubular capillary density and endothelial cell function, while the contribution of endothelial Tβ4 to renal outcome depends on disease model, whether a state of nonreversible interstitial fibrosis vs. toxic acute tubular injury, with beneficial effects of knockdown of Tβ4 in the former, contrasting impaired recovery in the latter. Tβ4 also affects M2 macrophage transition, but knockdown of Tβ4 only in macrophages did not change interstitial fibrosis. We conclude that thymosin b4 has cell and context-specific renal effects.

Funding: NIDDK Support

FR-PO375

Pharmacological Induction of ARNT/HIF1β Attenuates Chronic Organ Failure Michael Zeisberg, Desiree Tampe, Gerhard A. Mueller, Bjoern Tampe. *University Medical Center Goettingen, Goettingen, Germany*.

Background: Injury in any organ triggers a complex signaling cascade, ultimately culminating in tissue fibrosis and organ failure. Prompted by various studies across multiple organs demonstrating that preconditioning regimens to pre-emptively induce endogenous regenerative mechanisms protect from later incurring injury, we here aimed to gain insights into the molecular mechanisms underlying successful preconditioning, and to explore whether such pathways could be utilized to inhibit progression of chronic organ injury.

Methods: The effect of picomolar versus nanomolar FK506 was assessed in multiple models of chronic injury in the kidney (UUO), heart (AT II infusion) and liver (CCl_4 injection). Using murine and human cell cultures, molecular mechanisms were analyzed by qRT-PCR, immunostaining and Western blotting.

Results: Based on existing transcriptional profiling data, enrichment analysis and array-based screening, we identified a novel protective mechanism that is controlled by the transcription factor ARNT (synonym HIF1β), which effectively inhibits progression of chronic kidney injury in both, preconditioning as well as interventional regimens. We further report that ARNT expression itself is controlled by the FKBP12/YY1 transcriptional repressor complex, and that disruption of such FKBP12/YY1 complexes by either depletion of FKBP12 or YY1, or by picomolar FK506 concentrations at sub-immunosuppressive doses increases ARNT expression, leading to transcriptional ARNT induction. On a molecular level, we provide evidence that supraphysiological ARNT levels induce formation of distinct ARNT homodimers independent of hypoxia or xenobiotic signaling. For the first time, we detect ARNT homodimer formation in mammalian cells, facilitating unique transcriptional properties of ARNT/ARNT by direct targeting of a palindromic E-box binding motifs (5'-*CACGTG* core sequence) within the proximal *ALK3* promoter. Subsequent activation of ALK3-dependent canonical BMP signaling responses attenuate chronic organ failure in models of chronic kidney, cardiac and liver injuries.

Conclusions: We report a novel organ protective mechanism that depends on ARNT/HIF1β homodimers, which can be pharmacologically modulated and targeted by immunophilin ligand FK506.

FR-PO376

Increased Sodium Chloride Cotransporter Expression in a Rat Remnant Kidney Model Ito Sakuya,[4] Yusuke Kaida,[4] Yosuke Nakayama,[1] Eisei Sohara,[3] Shinichi Uchida,[3] Kei Fukami.[2] *[1]Department of Medicine, Division of Nephrology, Department of Medicine, Kurume University, Kurume, Japan; [2]Kurume University School of Medicine, Kurume, Japan; [3]Tokyo Medical and Dental University, Tokyo, Japan; [4]Department of Medicine, Kurume University School of Medicine, Kurume, Japan*.

Background: Antihypertensive therapies such as renin-angiotensin system (RAS) inhibitor and diuretics are the promising therapeutic strategy for inhibiting the progression of chronic kidney disease (CKD). The salt-sensitive hypertension is associated with the progression of CKD through the activation of the sodium chloride cotransporter (NCC). However, changes in the expression of NCC in the distal tubule of the different CKD stages are unknown. Thus, we investigated the blood pressure and the expression of NCC in the distal tubule of rats with mild to severe renal failure induced by nephrectomy(Nx).

Methods: Sprague Dawley (SD) rats were randomly allocated into the control and CKD groups. We assigned the Nx rats to three groups by the several degrees of kidney resection: sham (n=4), mild CKD (n=3), moderate CKD (n=4), severe CKD (n=3). The Nx and sham-operated rats were sacrificed at 4 weeks after operation. We examined the blood pressure, renal function, and urinary albumin excretion in rats with remnant kidney. Further, we explored the expression of NCC in renal tubule of the remnant kidneys by western blotting and immunostaining.

Results: Systolic blood pressure was significantly higher in the moderate and severe CKD rats compared with those in the sham-operated rats at 4 weeks after operation (148.3±17.9, 149.3±19.7 vs 114.8±12.8 mmHg; $P<0.05$, respectively). However, there was no difference of blood pressure between the mild CKD and the sham-operated rats (119.2±29.2 vs 114.8±12.8 mmHg; $P=0.79$). Serum blood urea nitrogen (BUN) and creatinine (Cr) levels, and urinary albumin excretion were significantly increased in all stages of CKD rats at 4 weeks after operation. The expression of total NCC were gradually up-regulated with the progression of CKD in the remnant kidney model.

Conclusions: In this study, increased NCC protein expression was observed in the remnant kidney model, which might induce the salt-sensitive hypertension in CKD. Therefore, the thiazide diuretics might be useful for controlling blood pressure in CKD patients. Further studies are needed to clarify the precise mechanisms of the increased NCC and its therapeutic strategy in CKD patients with hypertension.

FR-PO377

Targeting mTORC2/PKCα Inhibits Fibroblast Activation and Kidney Fibrosis Involving Blockade of Autophagic Flux Jiafa Ren, Chunsun Dai. *Nanjing medical university, Nanjing, China*.

Background: Our published study reported that mTORC2 plays a critical role in fibroblast activation and kidney fibrosis. However, the role and mechanisms for PKCα, one of the major downstream targets of mTORC2, in regulating fibroblast activation and kidney fibrosis remain to be determined.

Methods: Rat kidney interstitial fibroblasts (NRK-49F) were stimulated with TGFβ1 and kidney fibrosis was induced by unilateral ureter obstruction (UUO) in CD1 mice. Go6976, a synthetic compound which selectively inhibits PKCα signaling, was employed.

Results: Here, we found that TGFβ1 could activate PKCα in cultured NRK-49F cells with a time-dependent manner. Blocking PKCα signaling with either Go6976 or PKCα small interfering RNA could markedly inhibit TGFβ1-induced fibroblast activation. Additionally, Go6976 treatment could impair autophagic flux exhibited as decreased autophagosome-lysosome fusion and autophagic degradation accompanied by increased SQSTM1/p62 and LC3-II in NRK-49F cells. Similarly, 3-Methyladenine (3-MA) and Chloroquine (CQ), two classical authophagy inhibitors, could markedly suppress TGFβ1-induced fibroblast activation. In UUO kidneys, PKCα signaling was activated in the interstitial myofibroblasts and blocking PKCα with Go6976 could significantly ameliorate kidney fibrosis as well as inflammatory infiltration in the UUO kidneys compared to those treated with vehicle. Administration of Go6976 in mice could induce the accumulation of SQSTM1/p62 and LC3-II in the UUO kidneys, suggesting the blockade of autophagic flux in the fibrotic kidneys.

Conclusions: Together, these results suggest that blockade of PKCα attenuates TGFβ1-induced fibroblast activation may be through inhibiting autophagic flux. Targeting PKCα may provide a novel therapeutic strategy for patients with kidney fibrosis.

Funding: Government Support - Non-U.S.

FR-PO378

PBI-4050 Reduces Renal Injury and Anemia in a Mouse Model of Adenine-Induced CKD Jean-Francois Thibodeau,[1,3] Eldjonai Kamto,[1,2] Chet E. Holterman,[1] Rania Nasrallah,[1] Alex Gutsol,[1] Pierre Laurin,[3] Richard L. Hebert,[1,2] Chris R. Kennedy,[1,2] Lyne Gagnon.[3] *[1]Kidney Research Center, Ottawa Hospital, Ottawa, ON, Canada; [2]Department of Cellular and Molecular Medicine, University of Ottawa, Ottawa, ON, Canada; [3]Prometic BioSciences Inc., Laval, QC, Canada.*

Background: PBI-4050, a novel first-in-class orally active compound currently in clinical phase Ib/II in CKD patients, exerts antifibrotic effects via a novel mechanism of action. Through targeting of specific receptors expressed in proximal tubule cells, fibroblasts and macrophages, PBI-4050 decreases inflammation and fibrosis. The aim of this study was to investigate the effects of PBI-4050 in a model of adenine-induced CKD.

Methods: Eight-week old male C57BL/6 mice were fed standard chow, or a diet supplemented with 0.25% adenine. Following one week of adenine diet, daily doses of PBI-4050 (200 mg/kg) or water (vehicle) were administered by oral-gavage for three weeks. Longitudinal renal function was assessed by plasma creatinine via HPLC. At endpoint, blood analysis, plasma electrolyte and erythropoietin levels were measured in blood obtained by cardiac puncture. Tubulointerstitial inflammation/fibrosis and overall renal injury score was assessed in Masson's trichrome and PAS-stained kidney sections. Pro-inflammatory and pro-fibrotic gene expression and fibronectin expression were measured in kidney cortex samples by qPCR and western immunoblotting respectively.

Results: PBI-4050 treatment reduced adenine-induced polyuria and maintained urine osmolality. Renal function assessed by plasma urea and creatinine were significantly increased four and two-fold respectively in vehicle treated mice, while PBI-4050 lowered these values. Hematocrit, hemoglobin and mean corpuscular volume were significantly decreased in CKD-mice, while PBI-4050 maintained these levels in addition to increasing plasma erythropoietin levels. Renal pro-inflammatory gene expression was equally upregulated in both adenine-groups, while. Masson's trichrome staining, α-SMA mRNA and fibronectin protein expression were significantly upregulated in vehicle treated mice, and were decreased with PBI-4050. PAS-staining revealed decreased tubular injury and cyst formation in the adenine+PBI-4050 group compared to adenine+vehicle.

Conclusions: PBI-4050 treatment for three weeks decreased the severity of several adenine-induced sequelae including tubular injury, tubulointerstitial fibrosis and anemia. Taken together, these data reinforce its use as a potential renoprotective therapy.

Funding: Commercial Support - Prometic Life Sciences Inc.

FR-PO379

A Role for IL-27 in Limiting Renal Fibrosis Gaia Muallem, Lillian R. Aronson, Christopher A. Hunter. *University of Pennsylvania, Philadelphia, PA.*

Background: Immune processes that contribute to chronic kidney disease (CKD) represent important targets for prevention of disease in the kidney. Clinical and preclinical studies have established an association between Th17 cells and alternatively activated (M2) macrophages and renal fibrosis; however, a knowledge gap exists regarding how these cells promote fibrosis and how they may be regulated. In other systems, endogenous regulators have been used to successfully skew the immune response towards protection and away from pathology. The endogenous regulatory cytokine IL-27 has been shown to limit M2 macrophages and Th17 cells in other models of inflammation, leading to the hypothesis that it would be protective against renal fibrosis.

Methods: A) Renal fibrosis was induced in wild type (WT) C57Bl/6 mice and IL-27Rα$^{-/-}$ mice by unilateral ureteral obstruction (UUO). Kidneys were evaluated at day 14 post obstruction for immune cell infiltration and cytokine production by flow cytometry as well as fibrosis by trichrome staining and qPCR. B) Renal biopsy samples were collected from the following patient groups: control, CKD, diabetic kidney disease (DKD), diabetes alone (DM), and hypertension alone (HTN). Tubules were microdissected and RNA sequencing was performed on the tubular epithelium.

Results: In mice, IL-27 deficiency was associated with increased renal fibrosis, indicated by trichrome staining and higher expression of the fibrotic marker MMP9. There were increased M2 macrophages and Th17 cells in the fibrotic kidneys of IL-27Rα$^{-/-}$ mice with one subset of the Th17 cells also producing TNFα. IL-17 blockade in the IL-27α$^{-/-}$ mice attenuated fibrosis after UUO. RNA sequencing of human tubular epithelium indicated increased expression of the IL-17R in patients with kidney disease compared to controls and also a positive association of IL-17R expression with fibrosis scoring.

Conclusions: These data identify a role for IL-27 in modulating clinically relevant immune pathways in the kidney. IL-27 deficiency led to reduced renal fibrosis in mice after UUO injury and to the emergence of inflammatory Th17 responses and enhanced M2 macrophage polarization. Higher IL-17R expression was associated with increased kidney fibrosis in human samples, and blocking IL-17 abrogated renal fibrosis in IL-27α$^{-/-}$ mice. Further work will focus on treating WT mice with exogenous IL-27 in an attempt to ameliorate disease in the kidney.

Funding: Other NIH Support - NIAID, Private Foundation Support

FR-PO380

Relation of Uric Acid with Rapid Kidney Function Decline and Development of Kidney Disease: The Jackson Heart Study Stanford Mwasongwe,[2] Tibor Fulop,[1] Solomon K. Musani,[6] Mario Sims,[6] Adolfo Correa,[5] Bessie A. Young,[4] Michael F. Flessner.[3] *[1]FMC Organ Replacement Center, University of Debrecen, Debrecen, Hungary; [2]Jackson State University, Jackson, MS; [3]NIDDK, NIH, Bethesda, MD; [4]Uniiversity of Washington, Seattle, WA; [5]University of Mississippi Medical Center, Jackson, MS; [6]University of Mississippi Medical Center, JACKSON, MS.*

Background: Reports on whether elevated uric acid represents an independent risk factor for development and progression of chronic kidney disease (CKD) have been mixed. We evaluated the relationship of uric acid level with rapid kidney function decline (RKFD) and incident CKD among 3,702 Jackson Heart Study participants who had complete measures of uric acid at baseline (2000-2004) and estimated glomerular filtration rate (eGFR) available at both baseline and Exam 3 (2009-2013).

Methods: RKFD was defined as a decline in eGFR of ≥30% between Exams while incident CKD was defined as having eGFR < 60 mL/minute/1.73 m^2 at Exam 3 with ≥ 25% eGFR decline. Associations were evaluated using multiple logistic regression models. Odds ratios (OR, 95% confidence [CI]) were reported per 1 standard deviation (SD) increment.

Results: Mean baseline uric acid and eGFR were 5.4 ±1.6 mg/dL and 95.9 ±19.9 mL/min/1.73 m^2, respectively. During a median follow-up of 8.1 years, 422 (11.4%) and 268 (7.5%) participants experienced RKFD and developed incident CKD, respectively. In multivariable logistic regression, 1 SD increase in baseline uric acid concentration was associated with increased odds for RKFD (OR 1.8; 95% CI 1.25-2.49; p = 0.0013) and suggested a potential risk for incident CKD (OR, 1.39; 95% CI 0.89-2.16; p = 0.14). There was no interaction between sex and uric acid on both RKFD (p = 0.12) and incident CKD (p = 0.70).

Conclusions: In the community-based cohort of African Americans, elevated serum uric acid was significantly associated with RKFD and may represent a risk factor for development of CKD.

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FR-PO381

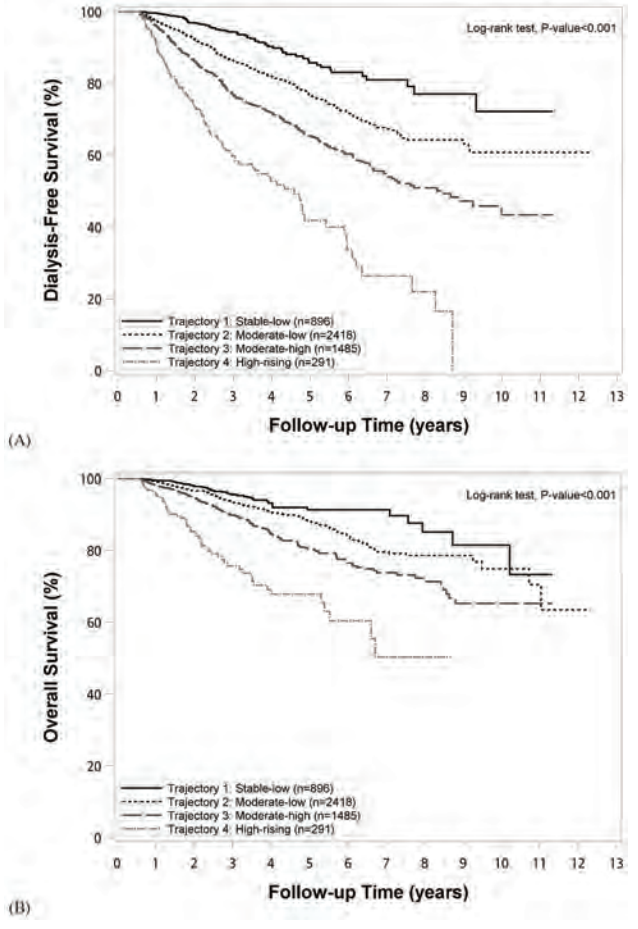
Uric Acid Predicts Adverse Outcomes in CKD: A Novel Insight from Trajectory Analyses Chin-Chi Kuo,[1] Ching-Wei Tsai.[2] *[1]Internal Medicine and Big Data Center, China Medical University Hospital, Taichung City, Taiwan; [2]Internal Medicine and Big Data Center, China Medical University Hospital, Taichung, Taiwan. Group/Team: CMUH Kidney Research Group.*

Background: Very little is known about longitudinal trajectories of serum uric acid (SUA) over the course of chronic kidney disease (CKD). We aimed to determine whether longitudinal SUA trajectories are associated with the risk of end-stage renal disease (ESRD) and all-cause mortality among CKD patients.

Methods: We conducted a prospective cohort study from a 13-year multidisciplinary pre-ESRD care registry. The final study population consisted of 5,090 CKD patients aged 20-90 years between 2003-2015. Individual's SUA trajectory was defined by group-based trajectory modeling in four distinct patterns: high-rising, moderate-high, moderate-low and stable-low. Time to ESRD and death was analyzed by multiple Cox regression.

Results: A total of 948 ESRD events and 472 deaths occurred with incidence rates of 57.9 and 28.7 per 1,000 person-years, respectively. Compared to those with a stable-low SUA trajectory, the adjusted hazard ratio (HR) of patients for incident ESRD was in a dose-response manner as follows: moderate-low: 1.89 (95% CI, 1.35-2.64); moderate-high: 2.74 (1.90-3.95), and high-rising: 3.24 (2.04-5.13), after considering the competing risk of death. For all-cause mortality, the corresponding risk estimate of the same SUA trajectory was 1.43 (95% CI, 0.93-2.21), 2.16 (1.35-3.44), and 5.18 (2.82-9.49), respectively.

Conclusions: Elevated SUA trajectories are associated with accelerated kidney failure and all-cause mortality in CKD patients. Adequate experimental evidence is urgently needed to inform when and how to optimize SUA in this population.



Kaplan-Meier curves of (A) dialysis-free survival and (B) overall survival by serum uric acid (SUA) trajectories based on group-based trajectory modelling (GBTM) (N = 5,090).

FR-PO382

Augmented Association between Blood Pressure and Proteinuria in Hyperuricemic Patients with Non-Nephrotic Chronic Kidney Disease Kentaro Kohagura, Tsuyoshi Miyagi, Ryo Zamami, Yusuke Ohya. *University of the Ryukyus, Nishihara-cho, Japan.*

Background: High serum uric acid levels (HU) may enhance susceptibility to hypertensive renal damage via disrupted autoregulation system of glomerular hemodynamics. However, effect of HU on the relationship between blood pressure (BP) levels and proteinuria is unknown in patients with chronic kidney disease (CKD).

Methods: A total of 109 patients with non-nephrotic CKD (55 men and 54 women) who underwent renal biopsy were recruited. Arteriolar hyalinosis was semiquantitatively assessed via arteriole grading. We examined the correlation between BP and urine protein levels (g/gCr) according to the presence of higher uric acid (HU) levels (mg/dl), defined as ≥7 in men and 5≥ in women, which were the levels from which risk of hyalinosis is increased in our previous study.

Results: The median for age, BP, estimated glomerular filtration rate (eGFR), and urine protein were as follows: 38 years, 124/74 mmHg, and 82 ml/min/1.73 m^2, and 0.8 g/gCr, respectively. In the patients with HU (n=58), log-transformed systolic BP was significantly correlated with log-transformed urine protein (r=0.49, p<0.0001). In contrast, there was no significant correlation between them in those without it (n=51). In the multiple regression model (R^2=0.18, p=0.0009), interaction of HU and log-transformed systolic BP for proteinuria was significantly correlated with logarithm-transformed urine protein (β=3.0, p=0.04) independent of age, sex and potential confounding factors. However, its statistical significance was completely disappeared after additional adjustment with arteriolar hyalinosis index.

Conclusions: These results suggested that HU might potentiate the susceptibility for hypertensive glomerular damage via disrupted autoregulation in non-nephrotic CKD patients.

FR-PO383

Uric Acid and Renal Pathological Features: A Cross-Sectional Study of 1070 Patients Receiving Renal Biopsy Li Wang, Daqing Hong. *Sichuan Provincial People's Hospital, Chengdu, China.*

Background: Hyperuricemia(HUA) is very common in Chronic kidney disease. Hyperuricemia increases the risk of cardiovascular events and accelerates the progression of chronic kidney disease. Our study attempt to determine the relationship between baseline uric acid levels and renal pathological features.

Methods: 1070 patients receiving renal biopsy in our center were involved in our study. The baseline characteristics at the time of kidney biopsy were collected from the medical records, including age, gender, serum uric acid(UA), glomerular filtration rate (eGFR), serum creatinine(Scr),Urea, 24 hours urine protein quantitation(24-u-pro),and serum albumin(Alb). Pathological morphological changes were evaluated with Oxford classification scoring system. Statistical analysis was done with SPSS 21.0.

Results: In the whole cohort, 429 of 1070 were IgA nephropathy(IgAN),641 of 1070 were non-IgAN. The prevalence of HUA was 61.2%(n=655), 56.2%(n=241), and 64.6%(n=414) in all patients, IgAN and non-IgAN patients, respectively. Serum uric acid levels were correlated to eGFR (r=-0.418, P<0.001), Scr(r=0.391,, P<0.001), Urea(r=0.410, P<0.001), and 24-u-pro(r=0.077, P=0.022). Univariate logistic regression analysis showed that HUA was associated with higher risk factor for segmental glomerulosclerosis (OR=1.918, 95%CI: 1.444-2.546) and tubular atrophy or interstitial fibrosis(OR=3.279, 95%CI:2.037-5.276). Multivariate logistic regression analysis showed that after adjustment of Scr,HUA was still a risk factor for segmental glomerulosclerosis (OR=1.783, 95%CI:1.327-2.397) and tubular atrophy or interstitial fibrosis(OR=1.715, 95%CI:1.000-2.942).

Conclusions: Hyperuricemia is prevalent in CKD patients receiving renal biopsy. Uric acid correlates not only to clinical renal injury indexes including serum creatinine, eGFR, urine protein, but also to renal pathology. Hyperuricemia is independently associated with segmental glomerulosclerosis and tubular atrophy or interstitial fibrosis. Reduce uric acid levels may delay the progression of worsening renal function.

FR-PO384

Developing a CKD Screening Algorithm for the Primary Care Setting Andy Y. Cheng, Manisha Jhamb, David Demoise, Amar R. Kohli. *University of Pittsburgh, Pittsburgh, PA.*

Background: CKD in the US not only has a significant prevalence, but also has an alarming projected incidence. Current guidelines for CKD screening are discordant, and few studies have been performed in evaluating various screening algorithms. This retrospective cohort study aims to propose a potential CKD screening algorithm for the primary care setting.

Methods: Adult patients aged 18-69 years seen for primary care visits at a tertiary hospital primary care clinic in Western PA were identified. Those with CKD, defined as two eGFR values of less than 60mL/min/1.73m^2 per MDRD calculation spaced at least 90 days apart in the EHR, were eligible for study inclusion. Characteristics including age ≥55, African American race, and comorbid DM or HTN were abstracted from the EHR. Statistical analyses, including percentage of CKD patients identified and number of patients needed to screen, were then performed using a reverse screening cohort of 650 patients to assess four potential screening algorithms.

Results: Known comorbid DM or HTN (81.8%) outperformed age ≥55 (69.7%) or African American race (49.5%) in identifying the largest percentage of CKD patients. Inclusion of age ≥55 to known comorbid DM or HTN yielded a greater percentage of CKD patients compared to addition of African American race to known comorbid DM or HTN (Table 1). A comprehensive screening algorithm including all four aforementioned variables mildly increased percentage of CKD patients identified, but at the expense of a moderate increase in number of patients needed to screen (Table 1).

Conclusions: A screening algorithm consisting of age ≥55 or known comorbid DM or HTN appeared to optimize percentage of CKD patients identified with number of patients needed to screen. Given that the proposed screening algorithm was derived via a reverse screening approach originating from a patient population with 100% CKD prevalance, further study applying the algorithm to a blanket primary care population is necessary to fully assess the algorithm's efficacy.

Funding: Private Foundation Support

Proposed Screening Algorithms & Associated Statistical Analyses

Screening Algorithm Components	% of CKD Cases Accounted (Number of Patients)	Number of Patients Needed to Screen (95% CI)
DM or HTN	81.8% (532)	5.5 (4.7-6.6)
DM or HTN or Age ≥55	92.0% (598)	12.5 (9.9-16.9)
DM or HTN or African American Race	87.2% (567)	7.8 (6.5-9.8)
DM or HTN or Age ≥55 or African American Race	94.6% (615)	18.6 (14.0-27.2)

FR-PO385

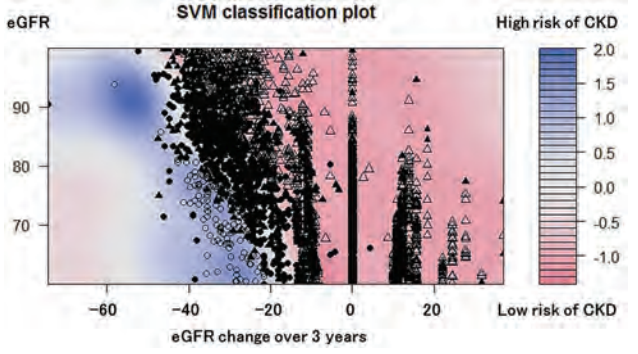
Evaluation of Glomerular Filtration Rate Change as an Indicator of Development of Incident CKD Using Support Vector Machine: Community-Based Prospective Cohort Study Eiichiro Kanda,[2] Bogdan I. Epureanu,[3] Kaname Suwa,[4] Kei Nakajima.[1] *[1]Kanagawa University of Human Services, Yokosuka, Japan; [2]Tokyo Kyosai Hospital, Meguro, Japan; [3]University of Michigan, Ann Arbor, MI; [4]Saitama Health Promotion, Saitama, Japan.*

Background: Chronic kidney disease (CKD) is a risk factor for cardiovascular disease and death. To decrease the number of CKD patients, it is important to identify people at high risk of developing CKD among healthy people from the public-health viewpoint. We investigated the role of estimated glomerular filtration rate (eGFR) change in the development of CKD in a community-based prospective cohort study using the support vector machine (SVM).

Methods: A total of 3295 healthy people (male, 72.7%) were enrolled in this prospective cohort study for 6 years (Saitama Cardiometabolic Disease and Organ Impairment Study) in Japan. The outcome event was incident CKD 6 years later. Subjects were categorized on the basis of eGFR change over 3 years by 10%.

Results: The mean±SD age was 38.8±10.1 years; eGFR, 81.8±17.3 ml/min/1.73m^2; and eGFR change over 3 years, -15.0±18.5%. Multivariate logistic regression models showed the relationship between eGFR change and incident CKD (reference 0 %): -10%, adjusted odds ratio 3.89 (95%CI, 2.0, 7.56); -20%, 40.3 (20.5, 79.0); -30%, 124.8 (59.9, 260.1); -40%, 297.9 (119.8, 741.1). Interaction between eGFR change and eGFR was also observed (p=0.0001). A receiver operating characteristic curve showed a cutoff value of -12.4% for CKD prediction. The use of SVM enabled the identification of high-risk patients and showed that cutoff values differ depending on eGFR: eGFR 90, eGFR change -40%; 80, -30%; 70, -20% (Figure 1).

Conclusions: eGFR change tends to be associated with the risk of CKD. The cutoff values for the prediction of CKD may differ depending on eGFR in the general population. The composite index of eGFR and eGFR change may have high potential use for detecting high-risk people for CKD.



FR-PO386

Lipodystrophy Increases the Risk of Developing CKD in HIV-Infected Patients in Switzerland: the LIPOKID Study Yassine R. Bouatou,[2] Angele Gayet-Ageron,[3] Alexandra Calmy,[1] Sophie M. De Seigneux.[2] *[1]HIV Unit, Geneva University Hospitals, Geneva, Switzerland; [2]Nephrology, Geneva University Hospitals, Geneva, Switzerland; [3]Clinical Epidemiology Unit, Geneva University Hospitals, Geneva, Switzerland. Group/Team: Swiss HIV Cohort Study.*

Background: Antiretroviral therapy (ART) improved HIV patient survival. However, metabolic complications such as dyslipidemia or lipodystrophy (LD) are the hallmark of first generation ART. Growing evidence points towards a role of lipid disturbances in chronic kidney disease (CKD). Also, as the HIV population is aging, identification of risk factors for (CKD) is crucial since both classical and HIV-related risk factors for CKD are highly prevalent among these patients. We studied the cumulative exposure to LD as an independent risk factor for CKD in HIV patients.

Methods: All patients from the Swiss HIV Cohort Study with an estimated glomerular filtration rate (eGFR) > 60 ml/min/1.73 m^2 at baseline (i.e. at entry in the cohort) and more than 3 months of follow-up from January 2002 to December 2015 were included. The primary endpoint was defined as a sustained eGFR < 60 ml/min/1.73 m^2. The secondary endpoint was sustained albuminuria (dipstick). Cox regression models were used to measure the risk to develop CKD associated with cumulative exposure to different patterns of LD.

Results: Among the 5'384 patients included, 4'246 did not have LD at entry in the cohort. 31.0% developed at least once LD during their follow-up after a median time of 17.1 months (IQR: 0-45.2 months) and 252 (4.7%) reached the primary endpoint after a median follow-up time of 43.7 months from baseline (IQR: 18.5-89.3 months). Overall exposure to LD increased significantly the risk of an eGFR < 60 ml/min/1.73 m^2 in univariate analysis with a hazard ratio (HR) 2.25 (95% confidence interval (CI): 1.68-3.00; p <0.001). After adjustment for main confounders, LD increased the risk of eGFR < 60 ml/min/1.73 m^2 by a HR 1.98 (95% CI: 1.31-2.99; p = 0.001). LD was not significantly associated with the development of albuminuria.

Conclusions: LD might be a risk factor for eGFR decline independently of previously reported risk factors for CKD.

FR-PO387

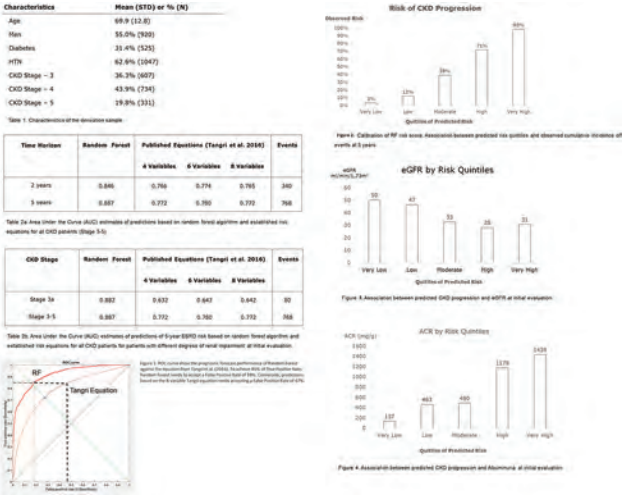
Artificial Intelligence Improves CKD Progression Forecasts Luca Neri, Francesco Bellocchio, Carlo Barbieri, Flavio Mari, Ulrich Tschulena, Stefano Stuard. *Fresenius Medical Care, Bad Homburg, Germany.*

Background: Accurate CKD progression forecasts are key to tailor interventions to real patients needs. Current prognostic tools rely on few dominant variables (e.g. eGFR, albuminuria) and do not incorporate potentially important patterns of association (e.g. interactions). Hence, their performance is suboptimal for high and low risk patients (i.e. early stages of CKD). We developed a risk score addressing such weaknesses with machine learning.

Methods: CKD patients (stages 3-5) registered in EuCliD® (2011-2015) entered the study cohort. Enpoints were Kidney Failure (KF) within 2 and 5 years. The algorithm was derived with random forest (RF) and tested in a partition of the original sample which was not used to develop the model. The RF algorithm exploited 82 variables. To reflect real-life clinical practice, in the validation study, the algorithm calculated a risk score for each patient based on non-missing variables abstracted from electronic clinical charts. We computed model AUC and calibration curves. We compared the predictive accuracy of RF against Tangri's Kidney Failure Risk Score (KFRS)

Results: Among 4064 patients, 2685 and 1672 patients had 2 and 5 years of follow up (fig. 1). Most influential variables for KF at 2 years were eGFR, its rate of change, proteinuria, body mass, haemoglobin, Charlson's index, phosphate. Most influential variables for KF at 5 years were blood pressure, CKD-BMD markers, eGFR, proteinuria, serum albumin, heart rate. FR outperformed KFRS both in the whole sample and among CKD3a patients (Fig 1).

Conclusions: Contrary to KFRS, the performance of RF was stable at different CKD stages and was less dependent on intial GFR and albuminuria. Differences in forecast accuracy between RF and KFRS equations may lead to very large reductions in health care cost and clinical risk due to unnecessary medical encounters.



FR-PO388

Time-Centered Approach to Understanding Progression of CKD Elaine Ku, Charles E. McCulloch, Kirsten L. Johansen. *University of California San Francisco, San Francisco, CA.*

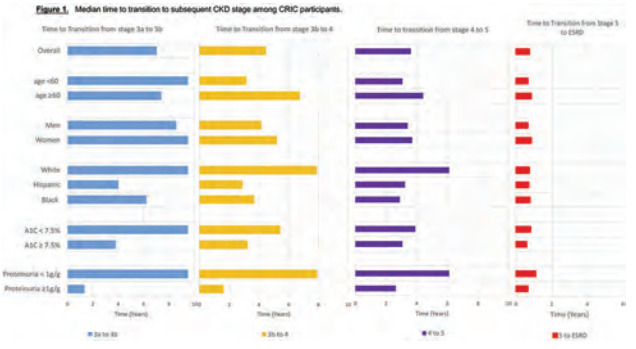
Background: Traditional approaches to modeling risk of CKD progression do not provide estimates of the *time* it takes for disease progression to occur by stage of CKD, or the extent to which risk factors may differentially affect the time spent in various CKD stages.

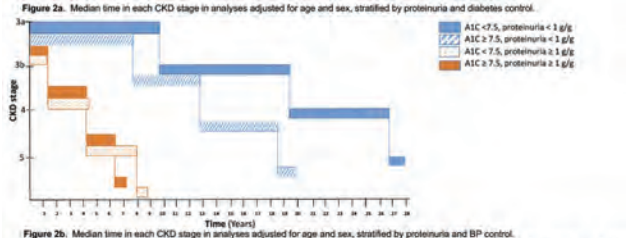
Methods: We used mixed models to estimate person-specific trajectories of renal function among 3682 participants of Chronic Renal Insufficiency Cohort (CRIC), a longitudinal study of persons with CKD. We then used these trajectories to estimate time spent in each CKD stage and compared these times according to combinations of risk factors associated with disease progression.

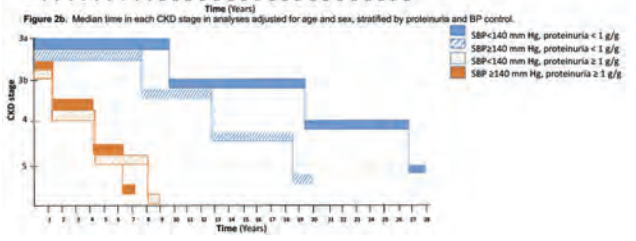
Results: During 9.5 years of median follow-up, participants spent longer in earlier than later CKD stages, ranging from 9.5 yrs in stage 3 to 0.7 yrs in stage 5 [Figure 1]. Risk factors were associated with larger differences in duration in the earlier vs. later stages of CKD. For example, median duration of CKD was over 8 years shorter in stage 3a, 6 years shorter in stage 3b, but only 5.3 months shorter in stage 5 for those with proteinuria ≥1g/g (vs. <1g/g) [Figure 1]. Participants with controlled diabetes (A1C < 7.5%) and without significant proteinuria spent the longest time in CKD stage 3 [Figure 2a], but spent similar amount of time in stage 5 as participants with uncontrolled diabetes and proteinuria. We also found profound differences in the time spent in CKD stages by presence or absence of proteinuria and uncontrolled systolic BP (≥140 mm Hg) [Figure 2b].

Conclusions: We found marked variations in the time spent in the different stages of CKD based on different risk factors. Time-based metrics of CKD progression may help convey prognostic information to patients and guide clinical decisions, such as timing of access placement and RRT.

Funding: Other NIH Support - NHLBI







FR-PO389

Long Term Effects of Intensive Low Salt Diet Education on Deterioration of Glomerular Filtration Rate among Non-Diabetic Hypertensive Patients with CKD Anna Lee,[1] Ho Jun Chin.[2] *[1]SNUBH, Gyeonggi-do, Democratic People's Republic of Korea; [2]Seoul National University Bundang Hospital, Seong nam, Republic of Korea.*

Background: We conducted a prospective cohort study to investigate whether lower dietary salt intake and the intensive low salt diet education are effective to reduce the rate of GFR decline among hypertensive CKD patients.

Methods: This study included 171 participants in the previous open-label, case-control, randomized clinical trial including 245 hypertensive CKD patients who took an olmesartan medoxomil until the end of the study and were assigned to receive an intensive low salt diet education or conventional education. We compared the eGFR change rate, the increase of serum creatinine ≥ 50%, the decrease of eGFR ≥ 30%, and the percent change of albuminuria during 36.3 ± 4.1 months after randomization between education groups.

Results: The mean differences of eGFR change rate between groups was 1.68 ml/min/1.73m^2/year and 1.64 ml/min/1.73m^2/year at 25.1 ± 4.0 months and at 36.3 ± 4.1 months after randomization, respectively. The percent of increment in serum creatinine ≥ 50% was 1.1 % in Intensive group and 8.2% in Control group (*p=0.025*), and the percent of decrease in eGFR ≥ 30% was 3.3 % in Intensive group and 11.1 % in Control group (*p=0.048*). Overall mean difference of 24-hour urine sodium excretion between groups were 10 mEq/day and did not show difference (*p=0.430*), however, in Control group, participants with higher urinary sodium excretion (≥200 mEq/day) showed rapid decline of eGFR (*p=0.012*) and participants with effective decrease of urinary sodium excretion during trial phase (decline≥ 25% of sodium excretion) showed more slow decline of eGFR (*p=0.035*).

Conclusions: This cohort study demonstrated intensive low salt diet education was independently related to slow eGFR decline during about 36 months follow-up period and higher salt intake resulted in more rapid decline of eGFR in participants with conventional low salt education.

Funding: Veterans Affairs Support, Commercial Support - Daiichi Sankyo Korea Co. Ltd., Clinical Revenue Support

Slope of eGFR(ml/min/1.73 m2/year) at each observation period compared to randomization period

Slope of eGFR	Intensive group	Control Group	Difference of mean	p-value
16-week-Randomization	-12.72 ± 83.20	0.77 ± 74.17	-0.16	0.269
1st cohort examination- Randomization	0.23 ± 5.05	-1.45 ± 4.95	1.68	0.031
2nd cohort examination- Randomization	0.11 ± 4.62	-1.53 ± 3.04	1.64	0.010

FR-PO390

Urinary Uromodulin Independently Predicts ESRD and Rapid Kidney Function Decline in CKD Patients Dominik Steubl. *Klinikum rechts der Isar, Munich, Germany. Group/Team: Munich Uromodulin Study Group.*

Background: Urinary uromodulin (uUMOD), exclusively secreted by the ascending limb of the loop of Henle and therefore a marker of tubular function has been shown to be a strong predictor of long term CKD progression and cardiovascular mortality. Data on risk factors predicting rapid progression to end-stage-renal-disease (ESRD) or rapid kidney function decline in chronic kidney disease (CKD) are rare but urgently needed to plan treatment. This article describes the predictive value of uUMOD for rapid progression of CKD.

Methods: We assessed uUMOD, demographic/treatment parameters, estimated glomerular filtration rate (eGFR) and proteinuria in 230 CKD patients stage I-V. ESRD or 25%-decline of eGFR was registered at the end of a follow-up of one year as the outcome variables. Association between logarithmic (log) uUMOD and (log) eGFR/proteinuria was calculated using linear regression analysis adjusted for demographic parameters. We performed multivariable Cox regression analysis to evaluate uUMOD as a predictor. Therefore, patients were categorized into quartiles. The predictive value was further assessed using receiver-operating-curve (ROC) analysis.

Results: Follow-up was 57.3±18.7 weeks. 47 (20.4%) patients reached the endpoint. (log) uUMOD concentrations were significantly associated with (log) eGFR and (log) proteinuria (r=0.554 and r=-0.429, p<0.001 resp.). In multivariable Cox-regression analysis, the two quartiles with the lowest uUMOD concentrations were at increased risk for ESRD/rapid eGFR loss with a hazard ratio (HR) of 3.589 (lowest quartile, uUMOD ≤ 2.6 µg/ml, 95%-confidence interval (CI) 1.002-12.992, p=0.049) and 5.409 (second lowest quartile, uUMOD 2.7-4.75 µg/ml, 95%-CI 1.444-20.269, p=0.011) in comparison to the highest quartile (≥ 11.45 µg/ml), respectively. In ROC-analysis, uUMOD predicted the endpoint with good sensitivity (74.6%) and specificity (76.6%) at an optimal-cut-off at 3.5 µg/ml and area-under-the-curve of 0.786 (95%-CI 0.712-0.860, p<0.001).

Conclusions: uUMOD was independently associated ESRD/rapid loss of eGFR. It might serve as a robust predictor of rapid kidney function decline and help to better schedule arrangements for future treatment.

FR-PO391

Anemia Is a Risk Factor for Incident ESRD Santosh Saraf,[6] Jesse Y. Hsu,[8] Jing Chen,[3] Teresa K. Chen,[1] Michael J. Fischer,[5] L. Lee Hamm,[4] Rupal Mehta,[2] James H. Sondheimer,[10] Matthew R. Weir,[7] Xiaoming Zhang,[9] Ana C. Ricardo,[6] James P. Lash.[6] *[1]Johns Hopkins University School of Medicine, Baltimore, MD; [2]Northwestern Univesrsity, Feinberg School of Medicine, Chicago, IL; [3]Tulane School of Medicine, New Orleans, LA; [4]Tulane University School of Medicine, New Orleans, LA; [5]University of Illinois Hospital and Health Sciences Center, Chicago, IL; [6]University of Illinois at Chicago, Chicago, IL; [7]University of Maryland School of Medicine, Baltimore, MD; [8]University of Pennsylvania, Philadelphia, PA; [9]University of Pennsylvania School of Medicine, Philadelphia, PA; [10]Wayne State University School of Medicine, Detroit, MI.*

Background: Although anemia is a consequence of chronic kidney disease (CKD), anemia itself may accelerate CKD progression. However, the data regarding the impact of anemia on the progression of CKD are inconsistent.

Methods: We used Cox proportional hazards to examine the association of baseline anemia (defined using the World Health Organization criteria of hemoglobin [Hgb] <12 g/dL in women and <13 g/dL in men) with incident end-stage renal disease (ESRD) and all-cause death using data from the Chronic Renal Insufficiency Cohort Study.

Results: The study included 3,919 participants with CKD (mean age 58 years, 45% female, 42% white, 42% black, 13% Hispanic, mean estimated glomerular filtration rate (eGFR) 45 ml/min/1.73 m^2, and median proteinuria 0.19 g/24h). At study entry, 1,859 (47.4%) of participants had anemia. Compared to individuals without anemia, those with anemia were older, more likely to be black or Hispanic, have lower mean eGFR and more proteinuria (P<0.001 for each). Over a median follow-up of 7.8 years, we observed 1,010 ESRD events and 994 deaths. The table below summarizes the results of our multivariable analyses.

Conclusions: In a large cohort of adults with CKD, anemia was independently associated with increased risk for incident ESRD but not all-cause death. Future work is needed to evaluate the optimal Hgb level for CKD patients.

Funding: Other NIH Support - NHLBI

		Anemia vs. No Anemia	Per 1gm Hgb Decrease
		Hazard Ratio (95% CI)	
ESRD	Model 1 (a)	2.54 (2.22-2.90)	1.31 (1.26-1.36)
	Model 2 (b)	2.44 (2.13-2.80)	1.34 (1.29-1.39)
	Model 3 (c)	1.31 (1.13-1.52)	1.10 (1.05-1.14)
Death	Model 1 (a)	1.64 (1.44-1.86)	1.13 (1.09-1.18)
	Model 2 (b)	1.43 (1.25-1.63)	1.13 (1.09-1.18)
	Model 3 (c)	1.03 (0.89-1.19)	1.01 (0.97-1.06)

(a) Adjusted for center

(b) Further adjusted for age, sex, race/ethnicity, education, income

(c) Further adjusted for systolic blood pressure, waist circumference, cardiovascular disease, HgbA1c, phosphate, C-reactive protein, eGFR, proteinuria, ACE-inhibitor/ARB, beta blocker, erythropoiesis stimulating agent

FR-PO392

The Association between Kidney Function and Genetic Polymorphisms among Japanese Male Employees Takahiro Imaizumi, Sawako Kato, Shoichi Maruyama. *Nagoya University Graduate School of Medicine, Nagoya, Japan.*

Background: Previous studies have implicated several single nucleotide polymorphisms (SNPs) in predisposition to chronic kidney disease (CKD). Though atherosclerotic disease is deeply involved in the incidence of CKD, whether SNPs related to arteriosclerosis are involved in CKD remains unclear. The purpose of this study was to identify SNPs that confer susceptibility to CKD and to examine whether the risk allele accumulation is associated with CKD.

Methods: We conducted a cross-sectional study using data of 4814 male workers which contained 432 participants with CKD to examine the association between eGFR and 59 candidate polymorphisms (17 CKD and 42 atherosclerotic diseases). We defined the genetic risk score (GRS) as the total number of risk alleles that showed a significant association in this analysis, and examined the relationship with CKD (eGFR < 60 ml/min/1.73m2).

Results: We found eight candidate SNPs with *P* value < 0.05 (*CX3CR1* rs3732379, *SHROOM3* rs17319721, *MTP* rs1800591, *PIP5K1B* rs4744712, *APOA5* rs662799, *BRAP* rs3782886, *SPATA5L1* rs2467853, and *MCP1* rs1024611) in the multivariate linear regression adjusted for age, BMI, systolic blood pressure, and fasting blood glucose. Among these 8 SNPs, *BRAP* rs3782886 and *SPATA5L1* rs2467853 were significantly associated with eGFR (false discovery rate < 0.05). GRS was significantly associated with CKD [Odds ratio; 1.17, 95% confidence interval, 1.09-1.26]. C-statisics improved from 0.775 to 0.780 but showed no statistical significance ($P = 0.061$). However, adding GRS significantly improved IDI and cNRI (0.0057, $P = 0.0028$, and 0.212, $P < 0.001$, respectively).

Conclusions: After adjustment for clinical factors, kidney function was associated with *BRAP* rs3782886 and *SPATA5L1* rs2467853 and the GRS for CKD that we developed was associated with CKD.

Funding: Commercial Support - Toyota motor corporation, Government Support - Non-U.S.

Associated SNPs

rs number	Near gene	Major/minor allele	Coefficient	95% confidence interval	P value
rs3732379	*CX3CR1*	C/T	1.25	(0.004, 2.50)	0.049
rs17319721	*SHROOM3*	G/A	-1.16	(-2.15, -0.16)	0.023
rs1800591	*MTP*	G/T	0.99	(0.26, 1.72)	0.0077
rs4744712	*PIP5K1B*	C/A	-0.75	(-1.31, -0.19)	0.0088
rs662799	*APOA5*	A/G	-0.61	(-1.18, -0.046)	0.034
rs3782886	*BRAP*	A/G	-1.63	(-2.25, -1.02)	<0.0001
rs2467853	*SPATA5L1*	G/T	2.07	(0.89, 3.24)	0.0006
rs1024611	*MCP1*	C/T	-0.65	(-1.22, -0.084)	0.025

FR-PO393

Fibroblast Growth Factor 23 and Kidney Function Decline: The Health Aging and Body Composition Study David A. Drew,[3] Ronit Katz,[6] Stephen Kritchevsky,[8] Joachim H. Ix,[5] Michael Shlipak,[1] Anne B. Newman,[2] Linda F. Fried,[7] Mark J. Sarnak,[3] Orlando M. Gutierrez.[4] *[1]San Francisco VA Medical Center, San Francisco, CA; [2]University of Pittsburgh, Pittsburgh, PA; [3]Tufts Medical Center, Boston, MA; [4]UAB School of Medicine, Birmingham, AL; [5]UCSD, San Diego, CA; [6]University of Washington, Seattle, WA; [7]VA Pittsburgh Healthcare System, Pittsburgh, PA; [8]Wake Forest School of Medicine, Winston-Salem, NC.*

Background: Fibroblast growth factor 23 (FGF-23) is a potential biomarker for kidney disease. Previous studies have shown FGF-23 to be a risk factor for incident end-stage renal disease (ESRD); however, there are less data on the association of FGF-23 with earlier kidney related outcomes.

Methods: Serum FGF-23 was assayed using an intact ELISA assay in 2,496 participants of the Healthy Aging and Body Composition Study, a cohort of well-functioning older adults. Kidney function was estimated by assaying cystatin C at baseline and years 3 and 10. The associations between FGF-23 and decline in kidney function (defined by estimated glomerular filtration rate (eGFR) decline ≥30% or ≥3 ml/min/year) and incident CKD (incident eGFR <60 ml/min/1.73 m^2 and ≥1 ml/min/year decline) were evaluated. Models were adjusted for demographics, baseline eGFR, urine albumin/creatinine ratio, comorbidity, and serum calcium, phosphorus and parathyroid hormone.

Results: The mean (SD) age was 75 (3) years, with 52% female, and 38% black. There were 405 persons with 30% decline, 702 with > 3 ml/min/year decline, and 536 with incident CKD. In fully adjusted continuous models, FGF-23 concentrations were not associated with kidney function decline (OR [95%CI] = 0.99 [0.82, 1.19] for ≥30% decline and OR= 1.16 [0.99, 1.36] for ≥3 ml/min/year decline), or incident CKD (IRR= 1.05 [0.91, 1.22] per two fold higher FGF-23 level). In quartile analysis, the highest quartile of FGF-23 was significantly associated with incident CKD (IRR= 1.26 [1.02, 1.57] for highest vs lowest quartile).

Conclusions: Higher FGF-23 concentrations were not consistently associated with decline in kidney function or incident CKD in community-dwelling older adults.

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Table. Association of FGF-23 with kidney function decline and incident CKD in the Health ABC Study

Doubling of FGF-23	N	N with outcome	Model 1 OR or IRR^ (95% CI)	Model 2 OR or IRR^ (95% CI)
≥ 30% decline	2496	405	1.03 (0.86, 1.23)	0.99 (0.82, 1.19)
≥ 3 ml/min/year decline	2496	702	1.21 (1.04, 1.41)	1.16 (0.99, 1.36)
Incident CKD*	1914	536	1.07 (0.93, 1.24)	1.05 (0.91, 1.22)

Model 1 = adjusted for age, sex, race, study site, baseline eGFR, urine ACR, diabetes, cardiovascular disease, and hypertension
Model 2 = Model 1 + adjustment for calcium, phosphorus, and PTH
^Incident rate ratio for incident CKD outcome
*Excludes those with eGFR < 60 ml/min/1.73 m2 at baseline

FR-PO394

Bilateral Oophorectomy and the Risk of CKD Andrea G. Kattah, Carin Y. Smith, Vesna D. Garovic, Walter A. Rocca. *Mayo Clinic, Rochester, MN.*

Background: Premenopausal women who undergo bilateral oophorectomy are at an increased risk for morbidity and mortality. Given the potential benefits of estrogen on renal structure and function, we hypothesized that women who undergo bilateral oophorectomy are at an increased risk of chronic kidney disease (CKD).

Methods: All premenopausal women who underwent bilateral oophorectomy for a noncancerous condition before age 50 years from 1/1/1988 to 12/31/2007 in Olmsted County, MN were identified and age-matched (± 1 year) to referent women who did not undergo oophorectomy. CKD was defined in 2 ways: (1) serum creatinine-based definition (Cr > 1.1 mg/dl on two occasions, greater than 90 days apart) and (2) medical record diagnosis of CKD (screening for diagnosis codes and confirmation by medical record review). The hazard ratio (HR) for CKD was estimated with Cox proportional hazards models using age as the time scale. Women with CKD before index were excluded from the analyses. Inverse probability weighting was used to balance the two cohorts with respect to 17 chronic diseases at the time of oophorectomy (or index date), age, education, race, BMI, smoking, and calendar year.

Results: There were 1,653 women with bilateral oophorectomy and 1,653 referent women, and the median length of follow-up was 14 years in both cohorts. Using the serum Cr-based definition, 69 referent women and 120 women with bilateral oophorectomy developed CKD, with an adjusted HR of 1.48 (95% CI 1.10-1.99). The adjusted HR was higher in women who underwent oophorectomy at age ≤ 45 years (HR 1.74 (95% CI 1.15-2.63). In a subgroup analysis of women without any chronic diseases at the index date, the risk of CKD remained significant (HR 1.85, 95% CI 1.12-3.05). Using the diagnosis of CKD confirmed at medical record review, 43 referent women and 61 women with bilateral oophorectomy developed CKD, with an adjusted HR of 1.17 (95% CI 0.79-1.74).

Conclusions: Premenopausal women who undergo bilateral oophorectomy are at an increased risk of developing CKD, even after adjusting for multiple chronic conditions. This risk may be due to the abrupt drop in systemic estrogen levels after surgery. Further research into the mechanism of renal injury and the correct dosage of hormone replacement after oophorectomy is needed.

Funding: Other NIH Support - The study used the resources of the Rochester Epidemiology Project, which is supported by the National Institute on Aging of the National Institutes of Health [R01 AG034676]. This study was also supported by funds from the Mayo Clinic Research Committee (to W.A.R.). W.A.R. was partly supported by the National Institutes of Health [R01 AG052425, P50 AG044170, U01 AG006786, and P01 AG004875].

FR-PO395

Non-Alcoholic Fatty Liver Disease Does Not Accelerate Progressive Renal Progression in Non-Dialysis CKD Rajkumar Chinnadurai, Diana Vassallo, Philip A. Kalra. *SALFORD ROYAL NHS FOUNDATION TRUST, Manchester, United Kingdom.*

Background: Non-Alcoholic Fatty liver disease(NAFLD) is strongly associated with increased incidence and high prevalence of Chronic Kidney Disease(CKD). The association of NAFLD with renal disease progression in non-dialysis dependent CKD(NDD-CKD) has not been explored. Our aim is to access the impact of NAFLD on the rate of progression of CKD.

Methods: All patients recruited in the Salford Kidney Study(SKS)(Large prospective CKD database) who had an Ultrasound(US) of the liver performed between January 2000 to December 2014 were sampled in this retrospective observational study. Estimated Glomerular Filtration Rate(eGFR) as measured by CKD-EPI formula was collected for all patients from study start date (date of Ultrasound) until the study end which included commencement of renal replacement therapy or reaching eGFR <10 ml/min, death, loss to follow-up or censoring at 31 December 2015. The rate of decline in eGFR was calculated by the slope of linear regression in the total sample and a matched group obtained after propensity score matching of all baseline characteristics. All analysis was undertaken in SPSS.

Results: Of the 3061 patients registered in the SKS, 1419 patients had US imaging of the liver, either bespoke or as part of a general abdominal scan, during the study period. After excluding patients based on pre-set criteria, a sample of 852 (183 NAFLD and 669 normal US) patients with complete datasets remained. By Propensity Score matching 138 patients with and without NAFLD were matched. At baseline, the median age of the study group was 66 years, and median eGFR was 33.5 mL/min/1.73m^2. Patients with NAFLD had more hypertension, diabetes mellitus and hypercholesterolemia. Body Mass Index was significantly higher in the NAFLD group 31 vs 27 kg/m^2(p= <0.0001). Median Follow-up time was 73 months with no difference between groups(p=0.176). In terms of CKD progression, there was no difference in the rate of decline of eGFR between

the two groups in the total sample (NAFLD: -2.54 ml/min/yr; normal liver: -2.09 ml/min/yr; p=0.088). Similar results were observed in the propensity score matched sample (NAFLD: -2.62 ml/min/yr; normal liver: -3.07 ml/min/yr; p-0.583).

Conclusions: In our Cohort of NDD-CKD patients the presence of NAFLD did not accelerate the rate of CKD progression.

FR-PO396

Particulate Matter Air Pollution and the Risk of Incident CKD and Progression to ESRD Benjamin C. Bowe,[1] Yan Xie,[1] Tingting Li,[1,3] Yan Yan,[1,4] Hong Xian,[1,2] Ziyad Al-Aly.[1,3] *[1]Clinical Epidemiology Center, Research and Development Service, Veterans Affairs St Louis Health Care System, St. Louis, MO; [2]Department of Biostatistics, Saint Louis University College for Public Health & Social Justice, St. Louis, MO; [3]Department of Medicine, Washington University School of Medicine, St. Louis, MO; [4]Department of Surgery, Washington University School of Medicine, St. Louis, MO.*

Background: Elevated levels of fine particulate matter of <2.5 μm in aerodynamic diameter ($PM_{2.5}$) are associated with increased risk of cardiovascular outcomes and death. However, whether higher concentrations of $PM_{2.5}$ are associated with increased risk of incident chronic kidney disease (CKD), CKD progression, and end stage renal disease (ESRD) is unknown.

Methods: We linked the Environmental Protection Agency and the Department of Veterans Affairs databases to build an observational cohort of 2,482,737 United States veterans, and used survival models to evaluate the association of $PM_{2.5}$ concentrations and risk of incident eGFR <60 ml/min/1.73m^2, incident CKD, eGFR decline ≥30%, and ESRD. County-level exposure was defined at baseline as the annual average $PM_{2.5}$ concentrations in 2004, and separately as time-varying where it was updated annually and as cohort participants moved.

Results: Over a median follow-up of 8.52 years (IQR:8.04-8.80); where exposure was defined at baseline (median 11.8 μg/m^3; IQR:10.1-13.7), a 10 μg/m^3 increase in $PM_{2.5}$ concentration was associated with increased risk of eGFR <60 ml/min/1.73m^2 (Hazard Ratio (HR)=1.21; 95% Confidence Interval (CI)=1.14-1.29); CKD (HR=1.27;CI=1.17-1.38); eGFR decline≥30% (HR=1.28;CI=1.18-1.39); and ESRD (HR=1.26;CI=1.17-1.35). In time-varying analyses, a 10 μg/m^3 increase in $PM_{2.5}$ concentration was associated with increased risk of eGFR <60 ml/min/1.73m^2 (HR=1.25;CI=1.17-1.34); CKD (HR=1.37;CI=1.26-1.48); eGFR decline≥30% (HR=1.36;CI=1.26-1.46); and ESRD (HR=1.31;CI=1.21-1.43). Spline analyses showed a linear relationship between $PM_{2.5}$ concentrations and risk of kidney outcomes. Exposure estimates derived from NASA's satellite data yielded consistent results.

Conclusions: Our findings demonstrate a significant association between exposure to ambient fine particulate matter and risk of incident CKD, eGFR decline, and ESRD.

Funding: Veterans Affairs Support

FR-PO397

Ambient Coarse Particulate Matter, Nitrogen Dioxide, Carbon Monoxide, and the Risk of Kidney Disease Benjamin C. Bowe,[1] Yan Xie,[1] Tingting Li,[1,3] Yan Yan,[1,4] Hong Xian,[1,2] Ziyad Al-Aly.[1,3] *[1]Clinical Epidemiology Center, Research and Development Service, Veterans Affairs St Louis Health Care System, St. Louis, MO; [2]Department of Biostatistics, Saint Louis University College for Public Health & Social Justice, St. Louis, MO; [3]Department of Medicine, Washington University School of Medicine, St. Louis, MO; [4]Department of Surgery, Washington University School of Medicine, St. Louis, MO.*

Background: Experimental and preliminary clinical evidence suggest that environmental air pollution adversely impacts kidney health. Prior work examined the association between fine particulate matter and risk of kidney disease. The relationship between ambient coarse particulate matter (PM_{10}), nitrogen dioxide (NO_2), and carbon monoxide (CO) and risk of incident chronic kidney disease (CKD), CKD progression, and end stage renal disease (ESRD) is not clear.

Methods: We merged multiple large databases including those of the Environmental Protection Agency and the Department of Veterans Affairs to build a longitudinal observational cohort of 2,201,969 United States veterans, and used survival models to evaluate the association of PM_{10}, NO_2, and CO concentrations and risk of incident eGFR <60 ml/min/1.73m^2, incident CKD, eGFR decline ≥30%, and ESRD. Exposure was treated as time-varying where it was updated annually and as cohort participants moved.

Results: Over a median follow-up of 8.52 years (IQR:8.05-8.80), an interquartile range (IQR) increase in concentrations of PM_{10}, NO_2, and CO was associated with increased risk of eGFR <60 ml/min/1.73m^2, HR=1.07 (CI=1.06-1.08), HR=1.09 (CI=1.08-1.10), and HR=1.09 (CI=1.08-1.10), respectively. An IQR increase in concentrations of PM_{10}, NO_2, and CO was associated with increased risk of incident CKD, HR= 1.07; (CI=1.05-1.08), HR=1.09; (CI=1.08-1.11), and HR=1.10; CI=1.08-1.11), respectively. An IQR increase in PM_{10}, NO_2, and CO concentrations was associated with increased risk of eGFR decline ≥30%; HR=1.08 (CI=1.07-1.09), HR=1.12 (CI=1.10-1.13), HR=1.09 (CI=1.08-1.10), respectively. An IQR increase in concentrations of PM_{10}, NO_2, and CO was associated with increased risk of ESRD; HR=1.09 (CI=1.06-1.12), HR=1.09 (CI=1.06-1.12), and HR=1.05 (CI=1.02-1.08), respectively. Spline analyses suggested a monotonic increasing relationship between PM_{10}, NO_2, and CO concentrations and risk of kidney outcomes.

Conclusions: Our results demonstrate that environmental exposure to higher levels of PM_{10}, NO_2, and CO is associated with increased risk of incident CKD, eGFR decline, and ESRD.

Funding: Veterans Affairs Support

FR-PO398

Urinary Iron and Oxidative Stress: Association with Megalin in CKD Shinya Nakatani,[5] Ayumi Nakatani,[5] Eiji Ishimura,[3] Norikazu Toi,[5] Akihiro Tsuda,[2] Shinsuke Yamada,[6] Katsuhito Mori,[5] Yoshiaki Hirayama,[1] Akihiko Saito,[4] Masaaki Inaba.[5] *[1]Denka-seiken co., ltd., Gosen-shi, Japan; [2]Department of Nephrology, Endocrinology, Metabolism, and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan; [3]Meijibashi Hospital, Osaka, Japan; [4]Niigata University, Niigata, Japan; [5]Osaka City University Graduate School of Medicine, Osaka, Japan; [6]Department of Metabolism, Endocrinology, and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan.*

Background: Megalin mediates the uptake of glomerular-filtered iron in the proximal tubules. Sandwich enzyme-linked immunosorbent assays have been developed to measure urinary ectodomain (A-megalin) and full-length (C-megalin) forms of megalin using monoclonal antibodies against the amino- and carboxyl-terminal of megalin, respectively. Urinary C-megalin excretion is increased via exocytosis in association with megalin-mediated metabolic load to the endo-lysosomal systems in the proximal tubules of residual nephrons. Thus, the present study investigated the association between urinary iron and megalin in chronic kidney disease (CKD) patients, and the possible harmful effect of iron in renal tubules.

Methods: The urinary levels of iron, megalin, and other markers were measured in 63 CKD patients, and their associations were evaluated by Pearson's and Spearman's analyses followed by multiple regression analyses.

Results: Urinary iron was 109 [69.3–166] μg/g Cr. Urinary total protein correlated significantly ($r = 0.528$, $p < 0.001$) with urinary C-megalin, but not with A-megalin. Although both urinary C-megalin and urinary total protein correlated with urinary iron (C-megalin: $r = 0.574$, $p < 0.001$; total protein: $r = 0.500$, $p < 0.001$, respectively), urinary C-megalin alone emerged as an independent factor associated positively with urinary iron ($\beta = 0.520$, $p < 0.001$) ($R^2 = 0.75$, $p < 0.001$). Furthermore, urinary iron was associated significantly and positively with urinary 8-hydroxydeoxyguanosine, an oxidative stress marker, whereas none of the tubular markers, including urinary β_2-microglobulin and N-acetyl-β-D-glucosaminidase, were associated with urinary 8-hydroxydeoxyguanosine

Conclusions: In conclusion, renal iron handling may be associated with oxidative stress in renal tubules and megalin-mediated endo-lysosomal metabolic load in the proximal tubules of residual nephrons.

Funding: Private Foundation Support

FR-PO399

Magnesium and Progression of CKD in Children Enrolled in the CKiD Study Martin A. Turman,[1] Aisha Betoko,[4] George J. Schwartz,[3] Susan L. Furth,[5] Bradley A. Warady.[2] *[1]Phoenix Children's Hospital, Phoenix, AZ; [2]The Children's Mercy Hospital, Kansas City, MO; [3]University of Rochester, Rochester, NY; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [5]The Children's Hospital of Philadelphia, Philadelphia, PA. Group/Team: CKD in Children Study.*

Background: Studies in adults with CKD demonstrate that lower magnesium (Mg) levels correlate with more rapid progression of CKD. We hypothesized that hypomagnesemia is associated with more rapid disease progression in children with CKD.

Methods: We measured the initial serum Mg level in 418 children enrolled in the first cohort of the Chronic Kidney Disease in Children (CKiD) study. Participants were grouped into low Mg (< 1.7 mg/dL, n=84; 20%), intermediate Mg (1.7-1.9 mg/dL, n=217; 52%) or high Mg (2.0-2.7 mg/dL, n=117; 28%) categories. Using parametric failure-time models, we evaluated the association between Mg level and CKD progression, defined as time to the composite event of renal replacement therapy (dialysis or kidney transplant) or 50% decline in estimated glomerular filtration rate (eGFR) after adjustment for the following potential confounders: initial eGFR, proteinuria, age, sex, race, BMI, Tanner stage, anemia, hypertension, and CKD diagnosis.

Results: Median age was 11 years, 62% were male and 58% non-Hispanic white. Median eGFR and urine protein-to-creatinine (UP/C) ratio were 45.3 ml/min/1.73m^2 and 0.4 mg:mg, respectively; 21% of the children had a glomerular diagnosis. The baseline characteristics of the patients in the three groups were not significantly different with regard to all potential confounders except initial eGFR and proteinuria. Participants in the low Mg group had a significantly higher baseline eGFR, and lower UP/C ratio compared to those in the high Mg category (median [IQR]: 51 [41, 63] *vs.* 37 [29, 50] and 0.3 [0.1, 1.0] *vs.* 0.6 [0.2, 1.7] respectively). Mg levels were not significantly different for participants on diuretics (n=28), calcineurin inhibitors (n=14), or Mg supplements (n=7). After adjustment for potential confounders, the relative times to either 50% decline in eGFR or renal replacement therapy were not significantly different among Mg groups.

Conclusions: Hypomagnesemia (Mg <1.7 mg/dL) is surprisingly prevalent (20%) in pediatric patients with CKD. This high rate of hypomagnesemia does not correlate with diuretic or calcineurin inhibitor use. Unlike studies in adult populations, hypomagnesemia does not correlate with more rapid progression of pediatric CKD. Higher Mg levels (Mg>2.0 mg/dL) do not correlate with more rapid progression of pediatric CKD either.

Funding: NIDDK Support, Private Foundation Support

FR-PO400

CKD Self-Management: Identifying Phenotypes and Associations with Renal and Cardiovascular Outcomes Sarah J. Schrauben,[1] Jesse Y. Hsu,[1] Sylvia E. Rosas,[2] Rajat Deo,[2] Bernard G. Jaar,[2] Georges Saab,[2] Swati Lederer,[2] Jing Chen,[2] Ana C. Ricardo,[2] James P. Lash,[2] Harold I. Feldman,[1] Amanda H. Anderson.[1] *[1]U Penn, Philadelphia, PA; [2]CRIC, Bethesda, MD.*

Background: In the effort to slow chronic kidney disease (CKD) progression and its complications, patients need to engage in self-management behaviors. This study evaluated CKD self-management behaviors (CKD-SMB) by identifying patterns of engagement into groups (or phenotypes), and evaluating the association of these phenotypes with renal and cardiovascular outcomes, and death.

Methods: Data from the Chronic Renal Insufficiency Cohort (CRIC) Study were analyzed using a clustering technique, latent class analysis (LCA), to identify CKD-SMB phenotypes stratified by diabetes status. The original CRIC cohort (N=3939) was the derivation cohort, and 1,560 participants subsequently recruited served as the validation cohort. LCA was based on the following measures of CKD-SMB: BMI, diet, physical activity, blood pressure, smoking status, and hemoglobin A1c (if diabetic), which were dichotomized into "recommended" and "not recommended". Cox proportional hazards models calculated hazard ratios (HRs, 95% CI) of phenotypes for CKD progression, atherosclerotic and heart failure (HF) events, and death.

Results: Three CKD-SMB phenotypes were identified separately among diabetics (DM) and non-diabetics (ND) that varied by level of engagement in recommended CKD-SMB, with Phenotype I being the most engaged, Phenotype II moderately engaged, and Phenotype III, the least engaged. In multivariable-adjusted models, Phenotype III was strongly associated with CKD progression, atherosclerotic events, and death among both DM and ND, and Phenotype II was associated with atherosclerotic events in DM and with death in ND (Table).

Conclusions: This study demonstrates there are potentially three CKD-SMB phenotypes that distinguish risk for clinical outcomes. Given the rise of CKD and its complications, CKD-SMB phenotypes could identify high-risk groups and guide management.

Funding: NIDDK Support

Associations (HR, 95% CI) of Clinical Outcomes by CKD-SMB Phenotypes

	Phenotype II-DM	Phenotype II-ND	Phenotype III-DM	Phenotype III-ND
CKD Progression	1.11 (0.91-1.35)	1.01 (0.82-1.25)	1.82 (1.32-2.52)	1.49 (1.06-2.09)
Atherosclerotic Events	1.40 (1.04-1.89)	1.15 (0.83-1.60)	2.54 (1.61-3.99)	1.90 (1.18-3.06)
HF Events	1.08 (0.84-1.40)	1.35 (0.97-1.86)	0.90 (0.56-1.45)	1.12 (0.66-1.92)
Death	1.22 (0.97-1.55)	2.80 (1.60-4.89)	1.95 (1.35-2.81)	4.14 (2.06-8.33)

Phenotype I as referent group.

FR-PO401

Factors Associated with Rapid CKD Progression in a Special Predialysis Population under Strict Volume Control Olimpia Ortega, Zsofia K. Baranyi, Melissa Vasquez, Diego Navazo, Rosa Camacho, Maria Sanchez, Cristina Di Gioia, Paloma Gallar, Aniana Oliet, Milagros Ortiz, Carmen Mon, Juan Carlos Herrero. *Nephrology, Hospital Severo Ochoa, Leganes, Spain.*

Background: Fluid overload has emerged recently as an independent predictor of chronic kidney disease (CKD) progression among patients with CKD. Fluid overload control has been our priority for many years in our predialysis outpatient unit using a strategy of strict volume control. The aim of this study was to analyse the hydration status achieved in our patient and to evaluate the independent factors associated with rapid CKD progression or the initiation of dialysis in this special population.

Methods: 99 patients with CKD stages 4 and 5 were enrolled and followed for 2.9 ± 1.4 years. All patients were under a strict volume control strategy based on clinical criteria. Body composition monitor was used to analyse the hydration status achieved in our patients. Patients were organized in tertiles of percentage annual GFR decline. Univariate and multivariate logistic regression analysis were used to evaluate the independent factors associated with rapid CKD progression (tertil 3, cutoff value>13%). Cox proportional hazard model was used to analyse the independent factors associated with the initiation of dialysis.

Results: Fluid overload in the whole population was 0.17 (-0.4 to 0.98) and median relative hydration status (fluid overload/ECW) was 1.4 % (-2.25 to 5.2%). During the study period 17 patients iniciate dialysis and 3 patients died. Multivariate logistic regression analysis shows that only NT-proBNP levels (OR 1.01; 95% CI 1.00-1.03; p=0.04) and proteinuria (OR 1.60; 95% CI 1.12-2.39; p=0.03) were associated with rapid CKD progression (tertil 3). The independent factors associated with the initiation of dialysis were NT-proBNP (HR 1.00; 95% CI 1.000-1.001; p=0.006), proteinuria (HR 4.4; 95% CI 1.23-16.1; p=0.02) and low plasma albumin (HR 0.002; 95% CI 0.000-0.69; p=0.04). Fluid overload was not associated with rapid CKD progression nor with the start of dialysis.

Conclusions: A practically normohydration status can be achived even in patients with advanced CKD using a strategy of strict volume control. In this setting, NT-proBNP levels, reflecting increased left ventricular filling pressure and not fluid overload by itself, are associated with rapid CKD progression and the initiation of dialysis.

FR-PO402

Biologic Use and Incident CKD in Rheumatoid Arthritis Keiichi Sumida,[1] Miklos Z. Molnar,[3] Praveen Kumar Potukuchi,[3] Fatima Hassan,[3] Fridtjof Thomas,[3] Kunihiro Yamagata,[4] Kamyar Kalantar-Zadeh,[2] Csaba P. Kovesdy.[3] *[1]Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; [2]University of California Irvine, School of Medicine, Orange, CA; [3]University of Tennessee Health Science Center, Memphis, TN; [4]University of Tsukuba, Tsukuba, Japan.*

Background: Rheumatoid arthritis (RA) is associated with reduced kidney function, possibly due to chronic inflammation or the use of nephrotoxic therapies. Little is known about the effects of RA therapy using novel non-nephrotoxic biologic agents on the risk of incident CKD.

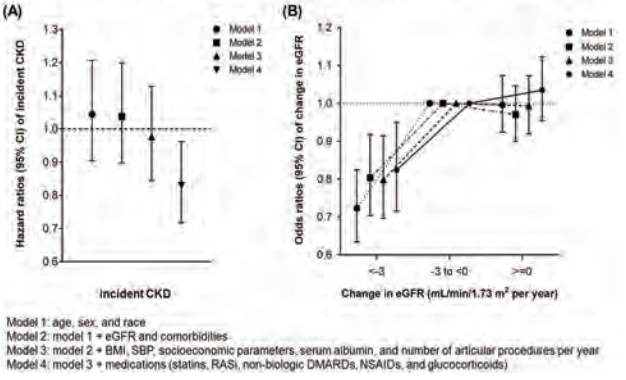
Methods: In a nationwide cohort of 20,757 U.S. veterans with an eGFR ≥60 mL/min/1.73 m^2 who were newly diagnosed with RA between 2004 and 2006, with follow-up through 2013, we examined the association of the use of biologic agents with incident CKD (>25% decrease in eGFR reaching <60 mL/min/1.73m^2) and change in eGFR (<-3, -3-<0 [reference], and ≥0 mL/min/1.73m^2/year), using time-dependent Cox models and multinomial logistic regression models, respectively, with adjustment for potential confounders.

Results: After multivariable adjustment, patients receiving (vs. not receiving) biologic treatment had a lower risk of incident CKD (adjusted HRs [95% CI], 0.83 [0.72-0.96]) and progressive eGFR decline (adjusted multinomial ORs [95% CI] for eGFR slopes <-3 and ≥0 [vs. -3-<0] mL/min/1.73m^2/year, 0.82 [0.72-0.95] and 1.03 [0.95-1.12], respectively) (Figure). A significant deceleration of eGFR decline was also observed after biologic administration in patients treated with biologics (-1.0±1.9 vs. -0.4±2.2 [mL/min/1.73m^2/year] before and after biologic use, respectively, *P* <0.001).

Conclusions: Biologic treatment was independently associated with lower risk of incident CKD and progressive eGFR decline. Clinical trials are warranted to test whether active interventions with biologic agents can prevent adverse renal outcomes associated with RA.

Funding: NIDDK Support

Association of biologic treatment with (A) incident CKD and (B) change in eGFR



Model 1: age, sex, and race
Model 2: model 1 + eGFR and comorbidities
Model 3: model 2 + BMI, SBP, socioeconomic parameters, serum albumin, and number of articular procedures per year
Model 4: model 3 + medications (statins, RASi, non-biologic DMARDs, NSAIDs, and glucocorticoids)

FR-PO403

Changes in Albuminuria and Subsequent Risk of Incident Kidney Disease Keiichi Sumida,[1] Miklos Z. Molnar,[4] Praveen Kumar Potukuchi,[4] Koshy K. George,[3] Fridtjof Thomas,[4] Jun Ling Lu,[4] Kunihiro Yamagata,[5] Kamyar Kalantar-Zadeh,[2] Csaba P. Kovesdy.[4] *[1]Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; [2]University of California Irvine, School of Medicine, Orange, CA; [3]University of Queensland, Memphis, TN; [4]University of Tennessee Health Science Center, Memphis, TN; [5]University of Tsukuba, Tsukuba, Japan.*

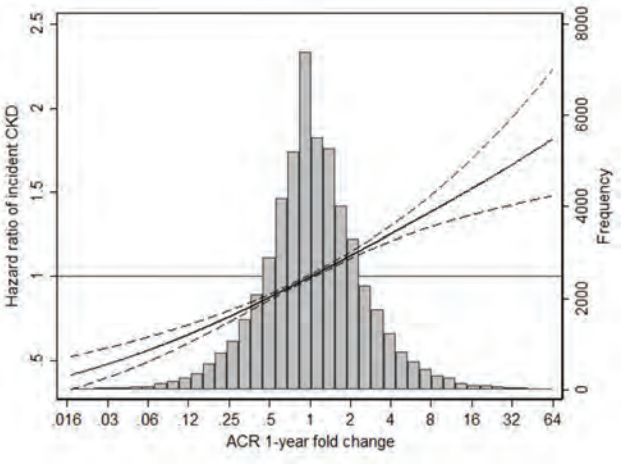
Background: Albuminuria is a robust predictor of CKD progression. However, little is known about the associations of changes in albuminuria with the risk of kidney events outside the settings of clinical trials.

Methods: In a nationwide cohort of 56,946 U.S. veterans with at least two albuminuria measurements and an eGFR ≥60 mL/min/1.73 m^2 between 2004 and 2006, we examined the associations of 1-year fold changes in albuminuria with incident CKD (>25% decrease of eGFR upon reaching <60 mL/min/1.73 m^2) and rapid eGFR decline (eGFR slope <-5 mL/min/1.73 m^2 per year), assessed using Cox models and logistic regression models, respectively, with adjustment for potential confounders.

Results: The mean (SD) age was 64.2 (10.4) years; 97% were male; and 91% were diabetic. There was a near linear association between 1-year fold changes in albuminuria and incident CKD (Figure). The multivariable-adjusted hazard ratios (95% CI) of incident CKD associated with 1-year albuminuria fold changes of <0.5, 0.5-<0.75, 1.25-<2, and ≥2 (vs. 0.75-<1.25) fold were 0.82 (0.76-0.88), 0.93 (0.86-1.00), 1.12 (1.05-1.20), and 1.29 (1.21-1.38), respectively. Qualitatively similar associations were present for rapid eGFR decline (adjusted odds ratios [95% CI] for albuminuria changes <0.5, 0.5-<0.75, 1.25-<2, and ≥2 [vs. 0.75-<1.25] fold, 0.86 [0.78-0.94], 0.98 [0.89-1.07], 1.18 [1.08-1.28], and 1.67 [1.54-1.81], respectively).

Conclusions: Changes in albuminuria were associated with subsequent risk of incident CKD and rapid eGFR decline. Further studies are warranted to test whether active interventions aimed at lowering elevated albuminuria can improve kidney outcomes.

Funding: NIDDK Support



FR-PO404

Complications of RAAS Blockade in Patients with Advanced CKD Miklos Z. Molnar,[4] Adnan Naseer,[6] Keiichi Sumida,[2] Ariel R. Riezenman,[5] Barry M. Wall,[7] Praveen Kumar Potukuchi,[4] Abduzhappar Gaipov,[4] Elani Streja,[1] Kamyar Kalantar-Zadeh,[3] Csaba P. Kovesdy.[4] *[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [2]Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; [3]University of California Irvine, School of Medicine, Orange, CA; [4]University of Tennessee Health Science Center, Memphis, TN; [5]University of Tennessee Health Science Center - Memphis, Memphis, TN; [6]VAMC, Germantown, TN; [7]Veterans Affairs Medical Center, Memphis, TN.*

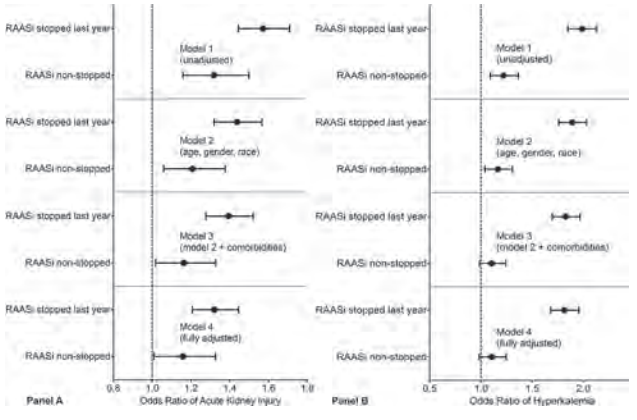
Background: Renin-Angiotensin-Aldosterone system inhibitors (RAASi) are associated with slower progression of chronic kidney disease (CKD) and lower mortality in patients with CKD, yet their discontinuation is frequent. The reasons for not using or for stopping RAASi in patients with advanced CKD are unclear.

Methods: We examined 15,966 US veterans initiating dialysis during 2007-2014, who displayed three RAASi use patterns in the last 3 years pre-dialysis: 1) never used (n=7,294), 2) discontinued in the last year before dialysis (n=6,833) and 3) uninterrupted use (n=1,839). We defined AKI as a >25% decrease in eGFR and hyperkalemia as a potassium >5.5 mmol/l during the 3 years prior to dialysis. Associations of RAASi use patterns with incidence of AKI and hyperkalemia were examined in logistic regression models adjusted for demographics, comorbidities, blood pressure and eGFR.

Results: Patients were 72±11 years old, 98% male, 23% African-American, and 65% diabetic. Compared to patients who never used RAASi, uninterrupted and interrupted RAASi use were associated with 16% and 32% higher multivariable adjusted risk of AKI [Figure Panel A], and with 11% and 81% higher multivariable adjusted risk of hyperkalemia [Figure Panel B], respectively.

Conclusions: RAASi before dialysis is associated with higher risk of AKI and hyperkalemia. These complications (especially hyperkalemia) may contribute to the discontinuation of RAASi in patients with advanced CKD. Additional studies are needed to determine if measures aimed at alleviating hyperkalemia and AKI could lead to higher RAASi use and improved outcomes.

Funding: NIDDK Support



FR-PO405

Association between Serum Albumin Level and Incidence of ESRD in Patients with Immunoglobulin A Nephropathy: A Possible Role of Albumin as an Antioxidant Agent Yasuhiro Kawai,[2] Kosuke Masutani,[2] Kumiko Torisu,[2] Ritsuko Katafuchi,[3] Shigeru Tanaka,[1] Akihiro Tsuchimoto,[2] Koji Mitsuiki,[2] Kazuhiko Tsuruya,[2] Takanari Kitazono.[2] *[1]Fukuoka Dental College, Fukuoka, Japan; [2]Kyushu University, Graduate School of Medical Sciences, Fukuoka City, Japan; [3]National Fukuoka-Higashi Medical Center, Koga, Fukuoka, Japan.*

Background: Serum albumin is the most abundant intravascular protein and the major intravascular antioxidant. The association between serum albumin and the incidence of end-stage renal disease (ESRD) in patients with IgA nephropathy (IgAN) is not fully understood.

Methods: We retrospectively investigated 1,352 patients who were diagnosed with IgAN by kidney biopsy from seven institutions in Japan between October 1979 and December 2010. Patients were divided into three groups by tertile of serum albumin value: Low group, Middle group, and High group (≤3.9 g/dL, 4.0–4.3 g/dL, ≥4.4 g/dL, respectively). The association between serum albumin level and the incidence of ESRD was assessed using a Cox proportional hazards model. We also conducted an experiment of dihydroethidium staining for detection of decrease in intracellular superoxide anion induced by hydrogen peroxide in albumin-pretreated mouse mesangial cells.

Results: During the median 5.1-year follow-up period, 152 patients (11.2%) developed ESRD. Participants in Low group had a 1.88-fold (95% confidence intervals, 1.15–3.20) higher risk of the incidence of ESRD than those in High group after adjustment for age, sex, systolic blood pressure, urinary protein excretion, body mass index, estimated glomerular filtration rate, total cholesterol, triglycerides, and pathological parameters of the Oxford classification (M, E, S, T) and extracapillary proliferation (Ex). Furthermore, in *in vitro* experiments, generation of intracellular superoxide anion, a major form of reactive oxygen species, by hydrogen peroxide was significantly attenuated in albumin-pretreated mouse mesangial cells compared with γ-globulin-pretreated cells.

Conclusions: Low serum albumin level is an independent risk factor of ESRD in patients with IgAN. The mechanism could be explained by the antioxidant capacity of serum albumin.

FR-PO406

Association of Elevated Urinary miR-126, miR-155, and miR-29b with Diabetic Kidney Disease Cristina Beltrami,[3] Kate A. Simpson,[2] Mark D. Jesky,[1] Alexa Wonnacott,[2] Lucy J. Newbury,[2] Robert H. Jenkins,[2] Donald Fraser,[2] Timothy Bowen.[2] *[1]Queen Elizabeth Hospital Birmingham, Birmingham, United Kingdom; [2]Cardiff University, Cardiff, United Kingdom; [3]Maastricht University, Eindhoven, Netherlands.*

Background: Around 9% of the adult global population has diabetes mellitus and approximately 40% of these individuals will develop diabetic kidney disease (DKD). Effective DKD biomarkers remain elusive, but urinary microRNAs (miRNAs) represent a potential source of novel non-invasive disease sentinels. The principal aim of this study was to analyse urinary miRNA biomarkers in DKD.

Methods: Unbiased RT-qPCR profiling of 754 miRNAs was compared in pooled urine samples from DKD patients (n = 20) and control subjects (n = 20). Candidate urinary miRNA biomarkers were then analysed by RT-qPCR in an independent cohort of 89 DKD patients, 62 diabetic patients without DKD and 41 controls. To locate the source of these miRNAs within the nephron, isolation of nephron regions from renal biopsy tissue by laser capture microdissection (LCM) was followed by RT-qPCR analysis of representative cell types.

Results: Significantly increased miR-126, miR-155 and miR-29b were detected in pooled DKD patient urine samples compared to control samples. These results were confirmed in our independent patient cohort: miR-126 (2.8-fold increase; $p<0.0001$), miR-155 (1.8-fold; $p<0.001$) and miR-29b (4.6-fold; $p = 0.024$). Combined receiver operating characteristic curve analysis for these miRNAs resulted in an area under the curve of 0.8. A relative quantification threshold equivalent to 80% sensitivity for each miRNA gave a positive signal for 48% of DKD patients compared to 3.6% of diabetic patients without DKD. LCM detected miR-155 in glomeruli, proximal and distal tubules, while miR-126 and miR-29b were most abundant in glomerular extracts. MiR-126 and miR-29b were enriched in glomerular endothelial cells (GEnCs) compared to podocytes, proximal tubular epithelial cells and fibroblasts. Significantly increased miR-126 and miR-29b were detected in GEnC conditioned medium in response to tumour necrosis factor-alpha and transforming growth factor-beta 1, respectively.

Conclusions: We have identified a urinary miRNA signature of increased miR-126, miR-155 and miR-29b detection that is associated with DKD, these miRNAs are therefore promising DKD biomarkers. MiR-126 and miR-29b were enriched in GEnCs and released from these cells in response to DKD-related cytokines, the pathological significance of this finding merits further evaluation.

FR-PO407

Tracking of Microalbuminuria and A1c in a High-Risk Zuni Population Vallabh O. Shah,[2] V. Shane Pankratz,[2] Robert G. Nelson,[1] Donica M. Ghahate,[2] Jeanette Bobelu.[2] *[1]National Institutes of Health, Phoenix, AZ; [2]University of New Mexico Health Science Center, Albuquerque, NM.*

Background: The Zuni Indians are disproportionately affected by diabetes and chronic kidney disease, signaling a need for effective community-based prevention efforts. We previously reported on the epidemic of kidney disease and its intermediate phenotypes, and described the heritability of these conditions. Recently, through a Patient Center Outcomes Research Institute (PCORI)-funded study of home-based kidney care (HBKC), we rescreened 314 Zuni participants and examined changes in a constellation of markers of kidney disease and diabetes in a subset of these participants.

Methods: Summaries of the risk factors in the 155 participants (73 [47%] female; mean [SD] age at baseline 33.7 [11.5] years) at three key time points shown in the table 1.

Results: The development of ESRD in 7 individuals in this study set of 155 participants with longitudinal follow-up underscores the high incidence of renal disease in this population. These incident cases of renal disease occurred in 2081.7 person-years of follow-up, leading to an estimated incidence rate of CKD in this population of 3.8 (95% CI: 1.9 – 7.7) events per 1000 person years.

Conclusions: This analysis of a cohort of individuals from the PCORI studied at 3 time points over up to 14.3 years shows significantly increasing UACR and A1C levels, and a high incidence of kidney disease. These findings reinforce the need for interventions to modify risk factors for CKD progression, such as our PCORI-supported pilot HBKC intervention in this high-risk population, particularly amongst young adult Zuni.

Funding: Other U.S. Government Support

Table 1	Time 1 (Yr 2000)	Time 2 (Yr 2007)	Time 3 (Yr 2014)	
A1C	6.1 (1.4)	6.1 (1.4)	7.0 (2.0)	<0.001
UACR	58 (156)	106 (337)	976 (2679)	<0.001

*Mean (SD). Repeated measures analysis of variance models were performed to test for trends in risk factors over time (P<0.05 indicates statistical significance).

FR-PO408

Arsenic Exposure and Incident ESRD in the Southern Community Cohort Study (SCCS) Kerri L. Cavanaugh,[1] Edmond K. Kabagambe,[1] Jennifer Morse,[1] Thomas G. Stewart,[1] Aaron B. Bowman,[1] Yaofang Zhang,[2] William J. Blot,[1] Talat Alp Ikizler,[1] Loren Lipworth.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Vanderbilt University, Nashville, TN.*

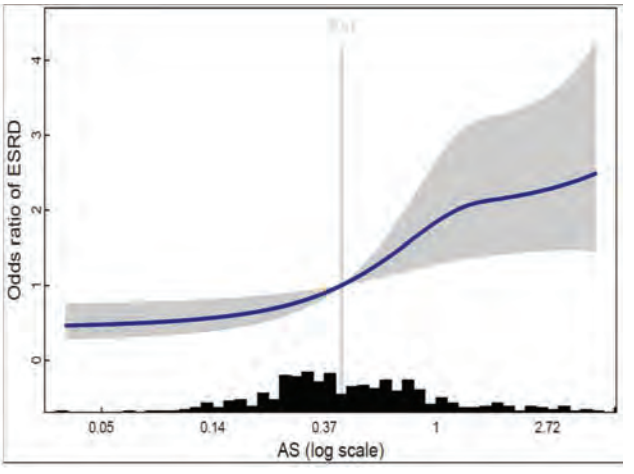
Background: Arsenic (As) is nephrotoxic at high doses. We hypothesized that long-term low to moderate exposure to As is associated with ESRD risk.

Methods: We conducted a nested case-control study within the SCCS, a prospective study of low income adults residing in underserved urban and rural communiities with potentially high toxicant burden in the southeastern US (2002-2009). Among 125 (63 black, 62 white) randomly selected incident ESRD cases and 250 controls, matched on age, race, sex and time of enrollment, baseline serum As was measured by inductively coupled plasma mass spectrometry. Data were modeled using conditional logistic regression, after log transformation of As. Generalized additive models examined the association of As exposure with ESRD probability adjusting for age, race, sex, diabetes, hypertension, and smoking.

Results: Mean age at SCCS enrollment of cases and controls was 55 years, and 55% were female. Median (25th, 75th percentile) levels of As (ng/ml) were significantly higher among ESRD cases (0.56; 0.32, 0.85) than among controls (0.39; 0.26, 0.73). An inter-quartile range increase in As log-transformed level was associated with significantly higher odds of ESRD (OR=1.58; 95% CI 1.21-2.06). The relative odds of ESRD as As varies from the median were computed from a multivariable logistic regression model controlling for hypertension, diabetes, enrollment age, race, sex, and smoking. The OR plotted against As (see Figure) shows the estimated association.

Conclusions: In summary, these results provide support for the hypothesis that chronic low to moderate exposure to As may be an important novel modifiable contributor to ESRD risk. Further work incorporating urinary As and geographic exposure modeling is ongoing.

Funding: Other NIH Support - NIEHS P30ES000267–47; National Cancer Institute (R01 CA092447); American Recovery and Reinvestment Act (3R01CA092447-08S1)



FR-PO409

Total Nephron Number Decreases with the Stage of CKD – A Study in Japanese Subjects Go Kanzaki,[3,4] Victor G. Puelles,[2] Luise A. Cullen-McEwen,[4] Yusuke Okabayashi,[3] Nobuo Tsuboi,[3] Akira Shimizu,[1] Takashi Yokoo,[3] John F. Bertram.[4] *[1]Department of Analytic Human Pathology, Nippon Medical School, Tokyo, Japan; [2]Department of Nephrology and Clinical Immunology, University Hospital RWTH Aachen, Aachen, Germany; [3]Division of Nephrology and Hypertension, The Jikei University School of Medicine, Tokyo, Japan; [4]Department of Anatomy and Developmental Biology, Monash University, Melbourne, VIC, Australia.*

Background: There is increasing evidence that low nephron number increases the risk for CKD. We have previously shown that nephron number predicts eGFR. However, changes in total nephron number across the stages of CKD have not previously been reported. In this study we assessed total nephron number and clinicopathological findings in Japanese subjects in order to determine the structural and functional changes associated with nephron loss in each CKD stage.

Methods: Kidneys from 58 Japanese subjects were collected at Nippon Medical School, Tokyo, Japan during autopsy and were divided into three groups; CKD stage 1 (n=13, eGFR>90 mL/min), CKD stage 2 (n=24, eGFR 89-60 mL/min), and CKD stage 3-4 (n=21, eGFR 59-15 mL/min). Total nephron number (Nglom) and mean glomerular volume (Vglom) were estimated by design-based stereology. Single nephron eGFR (SNeGFR) was calculated as eGFR divided by two times the number of non-sclerotic glomeruli.

Results: Total nephron number per kidney was significantly lower in CKD stage 3-4 (293,198±110,087; mean±SD; P<0.001) than in CKD stage 1 (591,377±238,149) and CKD stage 2 (505,303±132,917). Glomeruli were larger in CKD stage 3-4 (P<0.001) than in CKD stages 1 and 2. Kidney weights were similar in the three groups, even though subjects with CKD stage 3-4 had lower cortical volumes and total glomerular volume (combined volume of all non-sclerotic glomeruli) than with CKD stages 1 and 2. Although no differences in SNeGFR were observed between the three groups, SNeGFR/Vglom, which predicts glomerular capillary filtration, was reduced in CKD stages 2 and 3-4 (P<0.001).

Conclusions: Compared with subjects with eGFR>60 mL/min, CKD stage 3-4 patients had an apparent nephron deficit, with glomerular hypertrophy partially compensating for the nephron loss. Our findings also suggest that glomerular capillary filtration starts decreasing in CKD stage 2.

Demographic and renal functional and structural data with CKD stages

	CKD stage1 (N=13)	CKD stage2 (N=24)	CKD stage3-4 (N=21)	ANOVA (P value)
Nglom	591,377±238,149	505,303±132,917	293,198±110,087	<0.001
Vglom (x10^{6} μm^{3})	6.39±1.79	7.09±1.53	10.52±3.77	<0.001
total glomerular volume (cm^{3})	3.42±1.12	3.21±0.89	2.48±1.17	0.038
Cortical volume (cm^{3})	84.8±29.8	80.8±19.5	65.3±20.6	0.038
SNeGFR (nl/min/1.73m^{2})	119.3±54.1	86.8±24.8	97.3±44.8	0.2771
SNeGFR/Vglom (ml/min/1.73m^{2}/cm^{3})	19.0±8.1	12.6±3.7	10.3±6.3	<0.001

mean±SD

FR-PO410

Intrarenal Renin-Angiotensin System Activation in Nighttime Is Associated with Renal Arteriosclerosis in Normotensive IgA Nephropathy Patients Naro Ohashi,[1] Shinsuke Isobe,[1] Takashi Matsuyama,[1] Sayaka Ishigaki,[1] Naoko Tsuji,[2] Tomoyuki Fujikura,[3] Takayuki Tsuji,[3] Akihiko Kato,[4] Hideo Yasuda.[5] *[1]Hamamatsu University School of Medicine, Hamamatsu, Japan; [2]Hamamatsu University School of Medicine, Hamamatsu, Japan; [3]Hamamatsu University School of Medicine, Hamamatsu, Japan; [4]Hamamatsu University School of Medicine, Hamamatsu, Japan; [5]Hamamatsu University School of Medicine, Hamamatsu, Japan.*

Background: Intrarenal renin-angiotensin system (RAS) activation especially in nighttime plays an important role in the development of hypertension and renal damage. However, the association between intrarenal RAS activation in daytime and nighttime and renal structural damages has not been clearly investigated in IgA nephropathy patients without hypertension.

Methods: We investigated the urinary angiotensinogen (U-AGT) excretion in daytime and nighttime that reflects intrarenal RAS activity and renal structural damages in 27 normotensive IgA nephropathy patients (age 39.2 ± 13.6 years, 10 men and 17 women, blood pressure 112.0 ± 11.8 / 70.0 ± 9.5 mmHg, estimated glomerular filtration rate (eGFR) 74.0 ± 17.3 ml/min/1.73m^2, urinary protein excretion 0.58 ± 0.50 g/day). Renal structural damages of renal biopsy tissues were scored as follows: the levels of arteriolar hyalinosis; the proportion of arterioles affected (0: absent, 1: 1-25%, 2: 26-50%, 3: 51-100%), the levels of arteriosclerosis in arcuate and interlobular arteries (0: normal, 1: intima thickness and less than media thickness, 2: intima thickness and more than media thickness), and percentages of global sclerosis (GS) and tubulointerstitial fibrosis, as described previously.

Results: The levels of arteriosclerosis were significantly and positively associated with U-AGT excretion levels in daytime and nighttime. On the other hand, the levels of arteriolar hyalinosis and percentages of GS and tubulointerstitial fibrosis were not correlated with the U-AGT excretion levels in daytime and nighttime. Multiple liner regression analysis revealed that the levels of arteriosclerosis tended to be associated with U-AGT excretion levels in daytime, when age, sex, body mass index (BMI), and eGFR were adjusted (β=0.33, p=0.079). Moreover, the levels of arteriosclerosis were significantly and positively associated with U-AGT excretion levels in nighttime after adjustment of age, sex, BMI, and eGFR (β= 0.39, p= 0.043).

Conclusions: In normotensive IgA nephropathy patients, the activation of intrarenal RAS especially in nighttime is associated with renal arteriosclerosis.

Funding: Government Support - Non-U.S.

FR-PO411

Performance Evaluation and Potential Utility of Urinary L-FABP as a Point of Care Device in CKD Nicos Mitsides,[1] Ananya Saha,[1] Ian Read,[1] Philip A. Kalra,[2] Sandip Mitra.[1] *[1]Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom; [2]Salford Royal Hospital NHS Trust, Salford, United Kingdom.*

Background: Liver-type fatty acid binding protein(L-FABP) is expressed by the proximal renal tubule during oxidative stress. Urinary L-FABP is released with tubular damage & is an established biomarker in acute kidney injury. However its value in Chronic Kidney Disease(CKD) & its progression has not been defined. We evaluate the clinical performance of a semi-quantitative point of care(POC) device for the detection of urinary L-FABP & assess the value of urinary L-FABP as a biomarker at different stages of CKD.

Methods: We report the baseline analysis of ELUDE, a multicentre study involving patients with CKD. Urine samples were tested for urinary protein creatinine ratio(PCR in mg/mmol) and urinary L-FABP using a semiquantitative POC & a quantitative ELISA(ug/gCr). A concomitant serum sample was analysed to calculate estimated glomerular filtration rate(MDRD eGFR in ml/min/1.73 m^2). CKD was staged as per KDOQI.

Results: In 624 CKD participants, 15% had CKD1-2(eGFR=77±11.0;uPCR=103±210.3), 13 % CKD3a(eGFR= 51±4.5;uPCR=46±89.9), 25% CKD3b (eGFR=36±4.5;uPCR=72±120.4), 33% CKD4(eGFR=22±4.5;uPCR= 139±191.5) & 15% CKD5 (eGFR=11±2.4;uPCR=265±282.2). The mean urinary L-FABP ELISA measurement was 21.0 ug/gCr. L-FABP levels increased with advancing stages of CKD(1-2: 4.3±19.1;3a: 7.2±30.4ug/L; 3b: 9.0±23.6ug/L; 4: 25.4±51.5ug/L; 5: 62.5±33.6ug/L). L-FABP correlated negatively with eGFR (r= -0.516, p<0.01) and positively with uPCR (r=0.567, p<0.01). The association of L-FABP with eGFR was more pronounced at advanced stages of CKD. In an adjusted linear regression model for prediction of eGFR, L-FABP was an independent predictor in CKD stages 4 (beta= -0.185, p=0.02) & 5 (beta= - 0.241, p=0.03) while PCR was only an independent predictor in CKD 5(CKD4:beta= -0.001, p=0.99;CKD5:beta= -0.243, p=0.03). POC derived L-FABP measurements correlated well with ELISA(r=0.656, p<0.01).

Conclusions: The study findings suggest that in advanced stages of CKD, L-FABP may be a more reliable predictor eGFR than proteinuria. High levels of L-FABP in advanced CKD 4 & 5 could reflect dominant tubular damage & atrophy & may act as a useful biomarker of progressive disease. Longitudinal follow-up data from this study will further inform these findings. POC device used in this study provides a reliable way of measuring urine L-FABP & may be of utility in the clinical setting

Funding: Commercial Support - CMIC Holdings LTD

FR-PO412

Soluble ST-2 and Galectin-3 and Risk of CKD Progression Mariam L. Alam,[8] Ronit Katz,[7] Keith A. Bellovich,[4] Zeenat Y. Bhat,[6] Frank C. Brosius,[2] Ian H. de Boer,[7] Crystal A. Gadegbeku,[5] Debbie S. Gipson,[3] Jennifer J. Hawkins,[3] Jonathan Himmelfarb,[7] Bryan R. Kestenbaum,[7] Matthias Kretzler,[1] Susan P. Steigerwalt,[3] Nisha Bansal.[7] *[1]U.Michigan, Ann Arbor, MI; [2]University of Arizona, Tucson, AZ; [3]University of Michigan, Ann Arbor, MI; [4]St. John Hospital Medical Center, Detroit, MI; [5]Temple University, Philadelphia, PA; [6]Wayne State University, Detroit, MI; [7]Kidney Research Institute, Seattle, WA; [8]University of Washington, Seattle, WA.*

Background: Cardiac biomarkers soluble ST-2 (sST-2) and galectin-3 may reflect inflammation and fibrosis. sST-2 and galectin-3 have been shown to be associated with cardiovascular events, but less is known about their associations with kidney disease. We examined associations of sST-2 and galectin-3 with kidney function decline in two chronic kidney disease (CKD) cohort studies.

Methods: The Clinical Phenotyping Phenotyping and Resource Biobank (CPROBE) and Seattle Kidney Study (SKS) are prospective studies of CKD patients. We measured serum concentrations of sST-2 and galectin-3 at baseline. Outcomes were 1) progression to end-stage renal disease (ESRD) (need for dialysis/transplant or eGFR <15 ml/min/1.73m^2) and 2) annualized relative change in eGFR. We used Cox regression and generalized estimating equation models to study the association of biomarker levels with kidney outcomes, adjusting for eGFR, urine ACR (UACR), demographics, cardiovascular disease, diabetes, body mass index, blood pressure and anti-hypertensive use.

Results: Among the 561 participants in CPROBE, the mean age was 55 ± 16 years, 42% were male and 35% had diabetes. Baseline eGFR was 55 ± 31 ml/min/1.73m^2 and median UACR was 217 (interquartile range [IQR] 16, 885) mg/g. Among the 280 SKS participants, the mean age was 62 ± 13 years, 82% were male and 56% had diabetes. Baseline eGFR was 42 ± 16 ml/min/1.73m^2 and median UACR was 118 (IQR 15, 626) mg/g. Incidence rates of ESRD were 5.41 (110 events) and 3.73 (30 events) per 100 person-years in CPROBE and SKS, respectively. Higher sST-2 was associated with a greater annual decline in eGFR in both CPROBE and SKS, but was not associated with progression to ESRD. Higher galectin-3 was associated with an increased risk of ESRD in CPROBE only (**Table**).

Conclusions: Higher levels of sST-2 and galectin-3 are associated with progression of CKD, highlighting possible shared cardiac and renal mechanisms that contribute to these diseases.

Funding: NIDDK Support

Table. sST-2 and galectin-3 and progression of CKD.

	Change in eGFR		ESRD	
	β (95% CI)*	p-value	HR (95% CI)**	p-value
sST-2 (per doubling)				
C-PROBE	**-3.25 (-5.63, 0.87)**	**0.009**	1.15 (0.81, 1.62)	0.439
SKS	**-3.35 (-6.18, -0.52)**	**0.023**	1.61 (0.59, 4.40)	0.354
Galectin-3 (per doubling)				
C-PROBE	0.46 (-1.14, 2.06)	0.572	**1.46 (1.07, 1.99)**	**0.016**
SKS	-2.42 (-4.91, 0.08)	0.061	0.67 (0.276, 1.64)	0.381

*β reflects mean difference in percent change in eGFR per year associated with a two-fold higher baseline biomarker concentration.
**HR reflects risk of ESRD associated with a two-fold higher baseline biomarker concentration.
***Models adjusted for age, race, gender, BMI, log(eGFR), log(UACR), education, smoking, cardiovascular disease, diabetes, systolic blood pressure and anti-hypertensive use.

FR-PO413

CKD Progression in Patients with Sickle Cell Trait Kabir O. Olaniran, Nwamaka D. Eneanya, Andrew S. Allegretti, Dihua Xu, Ravi I. Thadhani. *Massachusetts General Hospital, Malden, MA.*

Background: Sickle cell trait (SCT) has been shown in recent studies to be independently associated with incident CKD and progression to end stage renal disease (ESRD). We sought to confirm the risk for ESRD and glomerular filtration rate (GFR) decline in a multi-hospital cohort.

Methods: This was a multi-hospital retrospective cohort study in Boston using adult KDIGO criteria CKD patients between 2005-2017. Chart review was used to ascertain the following exposures: SCT and the reference group (RG; black race with CKD and normal hemoglobin electrophoresis). Primary outcomes were ESRD on dialysis (identified by diagnosis codes) and GFR decline (defined as a decrease in GFR ≧1ml/min per follow up year). Exposures confirmed by diagnosis code only were then added for sensitivity analysis.

Results: 915 CKD subjects were initially included (241 SCT and 674 RG). Baseline age was 54±15 years in SCT CKD and 52±17 years in the RG, p=0.266. The mean baseline GFR in SCT CKD patients was similar vs the RG (69±33ml/min vs 70±36ml/min, p=0.57) with similar proportions per CKD stage. Treatment with renin-angiotensin system inhibitors was not significantly different (88% SCT CKD vs 85% RG, p=0.26). No other significant differences in the baseline characteristics of the SCT CKD vs the RG were noted including smoking status, co-morbidities and treatments. After adjustment for age, co-morbidities and medications, we found significantly increased odds for GFR decline in SCT CKD (OR 1.7, 95% CI 1.1-2.6) compared to the RG. SCT CKD patients also had significantly increased odds for dialysis (OR 1.8, 95% CI 1.04-2.98) after multivariable analysis. Sensitivity analysis of 8,580 subjects (360 SCT and 8,220 RG) found similar results for GFR decline (OR 1.6, 95% CI 1.2-2.2) and dialysis (OR 1.9, 95% CI 1.3-2.9).

Conclusions: SCT with concurrent CKD is associated with an increased risk for GFR decline and requirement for dialysis in our cohort. More detailed studies are needed to determine risk factors for progression in this patient population.

FR-PO414

Factors Associated with Clinically Significant CKD and Their Clinical Utility in Primary Care Clinics in Singapore Quan Lan J. Lew,[3] Francis N. Nguyen,[4] John C. Allen,[1] Ngiap chuan Tan,[2] Tazeen H. Jafar.[1] *[1]Duke-NUS Graduate Medical School, Singapore, Singapore; [2]SingHealth Polyclinics, Singapore, Singapore; [3]Singhealth Polyclinic, Singapore, Singapore; [4]SingHealth, Singapore, Singapore.*

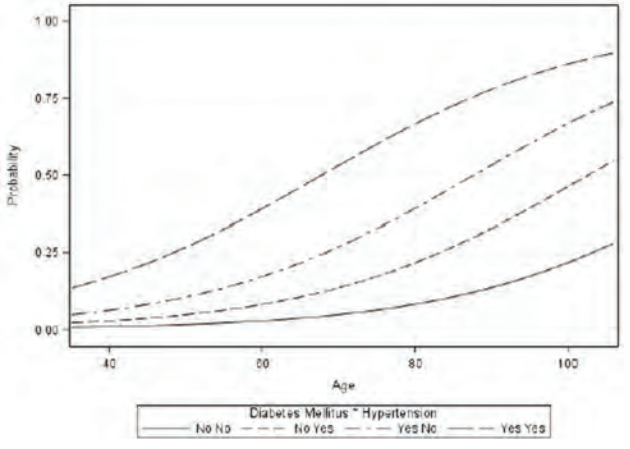
Background: Chronic kidney disease (CKD) is a major global public health challenge, including Southeast Asia. Factors associated with CKD in Singapore were determined by analyzing historical data on all individuals ≥ 40 years visiting 4 government polyclinics in Singapore from 1st Jan 2012 to 31st Dec 2015.

Methods: Clinically significant CKD patients had CKD-EPI serum creatinine-based estimated glomerular filtration rate < 60ml/min/1.73m^2 or 1+ dipstick proteinuria sustained ≥ 3 months. Multivariable and stepwise logistic regression analysis and receiver operator characteristic curve analysis were conducted for the outcome of clinically significant CKD.

Results: About 25.9% (95% CI: 25.6-26.2%) of the 88,765 individuals screened at Singapore Polyclinics (mean (SD) age of 65.9 (±11.1) years, and 53.3% women) had clinically significant CKD. Age [OR=1.06; 95% CI: (1.06-1.07) / year]; body mass index [1.02 (1.02-1.03) / kg/m^2]; male vs female [1.23 (1.17-1.27)]; Malay [1.31 (1.24-1.38)] and Indian [(0.80 (0.74-0.87)] vs Chinese; public vs private housing [1.25 (1.18-1.34)]; ever vs never smoker [1.08 (1.01-1.15)]; presence of hypertension [2.89 (2.69-3.11)], diabetes [7.23 (6.95-7.52)], or stroke [1.36 (1.27-1.45)] vs none were independently associated with clinically significant CKD. However, only age, presence of diabetes and hypertension incrementally added to the area under the curve of 0.808 (95% CI: 0.805-0.811) for clinically significant CKD.

Conclusions: Clinically significant CKD prevalence is high in primary care clinics in Singapore. Our results highlight the factors associated with clinically significant CKD and underscore the need for targeted screening of CKD in Southeast Asia.

Funding: Clinical Revenue Support



Probability of CKD increases with age, and presence of hypertension and diabetes.

FR-PO415

Long-term Prognosis and Predictive Factors of Non-Remission in IgA Nephropathy after Tonsillectomy and Steroid Pulse Therapy Kosuke Yamaka,[1] Keita Inui,[1] Yosuke Yamada,[1] Yuji Kamijo.[2] *[1]Shinshu University, Matsumoto CIty, Japan; [2]Shinshu University School of Medicine, Matsumoto, Japan.*

Background: Tonsillectomy and steroid pulse therapy (TSP) for IgA nephropathy (IgAN) is widely performed in Japan. However, the efficacy of TSP remains controversial, partly because even though IgAN is a chronic nephritis, most studies set the primary outcome as complete remission (CR) at 1 year after TSP and do not address long-term outcome. Therefore, we followed patients who had undergone TSP for a minimum of 3 years to clarify the long-term results and predictive factors of non-remission (NR) following TSP.

Methods: This retrospective, single-center, cohort study included 63 patients who were monitored for at least 3 years after TSP for IgAN at Shinshu University Hospital. The frequency of CR (urinary total protein <0.3 g/gCre and urinary red blood cells <5/high-power field) was assessed at 1 and 3 years following TSP. Using statistical methods, the predictive factors of NR at 3 years were investigated with relation to physical examination, serology, and urinalysis items.

Results: CR was observed in 29 (46%) patients at 1 year of follow-up. Of these, 6 (10%) experienced a recurrence and 23 (36%) maintained CR at 3 years. Among the 34 (54%) patients with NR at 1 year, 10 (16%) exhibited late remission and 24 (38%) remained unchanged at 3 years. Overall, tubulointerstitial fibrosis was significantly more severe in NR patients at 3 years than in CR patients (P<0.01). Among the 29 patients who showed CR at 1 year, tubulointerstitial fibrosis in patients with a recurrence at 3 years was significantly more severe as well (P<0.05). The most useful factor for predicting NR at 3 years was the well known tubulointerstitial injury marker urinary N-acetyl-β-D-glucosaminidase (U-NAG) according to receiver operator characteristic (ROC) analysis (cut-off: 4.35 U/gCre; sensitivity: 83%; selectivity: 75%; area under ROC curve: 0.817). Even in patients with CR at 1 year, those whose U-NAG was >4.35 U/gCre were more likely to relapse within 3 years (P<0.05).

Conclusions: At 3 years following TSP for IgAN, both recurrence and late remission are observed in relatively many patients. The severity of tubulointerstitial fibrosis is considered to be related to TSP resistance, and U-NAG represents a useful predictor of long-term prognosis.

FR-PO416

Epicardial Fat Is Associated with Traditional CV Risk Factors and Renal Function in Patients with Moderately Severe CKD Turgay Saritas,[5] Jonas Schmöe,[2] Jennifer Nadal,[1] Matthias Schmid,[10] Rolf Janka,[8] Christoph Wanner,[7] Kai-Uwe Eckardt,[6] Jürgen Floege,[4] Markus P. Schneider,[9] Georg Schlieper.[3,11] *[1]University of Bonn, Bonn, Germany; [2]University Hospital RWTH Aachen, Aachen, Germany; [3]University Hospital RWTH Aachen, Aachen, Germany; [4]University Hospital RWTH Aachen, Aachen, Germany; [5]University Hospital RWTH Aachen, Aachen, Germany; [6]University of Erlangen-Nuremberg, Erlangen, Germany; [7]University Hospital Wuerzberg, Wuerzburg, Germany; [8]University of Erlangen-Nuernberg, Erlangen, Germany; [9]Nephrology and Hypertension, University of Erlangen-Nuremberg, Erlangen, Germany; [10]University of Bonn, Bonn, Germany; [11]MVZ DaVita Karlstraße, Düsseldorf, Germany.*

Background: Pathological increase of epicardial adipose tissue (EAT) has been proposed as a novel, imaging-based predictor of CV events. How traditional CV risk factors associate with EAT enlargement in patients with moderately severe chronic kidney disease (CKD) has not been examined yet.

Methods: We analyzed data from 257 patients from CARVIDA (CARdioVascular In Depth Assessment), which is a multi-center substudy of the German Chronic Kidney Disease (GCKD) study. Patients were enrolled on the basis of an eGFR of 30-60 ml/min/1.73m^2 or overt proteinuria, and EAT was measured by computed tomography. Multivariable association of EAT with CV risk factors (age, gender, BMI, smoking, diabetes mellitus, hypertensive nephropathy, cholesterol, HDL, eGFR (CKD-EPI equation) and urine albumin-to-creatinine (UACR)) was assessed using linear regression analysis. Framingham 10-year CV disease risk score and ACC-AHA 10-year atherosclerotic CV disease (ASCVD) risk score were calculated for each patient.

Results: EAT showed a median level of 121 cm^3 (IQR: 81-162 cm^3). Prevalence of traditional CV risk factors increased with quartiles of EAT (all p < 0.05). Using multivariable analysis, higher EAT was significantly associated with the majority of investigated risk factors (age, gender, BMI, smoking, HDL) (Table 1). Of note, lower eGFR was independently associated with increased EAT (OR 0.997 (95% CI: 0.994-0.999), p<0.05). Finally, EAT correlated with estimated 10-year risk for CV disease by Framingham (spearman rho = 0.257, p =0.002; median risk score: 18.5%) and ASCVD (spearman rho =0.192, p =0.020; median risk score: 13.7%).

Conclusions: Epicardial fat is associated with traditional CV risk factors in the presence of CKD. Moreover, we observed that lower eGFR is also associated with EAT. EAT may thus be an integrative risk marker and follow-up of our patients will determine whether assessment of EAT improves the prediction of CV events in CKD.

Funding: Private Foundation Support, Government Support - Non-U.S.

Associations between Cardiovascular Risk Factors and Epicardial Fat Volume as obtained from Multivariable Adjusted Linear Regression

	Odds Ratio	95% CI	P-value
Age	1.010	1.006 - 1.014	<0.0001
Male	1.308	1.189 - 1.439	<0.0001
BMI	1.043	1.034 - 1.052	<0.0001
Smoking	(reference)	(reference)	(reference)
- Never smoked (reference)	1.146	1.048 - 1.253	0.003
- Former	1.183	1.035 - 1.352	0.014
- Current	0.982	0.885 - 1.091	0.738
Diabetes mellitus	1.087	0.970 - 1.219	0.150
Hypertensive Nephropathy	1.000	0.999 - 1.001	0.503
Cholesterol	0.997	0.995 - 1.000	0.048
HDL	0.997	0.994 - 0.999	0.005
eGFR	1.000	1.000 - 1.000	0.158
UACR			

FR-PO417

C-Reactive Protein Mediates the Association between Central Obesity and Microalbuminuria among Persons with the Metabolic Syndrome, Especially in African Americans Satyesh K. Sinha,[1,3] Magda Shaheen,[1,3] Deyu Pan,[1,2] Keith C. Norris,[2,3] Susanne B. Nicholas.[2,3] *[1]Charles R Drew University of Medicine and Science, Los Angeles, CA; [2]None, Westchester, CA; [3]University of California Los Angeles, Los Angeles, CA.*

Background: C-reactive protein (CRP), an inflammatory marker, is associated with the metabolic syndrome (MetS) and chronic kidney disease (CKD). However, little is known about the racial disparities of the effect of CRP on the association between individual components of the MetS and microalbuminuria (MA).

Methods: We analyzed National Health and Nutrition Examination Surveys (NHANES) data, (1999-2010) for adults (aged ≥20 years) with MetS (N=5700). We used multiple logistic regression to assess the independent relationship between MetS components and MA, adjusting for age, gender, race/ethnicity and estimated glomerular filtration rate (eGFR). We used the Sobel-Goodman mediation tests to examine the extent of how CRP influences the effect of MetS components on MA by race/ethnicity. We examined the association between CRP and MA and tested the ability of CRP to reclassify risk using the net reclassification index with and without CRP.

Results: In the multivariate model, CRP, as well as central obesity, blood pressure, fasting plasma glucose, and high-density lipoprotein (HDL), were independent predictors of MA, p<0.05. The mediation test showed that the proportion of total effect of the MetS components on MA, mediated by CRP, is: 0.11 for HDL and 0.40 for central obesity, p<0.05. These levels varied by race/ethnicity. The mediation effect of CRP for central obesity (highest prevalence in African Americans; AAs) was highest for AAs (0.94) compared to Whites (0.55) or Hispanics (0.18), p<0.05The addition of CRP to the adjusted model of MetS components, demographics and eGFR resulted in net reclassification improvement of 0.11 (standard error=0.03, p=0.002) but no significant change in the prediction of MA (receiver-operating characteristics–area under the curve; without CRP=0.66; with CRP=0.67).

Conclusions: We conclude that CRP mediates the association between MA and both HDL and central obesity. Importantly, for AAs, CRP mediates the relationship between MA and central obesity. **Grant Support:** Supported in part by NIH grants U54-MD-008149, UL1TR000124, P30AG021684, U54MD007598, and S21 MD000103.

Funding: Other NIH Support - U54-MD-008149, UL1TR000124, P30AG021684, U54MD007598, and S21 MD000103.

FR-PO418

A New Way to Assess CKD Progression: Correlation of Renal Ultrasound Measurements to Co-Morbidities, CKD Stages, and Total Renal and Parenchymal Cortical Volume Harish R. Alappan,[1] Raj Alappan,[3] Raj Sehgal.[2] *[1]Emory University - Undergraduate, Atlanta, GA; [2]Radiology Institute, Atlanta, GA; [3]Renal Associates, LLC, Columbus, GA.*

Background: Correlating Renal Ultrasound (US) data to co-morbidity and Chronic Kidney Disease (CKD) stages is sparse. Kidney's volumetric US data and trends have not been reported previously in CKD stages.

Methods: Initial CKD evaluation was conducted at Renal Associates. Clinical data and renal US done at the center were analyzed. Using the *M7-Mindray US System,* the same radiographer did the imaging and the same radiologist read images. 612 renal US images from Aug. 2014 to Jan. 2016 were analyzed. The Renal and Medullary sagittal, transverse and AP axis and cortical thickness for the right (RK) and left (LK) kidneys were measured in cm. Using Total Renal (TRV), and the Medullary (MV) volume, the Cortical (CV) volume was calculated. Using a correction constant for each kidney (RK=0.4891, LK=0.4886) the true renal Cortical tissue Volume (RCV) was determined for each kidney.

Results: Overall study (n=612): mean age was 63.87 yrs., 339 (55.3%) females, BMI 31.23, Cr 1.49 mg/dL, CrCl 73.02 mL/min, PTH 62.14 and HCO_3 at 25.52. The RK and LK sagittal size was 10.72 cm and 10.71 cm (p-NS), cortical thickness was 1.51 cm and 1.59 cm (p<0.004), renal stone 54(8.8%), and 204 had renal cysts (34.6%). CKD stages correlated to both RK and LK for corrected TRV of 171.23 cm^3 and 178.32 cm^3, Cortical tissue volume 151.09 cm^3 and 154.44 cm^3 (p<0.001), and Combined total cortical tissue volume in male 356.89 cm^3 and female 263.99 cm^3 (p<0.001). For 1mL of the RCV(cm^3), Cr Cl per mL ratio linearly increased as CKD Stages advanced (3.125 cm^3 in Stage-1 to 9.62 cm^3 in Stage-4). All males and diabetics had a larger sagittal, cortex and renal Cortical volume. Af. Am had thicker cortex (see Table).

Conclusions: This study is the first of its kind that correlates renal measurements on Total Renal Volume and Renal Cortical Volume to CKD Stages and other co-morbidities. Cortical thickness and volumetric corrected Renal Cortical Volume in cm^3 were accurate and significant. We propose with this study a new way to use ultrasound to monitor CKD progression.

SUB GROUP DATA ANALYSIS												
	Male	Female	p-Value	DM	No DM	p-Value	Caucasian	Af. Am	p-Value		TRCV cm^3	p-Value Comparison
Right Kidney – (All measurements in cm & cm^3)										Stage-1	393.551	
SAG	11.22	10.33	<0.0001	10.99	10.41	<0.00014	10.92	10.51	<0.0059	Stage-2	321.514	<0.0001
Trans	5.21	6.12	<0.0001	5.85	5.35	<0.0001	5.69	5.53	NS	Stage-3	257.347	<0.0001
AP	5.75	5.23	<0.0001	5.58	5.32	<0.0042	5.45	5.45	NS	Stage-4	238.493	<0.0001
Cortex	1.626	1.62	<0.0001	1.54	1.47	<0.015	1.459	1.56	<0.0014	Compared -Stage 1 to 2,3, & 4		
Cor. V	204.06	145.34	<0.0001	172.03	168.16	<0.0001	179.883	162.277	<0.009	CKD	cm^3/mL	mL/ cm^3
RCV	179.25	128.36	<0.0001	161.03	138.95	<0.00018	157.712	151.53	<0.013	Stage-1	3.125	0.319
Left Kidney – (All measurements in cm and cm^3)										Stage-2	4.425	0.225
SAG	11.9	10.31	<0.0001	10.93	10.45	<0.0047	10.94	10.496	<0.0071	Stage-3	5.487	0.182
Trans	6.39	5.72	<0.0001	6.16	5.87	<0.0028	6.02	6.04	NS	Stage-4	9.620	0.103
AP	5.41	4.97	<0.0001	5.25	5.05	<0.026	5.17	4.50	NS	AGE – (years)		
Cortex	1.693	1.5	<0.0001	1.55	1.47	NS	1.55	1.63	<0.019	<50	3.716	0.269
Cor. V	202.64	153.32	<0.0001	183.05	173.56	<0.015	182.17	170.19	<0.037	50-65	3.884	0.257
RCV	178.41	135.22	<0.0001	159.72	148.44	<0.036	156.98	151.54	NS	>65	4.616	0.216
TRCV	357.66	263.58	<0.0001	(TRCV = RK+LK RCV in cm^3)								

FR-PO419

Change in Creatinine-Based Estimated GFR versus Cystatin-C-Based Estimated GFR and Renal Outcome in Patients with CKD Su Hyun Kim,[6] Junseok Jeon,[5] Minjung Kim,[4] Hye Ryoun Jang,[1] Yoon-Goo Kim,[2] Dae Joong Kim,[6] Ha Young Oh,[6] Wooseong Huh,[3] Jung eun Lee.[4] *[1]None, Seoul, Republic of Korea; [2]Samsung Medical Center, Seoul, Republic of Korea; [3]Samsung Medical Center Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [4]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [5]Samsung medical center, Seoul, Republic of Korea; [6]Samsung medical center Sungkyunkwan University School of medicine, Seoul, Republic of Korea.*

Background: Many studies have demonstrated that an early change in estimated glomerular filtration rate (eGFR) predicts the risk of chronic kidney disease (CKD) progression. However, there are few studies comparing prognostic power between creatinine-based eGFR slope (eGFRcre slope) and cystatin-C-based eGFR slope (eGFRcys slope). This study examined which eGFR slope during first-year was superior in identification of high-risk group of progression to end-stage renal disease (ESRD) in patient with CKD.

Methods: From October 2010 to November 2016, patients who had simultaneous measurements of serum creatinine and cystatin-C more than 3 times for 1 year were identified. We calculated baseline eGFR values and first-year eGFR slopes using CKD-EPI equation and linear regression analyses. The patients with baseline eGFR ≥ 60 ml/min/1.73m² were excluded. We defined a rapid progression as eGFR slope < -5 mL/min/1.73m²/year. We assessed association between first-year eGFR slopes and progression to ESRD (defined as initiation of dialysis or kidney transplantation) by cox proportional hazard model.

Results: Total 857 patients were included. Forty% of subjects had diabetes. Baseline eGFRcre were 36.7 (25.8 – 47.2) ml/min/1.73m² and eGFRcys were 36.5 (25.3 – 49.1) ml/min/1.73m². During follow-up of 2.4 (1.3 – 3.3) years, 78 (9.1%) events occurred. Both eGFRcre slope and eGFRcys slope were associated with higher risk of ESRD independently of baseline eGFR (HR = 0.95 [0.93 – 0.97], HR = 0.96 [0.95 – 0.98], respectively). Both creatinine and cystatin-C based-rapid progression were associated with increased risk of ESRD (HR = 2.25 [1.44 – 3.52], HR = 1.77 [1.10 – 2.86], respectively). In subgroup analyses of rapid progression group by creatinine (N = 295), eGFRcys slope was not associated with risk of ESRD (HR = 0.99 [0.96 – 1.03], P = 0.68). Whereas, eGFRcre slopes contributed to further discrimination of higher risk of ESRD in subjects with rapid progression by cystatin-C (HR = 0.96 [0.93 – 0.98], P = 0.002).

Conclusions: These findings suggest that eGFRcre slope may be superior to eGFRcys in identification of high-risk group in patient with CKD.

FR-PO420

Laboratory Indices and Serum Biomarkers Associate with Prior Renal Functional Decline in CKD William P. Martin,[1] Serika D. Naicker,[1] Eibhlin M. Mccole,[2] Susan Logue,[1] Sarah Cormican,[1] Marie Mcgarvey,[2] Ciaran Richardson,[2] Ivan Mcconnell,[3] John Lamont,[3] John P. Ferguson,[4] Peter Fitzgerald,[3] Matthew D. Griffin.[1] *[1]Regenerative Medicine Institute, National University of Ireland, Galway, Ireland; [2]Randox Teoranta, Meenmore, Dungloe, Ireland; [3]Randox Laboratories Limited, 55 Diamond Road, Crumlin, United Kingdom; [4]HRB Clinical Research Facility, Galway, Ireland.*

Background: Prediction of renal functional decline in chronic kidney disease (CKD) is limited. We evaluated the relationship between laboratory indices and results from a novel serum biomarker chip assay with recent rate of decline of renal function.

Methods: Patients were recruited from Nephrology clinics at a tertiary referral center during 2014 and 2015, where they provided a serum sample for biomarker quantification with a novel multi-analyte chip assay. Relationships between laboratory indices and serum biomarkers at recruitment with slope of MDRD eGFR prior to recruitment were investigated using a custom weighted least squares algorithm adjusting for age, sex, and first eGFR during the study period.

Results: 170 subjects were identified (135 (79.4%) with native CKD, 35 (20.6%) with kidney transplants (KTs)). Mean age was 60.09 ± 17.38 years. 69 (40.6%) subjects were female. Native CKD stages were: 5 (3.7%) CKD1, 17 (12.6%) CKD2, 19 (14.1%) CKD3a, 40 (29.6%) CKD3b, 44 (32.6%) CKD4, and 10 (7.4%) CKD5. Median [IQR] number of eGFR measurements was 17.0 [10.8, 27.3] over 3.3 [2.4, 3.7] years prior to recruitment. Rate of eGFR decline was -2.59 ± 5.29 vs. -0.46 ± 5.27 mL/min/BSA/year in native CKD and KT subjects, respectively (p = .035). Analysis results for selected laboratory and biomarker indices are summarized in the Table.

Conclusions: Multiple serum biomarkers measured simultaneously with a novel chip assay and several laboratory indices were strongly associated with prior renal functional decline in CKD subjects. Retrospective eGFR trends may be of value for identifying biomarker signatures associated with rapid renal functional decline.

Funding: Commercial Support - Randox Teoranta, Meenmore, Dungloe, County Donegal, F94 TV06, Ireland

Association of serum laboratory indices and biomarkers with slope of MDRD eGFR by multivariable regression.

	n (%)	p
Serum Laboratory Indices		
Hemoglobin	170 (100.0%)	<001
Phosphate	169 (99.4%)	<001
Albumin	170 (100.0%)	<001
Serum Biomarkers		
Fatty acid-binding protein 1	130 (76.5%)	.009
Tumor necrosis factor soluble receptor 1	125 (73.5%)	<001
Tumor necrosis factor soluble receptor 2	129 (75.9%)	<001
Neutrophil gelatinase-associated lipocalin	130 (76.5%)	.006
Cystatin C	130 (76.5%)	<001

FR-PO421

Non-Steroidal Anti-Inflammatory Drug (NSAID) Use and ESRD in the Southern Community Cohort Study (SCCS) Fabian Bock,[1] Edward D. Siew,[1] Jennifer Morse,[2] Thomas G. Stewart,[2] William J. Blot,[1] Talat Alp Ikizler,[1] Loren Lipworth.[1] *[1]Div of Nephrology&Hypertension, Dept of Medicine, Vanderbilt University Medical Center, Nashville, TN; [2]Dept of Biostatistics, Vanderbilt University Medical Center, Nashville, TN.*

Background: Evidence suggests increased ESRD risk among NSAID users, but data are inconsistent and limited, particularly among blacks at high ESRD risk. The SCCS is a prospective study of ~86,000 individuals, two thirds black, in the southeastern US, where ESRD rates are high.

Methods: We assembled a case-cohort study from the SCCS, comprising 292 incident ESRD cases, identified by linkage with the US Renal Data System through March 2015, and a probability sample of 1453 SCCS participants, who donated a blood sample and had serum creatinine measured. Data were collected at baseline on regular use (2 times/week for ≥one month) of prescription and OTC analgesics, including NSAIDs. The analysis was restricted to those who reported using any analgesic. The association of NSAID use with ESRD was estimated with a logistic regression model adjusted for age, sex, race, smoking, hypertension, diabetes, arthritis, baseline eGFR, aspirin, acetaminophen, and an estimated propensity score (PS). The PS is the covariate-adjusted probability of being an NSAID user and was calculated with predictors of NSAID use as covariates.

Results: At enrollment, mean (SD) age was 53 (8) and 55 (9) years among ESRD cases and subcohort controls, and 78% and 62%, respectively, were black. Median (25th, 75th percentile) baseline eGFR of cases and controls was 78 (39, 109) and 98 (83, 113) ml/min/1.73 m², respectively. Overall, NSAID, aspirin and acetaminophen use were reported by 38%, 53% and 33% of ESRD cases, respectively, compared to 53%, 40% and 33% of controls. Table 1 shows the distribution of analgesic use by baseline eGFR. In adjusted analyses, compared to non-NSAID analgesic users, the OR (95% CI) for the association between NSAID use and ESRD was 0.83 (0.54-1.27).

Conclusions: Among analgesics users, 25% of cases with baseline eGFR<60 used NSAIDs, but NSAID use was not significantly associated with risk of ESRD.

Funding: Other NIH Support - National Cancer Institute (R01CA092447) and American Recovery and Reinvestment Act (3R01CA092447-08S1), Other U.S. Government Support

Table 1

	NSAID (%)	Aspirin (%)	Acetaminohen (%)
eGFR (ml/min/1.73 m2)	Case/Subcohort	Case/Subcohort	Case/Subcohort
<= 60	25.2/53.0	59.4/39.3	32.9/23.8
60 < eGFR <= 90	50.7/52.6	56.3/42.0	20.3/31.8
> 90	43.3/53.8	46.6/39.2	37.8/34.6

FR-PO422

Indian Chronic Kidney Disease (ICKD) Study: A Prospective Cohort Study of CKD Patients in India Ashok K. Yadav,[3] Vivek Kumar,[9] Shobhit Bhansali,[3] Gopesh K. Modi,[2] Sishir D. Gang,[7] Jai Prakash,[1] Dipankar Sircar,[5] Sreejith Parameswaran,[6] Narayan Prasad,[10] MANISHA SAHAY,[8] Santosh Varughese,[11] Shivendra Singh,[1] Vivekanand Jha.[4] *[1]Banaras Hindu University, Varanasi, India; [2]Samarpan kidney Institute & Research Ctr., Bhopal, India; [3]Nephrology, PGIMER, Chandigarh, India; [4]George Institute for Global Health, New Delhi, India; [5]IPGMER, SSKM HOSPITAL, KOLKATA, India; [6]JIPMER, Ponidcherry, India; [7]MULJIBHAI PATEL UROLOGICAL HOSPITAL, Nadiad, India; [8]OSMANIA HOSPITAL, HYDERABAD, India; [9]Postgraduate Institute of Medical Education and Research, Chandigarh, India; [10]SGPGIMS CAMPUS, Lucknow, India; [11]Nephrology, CMC, Vellore, India.*

Background: The Indian Chronic Kidney Disease (ICKD) study (https://ickd.georgeinstitute.org.in/) is a multi-centric, prospective, observational cohort study of early stage CKD patients in India which will ascertain rate and factors influencing progression of CKD in India.

Methods: Adult subjects with mild to moderate CKD [estimated glomerular filtration rate (eGFR) 30-60 ml/min/1.73m² or eGFR >60 ml/min/1.73m² with proteinuria/albuminuria] are eligible for enrolment. Approximately 5000 subjects would be enrolled over 18 months. Time to 50% decline in eGFR, need of renal replacement therapy, CVD event or death are primary end points. A central bio-repository with serial biological samples is coupled with this cohort. Socio-economic aspects of treatment will also be studied.

Results: A total of 1567 subjects have been enrolled in the ICKD cohort till May 2017. The cause of CKD could not be ascertained in 25% of subjects. Chronic glomerulonephritis, diabetic kidney disease and chronic interstitial nephritis are causes for CKD in 16.5%, 18% and 17% of subjects, respectively. Tables 1 shows selective demographic characteristics of enrolled subjects. Majority are males belonging to rural areas with occupation exposure to sand, dust, chemicals or animals etc. 24% subjects had used alternative drugs and 10% had history suggestive of AKI in the past.

Conclusions: This is the first and most comprehensive description of an early stage CKD cohort from a developing country.

Funding: Government Support - Non-U.S.

Table 1: Selected demographic details of ICKD study subjects (n=1567)

Characteristics	Mean ± SD or No. of subjects (% of total)
Age (Years)	50.1±12.0
Male sex	1066 (68.0)
BMI (Kg/m²)	25.5±23.8
Waist/Hip ratio	1.90±0.2
Systolic blood pressure (mmHg)	133.3±19.9
Diastolic blood pressure (mmHg)	83.5±10.5
Disease duration (months)	43.6±171.8
Education: graduates and above	470 (30.0)
Residence: rural or semi-urban	938(59.8)
Occupational exposure to sand, dust, chemicals, animals etc.	528(33.7)
Strict vegetarians	536(34.4)
Family history of kidney disease present	148(9.5)
History of hypertension	1061(67.7)
History of diabetes	474(30.2)
History of use of alternative drugs or medicines	377(24.1)
History of AKI	154(9.8)
History of NSAIDS use after diagnosis of kidney disease	48(3.1)
Smoking history	491(31.3)
History of vaccination against hepatitis B	406(25.9)
Medical insurance available	431(27.5)
Monthly income (USD)	232.7(93.1-465.8)
Monthly medication cost (USD)	33.8 (13.8-61.5)

FR-PO423

GDF-15 and FGF-23 Are Associated with Mortality in Type 2 Diabetic Patients with Microalbuminuria Marie Frimodt-møller,[1] Bernt Johan Von Scholten,[1] Henrik Reinhard,[1] Tine Hansen,[1] Frederik Persson,[1] Hans-Henrik Parving,[2] Peter Rossing.[1,3] *[1]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [2]Rigshospitalet, Copenhagen, Denmark; [3]Copenhagen University, Copenhagen, Denmark.*

Background: We evaluated growth differentiation factor 15 (GDF-15) and fibroblast growth factor 23 (FGF23) reflecting different aspects of renal pathophysiology as determinants of decline in estimated glomerular filtration rate (eGFR), incident cardiovascular disease (CVD) and all-cause mortality in patients with type 2 diabetes (T2D) and microalbuminuria, but without clinical coronary artery disease

Methods: Prospective study including 200 patients. GDF-15 and FGF23 were measured at baseline. Adjusted Cox models included sex, age, LDL cholesterol, smoking, HbA_{1c}, creatinine, systolic blood pressure urine albumin excretion rate (UAER) and for FGF23 also 25(OH)vitamin D. *Main outcome measures:* A decline in eGFR of >30%, at any time point during follow-up was the predefined endpoint of CKD progression. Hazard ratios (HR) are provided per 1 SD increment of log-transformed values of the biomarkers.

Results: Patients were (± SD) 59 ± 9 years old, eGFR 91.1 ± 18.3 ml/min/1.73m² and UAER (IQR) 103 (39–230) mg/24-h. During a median 6.1 years follow-up, there were 40 incident CVD events, 26 deaths and a total of 42 patients reached the renal endpoint after 4.9 years (median). Higher GDF-15 was a determinant of decline in eGFR >30% in unadjusted (HR (95% CI) 1.7 (1.3-2.4); p=0.001) and adjusted (HR 1.7 (1.1-2.5); p=0.018) models, a predictor of CVD in the unadjusted model (HR 1.4 (1.0-1.9); p=0.034) and of all-cause mortality in unadjusted (HR 1.8 (1.3-2.6); p<0.001) and adjusted (HR 1.9 (1.2-2.9); p=0.003) models. Higher FGF-23 was associated with all-cause mortality in unadjusted (HR 1.5 (1.1-2.0); p=0.010) and adjusted (HR 1.6 (1.1-2.2); p=0.011) models.

Conclusions: In patients with T2D and microalbuminuria, GDF-15 was independently associated with decline in kidney function and all-cause mortality, and higher FGF23 was associated with all-cause mortality.

FR-PO424

Cigarette Smoking Exacerbated the Pathology of Diabetic Nephropathy with Severity of interstitial Inflammation Infiltration: A Multi-Center Study in Male Adults Qian Q. Han. *West China Hospital, ChengDu, SiChuan, China.*

Background: Cigarettes smoking have been identified as a progression factor in various kidney diseases, but no exact statement has been shown in DN at present. So we aim to investigate the association between cigarette smoking and renal injury of biopsy-proven diabetic nephropathy (DN) in male adults from Southwest China to provide more evidence for management.

Methods: A total number of 171 male adult patients with DN proven by renal biopsy from multicenter in Southwest China were recruited in our study. The patients are divided

into three groups according to smoking state: non-smoker, ex-smoker, and current smoker. Clinical data and pathological characteristics of all three groups were collected. Logistic regression analyses, with or without multivariable adjustments for other risk factors for DN, were used to evaluate the risk of pathology of DN based on the smoking status.

Results: Cigarette smoking is associated with the pathology of DN. Both the unadjusted regression analyses and the multivariable adjusted regression analyses suggested cigarette smoking was a risk factor for severity of glomerular lesions (p=0.030 & 0.030 respectively) and interstitial inflammation infiltration (p= 0.009 & 0.009 respectively) when compared with non-smoking group, and arterial hyaline (p=0.014 and 0.015 respectively) when compared with ex-smoking group. Especially, both unadjusted (p=0.01, OR=14.73) and multivariable adjusted (p=0.01, OR=17.50) regression analyses strongly significantly suggested that smoking was risk for interstitial inflammation. When analysing the subgroups divided by eGFR and urine protein, the results were still significant.

Conclusions: Smoking may be an independent risk factor for glomerular lesions, interstitial inflammation infiltration of DN, while persistent smoking is a risk factor for arterial hyaline, which suggesting no smoking or cessation of smoking is recommended for patients with diabetic nephropathy.

Funding: Private Foundation Support, Clinical Revenue Support, Government Support - Non-U.S.

FR-PO425

Self-Reported Tobacco, Alcohol, and Illicit Drug Use and Progression of CKD: The CRIC Study

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Background: The associations of tobacco, alcohol, and illicit drug use with risk of chronic kidney disease (CKD) progression and all-cause mortality have not been well studied among patients with CKD.

Methods: The Chronic Renal Insufficiency Cohort (CRIC) Study is a prospective cohort study of 3939 adults with CKD recruited from seven US clinical sites. Self-reported questionnaires annually assessed current smoking, weekly drinking (consumed alcohol ≥1 days per week), any marijuana use, and any hard illicit drug use (use of cocaine, heroin, or methamphetamine). CKD progression was defined as halving of estimated glomerular filtration rate (eGFR) or initiation of dialysis or kidney transplant. Deaths were confirmed by death certificate. Multiple time-dependent Cox regression was used to assess the associations of drug use with progression of CKD and all-cause mortality.

Results: Over an average 5.4-year follow-up, 1287 participants had CKD progression and 1001 died. Current smoking and hard illicit drug use were significantly associated with increased risk of CKD progression or all-cause mortality (Table).

Conclusions: Among patients with CKD, current smoking and hard illicit drug use may increase the risk of CKD progression and all-cause mortality.

Funding: NIDDK Support

Table. Hazard ratios (95% confidence intervals) of CKD progression and mortality associated with annually-updated drug use

	Age, sex, race, and clinical site-adjusted		Multivariable-adjusted*	
	HR (95% CI)	P Value	HR (95% CI)	P Value
CKD progression				
Current smoking	1.17 (1.00-1.38)	0.05	1.10 (0.93-1.30)	0.26
Weekly drinking	0.62 (0.53-0.74)	<0.001	0.88 (0.74-1.05)	0.15
Marijuana use	0.92 (0.81-1.04)	0.18	0.88 (0.78-1.00)	0.06
Hard illicit drug use	1.33 (1.07-1.65)	0.01	1.27 (1.02-1.58)	0.03
All-cause mortality				
Current smoking	1.80 (1.52-2.14)	<0.001	1.80 (1.50-2.14)	<0.001
Weekly drinking	0.63 (0.52-0.77)	<0.001	0.78 (0.64-0.96)	0.02
Marijuana use	1.12 (0.96-1.29)	0.14	1.07 (0.92-1.24)	0.38
Hard illicit drug use	1.61 (1.26-2.06)	<0.001	1.30 (1.01-1.67)	0.04
CKD progression or all-cause mortality				
Current smoking	1.32 (1.16-1.51)	<0.001	1.23 (1.07-1.40)	0.003
Weekly drinking	0.67 (0.58-0.77)	<0.001	0.91 (0.79-1.05)	0.20
Marijuana use	0.95 (0.85-1.05)	0.31	0.90 (0.81-1.00)	0.06
Hard illicit drug use	1.36 (1.14-1.63)	0.001	1.22 (1.01-1.47)	0.04

*Adjusted for age, sex, race/ethnicity, clinical site, estimated glomerular filtration rate, history of diabetes, body mass index, systolic blood pressure, hemoglobin, use of non-steroidal anti-inflammatory drugs, and current smoking

FR-PO426

Lower School Educational Level Is Associated with Lower eGFR in Patients with Moderately Severe CKD: The GCKD Study

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Background: Low socioeconomic status (SES) is associated with increased prevalence of chronic kidney disease (CKD) and mortality. However, previous studies were mainly conducted in the U.S. population. This study evaluated the association between SES and kidney function in a large German cohort of patients with moderately severe CKD.

Methods: We analyzed data from 5111 patients of the German CKD (GCKD) study, who were enrolled on the basis of an eGFR of 30-60 mL/min or overt proteinuria. Patients were divided into three categories according to their school educational level: "low" (completed ≤ 9th grade), "intermediate" (10th grade) and "high" (≥12th grade). In addition, patients were stratified in four groups according to their annual household income: ≤25.000 €; 25.000 to <50.000 €; 50.000 to <100.000 €; ≥100.000 €. An ordinal logistic regression was run to determine the association of education and income on eGFR (<30, 30-44, 45-59, >60 mL/min) and urine albumin-to-creatinine ratio (UACR) (<30, 30-300, >300mg/g), adjusted for multiple confounders.

Results: In comparison with those who had high school education, patients with low education had lower eGFR (median eGFR 43 vs. 51 ml/min, $p < 0.001$). However, autoimmune disease was more prevalent and UACR was higher (median 78 vs. 48 mg/g) in patients with high education ($p < 0.001$). An association was also found between low education and low annual household income, and the prevalence of diabetes mellitus, hypertension, coronary heart disease, stroke, and arrhythmia ($p < 0.001$). Similar significant differences were observed by comparing patients with low income vs. high income. In multivariate analysis, the odds ratio of being in a lower category of eGFR for low educated vs. high-educated patients was 1.254 (95% CI: 1.077 - 1.459); $p = 0.003$. No significant association was found between income and eGFR levels. Furthermore, no association was found between education/income and UACR categories.

Conclusions: Within the GCKD cohort, low education level but not income was independently associated with lower eGFR. Furthermore, low education and low income were associated with a greater burden of comorbidities.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO427

Hyperfiltration Predicts Rapid GFR Decline in a General Non-Diabetic Population and in Type 2 Diabetes

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Background: An abnormally high glomerular filtration rate (GFR), or renal hyperfiltration, may predispose individuals to subsequent rapid GFR decline in diabetes, prediabetes, obesity, and hypertension. This hypothesis remains controversial; however, in diabetes, it is supported by clinical trials showing that treatments that acutely reduce the GFR, such as ACE inhibitors and sodium-glucose cotransport inhibitors, may reduce medium-term GFR decline.

Methods: We investigated whether a higher GFR predicts a steeper long-term GFR decline in two diverse populations, Pima Indians with type 2 diabetes (N=319) and non-diabetic Caucasians in Norway (the Renal Iohexol Clearance Survey [RENIS], N=1594). Because spurious correlations between initial values (e.g., GFR level) and subsequent changes may bias ordinary regression methods, we assessed this relationship as the correlation between the random intercept and random slope in a linear mixed model. This method separately estimates the error term (e.g., the day-to-day variation in the GFR) and random effects, eliminating bias because of regression to the mean.

Results: The mean (SD) baseline GFRs were 149.4 (43.3) and 104.0 (20.1) ml/min, and the median (IQR) follow-up times were 9.1 (4.0-15.0) and 5.6 (5.2–6.0) years in the Pima and RENIS cohorts, respectively. Higher body weight and higher fasting plasma glucose concentration were associated with a higher baseline GFR (a higher intercept) in both cohorts in multivariable adjusted linear mixed regression models with a random intercept and slope ($p<0.001$). The adjusted correlation between the random intercept and random slope was -0.42 (95% confidence interval, -0.55 to -0.26) in the Pima cohort and

-0.32 (-0.40 to -0.23) in the RENIS cohort, demonstrating that higher baseline GFRs were associated with a steeper GFR decline.

Conclusions: Renal hyperfiltration predicts accelerated long-term GFR decline in type 2 diabetes and in the general non-diabetic population.

Funding: NIDDK Support, Commercial Support - Boehringer Ingelheim, Government Support - Non-U.S.

FR-PO428

Predictors of Net Acid Excretion in the Chronic Renal Insufficiency Cohort (CRIC) Study Landon C. Brown,[1] Alison Luciano,[1] Jane F. Pendergast,[1] Pascale Khairallah,[1] Cheryl A. Anderson,[2] James H. Sondheimer,[3] L. Lee Hamm,[4] Ana C. Ricardo,[5] Panduranga S. Rao,[6] Mahboob Rahman,[7] Edgar R. Miller,[8] Daohang Sha,[9] Dawei Xie,[9] John R. Asplin,[10] Harold I. Feldman,[9] Myles S. Wolf,[1] Julia J. Scialla.[1] *[1]Duke University School of Medicine, Durham, NC; [2]University of California San Diego, La Jolla, CA; [3]Wayne State University School of Medicine, Detroit, MI; [4]Tulane University School of Medicine, New Orleans, LA; [5]University of Illinois at Chicago, Chicago, IL; [6]University of Michigan Health System, Ann Arbor, MI; [7]Case Western Reserve University, Cleveland, OH; [8]Johns Hopkins University, Baltimore, MD; [9]University of Pennsylvania, Philadelphia, PA; [10]Litholink Corp, Chicago, IL.*

Background: In prior work, higher urine net acid excretion (NAE) was associated with lower risk of chronic kidney disease (CKD) progression in patients with diabetes. In order to (1) evaluate potential mechanisms underlying associations between NAE and outcomes, and (2) assess modifiable components for future intervention, we now evaluate independent predictors of NAE in the CRIC Study.

Methods: CRIC is a cohort of adults with entry estimated glomerular filtration rate (eGFR) of 20-70 ml/min/1.73 m^2. 24h NAE was measured as the sum of urine NH_4^+ and titratable acidity in a subset, excluding those with urine pH <4 or ≥7.4 (n=20) and 2 extreme outliers (final n=978). We identified individual variables and sets of variables associated with NAE across the domains of demographics, comorbidities, laboratory measurements, diet, body composition, and medications using linear regression and domain-specific model adjusted R^2.

Results: Mean ± SD of NAE was 33.2 ± 17.4 mEq/day and was higher among those with diabetes (n=496) vs. without diabetes (n=482, 34.4 ± 18.7 vs. 31.9 ± 15.9 mEq/day; p=0.02). Multiple variables associated with NAE in models adjusted for age, sex, eGFR, race/ethnicity, and body surface area (Table). By domains, most variance was explained by demographics, body composition, and laboratory values including kidney function and serum bicarbonate. Among medications, several metabolically active agents including biguanides and allopurinol associated with NAE.

Conclusions: NAE relates to body composition and metabolic factors in addition to diet. This result may help explain previously observed associations between NAE and kidney outcomes in diabetes.

Funding: NIDDK Support

Table. Variable Domains and Selected Individual Variables Associated with NAE (mEq/day)

Domain*	Variance explained (adjusted R^2)	Selected variables from domain	Adjusted difference in NAE (95% CI) – Association	+ Association
Demographics	9.9%	-	-	-
Body Composition	13.0%	-	-	-
	-	Body Mass Index (per 5 kg/m^2) ‡		2.58 (1.95, 3.21)
	-	Body Surface Area (per 0.3 m^2)		1.70 (1.34, 2.06)
Comorbidities	2.9%	-	-	-
	-	HOMA-IR (per 1 mmol/L x mU/L) §		0.18 (0.05, 0.31)
	-	Systolic BP (per 5 mmHg)	-0.24 (-0.47, -0.01)	
Medicines	2.7%	-	-	-
	-	Allopurinol (n=111/978)		3.50 (0.28, 6.71)
	-	Biguanide (n=64/978)		4.66 (0.59, 8.74)
	-	Non-statin lipid lowering agent (n=137/978)		3.21 (0.33, 6.08)
	-	NSAID (n=509/978)		2.15 (0.11, 4.18)
Laboratory Values	13.4%	-	-	-
	-	eGFR (per 5 ml/min/1.73 m^2)		1.01 (0.66, 1.37)
	-	Serum Bicarbonate (per 1 mmol/L)	-0.60 (-0.92, -0.28)	
	-	Serum Albumin (per 1 g/dL)		3.18 (0.93, 5.42)
	-	Hemoglobin (per 1 g/dL)		0.64 (0.00, 1.29)
Diet	6.6%	-	-	-
	-	PRAL (per 10 mEq/day) ‖		0.89 (0.31, 1.46)
	-	Protein (per 10 g/day)		0.53 (0.18, 0.88)

* Domains include selected variables as listed plus the following: Demographics: Age, sex, race/ethnicity, education; Body Composition: Free fat mass by bioimpedance, waist circumference; Comorbidities: Diabetes, lung disease; Medicines: ACEI/ARB, diuretics, insulin, sulfonylurea; Laboratory values: Serum BUN, Diet: Potassium, total calories, sodium
‡ BSA removed from multivariable model when BMI added due to collinearity
§ HOMA-IR, a measure of insulin resistance is proportional to the fasting glucose concentration x fasting insulin concentration
‖ PRAL=potential renal acid load (mEq/day)

FR-PO429

Association of Low Bicarbonate with Increased Risk of Mortality, Dialysis, and Hospitalization in CKD Patients Jerry M. Buysse,[2] David A. Bushinsky,[4] Elizabeth Li,[1] Sarah McNulty,[3] Gerrit Klaerner.[3] *[1]PharmaStat, LLC, Newark, CA; [2]Tricida, Inc, South San Francisco, CA; [3]Tricida, Inc., South San Francisco, CA; [4]University of Rochester Medical Center, Rochester, NY.*

Background: Low bicarbonate has been associated with a higher risk of mortality, dialysis, and hospitalizations in CKD patients. Here we estimate these risks across different levels of low bicarbonate, compared to normal, in a database of 59,710 patients with stage 3-5 CKD (ICD9 585.4, 585.5) or eGFR <60 mL/min/1.73m^2 (Optum Electronic Health Record Dataset, 2007 – 2016).

Methods: Within this database, 43,777 patients were identified with a baseline bicarbonate of ≥12 to <29 mEq/L and baseline eGFR <60 mL/min/1.73m^2. Time-to-event analyses on this dataset evaluated death, progression to dialysis, and first hospitalization or emergency room (ER) visit by baseline bicarbonate groups: 12 – 20 (low), >20 – 22 (moderately low), and >22 – <29 (normal) mEq/L. Hazard ratios (HRs; 95% CIs) for these outcomes in the low and moderately low groups, compared with normal, were determined using a Cox regression model adjusted for time-independent covariates (age, gender, diabetes, hypertension, cerebrovascular disease, and baseline eGFR).

Results: Bicarbonate was low in 6,558 (15%), moderately low in 6,599 (15%) and normal in 30,620 (70%) of patients and the overall mean eGFR was 34.9 mL/min/1.73m^2. Compared with normal, the mortality HRs were 2.63 (95% CI, 2.46 to 2.80) in the low and 1.47 (95% CI, 1.36 to 1.59) in the moderately low bicarbonate groups (p<0.0001). The HRs for progression to dialysis and hospitalization/ER visits were 1.46 (95% CI, 1.32 to 1.62) and 1.46 (95% CI, 1.38 to 1.55), respectively, in the low bicarbonate group (p<0.0001); in contrast, the moderately low bicarbonate group had the same risk as normal for these outcomes [1.10 (95% CI 0.97, 1.24), p=0.13 and 1.08 (95% CI 1.01, 1.15), p=0.02, respectively, for dialysis and hospitalization/ER visits].

Conclusions: There is a strong correlation between low bicarbonate and risk of adverse outcomes (death, dialysis, hospitalizations or ER visits) in CKD, and the risk of these outcomes is significantly greater in patients with low bicarbonate levels (12 – 20 mEq/L) compared to those with normal bicarbonate levels (>22 – <29 mEq/L).

Funding: Commercial Support - Tricida, Inc.

FR-PO430

The Association of Metabolic Acidosis with Renal Progression in CKD: Results from the KNOW-CKD Study Hyo Jin Kim,[1] Hyunjin Ryu,[3] Eunjeong Kang,[3] Miyeun Han,[4] Curie Ahn,[3] Kook-Hwan Oh.[3] *[1]Department of Internal Medicine, Dongguk University College of Medicine, Gyeongju-si, Republic of Korea; [3]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, GyeongGi-Do, Republic of Korea; [4]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea.*

Background: Metabolic acidosis, usually manifested by low serum bicarbonate level, is prevalent in chronic kidney disease (CKD). However, its relationship to long-term outcomes is unclear in Korean CKD patients. The purpose of the present study is to evaluate serum bicarbonate as a risk factor for renal outcomes, cardiovascular events and mortality in large-scale Korean CKD cohort patients.

Methods: Among the subjects recruited in the KoreaN Cohort Study for Outcome in Patients With Chronic Kidney Disease (KNOW-CKD) between 2011 and 2016, we analyzed 1,809 participants who measured for serum bicarbonate levels. Serum bicarbonate level was categorized as low, lower normal, higher normal, and high (< 22, 22-26, 26.1-29.1, ≥30 mmol/L, respectively) groups. Metabolic acidosis was defined as serum bicarbonate < 22 mmol/L. The primary outcome was renal events defined as doubling of serum creatinine, 50% reduction in eGFR from the baseline values, or end-stage renal disease. The secondary composite outcome consisted of cardiovascular events and death.

Results: Patients were 53.6±12.3 years old. The mean serum bicarbonate level was 25.7±3.7 mmol/L. A total 240 (13.3%) patients had metabolic acidosis. Patients were followed for 36.3±17.5 months. After adjustment, there was no significant association between serum bicarbonate and renal outcomes. There was significant interaction of serum bicarbonate with eGFR (interaction *P*=0.029). In an analysis with adjustment, in a subgroup with eGFR ≤45ml/min/1.73m^2, the risk of developing renal outcomes was significantly increased with decreasing (HR, 0.91; 95% CI, 0.87-0.94; *P*<0.001) and the low bicarbonate group was associated with a HR of 1.72 (95% CI, 1.28-2.32; *P*<0.001) compared with lower normal group. Serum bicarbonate was not independently associated with renal outcomes in those with eGFR >45ml/min/1.73m^2 (HR 0.92; 95% CI, 0.78-1.08; *P*=0.297). Serum bicarbonate was not independently associated with secondary outcomes neither in eGFR ≤45 (HR 0.96; 95% CI, 0.89-1.04; *P*=0.339) nor in eGFR >45ml/min/1.73m^2 (HR 0.90; 95% CI, 0.79-1.02; *P*=0.086).

Conclusions: In a cohort of participants with CKD, metabolic acidosis was an independent risk factor for renal progression, particularly for those with advanced decreasing kidney function.

Funding: Government Support - Non-U.S.

FR-PO431

Urinary Citrate Concentrations in a Multi-Ethnic Asian Population of Healthy Participants and CKD Patients Clara L. Ngoh,[2] Boon Wee Teo.[1,2] *[1]Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore; [2]Department of Medicine, University Medicine Cluster, National University Health System, Singapore, Singapore.*

Background: Hypocitraturia is a risk factor for nephrolithiasis. Urinary metabolomics from non-Asian centres have suggested that urinary citrate is important for chronic kidney disease (CKD) progression. We studied clinical associations between urinary citrate concentrations and CKD in a multi-ethnic Asian population.

Methods: Data of 187 CKD patients and 87 healthy participants from the Asian Kidney Disease Study and the Singapore Kidney Function Study were used. Four ethnic groups (Chinese, Malay, Indian and Others) were included. Glomerular filtration rate (eGFR) was estimated using the CKD Epidemiology Collaboration (CKD-EPI) equation. Urine citrate concentration was assayed using fluorescence mass-spectrometry. Hypocitraturia was defined as 24-hour urinary citrate excretion (UCE) <320 mmol.

Results: The mean 24-hour UCE in healthy controls and patients were 336 (209 - 443) mmol and 143 (63 - 208) mmol (CKD 1 and 2); 63 (17 - 93) mmol (CKD 3) and 21 (4 - 39) mmol (CKD 4 and 5) respectively (P <0.001). Hypocitraturia was first observed when eGFR <89 ± 12 ml/min/1.73 m^2. Hypocitraturia was also significantly associated with dietary protein intake (P =0.045), eGFR (P <0.001), metabolic acidosis (P <0.001)

and 24-hour proteinuria (P <0.001). In each CKD strata, Malay patients had the lowest 24-hour UCE (difference of 17 ± 24 mmol, P =0.025), after adjusting for age, eGFR, dietary protein intake and chronic medications. In the Malay population, 24-hour UCE was also associated with a history of coronary artery disease (P <0.001), but was not a risk factor for urolithiasis (P =0.590). In healthy controls, there were no ethnic disparities.

Conclusions: Hypocitraturia is observed in early CKD, with Asian ethnic disparities in terms of degree of UCE reduction. This has prognostic implications for renal and cardiac function. Further urinary metabolomics studies should focus on UCE to identify key signature differences between different Asian ethnic groups.

FR-PO432

Acid Retention Worsens as CKD Progresses to More Advanced Stages Nimrit Goraya,[4,5] Jan Simoni,[3] Lauren N. Sager,[2] Donald E. Wesson.[1,6] *[1]Diabetes Health and Wellness Institute, Dallas, TX; [2]Biostatistics, Baylor Scott & White, Temple, TX; [3]Surgery, Texas Tech University Health Sciences Center, Lubbock, TX; [4]Internal Medicine, Texas A and M School of Medicine, Temple, TX; [5]Internal Medicine, Baylor Scott and White Health, Temple, TX; [6]Internal Medicine, Baylor Scott and White Health, Temple, TX.*

Background: Acid (H^+) retention, even without metabolic acidosis by plasma acid-base parameters, mediates eGFR decline in animal models of chronic kidney disease (CKD) and worsens with declining GFR. Patients with reduced eGFR but no metabolic acidosis also have H^+ retention (Wesson, et al. AJP 300:F830) and preliminary longitudinal studies showed that H^+ retention worsened as eGFR decreased over 10 years (Goraya, et al. JASN 26:58A, 2015). Because recent studies support that dietary H^+ reduction slows nephropathy progression, more advanced CKD patients might require more aggressive dietary H^+ reduction if their H^+ retention is indeed greater. Consequently, we further tested the hypothesis that H^+ retention worsens with declining eGFR by comparing cross-sectional measurements of H^+ retention across CKD stages 1 through 4.

Methods: Twenty-six CKD 1, 40 CKD 2, 36 CKD 3, and 36 CKD 4 macroalbuminuric, non-diabetic CKD subjects had H^+ retention measured by comparing the observed to the expected increase in plasma [HCO_3] in response to retained HCO_3 (dose-urine excretion) two hours after an oral $NaHCO_3$ bolus (0.5 meq/Kg bw), assuming 50% body weight HCO_3 space of distribution. Specifically, H^+ retention = [(retained HCO_3/0.5 x body weight) – observed increase in plasma [HCO_3]] x (0.5 x body weight). So, the greater the difference between the expected and observed increase in plasma [HCO_3], the greater the amount of "unaccounted HCO_3" which was assumed to have been HCO_3 that had been titrated by retained H^+.

Results: Cystatin C-calculated eGFR in ml/min/1.73m^2 was as follows: CKD 1=101±8, CKD2=76±6, CKD 3=40±7, and CKD 4=23±5. The Bonferroni correction required a p-value of < 0.0083 for significance among group comparisons for H^+ retention. Accordingly, H^+ retention was greater in CKD 2 vs. CKD 1 (17.4±8.9 vs. 3.0 ± 14.0 mmol, p<0.0001), in CKD 3 vs. CKD 2 (24.9±15.4 vs. 17.4±8.9 mmol, p=0.0079), but not for CKD 4 vs. CKD 3 (32.2±10.5 vs. 24.9±15.4 mmol, p=0.0108).

Conclusions: These cross-sectional data show that H^+ retention increased significantly and progressively from CKD stages 1 through 3 and, along with the previous longitudinal data, support that H^+ worsens as eGFR decreases. Greater H^+ retention in patients with lower eGFR might contribute to their faster eGFR decline and its resolution might require more aggressive dietary H^+ reduction to optimize eGFR preservation.

FR-PO433

Acid Retention Revealed by Urine Citrate Excretion Might Identify CKD Patients for Whom Dietary Alkali Is Kidney Protective Nimrit Goraya,[5,6] Jan Simoni,[4] Lauren N. Sager,[3] Nicolaos E. Madias,[2] Donald E. Wesson.[1,5] *[1]Diabetes Health and Wellness Institute, Dallas, TX; [2]Internal Medicine, Tufts University School of Medicine, Boston, MA; [3]Biostatistics, Baylor Scott & White, Temple, TX; [4]Surgery, Texas Tech University Health Sciences Center, Lubbock, TX; [5]Internal Medicine, Baylor Scott & White Health, Temple, TX; [6]Internal Medicine, Texas A and M School of Medicine, Temple, TX.*

Background: Despite data showing that dietary alkali slows eGFR decline in chronic kidney disease (CKD) stage 3 (CKD 3) patients with mild metabolic acidosis (plasma total CO_2 [$PTCO_2$] >22 mM) (Goraya, et al. KI 86:1031, 2014) and in CKD stage 2 (CKD 2) patients with H^+ retention but no metabolic acidosis ($PTCO_2$ >24.5 mM) (Wesson, et al. AJP 300:F830, 2011; Mahajan, et al. KI 78:303, 2010), KDIGO recommends alkali for only CKD patients with $PTCO_2$ < 22 mM. We tested the hypothesis that urine excretion of the pH-sensitive metabolite citrate identifies H^+ retention, a form of acid stress which causes GFR decline in animal models of CKD, in CKD patients for whom dietary alkali provides kidney protection but for whom current guidelines do not recommend alkali therapy.

Methods: Macroalbuminuric, non-diabetic subjects with CKD stage 1 (CKD 1) and $PTCO_2$ > 24 mM (n=26), CKD 2 with $PTCO_2$ > 24 mM (n=40), and CKD 3 with $PTCO_2$ 22-24 mM (n=36), had H^+ retention measured by comparing observed to expected increase in $PTCO_2$ in response to retained HCO_3 (dose-urine excretion) two hours after oral $NaHCO_3$ bolus (0.5 meq/Kg bw), assuming 50% bw HCO_3 space of distribution. Specifically, H^+ retention = [(retained HCO_3/0.5 x body weight) – observed increase in plasma [HCO_3]] x (0.5 x body weight). Eight-hour urine citrate excretion (8h $U_{cit}V$) was measured after overnight fast.

Results: $PTCO_2$ was similar in CKD 2 (26.2±0.6 mM) and CKD 1 (26.8±0.7 mM) but was lower in CKD 3 (22.8±0.7 mM). Bonferroni correction required p-value significance < 0.0083 for within-group comparisons of H^+ retention and 8h $U_{cit}V$. H^+ retention was greater in CKD 2 than CKD 1 (17.4±8.9 vs. 3.0±14 mM, p<0.0001) despite similar $PTCO_2$ and that for CKD 3 (24.9±15.4 mM) was higher than both CKD 1 (p<0.0001) and CKD 2 (p=0.0079). Furthermore, 8h $U_{cit}V$ was less than CKD 1 (335±125 mg) for both CKD 2 (187±40 mg, p<0.0001) and CKD 3 (159±15 mg, p<0.0001).

Conclusions: Lower than CKD 1 8h $U_{cit}V$ identified H^+ retention in CKD 2 and CKD 3 patients for whom alkali therapy has been kidney protective but whose $PTCO_2$ was not low enough for alkali therapy by current guidelines. Urine citrate excretion is easily measurable in clinical settings and should be further explored as a strategy to identify CKD patients for whom alkali therapy might provide kidney protection.

FR-PO434

Association of Galectin-3 and MMP-2 with Risk of CKD Progression in the Chronic Renal Insufficiency Cohort (CRIC) Study Amanda H. Anderson,[2] Paula F. Orlandi,[2] Jason Roy,[2] Nisha Bansal,[3] Katalin Susztak,[2] John W. Kusek,[1] Harold I. Feldman.[2] *[1]NIDDK, Bethesda, MD; [2]University of Pennsylvania, Philadelphia, PA; [3]The CRIC Study, Philadelphia, PA. Group/ Team: CRIC Study.*

Background: Kidney fibrosis is a final common pathway of progressive chronic kidney disease (CKD). Markers of fibrosis may be independently associated with risk for CKD progression.

Methods: We measured galectin-3 and matrix metalloproteinase-2 (MMP-2) at baseline in a multi-center, prospective cohort study of men and women with CKD, the CRIC Study (N=3,828; mean estimated glomerular filtration rate (eGFR): 45 mL/min/1.73m^2; age range: 21-75 years; 48% diabetes). CKD progression was defined as either the onset of end-stage renal disease or a 50% reduction in eGFR. Cox proportional hazards models were fit to estimate the relationships between galectin-3 and MMP-2 with CKD progression.

Results: Higher baseline galectin-3 levels were significantly associated with patient characteristics; in particular, strong associations existed for females, non-Hispanic blacks, lower eGFR, higher FGF23, and higher inflammatory markers. MMP-2 levels were elevated most significantly among those with higher systolic blood pressure, diabetes, higher urine protein excretion, and higher cardiac biomarker levels. Over a median follow-up of 6 years, the highest quartiles of galectin-3 and MMP-2 were associated with a 2-fold and 1.5-fold increased risk for CKD progression, respectively (Table), after adjusting for traditional risk factors with the exception of eGFR (Model 2), which may be an intermediate factor in this relationship. Although further adjustment for baseline eGFR attenuated this risk, it remained statistically significant.

Conclusions: Galectin-3 and MMP-2 were found to be independent risk factors for CKD progression. Future studies should investigate if these measures improve identification of high-risk subgroups within the population of individuals with CKD.

Funding: NIDDK Support

	Model 1	Model 2	Model 3
Galectin-3, ng/mL			
Q1 (<10.2)	Ref	Ref	Ref
Q2 (10.2-14.3)	1.48 (1.23-1.79)	1.29 (1.06-1.57)	1.06 (0.87-1.29)
Q3 (14.3-19.5)	2.24 (1.87-2.67)	1.82 (1.50-2.20)	1.38 (1.14-1.67)
Q4 (19.5-83.9)	2.97 (2.49-3.55)	2.01 (1.67-2.44)	1.25 (1.03-1.52)
MMP-2, ng/mL			
Q1 (<243)	Ref	Ref	Ref
Q2 (244-311)	1.20 (1.00-1.46)	1.17 (0.96-1.43)	1.16 (0.95-1.42)
Q3 (312-401)	1.67 (1.40-2.02)	1.32 (1.08-1.60)	1.27 (1.04-1.54)
Q4 (402-1379)	2.61 (2.20-3.11)	1.53 (1.27-1.85)	1.33 (1.10-1.61)

Model 1: unadjusted; Model 2: stratified by clinical site and adjusted for age, gender, race/ethnicity, urine protein, body mass index, systolic blood pressure, smoking, diabetes, and history of cardiovascular disease; Model 3: Model 2 + eGFR.

FR-PO435

Sleep Apnea and CKD Progression: A Prospective Observational Study Muna T. Canales,[1] Shahab Bozorgmehri,[2] Areef Ishani,[3] I. D. Weiner,[1] Richard Berry,[1] Rebecca Beyth.[1] *[1]Malcom Randall VAMC & Univ. of Florida, Gainesville, FL; [2]University of Florida, Gainesville, FL; [3]Dept of VA & Univ. of Minnesota, Minneapolis, MN.*

Background: Studies using retrospective data analysis or using diagnostic codes have suggested that sleep apnea (SA) accelerates kidney function decline. We report an interim analysis of the first large, prospective study in CKD assessing this interaction.

Methods: This is a planned 2-year interim analysis of the SNORE Study, an ongoing 3-year prospective study of 248 Veterans aged 18-89 years with eGFR 15-44 ml/min/1.73m^2 who were not on treatment for SA at time of enrollment. At baseline, Veterans underwent an overnight sleep study, and estimation of renal function (serum creatinine, SCr). Renal function was re-assessed annually and intercurrent SCr measures were obtained from the computerized medical record. We determined the association between baseline SA (defined by the apnea-hypopnea index, AHI) and 1) MDRD eGFR trajectory; and 2) risk of 30% decline in MDRD eGFR using linear mixed modeling and cox-proportional hazards regression, respectively.

Results: At entry into the study, mean ±SD age was 73±10 years; 95% were male; 78% were white; mean (±SD) body-mass-index(BMI) was 30±5 kg/m^2; 96% had HTN; and 55% had DM. Mean follow-up at time of this planned interim analysis was 2.2 ± 0.8 years. Median [IQR] number of SCr values was 10 [6-16]. Mean MDRD eGFR was 35±9 ml/min/1.73m^2. Median [IQR] AHI was 10 [4-22]. The proportion with no, mild, moderate or severe SA were 29%, 32%, 19%, and 20%, respectively. EGFR decline was faster among those with moderate to severe SA (-1.68 ± 0.61 ml/min/1.73m^2/year) vs none or mild SA (-0.68 ± 0.39 ml/min/1.73m^2/year) but this was not statistically significant (p = 0.10). Moderate to severe SA was associated with a 58% increased risk of 30% decline

in eGFR, despite adjustment for age and BMI (p=0.05) as compared to those with none or mild SA.

Conclusions: Among Veterans with CKD, the presence of moderate to severe SA is associated with a faster decline in eGFR and increased risk of 30% decline in eGFR over 2 years, but findings are of borderline statistical significance. Completion of 3-year follow-up as planned will provide additional power to make more definitive conclusions regarding the association between SA and CKD progression in this population.

Funding: Veterans Affairs Support

FR-PO436

Urinary Epidermal Growth Factor (uEGF) and Monocyte Chemoattractant Protein-1 (uMCP1) as Biomarkers of Renal Involvement in ANCA-Associated Vasculitis (AAV) Wenjun Ju,[1] Catherine Najem,[2] Viji Nair,[1] David D. Cuthbertson,[3] Rennie L. Rhee,[2] Laura H. Mariani,[1] Jeffrey P. Krischer,[3] Matthias Kretzler,[1] Peter A. Merkel.[2] *[1]University of Michigan, Ann Arbor, MI; [2]University of Pennsylvania, Philadelphia, PA; [3]University of South Florida, Tampa, FL. Group/Team: Vasculitis Clinical Research Consortium and NEPTUNE Network.*

Background: EGF mediates distal tubular epithelial cell function and regeneration. MCP-1 recruits leukocytes to areas of inflammation. This study examined the utility of uEGF and uMCP-1 as biomarkers of renal disease in AAV.

Methods: uEGF and uMCP-1 (normalized to urine creatinine) were measured at enrollment, an active renal disease visit (index), 1-2 visits prior to and after the index, and at 1 year follow-up utilizing urine samples from a multicenter longitudinal cohort of patients with AAV. Chronic kidney disease (CKD) was defined as eGFR< 60 mL/min/1.73 m2 for >3 months. Index visit was defined as the first visit with a new/worse BVAS/WG renal item since prior visit. To assess the association of each biomarker with disease activity, a mixed effect model was used, adjusting for ANCA type (MPO or PR-3), urinary albumin/creatinine ratio (ACR), eGFR, visit type. To assess time to CKD, a Cox proportional hazard model was used, adjusting for demographics, ANCA type, ACR, and eGFR.

Results: At baseline, 165/544 patients had CKD. After adjusting for sex, age, race, ANCA type, eGFR, and albumin/Cr, for each unit increase in baseline uEGF/Cr there was a lower risk of CKD [HR=0.62, (0.43, 0.88), p=0.01)]. Higher baseline uMCP-1/Cr didn't predict risk of CKD [HR=1.14, (0.88, 1.48), p=0.33)]. 112 patients had active renal disease. uEGF/Cr levels did not significantly differ between pre-, post-, and index visits. Compared to index visit, uMCP-1/Cr was lower at pre- and post-index visits (p=0.04 and p<0.01).

Conclusions: In AAV, uEGF predicts progression to CKD independently of ACR and eGFR. uMCP-1, but not uEGF, correlates with renal disease activity. uEGF and uMCP-1 are useful biomarkers in AAV.

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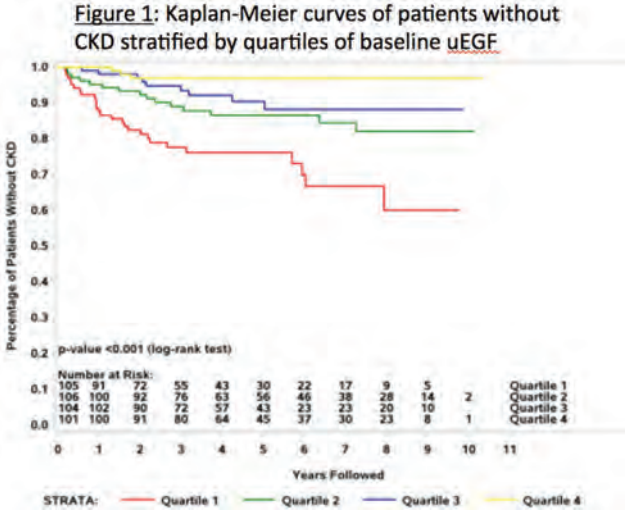

FR-PO437

Neighborhood Socioeconomic Status and Incident ESRD Milda R. Saunders,[6] Esteban A. Cedillo-Couvert,[8] Lawrence J. Appel,[2] Jiang He,[4] Edward J. Horwitz,[3] Jesse Y. Hsu,[10] Martha L. Daviglus,[8] Michael J. Fischer,[7] Ana C. Ricardo,[8] Hernan Rincon-Choles,[1] Susan P. Steigerwalt,[9] Daohang Sha,[5] James H. Sondheimer,[11] James P. Lash.[8] *[1]Cleveland Clinic, Cleveland, OH; [2]Johns Hopkins Medical Institutions, Baltimore, MD; [3]Solon, OH; [4]Tulane School of Public Health and Tropical Medicine, New Orleans, LA; [5]Uiversity of Pennsylvania, Philadelphia, PA; [6]University of Chicago, Chicago, IL; [7]University of Illinois Hospital and Health Sciences Center, Chicago, IL; [8]University of Illinois at Chicago, Chicago, IL; [9]University of Michigan, Ann Arbor, MI; [10]University of Pennsylvania, Philadelphia, PA; [11]Wayne State University School of Medicine, Detroit, MI. Group/Team: On behalf of CRIC Investigators.*

Background: Although individuals with lower socioeconomic status (SES) are disproportionately affected by end-stage renal disease (ESRD), the association of neighborhood SES with incident ESRD has not been thoroughly evaluated. Using data from the Chronic Renal Insufficiency Cohort Study, we evaluated the relationship between neighborhood SES and ESRD.

Methods: Cox proportional hazards to examine the association between neighborhood SES quartiles and incident ESRD. We constructed a neighborhood-level SES summary measure using z scores for 6 census-derived variables using a validated approach.

Results: Among 3291 adults with CKD (mean eGFR 45 ml/min/1.73m^2, median proteinuria 0.19 g/24h), 41% were non-Hispanic white, 42% non-Hispanic black, 13% Hispanic. At study entry, compared to those in the highest quartile SES neighborhoods (Q4), individuals in lowest SES quartile neighborhoods (Q1) were more likely to be younger, female, non-Hispanic black or Hispanic, current smokers, have lower healthy eating scores and physical activity (p<0.001 for each). In addition, Q1 individuals had lower eGFR, higher proteinuria, and were more likely to have diabetes, hypertension, and cardiovascular disease; however, they were as likely as their Q4 counterparts to be on aspirin, statin, and ACE/ARB. During median follow-up of 6.8 years, there were 878 ESRD events. Multivariable analyses are summarized below.

Conclusions: While individuals in low SES neighborhoods had a greater burden of kidney disease risk factors and higher ESRD rates, likelihood of reaching ESRD was explained in part by individual SES.

Funding: NIDDK Support

		Q1 (lowest SES)	Q2	Q3	Q4 (highest SES)
ESRD incidence per 100 person-year		5.6	4.8	3.7	2.1
ESRD	Model 1[a]	1.39 (1.09-1.77)	1.29 (1.02-1.64)	1.35 (1.08-1.68)	Ref
	Model 2[b]	0.95 (0.63-1.43)	0.95 (0.67-1.36)	1.10 (0.83-1.45)	Ref
	Model 3[c]	1.02 (0.63-1.66)	1.06 (0.70-1.61)	0.98 (0.70-1.36)	Ref

a. Adjusted for center, age, sex, race/ethnicity

b. Model 1 plus education, income, occupation

c. Model 2 plus physical activity, diet, BMI, smoking, systolic BP, diabetes, eGFR, proteinuria, ACE/ARB, aspirin, statin

FR-PO438

Human Kidney Tubule Cytosine Methylation Changes Can Improve Models for CKD Progression Caroline A. Gluck,[5] Chengxiang Qiu,[6] Sang Youb Han,[2] Jing Huang,[6] Ae Seo Deok Park,[4] Yi-An Ko,[6] Ioannis Mantzaris,[3] Yong Chen,[6] Amit K. Verma,[1] Matthew Palmer,[6] Katalin Susztak.[6] *[1]Albert Einstein College of Medicine, Bronx, NY; [2]Inje University, GoYang, Republic of Korea; [3]Montefiore Medical Center, Bronx, NY; [4]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [5]The Children's Hospital of Philadelphia, Philadelphia, PA; [6]University of Pennsylvania, Philadelphia, PA.*

Background: Chronic Kidney Disease (CKD) progresses at variable rates. Patients who progress rapidly are more likely to reach end stage renal disease (ESRD). Current models to predict CKD progression are centered on baseline GFR, age, and albuminuria. These clinical phenotypes do not explain the pathophysiology of progression and cannot account for environmental influence on progression. Cytosine methylation is a stable, cell type specific and environmentally responsive epigenetic signal that affects gene expression patterns. The aim of this project was to determine if genome wide cytosine methylation changes can improve baseline models for CKD progression and identify novel pathways underlying CKD progression.

Methods: Biobanked human kidney tissue was microdissected to isolate kidney tubules. The data set included 69 human kidney tubule samples with associated cross-sectional and longitudinal clinical data. Histopathology for samples were graded on 20 independent parameters. Genome wide cytosine methylation was analyzed using the Illumina Infinium 450K chip. Transcript level changes were determined using the Affymetrix RNA microarray. Subject-specific adjusted GFR slopes were determined using best linear unbiased prediction to account for random variation. Variables for CKD progression models were selected by a machine learning regression analysis method, "LASSO", to improve model accuracy and reduce model overfitting. Methylation and

transcript levels were added to baseline linear regression models and both R^2 and akaike information criterion (AIC) values were ranked to determine model fitness.

Results: The final model (M1) for CKD progression based on LASSO-selected variables included: baseline GFR, age, albuminuria (dipstick), CKD stage, diabetes, height, and vessel intimal fibrosis. Adding the top gene transcript level to M1 (M2) improved model fitness. Finally, addition of the methylation level at the top genome loci to M2 (M3) further improved model fitness.

Conclusions: Human kidney tubule cytosine methylation levels may improve CKD progression models even after gene expression levels are included. Methylation changes in kidney tissue may be useful biomarkers for CKD progression and may be functionally important in CKD progression.

Funding: NIDDK Support

FR-PO439

Urinary Epidermal Growth Factor Predicts Rapid GFR Decline in the General Non-Diabetic Population Jon V. Norvik,[4,3] Wenjun Ju,[5] Viji Nair,[5] Vidar T. Stefansson,[3] Jørgen Schei,[4,3] Trond G. Jenssen,[1] Marit D. Solbu,[4] Matthias Kretzler,[2] Bjorn O. Eriksen,[6] Toralf Melsom.[4] *[1]Oslo University Hospital, Oslo, Norway; [2]U.Michigan, Ann Arbor, MI; [3]UiT The Arctic University of Norway, Tromso, Norway; [4]University Hospital of North Norway, Tromsø, Norway; [5]University of Michigan, Ann Arbor, MI; [6]University of Tromsø, Tromsø, Norway*.

Background: Biomarkers are needed to distinguish people at high risk to develop chronic kidney disease (CKD) for early and targeted clinical care. Lower levels of urinary epidermal growth factor (uEGF) have been associated with increased tubular atrophy, interstitial fibrosis and rapid progression in CKD of various etiologies. We investigated whether lower uEGF predicted risk for rapid glomerular filtration rate (GFR) decline in the general non-diabetic population.

Methods: In the Renal Iohexol Clearance Survey of Tromsø 6 (RENIS-T6), we measured GFR by iohexol-clearance in 1,594 middle-aged persons without diabetes or chronic kidney disease. Of these, 1,299 (81%) had a follow-up GFR measurement after a median of 5.6 years in the RENIS-Follow Up and a random sample of 87 persons had a third GFR measurement. uEGF levels at baseline were measured using an ELISA assay. We used a linear mixed model with random intercept and slope to assess the relationship between uEGF and change in GFR and a multiple logistic regression model to examine the association between uEGF and rapid GFR decline (defined as annual GFR decline > 3 mL/min/1.73m^2).

Results: The mean (SD) annual GFR decline rate was -0.86 (2.13) mL/min/1.73m^2. Lower baseline uEGF was independently associated with a steeper GFR decline rate (-0.16 (95% confidence interval (CI) -0.26 to -0.05) mL/min/1.73m^2 per 1 SD decrease in log-transformed uEGF after adjusting for CKD risk factors such as urinary albumin-to-creatinine ratio (ACR)). The annual GFR decline rate for participants with uEGF levels below the median was -1.00 (95% CI -1.14 to -0.86) mL/min/1.73m^2 compared to -0.71 (95% CI -0.86 to -0.56) mL/min/1.73m^2 for those above the median level (P=0.006), adjusted for sex, age and ACR. The multivariable adjusted odds ratio for rapid decline was 1.91 (95% CI 1.27 to 2.88) for those with uEGF below the median level.

Conclusions: Lower uEGF levels predicted rapid GFR decline in the general non-diabetic population.

Funding: Government Support - Non-U.S.

FR-PO440

Rate of GFR Decline and Incident CKD among Primary Care Patients with Normal or Mildly Reduced Renal Function Farrukh M. Koraishy,[1,2] Joanne Salas,[1] Jeffrey F. Scherrer.[1] *[1]Saint Louis University, Saint Louis, MO; [2]Internal Medicine/Nephrology, John Cochran VA Medical Center, Saint Louis, MO*.

Background: Rapid GFR decline is associated with adverse outcomes. The risk factors associated with the rate of GFR decline in association with incident CKD among primary care patients with normal or mildly reduced GFR are not well defined.

Methods: From an academic primary care patient registry containing electronic health record data, we identified 2,219 adults with at least three eGFR values (calculated using the CKD-EPI equation) between July 1st 2008 – June 30th 2016. We required patients to have an initial (baseline) eGFR value between 60-119 ml/min/1.73 m^2. Rapid GFR decline was defined as a decline in eGFR of >5 ml/min/1.73 m^{2}per year and incident CKD was defined as an eGFR of <60 ml/min/1.73 m^2. The clinical and socio-demographic characteristics were compared using chi-square tests and independent samples t-tests. Adjusted logistic regression models were computed to measure the associations between covariates among rapid decliners stratified by baseline eGFR of 60-89 (mildly reduced) and 90-119 (normal) ml/min/1.73 m^2.

Results: Rapid GFR decline was significantly associated with incident CKD, older age, black race, unmarried status, lower neighborhood socioeconomic status (nSES), hypertension, type 2 diabetes, current smoking and initial eGFR (p<0.01). Incident CKD was significantly associated with unmarried status (p =0.028), and type 2 diabetes (p<0.0001) in rapid decliners and with anxiety (p = 0.005)and depression (p = 0.5) in slow decliners. Older age, hypertension and initial GFR were significantly (p< 0.0001) associated with incident CKD in both groups. Multivariate logistic regression analysis restricted to patients with rapid GFR decline and mildly reduced baseline eGFR, revealed only older age being significantly associated with incident CKD (OR = 1.04 [1.01-1.08]). A separate multivariate logistic regression model among rapid decliners with a normal baseline eGFR revealed only type 2 diabetes being significantly associated with incident CKD (OR = 3.83 [1.35-10.89]).

Conclusions: Among primary care patients with normal or mildly reduced GFR (who are typically not referred to nephrology), patient characteristics associated with incident CKD differ by the rate of GFR decline and by the baseline eGFR. Our findings identify high-risk patients in primary care and would inform development of risk prediction models for incident CKD.

Funding: NIDDK Support

FR-PO441

The Effect of Statin Therapy on Clinical Outcomes in Patients with CKD: The Results from the KNOW-CKD Seong yeong An, Ki Heon Nam, Jong Hyun Jhee, Seohyun Park, Seung Hyeok Han, Dae-Suk Han. *Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea*.

Background: Statin therapy is a main part of the management of lipid disorders in patients with CKD. However, the effects of statin use against CKD progression and cardiovascular events are still under debate in these patients. Also, it is unknown whether clinical outcomes are affected by lipophilic or hydrophilic nature of statins.

Methods: We studied the effects of use and types of statins on clinical outcomes in 2,238 patients using the database from the Korean Cohort Study for Outcome in Patients with Chronic Kidney Disease (KNOW-CKD). Statin users were defined if they were treated with statins at baseline. And, statin users were further classified into lipophilic or hydrophilic statin users depending on types of statins. Primary outcome was a composite of a 50% decline in eGFR, ESRD, cardiovascular events, and death.

Results: During a mean follow-up duration of 38 months, the composite outcome occurred in 74 (9.3%) patients among statin users as compared to 55 (7.1%) among non-users (P=0.119). In a multivariable Cox model after adjustment of confounding factors, statin use was not associated with a decreased risk of primary outcome (HR, 0.85; 95% CI, 0.67-1.07; P=0.168). However, in a subgroup of patients with eGFR of ≥ 30 ml/min/1.73 m^2, statin users were significantly associated with a 39% reduction in primary outcome as compare to non-users (HR, 0.61; 95% CI, 0.39-0.95; P=0.030). In addition, hydrophilic statin users had a lower risk of developing the endpoint than non-users in this subgroup (HR, 0.57; 95% CI, 0.34-0.97; P=0.037), whereas lipophilic statin users did not have such benefit (HR, 0.65; 95% CI, 0.38-1.09; P=0.104). However, there was no difference in HRs for primary outcome between hydrophilic and lipophilic statin users.

Conclusions: Statin use was associated with improved outcomes in early stages of CKD and the effectiveness was similar between hydrophilic and lipophilic statin users.

FR-PO442

The Association between Alcohol Consumption and Renal Outcome Is Modified by CKD Stages: The Results from the KNOW-CKD Heebyung Koh, Jaeyeol Kwon, Ki Heon Nam, Seong yeong An, Seung Hyeok Han. *Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea*.

Background: Several studies have suggested that moderate alcohol drinking exhibits beneficial effects on the development of CKD. However, studies that examined the association between alcohol consumption and progression of CKD in patients with CKD are scarce.

Methods: We analyzed drinking pattern according to CKD stages and examined the association between alcohol consumption and CKD progression using the database from the prospective KoreaN cohort study for Outcome in patients With CKD (KNOW-CKD). After excluding 641 patients who have missing data, a total 1597 patients were included. Alcohol consumption within last 1 year was categorized into none, ≤ 1 drinks/month, 2-4 drinks/month, 2-3 drinks/week, and ≥ 4 drinks/week. Primary outcome was a composite of halving of eGFR or the onset of ESRD.

Results: The mean age was 53.5 years and 61.6% were male. Patients with decreased renal function were less likely to consume alcohol (P for trend < 0.001). There was a significant interaction between alcohol consumption and eGFR (p < 0.001). During a median follow-up of 38.1 months, primary outcome occurred in 263 (16.5%) patients. In a multivariate Cox regression after adjustment of age, sex, BMI, SBP, CRP, total cholesterol, smoking and CCI score, more alcohol consumption was significantly associated with a lower risk for adverse outcome. Compared to non-drinkers, hazard ratios (HRs) for developing primary renal outcome who consumed 2-4 drinks/month, 2-3 drinks/week, ≥ 4 drinks/week were 0.67 (95% confidence interval [CI], 0.47-0.97; p=0.034), 0.59 (95% CI, 0.37-0.95; p=0.031) and 0.29 (95% CI, 0.11-0.79; p=0.015), respectively. However, beneficial effect of alcohol was lost after eGFR, urine protein-creatinine ratio, and hemoglobin were added to the model.

Conclusions: We demonstrated no association between alcohol consumption and renal adverse outcomes after adjustment of CKD-related factors. Thus, beneficial effects of alcohol on CKD progression should be interpreted cautiously with CKD severity taken into account.

FR-PO443

Self-Reported Snoring Is Associated with Incident CKD Development: A Community-Based Prospective Cohort Study Jaeyeol Kwon, Heebyung Koh, Ki Heon Nam, Seong yeong An, Tae-Hyun Yoo. *Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea.*

Background: Reports have shown sleep disordered breathing symptoms including habitual snoringto be clearly associated with the development ofmetabolic derangements and vascular diseases. However, the relationship between habitual snoring and renal function is not well investigated. Therefore, this study aimed to evaluate the association between habitual snoring and the development of incident chronic kidney disease in a cohort of subjects with normal renal function.

Methods: Data were retrieved from the Korean Genome and Epidemiology Study, a prospective community-based cohort study. A total of 9304 subjects with normal renal function were included in the final analysis. Subjects were classified into three groups, based on self-reported snoring frequency at baseline: non-snorer, infrequent snorer, frequent snorer. The primary endpoint of study was development of CKD, defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2.

Results: The mean age was 52 years. The non-snorer, infrequent snorer, frequent snorer groups each included 3573(38.4%), 3856(41.4%) and 1875(20.2%)subjects. During a mean follow-up duration of 101±53 months, 272(7.6%), 332(8.6%) and 197(10.5%) subjects developed CKD in the non-snorer, infrequent snorer and frequent snorer group. Cox Proportional Hazard model analysis revealed that snoring was an independent risk factor for incident CKD development [HR, 1.21; 95% CI,1.007-1.468; P 0.0043]. This finding was significant even after adjustments were made for confounding factors including the presence of metabolic syndrome and eGFR at baseline.

Conclusions: Snoring may increase the risk of CKD development in subjects with normal renal function. Managing sleep quality could play a role in preserving renal function.

FR-PO444

The Effects of Coffee Intake on the Incident CKD in General Population Heebyung Koh,[1] Ki Heon Nam,[1] Meiyan Wu,[2] Boyoung Nam,[2] Seung Hyeok Han.[1] *[1]Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea; [2]Department of Internal Medicine, College of Medicine, Severance Biomedical Science Institute, Brain Korea 21 PLUS, Yonsei University, Seoul, Republic of Korea.*

Background: The effects of habitual coffee consumption on health have been a public concern. However, the association between coffee intake and kidney disease is unknown. This study aimed to investigate whether coffee intake can have an impact on the development of chronic kidney disease (CKD) in general population.

Methods: Using the database from the Korean Genome and Epidemiology Study (KoGES) from 2001 to 2014, we analyzed 9644 subjects with normal renal function. Coffee consumption was categorized into 5 groups; 0/wk (n=2232), < 1 cup/wk (n=618), 1-6 cups/wk (n=1690), 1 cup/day (n=2645), and ≥ 2 cups/day (n=2459). All measurements such as blood pressure, body mass index, estimated glomerular filtration rate (eGFR), fasting glucose, hemoglobin, and lipid profiles during follow-up period were treated as time-varying covariates. The primary outcome was incident CKD defined as an eGFR < 60 mL/min/1.73m^2.

Results: The mean age was 52.0 years and 4594 (47.6%) were male. At baseline, higher coffee consumers were younger, had lower blood pressure, and had lower prevalence of hypertension and diabetes as compared to non-drinkers or lower consumers. Time-averaged blood pressure was also lower as coffee consumption was increased. A multivariate linear regression model showed that high coffee consumption independently associated with low systolic blood pressure (ß = -0.52, P < 0.001). During a mean follow up of 124.8 months, 839 (8.6%) participants developed CKD. The incident CKD occurred in 224 (10.0%), 69 (11.2%), 148 (8.8%), 209 (7.9%), and 174 (7.1%) individuals in the coffee consumption groups of 0/wk, < 1 cup/wk, 1-6 cups/wk, 1 cup/day, and ≥ 2 cups/day, respectively (P for trend < 0.001). In a time-varying Cox model after adjustment of confounding factors, coffee consumption of ≥ 1 cup/day [hazard ratio (HR), 0.74; 95% confidence interval (CI), 0.59-0.92; P = 0.01] and ≥ 2 cups/day (HR, 0.77; 95% CI, 0.60-0.98; P = 0.03) were significantly associated with a lower risk of CKD development.

Conclusions: Our findings suggest beneficial effect of coffee intake of ≥ 1 cup/day on the incident CKD. This can be partly explained by coffee intake-associated decrease in blood pressure.

FR-PO445

Optimal Target for Blood Pressure Control in Patients with CKD: The Results from the KNOW-CKD Study Seong yeong An, Seung Hyeok Han, Heebyung Koh, Jaeyeol Kwon. *Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea.*

Background: There has been a long debate regarding what level blood pressure (BP) should be lowered to in patients with chronic kidney disease (CKD). This study aimed to investigate the optimal target BP levels to retard the progression of CKD in participants in the KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD).

Methods: Between February 2011 and July 2016, a total of 2,238 patients were enrolled. After excluding 22 patients in whom systolic blood pressure (SBP) was not measured, 2,226 patients were included in the analysis. Patients were categorized into 7 groups according to baseline SBP levels; <110, 110-119, 120-129, 130-139, 140-149, 150-159, and ≥160 mmHg. Primary outcome was a composite of a 50% decline in estimated glomerular filtration rate, or end stage renal disease.

Results: The mean age of the patients were 53.6 years and 1,362 (61.2%) were male. At enrollment, 2,138 (96%) had hypertension and the mean SBP was 127.9±16.2 mmHg. During a mean follow up of 36.7 months, primary outcome occurred in 334 (15.0%) patients. There were increases in the number of the composite outcome as SBP increased (P for trend < 0.001). In a multivariate Cox analysis after full adjustment for confounding factors including age, sex, body mass index, smoking status, comorbidities, use of antihypertensive agents, eGFR, and overt proteinuria, SBP of < 110 mmHg [hazard ratio (HR), 0.52; (95% confidence interval (CI), 0.31-0.87, P=0.012] and SBP of 110-119 mmHg (HR, 0.62; 95% CI, 0.42-0.91; P=0.015) were significantly associated with a lower risk of the composite endpoint as compared to SBP of 130-139 mmHg. In contrast, HRs for the composite outcome were significantly higher in patients with SBP of 150 to 159 mmHg (HR, 1.47; 95% CI, 1.00-2.15; P=0.049) and those with SBP of ≥ 160mmHg (HR, 2.00; 95% CI, 1.30-3.09; P=0.002) than in patients with SBP of 130-139 mmHg. There was no difference in the risk of primary outcome between SBP categories of 120-129, 130-139, and 140-149 mmHg.

Conclusions: In this study, we found a significant linear relationship between SBP and adverse renal outcomes in patients with CKD. Thus, lowering the target BP below the levels proposed by the current guideline may be beneficial to attenuate deterioration of kidney function.

FR-PO446

Smoking Is a Risk Factor for the Progression of CKD: From the Korean Cohort Study for Outcome in Patients With CKD Arum Choi,[1] Meiyan Wu,[1] Seung Hyeok Han.[2] *[1]Department of Internal Medicine, College of Medicine, Severance Biomedical Science Institute, Brain Korea 21 PLUS, Yonsei University, Seoul, Republic of Korea; [2]Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea.*

Background: Smoking is a risk factor of developing incident chronic kidney disease (CKD). However, most studies included relatively healthy participants without CKD and studies on the association between smoking and deterioration of kidney function in patients with CKD are scarce. Therefore, we aimed to evaluate the effect of smoking on kidney disease progression and dose-response relationship by pack-years in these patients.

Methods: The KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD) is a nation-wide prospective observational cohort study from 9 centers in Korea. A total of 2218 patients were included in the final analysis. Patients were categorized into never-, former-, and current- smokers. Primary outcome was a composite of a reduction of eGFR of ≥ 50%, initiation of dialysis, or kidney transplantation.

Results: The mean age was 53.6±12.3 years and 1356 patients (61.1%) were male. Compared to never-smokers, former- or current- smokers had higher prevalence of diabetes (38.4% vs. 29.6%, P < 0.001) and cardiovascular disease (14.3% vs. 7.8%, P < 0.001) at baseline. In addition, these patients had higher blood pressure (128.9±16.7 vs. 127.0±15.8 mmHg, P = 0.007), lower eGFR (48.6±27.9 vs. 52.2±32.2 ml/min/1.73m^2, P = 0.004) and higher level of proteinuria [1.6 (0.2-1.8) vs. 1.2 (0.1-1.2) g/day, P < 0.001] than never-smokers. During a mean follow-up duration of 36.7±18.2 months, primary outcome occurred in 168 (16.5%) in former- or current-smokers as compared to 164 (13.6%) in never-smokers (P = 0.057). In a multivariable Cox regression analysis after adjustment of confounding factors, smokers were significantly associated with an increased risk of primary outcome (HR, 1.36; 95% CI, 1.05-1.77; P = 0.020). In addition, HRs for primary outcome were 0.94 (95% CI, 0.65-1.35; P = 0.723), 1.49 (95% CI, 1.04-2.14; P = 0.030), 1.83 (95% CI, 1.12-2.86; P = 0.008), and 2.21 (95% CI, 1.39-3.51; P = 0.001) for <14.9, 15-29.9, 30-44.4 and ≥45 pack-years, respectively, suggesting that there was a dose-response relationship between smoking consumption and CKD progression.

Conclusions: This study clearly showed that smoking is associated with deterioration of kidney disease. Thus, quitting smoking should be a part of preventative strategy in management of CKD.

FR-PO447

Secondhand Smoking Is a Risk Factor for Incident CKD Development Sukyung Kang,[1] Tae-Hyun Yoo,[2] Jaeyeol Kwon,[2] Heebyung Koh,[2] Youn kyung Kee.[2] *[1]Department of Internal Medicine, College of Medicine, Severance Biomedical Science Institute, Brain Korea 21 PLUS, Yonsei University, Seoul, Republic of Korea; [2]Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea.*

Background: Smoking is a well-known risk factor for renal function decline. However, the risk of CKD development in nonsmokers exposed to secondhand smoke is not well elucidated yet. This study aimed to investigate the association between secondhand smoking and the risk of CKD development among never-smoking adults.

Methods: Subjects who participated in the Korean Genome and Epidemiology Study (KoGES) from 2001 to 2014 were enrolled. A total of 4856 subjects with normal renal function and without a history of smoking were included in the final analysis. The subjects were divided into two groups depending on secondhand smoke exposure (SSE).

The primary outcome was development of CKD defined as estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2.

Results: In the SSE and non-SSE groups, the mean ages of the subjects were 49.5 ± 7.4 and 51.6 ± 7.9 years, the numbers of male subjects were 289 (14.0) and 466 (16.7), and the mean estimated glomerular filtration rates (eGFR) were 95.1 ± 12.7 and 93.9 ± 12.8 ml/min/1.73 m^2, respectively. Among the subjects in the SSE group, the duration of SSE showed a significant positive correlation with BMI and HbA1c. Cox analysis revealed that SSE was a significant risk of CKD development even after adjustments were made for confounding factors (Hazard ratio, 1.15; 95% confidence interval, 1.02-1.33; P = 0.049).

Conclusions: Secondhand smoking significantly increased the risk of CKD development. In addition, factors such as obesity and insulin resistance may be affected by SSE. Avoiding SSE may have an effect on preventing the development of CKD.

FR-PO448

Significance of Cardio-Ankle Vascular Index in the Long-Term Renal Prognosis for Patients with Non-Diabetic CKD Akihiro Shimizu, Hideo Okonogi, Tetsuya Kawamura, Shinya Yokote, Masahiro Suyama, Kei Matsumoto, Kentaro Koike, Nobuo Tsuboi, Yoichi Miyazaki, Masato Ikeda, Makoto Ogura, Takashi Yokoo. *Division of nephrology and hypertension, The Jikei university school of medicine, Tokyo, Japan.*

Background: Cardio-ankle vascular index (CAVI) is a non-invasive index of arterial stiffness and, theoretically, independent of blood pressure at the time of measurement. Although the role of CAVI as a predictor of cardiovascular events has been reported, few studies have considered the renal prognosis. The present retrospective cohort study was undertaken to investigate the association between CAVI and the long-term renal prognosis in patients with non-diabetic chronic kidney disease (NDCKD).

Methods: We included 44 NDCKD patients (CKD stages 1, 2, 3 and 4, and follow-up period ≥2 years), who were diagnosed by first time renal biopsy (RBx). Renal outcome was defined as reaching 30% decline in eGFR from baseline. We analyzed the association between CAVI and outcome, and risk factors affecting the incidence of outcome, by Cox proportional hazard model, receiver-operating characteristic (ROC) analysis, and Kaplan–Meier analysis.

Results: As a result, a median follow-up time was 86 months (range, 27–101 months), and 15 patients reached outcome. Baseline CAVI, eGFR, hypertension and uric acid were significantly associated with outcome by univariate Cox analysis (p<0.05). By ROC analysis, the areas under the curve for diagnosis of the future outcome by baseline CAVI was 0.838 (p=0.0007), and CAVI cut-off value was calculated as 7.50 (Sensitivity 93%, Specificity 62%). Then CAVI≥7.5 (HCAVI) and eGFR were independently associated with outcome by multivariate Cox analysis, (Hazard ratio (HR) 7.3, 95% confidence interval (CI) 1.2-141, p<0.05, and HR 0.97, 95%CI 0.94-0.99, p<0.05, respectively). Furthermore, Kaplan-Meier analysis showed that outcome-free survival was significantly lower in HCAVI group compared with CAVI<7.5 group (Log-rank test, p=0.0017).

Conclusions: These results indicated that CAVI at the time of RBx was independently associated with long-term renal prognosis in NDCKD patients.

FR-PO449

CKD Patients Are Exposed to More Proton Pump Inhibitors (PPIs) Compared to Non-CKD Patients in a Tertiary Single Center Heejeong Lee,[2] Songhee Oh,[3] Haekyung Lee,[4] Jin seok Jeon,[1] Dong-Cheol Han,[2] Soon hyo Kwon.[2] *[1]Soon Chun Hyang Univ. Hospital, Seoul, Republic of Korea; [2]Soon Chun Hyang University Hospital, SEOUL, Republic of Korea; [3]soon chun hyang university hospital, SEOUL, Republic of Korea; [4]Soonchunhyang University Hospital, SEOUL, Republic of Korea.*

Background: Proton pump inhibitor (PPI) is associated with incident chronic kidney disease (CKD), CKD progression and end-stage renal disease (ESRD). However, the extent of PPI in CKD patients comparing to non CKD patients is still unclear.

Methods: We conducted a retrospective study on patients (>18 years old) who received PPI in a single tertiary center out-patient clinic (750 beds, Seoul, South Korea) from Jan. 2014 to Dec. 2015. PPIs need doctor's prescription in South Korea. All data were collected from electronic medical record. The PPI prescription and their characteristics were analyzed according to CKD-EPI equation of the patients.

Results: Our sample consisted of 9,112 patients. Females were 50.3% were and CKD (eGFR<60mL/min) patients were 9.8%. Among CKD patients, 721 (7.9%) were categorized as stage 3 or 4, 176 (1.9%) were stage 5 or ESRD. Total 7 types of PPIs were prescribed. During the study period, median duration of PPI usage was 120days [interquartile range, 63-273] in CKD 3-4 group, 105 days [56-271] in CKD 5-ESRD group and 90 days [56-175] in non-CKD group. Patients with CKD stage 3 or 4 took longer duration of PPI than non-CKD paients (p<0.001). Main departments of medicine which prescribed PPIs in CKD group were gastroenterology (39.4%), cardiology (28.2%), nephrology (15.1%) and neurology (4.2%). Compared to the non-CKD group, the CKD stage 3 or 4 and CKD stage 5 orESRD group was taking more drugs simultaneously (6.9 ± 4.2 vs 4.5 ± 2.4; p<0.001, 5.6 ± 2.8 vs 4.5 ± 2.4 ; p<0.0001, respectively).

Conclusions: CKD patients are exposed to more PPIs compared to non-CKD patients. Physicians should pay careful attention when prescribing PPIs in patients with CKD.

FR-PO450

Augmented Effect of Blood Pressure on Renal Arteriolosclerosis via Increased Arterial Stiffness in CKD Ryo Zamami, Tsuyoshi Miyagi, Kentaro Kohagura, Masanobu Yamazato, Akio Ishida, Yusuke Ohya. *University of the Ryukyus, Nishihara-cho, Japan.*

Background: We reported arteriolar hyalinosis, a potential marker for disrupted autoregulation system may potentiate hypertensive glomerular damage. Arterial stiffness is suggested to relate hypertensive organ damage by interaction with arteriolar sclerosis. Therefore, we conducted a cross-sectional study to determine the effect of arterial stiffness on the relationship between blood pressure and renal arteriolar hyalinosis.

Methods: A total of 102 consecutive patients with chronic kidney disease (CKD) who underwent renal biopsy and had data of branchial-ankle pulse wave velocity (baPWV) were recruited. Arteriolar hyalinosis was semiquantitatively assessed via grading system (grade 0 –3).

Results: The mean value for age, blood pressure and estimated glomerular filtration rate (eGFR) were as follows: 46 years, 123/74 mmHg, and 72ml/min/1.73m^2. Patients were divided into four subgroup according to the median value of baPWV and systolic BP (SBP). Max hyalinosis grade was the highest in high baPWV / high SBP group. In multivariate logistic regression analysis, revealed that high baPWV / high SBP were significantly associated with the presence of highest max hyalinosis grade 3 (Odds ratio, 8.22; 95% confidence interval 1.79-37.7, P<0.01). Moreover, this group had the highest urine protein among four groups. Even in normal SBP, patients with high baPWV had higher max hyalinosis grade compared with low baPWV.

Conclusions: In CKD patients, arterial remodeling may cause progression of CKD via augmented effect of blood pressure on renal arteriolosclerosis.

FR-PO451

Even Overweight Relates to Proteinuria Accompanied with Glomerular Hypertrophy in Non-Nephrotic CKD Ryo Zamami, Tsuyoshi Miyagi, Kentaro Kohagura, Chisato Fukuhara, Masanobu Yamazato, Akio Ishida, Yusuke Ohya. *University of the Ryukyus, Nishihara-cho, Japan.*

Background: Glomerular hypertrophy (GH), a potential marker for glomerular hypertension is suggested to relate progression of chronic kidney disease (CKD). However, risk factors for GH are not clear. Thus, we conducted cross sectional study to elucidate clinical factors, which relate to the presence of GH among CKD patients.

Methods: A total of 107 patients with non-nephrotic CKD who underwent renal biopsy were recruited. The glomerular diameter of the biopsy specimen was measured. We compared clinical characteristics between the patients with GH and those without it, which defined as equal or larger than the 75th percentile value of glomerular diameter.

Results: The mean value for age, estimated glomerular filtration rate (eGFR), and body mass index (BMI) were as follows: 40 years, 86 ml/min/1.73m^2 and 24.0 kg/m^2. The median (quartile range) of maximal GD was 219 (202 – 245) mm, and the 75th percentile value was 245 mm. The group with GH had higher proportion of male and higher value of BMI, systolic blood pressure, uric acid and triglyceride. There was positive correlation between glomerular diameter and BMI. In the multivariate logistic regression analysis, overweight (BMI ≥ 25 kg/m^2) was significantly associated with GH (odds ratio 4.66, 95% confidence interval 1.33–16.3, P=0.02) independent of age, sex and some confounding factors such as diabetes mellitus. In the overweigh patients, glomerular diameter was significantly correlated with urine protein (r=0.52, P=0.0007).

Conclusions: Overweight is an independent determinant for glomerular hypertrophy. Even overweight may be a risk factor for progression of CKD in association with GH.

FR-PO452

The Impact of Prematurity on Postnatal Renal Medulla Development Joan Li,[5] Michael Guandalini,[2] Yoga Kandasamy,[4] Karen M. Moritz,[3] Peter Trnka.[1] *[1]Child and Adolescent Renal Service, South Brisbane, QLD, Australia; [2]Lady Cilento Children's Hospital, South Brisbane, NSW, Australia; [3]The University of Queensland, St Lucia, NSW, Australia; [4]Townsville Hospital, Douglas, NSW, Australia; [5]University of Queensland, Australia Institute for Bioengineering and Nanotechnology, Brisbane, QLD, Australia.*

Background: In humans, nephrogenesis ceases before birth but the renal medulla continues to develop postnatally and reaches full functional maturation at around 12-18 months of age. Premature birth is associated with reduced nephron number and increased risk of kidney and cardiovascular disease. However, the impact of prematurity on renal medulla remodelling and maturation and its contribution to the development of adult disease is unknown.

Methods: Preterm babies born at ~28 weeks of gestation and term babies without renal or urinary tract abnormalities were included in this study. Renal ultrasound was performed in 35 premature babies at 32 weeks and 37 weeks post menstrual age (PMA). In addition, 42 babies born at term were examined in the first week of life. Additional ultrasound images were taken at six months of age in all babies. Total kidney volume, renal cortical and pyramid thickness were measured.

Results: In premature babies the average kidney volume increased significantly from 32 weeks to 37 weeks PMA (post menstrual age) (6.89 ± 0.4 vs 10.38 ± 0.29, p ≤ 0.0001). However, at 37 weeks PMA the kidney volume and the pyramid/cortex ratio were still significantly smaller in premature babies compared to term babies (10.38 ± 0.29 vs 12.85 ± 0.48, p ≤ 0.0001; 2.22 ± 0.08 vs 2.79 ± 0.08, P = 0.0001 respectively). Premature infants

also had a significantly lower eGFR (73.6 vs. 79.3 mL/min/1.73 m^2; p = 0.03). By 6 months the average kidney volume was no longer different between premature and term babies due to significant catch-up growth of the premature kidney. The pyramid/cortex ratio remained significantly lower in the premature babies than term babies (2.01±0.05 vs 2.5±0.10, p = 0.0006). In term babies the medulla region continued to develop and mature; renal pyramid/parenchyma ratio increased from birth to 6 months (0.59±0.01 vs 0.62±0.05, p = 0.05). For premature babies the pyramid/parenchyma ratio didn't change significantly from birth to 6 month suggesting the medullary growth was significantly impaired.

Conclusions: Taken together, these results suggest that premature birth has sustained effects on postnatal renal medulla development and remodelling with potentially negative impact on renal function later in life.

FR-PO453

Urinary Epidermal Growth Factor as a Prognostic Marker for the Progression in Children with Alport Syndrome Baihong Li,[1] Fangrui Ding,[1] Fang Wang,[1] Viji Nair,[2] Matthias Kretzler,[2] Wenjun Ju,[2] Jie Ding.[1] *[1]Peking University First Hospital, Beijing, China; [2]University of Michigan, Ann Arbor, MI.*

Background: Alport syndrome (AS) is a rare hereditary kidney disease manifested with progressive renal failure, vast majority of the cases are caused by defects in type IV collagen genes. Considerable variation exists in terms of disease progression among patients with AS. Identification of patients at high risk of rapid progression remains an unmet need. Urinary epidermal growth factor has been shown to be independently associated with risk of progression to end stage kidney disease (ESKD) or 40% reduction of baseline eGFR in multiple independent adult CKD cohorts. In this study we aim to assess the prognostic value of uEGF in children with AS.

Methods: 117 pediatric patients with AS and 72 healthy children (3-18 year-old) were included in this study. uEGF was measured in duplicates in baseline urine samples using ELISA (R&D) and concentration was normalized by urine creatinine (uEGF/Cr). In patients with longitudinal follow up data (n=38), progression was defined as deteriorated kidney function (CKD stage increase) during follow-up period (average follow-up 29.92±16.18 months). The area under the receiver operating characteristic (ROC) curve was used to assess the discriminative power of the marker.

Results: uEGF/Cr decreases with age in both healthy children and pediatric patients with AS. The decrease rate of uEGF/Cr with age was faster in AS patients. uEGF/Cr is significantly correlated with GFR (r=0.75, p<0.001), after adjustment for age. In 38 patients with longitudinal follow-up, we observed a significant correlation between uEGF and eGFR slope (r=0.58, p<0.001). Patients with lower uEGF/Cr level were at increased risk of progression to a higher CKD stage. uEGF distinguished progressors from patients who do not show CKD stage advance with an AUC of 0.89, versus 0.80 by GFR and 0.79 by ACR.

Conclusions: Our work suggested that uEGF/Cr may be used as a biomarker for accelerated kidney function decline in pediatric patients with AS. It may help to identify patients at high risk of progression for targeted clinical care and improve the patients'stratification in interventional trials. Future validation with more patients and longer follow-up time will be required.

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FR-PO454

Analysis of the Plasma Proteome Reveals Dysregulation of Molecular Pathways in Patients with Stage 4 CKD Ewelina Kulikowski,[2] Sylwia Wasiak,[2] Laura Tsujikawa,[2] Christopher Halliday,[2] Stephanie Stotz,[2] Dean Gilham,[2] Ravi Jahagirdar,[2] Kamyar Kalantar-Zadeh,[3] Richard A. Robson,[1] Michael Sweeney,[4] Jan O. Johansson,[4] Norman C. Wong.[2] *[1]CHristchurch Clinical Studies Trust, Christchurch, New Zealand; [2]Resverlogix Corp, Calgary, AB, Canada; [3]University of California Irvine, School of Medicine, Orange, CA; [4]Resverlogix Inc., San Francisco, CA.*

Background: Chronic kidney disease (CKD) is associated with progressive loss of renal function. To gain insight into molecular mechanisms and biological consequences of pathway dysregulation in CKD, plasma proteome profiling of stage 4 CKD patients was performed using a novel somamer-based approach coupled to bioinformatics.

Methods: Eight subjects with stage 4 CKD not on dialysis (mean eGFR=20 ml/min/1.73m^2) and eight matched control subjects (mean eGFR=78.5 ml/min/1.73m^2) participated in the study. Plasma samples were collected for analysis with the SOMAscan® 1.3K platform, which detects 1305 proteins in a multiplexed, sensitive and reproducible manner. Proteomics data were analysed with Ingenuity Pathway Analysis (IPA®).

Results: SOMAscan® proteomic analysis of plasma from CKD versus control subjects identified 289 differentially expressed proteins (difference>10%, p<0.05). 191 of those proteins were upregulated by more than 50% in CKD plasma relative to controls. Many of the enriched markers correlate with CKD progression, including cystatin C, B2M, LCN2, LFABP and FGF23. Other differentially expressed proteins include cytokines and their soluble receptors, adhesion molecules, metalloproteases, complement, coagulation and fibrinolytic factors. IPA® bioinformatics of the plasma proteome confirmed an upregulation of pathways known to be activated in CKD such as the inflammatory and immune response, endothelial dysfunction, thrombosis, renin-angiotensin system, calcification and oxidative stress.

Conclusions: This study provides an exhaustive list of plasma proteins that are dysregulated in stage 4 CKD. In combination with pathway analysis, this CKD plasma proteome contributes new knowledge of molecular processes that accompany CKD and potential new disease markers.

FR-PO455

Mineralocorticoid Receptor Blockers and Renal Outcomes in Patients with Heart Failure and CKD Thomas Mavrakanas,[2,3] Nadia Giannetti,[1] Ruth Sapir-Pichhadze,[2] Ahsan Alam.[2] *[1]Division of Cardiology, McGill University Health Centre, Montreal, QC, Canada; [2]Division of Nephrology, McGill University Health Centre, Montreal, QC, Canada; [3]Division of General Internal Medicine, Geneva University Hospitals, Geneva, Switzerland.*

Background: The protective effect of mineralocorticoid receptor blockers (MRBs) against cardiovascular death or heart failure hospitalization has been demonstrated in patients with chronic kidney disease (CKD). However, safety concerns limit their use in this population. Furthermore, the effect of MRBs on CKD progression is unknown.

Methods: We conducted a retrospective cohort study including consecutive adult patients from the heart failure clinic of a tertiary care center who were already treated with an angiotensin converting enzyme inhibitor or an angiotensin receptor blocker. The exposure of interest was treatment with MRBs by 6 months from registration to clinic. Persistent doubling of serum creatinine was the primary efficacy outcome. The composite of doubling of serum creatinine or potassium >6 mmol/l was the primary safety outcome. The composite of death from any cause, myocardial infarction, or admission for decompensated heart failure was the secondary outcome.

Results: A total of 314 patients who were prescribed MRBs were compared to 1116 patients who were never treated with MRBs. Among them, 121 and 408 patients, respectively, had CKD. MRBs had to be discontinued in 34/121 patients with CKD (28.1%) and 55/165 patients without CKD (33.3%) (p-value=0.35). While MRB treatment increased the risk of persistent creatinine doubling in patients without CKD, in CKD patients a protective trend was seen (p-value for interaction 0.02). Similarly, the primary safety outcome occurred more commonly with exposure versus non-exposure to MRBs in non-CKD but not in CKD patients (p-value for interaction 0.02). CKD status did not alter MRB effect on death from any cause, myocardial infarction, or admission for decompensated heart failure (p-value for interaction 0.27).

Conclusions: CKD status significantly alters MRB effect on renal outcomes. Treatment with MRBs may be nephroprotective in heart failure patients with CKD.

Funding: Private Foundation Support

FR-PO456

Markers of the Adaptive Immune Response Are Associated with Advancing CKD Status Dana C. Crawford, William S. Bush, Jessica N. Cooke Bailey, John F. O'Toole, John R. Sedor. *Case Western Reserve University, Cleveland Heights, OH.*

Background: Germline and somatic genomic variation represent the bulk of 'omics data in precision medicine research. These data, however, may fail to capture the dynamic biological processes that underlie disease development, particularly for diseases of aging such as chronic kidney disease (CKD).

Methods: To demonstrate the value of additional dynamic precision medicine data, we sequenced somatic T-cell receptor rearrangements from genomic DNA collected during a clinical encounter from 15 CKD participants. Participants were consented as part of a larger precision medicine research project at a large urban public hospital. Genomic DNA was extracted from whole blood, and T cell receptors were sequenced with six replicates per sample using Adaptive Biotechnologies' immunoSEQ assays coupled with the Illumina NextSeq PE. All sequences were assembled using Adaptive Biotechnologies' ANALYZER bioinformatics pipeline. Demographic and clinical data closest to the time of blood draw were extracted from the electronic health record.

Results: The average age of patients was 61.73 years, more than half (60%) were female, and the majority were African American (80%). T-cell receptor diversity was estimated using productive clonality, a measure ranging from 0 (polyclonal samples; more diversity) to 1 (oligoclonal samples; less diversity). Productive clonality in this sample ranged from 0.0151 to 0.2565 with a mean of 0.1030 (standard deviation or SD=0.0669). Average productive clonality did not statistically differ by sex: females = 0.0811 (SD=0.0533) and males = 0.1358 (SD=0.0764). We then tested for correlations between T-cell receptor diversity and biomarkers of CKD, including disease status calculated using the CKD-EPI equation. Reduced T-cell diversity was associated with increased creatinine (R^2=0.0995). BUN (R^2=0.0258), and eGFR (R^2=0.066) but not with white blood cell count (R^2=0.0004). Reduced T-cell diversity was also associated with worsening CKD status (R^2=0.2362), with a higher on average productive clonality (0.0488) among stage 4 patients (n=5) compared with stage 3 (0.0330; n=8) and stage 2 patients (0.0149; n=2).

Conclusions: These data suggest an association between advanced CKD and premature aging of the adaptive immune system and highlight the potential of dynamic 'omic data to generate novel hypotheses about disease mechanisms.

FR-PO457

Remote Candidate Prognostic Biomarkers of CKD among People with Type 1 Diabetes Mellitus (T1DM) Jian Cai,[1] Michael Merchant,[1] Adam E. Gaweda,[1] Michael E. Brier,[1] Brad H. Rovin,[2] Minghao Ye,[3] Jan Wysocki,[3] Mark E. Molitch,[3] Daniel Batlle,[3] Jon B. Klein.[1,4] *[1]University of Louisville School of Medicine, Louisville, KY; [2]Ohio State University Wexner Medical Center, Columbus, OH; [3]Northwestern University Feinberg School of Medicine, Chicago, IL; [4]Robley Rex VAMC, Louisville, KY. Group/Team: For DCCT/EDIC study and CKD Biomarkers Consortium.*

Background: It has been difficult to identify biomarkers that antedate the development of CKD. We used a plasma proteomic approach to evaluate samples from participants in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications (DCCT/EDIC) with the goal to establish surrogate prognostic biomarkers of CKD in T1DM.

Methods: Samples from 23 cases (defined as participants who went on to develop CKD stage 3 (GFR<60ml/min/1.73m^2) were examined prior to developing CKD. Two samples from these cases were analyzed; an early sample during DCCT and a later sample from each same subject during EDIC. 23 controls were participants in whom GFR remained well above 60ml/min/1.73m^2 after collection of the two matching samples during DCCT and EDIC. Samples were immunodepleted, trypsinized, labeled with 10-plex tandem mass tag (TMT), and analyzed by high resolution 2D-LCMS. The data were processed prior to Wilcoxon Rank-Sum difference testing (p-value <0.05). Candidate biomarker selection was based on fold-changes (FC, <1.5 and >1.5) to identify case/control DCCT and EDIC differences.

Results: When the sample for proteomic analysis was obtained during DCCT, cases and controls had similar age, sex, GFR, HBA1C, blood pressure, albumin excretion rate (AER) and duration of DM. During EDIC, about 15 years later, there were differences (p<0.01) in GFR (83.9 vs 101.9 ml/min/1.73m^2), AER (810.5 vs 24.6mg/24h) and HbA1c (9.5 vs 8.3) between cases and controls. 1,667 identified protein groups were quantified. Cross sectional cases/control proteome differences were observed during DCCT (n=12) and EDIC (n=103) study time frames. Nine proteins were observed with >1.5FC (DCCT, n=2; EDIC, n=7), many involved in insulin signaling, inflammation, and coagulation/microvascular function. These differences in proteins were identified about 20 and 4yrs, respectively before the development of CKD.

Conclusions: In people with T1DM the plasma proteome, years prior CKD stage3, has unique proteins that are potential biomarkers of disease progression.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO458

Uromodulin Synthesis Is Reflected by Metabolic Profiles in the General Population Claire Boulange,[2,1] Eric G. Olinger,[4] Manuja Kaluarachchi,[2,1] John C. Lindon,[2,1] Natsuko Tokonami,[3] Tomoaki Takata,[3] Olivier Devuyst.[3] *[1]Imperial College london, London, United Kingdom; [2]Metabometrix Ltd, London, United Kingdom; [3]University of Zurich, Zurich, Switzerland; [4]University of Zürich, Zürich, Switzerland.*

Background: Uromodulin (UMOD) is the most abundant protein in mammalian urine, synthesized exclusively along the thick ascending limb (TAL) in the kidney and with highly variable urinary levels in the general population. GWAS associated common variants in the *UMOD* promoter region, driving higher UMOD production, with increased risk for chronic kidney disease (CKD). UMOD regulates TAL transport but the mechanisms linking UMOD and risk for CKD remain unknown. We hypothesize. We speculate that the production rate of this protein imposes a metabolic burden to the TAL that might be reflected by metabolic profiles.

Methods: Overnight urine was collected from male volunteers (eGFR>80mL/min) and overnight UMOD excretion was determined (14.71±0.60mg, n=279). gender Extreme low (2.79±0.26mg, n=25) and high (34.11±2.14mg, n=25) age-matched UMOD excretion groups were defined and urine was analyzed by ^{1}H NMR spectroscopy and UPLC-MS. Mitochondrial phenotyping was performed on isolated TAL's from *Umod*$^{-/-}$, *Umod*$^{+/+}$ and Tg$^{Umodwt/wt}$ mice on FVB background, mimicking variable UMOD production rates in humans.

Results: Unsupervised principal component analysis evidenced natural clustering of metabolic data for urine samples stratified according to UMOD excretion. Many significant metabolic features were associated with overnight UMOD excretion in both NMR and UPLC-MS datasets. Biological interpretation pinpoint to Metabolic pathways involving these metabolites are related to protein synthesis and degradation, energy metabolism (fatty acid metabolism, citric acid cycle) and oxidative stress. Mitochondrial phenotyping revealed lower oxygen consumption rates and mitochondrial ATP production at baseline in TAL samples from *Umod*$^{-/-}$ vs. *Umod*$^{+/+}$ mice; and an increased maximal respiratory capacity in those from Tg$^{Umodwt/wt}$ vs. *Umod*$^{+/+}$ mice.

Conclusions: These results indicate a particular specific urinary metabolic profile associated with divergent UMOD production in the general population, supported by specific changes in mitochondrial metabolism reflecting uromodulin production in mouse models. The metabolic burden of increased UMOD production may, over time, contribute to CKD susceptibility.

Funding: Government Support - Non-U.S.

FR-PO459

Risk of ESRD and Mortality in Stage 3 CKD Using a Risk Estimator Youngjun Park, Nawsheen Chowdhury, Candace D. Grant, Shayan Shirazian. *Department of Medicine, Division of Nephrology, NYU-Winthrop Hospital, Mineola, NY.*

Background: Accurate assessment of the risk of end stage renal disease (ESRD) is important in determining which patients with chronic kidney disease (CKD) to prepare for renal replacement therapy (RRT). This can be challenging in earlier CKD when the short term risk for ESRD can be low but the lifetime risk is high. We applied a short term (2-year) risk calculation method to a population of stage 3 CKD patients and carried out an observational study to assess outcomes.

Methods: This is a cross-sectional study of 409 patients with stage 3 CKD. The ESRD risk estimation was determined using the 2 year risk estimator developed and validated by Tangri et al. A 2-year risk of progression to ESRD of <2.5% was considered low risk (LR) and ≥ 2.5% was considered high risk (HR). Patients were then organized into groups by age (< 60, 60 to 79 and ≥80 years). Over the following 2 years development of ESRD and death were recorded.

Results: The average age for the entire group was 70±14 years, 68% were men, 78% were white, the mean GFR was 42 ml/min/1.73m2 and the mean 2 year ESRD risk was 2.2%. The 2 year calculator determined 76% (n=311) of our entire stage 3 cohort to be LR. None of the LR group reached ESRD versus 5% of the HR group and 5% of the LR group died versus 10% of the HR group. The 2 year risk of ESRD progressively diverged with younger age with a 4.2% risk for patients <60, versus a 1.9% and 1.1% risk for patients 60 to 79 and ≥ 80, respectively (p<0.001). For patients younger than 60, 46% of them were at high risk compared to 10% in the ≥ 80 year age group (p<0.001). We found none of the patients aged ≥ 80 versus 4% of the younger patients aged <60 years reached ESRD. In contrast, 11% of the older patients versus 4% of the younger patients died.

Conclusions: These results show that in our population age had a significant impact on 2 year estimated ESRD risk. Risk determinations and outcomes showed progressively higher ESRD risk with younger age and a higher risk of death with older age. A validated risk calculator to assign patients to LR and HR groups appears to help predict clinical outcomes and might be a useful tool in guiding proper selection of patients for preparation for RRT.

FR-PO460

Concomitant Acute Pyelonephritis and Obstruction Duration Affects Renal Outcome in Obstructive Uropathy by Urolithiasis Jung-ho Shin, So-hee Jeong, Jin Ho Hwang, Su Hyun Kim. *Chung-Ang University Hospital, Seoul, Republic of Korea.*

Background: Urolithiasis related obstructive uropathy is one of increasing causes of CKD, which commonly encountered in clinical field. Obstruction release from urolithiasis can be easily delayed with a lack of suggested golden time to prevent renal function deterioration. Here, we investigated the clinical significance and renal outcomes of urolithiasis related obstructive uropathy.

Methods: This is a pilot study of 414 from 2315 patients in urolithiasis related obstructive uropathy cohort which is recruited between Jan. 2005 and Dec. 2015. Clinical outcomes were evaluated with respect to obstruction duration, acute kidney injury (AKI), and acute pyelonephritis (APN) accompanied by obstructive uropathy.

Results: Median duration of obstruction (elapsed time to release obstruction) was 5 days and APN was accompanied in 17.1% of patients. In the patients whose obstruction was relieved within 2 days from the symptom onset, 14.5% showed spontaneous release of obstruction. In the patients with concomitant APN, mean age was older (57.67vs 52.5 years old, P=0.007), estimated GFR (eGFR) at the time of admission was lower (63.5 vs. 79.4 ml/min/1.73m2, P<0.001), and the use of NSAIDs were lower (49.3% vs. 74.9%, P<0.001). The eGFR decrease of >30% from baseline (P<0.001) and eGFR decrease of >50% (P<0.001) occurred significantly more in patients with concomitant APN. The AKI grades by KDIGO showed worse renal outcome in advanced stage (P=0.001). The patients whose obstruction was released within 2 days from the symptom onset, showed more favorable outcome in eGFR decrease of >30% (P=0.019). When we adjusted gender, age, HT, DM, use of NSAIDs, APN, AKI grades, and obstruction release over 2 days for a multivariate analysis, APN (HR 2.2, CI 1.01-4.65; P=0.047) and the obstruction release after 2 days (HR 3.55, CI 1.34-9.38; P=0.011) were independently associated with eGFR decrease of >30%. Concomitant APN was also associated with eGFR decrease of >50% (HR 8.006, CI 1.86-34.38, P=0.005). The use of NSAIDs was associated with favorable renal outcomes.

Conclusions: In urolithiasis related obstructive uropathy patients, concomitant APN was strongly associated with renal function deterioration after obstruction release. The elapsed time to release obstruction also affected to renal function.

FR-PO461

Prevalence and Severity of Dental Plaque and Dental Calculus in Patients with CKD Namita Kalra,[4] Ujjawal Roy,[1] Sunil Agarwal,[3] Ashok K. Tripathi,[5] Om P. Kalra.[2] *[1]Orchid Medical Centre, Ranchi, India; [2]Nephrology, Pt. B.D. Sharma University of Health Sciences, Rohtak, India; [3]Medicine, University College of Medical Sciences and GTB Hospital, Delhi, India; [4]Pedodontics, University College of Medical Sciences, Delhi, India; [5]Biochemistry, University College of Medical Sciences, Delhi, India*.

Background: Patients with CKD have impaired immune responses which may predispose them to various infections, such as dental plaque. Further, altered calcium phosphorus balance and high prevalence of mineral bone disease may result in poor dental health including dental calculus, decayed and missing teeth. The goal of this study was to assess the status of dental plaque, dental calculus and missing teeth in patients with CKD.

Methods: 150 age and sex matched subjects were recruited under 3 groups, 50 in each. These included : Group A - healthy controls; Group B - patients with CKD stage 3 to 5 not yet on maintenance hemodialysis (MHD) and Group C - patients of CKD stage 5 who were on MHD for >1 month. Detailed examination of the teeth for dental plaque and dental calculus was done. Severity of dental plaque and dental calculus was assessed by using dental plaque and calculus scores on a scale of 1 to 3. Dental plaque and dental calculus score was calculated after recording individual dental plaque and calculus score and dividing it by the number of teeth examined. Patients with history of recent tobacco use, diabetes mellitus, oral infection and drug intake such as calcium channel blockers, anticonvulsants, immuno-suppressants and allograft recipients were excluded.

Results: Mean dental plaque score and dental calculus score in patients with CKD were significantly higher as compared to healthy controls ($p<0.001$ for both). Mean dental plaque score was: healthy controls : 0.98±0.39, Group B : 1.56±0.52 and Group C : 1.81±0.53. Mean dental calculus score was: healthy controls : 0.91±0.65, Group B : 1.77±0.56 and Group C : 1.81±0.56. Further, it was found that the dental plaque score showed a progressive rise with increase in severity of kidney disease. Patients of CKD stage 5 who had been on MHD had significantly higher mean dental plaque score as compared to those with CKD stage 5 who had not yet been started on HD ($p=0.029$). Further, patients with CKD had higher number of missing teeth (Group B – 2.36±4.08, Group C – 2.64±3.60) as compared to healthy controls (1.10±2.28).

Conclusions: Patients with CKD have higher prevalence of dental plaque and dental calculus. The prevalence of dental plaque correlates with increase in severity of kidney disease. Higher prevalence of dental pathology may contribute to malnutrition in patients with CKD.

FR-PO462

Urinary Renin and Angiotensinogen for Predicting Antiproteinuric Effect of Angiotensin Receptor Blocker Do Hee Kim,[1,2] Junseok Jeon,[2] Hye Ryoun Jang,[2] Jung eun Lee,[2] Wooseong Huh,[2] Hye-Young Kim,[1,3] Dae Joong Kim,[2] Ha Young Oh,[2] Yoon-Goo Kim.[2] *[1]Division of nephrology, Department of Medicine, Chungbuk National University Hospital, Cheongju, Republic of Korea; [2]Division of nephrology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]Department of Medicine, Chungbuk National University College of Medicine, Cheongju, Republic of Korea*.

Background: Although urinary angiotensinogen (AGT) and renin were reported to reflect the activity of intrarenal renin-angiotensin system which is known to be activated in proteinuric chronic kidney disease patients, the clinical value of urinary AGT and renin during antiproteinuric treatment is yet to be determined. In this study, we investigated the clinical impact of baseline urinary AGT or renin on the antiproteinuric effect of angiotensin receptor blocker (ARB).

Methods: A multicenter, prospective observational cohort study was conducted in 205 patients with overt proteinuria (urinary protein/creatinine ratio [uPCR] ≥ 1 mg/mgCr) between April 2009 and December 2011. Low salt diet was thoroughly educated in all patients at the time of enrollment. Baseline urinary AGT/creatinine ratio (uAGT/Cr), renin/creatinine ratio (uR/Cr), and sodium/creatinine ratio (uNa/Cr) were measured before starting valsartan. The uPCR was followed up at 2 months and 6 months in all patients. A total of 60 patients were followed up for 5 years.

Results: The mean age of patients was 47.6 ± 12.5 years and 51.2% were male. The uPCR was 2.32 ± 1.43 mg/mgCr and the estimated glomerular filtration rate was 63.2 ±28.8 ml/min/1.73m^2. The uNa/Cr was 1.30 ± 1.25 mg/mgCr. Natural logarithms of uAGT/Cr (ln[uAGT/Cr]) and uR/Cr (ln[uR/Cr]) were significantly higher in 53 patients with uPCR decrement greater than 1mg/mgCr at 6 months. uNa/Cr was higher in patients with uPCR decrement greater than 1 mg/mgCr at 2 months. Multivariable regression analysis identified uNa/Cr as a significant factor associated with the degree of uPCR decrement at 6 months (β = -0.206, P = 0.047). Ln(uR/Cr) was identified as a predictive factor (OR 1.244, 95% CI 1.04-1.49, P = 0.018) for uPCR decrement higher than 1 mg/mgCr at 6 months in logistic regression analysis.

Conclusions: Our study showed that baseline ln(uR/Cr) and uNa/Cr have the potential to be used as prognostic markers predicting antiproteinuric effect of ARB. The clinical importance of low salt diet education was also shown.

FR-PO463

AKI after Radical Nephrectomy as Risk Factor for CKD: Retrospective Analysis from an Italian Cancer Center Laura Cosmai,[5] Camillo Porta,[2] Fabio Malberti,[1] Marina Foramitti,[3] Maurizio Gallieni.[4] *[1]Azienda Istituti Ospitalieri di Cremona, Cremona, Italy; [2]IRCCS San Matteo University Hospital Foundation, Pavia, Italy; [3]Istituti Spitalieri Cremona, Cremona, Italy; [4]Ospedale San Carlo Borromeo - ASST Santi Paolo e Carlo - University of Milano, Milano, Italy; [5]Nephrology and Dialysis, ASST Santi Paolo e Carlo, Milano, Italy*.

Background: Radical nephrectomy is a significant risk factor for chronic kidney disease (CKD), and there are few reports on the renal outcome after radical nephrectomy for cancer. The aim of this study was to determine the incidence of AKI and whether postoperative AKI is associated with new-onset CKD after radical nephrectomy for renal cell cancer (RCC).

Methods: We conducted a retrospective study of 650 adult patients (>40 years old), from an Italian Cancer Centers with normal renal function who underwent unilateral radical nephrectomy for a solitary renal cortical tumour and were pathologically diagnosed with RCC between January 2010 and February 2017. Post-operative AKI was classed using risk, injury, failure, loss and end-stage kidney disease (RIFLE) criteria. CKD was defined as a decrease in estimated glomerular filtration rate (GFR) to <60 mL/min/1.73 m2

Results: According to the RIFLE criteria, 195 of 216 patients fell into the AKI risk category 1, 16 patients fell into the AKI injury category and 5 patients fell into the AKI failure category. Multivariate analysis revealed as major result that higher preoperative GFR was an independent risk factor for postoperative AKI, although older age, male gender higher body mass index, smaller RCC size were independent risk factors too. New-onset CKD was more prevalent in the AKI risk group than in patients without AKI 1 year after surgery (56.1% versus 43.9%, respectively) and 3 years after surgery (52% versus 31%). Patients who experienced post-operative AKI had a 5.1-fold higher risk of new-onset CKD after multiple adjustments, that confirms other recent study.

Conclusions: AKI after radical nephrectomy in patients is a potent risk factor for new-onset CKD. Prevention of post-operative AKI, but also the assesment of kidney function pre-nephrectomy, is essential for reducing the incidence of CKD after nephrectomy.

FR-PO464

Elevated Time-Varying BP Is Associated with Greater Risk of Progression of CKD Than Elevated Baseline BP in Children with Non-Glomerular CKD Ben C. Reynolds,[3] Jennifer Roem,[1] Christopher B. Pierce,[2] Joseph T. Flynn,[4] Mina Matsuda-Abedini,[8] Susan L. Furth,[5] Bradley A. Warady,[6] Rulan S. Parekh.[7] *[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [2]Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; [3]Royal Hospital for Children, Glasgow, Glasgow, United Kingdom; [4]Seattle Children's Hospital, Seattle, WA; [5]The Children's Hospital of Philadelphia, Philadelphia, PA; [6]The Children's Mercy Hospital, Kansas City, MO; [7]The Hospital For Sick Children, Toronto, ON, Canada; [8]The Hospital for Sick Children, Toronto, Toronto, ON, Canada*.

Background: Effective treatment of hypertension in children with chronic kidney disease (CKD) slows the rate of progression to end stage renal disease (ESRD). Less clear is whether longitudinal (e.g. annual time varying) measures of blood pressure (BP) are associated with greater risk of progression. We quantified this risk with systolic or diastolic casual BP measurement > 90th centile at baseline or longitudinally in children with CKD.

Methods: Of 826 children (257 glomerular disease, 569 non-glomerular) enrolled in the CKiD cohort, we determined if BP <50th, 50th-90th, or >90th centile (for age, gender and height) was associated with a composite outcome of CKD progression: ESRD or GFR reduction of 50% from baseline. BP category was defined as time-fixed (baseline) and time-varying (last available). Pooled logistic models using inverse probability weighting were used to estimate the relative hazard odds of progression associated with each BP category and stratified by CKD diagnosis.

Results: Higher SBP percentile was associated with an elevated risk of progression, the time-varying metric estimating a higher magnitude of risk compared to time-fixed baseline measures (Table). Adjustment for potential confounders did not qualitatively change the risk in non-glomerular disease but nullified the estimate in glomerular disease.

Conclusions: Elevated time-varying systolic BP is associated with a greater risk of CKD progression than baseline BP in children with non-glomerular CKD. Clinicians can use updated BP to assess risk for progressive CKD and adjust management accordingly.

Funding: NIDDK Support

Table: Hazard Odds Ratio (95% confidence intervals)

		Unadjusted		Adjusted	
		Non-glomerular	Glomerular	Non-glomerular	Glomerular
Baseline SBP %	<50th	ref			
	50-90th	1.07 (0.76,1.52)	1.63 (0.96, 2.79)	1.15 (0.81,1.63)	1.14 (0.69, 1.89)
	>90th	1.67 (1.12, 2.47)	3.39 (1.91, 6.02)	1.79 (1.2,2.68)	1.34 (0.75,2.4)
Time-varying SBP %	<50th	ref			
	50-90th	1.59 (1.12, 2.27)	1.79 (1.05,3.07)	2.55 (1.64,3.97)	0.86 (0.42,1.79)
	>90th	3.35 (2.25,5)	4.48 (2.53,7.95)	3.16 (1.82,5.5)	0.85 (0.35,2.02)
Baseline DBP %	<50th	ref			
	50-90th	1.15 (0.8, 1.64)	1.28 (0.72,2.2)	1.17 (0.82,1.67)	1.02 (0.62,1.69)
	>90th	1.19 (0.77,1.85)	4.71 (2.6,8.52)	1.23 (0.79,1.91)	2.68 (1.42,5.07)
Time-varying DBP %	<50th	ref			
	50-90th	1.39 (0.98,1.96)	0.93 (0.53,1.63)	1.78 (1.15,2.76)	0.46 (0.22,0.94)
	>90th	1.81 (1.18,2.79)	5.28 (3.04,9.17)	1.64 (0.89,3.01)	1.45 (0.66,3.2)

* adjusted for GFR, proteinuria, antihypertensive use, immunosuppressant use (G only), age, male sex, black race, BMI z-score

FR-PO465

30% GFR Decline in 2 Years Was Observed among 62.5% of CKD Patients Initiated Hemodialysis: A Longitudinal GFR Trajectory Analysis Ahmad B. Kaihan,[4] Yoshinari Yasuda,[1] Takayuki Katsuno,[3] Sawako Kato,[3] Takahiro Imaizumi,[6] Takaya Ozeki,[5] Manabu Hishida,[2] Naotake Tsuboi,[3] Shoichi Maruyama.[3] *[1]Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Aichi-ken, Japan, Nagoya, Japan; [2]Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [3]Nagoya University Graduate School of Medicine, Nagoya, Japan; [4]Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan; [5]Nephrology, Nagoya University Graduate School of Medicine, Nagoya, AICHI-KEN, Japan., Nagoya, Japan; [6]Nephrology, Nagoya University Graduate School of Medicine, Nagoya, Japan.*

Background: GFR decline rate has been highlighted as a new renal outcome for the clinical trial to reduce the sample size and shorten the observation period. We aimed to evaluate the eGFR trajectory among CKD patients initiated hemodialysis (HD).

Methods: A longitudinal GFR trajectory analysis was conducted among consecutive 112 CKD patients initiated HD between 2014 and 2016 at Nagoya University Hospital. All serum creatinine (SCr) values were collected from the electronic medical record from 2000 to the initiation of HD and eGFR annual decline rate (ADR) was calculated. eGFR ADR stratified into quartile classification and 30%, 40% eGFR decline and doubling of SCr in 2 years were analyzed in association with eGFR ADR.

Results: The causative kidney diseases were 41 (37%) diabetic nephropathy, 37 (33%) nephrosclerosis, 14 (13%) chronic glomerulonephritis, and 20 (18%) others. Median follow-up period was 5.6 years. The proportion of 30%, 40% eGFR decline, and the doubling of SCr in 2 years were shown in Table 1. Kaplan-Meier survival curve analysis for 30% eGFR decline revealed significant difference among quartiles (log-rank p< 0.0001). The associating factors for eGFR ADR were in SCr, eGFR, protein creatinine ratio (PCR), Hb, and SUA univariate, and eGFR (OR 1.14, 95% CI 1.04-1.26, p=0.0008) and PCR (OR 3.27, 95% CI 1.20-8.92, p= 0.02) in multivariate logistic regression analyses. 30% eGFR decline was observed significantly earlier in the greater amount of PCR quartiles (p<0.001). In GFR categories, G3a showed a tendency to meet 30% eGFR decline later than other GFR categories.

Conclusions: Although 30% GFR decline was the earlier renal outcome in 2 years, approximately 40% of patients initiated HD were negative in this study. The longer observation period should be considered among slowly progressive CKD patients with mild proteinuria and mild-moderately impaired renal function.

Funding: Other U.S. Government Support

30%, 40% eGFR decline and serum creatinine doubling in 2 years among annual GFR decline rate quartiles.

	1st quartile (slow: n=28)	2nd quartile (moderate: n=28)	3rd quartile (fast: n=28)	4th quartile (very fast: n=28)
Annual eGFR decline rate (mL/min/1.73m^2/year)	2.1 [1.5-2.5]	4.3 [3.7-4.7]	7.4 [6.4-8.7]	14.7 [10.9-18.8]
30% GFR decline in 2 years (%)	13 (46.4)	16 (57.1)	18 (64.3)	23 (82.1)
40% GFR decline in 2 years (%)	7 (25.0)	11 (39.3)	13 (46.4)	21 (75.0)
Doubling of sCr in 2 years (%)	8 (28.6)	8 (28.6)	8 (28.6)	20 (71.4)

FR-PO466

Delayed Renal Recovery and Long-Term Renal Survival after Radical Nephrectomy for Renal Cell Carcinoma Hee jung Park,[3] Ha nee Jang,[5] Tae won Lee,[2] Hyun Seop Cho,[2] Hyun-Jung Kim,[4] Dong Jun Park,[2] Eunjin Bae,[1] Se-Ho Chang.[3] *[1]Gyeongsang National University Changwon Hospita, Changwon, SEOUL, Republic of Korea; [2]Gyeongsang National University Hospital, Jinju-si, Gyeongsangnam-do, Republic of Korea; [3]Gyeongsang national university hospital, Jinju, Jinju-si, Republic of Korea; [4]School of Medicine, Gyeongsang National University, Jinju, Republic of Korea; [5]Gyeongsang National Univ. Hospital, Jinju, Republic of Korea.*

Background: Radical nephrectomy has been associated with chronic kidney disease (CKD). It is unclear whether delayed renal recovery after surgery affects long-term renal outcome. We investigated the association between delayed renal recovery and long-term renal survival in patients undergoing radical nephrectomy for renal cell carcinoma. We assessed factors affecting the recovery of renal function.

Methods: We reviewed medical record database for all patients (>18 years old) who underwent radical nephrectomy for renal cell carcinoma between from January 2009 to December 2016. Among these, we included patients with a 3-month renal function test after surgery. Renal outcome was defined as a doubling in serum creatinine or End stage renal disease. Estimated GFR were evaluated at baseline, 3 months and the last follow-up. We excluded patients with estimated glomerular filtration rate (GFR) of less than 40 ml/min/1.73m2. Estimated GFR calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Delayed renal function was defined by creatinine did not decrease less than preoperative value.

Results: Among the 105 patients who met inclusion criteria, 70 (66.7%) were males. The median age at nephrectomy was 62 year (range 25-84 years). 60 (57.1%) were diagnosed with delayed renal recovery: The average serum creatinine was 0.85 ± 0.22 mg/dL, and average estimated GFR was 102.89 ± 29.46 ml/min/1.73m2. The average follow-up period was 39.55 ± 24.48 months. Multiple linear regression analysis shows delayed renal recovery, baseline estimated GFR to be significantly associated with long-term renal survival (p=0.05, p=0.040, respectively). Hypertension and increased baseline creatinine were the factors affecting early recovery of renal function.

Conclusions: Our results suggest that hypertension and renal impairment for renal cell carcinoma patients may delayed renal recovery after radical nephrectomy, and adversely affect kidney function over a long term period.

FR-PO467

Renal and Metabolic Complications of Long-Term Total Parental Nutrition (TPN) in Pediatric Patients Poornima Baddi,[4] Najeeb Zoubi,[2] Joseph L. Lelli,[1] Tej K. Mattoo.[3] *[1]Children's Hospital of Michigan, Detroit, MI; [2]Children's hospital of Michigan, Detroit, MI; [3]Children's Hospital of Michigan, Detroit, MI; [4]Pediatric Nephrology, Children's hospital of Michigan, Detroit, MI. Group/Team: Wayne state university.*

Background: The number of children requiring prolonged TPN is increasing and yet very little is known about its potential long term complications. The objective of this study was to evaluate renal and metabolic complications of prolonged TPN in patients at our institution.

Methods: We did a retrospective chart review with prospective follow-up of 26 patients who, with the exception of one patient, were followed at our Children's hospital Intestinal Rehabilitation Program (CHIRP) clinic. We included patients 1 to 15 (median of 4) years of age that had been on TPN for ≥ 6 months at the time of data collection. Patients who received <20% of nutrition as TPN and those with other co-morbidities were excluded. Variables that were studied included anthropometric data, indication and duration of TPN, TPN formulation and daily volume, intestinal anatomy, details on oral nutritional supplements, current medications, blood and urine chemistry results, renal imaging results, and number of acute kidney injury (AKI) episodes.

Results: Of the 26 patients, 8 (31%) received 100% nutrition as TPN; 10 (38%) patients received a mean of 80% and 8 received 20%-80% nutrition as TPN. The Median duration of TPN administration was 4 years (Range 1-15). Recurrent AKI was the commonest complication in 24 (92%) patients with a median of 8 (range 4 - 40) episodes per patient. Other complications were hypertension (38%), echogenic kidneys on ultrasound examination (27%), renal size asymmetry (15%), hydronephrosis (15%), renal calculi (11%), phosphaturia, hypophosphatemia and nephrocalcinosis (4%), and recurrent post-infectious Glomerulonephritis (4%). Glomerular hyper filtration, as defined by modified Schwartz eGFR of >135ml/min/m^2, was noted in 12 (46%) patients.

Conclusions: Children on long-term TPN are at risk of CKD due to recurrent AKI, hypertension, and glomerular hyperfiltration. Appropriate renal and metabolic monitoring is recommended.

FR-PO468

A Prediction Model for Progression to ESKD, Based on the Neural Network (ANN) Analysis, in IgA Nephropathy Patients Francesco P. Schena,[7] Vito walter Anelli,[5] Paolo Tomeo,[9] Tommaso Di noia,[6] Maria luisa Russo,[8] Graziella D'arrigo,[2] Giovanni Tripepi,[1] Vladimir Tesar,[4] Carmine Zoccali,[3] Rosanna Coppo.[4] *[1]CNR-IBIM, Reggio Calabria, Italy; [2]Clin. Epid. and Physiopath. of Renal Dis. and Hypertens., CNR-IBIM, Reggio Calabria, Italy; [3]Nephrology, Transplantation and Hypertension, Reggio Calabria, Italy; [4]Prague, Czech Republic; [5]Polytechnic University of Bari, Bari, Italy; [6]Polytechnic University of bari, Bari, Italy; [7]University of Bari, Bari, Italy; [8]University of Turin, Turin, Italy; [9]Polytechnic University of Bari, Italy, Bari, Italy. Group/Team: On behalf of VALIGA Study.*

Background: IgA nephropathy(IgAN) is the most common biopsy-proven glomerulonephritis in the world characterized by progressive deterioration of the renal function. Many statistical appoaches have been used to predict ESKD in IgN patients. The ANN is a non-linear statistical approach for pattern recognition in order to weight all the relationships between input and output variables. We have updated and used the clinical decision support system, previously published (NDT 2016), to estimate the ESKD risk.

Methods: A cohort of 680 adult patients from the European VALIGA study with complete dataset was used for this study. Of these 178 reached ESKD. Five indicators (age, sex, serum creatinine, daily proteinuria, hypertension) and MEST-C (mesangial and endocapillary hypercellularity, segmental glomerulosclerosis, tubular atrophy/interstitial fibrosis and presence of crescents) classification at time of kidney biopsy were used for

the training and validation process of the ANNs. Then, we included follow-up (years) and therapy. Two indipendent ANNs were used for predicting, first, ESKD and, then, the time occurring to ESKD. For every ANN, 80% of IgAN patients were included in the training set and 20% in the validation set. Four well-known classification metrics were used for the first ANN and two error-based metrics were used to evaluate the regression algorithm for the second ANN.

Results: The first model to predict ESKD by 15 years of clinical outcome had accuracy 98%, precision 93%, recall 87% and F1-measure 87%. The second ANN to predict the number of years to achieve ESKD showed a RMSE (root mean squared error) of 2.68 years and a MAE(mean absolute error) of 2.12 years.

Conclusions: We have developed a new clinical decision support system to estimate the risk of ESKD and its timing in IgAN patients. This tool showed an excellent performance. Interestingly, the VALIGA cohort included many patients who received or not ACEi or ARBs or immunosuppressive therapy that may influence the clinical course of the disease. Thus, the training and validation phase of our ANNs considered therapy exposure.

Funding: Government Support - Non-U.S.

FR-PO469

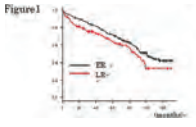
Can Early Referral to Nephrologists Reduce All-Cause and Cardiovascular Mortality and How Long Can the Effect of Pre-Dialysis Nephrology Care Last after Dialysis Initiation? Yukimasa Iwata, Taisuke Takatsuka, Daisuke Yoshimura, Hiroki Okushima, Rei Iio, Tatsuya Shoji, Terumasa Hayashi. *Osaka General Medical Center, Osaka-Shi, Japan*.

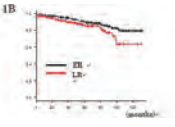
Background: Although early referral (ER) to nephrologists before dialysis initiation has been recognized to improve overall survival in patients on maintenance dialysis, we don't have any available data about how long the favorable effect of ER can last. Furthermore, its effect on cardiovascular (CV) mortality remains unclear. Thus, we conducted single center retrospective cohort study of incident dialysis patients to investigate the effect of ER on all-cause and CV mortality and how long ER could sustain its favorable effect on mortality after dialysis initiation.

Methods: A total of 875 patients with accurate clinical data and outcomes were extracted from 1131 patients who started chronic dialysis treatment from 2006 to 2015. Clinical status at dialysis initiation, all-cause and CV mortality were compared by referral timing (ER, referred to nephrologists more than 6 months before dialysis initiation; LR, other than ER). Cox and interval Cox proportional hazard model was used to evaluate the predictive factors for outcomes and how long favorable effect of ER on mortality could last after dialysis initiation.

Results: Median age and eGFR at dialysis were 70 years and 5.4 ml/min/1.73m^2, respectively. 654 patients were referred early (ER). 275 patients died and 82 of those from CV disease during the follow-up period (median, 40 months). Although, ER group showed fewer all-cause and CV mortality (Log-rank test; P=0.007, 0.019 respectively) than LR group (Figure1), multivariate Cox proportional analysis failed to show significant impact on all-cause and CV mortality. However, on the basis of the Kaplan-Meier curves, the excess overall survival among ER versus LR patients appeared limited to the several years of maintenance dialysis (Figure 1A). Thus, we built several interval Cox models: from onset of dialysis to 6, 12, 18, 24, 30 and 36 months of maintenance dialysis. The favorable effect of ER on overall survival was limited to the first 30 months on dialysis (Figure2).

Conclusions: ER was not associated with CV death, whereas ER may improve overall survival during early phase after dialysis initiation.





FR-PO470

Urinary Neutrophil Gelatinase-Associated Lipocalin Is a Possible Indicator of Tubulointerstitial Fibrosis and Glomerular Sclerosis in the Patients Undergoing Renal Biopsy Yoshifumi Hamasaki, Teruhiko Yoshida, Ryo Matsuura, Akihiro Tojo, Eisei Noiri, Masaomi Nangaku. *The University of Tokyo, Tokyo, Japan*.

Background: Renal tubulointerstitial fibrosis and glomerular sclerosis are common pathological changes occurring in association with chronic kidney disease (CKD). Non-invasive and reliable biomarkers which can predict the renal histopathological change will be helpful to decide the indication of renal biopsy. Neutrophil gelatinase-associated lipocalin (NGAL) is a promising marker of not only acute kidney injury but also CKD. We investigated whether urinary markers, including NGAL, can predict renal tubulointerstitial fibrosis (TF) and glomerular sclerosis (GS) in the patients undergoing percutaneous renal biopsy.

Methods: This study enrolled all consecutive adult patients undergone renal biopsy at The University of Tokyo Hospital from July 2014 to April 2017. We collected urine from these patients just before renal biopsy and measured N-Acetyl-β-D Glucosaminidase, L-type fatty acid binding protein, and NGAL. All markers were corrected by urinary creatinine (Cre) concentration. We also collected clinical parameters measured before renal biopsy. All biopsy specimens were evaluated by a pathologist for the medical purpose. We evaluated the relationships between urinary markers and the results of histopathological diagnoses.

Results: Ninety-six patients were enrolled in this study. Urinary NGAL/Cre (uNGAL/Cre) was significantly correlated with the severity of TF and the percentage of sclerotic glomeruli (Spearman's rank correlation coefficient ρ= 0.38 and 0.28, p <0.01 and <0.01, respectively) in the biopsy specimens. uNGAL/Cre was also significantly correlated with eGFR. When all patients were divided into two groups according to the severity of TF (less or more than 10% of interstitial area) or GS (less or more than 30% of total number of glomeruli), uNGAL/Cre in the severe group was significantly higher than in the mild group. When data from the patients with positive urine dipstick for both blood and protein (greater than 1+) were analyzed, uNGAL/Cre predicted severe TF and GS on ROC analysis (AUC [95%CI] = 0.72 [0.59-0.84] and 0.70 [0.56-0.83], respectively).

Conclusions: uNGAL/Cre may predict the severity of tubulointerstitial fibrosis and glomerular sclerosis in the patients undergoing renal biopsy.

FR-PO471

Incidence and Risk Factors of CKD in Thailand: Thai-SEEK Project Kraiwiporn Kiattisunthorn,[4] Pongsathorn Gojaseni,[1] Pornpen Sangthawan,[2] Atiporn Ingsathit.[3] *[1]Bhumibol Adulyadej hospital, Bangkok, Thailand; [2]Prince of Songkla University Hospital, Songkhla, Thailand; [3]Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [4]Siriraj Medical School, Mahidol University, Bangkok, Thailand. Group/Team: Thai-SEEK Steering Committee, Nephrology Society of Thailand* .

Background: Chronic kidney disease is one of the major public health problems which, in majority, can be preventable for progression to ESRD. Data from the first Thai-SEEK (Screening and Early Evaluation of Kidney Disease) survey completed in 2008, demonstrated prevalence of CKD for 17.5%. Data of incidence and etiologies of CKD in Thailand is scarce but is seriously concerned by policy makers of national health program for CKD prevention and slow progression. Therefore, we analyzed the data from the second survey to evaluate incidence and risk factors of CKD in Thailand.

Methods: A prospective cohort study was run from June 16, 2015 to December 15, 2016 by using subjects of the first survey. Data from history taking and physical examination, serum creatinine, urinalysis, and urine albumin creatinine ratio (UACR) were done in 2,396 subjects (70%) who gave responses for participating follow up program. One thousand, nine hundred and thirty-four subjects (71% of CKD-free in the first survey) were analyzed for CKD incidence and risk factors of new diagnosed CKD. Serum creatinine standardized with SRM967a (National Institute of Standards and Technology, MD, USA) was put in GFR calculation using CKD-EPI formula. Diagnosis and staging of CKD was based on KDIGO 2012 criteria, and rapid CKD progression was defined as a change in CKD staging plus a decline in GFR >25% or >5 ml/min/1.73m^2/year or renal replacement therapy was initiated.

Results: Mean age was 46.7±13.8 years old and 41% were male. Median follow-up time was 7.9 year (min-max 7.7, 9.1). The estimated incident CKD was 0.28 (95% CI: 0.26, 0.30) presented in 15.4%, 8.4%, 3.1%, 0.7% and 0.05%, for stage G1, G2, G3a, G3b and G4, respectively. The majority of CKD etiologies were hypertensive nephropathy (30.7%), diabetic nephropathy (19.2%), and tubulointerstitial nephritis (10.3%). Promoting factors of incident CKD were diabetes mellitus (RR 1.41; 95% CI: 1.15, 1.73), hypertension (RR 1.19; 95% CI: 1.01,1.41), and low socioeconomic status (<5,000 baht/month) (RR 1.54; 95% CI: 1.28,1.86).

Conclusions: Incidence of CKD was 28% in the 8-year cohort. Hypertension and diabetes mellitus were the most etiologies of CKD. Promoting primary prevention program for hypertension and diabetes mellitus, also effective screening in whom diagnosed hypertension and/or diabetes would be powerful in national CKD prevention policy.

Funding: Commercial Support - Janssen Cilag Thailand, Private Foundation Support, Government Support - Non-U.S.

FR-PO472

Post-Translational Modified Albumin in CKD Patients Joachim Jankowski,[1] Vera Jankowski.[2] *[1]RWTH Aachen, Aachen, Germany; [2]University hospital RWTH Aachen, Aachen, Germany*.

Background: Since post-translational modifications (PTM) of proteins may have an impact on the pathogenesis of diseases like atherosclerosis, diabetes mellitus and CKD, PTMs are currently gaining increasing interest. However, a comprehensive method for analysis of these PTMs is not established for the clinical diagnostic routine yet. Therefore, we have set up a MALDI-mass-spectrometric approach to detect post-translational modifications of plasma proteins for diagnostics.

Methods: In order to prove the significance of the approach, we analysed albumin – the most abundant plasma protein in human– isolated from CKD patients and healthy controls by mass-spectrometry. Post-translational modifications of albumin were identified after digestion by analysing mass-signal shifts of albumin peptides using pertinent mass-databases.

Results: Albumin isolated from plasma of CKD patients but not from healthy control subjects was specifically post-translationally modified by guanidylation of lysines. After identification of guanidylations as post-translational modifications of albumin isolated from CKD patients, these modifications were quantified by mass-spectrometry demonstrating a significant increase in the corresponding mass-signal intensities in CKD patients. The relative amount of guanidylation of lysine at position 468 in CKD patients was determined as 63% ± 32 (N=3). *In-vitro* guanidylation of albumin from healthy control subjects caused a decreased binding capacity of albumin in a time-dependent manner. Binding of indoxyl sulfate decreased from 82 ± 1 % of non post-translationally

modified albumin t o 5 6 ± 1 % after *in-vitro* g uanidylation w hereas t he b inding of tryptophan decreased from 20 to 4%. These results are in accordance with the binding of indoxyl sulfate to albumin from healthy control subjects and CKD patients. Thus, *in-vitro* post-translational guanidylation of albumin had a direct effect on the binding capacity of hydrophobic metabolites like indoxyl sulfate and tryptophan.

Conclusions: In conclusion, we established a mass spectrometry-based method for the characterisation of PTM and demonstrated the pathophysiological impact of a representative post-translational modification of plasma albumin. The approach described in this study may help to elucidate the pathophysiological role of protein modifications.

FR-PO473

Incidence and Outcomes of Syncope in Patients with CKD Manish M. Sood,[4] David Massicotte-Azarniouch,[3] John Paul Kuwornu,[6] Megan K. Mccallum,[6] Amit X. Garg,[1] Ngan Lam,[5] Amber O. Molnar.[2] *[1]London Health Sciences Centre, London, ON, Canada; [2]McMaster University, Hamilton, ON, Canada; [3]Ottawa, ON, Canada; [4]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [5]University of Alberta, Edmonton, AB, Canada; [6]Institute for Clinical Evaluative Sciences, Ottawa, ON, Canada.*

Background: Syncope is common condition, occurring in roughly 1 in 3 people during their lifetime, and may be a sign of life-threatening illness. CKD patients may be at an elevated risk of syncope due to concurrent medical conditions, medication usage or the etiology of CKD itself. We set out to examine the incidence of first episode and recurrent syncope and its outcomes in patients with CKD > 66 years of age.

Methods: A population-based, retrospective cohort study using administrative databases between 2006 and 2015. A total of 272,149 patients with no history of syncope, a urine albumin to creatinine ratio (ACR) and eGFR measure were included. First syncope by strata of eGFR and ACR was examined using Fine and Gray Models sub-distribution hazards ratio (sHR) and recurrent syncope by negative binomial models (RRR). Models were adjusted for demographics, resource utilization, demographics and medications. Among those with syncope, the incidence of adverse outcomes (ACS, arrhythmia, stroke, fracture and death) was determined by eGFR strata.

Results: A total of 15,074 (5.5%) first and 36,710 (13.5%) recurrent syncope events occurred during the study period. Lower eGFR was associated with a higher risk of first episode of syncope [eGFR 60-90: sHR 1.24(1.15-1.33), eGFR 45-60: sHR 1.45(1.34-1.57), eGFR 30-45: sHR 1.49 (1.36-1.62), eGFR < 30: sHR 1.40 (1.25-1.57), eGFR > 90 referent] whereas ACR was not. Recurrent syncope was associated with lower eGFR and higher ACR [eGFR 60-90: RRR 1.21(1.13-1.31), eGFR 45-60: RRR 1.46(1.34-1.58), eGFR 30-45: RRR 1.58 (1.44-1.73), eGFR < 30: RRR 1.73(1.53-1.94), eGFR > 90 referent; ACR 3-30: RRR 1.09 (1.04-1.13), ACR > 30: RRR 1.15(1.06-1.24), ACR < 3 referent]. Among those with a first syncope event, the event rate (per 100 pt-yrs) of all adverse outcomes was higher with lower eGFR strata compared to normal eGFR (ACS: eGFR < 30: 2.44, eGFR > 90: 0.98, Arrhythmia: GFR < 30: 21.63, eGFR > 90: 8.88, stroke: eGFR<30: 5.02, eGFR >90: 2.32, fracture: eGFR<30: 5.40, eGFR >90: 2.62, death: eGFR < 30: 23.23 eGFR>90: 5.31).

Conclusions: First episode and recurrent syncope events are associated with lower eGFR and only marginally with a higher ACR. The risk of all adverse events (cardiovascular, fracture and death) is higher post-syncope in patients with eGFR < 30.

FR-PO474

A First Assessment of Urinary Peptide Biomarkers Predictive of Cardiovascular Complications in Children with CKD Valerie Brunchault,[1] Benedicte Buffin-Meyer,[1] Benjamin Breuil,[1] Pedro Magalhães,[2] Petra Zürbig,[2] Kevin Kunzmann,[3] Franz S. Schaefer,[4] Joost Schanstra,[1] Julie Klein.[1] *[1]INSERM U1048, Toulouse, France; [2]Mosaiques Diagnostics GmbH, Hannover, Germany; [3]Institute of Medical Biometry and Informatics, Heidelberg University, Heidelberg, Germany; [4]University of Heidelberg, Heidelberg, Germany. Group/Team: 4C study consortium.*

Background: Cardiovascular disease (CVD) is the most important comorbidity affecting long-term survival in children and young adults with CKD. CVD is usually subclinical and early detection of pediatric CKD patients with high risk to develop CVD would be optimal. Our objective was to explore the urinary peptidome for biomarkers for early prognosis of CVD in children with CKD.

Methods: In this preliminary study, we used 86 pediatric patients from the Cardiovascular Comorbidity in Children with CKD (4C) cohort, which consists of children (6-17 years) with advanced CKD (eGFR=10–45 ml/min/1.73 m^2). During a 3-year follow-up, the carotid intima-media thickness (cIMT), pulse wave velocity (PWV) and left ventricular mass index (LVMI) were measured annually as surrogate markers of CVD complications. For each marker, the slope was calculated as a measure of CVD progression. Urine at baseline was analyzed by capillary-electrophoresis coupled to mass spectrometry for the identification of urinary peptides associated to progression of CVD.

Results: Among 7586 urinary peptides, 190, 22 and 14 urinary peptides were associated to progression of cIMT, PWV and LVMI, respectively ($p<0.05$). These peptides were combined in mathematical models to build the cIMT190P, PWV22P and LVMI14P classifiers. These classifiers were then validated using an independent validation cohort. The cIMT190P classifier predicted cIMT progression with 80% sensitivity [95% CI, 44.4 to 97.5], 100% specificity (95% CI, 66.4 to 100) and an area under the ROC curve (AUC) of 0.87 (95% CI, 0.68 to 1.00). The PWV22P classifier predicted PWV progression with 83% sensitivity (95% CI, 51.6 to 97.9), 70% specificity (95% CI, 34.8 to 93.3) and an AUC of 0.83 (95% CI, 0.64 to 1.00). However, the LVMI classifier was not validated.

Conclusions: These results indicate that urinary peptides could be used as a non-invasive tool for the early prediction of CVD complications associated to CKD in children. An additional 250 patients from the 4C study will now be used to refine and confirm these results. [Equal contribution JPS and JK]

Funding: Government Support - Non-U.S.

FR-PO475

Relationships between CKD and Progression of Left Ventricular Diastolic Dysfunction Yoshiyasu Miyajima, Tadashi Toyama, Shinji Kitajima, Akinori Hara, Yasunori Iwata, Norihiko Sakai, Miho Shimizu, Kengo Furuichi, Takashi Wada. *Kanazawa University Hospital, Kanazawa, Japan.*

Background: CKD is known as a risk factor for heart failure, but its role on the left ventricular diastolic dysfunction as a preliminary stage of heart failure has not been adequately studied.

Methods: To investigate the relationship between CKD and progression of left ventricular diastolic dysfunction, we included patients who received echocardiography examination in Kanazawa University Hospital for more than twice with intervals of more than one year. We excluded clinically diagnosed coronary artery disease, moderate valvular heart disorder and structural heart disease. Patients were examined their left ventricular peak velocity of blood flow across the mitral valve (E) and their diastolic peak velocities of mitral annulus (e'); E/e' ratio was used as an index of left ventricular diastolic function, and E/e' ratio >14 was defined as left ventricular diastolic dysfunction. Baseline estimated glomerular filtration rate (eGFR) and dipstick proteinuria were used as a status of chronic kidney disease (CKD). Time to development of left ventricular diastolic dysfunction and baseline CKD status were assessed using Cox proportional hazard models adjusted for known risk factors.

Results: A total of 1,163 subjects were included and the average observation period was 3.2 years. Compared to the patients with the estimated GFR ≥90 mL/min/1.73 m2 as a reference, hazard ratios (95% confidence intervals) for the development of diastolic dysfunction were 1.25 (0.87–1.79), 1.51 (0.96–2.38), 2.06 (1.25–3.40), and 3.54 (2.13–5.88) for patients with eGFR 60–89 mL/min/1.73 m2, 45–59 mL/min/1.73 m2, 30–44 mL/min/1.73 m2, <30 mL/min/1.73 m2, respectively. Compared to patients with proteinuria – or trace, patients with proteinuria more than 2+ or more were also a significant risk factor (hazard ratio 2.15, 95% confidence interval 1.40–3.29).

Conclusions: Low GFR and proteinuria were risk factors for the development of left ventricular diastolic dysfunction.

FR-PO476

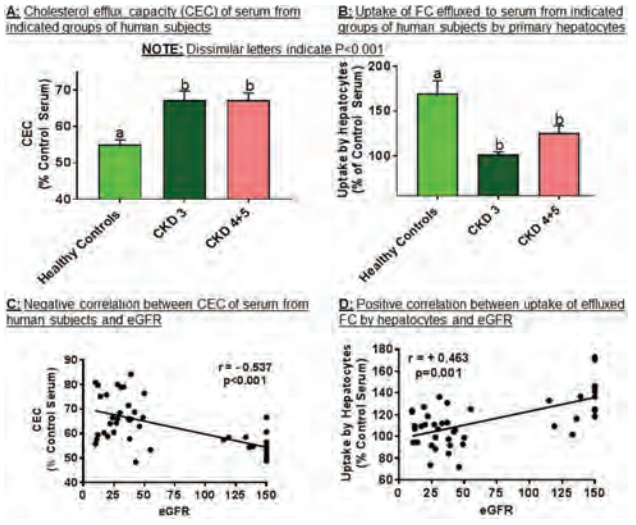
Impaired Delivery of Cholesterol to Hepatocytes by Serum from CKD Patients: Implications for the Associated CVD Risk Daniel E. Carl,[5] Graham T. Gipson,[3] Shobha Ghosh,[2] Salvatore Carbone,[3] Dave L. Dixon,[4] Ion S. Jovin.[1] *[1]McGuire VAMC/VCU, Richmond, VA; [2]VCU, Richmond, VA; [3]Virginia Commonwealth University, Richmond, VA; [4]Virginia Commonwealth University School of Pharmacy, Richmond, VA; [5]Internal Medicine, Virginia Commonwealth Univeristy, Richmond, VA.*

Background: Mortality in CKD patients is largely due to the development of CVD but the underlying mechanisms have not been elucidated. The flux of cholesterol through the body and final elimination by the liver rather than the plasma lipid profiles is now considered as a major contributor to development of CVD. Ability of the serum components to remove cholesterol from macrophage foam cells and deliver it to the liver for final elimination are the two critical steps in regulating cholesterol flux. Herein, we evaluated the ability of serum from CKD patients to facilitate these two processes.

Methods: Thirty-two consecutive patients with CKD (Stage 3, N=15 and Stage 4+5, N= 17) and 15 healthy subjects were enrolled in the study. Cholesterol efflux capacity (CEC) of the patient serum to remove cholesterol from human THP1 macrophage foam cells and the ability to deliver this effluxed cholesterol to primary hepatocytes was determined and compared between groups using the Mann-Whitney Test. Correlations between kidney function parameters, CEC and uptake by hepatocytes were performed using the Spearman's nonparametric rank test.

Results: CEC was significantly higher with serum from patients with CKD (Stages 3 and 4+5, $P<0.001$) compared to that from healthy subjects (Panel A). However, the ability of this effluxed FC to be delivered to hepatocytes was significantly lower in patients with CKD (Panel B, Stages 3 and 4+5, $P<0.001$). eGFR was inversely associated with CEC (Panel C) and positively associated with hepatocyte uptake (Panel D).

Conclusions: These data indicate that impaired delivery of cholesterol to the liver for final elimination from the body likely underlies the development of CVD in CKD patients. Studies are in progress to determine if this decrease in hepatocyte uptake in CKD is related to modifications of cholesterol carrying serum components (e.g., HDL or albumin) by reduced kidney function.



FR-PO477

Blockade of the Chemokine Receptor CX3CR1 with a Single Chain Antibody Reduces the Progression of Atherosclerosis and Glomerulosclerosis in Mice Steven W. Kerr,[7] Valentina Berger,[2] Jorge L. Villalona,[6] Rajvee Dave,[6] Hong Wang,[6] Margaret M. O'Neill,[8] Joshuaine Toth,[5] Mary Mcfarland,[1] Lynn Pantages,[3] Xingtie Nie,[4] Hu Sheng Qian,[3] John Broadwater.[5] *[1]Beoheringer Ingelheim Pharmaceuticals, Ridgefield, CT; [2]Boehringe-Ingelheim Pharm, Ridgefield, CT; [3]Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT; [4]Boehringer-ingelheim company, Danbury, CT; [5]Boehringer Ingelheim, Ridgefield, CT; [6]Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT; [7]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT; [8]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, AL.*

Background: The fractalkine receptor CX3CR1 regulates leukocyte trafficking during inflammation and is associated with cardiovascular disease risk. We developed a high-affinity, selective, single chain antibody that targets human CX3CR1, designated BI655088. Since cardiovascular disease is the major cause of morbidity and mortality in patients with chronic kidney disease, we used a cardiorenal model to evaluate atherosclerosis and renal parameters.

Methods: Therefore, BI655088 was administered at 30mg/kg i.p. 2x/wk for 12 weeks to hyperlipidemic ApoE$^{-/-}$ mice expressing the human CX3CR1 gene and induced renal insufficiency by performing a uninephrectomy.

Results: BI655088 significantly reduced atherosclerotic plaque area by 28% compared to vehicle-treated mice with no change in total cholesterol or triglycerides. In addition, BI655088 significantly reduced glomerulosclerosis incidence by 43% and severity in the remnant kidney. This effect was accompanied by a significant decrease in macrophage infiltration consistent with the mechanism of action. Plasma levels of fractalkine, used as a biomarker for antibody blockade of CX3CR1, were significantly increased in treated animals. In order to evaluate the potential effect of BI655088 for treating diabetic nephropathy, BI655088 was tested in streptozotocin-treated C57BL/6 mice transgenic for the human CX3CR1 gene. BI655088 dosed at 30, 3, and 0.3mg/kg i.p. 2x/wk for 12 weeks showed dose dependent decreases in both glomerulosclerosis, (-46%, -27%, and -15%), and interstitial lesions (-56%, -33%, and -16%), respectively, compared to vehicle-treated mice with no effect on glucose levels.

Conclusions: These results demonstrate that treatment with the CX3CR1 antagonist BI655088 can mitigate both renal and vascular injury induced in diabetic and hyperlipidemic mouse models.

FR-PO478

Urinary Orosomucoid Is Associated with Cardiovascular Risk Factors and Kidney Dysfunction: Cross-Sectional Data from the Tromsø Study Runa M. Andreassen,[1,2] Marit D. Solbu.[4,3] *[1]Department of Internal Medicine, Helgelandssykehuset, Sandnessjøen, Sandnessjøen, Norway; [2]Metabolic and Renal Research Group, UiT The Arctic University of Norway, Tromsø, Norway, Tromsø, Norway; [3]Metabolic and Renal Research Group, UiT The Arctic University of Norway, Tromsø, Norway, Tromsø, Norway; [4]Section of Nephrology, University Hospital of North Norway, Tromsø, Norway., Tromsø, Norway.*

Background: The acute phase protein orosomucoid is a component of the endothelial cell coat. It may be hypothesised that leakage of orosomucoid into the urine may be a more sensitive marker of a damaged filtration barrier than albuminuria. However, this has never been assessed in a general population. The aim of this cross-sectional study was to examine the univariate associations between urinary orosomucoid to creatinine ratio (UOCR), urinary albumin to creatinine ratio (UACR) and common cardiovascular (CV) risk factors, and to assess whether there is an independent association between eGFR and UOCR in a middle-aged cohort from the general population.

Methods: From the sixth wave of The Tromsø Study (2007/08) we included all participants who had measurements of urinary orosomucoid. Orosomucoid, albumin and creatinine were measured in three morning urinary specimens, and we used the median values from the three days for UACR and UOCR. The cohort was categorized according to some well known CV risk factors and the associations between UOCR, UACR, eGFR and risk factors were assessed by linear and logistic regressions analysis.

Results: A total of 3086 men and 4095 women were included; mean age was 63.5 (±9.2 SD) years. Mean eGFR was 88 (±14 SD) ml/min/1.73 m2. UOCR was significantly higher in men than in women and positively correlated with age. UOCR was also higher in subjects with BMI ≥25 kg/m2 than BMI <25 kg/m2 median 0.48 (IQR 0.24, 1.13) g/g vs. 0.37 (0.21, 0.85) g/g; P<0.001), as well as in hypertensive compared to normotensive subjects 0.56 (0.27, 1.31) g/g vs. 0.35 (0.20, 0.77); P<0.001) and smokers compared to non-smokers 0.50 (0.24, 1.18) g/g vs 0.43 (0.23, 0.99) g/g; P=0.002. UACR was positively associated with the same risk factors except BMI. In multivariable logistic regression analysis, both eGFR and UACR were independent risk factors for having UOCR above median (eGFR: odds ratio (OR) 0.83 (0.79-0,88) per 10 ml/min/1.73 m2, UACR: OR 2.05 (1.91-2.19)) per 0.5mg/mmol.

Conclusions: UOCR was positively associated with CV risk factors, and the association between eGFR and UOCR was independent of these factors and UACR. Our data indicate that increased UOCR may serve as a novel biomarker of atherosclerosis and kidney dysfunction, thereby supporting further research.

Funding: Government Support - Non-U.S.

FR-PO479

Increased Levels of Platelet Microparticles in CKD Patients with Acute Coronary Syndrome Josefin L. Mörtberg,[1,3] Kristina Lundwall,[1,3] Fariborz Mobarrez,[2] Hakan Wallen,[1,3] Stefan H. Jacobson,[1,3] Jonas Spaak.[1,3] *[1]Danderyd Hospital, Stockholm, Sweden; [2]Karolinska Institutet, Solna, Sweden; [3]Dept of Clinical Sciences, Karolinska Institutet, Danderyd hospital, Stockholm, Sweden.*

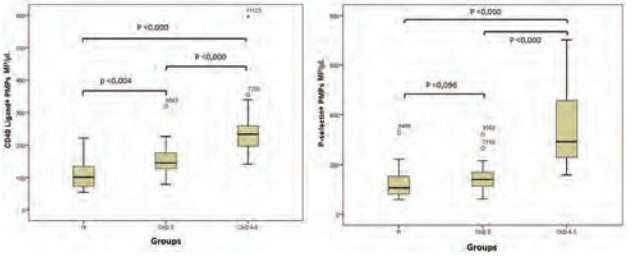
Background: Patients with CKD have worse outcome after an acute coronary syndrome (ACS). Traditional and nontraditional riskfactors, underutilization of coronary intervention, less active secondary prevention and lower adherence to medications all contribute to the poor prognosis. Microparticles MPs are circulating small sized vesicles shed from various cells upon activation, and they may induce biologically response and inter-cellular cross-talk. Platelet MPs(PMPs) are the most abundant MPs, and levels increase following myocardial infarction and in diabetes mellitus, hypertension, and CKD. We hypothesized that ACS patients with CKD had further elevated PMPs compared with non CKD patients.

Methods: 52 patients with ACS were included and fasting blood was acquired the day after admittance. Patients were divided in three groups according eGFR; average eGFR in group H (n=19) was 88 ml/min, in CKD 3 (n=16) 47 ml/min, and in CKD 4-5 (n=17) 19 ml/min. PMPs were measured by flow cytometry and phenotyped according to size (0.3 – 1.0 μm) and expression of CD41 (GPIIb; platelet specific marker) together with platelet activation markers, CD40ligand (CD154) and P-selectin (CD62P)

Results: Levels of PMPs were elevated in CKD 4-5 patients, and levels of PMPs expressing platelet activation markers CD40 ligand(CD 154)) and p-selectin (CD62p) were higher in both CKD groups, compared with non CKD patients

Conclusions: In ACS patients, levels of PMPs as well as levels of PMPs expressing CD40 ligand (CD154) and/or p-selectin (CD62p) are significantly higher in CKD patients compared with non CKD patients. These finding indicates a higher platelet activation in CKD patients, which might contribute to the poorer outcome for CKD patients following a myocardial infarction.

Funding: Government Support - Non-U.S.



FR-PO480

eGFR Trajectories and Risks of Death and Cardiovascular Events in Adults with Type 2 Diabetes Kenn B. Daratha,[1,2] Sterling McPherson,[1,2] Brad Dieter,[1] Radica Z. Alicic,[1] Katherine R. Tuttle.[1,3] *[1]Providence Health Services, Spokane, WA; [2]Washington State University, Spokane, WA; [3]University of Washington School of Medicine, Seattle, WA.*

Background: Diabetes is the most common cause of chronic kidney disease (CKD) worldwide. Most with diabetes and CKD will experience death or a cardiovascular disease (CVD) event before reaching end-stage kidney disease. Decline in estimated glomerular filtration rate (eGFR) may be an antecedent of such events. The aim of this study was to

determine the relationship of eGFR decline with death and CVD events among persons with type 2 diabetes.

Methods: The ACCORD trial tested intensive control of glycemia in adults with type 2 diabetes. In our study, group-based modeling classified eGFR trajectories of 10052/10251 (98%) ACCORD participants with at least 2 eGFR (CKD-EPI) measurements. Trajectory classification was based on greatest likelihood an individual trajectory fit within a hypothesized class structure (both in number and classes and order of each function). Cox proportional hazards models examined risk of the primary ACCORD outcome (CVD death, myocardial infarction, stroke) by eGFR trajectory assignment.

Results: Participants were followed up to 7 years. Baseline characteristics included: age 62.7±6.6 (mean±SD) years; women 38% (3857/10052); White race 62% (6281/10052); diabetes duration 10.7±7.6 years; HbA1c 8.3±1.1 %; eGFR 84.0±17.5 mL/min/1.73m^2; and urine albumin-to-creatinine ratio 13, 6-43 (median, IQR). Approximately 10% (1027/10052) of participants were classified in the lowest trajectory class with eGFR values persistently <60 mL/min/1.73m^2. In the next trajectory class, 21% (2101/10052) were classified with initial eGFR values above, but falling below, 60 mL/min/1.73m^2 over time. Three additional classes were defined with eGFR above 60 mL/min/1.73m^2 throughout the study. Fully-adjusted models controlled for baseline eGFR (isolating the independent effect of the trajectory slope), age, sex, race, diabetes duration, HbA1c, albuminuria, and treatment. Hazards for the primary outcome were greater for the two lowest compared to the highest eGFR trajectory class (HR_1=1.52; 95%CI=1.07-2.18; p=0.03 and HR_2=1.42; 95%CI=1.06-1.90; p=0.02).

Conclusions: More rapid eGFR decline in persons with type 2 diabetes independently predicted significantly greater risk of death and CVD events.

FR-PO481

Prevalence of Secondary Hyperparathyroidism among Patients with Diabetic Nephropathy Mahmoud H. Imam,[1] Ahmed W. Elshourbagy,[3] Amira Mohamady,[2] Rizk sayad rizk Sarhan.[2] *[1]Internal medicine, Benha University, Benha, Egypt; [2]Internal Medicine Department, Benha University, Benha, Egypt; [3]Internal Medicine Department, banha faculty of medicine, Benha, Egypt.*

Background: Both SHPT and diabetes mellitus have increased the risk for cardiovascular complication mainly through vascular calcification and endothelial dysfunction. The prevalence of SHPT among diabetic nephropathy patients is not previously studied. The aim of this study to evaluate the prevalence of SHPT among diabetic nephropathy patients attended to diabetes and nephrology outpatient clinic.

Methods: In this retrospective study, 437 diabetic patients were enrolled in this study from 864 diabetic patients who attended diabetes and nephrology outpatient clinics in our tertiary care hospital in Jeddah from Jan 2014 to Feb 2017. Inclusion criteria were: [1] Age ≥18 years, [2] Patient had diabetic nephropathy which was diagnosed based on the presence of urinary albumin/creatinine ratio (uACR) ≥ 30 mg/gm ± 24 hours' urinary protein measurement ≥ 300 mg/day. Exclusion criteria were|: [1] patients were already receiving cinacalcet and/or[2] patients had undergone neck surgery for parathyroidectomy. The intact parathyroid hormone, 25 vitamin D level, uACR and other kidney and biochemical investigation results were obtained from patients' medical records. Patients were divided into two groups: those with euparathyroidism (an iPTH level less than 65 pg/mL) and those with hyperparathyroidism with iPTH level above or equal to 66 pg/mL.

Results: Three hundred and seventy-four patients (85.5%) had an iPTH level above normal. When patients were divided according to their iPTH level into SHPT and euparathyroid groups, we found a significant mean difference between the two groups regarding uACR (2.38 ± 1.0 mg/g vs. 311 ± 180 mg/g; p <0.001), eGFR (49.15 ± 20.3 ml/min/1.73m^2 vs. 90.97 ± 3.93 ml/min/1.73m^2; p < 0.001), and serum urea (77.54 ± 26.19 mg/dL vs. 23.70 ± 5.66 mg/dL; p < 0.001). Our results showed that SHPT group had a statistically significant lower level of vitamin D and serum calcium. Furthermore, we found that there was a strong correlation between iPTH level and serum creatinine, eGFR, UACR, vitamin D.

Conclusions: Despite the absence of clinical manifestations, SHPT is common among diabetic nephropathy patients.

FR-PO482

The Effect of Digoxin on Renal Function in Patients with Heart Failure Parin M. Shah,[2] Sunil Bhandari.[1] *[1]Hull and East Yorkshire Hospitals NHS Trust and Hull York Medical School, East Yorkshire, United Kingdom; [2]Univerisity of Hull, Cottingham, United Kingdom.*

Background: We investigated the relation between digoxin use and change in renal function over time in patients with chronic heart failure (CHF).

Methods: 1241 patients with CHF (defined as symptoms/ signs of heart failure with either reduced left ventricular ejection fraction or raised amino terminal pro B type natriuretic peptide; NTproBNP >220 ng/l) were included. The patients were divided into four groups: never on digoxin (N=394); digoxin throughout (N= 449); started digoxin at some point after baseline (N=367); and stopped digoxin at some point after baseline (N= 31). The rate of change of estimated glomerular filtration rate (eGFR) was calculated using linear regression.

Results: The average age was 72 years (64% male), and median NTproBNP 1426 ng/L (IQR 632 - 2897). Patients on digoxin throughout had a significantly greater rate of decline in eGFR per year than patients not on digoxin throughout (mean (± standard deviation); -5 (13) ml/min/1.73m^2 per year *v* -2 (10) ml/min/1.73m^2 per year, P= 0.02). In those patients who started digoxin during follow-up, there was no significant difference in the rate of decline in eGFR before and after starting digoxin. There was no correlation between baseline eGFR (or rate of decline in eGFR) and age, body mass index, haemoglobin, or NTproBNP. Patients not taking angiotensin-converting enzyme inhibitors, angiotensin receptor blockers or beta blockers had a faster rate of decline in eGFR than those who were.

Conclusions: The rate of decline in renal function is greater in patients with CHF who are taking digoxin.

Correlation of eGFR with categorical variables

	Missing values	Mean Baseline eGFR (ml/min/1.73m2)		P value	Missing values	Mean Rate of decline in eGFR (ml/min/1.73m2 per year)		P value
Sex: male v female	19	58 (22)	54 (19)	<0.01	465	-2.5 (11.0)	-4.3 (11.8)	0.04
Sinus rhythm: yes v no	30	57 (22)	57 (20)	0.63	471	-2.9 (11.0)	-3.4 (11.6)	0.61
NYHA class: III/IV v I/II	41	54 (21)	59 (21)	<0.01	471	-2.6 (10.6)	-4.2 (12.4)	0.06
LV dysfunction: moderate/severe v normal/mild	51	56 (22)	57 (20)	0.59	483	-3.0 (11.2)	-3.1 (11.3)	0.88
ACEi /ARB: yes v no	19	57 (21)	56 (22)	0.22	465	-2.4 (10.8)	-5.7 (12.8)	0.04
BB: yes v no	19	58 (22)	56 (20)	0.18	465	-2.2 (10.9)	-4.6 (11.8)	<0.01
MRA: yes v no	19	58 (23)	57 (20)	0.30	465	-3.4 (13.6)	-3.0 (10.3)	0.66
Loop diuretic: yes v no	19	54 (21)	64 (19)	<0.01	465	-3.3 (11.7)	-2.6 (10.1)	0.44
Diabetes: yes v no	19	54 (21)	58 (21)	<0.01	465	-3.0 (10.5)	-3.2 (11.6)	0.78
Hypertension: yes v no	19	55 (20)	58 (22)	<0.01	465	-2.8 (10.4)	-3.3 (11.8)	0.51
IHD: yes v no	19	53 (21)	60 (21)	<0.01	465	-2.3 (10.9)	-3.9 (11.6)	0.05

eGFR: estimated glomerular filtration rate, NYHA: New York Heart Association, LV: left ventricular, ACEi: angiotensin-converting-enzyme inhibitor, ARB: angiotensin receptor blockers, BB: beta blocker, MRA: mineralocorticoid receptor antagonist, IHD: ischaemic heart disease.

FR-PO483

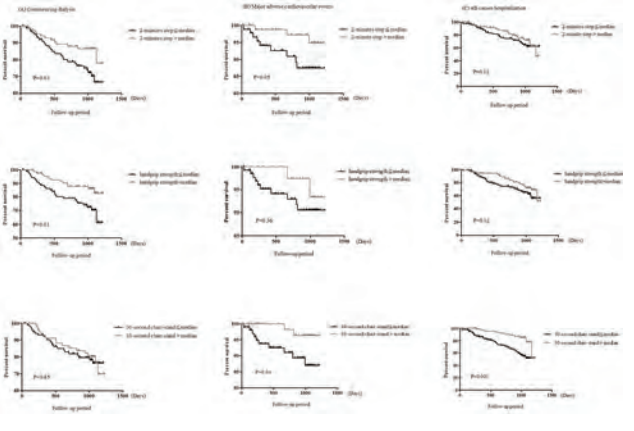
Association of Physical Activity with Cardiovascular and Renal Outcomes and Quality of Life in CKD Yi-chun Tsai,[2] Hung-Chun Chen,[2] Shang-Jyh Hwang.[1] *[1]Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [2]Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan.*

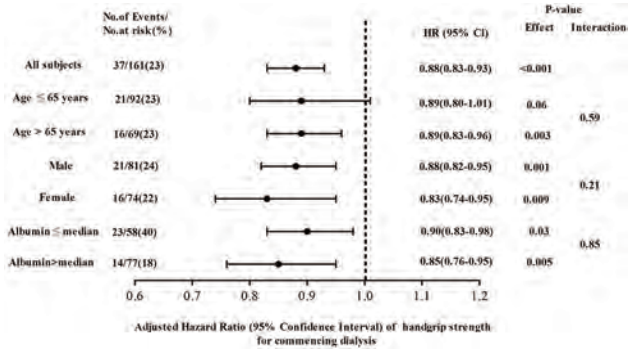
Background: Patients with chronic kidney disease (CKD) are more readily prone to have impaired physical activity than the general population. The aim of this study is to examine the relationship between physical activity and adverse clinical outcomes and quality of life (QOL) in CKD.

Methods: This cohort study enrolled 161 patients with CKD stages 1-5 from February 2013 to September 2013 and followed up until June 2016. Physical activity was measured using high handgrip strength, 30-second chair stand, and 2-minute step. The QOL was assessed using the Taiwan version of the WHOQOL-BREF. Clinical outcomes included commencing dialysis, major adverse cardiovascular events (MACEs), and first hospitalization.

Results: Of all participants, 1 kg/m^2 increase in handgrip strength was significantly associated with 0.13 score increase in total scores of QOL and 0.05 score increase in physical domain of QOL in adjusted analysis. One time increase in 30-second chair stand was significantly correlated with 0.14 score increase in psychological domain of QOL. Over a mean follow-up period of 29.1±11.2 months, 37 (23.0%) reached commencing dialysis, 11(6.8%) had MACEs, and 50(31.1%) had first hospitalization. High handgrip strength (hazard ratio (HR): 0.89, 95% CI: 0.84-0.96) and high 2-minute step (HR: 0.04, 95% CI: 0.01-0.95) were significantly associated with decreased risk for commencing dialysis in multivariate analysis. Thirty-second chair-stand was negatively associated with MACEs (HR: 0.65, 95%CI: 0.47-0.89) and first hospitalization (HR: 0.84, 95%CI: 0.74-0.95).

Conclusions: Physical activity is a potential predictor of QOL and clinical outcomes in CKD.





FR-PO484

Real Life Insights into the Use of Mineralocorticoid Receptor Antagonists in Patients with Diabetic and Non-Diabetic CKD with and without Heart Failure Michael Blankenburg,[2] Anne-Kathrin Fett,[4] Seline Eisenring,[4] Gabriele Haas,[3] Jonathan Korn,[4] Alain Gay.[1] *[1]Bayer AG, BERLIN, Germany; [2]Bayer AG, Berlin, Germany; [3]IMS Health, Frankfurt, Germany; [4]QuintilesIMS, Frankfurt, Germany.*

Background: Mineralocorticoid receptor antagonists (MRAs) are part of the treatment practice for patients with heart failure (HF) and/or hypertension. This study aimed to evaluate real-life MRA utilization in patients with chronic kidney disease (CKD) with or without diabetes mellitus (DM), HF and hypertension, respectively.

Methods: This retrospective cohort study used the US claims database PharMetricsPlus between 10/2009 and 09/2014. 229,143 patients ≥18 years with a first CKD diagnosis and 5,899 patients who initiated MRAs were included in two cohorts. Demographic characteristics, comorbidities, clinical events, medication use, and healthcare costs are reported for the overall cohorts and stratified by diagnosis: CKD (only), CKD+DM, CKD+HF and CKD+DM+HF, and MRA treatment (no MRA treatment, MRAs for < 6 and ≥ 6 months).

Results: We identified 114,129 CKD, 77,012 CKD+DM, 15,567 CKD+HF, and 22,435 CKD+DM+HF patients. The results showed low MRA usage in the population of interest. Overall, 2.3% of patients used MRAs. Use within the four diagnostic groups was 1.3%, 1.9%, 6.7%, and 6.7%, respectively. Hypertension was present in 78.5% of the overall population and in 94.1% of MRA users. HF was present in 16.6% of the overall population and in 46.6% of MRA users. 27.6% of patients who took MRAs had CKD stage 4, 5 or end-stage renal disease. MRA users generally presented with higher rates of comorbidities, medication use, and higher health-care costs. One-year persistence with MRA was less than 50%.

Conclusions: The use of MRAs in CKD patients is low and seems to be driven by the presence of hypertension and HF. Yet, MRAs are also given to CKD patients beyond stage 3, despite being contraindicated in the respective labels. Patients on MRAs tended to be more multi-morbid and to show higher healthcare resource use than patients without MRA.

Funding: Commercial Support - Bayer AG

FR-PO485

Impact of Transcatheter Aortic Valve Implantation on Renal Function Rita Calça, Rui C. Teles, Patricia Q. Branco, João Brito, Tiago Nolasco, Manuel D. Almeida, José P. Neves, Miguel Mendes, Domingos S. Machado, Andre L. Weigert. *Hospital Santa Cruz, Lisboa, Portugal.*

Background: Chronic kidney disease (CKD) is very prevalent in patients with aortic valve disease. Decreased renal perfusion as a consequence of diminished cardiac output may contribute to this patient's renal disfuncion. Given the potential reversibility of this mechanism after valve correction, the aim of this study was to verify the impact of percutaneous transcatether aortic implantation (TAVI) on kidney function.

Methods: We performed a retrospective analysis of 233 consecutive patients that underwent TAVI and were included in single center prospective registry between November 2008 and May 2017. Estimated Glomerular Filtration Rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and we considered 3 groups according their eGFR (mL/min/1.73 m^2); the categories sugested by Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines were mentioned for each group. *Group 1* with eGFR≥60 included patients without CKD or CKD G1-2; *Group 2* with 30≤eGFR<60 (CKD G3a-b)*;* and *Group 3* with eGFR<30 (CKD G4). Patients on dialysis were excluded from the analysis. Previous to TAVI, 43,1% were in *Group 1*, 44,0% in *Group 2* and the remaining 12,9% in *Group 3*.

Results: 56.7% were female and the mean age was 81.8±7.5years (from 47 to 94years). No age or gender differences were found between groups. In patients from *Group 1*, a 15% fall in eGFR was verified after 1year follow-up (table1*).* Conversely, in patients from *Group 2* and *Group 3* we observed a significant increase in eGFR after TAVI (table1).

Conclusions: The association between worse outcomes in CKD patients undergoing TAVI is well established, but little is known about the potential reversibility of renal function after aortic valve replacement. We concluded that, for patients with moderate-to-severe CKD, there is a gain of function in the first month post-TAVI, which increased further 1 year after the procedure. This is probably due to improved renal perfusion post-procedure. We postulate that when evaluating patients that might need TAVI, this 'reversibility of CKD effect' should be considered.

Table 1

	eGFR pre-TAVI (mL/min/1.73m2)	eGFR 1month after TAVI (mL/min/1.73 m2)	eGFR 1 year after TAVI (mL/min/1.73 m2)	p value
Group 1	74,9±9,0	65,6±20,0	63,4 ±19,2	<0.001
Group 2	45.4±8,5	50,1±15,1	52,6±16,4	<0.01
Group 3	24,4±5,1	34,9±18,1	38,4±18,8	<0.01

FR-PO486

The Use of Renin-Angiotensin System Inhibitors and Aldosterone Receptor Antagonists in Heart Failure Patients with CKD Shreya Ghetiya, Sheila Kalathil, Aref Obagi, Kimberly J. Mccourt, Arif Asif, Dawn Calderon. *Jersey Shore University Medical Center, Neptune, NJ.*

Background: In order to reduce morbidity and mortality, ACCF/AHA guidelines for heart failure with reduced ejection fraction (HFrEF), (EF≤40%), recommend angiotensin converting enzyme inhibitors (ACE-I) unless contraindicated (c/i). Angiotensin Receptor Blockers (ARBs) should be used in those pts who are intolerant to ACEIs. In those pts who are tolerant to ACEIs/ARBs, ACC/AHA 2016 updated guideline recommends replacing it with Angiotensin-Receptor/Neprilysin inhibitor (ARNI) to further reduce mortality. Guideline also recommend to add Aldosterone receptor antagonists (ARA) in all pts with NYHA class II-IV and who have EF ≤35%, or EF ≤40% with MI/diabetes who develop symptom, unless c/i.

Methods: We conducted a retrospective chart review of 118 patients with EF≤40% discharged from our tertiary care hospital between 01/2016-12/2016 to ascertain if the guidelines were met. Prevalence of stage 3 chronic kidney disease (eGFR<60) and proteinuria were also measured.

Results: Demographics revealed that out of 118 pts evaluated, 68% were male and 80% were White, 16% Black, 2% Hispanic, 1% Asian, and 1% others. Only 69 (58%) were on ACEIs/ARBs/ARNI and 61 (52%) were on ARA upon discharge. Of these 69 pts, 41(59%) were on ACEIs, 12(17%) on ARBs and 16(23.18%) on ARNI. 5 pts (7.24%) were switched to ARNI from ACEIs/ARBs upon discharge. 35pts(30%) had c/i to ACEIs/ARBs/ARNIs and 29 pts (24%) had c/i to ARA. In this cohort, 67 pts (57%) had CKD 3. The average eGFR was 35.74ml/min/1.73m^2. Proteinuria was present in 35 pts (30%) of all 118 and 21(31%) out of 67 pts with CKD. Average serum sodium and potassium upon discharge were 136.7 and 4.14 mmol/l, respectively. Hyperkalemia (>=5.0mmol/l) was found in only 8(7%) pts. Average EF was 25%. Average SBP: 117mmHg and DBP: 671mmHg.

Conclusions: This analysis reveals opportunity for improvement in the utilization of ACEACEIs/ARBs/ARNI and ARA, both for cardiac and renal benefits.

FR-PO487

Change in Albuminuria and Risk of ESKD in a Global Consortium Josef Coresh. *CKD Prognosis Consortium, Baltimore, MD.*

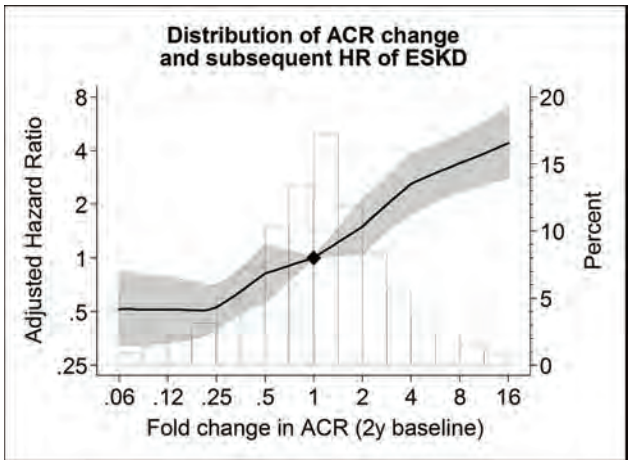
Background: Albuminuria and proteinuria are used in chronic kidney disease (CKD) staging, but it is uncertain how change in these markers is associated with ESKD risk in clinical settings.

Methods: CKD-PC cohorts with multiple albumin or protein to creatinine ratio (ACR & PCR) measurements within a 2-year baseline period and subsequent ESKD risk were analyzed using Cox regression. Random effects meta-analysis results are presented and absolute risk was modeled.

Results: 76,234 participants (age 59 y, 47% female, 64% diabetic) had ≥2 ACR or PCR measurements during a 2-year baseline period, and were subsequently followed for over 5 years during which 3,181 ESKD events occurred in 14 cohorts. Adjusted for initial levels of ACR, eGFR and covariates, changes in both ACR (Figure, 10 cohorts) and PCR (9 cohorts) were linearly related to log hazard ratio (HR) of ESRD: 4-fold decrease and 4-fold increase had HRs (95% CI) of 0.53 (0.4-0.7) and 2.6 (1.8-3.8) for ACR and 0.48 (0.3-0.7) and 2.2 (1.7-2.9) for PCR. Results were consistent in most subgroups (DM, HTN, RAASI use, BP change and age) except baseline ACR where HRs for 4-fold decrease in ACR were stronger at higher baseline ACR. Absolute risk differences of ESKD associated with a 4-fold decrease were much larger at higher baseline ACR or PCR and follow-up time.

Conclusions: Change in ACR and PCR were consistently associated with risk of ESKD, beyond baseline eGFR, ACR and change in eGFR, informing their use as outcomes in clinical practice, observational and clinical trial research, and for regulatory purposes.

Funding: NIDDK Support, Private Foundation Support



FR-PO488

Relationship of eGFR and ACR to Concurrent Abnormalities in a Global Consortium Lesley Inker. *CKD Prognosis Consortium, Baltimore, MD.*

Background: CKD is associated with many vascular and laboratory abnormalities. We describe the continuous relationship between abnormalities and CKD staged by eGFR and albuminuria (ACR; A1:<30, A2:30-299, A3:≥300 mg/g).

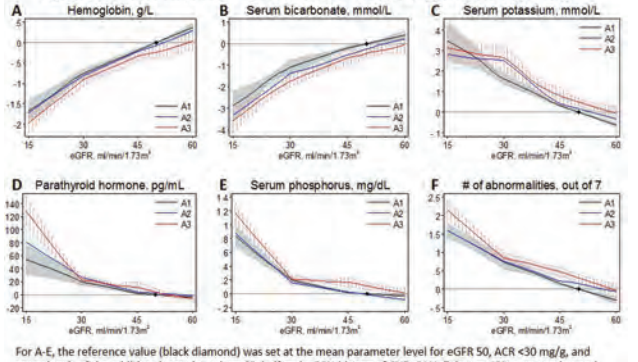
Methods: Using 12 CKD and 29 general population or high risk (GP/HR) cohorts, we performed random-effects meta-analyses for associations between eGFR (CKD-EPI creatinine equation, expressed as a linear spline with knots at 30, 45, 60, 75, 90 and 105) and the following parameters: systolic blood pressure (SBP, N=629,247), hemoglobin (N=405,633), bicarbonate (N=45,001, CKD cohorts only), phosphorous (N=128,769), parathyroid hormone (PTH, N=47,667), calcium (N=266,009), potassium (N=404,318), and total number of abnormalities (N=17,975, CKD cohorts only). Analyses were adjusted for demographics, comorbid conditions, and ACR stage. We assessed whether associations were modified by ACR stage and by diabetes by including interaction terms.

Results: The CKD cohorts were 52% female and 3% black, with mean age 67 (SD 14). The GP/HR cohorts were 53% female and 4% black, with mean age 53 (SD 18). In the CKD cohorts, lower eGFR was associated with lower hemoglobin and bicarbonate, and higher potassium, phosphorus, PTH and total number of abnormalities. (Figure) For phosphorus, there appeared to be a sharper increase in risk below eGFR <30. Associations with eGFR were relatively flat for SBP and calcium. There was no qualitative differences in associations by level of ACR or diabetes. In the GP/HR cohorts, there was a continuous association between eGFR and potassium; for hemoglobin, phosphorus and PTH, associations were present at eGFR <59, <51 and <70, respectively. Albuminuria was a weak risk factor for metabolic abnormalities.

Conclusions: There was a graded association between potentially reversible metabolic abnormalities and level of GFR with similar associations by ACR stage.

Funding: NIDDK Support, Private Foundation Support

Figure. Continuous associations between eGFR and laboratory parameters by A-stage



For A-E, the reference value (black diamond) was set at the mean parameter level for eGFR 50, ACR <30 mg/g, and mean levels of the additional covariates (age 60, half male, 20% history of CVD, 30% diabetes, 40% ever smoker and BMI 30). The y-axis reflects absolute difference in parameter value from the reference. For F, abnormalities were defined as hemoglobin <13 g/dL (12 g/dL for women), bicarbonate <22 mmol/L, potassium >5 mmol/L, PTH >65 pg/mL, phosphorus >5 mg/dL, calcium <8.5 mg/dL, SBP >140 mmHg or DBP >90 mmHg or taking antihypertensive medication, and the y-axis reflects the absolute difference in number of abnormalities compared to the mean number of abnormalities for an individual with eGFR 50, ACR <30 mg/g, and mean levels of additional covariates.

FR-PO489

Greater Variability in Kidney Function Is Associated with an Increased Risk of ESRD Yan Yan,[1,3] Benjamin C. Bowe,[1] Yan Xie,[1] Tingting Li,[1,2] Carlos E. Palant,[4,5] Ziyad Al-Aly.[1,2] *[1]Clinical Epidemiology Center, Research and Development Service, Veterans Affairs St Louis Health Care System, St. Louis, MO; [2]Department of Medicine, Washington University School of Medicine, St. Louis, MO; [3]Department of Surgery, Washington University School of Medicine, St. Louis, MO; [4]Research and Medical Service, Veterans Affairs Medical Center, Washington, DC; [5]George Washington University School of Medicine, Washington, DC.*

Background: Intra-individual variability in kidney function is an independent predictor of all-cause mortality, providing additional prognostic information beyond baseline kidney function and prior slope; however, its prognostic significance for ESRD is not known.

Methods: To examine this question we assembled a cohort of 1,004,741 United States veterans with an eGFR above 60 ml/min/1.73m^3 between October 2001-2002, where date of last measurement in this period was assigned T_0, and used adjusted Cox Proportional Hazard models to examine the association between eGFR variability and risk of ESRD. Variability in kidney function was defined for each participant as the coefficient of variation of the regression line modeled on all outpatient eGFR measures during the three years before T_0.

Results: After a median follow-up of 13.08 years, there were 2.76, 3.41, 4.01, and 5.57% cases of ESRD in the lowest to highest quartiles of eGFR variability, respectively. Compared with the referent category (lowest quartile), participants had a graded increase in risk of ESRD with a hazard ratio of 1.10 (95%CI: 1.06-1.13), 1.24 (1.20-1.28), and 1.73 (1.68-1.79) in quartiles 2, 3, and 4, respectively. Results were consistent across numerous sensitivity analyses.

Conclusions: Our results demonstrate that higher eGFR variability was associated with increased risk of ESRD.

Funding: Veterans Affairs Support

FR-PO490

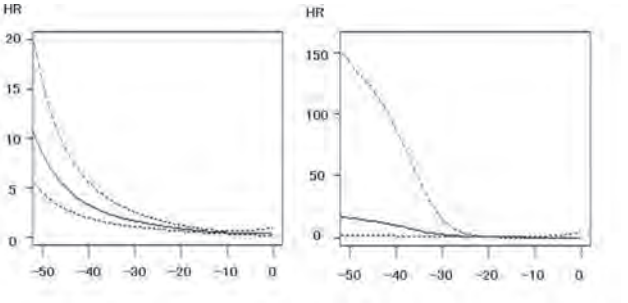
Importance of eGFR Change as a Surrogate End Point of ESRD in a Randomized Controlled Trial Eiichiro Kanda,[4] Enyu Imai,[3] Fumiaki Kobayashi,[1] Naoki Kashihara,[2] Masaomi Nangaku.[5] *[1]Daiichi Sankyo Inc, Somerset, NJ; [2]Kawasaki Medical School, Kurashiki City, Japan; [3]Nakayamadera Imai Clinic, Takarazuka, Japan; [4]Tokyo Kyosai Hospital, Meguro, Japan; [5]the University of Tokyo School of Medicine, Tokyo, Japan.*

Background: A use of a validated surrogate endpoint instead of a clinical endpoint could make a sample size small and shorten trial period. We evaluated a usefulness of an estimated glomerular filtration rate (eGFR) change as a surrogate endpoint using data from the randomized controlled clinical trial [Olmesartan Reducing Incidence of End-Stage Renal Disease (ESRD) in Diabetic Nephropathy Trial].

Methods: ESRD was defined as the true endpoint. eGFR changes over 1 to 3 years by 10% were defined as the surrogate endpoints. The relationship between eGFR changes and ESRD or the surrogate endpoints was evaluated using Cox proportional hazard models, which were adjusted for baseline characteristics. An effect of olmesartan on ESRD was compared with those on surrogate endpoints in terms of the ratio of the adjusted hazard ratio (aHR) of olmesartan to ESRD to those to surrogate endpoints by the bootstrap method.

Results: Diabetic kidney disease patients (n=566; male, 69.1%) were included in this analysis; average age±SD, 59.1±8.1 years; eGFR 37.1±9.8 ml/min. The Cox proportional hazard models with spline curves showed the relationships between eGFR changes over 1 and 2 years and ESRD (Figure 1). The ratios of aHR to ESRD to aHRs to surrogate endpoints near 1 were -30% or -40% over 2 years: -30%, 1.01 (95%CI 0.69-1.41); -40%, 1.0 (0.71-1.34). The events of eGFR changes of more than -30% showed good agreement with ESRD (0.6 < Cohen's kappas). The total sample sizes were 1004 for estimating eGFR change of -40% over 1 year; 800 for that of -40% over 2 years, which were smaller than that (1922) for one estimating ESRD.

Conclusions: eGFR change of more than -30% to -40% over 2 years would be a useful surrogate endpoint of ESRD in DKD patients.



FR-PO491

Identification and Prevalence of Pediatric CKD in a Large National Insurance Database Zubin J. Modi,[3] Ian T. Robinson,[3] Tanushree Banerjee,[2] Neil R. Powe,[2] Sharon Saydah,[1] Deborah Rolka,[1] Rajiv Saran,[3] Debbie S. Gipson.[3] *[1]Centers for Disease Control and Prevention, Atlanta, GA; [2]University of California, San Francisco, San Francisco, CA; [3]University of Michigan, Ann Arbor, MI.*

Background: Population-level surveillance of chronic kidney disease (CKD) in pediatrics is undeveloped. Children and adolescents with CKD are currently poorly identified in large databases, as existing surveillance systems focus primarily on adults. We examined 3 different claims-based algorithms to identify children and adolescents with CKD in a large, national, single-payer insurance database.

Methods: Using the Clinformatics™ data from 2014, children and adolescents < 21 years with potential CKD were identified by 3 ICD-9 code algorithms: 585-CKD codes alone, adult CKD stage-specific algorithm and a novel pediatric-specific CKD algorithm derived from chart review (N=110) at a large academic center. Patients were included if code was used at least once during the study period. Demographics were compared between patients identified via each method and concordance between methods was evaluated.

Results: 860, 8637, and 4294 children were identified via the 585-CKD, adult, and pediatric algorithms, respectively. Of all patients identified by at least 1 of the 3 methods, 44.6% were identified by both the adult and pediatric algorithms. All 860 patients identified by the 585-CKD algorithm were also identified by both adult and pediatric algorithms. Some code differences included prostatic obstruction, abnormal creatinine testing and acute renal failure in adult algorithm and specific genetic, autoimmune, and urologic disorders in pediatric algorithm. 144 patients were uniquely identified by the pediatric algorithm and 5861 were unique to the adult algorithm. Of the uniquely identified patients, those in the pediatric group were older, compared to the adult group (11 y vs 8 y). A higher prevalence of anemia was observed among patients uniquely identified by the pediatric algorithm compared to adult algorithm (43% vs 23%).

Conclusions: Adult and pediatric code algorithms examined identified substantially more potential patients with CKD than the 585-CKD algorithm. Refinement and validation of code algorithms for pediatric CKD as well as expansion to use of ICD-10 codes may be necessary to allow for current and historic case identification and pediatric CKD surveillance efforts.

Funding: Other U.S. Government Support

FR-PO492

Assessing Success in Transitioning of Young Adults from Pediatric to Adult Kidney Practice Cybele Ghossein,[1] Craig B. Langman,[1] Benjamin Joslin.[2] *[1]Feinberg School of Medicine, Northwestern University, Chicago, IL; [2]Northwestern University Feinberg School of Medicine, Chicago, IL.*

Background: Transfer from a pediatric to an adult medical setting is associated with many barriers. There are little data on patients' assessment of the transition process itself. Three years ago at Lurie Children's Hospital, we established a kidney transition program with the help of an adult nephrologist, physician assistant and social worker. After 18 months, we evaluated the patients' perception of the program.

Methods: Patients who had transitioned from pediatric care and were seen at least once in the adult clinic were asked to take an established 5-point Likert scale survey. Survey questions addressed readiness to transition, the transition process itself, and the perception of adult care. Responses were categorized into Top 2 Box ("strongly agree" or "agree") and Bottom 2 Box ("strongly disagree" or "disagree"). Surveys were followed with semi-structured interviews. Three readers rated each response as either "negative," "neutral," or "positive." Average, standard deviation and reader reliability were calculated. The readers also selected a word that best depicted each response and those most-common words were counted by question and overall.

Results: 17 out of 42 patients completed the survey. Average age at transition (mean ± SD) was 20 ± 2 years; the majority of patients (82%) felt ready to transfer to adult care but only 59% felt they were consulted on the timing. 88% of patients felt having a transition appointment and meeting the adult care providers in the pediatric setting to be valuable. Although 94% of patients ultimately felt comfortable in the adult care environment, 18% experienced noticeable differences in treatment recommendations. 13 semi-structured interviews were conducted. Overall, the patients responded positively (3±0, 100% reader reliability) to the transition. But, when asked what could have improved the transition, the word the patients used most was, "earlier."

Conclusions: Young adults transitioning to adult care often feel ready to transition earlier than their transfer of care date. They subjectively benefit from a transition program that outlines the process of transferring their care. Communication regarding differences in treatment between pediatric and adult nephrology care is warranted.

Funding: Private Foundation Support, Clinical Revenue Support

FR-PO493

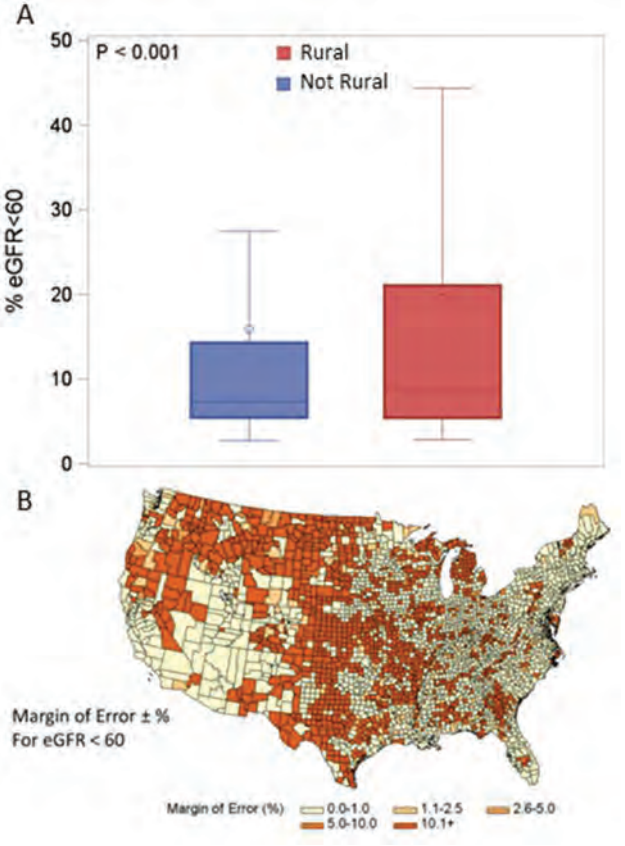
Spatial Analysis of CKD Prevalence in the US – A Joint Analysis of NHANES and KEEP Orrin Myers,[3] V. Shane Pankratz,[3] Keith C. Norris,[2] Joseph A. Vassalotti,[1] Mark L. Unruh,[3] Christos Argyropoulos.[3] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]UCLA, Marina Del Rey, CA; [3]UNM Health Sciences Center, Albuquerque, NM.*

Background: Chronic Kidney Disease (CKD) is a public health concern in the US, but it lacks a nationwide surveillance system that can describe regional variation. We investigate the feasibility of estimating county-level CKD prevalence from the large-scale community disease detection Kidney Early Evaluation and Program (KEEP).

Methods: KEEP participants were recruited from two-thirds of the nation's counties but were self-selected after targeted recruitment. We combined KEEP (N=127,149) and NHANES samples (N=27,565) from 2001–2012 to estimate sampling weights. The weights reduce self-selection bias in KEEP when estimating county-level prevalence of CKD (eGFR<60 mL/min/1.73m^2).

Results: Nationwide prevalence of eGFR<60 was 8.9% (7.5-10.7) from KEEP and 6.8% (6.3-7.2) for NHANES. CKD prevalence was significantly higher in rural counties (Fig 1A), which also had higher uncertainty (Fig 1B).

Conclusions: A joint analysis of NHANES and KEEP produced estimates of eGFR<60 that are adjusted for selection bias. Our analysis found that CKD rates are higher in rural counties. This approach makes it possible to enhance spatial CKD surveillance systems.



FR-PO494

Reported Awareness of CKD in the United States According to KDIGO Risk Groups for Prognosis Joanne E. Rodrigue,[1] Tanushree Banerjee,[1] Delphine S. Tuot,[1] Meda E. Pavkov,[2] Vahakn B. Shahinian,[3] Nilka Rios Burrows,[2] Rajiv Saran,[3] Neil R. Powe.[1] *[1]University of California, San Francisco, San Francisco, CA; [2]Centers for Disease Control and Prevention, Atlanta, GA; [3]University of Michigan, Ann Arbor, MI.*

Background: Chronic kidney disease (CKD) awareness in high risk populations is a critical public health challenge. CKD is characterized by marked differences in prevalence across race/ethnicity. Trends in awareness among those at various risks of prognosis to CKD have not been well characterized in the general United States population overall, or by race/ethnicity.

Methods: Prevalence of reported CKD awareness was assessed among non-pregnant adults aged ≥20 years in the National Health and Nutrition Examination Survey 1999-2014 with affirmative response to the question "do you have a routine place to go for healthcare?" Participants with and without CKD were categorized into three KDIGO risk groups for prognosis to CKD of low, moderate, and high, based on eGFR and albuminuria. CKD awareness was defined by affirmative response to the question "have

you ever been told that you had weak or failing kidneys?" We determined the proportions of awareness overall, by risk groups, and by race/ethnicity over time periods 1999-2004, 2005-2010, and 2011-2014. A propensity score for KDIGO risk groups was used to adjust for differences over time in demographics, hypertension, diabetes, and frequency of healthcare use.

Results: Among 23,762 adults, the adjusted proportion of reported CKD awareness across all risk groups increased from 1999-2004 to 2011-2014 (p-trend=0.04). Awareness among Mexican Americans at high risk, increased from 13.4% in 1999-2004 to 36.6% in 2011-2014, and among those at moderate risk 2.3% to 11.1% (combined p-trend=0.003). Awareness among non-Hispanic (NH) whites and NH blacks at high and moderate risk showed moderate increases over time, but the trend was not significant.

Conclusions: Overall, increases in reported awareness of CKD, particularly in Mexican-Americans at moderate and high risk of progression may be due to improvements in detection of disease or due to increases in the number of persons with CKD knowing they have the disease.

Funding: Government Support - Non-U.S.

Adjusted Prevalence of Awareness by Risk Groups

Risk Groups	1999-2004	2005-2010	2011-2014
Low	1.1 (0.9-1.4)	1.1 (0.8-1.4)	1.5 (0.9-2.1)
Moderate	3.1 (2.0-4.2)	4.5 (2.7-6.2)	5.1 (2.9-7.3)
High	14.4 (7.0-21.8)	9.9 (5.9-14.0)	19.8 (11.6-28.0)

FR-PO495

Racial Disparities in Trajectory of eGFR Decline in Patients with or at Risk for CKD Susanne B. Nicholas,[5] Kenn B. Daratha,[4] Jenny I. Shen,[1] Douglas S. Bell,[5] Radica Z. Alicic,[2] Katherine R. Tuttle,[3] Keith C. Norris.[5] *[1]LaBiomed at Harbor-UCLA, Torrance, CA; [2]Providence Medical Research Center, Spokane, WA; [3]University of Washington School of Medicine, Spokane, WA; [4]Washington State University, Spokane, WA; [5]Medicine, UCLA, Los Angeles, CA. Group/Team: UCLA-PHS CKD Registry Study Team.*

Background: Blacks have a 3.5-fold greater prevalence of advanced chronic kidney disease (CKD) compared to non-Blacks. However, less is known about patterns of CKD progression in Blacks relative to non-Blacks in real world settings. UCLA and PHS have formed the largest combined electronic health record (EHR) based CKD and at-risk for CKD Registry. This study compares trajectories of estimated glomerular filtration rate (eGFR) between Blacks and non-Blacks in the UCLA dataset.

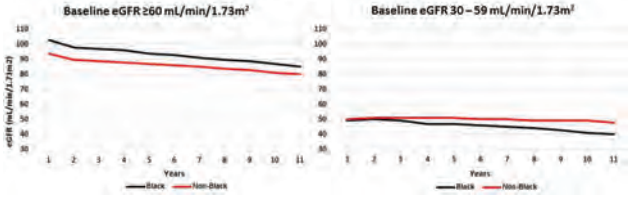
Methods: Data in the UCLA CKD and at-risk CKD Registry were analyzed from 176,406 patients who had at least two eGFR measurements from 2006-2016. Mean baseline eGFRs were compared using independent samples *t*-tests. Trajectories of eGFR of Blacks versus non-Blacks over the 11 years of the study were assessed using linear mixed models with random effects controlling for age and gender.

Results: Baseline characteristics of the overall cohort were: age 55±18 (mean±SD) years, CKD-EPI eGFR 90±24 mL/min/1.73m^2, 8% Black and 55% women. Among patients with baseline eGFR ≥60mL/min/1.73m^2, Blacks had higher mean baseline eGFR (103±23 versus 94±19 mL/min/1.73m^2, p<0.001), and higher mean difference in eGFR (6.8 mL/min/1.73m^2; 95% CI=6.6-6.9; p<0.001) than non-Blacks. Among patients with baseline eGFR 30-59 mL/min/1.73m^2, mean baseline eGFR was similar for Blacks and non-Blacks (49±8 versus 50±8 mL/min/1.73m^2, p=0.004). However, Blacks appear to have steeper trajectory of eGFR decline (mean difference in eGFR 1.8 mL/min/1.73m^2; 95% CI=1.4-2.3; p<0.001).

Conclusions: The trajectories of eGFR differed between Blacks and non-Blacks depending on baseline eGFR ≥60 or 30-59mL/min/1.73m^2, by a pattern shift from higher eGFR trajectories to lower, steeper eGFR trajectories. These data may signal critical windows for interventions to reduce disparities and improve kidney health in this high-risk group of Black patients.

Funding: Private Foundation Support

Figure 1. Mean eGFR Trajectories



FR-PO496

Decreased Kidney Function Among a Rural Population in Veracruz, Mexico: A Cross-Sectional Study Magdalena Madero,[1] Diego J. Aguilar,[2] Alejandro Raña,[2] Alejandro Escobar,[1] Antonio Villa,[2] Gregorio T. Obrador.[2] *[1]National Heart Institute, Division of Nephrology, Mexico, Mexico; [2]Universidad Panamericana School of Medicine, Mexico, D.F., Mexico.*

Background: An epidemic of CKD of unknown origin (CKDu) has emerged in Central America, particularly in young male sugarcane workers. CKDu cases have been reported from Tierra Blanca, Veracruz, a region with similar environmental and socioeconomic characteristics to those described in Central America. To date, there are no epidemiologic reports of CKD hotspots in Mexico.

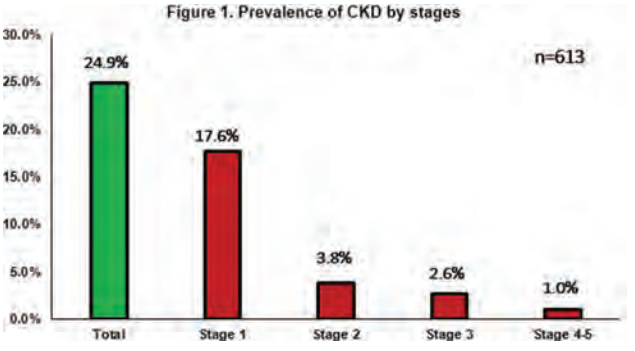
Methods: A cross-sectional study included adults with or without risk factors for CKD aged 20-60 from 3 communities in Tierra Blanca, Mexico. Sociodemographic, clinical, occupational and environmental data were collected from 613 participants. Standardized serum creatinine and albumin-creatinine ratio were measured; glomerular filtration rate (eGFR) was estimated using CKD-EPI equation. Patients were categorized with or without CKD according to KDIGO classification. Factors associated with lower eGFR were assessed using a multiple logistic regression model.

Results: Mean age was 41(±11), and 200(32.6%) were men. Prevalence of CKD (G1-G5) was 24.9%, mostly driven by albuminuria (Figure 1), and was similar between male and female participants. Presence of DM or HTN was more frequent in the group with CKD (33.9% and 33.9%); nevertheless, 68 (44.4%) of the participants identified with probable CKD did not have a traditional risk factor. Independent factors associated with an eGFR <90 mL/min/1.73 m^2 were older age(OR=1.07[1.04 - 1.10]), DM(OR=1.7[.99 - 3.19]), family history of CKD(OR=2.03[1.1 – 3.5]) and history of sugarcane work(OR=2.2 [1.1-4.3]).

Conclusions: This is the first epidemiologic report of a possible CKDu hotspot in Mexico. A high prevalence of CKD in these communities was found. Moreover, almost half of the cases could be classified as uCKD. Non-traditional risk factors, such as the history of sugarcane work, were associated with lower eGFR. The cross-sectional nature of the study prevents etiologic interpretations; a longitudinal assessment to further characterize this possible CKD hotspot is being planned.

Funding: Private Foundation Support, Government Support - Non-U.S.

Figure 1. Prevalence of CKD by stages



FR-PO497

Prevalence and Risk Factors for CKD in Adults of El Salvador Carlos M. Orantes,[7] Raúl Herrera,[4] Miguel M. Almaguer,[2] Moises N. Diaz,[1] Xavier F. Parada,[3] Esmeralda G. Gavarrete Escobar,[6] Luis C. Silva.[5] *[1]ISSS, San Salvador, El Salvador; [2]Instituto de Nefrologia, La Habana, Cuba; [3]Massachusetts General Hospital, Boston, MA; [4]National Institute of Nephrology, La Habana, Cuba; [5]National School of Public Health, Cuba, La Habana, Cuba; [6]University of El Salvador, San Salvador, El Salvador; [7]Renal Research Unit, National Institute of Health, San Salvador, El Salvador.*

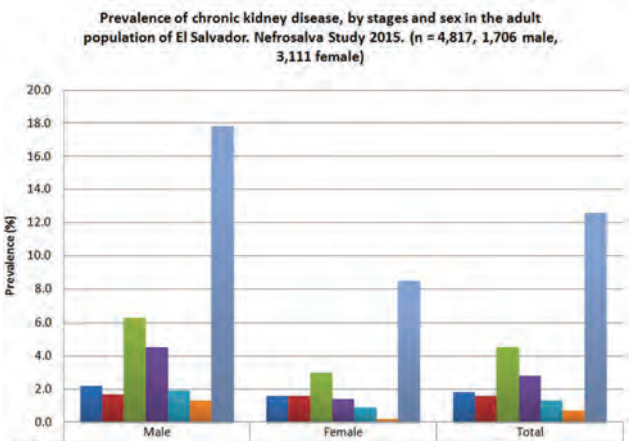
Background: An increase in deaths due to chronic kidney disease (CKD) has been observed in Central America. Mortality is 17 times higher in Nicaragua and El Salvador than in Cuba. Noted, CKD of unknown etiology (CKDu) is a major health problem in El Salvador

Methods: A cross-sectional analytical epidemiological study was conducted in a sample of 4,817 participants aged ≥20 years obtained from the national survey on non-communicable diseases to determine the prevalence and risk factors for CKD and CKDu. Stages of CKD (CKD-EPI equation) were estimated from serum creatinine and spot urine albumin. CKD-1 & 2 was confirmed at three months. Data analysis included descriptive, analytical, and bivariate measures

Results: Risk factors: diabetes mellitus (DM) 12.5%; hypertension (HTN) 37%; family history of CKD 8.7%; family history of DM 21.8%, family history of HTN 40.3%; obesity 27.3%, dyslipidemia 27%; current smoker 7.8%; alcoholism 9.4%; agricultural occupation 31.2%; NSAIDs 3.8%; nephrotoxic plants 3.8%, direct exposure to agrochemicals 12.6%. CKD prevalence was 12.6 (11.0-14.4) (Figure 1), of this one-third was CKDu 30.5% (25.9-35.5). Associations found were (OR; 95%CI): Age >64 (17.3; 11.7-25.6), DM (3.6; 2.9-4.7), obesity (3.5; 2.0-6.0), HTN (3.5; 2.8-4.5), male (2.3; 1.8-2.9), rural residency (1.3; 1.0-1.8), dyslipidemia (1.3; 1.0-1.6). At least 5 years of: use of agrochemicals (2.5; 1.9-3.4), exposure to agrochemicals in residency & work (2.4; 1.7-3.4), any agricultural activity (2.0; 1.5-2.5), direct exposure to agrochemicals (1.8; 1.4-2.4), drinking river water (1.8; 1.4-2.3), storage of products and hardware for fumigation (1.5; 1.2-2.0)

Conclusions: Adults in El Salvador have a double burden of risk factors (traditional and non-traditional) that can act synergistically to cause CKD

Funding: Government Support - Non-U.S.



	Male	Female	Total
CKD 1	2.2	1.6	1.8
CKD 2	1.7	1.6	1.6
CKD 3a	6.3	3.0	4.5
CKD3b	4.5	1.4	2.8
CKD 4	1.9	0.9	1.3
CKD5	1.3	0.2	0.7
CKD	17.8	8.5	12.6

FR-PO498

Survival of Patients with CKD Stage 3-5 in Iceland Arnar J. Jonsson,[1,2] Sigrun H. Lund,[2] Runolfur Palsson,[1,2] Olafur S. Indridason.[1] *[1]Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland; [2]University of Iceland, Reykjavík, Iceland.*

Background: The purpose of this study was to estimate hazard ratio (HR) for death in patients with chronic kidney disease (CKD) stage 3-5 and to estimate the survival benefit of renal replacement therapy in CKD stage 5.

Methods: We obtained all SCr values from all clinical laboratories in Iceland for the years, 2008-2013. Data on age, gender, diagnoses of comorbid conditions (ICD-9 and ICD-10 codes) and HbA1c measurements were retrieved from electronic medical records. Information on initiation of renal replacement therapy was also obtained. The CKD-EPI equation was used to calculate eGFR. CKD was defined and staged according to the KDIGO classification system. Computerized algorithms were used to identify and exclude episodes of acute kidney injury. For CKD stage survival analysis, Cox regression model, using age as time scale was used to calculate hazard ratios adjusted for age, sex, hypertension, diabetes, coronary artery disease and acute kidney injury. For hazard ratio calculations for stage 5 with RRT compared to no RRT we used cox regression model with time on study, adjusted for age as continuous variable, sex, hypertension, diabetes and coronary artery disease.

Results: We retrieved 1,230,563 SCr values for 183,931 individuals aged 18 years and older. The median age was 62 years (range: 18 – 108) and 47.5% were men. A total of 13152 (7.2%) patients had CKD, 8951 (4.9%), 3252 (1.8%), 798 (0.4%) and 151 (0.08%) in stage 3A, 3B, 4 and 5, respectively and 234 patients received RRT. Compared to individuals without CKD, the adjusted hazard ratio for death for CKD stage 3a, 3b, 4 and 5 were 0.94 (95%CI: 0.88 – 1.00), 1.15 (95%CI: 1.05 - 1.26), 1.84(1.59 – 2.14) and 3.08(2.31 – 4.09) respectively in men and 0.85 (95%CI: 0.80 – 0.91), 0.98 (95%CI: 0.90 - 1.07), 1.60(1.38 – 1.85) and 4.48(3.18 – 6.30) in women, respectively. For individuals with stage 5 and receiving RRT the HR for death was: 0.43 (95%CI: 0.27 – 0.68) compared to those that did not receive RRT. For individuals aged 65-74 the HR was 0.80 (95%CI: 0.33 – 1.92) and for individuals aged 75 or older the HR was: 0.32 (95%CI: 0.17 – 0.57).

Conclusions: This nationwide study, comprising the majority of the Icelandic populations does not confirm increased risk of death with stage 3a and 3b as previously reported. Renal replacement therapy seems to improve survival for patients with CKD stage 5, particularly for the aged

Funding: Government Support - Non-U.S.

FR-PO499

Temporal Changes in the Pattern of Kidney Disease: Analysis Based on 40,759 Biopsy-Proven Cases in China From 2003 to 2014 Huixian Zhu, Jin-Hua Hou, Minlin Zhou, Dandan Liang, Si-Jia Shao, Ye Liu, Zhi-Hong Liu. *National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing China, Nanjing, China.*

Background: Global burden of disease showed that spectrum of disease in China has changed from infectious disease to non-infectious disease over the past 20 years and the latter has become one of the most leading public health problems. Epidemiologic studies reveal the temporal changes in the pattern of kidney disease, which might reliably inform future hypothesis driven studies and public health interventions. Thus, in this study we aimed to determine the temporal trends in kidney disease in 40,759 cases from 2003 to 2014.

Methods: We identified all patients with a native kidney biopsy specimen referred to the National Clinical Research Centre of Kidney Diseases in Jinling Hospital between 2003 and 2014. Temporal era was categorized into three consecutive 4-year time intervals (2003–2006, 2007–2010, and 2011–2014) and patients age was categorized into four intervals (14-24, 25-44, 45-59, and ≥60).

Results: In total, 40,759 cases with renal biopsy were analyzed. The mean age of the patients were 36.59±14.12 years old and 52.0% was male. Mean age of renal biopsy patients increased continuously and he proportion of patients over 60 years old mounted up from 5.6% to 9.9%. Primary glomerulonephritis (PGN), Secondary glomerulonephritis (SGN), Tubulointerstitial disease (TIN) and inherited kidney disease accounted for 67.1%, 26.4%, 2.9% and 2.5% respectively among cases of renal biopsy. IgA nephropathy (IgAN) (52.7%) was most common in PGN, immune-mediated disease accounted for 59.20% in SGN. The proportions of IgAN and focal segmental glomerulosclerosis (FSGS) had a downward tendency (P<0.001); while the proportion of membranous nephropathy (MN) increased significantly (P<0.001). Lupus nephritis and Henoch-Schonlein purpura nephritis this kind of immune-mediated diseases decreased significantly (P<0.001), diabetic nephropathy increased by nearly one time (P<0.001) from 2011 to 2014.

Conclusions: PGN remained the predominant kidney disease in China, of which, IgAN was the most common one. What was noteworthy was that the proportion of MN increased significantly, with a maximum increase in adolescent patients. The changing spectrum of kidney disease presented in this study provided a certain reference and basis for clinical diagnosis, prevention and epidemiological study.

FR-PO500

Consistency of the Obesity Paradox across Different Stages of CKD in Over 2 Million Veterans Melissa Soohoo,[1] Elani Streja,[1] Yoshitsugu Obi,[1] Connie Rhee,[1] Christina Park,[1] Hamid Moradi,[1] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine, Orange, CA; [2]University of Tennessee Health Science Center, Memphis, TN.*

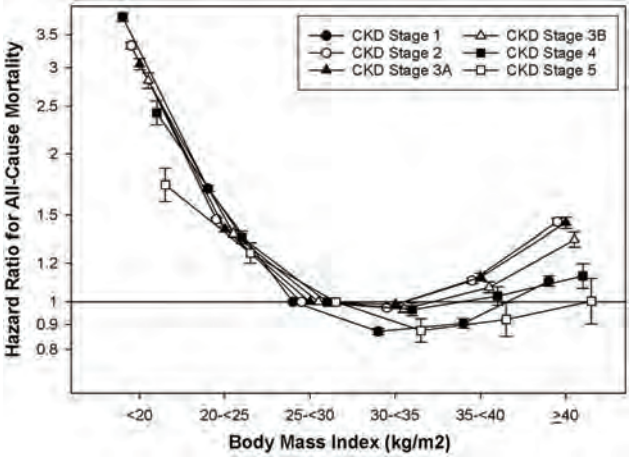
Background: The inverse relationship between body mass index (BMI) and mortality, also known as the "obesity paradox", has been described for both dialysis and non-dialysis dependent CKD patients. However, the relationship of BMI with mortality across all increasing CKD stages (including early CKD), is less well-known.

Methods: We investigated a cohort of 2.1 million US veterans with a BMI measurement between 2005-2006. CKD stages were created according to eGFR (estimated glomerular filtration rate) at the time of BMI measurement. Using Cox models adjusted for age, gender, race and diabetes status, we examined the relationship of BMI with all-cause mortality across strata of CKD stage.

Results: Patients were 64±14 years old, 5% female, 15% African-American, and 36% diabetic with a mean±SD baseline BMI 29±6 kg/m^2 and median[IQR] eGFR 75[61, 91] mL/min/1.73m^2. Patients were followed for a median[IQR] follow-up of 10.6[6.9, 11.1] years. We observed a reverse J-shaped association across all CKD stages compared to the referent BMI 25-<30 kg/m^2, where BMI≥40 kg/m^2 was associated with a higher risk of mortality across all CKD strata, except for CKD Stage 5 patients [HR(95%CI): 1.00[0.90, 1.12]. The relationship of BMI≥40 kg/m^2 with mortality incrementally declined towards the null across worsening kidney stages. However, across all stages of CKD, BMI<25 kg/m^2 was persistently associated with the highest risk of mortality. [Figure]

Conclusions: The relationship of morbid obesity with a higher risk of mortality in US veterans attenuates across worsening CKD stages, further supporting the notion of an "obesity paradox". Further studies are needed to understand the underlying mechanism of this relationship and whether weight management strategies are indicated in patients with worsening kidney disease.

Funding: NIDDK Support, Veterans Affairs Support



FR-PO501

Weight Loss in Veterans with CKD after Enrollment in a Weight Management Program Niraj Desai,[3] Cameron D. Carter,[4] Mirela A. Dobre,[2] Khaldoon Shaheen,[2] Sankar D. Navaneethan,[1] Mahboob Rahman.[2] *[1]Baylor College of Medicine, Houston, TX; [2]Case Western Reserve University, Cleveland, OH; [3]Cleveland VAMC, Case Western Reserve University, Cleveland, OH; [4]VHA, Cleveland, OH.*

Background: Though obesity is common in patients with CKD, interventions to reduce weight have not been well studied in this population. We examined the relationship between enrollment in a weight management program and weight loss across strata of eGFR.

Methods: We conducted a retrospective, observational analysis of patients enrolled in Managing Overweight/Obesity for Veterans Everywhere (MOVE!), a multidisciplinary weight management program within the Veteran's Affairs Medical Centers. Mean weight loss, and change in BMI for MOVE! participants was calculated comparing baseline weight measured upon enrollment to final weight measured at the last visit to the program. A control group not enrolled in MOVE! was evaluated for weight change over a similar time period. Paired t testing was used to assess statistical significance.

Results: 4935 veterans (age 59.5 +/- 9.4 yrs, weight 119.1 +/- 21.3 kg, BMI 37.4 +/- 6.5 kg/m2, 18% black, 67% diabetic) were enrolled in MOVE! between 2006 and 2011. Mean weight loss was 1.0 +/- 6.4 kg ($p<0.001$) and mean decrease in BMI was 0.33 +/- 2.1 kg/m^2 ($p<0.001$) after an average of 7.6 +/- 11.4 visits to the program. In an age, gender, BMI and weight matched cohort (n =4795), mean weight loss was 0.05 +/- 4.7 kg ($p=0.438$) and mean decrease in BMI was -0.05 +/- 1.7 kg/m^2 ($p=0.68$). Mean weight loss and decrease in BMI was similar for each stratum of eGFR in the intervention group (eGFR >90: 0.9 +/- 6.8 kg, 0.26 +/- 2.1 kg/m^2; eGFR 60-89: 1.1 +/- 6.6 kg, 0.36 +/- 2.2 kg/m^2; eGFR 45-59: 1.0 +/- 5.4 kg, 0.34 +/- 1.8; eGFR 30-44: 1.0 +/- 4.9 kg, 0.26 +/- 1.6 kg/m^2, all $p<0.001$). In the matched cohort, weight loss and decrease in BMI did not occur in any of the eGFR subgroups.

Conclusions: Enrollment in a multidisciplinary weight management program is associated with a modest weight loss across all strata of GFR.

FR-PO502

Weight Loss Has an Additive Effect on the Anti-Proteinuric Effects of Angiotensin II Receptor Blockers in Hypertensive Patients with CKD Shin-Young Ahn,[3] Dong Ki Kim,[7] Seung Seok Han,[6] Jung hwan Park,[2] Bumsoon Choi,[1] Chun Soo Lim,[4] Ho Jun Chin.[5] *[1]Division of Nephrology, Department of Internal Medicine, Seoul, Republic of Korea; [2]Konkuk University, Seoul, Republic of Korea; [3]Korea University Medical Center, Korea University Guro Hospital, Seoul, GYEONGGI-DO, Republic of Korea; [4]Seoul National University Boramae Medical Center, Seoul, Republic of Korea; [5]Seoul National University Bundang Hospital, Seong nam, Republic of Korea; [6]Seoul National University College of Medicine, Seoul, Republic of Korea; [7]Seoul National University Hospital, Seoul, Republic of Korea.*

Background: Because weight gain and obesity contribute to the development of chronic kidney disease (CKD) and end stage renal disease (ESRD), weight reduction is a lifestyle intervention that has been introduced for the prevention and management of CKD. However, CKD patients with obesity sometimes exhibit a slow progression of renal deterioration. We investigate the additive anti-proteinuric effect of weight reduction on the usage of an angiotensin II receptor blocker and the potential mechanisms of the beneficial effect in hypertensive CKD patients.

Methods: This study is a subanalysis of data from an open-label, randomized, controlled clinical trial (NCT01552954). Among the 235 participants, the body weight of 227 participants was measured and 24h urine samples were collected at baseline and after 16 weeks. The participants were assigned to subgroup according to changes in their body weight.

Results: Fifty-eight participants (25.7%) were assigned to group 1 (a ≥ 1.5% decrease in body weight after 16 weeks), 32 participants (14.1%) were group 2 (a 1.5% ~ 0.1% decrease in body weight), and 136 participants (60.2%) were group 3 (a ≥ 0.0% increase in body weight). Over the study period, unintentional weight loss independently increased the probability of reduced albuminuria (Group 1, RR 6.234, 95% CI 1.913 – 20.315, $p=0.002$). The relationship between weight loss and a decrease in albuminuria was even more significant in several subgroups, including participants who were female, younger (< 65 years), non-obese and obese (BMI ≥ 18.5 kg/m^2), as well as those who had a CKD stage ≥ 3a (≥ 45 ml/min/1.73m^2), consumed a low salt diet (urinary sodium excretion < 200 mEq/day) and a low protein diet (< 1.2 g/kg/day), and had a low baseline level of albuminuria (< 2000 mg/day). Among the urinary cytokines, only podocalyxin levels decreased significantly in participants who lost weight ($p=0.013$).

Conclusions: We observed that unintentional weight loss has additive effect on the anti-proteinuric effects of treatment with ARBs in hypertensive CKD patients, which is possibly related to the reduced damage of podocytes. Therefore, physicians could consider suggestion of weight reduction to hypertensive CKD patients even if they are not obese.

Funding: Private Foundation Support

FR-PO503

Daily Sedentary Time and Physical Activity Are Independently Associated with ESRD Risk Jacob M. Taylor,[2] Edmond K. Kabagambe,[2] Thomas G. Stewart,[1] Jennifer Morse,[1] Edward D. Siew,[2] William J. Blot,[2] Loren Lipworth,[2] Talat Alp Ikizler.[2] *[1]Biostatistics, Vanderbilt University Medical Center, Nashville, TN; [2]Medicine, Vanderbilt University Medical Center, Nashville, TN.*

Background: Lifestyle factors, such as sedentary time and physical activity, could independently contribute to the risk of end stage renal disease (ESRD).

Methods: We assembled a case-cohort study from the Southern Community Cohort Study (SCCS) which recruited ~86,000 low-income blacks and whites in the southeastern US (2002-2009). 546 incident ESRD cases, identified by linkage with the US Renal Data System through March 2015, and a probability sample of 4049 SCCS participants, who donated a blood sample and had serum creatinine measured, were included. Demographic, medical, and lifestyle information, including detailed sedentary time and physical activity data, were obtained via questionnaire at baseline. Sedentary time was calculated as hr/d from daily sitting activities, while physical activity was calculated as met-hrs and derived from engagement in light, moderate, and vigorous activities. Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of sedentary time and physical activity with ESRD were computed from multivariable Cox models that included the two variables and age, sex, race, education, income, body mass index, eGFR, smoking, history of diabetes, hypertension, and hypercholesterolemia.

Results: At baseline, the mean (SD) was 55.5 (8.8) years for age and 96 (24) mL/min/1.73m2 for eGFR. Median (25th, 75th percentile) for sedentary time and physical activity were 7.9 (5.5, 11.4) hrs/d and 15.7 (8.0, 29.1) met-hrs, respectively. Most participants were women (58%), black (67%), reached high school (65%), had low income (61%), were overweight or obese (77%), were current/former smokers (58%), and had hypertension (61%), while 25% had diabetes and 39% had hypercholesterolemia. After median follow-up of 9.7 years (range 0.08-12.8), risk of ESRD increased per IQR increase in sedentary time (HR=1.13, 95% CI 1.09-1.16), while risk decreased per IQR increase in physical activity (HR=0.93, 95% CI 0.90-0.97) in adjusted analysis.

Conclusions: In this population at high risk for ESRD, sedentary time appears to increase the risk of ESRD, whereas physical activity is inversely associated with ESRD risk. Sedentary time and physical activity appear to play independent roles in ESRD risk.

Funding: Other NIH Support - National Cancer Institute, Veterans Affairs Support, Other U.S. Government Support

FR-PO504

Conventional Measures of Body Composition Underestimate Sarcopenia and Overestimate Obesity in CKD Susan Ziolkowski,[4] Jin Long,[2] Glenn M. Chertow,[3] Mary B. Leonard.[1] *[1]Stanford School of Medicine, Stanford, CA; [2]Stanford University, Palo Alto, CA; [3]Stanford University School of Medicine, Palo Alto, CA; [4]Nephrology, Stanford University, Stanford, CA.*

Background: Fat and lean mass are directly correlated. Therefore, conventional definitions of sarcopenia (S) based on lean mass fail to capture low lean relative to fat, i.e. relative sarcopenia (RS) in those with greater adiposity. Recent data suggest RS better predicts incident morbidity than does S. Percent body fat (%BF) overestimates the prevalence of obesity if lean mass is low, while body mass index (BMI, kg/m^2) can underestimate. Fat mass indexed to height (kg/m^2) helps to address this limitation.

Methods: DXA appendicular lean mass index (ALMI, kg/m^2) and FMI were assessed in 13,980 NHANES participants. ALMI, FMI, and ALMI relative to FMI were expressed as sex- and race/ethnicity-specific standard deviation scores compared with young adults (T-scores) and for age. S was defined as ALMI T-score < -2, and RS as ALMI relative to FMI T-score < -2. Excess adiposity was defined using sex- and race/ethnicity specific FMI cutpoints and conventional BMI and %BF cutpoints. GFR was estimated using creatinine (eGFRcr) and cystatin C (eGFRcys).

Results: The prevalence of RS was higher than the prevalence of S, especially in CKD stages 3b (17 vs 6%) and 4 (36 vs 6%) using eGFRcr; these stages were associated with the highest FMI, accounting for the higher prevalence of RS vs S. In multivariable logistic regression, CKD stage was independently associated with lower ALMI relative to FMI for age, adjusted for smoking, physical activity and cardiovascular disease (OR stage 3b=1.47, stage 4=1.99, stage 5=2.38, vs eGFRcys > 90; p trend=0.05). The prevalence of obesity increased with CKD stage through stage 4, and was lower in stage 5 using FMI, BMI and %BF definitions. BMI and %BF under- and overestimated obesity prevalence, e.g., in CKD Stage 4, the prevalence of obesity was: BMI 42%, FMI 55%, %BF = 72%. CKD was not associated with obesity by FMI, adjusted for race, age, diabetes, liver disease, physical activity and cardiovascular disease.

Conclusions: In CKD, S underestimates muscle deficits and %BF overestimates the prevalence of obesity. CKD is independently associated with low lean mass relative to fat mass (RS) but is not associated with excess adiposity. Future studies are needed to determine how RS and excess adiposity (as defined by FMI) relate to morbidity and mortality in CKD.

Funding: NIDDK Support

FR-PO505

Association between Circulating Fibroblast Growth Factor 21 and Body Composition in CKD Mari Okada,[1] Takahiro Masuda,[1] Marina Kohara,[1,2] Hiromichi Yoshizawa,[1] Atsushi Miki,[1] Saki Nakagawa,[1] Ken Ohara,[1] Takuya Murakami,[1] Erika Hishida,[1] Hiroaki Myoga,[1] Miwa Shuto,[1] Yuko Watanabe,[1] Osamu Saito,[1] Tetsu Akimoto,[1] Shigeaki Muto,[1] Makoto Kuro-o,[2] Daisuke Nagata.[1] *[1]Division of Nephrology, Department of Internal Medicine, Jichi Medical University, Shimotsuke, Japan; [2]Division of Anti-aging Medicine, Center for Melecular Medicine, Jichi Medical University, Shimotsuke, Japan.*

Background: Fibroblast growth factor 21 (FGF21) is a liver-derived hormone that induces responses to stress including activation of the sympathetic nervous system and the hypothalamus-pituitary-adrenal axis. Circulating FGF21 levels increase in the progression of chronic kidney disease (CKD), but the mechanism has not yet been fully evaluated. In this study, we examined the association between circulating FGF21 and body composition in predialysis CKD patients.

Methods: Seventy-two predialysis CKD patients were enrolled in this study (age 51.3 ± 17.1 years, male 51.4%, estimated glomerular filtration rate [eGFR] 66.3 ± 28.3 ml/min/1.73m^2). Body composition was measured by bioelectrical impedance analysis (BIA). Patients were divided into low- and high-FGF21 groups by the median value. Multivariable logistic regression analysis was used to examine the association between serum FGF21 levels and body composition.

Results: The median value of serum FGF21 was 131 pg/mL. Age (56.7 ± 15.4* vs. 45.2 ± 17.0 years, *p <0.05), body mass index (BMI) (26.1 ± 5.7* vs. 23.7 ± 4.3 kg/m^2), systolic blood pressure 133 ± 16* vs. 122 ± 27 mmHg), extracellular water (ECW) (22.0 ± 5.2 vs. 21.2 ± 4.4 L, p=0.06), the ratio of ECW to total body water (ECW/TBW) (0.387 ± 0.021* vs. 0.376 ± 0.023) were high, eGFR (55.2 ± 27.0* vs. 79.2 ± 24.5 ml/min/1.73m^2) and serum albumin (3.2 ± 0.9* vs. 3.8 ± 0.7 g/dL) were low in the high-FGF21. On the other hand, percentage of fat mass (26.6 ± 10.6 vs. 25.1 ± 9.3 %, p=0.264) and skeletal muscle (26.7 ± 6.8 vs. 25.7 ± 5.8 kg, p=0.264) were similar among the groups. In logistic regression analysis, ECW/TBW was an independent risk factor for higher FGF21 level (odds ratio 1.38: 95% confidence interval 1.04-1.96, p=0.024) even after adjustment for gender, BMI, systolic blood pressure, and percentage of fat mass.

Conclusions: In predialysis CKD patients, higher circulating FGF21 level is associated with increase in ECW/TBW. This result indicates that fluid retention is a novel indicator for circulating FGF21 levels.

Funding: Government Support - Non-U.S.

FR-PO506

Association of Body Composition with Frailty Status among Patients with Moderate to Advanced CKD Cynthia Delgado,[3,2] Kirsten L. Johansen.[1] *[1]University of California, San Franicsco, San Francisco, CA; [2]Medicine, Division of Nephrology, University of California, San Francisco, San Francisco, CA; [3]Medicine, Nephrology Section, San Francisco Department of Veterans Affairs, San Francisco, CA.*

Background: Frailty disproportionately affects individuals with chronic kidney disease (CKD) and is associated with hospitalization and loss of independence. The Frailty In Chronic Kidney diSease Intervention pilot sTudy (FICKSIT) aimed to determine the feasibility of a multi-faceted intervention to address frailty. We compared body composition of frail and non-frail patients enrolled in FICKSIT.

Methods: We enrolled 68 patients with CKD stage III-IV over the age of 18 who were receiving nephrology care. Frailty was defined according to the Fried Frailty index, which includes 5 criteria (weak grip, exhaustion, weight loss, low physical activity, slow gait). Participants meeting three or more criteria were considered frail (F); those meeting 1-2 criteria were intermediate frail (IF); and those not meeting any frailty criteria were not frail (NF). We performed whole-body bioelectrical impedance spectroscopy (BIS) to estimate ICW/kg as a proxy for muscle mass (ICW)), fat mass (FM) and extracellular water (ECW) as a percentage of total body weight. We used ANOVA to compare frailty status (F, IF and NF) and logistic regression analysis with NF participants as the reference group to determine if body composition was associated with frailty status after adjusting for covariates.

Results: Participants' mean age was 67 ± 8, and 93% were male. The majority of participants met at least one frailty criterion; 49% were IF and 25% were F. ICW/kg was lower among IF (0.28 ± 0.3 L/kg) and F (0.26 ± 0.3 L/kg) than among NF participants (0.29 ± 0.03 L/kg, p=0.05). In regression analysis, higher percent muscle mass (ICW/kg) (OR 0.38 per 1%, 95%CI 0.17, 0.83) and percent FM (FM/kg) (OR 0.76 per 1%, 95%CI 0.58, 0.98) were associated with lower odds of frailty.

Conclusions: Among FICKSIT participants, higher muscle and fat mass were associated with lower odds of frailty

Funding: NIDDK Support, Veterans Affairs Support

FR-PO507

Frailty Affects Treatment Decisions and Outcomes for Patients with CKD Reid Whitlock,[2] Frederick Eng,[1] Ranveer S. Brar,[1] Claudio Rigatto,[2] Paul Komenda,[2] Clara Bohm,[2] Navdeep Tangri.[2] *[1]Seven Oaks General Hospital, Winnipeg, MB, Canada; [2]University of Manitoba, Winnipeg, MB, Canada.*

Background: Frailty is common in patients with Chronic Kidney Disease (CKD) and leads to accelerated aging. While there have been several studies examining frailty in patients with earlier stages of CKD and those on dialysis, little is known about the prevalence and impact of frailty on outcomes in patients with advanced CKD. We sought to determine the agreement between 3 different frailty measures and the association of these measures with dialysis modality decisions and mortality.

Methods: We studied 508 patients with advanced CKD who were enrolled in CKD clinics at 4 centers. We collected demographics, comorbid conditions, and laboratory results in addition to objective [Modified Fried Frailty Criteria (Fried) and Short Physical Performance Battery (SPPB)], and subjective measures (physician and nurse impression) of frailty. Our primary outcomes were choice of dialysis modality and all-cause mortality.

Results: Our cohort had a median age of 68 (interquartile range: 58, 77) and was 42.9% female. Estimates of frailty prevalence varied as 49.9% of the cohort were considered frail according to SPPB, 29.9% according to Fried, 33.4% according to physician impression, and 28.7% according to nursing impression. Agreement between objective frailty assessments (κ = 0.48) and subjective frailty assessments (κ = 0.46) was moderate. The objective frailty measures were not associated with choice of dialysis modality. In contrast, the subjective physician impression of frailty was associated with choosing hemodialysis (OR 3.74 [95% CI: 1.02-13.66]). The subjective frailty measures were not associated with choice of dialysis modality. Frailty measured objectively using Fried trended toward an association with mortality (OR 1.94 [95% CI: 0.97-3.88]).

Conclusions: In summary, we have demonstrated that the definition of frailty is important, as there is limited agreement between frailty construct and important differences in the relationship of each construct with clinical outcomes. Patients diagnosed as frail by Fried were more likely to die, and patients considered frail by physicians were more likely to choose in-center hemodialysis. Further research to understand the longitudinal trajectory of frailty and its impact on therapeutic choices, morbidity, mortality, and quality of life after initiation of dialysis is needed.

Funding: Government Support - Non-U.S.

FR-PO508

Recalibration and Validation of the Charlson Comorbidity Index in an Asian Population: The National Health Insurance Service – National Sample Cohort Study Jae shin Choi,[1] Myoung-Hee Kim,[2] Yong Chul Kim,[1] Jung Nam An,[3] Jae Yoon Park,[4] Dong Ki Kim,[1] Yun Kyu Oh,[3] Yon Su Kim,[1] Chun Soo Lim,[3] Jung Pyo Lee.[3] *[1]Seoul National University Hospital, Seoul, Republic of Korea; [2]Eulji University, Seongnam-si, Gyeonggi-do, Republic of Korea; [3]Seoul National University Boramae Medical Center, Seoul, SEOUL, Republic of Korea; [4]Dongguk University Ilsan Hospital, Gyeonggido, Republic of Korea.*

Background: Weights assigned to comorbidities to predict mortality may vary based on the type of index disease and advances in the management of comorbidities. We aimed to develop a modified Charlson comorbidity index (CCI) in an Asian nationwide database (mCCI-A), thereby predicting their mortality more precisely.

Methods: The main data source used in this study was the National Health Insurance Service-National Sample Cohort (NHIS-NSC) constructed from the National Health Insurance database, which includes health insurance claims between January 1, 2002 and December 31, 2013 in Korea. Of the 1,025,340 individuals included in the NHIS-NSC, 578,547 patients who were hospitalized at least once were analyzed for this study. mCCI-A score were calculated by summing up the weights which were assigned to individual comorbidities according to their relative prognostic significance determined by multivariate Cox proportional hazard model. The modified index was validated in the same cohort.

Results: The Cox proportional hazards model provided reassigned severity weights for 17 comorbidities that significantly predicted mortality. Both the CCI and the mCCI-A were correlated with mortality. However, the mCCI-A showed modest but significant increases in **c** statistics compared with the CCI. The analyses using continuous net reclassification improvement(cNRI) revealed that the mCCI-A improved net mortality risk reclassification by 23.1% (95% CI, 22.0-24.3; P<0.001).

Conclusions: The mCCI-A facilitates better risk stratification for mortality in Korean inpatients compared with the CCI, suggesting that it may be a preferred index for use in clinical practice and the statistical analysis of epidemiological studies.

FR-PO509

Self-Reported Sleep Problems and Mortality among US Adults with and without CKD: NHANES 2007-2010 Monica Shieu,[5] Jennifer L. Bragg-Gresham,[5] Hal Morgenstern,[5] Delphine S. Tuot,[4] Deborah Rolka,[1] Nilka Rios Burrows,[2] Neil R. Powe,[3] Rajiv Saran.[5] *[1]CDC, Atlanta, AL; [2]Centers for Disease Control and Prevention, Atlanta, GA; [3]Priscilla Chan and Mark Zuckerberg San Francisco General Hospital & University of California SF, San Francisco, CA; [4]University of California, San Francisco, San Francisco, CA; [5]University of Michigan, Ann Arbor, MI.*

Background: Sleep problems are associated with several medical conditions including kidney disease. However, little research has been done assessing associations of sleep problems with mortality. We estimated the effects of self-reported sleep problems on mortality, by CKD status, among nationally representative, US adults.

Methods: A sample of 11,338 adults, ages 20+, from the mortality-linked National Health and Nutrition Examination Survey (NHANES; 2007-2010) with complete data on estimated glomerular filtration rate (eGFR) and urine albumin-to-creatinine ratio (UACR) were included in the analysis. Data on self-reported sleep problems were obtained from questionnaires. CKD was defined as eGFR < 60 ml/min/1.73 m^2 or UACR > 30 mg/g. Cox regression, stratified by CKD status, was used to estimate hazard ratios (HR; 95% CIs) for mortality over a median of 34 months of follow-up, adjusting for survey year, age, sex, and race/ethnicity. A combined model including all the subjects was investigated (not shown) to test for differences in associations by CKD status.

Results: Self-reported sleep problems were common among participants with CKD. Among individuals with CKD, 4 of the 5 sleep problems were positively associated with mortality, adjusting for demographic factors (table). For diagnosed sleep disorders and <6 hours sleep per night, these associations in CKD patients were stronger than in persons without CKD (though both p-values for interaction were >0.15). Nocturia and >9 hours of sleep were associated with mortality in patients with and without CKD.

Conclusions: If these findings are replicated in other studies with more extensive control for confounders, especially among CKD patients, efforts should be made to understand if ameliorating sleep problems improves wellbeing and survival.

Sleep Outcome (With problems vs. no problems)	No CKD (n=9352)			CKD (n=2036)		
	**Prevalence (%)	Crude HR (95% CI)	*Adjusted HR (95% CI)	**Prevalence (%)	Crude HR (95% CI)	*Adjusted HR (95% CI)
Ever told a doctor of having trouble sleeping	23.8	1.3 (0.89, 1.9)	1.2 (0.82, 1.6)	31.6	0.83 (0.55, 1.3)	0.96 (0.63, 1.5)
Ever been told by a doctor of having sleep disorder	7.1	1.3 (0.59, 3.0)	1.1 (0.48, 2.5)	10.7	1.3 (0.85, 2.00)	1.5 (0.94, 2.3)
Nocturia	21.9	3.2 (2.2, 4.6)	1.7 (1.1, 2.5)	42.6	2.2 (1.3, 3.7)	1.5 (0.90, 2.5)
Sleep amount (hours)						
Inadequate (<6)	13.6	0.95 (0.55, 1.7)	1.0 (0.60, 1.7)	15.2	1.4 (0.86, 2.4)	1.5 (0.91, 2.6)
Normal (6-9)	84.7	1.00 (ref)	1.00 (ref)	79.9	1.00 (ref)	1.00 (ref)
Excessive (>9)	4.9	4.0 (2.2, 7.4)	3.4 (1.9, 6.3)	1.7	3.2 (2.1, 4.7)	2.5 (1.6, 3.6)

**Weighted with appropriate sampling weights, *Adjusted for survey year, age, sex, race/ethnicity

FR-PO510

Association of Chronic Insomnia with Mortality and Adverse Renal Outcomes Jun Ling Lu,[3] Amado X. Freire,[1] Miklos Z. Molnar,[3] Kamyar Kalantar-Zadeh,[2] Csaba P. Kovesdy.[3] *[1]UTHSC at Memphis, Memphis, TN; [2]University of California Irvine, School of Medicine, Orange, CA; [3]University of Tennessee Health Science Center, Memphis, TN.*

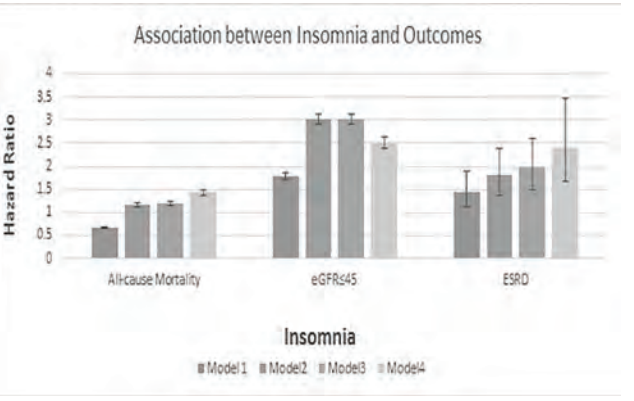
Background: Chronic insomnia is highly prevalent in the world. Its effects on the sympatho-adrenal system could potentially worsen hypertension and cause metabolic abnormalities. However, there is lack of evidence of the association between insomnia and adverse renal outcomes.

Methods: We examined associations of chronic insomnia (defined as the presence of ICD9 codes 307.42, 307.49 and 780.52 and long-term use of insomnia medications) with all-cause mortality and renal outcomes, (ESRD, incidence of eGFR <45 ml/min/1.73m^2, and eGFR slopes <-3.0 ml/min/1.73m^2) in a national cohort of 957,587 US veterans with baseline estimated eGFR >60 ml/min/1.73m^2. Associations were examined in Cox proportional hazards models and logistic regressions. Besides crude models (model 1), adjustments were made for demographics and baseline estimated GFR (model 2), BMI and blood pressure (Model 3), comorbidities, antihypertensive drugs, and social-economic status (Model 4).

Results: 41,928 patients (4.4%) had chronic insomnia. Over a 6.1-year median follow-up period, 23.1% of patients died [mortality rate: 39.4/1000 patient-years (PY)], 0.2% reached ESRD (event rate: 0.2/1000PY), 6.6% of them progressed to eGFR <45 (event rate: 11.6/1000PY), and 2.7% displayed rapid progression. Insomnia was associated with higher risk of all-cause mortality (hazard ratio (HR):1.43 [95%CI:1.37, 1.48], p<0.001), incidence of eGFR <45ml/min/1.73m^2 (HR: 2.51 [95%CI:2.39, 2.64], p<0.001), ESRD (HR: 2.41 [95%CI:1.66, 3.48], p<0.001), and rapid loss of kidney function (odds ratio: 1.46[95%CI: 1.33, 1.62], p<0.001) [Figure].

Conclusions: Chronic insomnia is associated with higher risk of all-cause mortality, incident CKD and progressive loss of kidney function. Further studies are needed to determine if interventions to alleviate insomnia could improve clinical outcomes.

Funding: NIDDK Support



FR-PO511

The Risk of Adverse Events in Polycystic Kidney Disease Patients with Advanced CKD Manish M. Sood,[1] Sonali N. De chickera,[4] Adeera Levin,[3] Mila Tang,[2] Ayub Akbari.[5] *[1]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [2]St. Paul's Hospital, Vancouver, AB, Canada; [3]St. Paul's Hospital and University of British Columbia, Vancouver, BC, Canada; [4]The Ottawa Hospital - University of Ottawa, Ottawa, ON, Canada; [5]University of Ottawa, Ottawa, ON, Canada.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) leads to progressive chronic kidney disease (CKD) with a subsequent increasing risk of adverse events such as cardiovascular disease (CV), infections, end-stage kidney disease (ESKD) and mortality. To date limited information exists regarding the risks of adverse events in ADPKD patients with advanced CKD. The objective of this study was to determine the risks of CKD-related adverse outcomes in ADPKD patients compared to non-ADPKD patients.

Methods: We examined data from the Canadian Study of Prediction of Death, Dialysis and Interim Cardiovascular Events (CanPREDDICT) cohort. CanPREDDICT was a prospective pan-Canadian cohort study from 2008-2013 involving 28 facilities caring for patients with advanced CKD (eGFR=15-45 ml/min/1.73m^2) with adjudicated outcomes. We used Cox proportional hazards and Fine and Gray models to examine the risk of CV (defined as coronary artery disease or CHF), infection, ESKD, or all-cause mortality in a propensity-score matched (4:1) cohort of non-ADPKD and ADPKD patients.

Results: Among a total of 2,370 patients, 105 with ADPKD were matched with 416 non-ADPKD patients with a baseline mean age and eGFR of 62.6 (SD 14.0) years and 27.8 (SD 9.0) mls/min/1.73m^2, respectively. During a total of 1,680 person-years of follow time (median follow-up 3.8 years), there were a total of 43 CV, 83 ESKD, 117 infectious and 39 all-cause mortality events. ADPKD was associated with a higher risk of cardiovascular events (9.5% vs. 7.9%, HR 1.46 95%CI 1.04-2.04) and ESKD (25.7% vs 13.5%, HR 2.00 95%CI 1.33-3.01), and with similar risks for infection (21.9% vs 22.6%, HR 1.16 95%CI 0.75-1.82) or all-cause mortality (6.7% vs 7.7%, HR 0.87 95%CI 0.40-1.91) compared to non-ADPKD. There were no differences in the types of infections (urinary, respiratory, hematologic or other) between the two groups (p=0.585).

Conclusions: ADPKD patients with advanced CKD are at higher risk of ESKD and cardiovascular events compared to non-ADPKD patients. These findings suggest that judicious monitoring, screening and treatment for adverse outcomes in ADPKD patients, especially related to cardiovascular disease, may be beneficial.

FR-PO512

Renal Resistive Index and Systematic Arterial Stiffness in the General Population Xiaohong Fan, Xuemei Li. *Peking Union Medical College Hospital, Chinese Academy of Medicine Sciences & Peking Union Medical College, Peiking, China.*

Background: Recent studies show that increased renal resistive index (RRI) is associated with kidney disease progression and cardiovascular disease (CVD). Greater arterial stiffness is also considered to be an independent predictor for CVD onset and associated with steeper decline in kidney function. RRI is presumed to be dependent on systematic vascular changes; however, the data about arterial stiffness and RRI is limited.

Methods: This study consisted of 3589 subjects ages between 35 and 85, recruited for a cross-sectional health survey in Pinggu, a suburb of Beijing, China in 2014. All subjects underwent assessment of ultrasonographic RRI and measurement of brachial-ankle pulse wave velocity (baPWV). Multiple linear regression modeling was performed to explore the RRI risk factors and the relationship between RRI and baPWV.

Results: The mean age of the study population was 53.7±9.1 years, 48.7% were males. RRI was positively associated with age (r=0.43; *P*<0.001). RRI in women was significantly higher than that in men (0.62±0.05 vs. 0.60±0.06; *P*<0.001) at all age groups, the sex difference existed even when adjusting for other factors. In all participants, baPWV was independently associated with increased RRI in multivariable analyses after adjustment for potential confounders. The other determinants of RRI in the general

population were age, sex, systolic and diastolic blood pressure, body mass index, estimate glomerular filtration rate and hemoglobin A1c(Table 1).

Conclusions: There was significantly association between systematic arterial stiffness and interenal RRI. The sex difference affect needs to be investigated in the future.

Funding: Government Support - Non-U.S.

Table 1: BaPWV was significantly associated with increased renal resistive index.

Variables	All participants(n=3598)			
	beta	95% CI		P value
Gender,Female vs. Male	0.023	0.020	0.026	<0.0001
baPWV, per 1 m/s	0.001	0.0004	0.0018	0.001
age,per 1y	0.002	0.0017	0.0021	<0.0001
BMI, per 1Kg/m2	0.0007	0.0002	0.0011	0.003
SBP, per 1mmHg	0.001	0.0009	0.0011	<0.0001
DBP, per 1mmHg	-0.001	-0.0021	-0.0018	<0.0001
eGFR, per 1ml/min/1.73m2	0.0002	0.00008	0.0004	0.004
HbA1c, per 1%	0.004	0.003	0.006	<0.0001

FR-PO513

The Association between Plasma PCSK9 Concentrations and CKD Ha yeon Kim,[2] Eun Hui Bae,[1] Seong Kwon Ma,[2] Soo Wan Kim.[2] *[1]Chonnam National University Hospital, Gwangju, Republic of Korea; [2]Chonnam National University Medical School, Gwangju, Republic of Korea.*

Background: Dyslipidemia commonly appear in patients with chronic kidney disease (CKD) presenting with unique characteristics. The proprotein convertase subtilisin/kexin type 9 (PCSK9) is a regulator of the low-density lipoprotein receptor and plasma cholesterol concentrations. We studied the association of circulating PCSK9 concentrations with both estimated glomerular filtration rate (eGFR) and serum lipid parameters in patients at different stage of CKD.

Methods: We evaluated plasma PCSK9 concentrations measured by ELISA in 90 non-dialysis patients at different stage of CKD. We assessed their lipid profile including total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), urine albumin creatinine ratio (UACR), C-reactive protein (CRP), use of statins or fibrate, presence of hypertension, diabetes, chronic kidney disease, smoking, malignancy and coronary artery disease.

Results: The mean plasma level of PCSK9 was 309.7 ± 74.6 ng/ml in the 90 patients. Plasma PCSK9 concentration has a positive correlation with UACR (r=0.261, *P* =0.029) and triglyceride (r = 0.316, *P* = 0.007), but not with total cholesterol (*P* =0.142), eGFR (*P* =0.058), HDL-C (*P* =0.319), LDL-C (*P* =0.101), ApoA1 (*P* =0.380), ApoB (*P* =0.805), ApoA1/B (*P* =0.893) and CRP (*P* =0.457). In the patients with UACR ≥ 1g/gCr, plasma PCSK9 levels increase compared to patient with UACR <1g/gCr, (361.9 ± 60.3 ng/ml vs. 299.3 ± 73.2 ng/ml, *P* =0.008). Plasma PCSK9 level was independently associated with existence of diabetes and statin/fibrate medication. The concentrations of PCSK9 according to CKD stages were 273.0 ± 56.5 ng/ml in the CKD stage 1, 317.5 ± 98.4 ng/ml in the CKD stage 2, 306.6 ± 68.7 ng/ml in the CKD stage 3, 333.1 ± 85.6 ng/ml in the CKD stage 4, and 306.0 ± 64.3 ng/ml in the CKD stage 5 without dialysis, respectively. The levels of PCSK9 in patients with CKD stage 1 were lower than those of other stages (*P* = 0.032).

Conclusions: Plasma PCSK9 concentrations are related to proteinuria, but not associated to eGFR in patient with CKD.

FR-PO514

The Risk of Venous Thromboembolism in Patients with Albuminuria and Normal or Reduced Kidney Function David Massicotte-Azarniouch,[3] Anan Bader eddeen,[8] Alejandro Lazo-Langner,[7] Amber O. Molnar,[2] Ngan Lam,[6] Deborah Lynn Zimmerman,[4] Amit X. Garg,[1] Ziv Harel,[3] Jeffrey Perl,[5] Ron Wald,[5] Manish M. Sood.[4] *[1]London Health Sciences Centre, London, ON, Canada; [2]McMaster University, Hamilton, ON, Canada; [3]None, Ottawa, ON, Canada; [4]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [5]St. Michael's Hospital, Toronto, ON, Canada; [6]University of Alberta, Edmonton, AB, Canada; [7]Western University, London, ON, Canada; [8]Istitution for Clinical Evaluative Sciences, Ottawa, ON, Canada.*

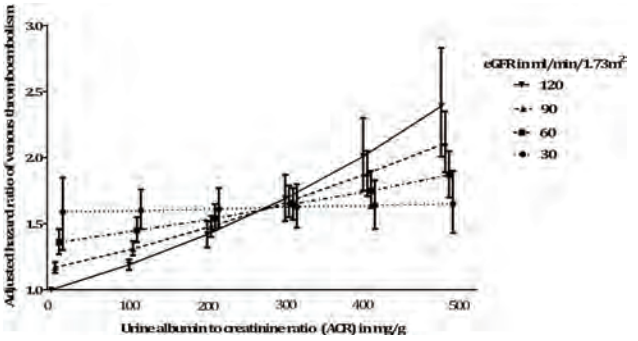
Background: Chronic kidney disease (CKD), defined by the presence of either albuminuria and/or reduced kidney function, is associated with a higher risk of venous thromboembolism (VTE). Whether the risk of VTE differs in CKD patients with albuminuria and normal or reduced kidney function remains unclear.

Methods: We conducted a retrospective population-based cohort study of 694, 956 patients in Ontario, Canada between 2002 and 2012. We included patients with a measurement of albuminuria (albumin-to-creatinine ratio, ACR) and serum creatinine (for estimated glomerular filtration rate, eGFR). The primary outcome was the time to a first VTE event examined across differing levels of albuminuria and kidney function using adjusted Cox proportional hazard models and accounting for the competing risk of death.

Results: A total of 15,180 (2.2%) VTE events occurred during the study period. Both albuminuria and kidney function were independently associated with VTE (p<0.0001). The association of albuminuria and VTE differed by the level of kidney function (ACR X eGFR interaction p=0.0001). The risk of VTE in patients with normal kidney function (eGFR 120 mL/min/1.73 m^2) and heavy albuminuria (ACR 500 mg/g) was HR 2.39 (95% CI 2.01-2.83) compared to those with normal kidney function and no albuminuria. Among those with reduced kidney function (eGFR 30 mL/min/1.73 m^2), the risk of VTE was increased, irrespective of albuminuria [ACR 0 vs. ACR 500 mg/g: HR 1.59 vs. 1.65).

Conclusions: Albuminuria increases the risk of VTE markedly in patient with normal kidney function but does not in those with reduced kidney function.

Funding: Government Support - Non-U.S.



Adjusted hazard ratio of venous thromboembolism by albuminuria at fixed levels of kidney function

FR-PO515

High Protein Intake Is Associated with Higher Mortality in Patients with Non-Dialysis Dependent CKD Jawed Akhtar,[2] Mahmoud A. Mahmoud,[2] Faisal M. Arif,[2] Angela M. Wallick,[1] Kamyar Kalantar-Zadeh,[3] Miklos Z. Molnar,[2] Barry M. Wall,[2] Csaba P. Kovesdy.[2] *[1]Department of Veterans Affairs, Memphis, TN; [2]University of Tennessee Health Science Center, Memphis, TN; [3]University of California Irvine, School of Medicine, Orange, CA.*

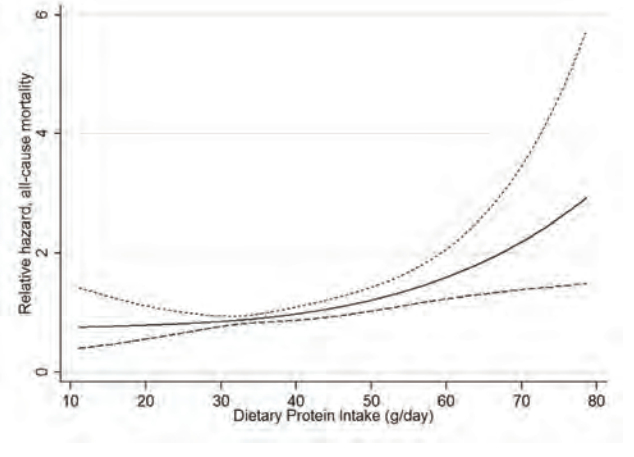
Background: High protein intake is associated with worse progression of CKD in patients with non-dialysis dependent CKD (NDD-CKD), but its effects on mortality are unclear.

Methods: We examined 854 NDD-CKD US veterans followed at a tertiary medical center. We estimated dietary protein intake (DPI) from urea nitrogen and creatinine measured from morning spot urine collections and using the Maroni formula. The associations of baseline DPI (analyzed as a continuous variable using splines, and divided into quartiles) with all-cause mortality was examined in Cox models adjusted for demographics, comorbidities, medication use, baseline estimated GFR and proteinuria.

Results: Patients were 66±11 years old, 96% were men, 59% were African American and 55% were diabetic. The baseline estimated GFR was 38±21 ml/min/1.73m^2. Higher DPI was associated with higher mortality (Figure). Compared to the second quartile, the hazard ratios (95%CI) of mortality associated with quartiles 1, 3 and 4 of DPI were 1.24 (0.76-2.01), 1.41 (0.88-2.26) and 2.17 (1.38-3.37), respectively.

Conclusions: In patients with moderate and advanced NDD-CKD, high DPI is associated with higher all-cause mortality. Further studies are needed to determine the amount of DPI providing optimal outcomes in this patient population.

Funding: NIDDK Support



FR-PO516

Caffeine Consumption and Mortality in CKD Miguel Bigotte Vieira,[1] Rita Magriço,[2] Catarina Viegas dias,[3] Lia Leitão,[4] João Sérgio Neves.[5] *[1]Nephrology and Renal Transplantation Department, Centro Hospitalar Lisboa Norte, Lisboa, Portugal; [2]Nephrology Department, Hospital Garcia de Orta, Almada, Portugal; [3]Dafundo Family Health Unit, Lisbon, Portugal; [4]Neurology Department, Hospital Prof. Doutor Fernando Fonseca, Amadora, Portugal; [5]Department of Endocrinology, Diabetes and Metabolism, São João Hospital, Faculty of Medicine, University of Porto, Portugal, Porto, Portugal.*

Background: An inverse relationship between coffee consumption and mortality has been reported in the general population. However, the association between caffeine consumption and mortality in patients with CKD remains unclear.

Methods: We examined the association of caffeine consumption with mortality among 2328 patients with CKD (defined by estimated GFR < 60 mL/min/1.73m^2, CKD-EPI) in a prospective nationwide cohort, using the continuous National Health and Nutrition Examination Survey (NHANES) 1999-2010. Caffeine consumption was assessed at baseline using 24-hour dietary recalls. Cox proportional hazard models were fitted to estimate hazard ratios (HR) for all-cause mortality according to quartiles of caffeine consumption, adjusting for potential confounders (age, gender, race, annual family income, education level, estimated GFR, albumin/creatinine ratio, hypertension, smoking status, dyslipidemia, body mass index, previous cardiovascular events and diet: consumption of alcohol, carbohydrates, polyunsaturated fatty acids and fibers). We assessed the extent to which CKD stage modified the effects of caffeine consumption on mortality with likelihood ratio tests for interaction.

Results: Quartiles of caffeine consumption were: 1st quartile (<29.5 mg of caffeine/day), 2nd (30.5 to 101.0 mg/day), 3rd (101.5 to 206.0 mg/day), and 4th quartile (206.5 to 1378.5 mg/day). A dose-dependent inverse association between caffeine and all-cause mortality was observed in patients with CKD. Comparing with 1st quartile of caffeine consumption, adjusted HR for death was 0.88 (95% CI, 0.68-1.44) for 2nd quartile, 0.78 (95% CI, 0.60-1.01) for 3rd quartile and 0.76 (95% CI, 0.59-0.97) for 4th quartile (p=0.027 for trend across quartiles). There were no significant interactions between caffeine consumption quartiles and CKD stages with respect to all-cause mortality.

Conclusions: Our study showed a dose-dependent protective effect of caffeine consumption on mortality among patients with CKD.

FR-PO517

The Effect of High Alcohol Consumption on Incidence of Proteinuria Was Different by Gender: A Retrospective Cohort Study Yoshiki Kimrua,[1] Ryohei Yamamoto,[2,1] Yoshitaka Isaka,[1] Kunitoshi Iseki,[3] Kunihiro Yamagata,[3] Kazuhiko Tsuruya,[3] Hideaki Yoshida,[3] Shouichi Fujimoto,[3] Koichi Asahi,[3] Toshiki Moriyama,[2,3] Tsuyoshi Watanabe.[3] *[1]Department of Nephrology, Osaka University Graduate School of Medicine, Suita, Japan; [2]Health and Counseling Center Osaka University, Toyonaka, Japan; [3]Steering Committee for the Research on the Positioning of Chronic Kidney Disease in Specific Health Check and Guidance in Japan, Fukushima, Japan.*

Background: Several studies reported that mild to moderate alcohol consumption reduced the risk of proteinuria, whereas a proteinuric effect of heavy alcohol consumption is controversial. The aim of this retrospective cohort study was to assess an association between high alcohol consumption and the incidence of proteinuria in males and females.

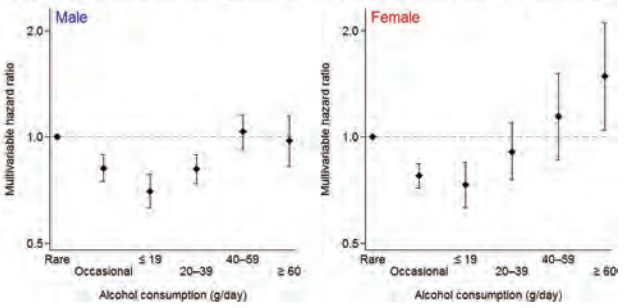
Methods: Participants who underwent annual health check examinations in Japan with dipstick urinary protein ≤± and/or eGFR <60 mL/min/1.73m^2 at their first examinations between 2008 and 2011 were included in this analysis. Main exposure was alcohol consumption categories defined as rare, occasional and daily drinkers with ≤19, 20-39, 40-59 and ≥60 g/day. The outcome was time to first incidence of proteinuria (dipstick urinary protein ≥1+). An association between alcohol consumption and incidence of proteinuria was assessed using Cox proportional hazards models.

Results: Background of participants in 78,327 males and 78,369 females; age 65 [57-69] (median [25%-75%]) and 64 [59-69] years; eGFR 75 [69-86] and 76 [68-90] ml/min/1.73m^2; respectively. Incidence of proteinuria was observed in 4,991 males and 3,040 females during 1.9 (1.0-2.1) years of the observational period. The association between alcohol consumption and incidence of proteinuria was U-shaped in males and J-shaped in females (Figure).

Conclusions: The effect of high alcohol consumption on incidence of proteinuria was different between males and females. The association was J-shaped in female and U-shape in males, respectively, suggesting that females were more vulnerable to alcohol than males.

Funding: Government Support - Non-U.S.

Figure. Association between alcohol consumption and incidence of proteinuria.



FR-PO518

Cannabis Use and Its Association with Clinical Characteristics and Post-ESRD Mortality Praveen Kumar Potukuchi,[4] Keiichi Sumida,[2] Miklos Z. Molnar,[4] Abduzhappar Gaipov,[4] Frank Park,[4] Hamid Moradi,[3] Fridtjof Thomas,[4] Elani Streja,[1] Melissa Soohoo,[3] Kamyar Kalantar-Zadeh,[3] Csaba P. Kovesdy.[4] *[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [2]Nephrology Center, Toranomon Hospital Kajigaya, Kawasaki, Japan; [3]University of California Irvine, School of Medicine, Orange, CA; [4]University of Tennessee Health Science Center, Memphis, TN.*

Background: The health effects of cannabis use in patients with advanced CKD are unknown.

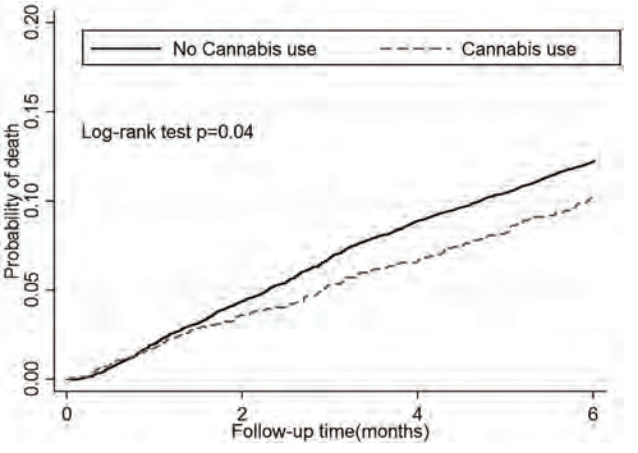
Methods: In 11,154 US veterans who transitioned to dialysis during 2007-2014 and had undergone urine toxicology tests (1,381 who tested positive for cannabis, and 9,773 who tested negative for cannabis), we examined the association of cannabis use with various clinical characteristics using logistic regressions and with 6-month all-cause mortality using multivariable adjusted Cox models.

Results: The mean (SD) age of the cohort was 61.9 (9.7) years; 97% were male, 45 % were African American and 69% were diabetic. Cannabis use was associated with younger age, higher mean pre-ESRD eGFR, unmarried status, smoking, cancer, liver disease, HIV and with the prescription of opioids and antidepressants (Table). Patients who tested positive for cannabis displayed lower mortality than patients who tested negative [Figure, unadjusted hazard ratio (95% CI): 0.83(0.7-0.99)], but the survival advantage was attenuated after multivariable adjustments [1.06 (0.86-1.31), p=0.6].

Conclusions: Among patients who underwent toxicology testing, cannabis use during the pre-ESRD period is associated with lower all-cause mortality in the immediate post-ESRD period. However, this association mitigates when adjusted for patient characteristics.

Funding: NIDDK Support

	Cannabis use yes vs no OR, (95% CI)
Age at dialysis	0.96 (0.95–0.97)
eGFR	1.01 (1.01–1.01)
Single vs married	1.29 (1.04–1.60)
Divorced vs married	1.47 (1.25–1.72)
Smoking	1.95 (1.62–2.35)
Cancer	1.51 (1.11–2.06)
Liver disease	2.03 (1.64–2.50)
HIV	3.00 (1.46–6.18)
Opioid use	1.45 (1.17–1.79)
Antidepressants use	1.51 (1.27–1.80)



FR-PO519

Iron Status and Mortality Risk in Diabetic and Non-Diabetic Veterans with CKD Monique E. Cho,[1,2] Jared Hansen,[1] Celena B. Peters,[1] Brian C. Sauer.[1,2] *[1]Veterans Health Administration, Salt Lake City, UT; [2]University of Utah, Salt Lake City, UT.*

Background: The mortality risk associated with abnormal iron balance has not been compared between diabetic and non-diabetic CKD populations.

Methods: We performed a historical cohort study using the Veterans Affairs Informatics and Computing Infrastructure. We identified a pre-dialysis CKD cohort (MDRD eGFR <60 mL/min/1.73m^2) with at least one set of iron indices between 2006-2015. The clinical characteristics were determined from the ICD-9 codes and laboratory data during the *baseline period*, defined as the year preceding the first available iron indices. Patients with ESRD, genetic and chronic disorders affecting iron metabolism were excluded. The cohort was divided into 4 iron groups based on the joint quartiles (Q) of transferrin saturation (Tsat) and ferritin: functional iron deficiency (FID), 1st Tsat Q + 3rd–4th ferritin Qs; Low Iron (LI), 1st Tsat+ferritin Qs; High Iron (HI), 4th Tsat+ferritin Qs; and Reference (R), 2nd–3rd Tsat+ferritin Qs. Matching weights were used to determine the effects of FID, HI, and LI on all-cause mortality, using R as the reference. Diabetes was examined as a potential effect modifier.

Results: Of the 1,159,371 Veterans with CKD, 148,611 met the inclusion criteria. The mean±SD for age and eGFR were 72±11 years and 43±11 mL/min/1.73 m^2, respectively. The median (IQR) Tsat and ferritin values were 20 (14, 26)% and 119 (64, 196) ng/mL. Of the study cohort, 42% could not be categorized into any of the 4 iron groups. In the remaining 83,439 Veterans, the prevalence for FID, HI, LI, and R were 13%, 17%, 20%, and 50%, respectively. After matching weights were implemented, the covariates were evenly distributed among the iron groups. During the mean±SD follow-up period of 4.0±2.7 years, FID exhibited the greatest risk for all-cause mortality [Risk Ratio, RR (95% CI): 1.21 (1.17, 1.25)], after being stratified by the diabetes status and matching for age, sex, race, BMI, dyslipidemia, eGFR, albumin, hemoglobin, eGFR, and CV history. The RRs for mortality with HI and LI were similarly increased, 1.09 (1.06, 1.13). The association between iron status and mortality risk was not modified by the diabetes status.

Conclusions: Abnormal iron status, particularly FID, is associated with increased all-cause mortality risk in pre-dialysis CKD, regardless of the diabetes status. Further studies are needed to investigate the underlying mechanism.

Funding: Veterans Affairs Support, Private Foundation Support

FR-PO520

Iron Status and the Risk of Incident ESRD in Veterans with CKD Monique E. Cho,[1,2] Jared Hansen,[1] Celena B. Peters,[1] Brian C. Sauer.[1,2] *[1]Veterans Health Administration, Salt Lake City, UT; [2]University of Utah, Salt Lake City, UT.*

Background: The risk for CKD progression associated with abnormal iron balance has not been evaluated in a large CKD population.

Methods: We performed a historical cohort study using the national data from the Veterans Affairs Informatics and Computing Infrastructure. We identified a pre-dialysis CKD cohort (MDRD eGFR <60 mL/min/1.73m^2) with at least one set of iron indices between 2006-2015. The clinical characteristics were determined from the ICD-9 codes and laboratory data during the *baseline period*, defined as the year preceding the first available iron indices. Patients with ESRD, genetic, and chronic disorders affecting iron metabolism were excluded. The cohort was divided into 4 iron groups based on the joint quartiles (Q) of transferrin saturation (Tsat) and ferritin: functional iron deficiency (FID), 1st Tsat Q + 3rd–4th ferritin Qs; Low Iron (LI), 1st Tsat+ferritin Qs; High Iron (HI), 4th Tsat+ferritin Qs; and Reference (R), 2nd–3rd Tsat+ferritin Qs. Incident ESRD was determined by the diagnosis and procedure codes reflecting renal transplantation or dialysis. Matching weights were used to determine the effects of FID, HI, and LI on incident ESRD, using R as the reference. Diabetes was examined as a potential effect modifier.

Results: Of the 1,159,371 Veterans with CKD, 148,611 met the inclusion criteria. The mean±SD for age and eGFR were 72±11 years and 43±11 mL/min/1.73 m^2, respectively. The median (IQR) Tsat and ferritin values were 20 (14, 26)% and 119 (64, 196) ng/mL. Of the study cohort, 42% could not be categorized into any of the 4 iron groups. In the remaining 83,439 Veterans, the prevalence for FID, HI, LI, and R were 13%, 17%, 20%, and 50%, respectively. After matching weights were implemented, the clinical covariates were evenly distributed among the iron groups. During the mean±SD follow-up period of 4.0±2.7 years, only HI exhibited increased risk for ESRD, [risk ratio, RR (95% CI): 1.16 (1.10, 1.23)]. The RRs for FID and LI were 0.97 (0.91, 1.03) and 0.78 (0.73, 0.83), respectively. The association between iron status and ESRD risk was not altered by the diabetes status.

Conclusions: High iron status is associated with increased risk for incident ESRD in CKD, while iron deficiency is associated with reduced risk for ESRD. Diabetes was not found to be an effect modifier. Further studies are required to confirm the finding and to investigate the underlying mechanisms.

Funding: Veterans Affairs Support, Private Foundation Support

FR-PO521

Functional Iron Deficiency and Incident Diabetes Risk in US Veterans with Pre-Dialysis CKD Monique E. Cho,[1,2] Jared Hansen,[1] Celena B. Peters,[1] Brian C. Sauer.[1,2] *[1]Veterans Health Administration, Salt Lake City, UT; [2]University of Utah, Salt Lake City, UT.*

Background: While the association between iron overload and diabetes is well established, the possible adverse metabolic effect of iron deficiency, both functional and absolute, has not been investigated in any population, including those with CKD.

Methods: We performed a historical cohort study using the national data from the Veterans Affairs Informatics and Computing Infrastructure. We identified a non-diabetic, pre-dialysis CKD cohort (MDRD eGFR <60 mL/min/1.73m^2) with at least one set of iron indices between 2006-2015. The clinical characteristics were determined from the ICD-9 codes and laboratory data during the *baseline period*, defined as the year preceding the first available iron indices. Patients with diabetes, ESRD, genetic and chronic disorders affecting iron metabolism were excluded. The cohort was divided into 4 iron groups based on the joint quartiles (Q) of transferrin saturation (Tsat) and ferritin: FID, 1st Tsat Q + 3rd–4th ferritin Qs; Low Iron (LI) reflecting absolute iron deficiency, 1st Tsat+ferritin Qs; High Iron (HI), 4th Tsat+ferritin Qs; and Reference (R), 2nd–3rd Tsat+ferritin Qs. Incident diabetes was determined by the ICD-9 codes. Matching weights were used to determine the effect of iron status on incident diabetes, using R as the comparison group.

Results: Of the 1,159,371 Veterans with CKD, 68,728 met the inclusion criteria. The mean±SD for age and eGFR were 74±12 years and 43±11 mL/min/1.73 m^2, respectively. The median (IQR) Tsat and ferritin values were 18 (13, 23)% and 98 (53, 150) ng/mL. Of the study cohort, 44% could not be categorized into any of the 4 iron groups. In the remaining 38,428 Veterans, the prevalence for FID, HI, LI, and R were 12%, 21%, 20%, and 47%, respectively. After matching weights were implemented, the covariates were evenly distributed among the iron groups. During the mean±SD follow-up period of 4.0±2.7 years, only FID was associated with increased risk for incident diabetes [Risk Ratio, RR (95% CI), 1.20 (1.09, 1.33)], after successful matching for age, sex, race, BMI, hyperlipidemia, CV history, albumin, hemoglobin, and eGFR. The RRs for HI and LI were 0.98 (0.90, 1.07)] and 1.04 (0.95, 1.13), respectively.

Conclusions: FID, but not absolute iron deficiency, is associated with increased risk for incident diabetes in CKD. Further studies are needed to investigate the underlying mechanisms.

Funding: Veterans Affairs Support, Private Foundation Support

FR-PO522

Review of Safety of IV Iron Therapy in Patients with Non-Dialysis CKD (CKD-ND) Vikki M. Meyer,[1] Richard P. Cooper,[3] Sunil Bhandari.[2] *[1]HEY Hospitals, HULL, United Kingdom; [2]Hull and East Yorkshire Hospitals NHS Trust and Hull York Medical School, East Yorkshire, United Kingdom; [3]Hull and East Yorkshire NHS Trust, Hull, United Kingdom.*

Background: Anaemia in patients with Chronic Kidney Disease not on dialysis therapy (CKD-ND) is common, and often necessitates the use of intravenous iron products to correct both functional and absolute iron deficiency and iron deficiency anaemia. There has been a large increase in use but concerns on safety have been correctly raised. JAMA highlighted a high rate of '*anaphylaxis*' in parenteral iron administration and mortality related to anaphylaxis. Short term reactions are known to occur including acute anaphylactic and labile iron reactions (*Fishbane effect*) while longer term effects include elevated oxidative stress, possible increased risk of infections, and risk of iron overload.

Methods: This retrospective observational single-centre study, examined our experience of short term adverse effects with parenteral iron administration in CKD-ND using two preparations, MonoFer and CosmoFer. Our database recorded patients' demographics, iron administered, baseline haemoglobin, iron parameters, clinical observations and side effects. A total of 909 doses of MonoFer (1g-1.5g) and 870 doses of CosmoFer (1g-1.5g) were administered to 1271 patients with a mean age of 68.67y for CosmoFer and 65.56y for MonoFer, with no known allergies.

Results: CosmoFer: a total of 1 anaphylactic event in 870 doses (0.11%) occurred and infusion discontinued due to hypotension and respiratory distress. Other reactions consisted of headache (2), diarrhoea (1), vomiting (1), flushing (2) and numbness (1). MonoFer: a total of 5 reactions, vomiting (1), lethargy (1), constipation (1), flare up eczema (1) and one collapse requiring discontinuation of infusion, hydrocortisone, oxygen support, but no other intervention. Reactions requiring drug discontinuation were CosmoFer, 1 in 870 doses; and MonoFer, 1 in 909 doses, which incidentally was the same patient in both cases.

Conclusions: Hyper-sensitivity reactions can occur in anyone receiving intravenous iron and at any time. Vigilance during administration is important and in the immediate 30 minutes following the infusion as per EMA guidelines. At present the balance between the benefits and the risks remains in favour of iron administration and patients should be reassured until new data is available but care should be taken. More studies are required to delineate the short and longer term safety of iron therapy.

Funding: Government Support - Non-U.S.

FR-PO523

Serum Fibroblast Growth Factor-23 Levels Are Associated with an Increased Risk of Developing Anemia in Patients with Non-Dialysis CKD Ki Heon Nam, Seong yeong An, Jong Hyun Jhee, Seohyun Park, Seung Hyeok Han, Dae-Suk Han. *Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea*.

Background: Fibroblast growth factor-23 (FGF23) is an established biomarker of adverse outcomes in patients with chronic kidney disease (CKD). Several cross-sectional studies have suggested possible association between FGF23 and anemia in these patients. Thus, we further explored this relationship and examined whether FGF23 level can predict the future development of anemia in a large-scale prospective cohort study.

Methods: Among 2,238 patients with non-dialysis CKD enrolled in the KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD), 2,089 patients who measured hemoglobin, hepcidin, iron profiles and intact FGF23 (iFGF23) level were included in the analysis. Anemia was defined as a hemoglobin level of < 13.0 g/dL and 12.0 g/dL for male and female, respectively.

Results: The mean age was 53.6 ± 12.2 years and 1,275 (61.0%) patients were males. At baseline, anemia was found in 925 (44.3%) patients. Log iFGF23 significantly correlated with hepcidin, but inversely with iron profiles and hemoglobin. A multivariate logistic regression model showed that log iFGF23 was independently associated with anemia (odds ratio [OR], 1.12; 95% confidence interval [CI], 1.03-1.23, P=0.01). Among 1164 patients without baseline anemia, 295 (25.3%) patients developed anemia during a median follow-up duration of 21 (interquartile range, 7-38) months. In the fully adjusted multivariable Cox models, risk of developing anemia was significantly higher in the 3rd (hazard ratio [HR], 1.74; 95% CI, 1.17-2.59; P =0.007) and 4th (HR, 1.73; 95% CI, 1.15-2.59; P= 0.02) quartile of iFGF23 as compared to the 1st quartile. Similar association was observed in a model when iFGF23 was treated as a continuous variable.

Conclusions: We showed that high serum iFGF23 levels are associated with an increased risk of developing anemia in patients with non-dialysis CKD. Our findings suggest that serum iFGF23 levels can emerge as an independent predictor of anemia.

FR-PO524

Serum 1,25 Dihydroxyvitamin D Is Independently Associated with Erythropoietin Deficiency and Endogenous Erythropoietin Resistance in Patients with CKD Il Young Kim,[2] In seong Park,[1] Min Jeong Kim,[2] Miyeun Han,[1] Harin Rhee,[1] Sang Heon Song,[1] Eun Young Seong,[1] Dong Won Lee,[2] Soo Bong Lee,[2] Ihm Soo Kwak.[1] *[1]Pusan National University Hospital, Busan, Republic of Korea; [2]Pusan National University Yangsan Hospital, Yangsan, Republic of Korea*.

Background: Erythropoietin (EPO) deficiency and resistance to endogenous EPO is an important pathophysiological feature in anemia of chronic kidney disease (CKD). 1,25 dihydroxyvitamin D [1,25$(OH)_2$D] deficiency is known to contribute to anemia of CKD. We aimed to investigate the associations between serum 1,25$(OH)_2$D, EPO deficiency and endogenous EPO resistance in patients with CKD.

Methods: This study included 409 patients with CKD [glomerular filtration rate (GFR) < 60 ml/min/1.73m^2] who were not on dialysis therapy. Patients on exogenous EPO therapy and patients with iron deficiencies were excluded. Endogenous EPO resistance was assessed by calculating the ratio of endogenous EPO to hemoglobin (Hb) (endogenous EPO/Hb ratio). The associations of Hb level, endogenous EPO level and the endogenous EPO/Hb ratio with clinical and laboratory variables were investigated by univariate and multivariate analyses.

Results: In univariate analysis, serum 1,25$(OH)_2$D level was correlated with the Hb level ($r = 0.705$, $P < 0.001$), endogenous EPO level ($r = 0.254$, $P < 0.001$) and the endogenous EPO/Hb ratio ($r = -0.132$, $P = 0.007$). Multiple regression analysis revealed that the serum 1,25$(OH)_2$D level remained significantly associated with the Hb level ($\beta = 0.530$, $P < 0.001$), endogenous EPO level ($\beta = 0.127$, $P = 0.025$) and the endogenous EPO/Hb ratio ($\beta = -0.106$, $P = 0.035$), even after adjusting for other confounding factors, including the levels of parathyroid hormone and the inflammatory marker C-reactive protein.

Conclusions: The serum 1,25$(OH)_2$D level exhibited significant associations with anemia, EPO deficiency and endogenous EPO resistance in CKD patients. These associations were independent of secondary hyperparathyroidism and inflammation status.

FR-PO525

CKD-MBD and the Use of Immunosuppressant in KNOW-pedCKD Joo Hoon Lee,[1] Hee Gyung Kang,[6] Eujin Park,[6] Yo Han Ahn,[2] Seong heon Kim,[5] Kyoung Hee Han,[3] Hyun Jin Choi,[6] Min Hyun Cho,[4] Young seo Park,[1] IL-Soo Ha.[6] *[1]Asan Medical Center, Seoul, Republic of Korea; [2]Hallym University Kangnam Sacred Heart Hospital, Seoul, SEOUL, Republic of Korea; [3]Jeju National University School of Medicine, Jeju, Republic of Korea; [4]Kyungpook National University Hospital, Daegu, Republic of Korea; [5]Pusan National University Children's Hospital, Yangsan, Republic of Korea; [6]Seoul National University Children's Hospital, Seoul, Republic of Korea*.

Background: CKD-MBD is abnormalities in mineral metabolism and bone structure in patients with chronic kidney disease (CKD). Many children with glomerulonephritis progress to CKD. In many patients with primary or secondary glomerulonephritis, the use of immunosuppresant may cause osteroporosis and growth retardation. We evaluated the effect of immunosuppresant on CKD-MBD in children.

Methods: KNOW-pedCKD is a Korean cohort study for outcomes in patients with pediatric CKD for 10 years which started from April 2011. 458 patients with CKD stage I to V below 20 years old were included. We divided the patients into 3 groups according to CKD stage: CKD stage I-II, III, IV-V. We compared calcium, phosphorus, alkaline phosphatase (ALP), intact parathyroid horome (PTH), vitamin D, FGF-23 and transtubular reabsorption of phosphorus (TRP) between patients who had immunosuppresants (IS group) and those without drug treatment (non-IS group) in each CKD group.

Results: In IS gruop, serum calcium level was lower in CKD stage I-II (10.18 vs 10.92 mg/dL, p=0.048), III (9.99 vs 10.87, p=0.001), IV-V group (9.45 vs 10.97, p=0.001), serum phosphorus level was higher in CKD stage I-II (4.93 vs 4.57, p=0.017), serum ALP was lower in CKD stage III (135 vs 262, p<0.001), IV-V (173 vs 265, p=0.017), serum calcidiol level was lower in CKD stage I-II (17.84 vs 22.43 mg/dL, p=0.003), III (15.68 vs 24.23, p=0.002), IV-V group (11.15 vs 23.02, p<0.001), serum calcitriol level and TRP was lower in CKD stage IV-V than non-IS group. Serum intact PTH and FGF-23 level did not show difference between IS and non-IS group.

Conclusions: The use of immunosuppressant in pediatric CKD patients may worsen CKD-MBD which was associated with hypocalcemia, hyperphosphatemia and vitamin D deficiency.

Funding: Government Support - Non-U.S.

FR-PO526

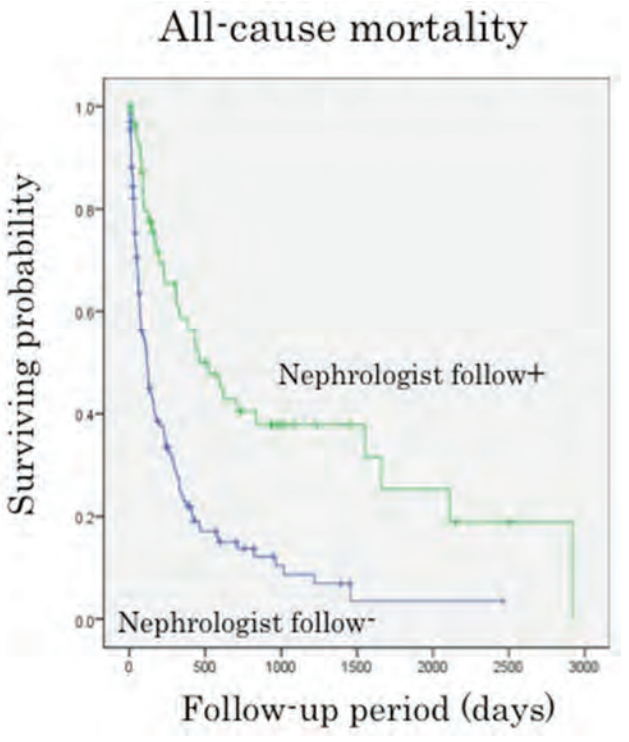
Survival Benefit of Nephrologist Follow-Up in Stage IV Cancer Patients with CKD Taisuke Ishii,[1] Takuya Fujimaru,[3] Eriko Nakano,[2] Yasuhiro Komatsu.[1] *[1]Nephrology, St.Luke's international hospital, Tokyo, Japan; [2]Medical oncology, St.Luke's international hospital, Tokyo, Japan; [3]Tokyo Medical and Dental University, Tokyo, Japan*.

Background: The prevalence of chronic kidney disease (CKD) is increasing among cancer patients. And CKD affects mortality of the patients with stage IV solid cancer. Several studies have shown that nephrologist follow-up resulted in improving survival of CKD patients. However, it is not clear whether nephrologist co-management could improve mortality.

Methods: In this single-center, retrospective cohort study, we collected data from all patients who were newly diagnosed as stage IV solid cancer with CKD from January 2007 to December 2016. The follow-up period lasted until April 2017. CKD was defined as eGFR ≤ 60 ml/min/1.73m^2 both at the time of cancer diagnosis and 90 days before the diagnosis. Nephrologist follow-up was defined as visit to nephrologist after diagnosed with the cancer. The primary endpoint was all-cause mortality. The secondary endpoint was cancer-specific mortality. Log-rank test and Cox proportional hazard analysis were used for analysis.

Results: 192 patients met inclusion criteria (age 78±9, 61.5% of males). CKD stage G3, G4, and G5 were 82.3%, 14.1%, and 3.6% respectively. In these patients, nephrologist follow-up were 24.7%, 48.1%, and 57.1%, respectively. During follow-up (median 134 days, IQR 46-415 days), 145 patients (75.5%) died. On Kaplan-Meier survival analysis, patients who visited nephrologist showed significantly better survival compared to those who did not visit at all (log-rank test, $p < 0.001$). After adjusting for age, gender, type of cancer, anticancer therapy, history of cardiovascular disease, baseline eGFR, serum WBC, CRP, proteinuria and ECOG Performance Status, nephrologist follow-up remained significant association with lower all-cause mortality and cancer specific mortality (HR 0.51, 95% CI 0.32-0.81 and HR 0.52, 95% CI 0.32-0.83, respectively).

Conclusions: Nephrologist follow-up was associated with lower risk of deaths in stage IV cancer patients with CKD.



FR-PO527

Lack of Nephrologist Follow-Up after Nephrectomy for Kidney Cancer Michael G. McCusker,[2,3] Naima Carter-Monroe,[1,4] Eric P. Cohen.[1,3] *[1]University of Maryland, Baltimore, MD; [2]University of Maryland Medical Center, Baltimore, MD; [3]Medicine, Baltimore VAMC, Baltimore, MD; [4]Pathology, Baltimore VAMC, Baltimore, MD.*

Background: Medical renal disease often accompanies kidney cancer. The American College of Pathology recommends that the tissue surrounding a resected kidney cancer be examined to identify significant medical renal disease, much as is done for a kidney biopsy done for non-cancerous disease. This can inform regarding pathogenesis of kidney cancer and is immediately important for nephrologic management of patients who have had nephrectomy, partial or complete.

Methods: We tested a prospectively maintained database at the Baltimore Veterans Affairs Medical Center to determine the adequacy of follow-up in such cases. Sixty six patients were identified from 2010 through 2016, who had at least six months of follow-up after surgery.

Results: All but one were men and 46 were black. The average age was 64 +/- 7 (sd). Forty-one had total and twenty-seven had partial nephrectomies. Two patients had partial followed by contralateral total nephrectomy. Twenty seven of the sixty eight had clear cell cancer, the rest were papillary. Thirteen patients with oncocytomas were not included. In the pathology reports, six had no comment regarding the non-cancerous renal tissue. Eight more reported no abnormality, but twenty four showed moderate or worse medical renal disease of the non-cancerous renal tissue. As reported by others, micro and macrovascular disease were present in the non-cancerous tissue of the majority of cases. The average preoperative serum creatinine (s creat) of the patients was 1.3 mg/dl +/- 0.6 (sd). The average discharge s creat was 1.7 mg/dl +/- 0.9 (sd). ($p<0.001$ vs preoperative s creat). The average s creat at one year was 1.8 mg/dl +/- 1.2 (sd). Only 23 of these 66 patients had any nephrology follow-up after their surgery, and only 13 had measurement of proteinuria.

Conclusions: We conclude that although Pathologists usually provide some report of the non-cancerous renal tissue, this is still not always done. The majority of cases show significant medical renal disease in the surrounding non-cancerous kidney. Importantly, nephrologic follow-up of these patients with chronic kidney disease is deficient. Because of the known risks of CKD, it is prudent to ensure Nephrologist follow-up for patients who have had a nephrectomy for kidney cancer.

Funding: Veterans Affairs Support, Clinical Revenue Support

FR-PO528

Independent Associations of eGFR and Albuminuria with Cancer Incidence Yejin Mok, Shoshana Ballew, Yingying Sang, Josef Coresh, Corinne Joshu, Elizabeth A. Platz, Kunihiro Matsushita. *Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.*

Background: Cancer is a potential complication of chronic kidney disease (CKD) recently attracting attention. However, no previous studies have simultaneously investigated two key CKD measures, estimated glomerular filtration rate (eGFR) and urinary albumin-to-creatinine ratio (ACR), for the risk of cancer incidence.

Methods: In 9,191 participants without prevalent cancer from the Atherosclerosis Risk in Communities (ARIC) study in 1996 to 1998, the associations of eGFR (based on creatinine and cystatin C) and ACR with overall and site-specific cancer incidence were evaluated with Cox proportional hazards model adjusted for conventional lifestyle and clinical risk factors for CKD and/or cancer.

Results: During a median follow-up of 14.7 years, 2,063 incident cancer cases occurred in 117,420 person years. eGFR was not associated with total cancer incidence after adjusting for risk factors. ACR was possibly positively associated after adjustment for age, sex, and race, but further adjustment for other potential confounders attenuated the association. By cancer site, a higher ACR was significantly associated with increased risk of lung and hematopoietic cancers (hazard ratio per 8-fold higher ACR was 1.29 [1.08-1.53] and 1.27 [1.02-1.59], respectively). The results were consistent for lung cancer even after excluding cancer in the first three years. These results were largely consistent in subgroups of sex, race, and current smoking status.

Conclusions: Kidney measures, particularly higher albuminuria, were modestly associated with cancer incidence. The association of ACR was especially robust for lung cancer and this finding is consistent with previous studies. Mechanisms underlying this association are not clear, and further studies exploring potential mechanism are needed.

Funding: Other NIH Support - The ARIC Study is carried out as a collaborative study supported by National Heart, Lung and Blood Institute contracts (HHSN268201100005C, HHSN268201100006C, HHSN268201100007C, HHSN268201100008C, HHSN268201100009C, HHSN268201100010C, HHSN268201100011C, and HHSN268201100012C). Studies on cancer in ARIC are also supported by the National Cancer Institute (U01 CA164975).

Table. Hazard ratios (95% CI) of incident cancer for categories of creatinine and cystatin C based eGFR and ACR

	eGFR, mL/min/1.73m^2					
	≥90 (N=2,155)	60-89 (N=6,071)	45-69 (N=671)	<45 (N=294)	Per 30 ml/min/1.73m^2 lower eGFR	P for trend
Case	459	1,375	162	67		
Model 1	1.0	0.96 (0.85-1.07)	1.06 (0.88-1.28)	1.24 (0.95-1.62)	1.40 (1.06-1.87)	0.248
Model 2	1.0	0.92 (0.82-1.04)	0.96 (0.79-1.16)	1.03 (0.79-1.35)	1.22 (0.91-1.64)	0.821
	ACR, mg/g					
	<10 (N=7,444)	10-29 (N=1,011)	30-299 (N=583)	≥300 (N=153)	Per 8-fold higher ACR	P for trend
Case	1,656	231	137	39		
Model 1	1.0	1.09 (0.95-1.25)	1.20 (1.01-1.43)	1.58 (1.15-2.17)	1.10 (1.03-1.18)	0.001
Model 2	1.0	1.03 (0.89-1.18)	1.05 (0.88-1.26)	1.34 (0.96-1.86)	1.05 (0.98-1.12)	0.119

Model 1: adjusted for age, sex, and race

Model 2: Model 1 + adjusted for BMI, hypertension, diabetes, total cholesterol, statin use, hs-CRP, history of CVD, family history of cancer, current smoker, current drinker and kidney measures (ACR was accounted for in the analyses for eGFR and vice versa)

FR-PO529

Prevalence and Mortality of CKD in Lymphoma: A Large Retrospective Cohort Study Masamitsu Ubukata, Masaki Hara, Teruhiro Fujii, Akihito Ohta. *Division of Nephrology, Department of Medicine, Tokyo Metropolitan Komagome Hospital, Bunkyo-ku, Japan.*

Background: The prevalence, incidence, and mortality of chronic kidney disease (CKD) in lymphoma patients have not been fully understood. The objective of this study was to evaluate the prevalence of CKD and its contribution to mortality in patients with lymphoma.

Methods: This was a retrospective cohort study on 429 consecutive lymphoma patients who were admitted or regularly visited our hospital from January 2013 to October 2016. The prevalence of CKD at enrollment was evaluated according to the modified CKD classification by the KDIGO (eGFR and proteinuria category). Dipstick proteinuria was classified into three grades: A1, for – and +/–; A2 for 1+ or 2+; and A3 for ≥3+. eGFR (mL/min/1.73 m^2) was classified into six stages: G1 for ≥90, G2 for 60–89, G3a for 45–59, G3b for 30–44, G4 for 15–29, and G5 for <15. CKD was defined as eGFR <60 mL/min/1.73 m^2 and/ or proteinuria ≥1+ that was sustained at least for 3 months. The severity of CKD was classified into the following four categories: no risk for G1A1 and G2A1; moderate risk for G1A2, G2A2, and G3aA1; high risk for G1A3, G2A3, G3aA2, and G3bA1; and very high risk for G3aA3, G3bA2, G3bA3, G4, and G5. The cumulative mortality rate was estimated using the Kaplan–Meier method, with stratification into two groups based on the presence or absence of CKD. Further, a multivariate Cox proportional hazards regression model was used to calculate the hazard ratio (HR) and its 95% confidence interval (CI) for all-cause mortality, after adjustments for age, gender, pathologic type, clinical stage of lymphoma, presence or absence of diabetes mellitus, hypertension, and cardiovascular disease.

Results: The mean follow-up period was 3.1 ± 1.0 years and the prevalence of CKD at study enrollment was 34.5%. The cumulative mortality rate was 20.7% and was significantly higher in the CKD group than in the group without CKD (36.4% vs. 18.0%, p = 0.02). In the multivariate analysis, mortality was significantly associated with CKD (HR 1.61; 95% CI 1.03–2.50), and this association was the most robust with very high risk CKD (HR 6.32; 95% CI 2.41–14.54).

Conclusions: CKD should be considered a risk factor for mortality among patients with lymphoma.

FR-PO530

Nephrologists' Perspectives on Cancer Screening in Patients with CKD Laura J. James,[3,5] Germaine Wong,[1] Jonathan C. Craig,[4] Allison Tong.[2] *[1]None, Auambie, NSW, Australia; [2]The University of Sydney, Sydney, NSW, Australia; [3]Sydney School of Public Health, The University of Sydney, Westmead, NSW, Australia; [4]University of Sydney/Children's Hospital, Sydney, NSW, Australia; [5]Centre for Kidney Research, Westmead, NSW, Australia.*

Background: Cancer is a leading cause of morbidity and mortality in patients with chronic kidney disease (CKD). However, cancer screening practices are highly variable among nephrologists, which may reflect uncertainties around the benefits and harms of screening in this setting, and the competing risk of death from other causes. Therefore we aimed to describe nephrologists' perspectives on cancer screening and understand the factors impacting their practice.

Methods: Semi-structured interviews were conducted with 21 nephrologists from 11 centres across Australia and New Zealand. Transcripts were analysed thematically

Results: Five themes were identified: empowering patients to make informed decisions (respecting patient preferences, communicating evidence-based recommendations, creating awareness of consequences, preparing patients for transplantation); justifiable risk taking (avoiding undue consequences in vulnerable populations, ensuring cost effectiveness, warranted by long term immunosuppression, assurance of reasonable survival gains); prioritising current or imminent complications; ambiguity of evidence in supporting decisions (absence of standardised recommendations, limited transferability of population-based data); and depending on a shared multidisciplinary approach (collaboration with primary health care, wary of inadequate dermatological services, generating targeted cancer preventative services).

Conclusions: Nephrologists approach decisions about cancer screening in patients with CKD based on patient preferences, assessment of risk, justifiable survival gains, and current health priorities. Evidence-based guidelines and specialist clinics that address cancer screening may support shared decision making about cancer screening in CKD.

Funding: Government Support - Non-U.S.

FR-PO531

Effectiveness of 12 Week Elbasvir/Grazoprevir (EBR/GZR) in Patients with Genotype 1 (GT1) Chronic Hepatitis C (HCV) and CKD Chizoba Nwankwo,[2] Bruce R. Bacon,[4] Michael P. Curry,[1] Steven Flamm,[3] Kris V. Kowdley,[5] Scott Milligan,[6] Naoky Tsai.[7] *[1]Beth Israel Deaconess Medical Center, Boston, AL; [2]Merck & Co, Lebanon, NJ; [3]Northwestern Feinberg School of Medicine, Chicago, IL; [4]Saint Louis University School of Medicine, Saint Louis, MO; [5]Swedish Medical Center, Seattle, WA; [6]Trio Health Analytics, La Jolla, CA; [7]University of Hawaii, Kailua, HI.*

Background: Elbasvir/grazoprevir (EBR/GZR) is recommended for use in the treatment of chronic HCV genotype (GT) 1 and 4 patients including those with renal impairment. The puprose of this study is to describe the real-world effectiveness of 12 week EBR/GZR in patients with GT1 chronic HCV and CKD.

Methods: Data were collected from US providers and specialty pharmacies through Trio Health's disease management platform. Patients with CKD and GT1 HCV who initiated 12 week EBR/GZR therapy between Jan 28, 2016 (FDA approval) to Dec 31, 2016 were included in the analyses. CKD was defined as renal impairment of baseline eGFR <90 ml/min. Effectiveness was defined as attainment of per protocol sustained virological response at week 12 post-treatment (PP SVR12).

Results: 228 patients with GT1 HCV and CKD were treated for 12 weeks with EBR/GZR and ribavirin (RBV) was added for 6 patients. 25% (56/228) of patients had mild stage 2 CKD, 21% (48/228) had moderate stage 3 CKD and 54% (124/228) had severe renal impairment (CKD stages 4-5). Other characteristics provided in (TABLE). At time of abstract submission, 144 of 228 were evaluable for PP SVR12; 98% (135/138) of patients treated with EBR/GZR and 100% (6/6) of patients treated with EBR/GZR+RBV achieved PP SVR12.

Conclusions: In the treatment of patients with GT1 chronic HCV and CKD, 12 week EBR/GZR was highly effective with an overall SVR12 (PP) of 98% (141/144).

Funding: Commercial Support - Merck & Co

Baseline Characteristics of EBR/GZR Treated G1 Patients	
CHARACTERISTICS - no. (%)	**12 week EBR/GZR (n=228)**
+RBV	6 (3%)
Treatment Naïve	191 (84%)
Cirrhosis	59/227 (26%)
Baseline Plts <100 K/ml	27/215 (13%)
Demographics	
Age - mean (range)	62 (24-88)
Male - no. (%)	141 (62%)
BMI – mean (SD)	28 (7) n=181
Virology - no. (%)	
Baseline Viral <800 IU/mL	86/226 (38%)
GT1A	144 (63%)
NS5A Resist. Tested	86/144 (60%)
NS5A Resist. Possible	3/86 (3%)
Comorbids - no. (%)	
Diabetes	83/224 (37%)
Hypertension	158/225 (70%)
Stage 4-5 CKD	124/228 (54%)

FR-PO532

Real-World Cost-Effectiveness of Elbasvir/Grazoprevir (EBR/GZR) for the Treatment of Chronic Hepatitis C (CHC) in Treatment-Naïve (TN) Genotype (GT) 1 Patients with CKD Chizoba Nwankwo,[2] Bruce R. Bacon,[6] Shelby L. Corman,[5] Michael P. Curry,[1] Steven Flamm,[4] Yiling Jiang,[3] Kris V. Kowdley,[7] Scott Milligan,[8] Naoky Tsai.[9] *[1]Beth Israel Deaconess Medical Center, Boston, AL; [2]Merck & Co, Lebanon, NJ; [3]Merck Sharp & Dohme Ltd., Hoddesdon, United Kingdom; [4]Northwestern Feinberg School of Medicine, Chicago, IL; [5]Pharmerit International, Bethesda, MD; [6]Saint Louis University School of Medicine, Saint Louis, MO; [7]Swedish Medical Center, Seattle, WA; [8]Trio Health Analytics, La Jolla, CA; [9]University of Hawaii, Kailua, HI.*

Background: EBR/GZR, a once-daily fixed-dose combination direct-acting antiviral (DAA) was shown in the C-SURFER trial to be safe and effective for the treatment of CHC patients with CKD. The objective of this analysis was to evaluate real-world cost-effectiveness of EBR/GZR compared to no treatment using data from the TRIO Network.

Methods: A state-transition model of CHC, liver disease, and CKD was developed using Microsoft Excel. The model consists of 10 health states reflecting degree of liver fibrosis (F0-4), decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), and liver transplant (LT); and 8 health states reflecting degree of CKD (Stages 1-5), hemodialysis, and kidney transplant. Baseline patient characteristics and the proportion of TN GT1 patients achieving sustained virologic response (SVR) were collected from a real-world study of 124 TN GT1 patients with CKD who were treated with EBR/GZR between January and October 2016, using data from the TRIO Network. Data on the rate of progression of hepatic and renal disease, annual costs for each health state, utilities, and risk of cardiovascular events were obtained from published literature. The primary outcome was the incremental cost-utility ratio (ICUR); secondary outcomes included the lifetime incidence of DC, HCC, LT, ESLD mortality, and life expectancy.

Results: TN GT1 patients who received EBR/GZR were less likely to develop DC or HCC, receive a liver transplant, or die of liver-related causes compared to untreated patients, with a 2.4-year increase in life expectancy. Discounted costs and QALYs were both greater in patients receiving EBR/GZR compared to no treatment, with an ICUR of $53,897 QALY.

Conclusions: The model projected that EBR/GZR significantly reduces the incidence of liver disease complications compared to no treatment, using real-world patient characteristics and treatment outcomes. In addition, EBR/GZR was cost-effective for the treatment of CHC in patients with CKD.

Funding: Commercial Support - Merck & Co

Lifetime incidence of liver disease complications, life expectancy, and ICUR for EBR/GZR vs. no treatment		
Outcome	**EBR/GZR**	**No treatment**
Decompensated cirrhosis (%)	2.35	9.79
Hepatocellular carcinoma (%)	0.77	11.41
Liver transplant (%)	0.01	0.64
End-stage liver disease mortality (%)	0.27	13.45
Life expectancy (years)	10.3	7.9
Discounted QALYs	5.52	4.31
Discounted costs, US$	312,682	247,335
ICUR, EBR/GZR vs. no treatment	$53,897/QALY	

FR-PO533

Uromodulin and Risk of Infection Related Hospitalizations Pranav S. Garimella,[8] Petra Buzkova,[3] Joachim H. Ix,[7] Tarek M. El-Achkar,[4] Prasad Devarajan,[1] Michael R. Bennett,[2] Michael Shlipak,[5] Mark J. Sarnak.[6] *[1]Cincinnati Children's Hospital, Cincinnati, OH; [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [3]UW, Seattle, WA; [4]Indiana University, Indianapolis, IN; [5]San Francisco VA Medical Center, San Francisco, CA; [6]Tufts Medical Center, Boston, MA; [7]UCSD, San Diego, CA; [8]University of california san diego, San Diego, CA.*

Background: Higher uromodulin levels are associated with lower rates of urinary tract infections in humans, and laboratory studies indicate that uromodulin may also be beneficial in sepsis and bacteremia. Studies have not confirmed the association between uromodulin and risk of all-cause infections in humans.

Methods: Using data from a random, sub-cohort of 958 older adults enrolled in the Cardiovascular Health Study, we evaluated whether spot urine uromodulin levels are associated with risk of infectious hospitalizations using Poisson and Cox regression analysis with several nested models.

Results: The mean age of participants was 78.1 years, mean eGFR was 70.9 ml/min/1.73m2 and 39.5% were men. The median (IQR) urinary uromodulin level was 25.88 (17.25, 38.83) units. There were 592 infections hospitalizations among 362 participants during a median follow up of 9.2 years. Rates of hospitalizations (per100 person-years) decreased across higher quartiles of uromodulin: 7.4, 6.0, 5.8, and 5.6. Each doubling of uromodulin was associated with 20% lower number of infectious hospitalizations (Rate Ratio 0.80, 95% CI 0.66, 0.97) when adjusted for demographics, comorbidities and laboratory variables. Uromodulin levels were not associated with the hazard of first infectious hospitalization. When Cox regression was used to model multiple events per person, each doubling of uromodulin was associated with 23% lower risk of infectious hospitalization (HR 0.77, 95% CI 0.64, 0.94) in adjusted analyses.

Conclusions: Higher levels of uromodulin are associated with lower rates and hazard of total infectious hospitalizations. Uromodulin levels may provide information about global immune defense that may not be limited to urinary tract infections alone.

Funding: NIDDK Support, Other NIH Support - NHLBI

Table: Rates of total infectious hospitalization by uromodulin quartiles

	Total	Q1	Q2	Q3	Q4
Sample/Infections	958/592	240/154	239/147	239/136	240/155
Rate per 100 PY (95%CI)	6.1(5.4,7.0)	7.4 (5.6,9.7)	6.0 (4.6,7.8)	5.8 (4.6,7.4)	5.6 (4.5,6.9)

Association of uromodulin (continuous scale) with total infectious hospitalizations

	All Rate Ratio	p-val
Log2umod*	0.88 (0.76,1.00)	0.06
log2umod1**	0.88 (0.755,1.00)	0.05
log2umod2†	0.89 (0.76,1.051)	0.17
log2umod3††	0.80 (0.66,0.97)	0.02

Adjustment in sequential models as follows
* Demographic adjusted: umod+ age (yrs)+gender+ black race+ urine creatinine
** Model 1: demographics+ BMI+ smoking status (current, never, former)
† Model 2: Model 1 + diabetes+ CVD+heart failure
†† Model 3: Model 2 +CRP+IL6
Log2umod = uromodulin log transformed to base 2

FR-PO534

Hospital Acquired Infections after Major Surgery among Patients with Clinical Comorbidities: The Stockholm Creatinine Measurements (SCREAM) Project Junichi Ishigami,[2] Marco Trevisan,[3] Hong Xu,[3] Josef Coresh,[4] Kunihiro Matsushita,[1] Juan J. Carrero.[3] *[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, AL; [2]Johns Hopkins School of Public Health, Baltimore, MD; [3]Karolinska Institutet, Stockholm, Sweden; [4]Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD.*

Background: Whether incidence of hospital acquired infections (HAIs) after major surgery differs by types of clinical comorbidity has not been well characterized.

Methods: We evaluated 66,820 patients (mean age, 64 years; 58% female) undergoing four major types of surgery (neuro [n=1,922], cardiothoracic and vascular [n=6,403], abdominal [n=26,542], and orthopedic surgery [n=31,953]) with available serum creatinine measurement for estimating GFR up to 365 days prior to the hospitalization between 2007 and 2011 in Stockholm, Sweden, for the in-hospital incidence of four HAIs (pneumonia, urinary tract infections, surgical site infections, and bloodstream infections) across clinical comorbidities including low eGFR <60 ml/min/1.73m^2, diabetes, coronary heart disease (CHD), congestive heart failure (CHF), stroke, chronic obstructive pulmonary disease (COPD), liver disease, and cancer.

Results: Among clinical comorbidities, cancer and low eGFR were most frequently identified (**Table1**). During hospital stay, 5.7% (n=3,784) had at least one type of HAIs. For each clinical comorbidity, the prevalence was disproportionally higher in patients with HAIs, and risk of HAIs was significantly higher in multivariable Poisson models (**Table1**). When population attributable fraction (PAF) was estimated, the PAF was highest for low eGFR (PAF, 0.13), followed by cancer, CHF, stroke and COPD (PAF, 0.11, 0.08, 0.06, and 0.05, respectively) (**Table1**). These findings were mostly consistent across the four types of infection.

Conclusions: For HAIs after major surgery, low eGFR posed the highest PAF among major clinical comorbidities, underscoring the importance of HAIs prevention measures for persons with low eGFR.

Funding: Other NIH Support - NHLBI Cardiovascular Disease Epidemiology Training Program grant (T32HL007024).

Table1: Prevalence of clinical comorbidity and relative risk of HAIs

	% in the overall population (n=66,820)	% among patients with HAIs (n=3,784)	Adjusted relative risk* (95%CI)	Population attributable fraction (PAF)
eGFR <60 ml/min/1.73m^2	18%	35%	1.62 (1.50-1.75)	0.13
Cancer	21%	34%	1.45 (1.35-1.56)	0.11
CHF	12%	24%	1.49 (1.36-1.62)	0.08
Stroke	11%	20%	1.41 (1.29-1.53)	0.06
COPD	12%	18%	1.33 (1.22-1.44)	0.05
Diabetes	12%	17%	1.11 (1.02-1.21)	0.02
CHD	8.8%	14%	1.12 (1.02-1.25)	0.02
Liver disease	2.6%	3.2%	1.28 (1.07-1.53)	0.01

*The model was adjusted for each clinical comorbidity, age, sex, and types for surgery

FR-PO535

Lactobacillus Plantarum 299v Prevents Clostridium difficile Infection in Patients Hospitalized in Nephrological and Transplantation Department Marcin Adamczak, Sylwia M. Dudzicz, Agata Kujawa-Szewieczek, Katarzyna Kwiecien, Andrzej Wiecek. *Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland.*

Background: *Lactobacillus plantarum 299v* (LP299v) has been introduced into the clinical practice in order to reduce gastrointestinal symptoms during antibiotic exposure. However, it remains controversial whether or not probiotics are also effective in the prevention of *Clostridium difficile* infections (CDI) among patients receiving antibiotics. The aim of this clinical, retrospective, single-centre study was to analyze the CDI among patients receiving antibiotics and hospitalized in the period before, during and after cessation of LP299v use, as a prevention of CDI, in the nephrological and transplantation department.

Methods: Among 5341 patients hospitalized in the nephrological and transplantation department during three years 40 patients with CDI were diagnosed and enrolled in this study. From November 2013 to December 2014 prevention of CDI with the oral use of LP299v was performed in all patients treated with antibiotics and after organ transplantation or receiving immunosuppressive drugs for any other reasons. For the further analysis the observation period was divided into three twelve-months periods: before, during LP299v use as the prophylactic manoeuvre against CDI and after cessation of such a prophylaxis

Results: A significant (p=0.0001) reduction of the number of cases with CDI was found during LP299v use (period 2) (n=2; 0.11% of 1791 hospitalized patients) compared two others periods i.e. before and after cessation of such a prophylaxis (n=21; 1.21% of 1742 hospitalized patients and period and n=17; 0.94% of 1808 hospitalized patients, respectively).

Conclusions: Routine use of *Lactobacillus plantarum 299v* during treatment with antibiotics may prevent *Clostridium difficile* infection in the nephrological and transplantation department.

Funding: Government Support - Non-U.S.

FR-PO536

Plasma Biomarkers and Response to Intensive Blood Pressure Control: The ACCORD Trial Girish N. Nadkarni,[1] Martine Pollack-Zollman,[1] Kinsuk Chauhan,[1] Veena Rao,[2] Priti Poojary,[1] Aparna Saha,[1] Chirag R. Parikh,[3] Steven G. Coca.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Yale University, New Haven, CT; [3]Yale University and VAMC, New Haven, CT.*

Background: Plasma biomarkers of inflammation [tumour necrosis factor 1 (TNFR1); monocyte chemoattractant protein (MCP1) and interleukin 18 (IL18)], renal injury [Kidney Injury Molecule 1 (KIM1)] and fibrosis [YKL40] are associated with estimated glomerular filtration rate (eGFR) decline. There are limited data on association between these markers and response to intensive sytolic blood pressure (SBP) control. We examined the relationship between baseline plasma biomarker levels and longitudinal SBP change in the ACCORD trial.

Methods: We used a multiplex platform to measure plasma biomarkers in baseline plasma specimens from randomly selected ACCORD trial participants with type 2 diabetes in intensive SBP arm (goal <120; n=260) vs. standard SBP arm (goal <140; n=269). We estimated the association between longitudinal SBP change and baseline biomarker tertiles after stratifying by intensive vs. standard SBP arm using linear mixed models.

Results: Mean age was 61.7 years, 46.6% were female and baseline eGFR was 88 ml/min. There were no significant differences between the intensive and standard SBP arm. Participants in the third tertile of KIM-1 had a higher SBP at baseline after adjusting for eGFR, UACR and demographics [+3.7 mmHg, SE 1.6]. After randomization, participants in the third tertile of KIM-1 in intensive SBP group had a smaller change in sBP compared to the first tertile [-5.1 mmHg; SE 1.5; p<0.001]. There were no associations with other biomarkers and SBP change in either arm. (Figure 1)

Conclusions: Higher levels of plasma KIM-1 at baseline are associated with attenuated SBP changes with intensive control. These findings indicate that subclinical renal tubular injury is associated with poorer response to intensive SBP control, even in persons with normal eGFR.

Funding: NIDDK Support

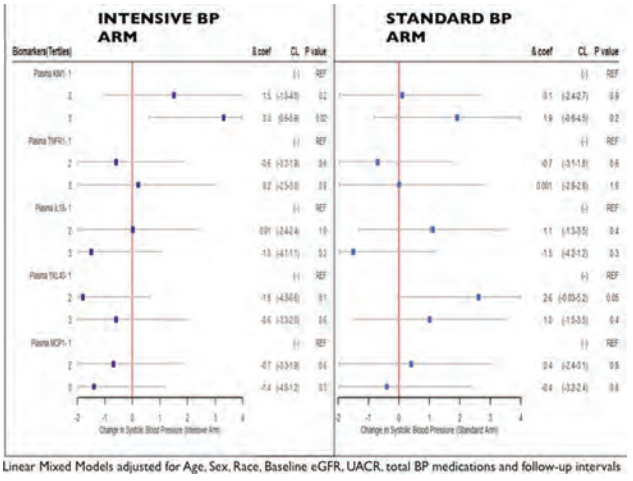


Figure 1. Relationship between Biomarker Tertiles and Response to Blood Pressure Control Stratified by Intensive vs. Standard Arms

FR-PO537

Did Non-Standard Withdrawal of Antihypertensive Agents Exaggerate Treatment Effect in SPRINT? Conor S. Judge, Alberto Alvarez-Iglesias, John P. Ferguson, Maria Costello, Andrew Smyth, Martin O'donnell. *HRB Clinical Research Facility, Galway, Ireland.*

Background: The control group in SPRINT targeted a blood pressure range of 130-140mmHg, which required down-titration of antihypertensive therapy when blood pressure was below 130mmHg on a single visit, or below 135mmHg on two consecutive visits. Such an approach would not be considered routine clinical care. We hypothesised that non-standard discontinuations of antihypertensive therapy in the control group, may have inflated the events rates and exaggerated the reported treatment effect.

Methods: Standard withdrawal of antihypertensive agents was defined as a withdrawal for systolic blood pressure less than 100mmHg at the current visit, or a reported, related adverse event occurring between the previous and current visit. We evaluated the association of antihypertensive withdrawal with CV events on follow-up using the Cox proportional-hazards regression. We repeated the primary analysis comparing the time to first occurrence of a primary outcome between treatment groups, adjusting for non-standard withdrawal in blood pressure medication, treated as time dependant covariates, to estimate the effect of intensive versus standard blood pressure control.

Results: Non-standard withdrawal of antihypertensive agents occurred in 9.3% of patient visits in the control group, compared with 5.1% in the treatment group ($p < 0.001$), and was associated with an increased risk of the composite outcome, which was significant for 2 follow-up periods (HR 1.65; 95% CI, 1.26-2.16 for initial 3 months, HR 1.47; 95% CI, 1.12-1.95 for 3 to 6-month period), which was independent of blood pressure effect. After adjusting for non-standard withdrawal/reduction of antihypertensive agents, the intensive-treatment group was associated with a lower risk of the composite outcome measure, compared to standard care (HR 0.81; 95% CI, 0.67 to 0.97).

Conclusions: Targeting a systolic BP range (130-140mmHg) in the control group of SPRINT, rather than a conventional blood pressure threshold (<140mmHg), resulted in withdrawals of antihypertensive medications that would not be considered routine care. An analysis that adjusted for non-standard withdrawal of blood pressure medications during the trial resulted in a significant, but diminished, treatment effect of intensive blood pressure control (HR 0.81 versus 0.75), and the effect on heart failure became non-significant.

FR-PO538

Influence of Baseline Diastolic Blood Pressure (DBP) Level on the Effects of Intensive Blood Pressure Lowering on Cardiovascular (CV) Outcome in SPRINT Srini Beddhu,[1] Glenn M. Chertow,[2] Alfred K. Cheung,[1] Mahboob Rahman,[3] Tom Greene,[1] Guo Wei,[1] William E. Haley,[5] William C. Cushman,[4] Paul K. Whelton.[6] *[1]Univ Utah, SLC, UT; [2]Stanford Univ, Palo Alto, CA; [3]Case Western Reserve University, Cleveland, OH; [4]VAMC, Memphis, TN; [5]Mayo Clinic, Jacksonville, FL; [6]Tulane Univ, New Orleans, LA. Group/Team: For SPRINT Research Group.*

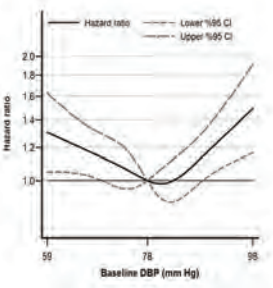
Background: Lowering systolic blood pressure (SBP) in persons with low DBP might affect tissue perfusion and thereby, ↑ risk for CV events.

Methods: SPRINT tested the effects of SBP goal < 120 vs. < 140 mm Hg on CV outcomes in 9361 participants. We tested for effect modification by baseline DBP of the intervention on primary CV outcome (a composite of non-fatal MI, ACS not resulting in MI, stroke, CHF, or CV death).

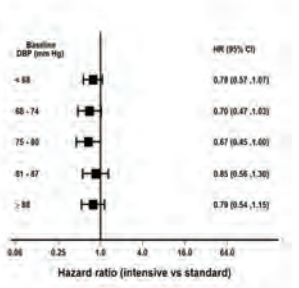
Results: Mean age was 67.9 ± 9.4 years, with 35.6 % being women and 31.5 % Black. Means (± SD) baseline SBP and DBP were 139.7 ± 15.6 and 78.1 ± 11.9 mm Hg, respectively. There were 562 primary outcome events over 29,277 person-years of follow-up. Adjusted for age, gender, race and the intervention arm, baseline DBP had a U-shaped association with the primary outcome (figure, panel A). Intensive SBP treatment reduced the risk of the primary outcome vs. standard treatment (hazard ratio [HR] 0.76, 95% CI 0.64 to 0.89). P-value for the linear treatment by baseline DBP interaction did not approach statistical significance for the primary outcome ($p = 0.85$). HR for primary outcome across DBP quintiles are summarized in figure, panel B. HR for the primary outcome was 0.78 (95% CI 0.57 to 1.07) within the lowest DBP quintile and 0.74 (95% CI 0.61 to 0.90) within the upper four DBP quintiles (interaction p-value = 0.78).

Conclusions: While baseline low DBP was associated with increased risk of CV events, there is no evidence that the beneficial effects of the SPRINT intervention were modified by the level of baseline DBP.

Funding: NIDDK Support, Other NIH Support - NHLBI



Panel A. Spline regression model relating baseline DBP to primary CV outcome (N = 9361)



Panel B. Comparison of the intensive vs. standard SBP intervention by baseline DBP quintile (N=9361)

FR-PO539

PTH, FGF23, and Effects of Intensive Blood Pressure Lowering in SPRINT Participants with CKD Charles Ginsberg,[12] Timothy Craven,[8] Michel Chonchol,[14] Alfred K. Cheung,[13] Mark J. Sarnak,[11] Anthony A. Killeen,[3] Kalani L. Raphael,[4] Udayan Y. Bhatt,[2] Jing Chen,[9] Glenn M. Chertow,[10] Barry I. Freedman,[8] Suzanne Oparil,[7] Barry M. Wall,[6] Clinton B. Wright,[1] Michael Shlipak,[5] Joachim H. Ix.[12] *[1]NINDS, Rockville, MD; [2]The Ohio State University, Dublin, OH; [3]University of Minnesota, Minneapolis, MN; [4]VA Salt Lake City Health Care System, Salt Lake City, UT; [5]San Francisco VA Medical Center, San Francisco, CA; [6]VA Medical Center, Memphis, TN; [7]University of Alabama at Birmingham, Birmingham, AL; [8]Wake Forest University School of Medicine, Winston-Salem, NC; [9]Tulane School of Medicine, New Orleans, LA; [10]Stanford University School of Medicine, Palo Alto, CA; [11]Tufts Medical Center, Boston, MA; [12]UCSD, San Diego, CA; [13]University of Utah, Salt Lake City, UT; [14]University of Anschutz Medical Center, Aurora, CO.*

Background: Serum FGF23 and PTH levels are elevated in CKD patients, and are associated with CVD events. Prior work has demonstrated that the association with CVD events may be modified by tubular resistance to FGF-23, thereby giving insight into kidney tubule function above and beyond eGFR. We hypothesized that the therapeutic benefits of intensive blood pressure (BP) control may also be modified by tubular resistance to PTH and FGF-23.

Methods: Among 2486 SPRINT participants with baseline eGFR < 60 ml/min/1.73m^2, we measured intact FGF23 and intact PTH. We evaluated whether the effect of randomization to intensive vs. standard BP arms on CVD, HF events, and all-cause mortality was modified by serum PTH or FGF-23 levels.

Results: Mean age was 73 yrs, 60% were female, mean eGFR was 46±9 ml/min/1.73m^2. Median [IQR] iFGF23 was 66 [52, 88] pg/ml, and median iPTH was 48 [35, 67] pg/ml. PTH modified the effect of intensive BP lowering for CVD events (p_{int}=0.01) and HF (p_{int}=0.003). In stratified analyses, intensive BP lowering was associated with lower risk of CVD (HR 0.68, 95% CI 0.45-1.00) and HF (HR 0.41, 95% CI 0.20-0.85) among participants with PTH <48 pg/ml; but not those with PTH >48 pg/ml. FGF23 did not modify the association of intensive BP control with any of the 3 outcomes.

Conclusions: Lower serum PTH levels may identify a subset of CKD patients who receive the greatest benefit from intense BP lowering. Further work is necessary to elucidate if tubular resistance to PTH is the mechanism responsible for these findings.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIA, NINDS, National Center for the Advancing Translational Sciences,, Veterans Affairs Support

Effect of Randomization to Intensive Blood Pressure Lowering for CVD and HF Events, Stratified by PTH Above vs. Below the Median

	Standard Arm # Event / # At Risk HR* (95% CI)	Intensive Arm # Event / # At Risk HR* (95% CI)
CVD Events		
≤ Median PTH	66/597 1.00 (Reference)	45/621 0.67 (0.45, 1.00)
> Median PTH	75/572 1.00 (Reference)	75/692 1.02 (0.72, 1.42)
Heart Failure Events		
≤ Median PTH	25/597 1.00 (Reference)	12/621 0.41 (0.20, 0.85)
> Median PTH	34/572 1.00 (Reference)	31/692 0.93 (0.55, 1.58)

Models adjusted for age, gender, race, randomized treatment arm, eGFR-Cr-Cys, urine ACR, prevalent CVD, prevalent HF, SBP, # anti-hypertensive meds at baseline, smoking, BMI, Total chol., HDL chol.

FR-PO540

Effect of Renal Function and Obstructive Sleep Apnoea on Nocturnal Blood Pressure in Patients with CKD Stage 3-4 Bodil G. Hornstrup,[3,1] Pia H. Gjørup,[2] Jost Wessels,[2] Thomas G. Lauridsen,[2,3] Erling B. Pedersen,[1] Jesper N. Bech.[3,1] *[1]Aarhus University, Aarhus, Denmark; [2]Department of Medicin, Holstebro, Denmark; [3]University Clinic of Nephrology and Hypertension, Holstebro, Denmark.*

Background: Many patients with chronic kidney disease (CKD) suffer from high nocturnal blood pressure (BP) and lack of nocturnal BP decrease. These are known to be associated with poorer outcome related to cardiovascular morbidity and mortality. Reasons for high nocturnal BP in patients with CKD are not known. In this case control study, we studied the effect of obstructive sleep apnoea (OSA) and renal function on nocturnal BP in CKD 3-4 subjects.

Methods: Seventy patients with CKD 3-4 (eGFR 15-59 mL/min) from the Renal Outpatients Clinic, Holstebro Hospital were compared with 56 healthy age-matched controls. 24 h ambulatory BP monitoring, blood samples (creatinine) and cardio respiratory monitoring (Apnoea Hypopnea Index, AHI) were performed in all participants.

Results: Non-dipping was seen in 44% (n=31) of CKD3-4 cases and 18% (n=10) of healthy controls (p=0.002). Moderate to severe OSA (AHI>15) was diagnosed in 26% (n=18) of CKD 3-4 cases and 2% (n=2) of controls (p<0.001). Regression analysis showed an association between BMI and nocturnal BP decrease in CKD (p = 0.001), but not in controls; eGFR or OSA were not associated with nocturnal BP. Compared to dipping CKD3-4 cases, non-dipping CKD3-4 cases had higher BMI (32 vs. 29 kg/m^2, p= 0.024) and HbA1c (52 vs. 43 mmol/mol, p=0.03), longer duration of antihypertensive treatment (10 vs. 6 years, p= 0.02), received more antihypertensive drugs (3 vs. 2, p<0.007), and more had history of AMI (29 vs. 5%, p=0.009).

Conclusions: Non-dipping and moderate to severe OSA were more frequently seen in CKD 3-4 than in healthy controls. In contrast to BMI, neither eGFR nor OSA were associated to nocturnal BP decrease in either group. Non-dipping CKD 3-4 had more obesity, diabetes and ischemic heart disease than dipping CKD. In addition, non-dipping in this CKD 3-4 population was associated with a longer duration and more complex hypertension treatment.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO541

The Effect of Night-Time versus Sleep-Time on Blood Pressure Dipping Ali Mirza Onder,[1] Songul Onder,[2] Tamekia Jones.[2] *[1]Pediatrics, Le Bonheur Children's Hospital, Memphis, TN; [2]University of Tennessee Health Science Center, Memphis, TN.*

Background: There is limited information on the sleep blood pressure profiles and sleep related blood pressure dipping (BPD) for subjects who work at night-time and sleep at daytime.

Methods: 84 medical professionals are evaluated with 24 hour ambulatory blood pressure monitoring (ABPM) during three work- sleep schedules; work daytime and sleep at night-time, work night-time and sleep at daytime, and awake at daytime and sleep at night-time during an off-work day. Subjects were divided into four distinct groups: subjects who only work at daytime and always sleep at night-time (Group A), subjects who switch from working day to night-time in frequent intervals such as every 3-4 days(Group B) or prolonged intervals such as every 3-4 months(Group C) and subjects who only work at night-time and always sleep during daytime(Group D). Sleep score is defined as the product of the sleep BPD percentage and duration of sleep in hours. The Kruskal Wallis test was used to compare differences among groups, and the Signed rank test was used to evaluate paired differences.

Results: Average reported sleep duration was indifferent between the four groups for both periods of work schedule. Although the median BPD profile (15.5 vs 12) and sleep score (112 vs 90) were higher for Group A than Group D, the differences were not statistically significant (p=0.31 and p=0.24). Groups B&C were compared for daytime and night-time work BPD; there was no difference for sleep BPD between two different work times (p=0.47). However, the median sleep score was significantly better when subjects were sleeping at night-time (127.5 vs 103, P=0.02). When the four groups were compared for their BPD during an off-work day, there was no difference for sleep BPD (p=0.43) and for sleep score (p=0.36).

Conclusions: In this preliminary study, the blood pressure dipping was predominantly associated with sleep time rather than night-time. Subjects who work at night had similar sleep BPD compared to subjects who work at daytime. However, subjects who switch shifts achieved a significantly higher sleep score when they slept at night-time, due to longer duration of sleep. The history of night-time work did not affect the sleep BPD on an off-work day, sleeping at night for any of the groups.

FR-PO542

Nocturnal Hypertension Is Common and Is Associated with CKD Progression in the Chronic Kidney Disease in Children Study (CKiD) Cohort Monica L. Guzman- Limon,[1] Shuai Jiang,[2] Derek Ng,[2] Bradley A. Warady,[3] Susan L. Furth,[4] Joseph T. Flynn,[5] Joshua A. Samuels.[1] *[1]Pediatric Nephrology & Hypertension, McGovern Medical School at UTHealth, Houston, TX; [2]Johns Hopkins University, Baltimore, MD; [3]The Children's Mercy Hospital, Kansas City, MO; [4]The Children's Hospital of Philadelphia, Philadelphia, PA; [5]Seattle Children's Hospital, Seattle, WA.*

Background: Hypertension (HT) affects nearly half of all of children with chronic kidney disease (CKD) and is a major modifiable cause of end organ disease. 24 hour ambulatory blood pressure monitoring (ABPM) has demonstrated the significance of nocturnal HT on CKD progression among adults. In children with CKD, the effect of nocturnal HT on CKD progression is unknown.

Methods: Stratified by CKD etiology, we investigated the relationships between daytime or nocturnal HT (or both), and a composite outcome (defined as RRT or a 50% decline in GFR) amonng CkiD participants using Cox proportional hazards models. Daytime and nocturnal HT were defined as: mean BP > 95th percentile and/or load > 25% for either systolic or diastolic BP within wake or sleep periods, respectively.

Results: 1195 ABPM studies from 693 CKiD participants were reviewed. In 501 children with non-glomerular (NG) CKD, 40% were normotensive, 7% had daytime only HT, 19% had nocturnal only HT, and 34% had diurnal HT. In 192 children with glomerular (G) CKD, 44% were normotensive, 6% had daytime only HT, 20% had nocturnal only HT and 30% had diurnal HT. In models adjusting for age, gender and race, among NG children, presence of nocturnal only HT was significantly associated with outcome when compared to normotensive children (HR: 1.80, p=0.02). The presence of dirunal HT in this group had a more pronounced association (HR: 2.37, p<0.001). Among children with G CKD, the presence of nocturnal only HT or daytime only HT was not significantly associated with outcome (HR: 1.60, p=0.30 and HR: 1.31, p=0.67, respectively), while the presence of diurnal HT was strongly associated with outcome (HR: 4.38, p<0.001).

Conclusions: Nocturnal hypertension is associated with a significantly faster decline in kidney function (GFR decline or RRT) when compared to normotensive patients with CKD. This outcome is even more pronounced in patients with diurnal HT. This confirms the utility of ABPM in patients with CKD. Identifying and controlling both daytime and nocturnal HT using ABPM may improve outcomes and delay CKD progression in this population.

Funding: NIDDK Support

FR-PO543

Ambulatory Blood Pressure and CKD Progression in the CKiD Cohort Janis M. Dionne,[1] Shuai Jiang,[3] Derek Ng,[2] Joseph T. Flynn,[4] Susan L. Furth,[5] Bradley A. Warady,[6] Joshua A. Samuels.[7] *[1]BC Children's Hospital/ University of British Columbia, Vancouver, BC, Canada; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [3]Johns Hopkins University, Baltimore, MD; [4]Seattle Children's Hospital, Seattle, WA; [5]The Children's Hospital of Philadelphia, Philadelphia, PA; [6]The Children's Mercy Hospital, Kansas City, MO; [7]University of Texas, Houston, TX.*

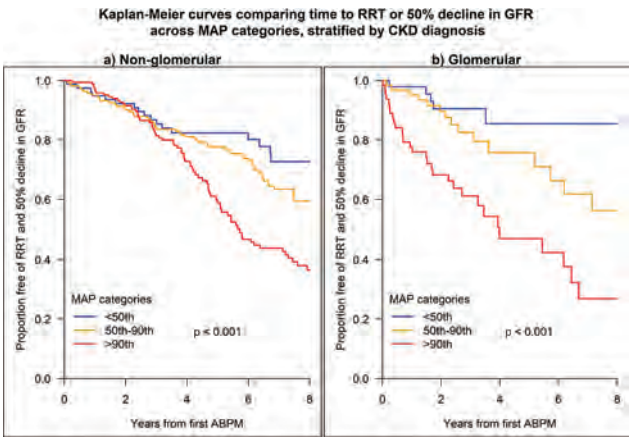
Background: We evaluated mean arterial pressure (MAP) by ambulatory blood pressure monitoring (ABPM) in the CKiD cohort to investigate if low-normal MAP (<50th %ile) was associated with a decreased rate of CKD progression compared to conventional (50th-90th %ile) or high (>90th %ile) MAP.

Methods: The primary outcome was time to renal replacement therapy (RRT) or 50% decline in eGFR. The primary exposure was time-varying MAP. Analyses were stratified by glomerular and non-glomerular diagnosis. 3 Cox models were fit with conventional MAP as the reference: unadjusted; age, gender and race adjusted; + proteinuria adjusted.

Results: 190 children with glomerular and 489 with non-glomerular CKD contributed at least one ABPM study. Those with high MAP were more likely to be African American, had more proteinuria and were less likely to take ACEi/ARB. Among children with glomerular CKD, those with high MAP had a 2.49 higher hazard ratio (HR) for the outcome compared to conventional MAP (95%CI: 1.35, 4.57); the HR for low-normal MAP was protective (0.42, 95%CI: 0.15, 1.15) (Figure 1). The HR with non-glomerular CKD with high MAP was 1.76 (95%CI: 1.25, 2.47) and 0.71 (95%CI: 0.42, 1.21) for low-normal MAP. After adjusting for age, race, and gender results were similar. Adjustment for proteinuria reduced the effect size but not the direction of association or glomerular significance.

Conclusions: Ambulatory MAP >90th %ile was associated with a more rapid progression of CKD in children. The benefit of MAP <50th %ile was slightly reduced after adjustment for proteinuria. The prevalence of ACEi/ARB use was lower among those with high MAP indicating potential for benefit with therapy.

Funding: NIDDK Support



FR-PO544

Reduction of Nocturnal Hypertension in Pediatric Renal Transplant Recipients Christine B. Sethna,[3] Shari Gurusinghe,[1] Rachel Frank,[2] Lulette Infante,[4] Kevin E. Meyers.[5] *[1]Cohen Children's Medical Center, New Hyde Park, NY; [2]Cohen Children's Medical Center, New Hyde Park, NY; [3]Cohen Children's Medical Center of NY, New Hyde Park, NY; [4]Cohen Children's Medical Center of New York, New Hyde Park, NY; [5]The Children Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA.*

Background: Nocturnal hypertension (nHTN) and non-dipper (ND) status are commonly found during ambulatory blood pressure monitoring (ABPM) in pediatric renal transplant recipients (Txp). These entities are associated with cardiovascular risk in adults. The aim was to investigate chronotherapeutic alteration of anti-hypertensive medication on nHTN and end-organ injury in ND Txp.

Methods: 33 ND Txp aged 5-21 with normal overall ABPM and eGFR >30 ml/min/1.73m^2 were randomized to intervention (enalapril, isradipine or propranolol added in the evening) or control (no medication change) in this open label, blinded endpoint clinical trial. ABPM, echocardiography for left ventricular mass index (LVMI) and pulse wave velocity (PWV) were performed at baseline, 3 and 6 months. ND was defined as a decline of <10% in average blood pressure (BP) from day to night. Differences were compared using Fisher's, t-test and paired t-test by intention-to-treat analysis.

Results: Txp included 17 intervention and 16 controls, age 13 (IQR 8,16) yr, 64% male. Baseline demographics, ABPM, LVMI and PWV were similar between groups. Conversion to dipper status occurred in 43% vs 10% at 3 months (p=0.08) and 53% vs 8% (p=0.02) at 6 months for intervention and controls, respectively. Although all ABPM parameters at 3 and 6 months were lower in intervention compared with controls, only systolic night BP at 6 months showed a significant difference (114.9±9.5 vs 106±8.3 mmHg, p=0.01). Changes over time in the intervention group are shown in the table. There were no significant changes over time in controls for ABPM, LVMI or PWV.

Conclusions: Reduction of nHTN and restoration of nocturnal dip in Txp is possible with chronotherapy. Future studies are needed with larger sample sizes to delineate the effect of improved nHTN on end-organ damage.

Funding: Private Foundation Support

Table. Pair-wise Comparison of Changes in the Intervention Group

N=17	Baseline	3 month	P-value*	6 month	P-value*
Systolic Dip (%)	4.8±6.7	7.9±7.6	0.07	10.9±	0.001
Diastolic Dip (%)	9.6±6.7	11.4±11.3	0.25	13.7±7.1	0.09
Night Systolic BP (mmHg)	113.9±10.1	96.9±30.9	0.08	106±8.3	<0.01
Night Diastolic BP (mmHg)	68.1±8.5	57.1±19.4	<0.01	63.1±7.3	0.19
Night Systolic Load (%)	56.8±32.5	26.6±3.8	0.05	31.5±27.5	<0.01
Night Diastolic Load (5)	55.6±37.6	28.6±35.9	0.045	35.5±32	0.04
LVMI (g/m$^{2.7}$)	48.7±14.4	43.3±13.7	0.01	44.6±12.9	0.38
PWV (m/s/)	7.56±0.91	7.78±1.7	0.73	7.8±2.1	0.51

* Compared to Baseline

FR-PO545

Ambulatory (ABP) Hypertension (HT) Over Time Is Associated with Subsequent GFR Decline in Children with CKD Joshua A. Samuels,[3] Derek Ng,[4] Shuai Jiang,[2] Joseph T. Flynn,[5] Susan L. Furth,[6] Bradley A. Warady,[7] Janis M. Dionne.[1] *[1]BC Children's Hospital/ University of British Columbia, Vancouver, BC, Canada; [2]Johns Hopkins University, Baltimore, MD; [3]McGovern Medical School at UTHealth, Houston, TX; [4]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [5]Seattle Children's Hospital, Seattle, WA; [6]The Children's Hospital of Philadelphia, Philadelphia, PA; [7]The Children's Mercy Hospital, Kansas City, MO.*

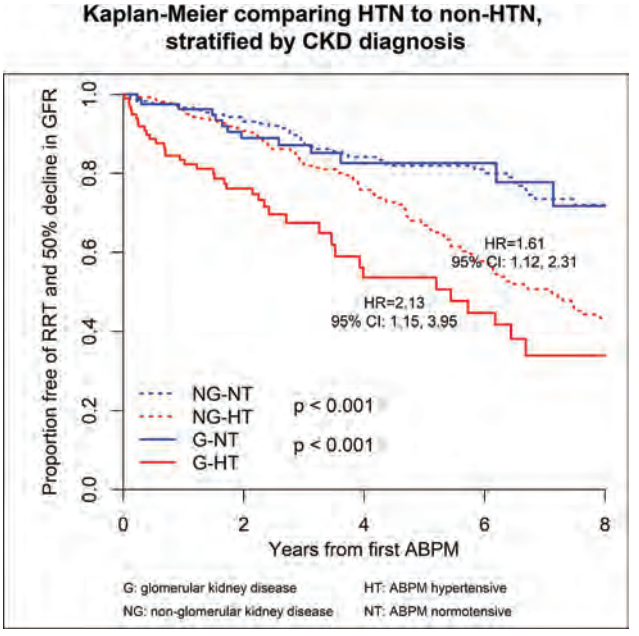
Background: Ambulatory HT is associated with CKD stage. Longitudinal changes in ambulatory blood pressure (ABP) and their relationship to subsequent pediatric CKD progression is poorly described. We characterize changes in ABP and GFR over time in children in the CKiD cohort.

Methods: BP based on ABP and HT defined by CKiD ABP criteria. HT status could change following repeat ABPM (every other year) and thus exposure varied over time. We quantified transitions from normotensive (NT) to HT, as well as the risk of progression to composite endpoint (RRT or 50% drop in GFR) by relative hazards (HR) using Cox proportional hazards models. Analyses adjusted for age, gender, and race and stratified by CKD diagnosis (i.e., glomerular (G=501) or non-glomerular (NG=192) etiology).

Results: A change in BP category was common. For G, 56% had HT at entry; 16% transitioned to a NT during ~6 years follow up. Of those with NT at entry, 20% transitioned to HT. For NG, 60% had HT at entry and 24% transitioned to NT. Among the 40% with NT at entry, 38% transitioned to HT. CKD progression was significantly greater during periods of HT compared to NT. Figure 1 displays the incidence of composite endpoint (GFR decline or RRT) by ABP status (HT= red; NT=blue) for G and NG CKD. Differences were significant by ABP (log rank p< 0.001 for both groups): HT was associated with 2.81 times higher hazard of endpoint among children with G (95%CI: 1.51, 5.24) and a 2.09 times higher hazard among those with NG CKD (95%CI: 1.46, 2.99) in adjusted models. HRs remained significant when adjusted for proteinuria.

Conclusions: Ambulatory HT is common (~58%) in children with CKD. NT transitioned to HT more than vice versa in both G and NG children. Ambulatory HT was strongly associated with CKD progression.

Funding: NIDDK Support



FR-PO546

Comparison of Blood Pressure (BP) Methods and Setting in Children with CKD Tammy M. Brady,[3] Shang-En Chung,[3] Michelle N. Eakin,[3] Andrea C. Goodman,[3] Cozumel S. Pruette,[3] Barbara A. Fivush,[3] Shamir Tuchman,[1] Susan R. Mendley,[4] Kristin Riekert.[2] *[1]Children's National Medical Center, Washington, DC; [2]Johns Hopkins School of Medicine, Baltimore, MD; [3]Johns Hopkins University, Baltimore, MD; [4]University of Maryland, Baltimore, MD.*

Background: Children with CKD are at greater risk for hypertension and high BP is a risk factor for CKD progression. Multiple methods exist to measure BP in clinical practice. We aimed to determine how differing methods of BP measurement:1) correlate with each other and 2) correctly identify hypertensive status.

Methods: Cross-sectional analysis of 116 children in the CKD: Hypertension Adherence in Teens (CHAT) study at baseline. Enrolled children were 11-19 years of age, had CKD, and were prescribed ≥1 BP medication. Children had a clinic BP, 3 consecutive

standardized home oscillometric BPs, and gold-standard 24-hour ambulatory BP (ABPM). BP index (BPi; measured BP/95th %ile BP; BP≥1 indicates hypertension) was calculated to standardize comparisons between BP measurements. Spearman correlation and Cohen's Kappa coefficient (k) were used to compare measurement methods.

Results: Mean age 15.6 +/-2.6 yrs, 53% African American, and 55% male. CKD Stage: I 23%; II 38%; III 26%; IV 6.3%; V 7.3%. 32% of children were classified as hypertensive via day ABPM measurements compared with 20% via home BP (mean or 1st value) and 26% via clinic BP. The prevalence of normotension was 37% using ABPM measurements. Compared to this gold standard, average home BP classified 70% as normotensive (k 0.23), 1st home BP classified 62% as normotensive (k 0.18), and clinic BP classified 53% as normotensive (k 0.2). Clinic BP did not correlate well with other methods of BP measurement [Table].

Conclusions: BP measured in clinic correlates poorly with other standardized measurements of BP and resulted in underdiagnosis of hypertension when compared to BPs obtained by gold-standard ABPM. Home BP measurements, used frequently in place of ABPM, also underdiagnosed hypertension. This underscores the importance of ABPM as part of routine care of children with CKD.

Funding: NIDDK Support

Spearman Correlation of Different BP Measurements

SBP	Home 1st SBP index	Home mean SBP index	Mean awake SBP index
Clinic SBP index	0.16	0.12	0.24
Home 1st SBP index		0.95*	0.52*
Home mean SBP index			0.53*
DBP	Home 1st DBP index	Home mean DBP index	Mean awake DBP index
Clinic DBP index	0.33*	0.32*	0.26*
Home 1st DBP index		0.94*	0.56*
Home mean DBP index			0.62*

*p<0.05

FR-PO547

Prevalence of Elevated Blood Pressure in Multiethnic School-Aged Children in New York City Bernarda Viteri Baquerizo,[3] Jeffrey M. Saland,[2] Clare Ceballos.[1] *[1]Mount Sinai School of Medicine, New York, NY; [2]Mount Sinai School of Medicine, New York, NY; [3]Mount Sinai School of Medicine, New York, NY.*

Background: Pediatric hypertension (HTN) is a public health problem defined by blood pressure (BP) ≥ 95th percentile relative to age, gender, and height on ≥ 3 occasions. Overweight increases the likelihood of elevated BP and HTN and is more common among minority, poor, and male children. These findings (28% overweight with 12% pre-hypertensive / 15% hypertensive range BP) were noted in School Based Health (SBH) centers by a team from this medical center 15 years ago. Our goal was to revisit these centers and a tertiary care hospital-based clinic to assess the quality of BP screening and follow-up and if needed to begin iterative quality improvement (QI) toward reducing consequences of HTN on childhood development and early-onset end organ damage.

Methods: Retrospective cross-section cohort, age 4-21 years, with at least one outpatient visit (SBH or hospital-based) between July 2015-June 2016.

Results: 5739 patients had 8225 encounters. 215 (3.74%) patients had at least one visit with elevated BP, out of which only 16 (7%) had follow-up within the period described. About 3/4 of the visits were at the hospital-based clinics and 2.65% of patients with elevated BP were seen in this setting vs. 4.39% seen at SBH clinics (p-value = 0.003). Appropriate follow-up in patients with elevated BP was noted in 14/126 seen at hospital-based clinics vs. 2/44 seen at SBH clinics. The children with or without elevated BP did not differ with respect to sex (female 52% and 48%, respectively), or AA race (40%), while Latinos were found in 46% patients with normal BP vs. 40% with elevated BP. Median age was 10 for the entire cohort. Obesity was noted in 63% of patients with elevated BP (median BMI 99th percentile.), vs. 34% in patients with normal BP (median BMI 82nd percentile (p-value 0.001;CI -13.65 to -13.56), despite a slightly higher prevalence of patients classified overweight (BMI ≥ 85th percentile) in the latter group.

Conclusions: Although the rate of elevated BP in this population was somewhat lower than other reports of general screening programs, there is nonetheless a significant population of children with elevated BP and overweight as a risk factor for elevated BP. The lack of follow-up among this group of patients with elevated BP highlights the need of quality improvement in the systematic screening and treatment of children in the East Harlem area of New York.

FR-PO548

Association of Creatinine Levels and Hypertension in an International Cross-Sectional Database of Pediatric Patients on Chronic Hemodialysis: The PICCOLO MONDO Initiative Alice Topping,[3] Ricardo Guerrero kanan,[2] Ana C. Alvarez-Elias,[5] Mara Medeiros,[1] Jochen G. Raimann,[3] Peter Kotanko,[3] Maria E. Ferris.[4] *[1]Hospital Infantil de México Federico Gómez, MEXICO, D.F., Mexico; [2]Instituto Nacional de Perinatologia, Mexico, Mexico; [3]Renal Research Institute, New York, NY; [4]University of North Carolina at Chapel Hill, Chapel Hill, NC; [5]MEXICO CHILDRENS HOSPITAL. FEDERICO GOMEZ, Tlalnepantla de Baz, Mexico.*

Background: Hypertension is a concern when treating pediatric chronic hemodialysis (cHD) patients due its association with cardiovascular morbidity and mortality. We aim to describe the association of laboratory markers and demographic information with hypertension in pediatric cHD patients from the PICCOLO MONDO Initiative.

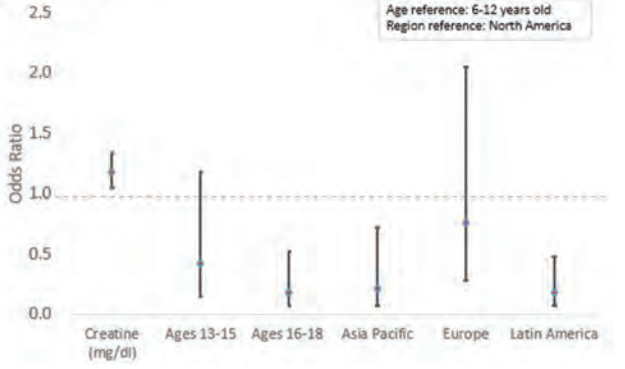
Methods: Routine treatment and laboratory information was compiled in the PICCOLO MONDO database from the years 2000 to 2010. Hypertension was classified as ≥ 95th percentile of pre-treatment systolic sitting blood pressure (SBP) based on age-, sex-, and height-specific percentiles. For subgroup analysis, patients were divided into 4 regions: Asia Pacific (AP), Europe (EU), Latin American (LA) and North America (NA) and 4 age groups: 0-5, 6-12, 13-15, 16-18 y.o.a. The study was approved by the University of North Carolina IRB.

Results: Data from 439 cHD patients < 18 y.o.a in 21 countries were analyzed. The median age was 16 y.o.a. (IQR 13 to 17) and 52.9% were male. Overall, 16.4% of patients were classified as hypertensive. This proportion varied by region: 31.9% of patients in NA, 26.5% in EU, 15.9% in AP and 12.4% of patients in LA were hypertensive (p=0.002). Creatinine was significantly higher in hypertensive patients (8.9±3.3 v. 7.7±3 p=0.02). Creatinine levels varied by age group and region (p=0.04 for regional and p=0.002 for age group comparisons). Logistic regression analysis shows that when controlling for region and age group, each one mg/dL increase in creatinine was associated with a 1.18 times increase in risk of having hypertension (95% CI 1.05 to 1.22).

Conclusions: We found differences in hypertension prevalence by region. Elevated creatinine was found to be a risk factor for hypertension, which may indicate that residual renal function protects against hypertension in pediatric cHD patients.

Funding: Commercial Support - Renal Research Institute

Figure 1: Odds ratios and 95% confidence intervals for logistic regression of hypertension



FR-PO549

Evolution of Systolic Blood Pressure in the First Year of Hemodialysis: A Comparison between Tassin, France, and Renal Research Institute, USA Alice Topping,[3] Hanjie Zhang,[2] Jochen G. Raimann,[3] Charles Chazot,[1] Peter Kotanko.[3] *[1]NephroCare Tassin Charcot, Sainte Foy-Les-Lyon, France; [2]Renal Research Institute, New York, NY; [3]Renal Research Institute, New York, NY.*

Background: Hypertension is common in hemodialysis (HD) patients. In HD patients blood pressure may be related to treatment practices. Currently the conventional HD in the US is prescribed as 3-4 hours, thrice per week. Tassin dialysis center in France performs long, 8-hour HD thrice per week and previously reported exemplary results regarding blood pressure control, fluid management, and phosphate clearance.

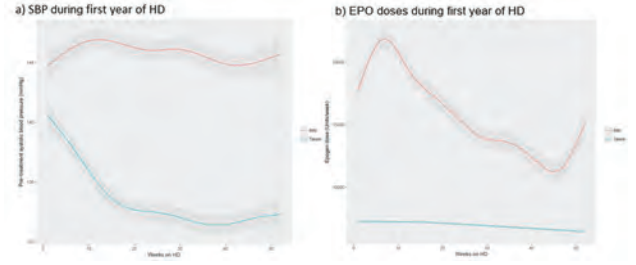
Methods: Patients from the Renal Research Institute (RRI) who started dialysis between 2000 and 2012 were propensity score matched to incident patients beginning HD between 2000 and 2013 from Tassin. RRI patients were matched on baseline (first week on HD) demographic, treatment and laboratory characteristics including age, sex, vascular access, dialysate and serum sodium levels and other relevant parameters. Weekly average SBP and weekly total Epogen doses (EPO) were plotted using generalized additive model over the first year of dialysis.

Results: 487 RRI patients were matched from a pool of 1,914 eligible patients to an equal number of Tassin patients. Patient groups were well balanced on age, sex, diabetes and other parameters. SBP declined steadily in the Tassin group until 18 weeks on HD then continued to decrease gradually until 40 weeks on HD. RRI patients had slightly higher SBP at baseline which increased in the first 12 weeks on dialysis, then declined gradually until week 42 (**Figure 1a**). EPO dose increased for RRI patients in the beginning of HD until 8 weeks, then decreased steadily during the first year of HD. Patients in Tassin showed a steady decrease in EPO use over the first year of HD (**Figure 1b**).

Conclusions: Patients in Tassin, France who receive longer HD times showed marked decreases in SBP compared to RRI patients. Weekly EPO dose decreased in both groups, but remained much higher in RRI patients throughout the first year of HD, particularly in the first weeks of HD. Sustained higher SBP in RRI patients may be related to the higher doses of EPO.

Funding: Commercial Support - Renal Research Institute

Figure 1 : Evolution of SBP and EPO doses in the first year of HD



FR-PO550

Radiological Imaging in Pediatric Renovascular Fibromuscular Dysplasia (FMD) Robert J. Louis, Anne marie Cahill, Kevin E. Meyers. *The Children Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA.*

Background: FMD is a non-inflammatory vascular disease that in children unlike adults has no sex-predilection. FMD is under-recognized, underdiagnosed, with unclear pathogenesis. Doppler Ultrasounds (US), Magnetic Resonance Angiography (MRA), Computed Tomography Angiography (CTA), and Catheter Based Angiography (Ang) are used to make a presumptive diagnosis of FMD.

Methods: We did a retrospective analysis of the clinical features and radiological findings in 26 children diagnosed with FMD at the Children's Hospital of Philadelphia (CHOP), all are entered into the national FMDSA database and have institutional IRB consent

Results: Mean age at diagnosis was 7.4 ± 4.7 yr (4m – 17yr). Family history HTN (54.2%) of FMD (8.3%), Caucasian (61.5%). Headache (46%) and HTN (89.7%) were the most prevalent symptoms and signs at presentation. FMD was unifocal single site 17/25 (68%) or unifocal multiple sites 7/25 (28%) and involved the main or first order renal branch in 17/25 (68%). Isolated deep vessel lesions beyond the 2nd order branches were found in 7/25 (28%) children (Table). Only Ang showed deep vessel disease. US imaging was significantly less sensitive (28% US vs 100% Ang, p = 0.003) and was the least sensitive imaging technique. The NPV of US (41.9%) was also less than that of Ang (100%). US had an equivalent specificity and PPV to that of Ang. This was true for the specificity and PPV of MRA imaging as well, but MRA imaging showed a lower NPV (40%) when compared with Ang. This was the lowest NPV of the imaging modalities. MRA had a better sensitivity (62.5%) than US. Overall, 3D CTA had the best sensitivity (84.2%) and NPV (70%) compared with Ang; but still had much lower specificity (70%) and PPV (84.2%) when compared with Ang.

Conclusions: Only Ang showed deep renal vascular disease. Ang should be done as part of the initial work-up of any child suspected of having renovascular FMD, no matter what the findings are on US, MRA, or 3D CTA.

Funding: Private Foundation Support, Clinical Revenue Support

Peripheral site of renal vasculature narrowing in 7/25 (28%) (more than 1 site often involved)

Location	Total stenoses (%)	Unifocal single site	Unifocal multiple sites	Multifocal	Patients n=25 (%)
2nd order	6 (9.4)	1	3	2	4 (16)
3rd order	5 (7.8)	2	1	2	4 (16)
4th order	3 (4.7)	1	0	2	2 (8)
Periphery	1 (1.6)	0	0	1	1 (4)

FR-PO551

Racial Disparities in Pediatric Hypertension Management Christopher Cates,[2] Bethany Crawford,[2] John Lin,[4] Nichaela A. Hoffman,[1] Thomas K. Davis,[3] Vikas R. Dharnidharka,[3] Laura Hesemann.[2] *[1]Barnes Jewish Hospital, St. Louis, MO; [2]University of Missouri School of Medicine, Columbia, MO; [3]Washington University School of Medicine, St Louis, MO; [4]Washington University in St. Louis, St. Louis, MO.*

Background: African American (AA) adults have a higher prevalence of HTN and lower rates of control when compared to non-Hispanic whites (non-AA). Evidence for a similar disparity in pediatric populations is mixed though there are differences in hypertension-related morbidity. Studies assessing differences in HTN control between ethnic groups are lacking for pediatric patients. The goal of this study was to evaluate rates of HTN control among pediatric patients of different ethnicity.

Methods: All patients with a diagnosis of HTN seen between May 2012 and April 2013 at a pediatric nephrology clinic in an academic center were evaluated. Patients with resolved HTN, ESRD, or history of kidney transplant were excluded. Blood pressure control was recorded as documented by the treating physician. Data were collected to evaluate risk factors for uncontrolled HTN, including race, age, gender, stage of HTN, number of medications, BMI, and presence of CKD.

Results: 126 subjects were included. 41 (33%) identified as African American, 85 (67%) identified as Caucasian, Asian, or Other. Median age was 14 (range 5 months-20 years). Among all subjects, 83% were documented as having adequate BP control. However, the rate of control among AA subjects was 68% compared to 87% among non-AA subjects (p=0.012). When comparing racial groups, there was no difference in BMI group, CKD, family history, use of multiple anti-hypertensive medications, or stage of HTN.

Conclusions: In this pediatric cohort, AA subjects were less likely to have adequately-controlled blood pressure when compared to non-AA despite no difference in commonly-assessed risk factors for HTN or the number of medications prescribed. This parallels results obtained through population-based studies showing lower rates of blood pressure control among AA adults compared to non-AA and highlights the need to further address racial disparities in pediatric health care.

Blood Pressure Control and Risk Factors by Ethnicity

	African American (N=41)	Non-African American (N=85)	p-value
Controlled	68%	87%	0.012
Overweight or obese	62%	60%	0.877
CKD	23%	28%	0.587
Family History of HTN	82%	76%	0.472
>1 medication	20%	29%	0.236

Pearson Chi-Square or Fisher's Exact Test as appropriate

FR-PO552

Ventricular Dysfunction in Children with Controlled Hypertension and CKD Wacharee Seeherunvong,[1] Aura J. Arenas Morales,[1] Arpit K. Agarwal,[2] Marissa J. Defreitas,[1] Chryso P. Katsoufis,[1] Gaston E. Zilleruelo,[1] Carolyn L. Abitbol,[1] Sethuraman Swaminathan,[2] Michael Freundlich.[1] *[1]University of Miami/ Pediatric Nephrology, Miami, FL; [2]University of Miami/ Pediatric Cardiology, Miami, FL.*

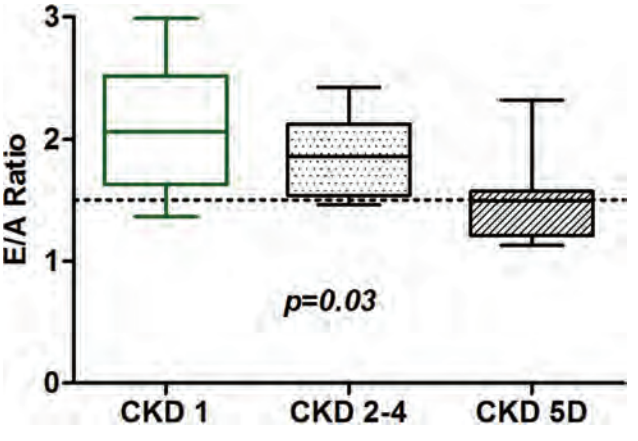
Background: Hypertension (HTN) contributes to left ventricular hypertrophy (LVH) and dysfunction, and accelerates cardiovascular (CV) disease in chronic kidney disease (CKD), but the thresholds linking blood pressure (BP) with eventual CV events in children are unknown. Suggested targets for optimal therapy are <95th %ile BP reference values, but whether sustaining BP within these targets averts LVH and ventricular dysfunction in children is uncertain.

Methods: From 70 patients (14.6±0.2 years) with an initial diagnosis of HTN and available echocardiographic evaluation, 33 (14 on renin-angiotensin system blockers) with controlled BP <95th %ile and eGFR-based CKD stages 1 (n=16), 2-4 (n=10) and 5D (n=7) were analyzed.

Results: BP Z-scores (Zs) were similar in all groups. Echocardiogram revealed LVH in 19%, 20% and 43% in stages 1, 2-4 and 5D, and abnormal relative wall thickness (RWT >0.37cm) in 44%, 60% and 71% respectively. While systolic function remained normal, diastolic function E/A ratio was reduced in 13%,20% and 71% of stages 1,2-4 and 5D and declined across stages (p<0.05) (Figure 1). E/Em and E/Es abnormal Zs were uncommon. At least 1 abnormal diastolic function was present in 25%, 50% and 86% in above stages (p<0.05). LVMI Zs correlated positively with BMI Zs, E/Em and E/Es Zs, and negatively with serum Ca (all p<0.05), but did not correlate with BP Zs. BP Zs did not correlate with any marker of diastolic function.

Conclusions: Despite controlled HTN, abnormal ventricular geometry and altered diastolic function were observed even in the earliest stages CKD. Other factors operative with declining kidney function may be responsible for the described changes. Longitudinal studies are needed to evaluate the effects of more stringent BP control on LVH and abnormal diastolic function in young CKD patients with HTN.

Funding: Clinical Revenue Support



FR-PO553

Epigenetic Clock and Biological Aging during Preeclampsia Natasa Milic,[2,3] Vesna D. Garovic.[1] *[1]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [2]Department for Medical Statistics and Informatics, School of Medicine University of Belgrade, Belgrade, Serbia; [3]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN.*

Background: Preeclampsia is a pregnancy-specific disorder clinically characterized by hypertension (blood pressure ≥140/90 mmHg) and proteinuria (≥300 mg per day).

Aberrant placental aging and increased placental senescence have been demonstrated in preeclampsia, as well as the role of epigenetic mechanisms, such as DNA methylation, in control of maternal gene expression in normal pregnancies, which can be disrupted in preeclampsia. The aim of this study was to test the hypothesis that biological aging is accelerated in women with preeclampsia vs. those with normotensive pregnancies.

Methods: Biological age was measured by "epigenetic clock," an estimate of DNA methylation age using the elastic net regression model, consisting of methylation values across 353 specific CpGs that were found to vary with age. Data from the 450k methylation of 44 blood samples from preeclamptic (n=11, mean age 30±7 years) and normotensive (n=34, mean age 31±4 years) patients during the first and second trimesters and at the time of delivery were used to compare longitudinally the estimated DNA methylation (epigenetic) ages during preeclamptic and normotensive pregnancies.

Results: Biological age for women with normotensive pregnancies have not changed over the course of pregnancy (32±6 years for all time points). In contrast, biological age significantly increased over the course of preeclamptic pregnancies: first trimester, 30±8 years; second trimester, 31±9 years; and delivery, 32±9 years ($p<0.05$).

Conclusions: Our data suggest that preeclampsia may behave as a premature-aging-like state. These findings set the stage for future studies that may identify novel mechanistic pathways in preeclampsia.

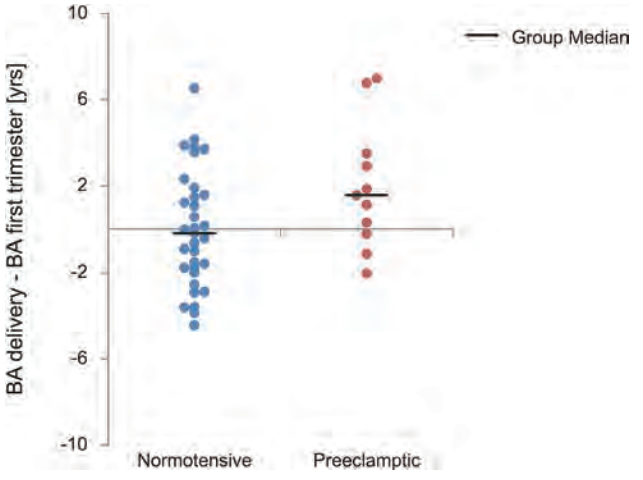


Figure 1. Difference in biological aging (BA) during course of pregnancy in normotensive and preeclamptic pregnacies

FR-PO554

Fetal but Not Maternal APOL1 Genotype Is Associated with Increased Risk for Preeclampsia among African-Americans Rebecca C. Hjorten,[3,11] Kimberly J. Reidy,[3] Claire L. Simpson,[8] A Z. Rosenberg,[12] Stacy Rosenblum,[4] Csaba P. Kovesdy,[10] Frances A. Tylavsky,[10] Joseph Myrie,[1] Bianca L. Ruiz,[1] Khyobeni Mozhui,[10] Soulin Haque,[1] Masako Suzuki,[1] Sandra E. Reznik,[5] Frederick J. Kaskel,[2] Jeffrey B. Kopp,[7] Cheryl A. Winkler,[6] Robert L. Davis.[9] *[1]Albert Einstein College of Medicine, Bronx, NY; [2]Albert Einstein College of Medicine, Children's Hospital at Montefiore, Bronx, NY; [3]Children's Hospital at Montefiore/ Albert Einstein College of Medicine, Bronxville, NY; [4]Montefiore Medical Center, Suffern, NY; [5]Montefiore Medical Center and Albert Einstein College of Medicine/St. John's University, Queens, NY; [6]NCI, NIH, Frederick National Laboratory, Frederick, MD; [7]NIDDK, NIH, Bethesda, MD; [8]UNIVERSITY OF TENNESSEE HEALTH SCI CTR, Memphis, TN; [9]University of Tennessee, Memphis, TN; [10]University of Tennessee Health Science Center, Memphis, TN; [11]Nephrology and Hypertension, Cincinnati Children's Hospital, Cincinnati, OH; [12]Pathology, Johns Hopkins University, Baltimore, MD.*

Background: African Americans are at increased risk for preeclampsia. Genetic variants in apolipoprotein L1 (*APOL1*) account for a substantial fraction of increased risk of kidney disease among African Americans. *APOL1* is expressed in human placenta, and transgenic mice expressing *APOL1* develop preeclampsia. The role of *APOL1* variants in human preeclampsia has not been studied.

Methods: Two studies were performed evaluating maternal and fetal *APOL1* genotypes in African American women with preeclampsia. At Albert Einstein College of Medicine (AECOM) Affiliated Hospitals, we studied 122 pregnancies in African American women with preeclampsia. At University of Tennessee Health Science Center (UTHSC), we studied 93 pregnancies in African American women with preeclampsia compared to 793 control birth mothers and infants.

Results: In both studies fetal *APOL1* high risk (HR) genotype was associated with preeclampsia in their mothers, relative risk at AECOM 1.65 (95% CI 1.11, 2.44) and odds ratio at UTHSC 1.92 (1.05,3.49). In both studies, maternal *APOL1* HR genotypes were not associated with preeclampsia. Gestational age, birth weight and Cesarean section did not vary by *APOL1* genotype. Fetal *APOL1* HR genotype births with preeclampsia were no more likely to have severe preeclampsia, but those mothers were more likely to have cerebral or visual disturbances (63% versus 37%, $p = 0.04$) and infants had lower APGAR scores at 5 minutes (8.0 versus 9.0, $p = 0.01$).

Conclusions: Fetal *APOL1* high-risk genotype confers an increased risk for preeclampsia, likely by adversely affecting placental function. *APOL1* genetic testing may have a clinical role to predict and perhaps improve pregnancy outcomes.

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FR-PO555

Determinants of Preeclampsia and Low Birth Weight in Pregnant Women with CKD Bogdan M. Sorohan,[1] Bogdan Obrisca,[1] Vlad T. Berbecar,[2,1] Andreea Andronesi,[1,2] Gener Ismail.[1,2] *[1]Fundeni Clinical Institute, Bucharest, Romania; [2]University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania, Bucharest, Romania.*

Background: Pregnant women with CKD are at high risk for adverse maternal and fetal outcomes, such as preeclampsia, low birth weight (LBW) and mortality, even those with mild CKD. Moreover, pregnancy itself is a risk factor for CKD progression. CKD and preeclampsia share common features, like proteinuria and hypertension, that make the differential diagnosis difficult during pregnancy. The aim of this study was to evaluate the clinico-biological determinants associated with preeclampsia and LBW in pregnant women with CKD.

Methods: We performed a prospective, observational cohort study on 32 pregnant patients with CKD. Exclusion criteria were eGFR <15ml/min and loss to follow-up. Definitions of preeclampsia in CKD and LBW were defined according to American College of Obstetricians and Gynecologists. To identify the predictors, we performed multivariate Cox and binary logistic regression.

Results: The median age was 23 years (IQR: 21.2-25) and 84.4% were nulliparous. Mean eGFR at referral was 46.5±16.1 mL/min//1.73m^2, 78.1% had CKD stage 3-4 and mean 24h proteinuria at referral was 1.01±0.6 g/24h, 50% of patients had >1.5g/24h. The most frequent primary disease for CKD was glomerulonephritis (78.1%), especially lupus nephritis (18.8%). The incidence of preeclampsia and LBW were 56.3% and 53.1%, respectively. Fetal death was present in one pregnancy (3.1%). Patients with preeclampsia were more hypertensive (61.3% vs 35.7%, p=0.15), proteinuric (1.23 vs 0.73 g/24h, p=0.02) and with a more decreased renal function (41.9 vs 52.4 ml/min/1.73m^2, p=0.004) at referral. By Cox multivariate analysis proteinuria >1.5g/24h at referral was independently associated with preeclampsia (HR=4.20, CI: 1.47-12.04, p=0.07) and preexisting hypertension presented a suggestive trend of association (HR=2.34, CI: 0.68-6.14, p=0.08). In multivariate logistic regression, proteinuria >1.5g/24h presented a close to significant association with LBW (OR=3.66, CI: 0.84-15.84, p=0.08).

Conclusions: In conclusion, proteinuria >1.5g/24h at referral is an independent determinant of preeclampsia, also presenting a trend of association with LBW and preexisting hypertension has a marginally significant tendency as a determinant for preeclampsia in pregnant women with CKD.

FR-PO556

Pregnancy Is Associated with Higher Central Systolic and Pulse Pressures in Later Life Karyne Pelletier,[2] Anne-Marie Cote,[1] Francois Madore,[2] Remi Goupil.[2] *[1]CHUS - Hopital Fleurimont, Sherbrooke, QC, Canada; [2]Hopital du Sacre-Coeur de Montreal, Montreal, AB, Canada.*

Background: Healthy pregnancy has been associated with increased arterial stiffness and central hemodynamics which normalises after delivery. Whether these changes portend to long-term changes in central blood pressures (BP) remains unknown.

Methods: Using the CARTaGENE populational database, central hemodynamic parameters were adjusted and compared between 1) women without previous pregnancies, 2) women with previous pregnancies of less than 20 weeks only and 3) women with previous pregnancies of longer term.

Results: Of 10,266 female CARTaGENE participants, 8,662 had previous pregnancies (666 with previous pregnancies ≤ 20 weeks only). Baseline characteristics are presented in the below table. After adjustment for important covariables, central systolic BP, central pulse pressure and augmentation index were higher in women with previous pregnancies ≤ 20 weeks than in women without pregnancies and with > 20 weeks pregnancies (p-values for trend <0.001, 0.001 and 0.04 respectively).

Conclusions: In this cohort, pregnancy was associated with increased central BP and indices of arterial stiffness in later life, the importance of which was greater when pregnancies longer than 20 weeks occurred. To what extent these differences could be explained by complications during pregnancy requires further investigations.

Characteristics	No pregnancy (n=1,604)	Pregnancy ≤ 20 weeks or less only (n=666)	Pregnancy > 20 weeks (n=7,996)
Age	54 ± 8	53 ± 7 [a]	54 ± 8 [b]
Age of first pregnancy	-	27 ± 7	25 ± 5 [b]
Diabetes	7%	7%	7%
Cardiovascular disease	4%	4%	4%
Treated hypertension	19%	15% [a]	22% [ab]
Brachial systolic BP	119 ± 15	118 ± 17	120 ± 16 [ab]
Brachial pulse pressure	47 ± 11	47 ± 11	48 ± 11 [ab]
Heart rate	70 ± 10	69 ± 11	69 ± 11 [a]
Adjusted central hemodynamic parameters			
Central systolic BP	113.2 (112.7, 113.7)	113.5 (112.9, 114.1)	114.1 (113.7, 114.6) [ab]
Central pulse pressure	41.1 (40.3, 41.8)	41.4 (40.6, 42.3)	42.4 (41.8, 43.1) [ab]
Augmentation index	31.2 (30.3, 32.0)	31.7 (30.6, 32.7)	31.8 (31.1, 32.6) [a]

[a] p<0.05 vs no pregnancy; [b] p<0.05 vs pregnancy 20 weeks or less.

Values are reported as mean ± standard deviation or as estimated marginal means (95%CI) adjusted for age, BMI, diabetes, cardiovascular disease, active smoking, total cholesterol, HDL-cholesterol, eGFR, uric acid, TSH, heart rate, mean BP and use of renin-angiotensin blockers, calcium channel blockers, diuretics, beta-blockers, statins and aspirin.

FR-PO557

Characterizing the Burden of Hypertension in High Alpine Himalayan Villages of Nepal

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Background: Villages in the Ganesh Himal mountains are located in a remote high altitude regions of the Himalayans where there is limited access to basic resources and medical care. The burden of hypertension (HTN) has never been assessed in these communities. The primary objectives of this evaluation were to determine the prevalence of HTN while providing clinical care at medical camps with Himalayan Healthcare (HHC).

Methods: We conducted a retrospective observational evaluation of adults ≥18 years living in Himalayan villages at ≥15,000 feet elevation who attended HHC clinics during the spring medical trek of 2017. HTN was defined as systolic (SBP) and diastolic blood pressure (DBP) ≥150/80 mmHg on two measurements by manual cuff. This cut off was selected given the limited medical resources available for treatment. Urine samples were sought for albumin and glucose in individuals with HTN.

Results: A total of 650 individuals (mean 50±19.9 years, 75%F) received care at the medical camps. BP was ≥150/80 mmHg in 43 patients (6.6%, mean age 65±13.8 years, 60%F) mean SBP among hypertensive patients was 172±18.3 mm Hg, and mean DBP was 96 ±11.6 mm Hg. There were 607 individuals (93.4%) without HTN (mean age 49 yrs ±19.8, 76%F, **Table 1**). Urine analysis was available in 48.8% of the HTN group of which 23.8% had trace albumin and 0.0% had glucosuria.

Conclusions: In high elevation Himalayan villages of Nepal the prevalence of HTN with BP ≥150/80mmHg was low but the severity of hypertension was high. Nearly one quarter of hypertensive individuals had albuminuria suggesting that end organ damage to the kidney is common. Our findings may under estimate the true prevalence of HTN given the predominance of females in the sample population and the high BP cut off. These results support a need for targeted interventions to diagnosis and manage HTN in high-altitude communities. They also have implications for public health policy in developing countries with limited resources.

Table 1: Blood Pressure in Ganesh Himal Villages of the Himalayan Mountains

	Overall	Sertung Village	Lapa Village
All Individuals, N	650	346	304
Age years, (mean ±SD)	50 ±19.9	51 ±20.2	48 ±19.4
Sex, Female N (%)	488 (75.0)	249 (72.0)	238 (78.3)
BP ≥150/80, N (%)	43 (6.6)	19 (5.5)	24 (7.9)
Age years, (mean ±SD)	64.8 ±13.8	62.6 ±19.1	66.5 ±13.4
Sex, Female N (%)	26 (60)	12 (63.2)	14 (58.3)
BP <150/80, N (%)	607 (93.4)	327 (94.5)	280 (92.1)
Age years, (mean ±SD)	49 ±19.8	50.8 ±20.3	46.9 ±14.3
Sex, Female N (%)	461 (76.0)	237 (72.5)	224 (80.0)

FR-PO558

Incidental Risk of Hypertension According to the Change of Body Weight (BW) in Korean Men

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Background: Despite accumulated evidence of strong relationship between obesity and hypertension, risk for hypertension according to the change of BW is not clearly identified. Therefore, this study was to evaluate the incidental risk of hypertension according to the change of BW.

Methods: 26,483 normotensive Korean men had been followed up from 2005 to 2010. Based on baseline BW in 2005, the changes of BW [(BW at censoring time – BW at baseline)/follow-up period (person-years)] were categorized into 5 groups according to their change levels from the lowest to the highest quintile (Q) (1st – 5thQ). On the base of 3rd Q, 1st and 2nd Q had negative changes of BW, and 4th and 5th Q had positive changes of BW. Cox proportional hazard models was used to evaluate the effect of BW change on the incidental risk of hypertension.

Results: During follow-up, 4,445 (16.8 %) cases of hypertension newly developed (Q 1-5: 19.0, 12.9, 12.4, 14.8, and 24.8% respectively). When quintile 3 was set as a reference in adjusted model, the hazard ratios (HRs) for incidental hypertension exhibited a J-shaped relationship with the BW changes (Q1: 1.66 [95% confidence interval (CI): 1.41–1.95], Q2: 0.96 [95% CI: 0.80–1.14], Q3: 1.00 [reference], Q4: 1.30 [95% CI: 1.10–1.54], and Q5: 3.39 [95% CI: 2.91–3.96], respectively).

Conclusions: The incidental risk of hypertension increased in weight loss as well as weight gain, which demonstrated J-shaped relationship. This finding warrants further studies to investigate the incidental relationship between BW changes and hypertension.

Table 1. Baseline characteristics of participants according to the BW changes per person-year in quintile groups

Characteristic	Overall	BW changes per person-year				
		Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Number (n)	26,483	5,296	5,297	5,296	5,298	5,296
Total person-year	97,713.3	16,898.2	21,590.3	21,903.2	21,218.3	16,103.3
Average person-year	3.69 ± (1.44)	3.19 ± (1.57)	4.07 ± (1.24)	4.13 ± (1.18)	4.00 ± (1.23)	3.04 ± (1.53)
Age (years)	42.7 ± (6.9)	43.6 ± (7.3)	42.9 ± (6.7)	42.8 ± (6.7)	42.2 ± (6.6)	42.9 ± (7.0)
Range of BW change/person-year	-13.16 – 12.07	-13.16 – -0.55	-0.58 – -0.06	-0.06 – 0.30	0.30 – 0.81	0.81 – 12.07
Range of BW change (kg)	-25.0–23.1	<-1.9	-1.9 – -0.2	-0.2–1.0	1.0–2.7	≥2.7
BW (kg)	71.3 ± (9.1)	74.2 ± (9.1)	71.3 ± (8.5)	70.4 ± (8.8)	70.1 ± (8.9)	70.6 ± (9.4)
Range of BMI change	-8.10–8.33	<-0.65	-0.65– -0.10	-0.10–0.35	0.35–0.91	≥0.91
BMI (kg/m²)	24.1 ± (2.7)	25.1 ± (2.6)	24.2 ± (2.5)	23.9 ± (2.6)	23.7 ± (2.6)	23.7 ± (2.8)
Systolic BP (mmHg)	110.8 ± (10.7)	112.1 ± (10.8)	110.8 ± (10.5)	110.2 ± (10.7)	110.2 ± (10.5)	110.8 ± (10.9)
Diastolic BP (mmHg)	74.6 ± (7.0)	75.6 ± (6.9)	74.7 ± (6.9)	74.3 ± (7.0)	74.1 ± (6.9)	74.5 ± (7.1)
SCr (mg/dL)	1.13 ± (0.11)	1.13 ± (0.12)	1.13 ± (0.12)	1.13 ± (0.10)	1.12 ± (0.10)	1.12 ± (0.11)
Current smoker (%)	43.3	40.7	40.7	41.8	44.6	48.9
Alcohol intake (%)	31.0	31.9	31.2	30.6	30.8	30.8
Regular exercise (%)	14.7	14.7	14.2	14.7	14.6	15.6
Family history of HTN (%)	31.3	31.0	30.6	30.1	32.5	32.3
Diabetes (%)	3.2	3.2	2.9	2.2	2.9	2.8
Development of HTN (%)	16.8	19.0	12.9	12.4	14.8	24.8

Data are shown as means ± (standard deviations), medians (interquartile ranges), or percentages. BW, body weight; BMI, body mass index; BP, blood pressure; SCr, serum creatinine; HTN, hypertension.

Table 2. Hazard ratios (HRs) and 95% confidence intervals (CI) for hypertension incidence according to the BW change per person-year in quintile groups

	Person-year	Range of body weight changes	Incidence cases	Incidence density	HR (95% CI)		
					Unadjusted	Model 1	Model 2
Body weight changes per person-year							
Quintile 1	16,898.2	<-1.9	1,069	59.6	1.59 (1.31–2.20)	1.46 (1.30–1.63)	1.49 (1.27–1.75)
Quintile 2	21,590.3	-1.9 – -0.2	661	31.5	1.08 (0.97–1.20)	0.95 (0.85–1.07)	0.90 (0.76–1.07)
Quintile 3	21,903.2	-0.2–1.0	657	30.0	1.00 (reference)	1.00 (reference)	1.00 (reference)
Quintile 4	21,218.3	1.0–2.7	766	36.9	1.30 (1.17–1.44)	1.30 (1.20–1.45)	1.30 (1.10–1.45)
Quintile 5	16,103.3	≥2.7	1,313	81.7	2.92 (2.66–3.20)	3.33 (2.83–3.50)	3.34 (2.79–3.76)
P for quadratic trend					<0.001	<0.001	<0.001

Model 1 was adjusted for age, baseline body weight, baseline blood pressure, total cholesterol, GGT, ALT, log(hsCRP), log(HOMA-IR), and eGFR.

Model 2 was adjusted for all factors in model 1 plus alcohol intake, family history of HTN, current smoking status, regular exercise, and diabetes.

FR-PO559

Global Variation in Blood Pressure Control and Anti-Hypertensive Therapy in CKD Patients with Hypertension

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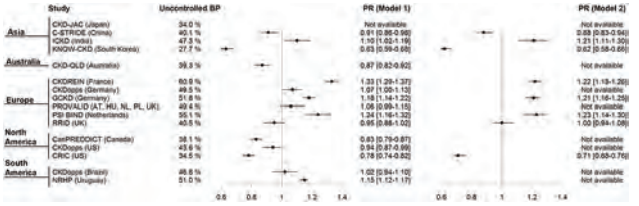
Background: Rates of blood pressure (BP) control in patients with CKD vary considerably worldwide. How differences in patient characteristics and antiHT treatment regimens relate to patterns of BP control is uncertain.

Methods: We used data from 14 studies participating in iNET-CKD, including 34,901 patients with eGFR <60 ml/min/1.73m2 and HT (defined as either BP ≥140/90 mmHg or antiHT drug use) to compare the prevalence of uncontrolled BP (≥140/90) across 16 countries using adjusted observed to expected prevalence ratios (PR).

Results: Rates of uncontrolled BP varied from 28% to 61% (Figure 1). After adjusting for age, gender, DM, and GFR, prevalence ratios remained higher in cohorts from continental Europe, India, and Uruguay. AntiHT use varied from 54% to 87% for RAAS inhibitors, 11% to 76% for diuretics, 26% to 75% for Ca channel blockers, and 22% to 68% for beta-blockers. In 8 out of 15 studies, >50% of patients with uncontrolled BP received <3 antiHT drugs. The number of prescribed antiHT classes was higher in cohorts from North America and Germany.

Conclusions: Global variation in BP control is only partly explained by patient characteristics. Heterogeneity of antiHT treatment practices may also play a role and would be potentially modifiable.



FR-PO560

Hypertension in High School Students: Genetic and Environmental Factors (HYGEF Study) Roberto Bigazzi,[1] Chiara Lanzani,[2] Laura Zagato,[2] Salvatore Lenti,[3] Simone Fontana,[2] Elisabetta Messaggio,[2] Nunzia Casamassima,[2] Valentina Batini,[1] Francesca Nistri,[1] Giada G. Santini,[1] Elena Brioni,[2] Simona Delli carpini,[2] Lorena Citterio,[2] Marco Simonini,[2] Stefano Tentori,[2] Filippo Cellai,[1] Cristiano Magnaghi,[2] Stefano Bianchi,[1] Vito M. Campese,[4] Paolo Manunta.[2] *[1]USL NO, Livorno, Italy; [2]Osp San Raffaele, Milan, Italy; [3]USL SE, Arezzo, Italy; [4]USC, Los Angeles, CA.*

Background: To evaluate the impact of gene pathways (Adducin (ADDs), Endogenous Ouabain (EO) genetic polymorphisms) in the transition from normotension to hypertension(HT) we performed an epidemiological study in 3 regions of northern(MI), central(Li), southern(Gr) Italy among young (age<18) high school students (St).

Methods: During a morning medical visit, we measured systolic (SBP) and diastolic (DBP) blood pressure, body weight, height, body mass index(BMI). A spot urine sample was collected to measure sodium (UNa), potassium (UK), creatinine, albumin. Finally, a saliva sample was obtained for DNA analyses. The 24 hour UNa was extimated according to Kawasaki's formula. Statistical analyzes were adjusted for age, sex, BMI and origin.

Results: Preliminary results on 2635 St (F1501, M1134, age 16,8±1,8 yrs) showed regional differences both for estimated UNa (Gt 196.4±2.5 mEq/24h; Mi 178.7±2.8; Li 171.5±2.1; p <0.001), and SBP (Li 121.1±0.4 vs Mi 118.9±0.4, Gt 118.4±0.4 mmHg). SBP was significantly correlated with BMI (r = 0.324, p <0.0001), and with UNa(r = 0.138 p <0.0001). Offspring with hypertensive parents (34%) showed higher SBP values than peers with negative familiarity (122±0.6 vs120±0.4 mmHg, p=0.04). In the analysis of the genotypes the Lanosterol Synthasi (LSS) polymorphism, the enzyme involved in the synthesis of EO, was associated with increased DBP (LSS AA 69.2±0.6; LSS AC 68.3±0.3; LSS CC 66.7±0.3 mmHg, p <0.0001). Carriers of both mutated variants of ADD1 and ADD2 (ADD1GT/ADD2 CT, n=167) showed greater (p = 0.015) UNa(192.9±4.3 mEq/24h) than St with genetic variants ADD1 GG/ADD2 CC (n = 826, 185.2±1.9 mEq/24h). The urine albumin/creatinine ratio was higher (12.3±2.3) in St with ADD3 GG / ADD2 CT(n=54) than in St with ADD3 AA / ADD2 CC (n=442, 8.1±0.8 mg/dl; p=0.05). The UNa/UK was greater in St carrying LSS AA/CYP1A1 CC (4 ± 0.4) vs. LSS GG/CYP1A1 AA (3.2±0.3; P=0.05).

Conclusions: These results confirm the role of the Adducin-EO genetic network in HT and identify interactions among environmental factors (Na and K intake) and genetic polymorphisms linked to HT.

Funding: Government Support - Non-U.S.

FR-PO561

Genetic Factors Predicting BP Response to Thiazides Differ in Hypertensive African Americans with and without APOL1 Genotypes Patrick Cunningham,[1] Zhiying Wang,[3] Rhonda M. Cooper-DeHoff,[2] Arlene B. Chapman.[1] *[1]University of Chicago, Chicago, IL; [2]University of Florida, Gainesville, FL; [3]University of Houston, Houston, TX.*

Background: Essential hypertension (HBP) is common, and disproportionately affects African Americans (AAs) with higher rates of cardiovascular and renal disease. Recently, variants of the APOL1 gene have been associated with a higher rate of kidney disease, with studies suggesting a complex role in cardiovascular disease. We investigated whether genetic background in APOL1 affected individuals predicted sensitivity to thiazide diuretics in in AA with HBP.

Methods: We combined AA patients from three HBP trials (PEAR1: NCT002465519, n=298, PEAR2: NCT01203852, n=190, and GERA1, n=280) to assess whether APOL1 genotype predicted BP response to thiazide diuretics. Subjects with elevated serum creatinine or significant proteinuria were excluded from these studies. Patient genetic data (*n*=570) was analyzed by Affymetrix or Illumina Human Omni1-Quad Beadchip with correction for age, gender, baseline BP, and racial admixture. G1 and G2 variant alleles were detected by imputation using the g1000 data set (PEAR1, PEAR2), or by direct sequencing (GERA1). GWAS was performed on this data set to detect SNPs associated with differential response to thiazides.

Results: 14.9% of this combined HBP cohort (n=85) was positive for two APOL1 risk alleles. SBP or DBP at baseline and SBP or DBP response to thiazides, as measured by office or home cuff were similar between APOL1 negative and positive individuals. GWAS performed after adjusting for APOL1 genotype found that an intronic SNP rs111955547, located in *ROBO2*, was associated with a significantly decreased response to thiazides for office DBP (p=4.8 x 10^{-8}). Similarly, rs12943080, located in an intronic SNP in *SNF8*, was associated with a significantly decreased response to thiazides for night time SBP (p=5.0 x 10^{-7}).

Conclusions: Although HBP APOL1 AA individuals demonstrated similar BP responses to thiazides, genetic variants of *ROBO2*, which has a known role in podocyte development, as well as *SNF8*, which interacts with TRPC6, responsible for autosomal dominant FSGS, may identify individuals with poor response to thiazide diuretics.

Funding: Other NIH Support - NIGMS

FR-PO562

APOL1 Hypertensive African Americans Show Greater BP Response and Urinary Albumin Reduction to Angiotensin Receptor Blockade with Different Genetic Predictors of Response versus Non-APOL1 Individuals Patrick Cunningham,[1] Zhiying Wang,[3] Rhonda M. Cooper-DeHoff,[2] Arlene B. Chapman.[1] *[1]University of Chicago, Chicago, IL; [2]University of Florida, Gainesville, FL; [3]University of Houston, Houston, TX.*

Background: Hypertension (HBP) is common and disproportionately affects African Americans (AAs). HBP AAs typically are salt sensitive and respond more to thiazide diuretics, with a relatively suppressed renin-angiotensin-aldosterone axis. Variants of the APOL1 gene specific to AAs are associated with a higher rate of kidney disease and a complex role in cardiovascular disease. We sought to characterize HBP *APOL1* AA individuals and their response to antihypertensive therapy.

Methods: HBP AA subjects from 4 trials (n=961) (PEAR1: NCT002465519 n=298, PEAR2: NCT01203852 n=190, GERA1 n=280, and GERA2 n=193: NCT 00005520) were evaluated at baseline after washout of BP meds. Genetic data was analyzed using Affymetrix or Illumina Human Omni1-Quad Beadchips. *APOL1* G1 and G2 variants were imputed using g1000 (PEAR1, PEAR2), or direct sequencing (GERA1, GERA2). Genome wide association analyses included age, gender, baseline BP, and racial admixture as covariates.

Results: 14.0% (n=135) were positive for two *APOL1* risk alleles. *APOL1* AAs had similar baseline office, home, ambulatory day and night SBP and DBP measures vs. others (n=827). *APOL1* AAs had significantly higher serum creatinine concentrations (0.93±0.24 vs 0.87±0.21 mg/dl, p=0.006) and lower eGFR (98.7±19.6 v. 104.4±18.7 ml/min, p=0.0008). AAs with an *APOL1* risk allele had a longer duration of HBP vs others (8.0±7.4 vs 6.7±7.5 yr, p=0.02). Subjects with an *APOL1* risk allele had a greater SBP response to candesartan (12.2±1.2 vs 7.5±1.8 mmHg, p=0.03; GERA2), a trend toward greater DBP response (8.9±0.9 vs 6.3±1.2 mmHg, p=0.08), and a greater decline in albuminuria (-8.3±3.1 vs -3.7±4.3 mg/day, p=0.03). An intronic SNP rs17825860, within *SDK1*, predicted greater office SBP response (p=6.9 x 10^{-7}) in *APOL1* AAs, and rs286856, an intronic SNP within *DPP6*, predicted greater office SBP response (p=3.2 x 10^{-7}) in *APOL1* negative individuals.

Conclusions: HBP APOL1 AAs demonstrate early differences in eGFR and serum creatinine with a greater SBP response to angiotensin receptor blockade (ARB) before clinical evidence of cardiac or renal disease. Genetic variants of the podocyte protein *SDK1*, and *DPP6*, which binds voltage gated potassium channels, may influence BP response to ARBs depending on *APOL1* status.

Funding: Other NIH Support - NIGMS

FR-PO563

Derivation and Validation of an Uplift Model to Personalize Blood Pressure Treatment Strategy Francis P. Wilson,[1] Aditya Biswas,[2] Chirag R. Parikh.[3] *[1]Yale School of Medicine, New Haven, CT; [2]Yale University, New Haven, CT; [3]Yale University and VAMC, New Haven, CT.*

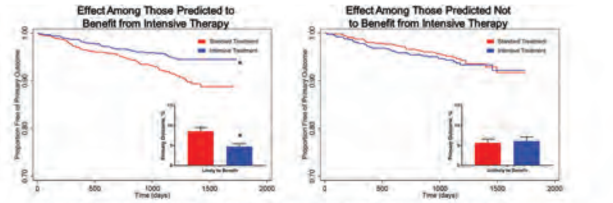
Background: The Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that, for non-diabetic patients with cardiovascular risk factors, a more intensive systolic blood pressure lowering strategy (<120 mm) was superior to a standard blood pressure lowering strategy to prevent cardiovascular outcomes. However, absolute risk reduction was low suggesting that the vast majority of patients exposed to lower systolic BP will not directly benefit. Uplift modeling is a novel strategy to predict the marginal benefit of an intervention at the level of an individual allowing for personalized targeting of interventions.

Methods: We divided the SPRINT cohort into a 70% training and 30% validation set. Using deep-phenotyping via auto-encoders and a random forest uplift model, we predicted the marginal benefit of the intensive blood pressure compared to standard strategy. We then dichotomized this metric into two groups - "likely to benefit" and "unlikely to benefit". We compared baseline factors in these two groups to examine factors strongly predictive of benefitting from intensive blood pressure control.

Results: In the test set, we identified 1,696 participants who would be likely to benefit from intensive blood pressure control and 1,112 who would be unlikely to benefit. The most common phenotypes of those likely to benefit included older white males with risk factors associated with the metabolic syndrome (such as higher serum glucose and microalbuminuria) but preserved eGFR. The hazard ratio (HR) of the intervention on the primary outcome in the "likely to benefit" group was 0.56 (95% CI 0.38 – 0.83, p=0.004) compared to 1.18 (0.71 – 1.98, p=0.53) among those unlikely to benefit (p-for-interaction 0.04).[Figure]

Conclusions: Use of an uplift-targeting approach in clinical practice would increase the efficacy of intensive blood pressure treatment, improve absolute risk reduction while simultaneously increasing the total number of cardiovascular events avoided at a population level.

Funding: NIDDK Support



Effect of intensive vs. standard treatment in the test set, stratified by predicted likelihood of benefit. Time-to Event analyses are presented with survival curves. Percent of patients experiencing the primary outcome appears in the inset bar charts. *p<0.005

	All Patient Strategy (n=2,808)	Uplift-Targeted Strategy (n=1,696)
HR (Intensive Vs. Control)	0.73 (0.54 - 0.99)	0.56 (0.38 - 0.83)
Absolute Risk Reduction (%)	0.64	1.68
Number Needed to Treat	156	60
Primary Outcome Events Avoided	18	28

Table: Treatment effects under a "treat all eligible patients" strategy vs. an uplift-targeted strategy in the test set. Uplift-targeting results in fewer individuals exposed to treatment while avoiding more primary outcome events. HR = Hazard Ratio

FR-PO564

Individualizing Hypertensive Treatment in Dialysis Population: Thinking beyond Intradialytic Blood Pressure Readings Rachana H. Jasani, Paras Dedhia, Viswanath Billa, SHRIRANG BICHU, Rajesh B. Kumar. *Apex Kidney Foundation, Mumbai, India.*

Background: Majority of hypertension treatment decisions are made based on dialysis unit BP readings. Out of dialysis unit blood pressure readings are shown to be associated with left ventricular hypertrophy and mortality.

Methods: Ambulatory BP monitoring (ABPM) performed for 44 hours in between 2 dialysis sessions. ABPM BP recorded every 20 min during the day (7am to 11pm) and every 30 min during the night (11pm to 7am) in non-fistula arm. Hourly means were averaged to obtain interdialytic systolic and diastolic blood pressure readings over 44 hours. Less than 70% readings were excluded from the study. Along with BP means, Percent Time Elevation (PTE-duration of day spent in high blood pressure state), dipping status at night, morning surge (the difference in systolic blood pressure during the first two hours after awakening and the lowest level recorded during night) and Pulse Pressure (PP) were assessed from ABPM data.

Results: Of 40 subjects, 68% were males. Average age was 54.5± 12.3 years. 45% had diabetes, 98% had hypertension and 20% had IHD. 80% subjects had >40% PTE. In terms of dipping status, 7.5% had normal dipping (10-20% drop in SBP at night), 67.5% were non-dippers (<10% drop in SBP at night) and 25% had reverse dipping status (nocturnal BP higher than diurnal BP). In our study, 10% had > 20% morning surge. We observed 27.5% had PP between 40 – 60 mm Hg, 45% had PP between 60 -80 mm Hg, 22.5% had PP between 80 – 100 mm Hg.

Conclusions: Blood pressure readings obtained from ABPM helps to individualize hypertension management in relation to timing and selection of anti-hypertensive agent. Also, it helps to provide a targeted approach in treating dialysis patients with diurnal variations in BP on dialysis and non-dialysis days.

FR-PO565

Cardiovascular Risk in Healthy Subjects Evaluated with Clinical-Genetic Test and Carotid Echography Francisco javier Lavilla, Pedro Errasti, Christian I. Alfaro Sanchez, Nuria Garcia-Fernandez, Pelayo M. Fdez-Felechosa, Jose maria Mora gutierrez. *Clinica Universidad de Navarra, Pamplona, Spain.*

Background: Evaluate cardiovascular risk (CVR) in healthy patients with clinical genetic test (Cardio inCode® test), and carotid echography.

Methods: cohort of 94 subjects (médium age 53 years 0.911, and male 73.5) We evaluate CVR with genetic test (Cardio inCode® that evaluated cardiovascular age -CVAGE- and global cardiovascular risk -GCVR-, using validated clinical and genetic score) and with carotid echography (intima.media thickness in left –IMTLC- and right -IMTRC- carotid). We evaluate levels of Glucose, Triglycerides, Total, HDL and LDL cholesterol, uric acid, creatinine (mg/dL) and creatinine clearance (ml/min) (MDRD-4 and CKD-EPI). We calculated the difference between cardiovascular (CVAGE) and biological age SPSS 20.0.

Results: Markers of CVR measure with Cardio inCode are associated with carotid and analytical parameters: **Carotid:** IMTLC is associated with AGE (r: 0.499, p: 0.001), CVAGE (r: 0.588, p= 0.001) and GCVR (r: 0.492, p: 0.001). IMTRC with AGE (r: 0.493, p: 0.001), CVAGE (r: 0.511, p= 0.001) and GCVR (r: 0.398, p: 0.001). **Renal function**:CKD-EPI is associated with AGE (r: -0.364, p: 0.001) and CVAGE (r: -0.361, p= 0.001) but MDRD not. **Metabolic parameters**: GLUCOSE is associated with CVAGE (r: 0.272, p= 0.008), GCVR (r: 0.224, p: 0.031), IMTLC (r: 0.254, p= 0.020), IMTRC (r: 0.214, p: 0.051) TG with CVAGE (r: 0.360, p= 0.001), GCVR (r: 0.453, p: 0.001), IMTLC (r: 0.400, p= 0.001), IMTRC (r: 0.241, p: 0.027) URIC ACID with CVAGE (r: 0.376, p= 0.001), GCVR (r: 0.353, p: 0.001) and IMTLC (r: 0.242, p= 0.001). **Differences between CVAGE and biological age** is associated with IMTLC (r:0.294, p: 0.007) and GCVR (r:0.363, p: 0.001). In 31.3% this difference is more than 10 years. No differences in biological age in this group.

Conclusions: Intima media thickness in left carotid is a good marker and better than in right carotid to evaluate CVR. CKD-EPI are better associated with CVR and Cardio inCode® than MDRD. Metabolic parameters (except cholesterol) are associated with Cardio inCode and intima media thickness. Difference between CVAGE and biological age are associated with cardiovascular risk. This difference depends on CVR, not biological age. In healthy subjects we can evaluated CVR with Cardio inCode® and carotid echography.

FR-PO566

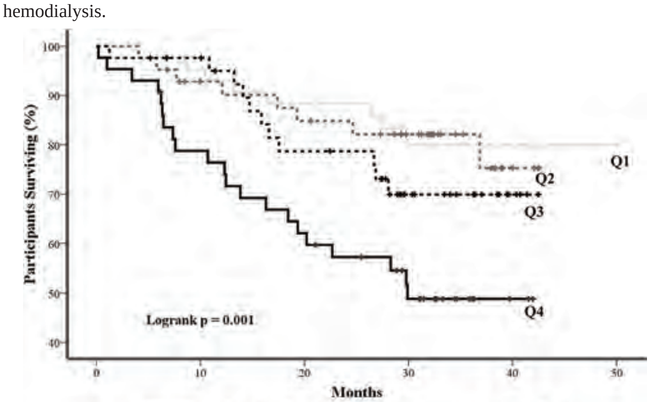
Short-Term Blood Pressure Variability Predicts Cardiovascular Events and All-Cause Mortality Better Than Office and Ambulatory Blood Pressure in Hemodialysis Patients Pantelis Sarafidis,[1] Charalampos Loutradis,[1] Antonios Karpetas,[2] George Tzanis,[1] Georgios Koutroumpas,[3] Athanasios Bikos,[4] Vasilios Raptis,[4] Christos Syrganis,[3] Vassilios Liakopoulos,[5] Aikaterini A. Papagianni.[1] [1]*Department of Nephrology, Hippokration Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece;* [2]*Therapeutiki, Hemodialysis Unit, Thessaloniki, Greece;* [3]*Hemodialysis Unit, Achillopouleion General Hospital, Volos, Greece;* [4]*Hemodialysis Unit, Pieria, Katerini, Greece;* [5]*Section of Nephrology and Hypertension, 1st Department of Medicine, AHEPA Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece.*

Background: Hemodialysis patients are subjected to severe blood pressure (BP) fluctuations during intra- and interdialytic periods. Long-term predialytic BP variability (BPV) is associated with increased cardiovascular risk. This is the first study to examine the prognostic significance of short-term BPV using ambulatory blood pressure monitoring (ABPM) in hemodialysis.

Methods: 170 patients underwent 48h ABPM during dialysis and a standard interdialytic interval and were followed for 28±11 months. BPV parameters calculated were: standard deviation(SD), weighted SD(wSD), coefficient of variation(CV), average real variability(ARV). The primary end-point was: combination of all-cause death, non-fatal MI or stroke. Secondary end-points were: (i) all-cause death (ii) cardiovascular death (iii) combination of cardiovascular death, MI, stroke, resuscitation after cardiac arrest, coronary revascularization or hospitalization for HF.

Results: In total, 37(21.8%) patients died and 46(27.1%) had cardiovascular events. Freedom from primary end-point was similar for quartiles of predialysis SBP, 48h SBP, and SBP-SD, but was progressively shorter for SBP-wSD (p=0.03), SBP-CV (p=0.047), and SBP-ARV (81.4%, 81.0%, 73.8%, 51.2% p=0.001; Figure 1). Hazard Ratios for all outcomes were similar for quartiles of pre-dialysis SBP and 48h SBP but were progressively increasing with higher quartiles of 48h SBP-ARV (for primary outcome: Q1:reference; Q2:1.11, 95%CI:0.42-2.95; Q3:1.64, 95%CI:0.66-4.09; Q4:3.45, 95%CI:1.53-7.81).

Conclusions: Short-term BPV is associated with future cardiovascular events and mortality in hemodialysis patients, but office and ambulatory BP are not. These results add to evidence suggesting that BPV is independent cardiovascular risk factor in hemodialysis.



	48hSBPARV	0	10	20	30	40	50
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Q2	10.7±0.5	42	35	32	24	4	0
Q3	12.1±0.5	42	38	29	16	4	0
Q4	15.9±2.5	43	33	26	17	2	0

Figure 1: Kaplan Meier curve and Life table for primary end-point and 48h SBP ARV

FR-PO567

Renal Functional Reserve Is Related to Exercise Heart Rate in Essential Hypertensive Patients: A Novel Link between the Kidneys and the Heart Aikaterini Damianaki,[2] Kyriakos Dimitriadis,[1] Aglaia Chalkia,[2] Konstantinos Tsioufis,[1] Dimitrios Petras.[2] [1]*First Cardiology Clinic, University of Athens, Hippokration Hospital, Athens, Greece;* [2]*Nephrology Department, Hippokration Hospital, ATHENS, Greece.*

Background: Renal functional reserve (RFR) refers to the capacity of the kidney to augment its level of function under the influence of certain stimuli and it constitutes a valuable diagnostic tool for recognizing high risk patients for acute kidney injury (AKI) and chronic kidney disease (CKD). The aim of our study was to assess the relation of RFR with diverse clinical parameters in patients with essential hypertension and GFR>60ml/min/1.73m^2.

Methods: 15 hypertensive subjects (mean age=57 years, BMI= 28.5 kg/m², office systolic/diastolic BP =148/90 mmHg) were included. All subjects underwent the exercise treadmill stress test, 24hour ABPM and cardiac ultrasound. Subjects who were on antihypertensive medication, stopped the agents for two weeks. All subjects were fasted for 8 hours and then baseline hydration status was recorded using bioimpedance analysis. Basal GFR was measured after hydration and stress GFR was achieved after ingestion of oral protein 1g/kg as cooked meal. Basal and Stress GFR were determined by Creatinine Clearance = Urine Creatinine/Serum CreatininexUrine Volume/time× 1.73/BSA). RFR was calculated as Stress GFR – Basal GFR.

Results: Patients with greater than 10years of HTN, had lower RFR values ($p<0.1$) (-14.59 ±43.26 ml/min/1.73m² vs 21.35±28.19 ml/min/1.73m²). There was no correlation of RFR values with respect to family history, smoking, BMI, age, dipping and office BP. In contrast, a statistically significant positive correlation was found between RFR and maximum heart rate (HR) during treadmill test ($r=0.880$, $p=0.009$). Hypertensives with high RFR were characterized by higher maximum HR during treadmill test.

Conclusions: RFR is related to treadmill exercise heart rate in essential hypertension, suggesting a link between the dynamic regulation of renal function and sympathetic overdrive influence on the heart. These findings suggest that treadmill test could be used to identify hypertensive patients with unfavorable RFR. Additionally, patients with greater than 10 years of HTN and/or on antihypertensive agents tend to have lower RFR values, indicating a possible susceptibility to renal injury.

FR-PO568

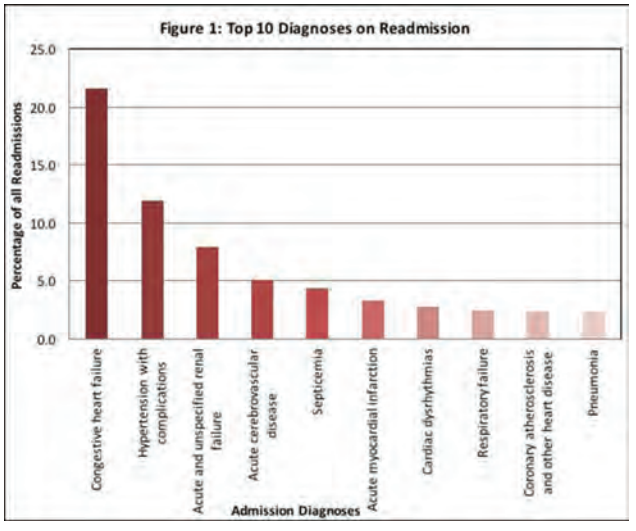
Thirty Day Readmissions in Patients Admitted for Hypertensive Emergency Aparna Saha, Lili Chan, Priti Poojary, Kinsuk Chauhan, Steven G. Coca, Girish N. Nadkarni. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Hypertensive (HTN) emergency accounted for 111/100,000 hospital readmissions in 2007 with increasing incidence. Few studies have examined 30-day readmission rates, reasons and outcomes in this growing population

Methods: Utilizing the Nationwide Readmission Database from year 2013, admissions for HTN emergency were queried by combining ICD-9 codes for malignant HTN and acute target organ damage. We excluded patients on dialysis, those<18 years old and admission occurring in December due to lack of 30 day follow up for readmissions. Index admissions were any admission without a preceding 30 day admission, while readmissions were any admission that followed a prior admission by less than 30 days

Results: In 2013, 30,936 index admissions were identified.15.4% of all index admissions had at least one 30-day readmission. When stratified by chronic kidney disease stage 3 or higher(CKD3) status, patients with CKD3 had higher readmission rate, 17% vs 14%, P<0.001. Of all index admissions, 44.8% were complicated by acute kidney injury(AKI) and AKI had higher rates of readmissions, 17% vs 14%, P<0.001. The top 10 causes for readmission are in Figure 1. While only 14% of readmissions were for repeat HTN emergency, 50% of all readmissions were likely related to complications from HTN emergency(congestive heart failure, HTN with complications, AKI, acute cerebrovascular disease and acute myocardial infarction). In-hospital mortality during index admission was 3%, while on readmission it was 4%

Conclusions: Over 1 out of 10 index admission for HTN emergency is followed by 30-day readmission. A high percentage of readmissions were for repeat HTN emergency. Both AKI and CKD are associated with higher readmission rates. Efforts should be directed towards identifying effective measures to improve blood pressure control and better follow-up post hospitalization, particularly in those with kidney disease



FR-PO569

Urinary Plasmin(ogen), Blood Pressure, and Progression of Diabetic Kidney Disease Evan C. Ray,[3] Rachel G. Miller,[4] John E. Demko,[5] Tina Costacou,[1] Carol L. Kinlough,[3] Casey Allen,[3] Mark L. Unruh,[2] Trevor J. Orchard,[1] Thomas R. Kleyman.[3,6] *[1]School of Public Health, University of Pittsburgh, Pittsburgh, PA; [2]Internal Medicine, University of New Mexico, Los Ranchos, NM; [3]Renal-Electrolyte Division, University of Pittsburgh, Pittsburgh, PA; [4]School of Public Health, University of Pittsburgh, Pittsburgh, PA; [5]Internal Medicine, University of California San Francisco, San Francisco, CA; [6]Cell Biology, University of Pittsburgh, Pittsburgh, PA.*

Background: Urinary plasmin and its precursor, plasminogen, are detectable in the urine of patients with diabetic or other proteinuric kidney diseases. Urinary plasmin(ogen) levels correlate with increased extracellular fluid volume and blood pressure and have been hypothesized to contribute to renal Na retention by activating the epithelial Na channel (ENaC) and to progression of chronic kidney disease through podocyte and tubular toxicity. We assessed whether urinary plasmin(ogen) levels predict subsequent increases in blood pressure or decline in kidney function in type 1 diabetes.

Methods: Individuals with childhood-onset type 1 diabetes were enrolled as part of the Pittsburgh Epidemiology of Diabetes Complications Study in 1986-1988 and followed prospectively for 25 years. The present nested-cohort study included 70 subjects chosen to represent a spectrum of baseline urinary protein levels. Clinical outcomes included 1) increased blood pressure over a two-year period, defined as any increase in systolic or diastolic blood pressure or addition of a new anti-hypertensive agent; 2) incident hypertension over the full 25 year study period, defined as new-onset blood pressure of 140/90 mmHg or hypertensive medication use; and 3) 50% decline in eGFR over the 25-year study period, calculated from baseline using the CKD-EPI formula. The predictive values of urinary plasmin(ogen) and albumin were compared.

Results: In those who experienced increased blood pressure, baseline plasmin(ogen) levels where higher, with a difference approaching significance ($p = 0.08$). Albumin did not differ ($p = 0.43$). Plasmin(ogen) predicted both incident hypertension (HR=2.05, $p=0.001$) and 50% decline in eGFR (HR=2.26, $p<0.001$), however adjusting for urinary albumin attenuated plasmin(ogen)'s 25-year predictive abilities ($p= 0.95$ and 0.45, respectively).

Conclusions: Over 2 years of follow-up, baseline urinary plasmin(ogen) was associated with an increase in blood pressure approaching significance, suggestive of a role in stimulating urinary Na retention. Over 25-years of follow-up, plasmin(ogen) predicted incident hypertension and 50% decline in eGFR, though not independently of albumin, suggesting that over the long-term, mechanisms non-specific to plasmin(ogen) contribute to hypertension and diabetic kidney disease progression.

Funding: NIDDK Support

FR-PO570

Inflammation and Apparent Treatment Resistant Hypertension in Patients with CKD – The Results from the CRIC Study Jing Chen,[7] Joshua D. Bundy,[10] L. Lee Hamm,[9] Chi-yuan Hsu,[11] James P. Lash,[12] Edgar R. Miller,[5] George Thomas,[3] Debbie L. Cohen,[15] Dominic S. Raj,[4] Hsiang-Yu Chen,[6] Dawei Xie,[16] Panduranga S. Rao,[14] Matthew R. Weir,[13] Jackson T. Wright,[1] Mahboob Rahman,[2] Jiang He.[8] *[1]Case Western Research University, Cleveland, OH; [2]Case Western Reserve University, Cleveland, OH; [3]Cleveland Clinic, CLEVELAND, OH; [4]GWU Medical Faculty Associates, Washington, DC; [5]Johns Hopkins University, Baltimore, MD; [6]The Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; [7]Tulane School of Medicine, New Orleans, LA; [8]Tulane School of Public Health and Tropical Medicine, New Orleans, LA; [9]Tulane University School of Medicine, New Orleans, LA; [10]Tulane University School of Public Health and Tropical Medicine, New Orleans, LA; [11]University of California San Francisco, San Francisco, CA; [12]University of Illinois at Chicago, Chicago, IL; [13]University of Maryland School of Medicine, Baltimore, MD; [14]University of Michigan Health System, Ann Arbor, MI; [15]University of Pennsylvania School of Medicine, Philadelphia, PA; [16]University of Pennsylvania School of Medicine Center for Clinical Epidemiology and Biostatistics, Philadelphia, PA.*

Background: Apparent treatment resistant hypertension (ATRH) is highly prevalent and associated with increased risk of cardiovascular disease (CVD) in patients with chronic kidney disease (CKD). Inflammation may be associated with blood pressure and is increased in CKD patients. It is unknown if inflammation is associated with increased likelihood of ATRH in CKD.

Methods: ATRH is defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic BP (DBP) ≥90 mmHg while taking ≥ 3 antihypertensive medications or taking ≥ 4 antihypertensive medications with SBP <140 mmHg and DBP <90 mmHg. 1359 Chronic Renal Insufficiency Cohort (CRIC) Study participants with ATRH and 2008 participants without ATRH, but with hypertension at the baseline visit, were included in this analysis. Multiple logistic regression models were adjusted for age, sex, race, clinical sites, diabetes, alcohol consumption, body mass index, physical activity, estimated glomerular filtration rate, 24-hour urinary protein, and 24-hour urinary sodium.

Results: Multiple-adjusted odds ratios (95% confidence intervals) of ATRH for the highest tertile comparing to the lowest tertile of the inflammatory biomarker levels were 1.31 (1.06-1.62, $p=0.026$) for tumor necrosis factor-α (TNF-α) and 0.75 (0.61-0.92, $p= 0.008$) for transforming growth factor beta (TGF-β). In addition, multiple-adjusted odds

ratios (95% confidence intervals) associated with one standard deviation difference in log-transformed TGF-β was 0.90 (0.83-0.98, p= 0.013). The levels of interleukin-6, interleukin-1 beta, and C-reactive protein were not significantly associated with odds of ATRH.

Conclusions: Higher levels of TNF-α and lower levels of TGF-β (as anti-inflammatory biomarker) were independently associated with odds of ATRH. Further study is warranted to investigate if targeting specific inflammatory pathways may improve blood pressure control among patients with CKD.

Funding: NIDDK Support, Other NIH Support - NATIONAL INSTITUTE OF GENERAL MEDICAL SCIENCES P20GM109036

FR-PO571

Diabetes Mellitus versus Vascular Calcification: Impact on Predialytic Blood Pressure and Incidence of Intradialytic Hypotension

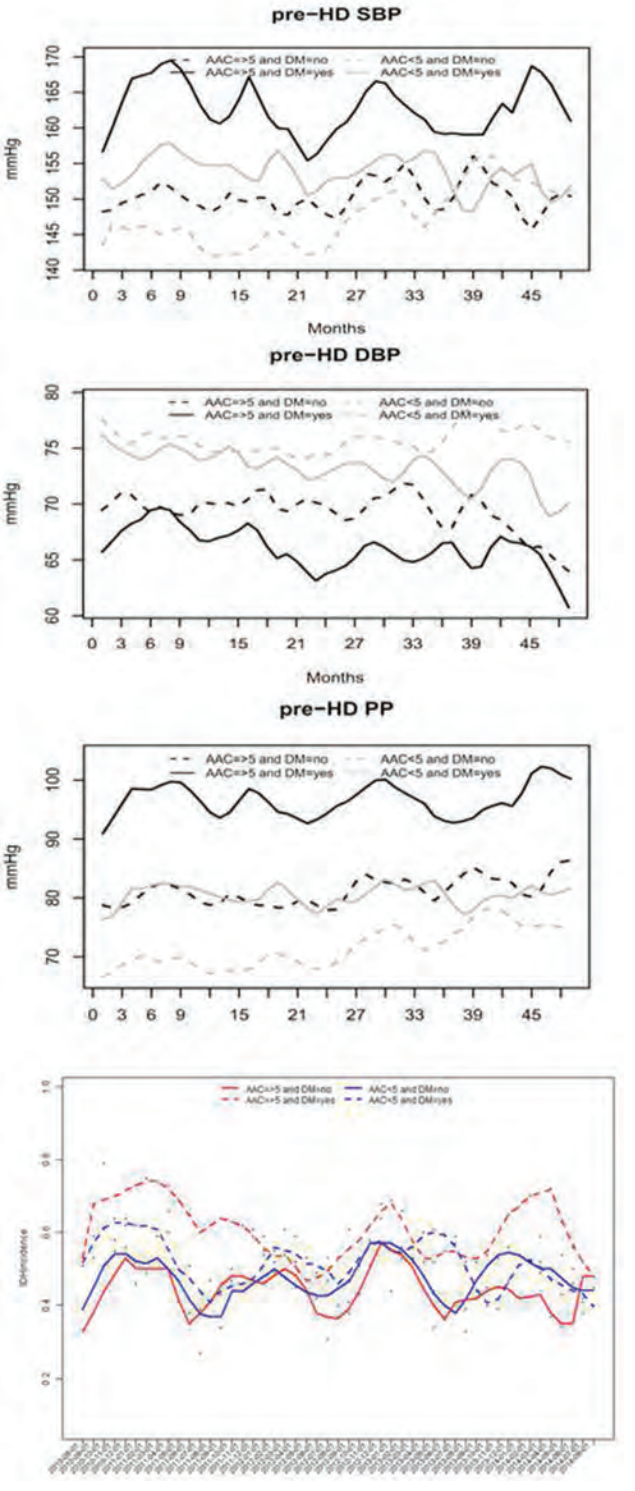
Sinae Lee,[1] Seoung Woo Lee.[2] *[1]none, Anyang-si, Republic of Korea; [2]Nephrology and Hypertension, Inha University Hospital, Incheon, Republic of Korea.*

Background: Diabetes mellitus (DM) and vascular calcification are highly prevalent in maintenance hemodialysis (HD) patients, but it has not known how they influence on pre-HD blood pressure (BP) and the incidence of intradialytic hypotension.

Methods: This study was performed from August 2010 to July 2014 in 66 patients who met the following criteria: HD duration for >6 months and HD 3 times weekly during the study. Four years of pre- and intradialytic BPs and laboratory data were collected. Abdominal aortic calcification (AAC) was assessed using the Kauppila score. Patients were classified as high (≥5) or low (<5) AAC. The KDOQI guideline was used to define IDH. IDH incidence was the number of sessions in which IDH occurred divided by the total number of monthly HD sessions. Subjects were classified into group 1 (high AAC, DM) (n=16), group 2 (high AAC, non-DM) (n=15), group 3 (low AAC, DM)(n=14), and group 4 (low AAC, non-DM) (n=21). Time series analysis (TSA) was performed to assess changes in pre-HD BP and the IDH incidence.

Results: Mean age was 61±11 years; 30 had DM; 50% were male; HD duration was 6.1±3.8 years; AAC score was 5.5±4.5; and HD sessions were 481±81. In TSA, pre-HD SBP, DBP, PP, and the IDH incidence were elevated by group in the order of 1>3>2>4, 4>2>3>1, 1>2=3>4, and 1>3>2=4, respectively (Fig. 1). Multiple regression showed that non-DM and low AAC was independently associated with pre-dialytic SBP (non-DM; β=-0.58, p<0.001; low AAC; β=-0.49, p=0.015), DBP (non-DM; β=0.34, p<0.001; low AAC; β=0.75, p<0.001), PP (non-DM; β=-0.57, p<0.001; low AAC; β= -0.69, p<0.001) and IDH incidence (non-DM; β=-0.31, p < 0.001; low AAC; β=-0.2, p=0.469).

Conclusions: Both DM and vascular calcification may influence pre-HD BPs and the IDH incidence; however, the effect of DM is more prominent.



FR-PO572

The Change of Glucose Metabolism in Primary Aldosteronism after Target Treatment

Yu-Fang Lin, Vincent Wu, Kwan-dun Wu. *Internal Medicine and College of Medicine, National Taiwan University Hospital, Taipei city, Taiwan.*

Background: Discrepant data have been published on the effects of aldosterone excess on abnormal glucose metabolism. There is no consistent result of follow-up glucose metabolism after adrenalectomy or spironolactone in patients with primary aldosteronism (PA).

Methods: Patients were enrolled during the screening test after adequate substitutive drug periods. Aldosterone, ARR(aldosterone renin ratio), glucose metabolism parameters

including HOMA-IR and HOMA-β were checked and calculated before and 1 year after on-target treatment.

Results: One hundred and thirty-eight PA patients were enrolled (mean age 50.6±11.5, 49% female), among them 72 patients with aldosterone producing adenoma (APA) received adrenalectomy (Group 1), 33 idiopathic hyperaldosteronism (IHA) treated with spironolactone (Group 2) and 33 APA treated with spironolactone (Group 3). There was no change of fasting glucose before and after treatment (P=0.056, 0.497, 0.575). Fasting insulin increased in group 1 and group 2 (P=0.019, 0007). Aldosterone decreased after adrenalectomy but increased after IHA treated with spironolactone. HOMA-β improved in patients in the former two groups (P=0.000, 0.015). HOMA-IR deteriorated significantly in group 2 (P=0.019) but not in group 1(P=0.109). The fasting glucose, fasting insulin, HOMA-IR and HOMA-β remained unchanged in group 3. At enrollment, APA had higher HOMA-IR (P=0.000) and fasting plasma glucose(P=0.019) than IHA. There was a negative correlation between aldosterone and HOMA-β or HOMA-IR after adjustment with serum potassium level, SBP, BMI, age, and sex.

Conclusions: At enrollment, APA had higher HOMA-IR and fasting plasma glucose than IHA. HOMA-β could improve in APA treated with adrenalectomy and IHA received spironolactone. HOMA-IR deteriorated in IHA patients but remained unchanged in other two groups. Thus, adrenalectomy of APA could improve glucose homeostasis other than spironolactone in APA.

Funding: Government Support - Non-U.S.

Glucose metabolism parameters in APA and IHA at baselines and at follow-up

	Group 1: APA adrenalectomy (n=72)			Group 2: IHA spironolactone (n=33)			Group 3: APA spironolactone (n=33)		
	Baseline	Follow-up	p	Baseline	Follow-up	p	Baseline	Follow-up	p
Plasma glucose(mg/dl)	100.1±22.5	95±12.7	0.056	94.8±12.3	97.4±19	0.497	108.1±28.7	106.2±40.5	0.575
Insulin (uU/ml)	10.5±8.9	13.5±10.3	0.019*	8.8±5.2	12.2±7.7	0.007*	16.1±36	13.4±12.6	0.669
HOMA IR	2.7±2.4	3.3±2.8	0.109	2.2±1.5	3±2	0.019*	4.3±8.4	3.8±4.4	0.748
HOMA-β	1.1±1	1.6±1.1	0.000*	1±0.6	1.4±1	0.015*	1.6±4.3	1.3±1.5	0.743

*p<0.05

FR-PO573

Hyperuricemia Is Associated with Worse Renal Outcomes in Patients Undergoing Percutaneous Transluminal Renal Angioplasty (PTRA) Xiaojun Chen,[1,3] Alfonso Eirin,[1] Ahmed Saad,[1] Amir Lerman,[2] Stephen C. Textor,[1] Lilach O. Lerman.[1] *[1]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [2]Department of Cardiovascular Diseases, Mayo Clinic, Rochester, MN; [3]Department of Nephrology, The Second Xiangya Hospital of Central South University, Changsha, China.*

Background: Hyperuricemia is associated with elevated risk for hypertension and chronic renal disease. PTRA improves blood pressure (BP) and renal function only in selected patients with atherosclerotic renovascular disease (ARVD), likely due to post-stenotic kidney injury. We hypothesized that hyperuricemia contributes to poor BP and renal functional outcomes in ARVD after PTRA.

Methods: Outcomes were compared among ARVD patients stratified by elevated serum uric acid (SUA) levels (>6.0mg/dl in women; >7.0mg/dl in men) undergoing PTRA. Multivariate analysis was used to determine significant predictors for renal and BP outcomes after PTRA.

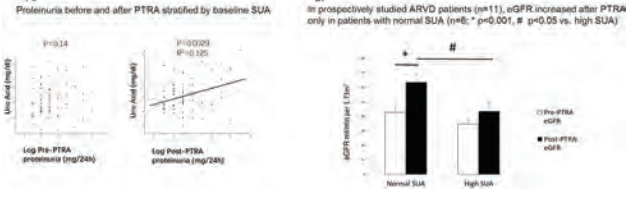
Results: In 94 patients with ARVD studied retrospectively, pre-PTRA eGFR was lower in hyperuricemic compared with normouricemic patients, and remained lower after PTRA (Table), after adjustment for body-mass index, number of antihypertensive drugs, baseline eGFR, diuretic use, and left ventricular (LV) mass (p<0.05). PTRA did not affect eGFR in either group, while diastolic BP decreased in both. In univariate analysis, lower SUA was associated with improved BP after PTRA (Hazard ratio 0.84, p<0.05), but multivariate analysis revealed that only age, coexisting cerebrovascular disease, and number of antihypertensive drugs remained independent predictors. Contrarily, in multivariate linear analysis SUA independently predicted post-PTRA proteinuria (odds ratio 68.5, p<0.05, Figure A) after adjustment for pre-PTRA proteinuria, LV ejection fraction, and eGFR, and for cerebrovascular, peripheral, and cardiovascular disease. In 11 additional ARVD patients studied prospectively under controlled sodium intake and antihypertensive regimens, PTRA improved renal function (Figure B) only in patients with normal SUA (n=6, p<0.05).

Conclusions: Hyperuricemia does not aggravate BP outcomes in ARVD patients, but may be associated with greater renal dysfunction and proteinuria after PTRA. Thus, SUA in patients with ARVD might be a predictor of worse outcomes after PTRA.

Funding: Other NIH Support - DK100081

Pre-PTRA eGFR is lower in hyperuricemic (n=44) compared with normouricemic (n=50) patients, and remains lower after PTRA

	Before PTRA				After PTRA			
	High SUA (N=44)	Normal SUA (N=50)	Unadjusted P value	Adjusted P value	High SUA (N=44)	Normal SUA (N=50)	Unadjusted P value	Adjusted P value
eGFR(ml/min /1.73m²)	41(16-84)	53(24-101)	0.002	0.0004	35(4.5-65.2)	53.1(10.5-85)	<0.0001	0.039



FR-PO574

The Benefit of Combined Calcium Channel Blockers with Angiotensin Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers on Renal Outcomes in Hypertensive Patients: A Meta-Analysis Paweena Susantitaphong,[1] Punnaka Pongpanich,[2] Pasvich Pitakpaiboonkul,[3] Kearkiat Praditpornsilpa,[1] Somchai Eiam-Ong.[1] *[1]Chulalongkorn University, Bangkok, Thailand; [2]Chulalongkorn university, Bangkok, Thailand; [3]Chulalongkron university, Bangkok, Thailand.*

Background: The prevalence of hypertension and its associated complications are likely to grow as the population ages. In addition, control of the disease is far from adequate, only fifty percent of persons with hypertension have their blood pressure under control, which was defined as a level below 140/90 mmHg. Most people need more than one drug to achieve blood pressure target. However, several guidelines only focus on the first line treatment. We conducted a meta-analysis to explore the benefits of combined calcium channel blockers (CCBs) with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) on renal outcomes in hypertensive patients.

Methods: A systematic literature search was conducted in MEDLINE, Scopus, Cochrane Central Register of Controlled Trials, and Clinical Trials.gov (until April 7, 2016) to identify randomized controlled trials comparing the benefits of combined CCBs with ACEIs or ARBs vs. other combinations on renal outcomes in hypertensive patients. Random-effect models were used to compute the weighted mean difference (WMD) for continuous variables.

Results: Sixty randomized controlled trials (48,913 patients) were identified. Although, the combined CCBs with ACEIs or ARBs did not have statistically significant difference on the WMD of systolic blood pressure and diastolic blood pressure (73 study arms) when compared with other combinations (0.25 mmHg; 95%CI -0.33, 0.84 mmHg, P=0.40 and 0.05 mmHg, 95%CI -0.36, 0.47 mmHg, P=0.80, respectively), the benefits on renal outcomes including the decreasing of serum creatinine (22 study arms, 1,791 patients, -4.08 mmol/L, 95%CI -5.71, -2.45 mmol/L, P< 0.001) and improving of estimated glomerular filtration rate (15 study arms, 1,853 patients, 4.13 mL/min/1.73m^2,95% CI 2.26, 6.00 mL/min/1.73m^2, P< 0.001) were observed when compared with other combinations. The significant increase of serum potassium was also observed. (25 study arms, 2,505 patients, 0.13 mEq/L;95% CI 0.07, 0.19 mEq/L, P<0.001)

Conclusions: The combination of CCBs with ACEIs or ARBs have a benefit on renal function in hypertensive patients. Therefore, this combination should be considered whenever monotherapy does not achieve guideline target.

FR-PO575

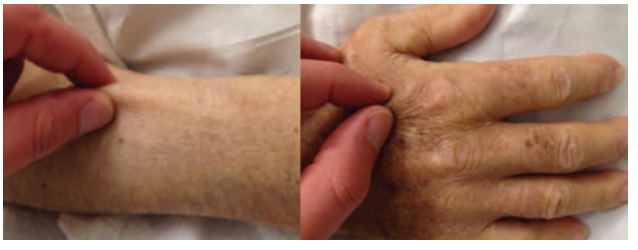
Scleroderma Renal Crisis Mimicking Rapidly Progressive Glomerulonephritis Ahmed Al-Sheyyab, Diego A. Beltran Melgarejo, Rachel B. Fissell, Jamie P. Dwyer. *Vanderbilt University Medical Center, Franklin, TN.*

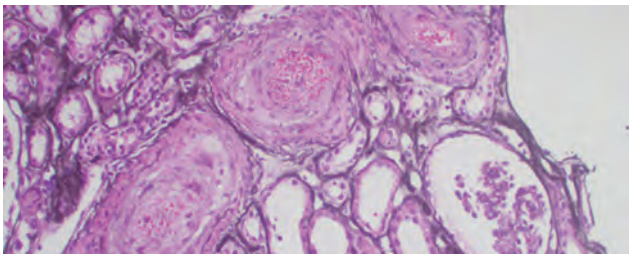
Background: Thrombotic microangiopathies are a group of disorders which overlap in their clinical features. We describe a case with ambivalent presentation, as it highlights some of the differentiating clinical features and the impact of treatment choices on the patient's outcome.

Methods: A 78 year-old man presented with edema of the lower extremities and hands. Clinic evaluation revealed serum creatinine 2.2 mg/dL(baseline 0.7mg/dL), new hypertension(BP 200/103), anemia (hemoglobin 9.1mg/dL) and thrombocytopenia (platelets 69 x10^3/mcL). Additional testing showed microscopic hematuria with proteinuria (protein:creatinine ratio 0.65), LDH 512U/L, haptoglobin <8 mg/dL, ADAMTS13 of moderate activity, and peripheral smear negative for schistocytes. A complete serologic work up was unrevealing except for a positive Antinuclear Antibody (1:2560). Despite pulse steroids therapy, renal failure worsened and ultimately required hemodialysis. Examination of the hands showed skin thickening. Captopril was started. Anti-RNA polymerase III antibodies were positive. Kidney biopsy was consistent with the clinical diagnosis of scleroderma renal crisis(SRC).

Results:

Conclusions: SRC can present similarly to Rapidly Progressive Glomerulonephritis(RPGN). The renal biopsy is able to differentiate between RPGN and SRC. However, thrombocytopenia can delay the performance of kidney biopsy. Clinical suspicion followed by careful hand examination and obtaining extractable nuclear antigen antibodies were key steps in revealing the diagnosis. Early diagnosis of scleroderma is critical to initiate timely therapy. Previous studies showed dramatic improvement of mortality with angiotensin-converting-enzyme inhibitors. In SRC, careful clinical examination for signs of scleroderma and appropriate serologic testing can guide early therapy. The astute clinician requires a high index of suspicion to make the diagnosis of SRC.





FR-PO576

Clinical and Histopathologic Features of Atherosclerotic Renal Artery Stenosis (ARAS): An Autopsy Study Madhuri Chengappa,[3] Ahmed Saad,[1] Sandra Herrmann,[1] Joseph P. Grande.[2] *[1]Mayo Clinic, Rochester, MN; [2]Mayo Foundation for Medical Research, Rochester, MN; [3]Mayo clinic, Rochester, MN.*

Background: ARAS is frequently seen in ageing population and contributes to morbidity in this group. Although a number of cohort studies have compared medical versus surgical therapies for ARAS, there are no previous autopsy-based studies correlating histopathologic and clinical features in patients with ARAS.

Methods: We queried Mayo Clinic database for autopsy cases with known diagnosis of ARAS between 1994 and 2013. We obtained 19 cases for which renal and cardiac histopathology slides were available. 6 patients had unilateral(UL) ARAS (4 medically managed, 2 stented) and 13 patients had bilateral(BL) ARAS (10 medically managed, 2 stented and 1 endarterectomy). All patients were treated for hypertension. Average systolic blood pressure (SBP) was 142mmHg. There was no significant difference SBP in BL or UL ARAS patients.

Results: Histopathology findings: Smaller kidney size correlated with increased SBP (p=0.02). There was a strong correlation with stenotic kidney(STK) size and corresponding STK weight(p=0.03). Glomerular filtration rate correlated with contralateral kidney(CLK) weight(p=0.01). STK/CLK weight ratio was significantly different between patients with UL(0.4) versus BL ARAS (0.7, p=0.002). Glomerular size strongly correlated with atrophy and kidney weight(p=0.0006). Intrarenal vascular disease correlated with glomerulosclerosis(GS) in both STK and CLK (p=0.004 and p=0.02 respectively). All patients with UL ARAS had medullary necrosis, only 1 patient with BL ARAS had medullary necrosis. Although 1 patient had atheroembolic disease documented, we identified 5 cases of intrarenal atheroemboli. Atheroemboli were not associated with presence of abdominal aortic aneurysms, but all 19 patients had severe aortic atherosclerosis. **Outcome:** Intrarenal vascular disease correlated with cardiovascular outcome making cardiovascular the most common cause of death in these patients. 57% of patients died either due to cardiovascular cause or stroke. All 19 patients had history of severe ischemic heart disease. 10.5% of patients developed end stage renal disease(ESRD) and died due to complications of ESRD.

Conclusions: Intrarenal vascular disease is a marker of severe atrophy and GS. Small glomerular size in STK was a robust marker of compensatory hypertrophy of CLK. Atheroembolic renal disease is an under-recognized complication of ARAS in this population.

FR-PO577

Percutaneous Intervention for Renal Artery Stenosis through the Years 2008 to 2014 Madhuri Ramakrishnan,[1] Siva sagar Taduru,[1] Reem Mustafa.[2] *[1]University of Missouri Kansas City, Kansas CIty, MO; [2]Nephrology, Kansas University Medical Center, Kansas City, KS.*

Background: Medical therapy remains the cornerstone of management of renal artery stenosis (RAS) with secondary hypertension. The indications of intervention by renal artery angioplasty with (PTRAS) or without (PTRA) stenting however, remains debated. Several trials in recent years have shown no difference in blood pressure control between medical management and percutaneous intervention. We aim to study the trends of utilization, outcomes, and complication rates of percutaneous intervention for RAS between 2008 to 2014.

Methods: We searched the National Inpatient Sample from 2008 – 2014 using International Classification of Diseases Clinical Modification (ICD-9-CM) codes to identify patients admitted with primary diagnosis of renal atherosclerosis, fibromuscular dysplasia (FMD), or reno-vascular hypertension. We excluded patients with vascular trauma, carotid stenosis, and mesenteric ischemia, to exclude patients who may have undergone endovascular procedures identified for these indications. We then identified patients who underwent PTRA and PTRAS. We identified complications of post-operative hematoma or bleeding, acute kidney injury (AKI), and atheroembolism. We described categorical variables as proportions and continuous variables as means. We analyzed the trend of utilization of the procedure using the Mantel-Haenzsel trend test.

Results: We identified 30,617 patients admitted with primary diagnosis of RAS. The mean age was 68.63 ± 15.5 years, 62.5% of patients were females, 79.5% were Caucasians, and the mean comorbidity score was 6.37 ± 7.33. Of these, 22,716 (74.2%) patients underwent percutaneous intervention. The mean age of these patients was 70.42 ± 12.6 years, 61.4% were females, 81.7% were Caucasians and the mean comorbidity score was 6.0 ± 7.1. We identified a trend towards lower rates of use of percutaneous interventions through our study period (84.1% in 2008 vs 50.7% in 2014, $P_{trend} < 0.0001$). Mortality rates were 0.2%, and the mean length of stay was 2.7 ± 3.3 days. Post-operative bleeding or hematoma was identified in 4%, AKI in 11.4% and atheroembolism in 0.3% of cases.

Conclusions: We found a significant downward trend of inpatient PTRA and PTRAS for RAS between 2008 and 2014. This is consistent with the lack of evidence to support the use of interventions. Patients who received intervention tended to be older, with lower comorbidity scores.

FR-PO578

Impedance Cardiography Informs Hypertensive Management Yossi Chait,[3] Barbara A. Greco,[2] Michael J. Germain.[1] *[1]Renal and Transplant Assoc of New England, Hampden, MA; [2]Renal and Transplant Associates of New England, Springfield, MA; [3]University of Massachusetts, Amherst, MA.*

Background: High blood pressure (BP) is a leading cause of death and disability in the US and worldwide. Approximately 1 of 3 U.S. adults (75 million) have high blood pressure, and only about half treated with antihypertensive protocol have their high blood pressure in recommended blood pressure target. Titration of medications involves a trial and error process, especially in resistant hypertension, and is typically guided by office blood pressure, an imprecise, indirect piece of overall hemodynamic status. It has been reported that cardiac power index (CPI) is the best hemodynamic correlate of mortality. Our aim was to follow standard hypertensive management using hemodynamic parameters as hypothesis generating. We measured hemodynamics (NICaS, NI Medical Israel) using a non-invasive, whole-body impedance cardiography technology. NICas reports stroke volume and pulse rate and therefore cardiac index (CI), and together with the measurement of BP it calculates total peripheral resistance index (TPRI).

Methods: We repeated NICaS measurements in 40 hypertensive patients with CKD, kidney transplant, and resistance hypertension over a follow up period up to 6 months (Treatment), andtitration was done after the first measurement (Baseline).

Results: We report results in 2 representative cases. BP was significantly reduced in both patients following medication changes. Hemodynamic changes from Baseline (Table, Figure) reveal that the reduction in TPRI in Patient A was associated with normalization of CI and CPI improving into their normal range after treatment. In Patient B an increase in TPRI was associated with decrease in CI and CPI out of normal range after treatment.

Conclusions: If BP alone was the single most important parameter, then the treatment could be considered a success. However, BP changes do not correlate well with direction of changes in other hemodynamic parameters, and can mask worsening CI and CPI. These results suggest that hemodynamics parameters should be guided using measurements of hemodynamics parameters beyond BP alone. Our hypothesis, to be tested in a large study in the near future, is that using impedance cardiography to guide hypertensive management will result in better BP control and patient experience (symptoms and compliance).

	SDP/DBP (mmHg)		Cardiac Index (L/min/m^2)		Total Peripheral Resistance Index (Dyn*sec/cm^5/m^2)		Cardiac Power Index (W/m^2)	
Patient	A	B	A	B	A	B	A	B
Baseline	142/70	188/88	2.2	2.2	3790	4272	0.41	0.58
Treatment	112/68	147/74	2.8	1.6	2324	4949	0.51	0.34

FR-PO579

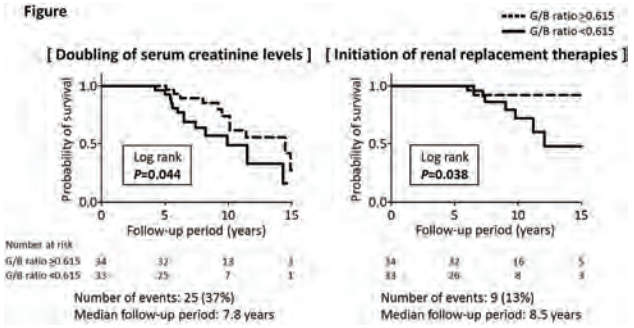
The Quantitative Evaluation of Glomerular Collapse Predicts the Long-Term Renal Outcome in Patients with Benign Nephrosclerosis Kotaro Haruhara, Nobuo Tsuboi, Hoichi Amano, Kentaro Koike, Go Kanzaki, Yusuke Okabayashi, Takaya Sasaki, Makoto Ogura, Takashi Yokoo. *Division of nephrology and hypertension, The Jikei university school of medicine, Tokyo, Japan.*

Background: Although the concomitant appearance of glomerular collapse and enlargement is a typical renal histological feature in benign nephrosclerosis (BNS), the definition of glomerular collapse has not been established. The aim of this study was to quantify the severity of glomerular collapse and to examine the predictive significance of this parameter regarding the renal outcome in patients with biopsy-proven BNS.

Methods: The clinical data and renal biopsy specimens from BNS patients with an eGFR of ≥30 mL/min/1.73m^2 were retrospectively reviewed. Based on the measurements of all cross-sectional areas of Bowman's capsules and glomerular capillaries in the specimens, the mean volume of the Bowman's capsules (BV) and the mean volume of the glomerular capillaries (GV) were separately calculated for each subject using Weibel's equation. The G/B ratio was defined as the ratio of GV to BV.

Results: This study included a total of 67 BNS patients, with a median G/B ratio of 0.615. The clinicopathological characteristics at the biopsy of the patients with a G/B ratio of ≥0.615 and those with a value of <0.615 were comparable, whereas the GV values of the patients with a G/B ratio of ≥0.615 were larger in comparison to the patients with a G/B ratio of <0.615. The survival analyses showed that a G/B ratio of <0.615 was associated with a worse renal outcome (**Figure**). In the Cox hazard analysis to determine the factors associated with the doubling of serum creatinine levels, a G/B ratio of <0.615 was found to be a significant predictor after adjustment by age, sex, and GV <median.

Conclusions: These results suggest that the G/B ratio of diagnostic biopsy specimens is a useful predictor of the long-term renal outcome in patients with BNS, the pathogenesis of which may involve glomerular collapse.



FR-PO580

Prevalence and Predictors of Orthostatic Hypotension at a Tertiary Care Hypertension Clinic with New Diagnostic Thresholds Mohammad A. Faraz,[1] Marcel Ruzicka,[2] Swapnil Hiremath.[1] *[1]University of Ottawa, Ottawa, ON, Canada; [2]None, Ottawa, ON, Canada.*

Background: Formal testing of orthostatic hypotension (OH), defined as a decrease of blood pressure (BP) of 20/10 mm Hg (systolic/diastolic) on change in posture from supine to standing, is seldom carried out in routine practice because of logistical constraints. A recent study reported a sit-to-stand decrease of 15/7 mm Hg as having high sensitivity and specificity. We measured the prevalence and risk factors associated with OH with the new threshold of sit-to- stand of either ≥15 mm Hg in systolic (SBP) or ≥ 7 mm Hg in diastolic BP (DBP).

Methods: We reviewed medical charts of patients being followed at Renal Hypertension Center, a referral centre for difficult to control hypertension. Sitting BP is measured after 5 minutes of resting, as an average of 5 measurements with an automated device. Standing BP is measured three times at one minute intervals and averaged. OH was determined on the basis of the difference in either average SBP or DBP. Demographic characteristics, comorbidities, medication details, laboratory values and BP measurements were extracted.

Results: Data from 219 patients was extracted. The overall difference in SBP (sitting - standing) was 0.94 and DBP was 2.1 mm Hg. 190 patients (87%) did not have OH, whereas 29 (13%) had OH using either SBP or DBP thresholds. The difference in SBP and DBP was 17 mm and 6 mm Hg in those with OH, versus 1.6 and 3 mm Hg amongst those without OH respectively. Higher sitting systolic BP was significantly associated with OH; age, gender, diabetes, number and hypertension medication class were not associated with OH.

Conclusions: Amongst referred patients to a specialist hypertension clinic, the prevalence of OH using a threshold of 15/7 mm Hg was 13%. The new diagnostic threshold allows for easy assessment of OH.

Categories	Overall	OH	No OH
Number (n/%)	219	29 (13%)	190 (87%)
Age (mean ± sd, years)	61.2 ± 17.7	63.8 ± 17.6	60.8 ± 17.8
Gender, male (N, %)	103 (47%)	15 (52%)	88 (46.3%)
BMI (mean ± sd, kg/m²)	31.2 ± 15.7	36.7 ± 39.3	30.3 ± 6.5
Ever Smoker (%)	55 (25.7%)	7 (24%)	48 (26.0%)
Comorbidities (N, %)			
Diabetes	73 (34.3%)	11 (37.9%)	62 (33.7%)
Cardiovascular disease	40 (18.9%)	4 (13.8%)	36 (19.7%)
Peripheral vascular disease	22 (10.4%)	4 (13.8%)	18 (9.8%)
Cerebrovascular disease	18 (8.5%)	2 (6.9%)	16 (8.7%)
Resistant hypertension	77 (35.2%)	10 (34.6%)	67 (35.3%)
Blood Pressure Measurements (mean ± standard deviation)			
Sitting SBP (mm Hg)	137.1 ± 22.2	151.3 ± 33.1	134.9 ± 19.2
Standing SBP (mm Hg)	136.2 ± 21.6	133.8 ± 32	136.5 ± 19.6
Sitting DBP (mm Hg)	76.6 ± 15.2	80.3 ± 23.1	76.0 ± 13.6
Standing DBP (mm Hg)	78.7 ± 14.9	74.5 ± 18.6	79.3 ± 14.2
Medications (N, %)			
ACEi or ARBs	157 (71.7%)	24 (82.8%)	133 (70%)
Beta blockers	103 (47%)	14 (48.3%)	89 (46.8%)
Calcium channel blockers	130 (59.4%)	12 (41.4%)	118 (62.1%)
Alpha-blockers	6 (2.7%)	0 (0%)	6 (31.6%)
Loop diuretics	15 (6.8%)	1 (3.5%)	14 (7.4%)
K-sparing diuretics	29 (13.2%)	2 (6.9%)	27 (14.2%)
Thiazide/ thiazide-like diuretic	96 (43.8%)	16 (55.2%)	80 (42.1%)

FR-PO581

Difference between Central and Peripheral Blood Pressure during Hemodialysis Jafar Al-Said, Corazon Suyao. *Bahrain Specialist Hospital, Manama, Bahrain.*

Background: Difference between the peripheral and central pressure had been confirmed in multiple studies. During hemodialysis, the blood pressure is measured regularly. Whether the difference between the peripheral and central pressure measurements is significant enough to favor checking the central rather than the peripheral pressure during the session is not known?

Methods: During regular hemodialysis treatments for 10 of our ESRD patients, we measured the central and the peripheral BP through one full session. The average systolic and diastolic pressures were estimated. The pulse pressure was calculated for the peripheral as well as the central pressure. The paired T test was used to determine the statistical significance.

Results: Among the 10 patients 70% were females. Mean age was 57.7 years (SE3.8). All of them were having hypertension and 80% were diabetic. The mean peripheral systolic pressure was 149mmHg. (SE 6.9). The mean central systolic pressure was 129mmHg (SE 5.8). The mean peripheral diastolic pressure was 77mmHg. (SE 4.8). The mean central diastolic pressure was 80mmHg (SE 4.6). The mean peripheral pulse pressure was 72mmHg (SE 6). The mean central pulse pressure was 49mmHg (SE 4.6). The difference between peripheral and central measurements for the systolic, diastolic and pulse pressure were statistically significant. The systolic pressure was 20mmHg higher in the peripheral measurement with P 0.012. The diastolic pressure was 3 mmHg lower in the peripheral measurement P 0.009. The pulse pressure was 22 mmHg higher in the peripheral measurement P 0.006.

Conclusions: There was a significant difference between the peripheral and central pressure measurements during dialysis. It suggests that monitoring of the central pressure would be more accurate than the peripheral pressure during the hemodialysis sessions. The difference was noticed more among patients with high CV risks.

FR-PO582

Pegloticase, a Mammalian Uricase, Significantly Decreases Mean Arterial Blood Pressure in Patients with Chronic Gout Peter E. Lipsky,[1] Richard J. Johnson,[3] Hyon Choi,[2] Anthony Yeo.[1] *[1]AMPEL BioSolutions, Charlottesville, VA; [2]Massachusetts General Hospital, Boston, MA; [3]University of Colorado Denver, Aurora, CO.*

Background: Hypertension is a recognized co-morbidity of hyperuricemia and gout,[1] and there are significant correlations between serum uric acid (sUA) and blood pressure (BP) in individuals with and without gout.[1] While some studies suggest lowering sUA may decrease BP,[2] a meta-analysis indicated no consistent effect of oral urate lowering

therapy.[3] Pegloticase persistently decreases sUA to <1 mg/dL in responders.[4] Results from the pegloticase randomized clinical trials (RCTs) permitted determination of the impact of persistent, very low sUA levels on BP in subjects with chronic refractory gout.

Methods: This analysis used results from two 6-month RCTs in which subjects received 8 mg pegloticase every 2 weeks or placebo.[4] sUA responders maintained sUA <6 mg/dL and usually <1mg/dL.[4] Sitting BP was measured at each visit and estimated glomerular filtration rate (eGFR) was determined at baseline and after 3 and 6 months.

Results: 29 sUA responders were assessed and their mean arterial pressure (MAP) at baseline was 94.9 ± 9.6 mm Hg. At baseline, 36%, 18%, 18%, 25%, and 4% of patients were in CKD eGFR categories G1, G2, G3a, G3b, and G4, respectively. There were significant reductions in MAP in responders throughout the 6-month trial (P=0.0029), with significant changes noted within 2 weeks of the first pegloticase dose. No consistent pattern of MAP decrease was noted in non-responders or subjects receiving placebo. Of the 29 sUA responders, 18 (62.1%) had persistent decreases in MAP. There were no significant differences in baseline age, gender, race, BMI, documented history of hypertension, duration of gout, MAP, sUA, cholesterol, eGFR or urinary uric acid /creatinine ratio in those who decreased MAP vs those who did not. There were no significant changes in eGFR in sUA responders to pegloticase and no significant correlation between changes from baseline MAP and eGFR in these subjects (r= -0.16, P=0.43).

Conclusions: sUA responders to pegloticase experienced significant reductions in MAP that were independent of changes in renal function. 1. Essex MN, *J Clin Rheumatol*. 2017;23:160. 2. Agarwal V, et al. *J Clin Hypertens*. 2013;15:435. 3. Franca GPH, deMoraes SER. Cochrane Database of Systematic Reviews 2017, 4:CD008652. 4. Sundy JS, et al. *JAMA*. 2011;306:711.

Funding: Commercial Support - Horizon Pharma

FR-PO583

The Impact on Central Blood Pressure and Arterial Stiffness Post-Renal Denervation (RDN) in Patients with Stage 3 and 4 CKD: The Prairie RDN Study Bhanu Prasad,[1] Shelley Giebel,[3] Michelle C. McCarron.[2] *[1]None, Regina, SK, Canada; [2]Regina Qu'Appelle Health Region, Regina, SK, Canada; [3]Regina QuAppelle Health Region, Regina, SK, Canada*.

Background: It is now recognized that central blood pressures (CBP) and arterial stiffness are better indicators of cardiovascular outcomes than brachial blood pressures (BBP's). Renal denervation (RDN) procedure has been shown to improve blood pressures by interrupting the afferent and efferent sympathetic nerves that traverse through the adventitia of the renal arteries. While there is evidence of improvement in BBP's in patients with stages 3 and 4 CKD, the impact of RDN on CBP's has not yet been examined.

Methods: We conducted a single-center, prospective study with pre and post-RDN follow-up. 26 patients with Stage 3 or Stage 4 CKD and resistant hypertension, with no radiological or laboratory evidence of secondary causes of hypertension underwent RDN between Jan 2014 to July 2015 at the Regina General Hospital, Canada. CBP's were measured by radial tonometry (Sphygmocor), ambulatory 24-hour blood pressure (Welch Allyn), office blood pressures (BP Tru) and pulse wave velocity (PWV) by Sphygmocor. Our primary outcome was to identify an improvement in CBP at 6 months post procedure. Secondary outcomes were to identify improvement in peripheral pressures, central pressures, pulse wave velocity at baseline, 6 and 24 months.

Results: 'There was a significant improvement in brachial blood pressures (median, mm Hg) (147.5/77) at baseline, (135/75) at 6 months and (133/74.5) at 24 months (**p=<0.001**). Mean central blood pressures (mm Hg) were (126/77) at baseline, (118/75) at 6 months and (118/67) at 24 months (p=0.18). Mean ambulatory 12-hour day (mm Hg) was (147/67) at baseline, (144/67) at 6 months and (150/69) at 24 months (p=0.27). Mean ambulatory 12-hour night BP (mm Hg) was (142/65) at baseline, (141/63) at 6 months and (143/65) at 24 months (p=0.93). Mean PWV (in m/s) was (13.8) at baseline, (13.3) at 6 months and (15.6) at 24 months time.

Conclusions: Our study demonstrates that there was a significant improvement in peripheral blood pressures from baseline to 6 months and was maintained at 24 months. There was a downward trend in central blood pressures although it did not reach statistical significance. There was no change in ambulatory blood pressures and PWV. It's the first study that looks at central blood pressures post RDN in CKD patients to our knowledge.

FR-PO584

Functional Sympatholysis Is Impaired in Chronic Renal Disease Ryan M. Downey,[2,3] Peizhou Liao,[1] Dana Dacosta,[2,3] Jeanie Park.[2,3] *[1]Department of Biostatistics and Bioinformatics, Emory University Rollins School of Public Health, Atlanta, GA; [2]Division of Renal Medicine, Emory University School of Medicine, Atlanta, GA; [3]Research Service Line, Atlanta VA Medical Center, Decatur, GA*.

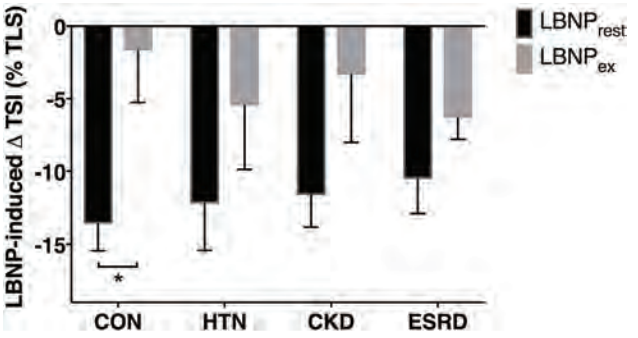
Background: Chronic renal failure is characterized by exercise intolerance. Although exercise induces reflex activation of sympathetic nerve activity (SNA), local metabolites within exercising skeletal muscle oppose SNA-mediated vasoconstriction, preserving blood flow and oxygenation to the working muscle, termed functional sympatholysis. We hypothesized that compared to healthy controls (CON), hypertensives without kidney disease (HTN), chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients have impaired functional sympatholysis.

Methods: Muscle oxygen tissue saturation index (TSI) was measured using near-infrared spectroscopy (NIRS) of the forearm in 46 subjects (10 CON, 8 HTN, 12 CKD, 12 ESRD). Sympathetic activation was induced using lower-body negative pressure (LBNP). Continuous muscle TSI was measured at rest, during LBNP, and during LBNP with concomitant rhythmic handgrip exercise at 30% of maximum voluntary contraction.

Results: Baseline muscle TSI was significantly lower in HTN, CKD, and ESRD compared to CON (CON, 69.30±1.86%; HTN, 65.74±1.94%; CKD, 66.88±1.08%; ESRD, 62.79±1.60%; p=0.042). Muscle TSI decreased in all groups during SNS activation induced by LBNP at rest. When compared to muscle TSI changes during LBNP at rest, the reduction in muscle TSI was significantly ameliorated during LBNP with handgrip exercise in CON (-11.94±2.04% vs. -6.25±1.82%, p=0.011), demonstrating intact functional sympatholysis.

Conclusions: There was no significant improvement in muscle TSI during LBNP with concomitant exercise in HTN, CKD or ESRD suggesting impaired functional sympatholysis that could contribute to exercise intolerance.

Funding: Other NIH Support - R01HL135183, DK-00756, GM-000680, Veterans Affairs Support, Private Foundation Support



Exercise significantly attenuated the LBNP-induced decrease in TSI in healthy controls, indicating functional sympatholysis (p=0.011). Exercise did not significantly attenuate LBNP-induced decreases in TSI in hypertensive, CKD, nor ESRD groups, indicating impaired sympatholysis.

FR-PO585

The Effect of Renal Denervation on Kidney Function – Does Estimating Equation Matter? The ReShape CV-Risk Study Marit D. Solbu,[1,3] Atena Miroslawska,[4,2] Jon V. Norvik,[1,3] Terje K. Steigen.[2,1] *[1]University Hospital of North Norway, Tromsø, Norway; [2]UiT The Arctic University of Norway, Tromsø, Norway; [3]Metabolic and Renal Research Group, UiT The Arctic University of Norway, Tromsø, Norway; [4]Department of Cardiology, University Hospital of North Norway, Tromsø, Norway*.

Background: Renal denervation (RDN) is considered as a treatment option for patients with treatment resistant hypertension (TRHT). However, the short and long term effect of RDN on kidney function has not been evaluated. Moreover, whether the various commonly used equations to estimate GFR perform equally in RDN patients has never been assessed. The aim of our study was to track changes of measured and estimated GFR (mGFR and eGFR) in patients treated with RDN for TRHT, and to compare the methods to assess GFR in this patient group.

Methods: In the ReShape CV-Risk Study, non-diabetic patients with TRHT and eGFR >45 ml/min/1.73 m^2 were recruited from out-patient clinics. TRHT was defined as ambulatory daytime systolic blood pressure (SBP) >135 mm Hg while treated with ≥4 antihypertensive drugs including a diuretic. Investigations, which included fasting blood tests and iohexol clearance (mGFR), were done before RDN and after 6 and 24 months. eGFR was calculated using the CKD-EPI equations for creatinine, cystatin C and the combination ($eGFR_{cre}$, $eGFR_{cys}$, $eGFR_{crecys}$).

Results: Among the 23 patients who underwent bilateral RDN in the study, 20 completed the follow-ups at 6 and 24 months and were included in this sub-study. At baseline, mean age was 54 (±9) years, mean body mass index was 32 (±5) kg/m^2, and 2 patients were women. Mean ambulatory SBP was 155 (±21) mm Hg at baseline, fell significantly by 9.9 (±24) mm Hg at 6 months and remained stable at 24 months. Before RDN, mGFR was 83 (±20) ml/min/1.73 m^2. The value was 76 (±22) ml/min/1.73 m^2 at 6 months (P for change from baseline =0.07), but 78 (±28) ml/min/1.73 m^2 at 24 months. Whereas $eGFR_{cre}$ was stable from baseline to the first 6 months' follow-up, $eGFR_{cys}$ and $eGFR_{crecys}$ increased significantly during the same period. However, at 24 months, mean GFR was 3.1 – 4.4 ml/min/1.73 m^2 lower than the baseline value regardless of method.

Conclusions: During the first months after RDN for TRHT, estimates of GFR varied with the method used, whereas measured GFR fell slightly. In this setting, eGFR may not reflect kidney function only. After longer follow-up, all estimates of GFR showed similar GFR decline as measured GFR. These findings may be considered when evaluating kidney function after RDN.

Funding: Government Support - Non-U.S.

FR-PO586

Activation of PI 3 Kinase (PI 3 K) by PDGF Receptor-Beta (PDGFRb) Regulates Akt-Dependent Hif1a to Express Glut1 for Mesangial Cell (MC) Hypertrophy in Response to High Glucose (HG) Falguni Das,[1] Nandini Ghosh-choudhury,[1] Balakuntalam S. Kasinath,[2] Goutam Ghosh-Choudhury.[2] *[1]UTHSCSA, SAN ANTONIO, TX; [2]University of Texas Health Science Center, San Antonio, TX.*

Background: Hyperglycemia increases PI 3 K/Akt to induce glomerular MC hypertrophy in diabetic nephropathy (DN). In DN, increased glomerular expression of PDGFRb is reported. As a mechanism of PI 3 K/Akt activation in DN, we hypothesized involvement of this receptor tyrosine kinase.

Methods: Human MCs, siRNA transfection, immunoblotting, protein synthesis and hypertrophy assays and rat model of streptozotocin-induced DN were used.

Results: HG significantly increased tyrosine phosphorylation-dependent activation of PI 3 K in MC, concomitant with increased tyrosine phosphorylation of PDGFRb at the catalytic loop and the PI 3 K binding sites. A specific PDGFRb inhibitor, JNJ-10198409 (JNJ), blocked these phosphorylations, which resulted in inhibition of association of PI 3 K with the PDGFRb. Similarly, siRNAs against PDGFRb and the PDGFRb mutant deficient in PI 3 K binding (PDGFRbM) inhibited HG-induced phosphorylation of PI 3 K and hence Akt. PI 3 K/Akt regulates Glut1 expression via Hif1alpha (Hif1a) transcription factor. siRNAs against Glut1 significantly inhibited HG-induced protein synthesis and hypertrophy of MCs. JNJ, siPDGFRb and PDGFRbM markedly suppressed the expression of Hif1a and Glut1 in response to HG. Interestingly, siRNAs against Hif1a inhibited HG-mediated protein synthesis and hypertrophy of MCs. Furthermore, JNJ, siPDGFRb and PDGFRbM inhibited MC hypertrophy induced by HG. This inhibition was reversed by the expression of constitutively active Akt kinase or Hif1a. Moreover, expression of Glut1 prevented the inhibition of hypertrophy induced by siPDGFRb or PDGFRbM. Finally, we observed increased phosphorylation of PDGFRb and PI 3 K in the glomerular fraction of STZ-induced diabetic rat. This increased phosphorylation was associated with Hif1a and Glut1 expression in the diabetic glomeruli.

Conclusions: Together our results provide the first evidence for a role of PDGFRb-mediated PI 3 K/Akt activation to control Hif1a/Glut1 axis in HG-induced MC hypertrophy.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO587

Gastric Bypass versus "Medical Bypass" – Impact on Experimental Diabetic Kidney Disease Meera Nair,[3] Aoife L. Canney,[3] Jessie A. Elliott,[1] naomi m. fearon,[3] Anna Casselbrant,[2] Lars Fandriks,[2] Carel W. Le roux,[3,2] Neil G. Docherty.[3,2] *[1]St. James's Hospital, Dublin, Dublin 8, Ireland; [2]University of Gothenburg, Gothenburg, Sweden; [3]University College Dublin, Dublin, Ireland.*

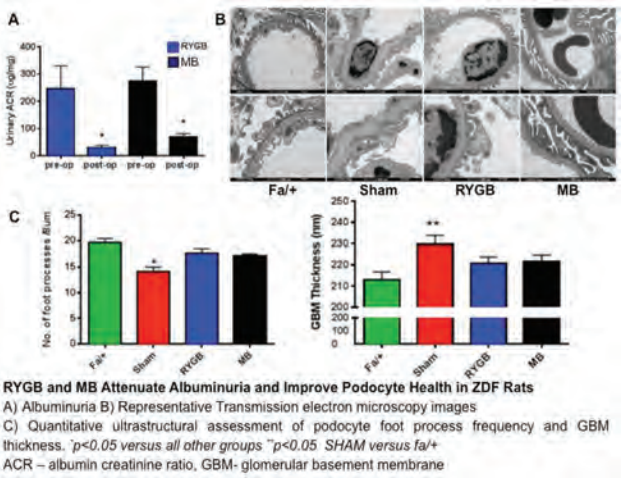
Background: Reductions in albuminuria are reported after Roux-en-Y gastric bypass (RYGB). Herein, we assess the impact of RYGB on podocyte injury in the Zucker Diabetic Fatty (ZDF) rat model of diabetic kidney disease (DKD) and compare glomerular injury and global renal transcriptomic responses of RYGB and matched "Medical Bypass"(MB).

Methods: Study 1: Adult male ZDF rats underwent sham surgery (n=8) or RYGB (n=7). Study 2: Adult ZDF rats underwent sham surgery (n=15) or RYGB (n=9). Nine sham-operated rats were calorie restricted and received insulin, liraglutide, metformin, ramipril, rosuvastatin and fenofibrate for 2 months (MB). Zucker Fa/+ rats acted as healthy controls throughout. Bodyweight, glycaemia, albuminuria and glomerular injury specifically podocyte number, density and ultrastructure were assessed at follow up. Renal transcriptomes were compared by RNA-seq.

Results: RYGB resulted in 20-30% weight loss, normalized glycaemia and albuminuria and reduced indices of glomerular injury, specifically podocyte injury (foot process effacement). RYGB equivalent outcomes were obtained on all parameters following MB. A number of RYGB-discrete changes appear to relate to procedure rather than correction of disease. MB recapitulates many of the gene expression alterations observed after RYGB, but modifies expression of a much larger number of genes. A discrete and potentially beneficial response to RYGB was the induction of ALOX15 expression, a potential source of anti-inflammatory lipids.

Conclusions: Equivalent improvements in DKD are obtained following RYGB and matched MB. Shared transcriptional change may underpin comparable ultrastructural improvements, but similarities therein understate the degree of diversity at the molecular level. ALOX15 upregulation may be a useful component of RYGB amenable to targeting in non-surgical bariatric mimetic approaches.

Funding: Government Support - Non-U.S.



RYGB and MB Attenuate Albuminuria and Improve Podocyte Health in ZDF Rats
A) Albuminuria B) Representative Transmission electron microscopy images
C) Quantitative ultrastructural assessment of podocyte foot process frequency and GBM thickness. *p<0.05 versus all other groups **p<0.05 SHAM versus fa/+
ACR – albumin creatinine ratio, GBM- glomerular basement membrane

FR-PO588

The Protective Effect of GSTK1 on Renal Injury in Diabetic Nephropathy by Anti-Inflammatory Chun Hu, Ming Yang, Peng Gao, Xianghui Chen, Yachun Han, Li Li, Xiaofen Xiong, Li Zhao, Li Xiao, Jun Li, Fuyou Liu, Lin Sun. *Departments of nephrology, Second Xiangya Hospital Central South University, ChangSha,Hunan, China.*

Background: Diabetic neprhropathy (DN) is one of the most serious microvascular complication in patients with diabetes mellitus. GSTK1 is a key protein which participate in adiponectin secretion and polymerization, it can also promote the expression of adiponectin. Our previous research has demonstrated that down-regulation of GSTK1 expression in the kidney of patients with DN, which consistent with decreased adiponectin levels in the serum. However, the role of GSTK1 in the development of DN is unclear.

Methods: C57BL/6 mouse were divided into four groups: normal group (control), STZ induced diabetic mouse group(STZ), overexpression GSTK1 group (GSTK1 transgenec mouse, fGSTK1) and fGSTK1 mouse with STZ iduced diabetc group (STZ fGSTK1)(n=8). In group of STZ and fGSTK1+STZ, mouse was feeding with high fat diet(HFD) for 4 weeks, and then single intraperitoneal injection of STZ 100mg/kg, continue with HFD feeding for 12 weeks. At the end of the experiment, blood and urine was collected for biochemical determination. The renal tissue was isolated and used for pathological examination,electron microscopy,DHE,IF,IHC,PCR and western blot analysis.

Results: Compared with the control group, the weight, blood sugar, blood lipid, urine protein levels, ROS were increased significantly in STZ mouse group. The pathological change were increased notable in the kidney in STZ mouse. In STZ mouse, the epithelial cell foot process effacement in kidney was seen as detected by electron microscope, in addition, both expression of GSTK1 and adiponectin were reduced compared to control($p<0.05$). Furthermore, the mRNA and protein expression of NLRP3, casepase1, IL1β, IL18 and NF-kB were increased significantly in the kidney of STZ mouse compared to control($p<0.01$), which accompany with the increased expression of FN, Collagen 1 and IV. All of this change were reversed partialy in fGSTK1+STZ group($p<0.01$). There was no significant difference between fGSTK1 and control groups

Conclusions: GSTK1 decreased the weight, blood glucose, blood lipid, urine protein, ROS level, increased adiponectinthe expression and reduced pathological changes in the kidney of STZ induced mouse. GSTK1 protected renal injury and reduce fibrosis in the kideny of diabetic mouse may through up-regulated expression of adiponectin and then inhibiting NLRP3 inflammation activity pathway

FR-PO589

Triptolide Alleviates Podocyte Injury in Hyperglycemia via Abrogating Activation of NALP3 Inflammasome and PI3K/Akt/mTOR Signaling Wenbei Han,[2] Yigang Wan.[1] *[1]Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China; [2]Nanjing University of Chinese Medicine, Nanjing, China.*

Background: *Triptolide* (TP), an extracted phytomedicine is frequently used for protecting against podocyte injury in early diabetic kidney disease (DKD) in China. However, the therapeutic mechanism remains unclear. In the process of DKD, the activation of NALP3 inflammasome and PI3K/Akt/mTOR signaling in kidneys is the important mechanisms by which renal inflammation contributes to podocyte damage. This study thereby aimed to examine the ameliorative effects of TP on podocyte lesion in hyperglycemia (HG), then to clarify its anti-inflammatory mechanisms in vitro by inhibiting the activation of NALP3 inflammasome and PI3K/Akt/mTOR signaling.

Methods: HG was used to induce murine podocyte to be in the state of damage. After the intervention of HG for 0, 3, 6, 12, 24 and 48 hours, firstly, the protein expressions of NALP3, active caspase-1 and active IL-1β were detected. Secondly, the protein expressions of desmin and synaptopodin were examined. Thirdly, the protein expressions of p-PI3K, p-Akt and p-mTOR were observed. And then, after the co-treatment of TP and HG without or with mTOR inhibitor (rapamycin), the protein expressions of the

key factors in NALP3 inflammasome activation, podocyte lesion and PI3K/Akt/mTOR signaling pathway were tested, respectively.

Results: The result showed that HG induced up-regulation of NALP3, active caspase-1, active IL-1β, p-PI3K, p-Akt and p-mTOR, and down-regulation of desmin and synaptopodin at protein expression level in podocyte. The co-treatment of TP and HG reversely regulated the protein expressions of NALP3, active IL-1β, desmin, synaptopodin, p-Akt and p-mTOR in HG-intervened podocyte significantly. The co-treatment of rapamycin, TP and HG recovered the level of NALP3 and p-mTOR protein expressions in HG-intervened podocyte obviously.

Conclusions: In conclusion, TP, as a natural regulator, attenuates podocyte injury in HG by abrogating the activation of NALP3 inflammasome and PI3K/Akt/mTOR signaling. This study may provide the first evidence that TP directly protects podocyte in HG via anti-inflammation.

Funding: Government Support - Non-U.S.

FR-PO590

Long-Term Empagliflozin Administration Downregulates Aquaporin 2 despite the Increased Expression of V2 Vasopressin Receptor in Diabetic Rat Kidneys Sungjin Chung,[1,2] Zhilian Li,[1,3] Soojeong Kim,[4] Seok Joon Shin,[2] Cheol Whee Park,[2] Chul Woo Yang,[2] Yong-Soo Kim,[2] Eun Sil Koh.[2] *[1]Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN; [2]Department of Internal Medicine, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea; [3]Department of Nephrology, Guangdong General Hospital, Guangzhou, China; [4]Department of Biochemistry, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea.*

Background: Beyond glucose lowering effect, it has been suggested that one of the possible mechanisms by which empagliflozin, a selective sodium-glucose cotransporter-2 (SGLT2) inhibitor, provides the remarkable cardiovascular and renal protection observed in a recent trial may relate to its effects on diuresis and natriuresis. However, the natriuretic effect of SGLT2 inhibitors is transient, and long-term data related to diuretic change are sparse.

Methods: This experiment assessed the effects of 12-week treatment with empagliflozin (3 mg/kg) on renal tubular function, related sodium transporters and water channels in diabetic OLETF rats by comparing it with other antihyperglycemic agents such as lixisenatide (10 μg/kg), a glucagon-like peptide receptor-1 agonist, and voglibose (0.6 mg/kg), an α-glucosidase inhibitor.

Results: At 12 weeks of treatment, serum sodium and potassium and fractional excretion of sodium did not significantly differ between empagliflozin-treated and control diabetic rats. Empagliflozin-treated diabetic rats produced slightly decreased but still high urine volume and glycosuria, and they showed significantly higher electrolyte-free water clearance than lixisenatide- or voglibose-treated diabetic rats. In empagliflozin-treated rats, renal protein expression of Na^+-K^+-$2Cl^-$ cotransporter (NKCC2), Na^+/H^+ exchanger isoform 3 (NHE3) and γ-epithelial Na^+ channel (ENaC) were decreased, and Na^+-Cl^- cotransporter (NCC) and α-ENaC expressions were unaltered compared with control diabetic rats. Empagliflozin increased the expressions of aquaporin (AQP)-3 and AQP7 but did not affect AQP1 protein expression in diabetic kidneys. Despite the increased expression in vasopressin V2 receptor (V2R), protein and mRNA levels of AQP2 in kidneys of empagliflozin-treated diabetic rats were significantly decreased than those of control diabetic rats. These were not observed in lixisenatide or voglibose-treated diabetic rats.

Conclusions: Taken together, longer use of empagliflozin may downregulate AQP2 expression regardless of the V2R activation by as-yet unidentified signaling pathways, contributing, in part, to polyuria in diabetic rats.

Funding: Government Support - Non-U.S.

FR-PO591

SGLT2 Inhibitor Dapagliflozin Is Renoprotective in Streptozotocin-Induced Diabetes Dora B. Balogh,[2,3] Lilla Lenart,[2] Judit Hodrea,[2] Adam Hosszu,[2,1] Ádám Vannay,[3,4] Laszlo J. Wagner,[1] Attila J. Szabo,[5] Andrea Fekete.[6,3] *[1]Department of Transplantation and Surgery, Semmelweis University, Budapest, Hungary; [2]MTA-SE Lendület Diabetes Research Group, Budapest, Hungary; [3]1st Department of Pediatrics, Semmelweis University, Budapest, Hungary; [4]MTA-SE Pediatrics and Nephrology Research Group, Budapest, Hungary; [5]1st Department of Pediatrics, Semmelweis University, Budapest, Hungary; [6]MTA-SE Lendület Diabetes Research Group, Budapest, Hungary.*

Background: Inhibitors of sodium-glucose co-transporter 2 (SGLT2) are a new class of antihyperglycemic drugs that act by inhibiting SGLT2 mediated glucose reabsorption in the proximal tubules. They have recently been approved type 2 diabetes, however their use is limited in renal impairment. They have not been registered yet in type 1 diabetes (T1DM) either. Previously we showed that in diabetic kidney injury activity of the hexosamine biosynthesis pathway is increased, resulting in protein *O*-linked N-acetylglucosamine modification (*O*-GlcNAcylation), which induces cellular processes leading to the progression of renal failure. The dynamic addition (by OGT) and removal (by OGA) of *O*-GlcNAc modulates signaling molecules which results in kidney fibrosis. Since there is still an unmet need for oral therapies in T1DM here we investigated the antidiabetic and possibly renoprotective effect of the highly selective SGLT2 inhibitor dapagliflozin (DAPA) in streptozotocin-induced model of DM.

Methods: T1DM was induced by streptozotocin (65 mg/bwkg, *ip.*) in male Wistar rats. Immediately following onset of DM the animals were treated *per os* for six weeks with DAPA (D+DAPA, 1 mg/bwkg/day). Metabolic, renal parameters and kidney histology was evaluated. Specific markers of tubular damage (NGAL, KIM-1), profibrotic factors (CTGF, PDGF, TGF-β), proinflammatory cytokines (IL-6, IL-1β, TNF-α) and α-SMA, *O*-GlcNAc, OGT and OGA protein levels were measured.

Results: Development of diabetic kidney injury was confirmed by impairment of renal function, massive proteinuria and structural damage of kidneys. DAPA reduced weight loss and decreased blood glucose level. DAPA Treatment improved GFR, ameliorated tubular damage and decreased of proinflammatory cytokines IL-6, IL-1β, TNF-α and profibrotic growth factors CTGF, PDGF, TGF-β. SGLT2 inhibition ameliorated DM-induced mesangial matrix expansion and tubulo-interstitial fibrosis. DM-induced elevated proteins *O*-GlcNAcylation, OGT, OGA and α-SMA levels were reduced by DAPA.

Conclusions: DAPA improved metabolic and renal parameters and decreased the histological lesions in the kidney. Decrease of *O*-GlcNAcylation by DAPA has a beneficial effect on profibrotic processes. These results support the effective and safe clinical application of DAPA in the prevention/treatment of T1DM and associated nephropathy.

FR-PO592

Dapagliflozin Alone or Combined with Ramipril Improves Hyperglycemia and Hypertension and Prevents Kidney Complications and GFR Decline in the Nephrectomized SDT Fatty Rat Model of Diabetic Nephropathy Francois Briand,[3] Masami Shinohara,[1] Emmanuel Brousseau,[3] Takeshi Ohta,[2] Yasushi Kageyama,[1] Thierry Sulpice.[3] *[1]CLEA Japan, Inc., Meguro, Japan; [2]Japan Tobacco Inc., Osaka, Japan; [3]PHYSIOGENEX, LABEGE, France.*

Background: Combination of sodium glucose cotransporter 2 inhibitor (SGLT2i) and angiotensin converting enzyme inhibitor (ACEi) represents a potential therapeutic strategy to prevent diabetic nephropathy progression to end stage renal disease (ESRD). Here we evaluated SGLT2i dapagliflozin (DAPA) alone or combined with ACEi ramipril (RAMI) in the uni-nephrectomized Spontaneously Diabetic Torii (SDT) fatty rat. This hypertensive/obese/type 2 diabetic model develops advanced renal complications and >50% glomerular filtration rate (GFR) decline within 10 weeks.

Methods: One week after unilateral nephrectomy, SDT fatty rats were put on a chow diet with 0.3% salt in drinking water for 10 weeks. Rats were treated without (CTRL) or with DAPA 1mg/kg/day alone or with DAPA + RAMI both at 1mg/kg/day in the diet upon diet start (10-week treatment).

Results: Compared to CTRL, DAPA reduced hyperglycemia by 70%, and % HbA1c by 4.7% (both $p<0.001$). DAPA reduced systolic and diastolic blood pressure by 17 and 14% (both $p<0.05$). While CTRL rats showed a 64% GFR decline (as measured by FITC-inulin injection) at 5 weeks of treatment, DAPA markedly prevented this decline with a 71% higher GFR vs. CTRL ($p<0.01$). At the end of the 10-week treatment, DAPA significantly reduced glomerulosclerosis, inflammation and fibrosis histopathology scores. However, GFR values were not different between CTRL and DAPA, even after a wash-out period, excluding a tubuloglomerular feedback effect. As DAPA alone, DAPA + RAMI reduced hyperglycemia by 74%, and % HbA1c by 4.7% (both $p<0.001$ vs. CTRL). DAPA + RAMI further reduced systolic and diastolic blood pressure by 29 and 24% (both $p<0.01$ vs. CTRL). As well, DAPA + RAMI prevented GFR decline at 5 weeks of treatment (39% higher, $p<0.05$), but also at 10 weeks of treatment (63% higher, $p<0.05$ vs. CTRL).

Conclusions: In the 10-week Unx SDT fatty rat, DAPA alone prevents kidney complications, while the combination with RAMI adds benefits by better delaying GFR decline. Our data suggest that SGLT2i/ACEi combination prevents progression to ESRD.

Funding: Commercial Support - PHYSIOGENEX

FR-PO593

PBI-4547 Prevents Renal Destruction and Fibrosis in Severely Obese db/db Mouse Model of Diabetes-Induced Kidney Disease Francois A. Leblond, Sylvie Létourneau, Jugurtha Ouboudinar, Liette Gervais, Pierre Laurin, Brigitte Grouix, Lyne Gagnon. *Prometic BioSciences Inc., Laval, QC, Canada.*

Background: Type 2 diabetes (T2D) is a major health problem worldwide. Comorbidities, such as kidney disease, associated to T2D are numerous and cause severe reduction of life expectancy. The uninephrectomized (NX) diabetic (*db/db*) mouse is a widely used model for the study of comorbidities associated to T2D. It also allows to study effects of obesity on diabetes-induced kidney disease. PBI-4547 is an orally active compound that displays anti-fibrotic and metabolic activities via a novel mechanism of action. The aim of this study was to investigate the protective effect of PBI-4547 on kidney health and function in NX *db/db* mice.

Methods: Total nephrectomy of the right kidney was performed on day 0 on 6-weeks old *db/db* (B6.BKS(D) and control C57BL/6 mice. Animals were treated with vehicle or PBI-4547 (25 mg/kg) from day 1 through 105 by daily oral gavage.

Results: PBI-4547 significantly improved diabetic condition of *db/db* mice, and lowered weight gain to that of control C57BL/6 mice. A significant reduction of fasting blood glucose, plasma insulin, and area under the curve in oral glucose tolerance test were observed in PBI-4547-treated *db/db* mice. PBI-4547 dosing also resulted in a reduction of plasma triglycerides and an increase in adiponectin. Moreover, PBI-4547 eventuated a significant reduction in the renal damage observed on *db/db* mice as shown by histopathological analysis of kidneys. When compared to control C57BL/6 mice, kidney glomeruli, tubules and capillaries of non-treated *db/db* mice were found significantly damaged. These modifications were almost absent on *db/db* mice treated with PBI-4547. Evaluation of numerous markers of fibrosis also confirmed that PBI-4547 significantly

reduced the fibrosis process in the kidney. Reduction of the mRNA expression of collagen type 1 (-40%), MCP-1 (-63%), TIMP-1 (-71%), MMP-2 (-47%) and GLEPP-1 (-13%) were shown in kidneys of PBI-4547-treated compared to untreated *db/db* mice. Neither BUN nor GFR were found significantly modified in the *db/db* non-treated mice (compared to NX C57BL/6 mice) and PBI-4547 had no impact on these parameters.

Conclusions: These studies suggest that, in addition to the improvement of T2D, PBI-4547 treatment precludes renal structure destruction and prevents fibrosis in the kidneys of severely obese *db/db* mice.

Funding: Commercial Support - Prometic Life Sciences Inc.

FR-PO594

PBI-4547, a Novel Anti-Diabetic Agent, Prevents Diabetic Nephropathy and Protects β-Cells in NOD Mice, a Model of Type 1 Diabetes Lyne Gagnon, Kathy Hince, François Sarra-Bournet, Mikaël Tremblay, Marie-Pier Cloutier, Sylvie Létourneau, Pierre Laurin, Brigitte Grouix, Francois A. Leblond. *Prometic BioSciences Inc., Laval, QC, Canada.*

Background: Kidney disease is a cause of substantial morbidity and mortality in type 1 diabetes (T1D). Up to 40% of patients with T1D develop macroalbuminuria, and up to 75% of these patients progress to end-stage renal disease (ESRD) within 10 years. PBI-4547 is a novel first-in-class orally active antidiabetic compound which displays pleiotropic activities and has been shown to reduce NASH, diabetes and fibrosis of kidney in different animal models. In the present study, we examined whether PBI-4547 may prevent diabetic nephropathy in NOD mice, a model of type 1 diabetes.

Methods: NOD/ShiLtJ female mice (8 weeks of age) received vehicle (water) or PBI-4547 (10 and 25 mg/kg/day) by daily gastric gavage for 23 weeks.

Results: In kidney, PBI-4547 protects against lesions by reducing glomerular volume and mesangial cross sectional area. Furthermore, tubular lesions were absent in PBI-4547-treated mice. Tubular dystrophy as PAS granular accumulation was constantly present in proximal tubules of NOD control mice and was completely abrogated by treatment with PBI-4547. Mice treated with PBI-4547 did not develop diabetes. OGTT was also normalized in PBI-4547-treated mice. PBI-4547 partially prevented islets destruction, which contributed to maintain normoglycemia.

Conclusions: This data suggests that PBI-4547 prevents diabetic nephropathy and complete destruction of β-cells and islets in type 1 diabetes model.

Funding: Commercial Support - Prometic Life Sciences Inc.

FR-PO595

Imbalance of Intestinal Microflora Disrupts LDL Receptor Pathway to Induce Lipid Accumulation at Renal Interstitium in Early Diabetic Nephropathy Zebo Hu, Kun ling Ma, Yang Zhang, Gui hua Wang, Peipei Chen, Jian Lu, Chenchen Lu. *Zhongda Hospital, Southeast University Medical School, Nanjing City, China.*

Background: Our previous studies demonstrated that lipid accumulation in kidneys contributes to the progression of diabetic nephropathy (DN). However, the exact mechanism of which caused lipid accumulation in kidney has not been completely elucidated. This study aimed to investigate the effect of imbalance of intestinal microflora on lipid deposition in the renal interstitium of DN.

Methods: Type 1 diabetic rats model were induced by streptozotocin injection. Broad-spectrum antibiotics were used to eliminate intestinal microflora. Intestinal microflora distribution was evaluated by 16S rDNA sequencing using samples from feces. Periodic acid-schiff (PAS) staining was used to observe basic structure and pathological changes of kidney. Lipid accumulation was detected by oil red O staining, Filipin staining, and intracellular free cholesterol quantitative assay. Immunohistochemical staining and Western blot were used to assess the protein expressions of low-density lipoprotein receptor (LDLr) pathway.

Results: Blautia, Roseburia, and Paraprevotella abundance were significantly increased in diabetic rats while Bacteroid abundance decreased when compared with the controls. Broad-spectrum antibiotics effectively cleared away intestinal microflora. PAS staining showed that tubular epithelium in diabetic mellitus group (DM group) exhibited obvious expansion, ballooning degeneration, cell detachment as well as increased glycogen deposition while antibiotics treatment alleviated those lesions. Lipid accumulation in tubular interstitium of diabetic rats was increased compared with the controls. After the application of antibiotics, the lipid accumulation in tubular interstitium of diabetic rats was significantly reduced. Moreover, immunohistochemical staining and Western blot suggested that LDLr expression in tubular interstitium was increased in DM group, while antibiotics treatment decreased LDLr expression.

Conclusions: Imbalance of intestinal microflora might disrupt LDLr pathway to induce lipid accumulation at renal interstitium in early diabetic nephropathy.

FR-PO596

Expression of Hepatic Cytochrome P450 Drug-Metabolizing Enzymes in a Mouse Model of Diabetic Nephropathy Cheng J. Fang,[4] Dylan Burger,[1] Chet E. Holterman,[2] Chris R. Kennedy,[1] Jean-Francois Thibodeau,[3] Brad Urquhart.[4] *[1]Kidney Research Centre, Ottawa, ON, Canada; [2]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [3]ProMetic BioSciences Inc., Laval, QC, Canada; [4]Western University, London, ON, Canada.*

Background: Out of 420 million diabetics, over a third will develop diabetic nephropathy. Studies in chronic kidney disease have demonstrated decreased expression of hepatic cytochrome P450 (CYP) drug-metabolizing enzymes. With polypharmacy in diabetic patients, diabetic kidney disease may lead to adverse drug reactions as a result of altered drug pharmacokinetics due to unexpected changes in CYP expression. This study evaluates the expression and metabolic activity of CYP3A11 and CYP2C29, mouse orthologues of human CYP3A4 and CYP2C9 in a mouse model of drug-induced diabetic nephropathy, as well as in a CYP3A4/PXR-humanized (TgCYP3A4/hPXR) mouse model.

Methods: Male C57BL/6 mice were treated with 50 mg/kg of streptozotocin (STZ; $n = 7$) intraperitoneally for 5 consecutive days. Control mice ($n = 8$) were injected with sodium acetate. After 16 weeks, blood glucose and kidney function (eGFR, urinary albumin-to-creatinine ratio (UACR)) were measured. Mouse livers were isolated for real-time PCR analysis and Western blot to determine CYP mRNA and protein expression. Activity of microsomes was assessed by metabolism of probe drugs (midazolam, testosterone) using liquid chromatography coupled to mass spectrometry (LC-MS).

Results: The UACR for STZ-treated mice was 667.3 μg/g compared to 145.5 μg/g in controls ($P < 0.001$). Similarly, eGFR was increased in STZ mice (20.2 mL/min/g body weight) compared to controls (10.2 mL/min/g body weight; $P < 0.001$). STZ-treated mice had higher plasma glucose (30.9 mM) compared to controls (6.4 mM; $P < 0.001$). Cyp3a11 mRNA expression showed a decreasing trend in diabetic nephropathy mice (-44%, $P = 0.10$) compared to control mice. Cyp2c29 mRNA expression was not significantly different in STZ mice compared to control.

Conclusions: Increased UACR, eGFR, and glucose are strong indicators of diabetic nephropathy, indicating reliability of the drug-induced diabetic mouse model. The same treatment is currently being used in studies investigating the impact of diabetic nephropathy on TgCYP3A4/hPXR mice. A decreasing trend in Cyp3a11 expression indicates possible down-regulation in diabetic nephropathy. Future directions will increase the sample size and evaluate hepatic differences caused by diabetic nephropathy by metabolomics in an effort to elucidate potential regulators of CYP expression.

Funding: Government Support - Non-U.S.

FR-PO597

TMX-049, a Novel Xanthine Oxidase Inhibitor, Attenuates Renal Injury in an Experimental Model of Diabetic Kidney Disease Yoshiki Tsubosaka,[1] Takashi Shirakura,[1] Shunsuke Tsujimoto,[1] Reiko Aizawa,[1] Chieko Matsui,[1] Yohei Sakamoto,[2] Naoki Hase,[1] Tsunefumi Kobayashi.[1] *[1]Pharmacology Research Department, Teijin Institute for Bio-medical Research, Teijin Pharma Limited, Tokyo, Japan; [2]Toxicology Research Department, Teijin Institute for Bio-medical Research, Teijin Pharma Limited, Tokyo, Japan.*

Background: Diabetic kidney disease (DKD) is a major chronic renal complication of diabetes. Since several non-clinical and clinical studies imply the contribution of xanthine oxidase (XO) to the DKD progression, inhibiting XO activity may be one of the attractive therapeutic approaches. TMX-049 is a newly developed XO inhibitor with non-purine structure. In this study, we evaluate the effect of TMX-049 on renal damage in rat model of type 2 diabetes.

Methods: 1. To examine the pharmacological profile of TMX-049, in vitro and in vivo inhibition of XO activity with TMX-049 treatment was measured in human primary hepatocyte and SD rat kidney, respectively. 2. To evaluate in vivo efficacy of TMX-049 on renal injury, 8 week-old male ZDF rats were orally administrated vehicle or TMX-049 once daily for 13 weeks. Normoglycemic ZDF-lean (ZL) rats were used as non-DKD control. The amount of urinary albumin and KIM-1, a biomarker for proximal tubular cell injury, were quantified on weeks 0, 2, 4, 6, 8, 10 and 12. Measurement of XO activity in renal cortex and histological analysis were determined at 13 weeks.

Results: 1. TMX-049 inhibited cellular XO activity ($IC_{50} = 2.43 \pm 0.54$ nM) in human hepatocyte and did not change other enzymatic activities related to purine metabolism. TMX-049 also showed sustained inhibition of XO activity in normal rat kidney 24 hours after oral administration, and its effect was more potent than that of launched XO inhibitor. 2. Compared with ZL rats, ZDF rats exhibited the renal structural changes, elevation of urinary parameters such as albumin and KIM-1 and increased XO activity in renal cortex. Immunohistological analysis revealed that XO/xanthine dehydrogenase expression was detected in the proximal tubules. Administration of TMX-049 reduced the urinary excretion of albumin and KIM-1, and ameliorated histological renal damage seen in ZDF rats without affecting any metabolic parameters.

Conclusions: TMX-049 attenuated renal injury in an experimental model of DKD. These results suggest the therapeutic potential of TMX-049 in DKD.

FR-PO598

Endoglin Mediates Endothelial Activation and Monocyte Adhesion and Is Correlated with Glomerular VCAM-1 in Patients with Diabetic Nephropathy Pascal Bus,[2] Tessa Gerrits,[1] Sharon Heemskerk,[1] Malu Zandbergen,[1] Jan A. Bruijn,[3] Hans J. Baelde,[2] Marion Scharpfenecker.[2] *[1]LUMC, Leiden, Netherlands; [2]Leiden University Medical Center, Leiden, Netherlands; [3]Leiden University Medical Center, Dept.Pathology, Leiden, Netherlands.*

Background: Diabetic nephropathy is characterized by microvascular injury driven by hyperglycemia and enhanced growth factor production. Altered growth factor expression causes an angiogenic imbalance resulting in endothelial activation and dysfunction. Endothelial activation promotes the adhesion and subsequent infiltration of inflammatory cells, which promote renal damage in diabetic animal models. Endoglin is crucial for angiogenesis and vascular development, and is associated with endothelial activation and inflammation in animal models of renal disease. Here, we investigated whether reducing

endothelial endoglin expression affects endothelial activation and monocyte adhesion under diabetic conditions *in vitro*, and we investigated which glomerular cells express endoglin and VCAM-1, and whether glomerular endoglin expression is associated with endothelial activation in patients with diabetic nephropathy.

Methods: Immortalized endothelial cells with either wild type or reduced endoglin expression were used to study endothelial activation and monocyte adhesion after stimulation with either glucose or VEGF-A. Glomerular endoglin and VCAM-1 expression was studied by immunohistochemistry in biopsies of patients with diabetic nephropathy. Data were analyzed using a Student's t-test or a Mixed Model Regression Analysis. Double-labeled immunofluorescence was performed for endoglin and CD31 or VCAM-1. Differences were considered significant at $p<0.05$.

Results: Lowering endoglin expression in endothelial cells *in vitro* significantly impaired VEGF-A- and glucose-mediated induction of activation markers *VCAM1* and *SELE*, and significantly reduced monocyte adhesion ($p<0.05$). In diabetic patients, endoglin was primarily expressed in endothelial cells. Glomerular VCAM-1 expression co-localized with endoglin. Furthermore, glomerular VCAM-1 was significantly increased in patients with diabetic nephropathy ($p<0.05$) and correlated with glomerular endoglin levels ($p<0.001$).

Conclusions: Targeting endoglin function is a promising future strategy to interfere with endothelial activation in order to prevent or stop inflammation and thereby the progression of diabetic nephropathy.

FR-PO599

FK506 Attenuates Proteinuria by Inhibiting Endothelial-to-Mesenchymal Transition in Rats with Diabetic Nephropathy

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Background: Many studies have shown that endothelial cell damage is present in the early stage of diabetic nephropathy(DN) and endothelium-podocytes crosstalk plays an important role in DN. FK506 was found to be beneficial for attenuating proteinuria in DN recently. However, the underlying mechanism is still unknown. In this study, we investigated whether endothelial-to-mesenchymal transition(EndMT) of DN could be attenuated by FK506.

Methods: Thirty-six **SD rats were randomly divided into three groups(n=12/ group)**: **control group,** DN **group,** FK506 **treatment group**. The DN model was established using strephozotocin(58mg/kg). The **diabetic** r**ats** were administered with FK506 **by** gavage **(0.15mg/kg/d) for 3**4 weeks. Some biochemical parameters, urinary albumin (UAL), and kidney weight/body weight (KW/BW) were measured. Nephrin and podocin were detected by Western blotting(WB) and Endothelial marker (CD31), FSP1 and α-SMA were detected by Double immunofluorescence staining, immunohistochemistry, real time-PCR and WB.

Results: There were significant increases in the levels of SCr, BUN, KW/BW, UAL, the glomerular volume, proliferative mesangial cells, width of the mesangial area in DN. However, these were reduced by FK506 treatment, compared with DN ($P<0.05$). Disorder, widening and fusion of podocyte processes were observed under the electron microscope in DN and they were reduced by FK506 treatment ($P<0.05$). The results of the WB showed that the expression of nephrin and podocin decreased in DN compared with the control and was significantly improved by FK506 treatment ($P<0.05$). Double immunofluorescence staining, Immunohistochemistry, real time-PCR and WB showed that the expression level of CD31 was downregulated in DN, whereas the expressions of FSP1, α-SMA were markedly upregulated. These changes were inhibited by FK506 treatment ($P<0.05$).

Conclusions: The results might provide a novel insight FK506 could attenuate the proteinuria by inhibiting endothelium-podocytes crosstalk in rats with DN. These results still need further study.

Funding: Government Support - Non-U.S.

FR-PO600

FK506 Attenuates Bone Loss by Inhibiting Endothelial-to-Adipocyte Transition in Diabetic Rats

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Background: FK506, a well known immunosuppressant drugs, was found to be beneficial for bone health recently. However, the underlying mechanism is still under study. Our previous research has shown that high glucose induced phenotypic changes of endothelial cells (EndMT) in vivo and in vitro. Therefore, we asked the question of whether high glucose induced EndMT could be transformed to MSCs and differentiated into adipocytes (endothelial-to-adipocyte transition), and subsequently be involved in the bone loss in diabetes.

Methods: Diabetic rats were divided into two groups: the diabetic group (DM) and the FK506-treated group (DM+FK506). Diabetic models were established by intraperitoneal injection with streptozocin. Healthy rats served as control (CTL). Skeletal changes were determined by dual energy x-ray absorption (DEXA), micro-computed tomography (micro-CT), and bone mechanics tests. Immunofluorescence staining was performed to detect the co-expression of endothelial marker (CD31) and fibroblast marker (FSP1), CD31 and adipocyte marker (LPL). The expression of CD31, FSP1, mesenchymal stem cell markers (CD10, CD44, STRO-1), and LPL were detected by immunohistochemistry, real time-PCR and western blots. Adipocytes were detected by oil red O staining.

Results: Increased bone loss was detected in the DM group, which could be attenuated by FK506 treatment: the bone mineral density (BMD) of femur and lumbar assessed by DEXA were decreased in the DM group, which attenuated by FK506 treatment ($P<0.05$); the trabecular BV/TV, trabecular number, cortical area, cortical thickness measured by micro-CT were decreased in the DM group, which were alleviated in the DM+FK506 group ($P<0.05$). The adipocytes infiltration in the DM group detected by oil red O staining was significantly increased compared with the CTL group, which was improved by FK506 treatment ($P<0.05$). The expression of CD31 was notable down-regulated in DM group, whereas the expressions of FSP1, CD10, CD44, STRO-1, LPL were markedly up-regulated. These changes were inhibited by FK506 treatment ($P<0.05$).

Conclusions: This study provides a novel insight that bone marrow endothelial-to-adipocyte transition might contribute to the bone loss in diabetes, and FK506 treatment could attenuate the skeletal changes by inhibiting this phenotypic transition.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

FR-PO601

Experimental Diabetic Nephropathy and Effect of Atrasentan Administration on Renin Angiotensin System

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Background: The endothelin A receptor specific blocker, atrasentan, has been shown to reduce residual albuminuria in diabetic nephropathy. However, edema has been described in some patients. We studied the effect of atrasentan in obese diabetic mice on renal pathology, renin angiotensin system and edema formation.

Methods: Male obese diabetic mice db/db(DB) and their controls(CONT) were used to study the effect of three doses of atrasentan(AS) administered for 16 weeks(10, 25 and 50mg/kgBW/day). Furthermore, a group receiving insulin(INS) was also included (10AS+INS). Body weight, glycemia, blood arterial pressure and bioimpedance were recorded throughout the follow-up and at the end of the study. WT1, ACE2 and AT1R were detected by IHC in kidney. ACE2 enzyme activity was detected in serum and renal cortex.

Results: DB animals showed higher blood glucose levels. Only the groups AS10+INS and AS50 showed significantly reduction of glycemia. Body weight in DB animals was higher than in control animals. Atrasentan significantly increased body weight in AS10+INS group reflected in the increase of extracellular fluid composition measured by bioimpedance. In kidney, DB animals showed lower number of podocytes than in controls. Only AS10 group recovered this number. Circulating and renal ACE2 activity were increased in DB and treatments with AS reduced these values to control level. IHC for ACE2 followed the same profile described for enzymatic activity. AT1R changed its expression in a dose-dependent fashion. AS10 group showed the same profile of expression as non-diabetic group.

Conclusions: In obese diabetic mouse, atrasentan treatment induced changes in body fluid composition when combined with insulin. Protective effects on kidney are observed at low doses of atrasentan by maintaining podocyte number in the glomeruli. Furthermore, atrasentan modulates ACE2 and AT1R, suggesting protective modifications in renin angiotensin system.

CONT	378.67 ± 3.60	34.30 ± 0.58	1.53 ± 0.01	0.54 ± 0.02	98.92 ± 0.52	118.48 ± 1.39	29.95 ± 0.96	513.57 ± 7.86	529.40 ± 20.75
DB	547.67 ± 34.29[#]	47.08 ± 2.69[#]	1.68 ± 0.10[#]	0.32 ± 0.05[#]	42.53 ± 7.6[#]	97.91 ± 2.80[#]	58.89 ± 0.86[#]	744.08 ± 13.41[#]	1126.60 ± 130.84[#]
DB+AS10	352.25 ± 22.23	47.33 ± 3.25	1.08 ± 0.05	0.52 ± 0.03	43.52 ± 0.43	90.33 ± 2.00	27.33 ± 1.00*	514.01 ± 5.34	816.91 ± 119.58
DB+AS25	579.92 ± 9.47	45.59 ± 2.70	1.13 ± 0.08	0.30 ± 0.07	42.89 ± 0.93	98.35 ± 2.35	29.23 ± 1.10	501.57 ± 5.80*	837.21 ± 65.84*
DB+AS50	452.80 ± 32.12*	36.93 ± 4.00	1.30 ± 0.13	0.40 ± 0.04	42.46 ± 0.85	104.26± 3.36	29.16 ± 1.09	594.80 ± 2.51*	837.19 ± 184.78*
DBins+AS10	266.58 ± 51.24*	53.11 ± 2.04*	0.84 ± 0.08	0.57 ± 0.02*	45.13 ± 0.81*	100.61 ± 2.11	32.60 ± 0.41	519.79 ± 11.55	1082.00 ± 133.27

Values are expressed as Mean ± SE. #p<0.05 vs CONT; *p<0.05 vs DB

FR-PO602

Renoprotective Effects of Aliskiren in a Non-Obese Type 2 Diabetic Model Rat

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Background: Previous experimental and clinical studies showed that various factors such as oxidative stress and renin-angiotensin system (RAS) were involved in pathogenesis of diabetic nephropathy (DN), and Aliskiren (ALS), which is a direct renin inhibitor, was useful for prevention of DN progression. However, there are no studies using non-obese type 2 diabetic animal models. The aim of our study was to elucidate the effects of ALS on DN in a non-obese type 2 diabetic rat model.

Methods: We used male Sprague-Dawley (SD) rats and Spontaneously Diabetic Torii (SDT) rats, which are known as non-obese type 2 diabetic animal models, in the present study. At 20 weeks of age, SD rats were assigned to the control group (SD group) and SDT rats were randomly divided into two groups: placebo-treated group (DM group) and ALS-treated group (ALS group). ALS was administered to the rats in the ALS group for 10 weeks. At 30 weeks of age, these rats were killed and then urinary and blood biochemical analyses and renal mRNA expression analysis were performed in all the groups.

Results: Despite similar blood pressure and renal function, urinary excretion of albumin was significantly lower in the ALS than in the DM group. Urinary excretion of angiotensinogen and 8-hydroxydeoxyguanosine (8-OHdG) were also significantly lower in the ALS compared to the DM group. Serum transforming growth factor-β (TGF-β) levels tended to be lower in the ALS than in the DM group. Renal mRNA expressions of angiotensin II type 1 receptor, nicotinamide adenine dinucleotide phosphate oxidase, and

TGF-β were significantly suppressed in the ALS compared to the DM group. Furthermore, renal nephrin mRNA expression was ameliorated by ALS treatment. Urinary excretion of albumin was positively and significantly correlated with urinary excretion of 8-OHdG as well as serum levels and renal mRNA expression of TGF-β.

Conclusions: The results of present study suggested that ALS provided renoprotective effects through RAS inhibition and reduction of oxidative stress and TGF-β even in a non-obese type 2 diabetic model rat.

FR-PO603

Protective Effect of an Oral Adsorbent AST-120 on Podocyte Injury Rieko Aoki, Ayako Fujieda, Atsuko Ezawa, Hiroko Iijima, Yusuke Yamashita, Kaori Kikuchi, Mariko Kato, Yoshiharu Itoh. *KUREHA CORPORATION, Tokyo, Japan.*

Background: Diabetic nephropathy is a major complication of diabetes and the leading cause of end-stage renal disease. An oral adsorbent AST-120 has been used clinically in Japan as a medicine for patients with chronic kidney disease (CKD) to slow down the progression of CKD. However, there is little evidence to support therapeutic efficacy of AST-120 for early stage overt diabetic nephropathy. Previously, we showed that the administration of AST-120 reduced the proteinuria and suppressed podocyte foot process effacement on SHR/NDmcr-cp (SHR/ND) rats, rodent model of metabolic syndrome/ type 2 diabetes. We also showed that AST-120 prevented the decrease of renal function and suppressed the levels of serum uremic toxins in unilateral nephrectomized (UNX) SHR/ND rats. In this study, we investigated whether the renal tissues of UNX SHR/ND rats were ameliorated by the administration of AST-120 and whether uremic toxins induced deleterious effects on the cultured podocyte cells *in vitro*.

Methods: Male SHR/ND rats, aged 8 weeks, underwent either UNX (n=20) or sham (n=6) surgery under anesthesia. Half of UNX rats were administered 8% AST-120 for 30 weeks in their diet, and serum and 24-hour urine samples were collected for biomedical studies. The gene expression of podocyte markers and fibrosis makers by real-time PCR in renal tissues from UNX-SHR/ND rats treated with or without AST-120. *In vitro* study, we evaluated effects of uremic toxins on the cytotoxicity and reactive oxygen species (ROS) production of mouse podocyte cells.

Results: AST-120-administered UNX-SHR/ND rats showed significantly lower levels of urinary protein excretion, serum creatinine, serum uremic toxins such as indole acetic acid (IAA) and kidney weight than UNX-SHR/ND rats. Nephrin, as a podocyte marker, in renal tissues was higher expressed in AST-120-administered UNX-SHR/ND rats than in UNX-SHR/ND rats. Plasminogen activator inhibitor-1 was lower expressed in AST-120-administered UNX SHR/ND rats. *In vitro* study, indoxy sulfate (IS) and IAA induced ROS production and the cytotoxicity of mouse podocyte cells, and N-acetyl-L-cysteine inhibited this effect.

Conclusions: These results indicate that the administration of AST-120 from the early stage of diabetic nephropathy has renoprotective effects. One of the mechanisms of the effect may be the reduction of uremic toxin by AST-120.

FR-PO604

P53 Mediates the Protective Effect of SRT2104 on Diabetic Kidney Disease Hao Wu, Junduo Wu, Shengzhu Zhou. *The Second Hospital of Jilin University, Changchun, China.*

Background: Silent mating type information regulation 2 homolog 1 (Sirt1) plays an important role in protection against diabetic kidney disease (DKD). Activation of Sirt1 by small molecules showed beneficial effects on experimental DKD. SRT2104 is a potent selective activator of Sirt1, and has been used in clinical trials, demonstrating both safety and tolerability. However, to date, the effect and mechanism of SRT2104 on DKD have remained unknown. P53 is an essential factor that induces the pathogenesis of DKD. Sirt1 deacetylates P53, leading to the inactivation of P53. Therefore, we hypothesize that SRT2104 inhibits P53 by activation of Sirt1, the effect of which ameliorates DKD.

Methods: Eight-week-old male C57BL/6 mice were induced to diabetes by streptozotocin, and were treated in the presence or absence of SRT2104, for a period of 24 weeks. To test whether or not P53 is required for SRT2104's action, mouse mesangial cells (MMCs) were treated with high glucose in combination with SRT2104, in the presence or absence of P53 siRNA.

Results: The diabetic mice exhibited remarkable renal inflammation, oxidative damage, fibrosis, pathological remodeling and albuminuria. These effects were significantly ameliorated by SRT2104. SRT2014 restored Sirt1 protein level and activity, and inactivated P53 in the kidneys of the diabetic mice. Interestingly, despite the activation of Sirt1, SRT2104 completely lost the protective effects in the presence of P53 siRNA in high glucose-treated MMCs.

Conclusions: The present study demonstrates, for the first time, that SRT2104 prevents DKD, the effect of which may be mediated by P53.

Funding: Government Support - Non-U.S.

FR-PO605

Pioglitazone Stabilizes Nephrin Expression via SUMOylation Irini Schaefer, Mario Schiffer, Hermann G. Haller. *Hannover Medical School, Nephrology, Hannover, Germany.*

Background: Pioglitazone belongs to a group of thiazoldinediones, antihypergycaemic drugs that increase peripheral insuline sensitivity. As peroxisome proliferator-activated receptor (PPAR) agonists they have been demonstrated to significantly decrease urinary albumin excretion in patients with type-2 diabetes. Furthermore, treatment with pioglitazone exerts anti-apoptotic effects on podocytes. However, the nephroprotective effects on a cellular and molecular level of these drugs remain elusive. We have investigated the effects of pioglitazone-treatment on nephrin expression "in vitro".

Methods: Differentiated podocytes were treated with 20 μm pioglitazone over 72 hours and western blot was performed. Subcellular fractionation shows expression of nephrin in the compartments. To show if pioglitazone also stabilize nephrin in "aged" podocytes we differentiated them over 8 weeks. Immunoprecipitation were performed for analyzing SUMOylation of neprin after treatment with pioglitazone.

Results: We found that nephrin expression was strongly enhanced in human and murine podocytes after pioglitazone exposure. Subcellular fractionation shows that the enhanced neprin expression was restricted to the plasma membrane. When we "aged" podocytes in vitro by keeping them under differentiating conditions for more than 8 weeks we detected a significant decrease of nephrin expression under normal culture conditions. However, nephrin expression remained stable over 8 weeks in the presence of pioglitazone. Interestingly, we found that SUMOylation of nephrin was significantly enhanced in the presence of pioglitazone.

Conclusions: Our data strongly suggest that membrane expression of nephrin in podocytes is modulated by pioglitazone treatment. The strong expression of nephrin in cultivated podocytes after treatment with pioglitazone indicates a direct molecular mechanism which is most likely responsible for the renoprotective and anti-proteinuric effects of pioglitazone treatments in vivo.

Funding: Government Support - Non-U.S.

FR-PO606

The Classic and Trans-Signaling of Interleukin-6 Are Both Injurious in Podocyte under High Glucose Exposure Chun-Tao Lei,[1] Hua Su,[1] Chun Zhang.[2] *[1]Huazhong Science and Technology University, Wuhan, China; [2]Union Hospital, Huazhong University of Science and Technology, Wuhan Hubei Provicne, China.*

Background: Interleukin-6 (IL-6) is a multifunctional cytokine that employs IL-6 classic and trans-signaling pathways, and these two signal channels execute different or even opposite effects in certain diseases. As a cardinal event of diabetic kidney disease (DKD), whether the podocyte abnormalities are associated with IL-6 signaling, especially the individual role of IL-6 classic or trans-signaling, remains unclear.

Methods: The circulatory IL-6, soluble IL-6R (sIL-6R) and soluble glycoprotein 130 (sgp130) levels in subjects with or without DKD were measured. Human podocyte cell line was employed in vitro study. RNA interfere targeting gp130 and gp130 or IL-6 neutralizing antibodies were utilized to block the entire IL-6 signaling. RNA interfere targeting IL-6R and recombinant sgp130 were used to inhibit IL-6 classic and trans-signaling respectively.

Results: Our findings elucidated that the circulatory IL-6, sIL-6R and sgp130 levels are elevated in patients with DKD. The expressions of membrane bound IL-6R (mIL-6R), sIL-6R, and gp130 are enhanced in kidney cortex of diabetic mice accompanying with activated STAT3 by tyrosine 705 residue phosphorylation, while not serine 727. Above data infer both classic and trans-signaling of IL-6 are activated during DKD. In cultured podocyte, high glucose (HG) upregulates the expression of mIL-6R and gp130, as well as STAT3 tyrosine 705 phosphorylation, in a time-dependent manner. Entirely blocking IL-6 signaling attenuates HG-induced podocyte injury. Interestingly, either inhibiting IL-6 classic signaling or suppressing its trans-signaling individually also dramatically alleviates HG-induced podocyte injury, suggesting both IL-6 classic and trans-signaling play a detrimental role in HG-induced podocyte injury. Consistently, activation of IL-6 classic or trans-signaling aggravates podocyte damage in vitro.

Conclusions: In summary, our observations demonstrate that either IL-6 classic or trans-signaling aggravates hyperglycemia mediated podocyte impairment. Accordingly, suppressing IL-6 classic and trans-signaling, especially simultaneously, is a promising therapeutic strategy for podocyte injury during DKD.

Funding: Government Support - Non-U.S.

FR-PO607

Attenuating Lymphatic Proliferation by Fenofibrate Ameliorates Diabetic Nephropathy and High-Fat Diet-Induced Renal Lipotoxicity Yaeni Kim,[1] Ji Hee Lim,[1] Min Young Kim,[1] Bumsoon Choi,[1] Yong-Soo Kim,[1] Seon Deok Hwang,[2] Cheol Whee Park.[1] *[1]The Catholic University of Korea College of Medicine, Seoul, Republic of Korea; [2]Inha University College of Medicine, Incheon, Republic of Korea.*

Background: In diabetic nephropathy, the proliferation of lymphatic vessels correlates with the extent of intrarenal inflammatory cell infiltration and tubulointerstitial fibrosis. Peroxisome proliferative-activated receptor (PPAR)α plays an important role against lipotoxicity under the control of AMP-activated protein kinase (AMPK).

Methods: We evaluated whether fenofibrate, a PPARα agonist, has a renoprotective effect by ameliorating lipotoxicityassociated with lymphangiogenesis.

Results: In male C57BLKS/J *db/db* mice, fenofibrate ameliorated albuminuria and mesangialand tubular fibrosis and inflammation. Fenofibrate inhibited the accumulation of intra-renal free fatty acid and triglycerides, which was associated with increase in the expression of PPARα, phosphorylation of AMPK, activation of PPARγ co-activator 1α-phosphorylated acetyl-CoA carboxylase, and suppression of sterol regulatory element-binding protein 1 (SREBP-1) and carbohydrate regulatory element-binding protein 1 (ChREBP). Fenofibrate significantly decreased lymphatic growth, as represented by decreases in the expression of lymphatic endothelial hyaluronan receptor-1 (LYVE-1) and podoplanin, along with decreases in vascular endothelial growth factor-C (VEGF-C)

and vascular endothelial growth factor receptor-3 (VEGFR-3). Consequently, fenofibrate reversed renal apoptosis and oxidative stress. In high-fat diet-fed spontaneously hypertensive rats (SHRs), fenofibrate also attenuated renal lymphatic proliferation and lipotoxicity-induced oxidative stress and apoptosis. In cultured HK2 cells, fenofibrate prevented palmitate- and high glucose-induced expression of VEGF-C, VEGFR-3, and LYVE-1 via activation of PPARα-AMPK-pACC signaling and suppression of SREBP-1 and ChREBP.

Conclusions: These results suggested that fenofibrate prevents diabetic nephropathy in *db/db* mice and high-fat diet-induced renal injury in SHRs by attenuating lymphatic proliferation, inflammation, andoxidative stress through activation of PPARα-AMPK pathway, especially in renal proximal tubule cells.

FR-PO608

Inhibition of High Glucose Induced Senescence of Human Glomerular Mesangial Cells by Metformin Up-Regulating Autophagy Level Xiuying Wang,[2] Lining Wang,[1] Shuang Yang,[2] Dan Sun.[2] *[1]Department of Nephrology, First Affiliated Hospital of China Medical University, Shenyang, P. R. China, Shenyang, China; [2]The First Hospital of China Medical University, Shenyang, China.*

Background: Autophagy has been found to be closely related to aging and human disease. However, the role of autophagy in the process of human mesangial cell senescence and its mechanism is unclear. In recent years the study found that metformin can activate the AMPK signaling pathway, inhibition of mTOR pathway and affect autophagy. Here we try to investigate the effects of metformin on autophagy and human glomerular mesangial cells senescence induced by high glucose.

Methods: Human glomerular mesangial cells (HGMCs) were cultured in vitro, and exposed to high glucose (30.0 mmol / L glucose) for 12,24,48 and 72 h and stimulated by high glucose with 10mmol/L metformin for 72 h. Normal control group(5.5mmol/L glucose)and hypertonic group(5.5 mmol/L glucose+24.5 mmol/L mannitol) were set up. The best stimulating concentration of metformin was filtered by Cell Counting Kit(CCK-8/WST-8). The cell senescence was evaluated byβ-galactosidase(SA-β-gal) staining. The activation of AMPK/mTOR pathway, aging related proteins p53,p21 and autophagy marker proteins LC3,p62 / SQSTMI were determined by Western blotting. Autophagic flux was detected by (mRFP-GFP-LC3)adenovirus observed using confocal microscopy.

Results: Compared with the normal control group, the cells exposed to high glucose for 12,24 and 48h showed up-regulated p53 and mTOR expression(P<0.05),the cells exposed to high glucose for 24 and 48h showed up-regulated p21 and p-mTOR expression(P<0.05),the cells exposed to high glucose for 24,48 and 72h showed down-regulated p-AMPK expression(P<0.05), up-regulated p62/SQSTM1 expression and increased percentage of SA-β-gal positive cells(P<0.05). The cells exposed to high glucose for 72h showed down-regulated LC3 expression and decreased autophagic flux level(P<0.05). Compared with those in high glucose group, The autophagic flux level and the expression of p-AMPK, LC3were increased dramatically in high glucose with metformin group (P<0. 05),while the protein expressions of p62,p53, p21, mTOR and p-mTOR decreased (P<0. 05),and SA -β-gal positive cells decreased(P<0. 05).

Conclusions: The senescence of human glomerular mesangial cells is associated with defective autophagy level under high glucose condition. Metformin could postpone high glucose - induced senescence of human glomerular mesangial cells by increasing aotophagy level via modulating AMPK/mTOR pathway.

Funding: Government Support - Non-U.S.

FR-PO609

miRNA-27b and miRNA-1228 Urinary Levels Discriminate Specific Classes of Histological Damage in Diabetic Patients Paola Pontrelli,[5] Francesca Conserva,[2] Mariagrazia Barozzino,[2] Francesco Pesce,[2] Rossella Menghini,[6] Annarita Oranger,[7] Antonella Di Franco,[2] Massimo Papale,[2] Francesco Giorgino,[2] Luigi Laviola,[3] Simona Simone,[1] M. Rossini,[4] Massimo Federici,[6] Loreto Gesualdo.[2] *[1]None, BARI, Italy; [2]University of Bari, Bari, Italy; [3]University of Bari Aldo Moro, Bari, Italy; [4]University of Bari, Department of Emergency and Organ Transplantation, Nephrology Unit, Bari, Italy; [5]University of Bari-Dept. of Emergency and Organ Transplantation, Bari, Italy; [6]University of Rome Tor Vergata, Rome, Italy; [7]University of Bari, Bari, Italy.*

Background: Diabetic nephropathy (DN) is the leading cause of end stage renal disease. Aim of our study was to identify novel urinary biomarkers which correlate with the histological damage. We focused on those miRNAs that modulate lysin63 ubiquitination, responsible of tubular damage in diabetic patients (PMID: 27881486).

Methods: Urinary samples were collected from 16 patients with type-2 diabetes (T2D) and DN, 7 with T2D and other nephrities (T2D-GN), including membranous nephropathy (MN) and Focal and Segmental Glomerulosclerosis (FSGS), 32 with other nephrities without T2D (GN), all with a biopsy proven diagnosis, 7 with T2D and normal renal function, 9 healthy subjects (HS). miRNAs expression was evaluated by qPCR in urines and in situ hybridization on tissues. Data were validated in a mouse model of DN (DBA2J mice treated with streptozotocin-STZ).

Results: miRNA-27b was down-regulated in urines of DN patients when compared to HS (p=0.03), to T2D (p=0.04) to T2D-GN (p=0.04), and to GN (p=0.05), such as miRNA-1228 (p=0.01 vs HS, p=0.01 vs T2D, p=0.04 vs T2D-GN, p=0.05 vs GN). Tissue expression of both miRNAs was also reduced at tubular level in DN vs T2D-GN (p<0.05) and was directly correlated with tubular-interstitial fibrosis (p<0.05). ROC curve from a predictive model (based on logistic regression) combining both miRNAs relative expression, was able to predict DN in the comparison with HS (AUC=0.93; p=5.9E-19), with T2D-GN (AUC=0.81; p=0.001), with T2D (AUC 0.90; p=2.7E-10) and with GN (AUC=0.69; p=0.002). miRNA-27b (conserved among species) was also down-regulated in urines of DBA2J/STZ mice vs DBA2J untreated controls (FC: -3.79; p<0.05) and was correlated with lysin63 protein accumulation and tubular-interstitial fibrosis (p<0.05).

Conclusions: miRNA-27b and -1228 expression correlate with increased fibrosis and discriminate DN patients vs other histological lesion in diabetic and non- diabetic patients.

Funding: Government Support - Non-U.S.

FR-PO610

MicroRNA-148b Influences High Glucose-Induced Endoplasmic Reticulum Stress in Rat Mesangial Cells by Targeting AMPKα1 Qiuling Fan. *Department of Nephrology, The First Hospital, China Medical University, Shenyang, China.*

Background: To verify the expression of microRNA-148b (miRNA-148b) induced by high glucose in rat mesangial cells, and to explore its effect on its target gene AMP-activated protein kinaseα1 (AMPKα1) and extracellular matrix excretion.

Methods: Rat mesangial cells were divided into 3 groups: normal glucose (NG, 5.5 mmol/L glucose) group, hypertonic (MA, 5.5 mmol/L glucose+ 19.5 mmol/L mannitol) group and high glucose (HG, 25.0 mmol/L glucose) group. miR-148b expression was detected by real time PCR. Then miR-148b inhibitor was transfected to rat mesangial cells. Their expressions of AMPKα1, glucose regulated protein78 (GRP78), C/EBP homologous protein (CHOP), fibronectin (FN)and collagen 4 proteins were detected by Western blotting; the expression of AMPKα1 mRNA was detected by real time PCR; the expression of COl 4 was also detected by immunofluorescence.

Results: Compared with NG group, HG group showed upregulated miR-148b expression, downregulated AMPKα1 mRNA and protein expression, and upregulated CHOP, GRP78, collagen 44 and FN expression (all P<0.05). HG-induced mesangial cells with miR-148b inhibitor had up-regulated AMPKα1 mRNA and protein expression, and downregulated CHOP, GRP78, collagen 4, FN expression as compared with HG-induced cells without miR-148b inhibitor (all P<0.05).

Conclusions: HG can upregulate miR-148b expression and downregulate AMPKα1 expression in rat mesangial cells, then activate endoplasmic reticulum stress to induce extracellular matrix excretion. miR-148b inhibitor upregulates AMPKα1 expression, inhibits endoplasmic reticulum stress and reduces extracellular matrix excretion.

FR-PO611

Transcriptional Regulation of Long Non-Coding RNA Tug1 in Diabetic Nephropathy Jianyin Long, Farhad R. Danesh. *The University of Texas MD Anderson Cancer Center, Houston, TX.*

Background: Long non-coding RNAs (lncRNAs) have been implicated in the pathogenesis of a myriad of diseases, including cancer, heart diseases and kidney diseases. We recently reported that lncRNA Tug1 (Taurine-upregulated gene-1) is a differentially repressed lncRNA in a mouse model of diabetic nephropathy (DN), and podocyte-specific Tug1 overexpression exerts a renoprotective phenotype. However, how the expression of Tug1 is regulated in the diabetic milieu is unknown.

Methods: Transcription factor binding prediction algorithms (rVista 2.0 and PROMO) were used to analyze Tug1 proximal promoter region. Standard PCR, site-directed mutagenesis techniques were used to generate mouse Tug1 promoter constructs. ChIP-qPCR, eletromobility shift assays (EMSA) and luciferase reporter assays were used to identify the elements responsible for glucose and/or TGF-β1-mediated transcriptional repression of Tug1.

Results: We have generated a series of Tug1 promoter reporter constructs which were used to study the transcriptional regulation of Tug1 by high glucose and TGF-β1 signaling. Bioinformatics analysis revealed several glucose responsive elements in the highly evolutionarily conserved 1kb Tug1 promoter fragment immediately upstream of the Tug1 TSS (transcription start site). Specifically, a consensus ChoRE (carbohydrate response element) motif (CAYGYGnnnnnCRCRTG), was identified in the proximal promoter region (CACGTGACCGGATCTTG, -324 to -307) of Tug1. This motif was reported as a specific peak in our recent publication about genome-wide ChIP-Seq of the glucose-responsive transcription factor ChREBP (carbohydrate response element–binding protein, also known as MLXIPL, MLX Interacting Protein Like) in mouse liver and fat. Binding of ChREBP to this motif in podocytes was further validated by ChIP-qPCR and EMSA. We are currently identifying the cofactors/corepressors for this ChREBP-mediated repression of Tug1 in podocytes.

Conclusions: We identified glucose-responsive transcription factor ChREBP binding to the evolutional conserved ChoRE in the proximal promoter, as the mechanism of Tug1 down-regulaton in diabetic milieu.

Funding: NIDDK Support

FR-PO612

Aerobic Exercise Training Reduces Renal Inflammatory Factors, Fibrosis, and Proteinuria in Diabetic Rats Rodolfo R. Rampaso,[2] Rafael Luiz,[2] Natalia Reinecke,[2] Edson A. Pessoa,[2] Kleiton A. Silva,[3] Luciana Jorge,[1] Maria A. Gloria,[2] Nestor Schor.[2] *[1]None, São Paulo, Brazil; [2]Universidade Federal de Sao Paulo/Escola Paulista de Medicina, Sao Paulo, Brazil; [3]University of Missouri, Columbia, AL.*

Background: The aim of this study was to evaluate the role of aerobic exercise in controlling the progression of diabetic nephropathy as proteinuria, fibrosis, inflammatory factors, and thus, its possible renoprotective effects

Methods: Adult male Wistar rats divided into 4 groups: Sedentary controls, (SED, n=8), Diabetes+Sedentary (DM-SED, n=8), Diabetes+Exercise (DM-EXE, n=8) and Exercise+Controls (EXE, n=8). DM was induced with streptozotocin (STZ), 50mg/kg i.v. The physical training was done on treadmill 60 min/day, 5 days a week for 8 weeks. Weekly it was determined the Maximal Exercise Test (set at 65-70% of MEtest). Fibrosis (m2), Glycemia 24h post training (glycemiapt), MEtest, creatinine clearance/BW (CrCl/BW), mean arterial pressure (MAP), proteinuria (uProt), renal inflammatory factors (IL-6, IL-10 and TNF-alpha) were measured

Results:

Conclusions: Reductions in glycemia, fibrosis and MAP comparing DM-EXE vs DM-SED. The DM-EXE controlled weight loss compared to DM-SED, but did not prevent alteration in the CrCl/BW. However, the effect of the EXE was strikingly observed in the reduction in both, mean uProt excretion (60% and 25%) and in inflammatory factors comparing DM-SED vs. DM-EXE. Therefore, preliminary data suggest that aerobic exercise can reduce proteinuria, renal fibrosis and inflammatory factors in diabetic animals and consequently diminish potential effects caused by diabetic and potentially could reduce the progression to renal failure

	SED	DM-SED	DM-EXE	EXE
uProt (mg/24h)	17 ± 0.88	46 ± 2.05 *#&	18 ± 0.72	16 ± 0.99
IL-6 (pg/ml)	541 ± 98	993 ± 40*#&	768 ± 74*&	391 ± 22
IL-10 (pg/ml)	545 ± 86	876 ± 34*#&	654 ± 31*&	453 ± 28
TNF-alpha (pg/ml)	3.05 ± 0.4	5.18 ± 0.76*#&	4.08 ± 0.22*&	2.32 ± 0.51
Fibrosis (m2)	5.87±0.92	11.42±1.84*#&	8.37±2.13*	7.47±1.27
CrCL/ (ml/min/BW)	5.65 ± 0.66	5.02 ± 0.43	4.19 ± 0.37	4.21 ± 0.29
glycemiapt (mg/dl)	103 ± 2.03	551 ± 7.03*&	491 ± 5.50*&	83 ± 2.57
MAP (mmHg)	122 ± 1.89	133.88 ± 1.79*#&	122 ± 1.35	121 ± 2.11
Weight (g)	455 ± 6.00	236 ± 14.41*#&	324 ± 9.34*&	387 ± 8.71
MEtest (m/min)	23.2 ± 0.49#&	19.5 ± 0.57*#&	35.1 ± 0.97	37.5 ± 0.57

FR-PO613

Quercetin Ameliorates Podocyte Injury by Inhibiting the ERK Signaling Pathway in Rats with Diabetic Nephropathy Fanfan Gao, Hongli Jiang. *Dialysis Centure of First Affiliated Hospital of Medicine School, Xi'an Jiaotong University, Xi'an, China.*

Background: An increasing number of investigations revealed that podocytes play a crucial role in the development and progression of diabetic nephropathy (DN). Quercetin, an antioxidant, may be a potential alternative to ameliorate podocyte injury in DN rats. The aim of this study was to investigate the protective effect and underlying mechanism of quercetin on podocyte injury in rats with diabetic nephropathy.

Methods: SD rats (180-200g) were randomly divided into four groups: normal control (NC, n=10), diabetic nephropathy (DN, n=10), DN treated with low-dose quercetin (DN+LQ, n=10) and DN treated with high-dose quercetin (DN+HQ, n=10). Diabetic nephropathy was induced by intraperitoneal injections of streptozotocin(STZ) (60mg/kg). DN+LQ rats were treated with 50mg/kg/d quercetin by gavage, DN+HQ rats were treated with 100mg/kg/d quercetin by gavage, NC and DN rats were treated with 100mg/kg/d DMSO by gavage. Blood glucose and body weight were obtained every two weeks, microalbuminuria and urine creatinine were obtained every four weeks. All animals were sacrificed after 12 weeks of treatments.

Results: In the present study, the levels of blood glucose, kidney hypertrophy index, microalbuminuria, SCr, BUN, TG were markedly increased in rats with STZ injection compared with NC rats, expectedly, these alterations were less intense in animals treated with quercetin. The picture of electron microscope showed foot process fusion in DN rats, while quercetin markedly inhibited foot process infusion. Immunohistochemical and western blotting results showed that the expression of nephrin and podocin in DN rats was significantly decreased, the expression of desmin, ERK, p-ERK in DN rats was significantly increased, whereas quercetin reversed these above changes. Additionally, the contents of nephrin and podocin in urine of DN rats were markedly higher than that of NC rats, while the contents of GSH and SOD in serum and kidney tissue of DN rats were significantly lower than that of NC rats. However, quercetin decreased the contents of nephrin and podocin in urine and increased the contents of SOD and GSH in blood and kidney tissue.

Conclusions: Quercetin treatment effectively ameliorated podocyte injury in rats with DN by inhibiting ERK signaling pathway. The manipulation of quercetin might act as a promising therapeutic intervention for diabetic nephropathy.

FR-PO614

TGF-Beta 1 Signaling May Be Mediated by Lysyl Oxidase-Like 2 in Human Podocytes in Diabetic Condition Beom Jin Lim,[2] Nara Jeon,[3] Hoon Young Choi.[1] *[1]Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Yonsei University College of Medicine, Seoul, Republic of Korea; [3]Yonsei University College of Medicine, Seoul, Republic of Korea.*

Background: Lysyl oxidase-like 2 (LOXL2) is a molecule known to be related with invasive growth and metastasis of malignant neoplasm. Recently, LOXL2 has been also reported to play an important role in target organ fibrosis including heart, liver and lung. In this study, we investigated the expression of LOXL2 in human kidney and podocyte, and its contribution to the transforming growth factor beta 1 (TGF-beta1) and collagen expression in podocyte with high-glucose condition.

Methods: We evaluated the expression of LOXL2 in human kidney using immunofluorescence staining. Real-time PCR and western blotting analysis for LOXL2 mRNA and protein expression were performed using cultured human immortalized podocytes. After fully differentiated, cultured human podocytes were exposed to high glucose (HG) for 48 hours. Lenti-virus mediated gene silencing of LOXL2 was done in human podocyte.

Results: By immunofluorescence staining, LOXL2 expression was identified in human glomerulus and was significantly increased in that with diabetic kidney disease compared with normal control. LOXL2 mRNA (2.40±0.15 vs. 1.17±0.11, P<0.05) and protein expression were significantly higher in human podocyte with HG condition than those with normal glucose condition. TGF-beta 1 mRNA expression was also increased in podocyte with HG condition (9.79±0.63 vs. 1.70±0.36, P<0.05). Gene silencing of LOXL2 significantly reduced TGF-beta mRNA and protein expression in human podocytes. Western blot analysis showed that collagen I and phosphorylated Smad2 protein expression were significantly decreased in LOXL2 knock-down podocytes.

Conclusions: Our results showed that TGF-beta 1 signaling may mediated by LOXL2 in podocytes in diabetic condition.

FR-PO615

TGFbeta (TGFb)-Stimulated PI 3 Kinase (PI 3 K)/Akt Downregulates DEPTOR to Increase Podocyte Hypertrophy and Matrix Protein Expression Falguni Das,[1] Nandini Ghosh-choudhury,[1] Balakuntalam S. Kasinath,[2] Goutam Ghosh-Choudhury.[2] *[1]UTHSCSA, SAN ANTONIO, TX; [2]University of Texas Health Science Center, San Antonio, TX.*

Background: TGFb contributes to kidney injury in diabetic nephropathy (DN). mTOR controls renal cell hypertrophy and matrix protein expression. We have recently shown that TGFb regulates the expression of deptor, a negative regulatory component of both mTORC1 and mTORC2. We hypothesized that PI 3 K/Akt signaling may contribute to deptor regulation.

Methods: Recombinant TGFb (2 ng/ml), rat podocytes, pharmacological inhibitors, dominant negative (dn) expression vectors and siRNAs transfection, immunoblotting, immunoprecipitation, protein synthesis and hypertrophy assays, glomeruli from rats with streptozotocin (STZ)-induced DN were employed.

Results: TGFb decreased the expression of deptor in a time-dependent manner, leading to increase in the mTORC1 and mTORC2 activity, as judged by the increase in phosphorylation of their substrates S6 kinase/4EBP-1 (mTORC1) and Akt (Ser-473)/NDRG1 (mTORC2). To explore the mechanism of deptor suppression, we used the PI 3 kinase and Akt inhibitors, Ly 294002 and MK 2206, and PTEN or dominant negative (dn) PI 3 K or dn Akt kinase, which reversed the TGFb-induced deptor downregulation, resulting in inhibition of mTORC1 and mTORC2 activation. TGFb inhibited the deptor-mTOR complex formation in co-immunoprecipitation experiments. Expression of PTEN or dn Akt kinase restored the complex formation in the presence of TGFb. Furthermore, dn PI 3 K or dn Akt kinase significantly inhibited the TGFb-induced hypertrophy. Interestingly, siRNAs against deptor alone induced hypertrophy of podocytes similar to TGFb; additionally they reversed the inhibition of hypertrophy induced by dn PI 3 K or Akt kinase. Moreover, expression of dn PI 3 K or dn Akt kinase significantly inhibited the TGFb-stimulated expression of fibronectin, which was reversed by siDeptor. Finally, we found significantly reduced expression of deptor, concomitant with increased activation of mTORC1 and mTORC2 in the glomeruli of STZ-induced diabetic rats.

Conclusions: Our data for the first time demonstrate the involvement of PI 3 K/Akt signaling in the suppression of deptor by TGFb to maintain high mTOR activity necessary for renal cell hypertrophy and matrix protein expression.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO616

The Impact of Glucagon-Like-Peptide-1on JAK-STAT Pathway in Diabetic Kidney Disease in db/db Mice and in Endothelial Cells Exposed to a Diabetic Environment Yael Einbinder,[2] Sydney Benchetrit.[1] *[1]Meir Medical Center, Kfar Saba, Israel; [2]Meir Medical Center, Kfar Saba, Kfar Saba, Israel.*

Background: The Janus kinase/signal transducer and transcription activator (JAK/STAT) proteins mediate the actions of many cytokines, chemokines, hormones, and growth factors critical to cell proliferation, differentiation, migration, and apoptosis. This study used db/db mice and endothelial cells (EC) to determine the effect of a diabetic

environment on the JAK-STAT pathway, and to assess the potential effect of GLP-1 analogue in both models.

Methods: C57BL/6 (WT) and BKS.Cg-*Dock7*^{m} +/+ *Lepr*$^{db/db}$ (db/db) mice were randomized to WT group, db/db mice (diabetic control group) and db/db mice treated with GLP-1 analog (Liraglutide) for 14 weeks. The kidneys were then perfused and removed for mRNA, protein analysis and Immunohistochemistry. EC obtained from Human umbilical vein were stimulated with AGE-HSA, glucose and GLP-1 for 24 hours.

Results: p-STAT3 (Ser 727) and p-STAT3 (Tyr 705) were significantly up-regulated in control db/db mice compared to WT mice. GLP-1 analog significantly down-regulated p-STAT3 (Ser 727, Tyr 705) protein expression compared to control db/db mice. P-STAT3 was mainly expressed in the glomeruli, while p-JAK2 was expressed in the tubules also. In EC stimulated with diabetic environment p-STAT3 (Tyr 705) and JAK2 were up regulated while GLP-1 analog significantly down-regulated there expression. The GLP-1 analog inhibited the target gene SIRT1 in db/db mice and in EC culture.

Conclusions: JAK-STAT pathway is activated in experimental models of diabetes mellitus. The GLP-1 analogue (liraglutide) inhibited STAT3 and JAK2 expression in db/db mice and in EC culture possibly through inhibition of SIRT1.

FR-PO617

Uromodulin Proteolytic Processing Is Altered in Youth with Type 1 Diabetes Julie Anh Dung Van,[4] Anne-Christin Hauschild,[3] Ihor Batruch,[1] Eleftherios P. Diamandis,[2] James W. Scholey,[4] Ana Konvalinka.[4] *[1]Mount Sinai Hospital, Toronto, ON, Canada; [2]Mount Sinai Hospital and University Health Network, Toronto, AB, Canada; [3]Princes Margaret Cancer Center, Toronto, Ontario, ON, Canada; [4]University of Toronto, Toronto, ON, Canada.*

Background: Dysregulated proteolytic activity in the kidney may induce early functional and structural changes in type 1 diabetes, and this activity may be specific to some proteases and their protein substrates. Thus, peptides generated within kidney may be excreted into the urine and provide a footprint of intrarenal proteolysis. We aim to compare urinary peptidomes of youth with type 1 diabetes in relation to healthy peers and to infer protease activity in the kidney from differentially excreted peptides.

Methods: We obtained second-morning, midstream urines from 15 cases with type 1 diabetes and 15 age- and sex-matched healthy controls. Urine volumes normalized to creatinine were subjected to 10kDa ultrafiltration to isolate naturally occurring peptides. Peptides were then fractionated and analyzed on Q-Exactive mass spectrometer. MaxQuant software was used for peptide identification and label-free quantification. Proteasix, an online tool, was used to predict proteases responsible for generating differentially excreted peptides.

Results: A total of 6323 naturally occurring peptides were quantified. Of these, 163 peptides were consistently detected across all thirty urine samples. Five peptides from this subset were differentially excreted between the groups (FDR, $q < 0.05$), and they derived from regions near the C-terminus of uromodulin and clusterin. Peptide intensities strongly correlated with glycated hemoglobin and blood glucose, and only weakly so with albumin/creatinine ratio. Interestingly, urinary excretion of the uromodulin protein was not different between groups, suggesting an increase in proteolysis of uromodulin in the kidney. The top predicted proteases included hepsin, neutrophil elastase, and plasmin.

Conclusions: Our analysis of the urinary peptidome revealed early differences in the excretion rates of uromodulin peptides in adolescents with diabetes in the absence of microvascular complications, compared to healthy age-matched subjects. We conclude that sustained hyperglycemia is associated with early activation of proteolytic enzymes in the kidney before the onset of microalbuminuria.

FR-PO618

Puerarin Attenuates Diabetic Kidney Injury through Suppression of NOX4 Expression in Podocytes Yifei Zhong,[1] Ruijie Liu,[2] Kyung Lee,[2] John C. He.[2] *[1]Longhua Hospital, Shanghai University of Traditional Chinese Medicine, China, Shanghai, China; [2]Mount Sinai School of Medicine, New York, NY.*

Background: *Radix puerariae*, a traditional Chinese herbal medication, has been used to treat patients with diabetic nephropathy (DN). Several studies demonstrated that puerarin, the active compound of *radix puerariae*, improves DN in streptozotocin (STZ)-induced rat and mouse models. However, as STZ injection alone results in mild kidney injury, the mechanisms of renoprotection afforded by puerarin remained inconclusive. Therefore in this study, we sought to clarify the role of puerarin by employing a STZ-induced diabetes in the mice lacking the endothelial nitric oxide synthase, which develop more advanced DN, and explored the mechanism of puerarin in cultured podocytes.

Methods: Diabetes was induced in the male eNOS homozygous knockout mice of 8 weeks old on a C57BL/6 background by injecting streptozotocin for 5 consecutive days. 2 weeks after diabetes was confirmed in mice, mice were given puerarin (Sigma-Aldrich) by oral gavage at a dose of 20mg/kg body weight/day, or vehicle as control, for 8 weeks. Urine albuminuria, kidney histology, IHC, and qPCR of isolated glomeruli were analyzed as desscribed. Conditionally immortalized murine podocytes were obtained from Dr. Peter Mundel. Podocytes were transfected using Viafect reagent and ROS and NAPDH oxidase activity were measured accordingly.

Results: Puerarin treatment of diabetic eNOS$^{-/-}$ mice significantly improved albuminuria and diabetic kidney injury. Puerarin also significantly reduced oxidative stress and inhibited the expression of NAPDH oxidase 4 (NOX4) in glomeruli of diabetic mice. In cultured conditionally immortalized murine podocytes, puerarin reduced superoxide production, as well as NOX4 expression at both mRNA and protein levels. Interestingly, we found that puerarin increased both mRNA and protein levels of Sirt1 in podocytes. Indeed, puerarin suppressed NOX4 expression through Sirt1-mediated deacetylation of NF-κB.

Conclusions: Our findings confirm the renal protective effects of puerarin in an animal model with more advanced DN and demonstrate a new mechanism that underlies the anti-oxidative effects of puerarin in kidney podocytes.

Funding: Government Support - Non-U.S.

FR-PO619

Deficient of Endothelial Function Exacerbates NLRP3-Inflammasome Activation in Podocyte of Diabetic Nephropathy Hajime Nagasu,[2] Yuji Sogawa,[1] Kengo Kidokoro,[2] Minoru Satoh,[2] Tamaki Sasaki,[2] Naoki Kashihara.[2] *[1]Kawasaki Medical School, Kurashiki, Japan; [2]Nephrology and Hypertension, Kawasaki Medical School, Kurashiki, Japan.*

Background: Previous studies have indicated that 30–40% of patients with type 1 DM develop overt nephropathy, but the detailed mechanism is not clear. Reactive oxygen species (ROS) are excessively produced in DM, and ROS production exacerbates nephropathy. We reported that the uncoupling of endothelial nitric oxide (NO) synthase (eNOS) is the source of glomerular ROS production. While NLRP3 inflammasome activation in podocytes plays an important role in the progression of DKD, whereas NO regulates inflammasome activation. However, it is unclear how the NLRP3 inflammasome is regulated in the kidney. In this study, we determined if eNOS/NO signaling suppresses inflammasome activation in DKD.

Methods: We used wild-type (WT) and eNOS-deficient mice (eNOSKO) to determine the role of the eNOS-NO pathway. Diabetes was induced by a single intraperitoneal injection of streptozocin (STZ; 65 mg/kg body weight). Subsequently, we divided mice into four groups: WT, WT-STZ, eNOSKO, and eNOS-STZ. Four weeks after the induction of DM, the mice were sacrificed, and their kidney tissues were harvested. Urinary albumin excretion was checked before the sacrifice, and glomerular damage was assessed by PAS staining. Next, the localization of inflammasome activation in glomeruli was evaluated with immunohistochemical analyses. To investigate inflammasome activation in glomeruli, glomeruli were isolated from the kidney tissue by using Dynabeads. The mRNA expression of inflammasome components NLRP3, IL-1β, and IL-18 were checked with real-time quantitative PCR.

Results: Urinary albumin excretion was increased in WT-STZ compared with WT. These urinary albumin excretions were increased much more in eNOS-STZ than in WT-STZ. The glomeruli were more damaged in eNOS-STZ compared with WT-STZ. In immunohistochemical analyses, the expression of ASC coexisted with podocytes detected by podocalyxin staining in eNOS-STZ. These data suggested that the NLRP3 inflammasome activation was located in podocytes. In isolated glomeruli, the mRNA of the inflammasome components were higher in eNOS-STZ than in WT-STZ.

Conclusions: eNOS/NO signaling attenuates glomerular injury in diabetic mice via suppression of inflammasome activation.

Funding: Private Foundation Support

FR-PO620

An N-Terminal Truncated Intracellular Isoform of Matrix Metalloproteinase-2 Is Induced by Hyperglycemia and Activates a Primary Innate Immune Response In Vitro Sang Heon Song,[2] In seong Park,[2] Miyeun Han,[2] Harin Rhee,[2] Eun Young Seong,[2] Dong Won Lee,[3] Soo Bong Lee,[3] Ihm Soo Kwak,[2] David H. Lovett.[1] *[1]Internal Medicine, University of California San Francisco, San Francisco, CA; [2]Internal Medicine, Pusan National University Hospital, Busan, Republic of Korea; [3]Pusan National University School of Medicine, Yangsan, Republic of Korea.*

Background: We have reported that matrix metalloproteinase-2 (MMP-2) exists in two discrete isoforms. The first consists of the classical full length isoform (FL-MMP-2) which is secreted as a latent proenzyme. A second novel isoform is generated by oxidative stress-mediated activation of an alternate promoter in the distal first intron of the MMP-2 gene. This results in synthesis of an N-terminal truncated isoform (NTT-MMP-2) that is intracellular, enzymatically active and concentrated within mitochondria. NTT-MMP-2 triggers mitochondrial-nuclear stress signaling via *NF-kB* transcriptional cascades. Renal proximal tubule-specific transgenic expression of the NTT-MMP-2 isoform results in regulated necrosis, activation of innate immunity and enhanced sensitivity to ischemia/reperfusion injury. In this study we examined the relationship between hyperglycemia and the induction of NTT-MMP-2 and innate immunity genes using the human HK2 proximal tubule cell line.

Methods: We manufactured the specific siRNA for NTT-MMP-2 and tested the inhibitory efficacy of NTT-MMP-2 for innate immunity-related genes using quantitative PCR in HK2 cells with high glucose stimulation.

Results: High glucose medium (30 mM) induced a 1.65±0.06 and a 3.20±0.18 fold increase in FL-MMP-2 and NTT-MMP-2 synthesis as determined by qPCR, respectively ($p<0.05$ for each). High glucose medium also resulted in statistically significant increases in the expression of the innate immunity genes *IFIT1, IRF7, IL6 and CXCL1* including *NF-kB.* To determine the relationship between high glucose medium enhanced NTT-MMP-2 and innate immune gene expression we developed an NTT-MMP-2 specific siRNA that targets the unique 5'UTR of this gene. Selective siRNA targeting inhibited high glucose mediated NTT-MMP-2 expression to 0.81±0.75 fold ($p<0.01$), with no effect on FL-MMP-2 expression (1.33±0.28 fold, $p>0.05$) compared with negative control. The selective NTT-MMP-2 siRNA suppressed high glucose mediated *NF-kB* expression, as well as *IFIT1, IRF7, IL6 and CXCL1.*

Conclusions: We conclude that selectively targeting NTT-MMP-2 with a siRNA approach offers a therapeutic approach for reduction of tubular epithelial cell necrosis and activation of innate immunity in the setting of diabetes mellitus.

Funding: Government Support - Non-U.S.

FR-PO621

TRAP Analysis of Podocyte Gene Expression in Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is the leading cause of end-stage renal disease, and podocyte injury plays a critical role in its development. To better understand the role of podocytes in DN, we have utilized Translating Ribosome Affinity Purification (TRAP) to analyze mRNA translation in podocytes isolated from kidneys of mice with early onset of diabetes.

Methods: TRAP allows for the isolation and quantification of cell-specific active mRNA translation. We utilized a podocin-Cre transgene for podocyte-specific activation of a TRAP allele ($Rosa26^{fsTRAP}$). Translated mRNAs were quantified by high-throughput rRNA-depleted total RNA sequencing. To determine responses to early diabetes, mice were made diabetic with streptozotocin and mRNA was isolated 3 weeks after onset of hyperglycemia. To date, 9 diabetics (5 female, 4 male) and 9 controls (3 female, 6 male) have been studied.

Results: With TRAP isolation, mRNA of podocin and nephrin, two podocyte markers, were enriched 50 to 70 -fold. Overall, 1255 genes were upregulated >1.5 fold and 406 genes were downregulated >1.5 fold. However, there were marked sex differences in male vs. female: Up: 1292 vs. 413; Down: 580 vs. 350; 100 genes were up and 40 genes were down in both sexes. Unlike females, in males, predominant clusters of upregulated genes were related to cell cycle, cell division and apoptosis. In both sexes, there were gene clusters related to inflammation and alterations in cell metabolism. Of interest, both sexes had increased gene clusters related to cell responses to interferons.

Conclusions: Analysis of translated mRNA from podocytes after early onset of a model of type I diabetes indicates significant differences between sexes, with evidence of more dedifferentiation and injury in males. Our ongoing studies in mice with more established DN and in models of type II diabetes should provide further insight into podocyte injury and gender responses.

Funding: NIDDK Support

FR-PO622

High Intensity Interval Training (HIIT) Attenuates Proteinuria and Improves Physical Capacity in STZ Diabetic Rats

Natalia Reinecke,[3] Rafael Luiz,[2] Alexandre Saud,[3] Rodolfo R. Rampaso,[2] Wesley Silva,[5] Samuel T. Filho,[5] Waldemar S. Almeida,[1] Nestor Schor.[4] *[1]EPM/UNIFESP, São Paulo, Brazil; [2]None, São Paulo, Brazil; [3]UNIFESP, Sao Paulo, Brazil; [4]Universidade Federal de Sao Paulo/Escola Paulista de Medicina, Sao Paulo, Brazil; [5]Universidade Federal de São Paulo, Sao Paulo [SP], Brazil.*

Background: The insertion of Diabetic patients on a physical training program is a challenge, given that 'lack of time' is one of the most cited barriers. HIIT has demonstrated to have several benefits to these subjects, even requiring a lower commitment time than current recommendation of exercise for this population. The purpose of this investigation was to examine the effects of HIIT on renal function and physical capacity in STZ Diabetic rats and compare these results with the effects of endurance moderated exercise.

Methods: Wistar rats were divided into four groups 6-8 animals: Sedentary Control(SC), Sedentary Diabetic(SD), Diabetic Endurance(DE) and Diabetic HIIT(DH). DH group were submitted to following protocol: 10bursts of 1min(90% of maximal test) intersected with 10 periods of low intensity walking(40% of maximal test) 3days/wk, 8weeks total. Endurance training consisted of 60min of moderated exercise(60% of maximal test) 5days/wk, 8weeks total. Diabetes was induced by a single STZ injection(50mg/kg i.v.). At the end of protocol animals underwent to an Ergospirometry test to detect the peak of oxygen consumption(VO_{2peak}).

Results: HIIT improved Exercise Capacity(VO_{2peak}:48±16 vs 32.8±7ml/kg/min, DH vs SD,p<0.05) as well as Endurance training(VO_{2peak}:53.1±11 vs 32.8±7ml/kg/min, DE vs SD,p<0.05). HIIT, but not Endurance training, attenuated the increase in proteinuria caused by Diabetes in comparison to SD(9.9±6 vs 19.6±1.9mg/dL/24h, p<0.05, respectively). Both training attenuated the increase in urinary volume, water ingestion, Serum Urea and partially prevent low Creatinine Clearance(CrCl) when compared to SD.

Conclusions: Results of this study show that HIIT can improve exercise capacity, partially prevent low CrCl and attenuate the increase in proteinuria and in other diabetic symptoms as polyuria and polydipsia. These data suggests that HIIT can be a time-efficient adjunct treatment to minimize Diabetes complications.

Funding: Government Support - Non-U.S.

	SC	SD	DE	DH
Glycemia(mg/dl)	112±7	460±70*	500±26*	465±51*
Urinary Volume(ml)	14±5	95±14 *	118±18*	93±24*#&
H2O Consumption(ml)	18±5	124±22*	146±18*	93±24*#&
CrCl(ml/dl)	0.8±0.1	0.4±0.2*	0.7±0.3	0.6±0.02
Ser Urea(mg/dl)	41±8	72±14*	55±16#	54±9#

*p<0.05vsSC; #p<0.05vsSD, &p<0.05vsDE

FR-PO623

Investigation of Protein Tyrosine Phosphatase, Non-Receptor Type 2 (PTPN2) and Its Interaction with Vitamin D Receptor (VDR) in Inflammation of Type 2 Diabetes Mellitus

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Background: To investigate the role of protein tyrosine phosphatase nonreceptor type 2 (PTPN2) in the inflammation of type 2 diabetes mellitus (T2DM) and its interaction with vitamin D receptor(VDR).

Methods: 101 T2DM patients were divided into three groups based on urinary albumin-to-creatinine ratio (uACR):normal albuminuria(30mg/g>uACR,n=29), microalbuminuria(30mg/g≤uACR<300mg/g,n=34), and macroalbuminuria(uACR≥300mg/g,n=38), with healthy individuals(n=18) as controls. Serum from these objects were analyzed for PTPN2 protein. Peripheral blood mononuclear cells (PBMCs) were cultured ex vivo to analyzed for PTPN2 and VDR in both protein and mRNA level. HK2 and THP1 cell were stimulated with tumor necrosis factor (TNF) or high glucose and treatment with paricalcitol. The expression of PTPN2 and VDR was analyzed by real-time PCR and Western blotting. The release of IL-6 and MCP-1 were analyzed by real-time PCR and ELISA after PTPN2 silencing or overexpression.

Results: PTPN2 expression was down-regulated in serum and PBMCs from T2DM patients with albuminuria and same with VDR expression in PBMCs. PTPN2 levels were negatively correlated with uACR. Logistic regression analysis revealed that PTPN2 down-regulation was an independent risk factor for the increase in uACR; PTPN2 expression was positively correlated with VDR expression in the PBMCs from T2DM patients. Stimulation of TNF-α or high glucose could both decrease the expression of PTPN2 and VDR in both protein and mRNA level in cultured HK2 and THP-1 cell, while treatment with paricalcitol can reverse the down-regulation of PTPN2 as well as VDR. After PTPN2 silencing in HK2 and THP-1 cell can significantly increased the production of the inflammatory cytokine IL-6 and chemokines MCP-1. Moreover, high PTPN2 levels contributed to decline the elevated IL-6and MCP-1. But treatment with paricalcitol after PTPN2 silencing could not reverse the up-regulation of IL-6 and MCP-1.

Conclusions: Down-regulation of serum PTPN2 is independently with the severity of albuminuria in T2DM.PTPN2 has anti-inflammatory activities in T2DM and the inflammation regulatory role may be associated with the Vitamin D/VDR pathway.

FR-PO624

Advanced Glycation End Products (AGEs) Interrupted Podocyte Autophagy Flux through mTOR Activation

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Background: Insufficient podocyte autophagy exacerbates podocyte injury and renal dysfunction under diabetic conditions. AGEs are a classic pathogenic factors under diabetic conditions. In present study, we studied the role of AGEs on podocyte autophagy and its underlying mechanism.

Methods: Db/db mice were gavaged by Pyridoxamine(inhibitor of AGE formation) to mimic diabetic conditions with low- AGEs serum levels. Autophagy were examed by Western blotting, immunofluorescent staining, transmission electron microscopy.

Results: 1. AGE inhibited podocyte autophagy and led to podocyte injury in vivo and in vitro (FIG 1A-D). 2. We further found that AGE blocked autophagy flux via interfering the formation of autophagosme, fusion of autophasome and lysosome in cultured podocyte(FIG1 E-F). 3. mTOR is an important autophagy negative regulator. Next, we found AGE activated mTOR activity in vivo and in vitro. mTOR activation mediated AGE-induced podocyte autophagy inhibition in vivo and in vitro(FIG2).

Conclusions: AGE interrupted podocyte autophagy flux through mTOR activation.

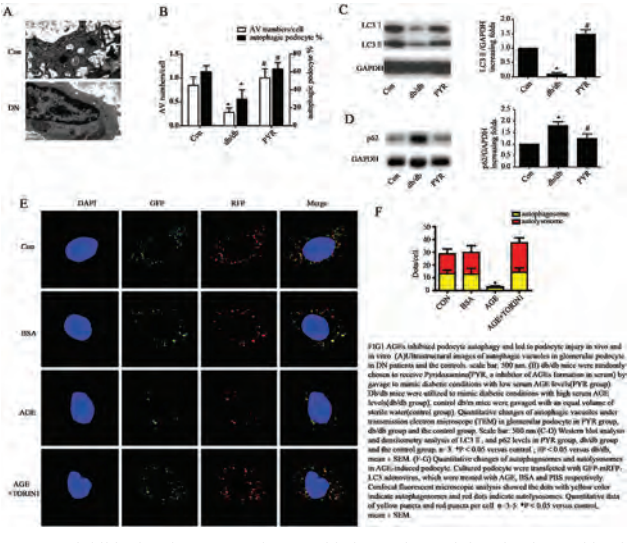

FIG1 AGEs inhibited podocyte autophagy and led to podocyte injury in vivo and in vitro

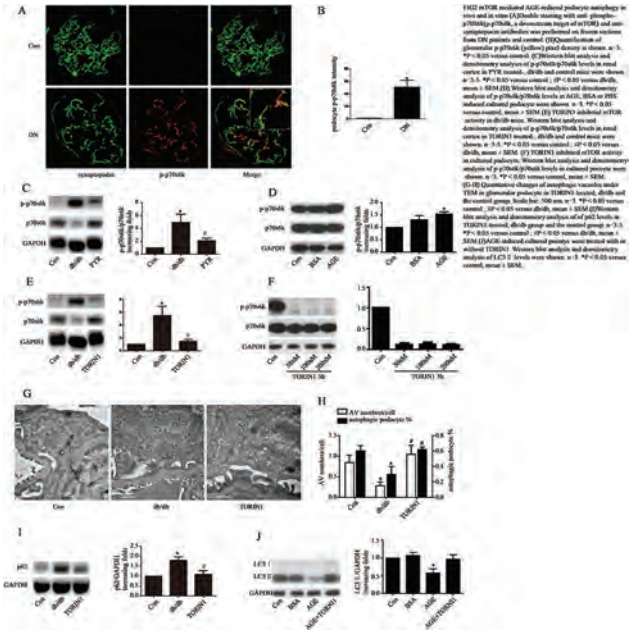

FIG2 mTOR mediated AGE-reduced podocyte autophagy in vivo and in vitro

FR-PO625

Endogenous Klotho May Play Direct Roles in the Pathogenesis of Diabetic Vascular Disease Langjing Zhu,[2,3] Qinghua Liu,[3,2] Yan Ding,[3] Yu-Chun Chang,[3] Li-Li Hsiao.[1] *[1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [2]Nephrology, The First Affiliated Hospital, Sun Yat-sen University, Shenzhen, China; [3]Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.*

Background: Diabetes is a known risk factor for cardiovascular disease (CVD) and chronic kidney disease. Dysfunction of vascular smooth muscle cells (VSMCs) plays a key role in the pathogenesis of diabetic vascular disease, which requires the migration and proliferation of VSMCs as well as the production of biological mediators such as TGF-β1, Fractalkine, and matrix metalloproteinases (MMPs). We previously showed that endogenous Klotho is a master regulator of CVD by reducing vascular calcification in the VSMC layer. This study aims to explore the functional roles of endogenous Klotho in the pathogenesis of diabetic vascular disease.

Methods: Diabetic model is created using Human Aortic-SMCs (HA-SMCs) with D-glucose under dose-response (5.5mM, 25mM, 35mM, and 50mM) and time-dependent fashion (0 day to 10 days); mannitol (35mM and 50mM) is used to assess the osmotic effects. Expression of endogenous Klotho, TGF-β1, Fractalkine, MMP2, and MMP9 are assessed by Western blot. The direct effects of endogenous Klotho are achieved by Klotho-siRNA and Klotho-plasmid transfection. MTS assay is used to assess the cell proliferation, flow cytometry with propidium iodide staining is used to study cell cycle, and the wound-healing migration assay is for the migratory activity.

Results: The Klotho expression in HA-SMCs is upregulated by high glucose (HG) in a dose-dependent manner; and the expression peaks at day 3 with 35mM D-glucose treatment. However, the Klotho expression is not affected by mannitol, indicating that differential expression of klotho is not caused by hyperosmolarity. HG (35mM D-glucose) also upregulates the expression of TGF-β1, Fractalkine, MMP2, and MMP9, which are further enhanced under the Klotho deficiency state using Klotho-siRNA transfection, and mitigated by Klotho over-expression using Klotho-plasmid transfection. Neither HG nor Klotho has effects on the migration or proliferation of HA-SMCs.

Conclusions: HG regulates the expression of endogenous Klotho and in an unique diphase pattern. Endogenous Klotho may play direct roles in the pathogenesis of diabetic vascular disease using the knock-down and knock-in Klotho system, which suggest that Klotho may serve as a potential treatment target in diabetic vascular disease.

Funding: Government Support - Non-U.S.

FR-PO626

Renal and Cardiovascular Dysfunction in db/db Diabetic Mice Is Associated with Increased Cardiac Angiotensin Converting Enzyme 2 (ACE2) and Neprilysin (NEP) Rucha Fadnavis, Meenasri Kumbaji, Salim El-Amouri, Nadja Grobe, Khalid M. Elased. *Wright State University, Dayton, OH.*

Background: The prevalence of diabetic kidney disease (DKD) has increased in the recent decades and is considered one of the main causes of ESRD. DKD is also a major risk factor for cardiovascular diseases. Proteinuria is now widely accepted as an independent risk factor for cardiovascular morbidity and mortality. The renin angiotensin system (RAS) plays an important role in regulating both the renal and cardiovascular systems. The deleterious actions of Ang II are antagonized by Ang (1-7), which is generated by ACE2 and NEP. ACE2 and NEP are multifunctional enzymes and their shedding in the urine have emerged as early biomarkers for DKD. ACE2 has been shown to have renoprotective and cardioprotective role in diabetic mice. In addition, a combination of AT1 receptor blockade and NEP inhibition, Sacubitril-Valsartan is used for management of heart failure. The aim of this study was to investigate whether shedding of urinary ACE2 and NEP could be a predictor of cardiovascular disease and index of intra cardiac ACE2 and NEP status in *db*/*db* diabetic mice.

Methods: Radio-telemetry was used to measure blood pressure. Control and diabetic *db/db* mice (8 weeks) were treated with pioglitazone (20mg/Kg/day) for 10 weeks. Western blot, immunostaining and RAS enzyme assays were used to study renal, urinary and cardiac protein expression and activities.

Results: *db*/*db* mice are normotensive at the ages of 8-12 weeks. There were no significant differences in cardiac ACE2 and NEP between *db*/*db* and control mice. However, at 18 weeks, *db*/*db* mice developed albuminuria and hypertension. In addition, at this age there was a significant increase in urinary and cardiac ACE2, NEP expression and activity. Pioglitazone treatment of *db*/*db* diabetic mice normalized hyperglycemia and attenuated albuminuria. In addition, pioglitazone increased expression and activity of cardiac ACE2 whereas it decreased expression and activity of cardiac NEP compared to untreated *db*/*db* mice.

Conclusions: Pioglitazone treatment could be used as a renoprotective and cardioprotective since it attenuated albuminuria, increased cardiac ACE2 and decreased cardiac NEP. Increased urinary ACE2 and NEP could be used to predict alteration of cardiac RAS status and possible risk of cardiovascular diseases.

FR-PO627

Increased Phosphorylation of the Ubiquitin Ligase Kelch-Like 3 in the Kidney of Db/Db Mice Shigeru Shibata,[2] Kenichi Ishizawa,[2,1] Yoshikazu Nemoto,[2] Chikayuki Morimoto,[2] Shunya Uchida.[2] *[1]Shinsen-Ikebukuro Clinic, TOKYO, Japan; [2]Teikyo University School of Medicine, Tokyo, Japan.*

Background: Although clinical studies have shown that diabetic patients display salt-sensitive hypertension, its pathogenesis remains unclear. Kelch-like 3 (KLHL3) is a component of an E3 ubiquitin ligase complex that regulates blood pressure by targeting With-No-Lyisne (WNK) kinases for degradation. Mutations and inactivation of KLHL3 cause hypertension resulting from increased Na-Cl cotransporter (NCC) activity in the kidney. Previously, we have reported that angiotensin II (Shibata et al. PNAS 2014) and potassium depletion (Ishizawa et al. BBRC 2016) inactivate KLHL3 by protein kinase C (PKC)-mediated phosphorylation at S433 in the Kelch-domain, thereby contributing to blood pressure elevation. In this study, we examined the possible involvement of KLHL3 in the diabetic kidney using a model of type 2 diabetes.

Methods: We examined the expression levels of total KLHL3 and KLHL3 phosphorylated at S433 ($KLHL3^{S433\text{-}P}$) in the kidney of Db/+ and Db/Db mice. We also determined the levels of Cl transporters including NCC, Na-K-2Cl cotransporter NKCC2, and Cl/HCO_3 exchanger pendrin in the membrane fraction of the kidney in this model.

Results: Western blotting revealed that $KLHL3^{S433\text{-}P}$ levels were significantly increased in the kidneys of Db/Db mice (2.2-fold increase versus Db/+ mice; $P < 0.01$), which was associated with the increased levels of WNK1/4. Moreover, NCC levels in the membrane fraction were significantly higher in Db/Db mice than Db/+ mice **(**2.3-fold increase, $P < 0.01$**)**. Interestingly, NKCC2 was also increased, whereas pendrin was decreased in Db/Db mice. The decreased pendrin in this model was associated with the increased levels of inactive, phosphorylated form of mineralocorticoid receptor in the kidney. To determine the mechanism for the increased $KLHL3^{S433\text{-}P}$ levels, we evaluated PKC activity in the kidney. Of note, active, phosphorylated PKC was increased in Db/Db mice, explaining the $KLHL3^{S433\text{-}P}$ induction in this model.

Conclusions: These data indicate that the inactivation of KLHL3 is involved in the increased NCC activity in Db/Db mice, and suggest that KLHL3 is involved in the pathogenesis of salt-sensitive hypertension in type 2 diabetes.

FR-PO628

Insulin Stimulates Urate Transporter 1 (URAT1) and Uric Acid Reabsorption Shigeru Shibata,[2] Daigo Toyoki,[2] Emiko Kuribayashi-Okuma,[2] Yoshikazu Nemoto,[2] Chikayuki Morimoto,[2] Yoshifuru Tamura,[2] Makoto Hosoyamada,[1] Shunya Uchida.[2] *[1]Teikyo University Faculty of Pharma-Sciences, Tokyo, Japan; [2]Teikyo University School of Medicine, Tokyo, Japan.*

Background: Accumulating data indicate that renal uric acid (UA) handling is altered in diabetes. In addition, hyperinsulinemia is associated with hyperuricemia and hypouricosuria. However, the underlying mechanisms remain unclear. In this study, we aimed to investigate how diabetes and insulin alter the levels of renal UA transporters.

Methods: Sprague-Dawley (SD) rats received intraperitoneal injection of streptozotocin. The rats were confirmed to be diabetic by measuring blood glucose after 72 hours (glucose levels > 250 mg/dl). Some rats received subcutaneous infusion of insulin *via* an osmotic minipump (3 U/day). In a separate experiment, non-diabetic SD rats received a low dose of insulin (0.75 U/day). We also performed in vitro experiments using NRK-52E cells, the rat kidney epithelial cell line.

Results: In insulin-depleted diabetic rats with streptozotocin treatment, both UA excretion and fractional excretion of UA (FEUA) were increased, suggesting that tubular handling of UA is altered in this model. In the membrane fraction of the kidney, the expression of urate transporter 1 (URAT1) was significantly decreased, whereas that of ATP-binding cassette sub-family G member 2 (ABCG2) was increased, consistent with the increased renal UA clearance. Importantly, administration of insulin (3 U/

day) to the diabetic rats decreased UA excretion and alleviated UA transporter level changes. To confirm the contribution of insulin in the regulation of urate transporters, normal rats received a low dose of insulin (0.75 U/day). Of note, insulin significantly increased URAT1 and decreased ABCG2 levels, resulting in increased UA reabsorption. Furthermore, URAT1 was present in NRK-52E cells, and the addition of insulin to the medium significantly increased the endogenous URAT1 levels in the membrane fraction of NRK-52E cells.

Conclusions: These results suggest a previously unrecognized mechanism for the anti-uricosuric effects of insulin, and provide novel insights into the renal UA handling in the diabetic state.

FR-PO629

Diabetes Aggravate Post-Ischemic Renal Fibrosis through Persistent Activation of Sonic Hedgehog Signaling Sang-Ho Lee,[3] Dong-Jin Kim,[4] Jun mo Kang,[5] Seon hwa Park,[3] Seok jong Song,[3] Su-Mi Kim,[2] Seo Jung-Woo,[2] Yu ho Lee,[3] Yang gyun Kim,[1] Ju young Moon,[3] So-young Lee.[5] *[1]Division of Nephrology Department of internal medicine Kyung Hee University College of Medicine, Seoul, Republic of Korea; [2]Kyung Hee University, Seoul, Republic of Korea; [3]Kyung Hee University Hospital at Gangdong, Seoul, Korea, Seoul, Republic of Korea; [4]KyungHee University, Seoul, Republic of Korea; [5]Bundang CHA Medical Center, CHA Univ., Bundang, Republic of Korea.*

Background: Diabetes has a high risk for chronic kidney disease (CKD) and increases the severity of acute kidney injury (AKI). AKI induces renal fibrosis, known as a key feature of CKD, and renal fibrosis is associated with transforming growth factor-β1 (TGF-β1) and sonic hedgehog (Shh) signaling pathway. However, it is not known whether diabetes accelerates CKD progression via Shh signaling after AKI. Here, we investigated the influence of diabetes on CKD progression after AKI.

Methods: We established unilateral renal ischemia–reperfusion injury (IRI) model in streptozotocin induced diabetic mice. Histological changes in the kidney were evaluated at 3 and 5 weeks after IRI. The expression levels of mRNAs and proteins related to fibrosis and inflammation were determined by qRT-PCR and western blot. The effect of hyperglycemia on the epithelial-mesenchymal transition (EMT) induced by TGF-β1 and Shh signaling pathway was demonstrated in HKC-8.

Results: When comparing between 3 and 5 weeks after IRI, there was no improvement of tubulointerstitial injury in diabetes. Renal fibrosis was significantly higher in diabetes than in non-diabetes at 5 weeks after IRI. The pattern of infiltrated T and B cell was also consistent with that of renal fibrosis. The mRNA and protein expression levels of related TGF-β1 and Shh signaling pathway were significantly higher in the diabetic IRI kidneys than in the non-diabetic IRI kidneys. In vitro, Hyperglycemia led to the expression levels of TGF-β1 and Shh, and then interacted with each other for the progression of fibrosis.

Conclusions: Taken together, we demonstrated that diabetes on IRI induced the persistent activation of TGF-β1 and Shh signaling pathway and aggravate the interstitial renal fibrosis. In addition, the susceptibility to TGF-β_1 and Shh was increased by hyperglycemia in renal tubular cells.

FR-PO630

Clusterin Is Increased in Glomeruli of Patients with Diabetic Nephropathy and after Induction of Damage in Podocytes In Vitro Junling He, Pascal Bus, Kimberley Veraar, Marion Scharpfenecker, Jan A. Bruijn, Hans J. Baelde. *Department of Pathology, Leiden University Medical Center, Leiden, Netherlands.*

Background: Clusterin is a glycoprotein which is ubiquitously expressed in many tissues, including the kidney. It is demonstrated that clusterin plays a role in apoptotic processes, and it is suggested to have protective properties on cells. The expression of clusterin has been reported to be up-regulated in diverse kidney injuries. In this study, we investigated whether clusterin is upregulated in glomeruli of diabetic nephropathy (DN), where clusterin is expressed in the glomeruli, and how clusterin is regulated under diabetic conditions.

Methods: Clusterin mRNA analysis was performed on kidney cortex and micro-dissected glomeruli from patients with DN (n=24), non-diabetic subjects were used as control (n=11). Clusterin protein expression was assessed by immunohistochemistry on renal tissue from patients with DN and non-diabetic subjects. Kidneys of streptozotocin-induced diabetic mice(n=10) and non-diabetic control mice (n=10) were sequentially stained for clusterin and WT1 (a podocyte marker). Furthermore, human podocytes (Moin Saleem, Bristol, UK) were cultured and incubated with glucose, VEGF-A, angiotensin II and puromycin aminonucleoside (PAN). qPCR was performed to investigate the regulation of clusterin under these diabetic conditions.

Results: Compared to non-diabetic subjects, clusterin mRNA expression was significantly increased in both glomeruli (2.3 times) and whole kidney lysates (3.6 times) of patients with DN ($p<0.05$). Clusterin protein levels were also increased in glomeruli of patients with DN compared to non-diabetic subjects($p<0.05$). Similar results were found in glomeruli of diabetic mice compared to non-diabetic control mice ($p<0.05$). Interestingly, clusterin partly co-localised with WT-1 in glomeruli of mice. Glucose, VEGF-A, and angiotensin II stimulation did not increase the clusterin mRNA expression in podocytes, whereas PAN-stimulation significantly increased the clusterin mRNA expression ($p<0.05$) *in vitro*.

Conclusions: Our data show that clusterin is increased in glomeruli of patients with DN and in podocytes after PAN-induced damage *in vitro*. Further studies have to elucidate whether clusterin has protective effects on podocytes upon damage during the development of DN.

FR-PO631

Renal-Selective Snx5 Gene Silencing Increases Insulin Resistance and Blood Pressure in Mice Xiaoyan Wang, Laureano D. Asico, Xiaobo Ma, Pedro A. Jose, Van Anthony M. Villar. *George Washington University School of Medicine, Washington, DC.*

Background: We have reported that sorting nexin 5 (SNX5) plays an important role in the positive regulation of insulin receptor expression and function in cultured renal proximal tubule cells and that renal-selective *SNX5* gene silencing increased blood pressure (BP) in WKY rats, via the D_1 dopamine receptor (D_1R).

Methods: In order to test the hypothesis that renal *Snx5* gene silencing increases insulin resistance and BP, we measured BP, blood glucose, serum insulin, urinary insulin excretion, and insulin sensitivity in C57Bl/6J mice treated with a 7-day renal subcapsular infusion of *Snx5*-siRNA; mock-siRNA was used as control (3 μg/kg/day, n=4/group).

Results: *Snx5* siRNA-treated mice had elevated BP (SBP: 119±5.2 *vs*. 101.5±0.5; DBP: 91.8±7.3 *vs*. 72±2.3, mm Hg, under pentobarbital anesthesia), non-fasting blood glucose (214±3 *vs*. 179±8, mg/dl) and fasting serum insulin (1.16±0.17 *vs*. 0.62±0.04, ng/ml) was increased while urinary excretion of insulin (0.15±0.03 vs 0.55±0.13, ng / mg of creatinine) was decreased. In another set of mice (n=4/group) that urine water/sodium excretion, and creatinine clearance between the two groups. Histologically, SNX5 was mainly located in the apical membrane of proximal tubules, thick ascending limbs of loop of Henle, and distal convoluted tubules. SNX5 colocalized with the insulin receptor β (IR-β), insulin-degrading enzyme (IDE), NHE3, NKCC2 and NCC. Renal protein expression (via immunoblotting) of SNX5 (29±10, % of control), IR-β (50±7) and IDE (57±6) were lesser while renal protein expression of NHE3 (172±29), NaPi2 (223±12), NKCC2 (440±12) and NCC (177±23) were greater in SNX5-depleted mice compared to control mice. Renal protein expressions of α/β/γ-ENaC, Na^+K^+ATPase, actin, and renal morphology(via H&E staining and brightfield microscopy) were similar in both groups.

Conclusions: Silencing of renal SNX5 expression with siRNA decreased renal IR-β/IDE and increased sodium transporters in proximal and distal nephron segments. These may impair the regulation of renal D_1R in insulin metabolism and sodium transport and cause increased BP and insulin resistance in SNX5 depleted mice.

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FR-PO632

Human Mesenchymal Stem Cells Suppress Glucose-Induced Inflammatory Responses of Stable Renal Proximal Tubular Epithelial Cell Monolayers Md nahidul Islam,[1] Tomas P. Griffin,[1,2] Stephanie Rocks,[1] Joana Cabral,[1] Thomas Ritter,[1] Tara McMorrow,[3] Timothy O'Brien,[1,2] Matthew D. Griffin.[1,4] *[1]Regenerative Medicine Institute, School of Medicine, National University of Ireland Galway, Galway, Ireland, Galway, Ireland; [2]Centre for Endocrinology, Diabetes and Metabolism, Galway University Hospitals, Galway, Ireland; [3]School of Biomolecular and Biomedical Science, Conway Institute, University College Dublin, Dublin, Ireland; [4]Department of Nephrology, Galway University Hospitals, Galway, Ireland.*

Background: Renal proximal tubular epithelial cells (RPTEC) are dysfunctional in diabetic kidney disease (DKD). Mesenchymal stem cells (MSCs) may modulate DKD pathogenesis. We aimed to investigate the pro-inflammatory effects of prolonged exposure to high-glucose concentration on RPTECs and to determine whether MSC-derived factors modulate this response.

Methods: Human RPTEC/TERT1 cells were cultured for 12 days to generate stable confluent monolayers. Media containing "Normal" (5mM) and "High" (25mM) D-Glucose or D-Mannitol (25mM) were added for a further 5 days. Supernatants/cells were collected for ELISA (IL-6, IL-8, MCP-1, NGAL) and flow-cytometry (cell death by Annexin-V/PI staining). 10X-concentrated "full" and "extracellular vesicle (EV) depleted" conditioned media (CM) from human bone marrow-derived MSCs were added for the final 2 days at 20:80v/v. Additionally, MSCs were co-cultured 1:10 with RPTEC for 2 days in a trans-well system. Results were statistically analysed with Graphpad Prism 6.0®.

Results: Five day exposure to high-glucose caused significant increases in RPTEC/TERT1 secretion of IL-6, IL-8, MCP-1 and NGAL compared to normal-glucose and mannitol without increasing cell death. The increases in cytokine secretion were only evident after 80-hours (IL-6, MCP-1, NGAL) or 96-hours (IL-8) of culture. Addition of either full- or EV-depleted-CM was associated with significantly reduced high glucose-induced RPTEC/TERT1 secretion of IL-6, IL-8 and MCP-1 (40%-125%), but not NGAL. Indirect contact of MSCs with RPTEC/TERT1 cells in trans-well cultures resulted in even more potent reduction in the secretion of IL-8, IL-6 and MCP-1 (90%-250%).

Conclusions: Prolonged high-glucose exposure induced secretion of pro-inflammatory mediators by RPTEC stable monolayers. Soluble factors released by MSC suppressed high-glucose-induced RPTEC secretion of inflammatory cytokines. EV depletion did not prevent this suppressive effect. Indirect contact of MSCs with RPTEC/TERT1 cells resulted in more potent anti-inflammatory effects.

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FR-PO633

The Effects of Açai (Euterpe oleracea) Extract in the Oxidative Stress and Inflammation in Mouse Mesangial Cells Stimulated with High Glucose Elisa M. Higa,[1] Deyse Lima,[2] Giovana Punaro,[2] Adelson Rodrigues,[2] Margaret G. Mouro.[2] *[1]Medicine Department/Unifesp, Sao Paulo, Brazil; [2]UNIFESP, Sao Paulo, Brazil. Group/Team: Laboratory of Nitric Oxide and Oxidative Stress.*

Background: *Diabetes mellitus* is a chronic disease characterized by hyperglycemia, which generates oxidative stress, with injuries to several organs. 20 to 30% of diabetic patients develop nephropathy, characterized by excessive production of extracellular mesangial matrix, marked initially by albuminuria, with gradual reduction of renal function. Açai is a native fruit from Amazon, which could provide beneficial effects on human health due to its antioxidant properties. The aim of this study was to evaluate the effects of açai extract (EA) in the oxidative stress and inflammation induced by high glucose in immortalized mouse mesangial cells (MiMC).

Methods: MiMC were cultured in DMEM with 5% fetal bovine serum. At 60-70% of confluence, they were cultured in media with normal glucose (NG – 6.7mmol/L), mannitol (osmolar control – 30mmol/L) or high glucose (30mmol/L) for 24, 48 or 72h. After the treatment, cell viability was assessed through an automated counter (Coutess™, Invitrogen, USA). The supernatant was collected for measuring NO by Nitric Oxide Analyzer (NOA™, Sievers, CO, USA). NO was also measured in the cells by DAF-FM staining; reactive oxygen species (ROS) were measured using DCFH-DA. Catalase, Nrf2, iNOS and NF-κB p65 were analyzed by Western blot.

Results: The cell viability after treatment with EA remained greater than 90% in all groups, showing no cytotoxicity of the extract. There was a significant increase of the cellular proliferation in the HG when compared to the NG group, while EA managed to decrease it in all times studied. NO, ROS and inflammatory mediators were increased in the HG vs NG group, being also decreased after treatment with EA, $p < 0.05$. HG showed a decrease in the protein content of the antioxidants catalase and Nrf2 vs NG group, which were partially recovered by EA, with $p < 0.05$.

Conclusions: In this study, EA was able to decrease the proliferation and oxidative stress induced by high glucose, in MiMC, by suppressing inflammatory mediators signalling (NF-κB p65 and iNOS), and at the same time activating Nrf2/ antioxidant response pathways. The use of extract of açai could be an additional protective strategy for increase the antioxidant defense system in diabetes, and delay the progression of this disease and its complications, such as the nephropathy.

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FR-PO634

Impact of P2X7 Receptor on the Progression of Diabetic Nephropathy in Rats Elisa M. Higa,[1] Robson S. Serralha,[2] Adelson Rodrigues,[3] Giovana Punaro,[3] Margaret G. Mouro,[3] Deyse Lima,[3] Camila Farias,[3] Daniela B. Rodrigues.[3] *[1]Medicine Department/Unifesp, Sao Paulo, Brazil; [2]Universidade Federal de São Paulo, Maua, Brazil; [3]UNIFESP, Sao Paulo, Brazil. Group/Team: Laboratory of Nitric Oxide and Oxidative Stress.*

Background: *Diabetes mellitus* (DM) is a chronic disease which occurs when there is a failure in insulin production or when the cells become resistant to this hormone, leading to hyperglycemia. This situation results in increase of extracellular ATP concentration, which is responsible for several biological functions, among them the activation of $P2X_7$ receptor. When rapidly activated, $P2X_7$ allows the cations influx to the cells, mainly calcium. Constant activation of $P2X_7$ results in opening of many non-selective pores and these in turn allow the passage of hydrophilic molecules with approximately 900 Da. In both processes, $P2X_7$ induces cell death by necrosis via cell swelling or apoptosis, through high concentrations of calcium. Studies from our Laboratory showed that $P2X_7$ expression and activation is associated with oxidative stress in DM. Our aim is to evaluate the effects of $P2X_7$ on the diabetic nephropathy progression in rats.

Methods: Male Wistar rats, 7 weeks old, were unilaterally nephrectomized and DM was induced using streptozotocin (STZ, 60mg/kg, i.v.). Control rats (CTL) received citrate buffer, STZ vehicle. The animals were placed in metabolic cages in different weeks for 24-hour urine collection and a small aliquot of 3-hour blood fasting, for biochemical analysis. The renal tissue was collected after euthanasia, under anesthesia, and prepared for Western blot (WB) test against $P2X_7$, from the 1st to 8th week of diabetes; the results were described as mean ± SEM, with significance at $p<0.05$.

Results: Plasma urea was significantly increased and urinary urea was significantly decreased in diabetic animals in all weeks of protocol when compared to the respective CTL. Proteinuria was increased in diabetic animals at 2nd to 8th week of protocol, when compared to the respective CTL. Analysis of $P2X_7$ expression by qPCR and protein analysis by WB presented a significant increase of this receptor at 6th week when compared to 1st week of DM. We observed a moderate positive correlation between $P2X_7$ protein and plasmatic urea, and a negative correlation between $P2X_7$ and urinary urea. We found a strong positive correlation between $P2X_7$ protein and proteinuria at 6th week ($p< 0.05$).

Conclusions: Our data, mainly proteinuria, suggest that $P2X_7$ plays a role on the progression of nephropathy in this model of DM.

FR-PO635

Vitamin D Receptor Agonist (VDA) Prevents Dedifferentiation of Podocytes through Down Regulation of MicroRNA193a in High Glucose Milieu Abheepsa Mishra,[4] Kamesh R. Ayasolla,[1] Vinod Kumar,[7] Xiqian Lan,[1] Rukhsana Aslam,[2] Ali Hussain,[3] Seyedeh Shadafarin Marashi Shoshtari,[6] Ashwani Malhotra,[8] Pravin C. Singhal.[5] *[1]Feinstein Institute for Medical Research, Great Neck, NY; [2]Feinstein Institute for medical research, Glenoaks, NY; [3]Feinstein Institute of Medical Research, New York, NY; [4]Feinstein Institute of Medical Research, Northwell Health, MANHASSET, NY; [5]North Shore LIJ Health System, Great Neck, NY; [6]The Feinstein Institute for Medical Research, Manhasset, NY; [7]Immunolgy and Inflammation, Fienstine Institute for Medical Research, New York, NY; [8]Immunolgy and Inflammation, Feinstein Inst. Med research and NSLIJ, Manhasset, NY.*

Background: Both podocytes (PDs) and parietal epithelial cells (PECs) are derived from the same mesenchymal cells during embryogenesis. Expression of miR193a, which inversely regulates Wilms tumor (WT) 1 gene (the transcriptor of nephrin and podocalyxin) determines the net phenotype. Vitamin D receptor agonist (VDA) has been shown to down regulate miR193a in differentiating PECs. We hypothesize that if high glucose dedifferentiate PDs through up regulation of miR193a then VDA could prevent PDs dedifferentiation via down regulation of miR193a.

Methods: Differentiated (DIF)-PDs were incubated in media containing either buffer or high glucose (30 mM) for 48 hours (n=4). To evaluate the effect of VDR agonist, DIF-PDs were incubated in media containing a buffer, high glucose with/without VDA (EB1089, 1 nM) for 48 hours. To determine the effect of WT1 repressor complex on the PAX2 promoter in high glucose milieu, cellular lysates of control and high glucose treated PDs were immunoprecipitated with WT1 antibody and IP fraction was probed for DNMT1, EZH2, and menin. *In vivo* studies, four- months old wild-type and $BTBR^{ob/ob}$ mice were administered either normal saline or normal saline + VDA (0.1 µg/Kg), intraperitoneally, every other day for 4 weeks. Renal cortical sections were labeled for WT1, synaptopodin, and PAX2. Renal cortical sections were labeled for miR193a by fluorescent *in situ* hybridization technique.

Results: High glucose down regulated ($P<0.05$ vs. control) PD expression of WT1, nephrin, podocalyxin but enhanced ($P<0.01$ vs. control) expression of PAX2 and miR193a. VDA not only down regulated PD expression of mIR193a and PAX2 but also upregulated ($P<0.05$ vs. control) expression of WT1. High glucose upregulated PD expression of PAX2 through disruption of WT1 repressor complex binding on PAX2 promoter. VDA treatment not only increased PD expression of WT1 but also displayed binding of WT1 repressor complex on the PAX2 promoter. Renal cortical sections of $BTBR^{ob/ob}$ mice displayed enhanced PD expression of miR193a, decreased PD expression of WT1 and enhanced expression of PAX2.

Conclusions: High glucose dedifferentiates PD via up regulation of miR193a and VDA preserves PD phenotype in high glucose milieu by down regulating miR193a.

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FR-PO636

TRAM34, an Inhibitor of KCa3.1: A Novel Therapy for Treatment of Established Diabetic Nephropathy Chunling Huang, Ling Zhang, Hao Yi, Ying Shi, Xinming Chen, Carol A. Pollock. *kolling institute, the University of Sydney, Sydney, NSW, Australia.*

Background: Existing treatments of established diabetic nephropathy have not been proven to have long term efficacy. Hence it is essential and indeed urgent to discover novel therapeutic targets to stabilize or reverse diabetic nephropathy. KCa3.1 is an intermediate/small-conductance calcium activated potassium channel. The most well defined role of KCa3.1 channels is to regulate calcium entry into cells and thereby modulate calcium-signaling processes. We have previously demonstrated in murine models of diabetes mellitus that gene silencing or pharmacological blockade of KCa3.1, when introduced at the induction of diabetes mellitus, confers significant protection against the subsequent development of diabetic induced interstitial fibrosis through inhibition of TGF-β1 signalling pathways. Therefore, this study aimed to investigate the therapeutic effect of the KCa3.1 inhibitor TRAM34 in a mouse model of established diabetic nephropathy.

Methods: Diabetic eNOS-/- mice with established nephropathy (24 weeks after induction of type 1 diabetes induced by streptozotocin) were treated with TRAM34 or DMSO (vehicle control) for a further 14 weeks. Preterminal kidney function and subsequent renal structure were assessed as well as inflammatory, fibrotic markers and the TGF-β1 signalling pathway.

Results: 24h urinary albumin was significantly increased in the diabetic animals compared to the non-diabetic controls ($P< 0.01$). Albuminuria was significantly reduced in TRAM 34 treated diabetic animals compared to the diabetic group ($P<0.05$). Immunohistochemistry demonstrated increased CD68 and F4/80 expression, indicating increased macrophage infiltration in the diabetic animals ($P< 0.05$), which was reversed by treatment with TRAM34 ($P< 0.05$). Similarly, TRAM34 reversed the increased mRNA and protein expression of type I and type III collagen and fibronectin observed in the diabetic animals ($P< 0.05$). Furthermore, blocking the KCa3.1 channel by TRAM34 led to the reduction of TGF-β1 signaling through inhibiting phosphorylation of Smad2/3 ($P< 0.05$).

Conclusions: Blockade of KCa3.1 by TRAM34 is a promising therapeutic intervention in established diabetic nephropathy.

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FR-PO637

GFR Correlates with the Homogeneity of Glomerular Capillary Blood Velocity in Diabetic Rats Jacob S. Engbjerg,[4] Donato Sardella,[5,4] Luca Bordoni,[4] Francesco Trepiccione,[3] George Rhodes,[2] Ruben M. Sandoval,[1] Leif Østergaard,[4] Giovambattista Capasso,[6] Bruce A. Molitoris,[1] Sebastian Frische.[4] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Indiana University School of Medicine Division of Nephrology, Indianapolis, IN; [3]Second University of Naples, Naples, Italy; [4]University of Aarhus, Aarhus, Denmark; [5]University of Camerino, Corridonia, Italy; [6]University of Campania Luigi Vanvitelli, Napoli, Italy.*

Background: Hyperfiltration is common in early diabetes, but the mechanisms behind the rise in GFR are not well understood. Theory predicts that glomerular capillary blood flow dynamics can influence GFR. We therefore aim to investigate if the heterogeneity of glomerular capilary blood velocity influence GFR in experimental diabetic rats.

Methods: 3 groups of male Munich Wistar Frömter rats were studied: Control (C) (n=8), Diabetic (D) (7 days after STZ-injection (40 mg/kg)) (n=10) and acutely hyperglycemic (H) (i.v glucose injections to reach blood glucose (BG) > 20 mM) (n=7). Rats were anesthetized with Inactin and prepared for 2-photon in vivo microscopy (2PM) by externalization of the left kidney. BP and HR were monitored. Blood plasma was labelled by injection of Setau-647-coupled 500kD dextran. Blood flow velocity was measured in ≧6 glomerular capillaries in each glomerulus using longitudinal linescans at >1.3 kHz in the capillary lumen. GFR was measured by fitting a double-exponential decay function to the FITC signal in the plasma recorded by 2PM during 30 min after a bolus of FITC-3kD-dextran. Blood samples were obtained before and after microscopy.

Results: A significant correlation between the homogeneity of glomerular capillary blood flow velocity and GFR was found in the D-rats (p = 0.028), but not in C- or H-rats. In C-rats GFR correlated significantly with BP (p=0.0047), age (p=0.026) and plasma osmolality (p=0.011). GFR did not correlate with these parameters in D-rats (p =0.08, p=0.84 and p=0.45) or H-rats (p=0.15, p=0.22, and p=0.68).

Conclusions: Homogenization of blood flow velocities in the glomerular capillaries seems a new powerful mechanism, which may underlie hyperfiltration in diabetic rats. Mechanistically, it may result from mesangial cell dysfunctionality and it appears to override the influence of parameters influencing GFR in control rats.

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Group means of the parameters investigated

	Mean and SD			p-value		
	C	D	H	C vs D	C vs H	D vs H
Age(days)	110 ±19	118 ±15	114 ±17	0.66	0.91	0.9
BG (mM)	5.4 ± 0.86	19.1 ± 4.5	24 ± 14.9	<0.01	<0.01	0.44
BP(mmHg)	135 ±17.5	130 ±7.3	152 ±9.6	0.63	0.06	0.01
Plasma osmolality (mOsm/kg)	314±17	331 ±7.6	328±8.8	0.04	0.13	0.89
GFR(ml/min)	2.73 ±0.86	3.72±1.83	5.08 ±2.33	0.47	0.04	0.28

FR-PO638

A New Model of Diabetic Nephropathy with Advanced CKD Progression in C57BL/6 Mice Xiaoyan Bai,[1] Xiao Li,[2] Jianwei Tian,[1] Wan Jiao,[1] Youhua Liu.[3] *[1]Nephrology, Nanfang Hospital, Southern Medical University, Guangzhou, China; [2]Emergency, Nanfang Hospital, Southern Medical University, Guangzhou, China; [3]University of Pittsburgh, Pittsburgh, PA.*

Background: Diabetic nephropathy (DN) is the leading cause of end-stage kidney disease in industrialized nations. However, there is a lack of robust mouse models with key features of advanced human DN. Very few options of murine models for studying DN include Akita and OVE26 type 1 diabetic mice, and C57BL/6J db/db, C57BL/KsJ ob/ob, eNOS(-/-) db/db and BT/BR ob/ob type 2 diabetic mice. The limitation of these mice is the requirement for mutation to be superimposed to obtain desired phenotypic characteristics. Most genetically modified mice are on the C57BL/6 background; however, they are notorious for resistance to develop DN. To overcome these conundrums, this study reports a novel DN model by challenging with advanced oxidation protein products (AOPPs) in streptozotocin-induced diabetic C57BL/6 mice.

Methods: Uninephrectomized male C57BL/6 mice were divided as follows: 1) non-diabetic; 2) AOPPs-challenged NC; 3) losartan-treated AOPPs-challenged NC; 4) diabetic; 5) AOPPs-challenged diabetic and 6) losartan-treated AOPPs-challenged diabetic mice. After 8, 12 and 24 weeks, biological parameters were evaluated and kidneys harvested for morphology and morphometry.

Results: Glomerular hypertrophy and accumulation of mesangial matrix were present by 8 weeks. By 24 weeks, glomerular lesions similar to those of advanced human DN were present, as demonstrated morphologically by significant mesangial expansion ($p<0.001$) and sclerosis resembling Kimmelstiel-Wilson nodules, diffuse podocyte foot process effacement ($p<0.05$), increased glomerular basement membrane width ($p<0.001$), and worsened tubulointerstitial fibrosis. Immunofluorescence microscopy excluded immune complex diseases for IgG, IgM, and IgA. These morphological changes recapitulate the renal pathology of advanced human DN. AOPPs-challenged diabetic C57BL/6 mice were more sensitive to develop progressive proteinuria beginning at 8 weeks. By 24 weeks, increased albumin excretion rate ($p<0.001$) was found and losartan treatment alleviated these changes.

Conclusions: AOPPs can accelerate the progression of DN in resistant C57BL/6 mice. This mouse model offers a homogeneous genetic background for studying the pathogenesis of advanced DN that resembles human diabetic kidney disease. It also makes it possible to interrogate the role of specific genetic modifications and to evaluate novel therapeutics in the preclinical setting.

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FR-PO639

Distinct Patterns of Dysregulated Autophagy in Type 1 and 2 Diabetic Nephropathy Shinsuke Sakai,[1] Takeshi Yamamoto,[1] Yoshitsugu Takabatake,[1] Atsushi Takahashi,[1] Tomoko Namba,[1] Satoshi Minami,[1] Ryuta Fujimura,[1] Jun Matsuda,[1] Tomonori Kimura,[1] Taiji Matsusaka,[2] Fumio Niimura,[2] Yoshitaka Isaka.[1] *[1]Osaka University Graduate School of Medicine, Suita, Japan; [2]Tokai University School of Medicine, Isehara, Japan.*

Background: Autophagy maintains cellular homeostasis and has protective roles against several stresses. Although it has been reported that high blood glucose can impair some nutrient signalings, suppress autophagy induction during type 2 diabetic nephropathy, how autophagy is dysregulated is still largely unknown.

Methods: 1) We accessed the autophagic flux *in vivo* by investigating the difference in the numbers of GFP-LC3-positive dots by chloroquine administration under fed or starved condition in streptozotocin (STZ)-treated GFP-LC3 transgenic mice (type 1 diabetes) or in obese db/db mice crossed with GFP-LC3 transgenic mice (type 2 diabetes). 2) We compared the inhibitory effects of glucose, insulin, and amino acids on autophagic activity in proximal tubules of 24 h-starved GFP-LC3 transgenic mice. 3) We examined the consequences of long-term autophagy deficiency using STZ-treated proximal tubular cell (PTC)-specific *Atg5*-deficient mice (*Atg5*$^{F/F}$;KAP) or *Atg5*$^{F/F}$;KAP crossed with db/db mice. Then, we examined the effects of rapamycin (an inhibitor of the mechanistic target of rapamycin; mTOR) on vulnerability to ischemia-reperfusion (I/R) injury in these mice.

Results: 1) Autophagy induction was suppressed even under starvation in the PTCs of db/db mice. In contrast, autophagic activity was enhanced in STZ-treated mice even under fed condition. 2) Insulin and amino acids, but not glucose, suppressed starvation-induced autophagy by activating mTOR pathway. 3) Urinary albumin excretion, mitochondrial damage (assessed by COX and SDH staining) and fibrosis (type I collagen immunostaining) were significantly increased in STZ-treated *Atg5*$^{F/F}$;KAP mice compared with control STZ-treated mice. In contrast, these were increased in db/db mice regardless of autophagy deficiency. I/R lead to more severe injury in both diabetic mice compared with nondiabetic mice. Rapamycin exaggerated I/R injury in STZ-induced mice, while it attenuated in db/db mice.

Conclusions: Distinct patterns of dysregulated autophagy in type 1 and 2 diabetic nephropathy should be considered in prevention and treatment.

FR-PO640

Inhibition of Prolyl Hydroxylase Domain (PHD) Reduces Glomerular Macrophage Infiltration and Improves Albuminuria in Mice with a High Fat Diet Hisako Saito,[2] Tetsuhiro Tanaka,[2] Mai Sugahara,[2] Kenji Fukui,[2,1] Takeshi Wakashima,[2,1] Masaomi Nangaku.[3] *[1]JT CPRI, Osaka, Japan; [2]The University of Tokyo graduate School of Medicine, Tokyo, Japan; [3]the University of Tokyo School of Medicine, Tokyo, Japan.*

Background: The epidemic of obesity and its complications is rapidly growing all over the world. Chronic hypoxia in the tubulointerstitium is a major pathogenic factor mediating progression of CKD, and kidneys of metabolic disorders suffer from significant degrees of tubulointerstitial hypoxia. Recent drug discovery established utility of prolyl hydroxylase domain (PHD) inhibitors as stabilizers of hypoxia-inducible factors (HIFs) in vivo, which are currently in human clinical studies for the treatment of anemia in CKD. Notably some clinical studies suggest a role of PHD inhibitors in ameliorating obesity and hyperlipidemia. In this study, we hypothesized that HIF activation using a PHD inhibitor, JTZ-951, protects from obesity-related glomerulopathy (ORG) in mice fed with high fat diet (HFD).

Methods: Eight-week-old, C57BL/6J mice were fed with HFD for 12 or 20 weeks with or without JTZ-951 (0.005%; mixed in chow). Renal consequences of PHD inhibition was investigated at 20 or 28 weeks of age.

Results: JTZ-951 caused a transient rise in hematocrit levels (at 12 weeks of age). Successful activation of HIF in the kidney was confirmed by immunostaining for HIF-1α. Body weight was significantly lower in the JTZ-951 group as compared with the vehicle group. Plasma cholesterol levels were also significantly lower in the JTZ-951 group. PHD inhibition reduced albuminuria (120.8 vs 89.3 μg/mgCr, $P<0.03$). Histologically, glomerular tuft area, mesangial expansion and podocyte density were comparable between groups, but the number of F4/80- positive infiltrating macrophages was lower in the JTZ-951 group. Arginase 1 mRNA expression was higher in the JTZ-951 group, suggesting a possible role of PHD inhibition in altering macrophage polarity, which may have contributed to reducing albuminuria.

Conclusions: Activation HIF by PHD inhibitors mediated multiple renal and non-renal consequences in mice with HFD. JTZ-951 significantly improved obesity and lowered total cholesterol levels. In the kidney, a decrease in albuminuria was associated with decreases in infiltrating macrophages and their possible skewing toward the M2 phenotype. Results of the present study offer a promising view that pharmacological PHD inhibition may be beneficial for the treatment of CKD associated with obesity.

FR-PO641

Does SGLT2 Inhibition with Dapagliflozin Overcome Therapy Resistance to RAAS Inhibition? Hiddo J. Lambers Heerspink,[2] Sergei Petrykiv,[1] Gozewijn D. Laverman,[3] Dick de Zeeuw.[2] *[1]None, Groningen, Netherlands; [2]University Medical Center Groningen, Groningen, Netherlands; [3]ZGT Almelo, Almelo, Netherlands.*

Background: Renin-Angiotensin-Aldosterone-System inhibitors (RAASi) is a mainstay for renal and cardiovascular protective treatment in patients with chronic kidney disease. However, individual patients show a large variation in their response to RAASi both in surrogates like albuminuria and the hard renal outcomes. Sodium-glucose co-transporter 2 inhibitors (SGLT2) lower albuminuria and confer cardiovascular and possibly renal protection. To establish whether individual therapy resistance to RAASi can be overcome by adding an SGLT2 inhibitor we assessed individual albuminuria responses in patients exposed both to RAASi and the SGLT2 inhibitor dapagliflozin.

Methods: We used data from a randomized controlled cross-over trial designed to assess the albuminuria lowering effect of 6-weeks treatment with dapagliflozin. The trial enrolled 33 patients with type 2 diabetes, albumin:creatinine ratio (U_{ACR}) between 100 and 3500 mg/g who were all using an ACEI or ARB at the time of enrollment. We extracted from the electronic medical records data on the U_{ACR} response upon start of RAASi before the trial period, and analyzed the individual albuminuria response to RAASi and to dapagliflozin.

Results: We retrieved data on RAASi from 26 patients (age 62 (SD 8); male gender 20 (77%); U_{ACR} 355 [150 – 533] mg/g. Thirteen patients started an ACEi, and 13 an ARB before entry into the study. The mean U_{ACR} lowering response to RAASi was 26.5% with a large between individual variability (range -76.1 to +135.1%). The addition of dapaglifozin resulted in a mean U_{ACR} lowering response of 34.9%, again with a large between individual variability (range -83.9 to +94.2). Interestingly, there was a significant positive correlation between the response to RAASi and dapagliflozin (Pearson correlation coefficient 0.635; p<0.001) indicating that patients who did not respond to RAASi also did not respond to dapagliflozin. Therapy adherence during the study was excellent with 97.5% of all medications being taken.

Conclusions: Individual therapy resistance to RAASi cannot be overcome with the addition of a completely different class of drugs, SGLT-2 inhibitors. These data suggest that the individual drug response is an intrinsic individual characteristic possibly unrelated to the type of intervention, unless the mode of action of dapaglifozin on albuminuria is through the RAAS.

Funding: Commercial Support - AstraZeneca provided dapagliflozin study medication

FR-PO642

The Study of Mechanisms of SGLT2 Inhibitors for Renoprotection in Human Diabetic Kidney Disease Saeko Sato. *Saitama Medical center, Saitama Medical University, Kawagoe, Japan.*

Background: SGLT2 inhibitor (SGLT2i) has been reported to suppress not only glomerular hyperfiltration, but also have direct action on renal proximal tubule cells in vitro. There have been no reports on detailed investigations of its mechanism in humans, and there are many discussions about that. Therefore, we explore the effect of verious SGLT2i on kidney function and kidney injury in patients with diabetic kidney disease (DKD).

Methods: In patients with type 2 diabetes (T2DM) with DKD, the usual dose of SGLT2 inhibitor (Iplagliflozin 50mg or Canagliflozin 100mg or Dapagliflozin 5mg or Luceogliflozin 2.5mg or Tofogliflozin 20mg or Empagliflozin 10 mg) (when the effect was insufficient, it could be increased to the maximum dose), we compared and examined the several items before administration and one month after, 12 months after.

Results: 73 cases was subjected. Administration of SGLT2i significantly reduced HbA1c and mean blood pressure in the examination room also decreased significantly after one month and 12 month (data not shown). In renal function, estimate glomerular filtration rate (eGFRcreat) decreased significantly after one month, but improved after 12 months (61.3 ± 21.8 → 59.7 ± 22.5 (p = 0.0201) → 61.4 ± 23.7 mg/gCr). The urine albumin-to-creatinine ratio (u-ACR) decreased significantly both after one month and 12 months (560.2 ± 882.7 → 323.4 ± 553.4 (p = 0.0082) → 281.5 ± 430.2 mg/gCr (p = 0.0054)). In inflammation or oxidative stress biomarkers, malondialdehyde modified LDL (MDA-LDL) was significantly decreased after one month and 12 months (133.4 ± 39.5 → 109 ± 28.2 U / L (p = 0.0141) after 12 months). Urinary monocyte chemoattractant protein 1 (MCP-1) did not change after one month, but it decreased significantly after 12 months (2.49 ± 1.75 → 1.27 ± 1.39 pg/gCr (p = 0.0169)). Urinary liver-type fatty-acid-binding protein (L-FABP) also did not change after one month, but it decreased significantly in 12 months (11.4 ± 21.7 → 8.0 ± 16.8 μg/gCr (p = 0.0004)). There was no correlation between the rate of change in HbA1c or the rate of change in blood pressure and the rates of change in eGFR, u-ACR, MDA-LDL, u-MCP-1 and u-L-FABP.

Conclusions: Renoprotection of SGLT2i for DKD in T2DM is considered to be the main mechanism of improvement of glomerular hypertension at early stage, but direct suppression of inflammation and oxidative stress acts in the long term.

FR-PO643

Insulin Use Is a Surrogate Marker of Insulin Resistance (IR) Christine K. Raj,[1] R. E. Boucher,[2] Guo Wei,[2] Terrence S. Bjordahl,[2] A. N. Habib,[2] Srini Beddhu.[2] *[1]UC Berkeley, Saratoga, CA; [2]Univ. of Utah, SLC, UT.*

Background: We previously noted that diabetics needing insulin therapy are at ↑ risk of reaching ESRD than those that do not need insulin adjusted for duration of diabetes mellitus (DM), concurrent use of other hypoglycemic agents and HbA1C levels. We hypothesized that need for insulin is a reflection of underlying IR.

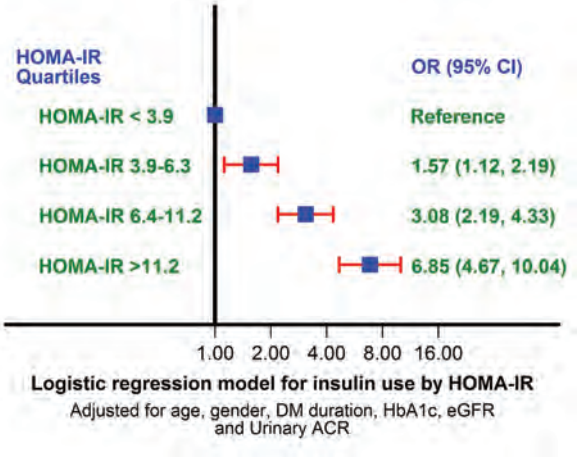
Methods: We examined whether insulin use is reflective of IR in 1756 participants with DM and non-missing data for insulin use and IR in the Chronic Renal Insufficiency Cohort. Insulin use was related to IR estimated by homeostatic model of assessment of insulin resistance (HOMA-IR) in logistic regression models.

Results: Mean age was 59 ±10 years, 55.4% were men and 44.0% were black. Baseline characteristics of diabetics on insulin and not on insulin are summarized in the table. Compared to the lowest quartile of HOMA-IR, there was a graded ↑ in odds of insulin use in the upper three quartiles in a multivariate logistic regression model (Figure).

Conclusions: We conclude that need for insulin use is a surrogate marker of insulin resistance and interventions that target insulin resistance might ↓ the need for insulin use in DKD.

Funding: NIDDK Support

Insulin Use	No (50.2 %) N = 881	Yes (49.8 %) N = 875	
Age (yrs)	61 ± 9	58 ± 10	<0.001
Male (%)	57.5	53.1	0.06
Black (%)	43.2	44.7	0.54
Atherosclerotic Conditions (%)	38.0	45.8	0.001
CHF (%)	11.1	16.0	0.003
Duration of DM (yrs)	12.0 ± 8.9	20.3 ± 10.3	<0.001
BMI (kg/m^2)	34.3 ± 8.1	33.6 ± 8.1	0.07
Hemoglobin-A1c (%)	7.2 ± 1.5	8.1 ± 1.7	<0.001
Sulfonylurea (%)	58.0	14.7	<0.001
Biguanide (%)	24.1	8.7	<0.001
TZD (%)	30.2	17.4	<0.001
Other Hypoglycemic Agents (%)	3.5	2.4	0.17
HOMA-IR	4.9 (3.1, 7.9)	8.4 (5.2, 15.1)	<0.001
CKD-EPI eGFR (ml/min/1.73 m^2)	42.9 ± 14.1	40.8 ± 13.7	0.001
Urine ACR (mg/g)	64.0 (12.3, 623.5)	268.2 (33.5, 1238.6)	<0.001



FR-PO644

The Role of the Renal Biopsy in 6003 Patients with Diabetic Nephropathy Dao-Fu Dai, Shree G. Sharma, Christopher P. Larsen, Patrick D. Walker. *Arkana Laboratories, Little Rock, AR.*

Background: Diabetic nephropathy (DN) is a leading cause of end stage renal disease (ESRD). Proteinuria and progressive decline in renal function in patients with diabetes mellitus (DM) are usually thought to be secondary to DN. However, recognition of superimposed non-diabetic renal disease (NDRD) is critical and, with appropriate diagnosis and treatment, may prevent accelerated progression to ESRD.

Methods: This was a retrospective clinical pathological study of 6003 patients with DM and a biopsy diagnosis of DN, to determine the spectrum of superimposed NDRD and to evaluate the relationship between the presence or absence of NDRD with various clinical manifestations, including rapid worsening of proteinuria and renal function, hematuria with or without an active urine sediment, or the acute nephritic syndrome.

Results: The renal biopsy identified superimposed NDRD in 36.6% of patients with DN. Importantly, the biopsy excluded NDRD in 16.7% of patients with systemic diseases and clinical/laboratory findings suspicious for a superimposed disease. Multivariate analysis identified that a rapid rise in serum creatinine is the strongest predictor for superimposed NDRD (OR: 2.19, p<0.001). Other independent predictors include the acute nephritic syndrome and clinical features suspicious for NDRD. The spectrum of

superimposed NDRD varied according to indications leading to renal biopsy. Acute tubular injury (21%) was most common in patients with rapid decline of renal function; focal segmental glomerulosclerosis was most common (7.1%) in patients with an unexpected swift rise in proteinuria; pauci-immune crescentic glomerulonephritis (15.7%) was most common in patients with rapidly progressive renal failure; infection-associated glomerulonephritis (16.5%) was most common in patients with the acute nephritic syndrome and IgA nephropathy was the most common in patients with hematuria (7.6%).

Conclusions: The renal biopsy is critical to identify the presence or absence of a superimposed NDRD in patients with DN. This study documents the relationship between various clinical manifestations of renal disease and specific NDRD. Finally, it demonstrates the importance of the biopsy in ruling in or out suspected non-diabetic renal disease in clinical settings that would support such a concern.

FR-PO645

Renal Biopsies in Diabetic Patients: Hematuria or Absence of Retinopathy Do Not Indicate Non Diabetic Renal Disease: A 10-Year Single-Center Experience

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Background: Diabetic nephropathy (DN) is usually a presomptive diagnosis based on clinical and biological evidences. However, renal biopsies (RB) may be performed in diabetic patients with glomerular proteinuria lacking classical features of DN and/or in patients with diabetes and another disease with potential renal involvement who could benefit from specific therapy. We compared the frequencies of Non Diabetic Renal Disease (NDRD) according to the RB indications to assess if RB performed for atypical findings are justified.

Methods: 144 RB were performed in diabetic patients with glomerular proteinuria in our center in ten years and divided into two groups: Group 1 (G1): atypical findings (absence of diabetic retinopathy (DR), hematuria (HU), rapid eGFR decline, rapid increase of proteinuria or sudden nephrotic syndrome); Group 2 (G2): clinical and/or biological features of suggesting NDRD. We compared frequencies of NDRD and RB related adverse events in each group.

Results: 68 patients were identified in G1 and 76 in G2. Gender, age, high blood pressure, serum creatinine, urinary protein-to-creatinine ratio, HU, DR, renin-angiotensin system blockade and diabetes duration were not different between both groups. Glycated hemoglobin was higher in G1 (7.8±2.2 vs 7.1±1.4, p=0.04). NDRD was diagnosed in 7 % of patients in G1 and 50% in G2 (p<0.001). None of the 37 patients who underwent RB for HU, and/or absence of DR had NDRD. Adverse events were more frequent in G1 than in G2 (10% vs 1%, p=0.027) (Table).

Conclusions: Absence of DR or presence of HU should not be the only motivation to indicate RB in diabetic patients as they convey an increased risk of adverse event without any benefit.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

Renal biopsies indication	n (%)	Non diabetic renal disease,n (%)	Adverse events, n (%)
Atypical findings	**68 (100)**	**5 (7)**	**7 (10)**
Haematuria and/or absence of diabetic retinopathy, n (%)	37 (53)	0 (0)	5 (14)
CKD progression, n (%)	15 (21)	2 (13)	1 (7)
Recently increased proteinuria, n (%)	10 (14)	1 (10)	1 (10)
Miscelleanous, n (%) (Previously unknown diabetes, Sudden nephrotic syndrom or Stage 5 CKD)	8 (11)	4 (50)	0 (0)
Other indications	**76 (100)**	**38 (50)**	**1 (1)**
Systemic disease with potential renal involvement, n (%) (Hyper IgG4 disease, Systemic lupus erythematosus without history of renal flare, Bullous pemphigoid, Autoimmune polyglandular syndrome, Sarcoidosis and ankylosing spondylitis, HBV, HCV, HIV seropositivity, Tuberculosis, or Amyloidosis)	26 (35)	12 (46)	1 (4)
Monoclonal gammopathy, n (%)	15 (20)	3 (20)	0 (0)
Acute kidney injury, n (%)	13 (18)	6 (46)	0 (0)
Known renal disease, n (%) (ANCA-associated disease, Lupus nephritis or IgA nephropathy/Henoch-Schonlein purpura)	8 (11)	6 (75)	0 (0)
Miscelleanous, n (%) (Anti-nuclear antibodies or Anti-neutrophil cytoplasmic antibodies, Proteinuria pre-diabetes onset or Cutaneous purpura)	14 (19)	11 (78)	0 (0)

FR-PO646

Metformin Is Renoprotective Only in Patients with Progressive Renal Function Decline

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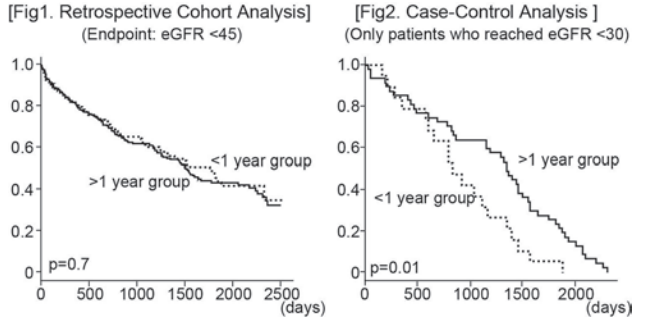
Background: SGLT2 inhibitors have renoprotective properties. Metformin is a first-line drug for treating diabetes mellitus, but it is unknown if it is renoprotective.

Methods: This was a retrospective observational study. From January 2009 to December 2015, we obtained medical records of patients prescribed metformin at our facility. The medical record sampling began on the day the patient demonstrated eGFR <60 ml/min/1.73m² (hereinafter, omit "ml/min/1.73m²") and ended on the day when eGFR <45 or <30. Exclusion criteria are as follows: (1) Short-term period between date reached eGFR <60 and the last creatinine (Cr) measurement date, (2) The same day reached eGFR <60 and <45. All patients were divided into two groups depending on whether metformin was prescribed for less than or more than 1 year ("<1 year group" and ">1 year group"). The survival curve for the outcome was illustrated using the Kaplan–Meier method.

Results: Of the 1,334 subjects who received metformin, 691 (51.8%) had recorded eGFR <60 more than once. Overall, 469 subjects meet the criteria (average age 68.5 years, 299 males, eGFR 55.5 ± 3.84, "<1 year group" was 162 people). 222 subjects with eGFR <45 and 66 subjects with eGFR <30 reached the study endpoint. First, we conducted a retrospective cohort study. No between-group differences were found for reaching the study endpoint(Fig1). Next, we conducted a case-control analysis in the people who reached the study endpoint. We found no differences at the endpoint of eGFR <45. But at the endpoint of eGFR <30, ">1 year group" demonstrated slower renal function decline than the "<1 year group" (Fig2. 47 vs 19 subjects; median 1354 vs 830 days, log-rank test p = 0.01). No subjects developed lactic acidosis over the course of the study.

Conclusions: Metformin exhibited a renoprotective effect in patients. However, it was limited to the progressive renal function decline group



FR-PO647

Effects of Hydrochlorothiazide and Amiloride on the Antialbuminuric Efficacy of Losartan in Patients with Diabetic Kidney Disease

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Background: The best strategy to slow progression of diabetic kidney disease (DKD) and reduce cardiovascular risk of DKD patients is controlling blood pressure (BP) and reducing albuminuria. The first line treatment for patients with DKD and hypertension is using renin-angiotensin-aldosterone system (RAAS) blockers. However, some DKD patients have persisted albuminuria after reaching the maximum tolerated dosage of RAAS blockers and proper BP control. Therefore, this study aims to prove an efficacy of alternative medicine which is a combination of HCTZ and amiloride (HCT+A) to reduce albuminuria apart from RAAS blockade therapy.

Methods: This prospective randomized, single blinded study assigned 75 patients with DKD, CKD stage 1-3 and urine albumin-to-creatinine ratio (UACR) > 300 mg/g received stable dosage of losartan during the last 3 months in Vajira hospital from 1 June 2016 to 31 January 2017. There were 39 cases received HCT+A group compared with 36 cases in placebo group. All patients were eligible to receive conventional therapy. The patients were followed for 4 weeks. The primary composite end point was the percent change in the median of UACR between the baseline and final value of each treatment period. The primary analysis was performed on the independent t test or Mann-whitney U test.

Results: The UACR showed a significant reduction with HCT+A 42.84% compared with placebo group – 7.95% (p < 0.001). There were a > 30% reduction in UACR in 24 patients (64.1%) treated with HCT+A and in 6 patients (16.7%) in placebo. The percentage of patients with >50% UACR reduction in the HCT+A group 16 patients (41%) compared with the placebo group (2 patients (5.6%)). Glomerular filtration rate (GFR), body weight decreased with HCT+A regimen. Blood pressure had no significant change after treatment. There was one patient developed severe hyperkalemia until stopped treatment.

Conclusions: The addition of HCTZ and amiloride to patients with DKD (CKD stage 1-3) with UACR > 300 mg/day on top Losartan induces a significant antialbuminuric effect and associated with the degree of GFR reduction.

Funding: Government Support - Non-U.S.

FR-PO648

Incremental Value of Renal Pathological Score to Kidney Failure Risk Equation in Advanced Diabetic Nephropathy

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Background: The Kidney Failure Risk Equation (KFRE) that enables to accurately predict end-stage renal disease (ESRD) in patients with chronic kidney disease (CKD) in stages 3 to 5 was developed and validated worldwide. We aimed to first assess the

performance of KFRE on individuals with biopsy proven diabetic nephropathy in advanced CKD stages at the time of biopsy and then evaluate the incremental value of pathologic information of renal biopsy to KFRE on them.

Methods: 296 individuals with biopsy proven diabetic nephropathy in CKD stages 3 to 5 at the time of biopsy was identified at four nephrology centers in Japan. Pathological classification was performed by three pathologists based on the Pathologic Classification of Diabetic Nephropathy. Individuals were randomly assigned to two cohorts (2:1 cohorts). The development cohort of 198 was used to validate the KFRE and to assess the incremental value of pathological score on diabetic nephropathy (D-score). Model performance was assessed by chi-squared test, Akaike information criterion, and Harrell's c-statistics. Incremental value of D-score to KFRE was evaluated with net reclassification improvement (NRI), integrated discrimination improvement (IDI), Integrated sensitivity (IS) and integrated specificity (IP). Validation of the models was performed in the validation cohort of 98.

Results: Median follow-up durations (25th, 75th percentiles) were 1.8 (1.0, 5.0) years and 2.0 (1.0, 3.8) years, respectively (p=0.89). Both KFRE and KFRE+D-score were significant predictors of ESRD in both the development cohort and validation cohort (Hazard Ratios of KFRE and KFRE+D-score in the development cohort were 2.44 (1.89-3.15) and 1.08 (1.04-1.13), and those in the validation cohort were 2.30 (1.57-3.38) and 1.08 (1.01-1.16), respectively). Incremental value of D-score using free cut-points showed positive overall NRI (0.5%; CI, 0.1-0.5%) but the IDI showed no significant change (0.0002; CI, -0.00007-0.0005). The KFRE+D-score model improved the both IS and IP but showed little differences.

Conclusions: KFRE worked well to identify individuals at high risk of ESRD in both the development and validation cohort. Adding pathological information to the KFRE improved the risk prediction of ESRD but did not statistically outperform the KFRE.

FR-PO649

The Effect of Ursodiol on Kidney Function: A Retrospective Case Series of Patients with Diabetic Kidney Disease Fabian Bock,[1] Moh'd Mohanad A. Al-Dabet,[2] Khurrum Shahzad,[2] Berend H. Isermann,[2] Talat Alp Ikizler.[1] *[1]Div of Nephrology&Hypertension, Dept. of Medicine, Vanderbilt University Medical Center, Nashvile, TN; [2]Dept of Clinical Chemistry and Pathobiochemistry, Otto-von-Guericke University, Magdeburg, Germany.*

Background: Experimental evidence suggests that bile acids are protective in diabetic nephropathy. *Ursodeoxycholic acid* (*UDCA, Ursodiol*) has been shown to attenuate renal damage in mouse models of diabetic nephropathy in part through reducing oxidative or ER stress. Ursodiol is in clinical use for the prevention of gall stone disease and in primary biliary cirrhosis (PBC) but clinical data on the effect on kidney function in patients with diabetic kidney disease (DKD) are lacking

Methods: We retrospectively screened Synthetic Derivative, a de-identified copy of over 2 million patient records at Vanderbilt University Medical Center for the following inclusion criteria: ICD9/10 code of diabetes with diabetic nephropathy, diabetic kidney disease or renal manifestation (diagnosed between 2000 and 2008), Ursodiol started for any indication (between 2010 and 2014) and serial eGFR assessments thereafter. Repeated measures ANOVA was used to examine the effect of Ursodiol on kidney function overtime.

Results: A total of 13 patients met the inclusion criteria. At inclusion, median age was 55 (30-72) years. The majority of cases was white (10/13) had hypertension (12/13) and were on ACEi or ARB (12/13) therapy. Gender distribution was equal. Five, one, five, two and zero patients had CKD Stage 1, 2, 3, 4, and 5, respectively. Median diabetes duration was 12 years, the median Ursodiol treatment duration was 1.25 (0.5-10) years and indications for Ursodiol included: gallstone prevention post bariatric surgery, cryptogenic cirrhosis or primary biliary cirrhosis. At 12 months after initiation of Ursodiol, 92% (12/13) patients had increased eGFR (p=0.02, compared to baseline). The mean eGFR (±SD) increase from baseline was 13.5 ± 18.4 ml/min/m^2 (median: 8.5 and 25-75 percentiles: 4.7-13.5).

Conclusions: This retrospective analysis showed a significant improvement in kidney function at 12 months after starting the bile acid Ursodiol in patients with diabetic kidney disease. While the results are limited by a small case number, the heterogeneity of clinical indications for Ursodiol and the number of potential confounding factors, there is precedent for prospective studies examining the use of Ursodiol as a potential treatment for amelioration of CKD progression in patients with DKD.

Funding: Other NIH Support - The Vanderbilt Synthetic Derivative database used in this study is supported by institutional funding and by the Vanderbilt CTSA grant ULTR000445 from NCATS/NIH.

FR-PO650

The Effects of Dapagliflozin on Urinary Metabolites in Patients with Type 2 Diabetes Michelle Pena,[1] Skander Mulder,[1] Manjula Darshi,[2] Benjamin F. Van espen,[2] Jiwan J. Kim,[2] Kumar Sharma,[2] Hiddo J. Lambers Heerspink.[1] *[1]University Medical Center Groningen, Groningen, Netherlands; [2]University of California San Diego, La Jolla, CA.*

Background: The cardiovascular and possibly kidney protective effects of SGLT2 inhibition are hypothesized in part due to improved mitochondrial function in the heart and kidney. To test this, we assessed the effects of dapagliflozin, an SGLT2 inhibitor, on a pre-specified panel of 13 urinary metabolites known to reflect mitochondrial function in patients with diabetes and elevated albuminuria.

Methods: Urine samples were used from a double-blind, randomized, placebo controlled crossover trial in 28 patients with type 2 diabetes, albumin/creatinine ratio >100 mg/g, and on a stable dose of an Angiotensin Converting Enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). Dapagliflozin and placebo treatment periods each lasted for 6 weeks. Urinary metabolites were quantified by gas-chromatography mass spectrometry, corrected for urinary creatinine, and combined into a single-valued index.

Results: Twelve of the 13 metabolites were detectable. At baseline, higher values of the metabolite index positively correlated with eGFR (pearson's r = 0.36, p = 0.05). Preliminary findings showed that after 6 weeks of dapagliflozin treatment, eight of the 12 metabolites were significantly increased from baseline. The metabolite index increased by 17% (95%CI: -3 – 49, p = 0.14) with placebo compared to 60% (26 – 102, p <0.001) with dapaglifozin. Accordingly, the placebo-adjusted effect was 45% (2 – 76, p = 0.03). Changes in the metabolite index during dapagliflozin treatment did not correlate with changes in HbA1c (r = 0.21, p = 0.28), eGFR (r = -0.16, p = 0.42), or albuminuria (r = 0.18, p = 0.37).

Conclusions: Dapagliflozin significantly increased a panel of mitochondrial metabolites previously associated with progressive diabetic kidney disease. These data suggest that SGLT2 inhibitors may improve mitochondrial function leading to kidney protection. Future studies of longer treatment duration and clinical outcomes are needed to confirm the clinical impact of these findings.

FR-PO651

Comparison between Liraglutide and Sitagliptin Effects on Cardiac Function in Diabetic Patients with Renal Failure Takeyuki Hiramatsu. *Konan Kosei Hospital, Konan Aichi, Japan.*

Background: Diabetes mellitus with renal failure (DM-CRF) is a progressive multifactorial disease associated with cardiovascular complications. To prevent progression of cardiovascular complications in DM-CRF, glycemic control is important. But in DM-CRF, using of anti-diabetic agents(ADAs) were limited. In this study, we examined the efficacy of liraglutide or sitagliptin to treat type 2 diabetes patients with renal failure.

Methods: Seventy two type 2 diabetes patients with renal failure (eGFR< 60mL/min/1.73m^2) were divided into two groups. Twenty four were used liraglutide 0.9 mg once a day (Group A), fourty eight were used sitagliptin 50mg once a day (Group B). ADAs were switched to these agents because of bad glycemic control. Moreover after that, all drugs were not changed during the study period. During 48 months of study period, we examined the blood pressure and renal function every three months. Echocardiography was examined at baseline and every 12 months after starting drugs to detect systolic and diastolic cardiac function.

Results: Hemoglobin A$_1$c, and systolic/diastolic blood pressure levels were gradually decreased in group A, but in group B was not. The eGFR value was not changed in both groups, however albuminuria was decreased significantly in both groups. Left ventricular ejection fraction(EF) was not changed during 48 months in both groups. But left atrial dimension(LAD) and tissue Doppler index(E/e') in group A were improved significantly. In group B, at 48 months after using agents, E/e' was worsened. No remarkable adverse events were seen in both groups.

Conclusions: These findings suggest that liraglutide and sitagliptin have similar effects on renal function, but according to cardiac diastolic function, liraglutide therapy is more beneficial for type 2 diabetes patients than sitagliptin therapy. Further studies with larger samples were needed to detect these effects.

Clinical Data

	Group A (n = 24)			Group B (n = 48)		
	at baseline	24 months	48 months	at baseline	24 months	48 months
eGFR (mL/min/1.73m^2)	35.9 ± 16.1	39.1 ± 20.8	35.6 ± 20.6	40.9 ± 15.6	40.8 ± 17.6	38.5 ± 18.5
Albuminuria(mg/day)	410.0 ± 270.9	330.9 ± 209.7	287.8 ± 187.0 *	349.8 ± 271.2	331.2 ± 265.3	296.3 ± 153.4 *
EF (%)	62.2 ± 12.1	67.1 ± 12.2	62.0 ± 9.7	67.2 ± 14.2	66.3 ± 16.2	65.1 ± 14.3
LAD (mm)	38.6 ± 6.3	35.6 ± 5.1 *	35.9 ± 3.6	35.4 ± 5.9	36.9 ± 5.7	37.6 ± 4.7 *
E/e'	15.1 ± 2.4	11.9 ± 2.0 **	13.1 ± 2.3 *	10.9 ± 2.0	11.9 ± 3.6	13.6 ± 4.4 **

*: P < 0.05, **: P < 0.01 vs. at baseline

In group A, diastolic funftion was improved, but in group B, was not.

FR-PO652

Metformin Use Does Not Increase Risk of Clinical Acidosis in Diverse Population of CKD Patients Rocco Ferrandino,[1] Tielman T. Van Vleck,[2] Jeremy S. Leventhal,[1] Bart Ferket,[1] Jaime Uribarri,[1] Girish N. Nadkarni,[1] Steven G. Coca.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Mount Sinai School of Medicine, New York, NY.*

Background: Metformin use in type 2 diabetes (T2D) patients with Stage 3a chronic kidney disease (CKD3a) has been cautioned because of concerns for associated metabolic acidosis. We used a large multiethnic urban cohort to assess both rates of acidosis and absolute difference in serum bicarbonate in new users of metformin compared to non-users.

Methods: We identified T2D with CKD3a from the Mount Sinai CKD Registry and propensity-matched metformin new-user: non-user pairs 1:1 on baseline data. We calculated incidence rate ratios (IRR) of acidosis (bicarbonate level ≤22 MEQ/L and serum anion gap (SAG)≥12) using negative binomial regression. We examined the longitudinal effect of metformin use on patient bicarbonate levels using linear mixed effect modeling.

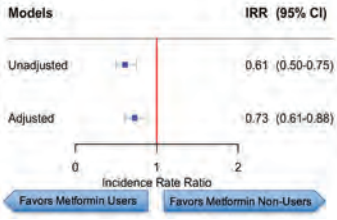
Results: We had data on 1494 patients (747 matched pairs). Median age was 74, 45.2% was male, baseline eGFR was 49.6. Baseline bicarbonate was similar in both metformin user (25.7 MEQ/L) and non-users (25.0 MEQ/L). Acidosis events in new metformin users and non-users were 13.8 and 23.0 events/100 patient years over follow up. Adjusted IRR over follow up were 0.73 (95% CI 0.61 – 0.88), respectively. The serum

bicarbonate over follow up was statistically higher but not clinically different in the user vs. non-user group (Difference= 0.18, SE=0.08, P=0.02).

Conclusions: In a large healthcare cohort of T2D patients with CKD3a, new prescription of metformin was not associated with either acidosis events or lower bicarbonate levels compared to non-users, suggesting that concerns for metformin associated lactic acidosis in this population may not be warranted.

Funding: Other NIH Support - 1TL1TR001434

A



B

	Non-User	New User	P
Events Per 100 Patient Years	23.0	13.8	
Bicarbonate	19.4 (2.2)	20.0 (1.8)	<0.001
Anion Gap	16.2 (3.3)	16.4 (3.0)	0.34

Figure 1. A. Unadjusted and adjusted IRRs for acidosis events are reduced in metformin users. B. Descriptive statistics of incidence and laboratory values during acidosis events.

FR-PO653

Presence of Kimmelstiel-Wilson Nodules in Diabetic Nephropathy Correlates with Duration of Diabetes and Poor Glycemic Control Monica Sircar, Ivy A. Rosales, Dihua Xu, Sahir Kalim, Ravi I. Thadhani. *MGH, Boston, MA.*

Background: Mesangial nodules are regarded as a major histologic correlate of diabetic nephropathy. However, whether there is an association between the presence of nodules with various stages of diabetic chronic kidney disease (CKD) is not known. Here we report clinicopathologic association between the presence of nodules in diabetic patients with varying stages of CKD.

Methods: All seventy-five available autopsy records and charts from 2013 to 2016 of type 1 and 2 diabetics were examined. Twenty-six patients had all necessary demographic data in their records, including age, sex, race, hemoglobin A1c level, duration of diabetes, hypertension status, at least 2 creatinine levels within the last six months prior to death, and treatment information. Archived autopsy kidney sections were reviewed by a pathologist blind to clinical data. Nineteen kidneys free of autolysis were systematically assessed for (i) percent global glomerulosclerosis, (ii) mesangial hypercellularity, (iii) percent glomeruli with nodules, and (iv) percent interstitial fibrosis.

Results: Mesangial nodules were present in diabetic patients with CKD II (50%, n=4), III (86%, n=7), IV (86%, n=7), and V (100%, n=1). Poor glycemic control, defined as HgbA1c ≥7.5% (Welch's t test p = 0.035), and duration of diabetes >10 years (p=0.036) showed strong associations with higher percent of nodules. Although a linear trend was evident, the correlation between percent of nodules and CKD stage was not statistically significant. The extent of glomerulosclerosis did not correlate with clinical factors such as age, sex, hypertension, treatment with RAAS blockade or longstanding diabetes.

Conclusions: The presence of nodules in diabetic kidneys showed significant associations with duration of diabetes >10 years and poor glycemic control. Mesangial nodules were present in kidneys of diabetic patients at all stages of CKD, with apparently more nodule formation in the later stages of the disease. These preliminary findings suggest a trend towards increased nodule formation as chronic kidney disease progresses. Together, our study suggests that diabetic nephropathy is associated with significant nodule formation, and the percentage of glomeruli with nodules may be a more definitive readout of CKD progression than determining just the presence or absence of nodules in glomeruli.

Funding: Private Foundation Support

FR-PO654

Lack of Diabetic Glomerulosclerosis in Patients with Longstanding Diabetic Complications Amy K. Mottl,[2] John M. Basgen,[5] Susan L. Hogan,[2] Susanne B. Nicholas,[4] J. Charles Jennette,[2] Ronald Klein,[3] Michael Mauer.[1] *[1]University of Minnesota, Minneapolis, MN; [2]University of North Carolina, Chapel Hill, Chapel Hill, NC; [3]University of Wisconsin-Madison, Madison, WI; [4]Department of Medicine, University of California, Los Angeles, CA; [5]Charles Drew University, Los Angeles, CA.*

Background: There is heterogeneity of renal complications in diabetes. We sought to determine the nephropathologic light microscopic characteristics and ultrastructural measurements in adults with type 2 diabetes undergoing research protocol kidney biopsy.

Methods: Inclusion criteria included type 2 diabetes ≥5 years duration, retinopathy and/or microalbuminuria or decreased estimated glomerular filtration rate (GFR) <60ml/min/1.73m^2. Nineteen participants (mean age 54y) underwent kidney biopsy, measured GFR using iohexol clearance, first morning void (FMV) urine albumin:creatinine ratio (UACR) and retinal photography. Nephropathologic characteristics were scored by a nephropathologist using usual methods. Stereologic ultrastructural parameters included glomerular basement membrane (GBM) thickness (measured using orthogonal methods) and fractional volume of mesangium (V/v(mes/glom). Typical diabetic glomerulosclerosis was diagnosed if V/v(mes/glom) exceeded 0.20 with GBM thickening (>470nm for women; >520nm for men). Predominant diabetic vasculopathy was diagnosed if V/v(mes/glom) was less than 0.20 in the presence of arterial hyalinosis and/or arteriosclerosis and GBM thickening. Arteriosclerosis without GBM thickening was attributed to nondiabetic arterionephrosclerosis.

Results: Results (see table) showed that 5 of 19 participants had nondiabetic arterionephrosclerosis, and while there were trends in the degree of albuminuria and retinopathy severity, this alone did not distinguish between diabetic and nondiabetic vasculopathy, nor the severity of vasculopathy.

Conclusions: Molecular studies aimed at deciphering between diabetic and nondiabetic complications will require research protocol kidney biopsies from patients with a wide spectrum of clinical disease characteristics.

Funding: NIDDK Support

	Age	Sex	Race/ Ethnicity	Diabetes duration	Global Sclerosis	GBM Width (nm)	Vv (mes/glom)	Arteriolar Hyalinosis	Arterio-sclerosis (0/1/2/3)	IFTA (0/1/2/3)	FMV UACR	Iohexol Clearance	Retinal Proliferation
Typical Diabetic Glomerulosclerosis:													
P1	46	F	NHB	17	0	859	0.549	1	1	1	2681	70	None
P2	48	F	Hispanic	21	2	652	0.465	2	2	1	1967	64	Severe
P3	38	F	NHB	19	0	684	0.344	3	1	1	154	109	Severe
P4	52	M	NHW	12	1	727	0.262	1	2	1	11	137	Severe
P5	63	M	NHW	23	2	546	0.329	2	1	3	383	81	Severe
P6	61	M	NHW	30	1	1075	0.396	3	2	1	170	89	None
P7	60	M	NHB	26	1	607	0.266	1	1	1	320	61	None
P8	47	F	NHB	13	2	584	0.349	0	2	2	156	132	Mild/Mod NPDR
P9	55	F	NHW	7	0	491	0.290	0	0	0	0	88	None
P10	61	M	Hispanic	22	0	507	0.233	1	1	1	7	127	None
P11	63	M	NHW	17	0	589	0.25	2	0	1	15	79	Mild/Mod NPDR
Predominant Diabetic Vasculopathy:													
P12	53	F	NHW	7	4	472	0.142	0	1	3	18	167	Mild/Mod NPDR
P13	56	M	NHW	16	0	528	0.167	0	1	0	97	178	None
P14	60	F	NHW	8	1	513	0.182	0	3	1	14	53	None
Nondiabetic Arteriosclerosis:													
P15	41	F	NHB	24	0	439	0.183	0	2	0	9	149	Mild/Mod NPDR
P16	36	F	NHB	23	0	401	0.192	1	3	0	54	94	None
P17	51	F	NHB	17	0	442	0.136	2	1	0	0	97	Mild/Mod NPDR
P18	64	F	NHB	13	4	467	0.160	0	3	3	91	83	None
P19	68	M	NHW	14	3	510	0.199	3	3	2	16	55	Severe

NHB=Non-Hispanic Black, NHW=Non-Hispanic White, IFTA=Interstitial Fibrosis and Tubular Atrophy, NPDR=Nonproliferative Diabetic Retinopathy

FR-PO655

Association between Severity of Diabetic Retinopathy and Renal Pathology or Renal Prognosis in Patients with Biopsy-Proven Diabetic Nephropathy in Type 2 Diabetes Mellitus Katsuhiko Morimoto,[1,2] Ken-ichi Samejima,[1] Masaru Matsui,[1] Tomoko Kanki,[1] Masatoshi Nishimoto,[1] Miho Tagawa,[1] Yasuhiro Akai,[1] Yoshihiko Saito.[1] *[1]First Department of Internal Medicine, Nara Medical University, Kashihara, Japan; [2]Department of Cardiology and Nephrology, Nara Prefecture General Medical Center, Nara, Japan.*

Background: Diabetic nephropathy and retinopathy are generally believed to develop concomitantly. However, much remains unclear about the association between renal pathology andretinopathy as renal biopsy is rarely indicated.

Methods: This is a retrospective observational study. Inclusion criteria were patients with type 2 diabetes, biopsy-proven diabetic nephropathy, and evaluation for retinopathy by ophthalmologists from 1984 to 2014. Exposure of interest was severity of retinopathy by the modified Davis and the Scheie Classification. Outcome variable was development of end-stage renal disease (ESRD). Statistical analyses were performed using Cox regression model. Correlation between severity of retinopathy and renal pathology were examined using Spearman's rank correlation.

Results: Data for 376 patients were available, Mean age was 57.5 years. Retinopathy was found in 168 (44.7%). During mean follow-up of 9.4 years, ESRD developed in 67. Renal prognosis was significantly poorer in the group with retinopathy. In terms of modified Davis classification, more severe retinopathy indicated poorer renal prognosis (log-rank p<0.001). In Cox regression analysis, severity of retinopathy was an independent risk factor for the development of ESRD (Table). Positive correlations with retinopathy were observed for diffuse glomerular lesions (ρ=0.48, p<0.001), nodular lesions (ρ=0.50, p<0.001), interstitial fibrosis and tubular atrophy (ρ=0.36, p<0.001), and arteriolar hyalinosis (ρ=0.34, p<0.001).

Conclusions: Only about half of patients with biopsy-proven diabetic nephropathy had retinopathy. The severity of retinopathy was an independent predictor of progression of nephropathy.

Relationship between diabetic retinopathy and ESRD (Cox regression)

	Adjusted HR	95% CI	P value
Non-proliferative retinopathy	3.51	1.68 to 7.64	<0.001
Preproliferative retinopathy	3.76	1.35 to 10.1	0.01
Proliferative retinopathy	15.5	6.33 to 38.9	<0.001

Covariates included age, sex, eGFR, systolic blood pressure, proteinuria (g/gCr), HbA1c.

FR-PO656

Collagen Type III Degradation Is Associated with Deterioration of Kidney Function in Patients with Type 2 Diabetes with Microalbuminuria Federica Genovese,[1] Tine Hansen,[3] Daniel Guldager Kring Rasmussen,[1,5] Signe Holm Nielsen,[1,4] Henrik Reinhard,[3] Hans-Henrik Parving,[2] Morten A. Karsdal,[1] Peter Rossing.[3,6] *[1]Nordic Bioscience, Herlev, Denmark; [2]Rigshospitalet, Copenhagen, Denmark; [3]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [4]Department of Biomedicine and Biotechnology, Technical University of Denmark, Kgs. Lyngby, Denmark; [5]Institute of Molecular Medicine, Cardiovascular and Renal Research, University of Southern Denmark, Odense, Denmark; [6]University of Copenhagen, Copenhagen, Denmark.*

Background: In diabetes one of the main features of the progression to diabetic kidney disease is a pathological deposition of extracellular matrix components triggering renal fibrosis. The main structural component of the fibrotic core is collagen. One of the most prominent collagens is collagen type III (COL III), which is excessively synthesized and incorporated into the fibrotic extracellular matrix. Multiple studies in both humans and mice have suggested that MMP-9 activity is increased in diabetic kidney disease. We investigated whether a neo-epitope fragment of COL III generated by MMP-9 (C3M) was associated with deterioration of kidney function in a well-characterised type 2 diabetic population with microalbuminuria and without symptoms of coronary artery disease.

Methods: The cohort included 200 participants, followed for 6.1 years. We measured C3M levels in serum (S-C3M) and urine (U-C3M) at baseline. To adjust for urine output levels of U-C3M were normalized for urinary creatinine. The investigated endpoint was a decline in eGFR of >30% (n=42). Cox proportional hazards regression analysis was performed for S-C3M and U-C3M both unadjusted and adjusted for traditional risk factors (sex, age, systolic blood pressure, LDL-cholesterol, smoking, HbA1c, creatinine and urinary albumin excretion rate). To assess whether S-C3M or U-C3M improved risk prediction beyond traditional risk factors we calculated the relative integrated discrimination improvement (rIDI).

Results: The hazard ratio per doubling of S-C3M was 3.00 (95% CI 1.52-5.90, p=0.002). When adjusted for traditional risk factors the hazard ratio per doubling of S-C3M was 2.84 (95% CI 1.35-5.97, p=0.006). Addition of S-C3M to a model containing traditional risk factors improved the relative discrimination by 19.8 percentage points (p=0.007). U-C3M was not associated with declining eGFR.

Conclusions: In conclusion, S-C3M was independently associated with decline in renal function, and added significant improved discriminatory power to a model containing traditional risk factors.

Funding: Commercial Support - Nordic Bioscience, Private Foundation Support

FR-PO657

Serum and Urine Markers of Collagen Type VI Formation (Pro-C6) and Type III Degradation (C3M) Reflect Renal Function in Type 1 Diabetes Tine Hansen,[6] Daniel Guldager Kring Rasmussen,[5] Sascha Pilemann-lyberg,[4] Signe Holm Nielsen,[3] Morten A. Karsdal,[5] Frederik Persson,[2] Simone Theilade,[1] Federica Genovese,[5] Peter Rossing.[2,7] *[1]Steno Diabetes Center Copenhagen, Hellerup, Denmark; [2]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [3]Nordic Bioscience A/S, Herlev, Denmark; [4]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [5]Nordic Bioscience, Herlev, Denmark; [6]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [7]University of Copenhagen, Copenhagen, Denmark.*

Background: Progression of diabetic kidney disease is associated with renal fibrogenesis and associated with increased extracellular matrix remodeling and release of collagen fragments in urine in progressive renal disease. We evaluated associations between kidney function and a marker of collagen type VI formation (Pro-C6) and a marker of collagen type III degradation (C3M) in type 1 diabetes.

Methods: Serum and urinary levels of Pro-C6 and C3M were measured with ELISA in 668 patients with type 1 diabetes. Kidney function was evaluated as eGFR (CKD-EPI) and urinary albumin excretion rate (UAER). We applied unadjusted and adjusted linear regression analyses. Adjustment included age, sex, LDL cholesterol, smoking, HbA_{1c}, systolic blood pressure, UAER (in analyses of eGFR) and eGFR (in analyses of UAER). To adjust for urine output levels, the urinary markers were normalized for urinary creatinine.

Results: Of the 668 patients, 368 (55%) were male, mean±SD age was 54.6±12.6 years and eGFR 81.6±25.5 ml/min/1.73m^2. Median (IQR) UAER was 17 (8-65) mg/g. Both higher serum and urinary levels of Pro-C6 were associated with lower eGFR (unadjusted: p<0.001; adjusted: p<0.001) and higher UAER (unadjusted: p<0.001; adjusted: p<0.001). Lower urinary levels of C3M were associated with lower eGFR (unadjusted: p<0.001; adjusted: p<0.001) and higher UAER in the unadjusted model (p<0.001), but significance was lost after adjustment (p=0.43). Higher serum levels of C3M were associated with lower eGFR (unadjusted: p<0.001; adjusted: p=0.001) and higher UAER (unadjusted: p<0.001; adjusted: p=0.007).

Conclusions: In type 1 diabetes, higher serum and urine levels of the collagen type VI formation marker Pro-C6 were associated with poorer kidney function. Moreover, higher serum levels and lower urine levels of the collagen type III degradation marker C3M were related to poorer kidney function. Longitudinal data are needed to clarify the predictive role of these markers.

Funding: Commercial Support - Nordic Bioscience A/S, Herlev, Denmark

FR-PO658

A Novel Marker of Collagen Type VI Formation Is Prognostic for Cardiovascular Disease, All-Cause Mortality, and Deterioration of Kidney Function in Patients with Type 2 Diabetes with Microalbuminuria Daniel Guldager Kring Rasmussen,[1,4] Tine Hansen,[3] Signe Holm Nielsen,[1,5] Henrik Reinhard,[3] Hans-Henrik Parving,[2] Morten A. Karsdal,[1] Federica Genovese,[1] Peter Rossing.[3,6] *[1]Nordic Bioscience, Herlev, Denmark; [2]Rigshospitalet, Copenhagen, Denmark; [3]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [4]Institute of Molecular Medicine, Cardiovascular and Renal Research, University of Southern Denmark, Odense, Denmark; [5]Department of Biomedicine and Biotechnology, Technical University of Denmark, Kgs Lyngby, Denmark; [6]University of Copenhagen, Copenhagen, Denmark.*

Background: Type 2 diabetes is a common risk factor for the development of renal fibrosis and chronic kidney disease (CKD). Recent findings have shown that type VI collagen (COL VI) is markedly upregulated during fibrosis. The role of COL VI has been sparsely investigated in fibrosis onset and progression. We evaluated a novel biomarker of COL VI formation as a prognostic marker for cardiovascular events, all-cause mortality, and decline in eGFR in patients with type 2 diabetes with microalbuminuria and without symptoms of coronary artery disease.

Methods: The cohort included 200 participants followed for 6.1 years. COL VI formation was assessed with the Pro-C6 assay, detecting a specific fragment of COL VI released upon deposition in the extracellular matrix. Pro-C6 levels were measured in serum at baseline. Endpoints included: 1) a composite of cardiovascular events (n=40); 2) all-cause mortality (n=26); and 3) decline in eGFR of >30% (n=42). Cox models were unadjusted and adjusted for traditional risk factors (sex, age, systolic blood pressure, LDL-cholesterol, smoking, HbA_{1c}, creatinine and urinary albumin excretion rate). Pro-C6 was assessed per doubling in the analysis. To assess if Pro-C6 improved risk prediction beyond traditional risk factors we calculated relative integrated discrimination improvement (rIDI).

Results: Levels of Pro-C6 were associated with an increased risk of cardiovascular events (unadjusted HR 2.65, 95% CI 1.47-4.79, p=0.0013; adjusted HR 2.32, 95% CI 1.08-5.01, p=0.032), all-cause mortality (unadjusted HR 3.95, 95% CI 1.98-7.86, p=0.0001; adjusted HR 6.98, 95% CI 3.06-15.9, p<0.0001), and decline in eGFR (unadjusted HR 3.00, 95% CI 1.72-5.21, p=0.0001; adjusted HR 2.67, 95% CI 1.21-5.89, p=0.015). Addition of Pro-C6 to a model containing traditional risk factors improved the rIDI by 14.5% (p=0.04) for cardiovascular events, 64.3% (p<0.001) for all-cause mortality, and 19.8% (p=0.007) for decline in eGFR.

Conclusions: In conclusion, Pro-C6 was associated with cardiovascular events, all-cause mortality, and decline in eGFR in patients with type 2 diabetes and microalbuminuria.

Funding: Commercial Support - Nordic Bioscience, Private Foundation Support

FR-PO659

A Novel Oxidative Stress Biomarker, APX-501 Protein as a Promising New Biomarker for Progression of Diabetic Nephropathy in Type 2 Diabetic Patients Ho jun Lee, Jin Joo Cha, Dae R. Cha, Young Sun Kang. *Korea University Medical College Ansan Hospital, Ansan city, Republic of Korea.*

Background: A large body of evidence indicates that oxidative stress is one of the most important mechanism link for the major pathways involved in the development and progression of diabetic vascular complications. Recently, we've identified that APX-501 protein was synthesized from renal cells, and found that APX-501 was involved in oxidative stress in the kidney. Therefore, we investigated the role of APX-501 as a new biomarker for diabetic nephropathy in type 2 diabetic patients.

Methods: Total 166 patients were enrolled and prospectively followed up for 6 months. Study patients were divided into four groups; 1) non-diabetic patients with nephrotic range of proteinuria (n=35), 2) type 2 diabetic patients with normoalbuminuria (n=34), 3) type 2 diabetic patients with microalbuminuria (n=26), 4) type 2 diabetic patients with overt proteinuria (n=71). Plasma level of APX-501 were measured at baseline and 6 months using ELISA. Addiitionally, we performed in vitro and in vivo experiment to further confirm the presence of APX-501 in diabetic nephropathy.

Results: Plasma APX-501 level was significantly higher in diabetic patients with microalbuminuria and overt proteinuria compared to non-diabetic patients with nephrotic range proteinuria and diabetic patients with normoalbuminuria. APX-501 level was positively correlated with systolic blood pressure, serum creatinine level and urinary albumin excretion. The level of APX-501 was significantly different after 6 months compared to the baseline in all diabetic patients, whereas there were no significant difference between the two time point in the level of microalbuminuria and proteinuria. The degree of increment of APX-501 were greater in patients with microalbuminuria and overt proteinuria. In cultured renal cells, high glucose and angiotensin II increased synthesis of APX-501 level. Gene silencing of APX-501 ameliorated high glucose-induced ECM synthesis and oxidative stress markers. in type 2 diabetic db/db mice, plasma level and renal expression of APX-501 was significantly increased in diabetic mice according to its age.

Conclusions: These findings suggest that APX-501 synthesis may be activated in early stage of diabetic environment, and may be increased according to the progression of diabetic nephropathy.

FR-PO660

What Is the Potential for RAAS Blockade Optimisation for Patients with Diabetic Kidney Disease in the Era of Potassium Binders? Stephanie Chong,[3,2] Katharine Pates,[3,1] Kieran Mccafferty.[3,2] *[1]Barts Health NHS Trust, London, United Kingdom; [2]NHS, LONDON, United Kingdom; [3]Royal London Hospital, London, United Kingdom.*

Background: Diabetes is the leading cause of renal failure in both worldwide and in the UK. For 2 decades RAAS blockade has been the cornerstone of management of diabetic kidney disease. Recent registry data suggest that RAAS dose maximisation is key to reduce population health care costs and improve outcomes. However, the use of RAAS blockade is often limited by hypotension or hyperkalaemia. Potassium binders may provide a novel strategy to safely enable dose maximisation of RAAS therapy, but it is unknown how many patients are not treated or sub-maximally treated due to fears of hyperkalaemia.

Methods: We performed a retrospective study, analysing our electronic patient record to establish how many patients were sub-maximally treated with RAAS therapy and the reasons for failure of dose maximisation. We included all adult patients with type 2 diabetes, in our tertiary renal unit which covers a population of 2.5 million ethnically diverse patients across North and East London. We excluded any patients due to commence dialysis imminently or already on renal replacement therapy and patients with secondary glomerular lesion or other clear cause of CKD.

Results: We identified 415 diabetic patients meeting the inclusion/exclusion criteria. We found that only 72% were on ACE or ARB therapy. Of these, only 50.3% were on maximum dose therapy. This means that only 37% of patients of the total cohort were on maximal RAAS therapy. The main limiting factors were hyperkalaemia (Potassium > 5.0mmol/L) in 30.8%, hypotension (BP < 120/70 and not on other blood pressure lowering agents) in 15.4%, both in 2.3% and dose was not maximised for no specified reason despite inadequate BP control and acceptable potassium levels in 51.3% of patients. Additional reasons found to explain the lack of dose maximisation in this group of patients, were historical hyperkalaemia, fear of new hyperkalaemia, progressive CKD or AKI.

Conclusions: Our study demonstrated the huge unmet potential for safe dose maximisation of RAAS therapy using potassium binders in a cohort of patients with diabetic kidney disease. We estimate that if these findings were extrapolated across the 3 million patients with diabetic kidney disease across the UK then almost 1 million patients may benefit from potassium binder enabled dose maximisation.

FR-PO661

Effect of Angiotensin Converting Enzyme (ACE) and Angiotensinogen (AGT) Gene Polymorphisms on the Anti-Proteinuric Efficacy of ACE Inhibitor Therapy in Patients with Type 2 Diabetes with Nephropathy Om P. Kalra,[6] Neerja Aggarwal,[7] Pawan K. Kare,[5] Parul Varshney,[9] Anil K. Yadav,[4] Alpana Raizada,[3] Ashok K. Tripathi,[8] Basu D. Banerjee,[2] Madhu V. S.[1] *[1]Medicine, University College of Medical Sciences, Delhi, India; [2]Biochemistry, University College of Medical Sciences and GTB Hospital, Delhi, India; [3]Medicine, University College of Medical Sciences, Delhi, India; [4]Medicine, GTB Hospital and University College of Medical Sciences, Delhi, India; [5]Biochemistry, University College of Medical Sciences, Delhi, India; [6]Nephrology, Pt. B.D. Sharma University of Health Sciences, Rohtak, India; [7]Biochemistry, University College of Medical Sciences, Delhi, India; [8]Biochemistry, University College of Medical Sciences, Delhi, India; [9]Biochemistry, University College of Medical Sciences, Delhi, India.*

Background: Diabetic nephropathy (DN) is the leading cause of chronic kidney disease worldwide and affects approximately 20-30% of diabetic patients. ACE inhibitor drugs are commonly prescribed for reno-protection; however, anti-proteinuric response is not uniformly observed in all patients. The aim of this study was to evaluate the role of genetic variants of ACE and AGT genes on the anti-proteinuric efficacy of ACE inhibitor therapy in patients with DN.

Methods: In the present study, 270 patients with Type 2 diabetes mellitus with nephropathy aged between 30 to 65 years and a duration of diabetes ≥5 years were enrolled and treated with ACE inhibitor (ramipril) and followed at regular intervals for 6 months for assessment of urinary albumin/creatinine ratio (ACR) and eGFR (MDRD). Patients were classified as responders when they had a decrease in urinary ACR ≥30% at the end of 6 month follow up. Genotyping of *ACE I/D* and *AGT M235T* polymorphisms were performed by using primer specific polymerase chain reaction and PCR-RFLP technique, respectively.

Results: An overall significant reduction in ACR 36.2% was observed in the whole group at the end of 6 months; however, macro-albuminuric patients (55%) showed better response to therapy as compared to micro-albuminuric patients (45%). Overall, 130 (48%) of patients with DN were found to be responders to ACEI. The frequency of ACE genotype II, ID and DD was found to be 31%, 53% and 16% respectively. The frequency of AGT genotype MM, MT and TT was found to be 25%, 53% and 22% respecively. A reduction in urinary ACR was found to be independent of genotypes of *ACE I/D* and *AGT M235T* polymorphisms although macro-albuminuric patients having TT genotype showed higher response (72%) although it was statistically not significant. eGFR decreased from the base line value of 73.65±24.71 ml per minute per 1.73 m^2 to 68.90±24.44 ml per minute per 1.73 m^2 at the end of 6 months (p<0.081).

Conclusions: ACE inhibitor therapy reduced urinary ACR by ≥ 30% in 48% of patients with diabetic nephropathy and macroalbuminuric patients exhibited better response. The anti-proteinuric response was found to be independent of *ACE I/D* and *AGT M235T* polymorphisms.

Funding: Government Support - Non-U.S.

FR-PO662

Relationship between Transition in CKD Category and Renal Outcome in Japanese Type 2 Diabetic Patients with Biopsy-Proven Diabetic Nephropathy Tomoaki Funamoto, Miho Shimizu, Tadashi Toyama, Shinji Kitajima, Kengo Furuichi, Takashi Wada. *Division of Nephrology, Kanazawa University Hospital, Kanazawa, Japan.*

Background: We examined the association between transition in chronic kidney disease (CKD) category over 5 years and 10 years after renal biopsy and renal outcome in Japanese type 2 diabetic patients with biopsy-proven diabetic nephropathy.

Methods: Based on up to 5 years and 10 years observation after renal biopsy, we determined transition in CKD category. We first evaluated the association of renal composite events (requirement of dialysis, or a 50% decline in estimated glomerular filtration rate (eGFR) from baseline (at the time of renal biopsy)) with progression of CKD categories over 5-years (n=54) and 10-years (n=54) after renal biopsy in patients with normo-/microalbuminuria with eGFR ≥ 15 mL/min per 1.73m^2. We subsequently evaluated the association of renal composite events with remission of macroalbuminuria to normo-/microalbuminuria over 5-years (n=58) and 10-years (n=42) after renal biopsy in patients with macroalbuminuria.

Results: (1) In the 5-year analysis in patients with normo-/microalbuminuria with eGFR ≥ 15 mL/min per 1.73m^2, 8 patients showed progression of albuminuria stage, whereas 9 patients showed progression of eGFR stage. The corresponding numbers in the 10-year analysis were 12 patients and 16 patients, respectively. Cumulative incidences of renal composite events in patients with progression of albuminuria stage and eGFR stage were higher than no progression. The risk for renal composite events was associated with progression of albuminuria stage rather than eGFR stage. The progression of albuminuria was associated with nodular lesions, whereas the progression of eGFR stage was associated with diffuse lesions. (2) In the 5-year analysis, 10 patients showed remission of macroalbuminuria. The corresponding number in the 10-year analysis was 16 patients. Cumulative incidences of renal composite events in patients with remission were lower than no remission. In the 10-year analysis, remission was a determinant for renal composite events. Low urinary protein excretion at renal biopsy and female were the determinants for remission.

Conclusions: Our study suggests that transition in CKD category over 5-years and 10-years as well as diabetic kidney lesions add significant prognostic information about risk for renal outcome in type 2 diabetes.

FR-PO663

Is Urinary KIM-1 a Predictor of EGFR Decline, Incident Cardiovascular Disease, and All Cause Mortality? Mie K. Eickhoff,[3] Bernt Johan Von Scholten,[1] Henrik Reinhard,[4] Tine Hansen,[3] Frederik Persson,[3] Hans-Henrik Parving,[2] Peter Rossing.[5] *[1]Novo Nordisk A/S, Soborg, Denmark; [2]Rigshospitalet, Copenhagen, Denmark; [3]Steno Diabetes Center, Gentofte, Denmark; [4]Steno Diabetes Center A/S, Gentofte, Denmark; [5]Steno Diabetes Center Copenhagen, Gentofte, Denmark.*

Background: Urinary levels of kidney injury molecule 1 (KIM-1) has shown to reflect tubular pathophysiology. We evaluated KIM-1 as a predictor of decline in estimated glomerular filtration rate (eGFR), incident cardiovascular disease (CVD) and all-cause mortality in patients with type 2 diabetes (T2D) and microalbuminuria without clinical coronary artery disease.

Methods: We performed a prospective study including 200 patients, all receiving multifactorial treatment. Urinary KIM-1 was measured at baseline and was available in 191 patients. Adjusted Cox models included sex, age, LDL cholesterol, smoking, HbA_{1c}, creatinine, systolic blood pressure and urine albumin excretion rate (UAER). A decline in eGFR of >30%, which has recently been suggested as a valid renal outcome, at any time point during follow-up was the predefined endpoint of CKD progression. Hazard ratios (HR) are provided per 1 SD increment of log-transformed values of the urinary biomarker.

Results: Patients were (± SD) 59 ± 9 years old, eGFR 91.1 ± 18.3 ml/min/1.73m^2 and UAER (IQR) 103 (39–230) mg/24-h. During a median 6.1 years follow-up, there were 40 incident CVD events and 26 deaths and a total of 42 patients reached the predefined CKD progression endpoint after 4.9 years (median). Higher urinary KIM-1 was a predictor of eGFR decline, unadjusted HR (95% CI): 1.9 (1.2-2.8); p=0.003, and in the adjusted model HR 1.7 (1.0-2.7); p=0.034. For CVD events urinary KIM-1 was a determinant in the unadjusted model (HR 1.4 (1.0-2.1); p=0.04) but not in the adjusted model (HR 1.4 (1.0-2.1); p=0.08), and of all-cause mortality in unadjusted (HR 2.0 (1.2-3.2); p=0.008) and adjusted (HR 2.3 (1.2-4.1); p=0.008) models.

Conclusions: In patients with T2D and microalbuminuria receiving multifactorial treatment, urinary KIM-1 was independently associated with deterioration in renal function and all-cause mortality.

FR-PO664

IL-6 Assessment as a Non-Traditional Risk Factor for Cardiovascular Risk and Hospital Admission in Type 2 Diabetes Patients with Diabetic Nephropathy Ana P. Pimentel,[1] Filipa B. Mendes,[1] Luisa H. Pereira,[1] Ana P. Silva,[2] Pedro L. Neves.[3] *[1]Centro Hospitalar do Algarve, Faro, Portugal; [2]Hospital de Faro E.P.E, Faro, Portugal; [3]Nephrology, CHA, Faro, Portugal.*

Background: Oxidative stress and inflammatory cytokines in diabetic nephropathy are major triggers regarding the development of microvascular complications of type 2 diabetes. Interleukin-6 (IL-6) is one proinflammatory cytokine, implicated in the pathogenesis of diabetic nephropathy where vascular inflammation and fibrosis are the rule with influence on the development of cardiovascular disease. The aim of this study is to verify the relationship between plasmatic IL-6 and non-traditional cardiovascular risk factors, inherent comorbidities, mineral metabolism parameters, insulin resistance score of type 2 diabetic (DM) patients with nephropathy and hospital admissions due to ischemic heart disease (IHD).

Methods: Retrospectively data from a cohort of 175 type 2 DM patients followed in an outpatient clinic from January 2008 to August 2011 were obtained, including Homeostatic Model Assessment (HOMA) for insulin resistance, homocysteine, fibrinogen and brain natriuretic peptide (BNP) levels and Charlson Comorbidity Index (CCI) was calculated. The patients were divided into groups using serum IL-6. Group 1 (N=113) was defined as having IL-6 <4.9pg/mL and group 2 (N=62) had IL-6 ≥4.9pg/mL.

Results: Statistically significant differences were found between the groups (p<0,003) with higher values of IL-6 being associated with greater CCI, higher phosphorus and PTH level, but also HOMA, BNP, diastolic pressure and albumin-creatinine ratio. CCI (OR 3.714 95% CI (1.6-8.2) p=0.001) and IL-6 (OR 1.5 95% CI (1.104-2.486) p=0.015) were predictive factors in terms of hospital admission for IHD, and using a generalized linear model, higher values of IL-6 were predictive for acute coronary syndrome (ACS) (Wald=0.1219; CI 95% (0.14-0.59) p=0.01) with an AUC=0.79, p=0.0001.

Conclusions: In type 2 diabetic patients, elevated serum levels of IL-6 are associated with the presence of non-traditional cardiovascular risk factors, as well as higher insulin resistance, worst mineral metabolism parameters and more comorbidity. In our cohort study, IL-6 levels were predictive of ACS and hospital admission for IHD.

FR-PO665

The Expression of Serum lncRNA GAS5 and miR-21 ceRNA Associated with Clinical and Pathological Changes in Patients with Diabetes and Diabetic Nephropathy Qiuling Fan. *Department of Nephrology, The First Hospital, China Medical University, Shenyang, China.*

Background: To analyze the expression of serum lncRNA GAS5 and miR-21 in patients with diabetes mellitus and diabetic nephropathy, and to analyze the correlation between the expression of them and the clinical and pathlogical parameters, and to testify the function of them in the pathogenesis of diabetes mellitus and diabetic nephropathy, in order to find novel therapeutic targets and biomarkers.

Methods: The patients were divided into three groups, diabetic nephropathy group: patients proven by renal biopsy, diabetes group: patients with diabetes of normal Urine albumin creatinine ratio, normal control group. The expression of lncRNA GAS5 and miR-21 in serum samples were detected by real-time quantitative PCR. The correlation of serum lncRNA GAS5 and miR-21 expression with the clinical parameters were analyzed.

Results: The expression of serum lncRNA GAS5 was significantly down-regulated and the expression of serum miR-21 was significantly up-regulatedin in diabetes mellitus and diabetic nephropathy patients comparing with the normal control group. The expression of serum miR-21 was gradually up-regulated (P=0.038) along with the progression of renal biopsy stage IIb-IV of DN. FBG and HbA1cwere significantly negatively correlated with serum lncRNA GAS5, and FBG was independently correlated with serum lncRNA GAS5. urine microalbumin, TC, Cr, Urea(r=0.516,P<0.001) and SBP were significantly positively correlated with serum miR-21. ALB and eGFRwere significantly negativly correlated with serum miR-21, and ALB was independently correlated with serum miR-21. The diagnostic efficiency of serum lncRNA GAS5, miR-21 and lncRNA GAS5/miR-21 as "diagnostic signature" for DM were good, for lncRNA GAS5, AUC=0.7302, p=0.03, cutoff point was 0.0056, sensitivity was 62.86%, specificity was 77.78%; for miR-21, AUC=0.8397, p=0.002, cutoff point was 0.6600, sensitivity was 77.14%, specificity was 77.78%. The diagnostic efficiency of serum miR-21 and lncRNA GAS5/miR-21 as "diagnostic signature" for DN were good, for miR-21, AUC=0.9179, p<0.0001, cutoff point was 0.9900, sensitivity was 76.00%, specificity was 94.74%.

Conclusions: Serum lncRNA GAS5 and miR-21 expression can be used as noninvasive diagnostic marker for diabetes and diabetic nephropathy.

FR-PO666

Reduced Sublingual Endothelial Glycocalyx in Type 1 Diabetic Patients with Diabetic Nephropathy Signe Abitz Winther,[1,2] Marie Frimodt-møller,[1] Emilie Hein Zobel,[1] Tine Hansen,[1] Peter Rossing.[1,3] *[1]Steno Diabetes Center Copenhagen, Gentofte, Denmark; [2]Novo Nordisk A/S, Maaløv, Denmark; [3]University of Copenhagen, Copenhagen, Denmark.*

Background: Glycocalyx is a glycoprotein layer that lines and protects the capillary endothelium. Damage to the glycocalyx may be an early stage in development of microvascular complications in diabetes. Insight into the function and thickness of glycocalyx in vivo, has been limited by the lack of easy and non-invasive quantification tools. With capillaroscopy it is possible to visualize the sublingual capillaries by sidestream dark field imaging and estimates the dimensions of the glycocalyx by measuring the perfused boundary region (PBR). We evaluated the glycocalyx thickness non-invasively in type 1 diabetic patients with different levels of historical and current albuminuria.

Methods: Cross-sectional study including 77 type 1 diabetic patients stratified by history of normoalbuminuria (<30 mg/g;n=26), microalbuminuria (30-299 mg/g;n=27) and macroalbuminuria (>300 mg/g;n=24). Glycocalyx thickness was assessed by 5 measurements with the GlucoCheck device (GlucoCheck BV, The Netherlands), a non-invasive hand-held microscope generating video recordings of the sublingual capillaries. Endothelial glycocalyx thickness was estimated from the PBR in capillaries with a diameter range of 5-25 μm. Higher PBR indicates smaller glycocalyx width. Urinary albumin-to-creatinine ratio (UACR) was measured in 3 morning samples.

Results: In normo-, micro-, and macroalbuminuric patients PBR was (mean±SD) 2.30±0.22 μm, 2.32±0.25 μm, and 2.49±0.35 μm, respectively. Differences between normo- and macroalbuminuric patients (p=0.020) and micro- and macroalbuminuric patients (p=0.042) were significant, but the difference between normo- and microalbuminuric patients was not (p=0.74). After adjustment for age, sex, HbA_{1c}, diabetes duration and systolic blood pressure, differences between normo- and macroalbuminuric patients (p=0.018) and micro- and macroalbuminuric patients (p=0.004) remained significant. In pooled (n=77) multivariate linear regression, higher level of current UACR was associated with a higher PBR (p=0.0007).

Conclusions: In type 1 diabetic patients with a history of macroalbuminuria, measurements with the non-invasive GlucoCheck device revealed significantly higher PBR, suggesting an impaired glycocalyx, compared to patients with normo- or microalbuminuria. Moreover, higher current level of albuminuria was associated with higher PBR.

Funding: Private Foundation Support

FR-PO667

Automatic Data Analysis for Standardization of Renal Diffusion Tensor MRI Keren Doenyas-Barak, Shai Efrati. *Asaf-Harofhe MC, Zerifin, Israel.*

Background: Diffusion tensor MRI (DTI) noninvasively evaluates renal microstructure, especially fibrosis. DTI parameters and creatinine clearance have shown good correlation. However, neither a uniform technique for data analysis nor standard values exists. DTI is analyzed using manual selection of regions of interest (ROIs). Subjectivity of operator's interpretation and poor reproducibility limit the clinical value of this technique. We evaluated standard protocols for renal DTI quantification.

Methods: Twelve adults with diabetic kidney disease, defined as eGFR<60 ml/min/1.73m2 or proteinuria, and 5 healthy volunteers were scanned in a 3T Siemens scanner. Data were analyzed using 3 definitions of ROI: Manual selection of ROI based on intensity: Four circle ROIs are placed on high and low signal intensity regions of the 4 anatomical slices to define the medulla and cortex, respectively. Automatic ROI selection: The cortex was defined as 5-10 mm from the external margin of the kidney and the medulla as the region from the internal margin of the cortex to the inner margin of the kidney of 4 slices. Fiber tracking: DTI fiber-tracking was performed on 4 coronal slices of the kidney medulla, reconstruction kidney fibrils. Fiber volume, calculated as a percent of the whole kidney volume, was extracted in 5 fractional anisotropy (FA) thresholds: 0.1-0.2.

Results: Mean age was 65.9 years (60.5-70.7) and mean eGFR 62.9 ml/min/1.73m2 (37.1-83.5). The mean cortical apparent diffusion coefficient (ADC) and FA were 0.0029(0.0026-0.0032) and 0.165(0.152-0.184) using manual ROI selection, and 0.0024 (0.0026-0.0029) and 0.175(0.172-0.196) using automatic selection. Respective values for medullary ADC and FA were 0.0028 (0.0026-0.0029) and 0.175(0.160-0.196); and 0.0022(0.0021-0.0034) and 0.023(0.126-0.182). A strong correlation with eGFR was demonstrated for medullary ADC and FA (r=0.748 and r=0.657 p<0.05) and for cortical ADC (r=0.617 p<0.05) using automatic ROI selection, but only for medullary FA using manual ROI selection (r=0.678 p<0.05). Fiber tracking at FA thresholds of 0.12, 0.15 and 0.17 showed a strong correlation with eGFR (r=0.783, 0.787, 0.712 p<0.05 for all).

Conclusions: Objective data analysis using anatomic ROIs or fiber tracking strongly correlate to renal function and may be used for standard analysis of renal DTI.

FR-PO668

Safety of Liraglutide versus Placebo in Patients with T2D and CKD in the LEADER Trial Johannes F. Mann,[6] Vivian A. Fonseca,[5] Ofri Mosenzon,[1] Itamar Raz,[2] Helle Frimer-Larsen,[4] Bernt Johan Von Scholten,[4] Thomas Idorn,[4] Neil Poulter.[3] *[1]Hadassah Hebrew University Hospital, Jerusalem, Israel; [2]Hadassah Hebrew University Hospital, Jerusalem, Israel; [3]Imperial College, London, United Kingdom; [4]Novo Nordisk A/S, Soborg, Denmark; [5]Tulane University Medical Center, New Orleans, LA; [6]KfH Kidney Center, Munich, Germany. Group/Team: On behalf of LEADER Trial Steering Committee and Investigators .*

Background: We assessed the safety of liraglutide vs placebo (PBO) in patients with chronic kidney disease (CKD) in the LEADER trial.

Methods: LEADER was a randomized, double-blind, multicenter, placebo-controlled cardiovascular (CV) outcome trial assessing CV and long-term safety of liraglutide up to 1.8mg/day vs PBO plus standard of care for 3.5-5 years in 9340 type 2 diabetes (T2D) patients at high risk for CV disease. We stratified participants according to baseline estimated glomerular filtration rate (eGFR) <60 (with CKD) or ≥60ml/min/1.73m^2 (without CKD) and analyzed: serious adverse events (SAEs), SAEs leading to discontinuation, acute renal failure, nausea leading to discontinuation, acute gallstone disease, severe hypoglycemia and foot ulcers.

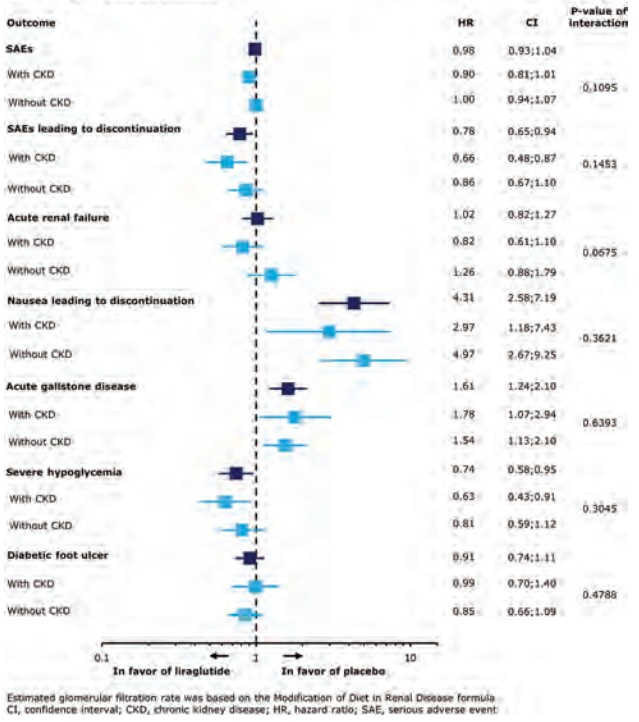
Results: Mean eGFR in patients with (n=2158) or without CKD (n=7158) was 45.7 ±10.9 and 90.8±21.6mL/min/1.73m^2, respectively. There was no increased risk of SAEs or SAEs leading to discontinuation with liraglutide vs PBO in those with and

without CKD (Fig); and no conclusive risk of acute renal failure in those with CKD (hazard ratio [HR] 0.82, confidence interval [CI] 0.61;1.10) or without CKD (HR 1.26, CI 0.88;1.79) with liraglutide vs PBO. There was no difference in the risk of nausea leading to discontinuation or acute gallstone disease in patients with and without CKD. Severe hypoglycemia risk was significantly reduced with liraglutide by 37% (with CKD, HR 0.63, CI 0.43;0.91) and non-significantly reduced by 19% (without CKD, HR 0.81, CI 0.59;1.12). Diabetic foot ulcer risk was not increased with liraglutide in those with and without CKD (Fig).

Conclusions: In LEADER, liraglutide was as well tolerated in patients with CKD as in those without CKD.

Funding: Commercial Support - Novo Nordisk A/S

Figure: Risk of selected adverse events with liraglutide vs placebo according to CKD at baseline



Estimated glomerular filtration rate was based on the Modification of Diet in Renal Disease formula
CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; SAE, serious adverse event

FR-PO669

Renal Histology Does Not Predict Progression of Diabetic Nephropathy Paraish S. Misra,[2] Adriana Krizova,[3] Richard E. Gilbert,[1,4] Darren A. Yuen.[1,4] *[1]Keenan Research Centre for Biomedical Sciences, St. Michael's Hospital, Toronto, ON, Canada; [2]University of Toronto, Toronto, ON, Canada; [3]St Michael's Hospital, Toronto, ON, Canada; [4]Faculty of Medicine, University of Toronto, Toronto, ON, Canada.*

Background: The ability to predict renal disease progression in diabetes remains limited, despite the identification of well-established risk factors including glycemic control, blood pressure, and albuminuria. The consensus pathologic classification system developed by the Renal Pathology Society (RPS) was designed to assist clinical and research assessment of diabetic nephropathy. While some reports have suggested that the RPS classification correlates with disease progression, its predictive potential has not yet been completely evaluated. Our aim was to determine the relationship between the RPS score and progression of diabetic renal disease.

Methods: Slope of estimated glomerular filtration rate (eGFR) decline was calculated for patients with biopsy-proven diabetic kidney disease, and correlated with RPS histologic classification scores. Results were adjusted for baseline eGFR and urine albumin-to-creatinine ratios (ACR) at the time of biopsy. Additionally, the correlation between slope of eGFR decline and histologic and clinic parameters was assessed, and renal survival curves (time off dialysis) were generated for subgroups of ACR, eGFR, and histology scores.

Results: 26 patients with biopsy-proven diabetic kidney disease and at least 6 months of eGFR follow-up data were identified among 394 biopsies performed at St. Michael's Hospital between 2011 and 2016. While renal survival was significantly worse with increasing glomerular and interstitial fibrosis/tubular atrophy scores ($p < 0.0001$ and $p = 0.0124$, respectively), patients with higher fibrosis scores had lower eGFR at the time of biopsy ($r = -0.6623$, $p = 0.0002$). Slope of eGFR decline did not correlate with either histologic classification or baseline clinical parameters on univariate or multivariate analyses.

Conclusions: Beyond establishing the diagnosis of diabetic nephropathy, our results suggest that renal biopsy does not provide any additional information regarding the rate of disease progression. While patients with higher fibrosis scores on biopsy tended to have poorer renal survival, such individuals also had lower baseline eGFR. Importantly, histologic scores did not correlate with future changes in eGFR. Larger studies are needed to confirm these observations.

Funding: Private Foundation Support

FR-PO670

Low Estimated Glomerular Filtration Rate (eGFR < 60 ml/min/1.73 m2) with Albumin-to-Creatinine Ratio [ACR)] <30 mg/g Is Associated with Increased Mortality Risk in Diabetics Holly J. Kramer,[1] R. E. Boucher,[3] Guo Wei,[2] Alfred K. Cheung,[3] William C. Cushman,[4] Srini Beddhu.[3] *[1]Loyola University Medical Center, Maywood, IL; [2]University of Utah, Salt Lake City, UT; [3]University of Utah School of Medicine, Salt Lake City, UT; [4]Memphis VA Medical Center, Memphis, TN.*

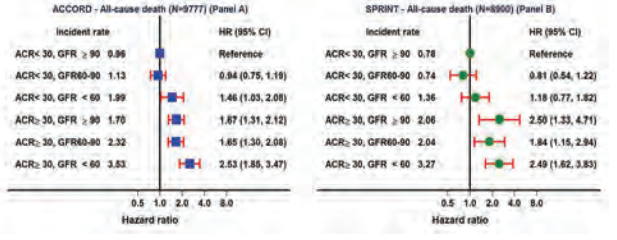
Background: Prevalence of low eGFR (< 60 ml/min/1.73 m^2) with an ACR < 30 mg/g is increasing, especially among adults with diabetes, likely due to better management of chronic kidney disease (CKD) risk factors. Determining the association between CKD phenotypes including low eGFR with ACR < 30 mg/g in adults with and without diabetes may help guide prevention efforts to reduce CKD associated morbidity and mortality.

Methods: We examined unadjusted mortality rates by CKD phenotype (based on eGFR and ACR grouops) using data from the Action to Control Cardiovascular Disease (ACCORD), which included 9777 adults with diabetes, and the Systolic Blood Pressure Intervention trial (SPRINT), which included 8900 adults without diabetes. Cox proprortional hazards models were used to calculate the hazard ratio of mortality by CKD phenotype in these two study populations with simultaneous adjustment for demographics, blood pressure and prevalent cardiovascular disease with the eGFR ≥90 ml/min/1.73 m^2 and ACR < 30 mg/g as referent group.

Results: The mean age was 62.8 (6.7) and 67.9 (9.4) years in ACCORD and SPRINT, respectively. In the ACCORD and SPRINT trials, mortality rates in the group with eGFR < 60 ml/min/1.73 m^2 and ACR < 30 mg/g were 1.99 and 1.36 deaths per 100 person-years, respectively. After adjustment for covariates, presence of eGFR < 60 ml/min/1.73 m^2 with ACR < 30 mg/g was associated with a 1.58-fold higher hazard rate for mortality (95% CI 1.19, 2.10) relative to eGFR ≥ 90 ml/min/1.73 m^2 with ACR < 30 mg/g in ACCORD. No significant association was noted with this CKD phenotype and mortality in SPRINT (hazard ratio 1.17; 95% CI 0.76, 1.80) (see Figure).

Conclusions: Low eGFR with ACR < 30 mg/g is associated with increased mortality risk in adults with diabetes. These data demonstrate the need to identify and implement interventions that reduce mortality in adults with diabetes and CKD, including those without albuminuria.

Funding: NIDDK Support



Hazard ratios for mortality by CKD phenotypes in ACCORD (panel A) and SPRINT (panel B)

FR-PO671

Urine sCD163 Is a Biomarker of Active Nephrotic Syndrome Sarah M. Moran,[2] Dearbhaile Dooley,[2] Matthias Kretzler,[1] Mark A. Little.[2] *[1]U.Michigan, Ann Arbor, MI; [2]Trinity Health Kidney Centre, Trinity College, Dublin, Ireland. Group/Team: Neptune Nephrotic Syndrome Study Network.*

Background: Prior work has demonstrated that urinary soluble CD163 (usCD163) displays excellent biomarker characteristics for detection of active renal vasculitis in patients with ANCA-associated vasculitis and Lupus. We sought to assess the levels of usCD163 in active and remission nephrotic syndrome.

Methods: Patients with biopsy proven nephrotic syndrome (Minimal change (MCD), focal and segmental glomerulosclerosis (FSGS) and membranous glomerulonephritis (MN) were included. Paired urine samples from time of remission (urine protein creatinine ratio (uPCR) <0.5mg/mmol) and of active nephrotic syndrome (uPCR >3.5mg/mmol) were selected from NEPTUNE a multicentre longitudinal cohort. Creatinine-normalised usCD163 levels were measured in urine by ELISA.

Results: 53 patients were included (MN n=22, MCD n=20, FSGS n=11). Median age at onset of NS was 34.5 years (IQR 13.5-59.8 yrs), median eGFR was 77.3mls/min/1.73m^2 (SD ±30.3mls/min/1.73m^2). Median usCD163 levels were higher in active nephrotic syndrome (536.3ng/mmol (IQR 222.7-1061 ng/mmol))) compared to remission (0.9ng/mmol (IQR 0-19.6 ng/mmol), $p<0.0001$) with median values in active FSGS of 372.9ng/mmol (IQR 151.4-639mg/mmol), active MCD of 539.2ng/mmol (IQR 114.3-1511/mmol), and active MN of 604.2ng/mmol (IQR 305.8-1423/mmol), $p=0.417$. (figure 1A). uProtein:Creatinine Ratio and usCD163 levels were significantly correlated with a low correlation coefficient – in active NS $r^2=0.14$, $p=0.006$ (figure 1B).

Conclusions: usCD163 levels are markedly elevated in active nephrotic syndrome. 14% of the observed variance in usCD163 was explained by total urine protein excretion. This suggests that, although some of the measurable usCD163 in urine of patients with

nephrotic syndrome is due to leak across the GBM, most appears to be derived directly from the glomerular immune process.

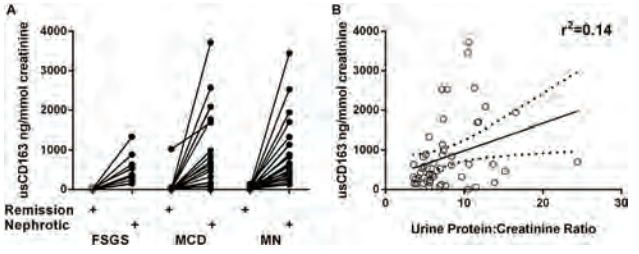


Figure 1A: usCD163 levels in remission and active nephrotic syndrome. FSGS=focal and segmental glomerulosclerosis, MCD=minimal change disease, MN= membranous glomerulonephritis. Figure 1B: Correlation between urine protein creatinine ratio and usCD163 in active nephrotic syndrome.

FR-PO672

Urinary CD80 as a Biomarker for Nephrotic Syndrome Marie C. Hogan,[2] Anatilde M. Gonzalez guerrico,[1] Adam M. Wright,[1] Jonathan P. Troost,[3] Fernando C. Fervenza,[1] John C. Lieske,[1] George G. Klee.[1] *[1]Mayo Clinic, Rochester, MN; [2]Mayo Clinic, Rochester, MN; [3]University of Michigan, Ann Arbor, MI.*

Background: The immune system appears to play a significant role in the pathogenesis of certain nephrotic syndrome (NS) patients with minimal change disease (MCD) and focal segmental glomerular sclerosis (FSGS). CD80/B7-1, a co-stimulatory receptor expressed on activated antigen presenting cells, has been implicated in certain cases. However, CD80 assays have suffered from lack of sensitivity and specificity.

Methods: Use a newly-validated ELISA to determine association of urinary CD80 with renal histology and disease status in biopsy proven MCD, FSGS, or other renal diseases (lupus nephritis, diabetic nephropathy, IgA, membranous nephropathy (MN), or polycystic kidney disease. We modified commercial CD80 ELISAs assays to increase sensitivity (biotinyl tyramide amplification) and analytically validated the assay for urine (uCD80). Cases were recruited from the Mayo and NEPTUNE cohorts(Table). Data is expressed as (mean, median (IQR)) and analyzed by t-test or GEE.

Results: uCD80 levels associated with MCD and FSGS compared to other pathologies, and also was higher in disease relapse (table). Using a GEE model of CD80 levels in all diagnsoses versus MCD we observed strong separation by disease type (MN β= -269; CI -469 to-69; p<0.01; FSGS β=-228, CI -429 to-27, p=0.03; IgA β=-289; CI-489 to-89, p<0.01).

Conclusions: Our results confirm that uCD80 excretion correlates with MCD and FSGS disease status. Further study (ongoing) is warranted to determine whether uCD80 is a useful biomarker for diagnosis, prognosis, and predictor of response to immunosuppression. These results also suggest that uCD80 may reflect immune pathways involved in the pathogenesis of certain MCD and FSGS cases, and further research is needed to understand its cellular source.

Funding: NIDDK Support, Commercial Support - Bristol -Myers-Squibb

Table 1. Description of MCD and FSGS and comparison cohort samples

	Remission			Relapse			
	n	CD80/Creat	UP/Creat	n	CD80/Creat	UP/Creat	p
Paired samples							
MCD	23	44 (22 to 103)	0.1 (0.02 to 0.2)	23	141 (83 to 232)	6.9 (3.3 to 11.7)	<0.01
FSGS	16	26 (9 to 75)	0.4 (0.1 to 0.9)	16	90 (55 to 116)	4.2 (3.3 to 7.7)	<0.01
Unpaired samples							
MCD	47	49 (27 to 86)	0.1 (0.1, 0.2)	34	140 (82, 224)	6.2 (3.4, 10.6)	<0.01
FSGS	19	25 (8, 74)	0.3 (0.1, 0.9)	42	80 (30 to 98)	4.0 (2.8, to 5.7)	<0.01
MN	13	38 (23 to 45)	0.2 (0.1 to 0.2)	29	46 (31 to 74)	2.6 (1.5 to 3.6)	0.10
Lupus	10	30 (8 to 64)	0.2 (0.2 to 0.5)	9	116 (70 to 293)	3.3 (1.7 to 11)	0.03
IgA	8	34 (12 to 41)	0.8 (0.3 to 0.9)	11	36 (21 to 57)	2.3 (1.1 to 3.1)	0.70
Diabetic	3	89 (21, 132)	1.1 (0.6 to 6.4)	6	234 (123, 334)	8.1 (6.0, 10.2)	0.20

FR-PO673

Beneficial Effects of Proteasome Inhibitors (PIs) Administered after Onset of Proteinuria in a Model of Minimal Change Disease (MCD) Himanshu Vashistha,[3] Allyson E. Bradley,[3] Frank C. Abbruscato,[3] Patrick D. Walker,[1] Sudhir V. Shah,[2] Radhakrishna Baliga.[3] *[1]Arkana Laboratories, Little Rock, AR; [2]University of Arkansas, Little Rock, AR; [3]Ochsner Health System, New Orleans, LA.*

Background: Proteasomes play a major role in the pathophysiology of several disease processes in part through its action on a crucial transcription factor, nuclear factor-kappa B (NF-κB). NF-κB regulates the expression of a variety of inflammatory genes including cytochrome P450 (CYP) which plays a major role in MCD. We have shown previously that administration of PIs prior to the onset of proteinuria resulted in marked protection against puromycin aminonucleoside (PAN) -induced proteinuria. However, the role of PIs in ongoing glomerular injury and their potential beneficial effects following the establishment of significant proteinuria have not been previously examined. The current study was designed to determine the effect of PIs administration following the onset of proteinuria in a model of MCD and to study the potential mechanism involved utilizing in vitro cultured human podocytes (HP)

Methods: MCD was induced in SD rats by injecting a single dose of PAN intravenously (IV). Proteinuria was measured as albumin to creatinine ratio (ACR) (μg/mg) until day 10. MG-132 was administered by osmotic pumps and Carfilzomib (CAR) was administered IV following onset of proteinuria. Proteins were analyzed by western blot and immunocytochemistry. Immunohistochemical analysis was also performed on the kidney cortical sections.

Results: Administration of MG-132 and CAR after the onset of PAN induced proteinuria (PAN 75±14, PAN+MG132 84±6, PAN+CAR 52±7; NS differences between groups; values are mean ±se) prevented the further increase until sacrifice (PAN 147±13, PAN+MG132 104±17*, PAN+CAR 98+13*; P<0.05* compared to PAN alone). This was accompanied by marked decrease in lipid peroxidation in PIs treated rats. MG-132 significantly decreased the nuclear translocation of NF-KB, activation of IL-6, up regulation of CYP, marked reduction in H_2O_2 release and 8-Oxo-dG expression in cultured HPs. MG-132 and CAR blunted the nuclear translocation of Nrf-2, preserved Keap-1 expression, upregulated PAN induced HO-1 and SOD with significant decrease in apoptosis.

Conclusions: These in vitro and in vivo data imply the crucial role of proteasome in progressive glomerular injury. CAR, which is currently used in humans should be considered as a potential therapeutic alternative in MCD.

Funding: Private Foundation Support

FR-PO674

Study of a Breakthrough Therapy Utilizing Alternative Actions of Vitamins A and D in a Murine Model of Minimal Change Nephrotic Syndrome Shoji Tsuji, Jiro Kino, Chikushi Suruda, Takahisa Kimata, Sohsaku Yamanouchi, Kazunari Kaneko. *Department of Pediatrics, Kansai Medical University, Osaka, Japan.*

Background: The etiology of minimal change nephrotic syndrome (MCNS) remains unclear, although recent research suggests that regulatory T cell (Treg) malfunction and associated functional and structural podocyte abnormalities play a role. Steroids are shown to have high efficacy against MCNS, and are utilized to correct the above-stated podocyte abnormalities. However, long-term steroid treatment may induce various adverse effects. In addition to their intrinsic vitamin functionality, vitamins A and D have recently demonstrated immunoregulatory functions, including effects on Treg differentiation and induction. Furthermore, they have been shown to restore damaged podocytes, directly [Okamura M, et al. *Nephrol Dial Transplant* 2009;24:3006]. The objective of this study was to investigate if vitamins A and D, which have fewer adverse effects, can correct the causes of MCNS in an animal model, and to search for a non-steroidal therapy for this syndrome.

Methods: Six-week-old MCNS model Wistar rats with puromycin aminonucleoside (PAN)-induced nephrosis were categorized into 4 treatment groups (n=3 per regimen): 1) VA Group received subcutaneous vitamin A 2.5 mg/kg dissolved in 1 mL dimethyl sulfoxide [DMSO]), 2) VD Group received intraperitoneal vitamin D 0.4 μg/kg dissolved in 0.2 mL phosphate-buffered saline [PBS]), 3) VAD Group received both the subcutaneous VA and intraperitoneal VD, 4) C (Control) Group received 0.2 mL subcutaneous DMSO and 0.2 mL intraperitoneal PBS. Starting two days pre-PAN administration, each regimen involved daily treatment for 12 days. Urinary protein excretion was measured and compared among the four groups. The Kruskal-Wallis Test was used for statistical analyses.

Results: Peak urinary protein excretion occurred at Day 9 post-PAN administration, when the median value was significantly lower in the VAD group than the C group (16.4 vs. 731.8 mg/kg/day; p=0.0144) and tended to be lower, although not significantly different, in the VAD group than the single-vitamin-treated rats (16.4 vs. 44.8 [VA] or 264.9 [VD] mg/kg/day.

Conclusions: Vitamins A and D exhibit an antiproteinuric effect with an additive action in MCNS model rats, and are potential therapeutic agents.

FR-PO675

APOL1-B3 Isoform Is Involved in the Processing of the IL-1β Production Hidefumi Wakashin,[1] Jeffrey B. Kopp.[2] *[1]Dokkyo Medical University, Shimotsuga, Japan; [2]NIDDK, NIH, Bethesda, MD.*

Background: *APOL1* genetic variants G1 and G2 increase risk for glomerular disease. Previously, we identified an intracellular splice isoform, APOL1-B3, that is expressed in glomerular cells and tubular cells *in vivo* (ms submitted). In transgenic mice, APOL1-B3-G2 expression enhanced podocyte injury, increased pro-IL-1β mRNA from isolated glomeruli, and increased renal IL-1β protein production. APOL1-B3 interacted with NLRP12, a negative regulator of Toll-like receptor signaling, potentially explaining elevation of pro-IL-1β mRNA in glomeruli. Here we examined the role of APOL1-B3 in inflammasome activation and production of mature IL-1β.

Methods: We generated stable THP-1 monocytic cell lines expressing APOL1 under the control of the chicken actin promoter, CAG-APOL1-B3-FLAG-G0 (common variant) or -G2 (renal risk variant); G1 variant cells were not viable. THP-1 cells were treated with phorbol myristate acetate to induce differentiation into macrophages, which were stimulated with lipopolysaccharide (LPS) and nigericin to activate inflammasomes. We generated CAG-APOL1-B3 transgenic mice, using linear DNA encoding CAG promoter-APOL1-B3 (G0 or G2), with FLAG-SV40 polyA signal sequence. Mice were studied at 6-8 w of age. Random urine was obtained prior to and 3 days after uninephrectomy.

Results: In THP-1 derived macrophages, over expression of APOL1-B3-G0 and –G2 significantly enhanced both LPS-stimulated IL-1β production (mean±SD:

control =193±3.8, G0=585±33, G2=669±79) (P<0.05) and release of caspase-1 into supernatant (control =3393±520, G0=9828±1541, G2= 6783±608) (P<0.05). Following uninephrectomy, increased urinary caspase-1 was seen in both APOL-B3 mice (G0, G2) and wild type mice, with no difference among groups. The ratio of IL-1β to pro-IL-1β in the kidney, assessed by Western blot, increased following uninephrectomy, and was numerically greater in APOL1-B3-G2 mice. These findings suggest enhanced processing of pro-IL-1β by the APOL1 risk variant. By Western blot, both APOL1-B3-G0- and -G2 interacted with NLRP3.

Conclusions: These findings suggest that under the conditions studied, the APOL1-B3 isoform affects processing of IL-1b and add a further dimension to the role of APOL1-B3 in modulating NLRP3 pathway signaling.

FR-PO676

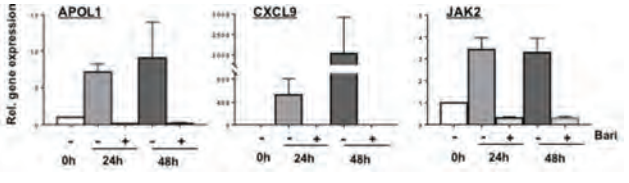
JAK1/2 Regulate APOL1, CXCL9 and JAK2 Expression in Human Kidney Cells Hongyu Zhang,[2] Gordon S. Wu,[3] V Vega-Warner,[2] Matt G. Sampson,[2] Frank C. Brosius.[1,2] *[1]University of Arizona, Tucson, AZ; [2]University of Michigan, Ann Arbor, MI; [3]Wayne State University School of Medicine, Ann Arbor, MI.*

Background: Chronic inflammation contributes to progression of all glomerular diseases. Recent data suggest that both APOL1 and JAK1/2 signaling contribute to the pro-inflammatory milieu in a variety of kidney diseases including FSGS, diabetic kidney disease, and other causes of nephrotic syndrome. Based on systems genetic and transcriptomic analyses of humans and of murine models of glomerular diseases, the expression of CXCL9, a T-cell chemoattractant belonging to the CXC chemokine family, is increased by APOL1 high risk genotype expression and by JAK2 overexpression in podocytes.

Methods: Human kidney 2 (HK-2) cell monolayers were grown to confluence and treated with interferon-gamma (IFN) (30ng/ml), interleukin-6 (IL-6) (10ng/ml), or tumor necrosis factor-alpha (TNF) (10ng/ml) from 30 min to 48 hr. mRNA levels of JAK2, APOL1 and CXCL-9 were determined at multiple timepoints in response to these agonists. A commercially available inhibitor of JAK1 and JAK2, baricitinib (Bari; 500nM), was then applied 30 min prior to agonist incubation.

Results: HK-2 cells were found to express APOL1, JAK2 and CXCL9. Stimulation of HK-2 cell monolayers of with IFN, but not IL-6 or TNF, resulted in a large, rapid and sustained (maximal at 48 hr) increases in mRNA expression of JAK2, APOL1 and CXCL9 (Figure). All of these increases were abrogated by 30 minutes of pretreatment with the JAK1/2 inhibitor as was the IFN induced increase in STAT3 phosphorylation.

Conclusions: In cultured human kidney cells, IFN stimulation triggers a cascade of events resulting in large increases in expression of pro-inflammatory mediators and APOL1. This cascade is completely abrogated by specific inhibition of JAK1/2 signaling. These findings suggest that JAK1/2-STAT3 signaling regulates APOL1, CXCL9 chemokine and JAK2 expression by parenchymal cells in the kidney. Future studies will examine effects of APOL1 modulation and genotype on this process.



IFN-induced increases in APOL1, CXCL9 and JAK2 (-) were completely inhibited by preincubation with Bari (+). N = 3 separate experiments for each timepoint.

FR-PO677

Flt3 Inhibitor Attenuates Renal Injury in Adriamycin Nephropathy by Suppressing CD103+ DC-Mediated T Cell Activation Qi Cao, Titi Chen, Vincent W. Lee, Guoping Zheng, Yiping Wang, David C. Harris. *The Westmead Institute for Medical Research, Westmead, NSW, Australia.*

Background: In our previous study, CD103+ DCs were shown to play a pathogenic role via activation of CD8 T cells in Adriamycin nephropathy (AN), a model of focal segmental glomerulosclerosis. FMS-like tyrosine kinase 3 (Flt3) is a receptor which is highly and specifically expressed on tissue resident CD103+ DCs. To test the effect on renal injury of inhibition of Flt3 on CD103+ DCs, we used a selective Flt3 inhibitor (AC220) to treat mice with AN.

Methods: AN was induced in BALB/c mice, who were treated daily for 14 days with 10mg/kg AC220 or Vehicle (n=8/group) from day 7 after adriamycin, when AN was established. Renal functional and structural injury, as well as inflammatory cytokine expression and cell infiltration were assessed.

Results: The number of kidney CD103+ DCs, but not CD103- DCs or plasmacytoid DCs, was significantly decreased in AN mice after AC220 administration. Treatment with AC220 significantly improved renal function (creatinine clearance: 22.8±4.9 vs. 50.2±13.3 μl/min) and reduced structural renal injury and fibrosis in AN mice. AC220-treated AN mice had decreased levels of inflammatory cytokines IL-1beta, IL-6 and TNF-a in kidney. AC220 treatment decreased infiltration of CD4 T cells, CD8 T cells and macrophages in kidney, and reduced inflammatory cytokine and cytotoxic molecule expression of kidney CD8 T cells in AN mice.

Conclusions: Flt3 inhibitor AC220 effectively reduced renal injury in AN mice, suggesting that this inhibitor might be a useful pharmaceutical agent to treat chronic kidney disease.

Funding: Government Support - Non-U.S.

FR-PO678

MBL2 Gene Polymorphism and IgG4 in Membranous Nephropathy Denise M. Costa,[2,1] Gisele Vajgel,[2] Maria Alina G. Cavalcante,[2] Camila B. Oliveira,[2,1] Carolina A. Vasconcelos,[1] Lucila Maria Valente.[2] *[1]Nephrology, Instituto de Medicina Integral Prof. Fernando Figueira, Recife, Brazil; [2]Nephrology, Hospital das Clinicas - UFPE, Recife, Brazil.*

Background: Although there is evidence regarding the involvement of the lectin pathway and IgG4 in idiopathic membranous nephropathy (IMN), the trigger responsible for the immune complexes formation is uncertain. It is known that IMN occurs in genetically susceptible individuals, however, very few studies have investigated the possible relationship between this glomerulopathy and polymorphisms of the *MBL2* gene, which is responsible for producing mannose-binding lectin (MBL) protein, a major component of the lectin pathway of the complement. We investigated the frequency of *MBL2* gene polymorphisms and the serum ratio of IgG4 in patients with membranous nephropathy (MN).

Methods: Polymorphisms in the exon 1 of the *MBL2* gene (codons 52, 54 and 57) and SNPs at positions -550 (HL) and -221 (XY) in the promoter region were evaluated in 60 patients compared to a control group of 101 blood donors. It established the frequency of polymorphisms and the serum ratio of IgG4 comparing the two main etiologies of membranous nephropathy: idiopathic (35 patients) and secondary to systemic lupus erythematosus (LMN) in 25 patients.

Results: The O allele, variant of exon 1, was more frequent in the group with MN compared to CG (42% × 22%; p <0.001). The heterozygous A/O was predominant among patients with MN compared to genotype A/A (OR = 11.16; 95% CI = 4.77 - 28.41). There was no difference for genotypes or alleles frequencies among patients and CG in H/L and X/Y promoter variants. When comparing the IMN and LMN groups there was no difference in the frequency of alleles or genotypes with a specific etiology. It was possible to reconstruct combined *MBL2* genotypes from 29 patients, and split in groups as high producers (HYA/HYA, HYA/ LYA, HYA/LXA, LYA/LYA and LYA/LXA), low producers (LXA/LXA, HYA/O and LYA/O) and deficient producers (LXA/O and O/O). A low-producer combined genotype was associated with a greater chance of developing MN (OR = 6.31, 95% CI = 2.26 - 19.7, p = 0.0001) when compared to CG. Serum levels of IgG4 and IgG were measured in 32 patients with IMN and 24 with LMN. The median of serum ratio IgG4 was 5% for IMN and 3% for LMN (p = 0.016).

Conclusions: Our data indicates that *MBL2* polymorphisms may be associated with the activation of lectin pathway by IgG4 subclass antibodies in MN.

FR-PO679

Immunodominant Epitope Regions and Clinical Outcome in THSD7A-Associated Membranous Nephropathy Larissa Seifert, Elion Hoxha, Anna M. Eichhoff, Gunther Zahner, Friedrich Koch-nolte, Rolf A. Stahl, Nicola M. Tomas. *University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*

Background: THSD7A has been identified as an autoantigen in patients with membranous nephropathy (MN). The epitopes targeted by patient autoantibodies are unknown.

Methods: In order to define the domain topology of THSD7A, we performed structure-based alignments with thrombospondin type 1 (TSP_1) domains in the protein data bank (pdb). We then cloned THSD7A fragments and tested for reactivity with serum from 31 patients with THSD7A-associated MN in a two-step approach using Western blotting. Clinical and serological follow-up was available from 16 of the 31 patients. We evaluated epitope profiles for associations with disease activity, incidence of malignancy, and clinical outcome.

Results: Protein structural analysis revealed a tandem string of 21 TSP_1 domains (d1 to d21). In a first unbiased approach, three consecutive fragments of the antigen (d1_d4, d5_d10 and d11_d21) were cloned, expressed in HEK293 cells, and tested for reactivity with patient autoantibodies. We found that 84% of patients recognized at least two of the constructs. Therefore, we cloned soluble fragments of 2-3 adjacent TSP_1 domains (d1_d2, d2_d3, d3_d4, d5_d6, d7_d8, d9_d10, d11_d12, d13_d14, d15_d16, d17_d18, d19_d21) in a second approach and tested again for serum reactivity. The d1_d2 fragment was recognized by 84% of the patients and therefore considered the immunodominant epitope region. However, epitope profiles among our patients varied greatly with 9 out of 11 TSP_1 domain fragments being recognized by at least three different sera. There was no association of epitope profiles with proteinuria, renal function or malignancy at the time of diagnosis. However, patients who recognized only one or two epitopes had lower anti-THSD7A antibody levels and less proteinuria. Among the patients with clinical and serological follow-up, 5 patients showed stable epitope profiles and persistent active disease, 8 patients lost reactivity with one or more constructs over time, and 3 patients showed a change in epitope profile during follow-up.

Conclusions: Our study demonstrates that autoantibodies in THSD7A-associated MN target a great variety of epitopes within the antigen. We could not identify epitope risk profiles regarding disease activity, clinical outcome during follow-up or incidence of malignancy.

Funding: Government Support - Non-U.S.

FR-PO680

Visualization of Myeloma Light Chain Filtration and Proximal Tubule Trafficking: Implication for MGUS Dawson Dean,[1] Ruben M. Sandoval,[1,2] Mark C. Wagner,[1,2] Silvia B. Campos-bilderback,[1,2] Bruce A. Molitoris.[1,2] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Roudabush VAMC, Indianapolis, IN.*

Background: Myeloma light chains are thought to cause acute and chronic kidney injury by several mechanisms including tubular obstruction and direct proximal tubule (PT) injury. Earlier forms of this disease, including Monoclonal Gammopathy of Undetermined Significance (MGUS), are detected by serum markers but their impact on the nephron is not fully understood.

Methods: To study directly the fate of serum myeloma light chains we isolated myeloma light chains from patient urines using gel sizing techniques, conjugated them to Texas Red, and injected either in a pulse chase or pulse with a continuous infusion.

Results: Using 2-photon microscopy of surface glomeruli of Munich Wistar Fromter rats, the glomerular sieving coefficients of these conjugated Myeloma proteins were determined to be 0.14 ± 0.02. Additionally, light chains attached to PT apical membranes within 20 seconds following IV injection, accumulated rapidly in a linear fashion within the apical aspect of the cell and subsequently trafficked to lysosomes. No transcytosis was visualized. Both S1 and S2 segments of PT participated equally in a saturable process with non-reabsorbed light chains being concentrated in distal tubule lumens. These data indicate myeloma light chains are readily filtered across the glomerulus, reabsorbed effectively by PT cells and do not appear in the urine until saturation of PT reabsorption has occurred.

Conclusions: This has important implications in MGUS where PT protein overload and subclinical injury could be occurring without serum or urine evidence of paraproteinemia.

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FR-PO681

Estrogen-Related Receptor α (ERRα) Plays Proapoptotic and Proinflammatory Roles in Mesangial Cells Wei Gong, Yue Zhang, Songming Huang, Zhanjun Jia, Aihua Zhang. *Nephrology Department, Children's Hospital of Nanjing Medical University, Nanjing, China.*

Background: Mesangial Cell **(**MC) apoptosis has been proposed as an important cell clearance mechanism during the uncontrolled MC proliferation. The present study is undertaken to investigate the role of ERRα in MC apoptosis under the normal and pathological conditions.

Methods: The mouse MC line was treated with vehicle or puromycin aminonucleoside (PAN). Then the regulation of ERRα and the role of ERRα in MC apoptosis and inflammation was examined.

Results: PAN induced MC apoptosis by 2.3 folds accompanied by the declined cell viability and enhanced inflammatory response. The apoptosis was further evidenced by the increments of BAX/Bcl-2 ratio and caspase-3 expression. In line with the apoptotic response, we also found a remarkable induction of ERRα, an orphan nuclear receptor, at both mRNA (>5-fold) and protein levels (>2-fold). Interestingly, ERRα silencing by a siRNA approach resulted in an attenuation of MC apoptosis by 45% caused by PAN. Meantime, the inflammatory response was also markedly ameliorated. More importantly, overexpression of ERRα in MCs significantly triggered MC apoptosis in line with increased BAX/Bcl-2 ratio and caspase-3 expression. In PAN-treated MCs, ERRα overexpression further aggravated PAN-induced apoptosis by 2.3-fold.

Conclusions: These data suggested a detrimental effect of ERRα on PAN-induced MC apoptosis and inflammatory response, which could help us to better understand the pathogenic mechanism of MC injury in PAN nephropathy and other glomerular diseases.

FR-PO682

Prescribed Chinese Herbal Medicine, Shen Ping Decoction, Blocks Activation of Human Mesangial Cells Induced by Different Pathogenic Mechanisms Xianwen Zhang,[1,3] Zhi qiang Huang,[3] Lin Wang,[1] Stacy D. Hall,[2] Bruce A. Julian,[3] Yiping Chen,[4] Jan Novak.[3] *[1]Longhua Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China; [2]UAB, Birmingham, AL; [3]University of Alabama at Birmingham, Birmingham, AL; [4]longhua hospital, SHANGHAI, China.*

Background: Mesangioproliferative glomerular diseases are characterized by increased proliferation of mesangial cells (MC), often due to the activation by PDGF and/or angiotensin II (AII). Shen Ping decoction (SP), an herbal medicine, has been prescribed to treat IgA nephropathy (IgAN) in China for decades; SP treatment effectively reduces proteinuria and stabilizes renal function. To investigate the pharmaceutical mechanisms of SP, we assessed the effects of SP in our model of primary human MC using MC activators PDGF-BB or AII.

Methods: MCs were treated using PDGF-BB for 15 min with or without SP. Phosphorylation of PDGF receptor-β (PGDFR-β), its down-stream signaling, and a TAM-family kinase Axl were assessed by Western blotting using MC lysates. Binding of biotylated PDGF-BB to its receptor was measured with or without SP. Cellular proliferation was determined using BrdU uptake. MCs were also treated with AII for 15 min with or without SP and transactivation of EGFR by AII was assessed.

Results: SP inhibited proliferation of MCs induced by PDGF-BB in a dose-dependent manner. SP blocked binding of PDGF to its receptor, thus inhibiting phosphorylation of PDGFR-β. Activation of down-stream signaling, including phosphorylation of ERK1/2 and AKT, was also blocked by SP. Moreover, SP inhibited PDGF-induced transactivation of TAM-family kinase Axl. Phosphorylation of EGFR in MCs was activated by AII treatment and was inhibited by SP in a dose-dependent manner. Activation of EGFR down-stream signaling, including ERK1/2 and AKT, was also inhibited.

Conclusions: Chinese herbal medicine SP blocked MC activation induced by PDGF-BB or AII through inhibition of multiple signaling pathways. These findings thus explain some of the mechanisms of SP treatment to benefit patients with IgAN.

Funding: NIDDK Support

FR-PO683

Heparanase II Inhibits Heparanase I-Mediated Cleavage of Endothelial Glycocalyx, Preserves Glomerular Integrity, and Prevents Microvascular Injury Yulia Kiyan,[1] Klaus Stahl,[4] Sergey Tkachuk,[5] Patricia A. Schroder,[6] Laura L. Beverly-Staggs,[3] Mario Schiffer,[1] Roman Kiyan,[2] Boris Chichkov,[2] Hermann G. Haller.[1,6] *[1]Hannover Medical School, Hannover, Germany; [2]Laser Zentrum Hannover e.V., Hannover, Germany; [3]Mount Desert Island Biological Lab, Salisbury Harbor, ME; [4]MHH, Hannover, Germany; [5]Medizinische Hochschule Hannover, Hannover, Germany; [6]Mount Desert Island Biological Laboratory, Salisbury Cove, ME.*

Background: Regulation of heparan sulfate (HS) chains of the glycocalyx is an important pathomechanism of vascular and renal diseases. Heparanase 1 (HPSE1) is the only known glucuronidase capable of degrading HS chains. Recently cloned heparanase 2 (HPSE2) is catalytically inactive and its functions are yet unclear. We have tested the hypothesis that HPSE2 antagonizes HPSE1, prevents HS chain cleavage and protects endothelial cell function.

Methods: In vitro study of endothelial cells (EC) were carried out (1) in cell culture and (2) in a microfluidic chip under flow conditions. We developed a lentiviral construct and upregulated HPSE2 expression in EC. To assess HSPE2 function in vivo we used a transgenic zebrafish model (Tg(I-fabp:GFP-DBP) and measured loss of fluorescent protein form the circulation.

Results: Addition of active HPSE1 led to the shedding of HS layer from endothelial cell surface. Overexpressing HPSE2 protected against HPSE1-induced glycocalyx shedding and damage of VE-cadherin junctions, cytoskeletal rearrangements and from glucose-induced ICAM expression and adhesion of AM-labelled monocytes. LPS stimulation with increased expression of IL-6, IL-1β, and RANTES, as well as phosphorylation of p65 subunit of NFκB, p38, and MEK kinases was diminished by HPSE2 overexpression. HPSE2 knockdown in zebrafish showed a phenotype characterized by general body edema and albuminuria. Diffuse leakage of from the intravascular compartment into the interstitial tissue of the fish tail was visualized. Simultaneous injection of human HPSE2 full length mRNA we partially rescued the proteinuric phenotype of HPSE2-KD fish.

Conclusions: HPSE2 is important for endothelial development and function in zebrafish model and in vitro under flow conditions. Our results suggest that HPSE2, expressed locally by EC or delivered with blood, fulfills protective role in microvasculature via several distinct mechanisms. First, it binds to and protects the HS glycocalyx from enzymatic shedding by HPSE1. In addition, HPSE2 binding to HS diminishes HS involvement in receptor-ligand interaction and is anti-inflammatory. We suggest that the C-terminal part of the HPSE2 protein containing HS-binding motif might be critical for endothelial function.

Funding: Government Support - Non-U.S.

FR-PO684

Podocyte Cross Talk with Parietal Epithelial Cells (PECs) Stimulates PECs Proliferation in HIV Milieu Vinod Kumar,[4] Xiqian Lan,[1] Rukhsana Aslam,[2] Ali Hussain,[3] Seyedeh Shadafarin Marashi Shoshtari,[6] Catherine Meyer-Schwesinger,[7] Ashwani Malhotra,[8] Pravin C. Singhal.[5] *[1]Feinstein Institute for Medical Research, Great Neck, NY; [2]Feinstein Institute for medical research, Glenoaks, NY; [3]Feinstein Institute of Medical Research, New York, NY; [4]Immunolgy and Inflammation, Fienstine Institute for Medical Research, New York, NY; [5]North Shore LIJ Health System, Great Neck, NY; [6]The Feinstein Institute for Medical Research, Manhasset, NY; [7]University of Hamburg, Hamburg, Germany; [8]Immunolgy and Inflammation, Feinstein Inst. Med research and NSLIJ, Manhasset, NY.*

Background: HIV-associated nephropathy is characterized by an abundance of proliferating PECs in Bowman's space. The involved mechanism of PECs proliferation in HIV milieu is not clear. Recently, we demonstrated that HIV stimulates IL-1β generation by PDs. We now hypothesize that cross talk between PDs to PECs and PECs to PECs promotes PECs proliferation.

Methods: Immortalized PECs and differentiated PDs were transduced with either vector (PECV/PDV) or HIV (PECHIV/PDHIV, NL4-3) and assayed for pyroptosis (morphologic assay). Control PECs/PDs, PECV/PDV, and PECHIV/PDHIV were incubated in serum-free media for 24 hours. Incubation (conditioned, C) media was collected and stored at -80°C. PECs were incubated in serum-free media containing 10% of control (PECV/PDV) and experimental (PECHIV/PDHIV) conditioned media for 48 hours. In another set of experiments, PECs were incubated in serum free media containing 10% control and experimental media with or without IL-1β (neutralizing) antibodies for 48 hours. Cells were evaluated for proliferation by MTT cellular viability

assay. To confirm the role of cross talk, PECs were grown in outer wells and PECHIVs/PDHIVs were seeded into inner wells (Trans-well plates). After 48 hours, cells in outer wells were assayed for proliferation. Cellular lysates/incubation media of PECs/PDs and PECHIV/PDHIV were assayed for IL-1β by ELISA. Additionally, PECs grown on coverslips were treated with 10% control and experimental media for 48 hours followed by immunolabeling for either PCNA or Ki67.

Results: Both PDHIV and PECHIV displayed a higher percentage of pyroptosed cells (P<0.01 vs respective controls). Cellular lysates and incubation media of PDHIV and PECHIV displayed enhanced (P<0.05 vs. PDHIV and PECHIV) generation of IL-1β. Conditioned media of PDHIV and PECHIV promoted PECs proliferation; however, anti-IL-1β antibody partially inhibited PDHIV/PECHIV-conditioned media-mediated proliferation. PECs growing in outer wells of trans-well plates containing PDHIV/PECHIV also displayed enhanced proliferation. PECs treated with PECHIV/PDHIV conditioned media higher percentage (P<0.01 vs. PECV/PDV) of PCNA/Ki67 +ve cells.

Conclusions: Cross talks between PDs to PECs and PECs to PECs promote PECs proliferation in HIV milieu.

Funding: NIDDK Support

FR-PO685

Vitamin D Receptor (VDR) Agonist Slows Down Progression of HIVAN via Down Regulation of HIV Gene Expression Seyedeh Shadafarin Marashi Shoshtari,[3] Rukhsana Aslam,[1] Vinod Kumar,[3] Ashwani Malhotra,[1] Pravin C. Singhal.[2] *[1]Feinstein Institute for medical research, Glenoaks, NY; [2]North Shore LIJ Health System, Great Neck, NY; [3]The Feinstein Institute for Medical Research, Manhasset, NY.*

Background: Activation of renin angiotensin system (RAS) has been demonstrated to play an important role for the progression of HIVAN. This effect of RAS has been attributed to modulation of hemodynamic factors as well as direct cytotoxicity to kidney cells. We have previously demonstrated that HIV enhances kidney cell renin expression. We now hypothesize that renin enhances HIV gene expression and this effect of renin could be prevented by VDR agonist, resulting in slowing down the progression of HIVAN.

Methods: Human podocytes (HPs) were transdudced with either vector (V/HP) or HIV (NL4-3, HIV/HP). To increase endogenous renin production, V/HPs and HIV/HPs were transfected with siRNA vitamin D receptor (siRNA-VDR/HIV/HPs) or scrambled (Scr-siRNA/HIV/HP) siRNA; protein blots were probed for renin and actin expressions. To evaluate the effect of renin in vivo, mRNA expressions of HIV genes from renal tissues of HIVAN (Tg26) mice with higher endogenous renin (Tg26 mice expressing 2, 3 and 4 copies of angiotensinogen [Agt] or lacking VDR) were quantified by qPCR. To down regulate renal tissue renin expression, Tg26 mice were treated with either vehicle or a VDR agonist (VDA) for 2 weeks and renal tissues were evaluated for HIV gene expression. In addition, gene expression and progression of renal lesions in Tg26 mice, Tg26 mice lacking renin, and Tg26 mice treated with VDA. were compared.

Results: HIV enhanced renin expression in HPs. Silencing of VDR in HIV/HPs further enhanced expression of Nef, Tat, and Vif. However, VDA down regulated HIV gene expression in HIV/HPs. Renal tissues of Tg26 with 4 Agt copies displayed 2-4 fold increase in mRNA expression of gp120, Vpr, Tat, Nef and Vpu vs. Tg26 (Agt 2 copies). Similarly, Tg26 mice lacking VDR displayed greater HIV gene expression when compared to Tg26 mice with intact VDR. VDA-treated of Tg26 mice not only down regulated renal tissue expressions of renin but also attenuated expression of HIV genes. Tg26 mice lacking renin or treated with VDA, displayed attenuated renal tissue HIV gene expression and slowed down the rate of progression of renal lesions.

Conclusions: Renin enhances renal tissue and podocyte HIV gene expression and induces accelerated progression of renal lesions; however, this effect of renin could be prevented by VDA treatment.

Funding: NIDDK Support

FR-PO686

IRAK4 Inactivation Eliminates Disease Phenotype in a Murine Model of Lupus/Lupus Nephritis Barry K. Horne, Ian R. Rifkin, Ramon G. Bonegio. *Boston University School of Medicine, South Weymouth, MA.*

Background: Toll-like Receptor (TLR) signaling has been shown to play a major role in the progression of lupus and lupus nephritis (LN). Interleukin-1 Receptor-Associated Kinase 4 (IRAK4) is a protein kinase that is critical to mammalian TLR signaling. Humans with homozygous loss-of-function (LOF) mutations in IRAK4 lead relatively normal lives upon reaching adulthood. Attempts at specific *in vivo* inactivation of kinases in other human diseases have met with great success, and they are currently considered attractive targets for the development of new therapeutics. Thus, we hypothesized that inactivation of IRAK4 would ameliorate disease in our murine model of lupus / LN, and validate it as a potential therapeutic.

Methods: We crossed lupus prone Yaa, FcγRIIb$^{-/-}$ mice to mice with inactive IRAK4 kinase to allow the comparison of lupus prone mice with (IRAK4$^{+/+}$) or without (IRAK4$^{KD/KD}$) functional IRAK4. We conducted a survival study, and analyzed the groups for markers of the lupus phenotype: body weight, spleen weight, cervical lymph node weight, perigonadal fat weight, and proteinuria.

Results: IRAK4$^{+/+}$ mice developed severe lupus and lupus nephritis, and died at a median age of 27 weeks (range: 22 to 28 weeks). In contrast, IRAK4$^{KD/KD}$ mice had a dramatic survival advantage (p<0.001), and mice analyzed at 1 year of age had no evidence of lupus. They exhibited no signs of nephritis, lacked proteinuria, and had normal spleen, cervical lymph node, and fat weights.

Conclusions: IRAK4 kinase activity is indispensable for the development of lupus and lupus nephritis in the Yaa, FcγRIIb$^{-/-}$ mice, indicating that the IRAK4 signaling pathway is an attractive therapeutic target.

Funding: NIDDK Support, Other NIH Support - NIAID T-32 (ITP) 5T32AI007309-27

FR-PO687

Increased MERTK Glomerular mRNA Expression in LN Multiethnic Populations: A Modulator of Innate Inflammation Iris J. Lee,[1] Paris Barkan,[1] Kalyani Perumal,[2] Sudha Visvanathan,[3] Matthias Kretzler,[4] Crystal A. Gadegbeku,[1] Brad A. Godfrey,[4] Celine C. Berthier.[4] *[1]Temple University School of Medicine, Philadelphia, PA; [2]Stroger Hospital, Chicago, IL; [3]Boehringer-Ingelheim, Ridgefield, CT; [4]University of Michigan, Ann Arbor, MI.*

Background: Inflammation and cytokine dysregulation contribute to disease pathogenesis in Systemic Lupus Erythematous (SLE) and lupus nephritis (LN). MERTK, a receptor protein tyrosine kinase, limits toll like receptor (TLR)-induced production of pro-inflammatory cytokines (IL-6, IL-1β and TNF-α) through the induction of suppressor of cytokine signaling proteins (SOCS). MERTK also mediates phagocytosis and clearance of apoptotic cells, a function known to be defective in SLE. Furthermore, mice deficient in MERTK develop glomerulonephritis. Therefore, we investigated MERTK mRNA expression in human LN renal biopsies.

Methods: Gene expression profiles of microdissected renal biopsies from LN patient (European and Multiethnic cohorts, including WHO class II, III, IV, V) were analyzed.

Results: In the European cohort, glomerular MERTK transcript was 2.6 fold up-regulated in LN compared to controls (q-value<0.0001), and was the most highly altered compared to kidney biopsies from other proteinuric diseases (FSGS, Hypertensive nephropathy, IgAN, Minimal change, Membranous). For diabetic nephropathy and rapidly progressive GN, fold-change was 1.2 and 1.7 respectively (q-value<0.005). Like the European cohort, glomerular MERTK was also 2.3 fold up-regulated in the Multiethnic cohort (q-value <0.0001). MERTK mRNA was not significantly regulated in the tubular compartment of any kidney disease. Finally, MERTK mRNA expression was not significantly different among CKD stages I-V, and did not correlate with GFR or level of proteinuria.

Conclusions: Our data show preferential expression of MERTK in the glomerular compartment of LN tissue compared to controls. In addition, expression was unrelated to level of GFR or proteinuria. MERTK is known to regulate innate inflammation, and its expression in LN likely represents an adaptive response to an upregulated immune system. Further research is necessary to understand how alterations in MERTK gene expression pattern contributes to pathogenesis of glomerular injury and inflammation in LN, or would be useful as a biomarker for LN outcomes.

Funding: Commercial Support - Boehringer-Ingelheim Pharmaceuticals

FR-PO688

Robust Improvement in Lupus Nephritis after Hyaluronidase Treatment Due to the Removal of Accumulated Hyaluronic Acid in Glomerular Endothelial Glycocalyx Hiroyuki Kadoya, Chaim O. Jacob, Janos Peti-Peterdi. *University of Southern California, Los Angeles, CA.*

Background: Lupus Nephritis (LN) is a major cause of morbidity and mortality in patients with systemic lupus. The exact pathomechanism of LN has been elusive, and therefore current non-specific therapies are limited to general immunosuppression. Recently, we developed an intravital multiphoton microscopy (MPM) imaging approach to visualize the interplay between cellular components of the immune system and local kidney tissue factors. We observed the glomerular homing of IL-17-producing activated memory T cells, which were the vast majority of all immune cells found in LN kidney. The present study tested the hypothesis that T cell homing is due to the accumulation of the CD44 ligand hyaluronic acid (HA) in the glomerular endothelial glycocalyx, and its removal by hyaluronidase improves LN.

Methods: Serial MPM was used to track the fate of endogenous T cells labeled with anti-CD3 and anti-CD44 antibodies in vivo in a model of rapid LN (BAFF transgenic New Zealand mixed (NZM) mice). FITC-labeled wheat germ agglutinin (WGA) lectin and Alexa594-labeled HA-binding protein (HABP) were used to evaluate glomerular endothelial glycocalyx and HA content, respectively.

Results: Glomerular size, microthrombi, albumin leakage, T cell homing were significantly increased at 4-6 weeks old LN mice compared with control healthy mice. Robust accumulation of endothelial glycocalyx and HA content (thickness and intensity of WGA and HABP fluorescence, respectively) were observed in LN mice, but not in control. Hyaluronidase injection significantly and dose-dependently (EC50=20U) reduced WGA and HABP fluorescence, T cell homing, and albumin leakage within 1 hour. Hyaluronidase treatment caused a 5-fold reduction in albuminuria and 4-fold increase in survival rate of LN mice.

Conclusions: Our results support the major importance of HA in the endothelial glycocalyx in the glomerular homing of memory T cells in the development and pathobiology of LN. Hyaluronidase treatment is a promising new therapeutic approach for LN.

FR-PO689

Neuraminidase Activity Mediates IL-6 Production by Lupus Prone Mesangial Cells Tamara Nowling, Kamala Sundararaj, Jessalyn I. Rodgers. *Medical University of South Carolina, Charleston, SC.*

Background: Glycosphingolipid (GSL) levels and neuraminidase (NEU) (an enzyme that mediates GSL catabolism) activity/expression are altered in the kidneys and/or urine of lupus mice and human patients with proliferative nephritis compared to their non-nephritic counterparts and healthy controls. Specifically, elevated GSL levels were observed in the mesangial region of glomeruli. We hypothesize that activation of mesangial cells (MCs) in the progression of lupus nephritis is mediated in part by NEU activity, contributing to renal inflammation in lupus nephritis. Here we investigated the role and possible mechanisms by which NEU activity contributes to MC activation.

Methods: For these studies, we used the MES13 mouse MC line and primary MCs grown out from glomeruli isolated from MRL/lpr lupus prone mice. MCs were analyzed in the absence or presence of heat aggregated IgG (mimic of immune complex deposition), inhibitors for NEU activity or MAP kinase pathways inhibitors include real-time RTPCR, NEU activity assays, IL-6 and MCP-1 ELISAs, immunohistochemistry of renal sections, and confocal immunofluorescence of MCs.

Results: While HA-IgG alone fails to activate MES13 cells to produce IL-6, over-expressing NEU1 or NEU3 alone results in significant production of IL-6. HA-IgG added to MES13 cells over-expressing NEU1 or NEU3 further increased IL-6 production over NEU1 or NEU3 alone. In primary MCs, Neu1 message levels, NEU activity, and IL-6 and MCP-1 production are dose-dependently and significantly increased following addition of HA-IgG. Addition of an FDA-approved inhibitor of NEU activity significantly and dose-dependently inhibited HA-IgG-induced IL-6 while higher concentrations were required to inhibit MCP-1 production. NEU1 and NEU3 appear to co-localize with HA-IgG at the surface of the MES13 and primary MCs. JNK and p38 MAP kinase inhibitors prevented IL-6 production in response to NEU1 or NEU3 over-expression in MES13 cells.

Conclusions: Together these results suggest that immune complex activated IL-6 production of MCs is mediated by NEU activity. This may occur at the cell surface in a complex of HA-IgG and surface receptor that recognizes HA-IgG. Furthermore, the NEU1/NEU3 mediated IL-6 production appears to involve the p38/JNK stress-activated MAPK pathways. Targeting NEU activity may reduce MC cytokine production and thus renal inflammation in lupus nephritis.

Funding: Other U.S. Government Support

FR-PO690

Effects of High Titers of Anti-Chimeric Antibodies Following Rituximab Dario Roccatello,[1] Savino Sciascia,[2] Roberta Fenoglio.[1] *[1]Ospedale San GIovanni Bosco, Torino, Italy; [2]Center of Research of Immunopathology and Rare Diseases (CMID), Division of Clinical Immunology, Giovanni Bosco Hospital and University of Turin, Ita, Torino, Italy.*

Background: Monoclonal antibodies (MoAbs) are highly successful in treating various immunological disorders. The development of anti-drug antibodies (ADA) against the therapeutic MoAb is relatively common. In recent years, knowledge of how to assess immunogenicity of biological drugs has improved. ADA are thought to form immune complexes with the MoAb, leading to accelerated MoAB clearance and low decrease levels in the blood stream. Several reports showed an inverse relationship between MoAb levels and anti MoAb antibody formation. Further, patients who develop ADA are more likely to present with infusion-related adverse effects. Acute infusion reactions, including anaphylaxis, develop in a close temporal relationship to MoAb infusion. Among the others MoAbs, Rituximab (RTX), an anti-CD20 monoclonal antibody, often results in the production of human anti-chimeric antibodies (HACA). In this study, we aimed to to evaluate the presence of HACA in patients with poor response to treatment with RTX

Methods: We assessed the incidence of HACA in patients with autoimmune diseases treated with the RTX and determine the potential relationship with trough drug concentration, efficacy, and patient-reported outcomes.

Results: When investigating 37 patients treated with RTX, we found very high-titer of HACA (> 1,000 AU) in 5 patients (13.5%): 2 with Systemic Lupus Erythematosus (SLE), 2 with Membranous Nephropathy (MN) and 1 patient with Mixed Cryoglobulinemia (MC). Details are given in table 1. In 4 of them, high titers of HACA were clearly related to unresponsiveness to RTX treatment. In the other case the appearance of high HACA titers was consonant with a severe hypersensitivity reaction during RTX re-treatment.

Conclusions: HACA detection and monitoring, especially in the cases of RTX re-treatment, could not only assure a safer administration, but also support a more rational strategy of treatment.

Table 1

Case	Disease	# of cycles of RTX	Steroids Therapy	HACA titers (AU)	RTX-level
1	SLE	1	Yes	15,720	ND
2	SLE	1	Yes	3,719	ND
3	MC	3	No	14,670	0
4	MN	1	No	1,007	0
5*	MN	2	No	10,363	0

Abbreviations are: NP: not determined. * Patient with severe hypersensitivity reaction

FR-PO691

CD11b Activation Reduces Inflammation in Lupus Nephritis by Downregulating TLR Pathways Samia Khan, Mohd Hafeez Faridi, Ha Won Lee, Mehmet M. Altintas, Shehryar J. Khaliqdina, David J. Cimbaluk, Vineet Gupta. *Rush University Medical Center, Chicago, IL.*

Background: Single nucleotide polymorphisms (SNPs) in the *ITGAM* gene, coding for CD11b subunit of the integrin CD11b/CD18, produce defective protein and confers a strong predisposition to systemic lupus erythematosus (SLE, lupus) and lupus nephritis. Elevated levels of IFN I in circulation is a heritable risk factor for SLE and play a pathogenic role and are likely driven by a combination of genetic variations and environmental stress. Here we investigate if variations in ITGAM are linked to high IFN I and whether pharmacological CD11b activation could be a therapeutic strategy.

Methods: To test for a direct link between ITGAM SNPs and the TLR induced IFN-I pathways, we measured serum IFN I activity in 171 SLE patients and determined their *ITGAM* genotype. Since ITGAM SNPs result in functionally deficient CD11b, we tested whether partial CD11b activation with small molecule agonist, leukadherin-1 (LA1) can suppress IFN-I pathways and determined TLR signaling components that are regulated by CD11b activation. To test the efficacy of LA1 in a lupus model, we used the MRL/*lpr* mice that develop IFN I-dependent multi-organ lupus similar to human lupus with renal inflammation.

Results: We report that SLE subjects carrying ITGAM SNPs have significantly elevated serum IFN-I activity indicating a direct link between reduced CD11b activity and elevated inflammation in patients. LA1 treatment reduced IFN I responses and protected lupus-prone MRL/*lpr* mice from kidney injury. LA1-treated mice had reduced glomerular damage, proteinuria, and IgG renal immune complex deposition as compared to vehicle-treated controls. CD11b agonist LA1 suppressed proinflammatory cytokine secretion by TLR-activated leukocytes and suppressed IFN I signaling, via an AKT-FOXO3-IRF7 pathway. TLR-stimulated macrophages from CD11b SNP carriers showed increased expression of IRF7 and IFNB, as well as increased nuclear exclusion of FOXO3, which was reversed by LA1.

Conclusions: LA1 suppresses TLR-induced cytokine production that has been directly linked to exacerbation of lupus nephritis. Hence pharmacological CD11b activation is a promising potential novel therapeutic target, particularly in patients identified as carriers of ITGAM variants.

Funding: NIDDK Support

FR-PO692

Exogenous Hepcidin Mitigates and Delays Onset of Lupus Nephritis Yogesh M. Scindia,[2] Ewa U. Mandziak,[3] Valentina Loi,[1] Saleh Mohammad,[3] Sundararaman Swaminathan.[3] *[1]AO Brotzu Cagliari, Cagliari, Italy; [2]Univerisity of Virginia, Charlottesville, VA; [3]University of Virginia, Charlottesville, VA.*

Background: Lupus nephritis (LN) is an end-organ manifestation of systemic lupus erythematosus (SLE) with a strong gender bias and affects mostly pre-menopausal women. Current interventions are imprecise and broadly immunosuppressive and hence there is a constant need for identifying new therapeutic targets. Recent human studies have identified Hepcidin (*Hamp*), the master regulator of iron metabolism as a biomarker of LN, and renal flares are associated with low *Hamp* levels. So far there are no mechanistic studies examining the role of hepcidin in the pathogenesis of SLE. We therefore hypothesized that *Hamp* treatment would mitigate SLE-induced kidney disease.

Methods: 7-week-old female MRL/*lpr* mice (a spontaneous model of SLE, n = 4-5) were treated bi-weekly with saline or 50 µg of hepcidin (i.p) for 10 weeks, following which outcomes like microalbuminuria, histopathology, circulating autoantibody levels and other markers of inflammation were examined.

Results: Saline treated mice developed severe LN by 17 weeks of age as indicated by high microalbuminuria, collagen deposition, renal IL-6, CXCL-1 and M-CSF transcripts, and an infiltration of CD45 cells, F4/80+ve macrophages and T cells. There was a concomitant increase in circulating autoantibodies and serum MCP-1, IL-6, GM-CSF and TNFa. *Hamp* treatment significantly reduced all theses manifestations of LN (Microalbuminuria; PBS, 914.6 ± 64.6 mg/gm vs *Hamp* 314.2 ± 111.2 mg/gm). *Hamp* treatment was associated with a systemic decrease in Cox-2, a mediator of inflammation. There was an increase in renal H-ferritin and a concomitant decrease in iron dependent enzymes, Rrm-1 and Rrm-2, both of which are required for DNA synthesis.

Conclusions: This is the first study to demonstrate therapeutic benefit of *Hamp* in LN. Our results indicate that *Hamp* protects against LN by decreasing Cox-2 and reducing inflammation as well as by reducing cell proliferation through the induction of cytoprotective H-ferritin. Further studies are required to investigate whether *Hamp* mediated protection leads to end-organ resistance to LN or through to modulation of immune responses.

Funding: NIDDK Support

FR-PO693

Antirenal CD4+ T Cells Arise in Lupus Nephritis, Are Mainly of the Th1 Phenotype, Are Only Partially Controlled by Their Regulatory Counterparts, and Invade the Inflamed Kidneys Philipp Enghard,[1] Sebastian Tesch,[2] Dimas Abdirama,[2] Gabriela Riemekasten.[3] *[1]Charité, Berlin, Germany; [2]Charité Universitätsmedizin Berlin, Berlin, Germany; [3]University Lübeck, Lübeck, Germany*.

Background: Lupus nephritis (LN) is associated with local MHC II upregulation and a T cell rich infiltration, suggesting an antigen-specific immune response. However, up to date no renal target antigens are known in LN. Here we report the identification of a set of target autoantigens and characterize the respective CD4+ T cell response.

Methods: Peripheral blood T cells from 57 SLE patients and 11 healthy controls (HC) were analyzed. In an initial cohort T cells were stimulated with kidney lysates from healthy kidneys. Subsequently five candidate autoantigens were identified based on the assumption that a corresponding autoantibody is present and that the respective antigen is upregulated in the inflamed kidney in LN. Enrichment via CD40L expression was performed and intracellular cytokine production was measured with flowcytometry (ARTE method). Regulatory T cells were assessed via CD137 enrichment. Urinary T cells from six patients with active LN were isolated and probed for the presence of autoreactive T cells.

Results: Only marginal T cell reactivity was detectable when stimulating peripheral blood T cells with kidney lysates. In subsequent experiments, a pool of renal candidate autoantigens was used and autoreactive CD4+ T cells were detected in patients with SLE and healthy controls. These cells were mainly IFN-y producing Th1 T cells and were significantly expanded in patients with active LN, compared to inactive SLE patients and HC. IL-4, IL-10 and IL-17 producing antirenal CD4+ T cells were present in lower frequencies, albeit also expanded in patients with active LN. Upon stimulation with renal autoantigens, CD137 expressing Tregs were also detected, and the ratio of IFN-y+ T cells to CD137+ Treg cells was significantly higher in active LN patients and correlated with disease activity. Using T cell libraries we identified Vimentin and Annexin A2 as the main, but not exclusive targets of the antirenal T cell response. Finally, we were able to also detect antirenal T cells in the urine of patients with active LN, indicating renal invasion of these cells.

Conclusions: An antirenal CD4+ T cell response arises in LN. These cells are mainly of the Th1 phenotype, invade the inflamed renal tissue and are only partly controlled by their regulatory counterparts.

Funding: Government Support - Non-U.S.

FR-PO694

Update about PEARL: Pathway Exploration and Analysis in Renal Disease in the Accelerating Medicine Partnership (AMP) Lupus Network Celine C. Berthier,[1] Arnon Arazi,[2] Deepak Rao,[3] Thomas Eisenhaure,[2] Nir Hacohen,[2] David J. Lieb,[2] Betty Diamond,[4] Matthias Kretzler.[1] *[1]University of Michigan, Ann Arbor, MI; [2]Broad Institute, Cambridge, MA; [3]Brigham and Women's Hospital, Boston, MA; [4]The Feinstein Institute for Medical Research, Manhasset, NY. Group/Team: PEARL team members*.

Background: Despite treatments, a substantial proportion of lupus nephritis (LN) patients progress to end stage renal disease and death. Detailed transcriptomic analyses of LN kidneys may identify new therapeutic targets. The AMP-PEARL Phase 1 project is to identify renal and urine LN single cell signatures.

Methods: Cells from urine and renal biopsies performed for clinical diagnosis from inform-consented patients (26 LN, 10 healthy controls) were isolated, frozen into Cryostor solution, sorted and profiled by RNAseq.

Results: A total of 15 immune cell populations active in the inflamed kidney were identified and revealed significant differences in subset frequencies across LN patients (e.g. B-cells, dendritic cells). Genes expression in cells from LN patients compared to those in healthy controls highlighted unique LN dysregulated genes/pathways (such as the expected IFN). The renal and urine signatures significantly correlated, suggesting that urine cells could be used as potential markers for longitudinal monitoring and assessment of kidney inflammation. Two chemokine receptors (CXCR4 and CX3CR1) were expressed on the surface of almost all infiltrating immune cells which may be new therapeutic targets.

Conclusions: Preliminary results from the AMP-PEARL-Phase 1 study identified LN active cells and pathways, that can be used to guide the development of novel therapies. Analyses at a bigger scale in the phase 2 of the project will accelerate discovery of new therapeutic targets and identification of biomarkers to guide therapeutic decisions in LN and integrate the treatment effect.

Funding: Other NIH Support - Accelerating Medicines Partnership (AMP)

FR-PO695

Synergetic B-Cell Immunomodulation with Rituximab and Belimumab Combination Treatment in Severe, Refractory SLE: The SynBiose Proof-of-Concept Study Tineke Kraaij,[1] Sylvia Kamerling,[1] Esther de Rooij,[1] Paul L. Van daele,[2] Edwin Bredewold,[1] Jaap A. Bakker,[3] Ingeborg M. Bajema,[4] Hans Ulrich Scherer,[5] Rene Toes,[5] Tom Huizinga,[5] Ton J. Rabelink,[1] Cees van Kooten,[1] Yoe Kie Onno Teng.[1] *[1]Nephrology, Leiden University Medical Center, Leiden, Netherlands; [2]Clinical Immunology, Erasmus MC, Rotterdam, Netherlands; [3]Clinical Chemistry, Leiden University Medical Center, Leiden, Netherlands; [4]Pathology, Leiden University Medical Center, Leiden, Netherlands; [5]Rheumatology, Leiden University Medical Center, Leiden, Netherlands*.

Background: Neutrophil extracellular traps (NETs) are auto-antigenic DNA strands and could give rise to SLE-specific autoantibodies that can deposit in glomeruli. It has been shown that autoantibodies can induce NETs, contributing to a vicious circle of immune activation in SLE. We hypothesized that eliminating autoantibodies can lead to decreased NET induction and thereby ameliorating disease in SLE. We designed a proof-of-concept study to eliminate autoantibodies and NET formation through synergetic B-cell immunomodulation with rituximab and belimumab (RTX+BLM) in severe refractory SLE.

Methods: We treated patients with severe, refractory SLE in a phase 2 study with RTX+BLM. The primary endpoint assessed reduction of pathogenic autoantibodies and NET induction at week 24. Anti-dsDNA autoantibodies were measured and high sensitivity FACS was performed to assess B-cell subsets. NET induction was measured with 3D confocal microscopy.

Results: We included 14 patients with severe, refractory SLE of whom 11 had a renal flare. At 24 weeks we observed significant reductions in anti-dsDNA autoantibodies ($p=0.0015$). CD19+ B-cells were depleted throughout the study ($p=0.0005$) while plasma cells (PCs) temporarily decreased but returned at week 24 despite persistent depletion of transitional B-cells. Taken together with reductions of autoantibodies and stable total IgG, there is no reconstitution of autoreactive PCs. We observed significant decrease in NET reduction ($p=0.0017$). In vitro studies elucidated this resulted in reduction of immune complexes by RTX+BLM. Importantly, beneficial immunological effects translated to amelioration of clinical disease activity: SLEDAI decreased from a median of 18 to 2 ($p=0.0002$). Ten out of 11 LN patients showed a response (4 complete renal responders). The response was achieved while tapering immunosuppressive drugs. Treatment was well-tolerated.

Conclusions: The SynBiose study is the first to demonstrate that RTX+BLM ameliorated disease in severe SLE in association with the reduction of pathogenic autoantibodies and immune complex-mediated NET induction. Therefore, RTX+BLM represents a novel treatment concept in SLE. ClinicalTrials.gov NCT02284984

FR-PO696

Erythropoietin (EPO) Ameliorates Lupus Nephritis by Inhibiting TFH and Increasing Treg Andrea Angeletti,[2,4] Chiara Donadei,[2,4] Vivette D. D'Agati,[1] Arun Cumpelik,[2] Joaquin Manrique,[3] Miguel L. Fribourg,[2] Gaetano La Manna,[4] Peter S. Heeger,[2] Paolo Cravedi.[2] *[1]Columbia University College of Physicians and Surgeons, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]Complejo Hospital de Navarra, Pamplona, Spain; [4]Nephrology, DIMES, Bologna, Italy*.

Background: Systemic lupus erythematosus (SLE) is characterized by impaired immune regulation and enhanced follicular helper T cell (Tfh)-dependent B cell activation, autoantibody production and tissue deposition/injury. Building upon evidence that EPO inhibits effector T cells (Teff) while promoting regulatory T cells (Treg) (JASN 2017), we tested the effects of EPO in murine lupus.

Methods: We treated MRL/lpr mice with rEPO (5,000IU/ml, 3/week mo 4-6) or vehicle, serially measured proteinuria and at 6 mo quantified anti-dsDNA, glomerular Ig deposition and splenic Treg/Teff/Tfh. We also administered EPO or vehicle to (bxd) F1 mice given B6 spleen cells and quantified splenic Tfh, Treg and germinal center (GC) B cells 2 weeks later.

Results: In MRL/lpr mice, rEPO increased Treg (20.1±3.3 vs. 11.5±4.2%; $P<0.05$) and reduced proteinuria, autoantibodies, glomerular IgG deposition, and histological score (is that right?) (**Fig 1A**). In the parent to F1 model, EPO inhibited T_{FH} and GC B cells formation (**Fig 1B-C**), while it increased Treg cells vs. vehicle (1.4±0.3 vs. 0.4±0.2%; $P<0.05$).

Conclusions: EPO administration inhibits T_{FH} and GC B cell formation while promoting Treg, together reducing the clinical and histological expression of murine lupus nephritis. Together with our published evidence that EPO promotes human Treg, the data support safety/efficacy testing of rEPO as an immunemodulating agent in lupus patients.

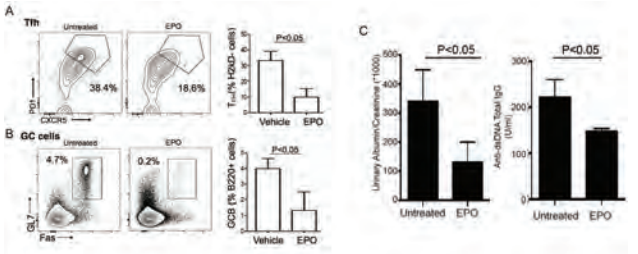


Figure. EPO reduces T_{FH} and germinal center (GC) B cells in GVHD lupus model and ameliorates MRL/lpr model. Donor ($H2kd^a$) $CD4^+PD1^+CXCR5^+$ Tfh cells (A, representative plots, left, and data quantification, right) and host ($H2kd^-$) $B200^+IgM^-IgD^-GL7^+Fas^+$ GC B cells (B) in B6 x BALB/c mice treated with or without EPO (5,000IU x 3/week) at 7 days after adoptive transfer of CD8-depleted splenocytes. C) Proteinuria and serum anti-dsDNA autoantibodies in MRL/lpr mice treated with or without EPO. Data are representative of 3-5 mice per group.

FR-PO697

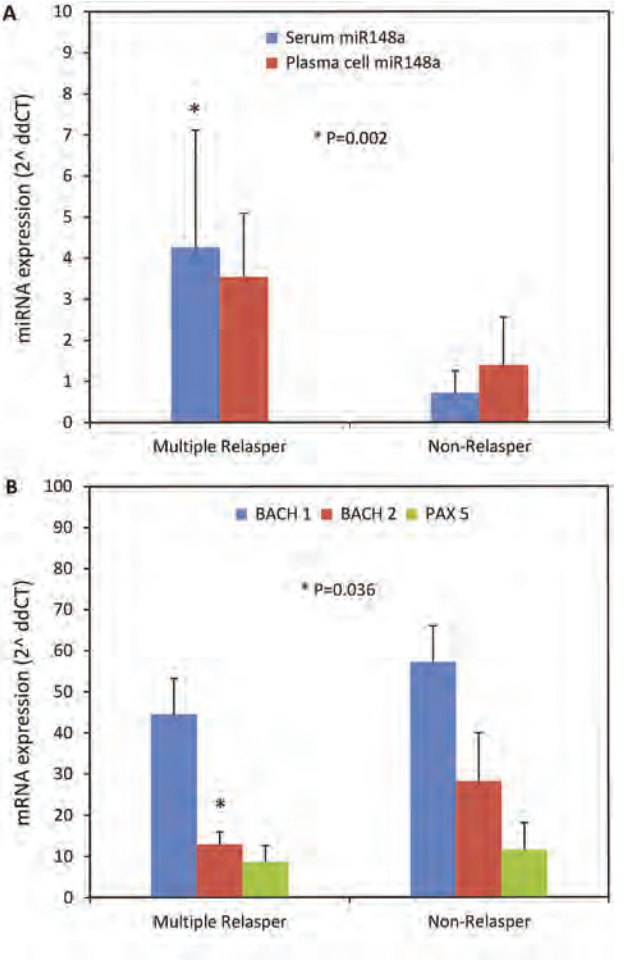
Relationship between B Cell Signatures and Disease Flare in Lupus Nephritis Patients Desmond Y. Yap,[1] Susan Yung,[2] Irene Yam,[2] Paul Lee,[2] Cheryl Tam,[2] Daniel Tak Mao Chan.[1] *[1]Queen Mary Hospital, Hong Kong, China; [2]The University of Hong Kong, Hong Kong, China.*

Background: Nephritic flares in patients with lupus nephritis (LN) reduce renal survival but factors contributing to flares remain elusive. Perturbations of B cell subsets have been implicated in the pathogenesis of LN, but the relationship between B cell signatures and relapse has not been investigated.

Methods: We compared circulating B cell subsets and signatures (miRNA148a, BACH1, BACH2 and PAX5) in the serum and plasma cells during disease quiescence between Class III/IV±V LN patients who are multiple relapsers (MR, defined as ≥3 relapses within 36 months unrelated to non-compliance) or non-relapsers (NR, defined as no relapse after the presenting episode).

Results: 33 patients were included (MR n=20; NR n=13). MR showed lower percentage of circulating naïve and memory B cells (0.48%, IQR 0.24%-3.15% vs. 4.52%, IQR 3.18%-8.25%; and 0.51%, IQR 0.26%-0.67% vs. 0.96%, IQR 0.86%-1.91%; p=0.014 and 0.014 respectively) and higher plasma cell-to-naïve B cell ratio (1.52±2.19 vs. 0.21±0.33, p=0.011) compared with NR. MR had higher miRNA148a in serum and plasma cells compared with NR [relative expression (RQ) 4.25±2.86 vs. 0.71±0.55 and 3.53±1.56 vs. 1.38±1.17, p=0.002 and 0.128] (Figure 1A). MR also showed lower BACH2 expression in circulating plasma cells [RQ 12.86±3.10 vs. 28.10±11.87, p=0.036)], but no difference in BACH1 and PAX5 (p>0.05 for both) (Figure 1B).

Conclusions: Elevated serum and plasma cell miRNA148a might be related to BACH2 downregulation in plasma cells and altered circulating B cell subsets, thereby increasing risk of LN relapse.



FR-PO698

Serum VCAM-1 Level in Patients with Lupus Nephritis and Its Clinical Associations Daniel Tak Mao Chan, Kelvin Yu, Mel Chau, Kwok Fan Cheung, Susan Yung. *Department of Medicine, The University of Hong Kong, Hong Kong SAR, Hong Kong.*

Background: Cardiovascular disease is more common in patients with lupus nephritis. Endothelial cell activation or injury is associated with shedding of adhesion molecules into the circulation. We investigated circulating VCAM-1 level in lupus nephritis patients and its clinical associations.

Methods: Archived paired serum samples, one during flare and the other during clinical remission, from 29 patients with biopsy-proven Class III/IV lupus nephritis were included. Serial samples obtained at intervals of 3-4 months over two years in 27 stable patients were included for longitudinal studies. Smokers and patients with serum creatinine above 450μmol/l or eGFR below 15ml/min were excluded. Age- and sex-matched patients with non-lupus glomerular diseases and healthy subjects (n=25 for each group) were included as controls. Serum VCAM-1 level was measured by ELISA.

Results: 482 serum samples from lupus nephritis patients (20 females and 9 males; age 39.0±10.2 years; disease duration 7.6±8.6 years) were studied. Only one patient had clinically evident vascular disease. Serum VCAM-1 level was significantly higher during active lupus nephritis, compared to remission samples, patients with non-lupus renal diseases or healthy subjects (P<0.001, for all). VCAM-1 level correlated with SLEDAI and the level of anti-dsDNA antibody, serum creatinine, urine albumin-to-creatinine ratio, and prevailing prednisolone daily dose, and inversely correlated with serum C3 and albumin levels. VCAM-1 level was not associated with lipid parameters. Longitudinal studies showed that increased circulating VCAM-1 level preceded clinically evident renal flare by 4.6±3.4 months, and persisted for 11.7±8.8 months after clinical disease quiescence. Analysis with ROC curve showed that serum VCAM-1 level distinguished patients with active lupus nephritis from healthy subjects with sensitivity and specificity rates of 96.5% and 96.0% respectively (P<0.0001), and from patients with non-lupus renal diseases with sensitivity and specificity rates of 89.6% and 82.6% respectively (P<0.0001).

Conclusions: Active lupus nephritis was associated with elevated VCAM-1 level in serum, which persisted for many months despite renal response after treatment. The findings suggest prolonged subclinical vascular endothelial injury and could have implications on the pathogenesis of cardiovascular complications.

Funding: Government Support - Non-U.S.

FR-PO699

Pathologic Findings in Monoclonal Glomerulopathy with Features of Cryoglobulinemic Nephropathy in the Kidneys of a Vk*MYC Transgenic Model of Multiple Myeloma Ping L. Zhang,[1] Guillermo A. Herrera,[3] Karen L. Lewinski,[1] Bei Liu.[2] *[1]Anatomic Pathology, Beaumont Health System, Royal Oak, MI; [2]Immunology, Medical University of South Carolina, Charleston, SC; [3]Pathology, Louisiana State University Health Sciences Center, Shreveport, LA.*

Background: There are only a few animal models of monoclonal light chain-associated renal diseases and no animal models of monoclonal cryoglobulinemic nephropathy (CN) that can be used to evaluate treatment modalities. The Vk*MYC transgenic model in 50-70 weeks old mice with renal involvement has been reported before (Chesi *et al*., 2008) but detailed renal pathologic changes have not been well documented. This study fully investigates pathologic changes in these kidneys.

Methods: The kidneys of 6 wild type and 12 Vk*MYC transgenic mice were investigated using routine light microscopy (LM), immunofluorescence stains for light chains (IF), and electron microscopy (EM). The EM score system developed to evaluate findings is as follows: 0 – no deposits, +/- minimal electron dense deposits, 1+ - mild deposits, 2+ - moderate deposits and 3+ - moderate to prominent deposits with subendothelial deposits.

Results: By LM, wild-type kidneys were unremarkable. However, the kidneys from transgenic mice showed either mesangial segmental expansion, some with associated hypercellularity and /or thrombotic obstruction of glomerular capillaries. By IF, the glomeruli of wild-type mice showed minimal or no staining for both kappa and lambda. In the transgenic mice, lambda was 2+, stronger than kappa 1+ staining in glomeruli as a reversed pattern in 3 mice. In the aging wild-type mice, minimal electron dense deposits can be seen in the mesangial areas by EM. Notably, in transgenic mice, 6 out of 12 kidneys showed mild mesangial deposits (1+). The other 6 kidneys from the transgenic mice showed 2-3+ electron dense deposits. The deposits were located in glomerular capillary lumina in 3 cases. Large luminal and subendothelial deposits were characterized by randomly disposed microtubular structures measuring up to 16 nm in diameter**,** with overall features consistent with findings CN. Segmental fusion of foot processes were seen, but no mesangial interposition was noted.

Conclusions: Our pathology evaluation suggests that 50% (6/12) of kidneys from the Vk*MYC model of MM had significant EM deposits with features of CN in 3 of them (most likely lambda dominant). This transgenic model of monoclonal-associated glomerulopathy may be useful to evaluate treatment of neoplastic B cell clones with renal manifestations.

Funding: Other NIH Support - NCI

FR-PO700

C4d Deposits in FSGS before the Development of Sclerosis Nina A. van de Lest,[1] Malu Zandbergen,[1] Reinhold Kreutz,[2] Jan A. Bruijn,[1] Ingeborg M. Bajema,[1] Marion Scharpfenecker,[1] Jamie S. Chua.[1] *[1]Leiden University Medical Center, Dept.Pathology, Leiden, Netherlands; [2]Charite-University Medicine Berlin, Berlin, Germany.*

Background: Immune deposits of complement components are occasionally seen in patients with FSGS. These deposits are non-diagnostic and are often considered as nonspecific entrapment in sclerotic lesions. However, deposits of IgM and C3 have also been observed in non-sclerotic glomeruli. Moreover, recent animal studies demonstrated a role for the complement system in the pathogenesis of FSGS. Here, we investigated the pattern of complement deposition in glomeruli of experimental and human FSGS, using the complement activation biomarker C4d.

Methods: Kidney sections of Munich Wistar Frömter (MWF) rats of 4 (no proteinuria), 8 (only proteinuria) and 24 (proteinuria with glomerulosclerosis) weeks of age were stained for C4d. Age-matched spontaneously hypertensive rats (SHR) with no proteinuria were used as controls. Also, we performed a C4d staining on 40 kidney biopsies of patients with FSGS and 46 control biopsies of patients with minimal change disease (MCD) who have proteinuria without segmental glomerulosclerosis. Prevalence and localisation of C4d deposition in glomeruli were investigated.

Results: The percentage of C4d positive glomeruli was significantly higher in MWF rats at 8 and 24 weeks of age compared to controls ($p<0.001$ and $p<0.01$ respectively). C4d deposits were also more frequently observed in rats of 4 weeks of age, yet not significant. At 24 weeks, 94% of sclerotic glomeruli were C4d positive, whereas 50% of C4d positive glomeruli showed segmental glomerulosclerosis. In human biopsies, glomerular C4d deposits were observed in 75% of FSGS and 35% of MCD cases ($p<0.001$). Of positive cases, 40% of glomeruli were positive in FSGS compared to 33% in MCD. In FSGS, C4d was co-localized with segmental sclerosis in 57% and was present in non-sclerotic glomeruli or non-sclerotic parts of sclerotic glomeruli in 45%.

Conclusions: Here, we show that in the MWF rat model for FSGS, C4d deposits are present before the development of glomerulosclerosis. Similarly, C4d deposits were present in non-sclerotic glomeruli of patients with FSGS and in patients with MCD who have proteinuria without segmental glomerulosclerosis. These results indicate that C4d deposition could be involved in the development of FSGS.

FR-PO701

Blockade of TNF Alpha Signaling Reverses Toxic Effects of Focal Segmental Glomerulosclerosis Sera on Podocyte Adhesion Independently of Serum TNFa Level Elena Torban,[1] Nadezda Kachurina,[1] Chen-Fang Chung,[1] Katarina S. Pessina,[1] Thomas Kitzler,[1] Nada Alachkar,[2] Paul R. Goodyer,[1] Andrey V. Cybulsky.[1] *[1]McGill University Health Center, Montreal, QC, Canada; [2]The Johns Hopkins University, Baltimore, MD.*

Background: Patients with primary FSGS often progress to end stage renal disease and require renal transplantation. In about half, the disease recurs in the allograft, suggesting a circulating podocyte-toxic factor in the host. We and others have reported clinical improvement following TNFα blockade in a subset of recurrent FSGS patients. Likewise, blockade of TNFα signaling in cultured human podocytes reverses the toxicity of some FSGS sera. In this study, we tested 100 FSGS serum/plasma samples for in vitro podocyte toxicity and responsiveness to TNFα blockade, and measured serum TNFα levels or serum effects on expression of podocyte TNFα pathway genes.

Methods: Plasma/serum samples from steroid-resistant nephrotic syndrome patients with biopsy-confirmed FSGS were tested for toxicity to human podocytes, as judged by disassembly of focal adhesion complexes (FACs) (Kachurina, AJP-R, 2016). Pre-treatment with blocking anti-TNFα Receptor I&II antibodies was used in some experiments. Expression of 8 TNFα pathway genes, whose expression differs significantly between FSGS and control samples in the Nephroseq database, was assessed by RT-qPCR.

Results: A significant loss of FACs (less than 60% of control) was induced by 47% of FSGS samples. Among these, TNFα blockade reversed podocyte toxicity in 24%. Neither serum toxicity nor responsiveness to TNFα blockade in podocytes correlated with circulating TNFα levels. Significant changes in expression of TNFα signaling pathway genes were induced by exposure to FSGS sera that disrupted podocyte FACs and that could be reversed by TNFα blockade, but not by sera from healthy controls or rheumatoid arthritis patients.

Conclusions: Sera from a subset of primary FSGS patients cause striking dispersion of podocyte FACs. This activity is unrelated to serum TNFα level but may be due to the effect of FSGS serum on activation of endogenous podocyte TNFα pathway signaling. Our assay may be useful in identifying patients at high risk for recurrence of FSGS in the renal allograft and who may potentially benefit from TNFα blockade to attenuate podocyte injury.

Funding: Government Support - Non-U.S.

FR-PO702

Proteomic Analysis of Glomerular Extracellular Matrix Demonstrates Differences between FSGS Variants Michael Merchant,[1] Dawn J. Caster,[1,2] Daniel W. Wilkey,[1] Michelle T. Barati,[1] Kenneth R. McLeish.[1] *[1]Department of Medicine, Division of Nephrology & Hypertension, University of Louisville, Louisville, KY; [2]Robley Rex VA Medical Center, Louisville, KY.*

Background: Abnormal remodeling of glomerular extracellular matrix (ECM) is a prominent feature of focal segmental glomerular sclerosis (FSGS). Changes in ECM that accompany FSGS have not been defined in humans. We postulated that FSGS is characterized by specific changes in ECM composition. The current study used laser capture microdissection (LCMD) of glomeruli from human biopsy specimens and mass spectrometry (MS) and immunohistochemical (IHC) methods to compare -ECM composition among patients with FSGS-NOS, collapsing FSGS (CFSGS), and normal subjects.

Methods: Glomerular sections were obtained by LCMD from de-identified FFPE tissue from FSGS-NOS (n=6), CFSGS (n=7), and from 2 kidneys retrieved, but not used, for transplantation. Samples were analyzed as recently published (Hobeika L, et al. Characterization of glomerular extracellular matrix by proteomic analysis of laser-captured microdissected glomeruli. Kidney Int. 2017 91:501-511). Abundance data were filtered by GO annotation and matrixome designation for confirmatory IHC studies using Human Proteome Atlas validated antibodies and an expanded disease/normal- control renal biopsy panel.

Results: IHC was performed on 7 of 25 ECM proteins unique to CFSGS, 3 of 6 unique to FSGS-NOS, and 2 of 20 present in both subtypes of FSGS but not normal. All ECM proteins identified from normal were present in FSGS glomeruli. Annexin 3, marker of parietal epithelial cells (PEC), and cathepsin C, an inflammatory protease, showed intraglomerular staining in 10% to 20% of glomeruli in biopsies from CFSGS patients, while only staining Bowman's capsule in biopsies of FSGS-NOS, minimal change disease, IgAN, primary membranous nephropathy, and congenital nephrotic syndrome. Annexin 3 and cathepsin C co-localized within CFSGS glomeruli, while staining with a marker of activated PEC (CD44), was negative.

Conclusions: PEC infiltration of glomerular tufts was characteristic of CFSGS, not FSGS-NOS. Although PEC did not express activation markers, they produced a protease unique to glomerular ECM. Cathepsin C may represent a novel mediator of PEC-mediated glomerulosclerosis leading to collapse.

Funding: NIDDK Support, Private Foundation Support, Clinical Revenue Support

FR-PO703

Role of Monocyte Interleukin (IL)-27 in Minimal Change Nephrotic Syndrome (MCNS) Chang-Yien Chan,[2,4] Wee Song Yeo,[2,4] Jinmiao Chen,[3] Henry H. Yang,[1] Hui Kim Yap.[2,4] *[1]Cancer Science Institute of Singapore, National University of Singapore, Singapore, Singapore; [2]Paediatrics, National University of Singapore, Singapore, Singapore; [3]Singapore Immunology Network (SIgN), (BMSI, A*STAR), Singapore, Singapore; [4]KTP-National University Children's Medical Institute, National University Hospital, Singapore, Singapore.*

Background: We have previously shown upregulation of lymphocyte IL-13 gene expression during nephrotic relapses in MCNS patients, associated with downregulation of pro-inflammatory cytokines, IL-8 and tumor necrosis factor (TNF)-α in lipopolysaccharide (LPS)-stimulated monocytes, and decreased monocyte CD14 expression, suggestive of an IL-13-induced anti-inflammatory effect. This study aimed to identify the monocyte 'gene signature' in MCNS patients and subsequently to validate the findings in human podocytes.

Methods: Monocyte RNA from 5 patients in relapse and remission were analysed using Illumina Human Ref8 chips. Subsequently plasma IL-27 levels were measured in 14 MCNS patients in relapse and remission and 20 healthy controls. The role of IL-27 in human podocytes was studied using cell migration assay (cultrex). Podocyte RhoA/Rac1 activity were measured using ELISA and STAT1/3 levels were studied using Western blot. Statistical analysis was done using Mann-Whitney test and Wilcoxon signed rank test for paired data.

Results: Metacore™ analysis on the monocyte transcriptome of MCNS patients in relapse compared to remission revealed involvement of genes in IL-1 signaling, regulation of actin cytoskeleton by RhoGTPases, toll-interleukin receptor (TIR)-domain-containing adapter-inducing interferon-β (TRIF) and IFN-induction (IRF4, IRF7, IFI6, IFI27, IFI35, IFI44, SERPING1, OAS1, OAS2, OAS3, OASL, CXCL9, CXCL10, DDX58) pathways. Of note gene expression of *IL27* was 2.7 times upregulated in MCNS patients in relapse. Consistent with the microarray results, plasma IL-27 levels were significantly higher in MCNS patients in relapse (1.56±0.19 pg/ml) compared to remission (0.95±0.13 pg/ml) ($p<0.05$) and controls (0.89±0.14 pg/ml) ($p\leq0.01$). IL-27 stimulation in human podocytes resulted in phosphorylation of both STAT1 and STAT3. RhoA activity in IL-27 stimulated podocytes remained largely unchanged whereas activated Rac1 levels in podocytes were 1.56-fold higher compared with unstimulated podocytes at 20 minutes. Moreover, IL-27 induced 6.35% podocytes migration, comparable to the 6.96% podocytes migration observed in LPS-stimulated podocytes.

Conclusions: Monocytes may play a role in the pathogenesis of MCNS relapses via production of IL-27 and subsequent activation of STAT1, STAT3 and Rac1 as well as induction of cell migration in human podocytes.

Funding: Government Support - Non-U.S.

FR-PO704

Loss of Mitf Aggravates PAN Induced Proteinuria in Zebrafish Philipp Niggemann,[1] Patricia A. Schroder,[2] Patricia Bolanos-Palmieri,[1] Janina Müller-Deile,[1] Heiko J. Schenk,[1] Laura L. Beverly-Staggs,[2] Beina Teng,[1] Hermann G. Haller,[1] Mario Schiffer.[1] *[1]Hanover Medical School, Freiburg, Germany; [2]Mount Desert Island Biological Laboratory, Salisbury Cove, ME.*

Background: We developed a standardized proteinuria model in zebrafish using puromycin aminonucleoside (PAN) through treatment via the water. We noticed, that fish with the *nacre* mutation show a significantly higher susceptibility to PAN than AB fish upon exposure to the same dosage of PAN. (AB is a standard wild-type line) *Nacre* is the name of a mutation yielding a truncated version of Microphthalmia-associated transcription factor (Mitf) in zebrafish. Mitf is an evolutionary conserved transcription factor that controls pigment cell fate in vertebrates. It is well known that a mutation in *mitf* leads to missing neural-crest-derived melanophores and results in a pigment-less phenotype, making this mutation a commonly used fish line to study organ development.

Methods: Tg(l-fabp:eGFP-DBP) zebrafish were backcrossed onto AB or *nacre* background and were exposed to PAN in the water at varying timepoints from 44 hours post fertilization (hpf) to 50 hpf. Loss of high molecular weight proteins from the circulation was measured at 96 hpf as a surrogate marker for proteinuria. In addition, we performed *mitf* knockdown experiments in AB zebrafish using morpholinos. Moreover, cultured human podocytes were examined after silencing of *MITF in vitro*.

Results: Zebrafish homozygous for the *nacre* mutation and AB zebrafish after knockdown of *mitf* exhibited stronger proteinuria after PAN treatment compared to control animals. Moreover, a treatment with PAN at 46 hpf yielded the strongest proteinuria. Treatments at later timepoints were less effective in proteinuria induction. Silencing of *MITF* in human podocytes led to a disrupted cytoskeletal organization after PAN treatment. At the same time the expression of MITF downstream partners like INF2 was changed, indicating that MITF plays an important role for cytoskeleton recovery in podocytes.

Conclusions: We present the first reproducible PAN-nephrosis model in zebrafish, which could serve as a suitable setting for drug testing in zebrafish. Furthermore, we can demonstrate that a mutation in *mitf* leads to a higher susceptibility for disruption of the glomerular filtration barrier upon PAN treatment, which results in stronger proteinuria.

FR-PO705

Heterogeneous Nuclear Ribonucleoprotein F Deficiency Aggravates Podocyte Loss via Down-Regulation of Sirtuin-1 Expression in Adriamycin-Induced Nephropathy in Mice Chao-Sheng Lo,[2] Isabelle Chenier,[1] Janos G. Filep,[4] Julie R. Ingelfinger,[6] Shao-Ling Zhang,[5] John S. Chan.[3] *[1]CHUM-Hotel Dieu Hosp, Montreal, QC, Canada; [2]CRCHUM, Universite de Montreal, Montreal, QC, Canada; [3]CRCHUM, University of Montreal, Montreal, QC, Canada; [4]Maisonneuve-Rosemont Hosp., Montreal, QC, Canada; [5]Research Center of Centre Hospitalier de l Universite de Montreal (CRCHUM), Montreal, QC, Canada; [6]The New England Journal of Medicine, Boston, MA.*

Background: We reported that overexpression of heterogeneous nuclear ribonucleoprotein F (hnRNP F) enhances sirtuin-1 expression and attenuates apoptosis in renal proximal tubular cells in db/db hnRNP F-transgenic mice (Diabetes 2017). In the present study, we investigated whether hnRNP F deficiency in podocytes would aggravate podocyte injury in adriamycin (ADR)-induced nephropathy in mice.

Methods: Podocyte-specific hnRNP F knockout (KO) mice were generated by crossbreeding podocin (Pod)-Cre mice with floxed hnRNP F mice on a C57BL/6 background. Male adult non-KO littermates (controls) and Pod-hnRNP F KO mice were studied at age 10 to 20 weeks. Body weight (BW) and urinary albumin/creatinine ratio (ACR) were monitored bi-weekly. To induce nephropathy, male controls and Pod-hnRNP F KO mice were administered ADR (doxorubicin) (18 mg/kg BW) via tail vein at the age of 10 weeks. Urinary ACR were assessed 7 and 11 days post-ADR. Mice were euthanized on day 12. Kidneys were processed for histology. Freshly isolated glomeruli were assessed for mRNA and protein expression by real time-qPCR and Western blotting, respectively. In addition, primary podocytes isolated from controls and Pod-hnRNP F KO mice ± ADR were studied in vitro.

Results: Pod-hnRNP F KO mice were phenotypically normal with a slight increase in ACR at week 20. Glomeruli isolated from POD-hnRNP F KO mice exhibited significantly lower mRNA and protein levels of sirtuin-1 and podocyte markers including nephrin, WT1 and synaptopodin than controls. Administration of ADR significantly increased urinary ACR and apoptotic podocytes in both groups. However, these changes were more pronounced in Pod-hnRNP F KO mice, parallel with significant decreases in sirtuin-1, nephrin, WT1 and synaptopodin expression. Finally, in vitro studies confirmed that primary podocytes from hnRNP F KO mice exhibited lower sirtuin-1 expression and higher acetylated p53 expression and apoptotic podocytes after ADR treatment.

Conclusions: HnRNP F deficiency aggravates podocyte apoptosis in ADR-induced nephropathy in mice, indicating a protective role for hnRNP F against podocyte injury.

Funding: Government Support - Non-U.S.

FR-PO706

Recombinant Mutated Human Angiopoietin-Like 4 Reduces the Progression of CKD Due to Diabetes and FSGS Maria Del Nogal Avila,[1] Hector Donoro blazquez,[1] Joubert B. Kharlyngdoh,[1] Ranjan Das,[1] Eduardo Molina-Jijon,[1] Szymon Filip,[1] Carmen Avila-Casado,[2] Camille E. Mace,[1] Lionel C. Clement,[1] Sumant S. Chugh.[1] *[1]Rush University Medical Center, Chicago, IL; [2]University Health Network, University of Toronto, Toronto, ON, Canada.*

Background: Angptl4 is a major molecular mediator of nephrotic syndrome secreted in two forms: a hyposialylated form secreted from podocytes that causes proteinuria in minimal change disease (MCD), and a sialylated circulating form secreted from skeletal muscle, heart and adipose tissue that reduces proteinuria and causes hypertriglyceridemia in nephrotic syndrome. Short-term studies with FSGS and diabetic nephropathy (DN) rats using recombinant mutant Angptl4 reduces proteinuria without causing hypertriglyceridemia.

Methods: We injected recombinant human mutated Angptl4 (protein 8520) or control albumin weekly subcutaneously into rats with FSGS (B. Mna; n=6/group) and DN (ZSF1; n=5/group) according to different dosing regimens. Recombinant sialylated Angptl4 mutant 8520 was produced in HEK923 cells growing in hollow fiber bioreactors. To study the effect of higher native circulating sialylated Angptl4 expression in FSGS, adipose tissue-specific Angptl4 TG (372) were backcrossed for 8 generations into B. Mna rats.

Results: ZSF1 rats treated with 500μg of 8520 had less proteinuria (38.95±6.6 mg per 18h) than controls (64.8±3.3 mg per 18h) after 3 weeks of weekly treatment ($p<0.05$). When the dose was reduced, proteinuria was not significantly different between the two groups. Differences were restored after increasing the amount of protein at week 13 (8520: 172.4±14.5 mg per 18h and control 210.6±13.5 mg per 18 h; $p<0.05$). BUN and creatinine levels were significantly lower in rats treated with 8520 at different time-points, with better histology morphology than controls after 28 weeks of treatment. After 15 weeks of Angptl4 mutant therapy, B. Mna rats had less prominent visceral epithelial cells, less VEP hypertrophy, less tubular-interstitial inflammation and less periglomerular fibrosis compare with control group. 8 month old male 372-B. Mna has less creatinine and BUN than non-TG B. Mna rats and remarkable improved histology. Female 372-B. Mna showed less proteinuria (238.5±39.4 mg per 18h) than non-TG B. Mna rats (307.8±15.7 mg per 18h) ($p=0.048$).

Conclusions: These findings suggest a protective effect of recombinant mutated human Angptl4, as well as increased circulating native rat Angptl4 in the progression of CKD.

Funding: NIDDK Support

FR-PO707

Albumin Modification Leads to Altered Glomerular and Podocyte Injury Shipra Agrawal,[1,2] Amanda P. Waller,[1] Jiro Kino,[1] Melinda A. Chanley,[1] Bryce A. Kerlin,[1,2] William E. Smoyer.[1,2] *[1]CCTR, The Research Institute at Nationwide Children's Hospital, Columbus, OH; [2]Pediatrics, The Ohio State University, Columbus, OH.*

Background: Albuminuria is associated with an increased risk of progressive glomerular disease. However, the molecular basis for potential causative roles for albuminuria and/or its modification [free fatty acid (FFA) binding and ionic forms] in progressive glomerular disease remains poorly understood. We hypothesized that albumin modification by altering its levels, FFA binding ratio, and charge can regulate glomerular and podocyte injury.

Methods: A model of chronic glomerular disease was studied in wild type (WT), Nagase Analbuminemic Rat (NAR), and NAR-Het on a Fischer344 background female rats (~160 g, N=4-5/group) by multiple puromycin-aminonucleoside (PAN) injections (100 mg/kg i.p., every 4 weeks) over a course of 3 months, with serial measurements of proteinuria, serum creatinine, urinary podocalyxin, and N-acetyl-b-D-glucosaminidase (NAG) activity. Moreover, direct podocyte injury was compared following exposure to albumin and FFA at varying molar ratios, as well as exposure to cationic vs. regular albumin.

Results: Consistent proteinuria was induced at week 11 in WT rats, which was significantly higher vs. NAR or NAR-Het rats. Moreover, comparable plasma protein levels were observed in NAR vs. WT rats, despite complete absence of albumin in NAR. Serum creatinine levels were similarly increased in both NAR and WT rats at week 12, while podocalyxin levels were slightly increased only in WT rats, and NAG activity was not altered in either group. Since the FFA:albumin ratio is massively altered in NAR, the ability of FFA to cause direct podocyte injury in vitro was measured in the absence/presence of albumin at different molar ratios. Both the absence of albumin and exceeding the FFA binding capacity of albumin (>10:1 FFA:albumin) resulted in increased podocyte toxicity, especially for oleic acid and arachidonic acid. Additionally, cationic albumin induced dramatically greater podocyte toxicity vs. regular negatively charged albumin, even at 400 times lower concentration (0.1 g/dL, 20 hr exposure vs. 4g/dL, 4-7 days exposure).

Conclusions: Modification of albumin by altering its levels, FFA:albumin ratio, or ionic charge dramatically alters its glomerular and direct podocyte toxicity.

FR-PO708

Inhibition of p53 Desumoylation by SENP1 Exacerbates Puromycin Aminonucleoside-Induced Apoptosis in Podocytes Lingyu Wang. *the First Affiliated Hospital of Dalian Medical University, Dalian, China.*

Background: Apoptosis is a major cause of reduced podocyte numbers, which leads to proteinuria and/or glomerulosclerosis. Emerging evidence has indicated that deSUMOylation, a dynamic post-translational modification that reverses SUMOylation, is involved in the apoptosis of Burkitt'slymphoma cells and cardiomyocytes; however, the impact of deSUMOylation on podocyte apoptosis remains unexplored. The p53 protein plays a major role in the pathogenesis of podocyte apoptosis, and p53 can be SUMOylated.

Methods: Therefore, in the present study, we evaluated the effect of p53 deSUMOylation, which is regulated by sentrin/SUMO-specific protease 1 (SENP1), on podocyte apoptosis.

Results: Our results showed that SENP1 deficiency significantly increases PAN-induced podocyte apoptosis. Moreover, SENP1 knockdown results in the accumulation of SUMOylated p53 protein and the increased expression of the p53 target pro-apoptotic genes, *BAX*, *Noxa* and *PUMA*, in podocytes during PAN stimulation.

Conclusions: Thus, SENP1 may be essential for preventing podocyte apoptosis, at least partly through regulating the functions of p53 protein via deSUMOylation. The regulation of deSUMOylationmay provide a novel strategy for the treatment of glomerular disorders that involve podocyte apoptosis.

FR-PO709

Antibody-Based Targeting of APRIL as a Therapeutic Strategy in the Treatment of IgA Nephropathy—A Case Study in a Grouped ddY Mouse Model James R. Myette,[2] Toshiki Kano,[1] Hitoshi Suzuki,[1] Hedy Adari,[2] Ketan Deotale,[2] Brian J. Pereira,[2] Yusuke Suzuki.[1] *[1]Juntendo University Faculty of Medicine, Tokyo, Japan; [2]Visterra, Inc., Cambridge, MA.*

Background: IgA nephropathy (IgAN) is a chronic, "autoimmune" glomerular disease of high unmet medical need. The cytokine APRIL (TNFSF13) is emerging as a key player in disease onset and progression, based on a recent convergence of biological and translational data. The pathogenic role of APRIL in IgAN has been previously established in grouped ddY (gddY) mice, an early-onset disease model which recapitulates many of the clinical hallmarks of IgAN pathophysiology and progression. VIS649, a humanized IgG2 specifically targeting human APRIL, is being developed as a therapy for IgA nephropathy. Based on its overlapping epitope and functional attributes, surrogate antibody mAb 4540, which neutralizes mouse APRIL, was used to evaluate anti-APRIL intervention in controlling disease in gddY mice.

Methods: 6-7 week old female mice were administered mAb 4540 (10-20 mg/kg) once weekly for up to eight weeks by i.p. injection. Relevant endpoints included serum immunoglobulin profiling by ELISA; IgA, IgG, and C3 deposition in kidney by IFC; proteinuria based on albumin:creatinine ratios (uACR) from spot urine; and glomerular histopathology by PAS staining. Cellular B-cell profiling in bone marrow was completed by flow cytometry.

Results: Treatment of gddY mice with mAb 4540, relative to the control groups, resulted in the suppression of serum IgA profiles and a markedly lower deposition of IgA, IgG, and C3 in the kidney mesangium. These observations correlated with a better glomerular histopathology profile and a lower uACR profile, indicative of reduced kidney injury. Treatment efficacy was observed as early as 4 weeks after the start of intervention and was sustained during the recovery phase of this study. Targeting APRIL with mAb 4540 demonstrated no overt differences in serum IgG levels or plasma cell profiles.

Conclusions: This study both confirms and extends the rationale for targeting the cytokine APRIL for treatment of IgAN. The demonstrated efficacy of mAb4540 in this model also highlights the potential therapeutic benefit of VIS649, a first-in-class human monoclonal antibody being developed for the treatment of IgAN.

Funding: Commercial Support - Visterra, Inc., Government Support - Non-U.S.

FR-PO710

Mesenchymal Stem Cells Acquire Phagocytotic Functions and Contractibility When They Repair Light Chain-Induced Mesangial Damage Chun Zeng, Guillermo A. Herrera, Man Liang, Hongzhi Xu, Elba Turbat-herrera, Jiamin Teng. *Pathology, LSUHSC-Shreveport, Shreveport, LA.*

Background: Using mesenchymal stem cells (MSCs) to repair the injured mesangium has been shown experimentally to be a promising approach. However, the precise role MSCs play in the repair process is still unclear. In this study, we investigated phagocytotic and contractibility capabilities of MSCs in the process of mesangial repair.

Methods: Mesangial cells (MCs) were incubated with AL-amyloidosis and light chain deposition disease G-LCs for 4 days to establish an in vitro mesangial cell injury model. Green fluorescent protein (GFP)-labeled MSCs were added together with florescent-labeled latex beads to assess phagocytotic activity of MSCs. A 6 dimensional (6D) live cell imaging system was used to record the process for 7 days after the introduction of the MSCs. Immunofluorescence, immunohistochemistry and electron microscopy were used to evaluate samples obtained at different time frames. Stains for smoothelin, CD68, CD29 and CD54 were used to monitor phenotypic expressions of MSCs. Collagen assay was used to evaluate contractibility.

Results: MSCs migrated to the damaged mesangial areas and morphologically transformed from an undifferentiated to a macrophage phenotype. MSCs lost CD29/54 stem cell makers after G-LCs treatment, acquiring CD68, and later expressed smoothelin / muscle specific actin. Significant amount of the florescent-labeled latex beads were engulfed by transformed MSCs indicating active phagocytosis during the initial cleaning phase of the repair. MCs revealed decreased contractibility after G-LCs treatment while MSCs exhibited contractability during the late phase of the process, but not at the beginning of the repair. The plasticity of MSCs was confirmed ultrastructurally with findings of macrophage and smooth muscle differentiation at different stages of the repair process.

Conclusions: MSCs undergo both morphological and functional transformations as they proceed to repair the damaged mesangium. In contrast to previous belief that MSCs only enhance repair via a paracrine mechanism, this study provides evidence that MSCs differentiate sequentially from uncommitted to macrophage and finally smooth muscle (mesangial cell) phenotypes during the process of mesangial repair. This permits the repair process to replace the damaged mesangium with fully differentiated mesangial cells.

FR-PO711

MicroRNA-181a (miR-181a) Drives Deptor Downregulation by TGFbeta (TGFb) to Induce Mesangial Cell (MC) Hypertrophy and Fibronectin Expression Soumya Maity,[3] Falguni Das,[1] Nandini Ghosh-choudhury,[1] Balakuntalam S. Kasinath,[2] Goutam Ghosh-Choudhury.[2] *[1]UTHSCSA, SAN ANTONIO, TX; [2]University of Texas Health Science Center, San Antonio, TX; [3]University of Texas Health Science Center at San Antonio, San Antonio, TX.*

Background: TGFb-stimulated noncanonical mTOR signaling contributes to MC hypertrophy and matrix protein expansion. The molecular mechanism of mTOR activation is not known. Deptor is a common inhibitory subunit for both mTORC1 and mTORC2.

Methods: MCs, qRT-PCR, reporter transfection, immunoblotting, anti-miR-181a and miR-181 mimic transfection, protein synthesis and hypertrophy assays were used.

Results: In MCs, TGFb reduced the expression of deptor in a time-dependent and prolonged manner. This deptor downregulation was associated with increased activation of both mTORC1 and mTORC2 as determined by the phosphorylation of S6 kinase and Akt (Ser-473), respectively. To study the mechanism of repression of deptor, we considered microRNA-mediated post-transcriptional regulation. Bioinformatic analysis revealed the presence of miR-181a recognition element in the 3'UTR (untranslated region) of deptor mRNA. In MCs, TGFb significantly increased the expression of miR-181a in time-dependent manner. Overexpression of miR-181a mimic inhibited the expression of deptor. To determine the responsiveness of the miR-181a recognition element, we used a reporter construct in which deptor 3' UTR was fused to the luciferase gene (3'UTR-Luc). Co-transfection of miR-181a mimic with this reporter plasmid showed significant reduction in luciferase activity, indicating the responsiveness of the recognition element. Incubation of 3'UTR-Luc-transfected MCs with TGFb significantly decreased the luciferase activity. Importantly, transfection of anti-miR-181a inhibited TGFb-induced phosphorylation of S6 kinase and Akt (Ser-473), two substrates of mTORC1 and mTORC2, respectively. In contrast transfection of miR-181a mimic increased the activity of mTORC1 and mTORC2. Furthermore, anti-miR-181a significantly inhibited TGFb-induced protein

synthesis and hypertrophy of mesangial cells. Similarly, anti-miR-181a attenuated TGFb-stimulated fibronectin expression.

Conclusions: Our results provide the first evidence for the mechanism of deptor downregulation by TGFb, involving miR-181a. Furthermore, we demonstrate for the first time that miR-181a contributes to TGFb-induced mesangial cell hypertrophy and matrix protein expression. Use of anti-miR-181a may be beneficial in TGFb-mediated fibrotic kidney disease.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO712

Exosomes from High Glucose-Treated Human Mesangial Cells Activate Renin Angiotensin System in Healthy Mesangial Cells Antonio S. Novaes,[1] Fernanda T. Borges,[2] Mirian A. Boim.[2] *[1]Federal University of São Paulo, São Paulo, Brazil; [2]UNIFESP, São Paulo, Brazil.*

Background: High glucose (HG) induced-intracellular angiotensin II (Ang II) accumulation is correlated with upregulation of Ang II target genes, such as pro-fibrotic cytokines. This effect can be propagated via microRNAs and peptides transferred to other cells via exosomes (Ex), which play a key role in cellular communication under physiological and pathological conditions.

Methods: To verify whether exosomal signaling initiated in HG stimulated human mesangial cells (HCM) would affect control cells function, HMC were cultured under standard (5 mM) or HG (30 mM) concentrations for 24 hr. Ex secreted to culture medium were purified by ultracentrifugation and analyzed by electron microscopy. The vesicles size/concentration ratio was determined by the particle tracking using a nanoparticles analyzer and the Ex were characterized by the presence of CD63 and CD81 by western blot. Ex from control (C-Ex) or HG stimulated-HMC (Ex-HG) were labeled with PKH26 and added in normal HMC. The Ex internalization was evaluated by confocal microscopy (CM). The presence angiotensinogen (AGT), renin and ACE in the Ex was analyzed by western blot. The bioactivity of the Ex was evaluated in Chinese Hamster Ovary cells (CHO-K1), which do not express components of RAS, and in CHO-K1 transfected ECA (ECA-CHO) in the presence of C-Ex or HG-Ex. The synthesis of Ang II in ECA-CHO was analyzed by CM. Expressions of fibronectin, AGT, renin, AT1, AT2 receptors and proliferation were used to assess the cellular response to signal transferred through the Ex in control HMC exposed to C-Ex or HG-Ex.

Results: HG stimulus induced a change in the amount, but not in the size of Ex. HG-Ex are internalized by normal HMC. C-Ex contained AGT and renin proteins, whose expressions were increased in cells exposed to HG-Ex. ACE was not detected in C-Ex and HG-Ex. The exposure of HG-Ex to ECA-CHO resulted in Ang II formation in these cells. The expression levels of fibronectin, AGT, renin, AT1 and AT2 were higher in control HMC treated with HG-Ex compared with those treated with C-Ex, indicating that HG-Ex can modify the function of target control HMC.

Conclusions: These results suggest that the intercellular communication through the exosomes may have pathophysiological implications in the diabetic kidney.

Funding: Government Support - Non-U.S.

FR-PO713

Connective Tissue Growth Factor (CTGF, CCN2) Is Sufficient to Drive Expression of Collagen IV, Fibronectin and Mesangial Expansion Yongxin Gao,[1,2] Charles W. Heilig,[1,2] Leighton R. James.[1,2] *[1]Medicine, University of Florida, Jacksonville, FL; [2]Diabetes Institute, University of Florida, Gainesville, FL.*

Background: CTGF has been linked to organ fibrosis. Using an animal model and cultured mouse embryonic fibroblast, we previously demonstrated that CTGF expression modulates response to hyperglycemia and diabetes mellitus. Accordingly, we hypothesized that CTGF directly influences expression of extracellular matrix protein to drive glomerulosclerosis. To test our hypothesis, we used animals that express 1 to 4 copies of mice CTGF gene to assess a) levels of ECM proteins (Fibronectin [Fn] and Collagen IV [Coll IV]), vascular endothelial growth factor (VEGF), mechano growth factor (MGF), as well as, b) mesangial expansion and.fibrosis.

Methods: CTGF knockout and gene-duplicated mice were generated using standard gene-targeting methodologies. Mice harboring 1 to 4 copies of CTGF were generated through breeding and have been previously described. Lysates were obtained from Kidney cortices retrieved from 6-month old mice and used for immunoblotting analysis of CTGF, Collagen IV, Fn, VEGF and MGF. Histologic examination was performed on fixed kidney sections using Hematoxylin and eosin (H&E), Periodic-schiff and Mason-trichrome staining. Immunohistochemistry utilized CTGF antibody and flourescent labelled secondary antibody.

Results: There was a graded increase in CTGF (3.5-fold), Coll IV (4-fold), Fn (7-fold), VEGF (8-fold) and MGF (7-fold) in 4-copy mice when compared with heterozygous (1-copy) animals. In addition, we observed mesangial matrix expansion and increased mesangial and perivascular fibrosis in kidney from 4-copy animals as compared with heterozygous and wild-type mice.

Conclusions: Graded CTGF expression directly increases expression of collagen, fibronectin, VEGF and MGF in mice kidney. Increased peri-vascular and glomerular sclerosis links CTGF expression with fibrosis, blood pressure and urine protein excretion previously observed in these models.

Funding: Private Foundation Support

FR-PO714

Down Regulation of Gamma-Adducin Diminishes Glomerular Function and Promotes Hypertension Related CKD Xiaochen He, Fan Fan, Bibek Poudel, Shaoxun Wang, Paige N. Mims, Richard J. Roman. *University of Mississippi Medical Center, Jackson, MS.*

Background: Fawn Hooded Hypertensive (FHH) rat is a genetic model of hypertension-induced chronic kidney disease (CKD). Using overlapping Chr 1 congenic strains, we identified a K572Q mutation in Add3 as a positional candidate gene for proteinuria in FHH rats. The present study examined whether knockin of wild type Add3 alters the development of proteinuria and hypertension induced renal injury in FHH rats.

Methods: Blood pressure and proteinuria were evaluated weekly in FHH and FHH.Add3 transgenic rats as they aged from 12 to 24 weeks of age or during the development of DOCA/salt induced hypertension. Renal injury was assessed by histology analysis. *In vitro*, Add3 was knocked down in normal rat kidney epithelial cells, a model system of podocyte, by using 27-mer Dicer-substrate RNAi, followed by MTS assay, F-actin immunostaining, or mitochondrial function assay.

Results: Blood pressure was similar in FHH and FHH.Add3 transgenic rats. Proteinuria increased from 37±2 to 260±32 mg/day as they aged in FHH rats (n=30), but this increase was attenuated in FHH.Add3 transgenic rats (24±3 to 170±16 mg/day, n=12). Moreover, DOCA hypertensive FHH rats (484±78 mg/day, n=21) exhibited more severe proteinuria than that seen in FHH.Add3 transgenic rats (259±5 mg/day, n=12). DOCA hypertensive FHH rats developed more severe renal injury than hypertensive FHH.1^{BN} and FHH.Add3 transgenic rats that express wt-Add3. The glomerular injury score averaged 3.31±0.01 in FHH versus 2.54±0.01 and 2.50±0.03, in FHH.1^{BN} and FHH.Add3 rats. The percentage of fibrosis in the renal cortex and vascular remodeling were significantly higher in DOCA treated hypertensive FHH rats than in FHH.1^{BN} and FHH.Add3 transgenic rats. In normal rat kidney epithelial cells, down-regulation of Add3 decreased cell proliferation by 50%, disrupted the actin cytoskeleton, and impaired mitochondrial function.

Conclusions: These results suggest that down regulation of Add3 may decrease glomerular function in FHH rats by disrupting the actin cytoskeleton and impairing mitochondrial function of podocytes, which may contribute to the development of renal end organ damage with aging and after the onset of hypertension.

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FR-PO715

Mice Deficient in Aminopeptidase A Have Augmented Albuminuria Following Renal Mass Reduction Wayne R. Fitzgibbon,[1] Ehtesham Arif,[1] Peifeng Deng,[1] Fengxia Xiao,[2] Dylan Burger,[3] Michael G. Janech,[1] Deepak Nihalani,[1] Juan Carlos Q. Velez.[4] *[1]Medical University of South Carolina, Charleston, SC; [2]Ottawa Hospital Research Institute, Ottawa, AB, Canada; [3]Kidney Research Centre, Ottawa, ON, Canada; [4]Ochsner Clinic Foundation, New Orleans, LA.*

Background: Aminopeptidase A (APA) is a membrane-bound metalloproteinase expressed in podocytes and tubular epithelia. We have previously shown that global deficiency in APA increases susceptibility to acute immune- or Ang-dependent glomerular injury. We hypothesized that APA acts to minimize podocyte damage during progressive chronic kidney disease.

Methods: To test this hypothesis we measured urine flow rate, urine albumin (Alb), creatinine (Cr), and microparticle (MP) levels in 129Sv/C57Bl6 wild type (WT, n=6) and APA KO (n=6) mice subjected to remnant nephropathy. Twenty-four hour (24h) urine collections were obtained prior to, and 2 and 4 weeks following 5/6 reduction in renal mass.

Results: Baseline values were not different between the two strains. Renal mass reduction induced albuminuria in both groups at 2 weeks; however, 24h albumin excretion (UAlbV) was markedly higher for the KO compared to the WT mice at both 2 weeks ($p<0.001$) and 4 weeks ($p<0.001$). UAlbV was 11 (6–21), 161 (57–497) and 169 (42–1230) μg/24h, and 17 (6–43), 1554 (712–2217) and 1400 (629–2882) μg/24h for baseline, 2 and 4 week periods for the WT and the APAKO mice, respectively. Similar findings were observed when albumin levels were expressed as albumin/creatinine ratio (UACR). UACRs were 277 (113–743) vs 1856 (842–2539) at 2 weeks ($p<0.001$) and 242 (116–1781) vs 1837 (618–3845) at 4 weeks ($p<0.001$) for the WT and APAKO respectively. Concomitant with the reduction in renal mass was a decrease in the generation of total urinary MP (uMP/Cr) that was similar in both groups. Further, the formation of podocyte-derived podoplanin-stained (ps) MP also decreased in both groups. For WT, the generation of psMP at baseline and 2 weeks was $2.2x10^6 \pm 1.0x10^6$ vs $4.8x10^5 \pm 9.2x10^5$ psMP/mg ($p=0.03$) and at 4 weeks $2.6x10^5 \pm 1.4x10^5$ psMP/mg ($p<0.01$). For the APAKO mice psMP at baseline and 2 weeks was $2.2x10^6 \pm 1.2x10^6$ vs $4.3x10^4 \pm 4.1x10^4$ psMP/mg ($p<0.01$) and at 4 weeks $1.7x10^5 \pm 2.4x10^5$ psMP/mg ($p<0.01$).

Conclusions: Our findings support a role for APA in ameliorating glomerular injury following 5/6 renal ablation. The finding that the formation of (ps)MP was not different between the 2 groups 2 weeks after renal injury, suggests that the chronic renoprotective role of APA may not be associated with attenuation of podocyte MP formation.

Funding: Private Foundation Support

FR-PO716

3D Analysis of Optically Cleared Kidney Slices Reveals Focal Podocyte Loss in Crescentic Nephritis Victor G. Puelles,[1,2] David Fleck,[3] Michael Vogt,[4] Stella Papadouri,[1] Thiago Strieder,[1] Turgay Saritas,[1] David J. Nikolic-Paterson,[2] Marc Spehr,[3] Marcus J. Moeller.[1] *[1]Nephrology and Clinical Immunology, University Hospital RWTH Aachen, Aachen, Germany; [2]Nephrology, Monash Medical Centre, Clayton, VIC, Australia; [3]Chemosensation, RWTH Aachen University, Aachen, Germany; [4]Core Facility "Two-Photon Imaging" IZKF, RWTH Aachen University, Aachen, Germany.*

Background: Podocyte depletion is a common feature of glomerulosclerosis (FSGS), but its role in crescentic nephritis remains unclear. This study combined genetic tagging of podocytes with three different optical clearing techniques to determine podocyte depletion in whole glomeruli from mice with crescentic nephritis.

Methods: Podocyte nuclei were labeled by eGFP-histone in of adult male Pod-rtTA/H2B-eGFP mice by oral doxycycline, followed by a 7-day wash out period, and a single intra-peritoneal injection of nephrotoxic serum (NTS; 5mg/g). Experimental mice were killed 10 days after NTS injection, and compared to age-matched controls. Kidney slices were optically cleared with SCALE-A4, CLARITY and Ethyl Cinnamate (ECi). High-resolution serial optical images were obtained by confocal and two-photon microscopy.

Results: Mean podocyte number per mouse showed very low variability within controls (1-5% variability, P>0.05) and within NTS-injected mice (1-9% variability, P>0.05) independent of the clearing technique. In NTS-injected mice, a similar degree of average podocyte depletion per mouse was identified with all clearing methods (60-63%, P<0.001). The technical (dis-)advantages of each clearing protocol were also analysed, including optimal penetration depth and resolution, compatibility with immunofluorescence, microscopy set-ups, and cost-efficiency. Importantly, total podocyte number per glomerulus showed great variability: controls (mean: 78,81; ranging from 49 to 128 podocytes per glomerulus) and in NTS-injected mice (mean: 29,99; ranging from 1 to 95 podocytes per glomerulus). Using the lowest value for podocyte number in controls as a cut-off reference, only 78% of analysed glomeruli (141 of 180) from NTS-injected mice had a certain degree of podocyte depletion. While deposition of the NTS within glomeruli occurred in a global and homogeneous fashion, podocyte loss was focal.

Conclusions: This study has identified early focal podocyte depletion in mice with crescentic nephritis suggesting a so far unrecognized role of podocyte depletion in the development of the focal crescentic lesions. The combination of lineage tracing and optical clearing provides a powerful new tool for analysis of podocyte depletion in large tissue samples.

FR-PO717

Metformin Ameliorates the Progressive Nephritis of an Experimental Alport Syndrome Mouse Model Kohei Omachi, Shota Kaseda, Tsubasa Yokota, Mary Ann Suico, Tsuyoshi Shuto, Hirofumi Kai. *Kumamoto University, Kumamoto, Japan.*

Background: Alport syndrome (AS) is a hereditary glomerular disease for which renin-angiotensin-aldosterone (RAAS) inhibitor is primarily prescribed. Although RAAS inhibitor is effective for proteinuria, it is not a cure for AS and most patients develop end-stage renal disease. Thus, there is a need to explore other therapeutic avenues. Here, we show the occurrence of metabolic disorder in the glomeruli of Alport mouse model, and that metformin, an anti-diabetic agent, ameliorated the progressive nephritis in AS mice.

Methods: To clarify the molecular underpinning of AS, glomerular samples were collected from 12-week-old wild type and Alport mice (*B6, Col4a5 G5X*), and global protein expression analysis was performed by LC-MS/MS. To improve the metabolic dysregulation, Alport mice were treated with metformin (6-11w: 5 mg/mL,12-20w: 2.5mg/mL, *po*) or vehicle from 6 to 20 weeks old. RAS inhibitor losartan (6-11w: 250μg/mL,12-20w: 125μg/mL, *po*) was used as positive control. Urine samples were collected once every two weeks. Plasma and kidney tissue samples were collected from 20-week-old mice and histological analysis (PAM and Masson trichrome staining) was performed. Expression of genes associated with kidney injury (*Lysozyme, Kim1*), pro-inflammatory cytokines (*Il-6, Il-1b, KC*) and pro-fibrotic factors (*Tgfb, Mmp9/12*) were assessed by qRT-PCR.

Results: Proteomics analysis revealed dysregulation of mitochondrial energy pathway (COX I biogenesis, respiratory electron transport, and ATP synthesis) in addition to already known glomerular damage-associated pathway (nephrin interaction and laminin interaction). Metformin suppressed proteinuria. Although the reduction of proteinuria was lower than losartan, metformin reduced the expression of pro-inflammatory cytokines and pro-fibrotic genes better than losartan. Correlated with these results, metformin suppressed fibrotic area and macrophage invasion histologically.

Conclusions: This study revealed that metabolic disorder occurs in Alport glomerulus and that metformin suppressed progressive nephritis. Metformin is an inexpensive drug that is applicable to pediatric patients. With these findings, metformin could be considered as a novel option for AS therapy.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO718

ENU-Induced Point Mutation in the Laminin Alpha 5 L4a Domain Results in Nephrotic Syndrome Sara Falcone,[2] Thomas Nicol,[2] Jeffrey H. Miner,[3] Frederick W. Tam,[1] Paul K. Potter.[2] *[1]Imperial College Kidney and Transplant Institute, London, United Kingdom; [2]Medical Research Council, Didcot, United Kingdom; [3]Washington University School of Medicine, St. Louis, MO.*

Background: Nephrotic syndrome (NS) is a heterogeneous group of disorders characterised by renal and extrarenal manifestations. Classic symptoms of NS include severe proteinuria and hypoalbuminemia, oedema and hyperlipidemia. Genetic studies of hereditary forms of NS have led to the identification of proteins playing a crucial role in slit diaphragm signalling, regulation of actin cytoskeleton dynamics and cell-matrix interactions. As part of the MRC Harwell ageing screen a missense mutation was identified in the gene *Lama5* coding for the laminin alpha 5 chain, a major component of the renal extracellular matrix. Homozygous mice showed symptoms of NS including a severe proteinuria that preceded histological lesions and alteration of renal markers in plasma.

Methods: The *Lama5*^{E884G} mouse line was derived from a G3 pedigree produced in the MRC Harwell N-ethyl-N-nitrosourea (ENU) mutagenesis screen. The mutation was identified by combining the use of a dense SNP panel and whole genome sequencing. *Lama5*$^{E884G/-}$ mice were then backcrossed for a total of 10 generations to C57BL/6J mice. Urine and plasma were collected at different time points and markers of kidney function were measured. Kidneys were also collected for pathological assessment and study of the molecular mechanism. Concurrently, an *in vitro* study is ongoing to look at the expression and secretion of LAMA5 and its interaction with other laminin chains.

Results: Time course studies of *Lama5*^{E884G} homozygotes showed high levels of proteinuria from 25 weeks of age but no other signs of kidney impairment. Affected mice also have significantly elevated cholesterol levels. The *Lama5*$^{E884G/-}$ compound heterozygote exhibited severe proteinuria, thus confirming the *Lama5*^{E884G} mutation as the causative allele. Alterations in the expression of genes and proteins associated with integrin signal-mediation show an abnormal response of the glomeruli that could possibly have an effect on the podocytes' F-actin bundles. Preliminary *in vitro* results show an impaired secretion of the LAMA5 short arm.

Conclusions: We have identified a novel mutant mouse line exhibiting NS resulting from a point mutation in *Lama5*. This gene has recently been associated with renal disease in patients. We are currently dissecting the molecular pathogenesis of disease in these animals to provide insight into human disease.

Funding: Government Support - Non-U.S.

FR-PO719

Proteomic Analysis of Renal Tissue in Lupus Nephritis Asmaa Abu Maziad,[1] Ram R. Singh.[2] *[1]Mattel Children's Hospital, UCLA, Los Angeles, CA; [2]UCLA School of Medicine, Los Angeles, CA.*

Background: Lupus nephritis (LN) occurs in 40-80% of children with systemic lupus erythematosus (SLE) and is a major cause of morbidity and mortality in childhood SLE. Pathogenesis of LN progression is unclear. Identification of molecules that are differentially expressed between early to late stages of LN may help in detecting the progression of kidney damage and to identify potential new targets of treatment.

Methods: This is a case-controlled study involving children and adolescents of 1-21 years of age who have biopsy-proven LN by the 2003 International Society of Nephrology/Renal Pathology Society classification. A total of 54 archived formalin-fixed and paraffin embedded kidney biopsy specimens obtained from UCLA Translational Pathology Core. These included 13 control specimens from transplanted kidneys with normal histology and 6-8 specimens for each of the six classes of LN. These tissues were subjected to proteomics analysis using nano-scale liquid chromatography tandem mass spectroscopy (nLCMSMS) by Tandom Mass Tag method for protein labeling. Quantitative relative expression data is extracted using Proteome Discoverer 2.0 Software. DAVID software was used for data analysis. Clinical /kidney biopsy data and outcomes were collected for both cohorts and entered in UCLA RedCap software.

Results: We have thus far completed the mass spectroscopy analysis of 22 kidney biopsies (2 class II, 2 class III, 5 class IV, 7 class V, 3 class VI, and 3 control), and identified a total of 2,000 proteins in the global analysis. Among these, 86 proteins were significantly different between control and LN specimens. Among the differentially expressed proteins, the following were upregulated: MHC Class I, LIM domain and actin binding 1, WD repeat domain 7, Rho GDP dissociation inhibitor beta, and cadherin 13. The significantly downregulated proteins included G protein subunit alpha i3, catenin beta 1, ubiquinol-cytochrome c reductase core protein I, heterogeneous nuclear ribonucleoprotein U-like 2, histone deacetylase 6, NFS1 cysteine desulfurase, and Thy-1 cell surface antigen. In-depth analyses of the data are in progress.

Conclusions: This preliminary work delineates proteins that are differentially expressed between control and LN kidneys. Ongoing work will complete the proteomic analyses of the remaining specimens, and perform pathway analyses of the controls and different classes of LN

Funding: Other NIH Support - University of California at Los Angles, Children`s Discovery and Innovation Institute

FR-PO720

Validation of the Prognostic Value of the Histopathological Classification of ANCA-Associated Glomerulonephritis: A Meta-Analysis Maria Wester Trejo,[1] Emma Van Daalen,[1] Jan W. Schoones,[2] Olaf Dekkers,[3] Jan A. Bruijn,[1] Ingeborg M. Bajema.[1] *[1]Pathology, Leiden University Medical Center, Leiden, Netherlands; [2]Walaeus Library, Leiden University Medical Center, Leiden, Netherlands; [3]Clinical Epidemiology, Leiden University Medical Center, Leiden, Netherlands.*

Background: In 2010, a histopathological classification of antineutrophil cytoplasmic autoantibody (ANCA)-associated glomerulonephritis (AAGN) was proposed by an international consortium of renal pathologists and nephrologists. It comprises four biopsy classes: focal, crescentic, mixed and sclerotic, the order of which was shown, in the initial publication, to correspond to increasing severity of renal impairment during follow-up. The aim of this meta-analysis was to evaluate the prognostic value of these phenotypical classes by means of validation studies that have been published since.

Methods: A literature search was performed using Web of Science, Google Scholar, PubMed and Embase in March 2017, selecting studies that associated histopathological class to renal outcome in adult patients with AAGN. The risk of developing end-stage renal disease (ESRD) during follow-up was compared between classes using a meta-analysis with random effects model. Weighted relative risks (RR) with 95% confidence intervals (95% CI) were reported.

Results: Nineteen studies were included with a total of 2,408 patients. Using sclerotic class as a reference category, ESDR risk was lower in the crescentic class (RR 0.53, 95% CI 0.43-0.64); RR in focal was lower than in crescentic class (RR 0.27 95% CI 0.20-0.37). RR in crescentic compared to mixed class was 1.18 (95% CI 0.95-1.45); RR in focal compared to mixed class was 0.34 (95% CI 0.25-0.47).

Conclusions: Our meta-analysis shows that the risk for developing ESRD increased with more severe histopathological lesions. We found no difference between the crescentic and mixed classes, pointing towards a comparable risk profile with regard to ESRD. We are currently performing an individual patient data meta-analysis, as this technique is better equipped to deal with study heterogeneity. For the moment, this meta-analysis confirms the use of the histopathological classification system as a predictor of renal outcome in the prognostication of patients with AAGN.

FR-PO721

Clinical Impact of Peritubular Capillaritis on Renal Prognosis in ANCA-Associated Glomerulonephritis Satoshi Hara,[3] Fae Suzuki,[4] Ichiro Mizushima,[4] Kiyoaki Ito,[5] Hiroshi Fujii,[1] Kazunori Yamada,[4] Mitsuhiro Kawano.[2] *[1]Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Kanazawa, Japan; [2]Division of Rheumatology, Kanazawa University Hospital, Kanazawa, Japan; [3]Kanazawa Graduate School of Medicine, Kanazawa, Japan; [4]Kanazawa University Graduate School of Medicine, Kanazawa, Japan; [5]Kanazawa universtiy, Kanazawa, Japan.*

Background: A predictive histopathologic classification of anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis has been widely used; however, the classification is based on only glomerular lesions, and tubulointerstitial lesions including peritubular capillaritis (PTCitis) are excluded. The present study was aimed to clarify the clinical impact of PTCitis on renal prognosis in ANCA-associated glomerulonephritis.

Methods: Sixty-one patients of ANCA-associated glomerulonephritis, diagnosed by kidney biopsy at our center between January 2003 and May 2016, were included in the study. PTCitis is defined as infiltration of inflammatory cells at least one leukocyte in ≧10% of cortical PTCs with ≧3 leukocytes in most severely involved PTC. According to the presence/absence of PTCitis, patients were retrospectively divided into 2 groups [PTCitis (+) or PTCitis (-)], and clinical and histological findings correlated with PTCitis were estimated. The primary predictor was the presence of PTCitis. The primary endpoint was the cumulative percentage of patients who developed end-stage renal disease.

Results: PTCitis was detected in 39 of 61 (63.9%) cases. Clinically, age, gender, serum C-reactive protein, kidney function, urinary protein were all insignificant between PTCitis (+) and PTCitis (-) groups. Histologically, arteritis of small artery and interstitial fibrosis were evident in PTCitis (+) group (p=0.005, p=0.033, respectively), although histological subclass type and tubular atrophy were not different. Renal survival at 6 months was 87.2% in PTCitis (+) group compared with 86.4% in PTCitis (-) group (p=0.96). When adjusted by renal function and other histologic parameters, PTCitis was not an independent predictor for renal survival (hazard ratio, 1.3; 95%confidence interval 0.3-6.1; p=0.71).

Conclusions: PTCitis may not affect renal prognosis in ANCA-associated glomerulonephritis, while PTCitis is correlated with interstitial fibrosis. The further studies of larger population would be required.

FR-PO722

Chemokine Receptor 8 in Peripheral Blood Mononuclear Cells Can Distinguish Active ANCA-Associated Vasculitis from Infectious Complications Satoru Sanada,[1] Yukako Akiyama,[2] Mitsuhiro Sato,[1] Toshinobu Sato,[1] Yoshio Taguma.[1] *[1]Japan Community Health Care Organization Sendai Hospital, Sendai, Japan; [2]Tohoku university, Sendai Miyagi, Japan.*

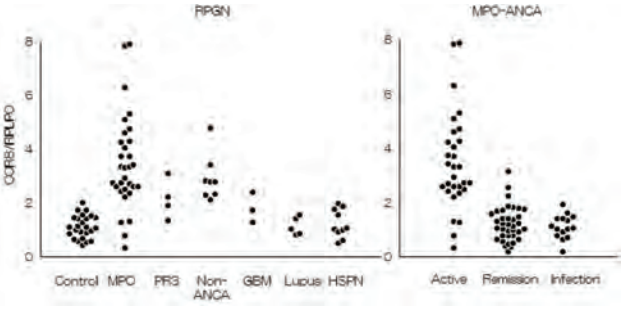
Background: Infectious complications are major causes of death in ANCA-associated vasculitis (AAV). Similar clinical symptoms between AAV and infection may cause diagnostic difficulty despite totally opposite treatment in two situations. Aim of this study is to identify a new biomarker for AAV, which enables to distinguish vasculitis and infections.

Methods: Peripheral blood mononuclear cells (PBMC) were collected from 222 patients with AAV, including patients in active, remission and infectious complications and patients with other rapidly progressive glomerulonephritis. Chemokine receptor 8 (CCR8) was assessed using quantitative PCR and flow cytometry. Quality of mRNA was measured by bioanalyzer before reverse transcription to provide reproducible results.

Results: CCR8 mRNA level in PBMC was significantly higher in patients with MPO-ANCA vasculitis compared to that in healthy control, which was confirmed by upregulated CCR8 protein expression in FACS. The area under ROC curve was 0.923 (95%CI: 0.842-1.000) with a sensitivity of 87.5% and a specificity of 100%. Lupus nephritis nor purpura nephritis did not show high CCR8 mRNA levels. Among MPO-ANCA vasculitis, CCR8 mRNA levels in patients with remission and patients with infectious complications during remission were lower compared to that in patients with active. The area under ROC curve was 0.924 (95%CI: 0.846-1.000) compared with active AAV and infectious complication.

Conclusions: CCR8 mRNA level in PBMC was associated with AAV activity, however, infectious complications did not affect CCR8 expression, suggesting that CCR8 could be a useful diagnosis biomarker for AAV.

Funding: Private Foundation Support



FR-PO723

Thrombotic Microangiopathy in Pauci-Immune Glomerulonephritis Jianling Tao,[3] Megan L. Troxell,[2] Jessica B. Lapasia,[1] Neeraja Kambham.[2] *[1]Medicine, Kaiser Permanente, San Francisco, CA; [2]Pathology, Stanford University School of Medicine, Stanford, CA; [3]Medicine, Stanford University, Stanford, CA.*

Background: Renal thrombotic microangiopathy (TMA) is occasionally seen in biopsies with pauci-immune necrotizing crescentic glomerulonephritis (NCGN). Recent studies indicate that NCGN patients with TMA have more severe renal injury and higher mortality rate.

Methods: Biopsies from 2 centers with diagnosis of NCGN and TMA changes were identified (5/2003- 4/2017) from Pathology records. Patients with connective tissue disorders, HBV, HCV, HIV, and monoclonal gammopathy were excluded. Biopsies were re-reviewed and detailed clinical and follow up data was documented.

Results: Ten patients met our inclusion criteria. Patients were predominantly female (9:1) and average age at biopsy was 48 years (range 10-72). Clinical presentation was nephritic syndrome +/- acute renal failure and 3 patients had nephrotic range proteinuria. ANCA was positive in 8 patients and schistocytes were noted on peripheral smear in 2 patients. Of 7 patients with available complement data, only 1 had low C3 at presentation; one patient with previously normal C3 developed hypocomplementemia and clinical TMA 3 years later. In addition to glomerular crescents and necrosis, prominent TMA changes (unrelated to GBM rupture or crescents) were seen in glomeruli/blood vessels on light microscopy in 6 patients and on EM in 4 patients. Glomerular mesangial C3 (+/- IgG) staining was documented in 3 patients, with ultrastructural confirmation of deposits in 2. The mean follow up was 40 months (range 0.5-156). At last follow up, 5 patients reached ESRD or died; 1 has mild chronic kidney disease and 2 have normal renal function. Treatment in most cases included steroids and Cytoxan, with a few receiving rituximab and plasmapheresis. One patient received anti-complement treatment after biopsy and another received it 3 years later; both were dialysis dependent at last follow-up.

Conclusions: NCGN patients rarely have clinical or biopsy-proven TMA. Based on this limited sample, the clinical outcome appears to be poor. The underlying mechanism has been postulated to be alternative complement pathway abnormality. The nephrologist should be alerted to the presence of TMA for potential therapeutic implications and further complement investigations.

FR-PO724

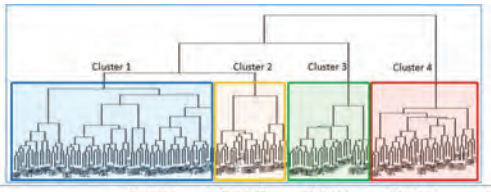
Unravelling the Pathophysiology of C3G/IC-MPGN and How to Predict Disease Progression and Orient Therapies Paraskevas Iatropoulos,[1] Erica Daina,[1] Manuela Curreri,[1] Rossella Piras,[1] Elisabetta Valoti,[1] Caterina Mele,[1] Elena Bresin,[1] Sara Gamba,[1] Marta Alberti,[1] Matteo Breno,[1] Ettore Sabadini,[2] Marina Noris,[1] Giuseppe Remuzzi.[1,2] *[1]IRCCS - Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy; [2]Unit of Nephrology and Dialysis, Ospedale Papa Giovanni XXIII, Bergamo, Italy. Group/Team: Registry of Membranoproliferative Glomerulonephritis/C3 Glomerulopathy*.

Background: Membranoproliferative glomerulonephritis (MPGN) was recently reclassified into alternative pathway (AP) complement-mediated C3 glomerulopathy (C3G) and immune-complex-mediated MPGN (IC-MPGN). However, genetic and acquired AP abnormalities are also observed in IC-MPGN. Here, in patients with C3G/IC-MPGN, we explored the presence of distinct disease entities characterized by specific pathophysiologic mechanisms.

Methods: We performed unsupervised hierarchical clustering, a data-driven statistical approach not biased by operator hypotheses, on 163 C3G/IC-MPGN patients using histology, genetic, serum complement and clinical features.

Results: This approach divided C3G/IC-MPGN patients into four clusters, characterized by specific histology, clinical and complements features indicating the existence of four different pathogenetic patterns. Specifically, patients with fluid-phase complement activation, showing low serum C3 and a high prevalence of AP gene mutations and/or C3NeF (clusters 1-3), were separated from patients with solid-phase complement activation (cluster 4), showing likely normal serum C3, late onset and poor renal survival. In patients with fluid-phase complement activation, clusters 1 and 2 were characterized by massive AP activation as far as the terminal pathway and the highest prevalence of subendothelial deposits, but cluster 2 was characterized by the additional activation of the classical pathway and the highest prevalence of nephrotic syndrome at onset. Patients in cluster 3 were characterized by prevalent activation of the C3 convertase and highly electron-dense deposits.

Conclusions: These clusters of C3G/IC-MPGN patients may be useful for better clarifying disease etiology, defining the risk of ESRD and paving the way for personalized treatment.



	Cluster 1	Cluster 2	Cluster 3	Cluster 4	*p*-value
Mutations† and/or C3NeF	70%	76%	81%	5%[A,B,C]	$8.5x10^{-10}$
Serum C3 (mg/dl)	38 (±30)	27.7 (±21.8)	33.1 (±29.2)	93.2 (±42.1)[A,B,C]	$2.3x10^{-16}$
Serum C4 (mg/dl)	21.3 (±10.2)	17.6 (±8.6)[C,d]	22.6 (±8.7)	24.9 (±10.6)	0.037
Plasma SC5b-9 (ng/ml)	1315 (±1300)[C,d]	1681 (±1334)[C,d]	519 (±501)	385 (±270)	$5.8x10^{-7}$
Intramembranous highly electron-dense deposits on EM	2%	0%	83%[A,B,d]	6%	$1.9x10^{-20}$
Glomerular C3 deposits on IF*	2.6 (±0.7)	2.8 (±0.3)	2.7 (±0.4)	2.6 (±0.5)	0.186
Glomerular C1q deposits on IF*	0.5 (±0.8)	1.4 (±1)[A,C,d]	0.2 (±0.5)	0.6 (±1)	$4.9x10^{-4}$
Age of onset (y)	13.6 (±11.1)	20.5 (±13.2)[A,C]	12.6 (±8.1)	30.8 (±19.3)[A,B,C]	$4.7x10^{-9}$
Nephrotic syndrome at onset	31%	65%[A,C,d]	28%	30%	0.007
ESRD along disease course	3%	8%	7%	22%	0.013

†Mutations in *CFH, CD46, CFI, CFB, C3* and *THBD*; C3NeF: C3 Nephritic Factor; EM: electron microscopy; IF: immunofluorescence; *graded using a scale of 0, trace (0.5+), 1+, 2+ and 3+; [A,B,C,D]: significantly different vs. cluster 1, 2, 3 and 4, respectively.

FR-PO725

More Than C3 Deposition: The Unique Characteristics of One Family with C3 Glomerulopathy Alexandria I. Leonhardt,[1] Nicole Meyer,[1] Nicolò Borsa,[2] Yuzhou Zhang,[1] Richard J. Smith,[1] Carla M. Nester.[1] *[1]University of Iowa, Iowa City, IA; [2]The University of Iowa, Iowa City, IA.*

Background: As a disease, C3 Glomerulopathy is currently defined by the single diagnostic criteria of a predominant immune fluorescent staining of C3 on renal biopsy. Additonal diagnositic requirements have not been defined. After cases are ascertained, infrequently, it may be discovered that those affected have a genetic abnormality in a complement gene – supporting the underlying complement abnormality as the disease causing agent. We present a familial case of C3G identified after a proband with predominant C3 staining was discovered to have a homozygous *C3* gene mutation.

Methods: After obtaining informed consent, a medical record review was completed on all available family members. The disease phenotype was confirmed by renal biopsies in persons with >1gm/24hr of urine protein. Comprehensive genetic screening was completed on all complement genes using standard procedures. An extensive complement analysis was performed that included serum levels of complement proteins and their cleavage products, assays of complement function, and screens for autoantibodies.

Results: A pathogenic variant in *C3* segregated with each patient with a renal phenotype: c.443G>A, p.R148Q. Both the matriarch and patriarch of the family were heterozygous for this variant, consistent with their relationship as first cousins. The spectrum of clinical renal disease ranged from asymptomatic hematuria (N=2) or proteinuria (N=1) to end stage renal disease (N=3). One family member had multiple cysts by ultrasound. Renal biopsies confirmed C3GN in 3 family members and FSGS in a fourth person. Serum C3 levels were normal in all asymptomatic individuals (both with and without the variant). C3 levels were low in individuals with symptomatic C3GN pathology. All persons carrying the p.R148Q mutation had elevated serum levels of C3c. Surface plasmon resonance assays, as well as an expanded functional and cofactor assessment of the mutation is ongoing.

Conclusions: We present a rare case of familial C3 Glomerulpathy. Unique to this case is an underlying gene abnormality that segregates not only with the diagnostic C3G requirement, but also with FSGS and cystic renal disease. This pedigree highlights not only the narrow nature of the C3G definition, but also calls into question whether the C3 protein may play a functional role in other renal abnormalities.

Funding: NIDDK Support

FR-PO726

C3G-Associated with Monoclonal Gammopathy Aishwarya Ravindran, Fernando C. Fervenza, Sanjeev Sethi. *Mayo Clinic, Rochester, MN*.

Background: Monoclonal immunoglobulins (MIg) may act a functional inhibitor of the alternate complement pathway thereby playing a causal role in the pathogenesis of C3 glomerulopathy (C3G). In this study, we describe the clinicopathological features, hematological evaluation, treatment and outcomes of C3G associated with MIg.

Methods: We identified 95 patients seen at the Mayo Clinic from 2007-2016 with a diagnosis of C3 glomerulopathy (C3GN or DDD) who were tested for a monoclonal protein.

Results: 36 (37.9%) patients were positive for MIg; 65.1% of patient ≥50 years were positive (17 times higher than the expected rate). The median age at diagnosis was 60 years (range: 20-85), 25 males and 11 females. The median serum creatinine and proteinuria was 1.9 mg/dL and 3000 mg/24 hours. Hematuria was present in 28 (93.3%) patients. Twelve (34.3%) patients had low C3 and 4 (11.4%) had low C4. Twenty-six (72.2%) patients were classified as MGUS/MGRS, 5 (13.9%) multiple myeloma, 2 (5.6%) smoldering myeloma, 1 (2.8%) CLL, 2 with cryoglobulins (5.6%) 1 of which was type I cryoglobulin and the other was associated with lymphoma of the stomach. The most common abnormality was the presence of C3 nephritic factor in 10 (43.5%) patients and autoantibodies to complement factor H or B in 3 patients (13%). Six (30%) patients had mutations in complement regulating proteins. Of the 36 patients, 33 (91.7%) received steroids and/or other immunosuppressive drugs. At a median follow-up of 43.5 months, the median serum creatinine and proteinuria was 1.4 mg/dL and 749 mg/24 hours. Nine (25%) patients progressed to end stage renal disease. Sixteen (44.4%) received targeted therapy for MIg. Of these 11 (68.8%) patients achieved stable renal function, while the remaining 5 (31.2%) progressed to ESRD, of which 3 (18.7%) had multiple myeloma and only 2 (12.5%) had MGUS/MGRS. With regards to non-targeted treatment for the MGUS/MGRS group, 4 (20%) patients progressed to ESRD.

Conclusions: Our study shows a high prevalence of MIg in C3G patients. C3 nephritic and autoantibodies were more common compared to mutations suggesting that the MIg likely acts as an autoantibody to complement regulating proteins. Targeted treatment of MIg, in particular with MGUS/MGRS, resulted in stabilization of renal function in a majority of the patients.

FR-PO727

Autoimmune and Genetic Workup in Post-Transplant C3 Glomerulopathy Ashwani Kumar,[1] Ritambhra Nada,[1] Raja Ramachandran,[2] Charan S. Rayat,[1] Krishan Lal L. Gupta.[2] *[1]Postgraduate Institute of Medical Education & Research, Chandigarh, India; [2]Nehru Hospital, Chandigarh, India*.

Background: Post-transplant C3 glomerulopathy (Tx-C3GP) is associated with alternate complement pathway (ACP) dysregulation and the literature is scanty. Hence, serological and genetic workup for Tx-C3GP was performed.

Methods: We performed Tx-C3GP workup in all patients reported during 2010-16. Tests included ACP functional assay (APFA), C3, C4 levels, complement factors H (CFH) and B (CFB) estimation. Paraproteins and autoantibodies to CFH (ab-CFH), CFB (ab-CFB), C3 convertase (C3Nef), PCR for CFH and complement factor H-related 5 (CFHR5) genes were done followed by Sanger sequencing. Clinical outcome of the patients was also recorded.

Results: Twenty-six cases of Tx-C3GP included 11 cases of dense deposit disease (DDD), 10 C3 glomerulonephritis (C3GN) and 5 C3GP (EM not available). Mean age was 31.88 years. Two-thirds presented with graft dysfunction (Mean time; <1 week-C3GN, 8 Months-DDD). Nephrotic syndrome and asymptomatic urine abnormality were present in 17%. Basic disease was known in 50% (DDD-4, C3GN-3, C3GP-5, & Diabetic nephropathy-2) cases. Native kidney histology ranged from normal to membranoproliferative (MP) morphology, whereas in early post-transplant recurrences, it was focal segmental proliferative and MP in late recurrences. We observed low APFA and C3 in all cases. Positive findings in DDD included, low CFH levels, ab-CFH, low CFB levels in 56, 25 and 11%, respectively. Low CFH levels (22%) and ab-CFH were present in 15% of C3GN. In contrast to DDD, 22% patients of C3GN had low CFB levels and ab-CFB (22%). C3NeF was positive in 44% DDD and 33% of C3GN. We found CFH SNP rs800292 (Val62Ile) in 44% and -18TT insertion in 22% cases of DDD and both SNPs were seen in 11% cases of tx-C3GN. SNP rs1061147 (p.Ala243Ala) and rs1061170 (p.His402Tyr) of CFH were more frequent in tx-C3GN (56% & 45%) and seen lesser in tx-DDD (33% and 11%). SNP rs2274700 (p.Ala473Ala) was equally present (22%) in both the groups. No variant of CFHR5 was present in any tx-C3GP case. 43% of the patients experienced graft loss.

Conclusions: Both DDD and C3GN reccur post-transplant. C3GN has an early recurrence compared to DDD. Low CFH and ab-CFH were evident in DDD, whereas low

CFB and ab-CFB are seen in C3GN. Genetic findings for CFH gene revealed difference among variants for these two entities.

Funding: Government Support - Non-U.S.

FR-PO728

Dense Deposit Disease: Is There a Racial Difference in the Prevalence? Anila Abraham,[2] Patrick D. Walker.[1] *[1]Arkana Laboratories, Little Rock, AR; [2]Renopath, Center for Renal and Urological Pathology, Chennai, India.*

Background: Dense deposit disease(DDD) is a rare glomerulonephritis that commonly affects children. It is defined at the ultrastructural level by the presence of extremely electron dense material in the lamina densa of the glomerular basement membrane. This results in various patterns of glomerular injury with mesangioproliferative and membranoproliferative patterns being the most common

Methods: Native kidney biopsies reported from August 2013 to November 2016 at Renopath, Chennai, Tamil Nadu, India were reviewed. Cases of DDD were identified and clinicopathologic features compared. We then compared our findings with data published in literature. The databases at Renopath and Arkana Laboratories were utilized to compare the rates of DDD diagnosis

Results: During the study period, there were 25 patients with DDD among the 7335 native kidney biopsies (0.34%) at Renopath. Arkana Laboratories in Little Rock, AR, USA, had 21 cases of DDD among their 26,319 native kidney biopsies (0.08%) during the same time period. The mean age of patients was 20.7 years, with only 9 (36%) patients < 16 years of age. Male to female ratio was 1.3:1. Serum C3 was decreased in all patients. At the time of biopsy, proteinuria was present in all patients, five were hypertensive, 2 had partial lipodystrophy and one had drusen. Membranoproliferative, mesangioproliferative, exudative and crescentic patterns were observed. Only 52% of the biopsies showed membranoproliferative pattern. Interstitial inflammation was significantly higher in the biopsies with this pattern. All the patients with crescentic pattern (16%) were below 16 years of age. Mesangioproliferative pattern was seen only in adults. Arteriosclerosis, interstitial fibrosis and tubular atrophy were significantly more frequent in adults

Conclusions: The mean age of patients in our study was 20.7 years, unlike many studies which considered DDD as a childhood disease. Only half of our patients had the membranoproliferative pattern of glomerular injury. Crescentic pattern was seen exclusively in children and mesangioproliferative pattern was seen only in adults. Although DDD is rare, it is much more common (>400%) in this Indian population when compared with the American population. In addition to genetic differences, environmental factors and chronic infections may possibly contribute to the high incidence in this South Indian population

FR-PO729

Urine Micro-RNAs as Histology Biomarkers in Lupus Nephritis Xiaolan Zhang,[1] Juan M. Mejia-Vilet,[2] Huijuan Song,[1] Samir V. Parikh,[1] Anjali A. Satoskar,[1] Tibor Nadasdy,[1] Brad H. Rovin.[1] *[1]Ohio State University Wexner Medical Center, Columbus, OH; [2]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico. Group/ Team: CKD Biomarker Consortium.*

Background: Urine micro-RNAs (miRNA) have emerged as potential biomarkers for lupus nephritis (LN). The relationship of urine miRNAs with renal histology in LN was investigated.

Methods: This study examined 98 biopsy-proven LN patients and 19 healthy controls. Total urine RNA was enriched using ExoQuick columns. miRNA was extracted and screened for differential expression of individual miRNAs between LN and controls using Nanostring miRNA profiling. The miRNAs showing the most significant differential expression on screening were validated by duplex real-time PCR after cDNA synthesis using a TaqMan Advanced miRNA cDNA Synthesis kit. miRNA levels were normalized to urine creatinine and the housekeeping miRNA, miR-191-5p. Urine miRNA expression and kidney histology were compared by t-test, ANOVA followed by Wilcoxon ranked-sum testing or multiple linear regression, as appropriate.

Results: Several miRNAs identified by Nanostring screening were confirmed by PCR. Of these, miR-29c-3p correlated with kidney biopsy chronicity index (R2=0.38, p=0.0022), and was significantly increased in the urine of patients with interstitial fibrosis (4.86-fold; p=0.006) and tubular atrophy (5.92-fold; p=0.0029). miR-1290 expression was 39-fold higher (p=0.007) in patients who did not have crescents compared to those with crescents. miR-200b-3p was also decreased in patients with crescents (7.78-fold; P=0.024), glomerular neutrophil accumulation (10-fold; P=0.006) and endocapillary proliferation (2.82-fold, P=0.01) compared to patients without these acute lesions.

Conclusions: A subset of miRNAs that are differentially-expressed in the urine of LN patients appear to correlate with acute or chronic changes on kidney biopsy and are candidate renal histology biomarkers that may be useful for non-invasively following changes in renal pathology during LN.

Funding: NIDDK Support

FR-PO730

Urine Epidermal Growth Factor, Monocyte Chemoattractant Protein-1, or Their Ratio in Lupus Nephritis: Relationship with Renal Histology and Response to Therapy Chagriya Kitiyakara, Pintip Ngamjanyaporn, Suchin Worawichawong, Khantong Khiewngam, Piyanuch Radinahamed. *Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.*

Background: The balance between pro-inflammatory cytokines such as monocyte chemoattractant protein- 1 (MCP-1) and protective cytokines such as epidermal growth factor (EGF) likely determines the disease activity and outcomes in glomerular diseases, but there is limited data in lupus nephritis (LN). In this study, we evaluated the relationship between urinary EGF, MCP-1 or their ratio at baseline with renal histology and the response to immunosuppressive therapy at 6 months follow-up.

Methods: This is a prospective study of biopsy-proven LN (n = 69). Urine samples were collected at biopsy. MCP-1 and EGF were analyzed by ELISA. Response to treatment was defined as 50% or greater reduction in proteinuria or proteinuria <0.5g/g Cr. Biomarker levels were compared between histological categories. Factors associated with treatment response at 6 months were analyzed by multivariate logistic regression in LN Classes III-IV.

Results: LN Classes were: II, III, IV, V, VI (n=9, 25, 21, 13,1). Compared to Class II, patients with Class III-V had higher MCP-1 and lower EGF/MCP-1 whereas EGF was not different. High MCP-1was independently associated with Class III-V. Patients with high activity index (AI ≥7) had higher MCP-1 and lower EGF/MCP-1 compared to patients with low AI. Patients with high chronicity index (CI≧3) had lower EGF/MCP-1 compared to patients with low CI. MCP-1 was higher in patients with wireloop, karryorhexis, tubulitis, tubular atrophy, interstitial fibrosis and EGF/MCP1 was lower in patients with PMN infiltration, wireloop, karryorhexis and cellular infiltration compared to patients without these features. In Class III-IV patients with 6 months follow-up (n= 41), 36 responded to immunosuppression and 27 were non-responders (NR). EGF was higher in Responders [EGF (ng/mg Cr): Responders: 141 (74, 283) vs NR: 57 (24, 87), p=0.025] whereas MCP-1 or EGF/MCP-1 were not different. EGF (per ng/ mg Creatinine) was independently associated with response to immunosuppression [OR (95%CI): 1.02 (1.00-1.034), p=0.034.]

Conclusions: Overall, MCP-1 was higher in LN with adverse histopathological features. Among Class III-IV patients, the response to immunosuppressive therapy at 6 months was independently associated with low baseline EGF, but not high MCP-1.

Funding: Government Support - Non-U.S.

FR-PO731

Lupus-Like Glomerular Immune Complex Deposits in a Subset of Patients with Liver Cirrhosis – Histologic Features and Clinical Correlates Anjali A. Satoskar,[2] Jessica Hemminger,[2] Vidya Arole,[2] Isabelle Ayoub,[1] Tibor Nadasdy.[2] *[1]Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, OH; [2]Pathology, Ohio State University Wexner Medical Center, Columbus, OH.*

Background: Glomerular IgA deposits have been previously reported in patients with liver cirrhosis as incidental findings, mainly in autopsy studies. We recently encountered patients with liver cirrhosis presenting with acute kidney injury and large lupus-like glomerular immune deposits. None had systemic lupus erythematosus. Our aim was to systematically elucidate their clinical and biopsy features, and treatment outcomes.

Methods: We searched our kidney biopsy database over a 13-year period, from January 2004 to December 2016 for all native kidney biopsies from patients with cirrhosis.

Results: We found 118 kidney biopsies from cirrhotic patients, 76/118 had glomerular IgA staining. Nine of these 76 had large IgA, IgG and C3 containing glomerular immune complex deposits (Fig 1) and proliferative glomerulonephritis. Six of 9 patients had concomitant acute bacterial infection, prompting a biopsy diagnosis of infection-associated glomerulonephritis and treatment with antibiotics. In the remaining 3/9 patients, infectious workup was negative and were administered steroids. Overall clinical outcomes were poor among the 9 patients, but 2/6 patients treated with antibiotics (1 with liver transplant), and 1/ 3 patients on steroids recovered renal function.

Conclusions: These cases provide support to the theory that advanced liver failure can compromise the ability to clear circulating immune complexes, contributing to the build-up of large immune complex deposits in the kidney and concomitant bacterial infection probably provides a "second-hit" triggering acute glomerulonephritis in at least a subset of these patients. A trial of antibiotics is recommended and caution is advised before administering immunosuppressive treatment. Bacterial infection can be subtle and difficult to diagnose. However, both diagnosis and management of glomerulonephritis in these patients remains a challenge.

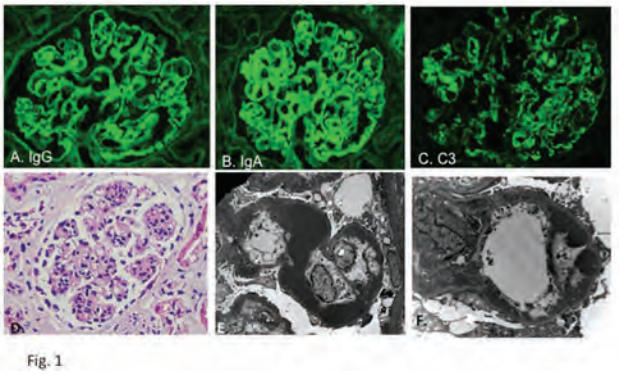


Fig. 1

Fig.1

FR-PO732

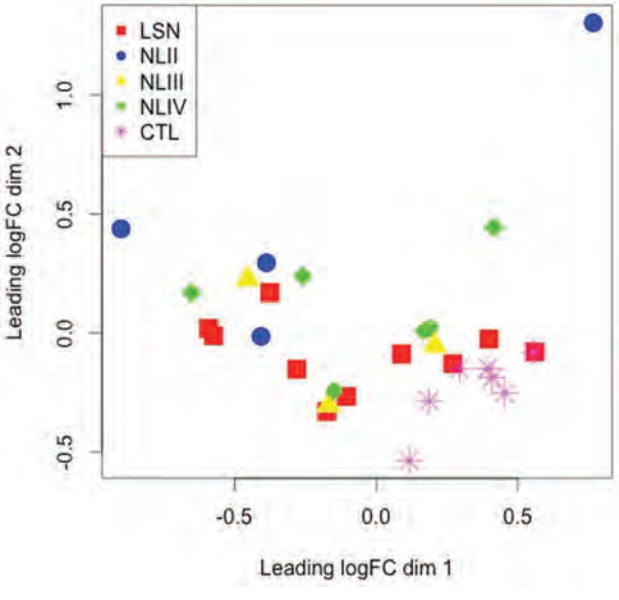
Lupus Nephropathy: Clinical-Pathological Description of 400 Cases of the Colombian Caribbean Region and Variations in the Expression of Plasma MicroRNAs Gustavo Aroca Martinez,[2,3] Alex Domínguez,[2] Elkin Navarro,[4] Henry J. Gonzalez Torres,[4] Diana Silva,[2] Juan C. Conde,[3] Lisneth Almendrales,[4] Eduardo Egea bermejo,[5] Antonio Iglesias Gamarra.[1]
[1]Universidad Nacional de Colombia, BOGOTA, Colombia; [2]Medicine, Universidad Simón Bolívar, Barranquilla, Colombia; [3]Nephrology, Clínica de la Costa, Barranquilla, Colombia; [4]Universidad Simon Bolivar, Barranquilla, Colombia; [5]Universidad del Norte, Barranquilla, Colombia.

Background: Lupus nephritis (LN) is one of the most serious manifestations of systemic lupus erythematosus (SLE). Renal biopsy allows diagnosing the histopathological classes of LN, however, it is an invasive technique associated with risk of hemorrhage. It is a priority to characterize noninvasive diagnostic tests and alterations in the differential expression of microRNAs (miRNAs) to measure LN activity. The objective was describe the clinical-pathological characteristics and to analyze the differential expression of a group of plasma miRNAs in patients with LN.

Methods: Retrospective analytical study. 400 patients are included with LN diagnosed by renal biopsy of the Caribbean Region between January 2008 and December 2016. Differentially expressed miRNAs were selected by Illumina and their diagnostic ability was validated by qPCR in 100 patients with LN.

Results: 400 patients, 86% were women. Average age of 37 ± 13.2 years. Mean follow-up time: 48 ± 20 months. Main syndromic diagnoses: nephritic syndrome (51%). Histological class: IV (70.7%), III (19.3%), II (6.5%). 234 (58%) patients did not achieve remission at 48 months. The miRNAs proposed as candidates were: miR-221-5p, miR-380-3p, miR-556-5p, miR-758-3p and miR-3074-3p, for their high sensitivity (97%) and specificity (70.3%); Positive predictive value (82.5%), negative predictive value (96%) and diagnostic efficacy (87.9%).

Conclusions: The miRNAs (miR-221-5p, miR-380-3p, miR-556-5p, miR-758-3p and miR-3074-3p) are possible diagnostic biomarkers and the differential expression pattern of miRNA would have significant implications in the pathophysiology of LN.



FR-PO733

Full House Immunofluorescence Nephropathy in Patients with Negative Clinicopathological Spectrum for Systemic Lupus Erythematosus Milagros M. Flores fonseca,[1] Arisbeth Villanueva-Perez,[1] Victor M. Martinez-Mejia,[1] Benjamin Gomez-Navarro,[1] Claudia A. Mendoza cerpa,[1] Viridiana Rodriguez,[1] Sandra F. Velasco,[2] Jorge Andrade-Sierra.[1]
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Background: The renal histologically evidence of Systemic Lupus Erythematosus (SLE) and its classic situation for full house positive immunostaining detection; IgA, IgM, IgG, C1q and C3 deposits; occurs in lupus nephritis (LN). However, these pattern may be present in the absence of SLE on other entities such as liver disease, diabetes mellitus, infections and other glomerulonephritis (GN).

Methods: Records of 22 kidney biopsies with full-house IF nephropathy with negative clinicopathological spectrum for SLE. We evaluated at the time of renal biopsy findings including demographics, clinical presentation, laboratory data, renal biopsy findings and clinical follow up.

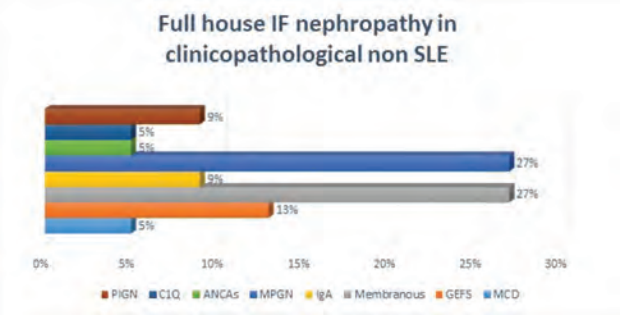
Results: Of the 22 full house IF nephropathy biopsies the histological diagnoses included minimal change disease (5%), focal and segmental glomerulosclerosis (13%), membranous GN (27%), IgA nephropathy (9%), membranoproliferative GN (27%), C1q GN (5%), post infectious GN (9%) and ANCA associated GN (5%). Six patients originally with full house with no SLE spectrum developed SLE in a range between 8 to 20 months of clinical follow up.

Conclusions: Full-house IF pattern it is commonly associated with morphologic evidence of LN. Although it is a characteristic not exclusively of LN, our report showed that full nephropathy is present in other type of GN. Furthermore, 6 of 22 patients on clinical follow up developed clinical and not just morphologic characteristics of SLE. Full house nephropathy is still a diagnostic challenge, may be associated with other systemic and infectious diseases. As clinicians we should insist in strict follow-up and always be alert of possible develop overt of SLE.

Characteristic Baseline

Sex – No. (%) Male/Female	12 (55) / 10 (45)
Age –yr	27 ± 11
Clinical presentations – No. (%) Nephrotic syndrome Nephritic syndrome Hematuria Non nephrotic proteinuria	 13 (60) 1 (5) 3 (13) 5 (22)
Laboratory variables Serum creatinine – mg/dl Albumin – g/dl Proteinuria – g/24hrs	 0.59 ± 0.46 2.98 ± 0.52 4.67 ± 4.36

Mean ± SD



FR-PO734

Idiopathic Non-Lupus Full House Nephropathy Compared to Lupus Nephritis Cristiane B. Dias,[1] Leonardo A. Testagrossa,[4] Denise M. Malheiros,[3] Lectícia Jorge,[4] Viktoria Woronik.[2] *[1]University of Sao Paulo, Brazil, São Paulo, Brazil; [2]None, Salvador, Brazil; [3]University of Sao Paulo, Sao Paulo, Brazil; [4]University of São Paulo, São Paulo, Brazil.*

Background: Full house pattern is defined by the concomitant deposition of immunoglobulins G, A and M and two components of the complement system in renal tissue identified by immunofluorescence. Non-lupus full house nephropathy (NLFN) is the patients with full house pattern but which did not fulfill criteria for the diagnosis of systemic lupus erythematosus. Due to the rarity of NLFN we studied our case series comparing with lupus nephritis.

Methods: All biopsies from January 2000 to September 2016 with full house pattern were collected from the Pathology and Nephrology Discipline at Hospital das Clinicas of São Paulo. Patients with confirmed diagnosis of Lupus Nephritis were used for comparison. Clinical and laboratory data at the time of renal biopsy and at the end of follow-up were retrieved.

Results: In this period, 16 patients had a diagnosis of non-lupus full house nephropathy, with a mean age of 36.8 ± 10.7 years, with 10 men (62.5%), median serum creatinine of 1.1 (0.8-1.0) mg/dL and mean proteinuria of 7.0 ± 4.6g/day. The most frequently optical

microscopy pattern found was membranoproliferative glomerulonephritis in 7 cases (43.80%) and membranous glomerulopathy in 4 cases (25%). Regarding the evolution, 3 patients fulfilled criteria for systemic lupus erythematosus, 2 patients were diagnosed with schistossomosis and 1 cryoglobulinemia. Ten patients with idiopathic form were compared with a group with lupus nephritis and did not have difference with respect to renal survival [Table1].

Conclusions: Non-lupus full house nephropathy is a rare condition, affecting equality men and women and has same renal survival than lupus nephritis.

Comparison of clinical and laboratory data on the diagnosis and renal outcomes of patients with idiopathic non-lupus full house nephropathy vs lupic nephritis

	Idiopathic Non Lupus Full House Nephropathy	Lupus Nephritis	p
Age (years)	31.5 ± 10.1	32.0 ± 8.7	0.89
Gender (M/F)	9/6	1/19	0.0006
Serum Creatinine (mg/dL)	0.9 (0.7-2.3)	0.9 (0.6-2.5)	0.94
Proteinuria (g/day)	6.3 (3.1-10.3)	4.1 (3.6-6.7)	0.55
Arterial hypertension (%)	50	60	0.20
Hematuria (%)	85.7	52	<0.0001
Dialysis or death (%)	40	30	0.69
Serum Albumin (g/dL)	2.2(1.9-2.9)	2.5(1.9-3.3)	0.54
Hemoglobin (g/dL)	12.1 (10.1-12.4)	11.9 (9.6-13.2)	0.60
Follow up (months)	72.4 ± 49.3	105.8 ± 2.6	0.0028

FR-PO735

A Novel Method of Urine Protein Isolation Allows for Identification of Kidney Disease Protein Biomarkers Using Mass Spectrometry Analysis John P. Shapiro,[1] Juan M. Mejia-Vilet,[2] Daniel J. Birmingham,[1] Brad H. Rovin.[1] *[1]Ohio State University Wexner Medical Center, Columbus, OH; [2]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico.*

Background: Characterization of the urine proteome using mass spectrometry (MS) provides an opportunity to identify kidney disease biomarkers. This approach has proven challenging due to salt content, pH and other physicochemical qualities that interfere with MS. We describe a novel, simple method that attenuates these properties of urine and allows for robust quantitative urine proteome characterization.

Methods: Urine (1ml) from healthy individuals (control) or patients with class IV lupus nephritis (LN-IV) was placed in Nunc MaxiSorp ELISA plates and incubated 16 hr at 4oC. Wells were washed 2x with PBS, 2x with 50 mM NH3HCO3 and incubated with trypsin in 50 mM NH3HCO3 for 7 hours at 37oC. Acetonitrile (ACN) was added to each well, mixed, collected and pooled. Peptides were dried, resuspended in 10 µl 2% ACN, 0.1% formic acid and analyzed by LC-MS/MS on a Thermo-Fisher Orbitrap XL mass spectrometer.

Results: MS identified 356 proteins, 63 of which demonstrated a ≥3-fold change in expression between control and LN-IV (all $p<0.05$). Several serum proteins such as albumin and serotransferrin were detected at higher levels in LN-IV (27-, 65-fold respectively) than control. In contrast, many proteins known to be expressed by the kidney were present in control urine but were undetectable or significantly decreased in LN-IV urine. Examples include uromodulin, extracellular sulfatase, EGF, kininogen-1, and cubulin, down-regulated (7-, 9-, 12-, 7- and 9-fold, respectively). Other attenuated proteins include amiloride-sensitive sodium channel subunit gamma and sodium/potassium-transporting ATPase subunit gamma, down-regulated 4- and 3-fold, respectively.

Conclusions: This method demonstrates the effects of lupus nephritis on urine protein profiles. As expected, serum proteins prominent in the urine of LN-IV are absent or present in small amounts in control urine. The absence or diminished expression of proteins in LN-IV urine that are present in control urine suggests specific attenuation due to LN-induced renal injury and may provide a way to assess the health of renal parenchyma. This method may provide a rapid means of preparing urine for clinical MS analysis.

Funding: Clinical Revenue Support

FR-PO736

Pure Lupus Membranous Nephritis with Only IgG Deposits on Immunofluorescence Behaves Like Full House Pattern Gisele Vajgel,[1] Camila B. Oliveira,[1,2] Denise M. Costa,[1,2] Carolina A. Vasconcelos,[2] Maria Alina G. Cavalcante,[1] Lucila Maria Valente.[1] *[1]Nephrology, Hospital das Clinicas - UFPE, Recife, Brazil; [2]Nephrology, IMIP, Recife, Brazil.*

Background: Pure lupus membranous nephritis (LMN) may present with only IgG deposits on immunofluorescence (IF) resembling idiopathic membranous nephritis. We aim to evaluate if patients with LMN and only IgG (±C3) have the same outcome as those with IgG plus other Ig/C1q deposits.

Methods: Adult patients with a diagnosis of lupus (≥ 4 SLICC criteria) and pure LMN between 2004 and 2016 were retrospectively evaluated. Complete response, partial response and relapse were defined by KDIGO criteria.

Results: Thirty-one patients out of 42 were selected; the remaining was excluded due to lack of data or follow-up less than 12 months. Clinical characteristics are shown in Table 1. Drugs used for treatment were different between groups at the beginning (p=0.02) and at 12mo (p=0.02), but more homogeneous at the end of follow-up (p=0.15). Complete and partial response for only IgG and IgG+Ig/C1q group were not different between groups at 12mo (71.4% vs 95%; p=0.16), 24mo (83.3% vs 92.3%; p=1.0) and at last follow-up (75% vs 95.6%; p=0.16).

Conclusions: Despite lack of full house pattern on IF, lupus membranous nephritis patients with only IgG deposits seems to have the same outcome as those with typical full house or IgG plus other Ig/C1q pattern.

Baseline characteristics	Only IgG N = 8	IgG+Ig/C1q N = 23	p-value
Age* (±SD)	31.4 (±9.7)	28.5 (±9.1)	0.46
Female, n(%)	7 (87.5)	21 (91.3)	1
Mixed Race, n(%)	2 (28.6)	13 (56.5)	0.39
SCr, mg/dL*	0.9	1.0	0.76
SAlb, mg/dL*	2.61	2.58	0.94
Proteinuria, g/24h*	4.23	4.22	1
Hematuria, n(%)	4 (57.1)	9 (47.3)	1
Hypertension, n(%)	6 (75)	11 (57.9)	0.41
ANA, n(%)	8 (100)	17 (94.4)	1
Low C3, n(%)	2 (25)	10 (62.5)	0.19
Low C4, n(%)	1 (14.3)	4 (28.6)	0.62
Outcome at last visit			
Complete or partial remission, n (%)	6 (75)	22 (95.7)	0.16
Relapse, n (%)	3 (37.5)	7 (30.4)	1
Doubling SCr, n (%)	1 (12.5)	0 (0)	0.26
CrCl < 30, n (%)	1 (12.5)	1 (4.3)	0.46
Follow-up, mo(±SD)	41.5 (±13.8)	38.2 (±18.3)	0.60

*Mean

FR-PO737

The Relationship between Immunological Activity Markers and the Presence of Crescents in Renal Biopsy in Patients with Lupus Nephritis Katarzyna Kanclerz,[3,4] Michal Komorniczak,[1] Barbara Bullo-Piontecka,[1] Agnieszka Perkowska-Ptasinska,[2] Alicja Debska-Slizien.[1] *[1]Department of Nephrology, Transplantology and Internal Medicine, Medical University of Gdansk, Gdansk, Poland; [2]Department of Transplantation Medicine, Nephrology and Internal Diseases, Transplantation Institute, Medical University of Warsaw, Warsaw, Poland; [3]Department of Nephrology, Transplantology, and Internal Medicine, Medical University of Gdansk, Gdansk, Poland; [4]Department of Occupational, Metabolic, and Internal Medicine, Medical University of Gdansk, Gdansk, Poland.*

Background: Among lupus nephritis (LN) patients (pts) various forms of crescents can be observed in the majority of glomeruli in renal biopsy. The objective of the study was to assess the relationship between the presence of crescents in renal biopsy and levels of immunological activity markers in LN pts.

Methods: The study group consisted of 29 W and 8 M, mean age 35.43 ± 11.22 years (range 18-66,) with biopsy proven LN. Anti-dsDNA and anti-C1q antibodies, complement component 3 (C3) and complement component 4 (C4), IgG concentrations and circulating immune complexes (C1q and C3d) represent the markers of immunological activity of the disease. Percentage of cellular crescents and percentage of all types (cellular, fibrous, fibrocellular) of crescents were evaluated in renal biopsy.

Results: The study revealed a statistically significant correlation between the percentage of all crescent types with the serum C3 level (r=-0.50; p=0.002) and anti-dsDNA antibodies (r=0.40; p=0.015). Furthermore, a substantial negative relationship between all types of cellular crescents with C3 (r=-0.55; p=0.002) and the IgG concentration (r=-0.34; p=0.039) was noted. However, no statistically important interrelation between the presence of renal crescents and anti-C1q antibodies of circulating immune complexes was found.

Conclusions: Activity of LN, evaluated using immunological markers (including a low level of C3 and a high level of anti-dsDNA), corresponds with a more aggressive form of nephropathy, associated with numerous crescents in renal biopsy.

FR-PO738

Concordance of Clinical and Histological Response on Lupus Nephritis Patients Diana A. Aguirre Campos, Jesus Arellano, Adolfo Navarro escamilla, Blanca Martinez-Chagolla, Luis A. Mariscal. *Hospital General Dr. Miguel Silva, Morelia, Mexico.*

Background: Renal response in lupus nephritis usually exclude the renal histology component. There are discordance between clinical findings and the histological activity. Recent studies has suggested that repeat biopsy after induction therapy may be useful to evaluate response to immunosuppressive therapy. The objective was to compare the concordance between clinical and histological response on proliferative lupus nephritis patients.

Methods: This retrospective study included patients between June 2010 and May 2017 with proliferative lupus nephritis who had a control biopsy after induction treatment. We evaluate complete clinical response (CCR), partial clinical response (PCR) and no clinical response (NCR) according to ACR criteria. The histological response (HR) was defined as an activity index less or equal to 3 in the control biopsy. For concordance analysis we evaluate by 2 criteria: the first (CR1) defined as Non Responders the patients with PCR and NRC. The second criteria (CR2) take as Non responders only the NRC patients. Concordance was evaluated by Kappa coefficient.

Results: We included 19 patients, 7 of them with lupus flare; 15 women (78.9%); mean age 27.4±5.79 years old and follow-up of 384±116 days. The control biopsy was performed between 6 to 12 months after the start of the treatment. At control biopsy 5 patients (26.31%) had CCR, 5 (26.31%) PCR and 9 (47.36%) NCR. Twelve patients

(63.1%) had histological response and 7 (36.8%) without histological response. The concordance between clinical and histological response was 0.53 in the CR1 criteria, and 0.47 in the CR2 criteria.

Conclusions: The study show a low concordance between clinical and histological response in proliferative lupus nephritis.

FR-PO739

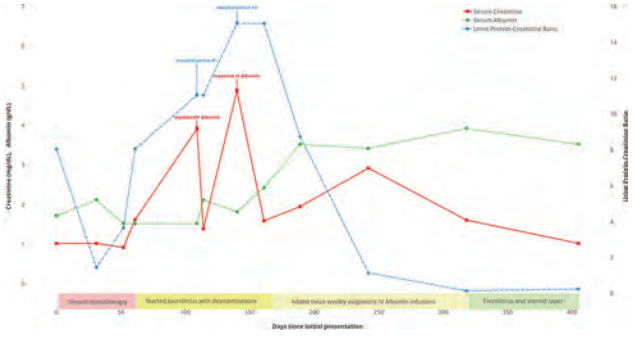
A Patient with "Albumin-Dependent" Focal Segmental Glomerulosclerosis Margaret Duffy,[2] Matthew Palmer,[1] Vishnu S. Potluri,[2] Jonathan J. Hogan.[2] *[1]Pathology, University of Pennsylvania, Philadelphia, PA; [2]Nephrology, The University of Pennsylvania, Philadelphia, PA.*

Background: Idiopathic focal segmental glomerulosclerosis (FSGS) can present with severe volume overload and acute kidney injury (AKI). Here we present such a patient with idiopathic FSGS complicated by multiple episodes of severe AKI and diuretic-resistant volume overload that was only responsive to IV albumin therapy.

Methods: A 54 year-old Jamaican woman developed nephrotic syndrome (SCr 0.86 mg/dL, UProt:Cr 8 g/g, SAlb 1.7 g/dL). A kidney biopsy revealed tip-variant FSGS. She achieved partial remission within four weeks with prednisone 120 mg/d, but then relapsed (UProt:Cr 3.6, SAlb 2.1 g/dL). She was hospitalized with oliguric AKI (Scr 3.89 mg/dL) and volume overload refractory to high-dose IV diuretics and developed candida esophagitis and *C. difficile* colitis. Steroids were tapered and she was treated with IV albumin (25%, 1 mg/kg q8h), with improvement in her SCr (1.37 mg/dL) and urine output (8L) within 24 hours (see image). Tacrolimus was started and she was discharged. She was then re-admitted for volume overload, hypoalbuminemia, and AKI that only responded to 25% IV albumin. Tacrolimus levels were undetectably low. We hypothesized that her acute anasarca led to her inability to absorb tacrolimus. We therefore treated her aggressively with 5 sessions of intermittent ultrafiltration, 5 sessions of plasma exchange therapy with albumin replacement, and pulse oral dexamethasone (40 mg/week). Her AKI again resolved and she was discharged on weekly dexamethasone, oral tacrolimus, and biweekly outpatient albumin infusions. With this therapy she achieved complete remission with target tacrolimus trough levels 6-8 µg/L. She was weaned off steroids and IV albumin. She has been in complete remission for five months on tacrolimus monotherapy.

Results:

Conclusions: We present a case of idiopathic FSGS with a rare and extreme phenotype of severe volume overload and recurrent AKI. In these cases, IV albumin therapy should be considered, particularly for patients who were previously steroid-responsive and may therefore be responsive to other immunosuppressive agents.



FR-PO740

Urinary Extracellular Vesicle-Derived Markers for Steroid Resistant FSGS Ilse M. Rood,[1] Michael Merchant,[2] Daniel W. Wilkey,[2] Johan Van der vlag,[1] Jack F. Wetzels,[1] Jon B. Klein,[2,3] Jeroen Deegens.[1] *[1]Radboud University Medical Center, Nijmegen, Netherlands; [2]University of Louisville Kidney Disease Program, Louisville, KY; [3]Robley Rex Veterans Administration Medical Center, Louisville, KY.*

Background: Urinary extracellular vesicles (uEV) contain many proteins that may serve as biomarkers in renal disease. We compared the proteome of uEV from patients with biopsy proven focal segmental glomerular sclerosis (FSGS) with a steroid resistant nephrotic syndrome (SRNS; n=3), FSGS with steroid sensitive nephrotic syndrome (SSNS; n=3), FSGS with a partial remission on steroids (PR; n=3), minimal change disease (MCD; n=3), secondary FSGS (n=3) and normal healthy controls (NC; n=3). We hypothesized that the proteome of uEV could reveal a marker to predict steroid resistance in patients with FSGS.

Methods: UEV were isolated and analyzed using a multiplexing approach (TMT-labeling) and LCMS methods (1D-RP-HPLC-ESI-LTQ-VELOS-Orbitrap and Proteome Discover Software).

Results: In total 503 different proteins were identified with at least two peptides (with peptide and protein threshold of 95% with a false discovery rate of 0.5%). Comparison of FSGS SRNS to SSNS (including FSGS-SSNS, PR and MCD) indicated changes (unadjusted t-test $p<0.05$) in abundance of 26 proteins. In FSGS SRNS 17 proteins were downregulated, of which four proteins without any overlap of abundance compared to SSNS, secondary FSGS and normal controls. Nine proteins were upregulated, of which three proteins without any overlap compared to SSNS, secondary FSGS and normal controls. Many of these are related to the complement system.

Conclusions: We identified 26 extracellular vesicle-derived proteins that were significantly different between FSGS SRNS, compared to SSNS. Further analysis will be conducted to identify (a subset of) proteins that maybe considered as candidate biomarkers for FSGS SRNS.

FR-PO741

Collapsing FSGS: Vascular Injury as a Cause of Secondary Collapsing Glomerulopathy? Francois Gougeon,[2,5] Harsharan K. Singh,[3] J. Charles Jennette,[4] Volker Nickeleit.[1] *[1]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]UNC-Chapel Hill Nephropathology, Chapel Hill, NC; [3]University of North Carolina School of Medicine, Chapel Hill, NC; [4]University of North Carolina at Chapel Hill, Chapel Hill, NC; [5]Pathologie, Université de Montréal, Montréal, QC, Canada.*

Background: Collapsing glomerulopathy (CG) has been associated with various diseases such as infections, diabetes mellitus or auto-immune diseases. In renal allografts CG has occasionally been linked to perfusion abnormalities. At present a systematic review of CG and concurrent other renal diseases is lacking

Methods: We searched our database for a biopsy diagnosis of CG in native and transplant kidneys between 01/2011 and 01/2016. Among 7641 cases 4.4% (322) showed CG in an initial index biopsy. Tip variant FSGS 51/7641 (0.7%) served as one control cohort. Cases were grouped as: 1) "pure": no other significant kidney disease, 2) presumptive "secondary": with concurrent other significant renal diseases

Results: CG was more often secondary than the tip-variant (152/322, 47% vs. 14/51, 28%; $p<0.01$; table 1). In the study set three disease categories were significantly more often diagnosed in secondary CG: severe arterionephrosclerosis (AS; 25%), membranous glomerulopathy (MGN, 15%) and thrombotic microangiopathies (TMA, 9%; all $p<0.01$). In comparison secondary tip variant FSGS showed tightest associations with MGN and no association with TMA. In transplants, 21/30 (70%) of CG cases were classified as secondary: 7/21 had prominent vascular sclerosis and 4/21 antibody mediated rejection with microvascular injury

Conclusions: In conclusion: CG but not tip-variant FSGS is commonly associated with concurrent renal diseases. Secondary CG is significantly linked to vascular injury (AS, TMA, rejection with capillaritis). These findings further understanding of CG and pending future studies can streamline diagnostic decision making

	CG	Tip lesion	Total cohort
Total	322	51	7319
Total "pure	170 (52.8%)	37 (72.5%)	N/A
Total "secondary"	152 (47.2%)	14 (27.5%) p=<0.01	N/A
Associations in "secondary" cohort			
Severe arteriosclerosis	38/152 (25.0%)	2/14 (14.3%)	757 (10.3%) p<0.01
Membranous glomerulopathy	22/152 (14.5%)	5/14 (35.7%) p<0.05	623 (8.5%) p<0.01
Lupus nephropathy	20/152 (13.2%)	1/14 (7.1%)	663 (9.1%)
Diabetic nephropathy	20/152 (13.2%)	1/14 (7.1%)	951 (13.0%)
Thrombotic microangiopathy	14/152 (9.2%)	0	187 (2.6%) p<0.01
Combined severe arteriosclerosis and diabetic nephropathy	12/152 (7.9%)	0	372 (5.1%)
IgA nephropathy (proliferative)	4/152 (2.6%)	0	320 (4.4%)
ANCA-associated glomerulonephritis	3/152 (2.0%)	0	406 (5.5%)
Other	19/152 (12.5 %)	5/14 (35.7%)	N/A

Table 1: Total biopsy cohort and tip lesion compared to secondary CG cases (natives). All statistics refer to comparison with the CG cohort.

FR-PO742

Clinical and Pathological Analysis of Patient Presenting Renal Lesion and Monoclonal Gammopathy: A Retrospective Study of 64 Patients with Biopsy-Proven Renal Diseases Chao Li, Yubing Wen, Hang Li, Jianfang Cai, Xuemei Li, Xuewang Li. *Nephrology, Peking Union Medical College Hospital, Chinese Academy of Medicine Sciences & Peking Union Medical College, Beijing, China.*

Background: Patients with monoclonal gammopathy can develop a variety of related renal lesions or possibly have kidney disease unrelated to their monoclonal gammopathy. We characterized the spectrum of renal diseases associated with monoclonal gammopathy and unrelated renal diseases.

Methods: Hospitalized patients in Peking Union Medical College Hospital who underwent renal biopsy between January, 2013 and December, 2015. They had monoclonal gammopathy on Serum protein electrophoresis (SPE), serum immunofixation electrophoresis (IFE), urine IFE and/or serum free light chain (FLC). 64 patients met the inclusion criteria and were classified as MGRS (n=36), MGUS (n=17) and hematologic malignancy (n=11).

Results: Renal lesions in MGRS subgroup included light chain amyloidosis(AL) (n=28, 77.8%), light chain deposition disease(LCDD) (n=7,19.4%), and fibrillary glomerulopathy (n=1, 2.8%). Renal diseases in MGUS subgroup included membranous nephropathy (n=10, 58.8%), FSGS (n=3, 17.6%), diabetic glomerulopathy (n=1, 5.9%), Henoch-Schonlein purpura nephritis (n=1, 5.9%), anti-GBM disease concurrent with membranous nephropathy (n=1, 5.9%) and glomerulomegaly (n=1, 5.9%). Various renal lesions related/unrelated to hematologic malignancy were seen in third subgroup, including light chain cast nephropathy (n=3, 27.3%), tubulo-interstitial lesions (n=2,

18.2%), LCDD(n=1, 9.1%), IgA nephropathy (n=1, 9.1%), MesPGN (n=1, 9.1%), endocapillary proliferative glomerulonephritis (n=1, 9.1%) and acute tubular necrosis (n=1, 9.1%). Positive rate of SPE, SIFE and UIFE in MGRS subgroup were 40.6%, 52.8% and 69.4%, respectively. Positive rate of SPE, SIFE and UIFE in MGUS subgroup were 68.8%, 100% and 37.5%, respectively. Positive rate of SPE, SIFE and UIFE in hematologic malignancy subgroup were 54.5%, 72.7% and 81.8%. MGRS and MGUS subgroups differed significantly in positive rate of SIFE (P<0.001). Abnormal rates of serum FLC ratio in above three subgroups were 83.3%, 17.6% and 90.9%, respectively, in which MGUS group was significantly lower than other two groups(P<0.001,P<0.001).

Conclusions: The significance of monoclonal gammopathy in patients with renal disease should be evaluated by other clinical data, as well as renal pathology.

FR-PO743

Clinical, Pathological, and Mass Spectrometry Analysis of AL Renal Amyloidosis

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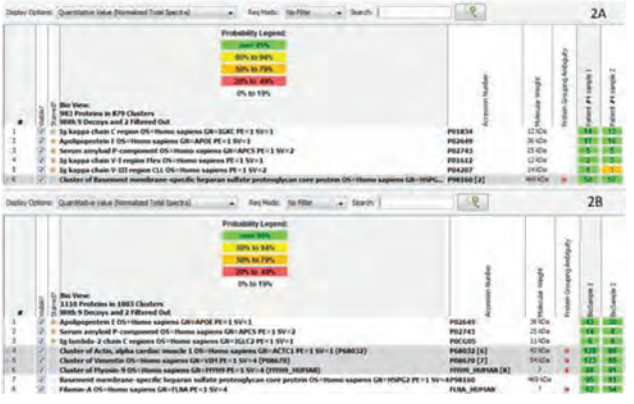
Background: In recent years, laser micro-dissection combined with mass spectrometry (LMD/MS) has been applied in the diagnosis of renal amyloidosis, it can be used for typing of amyloid deposits where routine immunohistochemistry (IHC) is equivocal and negative, as well as finding new causes of amyloidosis, In this study, we retrospectively analysis the patients with AL amyloidosis to evaluate the significance of immunoperoxidase (IP) and establish LMD/MS technique for diagnosing renal amyloidosis.

Methods: We analyzed 45 cases of AL amyloidosis patients diagnosed by Congo Red Staining (CRS) and EM who were admitted during last 5 years in a single centre, analyzed their clinical manifestations and pathological findings, then selected 20 cases with inconclusive immunofluorescence (IF) results, performed IP and LMD/MS for amyloid typing. For IP, both κ and λ were stained. For LMD/MS analysis, 7-μm sections were prepared and CRS positive area was collected by laser microdissection, the minimum area for each case was 200,000μm^2. Sample microdissected was digested by trypsin. Peptides were quantified using Thermo Fusion Lumos mass spectrometer. MASCOT software was used for identification of proteins. Scaffold 4 software was used to integrate the results.

Results: Patients with AL renal amyloidosis had mutiple organs involvement, including kidney, liver, heart and intestinal system. Eleven (55%) of the 20 cases could be typed by IP technique. Amyloid materials could be identified in eighteen (90%) of the 20 cases by LMD/MS. Figure 1A and 1B were Mascot results of AL-κ and AL-λ amyloidosis subtyped by LMD/MS respectively.

Conclusions: Our study showed IP is superior to IF and MS-based proteomic analysis is complementary to IHC in typing of renal amyloidosis.

Funding: Government Support - Non-U.S.



FR-PO744

Sensitivity and Specificity of Immunofluorescence for Diagnosing Renal Immunoglobulin-Derived Amyloidosis Compared to Mass Spectrometry

M. Lourdes Gonzalez Suarez, Pingchuan Zhang, Samih H. Nasr, Mary E. Fidler, Insara Jaffer Sathick, Wonngarm Kittanamongkolchai, Paul J. Kurtin, Nelson Leung. *Mayo Clinic, Rochester, MN.*

Background: Immunoglobulin light chain (AL) amyloidosis is the most frequent type of renal amyloidosis in the U.S., accounting for 81% of cases. Accurate typing is crucial for early diagnosis and treatment of immunoglobulin-derived (AIg)-amyloidosis (i.e. AL, AH (Ig heavy chain), AHL (Ig heavy and light chain)) and to avoid treating other types with potentially toxic chemotherapy. Immunofluorescence (IF) is the first step to type renal AIg-amyloidosis but the performance characteristics of this method are largely unknown. In this study, we aim to establish the sensitivity and specificity of IF for diagnosing AIg-amyloidosis in patients whose amyloid typing was performed by the current gold standard, laser microdissection/mass spectrometry (MS).

Methods: Renal biopsy pathology reports (2008-2015) from several institutions with diagnosis of amyloidosis by IF, which underwent a confirmatory diagnosis and typing by MS done at our center, were reviewed. Reported IF staining for kappa or lambda ≥ 2+, with weak or no staining (0, trace or 1+) for other antigens was considered positive for AL by IF.

Results: We reviewed 170 renal pathology reports. Of these, 104 cases were confirmed as AIg-amyloidosis on MS and 66 were non-AIg (including AA, ALECT2, AApo AI, AApo AII, AApo AIV, AGel, AFib) (table). IF sensitivity was 84.6%; 16 could not be diagnosed as AIg-amyloidosis by IF due to weak staining for all antigens. Lower sensitivity could be in part related to selection bias as cases with clear-cut IF findings of AL may not have undergone testing by MS. IF specificity was 92.4%; 5 cases were misdiagnosed as AIg-amyloidosis by IF.

Conclusions: In this study, IF failed to accurately differentiate AIg- from non-AIg amyloidosis in 12.3% of cases. Relying on IF alone for determining AIg vs. non-AIg amyloidosis may lead to misdiagnosis. Our data demonstrate that IF has inferior sensitivity and specificity as compared with MS in the typing of AIg-derived amyloidosis. Typing with MS is recommended in cases where IF is not certain.

Immunofluorescence results for the diagnosis of immunoglobulin- derived amyloidosis

Immunofluorescence	Positive MS	Negative MS	Total of cases
Positive	88	5	93
Negative	16	61	77

FR-PO745

Rapid Reduction in Urinary sCD163 Correlates with Clinical Benefit in the CLEAR Study of C5aR Inhibitor Avacopan in ANCA-Associated Vasculitis

Jun Deng,[1] Antonia Potarca,[3] Thomas J. Schall,[2] Pirow Bekker.[3] *[1]ChemoCentryx, Inc, Mountain View, CA; [2]ChemoCentryx, Inc, Mountain View, CA; [3]ChemoCentryx, Inc, Mountain View, CA.*

Background: Avacopan (CCX168), a potent C5aR inhibitor, induced rapid clinical benefit (measured by BVAS, proteinuria, and health-related quality of life measurements) in the Phase 2 CLEAR trial in ANCA-associated vasculitis, AAV (Jayne et al, JASN, 2017). Urinary soluble CD163 (sCD163) is a macrophage cell surface molecule known to correlate with renal histopathology, and it is a useful biomarker of kidney inflammation in AAV (O'Reilly et al, JASN, 2016). We evaluated urinary sCD163 in CLEAR patients at baseline and over the 12-week treatment period.

Methods: CLEAR comprised 3 patient groups: (1)Full dose prednisone (60 mg), standard care; (2)Avacopan 30 mg b.i.d. plus low dose prednisone (20 mg); (3)Avacopan 30 mg b.i.d. plus no prednisone. All patients received either IV cyclophosphamide or IV rituximab. sCD163 (ELISA) and creatinine were measured pre-dose, and days 8, 15, 29, 57, and 85.

Results: Avacopan treatment reduced sCD163/creatinine markedly by day 8, and further over the course of 12-weeks (see table). By contrast, standard care controls with full-dose prednisone therapy did not show improvement in urinary sCD163 until day 57. The urinary sCD163/creatinine levels were highly correlated with previously reported improvements in urinary albumin/creatinine ratio and MCP-1/creatinine ratio (p<0.0001).

Conclusions: Avacopan induced a rapid reduction of sCD163, which correlated with similarly rapid improvements of kidney inflammation markers and AAV signs and symptoms in the CLEAR trial. sCD163 may provide a valuable biomarker of clinical improvements derived from avacopan. Avacopan is currently in a Phase 3 clinical trial for AAV.

Funding: Commercial Support - Chemocentryx

Urine sCD163/creatinine ng/mmole

	Placebo + FD Prednisone				Avacopan + LD Prednisone				Avacopan + No Prednisone			
Time Points	N=	Geomean	95% CI Lower	95% CI Upper	N=	Geomean	95% CI Lower	95% CI Upper	N=	Geomean	95% CI Lower	95% CI Upper
Pre dose	19	258	148	448	21	408	280	596	18	250	137	458
Day 8	19	300	186	485	21	300*	207	436	18	180*	110	296
Day 15	19	249	147	423	21	213***	142	321	18	165*	89	306
Day 29	19	220	141	342	21	117***	78	173	17	117**	63	216
Day 57	19	116***	74	182	20	115***	70	188	16	125#	71	219
Day 85	19	120**	77	187	20	85***	50	145	18	97*	50	188

Paired t-test against baseline in each group: *p<0.05; **p<0.01; ***p<0.001; # p=0.076; FD = Full dose; LD = Low dose

FR-PO746

Serum B-Cell Activating Factor Levels Are an Early Predictor of the Response to Rituximab in Patients with Idiopathic Nephrotic Syndrome

Manuela Colucci, Francesco Emma, Marina Vivarelli. *Bambino Gesù Children's Hospital - IRCCS, Rome, Italy.*

Background: Treatment with rituximab (RTX), a B-cell depleting anti-CD20 antibody, has a prolonged efficacy in preventing relapses in pediatric idiopathic nephrotic syndrome (INS). Length of remission following RTX correlates with length of B cell, especially memory B cell, depletion. However, some patients experience early recurrence of INS following RTX treatment. Serological predictors of response to RTX are as yet unidentified.

Methods: Levels of serum B cell-activating factor (BAFF) and of B cell subsets were serially monitored by ELISA and flow cytometry respectively in 14 steroid-dependent INS children treated with RTX up to recurrence of NS. An initial dose of RTX (375 mg/m^2), repeated at 7 days in case of incomplete depletion of B cells, was administered.

Results: Three patients relapsed after 6.1±0.2 months (R) whilst the other 11 never relapsed during this period (NR). At baseline there was no significant difference between these two groups. One month after RTX treatment, all B cell subpopulations were

completely depleted, and total $CD19^+$ B cells started to reappear at 6 months in both groups, with no significant difference in the number of total B cells between R and NR. However, serum BAFF levels and the B cell subset repopulation were different in the two groups. In the NR group, serum BAFF levels significantly rose at 1 month and remained increased during the follow-up, sustaining the significant re-emergence of transitional and mature B cells ($p<0.05$ vs 1 months). Unexpectedly, serum BAFF levels never increased in the R group, and this was reflected by the reduced recovery of transitional and mature B cells. In contrast, R patients showed a significantly increased reconstitution of memory and in particular switched memory B cells at 6 months compared to the NR group in whom the memory B cells remained depleted ($p<0.05$ compared with R at 6 months).

Conclusions: Total B cell recovery is not a good predictor of relapse in INS pediatric patients treated with rituximab, as this population is composed of several B cell subsets with different functions and different reconstitution patterns following RTX treatment. On the contrary, serum BAFF levels post-RTX treatment and the re-emergence of memory and in particular of switched memory B cells may better predict the response to RTX in pediatric INS patients.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO747

Urine Epidermal Growth Factor, Monocyte Chemoattractant Protein-1, or Their Ratio as Biomarkers for Response to Therapy in Primary Glomerulonephritis

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Background: The balance between pro-inflammatory cytokines such as monocyte chemoattractant protein- 1 (MCP-1) and protective cytokines such as epidermal growth factor (EGF) likely determines the outcomes in primary glomerulonephritis (GN). Elevated urinary MCP-1 and decreased urinary EGF have been associated with renal fibrosis, but there is limited information on their prognostic roles. We evaluated the relationships of urinary EGF, MCP-1 or their ratio at baseline with subsequent response to therapy and renal function at 24 months in patients with primary GN.

Methods: This is a prospective study in primary GN (n=74). Urine samples were collected at the time of biopsy. MCP-1 and EGF were analyzed by ELISA kits and expressed as a ratio to creatinine (ng/mg Cr) or as EGF/MCP-1 (ng/ng). Complete remission (CR) was defined as proteinuria ≤ 0.3 g/gCr and other subjects were categorized as Not in remission (NR). The predictive role of the biomarkers and traditional clinical parameters for CR were analyzed by Cox multivariate regression analysis.

Results: The diagnoses were: IgA nephropathy (n=28), focal segmental glomerulosclerosis (n=16), minimal change disease (n=10) and membranous nephropathy (n=20). Median follow up was 20 (12, 28) months. Estimated glomerular filration rate (eGFR) at baseline correlated with positively with EGF, EGF/MCP-, and inversely with MCP-1. Proteinuria at baseline correlated positively with MCP-1, and inversely with EGF/MCP-1. After treatment with renin-angiotensin blockers and/or immune-modulating agents, 38 patients (51.4%) achieved CR. Baseline EGF and EGF/MCP-1 levels were higher in CR compared to NR, whereas MCP-1 was not different. High EGF (>75 ng/mgCr) at baseline was an independent predictor for subsequent CR (OR (95%CI): 2.86 (1.37-5.94), p=0.005). In the subset of patients (n=43) who completed 24 months follow-up, high baseline EGF (>75 ng/mgCr) had lower proteinuria at 24 months follow-up. Baseline EGF and EGF/MCP-1 correlated positively with eGFR at 24 months.

Conclusions: High urinary EGF at baseline was an independent predictor of subsequent CR. EGF and EGF/MCP-1 at baseline correlated positively with eGFR and inversely with proteinuria at 24 months. Larger studies are necessary to confirm the benefits in the management of primary GN.

Funding: Government Support - Non-U.S.

FR-PO748

Clinicopathological Implications of Urinary Soluble CD163 in Glomerulonephritis with Crescentic Formation

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Background: M2 macrophages contribute to crescentic formation in various types of glomerulonephritis. A recent report suggested that the level of urinary soluble CD163 (sCD163), a marker of M2 macrophage infiltration, associated very tightly with active renal vasculitis. In this study, the association of urinary sCD163 level with indices of disease activity was analyzed in patients with glomerulonephritis with crescents.

Methods: Subjects were fifty-seven patients with biopsy proven glomerulonephritis with crescentic formation, including microscopic polyangitis (n=14), anti-GBM glomerulonephritis (n=3), IgA vasculitis (n=10), IgA nephropathy (n=22), lupus nephritis (n=6), infectious glomerulonephritis (n=2). In advance of kidney biopsy, measurements of urinary sCD163 and urinary protein excretion (UP), effective glomerular filtration rate (eGFR) were performed.

Results: 1) In all subjects, urinary sCD163 correlated positively with the percentage of glomeruli with cellular crescents ($r=0.48$, $p<0.01$). In contrast, urinary sCD163 did not associate with the percentage of glomeruli with fibrocellular or fibrous crescents. Additionally, there was a positive correlation between urinary sCD163 and UP ($r=0.41$, $p<0.05$), whereas there was no association between urinary sCD163 and eGFR. 2) In thirty subjects followed for six months after immunosuppressive treatments, the positive relationships of urinary sCD163 levels with treatment-induced changes in eGFR ($r=0.49$, $p<0.01$) or UP ($r=0.41$, $p<0.05$) were observed.

Conclusions: In conclusion, urinary sCD163 may be a novel surrogate marker for disease activity of glomerulonephritis with crescentic formation.

FR-PO749

Diagnosis of Renal Vasculitis Flare Using usCD163: A Multi-Centre Prospective Study

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Background: Urinary sCD163 displays excellent potential for active renal vasculitis detection at AAV diagnosis. The clinical utility of usCD163 is in the diagnosis of renal vasculitis flare, potentially obviating the need for biopsy and detecting active renal vasculitis prior to further injury.

Methods: AAV patients were prospectively recruited with potential renal vasculitis flares from a multicentre cohort. Physicians judged the flare probability as *High* or *Possible*. An independent committee adjudicated on renal flare diagnosis (BVAS major criteria:RBC casts &/or 30% increase in creatinine or renal biopsy). Urine creatinine-normalised sCD163 levels were measured by ELISA.

Results: 44 patients were prospectively recruited, 32% with renal flare. Creatinine was 1.7mg/dL (IQR 1.0-3.2, 78% increase from baseline) and 1.5mg/dL (IQR 1.1-1.7, 2.8% increase) in flare and non-flare (p=0.02). Median usCD163 levels were significantly higher in patients with adjudicated renal flare (469.6 ng/mmol (IQR 363.8-2974)) compared to non-flare (25.4 (IQR 3.9-80.8), p<0.0001)). Median usCD163 levels were not elevated in potential renal flare mimics, including sepsis (62.1ng/mmol IQR 27.8-155.3), acute kidney injury (22.4ng/mmol IQR 0-78.7) or systemic flare (22.4ng/mmol, IQR 21-107.7).

Conclusions: usCD163 is diagnostic of renal vasculitis flare in prospectively observed patients with AAV, and is superior to initial physician assessment and BVAS major renal criteria.

Funding: Government Support - Non-U.S.

Table 1: Biomarker characteristics.

	Sensitivity	Specificity	PLR	NLR	PPV	NPV	AUC
usCD163 >300ng/mmol	91.7%	96.8%	28.4	0.09	91.7%	96.8%	0.93
Physician High Probability	47.4%	88%	3.95	0.6	75%	68.8%	0.71
BVAS WG Major Criteria	57.1%	82.8%	3.31	0.52	61.5%	68.1%	0.74

PLR= Positive Likelihood Ratio. NLR=Negative Likelihood Ratio. PPV=Positive Predictive Value. NPV=Negative Predictive Value. AUC=Area Under Curve

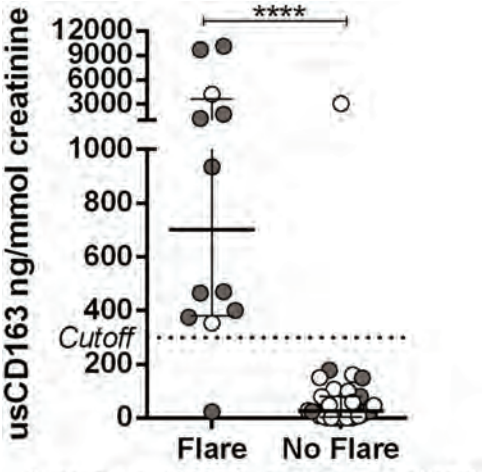


Figure 1:usCD163 levels normalised to urine creatinine.
Dark circles: High probability of renal flare.
Clear circles: Possible renal flare.

FR-PO750

Clinical Study Results of a Real-Time Point-of-Care Glomerular Filtration Rate Measurement Richard B. Dorshow,[3] Martin Debreczeny,[1] James R. Johnson,[1] jeng-jong Shieh,[1] Thomas E. Rogers,[2] Kevin J. Martin,[4] Daniel W. Coyne.[5] *[1]MediBeacon Inc., St Louis, MO; [2]MediBeacon Inc, St Louis, MO; [3]MediBeacon Inc., Saint Louis, MO; [4]Saint Louis University Med Ctr, St. Louis, MO; [5]Washington University School of Medicine, St. Louis, MO.*

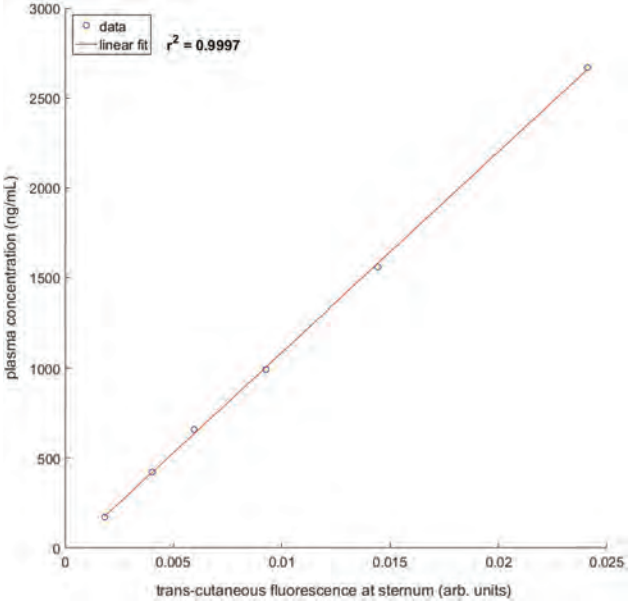
Background: Real-time point-of-care measure of glomerular filtration rate (mGFR) would permit rapid diagnosis of acute kidney injury and precise determination of CKD. Clearance pharmacokinetics of the fluorescent agent MB-102 was measured in the plasma and correlated with noninvasively measured transdermal fluorescence for subjects with normal kidney function to Stage 4 CKD.

Methods: Blood samples were taken in 60 subjects with eGFR from normal to 19 mL/min/1.73m² over a period of 12hr post simultaneous administration of MB-102 and iohexol, and urine collected to assess percent excretion. A noninvasive detection device simultaneously measured the transdermal fluorescence from MB-102.

Results: Plasma pharmacokinetics displayed the expected 2 compartment model of a vascular-tissue equilibrium phase followed by renal excretion only. The GFR measured from the MB-102 plasma pharmacokinetics was highly correlated with the GFR measured from iohexol over the entire measured range of GFR values (r^2=0.98). The time-dependence of the transdermal fluorescence from MB-102 monitored by our fluorescence detection device was highly correlated with that of the plasma (see figure from subject with normal mGFR). MB-102 was completely cleared by 12hr when mGFR was >60 mL/min/1.73m². No serious nor significant adverse events were reported.

Conclusions: Point-of-care clinically amenable measured GFR for a range of kidney function from normal to Stage 4 CKD is demonstrated using transdermal fluorescence detection of the novel fluorescence tracer agent MB-102.

Funding: Commercial Support - MediBeacon Inc.



FR-PO751

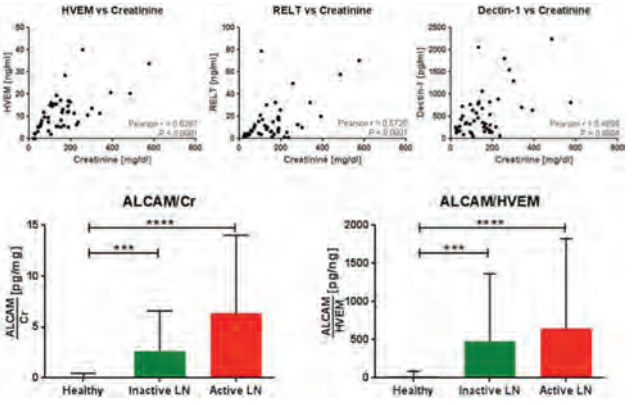
Unbiased Screening of Urinary Protein Biomarkers for Glomerular Filtration Rate Normalization Sanam Soomro, Samantha Stanley, Ramesh Saxena, Michelle Petri, Chandra Mohan. *University of Houston, Houston, TX.*

Background: To account for glomerular filtration rate, urinary creatinine is routinely used for the normalization of urine biomarkers related to disease. Because of the small size of this metabolite, antibodies are difficult and expensive to develop, limiting the applications of disease-specific urine protein biomarkers for antibody-based point of care applications.

Methods: An aptamer-based screening of 1129 proteins in 24 human urine samples (8 active lupus nephritis (LN), 8 inactive LN, 8 healthy controls (HC)) was carried out to identify urine proteins that correlated well with urine creatinine but not disease.

Results: The screen uncovered 18 proteins that correlated well with urinary creatinine but were similar in patients with or without nephritis. Further validation in an independent cohort of 48 subjects (16 active LN, 16 inactive LN, 16 HC) showed a significant positive correlation of urine HVEM, RELT, and Dectin-1 to urinary creatinine. The most promising marker, urine HVEM, was significantly correlated to urinary creatinine in both white (Pearson r = 0.7229, P = 0.0001) and black subjects (Pearson r = 0.6111, P = 0.0009). Finally, normalization of other urinary biomarker proteins against urine HVEM showed comparable fold change and statistical significance as normalization to urinary creatinine.

Conclusions: Instead of the metabolite creatinine, proteins such as HVEM, RELT, and Dectin-1 can be used for normalization of urine biomarkers. The use of proteins instead of metabolites for normalization paves the way towards novel diagnostic approaches.



Urine HVEM, RELT, and Dectin-1 were validated by ELISA and found to be significantly correlated with urinary creatinine. HVEM, the most promising marker for GFR normalization, was also used to normalize ALCAM, a biomarker for SLE, to have comparable fold change and statistical significance as normalization to urinary creatinine.

FR-PO752

Plasma Metabolomics in Steroid-Sensitive and Steroid-Resistant Nephrotic Syndrome Jessica Gooding,[3,4] Shipra Agrawal,[2,5] Susan Mcritchie,[1,4] Zachery J. Acuff,[3,4] William E. Smoyer,[2,5] Susan J. Sumner.[4,1] *[1]Nutrition Research Institute, University of North Carolina at Chapel Hill, Kannapolis, NC; [2]Center for Clinical and Translational Research, Nationwide Children's Hospital, Columbus, OH; [3]Discovery, Science and Technology, RTI International, Durham, NC; [4]NIH Eastern Regional Comprehensive Metabolomics Resource Core (ERCMRC), University of North Carolina Chapel Hill, Chapel Hill, NC; [5]Pediatrics, The Ohio State University, Columbus, OH.*

Background: Nephrotic syndrome (NS) is a common kidney disease in children. Steroids are the primary therapy; however, they are ineffective in ~20% cases. Children with steroid-resistant NS (SRNS) fail to enter remission after prolonged steroid treatment, and are at high risk for steroid-induced side effects as well as progression of disease to end-stage renal disease (ESRD) within five years. This study aimed to discover markers of steroid-resistance that could be used to predict SRNS at presentation and develop a mechanistic definition of SRNS.

Methods: Citrate plasmas (n=86) were collected from 30 steroid-sensitive NS and 15 steroid-resistant NS patients at presentation (prior to steroid therapy) and after an average of 7 weeks of steroid treatment. Broad spectrum ^{1}HNMR data was acquired, binned, and concentration fit. Multivariate analyses and hypothesis testing were used to determine the metabolites that best differentiated the phenotypic groups, and logistic regression using a stepwise variable selection method were used model the odds of steroid resistance at presentation.

Results: Treatment effects were observed between paired presentation and follow-up steroid-sensitive (SSNS) samples and between follow-up SSNS and SRNS samples. Metabolites affected by treatment included lipoproteins, adipate, tyrosine, valine, alanine, glutamine, glucose, pyruvate and creatine. After controlling for age, the step-wise logistic regression model selected glutamine (OR= 1.01; 0.99-1.02 95% CI). A similar model with children age >3 only, indicated that children with increased levels of malonate (OR=0.94; 0.89-1.00 95% CI) had an increased odds of responding to treatment.

Conclusions: Known effects of corticosteroid treatment were observed providing a proof-of-concept. The observed metabolic signature supports previous hypotheses that the proximal tubule is involved in the pathology of SRNS as reflected in circulating metabolites of renal gluconeogenesis. After controlling for age, logistic regression suggests that malonate concentration may be a potential biomarker for identifying SRNS at presentation.

Funding: NIDDK Support, Other NIH Support - NIGMS K01GM109320

FR-PO753

A Significance of Urine-Gravidity in Nephrotic Syndrome Shinichi Nishi,[1] Hideki Fujii,[1] Shunsuke Goto,[2] Keiji Kono,[1] Mikiko Yoshikawa,[1] Shuhei Watanabe,[1] Kentaro Watanabe.[1] *[1]Kobe University Graduate School of Medicine, Kobe, Japan; [2]Kobe University Graduate School of Medicne, Kobe, Japan.*

Background: Selectivity index (SI) has been used in the differentiation of nephrotic syndrome (NS), while the sensitivity of SI is not so high. We studied the significance of urine gravidity (UG) as an available differentiative marker for NS.

Methods: We selected 45 consecutive patients with primary NS that were admitted in Kobe University Hospital from 2012 to 2014. Secondary renal diseases associated with collagen diseases and diabetes were excluded. The cases already treated by glucocorticoid or diuretics were also excluded. We studied the relationship between histological and

clinical findings and clarified the availability of UG in the point of differentiation of NS due to MCNS, FSGS, MN.

Results: The subjective cases were comprised of 23 MCNS, 18 MN (stage 1=4), and 3 FSGS. The average age was 52.7±27.7 years-old. The means of amount of urine protein (AUP) and albumin were 8.1±3.7 g/gCr and 1.7±0.7 g/dL, respectively. Those of UG and SI were 1.032±0.013 and 0.340±0.563, respectively. We divided all cases into two groups; MCNS (n=23) and non-MCNS (n=22). In the comparison of two groups, UG was significantly higher in MCNS, 1.039±0.008 and 1.024±0.013 ($p<0.001$). SI did not show a significant difference; 0.216±0.476 in MCNS and 0.476±0.662 in non-MCNS ($p=0.9314$). In ROC analysis UG-AUC of MCNS was 0.831 and SI-AUC of MCNS was 0.796, respectively. We divided into all cases into other two groups; MCD (MCNS+stage1 MN+FSGS) and non-MCD groups. In the comparison of two groups, UG was significantly higher in MCD, 1.039±0.008 and 1.017±0.009, respectively ($p<0.001$). SI did not show significant difference in MCD and non-MCD, 0.222±0.384 and 0.574±0.787 ($p=0.943$). In ROC analysis UG-AUC of MCD was 0.978 and SI-AUC of MCD was 0.770.

Conclusions: UG was an available differentiative marker for MCNS vs. non-MCNS or MCD vs. non-MCD. When we combine UG and SI, we can effectively differentiate three groups MCNS, MN, and FSGS.

The mean parameters of NS cases

	AUP(g/gCr)	Alb(g/dL)	UG	SI
MCNS	8.4(3.7)	1.6(0.7)	1.039(0.003)	0.216(0.434)
MN stage1	7.0(3.0)	1.5(0.4)	1.037(0.006)	0.187(0.160)
MN stage2-4	7.1(3.5)	1.9(1.9)	1.017(0.009)	0.594(0.787)
FSGS	12.9(3.1)	1.7(0.8)	1.041(0.007)	0.311(0.065)

Mean(SD)

FR-PO754

Comparison of Spot Urinary Protein to Creatinine Ratio to 24 Hours Urinary Protein at Different Time Points During the Day: Is There a Variability During the Day? Omer Sabir, Muhammad M. Riaz, Nauman Tarif, Abaid U. Rehman, Kashif Rafique, Nabiha Rizvi. *Medicine, Division of Nephrology, Fatima Memorial School of Health Sciences, University of health Sciences, Lahore, Pakistan.*

Background: 24 hours urinary protein excretion is considered gold standard for the estimation of daily urinary protein loss, although cumbersome. We compared the spot urinary protein to creatinine ratio (PCR) collected at three different time points of the day with standard 24 urine protein collection to identify the best time for sampling.

Methods: This was an observational, cross sectional study carried out at Fatima Memorial Hospital Lahore, Pakistan over four years from January 2013. Sixty-seven (67) patients who were persistently dipstick positive for protein were included and informed consent was obtained. The patients were required to collect a twenty-four hours urine sample according to standard recommendations for protein and creatinine measurement. From the same collection 10 ml aliquots of urine were separated and sent for spot urinary protein and spot urinary creatinine for PCR at different time points (Morning: 8 AM – 10 AM; Evening : 2 PM – 6 PM; Night: 8 PM – 10 PM).

Results: Mean age of the cohort was 32.91± 13.12 years and 39 (58.2%) were males. Mean Serum Creatinine was 3.24 ± 2.50 mg/dL (mean eGFR by CKD-EPI equation: 45.1 ± 37.3 ml/min. Range: 5.7 – 147.5 ml/min). 37.3% were diabetic and were clinically designated as having diabetic nephropathy whereas the rest were undergoing evaluation or had biopsy proven glomerulonephritis. Patients were classified as CKD Class I: 18.6%, Class II: 15.3%, Class III: 23.7%, Class IV: 16.9% and Class V: 25.4%. None of the patient was on renal replacement therapy at the time of cross section. Mean serum albumin of the cohort was 3.23 ± 0.63 g/dL (Range: 1.9 to 4.7 g/dL.); whereas mean 24 hours urinary protein was 2.0 ± 1.58 g/day (Range: 0.73 – 6.5 g/day). Pearson's correlations for all three spot PCR samples were significantly correlated with the 24 hours urinary protein sample, however night time spot sample was found to have strongest correlation (Pearson's r: 0.64, $p < 0.05$) as compared to early morning and evening samples ($r = 0.41$ and $r = 0.37$ respectively, $p < 0.05$ for both).

Conclusions: Our study shows that nighttime sampling for spot PCR may better correlate with 24 hours urinary protein excretion. Further studies in different CKD stages and ethnicities could confirm the findings of our study.

FR-PO755

Prediction of Pathologic Type of Primary Nephrotic Syndrome Using a Machine Learning Algorithm Hui Xu. *Nephrology Department, Xiangya Hospital, Central South University, Changsha, Hunan, China, Changsha, China.*

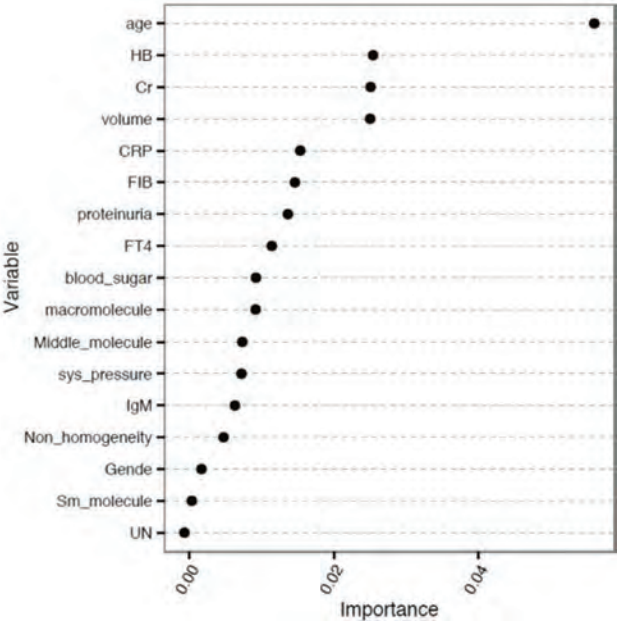
Background: Renal biopsy is the gold standard to determine the pathologic type of primary nephrotic syndrome. However, renal biopsy cannot be performed in some cases. Based on this, we tried to using a machine learning algorithm to predict the pathologic type in primary nephrotic syndrome patients without renal biopsy.

Methods: Clinical data and pathologic types of 203 patients with primary nephrotic syndrome were collected. We trained and validated a machine learning algorithm using data from 203 patients. Then the model was tested prospectively on another 63 biopsy-confirmed patients with primary nephrotic syndrome. Thirdly, Compared with the pathologic results of renal biopsy, the predictive effectiveness of the model was further verified.

Results: Overall accuracy of prediction from the retrospective set of 203 patients was 62.2% across all types of nephrotic syndrome. Among them, minimal-change disease (MCD), 52.2%; non-IgA mesangial proliferative glomerulonephritis, 64.1% (Non-IgAN); IgA nephropathy (IgAN), 57.1%; membranous nephropathy (MN), 76.1% and focal segmental glomerulosclerosis (FSGS), 10.5%. The accuracy of model prediction for the prospectively collected dataset of 63 patients was 61.9%. MCD, 85.7%; Non-IgAN, 60%; IgAN, 80%; MN, 63.6% and FSGS, 0%. Meanwhile, the algorithm identified 17 of 33 variables as contributing strongly to type of renal pathology. Among them, age, hemoglobin and serum creatinine were the top three(Figure 1).

Conclusions: The method has high precision and can be used to help those patients who are not suitable for renal biopsy to predict the pathologic type of primary nephrotic syndrome, which can guide the diagnosis, choice of treatment and evaluation of prognosis of primary nephrotic syndrome.

Funding: Government Support - Non-U.S.



FR-PO756

Urinary Podocyte mRNA and Urinary Podocalyxin Protein: Different Excretion Pattern between Proliferative and Non-Proliferative Glomerular Diseases Akihiro Fukuda,[1,2] Akihiro Minakawa,[2] Masao Kikuchi,[2] Yuji Sato,[2] Hiroyuki Kurosawa,[3] Masanori Hara,[4] Shouichi Fujimoto.[2] *[1]Oita University, Yufu, Japan; [2]University of Miyazaki, Miyazaki, Japan; [3]Denka Seiken Co., Ltd, Gosen, Japan; [4]Niigata Wellness (Iwamuro Health Promotion Center), Niigata, Japan.*

Background: Podocyte depletion causes glomerulosclerosis, and persistent podocyte loss drives progression to end-stage kidney disease in most forms of glomerular diseases. Podocytes are resident on the urinary space side of the glomerular basement membrane, so that as they detach or die, their products can be identified in urine. Thus, the podocyte products in urine might be potential biomarkers to monitor glomerular disease activity and progression. Recently, both the urinary pellet podocyte (u-pod) mRNA excretion rate and urinary podocalyxin (u-PCX) protein levels have been used to monitor disease activity in various glomerular diseases. However, differences in these markers between various pathologies have not yet been investigated. By comparing the u-pod mRNA excretion rate to u-PCX protein levels in biopsy-proven glomerular diseases, we examined the significance of these markers in various glomerular diseases.

Methods: From January 2013 to March 2016, early morning urine samples were collected from 12 healthy volunteers and 184 patients with various kidney diseases (minor glomerular abnormality, n=15; MCNS, n=16; MN, n=17; IgAN, n=62; crescentic GN, n=24; lupus nephritis, n=11; others, n=39). We examined the u-pod mRNA excretion rate, u-PCX protein levels and urinary protein/creatinine ratio (u-PCR).

Results: The u-pod mRNA excretion rate was statistically correlated with u-PCX protein levels ($r=0.37$, $p<0.001$). Both the u-pod mRNA excretion rate and u-PCX protein levels were statistically correlated with u-PCR ($r=0.52$, $p<0.001$ and $r=0.32$, $p<0.001$, respectively). Interestingly, the u-pod mRNA excretion rate was significantly increased in crescentic GN, IgAN and LN (especially class IV) compared with controls but not in MCNS and MN, whereas the u-PCX protein levels were significantly increased in MN and LN (tendency for class V) compared with controls but not in other glomerular diseases.

Conclusions: Although the u-pod mRNA excretion rate and u-PCX protein levels were positively correlated, a higher u-pod mRNA excretion rate and higher u-PCX protein levels might be associated with proliferative glomerulonephritis and non-proliferative glomerulonephritis, respectively.

FR-PO757

A Swine Model of Tunneled Dialysis Catheter (TDC) Infection and Dysfunction: Opportunities for Therapeutic Innovation Diego Celdran-Bonafonte,[1] Begoña Campos,[2] Aous Jarrouj,[1] Li H. Wang,[1] Lindsay N. Kohler,[1] Jaroslav Janda,[1] Keith L. Saum,[2] Frank C. Brosius,[1] Prabir Roy-Chaudhury.[1,3] *[1]University of Arizona, Tucson, AZ; [2]University of Cincinnati, Cincinnati, OH; [3]SAVAHCS, Tucson, AZ.*

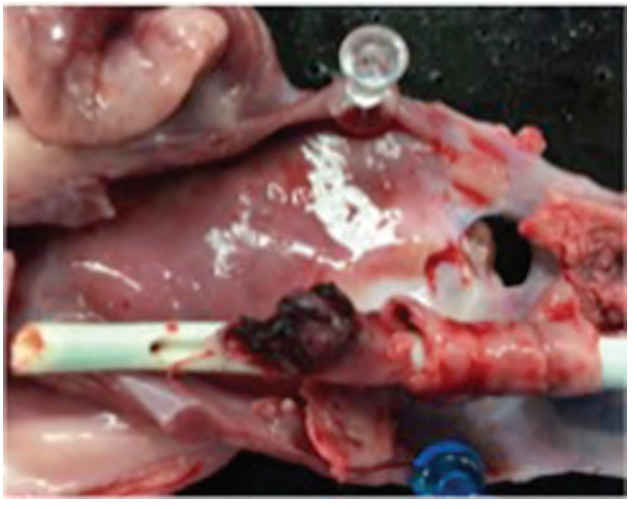
Background: TDC infection and dysfunction are important causes of morbidity and mortality in hemodialysis patients, with no truly effective therapies. An important reason for this is the absence of a validated large animal model. We herein describe a swine model that closely mimics the human condition.

Methods: TDC's were placed in the right jugular vein of 6 Yorkshire pigs. Blood was flushed in and out of each lumen twice weekly in order to mimic dialysis and assess for the onset of dysfunctional flow. Animals were monitored daily for infection. Blood cultures (BC) were obtained and antibiotics started when the temperature was > 103 degrees F. Animals were euthanized if they did not respond to treatment. Data on the time to infection (fever), dysfunction, and sacrifice, as also the BC profiles were collected. Data collection has been completed on 3 pigs and is ongoing in the others. We will present the available data from all 6 pigs.

Results: The average time to fever (infection) and TDC dysfunction was 9.2±5.2 and 8±6.2 days respectively. The arterial line was dysfunctional first in 83% of cases. Compacted fibrin sheaths were present in all sacrificed animals (Figure), together with jugular and central venous wall thickening. Importantly, the bacterial profile correlated with standard human data, showing growth of Klebsiella, Pseudomonas and Beta hemolytic strep (and from an earlier study Staphylococcus aureus).

Conclusions: We have, for the first time, described a large animal model of TDC infection and dysfunction which mimics the human condition. We believe that the availability of this model, with its well defined end points, will incentivize the product development pathway for novel, safe and effective therapies that target both TDC infection and dysfunction.

Funding: NIDDK Support



FR-PO758

Upper Extremity Swelling in ESRD: DVT or Central Venous Disease Adam Safdi,[1] Monnie Wasse.[2] *[1]Medicine, Northwestern University, Chicago, IL; [2]Rush University Medical Center, Chicago, IL.*

Background: Among end-stage renal disease (ESRD) patients, upper extremity deep vein thrombosis (DVT) and central venous disease (CVD) defined as stenosis or occlusion, may have similar clinical presentations, commonly a swollen arm ipsilateral to a functional dialysis access. However, management is different. Anticoagulation is prescribed for acute DVT, whereas angioplasty might be necessary for CVD. The objective of this study was to examine ESRD patients presenting with arm swelling who received a diagnosis of upper extremity DVT, the proportion undergoing central venous angiogram, and an alternate CVD diagnosis.

Methods: We retrospectively reviewed the medical records of all ESRD patients receiving hemodialysis admitted to a tertiary academic medical center between January 1, 2013 and June 30, 2015, and received a diagnosis of upper extremity DVT by ICD-9 code. Charts were reviewed to determine: 1) if duplex ultrasound was performed, 2) if referral was made for dialysis access angiogram and if CVD was determined, and 3) whether the patient was discharged on anticoagulation.

Results: An upper extremity ultrasound was ordered in 102 ESRD patients over 124 admissions, and one or more acute or chronic DVT was diagnosed in 118 of the 124 admissions. The most common vein location for DVT was the internal jugular (75%), followed by axillary (44%), subclavian (34%), brachial (23%), and brachiocephalic (14%). 25 of the 118 DVT cases (21.2%) were referred for angiography. Of these, only 4 of the 25 cases (16%) were diagnosed with DVT. In contrast, 18 of the 25 cases (72%) referred for angiogram had CVD. Of note, angiography was not always performed on the vessel noted to have a DVT by duplex ultrasound. Of 19 cases diagnosed with a DVT and subsequently studied with angiography, CVD was present in 18 cases (94.7%) and DVT was only observed in 4 cases (21.1%), all of whom had concurrent CVD. 39 of the 118 cases (33%) diagnosed with a DVT were discharged with a new prescription for anticoagulation.

Conclusions: Our retrospective study shows that when hemodialysis patients with ESRD receive a diagnosis of upper extremity DVT by ultrasound, and also have upper extremity venogram, they more often have CVD than DVT. This suggests that duplex ultrasound leads to an incorrect clinical diagnosis when hemodialysis patients present with a swollen arm, and suggests patients may be receiving inappropriate anticoagulation.

Funding: Other NIH Support - Grant Number UL1TR001422

FR-PO759

Incidence and Risk Factors for Central Venous Stenosis in Haemodialysis Patients Anamika Adwaney,[1] Neill D. Duncan,[2] Damien Ashby.[1] *[1]Imperial College, London, United Kingdom; [2]Imperial College Renal and Transplant Centre, London, United Kingdom.*

Background: Central venous catheters have traditionally provided haemodialysis access when a fistula is declined or not achieved, but are increasingly advocated as an acceptable option for older or more comorbid patients. Adverse effects of this type of dialysis access include central vein stenosis (CVS), which can lead to significant morbidity including access dysfunction or failure. The pathogenesis and risk factors for CVS are incompletely understood.

Methods: All patients starting haemodialysis in a single centre between December 2005 and February 2015 were prospectively identified. From this cohort, a random sample of patient records were retrospectively analysed for the presence of CVS, defined by cross-sectional or angiographic imaging.

Results: Out of 300 patients (aged 19 - 91, 64.7% male) followed for up to 10 years, CVS developed in 23 (7.67%). All CVS patients had a history of tunneled dialysis catheter use. Compared to those unaffected, patients with CVS had a larger number of previous catheters (2.3 vs 1.2, $p<0.001$) but not a greater duration of previous catheter use (28.7 vs 32.1 months). Non-dialysis risk factors, more frequent in patients with CVS, included pacemakers (13.0 vs 2.2%, $p=0.024$) and prior intensive care admission (56.5 vs 11.9%, $p<0.001$). There was no significant effect of ethnicity, but in older patients (over 70 at dialysis initiation, 35.0% of the group) the development of CVS was much less common (2.9 vs 10.3%, $p=0.023$).

Conclusions: In haemodialysis patients with prior tunneled catheter use, a significant minority may develop CVS, with the number of catheters, rather than catheter duration, being the primary risk factor, though non-dialysis risk factors are also important. The finding that patients over 70 at dialysis initiation are less likely to develop CVS, supports the selective use of tunneled catheters in some older patients.

FR-PO760

Tunneled Catheter-Related Bacteremia Preventive Protocol: Results Analysis Carmen Gonzalez corvillo, Maria angeles Rodriguez-Perez, Mercedes Salgueira. *NEPHROLOGY, HUVMACARENA, SEVILLA, Spain.*

Background: The increasing use of tunneled catheters for hemodialysis is associated with a number of complications, particularly catheter-related bacteremia(CRB). The implementation of a pre-emptive protocol during the preimplantation period and maintenance care could reduce the rate, although there is no consensus in the bibliography. Since 2006, our department has had a preimplantatory protocol, developed by nephrologists and infectologists, it includes nasal decolonization in case of staphylococcal aureus colonization, complete cleansing with chlorhexidine gel and prophylactic cefazolin before the procedure. We analyze the results obtained in our department regarding CRB in tunneled catheter implants in the last 11 years.

Methods: Our protocol has been implemented in 246 tunneled catheters, implanted in 107 patients. Mean age:63 years. Mean follow-up period for each catheter:132 months. Incidence of bacteremia, time of appearance of the bacteremia after the implantation, bacteria types and associated complications were analyzed.

Results: - Location:right jugular vein 71.1%, left subclavian 16.3%, right subclavian 11%, femoral 1.6% - 72 catheters were removed in 15(6.1%) cases, with infection being the main reason for removal. - 64 cases of catheter-related bacteremia were diagnosed, representing an incidence rate of 0.48 cases per 1000catheters per day. Mean time for appearance of CRB:579± 441 days after implantation(median 513days, minimum 42, maximum 1623) - Most frequent microorganisms: Staph. Epidermidis 36.7%, MSSA 26.5%, MRSA 6.1% Staph. Warneri 4%, pantoea agglomerans 4%, strep viridans 4%, candida 2%, pseudomonas 2%, cloacae 2%, klebsiella 2%, corynebacterium 2%, serratia 2%. - Infection recurrence was 26% in a mean time of 276 days. The most frequently recurring microorganisms were Staph. Epidermidis 31% and MSSA 26%. - Septic complications: 9 cases (1 septic arthritis, 1 spondylodiscitis, 4 endocarditis and 4 septicemia)

Conclusions: In our experience, the rate of tunneled CRB is in fact lower than reported in the bibliography. Implementation of our preemptive protocol has delayed the incidence of CRB, with the primo-infection presenting more than 1 year after tunneled catheter implantation. The recurrence rate was high and the most frequent microorganism was Staph. Epidermidis. The incidence of other complications and the need to remove the catheter is low.

FR-PO761

Efficacy of Alteplase (tPA) 1 mg versus 2 mg in Restoring Hemodialysis Catheter Function: A Randomized Double-Blind Controlled Study Albert Kadri,[1] Wasim El Nekidy,[2] Derrick Soong,[3] Maher M. El-Masri.[4] *[1]Windsor Regional Kidney Care Center, Windsor, ON, Canada; [2]Cleveland Clinic - Abu Dhabi, Windsor, ON, Canada; [3]Windsor Regional Hospital, Windsor, ON, Canada; [4]University of Windsor, Windsor, ON, Canada.*

Background: Hemodialysis catheters (HDC) are used to provide vascular access to patients with Chronic Kidney Disease on hemodialysis (HD). Late thrombus formation can result in HDC occlusion leading to its malfunction. Data about optimal alteplase (tPA) dose required to restore HDC is scarce. The purpose of the study was to examine the effectiveness of the commonly used tPA dose of 2 mg as compared to 1mg in restoring HDC function

Methods: A double blind, randomized, controlled clinical trial was conducted on hemodialysis patients who required tPA use to restore their HDC function. Eligible consented patients were randomly assigned to either of the two study groups (tPA 2 mg or 1 mg). Patients were included if they: were ≥ 18 years of age at the time of the study, were receiving HD using HDC, and had no medical contradiction for tPA use.

Results: Forty eight consenting patients contributed a total of 252 observations that were allocated to either group A (2 mg) or group B (1mg) based on randomization. Given the clustered nature of the observation, randomization was observation-based as opposed to patient-based. The rate of clot resolution at the catheter site in the A group was 85.7% as opposed to 84.9% with an insignificant absolute risk reduction of only 0.8 % percentage ($p = 0.5$). There were only six catheter removals; three of which were related to catheter malfunction. Catheter stripping was documented in 10 of the 252 observations. Kaplan Meier results indicated that the median time to occlusion after tPA resolution of the first catheter occlusion was 192 and 120 days for groups A and B, respectively (Log rank = 0.499; p = 0.480). Cox regression analysis indicated no difference in the hazard of occlusion between the two groups (p = 0.267; HR = 0.72; 95% CI 0.40–1.3). Further, correlated logistic regression with generalized estimating equations on all 252 observations indicated no difference in the rate of post tPA clot resolution (p = 0.336; OR = 2.4, 95% CI 0.399-14.6) between the two groups.

Conclusions: tPA 1 mg is as effective as 2 mg in restoring HDC function. The use of the lower dose will result in significant cost reduction in hemodialysis units.

Funding: Private Foundation Support

FR-PO762

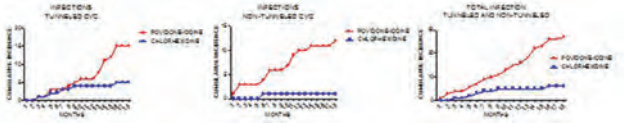
Infections of Tunneled and Non-Tunneled Central Venous Catheters Associated with the Use of 10% Povidone-Iodine versus 2% Chlorhexidine in Chronic Hemodialysis Mauricio Arvizu-Hernandez,[2] Olynka Vega,[1] Ricardo Correa-Rotter.[2] *[1]National Institute of Medical Sciences, Mexico, Mexico; [2]Nephrology and Mineral Metabolism, National Medical Science and Nutrition Institute Salvador Zubiran, México city, Mexico.*

Background: Vascular access (VA) infections are a problem in patients on hemodialysis (HD), representing the second cause of morbidity and mortality. The ideal VA is the arterio-venous fistula, in our environment a high number of patients start and stay for a longer than desired on catheters. The use of 2% chlorhexidine solution (2% CHX) for the management of exit site of VA on HD can impact positively the number of catheter infections.

Methods: Retrospective cohort study performed in our Institute HD unit, where 10% povidone-iodine solution (PI) was previously used and since March/2015, was substituted by 2% CHX. We assessed the rate of VA (cathether related) infections from Sep/13 to Aug/16 (Sept/13-Feb/2015 PI and Mar/15-Aug/16 use of 2% CHX). Incidence of infections was analyzed on a monthly basis, identifying number and clinical characteristics of the infection. We calculated the rate of infections per 1000 days/cath/patient. The use of PI vs 2% CHX periods were compared.

Results: During the 36 month study period, a total of 33 infections were identified (0,91 infect/month). The highest infection rate was observed during the use of the PI, both in tunneled and non-tunneled catheters. On the basis of cumulative incidence rates, calculating the RR; the use of PI in both types of catheters, as compared to use of 2% CHX, has a RR of 4.0 (tunneled RR=3.6 and non-tunneled RR=7.0).

Conclusions: Our study demonstrated clearly that the use of 2% CHX in patients with temporary cathether vascular accesses on HD, reduces the risk of infection of both the tunneled and non-tunneled catheters.



	Povidone-iodine 10%	Chlorhexidine 2%	p value
No. of patients	50.7	52.2	0.27
Median Age (ys)	41.4	44.9	<0.001
Men	36%	41.8%	
Follow-up	18	18	-
Tunneled CVC			
No. Tunneled CVC	20.1	24.4	<0.001
Days/patient/CVC	10,987	13474	
No. Infections	15	5	0.046
Rate Infection /1000 CVC days	1.36	0.37	0.024
RR of infection	3,6	0,28	
Non Tunneled CVC			
No. Non Tunneled	24.7	15.2	<0.001
Days/patient/CVC	13,487	8,313	
No. Infections	12	1	0.004
Rate Infection /1000 CVC days	0.92	0.13	0.011
RR of infection	7,07	0,14	
Tunneled and non-tunneled CVC			
Total Days/patient/ CVC	24,474	21787	
Rate Infection /1000 CVC days	1.1	0.27	0.0008
RR of infection	4,07	0,24	
Catheter withdrawal	7	2	0.056
Relapsed	2	0	-
Exit site infection	8	1	
Bloodstream infection	19	6	
Mixed	10	1	
Positive cultures	18	4	
Hospitalization	4	1	

FR-PO763

Substitution of Citrate with Tissue Plasminogen Activator (rt-PA) for Catheter Lock Does Not Improve Patency of Tunneled Hemodialysis Catheters Pavlina Richtrova,[1,2] Jan Mares,[1,2] Lukas Kielberger,[1,2] Jan Klaboch,[1,2] Jaromir Eiselt,[1,2] Tomas Reischig.[1,2] *[1]1st Medical Department, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic; [2]Biomedical Centre, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Republic.*

Background: The study aim was to establish if substitution of citrate with rt-PA for catheter lock once weekly can reduce the incidence of catheter-related blood stream infections (CR-BSI) or improve patency of tunneled hemodialysis catheters.

Methods: All incident patients undergoing insertion of a tunneled hemodialysis catheter were screened and included except those suffering infection or using anticoagulation. Study participants were randomized into two arms according to the solution applied as catheter lock: receiving either trisodium citrate (Citra-Lock™ 4%) only or rt-PA (Actilyse® 1mg/ml) on the middle session each week with citrate used on the first and third sessions. The incidence of CR-BSI (confirmed by positive blood culture), catheter non-function (complete obstruction), and malfunction (blood flow <250ml/min) was recorded. Statistical significance was tested with ANOVA, post hoc analysis was performed by means of multiple linear regression.

Results: Totally, 20 patients were included and followed during 655 hemodialysis sessions. No episode of CR-BSI was detected while 6 catheter non-functions (0.9% sessions) and 101 malfunctions (15.4% sessions) were recorded. The incidence of both events was equal between the study arms: 4 non-functions and 55 malfunctions in the rt-PA arm and 2 non-functions and 46 malfunctions in the citrate arm ($p=0.47$ and $p=0.24$, respectively). Additionally, the mean blood flow achieved did not differ significantly between the arms: 326±1,8 and 326±1,9 ml/min ($p=0.95$) in rt-PA and citrate arms, respectively. Post hoc analysis identified time elapsed since previous session ($\beta=0.12$, $p=0.005$) and malfunction on previous session ($\beta=0.25$, $p<0.001$) as significant factors affecting the occurrence of malfunction. By contrast, the study arm, rt-PA application on previous session, and catheter vintage did not enter the model.

Conclusions: Substitution of citrate with rt-PA for catheter lock does not reduce the incidence of catheter malfunction neither does it affect the blood flow achieved during hemodialysis. Catheter patency is related rather to the time interval between sessions and to previous malfunction. The incidence of CR-BSI within pre-selected hemodialysis population is sporadic (less than 1 per 4.3 patient years in our sample).

Funding: Government Support - Non-U.S.

FR-PO764

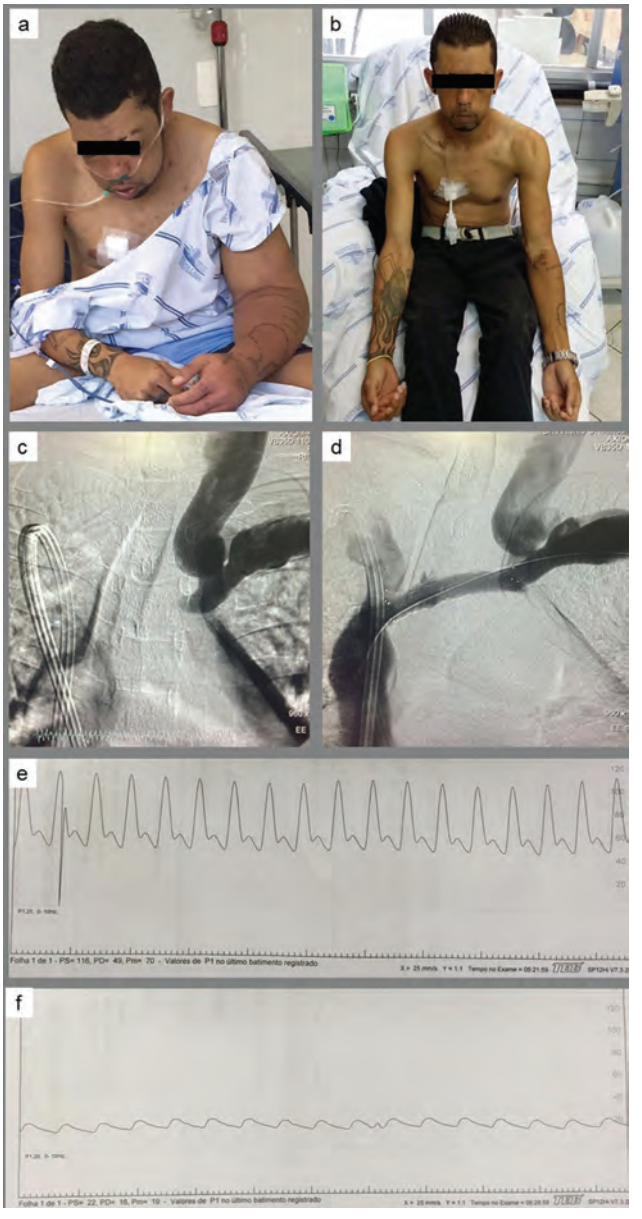
Sharp Recanalization of Central Venous Occlusions in Hemodialysis Patients Carlos rafael A. Felipe,[2] Andre S. Alvarenga,[2] Gerson M. Pereira jr,[2] Ana elisa S. Jorge,[2] Antonio carlos M. Bedeti.[1] *[1]Santa Casa, Belo Horizonte, Brazil; [2]Santa Casa de Belo Horizonte, Belo Horizonte, Brazil.*

Background: Central venous occlusion (CVO) is a severe vascular complication that causes massive upper extremity swelling and dysfunctional dialysis access. Management is aimed at providing symptomatic relief and maintaining hemodialysis access site patency.

Methods: A total of 14 hemodialysis patients with massive upper extremity swelling and dysfunctional dialysis access, who underwent endovascular recanalization for CVO at our institute between November-2013 and May-2016 were examined. We evaluated procedure sucess rate, complication rate, primary and secondary patency rate.

Results: There were 12 occlusions in brachiocephalic veins and 2 in suclavian veins. Until this procedure, each patient had lost on average 5.1 vascular access. First, we tried to traverse the occlusion using soft tip of hydrophilic wire under angiographic catheter (conventional technique); if failure, we switched to sharp recanalization technique using stiff end of hydrophilic wire to puncture the fibrotic cap to create a channel that was crossed by the soft tip of same hydrophilic wire. The procedure was considered successful when residual lesion was <30%. Succes of conventional technique were 28.6%. Switch to sharp recanalization resulted in overall success rate of 85.7% without any major complications. It maintained the patency of dialysis access and relieved the symptoms in all cases. At 12 months, the primary and secondary patency rates were 75% and 83.3% respectively. At an average follow-up of 12.8 months, there was one death not related to the procedure.

Conclusions: Sharp recanalization of symptomatic central venous occlusions in hemodialysis patients was an effective and safe method to maintain the patency of dialysis access and to relieve the symptoms.



FR-PO765

Predicting Vascular Access Thrombosis Using Vasc-Alert™ Based Scoring Algorithm Jeffrey J. Sands,[2,3] Brad C. Astor,[1] Kim Hirschman,[3] John B. Kennedy,[3] Anatole Besarab.[4] *[1]University of Wisconsin, Madison, WI; [2]Renal Systems Consulting LLC, Orlando, FL; [3]Vasc-Alert LLC, Evanston, IL; [4]Stanford University, Palo Alto, CA.*

Background: We evaluated a Vasc-Alert™ based multifactorial scoring algorithm to estimate the risk of developing vascular access (VA) thrombosis within the subsequent 60-days. Vasc-Alert™ VA surveillance utilizes data from each dialysis treatment (Tx) to calculate intra-access venous (VAPR) and arterial (AAPR) pressure ratios to identify those VA at high risk for thrombosis needing further evaluation ± elective intervention. Alerts are generated when the VAPR>0.55 or the AAPR>0.65 (AVF) and >0.60 (AVG) on 3 consecutive Tx.

Methods: We identified 985 patients (263 AVF; 722 AVG), including 304 (81 AVF, 223 AVG) who experienced VA thrombosis (TH) and 681 (182 AVF, 499 AVG) without TH (N-TH), from 86 HD facilities with electronic download of Tx and VA intervention data with up to 120 days Tx data/patient. Records were divided into 15 day intervals (total intervals = 7655; 2049 AVF and 5606 AVG) and assessed to determine outcome (TH vs N-TH) within the subsequent 60 days. Bivariate repeated-measures logistic regression identified 5 factors significantly associated ($p<0.05$) with TH (mean AAPR, mean VAPR, VAPR slope, #VAPR alerts, #Tx with delivered/prescribed blood flow rate <90%). Risk scores were then assigned for specific ranges of each factor based upon their predictive value for TH (0-1 for Mean AAPR, VAPR slope, Tx Blood Flow Rate (BFR)<90% prescribed; 0-3 for mean VAPR) and summed for each interval resulting in an assigned cumulative risk score from 0-7.

Results: A total of 15.3% intervals were associated with thrombosis in the subsequent 60 days. The cumulative incidence of thrombosis was greater with higher cumulative score (see table below). Scores ≤1 were associated with a relatively low incidence (9.5% AVF, 13.0% AVG) and scores ≥3 with a high incidence (AVF: 25.4%, AVG: 23.2%) of thrombosis.

Conclusions: Risk scores based upon a Vasc-Alert™ scoring algorithm successfully identified VA with low or high probability of developing thrombosis within the next 60 days. Because these scores are Tx record based, they may be easily automated to help guide VA patient care through a population management model.

Funding: Commercial Support - Vasc-Alert LLC

Cumulative Score

Cumulative Score		0	1	2	3	4	5	6	7	Total
AVF	Total Intervals	571	561	311	250	194	106	50	6	2049
	% Thrombosis	7.4	11.6	16.7	20.8	25.8	25.5	44.0	50.0	15.3
AVG	Total Intervals	940	2663	1374	473	121	29	6		5606
	% Thrombosis	7.9	14.8	17.6	20.9	27.3	37.9	50.0		15.3

FR-PO766

A Randomised Controlled Trial of Interrupted versus Continuous Suturing Techniques for Radiocephalic Fistulae: 3-Year Follow-Up Data Emma L. Aitken, David Kingsmore. *NHS Greater Glasgow and Clyde, Glasgow, United Kingdom.*

Background: Continuous suturing techniques have conventionally been used for the end-to-side anastomoses of radiocephalic fistulae (RCF), however only 50-60% of RCF retain patency at one-year. We hypothesised that interrupted sutures (utilised in many microsurgical procedures) may improve outcomes of fistulae constructed from small vessels by optimising anastomotic compliance.

Methods: Three year follow-up of a randomised controlled trial comparing interrupted (n=36) vs. continuous (n=42) suturing techniques for RCF is presented. Patients were excluded if vessels were <1.8mm diameter or if previous ipsilateral fistula had been attempted. The primary end point was primary patency at 6 weeks (assessed by a blinded observer for the presence of thrill and bruit). Secondary end points were functional patency (clinical and ultrasonographic) at 6 weeks and primary/ secondary patency at 1 and 3 years (NCT01704313).

Results: Groups were comparable for basic patient demographics, operating surgeon and vessel diameter (mean age: 58.9(13.3) yrs; 67.9% male). Primary patency at 6 weeks was higher in the interrupted group (71.4% vs. 47.2%; OR 2.9 P=0.01). There was no significant difference in functional patency at 6 weeks (52.4% vs. 36.1%; OR 2.0 P=0.18). At 3 year follow-up 34.6% of patients (n=27) had died, 24.3% (n=19) had been transplanted and only 34.6% (n=27) of the patients remained on haemodialysis. Primary patency at 1 year was comparable between the two cohorts (53.3% [16 of 30 patients] vs. 45.9% [17 of 37 patients]; OR 1.34, P=0.17 for interrupted and continuous cohorts respectively). Similarly 3 year patency rates were 50.0% [13 of 26 patients] vs. 60.0% [15 of 25 patients]; OR 0.67, P=0.54).

Conclusions: An interrupted suturing technique yielded higher early primary patency rates for RCF. Less than one third of the original cohort remained on dialysis at three year follow-up. The early improvements in patency observed in the interrupted arm were not seen at 1 and 3 year follow-up. This may be the result of a small sample size (the study was not powered for secondary end-points). This study highlights the high attrition rate and short survival of patients with end-stage renal disease and brings into question whether autologous access is appropriate for ever patient.

FR-PO767

Buttonhole Versus Stepladder Cannulation for Arteriovenous Fistulas for Home Hemodialysis Patients: A Randomized Controlled Feasibility Trial Deborah Lynn Zimmerman,[8] Jennifer M. MacRae,[7] Brittany Hollingsworth,[3] Christopher T. Chan,[5] Gihad E. Nesrallah,[4] Philip McFarlane,[2] Michael A. Copland,[6] Shih-Han S. Huang.[1] *[1]London Health Sciences Centre, London, ON, Canada; [2]St. Michael's Hospital, Toronto, AB, Canada; [3]The Ottawa Hospital Research Institute, Ottawa, ON, Canada; [4]The University of Western Ontario, Toronto, ON, Canada; [5]Toronto General Hospital, Toronto, ON, Canada; [6]University of British Columbia, Vancouver, BC, Canada; [7]University of Calgary, Calgary, AB, Canada; [8]Medicine, Ottawa Hospital, Ottawa, ON, Canada.*

Background: The need for more rigorous studies to address the uncertainty about the risk and benefits of buttonhole versus stepladder cannulation for arteriovenous fistula (AVF) was highlighted in the recently published Canadian Society of Nephrology guidelines on intensive home hemodialysis (HHD). Therefore, our purpose was to determine the feasibility of doing a multi-centre randomized controlled trial of buttonhole versus step-ladder cannulation in patients training to do HHD with an AVF.

Methods: Patients were to be recruited from 7 tertiary care Canadian hospitals with expertise in home hemodialysis. Inclusion criteria were 1) adult patients training for HHD, 2) AVF, 3) life expectancy greater than 12 months, and 4) able to give informed consent. Exclusion criteria were: 1) potential loss to followup within 12 months of training, 2) allergy to mupirocin, 3) need for intradermal lidocaine, 4) short segments or aneurysms in the AVF that the care team felt required buttonhole cannulation, and 5) mechanical heart values. For our feasibility outcome, we determined that 70% of eligible patients needed to be randomized.

Results: Patients were recruited from November 2013 to Sept 2015. A total of 167 patients began training for HHD; average age 54 (±15) years, 55% male, 53% had a central venous catheter (CVC) or arteriovenous graft (AFG). Sixty patients were eligible to participate; only 14 (23%) were randomized. Of the eligible patients that we not randomized, the majority either declined study participation (16) or stated a preference for buttonhole cannulation (12). Of the 107 patients who were ineligible to participate 79 patients had a CVC and 10 patients had an AVG. Other reasons for exclusion included; did not complete training (8), potential to be lost to followup (6), buttonhole required (4), stepladder required (1), and mechanical heart values (1).

Conclusions: In spite of the stated equipoise about the optimal cannulation technique for patients with an AVF who are training for HHD, we were unable to demonstrate that a randomized controlled trial would be feasible in Canada.

Funding: Commercial Support - Baxter

FR-PO768

Protecting Patients from Venous Needle Dislodgement (VND): An Improved AV Fistula Set PATRICK ROUSCHE.[1,2] *[1]Hemotek Medical Inc., Rohnert Park, CA; [2]Bioengineering, University of Illinois, Chicago, IL.*

Background: Venous needle dislodgement (VND) is a serious patient risk for any dialysis session at home or in the clinic. Inadvertent removal of the venous line during dialysis therapy is at very least inconvient, leading to spilled blood. At worst, even just one minute of unmitigated VND at 400 mL/min can lead to hemorrhagic shock; if the VND goes undetected for 5 minutes, patients can die from exsanguination. Clinics are faced with biohazard exposure, therapy disruption and patient injury/death. Hemodialysis machines are programmed to automatically detect pressure variations between fully inserted and dislodged needles during therapy, but often fail to accurately detect VND. We introduce here a patent-pending AV fistula modification which protects patients from the risks of VND.

Methods: The standard butterfly design of traditional AV fistulas was modified to incorporate a small 'sensing' feature on the underside of the needle used to determine if the inserted AV fistula remains in close contact with patient skin. When the system detects VND, flow through the needle is immediately restricted, resulting in quick and automatic shut-off of the machine pump. The needle is otherwise designed to look and feel the same as a traditional AV fistula needle.

Results: Essential to performance testing of the new AV fistula, is its ability to pass normal amounts of fluid flow in the 'ON SKIN' condition and its ability to restrict flow when in the 'OFF SKIN' position. We used a benchtop flow system to determine the forces associated with flow termination during simulated VND. Results suggest fluid flow disruption of up to 95% through the V-Needle during simulated 'dislodgement' is achievable with closing forces of ~15 grams, a force level that can easily be tolerated on the human skin over the typical dialysis therapy.

Conclusions: The V-Needle offers a simple and elegant solution to the problem of Venous Needle Dislodgement. Fluid flow termination in the event of dislodgement can be achieved with low forces, allowing a product solution which is easily implemented in the clinic or home.

Funding: NIDDK Support

Hemotek Medical's V-Needle protects patients from VND

FR-PO769

Environmental and Patient Specific Factors Associated with Absolute AVF Blood Flow David H. King,[4] Michael G. Taylor,[5] Mo Al-Qaisi,[4,3] Sumith C. Abeygunasekara,[2] Abdelgalil A. Ali.[1] *[1]Broomfield Hospital, Chelmsford, United Kingdom; [2]Broomfield hospital, Chelmsford, United Kingdom; [3]Imperial College London, London, United Kingdom; [4]Renal, Mid Essex Hospitals, Chelmsford, United Kingdom; [5]Kings College London, London, United Kingdom.*

Background: AVF blood pressure measurement using a novel monitoring device BluedopTM combined with Color Duplex blood flow measurement has been used to identify the incidence of Normal and Failing Arteriovenous Fistulae 1. The study protocol has been repeated in two widely different environments, Europe (UK) and Africa (Sudan).

Methods: A patented algorithm based on blood velocity waveform shape, was used to calculate mean distal brachial artery blood pressure P proximal to the a-v anastomosis. Dividing flow Q by pressure P yields venous conductance VC. A value of less than 10ml per minute per mmHg correlates with a significant venous outflow stenosis of 60% or greater.

Results: There were 54 dialysis patients in the Sudan cohort of which 9 were failing according to VC criteria leaving 45 normally functioning AVF. There were 68 dialysis patients in the UK cohort of which 10 were failing, leaving 58 normally functioning AVF in the study. There was no significant difference in the percentage of failing AVF in either group (Sudan = 17%, UK = 15%). Table 1 shows Mean ± 1SD for P, Q and VC in normally functioning AVF. AVF blood flow in the Sudanese cohort was 69% greater than the UK cohort. This is a highly significant difference. The following dependencies were tested and shown to be minor or not significant NS. The tests shown here were on the Sudanese cohort: AVF Flow vs Age = NS (R2= 0.0019), AVF Flow vs Gender = NS (female vs male = 1578 ± 567ml/min vs 1882 ± 910 ml/min). In contrast published values for minimum seasonal ambient temperatures show Khartoum is approximately 14 deg C hotter than London throughout the year, supporting the concept of a temperature related association with AVF development.

Conclusions: Further research into the influence of a range of low, medium and high seasonal temperatures on AVF blood flow may supply insight into early AVF failure as well as early maturation. [1] Volume blood flow, static pressure ratio and venous conductance in native arterio-venous fistulae: three surveillance methods compared: J Vasc Access 2015;16(3);211-217

Table 1

Location	P mmHg	Q ml/min	VC ml/min/mmHg
Sudan normal AVF	50 ± 19	1797 ± 843	38.8 ± 21.3
UK normal AVF	48 ± 11	1062 ± 543	22.4 ± 11.1

FR-PO770

Identifying a Core Vascular Access Outcome for All Trials in Hemodialysis: An International Survey with Patients and Health Professionals Andrea K. Viecelli,[1,2] Martin Howell,[3] Allison Tong,[3] Jonathan C. Craig,[3] David W. Johnson,[1,2] Carmel M. Hawley.[1,2] *[1]Department of Nephrology, Princess Alexandra Hospital, Brisbane, QLD, Australia; [2]School of Medicine, University of Queensland, Brisbane, QLD, Australia; [3]University of Sydney, Sydney, NSW, Australia.*

Background: Vascular access is an essential component for the care of patients requiring hemodialysis, yet clinical trials report a large and diverse range of vascular access outcomes that often cannot readily be compared across trials and have no clear relevance to patients and clinicians. This survey aims to identify a core outcome for vascular access, with the expectation that this will be measured and reported in all trials involving patients requiring hemodialysis, based on the shared priorities of patients/caregivers and health professionals.

Methods: Based on a systematic review, qualitative research and meetings with vascular access experts, 12 vascular access outcomes were included in an online survey conducted in English, Chinese, Spanish and Malay. Participants rated the absolute importance of outcomes using a 9-point Likert scale (7-9 being critically important), and the relative importance was determined by a Best-Worst Scale (BWS) using multinomial logistic regression.

Results: The survey was completed by 772 participants (187 [24%] patients/caregivers and 585 [76%] health professionals) from 58 different countries. Across both groups, the top two outcomes were function (mean 8.4, top 1 on BWS) and infection (mean 8.1, top 2 on BWS). There was consistency in the prioritization of outcomes between both groups but health professionals rated outcomes overall higher than patients/caregivers (mean differences ranging from 0.09 for interference with activities to 1.3 for access maturation) with the exception of aneurysms which was ranked higher by patients/caregivers (mean difference 1.1, top 3 vs 7 on BWS).

Conclusions: For patients/caregivers and health professionals, there was consensus on the primary importance of vascular access function. A core outcome measure for function will now be developed to improve the consistency and relevance of vascular access outcomes reported in trials in hemodialysis.

Funding: Government Support - Non-U.S.

FR-PO771

Age Is Not Everything – Vascular Access for Hemodialysis in the Elderly Dallit Mannheim, Tatiana Tanasiychuk, Victor Frajewicki. *Carmel Medical Center, Haifa, Israel.*

Background: Old patients are the fastest growing incidence dialysis age-group, having increased by 57% over the last decade. Indeed, people aged more than 75 are now over 1/5 of dialysis patients. Even though arteriovenous fistulas (AVF) are the preferred vascular access for hemodialysis, with the lowest rate of morbidity and mortality, the best vascular access in the elderly is still unclear. This controversy is further accentuated by a longer maturation time of AVF and shorter life expectancy. To promote a better planning and follow-up of patients undergoing operations for vascular access at our center we initiated a multi-disciplinary clinic: every single patient is routinely evaluated before and after the operation at least by a vascular surgeon and a nephrologist.

Methods: The goal of this study was to retrospectively evaluate the outcome in patients assessed by a multi-disciplinary clinic which have undergone operations for the creation of a vascular access during 2015-2016. Primary endpoint was the rate of a functioning mature vascular access, either a fistula or a graft.

Results: During the period 291 operations for vascular access were done. All patients were evaluated by a vascular surgeon and nephrologist before the operation. Patients without clinical obvious arm or forearm cephalic veins were further evaluated by venous mapping. Male:female ratio was 3:1, Diabetes was present in 58%. 119 patients (41%) were evaluated before onset of dialysis. A primary fistula was created in 92% of cases; radio- cephalic 39%, brachio- cephalic 43%, brachio- basillar in 11%. In 17 (6%), grafts were inserted. Five patients experienced post-operative complications (including 4 cases of steal syndrome and 1 of venous hypertension). Of these, only 1 was an elder patient. Maturity was achieved in 202 accesses (73%). In 2 cases an angioplasty was needed to assist maturation. Age did not correlate with maturation as both a categorical as well as a continuous parameter for all age groups (including over 75, 80 or 85)

Conclusions: Implementation of a multi-disciplinary trained team to take care of the growing elderly population requiring dialysis is highly advised. This kind of program not only leads to a higher rate of successful vascular access but also avoids unnecessary surgical interventions and complications in patients that will not enjoy from such procedures.

FR-PO772

Keep or Remove? Arteriovenous Fistula Functionality in Patients Returning to Haemodialysis after Transplant Failure Sarah Blakey,[1] Damien Ashby.[2] *[1]Imperial College Healthcare NHS Trust, London, United Kingdom; [2]Imperial College, London, United Kingdom.*

Background: The arteriovenous fistula is the preferred access type for haemodialysis patients, but following transplantation many patients are concerned about the appearance or potential for long-term complications with a fistula, particularly since it may no longer be functional should dialysis be required years later. Little is known about the long-term patency of fistulae when redundant, or the likelihood of functionality at the point of transplant failure.

Methods: In a prospectively identified cohort of haemodialysis patients with a fistula undergoing renal transplantation between April 2007 and October 2015, records were retrospectively analysed to identify those who returned to hemodialysis, and their vascular access at the time.

Results: Out of 224 patients (aged 19-77 at transplantation, 75.4% male) followed for up to 10 years (mean 49.1 months), 24 (10.7%) died with a functioning transplant and 21 (9.4%) returned to haemodialysis after a mean of 34.3 months post-transplantation (range 0-85.5). Of the 21 patients returning to haemodialysis, 15 (71.4%) were able to use their pre-transplant fistula. Compared to those returning to dialysis with a functional fistula, those requiring new access had a longer transplant duration (66.6 vs 21.3 months, p=0.007), but there was no difference in age at transplant failure (47.8 vs 56.1, p=0.2). All patients re-starting haemodialysis within 24 months of transplantation had a functional fistula, compared to only 40% of those returning to dialysis beyond 2 years. Of the 6 patients whose fistula was non-functional, 3 had undergone excision due to fistula complications (2 aneurysms and 1 high-output heart failure), 2 spontaneously failed, and 1 required alternative access whilst a procedure was performed to recover fistula functionality.

Conclusions: Following a period of haemodialysis via fistula and subsequent transplantation, around 10% of patients return to dialysis over 4 years. The majority of these will still have functional access, but fistula patency declines with time, due to fistula complications and spontaneous failure. These data may be helpful to those making fistula decisions with transplant patients.

FR-PO773

Maintaining Vascular Access for Haemodialysis after First Vascular Intervention Pablo Justo avila,[2] Terrina Abd rahim,[1] Kumar Abayasekara,[2] Lindsay J. Chesterton,[2] Richard J. Fluck.[2] *[1]Kettering General Hospital, Leicester, United Kingdom; [2]Royal Derby Hospital, Derby, United Kingdom.*

Background: Vascular access (VA) teams struggle with VA patency as they can stenose or thrombose entailing vascular intervention (VI). We explore predicting factors for prolongation of VA function following VI and the role of antiplatelet or anticoagulant medications (AAM) on primary (PGS) and secondary graft survival (SGS).

Methods: We analysed VA formations from Oct09 to Dec15, with follow-up ending Dec16. Patient demographics, comorbidities, cause of ESRD and medications were collated. We identified location of VA, first time of VI, number of VI, failure date and cause of HD withdrawal.

Results: 427 patients (260 M and 167 F) underwent VA formation. Mean age was 63 years. 168 had DM (39.3%) and 247 had HTN (57.8%). Causes of ESRD were unknown (41.0%), DM nephropathy (30.4%), GN (21.6%), PKD (3.75%) and HTN nephropathy (3.28%). 315 were on AAM; 19 (3.9%) on warfarin (W), 17 (3.5%) on clopidogrel (CL), 253 (52%) on aspirin (AP), 17 (3.5%) on AP and CL and 9 on W and AP. 538 VA were formed (209 radiocephalic [RC], 229 brachiocephalic [BC], 87 brachiobasilic [BB] and 13 AVGs); 487 usable for HD. Mean follow-up was 850 days (SD 718). 286 (58.7%) required VI; (8 revisions [RV], 278 angioplasty [AG], 33 RV and AG) comprising 116 RC, 109 BC, 51 BB and 10 AVG. Median time to AG was 371 days; while to RV was 443 days. Mean PGS was 356 days (SD 372). Median AG performed was 2.8 (SD 2.25). 153 patients discontinued HD due to death (24.8% [71]), thrombosis of VA (21.7% [62]) and functioning transplant (7%[20]). SGS was 760 days (SD 528). We excluded patients who died or received transplant from analysis. We found no correlation between having DM or HTN, cause of ESRD, and type of VA with graft patency. VI in the first 6 months after VA formation was associated with worse patency rates (27.27% vs 53.97% [p < 0.001]). HTN was associated with longer SGS (697.73 vs 550.76 days [p 0.004]) whilst DM was associated with shorter SGS (578.76 vs 673.12 days [p 0.039]). AAM was not associated with improved patency (59.09% vs 70.96% [p 0.076]) or SGS (626 vs 656 days [p 0.178]).

Conclusions: 1. VI in the first 6 months after VA formation is associated with worse patency rates. 2. Less stringent BP control but tight glycaemic control could potentially

increase patency rates of VAs. 3. AAM is not directly associated with higher patency rates or prolongation of SGS.

FR-PO774

Pre-Dialysis Cognitive Impairment and Pre-Emptive Placement of Dialysis Access: Findings from the Chronic Renal Insufficiency Cohort Study Meera N. Harhay,[16] Dawei Xie,[15] Chi-yuan Hsu,[9] Alan S. Go,[4] Jing Chen,[7] James P. Lash,[11] Sanjeev Akkina,[5] Xiaoming Zhang,[14] Eric Vittinghoff,[10] Stephen M. Sozio,[3] Stephen L. Seliger,[12] Mirela A. Dobre,[1] Jacob B. Blumenthal,[2] Rajat Deo,[13] Peter P. Reese,[13] Kristine Yaffe,[8] Manjula Kurella Tamura.[6] *[1]Case Western Reserve University, Cleveland, OH; [2]Department of Veterans Affairs, Baltimore, MD; [3]Johns Hopkins University School of Medicine, Baltimore, MD; [4]Kaiser Permanente Northern California, Oakland, CA; [5]Loyola University Medical Center, Chicago, IL; [6]Stanford University, Palo Alto, CA; [7]Tulane School of Medicine, New Orleans, LA; [8]UCSF, San Francisco, CA; [9]University of California San Francisco, San Francisco, CA; [10]University of California, San Francisco, San Francisco, CA; [11]University of Illinois at Chicago, Chicago, IL; [12]University of Maryland School of Medicine, Baltimore, MD; [13]University of Pennsylvania, Philadelphia, PA; [14]University of Pennsylvania School of Medicine, Philadelphia, PA; [15]University of Pennsylvania School of Medicine Center for Clinical Epidemiology and Biostatistics, Philadelphia, PA; [16]Drexel University College of Medicine, Philadelphia, PA. Group/Team: CRIC Study Investigators.*

Background: Cognitive impairment (CI) is a common finding in late-stage chronic kidney disease (CKD), but few studies have examined its direct impacts on dialysis preparedness. We assessed the independent association of pre-dialysis CI on the probability of pre-emptive permanent access placement among participants from the Chronic Renal Insufficiency Cohort (CRIC) Study who started dialysis.

Methods: We identified 630 CRIC participants who initiated dialysis. We defined pre-dialysis CI as a Modified Mini-Mental State Examination score < 80 measured prior to dialysis initiation. We estimated the association between CI and access placement using logistic regression models for the probability of 1) having permanent access placed before dialysis initiation, and 2) using the permanent access at the first dialysis session.

Results: The cohort had a mean age of 59 years (SD 12 years) and mean eGFR of 16 ml/min/1.73m^2 (SD 3 ml/min) at the pre-dialysis cognitive assessment. Pre-dialysis CI was present in 14% (n=89) of the cohort. Compared to participants without CI, more participants with CI reported low income status (64% vs 38%, p<0.001) and low educational attainment (71% vs 22%, p<0.001). Pre-emptive access was placed in 75% of the cohort (n=473), and 45% of participants initiated dialysis using a permanent access (n=279). After adjustment for eGFR slope, demographics, diabetes, hypertension, vascular disease, functional status, and smoking, pre-dialysis CI was associated with a 48% lower probability of pre-emptive access placement (aOR 0.52, 95% CI 0.29-0.91) and a 45% lower probability of starting dialysis using a permanent access (aOR 0.55, 95% CI 0.32-0.97). After adjustment for socioeconomic variables including income, these associations were no longer statistically significant.

Conclusions: In this study, we found an association between pre-dialysis CI and suboptimal access outcomes, though this finding was not independent of socioeconomic status. Given the known relationship between socioeconomic status and CI, future studies may consider incorporating measures of pre-dialysis CI when evaluating strategies to reduce disparities in dialysis preparedness.

Funding: NIDDK Support

FR-PO775

A Meta-Analysis of Randomized Clinical Trials of Blood Flow and Stenosis Surveillance of Hemodialysis Access Seon Deok Hwang,[1] Seoung Woo Lee,[2] Moon-Jae Kim.[3] *[1]Inha University College of Medicine, Incheon, Republic of Korea; [2]Inha University Hospital, Inchon City, Republic of Korea; [3]Kidney Center, Inha University Hospital, Incheon City, Incheon, Republic of Korea.*

Background: Regular vascular access blood flow (Qa) surveillance is recommended to detect graft or fistular stenosis. However, published studies have reported conflicting results of its utility that led healthcare professionals to doubt the benefits of this surveillance method. We find to access blood flow monitoring lowers the risk of AV access thrombosis or stenosis and that the outcomes differs between arteriovenous(AV) fistular (AVF) and arteriovenous graft (AVG)

Methods: We performed a systematic review of the available literature according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. An electronic search was conducted using the MEDLINE, EMBASE, and Cochrane Library databases from 1980 to 2017 for 9 RCTs involving dialysis access blood flow measurement. All studies combined included a total of 981 patients with hemodialysis vascular access of whom 649 had AVF and 332 had AVG.

Results: The estimated overall pooled risk ratio (RR) of thrombosis was 0.782 (95% confidence interval [CI], 0.553 to 1.107) favoring access blood flow monitoring. The pooled RR of thrombosis were 1.104 (95% CI, 0.672 to 1.816) in the AVG group. However, In AVF subgroup, the pooled RR of thrombosis statistically significant decrease surveillance group 0.562 (95% CI, 0.346 to 0.915).

Conclusions: The benefit of AV access surveillance using access blood flow monitoring to lower the risk of thrombosis is uncertain in AVG group. But, using access AVF surveillance is effective method in hemodialysis patients.

FR-PO776

Which Test Is Best for Detecting Stenosis and Predicting Thrombosis in Arteriovenous Graft? A Diagnostic Accuracy Comparative Study Nicola Tessitore,[2] Giuseppina Pessolano,[2] Giovanni Lipari,[3] Giancarlo Mansueto,[1] Valeria Bedogna,[2] Alberto Contro,[1] Albino Poli,[1] Antonio Lupo.[2] *[1]AOUI Verona, Diagnostics & Public Health Dpt, Verona, Italy; [2]AOUI Verona, Nephrology Unit, Verona, Italy; [3]AOUI Verona, Surgery Dpt, Verona, Italy.*

Background: Guidelines recommend regular screening of grafts for significant >50% stenosis (St) by surveillance (access blood flow[Qa], static venous pressure ratio[sVPR] or Duplex Ultrasound [D]) and state that there is insufficient evidence to prefer one tool over another due to the lack of studies comparing vis-a-vis all of the options

Methods: To identify optimal criteria for St detection and elective repair, we compared in 52 PTFE grafts the Area under Receiver Operator Curve (AUC[95%CI]), sensitivity (SE) & false positive rate (FPR) of clinical monitoring (M), Qa by ultrasound dilution (QaU), sVPR, & D to detect >50% St (StD) and measure Qa (QaD) for >50% St at angiography (StA) and incipient thrombosis (within 4-mo).

Results: Prevalence of StA was 52%. M could not detect StA (AUC 0.60[0.45-0.76]), while all surveillance tools had a similarly significant accuracy for StA: StD (AUC 0.91[0.79-0.97]; SE 85%, FPR 4%), QaU (AUC 0.89[0.77-0.96]; Qa<1300 ml/min: SE 78%, FPR 8%), sVPR (AUC 0.78[0.65-0.89]; sVPR>0.7: SE 89%, FPR 40%), QaD (AUC 0.73[0.59-0.84]; Qa<1300 ml/min: SE 76%, FPR 48%). 31 thromboses occurred during the follow-up. Only QaU (AUC 0.75[0.64-0.84], p<0.001; QaU<1200: SE 68%, FPR 29%), QaD (AUC 0.67[0.53-0.80], p<0.03; QaD<1300: SE 87%, FPR 57%) & StA (AUC 0.61[0.50-0.72], p<0.05; SE 73%, FPR 47%) were equally significant predictors of thrombosis, though their AUC was similar to StD (AUC 0.60[0.46-0.72]) & sVPR (AUC 0.59[0.47-0.70]). At Cox's multivariate analysis (in a model including StA or StD, QaU or QaD, sVPR, M & acute symptomatic Hypotension during the follow-up) the only significant & independent predictors of incipient thrombosis were Hypotension (with a 4-fold [95%CI:2-18] increased risk, p=0.001), QaU or QaD (with a 20% [95% CI:10-40] greater risk for each 100 ml/min drop in Qa, p<0.01). At univariate analysis, the risk of thrombosis increased significantly at QaU<1200 ml/min (RR 3.7 [95%CI:1.7-8.7], p<0.001) or QaD<1300 ml/min (RR 4.1 [95%CI:0.9-37.1], p<0.05).

Conclusions: Our comparative study suggests that in graft an effective screening program should be based on Qa surveillance (QaU or QaD) & the risk of thrombosis may be contained by avoiding acute hypotension & electively repairing St at a QaU<1200 ml/min or QaD<1300 ml/min.

FR-PO777

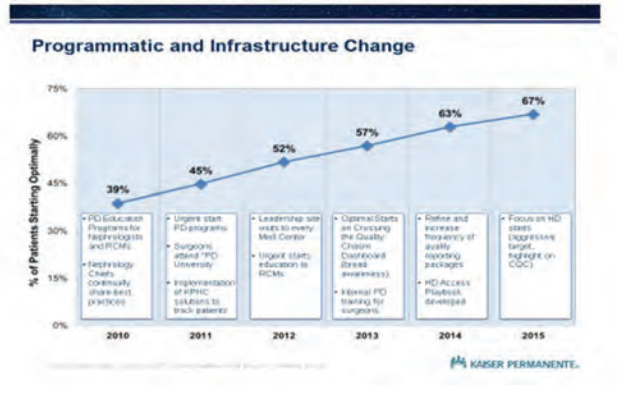
Optimal ESRD Starts as an Organizational Metric Enabling Reduction in CVC Use Leonid Pravoverov,[1] Sijie Zheng,[2] Joanna Mroz.[2] *[1]Kaiser Permanente, Walnut Creek, CA; [2]The Permanente Medical Group, Oakland, CA.*

Background: Patients who initiate dialysis with central venous catheters are associated with higher rate of infection, death and hospitalization. However in the United States, on average 80% of patients started hemodialysis are using central venous catheter instead of a matured AVF/AVG. Kaiser Permanente Northern California (KPNC) is an integrated health care system of 4 million members with an average of 1300 patients starting renal replacement therapy every year. Through a systemic multi-discipline approach, KPNC was able to gradually increase patients with and "optimal start" to 67% and reduce incident patients using CVC to initiate dialysis to 33%.

Methods: Since 2009 KPNC adopted Optimal ESRD Starts metric, targeting to (1) increase use of home dialysis modalities, Peritoneal Dialysis (PD) and home hemodialysis (HHD), (2) increase use of AVF/AVG in hemodialysis population and (3) increase number of pre-emptive transplants.

Results: Throughout systematic approach and advantages of integrated healthcare system, we are able to reduce use of CVC as an initial access for dialysis to less than 33%.

Conclusions: It is feasible to decrease CVC in patients starting renal replacement therapy by systemic and multi-disciplinary approach.



FR-PO778

Efficacy of Peri-Vascular Anesthesia in Dialysis Access Procedures – Experience from Saudi Arabia Danyal Hassan. *DaVita Saudi Arabia, Jeddah, Saudi Arabia.*

Background: Early and late venous stenosis within a dialysis access is a common complication requiring endovascular intervention. These procedures are typically done under sedation because of pain and discomfort to the patients. On the other hand use of sedation is associated with higher risk of complications.

Methods: We describe the use of peri-vascular local anesthesia (PVA), in a free standing vascular access center (VAC), to treat area of stenosis in dysfunctional dialysis access. The area of the stenosis was identified using standard angiogram and PVA was provided under ultrasound guidance. The pain experienced by the patients was recorded on a numeric score from 0-10; during the procedure and at the time of discharge. This was then divided into adequate, moderate and poor pain control.

Results: Data was collected for 83 patients who underwent 112 encounters over a period of 15 months. Mean age of the patients was 54 years, with 51% male patients. There were 54 cases of outflow stenosis, 34 inflow stenosis, 10 cases of both inflow and outflow stenosis treated during the same procedure, and 14 thrombectomy cases including 12 AVF thrombectomy and 2 AVG thrombectomy. During procedure 4 covered stents were placed, 2 of them to treat complications. Overall adequate pain control (0-3) during the procedure was achieved in 91 patients (81%), moderate pain control in 16 patients (14.2%) and poor pain control in 5 patients (4.4%). Post procedure 97% of the patient reported adequate pain control and 3% reported moderate pain control. For thrombectomy procedures 6 (43%) patients reported adequate, 6 (43%) reported moderate and 2 (13%) reported poor pain control. Overall procedure success rate was 98%, with 3 procedures related complications including two Grade I hematomas and one Grade II hematoma. In one case the procedure was stopped due to poor pain control, leading to anxiety, chest pain and transfer to the ER. No PVA related complications were reported except for mild local infiltration and erythema.

Conclusions: In this series, ultrasound guided PVA provided good pain control for endovascular procedures in outpatient setting with minimal complications. In case of thrombectomy, PVA should be decided on case to case basis, due to a higher moderate and poor pain control during the procedure.

FR-PO779

Correlation of Intradialytic Blood Pressure Variability with Vascular Access Outcomes in Hemodialysis Patients Hye mi Seo, Hyunwoo Kim, Ji young Kim, Miyeon Kim. *Jeju National University Hospital, Jeju City, Republic of Korea.*

Background: Hemodialysis vascular access dysfunction is a major cause of morbidity and hospitalization in patients on hemodialysis. Identifying risk factors of vascular access failure is important because it will likely allow early intervention for dysfunctional hemodialysis fistulas. Recent studies has shown that blood pressure variability during dialysis are associated with increased cardiovascular morbidity and mortality. But there have been no studies related to effect of intradialytic BPV on vascular access outcomes. This study aimed to investigate the correlation of intradialytic BPV with vascular access outcomes in hemodialysis patients.

Methods: We examined 130 end stage renal disease patients with created vascular access between January 2009 and December 2016 in our hospital. Blood pressure data were collected three month after the start of hemodialysis for adaptation period. We examined 12 dialysis session per patient and recorded five times blood pressure for each session. Blood pressure variability (BPV) was assessed using the standard deviation of the residual derived from linear regression model. The primary outcome was primary vascular access patency defined as time to first intervention including angioplasty or surgical revision. Cox proportional hazards regression anlysis was used to access the risk of primary outcome (reintervention) or secondary ouctome (failure).

Results: Patients were followed up an average of 3.7 years. Patient's mean age was 62 years. Among these, 64% of patients were male, 53% of patients had DM. We devided patients into two groups according to intradialytic blood pressure variability. The mean time to primary patency of high BPV group was 750 ± 131 days and low BPV group was 1613 ± 190 days. After adjustment for demographics, comorbidities and medications, high BPV was significantly associated with worse primary outcome (HR, 2.30; 95% CI 1.39-3.82; p = 0.01) and worse secondary outcome. (HR,2.81; 95% CI 1.14-6.93; p = 0.025)

Conclusions: We observed a significant correlation between intradialytic BPV and vascular access patency. Lowering Intradialytic BPV is important to improve vascular access patency in hemodialysis patients.

FR-PO780

Association between Post-Dialysis Hemoglobin Level and the Survival of Vascular Access Hiroki Nishiwaki,[7] Takeshi Hasegawa,[7] Naoto Tominaga,[3] Masahiko Yazawa,[1] Hiroo Kawarazaki,[6] Tatsuyoshi Ikenoue,[5] Yugo Shibagaki,[2] Shingo Fukuma,[4] Shunichi Fukuhara.[4] *[1]Division of Nephrology and Hypertension, Department of Internal Medicine, St.Marianna University School of Medicine, Kawasaki, Japan; [2]Division of Nephrology and Hypertension, St Marianna University Hospital, Kawasaki, Japan; [3]Georgetown University Medical Center, Washington, DC; [4]Kyoto University, Kyoto, Japan; [5]Kyoto University Graduate School of Medicine and Public Health, Kyoto, Japan; [6]None, Tokyo, Japan; [7]Showa University Fujigaoka Hospital, Yokohama, Japan.*

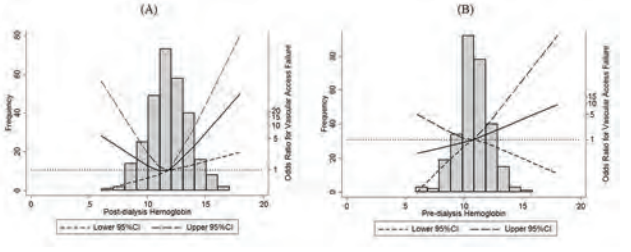
Background: Although a few dialysis facilities conduct a complete blood cell count for some patients at post-dialysis, including hemoglobin, clinical findings supporting the interpretation of results are scarce. The aim of this study was to investigate the association between post-dialysis hemoglobin level and vascular access failure with clinical data.

Methods: Study Design: Case crossover design Setting: Japanese dialysis facilities which routinely take post-dialysis blood samples, including complete blood cell counts at least once a month. Participants: Hemodialysis patients who experienced vascular access failure in Jan. 2010- Dec. 2014. Exposure: Post-dialysis hemoglobin level Main outcome: Vascular access failure treated with endovascular treatment or operation. Statistical analysis: Self-matched odds ratios and 95% confidence intervals were estimated by comparing post-dialysis hemoglobin just before events ("case") with levels at 6 and 12 months before events ("control") using conditional logistic regression, and presented with restricted cubic spline.

Results: 230 hemodialysis patients with vascular access failure were identified. Mean post-dialysis hemoglobin level before the failure was 11.8 g/dl (standard deviation 1.7). The spline curve showed that higher post-dialysis hemoglobin levels above 11.8 g/dl had a greater odds ratio for vascular access failure. Post-dialysis hemoglobin levels and odds ratios (95% Confidence Interval) for vascular access failure relative to the reference value (Hb 11.8 g/dl) were Hb 12.0 g/dl, 1.1 (1.0-1.1); Hb 14.0 g/dl, 3.3 (1.3-8.3); and Hb 16.0 g/dl, 12.7 (1.8-89.4).

Conclusions: A higher post-dialysis hemoglobin level was associated with vascular access failure. Higher post-dialysis Hb could be a factor which triggers vascular access failure.

Funding: Private Foundation Support



FR-PO781

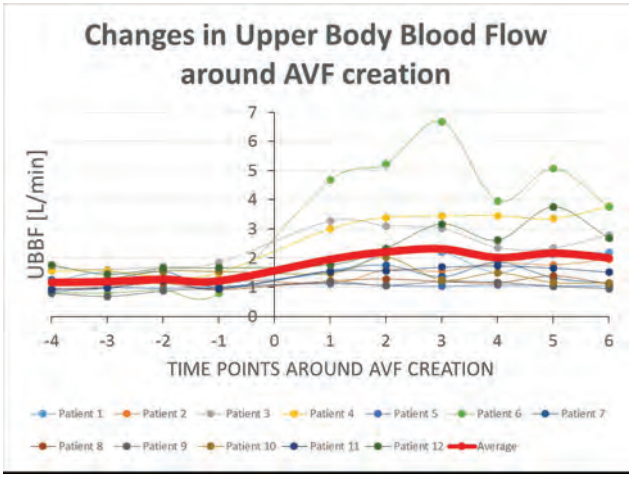
Changes in Upper Body Blood Flow after AV Fistula Creation in Hemodialysis Patients Israel Campos,[1] Hanjie Zhang,[2] Priscila Preciado,[1] Stephan Thijssen,[1] Peter Kotanko.[1] *[1]Renal Research Institute, Morelia, Michoacán, Mexico; [2]Renal Research Institute, New York, NY.*

Background: Hemodynamic changes occurs after AV fistula (AVF) creation. Cardiovascular adaptive mechanisms allow adequate AVF maturation, usually accompanied by an increase in cardiac output (CO). In hemodialysis (HD) patients with a central-venous catheter (CVC), upper body blood flow (UBBF) can be estimated [Campos et al., WCN 2017]. UBBF is expected to increase after AVF placement in the presence of normal AVF maturation and adequate adaptation

Methods: We estimated UBBF around AVF creation using averaged central-venous oxygen saturation and hemoglobin data from the Crit-Line® Monitor (CLM) (FMC, Waltham, MA) in HD patients from Renal Research Institute clinics. Brain mass was calculated using the Mehrpour formula [J Forensic Leg Med. 2010]. Arm muscle mass was set at 2.3kg for males and 1.2kg for females [Abe T, Br J Sports M. 2003]. Tissue-specific O2 consumption rates were taken from Sokoloff L [Handbook of Physiology. 1960]. Arterial O2 saturation was taken from a large HD population [Meyring-Wösten, CJASN. 2016]. We compared the four closest UBBF values before AVF creation, the first three UBBF estimates after AVF creation and the last three UBBF estimates before first AVF cannulation

Results: We analyzed 12 patients (8 males), mean age 60±12 y. While individual UBBF trajectories differed between patients, UBBF did rise on average after AVF creation (Figure). The average UBBF before and after AVF creation was 1.21±0.03L/min, and 2.15±0.76L/min respectively, and UBBF before the first AVF cannulation was 2.06±0.62L/min

Conclusions: Hemodynamic changes related to AVF creation can be detected non-invasively in HD patients using the CLM. As expected, UBBF increases on average after AVF creation. A prospective study with AVF flow rate measurements alongside UBBF estimation would be insightful and help define the expected UBBF trajectory in well-maturing AVFs



FR-PO782

Characteristics of Permanent Vascular Access of Young Children (≤12 Years Old) on Chronic Hemodialysis Reut R. Pagi, Gaurav Kapur, Rudolph P. Valentini, Amrish Jain, Tej K. Mattoo, Rossana Baracco. *Children's Hospital of Michigan, Detroit, MI.*

Background: Hemodialysis (HD) is the most commonly used dialysis modality in children with end stage renal disease. Because of perceived proximity to transplantation and smaller blood vessels in children, central venous catheters (CVC) remain the most commonly used access for children in the United States and are more frequently used over a permanent access: either an arteriovenous fistula (AVF) or arteriovenous graft (AVG). The aim of this study was to compare efficacy and complications of these HD accesses in young children.

Methods: This was a retrospective chart review of patients who started chronic HD at age ≤12yo from 2008 to 2016. Data collected and compared included age and weight of the patient, infectious and non-infectious complications and hospital admissions related to the access; as well as treatment characteristics at 6 months including adequacy of dialysis (Kt/V), hematocrit, albumin, erythropoietin dose and calcitriol dose.

Results: There were 39 accesses used by 19 patients (16 CVC's, 16 AVF's and 7 AVG's). Medians were 8 years (1 – 12) for age and 23.4kg (6.6 – 110.7) for weight. Median days on HD per patient was 696 (317 – 1826). Treatment characteristics at 6 months showed that Kt/V was 2 for permanent access and 1.42 for CVC (p=0.03). Albumin and hematocrit were not significantly different between the 2 groups. Patients with CVC required 33% more erythropoietin and 100% more calcitriol than the patients with permanent access, however, this difference was not statistically significant. Patients using permanent access had lower rates of infectious complications, total complications, hospital admissions and shorter hospital stays (p<0.01 for all categories).

Conclusions: Commitment to using permanent access (AVG or AVF) in young children on chronic HD led to more cost-effective care in view of decreased complications, hospitalizations and better adequacy of dialysis.

Access Related Complications per 100 Days of HD (mean)

	CVC	Permanent access	P value
Bloodstream infections (BSI)	0.61	0.03	<0.001
Hospital days secondary to BSI	2.32	0.13	<0.001
Antibiotic treatment days secondary to BSI	9.32	0.50	<0.001
Admissions related to access complications	0.95	0.40	<0.001
Total complications	0.93	0.52	<0.001
Hospital days related to access	3.05	1.21	<0.001

FR-PO783

Impact of a Compressive Therapy via Arm Sleeve on High Flow Arteriovenous Fistula and Cardiac Output in Patients with ESRD Jong-Hwan Jung, Seon-Ho Ahn. *Wonkwang University Hospital, Iksan, Republic of Korea.*

Background: Heart failure is among cardiac complications in patients with end-stage renal disease (ESRD) undergoing hemodialysis via arteriovenous fistula (AVF). AVF creation may result in several cardiac dysfunctions, such as increase of left ventricular end-diastolic diameter, left ventricular hypertrophy, and high output heart failure, particularly in patients with AVF flow over 2000 ml/min. Surgical reduction of AVF to improve cardiac dysfunctions may often result in complications, such as access thrombosis. Thus, we suggests non-invasive compressive method via arm sleeve to reduce blood flow of high flow AVF.

Methods: Data were collected from total 30 patients with ESRD and high flow AVFs. All patients have autologous AVFs and have undergoing hemodialysis of three times sessions per week. All patients also have high flow AVFs with blood flow rate over 1200 ml/min. Arm sleeve (Nambuk Surgical®, Seoul, Korea) with pressure of 30~40 mmHg was applied during 8 hours on non-hemodialysis dates for three months in only fifteen patients. We performed comparative analysis for changes of AVF flow rates, cardiac output, and arm edema after application of arm sleeve in two groups.

Results: The average change of AVF flow rate in group which arm sleeve was applied was – 60 ml/min. On the contrary, average change of AVF flow in control group was 19.33 ml/min. The average AVF flow rate in group which arm sleeve was applied decreased statistically significant. (p <0.001) Also, arm edemas decreased significantly in patient which arm sleeve was applied. (-0.28 ± 0.28 vs 0.23 ± 0.26, -0.32 ± 0.25 vs 0.12 ± 0.24, -0.36 ± 0.37 vs 0.31 ± 0.21, -0.37 ± 0.30 vs 0.31 ± 0.32, and -0.45 ± 0.44 vs 0.33 ± 0.34; p <0.001) We analyzed changes of cardiac output. However, there was no significant difference concerning of change of cardiac output in two groups. (-0.01 ± 0.005 vs 0.005 ± 0.17, p =0.091)

Conclusions: The non-invasive compressive method reduced arm edema and AVF flow rate in patients with high flow AVFs. High flow rate over 2000 ml/min of AVF can be a risk factor of development of high output heart failure in patients with AVFs. Although there was no an effective impact of the non-invasive compressive method on cardiac output, reduction of edema and AVF flow rate might inhibit development of high output heart failure in patients with high flow AVFs

FR-PO784

Acetate Free Dialysis and Mortality in the French Renal Epidemiology Information Network Registry (REIN) Lucile Mercadal,[1,6] Abdoulaye Ndoye,[4] Marie Metzger,[3] Christian Jacquelinet,[2] Benedicte Stengel.[5] *[1]nephrology, AP-HP, Pitié Salpetrière hospital, Paris, France; [2]Agence de la biomedecine, Saint-Denis La Plaine, France; [3]CESP U1018, INSERM, Villejuif, France; [4]INSERM, Villejuif, France; [5]Inserm ? CESP, Villejuif, France; 6team 5, INSERM-CESP, Villejuif, France.*

Background: We previously found a reduced mortality associated with the use of acetate free dialysis (AFD) in subjects older than 70 years old. As the use of these dialysates made with chlorhydric or citric acid steadily increases since 2010, we wonder whether this result can be reproduced in the last recent years.

Methods: All patients who started HD from 2010 to 2013 were classified according to their exposure to AFD: exposed in a 100% AFD dialysis center, exposed in a mixed center (both standard and AFD) and unexposed. Cox survival analysis was performed in 26 304 incident patients, adjusted for 15 baseline co-morbidities and biological data and accounting for patient clustering within facilities. Exposure to AFD and hemodiafiltration (HDF) status were analyzed as time-dependent variables. Analysis was censored at Dec 31, 2014, or at kidney transplantation, lost to follow-up, dialysis weaning or transfer to peritoneal dialysis. The Cox model was used for the overall population and by age group, <70 or ≥70 years.

Results: During the study period, 16 124 subjects were exclusively dialyzed in centers with standard dialysate, 380 in 100% AFD centers, 7538 in mixed centers and 6481 had a change in their AFD exposure. Being dialyzed in mixed centers was associated with a mortality HR of 0.53 (0.47-0.60) for subjects <70years old and of 0.57 (0.52-0.62) for those ≥70. Being dialyzed in 100% AFD centers was associated with a mortality HR of 0.80 (0.59-1.09) for subjects <70 years old and of 0.68 (0.54-0.87) for those ≥ 70. The Cox on the overall population found a mortality HR of 0.56 (0.51-0.61) for being dialyzed in mixed centers and of 0.73 (0.6-0.89) for 100%AFD centers.

Conclusions: Using an entirely new data set of subjects exposed to AFD in the REIN registry, we confirm that being dialyzed with AFD is associated with a reduced mortality risk. In a larger AFD exposed population, the mortality reduction seems more constant with age.

FR-PO785

Forecasts for 2030 for the ESRDDialysis Workforce in the US Ivo Abraham,[2] Chinmayee Katragadda,[2] Michael Katz,[2] Brian Erstad,[2] Karen Macdonald.[1] *[1]Matrix 45, Tucson, AZ; [2]University of Arizona, Tucson, AZ. Group/Team: For ESRD Workforce Investigators.*

Background: The continued rise in patients requiring renal replacement therapy impacts the ESRD/dialysis workforce demand. We aimed to estimate for 2030, on the demand side, the number of patients requiring dialysis; and on the supply side, workforce requirements for nephrologists, nurses (registered nurses and advanced practice nurses) and technicians (licensed practical/vocational nurses and dialysis technicians).

Methods: We forecasted the demand and supply sets using time series analysis with autoregressive integrated modeling (ARIMA). We used annual 2008-2014 USRDS data for the number of dialysis patients, dialysis centers, and FTE nurses and technicians; and 2008-2016 ASN data for nephrologists. We assumed similar dialysis practice patterns in 2014 and 2030.

Results: Forecasting models projected the following for 2030; all with adequate to superior goodness-of-fit. On the demand side, 689693 patients and 9911 centers. On the supply side 13107 nephrologists, 51381 FTE nurses, and 62243 FTE technicians. By 2030 the ratio of patients:nephrologist will have increased to 52.6:1; of patients:nurse to 13.4:1; and of patients:technician to 11.1:1. The supply differential of nephrologists is projected to be -386 shortage; of nurses +5679 surplus; and of technicians -2276 shortage.

Conclusions: Significant shortages of nephrologists and FTE technicians are anticipated by 2030 to meet the demand of patients requiring dialysis and the centers providing this dialysis. The shortage in centers can be addressed by enhanced operational efficiency and increased volume, but the latter is constrained by the need for geographically equitable access. Though the emerging use of advanced practice nurses may enable shifting some responsibilities' from nephrologists, in general nurses can assume few if any nephrologists' responsibilities. In addition to potentially being inappropriate professionally, wage differences make nurses fulfilling tasks of technicians economically not feasible. Funding for nephrology fellowship training needs to be

diversified and recruitment intensified (inter)nationally; while novel training programs between the dialysis sector and community/technical colleges are required to address the technician demand.

FR-PO786

Relative Blood Volume Changes and Mortality among Hemodialysis Patients Priscila Preciado, Hanjie Zhang, Stephan Thijssen, Peter Kotanko. *Renal Research Institute, New York, NY.*

Background: Ultrafiltration during hemodialysis (HD) is the only means to remove excess fluid. In most HD sessions the ultrafiltration rate exceeds the refilling rate (UFR), leading to decreased blood volume and potentially intradialytic hypotension and increased morbidity. While relative blood volume (RBV) monitoring is widely used, the relationship between RBV levels and outcomes is ill-defined

Methods: Retrospective multi-center study in HD patients from 17 Renal Research Institute (RRI) clinics between 1/2012-12/2016. A 6-months baseline period preceded follow-up period. Hematocrit-based RBV was reported 1x/minute by the Crit-Line® Monitor (CLM;Fresenius Medical Care, Waltham, MA). Hourly RBV levels were defined as the mean RBV between treatment minutes 50 and 70,110 and 130, and 170 and 190. The relationship between mortality and hourly RBV levels was analyzed using Cox proportional hazards models with spline terms

Results: We included 842 patients with 28,119 HD treatments (mean age 61.0±14.8 years, 50% whites, 62% males, 56% diabetes mellitus, 22% congestive heart failure). Median follow-up was 2.7 years. Hazard ratios for all-cause mortality were significantly reduced in patients who achieved RBV levels [%] of 93-96 at 1 hour, 89-94 at 2 hours, and 86-92 at 3 hours. Subgroup analysis by age, gender, race, comorbidities, pre-HD blood pressure, and UFR showed similar results

Conclusions: To our knowledge this is the first study to examine the relationship between achieved intradialytic RBV levels and all-cause mortality in a large and diverse HD population. Our key finding is the association of specific RBV levels with reduced mortality. Prospective studies are warranted to test the hypothesis that attainment of these levels improve outcomes

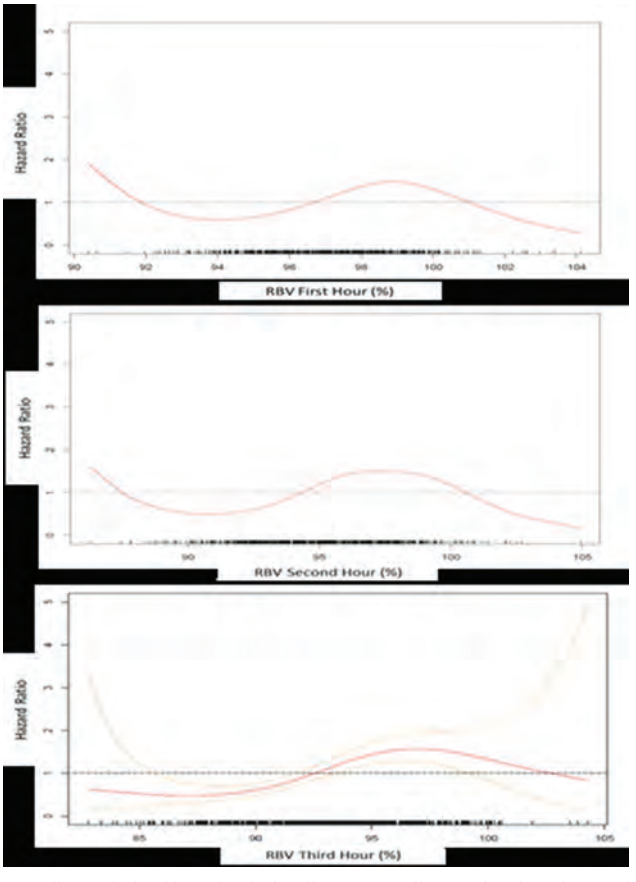


Fig 1 Spline analysis of hazard ratio for all-cause mortality as a function of RBV after 1, 2, and 3 hours

FR-PO787

Effects of Post-Dilution High Volumen On-line Hemodiafiltration in Comparison to High-Flux Hemodialysis: A One-Year Prospective and Controlled Study Fernando F. Hadad-Arrascue,[1,2] Gabriela I. Pimentel,[1,2] Barbara Fernandez-Lopez,[1,2] Maria D. Algaba,[1,2] Marisol Poma tapia.[3] *[1]Nephrology, Clinica RTS Murcia VII, Murcia, Spain; [2]Nephrology, Hospital Universitario Reina Sofia, Murcia, Spain; [3]Nephrology, Hospital Universitario Clinico San Carlos, Madrid, Spain.*

Background: It is suggested that post-dilution on-line Hemodiafiltration (OL-HDF) may improve clinical outcomes. Currently, the world-wide acceptance of HDF is low because higher costs and its benefits have not been well demonstrated. The aim of this prospective and controlled study was to compare the effects of post-dilution OL-HDF and conventional high-flux HD during one year.

Methods: One-hundred fifteen clinically stable HD patients were randomized in two groups: OL-HDF group (55 patients, ages 29-81 years, mean time on dialysis 5.2 years) and HD group (60 patients, ages 39-95 years, mean time on dialysis 6.5 years). All patients were scheduled sessions thrice weekly with a stable arteriovenous fistula, blood flow rate (QB) 364 ml/min (316-410 ml/min) in OL-HDF and QB 356 ml/min (306-400 ml/min) in HD. The same Polysulfone membrane high-flux dialysers and Artis Physio dialysis machines for both groups were used during the entire study period. OL-HDF procedure was performed in the post-dilution mode and the substitution volume was targeted to be above 20 L per session.

Results: During follow-up, there were no significant differences in mean hemoglobin (11.7±1.5 g/dl OL-HDF vs. 11.74±1.45 g/dl HD), mean transferrin saturation (24.6±14.3% OL-HDF vs. 22.9±16.4% HD), but the mean prescribed erythropoietin (EPO) dosage was significantly lower in OL-HDF than HD (14676±2889 vs. 15300±4550 U/month, P<0.05). The mean prescribed intravenous iron dosage was not different among the groups. OL-HDF group was lower the mean ferritin (483.3±45.7 ng/mL vs. 601.6±35.6 ng/mL, P<0.005), mean high-sensitivity C-reactive protein (0.42±0.1 mg/dL vs. 0.62±0.15 mg/dL), mean intact parathyroid hormone (327.09±45.7 pg/mL vs. 346.95±35.6 pg/mL, P<0.05), despite similar calcium (8.82±0.14 mg/dL vs. 8.89±0.16 mg/dL) and phosphorus (4.09±0.16 mg/dL vs. 4.01±0.11 mg/dL, P>0.05). The β-2 microglobulin remained lower (23.53±12.1 mU/mL vs. 26.94±12.43 mU/mL, P<0.05) and mean Kt was significantly higher (53.12±1.9 vs. 48.18±1.87, P< 0.05) in OL-HDF, despite the mean eKt/V was similar in both groups.

Conclusions: Post-dilution OL-HDF is a safe and well-tolerated treatment, increased dialysis dose, reduced inflammation and needed lower requirement for EPO to correct anemia compared with high-flux HD.

FR-PO788

Increased Levels of Extracellular Nucleosomes, Biomarkers of Cell Death, in Stage 5 Chronic Kidney Hemodialysis (CKD5-HD) Are Independent of Circulating Tissue Factor Microparticle Complex Vinod K. Bansal,[1] Trung Phan,[1] Ryan Mcmillan,[1] Amanda Walborn,[2] Debra Hoppensteadt,[1] Jawed Fareed.[1] *[1]Loyola University Medical Center, Maywood, IL; [2]Loyola University Medical Center, Maywood, IL.*

Background: Extracellular nucleosomes in plasma (PNs) are complexes of DNA and histones that are released during cell death. In both the chronic and acute kidney injury, there is an increased release of nucleosomes with decreased nucleosome clearance. Nucleosomes mediate inflammatory and thrombotic responses and could serve as biomarkers in chronic kidney diseases. Microparticle-associated tissue factor (MP-TF) are released during cell death and mediate thrombotic responses.

Methods: Plasma levels of PNs in CKD5-HD patients (n = 90) and healthy volunteers (n = 50) were measured using the Cell Death Detection ELISA PLUS assay (Roche Diagnostics, Mannheim, Germany). MP-TF levels were measured using the ZYMUPHEN MP-TF kit (Hyphen BioMed, Neuville-sur-Oise, France). The levels of both PNs and MP-TF were also correlated with WBCs, RBCs and platelets to determine the origin of measured PNs.

Results: In comparison to the plasma from healthy volunteers (6.74 ± 13.7 Arbitrary Units (AU)), the levels of PNs in CKD5-HD patients were higher (15.5 ± 14.1 AU; $p < 0.0001$). Similarly, MP-TF levels were elevated in CKD5-HD patients (3.00 ± 1.42 pg/mL; $p < 0.0001$) compared to normal (0.363 ± 0.263 pg/mL). There was no correlation between PNs and MP-TF in CKD5-HD patients ($r = 0.077$; $p = 0.501$). Moreover, there was no correlation between PNs and platelets ($r = 0.067$; $p = 0.543$) and RBCs ($r = 0.083$; $p = 0.447$). However, the PNs showed a positive correlation with WBCs ($r = 0.223$; $p = 0.042$). There was no correlation between MP-TF and WBCs ($r = -0.057$; $p = 0.632$) and RBCs ($r = -0.042$; $p = 0.722$), but a positive correlation was observed between MP-TF and platelets ($r = 0.237$; $p = 0.042$).

Conclusions: PNs were elevated in CKD5-HD patients, indicating an increased release of nucleosomes, suggesting increased cell death. The observed correlation between PNs and WBCs suggests that the detected PNs are derived from WBCs. A lack of correlation between PNs and MP-TF suggests that the MP-TF increase is independent of the pathophysiologic processes responsible for abnormal PN generation in CKD5-HD patients.

FR-PO789

The Interdialytic Creatinine Rise Is a Novel Marker of Volume Overload and Mortality Risk in Hemodialysis Patients Ljubomir M. Ilic, Robert S. Brown, Roger B. Davis, Stewart H. Lecker. *Beth Israel Deaconess Medical Center, Boston, MA.*

Background: Volume overload is a major contributor to morbidity and mortality in maintenance hemodialysis (HD) patients. Since serum creatinine increases between HD treatments, we theorized that the Interdialytic Creatinine Rise (IDCR), a change dependent upon net creatinine retention and dilution by fluid intake, might be used to evaluate volume overload and predict patient mortality. IDCR is calculated using two serum creatinine values from the same interdialytic period obtained at least 18h apart.

Methods: Three analyses were undertaken. A prospective cohort of 47 maintenance HD patients admitted to our hospital had IDCRs measured serially over a period of one week. IDCR change with time and after HD sessions were analyzed using mixed effects model. A prospective cohort of 25 outpatient maintenance HD patients was followed for 2 weeks with determination of the sensitivity and specificity of different IDCR cutoff values using patient volume assessments by their nephrologist as the gold standard. A retrospective cohort of 39 maintenance HD patients was studied longitudinally during inpatient admissions from 2012 until 2017 or death. The data were analyzed using Cox proportional hazards model with IDCR as a time varying covariate. In the same cohort, mixed effects logistic regression was used to correlate IDCR with mortality risk.

Results: IDCR decreases, changing by –0.014 per day without HD (95%CI –0.017, –0.010; p<0.001) due to volume gain. IDCR increases by 0.013 from before to after each successive hemodialysis session (95%CI 0.008, 0.017; p<0.001) due to fluid removal by ultrafiltration. An IDCR cutoff value of ≤ 0.1 mg/dL/h has a sensitivity of 82 %, specificity of 79 %, and accuracy of 80 % in diagnosing volume overload with AUC of ROC curve = 0.78 (95%CI 0.59, 0.97). The hazard ratio of death for each 0.01 mg/dL/h decrease in IDCR is 1.64 (95%CI 1.31, 2.07; p<0.001). If IDCR decreases to less than 0.05 mg/dL/h, the odds ratio of death within 2 months is 38 (95%CI 8, 131; p<0.001).

Conclusions: IDCR decreases with volume retention, can help detect volume overload, and has excellent prognostic value in identifying HD patients who are at high risk of dying over the following 60 days.

FR-PO790

The Effect of Isohydric Hemodialysis on Uremic Retention Solutes Jerome Lowenstein,[1] Aleksey Etinger,[2] Sumit R. Kumar,[3] William Ackley,[3] Leland R. Soiefer,[2] Eric B. Grossman,[1] Albert Matalon,[1] Robert Holzman,[5] Bjorn Meijers.[4] *[1]New York University Medical Center, New York, NY; [2]New York University School of Medicine, New York, NY; [3]Yale New Haven Hospital, New Haven, CT; [4]University Hospitals Leuven, Leuven, Belgium; [5]NYU School of Medicine, New York, NY.*

Background: There is growing evidence that the accumulation of protein- bound uremic retention solutes, such as indoxyl sulfate (IS), p-cresyl sulfate (PCS) and kynurenic acid (KA), play a role in the accelerated cardiovascular disease seen in patients undergoing chronic hemodialysis. Protein-binding, presumably to albumin, renders these solutes poor-dialyzable. We had previously observed that the concentration of free solute and its unbound fraction were markedly reduced at the end of hemodialysis. We hypothesized that solute binding might be pH-dependent and the changes attributable to the higher serum pH at the end of hemodialysis. *In vitro*, acidification of uremic plasma to pH 6 greatly increased the proportion of unbound indoxyl sulfate.

Methods: We tested our hypothesis by reducing the dialysate bicarbonate buffer concentration to 25 mEq/L for the initial half of hemodialysis ("isohydric dialysis"). Eight stable hemodialysis patients underwent "isohydric dialysis" and, midway, were switched to standard buffer (37 mEq/L). A second dialysis, 2 days later, employed standard buffer throughout.

Results: We found a clearcut separation of blood pH and bicarbonate concentrations 90 minutes following "isohydric dialysis" (pH = 7.37, HCO3 =22.4 mEq/l) and standard dialysis (pH= 7.49, HCO3 = 29.5). Analysis of free and bound concentrations of uremic retention solutes confirmed our prediction that binding of solute is affected by pH. However, in mixed models analysis, we found that the *reduction in total uremic solute concentration* during dialysis accounted for a greater proportion of the variation in free concentration, presumably an effect of saturation binding to albumin, than did the *relatively small change in pH* produced by isohydric dialysis.

Conclusions: These findings suggest that modification of dialysis technique that would expose blood to a transient decrease in pH might increase the free fraction of solute and enhance the efficacy of hemodialysis in the removal of protein-bound uremic retention solutes.

Funding: Private Foundation Support

FR-PO791

Intra-Dialytic Syndrome and Time to Recovery in Patients on In-Center Hemodialysis Luis Alvarez,[3,4] Sarah S. Prichard,[2] Dean Hu,[5] Glenn M. Chertow.[1] *[1]Stanford University School of Medicine, Palo Alto, CA; [2]Advisor role, Outset Medical, San Jose, CA; [3]Nephrology, Palo Alto Medical Foundation, Palo Alto, CA; [4]Outset Medical Inc, San Jose, CA; [5]Outset Medical, San Jose, CA.*

Background: Patients on hemodialysis (HD) experience a variety of symptoms during dialysis described here as Intradialytic Syndrome (IDS). Patients also feel unwell for a period of time post HD. The purpose of this study was to assess frequency and severity of intradialytic symptoms and time to recovery post dialysis in a broad cross section of HD patients.

Methods: An online questionnaire was sent to patients in the National Kidney Foundation database via email. Patients included were adults on in-center hemodialysis 3 times/week for 3 or more months. Demographic and basic clinical data were obtained. A 12-item symptom questionnaire asked about the type and severity of symptoms during HD sessions in the previous week. Severity was rated on a 5-point Likert scale - 1 "not severe" to 5 "very severe". It also asked how long it took to resume normal activities post dialysis, if they ever stopped dialysis early because of intradialytic symptoms, and for which symptoms they stopped.

Results: 5,000 e-mails were sent. 98 patients met the screening criteria and completed the questionnaire. Mean age 65±14 yrs, 39% female, 61% male, 65% White, 28% Black/African American, 46% diabetic, 35% history of coronary artery disease, and 87% with hypertension (100% on meds). 88% had intradialytic symptoms in the previous week, with a mean severity of 2.7 (range: 1 - 5). The most common adverse events are shown in Table 1: The median (10%, 90%) time to recovery and resume normal activities was 180 minutes (30 minutes, 13 hours). 35% reported having stopped dialysis early for symptoms. The most common symptom-related reasons to stop dialysis early were cramps and low blood pressure.

Conclusions: 88% of a broad based sample of in-center HD patients reported having symptoms during dialysis. Because intradialytic syndrome can cause patients to terminate dialysis prematurely, innovation in dialysis should target reducing these symptoms.

Funding: Commercial Support - Outset Medical Inc.

Table 1

Symptom	Proportion of patents reporting intradialytic symptoms in the past week	Severity (mean)
Fatique/feeling drained	59%	2.8
Cramps	48%	1.8
Low BP/hypotension	41%	2.1
Headaches	28%	2.0
Itchy skin	20%	2.0
Faintness/dizziness	17%	1.8

*For patients reporting symptoms

FR-PO792

Exploring Walking Pace, Physical Activity, and Readiness to Change in ESRD Yan Song,[1] Patrick J. Highton,[3] Amy L. Clarke,[1] James Burton,[1] Alice C. Smith.[2] *[1]University of Leicester, Leicester, United Kingdom; [2]John Walls Renal Unit, Leicester General Hospital, Leicester, United Kingdom; [3]Loughborough University, Leicester, United Kingdom.*

Background: Reduced physical function and walking speed in end stage renal disease (ESRD) patients are associated with increased morbidity and mortality and high healthcare costs. Physical activity (PA) and regular exercise may optimize physical function, but the majority of ESRD patients are sedentary. This study explored walking speed, PA and exercise, and readiness to change exercise behavior in patients on haemodialysis (HD).

Methods: 1156 patients (M: F 1.8:1, median (IQR) age 63.01(21.00) years) from 16 disparate HD networks completed a series of validated questionnaires: GP Physical Activity Questionnaire (GPPAQ providing Physical Activity Index [PAI] and Walking Speed [WS]), Leisure Time Exercise Questionnaire (LTEQ, providing an exercise Health Contribution Score (HCS) based on METS) and Stage of Change Questionnaire (SoCQ, defining readiness to change exercise behaviour).

Results: The distribution of PAI, WS, HCS and SoC are shown in Table 1. Walking pace was negatively associated with older age, female sex (P<0.01) and longer dialysis vintage (P<0.05), and positively associated with behavioural factors (physical activity, leisure time exercise), and readiness to change (all P<0.01).

Conclusions: GPPAQ and LTEQ responses highlight the inactive lifestyle of HD patients. The majority have slow walking speed which is a strong predictor of poor outcome and indicates the need for functional improvement. Exercise interventions have been shown to improve walking speed in older frail adults and may be beneficial for ESRD patients. However, walking speed was positively associated with stage of change indicating that the most vulnerable patients (slow walking pace, older age, female, low PA) may require targeted support to engage in exercise programmes to improve outcomes.

Funding: Private Foundation Support

Table 1 Distribution of Physical Activity Index, Walking Speed, Exercise Health Contribution Score and Stage of Change in HD patients

Questionnaire		HD patients in each category n (%)			
GPPAQ	PAI	Inactive	Moderately Inactive	Moderately Active	Active
		907 (78.5)	78(6.7)	59(5.1)	49(4.2)
	Walking speed	Slow	Steady	Brisk	Fast
		736 (63.7)	266 (23.0)	39(3.4)	18(1.6)
LTEQ	HCS	<14 (Insufficient for benefit)		14-23 (Some benefit)	≥24 (Substantial benefit)
		947 (81.9)		42(3.6)	73(6.3)
SoCQ		Pre-Contemplation	Contemplation	Preparation	Action / Maintenance
		460 (44)	215(20)	202(19)	48(5) / 129(12)

FR-PO793

Intradialytic Systolic Blood Pressure and Hemodynamics Are Predominantly Controlled by Baroreflex Mechanisms Dvora Rubinger, Michal Dranitzki Elhalel, Dan Sapoznikov. *Hadassah University Medical Center, Jerusalem, Israel.*

Background: Systolic blood pressure (SBP) is believed to be controlled by both baroreflex (BARO) and non-baroreflex (NON-BARO) sympathetically mediated central mechanisms.

Methods: To assess the relative contribution of these mechanisms during hemodialysis (HD), beat-to-beat SBP and interbeat interval (IBI) monitoring using Finometer device was performed during a 4 hr regular HD session in 51 non-diabetic patients, age 52±16 y. BARO and NON-BARO activity episodes were evaluated by the calculation of the slope of between IBI and SBP in 1 min sequences; a positive correlation coefficient (r>0.5) was considered to be representative of BARO activity, whereas a negative correlation was considered to represent NON-BARO sympathetic activity. LFα coefficient, a measure of predominantly BARO function was calculated as the square root of the ratio between average IBI power and average SBP power in the low frequency band (0.04-0.15 Hz). Cardiac output (CO), stroke volume (SV) and total peripheral resistance (TPR) were calculated using the Modelflow simulation method.

Results: The averaged variables for the 1st and the 4th HD hr (median and interquartile range) are shown in Table 1.(see table below) During HD, LFα increased from 3.76 (2.34) in the 1st to 4.17 (3.37) the last hr (p=0.013).

Conclusions: Our data show: 1. At the begining of HD, SBP is dually controlled by both BARO and NON-BARO mechanisms. 2. During ultrafiltration, the maintenance of constant SBP is achieved by predominant BARO activation. 3. The decrease in CO and SV during ultafiltration is compensated by an increase in TPR. The intradialytic hemodynamic stability seems to be dependent on the adequacy and the strength of the BARO response.

Table 1.

	HD 1st hr	HD 4th hr	p
SBP (mmHg)	133 (22)	131 (26)	NS
IBI (ms)	805 (129)	796 (183)	NS
% BARO episodes	62(61)	96 (67)	0.003
% NON-BARO episodes	38 (61)	4 (67)	0.003
CO (L/min)	6.78 (2.10)	5.64 (2.58)	0.001
SV (ml)	89 (28)	73 (38)	0.001
TPR (mmHg.s/ml)	0.875 (0.310)	1.009 (0.530)	0.001

FR-PO794

Hemodialysis Prescription Patterns in a Large Cohort of Pediatric Patients on Maintenance Hemodialysis Verena Gotta,[1] Olivera Marsenic Couloures,[3] Marc Pfister.[2] *[1]University of Basel Children's Hospital, Basel, Switzerland; [2]University of Basel Children's Hospital, Basel, Switzerland, Hilterfingen, Switzerland; [3]Yale University School of Medicine, New Haven, CT.*

Background: Hemodialysis (HD) prescription is relatively standardized in adults, compared to children. Limited systematic data on HD prescription behavior in children and adolescents is available. We aimed to provide reference ranges of real-life pediatric HD prescriptions.

Methods: This descriptive cohort study included 53903 HD sessions of 1852 patients <30 years on chronic HD since childhood, receiving thrice weekly HD between 2004 and 2016 in outpatient DaVita dialysis (6075 patient-years, 1-29 years, 8.3-168 kg). Median and 10th to 90th percentiles (80% reference ranges) of prescriptions were calculated over age and weight-bands of 10 kg, from median individual prescriptions per year for: blood flow (Q_B), dialysate flow (Q_D), mass-transfer coefficient for urea (*KoA)*, duration of HD session, resulting dialytic clearance for urea (K_D) and single pool variable-volume Kt/V (spKt/V). Both absolute and weight-normalized flows were investigated. Means ±standard deviation were summarized over five larger age and weight groups.

Results: Prescription parameters were correlated with age and weight, and showed non-linear dependencies. Inter-individual variability was larger between patients of same age (larger reference intervals) than of same weight. Systematic prescription differences were however more pronounced between patients of different weight (see Table). Generally, low-weight patients had higher weight-normalized Q_B, Q_D, KoA, K_D and spKt/V. More than 90% (70%) of patients 10-80 kg achieved target spKt/V of ≥1.2 (≥1.4). spKt/V was steadily decreasing with higher weight, with only 75% (36%) of patients 110-120 kg achieving target values of ≥1.2 (≥1.4).

Conclusions: HD prescription components are systematically different in children compared to adults, with smaller patients routinely receiving more intensified treatments. Adolescents and young adults with weight >80 kg appear to be at higher risk of receiving suboptimal HD treatment as compared to children ≤80 kg.

Weight	<25kg	25-50kg	50-75kg	75-100kg	>100kg
Q_B (mL/min/kg)	8.2±2.9	7.8±1.6	6.5±1.2	4.8±0.8	3.5±0.6
Q_D (mL/min/kg)	28.0±9.8	15.3±3.2	11.3±2.1	8.0±1.4	6.1±1.0
KoA (mL/min/kg)	22.8±8.2	24.5±5.1	18.5±3.0	13.7±2.0	10.5±1.6
K_D (mL/min/kg)	5.6±1.0	5.3±1.0	4.4±7.0	3.5±0.5	2.8±0.5
Duration (min)	181±20	192±24	205±25	217±24	232±27
spKt/V	1.63±0.31	1.73±0.33	1.59±0.26	1.44±0.22	1.33±0.22

mean ± standard deviation

FR-PO795

Use of a Validated Algorithm to Estimate Potentially Avoidable Readmissions in Hemodialysis Patients Matthew R. Sinclair,[1] Anna Mathew,[1] Lisa M. Rosen,[2] Jody-Ann McLeggon,[1] Steven Fishbane.[1] *[1]Northwell Health, Commack, NY; [2]The Feinstein Institute for Medical Research, Manhasset, NY.*

Background: Hemodialysis (HD) patients face up to 35% 30-day readmission, with associated anxiety and financial costs. There is no validated measure to identify potentially avoidable readmissions (PAR) in HD patients. In the general medicine population, the SqLape computer algorithm identifies PAR with 96% sensitivity and specificity. The aim of this study is to validate SqLape in the HD population.

Methods: We used chart review as the validation gold standard. We randomly selected 100 charts of HD patients with a 30-day readmission in Northwell Health, ending 9/30/2015. SqLape identified patients with a PAR and chart reviewers, blinded to algorithm results, conducted a simultaneous chart review. PAR chart review criteria was developed *a. priori*. To assess reliability of PAR classification by chart review, a second reviewer adjudicated a random 20% of charts. A 2x2 table cross classified algorithm and chart review identified PAR. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. All analysis used SAS version 9.4.

Results: The kappa statistic for inter-rater reliability of readmission classification was 0.667 (substantial agreement). 19% and 72% of readmissions were classified as potentially avoidable by chart review and algorithm, respectively. The sensitivity and specificity of SqLape was 60.0% (95% CI: 26.2, 87.8) and 25.6 (95% CI: 13.5, 41.2), respectively. The PPV and NPV was 15.8% (95% CI: 6.0, 31.3) and 73.3% (95% CI: 44.9, 92.2), respectively (Table 1).

Conclusions: We assessed the use of an algorithm to identify PAR in HD patients. The algorithm performed well to identify the proportion of patients without a potentially avoidable readmission, with acceptable sensitivity and NPV. Specificity and PPV of the algorithm were poor, perhaps related to unique causes of PAR in HD patients(i.e fluid and electrolyte abnormalities, vascular access issues). Future studies should focus on development of an accurate measure of potentially avoidable readmissions in HD patients, as a foundational starting point for further study of this topic.

Table 1: Classification of 30-Day Potentially Avoidable Readmission

		From chart review	
		PAR	Non-PAR
From Algorithm	PAR	6	32
	Non-PAR	4	11

PAR: 30-day Potentially Avoidable Readmission

FR-PO796

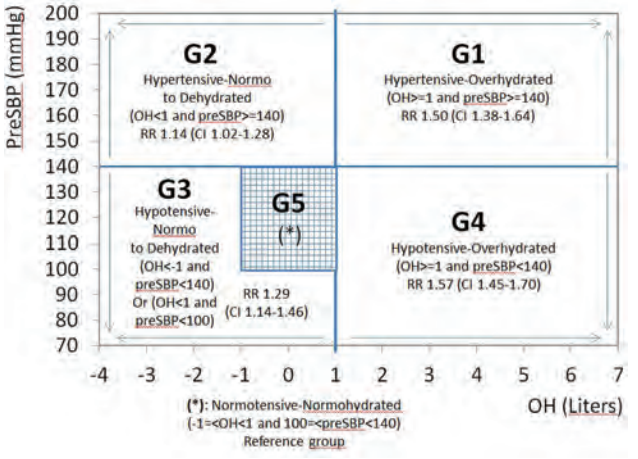
Relationship between Hydration Status (HS), Blood Pressure (BP), and Survival in Hemodialysis (HD) Patients (Pts) Marcelo D. Ferder, Adrian M. Guinsburg, Cristina Marelli. *Fresenius Medical Care Argentina, Buenos Aires, Argentina.*

Background: HS and BP are key factors to control in HD pts due both are closely related to mortality. We aimed to study their association with mortality in a large HD pts cohort from Fresenius Medical Care Latinamerica (FMCLA).

Methods: Pts undergoing HD at FMCLA between 09/2008 and 12/2016 were included. HS was assessed by multifrequency bioimpedance spectroscopy using a body composition monitor device (BCM©, FME Deutschland GmbH). Predialysis systolic BP (pSBP) was obtained as mean of 6 consecutive treatments prior to HS assessment (baseline). Lab data at baseline was used. Values expressed as mean±SD. All pts were assigned to one of five groups (G) based on pSBP and overhydration (OH). G1: Hypertensive-Overhydrated (OH>=1+pSBP>=140); G2: Hypertensive-Normo/Dehydrated (OH<1+pSBP>=140); G3: Hypotensive-Normo/Dehydrated (OH<-1+pSBP<140) or (OH<1+pSBP<100); G4: Hypotensive-Overhydrated (OH>=1+pSBP<140); G5 (Ref): Normotensive-Normohydrated (-1=<OH<1+100=<pSBP<140). Time at risk was counted between HS assessment and death or Dec 31, 2016. A Cox model was constructed to analyze independent relationship between groups and mortality.

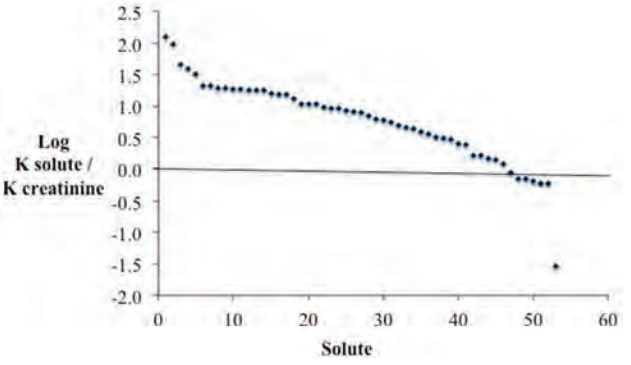
Results: 43,786 pts were included. Age 57.9±16.1 yrs, vintage 3.1±4.3 yrs, male 58.2%, OH 1.76±2.15 lts, pSBP 140.4±23.4 mmHg, Alb 3.8±0.5 (g/dl), Hgb 10.8±1.9 g/dl, serum Ca 8.8±0.9 mg/dl, serum P 4.7±1.4 mg/dl, serum Na 137.8±4.0 mEq/l, eKt/V 1.36±0.30, DBT 30.9%, CVD 8.0%, Cancer 1.0%. Mean follow up time was 4.45 yrs and 5,864 death events were observed. After controlling for demographic, comorbid and lab values, RR of death was G1 1.50 (1.38-1.64), G2 1.14 (1.02-1.28), G3 1.29 (1.14-1.46) and G4 1.57 (1.45-1.70).

Conclusions: Our study suggests that any combination of OH and pSBP outside the box of reference (-1<OH<1 and 100<pSBP<140) increases risk of death. Excesive OH (OH>=1) combined with pSBP<140 (G4) as well as >140 (G1) are groups at higher risk.



presence of additional colon-derived solutes for which chemical structures remain to be determined. Efficient renal clearance for many of these compounds, which are presumably of microbial origin, is achieved by tubular secretion. The large number of colon-derived solutes complicates the problem of identifying their potential toxicity.

Funding: NIDDK Support, Veterans Affairs Support



FR-PO797

Developing an Organized Approach to Symptom Screening, Assessment, and Management for Hemodialysis Patients in Ontario: A Pilot Project Alysha Glazer,[1] Marnie MacKinnon,[1] Esti Heale,[1] Carey Moolji,[1] Peter G. Blake,[2] Michael Walsh.[3] *[1]Ontario Renal Network, Toronto, ON, Canada; [2]London Health Sciences Centre, London, ON, Canada; [3]McMaster University, Hamilton, ON, Canada.*

Background: People living with chronic kidney disease (CKD) requiring dialysis experience a high degree of symptom burden. Symptom assessment, particularly the assessment of chronic symptoms, is not typically done systematically as routine care which may result in a care gap. A provincial approach to routine symptom assessment that can be customized by renal programs may provide an opportunity to improve patient-provider communication and patient experience with dialysis care. To improve the experience of people treated with in-facility hemodialysis and their care team by providing an organized approach to routine symptom screening, assessment, and management.

Methods: Eight Regional Renal Programs in Ontario were selected to participate in a one year pilot project. Participating Programs will routinely assess patients undergoing in-facility hemodialysis with the Edmonton Symptom Assessment Scale Revised – Renal (ESAS-r:Renal), a self-reported symptom questionnaire. The project is being developed by a Task Group with multi-institutional and multi-sectoral representation utilizing a co-design model that engages patients, healthcare providers, and administrators in project planning and development.

Results: Each pilot site has developed a new clinical workflow that includes symptom screening, assessment, and management every four to six weeks. Healthcare providers will be educated on symptom assessment and management through a train-the-trainer approach and the use of evidence-based clinical symptom management guides. Patients will also be educated about the project and use of the screening tool through various resources, including one-on-one education from the care team. Finally, an extensive evaluation framework was developed to guide the evaluation of the pilot project.

Conclusions: This pilot project will help determine the feasibility of a provincial approach to symptom screening, assessment, and management in Ontario. Furthermore, the project will increase awareness of CKD patient symptom burden.

Funding: Government Support - Non-U.S.

FR-PO798

Numerous Colon-Derived Solutes Are Efficiently Cleared by the Kidney Robert Mair,[1] Tammy L. Sirich,[1,2] Natalie Plummer,[1,2] Timothy W. Meyer.[1,2] *[1]Stanford, Palo Alto, CA; [2]VAPAHCS, Palo Alto, CA.*

Background: Previous studies have identified solutes derived from colon microbes that are normally excreted in the urine. The current study employed metabolomic analysis to identify additional solutes in this class and profile their renal clearance.

Methods: Samples from patients with total colectomies (n=12) and age matched controls (n=17) were analyzed using an established metabolomic platform. Solutes were considered colon-derived if they met both of the following criteria: 1) mean excretion rate was greater than four-fold higher in individuals with colons than without colons 2) the difference in excretion between the groups was assigned significance with a false discovery rate (q value) < 0.05.

Results: 91 urinary solutes were identified as colon-derived. Of these, 46 were named compounds with known structure and 45 were unnamed compounds without confirmed chemical structure. Only 11 of the 46 named compounds identified as colon-derived in the current study had previously been shown to be be colon-derived. Binding to plasma proteins allowed a urinary clearance expressed in terms of the free, unbound solute concentration. Plasma levels in normal subjects were sufficient to estimate clearance values for 53 of the 91 colon-derived solutes. As shown in the figure, the estimated urinary clearance exceeded the creatinine clearance for the great majority of these solutes, consistent with tubular secretion.

Conclusions: Comparison of patients with and without colons identified 35 novel colon-derived solutes which are normally excreted by the kidneys and revealed the

FR-PO799

Effects of Intradialytic Cycling on Exercise Capacity, Quality of Life, and Physical and Cardiovascular Function: A Systematic Review and Meta-Analysis Hannah M. Young,[4] Daniel S. March,[3] Matthew P. Graham-Brown,[4] Arwel W. Jones,[5] Ffion Curtis,[5] Charlotte E. Grantham,[3] Patrick J. Highton,[1] Alice C. Smith,[4] Sally J. Singh,[2] Chris Brile,[5] James Burton.[3] *[1]Loughborough University, Leicester, United Kingdom; [2]University Hospitals of Leicester NHS FT, Leicester, United Kingdom; [3]University of Leicester, Leicester, United Kingdom; [4]University of Leicester and University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; [5]University of Lincoln, Lincoln, United Kingdom.*

Background: There is growing interest in intradialytic cycling (IDC), to address a range of health & wellbeing issues associated with haemodialysis (HD). The aim of this systematic review was to identify & synthesise the available evidence on the effects of IDC on exercise capacity, quality of life (QOL), physical & cardiovascular function.

Methods: Databases of published, unpublished & ongoing studies (Medline, EMBASE, CINAHL, LiLACS, Web of Science, Sports Discus, PsycINFO, PEDRO, AMED, Cochrane, PROSPERO, DARE, BIOSIS previews, Index to Scientific & Technical Proceedings, Conference Papers Index, CENTRAL, ClinicalTrials.gov, Current Controlled Trials) were searched for randomised controlled trials (RCTs) of prevalent adult HD patients, comparing cycle training during HD to usual care. Sources were searched until March 2017 & supplemented by internet, hand searching & consultation with experts. No limits were placed upon publication language.

Results: Fourteen RCTs were eligible, but 5 did not provide data interpretable for use in meta-analyses. The remaining 9 RCTs included 187 participants and the length of IDC interventions ranged from 8-26 weeks. Most studies had an overall high risk of bias. Meta-analysis of available evidence indicated no significant change in VO_2 peak (MD 1.84, 95% CI -0.90 to 4.59 p=0.19), physical (mean change -0.06, -0.69 to 0.58 p=0.86) or mental component (mean change 1.68, -6.30 to 9.65 p=0.68) scores of the SF36, or pulse wave velocity (MD -0.36, -1.54 to 0.43, p=0.38) following IDC. IDC did lead to a mean improvement of 85m (25 to 144, p=0.005) on the six-minute walk test. The limited number of studies in the meta-analyses precluded planned sensitivity & subgroup analyses & assessment of publication bias.

Conclusions: There is insufficient evidence to support the use of IDC to influence exercise capacity, QOL, cardiac or physical function in practice. The point estimates of the meta-analyses on the 6MWT are greater than the smallest clinically important difference, but the imprecision of the individual study estimates means further RCTs are needed. The strength of the evidence could be greatly enhanced via transparent reporting & consensus on validated measures.

Funding: Government Support - Non-U.S.

FR-PO800

Coronary Artery Bypass Grafting (CABG) Is Not Associated with Worse Outcomes in Dialysis Patients Sirlei Silva, Rosa M. Moyses, Rosilene M. Elias. *Universidade de São Paulo, SAO PAULO, Brazil.*

Background: CABG is currently a good option of treatment for dialysis patients with multivessel coronary artery involvement. However, whether this population has a higher risk of Hospital worse outcomes than patients with normal renal function and patients with chronic kidney disease (CKD) not on dialysis is still debatable.

Methods: This is a prospective observational study to compare hospital mortality of patients who underwent elective CABG. Consecutive non-selected patients were included in the group with normal renal function (control; N=167), CKD with eGFR 30-60 ml/min (CKD30-60; N=78) and on maintenance dialysis (CKD5D; N=31). Demographic, clinical, biochemical and also fluid balance were evaluated in all patients from the day 1 (surgery) to the day 30 of admission. Sequential Organ Failure Assessment (SOFA) scores at intensive care unit (ICU) admission were also assessed.

Results: Age was similar among control, CKD30-60 and CKD5D groups (63±10, 63±9 and 65±6 years, respectively, p=0.585). Patients from the control group had less diabetes (p=0.019) and Hypertension (p=0.010) than other groups, although dyslipidemia, smoking and previous history of coronary disease did not differ significantly. Initial SOFA scores were higher when renal component was considered (0.3±0.6, 1.1±0.8 and 4.2±1.0 in groups control, CKD30-60 and CKD5D respectively, p=0.0001), though this difference disappeared when renal component was dismissed (p=0.507). Surgery time was similar among groups (p>0.05); endotracheal intubation time was shorter in the control group (p=0.001) as well as intensive care discharge time (p=0.002). There were 17 deaths in 30 days of admission that occurred in the ICU (7 from control, 7 from CKD30-60 and 2 patients from CKD5D; p=0.264). Kaplan-Meier curve showed no 30-day hospital mortality difference among groups (log-rank test 0.977), which was confirmed by Cox-regression survival analysis adjusted for age, diabetes and initial SOFA.

Conclusions: The CABG predictable short-term mortality seems not to be inferior among selected patients on maintenance dialysis. This is probably due to quality improvements in the in cardiologic centers and also because dialysis can be routinely planned in this population.

FR-PO801

Small Animal Study and Hemocompatibility of Small Form Factor Microfluidic Filtration System with Nitride Membranes

Dean G. Johnson. *University of Rochester, Rochester, NY.*

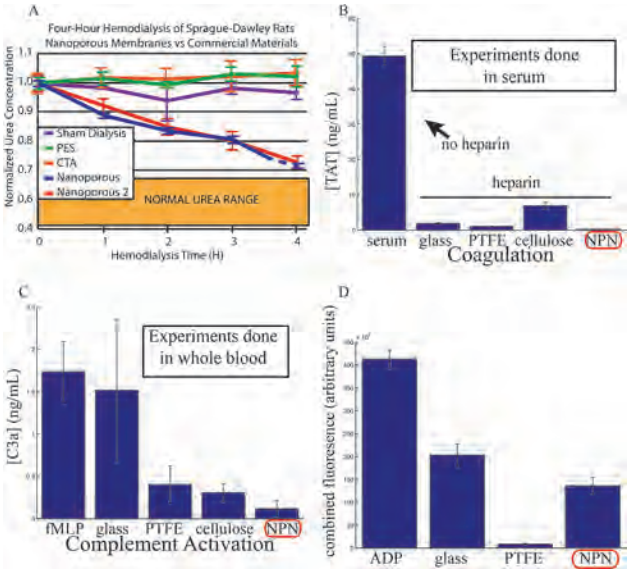
Background: Improving the health outcomes for End Stage Renal Disease (ESRD) patients on hemodialysis (HD) requires new technologies for wearable HD such as a highly efficient membrane that can achieve standard toxic clearance rates in small device footprints. Our group has developed nanoporous silicon nitride (NPN) membranes which are 100 to 1000 times thinner than conventional membranes and are orders-of-magnitude more efficient for dialysis.

Methods: Devices were constructed with polydimethylsiloxane (PDMS) and two NPN membrane chips. Uremic rats were dialyzed for 4 hours under anesthesia. The concentration of thrombin-anti-thrombin complex (TAT) and C3a complement was used as the indicator of coagulation and immune activation. For platelet adhesion and activation, platelet rich plasma (PRP) was incubated in microchannels then incubated with antibodies.

Results: The clearance results from the commercial membranes and the sham dialysis showed no reduction in urea concentration (Figure 1A). The NPN membranes from SiMPore, on the other hand reduced the urea by 26%. Albumin was retained during the 4-hour HD session (n=3) as expected. This indicates that the molecular weight cut-off was somewhere between the size of urea (60.06 Da) and that of albumin (66.5 kDa). The hemocompatibility results are shown in Figure 1B-D.

Conclusions: We had positive results from the NPN membranes clearing Urea better than commercial materials. Significantly, urea was cleared with very little membrane surface area. The favorable hemocompatibility results of the native silicon nitride are encouraging.

Funding: NIDDK Support



A: Sham dialysis, PES, and CTA membrane dialysis – no reduction in serum urea. 50 nm and 75 nm NPN membranes show a 24% decrease in serum urea. B: Coagulation (TAT) n = 3 C: Immune activation (C3a) n = 3 D: Platelet activation (CD62P) n = 15 for ADP, glass, and NPN; n = 5 for teflon.

FR-PO802

Bringing Down the Phosphorus: A Novel Approach to Improve the Quality of Hemodialysis Phosphate Management

Alexander Brauer,[1] Laura J. Maursetter.[2] *[1]UWSMPH, Madison, WI; [2]University of Wisconsin School of Medicine and Public Health, Madison, WI.*

Background: High phosphate levels are associated with vascular calcifications, osteodystrophy and an increased risk of cardiac mortality. According to major investigations such as the Dialysis Outcomes and Practice Patterns Studies, approximately 50% of dialysis patients have hyperphosphatemia. Hyperphosphatemia is both a common and serious complication for patients receiving dialysis therapy. Despite this fact, clinical management of hyperphosphatemia remains subpar. This is thought to be largely due to patient compliance with binders, cost of therapy and dietary constraints.

Methods: In this single center quality improvement project looking at the prevalence of phosphorus control and the willingness of patients to make a change. The serum phosphate levels from the previous 6 months were evaluated. Patients were classified into 3 groups: good control (phosphorus <6), fluctuating control (phosphorus with 2-3 values >6) or poor control (phosphorus >6 for more than 4 values). Anyone in the fluctuating or poor control group was scheduled into 4 weekly meetings for the purpose of using behavioral change theory, an intervention that has been shown effective in dialysis patients. Management modifications were developed by the patients based on the perceived needs. These included changes that have been proven effective such as specific dietary consultation, economic concerns, and meal planning/preparation. The intervention was documented for the patient.

Results: 115 patients that were included in this evaluation, 46 (40%) of patients fell into the fluctuating or poor control group; 21 in the poor control and 25 in fluctuating control. 96% of these patients were willing to meet regularly and 100% of these developed an intervention. The patients reported a positive view of this program.

Conclusions: Using theories of behavioral change, this interdisciplinary intervention showed that patients with poor or fluctuating control of phosphorus were willing to meet and create a plan for change. Belief that poorly controlled phosphorus patients would not care to make changes was disputed by these results. This model actively included the patient as part of the management plan and could be applied to many parts of the hemodialysis treatment to improve adherence to management guidelines.

FR-PO803

Risk Factors Associated with Early Mortality in Patients Commencing Maintenance Hemodialysis: A Systematic Review

Adil M. Hazara,[1] Sunil Bhandari.[2] *[1]Hull and East Yorkshire Hospitals NHS Trust, Hull, United Kingdom; [2]Hull and East Yorkshire Hospitals NHS Trust and Hull York Medical School, East Yorkshire, United Kingdom.*

Background: Early mortality rates are reported to be high in patients starting hemodialysis (HD) for end-stage renal disease (ESRD). We have conducted a systematic review of literature in order to evaluate the risk factors associated with early mortality in this patient population.

Methods: Medline and EMBASE databases were searched for studies published in English language between 1/1/1985 and 31/7/2015. Early mortality was defined as deaths within 180 days of starting HD. Case-control and cohort studies involving adult subjects commencing HD for ESRD were included. The Quality in Prognosis Studies tool was used to assess risk of bias in individual studies. Data extracted from the studies included information on population characteristics and settings. In addition, patient or treatment related factors studied with reference to their relationship with the risk of early mortality were documented. The findings were summarised and a narrative account was drawn from the available evidence.

Results: 21 studies with a combined population of 1,016,646 new dialysis starters were included (median number of subjects: 825; range: 148 - 498,566). There were 15 cohort and 6 case-control studies. Risk of bias was low, medium and high in 5, 3 and 13 studies respectively. A total of 39 different risk factors for early mortality were extracted; broadly, these belonged in 4 categories: clinical, demographic, laboratory and socioeconomic risk factors. Early mortality was associated with patient age, serum albumin at the start of dialysis, not starting HD with functioning arteriovenous fistula, having diabetes as the cause of ESRD, history of heart failure or malignancy, increased frailty, absence of previous nephrological care and deficiency of 25-OH vitamin D. Factors that were not associated with early mortality were gender, having diabetes (as a comorbid condition), serum haemoglobin, parathyroid hormone levels, serum calcium and phosphate.

Conclusions: This systematic review identifies several important modifiable risk factors for early mortality. Studies examining the effects of modification of these risk factors are urgently needed.

FR-PO804

In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems (ICH CAHPS) Survey Non-Responder and Responder Characteristics

Taimur Dad,[2] Hocine Tighiouart,[2] Megan Grobert,[1] Eduardo K. Lacson,[2,1] Klemens B. Meyer,[2] Dana Miskulin,[2] Daniel E. Weiner,[2] Michelle M. Richardson.[2] *[1]Dialysis Clinic Inc, Boston, MA; [2]Tufts Medical Center, Boston, MA.*

Background: The In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems (ICH CAHPS) Survey assessing patient experience is a

performance metric in the End Stage Renal Disease Quality Incentive Program administered twice yearly to adult, in-center hemodialysis patients. Response rates currently are approximately 35% and little is known about characteristics of non-responders.

Methods: Cross-sectional analysis of ICH CAHPS administration in 2012 to all ICH patients in Dialysis Clinic, Inc. (DCI) facilities nationally who met AHRQ eligibility criteria for survey administration (over 18 years old and receiving HD at their facility for at least 3 months). Patient-level covariates include demographic, clinical, laboratory, and functional characteristics. Outcome was survey response using AHRQ's definition of response (no proxy help and answers to at least 50% of pre-defined key questions).

Results: Among 11,055 patients eligible for ICH CAHPS, 6,541 (59%) did not return the mail survey or complete the alternative phone survey and 5,372 (82%) of these had complete covariate data. Of 3,918 responders with complete data (87% of responders), 549 (14%) did not meet AHRQ's definition of response. Using random effects multivariable logistic models, non-responders were more likely to be men, non-white, younger, single, dual Medicare/Medicaid eligible, less educated, non-English speaking, not active on the transplant list, have longer ESRD vintage, lower BMI, lower serum albumin, worse functional status, and more hospitalizations, missed treatments, and shortened treatments. Similar associations were found using more parsimonious multivariable analyses and after imputing missing data.

Conclusions: In 2012, survey non-responders significantly differed from responders raising concern for bias in survey results. Future research should assess and address reasons for non-response to improve survey applicability.

Funding: Other NIH Support - T32DK007777 - T32 Training Grant. "Epidemiology, Clinical Trials and Outcomes Research in Nephrology." Institutional Training Grant at Tufts University; PI: Andrew Levey MD, Commercial Support - Dialysis Clinic, Incorported

FR-PO805

World-Wide Early Mortality Rates after Commencement of Hemodialysis: A Systematic Review and Meta-Analysis

Adil M. Hazara,[1] Sunil Bhandari.[2] *[1]Hull and East Yorkshire Hospitals NHS Trust, Hull, United Kingdom; [2]Hull and East Yorkshire Hospitals NHS Trust and Hull York Medical School, East Yorkshire, United Kingdom.*

Background: In the care of patients with progressive decline in renal function, the start of maintenance hemodialysis (HD) marks a critical turning point. Mortality rates are reported to be high in this period due to multiple treatment and patient related factors. Our aim was to estimate world-wide early mortality rates after commencement of HD in patients with end-stage renal disease.

Methods: Medline and EMBASE were searched for studies published between 1/1/1985 and 7/31/2015 in English. Early mortality was defined as deaths within 180 days of starting HD. Case-control and cohort studies involving adult subjects commencing HD were included. Number of deaths within the early period were extracted and converted in to annualised mortality rates (expressed in 100 person-year). The Quality in Prognosis Studies tool was used to assess risk of bias in studies.

Results: 25 studies were included (population of 1,000,014 patients from 12 countries). Median follow-up: 90 days representing 255,079 person-years of observation. Mortality rates varied from 15.7 to 122.0 per 100 person-year (meta-analysis: 31.6 per 100 person-year [95% CI 31.0-32.2], figure 1). Rates were highest in studies based in Africa (87.2 vs Europe: 15.9 per 100 person-year), lower income countries (87.2 vs high income countries: 31.5 per 100 person-year), studies that restricted recruitment to elderly (37.5 vs unselected: 31.6 per 100 person-year), those that started recruiting in earlier decades (1970's: 37.3 vs 2000's: 31.6 per 100 person-year) and those with low risk of bias (33.6 vs high risk: 22.6 per 100 person-year).

Conclusions: High rates of early mortality after commencement of HD is a global phenomenon. Studies showing lowest rates generally carried high risk of bias suggesting likely under-reporting and incomplete follow-up.

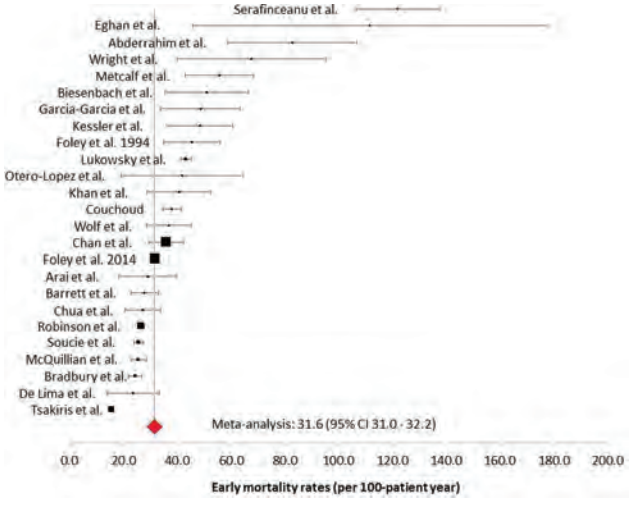


Figure 1: Meta-analysis of early mortality rates in patients newly started on hemodialysis

FR-PO806

Assessment of Wear Compliance, Differences in Step Counts, and Activity Levels of Fitbit and Jawbone Devices to the Actigraph GT3X+ in Hemodialysis Patients

Luis M. Perez, Hsin-Yu Fang, Brett Burrows, Sean P. Mullen, Ken Wilund. *University of Illinois, Urbana, IL.*

Background: The Actigraph GT3X+ (ACT) is a research standard in measuring steps and physical activity, but does not have the convenience of newer commercial devices. The objective of this study was to determine wear compliance and compare differences in steps counts of the Fitbit Flex (FLX), Fitbit Charge HR (CHR), and Jawbone Up2 (JWB) to the ACT in hemodialysis (HD) patients.

Methods: We recruited 29 HD patients (age: 53±10 y, BMI: 32.4±11.4 kg/m2, sex: 67% M) to simultaneously wear the ACT (hip), FLX, CHR, & JWB (wrist) for 7 days. A total of four days (2 dialysis & 2 non-dialysis) were selected for validation. We used self-reported wear-time and a validated algorithm to identify and select valid days for steps and sedentary, light, and moderate-to-vigorous (MVPA) activity.

Results: Adherence rate was for patients wearing and completing 4 days of valid data was 50% (13 excluded & 3 drop-outs). The average daily steps by device were: ACT=2666±1202, FLX=3735±1869, CHR=3660±1728, JWB=3041±1801; with a significant mean difference in steps from the ACT to the FLX & CHR ($p<0.01$), but not for the JWB ($p=0.35$). Regression of the mean steps to the difference in steps was significant for the FLX, CHR, & JWB to the ACT (all $p<0.05$). Patients had a greater step count on average for non-dialysis days compared to dialysis days. Each device had a significant correlation in steps to the Actigraph (FLX $r=0.84$, $p<0.01$; CHR $r=0.81$, $p<0.01$, JWB $r=0.67$, $p=0.01$). The correlation of light activity (min.) was significant for the FLX ($r=0.72$, $p<0.01$) & CHR ($r=0.67$, $p<0.01$) was significant, but not for sedentary & MVPA activity. Furthermore, the mean difference in light time was not significantly different for the FLX & CHR.

Conclusions: The FLX, CHR, & JWB provided similar step estimates, but each device overestimated steps compared to the Actigraph. The devices provided similar estimates of time spent in light activity, but not sedentary or MVPA activity. It is possible that the algorithms or different positioning of the devices contributed to this discrepancy. Additional studies are needed to confirm these data.

FR-PO807

Effect of Twice Weekly Hemodialysis on Plasma Levels of Uremic Solutes Normally Cleared by Secretion

Sheldon Leong, Natalie Plummer, Timothy W. Meyer, Tammy L. Sirich. *Stanford University/VAMC Nephrology, Palo Alto, AL.*

Background: Current guidelines allow twice weekly hemodialysis (HD) in patients with residual function. They require that patients receive a target standard Kt/V_{urea} (stdKt/V) calculated by combining the residual urea clearance (Kru) with dialytic dose assessed by Kt/V_{urea}. This urea-based calculation does not take into account the native kidney's secretory function. We hypothesized that because secretory function is not replicated by dialysis, plasma levels of normally secreted solutes may be better controlled in patients with residual function on twice (2X) weekly HD than in anuric patients on thrice (3X) weekly HD.

Methods: Dialytic clearance (Kd), residual clearance (Kr), and plasma levels for urea and 4 solutes normally cleared by secretion were measured in patients on 2X weekly HD with average stdKt/V 2.35 ± 0.49. Plasma solute levels were compared to those measured in anuric HEMO Study patients on 3X weekly HD with similar stdKt/V of 2.22 ± 0.24.

Results: Maintenance of secretion in the residual kidney was reflected by higher ratios of residual clearance to dialytic clearance (Kr/Kd) for the secreted solutes than for urea. The plasma levels for indoxyl sulfate, hippurate, and phenylacetylglutamine in the 2X weekly patients were significantly lower than in the 3X weekly anuric patients, while the plasma level for p-cresol sulfate was not different between the two groups (Table).

Conclusions: Residual kidney function removes a larger portion of secreted solutes than of urea. The plasma levels of secreted solutes may therefore be better controlled in patients with residual function on 2X weekly treatment than in anuric patients on 3X weekly treatment receiving the same weekly dose as assessed by Kt/V_{urea}. Consideration of secretory function may allow refinement of prescription guidelines for patients with residual kidney function.

Funding: Veterans Affairs Support

	2X weekly (n=9)				3X weekly (n=469)
	Kd (ml/min)	Kr (ml/min)	Kr/Kd	Plasma (mg/dl)	Plasma (mg/dl)
Urea Nitrogen	235 ± 30	2.8 ± 1.5	0.01 ± 0.01	67 ± 18	60 ± 18
Secreted Solutes					
Indoxyl Sulfate	28 ± 10	1.7 ± 1.4	0.08 ± 0.08	1.9 ± 0.9	2.7 ± 1.3 *
p-Cresol Sulfate	21 ± 8	0.7 ± 0.6	0.04 ± 0.04	4.2 ± 2.1	3.2 ± 1.8
Hippurate	122 ± 33	14 ± 8	0.12 ± 0.09	2.7 ± 2.7	6.0 ± 4.7 *
Phenylacetylglutamine	160 ± 29	10 ± 8	0.06 ± 0.06	2.3 ± 2.4	4.9 ± 3.2 *

(mean±stdev; *$p<0.05$, 2X vs. 3X weekly)

FR-PO808

Healthcare Provider Experiences in Emergent Dialysis of Undocumented Immigrants Areeba Jawed,[2] Alexia Torke,[3] Lucia Wocial.[1] *[1]Indiana University Health, Indianapolis, IN; [2]Wayne State University, Grosse Pointe Woods, MI; [3]Indiana University School of Medicine, Indianapolis, IN.*

Background: No national standards exist for chronic dialysis in undocumented (UD) immigrants posing a unique ethical dilemma for providers. The purpose of this survey was to explore provider perspectives.

Methods: Cross Sectional Internet Survey in April 2016 of Nephrology, ICU, ER, IM, Palliative Care nurses and physicians at a safety-net hospital. The last 4 open ended survey questions were included in this analysis (table 1). All authors individually explored the textual data inductively using an approach based on grounded theory to generate codes and broader themes. Coders then developed a shared code list. All responses were assigned ≥ 1 theme. We then calculated the number of participants with each of the codes.

Results: 299/765 participants completed the survey of which 185 included free texted comments. Nurses comprised 47% of the respondents. 483 responses were coded. The predominant coping mechanisms to moral distress were venting and team approach to patient care. We found that responses to the last 3 questions had overlapping themes. So, these items were coded using the same list of codes. Many participants spoke to the negative consequences of emergency dialysis for UD immigrants. This was noted to have a negative effect on providers, UD patients, other patients and the health system. Emotional and psychological distress was common (73.5%) along with concerns for emergent dialysis causing harm to UD immigrants (38.9%). Although far less common, some providers did note positive consequences of their experience caring for UD patients, most common being taking pride in provider role (13%). Attitudes about the right approach to this issue varied widely with both support (36.2%) for and opposition (7.6%) to dialysis for UD patients. Importantly emotions ran very high among those who supported regularly scheduled 3x\week dialysis and those who opposed dialysis altogether.

Conclusions: Provision of inadequate dialysis causes significant emotional distress in providers with varying attitudes towards the current practice of emergent dialysis. Policies need to be balanced with the strong ethical and moral commitments of providers.

How do you cope with the the Moral Distress that you encounter?
What do you perceive to be consequences of moral distress on you?
What Impact does providing care to UD immigrants have on you?
Please provide any other comments about the care of ESRD patients who are UD immigrants

FR-PO809

Socioeconomic Determinants of Outcomes among Patients Receiving Hemodialysis in India Abhinav Bassi,[1] Vivekanand Jha,[1] Kamal D. Shah,[3] Oommen John,[2] Venkatraman G,[3] Sumathi Kolli.[3] *[1]George Institute for Global Health, New Delhi, India; [2]The George Institute for Global Health, New Delhi, India; [3]NephroPlus Dialysis Centres, Hyderabad, India.*

Background: Dialysis in India is associated with a relatively higher mortality and early dropout when compared to developed countries. Poor clinical outcomes of dialysis patients are associated with socio-demographic predictors that have received limited attention thus far.

Methods: Data from a cohort of 9,058 subjects receiving HD between April 2014 and December 2016 at 92 centres of NephroPlus, India's largest dialysis center network was analysed retrospectively. We retrieved baseline demographics, medical history, treatment cost, dialysis frequency and erythropoiesis stimulating agent (ESA) use from the patient records. Univariate Cox proportional hazards model was used for the calculation of mortality and dialysis discontinuation hazard ratios (HR).

Results: The mean age of the subjects was 51±14 years. Subjects were predominantly male (70%), from metropolitan cities (37%) and paying out of pocket for dialysis (61%). A total of 16% of the subjects died, 46% discontinued dialysis and 37% continued dialysis. Out of the 1494 deaths, 60% and 75% subjects died within the 1st and the 2nd year from their first dialysis, respectively. Of the 4181 subjects discontinuing dialysis, 21% and 76% discontinued within the 1st and the 2nd year from their first dialysis respectively. Subjects younger than 40 years (HR 0.55, 95% CI, 0.47-0.65), residing in a metropolitan city (HR 0.56, 95% CI, 0.49-0.63), undergoing dialysis three times per week (HR 0.91, 95% CI, 0.84-0.98), on erythropoiesis-stimulating agents (ESAs) (HR 0.88, 95% CI, 0.78-0.99) and paying dialysis cost through health insurance (HR 0.89, 95% CI, 0.66-0.90) had lower mortality HR. Subjects not receiving ESAs (HR 2.56, 95% CI, 2.18-3.03) and paying out of pocket for dialysis (HR 1.15, 95% CI, 1.03-1.27) had higher odds of discontinuing dialysis. Gender was not found to be a predictor of outcomes.

Conclusions: The findings of the analysis of the data from this large cohort show high mortality and dropout rates and highlight the associated socio-economic and treatment related factors that will need to be addressed to reduce inequity in dialysis access and improve outcomes in India.

FR-PO810

A Simulation of Demand-Supply Imbalance in Dialysis Care in India Achintya Ray,[2,3] Bhabendra Putatunda.[1] *[1]Nephrology Associates PC, Murfreesboro, TN; [2]Tennessee State University, Nashville, TN; [3]Kidney Clinics and Research Centers International, Inc., Murfreesboro, TN.*

Background: About 10% of India's 1.3 Billion people suffer from Chronic Kidney Disease (CKD). An average of 15% of urban Indian population suffers from CKD. That number rises to 50% for some cities. Demand (CKD/ESRD treatment including dialysis) is growing at a rate of about 31% in India (compared to about 6% in the USA and 8% in the rest of the world.) About 30% of the CKD cases are estimated to be caused by diabetes and about 20% by hypertension. India has over 70 Million diabetes patients, a number that is estimated to double by 2040. A third of the diabetes cases will develop CKD. About 200,000 patients develop ESRD in India per year of which 70%-80% start dialysis treatment while about two-thirds of them are eventually ceasing the treatment due to resource limitations leading to premature death.

Methods: Published studies are used to extract economically meaningful numbers that can be used to draw quantifiable data measuring the demand-supply imbalance. Various projection methods are used to arrive at measures of long-term (through 2035) prevalence in the country for diabetes, dialysis and CKD cases. Furthermore, published studies are used to estimate the lower and upper bounds of CKD prevalence. Sparse evidences are scanned to estimate the number of dialysis centers and machines in different parts of the country and their abilities to meet the current demands. Reasonable assumptions are made to simulate the demand and supply of dialysis treatment based on the upper and lower bounds of the CKD estimates.

Results: About 87% to 93% of the demand for dialysis treatment may not be currently met in India. These estimates may be conservative. It is estimated that about 40,000-68,000 additional dialysis machines may be needed to serve India's current demand. These numbers may increase by 200%-300% by 2035 under various scenarios.

Conclusions: This study is of the first to harness a sparse and widely varying literature on the state of dialysis treatment to make meaningful estimates of demand-supply imbalance in Indian dialysis care market. The sparseness of the existing studies and the gravity of the magnitude of the imbalance point to need for more in-depth studies involving population health and healthcare marketplace data in India.

FR-PO811

Weight Perception in African-American Hemodialysis Patients Varun Gupta,[1] Milda R. Saunders,[2] Rita L. McGill,[2] Michelle A. Josephson.[2] *[1]Creighton University, Northbrook, IL; [2]University of Chicago, Chicago, IL.*

Background: The epidemic of obesity in the United States has been linked to greater risks of cardiovascular disease, diabetes, and kidney disease. However, in dialysis patients, increased body mass index (BMI) is paradoxically associated with better survival, as is African American race. We sought to determine the perception of ideal BMI in African American hemodialysis patients.

Methods: We surveyed African American hemodialysis patients at three dialysis facilities on the South Side of Chicago in June-July 2016. Patients were asked about ideal weight, exercise, eligibility for kidney transplant, and lifestyle. BMI was calculated from measured values. Results were tabulated into a descriptive analysis.

Results: Among 127 patients, 52% were female, and 82% had completed 12 or more years of school. Mean age was 57±16 years. Mean BMI was 28.8±7.3, 32 patients (25%) were overweight, and 50 patients (39%) were obese; proportions did not differ by sex. BMI>38 (our center maximum for transplant eligibility) was seen in 14 (11%). Among patients with normal BMI, 43% perceived a need to gain weight; among overweight patients, 79% wanted to maintain or gain weight (Table). The majority (70%) of obese patients wanted to lose weight.

Conclusions: African American hemodialysis patients perceive BMI of 25-30, which is classified as overweight, to be desirable. Further work is needed to determine whether this weight preference is in part responsible for African Americans' improved hemodialysis survival.

Funding: NIDDK Support

Perceived Need to Lose or Gain Weight, by BMI

BMI Category, n (%)	Should Lose	Should Maintain	Should Gain	Total
Underweight (BMI<18.5)	0	0	3 (100)	3
Normal/Ideal (BMI=18.5-24.9)	1 (2)	23 (55)	18 (43)	42
Overweight (BMI 25-29.9)	7 (22)	20 (63)	5 (16)	32
Obese (BMI>30)	35 (70)	14 (28)	1 (2)	50
Total	43	57	27	127

FR-PO812

Use of Poisson Regression Analysis with Restricted Cubic Splines Facilitates Cross-Sectional Comparisons of Mortality in a Large Provider Antonia Harford,[2] R. Schrader,[1] S. Paine,[1] Ambreen Gul,[1] Philip Zager.[2,1] *[1]DCI, Albuquerque, NM; [2]UNM, Albuquerque, NM.*

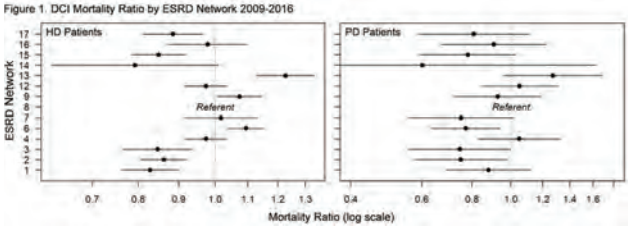
Background: Dialysis Clinic, Inc. (DCI) is a large not-for-profit provider. Assessing mortality across geographic regions served by a large provider is complicated by differences in demographics and local variations in overall healthcare. The use of Poisson regression analysis with restricted cubic splines may facilitate cross-sectional comparisons of mortality that are not influenced by differences in distributions of race, sex, age, vintage and diabetes.

Methods: We assessed mortality for HD and PD patients treated in DCI facilities in different geographic regions across the country for the years 2009 to 2016 combined. We used ESRD Networks to define the geographic regions. We conducted Poisson regression analysis using the rms package in R. Instead of using USRDS categories we used restricted cubic splines, which have flexible shapes, determined by the data. Models contained categorical (race, sex, and diabetes) and continuous (age, vintage, and year) variables. We fit all 2-way interactions among race, sex, diabetes status, and interactions

between age and vintage. Network 8, which has the largest number of DCI patients, was the referent.

Results: Standardized mortality ratios by ESRD Networks for HD and PD patients for the years 2009-2016 are shown. Results are expressed as ratios of mortality within a given Network to that in the referent Network. Among HD patients, clinics in Networks 1, 2, 3, 15, and 17 had lower mortality ratios vs. Network 8. Among PD patients, clinics in Networks 2 and 3 had lower mortality ratios vs. Network 8.

Conclusions: Within DCI there were significant variations in mortality across ESRD Networks for both HD and PD patients. The use of Poisson regression analysis, with restricted cubic splines, facilitates assessing mortality across different geographic regions served by a large provider. This technique provides estimates that are not influenced by demographic differences.



FR-PO813

Efficacy of Percutaneous Etelcalcetide Injection into the Parathyroid Glands on Serum Parathyroid Hormone (PTH) in Hemodialysis (HD) Patients with Secondary Hyperparathyroidism (SHPT): A Pilot Study Satoshi Funakoshi,[1] Takuhisa Uchino,[1] Subodh J. Saggi,[2] Yoko Obata,[3] Tomoya Nishino,[3] Jyunichiro Hashiguchi,[1] Takashi Harada.[1] *[1]Nagasaki Kidney Center, Nagasaki, Japan; [2]SUNY Downstate Medical Center, New York, NY; [3]Nagasaki University Hospital, Nagasaki, Japan.*

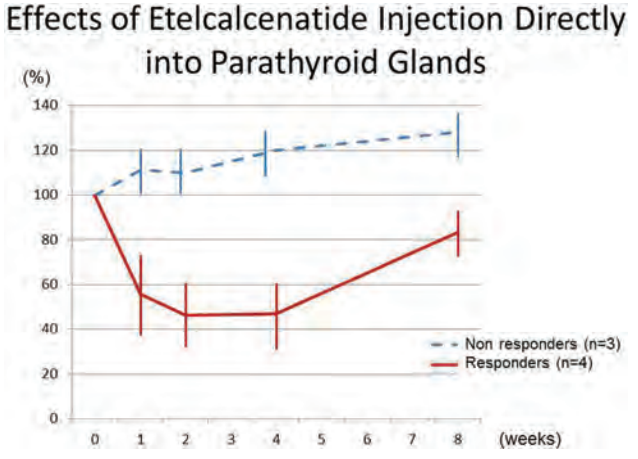
Background: The most popular treatment for SHPT in HD patients is oral administration of cinacalcet in Japan. Nausea and high cost limits its use long term. Etelcalcetide is a novel injectable calcimimetic agent that has a similar mechanism of action as cinacalcet. Direct injection of etelcalcetide into the PTH gland may prove to be cost effective as compared to its systemic administration.

Methods: HD patients with SHPT who complained of nausea while on cinacalcet for >2 years were enrolled in this study after their informed consent was obtained. Cinacalcet was withdrawn from all patients for > 2 weeks, and 1.0ml (2.5mg) of etelcalcetid for 1.25ml gland volume was injected under direst real-time ultrasonographic guidance, and serum PTH was determined for up to 8 weeks.

Results: Seven patients (mean age, 68.4±11.8 years old; median HD duration, 12 years; mean PTH 270.6±155.5 pg/ml; participated in the pilot trial. Four achieved >50% reduction in serum PTH up to 4 weeks as shown in figure. Three patients had no response to this therapy, but their PTH was promptly decreased with systemic etelcalcetide administration, suggesting the presence of undetected hyperactive glands by Ultrasound. Direct administration was safe and not associated with any hematoma or laryngeal nerve paresis as has been reported for direct ethanol injection.

Conclusions: Percutaneous etelcalcetide injection into the parathyroid glands appears to be cost effective, safe, and a superior option for the treatment of SHPT in HD patients.

Funding: Private Foundation Support



FR-PO814

Mortality Prediction in Hemodialysis Patients According to Dietary Protein Intake to Serum Phosphorus Ratio Dana Bielopolski,[1,4] Yoshitsugu Obi,[2] Elani Streja,[1] Kamyar Kalantar-Zadeh.[3] *[1]Harold Simmons Center for Kidney Disease Research and Epidemiology, Orange, CA; [2]University of California Irvine, Orange, CA; [3]University of California Irvine, School of Medicine, Orange, CA; [4]Nephrology and Hypertension, Rabin Medical Center, Petah-Tikva, Israel.*

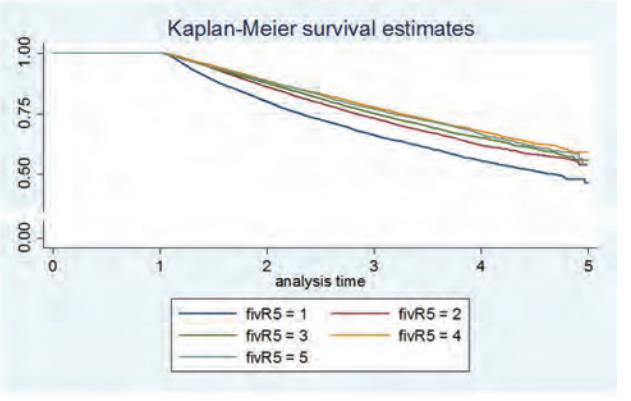
Background: Lowering serum phosphorus (P) in maintenance hemodialysis (MHD) patients may improve survival. However, prior studies have shown that restricting dietary protein intake (estimated by "normalized protein catabolic rate", nPCR), a major source of phosphorus, is associated with higher mortality. We hypothesized that combing these two risks, nPCR and P, in the form of a new score can improve survival prediction.

Methods: Dividing the variables by one another enabled them to influence the metric equally. We divided phosphorus by 5.8, to create nP, so that distribution ranges of the two variables better overlap. Then new metric R, was formulated: R=nPCR/nP Analysis was carried in 63,016 MHD pts, who were followed for 5 years (2007-11). Survival models were adjusted for case-mix and malnutrition-inflammation cachexia syndrome (MICS).

Results: Patients were divided to 5 groups according to R value. Group 1 had high phosphorus and low nPCR, the opposite of patients in group 5. After 1 year follow-up survival difference between groups was according to numerical order. Association of R with mortality was strengthened with adjustment for case-mix variables. Adjusting HR to albumin improved prediction of patients with good prognosis.

Conclusions: The novel protein to phosphorus ratio score can predict mortality in MHD patients and may allow a better phosphorus monitoring while adequate protein intake is ensured.

Funding: Private Foundation Support



Survival estimates according to fivR5 after 1 year 63,016 CEFDIM patients

FR-PO815

Effects of Citrasate® and Citrasate Dry ® on Serum Calcium and iPTH Robert J. Kossmann,[1] Ludmila Anderson,[1] Linda H. Ficociello,[1] Paul Balter,[2] Alice Topping,[2] Claudy Mullon.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Renal Research Institute, New York, NY.*

Background: Citrasate and Citrasate Dry provide hemodialysis dialysates (CD) containing 2.4 mEq of citric acid (citrate) per liter. Citrate binds calcium and is rapidly metabolized in the liver. The objective of this analysis was to explore CD effects on corrected serum calcium (CSC) and iPTH in chronic kidney disease patients on thrice weekly hemodialysis (HD) who were converted from acetate acidified dialysates without citrate (AD) to CD.

Methods: Data for CD treated patients from 18 clinics were analyzed. Mean pre-HD laboratory values for the last three months of AD were compared with mean values for the first three months of CD (paired t-test, McNemar, chi^2, α=.05). Subanalyses were carried out by CSC (<8.4, 8.4-9.5, 9.6-10.2, >10.2 mg/dl) and iPTH (<130, 130-600, >600 pg/ml) ranges during the three months of AD. Changes in concomitant medications (in-center vitamin D [VitD], Cinacalcet, Ca-based phosphate binders [CaPB]) were explored.

Results: In total, 1,321 patients were analyzed. Mean pre-HD values for three months of AD and changes following the CD conversion are summarized in the Table.

Conclusions: On average, CSC decreased -5.6% and iPTH increased +4.4% during the first three months of CD. Subanalyses indicated that observed changes in CSC and iPTH varied according to their range during the last three months of AD. Limitations of the analysis include the cross-sectional nature of our assessment and inability to account for all clinical practices.

Funding: Commercial Support - Fresenius Medical Care North America

	All Patients	AD CSC (mg/dl) <8.4	AD CSC (mg/dl) 8.4-9.5	AD CSC (mg/dl) >9.5<=10.2	AD CSC (mg/dl) >10.2	AD iPTH (pg/ml) < 130	AD iPTH (pg/ml) 130-600	AD iPTH (pg/ml) >600
Number of patients analyzed	1,120	195	742	169	14	60	670	390
AD iPTH (pg/ml)	596.8	646.7	595.9	540.9	624.8	79.2	364.5	1,075.5
CD iPTH Change	+26.1	-17.3	+21.6	+99.8	-16.1	+141.2	+74.9	-75.4
Number of patients analyzed	1,165	202	766	179	18	94	678	393
AD CSC (mg/dl)	8.9	8.0	9.0	9.7	10.6	9.1	8.8	8.9
CD iPTH change	-0.05	+0.2	-0.05	-0.3	-0.7	-0.2	-0.05	-0.01
AD in-center VitD use (%)	78.3	78.0	79.2	76.4	65.1	48.2	78.6	84.5
CD VitD use change	0	+2.8	+0.9	-2.8	-25.9	-3.2	+0.5	+2.1
AD CaPB use (%)	22.5	26.1	22.8	18.3	19.1	28.4	26.3	14.8
CD CaPB use change	+1.0	+4.6	+0.7	-1.5	-4.8	0	+1.2	+0.9
AD Cinacalcet use (%)	29.3	39.9	28.1	24.5	23.8	13.8	24.2	42.7
CD Cinacalcet use change	+2.7	+2.1	+3.0	+2.4	-4.8	-1.0	+2.1	+4.3

FR-PO816

Measured versus Prescribed Dialysate Sodium Using Dialysis Machines from Different Manufacturers Ambreen Gul,[1] Dana Miskulin,[2] Antonia Harford,[3] R. Schrader,[1] S. Paine,[1] Walter L. Bender,[4] Bijin Thajudeen,[5] Philip Zager.[3,1] *[1]DCI, Albuquerque, NM; [2]Tufts Medical Center, Sommerville, MA; [3]UNM, Albuquerque, NM; [4]Dialysis Clinic Inc., Kansas City, MO; [5]University of Arizona, Tucson, AZ.*

Background: The optimal dialysate sodium (DNa) is unknown. We previously reported that differences (measured - prescribed DNa) in facilities using Fresenius and Gambro machines ranged from +13 mEq/L to - 6 mEq/L (mean + 2.5 mEq/L), which may contribute to the disparate results of published studies. We extended these observations by assessing differences in facilities using B. Braun machines.

Methods: We studied 2 DCI facilities that use B.Braun Dialog+ machines with either NaturaLyte or Diasol dialysate. Technicians entered DNa orders into the machine, which were verified by a nurse. We turned on dialysate machines ≥ 30 minutes prior to sampling. We clamped the saline line and sampled dialysate from the dialysate port 10 minutes prior to the start of dialysis in clinics 5 (24 machines, 97 treatments) and 6 (25 machines, 54 treatments). We sampled dialysate 10 minutes prior to end of dialysis in clinics 5 (n=91) and 6 (n=54). The DCI lab measured DNa concentrations with an indirect ion selective electrode. We assessed the differences (measured- prescribed DNa) by computing least square means with a linear mixed model that accounted for random machine effects and repeated measures.

Results: Measured DNa was 3.36 mEq/L (95% CI 2.69 – 4.02) and 1.82 mEq/L (95% CI 1.08 – 2.56) higher than prescribed in Units 5 and 6, respectively. The percentages of DNa measurements within 2 mEq/L of that ordered were 22.2% and 59.5% in Unit 5 & 6, respectively. DNa in late in dialysis was also higher than prescribed in clinics 5 (4.14 mEq/L [95% CI 3.54 – 4.73]) and 6 (1.81 mEq/L, [95% CI 1.15 – 2.47]). Measured DNa in samples drawn pre- and late- dialysis were similar. In clinic 5 26 pairs (28.6%) matched and 67 (73.6%) were within 1mEq/L. Corresponding numbers in clinic 6 were 22 (40.7%) and 47 (87%). The weighted kappa was 0.63 indicating good agreement between pre- and late dialysis DNa.

Conclusions: Measured DNa is higher than prescribed with Fresenius, Gambro, and B.Braun machines. QAPI programs should incorporate measurements of DNa to ensure adherence to the dialysis prescription.

FR-PO817

The Amino Acid Losses Are Lower during Pre-Dilution On-Line HDF Than HD Shunichiro Urabe,[1,2] Yukie Kitajima,[3] Motoko Kato,[1] Asami Kurii,[1] Emi Hiyama,[1] Takashi Hosono,[1] Toru Hyodo,[4] Makoto Kitamura,[4] Miho Hida,[4] Yasuhisa Kurata,[4] Kenichi Kokubo.[5] *[1]Clinical Engeenering, Eijin Clinic, Hiratsuka, Kanagawa, Japan; [2]Kitasato University Graduate School of Medical Sciences, Sagamihara, Japan; [3]Tokyo Healthcare University, Tokyo, Japan; [4]Kurata Hospital & Eijin Clinic, Hiratsuka, Japan; [5]Kitasato University School of Allied Health Sciences, Sagamihara, Japan.*

Background: We analyzed the amino acid losses that occur on performing pre-dilution on-line HDF (O-HDF) and HD because the amino acid kinetics of O-HDF has been unknown until now.

Methods: We compared the total amino acid level, total non-essential/essential/branched-chain amino acid levels, urea/Cr removal amount, reduction rate, and Kt/V (urea) between 10 patients undergoing O-HDF (8 males, 5 diabetic, mean age: 70.5±2.11 years) and 10 patients receiving HD (7 males, 5 diabetic, mean age: 73.6±5.87 years). The mean blood flow rate in the former and latter was 240±20 and 200 mL/min, respectively. The dialysate flow rate was 347±26.4 and 450 mL/min, respectively. The replacement fluid flow rate was 253±26.4 and 0 mL/min, respectively. The replacement fluid volume was 57±6.0 and 0 L, respectively.

Results: In the O-HDF group, the total and total non-essential amino acid losses (6,097±1,507* and 4,070±967* mg, respectively) were significantly lower than in the HD group (9,093±1,965 and 6,529±1,469 mg, respectively) (* $p < 0.01$). Urea and Cr removal amount in the O-HDF group was 12.4±1.48 and 1.59±0.367 g, respectively. In the HD group, the values were 12.5±3.59 and 1.63±0.332 g, respectively. The values showed no significant differences between the O-HDF and HD group. In the O-HDF group, the urea and Cr reduction rates were 65.1±6.68 and 71.2±6.80%, respectively. In the HD group, the values were 64.2±5.95 and 70.6±6.01%, respectively. The values showed no significant differences between the O-HDF and HD group. The Kt/V (urea) values in the former and latter were 1.50±0.289 and 1.49±0.314, respectively; there was no significant difference.

Conclusions: Under the same dialysis dose of Kt/V for urea, the amino acid losses were lower during O-HDF than HD, suggesting that O-HDF is more favorable as a blood purification method from the viewpoint of nutrition.

FR-PO818

Adjustment of Target Weight Based on Absolute Blood Volume Reduces the Frequency of Intradialytic Morbid Events Daniel SCHNEDITZ,[3] Susanne Kron,[1] Til Leimbach,[2] Klemens Budde,[1] Joachim Kron.[2] *[1]Charite Universitatsmedizin Berlin, Berlin, Germany; [2]KfH Kidney Center Berlin-Köpenick, Berlin, Germany; [3]Medical University Graz, Graz, Austria.*

Background: Adequate ultrafiltration (UF) avoiding intradialytic morbid events (IME) remains a core problem in current hemodialysis (HD) therapy. The aim of this study was to investigate the suitability of absolute blood volume (Vs, in mL/kg) to prescribe UF volume and to reduce the frequency of IME.

Methods: Following a 4 week baseline phase to quantify the frequency of IME, volume status was determined in a specified HD study during which relative blood volume (RBV, %) was measured by the blood volume monitor (BVM), Vs was measured using on-line dialysate dilution, and volume overload (Vo, L) was measured using bioimpedance spectroscopy. Symptomatic IME was defined as a drop in systolic blood pressure (PSYS) by more than 20 mmHg, or a PSYS below 90 mmHg, or the occurence of symptoms such as dizziness, light-headedness, sweating, or cramps. Suitability of different variables to discriminate for IME was examined by analysis of receiver-operator-characteristics (ROC-analysis) and calculation of the area under the ROC-curve (AUROC). Target weight was then increased or decreased based on measured Vs, Vo, and occurence of IME, and the frequency of IME was recorded during 4 weeks of follow-up.

Results: 45 patients participated in this study. 22 (49%) patients experienced 66 IME in 12% of HD treatments during baseline. In 15 (33%) patients who experienced IME during the volume assessment study Vs (60.7±4.0 vs. 73.7±11.3 mL/kg, $p<0.001$) and Vo (1.1±0.9 vs. 2.5±1.8 L, $p<0.01$) was lower than in stable patients, while RBV (87.9±4.4 vs. 90.2±4.2%, p=n.s.) was comparable. AUROC was 0.92, 0.80, and 0.61 for Vs, Vo, and RBV, respectively. The sensitivity, specificity, and accuracy of the Vs≤65 mL/kg threshold to predict IME was 87%, 100%, and 91%, respectively. Target weight was increased (+1.5 kg) or decreased (-5kg) in 32 patients. The frequency of IME fell to 0.9% of all HD sessions in the following 4 weeks ($p<0.001$).

Conclusions: Absolute blood volume (Vs, mL/kg) is more accurate in assessing the risk for IME-prone patients than relative blood volume (RBV, %). Adjustment of target weight based on information of Vs, Vo, and IME appears as a feasible approach to reduce the frequency of IME.

FR-PO819

Use of Lung Ultrasonography to Determine the Accuracy of Clinically Estimated Dry Weight in Chronic Hemodialysis Patients Chuan Jiang, Satyam Patel, Andrew A. Moses, Maria V. DeVita, Michael F. Michelis. *Medicine / Nephrology, Lenox Hill Hospital / Northwell Health, New York, NY.*

Background: The use of lung ultrasound (LUS) to identify extravascular lung water has received increasing acceptance. Sonographic B-lines, discrete vertical lines that originate from the pleura, represent pulmonary interstitial edema and are correlated with the accumulation of fluid. The goal of this study was to evaluate the utility of LUS to determine the accuracy of prescribed dry weight (DW) in chronic hemodialysis (HD) patients admitted to our dialysis unit and to ascertain the adequacy of fluid removal.

Methods: LUS was performed pre and post HD in 20 patients. The HD prescription and DW challenge were done independent of the results of the LUS. The presence of B-lines was tabulated and compared to the intradialytic ultrafiltration parameters.

Results: The mean age of the patients was 66.4 ± 13.5 years, with 55% male, and a mean dialysis vintage of 70.2 ± 8.0 months. Of the 20 patients, 3 did not exhibit B-lines at the beginning of the dialysis session. Among the other 17 patients, B-lines disappeared in 7 patients at the end of the HD session (mean B-lines 4.2 to 0). One patient was 0.3kg away from the prescribed dry weight, but the mean variance in the other 6 patients was 1.7kg below the prescribed weight. Of the remaining 10 patients, eight decreased but did not eliminate the B lines (mean B-lines 15.5 to 3.8) and were 3.8kg below DW post HD. Two patients could not reach DW or eliminate the B-lines (mean B-lines 24.5 to 10.0) and were 3.2 kg above DW post HD. Both patients exhibited more cardiac insufficiency than initially recognized. Correlation analysis showed a statistically significant correlation ($P < 0.05$) between the intradialytic percent change in B-lines and the percent change in total body weight ($r = 0.40$) and ultrafiltration rate ($r = 0.33$). Seven of 10 patients with clear chest x-rays pre HD exhibited B-lines.

Conclusions: This study supports the hypothesis that reduction of B-lines during HD can provide accurate information regarding changes in pulmonary fluid content. Further, LUS is an invaluable diagnostic tool for recognizing both the adequacy of fluid removal and the occurrence of error in the estimation of dry weight by usual clinical parameters.

FR-PO820

Use of Lung Ultrasonography for Assessment and Follow Up of Asymptomatic Pulmonary Congestion in Hemodialysis Patients Salah S. Naga. *Nephrology, Alexandria Faculty of Medicine, Alexandria, Egypt.*

Background: Chronic fluid overload is a common problem in ESRD patients on HD. Even asymptomatic lung congestion results in increased cardiovascular morbidity and mortality. Lung ultrasound provides a non-invasive tool to assess fluid overload. The aim of the study was to assess asymptomatic pulmonary congestion using lung ultrasonography and to evaluate the effect of increasing hemodialysis dose on improvement of the lung comet scores.

Methods: One hundred patients were enrolled. Based on ultrasound lung comets (ULC) score, patients were divided into group A (65 patients) with no or mild pulmonary congestion (ULC<14) and group B (35 patients) with moderate to severe (ULC>14). Group B was further subdivided into group B1 (18 patients) who were subjected to intensified HD and group B2 (17 patients) who were maintained on their conventional HD, and both subgroups were followed for three months.

Results: Baseline ULC score showed a significant positive correlation with LAP (r=0.808, p <0.001), LAD (r=0.519, p<0.001), IVCD (r=0.669, p<0.001), SBP (r=0.578, p<0.001) and DBP (r=0.435, p<001) and a strong negative correlation with EF (r=0.542, p<0.001) and inferior vena cava collapsibility index (IVCCI) (r=0.571, p<0.001). After intensified HD, Group B1 showed a significant decrease in the ULC score (25.44±6.13 to 9.17 ± 3.65, p<0.001), left atrial pressure (LAP) (16.22 ± 1.72 to 12.16 ±1.90, p<0.001), left atrial diameter (LAD) (41.33 ± 4.06 to 39.53 ± 2.73, p=0.003), inferior vena cava diameter (IVCD) (12 .65 ± 1.74 to 9.86 ± 1.61, p<0.001), SBP (146.67 ± 17.15 to 130.0 ± 12.83, p<0.001) and DBP (87.22 ± 6.96 to 82.22 ± 4.28, p=0.001) in comparison to group B2.

Conclusions: The present study demonstarted that lung ultrasonography guided intensified HD dose improved patients lung comets score, LAP, LAD, IVCD, IVCCI and blood pressure. ULC monitoring is an easy tool to detect asymptomatic lung congestion and allows tailoring dialysis to treat it.

FR-PO821

Intradialytic Hemodynamics and Cerebral Perfusion Dawn F. Wolfgram. *Zablocki VA Medical Center, Milwaukee, WI.*

Background: Persons with end-stage renal disease on hemodialysis (HD) have significant cerebral ischemic disease and atrophy noted on brain imaging. Hemodynamic instability during HD may lead to cerebral hypo-perfusion and resultant ischemic injury. Risk of cerebral hypo-perfusion may be higher in a subset of HD persons with increased drop in blood pressure during HD. We sought to describe the changes in cerebral perfusion during HD and the relationship to changes in intradialytic blood pressures (BP) in a cohort of HD patients.

Methods: We used a clinically validated method of continuous cerebral oximetry monitoring as a marker of cerebral perfusion during HD. Demographic variables and co-morbidities were collected on each participant, along with hemodialysis variables of intradialytic BP, fluid removal and duration of HD session. Descriptive statistics and linear regression analysis was used to analyze the data.

Results: Thirteen participants were enrolled with 11 participants completing the study and included in the analysis. The mean (SD) age was 66.8 (7.7) years. All participants had hypertension and 73% had diabetes. Diabetes was the cause of ESRD in 55% of participants. The mean (SD) change in cerebral oximetry during HD was -3.5% (2.6). In participants with greater than 20mmHg drop in SBP during HD (n= 7) the mean (SD) change in cerebral oximetry was -4.1% (3.2) vs -2.6 (0.8) in those with less than 20mmHg drop in SBP (p = 0.39). In participant with diabetes the mean (SD) change in cerebral oximetry was -4.2 (3.2) vs -2.3 (1.3) in participants without diabetes (p = 0.24). In participants with both diabetes and a greater than 20mmHg drop during dialysis there was a change in cerebral oximetry of -5.1 (3.1) vs -2.2 (1.3) in participants not meeting both criteria (p = 0.06). In four participants there was a significant association between SBP and cerebral oximetry during HD.

Conclusions: On average cerebral oximetry declines during HD and in some participants the decline may be related to drop in systemic BP during HD. Greater intradialtyic drop in BP in the setting of diabetes may increase risk of cerebral hypo-perfusion and ischemic injury. Analysis of our data was limited due to small sample size and increase in participant number is needed to determine the relationship between changes in intradialytic blood pressures and cerebral oximetry.

Funding: Private Foundation Support

FR-PO822

Evaluation of Intradialytic Hypertension Using Bioelectrical Impedance Combined with Echocardiography in Maintenance Haemodialysis Patients Hongqi Ren. *National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China.*

Background: Although intra-dialytic hypertension(IDH) has been noted in clinical setttings for many years, its pathogenesis remains unclear. In this cross-sectional study, we aimed to analyze IDH incidence in our center and the correlation between postdialysis volume state and IDH.

Methods: 131maintenance haemodialysis (MHD) patients were enrolled in our study with bioelectrical impedance (BIA) and echocardiography (ECG) recorded. Demographic data was collected and laboratory examination was conducted. The patients were grouped into four groups according to the changes of systolic blood pressure (SBP) between postdialysis and predialysis.

Results: The incidence of IDH was10.7%. The proportion of extracellular water to total body weight (ECW/TW) evaluated by BIA, in the IDH group was significantly higher than those of the other three groups both in pre-and post- dialysis comparison. In particular, postdialysis SBP was highest in the highest tertile interval of ECW/TW. In addition, left ventricular volume (LVV) in the IDH group was the highest among all four groups. By binary logistic analyses, we found that predialysis SBP, postdialysis ECW/TW and LVV were independent risk factors of intradialytic hypertension. When predicting the probability of ECW/TW combined with LVV, ROC curve showed a AUC (0.752, 95 % CI was 0.613-0.896)was higher than the LVV and ECW/TW alone.

Conclusions: In this study, we found that the volume expansion of ECW and intravascular compartments after the dialysis measured by the combination of bioelectrical impedance and echocardiography in patients with MHD. Our study further showed that post-dialysis volume expansion is an important factor for the development of IDH.

Funding: Government Support - Non-U.S.

FR-PO823

Baseline Muscle Strength, Dry Weight, and Physical Activity Are Associated with Muscle Strengthening of Lower Extremities after 6-Month Resistance Training in Patients with Maintenance Hemodialysis Yoshifumi Moriiyama,[2] Sae Aratani,[3] Masahiko Hara,[4] Hideaki Ishikawa.[1] *[1]Konan Kosei Hospital, Konan, Japan; [2]Nagoya kyoritsu hospital, Nagoya, Japan; [3]Nippon Medical School Hospital, Tokyo, Japan; [4]Osaka City University Graduate School of Medicine, Osaka, Japan.*

Background: Rapid muscle wasting is a common complication in patients with maintenance hemodialysis, and it is associated with the risk of pratfall as well as with poor quality of life and survival.

Methods: We included 271 patients who underwent 6-month resistance training program during hemodialysis. Primary outcome measure was change in percent knee extension muscle power to body weight (pKEMP-BW; mean of right and left) during 6-month. We divided our patients into 2 groups; improve vs deteriorate groups. Multivariable logistic regression model was employed to evaluate parameters which are associated with improvement of pKEMP-BW at 6-month, using indices shown in the Table as explanatory variables such as baseline pKEMP-BW or short physical performance battery (SPPB).

Results: Median age was 71 (quartile 64-77) years old, 144 patients (53.1%) were men, and median dry weight was 54.2 (47.5-61.6) kg. After 6-month training, pKEMP-BW was improved in 177 patients (65.3%), and pKEMP-BW changed from 42.0 (32.4-52.3) % to 43.4 (34.8-55.0) % in total (p<0.001). As shown in the Table, baseline lower dry weight, higher handgrip, lower pKEMP-BW, and higher SPPB were associated with an improvement of pKEMP-BW at 6-month.

Conclusions: Six-month resistance training improved pKEMP-BW. Baseline lower dry weight, higher handgrip, lower pKEMP-BW, and higher SPPB were associated with an improvement of pKEMP-BW at 6-month in patients with maintenance hemodialysis.

	Standard Multivariable Model		Akaike Information Criterion Model	
Parameter	Adjusted odds (95% CI)	p-value	Adjusted odds (95% CI)	p-value
Age, years old	0.99 (0.96-1.03)	0.664	---	---
Male	1.22 (0.54-2.79)	0.632	---	---
Dry weight, kg	0.95 (0.92-0.98)	0.002	0.95 (0.92-0.98)	0.002
Handgrip, kg	1.08 (1.02-1.14)	0.011	1.08 (1.03-1.14)	0.003
pKEMP-BW, %	0.92 (0.89-0.95)	<0.001	0.92 (0.89-0.95)	<0.001
SPPB	1.23 (1.07-1.42)	0.005	1.22 (1.06-1.40)	0.004

FR-PO824

Urea Clearance Modelling Using 300 ml/min of Dialysate Flow J. Ken Leypoldt,[1] Sarah S. Prichard,[3] Glenn M. Chertow,[2] Luis Alvarez.[1] *[1]None, Menlo Park, CA; [2]Stanford University School of Medicine, Palo Alto, CA; [3]Outset Medical, San Jose, CA.*

Background: High dialysate flow rates (Q_D) of 500-700 mL/min are generally used in the outpatient setting to maximize urea removal in a time efficient manner. Lower dialysate flows of 100-200 mL/min are often employed in critically ill patients and in patients at high risk of dialysis disequilibrium. There are few data describing the use of a mid-rate Q_D (300mL/min) in a modern outpatient dialysis setting. We present urea kinetic modeling of 300 mL/min dialysate flow rates and investigate differential urea clearances between 300 and 500 mL/min Q_D.

Methods: Urea kinetic models were used to predict urea clearances at 300 mL/min dialysate flows. Using the FHN trial group urea model assumptions in combination with published dialyzer characteristics (KoA), a weekly urea concentration profile was obtained. The model was then applied to patients of different weights and volumes of distribution (VOD) at blood flows (Q_B) of 400 mL/min. Finally, a clearance relationship for spKt/V of 300 vs. 500 mL/min Q_D was obtained.

Results: Table 1 shows modelled spKt/V when Q_D is 300mL/min or 500 mL/min at the same Q_B of 400 mL/min. Across VOD, the model demonstrates a Q_D of 300 mL/min results in a predicted spKt/V that meets urea clearance targets. There was a small difference in spKt/V between a Q_D of 300 mL/min and 500 mL/min Q_D. Use of a larger KoA (LKoA) dialyzer and 15 minutes of additional time narrows the spKt/V difference.

Conclusions: A Q_D of 300mL/min can be expected to achieve urea clearance targets. Decreasing dialysate flow rate to 300 mL/min results in a modest, but clinically insignificant, spKt/V difference. For patients with clearance challenges at 500mL/min Q_D, the use of a 300 mL/min Q_D with a larger KoA dialyzer and incremental time can be considered, which may itself allow for lower rates of ultrafiltration and better-tolerated hemodialysis therapy.

Funding: Commercial Support - Outset Medical Inc

Table 1: Calculated spKt/V

Dialysate Flow (mL/Min)	500	300	300
Dialyzer	Standard Dialyzer	Standard Dialyzer	LKoA Dialyzer + 15 min
VOD=25L, Treatment Time=180 minutes	1.68*	1.46	1.60
VOD=30L, Treatment Time=210 minutes	1.64	1.42	1.56
VOD=30L, Treatment Time=240 minutes	1.84	1.59	1.72
VOD=35L, Treatment Time=240 minutes	1.61	1.39	1.51

*spKt/V

FR-PO825

In-Vitro Dialysis Clearances Using Dharma, the EasyDial Portable Hemodialysis Machine Timothy R. Mcnamara,[2] Osman S. Khawar,[1] Sarah L. Foster.[2] *[1]Balboa Nephrology Medical Group, Escondido, CA; [2]EasyDial, Irvine, CA.*

Background: Dharma is a unique, fully portable dialysis machine, which uses only 5 Liters of dialysate during each treatment. To determine the efficacy of Dharma in clearing blood waste products, in-vitro dialysis tests were run utilizing bovine blood.

Methods: Twenty-three treatments were conducted and all met the defined parameters of an effective dialysis over 90 – 120 minutes. A common protocol was utilized. Amendments were made for differences between studies inclusive blood flow rates, dialysate, reinfusion solutions and rates. Dharma machines were prepared with consumables (dialyzer, blood and dialysis circuit cassettes, blood and dialysate lines) and primed. Five liters of dialysate were added to a reservoir and warmed to 37 degrees centigrade. Five liters of bovine blood was spiked with urea, creatinine, potassium, calcium, magnesium and glucose to levels commonly found in dialysis patients. The blood was added to a vessel connected to the arterial line through a 16-gauge needle or a 10 French catheter. Treatments were run by dialysis technicians. Serum samples for waste products were collected at baseline, every 15 minutes and at the end of dialysis. Dialysate pH and conductivity were monitored.

Results: Desired clearances of waste products was achieved at all timepoints (Table 1). Mean clearances were: BUN 77.1% (126.3 mg/dL (±26.4) to 28.93 mg/dL(±6.89), creatinine clearance 88.9% (15.9 mg/dL (±4.2) to 1.76 mg/dL (±0.89) and urea clearance was of 77.5% (225.5mmol (±47.2) to 50.74 mmol (±19.03). Clearances for waste products were greater than 70% at all timepoints and were greatest in the 120-minute treatment group for BUN (78.6%), creatinine (89.5%) and urea (78.7%).

Conclusions: These results verify in-vitro efficacy of Dharma in dialysis treatments. Dharma offers the unique features of portability (18 lbs.), no fixed water connection (5 L dialysate) and the possibility for significantly reducing dialysis treatment times. These features may allow for improving the quality of life and reducing the burden of illness in ESRD patients on dialysis.

Funding: Commercial Support - EasyDial Inc

BUN, Creatinine and Urea Clearances

	Overall efficacy (n=23)	Clearance %	90 minute efficacy (n=6)	Clearance %	120 minute efficacy (n=17)	Clearance %
	Baseline / End of Treatment		Baseline / End of Treatment		Baseline / End of Treatment	Clearance %
BUN (mg/dL)	126.3 (+/- 26.4) 28.93 (+/- 6.89)	77.09%	101.5 (+/- 15.86) 26.3 (+/- 15.8)	79%	133.06(+/-6.89) 15.97 (+/-0.89)	78.06%
Creatinine (mg/dL)	15.9 (+/- 4.2) 1.76 (+/- 0.89)	88.9%	12.51 (+/-4.68) 1.96 (+/- 0.86)	87.7%	15.97(+/-4.12) 1.67 (+/- 0.89)	89.54%
Urea (mmol)	225.5 (+/- 47.2) 50.74 (+/- 19.3)	77.5%	181.23 (+/- 23) 44.04 (+/- 30.05)	75.7%	236.76 (+/-16.46) 50.31 (+/-12.3)	78.73%

FR-PO826

African American ESRD and Medication Adherence: What Are the Effects of Everyday Racism? Tamara Savage. *Social Work, UNC Pembroke, Pembroke, NC.*

Background: Poor medication adherence leads to increased hospitalizations, morbidity, and mortality in end-stage renal disease (ESRD) patients. African American ESRD patients have poorer rates of medication adherence when compared to Whites. Studies have not investigated the impact of broader social issues such as everyday racism on this racial disparity. This is the first study to explore how everyday racism within the healthcare system contributes to this disparity in medication adherence. A mixed methods study was conducted to investigate the relationship between everyday racism and medication adherence within the African American ESRD community.

Methods: Primary data were collected from 46 African American ESRD patients. All participants completed a questionnaire comprised of demographic information, a medication adherence survey, and an everyday racism in the healthcare setting survey. Additionally, 27 of the total sample (N=46) participated in in-depth interviews which lasting approximately one hour. Participants were recruited from attendees at two patient-centered meetings in Greensboro, NC and Nashville, TN. Pearson's Correlation was used to analyze quantitative data and Constructivist Grounded Theory was used to identify themes that emerged from interview transcripts.

Results: A statistically significant negative relationship was found between medication adherence and everyday racism in the healthcare system (r = -.477, p < .01). As everyday racism increased, medication adherence decreased. Furthermore, interviews revealed that everyday racism perpetuated within the healthcare system negatively affected participants' medication adherence. Three themes were identified: 1) Concern that medical providers were not knowledgeable about the medications they were prescribing 2) Concern that the medication was not safe 3) Information about medication and lab results withheld or given to participants without further consultation.

Conclusions: These findings provide the basis for development of future research that could lead to interventions with healthcare systems and professionals to address the medication adherence disparity.

Funding: Private Foundation Support

FR-PO827

Methylguanidine in Normal Subjects and ESRD Patients Ahmed Z. Alkhathlan,[1] Xin Hai,[2] Mirela A. Dobre,[2] Timothy W. Meyer,[3] Thomas H. Hostetter.[2] *[1]University Hospitals Case Medical Center, Beachwood, OH; [2]Case Western Reserve University, Cleveland, OH; [3]Stanford University, Palo Alto, CA.*

Background: Methylguanidine (MG), a guanidino compound, is a small water-soluble solute that accumulates in uremic patients and has been implicated in some uremic toxicities. We studied the behavior of MG in end-stage renal disease patients on chronic dialysis compared to normal controls.

Methods: We studied six normal controls and seven chronic hemodialysis patients. Blood and 24-hour urine samples collected from the control group; while blood and dialysate samples were collected from the dialysis group (start, mid, and end of dialysis sessions). Urea, creatinine (Cr), and MG were measured by a LC-MS/MS method. Mean levels, clearance, and production/excretion rates were calculated assuming first order kinetics, and statistical methods (Student's t test, Pearson correlation coefficient) were used for data analysis. Results are expressed as mean ± standard deviation (SD).

Results: The mean predialysis plasma MG level in chronic dialysis subjects was significantly higher (more than 100-fold) than in the control group (5.17 ± 2.61 vs. 0.047 ± 0.01 μM, respectively; P = 0.0005). In comparison, the mean predialysis urea level was only three-fold the normal level (44.05 ± 23.06 vs. 14.89 ± 3.23 mg/dL, respectively; P = 0.02), and Cr was 13-fold the normal level (10.8 ± 3.1 vs. 0.83 ± 0.18 mg/dL, respectively; P = 0.0001). The mean production rates of MG were 47.12 (± 13.6) and 4.21 (± 3.4) μmol/day in chronic dialysis patients and healthy individuals, respectively (P < 0.05). The effective clearance rates for urea and Cr in dialysis patients were 239 (± 69) and 173 (± 51) ml/min, respectively; which were significantly higher than the effective clearance rate for MG 122 (± 26) ml/min (P < 0.05).

Conclusions: MG accumulates to more than 100 fold the normal level in ESRD patients. This accumulation likely reflects 1) its clearance rate (and therefore its reduction ratio) is significantly less than that of urea and Cr, which is likely due to its previously described large distribution volume, and 2) increased production from Cr oxidation.

Table 1. Solute Plasma Levels, Clearance and Excretion Rates in Controls and ESRD Patients

	Plasma Levels a				Clearance b		Excretion/Removal c	
Solute	UN d (mg/dl)	Cr (mg/dl)	MG (μM)	Urea (ml/min)	Cr	MG	Urea (g/day)	MG (μmoles/day)
Normal (n=6)	14.89 ± 3.23	0.83 ± 0.18	0.047 ± 0.013	55.19 ± 13.75	119.07 ± 22.03	68.09 ± 62.07	24.89 ± 6.24	4.6 ± 4.2
ESRD (n=7)	44.05 ± 23.06	10.8 ± 3.1	5.17 ± 2.61	238.83 ± 69.4	173.04 ± 51.1	122.53 ± 26.5	12.65 ± 6.62	47.12 ± 18.35

FR-PO828

Capturing and Reporting Performance Measures for Chronic Hemodialysis Care: The Veterans Health Administration (VHA) Dialysis Dashboard Experience Michael J. Fischer,[2,4] Karen Sovern,[1] Susan T. Crowley.[3] *[1]Department of Veterans Affairs, Cincinnati, OH; [2]University of Illinois Hospital and Health Sciences Center, Chicago, IL; [3]Veterans Health Administration, West Haven, CT; [4]Jesse Brown VAMC and Hines VA Hospital, Chicago, IL.*

Background: End-stage renal disease (ESRD) is a common, burdensome, and costly chronic condition among Veterans. Assessment and improvement of the quality of Veteran chronic hemodialysis (HD) care is a VHA goal. However, VHA has historically been reliant on external vendors to provide assessments of chronic VHA HD facility-level performance and to meet stakeholder requests for quality reports.

Methods: The VHA National Kidney Program began a process of leveraging multiple kidney disease and dialysis informatics initiatives to build an internal kidney disease surveillance system in 2012. A four step process was used to develop and implement a national VHA Dialysis Dashboard for capturing and reporting of clinical performance measures (PMs) for approximately 3000 Veterans at 71 VHA HD facilities. This electronic dashboard is accessible by VA operations and clinical dialysis staff for quality assurance and improvement activities.

Results: First, the assembly of a diverse stakeholder committee was required to achieve broad consensus for PMs and ensure acceptance in the field. Second, a process for conducting an environmental scan of existing ESRD/HD PMs and vetting was developed. Through teleconference discussions and web-based voting on 78 PMs from recognized

reference organizations, 11 mature facility-level PMs were selected that encompass dialysis adequacy, vascular access, anemia, mineral metabolism, and infection. Third, collaboration across different VHA service lines proved essential to create this dashboard, which leveraged the VA electronic medical record and data warehouses, and created a web-based application for field reporting. Fourth, a coordinated series of national rollout calls, pilot testing, and user acceptance testing was essential for final implementation. The Dashboard was fully implemented in 2013, and by 2016 there was 100% VA dialysis facility participation and 96% usable records for PMs.

Conclusions: The VHA Dialysis Dashboard is a versatile surveillance and reporting tool to provide national and facility level assessment of the quality of chronic dialysis care, to guide and motivate high quality care, to target quality improvement efforts at a facility level, and to provide an atmosphere for promoting a cohesive approach to process improvement efforts at a national level.

Funding: Veterans Affairs Support

FR-PO829

Protein-Bound and Large Toxin Removals between Hemodialysis Using High Cut-off Dialyzers with Adsorptive Cartridge and High-Efficiency Online Hemodiafiltration: A Crossover Randomized Controlled Trial Nutchaya Khemnark,[1,2] Khajohn Tiranathanagul,[1,2] Maneerut Limjariyakul,[1] Supeecha Wittayalertpanya,[1] Paweena Susantitaphong,[1,2] Somchai Eiam-Ong,[1,2] Kearkiat Praditpornsilpa.[1,2] *[1]Chulalongkorn University, Bangkok, Thailand; [2]King Chulalongkorn Memorial Hospital, Bangkok, Thailand.*

Background: Protein-bound toxins especially indoxyl sulfate (IS) which could not be removed by standard hemodialysis (HD) using high-flux dialyzer are obviously correlated with high mortality in HD patients. High-efficiency online hemodiafiltration using high-flux dialyzer (OL-HDF) has been reported to enhance IS removal and improve patient survival. At present, there are certain limitations of OL-HDF including necessity for special machine and high investment cost. Therefore, we proposed a new HD modality which can be performed in any HD centers with standard HD machine by using high cut-off (HCO) dialyzer, PES-17Dα (Nipro, Japan) in combination with hemoperfusion (HP) using HA130 adsorptive cartridge (Jafron, China) and compared with OL-HDF.

Methods: This was a cross-over randomized control trial. Ten chronic hemodialysis patients were randomized to consecutively undergo dialysis with either new HD modality (HCO HD with HP) or OL-HDF before cross-over to the other modality for 8-week each period. The efficacy including percentage reduction after dialysis of IS, β2 microglobulin (β2m) and urea were assessed. Patient safety and dialysate albumin loss were monitored. IS was measured by high performance liquid chromatography.

Results: The plasma IS levels significantly decreased in both treatment modalities. The percentage reduction of IS were comparable between HCO HD with HP and OL-HDF (52.0±11.7 vs. 56.3±7.5 %, p=0.28). The percentage reduction of β2m did not differ (83.7±4.9 vs. 84.0±4.3 %, p=0.75). Two techniques provided adequate small solute removal. Although the dialysate albumin loss was significantly higher in HCO HD with HP than OL-HDF (4.2±2.4 vs. 0.5±0.8 g/session; P=0.008), there were no significant long-term changes in serum albumin levels of both modalities.

Conclusions: Standard HD using HCO dialyzer with HP using adsorptive cartridge, which could be performed in any HD centers, can effectively remove IS, β2m, and small toxin in comparable with high cost OL-HDF and could replace OL HDF where it is unavailable.

FR-PO830

Renal AA-Amyloidosis in Dialysis-Dependent Drug Addicts Camilla Madsen, Ingjerd W. Manner, Helga Gudmundsdottir. *Oslo University Hospital, Ulleval, Oslo, Norway.*

Background: A substantial increase of dialysis-dependent injecting drug abusers has been observed in Oslo, Norway. The incidence in other parts of the country is low. Longstanding chronic skin infections caused by subcutaneous administration ("skin popping") of illicit drugs, when the intravenous route is exhausted may induce AA-amyloidosis. The kidneys are the organs most frequently affected. Renal AA-amyloidosis is characterized by nephrotic syndrome and progression to end stage renal disease and the prognosis is poor. The diagnosis can only be confirmed by tissue biopsy. The prevalence of hepatitis B, C and HIV in this population of patients tends to high.

Methods: Retrospective investigation including all patients with past or present injecting drug abuse who started dialysis between January 2005 and June 2017 in the city of Oslo, Norway.

Results: A total of 46 injecting drug addicts were included in the study. All patients were Caucasian, 70% males, mean age was 50.2 ± 8.3 years and they had been injecting drug addicts for 27.3 ± 9.2 (range 9-47) years). A total of 54.3% were crash landers (i.e. referred within 4 months of requiring dialysis). Renal biopsy was performed in 34 patients (74%), and AA-amyloidosis was confirmed in all but one patient. All patients were positive for anti-hepatitis C virus antibodies, and 4.3% were HIV infected. All had a history of repeated chronic suppurative skin infections. All had ongoing drug abuse and all had been offered medication-assisted therapy. No patients fulfilled criteria for renal transplantation due to chronic infections and ongoing drug abuse. The prognosis after starting dialysis was poor with 34% mortality in 1 year. As of today, 16% of our dialysis population are past or present injecting drug addicts with renal failure caused by renal amyloidosis.

Conclusions: Renal AA-amyloidosis is the most common cause of end stage renal disease in injecting drug addicts in Oslo. Morbidity and mortality is high. It is a challenging and complex population without the option of transplantation. More focus is needed on prevention and early intervention.

FR-PO831

Effect of Different Dialysis Procedures on Mid-Term Protein-Bound Toxins Plasma Levels Detlef H. Krieter,[1] Simon Kerwagen,[1] Marieke Rueth,[2] Horst-Dieter Lemke,[2] Christoph Wanner.[1] *[1]University Hospital, Wuerzburg, Germany; [2]eXcorLab GmbH, Obernburg, Germany.*

Background: Protein bound uremic toxins (PBT) are involved in dialysis associated morbidity. If dialysis procedures differ in their effect on PBT plasma levels over longer periods has barely been studied. Purpose of the present trial was to monitor PBT plasma levels over a 6-week period in patients on different extracorporeal dialysis forms.

Methods: In a prospective, randomized, controlled, cross-over trial enrolling 15 maintenance dialysis patients (*DRKS00010788*), low-flux and high-flux hemodialysis (HD) were compared to high convective volume (≥25 L) postdilution hemodiafiltration (HDF). Each patient was subjected thrice weekly to each treatment mode for 6 consecutive weeks. Dialysis membrane material was always identical (PUREMA® L and H, resp.). Dialysate flow rates differed in HD and HDF (500 vs. 700 mL/min). Blood flow rates and treatment time were kept identical for individual patients. Plasma levels of free and total para-cresyl sulfate (pCS) and indoxyl sulfate (IS) were determined at baseline (t0), after 3 (t3) and 6 weeks (t6) of each treatment period. Reduction ratios were measured at t0 and t3. Serum CRP and albumin were also monitored.

Results: During HDF, plasma concentrations of total IS decreased from t0 (18.9±13.0 mg/L) to t3 (16.6±12.1 mg/L, P=0.027). Total IS levels at t0 and t3 during HDF were lower compared to low-flux HD (20.8±14.4 mg/L, P=0.046, and 20.0±12.7 mg/L, P=0.021, resp.), but did not differ from high-flux HD (20.1±12.6 and 19.3±11.6 mg/L). Total IS reduction ratio in HDF (t0, 48.1±9.6; t3, 46.0±18.3%) were much higher (P<0.001) compared to low-flux (36.5±10.7; 34.3±8.2%) and high-flux HD (35.9±8.7; 37.0±10.5%). Although, reduction ratios for free IS and pCS as well as for total pCS were also significantly higher in HDF, no differences in these PBT plasma levels were determined. Interestingly, free and total IS concentrations highly correlated with CRP (r 0.378 and 0.520, resp.; each P<0.001), but not with albumin.

Conclusions: Differences in instantaneous removal by dialysis therapies have only limited impact on mid-term plasma levels of PBT. The association of inflammation and IS further indicates that other factors are more important determinants of PBT concentrations.

Funding: Commercial Support - 3M Deutschland GmbH

FR-PO832

Plasma Total Matrix Gla Protein, Vitamin K Levels, and Vascular Calcification in Prevalent Hemodialysis Patients Sonoo Mizuiri,[3] Yoshiko Nishizawa,[3] Kazuomi Yamashita,[3] Kohji Usui,[1] Chie Tanji,[1] Shigehiro Doi,[2] Takao Masaki,[2] Kenichiro Shigemoto.[3] *[1]Ichiyokai Ichiyokai Clinic, Hiroshima, Japan; [2]Hiroshima University Hospital, Hiroshima, Japan; [3]Ichiyokai Harada Hospital, Hiroshima, Japan.*

Background: Hemodialysis (HD) patients suffer from accelerated vascular calcification. Vitamin K-dependent matrix Gla protein (MGP) is a potent inhibitor of vascular calcification but published data on plasma MGP levels of HD patients are inconsistent. This study investigated the associations between the plasma total MGP level and the vitamin K level or vascular calcification in HD patients.

Methods: Subjects were 73 prevalent HD patients aged≤60 years and 40 healthy controls. Plasma total (including inactive) MGP levels were assessed using an ELISA kit (Cloud-Clone Corp). Predictors of the plasma MGP level in patients were identified by regression analyses [variables: age, presence of diabetes, presence of cardiovascular disease, dialysis vintage, Agatston (coronary artery calcification) score, serum phosphate, calcium, intact parathyroid hormone, vitamin K1, and vitamin K2 levels, Kt/Vurea, and geriatric nutritional risk index (GNRI)]. The variables that displayed significance in the univariate analyses were subjected to multiple regression analysis.

Results: The healthy subjects' mean estimated glomerular filtration rate was 78±13 ml/min/1.73m^2. The HD patients' (including 25 patients with diabetes) median dialysis vintage was 78 (36-152) months. The age (50±6 vs.48±6 years), sex distribution, and body mass index and vitamin K2 levels were not significantly different, but the vitamin K1 levels were significantly lower (0.56±0.37 vs. 0.98±0.61 ng/ml, P<0.0001), and the MGP levels were significantly higher (290±50 vs.160±41 ng/ml, P<0.0001) in HD patients as compared to controls. Regression analyses indicated that age, dialysis vintage, presence of cardiovascular disease, vitamin K1 level, and GNRI were significantly associated with the MGP level [β (95% CI): 0.35 (2.11-6.52), P<0.001, 0.25 (0.01-0.23), P<0.05, 0.28 (2.79-27.15), P<0.05, -0.28 (-70.01--14.56), P<0.05, -0.25 (-4.36--0.18), P<0.05, respectively]. In the multiple regression analysis, only presence of cardiovascular disease was found to be significantly associated with the MGP level [β (95% CI): 0.24 (0.58-24.77), P<0.05].

Conclusions: HD patients had lower vitamin K1 levels than healthy subjects, and the plasma total MGP level is significantly associated with cardiovascular disease, but not the Agatston score, in HD patients.

Funding: Private Foundation Support

FR-PO833

Trends in Emergency Hospitalization for Cardiovascular and Infectious Diseases between Hemodialysis and Peritoneal Dialysis over 20 Years Masataka Banshodani, Hideki Kawanishi, Misaki Moriishi, Sadanori Shintaku, Shinichiro Tsuchiya. *Tsuchiya General Hospital, Hiroshima, Japan.*

Background: In hemodialysis (HD), volume and electrolyte status drastically change, whereas peritoneal dialysis (PD) is a continuous dialysis and thus maintain a stable volume and electrolyte status. However, no studies have evaluated trends of hospitalization for cardiovascular diseases (CVDs) and infectious diseases (IDs) according to dialysis modality over time.

Methods: This is a retrospective observational cohort study that evaluated 13,078 hospitalizations (1,955 HD and 497 PD patients with end-stage renal disease) to clarify associations between dialysis modality and emergency hospitalization for CVDs (HD, 1,704; PD, 261 times) and IDs (excluding PD-related infections; HD, 970; PD, 132 times) at a single institution over 20 years (1995–2014).

Results: The CVD hospitalization rate (per 100 person-years) in PD remained at the same level over 20 years (1995–1999, 2000–2004, 2005–2009, 2010–2014; 9.7, 6.5, 10.5, and 7.2, respectively), while in HD, the rate decreased (15.4, 8.3, 5.7, and 6.3; every $P < 0.001$, v.s. 1995–1999). The ID hospitalization rate in PD decreased in the last 5 years (5.0, 5.0, 5.4, and 2.5, respectively; $P = 0.001$, 2005–2009 v.s. 2010–2014). In HD, the rate increased (5.9, 3.9, 3.8, and 5.4; $P < 0.001$, 2005–2009 v.s. 2010–2014). In the logistic regression analyses, the odds of dialysis vintage (odds ratio [OR], 3.58; confidence interval [CI], 2.25–5.77; $P < 0.001$) and HD (OR, 2.04; CI, 1.57–2.68, $P < 0.001$) were significantly higher for CVD hospitalization in the first 10 years, but the significances disappeared in the last 10 years. Although no significance was found in first 10 years, the odds of male sex (OR, 1.27; CI, 1.08–1.51, $P = 0.004$) and HD (OR, 1.52; CI, 1.19–1.96, $P < 0.001$) were significantly higher for ID hospitalization in the last 10 years.

Conclusions: The risk of CVD hospitalization was significantly higher in HD than in PD in the first 10 years, but the risk disappeared in the last 10 years. However, the increased risk of ID hospitalization in HD should be solved. Further multicenter studies are needed to compare hospitalization rates among dialysis modalities.

FR-PO834

The Impact of Early Hospitalizations after Initiation of Dialysis on All-Cause Mortality in Incident Hemodialysis Patients Yu ah Hong,[1] Su Hyun Kim,[3] Yong-Lim Kim,[4] Yon Su Kim,[5] Shin-Wook Kang,[6] Seong il Jo,[1] Yoon-Kyung Chang,[2] Suk young Kim,[2] Yong Kyun Kim.[2] *[1]The Catholic University of Korea, Daejeon, Republic of Korea; [2]The Catholic University of Korea, Daejeon, Republic of Korea; [3]Chung-Ang University Hospital, Seoul, Republic of Korea; [4]Kyungpook National University Hospital, Daegu, Republic of Korea; [5]Seoul National University College of Medicine, Seoul, Republic of Korea; [6]College of Medicine, BK21, Yonsei Univ., Seoul, Republic of Korea.*

Background: Background/Aims: Hospitalization and mortality rates are relatively high within first several months after initiation of dialysis in end-stage renal disease (ESRD). Limited data are available about the association between early hospitalization after initiation of dialysis and clinical outcomes in ESRD patients. We investigate the association between early hospitalization and all-cause mortality in incident hemodialysis (HD) patients.

Methods: Methods: Incident dialysis patients were selected from the Clinical Research Center registry a prospective Cohort study on dialysis patients in Korea. Early hospitalization was defined as all-cause hospitalization within 90 days after initiation of HD. The primary outcome was all cause mortality and the secondary outcome was cardiovascular and infection-related mortality.

Results: Results: A total of 1,584 hemodialysis patients were included. The median follow-up period was 24.5 months. During follow up period, 150/1,584 (9.5 %) was died. 43/1,584 (2.7%) and 33/1,584 (2.1 %) was died of cardiovascular and infection-related cause. Kaplan-Meier analysis showed that the all-cause mortality rates ($P < 0.001$, Log-rank) as well as cardiovascular infection-related mortality rates ($P < 0.001$ and $P < 0.001$, respectively, Log-rank) were significantly higher in patients with early hospitalization than in patients with no hospitalization. The multivariate Cox regression analysis showed that patients with early hospitalization remained at higher risk for all-cause mortality than those without early hospitalization after adjusting for confounding variables (HR 2.888 [1.806-4.616], $P < 0.001$). In addition, cardiovascular and infection-related mortality were significantly higher in patients with early hospitalization than in patients with no hospitalization after adjusting for confounding variables (HR 7.547 [2.893-19.690], $P < 0.001$ and HR 2.900 [1.157-7.27], $P < 0.001$, respectively).

Conclusions: Conclusion: Early hospitalization within 90 days after initiation of dialysis was an independent predictor marker of all-cause mortality in incident HD patients, which suggest that careful attention for HD patients with early hospitalization is needed.

FR-PO835

Association of Waist-to-Hip Ratio with Sudden Cardiac Death and Cardiovascular Mortality in Incident Hemodialysis Patients Jessica Fitzpatrick,[1] Stephen M. Sozio,[2] Bernard G. Jaar,[2] Michelle M. Estrella,[4] Jose M. Monroy-Trujillo,[2] Larisa G. Tereshchenko,[3] Rulan S. Parekh.[1] *[1]University of Toronto, Toronto, ON, Canada; [2]Johns Hopkins University, Baltimore, MD; [3]Oregon Health and Science University, Portland, OR; [4]University of California, San Francisco and San Francisco VA Medical Center, San Francisco, CA.*

Background: Waist-to-hip ratio (WHR) is a predictor of cardiovascular disease (CVD) and mortality in the general population. Few studies, however, have examined the association of WHR and risk of CVD mortality, particularly sudden cardiac death (SCD), among end-stage renal disease (ESRD) patients undergoing hemodialysis.

Methods: This study included 379 incident hemodialysis patients enrolled in the Predictors of Arrhythmic and Cardiovascular Risk in ESRD (PACE) Study. WHR was calculated as the ratio of waist-to-hip circumference. CV death was defined as deaths arising from arrhythmias, ischemic CVD, and ischemic cerebrovascular disease, as well as SCD. Cox proportional hazards regression was used to estimate the association of baseline WHR with risk of CVD death, SCD, and non-CVD death.

Results: At baseline, the mean age was 54.9 years, 41% were female, 73% were African American, 57% had diabetes, the mean comorbidity index was 5.2, the mean body mass index (BMI) was 29.3 kg/m^2, the mean WHR was 0.95, and 85% were above the World Health Organization WHR threshold for metabolic complications. WHR and BMI were weakly correlated (r=0.21). During a median follow-up time of 2.5 years, there were 35 CVD deaths, 15 SCD, and 48 deaths from non-CVD causes. An increase in WHR was associated with higher hazard of CVD mortality and SCD, but not non-CVD mortality. In adjusted models, WHR was strongly associated with SCD. There was no evidence of interaction between WHR and race or BMI in any of the models.[Table]

Conclusions: WHR is associated with SCD and CVD death in incident hemodialysis patients. The easily measured WHR may be a useful metric to risk stratify ESRD patients for CVD mortality.

Funding: NIDDK Support

	Per 0.1 increase in WHR	
	HR (95% CI)	P-Value
Non-CVD Mortality		
Unadjusted	0.72 (0.49, 1.05)	0.09
Adjusted†	0.93 (0.59, 1.46)	0.75
CVD Mortality		
Unadjusted	1.35 (0.88, 2.07)	0.17
Adjusted†	1.69 (1.03, 2.76)	0.04
SCD		
Unadjusted	2.07 (1.09, 3.94)	0.03
Adjusted†	2.48 (1.19, 5.19)	0.02

† Model adjusted for age, sex, race, comorbidity index, BMI, and albumin

FR-PO836

A Scoring System to Guide Systemic Oral Anticoagulation Among Incident Dialysis Patients with a Preexisting Diagnosis of Atrial Fibrillation/Flutter Robert C. Albright,[2] John J. Dillon,[2] Dena E. Cohen,[1] Steven M. Brunelli.[1] *[1]DaVita Clinical Research, Minneapolis, MN; [2]Mayo Clinic, Rochester, MN.*

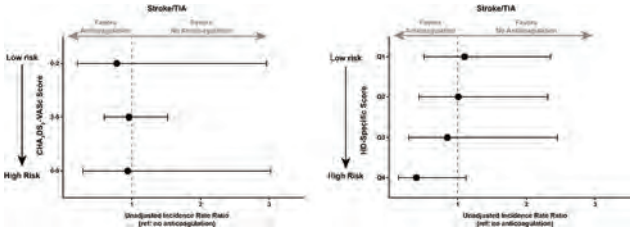
Background: Among the general population, patients with atrial fibrillation/flutter (Afib) and a CHA_2DS_2-VASc score ≥2 have high stroke risk and may receive systemic oral anticoagulation (SOA). Utility of CHA_2DS_2-VASc in patients initiating hemodialysis (HD) with pre-existing Afib is unclear.

Methods: We considered adult Medicare enrollees who initiated HD at a large US dialysis organization in 2010-2011 with pre-existing Afib, determined from claims. Exposures were risk scores and SOA, based on a prescription fill during the first 3 months of HD. Outcome (stroke/transient ischemic attack [TIA]) was considered from HD start until censoring or study end (Dec 2012), and compared using intention-to-treat principles and Cox proportional hazard models. An HD-specific risk score was developed using a logistic model fit by stepwise elimination of non-contributing variables ($p>0.1$). Positive outcomes were SOA and no stroke/TIA, and no SOA and stroke/TIA; negative outcomes were the converse.

Results: Among 2742 patients initiating HD with Afib, no association was observed between SOA and risk of stroke/TIA across CHA_2DS_2-VASc categories. Female sex, Hispanic race, use of a central venous catheter, congestive heart failure, and diabetes defined an HD-specific risk score. In the top quartile of this score, SOA (vs. no SOA) was associated, at near statistical significance, with a lower point estimate for risk of stroke/TIA.

Conclusions: We developed a risk score that, unlike CHA_2DS_2-VASc, may identify incident HD patients with Afib who will benefit from SOA. Further work is needed to refine and validate this HD-specific score.

Funding: Commercial Support - DaVita, Inc



FR-PO837

Dialysis Modality and Incident Atrial Fibrillation in Older Patients with ESRD Initiating Dialysis Jingbo Niu, Maulin Shah, Jose J. Perez, Medha Airy, Sankar D. Navaneethan, Wolfgang C. Winkelmayer. *Baylor College of Medicine, Houston, TX.*

Background: The incidence of atrial fibrillation (AF) in older patients with ESRD initiating hemodialysis (HD) is high, at 14.8 per 100 person-years, and AF is associated with increased morbidity and mortality. It has been posited that peritoneal dialysis (PD) may confer lower AF risk owing to lesser fluctuations of fluid and electrolyte status. We tested whether the incidence of AF differed between patients using PD versus HD for the initiation of dialysis in a national U.S. cohort.

Methods: Patients 67+ years who initiated dialysis for ESRD in the continental US were eligible if they had been continuously enrolled in Medicare A&B during the 2 years pre- and 90 days post-ESRD. Those with any diagnosis of AF prior to initiation of dialysis (=index date) were excluded. Patients were further required to have exclusively used a single modality for these first 90 days (or until they died or received a transplant during that period). Patients were then followed for AF incidence, which was ascertained from 1 inpatient or 2 outpatient diagnoses (ICD-9 code: 427.3x). Follow-up was terminated 3 years after index date or at loss of Medicare A&B coverage. Death and kidney transplantation were handled as either censoring or competing events in separate analyses. Multivariable Cox proportional hazards regression models were used to estimate the cause-specific and sub-distribution hazard ratios [HR (95% confidence interval)] for PD vs HD.

Results: We identified 251,092 patients with ESRD initiating dialysis between 1996 and 2011; 93.2% used HD and 6.8% used PD. During 447,253 years of follow up, 69,656 patients were newly diagnosed with AF; 3,324 received a kidney transplant and 102,202 died. The unadjusted AF incidence rates per 100 person-years were 15.7 for HD and 14.5 for PD, respectively. The unadjusted cause-specific HR for AF comparing PD to HD (referent) was 0.93 (0.91-0.96) and the sub-distribution HR was 0.97 (0.95-1.00). Multivariable adjustment yielded a cause-specific HR of 1.03 (1.00-1.06) and a sub-distribution HR of 1.00 (0.97-1.03).

Conclusions: In older individuals with ESRD initiating dialysis in the U.S., patients using PD had very similar adjusted rates of AF compared with otherwise similar patients using HD.

Funding: NIDDK Support

FR-PO838

Oral Anticoagulation Among Patients Initiating Dialysis with Existing Atrial Fibrillation/Flutter: Association with Outcomes and Risk Score Robert C. Albright,[2] John J. Dillon,[2] Dena E. Cohen,[1] Steven M. Brunelli.[1] *[1]DaVita Clinical Research, Minneapolis, MN; [2]Mayo Clinic, Rochester, MN.*

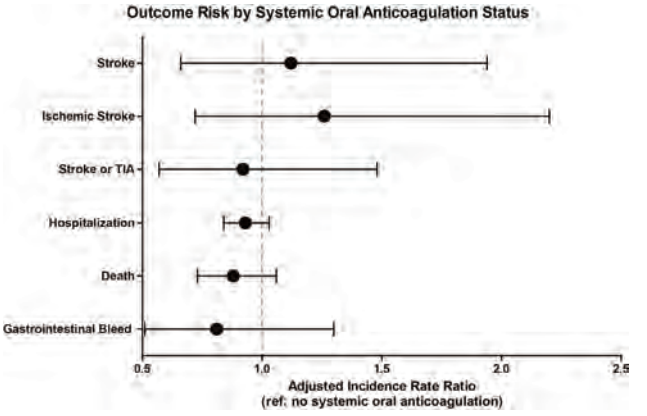
Background: In the general population, systemic oral anticoagulation (SOA) may reduce stroke risk among patients with atrial fibrillation/flutter (Afib). Patients who develop Afib after starting hemodialysis (HD) do not typically benefit from SOA. Guidance for use of SOA among patients who initiate HD with pre-existing Afib is scant.

Methods: This study considered adult Medicare A, B, and D beneficiaries who initiated in-center HD at a large US dialysis organization in 2010 or 2011 with a pre-existing diagnosis of Afib, ascertained from claims data. SOA (exposure) was based on a Medicare D claim for a prescription fill during the first 3 months of HD. Outcomes were considered from HD start until death, loss to follow-up, or study end (31 Dec 2012). Comparisons were made using intention-to-treat principles and negative binomial (hospitalization) or Cox proportional hazard (death, stroke, ischemic stroke, and stroke/transient ischemic attack [TIA]) models adjusted for imbalanced characteristics.

Results: Among 2742 patients initiating HD with Afib, 835 had a fill for SOA, and 1907 did not. No independent association was observed between SOA and any outcome considered. No protective association of SOA was observed in patients with high (or low) CHA_2DS_2-VASc risk score (*p*-interaction > 0.1 for each). No association was observed between SOA use and risk of gastrointestinal bleed.

Conclusions: Among patients who initiate HD with pre-exisiting Afib, traditionally accepted stroke risk scores cannot adequately guide clinicians with respect to possible benefit of SOA. Alternate methods are needed to guide use of SOA in such patients.

Funding: Commercial Support - DaVita, Inc



FR-PO839

Relationship between History of Stroke before Dialysis Initiation and All-Cause Mortality in Dialysis Patients Masayasu Kojima,[1] Daijo Inaguma,[2] Hideaki Shimizu,[1] Shigehisa Koide,[2] Kazuo Takahashi,[2] Hiroki Hayashi,[2] Midori Hasegawa,[2] Yukio Yuzawa.[2] *[1]Nephrology, Daido Hospital, Nagoya, Japan; [2]Nephrology, Fujita Health University School of Medicine, Toyoake, Japan.*

Background: Some reports have shown a relationship between stroke and all-cause mortality in pre-dialysis or maintenance dialysis patients. However, there are few previous studies describing the prognosis of dialysis patients whose baseline was set at the time dialysis was initiated. Therefore, we examined whether all-cause mortality differed between dialysis patients with and without a history of stroke before dialysis initiation.

Methods: The subjects were patients in the 17 centers participating in the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis (AICOPP) from October 2011 to September 2013. We determined by a survey conducted at the end of March 2015. Thus, we enrolled 1,520 subjects into the study. We classified patients into 2 groups according to the history of stroke (i.e., a stroke group and a non-stroke group). Propensity scores (PS) represented the probability of being assigned to a group with or without a history of stroke. All-cause mortality was compared in PS-matched patients by using the log-rank test for Kaplan-Meier curves. Factors contributing to all-cause mortality were examined using stepwise multivariate Cox proportional hazards analysis.

Results: There were 236 patients in each group after PS-matching. The median of follow up period was 1,318 days (interquartile range: 1,109-1,509 days). During observation, all-cause death occurred in 84 patients (35.6%) in the stroke group and 28 (11.9%) patients in the non-stroke group. Cardiovascular related death occurred in 32 patients (13.6%) in the stroke group and 10 (4.2%) patients in the non-stroke group. The all-cause mortality was significantly higher in the stroke group compared to the non-stroke group after PS-matching (Logrank test: $p < 0.001$). The all-cause mortality was significantly higher in the stroke group compared to the non-stroke group (hazard ratio = 5.00, 95% confidence interval = 2.81-8.90) in multivariate analysis adjusted for age, gender, comorbidity of diabetes, history of coronary artery disease, body mass index, blood pressure, hemoglobin, eGFR, use of loop diuretics, CRP, and bicarbonate.

Conclusions: History of stroke before dialysis initiation was associated with a higher all-cause mortality.

FR-PO840

Hemoglobin Concentrations and the Risk of Hemorrhagic and Ischemic Stroke in Patients Undergoing Hemodialysis: The Q-Cohort Study Ryusuke Yotsueda,[3] Shigeru Tanaka,[1] Masatomo Taniguchi,[2] Hideki N. Hirakata,[2] Kazuhiko Tsuruya,[3] Takanari Kitazono.[3] *[1]Fukuoka Dental College, Fukuoka, Japan; [2]Fukuoka Renal Clinic, Fukuoka City, Japan; [3]Kyushu University, Graduate School of Medical Sciences, Fukuoka City, Japan.*

Background: Several lines of evidence have suggested an association between low hemoglobin concentrations and hemorrhagic stroke, and an association between high hemoglobin concentrations and ischemic stroke. However, the contribution of hemoglobin concentrations to the separate incidence of hemorrhagic or ischemic stroke in patients undergoing hemodialysis remains unclear.

Methods: A total of 3,436 participants undergoing maintenance hemodialysis were followed up for 4 years. The primary outcome was incidence of first development of hemorrhagic or ischemic stroke. Hemoglobin concentrations were divided into quartiles based on baseline data (hemoglobin [g/dL]: Q1, ≤9.7; Q2, 9.8–10.5; Q3, 10.6–11.1; Q4, ≥11.2). The associations between hemoglobin concentrations with each types of stroke were examined using Kaplan–Meier method and Cox proportional hazards model.

Results: During the follow-up period, 77 (2.2%) patients experienced hemorrhagic stroke and 141 (4.1%) experienced ischemic stroke. The 4-year incidence rate of hemorrhagic stroke was significantly higher with lower hemoglobin concentrations. Compared with the quartile of the highest hemoglobin concentrations (Q4), the multivariable-adjusted hazard ratios for hemorrhagic stroke were 1.18 (95% confidence interval, 0.56–2.51), 1.65 (0.85–3.30), and 2.16 (1.14–4.64) in patients with Q3, Q2, and

Q1, respectively. There did not appear to be an association between the 4-year incidence rate of ischemic stroke and hemoglobin concentrations. Compared with the quartile of the lowest hemoglobin concentrations (Q1), the multivariable-adjusted hazard ratios for ischemic stroke were 1.19 (95% confidence interval, 0.75–1.92), 0.87 (0.50–1.49), and 1.11 (0.68–1.85) in patients with Q2, Q3, and Q4, respectively.

Conclusions: Low hemoglobin concentrations are associated with high risk of hemorrhagic stroke in patients undergoing hemodialysis. However, hemoglobin concentrations are not associated with the risk of ischemic stroke.

FR-PO841

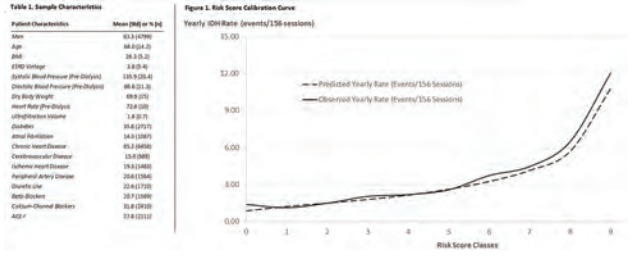
Identifying Patients at Risk for Intradialytic Hypotension Luca Neri, Milena Chermisi, Carlo Barbieri, Flavio Mari, Stefano Stuard. *Fresenius Medical Care, Bad Homburg, Germany.*

Background: Despite Intradialytic Hypotension is a prominent clinical problem for patients on dialysis, there currently is no valid risk prediction tool

Methods: All FME patients registered in Spain (2013 - 2015) have been enrolled in a historical cohort. We extracted medical data from de-identified electronic clinical charts (EuClid database). We partitioned the initial dataset in a training (90%) and validation (10%) sample. We implemented a two-part regression to evaluate correlates of Intradialytic Hypotension (IDH) and derived a risk score. Stage 1 identified patients at high risk of experiencing at least 1 IDH. Stage 2 predicted IDH rate in patients identified in stage 1 as the IDH cluster. AIC minimization was used for model selection

Results: Among 7582 patients (Validation set: 758), 4346 had at least one IDH during follow up time (mean=1.58 ±1.03 years). On average there were 5.1±9.5 events per patient during the follow up (incidence: 0.023±0.036 IDH/person-treatment). Factors associated with increased IDH risk: ESRD vintage, previous IDH, variability of intradialytic body weight drop, intradialytic blood pressure drop, ultrafiltration volume, pre-dialysis blood pressure, serum potassium, extracellular water volume, calcium, ferritin, body fat, female sex, use of diuretics, diabetes, CRP, history of stroke, dialysate bicarbonate and sodium, dementia, over-hydration. Factors associated with reduced IDH risk: intradialytic blood pressure variability, dry body weight, lower intracellular water volume, intradialytic heart rate variability, urea distribution volume, hematocrit, serum potassium. The risk score had excellent calibration and accurately discriminated across different risk classes (fig1)

Conclusions: We identified potentially modifiable risk factors for IDH. Additionally, our prediction algorithm provides a reliable tool for risk stratification



FR-PO842

Effects of Blood Pressure Variability on Mortality in Chronic Hemodialysis Patients: OCTOPUS Study Takayuki Adachi,[2] Kentaro Kohagura,[3] Hisatomi Arima,[1] Kunitoshi Iseki.[2] *[1]Fukuoka Uniuversity, Fukuoka, Japan; [2]Tomishiro Central Hospital, Tomigusuku city, Japan; [3]University of the Ryukyus, Nishihara-cho, Japan.*

Background: We examined the relationship between blood pressure variability and survival among chronic HD patients.

Methods: We previously reported the results of the multi-center prospective, open trial of the Olmesartan Clinical Trial in Okinawa Patients Under Okinawa Dialysis Study (OCTOPUS). In a multicenter, prospective, randomized, open label, blinded-endpoint trial, 469 patients with chronic HD and elevated BP (140–199/90–99 mmHg) were assigned to receive the angiotensin receptor blockade (ARB) olmesartan (at a dose of 10–40 mg daily; n = 235) or another treatment that does not include angiotensin receptor blockers and angiotensin-converting enzyme (ACE) inhibitors (n = 234). For this study, we examined of 435 patients after excluding those who died within 1 year after registration (N=28) and lack of blood pressure data for more than 2 time (N=6). We adopted the coefficient of variation (CV), which was obtained using 6 pre-HD blood pressure within the first year after registration, as a marker of blood pressure variability. Cox proportional hazard analysis was used to examine the relationship between blood pressure variability and mortality after the 1-year visit with adjustment for age, sex, smoking, DM, HD vintage, and use of angiotensin receptor blockade.

Results: During the mean follow-up of 2.5 years after the 1-year visit, we observed 58 deaths. We used five quintile groups of CV pre-HD systolic blood pressure (Q1 to Q5). The mortality rate was 9.2% (Q1), 12.8% (Q2), 9.1% (Q3), 16.1% (Q4), and 19.5% (Q5), respectively. The adjusted hazard ratio (95% confidence interval) was 1.83 (0.73-4.63) in Q1, 1.83 (0.73-4.63) in Q2, 1.84 (0.77-4.40) in Q4, and 2.42 (1.04-5.62) in Q5 when the Q3 was taken as reference.

Conclusions: Mortality rate was higher among patients with higher pre-HD variability of blood pressure.

FR-PO843

Association of Intradialytic Hypotension and Vascular Calcification in Hemodialysis Patients Ajin Cho,[3] Jung-woo Noh,[2] Dong Ho Shin.[1] *[1]College of Medicine, Hallym University, Seoul, Republic of Korea; [2]Hallym University, Seoul, Republic of Korea; [3]Hallym university Kangnam Sacred Heart Hospital, Seoul, Republic of Korea.*

Background: Intradialytic hypotension (IDH) is a common complication during hemodialysis (HD). IDH not only causes discomfort, but also increases patient mortality and cardiovascular events (CVEs). Vascular calcification is associated with structural and functional abnormality of the heart and blood vessels. It induces a reduction in vascular compliance and diastolic LV dysfunction. Therefore, IDH may be associated with vascular calcification in HD patients. We investigated the relationship between IDH and vascular calcification in HD patients, and their impacts on CVEs.

Methods: We enrolled 191 maintenance HD patients who underwent plain abdomen radiography for abdominal aortic calcification score (AACS). A nadir systolic blood pressure (BP) < 90 mm Hg or the requirement of bolus fluid administration was required to quantify the hypotension diagnosis. IDH was defined as > 2 hypotension episodes during 10 HD treatments.

Results: Among the 191 patients, IDH occurred in 32. AACS was higher in the IDH group compared with the no-IDH group (8.4 ± 6.0 vs. 4.9 ± 5.2, respectively; P = 0.001). High AACS was an independent risk factor after adjustment for age, diabetes mellitus, ultrafiltration, diastolic BP, and calcium level (odds ratio (OR) = 1.08, 95% CI = 1.002–1.16; P = 0.04). Patients with both IDH and AACS > 4 had the highest cumulative CVE rate (27.9%, P=0.008) compared with 11.2%, 12.5%, and 6% for those with AACS > 4 only, with IDH only, and neither, respectively. In multivariate analysis, the presence of both IDH and AACS > 4 was a significant predictor of CVE (hazard ratio (HR) = 2.84, 95% CI = 1.04–7.74, P = 0.04).

Conclusions: IDH is associated with abdominal aortic calcification and is an independent risk factor for IDH. Both IDH and high AACS were significant predictors of CVE.

FR-PO844

Peridialysis BP Levels and Risk of All-Cause Mortality: A Meta-Analysis Yu-Chen Han. *Zhongda Hospital, Southeast University School of Medicine, Nanjing, China.*

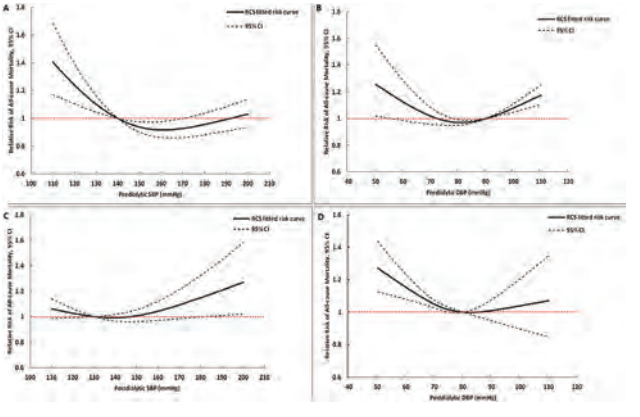
Background: Blood pressure (BP) management posed great challenge in hemodialysis (HD) population. The optimal peridialysis BP for HD population was unknown. We conducted a dose-response meta-analysis to investigate the quantitative features and the potential threshold effect of the associations between peridialysis BP levels and all-cause mortality risk in HD population.

Methods: We searched all of the prospective cohort studies (published before March 18, 2017) on the associations between peridialysis BP levels and all-cause mortality risk.

Results: A total of 229,688 prevalent HD patients from 8 studies were included. The non-linear associations were noted between peridialytic BP levels and all-cause mortality risk. Significant increased risk of death was found in four peridialysis BP ranges, that is, low levels of predialysis SBP (<135mmHg, 140mmHg as the reference), two extremes of predialysis DBP (<55 and >95mmHg, 90mmHg as the reference), high levels of postdialysis SBP (>180mmHg, 130mmHg as the reference), and low levels of postdialysis DBP (<75mmHg, 80mmHg as the reference). The peridialysis BP ranges with the peak survival were 160-165mmHg for predialysis SBP, 80-85mmHg for predialysis DBP, 135-140mmHg for postdialysis SBP and 80-85mmHg for postdialysis DBP. Threshold effect was determined in the associations between peridialysis BP and all-cause mortality risk, and potential BP thresholds were identified (149mmHg for predialysis SBP, 79mmHg for predialysis DBP, 147mmHg for postdialysis SBP and 76mmHg for postdialysis DBP).

Conclusions: The optimal peridialysis BP for HD population was unknown. By incorporating major hemodialysis databases in the world, major quantitative features of the peridialysis mortality associations were explicitly identified in our study. The proposed peridialysis BP ranges and the threshold values could help clinicians identify high risk patients and give guidance to BP-lowering therapy (dry weight probing and antihypertensive drugs) in HD population.

Funding: Government Support - Non-U.S.



RCS, restricted cubic spline

FR-PO845

Comparison between 44-Hours Ambulatory Blood Pressure Monitoring (ABPM) and 24-Hours Non-Dialysis Day ABPM in Indian Dialysis Subjects Rajesh B. Kumar, Rachana H. Jasani, SHRIRANG BICHU, Viswanath Billa, Paras Dedhia. *Apex Kidney Foundation, Mumbai, India.*

Background: ABPM is considered as a gold standard method to assess hypertension in dialysis population. However, 44 hours ABPM is cumbersome and usually enocunters reluctance from patients. 24 hours ABPM is more practical and convenient for patients.

Methods: Ambulatory BP monitoring (ABPM) performed for 44 hours in between 2 dialysis sessions. ABPM recorded every 20 min during the day (7 am to 11 pm) and every 30 min during the night (11 pm to 7 am) in non-fistula arm. Hourly means were averaged to obtain interdialytic systolic and diastolic blood pressure readings. 24 hours ABPM data were extracted from hourly means on non-dialysis day from 6am to 6am. ABPM data with less than 70% readings were excluded from the study. 24 hours mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) were compared with 44 hours measurement using paired t-test.

Results: 35 patients were included in the analysis. Mean age was 54.5 ± 12.7 years and 66% were males and 34% were females. Mean dialysis vintage was 2.7 ± 2.8 years. 49% were diabetic, 97% were hypertensive and 23% had IHD. Mean 44 hour BP was 151.9 ± 15.8/ 83.2±13.4 mm Hg and mean 24 hour BP was 151.5 ± 15.9/82.6± 13.7 mm Hg. There was no statistical difference between 44 hour and 24 hour mean SBP (*p* value: 0.45) and mean DBP (*p* value: 0.77).

Conclusions: Mean SBP and DBP of 44-hours ambulatory blood pressure monitoring and 24-hours non-dialysis ABPM were comparable in study subjects. We conclude that 24 hours ABPM on non-dialysis day is an alternate feasible option in assessing BP in dialysis patients.

FR-PO846

Use of Beta-Blockers Associated with Lower Orthostatic Response in Dialysis Patients Gustavo Laham.[1,2] *[1]Internal Medicine, Nephrology section, CEMIC, Ciudad de Buenos Aires, Argentina; [2]FME CEMIC Saavedra, Ciudad de Buenos Aires, Argentina.*

Background: Beta Blockers (BB) are widely used in dialysis patients (pts). However, the evidence supporting their utility in improving cardiovascular (CV) outcomes in this population is conflicting.

Methods: Within a CV evaluation program for pts with ESRD in our Hospital. We evaluated 102 pts attended the interdialysis day. BP and hemodynamics was determined with impedance cardiography in supine position and after the third minute of standing. Following variables: SBP, DBP, heart rate (HR), stroke volume (SV), systemic vascular resistance index (SVRI) and thoracic fluid content (TFC). At the same time, the variability of the frequency was evaluated during 3 minutes at rest and in standing position. Patients were classified into 2 groups according to the presence of Hypotension (HYPOT) or not (EST). Orthostatic hypotension was defined as a drop of 20mmHg or more of SBP and/ or 10mmHg or more of DBP when standing. Hemodynamic variables were analyzed : 1-baseline conditions and 2-differences (delta standing-lying) between the two groups (t-test and Mann-Whitney U test). Independent predictors of orthostatic hypotension were determined adjusting for age, sex, BP, anthropometric variables, time on dialysis and medication through a logistic regression.

Results: We included 81 patients: age: 59,8 ± 14 years, female 55,5%: SBP: 137,7± 27,2 mmHg, DBP: 83,5 ± 19,7 mmHg. Twenty nine pts (35,8%) had orthostatic hypotension. No significant differences were found in age, sex, BMI, time on dialysis, DM and CV events between both groups. 86.21% of the pts in the HYPO group received BB and 28.8 of the pts in the EST group with a significant difference (p<0, 0004). At rest position there were no hemodynamic or autonomic differences between both groups, but in Standing position, HYPO group, showed delta of SVRI (p < 0.037) lower, as well as lower delta DBP, delta Median Blood Pressure and delta SBP (p< 0,0001) compared to de EST group. There were no significant differences in the delta TFC as well as between autonomic variables. In logistic regression the use of BB was an independent variable for orthostatic hypotension.

Conclusions: In this group of dialysis pts the use of BB was a determining factor to attenuate or nullify the compensatory increase of the vascular resistance against the bipedestation. Therefore BB could collaborate with the development of hypotension when standing independently of the autonomic response.

FR-PO847

Association of Betaine with Blood Pressure in Dialysis Patients Lulu Wang,[2] Mingming Zhao,[3] Wenjin Liu,[1] Lemin Zheng,[3] Junwei Yang.[4] *[1]2nd Affiliated Hospital of Nanjing Medical University, Nanjing, China; [2]Center for Kidney Disease, Second Affiliated Hospital of Nanjing Medical University, Nanjing, China; [3]Peking University, Beijing, China; [4]Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.*

Background: Patients with chronic kidney disease have an increased risk of cardiovascular morbidity and mortality. Hypertension has been considered as one of the most important contributor to the increased risk. Betaine is a zwitterionic quaternary ammonium compound and distributed widely in rich dietary sources. Previous studies suggest a possible link between alteration of circulating betaine and hypertension. However, there is a paucity of data regarding patients on maintenance hemodialysis. We aimed to explore the association of betaine with blood pressure in this disease population.

Methods: Between July 2015 to July 2016, 368 patients on maintenance hemodialysis (4h / thrice weekly over 3 months) from six tertiary hospitals were recruited to participate an ongoing cohort study. Interdialytic blood pressure was evaluated by ambulatory blood pressure monitoring. Plasma betaine level was measured by high performance liquid chromatography–mass spectrometry for 327 subjects. The association between betaine and blood pressure was evaluated by multiple linear regression analysis.

Results: The mean age of the patients was 52.6±11.9 years, and 58.4% were male. Average interdialytic ambulatory systolic and diastolic blood pressure were 138.4±22.7 mm Hg and 84.4±12.5 mm Hg, respectively. Mean plasma betaine level was 37.6 umol/L. There was no significant difference of plasma betaine level across certain subgroups, including age (>60 vs. ≤60), gender (male vs. female), BMI (≥25 vs. <25), diabetes (yes vs no) and previous history of cardiovascular disease (yes vs no). Multiple linear regression analysis revealed significant associations of betaine with both systolic blood pressure (β=-3.66,P=0.003) and diastolic blood pressure (β=-2,P=0.004). The associations persisted even after extensive adjustment for cardiovascular covariates.

Conclusions: In conclusion, we demonstrated, for the first time, significant association between betaine and blood pressure level in a group of hemodialysis patients. Our data suggests that alteration of circulating betaine possibly contributes to blood pressure regulation in these patients.

Funding: Government Support - Non-U.S.

FR-PO848

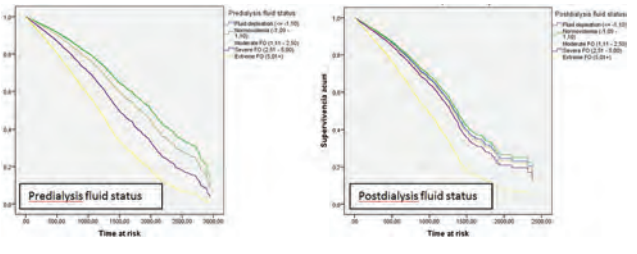
Fluid Status (FS) as Predictor of Long Term Survival in Hemodialysis (HD) Patients Adrian M. Guinsburg, Marcelo D. Ferder, Cristina Marelli. *Fresenius Medical Care, Moron, Argentina.*

Background: Extracellular fluid overload (FO) has been typically described as predictor of all-cause mortality in HD patients. A recent publication [Dekker et al, KI (2017), 91, 1214-1223] also demonstrated a beneficial effect of pre and postdialysis fluid depletion on survival. In this study we aim to analyze the relationship between FS and survival in a large cohort of patients from Fresenius Medical Care LatinAmerica (FMCLA)

Methods: Patients on HD at FMCLA between 09/2008 and 12/2016 were included. Body composition after 90 days of dialysis was assessed by multifrequency bioimpedance spectroscopy (BCM©, Fresenius Medical Care). Pre and postdialysis fluid status (FS) groups were defined according to overhydration (OH) as follow: fluid depletion (FD, <= -1.1 lts), normovolemia (NV, -1.1 to 1.1 lts), moderate FO (MFO, 1.1 to 2.5 lts), severe FO (SFO, 2.5 to 5 lts) and extreme FO (EFO, +5 lts). A Cox regression model was constructed to analyze independent relationship between FS and survival accounting for age, gender, vintage, diabetes, CVD, cancer, predialysis systolic blood pressure (preSBP), BMI, lean and fat tissue index, albumin, CRP, cholesterol, Hgb, Ca, P, Na and eKt/V. Values are expressed as mean±SD or [CI]

Results: 43,786 patients were included into initial dataset but only 9,501 had available data on all variables. Age 57.9±16.1 yrs, vintage 3.1 [3.06-3.14] yrs, male 58.2%, OH 1.76 [1.74-1.78] lts, preSBP 140.4±23.4 mmHg, alb 3.8±0.5 (g/dl), hgb 10.8±1.9 g/dl, Ca 8.8±0.9 mg/dl, P 4.7±1.4 mg/dl, Na 137.8±4.0 mEq/l, eKt/V 1.36±0.30. DBT 30.9%, CVD 8.0%, cancer 1.0%. Mean follow-up time was 4.45 years and 2,978 death events were observed. After controlling, RR of death for each group as compared to NV (ref) was a) for predialysis FS: FD 1.19 [NS], MFO 1.18 [1.08-1.30], SFO 1.61 [1.45-1.79], EFO 2.50 [2.09-2.98]; b) for postdialysis FS: FD 1.06 [NS], MFO 1.1 [NS], SFO 1.18 [NS], EFO 1.94 [1.36-2.76]

Conclusions: In our cohort and after multivariate adjustments predialysis MFO, SFO and EFO increased risk of death while there was no impact of FD. Postdialysis FS had no independent impact on survival except for EFO patients.



FR-PO849

Assessment of Pulmonary Congestion by thoracic Fluid Content Predicts Mortality in Hemodialysis Patients Jining Wu, Hong Ye, Junwei Yang. *Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.*

Background: Pulmonary congestion is prevalent and usually asymotomatic in patients with end-stage renal disease (ESRD). Thoracic fluid content (TFC) measured by thoracic electrical bioimpedance (TEB) is suggested to serve as a non-invasive measure of pulmonary congestion. We explored the clinical and echocadiographic correlates of thoracic fluid content as well as its prognostic value in hemodialysis patients.

Methods: In this prospective observational study, we enrolled 114 patients from a single hemodialysis unit. We used different methods of evaluation: thoracic bioimopedance (pre- and post-dialysis) and echocardiography (pre-dialysis). Our aim was to test the prognostic value of TFC in this population. Mortality was analysed after a median of 560.5-day follow-up. The primary outcome was all-cause death.

Results: TEB examination were successfully completed in 114 patients. Patients were divided into two categories based on the TFC measured before dialysis. TFC was strongly associated with left atrial diameter(LAD)(r=0.454,P=0.001), left ventricular posterior wall thickness (LVPW) (r=0.473,P=0.001)and ejection fraction (EF) (r=-0.527,P=0.001). After a median follow-up of 520-day, compaired with those patients having lower TFC, patients with higher TFC had 4.95–fold risk of death.

Conclusions: TEB is a technique that could detect pulmonary congestion at a pre-clinical stage in hemodialysis patients, and TFC emerged as a predictor for the mortality in this population.

Funding: Government Support - Non-U.S.

FR-PO850

Changes in Blood Pressure Following a Fluid Management Quality Improvement Project (QIP) during In-Center Hemodialysis (HD)

Paul Balter,[2] Ludmila Anderson,[1] Lisa A. Pacelli,[2] Patrice B. Taylor,[1] Claudy Mullon,[1] Robert J. Kossmann,[1] Linda H. Ficociello.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Renal Research Institute, New Haven, CT.*

Background: Fluid and sodium retention are leading causes of hypertension (HT) among HD patients. A QIP with a goal to improve fluid management among patients on thrice weekly HD was conducted. This analysis aimed to determine whether QIP initiation was associated with BP changes among HT patients.

Methods: The QIP utilized Crit-Line® Monitors (CLM III) that non-invasively assess intra-dialytic relative blood volume (RBV) and provide real-time data to allow for ongoing fluid monitoring and management. De-identified data from electronic medical records of active patients at QIP initiation were analyzed. Average values for parameters at baseline (BL; 1 mo. prior to QIP initiation) and during first 3 mos. of the QIP were assessed. Changes in RBV, ultrafiltration volume (UFV), treatment (TX) time, and BP were analyzed. Stratified analyses by BL hypertension (HT) status (HT defined as pre-HD SBP > 140 or pre-HD DBP > 90 mmHg) were conducted. T-test and α=.05 were used to compare the BL and the 3rd month of the QIP.

Results: In total, 54 out of 83 (65%) patients had HT at BL. Although UFV and TX time did not change between BL and mo.3 of the QIP, the majority of measured parameters of BP (Table) improved. On average, pre-HD SBP decreased from 163.3 to 157.8 mmHg (p=.01) and pre-HD DBP decreased from 88.0 to 85.1 mmHg (p=.05). Among normotensive patients (n=29), all BP parameters remained unchanged. The % of RBV removed during HD changed from 8.9% during mo.1 to 9.4% during mo.3 of the QIP among HT patients (p=0.7), and from 9.8% to 10.0% among normotensive patients (p=0.8).

Conclusions: QIP initiation was associated with a decrease in BP parameters among HT patients. Neither TX time nor UFV changed over 4 mos. of observation.

Funding: Commercial Support - Fresenius Medical Care North America

n=54	UFV (l)	TX Time (min)	Pre-HD SBP	Pre-HD DBP	Post-HD SBP	Post-HD DBP	Min-HD SBP	Min-HD DBP	Max-HD SBP	Max-HD DBP
BL	2.42	223.1	163.3	88.1	148.9	81.6	124.7	66.8	171.4	97.0
Mo.1	2.48	223.7	160.5	86.4	144.5	80.0	120.3	65.1	167.9	96.3
Mo.2	2.49	220.1	158.8	85.0	138.9	77.1	117.6	64.1	163.8	94.0
Mo.3	2.51	223.6	157.8	85.1	140.3	77.7	116.3	63.3	164.2	94.2
BL vs. Mo.3 p-value	0.4	0.4	0.01	0.05	0.003	0.008	0.003	0.02	0.005	0.05

FR-PO851

Defining the Extent of Replacement Myocardial Fibrosis in Hemodialysis Patients with Non-Contrast Cardiac Magnetic Resonance

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Background: Extent of replacement myocardial fibrosis predicts patient mortality in advanced renal disease. Gadolinium enhanced cardiac MRI (CMR) defines myocardial fibrosis in disease groups with normal renal function, but is not possible in patients with advanced renal disease due to the risk of nephrogenic systemic fibrosis. In this study we describe and assess a non-contrast native T1 CMR signal thresholding technique (T11SD) that may be used for the detection and quantification of myocardial scar burden in haemodialysis (HD) patients.

Methods: The T11SD technique defines the mean native T1 and standard deviation (SD) in regions of discretely increased signal on native T1 parametric maps. The mean +/- SD of the region of interest are then applied as a threshold to the entire myocardium to give a threshold percentage. We assessed the agreement between T11SD and late gadolinium enhanced CMR (LGE-CMR) defined myocardial scarring (using full width half maximum analysis) in patients with aortic stenosis (AS) (n=25). We then compared T11SD between patients with AS (n=25) and patients on HD (n=25) and assessed inter- and intra-observer variability of T11SD in HD patients (n=10).

Results: Myocardial scar assessed by LGE-CMR correlated with T11SD in AS patients (r=0.913) with moderate agreement (ICC=0.55). Bland-Altman showed T11SD systematically overestimated scar burden by 4.3% compared to LGE-CMR. Extent of myocardial scarring defined by T11SD was higher in HD patients compared to AS patients (21.92%±1.0 vs 18.24%±1.4). Global native T1 time was higher in HD patients compared to AS patients (1279ms±5.8 vs 1143ms±12.49) as was the region of interest defined as scar (1390±8.7 vs 1276ms±20.5). The difference between remote myocardium and regions defined as scar were no different between groups (111.4ms±7.6 vs 133.2ms±17.5) representing a 9.6% and 10.4% increase from background myocardium. Inter-and intra-observer variability of T11SD were excellent (ICC=0.87, and 0.96).

Conclusions: This study suggests that extent of replacement myocardial fibrosis can be defined quantitatively with the native T1 signal intensity thresholding technique T11SD in HD patients, which we describe for the first time. This has important implications for the assessment and risk stratification in future research and clinical practice.

Funding: Other NIH Support - Scans of haemodialysis patients from the NIHR funded clinical trial CYCLE-HD ISRCTN11299707. Scans of aortic stenosis patients from the NIHR funded study PRIMID-AS NCT01658345.

FR-PO852

The Impact of Left Ventricular Hypertrophy and Left Ventricular Geometry at Dialysis Initiation on Cardiovascular Events on Chronic Dialysis in Japanese CKD Patients

Taisuke Takatsuka, Daisuke Yoshimura, Yukimasa Iwata, Hiroki Okushima, Rei Iio, Tatsuya Shoji, Terumasa Hayashi. *Osaka General Medical Center, Osaka-Shi, Japan.*

Background: Although, left ventricular hypertrophy (LVH) is common and worsens as CKD stage progresses and is an independent predictor of mortality and cardiovascular events (CVE) in CKD patients on dialysis, there are conflicting reports on the association between left ventricular geometry (LVG) and clinical outcomes. Thus, we conducted retrospective cohort study in incident dialysis patients at two major tertiary referral hospitals in Japan to investigate the impact of LVH and LVG at dialysis initiation on CVE on chronic dialysis.

Methods: Study population comprised 371 and 400 consecutive patients who started maintenance dialysis from 2006 to 2015 at our hospital and from 2001 to 2009 at Rinku General Medical Center, respectively. Echocardiogram was basically performed just before dialysis initiation. We categorized into four groups using LVH [left ventricular mass index (LVMI) >49g/m$^{2.7}$ for men and >45g/m$^{2.7}$ for women] and relative wall thickness [≥0.42 or <0.42]; normal geometry (NG), concentric remodeling (CR), eccentric hypertrophy (EH), concentric hypertrophy (CH). We compared patients' status at dialysis initiation among four groups and Cox proportional hazard model was used to investigate the association of LVH and LVG with CVE on chronic dialysis.

Results: Median age was 69 (male, 60.4%) and eGFR was 4.9ml/min/1.73m^2. Median ejection fraction (EF) and LVMI were 64.1% and 60.8g/m$^{2.7}$, respectively. Among 771 patients, 81 (10.5%), 56 (7.3%), 322 (41.7%) and 312 (40.5%) were classified into NG, CR, EH and CH, respectively. Multivariate Cox model showed that male gender, history of heart failure, Hemoglobin and EF were independently associated with CVE, whereas LVMI and LVG were not. Subgroup analysis revealed that EF (P 0.004) and history of heart failure (P <0.001) had significant interactions on the association of LVMI with CVE.

Conclusions: LVG at dialysis initiation was not associated with CVE on chronic dialysis. On the other hand, LVMI may be predictive for CVE in patients with preserved cardiac function or without history of heart failure.

FR-PO853

Significant Improvement of Left Ventricular Mass Index (LVMI) in Pediatric Patients within 6-12 Months of Initiation of Chronic Dialysis

Poyyapakkam Srivaths,[4,2] Jessica Geer,[4] Sarah J. Swartz,[2] Alisa A. Acosta,[3] Shweta S. Shah,[4] Eileen D. Brewer.[1] *[1]Baylor College of Medicine and Texas Children's Hospital, Houston, TX; [2]Baylor College of Medicine, Texas Children's Hospital, Houston, TX; [3]None, Houston, TX; [4]Texas Children's Hospital, Houston, TX.*

Background: : Left ventricular hypertrophy (LVH) determined by increased left ventricular mass indexed for index allometric height^ 2.7 (LVMI) is highly prevalent in children receiving chronic dialysis (CD). Natural history of LVH in pediatric (ped) CD patients (pts) has not been well studied; only one study showed no change in LVMI observed after 6 months of starting CD. We sought to investigate changes in LVMI from the start of CD to 6-12 months after, and its association with hypertension (HTN).

Methods: Retrospective chart review for prevalent pts at a single center treated from 2014-2017. Pts with baseline echocardiogram (ECHO) within 3 months of starting CD, who had repeat within 6-12 months while continuing CD were included. Pts were excluded if follow up ECHOs was not available or pts initiated CD at another center. Charts were reviewed for demographics and hypertension (HTN) defined by ICD diagnosis and receiving antihypertensive meds. LVH by LVMI was defined using known age and gender norms

Results: 58 pts (32 male, 55%; 32 chronic HD, 55%), mean age 13.9 (range 5-19.7 years). Mean LVMI from initiation decreased significantly on follow up ECHO (initiation 56.7 ±23.7 g/m^2.7 vs. 43.7 ± 15.9 g/m^2.7, p= 0.00001), independent of CD modality or gender. 50/58 pts had HTN at CD initiation; 53/58 pts had LVH by elevated LVMI. 49/50 pts with HTN at initiation had LVH, while 4/8 normotensive pts also had LVH (exact test p=0.001). On follow up at 6-12 mon, 21/53 pts with LVH at CD initiation normalized LVMI. Only 1 pt developed new onset LVH. Uncontrolled HTN (persistent HTN and/or increased meds) was significantly associated with persistent LVH on follow up in the group who had LVH at initiation of dialysis (table).

Conclusions: Nearly all ped CD pts with HTN at initiation had LVH by LVMI. LVMI improved significantly within 6-12 mon of CD initiation. Persistent LVH was associated with uncontrolled hypertension in ped CD pts.

Funding: Clinical Revenue Support

Change in LVH in 53 pts with LVH on CD initiation

Total n=53	HTN improved	HTN not controlled
No LVH f/u ECHO	18	3
LVH f/u ECHO	19	13

Exact p=0.04

FR-PO854

Increased Stroke Volume Variability during Hemodialysis Is Associated with High Cardiac Output State and Enhanced Mortality Dan Sapoznikov, Rebecca Backenroth, Michal Dranitzki Elhalel, Dvora Rubinger. *Hadassah University Medical Center, Jerusalem, Israel.*

Background: Stroke volume (SV) variability (sdSV) is a measure of the consistency of myocardial responsiveness during hemodynamic alterations, but its significance and predictive value in hemodialysis (HD) patients (pts.) are not well defined. The present study was undertaken to assess:1. the relationship of intradialytic sdSV with clinical data and other hemodynamic measurements and, 2. its effect on survival in chronic HD pts.

Methods: Continuous beat-to-beat intervals (IBI) and systolic (SBP) blood pressure were monitored using Finometer recordings in 119 HD pts. and in 34 age-matched control (C) individuals. Cardiac output (CO), SV and total peripheral resistance (TPR) were assessed using Beatscope software and the ModelFlow simulation method. The standard deviations (sd) of the above indices were considered to represent their variabilities. Kaplan Meier analysis was performrd to assess survival. A cutoff point of sdSV of 6.9 ml was chosen for best Log Rank significance.

Results: Table 1 lists hemodynamic data in C, in pts. with lower sdSV (≦6.9 ml, n=72) and in those with higher sdSV (>6.9 ml, n=47) (see Table 1 below). Clinical data were similar in both HD groups with the exception of more prevalent peripheral vascular disease and use of antihypertensive drugs in pts. with higher sdSV. Kaplan-Meier analysis of 5y survival showed a significantly increased mortality in HD pts. with higher as compared with those with lower sdSV (p=0.01).

Conclusions: Our data show that a special group of HD pts are characterized by high CO, SV and sdSV and decreased TPR. Increased sdSV in HD pts. was associated with decreased survival, as previously reported in pts with high output cardiac failure and preserved renal function. The causes of this syndrome may include inadequate vascular compliance, excessive vasodilatation or the type of vascular access and deserve further investigation.

Table 1.

	C	HD Lower sdSV	p (vs. C)	HD Higher sdSV	p (vs.C)	p (Higher vs. Lower sd SV)
SBP (mm Hg)	125 (21)	136 (29)	0.015	141 (31)	0.081	0.860
sdSBP (mm Hg)	6.1 (2.0)	6.4 (2.3)	0.700	7.4 (2.7)	0.011	0.007
SV (ml)	76 (28)	75 (29)	0.213	108 (31)	0.001	0.001
sdSV (ml)	4.9 (1.8)	5.2 (1.3)	0.692	8.2 (2.5)	0.001	0.001
CO (L/min)	5.8 (1.8)	5.5 (2.2)	0.170	7.2 (2.7)	0.001	0.001
sdCO (L/min)	0.38 (0.16)	0.39 (0.17)	0.577	0.67 (0.31)	0.001	0.001
TPR (mmHg.s/ml	0.914 (0.368)	1.060 (0.534)	0.003	0.747 (0.271)	0.003	0.001

Data given as median (interquartile range).

FR-PO855

Changes in QT Interval in Long-Term Hemodialysis Patients Yoshihiro Matsumoto,[2] Yasuo Mori,[3] Shinji Kageyama,[1] Kazuo Arihara,[4] Hidemaro Sato,[5] Kijun Nagata,[5] Yasushi Shimada,[2] Youichi Nojima,[2] Koichiro Iguchi,[2] Sugiyama Toshikazu.[6] *[1]Kageyama Urological Clinic, Shziuoka city, Japan; [2]Shizuoka City Hospital, Shizuoka, Japan; [3]Shibukawa Clinic, Shizuoka, Japan; [4]Ohtemachi Clinic, Shizuoka, Japan; [5]Sawada Hospital, GIFU, Japan; [6]Sugiyama Clinic, Shizuoka, Japan.*

Background: Cardiovascular diseases, including sudden cardiac death (SCD), are the leading cause of death in hemodialysis (HD) patients. A prolonged QT interval on the electrocardiogram (ECG) is a risk factor for SCD in HD patients as well as in the general population. This study sought to investigate whether the heart rate-corrected QT (QTc) interval increases with dialysis vintage.

Methods: A total of 102 patients from 7 outpatient HD clinics were retrospectively studied. They had been undergoing HD for more than 7 years, and had ECG data at 1, 4, and 7 years after HD initiation. The control group comprised 68 age-matched individuals without chronic kidney disease who had two available ECG reports at an interval of more than 4 years. Patients with ECGs showing heart rates of <57 or >103, extrasystoles, or any rhythm other than sinus were excluded. QTc was measured according to the Bazett formula. The association between a prolonged QTc interval and dialysis vintage was estimated using Dunnett's multiple comparison test.

Results: Average QTc intervals at 1, 4, and 7 years after HD treatment were 437, 443, and 445 ms, respectively. Those at 4 and 7 years after HD treatment were longer than those at 1 year after HD treatment; the difference was statistically significant (p<0.05). On the other hand, QTc intervals in the control group were 392 in the first year and 394 ms after an average of 6 years, which were much shorter than those in our HD patients and did not show an increase during the 6 years.

Conclusions: The QTc interval at 1 year after HD initiation was longer than in control subjects and increased over several years of HD treatment. Larger-scale studies are recommended to evaluate the association between SCD and QTc prolongation in HD patients.

FR-PO856

Hemodiafiltration Is Associated with Reduced Inflammation and Oxidative Stress and Improved Endothelial Risk Profile Compared to High-Flux Hemodialysis in Children Ayse Agbas,[1] Nur Canpolat,[1] Salim Caliskan,[1] Alev Yilmaz,[2] Hakan Ekmekçi,[3] Mark Mayes,[4] Helen Aitkenhead,[5] Lale Sever,[1] Rukshana Shroff.[6] *[1]Department of Pediatric Nephrology, Istanbul University Cerrahpasa Faculty of Medicine, Istanbul, Turkey; [2]Department of Pediatric Nephrology, Istanbul University Istanbul Faculty of Medicine, Istanbul, Turkey; [3]Department of Biochemistry, Istanbul University Cerrahpasa Faculty of Medicine, Istanbul, Turkey; [4]Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom; [5]Department of Chemical Pathology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom; [6]Department of Pediatric Nephrology, Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom.*

Background: Randomised trials in adults have shown reduced all-cause and cardiovascular (CV) mortality on hemodiafiltration (HDF) compared to conventional hemodialysis (HD), but the mechanisms for improved outcome are not clear and pediatric data is scarce.

Methods: We studied CV risk factors for inflammation, oxidative stress, antioxidant capacity and endothelial function in 22 children (13 female, age 8.9 - 15.5 years) in two dialysis units. All children received HD for at least 3 months, and were then switched to HDF. Biochemical measures were performed after 3 months on HD followed by 3 months on HDF.

Results: After 3-months on HDF there was a significant improvement in ß2 microglobulin, IL-10, hsCRP, ADMA, SDMA, AGE, ox-LDL and TAC compared to levels on HD (Table). HDF was associated with a significant reduction in ADMA, SDMA, hs-CRP and AGE even in children with residual renal function. Clearance was not associated with the type of vascular access, but children with a lower blood flow had higher inflammatory status (higher IL-6/IL-10 ratio; p=0.045, r=-0.431). Children with a higher convective volume (≥median 12.8L/m2) had lower Ox-LDL (p=0.024). None of the measures, except IL-10 levels, correlated with time on dialysis, suggesting that even a short dialysis vintage of 3 months on HD increases inflammatory and endothelial markers.

Conclusions: A significant improvement in inflammation, antioxidant capacity and endothelial risk profile is seen even within a short time (3 months) of HDF compared to HD treatment.

Funding: Government Support - Non-U.S.

n=22	Hemodialysis	Hemodiafiltration	*p value
Nitrotyrosine, nM/ml	28.5 (23.7-56)	32 (24.4-43.7)	0.370
Total antioxidant capacity, mmol/L	0.43 (0.40-0.72)	1.68 (0.42-2.39)	<0.001
Pentraxim-3, ng/mL	1.29 (0.49-1.91)	1.09 (0.63-1.66)	0.641
Interleukine-6, pg/mL	3.72 (2.34-8.36)	3.76 (2.37-8.86)	0.499
High sensitive C-reactive protein, mg/L	2.80 (1.95-3.16)	1.92 (0.70-2.43)	0.002
Interleukine-10, pg/mL	8.93 (3.81-146)	5.73 (4.39-10.4)	0.030
Lipoprotein phospholipase A2, ng/mL	333 (294-412)	372 (278-424)	0.465
Oxidized low density lipoprotein,ng/mL	278 (203-384)	172 (114-211)	0.001
Asymmetric dimethylarginine, µmol/L	1.03 (0.92-1.21)	0.85 (0.75-1.02)	0.001
Symmetric dimethylarginine, µmol/L	3.54 (2.46-3.54)	2.58 (2.12-3.12)	0.003
Advanced glycation end-products, ng/mL	1338 (1221-1490)	982 (1029-1221)	0.001
Beta 2 microglobulin, mg/L	38.5 (33-43)	22.5 (16-26.2)	<0.001

* Wilcoxon signed-rank test, median (IQR)

FR-PO857

Mediterranean and Dietary Approaches to Stop Hypertension (DASH) Diets and Cardiovascular and All-Cause Mortality in Adults on Hemodialysis: The DIET-HD Multinational Cohort Study Valeria M. Saglimbene,[1,3] Germaine Wong,[1] Jonathan C. Craig,[2] Jorgen B. Hegbrant,[3] Giovanni F. Strippoli.[4,3] *[1]University of Sydney, Sydney, NSW, Australia; [2]University of Sydney/Children's Hospital, Sydney, NSW, Australia; [3]Diaverum Medical Scientific Office, Lund, Sweden; [4]University of Bari, Bari, Italy. Group/Team: For DIET-HD investigators.*

Background: Mediterranean and DASH diets are associated with reduced cardiovascular and all-cause mortality in the general population, but these benefits may not be transferable in patients on hemodialysis due to the high content of potassium and phosphate in these diets.

Methods: Mediterranean and DASH diet scores were measured from the GA²LEN food frequency questionnaire within the DIET-HD study, a prospective cohort study (January 2014-January 2016) of 9757 adults treated with hemodialysis in Europe and South America. Adjusted cox regression analyses clustered by country were conducted to evaluate the association between Mediterranean or DASH scores and cardiovascular and all-cause mortality.

Results: During a median follow up of 1.5 years (8108 person-years), there were 1214 deaths of which 515 were attributable to cardiovascular causes. The mean (standard deviation) Mediterranean and DASH scores were 4.0 (1.5) (scale 0 to 8) and 20.4 (3.7) (scale 0 to 34), respectively. Compared with the lowest Mediterranean score quartile (0-3), the adjusted hazard ratios (95% confidence intervals) for cardiovascular mortality in the second (3-4), third (4-5) and fourth (>5) quartile were 0.92 (0.72-1.17), 1.12 (0.87-1.43) and 1.05 (0.78-1.41), respectively; the adjusted hazard ratios for all-cause mortality were 1.05 (0.90-1.23), 1.16 (0.99-1.37) and 1.15 (0.95-1.40), respectively. Compared with the

lowest DASH score quartile (0-18), the adjusted hazard ratios for cardiovascular mortality in the second (18-20), third (20-23) and fourth (>23) quartile were 0.95 (0.72-1.24), 1.28 (1.00-1.64) and 1.14 (0.85-1.52), respectively; the adjusted hazard ratios for all-cause mortality were 0.98 (0.83-1.16), 1.04 (0.89-1.23) and 0.95 (0.78-1.14), respectively.

Conclusions: Mediterranean or DASH dietary patterns were not associated with cardiovascular and all-cause mortality for patients on hemodialysis.

FR-PO858

Long-Term Trends in the Co-Morbid Disease Burden of Incident Hemodialysis Patients Rita L. McGill,[3] Jennifer L. Bragg-Gresham,[2] Kevin He,[2] Eduardo K. Lacson,[1] Dana Miskulin,[1] Rajiv Saran.[2] *[1]Tufts University School of Medicine, Boston, MA; [2]University of Michigan, Ann Arbor, MI; [3]University of Chicago, Chicago, IL.*

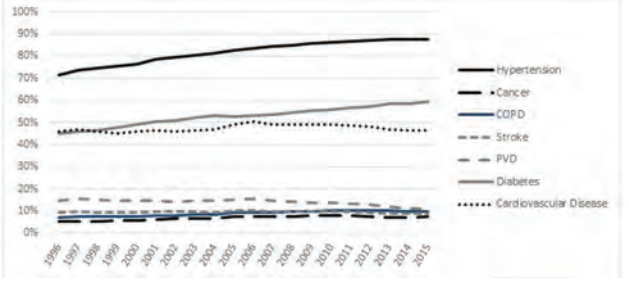
Background: Since April 1995, dialysis facilities and kidney transplant centers in the United States have been required to report the comorbid conditions of all new kidney failure patients to the US Renal Data System (USRDS). We examined the prevalence of several relevant comorbid diagnoses of all new hemodialysis (HD) patients reported to USRDS from 1996-2015.

Methods: All first-time HD patients initiating treatment between January 1996 and December 2015 were included, and analyzed by year of HD initiation. Diabetes and cardiac diagnoses were condensed into single variables, to align data obtained from the 1995 and 2005 versions of the Medical Evidence form. Five year prevalence trends in the proportions of each co-morbid condition were evaluated with logistic regression, treating year of HD initiation as a continuous variable and adjusting for age, sex, and race. Five year prevalence trends were expressed as odds ratios (OR) and 95% confidence intervals (CI), with OR > 1 representing increasing prevalence.

Results: 1,864,386 incident HD patients were assessed. Mean age increased gradually over time from 60.9 to 63.8 years. Time trends revealed linear increases in the prevalence of hypertension (OR=1.34, 95% CI=1.34-1.35) and diabetes (OR=1.16, 95% CI= 1.16-1.17). From 2006 onwards there was decreased prevalence of peripheral vascular disease (OR=0.91, 95% CI=0.91-0.91) and cardiovascular disease (OR=0.92, 95% CI=0.91-0.93). Prevalences of stroke, cancer, and lung disease showed no clinically significant changes.

Conclusions: The HD population in the United States is becoming older, with more hypertension and diabetes, but the prevalences of cardiovascular and peripheral vascular disease have decreased over the past ten years.

Funding: NIDDK Support



Prevalence of Co-morbid Diagnoses, by Year of HD Initiation

FR-PO859

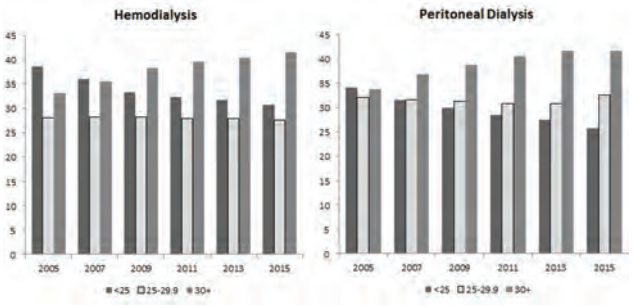
Impact of the Obesity Epidemic on Dialysis Patients Rita L. McGill,[3] Varun Gupta,[1] Klemens B. Meyer.[2] *[1]Creighton University, Northbrook, IL; [2]Tufts Medical Center, Boston, MA; [3]University of Chicago, Chicago, IL.*

Background: Obesity promotes chronic kidney disease directly via glomerular hyperfiltration, indirectly via increased diabetes and cardiovascular disease, and may reduce the likelihood of dying prior to kidney failure. We examined the impact of the US obesity epidemic on body mass index (BMI) of incident dialysis patients.

Methods: Cohorts of all incident adult USRDS patients between 2005 and 2015 with values recorded for BMI were examined, with stratification for hemodialysis (HD) and peritoneal dialysis (PD). BMI in kg/m^2 was categorized as <25, 25-29.9, 30-34.9, 35-39.9, and >=40. Age, race, sex, and end-stage renal disease (ESRD) network were also recorded. Multivariable linear regression was used to estimate the change in BMI over time separately for HD and PD patients.

Results: Among 1,007,774 incident HD patients and 78,745 incident PD patients, the proportions of patients with BMI<25 decreased, the proportions of patients with BMI 25-29.99 were stable, and the proportions of all groups with BMI≥30 increased between 2005 and 2015. After adjustment for age, sex, ESRD network, and race, BMI at dialysis initiation increased 0.147 kg/m^2 per year in HD patients and 0.126 kg/m^2 in PD patients (P<0.0001 for both).

Conclusions: Obesity and morbid obesity have been slowly increasing in the US dialysis population. Depending upon transplantation center criteria, 10-20% of patients enter dialysis with a BMI too high to be considered for kidney transplantation. Despite the paradoxical effects on survival, increasing obesity threatens the health of the dialysis patients, who face increased co-morbid disease burdens, reduced opportunities for optimal vascular access, and lower likelihoods that PD clearance will be adequate.



Distribution of BMI in Patients on HD and PD over Time

FR-PO860

A New, "Lighter" Operational Definition of Frailty in ESKD Ranjani N. Moorthi,[1] Keith Avin,[1] Ravi I. Thadhani,[2] Sharon M. Moe.[1] *[1]Indiana University-Indianapolis, Indianapolis, IN; [2]Massachusetts General Hospital, Boston, MA.*

Background: Frailty detection in incident patients on hemodialysis enables prevention strategies for disability, falls, hospitalizations and death. Traditional operational definitions of frailty developed with community-dwelling older adults includes self-report of "involuntary weight loss of >4.5 kg in the past year". Weight loss in ESKD is difficult to ascertain given volumetric flux during dialysis. We hypothesize that omitting weight criteria from the operational definition of frailty will reclassify incident dialysis patients to capture comorbidities, physical function and disability.

Methods: This is a cross-sectional analysis of subjects in the Indiana cohort in LUCID, a longitudinal study of incident dialysis patients. The 5 traditional frailty criteria are weight loss, exhaustion, low physical activity, slowness and weakness, with a sum score of ≥3 termed "frail". Our "Light" (weight free) definition excludes weight loss and categorizes a sum > 2 as "new-frail". SF36 scores, physical function (gait speed and grip strength), demographics as well as co-morbidities were compared between those "frail" and "new-frail". We also determined the % of subjects of identified as "disabled" in the frail and new-frail groups, using published FiND criteria (which are all self-report).

Results: Mean (SD) age of the 146 subjects was 54 (13) years; 54% male, 71% black, 53% had DM, and median (IQR) dialysis vintage was 90(65) days. New-frail criteria (4 elements) increased the number of participants identified as frail using the traditional 5 element definition from 43 to 90. The new frail compared to the traditional definition increased the odds of being identified as frail 1) in diabetics, (OR 1.56 to 2.31) and 2) for those with inability to walk several blocks (OR 3.032 to 7.792) (both p<0.001). (OR 1.381 to 3.047, p=0.003). The new definition also identified more subjects who are frail, but not yet disabled (n=37% vs traditional criteria 16.5% p<0.001).

Conclusions: Use of weight loss in traditional frailty definitions is complicated by its fluctuations during dialysis. The omission of weight and thus changing to a 4 element index demonstrated higher ORs for disease and function. This tool may be better at identifying frailty risk in women and those frail but not yet disabled. Longitudinal outcomes associated with this definition are currently being studied.

Funding: NIDDK Support

FR-PO861

Low Gait Speed and Difficulty with ADLs in Incident ESKD Patients Ranjani N. Moorthi,[1] Keith Avin,[1] Ravi I. Thadhani,[2] Sharon M. Moe.[1,3] *[1]Indiana University-Indianapolis, Indianapolis, IN; [2]Massachusetts General Hospital, Boston, MA; [3]VAMC, Indpls, IN.*

Background: A gait speed less than 0.8 m/s is associated with poor muscle strength and lower life expectancy in community dwelling elderly. In dialysis patients, low gait speed is associated with poor outcomes but this has not been robustly shown in incident patients. We hypothesized that a gait speed < 0.8 m/s is associated with poor muscle strength and difficulty with activities of daily living (ADL) in those new to dialysis.

Methods: "LUCID" is a longitudinal study of subjects incident to dialysis. This analysis was limited to Indiana University cohort who underwent measures of physical function; we examined the cross-sectional relationship between gait speed < 0.8 m/s and hand grip strength, demographics and ADLs collected on the SF36 by multivariate regression analyses. Data is presented as mean (SD) or median (IQR).

Results: Mean (SD) age of the 146 subjects was 54 (13) years; 54% were men, 71% were black, 53% had diabetes, and median dialysis vintage was 90(65) days. Median gait speed was 0.77(0.25) m/s. Hand grip strength was significantly lower in those with gait speed < 0.8 m/s: left hand 16 (10) vs 22 (16) kg, p<0.001; right gave similar results. Presence of diabetes significantly increased odds of lower gait speed by 2.9 fold (p=0.004), and a lower pre-dialysis diastolic BP, but not systolic, was associated with low gait speed (p=0.02). In a multiple logistic regression model, increased age, presence of DM and female gender were significantly associated with risk of gait speed less than 0.8 m/s. We then determined the association for a low gait speed of < 0.8 m/s to the SF36 questions: No difficulty climbing a flight of stairs decreased the risk by 0.11 times (P = 0.001); Inability to walk several blocks increased the risk by 3.4 times (p=0.008). Median gait speed was significantly lower in those subjects "who never exercised" compared to those were less sedentary: 0.68 (0.32) versus 0.79 (0.30), p=0.046. In a multiple linear

regression model, higher age, female sex, poor grip strength and the inability to walk several blocks were associated with lower average gait speed (adjusted R^2 0.38).

Conclusions: Lower skeletal muscle strength is associated with impaired mobility in patients new to dialysis. Older females with diabetes remain at greatest risk for mobility impairment. Poor gait speed is associated with decreased ability to perform ADLs in an incident dialysis population.

Funding: NIDDK Support

FR-PO862

Does Hemodialysis Impact Motor Performance beyond Diabetes and Peripheral Neuropathy? Objective Assessment of Gait and Balance Using Wearable Technology in a Hemodialysis Clinic

Noreen Siddiqi,[1] He Zhou,[1] Fadwa S. Al-Ali,[2] Abdullah Hamad,[2] Rania A. Ibrahim,[2] Talal Talal,[2] Sergio N. Sardon melo,[2] Bijan Najafi.[1] *[1]Baylor College of Medicine, Houston, TX; [2]Hamad Medical Corporation, Doha, Qatar.*

Background: Poor motor-performance is a serious problem for older adults undergoing hemodialysis (HD) treatment. HD process often leaves these patients too fatigued to engage in any physical activity or daily exercise; further deteriorating their gait and balance. In particular, little is known about how HD impacts gait and balance mainly due to difficulty of bringing these highly vulnerable population to a gait lab. In this study, we used wearable sensors to objectively examine the impact of HD on gait and balance.

Methods: 33 eligible subjects (age=66+6years, body mass index=31+7kg/m^2, male=58%) in 3 age-matched groups were recruited: 11 undergoing HD treatment, 11 with diabetes peripheral neuropathy (DPN) not requiring HD and 11 healthy controls (HC). Gait and balance performances were assessed using wearable sensors. Single task walking (ST), dual task waking (DT), and double stance balance under eyes open (EO) and eyes closed (EC) conditions were measured.

Results: The HD group had the worst gait performance compared to other groups, which reached statistical significant level after adjusting for demographic information. The highest effect size to discriminate between HD and DPN as well as between HD and HC, was ST stride velocity (d=4.825, p<0.001 and d=7.361, p<0.001). The HD group had the worst balance performance of all groups. Between-group differences of ankle sway and hip sway under both EO and EC conditions, reached statistical significance. The largest effect size to discriminate between the HD and DPN groups as well as between the HD and HC, occurred at EO hip sway (d=1.692, p<0.001) and EC hip sway (d=1.868, p<0.001).

Conclusions: To our knowledge this is the first study that utilize wearable technology to objectively characterize gait and balance in HD patients during clinic visit. Results demonstrated HD patients have significantly poorer gait and balance, even when compared to DPN patients. Poor balance and gait reduce the ability of HD patients to be active, which in turn may impact the outcomes and associated risk including poor lower extremities perfusion, foot problems, falls and early frailty.

Funding: Government Support - Non-U.S.

FR-PO863

Low Serum Uric Acid-Mortality Association in Incident Hemodialysis Patients

Yoshiko Nishizawa,[1] Sonoo Mizuiri,[1] Mariko Asai,[1] Kyoka Ono,[1] Kenichiro Shigemoto,[1] Kohji Usui,[3] Kazuomi Yamashita,[2] Michiko Arita,[4] Takao Masaki.[5] *[1]Division of Nephrology, Ichiyokai Harada Hospital, Hiroshima, Japan; [2]Ichiyokai Yokogawa Clinic, Hiroshima, Japan; [3]Ichiyokai Ichiyokai Clinic, Hiroshima, Japan; [4]Ichiyokai East Clinic, Hiroshima, Japan; [5]Nephrology, Hiroshima University Hospital, Hiroshima, Japan.*

Background: The association between serum uric acid (SUA) and mortality is contradictory in studies of hemodialysis (HD) patients. We hypothesized that nutritional status modifies the SUA-mortality association in the HD population.

Methods: We identified 462 patients who had HD treatment over 12 years (2004–2016) and had SUA measurements at HD initiation. Patients were followed-up until death. Kaplan-Meier survival analysis was assessed in each baseline SUA quartile (Q). Univariate Cox regression analyses of 1-year death were performed using data from HD initiation [variables: age, sex, presence of diabetes, hemoglobin, SUA (<5.0 mg/dl or Q4), creatinine, potassium, phosphate, C-reactive protein, geriatric nutritional risk index (GNRI), normalized protein catabolic rate (nPCR), and beta-2 microglobulin]. Multivariate Cox models were performed using significant variables from the univariate analyses. Regression analyses (RA) and multiple RA for SUA were performed using the same independent variables as univariate Cox models.

Results: The cumulative 1-year survival rate of patients belonging to the lowest UA Q1 (<6.2 mg/dl) was 81.1%, and was significantly lower (P<0.05) than patients in Q2 (92.7%, 6.2–7.2 mg/dl), Q3 (94.8%, 7.3–8.3 mg/dl), and Q4 (90.6%, ≥8.4 mg/dl). The cumulative 3 and 5 year survival rates of UA Q1 group were significantly (P<0.05) lower than those of the UA Q4 group (81.4% vs. 93.4%, and 80.7% vs. 89.6%, respectively). One-year all-cause mortality was found to be significantly associated with sex [hazard ratio (HR) 22.3, 95% confidence interval (CI) 2.56–338.6, P<0.01], serum creatinine (HR 0.26, 95% CI 0.10–0.52, P<0.01), serum phosphate (HR 3.22, 95% CI 1.40–8.20, P<0.01), SUA<5.0 mg/dl (HR 8.42, 95% CI, P<0.01), but not UA Q1. The HR of patients with SUA<5.0 mg/dl was 8.4 (P<0.05). In RA, SUA level was significantly associated with age, sex, hemoglobin, creatinine, potassium, phosphate, C-reactive protein, GNRI and nPCR (P<0.05). In multiple RA, SUA level was only associated with serum phosphate (β 0.20, P<0.01), creatinine(β 0.14, P<0.05), and GNRI (β 0.19, P<0.01).

Conclusions: Low SUA level but not high SUA level is associated with 1, 3, and 5-year mortality in incident HD patients, and a link between low SUA concentration and malnutrition status was present in this population.

FR-PO864

Pre-ESRD Uric Acid Levels and 1-Year Post-ESRD Hospital Admissions: A Transition of Care in CKD Study

Christina Park,[1] Melissa Soohoo,[1] Elani Streja,[1] Yoshitsugu Obi,[1] Hamid Moradi,[1] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine, Orange, CA; [2]University of Tennessee Health Science Center, Memphis, TN.*

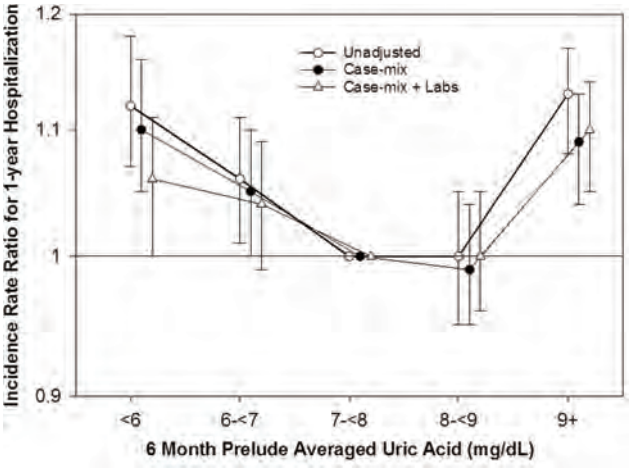
Background: Elevated serum uric acid (SUA) levels are associated with higher risk of mortality in patients with chronic kidney disease, yet are paradoxically associated with lower risk of mortality in hemodialysis patients. Though the relationship of SUA and mortality has been studied, the relationship of pre-ESRD (end-stage renal disease) SUA levels and early post-ESRD hospitalization rates is relatively unknown.

Methods: Among US veterans who transitioned to ESRD in 2007-2014, we identified 10,715 patients with SUA measurements within 6 months prior to the start of dialysis treatment (prelude). Using Poisson regression, we calculated incidence rate ratios (IRR) for hospitalizations during the first year after initiation according to prelude SUA strata, hierarchically adjusting for case-mix and laboratory covariates.

Results: Patients were 67 ± 11 years old, 2% female, 34% African-American and 69% diabetic. The 6-month prelude SUA was 8.1 ± 2.2 mg/dL. The median [IQR] number of hospital admissions during the first year on dialysis was 1 [0-3] with an incidence rate of 2 per 100 patient-years. A U-shaped association was observed between SUA and 1-year post-ESRD hospitalizations. In the fully adjusted model, compared with the reference group (7-<8 mg/dL), the IRR were higher among the low and high (IRR [95%CI]: 1.06 [1.00, 1.11] and 1.10 [1.05, 1.14], respectively), but not intermediate 6-month pre-ESRD SUA strata, for hospitalization within the first year of dialysis [Figure]

Conclusions: High and low prelude SUA levels were associated with a higher rate of hospitalization following the first year of dialysis initiation. Further investigation is needed to examine the mechanism behind pre-ESRD SUA levels and post-ESRD hospitalizations in this population.

Funding: NIDDK Support



FR-PO865

Depression Is Associated with Mortality Independent of Previous Screenings

John Sy,[1] Kirsten L. Johansen.[2] *[1]UCSF Medical Center, San Francisco, CA; [2]University of California, San Franicsco, San Francisco, CA.*

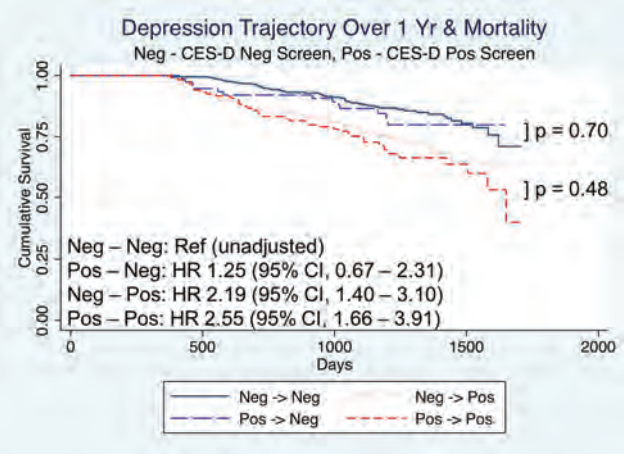
Background: Depression affects up to 40% of dialysis patients and is associated with 50% higher risk of mortality, but it is not known whether changes in depressive symptoms mitigate the risk. We used a longitudinal cohort to analyze the association between depressive symptoms and changes in symptoms with mortality.

Methods: We examined the association between depression screening (at baseline and 12 months) and mortality using Cox models among 762 prevalent dialysis patients enrolled from 6/2009 to 8/2011 in the ACTIVE/ADIPOSE prospective cohort. The CES-D Scale was used as a screening tool for depression. Death was ascertained through linkage with the USRDS as of 3/31/2014. Among 687 patients with paired baseline and 12m data, differences in mortality risk were assessed in 4 groups defined according to depression screening at baseline and 12 m (neg to neg; neg to pos; pos to pos; pos to neg). Models were adjusted for age, sex, race, frailty, comorbidities, and inflammatory makers.

Results: 30.0% screened positive for depression at baseline. After adjustment, screening positive at baseline (HR 1.73, 95% CI 1.28 – 2.34) or 12m (HR 3.50, 95% CI 2.59 – 4.74) was associated with higher mortality risk. Compared to those who never screened positive for depression, those who screened positive at 12m were at statistically significantly higher risk of mortality regardless of baseline depression status (figure). To formally test whether trajectory predicted mortality independently of depression at follow-up, we adjusted for CES-D scores at 12m. Screening positive for depression at 12m was associated with higher mortality, but trajectory was not.

Conclusions: Positive depression screening was associated with higher mortality risk at any time point regardless of changes over the preceding 12 months. Results suggest that effective treatment of depression has the potential to improve outcomes.

Funding: Veterans Affairs Support



FR-PO866

Adverse Outcomes of Subsequent Depression in ESKD Patients Undergoing Peritoneal Dialysis: A Longitudinal Prospective Study surapon nochaiwong,[3,4] Chidchanok Ruengorn,[2,4] Kiatkriangkrai Koyratkoson,[3,4] Chayutthaphong Chaisai,[3,4] Kajohnsak Noppakun,[5] Ratanaporn -. Awiphan,[2,4] Wilaiwan -. Chongruksut,[6,4] Sirisak Nanta.[1,4] *[1]Maesai District Hospital, Chiang Rai, Thailand, Chiang Rai, Thailand; [2]Facultty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand; [3]Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand; [4]Pharmacoepidemiology and Statistics Research Center (PESC), Chiang Mai University, Chiang Mai, Thailand; [5]Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [6]Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. Group/Team: Thai Renal Outcomes Research (THOR) Investigators.*

Background: Existing epidemiological studies demonstrated that depression subsequently predicts adverse outcomes in various populations. Nevertheless, evidences were inconclusive and limited with regard to dialysis patients, particularly in patients on peritoneal dialysis (PD).

Methods: We conducted a prospective single cohort study from the Kidney Center, general hospital, Chiang Mai, Thailand from May 2012 to December 2014, involving adults treated with long-term PD. Participants were followed up until December 2016. Depression was defined by the Beck Depression Inventory (BDI) II score ≥ 14 at baseline. Adverse outcomes of interest included all-cause mortality, cardiovascular (CV) mortality, CV hospitalization, and health-related quality of life (HRQOL). Multivariable Cox regression analyses were used to estimate mortality and hospitalization risk. HRQOL scores using the Kidney Disease Quality of Life (KDQOL-36) instrument were also compared by linear regression. Baseline sociodemographics and known risk factors were adjusted in the models.

Results: Our cohort consisted of 409 PD patients with mean age of 59.3 ± 12.4 years and 44.0% were female. Depression presented in 28.6% at recruitment. After a median follow-up of 1.73 years (835.2 person-year), 139 (34%) participants had died, of which 50 (36%) were attributable to CV death.

Conclusions: Depression is common in PD patients and is strongly associated with increased risk of death, CV hospitalization, and worse HRQOL scores. Further investigation is warranted to establish whether recognition and treatment of depression can improve patient outcomes.

Funding: Government Support - Non-U.S.

Adverse outcomes for depressive disorder (BDI-II ≥ 14) versus non-depressive disorders (BDI-II < 14)

Clinical Adverse Outcomes	No. of Events	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
• All-cause mortality	139	2.61 (1.87 – 3.64)	2.54 (1.61 – 4.02)
• CV mortality	50	3.42 (1.96 – 5.97)	3.36 (1.43 – 7.87)
• CV hospitalization	86	2.78 (1.82 – 4.25)	2.96 (1.67 – 5.26)
Patient-Reported HRQOL	**Outcome Mean**	**Unadjusted Difference (95% CI)**	**Adjusted Difference (95% CI)**
• KDQOL-36 physical component	49.9	-5.1 (-8.9 to -1.2)	-5.4 (-9.6 to -1.1)
• KDQOL-36 mental component	64.3	-4.2 (-7.8 to -0.5)	-4.7 (-8.6 to -0.8)
• KDQOL-36 kidney disease burden	74.2	-4.5 (-7.5 to -1.4)	-5.3 (-8.6 to -2.1)
• Summary KDQOL-36 scores	62.8	-4.6 (-7.8 to -1.3)	-5.1 (-8.6 to -1.7)

CI, confidence interval; HR, hazard ratio

FR-PO867

Temporal Variations in Hemoglobin before and after Transition to ESRD among Veterans: A Transition of Care in CKD Study Omesh N. Ranasinghe,[1] Melissa Soohoo,[2] Christina Park,[2] Connie Rhee,[2] Csaba P. Kovesdy,[3] Kamyar Kalantar-Zadeh,[2] Elani Streja.[2] *[1]UCLA, Los Angeles, CA; [2]UC Irvine, Orange, CA; [3]University of Tennessee Health Science Center, Memphis, TN.*

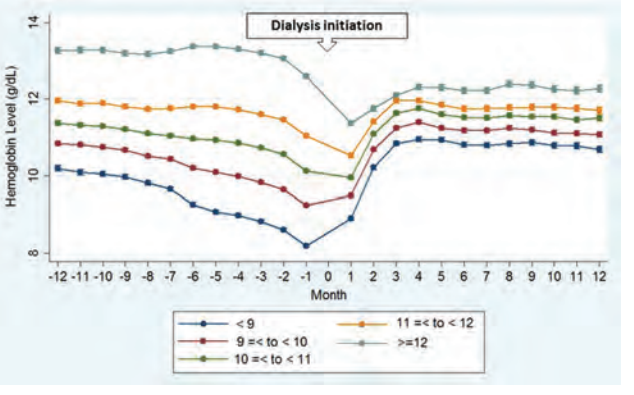
Background: Hemoglobin (Hgb) levels decrease as renal function deteriorates and higher Hgb variability is associated with poorer outcomes in patients transitioning to end-stage renal disease (ESRD). However, the relationship of pre- and post-transition Hgb trajectories as well as its association with post-ESRD outcomes is unclear.

Methods: We used a mixed-effects regression model to evaluate the trajectories of Hgb over the 1-year pre- and post-ESRD initiation periods in 31,472 US veterans who transitioned to ESRD in 2007-2014. Trajectories were stratified by baseline 6-month pre-ESRD (prelude) Hgb concentrations. With hierarchically adjusted Cox models, we examined the association of 1-year prelude Hgb slope with early post-ESRD mortality.

Results: The mean±SD age of the cohort was 68±11 years, with a median[IQR] 1-year prelude Hgb slope of -1.6[-2.6, -0.7] g/dL/year. In the prelude period, all Hgb groups showed a gradual decreasing trend and patients with a lower baseline Hgb (<10 g/dL) had the steepest drop before transition. Hgb levels were then corrected towards a normal range with reduced variation across groups in the post-ESRD period. Those with the steepest Hgb decline in the 1-year prelude (≤-3 g/dL/year) had the highest risk of early post-ESRD mortality (HR[95%CI]: 1.16[1.07, 1.26] ref: slope -2< to ≤ -1 g/dL/year) after demographics adjustment, yet the relationship was attenuated after further laboratory and medication adjustments (HR[95%CI]: 1.03[0.95, 1.12]).

Conclusions: Hemoglobin levels rapidly decrease before dialysis initiation and then quickly normalize after initiation and steep pre-ESRD Hgb decline is associated with higher early post-ESRD mortality risk. Further studies are needed to examine the impact of anemia management during the pre- and post-ESRD period on post-transition dialysis outcomes.

Funding: NIDDK Support



FR-PO868

Does Experience Matter? Nephrology Provider Experience and Patient Outcomes Scott Reule,[2] Robert N. Foley,[2] Paul E. Drawz,[2] Areef Ishani,[1] Mark E. Rosenberg.[2] *[1]None, Minneapolis, MN; [2]University of Minnesota, Minneapolis, MN.*

Background: Provider experience is associated with patient outcomes in select surgical settings. Similar associations have not demonstrated in other fields including nephrology, a field tasked with the care of patients with multimorbidity.

Methods: Using physician data within the AMA Masterfile combined with patient and Medicare claims data from the USRDS limited to the years 2010-2012, we determined associations between experience and survival after initiation of renal replacement therapy.

Results: We identified 360,787 patients on renal replacement therapy cared for by 7,535 providers. A total of 38,889 patients received care from 1,412 providers with 0-8 years of experience; 178,802 patients received care from 3,615 providers with 9-21 years of experience; and 129,855 patients received care from 2,508 providers with > 21 years of experience. Compared to both those with 9-21 and > 21 years of experience, providers with 0-8 years were more likely to be female (34.1% vs. 27.1% with 9-21 yrs.; 34.1% vs. 16.1% with > 21 yrs.) practice in the Midwest region of the US (20.8% vs. 18.9% with 9-21yrs.; 20.8% vs. 17.9%, with > 21 yrs.), and have graduated from an osteopathic training program (6.6% vs. 4.8%; with 9-21 yrs.; 6.6% vs. 2.2%, > 21 yrs.). No significant patient level characteristics were associated with provider experience. Overall, 31.4% of the cohort died at a mean of 5.8 years. Increased provider experience was associated with lower HR of death (AHR 0.95, 9-21 years; AHR 0.96, > 21 yrs. vs. 0-8 yrs.) adjusted for provider and patient level variables. One-year survival after initiation of renal replacement therapy was lowest for those receiving care from those with 0-8 years of experience (Log rank, P < 0.001).

Conclusions: In our limited sample, increasing provider experience is associated with decreased patient mortality on renal replacement therapy providing evidence that experience does matter.

FR-PO869

Screening for Peripheral Vascular Disease in Hemodialysis Patients by Measurement of Skin Perfusion Pressure Saad Mohammed Shariff, Alian Albalas, Ammar Almehmi, Vinay Narasimha Krishna, Timmy C. Lee, Ahmed K. Abdel Aal, Michael Allon. *University of Alabama at Birmingham, Birmingham, AL.*

Background: Peripheral vascular disease (PVD) is common in hemodialysis patients, but the optimal noninvasive screening test is unclear. Ankle Brachial Index (ABI) is the most commonly used test, but its accuracy in ESRD patients is limited by medial calcific sclerosis. Skin perfusion pressure (SPP) in the feet may be a more accurate measure of the severity of PAD, but its use in hemodialysis patients has not been evaluated. An SPP less than 50 mm Hg indicates significant PVD. We analyzed the association of SPP with clinical characteristics of these patients.

Methods: We studied 78 chronic hemodialysis patients. After administration of a brief screening questionnaire and physical examination of the lower extremities, SPP was measured in both lower extremities immediately before a dialysis session. We analyzed the association of SPP (the lower value between the 2 extremities) and individual clinical characteristics.

Results: Among the 78 study patients, 51% had diabetes, and 10% had a history of a lower extremity amputation. Seven patients (9%) had an SPP < 50 mm Hg. Among patients with a history of lower extremity amputation, the SPP in the remaining lower extremity was significantly lower than that measured in patients without prior amputation (p=0.01). There was no significant association of SPP with patient age, gender, diabetes, smoking history, history of stroke, claudication or LDL cholesterol (Table).

Conclusions: Of all the clinical risk factors evaluated, only a history of lower extremity amputation was significantly associated with a lower SPP. We are currently following these patients prospectively to determine the predictive value of SPP for future lower extremity ischemia.

Skin perfusion Pressure measurement in Hemodialysis patients (N=78)

	Skin Perfusion Pressure (mm Hg), Mean ± SE		p- Value
Patient Variable	Yes	No	
Age >= 65 yr (n=25)	78 ± 5	83 ± 4	0.44
Male (n=37)	82 ± 4	80 ± 4	0.71
Diabetes (n=40)	82 ± 4	81 ± 4	0.85
Hx of Amputation (n=8)	59 ± 8	84 ± 3	0.01
Ever Smoked (n=37)	84 ± 4	79 ± 5	0.43
Hx CVA	83 ± 17	81 ± 3	0.70
Claudication (n=12)	76 ± 6	82 ± 3	0.46
Excercise? (n=25)	83 ± 5	80 ± 4	0.69
LDL >= 100 (n=14)	90 ± 8	81 ± 5	0.35

FR-PO870

Understanding Early Mortality after Dialysis Initiation: The Role of Severity of Illness, AKI, and ESRD Certification Diane Steffick,[2] Kevin He,[1] Maggie Yin,[2] Jennifer L. Bragg-Gresham,[2] Vahakn B. Shahinian,[2] Michael Heung,[2] Rajiv Saran.[2] *[1]Kidney Epidemiology and Cost Center, University of Michgian, Ann Arbor, MI; [2]University of Michigan, Ann Arbor, MI.*

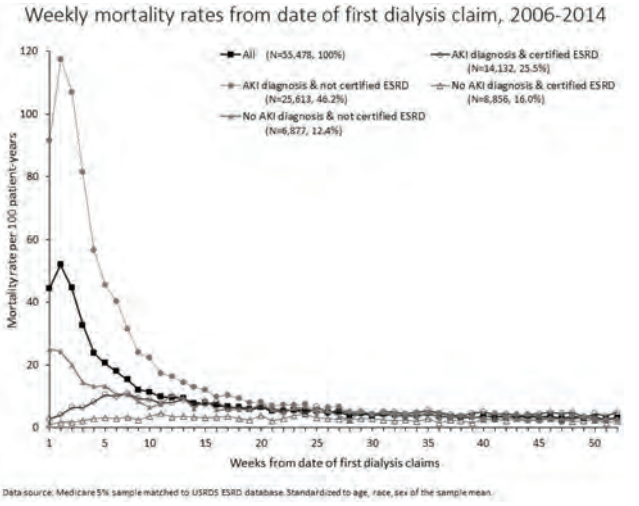
Background: Analysis of CMS-certified ESRD patient mortality has consistently shown an increase in the first weeks after dialysis initiation, peaking at 6-8 weeks and then declining. The factors underlying this mortality pattern are unclear. To explore this, we examined mortality rates from the first dialysis session, which often occurs prior to ESRD certification for many patients, for those patients on Medicare prior to ESRD.

Methods: This retrospective cohort study used the Medicare 5% sample of patients with a dialysis claim, merged with the USRDS ESRD database. Patients had no dialysis in 2005 and their first claim in 2006-2014 was selected. Patients with an ESRD first service date before the first dialysis claim were excluded. Poisson regression was used to calculate weekly mortality rates, standardized to the sample mean age, sex and race.

Results: N=55,478 patients had a first dialysis claim. 69% began as inpatients (39% ICU), 72% had a diagnosis of AKI, and 41% were eventually certified as ESRD. Most AKI patients who were never certified as ESRD started as inpatients (88%, 60% ICU) with high week 1 mortality that increased further in week 2 and then declined. ESRD-certified patients without AKI at first dialysis showed more gradual increase in mortality rates, peaking around week 11 and again at week 24. Only 29% started as inpatients (6% ICU). Non-AKI patients never certified as ESRD were more likely to start as inpatients (48%, 14% ICU) than the ESRD-certified. 69% of AKI patients that were ESRD certified started as inpatients, with 34% in the ICU [Figure].

Conclusions: Severity of illness at the time of dialysis initiation (with or without AKI) seems to drive the high early mortality seen following dialysis initiation. Low mortality rates at the time of ESRD certification are likely an artifact of clinical decision making that channels early survivors into the ESRD program.

Funding: NIDDK Support



FR-PO871

Comparative Effectiveness of Dialysis for Veterans in VA and Non-VA Settings Virginia Wang,[1,2] Cynthia Coffman,[1,2] Karen M. Stechuchak,[1] Paul L. Hebert,[3] Ann M. O'Hare,[3] David Edelman,[1,2] Hollis J. Weidenbacher,[1] Matthew L. Maciejewski.[1,2] *[1]Durham VAMC, Durham, NC; [2]Duke Univ, Durham, NC; [3]VA Puget Sound Health Care System, Seattle, WA.*

Background: Veterans with ESRD have different options for obtaining dialysis including: Medicare-funded community dialysis; VA in-house; and VA-purchased community dialysis (VA-PC). Differences in outcomes across these settings may reflect differences in patient characteristics or quality of care and care coordination, or both. This study compares hospitalization rates and days of care between Veterans receiving outpatient dialysis in VA, VA-PC, and Medicare settings.

Methods: We used VA and Medicare administrative data to construct a national cohort of VA-enrolled Veterans who initiated maintenance dialysis in 2008-2011. Cohort members were classified based on dialysis setting during the 2-year period immediately following dialysis initiation: 1) VA dialysis (VA); 2) VA-PC in non-VA dialysis units; 3) Medicare-financed dialysis in non-VA units (Medicare); or 4) "Mixed". We used logistic and negative binomial regression models to examine the associations between dialysis setting and hospitalization and hospital days (respectively) within 2-years after dialysis initiation (censoring at renal transplant or death), adjusting for patient demographic and clinical characteristics.

Results: Of the 27,301 cohort members, 67% received dialysis outside the VA under Medicare, 11% received dialysis outside the VA through VA-PC, 4% were treated in VA facilities, and 18% were treated in two or more of these settings (Table 1). Most Veterans were hospitalized (83%) and spent an average of 22.7 days in the hospital (median=14, IQR=8) during follow-up. Only Veterans receiving dialysis in two or more settings had higher rates of hospitalization versus those receiving dialysis under Medicare (OR= 1.3; 95% CI= 1.1, 1.5). There were no differences between groups in length of stay (p=0.26).

Conclusions: Veterans who received dialysis in more than one setting were at increased risk for hospitalization during the first two years after dialysis initiation.

Funding: Veterans Affairs Support

Table 1. Selected Descriptive Statistics N= 27,301	DIALYSIS SETTING							
	VA Dialysis Only N = 1,101		VA Purch Care Only N = 3,085		Medicare Only N = 18,267		Mixed N = 4,848	
	N	%	N	%	N	%	N	%
2-year Hospitalization (%)	905	(82.2)	2,501	(81.1)	15,161	(83.0)	4,117	(84.9)
2-year Hospital days (mean, median)	24.1 (12.0)		22.4 (13.0)		21.9 (14.0)		26.0 (14.5)	
2-year Mortality	269	(24.4)	925	(30.0)	7,621	(41.7)	1,104	(22.8)
Male	1,071	(97.3)	3,018	(97.8)	17,839	(97.7)	4,751	(98.0)
Age (mean, SD)	64.3 (10.9)		64.5 (10.5)		73.8 (10.9)		64.0 (10.6)	
Race: White	404	(36.7)	1,751	(56.8)	13,667	(74.8)	2,550	(52.6)
Black	555	(50.4)	1,013	(32.8)	3,462	(19.0)	1,783	(36.8)
Hispanic	111	(10.1)	210	(6.8)	656	(3.6)	356	(7.3)
Other	31	(2.8)	111	(3.6)	482	(2.6)	159	(3.3)
Urban residence	1,062	(96.5)	2,487	(80.6)	15,477	(84.7)	4,160	(85.8)
US Region: Midwest	250	(22.7)	580	(18.8)	4,366	(23.9)	1,039	(21.4)
Northeast	228	(20.7)	222	(7.2)	3,621	(19.8)	431	(8.9)
South	372	(33.8)	1,685	(54.6)	7,619	(41.7)	2,271	(46.8)
West	251	(22.8)	598	(19.4)	2,661	(14.6)	1,107	(22.8)
Home VAMC: ≥30 miles	146	(13.3)	1,785	(57.9)	9,756	(53.4)	2,179	(44.9)
Nearest VA dialysis: ≥30 miles	122	(11.1)	2,668	(86.5)	12,042	(65.9)	2,647	(54.6)
eGFR: <10	679	(61.7)	1,716	(55.6)	8,838	(48.4)	2,852	(58.8)
10-15	313	(28.4)	976	(31.6)	6,315	(34.6)	1,480	(30.5)
≥15	109	(9.9)	393	(12.7)	3,114	(17.0)	516	(10.6)
Dialysis access: Fistula/Graft	308	(28.0)	763	(24.7)	4,034	(22.1)	1,327	(27.4)
Catheter	714	(64.9)	2,155	(69.9)	13,018	(71.3)	3,359	(69.3)
Other/Unknwn	79	(7.2)	167	(5.4)	1,215	(6.7)	162	(3.3)

FR-PO872

Impact of Social Capital and Other Environmental Factors on Hemodialysis Patients' Health Outcomes Marta Reviriego-Mendoza, John W. Larkin, Dugan Maddux, Len A. Usvyat, Franklin W. Maddux. *Fresenius Medical Care North America, Waltham, MA.*

Background: While it is documented that environmental and societal factors impact general population's health outcomes, most focus of dialysis research is on traditional biomarkers. Social capital, which has been defined as "connections among individuals – social networks and the norms of reciprocity and trustworthiness that arise from them" (Putnam, 2000), has been shown to significantly affect patient's health (Kawachi et al., 1997; Yang et al., 2011). We thus aimed to investigate if social capital and other social determinants such as rurality and income have an effect on dialysis patients' hospitalization rates.

Methods: We included all patients who initiated dialysis treatment in the Fresenius Kidney Care clinics from Jan-2013 to Dec-2016. Patient's data was collected during the first 120 days on dialysis and included laboratory values and demographic data. Household income, educational level and rurality data was extracted from the United States Census Bureau at the zip code level. Data of county level measure of social capital was obtained from Rupasingha, et al., 2006. We calculated the impact of these variables on patients' hospital admissions for the reminder of the first year on dialysis using Poisson model with log of exposure days as offset variable.

Results: A total of 49,195 patients were included in the study. From the analysis, it was estimated that both household income (beta=-0.001, p=0.1052) and education (beta=0.0000, p=0.8255) had only a small, non-significant impact on patients' hospitalization rates. We also observed that patients who are married (-0.05, p less than 0.0001), living in a rural setting (-0.062, p=0.0017) and, to a lesser extent, in areas with more social capital (-0.020, p=0.1558), have a favorable impact on hospital admissions.

Conclusions: Rural settings and the existence of social networks may encourage neighbors' awareness. Our analysis suggests that, in addition to the health status and access of care, dialysis patients' clinical outcomes may be affected by their environmental and social surroundings. Deeper analyses are warranted to better understand the effects of social determinants on patients, outcomes.

Funding: Commercial Support - Fresenius Medical Care, North America

FR-PO873

Serum Levels of Resistin-Like Molecule Beta Is Associated with Gastrointestinal Complications in Patients with ESRD on Hemodialysis Kentaro Tanaka,[4,1] Akifumi Kushiyama,[1] Yoshihide Tanaka,[3] Shigeko Hara,[2] Takashi Ozawa.[3] *[1]Division of Diabetes and Metabolism, The Institute for Adult Diseases, Asahi Life Foundation, Tokyo, Japan; [2]Okinaka Memorial Institute for Medical Research, Toranomon Hospital, Tokyo, Japan; [3]Higashiyamato Nangai Clinic, Tokyo, Japan; [4]Higashikurume Ekimae Clinic, Tokyo, Japan.*

Background: Resistin-like molecule (RELM) β is a secretory protein homologous to resistin and reportedly contributes to local immune response regulation in gut and bronchial epithelial cells. RELMβ is experimentally associated with chronic inflammation such as metabolic syndrome, diabetes, dyslipidemia, colon cancer, IBD and atherosclerosis. However, there are no reports in patients with end-stage renal disease (ESRD). To investigate the roles of RELMβ in ESRD, we analyzed the serum levels of RELMβ in ESRD patients before and after hemodialysis and the association between serum RELMβ and gastrointestinal complications (GIC).

Methods: 69 patients with ESRD on hemodialysis provided written informed consent at our dialysis clinic in October 2015. We newly developed RELMβ ELISA and evaluated serum RELMβ from ESRD patients, compared with values from health check group as reference. Patients with severe bronchial asthma, abdominal operation just before measurement, and one failure measurement with non-specific signal were excluded. Then the remaining 66 patients (38 men, 28 women) were investigated for GIC in ESRD patients after serum RELMβ measurement. Onset date of complications were the day patients admitted to hospital for treatment. Statistical analysis was used by cox regression models.

Results: Serum RELMβ levels before dialysis which were markedly elevated as compared with those of control subjects (median 152 vs.60pg/ml, p=0.0008). Serum RELMβ was not eliminated after dialysis (p=0.54). Over median 14-month follow-up, 13 patients (19.6%) developed GIC (enteritis 2; bleeding 6; cancer 4; perforation 1). The patients in the lowest tertile of serum RELMβ (<90pg/ml) had no GIC. In a Cox univariate analysis, 10pg/mL increase of serum RELMβ was associated with GIC (hazard ratio 1.08, [95% CI 1.01-1.15], p=0.01). In Cox multivariate analysis, 10pg/mL increase of serum RELMβ was an independent predictor of GIC after adjusted by age, sex, diabetes, dialysis vintage, BMI, alb, CRP, Kt/V(1.12 [1.04-1.22], p=0.001).

Conclusions: Serum RELMβ is high in patients with ESRD, and high serum level of RELMβ is associated with the onset of GIC. These results suggest that the RELMβ plays a causal role in pathophysiology of GIC in ESRD and might be a useful marker.

FR-PO874

Association of Dialysis-Related Amyloidosis with Lower Quality of Life in Patients on Hemodialysis More Than 10 Years: The Kyushu Dialysis-Related Amyloidosis Study Kazuhiko Tsuruya,[5] Masayoshi Tsuji,[1] Hisatomi Arima,[2] Kunitoshi Iseki,[4] Hideki N. Hirakata.[3] *[1]Department of Preventive Medicine and Public Health, Fukuoka University, Fukuoka, Japan; [2]Preventive Medicine and Public Health, Fukuoka Uniuversity, Fukuoka, Japan; [3]Fukuoka Renal Clinic, Fukuoka City, Japan; [4]Tomishiro Central Hospital, Tomigusuku, Japan; [5]Department of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan. Group/Team: Kyushu Dialysis-Related Amyloidosis Study.*

Background: Dialysis-related amyloidosis (DRA) is one of the important critical issues in patients with long-term dialysis therapy. However, it remains unknown whether DRA is independently associated with patients' quality of life (QOL) and outcomes. Thus, we conducted a multicenter prospective cohort study to examine the association between DRA and QOL using cross-sectional and longitudinal study designs.

Methods: The major inclusion criteria were patients on dialysis for more than 10 years. Diagnosis of DRA was based on the clinical diagnostic criteria of DRA in Japan. Briefly, patients having two or more of five DRA-related findings (polyarthralgia, carpal tunnel syndrome, trigger finger, dialysis-related spondyloarthropathy, or bone cysts) were diagnosed with DRA. QOL was evaluated using EQ-5D health state utility scores. Decline in QOL was defined as an absolute change in EQ-5D scores from baseline to two years of follow-up (ΔEQ-5D scores) less than 0.

Results: A total of 1,314 patients from 72 dialysis facilities were enrolled in this study. Among them, 277 (21%) were diagnosed with DRA. EQ-5D scores were significantly lower in patients with DRA compared to those without DRA [median (interquartile range): 0.649 (0.533–0.768) vs. 0.768 (0.693–1.000); P<0.001]. Among the all patients, 931 (71%) could be followed for two years and were divided into three groups according to baseline and follow-up DRA status: patients with DRA at baseline (G1, n=190), those who had not DRA at baseline, but developed DRA during the follow-up period (G2, n=44), and those without DRA both at baseline and after two years (G3, n=697). Although G3 had shorter dialysis vintage (15 years) compared to G1 (27 years) and G2 (23 years), age, sex, and previous history of cardiovascular diseases were comparable among three groups. Decline in QOL was observed in significantly greater proportion in G1 (45%, P<0.05) and G2 (66%, P<0.01) compared to G3 (35%). Multivariable-adjusted odds ratios (95% confidence intervals) for the decline in QOL in G1, G2, and G3 were 1.40 (0.84–2.31) and 2.26 (1.01–5.09), and 1.00 (reference), respectively. The ΔEQ-5D scores were significantly lower in G2 than G3.

Conclusions: DRA was associated with lower QOL in hemodialysis patients with long-term dialysis therapy.

Funding: Commercial Support - KANEKA

FR-PO875

Randomized, Placebo-Controlled Study on the Efficacy of CR845 in Reducing CKD-Associated Pruritus in Hemodialysis Patients Robert H. Spencer, Catherine Munera, Maria S. Oberdick, Joseph W. Stauffer, Frederique Menzaghi. *Cara Therapeutics, Inc., Stamford, CT.*

Background: With no treatment approved in the US, patients with chronic kidney disease-associated pruritus continue to be afflicted by this debilitating condition. The present study evaluated the anti-pruritic efficacy of the novel potent and selective peripherally-acting kappa-opioid receptor agonist CR845 in hemodialysis (HD) patients with moderate-to-severe pruritus.

Methods: 174 HD patients experiencing pruritus for ~4.4 years with a mean baseline numerical rating score (NRS) >4 for worst itching intensity (0 [no itching] to 10 [worst itching imaginable]) were enrolled across 33 dialysis centers. Patients were randomized to receive one of 3 intravenous doses of CR845 (0.5 mcg/kg, n=44; 1 mcg/kg, n=41 and 1.5 mcg/kg, n=44) or placebo (n=45) at the end of each dialysis session over an 8-week treatment period. The primary efficacy endpoint was the change in the weekly mean of the daily 24-hour worst itching intensity NRS score from baseline (one week mean prior to randomization) to Week 8.

Results: Demographics and baseline features were well balanced across treatment groups, and CR845 was well tolerated at all doses. Average reduction in itch NRS scores from baseline (LS Mean ± SE) ranged from -2.8 (±0.38) in the 1.0 mcg/kg group (95% CI: -3.5 to -2.0) to -3.8 (±0.38) in the 0.5 mcg/kg group (95% CI: -4.5 to -3.1), with no significant differences between doses. The reduction in itch NRS scores was significantly different from placebo at the 0.5 and 1.5 mcg/kg dose (p≤ 0.019) with 64% (p=0.016) of patients in the 0.5 mcg/kg dose group reporting ≥ 30% reduction in worst itch NRS scores by Week 8, compared to 38% of the placebo patients. These results were supported by a significantly higher proportion of CR845 patients reporting that their itch was "very much improved" or "much improved" at the end of the study compared to placebo (66% CR845 vs 42% placebo; p=0.007) as measured by the Patient Global Impression of Change, along with a significant improvement in quality of life, including quality of sleep.

Conclusions: CR845 effectively and safely reduced itch intensity in HD patients with moderate-to-severe pruritus over 2 months of treatment.

Funding: Commercial Support - Cara Therapeutics, Inc.

FR-PO876

The Moisturizer Improves Pruritus of Dialysis Patients by Increasing Water Content in the Stratum Corneum Yukie Yoshida,[2,1] Kazumasa Hashimoto,[2] Hidehisa Saeki,[3] Seiki Fujimoto,[4] Shuichi Tsuruoka.[1] *[1]Department of Nephrology, Nippon Medical School, Tokyo, Japan; [2]Kidney Clinic, Nippon Medical School, Tokyo, Japan; [3]Department of Dermatorogy, Nippon Medical School, Tokyo, Japan; [4]Maruho Co., Ltd., Osaka, Japan.*

Background: In dialysis patients, skin disorder (dryness, itching, etc.) is frequently observed and treated with moisturizers without sufficient evidence. We therefore evaluated the usefulness of a moisturizer in the treatment of dry skin in dialysis patients in an exploratory manner.

Methods: This study was an open-label, randomized, before-after, parallel group comparison study conducted after approval by the Institutional Review Board of Nippon Medical School. The study was funded by Maruho Co., Ltd. (Osaka, Japan), and registered at the University Hospital Medical Information Network (UMIN) Clinical Trials Registry as UMIN000017016. Included were 12 maintenance hemodialysis outpatients in stable condition in our hospital, randomized to receive treatment with a lotion containing heparinoid (Maruho) for 2 weeks followed by 2-week washout (Group A: 6 subjects) or another 2-week treatment (Group B: 6 subjects). The primary efficacy measure was water content in the stratum corneum in the hypochondrium (flank). Secondary measures included visual analogue scale (VAS) itching score. Safety was evaluated based on adverse events. Efficacy data were collected on Day 1 and after 1, 2, 3, and 4 weeks of treatment, on which the water content was measured using a Corneometer (Courage-Khazaka) at 1 to 2 hours after the start of dialysis. Subjects additionally assessed their itching at the application site on a 100-mm VAS before dialysis.

Results: The moisture in the stratum corneum significantly increased at Weeks 1 and 2, then significantly decreased in Group A, in which study treatment was discontinued, but was almost maintained in Group B, in which treatment was continued. Itching VAS score significantly decreased at Weeks 1 and 2, indicating reduction of itching, then increased in Group A, suggesting that itching returned to the baseline condition. The score decreased in Group B, indicating further reduction of itching. At Week 4, the score was significantly different between Groups A and B. As for safety, mild upper respiratory tract infection was reported in 1 subject during treatment, but was not related to study treatment.

Conclusions: Continuous moisture retention with a preparation containing heparinoid may be effective and safe to reduce dry skin and maintain good skin condition in dialysis patients.

Funding: Commercial Support - Maruho Co., Ltd. (Osaka, Japan),

FR-PO877

The Present Status of Fatigue in Maintenance Hemodialysis Patients and Its Influencing Factors Bing Zhuang,[2] Junwei Yang.[1] *[1]Second Affiliated Hospital, Nanjing Medical University, Nanjing, China; [2]The second affiliated hospital of nanjing medical university, Nanjing, China.*

Background: Fatigue is a common and complex phenomenon in maintenance hemodialysis patients that significantly decreases the health-related quality of life, especially after hemodialysis treatment, frequently requiremore time to recover. The aim of this study was to analysis the fatigue status of hemodialysis patients in our dialysis center, explore the influencing factors of fatigue in these patients and proposeeffective intervention measures.

Methods: This study is a observational study. From June 2016 to February 2017,120 maintenance hemodialysis patients were enrolled the research in our center. The patients completed the questionnaires, including the Fatigue Assessment Scale(FAS) and the time of recovery from a dialysis session. The serum concentration of hemoglobin, albumin, electrolyte and the levels of PH, bicarbonate, lactic acidwere examined to statistics and analysis.

Results: 120 questionnaires were distributed and 111 were taken back, and 109 (90.8%) were effective among the questionnaires. The incidence of fatigue in maintenance hemodialysis patients was high, 63 of 109 (57.8%) patients enrolled in the study assessed of fatigue, 9.2% of patients had a severe fatigue. The time of recovery from hemodialysis (TIRD) is differently from 30 minutes to 24 hours. 66.1% of patients' recovery time was shorter than 2 hours, 29.3% was 2-12 hours, 4.6% of patients taked longer time to recover from a dialysis session. Most of them required more rest or sleep immediately after dialysis. The result of analysis is that the fatigue of patients was correlated with comorbidities (OR=0.202),the levels of lactic acid (OR=3.933) and the bicarbonate (OR=0.643) after dialysis. The rate of ultrafiltration,the levels of serum sodium and the levels of lactic acid after dialysis are different to the TIRD, the raised of lactic acid (OR=4.21) is associated of longer recovery time.

Conclusions: The incidence of fatigue patients in our dialysis center is more than a half,a few number of patients had a heavy fatigue,required more rest or sleep immediately after dialysis. The levels of lactic acid was the significant influencing factor of the fatigue in hemodialysis patients,TIRD was correlated with the raised of lactic acid during the dialysis process.

Funding: Government Support - Non-U.S.

FR-PO878

The Cataract Surgery Related Complications in Patients with ESRD Chia-Chun Wu. *Chi Mei Medical Center, Tainan, Taiwan.*

Background: Higher surgery risk in end stage renal disease (ESRD) patients is well known, but most reports focus on major surgeries. Cataract is the most common cause of visual loss worldwide. Although catarct surgery is a minor surgery, surgery related complications still happen. Herein, we want to know if ESRD patients have higher risk of cataract surgery related complications.

Methods: The National Health Insurance Research Database in Taiwan was used to identify patients who received cataract surgery. Patients with regular hemodialysis(HD) or peritoneal dialysis longer than 3 months were selected as study group. Control group is patients without chronic kidney disease and matched on age, gender and surgery year. Other exclusion criteria is any eye surgery within 3 years prior cataract surgery. The main outcome measures are cataract surgery–related complications within 3 months after surgery. Conditional logistic regression was used for the risk of complications.

Results: Patients with ESRD have higher percentage of hypertension, diabetes mellitus and more likely to have a cataract surgery in medical centers. Patients with ESRD have a 6.81 times higher risk to have vitreous hemorrhage within 3 months after cataract surgery. The odds ratios of vitreous hemorrage are 4.20, 4.86, 9.8 in the 1st, 2nd and 3rd month individually.

Conclusions: Patients with ESRD have a higher risk of vitreous hemorrhage after cataract surgery. Heparin is frequently used during HD to prevent clot formation in blood circuit, this analysis result might afford a reference to adjust the heparin dose in HD patients after receiving cataract surgery.

The multiple complications after cataract surgery within 3 months in ESRD patients and Control group

	ESRD patients (N=439)	Controls (N=1317)	Adjusted OR(95% CI)	P-value
Cornea edema	13(2.96)	27(2.05)	1.14(0.54-2.40)	0.7317
Glaucoma	40(9.11)	125(9.49)	0.72(0.47-1.10)	0.1257
Endophthalmitis	1(0.23)	5(0.38)	0.42(0.04-4.58)	0.4773
Vitreous hemorrage	20(4.56)	4(0.30)	6.81(1.98-23.35)	0.0023*
Retinal detachment	3(0.68)	5(0.38)	1.66(0.31-8.84)	0.5523
Dropped nucleus	10(2.28)	11(0.84)	2.28(0.83-6.31)	0.1119
Wound dehiscence	1(0.23)	4(0.30)	0.61(0.05-7.55)	0.7034

ESRD=End stage renal disease; OR=Odds ratio.

Adjusted factors :Hypertension, Diabetes mellitus, Myopia, Hospital level, use Anti-platelet drugs or anticoagulant

FR-PO879

Sex-Based Immunological Disparity in ESRD Patients Feng-Jung Yang,[1,2] Yen-Ling Chiu.[1,3] *[1]Graduate Institute of Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan; [2]Internal Medicine Department, National Taiwan University Hospital Yunlin Branch, Douliu, Taiwan; [3]Internal Medicine Department, Far Eastern Memorial Hospital, Banciao, New Taipei City, Taiwan.*

Background: Sex differences in the immune response and in infectious disease susceptibility have been well described, although the mechanisms underlying these differences remain incompletely understood. Patients with end-stage renal disease may face higher risk of infection. The activity and distribution of T cell and monocyte subsets between the sexes is still unknown.

Methods: The immunity in ESRD study (iESRD) recruited 412 hemodialysis patients from both northern and southern Taiwan. Peripheral blood were sampled before hemodialysis session and processed immediately for mononuclear cell isolation and staining. Using multicolor flow cytometry, lymphocytes were separated into subpopulations including naive Tn cells, central memory TCM, effector memory TEM, and terminally differentiated TEMRA. Monocytes were separated into three groups M1 M2 M3. Plasma levels of high-sensitivity C reactive protein was determined.

Results: Among CD4+/CD8+ T cell subsets, male patients showed decreased percentage of naïve CD4+/CD8+ Tn cell and increased percentage of effector memory CD4+/CD8+ TEM. Among monocytes subset, female patients showed increased percentage of classical monocytes and decreased percentage of nonclassical monocytes CD14+CD16+ monocytes. The M1 percentage of ESRD was lower than general population ~80%. Low M1 and high M3 indicating more inflammatory response in the this group. Besides, female patients have more numbers of naïve CD4+/CD8+ Tn cell and central memory CD8 TCM but less numbers of nonclassical monocytes M3.

Conclusions: Males and females differ in innate and adaptive immune responses. These sex-based immunological disparities contribute to variations in the incidence of autoimmune diseases and malignancies, susceptibility to infection. Our study showed the immune age of female was younger than male in ESRD. Male have more 'Non-classical' subtype monocytes which display more 'inflammatory' characteristics Sex associated immune response should be further investigated in the pathogenesis of infection and aging in ESRD.

FR-PO880

A Comparison between Hemodialysis and Peritoneal Dialysis on the Risk of Hip Fractures in Diabetics with Chronic Renal Disease Ammar Qureshi,[2] Fernando R. Aguilar,[1] Nesreen Benhamed.[3] *[1]Georgetown University Hospital, Washington, DC; [2]Internal Medicine, Marshall University, Huntington, WV; [3]Internal Medicine, MUSOM, Barboursville, WV.*

Background: It is well established that bone fragility and fractures are common complications of patients on dialysis, notably if they are diabetics. It remains uncertain if the risk of fractures changes depending on the dialysis modality either hemodialysis (HD) or peritoneal dialysis (PD). We aim in this study to set the risk of bone fractures between those two modalities in patients with DM2.

Methods: Data was extracted from the 2005 to 2012 Nationwide Inpatient Sample (NIS). Using propensity score matching, ESRD-DM patients on PD were matched with patients on HD at a 1:1 ratio. Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results: Among 586,238 patients with incident ESRD, 568,469(96.97%) and 17,769(3.03%) were initiated on HD and PD, respectively, during the hospitalization. After matching both groups, we find no difference in the rate of ulnar (0.1 vs 0.1; p=1) and hip fractures (0.3 vs 0.31; p=0.78) while spine (0.32 vs 0.21; p<0.0001) and humeral fractures (0.21 vs 0.15; p= 0.01) occur significantly more in the HD group.

Conclusions: Diabetic patients with ESRD on HD have higher risk for spine and humeral fractures. Further studies are needed to evaluate the different bone pathogenesis of both dialysis modalities to explain our findings.

FR-PO881

Association of Pre-ESRD Serum Bicarbonate with Post-ESRD Mortality among Incident Dialysis Patients: A Transition of Care in CKD Study Yoshitsugu Obi,[1] Christina J. Catabay,[1] Melissa Soohoo,[1] Christina Park,[1] Elani Streja,[1] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine, Orange, CA; [2]University of Tennessee Health Science Center, Memphis, TN.*

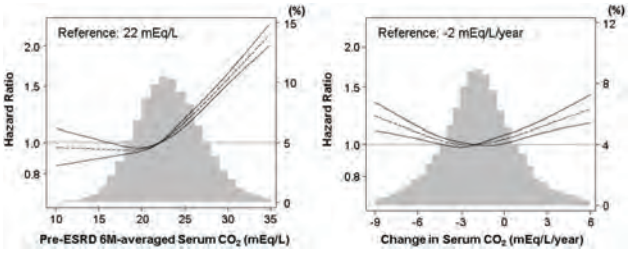
Background: Serum bicarbonate ($S\text{-}CO_2$) levels decline as CKD progresses and rise after dialysis initiation. While the current clinical guidelines suggest maintaining $S\text{-}CO_2$ > 22 mEq/L among pre-ESRD patients with CKD, there are scarce data on the impact of pre-ESRD $S\text{-}CO_2$ levels on post-ESRD mortality.

Methods: Among 32,655 US veterans who transitioned to dialysis between October 2007 and March 2014, we calculated 6-month averaged levels and annual decline rate of $S\text{-}CO_2$ during the last pre-ESRD period, and then estimated their risk for all-cause mortality with Cox regression adjusting for demographics, comorbidities, BMI, and eGFR.

Results: Mean baseline concentrations and rates of decline of $S\text{-}CO_2$ were 23±4 mEq/L and -1.8±2.4 mEq/L/year, respectively. Higher $S\text{-}CO_2$ >20 mEq/L showed higher adjusted mortality risk while there was no clear trend in the lower range. Compared to $S\text{-}CO_2$ of 22 mEq/L, adjusted HRs (95%CIs) were 0.96 (0.94–0.97), 1.09 (1.07–1.12), and 1.22 (1.18–1.27) at 20, 24, and 26 mEq/L, respectively. Consistent associations were observed irrespective of sodium bicarbonate use. There was a U-shaped association between the rate of decline in $S\text{-}CO_2$ and mortality with the lowest risk being approximately -2.0 mEq/L/year. Both faster decline and rise in $S\text{-}CO_2$ were more strongly associated with mortality among sodium bicarbonate users vs. non-users.

Conclusions: Pre-ESRD $S\text{-}CO_2$ levels above 20 mEq/L exhibited an incrementaly higher post-ESRD mortality risk. Further studies are needed to elucidate whether high S-CO2 is a surrogate of low protein intake, comorbid states, or other mechanisms.

Funding: NIDDK Support



FR-PO882

Phosphate Binder Use and Cost Trends in US Dialysis Patients Wendy L. St. Peter,[3] Lori Wazny,[1] Eric D. Weinhandl.[3,2] *[1]Manitoba Renal Program, Winnipeg, MB, Canada; [2]NxStage Medical, Inc., Victoria, MN; [3]University of MInnesota, Minneapolis, MN.*

Background: Phosphate binder costs for US dialysis patients having Medicare Part D was almost $1 billion in 2014. Our objectives were to examine current trends in use and cost data for phosphate binders and to determine gross Medicare Part D costs per equivalent phosphate binding dose.

Methods: Using data from United States Renal Data System, we report trends in phosphate binder use and costs for Medicare-covered dialysis patients with Medicare Part D prescription drug coverage from 2006-2013. We identified all medication fills for phosphate binders (calcium acetate, lanthanum carbonate, sevelamer carbonate, and sevelamer hydrochloride) and all Part D-covered drugs. For each year, we calculated percent of patients using phosphate binders (overall and by binder), weighted by cumulative follow-up time per patient, cumulative gross costs, gross costs per patient-year and gross costs per user-year. For each phosphate binder, we estimated gross costs per calcium carbonate-equivalent gram by applying relative phosphate binding capacities equal to 1.00 for calcium acetate, 2.00 for lanthanum, and 0.75 for sevelamer products.

Results: Number of dialysis patients with Medicare Part D coverage filling phosphate binder prescriptions steadily increased from 174,974 in 2006 to 263,404 in 2013 (50% cumulative increase), while percentages filling phosphate binder prescriptions remained stable at around 75% while gross costs per user-year for phosphate binders increased from $1433 to $3716 (159% cumulative increase, or 15% year-over-year increase). Gross costs per user-year for all other Part D-covered prescription medications in dialysis patients cumulatively increased by 44% (5.4% year-over-year growth). Between 2006 and 2013, gross costs per user-year for calcium acetate, sevelamer carbonate, and lanthanum carbonate increased by 153%, 284%, and 307%, respectively. Adjusted for relative phosphate binding capacity, gross costs of calcium acetate, lanthanum carbonate, and sevelamer carbonate were $0.79, $4.67, and $4.85, respectively, per one calcium carbonate-equivalent gram in 2013.

Conclusions: Growth in cost of phosphate binders outpaced growth in costs of other Medicare Part D medications in dialysis patients. To achieve an equal degree of phosphorus control in an average patient, Medicare expended roughly 6 times as much on sevelamer carbonate and lanthanum carbonate as on calcium acetate in 2013.

FR-PO883

Differential Effects of Hemodialysis and Transplantation on Cognitive Function in ESRD Mark D. Findlay,[1,2] Patrick B. Mark,[1,2] Jesse Dawson.[1,2] *[1]University of Glasgow, Glasgow, United Kingdom; [2]Queen Elizabeth University Hospital, Glasgow, United Kingdom.*

Background: Cognitive impairment (CI) is common in people receiving hemodialysis (HD). We examined for changes in cognitive function during the HD session and the effect of continued HD or renal transplantation on cognitive function at 12 months

Methods: Prospective observational study in adult patients on chronic HD. A neurocognitive battery was performed during a routine dialysis session and on a non-dialysis day. Cognitive tests included the Montreal Cognitive Assessment and additional tests of language, memory, processing speed and executive function. Mean flow velocity (MFV) was measured in the middle cerebral artery before, during and after dialysis using transcranial Doppler ultrasound. We compared cognitive function and MFV on and off dialysis and assessed the relationship between any changes using Spearman's rank correlation. Cognitive function was reassessed in a similar fashion 12 months later.

Results: 97 participants were enrolled (median age 59yr [IQR 51, 67], 40% female, median duration of end stage renal disease 1.76 years [IQR 0.6, 4.0]). 88 participants attended both intradialytic and non-dialysis day assessments. CI was present in 44(50%). Those with CI were more likely to have hypertension (95.5 v 81.8%, p<0.05). MFV declined during dialysis (mean; 49.8 to 43.2cm/s, p<0.001) correlating with UF volume, r=0.49 p<0.001. Participants scored lower on tests of processing speed and executive function during dialysis when compared to their non-dialysis day scores, p<0.001. Decline in test scores for language and executive function correlated with the dialysis-related fall in MFV, r=-0.27 p=0.02 and r=0.44 p<0.001 respectively. At 12 months, 59 remained on dialysis; 15 transplanted, 5 withdrew and 5 died. Improvements in language and attention tests were observed in those continuing HD, whereas those who received a transplant demonstrated improvements in executive function and processing speed, p<0.05.

Conclusions: Occult CI is common and cognitive function demonstrably worse during dialysis. Cerebral blood flow is reduced during HD, relating to UF volume and a measurable decline in cognitive function. The transient decline in executive function during dialysis does not appear to exert a progressive effect at 12 months, however its significant improvement following transplant highlights an aspect of cognitive function vulnerable to continued HD.

Funding: Government Support - Non-U.S.

FR-PO884

Implications of Variation in Cognitive Performance on Dialysis: A Pilot Study of an Electronic Cognitive Battery Meera N. Harhay,[2] Lucy Robinson,[1] Hasan Arif,[2] Karthik M. Ranganna,[2] Maria T. Schultheis.[1] *[1]Drexel University, Philadelphia, PA; [2]Medicine, Drexel University College of Medicine, Philadelphia, PA.*

Background: Cognitive impairment (CI) is common among dialysis patients, and some patients may exhibit transient CI during dialysis therapy. However, traditional neurocognitive testing has limited feasibility for use in clinical settings, and no studies have examined whether a decline in cognition during dialysis predicts health outcomes. We examined the association of variation in performance on the electronic Cogstate Brief Battery, consisting of four card-based cognitive tasks called Detection (processing speed), Identification (attention), One Card Learning (visual memory) and One Back (working memory), on the risk of subsequent hospitalization in a cohort of hemodialysis patients.

Methods: We enrolled 28 participants from a single dialysis unit in Philadelphia, PA. Participants completed the 10-minute Cogstate battery twice, once prior to dialysis and again during the last hour of dialysis therapy. For both sessions, participants were defined as "low" scorers on individual tasks if they scored below the cohort median score. We estimated age-adjusted Poisson regression models for the association of pre-dialysis and intradialytic cognitive performance and the number of hospitalizations participants experienced during six months of follow-up.

Results: The average age of the cohort was 58 years (SD 13), 97% were black, 60% were female. Mean dialysis duration was 6 years (range 2-20). After six months of follow-up, 35% of the cohort had at least 1 hospitalization, and 18% of participants (n=5) had >1 hospitalization. In age adjusted Poisson regression models, compared to participants who scored higher than the median both times for the Identification task, those who scored 1) higher pre-dialysis and lower during dialysis and 2) those that scored lower both times had a 9-fold and 7.5-fold increase in the expected number of hospitalizations in six months, respectively (p=0.03 for both). Reasons for hospitalization in low scorers included syncope and mechanical fall.

Conclusions: In this pilot study, we found that consistently low performance on a self-administered electronic cognitive task, or poorer performance during dialysis, signaled hospitalization risk among prevalent hemodialysis patients. Given limitations

due to low sample size, future studies should confirm and expand on these findings in larger cohorts.

Funding: NIDDK Support, Commercial Support - Frenova Renal Research, Private Foundation Support

FR-PO885

Fall Injury Prediction Using Quadriceps Thickness by Ultrasound Measurement of Patients with ESRD on Hemodialysis: A Prospective Study

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Background: Patients with end stage renal disease (ESRD) have an increased risk of fall injury. Recently, quadriceps muscle thickness (QT) by ultrasound (US) measurement has been reported as valid assessment of muscle wasting and physical function and easily applicable at the bedside. The aim of this study is to investigate if QT by US can prospectively predict fall injury in patients with ESRD on hemodialysis.

Methods: Within 732 patients with ESRD on hemodialysis at our 4 dialysis Clinics in April 2015, 182 patients provided written informed consent. The QT by US is indicated as the sum of both legs. The relative reliability of QT by US measurement was confirmed using intraclass correlation coefficient(ICC);right QT ICC(1,2)=0.99 and left QT ICC(1,2)=0.98. Patients with unstable condition such as discharge or initiation of oral steroid administration, or drop out before the first measurement were excluded. 179 patients (men127, women52) were studied. A fall was defined as an event in which a person was inadvertently located on the ground or other low position. Fall injury was defined as any injury with a fall, based on patient's self-report including bone fracture, crack, bleeding, bruise, and abrasion.

Results: Over median 12-month follow-up period, 42 patients (23.4%) developed the fall injury in 179 patients. When subjects were stratified by QT level into sex-specific tertiles, the patients in the lowest tertile (men<3.66cm, women<3.52cm) indicated a significantly higher risk of fall injury than the middle and highest tertiles by using Kaplan Meier estimate (logrank test, p<0.05). In a univariate analysis using Cox regression model, 1cm decrease of the QT by US indicated significant risk increase (hazard ratio 1.85, [95% CI 1.33-2.70], p=0.0002). In multivariate analysis, the hazard ration between the QT by US remained significant after adjusting various confounding factors such as sex, age, dialysis vintage, BMI, diabetes mellitus, nutritional state, grip strength (1.64, 1.04-2.63,0.03).

Conclusions: QT by US is an independent and useful predictor of fall injury in patients with ESRD on hemodialysis.

FR-PO886

Evaluating the Real-World Safety and Effectiveness of Sucroferric Oxyhydroxide in Dialysis Patients: An Interim Analysis of the VERIFIE Study

Marc G. Vervloet,[9] John N. Boletis,[12] Angel Luis M. De Francisco,[5] Denis Fouque,[11] Philip A. Kalra,[7] Markus Ketteler,[6] Piergiorgio Messa,[13] Manuela Stauss-Grabo,[3] Viatcheslav Rakov,[10] Sebastian Walpen,[10] Linda H. Ficociello,[1] Jacques B. Rottembourg,[4] Christoph Wanner,[8] Jorge B. Cannata-Andia.[2] *[1]Fresenius Medical Care - North America, Waltham, MA; [2]Hospital Universitario Central de Asturias, Oviedo, Spain; [3]Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany; [4]Groupe Hospitalier Pitié-Salpêtrière, Paris, France; [5]Marques de Valdecilla University Hospital, Santander, Spain; [6]Coburg Clinic and KfH-Dialysis Center, Coburg, Germany; [7]Salford Royal Hospital NHS Trust, Salford, United Kingdom; [8]University Hospital of Würzburg, Wuerzburg, Germany; [9]VU University Medical Centre, 2051 JN Overveen, Netherlands; [10]Vifor Fresenius Medical Care Renal Pharma, Glattbrugg, Switzerland; [11]University Claude Bernard, Pierre Benite, France; [12]Laiko University Hospital, Athens, Greece; [13]Maggiore Hospital, Milan, Italy.*

Background: Sucroferric oxyhydroxide (SFOH) is a non-calcium-, iron-based phosphate binder. The VERIFIE study aims to investigate the real-life safety and effectiveness of SFOH in prevalent dialysis patients with hyperphosphatemia.

Methods: This is a non-interventional, prospective, multicenter, European cohort study (scheduled observation period per patient: 12–36 months; planned enrollment: 1000 patients). The non-interventional design allows the observation of patients in a broad range of settings reflecting routine clinical practice. SFOH initiation was based on the physician's decision and was not influenced by study inclusion.

Results: This interim analysis presents data from 244 patients (mean age: 63.8 [standard deviation: 14.7] years; 64.0% male) included in the safety analysis set, of whom 219 were included in the full analysis set for the evaluation of laboratory parameters (serum ferritin and serum phosphorus). The mean observation period was 129 days. Phosphate binder use at baseline was reported in 64% of patients, mostly sevelamer (55%), calcium-based (39%) or lanthanum (34%). Mean initial dose of SFOH was 1175.4 mg (2.4 pills/day), rising to 1299.4 mg (2.6 pills/day) at the time of this analysis. The large majority of adverse drug reactions reported were gastrointestinal (Table). Serum phosphorus decreased from baseline to last visit by a mean of 0.8 mg/dL (p<0.0001). Serum ferritin levels were not significantly different from baseline by the last visit (p=0.23).

Conclusions: These interim real-world data show that SFOH is well tolerated, and no new safety risks were identified. In addition, SFOH was effective at reducing serum phosphorus in real-world practice.

Funding: Veterans Affairs Support

Table: Key safety and effectiveness measures

Parameter	Time point (N=244)
ADRs, n (%)	90 (36.9)
Serious ADRs, n (%)	8 (3.3)
Treatment discontinuation, n (%)	38 (15.6)
Gastrointestinal ADRs, n (%)	83 (34.0)
Discolored feces	43 (17.6)
Diarrhea	25 (10.3)
Serum ferritin, mean ng/mL (SD)	
Baseline (n=198)	431.1 (373.93)
Last visit (n=110)	444.1 (348.39)
Serum phosphorus, mean mg/dL (SD)	
Baseline (n=209)	6.5 (1.61)
Last visit (n=182)	5.7 (1.72)

ADR, adverse drug reaction; SD, standard deviation

FR-PO887

Mineral Bone Disorder Management in Hemodialysis Patients: Comparing PTH Control Practices in Japan with Europe and North America: The Dialysis Outcomes and Practice Patterns Study (DOPPS)

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Background: High circulating level of parathyroid hormone (PTH) is associated with elevated mortality. While the Japanese Society for Dialysis Therapy suggests a low/narrow PTH target, other international guidelines suggest much higher PTH targets. This discrepancy may help explain better survival in Japanese hemodialysis patients, and we analyzed PTH control practices in Japan compared with other regions.

Methods: We analyzed data from hemodialysis patients with ≥3 measurements of PTH during the first 9 months in DOPPS phase 4 and 5 (2009-2015). PTH control was defined by slope of log (PTH), parameterized as % change per month, and PTH mean was defined by the geometric mean of all measurements over the 9 month run-in period. Distribution of PTH slopes and means were assessed by regions [Europe/Australia/New Zealand (Eur-ANZ), Japan and North America] and dialysis vintage (<90 days, 90 days-1 year and >1 year). Mortality rates were compared across PTH slope and mean using Cox regression models.

Results: Our sample included 6035 patients in Eur-ANZ, 2644 in Japan and 18485 in North America. Mean PTH was much lower in Japan than in other regions across dialysis vintage categories. In patients with dialysis vintage <90 days, PTH level was more likely to decline >5% per month in Japan (49% of patients) vs. Eur-ANZ (34%) and North America(32%). In patients with dialysis vintage >1 year, Japanese patients were most likely to maintain steady PTH (ΔPTH within +/-5% per month: 47% in Japan vs 41% in Eur-ANZ and 41% in North America), with patients in Eur-ANZ and North America more likely to experience increase in PTH. During 13.5 (IQR, 5.9-22.9) months follow-up, prevalent patients with the highest mean PTH (>600 pg/mL) had the highest mortality rate [HR=1.22 (95% CI 1.02-1.47) vs. PTH 200-400 pg/mL]. PTH slope was not clearly associated with all-cause mortality.

Conclusions: PTH control, as measured by keeping a stable PTH level over 9 months, is better in Japan vs. other regions. No additional survival benefit for PTH control was observed, further study is needed to understand the reasons of keeping low PTH levels and its impact on survival advantage in Japan.

Funding: Commercial Support - Kyowa Hakko Kirin, Amgen, Baxter Healthcare, AstraZeneca, Hexal AG, Janssen, Keryx, Proteon, Relypsa, Roche, and Vifor Fresenius Medical Care Renal Pharma

FR-PO888

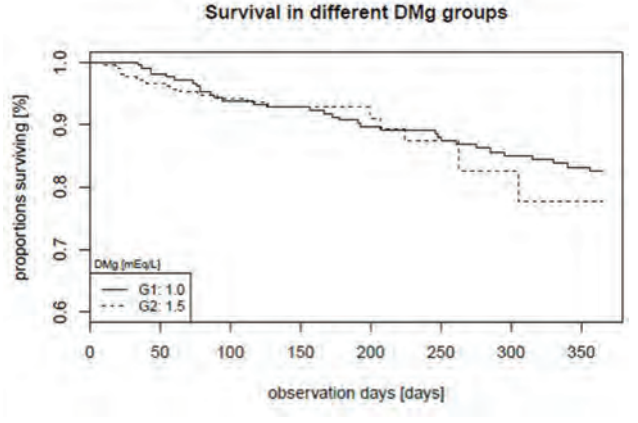
Associations between Dialysate Magnesium, Serum Magnesium, and Mortality: A Retrospective Cohort Study of the Monitoring Dialysis Outcomes (MONDO) Initiative Xiaoling Ye,[7] Adrian M. Guinsburg,[2] Cristina Marelli,[3] Bernard J. Canaud,[1] Stefano Stuard,[2] Xiaoqi Xu,[4] Jeroen Kooman,[6] Frank van der Sande,[6] Albert J. Power,[8] Len A. Usvyat,[5] Yuedong Wang,[9] John T. Daugirdas,[10] Peter Kotanko,[7] Jochen G. Raimann.[7] *[1]FMC Deutschland GmbH, Bad Homburg, Germany; [2]Fresenius Medical Care, Moron, Argentina; [3]Fresenius Medical Care Argentina, buenos Aires, Argentina; [4]Fresenius Medical Care Asia Pacific, Hong Kong, China; [5]Fresenius Medical Care North America, Melrose, MA; [6]Maastricht University Medical Centre, Maastricht, Netherlands; [7]Renal Research Institute, New York, NY; [8]Richard Bright Renal Unit, Bristol, United Kingdom; [9]University of California - Santa Barbara, Santa Barbara, CA; [10]University of Illinois College of Medicine, Burr Ridge, IL. Group/Team: MONDO initiative.*

Background: Serum magnesium (SMg) associated with mortality and particularly its deficiency substantially increases the risk of adverse outcomes. We studied the relationship between dialysate magnesium (DMg) and SMg and the effects DMg on all-cause mortality in a large global cohort.

Methods: All the patients(pts) started in-center hemodialysis(HD) between 2000 and 2012 were included. Following the first available DMg data point we established a 3 months baseline. All the value were average during baseline. Follow-up defined as 1 year after that. A multivariable regression model was applied to study the association of 1.0 versus 0.75 mEq/L DMg on SMg. Then we used 1:1 propensity score matching (age, gender, catheter, and vintage) to create two cohorts with DMg of 1.0 and 1.5 mEq/L, respectively. We compared survival times between these 2 cohorts using KM analysis, log rank-test and Cox regression analysis adjusted for age, gender, and catheter.

Results: We studied 15,211 pts (57.4 yrs, 58% males, 41% DM, 24% catheter; DMg 0.75: 2481 (16%), 1.0: 12,508 (82%) and 1.5: 222 (1%)]. In multivariate regression accounting for age, nPCR, NLR and albumin, a DMg increase by 0.25 mEq/L (from 0.75 to 1.0 mEq/L) was associated with a SMg increase by 0.09 (95%CI 0.03 to 0.14) mEq/L. Propensity score-matching created 2 well balanced cohorts with DMg of 1.5 and 1.0. Uni- and multivariate survival analysis did not show significant differences between the two DMg groups [**Figure 1**; adjusted HR of DMg 1.5: 1.1 (95% CI 0.6 to 2.0)].

Conclusions: Our results indicate a direct association between DMg and SMg. This finding is of importance, since higher SMg are associated with better outcomes in observational studies. Prospective studies are warranted to further delineate the complex interaction between DMg, SMg, and patient outcomes.



FR-PO889

Effect of Bioelectrical Impedance Analysis-Guided Comparing with Standard Clinical-Guided Dry Weight Assessment on Sleep Quality in Chronic Hemodialysis Patients Sethanant Sethakarun, Pariya Phanachet, Chagriya Kitiyakara, Sirimon Reutrakul, Arkom Nongnuch. *Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.*

Background: Sleep disturbances are common among chronic hemodialysis patients, leading to poor quality of life, increased morbidity and mortality. Hypervolemia has been linked to sleep problems in chronic hemodialysis patients, thus optimizing fluid status might improve sleep quality in such patients. This study aim to compare subjective and objectively measured sleep parameters, using Pittsburgh Sleep Quality Index (PSQI) questionnaire and actigraphy recordings, between bioelectrical impedance analysis (BIA)-guided and standard clinical-guided dry weight assessment during 6 months period.

Methods: We randomly assigned 19 chronic hemodialysis patients with subclinical hypervolemia; defined as clinically euvolemic status despite the ratio of extracellular water to total body water more than 0.4 on BIA, who were poor sleeper (PSQI>5) to either BIA-guided (BIA group) or standard clinical-guided dry weight group (clinical group). The outcomes were changes in PSQI score, and sleep parameters by actigraphy at 1, 3 and 6 months.

Results: Mean age was 63.53 ± 11.12 years and 42.11% were male. The baseline characteristic and sleep quality were comparable. At 3 and 6 months, subjective sleep quality in the BIA group significantly improved as reflected by a greater decline in PSQI score compared to the clinical group [3 months: mean difference -1.8 (-2.98 to -0.63), p= 0.003; 6 months: mean difference -3.11 (-4.31 to -1.92), p<0.01](figure 1). However, sleep parameters by actigraphy were not significantly different between groups.

Conclusions: Better optimization of fluid status using BIA significantly improves subjective sleep quality in chronic hemodialysis patients. This should be further explored in larger clinical trial.

Funding: Private Foundation Support

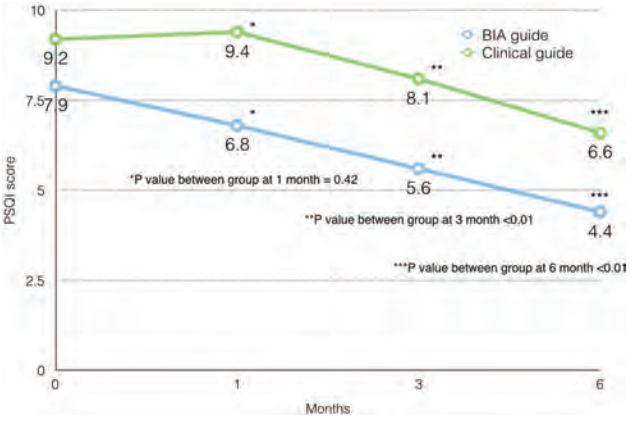


Figure 1. Change in PSQI score during study period.

FR-PO890

Ultrafiltration Profiling: Association with Clinical Outcomes among Incident Dialysis Patients Scott Sibbel, Adam G. Walker, Steven M. Brunelli. *DaVita Clinical Research, Minneapolis, MN.*

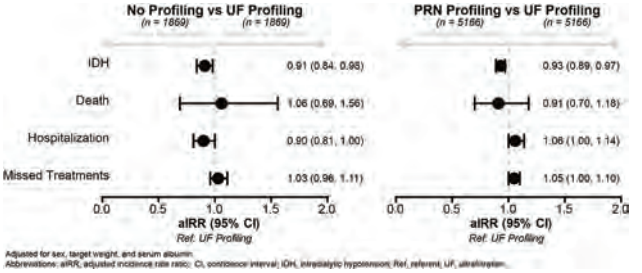
Background: Ultrafiltration (UF) profiling is the practice of varying the UF rate during dialysis in order to mitigate the consequences of decreased effective circulating volume. In practice, UF profiling may be used on a standing basis, a PRN basis, or not at all. We conducted parallel matched analyses comparing standing UF profiling to PRN UF profiling and to no profiling.

Methods: We considered all incident hemodialysis patients at a large dialysis organization (Jan 2010-Jun 2015). We identified all patients who received a first-ever order for standing UF profiling. We considered eligible controls of two types: PRN profile patients, who initiated a first-ever order for UF profiling on a PRN basis in the same vintage month; and patients who had not used UF profiling through the same vintage month. Each standing UF profile patient was matched (separately) to an eligible control of each type based on race and Charlson comorbidity index score using intention-to-treat methods. Rates of death, all-cause hospitalizations, missed dialysis treatments, and episodes of intradialytic hypotension (IDH) were assessed over the subsequent 12 months on an intention-to-treat basis.

Results: No UF profiling (vs standing UF profiling) was associated with lower rates of IDH and hospitalization, but indistinguishable rates of death and missed treatments. PRN UF profiling (vs standing UF profiling) was associated with lower rates of IDH, but higher rates of hospitalization and missed treatments; no difference in death rate was observed.

Conclusions: We did not detect a benefit of standing vs no UF profiling, nor evidence to suggest that PRN UF profiling is superior to standing UF profiling. These data call into question the rationale underlying commonplace use of UF profiling in clinical practice.

Funding: Commercial Support - DaVita, Inc



FR-PO891

Effects of Hemodialysis, Isolated Ultrafiltration, and Isolated Diffusion on Oxygen Extraction Ratio (OER) Silverio Rotondi,[5] Lida Tartaglione,[4] Luciano Carbone,[6] Maria luisa Muci,[1] Marzia Pasquali,[2] Sandro Mazzaferro.[3] *[1]Policlinico Umberto I Roma, Roma, Italy; [2]Policlinico Umberto I, Rome, Rome, Italy; [3]Sapienza University of Rome, Rome, Italy; [4]sapienza university of rome, Rome, Italy; [5]Nephrology and Dialysis Unit, ICOT Hospital, Polo Pontino, Sapienza University of Rome, Latina, Italy; [6]ICOT, Latina, Italy.*

Background: Hemodialysis sessions cause tissue hypoxia whis is not routinely measured. OER (n.v. 25-30%), obtained as the ratio between SaO_2 and Central Venous Oxygen Saturation ($SvcO_2$), is employed in ICU to quantify tissue hypoxic stress. We aimed to evaluate if the OER : a. Increases during dialysis session; b. is different after long (HD_{long}) or short (HD_{short}) dialysis intervals ; c. is differently affected by isolated ultrafiltration (iUf) or isolated diffusion (iD).

Methods: We enrolled 20 clinically stable patients on HD since >6 months, with Central Venous Catheter. We measured SaO_2 (by capillary oxymeter) and $ScvO_2$ (by blood gas analysis) to calculate the OER basally, 15', 30', 60', 120' and end of HD_{Long}. In 10 of them, OER was re-measured in the following two HD_{Short} sessions. Further in all patients, OER was re-measured during the first hour of the first and second HD_{Short} performed by applying, alternatively, iUF or iD. During each HD, UF rate was kept at<10 ml/kg/h and symptoms were recorded.

Results: In the HD_{Long} session, OER increased within 30' (post hoc test p<.05) and then progressively up to the end of HD, by 38%. Mean basal OER of HD_{Long} (34,4±7), HD_{Short1} (33,8±7) and HD_{Short2} (36,2±6) were not different (Tab.1). In the two HD_{Short} sessions, OER changes overlapped with those in HD_{Long}. During the first hour of the HD_{Short} session with iUF, the increment of OER was not significant, at variance with the significant increase recorded during the HD_{Short} with iD (Tab. 1). All HD sessions were asymptomatic with no change in blood pressure (systolic or diastolic) or heart rate. During sessions, no significant change was evident for capillary SaO_2 (98±1 %), while $ScvO_2$ progressively decreased.

Conclusions: a. OER increases significantly during HD sessions; b. HD intervals do not modify the adaptive process to hypoxia; c. iD affects this adaptive response possibly more than iUF. OER might be a marker of HD stress, potentially useful in fragile patients.

Funding: Clinical Revenue Support

HD, Type	Paz. (n)	Basal	15'	30'	60'	120'	HD end	Anova
HD_{Long}	20	34,4±7	39,0±7	40,0±8*	40,7±6#	42,5±8°	46,9±6^	.0001
HD_{Short1}	10	33,0±6	40,2±8*	41,3±6#	42,4±5#	42,0±7#	45,9±8°	.004
HD_{Short2}	10	36,2±6	40,6±9	42,2±7*	42,0±8*	42,9±10*	45,9±7°	.003
HD_{Short1}, iUF	20	33,0±6	35,9±7	36,6±6	37,5±7			n.s
HD_{Short2}, iD	20	32,4±6	37,6±6	38,8±5*	38,4±7			.04

Mean ± ES OER. iUF = isolated ultrafiltration; iD: Isolated Difussion;
Bonferroni Post-hoc test vs Baseline: *p<.05; # p<.005; ° p<.001; ^ p<.0001

Tab. 1

FR-PO892

Extended Weekly Hemodialysis Hours Selectively Improves Kidney Disease-Specific Quality of Life: A Secondary Analysis of the ACTIVE Dialysis Trial Brendan Smyth,[1,2] Oliver van den Broek-Best,[2] Li Zuo,[3] Nicholas A. Gray,[4] Christopher T. Chan,[5] Janak R. de Zoysa,[6] Kirsten Howard,[2] Kris Rogers,[1] Meg J. Jardine,[1] Vlado Perkovic.[1] *[1]The George Institute for Global Health, UNSW, Sydney, NSW, Australia; [2]University of Sydney, Sydney, NSW, Australia; [3]Peking University People's Hospital, Beijing, China; [4]Sunshine Coast University Hospital, Birtinya, NSW, Australia; [5]Toronto General Hospital, Toronto, ON, Canada; [6]Waitemata District Health Board, AUCKLAND, New Zealand.*

Background: End-stage kidney disease is associated with high symptom burden and poor quality of life (QOL). The ACTIVE Dialysis trial randomized 200 hemodialysis (HD) patients to standard (median 12) or extended (median 24) weekly HD hours for 12 months. Extended hours HD did not affect EQ-5D utility-based QOL but had a small but significant effect on generic health-related QOL, measured by the SF-36. We aimed to determine the impact of extended hours HD on kidney disease-specific QOL.

Methods: QOL assessments were administered by blinded interviewers at 3-monthly intervals during the trial. The Kidney Disease Component Summary (KDCS) is a disease-specific summary measure ranging from 0-100 including disease-specific dimensions such as disease impact, dialysis delivery and symptoms. The average intervention effect on KDCS was determined using mixed linear regression adjusted for time and baseline score. Pre-specified subgroups were defined by residence in China or other, dialysis in an institution or at home and dialysing for more or less than 6 months.

Results: Mean baseline KDCS scores were similar in participants randomised to standard and extended weekly dialysis hours (66.6 [95% CI 64.1-69.1] and 66.0 [95%CI 63.2-68.7] respectively). Extended weekly HD hours improved mean KDCS by 3.48 points (95%CI 1.44-5.51, p=0.0009). Subgroup analysis demonstrated the improvement in KDCS was individually significant in those from China, dialysing in an institution or of dialysis vintage >6 months (4.54 [95%CI 2.04-7.05], 4.05 [95%CI 1.83-6.27] and 4.20 [95%CI 1.92-6.48] respectively, all p<0.001).

Conclusions: Extended hours HD is associated with improvement in kidney disease-specific QOL despite having no effect on overall EQ-5D measured QOL. The impact in defined patient populations warrants further investigation. NCT00649298

Funding: Commercial Support - Baxter International Inc., Government Support - Non-U.S.

FR-PO893

Evaluation of Sex Difference in Fluid and Nutritional Statuses at the Initiation of Hemodialysis Using a New Bio-Impedance Spectroscopy Device Tatsunori Toida,[3,1] Shin Fukunaga,[1] Reiko Toida,[2] Shigehiro Uezono,[2] Hideto Nakagawa,[3] Yuji Sato,[3] Shouichi Fujimoto.[3] *[1]Nobeoka Prefectural Hospital, Nobeoka, Japan; [2]Chiyoda Hospital, Hyuga, Japan; [3]University of Miyazaki, Miyazaki, Japan.*

Background: Recently, the sex differences in health outcomes among patients undergoing maintenance dialysis were reported (JASN, 2017). The maintenance of an appropriate body fluid volume and nutritional status in hemodialysis patients is important for improving their prognoses. We herein cross-sectionally evaluated sex difference in over-hydration (OH) and the nutritional status (lean tissue index; LTI and skeletal muscle index; SMI) at the initiation of hemodialysis (HD) using a bio-impedance spectroscopy device (Body Composition Monitor, BCM).

Methods: 119 patients at the initiation of hemodialysis (female vs. male, 49 vs. 70; mean age, 69.7 ± 11.2 years; mean BMI, 23.9 ± 4.5 kg/m2, 59 diabetic patients) were enrolled between February 2015 and December 2016 at Nobeoka Prefectural Hospital and Chiyoda Hospital. Measurements were performed before HD in the early phase after the initiation of HD by BCM and relationships between clinical data were also assessed. Furthermore, the nutritional statuses of HD patients in the present study were compared with our previous findings obtained in healthy Japanese volunteers (Biomed Mater Eng, 2015).

Results: Patients with diabetes or pleural effusion showed significantly higher OH levels compared to those without diabetes or pleural effusion. Serum NT-proBNP values and BMI were positively correlated with OH levels, respectively. OH level was not different between male and female. LTI and SMI were negatively correlated with age in males, respectively, but not in females. LTI and SMI were not correlated with the levels of serum albumin or C-reactive protein. These indexes were not different between patients with or without diabetes. In males, LTI and SMI were lower in HD patients than in healthy volunteers, but not in females.

Conclusions: Present study suggests that BCM is a useful tool for evaluating the body fluid and nutritional status in patients at the initiation of HD. Furthermore, malnutrition is a concern in males at the initiation of HD. Follow-up observations using BCM may be useful for managing HD patients.

FR-PO894

HEMO Study Results Suggest that "Clinically Negligible" Residual Kidney Function (RKF) Is a Significant Contributor to Uremic Solute Clearance Stephanie M. Toth-Manikowski,[2] Tammy L. Sirich,[4] Thomas H. Hostetter,[1] Seungyoung Hwang,[2] Josef Coresh,[5] Neil R. Powe,[3] Tariq Shafi.[2] *[1]Case Western Reserve University, Cleveland, OH; [2]Johns Hopkins University School of Medicine, Baltimore, MD; [3]Priscilla Chan and Mark Zuckerberg San Francisco General Hospital & University of California SF, San Francisco, CA; [4]Stanford University, Palo Alto, CA; [5]Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD.*

Background: RKF is thought to exert its beneficial effects through improved clearance of uremic toxins but the level of native kidney function where this clearance becomes negligible is not known. The HEMO study excluded patients with RKF >1.5 mL/min, as a level below was regarded as "clinically negligible." We aimed to assess whether the levels of non-urea solutes associated with clinical outcomes differed among patients with this "clinically negligible" RKF compared to those with no RKF.

Methods: We measured 8 non-urea solutes in plasma from 1,280 patients of the HEMO Study 3-6 months post-randomization. We calculated the relative difference in solute levels among patients with and without RKF and compared it to the relative difference achieved by high vs standard hemodialysis (HD) dose (mean Kt/Urea 1.7 vs 1.3, respectively).

Results: At baseline, 34% of patients had "clinically negligible" RKF (mean 0.7±0.4 mL/min); 66% had no RKF. Those with RKF were older, had more recent onset of dialysis, and had lower UF requirements than those without RKF. Patients with RKF had significantly lower non-urea solute levels than patients without RKF. The differences were comparable or more pronounced than in those randomized to high HD dose (Table).

Conclusions: Even at a very low level, RKF is not "negligible" as it continues to provide clearance of solutes associated with clinical outcomes.

Funding: NIDDK Support

Effect of RKF on Uremic Solutes in 1,280 HEMO Participants

	RKF (N=433) vs No RKF (N=847)		High HD Dose (N=638) vs Standard HD Dose (N=643)*	
Solute	% Difference	p^	% Difference	p
P-Cresol Sulfate	8%	0.003	2%	0.46
Indoxyl Sulfate	-11%	0.001	-11%	<0.001
Hippurate	-24%	<0.001	-4%	0.34
Phenylacetylglutamine	-14%	<0.001	-7%	0.04
Trimethylamine-N-Oxide	-7%	0.04	-9%	<0.01
Methylguanidine	-14%	0.002	-22%	<0.001
Asymmetric Dimethylarginine	-4%	0.009	0.5%	0.74
Symmetric Dimethylarginine	-7%	0.001	-4%	0.02

*As reported previously (Meyer T. JASN.2016). ^Adjusted for age, sex, race, and Kt/Vurea

FR-PO895

Post-Hospitalization Dialysis Facility Processes of Care and Pulmonary Edema-Related Hospital Readmissions among Hemodialysis Patients Laura Plantinga,[1] Janice P. Lea,[1] Tahsin Masud,[1] John M. Burkart,[3] Bernard G. Jaar.[2] *[1]Emory University, Atlanta, GA; [2]Johns Hopkins University and Nephrology Center of Maryland, Baltimore, MD; [3]Wake Forest University School of Medicine, Winston-Salem, NC.*

Background: Both dialysis facilities and hospitals are accountable for 30-day readmissions among U.S. hemodialysis (HD) patients. Steps taken at the dialysis facility post-hospitalization may prevent pulmonary edema-related (PER) readmissions. We examined the association of post-hospitalization HD processes of care with PER readmissions.

Methods: Using electronic health record (EHR) data from 23 Southeastern dialysis facilities, starting in 2010 and linked with national registry data for complete follow-up through 2014, we identified 1454 in-center HD patients who had ≥1 hospitalization (first=index), survived ≥30 days, and had ≥3 contiguous dialysis sessions following the index discharge. Readmissions were defined as admissions that occurred within 30 days of the index discharge; PER readmissions were further defined by the presence of discharge codes for pulmonary edema, fluid overload, and/or congestive heart failure (CHF). Indicators of processes of care were defined by EHR data as present vs. absent in the first 3 sessions post-index discharge.

Results: Overall, 19.9% of patients were readmitted, and 8.3% had PER readmissions (38.7% of all readmissions). Compared to patients who did not, patients who had PER readmissions were slightly older (63.9 vs. 61.6 years; *P*=0.09), less likely to be black (54.6% vs. 63.4%; *P*=0.09) and more likely to have history of CHF (76.0% vs. 39.7%; *P*<0.001) or index admissions also related to pulmonary edema (72.7% vs. 35.1%; *P*<0.001). New dialysis orders, particularly with target weight changes, were more common among those with PER readmissions. Higher epoetin dose was less common in readmitted patients; drawing of labs was not different by readmission status (Table).

Conclusions: Patients who had PER readmissions were more, not less, likely to have target weight changes in dialysis orders and medication reductions within 3 sessions of index admission discharge. In general, these results suggest that usual post-hospitalization care at the dialysis facility may not prevent PER or all-cause readmissions.

Funding: Other U.S. Government Support

Post-hospitalization care indicator:	PER readmission			All-cause readmission		
	Yes	No	P	Yes	No	P
Labs drawn	80.0%	78.4%	*0.8*	80.2%	78.1%	*0.7*
New dialysis orders	63.6%	55.7%	*0.09*	57.9%	55.9%	*0.5*
Target weight change	47.9%	38.3%	*0.04*	40.0%	38.9%	*0.7*
Higher epo dose	15.6%	24.0%	*0.3*	14.1%	25.8%	*0.02*
≥1 medication stopped	31.6%	24.0%	*0.07*	29.3%	23.5%	*0.04*

FR-PO896

Factors Associated with Higher Risk of Emergency Department Use within 30 days of Hospital Discharge Jonathan H. Segal, John Stephen, Tempie H. Shearon, Bin Nan, Caitlin Hanna, Claudia Dahlerus. *University of Michigan, Kidney Epidemiology and Cost Center, Ann Arbor, MI.*

Background: Chronic dialysis patients visit the emergency department (ED) at 4-fould higher rates than Medicare beneficiaries in the general population yet little is known about outpatient ED use after hospital discharge. We examined clinical and sociodemographic/socioeconomic (SDS/SES) factors associated with increased ED use within 30 days after hospital discharge in the US Medicare dialysis population.

Methods: Data on ED visits (outpatient or observation stays) for dialysis patients in 2014 were obtained from Medicare Outpatient Claims. Adjustment was made for patient and area level clinical and SDS/SES characteristics. A two stage multivariate logistic regression model determined odds of an outpatient ED encounter within 30 days of an index hospital discharge adjusted for these SDS/SES and clinical factors.

Results: 14.5 % of the 423,165 index discharges among 201,674 unique patients in 2014 were followed by an outpatient ED visits within 30 days. Females, younger age, longer ESRD vintage and black race were associated with higher odds of an ED encounter within 30 days. Dually-eligible (DE) patients (Medicare and Medicaid) had 13% higher odds compared to Medicare Primary; Medicare secondary patients/Medicare HMO had 54% lower odds of an ED encounter.

Conclusions: Outpatient ED encounters within 30 days after a hospital discharge occur frequently for chronic dialysis patients. Patient characteristics of SDS/SES (DE status, younger age, female sex) are associated with a higher risk of ED use following a hospital discharge. These ED visits represent an opportunity for greater coordination to reduce potentially preventable acute care.

Funding: Other U.S. Government Support

Covariate	Odds Ratio
Sex: Female	1.09
Age (Ref: 60-74) 18-24	2.16
Age: 25-44	1.77
Age 45-59	1.29
Age 75+	0.86
Obese (Ref: normal weight)	0.94
ESRD Vintage 5+ years (Ref: 1-2 y)	1.08
Black Race (Ref: White)	1.15
Medicare primary + Medicaid (Ref: Medicare primary)	1.13
Medicare secondary/HMO	0.46
Area Deprivation Index (ADI)	1.06

all p-values <0.0001 except ADI where p=NS

FR-PO897

Effects of Predictive Modeling Assisted Care Interventions on Hospitalization Rates in Hemodialysis Patients David F. Sweet, Sheetal Chaudhuri, Hao Han, Anthony Chamberas, Dugan Maddux, Marta Reviriego-Mendoza, John W. Larkin, Len A. Usvyat, Franklin W. Maddux. *Fresenius Medical Care North America, Waltham, MA.*

Background: Hemodialysis (HD) patients continue to have high hospitalization rates regardless of advances in the treatment of end stage renal disease. We have developed and deployed a predictive model including more than 200 variables to identify in-center Hemodialysis (HD) patients at an increased risk for a hospitalization. In the pilot Dialysis Hospitalization Reduction Program (DHRP), we perform early identification of patients at risk for a critical event which may aid clinicians to intervene in a timely manner. We thus investigated the impact of DHRP on hospitalization rates in HD patients.

Methods: A total of 72 Fresenius Kidney Care clinics were included in the pilot; 141 clinics in neighboring regions to DHRP clinics were used as controls. We implemented the pilot in South Alabama/Florida Panhandle Region since Jan of 2015. For patients identified at high risk of hospitalization, Social Workers assessed and placed them on an intensive program employing community resources and integrated care. The dietitians utilized a high risk assessment looking at weight, nutrition, and access to food and supplements. The resident nurses assessed current care for anemia, adequacy, access, prior hospitalizations, and blood pressures. We compared mean quarterly hospital admission and readmission rates per patient year between groups.

Results: We analyzed the results 24 months after the start of the program and we found that DHRP patients exhibited: 1) 23% reduction in average yearly hospital admission rate compared to controls, and 2) 3.6% lower average yearly hospital readmission rate compared to controls. When fitting a linear regression model, both the quarterly hospital admission rate and quarterly readmission rate for the control group indicated an increasing trend with time, while the DHRP group indicated a small decreasing trend. Quarterly differences between groups for both admission rate and readmission rate increased over time ($p < 0.003$).

Conclusions: These findings suggest that care coordination based on predictive risk assessment in the DHRP is associated with lower hospitalization rates in HD patients, compared to controls. Further studies are needed to confirm these results.

Funding: Commercial Support - Fresenius Medical Care North America

FR-PO898

In-Patient Hospitalization of Dialysis Patients in Canada: Opportunities to Decrease the Burden on Patients Juliana Wu,[1] Michael Terner,[1] Kelvin Lam,[1] Frank Ivis,[1] Greg Webster,[1] Scott Klarenbach.[2] *[1]Canadian Institute for Health Information, Toronto, ON, Canada; [2]University of Alberta, Edmonton, AB, Canada.*

Background: All cause hospitalization rates for dialysis patients is high, with 1.7 hospitalizations per patient-year reported in the United States. In Canada, the Canadian Organ Replacement Register program at the Canadian Institute for Health Information examined hospitalization in Canada for both all-cause, and infections related to dialysis treatment.

Methods: A cohort of 38,369 incident dialysis patients between 2005 and 2014 were included in the study. Crude rates for hospitalization (all cause and infection) and in-hospital mortality were calculated. A frailty model was used to calculate hazard ratios for covariates including age, sex, race, income, comorbidity, primary diagnosis, year of dialysis start, care type, modality and pre-dialysis hospitalization.

Results: The all-cause hospitalization rate for dialysis patients was 1.1 hospitalizations per patient-year. Pediatric patients (HR = 2.73; p<0.001) and Indigenous patients (HR = 1.20; p<0.001) had higher risk than peers for hospitalization, and patients on home hemodialysis and peritoneal dialysis (HR = 0.84; p<0.001) had a lower risk of being hospitalized than in-centre patients. Similar results were observed for hospitalization for infections related to dialysis. All-cause hospitalizations were more frequent at dialysis initiation and decreased over time for both patients receiving peritoneal or hemodialysis.

Conclusions: Targeted national interventions such as promoting greater arteriovenous fistula use to reduce catheter infections, earlier transplantation for pediatric patients and expanding programs designed to improve care to Indigenous patients could be used to reduce the rate of hospitalization for higher-risk dialysis patients in Canada.

Cofactor	All-cause hospitalizations		Infection-related hospitalizations	
	Hazard ratio	95% CI	Hazard ratio	95% CI
Age group				
0–17	2.73	2.37–3.15	1.30	0.90–1.88
18–44	1.21	1.15–1.27	1.03	0.90–1.16
45–64	1.00	—	1.00	—
65–74	0.95	0.91–0.98	0.96	0.88–1.06
75+	1.01	0.97–1.05	1.02	0.92–1.12
Sex				
Female	1.08	1.05–1.11	1.03	0.96–1.11
Male	1.00	—	1.00	—
Race				
Asian	0.72	0.68–0.77	0.76	0.65–0.89
Indian subcontinent	0.78	0.73–0.84	0.86	0.73–1.02
Indigenous	1.20	1.12–1.28	1.30	1.11–1.53
Black	0.86	0.80–0.93	0.98	0.81–1.18
Caucasian	1.00	—	1.00	—

FR-PO899

Impact of Extended Weekly Hemodialysis Hours on Diverse Health-Related Quality of Life Domains: A Secondary Analysis of the ACTIVE Dialysis Trial Oliver van den Broek-Best,[1] Brendan Smyth,[2,1] Li Zuo,[3] Nicholas A. Gray,[4] Christopher T. Chan,[5] Janak R. de Zoysa,[6] Kirsten Howard,[1] Kris Rogers,[2] Vlado Perkovic,[2] Meg J. Jardine.[2] *[1]University of Sydney, Lewisham, NSW, Australia; [2]The George Institute for Global Health, UNSW, Sydney, NSW, Australia; [3]Peking University People's Hospital, Beijing, China; [4]Sunshine Coast University Hospital, Birtinya, NSW, Australia; [5]Toronto General Hospital, Toronto, ON, Canada; [6]Waitemata District Health Board, AUCKLAND, New Zealand.*

Background: The SF-36 quality of life (QOL) tool has been validated in multiple populations and conditions. The ACTIVE Dialysis trial randomised 200 haemodialysis (HD) recipients to standard (median 12) or extended (median 24) weekly HD hours for 12 months with no impact on overall EQ-5D utility-based QOL. Extended hours led to small but significant improvements in both SF-36 physical (PCS) and mental (MCS) composite scores (PCS 2.30, 95%CI 0.52-4.07; MCS 2.54, 95%CI 0.42-4.65). We aimed to examine the impact of extended weekly dialysis hours on individual SF-36 domains.

Methods: Generic health-related QOL was assessed by blinded interviewers every 3 months with SF-36 which includes PCS, MCS and 8 domains. The average intervention effect was calculated using mixed linear regression adjusted for baseline score and time.

Results: ACTIVE dialysis participants had a mean age of 51.6±11.5 years, with 62% recruited from China and 75% dialysing in-center. Extended dialysis had a significant, positive effect on 4 of the 8 domains: General Health Perceptions (7.33, 95%CI 2.85-11.81, p=0.002), Social Functioning (6.70, 95%CI 1.14-12.25, p=0.02), Role Emotional (8.17, 95%CI 0.03-16.30, p=0.05) and Mental Health (3.30, 95%CI 0.15-6.45, p=0.04). Although not reaching statistical significance, point estimates in other domains were also in a consistent positive direction: Physical Functioning (3.54, 95%CI -0.67-7.74, p=0.1), Role Physical (6.67, 95%CI -0.95-14.28, p=0.1), Bodily Pain (4.92, 95%CI -0.24-10.08, p=0.06) and Vitality (3.46, 95%CI -0.93-7.84, p=0.12).

Conclusions: Predominantly in-center extended weekly HD hours may have a positive effect on SF-36 measures beyond purely physical domains. Dialysis delivery involves multiple dimensions including biochemical, haemodynamic, social and health service access. Better understandings of the mechanisms for its impact on QOL are needed. NCT00649298

Funding: Commercial Support - Baxter International Inc., Government Support - Non-U.S.

FR-PO900

Hemodiafiltration and Mortality: Data from the Real World Ana Fernandes. *Centro Hospitalar Setubal, Setubal, Portugal.*

Background: Mortality remains high for hemodialysis (HD) patients and no single intervention has shown to decrease mortality. Online hemodiafiltration (HDF) is a promising technique, but randomized trials have shown inconsistent results.

Methods: We conducted a cohort study including all incident patients that started dialysis in 40 randomly selected units over a two-year period, and these patients were followed for at least 5 years, or until death or loss to follow up whichever occurred first. A descriptive statistic was used to characterize the population. To analyse time to mortality we used the Cox's Proportional Hazard model to evaluate the covariates that may modify the outcome. Covariates included in the model were comorbidities and vascular access type.

Results: 1,229 patients were included. Mean age was 65.2±15.5 years, 40.4% were male. Diabetes was the most frequent cause of CKD. At baseline, 23% had coronary artery disease (CAD), 43.7% had diabetes (DM), 31.3% had cerebrovascular disease (CBD) and 2.4% peripheral artery disease (PAD). Vascular access at the beginning of dialysis was a catheter in 45.9% of the patients, an arteriovenous fistula in 49.7% and a graft in 4.4%. Eight per cent of the patients were undergoing low flux HD, 66.5% high flux HD and 22% HDF. Three per cent of the patients were taking a calcimimetic, 37,9% were receiving a vitamin D analogue and the most common phosphate binding utilized was calcium carbonate. Median time of follow up was 48 months (Interquartile range 22-64) Univariate analysis showed that CAD (hazard ratio [HR] 1.89; 95%CI 1.54-2.32), DM (HR 1.32; 95%CI; 1.09-1.60), and PAD (HR 2.05; 95%CI 1.22-3.44) were associated with increased mortality. In multivariate analysis only CAD was associated with an increased risk of death (HR 2.00; 95%CI 1.61-2.46). Hemodiafiltration, as compared with low flux dialysis, was associated with a decreased mortality (HR 0.34, 95%CI 0.49-0.89). There was no difference in the risk of death between low-flux and high-flux hemodialysis (HR 1.19; 95%CI 0.92-1.55). Median survival time was not yet reached but it was longer in the hemodiafiltration group. (p< 0,0001)

Conclusions: This study suggests that HDF, as compared with low-flux dialysis, may reduce the risk of mortality. The magnitude of the effect size is possibly overestimated by the observational nature of study.

FR-PO901

Opioid Overdose Hospitalizations with Patients with ESRD – Nationwide Trends and Outcomes Swati Sakhuja,[2] Ankit Sakhuja,[1] Kianoush Banaei-Kashani.[1] *[1]Mayo Clinic, Rochester, MN; [2]University of Alabama at Birmingham, Birmingham, AL.*

Background: Opioid overdose is responsible for more deaths than firearms or motor vehicle crashes in the United States. Recent studies have shown opioid use to be widely prevalent in end stage renal disease (ESRD) patients, however, epidemiology and outcomes of opioid overdose in this population are unclear.

Methods: Using data from National/Natiowide Inpatient Sample database from year 2000-2013, we identified patients 20 years or older with opioid overdose admissions and those with ESRD using ICD-9-CM codes. Using data from US Census and USRDS render, we assessed the trend of incidence of opioid overdoses in ESRD and general population. We also examined the associated mortality and if ESRD is an independent predictor of mortality in these patients in a model adjusted for age, sex, race, primary payer, Charlson's score, hospital bed size, volume, region, location & teaching status, use of mechanical ventilation, classification of poisoning as suicidal, homicidal, accidental or unknown and year of admission.

Results: Of total 558,737 opioid overdose admissions, 7496 (1.3%) had ESRD. The incidence of opioid overdose (per 100,000 population) increased from 92 to 183 in ESRD and 19 to 31 in general population (Fig 1). Patients with ESRD were more often in 45-79 yr age-group, blacks or Hispanic and with higher co-morbidities. Inpatient mortality was higher in patients with ESRD (4.0% vs 2.5%; p<0.001). In addition, having ESRD was an independent predictor for mortality in these patients (OR 1.42; 95% CI 1.02-1.98).

Conclusions: The incidence of opioid overdose is higher in ESRD patients and is rising at a rapid pace. ESRD patients with overdose have higher mortality and ESRD is an independent predictor for mortality in patients with opioid overdose.

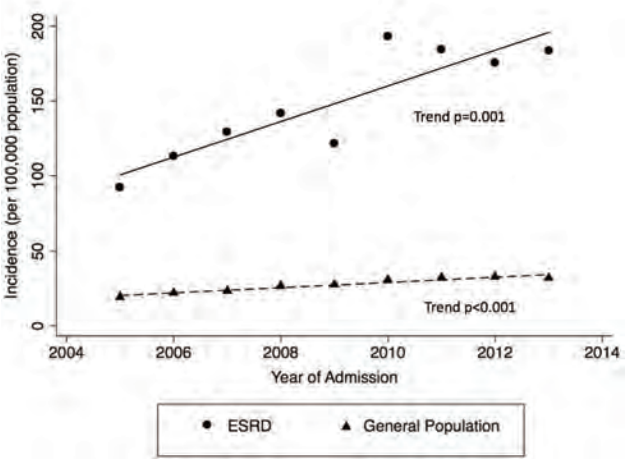


Fig 1: Trends of incidence of opioid overdose in ESRD and general population

FR-PO902

Novel Prediction Score for Early Death upon Transition to Dialysis: A Veterans Affairs (VA) and Kaiser Permanente Southern California (KPSC) Big Data Approach Yoshitsugu Obi,[1] Danh V. Nguyen,[1] Hui Zhou,[2] Elani Streja,[1] Melissa Soohoo,[1] Lishi Zhang,[1] Yanjun Chen,[1] Miklos Z. Molnar,[3] John J. Sim,[2] Steven J. Jacobsen,[2] Connie Rhee,[1] Csaba P. Kovesdy,[3] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine, Orange, CA; [2]Kaiser Permanente Southern California, Pasadena, CA; [3]University of Tennessee Health Science Center, Memphis, TN.*

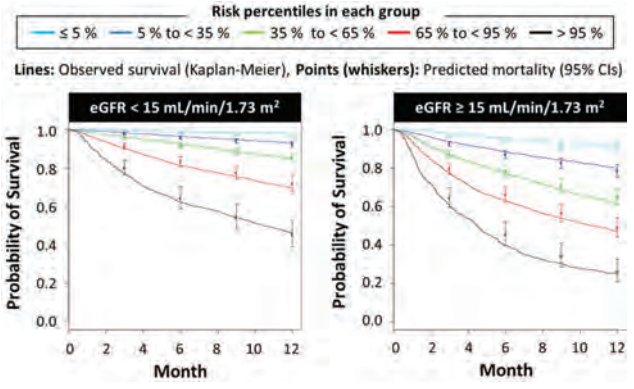
Background: Mortality is exceptionally high during the first year among incident dialysis patients. We aimed to establish a risk prediction tool for early mortality based on pre-ESRD conditions.

Methods: Among 35,853 US veterans who transitioned to dialysis over 6.5 years (10/2007–03/2014), we developed new risk scores based on demographics, primary ESRD causes, comorbid conditions, and pre-ESRD laboratory data. We stratified patients by low and high eGFR (i.e., <15 and ≥15 mL/min/1.73m^2, respectively), and then applied a Cox model with AIC-based backward variable selection to 14-month survival data. The final model was validated among 4,284 KPSC patients over 8.75 years (01/2007–09/2015).

Results: Observed 1-year mortality was 27% in the VA cohort, and was not significantly different from predicted mortality. C-index values in the VA cohort were 0.71 and 0.67 among patients with low vs. high eGFR, respectively. The external validation using the KPSC cohort showed C-index values of 0.77 and 0.74 among men vs. women with low eGFR, respectively, and 0.71 and 0.67 among men vs. women with high eGFR, respectively.

Conclusions: New risk scores for early mortality have been developed and externally validated among a cohort of racially, ethnically, and gender diverse ESRD patients transitioning to dialysis. It would help with the identification of a high risk population and provide information that may contribute to dialysis initiation planning.

Funding: NIDDK Support



FR-PO903

First-Year Mortality among Patients Initiating Hemodialysis with a Functional Arteriovenous Fistula Compared with Peritoneal Dialysis Purna Mukhopadhyay,[1] Kenneth J. Woodside,[2] Keith McCullough,[1] Kaitlyn Ratkowiak,[1] Douglas E. Schaubel,[2] Ronald L. Pisoni,[1] Vahakn B. Shahinian,[2] Rajiv Saran.[2] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]University of Michigan, Ann Arbor, MI.*

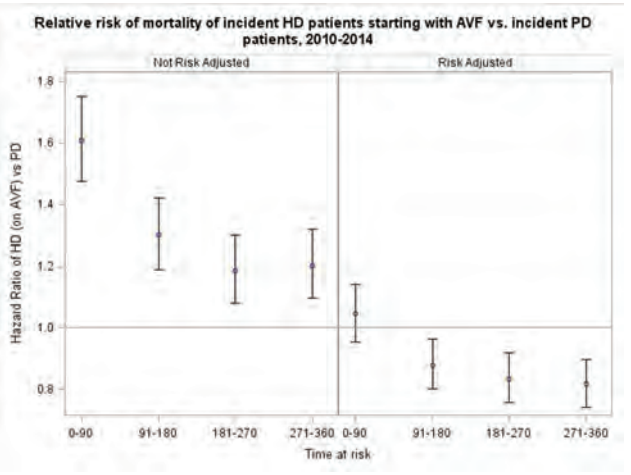
Background: Comparison of initial outcomes between in-center HD and PD are subject to bias, as typically PD patients (pts) are younger, healthier, & may have received longer pre-ESRD care. Restricting comparisons to better prepared pts who initiate HD with a functional arteriovenous fistula at start of renal replacement (HDAVF) may minimize this bias.

Methods: Five annual cohorts (USRDS 2010-2014, CMS Form 2728) of incident HDAVF pts (N=81,850) & PD pts (N=47,830) were followed up to 1 year for the outcome of death. Death & time at risk for cohorts were determined in each of 12 consecutive 30-day segments, censoring for transplantation, switch to PD (or HD), recovery of renal function, loss to follow-up, or end of study. Death rates are expressed per 100 patient years (PY). Unadjusted and adjusted hazard ratios for death averaged over 2010-2014 were calculated for four 90-day risk periods.

Results: HD pts were on average older (64 vs 57 years), male (63.4% vs 56.8%), had received pre-ESRD care (89% vs 85.8%), & had greater comorbid burden at start of ESRD. The average unadjusted mortality rate for the HD cohort was higher, with 9.9 PY deaths in the first 30-days vs 5.6 PY deaths for PD. The hazard ratio of HD vs. PD in the unadjusted model was 1.6 ($p < 0.001$) in the 0-90 day period, declining to 1.2 ($p < 0.001$) post-180 days. In the adjusted model, the HR for first 30 days was 1.05 ($p = 0.34$), & decreased to 0.88-8.82 ($p < 0.01$) in the post-90 day period (Figure).

Conclusions: After accounting for pt characteristics, those who start renal replacement therapy on HDAVF appear to have a survival advantage over those that initiate with PD, particularly after 90 days. These findings could guide providers in advising the patients on modality & vascular access choice at dialysis start, have policy implications, & provide impetus for future research.

Funding: NIDDK Support



FR-PO904

Options Education before Initiation of Dialysis Is Associated to Improved Hospitalization and Mortality Rates Marta Reviriego-Mendoza, Yue Jiao, John W. Larkin, Rob Lynch, Len A. Usvyat, Jeffrey L. Hymes, Franklin W. Maddux. *Fresenius Medical Care North America, Waltham, MA.*

Background: KDOQI guidelines recommend that chronic kidney disease patients receive options education to learn optimal ways to prepare for dialysis. Little is known about the impacts of options education on patient outcomes after the progression to end stage renal disease (ESRD). We investigated if options education is associated with improved hospitalization and mortality outcomes in incident dialysis patients.

Methods: We studied data from incident Fresenius Kidney Care (FKC) patients who initiated dialysis between 2009 and 2016. Patients were grouped by enrollment in FKC options education prior to initiating dialysis or not, as well as whether patients started dialysis as an outpatient or inpatient. In these groups, we calculated and compared the mean annual hospital admission and mortality rate during the first 120 days of dialysis.

Results: We analyzed data from a total of 300,818 patients; of these, 68,721 patients received options education prior to initiating dialysis. Throughout 2009-2016, patients who received options education generally exhibited lower rates of hospital admissions and mortality during the first 120 days of dialysis, as compared to those who did not receive education. Similar findings were observed, yet less pronounced, for admission and mortality rates in patients starting dialysis as an inpatient versus outpatient. Specifically, in 2016 outpatients without education had 1.74 admissions per patient year (ppy) and 0.19 deaths per 100 patient years (p100py). When compared to those with education, we observed a 23.6% decrease in admissions (1.33 admissions ppy) and a 52.6% decrease in death rate (0.09 deaths p100py). Inpatients without education had 2.1 admissions ppy and 0.27 deaths p100py, while patients with options education were observed to have a 7.14% decrease in admissions (1.95 admissions ppy) and a 37% decrease in death rate (0.17 deaths p100py).

Conclusions: The analysis herein indicates that receiving options education before progression to ESRD is associated with lower rates of hospital admissions and mortality in the incident dialysis period. More analyses are needed to confirm these observations.

Funding: Commercial Support - Fresenius Medical Care North America

FR-PO905

Race, Ethnicity, and End-of-Life Care in US Dialysis Patients, 2000 to 2011 Robert N. Foley,[2] Paul E. Drawz,[2] Donal J. Sexton,[1] Scott Reule.[2] *[1]The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin., Dublin, Ireland; [2]University of Minnesota, Minneapolis, MN.*

Background: End-of-life care is an increasingly prominent consideration, especially in situations where death appears imminent and quality of life is poor. As little is known regarding potential racial and ethnic disparities, we performed a national study to determine whether end-of-life care in US dialysis patients was subject to racial or ethnic disparity.

Methods: Retrospective United States Renal Data System files were used to examine the primary outcome, a composite of withdrawal of dialysis and death in a non-hospital or hospice setting (2000 to 2011, N=910,559). The following racial-ethnic groups were examined: (non-Hispanic) white, African American, Native American, Asian; Hispanic. Logistic regression was used to calculate odds ratios for end-of-life care outcomes per race-ethnicity.

Results: The primary outcome was less likely in patients from any minority group (10.1%) than in the non-Hispanic white population (21.5%, *P*-Value < 0.001). Corresponding values for dialysis withdrawal, hospice and non-hospital death were 16.3% Vs. 30.8%, 8.8% Vs. 15.7% and 33.1% Vs. 45.0%, respectively (*P*-Value < 0.001 for each comparison). After extensive covariate adjustment, the primary outcome was less likely in the combined minority group than in the white population (adjusted odds ratio [AOR] 0.53, 95% confidence interval [CI] 0.53-0.53, *P*-Value < 0.001); within individual minority groups, AOR values arrayed as follows (Vs. white, *P*-Value < 0.001 for each):

non-Hispanic Asian, AOR 0.43 (95% CI 0.41,0.46); non-Hispanic African American, AOR 0.48 (95% CI 0.47,0.49); non-Hispanic Native American, AOR 0.64 (95% CI 0.60, 0.68); Hispanic AOR 0.71 (95% CI 0.69,0.73). Minority-associated AORs for the primary outcome were < 1 in all 44 subgroups examined.

Conclusions: Compared to their non-Hispanic white counterparts, substantial, graded, unexplained disparities in end-of-life care practices appear to be present in all racial and ethnic minority groups.

FR-PO906

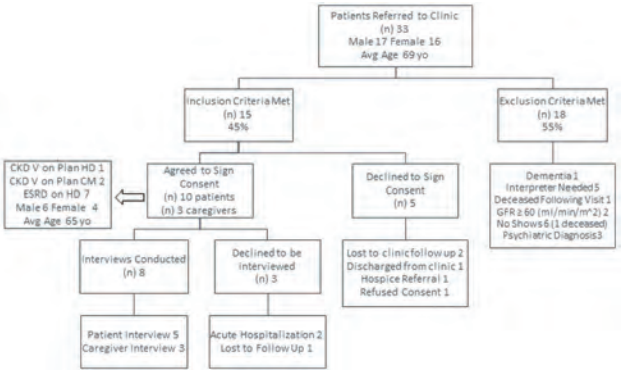
Challenges to Conducting Kidney Palliative Care Research Dana Assis,[1] Rebeca Wright,[2] Jennifer S. Scherer.[3] *[1]Nephrology, NYU School of Medicine, New York, NY; [2]Johns Hopkins University, Baltimore, MD; [3]NYU School of Medicine, New York, NY.*

Background: Despite having significant symptom burden and decreased quality of life, patients with advanced kidney disease have limited exposure to palliative care. This is partly explained by lack of research and evidence for the field. We report on challenges to conducting research in an outpatient kidney palliative care clinic (KPCC).

Methods: Patients with ESRD or CKD stage IV/V and their caregivers were approached to participate in a interview study on their experience in a KPCC. Consent was obtained in person during clinic visits from Jan - June 2017.

Results: Thirty three patients were referred to KPCC, with a no show rate of 18%. Fifteen patients met inclusion criteria; ten patients and three caregivers were consented. Cognitive impairment or psychiatric diagnosis led to patient exclusion. Hospitalization, fatigue, or pain led to attrition after consent and the potential bias towards a healthier population being interviewed. Some patients were confused by palliative care or became emotionally distressed during the interview. Patients could stop interviews and supportive conversations took place, however, maintaining a focus on the research question rather than immediately addressing clinical needs was complex. Logistically the consent process was difficult given patients had to stay past their already 60 minute long appointment. Patient physical and cognitive vulnerability, the emotional nature of palliative care topics, and provider-researcher conflict were observed challenges.

Conclusions: We uncovered barriers to palliative care research that are unique to patients living with advanced kidney disease. Future kidney palliative care research will need to consider the patient's emotional and physical state as well as the provider-researcher challenge when crafting study design to encourage patient participation and ongoing study of this essential field. *Funding: ASN Small Grants Program for Scholarly Work in Geriatric Nephrology and Renal Palliative Care*



CKD chronic kidney disease ESRD end stage renal disease CM conservative management HD hemodialysis

FR-PO907

Advanced Care Planning (ACP) among CKD and ESRD Patients: Kaiser Permanente Northern California (KPNC) Experience Sharina Belani,[1] Joanna Mroz.[2] *[1]Nephrology, Kaiser Permanente, San Rafael, CA; [2]The Permanente Medical Group, Oakland, CA.*

Background: Patients with advanced CKD and ESRD face difficult choices around extending life and managing quality of life with treatment burden. Yet, ACP choices related to dialysis therapy are rarely addressed. Nephrologists identify multiple barriers including lack of time, communication skills, and supportive tools. KPNC is an integrated health care delivery system providing care to more than 35,000 advanced CKD and 4,000 ESRD patients. KPNC Nephrology operationalized a structured ACP program called Life Care Planning (LCP) based on Respecting Choices® that follows the trajectory of CKD patients.

Methods: The KPNC LCP Nephrology program is an organized process to discuss future health care decisions and to create a written plan based on patient values and current health status. The program is operationalized with a three step staged approach using standardized communication including scripted conversations delivered by trained facilitators. First Steps is targeted to CKD 3 and 4 patients. Next Steps is targeted to prevalent ESRD patients on dialysis focusing on critical functions and trade-offs with dialysis therapy. Advanced Steps is targeted to ESRD patients with a predicted survival of less than 12 months based on clinical indicators. Registries in our EMR are used to identify at risk nephrology patients and identify the appropriate LCP step.

Results: Currently, 30% of our prevalent advaned CKD patients were able to both identify a decision maker for health care and provide verbal or written documentation in our EMR. Among our prevalent ESRD patients on dialysis, more than 30% of these patients have been invited to a Next Steps facilitated discussion and 16% of patients completed the discussion. Finally, 20% of highest risk ESRD patients have completed the Advanced Steps.

Conclusions: As an integrated health care system, KPNC is well suited to provide ongoing ACP and serious illness conversations for Nephrology patients. Future research is needed to identify effect of our LCP model at end of life including concordance with patient's identified wishes.

FR-PO908

External Validation of a Short-Term Prognostic Model for Patients Who Are on Maintenance Hemodialysis Wonngarm Kittanamongkolchai,[2] M. Lourdes Gonzalez Suarez,[1] James R. Gregoire.[1] *[1]Mayo Clinic, Rochester, MN; [2]Nephrology and Hypertension, Mayo Clinic, Rochester, MN.*

Background: Simple and accurate instruments for prognostication are needed to enable nephrologists to identify dialysis patients who have a poor prognosis and benefit from palliative care and advance care planning. Prognostic models have been developed but external validation studies are scarce. We aimed to externally validate a short-term prognostic model among our dialysis patients.

Methods: Between October 1 to October 31 2015, all of the adult HD patients (n =89) at a single dialysis facility in Rochester, MN were screened. Patient charts were reviewed for actuarial predictors (age, serum albumin, dementia and peripheral vascular disease) and nephrologists answered the "surprise" question, "Would I be surprised if this patient died within the next 6 months?". One-year survival was calculated using the prognostic calculator tool derived from a study by Cohen et al[1] (H:\QI palliative\ Prospective study\Prognosis calculator.htm) with each patient's individual covariates. Survival was monitored for 12 months. We assessed the predictive accuracy of the short-term prognostic model by calculating c-index based on the receiver operating characteristic curve.

Results: The mean predicted 1-year mortality was 19% compared with the observed mortality of 12%. The model had a C-index of 0.82 (p = 0.0001). Thirty eight percent of patients with 1-y predicted survival rate in the lowest quartile (equal or less than 66%) died compared to 3% of those with 1-Y predicted survival rate more than 66%. As seen in Figure 1, the model successfully predicted which patients had worse and better survival over time.

Conclusions: The short-term prognostic tool for dialysis patients may be of value for clinicians to improve end-of-life care by providing more accurate prognostic information. Reference: 1. Cohen LM, et al. Clin J Am Soc Nephrol. 2010 Jan;5(1):72-9

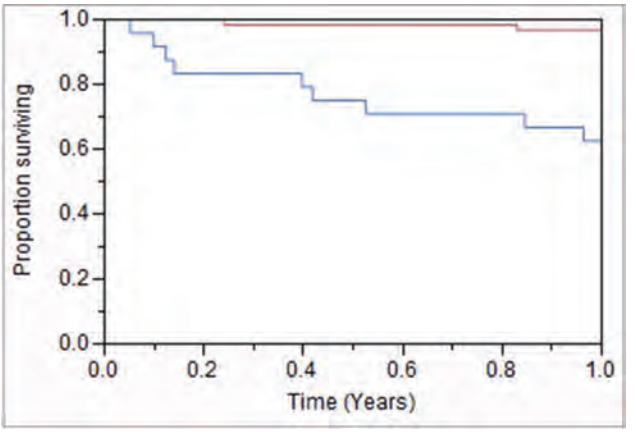


Figure 1: Survival of patients with predicted 1-Y survival in the lowest quartile (blue line) and higher quartiles (red line)

FR-PO909

Single Questions for the Diagnoses of Restless Legs Syndrome, Anxiety, and Depression in Hemodialysis (SQUIRREL) David T. Collister,[1,2] Jennifer C. Rodrigues,[1,2] Andrea E. Mazzetti,[2] Kelsi Salisbury,[2] Laura M. Morosin,[2] K. S. Brimble,[1,2] Michael Walsh.[1,2] *[1]McMaster University, Hamilton, ON, Canada; [2]St. Joseph's Healthcare Hamilton, Hamilton, ON, Canada.*

Background: Symptoms in patients with kidney disease, such as restless leg syndrome (RLS), depression and anxiety, are common, reduce quality of life and are potentially treatable. Simple, accurate screening tools are needed. We examined the operating characteristics of the single questions for RLS, depression and anxiety from the revised Edmonton Symptom Assessment System (ESAS-r) in hemodialysis patients.

Methods: We conducted a cohort study of adults receiving chronic hemodialysis in Hamilton, Canada. Diagnoses of RLS, anxiety and depression were made using the 2012 IRLSSG criteria and the Hospital Anxiety and Depression Scale. Participants were asked to the degree to which they experienced restless legs, anxiety and depression using the ESAS-r 11-point scales anchored at 0 (no symptoms) and 10 (worst possible symptoms). ESAS-r single questions were compared to their reference standards using cutoffs greater than 0 indicating the presence of symptoms using logistic regression from which receiver operating characteristics (ROC) curves were generated.

Results: We recruited 50 participants with a mean age of 64 (12.4) years, of whom 52% were male and 92% were on 3x weekly hemodialysis. Using the reference standards, 14 (28%) had a diagnosis of RLS, 27 (54%) had depression and 28 (56%) had anxiety. 27 (54%), 36 (72%) and 25 (50%) expressed symptoms of RLS, anxiety and depression. Areas under the ROC curves were 0.65, 0.81, 0.82 for RLS, anxiety and depression respectively (Figure 1). As a screening tool, an IRLS cutoff of 19 had the highest area under the ROC curve at 0.76 with a sensitivity of 71% and specificity of 81%.

Conclusions: The ESAS-r single question for RLS has poor discrimination for the diagnosis of RLS in a hemodialysis population although the ESAS-r single questions for anxiety, depression and the IRLS demonstrate reasonable discrimination.

Funding: Government Support - Non-U.S.

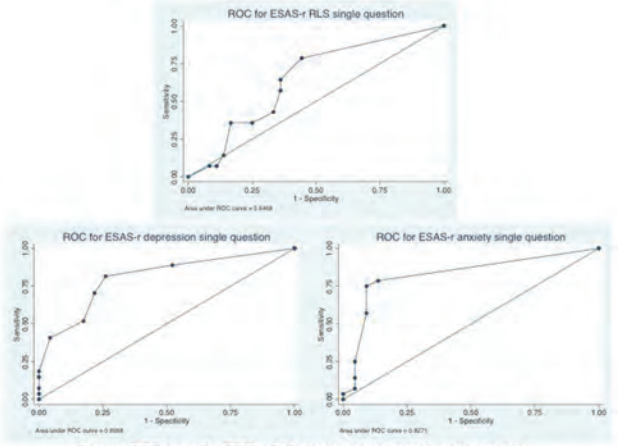


Figure 1: ROC curves for ESAS-r RLS, depression and anxiety single questions
Note: ROC = receiver operatoring characteristics,
ESAS-r = revised Edmonton Symptom Assessment System, RLS = restless legs syndrome

FR-PO910

Geographic Income Inequality and End-of-Life Care in US Dialysis Patients, 2000 to 2011 Robert N. Foley, Scott Reule. *University of Minnesota, Minneapolis, MN.*

Background: End-of-life care is increasingly considered in dialysis patients when death is imminent and quality of life is poor. Although end-of-life care can add financial and other burdens to dialysis patients and their families, associations with regional income dispersion have not been examined. As little is known regarding geographic income inequality, we performed a national study to examine potential associations with end-of-life care in US dialysis patients.

Methods: Retrospective United States Renal Data System files were used to end-of-life care parameters (all deaths from 2000 to 2011, N=910,559). The main exposure variable was county-level Gini index of income dispersion (range: 0 [perfect equality] to 1 [perfect inequality]; observed quartile thresholds 0.430, 0.453 and 0.481).

Results: The primary outcome-a composite of withdrawal of dialysis and death in a non-hospital or hospice setting-decreased monotonically with increasing income dispersion (20.9%, 18.6%, 17.0% and 10.2%, respectively, for Quartiles 1 to 4 of Gini index, *P*-Value < 0.001). Similarly, monotonic patterns (*P*-Value < 0.001 throughout) were seen for dialysis withdrawal (30.0%, 27.3%, 25.2% and 16.0%), hospice (15.1%, 14.1%, 13.3% and 9.0%) and non-hospital death (44.5%, 41.9%, 40.1% and 33.3%). After adjustment for age, sex, race-ethnicity, region, urban or rural domicile, kidney disease, mode of dialysis, previous transplant, insurance and dialysis facility characteristics, the primary outcome was similarly less likely in Quartiles 2 (adjusted odds ratio [AOR] 0.91 [95% CI 0.89-0.92], [Vs. Quartile 1]) and 3 (AOR 0.90 [0.88-0.91]) and even less likely in Quartile 4 (AOR 0.61 [0.61-0.62]), a pattern that was repeated when dialysis withdrawal, hospice and non-hospital death were examined (*P*-Value < 0.001 for each AOR). Multivariate associations between income dispersion and end-of-life care were present in all 45 subgroups examined.

Conclusions: End-of-life care in dialysis patients varies meaningfully by geographic income inequality.

FR-PO911

Improving Advanced Care Planning in Maintenance HD Patients with ESRD Bashir El-Khoury, Chandandeep Takkar. *University of Texas Health Science Center San Antonio, San Antonio, TX.*

Background: More than 80,000 Americans die every year while receiving maintenance dialysis therapy for ESRD. The adjusted mortality rate of maintenance dialysis patients is nearly twice that of adults with cancer and more than twice that of adults with CHF or stroke. Rates of hospitalization and ICU admission during last month of life are also higher in ESRD patients. Although studies have shown that dialysis patients with a treatment-limiting advance directive were less likely to be hospitalized, receive intensive procedures, and die in the hospital, advanced care planning (ACP) or completion of Advance Directives (AD)/Medical Power of Attorneys (MPOA) is lacking in the ESRD population compared to other chronic illnesses.

Methods: We conducted a pilot quality improvement project aimed at improving ACP in the maintenance HD community. Our goal was to increase the percentage of MWF second shift hemodialysis patients at University Dialysis Northwest (one of four dialysis units affiliated with us) with AD/MPOAs on file by 25% between November 2016 and February 2017. An inter-disciplinary team was convened. We surveyed our patients to obtain baseline information on current rates of AD/MPOA completion, knowledge of ACP, desire to participate in ACP, and identify barriers to completion. We collaborated with the Department of Palliative Medicine and implemented a series of interventions aimed towards facilitating the completion of ADs/MPOAs in our patients.

Results: We were able to increase the percentage of completed ADs/MPOAs to 29.2% from a baseline of 4.2% during our timeline. We are currently implementing measures including dedicated training in ACP for dialysis staff at all our outpatient dialysis facilities, incorporating ACP into interdisciplinary team meetings, establishing on-site notaries, and providing patient education in order to sustain results and expand the program to all UHS outpatient HD units.

Conclusions: Advance care planning is a vital aspect of patient-centered care at the end of life. Unfortunately it is lacking in the maintenance dialysis patient population due to a variety of cultural, provider and institutional barriers. We demonstrated that a comprehensive multidisciplinary approach to advance care planning improves AD/MPOA completion rates in our patient population.

FR-PO912

CKD Measures and Physical Function in Older Adults: The Atherosclerosis Risk in Communities (ARIC) Study Yugo Shibagaki,[1,5] Shoshana Ballew,[5] Priya Palta,[3] B G. Windham,[2] Josef Coresh,[4] Kunihiro Matsushita.[5] *[1]Division of Nephrology and Hypertension, St Marianna University Hospital, Kawasaki, Japan; [2]UMMC, Jackson, MS; [3]University of North Carolina at Chapel Hill, Chapel Hill, NC; [4]Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; [5]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD.*

Background: Reduced estimated glomerular filtration rate (eGFR) has been shown to be related to impaired physical function. However, data on the other chronic kidney disease (CKD) measure, albuminuria, in this context are sparse. Furthermore, whether cognitive function modifies these associations is unknown.

Methods: Among 4,608 community-dwelling older adults at ARIC visit 5 (2011-2013), we studied cross-sectional associations of eGFR with cystatin C (eGFRcys) and urine albumin-creatinine ratio (ACR) with physical function based on the Short Physical Performance Battery (SPPB). Cognitive function was classified as no cognitive impairment, mild cognitive impairment (MCI), or dementia according to a diagnostic review of neuropsychiatric, neurologic, and brain imaging assessments.

Results: Mean age of participants was 75.7 (SD 5.1) years, and median SPPB was 10 (IQR 8-11), with 13.8% (n=636) having impaired physical function (defined as SPPB score <6). Adjusted for potential confounders, the odds ratio of having impaired physical function was 1.98 (95%CI 1.21-3.24) in GFR <45 ml/min/1.73m^2, 1.42 (0.88-2.30) in GFR 45-59, and 0.98 (0.61-1.57) in GFR 60-89, compared to GFR ≥90 (Table). Similarly, the odds ratio was 1.92 (95%CI 1.20-3.05) in ACR ≥300 mg/g and 1.71 (1.38-2.14) in ACR 30-299, compared to ACR <30. When stratified by cognitive function (n=3,449 with normal and 1,159 with MCI/dementia), of the associations of eGFF and ACR with impaired physical function were stronger in normal cognition than in MCI/dementia (Table).

Conclusions: Both high albuminuria and low eGFR were independently associated with impaired physical function, with more evident results when cognition was preserved.

Adjusted odds ratios (95% CIs) of impaired physical function according to CKD measures.

	eGFRcys				UACR		
	>= 90 N=353	60 – 90 N=1,963	45 – 60 N=1,286	< 45 N=1,006	< 30 N=3,700	30 – 300 N=792	>= 300 N=116
Total N=4,608	1 (ref)	0.98 (0.61-1.57)	1.42 (0.88-2.30)	1.98 (1.21-3.24)	1 (ref)	1.71 (1.38-2.14)	1.92 (1.20-3.05)
Normal cognition N=3,450	1 (ref)	1.04 (0.57-1.89)	1.61 (0.88-2.97)	2.17 (1.16-4.05)	1 (ref)	1.91 (1.44-2.52)	2.14 (1.14-4.02)
MCI/Dementia N=1,158	1 (ref)	0.70 (0.31-1.58)	0.93 (0.41-2.11)	1.33 (0.58-3.06)	1 (ref)	1.39 (0.96-2.00)	1.46 (0.73-2.94)

Adjusted for age, race, gender, education, smoking, alcohol, body mass index, anemia, high sensitive CRP, diabetes, hypertension, history of stroke, history of coronary heart disease, heart failure, and peripheral arterial disease.

FR-PO913

Kidney Function Is Not Associated with an Accelerated Decline in Objective Tests of Physical Performance in Older Adults Mark Canney,[1,2] Daniel Carey,[1] Rose Anne M. Kenny,[1] Mark A. Little,[2] Conall M. O'Seaghdha.[3] *[1]The Irish Longitudinal Study on Ageing, Trinity College Dublin, Dublin, Ireland; [2]Trinity Health Kidney Centre, Trinity College Dublin, Dublin, Ireland; [3]Department of Nephrology and Transplantation, Beaumont Hospital, Dublin, Ireland.*

Background: Cross-sectional studies in older adults have identified an association between diminished estimated glomerular filtration rate (eGFR) and frailty. Whether kidney function is driving frailty, or both conditions have shared risk factors, is not well understood. Longitudinal studies could inform this question. We sought to examine whether baseline eGFR predicted an accelerated decline in gait speed or timed-up-and-go (TUG) in a large representative sample of older adults.

Methods: Prospective analysis from the first 3 waves (2009-2015) of The Irish Longitudinal Study on Ageing, a nationally representative cohort of community-based adults aged ≥50 years. Gait speed was measured at waves 1 and 3 in 3140 participants (mean age 60.9 years). TUG was measured at all 3 waves in 4930 participants (mean age 62.6 years). We calculated eGFR at wave 1 from cystatin C using the Chronic Kidney Disease Epidemiology equation. We used mixed effects linear regression to examine the association between categorical eGFR (>90, 60-89, <60mL/min/1.73m^2) and each outcome. Models were adjusted for age, sex, height, waist circumference, smoking, diabetes, pulse pressure, cardiovascular disease, polypharmacy, chronic health conditions. Each covariate was included as a main effect and its interaction with time (wave). The parameter of interest was the time*eGFR interaction. Analyses were weighted to account for differential non-response and attrition across waves.

Results: For gait speed the unadjusted time*eGFR interaction was strongly statistically significant (p<0.001) but did not retain significance after adjustment for age, sex and comorbidites (p=0.22). A similar pattern was observed for TUG: p<0.001 for unadjusted interaction, p=0.43 for multivariable-adjusted interaction. In a subgroup analysis, participants with eGFR<50mL/min/1.73m^2 (the median eGFR in the <60mL/min/1.73m^2 category) had some evidence of worse TUG over time compared to those with eGFR>60mL/min/1.73m^2, however the effect size was modest (0.3 seconds longer).

Conclusions: In this large cohort of older adults, a diminished eGFR did not predict an accelerated decline in objectively measured tests of physical performance. The strong association between eGFR and markers of frailty may be best explained by comorbidity rather than reduced kidney function per se.

Funding: Government Support - Non-U.S.

FR-PO914

Impact of Poor Functional Status on Outcomes among Elderly Dialysis Patients Silvi Shah, Anthony C. Leonard, Charuhas V. Thakar. *University of Cincinnati, Cincinnati, OH.*

Background: One-in-four incident end stage renal disease (ESRD) patients are > 75 years of age; and in prevalent trends for ESRD, the highest growth has occurred in those above 75 years. Hospitalizations and comorbidities are common in pre-ESRD patients, and along with age, can contribute to poor functional status at dialysis initiation.

Methods: We evaluated 49,645 adult incident dialysis patients (1/1/2008 to 12/31/2008) from the United States Renal Data System (USRDS) with linked Medicare data for at least 2 years prior to dialysis initiation. Poor functional status was defined by any of the three comorbidities listed in form 2728 – inability to ambulate, inability to transfer or need of assistance with daily activities. Using case-mix logistic regression adjusted models (16 variables including pre-ESRD hospitalizations), we examined the impact of poor functional status on type of dialysis modality (hemodialysis [HD] vs. peritoneal dialysis [PD]) and one-year all cause mortality. In a separate model among HD patients, we studied the effect of functional status on type of vascular access (arteriovenous [AV] access vs. catheter).

Results: Of the study cohort, 55% were male. Mean age was 72 ±11 years. At dialysis initiation, 26% were octogenarian, 20% reported poor functional status and 10% had reported nursing home stay. Patients with poor functional status were 10 times more likely have a nursing home stay than those without poor functional status. Only 4% of patients initiated PD. Of those who started HD, 82% initiated with a catheter. Overall, one-year mortality was 31%; it was 48% in patients with poor functional status and 57% in octogenarians with poor functional status. In adjusted analyses, patients with poor functional status were more likely to be started on HD (odds ratio [OR], 1.42; 95% confidence interval [CI], 1.18-1.69); and among those on HD, the odds for starting HD with AV access were lower (OR, 0.78; CI, 0.72-0.85). One-year adjusted mortality was higher in patients with poor functional status (OR, 1.5; CI, 1.42-1.59).

Conclusions: Poor functional status is associated with higher odds of initiating HD than PD; increases the risk of catheter use in those with HD, and is an independent predictor of one-year mortality. Patients with poor functional status, independent of age, should be counseled for shared decision-making and assessed for conservative treatment options.

FR-PO915

Racial and Gender Disparities in Long-Term Clinical Outcomes among Elderly Dialysis Patients Silvi Shah, Anthony C. Leonard, Charuhas V. Thakar. *University of Cincinnati, Cincinnati, OH.*

Background: Mortality in end stage renal disease (ESRD) patients is highest during the first year of dialysis. However, after considering the influence of pre-dialysis health status (defined as nephrology care and acute care hospitalizations) and dialysis access; the effects of race and gender on long-term mortality among incident Medicare dialysis patients are not known.

Methods: We evaluated 49,645 adult incident dialysis patients (1/1/2008 to 12/31/2008) from the United States Renal Data System (USRDS) with linked Medicare data for at least 2 years prior to dialysis initiation. Information on pre-dialysis health status was obtained from form 2728 and linked Medicare claims. Using case-mix adjusted logistic regression models (16 variables), we examined the effect of race and gender on one-year all cause mortality after dialysis initiation.

Results: Mean age of study population was 72±11 years. Of the study cohort, 26% were octogenarian; 55% were male; and 63% were White. Of those who started hemodialysis (HD), 82% initiated with a catheter. One-year mortality was 31%. Pre-dialysis nephrology care was associated with lower mortality in dialysis patients than those without nephrology care (26% vs. 39%, p<0.001). Pre-dialysis acute hospitalization was associated with higher mortality than those without pre-dialysis hospitalization (33% vs. 19%, p<0.001). As compared to patients with catheter, incident AV access was associated with lower mortality (35% vs. 16%; p<0.001). In adjusted analyses, as compared to Whites, one-year mortality was lower among Blacks (odds ratio [OR], 0.7; 95% confidence interval [CI], 0.66-0.74]), Hispanics (OR, 0.65; CI, 0.60-0.70) and Asians (OR, 0.65; CI, 0.57-0.74). Females were less likely to die within one year after initiating dialysis than males (OR, 0.95; CI, 0.91-0.99).

Conclusions: Among elderly dialysis patients; Blacks, Hispanics and Asians have a lower mortality than Whites; and females have lower mortality than males. These differences across race and gender exist independent of pre-dialysis health status and dialysis access type. Biological factors associated with these disparities need to be explored further to understand the reasons behind the survival advantage among minorities and women.

FR-PO916

Extracellular Volume Expansion and Inflammation Are Independently Associated with Malnutrition, Determined by Geriatric Nutritional Risk Index in Hemodialysis Patients Dong Ho Yang,[2] So-young Lee,[3] Mi Jung Lee,[2] Hye yun Jeong.[1] *[1]CHA Bundang Medical Center, Seongnam-si, Republic of Korea; [2]Internal Medicine, CHA Bundang Medical Center, CHA Univ., Seongnam-si, Not Applicable, Republic of Korea; [3]Internal Medicine, CHA Bundang Medical Center, CHA Univ., Seongnam-si, Not Applicable, Republic of Korea.*

Background: It is well known that malnutrition is implicated with increased morbidity and mortality in end-stage renal disease (ESRD) patients. Therefore, exploring risk factors for malnutrition has clinical relevance in these patients. In the present study, we aimed to investigate the significant association between fluid overload, inflammation, and malnutrition in ESRD patients on hemodialysis (HD).

Methods: A cross-sectional study was undertaken in 76 prevalent HD patients in South Korea. Geriatric nutritional risk index (GNRI) was calculated to determine nutritional status. Ratio of extracellular water (ECW) to total body water (TBW) was measured to determine fluid overload using multi-frequency bioimpedance (Inbody S20, Biospace, Seoul, Korea). Independent association between variables and GNRI were tested by linear regression analyses.

Results: The mean age was 59.1 ± 13.4 years, and 44 patients (57.9%) were mean. The mean GNRI value was 97.2 ± 6.6 (median 97.8, interquartile range 94.4 to 101.8). The mean ratio of ECW to TBW (ECW/TBW) was 0.38 ± 0.02. In univariate analysis, age (per 1 year, ß=-0.13, 95% confidence interval [CI]=-0.24 to -0.02), ECW/TBW (per 0.01, ß=-1.89, 95% CI=-2.58 to -1.19), and C-reactive protein concentrations (per 1 mg/l, ß=-4.73, 95% CI=-7.19 to -2.28) were negatively associated with GNRI, while serum potassium (per 1 mEq/l, ß=2.46, 95% CI=0.36 to 4.55) and calcium-phosphorous products (per 1 mg^2/dl^2, ß=0.18, 95% CI=0.06 to 0.29) were positively associated with GNRI. Moreover, men and patients with previous cardiovascular disease history had lower GNRI values. Multivariate analysis demonstrated that higher values of ECW/TBW (per 0.01, ß=-1.33, 95% CI=-2.06 to -0.59) and C-reactive protein (per 1 mg/l, ß=-2.88, 95% CI=-5.07 to -0.68) were independently associated with lower GNRI values after adjustment of confounding variables.

Conclusions: Extracellular volume expansion and inflammation showed an independent association with lower GNRI values in HD patients. This result suggest that avoiding fluid overload and inflammation could be helpful to mitigate malnutrition in these patients.

FR-PO917

Effect of Lower BMI on Mortality Risk in Older Patients Starting Dialysis Is Time-Dependent Harmke A. Polinder-Bos,[2] Ron T. Gansevoort,[2] Merel Van diepen,[1] Friedo W. Dekker,[1] Ellen K. Hoogeveen,[3,1] Casper F. Franssen,[2] Carlo A. Gaillard.[2] *[1]Leiden University Medical Center, Leiden, Netherlands; [2]University Medical Center Groningen, Groningen, Netherlands; [3]Jeroen Bosch Hospital, Den Bosch, Netherlands.*

Background: Lower body mass index (BMI) has consistently been associated with worse survival in older individuals in the general population and in chronic disease populations. Remarkably, in older dialysis patients no association of BMI with mortality was found. Therefore, we performed an in-depth analysis on this association in the NECOSAD cohort.

Methods: 908 patients aged ≥65 years were followed from start of dialysis until death or kidney transplantation, and were divided into tertiles by baseline BMI (BMI <23 (lower), 23-26 (reference), >26 (higher) kg/m^2). Because the hazards changed significantly during follow-up, the effect of BMI was modeled for the short-term (<1 year after dialysis initiation) and longer-term (≥1 years after dialysis initiation) using time-dependent Cox-regression models. Furthermore, differences between lower BMI patients who survived versus died during the first year of dialysis therapy were evaluated.

Results: During a median follow-up period of 3.8 year, 567 deaths occurred. Cumulative survival proportions at end of follow-up were 30%, 28% and 31% for the lower, middle and higher BMI groups, respectively. Lower BMI was associated with a higher short-term mortality risk (HR 1.57 [1.10-2.23] *P*=0.01), and a lower longer-term mortality risk (HR 0.77 [0.60-0.99] *P*=0.04), adjusted for age, sex, race, and smoking. Patients with a lower BMI who died during the first year of dialysis therapy had significantly more comorbidity, less physical mobility and ability to perform usual activities, and had lower albumin levels compared with those who survived the first year.

Conclusions: In older patients who start dialysis therapy lower BMI is associated with increased 1-year mortality. Remarkably, when surviving the first year of dialysis, patients with lower baseline BMI had a similar or even lower mortality risk compared with patients who had a normal or higher baseline BMI. Especially those older patients with lower BMI that have limited comorbidity and mildly or non-impaired physical function may benefit from having started dialysis.

FR-PO918

Importance of Skeletal Muscle Mass on the Long Term Patient Survival in the Elderly AKI Patients Who Underwent Continuous Renal Replacement Therapy Harin Rhee,[4] Sang Heon Song,[3] Miyeun Han,[7] Eun Young Seong,[3] Il Young Kim,[6] Dong Won Lee,[5] Soo Bong Lee,[2] Ihm Soo Kwak.[1] *[1]Busan National University Hospital, Busan, Republic of Korea; [2]None, Yangsan-si, Gyeongsangnam-do, Republic of Korea; [3]Pusan National University Hospital, Busan, Busan, Republic of Korea; [4]Internal medicine, Pusan National University Hospital, Busan, Republic of Korea; [5]Pusan National University School of Medicine, Yangsan, Republic of Korea; [6]Pusan National University Yangsan Hospital, Yangsan, Republic of Korea; [7]SEOUL NATIONAL UNIVERSITY HOSPITAL, SEOUL, Republic of Korea.*

Background: In patients with chronic kidney disease, survival has been shown to be better with increasing body mass index. Recently, it is also reported to be true in patients with acute kidney injury (AKI). However, few studies were conducted to reveal which of the two body components, muscle or fat, was beneficial to the patient survival. The aim of this study is to evaluate the impacts of skeletal mass and fat mass on the long term patient survival in elderly AKI patients who underwent CRRT.

Methods: This study was a single center retrospective study of elderly patients who survived from AKI needed CRRT from January 2013 to December 2015. Patient's long term survival was verified in March 2016 by individual phone call. Skeletal muscle mass (SMM) and fat mass (FM) were measured using bioimpedance analysis method at the time of CRRT initiation. SMM and FM were adjusted with height squared. Multivariable cox regression analysis was adjusted to evaluate the significant factors associated with long term patient survival.

Results: A total of 170 patients were included in this study. The mean patient age was 73.77±5.68 years old, and 57.1% of the patients were male. The mean BMI was 22.94±3.27 kg/m^2. During the median follow up period of 287.0 days, 40.0% (68/170) of the patients were dead. When we performed multivariable analysis to define factors associated with long term patient survival, lower SMM was associated with higher long term mortality (HR 0.830(0.697-0.988), p=0.036) along with older age (HR 1.062(1.105-1.110), p=0.009), history of sepsis (HR1.994(HR1.174-3.387), p=0.011) and prolonged prothrombin time (1.396, HR(1.155-1.688), P=0.001). However, lower FM was not associated with long term patient survival in this group.

Conclusions: In the elderly patients with AKI treated with CRRT, lower skeletal muscle mass rather than lower fat mass was associated with long term patient mortality.

FR-PO919

A Frailty Screening Tool for Use in CKD by Medical and Nursing Staff Andrew Nixon,[1,2] Theodoros M. Bampouras,[3] Alastair R. Petrie,[3] Atinuke J. Afolabi,[3] Neil Pendleton,[1] Sandip Mitra,[4] Ajay P. Dhaygude.[2] *[1]University of Manchester, Manchester, United Kingdom; [2]Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom; [3]University of Cumbria, Lancaster, United Kingdom; [4]Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom.*

Background: Frailty is associated with adverse clinical outcomes in chronic kidney disease (CKD) including an increased risk of hospitalisation and mortality. Nephrologists need a well-validated frailty screening tool.

Methods: Fifty-eight dialysis-dependent CKD and pre-dialysis stage 4 and 5 CKD patients were recruited. Patients were assessed by a doctor and nurses using the Clinical Frailty Scale (CFS). Frailty was also assessed using two operationalised frailty definitions: the frailty phenotype (FP) and the frailty index (FI). CFS scores were compared with FP and FI scores and ROC curves were calculated.

Results: Median age was 70 years old (IQR: 58.75-77.00) with 28 male patients. Half were receiving haemodialysis. Mean Charlson Comorbidity Index was 3.12 (SD: 1.29). Using the CFS, 29% were idenitified as frail by a doctor and 31% by nurses. Using the FP, frailty prevalance was 24%. Mean FI was 0.32 (SD: 0.13). Doctor and nurse CFS scores correlated well with each other (r=0.81, 95% CI: 0.70-0.89). Doctor CFS scores correlated well with FP (r=0.80, 95% CI: 0.70- 0.87) and FI (r=0.85, 95% CI: 0.75-0.92) scores. Nurse CFS scores correlated moderately well with FP (r=0.66, 95% CI: 0.51-0.77) and FI (r=0.67, 95% CI: 0.52-0.79) scores. The ROC AUC was 0.90 (95% CI: 0.82-0.98) for the doctor CFS and 0.81 (95% CI: 0.70-0.93) for the nurse CFS (figure 1). A CFS score ≥4 gave a sensitivity of 1.00 and 1.00 with a specificity of 0.41 and 0.43 for identifying frailty (as defined by the FP) by a doctor and nurse, respectively.

Conclusions: The CFS is a useful frailty screening tool in those with CKD and can be effectively used by medical and nursing staff. Further study is needed to evaluate its ability to risk stratify patients prior to the commencement of renal replacement therapy.

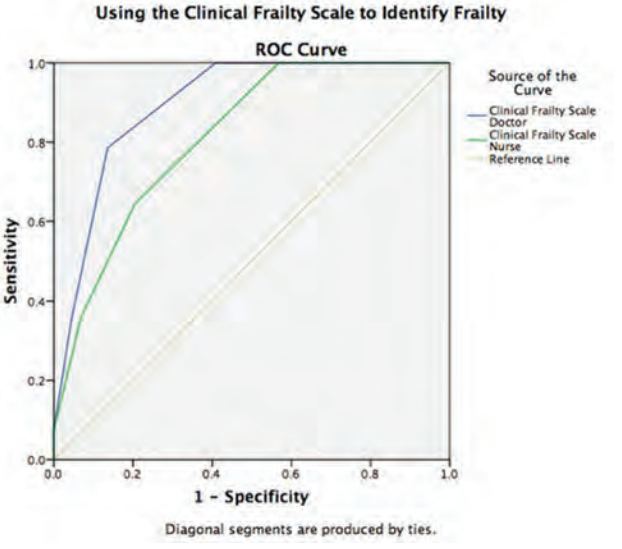


Figure 1. Using the CFS to Identify Frailty.

FR-PO920

Evaluation of a Patient-Directed Frailty Screening Tool for Use in CKD Andrew Nixon,[1,2] Theodoros M. Bampouras,[3] Alastair R. Petrie,[3] Atinuke J. Afolabi,[3] Neil Pendleton,[2] Sandip Mitra,[4] Ajay P. Dhaygude.[1] *[1]Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom; [2]University of Manchester, Manchester, United Kingdom; [3]University of Cumbria, Lancaster, United Kingdom; [4]Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom.*

Background: Frailty is associated with adverse outcomes in Chronic Kidney Disease (CKD). There is a need for a frailty screening tool that is well-validated in CKD. The British Geriatric Society (BGS) has suggested that the PRISMA 7 questionnaire is a useful self-assessment screening method for frailty in the general population. However, it has not yet been validated in those with CKD.

Methods: Fifty-eight dialysis-dependent CKD and pre-dialysis stage 4 and 5 CKD patients were recruited. Patients were asked to complete the PRISMA 7 questionnaire. As suggested by the BGS, a score of ≥3 was considered to identify frailty. Frailty was also assessed using two operationalised frailty definitions: the frailty phenotype (FP) and the frailty index (FI). The correlation between PRISMA 7 scores and FP and FI scores was assessed. ROC curves were calculated to assess the PRISMA 7 questionnaire's sensitivity and specificity.

Results: Median age was 70 years old (IQR: 58.75-77.00) with 28 male patients. Half were receiving haemodialysis. Mean Charlson Comorbidity Index was 3.12 (SD: 1.29). The PRISMA 7 identified 48% as frail. Using the FP, frailty prevalance was 24%. Mean FI was 0.32 (SD: 0.13). The PRISMA 7 scores correlated moderately well with FP (r=0.66, 95% CI 0.52-0.78) and FI (r=0.76, 95% CI 0.66-0.84) scores. Figure 1 demonstrates the ROC curve for the PRISMA 7. The ROC AUC was 0.87 (95% CI 0.77-0.97) for the PRISMA 7. A PRISMA 7 score ≥3 had a sensitivity of 0.93 and specificity of 0.66 for identifying frailty, as defined by the FP.

Conclusions: The PRISMA 7 questionnaire is an effective patient-directed frailty screening tool with excellent sensitivity for identifying frailty. It can be easily incorporated into routine clinical care. Further research is needed to evaluate its prognostic accuracy.

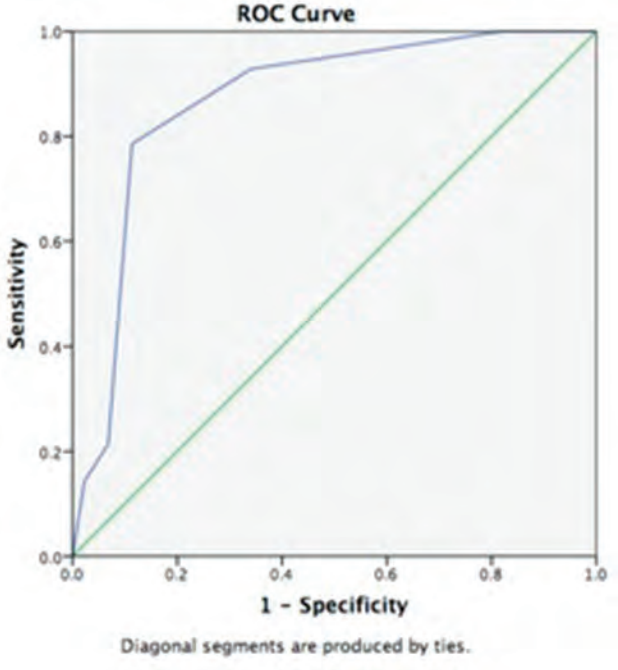


Figure 1. ROC Curve Assessing the PRISMA 7 Questionnaire's Ability to Identify Frailty

FR-PO921

Step Length as a Novel Predictor of Physical Function in Patients with CKD Rima N. Pai,[1] Rupinder singh Buttar,[8] William Paredes,[2] Matthew Custodio,[1] Hina Farooq,[4] BUSHRA ZAIDI,[6] Nabin R. Karki,[5] Aagat Sharma khatiwada,[7] Stephen Ansah-Addo,[1] Ashley Tran,[3] Meredith Hawkins,[1] Matthew K. Abramowitz.[1] *[1]Albert Einstein College of Medicine, New York, NY; [2]Albert Einstein College of Medicine, Bronx, NY; [3]Ambra Health, Holmdel, NJ; [4]Louis A. Weiss Memorial Hospital, Chicago, IL; [5]Medstar Harbor Hospital, Baltimore, MD; [6]ALBERT EINSTEIN COLLEGE OF MEDICINE, Bronx, NY; [7]University of Leicester, Leicester, United Kingdom; [8]Jacobi medical center, Bronx, NY.*

Background: Impaired mobility and disability are common in patients with CKD and contribute to morbidity and mortality. Novel predictors of functional decline could facilitate earlier identification of at-risk patients.

Methods: We measured average step length (SL) in 32 patients with CKD stages 4 and 5 who had physical function assessments performed every 3 months (median, 4 assessments). SL was calculated based on the number of steps needed to complete a 4m walk at usual pace. We also assessed lower extremity performance (Short Physical Performance Battery), muscle strength, endurance capacity (2 minute walk distance), self-reported physical function (SF-36 Physical Component Score (PCS)), and symptom burden (Renal Palliative Care Outcome Scale (POS)). Age and sex-adjusted linear regression and mixed effects models were used to test the association of SL with baseline characteristics and with physical function parameters over time, respectively.

Results: The mean age was 64±13 years, 44% were women, mean eGFR 20±10 mL/min/1.73m^2, mean BMI 32±7 kg/m^2, 59% had diabetes, and 16% had peripheral vascular disease. Lower PCS and higher POS associated with shorter SL (4.7cm (1.8-7.7) and 6.3cm (2.7-9.9) per 10 point difference, respectively), as did 2 SPPB domains (2.3cm (1.7-2.9) per 0.1m/s slower gait speed and 7.3cm (1.1-13.5) shorter SL with impaired balance). Over time, each 10cm shorter SL was associated with 1.4kg (0.2-2.7) weaker handgrip strength and 26.5ft (8.6-44.5) shorter 2-minute walk distance, and with 0.4 point (0.02-0.7) decrease in SPPB during follow-up. Furthermore, SL was shorter in patients experiencing a fall (46±11 vs. 56±8 cm, p=0.008).

Conclusions: In a cohort of patients with advanced CKD, shorter SL associated with poorer subjective and objective measures of physical function and with the likelihood of falling. SL may be a useful predictor of fall risk and functional decline in CKD patients.

Funding: NIDDK Support

FR-PO922

Serious Fall Injury History and Adverse Health Outcomes after Initiating Hemodialysis among Older US Adults C. Barrett Bowling,[1,3] Rasheeda K. Hall,[3,1] Anjali Khakharia,[2] Harold A. Franch,[2,4] Laura Plantinga.[2] *[1]Durham VA Medical Center, Decatur, GA; [2]Emory University, Atlanta, GA; [3]Duke University, Durham, NC; [4]Atlanta VAMC, Decatur, GA.*

Background: Although older adults with pre-dialysis CKD are at increased risk for falls, the prognostic significance of a serious fall injury prior to dialysis initiation has not been well described in the end-stage renal disease population.

Methods: We examined the association between a serious fall injury in the year prior to starting hemodialysis and adverse health outcomes in the year following dialysis initiation using a retrospective cohort study of U.S. Medicare claims data from the 2 years spanning dialysis start, among patients initiating dialysis in 2010-2012. Participants included Medicare beneficiaries aged ≥67 years. Serious fall injuries were defined using diagnostic codes for falls in combination with an injury code for a fracture, joint dislocation, or head injury. Outcomes were defined as time-to-event variables within the first year of dialysis for four outcomes: subsequent serious fall injury, hospital admission, post-acute skilled nursing facility (SNF) utilization, and mortality.

Results: Among this cohort of 81,653 initiating hemodialysis, 2,958 (3.6%) patients had a serious fall injury in the year prior to hemodialysis initiation. Compared to those without serious fall injuries, those with a serious fall injury in the prior year were older (mean age 78.1 vs 76.7), more likely to be female (57.7% vs. 46.8%) and white (73.5% vs. 65.2%), and more likely to need assistance with daily activities (27.2% vs. 17.8%). In the first year of dialysis, 7.6%, 67.6%, 30.7%, and 26.1% had a serious injury fall, hospitalization, SNF claim, or died. Multivariable adjusted hazard ratios (95% confidence intervals) for a serious fall injury, hospitalization, SNF claim, or death for those with vs. without a history of serious fall injury in the year prior to hemodialysis initiation were 2.94 (2.71-3.20), 1.20 (1.15-1.26), 1.62 (1.52-1.73), and 1.28 (1.20-1.43), respectively.

Conclusions: A serious fall injury in the year prior to dialysis was associated with an increased risk for adverse health outcomes. For older adults initiating dialysis, a history of a serious fall injury may be novel marker for frailty and provide prognostic information to support decision-making and establish expectations for life after dialysis initiation.

Funding: Veterans Affairs Support, Private Foundation Support

FR-PO923

Kidney Function Is Not an Independent Predictor of Falls among Community-Dwelling Older Adults Mark Canney,[1,2] Daniel Carey,[1] Rose Anne M. Kenny,[1] Mark A. Little,[2] Conall M. O'Seaghdha.[3] *[1]The Irish Longitudinal Study on Ageing, Trinity College Dublin, Dublin, Ireland; [2]Trinity Health Kidney Centre, Trinity College Dublin, Dublin, Ireland; [3]Department of Nephrology and Transplantation, Beaumont Hospital, Dublin, Ireland.*

Background: While several studies have identified a link between chronic kidney disease and markers of frailty in older age, it is largely unknown if this association translates into meaningful outcomes such as a greater risk of falls. We sought to examine the relationship between kidney function and falls in a large representative cohort of older adults.

Methods: Prospective analysis of 5060 participants from the first 3 waves (2009-2015) of The Irish Longitudinal Study on Ageing, a nationally representative sample of community-dwelling adults aged ≥50 years. All participants had estimated glomerular filtration rate (eGFR) calculated from cystatin C at wave 1. Data regarding falls (any fall in the last year or between waves) were captured via a computer-assisted personal interview at each wave. We used mixed effects logistic regression to examine the association between eGFR (≥90 [reference], 60-89, <60mL/min/1.73m^2) and reporting a fall. Models were adjusted for age, sex, frailty (pre-frail/frail versus robust), diabetes, cardiovascular disease, pulse pressure, polypharmacy and chronic health conditions. Each covariate was modelled as a main effect and as a time*covariate interaction. An inverse probability weight was applied to all estimates to account for differential non-response and attrition.

Results: Mean (standard deviation) age of participants was 62.8 (9.1) years, 46% were male and median (interquartile range) eGFR was 80 (67-93) mL/min/1.73m^2. After adjusting for age and sex, participants with eGFR <60mL/min/1.73m^2 had a 5.0% (95% confidence interval 1.3 to 8.6%) increased probability of a fall versus the reference group (eGFR ≥90mL/min/1.73m^2). This association was attenuated in the extended model (2.6% increased probability [-1.1 to 6.2%]). Results did not vary by age (over or under 65) or sex. The time*eGFR interaction was not statistically significant after adjusting for age and sex (p=0.65). Frailty and the number of chronic conditions were both independent predictors of falls in the multivariable model.

Conclusions: In this large prospective study of older community-based adults, kidney function was not found to be an independent predictor of falls. Our data suggest that, in the general population of older individuals, frailty status and comorbidity burden are more important predictors of falls than kidney function alone.

Funding: Government Support - Non-U.S.

FR-PO924

Improving Physical Function and Social Networks of Older Adults with ESRD: Development and Testing of Seniors Optimizing Community Integration to Advance Better Living with ESRD (SOCIABLE) Deidra C. Crews,[5] Alice M. Delaney,[7] Janiece L. Walker,[2] Thomas K. Cudjoe,[1] Allyson Evelyn-Gustave,[3] Jill Roth,[6] David L. Roth,[4] Sarah Szanton.[3] *[1]Johns Hopkins School of Medicine, Baltimore, MD; [2]Johns Hopkins School of Nursing, Baltimore, MD; [3]Johns Hopkins University, Baltimore, MD; [4]Johns Hopkins University, Baltimore, MD; [5]Johns Hopkins University School of Medicine, Baltimore, MD; [6]Johns hopkins School of Nursing, Baltimore, MD; [7]University of Maryland, Essex, MD.*

Background: Older adults with ESRD have increased morbidity, life constraining fatigue and decreased physical function. These conditions can inhibit self-care and social engagement while restricting ability to leave home. We developed a home-based program to improve physical and social functioning of low income, older adults on hemodialysis (HD).

Methods: We 1) identified daily functional needs and home environmental barriers to engaging social networks among low income older patients on HD through focus groups (n=7 patients); 2) mapped focus group findings onto aspects of an established program for low income older adults with physical limitations (which includes home visits with an occupational therapist, nurse and handyman to provide ≦$1300 worth of repairs, modifications and devices) tailoring the newly developed program (SOCIABLE) to the needs of HD patients; and 3) piloted the program among 12 patients. We used a randomized wait list design to deliver the services in a staggered fashion that allowed a control comparison.

Results: Focus group themes included those in the **Table**. We adapted the original program using these themes to produce SOCIABLE, which we tested. All participants were African American (50% male), mean age was 68 (SD= 5.9). From baseline to 6 month follow up, participants improved on average from 2.3 in Activities of Daily Living (ADL) difficulties (scale of 8) and improved 2.5 (scale of 8) Instrumental ADL difficulties. Participants' mean social network scores increased from 18.4 to 23.1 (out of a possible 40). Satisfaction with social support improved less.

Conclusions: Our results show that it is possible to improve physical and social function of low income older adults with ESRD via a home based intervention. As people with ESRD have low quality of life and account for substantial costs to the U.S. health system ($33 Billion), it is important to better understand how to improve life and decrease costs for this population with a full-scale efficacy trial.

Funding: Other NIH Support - National Institute on Aging

Representative Focus Group Quotes

Theme	Quote
Desire to live Independently	In reference to Nursing Home: "Where you have no independence. It's, you're at their beck and call for everything. Even when you don't want to eat, for an example, you're stuck."
Fatigue	"So after dialysis I am, I feel like I'm not tired until I actually leave. That's when it starts... That's my main thing, I have to rest."
Lack of Social Support	"They kind of like, they distance themselves, and they do it, they try to do it in different ways. And I can tell, because you don't hear from them as often as you did at first."

FR-PO925

Association of Kidney Disease Quality of Life (KDQOL-36) Subscale Scores with Mortality and Hospitalization in Older Dialysis Patients Rasheeda K. Hall, Alison Luciano, Carl F. Pieper, Cathleen Colon-emeric. *Duke University, Durham, NC.*

Background: The Kidney Disease Quality of Life (KDQOL-36) instrument is routinely administered to dialysis patients. Subscale scores may be useful for prognostication but their association with clinical outcomes has not been reported in older adults.

Methods: We conducted a longitudinal study of 3500 adults aged ≥ 75 years receiving dialysis through a large dialysis organization in 2012 and 2013. We used Cox and Fine and Gray models to evaluate the association of KDQOL-36 subscales (1- Burden of kidney disease, 2- Effects of kidney disease, 3- Symptoms of kidney disease, 4- SF-12 physical component score (PCS), and 5- SF-12 mental component score (MCS)) with risks of death and hospitalization, respectively. All models were adjusted for sociodemographic variables, hemodialysis access type, laboratory values, and Charlson index. We compared models with and without the KDQOL-36 subscales using likelihood ratio (LR) statistics.

Results: Among members of this cohort, 3,267 patients completed the KDQOL-36. From the date of KDQOL-36 completion, 929 (25.6%) patients died and 2,005 (61.4%) had at least one hospitalization over a median follow-up of 511 and 204 days, respectively. In unadjusted analyses, cohort members with KDQOL-36 scores in the lowest quintile (relative to the highest quintile) for all subscales had a higher probability of death. Cohort members with a SF-12 PCS in the lowest quintile had an increased adjusted risk of death [hazard ratio (HR), 1.53, 95% confidence interval (CI) 1.18-1.99] and hospitalization (HR, 1.33, 95% CI 1.12-1.58) compared with those with scores in the highest quintile. Cohort members with SF-12 MCS scores in the lowest quintile had an increased adjusted risk of hospitalization (HR, 1.41, 95% CI 1.19-1.68) compared with those in the highest quintile and those with Effects of kidney disease subscale scores in the lowest quintile had a lower risk of hospitalization (HR, 0.78, 95% CI 0.63-0.95). The magnitude of these associations was similar in competing risk models. Inclusion of KDQOL-36 subscales improved model fit both for death (LR 41.04; p-value = 0.004) and hospitalization (LR 68.14; p-value < 0.001).

Conclusions: Routinely administered KDQOL-36 subscales may improve risk stratification of older adults receiving dialysis for death and future hospitalizations.

Funding: Other NIH Support - NCATS, NIA, Private Foundation Support

FR-PO926

An Integrated Prognostic Model for Shared Decision-Making with Patients with Stage 4-5 CKD Daniel L. Landry,[1] Lewis Cohen,[2] Rebecca J. Schmidt,[3] Alvin H. Moss,[4] Brian H. Nathanson,[5] Michael J. Germain.[6] *[1]Department of Medicine, Section of Nephrology, Baystate Medical Center, Springfield, MA; [2]Department of Psychiatry, Baystate Medical Center, Springfield, MA; [3]Department of Medicine, Section of Nephrology, West Virginia University School of Medicine, Morgantown, WV; [4]Department of Medicine, Section of Nephrology, West Virginia University School of Medicine, Morgantown, WV; [5]OptiStatim, LLC, Longmeadow, MA; [6]Department of Medicine, Section of Nephrology, Baystate Medical Center, Springfield, MA.*

Background: Patients with advanced chronic kidney disease (CKD) have high mortality and often die before needing dialysis. Studies show that prognostic information is important to patients facing the decision to pursue or forgo dialysis. A model that integrates clinical intuition with objective measures to predict 12-month mortality in patients with advanced CKD could help inform decisions.

Methods: In this prospective, observational study, 749 patients with CKD stage 4 or 5 were followed for 2 years. Demographics and laboratory data were collected while providers assessed functional status by the Karnofsky Performance Scale Index (KPSI) and answered a "surprise" question (SQ), "Would you be surprised if your patient died within the next 6 months?" upon each clinic visit.

Results: Mean (SD) age of the cohort was 69.3 (14.6), 50.9% were male, and 83.6% were Caucasian. Mean (SD) Charlson Comorbidity Index score was 5.9 (2.1) and 136 patients (18.2%) had a KPSI score of 50 ("requires considerable assistance and frequent medical care") or worse. By 12 months, 101 (13.5%) died and 99 (13.2%) initiated dialysis. A logistic regression model was constructed with 3 predictors of mortality. Area under the ROC curve was 0.81 indicating good discrimination.

Conclusions: In this model, advanced age, poor functional status, and the SQ predicted 12-month mortality in advanced CKD patients. The model is being validated and may assist nephrologists in shared decision-making with CKD patients who are choosing between dialysis versus conservative management.

Funding: Private Foundation Support

Logistic Regression Model of 12-Month Mortality (n = 736 patients with complete data)

Covariate	Odds Ratio; 95% CI	P-Value
Surprise Question (SQ) = No; Baseline Category = Yes	6.63; (3.68, 11.96)	<0.001
Age per 10 year increase	1.49; (1.21, 1.83)	<0.001
Karnofsky Performance Scale Index (KPSI); Baseline Category = 80 to 100	1	
• KPSI = 50 to 70	2.22; (1.24, 3.98)	0.008
• KPSI = 10 to 40	3.15; (1.02, 9.68)	0.046

FR-PO927

Accelerated Brain Aging in ESRD Patients Yi-Fang Chuang,[4,2] Kai-Hsiang Shu,[1] Yu-sen Peng,[1] Yen-Ling Chiu.[1,3] *[1]Nephrology, Far Eastern Memorial Hospital, Banciao, New Taipei City, Taiwan; [2]School of Public Health, National Yang Ming University, Taipei, Taiwan; [3]Graduate Institute of Clinical Medicine, National Taiwan University, Taipei, Taiwan; [4]Psychiatry, Far Eastern Memorial Hospital, Taipei, Taiwan.*

Background: Patients with end-stage renal disease (ESRD) suffer from higher risk of cognition impairment and dementia compared to the general population. It is known that brain structure changes appear years before the development of cognitive impairments and dementia. However, the relationship between brain structure changes and cognitive functions in ESRD patients has never been studied.

Methods: Twenty-six patients on maintenance hemodialysis without dementia and fifty-two age-matched non-renal failure control individuals were recruited from the Far Eastern Memorial Hospital (For ESRD patients, average age: 59.9 years and 31% had diabetes). All patients lives an independent life and can attend hemodialysis treatment independently. Brain structure was measured by 3T-MRI and analyzed using Freesurfer. A battery of neuropsychological tests were also performed.

Results: Mini Mental State Examination (MMSE) scores were comparable between ESRD patients and control subjects (28.5 vs 28.6). However, ESRD patients showed poorer performance in psychomoter speed and executive function, measured by symbol search, sympbol substitution, trail making task and Stroop test after adjusting for age, gender, diabetes and education level (all $P < 0.05$). Neverthelss, there was no difference in both immediate recall or delayed recall memory tests. In addition, ESRD patients showed decreased volume in total gray matter and numerous brain structures, especially decreased volume of hippocampus (-0.98 mm^3), amygdala (-0.34 mm^3), and putamen (-1.61mm^3, all $P < 0.001$).

Conclusions: As the overall ESRD population grow older, how to prevent cognitive function decline and dementia is a pressing issue. Our study indicates that ESRD patients exhibit numerous accelerated brain aging represented by decreased brain volume in specific areas pertinent to the development of mild cogntive impairment (MCI) and dementia. Whether these changes are predicitive of further cognitive decline requires further study.

Funding: Government Support - Non-U.S.

FR-PO928

Octogenarians in the Emergency Room: AKI, Risk Factors, and Outcomes Mohsen Abu Alfeilat,[1] Itzchak N. Slotki,[1] Linda Shavit.[2] *[1]Share Zedek Medical Center, Jerusalem, Israel; [2]Shaare Zedek Medical Center, Jerusalem, Israel.*

Background: The prevalence of acute kidney injury (AKI) in the elderly is growing and the prognosis is dismal. The structural and functional changes of the aging kidney, multiple comorbidities and exposure to medications explain this susceptibility to AKI in elderly. The aim of this study was to evaluate the incidence, risk factors, clinical characteristics and outcomes of AKI in octogenarians admitted to the emergency room (ER) and to compare these parameters with those in a younger group of patients admitted in the same period.

Methods: This is a prospective, observational, single center study that enrolled adult patients admitted to the ER of Shaare Zedek Medical Center, Jerusalem, Israel. Patients were stratified by age (> or < 80 years) and followed up prospectively until discharge. Incidence of AKI, in hospital mortality and duration of hospital stay were recorded.

Results: Of 319 patients, 128 were octogenarians (mean age 86.7, range 80 to 105) and 191 were younger (mean age 60.6, range 18 to 79). The incidence of AKI and in hospital mortality was significantly higher in octogenarians (16.4 % vs 12.6 %, p= 0.039 and 15.6% vs 3.1 %, p= 0.001, respectively). In univariate analyses, sepsis and low blood pressure were associated with AKI in octogenarians, whereas history of CVA or CKD, hypoalbuminemia and anemia were associated with AKI in the younger group. In multivariate analysis, only low systolic blood pressure (SBP) at admission in octogenarians (p=0.002) and history of CKD and hypoalbuminemia in the younger patients (p<0.001; p=0.001) were independent risk factors for AKI.

Conclusions: Our results confirm the observation that AKI is common in octogenarians and is associated with significantly higher mortality. We identified SBP as the only independent variable associated with AKI. However, the role of therapeutic strategies aimed to increase SBP and diminish complications in octogenarians remains to be elucidated.

FR-PO929

Geriatric Nephrology: AKI in Elderly Patients; Differences in Etiology, Morbidity, and Mortality; Age Is Not a Prognostic Factor Francisco javier Lavilla, Pedro Errasti, Christian I. Alfaro Sanchez. *Clinica Universidad de Navarra, Pamplona, Spain.*

Background: Age is considered an acute kidney injury (AKI) prognostic factor. But can be more important than biologic age, the" clinical age" that include morbidity, acute and chronic health status. The objective is evaluate acute kidney injury (AKI) in elderly and very patient, and the influence of age as a prognostic factor.

Methods: In a cohort with 2714 hospitalizated patients (medium age 62 years, SD 0.3; 66.3 % males) with AKI (KDIGO), we made three groups (group A with age lower than 65 years, group B between 65 to 85 years and group C with more than 85 years). We evaluate AKI etiology, treatment and index prognosis (ISI –individual severity index-), chronic morbidity (cancer, chronic renal and cardiac failure, diabetes), health chronic status (Karnofsky) and acute morbidity (inflammatory status, lower hemoglobin level). We use SPSS 20.0.

Results: Exitus (%): (A: 19.5, B: 14.6, C: 14) (p=0.003) Etiology: AKI functional (%) (A: 33.1, B: 48, C: 64) (p=0.001). ATN (%) (A: 22, B: 18.7, C: 14) (p=0.001). Complex AKI (%) (functional and ATN) (A: 39.1, B: 27.6, C 20.9) (p=0.001). Renal replacement therapy (%) (A: 28.4, B: 24.4, C: 14) (p=0.001). Acute disease: Acute inflammatory disease (%) (A: 46.8, B: 35.6, C 29.1) (p=0.001). Surgical procedure (%) (A: 16.8, B: 25.3, C: 28.4) (p=0.001). Chronic disease: Diabetes (%) (A: 6.7, B: 12.3, C 16.3) (p=0.001). Previous chronic kidney disease (%) (A: 34.4, B: 55.1, C: 66.3) (p=0.001). Chronic Heart disease Previous chronic kidney disease (%) (A: 2.9, B: 4.9, C: 12.8) (p=0.001). Cancer (%) (A: 62.9, B: 41, C: 14) (p=0.001). Analytical parameters: C reactive protein peak (mg/dL) (A: 15.1 SD 0.4, B: 15.4 SD 0.42, C: 11.3 SD 1.39) (p=0.038). Lowe Hb level (g/L) (A: 8.5 SD 0.07, B: 9.2 SD 0.15, C: 9.82 SD 0.3) (p=0.001). Acute anc chronic health status: ISI (A: 0.2818, B: 0.3272, C: 0.3651) (p=0.001). Karnofsky (A: 69.5 SD 0.4, B: 68.28 SD 0.4, C: 61.3 SD 2.02) (p=0.001)

Conclusions: The AKI in very elderly patients were more functional and less complex, with lower mortality and acute disease, but more chronic disease. Age is not the more important prognostic factor in AKI. Is more important others (some acute diseases –inflammatory-, chronic diseases –cancer-, health chronic and acute status and AKI etiology–complexity related with previous factors-).

FR-PO930

Polypharmacy and Outcomes in Older Dialysis Patients Sashika Samaranayaka,[2] Robert J. Walker,[2] Ari Samaranayaka,[2] Sarah Derrett,[2] John B. Schollum.[1] *[1]Dunedin Hospital, Dunedin, New Zealand; [2]University of Otago, Dunedin, New Zealand.*

Background: The impact of polypharmacy on patients with end stage kidney disease (ESKD) and associated comorbidities is uncertain since a direct causation cannot be determined. More medications could be an indicator of more complex patients with a higher risk of poor health outcomes, regardless of polypharmacy. This study investigated the association between polypharmacy, comorbidities and patients' health outcomes as measured by hospital admissions and mortality in a cohort of ESKD patients ≥65 years

Methods: 225 participants aged ≥ 65 years, either already on dialysis or eligible for dialysis (eGFR<15 ml/mn/1.73m^2) were recruited and followed for 3 years[1]. Individual medications and the number of 'medication groups' (by therapeutic indication) per person were recorded at baseline. Hospitalisation, irrespective of cause, was measured as the number of days per person per 12 month follow up. Comorbidities were dichotomised to 0-2 and ≥3. Negative Binomial (NB) regression and Modified Poisson regression were used to assess associations medication had with hospitalisation rate and mortality respectively, first at univariate level, then after adjusting for confounders including comorbidities.

Results: Individual medications ranged from 2 to 20 (IQR 8 to 12) while the medication groups ranged from 2 to 15 (IQR 6 to 10). Most participants (83.5%) took between 3-8 'medication groups'. The most common 'medication groups' were metabolic bone disease related (87%), haemotenics (76%), cholesterol management (66%) and antithrombotics (65%). There was a significant increase in hospitalisation rates for each increase in medication group (RR 1.12, 95% CI: 1.02-1.23). Univariate analysis showed an 8% increase in the risk of mortality with each medication (RR 1.08, 95th CI 1.05-1.11) and an 11% increase in risk of mortality with each increase in 'medication group' (RR 1.11, 95% CI 1.09-1.13). Similarly, multivariate analysis showed an increase in individual medications increased the risk of death by 8% (RR= 1.08, 95% CI: 1.07-1.09) and each individual 'medication group' by 11% (RR= 1.11, 95% CI: 1.09-1.12)

Conclusions: In this high risk population, who may require polypharmacy, polypharmacy is also an indicator of increased risk of hospitalisation and mortality in those with ESKD ≥65 years. 1. Walker et al. BMC Nephrology 2013, 14:175

FR-PO931

Impact of Age and Glomerular Filtration Rate on Cardiovascular Drug Use in CKD Patients Cédric Villain,[7,8] Sophie Liabeuf,[6,8] Marie Metzger,[8] Christian Combe,[5] Denis Fouque,[4] Luc Frimat,[3] Christian Jacquelinet,[1,8] Maurice Laville,[4] Ronald L. Pisoni,[2] Benedicte Stengel,[8] Ziad Massy.[7,8] *[1]Agence de la biomedecine, Saint-Denis La Plaine, France; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]CHRU Nancy-Brabois, Vandoeuvre les Nancy, France; [4]CHU Lyon Sud, Pierre Benite, France; [5]CHU de Bordeaux, Bordeaux, France; [6]Service de Pharmacologie Clinique, CHU Amiens, Amiens, France; [7]CHU Ambroise Paré, APHP, Boulogne-Billancourt, France; [8]CESP, INSERM U1018, Univ. Paris-Sud, UVSQ, Univ Paris-Saclay, Villejuif, France.*

Background: Evidence for prescribing cardiovascular drugs is low in elderly patients (pts) with chronic kidney disease (CKD). We analyzed the impact of age and glomerular filtration rate (GFR) on use of drugs recommended for several cardiovascular diseases (CVD) among pts with CKD.

Methods: We used baseline data from the CKD REIN cohort including 3033 adult pts with CKD stage 3-4. We studied use of several CVD-specific drugs according cardiovascular antecedents: antiplatelet agents, renin-angiotensin-aldosterone system (RAAS) blockers, beta-blockers, and statins or ezetimibe in coronary heart disease; antiplatelet agents or oral anticoagulant drugs (vitamin K antagonist or oral direct anticoagulant) in stroke or transient ischemic attack; oral anticoagulant drugs in atrial fibrillation with CHADS2-VASc2 score ≥2. Odds-ratios (OR) of drug use according to age and estimated GFR were adjusted for sex, educational, activities of daily living, and other CVD specific relevant confounders.

Results: Mean age was 66.8 yr, and mean CKD-EPI GFR 32.9 ml/min/1.73m^2. Prevalence of coronary heart disease was 24.5% (81.3% of these pts were receiving antiplatelet agents, 75.7% RAAS blockers, 66.1% beta blockers, and 82.9% statins or ezetimibe), that of stroke or transient ischemic attack was 10.1% (88.3% pts receiving antiplatelet agents or oral anticoagulant drugs), and that of atrial fibrillation and CHADS2-VASc≥2 11.2% (69.0% receiving oral anticoagulant drugs). Results of logistic regression are shown in Table 1.

Conclusions: Although the management of CVD was appropriate in the majority of CKD patients, old age and to a lesser extend low eGFR were associated with underuse of certain recommended drugs. The cross-sectional design of our study, however, does not enable to show whether these drugs were never used or were discontinued due to side effect.

Funding: Commercial Support - Amgen, Baxter, GSK, Fresenius Medical Care, Lilly, MSD, Otsuka supported the CKD REIN cohort.

Table 1 – Adjusted odds-ratios (95% confidence interval) of CVD drug use according to age and GFR

History of CVD	Drugs	Age (years)				eGFR (ml/min)	
		<65	[65-75[	[75-85[	≥85	≥30	<30
Coronary heart disease	Antiplatelet agents[a]	1	1.31 (0.69-2.53)	1.31 (0.66-2.60)	0.81 (0.26-2.48)	0.67	1	0.84 (0.52-1.34)
	RAAS blockers[b]	1	1.21 (0.71-2.05)	0.98 (0.58-1.66)	0.37 (0.16-0.87)	0.10	1	0.54 (0.37-0.79)
	Statins or ezetimibe[c]	1	1.00 (0.53-1.91)	0.61 (0.33-1.15)	0.36 (0.18-0.95)	0.01	1	0.98 (0.64-1.50)
	Beta blockers[d]	1	0.46 (0.27-0.78)	0.31 (0.18-0.52)	0.58 (0.23-1.43)	<0.001	1	1.17 (0.82-1.63)
Stroke or transient ischemic attack	Antithrombotic drugs[e]	1	2.81 (0.99-7.97)	3.45 (1.14-10.45)	5.32 (0.52-54.52)	0.01	1	0.44 (0.19-1.05)
Atrial fibrillation CHADS2-VASc ≥2	Oral anticoagulant drugs[f]	1	1.81 (0.74-4.44)	0.95 (0.39-2.24)	0.87 (0.28-2.69)	0.13	1	0.63 (0.38-1.04)

Multivariable logistic regression adjusted for age, eGFR, sex, educational, activities of daily living, and [a] proteinuria, oral anticoagulant drug use, MMSE, marital status, and total number of drugs; [b] diabetes, kalemia, heart failure, and total number of drugs; [c] diabetes, body-mass index, serum albumin, marital status, and total number of drugs; [d] pulmonary disease, heart failure, marital status, and total number of drugs; [e] diabetes, marital status, and total number of drugs; [f] MMSE, marital status, and total number of drugs.

FR-PO932

ANCA Associated Vasculitis and Treatment Associated Morbidity in the Very Elderly – A Single Centre Experience Turren tarun S. Chaggar,[1] Marie B. Condon,[2] David Makanjuola.[2] *[1]Epsom and St Helier NHS Trust, London, United Kingdom; [2]St. Helier Hospital, Surrey, United Kingdom.*

Background: ANCA-associated vasculitis presents in later life and is not uncommon in the very elderly (>80 years) patients, but published data concerning the safety and

tolerability is lacking. Concerns about treatment toxicity and tolerability may be a barrier to starting appropriate immunosuppression.

Methods: Retrospective review of our local database identified all patients presenting between 2006 and 2015 with ANCA associated vasculitis, and data from those aged >=80 at presentation were analysed for the purposes of this study. Follow-up was until May 2017 or death. The incidence of treatment related complications; leucopaenia and infections was recorded. Survival data were analysed with respect to age, sex, renal function at diagnosis as well as treatment regime used. Cause of death was reviewed where available.

Results: We identified 32 cases with a mean age of 83.5 yrs (range 80-90), mean follow-up period of 35.5 months (range 0.2 – 106). Of these, 14 were PR3 positive and 18 were MPO positive. Mean admission creatinine was 406 μmol/L and 38% (12/32) required RRT within 72 hours. Induction therapy was combined with steroids and 78% received cyclophosphamide (25/32), 6% azathioprine (2/32), 3% MMF (1/32) and 3% rituximab. Maintenance therapy was with Azathioprine in 55% (16/29), MMF 17% (5/29) and steroid alone 21% (6/29). Leucopaenia was recorded in N = 5. Of these, cyclophosphamide induction therapy was associated with two episodes of leucopaenia. Azathioprine therapy was associated with 2 cases. The 5th case identified was following Rituximab induction therapy. There were 10 documented cases of infection. Three patients died during the induction therapy. Induction of remission was achieved in 24/25 patients with cyclophosphamide and steroid therapy. Renal survival was 79% (23/29) at 3 months and 85% (22/26) at 1 year. Patient survival was 91% (29/32) at 3 months and 90% (26/29) at 1 year. Overall 50% (16/32) patients died during the period up period with a mean time to death of 25.2 months.

Conclusions: The results of the retrospective study show that induction therapy with cyclophosphamide was generally well tolerated with low rates of leucopenia and infections occurring during the maintenance phase. Mean survival of 25.2 months was comparable in this cohort of patients when compared to elderly patients (aged > 80) with CKD 5.

FR-PO933

Progression of CKD4 to CKD5/ESRD versus Death in the Very Elderly and Factors Associated with Survival Hui Xue, Shayna L. Henry, Qiaoling Chen, Mark P. Rutkowski, Nichole Mihara, Mi Chang. *Kaiser Permanente Southern California, San Diego, CA.*

Background: Geriatrics is the fastest growing population with End Stage Renal Disease (ESRD), and there is limited knowledge of transition from CKD4 to CKD5/ESRD vs death in this group. This study aims to shed light on the rate of progression from CKD stage 4 to CKD stage 5 or ESRD vs death, and the factors associated with survival in patients with eGFR≤20 and >75yrs old.

Methods: From 2003 to 2008, 1,431 adults, mean age 81.1±4.7yrs (range 75-99), with 15< eGFR ≤ 20 for at least 3 consecutive months RRT, were followed for 5 years with censoring at Dec 31, 2013. Subjects were followed until death vs eGFR≤15/dialysis, and those who maintained eGFR> 15 were censored at 5yrs. Survival of those who transitioned to CKD5/ESRD were separated into conservative care vs. Renal Replacement Therapy (RRT) groups and followed until death vs censoring at 5yrs. Multivariable hazard ratios were calculated for survival for the study population.

Results: Among older adults with CKD4, 930 (65%) reached CKD5/ESRD first, while 432 (30.2%) reached death first, and 69 (4.8%) maintained CKD4 and were censored at 5yrs. Most individuals reached CKD5/ESRD before death up till age 90. Among the 930 individuals who transitioned to CKD5/ESRD, 214 received conservative care and 716 received RRT. In the conservative management group, 140/214 (65.4%) died, vs in the RRT group 467/716 (65.2%) died. Median survival was 46 and 37 months for RRT and no RRT groups, respectively, and not statistically different (p=0.314). Age was the greatest factor associated with death, followed by medical comorbidities except hyperlipidemia. Asian race, statin, phosphate binder, and ACEi/ARB use offered survival advantages.

Conclusions: Among >75yrs old CKD4 patients, the risk of progression CKD5/ESRD is still higher than death up to age 90. Factors associated with improved survival, statin, phosphorous binders, ACEi/ARB, use, hyperlipidemia, and Asian race, warrant closer evaluation in future studies.

Funding: Clinical Revenue Support

FR-PO934

Predicting Long-Term Renal and Patient Survival by Histological Diagnosis in Elderly Patients Undergoing a Renal Biopsy Arunraj Navaratnarajah, Candice A. Roufosse, H. Terence Cook, Michelle Willicombe. *Imperial College NHS Healthcare Trust, London, United Kingdom.*

Background: Evidence on long-term outcomes following renal biopsies in the elderly are lacking. This study aims to describe renal and patient outcomes in the elderly according to indication for biopsy, clinical parameters and histological diagnosis.

Methods: An analysis of 445 patients >70yrs old who had a renal biopsy between 2005 and 2015 was performed. Median age was 75.1yrs (70.1-91.0) and follow-up 5.8yrs.

Results: 180/445 patients progressed to ESRD or died. 83/445 died without renal replacement therapy (RRT), 97/445 required RRT and 49/97 died after requiring RRT. This equates to 1, 3 and 5yr renal survival of 86.1, 80.1 and 76.9% and patient survival of 92.6, 82.8 and 72.3% respectively. Patients who progressed to ESRD were at higher risk of dying compared with those who remained dialysis independent, HR 2.54(1.64-2.93), p<0.0001. Variables associated with risk of ESRD included higher serum creatinine (Cr) at time of biopsy [HR 1.005(1.004-1.007), p<0.0001] and biopsy for the indication of nephrotic syndrome (NS) with renal dysfunction [3.08(1.50-6.32), p=0.002]. Whilst having either histological features of GN [0.49(0.26-0.95, p=0.033] or TIN [0.075(0.01-0.55), p=0.01] were associated with dialysis independence. Variables associated with reduced patient survival included increasing age [1.09(1.04-1.15), p=0.0004], Cr at time of biopsy [HR 1.0018(1.008-1.0028), p=0.0003], biopsy for NS with renal dysfunction [2.80(1.69-4.63), p=0.000] and histological diagnosis of MGRS [2.81(1.47-5.37), p=0.0017]. Those with tubulointerstitial scarring without a definite cause [HR 2.19(1.33-3.62), p=0.0011], GN [HR 2.07(1.16-3.70), p=0.006] and vasculitis [HR 3.56(1.68-7.50), p<0.0001] were at risk of progressing to ESRD before dying. There was no difference in risk of ESRD or death in patients with TIN, who had a good prognosis. Patients with MGRS also had no increased risk of ESRD over death, 1.36(0.52-3.60), p=0.52, however prognosis was poor with median time to death or dialysis 0.91yrs.

Conclusions: Renal biopsies in the elderly not only provide a histological diagnosis but also prognostic information on renal and patient survival. Data from this study may be useful for informed decision making by patients and nephrologists.

Histological Feature	Glomerulonephritis excluding vasculitis (GN)	Vasculitis	Tubulointerstitial nephritis (TIN)	Monoclonal Gammopathy of Renal Significance (MGRS)	Tubulointerstitial scarring without a definite cause
No. of patients (%)	113 (25.4)	56 (12.6)	53 (11.9)	29 (6.5)	194 (43.6)

FR-PO935

Deletion of the Gene for Adiponectin Accelerates Age-Related Kidney Injury Eun Hui Bae,[1] Hong sang Choi,[3] Ha yeon Kim,[2] Chang Seong Kim,[1] Seong Kwon Ma,[2] Soo Wan Kim.[2] *[1]Chonnam National University Hospital, Gwangju, Republic of Korea; [2]Chonnam National University Medical School, Dongku, Republic of Korea; [3]Chonnam national university hospital, Gwangju, Republic of Korea.*

Background: Aging causes renal fibrosis, and aging related renal changes are characterized by oxidative stress. However, the role of adiponectin in aging process has not been elucidated. The present study was aimed to investigate the role of adiponectin in renal fibrosis in aging.

Methods: We used male 2 and 12 months old C57BL/6 (wild type, WT) mice and adiponectin knock out ($APN^{-/-}$) mice. The protein expression of transforming growth factor β (TGF- β), Smad-2/3, Smad-4, Smad-6, α smooth muscle actin (α-SMA), collagen IV, pro-apoptoic Bax and anti-apoptotic protein Bcl-2, phosphorylated AMP-activated protein kinase (p-AMPK) was determined by semiquantitative immunoblotting. For the in vitro experiments, human proximal tubular epithelial (HK2) cells were treated with TGF- β with or without pretreatment of adiponectin.

Results: 12 month old $APN^{-/-}$ mice exhibited decreased body weight, increased albuminuria and kidney to body weight ratio compared to 12 months WT mice. Fibrosis markers such as α smooth muscle actin and collagen IV were increased. The protein expression of TGFβ, Smad-2/3, and Smad-4 was increased, while inhibitory Smad-6 decreased in 12 months $APN^{-/-}$ mice compared to WT mice. ROS generation was also increased. Apoptosis marker such as Bax expression was increased while Bcl-2 expression was decreased in 12 months $APN^{-/-}$ mice compared WT mice. Phosphorylation of AMP-activated protein kinase (AMPK) was decreased in 12 months $APN^{-/-}$ mice compared to WT mice. TGFβ treatment showed decreased AMPK phosphorylation in HK2 cells. Pre-treatment of adiponectin attenuated fibrosis markers, apoptosis marker expression and ROS generation.

Conclusions: Our results suggest that adiponectin plays a role in the pathogenesis of progressive kidney injury associated with aging process.

FR-PO936

Impact of Aging on the Risk of Platinum-Related Renal Toxicity, Clinical Response, and Prognosis: A Systematic Review and Meta Analysis Guangyan Cai.[1,2] *[1]Nephrology, Chinese PLA Genaral Hospital, Beijing, China; [2]State Key Laboratory of Kidney Diseases, National Clinical Research Center of Kidney Diseases, Beijing, China.*

Background: Renal toxicity limits clinical use of platinum-based theray in the elderly. In order to clarify the impact of aging on (1) the risk of platinum-related nephrotoxicity; (2) clinical efficiency and prognosis of platinum therapy, the following meta analysis were carried out.

Methods: We searched multiple databases for the studies published before January 2017. The inclusion criteria were case-control, cohort studies published in any language.

Results: 34 studies with a total of 10,637 patients were included. The risk of platinum nephrotoxicity in the elderly group was 1.43 times higher than in the non elderly group (Risk Rate). The risk of grade I/II renal toxicity in the elderly group was 1.64 times higher than that in the non elderly group. There was no significant difference in the incidence of grade III/IV renal toxicity. Subgroup analysis of different platinum drugs confirmed carboplatin had less risk of nephrotoxicity than cisplatin. The risk of renal toxicity in the elderly patients from Asia is 2.63 times higher than that in young patients, which was significantly higher than those from Europe and North america. Although treatment with hydration, the risk in the elderly group was still 2.07 times higher than that in the control group. Presumably, the protective effect of hydration is more pronounced in non elderly patients who have better reserve of renal function. The risk of nephrotoxicities in the 60-70 year and more than 70 year group were 1.77 and 1.35 times greater than that in the non elderly group, respectively. There were no significant differences in the response rate, median survival time and 1-years survival rate between the elderly and the young patients with IIIB or IV grade of non-small cell lung cancer. The 1-year survival rate in the renal toxicity group is 44.8%, which is significantly higher than that in the non renal toxicity group (33.2%) (P=0.035).

Conclusions: Aging increases the risk of platinum nephrotoxicity by 43%, in which mild renal toxicity is dominant. There are no significant effects of aging on clinical efficiency and prognosis of platinum therapy. The 1-year survival rate of renal toxicity group is significantly higher than that without renal toxicity group.

FR-PO937

Kidney Size in Relation to Aging, Gender, Function, and CKD Risk Factors Antonello Pani,[5] Doloretta Piras,[5] Marco Masala,[6] Alessandro Delitala,[7] Silvana A. Urru,[1] Lenuta Balaci,[7] Liana Ferreli,[7] Francesco Loi,[7] Alice Atzeni,[5] Walter Racugno,[3] Laura Ventura,[4] Magdalena Zoledziewska,[6] Maristella Steri,[7] Edoardo Fiorillo,[7] David Schlessinger,[2] Francesco Cucca.[6,7] *[1]CRS4, Pula, Italy; [2]National Institute on Aging, Baltimore, MD; [3]University of Cagliari, Cagliari, Italy; [4]Università di Padova, Padova, Italy; [5]Nefrologia e Dialisi, Azienda Ospedaliera G. Brotzu, Cagliari, Italy; [6]Istituto di Ricerca Genetica e Biomedica (IRGB), CNR, Cagliari, Italy; [7]Center ProgeNIA, Istituto di Ricerca Genetica e Biomedica (IRGB), CNR, Cagliari, Italy.*

Background: Renal function is known to decrease progressively with age even in healthy individuals, in a process known as nephrosenescence. However, the relation of aging to renal volume is less clear. In our study we examined the relationship between renal function and kidney size, with a focus on the progressive effect of aging and the effect of several variables (heritability, CKD risk factors) on renal volumes.

Methods: Ultrasound kidney size parameters (total kidney volume, parenchymal kidney volume, and kidney length) were systematically determined using cross-sectional data from a general population cohort encompassing an age range 18-100. Among them, we separately analyzed 2,421 "healthy" and 1,539 "comorbid" individuals carrying CKD risk factors. Kidney volumes were adjusted for BSA.

Results: Gender and age effects on kidney size parameters were observed. In healthy volunteers, an early increase in kidney size was followed by progressive decrease in males, whereas in females the decline began earlier and continued throughout the lifespan. As a result, after the 3-4th decade, men had higher kidney volumes than women throughout life ($p< 0.001$). In comorbid individuals, a more evident early increase and a faster subsequent decrease in kidney sizes were seen ($p < 0.001$). The decline in kidney size parameters in the elderly was accompanied by a parallel decrease in eGFR. Heritability estimates for kidney size parameters ranged from 12% to 27%; the predominant influence of non-genetic parameters included effects of smoking and other CDK risk factors.

Conclusions: Our cross-sectional analysis showed dynamic changes in kidney size throughout life, which were influenced by both gender, age, and CKD risk factors. Heritability was overall relatively modest, while substantial effects of metabolic comorbidities and modifiable risk factors (e.g., smoking and lipid levels) were seen.

Funding: Other NIH Support - NIA

FR-PO938

How Do Creatinine Based GFR Equations Perform in Chinese Nonagenarians Mengjing Wang,[1] Xinyu Dong,[2] Minmin Zhang,[3] Li Ni,[2] Zuyun Liu,[5] Xiaofeng Wang,[4] Jing Chen.[2] *[1]Huashan Hosopital, Fudan Univeristy, Shanghai, China; [2]Huashan Hospital affiliated to Fudan University, Shanghai, China; [3]Huashan Hospital, Fudan Univerisy, Shanghai, China; [4]State Key Laboratory of Genetic Engineering and Ministry of Education Key Laboratory of Contemporary Anthropology, School of Life Sciences, Fudan University, Shanghai, China; [5]State Key Laboratory of Genetic Engineering and Ministry of Education Key Laboratory of Contemporary Anthropology, School of Life Sciences, Fudan University, Shanghai, China.*

Background: The clinical and prognostic meaning of evaluating Glomerular filtration rate (GFR) may be different in the very old population. This study aimed to elucidate the performance and predictive value of 4 GFR estimation equations in Chinese nonagenarians.

Methods: We calculated baseline eGFR from serum creatinine using the CKD epidemiology collaboration (CKD-EPI) equation, the Modification of Diet in Renal Disease Study (MDRD) equation, Berlin Initiative Study-1 (BIS1) equation, and modified MDRD equation from Chinese population in 278 nonagenarians from the Rugao longevity cohort over the period of 2007 to 2014. We compared the association of GFR estimated from 4 equations with risk of all-cause mortality using fully-adjusted Cox model. Overall improvement in reclassification based on clinical eGFR categories was assessed applying net reclassification improvement (NRI).

Results: Mean age of participants was 97±2 years old with 77% of women. Follow-up time was 2.8±1.8 years. Median (IQR) eGFR by CKD-EPI, MDRD, BIS, and modified MDRD equations were 73.9 (62.2–77.6), 87.5 (71.7–104.8), 56.4 (47.9–63.9), and 107.9 (88.4–129.2) ml/min per 1.73m², respectively. Higher $eGFR_{EPI}$ was associated with lower mortality after multivariate adjustment which includes frailty (for continuous $eGFR_{EPI}$: HR 0.987, 95%CI 0.976-0.998; for categorical $eGFR_{EPI}$: HR 0.782, 95%CI 0.628-0.945), while GFR estimated from other equations didn't show any associations with mortality. NRI for death by the CKD-EPI equation compared to MDRD, BIS1 and modified MDRD equations was 0.06, 0.06, and 0.03 (P>0.05 for all), respectively.

Conclusions: The CKD-EPI equation showed more appropriate estimation of GFR in long-lived individuals with respect to GFR distribution and risk of long-term mortality as compared to the other equations, suggesting improved clinical usefulness in Chinese nonagenarians.

Funding: Government Support - Non-U.S.

	Hazards ratio	95% Confidence interval		P*
eGFR (continuous, per 1ml/min/1.73m²)				
by EPI equation	0.987	0.976	0.998	0.026
by MDRD equation	0.996	0.991	1.002	0.179
by BIS equation	0.991	0.980	1.003	0.156
by modified MDRD equation	0.997	0.992	1.001	0.179
eGFR (categorical)**				
by EPI equation	0.782	0.628	0.975	0.029
by MDRD equation	0.969	0.823	1.140	0.7
by BIS equation	0.954	0.784	1.160	0.635
by modified MDRD equation	0.887	0.744	1.058	0.181

*Adjusted for following covariates: age, gender, marriage status, smoking, body mass index, level of education, systolic blood pressure, serum albumin, low-density lipoprotein cholesterol, frailty, hypertension, cardiovascular disease, cerebrovascular disease, and chronic obstructive pulmonary disease

** cut-off values of GFR were 40, 60, 80ml/min/1.73m²

FR-PO939

Value-Based Evaluation of Dialysis versus Conservative Care in Older Patients with Advanced CKD Wouter Verberne,[1] Janneke Dijkers,[1] Johannes C. Kelder,[1] Tom B. Geers,[1] Wilbert Jellema,[1] Hieronymus H. Vincent,[1] Johannes Van delden,[2] Willem Jan W. Bos.[1] *[1]St Antonius Hospital, Nieuwegein, Netherlands; [2]University Medical Center Utrecht, Utrecht, Netherlands.*

Background: Older patients approaching end-stage renal disease face the decision whether or not to start dialysis. Conservative care is argued to be a reasonable alternative as dialysis is not always associated with a survival benefit, as shown in our previous survival analysis. To truly foster decision-making, we analyzed more patient-relevant outcomes and treatment costs in an extended cohort.

Methods: We conducted a single-center cohort study in 366 patients ≥70 years old with stage 4/5 chronic kidney disease, who chose either dialysis (n=240) or conservative care (n=126) after careful counselling. Using a value-based health care approach (value = outcomes/cost), survival, quality of life, assessed with KDQOL-SF™ questionnaire in 98 patients, and treatment burden, determined as hospital free days, were evaluated, together with treatment costs.

Results: The survival advantage in patients choosing dialysis over patients choosing conservative care diminished or disappeared in patients ≥80 years or with severe comorbidity. There were no differences between patients managed conservatively (n=23) and patients started on dialysis (n=34) on physical and mental health summary scores (all P>0.1). Patients choosing conservative care had 353 versus 283 hospital free days per year, measured from date of treatment decision (incidence rate ratio: 1.15, 95% confidence interval 1.09 to 1.21, P<0.001). Annual hospital costs were significantly lower in the conservative care group (cost ratio: 0.43, 95% CI 0.28 to 0.67, P<0.001).

Conclusions: Choosing dialysis was associated with little or no survival benefit in patients with the highest ages or with severe comorbidity. In all patients, choosing conservative care was associated with similar quality of life, lower treatment burden, and lower treatment costs in comparison to choosing dialysis. By achieving similar outcomes against lower treatment burden and costs, value was created for older patients with advanced chronic kidney disease choosing conservative care.

Funding: Commercial Support - Roche, Private Foundation Support

FR-PO940

Outcomes in Dialysis versus Conservative Care for Older Patients: A Prospective Cohort Analysis of Stage 5 CKD Maharajan Raman, Philip A. Kalra, Darren Green. *Renal Medicine, Salford Royal NHS Foundation Trust, Salford, United Kingdom.*

Background: The benefits of dialysis in older people with ESKD are not clear. We aimed to establish whether dialysis has survival advantage compared to conservative care (CC) in older people who were medically suitable for dialysis therapy.

Methods: This was a prospective observational study of CKD patients aged ≥75 years when eGFR first reached ≤15ml/min/1.73m². Estimates of median survival and hazard ratios (HR) for death were compared between patients who chose dialysis versus those who chose conservative care from two time points: when first seen in pre-dialysis clinic (eGFR ≤15ml/min/1.73m²) and when initiation of dialysis first considered (eGFR ≤10ml/min/1.73m²). Patients with co-morbidities likely to significantly reduce life expectancy were excluded (NYHA class 3 or 4 heart failure, malignancy, dementia). Comparative data on number of days spent in hospital during follow up were also collected.

Results: There were 204 patient (123 dialysis, 81 CC) with eGFR was ≤15ml/min/1.73m². Of these, 115 went on to record an eGFR of ≤10ml/min/1.73m² (73 dialysis, 42 CC). The median survival from eGFR first ≤15ml/min/1.73m² for the dialysis and CC group were 42 (95% CI =33–50) and 31 (21-41) months respectively. The co-morbities adjusted HR for death in the dialysis group compared to CC was 0.61(0.41-0.61, p= 0.01). When eGFR first ≤10ml/min/1.73m², the respective median survival times were 36 (25–47) and 12 (0-5) months. The co-morbidities adjusted HR for death in dialysis group compared to CC was 0.36 (0.21-0.62, p <0.001). The median annualized number of hospital days (in-patient and outpatient) from eGFR ≤15mL/min/1.73m² was 23 (IQR 10-86) for dialysis patients, and 10 (5-25) for CC. The median annualized number of hospital days (in-patient and outpatient) from eGFR ≤10mL/min/1.73m² was 78 (IQR 18-125) for dialysis patients, and 21 (8-80) for CC.

Conclusions: This study is novel in being both prospective and in excluding patients with co-morbidly, which may limit suitability for dialysis. It indicates that dialysis increases survival in older patients, as the statistically significant difference in survival only appeared when eGFR was ≤10mL/min/1.73m². This advantage may be offset by the increase in time spent at hospital. Hence, a future focus on quality of life is needed to establish the true benefits of dialysis in older people.

FR-PO941

Hydrogen Sulfide Ameliorates Aging Associated Kidney Changes in Mice Hak Joo Lee,[1] Denis Feliers,[1] Jeffrey L. Barnes,[1] Sae Byeol Oh,[1] Goutam Ghosh-Choudhury,[1] Veronica Galvan,[1] Randy Strong,[1] James F. Nelson,[1] Adam Salmon,[1] Christopher G. Kevil,[2] Balakuntalam S. Kasinath.[1] *[1]University of Texas Health Science Center, San Antonio, TX; [2]Louisiana State University Health Science Center, Shreveport, Shreveport, LA.*

Background: Hydrogen sulfide (H2S) ameliorates renal fibrosis and proteinuria in chronic kidney disease. We examined the status of H2S in kidney aging.

Methods: First study: The status of H2S metabolism and signaling pathways related to synthesis of proteins including matrix proteins were studied in renal cortical extracts from C57BL/6 male young (5 months old, n=10) vs. old mice (30 months old, n=10). Second study: We randomized 18-19 month-old male mice to receive NaHS in drinking water (30 μmoles/L) (NaHS group, n=20 mice) vs. water alone (Control group, n=14 mice) for 5 months.

Results: First study: Compared to young mice, increase in renal cortical laminin and type 1-collagen content in old mice was associated with decreased generation of H2S, increase in tyrosine phosphorylation of insulin receptor (IR) and IRS2, decrease in AMPK activity and activation of Akt-mTORC1-mRNA translation signaling axis. Second study: Administration of NaHS to 18-19 month-old mice increased plasma free sulfide levels. Food, water intake and body weights were similar and blood glucose normal in the two groups throughout the study duration. Systolic, diastolic, and mean blood pressures (BPs) were high at baseline and continued to rise in the Control group; NaHS reduced the BPs. NaHS abolished the progressive increase in urinary albumin to creatinine ratio seen in control mice and reduced serum cystatin C levels. NaHS inhibited the increase in renal cortical content of laminin and type 1-collagen and ameliorated the increase in glomerular fractional mesangial matrix volume. NaHS inhibited tyrosine phosphorylation of renal cortical IR and IRS-2. NaHS restored decreased AMPK activity to normal and inhibited the Akt-mTORC1-mRNA translation axis that leads to increase in protein synthesis. Aging mice showed increase in renal cortical monocyte infiltration and content of p21, IL-1β, IL-6, components of Senescence Associated Secretory Phenotype, SASP, which contribute to tissue injury; NaHS inhibited these changes.

Conclusions: Aging-induced kidney changes are associated with H2S deficiency. Administration of H2S ameliorates aging-induced kidney changes; the mechanisms appear to involve reduced hypertension, inhibition of signaling pathways leading to matrix protein synthesis, and SASP.

Funding: Other NIH Support - Nathan Shock Center, Veterans Affairs Support

FR-PO942

Age-Related Changes in Nuclear Reduced Glutathione Levels in Rat Kidney Cortex and Medulla Marianna J. Zamlauski-Tucker, Bingwei Ye. *Ball State University, Muncie, IN.*

Background: Aging is associated with changes in the cell related to oxidative stress caused by free radicals produced in aerobic metabolism. Maintenance of reduced glutathione (GSH), the major antioxidant inside cells, provides protection against cell damage caused by free radicals. Although age-related changes in GSH levels in cell organelles, such as the mitochondria, have been reported in previous studies, there is limited information on GSH levels in the cell nucleus and age. The present study was undertaken to investigate the effect of age on changes in nuclear GSH levels in rat kidney cortex and medulla.

Methods: Young (3 months of age) and Old (22 months of age) female Lewis rats were used. The kidneys were harvested from anesthetized rats after being perfused with isotonic saline via a catheter in the abdominal aorta. The kidneys were separated into cortical and medullary sections and homogenized in isotonic saline. Differential centrifugation was used to isolate the nuclear fractions. GSH and oxidized glutathione (GSSG) levels were measured in the fractions using a spectrophotometric assay, and expressed as nmol/g kidney wet weight. Total GSH was determined from the sum of GSH and GSSG expressed in GSH equivalents. The redox ratio (i.e., GSH/GSSG) was also determined. Differences were evaluated using a a Student's t Test.

Results: There was a significant decrease in GSH, GSSG and TOTAL GSH levels with age in the nucleus from rat kidney cortex. There was not a significant decrease in the aforementioned variables with age in the nucleus from rat kidney medulla. The redox ratio was not changed with age in either the kidney cortex or medulla.

Conclusions: The findings indicate that nuclei from the rat kidney cortex do undergo a significant decrease in the antioxidant glutathione with age. This indicates the nucleus from rat kidney cortex is experiencing increased oxidative stress and thus, damage with age.

Age-Related Changes in Nuclear Glutathione Levels in Rat Kidney Cortex and Medulla

		GSH nmol/g kidney wet wt	GSSG nmol/g kidney wet wt	TOTAL GSH nmol/g kidney wet wt	GSH/GSSG (Redox Ratio)
Young rats (n = 6)	Cortex	310 ± 22	272 ± 49	811 ± 127	1.3 ± 0.2
	Medulla	213 ± 31	312 ± 83	837 ± 167	1.0 ± 0.3
Old rats (n = 6)	Cortex	203 ± 22 *	126 ± 40 *	455 ± 40 *	2.5 ± 0.6
	Medulla	158 ± 22	130 ± 43	419 ± 103	2.1 ± 0.6

All data expressed as X +/- SEM. * Significantly different ($p<0.05$) from Young rats.

FR-PO943

Outcomes of Peritoneal Dialysis Associated Peritonitis in the Elderly Population: A Single Centre Experience Htay Htay,[1] Suh C. Pang,[1] Mui hian Sim,[2] Jun Jie Benjamin Seng,[2] Sin yan Wu,[1] Marjorie W. Foo.[1] *[1]Department of Renal Medicine, Singapore General Hospital, Singapore, Singapore; [2]Department of Pharmacy, Singapore General Hospital, Singapore, Singapore.*

Background: The clinical outcomes of peritonitis in the elderly peritoneal dialysis (PD) patients have not been well studied before. The study aimed to determine the outcomes of peritonitis in elderly patients.

Methods: This was a single centre retrospective cohort study, including all peritonitis episodes between 2011 and 2014. The primary outcome was medical cure (defined as peritonitis episode cured by antibiotics without complicated by catheter removal, haemodialysis (HD) transfer, relapsed/recurrent peritonitis and/or death) in elderly patients, defined as ≥ 65 years old. The secondary outcomes were complications of peritonitis. These outcomes were compared between elderly and younger patients using multivariable logistic regression.

Results: Total 377 episodes of peritonitis occurred in 247 patients during the study period. Of these, 169 episodes occurred in 105 elderly patients. Of 105 elderly, 51% were male, 79% were Chinese, 65% had diabetes mellitus, 95% had hypertension and 54% had cardiovascular disease. Diabetes nephropathy (52%) was the commonest cause of renal failure. The causative organisms were Gram-positive (32%), Gram-negative (29%), culture negative (22%), polymicrobial (12%), fungal (4%) and mycobacterial (1%) organisms. Elderly patients were less likely to present with fever (17% versus 30%) and cloudy effluent (85% versus 92%) than younger patients. Total 112 episodes (66%) of peritonitis in elderly patients achieved medical cure. The remaining 57 episodes were not cured because of one or more of the following complications: catheter removal (n=29), haemodialysis transfer (n=20), relapsed/recurrent peritonitis (n=19), and/or death (n=11). There was no significant difference in the odds of medical cure (Odds ratio (OR) 0.93, 95% confidence interval (CI) 0.56 - 1.54; p=0.78) between the elderly and the younger patients after adjusting for cardiovascular disease, primary renal disease and causative organisms. Similar results were observed for complications of peritonitis (catheter removal, transfer HD, relapse/recurrence) except that the odds of peritonitis-related death was significantly higher in the elderly patients (adjusted OR 2.59, 95% CI 1.07-6.29; p=0.04).

Conclusions: Elderly PD patients achieved comparable medical cure but had higher peritonitis-related mortality than younger patients.

FR-PO944

Peritoneal Dialysis-Related Peritonitis in the Era of the Elderly Dialysis Population: A Retrospective, Multicenter Study in Thailand Kiatkriangkrai Koyratkoson,[4,5] surapon nochaiwong,[4,5] Chidchanok Ruengorn,[3,5] Chayutthaphong Chaisai,[4,5] Kajohnsak Noppakun,[6] Ratanaporn -. Awiphan,[2,5] Wilaiwan -. Chongruksut,[7,5] Sirisak Nanta.[1,5] *[1]Maesai District Hospital, Chiang Rai, Thailand, Chiang Rai, Thailand; [2]Chiangmai University, Chiangmai, Thailand; [3]Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand; [4]Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand; [5]Pharmacoepidemiology and Statistics Research Center (PESC), Chiang Mai University, Chiang Mai, Thailand; [6]Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [7]Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. Group/Team: Thai Renal Outcomes Research (THOR) Investigators.*

Background: Peritonitis, a major complication of peritoneal dialysis (PD), contributes to treatment failure, hospitalization, and mortality, particularly in elderly PD cases. Regardless of technical problems, social difficulties, and burden of comorbidities, it remains debated whether elderly patients have a significantly amplified risk of peritonitis than younger patients. Thus, we aimed to evaluate the impact of advanced age on the risk of PD-related peritonitis.

Methods: We conducted a retrospective cohort study using the PD registry database of an incident PD patients with aged ≥ 18 years. At PD initiation, subjects were categorized into <55, 55-65, and >65 years of age groups. Clinical characteristics regarding age groups were compared among participants from three large PD centers in Thailand between January 2006 and December 2016, and followed through April 2017. Time-to-first PD-related peritonitis and longitudinal rates were analyzed by multivariable Cox's proportional hazards model and Poisson regression, respectively.

Results: Among 1,023 PD patients included, 401 (39.2%), 312 (30.5%), and 310 (30.3%) patients aged <55, 55-65, and >65 years, respectively. After a total follow-up of 19,463.4 person-months, 519 (50.7%) were recognized as having PD-related peritonitis. There was no significant difference in spectra of causative microorganisms among patient age groups.

Conclusions: The risk of first episode peritonitis is not increased in elderly PD patients, however, compared with younger patients, the higher peritonitis rate was observed in elderly PD patients. Large prospective trials are needed to validate these findings.

Funding: Government Support - Non-U.S.

Hazard Ratios for First Episode PD-Related Peritonitis and Incidence Rate Ratio for Longitudinal PD-Related Peritonitis Rates by Patients' Age Group (n=1,023)

Patients by Age Group	Crude HR (95% CI)	P Value	Adjusted HR (95% CI)	P Value	Crude IRR (95% CI)	P Value	Adjusted IRR (95% CI)	P Value
< 55 years	Reference		Reference		Reference		Reference	
55 – 65 years	1.18 (0.96 – 1.45)	0.118	1.13 (0.74 – 1.72)	0.562	1.13 (0.98 – 1.30)	0.097	1.20 (0.91 – 1.59)	0.195
> 65 years	1.42 (1.14 – 1.75)	0.001	1.37 (0.78 – 2.40)	0.272	1.54 (1.32 – 1.79)	<0.001	1.66 (1.14 – 2.39)	0.007

Abbreviations: CI, confidence interval; HR, hazard ratio; IRR, incidence rate ratio; PD, peritoneal dialysis.

FR-PO945

Safety Profile of Outpatient Percutaneous Native Renal Biopsy: A Large Monocentric Single Operator Cohort Dario Roccatello,[2] Savino Sciascia,[3] Roberta Fenoglio.[1] *[1]None, TORINO, Italy; [2]Ospedale San GIovanni Bosco, Torino, Italy; [3]Center of Research of Immunopathology and Rare Diseases (CMID), Division of Clinical Immunology, Giovanni Bosco Hospital and University of Turin, Ita, Torino, Italy.*

Background: In the study we aim to evaluate the safety of performing percutaneous renal biopsy as an outpatient procedure compared to the traditional inpatient policy. Additionally, the rate and risk factors of complications after a procedure were investigated.

Methods: We ambispectively studied native kidney biopsies performed in our Institution between January 2000 and November 2015. Since January 2012, we began performing renal biopsies as outpatient procedures. Two groups of patients were considered: group I, in whom kidney biopsy was performed and followed by at least 1-day hospital admission; and group II, in whom renal biopsy was performed in the outpatient department and followed by 6 hours' observation period and then by regular outpatient visits. All biopsies were performed by a single nephrologist with the use of real-time ultrasound and automated biopsy needle (18 gauge), following a structured protocol.

Results: 462 biopsies were reviewed, 210 (45.5%) of patients were female and the mean age was 54.7 ± 17.9 years. One-hundred and twenty-nine (27.9%) of these biopsies were performed in outpatients. A total of 36 (7.8%) of patients developed a complication, and of those 9 (1.9%) suffered for a major complication [arteriovenous fistula (6 cases, 1.2%), ischaemic stroke (2, 0.4%), thromboembolic pulmonary embolism (1, 0,2%)] and 27 (5.8%) for minor [macroscopic haematuria (12 cases, 2,6%), haematomas on sonography not requiring intervention (15 cases, 3,2%)]. When comparing the complication rate between group I and II, no statically difference were observed [overall 24 (7,2%) complications in group 1 and 12 (9,3%) in group II; 5 (1,5%) and 4 (3,1%) major, 19 (5,5%) and 8 (6.2%) minor complications, respectively in group I and II]. When analysing together both groups, after multivariate analysis, serum creatinine >3 mg/dl (OR 2.03 95%CI 1.18-6.81) and known severe hypertension (OR 2.01 95%CI 1.2-4.7) were found to be independent risk factors for minor and major complications, respectively. Conversely, we found no association of risk with the number of biopsy passes, gender, age, diagnosis, presence of haematuria before the kidney biopsy nor the degree of proteinuria.

Conclusions: Outpatient biopsy could be a valuable, safe, and perhaps cost-effective method of obtaining diagnostic renal tissue in the majority of patients.

FR-PO946

Should Kidney Biopsies Be Done via CT-Guidance? Comparison of Percutaneous Native Kidney Biopsy Complications and Glomerular Yield between Interventional Radiologists and Nephrologists Brigani G. Amante,[1] Alkesh Jani.[2] *[1]UNIVERSITY OF COLORADO, HOUSTON, TX; [2]University of Denver Colorado, Aurora, CO.*

Background: Percutaneous native kidney biopsy (PNKB) is performed as an outpatient procedure by interventional radiologists (IR) & nephrologists. However, data on tissue yield & complication rates comparing IR performed (IRP) & nephrology performed (NP) PNKB are lacking. Also, there is no published study that directly compares outcomes of PNKBs performed via computed tomography (CT) vs. ultrasound (US) guidance.

Methods: 131 PNKBs performed at the University of Colorado Health System from 1/2014-12/2016 were included. Biopsies were performed by nephrologists using real-time US guidance or IR using CT guidance.

Results: 72 biopsies were done by nephrologists & 59 by IR. The NP group had a significantly longer duration of patient observation post-biopsy (20.7 vs 5.0 hrs, $p < 0.05$), used a larger biopsy needle (16G in 93% vs 18G in 100% of patients, $p < 0.05$), had lower number of needle passes (2.8 vs 3.5, $p < 0.05$), & had higher glomerular yield/needle pass (8.9 vs 6.4, $p = 0.05$) with lower rate of inadequate tissue (6.9% vs 18.6%, $p = 0.05$) than the IRP group. No differences in post-biopsy complications such as hematoma, hematuria, need for transfusion or intervention, analgesic use, emergency room visits, infection/sepsis, or patient death were observed between the groups.

Conclusions: Out-patient PNKB done via CT guidance had similar complication rates vs. real-time US guidance, and required a significantly shorter period of patient observation post-biopsy. Tissue yield was significantly better with real-time US guidance than with CT guidance, likely due to use of a larger-gauge needle. CT guided biopsy by IR offers similar complication rates for significantly less observation time vs US by Nephrology.

Table 1. Baseline Characteristics of Study Population.

Demographics	IR n= 59	Nephrology n= 72	P-value
Age (mean in yrs)	57.9	47.9	0.00000
Gender	M 53 (90%) F 6 (10%)	M 43 (60%) F 29 (40%)	0.0001
BMI	32.2	26.97	0.000002
Kidney size (cms)	11.49	11.12	0.186
Side of Biopsy	Left: 46 (78%) Right: 13 (22%)	Left: 64 (89%) Right: 8 (11%)	0.094
Blood Pressure Pre-Biopsy	Systolic: 134.9 Diastolic: 79.9	Systolic: 124.9 Diastolic: 71.0	0.0029 0.000008
Blood Pressure Post-Biopsy	Systolic: 126.5 Diastolic: 74.4	Systolic: 125.5 Diastolic: 70.5	0.422 0.112
Anticoagulant use	Anticoagulant: 1 Anti-platelet: 3 NSAID: 1	Anticoagulant: 0 Anti-platelet: 3 NSAID: 0	

Pre-Biopsy	IR n= 59	Nephrology n= 72	P-value
BUN	32.2	27.5	0.121
Serum Creatinine	2.11	1.77	0.160
eGFR (ml/min)	45.3	62.6	0.00297
[illegible]	13.57	12.85	0.082
Platelet count	230.7	229.6	0.935
INR	1.00	1.03	0.288
pRBC transfusion	0	0	n/a
Platelet transfusion	0	0	n/a
DDAVP	0	0	n/a

Table 2. Needle size, Glomerular Yield, and Duration of Patient Observation.

	IR n= 59	Nephrology n= 72	Difference	P-value
Needle Size	16G: 0 17G: 0 18G: 58 20G: 0	16G: 67 17G: 0 18G: 4 20G: 1	n/a	<0.00000
Needle passes per biopsy	3.47	2.79	0.68	<0.00000
Mean Glomerular yield (Ø + IF)	22.18	25.03	2.85	0.247
Glomerular Yield per Needle Pass	6.39	8.97	2.58	0.00024
Inadequate Tissue	11 (18.6%)	5 (6.9%)	11.7%	0.042
Duration of Patient Observation Post-Bx (Hrs)	5.03	20.73	15.7	<0.00000

Table 3. Complication Rate.

Complications	IR n= 59	Nephrology n= 72	P-value
Analgesic use acute from [illegible]	5 (8.4%)	3 (4.1%)	0.466
Emergency room visit [illegible]	2 (3.3%)	0	0.201
High change in Hct Pre-Post Bx (g/dL)	-0.675	-0.892	0.969
Femoral hematoma	14 (23.7%)	8 (11.1%)	0.064
Infection	2 (3.4%)	3 (4.2%)	1.000
Bleeding needing RBC transfusion	1 (1.7%)	1 (1.4%)	1.000
Bleeding needing Embolization	0	0	n/a
Bleeding needing Surgical intervention	0	0	n/a
Biopsy related death	0	0	n/a
Death	0	0	n/a

FR-PO947

Performance of Diagnostic and Interventional Nephrology (DIN) in Spain Haridian Sosa Barrios,[3] Jose Ibeas,[7] Angels Betriu,[6] Vicente Paraiso,[4] Pedro Quiros,[5] Ramon Roca-Tey,[1] Jose I. Cornago,[2] Maite Rivera.[3] *[1]Hospital De Mollet, Bancelona, Spain; [2]Hospital Galdakao, Bilbao, Spain; [3]Hospital Ramon y Cajal, Madrid, Spain; [4]Hospital U del Henares, Coslada, Spain; [5]Servicio Andaluz de Salud (Spain), El Puerto de Santa María, Spain; [6]IRB LLEIDA, LLEIDA, Spain; [7]LONDON, United Kingdom. Group/Team: GNDI.*

Background: Diagnostic and Interventional Nephrology (DIN) has gained drive in the last few years. Line insertion (whether ultrasound guided or not), renal biopsy (native and transplanted), renal ultrasound and peritoneal dialysis (PD) catheters or permanent dialysis lines insertion are vital to our specialty. Some of these procedures are delegated in other specialties. In our view, nephrologists should resume DIN as risk-benefit balance is better assessed, providing complete care for patients and reducing waiting times.

Methods: An online survey was sent by email to all Spanish Renal Departments in June 2015. The survey could be completed by any consultant and only one response per centre was allowed. Questions are listed in table 1. The survey was written, supervised and approved by the DIN Nefrology Group (GNDI, Spanish Society of Nephrology).

Results: Of 195 Nephrology Departments in Spain, 70 responded (35.8%). All centres had HD, 81.4% PD and 34.3% had a transplant program. 72.3% (52) had ultrasound equipment. Regarding catheter placement, 77.1% insert temporary jugular ones and 92.8% femoral. 75.7% perform native renal biopsies, of which 35.8% (19) are real-time ultrasound guided by nephrologists in full. Graft kidney biopsies are done in 26 centres, of which 46.1% are done by nephrologists. Tunnelled haemodialysis catheters are done in 38.5%, peritoneal catheter insertion in 25.7% and only 2 centres (2.8%) perform arteriovenous fistulae (AVF) angioplasty. In terms of ultrasound imaging, 28.5% do native kidneys ultrasound and 22.8% grafts. 71.4% of all centres offer carotid ultrasound assessment to evaluate cardiovascular risk, only 21% done by nephrologists. AVF's ultrasound scanning is done in 55.7% (39 centres).

Conclusions: DIN has spread in Spain, although there's still a long way ahead. It includes basic techniques to our specialty and allows more independency and efficiency. Therefore, appropriate training on different techniques should be warranted to nephrologists, implementing programs to do so aiming to minimize complication rates.

Funding: Government Support - Non-U.S.

FR-PO948

Preventing Unnecessary Renal Replacement Therapy for AKI: A Quality Improvement Project Adrianna Douvris,[3] Khalid Zeid,[3] Swapnil Hiremath,[3] Manish M. Sood,[1] Edward G. Clark.[2] *[1]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [2]The Ottawa Hospital and Kidney Research Centre - Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada; [3]University of Ottawa, Ottawa, ON, Canada.*

Background: AKI is a frequent complication in hospital with the highest mortality observed in patients requiring renal replacement therapy (RRT). Also, RRT for AKI may be harmful for renal recovery. There are no effective pharmacological interventions to treat established AKI. Treatment focuses on limiting further renal damage, and reducing the risk of requiring RRT. Our objective is to characterize events that contribute to potentially avoidable RRT for AKI patients at the Ottawa Hospital. Ultimately, our results will serve as a guide to create a clinical pathway for AKI to limit iatrogenic harm in this population.

Methods: This is a retrospective cohort study of 100 consecutive patients who required acute RRT for AKI while hospitalized at TOH between July 1, 2015-August 31, 2016. Inclusion criteria: age 18 or over, and all dialysis modalities except peritoneal dialysis. Exclusion criteria: end stage kidney disease (ESKD), and RRT within 72 hours of admission. The main outcome is the frequency of iatrogenic events in the period after AKI but prior to RRT that may cause harm.

Results: We screened 344 charts to include 100 patients. Admission diagnoses were sepsis (26%), cardiac (31%), surgical (18%) and renal (15%). 36% of patients required ICU, CCU, or cardiac surgery ICU (CSICU) care at one point. Possible AKI etiologies cited: pre-renal (51%), ATN (68%), AIN (16%), and post-renal (6%). Contrast-induced nephropathy was suggested in 27%. Volume overload was the most common indication for initiating RRT; hyperkalemia was cited as an indication in 32%. Relative hypotension from anti-hypertensives was cited as an AKI contributor in 7%. With regards to nephrotoxins post-AKI, NSAIDs were continued in 3%, ACEi/ARB in 16%, and spironolactone in 13%. Of the 32 patients dialyzed with hyperkalemia, only 43.7% were placed on a low K+ diet, and 7% received a form of additional K+ after AKI and with a serum K+≥5.

Conclusions: Our study includes many seriously ill patients with AKI where RRT is likely unavoidable. However, we have identified potentially harmful events. These include nephrotoxic medications, iodinated contrast dye, potassium supplementation, and hypertension management. Upon completion, we plan to use our data to create solutions that will hopefully reduce the risk of iatrogenic harm for hospitalized AKI patients.

FR-PO949

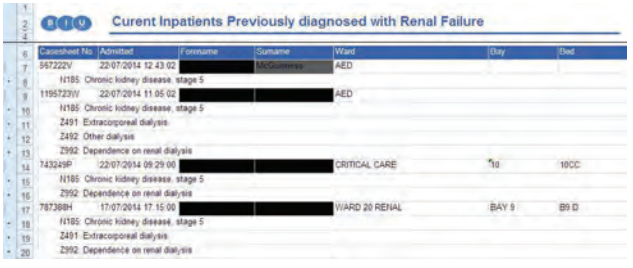
Patient Attendance Alert to Specialty System (PAASS): An Automatic Alert as a Novel Approach to Identify Patients with Advanced Kidney Disease for Early Specialty Input on Admission Bhavna Pandya, Samantha Dolan. *University of Liverpool, UK, LIVERPOOL, United Kingdom. Group/Team: Aintree Nephrology Dept; Aintree Business Intelligence System.*

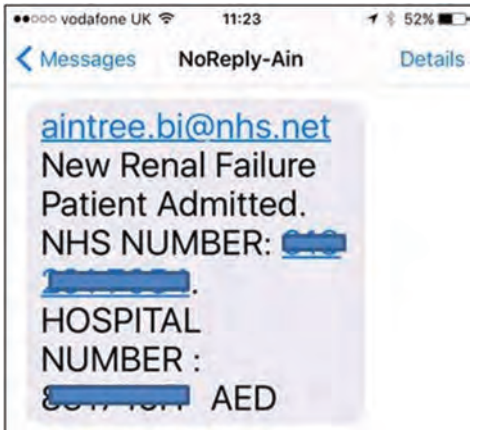
Background: Patients with pre-existing advanced renal disease admitted in emergency to hospital are managed by the admitting team. Renal specialists are involved at a late stage depending upon the mode of communication and rely on admitting team for notification. Delays in specialist input contribute to increased morbidity, length of stay, untoward incidences and even mortality. To avoid this delay, we designed an automatic, secure Patient Attendance Alert to Speciality System (PAASS) which alerts the renal team via e-mail and SMS message to notify the attendance of these patients to the appropriate specialist.

Methods: We carried out a retrospective analysis of patients admitted within several weeks between July-August 2016 with advanced renal disease. Comparison was made between PAASS alerted and manually referred patients. Length of stay, 30 day/ 6 month/ 12- month readmission rate and patient mortality rate were measured to compare with data prior to the implementation of PAASS alert. Trust's business intelligence system was used for alert details.

Results: The PAASS alert had acceptable sensitivity (95.2%) and specificity (100%). There was no difference in 6-month mortality and readmission rate between groups; however alerted patients had a significantly reduced 'length of stay' in hospital (p=0.0002, 95% CI -12.9,-7.6, SE 0.95), compared to those patients who were referred manually.

Conclusions: Our findings indicate that early notification of patient attendance to hospital using the PAASS alert contributed to reducing length of stay significantly.





FR-PO950

Disaster Preparation in Kidney Transplant Patients: A Survey-Based Assessment Shimi Sharief, Daniel J. Freitas, Deborah B. Adey, James A. Wiley. *University of California, San Francisco, San Francisco, CA.*

Background: Few quantitative assessments have been undertaken to assess the disaster preparedness of kidney transplant patients, a population at risk due to their dependence on immunosuppression. This is a survey-based assessment of the disaster preparedness of a cohort of 200 patients recruited from the UCSF Kidney Transplant clinic.

Methods: We recruited 200 kidney transplant recipients from the waiting room of the transplant clinic. They answered short pencil and paper questionnaires assessing their level of preparedness as well as what barriers they faced in becoming adequately prepared. Preparedness was scored based on the response to 7 different items and an index created. Medical and demographic data was extracted from the clinical chart. We analyzed the data using univariate analyses of different participant characteristics against three tertiles of preparedness – low (scores between 0-2), medium (scores of 3 or 4) and high (scores of 5-7). We created average scores of preparedness for various counties in California and geocoded them on maps created with Google Fusion Tables.

Results: Only 30 percent of patients were highly prepared for disasters. Participants were most prepared in stockpiling medications (78.5%) and least prepared in having a medical ID bracelet that identifies them as transplant patients (13%). A significant minority of patients (at least 40% of patients or more) were unprepared with lists of medications, important phone numbers and disaster kits. There were no major associations between preparedness and different participant characteristics such as age, race, gender, number of years since transplant or various clinical variables including type of immunosuppression or other comorbid conditions. Thirty-one of the 34 counties sampled were from California, of which Monterey County was the most prepared with an average preparedness score of 4.25 (out of 7).

Conclusions: Patients of all demographic and clinical backgrounds should be educated on the importance of disaster preparation. Since most deficiencies in preparedness are in general items, there should be a concerted effort on the part of city and medical services to address specialized populations in general preparedness planning.

Funding: NIDDK Support, Private Foundation Support

FR-PO951

Development and Usability Testing of a Patient Safety Educational Program in CKD Clarissa J. Diamantidis,[1] Jennifer St. clair russell,[1] Joseph Lunyera,[2] Janell R. Wylie,[1] Nikita Shah,[1] Jeffrey C. Fink.[3] *[1]Duke University School of Medicine, Durham, NC; [2]Duke University----, Durham, NC; [3]University of Maryland, Baltimore, MD.*

Background: Chronic kidney disease (CKD) threatens patient safety, yet few interventions educate patients about kidney-specific safety hazards. We sought to develop and usability test an educational program designed to promote patient awareness of relevant safety topics in CKD.

Methods: We included 4 patient safety objectives in a tablet-based educational program: 1) avoidance of non-steroidal anti-inflammatory drugs (NSAIDs); 2) hypoglycemia awareness (only for individuals with diabetes); 3) temporary cessation of certain medications while acutely volume deplete (i.e. "sick day protocol"); and 4) contrast dye risk awareness. Content was developed for each objective using plain language principles. Teaching strategies optimized human-computer interaction and content retention; audio, animation, and clinical vignettes reinforced themes. For example, using a vignette of a CKD patient with pain and pictures of common NSAIDs, participants are asked, "which of the following pain medicines are safe for Mr. Smith to take for his belly pain?" Assessment methods consisted of pre- and post- knowledge surveys, with provision of correct responses and explanations. Usability testing was performed among patients with CKD, and program tasks completion were rated as 1) no error, 2) non-critical error (self-corrected), or 3) critical error (not completed).

Results: All usability participants owned a mobile device and used it daily. Of 318 total tasks there were 3 non-critical errors (1%) and 6 critical errors (2%). One participant accounted for 7 of all total errors. All participants rated use of the tablet as 'very easy,' activity length as 'just right' (vs too long/short), the use of clinical vignettes as helpful, and would recommend this activity to others; the majority felt the program was 'very' or 'somewhat easy' to use (80%) and use of the audio was helpful (60%). All rated the activity between 8 (60%) and 10 (20%) on a scale of 1 to 10 (best). All usability testing recommendations were incorporated into the final version of the educational program.

Conclusions: A tablet-based patient safety educational program is acceptable and usable among individuals with CKD. Future studies will explore its impact on health outcomes in this high-risk population.

Funding: NIDDK Support

FR-PO952

Quality Improvement Pilot: A Novel, Personalised, Nurse Led Pathway for Patients Commencing Haemodialysis Shows Improved Outcomes Vicky Ashworth, Alexandra C. Mccrudden, Peter J. Cole, Asheesh Sharma. *Royal Liverpool & Broadgreen University Hospitals Trust, Liverpool, United Kingdom.*

Background: Commencing haemodialysis (HD) is a time of physical and psychological distress, with a high incidence of hospitalization. Despite good pre dialysis care many patients experience a suboptimal start to HD. Mortality is at its highest within

the first 90 days of commencing dialysis. **Aim:** To develop, test and evaluate the impact of a novel, personalised nurse led pathway for patients commencing HD on a range of patient centred process and outcome measures.

Methods: Sequential PDSA cycles were used to develop a personalised nurse led pathway for the first 6 sessions of HD (see fig). Patient distress was recorded at week 2, 4 and 8 using the validated Patient Distress Thermometer (Renal). Baseline control data were retrospectively collected for patients commencing HD from July 2015-June 2016. Our prospective pilot recruits patients from July 2016-June 2017, and we report 90 day follow-up data.

Results: There were 78 patients in the historic control cohort (mean age 58.4y, 62% male, 45% diabetic). 90 day follow up data are available for 37 patients who started HD using the new pathway (mean age 56.2y, 51% male, 27% diabetic). All outcome measures have improved (see table). Patient distress score has dropped from 4.3 (week 2) to 2.4 (week 8). Patient and staff feedback has been strongly positive.

Conclusions: These data suggest improvements in patient experience and outcomes using this novel intervention.

Funding: Private Foundation Support

Improvements in Patient Outcome Measures

	Historic control group	New patient pathway
% listed for transplant or in work up at 90d	21%	31%
% definitive vascular access at 90d	40%	56%
% with home therapy plan at 90d	8.5%	20%
Days in hospital in first 90d	12.2 days	8.6 days
Unadjusted 90d mortality	5.1%	2.7%

Novel Nurse Led Pathway	
Mandatory Interventions	**Personalised Interventions**
Early review of dialysis prescription	Patient experience questionnaire
Access plan	Priority of home therapies if appropriate
Early review of dry weight	Transplantation plan
Medication and dietary advice	Supportive approach for frailer patients
Anaemia and blood biochemistry	Individualised education support for both patients and families
Distress score & early psychology review	Support for both patients and families
Early consultant review	
Production of update letter for patient consultant and GP	

Components of nurse led pathway

FR-PO953

Prevalence of Depression in Patients with ESRD on Hemodialysis and Peritoneal Dialysis in the West Area of Puerto Rico Sherryl D. Mitchell. *Baylor College of Medicine, Houston, TX.*

Background: Depressive symptoms and depression are major public health problems and the most frequent psychological problems reported among ESRD patients being treated by hemodialysis. We assessed the prevalence of depressive symptoms among hemodialysis and peritoneal dialysis patients at West area of Puerto Rico. Despite these findings, depression may remain under recognized and undertreated, particularly among ESRD patients. A systematic assessment of depression in hemodialysis patients would supply information about patient feelings of well being. Existing data suggest that screening for depression may help identify patients at higher risk for death and hospitalization.

Methods: This cross-sectional study was represented with a sample of 146 hemodialysis patients selected from 3 dialysis centers of West Area at Puerto Rico. We provided written informed consent before filling questionnaires to patients. The Beck Depression Inventory (BDI-II) is considered to be the standard instrument for assessing symptoms of depression and screening for clinical depression. We used this scale of 21 short answer question for assess degree of depression in studied patients.

Results: The prevalence of depression in peritoneal dialysis patients is 36% in our study when we compare the depression between HD and PD patients we noted that there is more prevalence of depression in Hemodialysis patients with a 53% than in the peritoneal group. There is significant effect between these groups (DF= 1, Value= 2.9849 and P-Value= 0.084) with a significance level at 10%. For age ranges no significant effect was observed in depressive symptomatology (DF=1, P-value= 0.8453, Value=0.0381). In relation to the variable weather time in PD treatment and prevalence of depression there is not found significant differences (DF=2, P-value=0.8474, Value=0.3311). More results to discuss further.

Conclusions: Based on our investigation the prevalence of depression is present in ESRD on PD and HD patients at West area of Puerto Rico. This supports the recommendations of early implementation psychological measures and medical treatment in an effort to influence the prognosis associated with the progression related morbidity/ mortality and decrease hospitalization in ESRD on HD patients and improve quality of life!

FR-PO955

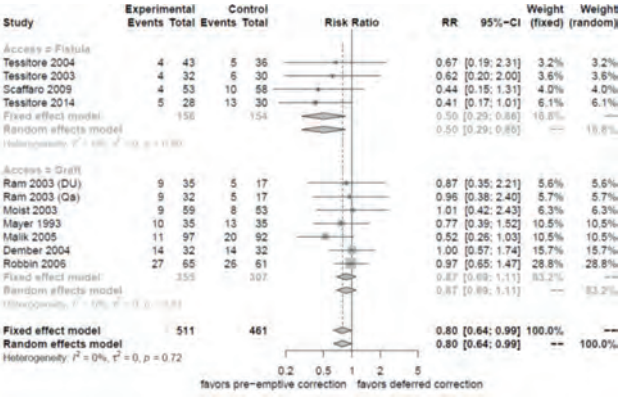
Meta-Analysis and Commentary: Preemptive Correction of Arteriovenous Access Stenosis Jochen G. Raimann,[2,1] Levi D. Waldron,[1] Elsie Koh,[3] Gregg Miller,[3] Murat Sor,[3] Richard J. Gray,[3] Peter Kotanko.[2,4] *[1]CUNY School of Public Health, New York, NY; [2]Research Division, Renal Research Institute, New York, NY; [3]Fresenius Vascular Care, Woodland Park, NJ; [4]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: A recent meta-analysis (Ravani et al., Am J Kidney Dis 2016) studied the effect of pre-emptive correction of arterio-venous (AV) vascular access versus deferred care, based on data from 10 trials. It reported a non-significant protective treatment effect of pre-emptive correction on access loss and a significant protective effect on thrombosis rates conferred by pre-emptive correction. We revisit this analysis, including data extraction and effects of heterogeneous study populations.

Methods: We repeated data extraction from referenced publications, and corrected event counts where applicable. As a next step we repeated the meta-analyses for studies that recruited patients with AV fistulae (AVF) and grafts (AVG), using a random effects model with VA access loss as the outcome.

Results: Our conclusions differ from the original findings: After amendment of the extracted event counts we find a significant overall positive effect of pre-emptive correction on AV access loss in the overall study population [RR 0.80 (95% CI 0.64 to 0.99), RD -0.07 (95% CI -0.12 to -0.02); Figure 1]. Whereas the data do not conclusively show a benefit of pre-emptive correction for AVG (RR = 0.87, 95% CI: 0.69 – 1.11), they show a strong protective effect for AVF (RR = 0.5, 95% CI: 0.29 to 0.86).

Conclusions: These findings corroborate clinical arguments such as superior long-term patency of AVF and the nature of AVG failure that often involve infectious causes. The available data indicate mild or no benefit of pre-emptive correction for AVG, but support tight monitoring of AV dialysis accesses and preemptive intervention and correction upon the detection of access stenosis for AVF. **Figure 1:** Meta-analysis of AV access loss, overall and by access type.



FR-PO956

Calculating Maximum Allowable Contrast Dose to Minimize Contrast Induced Nephropathy Following Coronary Angiography: Comparison of Validated Methods with Implications for Practice Habib Mawad,[4] Kelly M. Zerr,[4] Anurag Singh,[5] Simon Robinson,[3,1] Sean C. Hardiman,[1,3] Adeera Levin.[4,5] *[1]Cardiac Services BC, Vancouver, BC, Canada; [3]Department of Cardiology, Univ of British Columbia, Vancouver, BC, Canada; [4]St. Paul's Hospital and University of British Columbia, Vancouver, BC, Canada; [5]BC Renal Agency, Vancouver, BC, Canada.*

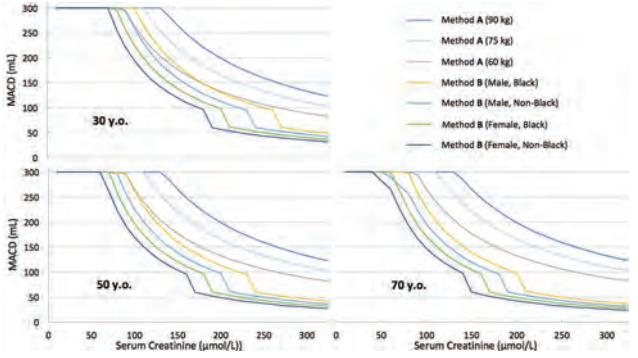
Background: The contrast volume used during angiographic procedures represents an important modifiable risk factor for contrast-induced nephropathy (CIN). As a result, attempts have been made to limit contrast exposure by determining maximum allowable contrast dose (MACD), using specific equations. Two published methods exist, but they use different components to derive the MACD: Method A uses weight and creatinine, Method B uses the estimated GFR (eGFR) multiplied by a specific ratio. Our study analyzed and compared the 2 methods with respect to concordance, and implications for incorporating into clinical practice. The goal was to find a simple equation to implement which would be safe (i.e. give the lowest MACD).

Methods: We calculated the MACD for a wide range of serum creatinine levels, weights and demographic variables (i.e. age, sex and race), using the 2 methods. Method A: MACD (mL) = (5* Body Weight (kg) * 88.42)/ Serum Creatinine (umol/L); and Method B: MACD (mL) = Ratio* eGFR (ml/min per 1.73m^2). A ratio of 3 was used if

eGFR >30 and a ratio of 2 if eGFR ≤30 ml/min per 1.73m^2. Irrespective of methodology, recommendations suggest that MACD should not exceed 300 mL.

Results: The results show a marked discordance in calculation of MACD depending on the equation used (see Figures). In the majority of cases method B gives a more conservative estimate of MACD. The difference is most marked for those who are heavier, older and are female, particularly non-black females.

Conclusions: Discrepancies in allowable contrast doses based on published formulae may lead to different and higher contrast exposure for some patients. We propose an alternative method which suggests lower contrast doses in those at highest risk of CIN. The impact of implementation of these methods on MACD used, subsequent incidence of CIN and dialysis as well as cardiovascular outcomes remains to be studied.



FR-PO957

Provider versus Pharmacy Led Initiation of ACEI or ARB Kelly Mazurek, Margaret E. Fleet, Bessie A. Young. *Uniiversity of Washington, Seattle, WA.*

Background: Guideline attainment in diabetes and early diabetic nephropathy is difficult. Primary care provider (PCP) directed recommendations can either be from a specialist or from a pharmacist. Studies looking at the efficacy of either approach have been mixed. The purpose of this study was to determine whether a provider (Nephrologist) versus pharmacy led invention, consisting of initiation of an ACEI or an ARB (Ac/Ar), was more effective.

Methods: Data were collected from the Diabetes Registry at the Veterans Affairs (VA) Puget Sound Health Care System. Search criteria were: diabetes mellitus, hypertension or blood pressure >140/90 mmHg, albuminuria >30 mg/g, and not being on an Ac/Ar. Exclusion criteria were taking an Ac/Ar, previously enrolled in pharmacy clinic, anaphylaxis or angioedema to an Ac/Ar, ESRD or no longer being a VA patient. Patients were followed over 7 months. Nephrology recommendations and guidelines were given to PCPs for starting an Ac/Ar. PCPs had the option to place an electronic nephrology consult to manage the intervention. On the other hand, the pharmacy team identified patients and placed referrals to a pharmacy clinic. The primary pharmacist made decisions on drug initiation, monitoring, titration and laboratory tests based on the same recommendations. The primary outcome was the rate of Ac/Ar initiation.

Results: A total of 34 patients were found in the provider group and 19 patients in the pharmacy group. There was a trend towards increased efficacy in the pharmacy led team (58%) over the provider led team (41%). However, there was no statistical difference (p 0.56). A post study survey showed that majority of participants favored that pharmacists identify, start and manage recommendations.

Conclusions: A pharmacy led intervention was no more effective than a provider led intervention in implementing current standards of care for diabetic patients. On the pharmacy arm, patients were more likely to have follow-up appointments if they were by telephone rather than in person. Telephone intervention is less burdensome and may lead to more successful interventions and continuity of care. PCPs are often overwhelmed with their patient panel and correct medication management can go overlooked. Pharmacists are just as effective, are more accessible health care practitioners and are well positioned to implement appropriate medication use.

FR-PO958

Renal Safety of Cisplatin-Based Chemotherapy in Urothelial Carcinoma Patients with a Solitary Kidney Masahiro Kondo,[1] Yuji Hotta,[2] Ryosuke Ando,[3] Takahiro Yasui,[3] Kazunori Kimura.[1,2] *[1]Pharmacy, Nagoya City University Hospital, Nagoya, Japan; [2]Hospital Pharmacy, Graduate School of Pharmaceutical Sciences, Nagoya City University, Nagoya, Japan; [3]Nephro-urology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.*

Background: There is little information on renal safety to cisplatin-based chemotherapies in patients with a solitary kidney after nephroureterectomy. We evaluated the nephrotoxicity and hematologic toxicities of gemcitabine plus cisplatin (GC) in urothelial carcinoma patients with a solitary kidney.

Methods: We retrospectively reviewed patients treated between August 2007 and December 2016. Eligible patients received GC as first-line chemotherapy, including as neo-adjuvant and adjuvant treatment. Patients with one kidney comprised the solitary kidney (SK) group; those with both kidneys comprised the BK group. Incidences of renal insufficiency and hematologic toxicities were examined and compared between the groups.

Results: There were 18 and 43 patients in the SK and BK groups, respectively. Mean serum creatinine [SCre] levels at baseline were significantly higher in the SK group than in the BK group (P<0.001). There were no significant differences in median numbers of administered cycles and doses of GC between the groups. No significant differences were observed between the groups in the incidence of acute kidney injury (SK: 11.1%, BK: 7.0%, P=0.627). SCre levels in both groups did not significantly increase during treatment (Fig.1); mean differences in SCre levels between baseline and each post-chemotherapy cycle were similar between the groups. The incidence of hematologic toxicity (grade 3/4) was not significantly different between the groups. Multivariate analysis revealed no statistically significant association between having a solitary kidney and severe hematologic toxicities.

Conclusions: Renal safety and treatment tolerability to GC chemotherapy is not inferior in patients with a solitary kidney.

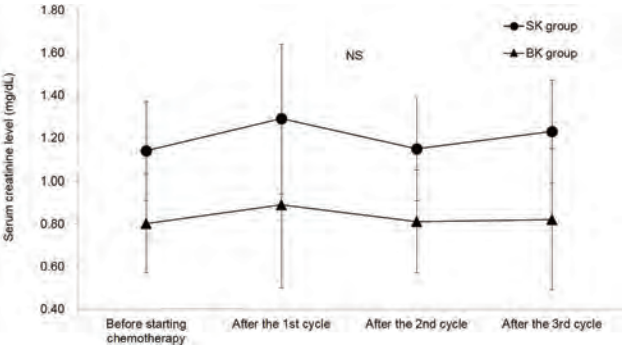


Fig.1: Change in serum creatinine levels between baseline and after each chemotherapy cycle of gemcitabine plus cisplatin in the solitary kidney (SK) and both kidneys (BK) groups. Repeated-measures analysis of variance: NS, not significant.

FR-PO959

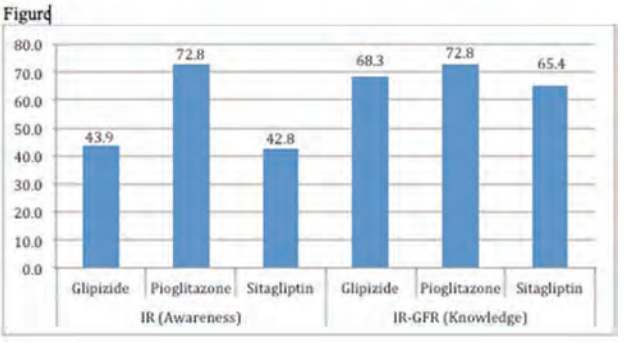
Awareness and Knowledge among Internal Medicine House-Staff for Dose Adjustment of Diabetes Medications in CKD Matthew S. Snyder,[1] Joshua Fogel,[2] Sofia Rubinstein.[1] *[1]Nephrology and Hypertension, Nassau University Medical Center, East Meadow, NY; [2]Brooklyn College, Brooklyn, NY.*

Background: Drug dosing errors result in adverse patient outcomes and are more common in patients with diabetes mellitus (DM) and chronic kidney disease (CKD). As internists treat the majority of patients with DM and CKD, we study if Internal Medicine house-staff (IMHS) have awareness and knowledge about the correct dosage of commonly used diabetes medications in those with CKD.

Methods: We surveyed 353 IMHS to evaluate incorrect awareness of whether a medication needs dose adjustment in patients with CKD (IR) and incorrect knowledge at what level of glomerular filtration rate a medication needs to be adjusted (IR-GFR) for Glipizide (GLI), Pioglitazone (PIO), and Sitagliptin (SIT).

Results: There were high percentages for lack of awareness and knowledge, with the highest for PIO at 72.8% (Figure). Multivariate logistic regression analyses showed that PGY1 had higher odds than PGY3 for GLI and SIT for both IR and IR-GFR and PGY2 had higher odds than PGY3 for PIO for both IR and IR-GFR. More Nephrology training and exposure in medical school or residency were each associated with lower odds for both IR and IR-GFR.

Conclusions: There is poor awareness and knowledge among IMHS for dose adjustment of diabetes medications in patients with DM and CKD. IMHS should receive more nephrology exposure and formal didactic educational training during medical school and residency to better manage complex treatment regimens and prevent medication dosing errors in those with DM and CKD.



Percentages for Incorrect Response to Medication Dose Needs Adjustment and Incorrect Response to Medication Dose Needs Adjustment at Appropriate GFR Level for Diabetic Medications

FR-PO960

Prevention of Medication Reconciliation Errors: Results of a QI Study Manisha Singh,[5] Temekis D. Hampton,[4] Sherida R. O'neal-wright,[3] Shree G. Sharma,[1] Michelle W. Krause.[2] *[1]Arkana Laboratories, Little Rock, AR; [2]University of Arkansas for Medical Sciences, Little Rock, AR; [3]DCI, Little Rock, AR; [4]UAMS, Little Rock, AR; [5]Nephrology/Internal medicine, University of Arkansas for Medical Sciences, Little Rock, AR.*

Background: Medication errors are one of the leading preventable causes of adverse patient outcomes. Accurate reconciliation can greatly decrease this risk. Dialysis patients have increased risk with polypharmacy of up to 5-10 medications/patient. We attempt to enable the patient himself to carry the information for their own care in a quality-improvement project using medication wallets.

Methods: Wallet design: Wallet contains contact information, care-buddy details, dialysis unit information, Physician and APN contacts, immunization record, current dialysis prescription with medications, known medical history and allergy information. The wallet has space to keep a driver's license, credit cards and cash. Method: Project consisted of 3 phases: Phase 1: Identify patients for participation.12/15 home dialysis patients consented for study. Phase 2: Review and compare medications in patient's record from available admission/discharge lists. Phase 3: Introduce intervention (Dialysis Wallet) and monitor its effectiveness through a questionnaire-based survey at each clinic visit.

Results: 67% of the patients had a medical visit since previous clinic visit. 17% of patients were hospitalized. Their dialysis prescription was unchanged during that hospitalization.100% of patients feel that their dialysis prescription were continued as prescribed.33% of patients felt that, after discharge from medical visit, their medication lists were not updated. They felt that the wallet contributed positively to their care. They reported that other providers appreciated this input at all physician and APN visits. Their immunization records helped expedite care. After the use of this wallet, participants report they would prefer continued use of wallet/hard copy. 67% of patient brought the wallet to clinic visits.

Conclusions: Our results indicate that the medication wallet may be a very effective way to minimize medication errors during transitions and an effective way to enable better patient care. The limitations are failure to update the wallet by some treating teams and patients forgetting to bring the wallet during some treatment visits. We hope that over time, this will get corrected as the importance of this step will be more apparent to providers as well as the patients.

FR-PO961

Medication Dosing in Dialysis Dependent ESKD Patients: A Retrospective Single Center Review Daryl U. Nnani,[3] Timothy V. Nguyen,[2] Archna Jariwala,[3] Vijay Lapsia.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Long Island University - AMS College of Pharmacy and Health Sciences, Little Ferry, NJ; [3]Mount Sinai Hospital, New York, NY.*

Background: Patients with hemodialysis (HD) dependent end stage kidney disease (ESKD) are more prone adverse events and poor outcomes due to inappropriate medication dosing. A significant number of medications are converted into active metabolites and failure to adjust doses may result in toxicity. Medication errors account for a majority of adverse events within the inpatient setting. The purpose of this study was to assess the appropriateness of medication dosing in hospitalized HD dependent ESKD patients.

Methods: This was an IRB-approved, single-center, retrospective medication chart review of adult HD-dependent patients diagnosed with ESKD admitted between 1/2016 – 8/2016. Patients were excluded if they were on peritoneal dialysis, admitted for kidney transplantation, or had missing pertinent information. The appropriateness of medication dosing was assessed by evaluating inpatient medication orders on day one of admission and was compared to drug manufacturer and tertiary reference renal dose adjustment recommendations.

Results: A total of 509 patients were included in this study and 6,964 medication orders were reviewed for a mean of 13.7±8.32 medications per patient. A total of 221 inappropriate medications orders were identified and 32.4% (165 of 509) of patients included in this study had an inappropriate medication order on admission. A total of 20 medication classes were ordered inappropriately on day one of admission. The most frequently inappropriately ordered medication classes were anticonvulsants 26.1% (58 of 221), opioids 25.6% (57 of 221), antibiotics 16.2% (36 of 221), histamine-2 receptor antagonists 8.1% (18 of 221) and HMG-CoA reductase inhibitors 6.3% (14 of 221). Morphine sulfate accounted for 83% (47 of 57) of inappropriate opioid medication orders. Gabapentin accounted for 66% (38 of 58) and levetircetam accounted for 28% (16 of 58) of inappropriate anticonvulsants medication orders in this study.

Conclusions: Anticonvulsants and opioids accounted for greater than 50% of inappropriate medications orders. Mandatory pharmacist medication reconciliation in this patient population and implementation of a best practice alert integrated into the computerized physician order entry system may result in a reduction of inappropriate medication orders in this patient population.

FR-PO962

Hydralazine-Associated Death and CKD Roman Zuckerman,[1] Mayurkumar P. Patel,[1] Rany Al haj,[1] Harry J. Dounis,[1] Seyedehsara Seyedali,[1] Ali Nayer,[2] Arif Asif.[1] *[1]Jersey Shore University Medical Center, Neptune, NJ; [2]Miami Renal Institute, North Miami Beach, FL.*

Background: Despite the widespread availability of effective anti-hypertensive agents (calcium channel blockers, ACE-Inhibitors/ARBs, diuretics, aldosterone receptor, and beta-blockers), hydralazine continues to be used as one of the first line agents in the management of hypertension. Hydralazine is known to cause drug-induced lupus (DIL) as well drug-induced anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis (DIV).

Methods: Herein we describe three male and one female patients (age: 53, 83, 57, 87) treated with hydralazine therapy, who presented with acute kidney injury, proteinuria, and hematuria. All demonstrated positive anti-histone antibodies. The two patents with DIV demonstrated pauci-immune, necrotizing crescentic glomerulonephritis on renal biopsy. The other two were found to have features consistent with drug-induced lupus (DIL) and immune complex deposition in the sub-endothelial, subepithelial and mesangial areas. Both patients with DIV were initiated on hemodialysis. One of them recovered successfully, whereas the other patient's condition deteriorated and hospice care was initiated. Of the two patients with DIL neither one required dialysis. One patient developed severe sepsis with subsequent withdrawal of care, while the other one was discharged home with renal function at baseline.

Results:

Conclusions: Our report calls for heightened awareness and prompt diagnosis of DIL and DIV associated with hydralazine therapy to minimize its morbidity and mortality associated with this agent. Given an extremely unfavorable side effect profile and multiple alternatives available on the market, hydralazine should generally be avoided. In situations where its use is necessary either due to other agents' unavailability, intolerance, or inefficiency, we find that it is imperative for a clinician to monitor closely the patients on a long-term/high dose hydralazine regimen.

FR-PO963

Tramadol Induced Severe Hypoglycemia in a Non Diabetic ESRD Patient Ameen Taleb,[1] Michael E. O'Brien,[4] Brianna D. Jewell,[2] Yuvaraj Thangaraj.[3] *[1]Mercy Medical Center-North Iowa, Mason City, IA; [2]Mercy North Iowa, Mason City, IA; [3]None, Mason City, IA; [4]University of Iowa, West Union, IA.*

Background: Tramadol is a generally well-tolerated medicine in ESRD patients on hemodialysis. We present a case of severe hypoglycemia in an ESRD patient within days of initiating tramadol for pain at appropriate dose and timing interval.

Methods: A 54 y/o man with a history of ESRD on hemodialysis, hypertension and chronic back pain presented with hypoglycemia on the day of dialysis after receiving dialysis treatment. He reported taking100 mg of tramadol after dialysis. He was noted to have severe symptomatic hypoglycemia with a blood sugar of 33 mg/dl. The patient required multiple ampules of IV dextrose 25g and subsequently received 50% dextrose infusion in the critical care unit for persistent hypoglycemia. Lab findings including drug screen and acid base status were unremarkable aside from hypoglycemia. Insulin levels, c-peptide level and IGF1 level were within normal limits. Screen for meglitinides and sulfonylureas were negative. CT abdomen and pelvis with contrast showed small hypodensities within the pancreas. The CT findings were not radiographically consistent with insulinoma and represented small cysts that appeared to be unchanged from the previous CT. Patient's clinical condition and hypoglycemia significantly improved within 48 to 72 hours after discontinuation of tramadol and receiving dialysis treatment. The patient did not have any further episodes of hypoglycemia in post hospitalization follow up.

Results: Tramadol's hypoglycemia effect appears to be due to a synergistic effect between mu opioid receptor stimulation and decreased serotonin and epinephrine reuptake in nerve endings, which subsequently promotes higher levels of intracerebral serotonin and epinephrine. Tramadol depends on a cytochrome P450 enzyme, the expression of which is highly variable for activation into its active metabolites. Those metabolites are renally cleared and dialyzable. Henceforth, the pain modulating effect and the hypoglycemic side effect of tramadol are not dose dependent.

Conclusions: This case illustrates the importance of early recognition and appropriate management of tramadol induced life threatening hypoglycemia in ESRD patients including the need for heightened vigilance and slow up-titration of dose to prevent severe hypoglycemia.

FR-PO964

Influence of Communication of Hyponatremia on Outcomes Kirsten Salline,[2] Jeffrey I. Silberzweig,[1,3] Stephanie Tsai,[2] Clara Oromendia,[2] Vesh Srivatana,[1,3] Gordon Hildick-Smith.[2] *[1]The Rogosin Institute, New York, NY; [2]Weill Cornell Medical College, New York, NY; [3]Medicine, Weill Cornell Medical College, New York, NY.*

Background: Despite the growing body of literature documenting the prognostic importance of hyponatremia, it is commonly treated as a peripheral issue during hospital admissions. We seek to quantify the degree to which hyponatremia is reported to outpatient providers and to evaluate factors associated with communication and associations between communication and standard outcome measures.

Methods: With IRB approval, we designed a retrospective cohort study of patients admitted to the Weill Cornell Campus of the New York-Presbyterian Hospital in January 2014 with corrected serum sodium <130 mEq/L who survived the hospitalization. Discharge summaries were manually reviewed for mention of hyponatremia; charts were reviewed for pertinent information. Patients who did and did not have hyponatremia mentioned in the discharge summary were compared using chi-square (or Fisher's Exact) and Kruskal-Wallis tests for categorical and continuous variables, respectively. Statistical significance was determined be at the 0.05 alpha level.

Results: Of 101 patients, hyponatremia was mentioned in discharge summaries in 37%. Patients with communicated hyponatremia were older (mean 77 vs. 66; p=0.004), and there was a non-significant trend towards Caucasian race (57% vs. 38% p=0.095), other demographic features did not differ. Nadir sodium (125.3 vs 127.3 mEq/L; p=0.001), and discharge sodium (132.2 vs. 134.7 mEq/L mEq/L, p=0.10) were lower for the group with communication. Mean duration of hospitalization was shorter (12 vs. 21 days, p=0.008). Communication of hyponatremia was not associated with one-year mortality, readmissions or readmissions with hyponatremia. Differences in subsequent outpatient providers' assessment of sodium levels were not significant (60% vs. 49%; n=50, p=0.665). Only 2 patients had hyponatremia labeled as a problem in the encounter note; in just one of these was it also mentioned in the discharge summary.

Conclusions: Despite its prognostic significance, our results suggest that hyponatremia is infrequently communicated to outpatient providers. Higher rates of communication were associated with severity of hyponatremia and shorter hospital stay. A lack of specific outpatient provider response to hyponatremia may explain the lack of association between communication of hyponatremia and outcome measures.

Funding: Clinical Revenue Support

FR-PO965

An Integrated Analysis of Safety and Tolerability of Etelcalcetide in Adult Patients on Hemodialysis (HD) with Secondary Hyperparathyroidism (SHPT) Geoffrey A. Block,[4] Glenn M. Chertow,[5] John T. Sullivan,[1] Hongjie Deng,[3] Omar Mather,[2] Holly Tomlin,[3] Michael Serenko.[1] *[1]Amgen, Thousand Oaks, CA; [2]Amgen Inc, Thousand Oaks, CA; [3]Amgen Inc., Thousand Oaks, CA; [4]Denver Nephrology, Denver, CO; [5]Stanford University School of Medicine, Palo Alto, CA.*

Background: Etelcalcetide (ETL) is a novel, IV calcimimetic for the treatment of SHPT in patients on HD. Here, the safety profile of ETL is summarized.

Methods: Safety was assessed by the nature, frequency, and severity of treatment-emergent adverse events (AEs) and changes in lab parameters in the integrated datasets of two 26-week randomized, placebo (PBO)-controlled (PC) studies, a 26-week randomized active-controlled (AC with cinacalcet [CIN]) study, and 2 single-arm open-label extension (OLE) studies. The ETL starting dose was 5 mg 3 times/week (TIW) at the end of HD. Depending on serum PTH and Ca values, the dose could be increased by 2.5 or 5 mg at 4-week intervals to a maximum dose of 15 mg TIW.

Results: 841 patients received ETL in the PC (n=503) and AC (n=338) studies and 1289 in the OLE studies for up to 3.4 yr. In the combined dataset of PC studies, common (≥5%) AEs occurring in the ETL group with a ≥1% greater frequency than PBO were blood Ca decrease (63.8% vs 10.1%), muscle spasms (11.5% vs 6.6%), diarrhea (10.7% vs 8.6%), nausea (10.7% vs 6.2%), vomiting (8.9% vs 5.1%), headache (7.6% vs 6.0%), and symptomatic hypocalcaemia (7.0 vs 0.2%). Rates of AEs of interest were similar between ETL and PBO for convulsions (0.8% vs 1.0%), fractures (1.6% vs 2.9%), hypersensitivity (4.4% vs 3.7%), infusion reaction (5.8% vs 5.7%), ventricular tachyarrhythmia (0.4% vs 0.8%), and GI bleeding (2.0% and 2.1%); a small numerical difference was noted in the rate of adjudicated cardiac failure (2.2% vs 1.2%). More patients in the ETL vs PBO groups experienced hypophosphatemia (1.4% vs 0.4%). ETL had no clinically significant effects on blood pressure, heart rate, weight, or hematology lab parameters. No clinically significant differences were observed in the safety profiles of ETL and CIN in the AC study. No new safety signals were identified with long-term ETL exposure in the OLE studies.

Conclusions: Consistent with its mechanism of action, the most important risks associated with ETL were serum Ca reductions and hypocalcemia-related AEs. Integrated safety assessment of ETL across both controlled clinical trials and OLE studies showed an overall favorable risk/benefit profile with no unexpected safety signals.

Funding: Commercial Support - Amgen Inc.

FR-PO966

Detection of Chlorite in Dialysis Water, an Unrecognized Safety Issue Edward T. Casey,[3] Susan T. Crowley,[2] Jeffrey Birdsong,[1] Paul M. Palevsky.[4] *[1]Orlando VAMC, Orlando, FL; [2]Veterans Health Administration, West Haven, CT; [3]Nephrology, Orlando VAMC, Orlando, FL; [4]University of Pittsburgh, Pittsburgh, PA.*

Background: Chlorine dioxide (ClO_2) is increasing used by medical facilities as a water disinfectant to mitigate risk of environmental Legionella infection. When exposed to water, ClO_2 generates chlorite (ClO_2^-), which may produce similar toxicity for dialysis patients as chlorine exposure. Although dialysis water is routinely tested for total residual chlorine that will detect chlorine, chloramines and ClO_2, these methods will not detect residual chlorite. No specific safe level for residual chlorite has been established.

Methods: Our medical center injects ClO_2 into the water supply due to Legionella concerns. Measurements of ClO_2 and ClO_2^- were taken throughout the medical center, including dialysis water, on a weekly basis using a Nelco ChlordioX Plus instrument. Feed water ClO_2 target level was 0.3-0.8 ppm, ClO_2^- maximum was 1 ppm. Water for dialysis is provided using portable RO with two pre-treatment granulated activated charcoal (GAC) filters. ClO_2 and ClO_2^- testing was performed from the sampling port between the two GAC filters. After 8 months of undetectable levels, we detected 0.04 mg/L ClO_2^- from 1 of 4 portable RO units, with undetectable levels of ClO_2. The GAC filters are replaced quarterly and had been replaced 7 weeks prior detection of ClO_2^-. Following replacement of the GAC, repeat testing showed undetectable levels of ClO_2^- and ClO_2.

Results:

Conclusions: When ClO_2 is used as a disinfectant for Legionella mitigation, it breaks down to yield chlorite, chlorate and chloride ions. While chlorate and chloride are effectively removed by GAC in dialysis water pretreatment, chlorite removal is not complete. We detected residual chlorite despite the GAC replacement 7 weeks earlier. After replacing the GAC filters, repeat sampling did not detect residual chlorite. Thus, the GAC appeared to remove ClO_2 appropriately, but became saturated with chlorite well before the scheduled GAC replacement date. Although ClO_2 is detected using the standard testing for total chlorine, chlorite is not. The effects of chronic low level exposure to chlorite are unknown, but potentially could lead to erythropoietin stimulating agent resistance and/or increased red blood cell destruction. Dialysis providers should be aware of this hazard, and recognize that more intensive monitoring and more frequent replacement of GAC may be required when ClO_2 is present in municipal or hospital water.

FR-PO967

Changes in Creatinine and Potassium after Initiating Renin Aldosterone Inhibitor and Diuretic Therapy in CKD: A Cohort Study from Outpatient Practices Katherine Garlo,[1] Diane Seger,[3] Julie Fiskio,[3] David W. Bates,[2] David M. Charytan.[1] *[1]Renal Division, Brigham and Women's Hospital, Boston, MA; [2]Brigham and Women's Hospital/Harvard Medical School, Brookline, MA; [3]Partners Healthcare System, Somerville, MA.*

Background: Clinical trials of renin aldosterone system inhibitors (RASi) have demonstrated major cardiovascular and renal benefits to patients with chronic kidney disease (CKD), but these benefits must be weighed against the risks of a decline in estimated glomerular filtration rate (eGFR) and hyperkalemia. Since randomized controlled trials do not include the breadth of patients in real world clinical settings, we assessed changes in creatinine (Cr), estimated glomerular filtration rate (eGFR), and potassium in a large cohort of CKD patients prescribed a new RASi or diuretic.

Methods: Retrospective cohort study of adults with pre-dialysis CKD stage 3-5 who received a new outpatient RASi or diuretic prescription during 2009-2011. Lab data was collected electronically and analyzed for changes in Cr, eGFR, and potassium.

Results: A total of 8,272 individuals (mean age 72 yrs ±13.5, 44% male, 86% white) with CKD (90% stage 3, 7% stage 4, 2% stage 5) were included; 52% received a RASi and 48% received a diuretic. Follow up labs were done within 2 weeks in 28% (RASi: 24%, diuretic: 31%). The mean percent change within 2 weeks of drug prescription in Cr was lower in the RASi group compared to the diuretic group (3.8%±19.6 and 5.6%±21.8 ml/min/1.732m^2, p<0.01). Over half of the subjects had <30% increase in Cr (RASi: 51.0%, diuretic: 52.2%) and over one third had an improvement in Cr (RASi: 37.5%, diuretic: 34.1%). Very few patients had a rise in Cr >50% (RASi: 2.2%, diuretic: 2.4%). The mean change in potassium was 0.07±0.5 in the RASi group and -0.03±0.6 in the diuretic group p <0.01. At follow up, the majority had a potassium <5.0 mmol/L (RASi: 80.4%, diuretic: 84.4%). Significant hyperkalemia (potassium >5.5) was rare (RASi: 1.9%, diuretic: 2.0%).

Conclusions: The low rate of meaningful changes in Cr and potassium following new prescriptions supports use in patients with moderate to advanced CKD. Further study is needed to determine lab monitoring strategies that improve safety and are cost-effective.

FR-PO968

Conversion of Single Glomerular and Tubule Segments into Proteomic Data for Discovery of Pathomechanisms in Proteinuric Kidney Diseases Markus M. Rinschen,[1] Tobias B. Huber,[2] Thomas Benzing,[1] Martin Höhne.[1] *[1]University Hospital Cologne, Cologne, Germany; [2]University Medical Center Hamburg, Hamburg, Germany.*

Background: Diseases of the kidney often originate in the glomerulus. Proteinuria, the leakage of the renal filter, is a hallmark and accelerator of renal disease. Virtually all glomerular diseases are histologically heterogeneous at early stages and affect a certain percentage of glomeruli to different extents. Our understanding of physiological kidney function is largely derived from the functional analysis of single nephron segments.

Methods: Here, we developed a nano-scale sample preparation protocol combined with targeted proteomics and single-unit bioinformatics analysis for the discovery of pathogenetic mechanisms in both single glomeruli and single tubuli. The method was applied to clinical samples, as well as different rodent models of glomerular disease.

Results: We analyzed the proteome of single glomeruli from mice and humans in different podocyte injury models. We could identify up to 2000 proteins (~10000 peptides) per single glomerulus. Analysis of 7 single glomeruli from patients with **congenital nephrotic syndrome and proven** *NPHS1* **mutations** discovered decreased amounts of nephrin but unchanged podocin amounts. A targeted podocyte sentinel assay was designed to acquire reproducible proteomic data across 24 glomeruli from two different podocyte damage models. The assay monitors podocyte actin cytoskeletal function, slit diaphragm function, glomerular basement membrane abundance and podocyte stress response. Bioinformatic analysis using hierarchical clustering and correlational approaches delineated common responses in glomerular damage across glomerular populations and across models. The method was also able to clearly discriminate microdissected tubular segments (e.g. S1 proximal tubule, mTAL and cortical collecting ducts), with potential applications in renal physiology.

Conclusions: These data demonstrate the potential of single segment proteomics for both basic research and translational medicine.

Funding: Government Support - Non-U.S.

FR-PO969

Metagenomic Analysis of Microbial Nanovesicle in Blood of Maintenance Hemodialysis Patients Un Sil Jeon,[1,2] Jinho Yang,[3] Seung Hee Yang,[4] Yoon-Keun Kim.[3] *[1]Nephrology, Sheikh Khalifa Specialty Hospital, Ras Al Khaimah, United Arab Emirates; [2]Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [3]MD Healthcare Inc., Seoul, Republic of Korea; [4]Kidney Research Institute, Seoul National University, Seoul, Republic of Korea.*

Background: Gut dysbiosis in uremic patients is known to contribute to progression and complications of chronic kidney disease (CKD). Extracellular vesicles (EVs) excreted from bacteria contain not only bacterial DNA and RNA, but also endotoxins and other virulent proteins. EVs can enter systemic circulation through intestinal mucosal membrane freely and be key communication messengers in host-microbe communication in human diseases.

Methods: We performed metagenomic analysis of bacteria-derived EVs in blood of 20 maintenance hemodialysis (HD) patients (10 diabetic and 10 non-diabetic) and 20 healthy controls. EVs in human serum were isolated using the differential centrifugation method as described previously (*Proteomics 2007;7:3143–3153*). DNA was extracted from 1 ug of serum EVs, and 16S ribosomal RNA (16S rRNA) gene sequencing was performed using high-throughput 454 pyrosequencing after amplification of the V1–V3 region of the 16S rDNA. Taxonomy assignment was carried out by using UCLUST and QIIME against the 16sRNA sequence database in GreenGenes.

Results: The value of alpha-diversity was lower in HD patients than in healthy controls, which means HD patients had a lower diversity of microbiome than healthy controls. The value of beta-diversity was significantly different between HD patients and controls. At the level of Phylum, HD patients had a significant higher level of *Acidobacteria EVs* than controls, but a lower level of *Proteobacteria* EVs. At the level of Genus, we found 37 biomarkers which revealed different levels between HD patients and controls (29 elevated and 18 decreased EVs in HD patients). *Streptococcus., Koribacteraceae(f), Ellin6513(o), and Burkholderia spp.* EVs were higher in HD patients than in controls, and *Enterobacteriaceae(f), Acinetobacter, Pseudomonas, Akkermansia, Proteus and Lactobacillus spp.* EVs were lower in HD patients. However, there were no differences between diabetic and non-diabetic HD patients.

Conclusions: In conclusion, we observed significant differences in the composition and amounts of bacteria-derived EVs in blood between HD patients and healthy controls using metagenomic analysis. Metagenomic analysis of bacteria-derived EVs could be a useful tool to investigate microbial dysbiosis and biomarkers in CKD patients.

FR-PO970

Comparing Raman Spectroscopy-Derived Metabolomic Signatures of Urine from Patients with CKD to Those with Normal Kidney Function James L. Pirkle,[2] John L. Robertson,[1] Mitchell Warren,[2] Ryan S. Senger.[1] *[1]Virginia Tech, Blacksburg, VA; [2]Wake Forest School of Medicine, Winston Salem, NC.*

Background: The field of metabolomics is being used increasingly in clinical research to improve aspects of clinical care ranging from early diagnosis to monitoring treatment progress and prognosis. It would be useful to have an affordable metabolomic test for urine that could identify patients with chronic kidney disease in the absence of albuminuria. Raman spectroscopy is an analytic tool used chiefly in solid state chemistry that has shown increasing application in analyzing molecular compositions of biological samples. We performed a pilot study to assess the ability of Raman spectroscopy analysis of urine samples to differentiate between patients with CKD and those with normal kidney function.

Methods: Free-catch urine samples were collected from 93 patients with CKD (on peritoneal dialysis) and from 25 generally healthy volunteers with normal kidney function. Raman spectra were analyzed using an Agiltron PeakSeeker Pro spectrometer with 785 nm laser excitation at 5 mW. A 1 s integration time was used, spectra were collected between 200-2000 cm^{-1}, and each sample was scanned 10 times. Spectra were analyzed by a multivariate statistical pipeline involving (i) principal component analysis and (ii) discriminate analysis of principal components following baseline correction and vector normalization of raw spectra.

Results: The individual raw spectra show that only the urea band at 1003 cm^{-1} is distinguishable. The multivariate statistical pipeline was used to determine whether differing molecular signatures existed elsewhere for urine from patients with CKD and those with normal kidney function. Results are shown in a canonical plot, where every data point represents an entire Raman spectrum. Distinct clusters of data points are observed between the urine of CKD patients (receiving PD) and those with normal kidney function, indicating recognizably different Raman signals and molecular compositions for each group.

Conclusions: Raman spectroscopy provides a rapid, cost-effective way to assess differences in the molecular composition of urine between patients with CKD and those with normal kidney function. Future research will focus on quantifying these differences and testing of unknown populations. Potential applications for this technology would include community screening for CKD using rapid urine testing.

FR-PO971

The Differential Expression of Circular RNAs in Exosomes from Serum and Urine in Patients with IMN Hualin Ma,[1,2] Xin-zhou Zhang.[1,2] *[1]Department of Nephrology, Shenzhen People's Hospital, Shenzhen, China; [2]Key Renal Laboratory of Shenzhen, Shenzhen, China.*

Background: To further explore the pathogenesis of idiopathic membranous nephropathy (IMN), the technique of gene-sequencing was used to analyze the differentially expressed circRNAs in exosomes from both the serum and urine of patients with IMN, which may lay the foundation for the research of circRNAs as a new class of exosome-based idiopathic membranous nephropathy diagnosis biomarkers.

Methods: Ten patients with idiopathic membranous nephropathy (IMN group) and ten normal controls (NC group) were recruited as experimental subjects in our study. The exosomes were extracted from the collected serum and urine by the ExoQuick Exosome Precipitation Solution and ultracentrifugation. Then, the pure circRNAs were extracted from the exosomes with a series of enzymatic reactions. Afterwards, the significantly differentially expressed circRNAs were chosen by the method of gene-sequencing to analyze the function of corresponding target genes.

Results: Compared with normal controls, the circRNAs were reduced in the exosomes from serum of patients with IMN, which mostly originated from intron gene regions. Meanwhile, a total of 89 circRNAs were significantly differentially expressed, which were also mostly derived from intron gene regions, including 49 up-regulated and 40 down-regulated genes. However, the species were increased in the exosomes from the urine of patients with IMN compared to normal controls, and they mainly originated from exon gene regions. Simultaneously, a total of 60 circRNAs were significantly differentially expressed, which primarily belonged to intron gene regions, including 54 up-regulated and 6 down-regulated regions. Compared with the circRNAs detected from urinary exosomes, a total of 59 circRNAs were significantly differentially expressed in the exosomes from the serum of patients with IMN, which also mostly originated from intron gene regions, including 32 up-regulated and 27 down-regulated regions.

Conclusions: The significant differential and specific expression of circRNAs in the exosomes from the serum and urine of patients with IMN were observed. For example, MUC3A, which originated from chr7:100550808|100551062, could be considered a potential diagnostic biomarker of IMN. Furthermore, these figures suggested that the significantly differentially expressed circRNAs can be used as a reference or supplement in the research of the pathogenesis of IMN.

FR-PO972

Integrity and Expression of Low-Input, Degraded Renal mRNA for Precision Medicine Applications Michael T. Eadon,[2] Tarek M. El-Achkar,[1] Yinghua Cheng,[3] Ken Dunn,[1] Samir V. Parikh,[4] Brad H. Rovin,[5] Seth Winfree,[3] Katherine J. Kelly,[1] Timothy A. Sutton,[3] Pierre C. Dagher.[1] *[1]Indiana University, Indianapolis, IN; [2]Indiana University Division of Nephrology, Indianapolis, IN; [3]Indiana University School of Medicine, Greenwood, IN; [4]Ohio State University Medical Center, Columbus, OH; [5]Ohio State University Wexner Medical Center, Columbus, OH.*

Background: Personalized medicine initiatives may entail the performance of molecular diagnostics on existing pathology samples from biological repositories. Technologies continue to evolve to define molecular signatures from low amounts of highly degraded RNA. We sought to understand the effect of differential tissue preservation and RNA degradation on renal expression using two different transcript expression platforms.

Methods: Kidneys from c57Bl/6 mice were subjected to one of five preservation conditions and RNA integrity was measured: frozen immediately (RIN 7.4 ± 0.2), stored 6 h in Michels solution (6.8 ± 0.6), stored 24 h in Michels solution (6.6 ± 0.3), stored 6 h in BE70 solution (3.3 ± 0.2), or formalin fixed (2.63 ± 0.2). In preparation for laser microdissection, tissue was subjected to immunofluorescence for the frozen (RIN 3.4 ± 0.2 post-stain) and formalin fixed (RIN 2.2 ± 0.1) conditions. Gene expression was measured using RNA sequencing and a microarray.

Results: Both platforms revealed a strong correlation between RNA from fresh frozen samples and highly degraded RNA from frozen stained (RNAseq: R = 0.922, Microarray: 0.964) or stained formalin fixed samples (RNAseq: R = 0.920, Microarray: 0.916). The inter-platform correlation ranged from R of 0.700 to 0.821. As compared to the microarray, both the dynamic range and coefficient of variation for RNAseq expression was larger.

Conclusions: Both the RNA sequencing and microarray platforms appear adequate to measure renal gene expression in highly degraded low-input RNA.

Funding: NIDDK Support

FR-PO973

Home Kidney Screening Device Ragwa Elsayed. *San Jose State University, Daly City, CA.*

Background: Kidney filters blood from wastes. As per USRDS, most CKD patients are between stage 1 to 3 and only 10% aware about their disease. The objective of this project is to design a new technique using mobile App to monitor the creatinine level in blood at home or at screening events and facilitate user at home to send the results to his physician.

Methods: Experiment based on Jaffe's reactions between picric acid and creatinine. Different concentrations of creatinine were prepared in 0.1 M Hcl solution. Picric acid was prepared 1.6% solution in an alkaline 0.75 M NaOH. Test Strip design: PVC or

Opaque plastic sheets (10 cm * 0.5 cm) Absorbable sheets (1 cm * 0.5 cm) immersed in picric alkaline solution for an hour then glued to test strip. 200 ul of creatinine solutions have been applied on test strips Using Matlab to measure creatinine color intensity from a mobile image of test strip

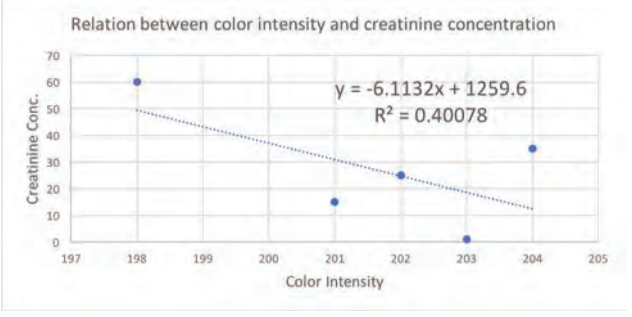
Results: A standard curve is established from results by using Matlab software image 1. A mobile app will be used to detect creatinine level from color intensity of test strip when apply a blood drop. We observed when applying higher creatinine concentration, test strip color become darker image 2

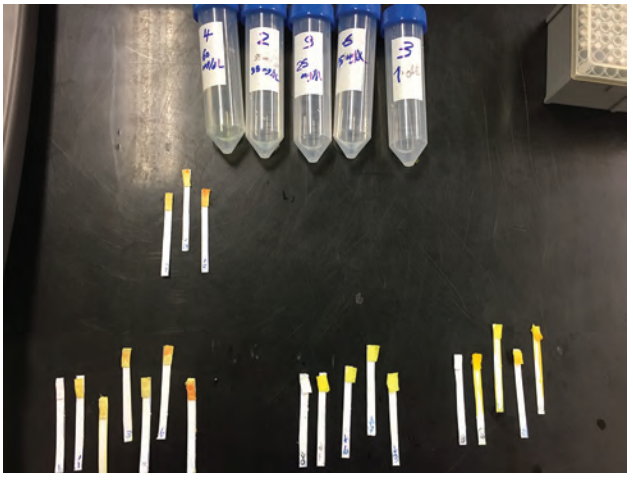
Conclusions: By using the chemical property of picric acid when react with creatinine, a relation is established as a standard curve between creatinine concentration and color intensity. Using the mobile phone cameras, anyone at home can measure creatinine level by taking an image of test strip.

Funding: Other U.S. Government Support, Private Foundation Support

Relation between color intensity and creatinine concentration

	Image 1	Image 2	Image 3	Image 4	Image 5
Red Intensity	204	202	203	204	199
Green Intensity	207	203	204	206	201
Blue Intensity	199	197	198	203	194
Creatinine Concentration	1	15	25	35	60





FR-PO974

Automatic Detection of Global Sclerosis in Pathological Glomerular Images with Deep Neural Networks Eiichiro Uchino,[1] Kei Taneishi,[2] Noriaki Sato,[1] Hideki Yokoi,[1] Yasushi Okuno,[1] Motoko Yanagita.[1] *[1]Kyoto University Graduate School of Medicine, Kyoto, Japan; [2]RIKEN Advanced Institute for Computational Science, Kobe, Japan.*

Background: Renal pathology is essential for diagnosis and treatment planning for patients with renal disease, and the application of digital pathology, which is a recent active field of automated histology analysis, to renal field is an important challenge. In recent literature, several studies have developed algorithm for detecting glomeruli from a whole slide image of kidney, but few studies have focused on detecting pathological features such as global sclerosis from those glomerular images.

Methods: We developed deep convolutional neural network (CNN) models which can automatically classify glomerular images as global sclerosis or not. Total 12422 glomerular images of periodic acid-Schiff (PAS) stain (n=3180), periodic acid methenamine silver (PAM) stain (n=3311), hematoxylin and eosin (HE) stain (n=2979), and Masson's trichrome (MT) or elastica-Masson (EM) stain (n=2952) were cropped from whole slide images of 133 patients who underwent renal biopsy in our hospital in 2013 and 2014, and were manually annotated based on clinical pathology reports. By each staining, CNNs were trained and validated by 5-fold cross validation with five patient groups assigned randomly. We evaluated area under the curve (AUC) of receiver operating characteristic (ROC), sensitivity, and specificity at optimal cut-point estimated from Youden's index.

Results: Out of 12422 glomeruli, 1743 (14.0%) were manually annotated as global sclerosis. For detecting global sclerosis, our CNN models for PAS stain had the best AUC in all staining (AUC, 0.977 ± 0.006 (mean ± SD); sensitivity, 95.8 ± 2.6%; specificity, 92.1 ± 2.3%). The models for the other staining showed similar performances for PAM (AUC, 0.971 ± 0.010; sensitivity, 90.3 ± 2.5%; specificity, 95.9 ± 2.4%), HE (AUC, 0.965 ± 0.010; sensitivity, 87.6 ± 2.3%; specificity, 95.4 ± 1.8%), and, MT or EM (AUC, 0.976 ± 0.010; sensitivity, 91.2 ± 3.2%; specificity, 95.2 ± 4.1%).

Conclusions: Our CNN models achieved good performance in detecting global sclerosis from glomerular images, which suggests that this approach is applicable for detecting other pathological features in future studies.

FR-PO975

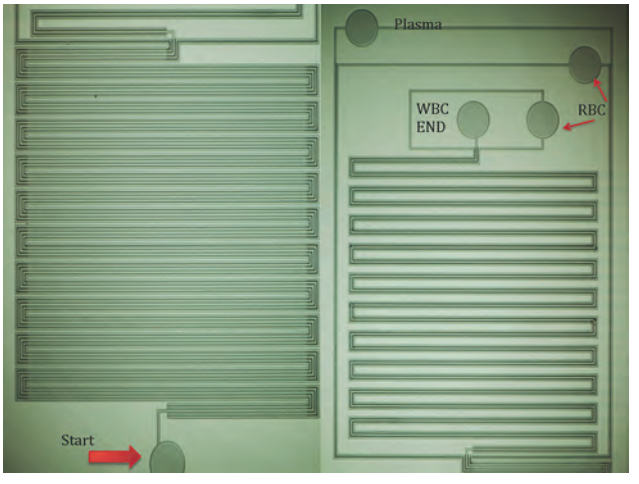
Parallel Cross-Flow Filtration Microfluidic Device for Renal Micro-Environment Emulation Zach Odeh. *Nephrology, First Affiliated Hospital of Dalian Medical University, Dalian, China.*

Background: Whole human blood, a non-Newtonian fluid, can effectively be filtered on a microfluidic device. Past microfluidic design approaches utilized dead-end filtration concepts that lead to clogging since the cells are trapped in the direction of flow. This limitation also precludes the filtration of plasma, an important component to investigate renal inflammation. There is a need for a novel design that can mimic capillary action and fenestrations gaps akin to the renal micro-environment. The primary aim of this study was to design, fabricate, and test a novel microfluidic device for separating whole human blood (plasma, white blood cells, and red blood cells).

Methods: Development of the microfluidic device utilizes photolithography and micro-molding techniques that involve the following basic components: silicon wafer (1 1 1), chrome masks, glass, and polydimethysiloxane (PDMS). Design assumptions called for human blood as the testing fluid. The design utilized a five-row filtration system in the first modular section with varying gap sizes (between pillar edges) from 6.5 microns to 2.5microns. The second modular design included three channels with the main channel flanked by weir micro filtration barriers of consistent gap slits of 3.5 micons.

Results: The combined (pillar and weir) cross-flow design was shown to rapidly separate different categories of blood cells simultaneously based on size-exclusion principles despite spacing anomalies. The pillar filtration segment appears to show gradient changes, especially in the last two filtration tunnels. The other weir filtration segment does not show as drastic a color gradient change.

Conclusions: This microfluidic chip, based on a multi-level parallel cross-flow design, offers enhanced features over prior microfluidic approaches. It effectively addressed dead-end filtration limitations with no visible clogging obstacles. It demonstrates a successful integration of modular micro-feature units (pillar and weir).



Modular Micro-Feature Systems

FR-PO976

Bioengineering an Organotypic Normal and Diseased Kidney Tubule Array Balaji karthick Subramanian,[1,2] Oguzhan Kaya,[1] Jing Zhou.[1] *[1]Medicine - Nephrology, Brigham and Womens Hospital /Harvard Medical School, Boston, MA; [2]Medicine - Nephrology, Beth Israel Deaconess Medical Center, Boston, MA.*

Background: Maintenance of homogenous kidney tubular structures is critical to retain kidney shape and function, and in accordance aberrations in their structures are manifested in disease conditions. Lack of *in vitro* kidney tubule models that are homogeneous in tissue geometry structures and also emulating aberrations in disease conditions have limited the understanding of their pathology and the therapeutics development.

Methods: Homogenous tubular tissue geometry micropatterns were imprinted in different extracellular matrix combinations as an array using a combination of photolithography and soft lithography techniques. Tubular kidney epithelial cells were then cultured in the3D micro-molded extracellular matrix array and were evaluated for

the morphogenic outcomes. Cystic kidney disease emulation was achieved by treatments with cAMP-elevating agents, while for acute kidney injury emulation cisplatin drug treatment was used.

Results: Both mouse and human kidney epithelial cells formed homogeneous tubular structures as defined by the tissue geometry yielding kidney tubular arrays. The tubule features in the array were validated based on the characteristic distributionof actin (f-actin), cilia (acetylated tubulin), tight junction (ZO-1), and Na+K+-ATPasepump. Further, the disease emulations of cystic kidney disease and acute kidney injury were confirmed for tubule to cyst transformation and Kidney injury molecule (Kim-1) expression respectively.

Conclusions: The tubule array yielded organotypic homogenous tubules with *in vivo*-scale dimensions, which can be utilized for assessing nephrotoxicity of drugs and the mechanistic studies of various tubular kidney disease, making it an alternative to animal studies.

FR-PO977

Development of Functional Vasculature in Decellularized Whole Porcine Kidneys with Human Endothelial Cells Pablo D. Cabral,[2,4] Dominique Seetapun,[2] Senthuran Atputhanathan,[2] Jeff Ross,[1] Morgan D. Black.[3] *[1]Miromatrix Medical, Eden Prairie, MN; [2]Miromatrix Medical Inc., Eden Prairie, MN; [3]Miromatrix Medical, Inc., Eden Prairie, MN; [4]Case Western Reserve University, CLEVELAND, OH.*

Background: End stage renal disease (ESRD) represents a major epidemic both in the US and worldwide. Patients with ESRD have two options: kidney transplantation or hemodialysis. Due to the organ donor shortage, only a few patients receive transplants. The alternative, hemodialysis, has a 5-year mortality rate of 35% compared to only 3% for transplantation. With ~500,000 hemodialysis patients in the US, a new therapy is needed. The ultimate solution would be a bioengineered kidney to solve the chronic shortage. A critical first step is the demonstration of a functional vasculature to continuously perfuse blood. We demonstrate that a functional vasculature can be achieved by repopulating decellularized kidneys with human primary cells.

Methods: Whole porcine kidneys were perfusion decellularized without compromising the native microarchitecture of both the vascular and tubular compartments. Human umbilical vein endothelial cells (HUVEC) and primary human epithelial cells (HRE) were perfused into the vascular and tubular compartments respectively. Whole organ culture was performed under continous perfusion and key metabolic parameters were monitored daily to assess cell proliferation and viability. Functional vasculature assessment was performed with blood loops using whole porcine blood to model in-vivo performance.

Results: Cellular engraftment and viability were measured by metabolic parameters including glucose consumption over 3 to 4 weeks (n=12) to achieve the desired level. These data were further corroborated by histological analysis of formalin fixed kidney sections demonstrating the presence of a single layer of engrafted cells on vascular and tubular compartments. Furthermore, cells positive for the endothelial cell marker CD31 were confined to the vascular compartment and cells positive for the epithelial cell marker e-cadherin were confined to the tubular compartment. Vascular functionality was characterized by blood loops and demonstrated long-term continuous perfusion of whole blood compared at physiological pressures compared to non-recellularized kidneys that demonstrated the lack of flow after a few minutes.

Conclusions: These results demonstrate the ability to generate a functional vasculature in recellularized kidney grafts, a critical first step in the engineering of a fully bioengineered kidney.

Funding: Commercial Support - Miromatrix Medical Inc.

FR-PO978

The Role of Endothelial Nitric Oxide Synthase Expression in Arteriovenous Fistula Remodeling and Hemodynamic Adaptation Timmy C. Lee,[1] Daniel Pike,[2] Tatyana Isayeva Waldrop,[1] Lingling Guo,[1] Maheshika S. Somarathna,[1] Yan-Ting Shiu.[2] *[1]University of Alabama at Birmingham, Birmingham, AL; [2]University of Utah, SALT LAKE CITY, UT.*

Background: Endothelial nitric oxide synthase (NOS3), via its role of producing nitric oxide (NO), plays an important role in arteriovenous fistula (AVF) maturation following AVF creation. NOS3 dysfunction may play an important role in AVF development.

Methods: Carotid (side)-jugular (end) AVFs were created in NOS3-/- (knockout), NOS3+/+ (wildtype), and NOS3 overexpression (OE) mice on C57/BL6 background. Serial AVF lumen and hemodynamic changes were characterized using non-contrast MRI-imaging and computation fluid dynamic imaging (Fig. 1). Mice were sacrificed at 21 days for histologic and biochemical studies.

Results: At day 21, NOS3 OE AVFs have large venous lumen at and near the anastomosis, smooth velocity streamlines, low vorticity, as well as relatively uniform and low wall shear stress (WSS), suggesting desired vascular remodeling and restoration of WSS. In contrast, both NOS3+/+ and NOS3-/- AVFs have small lumen, disturbed velocity streamlines, high vorticity, and high venous WSS. AVF vein MMP9 protein expression was reduced at 21 days in NOS3 OE mice compared to NOS3+/+ and NOS3-/- mice (p=0.09). AVF vein average intima/media thickness ratio was significantly lower in NOS3 OE mice compared to NOS3+/+ and NOS3-/- mice ($p<0.0001$) at 21 days. cGMP levels were significantly higher in NOS3 OE AVFs vs NOS3-/- and NOS3+/+ AVFs (p=0.05)

Conclusions: Increased NOS3 expression improves AVF hemodynamics and remodeling and reduces neointimal hyperplasia development. Future interventions that target increasing NOS3 expression and NO delivery may be beneficial to improving AVF development.

Funding: Clinical Revenue Support

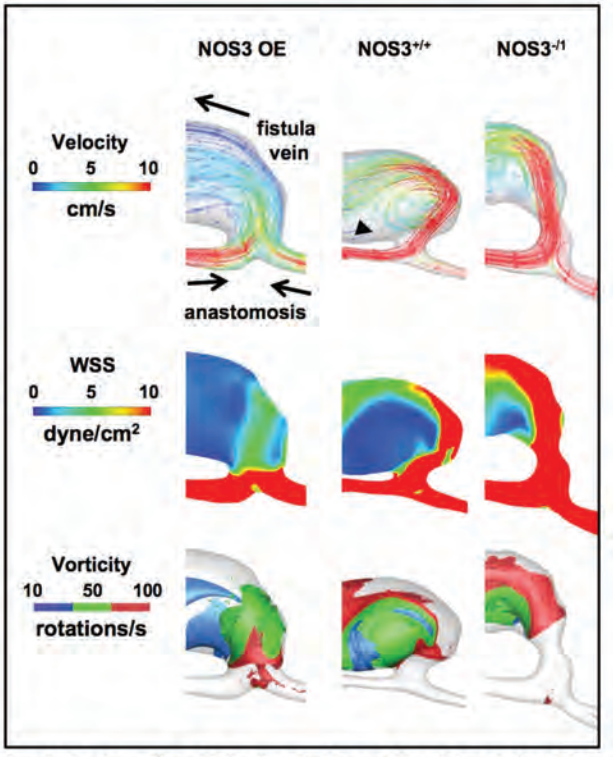


Fig. 1: 21 Day Flow Velocity, WSS and Vorticity Color Maps in Murine AVF. Note the different hemodynamic profiles in NOS3 OE, NOS3$^{+/+}$, and NOS3$^{-/-}$ mice at vein anastomoses and AVF veins. NOS3 OE mice had smoother velocity streamlines and lower WSS and vorticity (good adaptation) when compared to the NOS3$^{+/+}$ and NOS3$^{-/-}$ mice.

FR-PO979

Renal Protection during Cardiopulmonary Bypass (CPB) with a Leukocyte Modulatory Device (L-MOD) H. David Humes,[1] A. Westover,[3] D. Buffington,[3] K. Johnston.[2] *[1]Internal Medicine, University of Michigan Medical School, Ann Arbor, MI; [2]Innovative BioTherapies, Ann Arbor, MI; [3]Innovative BioTherapies, Inc., Ann Arbor, MI.*

Background: Leukocyte activation during cardiopulmonary bypass (CPB) contributes to a systemic inflammatory response that can cause organ injury and dysfunction, including the kidney. The therapeutic value of incorporating an extracorporeal leukocyte modulatory device (L-MOD) during and after CPB was investigated. Assessment of leukocyte mediated organ injury in a pre-clinical animal model was the primary outcome criteria.

Methods: Twenty-two pigs underwent a simulated cardiothoracic surgical procedure with 180 minutes of CPB and 5 hours post-operative observation. Pigs received CPB with no intervention (Group 1, n= 9), 3 hours of L-MOD therapy by incorporation of L-MOD into the CPB circuit (Group 2, n=6) or 8 hours of L-MOD therapy using a femoral veno-venous extracorporeal circuit during and after CPB (Group 3, n=7). Leukocyte counts and activation were serially measured. Hemodynamics, pulmonary parameters and urine output were monitored as indices of organ function. Serum troponin-I and urine neutrophil gelatinase-associated lipocalin (NGAL) served as biomarkers of organ injury for heart and kidney, respectively.

Results: Leukocyte activation at the end of CPB was significantly increased in Groups 1 and 2 but not Group 3. Leukocyte counts, namely neutrophils, significantly increased post-operatively in Groups 1 and 2 but not in Group 3. Systemic vascular resistance was not as reduced post CPB for the L-MOD treated pigs and at 5 hours post CPB, organ injury markers, troponin-I and NGAL, were lowest in Group 3.

Conclusions: 8 hours of L-MOD therapy limited leukocyte activation and the inflammatory response to CPB which resulted in less organ injury and dysfunction, including the kidney. Continuation of L-MOD therapy into the post-operative period was required for therapeutic impact.

Funding: Other NIH Support - HL127830

FR-PO980

A Comparison of Electronic Health Record (EHR) Phenotype Definitions for CKD C. Blake Cameron, John W. Stanifer, Rachel Richesson. *Duke University, Durham, NC.*

Background: Multiple methods for identifying patients with CKD using EHR-based phenotypes have been proposed. Few studies have systematically compared or prospectively validated these phenotype definitions.

Methods: In a rural, community-based healthcare system, we applied five distinct CKD phenotype definitions (A-E) to the EHR. Phenotype A defined CKD as ≥2 eGFR values <60mL/min/1.73m^2 separated by 90-730 days. Phenotype B was the same but also included individuals with albuminuria ≥30mg/g. Phenotypes C and D defined CKD by a single eGFR result <60 and <45 mL/min/1.73m^2 respectively. Phenotype E defined CKD as having ≥2 ambulatory encounters associated with an eligible ICD-9-CM or ICD-10-CM diagnosis code. We evaluated inter-rater agreement between each phenotype pair by calculating Chamberlain's percent positive agreement and Cohen's Kappa statistic.

Results: We identified 59,848 unique adults with at least one ambulatory encounter over a two-year period, of whom 6,620 (11%) were classified as having CKD by any one of the phenotypes. Only 666 (1%) were classified as having CKD by all five phenotypes. Phenotype C classified the most patients as having CKD (n=5,596; 9%), followed by phenotype B (n=3,837; 6%); phenotype A (n=3,268; 5%); phenotype D (n=2,552; 4%) and phenotype E (n=1,615; 3%). Phenotypes A and B showed the greatest agreement (Kappa=0.915), followed by phenotypes A and C (Kappa=0.718) and phenotypes B and C (Kappa=0.693). Phenotype E showed low agreement with any of the phenotypes.

Conclusions: In a rural, community-based healthcare system, several commonly used phenotype definitions showed poor agreement in classifying CKD. Additional studies using external reference standards that include prospective laboratory assessment of kidney function and albuminuria are required in order to validate performance characteristics of CKD phenotypes. Once validated, one or more CKD phenotypes could be promoted as a standard to define similar populations for clinical research and population health management.

Funding: Private Foundation Support

Positive overlap, percent positive agreement (PPA) and Kappa statistic for phenotype pairs

	Phenotype A (n=3,268)	Phenotype B (n=3,837)	Phenotype C (n=5,596)	Phenotype D (n=2,552)
Phenotype B (n=3,837)	n=3,268 PPA=85.2% Kappa=0.915			
Phenotype C (n=5,596)	n=3,268 PPA=58.4% Kappa=0.718	n=3,379 PPA=55.8% Kappa=0.693		
Phenotype D (n=2,552)	n=1,934 PPA=49.8% Kappa=0.648	n=1,967 PPA=44.5% Kappa=0.595	n=2,552 PPA=45.6% Kappa=0.603	
Phenotype E (n=1,615)	n=788 PPA=19.2% Kappa=0.297	n=848 PPA=18.4% Kappa=0.284	n=1,010 PPA=16.3% Kappa=0.249	n=801 PPA=23.8% Kappa=0.363

FR-PO981

VA MobileKidney App – A Mobile Educational and Clinical Engagement Tool for Veterans with CKD and Their Providers R. Brooks Robey,[1,2] Susan T. Crowley,[3,4] Devasmita Choudhury.[5,6] *[1]White River Junction VA Medical Center, White River Junction, VT; [2]Geisel School of Medicine at Dartmouth, Hanover, NH; [3]VA Connecticut Health Care System, West Haven, CT; [4]Yale School of Medicine, New Haven, CT; [5]Salem VA Medical Center, Salem, VA; [6]Virginia Tech Carilion School of Medicine, Roanoke, VA.*

Background: Patient health illiteracy and lack of accurate, reliable, and efficient mechanisms for evaluating self-care between clinic visits represent major barriers to optimal CKD management that are potentially amenable to digital telehealth solutions.

Methods: To address these barriers, we designed a secure digital application with 1) broad mobile device compatibility, 2) real time access to the CKD education and information resources housed in the cloud-based virtual VA *e*Kidney Clinic (*http://ckd.vacloud.us/*), and 3) novel electronic self-care journaling capabilities viewable remotely via a VA provider-facing interface.

Results: In addition to providing unrestricted mobile access to pertinent healthcare information and educational resources, the VA Mobile*e*Kidney app will allow Veterans with CKD to enter, annotate, and track self-gathered clinical information on personal mobile devices and securely share these data with their providers for asynchronous review, curation, and direct incorporation into the electronic health record (EHR). Graphical display of selected serial measures (e.g. weight, blood pressure, heart rate, and glucometer readings) permits both visual identification and monitoring of trends between visits. The corresponding ability to organize, curate, and import this information into the EHR in tabular form will also reduce associated transcription burdens and errors. In addition, free text annotations provide a vehicle for recording associated interval health questions and observations – and for recording special provider instructions during clinic visits.

Conclusions: Mobile*e*Kidney is scheduled for field testing and launch by Kidney Week 2017. It will provide accessible education resources to Veterans with CKD and their providers, as well as a mobile digital platform for sharing detailed self-gathered interval health information for joint review at regularly scheduled clinic visits. Free text journaling capabilities also afford flexibility to tailor application use to specific clinical needs. This novel digital tool for interval healthcare data acquisition, delivery, and review also provides a structured replacement for traditional hardcopy health diaries and promises to enhance patient buy-in and engagement in self-monitoring activities, as well as improve patient-provider communication, documentation, and coordination of care.

Funding: Veterans Affairs Support

FR-PO982

Engineering Design of Robust Ultrafiltration Profiles in Hemodialysis Rammah M. Abohtyra,[2] Christopher V. Hollot,[1] Joseph Horowitz,[3] Yossi Chait.[3] *[1]Department of Electrical and Computer Enginering, University of Massachusetts Amherst, Amherst, MA; [2]UMass, Florence, MA; [3]University of Massachusetts, Amherst, MA.*

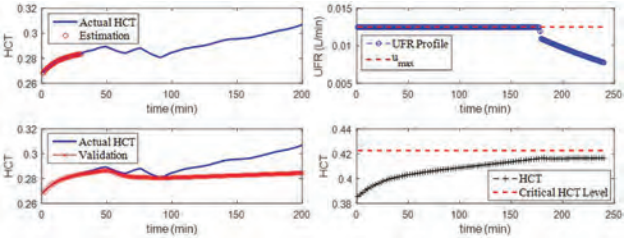
Background: Fluid removal during hemodialysis (HD) by ultrafiltration can lead to intradialytic hypotension, which is associated with an increase in morbidity and mortality. We design a robust, individualized ultrafiltration rate (UFR) profile to achieve a target volume removal under constraints on maximal UFR and maximal hematocrit (HCT) levels.

Methods: The fluid volume dynamics during HD was described by a validated nonlinear model comprising intravascular and interstitial pools, microvascular refilling/filtration, and lymphatic flow. Model parameters, red blood cells volume (V_{rbc}), plasma protein mass (m_p), and filtration coefficient (K_f), were estimated using 30 minutes of UFR and HCT clinical data and validated using remaining data. Anticipated parameter changes during HD and estimation errors were accounted for by allowing parameter uncertainty ranges of +/- 5%. The profile was designed using an optimization algorithm to remove 2.8 L in 4 hrs, with UFR not exceeding 10 ml/hr/kg, and HCT not exceeding 110% of initial HCT, and to guarantee performance over the entire range of parameter uncertainty.

Results: Model parameters (V_{rbc} =2.24 L, K_f =0.006 L/min/mmHg, and m_p=179.58 gr) of a 75 kg patient were estimated based on the initial 30 minutes of the HD session (Figure, top left) and validated over an additional 170 minutes of the session (Figure, bottom left). Simulation of the designed UFR profile (Figure, top right) over the range of model parameter uncertainty confirmed that all specifications were achieved (worst case HCT shown in Figure, bottom right); the worst case of HCT is simulated for a particular set of parameters within the parameter uncertainty range of the model.

Conclusions: The divergence of the validated response later in the HD period demonstrates that the underlying patient's response can deviate from model prediction due to, for example, autonomous adaption not captured in the model. This motivated the use of robust design of UFR profiles. Our UFR profile is designed to satisfy HCT and UFR constraints, and to guarantee that performance criteria are met over the entire model parameter uncertainty range.

Funding: NIDDK Support



FR-PO983

Machine Learning Model versus SOFA, APSIII, and OASIS in Prediction of Renal Replacement Therapy (RRT) within First 8 Days after ICU Admission in MIMIC-III (Medical Information Mart for Intensive Care III) Lukasz Kiljanek, Sandeep Aggarwal. *Drexel University College of Medicine, Philadelphia, PA.*

Background: There is a paucity of prediction tools for new onset RRT in ICU population. Computer based Machine learning models are being employed to create risk prediction tools using large databases. In this study we attempted the use of Gradient Boosting Machine (GBM) - Machine learning algorithm to create a RRT prediction tool using MIMIC 3 database

Methods: GBM algorithm from H2O.ai R project library was used to model 2008-2012 MIMIC 3 database. We defined 750 clinical and laboratory variables from first 24 hours after ICU admission. Patients with history of dialysis or RRT related events charted within first 24 hours of ICU stay were excluded. 17045 patients were divided 30 times randomly into training (90% of patients) and testing (10% of patients) datasets. **RRT within 8 days of ICU stay was defined as any RRT related event charted between 24 hours and 8 days mark**. Incidence of RRT was 27.8 [95% CI 25.9-29.6] for 30 testing sets. Each training dataset was used to build GBM for predicting need for RRT, which was validated on testing dataset. Area under curve (AUC) of receiver-operator characteristics curve (ROC) was recorded. For each of 30 testing datasets, AUC for prediction of RRT by SOFA, OASIS and APS III was also recorded.

Results: For 30 testing datasets, AUC of ROC for; GBM was 0.87 [95% CI 0.85-0.89], and SOFA was 0.83 [95% CI 0.82-0.84], APSIII was 0.82 [95% CI 0.81-0.83] and OASIS was 0.71 [95% CI 0.70 0.72], in predicting RRT within 8 days. GBM vs SOFA, GBM vs APSIII and GBM vs OASIS revealed statistically significant higher AUC of GBM (p<0.05 Wilcoxon signed-rank test). Most important predictors**,** seen within first 24 hours of ICU stay, from 1 of 30 runs, with their scaled importances were : last serum creatinine recorded (1), maximal serum creatinine recorded (0.94)

Conclusions: In our analysis GBM model showed statistically superior accuracy compared to conventional ICU severity scores to predict patients who survive until and require RRT after ICU admission. Additionally, we discovered applicability of conventional ICU severity scores to predict RRT in this setting. This can be employed to EMRs in hospitals for as an RRT event prediction too, but more research is warranted to assess clinical aplicability and robustness of our methods.

FR-PO984

Engineering-Based Individualized Anemia Management in Hemodialysis Patients Biro Alexander,[6] Sara Blumberg Benyamini,[7] Michael J. Germain,[2] Joseph Horowitz,[5] Zvi Barnea,[4] Relu Cernes,[3] Yossi Chait,[5] Eliezer Rachmilewitz,[7] Ze'ev Katzir.[1] *[1]Institute of Nephrology, Holon, Israel; [2]Renal and Transplant Assoc of New England, Hampden, MA; [3]WOLFSON MEDICAL CENTER, HOLON, ISRAEL, HOLON, Israel; [4]Wolfson Medical Center, Holon, Israel, Holon, Israel; [5]University of Massachusetts, Amherst, MA; [6]WOLFSON MEDICAL CENTER, HOLON, Israel; [7]Wolfson Medical Center, Holon, Israel.*

Background: Management of erythropoietin stimulating agents and parenteral iron in hemodialysis (HD) patients is performed according to protocols derived from population response data. This pilot study examined whether individualized dosing can reduce hemoglobin (Hb) variability and increase the proportion of Hb levels within range compared with standard protocol results, while transferrin saturation (TSAT) and Ferritin levels would remain similar, and that the use of medications could be reduced.

Methods: We enrolled 25 maintenance HD patients treated using a bi-weekly titration and dosing protocol. We switched into a computerized, individualized protocol based on feedback principles and a mathematical model [1]; The ESA protocol has been validated in prior studies while the IV Iron protocol was newly derived. In the individualized protocol dosing schedule was switched to weekly. Target and range Hb were 11.5 and (11,12) g/dl, respectively. Results are reported from the first 9 months of the year-long, crossover study with 3-month washout period; Hb variability measure was the standard deviation (sd). Baseline refers to the 6-month period prior to the study, and Study refers to the most recent 6-month. For normal data we used the t-test to compare means and Pitman's test for sds; medians of nonnormal data were compared by the signed rank test; and McNemar's test was used for binary data. and statistical significance is defined as P-value < 0.05.

Results: (Table)

Conclusions: The individualized anemia protocol has improved %Hb in range and reduced Hb variability compared with standard protocol, while Aranesp and Venofer doses were reduced. However, TSAT and Ferritin levels decreased suggesting that our Iron IV algorithm may require modification. 1. Chait Y, Horowitz J, Nichols B, Shrestha RP, Hollot CV, Germain MJ. Control-relevant erythropoiesis modeling in end-stage renal disease. IEEE Trans Biomed Eng. 2014

Funding: NIDDK Support

Parameter	Baseline	Study	P-value
Hb, mean (g/dL)	11.6	11.3	0.113
Hb, sd (g/dl)	0.95	0.53	0.003
Hb in range (%)	50	68	0.124
TSAT, mean (sd)	28.9 (7.5)	22.6 (5.7)	<0.0001
Ferritin, median [IQR] (ng/ml)	504 [405,725]	467 [310,638]	0.024
Aranesp, median [IQR] (mg/month)	184 [108,267]	115 [85,255]	0.027
Venofer, median [IQR] (mg/month)	200 [100,317]	154 [75,192]	0.062

FR-PO985

Sodium MRI Identifies Differences of Sodium Concentration with Age, Gender, and Race in Muscle and Skin of Healthy Subjects from the US Jonathan Dyke,[3] Anna Meyring-Wosten,[1] Yize Zhao,[3] Stephan Thijssen,[1] Peter Linz,[2] Peter Kotanko.[1] *[1]Renal Research Institute, New York, NY; [2]University Hospital Erlangen, Erlangen, Germany; [3]Weill Cornell Medical College, NY, NY.*

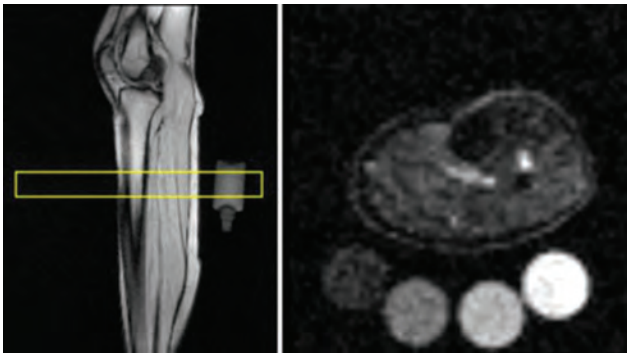
Background: Sodium (Na+) balance is important in managing hemodialysis patients; however, its assessment is difficult and incomplete. Experimental studies show that Na+ is stored without commensurate water accumulation in muscle and skin and may exceed levels measured in the serum. Our study implemented quantitative ^{23}Na MRI imaging of the calf muscle and skin of healthy subjects compared with ex-vivo reference standards. Contributions from age, gender and race were examined.

Methods: A total of 30 subjects were enrolled for the study [(15M/15F), 46.4±14.8 yrs, (10 White/20 African-American)]. Studies were performed on a 3.0 Tesla Siemens MRI using a ^{23}Na coil (Helmut Stark;Germany)[Fig 1]. Scan-rescan reproducibility was assessed the same day and 1 week later for a total of 4 time points/subject. Regions of interest were defined in the skin and following muscles: lateral gastrocnemius (LGM), medial gastrocnemius (MGM), soleus, tibialis anterior and peroneus. A mixed effects model was used based on repeated measures to determine the marginal multivariate effects of age, gender and race versus sodium MRI concentrations. A Bland-Altman plot assessed scan-rescan variability with the smallest real difference (SRD) calculated as 2.77*SEM.

Results: The Bland-Altman plots indicated high agreement between runs in all regions. The SRD was 9.7% and 4.1% within the same day and 10.9% and 12.2% comparing runs a week apart. Sodium increased in all muscles and skin with age. An association in muscle sodium was seen in the LGM (p=0.03), anterior (p=0.04) and peroneus (p=0.01) muscles with gender. No significant association was seen between sodium levels and race.

Conclusions: Tissue Na+ content was confirmed to increase with age in both muscle and skin of healthy controls. Differences in muscle sodium levels were also found with gender but not race. Reproducibility of ^{23}Na MRI in the muscle and skin resulted in an SRD that shows promise to assess serial changes in patients with renal insufficiency.

Funding: Private Foundation Support



FR-PO986

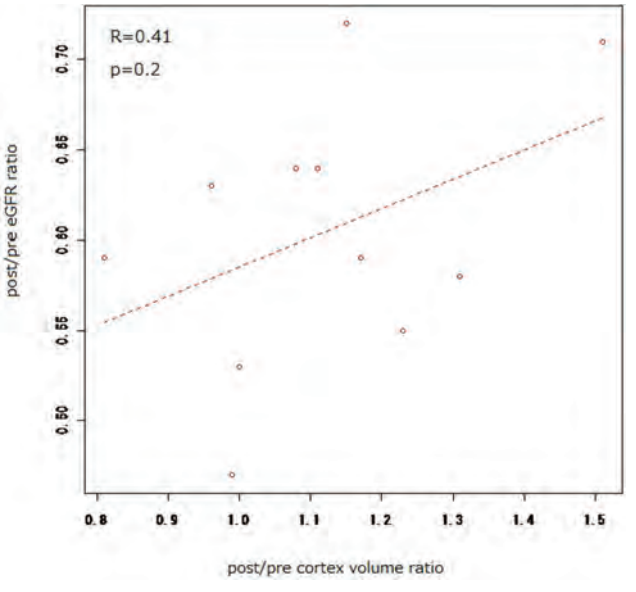
Computational Volume-Analysis of Compensatory Hypertrophy of the Kidney after Contralateral Nephrectomy Jun Nagayma. *Urology, Japanese Red Cross Nagoya First Hospital, Nagoya, Japan.*

Background: Kidney volume usually increases after contralateral nephrectomy according to the preoperative disease-affected kidney function. We preliminarily assessed post-nephrectomy-parenchymal volume divided into two regions (cortex and medulla) to examine compensatory hypertrophy in each using computational volume analyzer on new computational imaging technologies.

Methods: The arterial-phased enhanced imaging data (DICOM formatted) of 11 patients (age ranged between 51 and 86) were obtained from the institutional database. Nephrectomy was underwent in all patients in which 7 renal cell carcinoma, 3 pelvic and ureteral cancer and 1 pyonephrosis were included. Pre- and postoperative (after completion of compensatory hypertrophy) parenchymal volumes were calculated using Synapse Vincent, Fujifilm and compared regional increasing ratio in each area (total parenchyma, cortex and medulla).

Results: Mean preoperative volume of total kidney, cortex and medulla were 181.95 (31.38) ml, 112.53 (25.57) ml and 67.40 (16.85) ml and mean postoperative one were 200.81 (41.65) ml, 126.66 (34.94) ml and 74.15 (16.81) ml, respectively. Cortex volume increases significantly comparing to the preoperative status (p=0.04); however, medulla volume and cortex-medulla volume ratio did not change significantly. Body mass index, gender and preoperative estimated glomerular filtration ratio (eGFR) did not affect the cortex hypertrophy. When comparing the cortex increasing ratio to the change in eGFR, cortex hypertrophy indicated fewer decline in eGFR (fig: p=0.2, R=0.41).

Conclusions: Within the small preliminary experience, computational volume-analysis indicated kidney volume increase after nephrectomy in the cortex region superiority to the medulla. Cortex hypertrophy might correlate with better preservation of renal function in eGFR.



FR-PO987

Contrast Enhanced Ultrasound (CEUS): A Novel Marker of Kidney Disease Mona Shaban,[3] Emily H. Chang,[2] Anush Sridharan,[4] Paul Dayton.[1] *[1]UNC Chapel Hill and NC State University Raleigh, Chapel Hill, NC; [2]UNC Kidney Center, Chapel Hill, NC; [3]Nephrology, University of North Carolina at Chapel Hill, Chapel Hill, NC; [4]University of North Carolina, Chapel Hill, NC.*

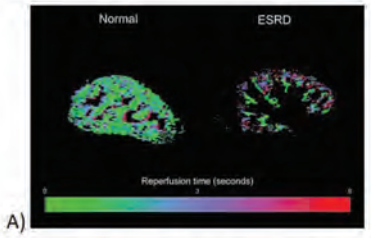
Background: The number of patients with chronic kidney disease (CKD) is on the rise and non-invasive methods of detecting early stages of kidney insufficiency are limited. Rise in creatinine often lags behind loss of kidney function and current ultrasound technology to evaluate severity of CKD hinges on kidney size and echogenicity, which is a subjective marker. Contrast enhanced ultrasound (CEUS) provides qualitative and quantitative measurements of perfusion, which may lead to earlier diagnosis of CKD and provide a better marker of kidney disease progression.

Methods: Patients with various stages of CKD were subjected to CEUS of the kidney. Contrast agent (Definity) was infused at a constant rate based on BMI. High mechanical index flash perfusion imaging was captured. Baseline serum creatinine and urinalysis was collected. Time-intensity curves (TICs) were generated for regions of interest (ROI) from the kidney parenchyma, as well as maximum intensity projections and reperfusion maps. TICs are used to generate a wash-in rate, area under the curve, and time-to-peak intensity.

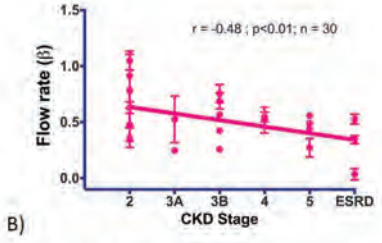
Results: A total of 30 patients with CKD and 3 healthy controls participated in this study. We have found that the enhancement of kidney parenchyma was markedly reduced in patients with lower glomerular filtration rate (GFR) (image 1A). Additionally, we have demonstrated a linear inverse correlation between reperfusion rate and stage of CKD (image 1B). These values will be compared to multiple metrics including GFR and proteinuria in hopes of establishing a novel technique that detects degree of CKD, particularly early stages.

Conclusions: CEUS is a novel, non-invasive imaging modality measuring kidney perfusion, which may be an earlier marker of kidney injury. The generation of wash-in rate, area under the curve, and time-to-peak intensity values will lead to quantitative measurements of kidney function. We are currently working to determine the diagnostic accuracy of these metrics.

Figure 1



Reperfusion maps of renal parenchyma comparing healthy volunteer (left) to ESRD patient (right)



The rate of kidney perfusion as measured by CEUS inversely correlates with stage of CKD

FR-PO988

Effect of Hemodialysis on T2 Relaxation Times in Body Tissues Kristin M. Corapi,[2] Lina A. Colucci,[4] Xavier F. Parada,[2] Herbert Y. Lin,[3] Michael J. Cima.[1] *[1]MIT, Cambridge, MA; [2]Massachusetts General Hospital, Boston, MA; [3]Massachusetts General Hospital/Harvard Medical School, Boston, MA; [4]Massachusetts Institute of Technology, Cambridge, MA.*

Background: Quantitative magnetic resonance (qMRI) can inform about the water content of different tissues. In this study we performed qMRI of the calf, pre and post-HD, to detect fluid changes in muscle and subcutaneous (SC) tissues.

Methods: Adult, male HD patients and healthy controls were enrolled. HD patients underwent qMRI before and after HD while controls underwent qMRI before and after 4 hours of bedrest. MRI scans were done on a 1.5T Siemens MRI Scanner using a knee coil. Quantitative T2 relaxation maps of the upper calf were generated using a spin echo sequences with 32 echoes, TR 3,300ms, TE 8ms, and 4 slices of 5mm thickness. Regions of interest (ROIs) enclosing SC tissue and muscle were manually drawn. Histograms of the T2 relaxation values in those ROIs were generated from the pre and post scans of all participants. The mean, median, and standard deviation of the T2 relaxation time distributions were calculated.

Results: Demographics are shown in table 1. HD patients have longer T2 relaxation times in both the muscle and SC tissue (figure 1a and 1b). We also observed a statistically significant (p=0.01) change in the T2 relaxation time for muscle, but not SC tissue (p=0.45), after treatment with hemodialysis (figure 1c and 1d).

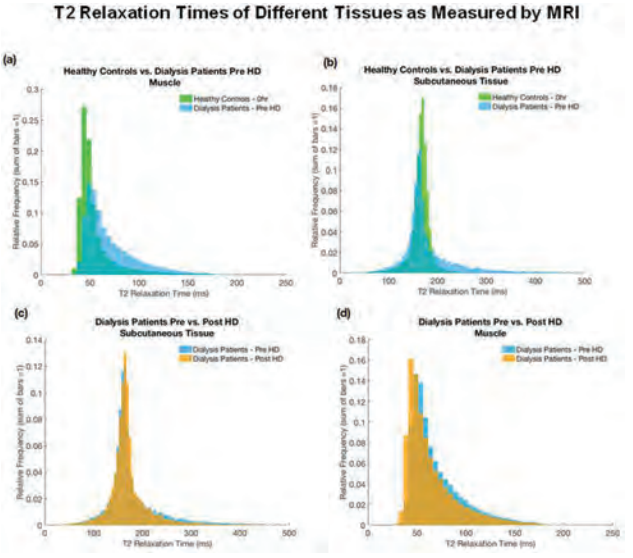
Conclusions: Our results suggest that there is a larger change in relaxation time in muscle than in SC tissue during hemodialysis. This suggests more water movement from the muscle compartment than the SC tissue. Devices to better understand the kinetics of fluid shifts during HD may help alter prescriptions and mitigate symptoms.

Funding: Private Foundation Support

Demographics of participants

	HD patients (n=4)	Health Controls (n=5)
Age (years)	56.8 (9.9)	55.2 (5.9)
Weight (kg)	84.7 (21.1)	76.4 (14.5)
BMI (kg/m2)	29.1 (7.0)	25.9 (5.3)
Fluid removal (mL)	2725 (1041)	NA

data presented as mean (SD)



FR-PO989

Portable Magnetic Resonance Sensor to Detect Volume Changes Lina A. Colucci,[4] Kristin M. Corapi,[2] Xavier F. Parada,[2] Herbert Y. Lin,[3] Michael J. Cima.[1] *[1]MIT, Cambridge, MA; [2]Massachusetts General Hospital, Boston, MA; [3]Massachusetts General Hospital/Harvard Medical School, Boston, MA; [4]Massachusetts Institute of Technology, Cambridge, MA.*

Background: Magnetic resonance technology provides information about the quantity, volume, and motion of water. In this study, we used portable, non-invasive MR sensors to monitor water movement in healthy controls and hemodialysis (HD) patients.

Methods: Adult, male HD patients and controls were enrolled. A custom, single-sided MR sensor developed by the Cima Lab at MIT was used to collect data from the upper calf of HD patients before and after dialysis. Controls had data collected before and after 4 hours of bedrest. The MR sensor collected T2 relaxation time measurements of a cubic centimeter voxel that included subcutaneous tissue and muscle. The T2 relaxation time measurements were analyzed with an inverse Laplace transformation to generate a relaxogram. The individual relaxograms were averaged together in each group.

Results: Demographics are shown in table 1. Free fluids are associated with long T2 relaxation times whereas bound hydrogen in connective tissues are associated with short T2 relaxation times. We observe that controls have nearly identical relaxograms at 0 and 4 hrs. Dialysis patients before treatment display an added peak in their relaxogram at higher relaxation times, representing excess free fluid. We demonstrate that this peak shifts to the left after dialysis and that the relaxogram of the HD patients becomes comparable to controls (Figure 1a-d).

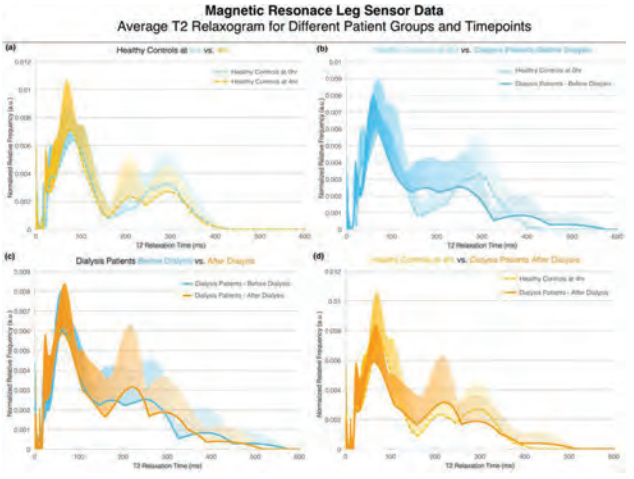
Conclusions: Portable MR sensors may quantify fluid overload in HD patients non-invasively. Further study is necessary to understand the sensitivity of these sensors to fluid shifts during HD and develop an absolute scale that relates relaxation time measurements to fluid overload.

Funding: Private Foundation Support

Demographics of Participants

	HD patients (n=4)	Healthy Controls (n=5)
Age (yrs)	56.8 (9.9)	55.2 (5.9)
Weight (kg)	84.7 (21.1)	76.4 (14.5)
BMI (kg/m2)	29.1 (7.0)	25.9 (5.3)
Fluid removal (mL)	2725 (1041)	NA

data presented as mean (SD)



FR-PO990

Evaluation of the Utility of [18F]DiFA as a Novel Kidney Hypoxia Imaging Tracer Norihito Nakata,[1] Masato Kiriu,[1] Yuki Okumura,[1] Hiroki Matsumoto,[1] Yuji Kuge.[2] *[1]Nihon Medi-Physics Co., Ltd., Sodegaura, Japan; [2]Hokkaido University, Sapporo, Japan.*

Background: It is reported that hypoxia is important as a final common pathway in which chronic kidney disease progresses to end-stage renal failure. Therefore, evaluation of hypoxic condition in the kidney is considered to be useful as a surrogate marker of drug treatment. However, it is difficult to evaluate the hypoxic condition in the kidney with the current in vitro diagnosis. We have investigated the basic properties of a new intratumoral hypoxic imaging agent 1- (2,2-Dihydroxymethyl-3- [^{18}F] Fluoropropyl) Azomycin ([^{18}F] DiFA) and have already reported its usefulness. In this study, we investigated whether [^{18}F]DiFA can evaluate the hypoxic condition in the kidney using a drug-induced renal impairment model. Furthermore, comparison with existing hypoxic imaging tracer, [^{18}F] FMISO, was also conducted.

Methods: [^{18}F]DiFA or [^{18}F]FMISO was administered to adriamycin-induced renal injury model rats and a PET imaging experiment was performed. Autoradiography was performed using [^{18}F]DiFA[S1] and compared with the results of immunohistochemistry using HIF-1α as a hypoxic marker.

Results: As a result of PET imaging of [^{18}F]DiFA, the uptake in the kidney cortex was observed at 80 minutes after administration, and an image visualized with high contrast was presented hypoxia of the renal cortex portion (Figure.1). These analysis results were shown in the following table. Since the localization of [^{18}F]DiFA in kidney and localization of HIF-1α were in good agreement, it was confirmed that [^{18}F]DiFA selectively accumulated in the hypoxic region in the kidney.

Conclusions: These results suggested that [^{18}F]DiFA may be useful as a hypoxia imaging tracer in the kidney compared to [^{18}F]FMISO.

Funding: Commercial Support - Nihon Medi-Physics Co., Ltd.

		[^{18}F]DIFA		[^{18}F]FMISO	
		model group	vehicle group	model group	vehicle group
SUVmax	右	5.17 ± 0.70**	1.42 ± 0.43	2.08 ± 0.21*	1.68 ± 0.14
	左	5.25 ± 0.55**	1.37 ± 0.28	1.97 ± 0.15*	1.74 ± 0.08
kidney-to-normal tissue ratio	右	11.33 ± 1.57**	3.77 ± 0.66	2.22 ± 0.10*	1.89 ± 0.13
	左	11.59 ± 1.88**	3.69 ± 0.37	2.11 ± 0.14	1.95 ± 0.05

(average ± SD), *p<0.05 (model group vs vehicle group), *p<0.001 ([^{18}F] DIFA vs [^{18}F]FMISO in model group), n = 4, student's t-test

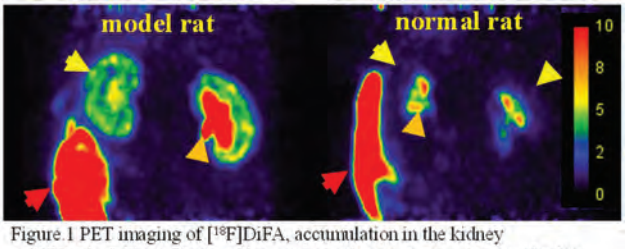


Figure.1 PET imaging of [^{18}F]DiFA, accumulation in the kidney
SUV scale: 0-10, p.i. 80 min, yellow arrow: renal cortex, orange arrow: renal pelvis
red arrow: intestinal tract

FR-PO991

Mesoscale Nanoparticles Selectively and Safely Target Renal Proximal Tubules Ryan M. Williams,[1] Janki Shah,[1] Xi Chen,[2,1] Edgar A. Jaimes,[1,2] Daniel A. Heller.[1,2] *[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Weill Cornell Medical College, New York, NY.*

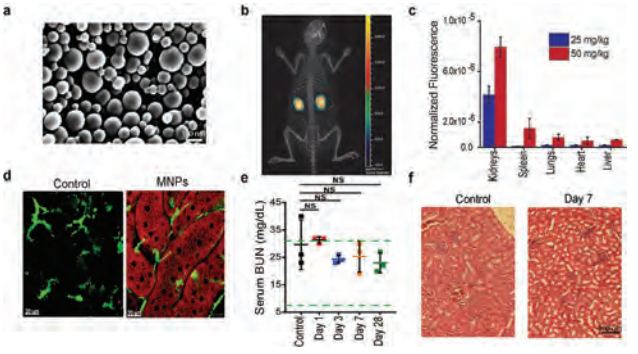
Background: Acute kidney injury accounts for 1% of hospital admissions in the US and over 20 million US adults (~11%) have chronic kidney disease. To address this problem, we developed mesoscale nanoparticles (MNPs) to selectively deliver therapies to the renal proximal tubules.

Methods: We synthesized MNPs from a biocompatible polymer (PLGA-PEG) to encapsulate a fluorescent dye for biodistribution and toxicology studies. Particles exhibited a size of approximately 400 nm and a negative surface charge. In vivo fluorescence imaging of mice determined the extent of renal localization via varying administration routes and doses. We used intravital and ex vivo fluorescence confocal microscopy to determine tissue-level distribution of MNPs. Finally, we performed toxicology experiments in mice via histology, blood counts, and renal biochemical panels to ascertain the safety of the particles up to one month in mice.

Results: We found that via intravenous administration, MNPs selectively localize to the kidneys up to 25-fold more than any other organ, uniquely selective among drug carrier systems. Within the kidneys, the localization was primarily to the proximal tubular epithelial cells, which is also novel to this system. Further, we found that these particles degrade and release their payload over weeks while they cause no renal or systemic toxicity.

Conclusions: Together, these results portend the pre-clinical development of therapeutic nanoparticles that are highly selective, safe, and provide long-term drug release with a single intravenous dose to treat renal diseases such as AKI and CKD.

Funding: Other NIH Support - DP2-HD075698; P30 CA008748, Private Foundation Support



a) Electron micrograph of MNPs. b) MNP localization to the kidneys. c) Relative renal MNP localization with varying IV doses. d) Tubular localization of MNPs (green is macrophages, red is MNPs). e) Serum BUN of mice treated with MNPs or control. f) Histology of kidneys in control or mice treated with MNPs.

FR-PO992

3-D Kidney-on-Chip Platform for Quantitative Screening of Podocyte Structural Integrity Smiti Bhattacharya,[2,5] Amit Ron,[1] Rhodora C. Calizo,[3] Robert Wiener,[3] John C. He,[4] Ravi Iyengar,[3] James C. Hone,[2] Evren U. Azeloglu.[3] *[1]Columbia University, New York, NY; [2]Columbia University, New York, NY; [3]Icahn School of Medicine at Mount Sinai, New York, NY; [4]Mount Sinai School of Medicine, New York, NY; [5]Department of Pharmacological Sciences, Ichan School Of Medicine at Mount Sinai, New York, NY.*

Background: Podocytes have an intricate *in vivo* morphology that is critical for their physiological function. Under disease conditions or upon isolation and culture, podocytes dedifferentiate and lose their specialized morphology, which prevents the use of primary or immortalized podocyte lines as translatable *in vitro* models of chronic kidney disease. In order to systematically study podocyte mechanobiology and drug response, we developed an *in vitro* culture system that utilizes microfabricated 3-D biochips to mechanically induce formation of fine peripheral processes in podocytes.

Methods: We microfabricated 3-D biochips using photolithography. We developed biochips of varying size formats from standard 96-well plates to 25-mm coverslips. Immortalized human podocytes were plated on 3-D biochips and differentiated for five days at 37 degrees Centigrade. Transcriptomic expression of differentiation markers was quantified using RT-PCR. Spatial localization and protein expression were quantified using immunofluorescence. Spatial biomechanics were quantified using atomic force microscope elastography.

Results: Podocytes in 3-D biochips displayed significant upregulation of a wide range of genes associated with the differentiated phenotype. The peripheral processes were selectively enriched for slit diaphragm components nephrin, podocin and neph1 as well as crosslinked actin bundles. Micropatterned podocytes exhibited heterogeneous biomechanical properties with significantly increased elastic modulus in peripheral processes. This spatial phenotype was lost when cells were treated with known nephrotoxic drugs or inhibitors of cytoskeletal integrity. When we looked at phenotypic signatures of protein localization, focal adhesion maturation and cytoskeletal integrity,

podocytes in biochips showed reduced cell-to-cell variability and high reproducibility compared to those on unpatterned glass surfaces.

Conclusions: We developed a 3-D kidney-on-chip system that provides a quantitative, high-throughput *in vitro* platform for studying podocyte morphology, biomechanics and drug response with high reproducibility.

Funding: NIDDK Support, Private Foundation Support

FR-PO993

Biomimetic Microenvironment Promotes In Vivo-Like Phenotype of Conditionally Immortalized Podocytes Matthew Ishahak, Ellery Jones, Alessia Fornoni, Ashutosh Agarwal. *University of Miami, Miami, FL.*

Background: Microenvironmental cues are integral in providing signals that modulate podocyte development and function. However, standard culture conditions fail to recapitulate the chemical, physical, and architectural cues presented by the glomerular basement membrane (GBM). We report the effect of an engineered GBM-mimic hydrogel on conditionally immortalized human podocyte cultures.

Methods: A hydrogel was developed through the enzymatic crosslinking of denatured collagen to serve as a GBM-mimic. 3D grooves were micromolded into the surface of the biomimetic hydrogel. Mechanical properties of the GBM-mimic hydrogel were characterized using a rheometer fitted with a metal parallel plate in oscillation mode. Conditionally immortalized human podocytes were cultured on various substrates in permissive conditions. Once cells reached ~90% confluence, they were moved to non-permissive conditions and cultured for 14 days to allow for differentiation. Phenotypic features were assessed by fluorescent imaging and scanning electron microscopy (SEM).

Results: A GBM-mimic hydrogel that recapitulates the protein composition, mechanical properties, and 3D surface topography of the GBM was successfully fabricated. The stiffness of the hydrogel (E=5.43±0.69 kPa) was much closer to the physiological stiffness of the glomerulus than that of other cell culture substrates (Fig 1A). SEM revealed the formation of processes branching from the main cell body of podocytes grown on the GBM-mimic hydrogels (Fig 1B).

Conclusions: These results demonstrate that microenvironmental cues induce in-vivo like podocyte morphology. Current studies are focused on incorporating additional GBM components (e.g. laminin) and dynamic physiological phenomenon (e.g. fluid flow, pressure differential, and protein gradient). Ultimately, an integrated platform that maintains and measures long term glomerular filtration will be developed to serve as a powerful addition to the toolkit for studying kidney disease and developing therapeutics.

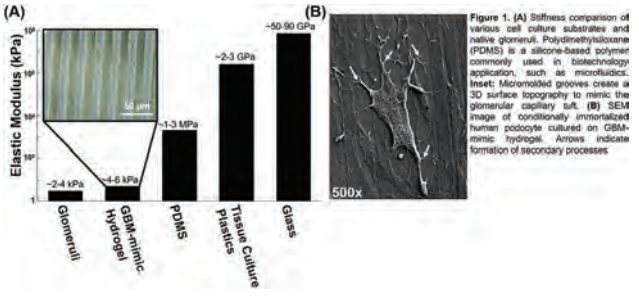


Figure 1. (A) Stiffness comparison of various cell culture substrates and native glomeruli. Polydimethylsiloxane (PDMS) is a silicone-based polymer commonly used in biotechnology application, such as microfluidics. Inset: Micromolded grooves create a 3D surface topography to mimic the glomerular capillary tuft. (B) SEM image of conditionally immortalized human podocyte cultured on GBM-mimic hydrogel. Arrows indicate formation of secondary processes

FR-PO994

Multiscale Mechanical Properties of Glycated Kidney Extracellular Matrix Nicholas J. Ferrell,[1] Sarah Dillender,[1] Rishabh Agarwal,[1,2] Minhal H. Abidi,[1] Gwyneth D. Walker.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]University of Illinois at Chicago, Lisle, IL.*

Background: Non-enzymatic glycation of the extracellular matrix (ECM) contributes to diabetic nephropathy. A subset of advanced glycation end-products (AGEs) crosslink the ECM and may increase ECM stiffness. Matrix stiffening is recognized as a contributor to progression of fibrotic diseases, but the role of non-enzymatic stiffening of kidney ECM in the progression of diabetic nephropathy is not well understood and may provide new targets for intervention. The aim of this work was to evaluate the degree to which ex vivo glycation increased the stiffness of cortical, glomerular, and tubular ECM using multiple biomechanical characterization techniques.

Methods: Cortical and glomerular ECM were isolated from porcine kidney cortex by gross dissection and differential sieving, respectively. Mouse tubules were isolated from wild type mouse kidneys by microdissection. ECM was decellularized and evaluated by histology and immunostaining to evaluate the effects of decellularization on ECM structure. ECM was glycated by incubation in glucose or ribose (0-500 mM) for 30 days. Following glycation, ECM was subjected to either compressive or tensile mechanical testing using custom microscale measurement techniques (for tubules and glomeruli) or commercial testing techniques (for cortical matrix).

Results: Histological examination and immunostaining for ECM proteins (collagen IV and laminin) showed that structural proteins were retained in the ECM and the matrix largely retained its three dimensional structure following decellularization. Biomechanical testing showed that glycation increased ECM elastic modulus (stiffness) following exposure to both glucose and ribose at concentrations >5 mM. This effect was more pronounced for ribose given its higher reactivity relative to glucose. The origin of the ECM (cortical, glomerular, or tubular) and the method of applied stress (tension or compression) had a significant effect on the measured stiffness. This variability is likely due structural differences between the matrix components and anisotropy in the tensile versus compressive mechanical properties.

Conclusions: These data suggest a potential role for ECM stiffening in progression of diabetic kidney disease. Care should be taken in interpretation of the measured elastic modulus depending on the origin of the matrix and the method of characterizing the ECM stiffness.

Funding: NIDDK Support

FR-PO995

Genomic Analysis of Primary Human Kidney Podocytes Reveals Numerous Differences from Widely Used Podocyte Cell Lines Karsten B. Sieber,[1] Shreeram Akilesh.[2] *[1]GlaxoSmithKline, King of Prussia, PA; [2]University of Washington, Seattle, WA.*

Background: Kidney disease is a major and increasing burden on society, affecting ~10% of adults worldwide and causing increased risk of all-cause mortality. The glomerular podocyte is an important cell type with limited proliferative/regenerative potential that is the target of many proteinuric kidney diseases. Despite extensive cell biological characterization, very few studies have focused on characterizing the podocyte-specific epigenetic architecture and transcriptome. Such studies promise to shed light on the mechanisms of genome regulation in this important cell type and to calibrate and improve commonly used and emerging (e.g. iPSC-derived) podocyte cell culture systems.

Methods: We generated high resolution chromatin accessibility (DNase-seq) and gene expression (RNA-seq) data for primary cultures of human podocytes (n=4), and compared them to similar datasets generated from a widely used conditionally immortalized human podocyte cell line cultured under growth-permissive and differentiation-inducing conditions.

Results: Initial transcriptomic analyses revealed that nearly 2000 genes are differentially expressed between the primary podocytes and a widely-used podocyte cell line. Of these genes, more than 100 transcription factors are differentially expressed; notably, primary podocytes retain strong expression of the lineage-defining transcription factor WT1, in contrast to the podocyte cell line which has weak expression of this gene. Many of the other differentially expressed transcription factors have not been specifically studied in podocytes. To understand their functional consequence, we are analyzing recently generated chromatin accessibility data to elucidate the transcription factor regulatory networks that drive the unique podocyte phenotype.

Conclusions: Compared to primary podocytes, these findings indicate widespread genome regulatory differences in the conditionally immortalized podocyte cell lines and suggest caution in their use. Ongoing studies are focusing on the impact of these differentially expressed transcription factors on the unique chromatin accessibility landscape of primary podocytes.

Funding: NIDDK Support, Private Foundation Support

FR-PO996

Targeting Renal Fibrosis Using Self-Assembled Nanoparticles Joan Li,[1] Justin Cooper-White.[1,2] *[1]The University of Queensland, Brisbane, QLD, Australia; [2]Biomedical Manufacturing, Manufacturing Flagship, CSIRO, Melbourne, VIC, Australia.*

Background: MicroRNAs (miRNAs) are emerging as potential therapeutics for Chronic Kidney Disease (CKD) to reduce fibrosis, and myofibroblast proliferation. However, the lack of targeted delivery of miRNAs with sustained expression or suppression are major challenges in translating microRNA therapy to treat CKD. We have developed a novel self-assembled nanoparticle (*SAnP*) delivery system that, when functionalised with a specific cell-targeting ligand, is recognised by both interstitial fibroblasts and injured epithelial cells within the kidney, enabling cell-specific delivery of miRNA via receptor-mediated uptake.

Methods: *In vitro* Epithelial-to-mesenchymal transition (EMT) model was induced in cultured MDCK cells with TGF-β (10ng/ml) and treated with or without miR-29 (1nM) for 72 hours. Renal fibrosis model was created using *Postn*-Cre;Rosa26R-Zsgreen mice (~ 20 weeks), subjected to Unilateral Ureteral Obstruction (UUO). The miR-29 mimic (0.1mg/kg), either packaged into the *SAnP* system targeting receptor "X" or as "naked" microRNA, was directly delivered into the renal parenchyma of the UUO model, at the time of the obstruction. Mice were euthanized 7 days after UUO. Kidneys were collected and processed for histology analysis.

Results: To test the specificity of our *SAnP* delivery system, we packaged Cy3-labelled miR into the SAnP and infected cells expressing receptor "X": MDCK cells. Uptake of Cy-3 was only detected in cells transfected with *SAnP-Cy3-miR* (97% vs 0.4% for Cy3-miR only), confirming receptor-mediated uptake. In cultured MDCK cells, TGF-β induced EMT was partially blocked by administration of the miR-29 mimic, as treated cells maintained the *cobblestone*-like morphology and preserved E-cadherin expression on the cell membrane. At 7 days post-UUO, our *SAnP*-delivered miR-29 mimic was able to reduce tubular dilatation and perivascular infiltration. Quantification of Picrosirius red staining indicated a 24% decrease in collage deposition. Delivery of "naked" miR-29 mimic did not show any beneficial effect in the UUO model.

Conclusions: Our preliminary data demonstrate that whilst miR-29 alone can inhibit the EMT transition *in vitro*, "naked" miR-29 had no effect *in vivo*. Our *SAnP* system however could affect cell-specific targeted delivery of miR29, significantly reducing tubular dilatation, interstitial infiltration and collagen deposition in the UUO model.

FR-PO997

Transcriptome Signatures for Dietary Fructose Induced Changes in the Proximal Tubule Ulrich Hopfer, Agustin Gonzalez-Vicente, Jeffrey L. Garvin. *Case Western Reserve University, Cleveland, OH.*

Background: Fructose consumption has been associated with renal dysfunction and salt-sensitive hypertension. Proximal tubules reabsorb and metabolize fructose.

Methods: To study the effect of fructose on genetic programs in proximal tubules, rats were given a 20% fructose (FRU) or water for 7 days. We used 4 groups of rats fed either chow 1 (normal salt) or 2 (high salt) +/- FRU. Each group contained 4 rats. The exposure time to FRU was short enough so that the rats showed no signs of metabolic syndrome. Total RNA from the superficial kidney cortex was analyzed using the Affymetrix microarray *RaGene*-2_0-st. Differential expression (DE) analysis of FRU vs. water on chow 1 or 2, was carried out using 3 different statistical methods: 1) Univariate ANOVA (Affymetrix TAC software), 2) Bayesian (BAMarray), and 3) Multivariate Characteristic Direction (CD). CD analysis of DE includes also information from the co-variance matrix between pairs of groups and calculates a vector of co-regulated genes ranked on a quantitative relative scale.

Results: Cosine similarity comparison of the FRU/water vectors from the 2 different chows showed greater similarity than FRU/water vector under either chow versus chow-alone vector. Intersection of the high ranking genes from the two FRU/water vectors (under diet 1 or 2) yielded 139 FRU-specific genes. Only 6 of these genes were also identified as DE genes by both univariate methods. They include the 2 most highly ranked CD genes as well as some lower ranked ones, suggesting that the univariate methods miss many DE genes because of high FRU-unrelated variance. DE genes identified by CD include G6pc, Slc5a8, Tkfc, Slc2a5, Khk, which directly transport or metabolize fructose in proximal tubules. Enrichment for GO:Biological Processes identified "response to nutrient" (GO:0007584), "cellular response to fructose stimulus" (GO:0071332) and "response to fructose" (GO:0009750). Enrichment for GO:Cellular Constituents identified 11 mitochondrial enzymes, suggesting amino acid catabolism, cataplerosis, ketogenesis, and fatty acid synthesis. DE of the cytosolic enzymes Pck1 and G6pc in FRU regardless of chow, suggest increases in gluconeogenesis and glyceroneogenesis.

Conclusions: In summary, the CD method outperforms commonly used univariate methods and provides a meaningful transcriptome signature of FRU in proximal tubules.

Funding: Other NIH Support - R01 HL128053, P30 CA43703

FR-PO998

Development of Method for Assessing Chemical-Induced Toxicity against Kidney Cells by In Vivo Live Imaging Technique Using Nephron-Visualized-Transparent-Zebrafish Shin'ichi Akiyama, Shoichi Maruyama. *Nagoya University Graduate School of Medicine, Nagoya, Japan.*

Background: Zebrafish is a well-established vertebrate model for studying genetically higher levels of biological phenomena and it is suitable for the identification of toxic- or therapeutic-compounds on a larger scale. Larva of zebrafish are transparent, so they are often used for in vivo phenotype-based toxicological assay, but because the body of juvenile or adult fish body is not transparent, it is not suitable for that. In this study, we tried to develop a new platform for assessing chemicals safety and toxicity against kidney by using a nephron-visualized-transparent-zebrafish.

Methods: We generated nephron-visualized-transparent zebrafish, which expressing green fluorescent protein (GFP) in glomeruli and proximal-mid tubule, by bioengineering technique using a promoter region of slc20a1a gene, a Gal4-UAS system, GFP cDNA and transparent zebrafish (Casper line). The larvae, juvenile and young adult of this fish were administrated a gentamicin, as positive control of nephrotoxicin, or several compounds by microinjection or exposure. Further, when evaluating protein leakage from the glomeruli, the dye-labeled dextran (MW, 70k) was administered by microinjection. At 24 or 48 hours post administration, we evaluated the survival, edema formation, form and number of nephron, and leakage of dextran.

Results: Live nephrons of the nephron visualized transparent zebrafish, could be clearly observed through the skin from outside the body from larva to young adult fish (2 months post-fertilization). In the fish treated with nephrotoxicin, edema increase, nephron loss, and dextran leakage were observed in a dose-dependent manner.

Conclusions: These results suggest that our in vivo assessing technique using the nephron-visualized-transparent-zebrafish have the potential to provide more easy and advanced platforms for assessing kidney health impacts of chemicals.

Funding: Government Support - Non-U.S.

FR-PO999

Effects of Nitric Oxide Releasing Bionanomatrix Gel on Reducing Neointimal Hyperplasia and Inflammation Maheshika S. Somarathna,[1] Patrick Hwang,[2] Tatyana Isayeva Waldrop,[1] Grant Alexander,[1] Lingling Guo,[1] HO-WOOK JUN,[1,2] Timmy C. Lee.[1] *[1]The University of Alabama at Birmingham, Birmingham, AL; [2]Endomimetics LLC, Birmingham, AL.*

Background: Vascular access is the lifeline for hemodialysis patients. An arteriovenous fistula (AVF) is the preferred type of vascular access. However, nearly 60% of the time, AVF maturation failure occurs due to early venous neointimal hyperplasia (NIH) formation and poor vascular remodeling. We hypothesize that local nitric oxide (NO) therapy administered at the time of AVF creation can inhibit venous NIH development and reduce local AVF inflammation. The aims of this study are to evaluate in a rat AVF model the effects of a NO-releasing bionanomatrix gel on: 1) NIH formation and 2) expression of inflammatory biomarkers such as MCP-1, IL-1, IL-6 and TNF-α in AVF vein.

Methods: Femoral vein to artery AVFs were created. After AVF creation, the NO-releasing gel was applied on the AVF anastomosis in 16 week old Sprague-Dawley rats (Figure 1). Rats were sacrificed at 7 days to perform: 1) Morphometric analysis of the AVF vein to access the changes in NIH development and 2) Western blot analysis from the vein segments to evaluate changes in expression levels of inflammatory biomarkers.

Results: The NO-releasing gel treatment group showed a significant reduction in NIH development at 7 days after AVF creation (Figure 1) when compared to the control group. MCP-1, IL-1, IL-6 and TNF-α protein expression in AVF vein was significantly lower in the NO-releasing gel treated group.

Conclusions: NO-releasing gel therapy applied locally on the AVF has great potential to promote AVF maturation by reducing NIH and mitigating local inflammation following AVF creation.

Funding: NIDDK Support

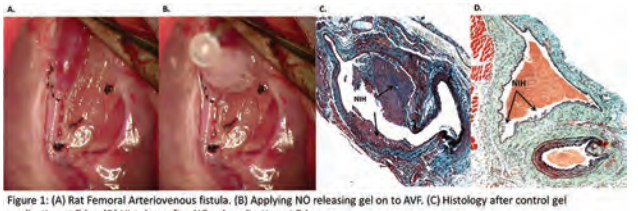


Figure 1: (A) Rat Femoral Arteriovenous fistula. (B) Applying NO releasing gel on to AVF. (C) Histology after control gel application at 7day. (D) Histology after NO gel application at 7day.

FR-PO1000

Autonomic Nervous System Dysfunction Status Post Solid Organ Transplant Nina Tazi,[2] Mira T. Keddis.[1] *[1]Mayo Clinic, Phoenix, AZ; [2]Internal Medicine, Mayo Clinic, Scottsdale, AZ.*

Background: Introduction: Autonomic nervous system (ANS) dysfunction has been reported to stabilize or improve following solid organ transplantation. This paper describes the phenomenon of ANS dysfunction, that happens within 30 days of solid organ transplant (kidney, kidney-pancreas or liver), requiring multiple medications, and ultimately resolves over several months.

Methods: Materials and methods: All patients who underwent solid organ transplant from 2012-2016 and were evaluated by neurology after transplant were included (n=8). Data gathered included pre transplant autonomic dysfunction, post-transplant BP, laboratory variables and paraneoplastic antibodies.

Results: Results: A total of 8 patients were identified who suffered severe symptoms of ANS dysfunction including symptoms of orthostatic intolerance and syncope in all, and significant gastrointestinal symptoms in 7 that began concurrently with adrenergic failure. Symptoms of ANS dysfunction occurred 1 - 3 weeks post-transplant. Symptoms present post-transplant included lower blood pressure, hypoalbuminemia, anemia requiring transfusion in 5 of 8 patients. Paraneoplastic autoantibody panel was drawn in 4 patients and abnormal in 3. Complications of autonomic failure in these patients resulted in prolonged and recurrent hospitalizations.

Conclusions: Conclusion: Autonomic testing confirmed the presence of significant autonomic neuropathy in those tested, and autoantibodies associated with autoimmune autonomic neuropathy were present in 3 of 4 patients tested, suggesting a potential autoimmune cause. Ultimately, the autonomic failure resolved in all patients with established long-term follow-up.

FR-PO1001

Organ-Specific Immunosuppression in Kidney Transplantation Dominik R. Kentrup,[3] Katharina Schütte-Nütgen,[3] Helga Pawlski,[3] Hermann Pavenstädt,[3] Sven Hermann,[1] Michael Schaefers,[1] Gregor Larbig,[2] Armin Kuebelbeck,[2] Stefan Reuter.[3] *[1]European Institute for Molecular Imaging - EIMI, Muenster, Germany; [2]Merck KGaA, Darmstadt, Germany; [3]University Hospital Münster, Münster, Germany.*

Background: Severe side effects attributable to immunosuppressive therapy are a major obstacle in organ transplantation. In this study we assessed a kidney-specific drug delivery mechanism and show that prednisolone, coupled to a specific polypeptide is selectively taken up by the kidney in rats which underwent renal transplantation, avoiding adverse systemic effects.

Methods: All experiments were performed using male rats, ten groups of animals were assessed (N=5-6): Syngeneically (Lewis Brown Norway F1 to Lewis Brown Norway F1) and allogeneically (Lewis Brown Norway F1 to Lewis) transplanted rats without immunosuppression, as well as allogeneically transplanted rats receiving either normal or modified prednisolone at two different concentrations (4mg/kg/12h or 16mg/kg/12h, i.p). Immunosuppressive treatment was either preventive (continuous treatment until the end of the experiment 4 days post surgery; six groups) or therapeutic (started 4 days after surgery and maintained for 3 days until day 7 post surgery; 4 groups, no low dose treatment). Treatment efficiency was evaluated by ^{18}F-FDG positron emission tomography in the preventive experimental setting 4 days post surgery, as well as on day 4 (baseline), day 5 and day 7 post surgery in the therapeutic setting. Moreover, histological analyses were performed and blood glucose levels were measured to assess systemic effects.

Results: High dosage treatment with normal prednisolone significantly reduced renal ^{18}F-FDG accumulation and histological signs of rejection both in the preventive and the

therapeutic setting, low dose treatment had no effect. In comparison, animals treated with modified prednisolone showed significantly reduced signs of renal graft rejection even under low dose treatment in the preventive setting, high dose treatment was at least as effective as conventional treatment in both the preventive and therapeutic setting. Moreover, treatment with modified prednisolone did not result in elevated blood glucose levels, contrary to normal prednisolone.

Conclusions: Immunosuppressive treatment with the modified, kidney specific prednisolone proved to be as least as effective as normal prednisolone and may even outperform the latter. In the case of renal transplantations, organ-specific immunosuppression is possible.

FR-PO1002

In Proximal Tubular Cells, Cyclosporine Triggers Actin Reorganization and MRTF-SRF Inhibition through Changes in Cofilin Oligomerization and Activity Bastien Burat,[2] Pierre Marquet,[2] Marie Essig.[2,1] *[1]CHU Limoges, Limoges, France; [2]INSERM UMR U850, Limoges University, Limoges, France.*

Background: Calcineurin Inhibitors, Cyclosporine A (CsA) and Tacrolimus, are the keystones of immunosuppressive regimens in solid organ transplantation. However, they induce a nephrotoxicity whose mechanisms remain widely elusive. We have previously shown that CsA affect actin organization in proximal tubular cells. Here, we explored the intracellular pathways leading to this actin reorganization and its downstream consequences.

Methods: Porcine proximal tubular LLC PK-1 cells were exposed for 24 hours to CsA (5μM), and S3R (10μM) a specific inhbibitor of cofilin phosphorylation. LLC PK-1 proteome was analyzed with iTRAQ shotgun proteomics by nano-LC-QTOF tandem mass spectrometry. Actin cytoskeleton was analyzed by TRITC-phalloidin labeling of F-actin. Cofilin oligomerization state was investigated by Western blot in non-reducing conditions after formaldehyde cross-linking Na/K-ATPase activity was quantified by colorimetric assay of inorganic phosphate. Serum response factor (SRF) activity was assessed by luciferase gene reporter assay.

Results: CsA induced a decrease in perimembranous branched F-actin meshwork with a significant decrease in Factin fluorescence positive area, (-3.3%, $p < 0.0001$). iTRAQ analysis showed that CsA induced a decrease in F-Actin/G-Actin ratio and a decrease in cofilin/actin ratio resulting from a global actin overexpression. Furthermore, CsA induced a 20% shift from tetramer to dimer's forms of cofilin. These modifications of F-actin/G-actin ratio and cofilin oligomerization were associated with an inhibition of SRF activity (-56% of control activity). CsA induced a 21% inhibition of the Na/K-ATPase activity. Such inhibition has been previously demonstrated to activate cofilin. The cofilin inhibitor S3-R, which has no significant impact on F-Actin/G-Actin ratio or SRF, blocked CsA effects on actin organization and SRF activity.

Conclusions: Our results suggest that CsA deeply affects the actin cytoskeleton of proximal tubular cells through the decrease in the tetrameric, polymerizing form of cofilin. This effect favored the depolymerization activit of cofilin leading to a decrease in branched actin microfilament. This reorganization of actin cytoskeleton leads to G-Actin increase and SRF inhibition, which may trigger tubular atrophy, one of the typical lesions of CsA toxicity.

FR-PO1003

Ginseng Extract Reduces Tacrolimus-Induced Oxidative Stress by Modulating Autophagy in Pancreatic Beta Cell Sun Woo Lim,[2] Yoo-Jin Shin,[2] Kang Luo,[2] Chul Woo Yang.[1,2] *[1]Seoul St. Mary's Hospital, Seoul, Republic of Korea; [2]The Catholic University of Korea, Seoul, Korea., Seoul, Republic of Korea.*

Background: Growing evidence suggests that regulation of autophagy may be an effective approach to protect beta cells against various extra-/intracellular stimuli. We previously demonstrated that long-term treatment of calcineurin inhibitor causes excessive autophagosome burden and impaired autophagy clearance in pancreatic beta cells. This study investigated the effect of Korean red ginseng extract on autophagy modulation focused on oxidative stress.

Methods: The rat insulinoma cell line INS-1 was treated with Tac (40 ug/mL) and KRGE (100 pg/mL) with or without 3-methyladenine (3-MA, 10 mM) or bafilomycine A1 (BA, 2nM) for 6h. Mice were treated with Tac (1.5 mg/kg, subcutaneous) and KRGE (0.4 g/kg, orgal gavage) for 4 weeks. The effect of KRGE on Tac-induced diabetes was evaluated by assessing intraperitoneal glucose tolerance test, plasma insulin level, beta cell area, and 8-hydroxy-2'deoxyguanosin in serum and islet. Autophagy and mitochondria functions were examined by measuring either microtubule-associated protein 1 light chain 3 beta expression, the number of autophagic vacuoles, and lysosome function or oxygen consumption and mitochondrial membrane potential.

Results: In mice with Tac-induced diabetes mellitus, KRGE improved islet dysfunction, and decreased oxidative stress and autophagic vacuoles. In vitro study, KRGE decreased autophagosome formation and improved lysosomal degradation, accompanied by improved beta cell viability and insulin secretion. Addition 3-methyladenine (3-MA), an inhibitor of autophagosome, to KRGE further improved cell viability and insulin secretion, and bafilomycin A (BA), an inhibitor of lysosomal function, reduced those effects of KRGE. At subcellular level, Tac caused mitochondrial dysfunction (impaired mitochondrial oxygen consumption, ATP production, and increased reactive oxygen species production). But, KRGE improved these parameters. The effect of KRGE on the mitochondrial function enhanced by 3-MA but decreased by BA, suggesting causal relationship between KRGE effect and autophagy modulation in Tac-induced mitochondrial dysfunction.

Conclusions: These findings indicate that KRGE modulates autophagy favorably by reducing Tac-induced oxidative stress, and this effect is closely associated with improvement of mitochondrial function.

FR-PO1004

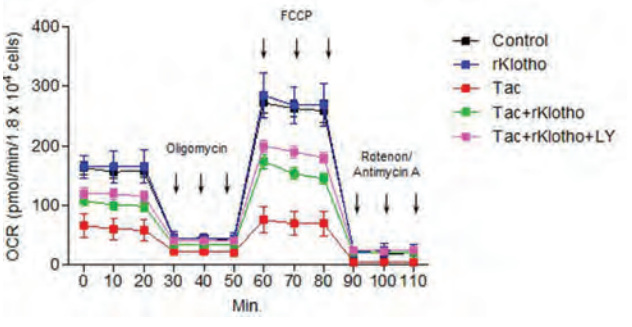
Klotho Enhances FoxO3-Mediated Manganese Superoxide Dismutase Expression by Negative Regulation of PI3K/AKT Pathway in Tacrolimus-Induced Oxidative Stress Sun Woo Lim,[1] Yoo-Jin Shin,[1] Kang Luo,[1] Chul Woo Yang.[2,1] *[1]Transplant Research Center, The Catholic University of Korea, Seoul, Republic of Korea; [2]Internal Medicine, Seoul St. Mary's Hospital, Seoul, Republic of Korea.*

Background: Mammalian forkhead members of the class O (FoxO) transcription factor are implicated in the regulation of oxidative stress, and FoxO proteins are negatively regulated by the phosphatidylinositol 3-kinase (PI3K)–AKT signaling pathway. We examined the effect of Klotho on PI3K/AKT pathway and manganese superoxide dismutase (MnSOD) in tacrolimus (Tac)-induced oxidative stress.

Methods: Mice were treated with Tac (1.5 mg/kg, subcutaneously) and recombinant Klotho (rKlotho, shedding form, 10 ug/kg once every 2 days, IP injection) for 4 weeks. For in vitro study, HK-2 cells were seeded in culture plates and treated with Tac (60 ug/mL) and rKlotho (1 ug/mL) with or without LY294003 (25 uM) for 12 h. We examined whether the oxidative stress and signaling pathway are involved in the protection by Klotho using immunoblot, immunostaining, RT-PCR, ChIP assay, oxygen consumption, ect.

Results: Klotho-treated mice showed decreased Tac-induced oxidative stress accompanied by functional and histological improvement. Klotho inhibited the PI3K/AKT-mediated phosphorylation of FoxO3a and enhanced FoxO3a binding to the MnSOD promoter. Klotho increased MnSOD mRNA and protein in mitochondria, and overexpressed MnSOD reduced Tac-induced toxicity in HK-2 cells. In mitochondria, Klotho improved Tac-induced mitochondrial dysfunction and decreased mitochondrial ROS, and this effect was enhanced by blocking PI3K activity with LY294002.

Conclusions: Collectively, Klotho protects Tac-induced oxidative stress by negative regulation of PI3K/AKT pathway, and subsequently enhances FoxO3a-mediated MnSOD expression. Through this mechanism, Klotho may protect against Tac-induced oxidative damage and apoptotic cell death. Finally, our results suggested that Klotho protein or Klotho-enhancing compounds may provide treatment options for nephrotoxicity in the future.



Klotho preserves Tac-induced mitochondrial dysfunction in HK-2 cells.

FR-PO1005

Dehydropeptidase-I Inhibitor Reduces Tacrolimus-Induced Kidney Injury by Anti-Oxidative and Anti-Apoptotic Effect Kang Luo,[3,1] Sun Woo Lim,[2,1] Chul Woo Yang.[3,1] *[1]Seoul St. Mary's Hospital, Seoul, Republic of Korea; [2]The Catholic University of Korea, Seoul, Republic of Korea; [3]The Catholic University of Korea, Seoul, Republic of Korea.*

Background: Cilastatin is an inhibitor of dehydropeptidase-I which enhances the antibacterial activity of imipenem. Dehydropeptidase I is associated with not only the metabolism of the enzyme but also the formation of possible renal toxic products. At present, role of cilastatin in chronic Tacrolimus (TAC) nephropathy still unclear.

Methods: Chronic TAC nephropathy was induced by administering TAC (1.5 mg/kg/day, subcutaneously) to rats on a low-salt diet (0.05%) with cilastatin (75 or 150 mg/kg/day, intraperitoneal injection) for 4 weeks. The effects of cilastatin on TAC-induced renal injury were evaluated in terms of renal function, tubulointerstitial inflammation and fibrosis. As a possible mechanism, we evaluated the effect of cilastatin on TAC-induced oxidative stress and apoptosis.

Results: Chronic TAC nephropathy was confirmed with impaired renal function and typical striped interstitial fibrosis. Combined treatment of TAC and cilastatin attenuated TAC-induced kidney dysfunction (serum creatinine, blood urea nitrogen, creatinine clearance, urine microalbumin) and interstitial fibrosis and maker of profibrotic cytokine (α-smooth muscle actin, transforming growth factor β1). Also, cilastation treatment decreased TAC-induced interstitial inflammation, demonstrated by decreased the ED-1-positive cells and pro-inflammatory cytokine (osteopontin) expression. Oxidative stress, a common mechanism of calcinurin inhibitor nephrotoxicity, was decreased with cilastatin treatment, demonstrated by decreased 8-OHdG and increased manganese superoxide dismutase. The increased number of TUNEL-positive cells and pro-apopptic

active caspase-3 and decreased antiapoptotic Bcl-2 expression by TAC was reversed with cilastatin treatment.

Conclusions: Cilastatin has anti-oxidative and anti-apoptotic properties and this may be responsible for protection of TAC-induced nephrotoxicity.

FR-PO1006

Effect of Conversion to Belatacept on Tacrolimus-Induced Diabetes Mellitus in Rats Long Jin. *The First Affiliated Hospital of Dalian Medical University, Dalian, China.*

Background: Belatacept is a promising immunosuppressant for replacing calcineurin inhibitors (CNIs). However, its effect on CNIs-induced diabetes mellitus (DM) is not adequately studied. Therefore, we tested the effect of conversion to belatacept on tacrolimus-induced DM.

Methods: Two separate experiments performed. The first experiment was conducted to determine diabetogenicity of belatacept. We administered five doses of belatacept via tail vein injection at the weekly basis for four weeks. The second experiment was conversion study. After inducing tacrolimus-induced DM with three weeks treatment with tacrolimus (TAC), TAC was converted to belatacept for three additional weeks. The effect of belatacept on TAC-induced pancreatic islet dysfunction was evaluated. The influence of oxidative stress was evaluated by measuring markers of oxidative stress 8-OHdG and antioxidant enzyme maker of MnSOD in pancreas tissues. The effect of conversion to belatacept on macrophage infiltration and apoptosis were detected by ED-1 and caspase-3. We also measured cell viability AO/PI staining in isolated rat islets. Finally, the direct effect of belatacept on TAC-induced ROS production and cell viability in vitro were investigated.

Results: The first experiment showed that treatment with belatacept showed similar blood glucose level compares with VH group. However, there was no difference between the other groups and time course. From the first study, we found that 1 and 2 mg/kg of belatacept have a clinically relevant therapeutic level. As expected, conversion from TAC to belatacept groups improved TAC-induced pancreatic beta-cell dysfunction compared with the TAC and TAC withdrawal groups. TAC treatment increased the level of 8-OHdG and reduced the level of MnSOD, and conversion could recover this effect. Conversion to belatacept significantly decreased the level of ED-1 and caspase-3 compared with that in the TAC and TAC withdrawal groups. AO/PI staining showed that conversion to belatacept effectively decreased TAC-induced islet cell death. In vitro study revealed that belatacept treatment significantly decreased ROS production and cell viability compared with that reported with TAC alone

Conclusions: Our study indicated that conversion from TAC to belatacept is effective in improving TAC-induced DM, and belatacept has a protective effect against TAC-induced pancreatic islet injury.

FR-PO1007

Insuline Resistance Promoting the Progression of Chronic Renal Allograft Dysfunction via the ERK1/2-GSK3β-NF-κB Signaling Pathway Qin Zhou,[1] Zhihong Zhao,[1] Hequn Zou.[2] *[1]The Third Affiliated Hospital of Southern Medical University, Guangzhou, China; [2]The 3rd Affiliated Hospital of Southern Medical University, Guangzhou, China.*

Background: Several studies had reported that insuline resistance (IR) was an important nonimmunological risk factors for chronic renal allograft dysfunction (CRAD). However, the pathogenesis of IR-mediated CRAD is still unclear. The aim of this study is to investigate the effect of rosiglitazone on ERK1/2-GSK3β-NF-κB signaling pathway in renal transplantation rats with insulin resistance.

Methods: The rats in CRAD group received classical orthotopic F344-Lewis kidney transplantation and then fed with normal diet. The rats in CRAD+IR group administrated with high fat diet for 8 weeks after kidney transplantation. The rats in CRAD+IR+ERK1/2 Inhibitor group and those in CRAD+IR+GSK-3β Inhibitor group were respectively treated with rosiglitazone (ERK1/2 inhibitor, 5mg/kg/d, gavage) and TDZD8 (GSK-3β inhibitor, 1mg/kg/week, tail vein injection) based on above CRAD+IR model. The controls were F344 and Lewis uninephrectomized rats fed with normal diet. Renal tissue was stained with HE and PAS. The expression of ERK1/2-GSK3β-NF-κB signaling proteins and its downstream inflammation factors were evaluated by means of immunohistochemical and western blot assays.

Results: (1) Function and histology: Compared with CRAD group, serum creatinine and 24-hour urinary protein output were significantly increased in CRAD+IR group. Compared with CRAD+IR group, the above indexes were significantly decreased and the infiltration of inflammation cell in transplanted kidney was significantly alleviated in CRAD+IR+ERK1/2 Inhibitor group. (2) Signaling pathway: Compared with CRAD group, the expression of P-ERK1/2, P-GSK3β and P-NF-κB P65 were significantly increased in CRAD+IR group, and the expression of the downstream inflammation proteins MCP-1 and ICAM-1 were increased in CRAD+IR group; Compared with CRAD+IR group, the expression of P-ERK1/2, P-GSK3β, P-NFκB P65, MCP-1 and ICAM-1 were significantly down-regulated in CRAD+IR+ERK1/2 Inhibitor group. The expression of P-NFκB, MCP-1 and ICAM-1 were inhibited by GSK-3β inhibitor.

Conclusions: It is shown that IR promoted CRAD in our rat model and ERK1/2 inhibitor and GSK-3β inhibitor improved the infiltration of inflammation cells in renal allograft tissue at the early stage of CRAD promoted by IR.ERK1/2-GSK3β-NF-κB signaling pathway participant in the pathogenesis of the early stage of CRAD promoted by IR.

Funding: Government Support - Non-U.S.

FR-PO1008

Everolimus Has Effect on the Tacrolimus Concentration within the Renal Proximal Tubular Cells in Dose Dependent Manners Haewon Lee,[1] Yang Wook Kim,[1] Bongsoo Park,[1] Sihyung Park,[1] Yoo jin Lee,[1] Seok ju Park,[2] Sang Youb Han.[2] *[1]Haeundae Paik Hospital, inje university, Pusan, Republic of Korea; [2]Inje University, Busan, Republic of Korea.*

Background: It was reported that everolimus in combination with varying levels of Tacrolimus is efficacious and associated with good kidney function. We aimed to investigate the effect of everolimus on the tacrolimus intracelluar concentration in the kidney cells when it is used concomitantly.

Methods: HK-2 Cells(immortalized Human Renal Proximal Tubule Cells) were treated with tacrolimus at the dose of 5 ng/ml, 10 ng/ml and 15 ng/ml. After 30 minutes, we treated with everolimus at the dose of 3 ng/ml, 9 ng/ml and 15 ng/ml, additionally, in the absence or presence of tacrolimus for 1 hour. We measured the intracelluar tacrolimus concentrations using LC/MSMS.

Results: Tacrolimus intracellular accumulation was significantly decreased by everolimus in a concentration dependent manner. At the concomitant treatment with 5 ng/ml of tacrolimus and everolimus (3 ng/ml, 9 ng/ml, 15 ng/ml), the intracellular tacrolimus concentrations was significantly decreased compared with abscence of everolimus. The intracellular tacrololimus was decreased by everolimus showing 0.348± 0.025 ng/ml/1x10^{6}cells, 0.279± 0.034 ng/ml/1x10^{6}cells, 0.232± 0.025 ng/ml/1x10^{6}cells vs 0.643± 0.087 ng/ml/1x10^{6}cells (P=0.01), respectively. At the concomitant treatment with 10 ng/ml of tacrolimus and everolimus (3 ng/ml, 9 ng/ml, 15 ng/ml), the intracellular tacrolimus concentrations was significantly decreased compared with abscence of everolimus, The intracellular tacrololimus was decreased by everolimus showing 0.544± 0.103 ng/ml/1x10^{6}cells, 0.393± 0.042 ng/ml/1x10^{6}cells, 0.376± 0.06 ng/ml/1x10^{6}cells vs 0.71± 0.177 ng/ml/1x10^{6}cells,(P=0.042), respectively. The effect of everolimus on intracelluar tacrolimus concentration decreased as the dose of tacrolimus increased. At the concomitant treatment with 15 ng/ml of tacrolimus and everolimus (3 ng/ml, 9 ng/ml, 15 ng/ml), the intracellular tacrolimus concentrations was significantly decreased compared with abscence of everolimus. The intracellular tacrololimus was decreased by everolimus showing 0.654± 0.043 ng/ml/1x10^{6}cells, 0.635± 0.096 ng/ml/1x10^{6}cells, 0.579± 0.251 ng/ml/1x10^{6}cells, vs 0.822± 0.168 ng/ml/1x10^{6}cells,(P=0.038), respectively.

Conclusions: We suggest that everolimus has effect on the tacrolimus concentration within the kidney proximal tubular cells in dose dependent manners.

FR-PO1009

Non-Invasive Proteomics to Detect Biomarkers for Kidney Allograft Dysfunction Maura A. Watson,[6] Meera Srivastava,[2] Dustin J. Little,[1] Ofer Eidelman,[5] Robert Nee,[6] Alakesh Bera,[3] David K. Oliver,[6] Harvey Pollard,[5] Rahul M. Jindal.[4] *[1]AstraZeneca, Gaithersburg, MD; [2]USU School of Medicine, Bethesda, MD; [3]Uniformed Services University, Bethesda, MD; [4]Uniformed Services University of Health Sciences, SILVER SPRING, MD; [5]Uniformed Services University of the Health Sciences, Bethesda, MD, MD; [6]Walter Reed National Military Medical Center, Vienna, VA.*

Background: Non-invasive biomarkers are needed for monitoring patients with transplant-associated renal injury to predict early acute rejection (AR). Currently, invasive allograft biopsy is required to make a definitive diagnosis of AR. We hypothesized that protein biomarkers released from rejecting allograft tissues can be detected early in the systemic circulation.

Methods: Serum from healthy individuals, transplant patients with either stable allograft function or chronic kidney disease (CKD), transplant patients requiring kidney biopsy, and CKD patients awaiting transplant (25 patients per category) were labeled with the fluorescent dye Cy3, and assayed on 1275 feature phosphoprotein microarray platform from Fullmoon biosystems. We validated these biomarkers associated with disease severity using a quantitative Reverse Capture Protein Microarray (RCPM) platform. Serum samples were spotted individually in serial dilutions and probed with a specific antibody predicted by the antibody microarray platform.

Results: Bioinformatic analysis compared healthy individuals, pre and post-transplant CKD patients and identified proteins that were present in higher serum concentrations in pre-transplant CKD and transplant allograft rejected patients. These included ATM, p38MAPK, HDAC8, SAPK/JNK, GSK3a-b, NFkappa B and RelB which pointed to an affected p53 signaling pathway. Among the tested phosphorylated proteins, phospho-species of SAPK/JNK and RelB were elevated in stable allograft function compared with CKD pre-transplant and graft rejected serum.

Conclusions: These novel serum analytes, together or independently, may constitute a robust and quantitative serum proteomic signature for AR in renal allografts. Detection of kidney allograft AR by affinity proteomics offers a promising non-invasive tool for surveillance of transplant recipients and for guiding treatment of graft rejection. The views expressed are the authors and do not reflect official policy of the Department of Army/Navy/Air Force, Department of Defense, or U.S. Government.

Funding: Other U.S. Government Support

FR-PO1010

A Role for IgE-Mediated Immune Response in the Pathogenesis of Chronic Antibody-Mediated Rejection (CAMR) F. Rascio,[1] Paola Pontrelli,[4] Elisabetta Manno,[1] Giuseppe S. Netti,[1] Barbara Infante,[1] Giulia Cocina,[1] Simona Simone,[3] Giuseppe Castellano,[3] Loreto Gesualdo,[3] Giovanni Stallone,[1] Giuseppe Grandaliano.[2] *[1]University of Foggia, Foggia, Italy; [2]Nefrologia/ Dialisi/Trapianto, Foggia, Italy; [3]University of Bari, Altamura, Italy; [4]University of Bari-Dept. of Emergency and Organ Transplantation, Bari, Italy*.

Background: CAMR is the main cause of graft loss and share with systemic lupus erythematosus (SLE), an autoimmune disease, the antibody-mediated kidney damage, the development of autoantibodies, and the activation of the interferon-alpha (IFN-alpha) pathway. IgE-mediated immune response play a key role in the development of SLE nephritis and is associated with IFN-alpha secretion. The aim of our study was to investigate IgE-mediated immune response in CAMR grafts.

Methods: We enrolled 40 biopsy-proven CAMR patients (pts), 15 transplant pts with normal graft function/histology (CTRL), 15 pts with interstitial fibrosis/tubular atrophy (IFTA) and 6 SLE pts. IgE deposition as well as recruitment of basophil and mast cells, the two main cell types activated by IgE, were studied by confocal microscopy. The IFN-alpha response was assessed measuring serum MxA, an IFN-alpha-induced protein, by ELISA.

Results: We observed a significant increase in tubular and glomerular deposition of IgE in CAMR patients (1876±197 pixels/area) and SLE (1678±178 pixels/area) compared with IFTA (379±87 pixels/area) and CTRL (355±93 pixels/area) (p<.001). Interestingly, the stainings for triptase, a marker of mast cells, and CD203c, a specific marker of basophil activation, revealed a significant infiltration of both cell types IgE in CAMR grafts (triptase+cells/field: CAMR 15±5 vs. LES 3.0±.4 and CTRL 0.2±0.4, p=.02. Cd203c+cells: CAMR 21±5 vs. LES 2.0±.4 and CTRL .2±.4, p=.02). We also observed that the absolute number of circulating basophils was significantly increased in CAMR (48±3/ul) compared to CTRL (20±1/ul) and IFTA (15±.5/ul, p=.02). MxA serum levels were significantly higher in CAMR compared to CTRL (123.3±22.6 vs 42.9±37.9 ng/ml, p=.002) and directly associated with the extent of IgE deposits (r=.347, p=.01).

Conclusions: Our data suggest that IgE deposition and the subsequent recruitment of basophils and mast cells within the graft may play a key pathogenic role in CAMR. The genesis of these events appears to be linked, as in SLE, to the systemic activation of the IFN-alpha pathway.

Funding: Government Support - Non-U.S.

FR-PO1011

Development of De Novo Donor-Specific Antibodies, Intra-Graft B Cell Populations, and Allograft Function and Morphology in a Rat Model of Non-Adherence to Therapy after Renal Transplantation Louisa Kühne. *University Hospital Regensburg, Regensburg, Germany*.

Background: Introduction: Non-adherence to immunosuppressive therapy has been associated with *de novo* donor-specific antibodies (dnDSA) and antibody-mediated rejection (ABMR). The aim of this study was to investigate the development of *dnDSA,* intra-graft leukocyte and specifically B cell subpopulations, as well as allograft function and morphology in a model of renal transplant simulating non-adherence.

Methods: Methods: We used a rat model of renal transplantation (Brown Norway -> Lewis) with intermittent cyclosporine A administration (CyA 5mg/KG) on every other day (daily application until d7), to simulate non-adherence. Transplanted rats were sacrificed after 6, 28, and 56 days. *DnDSA* were measured by flow crossmatch and complement-dependent cytotoxicity (CDC) assay. DSA IgG subclasses were also assessed. Flow cytometry was used to assess changes in leukocyte (CD11b/c, CD3, CD45R) and B cell subsets (CD45R, CD38, CD27, IgM) in renal allografts. The intra-graft distribution of leukocyte and B cell subsets was assessed by immunohistochemistry and immunofluorescence. Intra-graft transcription of chemokines and cytokines was analyzed by qPCR. Allograft fibrosis was stained using trichrome method. Functional parameters, including urinary protein excretion and serum creatinine concentration were measured by ELISA.

Results: Results: Simulation of non-adherence to immunosuppressive therapy led to development of *dnDSA*, predominantly of the complement-fixing IgG subclass IgG1 and IgG2b. Flow cytometric analysis of leukocyte populations showed a reduction in the absolute number of intra-graft leukocyte subsets (CD11b/c, CD3, CD45R) and specific B cell subsets (CD38, CD27, IgM) over time. Intra-graft mRNA expression of specific chemokines (lymphotoxin-ß) and IgG were increased over time. Functional and morphological changes indicating chronic allograft injury, such as fibrosis, proteinuria and serum creatinine were detected and increased over time in this model of non-adherence.

Conclusions: Conclusion: Using a rat model of non-adherence to immunosuppressive therapy in renal transplantation, we found an induction of dnDSA. Although intra-graft leukocyte and B cell numbers were reduced over time, a mild increase in functional and morphological indicators of chronic allograft injury was noted after non-adherence.

Funding: Private Foundation Support

FR-PO1012

Podocyte Injury Is a Feature of Transplant Glomerulopathy Sara Moradi,[2] Hui Chen,[1] Jean M. Francis,[3] Joel M. Henderson.[3] *[1]BMC, Boston, MA; [2]Boston University, Worcesterr, MA; [3]Boston University Medical Center, Boston, MA.*

Background: Transplant Glomerulopathy (TG) is a chronic progressive glomerular lesion seen in about 20% of human renal allografts at five years post-transplant. TG is primarily a result of endothelial injury and is analogous to the glomerular lesion of thrombotic microangiopathy. Diagnosis of TG is strongly associated with poor long-term graft survival; however there is no effective treatment to prevent the development or progression of TG. Since proteinuria is a key feature of TG, we hypothesize that podocyte injury is associated with its development and progression.

Methods: We examined diagnostic electron micrographs from 21 kidney allograft biopsies (range 1 month to 15 years post-transplant), and scored these images for ultrastructural features of podocyte and endothelial injury. Podocyte injury in the form of foot process (FP) effacement, and endothelial injury in the form of cell swelling and loss of fenestrations, were scored on a 0 to 3 scale corresponding to percentage of capillary loop surface involved by the lesion throughout the biopsy (0=0-10%, 1=10-25%, 2=25-50%, 3=50%+). We also immunostained formalin-fixed, paraffin-embedded sections with primary antibodies against a panel of podocyte-specific proteins, and molecular markers of podocyte injury. Features of podocyte injury were correlated with severity of TG (Banff "cg" score for the biopsy) and endothelial injury.

Results: We found a significant correlation between podocyte injury severity and both "cg" score and endothelial injury severity. FP effacement score increases with increasing cg score; Kruskal-Wallis test reveals that median vary significantly (P<0.05). FP effacement also correlates with endothelial injury; linear regression of these data reveals a significantly non-zero slope (P<0.0001) and R-squared = 0.5673. Immunohistochemical staining suggests loss of differentiating features in podocytes in association with transplant glomerulopathy and endothelial injury.

Conclusions: These findings support the contention that podocyte injury is a common feature of TG, and its severity (and potentially its pathogenesis) is closely tied to extent and severity of the endothelial injury.

Funding: Clinical Revenue Support

FR-PO1013

Novel Approaches to Modulate T Cell Responses Based on Insights from Tumor Metabolism: Lactate and Pyruvate Control T Cell Function through NAD Redox Metabolism Ulf H. Beier,[2] Jing Jiao,[2] Zhonglin Wang,[1] William J. Quinn,[1] Joseph A. Baur,[1] Wayne W. Hancock,[2] Matthew H. Levine.[1] *[1]University of Pennsylvania, Philadelphia, PA; [2]Children's Hospital of Philadelphia, Philadelphia, PA.*

Background: Solid tumors can evade host immunity due to their distinctive metabolic properties; e.g. the tumor microenvironment can be glucose-depleted but rich in lactic acid, thereby weakening anti-tumor immunity, since cytotoxic and effector T cells require glycolysis to function. We questioned if such insights might suggest novel approaches for T cell suppression in transplant recipients.

Methods: We co-stimulated human and murine CD8+ and CD4+ T cells and exposed them to pH-neutral 5-40 mM sodium L-lactate, D-lactate, or pyruvate, using equimolar NaCl as a control, and measuring T cell proliferation and cytokine production (IL-2, IFN-g, IL-17), and bioenergetics profiles by Seahorse. We measured nicotinamide adenine dinucleotide both in oxidized (NAD+) and reduced (NADH) form, and tested the effects of drugs that oxidize NAD (alpha-ketobutyrate, beta-lapachone, pyrroloquinoline quinone), or impair NAD recycling (FK 866) or NAD oxidation/reduction via lactate dehydrogenase (LDH) inhibition (GSK 2837808A). We induced a tumor-like glycolytic metabolism in MHC-mismatched cardiac allografts by perfusing BALB/c hearts with UW solution containing 1 mM phenformin, 1-2 μM oligomycin, 2 μM nicolsamide, or 2.5 μM UK5099 for 1 hour prior to their engraftment in untreated C57BL/6 recipients.

Results: Sodium L- (& D-) lactate reduced NAD+ to NADH in an LDH(D)-dependent manner, impaired T cell proliferation, and increased induced Foxp3+ Treg formation. Sodium pyruvate achieved the opposite, oxidized NADH to NAD+, reduced iTreg formation, and increased effector T cell proliferation. Bioenergetic measurements showed that in activated effector T cells, NAD+ oxidation increased, while NADH reduction impaired glycolysis, showing that T cell function depends on the NAD:NADH redox status, and less on the absolute amount of NAD. Interestingly, transiently inducing a glycolytic metabolism in MHC-mismatched cardiac allografts prolonged allograft survival for several days.

Conclusions: NAD redox metabolism controls T cell function through aerobic glycolysis, and inducing glycolytic metabolism in cardiac allografts can promote allograft survival. These data provide a rationale for testing further approaches to modulate NAD redox metabolism in allograft recipients.

Funding: Other NIH Support - NIAID, Private Foundation Support

FR-PO1014

Adenosine Pathway Implication in M2 Macrophage Phenotype Switch in Deceased Renal Donors Montserrat M. Diaz Encarnacion,[2,5] Elena Guillen-gomez,[3] L. Guirado,[1] Jose Ballarin.[4] *[1]Fundació Puigvert, Barcelona, Spain; [2]Fundación Pugvert, Barcelona, Spain; [3]Fundación Puigvert, Barcelona, Spain; [4]None, Barcelona, Spain; [5]Medicine, Autonoma de Barcelona University, Barcelona, Spain.*

Background: A recent publication from our group shows that before kidney transplantation there is an activation and infiltration of immune cells in grafts from deceased donors. Adenosine levels increase during inflammation and hypoxia, principally through the hydrolysis of ATP, which is released after cell damage/death. This adenosine increment could initiate a macrophage phenotype shift from an ATP-driven pro-inflammatory environment to an anti-inflammatory and even pro-fibrotic milieu.

Methods: The aim of this study is to address the implication of purinome membrane elements in inflammation and fibrosis driven by macrophages in renal grafts. Purinergic markers from pre-implantational renal allograft biopsies from living (LD) and deceased donors (DD) were quantified by qPCR and western-blot.

Results: Kidney samples from DD showed activation of both macrophage M1 inflammatory and M2 anti-inflammatory pathways evidenced by an increased expression of M1 and M2 markers. This result point to an early inflammatory response followed by activation of mechanisms for inflammation resolution. We found that expression of CNT2, a high-affinity Na^+-dependent adenosine transporter, is decreased. This is consistent with the need to increase extracellular adenosine concentration by inhibiting its uptake, since the extracellular conversion to adenosine is also limited by the ecto-5'-nucleotidase CD73 inhibition. In addition, CNT2 correlated with the adenosine receptor A2a ($A_{2A}R$), which suggests that extracellular adenosine would activate $A_{2A}R$ to trigger anti-inflammatory processes through cAMP increase. Western-blot results indicate an activation of $A_{2A}R$-PKA-CREB pathway as well as an increase of the M2 macrophage marker CD163, in DD biopsies. Moreover $A_{2A}R$ expression correlates with pro-fibrotic markers such as α-SMA, fibronectin, vimentin and collagen.

Conclusions: Persistent inflammation in DD and M2 macrophage activation by extracellular adenosine even before implantation would contribute to the induction of pro-fibrotic processes in grafts from DD.

FR-PO1015

Role of Ubiquitin Proteasome System during Renal Cold Storage and Transplantation Nirmala Parajuli, Sorena B. Lo, Lee Ann MacMillan-Crow. *University of Arkansas for Medical Sciences, Little Rock, AR.*

Background: We previously reported that renal cold storage (**CS**) leads to increased mitochondrial injury and renal damage following transplantation (**Tx**). However, CS induced molecular pathways responsible for worsening mitochondrial and renal damage following Tx are poorly understood. Alteration of Ubiquitin Proteasome System (**UPS**) has been reported in numerous diseases. The goal of this study was to evaluate if UPS was altered, and if this contributes to mitochondrial and renal damage after CS plus Tx (CS/Tx).

Methods: Rat kidneys exposed to **CS** (18hr) followed by Tx (**CS/Tx**) were used. Sham, autotransplant (ATx, a Tx without CS), and CS alone kidneys were used as control. The proteasome function in the renal extracts was measured using fluorogenic peptide substrates and spectrofluorometer. Mitochondrial function was assessed via high resolution respirometry.

Results: Proteasome function (chymotrypsin-like) was compromised after CS/Tx, but not in sham, ATx, or CS alone kidneys. A selective reduction of β5 (catalytic) subunit of the proteasome was observed only after CS/Tx. None of the groups showed change in expression of the predicted molecular weight of Rpt6 subunits of the proteasome. However, only CS/Tx kidneys showed an intense Rpt6 reactive bands of high and low molecular weights. Co-immunoprecipitation of renal extracts with Rpt6 antibody showed an association of Rpt6 subunit with heat shock proteins, which was significantly altered after CS/Tx. Similarly, compromised mitochondrial function was evident after CS, which was exacerbated after CS/Tx. Proteasome inhibition of NRK cells with Bortezomib showed reduced activity for mitochondrial complexes I, II and III. Similarly, antimycin A, a mitochondrial complex III inhibitor, treatment of NRK cells showed compromised proteasome function.

Conclusions: These data suggest, for the first time, that renal CS/Tx leads to altered expression/function of the UPS as well as its compromised association with heat shock proteins. Similarly, *in vivo* data suggest that the mitochondrial dysfunction precedes proteasome inactivation during CS/Tx. *In vitro* studies confirmed that a functional interaction exists between renal mitochondria and the UPS. New studies designed to preserve the UPS/mitochondrial function may have promising therapeutic implications for better outcomes after renal transplantation.

Funding: Other NIH Support - American Heart Association

FR-PO1016

Caspase Inhibition during Cold Storage Improves Graft Function and Histology of Transplanted Kidneys Swati Jain,[1] Trevor L. Nydam,[2] Robert J. Plenter,[2] Alkesh Jani.[3] *[1]UC Denver, Aurora, CO; [2]University of Colorado Denver, Aurora, CO; [3]University of Denver Colorado, Aurora, CO.*

Background: Prolonged cold ischemia is a risk factor for delayed graft function (DGF) of kidney transplants, and is associated with caspase-3 mediated apoptotic tubular cell death. We hypothesized that treatment of a donor organ with the caspase inhibitor, QVD-OPh, prior to kidney transplantation would be associated with significantly reduced renal tubular epithelial cell (RTEC) apoptosis, histology and improved renal function post-transplant in a mouse kidney transplant model of DGF.

Methods: For in vitro studies, mouse RTECs were incubated with either DMSO or QVD-OPh during cold storage in saline followed by rewarming in RPMI media. For in vivo studies, donor kidneys from C57BL/6 mice were perfused with either cold saline, DMSO (vehicle), or QVD-OPh, recovered, stored in the same solution at 4°C for 60 minutes, and transplanted into syngeneic C57BL/6 recipients. RTEC apoptosis, histological changes and sCr were quantitated

Results: Tubular cells treated with the caspase inhibitor QVD-OPh had significantly reduced capsase-3 protein expression, caspase-3 activity, and apoptotic cell death vs saline or DMSO (vehicle) in a dose dependent manner. Treatment of donor kidneys with QVD-OPh significantly reduced sCr, and resulted in significantly less tubular cell apoptosis, brush border injury, tubular injury, cast formation, and tubule lumen dilation vs. DMSO and saline treated kidneys (Table 1).

Conclusions: Treatment of RTECs and donor kidneys with Q-VD-OPh significantly reduces apoptosis, histological injury and improves renal function in a mouse model of kidney transplantation. Caspase inhibition may be a useful strategy to prevent DGF and increase the donor pool.

Funding: Veterans Affairs Support

in vitro (cold storage and rewarming) n=3				
	Saline	DMSO	QVD-OPh	
Caspase-3 protein	+++	+++	–	
Caspase-3 activity	0.149 ± 0.003	0.139 ± 0.007	0.029 ± 0.003*	
Apoptotic cell death	21.98 ± 1.07	19.12 ± 1.31	9.53 ± 0.66*	
in vivo (kidney transplant)				
	Control (n=4)	Saline (n=11)	DMSO (n=7)	QVD-OPh (n=7)
Serum creatinine (mg/dl)	0.33 ± 0.02	2.71 ± 0.21	1.85 ± 0.29	0.99 ±0.41*
Apoptotic cell death/hpf	0.5 ± 0.1	3.3 ± 0.24	2.78 ± 0.28	1.1 ± 0.19*
TUNEL assay	0.02 ± 0.02	1.31 ± 0.15	0.79 ± 0.1	0.3 ± 0.09*
Brush Border Injury	1.03 ± 0.02	3.5 ± 0.08	3.29 ± 0.14	2.5 ± 0.23*
Tubular Injury	0	7.64 ± 0.48	4.46 ± 0.47	3.2 ± 0.52*
Cast	0	1.88 ± 2.34	1.92 ± 0.21	0.8 ± 0.15*
Lumen area	22.5 ± 9.06	2030 ± 143.6	1887 ± 180.5	1166 ± 201.2*

*p<0.05 vs. Saline & DMSO

FR-PO1017

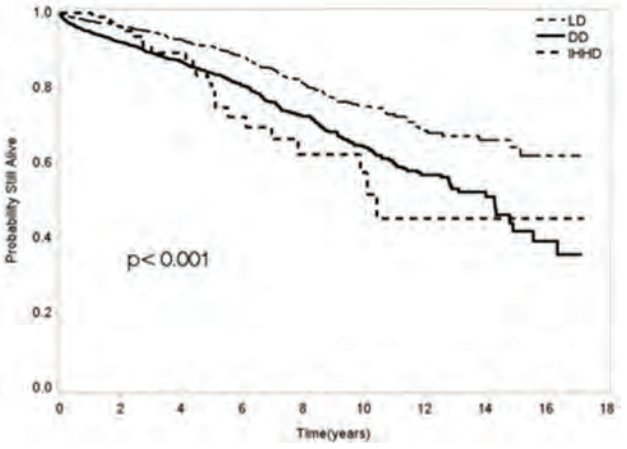
Intensive Home Hemodialysis Survival Is Comparable to Deceased Donor Kidney Transplant Angie G. Nishio-Lucar,[1] Genevieve R. Lyons,[1] Subhasish Bose,[2] Robert S. Lockridge.[1,2] *[1]University of Virginia HS, Charlottesville, VA; [2]Lynchburg Nephrology Physicians, Lynchburg, VA.*

Background: Kidney transplant (KT) is the treatment of choice for end-stage renal disease (ESRD) but, unfortunately, kidney donors are scarce. A prior Canadian study suggested intensive home hemodialysis (IHHD) had similar survival to deceased donor (DD) KT. Herein; we compare the survival of a large cohort of IHHD patients with kidney transplant recipients (KTR) in the same U.S. region.

Methods: We included all consecutive adult patients who received a first KT or started IHHD in the same Virginia region between October 1997 and June 2014. We obtained data on KTR from the Scientific Registry of Transplant Recipients and data on IHHD patients from Lynchburg Nephrology Physicians practice in Lynchburg, Virginia. We excluded recipients of en-bloc kidneys, multi-organ transplants and subsequent KT. Those receiving other home dialysis therapies, in-center hemodialysis (HD) or home HD getting < 20hrs/week or <4 sessions/week were also excluded. Kaplan-Meier method was used to estimate the overall survival (OS) among different modalities: IHHD versus living donor (LD) and DD KT. Adjusted hazard ratios (HR) were estimated using multivariate Cox proportional hazards regression.

Results: We identified 3097 KTR and 116 IHHD patients. Both cohorts had similar proportion of females (40.5% KTR vs 41.4% IHHD), African Americans (48.9% vs 50.9%) and diabetics (36.51% vs 37.1%). Compared to KTR, IHHD patients were more likely to be obese and have history of malignancy. LD KTR had the highest patient survival (Figure 1). At 5 years, the survival probability in IHHD patients was 79% (CI 0.69-0.90) compared to 84% (CI 0.82-0.86) in DD KTR, however the HRs did not significantly differ (HR 1.05, CI 0.68-1.62, p=0.837) after adjusting for ESRD cause, sex, age, and peripheral vascular disease.

Conclusions: In this study, survival of IHHD patients was not statistically different from DD KTR suggesting IHHD could be a reasonable alternative to DD KT. .



FR-PO1018

The Effect of Donor-Recipient Size Mismatch on Graft Survival Is Modified by Kidney Transplant Recipient and Donor Age Fanny Lepeytre,[5] Catherine Delmas-Frenette,[4] Xun Zhang,[3] Ruth Sapir-Pichhadze,[1] Bethany J. Foster,[2] Heloise Cardinal.[5] *[1]McGill University, Montreal, QC, Canada; [2]McGill University Health Center, Montreal, QC, Canada; [3]McGill University Health Centre, Montreal, QC, Canada; [4]None, Westmount, QC, Canada; [5]Centre de Recherche du CHUM, Montreal, QC, Canada.*

Background: Advanced donor age, recipient age and donor-recipient size mismatch are all independent risk factors for poorer kidney graft survival, but how these variables interact is unknown.

Methods: We performed a retrospective cohort study using the Scientific Registry of Transplant Recipient (SRTR). All first deceased donor kidney transplantations performed between Jan 1st 2000 and Jan 1st 2015 in recipients aged ≥18 years were included. We used multivariable Cox proportional hazards models to assess the association between donor-recipient body surface area (BSA) ratio (≤ 0.9 vs. >0.9) and overall graft survival, defined as death with function, return to dialysis or retransplantation. We considered interactions between BSA ratio and each of recipient age (≤54 vs. >54 years; the median age) and donor age (≤60 vs. >60 years), as well as a 3-way interaction term of BSA ratio by recipient age and donor age.

Results: From a total of 118,101 patients, 39,330 (33.3%) experienced graft loss over a median follow-up of 4.8 years. The 3-way donor-recipient BSA ratio by donor age by recipient age interaction was statistically significant (p=0.02). Among recipients ≤54 years, a donor-recipient BSA ratio ≤ 0.9 was associated with a higher risk of graft failure when donors were younger than 60 (hazard ratio (HR): 1.11, 95% confidence interval (CI) 1.07-1.14); when the donor was older than 60, donor-recipient BSA ratio ≤ 0.9 was not associated with graft survival (HR: 0.92, 95% CI 0.81-1.04). In recipients >54 years, donor-recipient BSA ratio ≤ 0.9 was significantly associated with graft failure regardless of donor age (HR: 1.07, 95% CI 1.03-1.10 for donors ≤60 and HR: 1.09, 95% CI 1.02-1.16) for donors >60.

Conclusions: We find donor-recipient size mismatch to have a small but significant impact on graft survival in all but younger recipients of older deceased donors. We hypothesize that in the latter group, the adverse impact of donor age superscedes the effect of donor-recipient size mismatch, and a size mismatch should not be considered as adversely affect graft survival in this patient population.

FR-PO1019

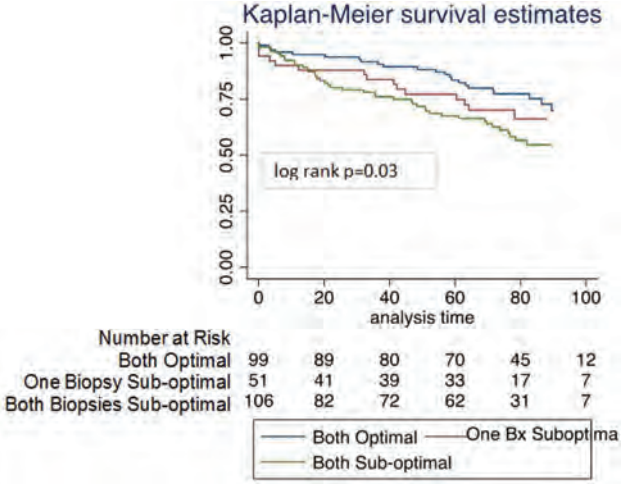
Contralateral Deceased Donor Kidney Procurement Biopsy Predicts Allograft Outcomes Syed A. Husain,[2] Dustin Carpenter,[1] Raphael Rosen,[3] Dominick Santoriello,[2] Mariana C. Chiles,[2] Leigh-Anne Dale,[4] Lloyd E. Ratner,[1] Sumit Mohan.[1] *[1]Columbia University, New York City, NY; [2]Columbia University Medical Center, New York, NY; [3]New York Presbyterian - Columbia, New York, NY; [4]New York Presbyterian Columbia, New York, NY.*

Background: Deceased donor kidney (DDK) procurement biopsies are often used to assess organ quality but have limited ability to predict outcomes, likely due to sampling error. We studied whether combining bilateral kidney biopsy results improves the prediction of allograft survival.

Methods: We identified all DDKs transplanted at our center from 2005-2009 that had procurement biopsies performed. Biopsy results from these kidneys and their contralateral partners (if available) were obtained from donor charts. Histology was classified as optimal if glomerulosclerosis (GS)≤10%, interstitial fibrosis/tubular atrophy (IFTA)≤10%, and vascular disease was none/mild. We compared death-censored graft failure for kidneys based on histologic category.

Results: 256 donors had a procurement biopsy on both kidneys, among whom 80.1% had concordant bilateral histologic categorization (99 both optimal, 106 both suboptimal) (κ=0.60, p<0.001). Agreement was higher for IFTA and vascular disease (both 75.8%) than GS (58.6%). When bilateral kidney biopsy results were combined, death-censored graft failure was highest for suboptimal kidneys with suboptimal partners, lower if only one kidney in the pair had optimal histology, and lowest for optimal kidneys with optimal partners (p=0.03) (Figure1). 43 kidneys (16.8%) had contralateral partners that were discarded. Discarded contralateral kidneys were more likely to have GS>5% (58.1% v 38.0%, p=0.02), as were their transplanted partners (60.5% v 41.3%, p=0.02). IFTA and vascular disease were not associated with discard. Partner discard did not predict transplanted kidney outcomes beyond biopsy results.

Conclusions: Adding contralateral kidney biopsy findings to DDK procurement biopsy appears to improve predictive power. When available, contralateral kidney biopsy findings should be provided to clinicians as part of the organ offer.



FR-PO1020

Outcomes of HLA-Incompatible Living Donor Kidney Transplantation Compared to Deceased Donor Kidney Transplantation or Dialysis and HLA-Compatible Living Donor Kidney Transplantation Tai yeon Koo, Jung-hwa Ryu, Ji-Jing Yan, Kyungok Min, Jaeseok Yang. *Seoul National University Hospital, Seoul, Republic of Korea.*

Background: HLA-incompatible(HLAi) living donor(LD) kidney transplantation(KT) is one of efforts to increase opportunity for sensitized end-stage renal disease patients due to organ shortage. Recently there are controversies for outcomes of HLAi KT. US data showed better outcomes of HLAi LDKT compared to HLA-compatible(HLAc) deceased donor(DD) KT or dialysis, whereas UK data demonstrated that waiting for DDKT or HLAc LDKT has good outcomes comparable to HLAi LDKT. Therefore, we tried to compare outcomes of HLAi LDKT with those of DDKT or dialysius, and HLAc LDKT in Korea

Methods: Forty-eight patients underwent HLAi LDKT after desensitization between 2006 and 2017. Indications of desensitization were positive complement-dependent cytotoxicity cross-match, positive flow-cytometric cross-match, high panel-reactive antibody tests, and positive donor-specific antibodies. We compared outcomes among HLAi LDKT patients, wait-listed patients who had continued to undergo dialysis(n=2047), patients who underwent either dialysis or DDKT(dialysis-or-transplantation group; n=2610), DDKT patients(n=563) and HLAc LDKT patients(n=654).

Results: In the HLAi LDKT group, patient survival rates were 97.8% at 1 year, 97.8% at 5 years and 97.8% at 8 years, as compared with rates of 98.4%, 96.4%, and 94.8% respectively in dialysis-group, rates of 98.3%, 97.2%, and 95.2% repectively in dialysis-or-transplantation group, rates of 99.7%, 99.4% and 98.6% respectively in LDKT group. There was no significant difference in patients survival rate among the groups. Although 6-month graft survival rate in HLAi LDKT was worse than that in HLAc LDKT, there was no significant difference in graft survival rates after 6 months between HLAi LDKT and any other group. Patient and graft survival rate of HLAc LDKT were better than dialysis or DDKT. In safety aspects, incidence of either antibody-mediated rejection or infectious complication did not differ among the groups.

Conclusions: In conclusion, outcomes of HLAi LDKT were comparable with those of dialysis or DDKT, dialysis alone, and HLAc LDKT. Therefore, we should consider many factors such as outcomes of dialysis, mean waiting time for HLAc DDKT, donor exchange program and experience of desensitization before decision of HLAi LDKT in sensitized candidates.

FR-PO1021

Predicting Expanded Criteria Donor Transplant Outcomes Ruth Sapir-Pichhadze,[1] Jean Tchervenkov,[2] Carly Rabin,[3] Dana Baran,[4,1] Justin Morein,[1] Paramita Saha chaudhuri.[1] *[1]McGill University, Montreal, QC, Canada; [2]McGill Unversity Health Center, Montreal, AB, Canada; [3]Royal College of Surgeons in Ireland (RCSI), Montreal, QC, Canada; [4]Royal Victoria Hospital, Montreal, QC, Canada.*

Background: Decisions on expanded criteria donor (ECD) organ utilization or discard rely primarily on selected clinical and histological features of ECD grafts. We

sought to identify which of the donor, recipient, and transplant characteristics are most predictive of long-term ECD transplant outcomes.

Methods: We conducted a retrospective cohort study in first time ECD kidney transplant recipients (KTR) transplanted between January 1, 2008 and December 31, 2014 at a Canadian Centre. The value of baseline donor (kidney donor risk index (KDRI), eGFR, and histology on frozen sections of procurement biopsies), recipient (age, sex, and cause of ESRD) and transplant (HLA mismatch, pulsatile perfusion, cold ischemia time, induction therapy, maintenance immunosuppression, and delayed graft function (DGF)) characteristics in predicting all-cause graft failure, defined as return to dialysis, re-transplantation, and death with function, was evaluated in univariate Cox proportional hazards models. Given the small sample size, variables that were statistically significant at level = 0.1 in the univariate analysis were considered for inclusion in multivariable models. In addition to baseline characteristics, a multivariable model including time-varying post-transplant eGFR measured at 3-months intervals was also fit. For the multivariable Cox proportional hazards models, p-value <0.05 was considered statistically significant.

Results: A total of 163 first-time ECD KTR with a median post-transplant follow-up of 3 years were included. Of the baseline donor, recipient and transplant characteristics, recipient age, cause of ESRD, and DGF were statistically significantly associated with all-cause graft loss in univariate analyses (p-value of likelihood ratio test 0.04, 0.07, and 0.01, respectively). In the time-fixed and time-varying multivariable Cox proportional hazards models, only recipient age (hazard ratio (HR) 1.04 [95% confidence interval (CI): 1.00, 1.09]; p-value=0.06) and time-varying eGFR (HR 0.96 [95%CI: 0.94, 0.98]; p-value=0.001), respectively, were independently associated with all-cause graft loss. C-indeces were 0.62 and 0.696 (SE=0.05), respectively.

Conclusions: In our study, recipient age and post-transplant eGFR were most predictive of ECD transplant outcomes. Caution should be exercised when considering organ discard based on ECD donor characteristics alone.

FR-PO1022

Inter-Correlations between Psychosocial Pre Transplant Determinant of Post-Transplant Kidney Allograft Function Sujan P. Shah, Brittany L. Schreiber, Flor Espinoza, Ann Kathleen N. Gamilla-Crudo, Rohan Patankar, Omar A. Aleter, Wayne G. Fischer, Muhammad A. Mujtaba. *University of Texas Medical Branch, Galveston, TX.*

Background: Psychosocial factors are common in patients with advanced and end stage kidney disease and they may be associated with post kidney transplant outcomes. When these patients are referred for transplant evaluation psychosocial and nutrition history is an important component of evaluation however there is lack of data on post-transplant implication of these factors. The aim of this study was to determine the correlations between pretransplant, nonclinical and psychosocial factors to post-transplant clinical outcomes.

Methods: We selected the following pre-transplant factors: gender, food stamp, marital relationship, insurer, education, Karnofsky score, history of depression, exercise, albumin level history of substance abuse, distance from transplant center. The posttransplant clinical outcomes selected were quality of kidney allograft at 6 months expressed as serum creatinine. The study involved retrospective analysis of 136 kidney transplant patients. There were 56 female patients and 75 male patients. We had 72 Hispanics (53%), 33 African Americans (24%), 22 Whites (16%), 9 Asians (7%). Patients age ranged from 25 years to 77 years. We used nominal logistic regression analysis and multinominal logistic regression analysis to identify the significant relationship between one dependent nominal variable and one or more continuous-level independent variables. A p-value of ≤ 0.05 was considered significant.

Results: Factors associated with significantly better serum creatinine at 6 months included: Female gender (p 0.014), active pre listing clinic follow up (0.0001), compliance with dialysis (0.06), and serum albumin >3.5 gm/dl (0.007). Patient primary insurer, family support, mariatal status, exercise, food stamp status, history of depression, history of substance abuse, education level, race, distance from transplant center, and retransplant status was not found to be associated with 6 months serum creatinine.

Conclusions: Pretransplant psychosocial factors are associated with the post transplant kidney allograft function. This also shows the pre transplant psychosocial history is an integral but often ignored part of evaluation and should be stressed upon. More prospective trials are required to confirm our findings.

FR-PO1023

The Reproducibility and Prognostic Capability of Procurement Frozen Section Renal Allograft Biopsies Dustin Carpenter,[2] Syed A. Husain,[3] Raphael Rosen,[4] Dominick Santoriello,[3] Mariana C. Chiles,[3] Lloyd E. Ratner,[2] Sumit Mohan.[1] *[1]Columbia University, New York, NY; [2]Columbia University, New York City, NY; [3]Columbia University Medical Center, New York, NY; [4]New York Presbyterian - Columbia, New York, NY.*

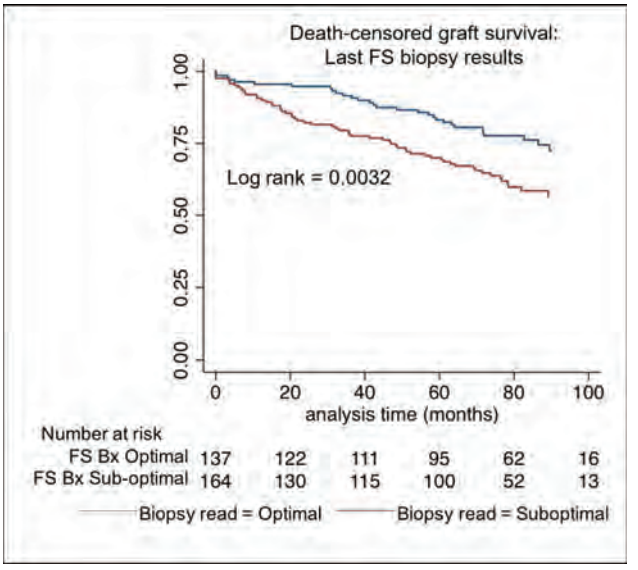
Background: Biopsies taken at the time of deceased donor kidney procurement are frequently used to assess organ quality and are cited as a leading reason for discard. However, the reproducibility and prognostic capability of these biopsies are controversial.

Methods: We compiled a retrospective, single institution, continuous cohort of deceased donor kidney transplants with complete biopsy reads from 2006-2009 (n=301). Histology was classified as optimal if glomerulosclerosis and interstitial fibrosis/tubular atrophy were each ≤10%, and vascular disease was mild or none. Cox proportional hazards and Kaplan-Meier methods were used for time to event analysis.

Results: The reproducibility of procurement biopsies was poor: in the 119 kidneys that were biopsied twice, 44.5% had histologic category (optimal vs. suboptimal) discrepancies comparing the first and second biopsies (κ=0.11, p=0.11). Using the frozen section biopsy nearest the time of procurement, graft survival was worse for kidneys with suboptimal vs.optimal histology (HR 1.91, p=0.004) (figure 1). This discriminatory ability of procurement biopsies to predict graft failure was stronger when they were obtained and read in our local OPO (p=0.04) compared to the donor OPO (p=0.18). Regardless of histologic category, transplantation was associated with a significant survival advantage compared to remaining on dialysis (5-year overall patient survival 87.1% [optimal] vs. 83.4% [suboptimal] vs. 35% [dialysis]).

Conclusions: Frozen section procurement kidney biopsies are poorly reproducible, but may help determine long term allograft function. However, even DDRT kidneys with suboptimal histology will result in a significant survival advantage compared to dialysis suggesting that biopsy findings alone should not be used to discard an organ.

Funding: Other NIH Support - NIH T-32 Training Grant, Other U.S. Government Support



FR-PO1024

The Deceased Donor Implantation Biopsy and Histopathological Characteristics for Predicting Graft Outcomes in Kidney Transplant Recipients Diping Wang,[2] Cindy S. Yip,[2] Christopher Dodoo,[1] Aijaz A. Gundroo,[2] Alok K. Dwivedi,[1] Lin Liu,[2] Shirley S. Chang,[3] Mareena S. Zachariah,[3] John E. Tomaszewski.[2] *[1]Texas Tech University Health Sciences Center El Paso, El Paso, TX; [2]University at Buffalo, Buffalo, NY; [3]Nephrology, Erie County Medical Center, Buffalo, NY.*

Background: The allocation of deceased donor kidneys has become more complex because of the increasing spectrum of donor and recipient co-morbidities. The kidney donor risk index (KDRI) was designed to capture the donor factors known at the time of organ procurement, but donor gender, cigarette use, polysubstance abuse, glomerulonephritides, and interstitial disease are not included in the KDRI and can influence graft outcomes. In this study, we evaluted the prognostic value of pre-implantation histopathological parameters in predicting the graft function after transplantation.

Methods: Deceased donor recipients transplanted between January 2012 and March 2016 were followed up to four years were included in this study. Pre-implantation biopsies were re-evaluated per the Banff 97 classification and chronic allograft damage index (CADI) and graft function was monitored. Glomerular filtration rate (GFR) at the last visit was categorized into a staging variable (Stage) after which multinomial logistic regression was used to assess the association between stage and the cofactors. Ordinary linear regression was also used to assess the association between GFR at last visit and the cofactors. Logistic and linear regressions were used to assess the association between Banff and CADI scores and the cofactors.

Results: Inter-observer correlation between the two pathologists for total Banff score (ICC = 97%) and CADI score (ICC = 92%) were excellent. The presence of glomerulosclerosis (GS, -10.15) and tubular atrophy (TA, -10.39) in CADI score were found to be associated with final GFR. In addition to GS, glomerular mesangial matrix (GM) in CADI was also associated with stages of GFR. Only presence of glomerular mesangial matrix (CM) parameter in Banff score was found to be associated with stage and graft function. In separate multivariable analyses after adjusting for other significant variables, GM present and CM present were associated with chronic kidney disease stage.

Conclusions: A multiparametric approach may be developed by incorporating pre-implantation biopsy information along with important clinical variables to predict outcome.

FR-PO1025

Is There a Role for Implantation Biopsies in the Era of Kidney Donor Profile Index (KDPI)? Luis C. Francalacci, Ling-Xin Chen, Richard V. Perez, Angelo M. De Mattos. *University of California, Davis, Sacramento, CA.*

Background: Implantation biopsies (**IBx**) are commonly performed after deceased donor kidney transplantation (**DD**). However, its role in the management of these grafts and the impact on outcomes are not fully described. We evaluated the role of IBx on short and long term graft outcomes and their relationships with KDPI.

Methods: We analyzed all the DD performed at our center between 2007 and 2013. Grafts not eligible for IBx (en-bloc pediatric) were excluded. Multivariable analysis was used to adjusted for confounding variables.

Results: Out of 885 DD performed, 477 had a IBx and 411 had not. The two groups were not different in terms of gender, age, race (donors and recipients), re-transplant, diabetes, PRA, or HLA mismatches, proportions of ECD, DCD, deaths from CVA, local procurement, pulsatile perfusion, terminal creatinine, and distribution of KDPI. There was a lower proportion of DCD in the IBx group (15 vs 21%, p=.02) and lower mean cold ischemic time - **CIT** (23 vs 25h, p=.006). The IBx group had a significantly better one year graft survival (96 vs 91%, p=.001). By multivariable analysis IBx was associated with 60% (CI 21.9 – 72.1%, p=.002) decreased risk of graft loss within the first year when adjusted by DCD, KDPI, and cold ischemia time. Long term graft survival was worse across strata of KDPI (p=.006). However, there were no difference in graft survival between the IBx and no-IBx groups (p=.16), even within the strata of KDPI: <35% (p=.7), 35 – 85% (p=.1), and >85% (p=.7). The composite chronicity score: (glomerulosclerosis-**GS** plus interstitial fibrosis-**IF**) was different across strata of KDPI (14, 44, and 66%, p<.001). However, there were no differences in graft survival by the percentage of GS (p=.4), IF (p=.4), or GS+IF (p=.08) on IBx. There was a lower incidence of delayed graft function on the IBx group (19 vs 31%, p<.001) that persisted even after adjustment for CIT and DCD. There were differences in e-GFR at 1, 3, and 5 years across strata of KDPI. However, no differences in e-GFR were found between the IBx and no IBx groups at the same time points.

Conclusions: Implantation biopsy is independently associated with better one year graft survival. However, KDPI becomes the most important factor associated with long term graft survival. The specific management modifications based on the results of IBx should be the focus of future investigation.

Funding: Clinical Revenue Support

FR-PO1026

Histologic Findings on Time-Zero Allograft Biopsies Correlate with Kidney Donor Profile Index (KDPI) and 30-Day Serum Creatinine Kuang-Yu Jen, Ling-Xin Chen, Luis C. Francalacci, Richard V. Perez, Angelo M. De Mattos. *University of California, Davis, Sacramento, CA.*

Background: KDPI is used as a numerical measure of deceased donor kidney quality relative to other recovered kidneys. It uses 10 donor factors but does not consider histologic findings. Correlation of KDPI to histologic findings is lacking. In this study, we examined the correlation between KDPI and chronic changes seen in time zero biopsies. We also assess whether such histologic findings add to the predictive ability of KDPI for 30-day serum creatinine and delayed graft function.

Methods: All deceased donor kidney transplants at our institution from 07/01/2016 to 03/15/2017 that had a time-zero biopsy were included. The biopsies were graded according to Banff 2015 guidelines. Distribution of KDPI was compared by Banff scores for chronicity (ci and ct) as well as chronic vascular disease (ah and cv). Linear regression was used to assess: 1) correlation between Banff scores and donor KDPI and 2) the ability of KDPI and Banff scores (either individually or together) to predict 30-day serum creatinine. Logistic regression was used to assess the ability of KDPI and/or Banff scores to predict delayed graft function.

Results: 134 recipients had a time-zero biopsy performed. There was correlation between the following Banff scores and KDPI: ci, ct, ah and cv (Table 1). ah score of greater or equal to 2 most closely correlated with KDPI. 30-day serum creatinine was predicted by KDPI, as well as ci, ct and ah scores. Using KDPI with ci + ct scores resulted in the best prediction of 30-day serum creatinine, with a correlation coefficient of 0.27. There was no correlation between Banff scores and the occurrence of delayed graft function. A KDPI score of 20-85% predicted delayed graft function at an OR of 8.18 (95% CI 1.80-37.2, p-value 0.007).

Conclusions: Chronic changes seen in time zero allograft biopsies correlate with KDPI and may be useful for predicting early graft outcomes.

Histologic variables, mean 30-day SCr and DGF by KDPI categories

KDPI	N	ci + ct ≥ 2	ah ≥ 2	cv ≥ 2	Mean 30-day SCr (mg/dL)	DGF, n (%)
0-20%	19	1 (5%)	1 (5%)	4 (21%)	1.32	2 (11%)
21-85%	104	33 (32%)	40 (38%)	39 (38%)	2.25	51 (49%)
86-100%	11	4 (36%)	6 (55%)	3 (27%)	2.83	3 (27%)
p-value*		0.03	0.003	0.38	0.01	0.003

*p-values obtained via Fisher's exact test for categorical variables and ANOVA for continuous variables

FR-PO1027

Clinical Outcome of Kidney Transplantation from Deceased Donors with Marginal Kidney Function Seong Sik Kang,[1,2] Hayeon Park,[1] Sang Mok Yeo,[1] Woo Yeong Park,[1,2] Kyubok Jin,[1,2] Sung Bae Park,[1,2] Seungyeup Han.[1,2] *[1]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Republic of Korea; [2]Keimyung University Kidney Institute, Daegu, Republic of Korea.*

Background: Deceased donor kidney transplantation (DDKT) in Korea has been activated recently. However, organ shortage for transplantation is getting worse, and DDKT using acute kidney injury (AKI), expanded criteria donor (ECD), or high kidney donor profile index (KDPI) kidney is increasing. Herein, we evaluated the clinical outcome of KT recipients (KTRs) who received marginal kidneys.

Methods: We retrospectively reviewed DDKT performed at Keimyung university hospital between January 2010 and December 2014. Ninety four DD and their corresponding 95 KTRs were included. We analyzed the clinical outcomes of DDKT according to AKI, ECD, and high KDPI (> 85%).

Results: KTRs belonging to the AKI group were 42 (44.2%), ECD group were 23 (24.2%), and high KDPI group were 16 (16.8%). The mean follow-up period was 42.6 ± 17.4 months (range 2-81). The incidence of delayed graft function (DGF) was significantly higher in the AKI group than in the non-AKI group ($P = 0.011$), but not in the ECD group and the high KDPI group. The estimated glomerular filtration rate (eGFR) of the AKI group was significantly lower at 1 week, 2 weeks and 1 month after KT compared to the non-AKI group. After 3 months of KT, there was no significant difference in eGFR between the AKI group and non-AKI group, the ECD group and standard criteria donor group, and the high KDPI group and low KDPI group. Patient survival rate showed no significant difference, according to AKI, ECD, or high KDPI. Allograft survival rate showed no significant difference in the AKI, ECD, and high KDPI groups compared with the control groups. However, allograft survival rate was significantly lower only in the group with acute rejection (AR) than in the group without AR ($P < 0.001$). In a multivariate analysis, AR was an independent risk factor for graft failure (hazard ratio 85.75, 95% confidence interval, 7.02-1047.77, $P < 0.001$), but AKI, ECD, or high KDPI were not.

Conclusions: AKI of DD kidney showed significant association with increased incidence of DGF. However, KT using AKI, ECD, or high KDPI donor kidney performed similarly to the control group in terms of graft function, graft survival, and patient survival. More detailed criteria for selecting a proper DD will be needed.

FR-PO1028

Impact of the Kidney Allocation System (KAS) in Highly Sensitized Patients Vineeta Kumar, Jayme E. Locke, Robert S. Gaston. *University of Alabama at Birmingham, Birmingham, AL.*

Background: Highly sensitized (HS) patients, defined as a PRA of 99-100% are awarded additional priority points in the new KAS instituted December 2014. We evaluated the impact of these changes at our institution at 1 and 2 year post transplantation

Methods: HS candidates who received a transplant on or after 12/4/2014 were prospectively monitored. Treatment included induction with anti-thymocyte globulin & IV corticosteroids, maintenance with tacrolimus, mycophenolate & prednisone. Designated care providers followed the HS recipients with more intensive frequency, donor specific anti HLA antibody (DSA) & viral monitoring, implantation & 6 month surveillance biopsies. Outcomes of interest were rate of transplantation, patient & allograft survival and function, acute cellular or antibody mediated rejection (AbMR). and were compared in a matched control population in a 1:2 fashion for age, race, and time of transplant.

Results: There were 15 HS patients transplanted between 12/8/14-10/5/15. The rate of transplant has risen from 1.6% in 2012 to 12.6% in 2015.60% of these were from national offers in contrast to 37.5% in the past. All 15 recipients have >1 year follow up time with 100% patient & graft survival. 12 out of 15 have 2 year follow up time with 2 graft losses (for recurrent FSGS) and 1 death for sepsis in this group. Rate of patient and graft survial in the matched cohort was 100% at 1 & 2 years post transplant. Graft function was equivalent in the two groups with serum creatinine (1.4vs.1.6mg/dl, Pvalue 0.7), eGFR (52vs.48ml/min/m2, pvalue 0.9), random urine protein/creatinine ratio (1.1vs.2.3). Rate of denovo DSA formation at 2 years was similar in the two groups at 23vs.26%, p value 0.1. All the high PRA patients in this study were followed by a specialized team with an average of 16 clinic visits per patient vs. 9 in the control population

Conclusions: There has been a shift to increased national offers under the new KAS within the HS candidates at our institution as was intended by the new KAS. All of them have had acceptable early patient and allograft survival and function with intensive and individualized monitoring and follow up. However care of these patients is very resource itensive and needs a dedicated and specialized group of care givers for post transplant care for a successful outcome that benefits a very specific subset of patients.

FR-PO1029

Recipient Age Is Significantly Associated with Immunological and Infective Complications Post Kidney Transplantation Rachel Hung,[3] Sumoyee Basu,[2] Gabrielle Goldet,[1] Raymond Fernando,[5] Sacha A. De Serres,[6] Paul Bass,[2] Mark Harber,[4] Alan D. Salama,[5] Ciara N. Magee.[1] *[1]None, Boston, MA; [2]Royal Free Hospital, London, United Kingdom; [3]Royal Free Hospital, London, London, United Kingdom; [4]UCL centre for Nephrology, London, United Kingdom; [5]University College London, London, United Kingdom; [6]University Health Center (CHU) of Quebec, Laval University, Quebec, QC, Canada*.

Background: In recent years, there has been a marked increase in the number of older patients (> 65) undergoing kidney transplantation. While there is increasing evidence that the ageing immune system is characterised by immunosenescence, many centres do not have age-specific protocols for immunosuppression. In this study, we sought to examine the effect of recipient age on the development of complications of over- and under-immunosuppression post-transplantation.

Methods: We investigated the outcomes of 90 patients aged > 65 who underwent kidney transplantation in our centre between April 2009-March 2016, 42 of whom were aged >70; these patients were compared to 57 controls aged 18 – 64, who were matched for number of HLA mismatches. Recorded variables included % cRF pre-transplant, rejection, development of *de novo* donor-specific anti-HLA antibodies (DSA) and development of CMV viraemia post-transplantation.

Results: Interestingly, there were significant differences in the mean %cRF pre-transplant across the groups:18-34, 17.75%; 35-49, 29.65%; 50-64, 36.29%; 65-69, 17.1%; and >70, 8.4%; p=0.008. The rate of rejection was markedly increased in the control group compared to those aged > 65 years (19.3% vs. 11.1%), although this did not reach statistical significance. Conversely, rates of CMV viraemia were significantly elevated in recipients >65 when compared to recipients <65 (75.6% vs 50.9%, p=0.03). Rates of *de novo* Class I DSA were also significantly higher in the younger age groups (18.8%, 0% & 23.8% in patients aged 18-34, 35-49 & 50-64, compared to 4.2% & 7.1% in recipients aged 65-69 & >70, respectively; p=0.025), while the development of *de novo* Class II DSA followed a similar trend (6.3%, 20% & 14.3% in patients aged 18-34, 35-49 & 50-64, versus 2.1% & 4.8% in recipients aged 65-69 & >70, respectively; p=0.077).

Conclusions: These data indicate that older recipient age is associated with reduced rates of rejection and *de novo* DSA but significantly increased infectious complications post-transplantation. Given the significant morbidity consequent to over-immunosuppression, consideration should be given to the development of age-specific protocols for immunosuppression.

FR-PO1030

Impact of Modifiable and Non-Modifiable Factors on Patient and Kidney Allograft Outcomes: A Twin Kidney Analysis of Left/Right Deceased Donor Kidney Pairs Natalie M. Otto,[1] Thomas Schachtner,[1] Petra Reinke.[2] *[1]Charite Campus Virchow Clinic, Berlin, Germany; [2]Charité, Campus Virchow Klinikum, Berlin, Germany*.

Background: The impact of donor factors on kidney allograft outcomes and infectious complications has been suggested in many previous studies. However, analysis of left or right donor kidney pairs are rarely performed, although individual recipients risk factors may be analyzed in a paired difference test and significantly reduce donor cofounders.

Methods: Here, we studied all transplanted left/right deceased donor kidney pairs at our center between 2003 and 2015. A total of 174 paired kidney transplantations were performed from 87 donors. To account for identical donor characteristics among left/right donor kidney pairs a paired difference testing was performed.

Results: Patient survival, allograft survival and allograft function were not correlated among left/right donor kidney pairs (p>0.05). In a paired analysis recipient age, gender, BMI, preformed diabetes, cold ischemia time, HLA-match did not impact allograft outcomes among left/right kidney pairs (p<0.05). Delayed allograft function was more likely detected in both kidney pairs than one pair only (p<0.05). Male gender was associated with delayed allograft function among kidney pairs (p=0.021). Primary nonfunction, acute cellular rejection, BK viremia, EBV viremia, sepsis, and cancer were more likely detected in one pair only (p<0.05). All 20 cases of BK viremia were detected in one pair only (p<0.001). A higher number of HLA-mismatches was associated with BK viremia among kidney pairs (p=0.006). Re-transplantation in one pair was associated with a higher incidence of acute cellular rejection.

Conclusions: Despite an increased incidence of delayed allograft function in left/right kidney pairs, our results suggest low impact of donor factors on patient and allograft outcomes. In contrast, our data suggest a strong impact of individual recipient characteristics as common infectious complications as CMV or BKV don't appear solely attributable to donor origin, but to impaired immunity of the recipient.

FR-PO1031

Factors Impacting Racial Disparity in Kidney Transplant Wait-Listing Yue-Harn Ng,[1] V. Shane Pankratz,[1] Kellee Bornemann,[2] Emilee J. Croswell,[2] John R. Pleis,[2] Ron Shapiro,[3] Mark L. Unruh,[1] Larissa Myaskovsky.[2] *[1]University of New Mexico, Albuquerque, NM; [2]University of Pittsburgh, Pittsburgh, PA; [3]RECANATI/MILLER TRANSPLANTATION INSTITUTE, New York, NY*.

Background: African Americans (AA) have a higher incidence of end-stage renal disease but lower rates of kidney transplantation (KT) compared to whites (WH). Disparities persist after adjusting for medical factors. We assessed the relationship of non-medical (eg. cultural, psychosocial, knowledge) factors with KT wait-listing (WL) within the context of racial differences.

Methods: We conducted a longitudinal cohort study with 1057 patients who were referred for KT evaluation. We used Kruskal-Wallis and chi-square test to examine race differences in non-medical factors. We assessed differences in time to KT WL with propensity weight adjustments. We then identified variables associated with early(<100d) vs late WL(>100d).

Results: We found significant racial differences in baseline characteristics[Tab1]. Both with and without propensity weight adjustment, AAs were less likely to be wait-listed compared to WH. This disparity was evident in the late wait-listers[Fig1]. KT knowledge, income and having live donors were positively associated with WL. Age, comorbidities, low SES, and being on dialysis were negatively associated with early WL. Among the late wait-listers, trust in physicians, family loyalty, and social support were positively associated but being AA was negatively associated with WL.

Conclusions: Non-medical factors affect racial disparities in KT WL. Developing interventions targeting cultural and psychosocial factors that put patients at greater risk for later WL may promote equal access to KT.

Funding: NIDDK Support

Table 1. Baseline Characteristics

	Non-Hispanic White (n=792)	Non-Hispanic Black (n=265)	p-value
Demographic Characteristics			
Age	57.6 ± 13.6	54.0 ± 12.4	<0.001
Female	301 (38.0)	102 (38.5)	0.89
Education (HS or less)	356 (45.2)	136 (51.7)	0.07
Occupation (≥ skilled manual worker)	406 (52.8)	95 (36.5)	<0.001
Income: (<15K)	162 (21.3)	108 (43.9)	<0.001
Insurance: Public	247 (31.6)	124 (47.5)	<0.001
Private/Public	310 (39.7)	80 (30.7)	
Married	456 (57.9)	87 (33.1)	<0.001
Medical Factors			
Charlson co-morbidity score	4.1 ± 3.4	5.9 ± 4.0	<0.001
Burden of kidney disease	3.7 ± 1.1	3.6 ± 1.1	0.37
Number of potential donors	21.5 ± 16.5	26.2 ± 21.0	0.004
On dialysis (Yes)	447 (58.8)	192 (79.3)	<0.001
Cultural Factors			
Racism in healthcare	2.2 ± 0.7	2.7 ± 0.8	<0.001
Medical mistrust index	2.4 ± 0.5	2.6 ± 0.5	<0.001
Trust in physician	2.2 ± 0.5	2.3 ± 0.5	<0.001
Family loyalty scale	49.0 ± 8.7	52.4 ± 11.0	<0.001
Religious objection to LDKT	2.0 ± 0.5	2.1 ± 0.5	<0.001
Experienced discrim. in health care	134 (17.0)	133 (51.0)	<0.001
Psychosocial Factors			
Social support - Total	42.7 ± 5.6	41.3 ± 6.7	0.007
Self esteem scale	3.2 ± 0.5	3.2 ± 0.5	0.25
Anxiety (> moderate)*	35 (4.4)	13 (4.9)	0.74
Depression (>moderate)	27 (3.4)	15 (5.7)	0.10
Transplant Knowledge			
Transplant knowledge	21.6 ± 2.7	20.2 ± 3.0	<0.001
Number of learning activities	4.6 ± 1.6	4.3 ± 1.6	0.002
Hours engaged in learning activities	20.2 ± 24.1	15.5 ± 22.8	<0.001
Total transplant concerns	10.8 ± 4.6	11.2 ± 4.9	0.30

Continuous variables are expressed as mean ± SD while categorical variables are expressed as n (%)
* Anxiety & depression was measured using the Brief Symptom Inventory (BSI) [Scale 1-5 with >3 being moderate]

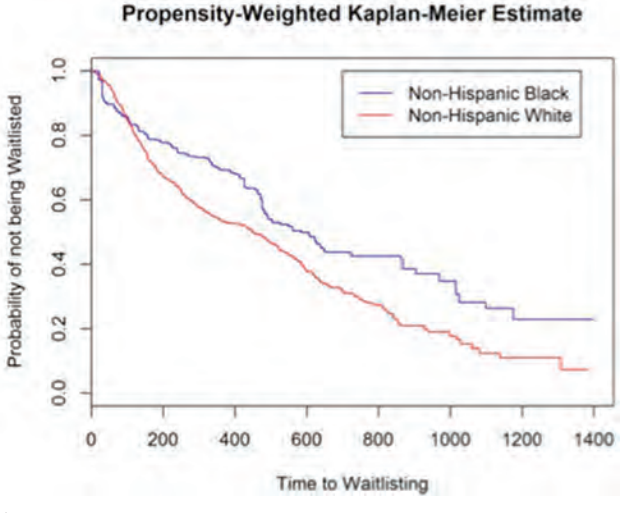


Fig1

FR-PO1032

Long-Term Outcomes of Kidney Transplantation Using Non Conventional Donors Luis C. Francalacci, Ling-Xin Chen, Richard V. Perez, Angelo M. De Mattos. *University of California, Davis, Sacramento, CA.*

Background: With the donor-recipient gap widening the pressure to utilize more non-conventional deceased donors (NCD) has increased. However, analysis of long term outcomes of such transplants is lacking. We described our experience with NCD over the past decade.

Methods: We included all deceased donor transplants performed at our center between 2005 and 2013 using donors with cardiac death, dual grafts, extended criteria, and with acute kidney injury: the **NCD** group. We compared their graft survival (Kaplan-Meier and Cox-regression) and renal function (MDRD eGFR) with our standard criteria donor (**SCD**) cohort.

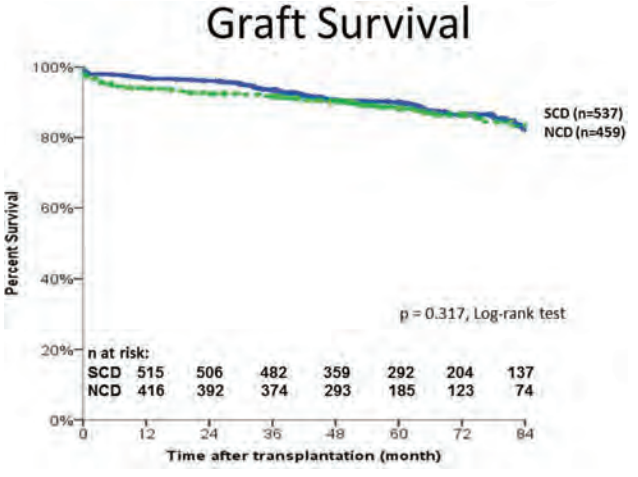
Results: Of all 996 adult deceased donors transplants 459 were NCD and 537 were SCD. The groups were not different in terms of gender, race, dialysis or HCV exposure, type of insurance, and BMI at transplant, The NCD group was older and had more diabetics, PRA was lower and less re-transplants. More often their kidneys came from older donors, were non-local, had a longer cold ischemic time, placed on pulsatile perfusion, and donor death by CVA (p<.001, all comparisons). Death censored graft survival was not different between groups (fig 1). After adjusting for all significant variables only age of recipients (p=.02) and donors with CVA (p=.002) were significant factors for graft failure. Renal function was lower on the NCD group at all time points. However, the eGFR was stable (and above 50 ml/min) within the groups for up to 7 years (table 1).

Conclusions: The use of NCD kidneys resulted in similar long term outcomes in terms of graft survival and function, as compared to SCD. The nephrology community and their patients should be aware of the benefits of accepting these grafts.

Funding: Clinical Revenue Support

Graft function (e-GFR, mean ± SD)

	NCD	SCD	p value
1 year	55 ± 19.5	63 ± 20.8	p < 0.001
3 years	56 ± 19.1	65 ± 22.9	p < 0.001
5 years	56 ± 22.6	64 ± 24.1	p < 0.001
7 years	55 ± 23.2	67 ± 23.3	p < 0.001



FR-PO1033

Factors Affecting Kidney Transplant Outcome in Very Old Recipients of Grafts from Very Old Donors Hernando Trujillo Cuellar,[1] Amado Andres,[1] Garcia A. Santiago,[1] Teresa Cavero escribano,[1] Candela Moliz,[1] Beatriz Redondo navarro,[2] Teresa Bada bosch,[2] Manuel Praga,[1] Esther Gonzalez monte.[1] *[1]Hospital 12 de Octubre, Madrid, Spain; [2]Hospital Universitario 12 de Octubre, Madrid, Spain.*

Background: Kidney transplantation is the best option for elderly patients with end stage renal disease. The major limitation in this group of patients is shortage of donors since kidneys from young donors are assigned to younger recipients. Spain had 43,4 donors pmp in 2016, 30% of them were aged over 70 years. Kidneys from these donors can be assigned to older patients without detriment to young recipients.

Methods: We performed a retrospective analysis of pretransplant clinical factors associated with graft and recipient survival in elderly patients (≥70 years) that received a kidney transplant from a very old donor (≥70 years) at our institution from October 2004 to December 2013 (and followed through April 25, 2017) (n = 155).

Results: Median age of donors and recipients was 77 (74-79) and 75 (73-78) years, respectively. The 3-year and 5-year patient survival was 73.1% and 67.1%. Mortality in the first year was 15.9%. Death censored graft survival was 83.4% at year 3 and 80.8% at year 5. History of cerebrovascular disease in the recipient was the only factor associated with patient survival (HR 5.12, p=0.027), while history of diabetes mellitus in the recipient was the only factor associated with the risk of graft loss (HR 4.40, p=0.0001).

Conclusions: Kidney transplantation from very old donors in patients over 70 years offers a survival advantage over staying on dialysis. History of cerebrovascular disease in the recipient was associated with an increased risk of recipient mortality, while history of diabetes in the recipient was associated with increased risk of graft loss. Further studies are needed to identify pretransplant clinical factors associated with increased risk of graft failure and recipient mortality in this population in order to improve allocation of these old allografts in the elderly patients.

Funding: Private Foundation Support

Donor characteristics	n = 112
Sex, n(%), male	50 (44.6)
Age, Md (IQR), years	77 (74-79)
Weight, Md (IQR), kg	70 (65-80)
SCr, Md (IQR), mg/dL	0.8 (0.7-0.9)
Hypertension, n(%)	72 (66.1)
Diabetes mellitus, n(%)	35 (32.1)
Cerebrovascular cause of death, n(%)	16 (14.3)
Glomerulosclerosis on kidney biopsy, n(%)	72 (87.8)
<15%	8 (9.8)
15-20%	1 (1)
21-30%	1 (1)
31-50%	
Recipient characteristics	**n = 155**
Sex, n(%), male	95 (61.3)
Age, Md (IQR), years	75 (73-78)
Weight, Md (IQR), kg	68 (61-75)
Dialysis duration before transplantation, Md (IQR), months	12 (5-24)
Previous kidney transplant, n(%)	16 (10.3)
Diabetes mellitus, n(%)	61 (39.4)
Coronary artery disease, n(%)	17 (11)
Cerebrovascular disease, n(%)	18 (11.6)
HLA mismatch, n(%)	4 (4-5)
Cold ischemia time, Md (IQR), hours	22 (19.5-25)

FR-PO1034

Referral Rates for Renal Transplant in Dialysis Clinic, Inc. Antonia Harford,[1] S. Paine,[2] R. Schrader,[2] Ambreen Gul,[2] Philip Zager.[1,2] *[1]UNM, Albuquerque, NM; [2]DCI, Albuquerque, NM.*

Background: Kidney transplantation (TXP) is the treatment of choice for medically appropriate End-Stage Renal Disease (ESRD) patients. Dialysis facilities play pivotal roles in (1) referring ESRD patients for the initial TXP evaluation; (2) assisting in the evaluation process; and (3) listing. Renal transplantation rates reflect significant racial disparity. Among ESRD patients incident in the US in 2011, overall the percent waitlisted or transplanted (WL/TXP) within 3 years was 13.7% but varied greatly by race, highest among Asians (32.7%) & lowest among Native Americans/Alaskan Native (11.1%). Dialysis Clinic, Inc. (DCI), a large not-for-profit provider, founded by a transplant nephrologist, is developing an innovative education program to enhance referral, WL/TXP & reduce health disparities.

Methods: The present study was conducted to obtain baseline data that will facilitate future annual assessments of the impact of this program. We studied 2,677 dialysis patients under age 70 who began dialysis in 2015, in 230 facilities operated by DCI. We used DCI's MIS to calculate referral, WL/TXP, & refusal rates, stratified by race, sex & diabetes status within the first year of dialysis.

Results: Overall, the referral rate was 62.6; 19.0% were WL/TXP, 43.6% were referred but not yet WL/TXP, 18.4% refused referral, & 28.3% were not referred. The rates, expressed per 100 patient years (95% CI), for referrals, not referred, WL/TXP & refusals, stratified by race, diabetes status, & sex are shown. There were no significant differences in referral or refusal rates across racial groups. Referral & refusal rates, respectively, did not differ significantly by race, sex or diabetes status. However, the point estimates for WL/TXP were lower in Blacks & Native Americans vs. Whites & in diabetics vs. non-diabetics.

Conclusions: Excellence in patient & staff education is essential to maximize transplant referral, WL/TXP, and minimize TXP related disparities. To accomplish these objectives innovative educational programs need to be developed & implemented for both dialysis facility staff & patients across the full-range of providers.

Rates, expressed as per 100 patient years (95% CI), for patients incident in 2015

	Total Referred	WL/TXP	Not Referred	Refused
Black	61.7 (56.3 – 67.0)	16.2 (13.4 – 18.9)	29.5 (25.8 – 33.2)	16.3 (13.5 – 19.0)
Native American	60.1 (39.3 – 80.9)	7.5 (0.2 – 14.9)	28.2 (13.9 – 42.4)	22.5 (9.8 – 35.3)
White	62.5 (58.0 – 66.9)	20.8 (18.2 – 23.4)	27.1 (24.1 – 30.0)	21.0 (18.4 – 23.6)
Female	57.8 (53.2 – 62.4)	17.6 (15.0 – 20.1)	28.9 (25.7 – 32.1)	22.6 (19.7 – 25.4)
Male	66.3 (62.0 – 70.6)	20.1 (17.8 – 22.5)	27.8 (25.1 – 30.6)	15.3 (13.2 – 17.3)
Diabetes Yes	58.5 (54.0 – 62.9)	12.2 (10.2 – 14.3)	28.6 (25.5 – 31.7)	21.4 (18.7 – 24.1)
Diabetes No	66.1 (61.7 – 70.5)	24.8 (22.2 – 27.5)	28.0 (25.2 – 30.9)	15.9 (13.8 – 18.1)
All	62.6 (59.5 – 65.7)	19.0 (17.3 – 20.8)	28.3 (26.2 – 30.4)	18.4 (16.7 – 20.1)

FR-PO1035

Discrepancy in the Documented Causes of Death among Kidney Transplant Recipients between USRDS and UNOS Databases Jingbo Niu,[1] Sankar D. Navaneethan,[1] Sreedhar A. Mandayam,[2] Jenny S. Pan,[1] Kevin F. Erickson,[1] Wolfgang C. Winkelmayer,[1] Venkat Ramanathan.[1] *[1]Baylor College of Medicine, Houston, TX; [2]None, Bellaire, TX.*

Background: Accurate reporting of cause of death is critical towards identifying specific interventions to improve survival. For U.S. kidney transplant recipients (KTR) cause of death is reported in the United Network for Organ Sharing (UNOS) and United States Renal Data System (USRDS) registries. Herein, we compared the causes of death reported in these two national databases.

Methods: We identified all adult first-time KTRs (1996-2012) with functioning graft when died and separately ascertained their reported causes of death from the USRDS and UNOS databases. Deaths were classified into: a) cardiovascular, b) infectious, c) malignancy, d) others, and e) unknown.

Results: Of 196,748 KTRs, for whom USRDS reported causes of death for 40,742 and UNOS reported causes of death for 40,424 patients, we included 30,721 patients with cause of death information available in both databases. As shown in Table 1, cause of death was coded as unknown for 28% in UNOS and for 57% in USRDS among KTRs. Among 12424 (40%) KRTs with exact cause of death documented in both databases, the agreement between the two databases on the cause of death was 76%.

Conclusions: In both national registries, the exact cause of death is unknown for a sizable proportion of patients who die with a functioning graft. There is considerable discrepancy between the two national registries for causes of death that are reported. Documenting the correct diagnosis is pivotal to design future clinical studies to extend survival of KTR.

Table 1. Cause of death among kidney transplant recipients from two national databases

Cause of death (USRDS data)	Cause of death (UNOS data)					
N (%)	Cardiovascular	Infectious	Malignant	Others	Unknown	Total
Cardiovascular	3526 (11.5)	98 (0.3)	25 (0.1)	841 (2.7)	395 (1.3)	4885 (15.9)
Infectious	110 (0.4)	1564 (5.1)	17 (0.1)	938 (3.0)	163 (0.5)	2792 (9.1)
Malignant	22 (0.1)	25 (0.1)	1658 (5.4)	156 (0.5)	88 (0.3)	1949 (6.3)
Others	414 (1.3)	202 (0.7)	191 (0.6)	2635 (8.6)	272 (0.9)	3714 (12.1)
Unknown	2973 (9.7)	1208 (3.9)	1324 (4.3)	4159 (13.6)	7717 (25.1)	17381 (56.6)
Total	7045 (22.9)	3097 (10.1)	3215 (10.5)	8729 (28.4)	8635 (28.1)	30721 (100)

FR-PO1036

Impact of Donor Ethnicity on Long-Term Kidney Transplant Outcomes Bhavna Chopra, Kalathil K. Sureshkumar. *Nephrology and Hypertension, Allegheny General Hospital, Pittsburgh, PA.*

Background: African American (AA) ethnicity increases the risk for developing chronic kidney disease (CKD). There is limited data on graft outcomes based on donor ethnicity. Donor ethicity is a variable in the kidney donor profile index (KDPI) designed to aid in organ allocation and in predicting long-term transplant outcomes. We aimed to evaluate long-term kidney transplant outcomes based on donor ethnicity under different KDPI groups.

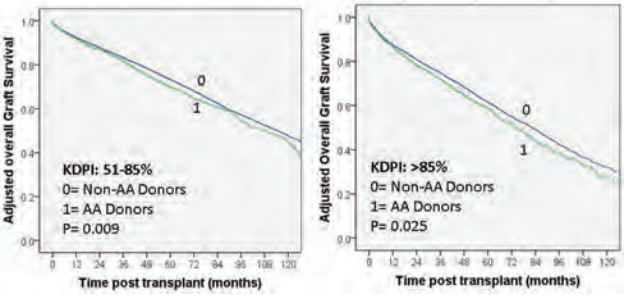
Methods: Using the OPTN/UNOS database, adult deceased donor kidney (DDK) transplant recipients from 2000 to 2015 who received induction therapy and were discharged on calcineurin inhibitor/ mycophenolate mofetil-based maintenance were identified. Patients were further divided into 4 KDPI categories (0-20%,21-50%,51-85% and >85%). Long term graft and patient outcomes were compared for recipients of AA vs. non-AA donor kidneys under each KDPI group in a multivariate Cox model.

Results: There were 59,648 participants in the study cohort with a median follow up of 48 months. Adjusted graft and patient outcomes among recipients of AA vs.non-AA donor kidneys by KDPI groups are shown in Table 1 and Figure 1. Overall and death-censored graft failure risks were higher for recipeints of AA donor kidneys among higher KDPI (51-85% and >85%) groups but similar among lower KDPI (0-20 and 21-50%) groups. Patient survivals were similar.

Conclusions: Our study showed inferior graft outcomes among recipients of AA donor kidneys in higher KDPI groups despite ethnicity being a variable in deriving KDPI. One could speculate that higher prevalence of risk factors for CKD progression such as APOL1 and sickle cell trait gene mutations among other factors in AA population as contributing to inferior graft outcomes. Prospective studies are needed to further elucidate these findings.

Table 1	KDPI 0-20% AA donor; n=560 Non-AA donor; n=14690		KDPI 21-50% AA donor; n=2807 Non-AA donor; n=16548		KDPI 51-85% AA donor; n=2774 Non-AA donor; n=16638		KDPI >85% AA donor; n=1670 Non-AA donor; n=3961	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Adjusted overall graft failure risk	1.18 (0.99-1.41)	0.61	1.05 (0.95-1.15)	0.32	1.12(1.02-1.20)	0.009	1.12 (1.04-1.24)	0.03
Adjusted death-censored graft failure risk	1.19 (0.93-1.50)	0.16	1.11 (0.97-1.25)	0.11	1.12 (1.01-1.25)	0.03	1.33 (1.16-1.51)	<0.001
Adjusted patient death risk	1.22 (0.99-1.50)	0.07	1.02 (0.91-1.15)	0.70	1.09 (0.99-1.20)	0.09	1.03 (0.91-1.16)	0.63

Figure 1: Adjusted graft survivals of AA vs. non-AA donor kidney recipients among the high KDPI groups



FR-PO1037

Living Kidney Donor Evaluation Time and Pre-emptive Kidney Transplantation Steven Habbous,[1] Amit X. Garg.[2] *[1]Western University, London, ON, Canada; [2]London Health Sciences Centre, London, ON, Canada.*

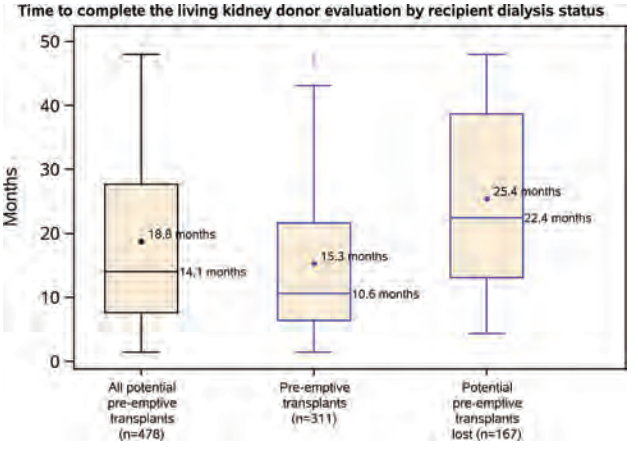
Background: A pre-emptive kidney transplant avoids the risks of initiating dialysis and may result in better outcomes than other treatment options available to patients with kidney failure.

Methods: Using healthcare databases in Ontario, Canada, we retrospectively studied 478 living donor kidney transplants from 2004-2014 where the recipients were not receiving dialysis when their donors' evaluation was underway (for at least three months). We assessed how often dialysis was initiated before transplantation, and explored factors associated with a higher likelihood of dialysis initiation prior to transplant. Results are presented as median (25th, 75th percentile).

Results: A total of 167/478 (35%) of patients with kidney failure initiated dialysis 9.7 (5.4, 18.7) months after their donor candidate began their evaluation, and received dialysis for 8.8 (3.6, 16.9) months before transplantation. The total cost of initiating and receiving dialysis was CAD $8.1 million and 44/167 (26%) patients initiated their dialysis urgently in hospital. The median total donor evaluation time (time from evaluation start to donation) was 10.6 (6.4, 21.6) months for pre-emptive transplants and 22.4 (13.1, 38.7) months for donors whose recipients started dialysis prior to transplant. Characteristics associated with a higher likelihood of the recipient initiating dialysis prior to transplantation included donor female sex, non-white donors, lower donor and recipient neighbourhood income quintile, and a longer time until the transplant program received the recipient referral. Results varied across transplant centres.

Conclusions: One-third of living donor kidney transplant recipients start dialysis prior to transplantation with significant costs to the healthcare system.

Funding: Government Support - Non-U.S.



Distribution of living donor evaluation times by recipient dialysis status when the living donor started the evaluation. Recipients who started dialysis before transplant were potential pre-emptive transplants lost.

FR-PO1038

Limitation of Terminal Serum Creatinine as a KDPI Variable in Predicting Long-term Kidney Transplant Outcomes Bhavna Chopra, Richard J. Marcus, Kalathil K. Sureshkumar. *Allegheny General Hospital, Pittsburgh, PA.*

Background: Terminal serum creatinine (Cr) is a varible in deriving kidney donor profile index (KDPI) which is used for deceased donor kidney (DDK) allocation and predicting transplant outcomes. Terminal Cr is a dynamic variable and can increase from reversible causes. We hypothesize that transplantation of DDKs with higher terminal

Cr within a KDPI group results in better long-term outcomes since these kidneys likely undergo procurement biopsy and transplant centers generally accept these kidneys only if the biopsy shows predominantly acute tubular injury with minimal chronicity.

Methods: Using the UNOS database, we identified adult DDK transplant recipients from 2000 to 2015 who received induction and were discharged on calcineurin inhibitor and mycophenolate mofetil maintenance. Patients were divided into 4 KDPI categories (0-20%, 21-50%, 51-85% and >85%). Using a Cox model, adjusted long-term graft and patient outcomes were compared between recipients of kidneys with terminal Cr >2.0 vs. ≤2.0 mg/dL under each KDPI category.

Results: Study comprised of 59,645 patients with a median follow up of 48 months. Adjusted graft and patient outcome comparisons based on terminal Cr for different KDPI groups are shown in the table. Adjusted overall graft failure and patient death risks were lower in patients who received DDKs with termial Cr >2 vs. ≤ 2 mg/dL in KDPI 21-50% and 51-85% groups but not in best quality (KDPI 0-20%) and marginal kidney (KDPI >85%) recipients. There were no differences in death-censored graft failure risks. Lower overall graft failure and similar death-censored graft failure in recipients of DDK with terminal Cr >2.0 mg/dL indicated reduced death with functioning graft.

Conclusions: The finding of reduced risk for death with functioning graft in patients who recieved DDK with termial Cr >2 mg/dL in the mid KDPI ranges likely reflects the selective use of these kidneys when procurment biopsy findings are favorable resulting in better long-term allograft function. Our study highlights limitations of using elevated terminal Cr in derivng KDPI.

Adjusted graft and patient outcomes by terminal creatinine (Cr) under different KDPI groups

	KDPI 0-20% Cr >2; n=478; Cr≤ 2; n=14769		KDP 21-50% Cr >2; n=1592; Cr≤2; n=17,762		KDPI 51-85% Cr>2; n=1388; Cr≤2; n=18.024		KDPI>85% Cr >2; n=349; Cr≤2; n=5282	
	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p	HR (95% CI)	p
Overall graft failure risk	0.92 (0.75-1.14)	0.46	0.88 (0.77-0.99)	0.04	0.86 (0.76-0.96)	0.007	1.02 (0.86-1.21)	0.85

FR-PO1039

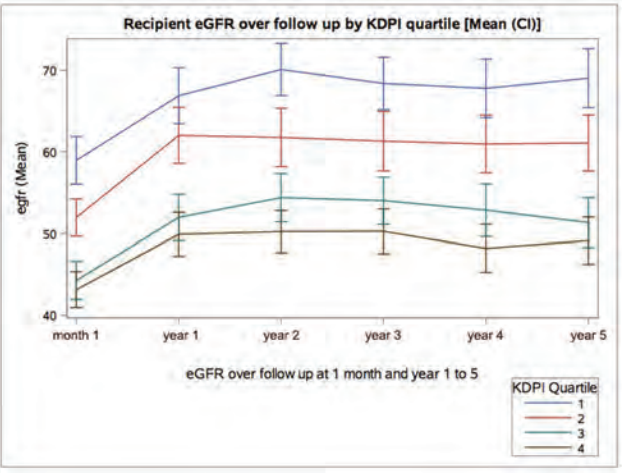
KDPI and Allograft eGFR in Deceased Donor Kidney Transplant Recipients over Follow Up: 1995-2013 Donal J. Sexton,[2,1] Patrick O'kelly,[1] Claire Kennedy,[1] Declan G. de Freitas,[1] Conall M. O'Seaghdha,[1] Peter J. Conlon.[1] *[1]Beaumont Hospital, Dublin 9, Co Dublin, Ireland; [2]The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin., Dublin, Ireland.*

Background: The KDPI has been validated for prediction of deceased donor graft outcomes and popularized in organ allocation in the United States. Whether KDPI predicts eGFR over long-term follow up has not been extensively characterised.

Methods: We performed a retrospective analysis of eGFR (CKD EPI equation) and graft outcomes over follow up in the National Kidney Transplant Service of Ireland database for the years 2006–2013. Associations of the composite KDPI score with eGFR at various time points over follow up were modeled using linear regression, linear mixed effects models and time to event strategies respectively.

Results: N=877 patients had complete data regarding KDPI calculation, N=148 allografts failed. Median (IQR) KDPI score was 52 (49). *At year 1* eGFR ml/min/1.73m^2 were*:* 69.2 (57.6-82.5) (N=172) quartile 1 of KDPI, 59.4 (50.2-74.5) (N=171) in quartile 2 KDPI, 51.9 (42.2-62.2) (N=176) in quartile 3 KDPI, 48.3 (38.5-58.5) (N=162) in quartile 4 KDPI, P<0.001. *At year 5* eGFR in these quartiles were 74.5 (60.5-88.2) (N=110), 64.6 (51.7-83.2) (N=104), 48.8 (34.4-61.6) (N=85), and 43.6 (37.5-58.1) (N=69), P<0.001. On repeated measures analysis with linear mixed effects models with a random participant specific intercept and a random time effect, KDPI (fixed effect covariate) associated with eGFR over follow up (see Fig 1): estimate (se) -0.25 (0.02) P<0.001 for KDPI. The variability in eGFR over 5 years alligned with KDPI score was 21% after adjusting for recipient age (time-varying covariate).

Conclusions: KDPI score predicted eGFR at multiple time points over long term follow up in this study. However, taking the KDPI as a composite of non-modifiable donor factors, a considerable portion of eGFR variability is likely attributable non-donor factors.



A plot of mean eGFR by quartile of KDPI score in deceased donor transplants in Ireland over 5 years follow up.

FR-PO1040

SCD ≠ KDPI <0.85 Shan Shan Chen, V. Shane Pankratz, Rawan T. Al-Odat, Mark L. Unruh, Yue-Harn Ng. *University of New Mexico, Albuquerque, NM.*

Background: The new kidney allocation system (KAS) assigns a kidney with Kidney Donor Profile Index (KDPI) > 0.85 [K>85] as high risk for allograft failure. Differences exist between the previous and current KAS: previous study showed that 8.3% of Expanded Criteria Donor (ECD) kidneys have a KDPI of < 0.85 (K<85). Outcomes following transplant of "discordant kidneys" (DK) is unclear. In this study, we compared the outcomes of DKs vs "concordant kidneys" (CK) using data from the Scientific Registry of Transplant Recipients.

Methods: We retrospectively calculated the KDPI of all kidneys transplanted from 2003 to 2016 and divided them into standard CK (Standard Criteria Donor [SCD] + K<85), expanded CK (ECD+K>85), standard DK (SCD+K>85) or expanded DK (ECD + K<85). We compared the characteristics of recipients who received different kidneys and assessed the rates of allograft failure for these kidneys.

Results: From 2003 to 2016, 148,887 kidney transplants were performed in the US with 16,222 (10.9%) DK transplanted. Significant differences were noted among the recipients of different donor kidney types [Table1]. Recipients of K>85 kidneys had poorer allograft survival compared to recipient of K<85 kidneys. Standard DK recipients had higher risk of allograft loss compared to expanded CK recipients. Recipients of expanded DK had higher risk of allograft failure compared to standard CK recipients [Fig1].

Conclusions: The new KAS is superior to the old KAS at predicting allograft failure. However, recipient of expanded DKs need to be counseled about the higher risk of graft loss compared to standard CKs.

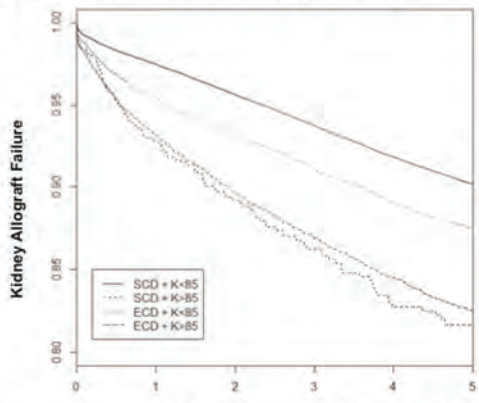
Funding: Commercial Support - Dialysis Clinic Inc.

Table. 1 Recipient Characteristics by Donor Type

	Standard CK	Standard DK	Expanded DK	Expanded CK	p-value
Age	45.7 ± 15.2	49.4 ± 17.7	57.1 ± 10.8	60.0 ± 9.8	< 0.01
Gender (Female)	50540 (40.2)	343 (40.7)	5549 (36.1)	2557 (36.2)	< 0.01
Race:					< 0.01
White	78147 (62.2)	362 (42.9)	9310 (60.5)	3998 (56.5)	
African Americans	38266 (30.5)	379 (45)	4676 (30.4)	2398 (33.9)	
Hispanic	20050 (16)	123 (14.6)	2155 (14)	1008 (14.3)	
Asians	6867 (5.5)	92 (10.9)	1096 (7.1)	567 (8)	
Native American	1277 (1)	7 (0.8)	187 (1.2)	78 (1.1)	
Others	1035 (0.9)	3 (0.3)	126 (0.7)	32 (0.5)	
BMI	27.3 ± 5.9	26.3 ± 5.8	28.2 ± 5.4	27.8 ± 5	< 0.01
Cause of Kidney Disease:					< 0.01
Diabetes	37650 (30)	228 (27)	5410 (35.2)	2527 (35.7)	
HTN	26909 (21.4)	255 (30.2)	3971 (25.8)	2064 (29.2)	
GN	24874 (19.8)	127 (15.1)	2202 (14.3)	856 (12.1)	
PKD	8954 (7.1)	43 (5.1)	1228 (8)	511 (7.2)	
Others	27205 (21.7)	190 (22.5)	2568 (16.7)	1115 (15.8)	
Comorbidities:					< 0.01
Diabetes Mellitus	107791 (86.1)	764 (90.8)	12935 (84.5)	6022 (85.4)	
HTN	97934 (83.7)	566 (85.4)	11441 (87)	5234 (88.4)	
CAD	101691 (81.8)	732 (87.6)	12011 (79.6)	5593 (80.4)	
PVD	6015 (5)	32 (4)	997 (6.8)	459 (6.8)	
Malignancy	5586 (4.6)	56 (6.9)	1052 (7.1)	547 (8)	
On Dialysis	96025 (78.7)	652 (82.5)	12417 (80.8)	5728 (81)	< 0.01
Years on Dialysis	4.4 ± 3.3	4.3 ± 3.1	4.3 ± 2.8	4.1 ± 3	< 0.01
Previous Kidney Transplant	16885 (13.4)	58 (6.9)	1071 (7)	319 (4.5)	< 0.01
Peak PRA	20.2 ± 32.4	17.9 ± 30.2	12.9 ± 24.8	12.1 ± 23.4	< 0.01
On Expanded Donor List	42519 (41.2)	399 (59.9)	13787 (93.4)	6525 (96.2)	< 0.01

Continuous variables are expressed as mean ± SD while categorical variables are expressed as n (%)

Figure 1. Association between Kidney Type and Allograft Failure



	HR	95% CI	5-year Graft Survival	95% CI	p-value
SCD + K<85	1.0	REF	90.2%	90.0% – 90.4%	
SCD + K>85	2.10	1.74 – 2.55	81.7%	78.5% – 84.9%	
ECD + K<85	1.34	1.27 – 1.41	87.5%	86.9% – 88.0%	
ECD + K>85	1.98	1.85 – 2.11	82.4%	81.4% – 83.4%	<0.001

FR-PO1041

Kidney Donor Profile Index (KDPI) Predicts Outcome of Deceased Donor Kidney Transplant in a Brazilian Center Carlos rafael A. Felipe,[3] Andre S. Alvarenga,[3] Silvana Maria C. Miranda,[1] Ana elisa S. Jorge,[3] Pedro Augusto M. Souza,[2] Izabela L. Piana.[4] *[1]Hospital Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; [2]None, Belo Horizonte, Brazil; [3]Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; [4]Faculdade de Minas Faminas BH, Belo Horizonte, Brazil.*

Background: Kidney Donor Profile Index (KDPI) is a well-established index to predict the outcome of deceased donor renal transplant (DDRT), but it has not been established for brazillian population.

Methods: We retrospectively calculated the KDPI and analyzed the outcomes of 45 consecutives DDRT from November/2014 to March/2016: mean cold ischemia time (CIT) was 13.9 hours; the incidence of delayed graft function (DGF). The median of KDPI was 53%.

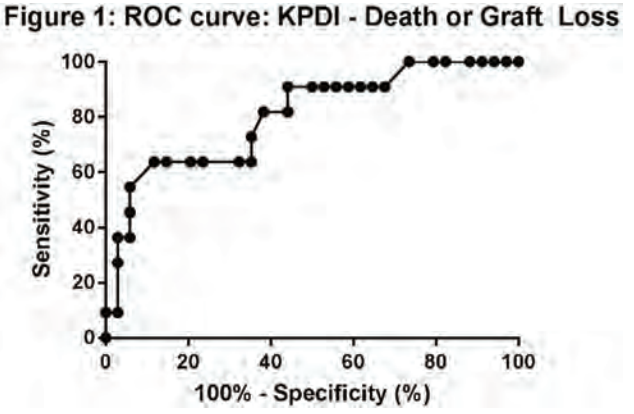
Results: Patients who died had higher KDPI (median 82.0% vs 50.5%; p 0.018), as well as those with allograft failure (median 77.0% vs 50.5%; p 0.021). The area under the KDPI ROC curve for the composite outcome of death or graft loss was 0.80 (Figure1), similar to donor serum creatinine. One year graft survival was 40% for kidneys with KDPI ≥ 70% versus 84.5% for kidneys with KDPI < 70% (relative risk = 4.81; p 0.003). There was no association between KPDI > 70% and cytomegalovirus (CMV) infection. Donor age, final donor creatinine and expanded criteria donor were also associated with death and allograft failure (Table 1).

Conclusions: KDPI accurately predicted graft survival after DDRT and may be helpful in selecting and allocating a deceased kidney in Brazilian population.

Table 1: Study population data and outcomes

	Functioning Graft (n=34)	Graft Loss/Death (n=11)	p
KDPI (%) – mean	48.7	72.3	0.002
Donor age (years) – mean	41.2	49.9	0.037
Final donor creatinine (mg/dl.) – median	0.92	2.60	0.002
Expanded criteria donor (%)	12.5	54.5	0.003
Cold ischemia time (h) - mean	12.7	16.2	0.055
Receptor age (years) - median	54.2	51.4	0.931
DGF (%)	55.9	81.8	0.164
Stroke (%)	61.8	90.1	0.131
Female donor (%)	41.2	36.4	>0.999
Biopsy proven acute kidney rejection (%)	27.3	9.0	0.4082
CMV disease (%)	45.5	18.2	0.1585

Figure 1: ROC curve: KPDI - Death or Graft Loss



FR-PO1042

Can Kidneys from Deceased Donors with AKI and Circulatory Death Be Transplanted? Swati Rao, Iris J. Lee, Avrum Gillespie, Serban Constantinescu. *Temple University School of Medicine, Philadelphia, PA.*

Background: Kidneys from deceased donors with acute kidney injury (AKI) are often not transplanted despite similar 1 year outcomes as donors without AKI. Our center utilizes a high percentage of AKI donors (15%), including donors with severe AKI requiring renal replacement therapy. We compared the 3 year outcomes of AKI donors after brain death (DBD) and circulatory death (DCD), with non-AKI donors.

Methods: We conducted a retrospective chart review of deceased donor kidney transplant (DDKT) recipients from 1/2011 to 6/2016. AKI was defined as terminal serum creatinine (SCr) of ≥ 1.5mg/dl.

Results: 138 eligible DDKT recipients were divided into 4 groups based on donor characteristics: Group 1 [DBD non-AKI, n=73(53%)], Group 2 [DCD non-AKI, n=44 (32%)], Group 3 [DBD-AKI, n=14(10%)], and Group 4 [DCD-AKI, n=7(5%)]. The terminal SCr was significantly higher in DBD-AKI (2.8mg/dl) and DCD-AKI (2.1mg/dl) compared to DBD non-AKI (0.9mg/dl) and DCD non-AKI (0.8mg/dl) (p <0.01). Recipients were 60% male, 65% Caucasian, and mean age of 57±12yrs, with no significant differences among groups. Donors in DCD-AKI group were younger than other groups (24yr vs 35-40yr p=0.02), but all had similar KDPI (43%, p=0.6). Although delayed graft function (DGF) was not different between the groups, the duration of DGF was longer in the DCD non-AKI group than other groups (16d vs 7.5-9d, p=0.04). Patient survival at 1yr, 2yr, and 3yr was 97%, 94% and 97% in group 1, 98%, 93% and 84% in group 2 respectively, and 100% for all years for group 3 and group 4 (p= 0.76, 0.91, and 0.62). Death censored allograft survival at 1yr, 2yr and 3yr was similar between the groups, 98%, 96% and 93% in group 1, 98%, 88%, and 87% in group 2 respectively, and 100% for all years in group 3 and group 4 (p=0.53, 0.70, and 0.93). The SCr was higher and eGFR was lower at 1 month post-KT in the DCD non-AKI group compared to other groups (p <0.01), but both became similar to other groups at 1 yr and remained comparable at 3yr post-transplant. At 3yr, 92% of DBD non-AKI, 86% of DCD non-AKI and 100% of DBD-AKI and DCD-AKI donors had eGFR of more than 30ml/min (p=0.9).

Conclusions: Judicious use of AKI donors had excellent 1yr and 3yr patient and allograft outcomes with no difference between DCD and DBD donors. Selected AKI donors, especially young donors, can be safely utilized to expand the donor pool.

FR-PO1043

Effect of Spontaneous Donor Hypothermia on Graft Outcome in Organ Transplantation Bernhard K. Krämer,[1] Urs Benck,[2] Peter Schnuelle.[2,3] *[1]Vth Department of Medicine, University Hospital Mannheim, Mannheim, Germany; [2]University Medicine Mannheim, Mannheim, Germany; [3]Nierenzentrum, Weinheim, Germany. Group/Team: Randomized Dopamine Trial Study Group.*

Background: A previous controlled donor intervention trial found that therapeutic hypothermia reduced delayed graft function (DGF) after kidney transplantation.

Methods: This retrospective cohort study nested in the randomized dopamine trial (ClinicalTrials.gov identifier: NCT000115115) investigates the effects of spontaneous donor hypothermia on initial kidney graft function, and evaluates graft survival including heart and liver transplants. All 264 donors who met the eligibility criteria for enrollment in the randomized dopamine trial were grouped by occurrence of spontaneous hypothermia. Hypothermia was defined by a core body temperature of less than 36.0°C before organ procurement. Accordingly, we assigned 54 donors to the hypothermia group and the remaining 210 donors served as controls.

Results: Hypothermia was associated with less DGF after kidney transplantation (OR 0.56, 95%CI 0.34 – 0.91). The benefit was greater when need for more than a single post-transplant dialysis session was analyzed (OR 0.48, 95%CI 0.28 – 0.82). Donor dopamine ameliorated dialysis requirement independently from hypothermia in a time-relationship with exposure (OR 0.93; 95%CI 0.87 – 0.98, per hour). Hypothermia did not alter kidney graft survival (HR 0.83, 95%CI 0.54 – 1.27), while dopamine treatment was associated with improved long-term outcome (HR 0.95, 95%CI 0.91 – 0.99 per hour). Stratified

analyses of non-renal organs in tertiles of the donor's core body temperature disclosed negative effects on heart allograft survival (HR 1.89, 95%CI 1.09 – 3.27).

Conclusions: Spontaneous donor hypothermia is associated with less DGF but does not appear to affect long-term outcome of the kidney graft. Our data raise safety concerns against therapeutic hypothermia in multi-organ donors when a thoracic transplantation is considered.

FR-PO1044

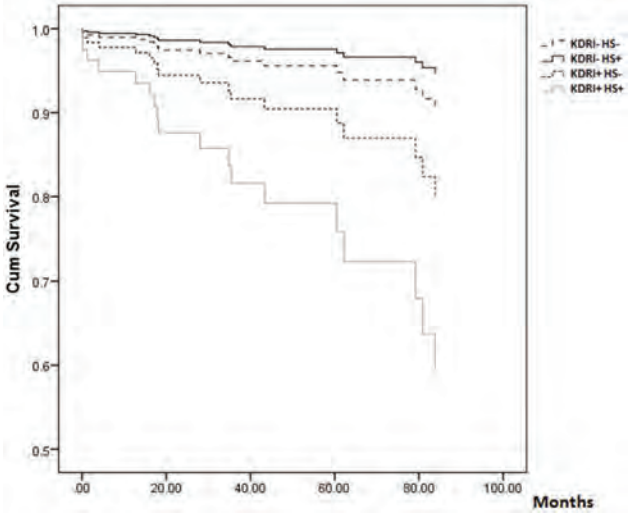
The Combination of KDRI and the Histological Score Improves the Risk Stratification of Marginal Organs in Kidney Transplantation Marco Fiorentino,[1] Francesco Pesce,[1] Giuseppe Castellano,[1] Simona Simone,[1] Pasquale Gallo,[1] Giuseppe Grandaliano,[2] Michele Battaglia,[3] Loreto Gesualdo.[1] *[1]Department of Emergency and Organ Transplantation, Nephrology, Dialysis and Transplantation Unit, University of Bari, Bari, Italy; [2]Nephrology, Dialysis and Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy; [3]Department of Emergency and Organ Transplantation, Urology, Andrology and Kidney Transplantation Unit, University of Bari, Bari, Italy*.

Background: The organ shortage has led to increase the procurement of kidneys from marginal donors, but the risk of graft failure is still object of debate. The aim of the study is to assess whether using both clinical and histological scores can better assess the risk for worse outcome for marginal organs.

Methods: We analyzed 210 kidney transplant recipients from donors aged >50 years. We retrospectively calculated the Kidney Donor Risk Index (KDRI) for each donor and we divided the population according to the KDRI (-, if KDRI ≤ median; +, if KDRI > median) and the histological score (HS, -, if HS ≤ 3; +, if HS > 3) in 4 groups: KDRI-HS- (low KDRI and HS), KDRI-HS+ (low KDRI and high HS), KDRI+HS-(high KDRI and low HS) and KDRI+HS+ (high KDRI and HS). We compared graft function between groups at 2 years and Cox regression analysis was performed to assess the risk for end stage renal disease (ESRD) between groups.

Results: Overall, median KDRI was 1.44 (1.25-1.65), while mean total HS was 3.04±1.62. Median follow-up was 51.9 (26.4 – 99.4) months. Graft function at 2 years was significantly worse in groups with high KDRI (KDRI+HS- and KDRI+HS+) compared to those with low KDRI (p<0.001), while no differences were found according to the HS. By contrast, the best ROC curve in predicting the development of ESRD is for the model that included both KDRI and histological score (AUC 0.81, 95%CI 0.708-0.914, p<0.001). A Cox model adjusted for recipient age, gender, acute rejection, DGF and chronic allograft dysfunction, patients with high KDRI and high HS are more likely to develop ESRD compared to the other groups (OR 5.6, 95%CI 1.3 to 24.5, p=0.02).

Conclusions: Patients with high KDRI and HS have worse outcome compared to patients with high KDRI but better histology. The integration of histology to clinical score may improve the assessment of the risk for graft failure in patients receiving organs from marginal donors.



FR-PO1045

Practice Variation in PHS-IR Kidney Transplants Corey Brennan,[1] Syed A. Husain,[2] Sumit Mohan,[1] Mariana C. Chiles.[2] *[1]Columbia University, New York, NY; [2]Columbia University Medical Center, New York, NY*.

Background: There is significant center level practice variation for accepting deceased donor organs in the U.S. We hypothesized that this variation occurs even for kidneys with good outcomes such as those from PHS-IR donors.

Methods: Using data from the Scientific Registry of Transplant Recipients (SRTR) from 2010-2016, we identified 78,087 kidney-alone deceased donor transplant recipients to evaluate transplant center use of PHS-IR organs in the U.S. Additionally, Cox regression analysis was used to assess the difference in allograft outcomes between PHS-IR and non-PHS-IR kidneys.

Results: 12,751 (16.3%) of kidneys were procured from PHS-IR donors who were younger (33.1±12.2 vs 38.9±16.5 years), with less hypertension (17.5 vs 29.3%), diabetes (4.1 vs 7.8%), marginally higher terminal SCr (1.31±1.15 vs 1.13±1.06) and lower KDPI (36.7 vs 49.2%) than non-PHS-IR donors (all p<0.001). PHS-IR kidneys demonstrated lower all-cause (12.2 vs 16.7%) and death-censored (5.5 vs 8.2%) graft failure (p<0.001). Despite the objectively higher quality, nearly a third (32.9%) of all PHS-IR kidneys were transplanted by just 10 transplant centers while 20 centers performed no PHS-IR transplants over the 7 year study period (**Figure 1**). PHS-IR kidneys were also significantly more likely to be shared between OPOs (30.6% vs 23.9%, p<0.001), underscoring the reluctance by some centers to use PHS-IR kidneys. PHS-IR kidneys experienced a reduced risk of graft failure (HR=0.787, p<0.001), persisting even after adjusting for KDPI and EPTS (HR=0.921, p=0.046).

Conclusions: Considerable variation in acceptance of PHS-IR donor kidneys exists despite evidence of the low risk of disease transmission and excellent outcomes. Although the number of potential donors who meet PHS-IR criteria is likely to rise during the opioid epidemic, the reluctance to use these organs is likely to adversely impact organ procurement and kidney discard in the U.S and reaffirms that deceased donors are often declined for factors other than organ quality.

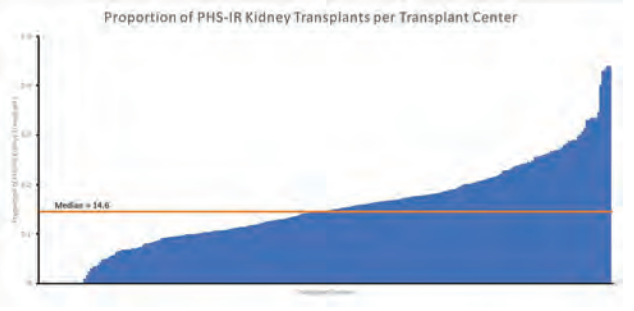


Figure 1.

FR-PO1046

Impact of Cold Ischemia Time, Independent of DGF, on Allograft Outcomes Mariana C. Chiles, Jordan G. Nestor, Syed A. Husain, Russell J. Crew, Heather K. Morris, Geoffrey K. Dube, Rachel E. Patzer, Stephen O. Pastan, Sumit Mohan. *Columbia University, New York, NY*.

Background: The rate of deceased donor kidney (DDK) discard is rising in the U.S., and prolonged cold ischemia time (CIT) is a frequently cited reason for discard. Although long CIT is associated with delayed graft function (DGF), the impact of both CIT and DGF on long-term survival is unclear.

Methods: To assess the risks associated with transplanting DDKs that have accrued long CIT, we used Scientific Registry of Transplant Recipients data to perform a paired kidney analysis and evaluated post-transplant death-censored graft failure. From 2000-2015, we identified 5,773 pairs (11,546 kidneys) that had a difference in CIT ≥5 hours, where 1 kidney developed DGF. The kidney from each pair with shorter CIT was included in the "short CIT" group and the kidney with longer CIT was included in the "long CIT" group.

Results: CIT for the long CIT kidneys was 24.8±8.9 hours versus 13.9±7.2 hours for the short CIT group (p<0.001). Long CIT kidneys were more likely to develop DGF (26.0% vs 22.4%, p<0.001). When examining pairs in which at least 1 kidney developed DGF and using the kidneys with short CIT and no DGF as the reference, kidneys that developed DGF had a higher probability of graft failure over the study period regardless of CIT (long CIT with DGF OR=1.87, p<0.001; short CIT with DGF OR=1.81, p<0.001; Figure 1), but kidneys with long CIT had no difference in graft failure (OR 0.98, p=0.71). In multivariable analysis, only recipients who developed DGF (whether with short or long CIT) had a higher risk of allograft failure compared to recipients of short CIT kidneys that did not experience DGF (long CIT with DGF OR=2.07, p<0.001; short CIT with DGF OR=1.98, p<0.001).

Conclusions: Kidneys with longer CIT had a marginally increased incidence of DGF, but long CIT was not associated with increased graft failure after stratifying recipients by DGF development. DGF describes a clinically heterogeneous entity resulting from multiple factors beyond prolonged CIT.

Funding: Other U.S. Government Support

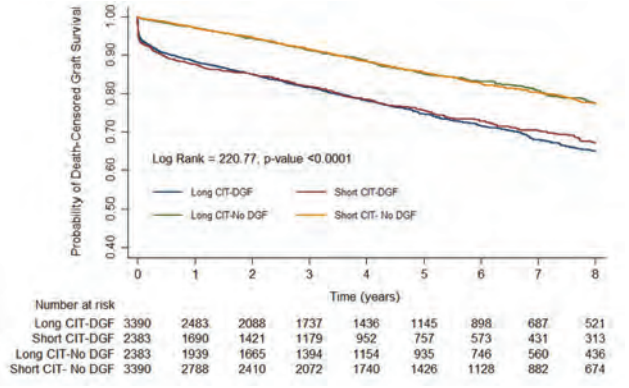


Figure 1

FR-PO1047

Perceptions of Patients with ESRD about Reasons for Transplant Non-Referral and Non-Listing Mary Morrow-Sutton, Hafiz Z. Mahmood, Umar Farooq, Nasrollah Ghahramani. *Penn State College of Medicine, Hershey, PA.*

Background: Kidney transplant (KT) is the treatment of choice for most patients with end stage renal disease (ESRD). We explored patients' understanding of reasons for non-referral for transplant and reasons for not having been placed on the transplant waiting list.

Methods: We sent flyers to 1,283 dialysis units. Of 2536 interested participants who fulfilled inclusion criteria, we randomly selected and invited 1400 to complete a survey which included questions regarding referral, evaluation and listing for KT.

Results: Of 673 participants, 401 had been referred, 361 had been evaluated and 201 were listed for transplant. A total of 272 patients (40%) indicated that they had not been referred for evaluation. The most common reasons cited by patients for not being referred for evaluation included: patient choice (24%), age (10%), weight (10%), and being too sick (9%). In 10% of cases, the patients indicated that their nephrologist had not mentioned KT as an option. The reason for non-referral was unknown to 16% of the patients. Forty patients indicated that they had been referred but never evaluated for listing. Patient choice was the most common cause for not being evaluated (26%), followed by being overweight (10%) and being too sick (8%). The reason for not being evaluated was unknown to 17% of referred patients. Of the patients who had undergone the evaluation process, 160 (44%) were not listed. Patient choice was the most common reason for not pursuing the listing process (33%), being too sick (13%), and being overweight (10%). The reason for not being listed was unknown to 12% of the evaluated patients.

Conclusions: Patient choice is the most commonly cited reason for not being referred, evaluated or listed for KT. A significant proportion of patients are not aware of the reason they have not been referred, evaluated or listed for KT.

Funding: NIDDK Support

FR-PO1048

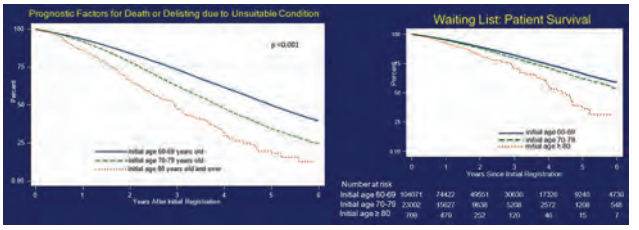
Removal Rates and Reasons from Waitlist in Elderly Kidney Transplant Candidates in the United States Korntip Phonphok,[2] Yong W. Cho,[1] Suphamai Bunnapradist.[2] *[1]Mendez National Institution of Transplantation, Los Angeles, CA; [2]UCLA, Los Angeles, CA.*

Background: The number of kidney transplant candidates on waiting list has been increasing over year, as well as the median age at initial registration. Since now there are 97,621 candidates on waitlist, among these 22,290 (22. 8%) are 65 years old and older (Data of June 1, 2017). Over 30,000 patients were removed from waiting list by year due to various reasons. We hypothesized that elderly candidates would have higher waitlist removal rates and less likely to achieve successful transplantation.

Methods: We used data from the Organ Procurement Transplant Network (OPTN/UNOS) as of December 8, 2016. We examined rates and reasons of waitlist removal in 137,553 kidney transplant candidates registered between January 1, 2000, and September 30, 2015. To allow for a sufficient follow-up period, candidates registered for transplantation up to September 31, 2015 (1 year before the date of last follow-up in the database) were included. Those candidates who were put on waitlists for organs other than kidney or multiple organs were excluded. We divided patients into 3 groups based on age at initial registration; 1) aged 60-69 years, 2)aged 70-79 years, and 3)aged ≥ 80 years. Reasons for waitlist removal were defined as being transplanted, delisted, and death.

Results: A total of 56,544 (48.3%) candidates were removed from waitlist over the study period due to reasons other than being transplanted. Delisting rate was increased by age group and was highest in aged ≥ 80 group. Among these, 22,908 (19.6%) were removed due to death during on waiting list. Candidates aged ≥ 80 years had the highest number of delisting due to condition unsuitable for transplant and also demonstrated worst patient survival while waiting for a transplant. ($p<0.01$) (graph)

Conclusions: Elderly kidney transplant candidates had high delisting rates due to death and condition unsuitable for transplant especially in those aged ≥ 80 years at initial registration, with decreased patient survival. Only half of them received successful transplantation. These results imply that patient selection before waitlist registration could avoid high rate of delisting.



FR-PO1049

The Impact of Donor Chemical Urine Toxicology on Outcomes of Kidney Transplantation Blaithin A. McMahon, Christopher A. Molini, Tessa K. Novick, Steven Menez, Edward S. Kraus. *Medicine, Johns Hopkins University, Baltimore, MD.*

Background: Most transplant centers now accept kidney grafts from victims who have acute chemical intoxications. Despite the widely acceptance of many of these donors the effect of the acute intoxication on kidney graft outcome is poorly understood.

Methods: This is a single center retrospective cohort analysis of 500 patients undergoing deceased donor kidney transplantation (DDKT). Urine toxicology agents tested from donor urine included: alcohol, heroin, cocaine, opioids/methadone, cannabinoids, benzodiazepines and methamphetamine. Delayed graft function (DGF) was defined as the need for dialysis within 1 week of kidney transplantation (KT). Graft failure was defined as the need to return to dialysis. Multiple logistical regression (MLR) analysis was used to assess the odds ratio for DGF and graft failure. MLR models were adjusted for donor age, donor race, donor terminal creatinine, recipient race, cold ischemic time, donation after cardiac death, and preemptive KT.

Results: Of 500 random DDKTs performed at our institution between January 2010 and October 2015, 230 deceased kidney donors (46%) were current drug users. The main chemical toxins detectable in donor urine were: alcohol (n=132, 26 %), heroin (n=80, 16%), opioid/methadone (n=40, 8%), cocaine (n=57, 11%), cannabinoids (n=90, 18%), benzodiazepines (n=15, 3%), methamphetamine (n=19, 4%). 23% of donors had more than one urine toxicology test positive, 13% had more than two tests positive and 5% more than two tests positive. The urine chemical toxicology of kidney donors did not have a significant effect on KT outcomes of DGF and graft failure on adjusted MLR analysis (median follow up of 24 months) (P for odds ratios > 0.05). There was also no association between donors with multiple positive urine chemical toxicology results (greater than 1 or 2 or 3 or 4 agent's positive in urine) and DGF or graft survival on MLR ($p > 0.05$).

Conclusions: The use of deceased donor kidney grafts from donors with positive urine chemical toxicology may be a worthwhile method of increasing the availability of scarce donor kidney organs as urine chemical toxicology is not associated with major transplant outcomes.

FR-PO1050

A Donor and Recipient Genome-Wide Association Study of Renal Allograft Function Caragh P. Stapleton,[3] Graham M. Lord,[6] Martin H. De Borst,[9] Harold Snieder,[9] Claire Kennedy,[4] Maria P. Hernandez-Fuentes,[6] Michael Weale,[6] Florence R. Delaney,[5] Patrick B. Mark,[10] Paul J. Phelan,[2] Fiona A. Chapman,[7] Alexander P. Maxwell,[1] A.J. McKnight,[1] Donal J. Sexton,[8] Kelly A. Birdwell,[12] Brendan Keating,[11] Gianpiero Cavalleri,[3] Peter J. Conlon.[4] *[1]Queen's University Belfast, Belfast, United Kingdom; [2]Royal Infirmary of Edinburgh, NHS Lothian, Edinburgh, United Kingdom; [3]Dept of Molecular and Cellular Therapeutics, Royal College of Surgeons, Dublin, Ireland; [4]Beaumont Hospital, Dublin 9, Co Dublin, Ireland; [5]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [6]King's College London, London, United Kingdom; [7]NHS Scotland, Glasgow, United Kingdom; [8]The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin., Dublin, Ireland; [9]University Medical Center Groningen, Groningen, Netherlands; [10]University of Glasgow, Glasgow, United Kingdom; [11]University of Pennsylvania, Philadelphia, PA; [12]Vanderbilt University, Nashville, TN. Group/Team: UK and Ireland Renal Transplant Consortium; International Genetics and Translational Research in Transplantation Network.*

Background: Previous studies have suggested the influence of common genetic variation on renal transplant outcome. Our aim was to expand on these studies and examine single variant effects of both donor and recipient genotypes on graft function (using estimated glomerular filtration rate (eGFR) as a proxy) taking a genome-wide association study (GWAS) approach.

Methods: We meta-analysed donor and recipient genetic variants across two cohorts (Netherlands cohort and UK/Ireland cohort). We carried out both donor and recipient GWAS of eGFR at 1 year (n donors=2,344; n recipients=2,840) and 5 years (n donors=2,190; n recipients=2,606) post-kidney transplant and examined change in eGFR between 1 and 5 years (Δ eGFR; n donors=1,678; n recipients=2,002). For the 1 year and 5 year analysis, where eGFR was missing due to death/failure the last known eGFR was used and death/failure was included as a covariate in the analysis. Samples with death/failure before 5 years were excluded in the Δ eGFR GWAS. Other covariates included the first eight principle components, donor and recipient age, donor type (living/deceased) and donor gender.

Results: No genome-wide significant associations were found in the three donor GWAS. In the recipient 5 year eGFR GWAS a significant association was observed with a locus on chromosome 19 (combined $p=2.59x10^{-8}$). The presence of the minor allele correlated with a decrease in eGFR (beta= -0.15). This region contains the gene *ZSCAN18* which may play a role in transcriptional regulation.

Conclusions: No single common genetic variant was associated with 1 year, 5 year or Δ eGFR in the donor GWAS. We detected a locus on chromosome 19 that associated with 5 year eGFR in the recipient GWAS suggesting that recipient genotype may be used to predict medium-term renal allograft outcome. Further work is required to assess the robustness of this signal and to replicate these findings.

Funding: Government Support - Non-U.S.

FR-PO1051

Genome-Wide Donor-Recipient Genetic Differences Influence Renal Allograft Survival Independent of HLA Madhav C. Menon,[2] Zhongyang Zhang,[1] Weijia Zhang,[2] Eli A. Stahl,[1] Ke Hao,[1] Barbara T. Murphy.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Mount Sinai School of Medicine, Forest Hills, NY.*

Background: Renal interstitial fibrosis (IF-TA) is a non-specific histologic entity identified in 30-40% of all allografts that fail. Transcriptomic studies of human allograft biopsies show that gene-signatures of ongoing alloimmune activity persist in these IF-TA lesions. Conventionally, anti-donor alloimmunity is attributed to HLA-mismatching. However, non-HLA loci have recently been shown to determine allo-recognition & responses.

Methods: We utilized unique genome-wide SNP array data encompassing Donor-Recipient pairs (D-R) from our recently completed multicenter GoCAR study [PI- Barbara Murphy] to study the role of D-R differences on death-censored allograft survival (DCGS) after excluding HLA-regions (n=385). We used ADMIXTURE analysis on genome-wide genotype data to plot the actual genomic race (AGR) of D-Rs using 1000-genome data (Fig-1). Long term survival data were obtained from UNOS/ANZDATA.

Results: AGR was more accurate than self-reported race (reclassifying 2.7-54% D-Rs among different races). Recipient AGR impacted DCGS in adjusted cox survival models (aHR-2.25 for African-American AGR), while donor AGR had minimal effect. Euclidean D-R genetic distance calculated from AGR significantly associated with DCGS. HLA-matching did not impact DCGS in adjusted analysis. In D-R pairs of similar ancestry, proportion of genome-shared identity-by-descent (pIBD), was predictive of allograft survival (n=224; Log rank P<0.01; pIBD<0.1 vs > 0.1). Notably, pIBD and AGR were not significantly associated with clinical/subclinical rejection at any time post-transplant. In multivariate analysis, lower pIBD scores strongly associated with histologic vascular intimal fibrosis and IF-TA in biopsies obtained less than 1-year (n=199; P<0.01). External validation of these results is ongoing.

Conclusions: Together our novel data show that non-HLA D-R differences determine vascular intimal fibrosis, IF-TA and impact allograft survival.

Funding: NIDDK Support, Private Foundation Support

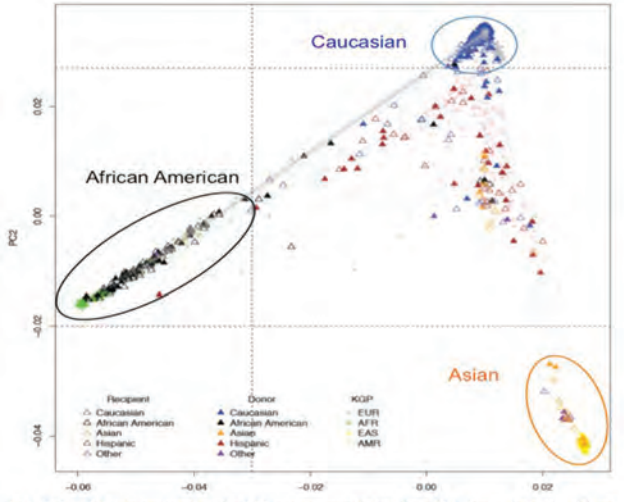


Fig 1. GoCAR D-R pairs projected on the 2-PC ancestry map derived from KGP. Donors (solid triangle) and recipients (empty triangle) are colored based on self-reported race and connected by dashed lines. PC: principle component; KGP: 1000 Genome Project; EUR: European; AFR: African; EAS: East Asian; AMR: American.

FR-PO1052

Circulating Fibrocytes Predict eGFR Slope Post Transplant and Are Associated with Chronic Tubular Changes Michael H. Lee, Christine M. Ribic, Azim S. Gangji, Peter Margetts. *McMaster University, Hamilton, ON, Canada.*

Background: Interstitial fibrosis and tubular atrophy predicts renal transplant outcomes. Circulating fibrocytes are associated with fibrogenic disease in other organs. We aim to evaluate the role of fibrocytes in predicting long-term renal function and the extent of graft fibrosis.

Methods: A single center observational study was conducted in patients undergoing a first kidney transplant. Blood was drawn pre-transplant, 1, 3, 6, and 12-months post-transplant. Circulating fibrocyte levels were identified by flow cytometry using cell surface CD45 and intracellular collagen I. Biopsy samples were stained for a-smooth muscle actin (SMA) and tissue fibrocytes were identified using dual labeling of CXCR4 and Prolyl-4-hydroxylase. The Banff classification was used to evaluate chronic biopsy changes.

Results: Eighty enrolled patients were followed to 12-months post-transplant. One-month circulating fibrocyte levels correlated inversely with the slope of the eGFR from 3 to 12 months (R=-0.257, p=0.03). Thirteen patients had a clinically indicated biopsy. The number of tissue fibrocytes correlated with a-SMA staining (R=0.637, p=0.026). Increased chronic tubular changes were associated with elevated 1-month circulating fibrocyte levels (p<0.001). Increased chronic interstitial changes were associated with increased numbers of tissue fibrocytes (p=0.028).

Conclusions: Elevated circulating fibrocytes at 1-month post-transplant may be prognostic of transplant outcome. Also, increased circulating fibrocytes at 1-month is predictive of chronic tubular changes on biopsy. The number of tissue fibrocytes correlates with interstitial fibrosis and a-SMA staining. Circulating fibrocytes at 1-month can be a biomarker for graft dysfunction and may predict the severity of graft fibrosis.

Funding: Commercial Support - Pfizer

SA-PO001

AKI Following Coronary Angiography: Survival and Development of CKD Dadi Helgason,[3,2] Thorir E. Long,[3,2] Sólveig Helgadóttir,[1] Runolfur Palsson,[2,3] Gisli H. Sigurdsson,[2,3] Tomas Gudbjartsson,[2,3] Ingibjorg J. Gudmundsdottir,[2] Martin I. Sigurdsson,[4] Olafur S. Indridason.[2] *[1]Akademiska Hospital Uppsala University, Uppsala, Sweden; [2]Landspitali - The National University Hospital of Iceland, Reykjavik, Iceland; [3]Faculty of Medicine, University of Iceland, Reykjavik, Iceland; [4]Duke Univeristy Medical Center, Durham, NC.*

Background: Acute kidney injury (AKI) is a recognized complication following coronary angiography (CA) and has been associated with adverse short-term outcomes. We studied the association of AKI following CA with survival and the development and/or progression of chronic kidney disease (CKD).

Methods: This was a retrospective study of patients undergoing CA in Iceland in 2008-2015. Excluded were patients on chronic dialysis, those without baseline serum creatinine (SCr) and patients who underwent open heart surgery in the first 3 days following CA. AKI was defined according to the KDIGO SCr criteria, CKD was defined as eGFR <60 mL/min/1.73 m^2 for at least 3 months, and progression of CKD as worsening of at least one stage sustained over 90 days. Clinical information was obtained from hospital medical records and a prospective CA registry (SCAAR-Swedeheart) and mortality data from Statistics Iceland. Survival was estimated with Kaplan-Meier method and compared to non AKI patients for the whole group (log rank test) and after 1:1 propensity score matching (Klein test). Cox proportional hazards model was used to determine predictors of CKD development/progression.

Results: AKI was diagnosed in 251 out of 13465 cases (1.9%). The 30-day mortality was 23.1% vs. 1.1%, and 1-year survival was 68.6% vs. 97.1%, in the AKI and non-AKI group, respectively (p<0.0001). After excluding patients who died within 30 days, the AKI patients had worse 1-year survival compared with a propensity score-matched control group, or 89.2% vs. 96.2% (p=0.03). While 2343 patients (17.4%) had CKD at baseline, 1935 of the 13465 cases (14.4%) developed incident CKD or progression of pre-existing CKD following CA, with a median time of follow-up of 3.5 (range 0.2-8.0) years. In multivariate analysis, AKI was a predictor of development/progression of CKD (HR 2.5; 95%-CI: 2.0-3.1).

Conclusions: Short-term mortality of patients with AKI following CA is high. However, even after excluding early deaths, AKI appears associated with less favorable long-term survival and the development and/or progression of CKD.

Funding: Government Support - Non-U.S.

SA-PO002

Temporal Trends in the Incidence of AKI after Coronary Revascularization in a Nationwide Study Wen Shen,[3] Siddartha Bhandary,[2] Jaeil Ahn.[1] *[1]Georgeotown University, Washington, DC; [2]Providence Hospital, Derwood, MD; [3]Georgetown University Hospital, DC, WA.*

Background: The major modalities of coronary revascularization - coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) both carry high risk of acute kidney injury (AKI). Our previous study has shown that CABG was associated with higher incidence of post-procedural AKI compared with PCI. Since the temporal trends of AKI incidence in the general population have been changing, it is important to study the temporal changes of AKI incidence in CABG and PCI which could help us better understand the risk profile migration over the years in the coronary revascularization modalities.

Methods: We generated a propensity-matched cohort of 274,464 hospitalizations that had first time CABG or PCI for multivessel coronary disease in 2004 to 2012 from the National Inpatient Sample. Patients received concomitant valvular repair or both CABG and PCI on the same admission, history of organ transplant, CKD stage V or ESRD on dialysis were excluded. Both groups were propensity score matched for age, gender, race, payer, prior MI, unstable angina, heart failure, CVA, peripheral arterial disease,

valvular disease, atrial flutter or fibrillation, CKD, diabetes, HTN, dyslipidemia, smoking, cirrhosis, COPD, systemic cancer, obesity, and anemia. The odds ratios were estimated by the random intercept logistic regression model.

Results: The temporal trends of AKI incidence in both CABG and PCI groups had been increasing over the years from 5.9% in 2004 up to 14.2% in 2012 for CABG, 2.7% in 2004 up to 8.8% in 2012 for PCI. Compared with PCI, CABG was associated with higher incidence of post-procedural AKI in each individual year from 2004 to 2012 (Time effect: OR 1.138, 95% CI: 1.113-1.164, P <0.01). Interestingly, although CABG had higher likelihood to develop AKI throughout the study period than PCI, the odds had been decreasing gradually (OR 3.29, 95% CI 3.08-3.54, P<0.01 in 2006; OR 1.73, 95% CI 1.58-1.88, P<0.01 in 2012).

Conclusions: Both CABG and PCI were associated with increasing temporal trends in AKI incidence over the years. Although CABG was associated with higher likelihood of developing post-procedural AKI in each individual year compared to PCI, the odds had been decreasing yearly.

Funding: Clinical Revenue Support

SA-PO003

Epidemiology of AKI in Cancer Patients Young Lee Jung,[1] Eunjeong Kang,[1] Minsu Park,[2] Namyong Park,[3] Hajeong Lee.[1] *[1]Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [2]Biomedical Engineering, Seoul National University College of Medicine, Seoul, Republic of Korea; [3]Computer Science and Engineering, Seoul National University College of Engineering, Seoul, Republic of Korea.*

Background: Acute kidney injury (AKI) is common in patients with cancer because of malignancy itself, treatment regimen, contrast exposure and coexisting morbidities. However, epidemiologic data for AKI in cancer patients are still lacking.

Methods: We retrospectively assembled newly diagnosed cancer patients at Seoul National University Hospital between January 2004 and December 2013. Among a total of 106,004 cancer patients, we excluded patients with dual primary cancer, age under 18 years-old, advanced renal dysfunction with eGFR less than 15 ml/min/1.73m^2. Patients who could not define AKI due to lack of data were also excluded. AKI was defined as the KDIGO guideline. We categorized patients according to involved organs. We collected demographic information, comorbidities such as diabetes and hypertension, laboratory tests, contrast exposures represented by CT count, and treatment regimen including surgery and chemotherapeutic agents use. AKI incidence was showed as incidence rate estimated by the person-years at risk.

Results: After exclusion, we finally included 68,036 patients. Among them, 23,024 (33.8%) patients developed AKI after cancer diagnosis. More than half of AKI patients experienced recurrent AKI events and 15.9% went through more than 5 times of AKI events. Interestingly, AKI in cancer patients tend to be increasing over time continuously. When compared AKI incidence rate according to cancer type, respiratory tract cancer revealed the highest incidence rate (289.5 cases/1,000 person-year), followed by genitourinary tract cancer (260.8 cases/1,000 person-year) and hematologic malignancies (217.1 cases/1,000 person-year). Patients with AKI experience were older, more men, and had more coexisting diseases such as diabetes and hypertension. They had lower initial renal function, lower serum albumin, and serum hemoglobin. In addition, they exposure more frequent contrast CT scan and chemotherapeutic agents.

Conclusions: In this study, we find that AKI events are increasing, and develop quite frequently and repetitively. Notably, respiratory tract cancer is proved to be the highest risk of AKI incidence. Not only demographic and co-existing factors but also treatment related factors may contribute to the AKI development.

SA-PO004

AKI in Cancer Patients: Risk Factors and Impact on Mortality Eunjeong Kang,[1,2] Minsu Park,[3] Namyong Park,[4] Peong gang Park,[5] U Kang,[4] Hee Gyung Kang,[1,5] Hyung-Jin Yoon,[3] Hajeong Lee.[1,2] *[1]Seoul National University College of Medicine, Seoul, Republic of Korea; [2]Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [3]Biomedical Engineering, Seoul National University College of Medicine, Seoul, Republic of Korea; [4]Computer Science and Engineering, Seoul National University College of Engineering, Seoul, Republic of Korea; [5]Pediatrics, Seoul National University Children's Hospital, Seoul, Republic of Korea.*

Background: Burden of acute kidney injury (AKI) has been demonstrated in a variety of clinical settings including surgery, intensive care unit, and exposures of nephrotoxic agents, although it remains unclear the impact of AKI on mortality in cancer patients.

Methods: We enrolled all patients who were diagnosed any type of cancer in a tertiary hospital during 10 years. Patients with double primary cancer, age less than 18 years, advanced renal dysfunction with estimated glomerular filtration rate (eGFR) <15mL/min/1.73m^2 were excluded. Initial serum creatinine (sCr) level was defined as first measured sCr within 2 months before and after cancer diagnosis, and baseline sCr was defined as minimum value of sCr from the previous 3 weeks by shifting the reference point every 3 weeks based on cancer diagnosis. AKI was defined according to KDIGO-AKI guideline. Demographic factors, co-morbidities, cancer type, eGFR, count of enhanced computed tomography (CT), and treatment options such as surgery and chemotherapy were included as covariates.

Results: Total 67,986 patients were included. Mean age was 56.9±13.0 years and 50.6% were male. AKI occurred in 22,990 (33.8%) of cancer patients during the follow-up period. More than half of patients (n=5,442, 23.7%) experienced 3 or more AKI events per year. Patients who developed AKI had lower eGFR at cancer diagnosis and was experienced more contrast CT exam. In multivariate logistic regression analysis, AKI developed in patients with older age, male, underlying hypertension, diabetes, lower serum albumin and hemoglobin levels, lower initial eGFR, genitourinary cancer type and receiving chemotherapy. A total of 23,140 (34.0%) deaths occurred during 48.5±40.3 months of follow-up. AKI development was demonstrated as an independent risk factor for mortality with graded response (AKI >0-3/year, hazard ratio [HR] 1.07, 95% CI 1.04-1.11, *P*<0.001; AKI ≥3/year, HR 2.31, 95% CI 2.20-2.43, *P*<0.001; reference, no AKI).

Conclusions: AKI development was common in cancer patients, especially in those with co-morbidities, impaired renal function, exposure of nephrotoxic agents such as radiocontrast and chemotherapy. Notably, AKI was an important and independent risk factors for mortality in cancer patients with dose-responsive manner.

SA-PO005

Obesity and Recovery from AKI: An Observational Feasibility Study Helen L. MacLaughlin,[1,4] Gerda K. Pot,[4] Iain C. Macdougall,[1] Christopher W. McIntyre,[3] Nicholas M. Selby.[2] *[1]King's College Hospital, London, United Kingdom; [2]University of Nottingham, Derby, United Kingdom; [3]London Health Sciences Centre, London, ON, Canada; [4]Diabetes and Nutritional Sciences Division, King's College London, London, United Kingdom.*

Background: Acute kidney injury (AKI) occurs in ⟩5% of hospital admission in the UK, and is associated with an increased risk of developing or worsening chronic kidney disease (CKD). The effect of obesity on recovery of kidney function after AKI, and the combined risk of obesity and AKI on subsequent development of CKD is not known.

Methods: A study was conducted to determine the feasibility of recruitment, retention and data collection procedures for the planned Ob-AKI cohort study in a sample of 100 patients hospitalised with an episode of AKI. Feasibility outcomes for recruitment, retention and trends in exploratory measures of recovery from AKI (⟩75% of preAKI eGFR) and development/progression of CKD (decrease in eGFR of ≥25% + rise in CKD category) were examined by BMI (⟨25, 25-29.9, 30+) over 12 months. Potential participants were identified by referral and electronic detection of episodes of AKI during hospital admissions. Inclusion criteria were 18-85 years, episode of AKI (KDIGO 2012), and pre AKI creatinine measured within the previous 12 months.

Results: 41% of eligible patients consented to participate in the study, exceeding the feasibility target of 15%. 101 patients were recruited to the study (67M, 34F, mean age 63.5 (±12.6) years and mean BMI 29.9kg/m^2, range 18.1 to 54.3kg/m^2); 28.3% with stage 1, 21.2% stage 2 and 50.5% stage 3 AKI. Retention was 86% at 6 months and 80% at 12 months; there were 10 deaths and 3 patients commenced dialysis during the study. There may be an interaction between obesity, pre-existing CKD and renal function after AKI. In obese patients with pre-existing CKD, recovery of kidney function at 6 months may be higher with subsequently greater progression at 12 months, compared to patients with normal BMI with CKD (71% (10/14) vs 61% (8/13)) and (31% (5/16) vs 27% (3/11)) respectively. Conversely, obese patients without CKD at baseline may have lower renal recovery at 6 months (35% (8/17) vs 47% (6/17)), yet develop less CKD at 12 months (37% (6/16) vs 69% (9/13)), compared to patients with normal BMI.

Conclusions: We have demonstrated that it is feasible to perform long term observational studies addressing AKI outcomes associated with obesity. A fully powered prospective cohort study to examine the relationships between obesity and outcomes afrer AKI is warranted.

Funding: Government Support - Non-U.S.

SA-PO006

Survival after Initiation of Renal Replacement Therapy for AKI in Cirrhosis Andrew S. Allegretti,[2] Xavier F. Parada,[2] Nwamaka D. Eneanya,[2] Raymond T. Chung,[1] Ravi I. Thadhani,[2] Hannah M. Gilligan.[2] *[1]MGH, Boston, MA; [2]Massachusetts General Hospital, Boston, MA.*

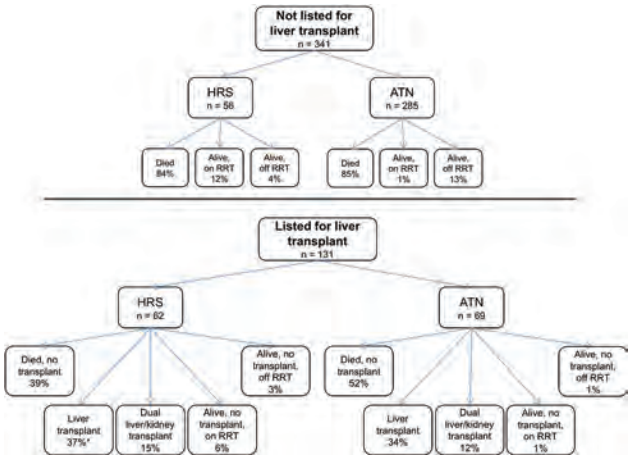
Background: Mortality is high after initiation of renal replacement therapy for acute kidney injury in cirrhosis. Literature on the appropriateness of dialysis in hepatorenal syndrome is sparse and is confounded by liver transplant eligibility. An update on outcomes in the non-listed subgroup is needed. Our objective is to compare survival after initiation of renal replacement therapy in cirrhosis between hepatorenal syndrome and acute tubular necrosis, stratifying by liver transplant listing status.

Methods: Retrospective cohort study of patients with cirrhosis acutely initiated on hemodialysis or continuous renal replacement therapy at five hospitals, including one liver transplant center. Multivariable regression and survival analysis were performed.

Results: 472 subjects were analyzed, 131 listed and 341 not listed for transplant. 24% (114/472) were alive at six months. Among those who did not receive a transplant, 14% (59/409) were alive at six months. Using stepwise regression, significant predictors of mortality were: non-listed transplant status, MELD score, age, admission to the intensive care unit, serum ALT, mechanical ventilation, and initiation with continuous renal replacement therapy. When stratified by transplant listing, adjusted Cox models showed similar survival between hepatorenal syndrome and acute tubular necrosis (HR 0.81 [95% CI 0.59, 1.11]; p = 0.19 among those not listed; HR 0.73 [95% CI 0.44, 1.19]; p = 0.21 among those listed).

Conclusions: After initiation of renal replacement therapy in cirrhosis, mortality is high at six months. Transplant listing status, MELD score, and indicators of critical illness best predicted mortality. Etiology of acute kidney injury (hepatorenal syndrome versus acute tubular necrosis) was not significantly associated with mortality.

Funding: NIDDK Support



Raw outcomes at six months

SA-PO007

Inflammation and Malnutrition Are Predictors of Long-Term Outcomes after Postoperative AKI in Non-Cardiac Surgery Masatoshi Nishimoto,[1] Miho Tagawa,[1] Takayuki Hamano,[3] Kokubu Maiko,[1] Masaru Matsui,[2] Kenichi Samejima,[1] Yasuhiro Akai,[1] Yoshihiko Saito.[1] *[1]Nara Medical University, Kashihara, Japan; [2]First Department of Internal Medicine, Nara Medical University, KASHIHARA, Japan; [3]Osaka University Graduate School of Medicine, Suita, Japan.*

Background: Previous studies showed that AKI is an independent predictor of long-term mortality after adjustment for comorbidities. However, these studies did not account for inflammation and malnutrition, which is associated with increased mortality in CKD.

Methods: This is a retrospective cohort study. Inclusion criteria were adult patients who underwent non-cardiac surgery under general anesthesia from 2007 to 2010. Exclusion criteria were urological or obstetric surgery, missing creatinine values, and preoperative dialysis. The exposure of interest was AKI, defined by KDIGO criteria, within 1 week postoperatively. Outcome variable was all-cause mortality. Statistical analyses were performed using Kaplan-Meier curve and Cox regression model.

Results: Among 1,704 patients, 129 developed AKI. During median follow-up of 3.9 years, the mortality of patients with AKI and without AKI were 27.9%, and 14.7%, respectively. AKI was independently associated with all-cause mortality after adjustment for comorbidities. After further adjustment for C-reactive protein (CRP) and albumin, the association between AKI and mortality was not significant (Table). Among non-users of statin and users of statin, adjusted HR of mortality (AKI vs no-AKI) was 1.92 (1.32-2.81) and 0.57 (0.15-2.23), respectively.

Conclusions: Attenuation of the association between AKI and all-cause mortality by adjustment for albumin and CRP suggested that inflammation and malnutrition, which predisposing patients to AKI, are predictors of increased all-cause mortality after AKI. Anti-inflammatory agents, such as statins, may improve long-term outcome after AKI.

The association between postoperative AKI and all-cause mortality

	HR(95%C.I)
Model 1	1.72(1.19-2.46)
Model 1 + CRP	1.59(1.10-2.31)
Model 1 + CRP + Alb	1.17(0.77-1.76)

Model 1 was adjusted for age, sex, eGFR, and history of DM, hypertension, malignancy, and cardiovascular diseases.

SA-PO008

Renal Recovery after Dialysis-Requiring AKI Is Associated with Decreased Short-Term Mortality Benjamin J. Lee,[2] Chi-yuan Hsu,[2] Rishi V. Parikh,[1] Thomas Leong,[1] Thida C. Tan,[1] Sophia Walia,[1] Raymond K. Hsu,[2] Kathleen D. Liu,[2] Alan S. Go.[1,2] *[1]Kaiser Permanente Northern California, Oakland, CA; [2]University of California, San Francisco, San Francisco, CA.*

Background: Dialysis-requiring acute kidney injury (AKI-D) is associated with increased risk of death even after hospital discharge and higher subsequent rates of cardiovascular disease. We examined whether renal recovery after AKI-D mitigates these risks in a diverse, community-based cohort.

Methods: We evaluated all adult members of Kaiser Permanente Northern California who experienced AKI-D between January 2009 and September 2015. We compared AKI-D patients who recovered adequate kidney function to come off dialysis to AKI-D patients who did not. The primary outcomes were all-cause death, heart failure hospitalization, acute coronary syndrome (ACS), and acute ischemic stroke or transient ischemic attack (TIA) within 1 year of acute renal replacement therapy initiation. Baseline demographics, eGFR, dipstick proteinuria, other labs, comorbidities, and medication use were identified from electronic health records and used for multivariable adjustment.

Results: Compared to AKI-D patients who did not recover (n=1,865), AKI-D patients who recovered (n=1,347) were younger, had higher baseline eGFR and less proteinuria, and were less likely to have pre-existing cardiovascular disease, hypertension, or diabetes. In multivariable Cox regression, recovery after AKI-D was independently associated with a 30% lower relative risk of all-cause death (adjusted hazard ratio [aHR] 0.70, 95% CI 0.55-0.88). Recovery after AKI-D was not statistically significantly associated with adjusted differences in heart failure hospitalization, ACS, or acute ischemic stroke/TIA events (**Table**).

Conclusions: Recovery after AKI-D was independently associated with lower short-term mortality. Interventions to promote early recovery of renal function after AKI-D should be evaluated.

Funding: NIDDK Support

Multivariable-adjusted associations for death and cardiovascular outcomes at 1 year after initiation of renal replacement therapy, by recovery status after AKI-D.

Outcome	Subgroup	Adjusted Hazard Ratio (95% Confidence Interval)
All-Cause Death	Not Recovered	Reference
	Recovered	**0.70 (0.55-0.88)**
Heart Failure Hospitalization	Not Recovered	Reference
	Recovered	1.38 (0.88-2.17)
Acute Coronary Syndrome	Not Recovered	Reference
	Recovered	0.97 (0.56-1.69)
Acute Ischemic Stroke or TIA	Not Recovered	Reference
	Recovered	0.52 (0.26-1.05)

SA-PO009

AKI and Associated Risk Factors for Mortality in Influenza Patients Raymundo A. Sánchez, Luis I. Bonilla, Raymundo Vera, Israel A. Villegas-Gasson, Alan L. Reyes, Jesus Cruz Valdez, Lilia M. Rizo Topete. *Hospital Universitario Dr. José Eleuterio González, Monterrey, Nuevo León, Mexico.*

Background: In 2009, a pandemia of influenza A(H1N1) virus severely affected Mexico. Several reports described the presentation of this disease in critically ill patients. Acute kidney injury (AKI) and mortality showed high prevalence in these studies. AKI incidence has been reported between 33.6%and 51% in A(H1N1) patients, with mortality rates between 36.3 and 51%.

Methods: We conducted a retrospective, observational study in patients admitted to the ICU during the 2016-2017 influenza season. All patients were diagnosed as ARDS and had suspicion of influenza infection. We obtained demographic, clinical and laboratory data. AKI was defined according to Acute Kidney Injury Network criteria. Patients were divided into two groups, survivors and non survivors.

Results: 30 patients were included in the study;20(66.6%) were male, median age was 46.4(±11.91). Mortality in the ICU was 60% and AKI was present in 66.6% of the patients. The mean APACHE II score was 24.2 ± 7.97, mean stay in ICU was 10 days(IQR: 6-15). Use of double vasopressor in 14(46.6%). All patients required invasive mechanical ventilation with PEEP 10.13(± 5.68), PaO2/FIO2 126.42(IQR: 75.9-171.25), tidal volume of 185(IQR:150-205). The diagnosis of influenza was confirmed in 12(40%), 3(16.7%) with influenza rapid diagnostic test (RIDTs) and 9(83.3%) with reverse transcriptase PCR(RT-PCR);of these 5(41.6%) confirmed influenza A(H1N1). The main comorbidities recorded were obesity(n=14, 46.7%), smoking(n=12, 40%), and diabetes mellitus type 2(n=11, 36.7%). The risk factors associated with mortality were obesity OR=2.62(IC=0.881-7.824, p=0.82), A(H1N1)influenza infection confirmed by PCR OR=3.824(IC=1.006-14.536, p=0.016), presence of AKI OR=2.8(IC=1.184-6.622, p=0.18), specially KDIGO 3 OR 10 (p=0.007), and renal replacement therapy(RRT) OR=11 (IC=1.164-103.94, p=0.018).

Conclusions: Influenza A(H1N1) is still a cause of great morbidity and mortality in the young Mexican population. In our cohort we found consistent data that can help the treatment of these patients in the setting of the ICU. The presence of acute kidney injury, obesity, and the need for RRT were strong risk factors for mortality in this study. Modifiable factors should be early identified to improve outcomes in critically ill.

SA-PO010

Differential Trends in Incident Rates of AKI by Severity Stage in the Irish Health System Leonard Browne,[5,1] Alaa Mohamed Alamin Abdelrahim Mohamed ALi,[3] Arunkumar Aruna udayakumar,[4,1] Wael F. Hussein,[2] Rajiv Saran,[6] Austin G. Stack.[1,7] *[1]Graduate Entry Medical School, University of Limerick, Limerick, Ireland; [2]Limerick University Hospital, Limerick, Ireland; [3]University Hospital Limerick, Limerick, Ireland; [4]University Of Limerick, Limerick, Ireland; [5]University of Limerick, Limerick, Ireland; [6]University of Michigan, Ann Arbor, MI; [7]Health Research Institute, Limerick, Ireland. Group/Team: UL Kidney Consortium.*

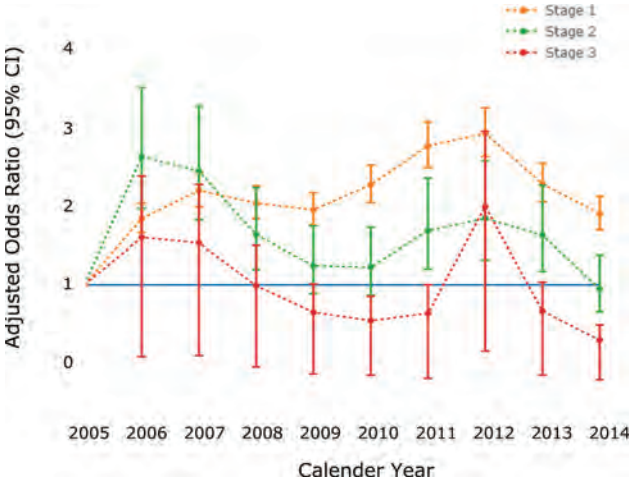
Background: Surveillance of Acute Kidney Injury (AKI) is a fundamental component of prevention strategies in health systems in order to reduce adverse outcomes. Recent studies have shown rising incident trends for dialysis-requiring AKI. We determined incident rates of first AKI by stage from 2005-2014 in the Irish Health System

Methods: We utilised data from the National Kidney Disease Surveillance System in Ireland to explore trends in incident AKI within the health system from 2005 to 2014 (n= 453, 509). AKI events were identified per KDIGO guidelines and classified by stage (1 to 3) and incidence rates per 100 patients were calculated for each year. Multivariable logistic models explored the relationship of calendar year with AKI incidence expressed

as odds ratio (OR) and 95% Confidence Intervals (CI) with adjustment for age, sex, county of residence, location of medical supervision and laboratory indicators of health.

Results: From 2005 to 2014, incidence rates of AKI per 100 patients increased from 5.5 % (5.4, 5.7) to 11.8 % (11.4, 12.1) in Stage 1; 0.58 % (0.53, 0.63) to 1.32 % (1.19, 1.45) in Stage 2, and from 0.46 % (0.41, 0.51) to 0.71 % (0.61, 0.81) in Stage 3. With adjustment for age, sex and baseline eGFR, a pattern of increasing odds of AKI was observed across all 3 stages (P<0.001 for trend). With further adjustment for county of residence, hospital, location of medical supervision and laboratory health indicators, a rising trend in incidence was observed only AKI Stage 1, while the reverse was seen for AKI Stage 2 and 3 (Figure 1), all P<0.001.

Conclusions: Increasing incidence of Stage 1 AKI is primarily responsible for overall growth of AKI in the Irish Health System. Accounting for changing demographic, clinical and geographic profiles, incident rates of Stage 2 and Stage 3 AKI have fallen in recent years and suggest improved preventive strategies.



SA-PO011

Prediction Model for AKI after Non-Cardiac Surgery Kokubu Maiko,[3] Miho Tagawa,[3] Takayuki Hamano,[1] Masatoshi Nishimoto,[4] Masaru Matsui,[2] Ken-ichi Samejima,[2] Yasuhiro Akai,[4] Yoshihiko Saito.[4] *[1]Osaka University, Suita, Japan; [2]Nara Medical University, Kashihara, Japan; [3]nara medical university, NARA, Japan; [4]Nara Medical University, Nara, Japan.*

Background: There are many prediction models for AKI after cardiac surgery, but few reports exist for non-cardiac surgery.

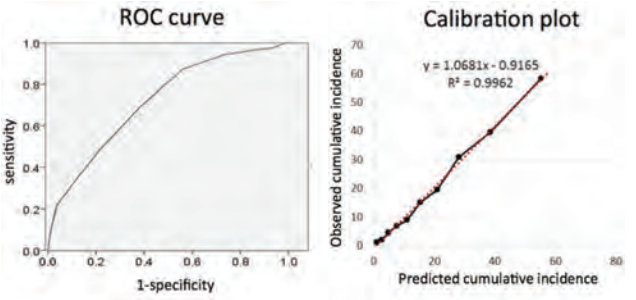
Methods: This is a retrospective cohort study in adults who underwent non-cardiac surgery under general anesthesia from 2007-2010. We exclude patients who had preoperative dialysis, urologic, and obstetric surgery or did not have creatinine level preoperatively. Predictive variables were patients' demographics and characteristics of surgeries. Outcome variable was AKI within 1 week postoperatively according to the KDIGO criteria. The cohort was divided into derivation and validation cohorts (2:1). In derivation cohort, predictors of AKI were analyzed by multivariate logistic regression analysis and prediction model was created using regression coefficients. Validity of the model was tested in validation cohort using ROC curve and calibration slope.

Results: Among 2,912 patients in the derivation cohort, 172 (5.9%) patients developed AKI. Variables independently associated with AKI and points according to the model are shown (Table). In the validation cohort, AUC was 0.72 (0.67-0.77) and there was no significant difference in predicted and observed incidence (p=0.12) (Fig).

Conclusions: Our prediction model for AKI after non-cardiac surgery was well calibrated. The model needs to be validated in other cohorts.

Prediction model

Male	2 points
Hypertension	1 point
Cerebrovascular accident	1 point
Thoracic surgery	3 points
Abdominal surgery	2 points
Pelvic surgery and replacement of major joints	2 points
Emergency surgery	2 points
Insulin	2 points
Vasopressor	1 point
Hct<40	1 point
BMI>23	1 point
eGFR<30	3 points
30 < eGFR < 60	1 point



SA-PO012

Prevalence and Variation of Best Practices in AKI: A Multi-Center Study Francis P. Wilson,[3] Aditya Biswas,[2] Dennis G. Moledina,[3] Sherry Mansour,[1] Chirag R. Parikh.[4] *[1]None, New Haven, CT; [2]Yale University, New Haven, CT; [3]Yale School of Medicine, New Haven, CT; [4]Yale University and VAMC, New Haven, CT.*

Background: AKI is common in hospitalized settings and is associated with increased morbidity, mortality, and length of stay. While there is no specific therapy for AKI, guidelines recommend certain best practice measures that could potentially form the basis of a standardized set of responses to AKI and the development of an AKI "report card". Adherence to such metrics in real-world settings is unknown.

Methods: Using guidelines published by the Kidney Disease: Improving Global Outcomes and National Institute for Health and Care Excellence, we identified four potential universal best practice metrics for hospitalized patients post-AKI including: subsequent creatinine measurement, urinalysis, urine output monitoring and avoidance of certain nephrotoxins (including aminoglycosides, non-steroidal anti-inflammatory drugs, and contrast media). We examined patients with AKI at three Connecticut hospitals to determine the rates of performance of these best practices within 24 hours of AKI onset. Patients discharged within 24 hours of AKI onset were excluded.

Results: Over three years, we identified 26,333 individuals (49.8% male, 18% black) with AKI based upon KDIGO-Creatinine criteria. The Table documents the rates of best practices across the three study hospitals and demonstrates significant variation. A multivariable model demonstrated that surgical patients, male patients, those with private insurance, and those with electrolyte abnormalities at AKI onset had more best practices performed. Of those *without* a creatinine measurement within 24 hours of AKI, 13.8% had progression to a higher stage of AKI, 1.5% went on to inpatient dialysis, and 6.2% died during the hospitalization.

Conclusions: Adherence to AKI best practice varies by hospital, ward, and patient factors. Standardization of best practice guidelines may help to reduce variation and improve outcomes.

Funding: NIDDK Support

Table 1 - Performance of Best Practices

	YNH	SRH	BH	Total	P-value
N	16,108	6,544	3,681	26,333	<0.001
Subsequent Creatinine, %	68.9	56.3	57.0	64.1	<0.001
Urinalysis, %	17.5	13.8	14.2	16.1	<0.001
Urine Output Monitoring, %	78.8	79.7	56.4	75.9	<0.001
Nephrotoxin Avoidance, %	92.4	92.3	94.1	92.5	<0.001

Table: Performance of best practice metrics at 3 study hospitals. YNH = Yale New Haven Hospital, SRH = St. Raphael Hospital, BH = Bridgeport Hospital

SA-PO013

Evaluation of the Accuracy of Estimated Baseline Serum Creatinine for Diagnosis of AKI in the Japanese Population Taro Horino, Yutaka Hatakeyama, Tatsuki Matsumoto, Keitaro Nagata, Kosuke Inoue, Yoshio Terada, Yoshiyasu Okuhara. *Kochi Medical School, Nankoku, Japan.*

Background: Modern epidemiologic studies of acute kidney injury (AKI) have been facilitated by the increasing availability of electronic medical records. However, pre-morbid reference serum creatinine (SCr) data are often unavailable in such records. Investigators substitute estimated baseline SCr with the eGFR 75 approach, instead of using actually measured baseline SCr. Here, we evaluated the accuracy of estimated baseline SCr for AKI diagnosis in the Japanese population.

Methods: Inpatients and outpatients aged 18-80 years were retrospectively enrolled. AKI was diagnosed according to the Kidney Disease Improving Global Outcomes criteria, using SCr levels. The non-AKI and AKI groups were selected using the following criteria: increase 1.5 times greater than baseline SCr, "baseline SCr" or increase 0.3 mg/dL greater than baseline SCr in 48 h, "increase in 48 h". AKI accuracy defined by the estimated reference SCr, the average SCr value of the non-AKI population, eb-GFR-A approach, or the back-calculated SCr from fixed eGFR = 75 mL/min/1.73 m^2, eGFR 75 approach, or, eb-GFR-B approach in this study, was evaluated.

Results: We analyzed data from 131,358 Japanese patients. The number of patients with reference baseline SCr in the non-AKI and AKI patients were 29,834 and 8,952, respectively. For AKI patients diagnosed using "baseline SCr", the AKI diagnostic accuracy

rates as defined by eb-GFR-A and eb-GFR-B were 63.5% and 57.7%, respectively, while in AKI diagnosed using "increase in 48 h", the AKI diagnostic accuracy rates as defined by eb-GFR-A and eb-GFR-B were 78.7% and 75.1%, respectively. In non-AKI patients, false positive rates of AKI misdiagnosed via eb-GFR-A and eb-GFR-B were 7.4% and 6.8%, respectively.

Conclusions: AKI diagnosis using the average SCr value of the general population may yield more accurate results than diagnosis using the eGFR 75 approach when the reference SCr is unavailable.

SA-PO014

Racial Differences in the Risk for AKI after Cardiac Surgery James F. George,[1] Rongbing Xie,[1] Margaret Tresler,[1] James K. Kirklin,[1] Anupam Agarwal.[2,3] *[1]Surgery, University of Alabama at Birmingham, Birmingham, AL; [2]Medicine, University of Alabama at Birmingham, Birmingham, AL; [3]Department of Veterans Affairs, Birmingham, AL.*

Background: The effects of race on developing AKI following cardiac surgery are unknown. To determine the extent of this disparity, we studied risk factors for AKI after cardiac surgery at a tertiary referral center.

Methods: AKI was defined using the KDIGO working group definition. Pre-op or baseline creatinine (CRE) was defined as the minimum value within 30 days before surgery. Post-op CRE was defined as the maximum value within 48 hours after surgery. Post-operative risk factors for AKI were determined using multivariable logistic analysis to predict the probability of AKI KDIGO stage >1.

Results: Among 5347 patients (pts) who underwent cardiac surgery between July 1, 2010 and December 31, 2015, the study included 2175 pts who had coronary artery bypass grafts (CABG, 1309, 60%), valve procedure (585, 27%), or combined CABG and valve procedures (279, 13%). The remaining 3172 pts were excluded due to concomitant other surgeries, assist devices, a prior dialysis, race other than black or white, death or discharge within 48 hours, or missing CRE values. 1791 of included pts were white (82%) and 382 were black (18%). 1589 pts were KDIGO=0, 522 were KDIGO=1, and 62 were KDIGO>=2. By multivariable analysis, factors predictive ($p<0.001$) of KDIGO stage >1 included black race (OR 1.57, $p=0.0005$), increased BMI at time of surgery (OR 1.02, $p<0.0001$), older age (OR 1.02, $p<0.0001$), higher number of diseased vessels (OR 1.21, $p=0.0002$), and mitral valve procedure (OR 2.05, $p=0.0007$). Mean pre-op CRE among blacks was 1.21 (0.9-1.3, 25th to 75th percentile) and 1.07 (0.8-1.2) in whites, a difference of 0.14 ($p<0.0001$). Mean post-op CRE among blacks was 1.45 (1.0-1.6) and 1.22 (0.9-1.4) in whites. Notably, the mean difference between post-op and pre-op CRE was significantly larger in blacks at 0.24 (0.0-0.3) versus 0.15 (0.0-0.3) in whites ($p=0.0011$). Review of Medicare billing data showed 53 (3%) whites and 20 (5%) blacks received a Nephrology consult during hospitalization ($p=0.03$). Only 16 (1%) of white and 9 (2%) of blacks required dialysis ($p=0.02$).

Conclusions: Black race was a significant risk factor for AKI after cardiac surgery, with blacks exhibiting larger increases in CRE after surgery. These results indicate that a larger, multicenter study examining race and AKI post-cardiac surgery is clearly warranted and tailored interventions to prevent AKI in blacks are needed.

Funding: Clinical Revenue Support

SA-PO015

Risk Factors for Community-Acquired AKI in Patients with and without CKD and Impact of Its Initial Management on Prognosis: A Prospective Observational Study Patrick Saudan,[3] Fabien Stucker,[1] Thomas Perneger,[2] Cyrielle Alves,[3] Pierre-Yves F. Martin.[3] *[1]Nephrology Unit, Hôpital de la Providence, Neuchatel, Switzerland; [2]Department of Clinical Epidemiology, Geneva University Hospitals, Geneva, Switzerland; [3]Department of Nephrology, Geneva University Hospitals, Geneva, Switzerland.*

Background: We aimed to describe clinical characteristics of patients with community-acquired acute kidney injury (CA-AKI), the effectiveness of initial management of CA-AKI, its prognosis and the impact of medication on its occurrence in patients with previous chronic kidney disease (CKD).

Methods: We conducted a prospective observational study within the Emergency Department (ED) of a University Hospital including any patient > 16 years admitted with an eGFR < 60 ml/mn/1.73m^2. With the help of a computer-based database, we identified daily the patients admitted with an eGFR < 60ml/mn/1.73m2 and a panel of nephrologists reviewed the files to assess the presence of AKI. We then analysed the clinical and demographic characteristics of the patients, the use of medications, and the adequate management of CA-AKI within the ED. The files were reviewed in the subsequent days and at one and three-years and mortality, renal recovery and renal function decline were analyzed.

Results: From May 1st to June 21st 2013, there were 8464 admissions in the ED, of which 653 had an eGFR < 60 ml/mn/1.73m^2. Of these, 352 had previous CKD, 341 had CA-AKI, and 104 had superimposed CA-AKI on CKD. Occurrence of superimposed CA-AKI in CKD patients was associated with male gender and with use of diuretics, but not with use of ARBs or ACEIs. Adequate management of CA-AKI defined as identification, diagnostic procedures and therapeutic intervention within 24 hours, was recorded in 45% of the cases and was not associated with improved outcomes. Three-year mortality was 21 and 48 % in CKD patients, respectively, without or with CA-AKI, and 40 % in patients with only CA-AKI ($p<0.001$). Mortality was significantly associated with age, hypertension, ischemic heart disease and CA-AKI. Progression of renal insufficiency was associated with male gender and age.

Conclusions: CA-AKI is more frequently encountered in male patients and those treated with diuretics and is an independent risk factor for long-term mortality. Its initial adequate management failed to improve outcomes.

SA-PO016

Furosemide Stress Test and Renal Angina Index for the Prediction of AKI Rolando Claure-Del Granado,[1,2] Yamile Serrano-Pinto,[2] Daniela Torrico-Guillen.[2] *[1]Universidad Mayor de San Simon, School of Medicine, Cochabamba, Bolivia, Plurinational State of; [2]Hospital Obrero #2 - C.N.S., Cochabamba, Bolivia, Plurinational State of.*

Background: In recent years several approaches for identifying patients at risk of acute kidney injury (AKI) were used; among them two have been of increasing interest: the Furosemide Stress Test (FST) and the Renal Angina Index (RAI). These two different approaches aim to identify patients at risk for subsequent AKI, and also have been used for the prediction of AKI severity. We assessed the performance of these two different approaches to identify patients at risk of AKI in an ongoing cohort of adult critically ill patients.

Methods: We analyzed data from 58 hospitalized patients admitted to a Medical ICU. We measured serum creatinine (sCr) every 24 hours for 7 consecutive days following ICU admission, and urinary volume was assessed hourly each 24 hours. At admission (day 0), **RAI (1-40)** was calculated using the following formula: **Risk level** (presence of sepsis = 1 point, presence of diabetes = 3 points, and vasopressors and use of invasive mechanical ventilation = 5 points) *x* **Injury level** (changes in eGFR: no change = 1 point, 0-24.9% = 2 points, 25-50% = 4 points, ≥ 50% = 8 points); and we applied the **FST** at day 0 (as describe by Chawla et. al. in Crit Care 2013 Sep 20; 17(5): R207). We assessed the performance of the FST and the RAI to predict the subsequent development of AKI using KDIGO sCr and urinary volume criteria.

Results: Of the 58 patients included in this study, 5 (8.6%) patients met the primary end point of AKI (sCr KDIGO criteria) and 4 (6.8%) using urinary volume KDIGO criteria. The performance of **Furosemide Stress Test** and the **Renal Angina Index** are shown on figure 1. Of note, we consider a cut-off point of <725 cc of urine at 2 hours for **Furosemide Stress Test** since none of the patients who developed AKI had <200 cc of urine at 2 hours as the original cut-off proposed value.

Conclusions: The Furosemide Stress Test and the Renal Angina Index have robust predictive capacity to identify critically ill patients at high risk of developing AKI before a rise in sCr occurs. These preliminary data of our ongoing study warrants future studies to validate these findings.

Performance	Furosemide Stress Test	Renal Angina Index
Sensitivity (%)	100	100
Specificity (%)	79.2	96.2
PPV (%)	31.2	71.4
NPV (%)	100	100
ROC-AUC (*p* value)	0.909 (0.003)	1.00 (< 0.001)

Figure 1. Performance of the Furosemide Stress Test and the Renal Angina Index

SA-PO017

Incidence and Costs of AKI in Hospitalized Patients with Infective Endocarditis Katherine M. Donaldson,[1] Mark Rudy,[1] Daniel E. Cleland,[1] Gaixin Du,[4] Moises A. Huaman,[3] Alice Thornton,[1] Laura Fanucchi,[1] Javier A. Neyra.[2] *[1]University of Kentucky, Lexington, KY; [2]University of Kentucky Medical Center, Lexington, KY; [3]University of Cincinnati, Cincinnati, OH; [4]UKY, Lexington, KY.*

Background: Acute kidney injury (AKI) is a frequent complication of hospitalized patients with infective endocarditis (IE) and carries adverse outcome. We examined the incidence, costs and characteristics associated with AKI in hospitalized patients with IE.

Methods: Retrospective cohort study of patients with IE admitted to UK hospital from 1/2013 to 12/2015. IE was defined by the modified Duke criteria. AKI was defined by the serum creatinine-KDIGO criteria. Patients with end-stage renal disease, kidney transplant, or baseline eGFR<15 were excluded. Multivariable logistic regression analysis of AKI as the dependent variable was used.

Results: 297 patients were included in the analysis. Of these, 40.4% were women and 94.9% were white. Mean age (SD) was 45.2 (16.3) years. AKI occurred in 186 (66.0%) patients: 54 (29.0%) developed AKI within the first 72 h and 132 (71.0%) after 72 h of admission. AKI was more common in women than in men (70.8% vs 57.0%, $p=0.016$). Hospital mortality in patients with AKI was 18.8% vs 14.4% in those without AKI, $p=0.33$. Patients who developed AKI had a longer hospital stay: median (IQR) 30 (15–47) vs 9 (5–18) days, $p<0.001$. AKI occurred more often in patients of poor socioeconomic status, with a diagnosis of hepatitis B and C or bacteremia, with exposure to aminoglycosides or diuretics and with a history of recurrent IE (all $p<0.01$). The median total direct cost of hospitalization in those with AKI vs without AKI was $51,488 (23,325–73,985) vs $14,801 (6,722–31,910), $p<0.001$. Female gender (OR 1.77, 95% CI 1.03–3.07), hepatitis C diagnosis (OR 1.98, 1.15–3.41) and comorbidity risk of mortality score=4 (OR 4.51, 2.64-7.69) were independently associated with incident AKI.

Conclusions: Two out of three hospitalized patients with IE develop AKI. Most episodes of AKI occurred after 72 h of hospital admission. Patients with AKI had a longer

hospital stay, incurring higher total direct costs. Female gender, hepatitis C diagnosis and risk of mortality score=4 were independently associated with the occurrence of AKI in this susceptible population.

Funding: Other NIH Support - University of Kentucky Center for Health Services Research Data, Analytics, and Statistical Core

SA-PO018

AKI Associated with Antibiotic Exposure in Critically Ill Children Emily L. Joyce,[1,2] Priyanka Priyanka,[1] John A. Kellum.[1] *[1]The University of Pittsburgh, Pittsburgh, PA; [2]Children's Hospital of Pittsburgh, Pittsburgh, PA. Group/Team: Critical Care Nephrology, CRISMA.*

Background: Acute kidney injury (AKI) is associated with adverse outcomes including prolonged hospital stay, increased healthcare costs, and delay in other organ recovery as well as development of chronic kidney disease. It is unclear which medications are associated with increased risk of AKI in pediatric critically ill patients.

Methods: Data was obtained from a convenience sample taken from the Pediatric HiDenIC database which contains > 12,000 critically ill patient records from the Children's Hospital of Pittsburgh between 2010 and 2014. Patients were categorized regarding exposure to any antibiotic within the first 24 hours of ICU admission with subsequent development of AKI using KDIGO staging.

Results: Out of 2890 critically ill pediatric patient encounters, 18% developed stage 2 or 3 AKI within the first week of admission to the ICU. Those who developed AKI had a longer ICU length of stay (p<0.001), longer hospital length of stay (p<0.01) and higher mortality rate (p<0.001). Within the cohort, 2254 patient encounters (78%) were exposed to any antibiotic within the first 24 hours of ICU admission. On univariate analysis, exposure to antibiotics including cefepime (OR 1.59, n=225, p<0.01), linezolid (OR 3.99, n=28, p<0.001), piperacillin/tazobactam (OR 2.04, n=546, p<0.001), and vancomycin (OR 1.45, n=1028, p<0.001) was associated with increased odds of developing AKI.

Conclusions: AKI is prevalent in critically ill children and associated with poor outcomes. Antibiotic use in this population is common and is associated with increased risk for development of AKI.

Funding: NIDDK Support

Descriptive Characteristics

	No AKI (Stage 0/1) N = 2366	AKI (Stage 2/3) N = 524	P-value
Age (years), mean ± SD	9.2 ± 7.9	9.5 ± 9.1	0.415
Males, N (%)	1322 (55.9)	294 (56.1)	0.923
ICU LOS (days), median (Q1-Q3)	2.8 (1.4-5.8)	4 (1.9-9.4)	<0.001
Hospital LOS (days), median (Q1-Q3)	7.3 (4.3-14.2)	9.7 (5.4-18.4)	0.009
Hospital Mortality, N (%)	44 (1.9)	36 (6.9)	<0.001

SD, standard deviation

ICU, Intensive care unit

LOS, length of stay

OR, Odds ratio

SA-PO019

Direct-Acting Oral Antiviral Therapy in the Treatment of Chronic Hepatitis C Is Associated with an Interim Increase in Serum Creatinine Levels Avinash G. Adiga,[2] Praveen Ratanasrimetha.[1] *[1]Texas Tech University, Lubbock, TX; [2]Texas Tech University Health Sciences Center, LUBBOCK, TX.*

Background: The introduction of newer all-oral, direct-acting antiviral therapy in place of traditional interferon-based therapy has revolutionized the management of CHC infection. The aims of our study are to evaluate i) Renal adverse effects related to all oral direct- acting, antiviral therapy for hepatitis C ii) relationship between changes in viral load and renal function tests in chronic hepatitis C patients.

Methods: A retrospective study involving 164 patients with chronic hepatitis C infection followed up in outpatient clinics between October 1, 2014, and September 30, 2015. Ninety- five patients who received antiviral therapy were included as cases and sixty-nine patients who did not receive treatment were included as controls. Creatinine levels of cases were noted at four- time points: pre-treatment, at four weeks, at the end of treatment (3 months), and at 12-week post-treatment (6 months) and at the similar time frame for controls. Patients with CKD stage 3 or more and patients with missing values were excluded.

Results: The rate of kidney disease in our study population is 8.7%. Baseline creatinine in the studied population was 0.92mg/dl. Viral clearance was seen in 98.9% of patients, who received the treatment. At the end of treatment, higher creatinine levels were seen in the treatment group than the control group. However, no significant differences in creatinine levels were seen at 6 months. When compared to baseline statistically significant increase in creatinine levels were seen at 3 months and 6 months were seen in both groups.

Conclusions: Serum creatinine levels are higher at the end of treatment in patients receiving anti-viral therapy when compared to controls. This difference tends to cease with further time duration. A decrease in the hepatitis C viral load is not associated with a concurrent decrease in creatinine levels.

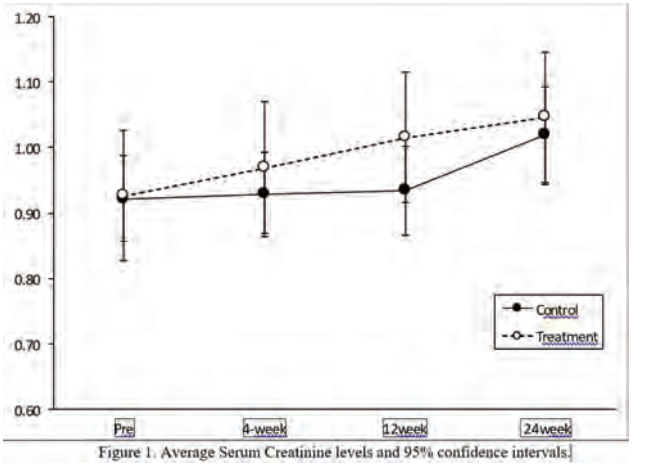


Figure 1. Average Serum Creatinine levels and 95% confidence intervals.

SA-PO020

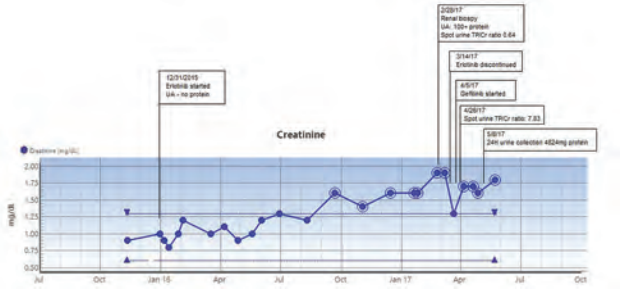
Reversible AKI from Erlotinib Due to Glomerular Endotheliosis Sheron Latcha,[1,3] Victoria Gutgarts,[3] Surya V. Seshan.[2] *[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Weill Cornell Medical Center, New York, NY; [3]Medical College, Weill Cornell, New York, NY.*

Background: Erlotinib is an oral epidermal growth factor receptor associated tyrosine kinase inhibitor approved for the treatment of metastatic non small cell lung (NSCLC) with exon 19 deletions or L858R substitution mutations. Renal toxicity is rare with one report of crescenteric glomerulonephritis.

Methods: A 67 year old female with metastatic lung adenocarcinoma (+EGFR L858R) was sent for renal evaluation for AKI. At start of erlotinib, creatinine (SCr) was 0.9mg/dl and UA showed no proteinuria. Thereafter, the SCr increased. At evaluation, blood pressure (BP) was 146/72 (no change from baseline), no edema was present, UA showed 100+ protein and spot urine total protein creatinine ratio was 0.64. Renal biopsy showed diffuse glomerular endothelial injury, global glomerulosclerosis (16/44 glomeruli), mild to moderate acute tubular injury, moderate widespread tubular atrophy, severe arterio and arteriolosclerosis and extensive arteriolar intimal hyalinosis. No proliferative or immune complex glomerular lesions were seen. The foot processes were partially effaced. Her disease had been well controlled on erlotinib so it was continued at a reduced dose. Subsequently it stopped for increases in SCr. After stopping erlotinib, the SCr decreased to 1.3mg/dl. Because of previously good response to an EGFR TKI, gefitinib was started. Subsequently, an increased SCr, proteinuria and BP were noted. At last followup on gefitinib, the BP was 167/83, no edema was present, SCr was 1.8mg/dl, a 24H urine collection showed 4.8gms of protein and there was no progression of disease on CAT scan.

Results:

Conclusions: Erlotinib treatment was associated with mild proteinuria and reversible AKI. The renal biopsy was consistent with glomerular endothelial injury which may be consistent with a mild form of thrombotic microangiopathy. The presence of significant arteriolar intimal hyalinosis may represent healed endothelial injury. The recurrence of AKI and worsening proteinuria with gefitinib may indicate that this is a "class effect" of EGFR TKIs.



SA-PO021

Carfilzomib Treatment and AKI in Patients with Multiple Myeloma Marianne Camargo,[2] Kinsuk Chauhan,[1] Steven G. Coca.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Nephrology, Mount Sinai Hospital, New York, NY.*

Background: Carfilzomib is a selective proteasome inhibitor approved for the treatment of relapsed and refractory multiple myeloma in patients who have been previously treated with at least two other agents. Initial clinical studies reported renal injury in 25-33% of patients treated, yet clinical trials reported the incidence of acute

kidney injury (AKI) between 4-8% when compared to other anti-myeloma agents. Our objective was to evaluate the real-world incidence and severity of AKI that is presumed due to carfilzomib treatment.

Methods: Electronic medical record (EMR) data was extracted from patients who received carfilzomib between 1/2012 and 12/2016 at a major academic medical center. Data included baseline demographics, medical history, and laboratory results including baseline creatinine and follow-up values during the course of treatment. AKI was defined as rise in creatinine by 0.3mg/dl or by 1.5 times increase from baseline. To estimate the incidence of AKI, a Poisson regression was used, adjusting for age, gender, kappa-lambda ratio, adjusted serum calcium, and history of hypertension, heart failure, and chronic kidney disease.

Results: Out of 429 patients identified between 1/2012-12/2017, 86 patients had received more than one dose of carfilzomib and had complete data. The average age was 65 years old, 42% women, 51% White. Forty-one percent of patients had at least one event of AKI. AKI was more common in women (IRR 2.2, 95% CI 1.7-2.8, p<0.01), older age (IRR 1.02 for each year of age, 95% CI 1.01-1.03 p<0.01), and African Americans (IRR 4.75, 95% CI 3.05-7.39, p<0.01).

Conclusions: Carfilzomib is a third line therapeutic agent for patients with refractory/relapsed multiple myeloma. Our analysis showed higher incidence of AKI events when compared to previous trials. Further studies are needed to clarify the epidemiology and risk factors for AKI in this population.

SA-PO022

Weighting the AKI Risk of Individual Nephrotoxins Karyn Yonekawa,[1] Chuan Zhou.[2] [1]*Seattle Children's Hospital/UW, Seattle, WA;* [2]*Seattle Children's Research Institute, Seattle, WA.*

Background: Seattle Children's Hospital's AKI surveillance system monitors the use of medications suspected to be nephrotoxic and for nephrotoxin-related AKI. An alert to the prescriber is triggered when ≥3 nephrotoxins are ordered. Our current system's sensitivity is 32% in detecting nephrotoxin-related AKI. To improve surveillance, we aimed to determine an individual risk weight for each nephrotoxin and develop a new alert system based on a scoring rule rather than on the number of nephrotoxins prescribed.

Methods: Nephrotoxin orders and AKI alert information (n=23,744) for 2 years (2013-2015) from a large tertiary-care children's hospital were analyzed. A risk weight was constructed for each nephrotoxin using the estimated probability of AKI when the nephrotoxin was present (either alone or in combination with other nephrotoxins). Nephrotoxic medication orders were scored by totaling the constructed risk weights of the individual nephrotoxins. We conducted ROC analysis on the final scores to determine alert thresholds and assess sensitivity and specificity.

Results: Using a total score threshold of 16 to trigger an alert, our model system's sensitivity and specificity was 70% and 80%, respectively. A total score threshold of 14 delivered a sensitivity of 83% and a specificity of 75%.

Conclusions: A surveillance system using individual risk weights for nephrotoxins and a scoring rule delivers improved nephrotoxin-related AKI detection. Additional work is needed to expand our analysis beyond the original list of suspected nephrotoxins to include other medications frequently prescribed in patients who are at risk for AKI.

Individual Weigths of Nephrotoxins

CIDOFOVIR FOSCARNET CYCLOSPORINE GANCICLOVIR TOBRAMYCIN	>16
VALACYCLOVIR PIPERACILLIN/TAZOBACTAM VANCOMYCIN SIROLIMUS VALGANCICLOVIR ENALAPRIL	15
INDOMETHACIN	13
CYTARABINE	12
ACYCLOVIR AMIKACIN TACROLIMUS CEFTAZIDIME	11
GENTAMICIN	10
CARBOPLATIN CAPTOPRIL METHOTREXATE IOVERSOL	9
LISINOPRIL	8
NEOMYCIN	7
LOSARTAN	6
ASPIRIN	4
NAPROXEN	2
IBUPROFEN BLEOMYCIN KETOROLAC CISPLATIN	1
PENTAMIDINE PAMIDRONATE MESALAMINE MELOXICAM ENALAPRILAT	0

SA-PO023

Association between Statin Therapy and Occurrence of AKI in Patients with Peripheral Artery Diseases Daisuke Kanai,[1,2] Kentaro Nakai,[2,3] Hideki Fujii,[3] Shinichi Nishi.[3] [1]*Department of Internal Medicine, Nishiwaki Municipal Hospital, Nishiwaki, Japan;* [2]*Division of Nephrology, Kakogawa Central City Hospital, Kakogawa, Japan;* [3]*Division of Nephrology and Kidney Center, Kobe University Graduate School of Medicine, Kobe, Japan.*

Background: Acute kidney injury (AKI) is an important clinical problem in diagnosis and treatment of cardiovascular diseases. Though may studies have reported that statin therapy before coronary angiography and/or intervention significantly decreased the occurrence of AKI, the association between pretreatment by statin and occurrence of AKI in patients with peripheral arterial diseases (PAD) remains unclear. Therefore, we researched the association between statin therapy and occurrence of AKI in patients with PAD.

Methods: We retrospectively analyzed data from the endovascular treatment (EVT) database in our hospital. The angiography and/or intervention for PAD were performed for 377 patients between October 2011 and March 2016. Sixty nine hemodialysis patients and 13 patients without sufficient data were excluded from a present study. Remaining 295 patients were enrolled and divided into the two groups; those without statin (control group; N=157) and those with statin (statin group; N=138) for at least one months before admission. AKI was defined by absolute increase in serum creatinine (SCr) of ≥0.5 mg/dl or a relative increase of ≥25% measured 1week after procedure.

Results: Before procedure, sex, SCr, amount of contrast medium, use of renin angiotensin system inhibitor, smoking and blood pressure were similar in both group. The statin group has significantly younger patients, more diabetes patients, higher body mass index (BMI) and lower low density lipoprotein-cholesterol (LDL-C) (100±32 mg/dL vs 108±31 mg/dL) than the control group. As for occurrence of AKI, there was significantly lower incidence in the statin group compared to the control group (5% vs 16%, p<0.05). We performed a multivariate analysis adjusted for age, BMI, diabetes mellitus, LDL-C, SCr and statin therapy. The result of multivariate analysis showed that statin therapy was significantly correlated with the lower occurrence of AKI (p<0.05).

Conclusions: The results of our study suggested that statin therapy may prevent the occurrence of AKI after angiography and/or intervention for PAD.

SA-PO024

Hydration Protocols with Cisplatin: Need for Consensus and Cost Curtailment Sandhya Manohar, Wonngarm Kittanamongkolchai, Jennifer Mcdonald, Jeffrey A. Betcher, Heidi D. Finnes, Nelson Leung. *Mayo Clinic, Rochester, MN.*

Background: Platinum based drugs use is often restricted due to the high risk of nephrotoxicity. The incidence of nephrotoxicity for Cisplatin is reported to be 25-30%. Many nephroprotective measures have been studied with hydration being the most commonly used. We sought to compare the incidence of Acute Kidney injury (AKI) at two large tertiary referral centers that use different nephroprotective protocols

Methods: We retrospectively reviewed all adult patients that received first dose of Cisplatin at Mayo Clinic Rochester (MCR) and Arizona (MCA) from 2010-2015 and had at least one creatinine value 7 days before and 72 hours after the drug administration. MCR utilizes a limited dose dependent hydration fluid with mannitol in the bag containing Cisplatin whereas MCA uses a liberal 1 liter pre- and post-hydration without mannitol.

Results: Out of the 2188 patients that had received Cisplatin at the 2 centers, only 191 patients met the inclusion criteria. Among them the overall incidence of AKI was 9.4% (18/191) with MCR having 10% (11/110) and MCA 8.6% (7/81) and the difference was not statistically significant. Only one patient had AKIN Stage 2 AKI and the rest were AKIN Stage 1. The average dose of Cisplatin received was higher in MCA (85.5 mg vs 74.9 mg) which was statistically significant (p 0.05). The average dose of fluids was 1316.7 ml (SD 615) in the 2 cohorts. There was no significant difference in the age, gender, history of chronic kidney disease, diabetes, hypertension, baseline creatinine, 30 day hospitalization and time to death after initiating chemotherapy among the two cohorts.

Conclusions: Our study showed that despite the marked differences in the nephroprotective protocols used at each of the center there was no difference in the AKI rate. In this time when the need for cost effective medicine is paramount we must try to be judicious in the drugs we use. We have since converged our Cisplatin hydration protocol, to be dose directed and without routine mannitol use, across the Mayo Clinic enterprise.

SA-PO025

The Risk of Contrast Induced AKI Is Still Present Despite Normal Renal Function Jasarat Chowdhury, Seema Jain, Masud Khan, Jasmine B. Lee. *Acute Medicine, Lewisham and Greenwich NHS Trust, London, United Kingdom.*

Background: Iodinated contrast CT studies are a common investigation for patients admitted to hospital. Contrast induced AKI (CI-AKI) is quoted to be the third most common contributor to in hospital AKI with patients with pre-existing CKD, cardiac dysfunction, diabetes and hypertension most at risk. However these studies were done before newer, low osmolality contrast media was common practise. This study investigates the incidence of contrast induced AKI (CI-AKI) in patients admitted to a UK district general hospital who underwent contrast CT studies.

Methods: All patients who had contrast CT studies over a 2 week period in November 2016 were included in the study. For these studies, 50-100ml of non-ionic, low osmolar contrast agent was injected. CI-AKI was defined using the KDIGO classification for AKI.

Results: 92 patients had contrast CT studies over the time period. Of these patients, 13% had pre-existing CKD, 11% had cardiac dysfunction, 15% had Diabetes and 36% had Hypertension. 5% of patient developed CI-AKI. 4% had stage 1 and 1% had stage 2, no patients had stage 3. However of the 5 patients who developed CI-AKI, none had pre-existing CKD or cardiac dysfunction, 1 had diabetes and 2 had hypertension.

Conclusions: The incidence of CI-AKI in our cohort was lower and less severe than quoted in previous studies which may be due to the lower osmolality contrast agent used. However, despite risk factors being present in this cohort, none of the patients who developed CI-AKI had pre-existing CKD which is thought to be the most significant risk factor and therefore features most highly in CI-AKI prevention guidelines. This study suggests that guidance given to prevent CI-AKI should be followed in all patients irrespective of pre-existing risk factors and that having existing CKD should not preclude a contrast study if necessary.

SA-PO026

Risk Factors for Polymyxin-Induced AKI in Critically Ill Patients Cassiane D. da Fonseca,[4,6] Mirian Watanabe,[6] Maria De Fatima Vattimo,[1] Sheila M. Fernandes,[4] Luciana soares C. Santos,[5] Filipe U. Coelho,[3] Natalia A. Oliveira.[2] *[1]Sao Paulo, Brazil; [2]Organization University of São Paulo, São Paulo, Brazil; [3]University of São Paulo, São paulo, Brazil; [4]School of Nursing, University of São Paulo, Carapicuíba, Brazil; [5]Universidade de São Paulo, SÃO PAULO, Brazil; [6]University of Sao Paulo, Sao Paulo, Brazil. Group/Team: Research Group on Acute Kidney Injury-GERA.*

Background: Critically ill patients with infections and sepsis frequently need robust antimicrobial agents, such as polymyxins (Pmxs), for efficacy against multi-resistant gram-negative bacteria. However, acute kidney injury (AKI) may be the most important limiting adverse effect of Pmxs. This study evaluated the incidence and identified the risk factors for the development of AKI in critically patients receiving Pmxs.

Methods: A multicenter retrospective cohort study enrolling 1009 intensive care patients Wwas performed. AKI was defined by KDIGO criteria. Primary outcome was patients who received Pmxs and developed AKI. The main secundary outcomes were clinical risk factors for Pmxs-induced AKI. Multivariate analyses with logistic regression were performed.

Results: A total of 936 patients were included. AKI was detected in 404 (43%) patients. Mean age was 59.1 ± 17.0 years, 63% were male. Systemic arterial hypertension (45%), Diabetes Mellitus (26%), sepsis (22%) and shock state (57%) were observed in AKI individuals. The mortality was 37% for AKI patients (P<0.001). Among 75 patients treated with Pmxs, rate of AKI was 88%. The risk factor of AKI associated with Pmxs were prolonged hospital stay, mechanical ventilation and shock state (P<0.001).

Conclusions: This data highligted that the rate of Pmx-induced AKI was greather than other studies. Critically ill patients are at higher risk due to the presence of prolonged hospital stay, mechanical ventilation and shock state.

Funding: Government Support - Non-U.S.

Risk factor of AKI associated polymyxins use

Variable	OR (IC 95%)	p value
Age	0.05 (0.9-1.0)	0.059
Shock	4.91 (1.6-14.8)	0.005
Vasoactive drug	0.59 (0.2-1.3)	0.212
Mechanical ventilation	1.07 (1.0-1.1)	<0.001
Clinical hospitalization	1.39 (0.7-2.7)	0.337
ICU hospital stay	1.09 (1.0-1.1)	<0.001

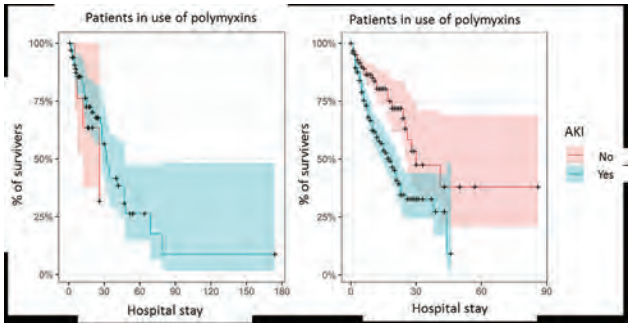


Figure 1. Survivel curve of patients in use of polymyxins.

SA-PO027

Vancomycin-Associated AKI with a Steep Rise in Serum Creatinine Juan Carlos Q. Velez,[4] Ndidiamaka O. Obadan,[2] Mohammed Alzubaidi,[2] Bhavna Bhasin,[1] John M. Arthur,[5] Gautam M. Phadke.[3] *[1]Medical College of Wisconsin, Milwaukee, WI; [2]Medical University of South Carolina, Charleston, SC; [3]University of North Dakota School of Medicine, Fargo, ND; [4]Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA; [5]University of Arkansas for Medical Sciences, Little Rock, AR.*

Background: The incidence of vancomycin-associated (VA) acute kidney injury (AKI) has increased after the Infectious Diseases Society of America updated their recommendations for higher therapeutic trough levels for methicillin-resistant *Staphylococcus aureus* infections. However, distinct laboratorial features of VA-AKI have not been described.

Methods: We defined precipitous AKI as a case with an increase in serum creatinine (sCr) ≥ 1.5 mg/dL/day. After encountering 2 cases of adults with VA-AKI presenting with an unusually steep rise in sCr, we probed for similar cases by surveying nephrologists at the American Society of Nephrology Communities online forum and by searching for published cases of VA-AKI via PubMed or Google to extract those with criterion for precipitous AKI. We also collected daily sCr values of consecutive AKI cases not associated with vancomycin exposure as a control group (non-VA-AKI).

Results: Seven original cases of VA-AKI characterized by an abrupt and exceedingly large rise in sCr shortly after a cumulative dose of vancomycin of ≥ 5 g given over 1 - 4 days were compiled from 4 different medical centers (mean age 41.6 years, 43% women, 57% black, mean body mass index 32 kg/m^2). In 3 cases, simultaneously obtained serum cystatin C (sCy) values did not reveal relative steep increments from the upper limit of normal (mean: 2.6 vs. 0.5 mg/dL, for sCr and sCy, respectively), suggesting that the reductions in glomerular filtration rate were overestimated by the sCr increase. In addition, we extracted 4 published cases of precipitous AKI due to vancomycin. The median initial 24-hour rise in sCr in all 11 VA-AKI cases compiled was 2.5 mg/dL (range 1.4 – 3.5 mg/dL). The slope of the initial 48-hour sCr rise of the VA-AKI (n = 11) cases was greater than that of non-VA-AKI (n = 44) cases [2.01 (CI: 1.6-2.4) vs 0.61 (CI: 0.5-0.7) mg/dL/day; p<0.0001]. A concomitant steep rise in blood urea nitrogen was not observed in these VA-AKI cases.

Conclusions: VA-AKI can occasionally manifest with a precipitous rise in sCr after a high cumulative dose of vancomycin. True toxic tubular injury overrepresented by the sCr rise is possibly present in these cases. Whether interference of vancomycin with tubular secretion of creatinine explains the phenomenon requires further study.

SA-PO028

Colistimethate Sodium and AKI: Incidence, Evolution, Risk Factors, and Prognosis Saul Pampa-Saico. *Hospital Ramon y Cajal, MADRID, Spain.*

Background: Colistimethate sodium (CMS) treatment has increased in the last years due to exponential increase in multidrug-resistant bacterial infections with the risk of CMS nephrotoxicity. The aim of this study was to determine the incidence and risk factors of AKI attributable to CMS based on KDIGO criteria. To identify prognostic factors which conditioning kidney function outcome at six months of follow-up.

Methods: Retrospective observational study, including patients >18 years old admitted from January 2007 to December 2013 who received CMS for > 48hours. Demographic, clinical and biochemical parameters of prognostic interest were collected. A multivariate logistic regression analysis was used to identify the risk factors associated with the development of AKI. To evaluate the renal function outcomes at 6 months after discharge (by eGFR (MDRD-4)) were analyzed by multivariate lineal regression. Unfavorable kidney evolution at six months was defined as residual impairment of kidney function indicated by a eGFR less than 60 ml/min/m2 or a reduction of creatinine clearance >25% at 3 months in comparison with baseline

Results: 126 patients (mean age 64.4±14 years) were included in the study; 61 patients developed AKI (48%). Independent predictors of AKI were the infection grade: severe sepsis (OR 3.1; p=0.026); septic shock (OR 11.9; p=0.0004), intravenous iodinated contrast media (OR 2.9; p=0.024) and serum creatinine at hospital admission (OR 2.9, p=0.031). Eighty-four patients (67%) survived at discharge. Independent predictors of decline in renal function after 6 months were eGFR at hospital admission (p=0.016) and hospital discharge (p=0.0004) (R^2_c = 0.823). 56% (34/61) patients who developed AKI during admission survived, 32% of them (11/34) had an unfavorable kidney outcome at 6 months, the main determinants were eGFR at hospital admission (p=0.023), at the start CMS (p=0.002) and at hospital discharge (p=0.0003).

Conclusions: The development of AKI associated with CMS treatment was correlated with the infection grade, intravenous iodinated contrast and serum creatinine at hospital admission. Neither doses nor length of therapy with CMS were associated with AKI. The eGFR levels at hospital admission and hospital discharge were independently factors associated with renal function outcome at six months. These predictors may assist in clinical decision making for this patient population.

SA-PO029

Angiotensin 2 Receptor Blocker (ARB) and Angiotensin Converting Enzyme-Inhibitor (ACE) Therapy Indications and Risks in Patients Who Develop an AKI During Hospital Admission Toby Humphrey, Oshini Shivakumar, Kate Berresford, Clare Morlidge, Andrew Findlay, Suresh Mathavakkannan. *East and North Hertfordshire NHS Trust, Stevenage, United Kingdom.*

Background: ACE/ARB are the second most prescribed medicine from primary care in England. Despite an aged and co-morbid population prescription of ACE/ARB is increasing. There are defined benefits for patients on ACE/ARB in certain clinical situations but there is concern in frail, elderly patients at risk of AKI. We sought to review the indications and risk factors for ACE/ARB use in patients (prescribed ACE/ARB in the community) who developed AKI during admission to a 700 bed secondary care hospital.

Methods: Adult elective and non-elective patients who developed AKI during an admission episode in February to April 2016 were identified by electronic AKI alert. 311 AKI events were reviewed by an AKI specialist nurse over this time period. Demographic details and medications including ACE/ARB were documented. All AKI patients admitted on ACE/ARB therapy had retrospective searches of their co-morbidities and indications for ACE/ARB therapy on electronic patient record and pathology database.

Results: 311 AKI events were reviewed by the AKI nurse between February - April 2016. 102 /311 (32.8%) of those patients had been prescribed ACE/ARB therapy up until admission. Of those 102 patients (M:F, 52:50), the mean age was 81.44 years, median age adjusted Charlson Co-Morbidity score was 6. 65 patients (63.73%) had a prior history of AKI whilst only 38 patients (37.25%) had a diagnosis of type 2 Diabetes, 24 (23.53%) had heart failure diagnosed by echocardiogram, 17 patients (16.67%) had documented proteinuria prior to admisison, 34 (33.33%) had a prior history of ischaemic heart disease. 13 patients (12.75%) had a diagnosis of cancer and 24 (23.53%) had a diagnosis of dementia.

Conclusions: Our data indicates patients on ACE/ARB therapy who develop an AKI during hospital episode are frequently elderly and co-morbid with a high likelihood of previous AKI. They frequently do not have good indications for ACE/ARB therapy with few diabetics, few diagnoses of cardiac failure, ischaemic heart disease and proteinuria. This data should be used to support further studies to identify elderly patient populations in the community prescribed ACE/ARB therapy who may benefit from rationalisation of their medication.

SA-PO030

Statins Can Offer Renal Protection in Patients with CKD or DM Afflicted with AKI Rabia Akhtar, Ghada Elshimy, Seme Tabassum, Chandra B. Chandran. *St Joseph Regional Medical Center/New York Medical College, Paterson, NJ.*

Background: Statins are some of the most commonly prescribed medications in the United States. Aside from the lipid-lowering effects, this class of medications may offer benefits to other organ systems and may play a role in preventing AKI through these pleiotropic effects. This has been studied most specifically in patients undergoing cardiac catheterization or cardiac surgery. Our study is unique in that it seeks to analyze whether the general population with CKD or diabetes not undergoing any cardiac surgery could also stand to benefit from statin therapy.

Methods: We conducted a chart review of 339 patients admitted to a major teaching hospital in New Jersey during the time period between 2000-2010 and had the diagnosis of AKI and then stratified patients as statin users and non-statin users. We aimed to study whether these groups had differences in their rates of recovery. A series of logistic regressions were conducted to investigate predictors of patients recovery. The predictors that were included in this analysis were race, HTN, DM, CKD, rhabdomyolysis, statin intensity, stage of CKD and mean HbA1c value.

Results: We found that in patients with normal kidney function, those who were on statins were not more likely to recover than patients not on statins ($p > .05$). However, among patients with chronic kidney disease, statins increased the odds that they would recover by a factor of 3.56 ($p < .05$). In addition, for patients with Diabetes Mellitus, statins increased the odds that a patient would recover by a factor of 3.81 ($p < .05$).

Conclusions: The results of our study show that statins may offer renal protection to patients with chronic kidney disease or diabetes and not just those undergoing cardiac catheterization or cardiac surgery. The results of our study also emphasize the need for further studies looking at statin use and outcomes in AKI. Further matched-analyses would be helpful to look at whether our results are reproducible.

SA-PO031

Oral Hydration to Prevent Contrast Induced Nephropathy Corinne E. Balemans,[1] Yvonne R. de Waal,[1] Marc A. Ten Dam,[2] Jack F. Wetzels.[1] *[1]Radboud University Medical Center, Nijmegen, Netherlands; [2]Canisius Wilhelmina Hospital, Nijmegen, Netherlands.*

Background: Contrast Induced Nephropathy (CIN) complicates the use of iodinated contrast media. Guidelines advise intravenous hydration as preventive measure in high risk patients. However, i.v. hydration requires complicated logistics and is associated with high costs and adverse events (de Waal, ASN 2015). We showed in a small sized study that oral hydration might be as effective as i.v. hydration (Balemans, ASN 2015). We now report the efficacy of oral hydration in a large prospective cohort.

Methods: Two hospitals participated in the study. Between January 2015 and May 2017 high risk patients were screened and if eligible hydrated with sodiumchloride tablets 1g/10kg of body weight/day on day -2 and -1 before contrast exposure. Patients with eGFR <30ml/min/1.73m2, overt heart failure, Multiple Myeloma or an emergency procedure were excluded and hydrated intravenously with sodiumbicarbonate. We evaluated the incidence of CIN (defined as a rise in serum creatinine ≥25% or ≥44umol/L 48-96hrs after contrast injection) and adverse events.

Results: In the study period 927 radiological procedures were planned in high risk patients. 393 patients gave informed consent, 20 were lost to follow up, 10 CT scans were cancelled. We eventually evaluated 363 procedures, 99 patients were treated with iv hydration mainly because of heartfailure and eGFR < 30ml/min/1.73m2. 264 patients (30.7% female) received oral hydration, mean age 70.6±8.3 yrs, mean eGFR 44.1±7.1 ml/min/1.73m2. The incidence of CIN after oral hydration was 3.0% (95%CI 1.44-5.97). In a historical control group, treated with iv hydration the incidence of CIN was 2.4% (95%CI 1.61-3.65) (Balemans, Radiology 2012). The main adverse event in the oral hydration group was nausea, in one case leading to conversion to iv hydration. One case of overhydration was reported (0.4%) compared to 12/490 (2.4%) after i.v. hydration (de Waal, ASN 2015)

Conclusions: Oral hydration is as effective as intravenous hydration in preventing CIN and can be used safely. Oral hydration obviates the need for hospital admission, and thus reduces costs.

Funding: Government Support - Non-U.S.

SA-PO032

Contrast-Nephropathy Following Intra-Arterial and Intravenous Contrast Administration in CKD Patients Pulkit Chaudhury,[3] Stacey Jolly,[2] Serge Harb,[3] Jesse D. Schold,[2] Susana Arrigain,[2] Victoria Konig,[2] Joseph V. Nally,[2] Sankar D. Navaneethan,[1] Georges Nakhoul.[3] *[1]Baylor College of Medicine, Houston, TX; [2]Cleveland Clinic, Cleveland, OH; [3]Cleveland Clinic Foundation, Cleveland Heights, OH.*

Background: Contrast-induced nephropathy (CIN) refers to acute kidney injury (AKI) that develops after administration of iodinated radiocontrast agents. It has been described following coronary intraarterial (IA) contrast administration. However, true risk of CIN after intravenous (IV) contrast administration is debated. Recent retrospective analyses have questioned any assocation between iodinated contrast and nephrotoxicity following IV administration. Here, we measure the risk of AKI and specifically CIN after IA and IV contrast administration in a high-risk population of hospitalized patients with CKD.

Methods: Pre-existing Cleveland Clinic CKD registry was used to conduct a propensity-matched analysis of patients getting inpatient left heart catheterization (LHC), contrast CT (CCT) and noncontrast CT (NCCT) scans between 2010 and 2015, with adequate creatinine measurements before and after scans. Propensity scores were developed using several variables including: age, gender, race, CKD stage, cardiovascular comorbidities, malignancy, hemoglobin and medications. One-to-one greedy matching with 0.1 caliper was used to match LHC patients to CCT and then to NCCT patients. Charts were independently reviewed to determine the etiology of the AKI. Chi-square tests were used to compare the proportion of AKI and CIN across matched groups.

Results: A total of 163 of 244 (67%) patients with LHC were matched to CCT and NCCT patietns. Patients had a mean age of 74 years with 55% males. The incidence of AKI was 25.8% in LHC, 21.5% in CCT and 22.7% in NCCT (P=0.64). The incidence of CIN was 20.2% LHC and 12.3% in CCT (P=0.05).

Conclusions: CIN can be observed following administration of both IA and IV contrast but is more frequently associated with administration of IA contrast. Although, the incidence of AKI was similar in the three groups, the distribution of AKI etiologies were significantly different as expected. Extrapolating the risk of CIN by comparing the incidence AKI in these fundamentally different populations, as has been recently published, should be done with caution.

Incidence of AKI and CIN after Contrast Media Administration

	Coronary Angiogram (n=163)	Contrast CT (n=163)	Non-Contrast CT (n=163)
All AKI	42 (25.8%)	35 (21.5%)	37 (22.7%)
CIN	33 (20.2%)	20 (12.3%)	0 (0%)

SA-PO033

Antithrombin III Is a Novel Predictor for Contrast Induced Nephropathy after Coronary Angiography: An Observational, Cross-Sectional Study Jianyong Yin, Feng Wang, Niansong Wang. *Department of Nephrology, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China.*

Background: Antithrombin III (AT-III) functions as an important endogenous anticoagulant and has powerful anti-inflammatory effects. Low AT-III activity is considered to be a predictor of poor outcomes in several conditions, including acute kidney injury after cardiac surgery. However, whether the AT-III levels are related to the incidence of contrast induced nephropathy(CIN) has not been identified yet.

Methods: A cross-sectional study on CIN after CAG was conducted to identify the potential predictive value of AT-III for CIN. A total of 460 patients who underwent coronary angiography(CAG) from January 2015 to December 2016 in coronary care units(CCU) were enrolled. CIN was diagnosed according to the KDIGO guideline. Plasma AT-III activity was measured before CAG and <75% was recognized as low activity according to reference values.

Results: Of 460 patients undergoing CAG, 125(27.17%) developed CIN. The incidence of CIN was significantly higher in patients with low AT-III activities than that in normal group (Pearson's chi-squared test P=0.002). Besides, with the decline of AT-III activity, the prevalence of CIN progressively rise, with the highest value(58.8%) in patients with AT-III activity<60%. Moreover, the AT-III activity was significantly lower in CIN patients than that in non-CIN ones(84.43±16.3% vs. 92.14±13.94%, P<0.001). After multivariable analysis, low AT-III activity remained a significant independent predictor of CIN(OR 2.207,95%CI[1.29-3.777];P=0.004) as well as baseline serum creatinine(OR 1.009,95%CI[1.001-1.016];P=0.026).

Conclusions: Patients with low AT-III activities presented a higher risk of developing CIN after CAG. And the initial AT-III activity may be an independent predictor for CIN.

Funding: Government Support - Non-U.S.

SA-PO034

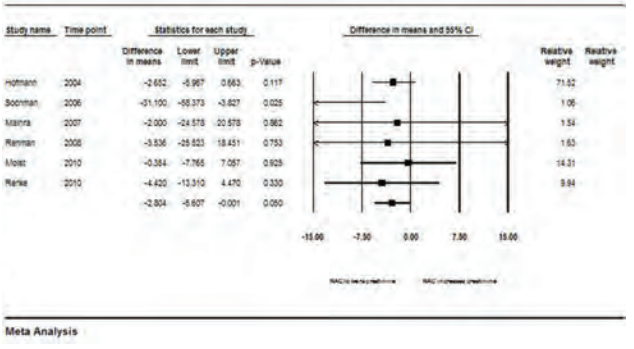
The Effect of N-Acetylcysteine on Serum Creatinine: A Systematic Review of the Evidence Johnny Huang, Ayub Akbari, Swapnil Hiremath. *University of Ottawa, Ottawa, ON, Canada.*

Background: Contrast-induced acute kidney injury (CI-AKI) is a major iatrogenic concern with contrast imaging procedures. N-acetylcysteine (NAC) has been tested in prevention of CI-AKI with conflicting reports of efficacy, and there has not been a good scientific explanation for this heterogeneity reported in the literature. Interference of NAC with serum creatinine measurement has been proposed to be one explanation, but the research on this topic has been discrepant. One possibility is that the interference may vary with the type of assay used to measure creatinine. **Objective:** What is the effect of NAC on serum creatinine, administered in the absence of any other confounding events (eg contrast administration, surgery)?

Methods: A systematic search was performed in MEDLINE, EMBASE, and Cochrane Library to identify studies with participants receiving NAC and before/after serum creatinine measurements, without confounding factors. Two authors independently screened the citations, and data of relevant articles was extracted for meta-analysis.

Results: The literature search produced 503 citations, of which 6 were eligible and included in the review. There is clinical heterogeneity in the studies in terms of study population (healthy volunteers, patients with normal and decreased kidney function), dose of NAC used and method of creatinine estimation. Overall, all studies did show a numerically lower creatinine after NAC administration, ranging from 0.35 to 31.1 µmol/L. The summary weighted mean difference was -2.8 µmol/L (95% CI -0.001, -5.6, p = 0.05). There was no statistical heterogeneity in the results.

Conclusions: Conclusion: There is a small decrease in serum creatinine with NAC administration, but, given the small sample sizes and clinical heterogeneity, a definitive study should be done to establish the true magnitude and nature of the effect.



SA-PO035

Effects of Fluid Resuscitation on Macro and Microcirculatory Perturbations in Ovine Septic Shock Yugeesh R. Lankadeva,[2] Junko Kosaka,[2] Naoya Iguchi,[2] Roger G. Evans,[3] Lindsea C. Booth,[2] Rinaldo Bellomo,[1] Clive N. May.[2] *[1]Austin Health, Melbourne, NSW, Australia; [2]Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, NSW, Australia; [3]Monash University, Melbourne, NSW, Australia.*

Background: Aggressive fluid resuscitation, with multiple boluses of crystalloids remains the first-line intervention to maintain systemic hemodynamics in septic shock, but its effects on the renal microcirculation are unknown. We therefore examined the effects of three successive boluses of sodium lactate on intra-renal and urinary oxygenation (pO_2) in conscious sheep with established septic acute kidney injury (AKI).

Methods: Sheep were instrumented with fiber-optic probes in the renal cortex, medulla and within a bladder catheter. Sheep received an infusion of *Escherichia coli* or vehicle-saline for 30 hours. A 500-mL bolus of sodium lactate was infused intravenously every hour at 24, 25 and 26 h of sepsis (N=8) over 15 min time-intervals.

Results: Septic AKI was characterized by hypotension (80±2 to 68±2 mmHg) and reduced creatinine clearance (82±8 to 40±6 mL/min)) (both P<0.01). Medullary tissue pO_2 (43±4 to 19±4 mmHg) and urinary pO_2 (44±4 to 20±3 mmHg) were simultaneously reduced (both P<0.001). Infusion of crystalloids briefly increased blood pressure (to 74±6 mmHg), creatinine clearance (to 71±16 mL/min) and improved medullary pO_2 (to 35±4 mmHg) and urinary pO_2 (to 28±6 mmHg). These effects were short-lived and rapidly diminished within the 3-h recovery period. Sheep with septic AKI retained 70% of the total volume of crystalloids infused.

Conclusions: Infusion of three successive boluses of crystalloids briefly reversed renal medullary hypoxia and improved kidney function in septic AKI. However, the transient nature of these effects challenges the long-term benefits of aggressive volume resuscitation in septic shock. In septic AKI, excessive fluid retention may lead to increased cardiac filling pressures and tissue oedema. Urinary pO_2 may be a real-time surrogate marker of medullary tissue pO_2 during fluid resuscitation in septic AKI.

Funding: Government Support - Non-U.S.

SA-PO036

Long-Term Survival in Patients with Septic AKI Is Strongly Influenced by Renal Recovery Marco Fiorentino,[1,2] Fadi Tohme,[1,3] Shu Wang,[1,4] John A. Kellum.[1,3] *[1]Center for Critical Care Nephrology, CRISMA, Department of Critical Care Medicine, University of Pittsburgh, Pittsburgh, PA; [2]Department of Emergency and Organ Transplantation, Nephrology, Dialysis and Transplantation Unit, University of Bari, Bari, Italy; [3]Renal & Electrolyte Division, Department of Medicine, University of Pittsburgh, Pittsburgh, PA; [4]Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA.*

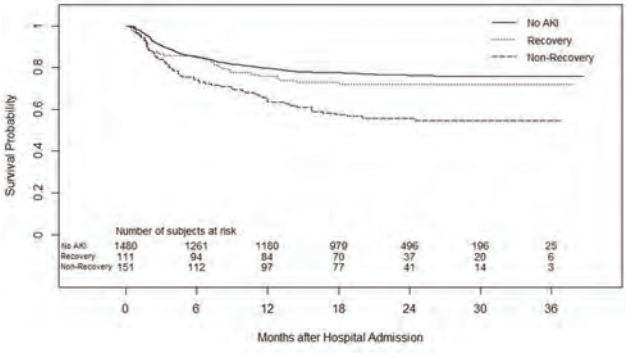
Background: Prior studies have found that long-term survival after critical illness is influenced by acute kidney injury (AKI) even in patients who appear to recover renal function. In the current report, we sought to examine the effects of septic AKI on longer-term survival as a function of recovery by discharge.

Methods: We analyzed patients with community-acquired pneumonia from a large multicenter cohort. Patients who developed AKI (KDIGO stages 2- 3) were included and renal recovery was defined as being alive at hospital discharge with return of SCr to within 150% of baseline without dialysis. Our primary outcome was survival up to 3 years analyzed using Kaplan-Meier and Gray's models.

Results: Stage 2-3 AKI occurred in 262/1742 (15%) patients of which 111 (42.4%) recovered. Patients without recovery were older (75±14 vs 69±15 years, p=0.001), and were more likely to have at least stage 1 AKI on day 1 (83% vs 52%, p<0.001). 11/262 (4%) patients developed ESRD by 1 year of follow-up. Mortality rates were 23.4% (347/1480) for no AKI, 28% (31/111) for AKI with recovery and 44.3% (67/151) for AKI without recovery. Non-recovery at hospital discharge was associated with lower survival compared to no AKI (p<0.001), while patients with recovery had similar survival compared to no AKI (p=0.2)(**Figure 1**). In a covariate-adjusted Gray's model, patients who did not recover had a greater hazard for mortality compared to no AKI (HR range 1.05–2.46, overall p=0.001), while recovering patients had similar risk for mortality compared to no AKI (HR range 0.6-0.28, overall p=0.43). Absence of AKI on day 1, no in-hospital RRT, higher Apache III score and higher baseline SCr were associated with recovery after AKI.

Conclusions: Recovery by hospital discharge is associated with improved long-term survival in patients with sepsis-associated AKI. Measures to enhance renal recovery by discharge might reverse the long-term adverse consequences of sepsis-associated AKI

Funding: Other NIH Support - R01GM61992



SA-PO037

The Clinical Significance of Alkaline Phosphatase Activity in Patients with Septic AKI Seung don Baek. *Mediplex Sejong Hospital, Gyeyang-gu, INCHEON, Republic of Korea.*

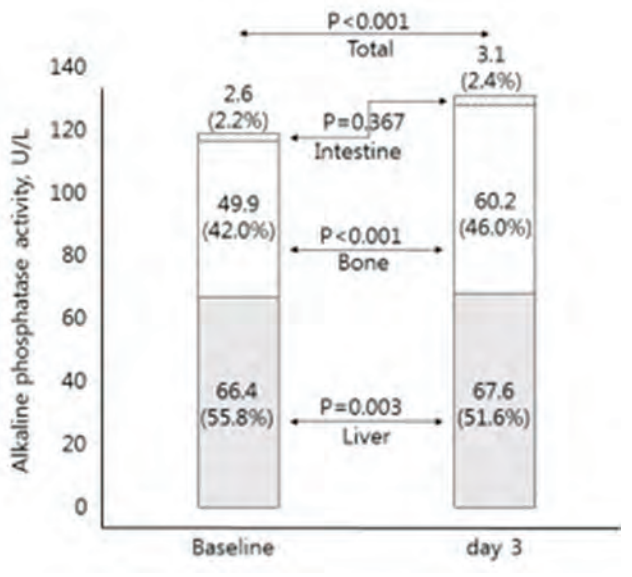
Background: Evidences suggested that alkaline phosphatase attenuate inflammatory response in sepsis by lipopolysaccharide detoxification and adenosine triphosphate dephosphorylation. We sought to determine alkaline phosphatase (AP) activity change during septic acute kidney injury (AKI) and clinical parameters associated with AP activity.

Methods: In a retrospective study of the patients who underwent continuous renal replacement therapy (CRRT) due to septic AKI, we investigated the baseline, follow-up AP activity on day 3 and the associated outcomes.

Results: We analyzed baseline AP activity of 155 patients and day 3 AP activity of 123 patients. Baseline AP activity of 90 (59–133) U/L increased to 105 (79–156) U/L on day 3, of which liver and bone isoforms increased significantly, but intestine isoforms did not reach statistical significance. Baseline AP activity did not show an association with renal and inflammatory biomarkers, or outcomes. Also, it did not differ significantly

between 75 survivors and 80 non-survivors (p=0.155). Day 3 AP activity increased in 70.6% of patients with mean difference of 19 (-3 to 53) U/L. Day 3 AP activity showed weak correlation with length of ICU stay (r=0.205, p=0.023) and length of hospital stay (r=0.190, p=0.036), however, not with survival (r=-0.035, p=0.698).

Conclusions: Endogenous AP activity modestly, but significantly increased in 70.6% of patients with septic AKI. However, neither baseline nor follow-up AP activity was associated with survival.



SA-PO038

Spanish Experience of Pregnancy-Associated Atypical Hemolytic Uremic Syndrome Ana Huerta,[5] Santiago Rodriguez de Cordoba,[4] Emilia Arjona,[1] Manuel Praga,[2] Jose M. Portoles.[3] *[1]Centro de Investigaciones Biologicas-CSIC, Madrid, Spain; [2]Hospital 12 de Octubre, Pozuelo De Alarcon, Spain; [3]Hospital Universitario Puerta de Hierro, Majadahonda, Spain; [4]Consejo Superior de Investigaciones Cientificas, Madrid, Spain; [5]Puerta de Hierro Hospital-Nephrology Department., Madrid, Spain. Group/Team: Spanish Group for Study of Complement and Renal Disease.*

Background: Pregnancy-associated atypical hemolytic uremic syndrome (P-aHUS) refers to the thrombotic microangiopathy that result from uncontrolled complement activation during pregnancy or the postpartum period. P-aHUS is a devastating disease for which we still have a limited clinical understanding and treatment experience. Here we report a retrospective study to analyze the clinical and prognostic data under different treatments of the cohort of P-aHUS patients from the Spanish aHUS Registry.

Methods: In the Spanish aHUS Registry we identified 242 adult female patients, of whom 22 fulfilled P-aHUS criteria. We performed a functional and genetic study of the complement system in all of them. We retrospectively collected the clinical, analytical, treatment and evolution characteristics of these patients. We present the data as median and interquartile range.

Results: The age of presentation was 34 years. It was the first pregnancy in 16 patients (73%). 73% of the cases occurred postpartum. Of these, 81% required cesarean section. 41% required acute hemodialysis. 19 patients associated hypertension, 7 neurological disorders, 4 gastrointestinal problems and 3 cardiac symtoms. A renal biopsy was performed in 11 patients: 10 presented MAT lesions and 3 an associated glomerulonephritis. Abnormalities in the complement system related genes were detected in only 41% of the cohort. 16 patients underwent plasma replacement, achieving haematologic response in 5 and renal response in 2. 3 patients received infusion treatment of fresh frozen plasma, with haematological response in 3 but renal response in 2. 10 of the 22 patients (45%) received treatment with Eculizumab, achieving haematological and renal response in 100% of them. 3 of the patients treated with Eculizumab required acute hemodialysis, but none of them required renal replacement therapy during follow-up.

Conclusions: P-aHUS seems to have similar characteristics than other types of aHUS. It seems to be an association between cesarean delivery and the development of P-aHUS. Treatment with Eculizumab was effective in 100% of our cohort. More studies are needed to confirm our findings.

SA-PO039

Obstetric AKI and Renal Outcomes Secondary to Pre-Eclampsia Frances I. Conti-Ramsden,[1] Hannah L. Nathan,[1] Annemarie De greeff,[2] Daniel W. Steyn,[3] David Hall,[4] Lucy C. Chappell,[1] Andrew H. Shennan,[1] Kate Bramham.[1] *[1]Kings College London, London, United Kingdom; [2]Accuracy Assessed Medical Devices CC, Diamond, South Africa; [3]Stellenbosch University, Parow, South Africa; [4]Stellenbosh University and Tygerberg Hospital, Cape Town, South Africa.*

Background: Introduction: Pre-eclampsia (PET) is a common cause of acute kidney injury (AKI) but AKI incidence, risk factors, maternal and renal outcomes in a middle-income setting are unknown. Objectives: To define the incidence of obstetric AKI in the CRADLE-II pre-eclampsia cohort, explore the association between maximal creatinine and maternal outcomes, and to identify the proportion of women with persistently elevated serum creatinine (Cr) before and after discharge.

Methods: A prospective observational study of women with PET at 3 centres in South Africa was conducted (Jan 2015-May 2016). Pre-specified outcomes were eclampsia, stroke, maximal Cr during admission ≥90 μmol/L (MaxCr90), maternal and perinatal death. Serial Cr (pre-pregnancy to May 2017) were subsequently extracted from national databases in all women with MaxCr90.

Results: 272/1547 (17.6%) of women had MaxCr90 (median 114, range 90-1097). Relative risk of death in women with MaxCr90 was 6.2 (95% CI 2.2,17.8). 236 (15.2%) women had AKI (KDIGO criteria; 123 (52.1%) Stage 1; 63 (26.7%) Stage 2; 50 (21.2%) Stage 3) with 188/236 (79.7%) cases occurring within 48hrs of admission. 138 women (58.5%) had AKI recovery at discharge (Cr returned to <1.5x baseline or <90 μmol/L if no baseline), 92 women (39.0%) did not have AKI recovery at discharge (Cr >1.5x baseline or >90 μmol/L if no baseline) and 6 (2.5%) women died. Serum Cr was repeated post discharge in 25 (27.1%) women without AKI recovery: 19 (76%) had AKI recovery; 6 (24%) no recovery. Overall, 96.3% (157/163) of women with repeat Cr assessment had AKI recovery but 3.7% (6/162) did not. Repeat Cr was not assessed in 67/92 (72.8%) women without AKI recovery at discharge.

Conclusions: Obstetric AKI was common in women with PET in this middle-income cohort. Maximal Cr ≥90 μmol/L was associated with a significantly increased risk of maternal death. Approximately two in five women had persistently raised serum Cr at discharge, which was not subsequently repeated in almost three quarters of these women. However, recovery from obstetric AKI in those assessed was high. Few women had persistently raised Cr reflecting new or pre-existing chronic kidney disease (CKD). The long term impact of recovered obstetric AKI on future CKD development requires further study.

Funding: Private Foundation Support

SA-PO040

NephroCheck AKIScore for AKI Prediction in Pregnancy Jennifer R. Joslin,[2] Sittiga Hassan-reshat,[1] Maria Ostermann,[1] Frances I. Conti-Ramsden,[2] Carolyn Gill,[2] Lucy C. Chappell,[2] Kate Bramham.[2] *[1]Guy's & St Thomas' Hospital, London, United Kingdom; [2]King's College London, London, United Kingdom.*

Background: NephroCheck AKIScore is a urinary assay of G1 cell cycle arrest markers: Tissue Inhibitor of Metalloproteinase-2 (TIMP-2) and Insulin-like Growth Factor Binding Protein-7 (IGFBP-7). Numerous studies have demonstrated incremental risk Acute Kidney Injury (AKI) with AKIScores >0.3 and 2.0 $(ng/ml)^2/10^3$ but its predictive role in pregnancy is unknown Aims: To determine AKIScore predictive value for AKI in pregnancy; to explore relationships between AKIScore and gestation, protein-creatinine ratio (uPCR) and pre-eclampsia diagnosis (PE).

Methods: Women recruited to the Pre-EclampsiA, Chronic Hypertension, rEnal and SLE (PEACHES) study with suspected or confirmed PE without pre-existing maternal disease with ≥1 creatinine concentration after baseline urine sampling were included. Urinary AKIScore (TIMP-2*IGFBP-7) was assessed. AKI was defined according to KDIGO criteria.

Results: 116 women were included with Median creatinine 58μmol/L (IQR 52-66) at baseline. Proportion of women according to AKIScore thresholds are shown in Table 1. AKIScore >2.0 had high specificity (94.7%; 95% CI: 85.4-98.9) and NPV (92.9%; 84.8-96.8) but low sensitivity (33.3%; 0.8-90.7) and PPV (25.0%; 4.6-70.0) for prediction of AKI within 48 hours; AKIScore >0.3 had low sensitivity and specificity (<50%). 31 (54%) of women without AKI had AKIScore >0.3 (25-31% risk of AKI in non-pregnant populations). 86 women had a repeat creatinine within 7 days. There was no relationship between AKIScore and baseline or peak creatinine within 7 days. There was no difference in AKIScore between women with (Median 0.4; Range 0-8.4) and without PE (0.3; 0.1-1.5) and no correlations between AKIScore and uPCR or gestation.

Conclusions: The majority of women with suspected or confirmed PE had high AKIScores without developing AKI which were independent of gestation or PE diagnosis. Further study to determine if different AKIScore thresholds are required for prediction of pregnancy AKI is needed, and if pregnancy and/or PE are associated with subclinical renal tubular stress.

Table 1: AKIScore and development of AKI within 48 hours

AKIScore (ng/ml)^2/10^3	AKI	No AKI
≤0.3	2 (66.6%)	26 (45.6%)
0.3-2.0	0	28 (49.1%)
>2.0	1 (33.3%)	3 (5.3%)
Median AKIScore (range)	0.23 (0.22-3.64)	0.32 (0-8.44)

SA-PO041

Clinical Profile of Pregnancy Related AKI (PRAKI): A Single Center Experience Mayur V. Patil. *Department of Nephrology and Clinical Transplantation, Institute of Kidney Disease and Research Centre and Institute of Transplantation Sciences, Ahmedabad, India.*

Background: Acute renal failure (ARF) of obstetric origin is one of the most common complication of pregnancy and leads to poor maternal and fetal outcome. The incidence of PRAKI in developed country is 1 in 20,000 pregnancies, where as in developing country like India is 1 in 50. Septic abortion, poor follow up of pregnancy, limited screening of pregnant patients with hypertensive complications and late referrals to tertiary center are responsible for high incidence of ARF in developing countries.

Methods: The study was conducted at government aided tertiary care hospital between April 2016 to March 2017. A total 1021 patients of ARF were admitted out of which 96 were PRAKI. ARF was defined according to KIDIGO guidelines. Renal biopsy was performed if the patient was oliguric or creatinine still >2mg/dl at the end of three weeks.

Results: The incidence of PRAKI was 9.4%. Most common age group was 24-29 years(53.13%). 45.83% patients presented in late pregnancy while 36.46% presented in postpartum period. Antenatal care was recieved by only 30.21% patients. 25% patients required termination of pregnancy. Most common cause for PRAKI was puerperal sepsis followed by pre eclampsia. 18.75% patients were managed conservatively while 69.79% were kept on intermittent hemodialysis and 11.46% required SLED/CRRT. Acute patchy cortical necrosis was most common histological finding, others were thrombotic microangiopathy and glomerulonephritis. Complete recovery occured in 43.75%, whereas 16.67% had partial recovery (became dialysis independent but with persistent renal impairment), 19.79% were kept on renal replacement therapy. Maternal mortality was seen in 19.79% of cases.

Conclusions: In our study, puerperal sepsis was the most common etiological factor for pregnancy-related AKI. Sepsis, thrombocytopenia, disseminated intra-vascular coagulation were associated with increased mortality.

SA-PO042

Pregnancy Related AKI: A Single Center Experience Umesh L. *Nephrology, Institute of nephrourology, Bangalore, India.*

Background: The incidence of pregnancy-related acute renal failure (PRAKI) in the developed countries is 1–2.8%, About 25% referrals to dialysis centres in the developing world comprise of pregnancy related acute kidney injury (PRAKI). It is associated with siginificant maternal and fetal mortality.

Methods: A prospective longitudinal observational study between February 2012 to april 2017. To evaluate the clinical, etiological and final outcome of AKI with special reference to pregnancy related acute kidney injury. AKI was diagnosed as per AKIN criterion with or without requiring hemodialysis.

Results: A total of 712 patients were studied. Among them 152 (21.34%) patients had PRAKI. The mean age among PRAKI was 21±5 years. The mean duration of hospital stay was 10.17± 6.7 days. Etiological factors include puerperal sepsis in 77 (50.65%), pregnancy induced hypertension in 37(24.34%), 17(11.18%) patients had post partum hemorrhage, 9 (5.92%) ante partum hemorrhage, postpartum hemolytic uremic syndrome in 3 patients (1.97%) and miscellaneous causes was seen 9 (5.92%). Biopsy was done on 34 patients who found to be oliguric or who needed dialysis support at the end of three weeks. seventeen showed acute tubular necrosis. eleven of them had patchy cortical necrosis .three with features of acute interstitial nephritis Three patients had thrombotic microangiopathy. Out of 152, 113 (74.34%) patients recovered from acute kidney injury, 10 patient remained on dialysis and seven patients had partial recovery from renal failure. 22 patients died with mortality rate of 14.47%. Out of these 11 patients died within 48 hours of admission. Sepsis, multiorgan dysfunction, coagulation abnormalities and retained products of conception were factors associated with mortality.

Conclusions: PRAKI is a significant cause of AKI in developing countries. Puerperal sepsis is the most frequent etiological factor and accounted for a majority of maternal mortality

SA-PO043

Preeclampsia: Long-Term Effects on Pediatric Social Disability Carmen Mercurio,[4] Patrocinio Rodriguez benitez,[2] Maria rosa Elero,[3] Alberto Tejedor jorge.[1] *[1]Fundación para la Investigación Biomédica del Hospital General Universitario Gregorio Marañón, Madrid, Spain; [2]Hospital General Universitario "Gregorio Marañón", Madrid, Spain; [3]Hospital Genral "Gregorio Marañón", Madrid, Spain; [4]Universidad Complutense Madrid, Madrid, Spain.*

Background: Preclampsia affects up to 10% of pregnancies worldwide and is one of the main causes of fetal morbi-mortality. Although its effects on maternal renal function are well established and have been attempted to relate to delayed pediatric development, its long-term effects on the child have not yet been quantified. **Objectives.** Our aim is to evaluate whether the preclampsia's severity and its obstetric management correlate to fetal morbidity and the degree of developmental delay in these infants.

Methods: This is an observational and descriptive study performed on a population of 96 women who were diagnosed with severe preclampsia at Hospital General Universitario Gregorio Marañón between 2007 and 2014, and their 111 children. To assess the mother, we gathered data from her medical history, blood analytics, medical management of the preeclampsia, evolution of renal function at 12 weeks and discharge from nephrology. To assess the children, we collected information of the pregnancy and delivery, as well as main diagnoses at birth. We used the Pediatric Evaluation of Disability Inventory in its computerized adaptive test version (PEDI-CAT) to study neurodevelopment, the TNO-AZL Preschool children Quality of Life (TAPQOL) to estimate quality of life, and M-CHAT (Modified Checklist for Autism in Toddlers) for Autism screening.

Results: Preclampsias with greater impact on maternal fidney function correlated with higher periventricular-intraventricular hemorrhage rates in the newborn. In terms of functional activity, PEDI-CAT percentiles were consistently lower in the Social/Cognitive domain, and these were associated to both lower maternal IgG levels, to low maternal platelet levels and maternal high urinary osmolality. High rates of maternal proteinuria were associated to greater risk of perinatal death. The presence of neonatal necrotizing enterocolitis was also associated with lower Social/Cognitive percentiles.

Conclusions: A connection between preclampsia and poor social/cognitive outcomes exists. This association is stronger when the mother has thrombocytopenia and increased ADH. Renal involvement and proteinuria are associated with higher morbi-mortality attributable to prematurity but not with alterations in subsequent social-cognitive development. ADH deficit in the newborn could have implications or could be responsible for a behavior of social retraction.

SA-PO044

The Effect of a Hourly Urine Output on the Clinical Outcomes in Nontraumatic Exercise-Induced Rhabdomyolysis Won jae Shin, Young kyung Ko, Young-Il Jo. *Nephrology, Konkuk University Medical Center, Seoul, Republic of Korea.*

Background: Rhabdomyolysis-induced renal failure is a relatively rare condition, but its clinical consequences are occasionally serious and dramatic. Early and aggressive fluid resuscitation is commonly used to prevent renal failure in rhabdomyolysis. However, the optimal fluid and rate of repletion are unclear. The purpose of this study is to evaluate the effect of the degree of urine output following fluid repletion on the clinical outcomes in nontraumatic exercise-induced rhabdomyolysis (EIR).

Methods: The medical records of all nontraumatic EIR patients admitted to Konkuk University Medical Center between 2011 and 2015 were reviewed. After establishing a definitive diagnosis of nontraumatic EIR, fluid infusion was promptly initiated, with the goal of maintaining a urinary flow of 150-300 mL/h according to existing protocol.

Results: Total 45 cases were analyzed. Patients were categorized according to the hourly urine output during initial 48 hours following fluid resuscitation: the high urine output (≥200 mL/hr) and the low urine output (<200 mL/hr) group. No significant differences were noted between two groups in initial levels of CPK, serum myoglobin, and creatinine. The fluid rate of initial repletion was significantly higher in the high urine output group (4.6±1.5 vs. 2.5±0.7 mL/kg/hr, p<0.001). The hourly urine output was also significantly high in the high urine output group (307.5±116.6 vs. 138.7±42.8 mL/hr, p<0.001). There was no differences in the clinical outcomes including maximal level of CPK, incidence of AKI and mean hospital stay between two groups (Table).

Conclusions: Our results indicated early fluid resuscitation, even though a urine output was less than 200 mL/hour, was effective for prevention of acute kidney injury in nontraumatic exercise-induced rhabdomyolysis. A prospective, controlled, multicenter trial is necessary to determine optimal fluid therapy to prevent acute kidney injury in nontraumatic EIR.

Table 1. Clinical Parameters of the low urine output and the high urine output group.

	Low urine output group (<200ml/hr) (n=17)	High urine output group (≥200ml/hr) (n=28)	P-value
Baseline Characteristics			
Age (years)	34.2 ± 0.7	27.7 ± 0.5	NS
Male gender (%)	52.9%	64.2%	NS
CPK, initial (U/L)	45097.0 ± 44495.1	59969.7 ± 41900.8	NS
Creatinine, initial (mg/dL)	1.2 ± 1.3	1.0 ± 0.9	NS
Treatment			
Hourly urine output (ml/hr)	138.7 ± 42.8	307.5 ± 116.6	<0.0001
Rate of fluid repletion (ml/kg/hr)	2.5 ± 0.7	4.6 ± 1.5	<0.0001
Use of bicarbonate (%)	23.0%	37.0%	NS
Clinical Outcomes			
Peak CPK (U/L)	46853.1 ± 44439.9	56263.8 ± 38803.1	NS
Development of AKI, (number [%])	1 (7.6%)	0 (0.0%)	NS
Mean hospital stay (day)	8.3 ± 8.0	7.0 ± 2.8	NS

SA-PO045

Renal Fibrosis and Tubular Transport Adaptation Caused by Cardiac Arrest and Cardiopulmonary Resuscitation (CA/CPR) in Mice Michael Hutchens,[1] Rumie Wakasaki,[3] Ian P. Coe,[3] Mohammed Z. Ferdaus,[2] James A. McCormick,[2] Sharon Anderson.[3] *[1]Oregon Health & Science, Portland, OR; [2]Oregon Health & Science University, Portland, OR; [3]Oregon Health and Science University, Portland, OR.*

Background: Studies of of cardiorenal AKI-to-CKD transition report higher incidence of CKD than studies of all-cause AKI-to-CKD transition. The mechanism is unknown because animal models of AKI-CKD transition exclude cardiac disease. We have reported that murine cardiac arrest and cardiopulmonary resuscitation (CA/CPR) is an experimental model of acute cardiorenal syndrome (Ikeda, AJPR 2017). Here, we show that CA/CPR causes essential findings of CKD.

Methods: CA was induced in mice with potassium chloride and confirmed as described. Mice were resuscitated 8 min later with CPR and epinephrine. 28 days later GFR was measured and the right kidney stained for alpha-smooth muscle actin and picrosirius red, which were quantified in unbiased fashon. Immunoblotting was performed for the tubular transporters NKCC2, pNKCC2, NCC, and pNCC.

Results: 28d after CA/CPR, mice demonstrate reduced GFR and elevated serum urea nitrogen (sham 33±4, CA/CPR 49±3 mg/dL, p=0.01). Tubulointerstitial collagen deposition is markedly increased 1 month after CA/CPR compared with sham. Quantification of αSMA revealed a CA/CPR-induced 20-fold increase in tubulointerstitial fibrosis compared with sham (figure 1). pNKCC2 was markedly reduced by CA/CPR compared with sham (49.7%, p=0.001, n=9).

Conclusions: Renal fibrosis and loss of renal function follows resolution of acute kidney injury in experimental acute cardiorenal syndrome. Because CKD damages tubular structure and leads to hypertension, we determined whether tubular sodium transporters critical to blood pressure regulation were altered by CA/CPR. Our findings are consistent with reduced tubular sodium reabsorption, which may reflect a compensatory response to sodium retention. Overall these findings suggest that experimental acute cardiorenal syndrome models AKI-CKD transition.

Funding: NIDDK Support

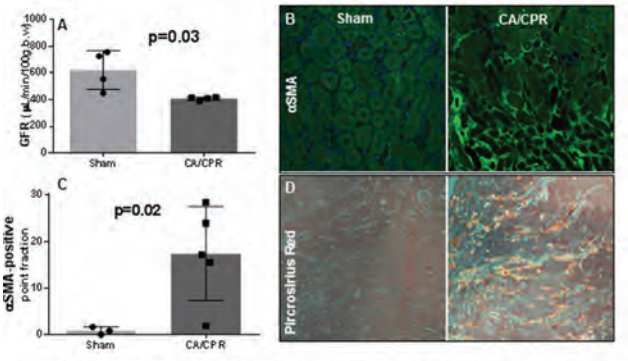


Figure 1: Renal failure and fibrosis 1 month after CA/CPR. A. GFR is reduced by 30% compared with sham. B. Renal αSMA (green) IHC in sham and CA/CPR. Tubulointerstitial αSMA is markedly enhanced in 1 month CA/CPR mice. C. Quantification of αSMA signal, n=8. D. Collagen stained with picrosirius red demonstrated with polarized light.

SA-PO046

Clinical Determinants of Complicated Hyperkalemia in Hospitalized Patients Etienne Macedo,[1] Linda Awdishu,[2] Ravindra L. Mehta.[1] *[1]Medicine, University of California San Diego, San Diego, CA; [2]UCSD Skaggs School of Pharmacy and Pharmaceutical Sciences, La Jolla, CA.*

Background: Hyperkalemia (HighK) is common in hospitalized patients and can be life-threatening. Preventive and management strategies differ based on patient presentation, underlying co-morbidities, concurrent medications and availability of health care resources. In this study we evaluated risk factors for complicated hyperkalemia and its association with patient course and outcomes during hospitalization.

Methods: Adult patients with at least 2 consecutive K>5mmol/L during a hospital stay were identified from electronic medical records (EMR). Data regarding patient location, comorbidities, medications in use prior to and after HighK detection and outcomes were extracted from the EMR. Complicated hyperkalemia(CK) was defined as reaching max K>6.5mmol/L, time to normalization of K levels>200 hours, death with K>5, more than 3 drugs prescribed for HighK treatment, need for ICU level care after HighK diagnosis and need for dialysis.

Results: Of 91,709 patients hospitalized over 24 months, 9,391 (8%) had two K>5mmol/l, and in 1,203 (1.3%) these were consecutive. 47% of the HighK episodes were present at hospital admission; in ER (67%). CK occurred in 577 (47%) of patients and was more frequent in males 51% vs. 32% of females. 711 patients had acute kidney injury (AKI) and CK was more commonly seen in AKI 227 (39%) than in AKI in CKD patients 117 (20%), no AKI/CKD 106 (18%) or ESRD 97 (16%) patients. Most AKI patients, 63%, were using at least one drug associated with hyperkalemia development before AKI diagnosis. The most common diagnoses associated with CK were heart diseases, sepsis, hepatic failure/hepatorenal syndrome, and fluid overload. Most frequent drugs used to treat CK were calcium 58%, insulin/dextrose 49%, albuterol 17% and sodium bicarbonate 28%. Recurrence of HighK during hospitalization ocurred in 720 (60%), of whom 250 (21%) were discharged and 75 (6.2%) died with K>5mmol/l. Length of hospital stay (CK vs HighK 16 (7—32) vs 7 (3-12) days; p<0.001) and mortality (CK 123 (21.3%) vs HighK 39 (6.2%); p<0.001) were significantly higher in patients with CK.

Conclusions: HighK is common in hospitalized patients and associated with high mortality. Clinical and process of care factors can help determine patients with HighK who are at highest risk for complications. These data can be utilized to identify high-risk patients in order to improve patient care and reduce complications.

Funding: Commercial Support - Relypsa

SA-PO047

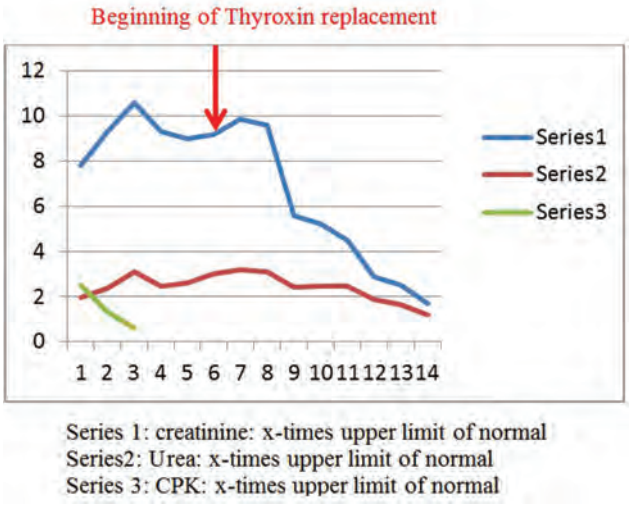
Hypothyroidism: A Known but Neglected Cause of AKI Chandra M. Jha,[1] Hormaz D. Dastoor,[2] Yassin El shahat,[3] Sarah H. Khan,[4] Ammar M. Jabar.[3] *[1]Gulf Diagnostic Center Hospital, Abu Dhabi, United Arab Emirates; [2]Rahba Hospital, ABU DHABI, United Arab Emirates; [3]Burjeel Hospital, Abu Dhabi, United Arab Emirates; [4]Mafraq Hospital, Abu Dhabi, United Arab Emirates. Group/Team: ADHARR.*

Background: Acute Kidney injury (AKI) of variable severity is common. Its recovery rests upon early diagnosis & specific intervention. We report a case of severe AKI due to hypothyroidism which recovered completely with the treatment of hypothyroidism. Literature review revealed that association of AKI with hypothyroidism has been recognized but standard textbooks on medicine, Endocrinology & Nephrology have failed to mention either AKI caused by hypothyroidism or hypothyroidism due to AKI.

Methods: A 26 year old Bangladeshi male electrician, smoker and occasional alcohol user, had symptoms of "not being well" & low back pain of one week duration. He had nonoligouric severe AKI (urea 6.3 mmol/L, creatinine 860 μmol/L, Creatinine clearance 5.02 ml/minute) without significant proteinuria (244 mg/day), normal electrolytes & normal ultrasonological study of Kidney, ureter and bladder. Moderately high CPK (1078 IU/L) without myoglobuniuria normalized within 72 hours but creatinine continued to rise. A history of weight gain & constipation of two months duration prompted us to check for thyroid function test. TSH was 590 miU/L, more than 140 times upper limit of normal. T3 & T4 were low. Thyroglobulin antibody & TSH receptor antibody were normal while microsomal antibody was elevated (326.8 KIU/L).

Results: Institution of levothyroxine therapy resulted in rapid decline of creatinine and symptomatic improvement of patient. His Creatinine clearance increased from 5.02 ml/minute to 49 ml/minute over two weeks and his creatinine level normalized over 4 weeks period. It saved the patient from kidney biopsy and dialysis.

Conclusions: We suggest that thyroid function test should *always* be part of investigation of AKI and renal function test should be part of investigation of hypothyroidism. Hypothyroidism should be included in the table of causes of AKI in standard textbooks.



High Creatinine and its response to Thyroxine treatment

SA-PO048

Clinical Aspects of IgG4-Related Retroperitoneal Fibrosis in a Single Center Study Yoon kyung Choi, Sang-Kyung Jo, Won-Yong Cho, Myung-gyu Kim, Jihyun Yang, Taeyeon Hwang, Woori C. Cho. *Korea University Hospital, Seoul, Republic of Korea.*

Background: Retroperitoneal fibrosis (RF) is a rare condition characterized by the proliferation of fibrous tissue in the periaortic and periiliac retroperitoneum. Along with increasing awareness of IgG4 related disease, we try to find the prevalence of IgG4-related retroperitoneal fibrosis (IgG4-related RF) and compare its clinical feature with non IgG4-related RF.

Methods: The material of this retrospective single center study included 21 patients with retroperitoneal fibrosis between January 2006 to December 2016. We entered all clinical and laboratory information for statistical analysis to determine the prevalence, clinical feature and outcomes of IgG-related RF.

Results: In total 21 patients with retroperitoneal fibrosis, 18 (85.7%) were idiopathic, and remaining 3 (14.3%) had secondary causes for retroperitoneal fibrosis. Among 18 idiopathic RF patients, 10 (55.5%) were diagnosed with IgG4-related RF (2 patients classified as 'definite' IgG4-related RF, 2 as 'probable', and 6 as 'possible'). The average age was 62.2 years (range, 41-79) and 6 (60%) were male. All lesions were detected around the infrarenal portion of the abdominal aorta and 7 cases simultaneously affected the iliac arteries. Hydronephrosis was present in 8 cases (80%) and acute kidney injury was observed in 6 patients. The median serum IgG4 at diagnosis was 641 (range, 24.8-3660). The elevation of serum IgG4 level was not observed in 2 patients. Eight patients were initially treated with steroid therapy. Seven of them (87%) showed radiological response, which showed poor correlation with serum IgG4 level. Comparing with 11 patients of non IgG4 related retroperitoneal fibrosis (52.4%), there were no statistically significant difference between the groups in age, gender distribution, incidence of hypertension, diabetes mellitus, heart failure, malignancy, acute kidney injury, proteinuria, or hematuria, concentration of hemoglobin, white cell counts, inflammatory markers, and complements.

Conclusions: This is a pilot study to evaluate the clinical and laboratory features of IgG related retroperitoneal fibrosis. Larger studies are needed for prevalence and prognosis of IgG4 related or non related RF.

SA-PO049

Not Such a Fun-gi Rebecca Blonsky, Leal C. Herlitz, Evamaria Anvari. *Cleveland Clinic, Cleveland, OH.*

Background: *Amanita Phalloides* is a poisonous mushroom known as death cap, found in central Europe and the northeastern United States. Its toxicity arises from amatoxins, which when ingested can lead to severe gastrointestinal (GI) malady, renal and liver failure and in some cases, death.

Methods: A 55-year-old Nepali male presented with nausea and vomiting for four days. He and his family were in a park and they saw mushrooms similar to those in Nepal which they collected and consumed. They then developed abdominal pain, nausea, vomiting and diarrhea. As their symptoms persisted, they sought care and it was found they had ingested *amanita phalloides*. Initial labs showed a creatinine (Cr) of 4.67 mg/dL, AST 1551 U/L, ALT 1103 U/L and total bilirubin 1.8 mg/dL. The patient was admitted to intensive care and nephrology was called for acute kidney injury (AKI). Urinalysis and renal ultrasound were normal but urine microscopy showed many unusual crystals, but no signs of acute tubular necrosis (ATN). The patient was treated with intravenous fluids, N-acetyl cysteine, octreotide and was enrolled in a trial using silibinin derived from *Silybum marianum* (milk thistle) being studied in amatoxin ingestion. With treatment, liver function improved and renal function normalized and was discharged after three days with a Cr of 0.8 mg/dL. Ten days later he returned complaining of edema, shortness of breath, anorexia and bitter taste. Labs showed BUN of 45 mg/dL and Cr of 8.69 mg/dL. Renal biopsy was done and showed ATN. After a total of two sessions of intermittent hemodialysis, he regained renal function and was discharged with a Cr of 3.95 mg/dL. On three month follow up, he achieved partial renal recovery to a stable Cr of 1.7 mg/dL.

Results:

Conclusions: AKI frequently occurs in amatoxin ingestion. It causes pre-renal azotemia as well as direct tubular toxicity through the amatoxins' inhibition of RNA polyermase II causing ATN. Though not well described, renal injury could be as a result of crystal deposition. Renal failure has also been reported following normalization of liver function. This pathophysiology is not well defined and has been hypothesized to be a result of the formation of free radicals causing ATN as the toxin is cleared after treatment. Patients who have ingested *amanita phalloides* require close follow up even with normalization of hepatic and renal function.

SA-PO050

Interim Analysis of Randomised Controlled Trial Comparing Effects of Intravenous versus Oral Hydration on Subclinical AKI in Laparoscopic Live Kidney Donors Ryan Ghita,[1] David Bruce,[2] Shona Mackinnon,[2] Emma L. Aitken,[1] Marc J. Clancy.[1] *[1]NHS Greater Glasgow and Clyde, Glasgow, United Kingdom; [2]University of Glasgow, Brighton, United Kingdom.*

Background: Laparoscopic donor nephrectomy is the gold standard for kidney donation due to improved donor convalescence. Pneumoperitoneum required for this procedure exposes patients to increased risk of renal injury. Intensive pre-operative intravenous hydration has shown to improve intraoperative haemodynamics but shows no improvement to creatinine clearance. This is potentially due to the reduced sensitivity of creatinine as a marker for renal injury in the acute setting. Neutrophil gelatinase-associated lipocalin (NGAL) is a biomarker with high sensitivity for acute kidney injury.

Methods: Patients were randomised 1:1 to receive 3L of preoperative intravenous fluids or ad-libitum oral hydration. NGAL samples were taken prior to intervention on day -1, day 0 pre- and post-operatively and on day+1. During the procedure, intraoperative urine output and haemodynamics were recorded. Data for baseline characteristics, eGFR from day -1 to 1 year and peri-operative outcomes were collected.

Results: 49 patients consented to take part. After removing withdrawals, 19 participants in the control group and 22 participants in the intravenous fluid group were analysed. All baseline characteristics were balanced between groups. On day 1 post-operatively 29.4% of patients in the intravenous fluids group had acute kidney injury compared to 40% of patients in the control group (p=0.529). Mean NGAL level was lower in the intravenous fluid group at every time point however with current numbers this was not found to be statistically significant. Percentage change in eGFR from baseline was also less pronounced in the intravenous fluid group at every time point but again was not statistically significant. Statistical analysis for all other outcomes showed that significant differences between groups were only found for intraoperative urine output and post-pneumoperitoneum stroke volume.

Conclusions: At this midpoint analysis the study was unable to fully establish a definitive effect of pre-operative hydration upon renal function in laparoscopic donor nephrectomy patients. There is a potential reduction in postoperative AKI and improvement of eGFR however a fully powered clinical trial should give definitive findings with relevant clinical applications.

SA-PO051

Nephrology Follow-Up Post AKI: Effects on Outcomes and Re-Hospitalization Arpita Basu,[2] Edward J. Horwitz,[1] Yasir Tarabichi.[1] *[1]MetroHealth, Cleveland, OH; [2]University Hospitals- Case Medical Center, Cleveland, OH.*

Background: AKI complicates 20% of all hospitalizations resulting in higher mortality, readmissions and costs. Mortality across all AKI stages is estimated at 21%. In a retrospective study, those with AKI were more likely to be rehospitalized within 30 days of discharge with cardiovascular events, mainly heart failure and acute myocardial infarction. Despite this, less than 20% of patients see a nephrologist within 3 months of discharge.

Methods: We retrospectively collected data on patients 18 years or older discharged after a hospitalization with AKI diagnosis during 1/1/14 to 12/31/16. Data on age, sex, length of stay and discharge diagnoses by ICD-9 or 10 codes was collected and categorized into Elixhauser comorbidity classification. Data also included time to outpatient provider visit, provider specialty and time to next admission. Cox proportional survival analysis was used to model time to readmission and death. Censoring was at 180 days post discharge or 12/31/2016. Hypothesis was tested with NephroOPTF registered as TRUE for patients having seen Nephrology versus FALSE for those seen by another specialty.

Results: 4563 discharges were included, with 1534 events (readmissions or death) documented. The cox-proportional hazards model showed that of patients who saw an outpatient provider, those that saw a Nephrologist had a significant reduction in time to readmission or death compared to those that did not (adjusted hazard ratio of 0.79 [95% CI 0.65 to 0.94, p<0.001].

Conclusions: Patients with AKI if seen by a nephrologist on discharge have lower risks of death or readmission in the acute setting when compared to those evaluated by non-Nephrologists. This study is limited in its retrospective nature, but provides a model for randomized studies to better evaluate and optimize outpatient care post discharge after AKI.

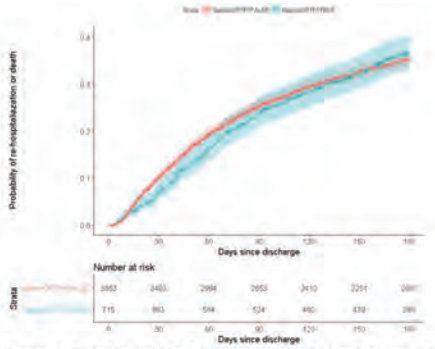


Figure 1: Unadjusted Kaplan Meir Curves for each group. NephroOPTF = TRUE represents patients that did see Nephrology in the outpatient setting. Shaded areas represent the confidence intervals for each group.

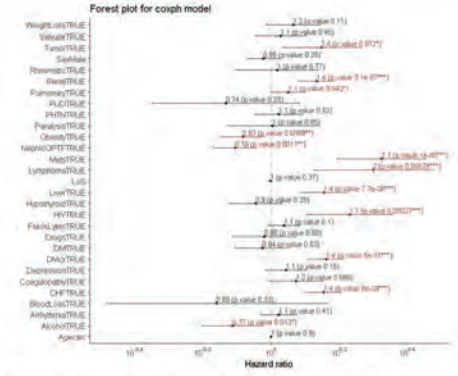


Figure 2: Forest Plots for coefficients tested. Age, LOS were continuous while the rest are categorical variables. The coefficient is listed above the curve with standard errors represented by the horizontal lines. * = p < 0.05, ** = p<0.01 and *** = p<0.001.

SA-PO052

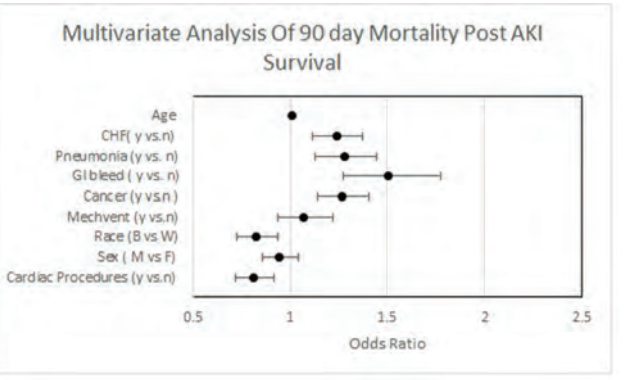
Race and Post-Hospitalization Mortality in AKI Itunu O. Owoyemi, Wenjun Xin, Emaad M. Abdel-Rahman, Rasheed A. Balogun. *University of Virginia, Charlottesville, VA.*

Background: Acute Kidney Injury (AKI), like ESRD, is known to be associated with increased mortality. Racial differences in outcomes exist in patients with multiple medical conditions and "access to care" is one of the linked variables. This study aims to determine if racial differences in mortality exists after hospital discharge for AKI when access to care may be inconsistent.

Methods: Retrospective cohort study of adults admitted to the University of Virginia Medical Center between January 1, 2001 and December 31, 2015 who had AKI during hospitalization. AKI definition of ≥ 0.3 mg/dl rise in serum creatinine, SCr, within 48 hours was used (Kidney Disease Improving Global Outcomes, KDIGO). Patients' characteristics or risk factors were summarized as frequencies and percentages for categorical variables and as mean ± standard deviation for continuous variables. The associations of these factors with the outcome of 90-day mortality post hospitalization were evaluated in logistic regression, measured by odds ratios (ORs) for the likelihood of post-hospitalization mortality. The 95% confidence intervals (CIs) for ORs and the corresponding p-values are reported. A p-value < 0.05 was considered to be statistically significant.

Results: We had a total of 11, 837 patients in our cohort with 79.7% whites and 17.8% blacks. Mean age was 62.41±15.52. Mean baseline SCr was 1.33±0.78 and mean Charlson index score of 4.13 ± 3.21. A total of 9808 were followed post hospital discharge while 1914 patients died in hospital and 88 patients did not have a last follow up date. A multivariate assessment adjusting for several co-morbidities showed a lower mortality rate at 90 days in black patients versus Caucasians.

Conclusions: Black patients with AKI had lower post-hospitalization 90-day mortality. This outcome is similar to that seen in black patients treated for ESRD in USA. A better understanding of mechanisms underlying a possible survival advantage in black Americans with AKI needs further investigation.



SA-PO053

Association of Kidney Function Decline with Survival in Primary Myelofibrosis Umut Selamet, Shouhao Zhou, Juhee Song, Srdan Verstovsek, Ala Abudayyeh. *MD Anderson Cancer Center, Houston, TX.*

Background: Primarymyelofibrosis (PMF) is a type of myeloproliferative neoplasm which causes megakaryocyte and granulocyte proliferation in bone marrow leading to fibrous tissue deposition and extramedullary hematopoiesis. Renal involment in PMF is rare however acute kidney injury may develop during the disease course due to thrombosis of the renal vessels, occlusion of the urinary tract by blood clots or megacaryocyte infiltration of the kidney interstitium. PMF is a rare disease, and the impact of kidney function on survival has not been studied well.

Methods: We retrospectively evaluated 107 patients with PMF treated with Ruxolitinib between 2007 and 2015. The mean follow-up was 51.2 months (95% CI: 43.4, 66.7). Patient characteristics are summarized in Table 1. Seventy-six percent (n=81) of patients were dead at the time of analysis. Multivariate logistic regression model was used to assess predictors of treatment response, and dynamic prediction model was used for modeling associations with survival.

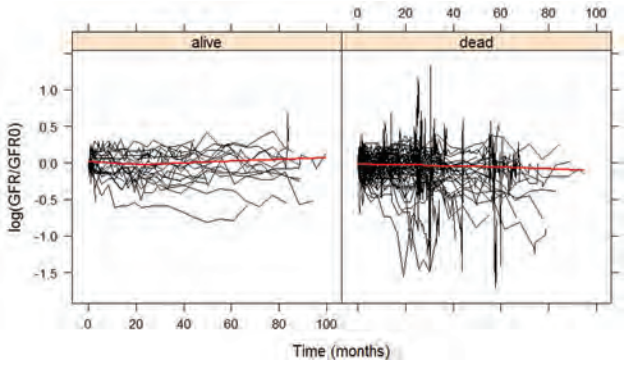
Results: We observed that estimated glomerular filtration rate (eGFR) was strongly associated with the risk of overall survival. Halving of eGFR levels resulted in 1.4-fold (95% CI: 1.06-1.78, p=0.042) increase of risk. No significant associations were observed between eGFR and clinical response including spleen response.

Conclusions: We have shown that kidney function decline is a risk factor for survival in PMF. Larger prospective studies are needed to evaluate the impact of kidney function both on clinical response and survival in this rare condition.

Funding: Clinical Revenue Support

Table 1: Characteristics of Study Participants

Variable	
Age (years ± SD)	65.5 ± 8.2
Male, n (%)	61 (57 %)
White, n (%)	101(94 %)
Baseline serum creatinine (mg/dL ± SD)	1.1 ± 0.34
Baseline blood urea nitrogen (mg/dL ± SD)	22 ± 11
Baseline eGFR (mL/min/1.73m^2 ± SD)	68 ± 22
Baseline serum albumin (g/dL ± SD)	7.6 ± 2.4
Baseline spleen length (cm ± SD)	19 ± 6
Overall response to treatment	
Clinical improvement, n (%)	69 (64 %)
Progressive disease, n (%)	36 (34 %)
Response evaluation missing, n(%)	2 (2 %)



SA-PO054

Effect of Community Acquired AKI on Long Term Outcomes in Patients Presenting with an Acute Myocardial Infarction Roy Mathew,[4] Mandeep S. Sidhu,[5] Jennifer Othersen,[3] Robert R. Moran,[6] Arif Asif,[1] Sripal Bangalore.[2] *[1]Jersey Shore University Medical Center, Neptune, NJ; [2]New York University School of Medicine, New York, NY; [3]WJB Dorn VA Medical Center, Columbia, SC; [4]William Jennings Bryan Dorn VAMC, Blythewood, SC; [5]Albany Medical College, Stratton VAMC, Albany Medical Center, Albany, NY; [6]Epidemiology, USC, Columbia, SC.*

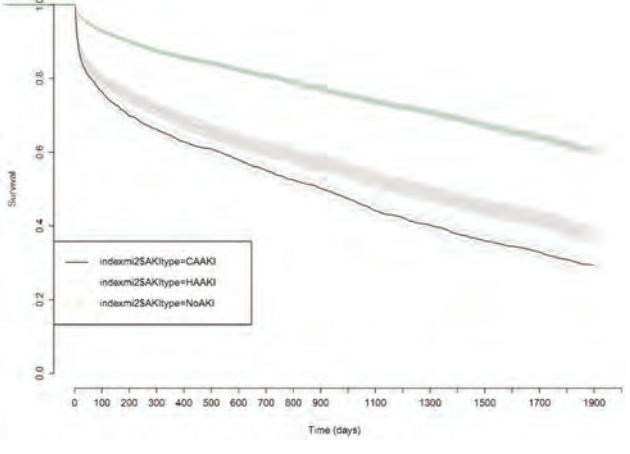
Background: We sought to examine long-term outcomes in patients admitted for a myocardial infarction (MI) based on whether they experienced community acquired acute kidney injury (CAAKI), hospital acquired acute kidney injury (HAAKI), or no acute kidney injury (no AKI).

Methods: Methods: Retrospective parallel cohort analysis of Veterans admitted for acute MI between 2005 and 2008. Data was obtained from the corporate data warehouse (CDW) using the VA Informatics and Computing Infrastructure (VINCI) computing environment. AKI was determined by assessing for changes in serum creatinine according to the KDIGO AKI classification system. Outcomes were death, hospitalization for cardiovascular (CV) events (MI, congestive heart failure, or stroke).

Results: Results: 11,580 patients with an MI were identified. Of these patients 15.1% had CAAKI, 14.5% had HAAKI and 70.4% had no AKI. Patients who developed AKI (CAAKI or HAAKI) were older, and had greater number of comorbidities as well as severity of initial admission (ICU stay, ventilation requirement or dialysis requirement) than no AKI. Patients with CAAKI were less likely to get cardiac catheterization during admission than those with HAAKI or no AKI (44.7%, 57.9%, 67.3%, respectively, p<0.001). Mortality was higher in both AKI groups as compared to the no AKI group at 5 year follow-up (adjusted HR and 95%CI: CAAKI 1.96, 1.83-2.09; HAAKI 1.60, 1.50-1.72). Patients with AKI (CA or HA) were more likely to have a repeat CV hospitalization than patients with no AKI (CAAKI adjusted HR 1.14 p=0.004; HAAKI adjusted HR 1.11, p=0.02; no difference between AKI groups).

Conclusions: Conclusions: In patients admitted with an acute MI, the presence of CAAKI was associated with long term outcomes as poor as HAAKI. Further research is needed to understand these associations.

Funding: Veterans Affairs Support



SA-PO055

Risk Factors and Long-Term Prognosis of Post-Operative AKI under Non-General Anesthesia Soojin Lee,[4] Sehoon Park,[3] Anna Lee,[1] Ho Jun Chin,[2] Ki Young Na,[2] Sejoong Kim.[2] *[1]SNUBH, Gyeonggi-do, Democratic People's Republic of Korea; [2]Seoul National University Bundang Hospital, Seong nam, Republic of Korea; [3]Seoul National University Hospital, Jongno-gu, SEoul, Republic of Korea; [4]Seoul national university hospital, Seoul, Republic of Korea.*

Background: The patients who receive surgeries under non-general anesthesia are less likely to be evaluated for their post-operative acute kidney injury (AKI) risks in detail than patients who undergo major operation. Risk factors and long-term prognosis data of these patients are scarce.

Methods: We conducted a retrospective cohort study on all adult patients who underwent surgeries under non-general anesthesia during the year 2013. Patients who had other surgeries within 1 month from their index operation, those with kidney injury prior to the surgery and those who lacked information of baseline or follow-up serum creatinine (sCr) measurement were excluded. Postoperative AKI was defined as 0.3 mg/dL or 1.5 times elevation of the patients' sCr from the baseline within 2 weeks from the surgery. Long-term outcomes were a composition of doubling of sCr and eGFR decrement for 30%, at 3 months or 6 months after operation. Risk factors for AKI were evaluated by multivariable logistic regression analyses.

Results: As a result, a number of 1,737 patients were included in our study cohort. Among them, 158 cases experienced post-operative AKI. Most of the AKI cases occurred after pulmonary or orthopedic surgeries with non-general anesthesia. Presence of baseline diabetes mellitus (adjusted OR 1.87, 95% CI 1.27-2.75, P < 0.001) and anemia (hemoglobin < 11 g/dL, adjusted OR 1.76, 95% CI 1.14-2.72, P=0.01) were significant risk factors for the AI events. When the long-term prognosis was evaluated, those who experienced AKI after non-general anesthesia surgeries significantly had worse renal outcomes at 3 month (adjusted OR 5.57, 95% CI 3.28-9.39, P < 0.001) or 6 month (adjusted OR 5.29, 95% CI 2.72-10.19, P < 0.001).

Conclusions: Therefore, postoperative AKI occurs in non-negligible portion of patients who underwent surgeries under non-general anesthesia, and their long-term renal prognoses were worse than of those without the event. Robust evaluation of underlying risk factors for post-operative AKI and careful follow-up for those who developed AKI should be warranted, regardless of anesthesia method used for the surgery.

SA-PO056

Risk of Hypoglycemia after Hospital Discharge Following AKI Adriana Hung,[1,3] Edward D. Siew,[3,1] Otis D. Wilson,[2] Amy Perkins,[2] Robert Greevy,[2,1] Khaled Abdel-Kader,[3,1] Sharidan Parr,[1,3] Talat Alp Ikizler,[3,1] Theodore Speroff,[2,1] Michael E. Matheny.[1,2] *[1]TVHS Veterans Administration, Nashville, TN; [2]Vanderbilt University Medical Center, Nashville, TN; [3]Vanderbilt Division of Nephrology and Hypertension, Nashville, TN.*

Background: Hypoglycemia remains a common life-threatening complication in patients with diabetes. The risk of hypoglycemia after acute kidney injury (AKI) is not well defined. In this study we evaluate the risk of hypoglycemia in patients with diabetes within 90 days post-discharge between hospitalizations with and without AKI.

Methods: We performed a propensity-matched analysis of patients with and without AKI using a retrospective national cohort of Veterans with diabetes hospitalized between 2004 and 2012. AKI was defined as a 0.3 mg/dl or 50% increase in serum creatinine from baseline to peak serum creatinine during hospitalization. Hypoglycemia was defined as hospital admission or an emergency department visit for hypoglycemia, or an outpatient blood glucose < 60 mg/dL. Time to incident hypoglycemia within 90 days was examined using Cox proportional hazards models. Pre-specified subgroup analyses by renal recovery and baseline CKD and HbA1c status were performed

Results: We identified 65,206 propensity score matched pairs with and without AKI. The incidence per 100 person-years for hypoglycemia was 29.7 (95% confidence interval [CI]: 28.9-30.4) for patients with AKI and 23.7 (95% CI: 23.0-24.4) for patients without AKI, hazard ratio (HR): 1.25 (95% CI: 1.19-1.30). After adjustment, AKI was associated with 26% increased risk of incident hypoglycemia HR: 1.26 (95%CI: 1.21-1.32). The risk of hypoglycemia varied by degree of renal recovery. For patients with full recovery, the HR was 1.17 (95% CI: 1.11-1.24), for partial recovery, the HR was 1.29 (95% CI: 1.22-1.37), and for no recovery, the HR was 1.45 (95% CI: 1.34-1.57) compared to those with no AKI.

Conclusions: AKI is a risk factor for developing hypoglycemia in the 90 days following discharge from a hospitalization, and the risk is modified by the degree of renal recovery. Guidelines for increased monitoring and treatment modification post-AKI need to be developed

Funding: Veterans Affairs Support

SA-PO057

Incidence and Outcomes of AKI in Octogenarians in Northern Jordan Ashraf O. Oweis,[1] Sameeha A. Alshelleh.[2] *[1]Medicine, Jordan University Of Science and Technology, Irbid, Jordan; [2]Medicine, University Of Jordan, Amman, Jordan.*

Background: Due to improvements in the health care system worldwide, human life expectancy has increased, resulting in a greater number of geriatric patients diagnosed

with acute kidney injury (AKI). We evaluated the incidence and outcome of AKI in octogenarians, as studies in this age group are few.

Methods: Design: Retrospective chart review. **Setting**: The medical ward of our tertiary-care hospital in northern Jordan. **Participants**: All patients aged 80-89 admitted to our medical ward between January 2010 and December 2013. Patients with stage IV and V chronic kidney disease were excluded. **Measurements**: The incidence of AKI determined by the Acute Kidney Injury Network classification, mortality, and hospital length of stay.

Results: There were 850 patients admitted during the study period. Of these, 135 were excluded from our analysis. The most common admission diagnoses were uncontrolled diabetes mellitus and acute coronary syndrome. AKI occurred in 216 patients (30.2%). In these cases, Stage 1, Stage 2, and Stage 3 disease were present in 59%, 17.5%, and 23.5%, respectively. Of the 115 patients who died before discharge (16.1%), 87 (75.6%) had developed AKI. Hypertension, the use of angiotensin receptor blockers and non-steroidal anti-inflammatory drugs, heart failure, and exposure to radiologic contrast media were significant risk factors for AKI.

Conclusions: Appropriate management of diabetes and hypertension in octogenarians will likely decrease the incidence of AKI in this age group leading to reduced hospital length of stay and mortality.

Funding: Government Support - Non-U.S.

Baseline characteristics

Variable	N (%)
Gender, Male	355 (49.6%)
Female	360 (50.4%)
Diabetes mellitus	115 (16.1%)
Hypertension	125 (17.5%)
Coronary artery disease	111 (15.5%)
Congestive heart failure	49 (6.9%)
Cerebral vascular accident	71 (9.9%)
Peripheral vascular disease	140 (19.9%)
Cancer	34 (4.8%)
Angiotensin converting enzyme inhibitor	191 (26.7%)
Angiotensin receptor blockers	110 (15.4%)
Non-steroidal anti-inflammatory drugs	20 (2.8%)
Contrast	153 (21.4%)
Baseline creatinine, mean SD	123.8 (105.5)

SA-PO058

Nutritional Assessment of Patients in the Recovery Phase of Moderate to Severe AKI Etienne Macedo,[1] Vivek Kumar,[4] Nancy Sahni,[2] Krishan Lal L. Gupta,[3] Ravindra L. Mehta.[1] *[1]Medicine, University of California San Diego, San Diego, CA; [2]Post Graduate Institute of Medical Education and Research, Chandigarh, India; [3]Postgraduate Institute of Medical Education & Research, Chandigarh, India; [4]Postgraduate Institute of Medical Education and Research, Chandigarh, India.*

Background: The role of nutritional status has not been studied in the recovery phase of AKI. Although protein restriction could reduce the tubular workload in the recovering kidney, malnutrition is common and may affect overall patient outcome. In order to further our understanding of the role of nutrition, we evaluated parameters of nutrition status in patients during the recovery phase of AKI.

Methods: This is an analysis of preliminary data from a pilot single center, open-label, randomized controlled, trial of patients who have an episode of Stage 2/3 AKI. Baseline CKD Stage 4 or higher, need of RRT for>2weeks or dialysis dependency at hospital discharge were exclusion criteria. A screening and comprehensive nutritional assessment was performed by a dietitian and quality of well-being, along with bioelectrical impedance measurments, blood and urine tests.

Results: Of 32 enrolled patient, mean age was 41yo, 43% were male, 38% had hypertension and 13% DM. Of 26 patients with complete nutritional assessment, 23% were classified as normal nutritional status, 46% at risk of malnutrition and 30% as malnourished. Only 3 patients were admitted to an ICU and 23 were dialyzed during hospital stay. Most patients lost weight at discharge, mean difference from admission was 5.5 kgs, with a trend to be higher in patients at risk of malnutrition (7kg) and malnourished (6kg), as compared to normal nutritional status (4.5kg). At hospital discharge charlson comorbidity index, EQ-5D-5L, albumin (3.8±0.7g/dl) and sCR (3.3±1.7mg/dl) values were not different by nutritional category status. Evaluation of body composition showed that all patients had decreased muscle mass according to normal age/gender composition. Fat mass was increased in 41% of patients at risk for malnutrition, as compared to 17% in normal and 24% in malnourished patients. The mini nutritional assessment (MNA) screening had a good correlation with the complete nutritional assessment; r=.842 (p<0.001).

Conclusions: Patients recovering from an AKI episode are at increased risk for malnutrition, particularly those undergoing dialysis during hospital stay. Nutritional screening is a simple, rapid and sensitive process that can detect all or nearly all of the patients at nutritional risk. Further evaluation including body composition may help to determine patients in need of nutritional follow up.

SA-PO059

Incident Trends in Hyperkalaemia among Patients with AKI in the Irish Health System Leonard Browne,[3,5] Arunkumar Aruna udayakumar,[6,1] Natalie Hsiao-Fang-Yen,[2,1] Rajiv Saran,[4,7] Austin G. Stack.[1,5] *[1]Graduate Entry Medical School, University of Limerick, Limerick, Ireland; [2]University Hospital Limerick, Limerick, Ireland; [3]University of Limerick, Limerick, Ireland; [4]University of Michigan, Ann Arbor, MI; [5]Health Research Institute, Limerick, Ireland; [6]Nephrology, University Of Limerick, Limerick, Ireland; [7]Kidney Epidemiology and Cost Centre, Ann Arbor, MI.*

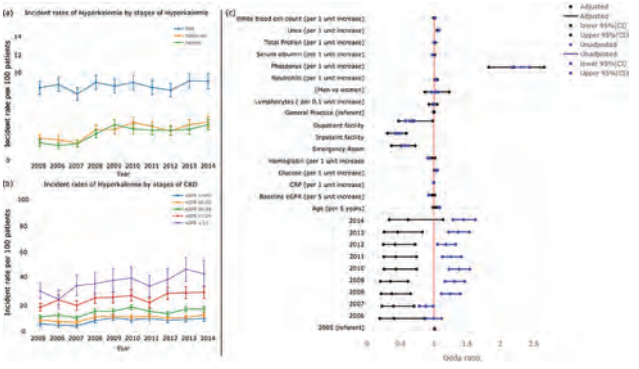
Background: Acute Kidney Injury (AKI) is increasingly common and associated with adverse clinical outcomes in the health system. Hyperkalaemia is an equally dangerous electrolyte disorder that frequently develops in the setting of AKI but little is known regarding its occurrence in this setting.

Methods: We utilised data from the National Kidney Disease Surveillance System in Ireland to explore trends in incident hyperkalaemia occurring in the setting of AKI from 2005 to 2014 (n= 47,259). AKI was identified from laboratory system per KDIGO guidelines and serum potassium recorded concurrently were graded as mild> 5.0, moderate 5-5-6.0, and severe > 6.0 mmol/L. Incidence rates per 100 patients were computed and multivariable logistic models explored the relationship of calendar year with incidence of hyperkalaemia expressed as odds ratio (OR) and 95% Confidence Intervals (CI) with adjustment for age, sex, county of residence, location of medical supervision and laboratory variables.

Results: From 2005 to 2014, incident rates of hyperkalaemia increased from 12.6% (11.7, 13.5) to 17.3 % (16.1, 18.4), P<0.001. Rates of mild hyperkalaemia remained relatively overall stable during period [from 8.2% ((7.5, 9.0) to 9.0% (8.1, 9.8) respectively], while rates of moderate and severe hyperkalaemia increased significantly [from 2.5% (2.05, 2.9) to 4.3% (3.7, 4.9) and from 1.9% (1.6, 2.3) to 4.0 % (3.4, 4.6) respectively, P<0.001. With adjustment for age, sex and baseline eGFR, the OR of hyperkalaemia > 5.0 mmol/L increased with calendar year from 2005 (OR, 1.00) to 2014 (OR,1.55, 95% CI 1.38-1.75). With additional adjustment for location of medical supervision, county of residence, laboratory indicators of health, the likelihood decreased

Conclusions: The incidence of hyperkalaemia has increased in the Irish Health system in well-defined demographic and clinical settings. The increasing trend is largely explained by changes in health status and practices in location of supervision.

Funding: Government Support - Non-U.S.



SA-PO060

A Predictive Model for CKD Development after Severe AKI in Children: A Single Center Prospective Study Stuart Goldstein,[1] Donna J. Claes,[1] Jacob R. Englert,[2] Parker J. Kain,[2] Rachel M. Driehaus,[2] Dhanuja Kasturiratna.[2] *[1]Cincinnati Children's Hospital, Cincinnati, OH; [2]Northern Kentucky University, Highland Heights, KY.*

Background: The association between hospital acquired AKI and CKD development in children has only been studied in either select cohorts comprised of convenience samples of available patients (pts) or from administrative data.

Methods: We conducted a prospective study of all non-BMT pts who developed severe AKI (sAKI, Pediatric Modified RIFLE-I or F) for at least 2 days to assess for CKD development after sAKI. Risk factors included standard of care lab data, AKI severity and duration, solid organ transplant status and nephrotoxic medication burden. The primary outcome was eGFR <90 ml/min/1.73m2 (CKiD Schwartz formula) at 6 months after sAKI. Significant predictors were identified based on a series of bivariate analyses (p<0.3), which were used to build several logistic regression models. The models were then compared and validated by Receiver Operator Characteristic (ROC) and Leave One Out Cross Validation (LOOCV).

Results: 193 pts who developed Stage 2 AKI were enrolled in this study (99M, 94F, mean age 10.5±6.2yrs, mean weight 43.7±31.0 kg). The median [IQR] AKI duration was 12 days [7, 21]. 45 pts required RRT. 79 pts had an eGFR assessment at 6 months, 24 of whom had an eGFR <90. On bivariate analysis, age, AKI duration, number of nephrotoxic medications, history of transplantation, lower eGFR, and lower serum albumin at AKI diagnosis was associated with CKD development at 6 months. Interestingly, RRT provision was not associated with CKD development. Seven candidate models were developed with AUCs that ranged from 0.81 to 0.82 and LOOCV that ranged from 0.67 to 0.76. The best candidate model (see table) based on a combination of AUC, LOOCV

and simplicity (5 variables vs. 7) had an AUC 0.81 [95%CI 70.2-92.6] and LOOCV value of 0.76.

Conclusions: A simple 5 variable model was developed to predict presence of CKD at 6 months in children who developed pRIFLE-I/F AKI from any cause. Further prospective work will need to be conducted to validate and calibrate this model.

Best Predictive Model for AKI to CKD Development

Variable	Coefficients	p-values	Odds Ratios	(95% CI)
Age	0.0904	0.12	1.09	(0.98,1.24)
AKI Days	0.0383	0.09	1.04	(1.0,1.1)
RRT (yes)	-1.6967	0.13	0.18	(0.013,1.3)
eGFR (nadir)	-0.0284	0.004	0.97	(0.95,0.98)
Transplant (yes)	1.8916	0.03	6.63	(1.27,43.4)

SA-PO061

AKI by KDIGO and AKIN Criteria in Patients with Non-ST Elevation Myocardial Infarction: Association with Risk Scores Avantee V. Gokhale,[3] Samuel Mon-Wei Yu,[2] Hector Alvarado verduzco,[1] Pitchaphon Nissaisorakarn,[2] Poonam Mahato,[2] Anjali Acharya.[3] *[1]JACOBI MEDICAL CENTER, BRONX, NY; [2]Jacobi Medical Center, Bronx, NY; [3]Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY.*

Background: Acute kidney injury (AKI) is commonly associated with the acute coronary syndrome, both STEMI and NSTEMI. We aimed to assess the incidence of AKI, as defined by AKIN and KDIGO criteria, in patients with NSTEMI at a safety net hospital catering to minority populations, and examined the association between the scores used for risk stratification in NSTEMI and AKI.

Methods: 170 out of 296 consecutively admitted patients between 1.1.2015 and 7.1.2016 with a primary diagnosis of NSTEMI were included in this study. 126 were excluded, mainly due to primary diagnosis of STEMI, and transfer to outside hospital. Their data were collected by retrospective chart reviews. GRACE and Killip scores were calculated for NSTEMI characterization. AKI was assessed as present/absent by 2 different criteria viz. AKIN and KDIGO. Statistical analyses included descriptive statistics and multivariable logistic regression.

Results: Out of 170 patients (mean age=69, 56% males), 39% were Hispanic. 28% had CKD, while, hypertension prevalence was 84%. Median baseline serum creatinine in the study group was 0.9. Median GRACE score was 119 and majority patients fell under Killip class 1 (78%). KDIGO and AKIN scores diagnosed AKI in equal number of NSTEMI patients (45%). While Killip class failed to predict AKI, GRACE score significantly associated with AKI by both AKI criteria [OR 1.03, 95% CI 1.01-1.04; p<0.001 for both]. Finally, when adjusted for age, sex, ACE-inhibitor, aspirin, statin, beta-blocker, diuretic use, history of diabetes and contrast exposure, GRACE score remained significantly associated with AKI by both criteria [1.03 (1.01-1.05), p=0.001 for both].

Conclusions: In a single-center, inner-city safety net hospital cohort of NSTEMI patients with predominantly Hispanic population, GRACE score, which incorporates initial creatinine into the score, was associated with AKI after adjustment for traditional risk factors for AKI. Furthermore, contrary to observations in STEMI, both AKIN and KDIGO predicted AKI to a similar extent in NSTEMI patients. However, larger population-based prospective studies are needed to confirm our findings and further assess the association with mortality.

SA-PO062

AKI in Hospitalized Dermatology Patients: An Epidemiology Study in Two Chinese Centers Yuanhan Chen,[2] Xinling Liang.[1] *[1]Guangdong general hospital (Guangdong Academy of Medical Sciences), Guangzhoou, China; [2]Guangdong General Hosiptial (Guangdong Academy of Medical Sciences), Guangzhou, China. Group/Team: China collaborative study on AKI.*

Background: Acute kidney injury (AKI) has become a worldwide public health problem, but little information is available in patients with skin diseases.

Methods: This study comes from the China collaborative study on AKI (ClinicalTrails.gov: NCT03054142; Ethical approval: GDREC.2016327H). The electronic medical information were collected retrospectively and the results of creatinine tests were analyzed by data mining. Total 4,710 hospitalized patients in the Department of Dermatology with at least two creatinine tests within 7 days were screened out from Sichuan Provincial People's Hospital (n=3,978) and Guangdong General Hospital (n=732). AKI was defined and staged according to Kidney Disease Improving Global Outcomes criteria on the basis of changes in serum creatinine.

Results: Two-hundred and ninety-five (6.3%) patients were classified into AKI, including 121(41.0%) hospital-adquired and 174 (59.0%) community-adquired AKI. In the top 15 general skin diseases (more than 1% in hospitalized dermatology patients), the AKI incidences of psoriasis with systemic reaction (14.8%), erythroderma (12.8%), drug eruption (12.6%) and systemic lupus erythematosus (12.5%) were significant higher than the total incidence (Figure 1). In multivariate logistic regression model, these 4 skin diseases were associated with AKI after adjusted by chronic kidney disease and diabetes mellitus. The Odds ratio were 2.970, 1.932, 2.446 and 2.254, respectively. The mean lenth of hospital stay was 2 days longer and the median hospital cost was about $500 higher in patients with AKI than those without. In addition, the mortality was much higher in patients with AKI than those without (3.1% *vs* 0.1%, $P < 0.001$). After adjusted by age and comorbidities, the AKI was related to in-hospital death (Odds ratio 24.630).

Conclusions: AKI was common in the hospitalized dermatology patients. It is associated with significantly higher in-hospital mortality and resource utilization.

Funding: Government Support - Non-U.S.

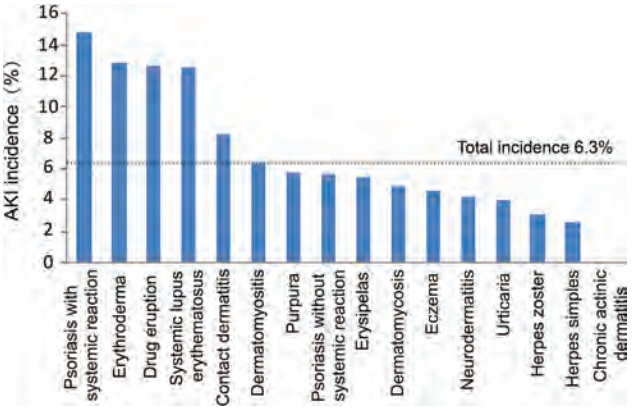


Figure 1. AKI incidence in the top 15 general skin diseases

SA-PO063

Patient Perspectives on Participation in Biopsy-Based AKI Research Dennis G. Moledina,[2] Bettina Cheung,[2] Randy L. Luciano,[3] Aldo J. Peixoto,[3] Francis P. Wilson,[1] Sandra L. Alfano,[2] Chirag R. Parikh.[4] *[1]Yale School of Medicine, New Haven, CT; [2]Yale University, New Haven, CT; [3]Yale University School of Medicine, New Haven, CT; [4]Yale University and VAMC, New Haven, CT.*

Background: As part of its new precision medicine initiative, the NIH/NIDDK has proposed collecting human kidney tissue to discover novel therapeutic targets in patients with acute kidney injury(AKI). Patient perspectives on participating in kidney biopsy-based AKI research are unknown

Methods: We surveyed participants enrolled in the Yale Acute Interstitial Nephritis(AIN) study who underwent a clinically-indicated kidney biopsy for AKI evaluation between 1/2015-10/2016, asked open-ended questions, and classified their answers into pre-defined categories

Results: Out of the 177 participants alive at contact, 117(66%) agreed to participate in the survey. Our survey included 59(50%) female, 34(29%) African-American, and 14(12%) Hispanic participants. 85(73%) reported that, if they hypothetically needed another clinically-indicated kidney biopsy, they would allow additional needle passes to donate kidney tissue for research. The major reasons described by participants for their choice are shown in **Figure**. Older [64(51-72) vs. 54(43-65) years, P=0.02] and African-American [16(50%) vs. 18(21%), P=0.002] participants were less likely to allow an extra pass with kidney biopsy; however, participants did not differ on self-reported biopsy complications such as pain, anxiety, and hematuria. 23(20%) participants agreed to participate in a study that obtained kidney tissue for research purposes even if another clinically-indicated biopsy was not needed

Conclusions: Among patients who had experienced a kidney biopsy, a majority were amenable to additional needle passes to donate kidney tissue for research at the time of a hypothetical, future, clinically-indicated biopsy

Funding: NIDDK Support, Private Foundation Support

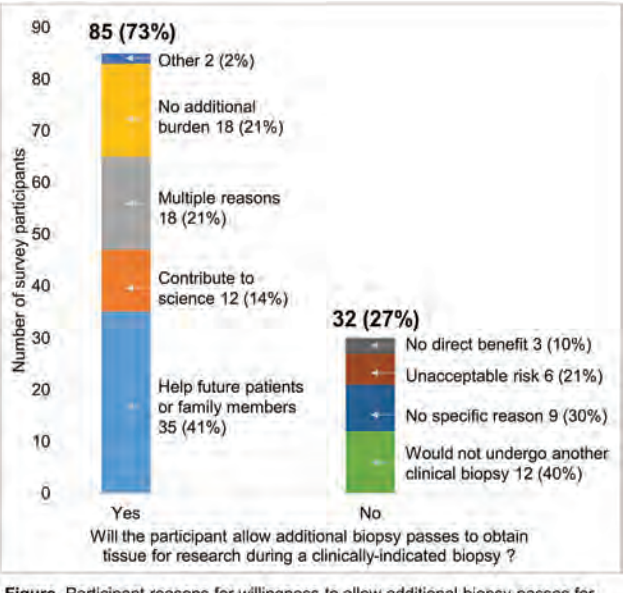


Figure. Participant reasons for willingness to allow additional biopsy passes for research during a clinically-indicated biopsy

SA-PO064

Is Reduced Telomere Length Associated with an Increased Risk of AKI Following Cardiac Surgery? Damian C. Balmforth,[2] Vasantha M. Muthuppalaniappan,[2] Sai Krishna Duraisingham,[2] Steven M. Harwood,[2] Julius E. Kieswich,[2] Rakesh Uppal,[1] Muhammad M. Yaqoob.[2] *[1]Barts and the London NHS Trust, London, United Kingdom; [2]William Harvey Research Institute, London, United Kingdom.*

Background: Patients undergoing cardiopulmonary bypass are at risk of post-operative acute kidney injury (AKI) due to renal ischemia. Several studies have demonstrated an association between cardiac surgery associated-AKI (CSA-AKI) and reduced long-term survival which persists even when the degree of AKI is mild and where there is complete resolution of the injury prior to discharge. The mechanism by which CSA-AKI is associated with increased mortality is not currently understood. Telomere length has been proposed as a biomarker for cellular senescence and aging and shortened telomeres have been shown to delay recovery after ischemia induced renal injury in animal models. We hypothesised that patients with reduced telomere length undergoing cardiac surgery may have increased long-term mortality and be more susceptible to ischemia-induced AKI.

Methods: Blood samples were taken immediately prior to surgery and mean leukocyte telomere length (TL) measured by quantitative real time polymerase chain reaction (rt-PCR). The primary outcome was the development of AKI in the first 7 days post-operatively, defined by the Adult Kidney Injury Network (AKIN) criteria. All patients were entered into a study database that recorded a range of pre-operative, intra-operative, and post-operative variables. Univariate statistical analysis was performed.

Results: Between January 2016 and March 2017, 243 patients at a single institution were recruited. Of these, 51 developed post-operative AKI (21%) as defined by the AKIN criteria (stage 1 = 45; stage 2 = 6; stage 3 = 4). No differences were found between the AKI and non-AKI groups in terms of male gender (79.4% Vs 79.4%; p = 1), mean age (67.0 Vs 63.1 years; p = 0.061), or ethnicity (p = 0.223). As expected, mean length of stay was significantly longer in the AKI group at 14.8 days compared to 9.3 days in the non-AKI group (p <0.0001). No difference in mean telomere length was found between the groups with a mean relative TL of 0.73 and 0.76 in the AKI and non-AKI groups respectively (p = 0.334).

Conclusions: No association was found between mean telomere length and the development of AKI following cardiac surgery.

SA-PO065

Renal Oximetry Measured by Near-Infrared Spectroscopy before Cardiopulmonary Bypass Predicts Cardiac Surgery-Associated AKI Rachel Joffe,[2] Mohammed M. Al aklabi,[1] Sudeshna Bhattacharya,[3] Dominic A. Cave,[1] Daniel Garros,[1] Lindsay Ryerson,[3] Catherine Morgan.[3] *[1]Stollery Children's Hospital, Edmonton, AB, Canada; [2]Stollery Children's Hospital, University of Alberta, Edmonton, AB, Canada; [3]University of Alberta, Edmonton, AB, Canada.*

Background: Cardiac surgery-associated acute kidney injury (CS-AKI) is common in children and associates with negative outcomes. Novel interventions to reduce CS-AKI require knowledge of its pathophysiology. States of altered perfusion, oxygen delivery and energy consumption occur during cardiopulmonary bypass (CPB) and could protect against or contribute to renal cellular injury and recovery. NIRS (near-infrared spectroscopy) is noninvasive technology for monitoring regional blood flow and tissue oxygenation. This study evaluated the relationship between renal regional oxygen saturation (rSO_2) and CS-AKI, using NIRS monitoring before, during, and after CPB in children.

Methods: Design, setting, and patients: We conducted a prospective cohort study evaluating children ≤10 kg who underwent CPB (Stollery Children's Hospital, Edmonton, Alberta, Canada). Heart transplant, preoperative dialysis, sepsis, extracorporeal life support, congenital renal disease, and preoperative nephrotoxins were exclusions. **Measurements:** Outcome measure was development of AKI after cardiac surgery (defined according to Kidney Disease: Improving Global Outcomes criteria). rSO_2 was measured continuously using NIRS (INVOS™ 5100C Cerebral/Somatic Oximeter, Troy, MI, USA) from time of anesthesia to time of transfer to intensive care.

Results: Main Results: CS-AKI occurred in 65%. Lower baseline (preoperative) rSO_2 associated with decreased risk of CS-AKI (p=0.01); children with baseline rSO_2 in the highest tertile were 7.14 times more likely to get CS-AKI (vs lowest tertile). Area under the curve for ability of baseline rSO_2 to predict CS-AKI was 0.73 (95%CI 0.60 to 0.85). Children with lower baseline glomerular filtration rate had lower mean renal rSO_2.

Conclusions: Conclusions: Findings demonstrate that preoperative oxygen supply/demand balance is an important predictor of CS-AKI, suggesting lower preoperative (and intraoperative) renal blood flow may be protective. There is not yet a definite link between remote ischemic preconditioning and prevention of CS-AKI, however renal protective effects of sublethal ischemia should continue to be explored.

Funding: Private Foundation Support

SA-PO066

Impact of Standard Mean Arterial Pressure on AKI in Patients with Shock According to Age Groups Sarah Y. Atallah,[1] Mazen Zaarour,[4] Chanudi Weerasinghe,[3] Julie Zaidan,[1] Bader Kfoury,[1] Elias Moussaly,[1] Ahmed Mahgoub,[1] Elie El-Charabaty,[2] Suzanne E. El Sayegh.[2] *[1]Internal Medicine, Staten Island University Hospital, Staten Island, NY; [2]Nephrology, Staten Island University Hospital, Staten Island, NY; [3]Hematology and Oncology, Staten Island University Hospital, Staten Island, NY; [4]Hematology and Oncology, Tulane University, New Orleans, LA.*

Background: Management of mean arterial pressure (MAP) to a target value is crucial in shock. Recent studies advocate the use of higher MAP target in patients in shock who are at risk acute kidney injury (AKI). However, there is limited clinical data to support this approach. Our objective was to compare the AKI outcome in patients with shock according to age and the achieved MAP.

Methods: We performed a retrospective chart review of patients admitted to the Intensive Care Unit (ICU) of one tertiary care center from Jan 2012 to May 2015. We obtained 3 MAP readings per day for the first 3 ICU days (D 0,1,2), with one mean value per day. Patients were stratified into 3 MAP groups (65-70,70-75 and 75-80mmHg). Patients were also grouped according to age (<60 year of agr and ≥60 year of age). The study's primary outcome was the incidence of AKI according to both age and MAP.

Results: Our sample size included 255 patients (104 <60 y.o, 151 ≥60 y.o). The incidence of AKI was higher in older patients (75.5%) compared to younger ones (69.2%). The incidence of AKI was similar regardless of the achieved MAP (Table 1). Within each age group, MAP did not have an impact on the incidence of AKI (incience of AKI in age <60 on D0: 86.6% in MAP 65-70 mmHg, 73.9% in MAP 70-75 mmHg, 78.9% in MAP 75-80 mmHg, p=0.65; incience of AKI in age≥60 on D0: 67.8% in MAP 65-70 mmHg, 76% in MAP 70-75 mmHg, 75% in MAP 75-80 mmHg, p=0.81). Furthermore, there were no statistically significant differences in the incidence of AKI for all age and MAP groups on all studied days (D0, D1, D2).

Conclusions: Older adults with shock have a higher incidence of AKI compared to younger patients, with no associated reduction in AKI incidence with higher MAP. Larger studies are needed to confirm whether a more conservative MAP target achieves the similar AKI outcomes compared to a higher, more aggressive one.

Table 1: Incidence of AKI across the three mean MAP groups in the total population

	Day 0	Day 1	Day 2
MAP 65-70	74.4%	70.0%	73.5%
MAP 70-75	75%	40.4%	80%
MAP 75-80	76.6%	30.1%	69.5%
	p=1	p=0.97	p=0.49

SA-PO067

Admission Hyperphosphatemia Increases Risk of AKI in Hospitalized Patients Wisit Cheungpasitporn,[2] Charat Thongprayoon,[1] Michael A. Mao,[2] Wonngarm Kittanamongkolchai,[2] Ankit Sakhuja,[2] Stephen B. Erickson.[2] *[1]Bassett Medical Center, Cooperstown, NY; [2]Mayo Clinic, Rochester, MN.*

Background: The association between elevated admission serum phosphate and risk of in-hospital acute kidney injury (AKI) is limited. The aim of this study was to assess the risk of AKI in hospitalized patients stratified by various admission serum phosphate levels.

Methods: This is a single-center retrospective study conducted at a tertiary referral hospital. All hospitalized adult patients who had admission phosphate levels available between January and December 2013 were enrolled. Admission phosphate was categorized based on its distribution into six groups (<2.4, 2.4 to 2.9, 2.9 to 3.4, 3.4 to 3.9, 3.9 to 4.4, and ≥4.4 mg/dL). The primary outcome was in-hospital AKI occurring after hospital admission. Logistic regression analysis was performed to obtain the odds ratio of AKI for various admission phosphate strata using the phosphate 2.4 to 2.9 mg/dL level (lowest incidence of AKI) as the reference group.

Results: After excluding patients with ESRD, without serum creatinine measurement, and those who presented with AKI at the time of admission, a total of 5,036 patients were studied. Phosphate levels of <2.4 mg/dL and ≥4.4 mg/dL were found in 458 (9.1%) and 585 (11.6%) patients, respectively. In-hospital AKI occurred in 595 (11.8%) patients. The incidence of AKI was 10.5%, 9.5%, 11.8%, 10.0%, 12.8%, and 17.9% in patients with admission phosphate <2.4, 2.4-2.9, 2.9-3.4, 3.4-3.9, 3.9-4.4, and ≥4.4 mg/dL, respectively. After adjusting for potential confounders, admission serum phosphate levels >4.4 mg/dL was associated with an increased risk of developing AKI with an odds ratios of 1.72 (95% CI 1.20-2.47), whereas admission serum phosphate level <4.4 mg/dL was not associated with development of AKI during hospitalization.

Conclusions: Elevated admission phosphate was associated with an increased risk for in-hospital AKI.

SA-PO068

Complex Relationship Among Obesity, AKI, and Long-Term Mortality in Coronary Artery Bypass Grafting Hongran Moon,[2] Yeonhee Lee,[2] Sejoong Kim,[1] Dong Ki Kim,[2] Ho Jun Chin,[1] Yon Su Kim,[2] Ki Young Na,[1] Seung Seok Han.[2] *[1]Seoul National University Bundang Hospital, Seongnam, GYEONGGI-DO, Republic of Korea; [2]Seoul National University College of Medicine, Seoul, Republic of Korea.*

Background: Obesity is an important health concern and related with several comorbidities and mortality. However, its relationship with acute kidney injury (AKI) and long-term mortality remains unresolved, particularly in Korean patients undergoing coronary artery bypass grafting (CABG).

Methods: A total of 3018 patients (aged ≥18 years) were retrospectively reviewed from two tertiary referral centers between 2004 and 2017. Obesity was defined using body mass index (BMI), according to the World Health Organization recommendation. The odds ratios (ORs) and hazard ratios (HRs) for post-surgical AKI and all-cause mortality were calculated after adjusting for multiple covariates. Patients were followed for 90 ± 40.9 months (maximum 13 years).

Results: The proportions of normal weight, underweight, overweight at risk, obese I, and obese II status were 31.7%, 2.4%, 27.8%, 35.1%, and 4.0%, respectively. Post-surgical AKI developed in 799 patients (26.5%). The obese group had a higher OR of AKI [1.72 (1.149-2.560)] than the normal weight group (P=0.008), whereas other groups with abnormal weight status did not confer the higher risk of AKI than the normal weight group. This result suggest that obesity was an indicator of the AKI risk in the CABG subset. However, the relationship trend with mortality was different from the above one. During the follow-up period, 787 patients (26.1%) died. The group with underweight status had a higher HR of mortality [2.69 (1.957-3.687)] than the normal weight group, whereas the groups with overweight at risk, obese I, and obese II status had lower HRs than the normal weight group, as follows: 0.59 (0.486-0.706), 0.61 (0.512-0.720) and 0.62 (0.410-0.926), respectively. These results suggest that normal weight status did not guarantee the lowest mortality in the CABG subset.

Conclusions: Obesity is related with the high risk of AKI, but not with the high mortality in Korean patients undergoing CABG. Rather, the patients with overweight at risk, obese I status showed better survival rates than the patients with normal weight. These results should be monitored in clinical practice, based on the consideration for several confounding factors, such as inflammation and malnutrition.

SA-PO069

Extracellular and Cardiothoracic Hypervolemia Evaluated with Bioimpedance Analysis as a Prognostic Marker in AKI Francisco javier Lavilla, Pedro Errasti, Christian I. Alfaro Sanchez, Nuria Garcia-Fernandez, Pelayo M. Fdez-Felechosa, Jose maria Mora gutierrez. *Clinica Universidad de Navarra, Pamplona, Spain.*

Background: The bioelectrical impedance analysis (BIA) can offer information about volemia. We evaluate corporal, hemodynamic BIA, and volemic parameters (Extracelular/intracelular watter ratio –ECW/ICW-, Extracelular/Total body watter ratio –ECW/TBW-, and Fluid thoracic volumen –FTV-) in acute kidney injury (AKI).

Methods: We include a cohort of 159 patients (médium age 66 years SD 1.3, and male 73 %) with AKI and corporal BIA (Study A), and another cohort of 50 patients (mean age 71.2 years SD 1.6, 79.6% males) with AKI and hemodynamic BIA (Study B). We evaluate clinical prognostic index (individual severity index –ISI-), analytical inflammatory parameter (C-reactive protein) and chronic health index (Karnofsky –K-). We evaluate mortality and renal replacement therapy requeriment. We use SPSS 20.0.

Results: Study A: Exitus 27%. ECW/ICW and ECW/TBW was associated with prognosis index, clinical and analytical parametes in AKI. ECW/ICW was associated with ISI (r=-0.240, p=0.002) and CRP (r=0.224, p=0.006) and Karnosky(r=-0.253 p<0.002). ECW/TBW was associated with ISI (r=-0.115 p=0.148) and CRP (r=0.116 p=0.158) and Karnosky(r=-0.242 p=0.002). ECW/ICW was associated with risk mortality (OR 2.313 p=0.004 CI 95% 1.308-4.092), and ECW/TBW also (OR 5.539 p=0.018 CI 95% 1.333-23.007). The AUC with ECW/ICW was 0.773 (p=0.001, CI 95% 0.672- 0.874) and with ECW/TBW was 0.734 (p=0.003, CI 95% 0.625- 0.844) respect to survive. Extracelular corporal volumen not was associated with renal replacement therapy requeriment. **Study B:** Renal replacement therapy was associated with higher FVT (p= 0.005 37/49.2 l/kOhm), and ventilatory support also (p=0.005 37 vs 49.2 l/kOhm). FVT was associated with C reactive protein (r=-0.310, p= 0.046). FVT not was associated with mortality.

Conclusions: Higher ECW/ICW or ECW/TBW are associated with poor prognosis in AKI. Extracelular hypervolemia are related with inflammatory, proteín metabolism, and health status prior to the event. Thoracic hypervolemia was associated with respiratory failure and renal replacement therapy requeriment. Both BIAs can used to made a better AKI patient management (use of diuretic, intravenous solutions) and triage (mortality, respiratory failure with renal replacement theraphy risk).

SA-PO070

The Incidence and Risk Factors of AKI in Patients with Pulmonary Infection-Associated Acute Respiratory Distress Syndrome Xin Wan,[1] Changchun Cao.[2] *[1]Nanjing Hospital Affiliated to Nanjing Medical University (Nanjing First Hospital), Nanjing, China; [2]Sir Run Run Hospital Affiliated to Nanjing Medical University, Nanjing, China.*

Background: Acute kidney injury (AKI) is a common complication in critically ill patients and is a major risk factor for death. Among critically ill patients, AKI occurred in 31.3% of patients and was more common in patients with ARDS (44.3% versus 27.4% in patients without ARDS. Infection (44.1%) was the most common risk factor for the development of ARDS. Lung was the most common infection site in infection-related ARDS, and also the only infection site significantly associated with increased risk of developing ARDS.there is no a study pay a attention to AKI in patients with pulmonary infection -associated ARDS (PI-ARDS). Therefore, we aimed to explore the incidence and risk factors of acute kidney injury in patients with PI-ARDS.

Methods: This retrospective cohort study included patients aged 18 or more who was admitted to hospital for pulmonary infection combined with or secondary to ARDS at Nanjing First Hospital in Nanjing, China, between January 2014 and March 2017. Univariate and multiple logistic regression models were used for determining the association between the development of AKI and risk factors. Multiple Cox-proportional hazards modeling was performed to evaluate the impact of AKI on the in-hospital mortality and hospital length of stay (LOS).

Results: Of 846 patients with ARDS result from pulmonary infection, the incidence of patients with PI-ARDS developed AKI was 53.1% (449/846). A total of 36(8.0%) PI-ARDS patients required renal replacement therapy. In the multivariate analysis, factors independently associated with AKI were male, age, white blood cell, platelets, several nephrotoxic drugs (diuretic, vancomycin, Aminoglycosides), proteinuria and invasive ventilation. The model was well calibrated and an area under the receiver operator curve (AUC) was 0.766. Furthermore, subjects with proteinuria of trace to 1+, 2+, 3+, had a 1.45(P = 0.037, 1.02 to 2.06), 3.36(P <0.001, 1.78 to 6.35), 11.26(P < 0.001, 3.11 to 40.80) fold increase in adjusted odds ratio of AKI compared with subjects with negative, respectively. AKI was also significantly associated with in-hospital mortality, especially in patients needing RRT, and prolonged hospital length of stay.

Conclusions: Proteinuria is an independent risk factor for AKI in PI-ARDS patients, and patients with PI-ARDS develop AKI would have a grave prognosis.

SA-PO071

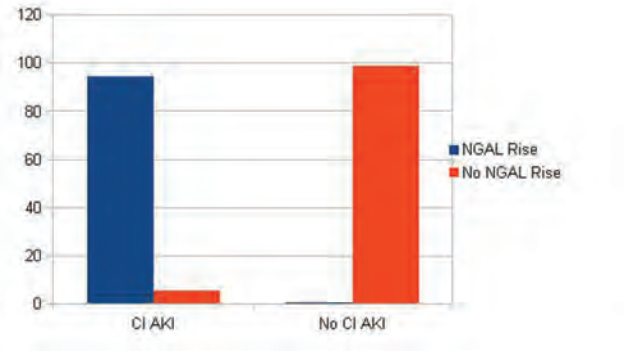
Role of Urinary NGAL at 4 Hours Post Coronary Angiogram in Detecting Contrast Induced AKI Madhav Venkatesan. *Amrita Institute of Medical Sciences, Trichy, India.*

Background: Serum creatinine is an unreliable biomarker of acute kidney injury(AKI). Newer biomarkers can diagnose AKI earlier. We attempted to determine the sensitivity, specificity, positive and negative predictive values of urine NGAL in detecting CI-AKI post a coronary angiogram, and to study the risk factors of CI-AKI.

Methods: 240 patients undergoing coronary angiogram were prospectively studied. Patients with a starting serum creatinine of more than 1.4mg/dl were excluded from the study. Serum creatinine and urine NGAL were measured before the procedure. Urine NGAL was measured 4 hours post procedure and serum creatinine was measured at 48 hours post procedure.

Results: The incidence of CI AKI in patients who underwent coronary angiogram was 8%. There was a rise in urinary NGAL in 95% of these patients (n=18). The sensitivity and specificity of urine NGAL at 4 hours were 94.7% and 99.1% respectively. The positive and negative predicitve values were 90% and 99.5% respectively. Age more than 75 years, presence of diabetes mellitus, congestive heart failure, prior history of CI-AKI and anemia had significant association with CI-AKI. Multivariate analysis showed that CHF and anemia were significantly associated with increased risk of CI-AKI.

Conclusions: Urine NGAL has a high sensitivity and specificity in the diagnosis of contrast induced acute kidney injury post coronary angiogram. Age above 75 years, diabetes mellitus, congestive heart failure, anemia and previous history of contrast induced AKI were significant risk factors for CI-AKI. Congestive heart failure and anemia were the risk factors with highest association with CI AKI. Based on our study we suggest that urine NGAL may be used for early detection of contrast induced acute kidney injury post a coronary angiogram with sensitivity and specificity of 94.7% and 99.1% respectively and with positive and negative predicitve values of 90%. and 99.5% respectively.



Association of rise in urine NGAL with CI-AKI

SA-PO072

Identification of Urine Apolipoprotein A-I as a Biomarker for Early Diagnosis of AKI Following Percutaneous Coronary Intervention by ITRAQ-Based Quantitative Proteomics Fangfang Zhou,[1,2] Qun Luo,[1,2] Gen Shen,[3,2] Honghua Ye,[3,2] Lina Han,[1,2] Lulu Huang,[1,2] Yumei Li,[1,2] Zemin Wang.[1,2] *[1]Department of Nephrology, Ningbo NO.2 Hospital, Ningbo City, China; [2]School of Medicine, Ningbo University, Ningbo, China; [3]Department of Cardiology, Ningbo NO.2 Hospital, Ningbo, China.*

Background: Acute kidney injury(AKI) has been recognized as a common complication of percutaneous coronary intervention(PCI). Our study aimed to discover and validate novel diagnostic biomarkers of acute kidney injury(AKI) following PCI by Isobaric Tags for Relative and Absolute Quantitation(ITRAQ) technology dynamically, and to explore potential mechanisms of AKI.

Methods: We performed a prospective nested case-control study. 14 older patients(>60yr) were identified with PCI-AKI. 12 patients were selected as controls, matched by age and gender. Urine were collected at different time points of pre-PCI, 6hrs, 24hrs, and 48hrs post-PCI. A training set of 56 urine samples(AKI group, n=6 and control group, n=6) were subjected to ITRAQ technology. Proteins were considered to be differentially expressed if the difference was statistically significant($p<0.05$) and the fold change was >1.2 or <0.83. Differentially expressed proteins, also analyzed by bioinformatics analysis, were then investigated in a validation set of 48 urine samples (AKI group, n=8 and control group, n=6) via parallel reaction monitoring(PRM) based targeted proteomics.

Results: A total of 14 overlapped proteins at all the different time points post-PCI showed an abundance change in AKI group as compared to those before PCI and controls. Among them, the accumulation of apolipoproteins A-I(apoA-I) were 14.86-, 18.88-, and 7.44-fold higher at 6h, 24h, and 48h post-PCI in AKI group, as compared to pre-PCI value respectively ($p=0.0409$, =0.0338, $p=0.1009$). Using the PRM approach, we successfully confirmed the differential accumulation of apoA-I at different time points post-PCI in the validation set. We also confirmed that serum level of high density lipoprotein (HDL) and apoA-I were significantly lower in AKI patients ($p=0.023$, $p=0.047$) as compared with controls. Bioinformatics analysis described that apoA-I may involved in Peroxisome Proliferator Activated Receptor(PPAR) signaling pathway.

Conclusions: The presence of urine apoA-I demonstrated in our study a potential diagnostic biomarker for PCI-AKI, suggesting lipid abnormalities in AKI, which may be related to HDL deficiency. Comparatively little is known regarding the role of lipids in pathogenic mechanisms of AKI, which deserve further study.

Funding: Government Support - Non-U.S.

SA-PO073

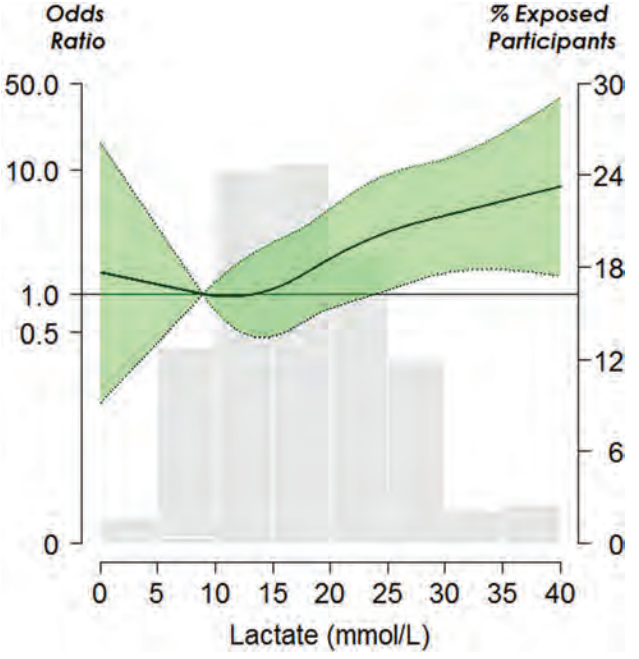
Serum Lactate Level Predicts Mortality among Patients with Metformin-Associated Lactic Acidosis Requiring Renal Replacement Therapy Chin-Chi Kuo,[2] Ching-Wei Tsai.[1] *[1]Internal Medicine and Big Data Center, China Medical University Hospital, Taichung City, Taiwan; [2]Internal Medicine and Big Data Center, China Medical University Hospital, Taichung City, Taiwan. Group/Team: CHMU Kidney Research Group.*

Background: The risk factor for mortality and the best practice concerning timing, mode, and dose of renal replacement therapy (RRT) for patients with metformin-associated lactic acidosis (MALA) with renal failure remain undetermined.

Methods: We searched case reports and case series published in PubMed/Medline and EMBASE from inception to Sep 2014 and applied predetermined exclusion criteria. Case-level data including case's demographics and clinical information related to MALA were abstracted. Multiple logistic regression modeling was used to examine the predictors of mortality.

Results: A total of 253 unique cases were identified with cumulative mortality of 17.2%. Eighty-seven percent of patients had acute kidney injury. Serum lactate level was significantly higher in non-survivors (median 22.5 mmol/L) than in survivors (17.0 mmol/L, *p*-value <0.01) and so did the median blood metformin concentrations (58.5 vs. 43.9 mg/L, *p*-value=0.05). The survival advantage was not significantly different between the modalities of RRT. The adjusted odds ratio of mortality for every one mmol/L increase in serum lactate level was 1.09 (95% CI 1.02-1.17, *p*-value=0.01). The dose-response curve indicated a lactate threshold greater than 20 mmol/L was significantly associated with mortality.

Conclusions: Our study suggests that predialysis level of serum lactate level is an important marker of mortality in MALA patients requiring RRT with a linear dose-response relationship. To better evaluate the optimal prescription of RRT in MALA, we recommend fostering an international consortium to support prospective research and large-scale standardized case collection.



Odds ratio for MALA mortality by serum lactate level. Solid lines: adjusted odds ratios based on restricted quadratic splines for the serum lactate level, with knots at the 10th, 50th, and 90th percentiles. The shaded green region: upper and lower 95% CIs.

SA-PO074

Preoperative Risk Assessment Improves Biomarker Detection for Predicting AKI After Cardiac Surgery Cheng chia Lee,[1,2] Chih-Hsiang Chang,[1,2] Chih-Wei Yang.[1,2] *[1]Chang Gung Memorial Hospital, Taoyuan, Taiwan; [2]Chang Gung University, Taoyuan, Taiwan.*

Background: The major challenge in managing acute kidney injury (AKI) lies in making an early diagnosis. Although urinary neutrophil gelatinase-associated lipocalin (NGAL) has emerged as a promising biomarker for the early detection of kidney injury, previous studies of adult patients have reported only moderate discrimination. The age, creatinine, and ejection fraction (ACEF) score is a preoperative validated risk model for predicting AKI following cardiac surgery. It remains unknown whether combined preoperative risk assessment through ACEF scores followed by urinary NGAL is an optimal approach with improved predictive performance.

Methods: This prospective study was performed in a tertiary referral center in Taiwan between July 2014 and February 2015. A total of 177 consecutive patients who underwent cardiac surgery were enrolled. Clinical characteristics, prognostic model scores, and outcomes were assessed. The ACEF scores were calculated as age (years)/ejection fraction (%) + 1 (if creatinine > 2.0 mg/dL). NGAL were examined within 6 hours after cardiac surgery. Patients were stratified according to preoperative ACEF scores, and comparisons were made using the area under the receiver operator characteristic (AUROC) curve for the prediction of AKI.

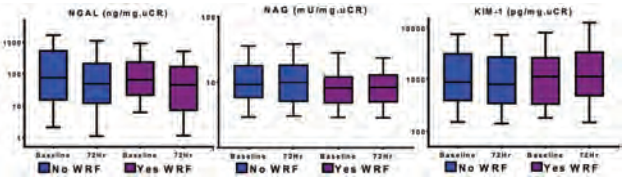
Results: A total of 45.8% (81/177) of the patients had AKI. Patients with ACEF scores ≥ 1.1 were older and more likely to have diabetes mellitus, myocardial infarction, peripheral arterial disease, and class III or IV heart failure. Urinary NGAL alone moderately predicted AKI, with an AUROC of 0.732. Risk stratification by ACEF scores ≥ 1.1 substantially improved the AUROC of urinary NGAL to 0.873 (95% confidence interval, 0.784–0.961; $P < .001$).

Conclusions: Risk stratification by preoperative ACEF scores ≥ 1.1, followed by postoperative urinary NGAL, provides more satisfactory risk discrimination than does urinary NGAL alone for the early detection of AKI after cardiac surgery. Future studies should investigate whether this strategy could improve the outcomes and cost-effectiveness of care in patients undergoing cardiac surgery.

Funding: Government Support - Non-U.S.

Performance of NGAL in discriminating AKI, stratified by ACEF scores

Population	AUROC (95% CI)	P value	Optimal cut-off (ng/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
ACEF < 1.1	0.606 (0.492–0.720)	0.071	>45.1	61.5	61.5	50.5	68.5
ACEF ≥ 1.1	0.873 (0.784–0.961)	<0.001	>77.5	83.3	87.2	81.2	88.7
Total	0.732 (0.656–0.808)	<0.001	>82.6	60.5	80.2	67.1	75.3



Baseline and 72 hour Biomarkers of Tubular Injury According to WRF Status.

SA-PO075

AKI Biomarkers and Cystic Fibrosis (CF): Does Having CF or Being a Girl Make a Difference? Courtney B. Munro.[1,2] *[1]Murdoch Childrens Research Institute, Melbourne, Victoria, NSW, Australia; [2]Paediatrics, University of Melbourne, Melbourne, VIC, Australia.*

Background: Novel urinary biomarkers are useful for prediction of acute kidney injury (AKI). Cystic fibrosis (CF) is a life limiting disease, caused by a gene defect in Cystic Fibrosis Transmembrane Regulator (CFTR), that predisposes the individual to recurrent respiratory infections which are often treated with nephrotoxic antibiotics. CFTR is highly expressed in the kidney, yet its effects in the human kidney in CF have not been closely examined. Previous studies have demonstrated renal glomerular hyperfiltration in children with CF. We set out to determine if novel urinary biomarkers could be used in children with CF, by determining reference levels in a paediatric CF population, and if this differed to healthy age-matched controls.

Methods: Urine was collected and analysed for kidney injury molecule-1 (KIM-1), neutrophil gelatinase associated lipocalin (NGAL) and fibroblast growth factor-23 (FGF-23) using ELISA and normalised to urinary creatinine (UCr). Analysis of biomarkers by cohort (CF vs. healthy controls), age and sex was performed.

Results: Urine was collected on 448 occasions (CF *n*=229; healthy controls *n*=219) from children aged 1 to 6-years, median 4-years. Median values were: KIM-1 205.44 pg/mL (Interquartile range (IQR) 107.11 to 427.93), NGAL 1.03 ng/mL (IQR 0.01 to 3.65), FGF-23 45.25 pg/mL (IQR 17.05 to 96.21) and UCr 4.21 mmol/L (IQR 2.56 to 6.26). KIM-1, NGAL and UCr were higher in healthy controls than in CF (p=0.0000), suggesting a concentrating defect. FGF-23 was higher in CF (p=0.0101) which may reflect inflammation and infection. In healthy controls KIM-1 and UCr increased with age (p=0.0000), whereas NGAL decreased with age (p=0.0141). In CF, only UCr increased with age (p=0.0166). In healthy controls there were significant sex differences with KIM-1 and UCr higher for boys (p=0.0002 and p=0.0006), whereas NGAL was approximately 5 times higher for girls (p=0.0003). Sex differences were not observed in CF.

Conclusions: This is the first reference range study for urinary KIM-1, NGAL and FGF-23 in young children with CF and highlights significant differences in AKI biomarkers in CF, and for age and sex in healthy children. This information is essential for interpreting AKI biomarkers in the context of CF. Further research is required as to the role of CFTR in the kidney and why children with CF express not only lower biomarker levels, but the absence of sex differences.

Funding: Private Foundation Support

SA-PO076

Worsening Renal Function During Aggressive Diuresis Is Not Due to Kidney Injury in Acute Heart Failure Patients Joshua L. Rein,[1] Keyanna Jackson,[2] Veena Rao,[2] Steven G. Coca,[1] Jeffrey M. Testani.[2] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Yale University, New Haven, CT.*

Background: The mechanisms underlying worsening renal function (WRF) in the setting of aggressive diuresis for acute heart failure (AHF) treatment may reflect renal tubular injury or simply indicate a hemodynamic or functional change in glomerular filtration. Well-validated tubular injury biomarkers—NAG, NGAL, and KIM-1— are now available that can quantify the degree of renal tubular injury. The ROSE trial provides an ideal experimental platform for the study of mechanisms of WRF during aggressive diuresis for AHF as the ROSE protocol dictated high dose loop diuretic therapy in all patients. We sought to determine whether kidney injury is a predominant mechanism for WRF in the setting of aggressive diuresis and its impact on prognosis.

Methods: Patients in the multicenter ROSE trial with baseline and 72-hour urine injury biomarkers were analyzed (*N*=277). WRF was defined as a ≥20% decrease in glomerular filtration rate estimated using cystatin C.

Results: Levels of NAG and KIM-1 did not change with aggressive diuresis (*P*>0.49, both), whereas levels of NGAL decreased slightly [-8.0 ng/mg (-169, 35 ng/mg), *P*<0.001]. WRF occurred in 21.7% of the population and was not associated with an increase in any marker of renal injury: NGAL (*P*=0.23), NAG (*P*=0.49), or KIM-1 (*P*=0.22). WRF was not associated with reduced survival (*P*=0.51). However, increases in NGAL, NAG, and KIM-1 were paradoxically associated with improved survival (adjusted HR: 0.78 per 10 percentile increase, 95% CI: 0.69-0.91; *P*=0.001). Change in injury biomarkers could not differentiate high versus low risk forms of WRF ($P_{interaction}$=0.35).

Conclusions: Renal injury was not a dominant mechanism for WRF in the context of aggressive diuresis of ADHF patients. Moreover, neither WRF nor renal injury was associated with an increased risk of death. These findings reinforce the notion that small to moderate "bumps" in creatinine commonly encountered with aggressive diuresis are mechanistically and prognostically different from traditional causes of acute kidney injury.

SA-PO077

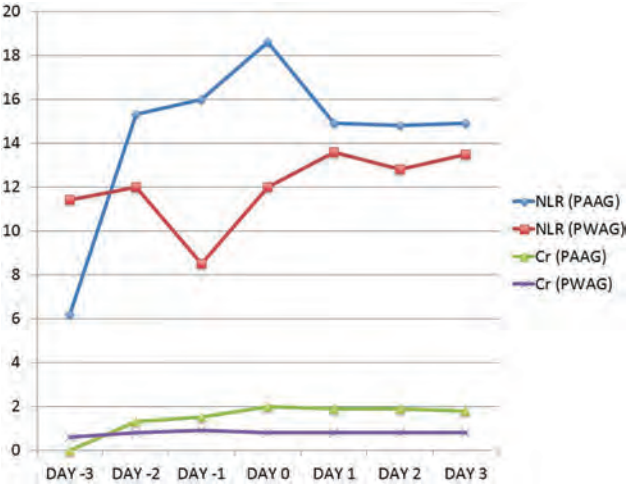
Utilizing CBC to Predict AKI and Its Recovery Asif Khan,[2] Anna S. Gutman,[1] Elie El-Charabaty,[2] Suzanne E. El Sayegh.[2] *[1]Northwell Health, Brooklyn, NY; [2]Staten Island University Hospital, Brooklyn, NY.*

Background: The difficulty in diagnosing acute kidney injury (AKI) prior to an elevation of serum creatinine, or a decrease in urine output, continues to pose challenges for nephrologists. Multiple new biomarkers of kidney damage have been evaluated, but their clinical value remains limited. The value of the neutrophil to lymphocyte ratio (NLR) is an indicator of systemic inflammation, which is easily calculated from a CBC. We investigated the hypothesis that a high NLR may predict the development of AKI.

Methods: This retrospective study identified patients of 18 years and older. We compared the NLR trends between patients with pneumonia and AKI as the experimental group (PAAG), to patients with pneumonia without AKI as the control group (PWAG). Day 0 was labeled as the day of AKI diagnosis, and the day of pneumonia diagnosis in the PAAG and the PWAG respectively. We documented trends of NLR and kidney function from 3 days before Day 0 until 3 days after Day 0.

Results: Of the 222 patients enrolled, 115 were in the PAAG, and 107 in the PWAG. Both groups had similar percentages of sexes, ethnicities, underlying hypertension, coronary artery disease, heart failure, and a similar median age. The PAAG had a significantly higher number of patients with chronic kidney disease and diabetes mellitus compared to the PWAG (47.9% vs. 4.8% (P<0.001) for CKD, and 40.4% vs. 24.1% (p=0.02) for DM). There was an increase in the mean NLR from day -3 to day 0 of 12.4 in the PAAG, and only a 0.6 in the PWAG group. These results suggest a positive correlation between a certain net change in NLR and the development of AKI.

Conclusions: The potential of NLR as an indicator of systemic inflammation is well established. A timely use of NLR within twenty-four hours of admission may predict an impending AKI. Further studies are necessary to establish the trends in NLR prior to the diagnosis of AKI.



Graph showing the trends in NLR in the PAAG compared to the PWAG, and trends in the serum creatinine of both groups.

SA-PO078

Efficacy of Urinary Output for the Early Diagnosis and Urinary NGAL for the Prognosis of AKI after Major Elective Non-Vascular Abdominal Surgeries Graziela R. Souza,[1] Emmanuel A. Burdmann,[4] Lia J. Marçal,[2] Luis Yu,[3] Dirce M. Zanetta.[5] *[1]São Paulo University, São Paulo, Brazil; [2]UNIVERSIDADE DE SAO PAULO, Sao Paulo - SP, Brazil; [3]University of Sao Paolo School of Medicine, Sao Paulo, Brazil; [4]University of Sao Paulo Medical School, Sao Paulo, Brazil; [5]University of São Paulo, S Paulo, Brazil.*

Background: Data comparing the efficacy of urinary output (UO) and serum creatinine (SCr) changes using RIFLE and KDIGO AKI definitions after major elective non-vascular abdominal surgeries (MENVAS) are scarce. The role of urinary NGAL as an outcome predictor in these patients is unknown. The aims of this study are to compare the efficacy of RIFLE and KDIGO SCr and UO criteria for AKI diagnosis and the role

of NGAL changes in the outcome of patients (pts) submitted to MENVAS admitted to the ICU.

Methods: One hundred and seventy one pts were prospectively evaluated, peri-operatively and from the ICU admission up to 7 days. SCr (mg/dl) was assessed before surgery and once a day up to 7 d or until ICU discharge. Hourly UO (ml/kg/h) was measured daily. AKI was diagnosed using either SCr or UO according RIFLE and KDIGO definitions. Urine samples were collected at the pre-operatory, at ICU admission, and 12 and 24 hours after ICU admission for NGAL (ng/mg urinary Cr) analysis. Data are presented as mean ± SD, median (minimal and maximum value) or frequency. Statistical significance was $p<0.05$.

Results: According to RIFLE criteria 101 pts (59.1%) developed AKI: 5 by SCr, 76 by UO and 20 by SCr+UO. Using KDIGO criteria 102 pts (60%) developed AKI: 6 by SCr, 67 by UO and 29 by SCr+UO. Pts with AKI diagnosed by UO, SCr and SCr+UO had, respectively, hospital length of stay (LoS) 19±19, 14±10 and 24±22 d (NS), ICU LoS of 3±1, 4±3 and 5±3 d ($p<0.001$ UO vs. SCr+UO) and mortality 4.5, 33.3 and 17.2%, respectively ($p=0.0211$). If the SCr criteria alone was utilized for AKI diagnosis, 25 pts in RIFLE group and 35 in the KDIGO group would be overlooked. Pts who died had higher NGAL values in the immediate post-surgery [108 (24-31642) vs. 45 (4–3763) no death, $p=0.0085$] and 24 h post-surgery [222 (59-8482) vs. 54 (3–6579) no death, $p=0.0026$] periods.

Conclusions: UO measurement seems to be pivotal for early AKI recognition, since the use of SCr criteria alone would miss a high number of AKI diagnoses, using either RIFLE or KDIGO definitions. Early NGAL increase after major elective non-vascular abdominal surgeries was associated with higher mortality in this group of patients.

Funding: Government Support - Non-U.S.

SA-PO079

Interval Change Plasma Neutrophil Gelatinase-Associated Lipocalin Level and Urine Output as a Predictor for Survival in Critically Ill Patients Undergoing Continuous Renal Replacement Therapy

Ha yeon Kim,[2] Eun Hui Bae,[1] Soo Wan Kim,[2] Seong Kwon Ma.[2] *[1]Chonnam National University Hospital, Gwangju, Republic of Korea; [2]Chonnam National University Medical School, Gwangju, Republic of Korea.*

Background: Continuous renal replacement therapy (CRRT) is increasingly modality of treatment in hemodynamic unstable ICU patients with AKI. Several biomarker have been attempted an early detection or assisted predicting prognosis. The neutrophil gelatinase-associated lipocalin (NGAL) is a one of them used early kidney injury marker. The aim of this study was to determine the outcome and identify the predictors of mortality of critically ill patients treated with CRRT for AKI in the ICU.

Methods: Protocol 1: In the single tertiary medical center retrospective study of 1,527 patients admitted ICU and undergoing CRRT from January 2011 to December 2013 was performed. Univariate and multivariate regression analyses were conducted to examine the independent predictor of patients' survival. **Protocol 2**: This retrospective observational study included 404 AKI patients treated with CRRT. The levels of serum creatinine (Cr), plasma NGAL obtained at baseline and at 48 hour after starting CRRT were analyzed.

Results: In total, 1,527 patients with AKI treated with CRRT, the overall in-hospital mortality rate of the CRRT treated AKI patients was 50.6%. Multivariate cox proportional hazards analysis identified that a urine output less 30 ml for initial first hour at the initiation of CRRT was independent predictor (HR; 1.73, CI; 1.45-2.07, p value; <0.001) besides APACHE II score and older age per 10 years and congestive heart failure also showed the significant predictors. Plasma NGAL was not different between survivor and non-survivor, whereas the difference of plasma NGAL between at baseline and at 48 hour after starting CRRT was significant different. However, univariate analysis revealed that delta plasma NGAL was not significant factor for the survival.

Conclusions: Plasma NGAL have limitation of early biomarker of predictor of survival. At initiation of CRRT, a urine output less 30 ml for initial first hour is a predictor of survival. Urine output is still a robust prognostic biomarker in these patients with AKI treated with CRRT.

SA-PO080

Development and Validation of 7-Plex Assay Panels to Measure Urine and Plasma Biomarkers Implicated in Prediction of CKD

Venkata Sabbisetti,[1,2] Emily Christie,[1,2] Sushrut S. Waikar,[1,2] Joseph V. Bonventre.[1,2] *[1]Brigham and Women's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA.*

Background: Biomarkers including TNFR1, TNFR2, suPAR, KIM-1, YKL 40, MCP-1 and BMP 7 have been shown to be associated with progression of kidney disease. We have developed and validated multiplex assays on the Meso Scale Discovery (MSD) platform to measure these 7 analytes simultaneously in both urine and plasma matrix.

Methods: We have developed a 7-Plex assay using MSD U-PLEX technology. Capture antibodies were biotinylated and conjugated to unique U-PLEX linkers and coupled to MSD 7-spot U-PLEX plates by incubating overnight at 4°C. Plates were coated with specific antibodies and then incubated with recombinant proteins, plasma or urine specimens from CKD patients for 1h followed by incubation with GOLD SULFO-TAGGED secondary antibodies for 1h. The amount of chemiluminescence in each well was measured using MSD SQ120 instrument.

Results: The MSD 7-plex assay demonstrated excellent linearity of dilution and spike recovery with no interference of various substances including glucose, bilirubin and albumin in both urine and plasma matrix. The intra and inter-assay coefficient of variation was below 15%.

Conclusions: We have developed a robust and reliable 7-plex assay on MSD platform to measure biomarkers implicated as potentially predictive of progression of kidney disease in plasma and urine specimens.

Funding: NIDDK Support

Biomarker	Assay Range (pg/ml)	LLOD (pg/ml)	Linearity of dilution	Intra-assay %CV (Urine)	Intra-assay %CV (Plasma)	Inter-assay %CV (Urine)	Inter-assay %CV (Plasma)	Volume Required (Urine/Plasma)
KIM-1	1.98-20000	1.98	1:2-1:16	7.1	4.8	8.6	7.8	10 µl
TNFR1	0.667-16000	0.667	1:2-1:16	8.9	6.6	9.5	9.9	10 µl
TNFR2	0.168-20000	0.168	1:2-1:16	5.7	3.6	8.7	10.1	10 µl
MCP-1	0.313-3900	0.313	1:2-1:16	6.8	7.9	8.8	8.4	10 µl
suPAR	53-64000	53	1:2-1:16	6.5	4.2	10.1	9.7	10 µl
YKL-40	140-192000	140	1:2-1:16	6.3	5.5	11.2	8.7	10 µl
BMP-7	5.50-8000	5.5	1:2-1:16	8.3	7.1	9.7	11.3	10 µl

SA-PO081

Establishment of a Tubule-Specific Renal Panel in AKI

Brent J. Portz, Michael A. Moore. *Danville Regional Medical Center, Danville, VA.*

Background: Early recognition to allow prevention of Acute Kidney Injury (AKI) is an ongoing inpatient challenge due to AKI's high morbidity and mortality. The traditional use of changes in serum creatinine and urinary output only define AKI after it is well established and kidney injury has begun. Better biomarkers of early acute renal injury are needed. Developments in systems biology techniques and advancements of genomic and proteomic technologies have provided an emerging list of novel glomerular and renal tubular cell biomarkers.

Methods: A comprehensive literature review was completed utilizing PubMed and MEDLINE databases from inception to January 2017 searching for 'AKI Biomarkers and Systems Biology'. Validated and Non-Validated novel AKI biomarkers discovered at tubule-specific sites via genomic, proteomic and systems biology techniques were identified. Unique biomarkers at distinct nephron segments were composited in a Tubule-Specific Renal Injury Panel.

Results: Amongst other identified markers, KIM-1 (Proximal Tubule), CNTF (Loop of Henle), bcl-2 (Distal Tubule), and NGAL (Collecting Tubule) suggested the highest potential for clinically applicable AKI biomarkers (Table 1).

Conclusions: The establishment of a tubule-specific renal panel is proposed to provide increased sensitivity/specificity to enable diagnosis earlier in acute renal injury.

SEGEMENT:	NOVEL BIOMARKER:	STUDY ORGANISM:	VALIDATED ASSAY (Y/N):
Proximal Tubule:	1. L-FABP	1. Human	1. N
	2. Urine KIM- 1 *	**2. Rat**	**2. Y**
	3. ADAM10	3. Rat	3. N
	4. Urine Interleukin-18	4. Human	4. N
	5. meprin B	5. Rat	5. N
	6. HNK-1	6. Human	6. N
	7. Urine DDRGK1	7. Human	7. N
Loop of Henle:	1. Urine and Serum NGAL	1. Human/Mouse	1. Y
	2. CNTF *	**2. Rat**	**2. N**
Distal Tubule:	**1. bcl-2 ***	**1. Rat**	**1. N**
	2. Urine elfin	2. Human	2. N
Collecting Tubule:	**1. Urine and Serum NGAL ***	**1. Human/Mouse**	**1. Y**

Table 1: List of Identified Novel Biomarkers at Segment Specific Sites, organism biomarker identified in and availability of commercially validated assays. **Bolded** *, denotes highest clinically applicable AKI biomarker at each segment. Literature references listed separately.

SA-PO082

Early Detection of Urine Neutrophil Gelatinase-Associated Lipocalin for 90-Day Mortality Prediction in Cirrhotic Patients with AKI

Zemin Wang, Fangfang Zhou. *Ningbo NO.2 Hospital, Ningbo City, China.*

Background: Our study was to investigate the prediction role of early detection of urine neutrophil gelatinase-associated lipocalin (uNGAL) after risk factors for 90-day mortality in cirrhotic patients with acute kidney injury (AKI).

Methods: We conducted a prospective nested case-control study of 90 cirrhotic patients with risk factors (bacterial infections, bleeding from oesophageal varices, large volume paracentesis (>3L/d), increased dosage of diuretics, and receiving contrast medium). Urine samples were collected at the time of risk factors occurred and 1d, 2d and 3d after the risk factors. Among these patients, 11 patients diagnosed as AKI(KDIGO AKI criteria, 2012). 9 patients were selected as controls, matched by age and gender. uNGAL was measured by ELISA. All the patients were followed up for 90 days.

Results: There were no significant differences in terms of baseline characteristics between AKI and control group. In the AKI group, the levels of uNGAL of 1-day, 2-day and 3-day after risk factors were significantly higher than those at the time of risk factors happened($P=0.013$, $P=0.009$, $P=0.012$). Totally 6 patients (30%) died during the 90-day follow-up period. The rate of mortality was much higher in patients with AKI compared with control group patients ($P < 0.05$). uNGAL level of 1d and 2d after risk factors was significantly higher in deceased patients compared with those in surviving patients (189.43(108.88,368.27) vs. 66.03(20.55,115.42), $P=0.049$; 148.31(70.06,326.68) vs.45.42(20.43,97.33), $P=0.039$). The serum Na, albumin, total bilirubin, levels of

uNGAL, and scores of Child-Pugh and MELD were signficantly associated with prognosis. Multivariate Cox regression analysis showed that uNGAL value of 2d after risk factors and MELD score independently predict 90-d mortality. ROC curve analysis showed that the plot of the uNGAL of 1-day and 2-day after risk factors could predict the risk of 90-day mortality in cirrhotic patients (AUC=0.792 (95%CI: 0.526-1.000), P=0.049; AUC=0.806 (95%CI: 0.584-1.000), P=0.039, respectively).

Conclusions: Early detection (1-2 days) of uNGAL after risk factors could predict 90-day mortality in cirrhotic patients with AKI, independent of other commonly used risk factors.

Funding: Government Support - Non-U.S.

SA-PO083

Usefulness of L-FABP as a Predictive Biomarker of AKI in Children with Cancer Sohsaku Yamanouchi, Takahisa Kimata, Shoji Tsuji, Kazunari Kaneko. *Kansai Medical University, Hirakata-shi, Japan.*

Background: Acute kidney injury (AKI) is one of severe complications during the course of administration of anti-cancer chemotherapy. Lahoti et al. have reported that 36% of adults with acute myelogenous leukemia or high-risk myelodysplastic syndrome developed AKI associated with chemotherapy, and 8-week mortality rates were approximately 15% in patients with AKI compared to 3% in non-AKI patients (Lahoti A, Cancer, 2010). Therefore, early and accurate diagnosis of AKI is essential even in children though the available information is scarce. Purpose: To identify predictive biomarkers of AKI in children with pediatric cancers.

Methods: We enrolled 16 children with cancer (acute leukemia in 11, and brain tumor in 5). Pediatric-modified RIFLE criteria modified by AKI Network were used to evaluate AKI. Urine samples were evaluated for: TP, Alb, NAG, BMG, and L-FABP. We obtained laboratory data thrice a week in 16 children with cancers who received 58 courses of chemotherapy consisting of Vincristine, Cisplatin, Cyclophosphamide, Carboplatin, Etoposide, Daunorubicin, L-asparaginase and Methotrexate. A course was between 4 and 8 weeks. AKI was noted in 14 out of 16 patients (87.5%) and 31 (53.4%) of 58 courses. Values of urinary biomarkers such as TP, Alb, NAG, BMG, and L-FABP were corrected using creatinine and compared between the courses with regard to patients showing AKI (n=31) and those without AKI (n=27). To assess the usefulness of these biomarkers in predicting AKI during chemotherapy, the receiver operating characteristic (ROC) curve was analyzed using the maximum value before developing AKI.

Results: Among urinary biomarkers, L-FABP and BMG (median value 15.5 μg/gCr and 320 μg/mgCr), demonstrated significantly higher levels in children who developed AKI than values in children without AKI (median value 6.8 μg/gCr and 201 μg/mgCr, P = 0.0007 and 0.003). Among the area under the curve in receiver operating characteristic curve calculated for each urinary biomarker, urinary L-FABP yielded the highest value: L-FABP (0.75) > BMG (0.72) > TP (0.64) > Alb (0.61) > NAG (0.53). Using the point on the curve closest to the (0, 1) point, cut-off for urinary L-FABP was 8.53 μg/gCr. Test sensitivity was 77.4 %, and specificity was 63.3 %.

Conclusions: We conclude that L-FABP is a possible predictive biomarker of AKI in children with cancer undergoing chemotherapy.

SA-PO084

Assessment the Utility of Finger-Nail Creatinine to Differentiate between AKI and CKD Nilesh Shinde,[1] Atul Sajgure,[1] Atul Mulay,[1] Charan B. Bale,[1] Ashwini Sharma,[1] Abhishek Goel,[1] Vajed Mogal,[1] Pratik Shete,[1] Shirin Telang,[2] Tushar A. Dighe.[1] *[1]Nephrology, Dr. D Y Patil Medical College, Pune, India, Pune, India; [2]shayadri hospital, kothrud, pune, Pune, India.*

Background: It is necessary to establish if azotemia is acute or chronic as it plays vital role in initiating treatment and in preventing its progression. When a patient presents with renal failure, it is often difficult to ascertain whether the individual is suffering from acute or chronic renal failure. Efforts were made to use fingernail creatinine to differentiate between the two. While some studies found this useful, there are studies which were inconclusive. OBJECTIVE: - To determine usefulness of finger-nail creatinine to differentiate between Acute Kidney Injury and Chronic Kidney Disease.

Methods: In this prospective observational cohort study conducted at tertiary health care centre, 20 patients were selected for the study. Out of which 10 patients were diagnosed as Acute Kidney Disease (AKI) and 10 patients were diagnosed as chronic Kidney disease (CKD) with 30 days of dialysis vintage. 10 healthy volunteers were also included in the study as controls. For estimating finger-nail creatinine concentrations, fingernails of all participating subjects were clipped and collected separately in plain tubes. The nails were cleaned under tap water, dried & the weight was recorded. The Nail creatinine was extracted in water first by pulverization, followed by mechanical powdering. Sample powder incubated at 45°C for 2 hrs, centrifuged and then assayed by Alkaline Picrate-method on semi Auto Biochemistry Analyzer (Robonik).

Results: We found that when nail creatinine level in AKI (30.41 +/- 4.32 micrograms/g of nails) was significantly low compared with nail creatinine in CKD (91.59 +/- 47.76 micrograms/g of nails) [p-value (Two-tailed unpaired T test) 0.0013]. However, when nail creatinine level in AKI compared with nail creatinine in healthy volunteer (33.99 +/- 4.54 micrograms/g of nails), there was no significant difference [p-value (Two-tailed unpaired T test) 0.088].

Conclusions: The finger-nail creatinine level in AKI was significantly low than finger-nail creatinine in CKD. Hence nail creatinine can be used as a one of the diagnostic tool to differentiate between AKI & CKD in patients presenting with renal failure.

SA-PO085

Use of Biomarkers in the Early Diagnosis of AKI in Critically Ill Patients: Systematic Review Luana A. Pedroso,[1] Vandack Nobre,[4] Claudmeire D. De almeida,[2] Nathalia S. De,[4] Rafael Souza,[4] Ana cristina Simões e silva,[3] Maria auxiliadora P. Martins.[4] *[1]Federal University of Minas Gerais, Ouro Preto, Brazil; [2]UFMG, Belo Horizonte, Brazil; [3]UFMG, Brazil, Belo Horizonte, Brazil; [4]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil.*

Background: Acute kidney injury (AKI) is a recognized condition among hospitalized patients and it is more common in intensive care units (ICU). AKI can be assessed by measuring serum creatinine; however, is considered a poor and delayed marker. New circulating and urinary biomarkers emerged in recent decades as promising in the early diagnosis of AKI, with better sensitivity (s) and specificity (sp) profile. Given its potential benefits in the diagnosis and prognosis of AKI, the need of using these new biomarkers in clinical practice is consensual. This study aims to perform a systematic review of literature, that evaluated the performance of biomarkers for the early diagnosis of AKI.

Methods: A systematic review of the medical literature, including experimental and observational studies published in MEDLINE, BVS, CINAHL and EMBASE, published between 2006-2016. The review will include experimental and observational studies, involving patients with 18 years or older more admitted to an ICU. The systematic review protocol was submitted and approved by the International Prospective Register of Systematic Reviews (PROSPERO), under the code CRD42016037325.

Results: Eight studies were selected. The main biomarkers investigated were neutrophil gelatinase-associated lipocalin (NGAL), L-type fatty acid binding protein (L-FABP), *N-acetyl glucosamine* (NAG) and cystatin C. In 16 out of 23 (66.7%) tests performed by the studies, analyzes have used urine samples. The biomarkers that presented the highest s and sp profile were the heat shock protein-72 (s=100%, sp=90%) and Interleukin 18 (s=92%, sp=100%). Cystatin C showed poor performance in two studies. Overall, two studies presented unfavorable results for the use of biomarker because their levels were significantly affected by comorbidities even in the absence of AKI.

Conclusions: All biomarkers have suffered some influence of other factors, such as comorbidities or etiology of AKI. An understanding of a single biomarker is unable to help identifying the etiology and mechanisms of AKI. Thus, the use of a diagnostic kit combining different biomarkers could be suggested for early diagnosis of AKI. Besides, the identification of AKI etiology may be helpful to guide the implementation strategies.

SA-PO086

A Study of Cell Therapy for Subjects With AKI Who Are Receiving Continuous Renal Replacement Therapy Brian Miller. *Sentien Biotechnologies, Inc., Medford, MA.*

Background: Sentien Biotechnologies, Inc. is developing SBI-101, a combination product containing allogeneic human mesenchymal stromal cells (MSCs) inoculated into a hollow-fiber unit for the treatment of patients with acute kidney injury (AKI) and the need for continuous renal replacement therapy (CRRT). MSCs are a unique source of therapeutic secreted factors that modulate the immune-mediated inflammatory response to acute organ injury and can enhance the repair of injured tissue. SBI-101 therapy is a novel approach designed to overcome the limitations of infusion of MSCs via the utilization of an extracorporeal, blood-contacting device. By immobilizing the MSCs outside of the patient, SBI-101 therapy is designed to facilitate dynamic, continuous blood conditioning in patients undergoing severe organ injury, including AKI requiring CRRT, combining an active therapy with standard of care for these patients.

Methods: The study is a prospective, multi-center, randomized, double-blind, sham-controlled, study of subjects with a clinical diagnosis of AKI due to various etiologies who are receiving CRRT. Subjects must have tolerated CRRT for at least 12 hours after commencement of CRRT and at the time of randomization and treatment with SBI-101. Up to 32 subjects may be enrolled to provide 24 subjects evaluable (as a per protocol population). -Low dose: (250 x106 MSCs) SBI-101 device -High dose: (750 x 106 MSCs) SBI-101 device -Control: Sham SBI-101 (no MSCs) For the low and high dose cohorts, 8 subjects will receive active treatment and 4 subjects will receive sham control.

Results: This study is actively recruiting patients with results expected in 2018.

Conclusions: This first-in-human clinical trial will evalute the safety and tolerability of SBI-101 in patients with AKI requiring CRRT. The study will also measure renal efficacy parameters as well as exploratory biomarkers chosen to characterize the pharmacodynamic effect of SBI-101 in treated subjects.

Funding: NIDDK Support, Commercial Support - Sentien Biotechnologies, Inc.

SA-PO087

Renal Recovery among Patients with AKI Who Require Outpatient Dialysis: Impact of ESRD Certification Michael Heung,[3] Maggie Yin,[3] Diane Steffick,[3] Kevin He,[1] Csaba P. Kovesdy,[4] Kamyar Kalantar-Zadeh,[2] Vahakn B. Shahinian,[3] Rajiv Saran.[3] *[1]Kidney Epidemiology and Cost Center, University of Michgian, Ann Arbor, MI; [2]University of California Irvine, School of Medicine, Orange, CA; [3]Internal Medicine - Nephrology, University of Michigan, Ann Arbor, MI; [4]University of Tennessee Health Science Center, Memphis, TN.*

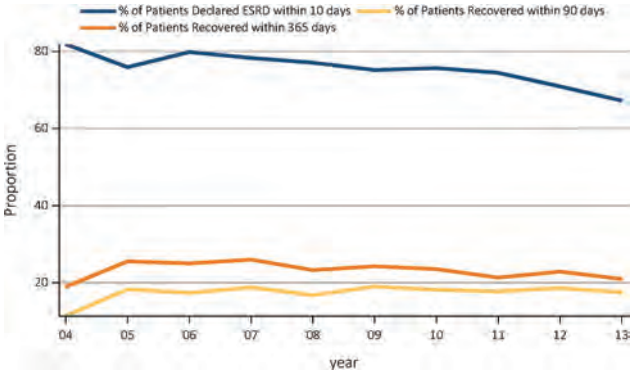
Background: AKI patients requiring outpatient dialysis are a vulnerable and growing population. We examined factors associated with ESRD certification and its impact on subsequent renal recovery.

Methods: Using a national Medicare 5% sample from 2004-2014, we identified a cohort of hospitalized patients with AKI-D who survived to discharge and required outpatient dialysis (n=5861). We compared patient characteristics between those declared ESRD (CMS Form 2728) within 10 days of hospital discharge (ESRD group) to those who were not (AKI group). We also examined renal recovery (dialysis independence for ≥30 days) at 90 and 365 days post-discharge, and time trends.

Results: Among the AKI-D outpatient cohort, 76% were declared ESRD while 24% remained AKI. There were no differences between the ESRD and AKI groups in sex or age distribution. Blacks were more likely to be ESRD than whites. The ESRD group had greater proportions of DM, CHF and pre-existing CKD. By 90 days 9.3% of ESRD and 41.2% of AKI patients recovered renal function. At 365 days these rates rose to 15.5% and 44.9%. In a multivariate model, lower odds of 90 day renal recovery were associated with ESRD declaration (OR 0.14, 0.12-0.17), CKD, CHF and black race. During the study period, a decreasing proportion of AKI-D patients were declared ESRD; 90 day recovery rates also decreased slightly, while 365 day rates remained stable (Figure). A significant proportion of AKI-D patients recovered renal function after hospital discharge, including those declared ESRD. After adjusting for clinical factors, ESRD certification remained the strongest independent predictor of renal non-recovery.

Conclusions: Further study is needed to determine the impact of ESRD versus AKI dialysis protocols on renal recovery.

Funding: NIDDK Support



Post-hospitalization outcomes for Medicare AKI-D patients, 2004-2014

SA-PO088

Risk Factors Associated with Early Mortality in Continuous Renal Replacement Therapy for AKI Haewon Lee,[1] Yang Wook Kim,[1] Bongsoo Park,[1] Sihyung Park,[1] Seok ju Park,[2] Yoo jin Lee.[1] *[1]Haeundae Paik Hospital, inje university, Pusan, Republic of Korea; [2]Inje University, Busan, Republic of Korea.*

Background: Continuous renal replacement therapy (CRRT) is a modality favored in hemodynamically unstable acute kidney injury (AKI) patients. However, the mortality of AKI is high despite the use of CRRT in intensive care units. In this study, we aimed to identify factors associated with an increased risk for 72-hour mortality in CRRT.

Methods: We conducted a retrospective observational study among 154 patients who received CRRT from March 2010 to December 2016. Laboratory parameters, demographic characteristics, administration of vasopressors, ventilator use, comorbidities, presence of anuria and fluid overload before starting CRRT were analyzed for any association with mortality.

Results: A total of 154 patients were enrolled in this study. Among them, 137 (89%) died in the ICU while on CRRT. Survivors and non-survivors showed significant differences in total bilirubin (1.61 ± 1.6 vs. 6.06 ± 7.73 mg/dl, p=0.01), mean BP (77.7 ±16.69 vs 66.91 ± 13.98 mmHg, p=0.01), systolic BP (108.53 ± 22.07 vs. 90.12 ± 19.63 mmHg, p=0.01), and amount of fluid overload for 3 days before initiating CRRT (5.02 ± 5.73 vs. 8.21 ± 5.44 L, p=0.01). Univariate analysis revealed parameters associated with mortality included ventilator use (OR 10.75, 95% CI 0.031~0.283), vasopressors (OR 4.16, 95% CI 0.085~1.71), malignancies (OR 4.76, 95% CI 0.04~0.9), and pre-CRRT fluid overload more than 2.5L (OR 3.91, 95% CI 1.06~14.3). Cox multivariate regression analysis was performed to exclude confounding factors. Use of vasopressors (HR 0.32, p=0.01), malignancy (HR 0.55, p=0.02), and pre-CRRT fluid overload (HR 0.63, p=0.03) were independent factors for death within 72 hours after initiating CRRT.

Conclusions: In conclusion, comorbidities such as malignancies, systolic blood pressure, and pre-CRRT fluid overload were closely related with 72-hour mortality in CRRT which may require close attention during ICU care. We emphasize the need to identify clinical or laboratory factors, especially those that are correctable, in the management of critical acute kidney injury.

SA-PO089

AKI Requiring Dialysis in ECMO Cristina E. Pinal,[1,2] Maaz Syed Ahmed,[1,2] Luis A. Concepcion.[1,2] *[1]Medicine, Baylor Scott&White, Temple, TX; [2]Texas A&M Health Science center, Temple, TX.*

Background: ECMO is used in critically ill patients with life threatening acute respiratory or circulatory failure. AKI requiring dialysis (RRT) is a frequent complication. Purpose: single center retrospective study to determine the incidence of AKI requiring dialysis, the outcome and survival in patients requiring ECMO.

Methods: Adult patients requiring ECMO (2012-1015) included. Demographic, laboratory and dialysis data obtained from the EMR. ECMO in VA/VV configuration by standard methods. Dialysis performed placing a dialyzer(Sorin SH14) in line w/ ECMO circuit and running dialysate (Nxstage[tm] bicarbonate based), using IV pumps 2 L per hour x 24 h a day, Ultrafiltation controlled with IV pump. No heparin used other than for the ECMO circuit. Results as mean and standard deviation, statistical analysis done w/ SPSS version 13.

Results: 169 patients, age 53(15) y, weight 92.7 (22) kg, BMI 31(6)EF 49(15)%. 77% white, 10%AA,28%DM,61%HTN 13%CKD, 41%CHD, 39% sepsis, 82% anemia(Hb<13). ECMO type:52% VA 48%VV. AKI requiring dialysis occur in 89(52.4%). Overall mortality 53%(64%VA 42%VV ECMO). The patients that required RRT had 51.7%mortality vs 54.4% not requiring RRT. Indications for RRT:75%fluid overload, 7.7%hyperkalemia, 3.6%acidosis. Within 4 days of admission 69.3%were on ECMO. Within 4 days in ECMO 60.7%of the patient with AKI required RRT.53%of the dialysis treatments done w/ 3K bath, 31% 2K, 11% 4K. The mean time on dialysis was 15.7 days(23).52.1% required 8 d of RRT and 75% required 22days of RRT. The patients had 6.7(7)liters of positive fluid balance at the start of RRT. The UF per day was 1.1(1.7)L with 75% of the patients the average daily UF was 2.3L. Serum creatinine at the start of ECMO was 1.57(1.1), at the start of RRT 2.94(1.3)mg/dl. BUN at the start of RRT was 67(37) mg/dl. The number of pressors in RRT 2.9 (1.2) vs 2.6(1.1) in non RRT patients($p<0.05$). By Kaplan-Meier analysis the median survival was 31 days(all population), No difference between VA and VV ECMO. For RRT the median survival was 41.6days, not RRT 45 days (NS) by log rank. No difference by diabetic status in survival.

Conclusions: AKI requiring dialysis is a frequent event in patients requiring ECMO. On line dialysis can be performed without the need of a dialysis machine. The mortality was not influence by the need of dialysis support in this critically ill patients. More pressors were needed in the patients that required dialysis support.

Funding: Private Foundation Support

SA-PO090

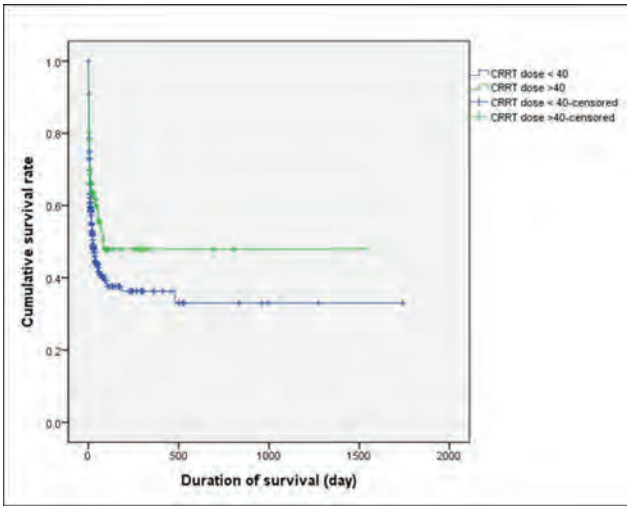
The Influence of Hypophosphatemia on Outcomes during CRRT in AKI Patients Yeonsoon Jung, Weon hyung Lee, Ho Sik Shin, Hark Rim, Hyo jong Kim, Ye na Kim. *Kosin University College of Medicine, Gospel Hospital, Busan, Republic of Korea.*

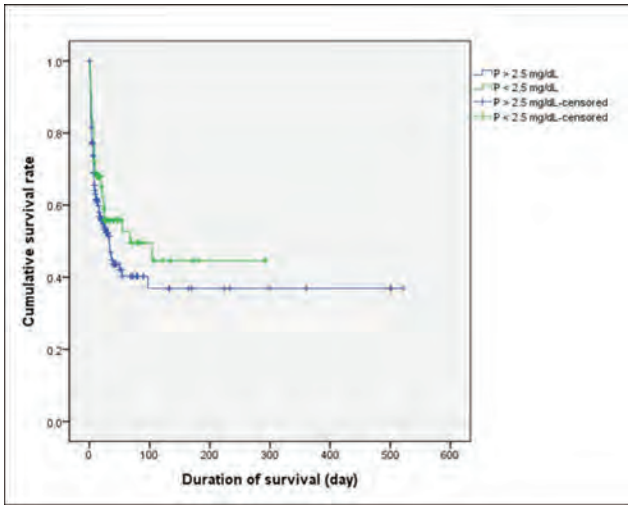
Background: To assess the role of hypophosphatemia in major clinical outcomes in patients treated with low-or high-intensity continuous renal replacement therapy(CRRT).

Methods: We performed a retrospective analysis of data collected from 620 patients. We divided the patients into two different groups of CRRT intensity (more than or less than 40 mL/kg/hour of effluent generation) and measured serum phosphate level daily.

Results: We obtained a total of 1800 phosphate measurements on days 0,1 and 2 and identified 49 patients (8%), 93 patients (15%), and 142 patients (23%) with hypophosphatemia on each of these respective days. In patients treated with lower-intensity CRRT, 23 episodes of hypophosphatemia/1000 patinet days were identified, compared with 83 episodes/1000 patient days in patients receiving higher-intensity CRRT ($P < 0.01$). Multiple Cox proportional hazards analyses showed that APACHE score, utilization of vasoactive drugs, and arterial pH on the third CRRT day were significant predictors of mortality; however, serum phosphate level was not a sinificant contributor.

Conclusions: The APACHE score, use of vasoactive drugs, and arterial pH on the 2nd CRRT day were significant predictors of mortality. Hypophosphatemia might not eb a major risk factor of increased motality in patients treate with CRRT.





SA-PO091

Effect of Low Dialysate Temperature on Blood Pressure During SLED in Patients with AKI Fahad Y. Edrees, Anitha Vijayan. *Washington University in St. Louis, St. Louis, MO.*

Background: AKI requiring RRT is associated with high mortality and morbidity. Intradialytic hypotension (IDH) may delay renal recovery by perpetuating ischemic injury. Studies have shown that lowering dialysate temperature to 35.5-36°C in ESRD patients is associated with decrease in the incidence of IDH. However, data in AKI patients undergoing CRRT or sustained low-efficiency dialysis (SLED) are scarce. We conducted a prospective, randomized, cross-over study to evaluate the effect of lower dialysate temperature on the hemodynamic status of critically ill patients with AKI during SLED.

Methods: We obtained approval from Washington University IRB. Patients were randomized to start SLED on either high (37°C) (Group A) or low (35°C) dialysate temperature (Group B) and then alternate treatments. Patients who had a single treatment, required antihypertensive medication after enrollment, or were on 3 pressers before starting treatment were excluded. SLED was performed using the NxStage System One®, with blood flow at 300ml/min and dialysate flow of 33 -126ml/min. Hypotensive event was defined by any of the following: ↓SBP ≥ 20mmHg, ↓MAP ≥ 10mmHg, decrease in ultrafiltration or change in vasopressors requirement. The number of events was analyzed by Poisson regression and other outcomes with repeated-measures ANOVA.

Results: We enrolled 21 patients who underwent a total of 78 SLED sessions, 39 in each arm. The mean age was 56.1 and mean SOFA score at time of enrollment 9.4 ± 2.6. There was doubling of hypotensive events in high temperature (1.4±1.0) compared to low temperature (0.7±0.6) sessions (P=0.007).(Table1)

Conclusions: AKI patients undergoing SLED with low dialysate temperature, experience significantly less intradialytic HoTN. Prevention of IDH may help to achieve UF targets, thereby preventing volume overload and may also help to promote renal recovery. A larger study is required to confirm our findings.

Primary and Secondary Outcomes

Outcome	Estimate ± SEM	Mean ± SEM		IRR	95% CI	p-value
		High Temp	Low Temp			
Events	0.75 ± 0.14	1.4 ± 1.0	0.7 ± 0.6	2.11	1.59 - 2.79	0.007
Ultrafiltration Difference	238 ± 104	421 ± 78	182 ± 79		21 - 456	0.03
Ultrafiltration % Achieved	-8.0 ± 4.1	84.0 ± 32.3	93.0 ± 3.3		-17 - -0.26	0.04
Lowest temp during SLED	0.02 ± 0.10	36.6 ± 0.1	36.5 ± 0.1		-0.20 - 0.23	0.88
Temp at end of SLED	0.10 ± 0.14	36.9 ± 0.1	36.8 ± 0.1		-0.19 - 0.38	0.48
Kt/Vurea	-0.03 ± 0.03	0.78 ± 0.04	0.81 ± 0.04		-0.09 - 0.03	0.28
URR	-1.71 ± 1.32	42.9 ± 2.1	44.6 ± 2.1		-4.56 - 1.14	0.22

IRR- incidence rate ratio; URR: urea reduction ratio

SA-PO092

Improving CRRT Lifespan: A QI Initiative Nathaniel C. Reisinger, Behdad Besharatian, Akash N. Sethi, Margaret Duffy, Ramnika I. Gumber, Joseph A. Messana, Jordana B. Cohen, Alan G. Wasserstein, Michael Chaknos, Dan Negoianu. *Penn, Philadelphia, PA.*

Background: Unplanned interruptions of continuous renal replacement therapy (CRRT) can impact patient care, nursing workflow, and value of care. At our center, a rapid blood flow rate (Qb) of 300 mL/min is used to minimize the need for anticoagulation. At this Qb, circuit lifespan should be 48 hours. Retrospective review of 4 weeks of data showed that over 50% of treatments last less than 24 hours. The optimal Qb to maximize filter life is not known. Furthermore, short catheter length is associated with decreased CRRT filter life in a randomized trial. We wished to explore whether increased blood flow and/or catheter position would be associated with improved filter life.

Methods: CRRT treatments were tracked prospectively for one month before and one month after our standard Qb was increased from 300 mL/min to 350 mL/min. The duration of treatment, reason for circuit discontinuation, and position of the tip of the catheter was noted. Kruskall-Wallis rank sum test was used to compare median circuit life as categorized by catheter position for the pre-intervention data set.

Results: Pre-intervention versus post-intervention, respectively, 23% versus 22% of CRRT circuits failed within 24 hours, 13% versus 13% failed between 24 and 48 hours, and 64% versus 65% expired having met their approved lifespan. Catheters in the upper 1/3 superior vena cava (SVC) had median lifespan of 36.5 hours (interquartile range 21-47). Catheters in the mid 1/3 SVC had median lifespan of 21 hours (interquartile range 14-27). Catheters in the lower 1/3 SVC had median lifespan of 48 hours (interquartile range 46.5-48). Catheters in the right atrium (RA) had median lifespan of 47 hours (interquartile range 40.5-48). p=0.0013 for the overall comparison.

Conclusions: Increasing blood flow rate to 350 mL/min did not decrease the percentage of treatments which clogged or clotted before 24 hours. However, more central catheter position was significantly associated with improved filter life. We intend to explore methods to improve catheter placement in the future.

SA-PO093

Inferior Vena Cava Diameter Correlates with Ultrafiltrate Removal in Septic Patients with AKI Jung Hee Chae,[1] Jennifer L. Waller,[1] Azeem Mohammed,[1] John J. White,[1] Matthew J. Diamond,[1] Muhammad O. Saleem,[1] N. Stanley Nahman.[1,2] *[1]Augusta University, Augusta, GA; [2]Norwood VAMC, Augusta, GA.*

Background: The physical examination in septic patients with acute kidney injury (AKI) may over or under estimate effective circulating blood volume. As a result, target ultrafiltration goals (UF) are frequently empiric, often defined in retrospect by hypotension or cardiac instability. We previously showed pre-dialysis inferior vena cava diameter (IVCD) correlated with volume removal in volume-expanded hemodialysis (HD) patients (Mohammed JASN 27:573A). In the present study, we theorized that pre-dialysis IVCD would better estimate and correlate with safe UF removal from septic AKI patients.

Methods: Septic AKI patients were studied before and during the first session of dialysis. Prior to dialysis, systolic blood pressure (SBP), the presence of rales or edema was recorded, and a UF goal was empirically assigned. Two trained operators (JC and AM) assessed IVCD using a GE Sonosite machine prior to the institution of dialysis. Linear regression (LR) was used to examine the association between pre-IVCD and volume removal.

Results: 20 septic AKI consented patients (see table) were studied: 60% black, 55% male, 70% hypervolemic (based on the presence of edema or rales), 40% on vasopressors, 55% intubated. Dialysis modalities included HD (n=16) and CRRT (n=4). Pre-dialysis parameters (mean±SD) included: age 59.7±12 yrs, SBP 128.3±22.2 mmHg, IVCD 2.65±0.7 cm. The average volume removed with dialysis was 2.50±1.9L. In the final multiple LR model, only IVCD predicted UF removal controlling for age, edema, volume status, intubation and pre-SBP, where for every one cm increase in pre-IVCD, 2.14 kg of volume was removed ($R^2 = 0.5182$, $p < 0.0003$). Neither edema nor rales was statistically predictive.

Conclusions: In septic AKI patients, the physical examination is not predictive of UF removal with dialysis, but the pre-dialysis IVCD correlates strongly with the ability to remove excess fluid. Measuring IVCD may improve UF removal estimates in septic patients with AKI, and reduce hypotensive and cardiac events associated with dialysis.

Dialysis modality	Age (yrs)	Black race (%)	SBP (mmHg)	IVCD (cm)	Volume removed (L)
HD	61.7±9.8	62.5	129.3±23.4	2.71±0.68	2.72±1.78
CRRT	52±16.5	50	124.2±11.1	2.46±0.7	1.63±1.71
Total	59.7±12	60	128.3±22.2	2.65±0.7	2.50±1.9

SA-PO094

Comparison of Measured versus Online Urea Kinetics in Patients with AKI Undergoing Hemodialysis Owais Bhatti, Yifei F. Zhang, Anitha Vijayan. *Washington University St Louis, Saint Louis, MO.*

Background: In patients with acute kidney injury (AKI) on intermittent hemodialysis (HD), KDIGO guidelines recommend a target single pool Kt/V (spKt/V) of 1.3, three times per week. Currently, the standard method of monitoring dialysis adequacy is by calculating spKt/V using pre and post serum BUN. This requires additional blood draws which are associated with nursing labor and laboratory costs. Online urea kinetic monitor systems, such as continuous dialysate UV-adsorbance monitoring, can potentially measure real time spKt/V without added cost. Unlike ESRD, AKI patients have fluctuating volume of distribution of urea and data on online urea monitoring in AKI are scarce.

Methods: We instituted a QI project to compare online monitoring to measured Kt/Vurea. After approval from the Washington University IRB we conducted a retrospective analysis of this data. For a single dialysis session per patient, spKt/V was calculated via Daugirdas equation, and compared to Kt/V measured by dialysate online urea monitoring. All patients underwent HD using B.Braun Dialog$^{+(R)}$ machines. Data were analyzed using Bland-Altman analysis.

Results: We reviewed 43 dialysis treatments of 20 patients with AKI. The mean age was 53 years, 60 % (12) were men and 65 % (13) had ATN. Bland- Altman analyses of the data showed that both methods were in agreement (Fig 1).

Conclusions: In this pilot study, data suggest that spKt/V calculated via pre and post serum BUN is comparable to the Kt/Vurea measured by continuous dialysate monitoring using UV-adsorbance. This has major implications regarding cost savings while ensuring that AKI patients are receiving adequate dialysis. A larger prospective study is needed to

determine whether online urea kinetics monitoring can be substituted for measured Kt/Vurea in patients with AKI.

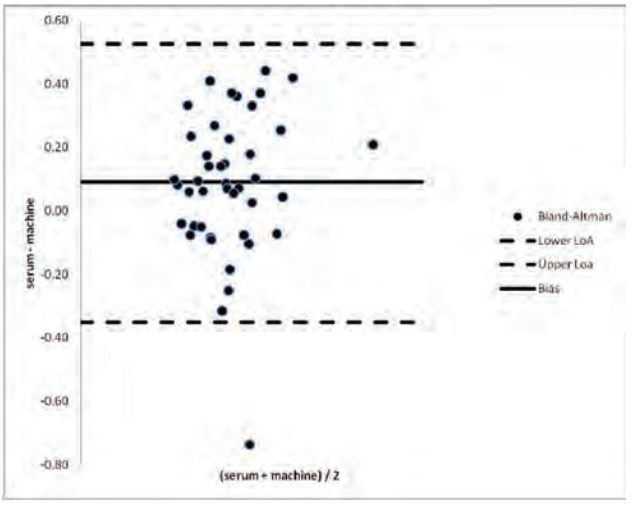


Figure 1

SA-PO095

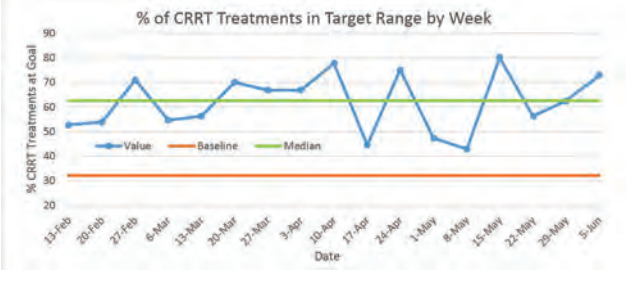
Continuous Renal Replacement Therapy Dosing in Critically Ill Patients Benjamin Griffin,[4] Amanda Thomson,[7] Mark Yoder,[2] Shannon J. Bortolotto,[3] Deb G. Bonnes,[2] Lisa M. Dufficy,[7] Adam P. Bregman,[1] Sarah Faubel,[5] Diana I. Jalal.[6] *[1]None, Denver, CO; [2]UCHealth, Aurora, CO; [3]Univeristy of Colorado Hospital/UCHealth, Aurora, CO; [4]University of Colorado, Aurora, CO; [5]University of Colorado Denver, Denver, CO; [6]University of Colorado Denver Health Science Center, Aurora, CO; [7]University of Colorado Hospital, Aurora, CO.*

Background: Continuous Renal Replacement Therapy (CRRT) is a commonly performed procedure in critically ill patients with acute kidney injury (AKI) in the intensive care unit (ICU). National guidelines from Kidney Disease Improving Global Outcomes (KDIGO) give a level 1A recommendation that CRRT should be prescribed to achieve a daily dose of 20-25 ml/kg/hr. Unfortunately, nationwide prescribing practices are quite variable, including among renal staff at the University of Colorado Hospital (UCH).

Methods: Our aim was to deliver a 20-25 mL/kg/hr average daily dose of CRRT in >80% of daily sessions. All patients at UCH who received CRRT were included. Key interventions included modifications to the CRRT flowsheet in EPIC to display actual delivered dose in terms of mL/kg/hr, development of a "CRRT Provider Protocol" to standardize CRRT delivery across the division, implementation of a CRRT didactic session within the clinical fellows' core curriculum, and an update of the standard CRRT procedure note to include the 24-hour average delivered dose. The outcome variable was % of patients with CRRT dosing in the range of 20-25 mL/kg/hr. Process variables included % of CRRT hours charted correctly by the nursing staff, and % of nephrology notes that record the dose. Balancing measures included nursing satisfaction and time spent charting.

Results: The above implementations were employed starting in February 2017. Prior to then only 32% of patients had an average daily delivered CRRT dose in the range of 20-25 mL/kg/hr. The median value since implementation in 62% (Figure 1). Nurses accurately charted the dosing variables 87% of the time when the new flowsheet was implemented, which has since risen to 96% charting accuracy. 100% of nurses surveyed feel their workload is the same or less with the new flowsheet.

Conclusions: Achieving the KDIGO recommended guidelines of delivering CRRT at 20-25 mL/kg/hr is achievable using EMR tools, and does not significantly increase the workload for nephrologists or nursing staff.



SA-PO096

Performance of Immunoglobulin E, Immunoglobulin G, and Combined Both in Predicting Minimal Change Disease before Renal Biopsy Kun-Hua Tu,[2] Cheng chia Lee.[1] *[1]Chang Gung memorial hospital, Taipei, Taiwan; [2]Chang gung memorial hospital, Taoyuan, Taiwan.*

Background: The diagnosis of minimal change disease (MCD) in adults rely mainly on renal biopsy. Procedure of renal biopsy brings not only the diagnostic benefit but also risk of complications. Although advance in image modality of percutaneous renal biopsy, biopsy-related complication still occurs. Bleeding is one of the major complications that may lead to hemodynamic instability and even death in few cases. Thus, development of model to predict MCD for high risk patients unsuitable for renal biopsy is necessary.

Methods: 142 patients with nephrotic syndrome who received renal biopsy between October 2007 and April 2011 at one tertiary medical center were enrolled in this study. Demographic, clinical, and pre-biopsy laboratory variables were retrospectively recorded and analyzed.

Results: The overall prevalence of MCD in this study was 26.8%. Age, hemoglobin levels, 24hrs urine protein, IgG, IgE differ significantly between MCD and non-MCD group. Further analyses demonstrated combined above clinical model and this two Ig risk factors (IgG < 450 and IgE > 110) exhibited best discrimination power in predicting the diagnosis of MCD, with the AUROC of 0.91 (95% CI 0.85-0.97, p<0.001).

Conclusions: The current study demonstrated that age, hemoglobin, 24-hours urinary protein are significant predictors of minimal change disease before renal biopsy. Combined above clinical model and this two Ig risk factors provide medical physician simple and valuable clinical markers to diagnose MCD. Further studies are warranted to examine the role of Ig as diagnostic, pathogenic, and prognostic marker in MCD

SA-PO097

Clinical Consequences of Different Albumin Measurement Methods in Patients with Membranous Nephropathy Coralien Vink- van Setten,[1] Anne-Els van de Logt,[1] Jack F. Wetzels.[2,1] *[1]Radboud UMC, Nijmegen, Netherlands; [2]Radboud University Medical Center, Nijmegen, Netherlands.*

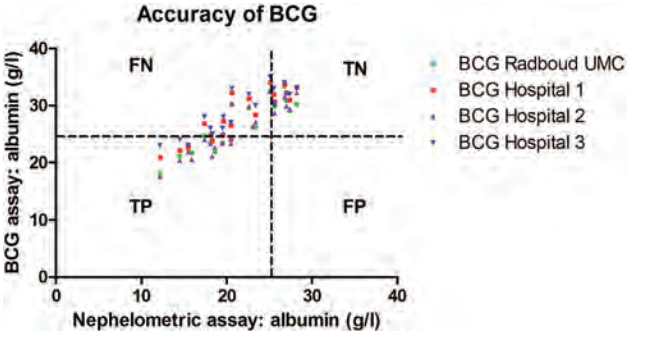
Background: Albumin levels are often used to define disease or predict risk. Cut off values are used to define nephrotic syndrome or advise toward the use of prophylactic anticoagulant therapy in patients with membranous nephropathy (MN). However, differences between albumin assays, although recognized (Bachmann 2016) are often unnoticed. In this study we aimed at quantifying differences between different albumin assays (immunonephelometry (reference), bromcresol green (BCG) and bromcresol purple (BCP)) in nephrotic patients with MN.

Methods: Plasma samples were collected from nephrotic patients with MN. Samples were stored at -80 °C. Albumin was measured with BCG, BCP and immunonephelometry in plasma in our hospital. A round robin was organized to compare the results of the BCG assay used in three regional hospitals.

Results: We included 23 MN patients (83% male), mean age was 60 ± 13 years, median serum creatinine level was 107 µmol/l (IQR 83-152) and median protein creatinine ratio 6.3 g/10 mmol (IQR 3.9-8.9). Mean serum albumin in nephelometric assay was 21.1±4.5 g/l. Whereas bias with the BCP was limited (0.3±1.8 g/l), BCG reported higher bias (5.1±1.9 g/l). Three regional hospitals, that used BCG, also reported higher serum albumin values. Variation between centers was large (Figure 1). Bias in hospital 1 and 3 was very high; respectively 6.7±2.1 g/l and 7.7±2.3 g/l. In hospital 2 a bias comparable with our assay (4.8±1.9 g/l) was noticed. Calculated accuracy of prophylactic anticoagulant therapy using a cut-off value of 25 g/l ranged between 53 % and 83 %, indicating that up to 47 % of patients might not receive appropriate therapy.

Conclusions: A large bias and impression was noticed between different albumin assays in patients with MN. The BCG assay overestimates serum albumin values. There were large between-centers differences. Inaccuracy of serum albumin assays will contribute to incorrect treatment decision. Clinicians should be aware of these variations. More attention to calibration and standardization is urgently needed.

Funding: Government Support - Non-U.S.



SA-PO098

Urinary Metabolomic Study in Patients with Membranous Nephropathy Hyung Ah Jo,[2] Seung Hee Yang,[1] Dong Ki Kim.[2] *[1]Kidney Research Institute, Seoul National University, Seoul, Republic of Korea; [2]Seoul National University Hospital, Jong ro Gu, SEOUL, Republic of Korea.*

Background: Membranous nephropathy (MN) is a leading cause of adult-onset nephrotic syndrome. Primary MN is an autoimmune disease caused by autoantibodies such as phospholipase A2 receptor antibody (PLA2RAb) and thrombospondin type 1 domain-containing 7A antibody against the podocyte antigen. Many previous studies showed that the prognosis of patients with MN can be predicted by measuring the levels of these autoantibodies. However, the treatment response varies among individuals, and adverse reaction to immunosuppressive agent (ISA) is significant. The treatment response should be optimized and the adverse reaction to ISA should be minimized. Thus, we performed a urine metabolomic study to identify the predictive biomarker of the prognosis and treatment response in patients with MN.

Methods: We used urine samples from patients with biopsy-proven primary MN that were stored at the time of kidney biopsy in Seoul National University Hospital Biobank to find differences in urine metabolites between the MN (n = 79), minimal-change-disease (n = 74), and control groups (n=82). The 800-MHz nuclear magnetic resonance-based metabolomic method was used. We investigated the urine metabolites specific to MN after excluding outliers and matching factors such as age, sex, and presence of diabetes mellitus. Serum PLA2RAb level was examined using an enzyme-linked immunosorbent assay. Hard outcome was defined as initiation of dialysis, a 50% decrease in the estimated glomerular filtration rates, and doubling of serum creatinine levels. We reviewed the association of urine metabolites with each patient's ISA response and the presence of hard outcome.

Results: After excluding outliers and matching for age, sex, and presence of diabetes mellitus, the levels of urine metabolites such as tyrosine, alanine, fumarate were higher than those measured in the control urine samples. The urinary fumarate level was significantly higher in the patients with steroid-resistant MN than that measured in the urine sample from the steroid-responsive patients. In this study, the patients with a hard outcome during the follow-up period showed urine fumarate levels 2.53-fold higher than those of the patients with a non-hard outcome.

Conclusions: Fumarate is a reliable biomarker for predicting the prognosis and treatment response of patients with MN. We have a plan to validate this metabolomic study.

SA-PO099

Dysbiosis of Gut Microbiota in Children with Relapsing Idiopathic Nephrotic Syndrome Chikushi Suruda,[1] Takahisa Kimata,[2] Sohsaku Yamanouchi,[2] Shoji Tsuji,[2] Kazunari Kaneko.[2] *[1]Department of Pediatrics, Kansai Medical University, Osaka, Japan; [2]Kansai Medical University, Hirakata-shi, Japan.*

Background: Background and Aims: Although the etiology of idiopathic nephrotic syndrome (INS) remains unknown, it is suggested that an abnormality in regulatory T cells (Treg), which have a central role in the suppression of inflammatory and allergic responses is involved. We also reported that the Treg is suppressed in number at the onset or relapse of INS in childhood (Pediatr Int., 2017). It was recently reported that *Clostridium* species, particularly clusters IV and XIVa of the genus *Clostridium* composing gut microbiota enhance the frequency of Treg in the colon. Taken together, we wonder whether a dysbiosis of gut microbiota leads to insufficient induction of Treg resulting in the relapse of INS. This study was conducted to clarify the dysbiosis in patients with INS and its association with their relapse.

Methods: Subjects and Methods: We collected naturally excreted feces (at onset of INS) from eight INS patients who relapsed (group R; median age: 3.0 years, 5 males and 3 females), four INS patients who did not relapse (group NR; median age: 4.3 years, 2 males and 2 females), and seven healthy children (group C; median age: 3.7 years, 4 males and 3 females). We conducted metagenome analysis using bacterial DNA that was extracted from the feces, The composition of colonizing bacteria was assessed by 16S ribosomal RNA gene sequencing of fecal samples using the Ion 16S Metagenomics Kit and the Ion Torrent Personal Genome Machine platform and compared the proportion of *Clostridium* species, clusters IV and XIVa of gut microbiota among 3 groups. Kruskal-Wallis test was used for statistical analysis.

Results: The proportion of *Clostridium* species, clusters IV and XIVa was significantly lower in the group R (median 0.8%) than those in the group C (14.3%) (P = 0.002, respectively). In contrast, there was no significant difference in the proportion between the group NR(11.4%) and group C (P = 0.83).

Conclusions: Discussion and Conclusion: Gut dysbiosis characterized by the lower proportion of clusters IV and XIVa of the genus *Clostridium* might be contributed to relapse of INS.

SA-PO100

Lupus Nephritis Is Linked to Immunity to an Intestinal Commensal Lachnospiracaea Species Brad H. Rovin,[1] Doua F. Azzouz,[2] Jill P. Buyon,[2] Alexander Alekseyenko,[3] Gregg Silverman.[2] *[1]Ohio State University Wexner Medical Center, Columbus, OH; [2]NYU School of Medicine, New York, NY; [3]Medical University of South Carolina, Charleston, SC.*

Background: A transmissible agent has long been suspected in the pathogenesis of SLE. We therefore investigated the potential contribution of the intestinal microbiome to LN.

Methods: Blood and fecal samples from SLE patients were obtained, unless a patient had selective IgA deficiency, prior cytotoxic drugs, or antibiotics within four months. Fecal 16S rRNA NGS was performed. Sera samples were profiled for autoantibodies. Sera from two independent lupus cohorts were studied for validation.

Results: Compared to controls, the intestinal microbiome from SLE patients (N=61) showed decreased species richness diversity. The microbiomes of patients in clinical remission (based on SLEDAI) were most similar to healthy controls, while reductions in taxonomic complexity were most pronounced in those with high disease activity. Notably, SLE patients had an overall 5-fold greater representation of a particular species in the Blautia genus of the Lachnospiracaea family of obligate anaerobic Gram-positive cocci. Abundance of this species significantly correlated with serum IgG to a cell wall moiety from a strain of this species (P=0.002, N=61, Spearman) but not with 7 other strains. There was also a significant correlation between the distribution of SLEDAI scores and levels of these circulating anti-strain IgG antibodies (P=0.02, N=48). Using antigen treated with DNAse/proteinase K, levels of IgG anti-strain antibodies were significantly higher in those with active nephritis at time of sampling compared to SLE without renal activity (Cohort 1 P=0.01 N=48; Cohort 2 P=0.001, N=53, Mann-Whitney). Levels of anti- strain antibodies also significantly correlated with high-titer serum IgG to native DNA (P<0.0001, N=27), and inversely correlated with C3 and C4 (each P<0.01, N=61). High titers of these anti-bacterial antibodies were found in active Class III, IV and V LN.

Conclusions: These findings suggest a novel paradigm for the pathogenesis of LN: Specific strains of common intestinal commensal bacteria affect IgG-autoantibody responses in patients with LN. This is reminiscent of post-streptococcal GN, although the postulated intestinal bacterial bloom occurs without clinical infection.

Funding: Private Foundation Support

SA-PO101

Molecular Profiling of the Kidney Biopsy in Class V Lupus Nephritis: Implications for Therapy Juan M. Mejia-Vilet,[1,2] Samir V. Parikh,[1] Huijuan Song,[1] Paolo Fadda,[1] Norma O. Uribe-uribe,[2] John P. Shapiro,[1] Lianbo Yu,[1] Brad H. Rovin.[1] *[1]Ohio State University Wexner Medical Center, Columbus, OH; [2]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico.*

Background: Class V lupus nephritis (LN) is often grouped with proliferative LN in clinical trials of experimental therapeutics. Given its distinctly different histology there is concern that class V patients may confound trial results of proliferative LN. We used molecular profiling of the kidney biopsy to identify potential differences in the immune pathogenesis of class V LN and proliferative LN.

Methods: Kidney biopsies from 21 patients having their first episode of LN were used. The glomeruli and tubulointerstitium (TI) were isolated by laser capture microdissection. RNA was extracted from each compartment and a panel of 578 immune-response genes was measured by Nanostring. Transcript expression was compared between proliferative (PF; classes III/IV) LN (n=7), membranous (MLN, class V) LN (n=5) and mixed (MT, classes III/IV+V) LN (n=9). Living transplant donor kidneys (n=10) were used as normal controls (NC).

Results: Principal component analysis showed clustering of patients by LN class in both renal compartments, but this was particularly striking for MLN and NC groups. A total of 42, 29 and 8 genes were differentially expressed in the glomeruli between MLN and MT, MLN and PF and MT and PF groups, respectively. Interferon-α2 (IFNA2)-regulated genes had higher expression in MLN glomeruli compared to MT and PF glomeruli. In contrast, 20 transcripts regulated by TGF-b1 had lower expression in MLN glomeruli compared to MT. In the TI, a total of 108, 21 and 25 genes were differentially expressed between MLN and MT, MLN and PF and MT and PF. In par ticular, transcripts regulated by IL-3 and IL-18 had higher expression in MLN than MT.

Conclusions: MLN has a distinctive gene expression pattern when compared to MT and PF LN which likely reflects a different pathogenesis. This has implications for treatment and for inclusion in clinical trials of experimental therapeutics.

Funding: Other NIH Support - SPARC

SA-PO102

Characterizing the Glomerular Immune Response to Induction Therapy in Lupus Nephritis (LN) through Molecular Imaging of Serial Kidney Biopsies Samir V. Parikh,[3] Ana Malvar,[1] Huijuan Song,[3] John P. Shapiro,[3] Valeria G. Alberton,[4] Juan M. Mejia-Vilet,[3] Isabelle Ayoub,[3] Anjali A. Satoskar,[3] Jianying Zhang,[3] Paolo Fadda,[3] Michael T. Eadon,[2] Daniel J. Birmingham,[3] Brad H. Rovin.[3] *[1]HOSPITAL FERNANDEZ, Buenos Aires, Argentina; [2]Indiana University Division of Nephrology, Indianapolis, IN; [3]Ohio State University Wexner Medical Center, Columbus, OH; [4]hospital Fernandez, Buenos Aires, Argentina.*

Background: The effects of LN therapy on the molecular profile of kidney is unknown. To address this question we examined the glomerular transcriptomes before and after induction therapy.

Methods: Patients with proliferative LN (n=56) were diagnosed by kidney biopsy (Bx1), treated with steroids plus cyclophosphamide (CYC) or mycophenolate (MMF) and re-biopsied after induction (Bx2). At Bx2 14 CYC and 13 MMF patients achieved a complete renal response (CR) and 6 CYC and 3 MMF patients had no response (NR). Glomeruli were isolated by laser capture microdissection and RNA was analyzed by Nanostring technology. Transcript expression was compared between Bx1 and Bx2 for each group. Only transcripts with at least 2-fold change (FC) and p<0.01 were considered differentially-expressed.

Results: After treatment, transcripts that were differentially overexpressed at Bx1 decreased in expression at Bx2 in CR treated with CYC or MMF. This included significant downregulation of pro-inflammatory, complement and fibrosis genes including *FCER1G, C1QB, CCL2, FN1, and TGFBI.* Conversely, NR after CYC showed persistent overexpression of transcripts upregulated at Bx1 and increased expression of additional transcripts including *CR1* (FC: 2.0, P=0.001), *C8G* (P=2.1, FC=0.002), *MIF* (FC-2.0, P=0.009), *STAT6* (FC: 1.9, P=0.0009) and *LGALS3* (FC: 1.9, P=0.005). NR after MMF also showed persistent overexpression of transcripts upregulated at Bx1 but also increased expression of over 20 additional transcripts, including dendritic cell, neutrophil, and NK cell signatures, such as *IL3 (FC: 2.5, P=0.0004), CSF2RB* (FC: 3.1, P=0.0001), *KLRF1* (FC: 3.4, P=0.0003), *TNFSF12* (FC: 2.7, P=0.001), *IL21R* (FC: 3.5, P=0.0003), *FN1* (FC:3.9, P=0.001), and *LAMP3* (FC:2.2, P=0.0003).

Conclusions: The glomerular immune signature in NR after MMF therapy is different than after CYC. These data suggest that different approaches may be needed to rescue NR depending on choice of induction treatment.

Funding: Other NIH Support - CCTS - Strategic Pharma-Academic Research Consortium

SA-PO103

Elevated BAFF Following Rituximab for Lupus Nephritis (LN) Is Associated with Higher Anti-dsDNA Titers in Patients with B Cell Recovery Liliana M. Gomez Mendez,[3] Matthew Cascino,[1] Brad H. Rovin,[2] Paul R. Brakeman,[3] Jay P. Garg,[1] Paul Brunetta,[1] Leonard L. Dragone.[1] *[1]Genentech, South San Francisco, CA; [2]Ohio State University, Columbus, OH; [3]UCSF, San Francisco, CA.*

Background: B-cell activating factor (BAFF) increases following B cell depletion by rituximab (RTX) in lupus. This has been associated with increased anti-dsDNA titers and may contribute to lupus relapses. The relationship between treatment with RTX, changes in BAFF, and anti-dsDNA titers at time of B cell recovery has not been previously assessed using clinical trial data.

Methods: We analyzed data from LUNAR (NCT00282347), a randomized trial that compared the addition of RTX or placebo (PBO) to background therapy of mycophenolate mofetil and steroids for the treatment of LN. At 78 weeks (12 months after final RTX infusion), linear regression was used to estimate the association between treatment, change in BAFF, B cell recovery, and anti-dsDNA titers. B cell recovery was defined as CD19 counts ≥ 50 cells/μL.

Results: Complete data was available for 99 patients. At baseline, median BAFF did not differ by treatment arm (3145 vs 3150 pg/mL) but was higher in patients who were anti-dsDNA positive (3540 vs 2380 pg/mL, p=0.002). BAFF increased in both arms at week 28 vs baseline (PBO 1674 pg/mL, p<0.001; RTX 4940 pg/ml, p<0.001). Between weeks 28 and 78, BAFF fell in both treatment arms but did not return to baseline. At week 78, 25 RTX patients had B cell recovery. In this subgroup, every increment of 1000 pg/mL in BAFF predicted a 9% higher anti-dsDNA at week 78 (p=0.019). This association was not seen among patients without B cell recovery or in PBO arm. However, absolute anti-dsDNA levels at week 78 were similar in the B cell recovery group vs patients without recovery (42 vs 24 IU/mL, p=0.8). Furthermore, anti-dsDNA levels were significantly lower in RTX-treated patients than PBO patients at week 78 (37 vs 66 IU/mL p=0.03).

Conclusions: BAFF increased in both treatment arms of the LUNAR trial, but with a larger increase in the RTX arm. In patients with B cell recovery at week 78, increased BAFF levels correlated with increased anti-dsDNA levels. Despite higher BAFF, anti-dsDNA levels remained significantly lower in the RTX group compared to the PBO group throughout 78 weeks. Therefore, the overall effect RTX has on lowering antibody titers may offset the effects of RTX-induced increases in BAFF.

Funding: Commercial Support - Genentech, Inc., South San Francisco, CA, USA

SA-PO104

Molecular Heterogeneity of the Kidney in Lupus Nephritis (LN) in Patients of Different Races and Ethnicities Isabelle Ayoub,[1] Juan M. Mejia-Vilet,[2] Daniel J. Birmingham,[1] Samir V. Parikh,[1] Huijuan Song,[1] John P. Shapiro,[1] Paolo Fadda,[1] Anjali A. Satoskar,[1] Lianbo Yu,[1] Brad H. Rovin.[1] *[1]Ohio State University Wexner Medical Center, Columbus, OH; [2]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico. Group/ Team: CKD Biomarker Consortium.*

Background: Black and Hispanic LN patients often have a more severe course and worse renal outcomes than white patients. This has been attributed to several factors, including socioeconomic status. We postulated that activation of different pathogenic pathways during LN may account, in part, for these racial/ethnic differences. To test this hypothesis the kidney transcriptomes of black, Hispanic and white patients were examined at LN flare.

Methods: Kidney biopsy was done at the first episode of LN in black (n=5), white (n=2) and Hispanic (n=3) SLE patients. All showed class III or IV LN. Glomeruli were isolated using laser capture microdissection. RNA was extracted and transcript expression analyzed by Nanostring technology. The expression of 358 immune/inflammatory genes was compared in blacks, whites and Hispanics

Results: As shown in the table, 3 transcripts were significantly upregulated and 3 transcripts were significantly decreased in glomeruli from black and Hispanic patients compared to glomeruli from white patients. Two transcripts were significantly upregulated in glomeruli from black and white patients compared to Hispanic patients (table)

Conclusions: Intra-renal molecular signatures appear to be different for the same histologic classes of LN among different races and ethnicities. The data suggest, for example, that interferonγ may be higher in black and Hispanic patients given the upregulation of SPP1 and CD276. In contrast, downregulation of the protective HLA-DRB1and HLA-DQA1 in black and Hispanic patients may predispose to more severe injury. Such differences may help explain why standard treatments appear to be less effective in black and Hispanic than white patients. Understanding these pathways may allow more targeted therapies for specific groups of patients and improve long-term kidney outcomes.

Funding: NIDDK Support

Table

Gene	Black vs White	Hispanic vs White	Black vs Hispanic	White vs Hispanic
SPP1	5.0-fold; p=0.02	6.3-fold; p=0.02	-	-
CXCL12	4.3-fold; p=0.04	6.3-fold; p=0.02	-	-
CD276	2.0-fold; p=0.02	2.3-fold; p=0.02	-	-
CD34	0.3-fold; p<0.03	0.3-fold; p=0.03	-	-
HLA-DQA1	0.04-fold; p<0.05	0.04-fold; p<0.001	-	-
HLA-DRB1	0.04-fold; p<0.001	0.017-fold; p=0.02	-	-
TNFSF12	-	-	2.3-fold; p=0.02	3.9-fold; p=0.006
NFATC1	-	-	2.0-fold; p=0.01	3.0-fold; p=0.01

SA-PO105

Anti-CRP Antibodies in Patients with Lupus Nephritis: Extended Follow-Up Satu S. Pesickova,[3,1] Martin Lenicek,[2] Romana Rysava,[3] Zdenka Hruskova,[3] Vladimir Tesar.[3] *[1]Hemodialysis unit, Dialcorp, s.r.o., Prague, Czech Republic; [2]Department of Clinical Biochemistry and Laboratory Diagnostics, First Faculty of Medicine, Charles University, Prague, Czech Republic, Prague, Czech Republic; [3]Department of Nephrology, General University Hospital and First Faculty of Medicine, Charles University, Prague, Czech Republic, Prague, Czech Republic.*

Background: Antibodies against monomeric CRP (anti-CRP-Ab) in patients with lupus nephritis (LN) seemed to be strong risk factor for poor outcome: non response to therapy, renal flare, end stage renal disease (ESRD) after two years of standard therapy, as it was shown in our previous study. The aim of this retrospective study is to verify the utility of anti-CRP- Ab in longer term follow-up.

Methods: Twenty three patients (1 male) with new diagnosis of LN proven by renal biopsy were followed-up for median (25-75%) of 8.9 (7.8-9.35) years. At the end of follow up (May 2017) renal and mortality data were collected. Unfavorable outcome was defined as ESRD, renal flare and non response to therapy. Baseline anti-CRP-Ab levels were measured by an in-house ELISA and compared regarding to the outcome (Mann Whitney test). ROC curve was constructed to define anti-CRP- Ab threshold level. Predictive value of anti-CRP-Ab positivity was tested by Fisher exact test.

Results: During the long term follow-up 1 patient (without response to therapy) died (anti-CRP-Ab positive), 6 patients experienced at least one renal flare (4 were anti-CRP-Ab positive), 3 patients progressed to ESRD (2 were anti-CRP-Ab positive). Baseline levels of anti-CRP-Ab were higher in patients with unfavorable outcome (53.9 vs 31.6 AU) p=0.023. Area under ROC curve was 0.81, sensitivity and specificity for given threshold (44 AU) was 81% and 70%, respectively. Anti-CRP-Ab positive patients seemed to have higher risk of unfavorable outcome when compared to those anti-CRP-Ab negative: OR=6.00 (0.67-75.61), p=0.089.

Conclusions: Anti-CRP- Ab seem to be promising prognostic marker of theraputic outcome. Further studies on larger groups should be performed.

SA-PO106

AKI Biomarker Expression in Glomeruli of Lupus Nephritis Biopsies Kelly V. Liang,[1] David R. Emlet,[2] Sheldon Bastacky,[1] Paul M. Palevsky,[1] John A. Kellum.[1] *[1]University of Pittsburgh, Pittsburgh, PA; [2]University of Pittsburgh School of Medicine, Pittsburgh, PA.*

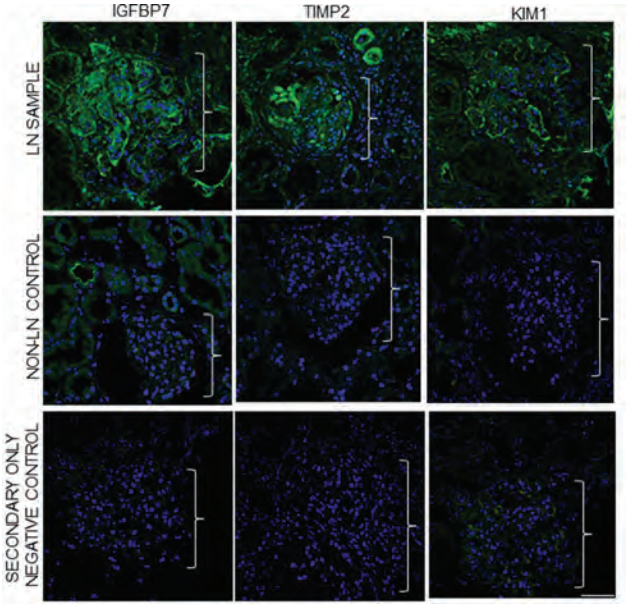
Background: Acute kidney injury (AKI) biomarkers urine insulin-like growth factor-binding protein 7 (IGFBP7), tissue inhibitor of metalloproteinases-2 (TIMP-2), and kidney injury molecule 1 (KIM-1) have been validated in critically ill as markers of tubular injury and cell-cycle arrest, but they have not been studied extensively in lupus nephritis (LN). Studies in animal models of LN suggest they may play a pathophysiologic role. Therefore, we sought to determine if IGFBP7, TIMP-2, and KIM-1 are expressed in human LN tissues.

Methods: Five frozen renal biopsies with LN class IV were identified from the Renal Pathology Department. Controls were human tissue from kidneys rejected for transplant. The samples were subjected to standard double-label indirect immunofluorescence with antibodies to IGFBP7, TIMP-2, and KIM-1 and appropriate fluorochrome-conjugated secondary antibodies. In vivo expression of biomarkers were determined semi-quantitatively using confocal microscopy.

Results: While the level of expression was variable from sample to sample, in every case, the levels of expression of IGFBP7, TIMP2, and KIM-1 were greater in glomeruli of LN biopsies compared to control kidney tissues. Figure 1 shows sample immunofluorescence images from a LN sample, a non-LN control tissue sample, and a negative control for each biomarker.

Conclusions: This is the first study to evaluate glomerular expression of TIMP-2 and IGFPB7 in glomeruli of patients with LN. IGFBP7, TIMP2, and KIM-1 expression was greater in glomeruli of LN biopsies compared to control kidney tissues. Therefore, further studies are warranted to determine if they may be useful biomarkers in LN and other glomerular disorders.

Funding: NIDDK Support



SA-PO107

Characterization of the Molecular Profile of the Kidney at the Initial Episode of Lupus Nephritis and at Renal Flare in the Same Patients Juan M. Mejia-Vilet,[1,2] Samir V. Parikh,[1] John P. Shapiro,[1] Paolo Fadda,[1] Norma O. Uribe-uribe,[2] Huijuan Song,[1] Lianbo Yu,[1] Brad H. Rovin.[1] *[1]Ohio State University Wexner Medical Center, Columbus, OH; [2]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico.*

Background: Renal flares are common in lupus nephritis (LN), and are generally treated in the same way as previous episodes of active LN. It is conceivable however, that after long-term immunosuppression the immune pathogenesis of a flare is different than the first episode of LN. We tested this hypothesis.

Methods: A cohort of 14 patients had kidney biopsies done at their first episode of LN, were successfully treated but subsequently flared and were biopsied again. These 28 pairs of renal biopsies were studied. LN class was the same between first and repeat biopsy. Glomeruli and tubulointerstitium (TI) were isolated by laser capture microdissection, RNA was extracted from each compartment and the expression of 578 immune-response genes was measured by Nanostring technology. Intra-renal transcript expression was compared between the first biopsy and the flare biopsy for each patient. Living transplant donor kidney biopsies at implantation (n=10) were used as normal controls.

Results: All patients were female and naïve to LN induction treatment at the time of the first biopsy. A principal component analysis did not show broad differences in gene expression between first and recurrent episodes of LN. However, glomeruli from flare biopsies demonstrated a significantly higher expression of complement pathway genes (CFH, C3, C1R, C1QB), TNF-regulated genes, and FN1, ITGA5, VCAM1 and IGF2R transcripts Conversely, in the TI there was lower expression of genes regulated by interferon-alpha 2 (CCL3, CXCL9, MX1, PML).

Conclusions: Although the expression of most immune genes was similar in the glomeruli and TI from initial and flare kidney biopsies, there were several differentially-expressed transcripts at flare. Knowledge of these differences may allow optimization of LN flare treatment, especially as targeted therapies become available.

Funding: Other NIH Support - SPARC

SA-PO108

Interferon-Inducible Protein 10 and Disease Activity in Patients with Systemic Lupus Erythematous and Lupus Nephritis: A Systematic Review and Meta-Analysis Pongpratch Puapatanakul,[2] Sonchai Chansritrakul,[1] Paweena Susantitaphong,[2] Somchai Eiam-Ong,[2] Kearkiat Praditpornsilpa.[2] *[1]Chonburi Hospital, Chonburi, Thailand; [2]Chulalongkorn University, Bangkok, Thailand.*

Background: There has been increasing evidence regarding correlation between serum as well as urine interferon-inducible protein 10 (IP-10) and disease activity of systemic lupus erythematous (SLE) patients.

Methods: We conducted a comprehensive search on PubMed, Scopus, and Cochrane electronic database through the end of December 2016. All studies that measured serum or urine IP-10 using enzyme immunoassay (EIA) in SLE patients with or without lupus nephritis (LN) were retrieved. Meta-analysis of correlation between each test and disease activity was performed using a random-effects model.

Results: Thirteen studies measured either serum or urine IP-10 levels in SLE/LN patients. However, only 9 and 4 studies provided adequate data of serum and urine IP-10 levels, respectively in 396 active SLE,175 active LN, 442 inactive SLE patients, and 310 non-SLE controls. Serum IP-10 levels were significantly higher in active SLE than in non-active SLE patients (mean difference [MD] 365.8 pg/mL, 95% CI 262.8 to 468.7, $p < 0.001$) but were indifferent between patients with active and non-active LN (MD 18.8 pg/mL, 95% CI -136.7 to 174.3, $p = 0.813$). Serum IP-10 also showed positive correlation with disease activity in SLE and LN patients (pooled r = 0.28, 95% CI 0.20 to 0.37, $p < 0.001$; pooled r = 0.26, 95% CI 0.08 to 0.43, $p = 0.006$; respectively). Urine IP-10 levels were comparable between active and non-active SLE patients (MD 2.44 pg/mgCr, 95% CI -0.50 to 5.38, $p = 0.10$) but were significantly higher in active LN patients compared to non-active LN patients (MD 4.57 pg/mgCr, 95% CI 1.68 to 7.47, $p = 0.002$). Urine IP-10 also had positive correlation with disease activity in SLE and LN patients (pooled r = 0.21, 95% CI 0.05 to 0.36, $p = 0.011$; pooled r = 0.40, 95% CI 0.13 to 0.62, $p = 0.005$; respectively).

Conclusions: Serum and urine IP-10 levels demonstrate positive correlation with disease activity in both SLE and LN patients. However, an increase in serum IP-10 is more pronounced in active SLE while urine IP-10 showed a significant increase mainly in active LN.

SA-PO109

The Ability of Serial Spot Urine Protein/Creatinine Ratios to Correctly Identify Proteinuria Trend in Lupus Nephritis Varies Greatly from Patient to Patient Isabelle Ayoub,[4] Ganesh B. Shidham,[1] Daniel J. Birmingham,[1] Brad H. Rovin,[3] Lee A. Hebert.[2] *[1]Ohio State University, Columbus, AL; [2]Ohio State University Medical Center, Columbus, OH; [3]Ohio State University Wexner Medical Center, Columbus, OH; [4]Medicine, The Ohio State Wexner Medical Center, Columbus, OH.*

Background: In most clinical laboratories the vast majority of testing for proteinuria in adult patients is based on spot protein/creatinine ratio (PCR). This follows KDIGO recommendations. It is widely recognized that spot PCR is more variable than 24h PCR testing. This is assumed to be a random property of spot PCR. In research, spot PCR variability is mitigated when data sets are averaged. However, in individual patient management, spot PCR's variability could confound management. Here we show for the first time that spot PCR in many patients are highly unreliable estimates of proteinuria trend.

Methods: We analyzed the variability of longitudinal testing of spot PCR and 24h PCR in 103patients with stage III or IV lupus nephritis (LN) participating in the ACCESS multicenter randomized trial. The gold standard estimate of proteinuria trend is that described by the line joining the serial 24h PCR values. To assess spot PCR reliability we compared in each patient the trend in serial spot PCR values to that of their 24h PCR trend line. Using semi-quantitative technique we stratified the patients according to whether the sequential spot PCR were deemed to be reliable, problematic or unreliable in identifying proteinuria trends based on the gold standard, the 24h PCR trend line.

Results: Of the 103 patients who had follow up testing of concurrent spot PCR and 24h PCR, 41% (42/103) had reliable, 24% (25/103) had problematic, and 35%(36/103) had unreliable spot PCR. No baseline predictors were significantly associated with any of the three categories. Patients with unreliable spot PCR were more likely to have unfavorable outcomes of their LN.

Conclusions: Clinical decision making in LN management should not be based on spot PCR testing. Instead, a reliable estimate of proteinuria magnitude can be obtained with the PCR of intended 24 hour urines that are at least 50% complete based on their creatinine content.

Funding: NIDDK Support

SA-PO110

Circulating Cell Free DNA Is Associated with Dynamics in FOXP3 Expression in Peripheral CD4+CD25+CD127+ T Cells in Patients with Lupus Nephritis

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Background: Lupus nephritis (LN) is a manifestation of systemic lupus erythematosus (SLE) associated with poor outcome. The pathophysiology of LN is multifactorial and the search continues for a set of suitable biomarkers to assess the status of the disease. Recently, attention has been drawn to abnormally elevated circulating cell free DNA (cfDNA) as a potential biomarker of SLE progression towards LN. However, it is unclear how concentrations of cfDNA correlate with the pattern and changes within functional subpopulations of T cells in LN patients. We carried our such an assessment in our study.

Methods: Forty eight LN patients were enrolled. Their blood was collected twice: at baseline and after six months for biochemical tests and biomarker evaluation. Flow cytometry was used for analysis of T cells populations for the expression of CD4, CD25, CD127 and intracellular FOXP3. cfDNA was isolated by use of QIAamp Circulating Nucleic Acid Kit (QIAGEN, Hilden, Germany).

Results: We found significant associations between cfDNA concentrations at baseline and also cfDNA change over six months with the changes in intracellular FOXP3 content in subpopulation of CD4(+)CD25(+)CD127(+) T cells.

Conclusions: CD4(+)CD25(+)CD127(+)FoxP3(+) subpopulation of T cells has been proposed to act as a suppressor of autoimmunity. The exact biomarker potential of this subpopulation of T cells in autoimmune diseases, including LN, has not been fully explored. Our study suggests that this particular subpopulation of T cells may become useful as an attractive indicator of disease activity in LN, which warrants further investigation.

Funding: Government Support - Non-U.S.

SA-PO111

Urine VCAM-1 and ICAM-1 as Biomarkers for Active and Chronic Kidney Injury in Lupus Nephritis

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Background: Urine levels of the adhesion molecules VCAM-1 and ICAM-1 may reflect active kidney disease in patients with lupus nephritis (LN), but it is unknown if these analytes are biomarkers of kidney pathology. This study investigated the relationship of urine (u)VCAM-1 and uICAM-1 to renal histology in LN.

Methods: uVCAM-1 and uICAM-1 were measured by ELISA at the time of kidney biopsy in 129 LN patients. SLE patients without kidney involvement (non-renal (nr) SLE, n=35) served as controls. Urine analyte levels were normalized to urine creatinine concentration, log-transformed and then examined in relation to ISN/RPS histologic class and specific histologic lesions using ANOVA, nonparametric Wilcoxon ranked-sum testing and linear regression as appropriate.

Results: uVCAM (R=0.57; p<0.0001) and uICAM (R=0.52; p<0.0001) correlated with proteinuria. Mean uVCAM and uICAM levels from LN patients were 5.4 and 2.2-fold higher, respectively than levels from nrSLE (p<0.0001). Significance was maintained when classes II-V LN were compared individually to nrSLE. In proliferative LN, uVCAM and uICAM levels positively correlated with biopsy activity index (R=0.32; p= 0.0037 and R=0.26; p=0.0143 respectively). uVCAM and uICAM levels were elevated in patients whose biopsies had karyorrhexis/fibrinoid necrosis (p<0.006; p<0.02, uVCAM; uICAM), hyaline deposits (p<0.006; p<0.02, uVCAM; uICAM) and PMN infiltrates (p < 0.003; p<0.03, uVCAM; uICAM). Only uVCAM was elevated in the presence of cellular crescents (p=0.002), and neither analyte reflected interstitial inflammation. Conversely, uICAM was negatively associated with biopsy chronicity index (R=0.32; p=0.0026), and was significantly lower in patients whose biopsies showed glomerular sclerosis and fibrous crescents (p=0.03; p=0.002). uICAM did not reflect interstitial fibrosis or tubular atrophy.

Conclusions: uVCAM-1 and uICAM-1 are biomarkers for glomerular injury in LN. uVCAM-1 levels reflect glomerular inflammation while uICAM-1 levels indicate chronic glomerular damage.

Funding: NIDDK Support

SA-PO112

Early Renal Response Biomarkers in Lupus Nephritis: Data from the AURION and AURA Trials

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Background: During treatment of lupus nephritis (LN) early biomarkers of complete, partial and no renal response (CR, PR, NR) would allow changing therapy in patients destined to not respond to their current treatment. Changes in complement and proteinuria after 8 weeks of therapy were shown to predict renal response at 6 months in the ALMS LN trial. To validate these biomarkers their performance was tested in the recently completed AURION and AURA LN trials.

Methods: Data was taken from the AURION 10 patient open-label study of voclosporin (VCS) 23.7 mg po BID, MMF and steroids in active LN, and from the AURA 265 patient randomized double-blind study of voclosporin in active LN. In AURA patients were dosed with voclosporin 23.7 mg po BID, 39.5 mg po BID or placebo, MMF and steroids. First morning voids (FMVs), 24 hour urine collections C3, C4 and anti-dsDNA were collected throughout. Normalization of C3 or C4 at week 12 and 25% reduction in Week 8 UPCR (25%UPCR) were used as predictors of CR at 24 and 48 weeks.

Results: In AURION, a 25%UPCR was 71% and 75% sensitive in predicting CR at weeks 24 and 48, but specificities were 33% and 25% respectively. Similar sensitivities (99% and 90%) for predicting 24 and 48 week CR were seen for a 25%UPCR, specificity remaining low (33% and 33%). In AURION C3 or C4 normalization at week 12 was not sensitive (29 and 25%), but specific (100% and 75%) for predicting 24 and 48 week CR. Similarly in AURA, C3 or C4 were not sensitive, but C3 was 80% and 81% specific while C4 was 77% and 76% specific for predicting 24 and 48 week CR. Change in anti-dsDNA has similar specificities as C3 or C4 but lower sensitivity for predicting CR at 24 and 48 weeks.

Conclusions: As active lupus nephritis flares cause damage within the renal matrix, a more rapid way of predicting CR at 24 or 48 weeks is needed. A rapid predictor should demonstrate both high sensitivity and specificity providing clinicians confidence for changing therapy earlier rather than waiting for 24 or 48 weeks. Use of a 25% reduction in Week 8 UPCR plus C3 normalization at week 12 provides clinicians a sensitive (99%) and specific (80%) method of predicting CR at 24 weeks. This same combination also provides clinicians a sensitive (90%) and specific (81%) method of predicting CR at 48 weeks. Future clinical trials should consider the use of this methodology.

Funding: Commercial Support - Aurinia Pharmaceuticals

SA-PO113

Accurately Representing the Heterogeneity of IgA1 O-Glycosylation in Patients with IgA Nephropathy

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Background: Patients with several autoimmune disorders, chronic inflammatory diseases, and some infectious diseases exhibit abnormal glycosylation of serum immunoglobulins and other glycoproteins. The biological functions of these modifications in health and disease continue to be a significant area of interest in biomedical research. Specifically, the task of defining site-specific glycoprotein heterogeneity is recognized as an area that still needs a considerable amount of effort to fully understand the role of glycan heterogeneity in biological processes and disease pathogenesis.

Methods: We have developed robust workflows for the analysis of the IgA1 clustered *O*-glycan heterogeneity in clinical samples from patients with IgA nephropathy (IGAN).

Results: IgAN is the leading cause of glomerulonephritis in the world with as many as 20-40% of patients progressing to end stage renal disease. Patients with IgA nephropathy have increased levels of nephritogenic circulating immune complexes that contain the immunoglobulin, IgA1. We and others have shown that IgA1 in patients with IgAN have altered *O*-glycan heterogeneity. This work demonstrates the progress we have made in characterizing the differing patterns of IgA1 O-glycan heterogeneity in patients with IGAN. IgA1 was isolated from serum of healthy controls and patients with IGAN, in order to determine each samples' specific *O*-glycosylation profile. Each patient's monomeric, polymeric, and circulating immune complex IgA1 were analyzed separately to determine if there was a difference in the glycan signature of the specific type of IgA1. The HR-MS profile of both the IGAN patients and healthy controls was also tested using existing lectin ELISA test for Gd-IgA1.

Conclusions: The detailed characterization of glycoprotein site occupancy and glycan heterogeneity is required for a better understanding of the biological roles of induvial glycoproteins and to determine the impact of the glycosylation on the proteins functionality. Our current results will demonstrate our ability to reliably provide quantitative comparison of individual sites of glycosylation across a range of *O*-linked glycosylation sites in order to determine a protein's Glycan Signature and how that signature relates to the proteins function. This work is supported by the NIH (GM098539).

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SA-PO114

Assessment of the Impact of Serum Levels of Gd-IgA1-Specific IgG Autoantibodies on the Prediction of the Course of Disease in Czech Patients with IgA Nephropathy Dita Maixnerova,[4] Stacy D. Hall,[1] Colin Reily,[1] Michaela Neprasova,[4] Jelena Skibova,[3] Miloslav Suchanek,[2] Eva Honsova,[3] Rhubell T. Brown,[1] Jan Novak,[1] Vladimir Tesar.[4] *[1]University of Alabama at Birmingham, Birmingham, AL; [2]University of Chemical Technology Prague, Prague, Czech Republic; [3]Institute of Clinical and Experimental Medicine, Prague, Czech Republic; [4]Dept. of Nephrology, General Teaching Hospital, 1st Faculty of Medicine, Charles University, Prague, Czech Republic.*

Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis, often leading to end-stage renal disease. The diagnosis and assessment of disease severity requires renal biopsy. Due to its inherent risks, non-invasive approaches would be very helpful.

Methods: We examined 94 patients with biopsy-proven IgAN who were assessed at the time of diagnosis for renal function, proteinuria, microscopic hematuria, and hypertension, and followed-up clinically since then. Using serum samples collected the time of diagnosis, we determined levels of galactose-deficient IgA1 (Gd-IgA1) and IgG autoantibodies specific for Gd-IgA1 (IgGAb) using lectin and immunodetection methods. Discriminant analysis and logistic regression model were used for statistical analyses.

Results: Clinical data (serum creatinine and eGFR), serum biochemical markers (Gd-IgA1, IgGAb) and histological scoring (Oxford MEST system) were used to develop a formula predicting the risk of disease progression at the time of biopsy. We observed higher levels of IgG autoantibodies in IgAN patients with progressive renal insufficiency at diagnosis compared to IgAN patients with stable renal function at the onset. We confirmed the association of IgG autoantibodies with the progression of Czech patients with IgAN.

Conclusions: Elevated serum levels of IgGAb may serve as marker of disease activity and/or decline of renal function and, thus, unfavorable predictor of disease progression in patients with IgAN. Longer clinical follow-up of this group and further evaluation of these results in larger cohorts are needed. The authors (JN, CR, BAJ) have been supported in part by grants DK106341, DK079337, DK078244, DK082753, GM098539 from the National Institutes of Health and a gift from the IGA Nephropathy Foundation of America and the authors (DM, VT) by grant LH15168 and PRVOUK- P25/LF1/2.

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SA-PO115

Proteomics of Glomeruli with IgA Nephropathy Reveals the Concomitant Abnormalities of Cytoskeleton in the Podocytes Hiroki Yamaguchi,[1] Shin Goto,[1] Yoshitoshi Hirao,[2] Bo Xu,[2] Keiko Yamamoto,[2] Suguru Yamamoto,[1] Yoshikatsu Kaneko,[1] Tadashi Yamamoto,[2] Ichiei Narita.[1] *[1]Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [2]Biofluid Biomarker Center, Institute for Research Collaboration and Promotion, Niigata University, Niigata, Japan.*

Background: Previously, extensive molecular research had been carried out to disclose the mechanism of glomerular injuries in IgAN, however, comprehensive analysis targeted to human glomeruli have been rarely reported. To investigate the molecular network of IgAN, we conducted quantitative proteomic analysis of dissected glomeruli of patients with IgAN.

Methods: We enrolled 12 IgAN patients (mean eGFR, 90.9 ml/min/1.73m^2; mean urinary protein, 0.61 g/day; crescentic lesion in kidney biopsy < 10%), and 4 nephrectomized patients due to urological cancers as normal samples (Nor). The glomerular samples were collected by laser microdissection and digested peptides were subjected to LC–MS/MS analysis. Their MS/MS spectral data were searched against Swiss-Prot database. Finally, we performed label-free quantitation using Normalized Spectral Index and extracted proteins which were significantly and distinctively expressed in glomeruli of IgAN or Nor. These proteins were assigned to web-accessible program, DAVID to discover enriched functional related-protein groups.

Results: A total of 3143 proteins were identified with peptide FDR < 1%, and 394 and 563 proteins were selected as expressed differentially in IgAN and Nor respectively. Functional annotation clustering on the glomerular proteins in IgAN ranked several metabolic and biosynthesis pathways as top categories, while that on the glomerular proteins in Nor gave higher enrichment scores to cytoskeletal proteins rich in the podocytes. Especially, the abundance of Actinin-alfa-4, synaptopodin, and RhoA-specific GEF were significantly lower in IgAN. Between the IgAN groups divided by the level of urinary protein (0.5 g/day), the expression of synaptopodin was significantly lower in the group with higher proteinuria.

Conclusions: These results suggest that mesangial inflammation in IgAN could cause the cytoskeletal abnormalities in podocytes, resulting to significant proteinuria and glomerular injury.

SA-PO116

Renal Immune Deposits of Patients with IgA Nephropathy Are Enriched for IgG Autoantibody Specific for Galactose-Deficient IgA1 Manish K. Saha,[3] Dana Rizk,[2] Stacy D. Hall,[1] Rhubell T. Brown,[3] Lea Novak,[3] Bruce A. Julian,[3] Jan Novak.[3] *[1]UAB, Birmingham, AL; [2]University of Alabama, Birmingham, AL; [3]University of Alabama at Birmingham, Birmingham, AL.*

Background: Patients with IgA nephropathy (IgAN) have circulating immune complexes (ICs) consisting of galactose-deficient IgA1 (Gd-IgA1) bound by Gd-IgA1-specific IgG autoantibodies. Some ICs deposit in the kidney, inciting injury. Renal biopsy examination by routine immunofluorescence reveals IgA, usually with C3 and variably with IgG. We assessed whether patients with IgAN have Gd-IgA1-specific IgG autoantibodies in renal biopsy tissue.

Methods: Frozen remnant renal biopsy specimens from patients with IgAN with (n=5) or without (n=10) IgG glomerular co-deposits (determined by routine immunofluorescence) and a patient with membranous nephropathy (MN; disease control) were used. Tissues were washed with PBS to remove interstitial and blood IgG. IgG from immunodeposits was then extracted by acidic buffer (*N Engl J Med* 361:11,2009). IgG concentrations were determined by ELISA. IgG molecular integrity was assessed by SDS-PAGE western blots. IgG autoantibodies were determined by their binding to Gd-IgA1 (*J Clin Invest* 119:1668,2009). Confocal microscopic evaluation was performed using frozen tissue specimens stained with fluorochrome-labeled antibodies specific for IgA, IgG, and C3.

Results: IgG was isolated from washes and extracts of all biopsy specimens, as determined by ELISA and confirmed by western blotting. This finding, suggesting that routine immunofluorescence has low sensitivity and underestimates IgG in immunodeposits, was confirmed by high-resolution confocal microscopy. Line intensity analysis confirmed co-localization of IgA and IgG. Moreover, IgG autoantibodies specific for Gd-IgA1 were detected in extracts of all biopsy specimens from patients with IgAN, but not MN control. Washes had no or very low amounts of IgG autoantibodies.

Conclusions: IgG autoantibodies specific for Gd-IgA1 were detected in renal immunodeposits of patients with IgAN, even in those without IgG by routine immunofluorescence. These findings support the pathogenic significance of IgG autoantibodies in IgAN.

Funding: Other NIH Support - National Institutes of Health Grant T32DK007545

SA-PO117

Gut Microbiota in IgA Nephropathy: What Is the Possible Association with Clinical Manifestations? Wen Tang. *Peking University Third Hospital, Beijing, China.*

Background: Few study have investigated the microbiota in IgA nephropathy (IgAN) and their association with clinical disease progression factors. In the present study, we investigated the microbiota in IgAN patients with relative normal renal function and further examed the association between clinical risk parameters of IgAN and microbial groups.

Methods: Fecal microbiota was studied in nineteen new diagnosed IgAN and fifteen matched healthy control. Microbiota composition and functional capacity were characterized using sequencing of the 16S rRNA gene on Illumina MiSeq platform Patients' clinic parameters were also collected to investigate their association with the microbiota.

Results: The proportion of *Bifidobacterium* was higher but Bacteroidetes was lower in the patients with IgAN as compared to healthy control. Additionally, CCA (canonical correlation analysis) analyse (Figure 1) revealed that Bifidobacterium was positively associated with serum IgA level and 24 hour proteinuria. Lachnoclostridium was positively associated with present of hypertension. Bacteroides and Prevotella were negative with them. Escherichia-Shigella was positive with urinary red blood cell account.

Conclusions: This study has for the first time revealed the association between microbiota and the factors associated with IgAN progression, which found that Bifidobacterium was positive associated with disease progressive factors. Further research are need to understand the potential role of the Bifidobacterim in the IgAN

Funding: Government Support - Non-U.S.

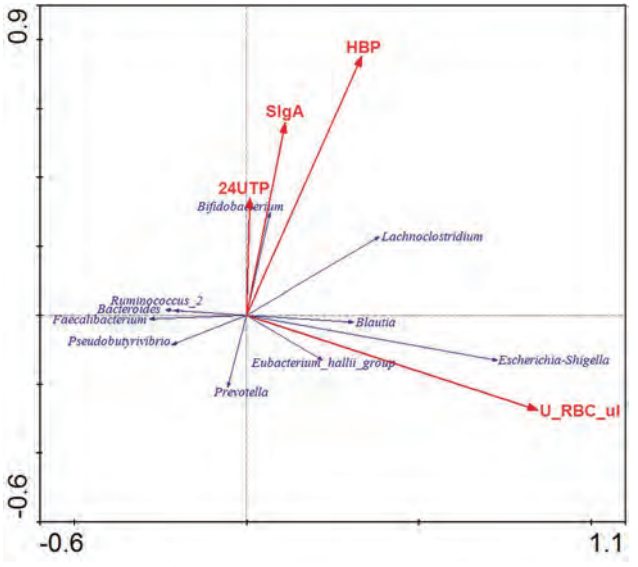


Figure 1 The correlations between bacterial community and hypertension(HBP), urine red blood cell count (U_RBC_ul), 24 hour urinary protein (24UTP) and serum IgA level (serum IgA)

SA-PO118

Plasma CX3CL1: A Biomarker Predicts Renal Inflammation and Progression of IgA Nephropathy Ran Luo, Shuiming Guo, Gang Xu, Shuwang Ge. *Dept of Nephrology, Tongji Hospital, Tongji Medical College, Huazhong Univ of Science and Technology, Wuhan, China.*

Background: Plasma biomakers of IgA nephropathy (IGAN) are still relatively unknown to date. This study was to investigate whether CX3CL1 was associated with pathology and renal outcome in IGAN.

Methods: 229 patients with IGAN diagnosed by renal biopsy between 2012 and 2014 at Huazhong University of Science and Technology Tongji hospital, were included in the study. Follow-up time was up to 42.5 months. Renal outcome was defined as composite endpoints, including ESRD and doubling of plasma creatinine. Plasma CX3CL1 level was measured by ELISA. Inflammatory cells including CD4+, CD8+, CD20+ and CD68+ cells in renal biopsy tissues were detected by immunohistochemistry. The two single nucleotide polymorphisms (SNPs) of CX3CR1, rs3732378 and rs3732379, were assessed with IGAN leukocyte.

Results: Plasma CX3CL1 levels correlated with serum creatinine (p<0.0001, r=0.344), estimated glomerular filtration rate (eGFR) (p<0.0001, r=-0.370), albumin (p=0.0002, r=-0.249). In renal biopsy specimens, the density of CD68+ (p<0.0270, r=0.461) and CD20+ (p<0.0014, r=0.363) cells was significantly associated with plasma CX3CL1. The study showed that mesangial hypercellularity (M1), endocapillary hypercellularity (E1), tubular atrophy/interstitial fibrosis (T2) according to the Oxford classification were associated with the levels of CX3CL1. ROC curve showed that plasma CX3CL1 had a predictive value for composite endpoints (cut-off CX3CL1=0.511ng/ml, AUC=0.780, sensitivity=0.818, specificity=0.693). Higher CX3CL1 predicted worse renal outcome during follow-up (Log rank, p=0.0016) by Kaplan-Meier analysis. In multivariate Cox proportional hazard analysis, CX3CL1 levels at the time of renal biopsy was found to be an independent predictor of composite endpoints after adjustment for age, gender, mean arterial blood pressure, prior tonsillectomy (per 1% increase, hazard ratio=27.94, 95% confidence interval=2.06-374.74, p=0.012). The haplotype frequency of rs3732378 and rs3732379 was 5.43% and 5.88%. There was no association of plasma CX3CL1 with these genotypes. Neither of the SNPs was associated with composite endpoints.

Conclusions: Plasma CX3CL1 correlates with IGAN pathology and prognosis. CX3CL1 may be a risk factor for progression of IGAN.

SA-PO119

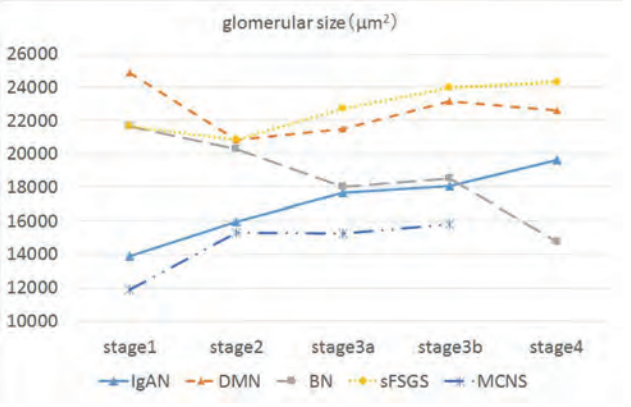
The Change in the Glomerular Size According to the Type of Glomerular Disease and the Renal Function Toshiyuki Imasawa, Masaki Uehara, Takafumi Yamakawa, Takehiko Kawaguchi. *Department of Nephrology, National Hospital Organization, Chiba-East Hospital, Chiba, Japan.*

Background: The glomerular size differs in each patient. Although it is assumed that the glomerular size should change according to the type of kidney disease and the hemodynamic state of the glomeruli, no clinical studies have investigated the impact of these factors on the glomerular size.

Methods: PAM-stained images of paraffin-embedded kidney sections were imported into a vertical slide system. The glomerular size was automatically calculated by manually outlining the glomerular tuft area on the display. We measured a total 18,673 glomeruli (with the exception of for globally sclerosed glomeruli) from 677 patients who underwent kidney biopsy in our hospital. All measurements were performed by a technical assistant in a blinded manner. In the present study, we especially focused on the glomerular sizes of patients with IgA nephropathy (IgAN) (n=212), diabetic nephropathy (DMN) (n=107), benign nephrosclerosis (BN) (n=78), and secondary focal segmental glomerulosclerosis (sFSGS) (n=53), and minimal change nephrotic syndrome (MCNS) (n=28). We also analyzed the glomerular sizes in patients with each stage of CKD.

Results: As shown in Figure, in CKD stages 1 and 2, the glomerular sizes of patients with diabetic nephropathy, benign nephrosclerosis, and secondary FSGS were significantly larger in comparison to patients with IgAN or MCNS ($p < 0.05$). In DMN and sFSGS, the sizes are similar in all CKD stages, while those in BN gradually decreased with the progression of the CKD stage. Conversely, the glomerular sizes of patients with IgAN gradually increased with the progression of the CKD stage.

Conclusions: The changes in glomerular size depend on the individual kidney disease. The pattern of the changes that occur with the progression of CKD should also differ according to the kidney disease.



SA-PO120

Transcriptomic Profiling of BTBRob/ob and eNOS-/-db/db Kidneys Sheds Light on Contrasting Morphological Phenotypes Anette E. Ericsson,[4] Anna Reznichenko,[4] Haichun Yang,[1] José Sanchez,[3] Lena William-Olsson,[4] Magnus Soderberg,[2] Agnes B. Fogo,[1] Anna Granqvist.[4] *[1]Department of Pathology, Microbiology and Immunology, Vanderbilt University School of Medicine, Nashville, TN; [2]Drug, Safety and Metabolism, AstraZeneca, Gothenburg, Sweden; [3]Discovery Sciences, AstraZeneca, Gothenburg, Sweden; [4]Innovative Medicines and Early Development, Cardiovascular and Metabolic Diseases, AstraZeneca, Gothenburg, Sweden.*

Background: There is a need for robust and translatable pre-clinical models for diabetic nephropathy (DN). The BTBRob/ob and eNOS-/-db/db mouse models develop progressive albuminuria and morphological lesions resembling early to moderate human disease. Mesangial expansion was evident in both models, however, podocyte foot process effacement was only local and minor in BTBRob/ob but widespread in eNOS-/-db/db.

Methods: This prompted us to perform RNA sequencing of kidney cortex and isolated glomeruli with parallel analysis of blood glucose, UACR and histology. To test whether transcriptional differences underlie the histologically disparate phenotypes, we performed an unbiased as well as targeted analysis of the RNA-seq data comparing expression profiles of a panel of known glomerular cell-specific markers that included genes for podocytes (n=50), mesangial (n=53) and glomerular endothelial cells (n=19).

Results: Obesity and hyperglycemia were present (BTBRob/ob, 16.5±2.0 mM; eNOS-/-db/db 16.1±2.5 mM blood glucose) as well as significant albuminuria in both models (BTBRob/ob, 10-fold vs lean; eNOS-/-db/db, 14-fold vs lean) at 20 (BTBRob/ob) and 18 (eNOS-/-db/db) weeks age. Transcriptomic analysis revealed a set of podocyte markers exclusively modulated in eNOS-/-db/db but not BTBRob/ob (Cd80, Kirrel, Nes, Podxl, Efnb1, Actn4, Utrn), while endothelial genes Eng, Pecam1, Kdr, Ehd3, Flt1, Tek, and Emcn were modulated in BTBRob/ob only. A number of these genes were also changed in glomeruli from human DN biopsies.

Conclusions: In summary, the two models share features of DN, however the eNOS-/-db/db mouse present more pronounced glomerular injury and podocyte effacement. Identified gene signatures suggest that the phenotype in eNOS-/-db/db has a stronger component of podocyte changes whereas BTBRob/ob has a stronger endothelial component, which may explain in part some of the differences in morphology and will be the subject for further studies.

Funding: Commercial Support - AstraZeneca

SA-PO121

High Protein Diet Accelerates Development of Diabetic Nephropathy in db/db Mice Sisse A. Nørgaard,[2,3] Dorte B. Sørensen,[3] Elisabeth D. Galsgaard,[1] Fredrik Wolfhagen Sand,[2] Henrik Søndergaard.[4] *[1]Liver Disease Pharmacology, Novo Nordisk A/S, Maaloev, Denmark; [2]Diabetes & Cardiovascular Pharmacology, Novo Nordisk A/S, Måløv, Denmark; [3]Veterinary Disease Biology, University of Copenhagen, Copenhagen, Denmark; [4]Diabetes Complications Pharmacology, Novo Nordisk A/S, Måløv, Denmark.*

Background: Diabetic and obese db/db mice are widely used in diabetic nephropathy (DN) research. However, this model only mimics the early changes in human DN with mild albuminuria and mesangial expansion (ME) as primary readouts. Both in humans and in diabetic models, a high protein diet (HPD) has been reported to affect the progression of nephropathy. Here, the objective was to explore if a HPD could accelerate nephropathy in db/db mice with the perspectives to study more advanced aspects of DN (e.g. interstitial fibrosis) and improve the therapeutic window.

Methods: 32 diabetic (C57BLKS-Lepr$^{db/db}$) and 20 non-diabetic (C57BLKS-Lepr$^{db/+}$) were fed either regular chow diet (21 kcal% protein) or HPD (60 kcal% protein) from 6 weeks of age (WoA) until termination at 21 WoA. In-life readouts were: body weight, blood glucose (BG), %HbA1c and albuminuria. At termination the kidneys were weighed and processed for histology and qPCR analysis. ME was scored on a scale from 0 to 3, on blinded PAS stained sections.

Results: Feeding db/db mice HPD was well tolerated and all db/db mice were diabetic throughout the study (BG >16.6mM) although mildly reduced compared to db/db mice fed regular chow. HPD increased albuminuria more than 10-fold at 21 WoA and kidney size at termination compared to db/db mice fed regular chow. The ME score revealed a significant increase in db/db mice on HPD compared to regular chow ($p<0.0001$). Further histopathological assessment of renal lesions (e.g. fibrosis) and gene expression profiling of the kidney by qPCR will be performed to extend these findings. No changes were found in db/+ mice given HPD for either of the readouts.

Conclusions: Feeding db/db mice HPD instead of regular chow seems to accelerate the development of diabetic nephropathy without affecting lean non-diabetic mice. Thereby, HPD could potentially improve the overall quality of this model through an accelerated disease progression and an increased therapeutic window. Further histopathological assessment of the kidney will reveal if HPD additionally enhances other readouts associated with advanced nephropathy e.g. fibrosis.

Funding: Commercial Support - Novo Nordisk A/S, Government Support - Non-U.S.

SA-PO122

Linagliptin Treatment versus RAAS Inhibition Alone Improves Murine Diabetic Nephropathy Anna Batorsky,[2] Monica Sanchez avila,[2] Kelly L. Hudkins,[1] Charles E. Alpers.[3] *[1]University of WA, Seattle, WA; [2]University of Washington, Seattle, WA; [3]University of Washington Medical Center, Seattle, WA.*

Background: Linagliptin (LIN) and other DPP4 inhibitors have proven effects as treatments for diabetes (DM), but the renal benefit is not well understood. We explore effects of LIN, and LIN in combination with the ARB, losartan (LOS), on diabetic nephropathy (DN). The leptin-deficient BTBR *ob/ob* (OB) mouse is shown to mimic morphologically advanced human DN and type II DM. Administration of leptin (LEP) is shown to reduce body weight by 20-40%, return mice to normoglycemic levels, and improve functional and structural characteristics of DN.

Methods: Cohorts of female mice (n=12) were treated with LIN (83mg/kg in chow), LOS (100mg/mL in drinking water), combined LIN/LOS or LEP for 6 weeks starting at 18 weeks of age. We collected 6-hour fasting glucose and protein excretion measurements for all mice at 18 and 24 weeks. Baseline structural characteristics for WT and OB mice were determined by sacrificing untreated mice at 18 weeks. Glomerular abnormalities assessed at 24 weeks include expansion of silver stained mesangial matrix by computer morphometry, and podocyte density using the p57 marker of mature podocytes. Renal function was assessed by measurement of urine albumin/creatinine ratio (UACR) and measurement of 8-OHdG in urine as a marker of DNA/RNA damage.

Results: LIN-treated mice exhibit reduced mesangial expansion (13.6% silver positive matrix per glomerular cross section) compared to untreated mice (18.4%) at 24 weeks ($p=0.02$). Treatment with LOS, or LIN/LOS resulted in statistically significant reduction in UACR when paired 18 and 24 week urine samples were analyzed ($p=0.032$, 0.035 respectively). An ELISA assay for 8-OHdG in urine showed all treatment groups have significantly lower levels of oxidative damage compared to untreated controls at 24 weeks (WT 28.2, 24wk OB 93.1, 24wk OB LIN 35.4, 24wk OB LIN/LOS 30.5, 24wk OB LOS 41.4, 24wk OB LEP 39.6 ng 8-OHdG/mg Cre, $p<0.001$). LEP-treated mice had restored podocyte density, but no significant difference was detected between other treatment groups and untreated controls.

Conclusions: Our results suggest that DPP4- and RAAS-inhibition may ameliorate features of DN via mechanisms independent of restored podocyte density.

Funding: Commercial Support - Boehringer Ingelheim

SA-PO123

Omentin1 Ameliorates Hyperglycemia or Hypoxia-Induced Podocyte Dysfunction by Activating AMP-Activating Protein Kinase Hidetoshi Kobayashi, Fumihiko Furuya, Toshihisa Ishii, Kenichiro Kitamura. *University of Yamanashi, Chuo, Japan.*

Background: Increased albuminuria is associated with the loss of capillary wall permselectivity in podocytes and is one of the risk factors for end stage kidney disease (ESKD). Omentin1 is an adipocytokine and has anti-inflammatory and anti-atherogenic properties. The aim of this study is to elucidate whether serum omentin1 levels are associated with the progression of diabetic kidney disease (DKD) and to explore the molecular mechanisms by which omentin1 induces anti-diabetic properties.

Methods: One hundred twenty-five diabetes patients were followed up for 7 years. Logistic regression models were used to evaluate the association with progression of DKD. To explore the protective function of omentin1, we focused on the AMPK pathway in podocytes. We exposed cultured podocytes to hyperglycemia or hypoxia and analyzed the kinase activities and the expression of downstream pathway in the presence or absence of omentin1.

Results: During the observation, progression either to the next albuminuria level in 16 patients or to ESKD occurred in 5 patients. In these progressors of DKD, baseline of serum omentin1 was significantly low compared with non-progressors. Multiple regression analysis revealed that a significant inverse association between serum omentin1 levels and the progression of DKD. In cultured podocytes, omentin1 administration was associated with increased activity of AMPK, and AMPK activation reduced podocyte permeability to albumin and podocyte dysfunction under hyperglycemia or hypoxia, as evidenced by zona occludens1 translocation to the membrane. These omentin1-induced activation of AMPK pathways are mediated through the adiponectin receptor1 (AdipoR1) in podocyte since it was diminished by siRNA-mediated knockdown of AdipoR1. These effects seemed to be caused by reduction of oxidative stress, as AdipoR1 and AMPK activation both reduced protein levels of NADPH oxidative Nox4 in podocytes.

Conclusions: Decreased serum omentin1 levels predict the progression of DKD in diabetes patients. Our in vitro findings demonstrated that omentin1-bound AdipoR1 is one of the key regulator of albuminuria and progression of DKD, likely acting through the AMPK pathway to modulate oxidative stress in podocytes.

SA-PO124

Inappropriate Expression of Angiopoietin-Like 2 Promotes Podocytes Dysfunction by Activating Focal Adhesion Kinase in Diabetic Kidney Disease Toshihisa Ishii, Fumihiko Furuya, Hidetoshi Kobayashi, Kenichiro Kitamura. *University of Yamanashi, Chuo, Japan.*

Background: Angiopoietin-like protein 2 (Angptl2) is an adiopokine which was secreted by adipose tissue or macrophages and that its circulating level was closely related to systemic insulin resistance, and inflammation in both mice and humans. We assessed the relationship between Angptl2 and the prevalence of the progression of diabetic kidney disease (DKD) and clarified the molecular mechanism of Angptl2-associated dysfunctions of podocytes.

Methods: One hundred forty eight diabetes patients were followed up for 7 years. Logistic regression models for the progression at every stage of DKD were used to evaluate the predictive value of Angptl2. The potential benefit of using Angptl2 alone or together with albumin excretion rate (AER) and eGFR was assessed by receiver operating characteristic (ROC) curve analysis. Furthermore, we investigated the expression of Angptl2 in macrophages and the effects of recombinant Angptl2 on podocyte *in vitro*.

Results: Progression of DKD was defined as the passage from one stage to the next based on AER or eGFR. The odds ratio for the prevalence of the presence diabetes, fatty changes of liver, and chronic kidney disease increased with higher serum Angptl2 levels. Cohort study indicated that baseline of Anptl2 was an independent predictor of progression at all stages of DKD. Reduced leukocyte DNA methylation in the promoter region of Angptl2 is associated with the pro-inflammatory environment that characterized with diabetic patients with ESKD from controls. In murine podocytes, Angptl2 induced the activation of focal adhesion kinase (FAK) via integrin α5β1-integrin-linked kinase and translocation of zona occludens-1 in the membrane and alubumin permeability.

Conclusions: Increased serum Angptl2 levels predict the progression of DKD in diabetes patients. Our in vitro findings suggest that Angptl2 is a key regulator of albuminuria, likely acting through the FAK pathway.

SA-PO125

Role of Wnt-β Catenin Pathway in Mediating Salutary Effects of Paricalcitol in Experimental Diabetic Nephropathy Sharma S. Prabhakar, Madhura Bose. *Texas Tech University Health Sciences Center, Lubbock, TX.*

Background: Diabetic nephropathy (DN) remains the most frequent cause of end stage renal disease but its pathogenesis remains unclear and consequently the treatment is not optimal. Many investigations including ours have shown renoprotective effects of paricalcitol (PAR) in DN. The aim of the current studies is to examine the role of Wnt- β catenin signaling in the beneficial effects of PAR in DN.

Methods: Obese ZSF rats, an established model of DN (type 2 diabetes), were treated with PAR (0.2 μg sc. twice a week) for 10 weeks from 21 weeks of age while control rats received none. Urine and blood samples were collected at the start and end of study. At 31 weeks rats were sacrificed, kidneys harvested and homogenates of one kidney in each rat were used to study expression of Wnt proteins and other pathogenic mediators by immunoblotting while the other kidney was used for RNA isolation and Next Gen

Sequencing (NGS) analysis. Kidney RNA seq data from ZSF obese and PAR treated rats were compared. Genes that were significantly altered based on 95% confidence and Log 2 fold change were filtered and mapped to canonical pathways in the IPA Knowledge Base. The dataset was filtered and a student t test was used to identify the genes most significantly altered following PAR treatment.

Results: PAR decreased proteinuria (970 mg/dl vs.1750 mg/dl in control) and slowed the decline of GFR (Ccr 3.6 L/Kg/BW vs.2.7 L/Kg/BW in control) in obese ZSF rats. NGS analysis of kidneys revealed that Wnt-β catenin signaling (which was differentially expressed compared to non-diabetic lean ZSF rats, per previous studies) is significantly altered in treated rats suggesting that changes in these pathways could account for the salutary effects of PAR. Western blot data confirmed that PAR inhibited the expression of many proteins in the Wnt signaling pathways specifically Wnt-3, Wnt-11 and c-myc. Other significant changes included Nitric Oxide, and OX-40 pathways in NGS and upregulation of phospho-eNOS, and inhibition of CTGF and NFkB protein expression.

Conclusions: We conclude that Wnt- β catenin is one of the important canonical pathways differentially modified by PAR and inhibition of Wnt proteins, along with changes in eNOS and CTGF may significantly contribute to renoprotective effects of PAR. These observations could potentially aid the development of novel therapies for DN.

Funding: Private Foundation Support

SA-PO126

Effective Therapy of Type 2 Diabetic Nephropathy by Protecting Pancreatic and Glomerular Endothelium with AAV10.COMP-Ang1 Yufeng Huang, Mi Tian, Li Tang, Christof Westenfelder. *Division of Nephrology, University of Utah Health, Salt Lake City, UT.*

Background: Diabetic hyperglycemia causes progressive and generalized damage to the microvasculature. In the kidney, this results in the loss of podocytes and thereby constitutive angiopoietin (Ang)-1 signaling required for maintenance and stabilization of the glomerular endothelium. As a consequence, glomerular endothelial cells are damaged, leading to leakage, glomerulosclerosis, and renal failure, i.e., diabetic nephropathy (DN). Therefore, we hypothesized that replacing Ang1 by constitutively expressing it with the plasmid AAVrh10.COMP-Ang1 would improve glomerular architecture and function thereby reducing glomerulosclerosis in db/db mice, a model of T2DM.

Methods: Uninephrectomy was performed on all experimental mice at 8 wks of age. Three groups included non-diabetic db/m, untreated diabetic db/db control and diabetic db/db mice treated with a single dose of AAVrh10.COMP-Ang1 ($2x10^{11}$ particles) injected via left carotid artery at 10 wks of age.

Results: The overexpression of COMP-Ang1 was confirmed not only in glomeruli but also in pancreatic and hepatic capillaries, which corrected the diabetes-induced dysregulation of tissue Ang2/Ang1 balance. Untreated db/db mice had substantial hyperglycemia (BG, 576±31mg/dl; Hb1Ac, 11.3±1.3%) and developed progressive increases in albuminuria and glomerular mesangial matrix expansion, associated with increased renal PAI-1, a1(IV) collagen and fibronectin expression compared with db/m mice at 18wks of age. Treatment with COMP-Ang1 yielded a significant reduction of glycemia (BG, 241±193mg/dl; Hb1Ac, 7.2±1.5%) and slowed the progression of albuminuria and glomerulosclerosis in db/db mice by 70% and 61%, respectively. Furthermore, renal expression of NF-kBp65, Nox2 and p47phox and pancreatic production of myeloperoxidase were increased while tissue SirT1 levels were decreased in untreated db/db mice, which were ameliorated by COMP-Ang1 overexpression.

Conclusions: These observations confirm our hypothesis and suggest that overexpression of COMP-Ang1 locally not only improves pancreatic function but also slows the progression of diabetes-associated glomerulosclerosis by improving both pancreatic and glomerular endothelial function via potently stimulating Ang1-Tie2 signaling. We conclude that upregulation of Ang1 expression locally has promise in improving glucose control and DN in T2DM.

SA-PO127

Intraperitoneal Administration of Human "Neo-Islets" Composed of Equal Numbers of Mesenchymal Stem and Pancreatic Islet Cells Durably Corrects Hyperglycemia in Diabetic NOD/SCID Mice Christof Westenfelder, Anna Gooch, Zhuma Hu, Ping Zhang. *University of Utah and VA Medical Centers, Salt Lake City, UT.*

Background: Globally, individuals with autoimmune Type 1 Diabetes mellitus (T1DM) continue to depend for survival on insulin injections. While pancreas and intrahepatic pancreatic islet transplants can produce insulin-independence and ameliorate serious complications, both therapies depend on potentially toxic anti-rejection drugs. Furthermore, the scarcity of pancreas donors, islet transplant failures, and the inability to adequately culture expand insulin-producing β-cells significantly limit the general availability of such and other cell-based interventions. Encapsulation of islets to protect them from allo- and auto-immune destruction has shown both promise and failures. We reported recently [STEM CELLS Translational Medicine, 7, 2017] that allogeneic "Neo-Islets" (NI) are immune protected and correct autoimmune diabetes in NOD mice. Furthermore, we are conducting an FDA-approved Pilot Study with canine NIs in insulin-dependent dogs using identical technology. As there remains a critical need for curative therapies of T1DM, we engineered human NIs and tested their ability, after i.p. administration, to reestablish euglycemia in streptozotocin (STZ)-diabetic NOD/SCID mice.

Methods: We generated *ex vivo* islet-sized NIs in which culture-expanded islet cells were aggregated in cell clusters with equal numbers of MSCs. NIs (5x10e6/kg b.wt.) or vehicle were administered i.p. to groups (n=6 each) of STZ-diabetic NOD/SCID mice.

Results: This minimally invasive i.p. administration of NIs durably normalized blood glucose levels in diabetic NOD/SCID mice. This was achieved by the spontaneous engraftment of NIs in the animals' omenta, and spontaneous redifferentiation of NI-intrinsic islet cells that physiologically secrete insulin into the hepatic portal vein.

Conclusions: Human NIs, as engineered here, show promise as a novel therapy that, we posit, has significant translational relevance to clinical T1DM. Specifically, this technology addresses the need for anti-rejection drugs and overcomes the scarcity of suitable donors.

Funding: Commercial Support - SCT

SA-PO128

A Novel SHIP2 Inhibitor Reduces the Catalytic Activity of SHIP2 in Kidney, Muscle, and Liver and Enhances Insulin Sensitivity Sanna H. Lehtonen,[2] Zydrune Polianskyte-prause,[2] Tuomas A. Tolvanen,[2] Sonja Lindfors,[2] Kanta Kon,[3] Hong Wang,[2] Vincent Dumont,[2] Per-Henrik Groop,[1,5] Tsutomu Wada,[3] Hiroshi Tsuneki,[4] Toshiyasu Sasaoka.[3] *[1]Folkhälsan Institute of Genetics, Folkhälsan Research Center, University of Helsinki, Helsinki, Finland; [2]Department of Pathology, University of Helsinki, 00290 Helsinki, Finland; [3]University of Toyama, Toyama, Japan; [4]University of Toyama, Toyama, Japan; [5]Division of Nephrology, Helsinki University Hospital, Helsinki, Finland.*

Background: The expression of lipid phosphatase SHIP2 is elevated in kidney, muscle and adipose tissues in experimental models of diabetes. Thus, SHIP2 is a potential therapeutic target to treat diabetic kidney injury and insulin resistance. To date, only few chemical compounds possessing an inhibitory effect on SHIP2 are known. All of them have poor bioavailability and none have reached clinical use.

Methods: To identify novel small molecules that inhibit SHIP2 we performed virtual screening of chemical libraries. The most potent SHIP2 inhibitors were validated by using recombinant SHIP2 fusion protein, cultured cells and diabetic db/db and SHIP2 overexpressing (SHIP2-Tg) mice.

Results: Virtual screening of chemical libraries containing 88680 molecules revealed compound II as a potential SHIP2 inhibitor. Compound II inhibits the catalytic activity of the recombinant SHIP2 phosphatase domain with an IC_{50} value of 0.75 μM. It also inhibits the activity of SHIP2 in cultured podocytes, myocytes and hepatocytes. Compound II increases glucose uptake in myocytes, and SHIP2 overexpression abrogates its insulin-mimetic properties. Treatment of SHIP2-Tg mice for 12 days with compound II reduces SHIP2 activity in kidney, skeletal muscle and liver and enhances insulin sensitivity. Treatment of db/db mice with compound II for 10 weeks enhances insulin sensitivity, decreases SHIP2 activity in the kidney and tends to reduce urinary albumin excretion.

Conclusions: Compound II inhibits the activity of SHIP2, enhances glucose uptake, and increases insulin sensitivity of both SHIP2-Tg and db/db mice. The db/db mice also show a trend of reduced albuminuria. This highlights the potential of SHIP2 as a drug target to treat diabetic kidney injury and insulin resistance. The data also propose that compound II and its derivatives have potential to be used for developing new insulin sensitizers.

Funding: Private Foundation Support

SA-PO129

Phenotype Agglomeration Analysis of Clinical and Histological End Points of Diabetic Kidney Disease Defines Modules with Improved Transcriptional Associations Paolo Guarnieri,[1] Jonathan Hill,[1] Viji Nair,[2] Jennifer L. Harder,[2] Junke Wang,[1] Julie Hawkins,[1] Steven S. Pullen,[1] Robert G. Nelson,[3] Carine Boustany,[1] Behzad Najafian,[4] Michael Mauer,[5] Matthias Kretzler.[2] *[1]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; [2]University of Michigan, Ann Arbor, MI; [3]National Institutes of Health, Phoenix, AZ; [4]University of Washington, Seattle, WA; [5]University of Minnesota, Minneapolis, MN.*

Background: Diabetic kidney disease (DKD) is the primary cause of end stage renal disease worldwide. While the structural and functional determinants of DKD have been studied extensively in various populations, comprehensive aggregation of longitudinal phenotypic measures with molecular mechanisms is lacking.

Methods: We collected an extensive set of clinical and histological endpoints from a cohort of 70 Pima Indians with type 2 diabetes and DKD. Patients underwent annual research examinations that included measurement of glomerular filtration rate (GFR, iothalamate) and had 2 research kidney biopsies performed 10 years apart. We developed a method in which missing values were interpolated with the mean, normalized and log transformed, if applicable. For inter-related traits only the most representative measurement was selected. The remaining traits were then clustered across samples balancing silhouette coefficients with minimum cluster size. A single composite trait – eigentrait – was then generated by averaging its components. Weighted gene co-expression network analysis was used to generate modules of genes with highly correlated expression, associated with either measured traits or eigentraits. Enriched biological functions were determined using Ingenuity Pathway Analysis on composite genes of significantly associated modules.

Results: We identified 7 eigentraits defining modules of mixed clinical and histological endpoints. A highly robust module included the slope of GFR, glomerular basement membrane thickening and mesangial expansion, and was associated in the first biopsy with immune cell migration while in the second biopsy with extracellular matrix synthesis, thereby supporting a role for inflammation in the initiation of DKD.

Conclusions: Phenotype agglomeration analysis provided a means of distilling biologically meaningful signals from a complex collection of traits in Pima Indians with DKD.

Funding: Commercial Support - Boehringer Ingelheim

SA-PO130

Adiposity and Renal Hemodynamic Function in Adults with Longstanding Type 1 Diabetes with and without Diabetic Kidney Disease Petter Bjornstad,[1] Julie A. Lovshin,[9] Yuliya Lytvyn,[9] Genevieve Boulet,[4] Leif E. Lovblom,[3] Omar N. Alhuzaim,[9] Mohammed A. Farooqi,[5] Vesta S. Lai,[8] Josephine Tse,[8] Leslie Cham,[7] Andrej Orszag,[6] Alanna Weisman,[9] Hillary A. Keenan,[2] Michael Brent,[9] Narinder Paul,[8] Vera Bril,[9] Bruce A. Perkins,[9] David Cherney.[9] *[1]Children's Hospital Colorado, Aurora, CO; [2]Joslin Diabetes Center, Boston, MA; [3]Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON, Canada; [4]Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital. Toronto, Ontario, Canada, Quebec City, QC, Canada; [5]None, Oakville, ON, Canada; [6]Sinai Health System, Toronto, ON, Canada; [7]Universal Health Network, Toronto, ON, Canada; [8]University Health Network, Toronto, ON, Canada; [9]University of Toronto, Toronto, ON, Canada.*

Background: Central adiposity is considered an important cardio-renal risk factor in the general population and in type 1 diabetes (T1D). We sought to determine the relationship between central adiposity and renal hemodynamic function in adults with longstanding T1D with and without diabetic nephropathy (DN).

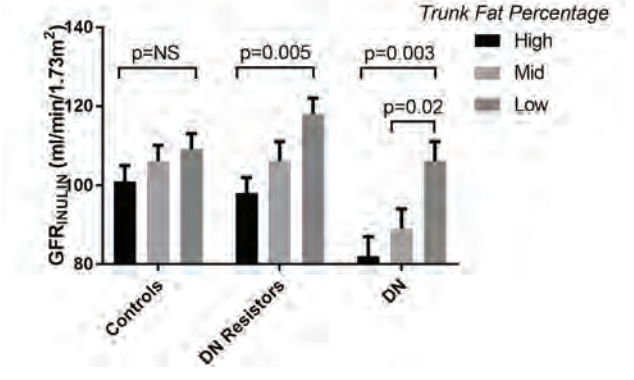
Methods: Patients with longstanding T1D (n=75, duration >50 yrs) and age/sex-matched healthy controls (HC, n=75) were studied. The T1D cohort was stratified into 50 DN Resistors (eGFR >60mL/min/1.73m^2 and <30 mg/day urine albumin) and 25 with DN. Renal hemodynamic function (glomerular filtration rate [GFR_{INULIN}], effective renal plasma flow [$ERPF_{PAH}$] was measured. Afferent arteriolar resistance (R_A), efferent arteriolar resistance (R_E), renal blood flow [RBF], renal vascular resistance [RVR], filtration fraction [FF], glomerular pressure (P_{GLO}) derived from Gomez' equations. Fat and lean mass were quantified by DXA.

Results: In healthy controls, measures of adiposity did not associate with GFR_{INULIN} or $ERPF_{PAH}$. In T1D, trunk fat mass inversely correlated with GFR_{INULIN} (r: -0.46, p<0.0001), $ERPF_{PAH}$ (r: -0.31, p=0.01) and positively with RVR (r: 0.53, p=0.0003). In analyses stratified by DN status, greater central adiposity related to lower GFR_{INULIN} in both DN and DN resistors, but the relationships between central adiposity, $ERPF_{PAH}$ and RVR were attenuated and/or reversed in DN compared to DN resistors. GFR_{INULIN} across tertiles of trunk fat percentage are shown in Fig 1.

Conclusions: The adiposity-renal hemodynamic function relationship may be modified by the presence of T1D and of DN, requiring further study of the mechanisms by which adiposity influences renal hemodynamic function in health and disease.

Funding: NIDDK Support

Fig 1. Sex-adjusted means of GFR across tertiles of trunk fat percentage



SA-PO131

Policy Impact on Diabetes Detection in Vulnerable Populations Kate Cartwright, David N. van der Goes. *University of New Mexico, Albuquerque, NM.*

Background: Earlier detection of type 2 diabetes is associated with improved management of diabetes. Populations with barriers to care are more likely to have type 2 diabetes and are more likely to be diagnosed at an advanced stage of the disease. US residing Hispanics are not only more likely to be diagnosed with diabetes than their non-Hispanic counterparts, but they are also more likely to die of a diabetes-related cause. Before the ACA, Hispanics were the most likely to be uninsured or underinsured in all states. After the ACA, in states which expanded Medicaid, the uninsured rate for Latinos was reduced to 9% compared to 7% for non-Hispanic whites. However, in states which did not adopt Medicaid expansion, 24% of Latinos are uninsured compared to 10% of non-Hispanic whites. California went further by expanding coverage to non-citizens, which increased the number of non-citizens covered by about 31%. In this project, we analyze the change in self-reported diabetes among non-citizen Hispanic women in expansion and non-expansion states.

Methods: In a multivariate regression framework, we use the 2011-2015 NHIS to analyze the change in self-reported diagnosis of diabetes among Hispanic non-citizen women before and after the ACA Medicaid expansion. Less than 5% of Hispanic women in the South lived in states that expanded Medicaid, while approximately 97% of Hispanic women in the West lived in states that expanded Medicaid under the ACA. We use a difference-in-difference model with our second difference comparing the Southern US to the Western US.

Results: Non-citizen Hispanic women living in Medicaid expansion states saw an 80% (1.81 OR; CI 1.11-2.93) relative increase in self-reported diabetes (compared to non-citizen Hispanic women in non-expansion states). Comparing the same group's changes in self-assessed health and BMI showed no change. This indicates the change in self-reported diabetes in unlikely due to changes in health status, but instead due to improved detection of diabetes.

Conclusions: This investigation supports the argument that expanding health coverage is associated with improved health knowledge. One of the most vulnerable groups in the US, non-citizen Hispanic women, seems to have benefited from Medicaid coverage expansion. Improved detection of diabetes in this population creates an opportunity to better manage this condition and improve health outcomes, survival odds, and heatlh equity.

SA-PO132

Systems Biology Identified Molecular Pathways and Biomarkers Associated with Diabetic Kidney Disease Progression Skander Mulder,[1] Viji Nair,[2] Wenjun Ju,[2] Kelli M. Sas,[2] Hiddo J. Lambers Heerspink,[1] Matthias Kretzler.[2] *[1]University Medical Center Groningen, Groningen, Netherlands; [2]University of Michigan, Ann Arbor, MI.*

Background: Diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease (ESKD). Understanding of molecular pathways involved in the initiation and progression of DKD facilitates biomarker development and drug target identification. We aim to identify molecular pathways associated with progressive loss of kidney function in both early and advanced stages of DKD.

Methods: We included 810 patients with early DKD from the DIRECT-2 trial (eGFR 69 ±11ml/min/1.73m^2 and normoalbuminuria) and 911 patients with advanced DKD from SUN-Macro (eGFR 33 ±10 and macroalbuminuria). Baseline urine proteomics, serum metabolomics and proteins were mapped to intra-renal transcriptional profiles of DKD biopsies from the European Renal cDNA Biobank (ERCB, n=19). All molecular features were associated with the primary end point of 30% eGFR decline or ESKD (n= 288), and subsequently with the secondary endpoint of eGFR slope < -3ml/year (n=704). Ingenuity pathway analysis identified significantly enriched canonical pathways and disease networks in associated features.

Results: The systems biology integration identified canonical pathways significantly enriched in molecular features associated with renal end points in early (3 pathways), advanced (1) and both stages (5) of DKD, respectively (Figure 1). These pathways include novel (Intrinsic Prothrombin Activation) and known DKD associated pathways (NAD biosynthesis and LXR/RXR activation). Antibody based assay results confirmed 11 (10 serum, 1 urine) biomarkers to be predictive for endpoints, including MMP7, TNFR1 and Endostatin representing the 5 enriched pathways in both early and late DKD.

Conclusions: By integrating intra-renal transcriptomic data with unbiased proteomics and metabolomics we identified stage-specific and shared molecular pathways, as well as their representing biomarkers, that are associated with DKD progression in early and late stages of DKD. Our work sets the stage for investigations of these biomarkers and molecular pathways for prognostic and interventional purposes.

Funding: Government Support - Non-U.S.

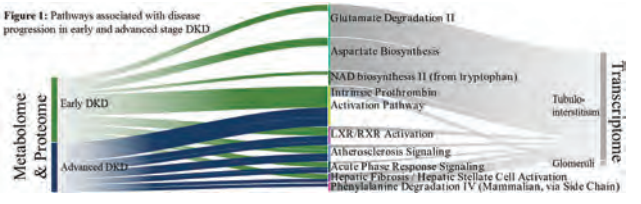


Figure 1:Pathways associated with disease progression in early and advanced stage DKD

SA-PO133

Identification of Novel Genetic Factors Linked to Diabetic Nephropathy Paolo Guarnieri,[1] Chengxiang Qiu,[2] Julie Hawkins,[1] Jonathan Hill,[1] Weiling Niu,[1] Matthew Palmer,[2] Yong G. Yue,[1] Steven S. Pullen,[1] Carine Boustany,[1] Katalin Susztak.[2] *[1]Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT; [2]University of Pennsylvania, Philadelphia, PA.*

Background: Diabetic nephropathy (DN) is serious kidney condition and the leading cause of chronic kidney disease in the USA contributing to 30-40 % of all end-stage renal disease cases. In order to provide a better insight into its molecular mechanism, genetic determinants and finally identify novel targets, we first generated a novel dataset from a cohort of 250 patients undergoing nephrectomy and then we analytically integrated the results with public domain data from genome-wide association studies (GWAS).

Methods: Patients in the study were genotyped using high density Axiom arrays and phenotyped using collected clinical records. Each matched kidney specimen was histologically assessed and RNA-seq transcriptionally profiled separating tubules from glomeruli.

Results: Our analysis identified several genes associated with kidney function decline (estimated glomerular filtration rate), many also responsible for the progressive increase in interstitial fibrosis and/or associated with lymphocytic infiltration. Cell type specific gene signatures used with deconvolution algorithms revealed that several immune cells, mostly T lymphocytes, are active since the early stages of the disease. Our distinctive study design enabled the first human kidney specific eQTL analysis and helped focus on genes for which expression in kidney is genetically determined either in tubules, in glomeruli or both. We completed the expression to genotype to trait associations by performing a Bayesian co-localization analysis between our results with those available from GWAS and then matched the direction of the expression change with the effect on the trait.

Conclusions: In this study we generated a high resolution tissue and disease specific transcriptome database which allowed the study of genes and processes implicated in DN.

Funding: Commercial Support - Boehringer Ingelheim

SA-PO134

Fluorescence Lifetime Imaging Microscopy Reveals Gradual Accumulation of Collagens and NADH Lifetime Decrease in Human Kidney Glomeruli with Diabetic Disease Progression Evgenia Dobrinskikh,[3] Kammi J. Henriksen,[1] Moshe Levi.[2] *[1]The University of Chicago, Chicago, IL; [2]University of Colorado Denver, Aurora, CO; [3]University of Colorado, Denver, Aurora, CO.*

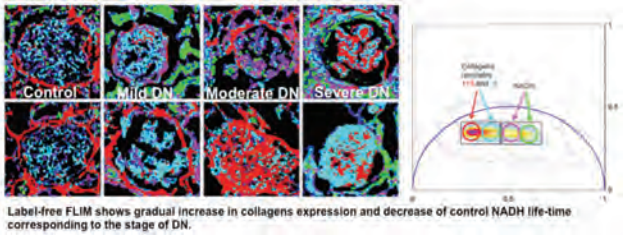
Background: Diabetes mellitus is a heterogeneous group of diseases which is a leading cause of renal cell and tissue damage, fibrosis and eventual renal failure. In view of recent therapies aimed at the pathogenesis of fibrosis generation and progression, sensitive and quantitative techniques for recording fibrosis becomes necessary.

Methods: We have applied Two Photon Excitation (TPE), Second Harmonic Generation (SHG) and Fluorescence Lifetime Imaging Microscopy (FLIM) for label-free imaging of kidney sections from kidney biopsies from human diabetic subjects. We have applied the phasor approach for FLIM analysis, which allows for the visual determination of collagens and other extracellular matrix components localization, and metabolic state of the kidney (free to bound NADH ratio) taking advantage of the specific autofluorescence characteristics of these molecules.

Results: In kidney biopsies obtained from diabetic humans, compared to biopsies obtained from nondiabetic subjects, we have determined that there is a strong SHG signal around the glomerulus and tubulointerstitial areas, which indicates presence of fibrosis. FLIM shows graduate increase of different types of collagens in the glomerulus and tubulointerstitial areas with the diabetes progression, which suggests different organization of extracellular matrix. NADH signal decreases and its lifetime shifts to the shorter lifetime in diabetic's kidneys that corresponds to different metabolic state of the tissue. FLIM also might determine relative degree of the disease progression based on the ratio of NADH lifetimes in different regions in diabetic compared to nondiabetic control kidneys.

Conclusions: TPE-SHG and FLIM imaging is a sensitive technique for label-free imaging, which can show metabolic state and ECM accumulation with the disease progression of the kidney based on the autofluorescence of the ECM components and NADH.

Funding: NIDDK Support



Label-free FLIM shows gradual increase in collagens expression and decrease of control NADH life-time corresponding to the stage of DN.

SA-PO135

Alternative Splice Isoforms in Human Diabetic Kidney Disease (DKD) Rajasree Menon,[1] Viji Nair,[1] Brad A. Godfrey,[1] Felix H. Eichinger,[1] Yuanfang Guan,[1] Maria Luiza A. Caramori,[2] Michael Mauer,[2] Matthias Kretzler.[1] *[1]University of Michigan, Ann Arbor, MI; [2]University of Minnesota, Minneapolis, MN.*

Background: mRNA transcript splice isoforms add a substantial complexity to gene regulation, but their expression and differentiated function have not been explored in renal disease. The goal of this study was to identify whether or not alternative splice isoforms were expressed in biopsy tissues from patients with diabetes.

Methods: TruSeq RNA Access based mRNA-Sequencing was performed on research kidney biopsy samples from 10 living kidney donors and 18 research volunteers with Type 1 diabetes (T1D) followed by weighted correlation network analysis (WGCNA) of the top 5,000 highly expressed variable transcripts. T1D patients were classified as fast-(n=10) and slow-progressors (n=8) for DKD. Alternative splice isoforms, defined by UniProt annotation, had to be differentially expressed (FDR< 0.3) between T1D and controls and to be contained in modules associated with disease progression. As alternative splice isoforms are poorly annotated, an integrated analysis using structure, function and motif predictions was performed and non-canonical isoforms with differential regulation and function from their canonical isoforms were further studied.

Results: 39 protein coding transcripts contained in three WGCNA modules were differentially expressed. EGF signaling, extra-cellular matrix and epithelial differentiation were among the top enriched processes. The protein products of 9 of these 39 transcripts are annotated as alternative /non-canonical isoforms. Analysis of the non-canonical isoform 3 of ATF3 was predicted to be involved in type I interferon and cell-substrate junction assembly compared to the canonical isoform. Consistent with this prediction, expression of the non-canonical, but not of the canonical ATF3 isoform, correlated highly with DUSP1 and EGR1 transcripts, known to be regulated by type I interferon. Structure predictions of the ATF3 isoform showed structural differences with RMSD of 3.5 from that of the canonical form with part of the basic leucine zipper domain missing in isoform 3 of ATF3.

Conclusions: We have identified alternative splice isoforms with substantial differential regulation and function prediction associated with key progression pathways in DKD, opening an analytical window to address the complexity of the transcriptome in renal disease.

Funding: NIDDK Support

SA-PO136

Type 1 Interferon Is Associated with Kidney Dysfunction in Type 2 Diabetes James Conway,[1] Felix H. Eichinger,[3] Brad A. Godfrey,[3] Viji Nair,[3] Anna Reznichenko,[2] Tim Slidel,[1] Clemens D. Cohen,[4] Brandon W. Higgs,[1] Carol P. Moreno Quinn,[1] Matthias Kretzler.[3] *[1]MedImmune, Gaithersburg, MD; [2]AstraZeneca, Molndal, Sweden; [3]University of Michigan, Ann Arbor, MI; [4]Klinikum Munchen, Munchen, Germany.*

Background: Type I interferon (IFN) is linked to the pathogenesis of autoimmune and inflammatory diseases known as interferonopathies. A portion of patients show aberrant type I IFN signaling, which can be measured by a gene expression signature composed of IFN-inducible genes (IFNGS). Chronic kidney disease (CKD) is characterized by chronic inflammation and interstitial fibrosis, yet little is known regarding type I IFN signaling in type 2 diabetics (T2D) with diabetic nephropathy (DN). Here we evaluated a type I IFNGS in these patients and identified an association with immune response and kidney dysfunction.

Methods: Tissue from human glomeruli (DN, n_1=12), tubulointerstitium from two independent patient sets (DN; n_1=17, n_2=31), and living donors (n_1=46) were obtained from the European Renal cDNA Bank and profiled by Affymetrix array. Gene-set variation analysis (GSVA) quantified a 21-gene type I IFNGS identified by Yao Y *et al* (PMID: 20948567) and other function-specific signatures. Patients were assigned to type I IFN-low or IFN-high groups based on median GSVA score. Gene signatures for which IFN-high patients differed from IFN-low were identified. P-values were adjusted for sex and age. A Fisher's combined probability was applied to summarize both studies (p_{chi}).

Results: Type I IFNGS was elevated in the tubulointerstitium (p_{chi}=1.3x10^{-4}), but not the glomeruli of DN patients compared to living donors. IFN-high patients associated with lower glomerular filtration rate (GFR) compared to IFN-low patients (p_{chi}=0.02). Although a high collagen signature associated with decreased GFR (p_{chi}=0.001), it did not correlate with type I IFNGS, suggesting an independent mechanism. IFN-high patients displayed increased T cell activation (p_{chi}=6.6x10^{-6}), TLR4 signaling (p_{chi}=5.7x10^{-5}) and innate immune response (p_{chi}=1.9x10^{-5}).

Conclusions: A significant decrease in GFR was observed in T2D patients with elevated Type I IFN signaling, which was also linked to increases in immune response signatures. This link between type I IFN signaling and kidney dysfunction may inform on patient selection for therapies targeting immune response pathways. This hypothesis should be confirmed in an independent study.

Funding: Commercial Support - MedImmune, AstraZeneca, Novo Nordisk, Eli Lilly, Gilead

SA-PO137

Integrated Score from Glomerular Structure and Molecular Profiles Predicts ESRD in Diabetic Kidney Disease (DKD) Viji Nair,[1] Jennifer L. Harder,[1] Paolo Guarnieri,[2] Jonathan Hill,[2] Brad A. Godfrey,[1] Carine Boustany,[2] Behzad Najafian,[3] Michael Mauer,[4] Robert G. Nelson,[5] Matthias Kretzler.[1] *[1]University of Michigan, Ann Arbor, MI; [2]Boehringer Ingelheim, Ridgefield, CT; [3]University of Washington, Seattle, WA; [4]University of Minnesota, Minneapolis, MN; [5]National Institutes of Health, Phoenix, AZ.*

Background: DKD progression is the major cause of ESRD and increased mortality risk globally. We used systems biology tools to identify predictors of DKD progression through the integration of kidney structural changes with transcriptional profiling.

Methods: Glomerular specific gene expression profiling and quantitative morphometric analyses were performed on protocol kidney biopsies from 70 Pima Indians with type 2 diabetes [iothalamate (iGFR) 145 ± 52 ml/min and ACR 25.9[139.5]) mg/g]. Transcriptional co-expression modules were associated with glomerular morphometric traits using Weighted Gene Coexpression Network Analysis (WGCNA). Traits included glomerular basement membrane width (GBMW), mesangial fractional volume per glomerulus [Vv(Mes)], foot process width (FPW) and % peripheral capillary endothelial surface which is fenestrated (%EF), all associated with clinical expression of DKD. A z-score was computed from the gene set that correlated with these traits and associated

with the ESRD outcome. The prediction ability of this score for ESRD over a median of 15 years of follow up was evaluated using the Area Under the Curve Statistic (AUC).

Results: WGCNA analysis identified 14 modules of coexpressed genes. Glomerular structural traits of DKD showed strong associations with molecular signatures. Inflammatory responses and cellular signaling and proliferation pathways were the prominent functions enriched within these shared structural traits. The glomerular lesions gene score discriminated patients with and without progression to ESRD (AUC 0.85[0.75 - 0.96], p <0.001) where cross sectional iGFR performed poorly 0.43[0.27-0.56]. The score also correlated significantly with iGFR slope (r= -0.55, p <0.001).

Conclusions: Early glomerular lesions of DKD and the gene expression pathways associated with these lesions strongly predicted progressive DKD in type 2 diabetes. Further evaluation of these pathways could provide early intervention targets and novel noninvasive biomarkers with predictive clinical utility.

Funding: NIDDK Support, Commercial Support - Boehringer Ingelheim

SA-PO138

Reduction of H3K27Me3 and Metabolic Memory Associated Inflammation in Podocytes Brad Dieter,[1] Rick L. Meek,[1] Robert J. Anderberg,[1] Sheryl K. Cooney,[1] Katherine R. Tuttle.[1,2] *[1]Providence Sacred Heart, Spokane, WA; [2]University of Washington School of Medicine, Spokane, WA.*

Background: Poor glycemic control, even with subsequent periods of well-controlled glycemia, increases risk for diabetic complications. This phenomenon, known as metabolic memory, may cause epigenetic changes such as reduction of histone 3 lysine 27 trimethylation (H3K27Me3), which increases expression of inflammatory mediators including serum amyloid A (SAA) in the diabetic kidney. The aim of this study was to determine if a sustained inflammatory response to metabolic memory may be mediated by increased SAA expression due to H3K27Me3 demethylation near the SAA promoter in podocytes, a cell centrally involved in diabetic kidney disease.

Methods: SAA knockout podocytes were generated using CRISPR-Cas9. In experiments to model metabolic memory, wild type and SAA knockout mouse podocytes were differentiated for 8-10 days, then exposed to advanced glycation end products (AGE, 300 μg/ml) for 7 days, followed by AGE removal and ongoing culture in control conditions for 7 more days. Chromatin immunoprecipitation measured H3K27Me3 near the SAA promoter. qRT-PCR was used to measure mRNA expression of inflammatory mediators: SAA, CXCL5, CCL2, and CCL5. Podocytes were exposed to AGE (300 μg/ml) for 1 day while H3K27Me3 demethylation was prevented by inhibiting the H3K27me3 specific demethylase, jmjd3, with GSK-J1 (20 μM).

Results: In metabolic memory experiments conducted in podocytes (n=6), histone H3K27Me3 near the SAA promoter was markedly reduced (95%) at day 14, while SAA mRNA increased (17±6-fold, p=0.025), as were SAA-dependent inflammatory mediators: CXCL5 (18.5±12-fold, p=0.004), CCL2 (2.0±0.7-fold, p=0.001), and CCL5 (1.6±0.6-fold, p=0.026). SAA knockout in podocytes reduced expression of CXCL5, CCL2, and CCL5 by ≥60% (p<0.05 for all) in metabolic memory experiments. jmjd3 inhibition reduced AGE-induced expression of SAA and each of the SAA-dependent inflammatory mediators by ≥60% (p<0.05 for all) in podocytes.

Conclusions: Short term exposure of podocytes to hyperglycemia-related perturbations causes sustained H3K27Me3 demethylation and increased SAA expression, leading to a sustained SAA-dependent inflammatory response.

Funding: Private Foundation Support

SA-PO139

Atrasentan Treatment Combined with RAAS Inhibition Increases Parietal Epithelial Cell Activation and Restores Podocyte Number Kelly L. Hudkins,[1] Tomasz A. Wietecha,[3] Floortje Steegh,[2] Charles E. Alpers.[4] *[1]University of Washington, Seattle, WA; [2]Academic Hospital Maastricht, Maastricht, Netherlands; [3]University of Washington, Seattle, WA; [4]University of Washington Medical Center, Seattle, WA.*

Background: BTBR *ob/ob* (OB) mice develop robust type 2 diabetes and nephropathy that resembles human DN, with mesangial expansion, podocyte loss and proteinuria. This study tested the treatment effect of atrasentan (A), an endothelin-1 receptor antagonist, with or without concurrent RAAS inhibition by losartan (L) in mice with established DN.

Methods: Groups of 18 week old OB and WT littermates were treated via drinking water with A (5 mg/kg/day), A plus L (25 mg/kg/day) or normal drinking water for 6 weeks. Mice were analyzed for renal function and morphologic manifestations of DN, including proteinuria, podocyte number, mesangial matrix expansion, glomerular inflammatory infiltration, ultrastructural morphology and parietal epithelial cell (PEC) activation.

Results: Mice treated with A or A plus L had a 3 fold decrease in average albumin creatinine ratio (ACR) after 6 weeks of treatment. Analysis of paired urine samples at 18w and 24w showed significant ACR reduction in 5 of 6 OB mice (p=0.017) treated with A. Serum creatinine levels also decreased in OB mice treated with A and A plus L (p< 0.05). Renal function improvement was accompanied by decreased glomerular mesangial matrix, increased macrophage infiltration, restoration of podocyte foot processes and an increase in podocyte number. Expression of CD44 and pERK 1/2, both markers of PEC activation, were significantly increased in OB vs. WT (p<0.05). Treatment with A alone increased CD44 and pERK 1/2 PEC expression, while A plus L treatment showed a further increase in CD44 expression but a decrease of pERK1/2. Glomerular expression of pS6, a surrogate of mTOR activation, is increased in OB vs. WT mice (p<0.05), and treatment with A and A plus L resulted in a significant decrease.

Conclusions: Atrasentan treatment resulted in improvement of renal function, matrix accumulation and podocyte number in BTBR *ob/ob* mice with established DN. Combined treatment with A plus L resulted in increased restoration of podocyte number compared to A alone. PEC activation was also increased in treated mice, while activation of the mTOR pathway was reduced by treatment. The benefit of combined A plus L treatment in patients with DN may occur through restoration of podocyte number, potentially via PEC cell activation and migration, and foot process integrity.

Funding: Commercial Support - Abbvie, Government Support - Non-U.S.

SA-PO140

Exogenous miRNA-23a/27a Attenuates Diabetes-Related Muscle Atrophy and Renal Fibrotic Lesions Bin Wang,[1,2] Aiqing Zhang,[1,3] Faten Hasounah,[1] Xiaonan H. Wang.[1] *[1]Emory University, Atlanta, GA; [2]Institute of Nephrology, Zhong Da Hospital, Southeast University, Nanjing, China; [3]Department of Pediatric Nephrology, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China.*

Background: Muscle atrophy is a frequent complication of diabetes mellitus. The microRNA-23a, -27a and 24-2, are located together in a gene cluster on chromosome 8. MiR-23a and miR-27a are known to regulate proteins that are involved in the atrophy and fibrosis process. We hypothesized that treatment with miR-23a/27a would reduce both diabetes-induced muscle wasting and renal fibrosis through exosome-mediated muscle-kidney crosstalk.

Methods: We generated an adeno-associated virus (AAV) that overexpresses miR-23a~27a~24-2 precursor RNA (and an AAV-GFP control) and injected it into the tibialis anterior (TA) muscle of STZ-induced diabetic mice. After 3 months, mice were killed and muscles and kidneys were analyzed for protein markers of atrophy and fibrosis. In-Vivo Xtreme camera system was used to track GFP migration to kidney in vivo.

Results: Injection of AAV-miRs into muscle increased miR-23a and miR-27a. The insulin/IGF signaling pathway was upregulated in skeletal muscle; e.g., increased phosphorylated Akt, attenuated FoxO1 and PTEN, reduced TRIM63/MuRF1 and FBXO32/atrogin-1. Myostatin signaling was downregulated; e.g., decreased myostatin and phosphorylated SMAD2/3 protein levels. Curiously, the serum BUN of diabetic animals was reduced in mice undergoing the miR-23a/27a intervention in muscle. Renal fibrosis, evaluated by Masson trichrome, was decreased as were pSMAD2/3, alpha smooth muscle actin, fibronectin and collagens. When diabetic mice were injected intramuscularly with AAV-GFP, the kidneys showed GFP fluorescence at levels that correlated with the levels in injected muscle, examined by linear regression. The abundance of GFP protein in skeletal muscle, serum exosomes and kidney increased over time after injection. Serum exosomes and kidneys of mice that received intramuscular injections of miR-23a/27a showed levels of those miRs that were higher than the un-injected control mice. No viral DNA was detected in the kidney.

Conclusions: Overexpression of miR-23a/27a in muscle prevents diabetes-induced muscle loss and attenuates renal fibrosis lesions via exosome-mediated muscle-kidney crosstalk.

Funding: Other NIH Support - National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health under Award Number R01 AR060268

SA-PO141

Dietary Acid Reduction with Either Fruits and Vegetables or Oral NaHCO3 Reduces Oxidative Stress and Slows Progression of Kidney Injury in Stage 1 CKD Nimrit Goraya,[2,5] Lauren N. Sager,[1] Jan Simoni,[3] Donald E. Wesson.[4,3] *[1]Biostatistics, Baylor Scott & White, Temple, TX; [2]Internal Medicine, Baylor Scott and White Health, Temple, TX; [3]Internal Medicine, Baylor Scott & White Health, Temple, TX; [4]Diabetes Health and Wellness Institute, Dallas, TX; [5]Internal Medicine, Texas A and M School of Medicine, Temple, TX.*

Background: Chronic kidney disease stage 1 (eGFR > 90 ml/min/m^2, CKD 1) patients with macroalbuminuria (urine albumin-to-creatinine ratio > 200 mg/g creatinine) are at increased risk for CKD progression with higher morbidity, mortality, and costs. Dietary acid (H^+) induces nephropathy progression in animal models of CKD, mediated in part though angiotensin II (AII)-induced oxidative stress. We tested the hypothesis that dietary H^+ reduction with base-producing fruits and vegetables (F+V) or oral $NaHCO_3$ (HCO_3) prevents further kidney injury in CKD 1.

Methods: Seventy-one macroalbuminuric, non-diabetic CKD 1 subjects had systolic blood pressure (SBP) reduced to < 150 mm Hg with regimens including ACE inhibition and were then randomized to receive F+V (n=23) in amounts to reduce dietary potential renal acid load by half, oral $NaHCO_3$ (HCO_3, n=23) 0.4 meq/Kg bw/day, or no additional intervention (Usual Care, n=25). Creatinine-based eGFR and spot urine levels of the following, factored per g creatinine, were measured at baseline and yearly for five years: albumin (Ualb), an index of kidney injury, angiotensinogen (UAGT), an index of kidney angiotensin II, and isoprostane 8-isoprostaglandin F_{2a} (8-iso), an index of oxidative stress.

Results: Baseline eGFR, Ualb, UAGT, and U8-iso were not different among the groups. The five-year course (mean, 95% confidence limit or CI) of Ualb was lower than Usual Care (406 mg/g, CI=376-435) in both F+V (332 mg/g, CI=312-352) and HCO_3 (324 mg/g, CI=299-349), consistent with less kidney injury in each dietary acid reduction group. Combining F+V and HCO_3 into one dietary acid reduction group, UAGT course was lower than Usual Care (p<0.02), consistent with lower kidney AII. The five-year course of U8-iso was lower than Usual Care (1.24 ug/g, CI=1.19-1.29) in both F+V (1.10 ug/g, CI=1.06-1.15) and HCO_3 (1.11 ug/g, CI=1.07-1.14), consistent with less oxidative stress in both dietary reduction groups. There was no significant change in eGFR over the five years in any of the three groups.

Conclusions: Dietary acid reduction in CKD 1 with either F+V or $NaHCO_3$ yielded less kidney injury and less oxidative stress than Usual Care, possibly mediated though reduced kidney AII, supporting that dietary acid reduction reduces the risk for progression to advanced CKD stages.

SA-PO142

Changes in Protein Intake among Adults with and without CKD: NHANES 2003-2014 Karen R. Siegel, Meda E. Pavkov. *Centers for Disease Control, Atlanta, GA.*

Background: Consuming a diet with moderate amounts of protein is recommended for all individuals, including those with Chronic Kidney Disease (CKD).

Methods: Using the National Health and Nutrition Examination Surveys (NHANES) 2003-2008 (T1) and 2009-2014 (T2), we estimated changes in protein intake over time and the percentage of adults consuming above the RDA average recommended amount of protein (56 gram[g]/day for men, 46 g/day for women), overall and by CKD status. We included adults ≥19 years old, excluded those pregnant or lactating, those with missing data on CKD status, diabetes status, or protein intake. The final analytic sample yielded 12,302 adults for T1 and 13,293 adults for T2. An average of 2 days of 24-hour dietary recalls were used to estimate protein intake. Protein intake was converted to kcal by multiplying each g by 4 kcal; to calculate protein intake as percentage of dietary intake, we divided by total daily kcal. CKD status was defined by albuminuria and/or eGFR <60 ml/min/1.73 m^2.

Results: Overall, protein intake was 98.8 g (Standard Error: 0.7), or 395 kcal, for men and 68.8 g (0.5), or 275 kcal, for women in T1; 97.3 g (0.6), or 389 kcal, for men and 69.3 g (0.4), or 277 kcal, for women in T2. This translates into 84.3% (0.7) of men and 77.8% (0.8) of women consuming above the recommended amount in T1, and 84.5% (0.5) of men and 78.2% (0.5) of women exceeding recommended protein intake in T2. In both time periods adults with CKD were less likely than those without CKD to consume above the recommended protein intake (83.1% vs 90.5% among men and 77.2% vs 83.7% among women in T1, and 82.7% vs 90.8% among men and 76.5% vs 84.1% among women in T2).

Conclusions: The percentage of the population exceeding protein intake recommendations remained high in 2003-2008 and 2009-2014. There is much room for improvement in reducing protein intake and potentially slowing disease progression in those with CKD. In ongoing work we also examine types of protein (e.g., animal, dairy, plant) and how their intake varies by CKD status.

SA-PO143

Osteoprotegerin Is a Strong Independent Marker of Cardiovascular Mortality in Patients with CKD Stage 3 to 5 Marcelo M. Nascimento,[1,4] Gustavo L. Marques,[1] Shirley Hayashi,[2] Anna Bjällmark,[2] Matilda Larsson,[2] Miguel C. Riella,[3] Bengt Lindholm.[4] *[1]UFPR, Hospital de Clinicas, Curitiba, Brazil; [2]Royal Institute of Technology (KTH), Huddinge, Sweden; [3]Evangelic School of Medicine of Parana, Curitiba, Brazil, Curitiba, Brazil; [4]Renal Medicine and Baxter Novum, Karolinska Institutet, Stockholm, Sweden.*

Background: Osteoprotegerin (OPG) regulates bone mass by inhibiting osteoclast differentiation and activation, and might play a role in vascular calcification. Increased levels of circulating OPG in patients with chronic kidney disease (CKD) have been reported to be associated with both aortic calcification and increased mortality. Here we assessed the mortality predictive role of OPG in CKD stage 3-5 patients followed for up to 5 years.

Methods: We evaluated the relationship between OPG and mortality (general and due to cardiovascular cause) in 143 CKD patients including 36 patients on hemodialysis, 55 patients on peritoneal dialysis, and 52 conservatively treated patients with CKD stages 3-5. Clinical characteristics, markers of mineral metabolism (including fibroblast growth factor-23 [FGF-23]), inflammation (high-sensitivity C-reactive protein [hsCRP] and interleukin-6 [IL-6]), intima-media thickness (IMT) in the common carotid arteries as assessed by ultrasound, and cardiac status by color tissue Doppler echocardiography, were measured at baseline, and correlations with OPG levels were analyzed.

Results: OPG levels were positively associated with IL-6 ($r = 0.44$, $P<0.01$), FGF-23 ($r = 0.26$, $P<0.01$) and hsCRP ($r = 0.27$, $P<0.01$), troponin I ($r = 0.55$, $P<0.01$) and IMT ($r = 0.39$, $P<0.01$), as well as with higher left ventricular mass. After 60 months follow-up, the survival rate by Kaplan-Meier analysis was significantly worse in those with higher baseline OPG levels for all cause as well as cardiovascular mortality (both Chi-Square: 15.60 $p<0.0001$). The Cox model for all cause and cardiovascular mortality demonstrated that only OPG (per pg/mL; HR=1.07, 95%CI=1.02-1.13, and HR=4.46, 95%CI=1.4-13.5, respectively) and hsCRP (per mg/dL; HR=1.02, 95%CI=1.01-1.04, and HR=5.71, 95%CI=1.17-27.9, respectively) were independently associated with increased all-cause and cardiovascular risk of death, respectively.

Conclusions: Elevated levels of serum OPG associate with markers of inflammation and mineral metabolism, signs of atherosclerosis and cardiovascular deaths in patients with CKD stage 3-5. OPG is a strong independent predictor of cardiovascular mortality in this patient population.

Funding: Commercial Support - Baxter Healthcare Corporation, Government Support - Non-U.S.

SA-PO144

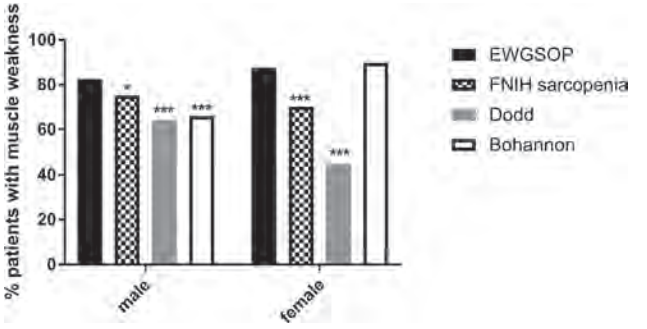
Differences in Prevalence of Muscle Weakness (Sarcopenia) in Haemodialysis Patients Determined by Hand Grip Strength According to Variation in Sarcopenia Guidelines Rachel Hung,[2] Kamonwan Tangvoraphonkchai,[1] Omid sadeghi-alavijeh,[3] Andrew Davenport.[3] *[1]Chulalongkorn University, Bangkok, Thailand; [2]Royal Free Hospital, London, London, United Kingdom; [3]Royal Free Hospital, London, United Kingdom.*

Background: Muscle weakness is associated with increased mortality, and patients on haemodialysis (HD) are at increased risk of muscle loss. There is no universal agreed definition for muscle weakness, so we wished to determine whether using different cut off criteria recommended by clinical guideline groups altered the prevalence in HD patients.

Methods: We measured hand grip strength (HGS) in HD outpatients comparing HGS with clinical guideline cut offs (European Working Group on Sarcopenia in Older People (EWGSOP), National Institutes of Health Sarcopenia Project (FNIH)) used to define muscle wasting (sarcopenia), as well as age and gender matched normative data.

Results: We studied 459 patients, 61.4% male, 47.3% diabetic. The prevalence of muscle weakness was significantly different when measuring HGS; 84.5% using the EWGSOP cut off, 73.2% with FNIH criteria and 75.2% using North American and 56.6% UK normative data ($p<0.01$). On logistic regression, muscle weakness was associated with age (odds ratio (OR) 1.05, $p<0.001$), weight (OR 0.96, $p<0.001$), serum albumin (OR 0.89, $p=0.007$)and being a non-diabetic (OR 0.31, $p=0.001$) whereas gender is not a significant factor. In addition, 66.7% of patients with no-comorbidities were weak, compared to 93.8% with highest co-morbidity score, $p<0.001$.

Conclusions: There is currently no agreed universal definition for muscle wasting (sarcopenia), but the EWGSOP and FNIH advocate HGS cut offs as part of their definition of sarcopenia. The prevalence of muscle weakness varies according to cut off, and whether age and gender matched normative data is used. In addition, patient characteristics in terms of age and co-morbidity also determine the prevalence of muscle weakness.



Male and female cut off points for different sarcopenia guidelines.* $p<0.5$, ** $p<0.01$, *** $p<0.001$ for EWSOP vs others

SA-PO145

Effect of Statin Therapy on Markers of Thrombosis and Inflammation in ESRD Daniel Chang,[2] Carlos H. Moreno Castaneda,[2] Farhanah Yousaf,[2] Hafiz Hussain,[2] Chaim Charytan,[2] Bruce S. Spinowitz.[1] *[1]New York Hospital Medical Center of Queens, New Rochelle, NY; [2]New York Presbyterian / Queens, Fresh Meadows, NY.*

Background: Large platelets have more granules, aggregate more rapidly with collagen, have higher thromboxane A2 levels and express more glycoprotein Ib and IIb/IIIa receptors. Upper quintile limit of mean platelet volume (MPV) predicts coronary artery disease in the hemodialysis population. Evidence suggests that statins may reduce MPV.

Methods: Medical records of prevalent hemodialysis patients as of 30Jun2016 were reviewed. Statins group included patients taking statins ≥6 months prior to 1Jan2016 and continued statins until 30Jun2016. No statins group included patients never taking statins or who stopped taking statins >6 months prior to 1Jan2016. Basic demographic, comorbidity, and laboratory data was tabulated. Independent t-test was used to compare 6-month (1Jan–30Jun2016) average MPV, WBC to MPV ratio, and ferritin levels in no statins versus statins groups.

Results: 224 patients were prevalent as of 30Jun2016. Exclusion consisted of 20 new patients, 98 with active infection or hospitalization, 5 on omega-3, 6 on steroid, 9 on statins <6 months, 7 started statins after 31Dec2015, 3 stopped statins between 1Jan-30Jun2016, and 5 received blood transfusion. In remaining 71 patients, 36 patients (24 males, 11 diabetics) aged 61±17 years never used or discontinued statins >6 months prior to 1Jan2016 while 35 patients (22 males, 22 diabetics) aged 70±13 years ($p=0.018$) taking statins ≥6 months prior to 1Jan2016 and continued statins until 30Jun2016. In statins group, 2 were on low intensity, 26 were on moderate intensity, and 7 were on high intensity statins. No statins group had higher mean cholesterol (159±34 vs 134±40 mg/dL) and LDL level (94±28 vs 73±34mg/dL) compared to statins group. After controlling for age and diabetes ($r^2=0.2$), mean MPV was significantly higher in statins group (11.2±1fL) versus no statins group (10.4±1fL) [$p=0.013$] while WBC to MPV ratio and ferritin levels were similar.

Conclusions: Our findings suggest that statin therapy in hemodialysis population is not associated with lower but rather higher MPV. Moreover, WBC to MPV ratio and

ferritin levels are unaffected by the use of statins. Lack of statins impact on markers of thrombosis and inflammation in end stage renal disease may explain lack of mortality benefit observed in previous literature.

SA-PO146

Exercise Capacity Predicts Mortality and Morbidity in Patients across the CKD Trajectory Sharlene A. Greenwood,[1,2] Ellen M. O'Connor,[1] Helen L. MacLaughlin,[1] Iain C. Macdougall.[1] *[1]King's College Hospital, London, United Kingdom; [2]King's College London, London, United Kingdom.*

Background: Exercise capacity is reduced in patients with chronic kidney disease (CKD). Low exercise capacity has been shown to be an independent predictor of mortality in patients with end-stage renal disease. We analysed the value of exercise capacity, characterised as the incremental shuttle walk test (ISWT) for predicting mortality and morbidity in a cohort of 438 patients (male 54%) from across the CKD trajectory (124 haemodialysis patients, 126 kidney transplant recipients, 31 peritoneal dialysis patients, 157 non-dialysis patients) over a 12-year period from 2005 to 2017 (median follow-up of 34 months).

Methods: Survival status was determined for 438 patients with CKD who were referred to an outpatient renal rehabilitation programme for which the ISWT and other clinical data had been determined. Chi-square and Kaplan-Meier survival analyses were performed. Risk of mortality was investigated independent of modality, BMI, diabetic status, age, gender, ethnicity, and smoking status using Cox proportional hazards model.

Results: There were a total of 108 combined events (death, cerebrovascular accident and hospitalisation for chronic heart failure) during the follow-up period. ISWT (>270m; p<0.0001 by Kaplan-Meier) was a strong predictor of mortality and morbidity. Determinants of functional ability, Sit to Stand 60 test (>18 complete transfers; p<0.0001 by Kaplan-Meier), Timed Up and Go 3m test (>8.05s; p=0.0001 by Kaplan-Meier), the Duke's Activity Status Index (>23.45; 0.003 by Kaplan-Meier) were also strong predictors of survival. On multivariate analysis, ISWT contributed significantly to the minimal explanatory model relating clinical variables to mortality and morbidity (overall x2 37.4, p=0.001). Patients who were able to walk >270m had a 2.3-fold (Hazard Ratio = 2.3; 95% confidence interval: 1.1 to 4.7) independent greater risk of a combined event (P = 0.02).

Conclusions: Exercise capacity is strongly predictive of mortality and morbidity in patients across the CKD trajectory. Exercise training interventions to improve clinical outcome in patients with CKD should be explored.

SA-PO147

Randomized Controlled Clinical Study to Prevent Decline in Renal Function and Nutritional Status in Predialysis Patients Using Ketoanalogue Supplementation Anita Saxena,[2] Amit Gupta,[1] Trisha Sachan,[4] Chandra M. Pandey.[3] *[1]Department of Nephrology, Lucknow, India; [2]Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India; [3]Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, India; [4]department of nephrology, sanjay gandhi post graduate institute of medical sciences, Lucknow, India.*

Background: Low protein diet is a means to protect residual renal function and to slow down progression of CKD to end stage renal disease. Study was conducted to evaluate effect of combined therapy of very low protein diet (vLPD) and ketoanalogues on renal function of predialysis patients and compliance to very low protein diet.

Methods: Prospective randomized controlled study. **Forty patients** divided into two groups of 20 each. CKD patients with GFR <60 but >30 ml/minute were included. Group I was supplemented with 300 mg/d of ketoanalogues combined with 0.4 gram /kg day protein (vLPD) and 35 kcal/kg/d of energy for 10 months. Group 2, control, was kept on low protein diet 0.6 g/kg /day and 35 kcal/kg /day energy. Biochemical investigations, included serum albumin, hemoglobin, sodium, potassium, calcium, phosphorus, and blood glucose were done at baseline (visit 1) and at 10 months (Visit 2). Dietary intake was taken by dietician. Nutritional status was assessed using SGA.

Results: At baseline, the GFR was higher in controls (51.14±15.1 ml/min). compared to ketoanalogue group (47.79±13.2 ml/min). GFR declined in the control group from 51.14 ml/min at baseline to 35.5±7.94 ml/min over a period of 10 months. In ketoanalogue group the GFR remained stable after 10 months 47.65±13.26.ml/min (47.79±13.2 at baseline). Serum albumin was preserved at 4.03 ±0.52 g/dL after10 months (4.11±0.43 g/dL at visit 1) in ketoanalogue group. In control group serum albumin decreased from 3.8±0.90 g/dL at visit 1 to 3.09±0.38 after 10 months (visit 2). GFR (p = 0.023) and serum albumin (p =0.000) were significantly higher in ketoanalogue vLPD group compared to controls at visit 2. Group 1 patients were noncompliant to vLPD as protein intake was 0.62±0.24 g/kg/d instead of 0.4 g/kg/d but GFR remained stable at 47.7 ml/min over 10 months. Energy intake was low 19.48±6.84 kcal/kg/d and 16.15±5.85 kcal/kg/d in group 1 and 2 respectively compared to RDA.

Conclusions: Ketoanalogue supplementation preserves nutritional status and prevents decline renal function.

SA-PO148

The Effect of a Renal Specific Oral Nutritional Supplement on Nutritional Status in Non-Dialytic CKD Wen-Yi Cheng,[2] Shang-Jyh Hwang,[3] Chih-Ching Lin,[4] Meng-Chuan Huang,[3] Owen J. Kelly.[1] *[1]Abbott Laboratories, Columbus, AL; [2]Abbott Laboratories Services Corp., Taipei, Taiwan; [3]Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [4]Taipei Veterans General Hospital, Taipei City, Taiwan.*

Background: The purpose of this study was to determine if 1-2 servings/d of a renal specific ONS (oral nutrition supplement) aids in maintaining nutritional status and avoids potential deleterious consequences in non-dialyzed stage 3b-5 CKD patients due to low dietary protein intake.

Methods: This is a prospective, multicenter, single arm, and open label study. Non-dialyzed stage 3b-5 CKD patients, with or without type 2 diabetes mellitus, with serum albumin ≥ 3.0 g/dl, and currently receiving standard medical care but not scheduled for dialysis treatment within 18 months were recruited. Subjects were requested to consume 1-2 servings per day (475 kcal, 10.6 g protein per serving), renal specific ONS for 6 months based on individual needs under dietitian's assessment. The change of serum albumin, body weight, and BMI were assessed for nutritional status. Protein and energy intakes were estimated from the dietary records. The outcomes on handgrip strength, blood biochemistries, appetite change, and quality of life were also examined.

Results: Totally 45 patients completed the intervention trial. Daily protein and energy intakes were elevated significantly 6 months later (+9.42 g/day, p<0.02; +175.37 kcal/day, p<0.001). Mean body weight and BMI increased significantly (+1.18 kg, p<0.001; +0.47 kg/m^2 p<0.001) but there was no significant difference in serum albumin (4.09 g/dl to 4.13 g/dl) after intervention for 6 months. However, handgrip strength and appetite improved significantly (+1.28 kg, p<0.001; +0.20 scores, p=0.03). There was no significant difference in the parameters of quality of life and the profiles of blood biochemistries.

Conclusions: The addition of renal specific ONS can maintain albumin level and improve anthropometry, handgrip strength, and appetite in non-dialyzed stage 3b-5 CKD patients compared to those who received standard diet counseling.

Funding: Commercial Support - Abbott Laboratories Services Corp. Abbott Nutrition, Taiwan

SA-PO149

Effects of Resistant Starch Supplementation on Inflammatory and Oxidative Stress Status in Hemodialysis Patients: A Pilot Randomized, Double-Blind, Placebo-Controlled Clinical Trial Denise Mafra, Marta Esgalhado, Milena B. Stockler-Pinto, Natalia A. Borges, Ludmila F. Cardozo, Bruna Paiva, Mariana Z. Jardim, Julie ann Kemp. *Federal Fluminense University, Niterói, Brazil.*

Background: In recent years, researchers have suggested that gut microbiota imbalance may be considered as a new cardiovascular risk factor in chronic kidney disease (CKD) patients, once it is associated with inflammatory and oxidative stress state. In this context, prebiotics use has been pointed out as a promising non-pharmacological therapeutic strategy by reestablishing the gut microbiota balance. The aim of this study was to determine the effect of resistant starch (RS) (as prebiotic source) supplementation on inflammatory and oxidative stress status on hemodialysis (HD) patients.

Methods: This randomized, double-blind, placebo-controlled clinical trial evaluated 20 CKD patients on HD (55% male, 55.6 ± 10.7 years, 30.5 (14.2 – 62) months HD vintage, BMI, 26.5 ± 4.8 kg/m^2). Patients were randomized to receive prebiotic (10 patients received 9 cookies/d in the dialysis days and 1 sachet/d in non-dialysis days, containing 16g of RS- Hi-Maize 260, Ingredion®) or placebo (10 patients received cookies and sachets - containing manioc flour) for 4 weeks. High sensitive C-reactive protein (hs-CRP) was analyzed using Bioclin® kit by automatic biochemical analyzer, interleukin (IL)-6 plasma levels were performed by ELISA and, malonaldehyde (MDA) plasma levels, a common marker of lipid peroxidation, were measured by thiobarbituric acid reaction. Routine biochemical parameters and nutritional status were also obtained.

Results: There was no significant difference between baseline values for any variable in both groups. After 4 weeks of RS supplementation, there was a significant reduction in IL-6 (from 3.47 ± 0.004 to 3.46 ± 0.001 pg/mL, p= 0.001) and MDA (from 4.64 ± 2.47 to 2.33 ± 1.57 nmol/mL, p=0.04) plasma levels. *No change was observed* in *placebo group.*

Conclusions: Data from this randomized study suggest that RS supplementation may modulate inflammation and oxidative stress in HD patients. These findings support the need for more studies with prebiotics in CKD patients to confirm the hypothesis that they could be a new non-pharmacological therapeutic strategy to modulate gut microbiota in these patients and reduce complications related to its imbalance.

Funding: Government Support - Non-U.S.

SA-PO150

Optical Analysis of Mitochondrial Dynamics and Function in Renal Physiology and Pathology In Vivo Using Metabolic Biosensor Transgenic Zebrafish Yuya Sugano,[2,3] Jacob P. Keller,[4,5] Ritu Tomar,[2,3] Hugo L. Siegfried,[2,3] Loren Looger,[4,5] Iain A. Drummond.[1,3] *[1]Massachusetts General Hospital, Charlestown, MA; [2]Massachusetts General Hospital, Charlestown, MA; [3]Harvard Medical School, Boston, MA; [4]Janelia Research Campus, Ashburn, VA; [5]Howard Hughes Medical Institute, Ashburn, VA.*

Background: Accumulating amounts of evidence suggest that mitochondria play a major role in maintenance of renal function and pathogenesis of kidney diseases. Despite

the apparent importance, however, little is known about mechanisms by which altered mitochondrial function leads to development of renal disease due to lack of appropriate tools. Mitochondria are a dynamic organelle that actively changes its shape, number and site of residence, thereby making it critical to analyze them *in vivo*. In order to establish *in vivo* tools to study mitochondria, we applied the genetically encoded biosensor technology to the zebrafish, an optically accessible and genetically tractable model system.

Methods: A transgenic zebrafish line incorporating a mitochondria targeted redox sensor (mitoGrx1-roGFP2) under the UAS effector element was generated. By crossing this UAS effector line into Gal4 driver lines with *podocin* and *cdh17* promoter [Tg(podo:Gal4) and Tg(cdh17:Gal4)], mitoGrx1-roGFP2 was expressed in glomerular podocytes and tubular epithelial cells, respectively, in the pronephros. Live imaging of the transgenic zebrafish was performed by sequential excitation at 405 nm and 488 nm for ratiometric measurements.

Results: We found that mitochondrial structure and dynamics in podocytes can be imaged in living zebrafish by two-photon microscopy. Time lapse imaging of Tg(podo:Gal4, UAS:mitoGrx1-roGFP2) demonstrated that mitochondria are stationary in pronephric podocytes. Upon exposure to a nephrotoxic antibiotic, puromycin aminonucleoside, mitochondria appeared to relocalize to primary and secondary processes from the cell body. Furthermore, ratiometric measurements of mitoGrx1-roGFP2 reported changes in oxidative stress levels in mitochondria in renal tubular epithelia in response to tert butyl hydroperoxide.

Conclusions: These transgenic zebrafish represent a novel tool to investigate mitochondrial structure and function *in vivo*. In addition, transgenic zebrafish with biosensors for other metabolic parameters, such as glucose, are also being validated. These transgenic zebrafish offer a versatile and accessible *in vivo* system to study mitochondrial dynamics and activity as well as their associated metabolism in the kidney in health and disease.

Funding: NIDDK Support, Government Support - Non-U.S.

Table 1 a). Association between lipoproteins and infection-related hospitalization and death

	Multivariate Model	Model with NLR	Model with CRP
Variable	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age [years]	1.024 (1.017, 1.031)***	1.024 (1.106, 1.031)***	1.022 (1.104, 1.029)***
Albumin [g/dL]	0.427 (0.360, 0.507)***	0.444 (0.374, 0.527)***	0.496 (0.416, 0.592)***
Access: catheter	1.001 (0.804, 1.246)	0.992 (0.797, 1.235)	0.995 (0.799, 1.238)
LDL [per 10 mg/dL]	0.94 (0.915, 0.966)***	0.94 (0.915, 0.966)***	0.994 (0.992, 0.997)***
HDL [per 10 mg/dL]	1.051 (0.986, 1.119)	1.051 (0.987, 1.12)	1.005 (0.999, 1.102)
Log triglycerides [mg/dL]	1.061 (0.878, 1.282)	1.064 (0.881, 1.286)	1.06 (0.877, 1.281)
NLR		1.03 (1.105, 1.045)***	
Log CRP [mg/L]			1.221 (1.151, 1.296)***

Table 1 b). Association between lipoproteins and cardiovascular hospitalization and death

	Multivariate Model	Model with NLR	Model with CRP
Variable	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age [years]	1.035 (1.028, 1.042)***	1.035 (1.028, 1.042)***	1.033 (1.027, 1.040)***
Albumin [g/dL]	0.636 (0.544, 0.742)***	0.647 (0.554, 0.756)***	0.701 (0.598, 0.821)***
Access: catheter	1.035 (0.861, 1.245)	1.030 (0.856, 1.239)	1.028 (0.855, 1.236)
LDL [per 10 mg/dL]	0.983 (0.962, 1.005)	0.983 (0.961, 1.004)	0.985 (0.964, 1.007)
HDL [per 10 mg/dL]	0.902 (0.849, 0.959)*	0.903 (0.849, 0.960)*	0.901 0.847, 0.958)***
Log triglycerides [mg/dL]	1.053 (0.894, 1.240)	1.055 (0.896, 1.243)	1.052 (0.893, 1.239)
NLR		1.017 (1.001, 1.034)*	
Log CRP [mg/L]			1.141 (1.084, 1.200)***

Table 1 c). Association between lipoproteins and all-cause mortality

	Multivariate Model	Model with NLR	Model with CRP
Variable	HR (95% CI)	HR (95% CI)	HR (95% CI)
Age [years]	1.035 (1.032, 1.038)***	1.035 (1.032, 1.038)***	1.034 (1.031, 1.036)***
Albumin [g/dL]	0.486 (0.458, 0.517)***	0.500 (0.470, 0.532)***	0.529 (0.497, 0.563)***
Access: catheter	0.932 (0.862, 1.008)	0.931 (0.861, 1.007)	0.927 (0.857, 1.003)
LDL [per 10 mg/dL]	0.980 (0.971, 0.989)***	0.980 (0.971, 0.989)***	0.981 (0.972, 0.990)***
HDL [per 10 mg/dL]	0.919 (0.897, 0.942)***	0.920 (0.898, 0.943)***	0.919 (0.897, 0.943)***
Log triglycerides [mg/dL]	0.852 (0.795, 0.914)***	0.856 (0.799, 0.918)***	0.856 (0.799, 0.918)***
NLR		1.024 (1.109, 1.029)***	
Log CRP [mg/L]			1.124 (1.100, 1.148)***

* statistical significant *** highly statistical significant

SA-PO151

Low Density Lipoprotein Cholesterol Is Associated with Decreased Infectious Death and Hospitalization in Hemodialysis Patients

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Background: Reduction in low density lipoprotein (LDL) does not decrease mortality in hemodialysis (HD) patients. The second leading cause of death in HD after cardiovascular (CV) diseases is infectious. LDL absorbs and inactivates bacterial toxins. Injected human LDL prevents endotoxin induced lethality in mice. We examined the effect of LDL, High Density Lipoprotein (HDL) and triglycerides (TG) on infectious, CV events and all cause mortality.

Methods: We explored relationships between blood lipids and outcomes in databases from Renal Research Institute (RRI) clinics in US and Fresenius Medical Care (FMC) clinics in Europe, and west Asia (14,650 patients, 60.2% male). All incident and prevalent patients starting in-center HD between Jan 1, 2000 and Dec 31, 2012 with at least one lipid measurements and inflammatory measures (C reactive protein (CRP)) or neutrophil lymphocyte ratio (NLR) measured were selected. Time to bacterial infectious, CV hospitalization or death or all cause death during up to 4 years of following the last lipid measurement were analyzed by Cox time varying proportional hazards.

Results: LDL reduced risk of infectious death and hospitalizations, and all-cause mortality (HR 0.98 0.971-0.989, (P< 0.001). HDL was associated with a reduction in CV death and hospitilization (HR 0.901 0.847-0.958 P = 0.0009) and all-cause mortality (HR 0.919 0.897-0943 P <0.001) and TG was associated with a reduction in all cause mortality (HR 0.683 0.642-0.726 P <0.001).

Conclusions: Higher LDL is associated with decreased all cause death and infectious death and hospitalizations, but not with increased CV risk, possibly accounting for the observation that reducing LDL cholesterol has a limited effect on outcomes in patients undergoing hemodialysis.

Funding: Commercial Support - Fresenius, MONDO

SA-PO152

Low Plasma Insulin-Like Growth Factor-1 Associates with Increased Mortality in CKD Patients with Reduced Muscle Strength

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Background: Chronic kidney disease (CKD) leads to metabolic and nutritional abnormalities including resistance to insulin-like growth factor-1 (IGF-1) action. Low plasma IGF-1 concentration as well as low handgrip strength (HGS), a reliable and easy-to-perform nutritional parameter, are independent predictors of increased mortality in CKD patients (pts). We hypothesized that low muscle strength enhances the negative impact of low IGF-1 on survival in CKD.

Methods: We included 685 CKD pts (62% males; median age 58 years) including 75 CKD 3-4 pts, 361 incident dialysis pts, 70 prevalent peritoneal dialysis pts and 179 prevalent hemodialysis pts. Baseline measurements of IGF-1, HGS, nutritional status (by subjective global assessment, SGA), lean body mass index (LBMI), and metabolic and inflammatory biomarkers potentially linked to IGF-1 were analysed in relation to mortality during follow up period of up to 5 years during which 208 pts (30.4%) died. We compared survival in four groups with high or low (cut-offs defined by ROC curve analysis) levels of IGF-1 and HGS.

Results: Pts with low IGF-1 were older, had lower body mass index (BMI), HGS and LBMI, more likely to have diabetes, CVD and malnutrition (SGA >1), and had sensitivity C-reactive protein (hsCRP) levels. During 5 years of follow-up, 208 pts (30.4%) died. Pts with Low IGF-1 + Low HGS had markedly increased mortality rate: In competing-risks regression analysis, sub-hazard ratio (SHR) of pts with Low HGS + Low IGF-1 was 2.3 times higher than for pts with High HGS + Low IGF-1. Low IGF-1 + Low HGS was independently associated with all-cause mortality after adjustments for age, sex, diabetes, CVD, SGA, smoking, hsCRP, albumin and LBMI.

Conclusions: Low IGF-1 together with low HGS - but not low IGF-1 together with high HGS - was independently associated with increased all-cause mortality suggesting that the effect of IGF-1 on mortality in CKD patients depends on nutritional status.

Funding: Commercial Support - Baxter Healthcare Corporation, Government Support - Non-U.S.

SA-PO153

Influence of Diabetes on Sarcopenia in Hemodialysis Patients

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Background: Recently, the associations between sarcopania and diabetes and between sarcopenia and chronic kidney disease, including hemodialysis (HD) condition, have been reported. However, there have been few reports that examine the relationship between sarcopenia and diabetes in HD patients. Little is known how far diabetes affects sarcopenia in HD patients. Moreover, definition of sarcopenia was made only in considering the low muscle mass in most of the previous studies. The purpose of this study was to assess sarcopenia which was strictly assessed by both muscle mass and muscle strength, and was to examine the association of diabetes with sarcopenia in HD patients.

Methods: A total of 308 patients on maintenance HD (age 58.1 ± 11.9 years, HD duration 6.5 ± 6.0 years, 60 % males, and 33 % diabetics) were examined. Appendicular

skeletal muscle mass was measured by dual energy X-ray absorptiometry (DXA). Low muscle mass was defined as skeletal muscle mass index (SMI) of < 6.87 kg/m² for males and < 5.46 kg/m² for females. Low muscle strength was defined as hand grip strength of < 26 kg for males and < 18 kg for females. Sarcopenia was defined as decline in both SMI hand grip strength.

Results: There were no significant differences in HD duration or in hemoglobin between patients with and without sarcopenia. Age was significantly higher, and body mass index and serum albumin were significantly lower in patients with sarcopenia than in those without sarcopenia (63.5 ± 11.0 *vs.* 54.1 ± 11.0 years, p < 0.0001; 19.4 ± 2.5 *vs.* 21.2 ± 2.3 kg/m², p < 0.0001 and 3.9 ± 0.3 *vs.* 4.1 ± 0.3 g/dL, p < 0.0001, respectively). Prevalence of sarcopenia in diabetic patients was significantly higher than that in non-diabetic patients (51 % *vs.* 36 %, p = 0.0151). In a multiple logistic regression analysis, presence of diabetes (OR = 3.02, p = 0.0008) was significantly, independenly associated with sarcopenia after adjustment with age, gender, HD duration, body mass index, hemoglobin, serum albumin, and C-reactive protein levels (R^2 = 0.273, p < 0.0001).

Conclusions: Present study clearly demonstrates, for the first time, that, in HD patients who are considered to be at higher prevalence of sarcopenia, diabetes is further an additional, strong risk factor for sarcopenia, which was strictly assessed by both muscle mass and muscle strength.

SA-PO154

Severe Vitamin D Deficiency Is a Risk Factor for Renal Hyperfiltration Jong Hyun Jhee,[1] Tae-Hyun Yoo,[1] Sukyung Kang,[2] Arum Choi.[2] *[1]Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea; [2]Department of Internal Medicine, College of Medicine, Severance Biomedical Science Institute, Brain Korea 21 PLUS, Yonsei University, Seoul, Republic of Korea.*

Background: Recent studies suggested that renal hyperfiltration (RHF) is significantly associated with increased risk of all-cause and cardiovascular mortality in relatively healthy adult population as well as diabetic patients. On the other hand, vitamin D deficiency is well known risk factor for renal progression in various diseases. This study aimed to investigate the association between RHF and vitamin D deficiency among relatively healthy adult population.

Methods: The data from subjects participated in the Korean National Health and Nutrition Examination Survey (KNHANES) from 2008 to 2015 were collected. A total of 33,210 subjects with normal renal function were included in the final analysis. Estimated GFR (eGFR) was calculated with the Chronic Kidney Disease Epidemiology Collaboration creatinine equation, and RHF was defined as eGFR > 95th percentile after adjustment for age, sex, and history of diabetes and/or hypertension. Severe vitamin D deficiency was defined as serum 25(OH)D < 10 ng/mL.

Results: The mean ages of the subjects were 48.1 years and the numbers of female subjects were 18,779 (56.5%). 1,637 (4.9%) subjects were categorized into RHF group. The proportions of hypertension and diabetes were significantly higher in RHF group than those in patients without RHF. According to serum 25(OH) level, the prevalence of renal hyperfiltration was significantly higher in the lowest 25(OH)D group (5.7%, P<0.001). Furthermore, multivariate linear regression analysis showed that 25(OH)D level was negatively associated with eGFR (β=-0.04, P < 0.001), systolic blood pressure (β=-0.01, P < 0.001), and fasting plasma glucose (β=-0.01, P < 0.001). In multivariate logistic regression model, severe vitamin D deficient group showed significantly high odds ratio (OR) for renal hyperfiltration than that in group with 25(OH)D ≥ 30 ng/mL (OR, 2.23; 95% confidence interval, 1.65-2.99; P <0.001).

Conclusions: Severe vitamin D deficiency is significantly associated with increasing prevalence of renal hyperfiltration in a relatively healthy population.

SA-PO155

Thiamine Deficiency in End-Stage CKD Patients Yosuke Saka, Tomohiko Naruse. *Nephrology, Kasugai Municipal Hospital, Kasugai, Japan.*

Background: Thiamine deficiency presents with several clinical manifestations such as heart failure, peripheral neuropathy and encephalopathy. Thiamine deficiency is observed also in patients with chronic kidney disease (CKD), resulting from malnutrition and long-term diuretic therapy. The risk of thiamine deficiency might be enhanced, especially in end-stage CKD patients. Thereby, we assessed thiamine status on incident dialysis patients.

Methods: This study included 188 consecutive patients initiated into dialysis between April 2013 and March 2016 in our hospital. Of 188 patients, 14 patients taking thiamine supplements were excluded. Thiamine status was evaluated by high-performance liquid chromatography (HPLC) measurement of thiamine in whole blood. We evaluated the association between blood thiamine concentration and other clinical parameters.

Results: The median value of blood thiamine concentration was 29.7 ng/mL [IQR:24.4–38.8]. In 21 patients (12.1%), blood thiamine concentration was lower than the normal lower limit (21.3 ng/ml). In Spearman univariate correlation analysis, blood thiamine concentration was correlated with age, Barthel index (BI) score and body mass index (BMI). Serum albumin concentration and loop diuretics therapy had no correlation with blood thiamine concentration. Multivariate regression analysis indicated that age (β-coefficient = –0.24, p = 0.043) and BI score (β-coefficient = 0.14, p = 0.025) were independent risk factors of thiamine deficiency.

Conclusions: This study shows that the proportion of end-stage CKD patients with low blood thiamine concentration was high. In addition, this study suggest that age and low physical activity (low score on BI) are independent risk factors of thiamine deficiency. Clinicians should be aware of thiamine deficiency when end-stage CKD patients, especially elderly patients with low physical activity, present unexplained cardiac or neurologic symptoms.

SA-PO156

Thyroid Status and Body Composition in a Prospective Hemodialysis Cohort Connie Rhee,[3] Yanjun Chen,[3] Amy S. You,[5] Csaba P. Kovesdy,[6] Matthew J. Budoff,[2] Tracy Nakata,[1] Alejandra Novoa,[5] Gregory Brent,[7] Kamyar Kalantar-Zadeh,[4] Danh V. Nguyen.[5] *[1]UC Irvine, Orange, CA; [2]UCLA School of Medicine, Torrance, CA; [3]University of California Irvine, Huntington Beach, CA; [4]University of California Irvine, School of Medicine, Orange, CA; [5]University of California, Irvine, Orange, CA; [6]University of Tennessee Health Science Center, Memphis, TN; [7]VA Greater Los Angeles Healthcare, Los Angeles, CA.*

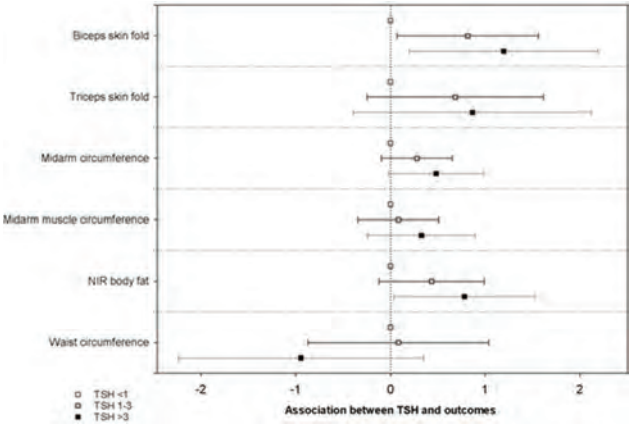
Background: Thyroid status is known to control metabolism, with subsequent effect upon body composition. In addition to causing excess adiposity, hypothyroidism also increases development and growth of skeletal muscle. Whereas hypothyroidism is highly prevalent in hemodialysis (HD) patients, there has not been prior study of thyroid status and trajectory of body composition parameters in this population.

Methods: Among 590 HD patients from the prospective *Malnutrition, Diet, and Racial Disparities in Kidney Disease* study, we examined the association of thyroid status, defined by baseline serum TSH, with body composition parameters over time using case-mix+laboratory linear mixed effects models. Over 2013-17, patients were recruited from 17 outpatient HD facilities and underwent protocolized TSH testing and body anthropometry testing: subcutaneous fat (biceps and triceps skinfold [SF]); skeletal muscle (mid-arm circumference [MAC], mid-arm muscle circumference [MAMC]; total body fat (near infra-red [NIR] body fat); and visceral fat (waist circumference).

Results: Higher TSH levels were incrementally associated with greater biceps SF (ref: TSH <1mIU/L): β=+0.8mm (p=0.03) and β=+1.2mm (p=0.02) for TSH levels 1-3 and >3mIU/L, respectively (Figure). Similarly, incrementally higher TSH levels were associated with greater NIR body fat: β=+0.4% (p=0.13) and β=+0.8% (p=0.04) for TSH levels 1-3 and >3mIU/L, respectively. There was a trend between higher TSH levels and higher MAC: β=+0.3cm (p=0.15) and β=+0.5cm (p=0.06) for TSH levels 1-3 and >3mIU/L, respectively.

Conclusions: In HD patients higher TSH levels are associated with greater markers of subcutaneous and total body fat, and may potentially be associated with greater muscle mass. Future studies are needed to determine if thyroid-modulating therapy alters the body composition of hypothyroid HD patients.

Funding: NIDDK Support



SA-PO157

The Best Cut-Off Value of Malnutrition-Inflammation Score (MIS) for Predicting Death in Maintenance Hemodialysis Patients Yanet Parodis Lopez,[6,2] Nery N. Sablón gonzalez,[1] Francisco Javier Rodriguez-Esparragon,[1,5] Noel Lorenzo villalba,[7] Gloria Anton,[2] Fayna Gonzalez cabrera,[3,1] Elena Oliva-Damaso,[4,3] Eduardo Baamonde,[3] Jose carlos Rodriguez perez.[1,3] *[1]Nephrology, Hospital Dr. Negrin, Las Palmas de GC, Spain; [2]Avericum, Telde, Spain; [3]Hospital Dr. Negrin, SANTA BRIGIDA, Spain; [4]Hospital General Universitario de Gran Canaria Dr Negrin, Las Palmas, Spain; [5]Unidad de Investigación, Hptal Dr. Negrín, Gran Canaria, Spain; [6]Nephrology, Centro de Hemodiálisis AVERICUM, Las Palmas de Gran Canaria, Spain; [7]Néphrologie, Centre Hospitalier Saint Cyr, France, France.*

Background: Mis score is associated with morbidity and mortality; however, there are few studies about cut-off value of MIS to categorize patients into high or low risk patients.

Methods: A total of 221 patients from the peripheral hemodialysis center of Dr Negrín University Hospital of Las Palmas de Gran Canaria were included. Demographic and biochemical data were obtained as well as MIS score. A three-year follow-up was carried out to evaluate the best cut-off value of MIS score for predicting death as the primary outcome.

Results: The MIS mean was 7,33 ± 4,57 and was higher in deceased patients (8,34 ± 4,56) than in the non-deceased patients (6,5 ± 4,26) (p = 0,002). In the ROC analysis, the optimal cut-off value of MIS for predicting death was 5 with 81,5 percent sensitivity and 42,6 percent specificity (Figure 1). MIS ≥ 5 was found in 67,3% of patients. 81,5% of the deceased patients had a MIS ≥ 5 compared to only 57,4% of the non-deceased patients (p <0,001) High MIS and Charlson index, advanced age and low lymphocytes were found to be predictors of mortality in the multivariate logistic regression analysis. As the MIS increases, overall survival is lower according to the Kaplan Meier's statistical analysis (p = 0,003) (Figure 2).

Conclusions: MIS was a practical, simple and independent predictor of mortality in hemodialysis patients, being 5 the best cut-off point to predict mortality. Additional risk factors associated with mortality were high Charlson Index, advanced age as well as lymphopenia.

Figure 1 :"The optimal cut-off value of MIS for predicting death in maintenance hemodialys patients"

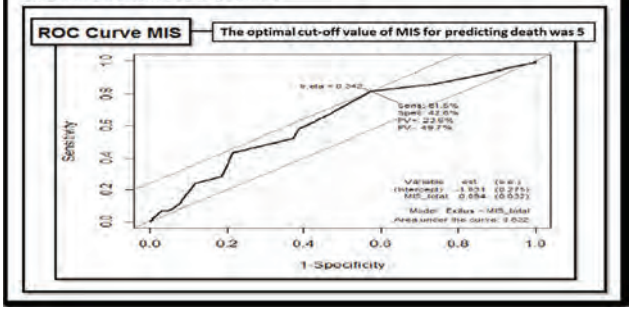
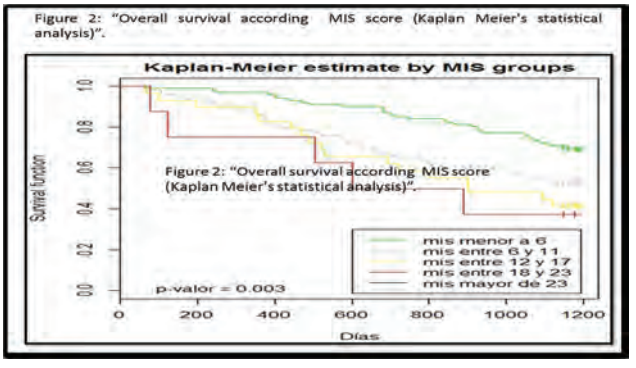


Figure 2: "Overall survival according MIS score (Kaplan Meier's statistical analysis)".



SA-PO158

Effects of Intravenous Iron Therapy on the Mortality and Hospitalization in Hemodialysis Patients Chun Soo Lim, Yun Kyu Oh. *Seoul National University Boramae Medical Center, Seoul, Republic of Korea.*

Background: Iron replacement therapy is inevitable to correct iron deficiency anemia in advanced chronic kidney disease patients. Intravenous (IV) iron therapy has been known as an efficient method to replace iron, especially in patients who are intolerant to oral iron. However, there have been concerns of considerable side effects with IV iron usage including increased risks of infection or cardiovascular disease (CVD). In this study, we compared IV iron usage with oral iron to assess the adverse effects in the prospective cohort of Korean patients.

Methods: We conducted multicenter prospective cohort study using Clinical Research Center for end stage renal disease. We enrolled 1,721 adult patients who were on hemodialysis between 2008 and 2013. Basic patient characteristics, laboratory data, dose of erythropoiesis stimulating agents (ESA) and 3-month iron dose were collected after enrollment. All-cause mortality, death and hospitalization due to infection or CVD were compared and propensity score matching were conducted to exclude the effects of other factors in outcome.

Results: In total 1,721 patients, 505 patients received IV iron therapy and 658 patients received oral iron only. Median IV iron dose during 3 months was 600mg (100 – 9,000 mg). In IV iron usage group, hemoglobin, ferritin, serum iron and transferrin saturation were significantly lower and total iron-binding capacity, ESA dose and erythropoietin resistance index were higher compared to oral iron group. During mean follow-up duration of 743.6±578.4 days, all-cause mortality, death due to infection or CVD and both death and hospitalization due to infection or CVD did not differ between two groups. Even in subgroup analysis of patients with higher IV iron usage (>600 mg/3 months), there were no significant differences in adverse outcomes. However, in subgroup analysis of prevalent patients, IV iron usage group tend to show higher hospitalization and death due to infection and CVD. After propensity score matching, similar trends were observed.

Conclusions: The current clinical usage of IV iron in hemodialysis patients did not increase all-cause mortality or death and hospitalization due to infection or CVD compared to oral iron therapy. A well-designed randomized controlled trial is needed to clarify both short-term and long-term effects of IV iron therapy.

SA-PO159

Association of Adiposity with Hemoglobin Levels in Patients with CKD Not on Dialysis Hirokazu Honda,[1] Kota Ono,[5] Tadao Akizawa,[2] Kosaku Nitta,[3] Akira Hishida.[4] *[1]Showa University Koto Toyosu Hospital, Tokyo, Japan; [2]Showa University School of Medicine, Tokyo, Japan; [3]Tokyo Women's Medical University, Shinjuku-ku, Japan; [4]Yaizu City Hospital, Yaizu, Japan; [5]Hokkaido University Hospital, Sapporo, Japan.*

Background: Adiposity influences erythropoiesis and iron metabolism in the general population. We therefore hypothesized that adiposity could be associated with erythropoiesis or impaired iron metabolism in patients with CKD; however, and that these associations would be influenced by the severity of CKD. The present study aimed to assess the relationship between adiposity—as estimated by body mass index (BMI) and abdominal circumference (AC)—and biomarkers of erythropoiesis in patients with chronic kidney disease (CKD) not on dialysis.

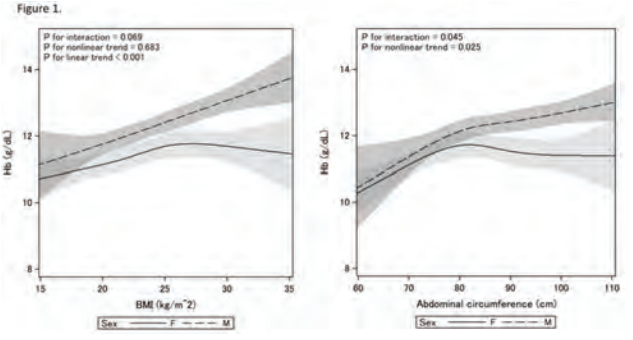
Methods: A total of 2,322 patients from the Chronic Kidney Disease Japan Cohort study were analyzed. Patients were grouped according to BMI category (low: BMI <18.5, normal: BMI 18.5-24.5, and high: BMI ≥25) and AC category (large: AC ≥90 cm for males and AC ≥80 cm for females, and; small: AC measurements below the large values<90 cm and <80 cm). Body composition and laboratory data were measured at baseline, 1 year, and 2 years.

Results: Multivariate regression analysis at 3 time points showed that a high BMI and large AC in male patients were significantly associated with higher hemoglobin levels. Hemoglobin levels in female patients with BMI<18.5 and small AC were lower than with 18.5≤BMI<25 and large AC, respectively (Fig. 1). However, hemoglobin levels were plateaued above threshold of 25 of BMI and 80cm of AC, respectively (Fig. 1). While BMI and AC were positively associated with C-reactive protein levels, they were not associated with levels of transferrin saturation, ferritin, and erythropoietin in multivariate models.

Conclusions: In conclusion, body composition may be associated with erythropoiesis;, however, adiposity may be only associated with increased erythropoiesis in male patients. It does not appear to hamper iron metabolism in CKD patients not on dialysis.

Funding: Commercial Support - Kyowa Hakko Kirin Co., Ltd

Figure 1.



SA-PO160

Falls and Fall-Related Injuries in Older Americans with CKD Brandon Kistler,[1] Jagdish Khubchandani,[1] Gina Jakubowicz,[1] Ken Wilund,[2] Jacob J. Sosnoff.[3] *[1]Ball State University, Muncie, IN; [2]University of Illinois, Urbana, IL; [3]University of Illinois at Urbana-Champaign, Urbana, IL.*

Background: Falls are among the leading causes of morbidity and mortality in older adults (age ≥65 years). Within older adult populations, few studies have identified the risk factors for falls in chronic kidney disease (CKD) patients. Previous studies have primarily been based on small convenience samples from healthcare facilities, emphasized severely ill patients, and explored only a few predictors of falls. This has led to conflicting data on risk factors for falling. Therefore, our objective was to examine the prevalence and predictors of falls in older adults with CKD from a large non-hospitalized population-based sample.

Methods: Using complex sample data analysis procedures, we analyzed the US Behavioral Risk Factor Surveillance System (BRFSS) to assess the prevalence and predictors of falls and fall-related injuries among older adults with CKD.

Results: The sample contained 157,753 older adults (56% female, 77% White, 57% in the age range of 65-75 years) with a fall prevalence of 28.7% within the last year. Within the sample, 9,116 (6.1%) had a diagnosis of CKD and 32,669 (23.5%) had diabetes. In multiple logistic regression models, individuals with CKD were more likely than those without CKD to report falls (OR 1.81 [95% CI] (1.63-2.01)) and fall-related injuries (OR 1.49 (1.26-1.77)) even after adjusting for demographic characteristics and chronic conditions. Within the CKD group, females (OR=1.71, p<0.01), non-whites (OR=1.17, p<0.05), diabetics (OR=1.21, p<0.05), those who used any special equipment, such as cane/wheelchair (OR=2.79, p<0.001), and those who had limited activity due to physical or mental problems (OR=2.23, p<0.001) had the highest odds of reporting falls. Furthermore, there was a trend for increased falls with increasing age category (p=0.06).

Conclusions: Falls and fall-related injuries are highly prevalent in elderly individuals with CKD, particularly in women, special equipment users, and those with limited activity. Multifactorial fall prevention strategies should be designed to target these at-risk populations.

SA-PO161

Effect of Fructooligosaccharide on Microbiota-Derived Uremic Toxins in Predialysis Patients: A Randomized Controlled Trial

Christiane I. Ramos,[1,3] Rachel G. Armani,[1] Lia S. Nakao,[4] Maria Eugenia F. Canziani,[1] Katrina L. Campbell,[2,3] Lilian Cuppari.[1] *[1]Federal University of Sao Paulo, Sao Paulo, Brazil; [2]Princess Alexandra Hospital, Brisbane, NSW, Australia; [3]Bond University, Robina, QLD, Australia; [4]Federal University of Parana, Curitiba, Brazil.*

Background: Microbiota-derived uremic toxins, p-cresyl sulfate (PCS) and indoxyl sulfate (IS), have been associated with poor outcomes in chronic kidney disease (CKD). This has encouraged the investigation of alternative approaches to modulate gut environment and to attenuate toxin production. The present trial aimed to evaluate the effect of the prebiotic fructooligosaccharide (FOS) on changes in PCS, IS, indole 3-acetic acid (IAA), kidney damage (eGFR and proteinuria) and insulin resistance in predialysis patients (stages 3b, 4 and 5).

Methods: The 3-month double-blind randomized controlled trial included 46 non-diabetic CKD patients [52% men; 57.6±14.4 years; eGFR: 21.3±7.3 mL/min/1.73m^2]. Intervention and placebo consisted in 12g/day of FOS or maltodextrin, respectively. PCS, IS and IAA were determined by high performance liquid chromatography. Dietary intake was assessed by 3-day food records; supplement adherence (sachet count) and gastrointestinal events by the Gastrointestinal Symptom Rating Scale.

Results: Aside for the intervention group being older (53.4±16.0 vs 61.9±11.4 years, p=0.04) the groups were homogeneous. Overall sachet adherence was excellent (mean consumption: 93.1±8.1%). No changes in the ratio of dietary protein/fibre intake or gastrointestinal symptoms were observed during the follow-up. Changes in the outcomes are depicted in the table.

Conclusions: FOS was well tolerated and resulted in a trend for reduced PCS. No effect of FOS on IS, IAA, kidney damage or insulin resistance was observed.

Funding: Government Support - Non-U.S.

Δ	Placebo (n=23)	Intervention (n=23)	Treatment effect Mean [95% CI]	p
PCS (mg/L)	1.3±24.6	-12.3±25.1	-13.5[-29.2–2.3]*	0.09*
IS (mg/L)	-0.2(-1.5–1.8)	-0.2(-0.9–1.0)	-0.1[-1.6–1.4]	0.90
IAA (µM/L)	-0.7(1.8–1.0)	0.1(-1.7–1.6)	1.8[-4.4–8.1]	0.44
eGFR (ml/min/1.73m^2)	0.2±2.8	0.2±3.4	0.6[-3.7–5.0]	1.00
Proteinuria (mg/24hr)	70.0(-130.0–620.0)	80.0(-130.0–620.0)	1.2[-0.6–3.0]	0.78
HOMA-IR	0.0(-0.7–0.5)	0.0(-0.3–0.6)	-0.1[-1.0–0.8]	0.44

Mean±sd or median (interquartile range). CI: confidence interval. *Adjusted by baseline PCS, dietary protein/fibre ratio and age.

SA-PO162

The Effects of More Frequent Hemodialysis (HD) on Plasma Vitamin C Concentration: An Ancillary Study of the Frequent Hemodialysis Network (FHN) Daily Trial

Jochen G. Raimann,[5] Samer R. Abbas,[5] Li Liu,[4] Brett Larive,[1] Yuguan Liu,[6] Gerald J. Beck,[2] Peter Kotanko,[5,7] Nathan W. Levin,[5] Garry J. Handelman,[6] The FHN Trial Group.[3] *[1]Cleveland Clinic, Cleveland, OH; [2]Cleveland Clinic Foundation, Shaker Heights, OH; [3]NIDDK, NIH, Bethesda, MD; [4]Peking University First Hospital, Beijing, China; [5]Renal Research Institute, New York, NY; [6]University of Massachusetts, Lowell, MA; [7]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Reports on vitamin C in HD patients have shown effects of vitamin C deficiency (Raimann, Semin Dial 2013) in association with scurvy symptoms. Dialyzability of water soluble vitamins is high and substantial losses in those who are dialyzed more frequently were hypothesized. The randomized FHN Daily Trial compared the effects of in-center HD six versus three times per week. We studied baseline correlations between vitamin C and potentially associated parameters, and the effect of more frequent HD on circulating vitamin C.

Methods: We studied vitamin C levels at baseline, and at months, 3, 5 and 11. Patients enrolled between 2007 and 2009 into the main trial in the East Coast consortium were approached for participation, and informed consent was obtained. Pre HD samples were processed with metaphosphoric acid and frozen at -70 C for measurement with HPLC. Regression models between baseline log-transformed vitamin C and hemoglobin, CRP, eKt/V, ePCR and PTH, and a linear mixed-effects model to estimate the effect size of more frequent HD on plasma vitamin C, were constructed.

Results: We studied 44 subjects enrolled in the FHN Daily trial (50±12 years, 36% female, 29% Hispanics and 64% blacks, 60% anuric). Vitamin C correlated significantly with pre HD hemoglobin (r=0.3; P=0.03) and PTH (r=-0.3, P=0.04), respectively. Vitamin C did not significantly differ at baseline (6x/week: 25.8 ± 25.9 versus 3x/week: 32.6 ±39.4 µmol/L) and no significant treatment effect on vitamin C concentrations was found [-26.2 (95%CI -57.5 to 5.1) µmol/L at Month 4 and -2.5 (95%CI -15.6 to 10.6) µmol/L at Month 12.

Conclusions: Based on data from this randomized-controlled trial no significant effect of the intervention on circulating plasma vitamin C concentrations was found. While admittedly no information on supplements were available, these data allays the concerns that more frequent HD would affect the concentrations of water-soluble vitamins and adversely affect patient's well-being. Correlations between vitamin C and hemoglobin and PTH support the importance of vitamin C for normal bone and mineral metabolism and anemia management.

SA-PO163

Pyridoxine Lowers Urine Oxalate in Kidney Stone Formers with Enteric Hyperoxaluria

Jennifer Scott, Mitchell Humphreys, Sean Mcadams, Mira T. Keddis. *Mayo Clinic, Phoenix, AZ.*

Background: Pyridoxine is commonly deficient in patients with enteric hyperoxaluria. We hypothesize that pyridoxine replacement may reduce urine oxalate in stone formers with enteric hyperoxaluria.

Methods: All patients with nephrolithiasis and urine metabolic analysis between 2008-2016 at Mayo Clinic Arizona were identified. Patients with 24-hour urine oxalate >40 mg and prescribed pyridoxine were included in the study (n=13). Patients with primary hyperoxaluria were excluded.

Results: 13 patients with risk factors for enteric hyperoxaluria were prescribed pyridoxine for treatment of nephrolithiasis. 10 (77%) patients had urine metabolic studies performed post-treatment. 5 were male, with mean age of 57.7± 10.7 years. 5 had <2 L/24hr of urine volume, 3 had hypocitraturia (<440mg/24hr), and 3 had hypercalcuria (>200mg/24hr). The mean baseline 24-hour urine oxalate was 70.67 ± 39.40 mg/d. Pyridoxine dose ranged from 25-100mg/d. Repeat urine was performed after median of 10 months (1.5-21). Mean 24-hour urine oxalate was 57.86 ± 33.09 mg/d after treatment (mean difference 12.8 ± 29 mg/d). Urine oxalate level improved in 7 and normalized in 4 patients post-treatment. There was no statistically significant difference between urine oxalate levels pre- and post- pyridoxine treatment (p 0.31). 7 patients had stone analysis performed, 6 of whom had predominately calcium oxalate stones. Only 3 of 10 patients treated had recurrent kidney stones after pyridoxine treatment.

Conclusions: In our cohort, pyridoxine improved hyperoxaluria and decreased risk of recurrent nephrolithiasis in 70% of patients. Future studies are required to evaluate the dose of pyridoxine and validate our findings in a larger cohort of patients with malabsorptive enteric hyperoxaluria.

Patient	Pyridoxine dose(mg)	Urine volume(L) 24hr baseline	Oxalate(mg)	Citrate(mg)	Calcium(mg)	Urine volume(L) 24hr post-treatment	Oxalate(mg)	Citrate(mg)	Calcium(mg)
1	50	1.11	74.4	289.6	22.7	1.58	87	411	37
2	50	1.37	41.3	951.1	133.7	1.35	35.7	807.4	442
3		2.51	44.3	855.6	196.8	1.17	26.5	167.5	134.5
4	50	4.03	50.7	915.5	327.2	2.7	45	1095	514
5	50	1.51	90.3	22.7	90.3	1.13	56.5	16.9	98.4
6		3.49	173.6	52.3	110.3	2.96	111.1	44.5	61.6
7	50	0.92	48.6	621.2	85.7	1.25	54.4	430.6	87.3
8	25	2.41	65.5	553.1	315.4	2.25	22	285	258
9	100	1.81	69.4	740.3	96	3.66	108.5	573.7	188.5
10	50	2.89	48.4	656.8	218	3.61	32	479	239

SA-PO164

Low Leptin Level Is Associated with Poor Nutritional Status in ESRD

Jun young Lee,[3] Jae seok Kim,[5] Jae Won Yang,[2] Seung-Ok Choi,[4] Byoung Geun Han.[1] *[1]None, Wonju, Republic of Korea; [2]Wonju Christian Hospital, Wonju, GangWon-Do, Republic of Korea; [3]Wonju christian severance hospital, Wonju, Kangwon do, Republic of Korea; [4]Yonsei University Wonju College of Medicine, Wonju, Kangwon, Republic of Korea; [5]Yonsei wonju college of medicine, Won-ju, Republic of Korea.*

Background: Poor nutritional status is associated with poor prognosis in end stage renal disease (ESRD) patients. Bio-impedance spectroscopy (BIS) is a useful method to estimate body fluid and nutritional status. Particularly, phase angle (PhA, °) is a parameter that represents nutritional status well. In the study, we aim to identify factors related to nutritional status in ESRD patients not undergoing dialysis.

Methods: We enrolled total 91 ESRD patients not undergoing dialysis. We measured routine serum markers including albumin and NT-proBNP, and appetite regulating hormones, leptin and ghrelin. With BIS, we measured OH (overhydration, liter) and OH/ECW (OH/extracellular water ratio) values to estimate body fluid amounts, and PhA to determine nutritional status. We defined poor nutritional status as a PhA <4.5°, and proper nutritional status as a PhA ≥4.5°. Lastly, we evaluated patient's nutritional status by assessing geriatric nutritional risk index (GNRI).

Results: Forty-one patients (45%) had poor nutritional status. The patients with poor nutrition, compared to proper nutrition, had significantly higher levels of NT-proBNP (14,477.8±12,712 vs. 4,965.2±8,824 pg/mL, p<0.001) and OH/ECW (29.6±12.7 vs. 6.2±10.3 %, p<0.001), and lower levels of albumin (3.0±0.5 vs. 3.7±0.5 g/dL, p<0.001), leptin (3.8±3.1 VS. 7.0±6.2 ng/mL, p=0.004) and GNRI (85.1±7.1 vs. 96.5±7.7, p<0.001). In Pearson's correlation test, leptin had negative correlations with NT-proBNP (r= -0.237, p=0.026) and OH/ECW (r= -0.288, p=0.006). On the contrary, leptin had positive correlations with BMI (r=0.351, p=0.001), PhA (r=0.263, p=0.012) and GNRI (r=0.281, p=0.007). In multivariate logistic regression test, high level of leptin (OR 6.12, 95% CI 1.01-37.13) and albumin (OR 10.14, 95% CI 1.51-68.20) predicted proper nutrition well, while increased level of NT-proBNP (OR 0.07, 95% CI 0.01-0.84) and OH/ECW (OR 0.04, 95% CI 0.01-0.19) were related to poor nutrition.

Conclusions: Our study demonstrates that ESRD patients with poor nutrition generally have a problem of excessive body fluid as well. Leptin is well correlated positively with nutritional status. Low leptin level suggests poor nutrition in ESRD patients. We believe that these relationships may be due to a counter-regulatory mechanism of leptin to nutritional status as an appetite suppressing hormone.

SA-PO165

Oral Alkali Supplementation to Reduce Uremic Toxin in Early Stage CKD Patients Michiaki Abe,[4] Tomokazu Souma,[3] Hiroshi Sato,[1] Sadayoshi Ito.[2] *[1]Clinical Pharamacology and Therapeutics, Graduate School of pharmaceutical Sciences, Tohoku University, Sendai, Japan; [2]Tohoku Graduate School of Medicine, Sendai Miyagi, Japan; [3]Northwestern University Feinberg School of Medicine, Chicago, IL; [4]Tohoku University Hospital, Sendai, Japan. Group/Team: CKOALA study group.*

Background: Patients with chronic kidney disease (CKD) has increased plasma uremic toxins (UTxs) and they develop metabolic acidosis and aciduria. These metaboic dsysregulations affects CKD progression and cardiovascular and bone complicaitons. Recently, oral alkali therapy has been suggested to slow the progression of CKD pathologies. To investigate the effects of alkali supplementation on UTx accumulation, we have initiated a double-blinded randomized control cohort study of "Estimating the efficacy of the Oral ALkALizers in patients with CKD; CKOALA study." Two types of alkalizers, Na/K citrate and Na bicarbonate, were used.

Methods: Total 47 CKD patients (CKD stage G2, G3a, G3b) were randomized to divide into 3 groups, control (n=15), Na bicarbonate (n=16) and Na/K citrate (n=16). The urine and plasma samples at 0, 6, 12 and 24 weeks after the intervention were collected and anonymized. Five UTxs including (Indoxyl sulfate (IS), p-cresyl sulfate (PCS), phenylacetyl L-glutamine (PAG), and argininosuccinate (ASA) and hippuric acid) were quantified by a quantitative-target LC-MS/MS. Individual change of UTx abundance were compared and Mann-Whitney test was used for statistical analysis. This research was approved as a secondary use of CKOALA study by Tohoku University Hospital Ethics Committee.

Results: %change of urinary concentrations of IS, PCS, PAG and ASA from was compared among groups. Urinary UTx levels in the Na/K citrate-treated group were significantly increased compared to the other two groups [IS; 93% (control) vs. 145% (bicarbonate), p=0.017; PCS, 116% (control) or 181% (bicarbonate) vs. 351% (citrate), p=0.001 or p=0.015; PAG, 94% (control) or 100% (bicarbonate) vs. 160% (citrate), p=0.016 or p=0.019; ASA, 87% (control) vs. 126 (citrate), p=0.003]. Furtheremore, plasma concentrations for IS was significantly reduced by Na/K citrate-treatment (control 1.2 μg/mL or bicarbonate 1.4 μg/mL vs. citrate 1.1 μg/mL, p=0.029 or p=0.035).

Conclusions: Our feasiblity study shows that an alkali therapy reduces some kinds of UTxs abundance in CKD patients and may represent a mechanism whereby oral alkali supplementation prevents CKD progression.

Funding: Other NIH Support - JSPS KAKENHI Grant-in-Aid for Scientific Research (C)

SA-PO166

Leptin Levels Are Not Reduced by High-Flux Compared with Low-Flux Haemodialysis: Results of a Randomized Trial Andreas Schneider,[1] Markus P. Schneider,[5] Detlef H. Krieter,[4] Hubert Scharnagl,[2] Christoph Wanner,[3] Christiane Drechsler.[3] *[1]University of Wuerzburg, Wuerzburg, Germany; [2]Medical University of Graz, Graz, Austria; [3]University Hospital Wuerzburg, Wuerzburg, Germany; [4]University Hospital Würzburg, Würzburg, Germany; [5]University of Erlangen-Nuremberg, Erlangen, Germany.*

Background: Leptin, in addition to its well described effects on glucose homeostasis, might be directly involved in the progression of atherosclerosis, as it promotes chronic inflammation and vascular smooth muscle cell proliferation. Interestingly, leptin levels are significantly increased in haemodialysis (HD) patients compared with healthy controls. Interventional strategies able to reduce levels of leptin in HD patients are of particular interest. The low molecular weight of leptin (16 kD) suggests that its elimination might depend on the specific HD modality.

Methods: We performed a randomized controlled trial on the effects of high-flux versus low-flux HD. 127 maintenance HD patients were randomized to low-flux (n=62) or high-flux (n=65) HD for 52 weeks. The primary endpoint of the study was the effect on parameters of anaemia, which has been published previously. The secondary endpoint included the effect on leptin levels. Leptin levels were measured by ELISA at baseline and after 52 weeks of treatment.

Results: Patients in both groups were 66 years (mean age). Underlying kidney disease was diabetic nephropathy in most cases (28% in the low-flux group and 38% in the high-flux group). Compared to baseline, a significant increase in leptin levels after one year of low-flux HD was observed (Delta leptin 41.7 ng/ml; p=0.032). In contrast, leptin levels remained more stable in the high flux group (Delta leptin 32.8 ng/ml; p=0.062). However, there was no difference in absolute change of leptin levels over time between the two randomization groups (p=0.743).

Conclusions: In this randomized controlled trial, we found that leptin levels increased after one year in patients allocated to low-flux HD, but remained more stable in those allocated to high-flux HD. However, the lack of a significant treatment difference suggests that high-flux HD is not more effective than low-flux HD. Future studies should investigate whether enhanced convective solute transport (e.g. by haemodiafiltration) would be able to improve leptin removal and patient outcome.

SA-PO167

The Discrepancy in the Predictability of Subjective Global Assessment for Mortality According to Dialysis Vintage in Hemodialysis Patients Ye Eun Ko,[1] Taeyoung Yun,[2] Dong-Ryeol Ryu.[1] *[1]Ewha Womans University, Seoul, Republic of Korea; [2]Ewha womans university, Seoul, Republic of Korea.*

Background: Subjective Global Assessment (SGA) is used to gauge nutritional status in dialysis patients. Still, SGA is not reliable for predicting mortality. There is no study on the predictability of SGA regarding mortality between incident and prevalent hemodialysis (HD) patients.

Methods: *A total of 2,798 dialysis patients were enrolled from CRC for end-stage renal disease between May 2009 and December 2015. The cohort was divided into two groups: incident (n=1,481) and prevalent HD (n=1,317). Each was stratified into two groups based on SGA: 'Good nutrition (G1)' and 'Mild to severe malnutrition (G2).' Kaplan-Meier (KM) and multivariate Cox analyses were performed to evaluate the relation between SGA and mortality in each HD group. Prevalent HD patients were divided into 'short-term' and 'long-term' groups based on median dialysis duration (36.7months), and multivariate Cox analyses were conducted. Incident HD patients were divided based on the presence of diabetes mellitus, age of 65 years or older, and obesity (BMI≥25 kg/m²). The relationship between SGA and mortality was further examined in sub-analyses.*

Results: During a median 3.1 years of follow-up period, 590 (21.1%) patients died. The KM survival curve showed that the cumulative survival rate in G1 was significantly higher than that in G2 among all patients (P<0.001) as well as in each group stratified based on dialysis vintage (P<0.001). Multivariate Cox analyses revealed that G2 was significantly associated with an increase in mortality (HR; 1.27, 95%CI; 1.10-1.47, P=0.002) compared with G1 among all patients. G2 was also significantly related to an increase in mortality in prevalent HD patients, but not incident HD patients (HR; 1.33, 95%CI; 1.01-1.75, P=0.04). Yet, in short-term, not long-term prevalent patients, G2 was significantly associated with an increase in mortality compared to G1 (HR; 1.52, 95%CI; 1.04-2.24, P=0.03). There were no significant relations between the SGA and mortality in the sub-analysis among incident HD patients.

Conclusions: Nutrition status according to SGA might be helpful for predicting mortality especially in prevalent HD patients, whereas SGA alone do not reflect the adverse clinical outcomes in incident HD patients. Further evaluation is needed to determine the discrepancy in association with mortality between two HD populations.

SA-PO168

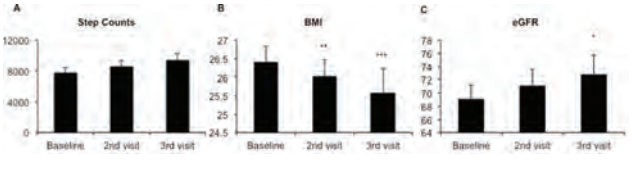
Exercise Favorably Affects Renal Function in Metabolic Syndrome without CKD: A Prospective Single-Center Study Atsushi Ueda,[1] Kei Nagai,[3] Aki Hirayama,[4] Chie Saito,[2] Kunihiro Yamagata.[2] *[1]Tsukuba University Hospital Hitachi Medical Education and Research Center, Hitachi, Ibaraki, Japan; [2]University of Tsukuba, Tsukuba, Japan; [3]University of Tsukuba hospital, Tsukuba-city Ibaraki, Japan; [4]Tsukuba University of Technology, Tsukuba, Japan.*

Background: A high body mass index (BMI) predicts an onset of CKD in population with normal renal function (Kidney Int. 2017; 91:1224-1235). It is expected that lifestyle-modification in obese individuals without CKD has favorable effects on renal function through the normalization of body weight and BMI. However, whether exercise can improve the renal function in obese individuals without drug-medications has not been fully resolved.

Methods: We studied 29 patients with high BMI (>25 kg/m²) and/or hypertensive (>grade 1 hypertension) and/or high LDL-C (>140 mg/dL) and/or moderately high HbA1c (6.5–7.5%), with no abnormality of urinalysis and no drug-medications. We provided education regarding resistance-exercise and aerobic exercise to the subjects for one hour at the first (baseline) visit. We measured their weight, waist circumference, blood pressure, and laboratory data at every visit. In addition, step-counts per day were calculated from cumulative records for every day by the pedometer during visits.

Results: Compared to first (baseline, visit 1), one month (visit 2), and two month later (visit 3), the mean step-counts of the subjects tend to increase (P=0.07, **Fig 1A**). The mean body weight and BMI were 71.9, 70.8 and 69.3 kg (P<0.01), and 26.4, 26.0, and 25.6 kg/m² (P<0.01, **Fig 1B**), respectively. Changes in step-counts and that in body weight were negatively correlated (r=-0.51, P=0.01). While serum LDL-C and HbA1c were not significantly declined, serum creatinine (P=0.01) and eGFR (P=0.01, **Fig 1C**) were improved during the follow-up.

Conclusions: Though the changes in most of parameters (blood pressure, lipid status and glycemic status) were not significant in this limited follow-up time, significant changes in renal function (serum creatinine and eGFR) were identified. It is suggested that exercise among obese individuals has a potential to improve their renal function independent of drug-medications.



SA-PO169

Protein Energy Wasting Is Correlated with Irisin and Over Load Fluid in Peritoneal Dialysis Patients Sijia Zhou, Ai Hua Zhang. *Peking University Third Hospital, Beijing, China.*

Background: Protein energy wasting (PEW) is a common phenomenon in maintenance dialysis patients and increased morbidity and mortality. The mechanisms are unclear. Over load fluid may also induce PEW in peritoneal dialysis patients. Irisin is a newly discovered myokine which can alleviate insulin risistance, is one kind of regulators of energy homeostasis and metabolism in humans. The aim of this study is to assess the relationships between irisin, over load fluid and PEW in PD patients.

Methods: This study is a cross-sectional study with 160 patients on maintenance peritoneal dialysis in peritoneal dialysis center of Peking University Third Hospital involved and 35 healthy people in a control group. PD patients were divided into two groups: protein energy waste group (PEW group) and non-protein energy waste group (non-PEW group) according to PEW diagnosis criteria. Serum irisin concentrations were measured by ELISA methods. The body composition consisting of over load fluid status [over hydration (OH) value >=2)] was analyzed by bioelectrical impedance.

Results: The serum irisin levels were significantly lower in PD patients compared with controls [113.2±11.8ng/ml vs. 464.2±37.4ng/ml, P<0.01]. The serum irisin levels were lower in PD patients with protein energy wasting than those of the patients without protein energy wasting[107.8±9.6ng/ml vs. 119.0±11.3ng/ml, P<0.01]. Existing over load fluid patients with higher prevalence of PEW (59.8%Vs.40.2%, x2=6.223, P=0.013). But there was no direct relationship between irisin level and over load fluid. The independent determinants of PEW were serum irisin and serum albumin.

Conclusions: Our results provide clinical evidence of the association between irisin, over load fluid and protein energy wasting in PD patients. Low irisin and over load fluid may aggravate protein energy wasting.

Funding: Government Support - Non-U.S.

SA-PO170

Bariatric Surgery Reduces Proteinuria in Severely Obese Patients with Normal Kidney Function by Reducing Systemic Inflammation Nam-Jun Cho, Hyo-Wook Gil, Chi-Young Choi. *Soon Chun Hyang University College of Medicine, Cheonan Hospital, Cheonan, Republic of Korea.*

Background: Obesity are associated with renal disease, including proteinuria, chronic kidney disease (CKD) and progression to end-stage renal disease. Bariatric surgery (BS) reduce proteinuria and improve renal function. The mechanism include improved blood pressure, improved glucose homeostasis, and reduced systemic inflammation associated with weight loss. However, it is unclear whether the mechanism by which BS reduces albuminuria is due to weight loss per se or by improved systemic inflammation induced by weight loss. To elucidate whether weight loss directly reduces albuminuria or via improvement of systemic inflammation induced by weight loss, a prospective cohort study was performed.

Methods: Patients older than 18 years who received BS in Soonchunhyang University Hospital from 1 January 2011 to 31 December 2011 were included. Other including criteria were followed: body mass index (BMI) ≥ 30, serum creatinine level ≤ 1.0, and without over proteinuria (dip stick ≤ trace). The patients were followed at 1, 6 months after BS.

Results: Forty-three patients were included. Three patients were men, 10 patients had diabetes, 12 patients had hypertension. eGFR estimated by CKD-EPI equation were 115.7 ± 16.5. There were significant reduction in body weight (98.9 ± 17.6 to 78.1 ± 14.8 kg), BMI (36.9 [34.0 – 42.8] to 29.5 [26.6 – 32.2] kg/m^2), high-sensitivity C-reactive protein (hs-CRP, 0.39 [0.24 – 0.69] to 0.09 [0.05 – 0.23] mg/L), and urine albumin-to-creatinine ratio (17.95 [6.81 – 72.89] to 8.11 [4.67 – 15.92] mg/g). There were positive correlations between delta hs-CRP and delta body weight (r = 0.349, p = 0.043) or delta BMI (r = 0.362, p 0.035); between hs-CRP and body weight (r = 0.374, p = 0.001) or BMI (r = 0.431, p < 0.001). In a multivariate analysis using linear mixed model demonstrated that hs-CRP (β = 0.5451, p = 0.022) is independent risk factors to affect ACR.

Conclusions: Our results suggests that weight loss by BS directly improve systemic inflammation, which subsequently leads to reduce albuminuria.

SA-PO171

The Additional Benefit of Weighted Subjective Global Assessment (SGA) for the Predictability of Mortality in Incident Peritoneal Dialysis Patients Taeyoung Yun, Dong-Ryeol Ryu. *Ewha Womans University, Seoul, Republic of Korea.*

Background: Although Subjective Global Assessment (SGA) is a widely-used tool for the nutritional investigation, it has limitation to assess nutritional status for the dependence on inspectors' subjective opinion. Moreover, there is no study for the usefulness of SGA and modified SGA in incident peritoneal dialysis (PD) patients.

Methods: A total of 365 incident PD patients between May 2009 and December 2015 at the 36 centers of the Clinical Research Center for end-stage renal disease in Korea were initially recruited, and we measured SGA and calculated weighted SGA using serum albumin and total iron binding capacity (TIBC) levels based on the normal values. Cox proportional regression analyses were performed and receiver operating curve was also conducted.

Results: During median 3.2 years of follow-up period, 61 patients (16.7%) were dead. Kaplan-Meier curve showed that the cumulative survival rate in 'Good nutrition (G1)' was significantly higher compared to that in 'Mild to severe malnutrition (G2)' (*P* < 0.001). G2 was also significantly associated with increase of all-cause mortality even after adjusting for age, gender, several comorbidities and TIBC (HR; 1.78, *P* = 0.038) compared with G1. Moreover, 1 unit increase of weighted SGA was still significantly correlated with the development of the mortality after adjustment of the same covariates (HR; 1.65, *P* = 0.013). However, G2 was significantly associated with increase of all-cause mortality in non-DM, DM, and old-aged group (in non-DM; HR; 2.86, *P* = 0.049, in DM; HR; 2.04, *P* = 0.021, and in old-aged; HR; 2.96, *P* = 0.026, respectively) except for young-aged group after adjusting for several covariates, whereas 1 unit increase of weighted SGA was revealed to be significantly related to increase of the mortality in all the subgroup analyses. Furthermore, the AUC of SGA and weighted SGA for all-cause mortality was 0.616 (*P* = 0.004) and 0.708 (*P* < 0.001). In addition, the AUCs of weighted SGAs in all the groups were significantly increased compared with those of SGA alone.

Conclusions: The evaluation of nutritional status based on SGA in incident PD patients may be useful for predicting mortality. However, weighted SGA with objective parameters including serum albumin and TIBC can provide an additionally predictable power for all-cause mortality compared with SGA alone.

SA-PO172

Serum Albumin Concentration, Estimated Glomerular Filtration Rate, and Cardiovascular Mortality among 1999-2010 NHANES Participants Amanda R. Tortorici,[1] Elani Streja,[1] Melissa Soohoo,[1] Daniel L. Gillen,[1] Connie Rhee,[1] Keith C. Norris,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine, Orange, CA; [2]UCLA, Los Angeles, CA.*

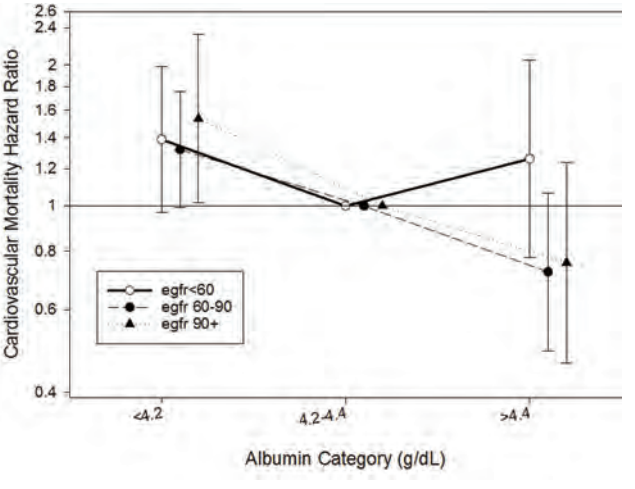
Background: As a potential strong predictor of longevity in persons with chronic kidney disease, we sought to examine whether higher serum albumin (Alb) levels are associated with reduced cardiovascular mortality in a nationally representative cohort of NHANES participants.

Methods: We identified 31,274 participants from the 1999-2010 continuous NHANES survey who had available Alb measurements and laboratory values for calculation of eGFR, as well as cardiovascular mortality data. Follow up time began the day after Alb measurement until December 31, 2011. We analyzed the association of Alb (<4.2, 4.2-<4.4 and ≥4.4 g/dL) with cardiovascular mortality across strata of eGFR (<60, 60-<90, and ≥90 ml/min/1.73m^2) using Cox proportional hazards models adjusted for age, sex, race, smoking, diabetes and education.

Results: The mean±SD age of the cohort was 48±20 years, among whom 52% were female, 20% were African-American, 22% were Mexican-American, and 7% were other Hispanic American. Across all eGFR strata, participants with Alb levels <4.2 g/dL (n=11,384 people) trended towards higher cardiovascular mortality risks compared to the reference group (Alb 4.2-<4.4 g/dL, n=10,793 people). When stratified by eGFR, participants with Alb levels >4.4 g/dL (n=9,097 overall) trended toward better cardiovascular survival among those with eGFR >60 ml/min/1.73m^2 (n=8,779), but worse cardiovascular mortality among those with eGFR <60 ml/min/1.73m^2 (n=318). [Figure]

Conclusions: Among 1999-2010 continuous NHANES participants, lower Alb levels trended toward 30% to 50% higher cardiovascular mortality risk irrespective of the eGFR level. Mortality predictability of Alb and the implications of its screening across the population at large warrants comparison to a lipid panel screening.

Funding: NIDDK Support



Figure

SA-PO173

The Effect of Selenium Deficiency on Thyroid Function and Cardiovascular Diseases in Peritoneal Dialysis Patients Jong tae Cho, So Mi Kim, Eun kyoung Lee, Chang hyun Park, Jihyen Jeon. *Division of Nephrology, Department of Internal Medicine, Dankook University Hospital, Dankook University, College of Medicine, Cheonan, Chungnam, Republic of Korea*.

Background: Trace element, selenium deficiency is known to be associated with impairment of thyroid hormone, and it can cause cardiovascular diseases, such as ischemic heart disease (IHD), heart failure (HF) or cardiomyopathy. In peritoneal dialysis (PD) patients, various causes may contribute to selenium deficiency, including dietary restriction, malabsorption, alteration of metabolism, and removal through dialysis itself. Therefore, we tried to investigate the effect of selenium deficiency on thyroid hormone and cardiovascular diseases in PD patients

Methods: This cross-sectional study enrolled 86 end-stage renal disease patients who underwent PD. The patients were divided into 2 groups based on serum seleium levels : 62 patients were normal level and 22 patients were selenium deficient. Thyroid hormones, including TSH, free T4 were measured. And presence of cardiovascular diseases, using echocardiography, coronary computed tomography or coronary angiography were evaluated.

Results: There were no significant differences in baseline characteristics, including age, sex, presence of diabetes mellitus, duration of PD and weekly Kt/V between the two groups. Although there was no significant difference, thyroid hormone impairment showed higher tendency in selenium deficient group than that in non- selenium deficient group (25 % vs 10 % p=0.06). The prevalence of IHD was significantly higher in selenium deficient group than that in the non-selenium deficient group (55 % vs 21 %, p=0.04). But, there was no difference in HF defined as ejection fraction with below 40 %, and cardiomyopathy between the two groups. All patients with thyroid hormone impairment showed high prevalence of IHD and the coincidence of thyroid impairment and IHD was significantly higher than that in selenium deficient group than that in non-selenium deficient group (63 % vs 31 %, p=0.01).

Conclusions: This study showed higher prevalence of thyroid hormone impairment and IHD in PD patients with selenium deficiency. Selenium deficiency may be related to thyroid hormone impairment, leading to cardiovascular diseases.

SA-PO174

A Pilot Study Characterizing Dysgeusia in Hemodialysis Patients Ciara Fitzgerald,[3,2] Ranjani N. Moorthi,[1] Sharon M. Moe,[1] Kathleen M. Hill Gallant,[2,1] Cordelia A. Running.[2] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Purdue University, West Lafayette, IN; [3]The Dublin Institute of Technology, West Lafayette, IN*.

Background: Dysgeusia is common in dialysis patients and contributes to poor nutritional intake. But, its underlying mechanisms are poorly understood. Studies have shown that taste improves after dialysis sessions, which implicates abnormal serum and salivary parameters as playing a possible role in how dialysis patients perceive taste stimuli. The goal of this pilot study was to characterize altered taste perceptions in dialysis patients compared to healthy adults, and to evaluate relationships between serum levels of potassium, sodium, phosphate, and urea with taste perceptions of these compounds. Our hypotheses were that dialysis patients would have blunted taste compared to controls, and that related serum levels would be inversely related to taste perception of compounds.

Methods: Using a cross-sectional design, we performed suprathreshold taste tests of stimuli (NaCl, KCl, $CaCl_2$, $NaPO_4$, $FeSO_4$, H_3PO_4, MSG, & urea solutions) in hemodialysis patients at a single center(n=16, 10 60±18 y) and healthy adults (n=27, 32±12 y). Participants rated a number of solutions on a 100mm visual analog scale to determine flavor and liking perception and scores were adjusted for each individual's perception of water. In the dialysis cohort, flavor scores were correlated against serum biochemistries drawn pre-dialysis.

Results: No significant differences were observed between how dialysis patients and controls rated each stimuli for flavor and liking (P=0.9). However, when flavor and liking were adjusted for each individual's perception of water, significant differences emerged, especially for compounds containing sodium ions (MSG, NaCl & $NaPO_4$) p<0.05. These differences all showed that dialysis patients experience a larger increase in flavor from the stimuli compared to water than the controls. No significant relationships were observed between serum ion levels and taste perceptions in the dialysis patients.

Conclusions: Our results did not support our original hypotheses. Interestingly, dialysis patients appeared to have stronger taste perception of sodium solutions compared with controls. These results should be considered preliminary due to the limited sample size and lack of age-matched controls. Larger, longer term studies are needed to fully evaluate how dysguesia is experienced by CKD patients pre- and post-dialysis using whole foods in addition to isolated compounds.

Funding: NIDDK Support, Other NIH Support - Indiana CTSI Project Development Team grant (NIH UL1TR001108)

SA-PO175

Risk Factors for the Decreased Upper Limb Muscle Strength in MHD Patients Qian Zhang,[1] Jiaying Zhang,[2] Minmin Zhang,[3] Jing Chen.[4] *[1]Huashan Hospital, Fudan University, Shanghai, China; [2]Fudan University, Shanghai, China; [3]Huashan Hospital, Fudan Univerisy, Shanghai, China; [4]Huashan Hospital affiliated to Fudan University, Shanghai, China*.

Background: To assess the risk factors for the decreased biceps muscle strength in young (<65 years) and old (≥65years) MHD patients

Methods: This is a cross-sectional analysis with prospective follow-up from MHD patients. All patients underwent assessment of strength of the biceps, body composition, anthropometry, dietary intake, nutritional status and the daily steps. Blood samples were obtained on the midweek dialysis day. Univariate and multivariate regression analysis was used to analyze the predictors of the decreased upper limb muscle strength. Survival analysis was made with the Kaplan–Meier survival curve and the Cox proportional hazard model.

Results: 174 patients were selected, 93 were male and 81 were female patients. The mean age was 63.05±12.29 ys, and the dialysis vintage was 9.19±6.66 ys. Patients were divided into young MHD group (n=97) and elderly MHD group (n=77). In young MHD group, gender (β = -2.01, P = 0.003), modified SGA score (β = -0.29, P = 0.03), muscle mass (β = 0.09, P = 0.03), 25(OH)D level (β = 0.04, P = 0.03) and IL-6 (β = -0.09, P = 0.002) were associated with the decreased biceps muscle strength. In the elderly MHD group, age(β=-0.25, P<0.001), muscle mass(β=0.08, P=0.03), 25(OH)D(β=0.08, P=0.001)and Log NT-proBNP(β=-1.62, P=0.008) were associated with the decreased biceps muscle strength. Patients were further divided into four groups according to 25(OH)D<25,25-50,50-75 and ≥75 nmol/L. Comparing the biceps muscle strength between the groups, it was found that the biceps muscle strength gradually increased with the gradual increase of 25(OH)D levels. During the follow-up of 52 weeks, 16 patients died. 14 of whom died of cardiovascular and cerebrovascular diseases and 2 died of tumor. Kaplan-Merier showed that the survival rate was significantly high in the high muscle strength group than that in low muscle strength group (P=0.002). Cox multivariate analysis showed that the association between low muscle strength and higher mortality risk remained strong in fully adjusted models.

Conclusions: In young MHD group, gender, modified SGA score, muscle mass, 25(OH)D and IL-6 were associated with the decreased biceps muscle strength. In the elderly MHD group, age, muscle mass, 25(OH)D and NT-proBNP were associated with the decreased biceps muscle strength. The biceps muscle strength was an independent risk factor for the survival of MHD patients.

SA-PO176

Tissue Content of Advanced Glycation End-Products and Augmentation Index, a Marker of Vascular Stiffness, Are Linked to Cardiovascular Disease and Mortality in CKD Patients Hideyuki Mukai,[1] Bengt Lindholm,[1] Dai Lu,[1] Jonaz Ripsweden,[2] Torkel Brismar,[2] Olof Heimburger,[1] Peter F. Barany,[1] Peter Stenvinkel,[1] Abdul Rashid T. Qureshi.[1] *[1]Renal Medicine and Baxter Novum, Karolinska Institutet, Stockholm, Sweden; [2]Medical Imaging and Technology, Karolinska Institutet, Stockholm, Sweden*.

Background: Accumulation of advanced glycation end-products (AGEs) may contribute to cardiovascular disease (CVD) and increased mortality in chronic kidney disease (CKD) patients. Skin autofluorescence (SAF), a noninvasive measurement of tissue AGE accumulation, and augmentation index (Aix) by applanation tonometry, may be markers of vascular damage and arterial stiffness respectively. We investigated associations of SAF, AIx and Framingham's CVD risk score with mortality in CKD patients.

Methods: SAF (AGE Reader) and Aix (SphygmoCor; adjusted for 75 heart beats per minute) were measured in 261 CKD patients (median age 56 years, 66% male, 20% diabetes; 130 non-dialyzed, 93 on peritoneal dialysis and 38 on hemodialysis). In 201 patients, coronary artery calcium score was assessed by computed tomography. Associations of SAF, AIx, and Framingham's CVD risk score (FRS) with all-cause mortality was evaluated by multivariate Cox models. During follow-up for median 25 months, there were 46 deaths.

Results: SAF associated with FRS (rho=0.51), hsCRP (rho=0.31), handgrip strength, HGS (rho=-0.30), fat body mass index, FBMI (rho=0.24), and bone mineral density, BMD (rho=-0.22). AIx associated with HGS (rho=-0.43), FRS (rho=0.41), albumin (rho=-0.26), hsCRP (rho=0.25), BMD (rho=-0.23) and lean body mass index, LBMI (rho=-0.20). ROC curve analysis of classifiers of CVD and predictors all-cause mortality showed as expected high values for FRS (AUC=0.75 and 0.77), however closely followed by SAF (AUC=0.71 and 0.75) and AIx (AUC=0.64 and 0.70). The highest tertile of Aix associated with all-cause mortality, HR 2.52 (95% CI 0.98-6.46; p=0.05), after adjusting for FRS.

Conclusions: SAF and AIx were associated with presence of CVD and mortality in ROC curve analysis; however, only AIx - and not SAF associated (p=0.05) with increased mortality risk after adjusting for Framingham's CVD risk score in CKD patients.

Funding: Commercial Support - Baxter Healthcare Corporation, Government Support - Non-U.S.

SA-PO177

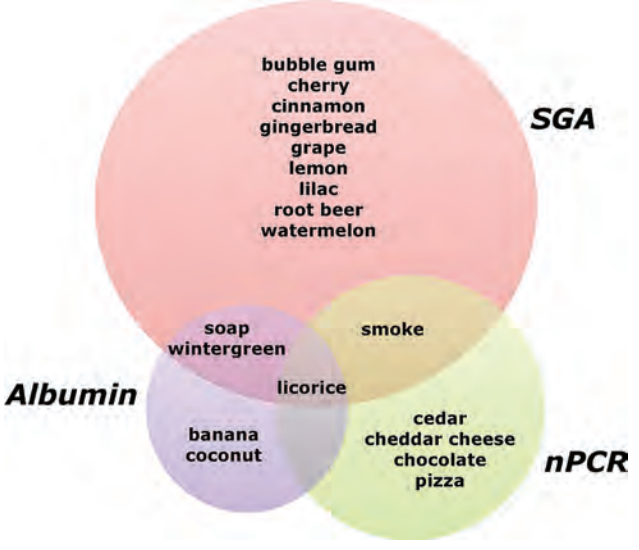
Olfaction–Nutrition Association in Patients with Kidney Disease: Odorant Specificity Teodor G. Paunescu, Dihua Xu, Sahir Kalim, Ravi I. Thadhani, Sagar U. Nigwekar. *Massachusetts General Hospital, Boston, MA.*

Background: Malnutrition is common in patients with chronic kidney disease (CKD) and especially end-stage renal disease (ESRD). Most of these patients have odor identification deficits, and a reduction in odor identification score is associated with higher subjective global assessment (SGA) score and lower total cholesterol, LDL cholesterol, and albumin. We investigated whether the identification of specific odorants is linked to abnormalities in nutritional markers.

Methods: We quantified odor identification in CKD (n=36) and ESRD patients (n=100) and healthy volunteers (HV, n=25) using the University of Pennsylvania Smell Identification Test (UPSIT). We assessed the correlation between the percentage of correct answers for each of the 40 odorants on the UPSIT test and nutritional markers.

Results: Correct identification of multiple odorants significantly correlates with levels of albumin (14 odorants), LDL (15 odorants) and total cholesterol (20 odorants). In analyses restricted to ESRD patients, lower SGA scores correlate with the correct identification of 13 odorants, while higher nPCR and albumin levels correlate with the correct identification of 6 and 5 odorants, respectively. Odorant-based analysis reveals that correct identification of certain odorants correlates more closely with nutritional markers: *licorice* correlates with albumin, nPCR, SGA, and triglycerides; *banana* correlates with albumin, pre-albumin, total and LDL cholesterol, and triglycerides; *watermelon* correlates with albumin, pre-albumin, SGA, and triglycerides. Some odorants, such as *gasoline, lime,* and *natural gas,* show no correlation with any of the nutritional markers we assessed.

Conclusions: Patients with kidney disease have odor identification defects that correlate with nutritional markers. Correct identification of specific odorants by ESRD patients is linked with levels of nutritional markers. These odorants should be followed to assess occurrence of malnutrition.



SA-PO178

Could a Low Protein Diet Exert Influence on Uremic Toxin Levels in Non-Dialysis CKD Patients? Denise Mafra,[1] Ana paula B. Dreux,[1] Juliana S. Anjos,[1] Milena B. Stockler-Pinto,[1] Ludmila F. Cardozo,[1] Carla J. Dolenga,[2] Lia S. Nakao,[2] Dennis C. Ferreira,[4] Flavia L. Carmo,[3] Alexandre S. Rosado,[3] José C. Carraro-Eduardo,[1] Natalia A. Borges.[1] *[1]Federal Fluminense University, Niteroi / Rj, Brazil; [2]Federal University of Parana, Curitiba, Brazil; [3]Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; [4]UNESA-UVA, Rio de Janeiro, Brazil.*

Background: Among many benefits for non-dialysis CKD patients, low protein diet (LPD) can be effective to modulate the gut dysbiosis reducing the influx into plasma of uremic toxins such as indoxyl-sulfate (IS), p-Cresyl Sulfate (p-CS) and Indole-3-Acetic Acid (IAA). The aim of this study was to evaluate the effects of LPD on uremic toxins serum levels and gut microbiota profile in non-dialysis CKD patients.

Methods: In this longitudinal study, LPD was prescribed for 30 non-dialysis CKD patients and anthropometric and biochemical parameters were evaluated at baseline and after 6 mo. Adherence to the diet was evaluated based on nPNA. Total concentrations serum of uremic toxins (IS, p-CS, IAA) were obtained by RP-HPLC. Fecal samples were collected to evaluate the gut microbiota profile by Polymerase Chain Reaction (PCR) and Denaturing Gradient Gel Electrophoresis analysis (DGGE). Patients were divided into 2 groups: patients who adhered to the LPD (N=14, 52.0 ±12.2yrs, eGFR, 35.2 ± 10.8 mL/min, BMI, 28.0 ± 5.0 Kg/m^2) and patients who not adhered to the diet (N=16, 59.6 ±16.1 yrs, eGFR, 36.0 ± 13.7 mL/min, BMI, 30.1 ± 6.6 Kg/m^2).

Results: Patients who adhered to the diet, presented a significant improvement in renal function and reduction in total and LDL cholesterol. After 6 months, the p-CS serum levels were reduced from 19.3 (9.6-24.7) to 15.5 (9.8-24.1) mg/L (p=0.03) in patients who adhered and, in contrast, levels were increased significantly in patients who not adhered to the LPD. There was no change in the average number of bands according DGGE. However, the average number of bands was positively associated with protein intake (r=0.44, p= 0.04).

Conclusions: Additionally to the improvement of renal function, LPD may be a good strategy to reduce the uremic toxins production by the gut microbiota in non-dialysis CKD patients.

Funding: Government Support - Non-U.S.

SA-PO179

Diagnostic Discordance between Body Mass Index and Body Fat Percentage for Obesity among Patients with CKD Ting-yun Lin, Szu-Chun Hung. *Teipai Tzu Chi Hospital, Taipei City, Taiwan.*

Background: In contrast to the general population, a higher body mass index (BMI) appears to be associated with a greater survival among patients with CKD, referred to as "obesity paradox". This may be explained by limitation of BMI as a measure of adiposity in CKD. Both BMI and body fat percentage (BF%) are used to classify obesity but outcomes may vary.

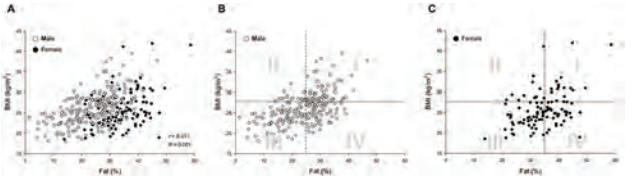
Methods: We investigated the two different cutoffs for diagnosing obesity (BMI ≥28 kg/m^2 or BF% >25% for male or >35% for female) and the impact on all-cause mortality in 326 nondialysis-dependent CKD patients with a median follow-up of 4.6 years. Body fat mass was determined using the Body Composition Monitor, a novel multifrequency bioimpedance spectroscopy device.

Results: Using BMI, 27.9% of patients were obese. However, 48.8% of patients were obese according to BF%. Although obesity defined by BMI was associated with a significantly lower risk of death, the result tended to be reverse when obesity was defined by BF%. When patients were classified into four distinct groups based on both BMI and BF% cutoffs for obesity, a considerable proportion of patients (29.4%) had excess body fat in the context of a normal BMI. These patients were more likely to have lower lean body mass and had higher mortality as compared to patients with obesity defined by both BMI and BF%.

Conclusions: Thus, diagnostic discordance between BMI and BF% may explain the "obesity paradox" because using BMI to detect obesity among those with CKD may miss a large number of patients with excess body fat. Proper diagnosis of obesity in patients with CKD is required for both risk prediction and treatment.

Cox models for relative risk of all-cause mortality calculated for obesity or not defined by BMI or BF%

Characteristics	Unadjusted		Model 1		Model 2	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
BMI-defined						
Nonobese	Reference		Reference		Reference	
Obese	0.26 (0.09–0.74)	0.012	0.32 (0.11–0.92)	0.034	0.26 (0.09–0.79)	0.017
BF%-defined						
Nonobese	Reference		Reference		Reference	
Obese	1.93 (1.01–3.71)	0.047	1.55 (0.79–3.02)	0.20	1.46 (0.73–2.90)	0.282



Relationship of BF% versus BMI

SA-PO180

The Use of Phase Angle to Evaluate Fluid Status in Dialysis Patients Laura Rosales,[1] Fansan Zhu,[1] Priscila Preciado,[1] Ohnmar Thwin,[1] Xia Tao,[1,2] Stephan Thijssen,[1] Peter Kotanko.[1,2] *[1]Renal Research Institute, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Phase angle (PA) has been suggested as an indicator for assessing body composition and fluid status in hemodialysis (HD) patients. PA is calculated by the ratio of reactance and resistance. Resistance represents body water content and reactance relates to body cell mass. The primary aim of this study was to evaluate the relationship between peridialytic fluid and phase angle changes in different fluid status in HD patients and healthy subjects (HS).

Methods: Ten HD patients (8 males, age 58.1±12 years, height 167±11 cm) and 12 healthy subjects (HS; 7 females, age 33±6 years, height 169±10 cm) were studied with the Seca mBCA 514 bioimpedance device (Seca North America, Chino, CA USA). Resistance (R, Ohm), reactance (Xc, Ohm), impedance (Imp, Ohm), and phase angle (PA, degrees) were measured pre- and post-HD treatment. HS were measured once. R, Xc, Imp and PA were compared between pre- and post-HD. In addition, we compared the post-HD levels with HS using 1-way ANOVA. Pre- and post-HD weights and body mass index (BMI) were recorded.

Results: Peridialytic body weight reduction was 2.63±0.54 kg. This weight change was accompanied by increased in PA and decreased in Xc. Average PA and Xc differed significantly from various hydration groups (pre-, post-HD and HS) by a nonparametric test (Fig. 1 A and C). Of note, pre- and post-HD R and Imp did not differ significantly in

HD patients (Fig. 1 B and D). BMI and PA were not correlated. Coefficient of variation of PA is 12.7% in HS group.

Conclusions: PA reflects peridialytic fluid status changes and thus is useful for evaluating relative changes in a given patient. However, PA may not be used to identify normal fluid status due to its large variability in HS (Fig 1 A). This variability is possibly due to the fact that PA is computed as the ratio of two variables, resistance and reactance, which represent different body components.

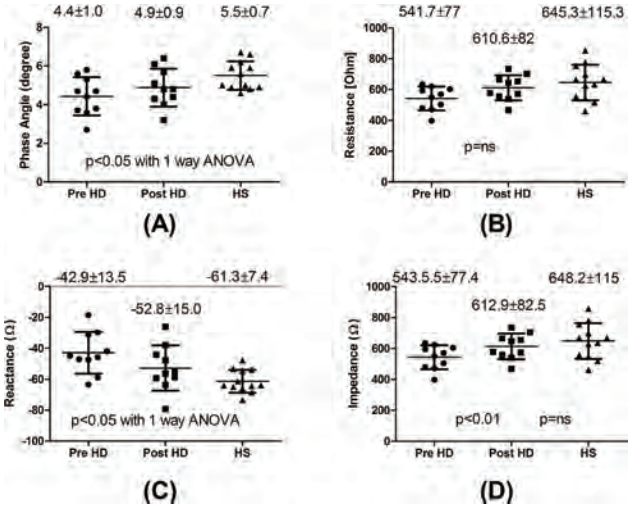


Fig. 1

SA-PO181

Is Zinc-Alpha2-Glycoprotein (ZAG) a Predictor of Mortality in Patients on Hemodialysis? Anaïs Bouchara,[2] Dan Yi,[5] Myriam Pastural,[3] Maurice Laville,[2] Solenne Pelletier,[1] Denis Fouque,[2] Christophe O. Soulage,[4] Laetitia Koppe.[2] *[1]Centre hospitalier Lyon Sud, Pierre-Bénite, France; [2]Hôpital Lyon Sud, LYON, France; [3]AURAL, LYON, France; [4]CarMeN, INSERM u1060, INSA LYON, VILLEURBANNE, France; [5]INSA-Lyon, VILLEURBANE, France.*

Background: Zinc alpha 2 glycoproteine (ZAG) is a new adipokine involved in cachexia due to its potent lipolytic effects. It has been shown that plasma ZAG concentration was increased in chronic kidney disease (CKD) and patients on hemodialysis treatment (HD). However, the impact of ZAG accumulation on mortality and cardio-vascular risks has never been studied.

Methods: Plasma ZAG concentration was measured by enzyme immuno-assays (EIA ZAG, Raybiotech, USA) in 253 patients on HD for at least 3 months, without progressive cancer. Mortality and cardio-vascular events have been registered during 4 years.

Results: During the follow-up period (31.3 ± 17.1 months), a total of 49 patients died (among which 16 from cardio-vascular events). Plasma ZAG concentration was inversely correlated with serum albumin (p=0.008), creatinine (p=0.007) and triglycerides (p=0.04). By contrast, it was positively correlated with age (p=0.002). Plasma ZAG concentration was independent of serum CRP, parathyroid hormone, LDL cholesterol and glycated hemoglobin. Kaplan-Meier analysis showed a significant correlation between plasma ZAG concentration and overall mortality (log rank, p<0.05) and cardio-vascular events (log rank, p<0.01). After Cox multivariate analysis, the association between plasma ZAG concentration and cardio-vascular events persisted after adjustment for demographic factors (age, sex, dialysis vintage), metabolic parameters (serum albumin, prealbumin, triglycerides, nPCR, BMI) and cardio-vascular risks (diabetes, dyslipidemia, hypertension, tobacco). Plasma ZAG concentration was however not associated with protein energy wasting.

Conclusions: Plasma ZAG accumulation does not correlate with protein energy wasting by contrast with patients having a cancer. ZAG does not seem to be involved in metabolic disturbances (type 2 diabetes, dyslipidemia) as observed in obese patien. ZAG accumulation seems to be associated with an excess overall mortality and cardiovascular mortality risk in HD patients. Complementary studies will be necessary to define the role of ZAG and the pathophysiological mechanisms in cardiovascular events in patients with CKD.

SA-PO182

Different Measures of Dietary Protein Intake and Correlations with Laboratory Markers across Race in Hemodialysis Patients Jui-Ting Hsiung, Elani Streja, Melissa Soohoo, Connie Rhee, Kamyar Kalantar-Zadeh. *UC Irvine, Orange, CA.*

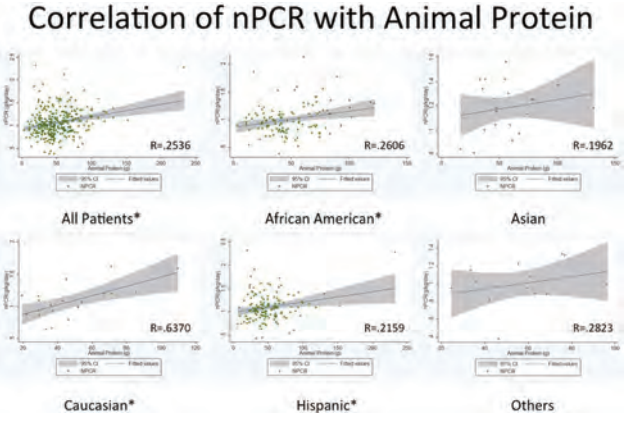
Background: Clinical practice guidelines recommend higher protein intake in hemodialysis (HD) patients, given their heightened risk of protein catabolism and protein energy wasting. Little is known how different components of protein intake correlate with laboratory markers, and whether this differs by race/ethnicity.

Methods: We examined HD patients from three prospective studies, the Anti-Inflammatory and Anti-Oxidative Nutrition in Hypoalbuminemic Dialysis Patients (AIONID), Nutritional and Inflammatory Evaluation in Dialysis (NIED), and Fosrenal for Enhancing Dietary Protein Intake in Hypoalbuminemic Dialysis Patients (FrEDI). We analyzed the correlations of dietary protein (total, animal, and vegetable) ascertained by three-day dietary record with laboratory measures including normalized protein catabolic rate (nPCR), serum albumin, and serum bicarbonate (CO2) stratified by race/ethnicity.

Results: The cohort was comprised of 336 HD patients, among whom 46% and 37% of patients were Hispanic White and African-American, respectively, 48% of patients were female and the mean±SD age was 55±14 years. In the overall cohort, nPCR strongly correlated with total protein (r=0.25, p<0.001) and animal protein (r=0.25, p<0.001), as well as within strata of African American, Caucasian, and Hispanic patients. However, there was no correlation between nPCR and vegetable protein (r=0.07, p=0.22) in any of the racial/ethnic groups. Serum albumin and CO2 showed weaker correlations with total protein, animal protein, and vegetable protein across all patients.

Conclusions: These findings suggest that nPCR has a stronger correlation with total and animal protein intake than with serum albumin and CO2 across all racial/ethnic groups. Further studies are needed to determine whether nPCR may be a more accurate tool for monitoring dietary protein among HD patients in the clinical setting.

Funding: NIDDK Support



Figure

SA-PO183

Does Thyroid Hormone (TH) Substitution Alter Hormonal Metabolism in Patients with Hypothyroidism and Renal Failure (RF)? Longin Niemczyk,[1] Ivanna Dubchak,[3] Malgorzata Gomolka,[3] Katarzyna Szamotulska,[2] Stanislaw Niemczyk.[3] *[1]Medical University of Warsaw, Warszawa, Poland; [2]National Research Institute of Mother and Child, Warsaw, Poland; [3]Military Institute of Medicine, Warsaw, Poland.*

Background: RF disrupts the metabolism of TH, and disorders are exacerbated by concomitant hypothyroidism. TH replacement therapy should equalize hormone levels but lack comprehensive research in this area. In patients with ESRD there is a tendency for higher TSH and lower triiodothyronine (T3) and thyroxine (T4) levels probably due to reduced TH conversion (T4 to T3). **The aim of the study** was to evaluate the effect of TH substitution on conversion factors and rT3 concentration in patients with coexisting RF and hypothyroidism.

Methods: The study involved 2 groups of patients with hypothyroidism and TH replacement therapy: Group A - 13 pts. without RF (12 F, 1 M) 48,4±10,67y.o., Group B - 26 pts. with ESRD treated with HD (16 F, 10 M) 58,8±15,52y.o. Pts. with ESRD, treated with HD, were studied during planned dialysis. CRP, creatinine, urea, PTH, TSH and TH: total - (TT4), (TT3), free fractions - (fT4), (fT3), and rT3 were measured and conversion factors (rT3/TT4, rT3/TT3) were calculated. Basic descriptive statistics, Pearson's linear correlation, the Mann-Whitney nonparametric test and Fisher's test were used. Adopted significance level was 0,05.

Results: Results were shown in table.

Conclusions: There is a tendency for a higher rT3 levels during thyroid hormone substitution in hypothyroid patients without renal failure. The inhibitory effect of renal failure on rT3 production in hypothyroid patients is still present during thyroid hormones substitution.

HORMONES LEVELS AND CONVERSION FACTORS

Group		TSH	TT4	TT3	fT4	fT3	rT3	rT3/TT4	rT3/TT3
A	N	13	13	13	13	13	13	13	13
	Mean	2,35	107,47	1,74	17,65	4,21	488,13	4,65	285,51
	SD	1,93	14,26	0,23	5,71	0,83	175,27	1,73	107,85
	Median	1,57	104,3	1,82	16,84	4,1	501,81	4,82	281,38
	Min.	0,17	87,74	1,35	11,63	2,4	24,32	0,2	14,22
	Max.	6,47	132,9	2,13	35,6	5,37	724,09	6,54	399,93
B	N	19	20	20	20	20	20	20	20
	Mean	2,9	90,54	1,23	16,03	3,21	198,72	2,32	169,61
	SD	2,45	22,41	0,26	3,98	1,37	91,84	1,23	87,76
	Median	1,56	90,15	1,22	15,37	2,93	185,36	2,16	170,77
	Min.	0,14	44,52	0,59	9,95	1,54	61,79	0,92	51,92
	Max.	8,56	134,7	1,94	26,18	8,24	367,87	4,79	357,16
p		NS	=0,022	=0,001	NS	=0,025	<0,001	<0,001	=0,002

SA-PO184

Association between Decrease in Skeletal Muscle Mass Index and Renal Atrophy in Patients with Non-Dialysis CKD Rei Iio, Rika Kumamoto, Taisuke Takatsuka, Daisuke Yoshimura, Hiroki Okushima, Yukimasa Iwata, Mitsumoto Kensuke, Tatsuya Shoji, Terumasa Hayashi. *Osaka General Medical Center, Osaka, Japan.*

Background: The frequency of sarcopenia increases as chronic kidney disease (CKD) progresses. CKD patients should be screened for sarcopenia and presarcopenia in order to detect them during an earlier stage of CKD and improve prognosis. Kidney size is associated with aging, inflammation, and decreased renal function, as seen with sarcopenia. We investigated the association of kidney size with muscle mass and muscle mass change in CKD patients.

Methods: We performed a single-center retrospective cohort study of 180 non-dialysis dependent CKD patients (age 66.4±12.5 years; male 66.1%; eGFR 31.4±17.5 mL/min/1.73m^2; etiology glomerulonephritis 22.2%, diabetic nephropathy 23.9%). We measured kidney size by ultrasonography and calculated total kidney volume (TKV) using an ellipsoid equation. Skeletal muscle mass index (SMI) were estimated using bioelectrical impedance analysis, and presarcopenia was defined as SMI ≤7.0 kg/m^2 for men and ≤5.7 kg/m^2 for women. The rate of change in SMI over a 6-month period was evaluated.

Results: The mean rate of change in SMI in six months was -1.5±7.1%. Multivariate logistic regression analysis showed that TKV was associated with presarcopenia (OR: 0.98, 95% confidential interval: 0.97-1.00, p=0.041). Multivariate regression analysis showed that SMI (β: -3.95, SE: 0.92, p<0.001) and TKV (β: 0.037, SE: 0.015, p=0.016) were associated with the rate of change of SMI in six months adjusted for age, sex, BMI, diabetes mellitus, history of cardiovascular disease, serum albumin, and proteinuria.

Conclusions: Among patients with CKD, presarcopenia is significantly associated with TKV, and patients with a small TKV are more prone to developing a decrease in skeletal muscle mass.

SA-PO185

8-Hydroxy-2-Deoxyguanosine (8-OHdG), a Marker of Oxidative DNA Damage, Is Associated with Mortality Independent of Inflammation in CKD Patients Dai Lu, Abdul Rashid T. Qureshi, Hideyuki Mukai, Anna Machowska, Olof Heimburger, Peter F. Barany, Peter Stenvinkel, Bengt Lindholm. *Renal Medicine and Baxter Novum, Karolinska Institutet, Stockholm, Sweden.*

Background: Oxidative stress and inflammation are two common interlinked features of CKD that associate with poor outcomes. We tested the hypothesis that inflammation modifies the mortality predictive capacity of serum 8-OHdG in CKD patients.

Methods: In 376 clinically stable CKD stage 1-5 patients (63% male; median age 57 years) including 53 CKD stage 1-2, 60 CKD stage 3-4 and 263 CKD stage 5 non-dialysis patients, 8-OHdG, and high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF), were measured at recruitment. The effect of inflammatory markers on the association between baseline 8-OHdG and 5-year mortality risk was investigated using multivariable modeling strategies using cut-off levels of each marker as determined by ROC curve analysis.

Results: The crude mortality rate was markedly increased in patients with high 8-OHdG especially when combined with high hsCRP and IL-6 **(Figure 1)**. In multivariable analysis, adjusting for age, sex, comorbidity, calendar year and eGFR, high 8-OHdG associated with increased relative risk ratio of death, 1.15 (1.07-1.25), 1.16 (1.07-1.25) and 1.17 (1.08-1.26) respectively, when adjusted also for hsCRP, IL-6 and TNF-α, respectively **(Table 1)**.

Conclusions: All-cause mortality risk was increased - independent of inflammation - in CKD patients with elevated 8-OHdG.

Funding: Commercial Support - Baxter Healthcare Corporation, Government Support - Non-U.S.

SA-PO186

Low Dose Aspirin Increases 15-Epi-Lipoxin A4 Levels in CKD Patients Marian Goicoechea,[1] Maria Dolores Sanchez-Nino,[2] Alberto Ortiz,[2] Maria soledad Garcia de vinuesa,[3] Borja Quiroga,[4] Enrique Morales,[5] Gema Fernandez Juarez,[6] Patricia De Sequera,[7] Ursula Verdalles,[1] Eduardo Verde,[3] Jose Luno.[1] *[1]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [2]Fundacion Jimenez Diaz, Madrid, Spain; [3]Hospital General Universitario Gregorio Marañon, Madrid, Spain; [4]Hospital de La Princesa, Madrid, Spain; [5]HOSPITAL 12 DE OCTUBRE, MADRID, Spain; [6]HOSPITAL DE ALCORCON, ALCORCON, Spain; [7]University Hospital Infanta Leonor, Madrid, Spain.*

Background: Resolution of inflammation is regulated by endogenous lipid mediators, such as lipoxins and their epimers, including 15-epi-lipoxin A4 (15-epi-LXA4). However, there is no information on 15-epi-LXA4 and its in vivo regulation in chronic kidney disease (CKD) patients.

Methods: Study Design: Open label randomized clinical trial. **Setting & Participants:** 50 participants with chronic kidney disease (CKD) stage 3 and 4 without prior cardiovascular disease (25 in the aspirin group and 25 in the standard group) followed for 46 months. **Intervention:** Aspirin (100 mg/day) or standard treatment. **Aim:** To analyze the effect of aspirin on plasma 15-epi-LXA4 levels and inflammatory markers in CKD patients.

Results: Baseline plasma15-epi-LXA4 levels were lower in diabetic (1.22±0.99 ng/ml) than in non-diabetic CKD patients (2.05±1.06 ng/ml, p<0.001) and inversely correlated with glycosylated hemoglobin levels (r=-0.303, p=0.006). In multivariate analysis, diabetes was associated with lower 15-epi-LXA4 levels, adjusted for age, inflammatory markers and renal function (p=0.005). In the whole study population, 15-epi-LXA4 levels tended to increase after twelve months on aspirin (from mean±SD 1.84±1.06 to 2.04±0.75 ng/ml) and decreased in the standard care group (1.60±1.15 to 1.52±0.68 ng/ml, p=0.04). The aspirin effect on 15-epi-LXA4 levels was more striking in diabetic patients, increasing from 0.94±0.70 to 1.93±0.74 ng/ml, p=0.017.

Conclusions: Diabetic patients with CKD have lower circulating 15-epi-LXA4 levels than non-diabetic CKD patients. Low dose aspirin for 12 months increased 15-epi-LXA4 levels, especially in diabetic patients. Given its anti-inflammatory properties, this increase in 15-epi-LXA4 levels may contribute to the beneficial effects of low dose aspirin.

Funding: Other NIH Support - Grant support: AASER was supported by Sociedad Española de Nefrologia (SEN) and SOMANE, additional support: Grant support: ISCIII and FEDER funds CP14/00133, PI15/00298, PI16/02057, DiabetesCancerConnect PIE13/00051, FRIAT, ISCIII-RETIC REDinREN RD016/009, Salary support: ISCIII Miguel Servet to MDSN. Programa Intensificación Actividad Investigadora (ISCIII/ Agencia Laín-Entralgo/CM) to AO.

SA-PO187

AGE Content of a Protein Load Is Responsible for Renal Hemodynamical Modifications Gabrielle L. Normand,[5] Sandrine Lemoine,[4] Marjorie Villien,[3] Didier Le bars,[1] Ines Merida,[1] Zacharie Irace,[8] Thomas Troalen,[6] Nicolas Costes,[2] Laurent Juillard.[7] *[1]CERMEP, BRON, France; [2]CERMEP - Imagerie du vivant, Lyon, France; [3]CERMEP imagerie du vivant, Tassin la demi lune, France; [4]Edouard Herriot Hospital, Lyon, France; [5]Hospices Civils de Lyon, Lyon----, France; [6]Siemens Healthcare S.A.S., Lyon, France; [7]University of Lyon, Lyon, France; [8]cermep, BRON, France.*

Background: Low-protein diet is recommended to slow down chronic kidney disease progression because each protein load leads to a detrimental glomerular hyperfiltration. Protein preparations used to demonstrate protein-mediated renal hemodynamic effects were rich in AGE. The aim of our study was to evaluate if the AGE content of a protein load is responsible for protein-induced renal hemodynamic modifications.

Methods: Ten healthy subjects were assigned to a high-protein (1g/kg) low-AGE (3.000 kU AGE) versus high-AGE (30.000 kU AGE) meal, during imaging sessions performed on two different days. Renal perfusion assessed by PET using [^{15}O] H2O, and renal oxidative metabolism measured by PET using [^{11}C] labeled acetate, were measured before and 120- minutes after each meal.

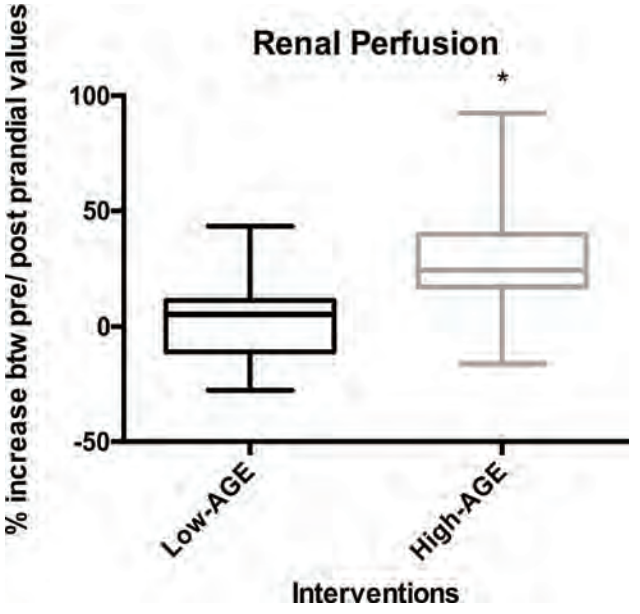
Results: Renal perfusion increased significantly (3.16 ± 0.55 to 3.80 ± 0.42 mL/ min/g, p=0.0002) after the high-AGE meal whereas it was not modified after the low-AGE meal (3.35±0.65 to 3.38±0.53 ml/min/g, p=0.88) (Table 1 and Figure 1). Oxidative metabolism increased significantly after the high-AGE meal (0.3 ± 0.04 vs 0.36 ± 0.08 min-1, p=0.005) compared to the low-AGE meal (0.30 ± 0.02 vs 0.31 ± 0.06 min-1, p=0.76) for both cortices.

Conclusions: This is not the high protein content of a meal that increases renal perfusion and oxidative metabolism but its high-AGE content. This study suggests that prevention of CKD progression should aim predominantly at reducing food AGE content.

Renal functional parameters.

	Low-AGE (n = 9)		High-AGE (n = 10)	
Acquisitions	Baseline	Post prandial	Baseline	Post prandial
15O-water PET (ml/g/min)-	3.35 ± 0.65	3.38 ± 0.53	3.16 ± 0.55	3.8 ± 0.42 *
11C- acetate PET (min-1)-	0.30 ± 0.02	0.31 ± 0.06	0.30 ± 0.04	0.36 ± 0.08 *
BOLD-MRI (Cortical R2*)	18.3 ± 1.3	20.4 ± 2.7 *	17.9 ± 1.2	20.1 ± 3.3
BOLD-MRI (medullary R2*)	27.6 ± 3.2	32.2 ± 4.1*	27.1 ± 4.9	32.4 ± 5.7 *

* means p < 0.05



SA-PO188

Nocturnal Intermittent Hypoxia Is Associated with Elevated Circulating Fibroblast Growth Factor 21 in ESRD Takuya Murakami,[1] Takahiro Masuda,[1] Marina Kohara,[1,2] Kazuhiro Shiizaki,[2] Tetsu Akimoto,[1] Sumiko Honma,[3] Yuko Watanabe,[1] Osamu Saito,[1] Eiji Kusano,[4] Yasushi Asano,[3] Makoto Kuro-o,[2] Daisuke Nagata.[1] *[1]Division of Nephrology, Department of Internal Medicine, Jichi Medical University, Shimotsuke, Japan; [2]Division of Anti-aging Medicine, Center for Molecular Medicine, Jichi Medical University, Shimotsuke, Japan; [3]Department of Nephrology, Japanese Red Cross Koga Hospital, Koga, Japan; [4]JCHO Utsunomiya Hospital, Shimotsuke, Japan.*

Background: Fibroblast growth factor (FGF) 21 is an endocrine factor mainly produced in the liver in response to various stress including inflammation and oxidative stress. We recently reported that higher circulating FGF21 predicts all-cause mortality in end-stage renal disease (ESRD) (Kohara M et al. PLoS One 2017), but the regulator to increase circulating FGF21 remains unclear. We therefore examined the association between circulating FGF21 and sleep-disordered breathing (SDB), characterized by nocturnal intermittent hypoxia and a mediator for chronic inflammation in ESRD.

Methods: Sixty-three ESRD patients receiving maintenance hemodialysis (age 64.2 ± 13.0 years, male 50.8%) were enrolled in this study. Overnight pulse oximetry was performed on a dialysis day, and numbers of over 3% desaturation per hour were defined as the 3% oxygen desaturation index (3%ODI). Patients were categorized into low- and high-FGF21 groups by the median value. Multivariable logistic regression analysis was used to examine the association between serum FGF21 levels and 3%ODI.

Results: The median value of serum FGF21 was 2021 pg/mL. The 3%ODI (6.8 ± 0.9 vs. 3.8 ± 1.0 times/hour, p=0.023) and the percentage of male (63.6 vs. 36.7 %, p=0.031) were significantly higher in the high-FGF21 group than in the low-FGF21 group. On the other hand, the mean oxygen saturation at night did not differ between the two groups (96.2 ± 1.6 vs. 96.4 ± 1.6 %, p=0.34). The 3%ODI was an independent risk factor for higher serum FGF21 levels (odds ratio 1.16: 95% confidence interval: 1.01-1.36, p=0.028) even after adjustment for age, gender, duration of dialysis and presence of diabetes.

Conclusions: Nocturnal intermittent hypoxia, but not mean oxygen saturation, is associated with elevated circulating FGF21 in ESRD. This result suggests that SDB is a novel therapeutic target for regulating circulating FGF21 levels.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO189

Body Fat Mass Is Predictive of Coronary Artery Calcification in Non-Dialysis CKD Patients: A Cross-Sectional Study Denise Mafra, Greicielle S. Da silva, Mariana Z. Jardim, Juliana S. Anjos, Ana paula B. Dreux, Daniel G. Neves, Natalia A. Borges, Milena B. Stockler-Pinto, Marcelo Nacif. *Federal Fluminense University, Niteroi / Rj, Brazil.*

Background: The most common cardiovascular disease (CVD) is coronary artery disease (CAD), which is an important cause of death in patients with chronic kidney disease (CKD). Several CVD risk factors are present in these patients since the early CKD stages, including obesity that is the cause of a variety of metabolic disorders which can increase the risk of CVD in CKD patients. The aim of this study was to evaluate the presence of atherosclerosis and possible association with body composition in non-dialysis CKD patients.

Methods: Twenty-eight patients [53.6% of men, 59.0 ± 13.4 years, creatinine clearance of 32.3 ± 16.6 mL/min, Body Mass Index (BMI) 26.6 ± 5.2kg/m^2] were evaluated in this cross-sectional study. Coronary atherosclerosis was assessed by coronary artery calcium (CAC) scoring done with non-contrast computed tomography. CAC scores as 0 Agatston units was classified without risk, and higher than 100 Agatston were considered representative of significant atherosclerotic disease. Routine biochemical tests, such as lipid profile and C-reactive protein (CRP), were evaluated using standard laboratory methods. Nutritional status was evaluated by BMI, % body fat and waist circumference.

Results: The median of calcium score was 323.7 (125.4- 700) Agatston, 18 patients had no risk for atherosclerosis (calcium score = 0), and 10 patients had risk for atherosclerosis (Ca Score > 100). The median of number of atherosclerosis lesions was 14 (9.2-44). There was correlation between Ca score and BMI (r= 0.37; p= 0.047), % fat body (r= 0.43; p= 0.03) and waist circumference (r= 0.53; p= 0.003). Multivariable logistic regression analysis revealed that % body fat mass and waist circumference were predictors for atherosclerosis risk, regardless of age, creatinine clearance, BMI, sex and CRP (R^2adjusted model = 0.76).

Conclusions: The present study suggests that non-dialysis CKD patients with high body fat mass showed the highest risk for CAC. In this sense, more longitudinal studies are required to confirm this association.

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SA-PO190

HDL Subclasses Alter with CKD Progression and Are Associated with ABI and Klotho Level in CKD-Stage-Specific Manner Eiichiro Kanda,[1] Yoshitaka Maeda.[2] *[1]Tokyo Kyosai Hospital, Meguro, Japan; [2]JA Toride Medical Center, Ibaraki, Japan.*

Background: Atherosclerosis is a complication of chronic kidney disease (CKD). Lipoprotein subclasses consist of a continuous spectrum of particles of different sizes and densities, and high-density lipoproteins (HDLs) are grouped into various subclasses (Table 1). We investigated the roles of lipoprotein subclasses in atherosclerosis and CKD-mineral and bone disorder.

Methods: Seventy one CKD patients (male, 70.4%; diabetic nephropathy, 23.9%) were enrolled in this prospective cohort study in Japan. The proportion of cholesterol level to total cholesterol level and the lipoprotein particle number in 20 lipoprotein fractions were measured by a newly developed method of high-performance gel permeation chromatography (HGPC).

Results: The average age (SD) was 75.0 (11.1) years and the estimated glomerular filtration rate (eGFR) was 17.2 (8.3) ml/min/1.73m^2. Although no statistically significant difference in cholesterol levels in lipoproteins or triglyceride levels between CKD stages 4 and 5 was shown by HGPC, the method showed that the lipoprotein particle number in small HDLs was higher in Stage 4 than in Stage 5 (p=0.002). Multivariate regression analysis adjusted for baseline characteristics showed that the cholesterol proportion in very small HDLs was negatively associated with eGFR change rate [fraction (F) 19 β=-17.63, p=0.036] and was associated with ABI [F19 β= 0.047, p=0.047] in Stage 4. Moreover, serum soluble α-Klotho level was associated with the number of very small HDL particles [F19 β=0.00026, p=0.012; F20 β=0.00041, p=0.036] in Stage 5.

Conclusions: This study showed that HDL subclasses alter with CKD progression and are associated with ABI and Klotho level in a CKD-stage-specific manner.

Definitions of classes and subclasses of lipoproteins

Fraction	F1-2	F3-5	F6	F7	F8	F9	F10	F11-13	F14-15	F16	F17	F18	F19-20
Subclass	CM	Large VLDL	Medium VLDL	Small VLDL	Large LDL	Medium LDL	Small LDL	Very small LDL	Very large HDL	Large HDL	Medium HDL	Small HDL	Very small HDL

SA-PO191

Diagnostic Biomarkers of Endoplasmic Reticulum Stress in Glomerular Disease Nihad T. Abouelazm,[3] Joan Papillon,[4] Julie Guillemette,[1] Andrey V. Cybulsky.[2] *[1]Medicine, McGill University, Montreal, QC, Canada; [2]Medicine, McGill University, Montreal, QC, Canada; [3]Medicine, McGill University, Montreal, QC, Canada; [4]Medicine, McGill University, Montreal, QC, Canada.*

Background: Endoplasmic reticulum (ER) stress has been implicated in the pathogenesis of various glomerular and tubular diseases. ER chaperones lacking the KDEL motif, e.g. ERdj3 and mesencephalic astrocyte-derived neurotrophic factor (MANF), can be secreted extracellularly. We propose that induction of ER stress in glomerular diseases may lead to accumulation of secreted ER chaperones in the urine. Such chaperones may potentially serve as biomarkers for diagnosis and therapy.

Methods: ER stress was induced in cultured glomerular epithelial cells (GECs) and in vivo with tunicamycin (TM). In addition, complement-induced ER stress in podocytes was studied in passive Heymann nephritis (PHN), a rat model of human membranous nephropathy. Intracellular expression and secretion of ER chaperones was monitored by immunoblotting. The protective effect of the chemical chaperone, 4-phenyl butyric acid (4-PBA), on complement-mediated podocyte injury was examined by adding 4-PBA to the drinking water of rats with PHN.

Results: In cultured GECs, TM upregulated ER chaperones, ERdj3 and MANF, intracellularly and in culture medium, whereas GRP94 (KDEL chaperone) increased only intracellularly. ERdj3 and MANF extracellular secretion was blocked by the secretory trafficking inhibitor, brefeldin A. ERdj3 and MANF immunoreactivity was stimulated in urines and glomerular lysates of TM-injected rats after 24 h and was independent of proteinuria. Compared to control, ERdj3 and MANF were increased significantly in the urine of PHN rats on days 7-14 after injection of nephritogenic antibody, and coincided with the onset of proteinuria on day 7. Moreover, in PHN, there were concomitant

increases in glomerular ER chaperones, GRP94, ERP57, and MANF, compared to control. Rats with PHN were treated with 4-PBA starting at the time of disease induction, or on day 7, until day 14. In both protocols, 4-PBA reduced proteinuria (on days 7-14), as well as urinary ER chaperone secretion, compared to PHN rats treated with saline.

Conclusions: ERdj3 and MANF secreted into the urine reflect glomerular ER stress. 4-PBA protected against complement-mediated podocyte injury and the therapeutic response could be monitored by ERdj3 and MANF secretion. Urinary ER chaperones may potentially serve as diagnostic biomarkers for identifying patients with glomerular ER dysfunction.

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SA-PO192

Whole Glomerular Transcriptome Analysis from CKD Biopsies Predicts Cell Lineage-Specific Transcripts Sean Eddy,[1] Viji Nair,[1] Tao Wei,[2] Anna Reznichenko,[3] Rajasree Menon,[1] John R. Hartman,[1] Edgar A. Otto,[1] Mark Tomilo,[1] Wenjun Ju,[1] Felix H. Eichinger,[1] Brad A. Godfrey,[1] Yu Chen,[2] James Conway,[4] Maja Lindenmeyer,[5] Clemens D. Cohen,[5] Shawn S. Badal,[6] Johnna D. Wesley,[7] Uptal D. Patel,[6] Matthew D. Breyer,[2] Kevin L. Duffin,[2] Maria chiara Magnone,[3] Carol P. Moreno Quinn,[4] Matthias Kretzler.[1] *[1]University of Michigan, Ann Arbor, MI; [2]Eli Lilly and Company, Indianapolis, IN; [3]AstraZeneca, Mölndal, Sweden; [4]MedImmune, Gaithersburg, NJ; [5]Ludwig-Maximilians-Universität München, München, Germany; [6]Gilead Sciences, Inc., Foster City, CA; [7]Novo Nordisk Research Center, Seattle, Seattle, WA.*

Background: Single cell transcriptome analysis yields a wealth of information on cell type specific transcripts but is not feasible on a large scale, while tissue-level transcriptomic analysis yields a wealth of information on gene regulation but lacks cell type specificity. Coupling whole tissue transcriptome analysis with single cell transcriptome analysis can yield insights into cell type markers and expression profiles.

Methods: Transcriptomic profiles of microdissected glomeruli from clinically indicated renal biopsies were generated from 170 CKD patients in the European Renal cDNA Bank cohort. Gene expression modules were generated using weighted gene co-expression network analysis. Cell lineage signatures curated from published literature were used to compare with modules.

Results: Across the glomerular transcriptome, 22 co-expression modules were identified ranging in size from 76 to 2012 genes. Limiting the analysis to the most variant transcripts yielded 16 co-expression modules ranging in size from 99 to 1046 genes. Re-sampling analysis indicated that modules were stable. From the most variant transcript analysis, eigengenes were compared to cell type specific signatures and two modules (698 genes) were strongly correlated ($r>0.75$, $p<10E-30$) with a podocyte signature generated from podocyte gene set (Ju et al., 2013). Functional enrichment of these modules identified biology associated with podocyte dysfunction, fibrosis, and glomerular toxicity. These two modules contained 62% (21/34) of the podocyte genes expressed in the variant filtered dataset including NPHS1 and WT1, and 69% (93/134) of previously predicted podocyte genes; 11-33% of the remaining genes in the podocyte signature-associated modules were expressed in podocytes from single cell RNA-seq analysis of human kidney tissue (based on different thresholding criteria for defining single cell expression).

Conclusions: This approach allows for the identification of cell-lineage specific transcripts in whole tissue transcriptome datasets and offers the opportunity to identify novel cell lineage transcripts.

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SA-PO193

Transcriptional Reprogramming by Wilms' Tumor 1 and FoxC2 Mediates a Repair Response during Podocyte Injury Sandrine S. Ettou,[1] Youngsook L. Jung,[2] Martin Kann,[3] Peter Park,[2] Jordan A. Kreidberg.[1] *[1]Boston Childrens Hospital- Harvard Medical School, Boston, MA; [2]Center for Biomedical Informatics, Harvard Medical School, Boston, MA; [3]Nephrolab Cologne, Kidney Research Center Cologne, Cologne, Germany.*

Background: Foot process effacement and proteinuria, representing a breakdown of the glomerular filtration barrier (GFB), may be caused by decreased expression of key podocyte proteins. We previously reported a Wilms' tumor-1 (WT1) ChIP-Seq study that identified components of the GFB and many other important podocyte genes as WT1 target genes. Many WT1 target genes in podocytes also appear to be bound by FoxC2, including *Nphs2*, and *Synpo*. In the present study we demonstrate that WT1 and FoxC2 transcriptionally program a repair response after podocyte injury induced by Adriamycin.

Methods: We used ChIP-Seq to study the DNA binding of WT1 and Foxc2 to target genes in normal podocytes. We used Adriamycin-induced podocyte injury as a model for human FSGS. WT1 and FoxC2 binding was determined by direct ChIP-qPCR at time points after injury using isolated glomeruli from 3, 5 and 7 days post-injection or control Balb/C mice.

Results: Our ChIP-Seq results demonstrate that WT1 and FoxC2 have multiple binding sites at target genes including *Nphs2* and *Synpo*. We previously observed that after the onset of heavy proteinuria, *Nphs2* and *Synpo* expression decreases, as does WT1 and FoxC2 binding to their respective target sites. However, in examining mice prior to, or during the early phase of proteinuria, WT1 and FoxC2 binding to target genes actually undergoes a transient increase at specific enhancer and promoter sites, and *Nphs2* and *Synpo* expression dramatically increases. Using immortalized podocytes, we also demonstrate that WT1 and FoxC2 binding to target genes is interdependent and that knockdown of WT1 or Adriamycin treatment results in epigenetic silencing of the *Nphs2* and *Synpo* genes.

Conclusions: Thus, our results reveal a previously unrecognized repair attempt in podocytes immediately after Adriamycin injury mediated by WT1 and FoxC2 to transcriptionally activate target genes required to maintain the GFB. In the Adriamycin model this repair attempt is ultimately unsuccessful, but transcriptional reprogramming may represent a therapeutic modality to maintain the GFB after podocyte injury.

Funding: NIDDK Support

SA-PO194

Acute Kidney Slices as a Tool to Dissect Calcium Signals in Podocytes Julia Binz,[1] Hadiseh Khalili,[2] Bernhard Schermer,[1] Thomas Benzing,[3] Matthias Hackl.[1] *[1]University Hospital Cologne, Cologne, Germany; [2]University Hospital of Cologne, Köln, Germany; [3]University of Cologne, Köln, Germany.*

Background: Calcium signaling in the kidney has been a focus of research for many years. Especially calcium handling in podocytes has been of great interest since it is implicated to play a role in podocyte injury. As isolated podocytes in cell culture are lacking their physiologic microenviroment and isolated glomeruli are prepared with several treatment steps, acute kidney slices (AKS) represent an ex vivo model where the structural complexity of the glomerulus is preserved and which can be prepared within minutes after sacrificing the animal.

Methods: Prior to the preparation of AKS 8-week old C57BL6 mice expressing GCaMP3 under the Pod:Cre promoter were treated with Adriamycin (25mg/kg) for five days. Untreated mice were used as control group. For AKS preparation mice were sacrificed, the kidneys were removed and cut into 500 µm thick slices. During imaging a multiphoton laser was used at 940nm and AKS were treated with an angiotensin-II containing solution to induce calcium signaling in podocytes. As control experiments we used laser-induced calcium signaling and propidium iodide to show that podocytes remain viable and able to produce calcium signals.

Results: The podocytes with genetically encoded calcium indicator are viable and able to produce a calcium wave after laser injury as published in vivo. High doses of angiotensin-II elicit calcium signals in podocytes of untreated animals. Furthermore, there is an increase in calcium response after induction of Adriamycin nephropathy.

Conclusions: Acute slices of the kidney are a great tool to study podocytes, retaining the complex microarchitecture of the glomerulus, and provide results comparable to in vivo imaging. They allow testing of different dosages and compounds on individual kidney slices as the two kidneys provide enough material for at least 5 slices each. The technical setup needed for preparation is limited and the technique can be quickly taught. A confocal imaging setup is sufficient to image AKS. Therefore, AKS have the potential to become a widely used tool in glomerular research.

SA-PO195

Podocyte De-Differentiation Repatterns Energy Metabolism and Promotes Cellular Crescent Formation Jiao Miao,[1] Qi Sun,[2] Junwei Yang.[2] *[1]Center for Kidney Disease, Second Affiliated Hospital of Nanjing Medical University, Nanjing, China; [2]Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.*

Background: The role of podocytes in human crescentic glomerulonephritis (GN) has been underestimated. This may be due to the confounding fact that "dysregulated" podocytes are able to proliferate, lose their markers, and undergo de-differentiation. Specific deletion of *Tsc1* in podocytes led to spontaneous cellular or mixed cellular and fibrous crescents at 12 wk of age. These cellular crescents were immunostaining positive for WT-1 and Ki-67, suggesting that podocytes proceed profound phenotype changing in this model. This study is to investigate the mechanism that governs podocyte de-differentiation. Here we demonstrated that a switch of metabolism from oxidative phosphorylation to aerobic glycolysis was the primary feature during podocyte de-differentiation and also might be the initial step to promote proliferating.

Methods: Renal biopsies from patients with anti-GBM disease, lupus GN and IgA nephropathy were studied by immunofluorescence for WT-1 for podocyte identification and Ki-67 for cell cycle assessment. The de-differentiated podocyte undergoing proliferation was assessed by flow cytometry and fluorescent. Western blot and quantitative real-time PCR were performed to examine the expression level of glycolysis related enzymes. Meanwhile, podocyte-specific *Tsc1* knockout mice were generated as a model for crescentic GN.

Results: Both gene and protein assay showed that the expression of glycolysis enzymes were upregulated in *Tsc1KO* mouse kidneys or in TGFβ1-treated podocytes. Aerobic glycolysis flux, indicated by glucose uptake and lactate production, was increased in TGFβ1-treated podocyte and positively correlated with cell de-differentiation and proliferation. Furthermore, continuously administrating 2-DG starting at 4 wk of age for 8 wk alleviateed crescents formation as well as the induction of p-S6, HIF1a, and PFK in the glomeruli from the *Tsc1*-knockouts.

Conclusions: Our findings demonstrate the critical role of aerobic glycolysis in podocyte de-differentation and proliferation and provide the treatment with aerobic glycolysis inhibitors as a potential anti-crescentic GN strategy.

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SA-PO196

Role of Exocyst Complex in Podocytes Ashish K. Solanki,[5] Deepak Nihalani,[5] Ehtesham Arif,[5] Pankaj Srivastava,[1] Joshua H. Lipschutz,[5] Xiaofeng Zuo,[1] Yanhui Su,[4] Yujing Dang,[5] Habeeb Alsudani,[2] Soumitra Ghoshroy.[3] *[1]MEDICAL UNIVERSITY OF SOUTH CAROLINA, CHARLESTON, SC; [2]USC, Columbia, SC; [3]University of South Carolina, Columbia, SC; [4]MUSC, Charleston, SC; [5]Medical University of South Carolina, Charleston, SC.*

Background: Exocytosis is mediated through the exocyst complex, which is critical for protein transport and its disruption causes defects in various cellular processes including cell polarity, migration, ciliogenesis and autophagy. Since various glomerular injuries disrupt these processes, we hypothesized that disruption of exocytosis in podocytes will lead to a disease phenotype. In this study, we generated podocyte-specific Exoc5 (a central component of the octameric exocyst complex) knockout mice that showed massive proteinuria and died within 4 weeks of birth.

Methods: Exoc5 was genetically deleted in podocytes by crossing Exoc5f/f with pod-CreTg/+ mice. Mice were analyzed using biochemical, histological, morphological and immunofluorescence approaches. Exoc5 knocked down stable cultured podocyte cells were created using Exoc5-specific shRNA and stained with acetylated tubulin and ciliary phenotype was evaluated by superresolution microscopy.

Results: The Exoc5f/f;PodCreTg/+ mice were proteinuric and died between 21-27 days after birth. Kidney section analysis showed severe glomerular defects with increased fibrosis and proteinaceous casts. Ultrastructural analysis showed effaced podocytes with loss of slit diaphragm. Immunofluorescence analysis showed significant mislocalization of junctional proteins Neph1 and ZO-1, and decreased Nephrin protein expression. To study ciliogenesis defects, we stained isolated mice glomeruli with tubulin antibody, which showed numerous cilia on wild type (WT) glomeruli (Fig1), while cilia in Exoc5 KO glomeruli were absent. In contrast, cultured podocytes showed reduced cilia number with shortened length.

Conclusions: This is the first report that highlights role of exocyst complex in podocytes and shows that loss of Exoc5 results in massive glomerular damage, loss of cilia and death in mice.

Funding: NIDDK Support

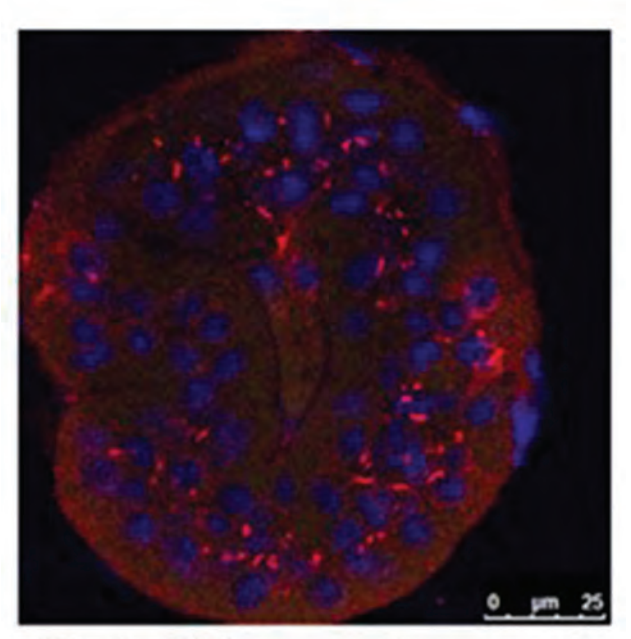

Fig1: Cilia on a glomerulus

SA-PO197

Beclin 1 Regulates Podocyte Secretory Pathways Tillmann Bork,[1] Wei Liang,[2] Kosuke Yamahara,[1] Tobias B. Huber.[3] *[1]University Hospital Freiburg, Freiburg, Germany; [2]Renmin Hospital of Wuhan University, Wuhan, China; [3]University Medical Center Hamburg, Hamburg, Germany.*

Background: Podocyte crosstalk with other glomerular cells might be a common theme of glomerular health and disease. However, very little is known how podocyte secretory pathways are being regulated. The complex molecular structure of the autophagy initiating protein Beclin 1 (ATG6) suggested an additional involvement in membrane dynamics. Using podocyte-specific knock-out of Beclin 1 we aimed to further elucidate the specific role of Beclin 1 in podocytes.

Methods: Mice with podocyte-specific loss of Beclin 1 were generated by using cre-loxp technique and analyzed. For autophagy assessment and primary cell culture these mice were crossed to Tomato/eGFP and GFP-LC3 reporter strains, respectively.

Results: Podocyte-specific knock-out of Beclin 1 results in proteinuria and decreased life span. Strikingly, podocytes show massively enlarged Golgi apparatus promoted by increased PI4P production leading to aberrant vesicle formation and vesicle accumulation indicating a functional disruption of the secretory pathway. In fact, VEGF secretion was massively decreased in of Beclin 1-deficient podocytes resulting in severe endothelial damage.

Conclusions: Here we identify a key regulatory protein of the secretory pathway by unravelling a novel function of Beclin 1 in podocytes. Promoting the delivery of secreted factors such as VEGF Beclin 1 is required for glomerular maintenance and might represent a novel pathway being affected in glomerular diseases.

Funding: Government Support - Non-U.S.

SA-PO198

Deiodinase 3 Downregulation: A Thyroid Hormone Associated Renoprotective Mechanism Nicholas J. Tardi,[2] Chuang Chen,[1] Ranadheer Dande,[2] Jochen Reiser.[2] *[1]Rush University, Chicago, IL; [2]Rush University Medical Center, Chicago, IL.*

Background: Deiodinase 3 (D3) is a membrane-bound, catabolic enzyme that regulates cellular metabolism by deactivating tri-iodothyronine (T3), the metabolically active thyroid hormone. As evident by the embryonic lethality of D3 knockout animals, proper regulation of thyroid hormone activity is vital in nearly all cell types. In the kidney, hyperthyroidism increases renal filtration pressure and absorption capacity, while hypothyroidism thickens the glomerular basement membrane and reduces filtration rate. Despite the prevalence of overlapping complications of thyroid hormone disorders and kidney disease, a unifying mechanism regulating T3 homeostasis in the kidney is absent. Though well studied in endocrine tissues, the role of D3 in local regulation of thyroid hormone in renal tissue has not been addressed. To fill this void, we initially assayed for deiodinase expression in podocytes, as they have a significant role in energy metabolism; having mechanisms that respond to both glomeruli derived and circulating changes in hormone levels. After discovering D3 was highly expressed in podocytes and downregulated in injury models, we aimed to determine the significance of D3 dysfunction in glomerular kidney disease.

Methods: The T3 regulatory capacity of D3 was analyzed via cleavage assay using a radioisotope labeled substrate in cultured podocytes treated with puromycin aminonucleoside (PAN). The role of D3 in proteinuric kidney disease was evaluated using podocyte specific D3 KO mice. Glomerular D3 expression was measured in renal biopsies from kidney disease patients by immunofluorescence.

Results: D3 expression and activity was downregulated in response to PAN induced podocyte injury *in vitro*. D3 expression was prominently diminished at the cell membrane, yet remained concentrated in the golgi and perinuclear region where metabolically active T3 resides. Podocyte specific D3 KO mice responded poorly to LPS-induced acute kidney injury, resulting in heavy proteinuria compared to control. D3 expression in glomeruli of kidney disease patients suffering from minimal change disease, diabetic nephropathy, or focal segmental glomerulosclerosis showed unique profiles amongst diseases.

Conclusions: Our data shows D3 downregulation in podocytes as a response to injury, and suggests D3 may have a renoprotective role in thyroid hormone associated kidney disease.

SA-PO199

DDR1 Inhibition Preserves Renal Function in a Mouse Model of Alport Syndrome Judith T. Molina David,[1,2] Jin Ju Kim,[1,2] Javier T. Varona Santos,[1,2] Anja Harmeier,[3] Hans Richter,[3] Rodolfo Gasser,[3] Christian Faul,[1,2] Marco Prunotto,[3] Alessia Fornoni.[1,2] *[1]Katz Family Division of Nephrology and Hypertension, University of Miami Miller School of Medicine, Miami, FL; [2]Katz Family Drug Discovery Center, University of Miami Miller School of Medicine, Miami, FL; [3]Hoffmann-La Roche, AG, Basel, Switzerland.*

Background: Alport Syndrome (AS) is a hereditary disease condition caused by mutations in the type IV collagen genes, leading to progressive renal fibrosis, hearing loss and ocular changes. Discoidin domain receptor 1 (DDR1) is a receptor tyrosine kinase that is activated by collagen and that promotes fibrosis, whereas genetic deletion of DDR1 in mice protects from renal failure in AS. Our study was aimed at identifying a selective DDR1 inhibitor to prevent kidney disease in Col4a3 knockout (KO) mice.

Methods: Approximately 56.000 compounds were screened in *in vitro* binding assay and a fraction of those (circa 1000) were further evaluated in a cell based assay aimed at evaluating DDR1 phosphorylation in dose response. Five compounds were finally selected based on their selectivity, potency and pharmacokinetic and pharmacodynamics profile for further *in vivo* testing and a unique lead compound (cpd) was identified for further in depth *in vivo* analysis. Four-week-old Col4a3 KO and wildtype (WT) mice were injected intraperitoneally with cpd (90 mg/kg) or vehicle on a daily basis. Experimental groups included: WT+vehicle (n=10), WT+cpd (n=11), KO+vehicle (n=11), and KO+cpd (n=14). At 8-weeks of age, mice were sacrificed and kidney tissue, blood and urine were collected for further analysis. Histological analysis was performed by H&E, PAS, Picrosirius Red and immunofluorescence staining (IF). Serum and urine samples were used to determine BUN, albumin, creatinine. Total and pDDR1 levels were measured in kidney cortex by immunoprecipitation.

Results: Fibrosis was assessed by IF for smooth muscle actin (αSMA), Collagen type 1 and laminin. Cpd treatment significantly improved serum BUN, urine albumin/creatinine ratio and fibrosis in KO mice in association with reduced levels of total and phosphorylated DDR1.

Conclusions: These results indicate that drugs targeting DDR1 may represent a novel strategy to treat kidney disease in patients with AS.

Funding: Commercial Support - Hoffmann-LaRoche AG

SA-PO200

The Role of DDR1 in Podocyte Lipotoxicity and Progression of Alport Syndrome Jin Ju Kim,[1,2] Judith T. Molina David,[1,2] Javier T. Varona Santos,[1,2] Marco Prunotto,[3] Sandra M. Merscher,[1,2] Jeffrey H. Miner,[4] Alessia Fornoni.[1,2] *[1]Katz Family Division of Nephrology and Hypertension, University of Miami Miller School of Medicine, Miami, FL; [2]Katz Family Drug Discovery Center, University of Miami Miller School of Medicine, Miami, FL; [3]F. Hoffmann-La Roche Ltd., Basel, Switzerland; [4]Washington University School of Medicine, St. Louis, MO.*

Background: The GBM is primarily composed by laminin and Collagen type IV. *De novo* production of collagen type I (Col I) has been observed in a mouse models of Alport Syndrome (AS-Col4a3KO). Discoidin-domain-receptor1 (DDR1) is a unique receptor tyrosine kinase that is activated by collagens. Deletion of the DDR1 in Col4a3KO mice improves survival and renal function. However, how DDR1 activation by aberrant collagen production contributes to podocyte injury and proteinuria is poorly understood.

Methods: Differentiated human podocytes were serum starved, followed by 18hrs treatment with 50ug/mL Col I (Corning). Podocyte lipid content was determined by BODIPY 493/503 and Cell Mask Blue staining. Free Fatty acid (FFA) uptake assessed using the fluorometric free fatty acid uptake kit (abcam). Col4a3KO mice (Jackson Laboratory) were utilized for the determination of kidney cortex DDR1 phosphorylation. HEK293 transfected with Dominant active (DA) and dominant negative (DN) constructs were utilized in selected experiments.

Results: DDR1 phosphorylation was increased in kidney cortex from Col4a3KO mice ($p<0.05$), whereas the expression of podocin and synaptopodin was decreased. pDDR1 correlated with blood urine nitrogen (BUN, $R^2=0.7$, $p<0.01$). *In vitro*, podocyte DDR1 was phosphorylated by Col I at 18 hours. Increased intracellular lipid accumulation ($p<0.05$) and FFA uptake ($p<0.001$) were also observed in Col I treated podocytes. DDR1 DA transfected HEK293 cells showed increased expression of CD36, a protein involved in FA uptake, and FFA uptake compared to cells transfected with DDR1 WT and DN ($p<0.05$). Glomeruli isolated from Col4a3KO mice showed increased lipid deposition and expression of CD36.

Conclusions: Our data suggest that col I-induced/DDR1-mediated lipotoxicity may represent a novel mechanism leading to podocyte injury in AS.

Funding: Commercial Support - Hoffmann-La Roche

SA-PO201

Inducible Podocyte-Specific Deletion of CTCF Leads to Progressive CKD with Severe Bone and Mineral Disease in the Absence of Renal Fibrosis Marta Christov,[6,5] Abbe R. Clark,[4] Eugene P. Rhee,[5] Hiroaki Saito,[7] Eric Hesse,[7] Mary L. Bouxsein,[3] Astrid Weins,[1] Peter H. Mundel,[2] Harald Jüppner,[5,3] Anna Greka.[1,3] *[1]Brigham & Women's Hospital, Boston, MA; [2]Goldfinch Bio, Cambridge, MA; [3]Harvard Medical School, Boston, MA; [4]Harvard University, Boston, MA; [5]Massachusetts General Hospital, Boston, MA; [6]New York Medical College, Valhalla, NY; [7]University Medical Center Hamburg-Eppendorf, Hamburg, Germany.*

Background: Progressive chronic kidney disease (CKD) is on the rise worldwide with more than 500 million people affected. However, the sequence of events resulting in onset and progression of CKD remain poorly understood. Likewise, while FGF23 elevations are associated with increased mortality, its utility as a biomarker of early CKD remains uncertain, and whether it can be manipulated through dietary or pharmacologic interventions is controversial. Animal CKD models exploring these issues are confounded by systemic toxicities or artificial surgical interventions.

Methods: Floxed CTCF mice ($CTCF^{fl/fl}$) were mated with doxycycline-inducible, podocyte-specific CRE transgenic mice ($iCre^{pod}$). Treatment of Cre^{pod}-$CTCF^{fl/fl}$ mice with doxycycline started at 6 weeks of age to generate $iCTCF^{pod-/-}$ mice, and treated wild-type (WT) mice served as controls. We assessed kidney histology for podocyte loss and interstitial fibrosis, as well as mineral metabolism parameters at 2, 4, 6 and 8 weeks. We determined bone parameters by microCT and histomorphometry in $iCTCF^{pod-/-}$ and WT mice at 8 weeks.

Results: We generated a novel CKD mouse model through the selective and inducible podocyte-specific deletion of an essential endogenous molecule, the chromatin structure regulator CCCTC-binding factor (CTCF), which leads to rapid podocyte loss ($iCTCF^{pod-/-}$). As a consequence, $iCTCF^{pod-/-}$ mice develop severe progressive albuminuria, hyperlipidemia and hypoalbuminemia, the hallmarks of the nephrotic syndrome, and die within 8-10 weeks. Progressive CKD in $iCTCF^{pod-/-}$ mice leads to high serum phosphate and low ionized blood calcium levels, and consequently to profound elevations in FGF23 and PTH levels that rapidly cause bone mineralization defects, increased bone resorption and bone loss.

Conclusions: Dissection of the timeline leading to glomerular pathology in this new CKD model led us to the surprising observation that podocyte ablation and the resulting glomerular filter destruction is sufficient to drive progressive CKD in the absence of interstitial fibrosis. This work highlights podocyte-protective strategies rather than the prevention of renal fibrosis as the most promising therapeutic approach for CKD.

Funding: NIDDK Support

SA-PO202

Loss of Function of Rhpn1 Leads to Proteinuria through Downregulation of Wt1 via Wtip Kan Katayama.[1,2] *[1]Cardiology and Nephrology, Mie university graduate school of medicine, Tsu, Japan; [2]Medical Biochemistry and Biophysics, Karolinska Institute, Stockholm, Sweden.*

Background: Rhophilin-1, Rhpn1 was identified as one of podocyte-enriched proteins and Rhpn1 inactivation in mice showed proteinuria at an early stage. Although the onset of proteinuria was suggested by a mechanism due to the altered actin cytoskeleton structure, the underlying pathogenesis is not fully clarified. Moreover, there is no report in human so far.

Methods: Therefore, we investigated the function of rhpn1 in zebrafish to evaluate whether the phenotypic change was conserved in zebrafish.

Results: Knockdown of rhpn1 in zebrafish caused proteinuria, which was confirmed by the uptake of 500 kDa Fluorescein isothiocyanate-conjugated dextran in proximal tubules. To further analyze the function of Rhpn1, yeast two hybrid screening was performed and Wilms tumor protein 1-interacting protein, Wtip, was identified as an interaction partner of Rhpn1. rhpn1 knockdown in zebrafish or Rhpn1 knockout in mouse resulted in downregulation of mRNA of Wilms tumor protein 1, WT1. In kidneys from Rhpn1 knockout mouse, nuclear translocation of Wtip protein was observed more commonly compared to wild-type mouse kidneys.

Conclusions: Taken together, loss of interaction between Rhpn1 and Wtip might be involved in the development of proteinuria through downregulation of Wt1.

SA-PO203

Ezrin Plays Important Roles in the Regulation of Foot Process Morphology in the Glomerular Podocytes Ryo Hatano. *Ritsumeikan University, Kusatsu, Japan.*

Background: Ezrin is highly expressed in the glomerular podocytes, and is reported to form multi-protein complex with a scaffold protein Na^+/H^+ exchanger regulatory factor 2 (NHERF2), and podocalyxin, a major sialoprotein. Podocalyxin deficient mice died within 24 hrs after birth with anuric renal failure, whereas NHERF2 knockout mice did not show apparent renal phenotype. On the other hand, physiological roles of ezrin in glomerular podocytes still remain unclear.

Methods: To investigate the physiological roles of ezrin in the regulation of glomerular podocyte function, ezrin knockdown mice ($Vil2^{kd/kd}$) were used in this study. Histological analysis of glomerulus was performed by H&E staining and electron microscopy. Western blotting and immunofluorescent analysis were performed the expression and localization of related proteins in the podocytes. Rho activities were investigated by ELISA-based pull down assay using isolated mouse glomeruli from WT and $Vil2^{kd/kd}$ mice and glomerula podocyte cell line, E11.

Results: $Vil2^{kd/kd}$ mice did not exhibit apparent glomerular dysfunction, morphological defects, and disturbance in the localizations of podocalyxin and NHERF2 in podocytes. In $Vil2^{kd/kd}$ glomeruli, Rac1 activity was significantly decreased in $Vil2^{kd/kd}$ glomeruli compared to WT glomeruli although RhoA activity was increased. Then, we examined Rho-activities in E11 cells, in which ezrin expression was downregulated by siRNA. Rac1 activity was significantly decreased in ezrin knockdown E11 cells, whereas significant change in the RhoA activity was not observed. On the other hand, transfection of constitutively active ezrin (T567D) increased the activity of Rac1. Furthermore, increased lamellipodia formation was observed in the T567D-transfected E11 cells.

Conclusions: Our results suggest that ezrin regulates the foot process formation via the Rac1 activity in the podocytes. Ezrin is known to interact with Rho-GDP dissociation inhibitor (RhoGDI). Since ezrin promotes the activation of Rho via the striping RhoGDI from GDP-bound Rho, activation of ezrin might be involved with Rac1 activation in the glomerular podocytes.

SA-PO204

The Protective Role of Podocyte Hypertrophy via mTOR Signalling after Mild Podocyte Depletion Victor G. Puelles,[1,2] James W. Van der wolde,[1] Luise A. Cullen-McEwen,[1] Luc Furic,[1] Kate M. Denton,[3] Marcus J. Moeller,[2] David J. Nikolic-Paterson,[4] John F. Bertram.[1] *[1]Anatomy and Developmental Biology, Monash University, Melbourne, VIC, Australia; [2]Nephrology and Clinical Immunology, University Hospital RWTH Aachen, Aachen, Germany; [3]Physiology, Monash University, Melbourne, VIC, Australia; [4]Nephrology, Monash Medical Centre, Melbourne, VIC, Australia.*

Background: Marked podocyte depletion is an established key feature of glomerulosclerosis (FSGS). However, little is known about the consequences of mild podocyte loss. In addition, activation of parietal epithelial cells (PECs) has been proposed as a major effector in FSGS. This study investigates the consequences of graded podocyte depletion, the hypertrophic response of podocytes and associations with PEC activation and thereby glomerulosclerosis.

Methods: We induced selective podocyte depletion in Pod^{Cre}iDTR mice by injection of diphtheria toxin (DT) at different doses. L-NAME induced hypertension was used as a second hit challenge after mild podocyte loss. The mammalian target of rapamycin (mTOR) signalling pathway was manipulated using mTOR inhibitors (RAD001 and INK128). Podocyte depletion and hypertrophy were examined by 3D analysis of whole glomeruli in optically-cleared kidney slices.

Results: Pod^{Cre}iDTR mice injected with a low dose of DT presented mild podocyte depletion, compensatory podocyte hypertrophy and reversible albuminuria without PEC

activation or glomerulosclerosis, even following a second hit challenge (high blood pressure), suggesting a protective role of podocyte hypertrophy. Injection of a higher dose of DT in Pod^{Cre}iDTR mice led to greater podocyte loss and hypertrophy. However, these mice showed PEC activation, glomerulosclerosis and persistent albuminuria, suggesting there is a limit for the protective role of podocyte hypertrophy. Pharmacological inhibition of mTOR during the induction of mild podocyte depletion led to persistent and exacerbated albuminuria, impairment of podocyte hypertrophy, PEC activation and glomerulosclerosis.

Conclusions: Podocyte hypertrophy via mTOR signalling is required for the adaptive hypertrophic response of remaining podocytes after mild podocyte depletion. These results are relevant for the use of mTOR inhibitors in the context of FSGS and CKD.

SA-PO205

HMGA1-Driven Long Non-Coding RNAs Mediate Endothelial-to-Mesenchymal Transition in Kidney Fibrosis Roel Bijkerk,[1] Atefeh Lafzi,[2] Wendy Stam,[1] Angela Koudijs,[1] Ellen Lievers,[1] Ton J. Rabelink,[1] Hilal Kazan,[3] Anton J. Van Zonneveld.[1] *[1]Leiden University Medical Center, Leiden, Netherlands; [2]CNAG-CRG, Barcelona, Spain; [3]Antalya International University, Antalya, Turkey*.

Background: Chronic kidney disease associates with the development of interstitial fibrosis characterized by a loss of the microvasculature and myofibroblast formation. Endothelial cells (ECs) are important for maintaining a healthy microvasculature while ECs also provide a potential source for myofibroblasts through endothelial-to-mesenchymal transition (EndoMT). Here, we aimed to identify a role for long non-coding RNAs (lncRNAs), novel central post-transcriptional regulators, in ECs in the development of kidney fibrosis.

Methods: We used VE-cadherin-ERT2;tdTomato mice to label and trace endothelial cells. We applied both the ischemia-reperfusion injury (IRI) and unilateral urethral obstruction (UUO) models followed by FACS sorting of the tomato-positive cells from healthy and diseased kidneys. Subsequently, we isolated RNA from these cells and profiled for lncRNAs, as well as gene expression, using comprehensive genome-wide transcript arrays.

Results: Upon kidney injury, we observed substantial co-localization of VE-cadherin-derived tomato positive signal with a-SMA staining, indicating that a significant portion (~15-20%) of myofibroblasts originated from ECs. We confirmed that ECs acquired a myofibroblast phenotype by using qPCR on FACS sorted tomato-positive cells showing reduced expression of EC markers CD31 and VE-cadherin while myofibroblast markers α-SMA and col1α1 increased. In UUO and IRI, we found 586 and 416 lncRNAs to be differentially expressed (>2-fold, $p<0.05$) in the VE-cadherin-derived tomato-positive cells, respectively. Using bioinformatic analyses to determine transcription factor motif-enrichment amongst differentially expressed lncRNAs we found strong enrichment for HMGA1 binding sites, a transcription factor previously described to be essential in EndoMT. Using ChIP-seq, we validated binding of HMGA1 to lncRNA promoters, including that of MALAT1, one of the differentially expressed and conserved lncRNAs, and subsequently demonstrated in an in vitro model for EndoMT that blocking MALAT1 with gapmers enhanced TGF-β induced EndoMT.

Conclusions: We demonstrated that HMGA1-induced lncRNAs mediate EndoMT which may provide novel strategies to counteract the development of kidney fibrosis.

SA-PO206

Rap1 and Its Guanine Nucleotide Exchange Factor C3G Are Critical for Drosophila Nephrocyte Filter Function Christopher P. Dlugos,[1] Cara Picciotto,[2] Astrid Jeibmann,[4] Michael P. Krahn,[3] Roland Wedlich-Söldner,[3] Hermann Pavenstädt,[5] Christian Klämbt,[3] Britta George.[1] *[1]Medizinische Klinik D, Universitiy Hospital Münster, Münster, Germany; [2]University Hospital Münster, Münster, Germany; [3]University of Muenster, Muenster, Germany; [4]Institute of Neuropathology, Münster, Germany; [5]UKM Münster, Münster, Germany*.

Background: Podocytes are crucial for kidney filter function. Podocyte damage is associated with a broad range of glomerular diseases with defective filter function based on aberrant intercellular junctions (slit diaphragms) and actin cytoskeletal dynamics resulting in renal failure and over time to end stage renal disease. Patients with mutations in the human gene encoding the slit diaphragm protein Nephrin do not develop functional slit diaphragms leading to a severe proteinuria. *Drosophila* nephrocytes form a slit diaphragm-like filtration barrier and express the Nephrin orthologue sticks-and-stones (sns). Nephrocytes represent a genetically tractable model to study Nephrin signaling *in vivo*. This study aims to elucidate Nephrin signal transduction to the actin cytoskeleton and focal adhesions.

Methods: To characterize the role of genes of interest in *Drosophila* nephrocyte filter function the secreted protein Atrial Natriuretic Factor (ANF-GFP-GFP) which is taken up by nephrocytes with functional filtration slits was ectopically expressed by the *ubiquitin* promoter (*ubi::ANF-GFP-GFP*). The *sns::Gal4* transgene allowed nephrocyte-specific expression of *UAS-dsRNA* by crossing the respective strains. Standard immunofluorescence and transmission electron microscopy were employed to analyze nephrocyte phenotypes.

Results: Co-immunoprecipitation experiments revealed an interaction of Nephrin and guanine nucleotide exchange factor C3G in HEK lysates. Engagement of a chimeric Nephrin molecule which results in downstream signaling events led to activation of integrin beta1 in podocytes. *In vivo*, nephrocyte-specific knockdown of the Nephrin orthologue *sns* as well as *C3G* or *roughened* (mammalian Rap1) compromised filtration, shown by impaired ANF-GFP-GFP uptake into *Drosophila* nephrocytes. Altered localization of integrin and the integrin-associated protein talin was observed following knockdown of *sns*. Ultrastructurally, knockdown of either *sns*, *C3G* or *roughened* resulted in loss of nephrocyte filtration slits.

Conclusions: *Drosophila melanogaster* is an effective model system to study nephrocyte function and Nephrin signaling. C3G interacts with Nephrin and is necessary for nephrocyte function.

Funding: Government Support - Non-U.S.

SA-PO207

KAT5-Mediated DNA Damage Repair Is Essential for the Maintenance of Podocytes Akihito Hishikawa,[1] Kaori Hayashi,[1] Toshiaki Monkawa,[2] Hiroshi Itoh.[1] *[1]Internal Medicine, Keio University School of Medicine, Tokyo, Japan; [2]Medical Education Center, Keio University School of Medicine, Tokyo, Japan*.

Background: We have recently reported the gene-selective epigenetic control in podocytes via KLF4 (Hayashi et al, JCI 2014. KI 2015). However, the precise formation process of epigenetic changes involved in diseases states remains unclear. Here we focused on KAT5, a histone acetyltransferase which has been reported as a KLF4 interacting protein and an important factor in repairing DNA, to investigate the possible role of DNA damage repair process in formation of epigenetic changes.

Methods: Expression of KAT5 was examined in streptozotocin (STZ)-induced diabetic mice model and the effect of KAT5 gene transfer was evaluated. To analyze the physiological role of KAT5, we generated podocyte-specific KAT5 knockout (KO) mice, and investigated the epigenetic changes and DNA damage status. We performed in vitro studies using cultured human podocytes to examine the mechanism of KAT5-associated epigenetic changes.

Results: KAT5 expression was significantly decreased in isolated podocytes in STZ mice and a marker of DNA double strand breaks γH2AX was increased in glomeruli of STZ mice. Restoration of KAT5 expression in STZ mice using a hydrodynamic-based gene transfer method ameliorated albuminuria, γH2AX and nephrin expression. KAT5 KO mice developed massive proteinuria (6 week-old, WT 33±16 mg/gCr, KO 3326±1023 mg/gCr, $p<0.05$) with segmental glomerurosclerosis and diffuse effacement of podocyte foot process. In KO mice, nephrin expression in isolated podocytes was decreased, and WT1-positive podocyte number was reduced with an increase in TUNEL positive cells. Epigenetic changes and an increase in γH2AX expression were observed in glomeruli of KO mice. In cultured human podocytes, high-glucose treatment (30mM) induced KAT5 reduction and overexpression of KAT5 increased nephrin expression. It was revealed that overexpression of KAT5 induced a decreased methylation and a decreased binding of DNMT1 in the nephrin promoter region by methylation-specific PCR method and ChIP analysis.

Conclusions: DNA damage repair through KAT5 is essential for the maintenance of podocytes and has relation to the changes in podocyte epigenome. Increased KAT5 in podocytes ameliorates diabetic nephropathy with promoted DNA damage repair and elevated nephrin expression.

Funding: Government Support - Non-U.S.

SA-PO208

Isoform Specific Phosphorylation of Dynamin1 in Regulating the Cortical Actin Cytoskeleton in Podocytes Changkyu Gu,[2] Nikolina Stojanovic,[2] Mario Schiffer,[1] Sanja Sever.[3] *[1]Hannover Medical School, Hannover, Germany; [2]Massachusetts General Hospital, Charlestown, MA; [3]Massachusetts General Hospital, Charlestown, MA*.

Background: Dynamin is an essential actin regulatory protein in podocyte, and loss of its function is closely connected to podocyte injury and proteinuria. Recently, our studies have shown that dynamin directly regulates actin cytoskeleton via its oligomerization state. Importantly, dynamin specific small drug (Bis-T-23) that induces its oligomerization ameliorates proteinuria in diverse proteinuric animal models through recovering functional actin structures in injured podocytes. Threrfore, it is important to maintain balance between dynamin assembly and disassembly. This dynamin oligomerization can be regulated through interaction with diverse cellular proteins, and it was reported that dynamin1 can differentially alter the affinity for its protein binding partners via phosphorylation by two different serine/thronine kinases, GSK3β and CDK5, in neurons. Based on these data, we hypothesize that phosphorylation-dependent dynamin1 oligomerization is an important molecular mechanism that regulates actin dynamics in podocytes.

Methods: Dynamin1 phosphorylation in podocytes was detected by western blot using phospho-dynamin1 specific antibodies in the presence of GSK3β or CDK5 inhibitor. Actin and paxillin in podocytes were stained to observe actin structures and focal adhesions. Cell migration and spreading assays were performed with podocytes expressing phosphor-dynamin1 mutants. For zebrafish experiments, each phosphor-dynamin1 mutant was expressed in dynamin2^{KD} zebrafish.

Results: 1. Dynamin1 is phosphorylated by GSK3β and CDK5 in podocytes. 2. Expression of phosphor-dynamin1 mutants alters cortical actin networks during cell spreading. 3. Expression of phosphor-dynamin1 mutants attects cell migration. 4. Expression of phosphor-dynamin1 mutants fails to rescue proteinuria in dynamin2^{KD} zebrafish.

Conclusions: The role of dynamin in actin cytoskeleton in podocytes is essential to maintain the glomerular filtration barrier. Dynamin directly regulates actin structures via its oligomerization state. Our data suggest that dynamin1 phosphorylation is implicated

in cortical actin dynamics in podocytes, and its balanced phosphorylation by GSK3β and CDK5 is crucial to podocyte's function in glomerular filtration.

Funding: NIDDK Support

SA-PO209

Flotillin-2 Is Required to Recruit Slit Diaphragm Protein into Rafts and Mediates Podocyte Injury and Proteinuric Glomerular Disease Li Zhang, Hong Zhang, Wei Shi, Xinling Liang. *Division of Nephrology, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China*.

Background: Podocytes are critical in the maintenance of the normal glomerular filtration barrier and is believed to be the target of numerous glomerular diseases leading to proteinuria. Lipid microdomains in podocytes play important roles in the normal cell morphology and glomerular barrier function. Raft proteins are thought to mediate diverse cellular processes. Flotillin-2/reggie-1(Flot-2) is a ubiquitously expressed and highly conserved raft protein. However, the biologic function in podocyte and proteinuric glomerular disease remains unknown.

Methods:

Results: Here, we identify and describe the functional role of Flot-2 as a novel podocyte-protein of the kidney glomerulus. Our novel studies demonstrate that flot2 expression is significantly reduced in glomerular podocytes of subjects with proteinuric glomerular diseases, and is also markedly reduced in response to podocyte injury induced by Lipopolysaccharide (LPS)/Adriamycin (ADR) in vitro and in vivo. We further find by immunoelectron microscopy that flot2 localizes to the insertion site of the slit diaphragm (SD) of podocytes. Reduced flot2 expression in vitro and in vivo using small interfering RNA and podocyte- specific flot2 knockout causes cytoskeleton disruptions and fails to recruit podocin, nephrin and CD2AP into rafts. Podocyte-specific flot2-deletion develops worse albuminuria, podocyte injury and glomerular pathology in LPS or ADR-induced nephropathy mice. Conversely, overexpression of flot2 in vitro and in vivo podocytes attenuates cytoskeleton disruptions and inhibits the reduction of SD-associated protein podocin, nephrin and CD2AP in lipid rafts. Meanwhile, podocyte injury, albuminuria and pathologic aberrance are prevented in podocyte-specific flot2 overexpression of transgenic mice when challenged with LPS or ADR. Mechanistically, we show that Flot2 and podocin directly interacts with each other via their SPFH domain. Further studies reveal that Krüppel-like factor 15(KLF15) directly bound to the flot2 promoter region, and regulate the expression of flot2 protein.

Conclusions: Thus, our results first indicate that flot-2 is required to recruit slit diaphragm protein into rafts and mediates podocyte injury and proteinuric glomerular disease. Maintaining necessary flot2 would be one potent way to prevent proteinuria kidney diseases.

Funding: Government Support - Non-U.S.

SA-PO210

In Vivo Investigation of Calcium Dynamics in Developing Podocytes during Glomerular Morphogenesis Lydia Djenoune,[1,2] Ritu Tomar,[1,2] Erin Merkel,[1,2] Iain A. Drummond.[1,2] *[1]Massachusetts General Hospital, Charlestown, MA; [2]Harvard Medical School, Boston, MA.*

Background: Podocytes are highly specialized epithelial cells in the kidney glomerulus that play critical roles in maintaining the glomerular filtration barrier. Nephrotic syndrome genes, including TrpC6 and PLCe1, affect podocyte calcium signaling. However, the role of calcium signaling during podocyte development *in vivo* remains unknown.

Methods: Here we aim at understanding the role of calcium signaling during glomerular development using live imaging of zebrafish.

Results: Live imaging showed that immature podocytes (48 hours post fertilization) are dynamic and interact with the dorsal aorta to form glomerular capillaries. By 4 days post fertilization (dpf) podocytes stabilize and the filtration barrier is functionally mature. Using the calcium biosensor GCaMP3, we observed spontaneous intracellular calcium transients in podocytes at early stages (2-3 dpf) of development in the zebrafish larva which were silenced by 4 dpf suggesting a role for calcium signaling in podocyte maturation. To determine the source of calcium, larvae were treated with calcium inhibitors and we observed that calcium transients were blocked by cyclopiazonic acid, thapsigargin and 2APB but not by cilnidipine or nifedipine, indicating calcium release from intracellular stores. *plce1* knockdown resulted in podocyte defects, disorganized capillaries, and loss of podocin expression suggesting a requirement for calcium signaling in podocyte differentiation. Using an unbiased whole glomeruli RNAseq transcriptome approach we identified multiple candidate signaling receptors potentially responsible for developmental podocyte calcium signaling.

Conclusions: These studies will help to identify new targets for intervention in glomerular diseases and establish zebrafish as a model for glomerular diseases caused by impaired calcium signaling.

Funding: NIDDK Support

SA-PO211

Loss of DUSP4 Promotes Insulin Resistance in Podocytes through JNK Activation Benoit Denhez,[3] Marina Rousseau,[3] Farah Lizotte,[3] Mannix Auger-Messier,[4] Anne-Marie Cote,[1] Pedro M. Geraldes.[2] *[1]CHUS - Hopital Fleurimont, Sherbrooke, QC, Canada; [2]University of Sherbooke, Sherbrooke, AB, Canada; [3]University of Sherbrooke, Sherbrooke, QC, Canada; [4]Université de Sherbrooke, Sherbrooke, QC, Canada*.

Background: Diabetic nephropathy is characterized by early damages to podocytes which lead to their dysfunction and loss. Insulin action in podocytes has been shown to be essential for their integrity. Multiple evidences suggested that the activation of JNK can lead to insulin resistance in various cell types. Data from our laboratory showed that the expression of DUSP4, a protein known to inhibit JNK, is reduced in the renal cortex of type 1 diabetic mice and cultured podocytes exposed to high glucose levels. Deletion of DUSP4 in diabetic mice resulted in significant increase of albuminuria, podocyte apoptosis and activation of JNK. The objective is to evaluate the effect of JNK activation induced by the loss of DUSP4 expression on insulin signaling pathway in cultured podocytes exposed to high glucose and diabetic mice.

Methods: Non-diabetic (NDM) and diabetic (DM) mice with the deletion of DUSP4 (D4KO) were stimulated with insulin to evaluate its downstream signaling pathway on the activation of IRS1 and Akt in the renal cortex. Mouse podocytes were exposed to normal (NG; 5.6 mM) or high (HG; 25 mM) glucose levels for 72 hours with or without the overexpression of DUSP4 adenoviral vector to evaluate the phosphorylation of JNK and the insulin signaling pathway.

Results: Insulin-stimulated Akt and ERK phosphorylation in the renal cortex of DM mice was decreased compared to NDM mice, and was further reduced in DM D4KO mice. Loss of insulin effects in DM D4KO mice was associated with increased phospho-serine 307 of IRS-1, which is known to inhibit IRS1 activity. In cultured podocytes, HG exposure inhibited insulin-induced activation of Akt, which was associated with a reduction in DUSP4 expression and a 2.8 fold increase in phospho-serine 307 of IRS-1. Overexpression of DUSP4 prevented both the HG-induced increased phosphorylation of JNK and phospho-serine 307 of IRS-1, and restored insulin-stimulated Akt activation in podocytes.

Conclusions: In conlusion, the reduction of DUSP4 expression by hyperglycemia in podocytes contributed to insulin resistance by promoting JNK activation.

Funding: Government Support - Non-U.S.

SA-PO212

The Role of the Atypical Cyclin-Dependent Kinase Cdk5 on Development and Function of Podocytes Nicole C. Mangold,[3] Henning Hagmann,[2] Stuart J. Shankland,[4] Markus M. Rinschen,[1] Thomas Benzing,[3] Paul T. Brinkkoetter.[2] *[1]CECAD, Cologne, Germany; [2]University Hospital Cologne, Cologne, Germany; [3]University of Cologne, Köln, Germany; [4]University of Washington, Seattle, WA.*

Background: The atypical Cyclin-dependent kinase 5 (Cdk5) controls migration, cell adhesion and synaptic plasticity in neurons. In the kidney Cdk5 expression is restricted to the podocytes. In these visceral epithelial cells Cdk5 is activated by three known activators, p35, p25 and Cyclin I and mediates anti-apoptotic function via MEK/ERK and BCL-2. This led to the hypothesis, that Cdk5 is a master regulator of podocyte apoptosis or detachment from the glomerular basement membrane. In the mouse model of nephrotoxic nephritis the conventional knockout of Cyclin I and p35 as well as the conventional double knockout of these alleles were shown to cause increase susceptibility to glomerular damage. Prolonged and mislocalized activity of Cdk5 by increased levels of p25 in neurons leads to neurodegeneration phenotypes and dementia.

Methods:

Results: To evaluate the role of the Cdk5 effector kinase in podocytes, podocyte specific Cdk5 knockout mice were generated by crossing Cdk5 floxed mice to a podocyte-specific Podocin:Cre line. Mice were born according to Mendelian rules and did not develop a phenotype until the age of 72 weeks as documented in urine and serum analyses as well as immunohistochemical stainings. In the nephrotoxic nephritis model Cdk5-deficiency resulted in increased susceptibility to glomerular injury, aggravated proteinuria and glomerular sclerosis and a decreased number of podocytes per glomerulum. In addition, a transgenic podocyte cell line expressing MYC-tagged p25 was generated by lentiviral gene transfer to investigate Cdk5 hyperactivity in podocytes. As compared to control podocytes, p25-transgenic cells showed an enhanced migratory phenotype, survival was not affected. Proteomic using MS/MS analysis revealed enhanced expression of proteins modulating cytoskeletal remodeling.

Conclusions: Whereas Cdk5 deficient mice develop no phenotype at baseline, this study highlights the anti-apoptotic effect of Cdk5 in the model of nephrotoxic nephritis. Whether activity of Cdk5 is protective in disease most likely depends on the balance of specific Cdk5-activators in the cell.

Funding: Government Support - Non-U.S.

SA-PO213

The Essential Role of Cofilin1 in Podocytes under Diabetic Conditions Beina Teng, Irini Schaefer, Hermann G. Haller, Mario Schiffer. *Nephrology, Medical School Hannover, Hannover, Germany*.

Background: Cofilin1 is known as actin filament severing protein and thus a key regulator of actin dynamics. Its deficiency results in the loss of a precisely organized actin

cytoskeletal architecture and can reduce cell migration and motility. In podocytes, Cofilin1 dysregulation leads to loss of secondary foot processes and FP effacement. Cofilin1 is also described as a part of a complex with actin and phosphorylated RNA polymerase (Pol) II, playing a major role in the regulation of gene transcription. In mammalian cells, Cofilin1 is inactivated via phosphorylation and translocated to the nucleus

Methods: To study the role of Cofilin1 in diabetes, sections of Type I diabetic mice induced by STZ, Type II diabetic db/db mice and Type II diabetic patients were evaluated by IF stainings against Cofilin1 and p-Cofilin1. Human and murine podocytes stimulated with glucose or TGF-β were analyzed for Cofilin1, its colocalization with Pol II and the distribution of F-actin. We also analyzed the phosphorylation profile of Cofilin1 at different time points using westernblot. After glucose treatment, migration assays were perfomed to compare the capability of podocytes to migrate into to the scratched wound with or without addition of p-Cofilin1 blocking peptide.

Results: Phosphorylated Cofilin1 is strongly detected in the nucleus of podocytes in diabetic mice and patients. Stimulation of cultured podocytes with glucose or TGF-β induced the translocation of Cofilin1 into the nucleus and led to a dysregulation of actin filaments, and Cofilin1 phosphorylated on Ser3 is mainly localized to the nucleus. Westernblots indicated an increased phosphoylation of Cofilin1 30 minutes after glucose treatment. Comparing the location of p-Cofilin1 with phosphorylated Pol II indicated a redistribution of Pol II away from areas with p-Cofilin1/actin, which most likely impacts transcriptional elongation. Podocytes remained static after glucose treatment in culture, but their migration ability was restored when p-Cofilin blocking peptide was added.

Conclusions: Localization of p-Cofilin1 to the nucleus is a strong indicator of diabetes induced dysfunction of podocytes; impacting the reorganization of the actin cytoskeleton as well as transcription. The phospho-inhibitor of Cofilin1 is a novel potential candidate to prevent p-Cofilin1 mediated progression of podocyte dysfunction and podocyte damage in diabetes.

SA-PO214

Paricalcitol Prevents PAN-Induced Podocyte Morphological Change via Direct Regulation of Nestin Transcription through the Interaction of VDR/VDRE Yuling Zhang,[1] Xinxin Jiang,[1] Xinyu Dong,[2] Jing Chen.[2] *[1]Huashan Hospital, Shanghai, China; [2]Huashan Hospital affiliated to Fudan University, Shanghai, China.*

Background: Podocyte morphological change is a pathologic feature of a variety of chronic kidney disease. Several lines of evidence suggested a potential protecting role of vitamin D in podocytes, but the underlying mechanism remained unclear. We hypothesized that vitamin D analogue paricalcitol restored podocytes morphology in puromycin aminonucleoside (PAN) induced nephrosis by modulating nestin gene expression

Methods: A rat model of podocyte injury was created by a single intraperitoneal injection of PAN and subjected to either saline or paricalcitol. Proteinuria, podocyte foot process effacement (FPE), expression of nestin and vitamin D receptor (VDR) in glomeruli was evaluated. The influence of PAN or paricalcitol on cultured mouse podoctyes were also observed. VDR expression was silenced by VDR siRNA or plasmids containing VDR shRNA transfection. Chromatin immunoprecipitation (ChIP) and luciferase reporter assays were performed to study the connection between VDR and nestin gene expression.

Results: Paricalcitol significantly alleviated PAN-induced proteinuria and podocyte FPE. This protective effect was accompanied by an increased expression of VDR in the glomeruli. Paricalcitol also inhibited PAN-induced glomeruli nestin overexpression. In vitro study showed that PAN significantly inhibited VDR protein expression and stimulated nestin protein expression which resulted in nestin filament derangement. Paricalcitol treatment abolished the effect. Downregulation of VDR in cultured podocytes also resulted in overexpression and derangement of nestin. ChIP assays revealed a VDR response element (VDRE) in nestin promoter and paricalcitol enhanced the binding of VDR and VDRE. Luciferase reporter assays of the nestin promoter fragment showed paricalcitol effectively repressed nestin reporter gene expression after PAN treatment. However, paricalcitol treatment alone showed no influence on luciferase activity. Mutation of VDRE abolished the effect.

Conclusions: Paricalcitol prevents morphological change of podocytes in PAN nephrosis via direct regulation of nestin trascription through the interaction of VDR/VDRE.

Funding: Government Support - Non-U.S.

SA-PO215

The Melanocortin-1 Receptor Protects Podocytes by Downregulating the Epidermal Growth Factor Receptor Lovisa Bergwall,[2,3] Johannes Elvin,[2,4] Roberto Boi,[2,3] Hanna I. Wallentin,[2,3] Borje Haraldsson,[1] Jenny C. Nystrom,[2,3] Lisa Buvall.[2,3] *[1]Novartis, Gothenburg, Switzerland; [2]University of Gothenburg, Gothenburg, Sweden; [3]Institution of Neuroscience and Physiology, Sahlgrenska Academy, Gothenburg, Sweden; [4]Institution of Medicine, Sahlgrenska Academy, Gothenburg, Sweden.*

Background: The Melanocortin-1 receptor in podocytes has been suggested as the mediator of the renoprotective effects seen in ACTH treatment of nephrotic syndrome. The protective effect has been proposed to be through stabilization of the actin cytoskeleton in podocytes.

Methods: Using phosphoproteomic mass spectrometry, actin regulatory pathways were identified downstream of the MC1R in podocytes over-expressing the MC1R and treated with the MC1R specific agonist BMS. Confirmation of regulated proteins and pathways was done using western blot. Actin dynamics was studied using phalloidin labeling. To evaluate the protective effect of MC1R-induced ERK phosphorylation and EGFR signaling, protamine sulfate was used on cultured podocytes in the presence or absence of the ERK-inhibitor PD98059.

Results: Actin cytoskeleton signaling was the toped ranked regulated pathway in podocytes identified in the phosphoproteomic data following BMS treatment. The activity of MAP-kinases, ERK and the EGFR was found to be significantly regulated. To confirm the proteomics data, western blot analysis was performed. Increased phosphorylation of ERK1/2 following BMS treatment was observed already after 5 minutes. This was followed by an increase in phosphorylation on EGFR T669, a site commonly phosphorylated by ERK and known to inactivate the receptor. Perturbed EGFR signaling was observed in MC1R activated podocytes shown by increased downregulation of the EGFR following EGF treatment in BMS exposed cells. MC1R was shown to protect podocytes from protamine sulfate induced EGFR activation and actin cytoskeleton rearrangement in podocytes. The rescue effect was shown to be attenuated by inhibiting ERK.

Conclusions: In this study, we show that MC1R activation leads to the ERK-dependent phosphorylation of EGFR T669, with ensuing downregulation of the receptor. Activation of the EGFR has previously been shown to be a negative regulator of actin cytoskeleton dynamics in podocytes. These data thereby suggest that the MC1R protective effect on the actin cytoskeleton in podocytes is due to its inhibitory role on EGFR signaling.

Funding: Government Support - Non-U.S.

SA-PO216

Dynamin: A Potential Regulator of Actin-Microtubule Interplay in Podocytes Kamalika Mukherjee,[1] Changkyu Gu,[2] Sanja Sever.[1] *[1]Massachusetts General Hospital, Charlestown, MA; [2]Massachusetts General Hospital, Charlestown, MA.*

Background: Podocytes are a critical component of the glomerular filtration unit. Structural and functional anomalies in podocytes have been implicated in renal diseases such as focal segmental glomerulosclerosis and diabetic nephropathy. Podocyte injury, dysfunction and loss are correlated with aberrations in cytoskeletal organization of these specialized cells. Microtubules and actin are the prevalent cytoskeletal components of major processes and foot processes in podocytes. We therefore sought to decipher the interplay between microtubules and actin in podocytes and identify regulatory proteins that may facilitate this interaction.

Methods: Immunocytochemistry was performed to detect changes in the cytoskeleton. Spin-down- and GTP hydrolysis- assays were used to assess dynamin and microtubule interaction. Microtubule polymerization and depolymerization were studied in an isolated system using fluorescence based assays.

Results: 1. Microtubule-regulating drugs alter actin cytoskeleton in podocytes. 2. Actin active drugs reorganize microtubule network. 3. Dynamin-modulating small molecules alter both microtubules and actin organization in podocytes. 4. Microtubule depolymerization is initiated in the presence of dynamin. 5. Tubulin polymerization is inhibited by dynamin. 6. Dynamin-regulating small molecules, in the presence of dynamin, alter polymerization state of microtubules.

Conclusions: Small molecule mediated alteration of actin cytoskeleton culminates in reorganization of microtubule network and *vice versa*. These observations demonstrate that the two cytoskeletal proteins are involved in constant communication with each other in podocytes. Moreover, altering the oligomerization state of dynamin affects both microtubule- and actin- cytoskeleton, which indicates that dynamin may qualify as one of the regulators of actin-microtubule crosstalk. Dynamin's ability to promote actin polymerization has already been documented. Our current findings show that dynamin oligomerizes on microtubule templates and induces its depolymerization. Additionally, tubulin polymerization into microtubules is inhibited by dynamin. Therefore, dynamin oligomerization affects the polymerization state of both actin and microtubules. Taken together, we provide evidence that dynamin may regulate the interplay between microtubules and actin in podocytes.

Funding: NIDDK Support

SA-PO217

Podocyte Expressed miR-146a Protects against Diabetic Glomerulopathy via Suppression of ErbB4 and Notch-1 Terese D. Geraghty,[3] Samia Khan,[2] Shehryar J. Khaliqdina,[4] Ha Won Lee,[4] Mehmet M. Altintas,[3] Pierre-Louis Tharaux,[1] Tobias B. Huber,[5] Markus Bitzer,[6] Jochen Reiser,[4] Vineet Gupta.[4] *[1]INSERM, Paris, France; [2]None, Chicago, IL; [3]Rush University, Chicago, IL; [4]Rush University Medical Center, Chicago, IL; [5]University Medical Center Hamburg, Hamburg, Germany; [6]University of Michigan, Ann Arbor, MI.*

Background: Diabetic glomerulopathy is a major complication of Diabetes Mellitus (DM) and is the leading cause of end stage renal disease (ESRD). MicroRNA-146a (miR-146a) is a negative regulator of inflammation and is highly expressed in myeloid cells and in podocytes. We have previously shown that miR-146a levels are significantly reduced in the glomeruli of diabetic nephropathy (DN) patients. To study its role in podocyte function, we have generated mice with selective deletion of miR-146a in podocytes. Here we will present our results from studies in these animals.

Methods: We generated and characterized podocyte-specific miR-146a deficient mice. To investigate the role of miR-146a in glomerular function in vivo, we induced hyperglycemia in C57BL/6 wildtype mice (WT), global miR-146a knockout mice (miR-

146a-/-) and podocyte-specific miR-146a knockout (KO) animals using streptozotocin (STZ).

Results: We further confirmed that podocytic miR-146a expression decreased in the glomeruli of type 2 diabetes (T2D) patients and correlated with increased albuminuria and glomerular damage. Mice lacking miR-146a globally or selectively in podocytes showed accelerated development of glomerulopathy upon STZ-induced hyperglycemia. miR-146a targets, Notch-1 and ErbB4, were significantly upregulated in the diseased glomeruli and TGFβ signaling was induced. Treatment of podocytes in vitro with TGFβ resulted in increased levels of Notch-1 and ErbB4, increased ErbB4 phosphorylation, and increased expression of inflammatory chemokine MCP-1, which suppresses miR-146a via an autocrine loop. Similarly, administration of low-dose LPS to podocyte-specific miR-146a KO mice resulted in increased albuminuria as compared to the WT mice, further suggesting that podocyte-expressed miR-146a protects from glomerular damage.

Conclusions: We suggest a novel role for miR-146a in protecting against glomerular injury via protecting podocytes from injury and cell death. This indicates that miR-146a might have a therapeutic potential in DN.

Funding: NIDDK Support

SA-PO218

Cell Adhesion Function of β-Catenin in Podocytes Is Crucial for Glomerular Filtration Barrier Michelle Duong,[1] Beina Teng,[3] Hermann G. Haller,[2] Mario Schiffer.[2] *[1]Hanover Medical School, Hannover, Germany; [2]Hannover Medical School, Hannover, Germany; [3]Medical School Hannover, Hannover, Germany.*

Background: β-Catenin has two functions: it mediates cell adhesion and Wnt signaling. Its function depends on its subcellular localization, as membranous β-catenin locates at cell adhesion complexes with cadherin and α-Catenin. On the other hand, β-catenin transcriptional activity is regulated by a nuclear β-catenin localization. We have shown β-catenin interacts with PKCε and PKCε deficiency leads to a nuclear localization of β-catenin. PKCε -/- podocytes show a increased cell detachment, apoptosis and reduced differentiation. P-cadherin and IQGAP1 are proteins involved in membranous β-catenin stability. We therefore investigated the relationship of this complex in podocytes.

Methods: We performed time course Western blot of cell lysates of murine PKCε -/- podocytes and tested the IQGAP and P-cadherin expression. We used adenoviral PKCε and β-catenin constructs to overexpress these proteins in PKCε deficient podocytes. Immunofluorescent staining was performed on murine kidney sections and podocytes to examine the P-cadherin and vinculin expression. Zebrafish larvae were injected with β-catenin1 morpholino and localization mutant β-catenin RNAs to investigate their function *in vivo*.

Results: During the differentiation of PKCε -/- podocytes, IQGAP1 and p-cadherin expression was reduced compared to WT cells. Overexpression of not only PKCε, but also ß-catenin, could reverse this effect and led to an normal IQGAP1 expression. We saw in immunofluorescence and western blot analysis a downregulated vinculin expression in PKCε -/- podocytes, which could be reversed by β-catenin overexpression. β-Catenin1 knockdown in zebrafish led to with proteinuria and edema. This could be partially rescued with overexpression of a β-catenin mutant expressed in the membrane, while a β-catenin mutant expressed in the nucleus could not reverse proteinuria.

Conclusions: We show β-catenin as a upstream mediator of cell-adhesion by its regulation of the adherens junction proteins P-cadherin, IQGAP1 and focal adhesion molecules such as vinculin. This complex is disturbed in functionally disabled podocytes. ß-catenin is translocated to the nucleus in unhealthy podocytes and the cell-adhesion function of β-catenin plays a more important role in the maintenance of the glomerular filtration barrier in zebrafish. The Wnt signaling function of β-catenin alone seems not to promote kidney health.

SA-PO219

Podocytes from 129S1 Mouse Glomerular Outgrowths Can Be Used for Functional Studies Hong Wang,[3] Kathleen A. Lincoln,[4] Christina S. Bartlett,[1] Jay Kuo,[2] Steven S. Pullen.[3] *[1]Boehringer Ingelheim, Ridgefield, CT; [2]Boehringer Ingelheim Pharmaceutical, Inc., Ridgefield, CT; [3]Boehringer Ingelheim Pharmaceuticals, Ridgefield, CT; [4]Boehringer-Ingelheim Pharmaceuticals, Ridgefield, CT.*

Background: Podocytes are specialized, terminally differentiated epithelial cells which are essential for integrity of the glomerular filtration barrier. Efforts to develop podocyte-directed therapies have been hampered by lack of *in vitro* systems for studying podocyte functions. Immortalized podocyte cell lines fail to represent native gene expression profiles, while the anatomic location of podocytes makes it difficult to study cell behaviors *ex vivo*. The 129S mouse strain is susceptible to and commonly used for models of renal disease, while currently primary mouse podocyte culture has been limited to use of the resistant C57BL/J strain. Therefore, we sought to isolate and characterize podocytes from glomerular outgrowths from 129S1 mice, a strain for which podocyte glomerular outgrowths have not been evaluated.

Methods: Glomeruli were isolated from 129S1/Svlm mice using Dynabead perfusion and magnetic isolation. We modified our protocol to include a brief collagenase incubation and MACS cell dissociation step to reduce handling time and increase viability. Purified glomeruli were resuspended in culture media and seeded on collagen IV coated plates. Intact glomeruli were removed after 4 days in culture. After 6 days, cells were treated with puromycin aminonucleoside (PAN) for 24 hours. Podocyte markers were measured using Taqman gene expression, and F-actin was visualized using fluorescent phalloidin.

Results: Expression of podocyte specific markers (nephrin, podocin, podocalyxin, synaptopodin, WT1, Glepp-1) was observed at 6 days of culture from 129S1 glomerular outgrowths. Nephrin gene expression was lost by 10 days of culture, although expression of other podocyte markers persisted. PAN treatment dose dependently up-regulated apoptotic genes, Caspase-3 and BAD, while podocyte markers and integrin gene expression were significantly reduced. Phallodin staining showed highly organized actin fibers present within the cytoplasm of cultured cells and was reduced by PAN treatment.

Conclusions: We successfully cultured primary mouse podocytes from the 129S1 mouse strain, modified the standard protocol to reduce glomerular isolation time, and identified the useful window of utility. This method will be valuable for rapid evaluation of genetic mouse models of podocytopathy and development of assays for podocyte functional assessment.

SA-PO220

Yap Dependent Mechanotransduction Determines the Podocyte's Response to Injury Markus M. Rinschen,[1] Tobias B. Huber,[2] Thomas Benzing,[1] Bernhard Schermer.[1] *[1]University Hospital Cologne, Cologne, Germany; [2]University Medical Center Hamburg, Hamburg, Germany.*

Background: Podocytes, terminally differentiated cells of the kidney filtration barrier, are subjected to considerable mechanical strain by physiological filtration pressure, which can even be increased by severe hypertension. When injury causes cytoskeletal reorganization and morphological alterations of these cells, the filtration barrier may become compromised and allow proteins to leak into the urine (proteinuria). The activities of the transcriptional co-activators YAP and TAZ are tightly controlled by the Hippo signaling pathway and are sensitive to mechanical cues.

Methods: We used time-resolved quantitative proteomics in the in vivo and in vitro PAN model of podocyte injury.

Results: We show that podocyte injury stimulates YAP activity and the expression of YAP-dependent target genes in a rat model of glomerular disease prior to the development of proteinuria. In contrast, injury of cultured human and mouse podocyte cell lines reduced YAP and TAZ activity when the cells were grown on stiff substrates. However, culturing these cells on soft matrix or inhibiting stress fiber formation recapitulated the damage-induced YAP upregulation observed in vivo, indicating a mechanotransduction-dependent mechanism of YAP activation in podocytes. YAP overexpression in cultured podocytes enhanced the abundance of extracellular matrix–related proteins. YAP activity was increased in mouse models of diabetic nephropathy, and expression of the YAP target *CTGF* was observed in renal biopsies from patients with glomerular disease. Whereas overexpression of human YAP in mice induced mild proteinuria, pharmacological inhibition of the interaction between YAP and its partner TEAD in rats ameliorated glomerular disease and reduced damage-induced mechanosignaling in glomeruli.

Conclusions: We conclude that perturbation of the mechanosensitive Hippo signaling pathway is a potential therapeutic target for treating some glomerular diseases.

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SA-PO221

Loss of OMA1 Activates the mTOR Pathway but Fails to Rescue PHB2 Deficient Podocytes Independent of Stress-Induced OPA1 Processing Paul T. Brinkkoetter,[1] Alexander Kuczkowski,[1] Kristina Schoenfelder,[2] Bernhard Schermer,[1] Thomas Benzing.[3] *[1]University Hospital Cologne, Cologne, Germany; [2]University Hospital of Cologne, Cologne, Germany; [3]University of Cologne, Köln, Germany.*

Background: The dynamin-like GTPase OPA1 is conceived as a central regulatory hub that controls mitochondrial dynamics, fusion and fission respectively, under stress and in states of disease. Stress-induced OPA1 processing by the metalloendopeptidase OMA1 triggers mitochondrial fission as seen in podocyte-specific knock-out mice lacking prohibitin membrane scaffolds as a model of impaired mitochondrial function.

Methods:

Results: As reported previously, loss of prohibitins resulted in increased insulin and mTOR signaling and, subsequently, renal failure and premature death after 4-5 weeks after birth. Here, we studied the interplay between the peptidase OMA1 and prohibitins and their effect on mitochondrial function and the activation of the mTOR signaling cascade in glomerular podocytes. In contrast to neurons, genetic depletion of OMA1 failed to rescue renal function in PHB2 deficient podocytes and did not prolong animal survival despite stabilizing mitochondrial morphology. OMA1 single knock-out animals showed increased mTOR signaling activity at baseline without compromising renal function or animal survival. This activating effect on mTOR was additive to the PHB2 effect as OMA1/PHB2 double knock-out animals showed even stronger levels of mTOR activation.

Conclusions: Taken together, impairment of mitochondrial dynamics results in activation of mTOR, which is not sufficient to cause podocyte disease at baseline. Additional insults, such as increased cellular stress or a destabilized slit-diaphragm as shown for PHB2 are required to induce podocyte disease. These findings not only emphasize the central role of mitochondria to control insulin and mTOR signaling in podocytes but also provide additional evidence for an additional function of prohibitins in podocytes beyond their established role as protein scaffolds at the inner mitochondrial membrane to control mitochondrial fusion and fission.

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SA-PO222

Dlg1 Is a Novel Regulator of Slit Diaphragm Formation in the Drosophila Nephrocyte John S. Poulton. *University of North Carolina at Chapel Hill, Chapel Hill, NC.*

Background: Proper glomerular filtration requires the formation and maintenance of slit diaphragms (SDs) between podocyte foot processes. Mutations affecting SD formation/function result in nephrotic syndrome. SD formation is coupled to podocyte maturation, which involves changes in cell polarity. Previous work in mammals has revealed that apical polarity proteins play important roles in SD formation, however the basolateral polarity complex appears dispensable.

Methods: To further explore the role of polarity proteins in SD formation, I took advantage of the Drosophila nephrocyte, which form SDs analogous to vertebrate podocytes. The facile genetics of Drosophila allowed efficient screening of multiple RNAi lines targeting components of the basolateral polarity complex.

Results: Consistent with previous findings in mouse podocytes, I found no obvious role for the basolateral protein Scrib in SD formation. In addition, knockdown of Lgl, another key component of the basolateral complex also produced no defects in SD formation. Surprisingly, loss of Discs Large1 (Dlg1) led to dramatic mislocalization of core SD components, including the fly homologues of Nephrin, Neph1, and ZO-1. Transmission electron microscopy of Dlg1 knockdown nephrocytes revealed significant reduction in the number of SDs, though some small patches of nephrocyte surface did retain SDs. Intriguingly, numerous ectopic SDs were observed internal to the cell surface, lining the labyrinthine channels—a phenotype not observed in wildtype nephrocytes.

Conclusions: These data identify Dlg1 as a novel and vital regulator of SD formation and localization. Dlg1 is a highly conserved PDZ protein best known for its role as a scaffold in the basolateral polarity complex, where it helps define apicobasal polarity in polarized epithelia. However, our findings indicate that Dlg's function in SD formation is independent of its role in cell polarity. I am currently working to determine Dlg's mechanism of action in this new context and also test Dlg's potential role in SD formation in vertebrate podocytes.

SA-PO223

Novel Genetic Modeling of Podocyte Diseases and Early Mesodermal Development Bridgette Drummond, Rebecca A. Wingert. *University of Notre Dame, Notre Dame, IN.*

Background: Specialized renal epithelial cells known as podocytes create an essential filter that when comprimised is causitive of numerous kidney diseases. Podocyte morphology and genetic regulatory systems are conserved in zebrafish, making them a simplified and accessible model to study podocyte development and disease states.

Methods: To systematically elucidate the network of podocyte development genes, we have developed a haploid ethylnitrosurea (ENU) screen to identify novel podocyte regulators.

Results: In the emerging panel of these new congenital models of podocyte genesis, we have isolated classes of defects including podocyte abrogation, reduction of podocyte number suggesting alterations in proliferation or survival of the lineage, and delayed differentiation. Of these, one mutant that has been identified has a complete loss or significant reduction of several established podocyte markers. In conjunction with this, the pronephros is proximally abrogated and has a dramatic decrease in several solute-transporter cells that distinguish both proximal and distal tubule segments. Interestingly, several known renal progenitors that demarcate the intermediate mesoderm also reduced in these mutants.

Conclusions: Elucidation of the genetic lesions in these mutants will provide valuable insights into the molecular components that are involved in podocyte development, and possibly provide models for congenital defects and other kidney diseases.

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SA-PO224

TRPC5 Overexpression and Activation Do Not Per Se Cause Nor Augment Kidney Disease Xuexiang Wang, Ranadheer Dande, Hao Yu, Mehmet M. Altintas, Jochen Reiser. *Rush University Medical Center, Chicago, IL.*

Background: The transient receptor potential canonical cation channel, subfamily C, member 5 (TRPC5) is broadly expressed in brain and kidney with the capability to mediate the calcium (Ca^{2+}) influx as well as cell migration. It was reported that TRPC5 is vital for Ca^{2+} homeostasis in podocytes due to its location in podocyte foot processes. It is believed to regulate podocyte cytoskeletal remodeling through its association with active Rac1 GTPase. Genetic knockout or pharmacological inhibition of TRPC5 protects mice from albuminuria. However, the gain in function role of TRPC5 *in vivo* has not been explored.

Methods: Two novel transgenic mouse models (C57BL/6, B/6) were developed by overexpressing either wild-type TRPC5 (TG) or the dominant negative TRPC5 (DN, pore mutant), respectively. Highly expressed TRPC5 was validated by mRNA expression, Western blot and glomerular immunofluorescence (IF). The natural progression of proteinuria was quantified over time and histology was examined by the end at 8 months old mice. LPS-induced albuminuria was measured at 24 and 48 hours after two experiments with separate injection regimens and TEM of podocytes was analyzed. Treatment with TRPC5 agonist Englerin A and antagonist ML204 were performed and proteinuria was compared.

Results: TRPC5 mRNA and protein level were significantly higher in TG and DN compared with B/6. Glomerular IF exhibited stronger TRPC5 staining in two transgenic mice than B/6 mice. Neither TG nor DN developed increased proteinuria at 8 months old. Histology analysis showed no noticeable abnormalities at this age. Both single high dose LPS challenge and two lower doses LPS challenge demonstrated substantially augmented proteinuria. However, no difference in proteinuria was found among TG, DN and B/6. TEM analysis revealed a similar level of foot process effacement among three groups of animals. TRPC5 activator Englerin A injection induced no change in proteinuria. TRPC5 inhibitor ML204 treatment did not rescue kidney filtration barrier injury from LPS challenge.

Conclusions: Overexpression of TRPC5 does not cause kidney injury over time per se or more podocyte damage to LPS challenge. Neither agonizing nor antagonizing TRPC5 by drug affects the podocytes function and proteinuria level. TRPC5 appears not as a mediator of glomerular kidney disease. Its role in other renal diseases requires further study.

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SA-PO225

Ephrin-B1 Bound to Nephrin at the Slit Diaphragm Controls Podocyte Function through the JNK Pathway Independently with Nephrin Phosphorylation Yoshiyasu Fukusumi, Ying Zhang, Hiroshi Kawachi. *Dept. Cell Biology, Kidney Research Center, Niigata University, Niigata, Japan.*

Background: We have reported ephrin-B1 is a novel component of the slit diaphragm (SD), and interacts with nephrin via their extracellular domains in cis form. We also reported that the podocyte-specific ephrin-B1 conditional knockout (CKO) mice showed proteinuria and disarrangement of the SD molecules. However, the precise function of the ephrin-B1 and nephrin at the SD is not well elucidated yet.

Methods: The mechanisms of the phosphorylations of ephrin-B1 and nephrin, and their downstreams were analyzed with HEK293 cell system, the rat nephrotic model and the ephrin-B1 CKO mice. The role of the nephrin-binding ephrin-B1 in regulating cell function was analyzed.

Results: Analyses with the HEK cells showed that not only nephrin but also the nephrin-binding ephrin-B1 was phosphorylated by the anti-nephrin antibody stimulation, and that the phosphorylation was Src kinase dependent. By contrast, the nephrin bound to ephrin-B1 was not phosphorylated by the stimulation to ephrin-B1. The ephrin-B1 co-transfected with the truncated nephrin lacking phosphorylation sites was phosphorylated more evidently, indicating the nephrin phosphorylation lowered the phosphorylation of the nephrin-binding ephrin-B1. Although the phosphorylation of nephrin was enhanced by the co-expression with ephrin-B1, the co-expression of the ephrin-B1 lacking tyrosine residues did not enhance, indicating the phosphorylation of ephrin-B1 is necessary for the enhancement of nephrin phosphorylation. Ephrin-B1 phosphorylation was also detected in glomeruli of the nephrotic model caused by anti-nephrin antibody. The phosphorylated ephrin-B1 phosphorylated JNK evidently. By contrast, nephrin signaling did not phosphorylate JNK. JNK phosphorylation was not detected in glomeruli of the ephrin-B1 CKO mice. The wound-healing assay with the HEK cells showed that the phosphorylation of ephrin-B1 promoted the cell motility, while nephrin did not promote it.

Conclusions: The phosphorylations of nephrin and the nephrin-binding ephrin-B1 were causally regulated, and the phosphorylation of the ephrin-B1 transferred the signals to downstream via another route of the nephrin signaling. Ephrin-B1 controls podocyte function through JNK pathway. The ephrin-B1 resided together with nephrin at the SD plays an essential role in maintaining the podocyte function.

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SA-PO226

Nephrin Is Necessary for Podocyte Recovery Following Injury in an Adult Mature Glomerulus Rakesh Verma, Madhusudan M. Venkatareddy, Theodore Z. Li, Sanjeevkumar R. Patel, Puneet Garg. *University of Michigan, Ann Arbor, MI.*

Background: Nephrin (*Nphs1*) is an adhesion protein and is expressed at the podocyte intercellular junction in the glomerulus. *Nphs1* mutations in humans or deletion in animal genetic models results in a developmental failure of foot process formation. Though nephrin is essential for foot process (FP) development, its role following development is not well defined. In order to understand the role of nephrin following developent we initially generated a nephrin flox mouse. Using this mouse we were able to delete nephrin in an inducible manner using tamoxifen (*Nphs1*$^{Tam\text{-}Cre}$).

Methods: Mice with podocyte specific deletion of nephrin were generated by breeding *Nphs1*$^{fl/fl}$ mice with *NPHS2*-Cre and tamoxifen-inducible (*NPHS2-Cre)* mice. We used biochemical and cell biology techniques to assess nephrin expression in the glomeurlus. Protamine sulfate (PS) and nephrotoxic serum (NTS) were used to study the role of nephrin following injury and in recovery.

Results: Deletion of nephrin using *Nphs2-Cre* resulted in FP spreading and proteinuria by 10-12 d following birth. Nephrin expression decreased by 85% at 10 days post-induction with tamoxifen. The *Nphs1*$^{Tam\text{-}Cre}$ mice had normal FP ultrastructure and intact filtration barrier upto 4-6 weeks post-induction. Interestingly, nephrin expression persisted at the slit diaphragm upto 16-20 wks post-tamoxifen. *Nphs1*$^{Tam\text{-}Cre}$ mice developed proteinuria 8 wks following induction along with FP structural changes. Nphs1$^{Tam\text{-}Cre}$ mice 2 wks post induction subjected to PS model of podocyte injury, demonstrated failure of recovery following heparin sulfate. Similarly, Nphs1$^{Tam\text{-}Cre}$ mice failed to recover following NTS with persistence of proteinuria and FP effacement.

Conclusions: As in development nephrin is necessary for maintenance of a healthy glomerular filter. Interestingly, nephrin expression persists for several months following

deletion. The small fraction of nephrin that remains is relatively stable and is sufficient to maintain the junction for 4-6 wks. It is likely that some nephrin is either recycled continously at the membrane or is stably linked to actin. Following injury, recovery requires larger amount of nephrin as evident by failure of recovery following PS and NTS injury. This would suggest that induction or maintanence of nephrin expression would be benefical to prevent proteinuric kidney diseases.

Funding: NIDDK Support

SA-PO227

Novel Methods to Analyze Mechanisms of TRPC6 Activation

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Background: TRPC6 is a calcium channel activated by diacylglycerol (DAG) and reactive oxygen species (ROS). TRPC6 mutations are associated with proteinuria in human focal segmental glomerulosclerosis. New data suggest that circulating factors in diabetes induce kidney injury via TRPC6-mediated calcium flux. It is unknown how different factors activate TRPC6. The goal of this study was to develop a platform for analysis of DAG and ROS in TRPC6 activation.

Methods: Full length human TRPC6 cDNA was cloned into pcDNA5/TO (Thermo Fischer) under CMV promoter and transfected into HEK293 cells. Stable clones were selected based on the TRPC6 expression. Calcium signaling was analyzed using FLIPR membrane potential assay. DAG synthesis was monitored using recombinant circularly permutated probe, Downward DAG (Montana Molecular). Cells were infected with baculovirus carrying the biosensor construct. Fluorescent signal was captured using FLIPR. For ROS detection, cells were stained with Cell-ROX dye and analyzed using confocal microscope.

Results: The stable cell line, C11, showed >7000x increase in hTRPC6 gene expression. Calcium signaling was stimulated in a dose-dependent manner by angiotensin II (AngII), 1-oleoyl-2-acetyl-sn-glycerol (OAG), endothelin 1 and hyperforin 9 (Hyp9), specific activator of TRPC6. DAG signal was increased by Hyp9 and endothelin 1, but not by AngII. However, AngII but neither Hyp9 nor endothelin 1 induced ROS formation.

Conclusions: We generated novel tools to investigate mechanisms of TRPC6 activation and demonstrated differential involvement of DAG and ROS in TRPC-induced calcium flux.

SA-PO228

The Role of APOL1 and Cholesterol Dependent Podocyte Injury in Focal Segmental Glomerulosclerosis

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Background: Focal segmental glomerulosclerosis (FSGS) is the most common primary glomerular disorder causing chronic kidney disease (CKD). Susceptibility to FSGS in African Americans is associated with the presence of genetic variants of the Apolipoprotein L 1 gene (APOL1) named G1 and G2. APOL1 is an integral component of high-density lipoprotein (HDL) particles suggesting it might be involved in cholesterol efflux from cells. We recently established that the pathogenesis of FSGS is linked to tumor necrosis factor (TNF)-mediated, ATP-binding cassette transporters A1 (ABCA1) dependent impairment of cholesterol efflux from podocytes, which are key cells of the glomerular filtration barrier preventing the development of proteinuria in kidney disease. In addition to ABCA1, ABCG1 was shown in other cells to play an important role in cholesterol efflux from cells.

Methods: HeLa cells were stably transfected with lentivirus carrying the APOL1 risk variants under the CMV promoter. Immortalized human urine derived epithelial cells (HUPECs) were established from patients with FSGS carrying different APOL1 genetic variants.

Results: Here we tested the hypothesis that APOL1 confers susceptibility to proteinuric kidney disease by modulating cholesterol efflux from podocytes. We show that APOL1 risk variant expression in HeLa cells leads to decreased cholesterol efflux. The expression of APOL1 risk alleles in HUPECs was not associated with significantly decreased cholesterol efflux from podocytes. However, we observed decreased ABCG1 and APOL1 expression ($p<0.01$) in the absence of ABCA1 repression. TNF and Interferon (IFN) treatment increased the expression of APOL1 ($p<0.001$) in urinary podocytes.

Conclusions: Our data reveal that APOL1 risk variant expression may play a role in modulating cholesterol efflux from podocytes, which may contribute to APOL1 mediated genetic susceptibility to FSGS.

Funding: NIDDK Support

SA-PO229

Vangl2 Is Associated with Ephrin-B1, a Novel Critical Component of the Slit Diaphragm, and Its Downregulation Is Involved in the Initiation Event of the Podocyte Injury

Yoshiyasu Fukusumi, Ying Zhang, Hiroshi Kawachi. *Dept. Cell Biology, Kidney Research Center, Niigata University, Niigata, Japan.*

Background: Podocyte-specific ephrin-B1 conditional knockout (CKO) mice showed proteinuria and disarrangement of the slit diaphragm (SD) molecules. However, the interaction of ephrin-B1 with other podocyte molecules is not well analyzed. To identify the molecules related with ephrin-B1, the gene expression profile in glomeruli of the CKO mice was analyzed by RNA-seq. The profile showed 260 molecules were downregulated to less than 50% in glomeruli of the CKO mice. We found a planar cell polarity protein vangl2 was evidently downregulated. It is reported that vangl2 plays an important role in podocyte maturation. However, the interaction of vangl2 with ephrin-B1 and the role of vangl2 in the development of nephrotic syndrome were not investigated.

Methods: The expression of vangl2 and its interaction with ephrin-B1 and other SD molecules were analyzed in glomeruli of the ephrin-B1 CKO mice and three types of rat nephrotic models, the SD specific injury caused by the anti-nephrin antibody (ANA), puromycin aminonucleoside (PAN) nephropathy, a mimic of MCNS, and adriamycin (ADR) nephropathy, a mimic of FSGS.

Results: The decrease of vangl2 mRNA expression in glomeruli of the ephrin-B1 CKO mice was confirmed by the qRT-PCR ($33 \pm 21\%$ to control, $p < 0.01$). The immunostaining of vangl2 was evidently decreased in the CKO mice. In ANA nephropathy, mRNA expression of vangl2 was already decreased at 1 h (1h, 27%, $p < 0.05$; day 1, 13%, $p < 0.01$; day 5, 34%, $p < 0.05$). The intensity of the vangl2 staining clearly decreased at 1 h when the nephrin staining was not decreased yet. The staining of vangl2 decreased also in PAN nephropathy, although the mRNA expression was not altered. In ADR nephropathy, the intensity of the vangl2 staining was clearly decreased on day 7 and 28. By contrast, the mRNA expression of vangl2 was upregulated.

Conclusions: Vangl2 was clearly downregulated in the ephrin-B1 CKO mice. The decrease of the vangl2 staining in the nephrotic models advances the decrease of the expressions of ephrin-B1, nephrin and other SD molecules. It is plausible that the alteration of vangl2 expression is involved in the initiation event of the nephrotic syndrome. Vangl2 could be an early marker to detect podocyte injury.

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SA-PO230

Studying the Role of Tcf21 In Vitro and In Vivo

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Background: Dedifferentiation and loss of podocytes are the major causes of chronic kidney disease. The basic helix-loop-helix (bHLH) transcription factor Tcf21 plays an important role for the differentiation of podocytes and is strongly expressed in mature podocytes *in vivo*. Tcf21 -/- mice die in the perinatal period due to the failure in the development of the lung and the kidney glomeruli.

Methods: Since parietal epithelial cells (PECs) are still under debate to be a type of progenitor cell for podocytes, we performed comparative gene expression analysis between freshly isolated podocytes, cultured primary PECs and cultured primary podocytes of mice. Furthermore, we performed ChIP-Seq analysis to identify new putative interaction partners and target genes of Tcf21.

Results: We identified 644 differentially regulated genes in freshly isolated podocytes in comparison to PECs and podocytes in culture. Tcf21 was identified as one of the most upregulated genes in freshly isolated podocytes (24- and 15-fold, respectively) as compared to PECs and podocytes, respectively, in culture. Interestingly, the expression of Tcf21 in PECs induced **m**ultilobulation and **b**udding of the nuclei, and the formation of **mi**cronuclei (MBM). Furthermore, we found an increased number of tetraploid cells. The multilobulation of nuclei was reversible after the addition of nocodazole and taxol indicating an involvement of microtubules. By qRT-PCR and Western blot analysis we found that Tcf21 downregulates the transcription factor YY1. Co-expression of YY1 and Tcf21 rescued the formation of MBM. Moreover, we observed that Tcf21 levels regulate the expression of cyclins like cyclin D1 and cyclin D2, suggesting a role of Tcf21 in cell cycle control. Additionally, by ChIP-Seq analysis we identified a genome-wide Tcf21-binding site (CAGCTG), which matched the CANNTG sequence that is the common E-box binding motif used by bHLH factors. Interestingly, many of the Tcf21 targets genes are involved in the regulation of the cell cycle, cell division, microtubule-based processes and chromosome segregation.

Conclusions: Taken together, Tcf21 is a transcription factor that appears to be importantly involved in the cell cycle regulation and function of podocytes.

SA-PO231

Loss of Glomerular Endothelial Surface Layer and Cell Integrity Is Mediated by Increased Ednra and Crosstalk with Podocyte Derived Edn1 Kerstin Ebefors,[3] Robert Wiener,[1] Evren U. Azeloglu,[1] Borje Haraldsson,[3,2] Ilse S. Daehn.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Novartis, Gothenburg, Switzerland; [3]University of Gothenburg, Gothenburg, Sweden.*

Background: Chronic kidney disease is increasing in prevalence worldwide with the majority of cases caused by glomerular diseases, including diabetic and hypertensive nephropathy and glomerulonephritis. There is emerging evidence that the specialized fenestrated glomerular endothelial cells (ECs) maintain the charge selective barrier to proteinuria via the endothelial surface layer (ESL) or glycocalyx. The ESL is a polysaccharide gel that lines the luminal surface composed of glycosaminoglycans (GAGs). We have previously demonstrated that activated podocytes can release endothelin-1 (Edn1) causing stress and dysfunction of ECs via increased Edn receptor A (Ednra) and consequently, podocyte loss in mice. We hypothesize that podocyte-EC crosstalk results in loss of early glomerular endothelial integrity.

Methods: Ultrastructural assessment of glomerular ECs by scanning EM at different time points of Dox induced TGF-β type I receptor signaling specifically in podocytes (PodTbrI mice). We measured ESL thickness by intralipid infusion EM and IsolectinB4 (IB4). Atomic force microscopy (AFM) measured the nanomechanical properties of the ESL in murine glomerular ECs (mGEC), we measured IB4, heparan sulfate (HS) by FACS, Heparanase (Hpse) and Hyaluronidase (Hyal) expression by RT-PCR.

Results: Compared to ECs of control mice showing extensive fenestration, we detected a striking loss of fenestrae and significant cellular blebbing after 4d of Dox in the absence of foot process effacement and significant microalbuminuria. After 4d of Dox, there was a robust reduction of ESL thickness, decreased further over time, and the ESL loss was prevented by Ednra inhibitor BQ-123. We examined whether loss of ESL is mediated by podocyte released Edn1. mGEC were treated with Edn1, or co-incubated with supernatant from Control (CtrlSN) or Dox (DoxSN) treated PodTbrI podocytes. AFM measurements showed a significant reduction in ESL by Edn1 and DoxSN, concomitant with decreased IB4 and HS, and prevented by BQ123. Upregulation of Hpse and Hyal expression denoted increased GAG degradation and remodeling by ECs in response to podocyte Edn1.

Conclusions: We show evidence of early crosstalk between podocytes and glomerular ECs that results in loss of EC integrity preceding podocyte foot process effacement in glomerular disease.

Funding: NIDDK Support, Private Foundation Support

SA-PO232

CLIC5A Protects Renal Glomeruli from Diabetes-Induced Damage Xin Wang, Laiji Li, Barbara J. Ballermann. *University of Alberta, Edmonton, AB, Canada.*

Background: Podocyte injury, including foot process (FP) effacement, is a critical early step in the development of diabetic nephropathy. Activated ezrin, podocalyxin and CLIC5A form a complex at the apical plasma membrane of FPs, coupling podocalyxin to actin. Disruption of this complex leads to FP effacement. We have shown that CLIC5A stimulates ezrin activation through Rac1-dependent $PI(4,5)P_2$ accumulation (*J Cell Sci 127:5164; 2014 & Kidney Int 89:833; 2016*). Here, we studied the role of CLIC5A in FP formation and diabetic nephropathy.

Methods: Conditionally immortalized mouse podocytes were differentiated for 14 days and infected with adenovirus-CLIC5A or vector. Cdc42 and Rac1 activity were determined by GTPase pull-down. Podocyte morphology was assessed by scanning electron microscopy (SEM) and confocal actin immunofluorescence (IF). Diabetes was induced with streptozotocin (50 mg/kg, IP X 5 days) in wild-type (WT) or CLIC5A deficient (KO) mice. Controls were given buffer IP. Histology was evaluated on Masson-Trichrome stained sections (n= 3-6 mice/group).

Results: In differentiated podocytes, CLIC5A raised active GTP-Cdc42 and Rac1 levels, it activated ezrin, and induced FP-like projections, observed by SEM and actin IF. In glomerular lysates of WT diabetic mice, CLIC5A, active ezrin and podocalyxin levels were reduced compared to nondiabetic WT mice. GTP-Cdc42/Rac1 complexes from renal cortex lysates of WT mice contained both, CLIC5A and the $PI(4,5)P_2$ generating enzyme PI4P5Kα (n=6). Notably, PI4P5Kα was absent from GTP-Cdc42/Rac1 pulldowns of KO mice (n=6). Diabetes strongly activated Cdc42 and Rac1 in WT and KO mice (n=3 each), but active ezrin was profoundly reduced in lysates and GTP-Cdc42/Rac1 complexes from KO compared to WT diabetic mice. Albuminuria, segmental glomerular sclerosis and interstitial fibrosis were significantly greater in CLIC5A KO diabetic mice than in WT diabetic mice.

Conclusions: In podocytes, CLIC5A activates Rac1 and Cdc42 and stimulates FP formation. The findings in mice that CLIC5A is necessary for the association of PI4P5Kα with GTP-Rac1/Cdc42, and that ezrin activation is profoundly reduced in diabetic CLIC5A deficient mice despite Rac1/Cdc42 activation, indicate that CLIC5A forms the critical link between the active GTPase(s) and PI4P5Kα which leads to $PI(4,5)P_2$-dependent ezrin activation. Inhibition of this novel mechanism contributes to diabetic nephropathy.

Funding: Private Foundation Support

SA-PO233

A Syndrome of IgA-Related Polycythemia Camille Cohen,[8,15] Séverine Coulon,[14] Kanit Bhukhai,[10] Michaël Dussiot,[9] Antoine Neuraz,[4] Martin Flamant,[1] Francois Vrtovsnik,[12] Aurelie Hummel,[16] Bertrand Knebelmann,[15] Laurent Mesnard,[13] Eric Rondeau,[2] Marc Benhamou,[7] Christophe M. Legendre,[3] Olivier Hermine,[11] Khalil El Karoui,[6] Ivan C. Moura.[5] *[1]APHP, Paris, France; [2]APHP; University Paris 6, PARIS, France; [3]Hôpital Necker, Paris, France; [4]Hopital Necker-Enfants Malades, APHP, Paris, France; [5]IMAGINE INSTITUTE, Paris, France; [6]IMRB, U955 Inserm Universite Paris Est Creteil, UPEC, CRETEIL, France; [7]INSERM, Paris, France; [8]U1151, INSERM, Paris, France; [9]INSERM U 1163 / CNRS ERL 8254, Paris, France; [10]Institut Imagine, Paris, France; [11]NECKER HOSPITAL, PARIS, France; [12]Hopital Bichat, AP-HP, Paris, France; [13]INSERM U702, PARIS, France; [14]Pharmacie, Grand Hôpital de l'Est Francilien, Meaux, France; [15]Nephrology, Hôpital Necker, Paris, France; [16]Nephrology, Necker hospital, Paris, France.*

Background: IgA nephropathy (IgAN) is associated with elevated levels of polymeric IgA (pIgA1) and circulating IgA1 complexes. We previously reported that pIgA1 controls erythropoiesis through activation of transferrin receptor (Coulon et al, Nat Med 2011), but data in patients are still lacking to involve pIgA1 in normal or pathologic erythropoiesis. In patients with IgAN and unexplained polycythemia, we hypothesized that pIgA1 could also be involved in the increased red blood cell production.

Methods: Sera from patients with IgAN and unexplained polycythemia (IgAN-Pcy, persistent hematocrit (Ht) >54%) were collected after written consent. Human progenitor $CD34^+$ cells with addition of IgAN-Pcy or control serum were plated in semi-solid methycellulose medium and quantified, and IgA1 depletion was performed as previously described (Coulon et al, Nat Med 2011). We performed a multivariate linear regression to analyze Hb levels among various groups of a CKD cohort (696 patients with glomerulonephritis but no ESRD, IgAN n=171), and in a post-transplant cohort (2600 patients, IgAN n=271).

Results: We report 6 patients with IgAN-Pcy who developed polycythemia (median Ht55%). No JAK2 mutations were found. All patients had normal blood oxygen level, as well as EPO levels (median 7.6 mUI/L, range 5.8-9.9) and abdominal ultrasound. In contrast, *in vitro* at low dose of Epo, we found that the number of erythroid burst forming unit (BFU-E)-derived colonies was increased in the presence of IgAN-Pcy serum compared to control (73 vs 52, $p<0.05$). Removal of IgA1 from IgAN-Pcy patients normalized the number of colonies while add-back of these IgA1 increased it to initial values. Emphasizing our finding, among glomerulonephritis, Hb level was significantly higher in patients with IgAN by multivariate analysis (13.1g/dL vs 12.2 g/dL, p=0.01). In the post-transplant cohort, the mean elevation of Hb at M3 and M12 compared to M0 was higher in IgAN compared to other patients (Δhb M0-M3 0.87 and 0.22g/dL; ΔM0-M12 1.36 and 0.71g/dL respectively), suggesting that Hb recovery is faster after acute anemia following renal transplantation.

Conclusions: These data suggest a role of pIgA1 in erythropoiesis regulation and describe a new etiology of polycythemia.

SA-PO234

The Loss of Heparin Sulphate Editing Enzyme Sulf1 Reduces VEGF Signaling and Enhances Endothelial Glomerular Injury and Albuminuria Anna K. Masseli,[1] Patricia A. Schroder,[4] Laura L. Beverly-Staggs,[3] Mario Schiffer,[1] Janina Müller-Deile,[2] Heiko J. Schenk,[1] Joon-Keun Park,[1] Hermann G. Haller.[1] *[1]Hannover Medical School, Hannover, Germany; [2]MHH, Hanover, Germany; [3]Mount Desert Island Biological Lab, Salisbury Harbor, ME; [4]Mount Desert Island Biological Laboratory, Salisbury Cove, ME.*

Background: The endothelial cell surface is covered by the heparin sulphate proteoglycans (HSPG). Alterations in the level of 6-*O*-sulfation of the HS chains modulate the binding and release of signaling molecules and affect vascular function. The regulation of the glycocalyx is not well understood. Heparan sulfate 6-*O*-endosulfatases (sulf1 and -2) regulate the binding properties of the glycocalyx. We tested the hypothesis that 6-*O*-sulfation is important for glomerular stability and that changes in 6-*O*-sulfation lead to glomerular damage and albuminuria.

Methods: To assess sulf-1 and -2 function *in vivo* we used a transgenic zebrafish model (Tg(*I-fabp*:eGFP-DBP) and measured edema formation and loss of fluorescent protein from the circulation after knock-down of sulf-1 and -2. We further tested whether loss of sulf enhanced glomerular injury in zebrafish using PAN injury. In addition, mice deficient for Sulf-1 and -2 were analyzed. Urinary albumin was measured by ELISA. Immunohistochemistry was performed on cryostat or on paraffin sections.

Results: Loss of Sulf-1 and -2A/B led to a dose-dependent increase in edema formation and albuminuria in zebrafish. Vascular permeability was enhanced after sulf-2 knock down. Reduction of sulfatases enhanced the PAN-induced albuminuria significantly. Vascular patterning was slightly affected by Sulf-2, indicating a role in vascular development of the isoform. In Sulf-2 deficient mice albuminuria occurred after week 4. The glomerular mesangium showed increased proliferation. Glomerular VEGF165 as well as p38 and pERK immunoreactivity were increased.

Conclusions: The level of 6-*O*-sulfation of HS chains of the glycocalyx is an important determinator of glomerular health and pathophysiology. Our results suggest that Sulf-1 and -2 regulate the signaling properties of VEGF and other growth factors in the renal microcirculation.

Funding: Government Support - Non-U.S.

SA-PO235

Endothelial Epas1 Deficiency Is Sufficient to Promote PEC Activation and FSGS in Experimental Hypertension Olivia Lenoir,[3] Yosu Luque,[4] Veronique Baudrie,[5] Placier Sandrine,[4] Laurent Mesnard,[4] Eric Rondeau,[1] Pierre-Louis Tharaux.[2] *[1]APHP; University Paris 6, PARIS, France; [2]INSERM, Paris, France; [3]U970, INSERM, Paris, France; [4]INSERM U702, PARIS, France; [5]inserm U970, Paris, France.*

Background: Focal segmental glomerulosclerosis (FSGS) is the most common primary glomerular disorder causing end-stage renal disease. It is still a complex, only partially understood disease. Progressive sclerosis represents a hallmark of focal segmental glomerulosclerosis. Genetic tracing studies showed that parietal epithelial cells participate in the formation of sclerotic lesions. The loss of podocytes triggers a focal activation of parietal epithelial cells, which subsequently form cellular adhesions with the capillary tuft. Meanwhile, in the absence of intrinsic podocyte alteration, the origin of the pathogenic signal that could trigger parietal epithelial cells recruitment is elusive. We studied the role of the endothelial PAS domain protein 1, a regulatory α subunit of the Hypoxia Inducible Factor complex, during angiotensin II-induced hypertensive nephropathy. Here, we hypothesized that endothelial EPAS1 could drive protection against Ang II-induced hypertension and glomerular injury leading to CKD.

Methods: To understand the role of endothelial EPAS1 during hypertensive nephropathy, we used a genetic approach to abrogate EPAS1 from endothelial cells in Ang II-induced hypertension in mice.

Results: We found that endothelial EPAS1 protects from glomerular injury induced by chronic hypertension. We also observed that endothelial EPAS1 abrogation aggravates podocyte and parietal epithelial cell (PEC) injury in a blood pressure-independent manner and impairs renal local vasoreactivity to Ang II.

Conclusions: The murine Ang II-induced hypertension developed in this study revealed a protective role of endothelial EPAS1 maintaining glomerular integrity during the hypertensive chronic insult. Interestingly, endothelial *Epas1* gene deficiency promoted podocyte damage and parietal epithelial cells activation and segmental sclerosis, supporting proof of principle that endothelial-derived signal can trigger FSGS. This also suggests that endothelial EPAS1 dysfunction could be a susceptibility factor for hypertension-associated FSGS lesions and CKD progression with endothelial *Epas1* functional variants or interacting pathways being potential key modifiers to understand secondary FSGS-lesions.

Funding: Government Support - Non-U.S.

SA-PO236

Sphingosine 1-Phosphate (S1P) as a Novel Paracrine Mediator of Classic and Regenerative Functions of Macula Densa Cells Ina M. Schiessl, Anne Riquier-brison, Dorinne Desposito, Janos Peti-Peterdi. *University of Southern California, Los Angeles, CA.*

Background: Macula densa (MD) cells play a key role in the regulation of renal hemodynamics. Newly emerging non-classic MD functions include the release of tissue remodeling factors and the recruitment of renal progenitor cells. S1P-signaling contributes to cell migration and proliferation and regulates renal vascular development. Also, in vitro studies demonstrated that S1P-signalling acutely regulates glomerular hemodynamics. Hence, we hypothesized that S1P may be synthesized locally in the MD, and that MD-derived S1P may contribute to classic and regenerative cell functions.

Methods: To investigate if S1P signaling regulates glomerular hemodynamics in vivo, we evaluated the acute effects of the S1P analogue FTY720 [1 mg/kg] on single nephron GFR (snGFR) using intravital multiphoton microscopy (MPM) of C57BL6 mice. Cell proliferation was determined using Ki67 staining of frozen kidney sections from mice treated with L-NAME [500mg/L, per os] for one week with or without daily FTY720 injections [3 mg/kg]. The expression and regulation of known S1P synthesizing or activating enzymes in MD cells was studied using MD gene profiling with the translating ribosome affinity purification (TRAP) technique. To isolate translated mRNA from MD cells, adult nNOS-eGFR-L10a mice were used, which were either treated with low salt/enalapril [100 mg/L] or a normal diet for 2 weeks.

Results: FTY720 administration reduced afferent arteriole diameter by 10 % (n=7, p=.0232) and snGFR by 24% (n=11, p=.0013). In the L-NAME injury model, we found significantly more Ki67+ proliferating cells in FTY720-treated kidneys compared to control (8.3±1.3 vs. 5.1±0.7 cells/area, n=12, p<.05). Screening the MD gene profile for S1P-relevant enzymes revealed the expression of sphingosine kinase 1, ceramide synthases (CS) 1, 2, 4 and 6, and a 2-fold upregulation in response to MD-stimulating treatment for CS 4 and 6 (p<.05) as well as a 2.5-fold reduction of sphingosine-1-phosphate phosphatase 2 mRNA abundance (p<0.01).

Conclusions: Our data show that S1P acutely decreases glomerular blood flow and snGFR in vivo, enhances kidney cell proliferation, and that MD cells express and regulate several S1P synthesizing or activating enzymes. This suggests that MD cell-derived S1P may act as a paracrine regulator of classic and new tissue regenerative MD cell functions.

Funding: NIDDK Support

SA-PO237

Tripartite Motif-Containing 55 (TRIM55) Participates in the Immune Response in Experimental Anti-Thy1 Glomerulonephritis Lei Chen,[2] Hongli Jiang.[1] *[1]Dialysis Center of First Affiliated Hospital of Medicine School, Xi?an Jiaotong University, Xi'an, Shaanxi, China; [2]Dialysis Department of Nephrology Hospital, First Affiliated Hospital of Medicine School, Xi'an Jiaotong University, Xi'an, China.*

Background: Mesangial proliferative glomerulonephritis (MsPGN) is considered as an immune-related disease. Its pathogenesis is involved with activation of mesangial cells and the subsequent immune inflammatory response. However, the mechanism underlying the regulation of immune response remains largely elusive. Tripartite motif family was reported to be closely related to immune regulation. In this study, we performed a series of experiments in vivo and vitro to investigate the role of tripartite motif-containing 55 (TRIM55), a member of tripartite motif family, in the progression of MsPGN.

Methods: 36 male SD rats were randomly divided into 6 groups, 5 of which were received tail vein injection of anti Thy-1 antibody (2.5 mg/kg body weight), and the remaining group was received PBS injection as negative control(NC). Specimens of the NC group were collected at 0d after the injection, while those of other groups were collected at 1d, 2d, 3d, 4d, and 5d, respectively. Immunohistochemical stainig of CD68 was performed to evaluate the level of macrophages infiltration. qPCR analysis of glomerulus was performed to examine the expression of TRIM55. Primary RMCs with overexpression of TRIM55 were obtained through plasmid transfection. In addition, si-RNA tranfection was used to knock down the expression of TRIM55 in primary RMCs. qPCR analysis was conducted to detect the level of cytokines, such as TNF-α, CCL2, CXCL6, CXCL10, and IL-6.

Results: PAS staining results indicated mesangial dissolution occurred since 1d, followed by inflammatory cell infiltration. CD68 immunohistochemical staining results showed that macrophages infiltration peaked at 1d and then decreased gradually. The expression of TRIM55 mRNA also peaked at 1d and decreased gradually, which was consistent with the trend of macrophages infiltration. In primary RMCs, knockdown of DBP led to down-regulation of the expression of cytokines (TNF-α, CCL2, CXCL6, CXCL10 and IL-6). On the other hand, the expression of those cytokines(TNF-α, CCL2, CXCL6, CXCL10 and IL-6) significantly increased in TRIM55-overexpressed primary RMCs.

Conclusions: The above results indicate that TRIM55 participates in the immune response in anti-Thy1 nephritis by regulating the production of cytokines. We duce TRIM55 may be a promising therapeutic intervention to ameliorate leukocyte infiltration in MsPGN.

SA-PO238

Nephronectin Is a Component of Novel Glomerular Adhesions That Regulate Mesangial Adhesion and Behavior Chitkale Hiremath, Denise K. Marciano. *University of Texas Southwestern Medical Center, Dallas, TX.*

Background: Defects in the glomerular basement membrane (GBM) cause heritable glomerular disease and are associated with the majority of acquired glomerular diseases, although their role in pathogenesis of the latter is unclear. The GBM contacts all cells of the glomerular tuft, namely podocytes, endothelia, and mesangial cells, whose function is coordinated to form an integrated filtration unit. Much of the GBM is deposited between podocytes and endothelia, where it is well known to form a critical part of the permeability barrier. However, the GBM also interacts directly with mesangial cells. Currently, little is known of specific GBM-mesangial interactions and their role in glomerular development, maintenance, and disease.

Methods: We utilize several mouse models in this study including conditional deletion of *Npnt*, the gene encoding nephronectin, using the *Six2-cre* line and *Podocin-cre* line.

Results: We find nephronectin, a GBM component and known ligand of α8β1 integrin, is produced by podocytes and deposited into the GBM, where it is required for formation of a novel GBM-mesangial cell adhesion structure. These specialized adhesions occur at sites of mesangial cell protrusion that are highly enriched in α8β1 integrin and appear to anchor capillary loops. Absence of nephronectin disrupts these adhesion structures, leading to mislocalization of α8β1, a pronounced increase in mesangial cell number, and mesangial sclerosis.

Conclusions: These results demonstrate a novel role for nephronectin-α8β1 integrin in a newly described adhesion complex.

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SA-PO239

Impact of Tryptophan Metabolism Alteration by Kynurenine 3-Monooxygenase Inhibition on Renal Cells and Its Role in Diabetic Kidney Disease Patricia Bolanos-Palmieri,[1] Patricia A. Schroder,[2] Heiko J. Schenk,[1] Janina Müller-Deile,[1] Hermann G. Haller,[1] Mario Schiffer.[1] *[1]Hannover Medical School, Hannover, Germany; [2]Mount Desert Island Biological Laboratory, Salisbury Cove, ME.*

Background: The kynurenine pathway (KP) is the major route for tryptophan catabolism, and changes in KP metabolites correlate with renal complications in a diverse range of pathologies. Previous work from our group identified the enzyme kynurenine 3-monooxygenase (KMO) as a factor underlying the onset of proteinuria in diabetes by

contributing to morphological changes in podocyte foot processes. However, in spite of the correlational evidence for kynurenine involvement in the worsening of renal function, the pathological and functional significance of the increase in KP metabolites on renal cells remains unkown.

Methods: To assess if the enzymes of the KP are altered in diabetic kidney disease we performed IF staining of mouse kidney sections after Streptozotocin (STZ) injections, as a model for type I diabetes. Alongside this, cultured murine and human podocytes were analyzed upon inhibition of KMO to define the impact of KP dysregulation. Cell shape, size and substrate adherence were monitored. Finally, since KMO is an integral part of the mitochondrial membrane and the KP plays a role in the production of NAD^+, we assessed mitochondrial function of podocytes after KMO inhibition by measuring bioenergetics parameters in a microplate-based live-cell metabolic assay.

Results: In line with our previous results, STZ-injected mice show reduced KMO expression in the renal cortex. Similarly, the expression of Arylformamidase, that catalyzes the production of kynurenine, is altered in diabetes. This change is more prominent in the glomeruli, where a reduction in the nuclear localization of AFMID was observed. Furthermore, KMO inhibition in cultured podocytes resulted in a substantial reduction in average cell size, and changes in Paxillin staining show alterations in the focal adhesions, which correlate with an increase in cellular detachment. Moreover, the changes in spare respiratory capacity observed after KMO inhibition are consistent with mitochondrial dysfunction which could affect the cells' ability to respond to variations in energy demand.

Conclusions: Taken together, these results highlight the prominent role of the KP in the maintenance of podocyte function as its dysregulation has an impact on cell morphology, substrate adherence and metabolic profile.

Funding: Government Support - Non-U.S.

SA-PO240

Macrophage Activation Syndrome (MAS) and Systemic Lupus Erythematosus (SLE): Early Diagnosis Improves Outcomes – Case Series from a Tertiary Centre Iolanda Godinho, Liliana Cunha, Allyson C. Egan, Tom Cairns, Matthew C. Pickering, Liz Lightstone. *Imperial College Lupus Centre, Hammersmith Hospital, London, United Kingdom.*

Background: MAS is a life-threatening complication of SLE, characterised by fevers, hyperferritinaemia, paenias, high triglycerides, abnormal liver, neurological & renal function. We report our case series & growing experience which led to improved recognition & outcomes

Methods: From clinical records & identifying all those patients in our lupus nephritis biopsy database (1997-2016, 475 patients, 806 biopsies) aged >18yrs with serum ferritin >2000ng/ml not explained by other causes, we report clinical & laboratory features & outcomes of 17 patients with 18 episodes of MAS.

Results: Of the 17 patients, 82% were female, median age 45 yrs (29-62). At time of acute MAS, 59% had new-onset SLE & 41% were flaring. Clinical & biochemical features summarised in table 1(image). Aggressive therapy with a combination of IV cyclophosphamide, plasma exchange, IV & oral steroids, IVIg & anti CD20 mAb was used. Where tolerated, tacrolimus given for 2 wks at presentation. Compared to dismal outcomes in the literature (as low as 34%), majority of patients responded to therapy (83%) though 3 (17.6%) died: 1 refractory to therapy & 2 in whom immunosuppression limited by infections.

Conclusions: This case series likely underestimates incidence: a) only a minority of patients with features of MAS have renal biopsies; b) until recently, few patients with severe SLE had ferritin measured acutely. MAS develops in context of a highly active SLE & should be screened for using serum ferritin, LDH, blood film, amylase & triglycerides to ensure early diagnosis. Our relatively low mortality & very high response rates reflect rapid diagnosis allowing early aggressive therapy aimed at quenching the inflammatory storm & treating the underlying SLE.

TABLE 1. CLINICAL and LABORATORY FEATURES	Number (%) of episodes
Fever	18 (100)
Splenomegaly (n=11)	2 (18)
Hepatomegaly (n=11)	2 (18)
Lymphadenopathy (n=13)	6 (46)
Neurological involvement	14 (78)
Cytopenias	
Hemoglobin < 90 g/L	17 (94.4)
Platelets < 100×10^9/L	17 (94.4)
Neutrophils < 1.0×10^9/L before CYP	1 (0)
Neutrophils < 1.0×10^9/L in total	6 (33.3)
≥2 cytopenias	16 (88.9)
Fibrinogen ≤1.5 g/L	8 (44.4)
Triglycerides ≥2.99mmol/L	13 (72.2)
LDH > 280 U/L	17 (94.4)
Albuminemia < 40 g/L	18 (100)
Sodium <135mmol/L	9 (50)
Liver dysfunction	
ALT > 100 U/L	10 (55.6)
AST > 48 U/L (n=12)	8 (66.7)
CRP > 80 mg/L	9 (50)
Bone marrow biopsy (n=8) with Hemophagocytosis	4 (50)
Schistocytes on blood film	9 (50)
Amylase >90 IU/L	13 (72.2)
AKI (n=17)	
Doubling of serum creatinine	12 (71)
Dialysis	3 (18)
SLE activity	
dsDNA positive, > 500	18 (100) and 8 (44.4)
C3 < 0.7 g/L	17 (94.4)
C4 < 0.16 g/L	16 (88.9)
Proteinuria >1g/day (n=16)	14 (87.5)
Nephrotic proteinuria (n=16)	9 (56.3)
Biopsy showing lupus nephritis at time MAS (n=6)	
Class II	2 (33.3)
Class III +V	1 (16.7)
Class IV or IV + V	3 (50.0)

SA-PO241

Urinary AlphaM Subunit of Integrin Mac-1 Associates With Glomerular Inflammation in Lupus Nephritis Akimitsu Kitagawa, Naotake Tsuboi, Yutaka Kamimura, Takayuki Katsuno, Shoichi Maruyama. *Nagoya University Graduate School of Medicine, Nagoya-shi, Aichi, Japan.*

Background: One of the pathogenesis of glomerulonephritis is glomerular accumulation of leukocytes. Integrin Mac-1 is composed of a unique α (α_m; CD11b) complexed to a common β2 subunit (CD18) on neutrophils and monocytes/macrophages. Mac-1 has been demonstrated to support various immunological functions on glomerular endothelium including leukocyte recruitment and immune-complex clearance. Interestingly, leukocytes have been shown to release Mac-1 from the surface upon cell activation under inflammatory conditions. In the current study, we evaluated the association of urine levels of CD11b (U-CD11b) with histological disease activity in experimental animals with glomerulonephritis and patients with various glomerular diseases, in particular lupus nephritis (LN).

Methods: Antibody-mediated glomerulonephritis was induced by rabbit anti-mouse nephrotoxic serum in male C57BL/6J mice (NTS-GN). Urine and kidney samples from NTS-GN mice and from 272 patients with glomerular diseases including LN between 2008 and 2014 in Nagoya University were subjected to the study. Urinary concentrations of CD11b, hemoglobin scavenger receptor CD163 (U-CD163), and MCP-1 (U-MCP-1) were measured by ELISA. Glomerular $CD11b^+$ cells for neutrophils and monocytes/macrophages were also immunohistologically analyzed. In 118 LN patients, histological disease activity was evaluated semiquantitatively using the biopsy activity index (BAI).

Results: U-CD11b was evident on day 14 and elevated until day 21 in NTS-GN mice. In human patients, U-CD11b levels were significantly increased in ANCA-associated vasculitis and LN group, particularly in the ISN/RPS class IV. In LN, the number of

glomerular CD11b$^+$ cells was correlated with U-CD11b concentration (r=0.547) and BAI (r=0.643). It is of note that corticosteroid treatment significantly reduced U-CD11b excretion associated with the disease amelioration both in experimental animals with NTS-GN and human LN patients. In the ROC curve generated to predict ISN/RPS class III and IV subpopulations, area under the curve of U-CD11b (0.904, sensitivity: 89.7%, specificity:84.7%) was greater than that of U-CD163 and U-MCP-1.

Conclusions: These data collectively suggest that U-CD11b can be a useful biomarker for prediction of histological disease activity in LN.

Funding: Government Support - Non-U.S.

SA-PO242

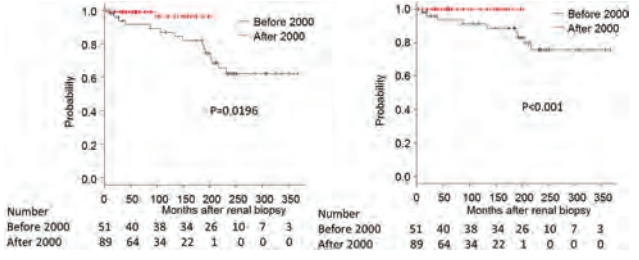
Improvement of Prognosis of Lupus Nephritis in Recent Years: A Single Center Retrospective Study Junya Suwa,[1] Hidekazu Ikeuchi,[1] Masao Nakasatomi,[2] Toru Sakairi,[1] Yoriaki Kaneko,[1] Akito Maeshima,[1] Yoshihisa Nojima,[2] Keiju Hiromura.[1] *[1]Department of Nephrology and Rheumatology, Gunma University Graduate School of Medicine, Maebashi, Japan; [2]Department of Rheumatology and Nephrology, Japan Red Cross Maebashi Hospital, Maebashi, Japan.*

Background: The treatment of SLE has been changing year by year, but it is not clear how the change actually relates to the improvement of the prognosis.

Methods: The treatment of lupus nephritis (LN) has been changing. In the present study, we examined the change of prognosis of LN in our facility.

Results: Median age was 34 years (IQR 28-47), median observation period was 105 months (IQR 47-189). ISN/RPS Class was follows: III(±V), 35 pts; IV(±V) 82 pts; pure V, 23 pts. The prognosis was significantly better in patients after 2000 in both renal events + patient death or renal events alone (P=0.0196 and P<0.001, respectively, Figure). In addition, frequency of proteinuric remission was significantly better in patients after 2000 at both of 6 months and 12 months after treatment (43.1% vs 68.9%, P<0.001; 60.7% vs. 78.7%, P= 0.031; respectively). There was no significant difference in levels of SCr and complements, and frequency of anti-DNA antibodies at baseline. Regarding the treatments, frequencies of steroid pulse therapy and dose of prednisolone were not different between the 2 groups, However, frequencies of immunosuppressants for the first induction therapy were different between before and after 2000: p.o. cyclophosphamide, 45.0% vs 3.3%, P<0.01; tacrolimus, 0.0% vs 11.2%, P=0.014; mycophenolate mofetil + tacrolimus, 0.0% vs 23.5%, P<0.01.

Conclusions: In our facility, the prognosis of active LN has been improved in recent years. The changes of immunosuppressants might contribute to better proteinuric remission rate at 6 and 12 months after induction therapy and lead to better long-term prognosis of LN.



Left: Renal events + Patient death, Right: Renal events

SA-PO243

Acute Tubular Necrosis in Lupus Nephritis Shikha Wadhwani, Joshua Leisring, Anjali A. Satoskar, Samir V. Parikh, Brad H. Rovin. *Ohio State University Wexner Medical Center, Columbus, OH.*

Background: Glomerular pathology drives management of lupus nephritis (LN) although acute tubular necrosis (ATN) is frequently seen on biopsy. The prevalence and significance of ATN in LN is unknown. To address these questions, we queried our native kidney biopsy data base.

Methods: 309 patients who underwent kidney biopsy from 2004 to 2011 were found to have LN. Pathology reports were reviewed for ISN/RPS class, glomerular histology, and tubulointerstitial damage, including presence of ATN. The relationship of ATN to patient demographics, pathology findings, and long-term outcomes were examined using Fischer's exact or Mann-Whitney tests, as appropriate.

Results: ATN was found in 78 (25%) LN patients. Patients with ATN had significantly higher serum Cr (2.18 ± 29 vs 1.55 ± 1.37 mg/dL; p<0.001) and proteinuria (4.66 ± 4.33 vs 3.22 ± 3.05 g/g; p=0.032) at time of biopsy than those without ATN. The presence of ATN was not affected by race or gender. Patients with active crescents (p = 0.006), glomerular capillary necrosis (p=0.035), or interstitial inflammation (p<0.001) were significantly more likely to have ATN than patients without these lesions. The degree of interstitial fibrosis and tubular atrophy was not increased in patients with ATN. Of the patients with at least 3 years of follow-up (mean 7.3 ± 2.2 years in ATN group, 8.4 ± 2.3 years in no ATN group), serum Cr at follow-up was not significantly different in those with ATN (n=20) and those without (n=62).

Conclusions: ATN commonly accompanies severe glomerular injury in LN, and is associated with impaired kidney function and high levels of proteinuria. However patients with ATN do not seem to have more long-term renal damage than patients without ATN.

Funding: Clinical Revenue Support

SA-PO244

Male Pediatric Lupus Nephritis Patients Experience Greater Mortality but Less Progression to ESKD Halei Benefield,[4] Meghan A. Jobson,[4] Anna L. Baldwin,[3] Eve Wu,[1] William F. Pendergraft,[2] Keisha L. Gibson.[2] *[1]The University of North Carolina, Chapel Hill, NC; [2]University of North Carolina Kidney Center, Chapel Hill, NC; [3]University of North Carolina School of Medicine, Chapel Hill, NC; [4]University of North Carolina at Chapel Hill, Chapel Hill, NC.*

Background: Epidemiological data on pediatric lupus nephritis are lacking. Here we present characteristics and outcomes of a racially diverse cohort of pediatric lupus nephritis patients.

Methods: We evaluated disease history and outcomes of patients age ≤ 19 years with tissue read by the UNC Nephropathology department as biopsy-proven lupus nephritis. Primary outcomes were end-stage kidney disease (ESKD) and death. Secondary outcomes included kidney transplant and adverse events per years of follow-up. Univariate logistic regression was used to calculate odds ratios and 95% confidence intervals with race (black or white) and sex coded as dichotomous categorical variables.

Results: Of 87 patients identified, 52 (60%) were female, 54 (62%) were black, 21 (24%) were white, and 12 (14%) were other. The mean follow-up duration was 11.6 years (SD 8.0). At diagnosis, 80% of patients presented with renal involvement, 59% with cutaneous symptoms, and 43% with hematological manifestations. The median age at biopsy was 14.6 years (IQR: 12.4, 17.2). 17 patients (20%) died with a median age at death of 20.8 years (18.9, 24.7). 18 patients (21%) progressed to ESKD with a median time to ESKD from first biopsy of 5.1 years (1.9, 7.4). Four patients (5%) underwent kidney transplant. Black patients experienced a median of 1.1 (0.4, 3.4) adverse events per 5 years of follow-up versus 0.6 (0.4, 1.2) in white patients; male patients experienced 0.6 (0.4, 1.7) events versus 1.6 (0.5, 4.0) in female patients. Black patients had 1.7 times the odds of death (95% CI: 0.4, 6.8) and 3.0 times the odds of ESKD (0.6, 14.7) compared to white patients. Male patients had 1.4 times the odds of death (0.5, 4.1) but 0.2 times the odds of ESKD (0.06, 0.9) as compared to female patients.

Conclusions: Our findings suggest that black pediatric patients with lupus nephritis have higher morbidity and mortality than white patients and that male patients have higher mortality but less renal morbidity than female patients. Longer follow-up and continued cohort enrollment will be important to broaden our knowledge of pediatric lupus nephritis.

SA-PO245

Evaluation of the slope of Change in eGFR as a Treatment Response Variable in Lupus Nephritis Ingrid R. Bispo, Evandro Klumb, Jose H. Suassuna. *Rio de Janeiro State University, Rio De Janeiro, Brazil.*

Background: In spite of treatment advances, up to 60% of lupus nephritis (LN) patients may eventually develop CKD. The commonest manifestations of LN include an active urinary sediment, proteinuria, and a loss of GFR. They are also the main tools determine treatment response, usually in a static fashion. We are not aware of any study that examined the predictive value of the slope of changes in renal function over time.

Methods: Out of 660 patients with SLE that attended our institution, between August of 2014 and June of 2016, we found and analyzed 227 patients with established LN. Estimated GFR by the CKD-EPI equation was evaluated longitudinally by linear regression and slopes calculated as ΔGFR in mL/min/month. Patients were grouped in tertiles of ΔGFR. Each tertile was analyzed by social-demographic, clinical, laboratorial and histopathologic features. Results were compared to treatment response variables as established in the literature. CKD and time to ESRD were analyzed as secondary outcomes.

Results: Women comprised 87% of the patients and mean age was 30 years. Proliferative GN predominated (77%) and mean of proteinuria at presentation was 3,6g/24h. The lowest tertile (worst response) was independently associated with race (Afro-Brazilians, p=0,05), lower levels of education (p=0,002) and with proliferative nephritides (p=0,03). Patients in this tertile also had more flares (p=0,003) but less active urinary sediment (p=0,03). On the other hand, the upper tertile (better response) was associated with higher education (p< 0,001), lower number of flares (p< 0,001), higher creatinine in the acute phase (p< 0,001). Subjects in low tertile and those that did not achieve complete response were more like to present CKD and ESRD.

Conclusions: The combination of traditional response variables along with slopes of change in GFR may provide an added discriminatory predictive value for evaluation of the treatment response in lupus nephritis.

SA-PO246

Impact of Extraglomerular Involvement on Clinical Presentation and Outcomes in Patients with Lupus Nephritis Krishan Lal L. Gupta, Hari A. Prasad, Manish Rathi, Aman Sharma, Ritambhra Nada. *Post Graduate Institute of Medical Education & Research, Chandigarh, India.*

Background: In patients with lupus nephritis, treatment and prognosis is characterized by its class which is based on glomerular pathology. Extra glomerular involvement, seen frequently was not considered in classification of lupus nephritis. Aim of this study was to analyze the incidence of tubulointerstitial and vascular involvement in lupus nephritis and their correlation with clinical presentation and outcomes.

Methods: This was a prospective retrospective cohort study including patients with biopsy proven lupus nephritis. A total of 241 patients were included in the study period between January2010 - June2016.

Results: The mean age of study population was 29 years. Among 241 patients in the study group, male: female ratio was 1:7. Although the clinical parameters at presentation were similar between the two groups, male patients had poor outcomes when compared with females (response rates 58.6%vs79.7%, P-0.04; resistant disease 34.5%vs15.7%, P-0.01). Interstitial involvement including interstitial inflammation, interstitial fibrosis and tubular atrophy was seen in 60.1% and vascular involvement was seen in 32.3% of biopsies (**Table1**). Patients with interstitial involvement had worse clinical parameters at presentation and poor outcomes at the end of 6 months of therapy (response rates 65.5%vs82.7%, P<0.01; resistant disease - 21.3%vs10.7%, P-0.03). Similarly in those with vascular involvement also had worse clinical parameters at presentation and poor outcomes (complete remission 38.2%vs61.9%, P<0.01; resistant disease - 26.3%vs14.3%, P=0.02). This trend of poor outcomes was especially seen in those with vascular TMA (response rates - 60%vs79.1%, P-0.04)(Table1).

Conclusions: The involvement of extraglomerular compartment in lupus nephritis patients is common and they play an important role in determining the outcomes along with glomerular lesions.

Distribution of Extra glomerular lesions on renal biopsy

TUBULOINTERSTITIAL INVOLVEMENT	145 (60.1%)	VASCULAR INVOLVEMENT	78 (32.3%)
Interstitial inflammation	93 (38.5%)	Asymptomatic vascular immune deposits	13 (5.3%)
Interstitial fibrosis/ Tubular atrophy	115 (47.7%)	Vasculopathy	5 (2%)
		Vasculitis	2 (0.8%)
		Vascular TMA	27 (11.2%)
		Arteriosclerosis	55 (22.8%)

SA-PO247

Eculizumab in Refractory Lupus Nephritis with Thrombotic Microangiopathy Jessica M. Nelson,[1] Daniel J. Birmingham,[1] Huijuan Song,[1] James A. Tumlin,[2] Brad H. Rovin.[1] *[1]Ohio State University, Columbus, OH; [2]University of Tennessee College of Medicine, Chattanooga, TN.*

Background: A patient with refractory lupus nephritis (LN) developed thrombotic microangiopathy (TMA) and was treated with the anti-C5 monoclonal antibody eculizumab (ECU). The response to ECU was minimal, so we characterized C5 cleavage during ECU therapy.

Methods: Complement component C5 and the membrane attack complex (C5b-9) were measured by the complement laboratory at the University of Iowa. Urine C5a were measured by sandwich ELISA. The C5 cDNA was directly sequenced by Sanger methodology.

Results: A 38 year old Asian woman with SLE had an LN flare (class IV+V) and was treated with 6 months of pulse cyclophosphamide + methylprednisolone. Proteinuria and hematuria persisted and serum complement levels remained depressed. The patient developed Coomb's negative hemolytic anemia and thrombocytopenia with elevated LDH, prothrombin fragments, and fibrin split products, and was diagnosed with TMA. ECU was started. Complement levels after 3 months of ECU are shown (Table). Although the patient's platelets improved hemolysis continued, circulating C5b-9 was not suppressed and C5a levels were elevated in the urine. Paradoxically concurrent serum C5 levels were above normal. The C5 exons were sequenced but the single nucleotide polymorphisms (SNP) that alter arginine 885 and block ECU binding were not found. However 2 SNPs that affected the amino acid sequence (V802I and E1437D) were found.

Conclusions: ECU did not effectively block C5 cleavage in this patient, and may have caused elevated circulating C5. These findings may be due to genetic variants in the patient's C5 gene.

Funding: Clinical Revenue Support

Test	Pre-ECU	During ECU	Reference Range
Serum Creatinine (mg/dL)	0.7	0.5	0.5-1.2
Urine Protein:Creatinine	7.3	11	<0.2
Hemoglobin (g/dL)	6.8	11 (transfused)	11.7-15.5
Platelets (k/uL)	132	196	150-400
Haptoglobin (mg/dL)	-	<30	44-215
C3 (mg/dL)	26	52	87-200
C4 (mg/dL)	2	undetc	18-53
C5 (mg/dL)	-	36	10-21
Urine C5a (ng/mg creatinine)	-	20	<1
Soluble C5b-9 (mg/L)	-	0.4	<0.3

SA-PO248

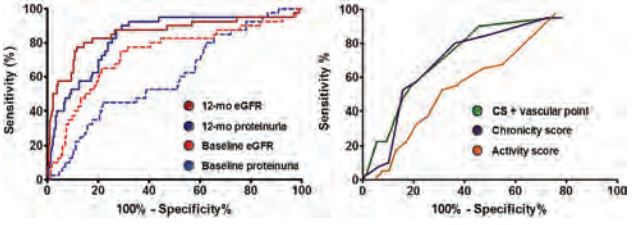
Clinical Parameters after Induction Treatment Are Better Predictors of 36-Month Renal Survival Than the Baseline Biopsy Histopathological Scores in Lupus Nephritis Sonia Rodriguez,[3] Luis E. Morales-Buenrostro,[1] Norma O. Uribe-uribe,[2] Juan M. Mejia-Vilet.[1] *[1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico; [2]Instituto Nacional de Ciencias Medicas y Nutricion, "Salvador Zubiran", Mexico City, Mexico; [3]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico.*

Background: Baseline clinical parameters and histopathological scores have been associated with lupus nephritis (LN) outcomes. Recently, it was suggested that adding intimal hyperplasia findings to the NIH chronicity score (CS) may enhance its predictive value. We evaluated the capacity of before and after-treatment clinical and histopathological parameters to predict 36-month renal survival.

Methods: We included a cohort of 255 patients with class III, IV or V LN and a minimum 36-month follow-up. We registered clinical and histopathological parameters and determined their predictive value for 36-month renal survival by means of logistic regression and ROC curves. A new chronicity score (CS+vasc) was created by adding 0 or 1 point to the NIH chronicity score based on vascular intimal thickening findings.

Results: The cohort comprised 89% female patients, median age 28 years (IQR 23-37). Median baseline eGFR and proteinuria were 81ml/min (IQR 45-117) and 3.2g/g (IQR 1.9-5.3) respectively. Forty patients (15.7%) developed end-stage renal disease by 36 months. The ROC curves area under the curve were 0.732 for baseline eGFR, 0.602 for baseline proteinuria, 0.620 for the NIH activity score, 0.739 for the chronicity score, 0.760 for CS+vasc 0.760, 0.857 for 12-month eGFR, 0.835 for 12-month proteinuria (figure). A 12-month proteinuria <0.8 had 71% sensitivity and 88% specificity for 36-month survival (LR 5.70) The activity score was associated with lower renal survival exclusively at a cutoff over 10 points.

Conclusions: Post-treatment 12-month proteinuria is an individual good renal survival predictor. At baseline, the best predictor is the histopathological NIH CS, which improves little with the addition of points for intimal thickening evaluation.



SA-PO249

Comparison of Tacrolimus and Mycophenolate Mofetil for Induction of Remission in Lupus Nephritis in Thailand: A Multicenter Randomized Controlled Trial Vuddhidej Ophascharoensuk,[1] Atiporn Ingsathit,[2] Sirirat Anutrakulchai,[3] Yingyos Avihingsanon,[4] Ratana Chawanasuntorapoj,[8] Pornpen Sangthawan,[5] Nuntana Kasitanon,[1] Warangkana Pichaiwong,[6] Pintip Ngamjanyaporn,[7] Vasant Sumethkul.[7] *[1]Chiang Mai University, Chiang Mai, Thailand; [2]Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [3]Khon Kaen University, Khon Kaen, Thailand; [4]King Chulalongkorn Memorial hospital, Chulalongkorn University, Bangkok, Thailand; [5]Prince of Songkla University Hospital, Songkhla, Thailand; [6]RAJAVITHI HOSPITAL, Bangkok, Thailand; [7]Ramathibodi Hospital, Bangkok, Thailand; [8]Siriraj Hospital, Bangkok, Thailand. Group/Team: warangkana.*

Background: We conducted a prospective multi-center, opened-label, parallel, randomized, controlled trial to compare tacrolimus (TAC) and mycophenolate mofetil (MMF) for induction of remission in lupus nephritis (LN).

Methods: Adult patients with biopsy-proven LN ISN/RPS Class III-V and active nephritis were receive prednisolone (0.7-1.0 mg/kg/day for 4 weeks of run in period and tapered) and randomly assigned to receive TAC (0.1 mg/kg/day) or MMF (1.5–2 g/day) for 6 months. All patients who had remission received AZA 1-2 mg/kg/day as standard treatment in the maintenance phase. The primary outcome was the probability of complete remission (CR) at 6 and 12 months and the secondary outcomes included CR or partial remission (PR), renal parameter (UPCR, serum creatinine, and GFR), adverse events (infection, leukopenia, GI symptoms, new onset DM/hyperglycemia, and alopecia) and health related quality of life scores (EQ5D).

Results: 84 patients were randomized. One patient who was randomized to TAC group withdrew from the study immediately after randomization. Therefore, 42 patients were received MMF and 41 patients were received TAC. Median times to complete remission were 6.1 months and 5.1 months in MMF and TAC groups (P= 0.82). The probability of CR was similar between 2 groups (HR=0.99; 95%CI 0.53 to 1.85; P=0.97). The reduction in UPCR were similar between 2 groups during induction period but there were significantly increasing UPCR in TAC group at 12 months (P=0.03). There were worsening serum creatinine and GFR in TAC group compared with MMF group during induction period but both serum creatinine and GFR were similar after maintenance therapy. Infection occurred more frequently in MMF group. Other adverse events and EQ5D scores were similar between 2 groups.

Conclusions: TAC is effective as MMF for induction therapy of active LN class III-IV. It have less infections than MMF but transiently increased serum creatinine and decreased GFR compared with MMF. ClinicalTrials.gov ID: NCT01580865

Funding: Commercial Support - Astellas

SA-PO250

The Long Term Outcome and Histological Transformation of ISN/RPS Class II Lupus Nephritis Abdulkareem Alsuwaida,[4] Amaar A. Bakhit,[5] Sufia Husain,[3] Feras A. Alsuwaida,[4] Junaid Wadera,[1] Hala M. KFoury.[2] *[1]KING KHALID UNIVERSITY HOSPITAL, RIYADH, Saudi Arabia; [2]KSU-KKUH, Riyadh, Saudi Arabia; [3]King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia; [4]King Saud University, Riyadh, Saudi Arabia; [5]King Saud University Medical City, Riyadh, Saudi Arabia.*

Background: There are discrepancies on the guidelines of the treatment of Class II LN due to the lack of scientific evidence. The role of immunosuppression, however, is less clear. The primary objective of this study is to assess the response of immunosuppressive therapy, the long-term prognosis and the histological transformation to other ISN/RPS classes among those who underwent a repeated biopsy.

Methods: A retrospective study was carried out that included patients who had received a diagnosis of LN class II on their first renal biopsy, between the years 1996 till 2016. The rate of complete remission, defined as Proteinuria less than 0.3 gm per day, with normal creatinine 6 month after biopsy were also evaluated. We also compared the histological transformation among those who underwent a repeated biopsy during the follow up.

Results: The study included 32 female patients with SLE and class II LN with the mean age of 31.2 years. The most frequent presentation (72%) was asymptomatic hematuria and/or subnephrotic range Proteinuria. The median serum creatinine and proteinuria at presentation were 78 umol/l and 0.8 gm per day, respectively. Acute kidney injury was noted in 7 patients (22%) and 3 patients (9.4%) had a nephrotic range proteinuria. The management was steroid alone in 25 patients (78%), Mycophenolate Mofetil in 6 patients (18.8%) and cyclophosphamide in 1 patient. Among the 25 patients treated with prednisolone alone (0.5-1 mg/kg), complete remission was seen in 23 patients (92%). After a median follow up of 8 years, two patients doubled their serum creatinine. The repeated biopsy was done in 17 patients (53%) and the detail of transformation to other classes is shown in table 1. The repeated biopsy showed transformation to other classes in 11 patients (65%).

Conclusions: Daily steroid monotherapy may be an appropriate first-line treatment for class II LN. Larger, prospective, trials are needed to validate this strategy and identify those patients who are less likely to obtain remission.

Funding: Government Support - Non-U.S.

Table 1. ISN/RPS classifications on repeat biopsy among 17 patients with baseline ISN/RPS Class II Lupus Nephritis

ISN/RPS II	ISN/RPS III	ISN/RPS IV	ISN/RPS VI
6 patients (35.3%)	5 patients (29.4%)	4 patients (23.5%)	2 patients (11.8%)

SA-PO251

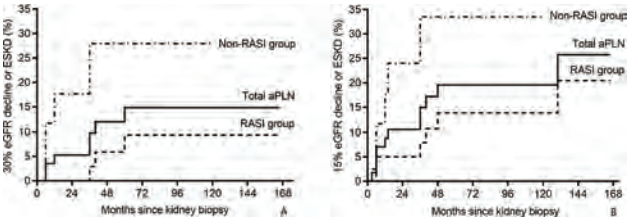
Early Renin-Angiotensin System Blockade Improved the Short-Term and Long-Term Renal Outcomes of Lupus Patients with Antiphospholipid-Associated Nephropathy Cai Yue, Guanhong Li, Xuemei Li, Ruitong Gao. *Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China.*

Background: Antiphospholipid-associated nephropathy (aPLN) represents a constellation of renal vasculopathies associated with antiphospholipid antibodies. Coexisting aPLN is associated with more severe renal involvement and worsened renal outcome in patients with lupus nephritis. Our aim with this research was to investigate the renal protective effects of early renin-angiotensin-aldosterone system (RAAS) blockade in lupus patients with aPLN.

Methods: Medical data of 57 lupus patients with biopsy proven aPLN were analyzed. Early RAAS blockade was defined as administration of renin-angiotensin system inhibitors (RASI) within 3 months after kidney biopsy and continued for at least 12 months.

Results: Patients were comparable in demographic data, laboratory findings, and renal histology by the time of kidney biopsy, except that the RASI group had higher proteinuria level (5.2 [2.8-8.8] vs 1.9 [0.6-2.8]g/d, p=0.005) and higher prevalence of hypertension (75 vs 29%, p=0.001). The two groups were comparable in estimated glomerular filtration rate (eGFR), mean arterial pressure (MAP), and proteinuria level at 12 months after kidney biopsy. The improvement ratio of eGFR at 12 months was significantly higher in the RASI group (26 [-5, 86] vs -2 [-20, 20]%, p=0.028), and the rate of change in eGFR after 12 months were comparable between groups. During a mean 80-months follow-up, 4 (23%) patients in the non-RASI group and 3 (8%) patients in the RASI group developed kidney disease progression. Early RAAS blockade significantly decreased the risk of kidney disease progression (HR 0.11 [0.02-0.59]; p=0.009). Proteinuria and hypertension controls were comparable between groups.

Conclusions: Early RAAS blockade improved the short-term and long-term renal outcomes in lupus patients with aPLN. The renal protective effect of RASI was independent of its antihypertensive and antiproteinuric effects.



Cumulative incidence of kidney disease progression in lupus patients with aPLN. A, kidney disease progression defined as 30% decline of eGFR or ESKD. 2B, kidney disease progression defined as 15% decline of eGFR or ESKD.

SA-PO252

Successful Multitarget Therapy in Refractory Lupus Nephritis: A Retrospective Cohort Camila B. Oliveira,[1,2] Denise M. Costa,[1,2] Gisele Vajgel,[1] Carolina A. Vasconcelos,[2] Maria Alina G. Cavalcante,[1] Lucila Maria Valente.[1] *[1]Hospital das Clínicas - UFPE, Recife, Brazil; [2]IMIP, Recife, Brazil.*

Background: Multitarget therapy (MT) with mycophenolate mofetil (MMF), calcineurin inhibitor and steroids has been studied for induction treatment of lupus nephritis (LN). Nevertheless, its use in refractory LN is still being evaluated.

Methods: Retrospective cohort study of adult patients with refractory LN (EULAR/ERA-EDTA recommendations) treated with MT. Clinical characteristics, serological data and long-term follow-up were analyzed. Complete response (CR) and partial response (PR) were defined by KDIGO Clinical Practice Guideline for Glomerulonephritis.

Results: Data from 8 patients with refractory LN are shown in Table 1. The mean age was 34.6 ± 6 years and 87.5% were female. Mean sCr was 0.8 ± 0.2 mg/dl and median proteinuria was 3.7 (3.1 – 4.1) g/24h. All patients were treated with MMF (1 – 2g/day) plus cyclosporine A 2.5 – 4.0 mg/Kg/day (7 patients) or tacrolimus 0.06 mg/Kg/day (1 patient) plus steroids. After a follow-up of 18 (7.5 – 29.8) months, 7 patients had CR or PR, mean sCr was 1.0 ± 0.3mg/dl and median proteinuria was 1.4 (0.8 – 2.0) g/24h. There were no major adverse events (severe infections or drug nephrotoxicity).

Conclusions: MT successfully induced CR or PR in most patients with refractory LN with no major adverse events.

Table 1. Patients characteristics and long-term follow-up of Multitarget Therapy in refractory lupus nephritis

No	Age (yrs)	Gender	ISN/RPS Classification	Before Multitarget Therapy			Multitarget Therapy							
				Induction Treatment	sCr mg/dl	Prot g/24h	6 months		12 months		Last visit			
							sCr mg/dl	Prot g/24h	sCr mg/dl	Prot g/24h	Time (months)	sCr mg/dl	Prot g/24h	Response
1	27	Female	V	CYC/MMF/ RTX	0.6	5.70	0.8	1.60	0.8	3.00	12	0.8	3.00	PR
2	31	Male	V	CYA/MMF	1.0	1.60	0.9	0.09			6	0.9	0.09	CR
3	41	Female	IV-S A/C + V 67% crescents	MMF/CYC	1.0	4.40	1.4	2.70			8	1.4	3.30	NR
4	25	Female	III A + V 10% crescents	CYC/MMF	0.9	3.30	0.8	1.30	0.9	1.90	27	1.0	0.97	PR
5	39	Female	IV-G A/C + V 42% crescents	MMF/CYC/ RTX	0.6	4.50	0.7	1.10			6	0.8	1.10	PR
6	34	Female	III A + V	MMF/CYC	0.6	4.00	0.7	1.80	0.6	1.30	39	0.6	1.70	PR
7	35	Female	III A/C + V	CYC/MMF	1.1	2.40	1.2	2.5	1.4	1.20	24	1.3	1.70	PR
8	42	Female	IV-S A/C + V 32% crescents	CYC/MMF	1.1	4.00	0.9	1.2	1.1	0.05	38	0.9	0.23	CR

ISN/RPS: International Society of Nephrology / Renal Pathology Society – CYC: Cyclophosphamide – MMF: mycophenolate mofetil – RTX: Rituximab – CYA: Cyclosporine A – sCr: creatinine – Prot: proteinuria – CR: complete response – PR: partial response – NR: no response

SA-PO253

Predictors of Renal Outcomes in Sclerotic Class ANCA GN Steven Menez,[5] Sami Alasfar,[3] Zdenka Hruskova,[1] Jennifer O. Scott,[3] Min Chen,[6] Mark A. Little,[4] Vladimir Tesar,[3] Duvuru Geetha.[2] *[1]Department of Nephrology, General University Hospital and First Faculty of Medicine, Charles University, Prague 2, Czech Republic; [2]John Hopkins Bayview Medical Center, Baltimore, MD; [3]None, Rosedale, MD; [4]Trinity College Dublin, Dublin, Ireland; [5]Medicine, Div. of Nephrology, Johns Hopkins Medicine, Baltimore, MD; [6]Peking University First Hospital, Peking, China.*

Background: The ANCA GN classification has been shown to have prognostic value in ANCA associated glomerulonephritis (GN) with sclerotic class portending poor renal outcomes. Relevant published data on factors predicting outcomes in sclerotic ANCA GN is limited and these patients are not well covered in published guidelines.

Methods: Patients were recruited from 1998-2016 from 4 centers worldwide (N= 45) for this retrospective cohort study. All patients had biopsy proven sclerotic ANGN with > 50% of sampled glomeruli showing global sclerosis. We describe the clinical characteristics of this cohort and evaluate predictors of one year GFR and ESRD.

Descriptive data are described as mean (SD). Logistic and linear regression models were used as appropriate.

Results: Of the 45 patients, 91% were Caucasian and 58% male with a mean age of 60 years. 80% had new diagnosis, 71% had renal limited disease and 84% were MPO ANCA positive. Kidney biopsies contained a mean (SD) 25 (18) glomeruli, mean (SD) % sclerosed glomeruli was 69(12) with 96% showing moderate to severe interstitial fibrosis (IF). 43 patients received immunosuppressive therapy: 69% pulse solumedrol, 71% cyclophosphamide, 24% rituximab and 18% received plasmapheresis. Disease remission was achieved in all. The mean (SD) eGFR at entry was 15 (18) and at 1 year was 17(13) ml/min/1.73m^2. Entry GFR, rituximab use and IF but not % normal glomeruli were predictive of 1 year GFR (Table1). Over a mean (SD) follow up of 60 (58) months, 25 patients reached ESRD and baseline GFR predicted risk of ESRD (p=0.04).

Conclusions: Entry GFR, use of RTX and lesser degree of IF predicted better GFR at 1 year in sclerotic ANCA GN. Further studies are needed to validate these findings.

Predictors of GFR at 12 Months

	Correlation coefficient or mean difference	Confidence interval	P-value
Age	0.15	(-0.15 - 0.45)	0.31
Gender (Female)	0.67	(-8.33 - 9.68)	0.88
ANCA type (PR3)	3.6	(-9.29- 16.59)	0.57
GFR at Entry	1.27	(.90 - 1.63)	<0.0005
Use of RTX versus CYC	19.285	(10.65 - 27.91)	<0.0005
Glomerular Sclerosis >75%	6.15	(-4.016 - 16.31)	0.23
Percentage of normal glomeruli >2%	-1.69	(-10.80 - 7.4)	0.75
Degree of Interstitial Fibrosis	-8.56	(-15.88 -- -1.23)	0.0001

SA-PO254

Pulmonary and Renal Outcomes in Patients with Pulmonary Renal Syndromes Treated with Plasmapheresis at VCU Christen Vagts, Catherine Grossman, Jason M. Kidd. *VCUHS, Richmond, VA.*

Background: Pulmonary renal syndromes (PRS) are a group of vasculitis syndromes characterized by pulmonary capillaritis, often resulting in diffuse alveolar hemorrhage, and glomerulonephritis. This includes anti-GBM disease and ANCA-associated vasculitis. The indications for plasmapheresis vary based upon the type of pulmonary renal syndrome and their presenting kidney function. The purpose of this study was to characterize patients with PRS treated with plasmapheresis at VCU, identify outcomes of pulmonary and renal functions of these patients, and to correlate estimated 30 day mortality with use of APACHE-II scoring with actual 30 day mortality.

Methods: A retrospective review of patients with PRS treated with plasmapheresis between 2006 and 2014 at VCU was conducted from a pre-existing database. Data regarding presentation, clinical course, follow up, and mortality were collected and evaluated.

Results: A total of 17 patients treated with plasmapheresis for a PRS were identified; eight had anti-GBM disease and nine had ANCA-associated vasculitis (AAV). 66% of patients with AAV were African American and 37.5% of patients with anti-GBM disease were African American. More patients with anti-GBM disease were tobacco users. Patients with AAV had a higher incidence of diffuse alveolar hemorrhage (78% vs. 25% patients with anti-GBM disease) and higher rates of intubation (78% vs. 11% patients with anti-GBM disease). More patients with anti-GBM disease presented with high degree renal failure, defined as Cr >5.7 (50% vs. 22% of patients with AAV). All patients with anti-GBM disease required hemodialysis (HD) during the plasmapheresis treatment period and all required chronic dialysis. In-hospital mortality was higher in patients with AAV (55% vs. 0% of patients with anti-GBM disease). APACHE-II scores appeared similar between the two groups, while both 30 day and 1 year mortality was higher in AAV (44% 30-day and 55% 1-yr mortality vs. 0% and 12.5% in anti-GBM disease respectively).

Conclusions: Patients with PRS requiring treatment with plasmapheresis had varying outcomes, with anti-GBM disease having overall worse renal-related morbidity but improved mortality when compared to ANCA associated disease.

SA-PO255

The Steroid Tapering in ANCA Vasculitis Evaluation Study (STAVE) 2: A Systematic Review and Meta-Analysis Jennifer C. Rodrigues,[1] David T. Collister,[1] Amy Archer,[3] Kim P. Cheema,[6] Christian Pagnoux,[2] Lehana Thabane,[7] Peter A. Merkel,[5] David R. Jayne,[4] Michael Walsh.[1] *[1]Nephrology, McMaster University, Toronto, ON, Canada; [2]Rheumatology, Mount Sinai Hospital, Toronto, ON, Canada; [3]Rheumatology, Northwestern University, Chicago, IL; [4]Rheumatology, University of Cambridge, Cambridge, United Kingdom; [5]Rheumatology, University of Pennsylvania, Philadelphia, PA; [6]Nephrology, University of Calgary, Calgary, AB, Canada; [7]Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada.*

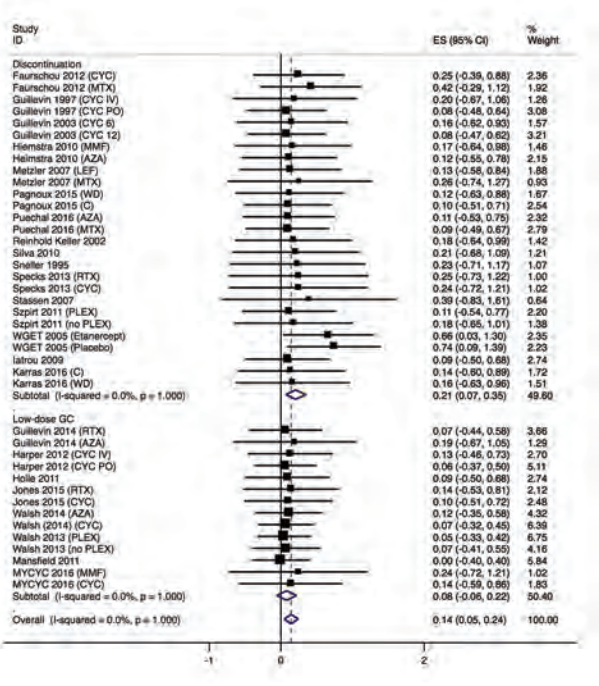
Background: Relapses of ANCA-associated vasculitis (AAV) are associated with death, decreased renal function, and ESRD. The role of glucocorticoids (GC) in relapse prevention is unclear.

Methods: MEDLINE, EMBASE, Cochrane Clinical Trials, and Grey Literature were searched from January 1, 2008 until May 26, 2016 without language restriction for studies with patients with AAV. GC use was specified *a priori* with minimum follow up of 18 months. Randomized controlled trials (RCT) and prospective cohort studies were included. Quality of evidence was assessed using modified Newcastle-Ottawa criteria. Meta-analysis was completed using a random-effects model of DerSimonian and Laird.

Results: 24 studies met criteria with 2272 patients. 13 (54%) discontinued GC in < 1 year. The pooled relapse rate was 14.3 per 100 patient years (95% CI 4.5,24.0). Relapse was more frequent when discontinuation was compared to long-term, low-dose GC (20.7 per 100 patient years, 95% CI 6.8,34.5 vs. 8.0 per 100 patient years, 95% CI 5.7,21.7 Figure 1). Multivariable linear meta-regression confirmed that long-term, low-dose GC was associated with lower relapse rates (β = -0.16, 95% CI -0.26,0.07, P = 0.001) and follow up time was associated with increased relapse rates (β = 0.003, 95% CI 0.001,0.006, P = 0.002). Multivariable linear meta-regression did not demonstrate any association of GC dosing with infections.

Conclusions: Long-term, low-dose GC was associated with decreased relapse rates in patients with AAV. Characterization and reporting of adverse events limited analysis. RCT are needed to determine optimal GC administration.

Funding: Private Foundation Support



Random effects meta-analysis of long-term, low dose GC as compared to GC discontinuation on relapse per patient year.

SA-PO256

Outcome Predictors in Childhood-Onset Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis: Clinicopathological Analysis in a Nationwide Japanese Survey Daishi Hirano,[3] Kazumoto Iijima,[2] Shuichi Ito.[1] *[1]Department of Pediatrics, Graduate School of Medicine, Yokohama City University, Yokohama, Japan; [2]Dept. of Pediatrics, Kobe Univ. Graduate School of Medicine, Kobe, Japan; [3]The Jikei university school of medicine, Tokyo, Japan.*

Background: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) occurs mainly in adults (estimated annual incidence ~ 10–20 per million, peak age at onset 60 years). Little is known about the disease in children. Here, we examined clinicopathological predictors of patient and renal outcomes in childhood-onset AAV.

Methods: This was a retrospective nationwide multicenter survey of patients with AAV diagnosed before age 16. Eligibility criteria were: (1) fulfilled the Chapel Hill Consensus Conference criteria for microscopic polyangiitis (MPA) or granulomatosis with polyangiitis (GPA), and (2) kidney biopsy showing histology consistent with AAV.

Results: The cohort consisted of 46 children; 35 (76%) were female, 38 (83%) had MPA, 9 (17%) had GPA, 83% were MPO-ANCA-positive, 13% were PR3-ANCA-positive. Median age at onset was 10.7 years, and median time to diagnosis was 2.0 months. Initial symptoms included fever and fatigue (43%), renal (74%), pulmonary (30%), ocular (20%), and mucocutaneous involvement (22%). Clinical features differed between MPA and GPA. Remission was achieved after induction therapy in 27 (55%) cases. After a median follow-up of 3.6 years, 14 (30%) patients had chronic kidney disease stages 2–3. Seven (15%) patients progressed to end-stage renal disease (ESRD). Renal outcome was better in GPA than MPA. In univariate analysis, although sex, age at onset, and diagnosis delay were not associated with risk of progression to ESRD, type of AAV, nephrotic-range proteinuria, and histological chronicity indices predicted renal outcome. Nephrotic-range proteinuria was significantly correlated with histological chronicity ($r = 0.50$, $P < 0.01$) and was an independent predictor of ESRD on logistic regression ($P < 0.01$).

Conclusions: There were significant differences between two types of AAV in terms of clinical features and outcomes. Nephrotic-range proteinuria was an independent

predictor of ESRD. Nearly 90% of the cohort did not need renal replacement therapy at a median follow-up of 3.6 years, indicating that renal survival in childhood-onset AAV has improved with the development of modern therapies.

Funding: Government Support - Non-U.S.

SA-PO257

Design of the Maintenance of ANCA Vasculitis Remission by Intermittent Rituximab Dosing Based on B Cell Reconstitution versus a Serologic ANCA Flare (MAINTANCAVAS) Trial Frank B. Cortazar,[2] William F. Pendergraft,[1] Colleen B. Dunbar,[2] Karen A. Laliberte,[2] John Niles.[2] *[1]University of North Carolina Kidney Center, Chapel Hill, NC; [2]Nephrology, Massachusetts General Hospital, Boston, MA.*

Background: B cell depletion with rituximab (RTX) is an effective strategy for maintenance of remission in ANCA vasculitis. Unfortunately, cessation of therapy is associated with a high rate of relapse, while indefinite continuation of fixed-dose treatment is associated with significant complications. No clinical trial data exists to guide the optimal use of RTX after two years of maintenance therapy. To address this unmet need, we designed the MAINTANCAVAS Trial.

Methods: The MAINTANCAVAS Trial is an open-label, randomized, and two-arm controlled trial to evaluate the efficacy of two RTX dosing strategies to prevent disease relapse: 1) RTX dosing upon B cell reconstitution (B cell arm), and 2) RTX dosing upon a significant rise in ANCA titer (ANCA arm). Eligible patients have a history of ANCA vasculitis and have completed at least 24 months of fixed-interval (i.e., every 4-6 months) RTX maintenance therapy in remission (BVAS-WG=0 and prednisone ≤ 7.5 mg/day). Upon randomization, patients discontinue fixed-interval RTX and are followed with clinical assessment and laboratory monitoring every three months. Patients assigned to the B cell arm are re-dosed with RTX 1 gm x 1 when the CD20 count rises above 10 cells/mm^3, while patients in the ANCA arm are re-dosed with RTX 1 gm x 2 (separated by 2 weeks) when the ANCA titer rises by pre-specified level. The primary outcome is disease relapse at 36 months. Secondary outcomes include significant adverse events, vasculitis damage, and RTX utilization. At an alpha level of 0.05 and power of 0.80, 180 patients are required to detect a 15% difference in relapse between the strategies.

Results: Enrollment commenced 6/7/2016. To date, a total of 43 patients have been enrolled. No relapses have occurred. Six patients in the B cell arm (n=22) have been re-dosed with RTX at the following times: 6 months (n=2), 9 months (n=3), and 1 year (n=1). No patients in the ANCA arm have been re-dosed. There have been no serious adverse events.

Conclusions: The optimal long-term RTX dosing strategy for maintenance of remission in ANCA vasculitis remains unknown. The MAINTANCAVAS trial should provide useful information to address this important question.

SA-PO258

Associated Clinical Characteristics in Anti-Neutrophil Cytoplasmic Antibody Negative, Pauci-Immune Crescentic Glomerulonephritis: Results of a Case Series at a Tertiary Care Center Prince Amaechi,[1] Evelyn Bruner,[3] Milos N. Budisavljevic.[2] *[1]Medical University of South Carolina, Charleston, SC; [2]Medical University of South Carolina----, Charleston, SC; [3]Medical university of south carolina, Charleston, SC.*

Background: Pauci-immune crescentic glomerulonephritis (PCGN) is the most common cause of rapidly progressive glomerulonephritis in adults and elderly patients. Approximately 10-30% of patients with PCGN have anti-neutrophil cytoplasmic antibody (ANCA) negativity. However the etiology of idiopathic ANCA-negative PCGN has never been clearly characterized besides a few case reports. We therefore conducted a case series of patients in our tertiary care center diagnosed with pauci-immune crescentic glomerulonephritis in the last 33 years to see if there was any specific associated factors.

Methods: We looked at all the patients in our hospital that had a diagnosis of pauci-immune crescentic glomerulonephritis from November 1994- June 2017. Those with additional diagnosis such as glomerular basement membrane disease or other autoimmune disorders were excluded. We identified 59 patients however, some had incomplete records and they were further excluded. The final number was 14 patients, of which 10 were ANCA- positive and 4 were ANCA-negative. Their medical records were evaluated for any associated medical conditions.

Results: Out of the 4 patients who were ANCA-negative, all of them had an infection that preceded their illness and that was clearly present at the time of renal failure diagnosis (100%); whereas, only 2 out of the 10 who were ANCA-positive had an associated infection with their illness (20%). In this small series of patients, the two categories of patients had a similar severity of illness as estimated by their Sequential Organ Failure (SOFA) Assessment Scores (averaging 3.6 and 3 respectively).

Conclusions: 100% of our patients with a diagnosis of ANCA-negative PCGN had associated infections preceding their illness, whereas this was true of only 20% of the ANCA-positive ones. The infections involved included BK virus, Parvovirus, Staph aureus pneumonia and streptococcal pneumonia. Our results suggest that there is a positive link between otherwise idiopathic ANCA-negative crescentic pauci-immune glomerulonephritis and a preceding episode of infection.

Relationship between ANCA positive vs negative with infection

ANCA- positive (+) infection = 2	ANCA- negative (+) infection= 4
ANCA-positive (-) infection = 8	ANCA- negative (-) infection = 0

ANCA- positive total n= 10, ANCA-negative total n= 4

SA-PO259

Relapse Free Survival after Steroid Withdrawal in ANCA Vasculitis Eirini LIOUDAKI,[5] Marie B. Condon,[4] Lubna Rashid,[3] Fiona E. Harris,[1] David Makanjuola,[4] Bhrigu Raj Sood.[2] *[1]Epsom and St Helier NHS Trust, Surrey, United Kingdom; [2]South West Thames Renal Unit, Carshalton, United Kingdom; [3]St Helier Hospital, London, United Kingdom; [4]St. Helier Hospital, Surrey, United Kingdom; [5]ST HELIER HOSPITAL, London, United Kingdom.*

Background: Current immunosuppressive regimens have made a marked difference to patient and organ survival; toxicity associated with long term treatment is recognised. Withdrawal of treatment is associated with disease relapse. It is unclear if there are cohorts of patients in whom immunosuppression can be withdrawn and if so when. We report, from our centre on the long term outcomes on 93 patients(pts) in whom steroid maintenance treatment was withdrawn after a stable remission was achieved.

Methods: 93 pts identified from a long term cohort of 219 pts presenting over a 13 year period. Data collected from medical records. Follow up ranged from 6 - 168 mths (median 60mths). Remission was achieved with standard induction (Plasma Exchange, Cyclophosphamide (cyclo) (oral or intravenous), mycophenolate mofetil (MMF) or Rituximab; all in combination with corticosteroid) and maintained with Azathioprine or MMF in combination with corticosteroid. In patients in whom a stable remission was achieved, withdrawal of corticosteroid would begin at 18 to 24 mths. We have looked at steroid withdrawal and subsequent disease activity.

Results: 38 female; 87 white ethinicity; median age at diagnosis of 69 yrs (range 18-89). Median creatinine (creat) at presentation was 309umol/L; 22 pts with a serum creat >500. Induction: 86 pts cyclo (6 oral, 80 IV); 1 Rituximab, 1 Azathioprine, 5 MMF. 30 pts received plasma exchange. Median time to cessation of prednisolone from induction was 25mths (4-93). 72 pts (77%) remain relapse free at a median of 39 months since steroid withdrawal (3-126). Antibody class or induction treatment did not predict relapse free status; neither did presentation renal function (median creat 309 in non relapse pts / creat 330 in relapse). Follow up of patients who had relapsed was longer than for those who are disease free; 110 (53-163) versus 66 (14-165) mths, however 62 patients have remained disease free for over 18mths off steroid. (median 24 (range 4-93)).

Conclusions: In this cohort we have so far not identified a clear predictor of steroid withdrawal without relapse, however 77% of our patients remain relapse free off steroid with significant follow up period. We would suggest that withdrawal of steroid should be the aim when patients have achieved a stable remission, and that this can be achieved safely with close monitoring.

SA-PO260

Combination Therapy with Rituximab and Cyclophosphamide for Remission Induction in ANCA Vasculitis Frank B. Cortazar,[3] Saif A. Muhsin,[3] William F. Pendergraft,[2] Zachary S. Wallace,[1] Colleen B. Dunbar,[3] Karen A. Laliberte,[3] John Niles.[3] *[1]Massachusetts General Hospital, Boston, MA; [2]University of North Carolina Kidney Center, Chapel Hill, NC; [3]Nephrology, Massachusetts General Hospital, Boston, MA.*

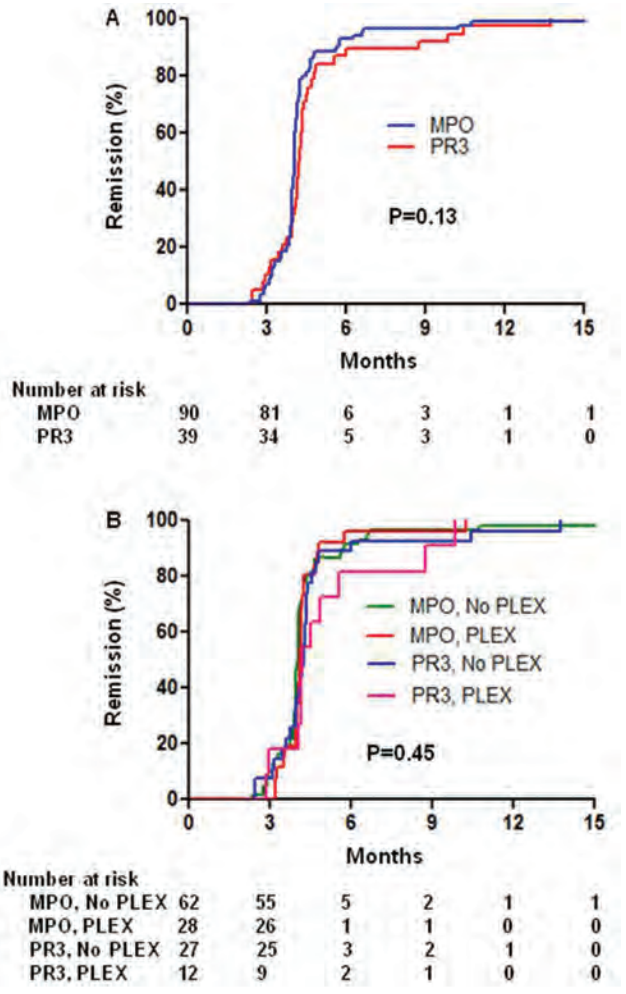
Background: Remission induction in ANCA vasculitis may be complicated by slow response to treatment and toxicity from glucocorticoids. More effective and less toxic regimens are needed.

Methods: Patients were included if they had ANCA vasculitis and were treated with a standardized remission induction regimen (SIR): Rituximab 1000 mg Q 2 weeks x 2 doses, oral cyclophosphamide 2.5 mg/kg x 1 week and 1.5 mg/Kg x 7 weeks (adjusted for eGFR), and a rapid prednisone taper that lowers the dose to ≤ 15mg/d by 1 month. Complete remission (CR) was defined as a BVAS-WG of 0 and a prednisone dose ≤ 7.5 mg/d.

Results: We identified 129 patients treated with the SIR, 31% of whom also received PLEX for RPGN or pulmonary hemorrhage (PH). Seventy percent of patients had MPO-ANCA and 30% had PR3-ANCA. Median time to CR was 4 months (IQR, 3.9 to 4.4), and by 5 months 84% of patients were in CR. Prednisone was tapered to discontinuation as tolerated, such that the median prednisone dose at 8 months was 0 mg/day (IQR, 0 to 2.5). In patients with RPGN (n=75), PR3-ANCA was associated with a greater increase in eGFR at 6 months compared with MPO-ANCA (16.1 [IQR 0.0 to 22.5] versus 5.6 [IQR, -0.4 to 15.6] ml/min/1.73m2; p=0.028). During the first year following CR, 1 major relapse occurred over 122 patient-years. Serious infections occurred more frequently in patients receiving PLEX and were associated with increasing age and PH. Four deaths occurred, 3 of which were associated with serious infections.

Conclusions: Combination therapy with rituximab and cyclophosphamide was efficacious, allowed for rapid tapering of high-dose glucocorticoids and was well tolerated.

Funding: NIDDK Support, Clinical Revenue Support



SA-PO261

Plasmapheresis, Rituximab, and Low-Dose Cyclophosphamide for Remission Induction Therapy in Severe ANCA-Associated Vasculitis Kavita Gulati, Stephen P. McAdoo, Jack W. Galliford, Megan Griffith, Tom Cairns, Charles D. Pusey. *Imperial College London, London, United Kingdom.*

Background: Rituximab (RTX) is an established treatment for remission-induction in ANCA-associated vasculitis (AAV), though data regarding its use in immediately organ- or life-threatening disease are limited. We have studied the use of RTX as adjuctive therapy to plasmapheresis (PEX), cyclophosphamide (CYC) and oral steroids in patients presenting with diffuse alveolar haemorrhage (DAH) or severe renal failure (presenting requirement for dialysis or serum creatinine >500μ/L).

Methods: This is a cohort study of patients treated for severe AAV between 2011-15 with a combination of PEX, low dose pulsed i.v. CYC (6x500-750mg) and RTX (2x1g after completion of PEX) and tapered oral corticosteroids (initial dose 1mg/kg, maximum 60mg od) without intravenous steroids. Maintenance therapy was commenced at 3 months with azathioprine (MMF if intolerant) and patients received prophylactic treatment for PCP, peptic ulcer disease and osteoporosis. Data are reported as median & IQR.

Results: Thirty patients have been treated with this regimen, with median follow-up 2.1 yrs. Median age was 62 yrs (IQR 55-75); 50% were PR3-ANCA+ve, 50% MPO-ANCA+ve. Presenting BVAS was 21 (16-25), creatinine 452 μmol/L (338-590), and 43% required dialysis. DAH was present in 43%. Patients received 7 (7-10) plasma exchanges, and cumulative RTX and CYC doses were 2g (all patients) and 3g (2.5-3.5), respectively. At 6 months, 90% of patients were in remission (BVAS=0). All patients achieved B cell depletion (<1 cell/μL) and 83% became ANCA negative at median 5.1 months. The median time to B cell repopulation (>10 cell/μL) was 35 months. Sustained B cell depletion was associated with low rates of relapse during long-term follow up: at 1, 3 and 5 years, 96%, 84% and 75%, of patients, respectively, were in sustained remission. The serious infection rate was 0.4/yr and 6 patients developed hypoIgG. Renal survival was 72%, 64%, 64% at 1, 3 and 5 years. Overall patient surival was 93%, 79% 79% at the same respective time points.

Conclusions: This combination regimen was an effective remission-induction strategy in severe AAV. Long-term relapse rates and renal and patient survival were favourable in a cohort of patients presenting with life-threatening disease manifestations. Combination regimens warrant further investigation in severe AAV.

SA-PO262

ATwo-CentreCohortExperienceofAnti-GBMDisease MarilinaAntonelou,[2] Benjamin A. Oliveira,[2] Astrid Baumann,[1] Mark Blunden,[3] Mark Harber.[2] *[1]Royal Free Hospital, London, United Kingdom; [2]UCL centre for Nephrology, London, United Kingdom; [3]Royal London Hospital, London, United Kingdom.*

Background: The important determinant for the response of therapy and long term prognosis in anti-glomerular basement membrane (GBM) disease is early diagnosis. The aim of this study is to identify possible delays in the recognition and treatment of the disease and determine renal outcomes.

Methods: Retrospective review of cases of all patients identified as anti-GBM positive presenting in two tertiary referral centres and associated district hospitals between 1978 and 2016. Case notes, pathology archives and laboratory results were reviewed to collect demographic and clinical data at presentation and last follow-up.

Results: Forty nine patients presented across both sites with anti-GBM disease (28 at the Royal Free and 21 at the Royal London Hospital), 17 (34.7%) of which initially presented to a district hospital prior to transfer. Twenty five (51%) were male. Their median age was 58 (10-82) years and GBM titre 134(31-779) U/ml. Thirty (61%) had a renal biopsy. Seven (14%) had pulmonary haemorrhage at presentation. Figure1 shows different time interval points where delays can occur from presentation to treatment. The median follow up was 4 (0.5-37.9) years. 70% became dialysis dependent within a month of presentation. At last follow-up (n=41), 12(29.3%) were renal replacement therapy (RRT) dependent, 12(29.3%) had received a renal transplant and three (7.3%) were RRT independent. Fourteen (34,1%) patients died.

Conclusions: Patients with (GBM) disease are at increased risk of morbidity and mortality. Local review of clinical practice is crucial to avoid delays in establishing a diagnosis and initiating treatment.

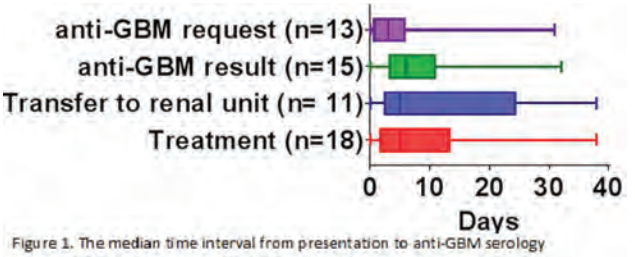


Figure 1. The median time interval from presentation to anti-GBM serology request 3(0.5-6) days, result 6(3-11)days, transfer to a tertiary unit 5(2-24) days and treatment 5(1.5-13.5) days.

SA-PO263

Describing the Natural History of C3 Glomerulopathy Chloe E. Gumpert,[1,2] Richard J. Smith,[2,3] Carla M. Nester.[2,3] *[1]University of Iowa Carver College of Medicine, Iowa City, IA; [2]Molecular Otolaryngology and Renal Research Laboratories, University of Iowa, Iowa City, IA; [3]Rare Renal Disease Clinic, Department of Pediatrics and Internal Medicine, University of Iowa, Iowa City, IA.*

Background: C3 glomerulopathy (C3G) is a rare, aggressive form of complement-mediated glomerular disease that carries the highest risk for irreversible renal failure of the known glomerular diseases. This dismal outlook results not only from a poor understanding of the natural history of disease (i.e. both what marks disease activity and what constitutes treatable disease), but also from the lack of disease-directed therapeutics. We have recently expanded the clinical data capture for our research subjects, and now include all patients with C3G seen in the University of Iowa's Rare Renal Disease Clinic. The following is the initial clinical cohort.

Methods: Data are derived from the clinic records of a contemporary cohort of 36 patients with a biopsy-proven diagnosis of C3G who have at least 1 year of clinical follow-up. Data are reported (without censoring for broader pathology characteristics) from time of presentation and at last follow-up.

Results: 29 C3GN and 7 DDD patients met criteria for evaluation. There was no difference in C3 at presentation or follow-up between the two disease types. No statistically significant difference was noted in eGFR at presentation. At last follow-up, 38% and 57% of C3GN and DDD patients respectively were at CKD Stage 3 or greater. DDD patients were more likely to progress to transplant.

Conclusions: C3GN and DDD are clinically similar, aggressive diseases with high risk for progression to late stage CKD. Routine clinical parameters and biomarkers of disease do not distinguish the two groups. Expansion of the cohort size and longitudinal re-evaluation is ongoing. Analyses of pathology and expanded biomarkers are ongoing. We expect this data will be critical for devising effective treatments for this group of patients.

Funding: NIDDK Support

Table 1. Clinical and biological data according to histological type

	C3GN (n=29)	DDD (n=7)	p value (α=0.05)
At Time of Disease Onset			
Serum Cr (mg/dL)	1.5	1.6	0.80
eGFR (mL/min/1.73m^2)	54.3	52.0	0.76
Serum C3 (mg/dL)	50.3	66.7	0.62
At Time of Last Follow-Up			
Mean Follow-Up (yrs)	4.6	3.8	0.97
Serum Cr (mg/dL)	2.7	3.7	0.61
eGFR (mL/min/1.73m^2)	53.4	46.5	0.91
≥ Stage 3 CKD	11 (38%)	4 (57%)	0.48
Serum C3 (mg/dL)	75.9	79.6	0.92
% Transplant	10.7	42.9	0.04
% Transplant Recurrence	0	14.3	0.04

SA-PO264

Overlap of C3 Glomerulonephritis and Thrombotic Microangiopathy Aishwarya Ravindran, Fernando C. Fervenza, Sanjeev Sethi. *Mayo Clinic, Rochester, MN.*

Background: Dysregulation of the alternate pathway (AP) of complement underlies the pathogenesis of both C3 glomerulonephritis (C3GN) and thrombotic microangiopathies (aHUS/TMA). In this study, we describe both the disease entities occurring in a series of 5 patients.

Methods: We identified 114 patients seen at the Mayo Clinic from 2007-2016 with a diagnosis of C3 glomerulopathy (C3GN or DDD) in native kidney biopsies. Patients with tissue diagnosis of thrombotic microangiopathy along with C3G were included.

Results: The median age at diagnosis was 58 years (range: 28-69), all were male. The median serum creatinine and proteinuria at presentation were 2.2 mg/dL (range: 1.7-3.2) and 2089 mg/24 hours (range: 250-5220). Monoclonal protein was present in 1 of the 3 patients tested. None of the patients had a history of infection or autoimmune disease. Light microscopy showed a membranoproliferative GN in 3 patients and a mesangioproliferative GN in 2 patients. Immunofluorescence showed bright C3 staining in the mesangium and/or capillary walls. On electron microscopy, capillary loops showed marked subendothelial expansion by fluffy material (and absence of deposits in these loops). However, capillary wall deposits were present in other loops in 4 (80%) of 5 biopsies. Mesangial deposits were present in all the biopsies. Ultrastructural features of DDD were not present; thus all biopsies were consistent with C3GN and aHUS/TMA. Complement studies showed low C3 in 4 (80%) patients, low C4 in 2 (40%) patients. Genetic evaluation of the AP showed positive CFH mutation and polymorphisms of CFB/CFH/CFHR5 genes in 1 patient tested. One patient had normal ADAMTS13, others were not tested. Of the 5 patients, 1 recieved steroid only; 1 received steroid and mycophenolate mofetil; 1 received therapeutic plasma exchange, steroid, eculizumab, cyclophosphamide; 1 was managed conservatively, and 1 was recommended therapeutic plasma exchange but lost to follow-up. At a median final follow-up of 18.3 months (range: 4-47.2), 1 progressed to ESRD, and for the remaining, the median creatinine and proteinuria were 2.5 mg/dL (range:1.4-3.6) and 1169 mg/24 hours (range: 947-2172), respectively.

Conclusions: We describe the clinicopathological features and renal outcomes of patients with features of both C3GN and aHUS/TMA. Dysregulation of the AP of complement can result in either C3GN, aHUS/TMA, or overlapping C3GN/aHUS.

SA-PO265

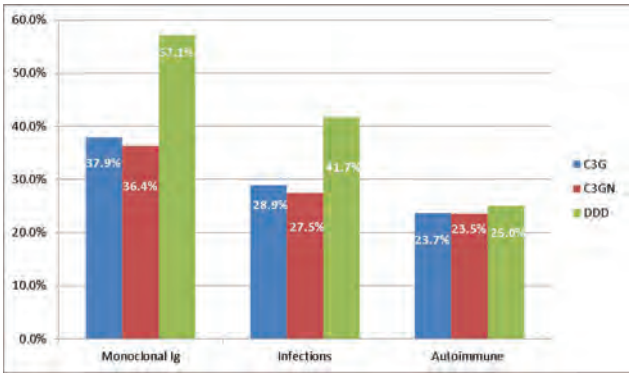
Triggering Factors and Associated Conditions in C3 Glomerulopathy Aishwarya Ravindran, Fernando C. Fervenza, Sanjeev Sethi. *Mayo Clinic, Rochester, MN.*

Background: C3 glomerulopathy (C3G), comprising C3 glomerulonephritis (C3GN) and dense deposit disease (DDD), is characterized by glomerular accumulation of complement proteins due to over activation of the alternative pathway of complement. Most of the reports on C3G are based on individual cases or small series of C3GN/DDD patients. There are no large scale studies describing the triggers/acquired conditions associated with C3G.

Methods: We identified 114 patients seen at the Mayo Clinic from 2007-2016 with a diagnosis of C3G, of which 102 (89.5%) had C3GN and 12 (10.5%) had DDD.

Results: Our study revealed 3 main triggers/acquired conditions associated with C3G: monoclonal Ig, infections and autoimmune diseases (figure 1). 1) Ninety five (83.3%) of the 114 patients were evaluated for a monoclonal Ig. Overall, 36 (37.9%) had a monoclonal Ig; furthermore 28 (65.1%) patient's ≥ 50 years had a monoclonal Ig. Twenty-six patients were classified as MGUS/MGRS, 5 as multiple myeloma, 2 as smoldering myeloma, 1 as CLL, 2 with cryoglobulins of which one was associated with lymphoma of the stomach. 2) Thirty-three (28.9%) patients had a history of infection at the time of diagnosis, with upper respiratory tract infection as the most common infection associated with C3G. Post-infectious GN was ruled out as these patients continued to have persistent hematuria long after resolution of the infection. 3). Twenty-seven (23.7%) patients had history of autoimmune diseases. The most common findings of autoimmunity was a positive ANA in 12 (12.2%), positive dsDNA in 6 (8.2%) and positive antiphospholipid antibody in 3 (4.1%) patients.

Conclusions: Triggering factors and acquired conditions are commonly present and can be the principal drivers of C3G. Each case should be evaluated for these conditions as these disorders can be important therapeutic targets in the management of C3G.



SA-PO266

The Cure Glomerulonephropathy (CureGN) IgA Nephropathy and IgA Vasculitis Cohort David T. Selewski,[13] Josephine M. Ambruzs,[2] Gerald B. Appel,[5] Andrew S. Bomback,[4] Daniel C. Cattran,[10] Melissa Fava,[1] Brenda W. Gillespie,[13] Margaret Helmuth,[1] Jonathan J. Hogan,[6] Bruce A. Julian,[12] Richard A. Lafayette,[8] Patrick H. Nachman,[14] Cynthia C. Nast,[3] Jan Novak,[12] Michelle M. O'Shaughnessy,[9] Matthew Palmer,[15] Heather N. Reich,[10] Dana Rizk,[11] Bruce M. Robinson,[1] Neil S. Sanghani,[16] Melissa Sexton,[1] John Sperati,[7] Jarcy Zee,[1] Krzysztof Kiryluk.[4] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]Arkana Laboratories, Little Rock, AR; [3]Cedars-Sinai Medical Center, Los Angeles, CA; [4]Columbia University, New York, NY; [5]Columbia University College of Physicians and Surgeons, Scarsdale, NY; [6]Hospital of the University of Pennsylvania, Philadelphia, PA; [7]Johns Hopkins University School of Medicine, Baltimore, MD; [8]Stanford University, Stanford, CA; [9]Stanford University Medical Center, Palo Alto, CA; [10]Toronto General Hospital, Toronto, ON, Canada; [11]University of Alabama, Birmingham, AL; [12]University of Alabama at Birmingham, Birmingham, AL; [13]University of Michigan, Ann Arbor, MI; [14]University of North Carolina School of Medicine, Chapel Hill, NC; [15]University of Pennsylvania, Philadelphia, PA; [16]Vanderbilt Nephrology, Nashville, TN. Group/Team: On behalf of the CureGN IgA writing group.*

Background: Cure Glomerulonephropathy (CureGN) is a multi-center(66 sites), NIDDK-funded longitudinal observational cohort study of 2400 prevalent (biopsy within 5 years) patients with minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, and IgA nephropathy (IgAN), including IgA vasculitis (IgAV, previously referred to as Henoch-Schonlein Purpura). We present enrollment data for the fully enrolled IgAN/IgAV cohort comparing children and adults.

Methods: Study data of 590 patients with biopsy confirmed IgAN or IgAV were reviewed. Lab and treatment data up to the time of enrollment are shown using descriptive statistics and univariate tests. We analyzed data to compare adults and children with IgAN and IgAV. Data are presented as median(IQR) and N(%).

Results: A total of 590 patients (355 adult and 235 pediatric) are in the IgAN/IgAV cohort. A comparison of adult to pediatric patients with IgAN and IgAV is in Table 1. Adults had lower eGFR at both time-points and lower enrollment albumin. For IgAN, adults had more proteinuria at both time-points. Patients with IgAV received more immunosuppression (83%v53%, p<0.001) and corticosteroids (81%v50%, p<0.001). 30% of children and 28% of adults with IgAV received either cyclophosphamide or mycophenolate mofetil.

Conclusions: This study reveals significant differences in the disease presentation and early disease course between children and adults with IgAV and IgAN. Furthermore, there were significant differences in treatments between IgAV and IgAN. This is the largest North American prospective IgAN/IgAV cohort initiated to date and will serve as an important resource to answer pathobiology questions in the future.

Funding: NIDDK Support

	IgAN (N=452)			IgAV (N=138)		
	Peds (N=143)	Adult (N=309)	p-value	Peds (N=92)	Adult (N=46)	p-value
Age at diagnosis (yrs)	11.9 (9.0-14.6)	38.6 (29.3-50.0)	<.001	8.9 (6.5-13.5)	35.0 (25.8-46.5)	<.001
Disease duration (yrs)	1.8 (0.3-2.8)	1.1 (0.3-3.3)	0.823	0.7 (0.2-1.5)	0.8 (0.2-2.0)	0.518
Sex: Male	88 (62%)	187 (61%)	0.836	57 (62%)	26 (57%)	0.539
Race: White	117 (82%)	223 (72%)	0.063	81 (88%)	37 (80%)	0.162
At Biopsy						
Urine P:C	0.8 (0.3-2.4)	1.5 (0.8-3.1)	<.001	1.9 (0.6-4.9)	1.3 (0.6-2.2)	0.159
Serum albumin (g/dL)	3.8 (3.3-4.1)	4.1 (3.6-4.7)	<.001	3.4 (3.0-3.8)	3.7 (3.2-4.3)	0.043
eGFR (mL/min/1.73m²)	100.1 (79.6-122.1)	51.8 (36.7-87.2)	<.001	108.1 (79.7-124.1)	64.5 (34.2-105.4)	<.001
At Enrollment						
Urine P:C	0.8 (0.1-0.9)	1.2 (0.4-2.1)	<.001	0.5 (0.2-1.5)	1.2 (0.4-1.9)	0.099
Serum albumin (g/dL)	4.1 (3.8-4.4)	4.0 (3.7-4.3)	0.268	3.9 (3.3-4.3)	4.0 (3.6-4.2)	0.425
eGFR (mL/min/1.73m²)	102.2 (85.2-124.7)	50.9 (33.5-84.4)	<.001	113.4 (96.5-125.8)	81.6 (47.5-111.2)	<.001
Monthly average change in eGFR between biopsy and enrollment	0.0 (-0.7-0.8)	-0.1 (-0.6-0.1)	0.085	0.0 (-0.5-2.2)	0.2 (0.0-1.4)	0.518
Treatment prior to enrollment						
Number of Immunosup. meds	1 (0-1)	1 (0-1)	0.916	1 (1-2)	1 (1-2)	0.946
Any immunosup. exposure	72 (50.3%)	166 (54%)	0.504	74 (80%)	41 (89%)	0.196
Cyclophosphamide	5 (4%)	13 (4%)	0.719	5 (5%)	8 (17%)	0.023
Mycophenolate Mofetil	22 (15%)	33 (11%)	0.155	23 (25%)	5 (11%)	0.052
Corticosteroid	67 (47%)	157 (51%)	0.434	72 (78%)	40 (87%)	0.218

Median (IQR) or N(%), Urine P:C=Urine Protein to Creatinine Ratio

Table 1: Comparison of IgA Nephropathy and igA Vasculitis between Children and Adults

SA-PO267

Routine Urinalysis Does Not Correlate with Kidney Pathology in IgA Nephropathy after Steroid Therapy Hyaejin Yun,[3] Byoung-Soo Cho,[2] Sung min Jung,[2] Wang kwang Hong,[4] Daeyoung Kim,[5] Sung-gyu Ha,[1] Haengil Ko.[1] *[1]MIRAE ING Kidney Center, Seoul, Republic of Korea; [2]Mirae Kidney Center, Seoul, Republic of Korea; [3]MIRAE ING kidney center, Seoul, Republic of Korea; [4]ByulE plastic surgery, Seoul, Republic of Korea; [5]n-biotek, Seoul, Republic of Korea.*

Background: Routine urinalysis, especially hematuria and proteinuria, has long been used as the most important laboratory tools in the diagnosis of glomerulonephritis and also widely adopted as a screening tool for kidney problems at school screening or health checking program. Recently other newly developed markers for kidney injury, such as cystatin-c, KIM-1, L-FABP, NGAL etc., were developed but not routinely used because lack of accumulated convincing data as yet.

Methods: We performed follow up kidney biopsy who showed normal urinalysis and serum cystatin-c for more than 3 months after steroid therapy to check the kidney status in 25 patients with IgA nephropathy. All 25 patients took longterm steroid therapy more than 6 months. Mean age was 28.1 years old. Mean follow up biopsy interval was 13.3 months. All kidney biopsy were performed at the OPD level without admission. We used ACE-Cut disposable biopsy needle under the ultrasound guide(LOGIQ E9).

Results: All 25cases showed abnormal urinalysis such as persistent hematuria, persistent proteinuria or associated with hematuria and proteinuria at initial kidney biopsy, and showed persistent normal urinalysis findings include hematuria and proteinuria more than 3 months at the time of follow up renal biopsy. Twenty cases showed persistent original diseases although slight to moderate degree pathological improvement. However only 5 cases progressed renal pathologies at the time of follow up biopsy. Among five pathologically progressed cases, 3 cases showed improvement of urinalysis findings and urine protein to creatinine ratio.

Conclusions: Although further studies are needed, anyone who showed segmental or global sclerosis, when associated with moderate to severe tubular atrophy and interstitial fibrosis at initial kidney biopsy, follow up kidney biopsy is mandatory even showed persistent normal urinalysis and lab findings before finishing steroid therapy.

SA-PO268

The Cure Glomerulonephropathy (CureGN) IgA Nephropathy and IgA Vasculitis Pediatric Cohort David T. Selewski,[20] Raed Bou Matar,[17] Yi Cai,[12] Aftab S. Chishti,[19] Vivette D. D'Agati,[8] Cynthia J. D'Alessandri-Silva,[9] Rasheed A. Gbadegesin,[10] Debbie S. Gipson,[20] Margaret Helmuth,[4] Sandra Iragorri,[17] Myda Khalid,[13] Helen Liapis,[5] Francesca Lugani,[11] Sherene Mason,[9] Carla M. Nester,[18] Damien G. Noone,[3] Michelle N. Rheault,[21] Rajasree Sreedharan,[15] Tarak Srivastava,[7] Agnieszka Swiatecka-Urban,[6] Katherine Twombley,[16] Tetyana L. Vasylyeva,[17] Donald J. Weaver,[14] Hong Yin,[1] Krzysztof Kiryluk.[2] *[1]Childrens Health Care of Atlanta, Atlanta, GA; [2]Columbia University, New York, NY; [3]The Hospital for Sick Children, Toronto, ON, Canada; [4]Arbor Research Collaborative for Health, Ann Arbor, MI; [5]Arkana Laboratories, Munich, Germany; [6]Children's Hospital of Pittsburgh of UMPC, Pittsburgh, PA; [7]Childrens's Mercy Hospital, Kansas City, MO; [8]Columbia University College of Physicians and Surgeons, New York, NY; [9]Connecticut Children's Medical Center, Hartford, CT; [10]Duke University Medical Center, Durham, NC; [11]G.Gaslini Children's Hospital, Genova, Italy; [12]Helen DeVos Children's Hospital, Grand Rapids, MI; [13]Indiana University, Indianapolis, IN; [14]Levine Children's Hospital at Carolinas Medical Center, Charlotte, NC; [15]Medical College of Wisconsin, Wauwatosa, WI; [16]Medical University of South Carolina, Charleston, SC; [17]Cleveland, OH; [18]University of Iowa, Iowa City, IA; [19]University of Kentucky, Lexington, KY; [20]University of Michigan, Ann Arbor, MI; [21]University of Minnesota, Minneapolis, MN. Group/Team: On behalf of the CureGN IgA writing group.*

Background: Cure Glomerulonephropathy (CureGN) is a multi-center(66 sites), NIDDK-funded longitudinal observational cohort study of 2400 prevalent (biopsy within 5 years) patients with minimal change disease, focal segmental glomerulosclerosis, membranous nephropathy, and IgA nephropathy (IgAN), including IgA vasculitis (IgAV, previously referred to as Henoch-Schonlein Purpura). The IgAN/IgAV cohort has recently filled and we present the enrollment data for pediatric IgAN and IgAV.

Methods: Data for all pediatric patients (<18 years) with biopsy confirmed IgAN or IgAV were reviewed. This analysis compares those with IgAN and IgAV. Data (lab, treatment) up to the time of enrollment are shown using descriptive statistics and univariate tests with results as median(IQR) or N(%).

Results: 590 patients are enrolled in the IgAN/IgAV cohort including 235 pediatric patients (143 (61%) IgAN and 92 (39%) IgAV). A comparison of IgAN and IgAV is presented in Table 1. Those with IgAV differed significantly in age at diagnosis, disease duration, proteinuria at biopsy, and serum albumin at biopsy. Those with IgAV were significantly more likely than those with IgAN to receive immunosuppression and corticosteroids (Table 1).

Conclusions: This study reveals significant differences in the demographics, disease presentation and treatments in children with IgAV and IgAN. Participants will now be followed longitudinally as part of CureGN to further define disease characteristics such as disease progression, pathophysiology and response to therapy.

Funding: NIDDK Support

	All (N=235)	IgAN (N=143)	IgAV (N=92)	p-value
Age at diagnosis(yrs)	11.0 (7.8-14.2)	11.9 (9.0-14.6)	8.9 (6.5-13.5)	0.001
Disease duration(yrs)	1.3 (0.3-2.8)	1.3 (0.3-2.8)	0.7 (0.2-1.5)	0.003
Sex:Male N(%)	145 (61.7%)	88 (61.5%)	57 (62%)	0.949
Race:White N(%)	198 (84.3%)	117 (81.8%)	81 (88%)	0.106
At Biopsy				
Urine P:C	1.4 (0.3-3.3)	0.8 (0.3-2.4)	1.9 (0.6-4.9)	0.005
Serum albumin(g/dL)	3.7 (3.1-4.0)	3.8 (3.3-4.1)	3.4 (3.0-3.8)	0.003
eGFR(mL/min/1.73m^2)	104.1 (79.6-123.9)	100.1 (79.6-122.1)	108.1 (79.7-124.1)	0.434
At Enrollment				
Urine P:C	0.4 (0.2-1.1)	0.3 (0.1-0.9)	0.5 (0.2-1.5)	0.048
Serum albumin (g/dL)	4.0 (3.6-4.3)	4.1 (3.8-4.4)	3.9 (3.3-4.3)	0.022
eGFR(mL/min/1.73m^2)	107.6 (87.2-124.8)	102.2 (85.2-124.7)	113.4 (96.5-125.8)	0.020
Monthly average change in eGFR between biopsy and enrollment	0.0 (-0.6-1.0)	0.0 (-0.7-0.8)	0.0 (-0.5-2.2)	0.160
Treatment Prior to Enrollment				
Number of immunosup. meds	1 (0,1)	1 (0,1)	1 (1,2)	0.001
Any immunosup. exposure N(%)	146 (62.1%)	72 (50.3%)	74 (80.4%)	<.001
Cyclophosphamide N(%)	10 (4.3%)	5 (3.5%)	5 (5.4%)	0.473
Imuran N(%)	15 (6.4%)	5 (3.5%)	10 (10.9%)	0.024
MMF N(%)	45 (19.1%)	22 (15.4%)	23 (25%)	0.068
Steroid N(%)	139 (59.1%)	67 (46.9%)	72 (78.3%)	<.001

Median (IQR) unless otherwise noted, Urine P:C=Urine Protein to Creatinine Ration, MMF=Mycophenolate Mofetil

Table 1: Comparison of Pediatric IgAV and IgAN

SA-PO269

Occurrence of IgA Nephropathy with Lupus Nephritis Ana Malvar,[3] Valeria G. Alberton,[4] Bruno J. Lococo,[5] Renzo Tais,[1] Matias Ferrari,[1] Pamela Delgado,[1] Angelica Sarabia,[1] Brad H. Rovin.[2] *[1]Fernandez Hospital, Buenos Aires, Argentina; [2]Ohio State University Wexner Medical Center, Columbus, OH; [3]HOSPITAL FERNANDEZ, Buenos Aires, Argentina; [4]hospital Fernandez, Buenos Aires, Argentina; [5]DIAVERUN, Buenos Aires, Argentina.*

Background: IgA nephropathy (IgAN) without lupus nephritis (LN) has been seen in a small number of patients with SLE who developed proteinuria. The coincident occurrence of IgAN and LN has not been previously reported. We describe 5 patients with LN who had prominent mesangial IgA deposits that persisted after induction therapy for LN resulted in resolution of the other immune complexes.

Methods: A cohort of 131 proliferative LN patients had a kidney biopsy for diagnosis (Bx1) and again after induction with steroids plus MMF or cyclophosphamide (Bx2). Mean follow up was 42 ±7 months.

Results: Five patients (4 females; average age 38) were found to have dominant IgA deposits before and after induction therapy for LN. LN class, immunofluorescence pattern, serum creatinine (Scr), and 24-hour proteinuria (prot) are described in the table. At Bx2 20% of IgA-dominant patients achieved a complete renal remission (prot ≤ 0.5g/d; normal SCr mg/dl) compared to 41% of the whole cohort. CKD developed in 60% of the IgA-dominant patients and 20% of the whole cohort after 4 years of follow-up.

Conclusions: We identified a small subset of patients with proliferative LN who simultaneously appeared to have IgAN. This subset of patients did not appear to do as well as with induction therapy or during long-term follow-up of a contemporaneous cohort of proliferative LN patients

subject	Bx1 class	Bx1 IgA/G/M	Bx1 C1q/C3	Bx1 Scr/prot	Bx2 igA/G/M	Bx2 C1q/C3	Bx2 Scr/prot
1	3	3/3/2	2/1	0.7/3.5	3/1/2	0/0	0.6/0.7
2	4	3/3/0	2/2	2.2/5	3/1/0	0/2	1.3/0.8
3	3	3/1/3	2/1	0.9/4.3	3/1/0	0/1	0.8/0.2
4	4	3/3/2	1/2	1.2/6.5	3/0/0	0/0	1.2/1.1
5	3	3/3/2	2/2	1.3/4	3/0/0	0/2	1.5/1.4

SA-PO270

Chronic HBV Infection Was Associated with Failure to Complete Remission of IgA Nephropathy Haiting Wu,[2] Zhen Wu,[1] Yubing Wen,[2] Jianfang Cai,[2] Hang Li,[2] Xuemei Li,[2] Xuewang Li.[2] *[1]Beijing Frendship Hospital, Capital Medical University, Beijing, China; [2]Peking Union Medical College Hospital, Chinese Academy of Medicine Sciences & Peking Union Medical College, Beijing, China.*

Background: Chronic HBV infection is associated with Glomerulopathies including IgA nephropathy. We conducted a retrospective study to investigate the association between chronic HBV infection and remission of IgA nephropathy.

Methods: In this retrospective cohort, 715 patients with biopsy-proved IgA nephropathy were included, of whom 95 were diagnosed as chronic hepatitis B virus (HBV) infection defined as persistent positivity of hepatitis B virus surface antigen. Data on age, sex, body mass index, presence of hypertension and diabetes mellitus, laboratory tests prior to treatment, and therapeutic regimens were retrospectively retrieved from medical records. Complete remission (CR) was defined as a 24-hour urinary protein <0.3g with a stable estimated glomerular filtration rate (eGFR). Multiple logistic regression analysis was used to estimate the association of HBV infection with CR and a 30% decline in eGFR.

Results: Patients with chronic HBV infection were younger (27.31±35.64 vs 35.64±11.51, P=0.005) and more likely to present heavier proteinuria (3.02±3.44, 2.02±2.18g P < 0.001) and avoid using immunosuppressive agents (10.52%, 58.57%, P < 0.001) as compared with those free of chronic HBV infection. However, the two groups did not differ in baseline eGFR, presence of hypertension and diabetes, administration of RAAS inhibitors and glucocorticoids. In one-year follow-up, HBV infection was associated with failure to CR in proteinuria (OR [95% CI], 2.10 [1.173-3.758], P=0.013),

but not with a 30% decline in eGFR(OR [95% CI], OR 1.192 [0.438-3.249], P=0.731), independently of gender, age, diabetes, hypertension, baseline eGFR, 24-hour urinary protein, use of glucocorticoids, immunosuppressive agents and RAAS inhibitors.

Conclusions: Chronic HBV infection may be associatited with failure to complete remission of IgA nephropathy.

SA-PO271

The Derivation and Validation of an International Multi-Ethnic Risk Prediction Model in IgA Nephropathy Sean Barbour,[6] Rosanna Coppo,[2] Yusuke Suzuki,[3] Zhi-Hong Liu,[4] Gabriela Espino-Hernandez,[1] Heather N. Reich,[5] Daniel C. Cattran.[5] *[1]BC Renal Agency, Vancouver, BC, Canada; [2]Torino, Italy; [3]Juntendo University, Tokyo, Japan; [4]Nanjing University, Nanjing, China; [5]University of Toronto, Toronto, ON, Canada; [6]University of BC, Vancouver, BC, Canada. Group/Team: International IgAN Collaboration.*

Background: Predicting renal outcome in IgA nephropathy (IgAN) is challenging. A prediction model is needed to improve risk stratification that is properly validated in multiple ethnic groups worldwide and can be used in clinical practice. To overcome these obstacles, we used large datasets from international collaborators to generate an accurate prediction model in IgAN.

Methods: The derivation dataset was from European, Japanese and Chinese adult cohorts; the validation dataset was from separate North/South American, European, Chinese and Japanese cohorts. Time from biopsy to the composite outcome (50% decline in eGFR or ESRD) was analyzed using Cox survival models.

Results: The validation dataset (N=2784) is 42% Caucasian, 21% Japanese and 37% Chinese; 18% (N=495) experienced the composite outcome over a median 4.8 years of follow-up. Two models were considered: a reduced model containing eGFR, blood pressure, proteinuria at biopsy, and MEST score; and a full model that also contained age, sex, race, use of RAS blockade/immunosuppression, and crescents. Compared to the reduced model, the full model had improved prediction with better AIC (5679 vs 5648), R^2 (19 vs 21%), ΔC-statistic (0.01, 95%CI 0.008-0.03), continuous NRI (0.17, 95%CI 0.11-0.27) and IDI (0.03, 95%CI 0.01-0.05), with similar calibration curves. We will next externally validate the full model in the validation dataset (N=1401), and convert the model into web and mobile app calculators for implementation in clinical practice.

Conclusions: Using the largest and most diverse datasets to date in IgAN, we will generate the first risk prediction tool that is externally validated in multiple ethnic groups worldwide and can be easily implemented in clinical practice using web/app-based calculators. We expect the prediction model will become the international standard for risk stratification in IgAN, and will facilitate both clinical trial recruitment of high-risk patients and testing the added prediction benefit of novel biomarkers.

SA-PO272

Short-Term Anti-Proteinuric Effect of Tacrolimus Is Not Related to Preservation of Glomerular Filtration Rate during 5 Year-Follow Up Period in IgA Nephropathy Mi-yeon Yu,[1] Yong Chul Kim,[1] Ho Jun Chin.[2] *[1]Seoul national university hospital, Seoul, Republic of Korea; [2]Seoul National University Bundang Hospital, Seong nam, Republic of Korea.*

Background: It has been known that tacrolimus reduced proteinuria in IgA nephropathy for a short period of time. We investigate persistent effects of proteinuria reduction and improvement of kidney function after discontinuation of the tacrolimus administration.

Methods: Patients with biopsy-proven IgA nephropathy were randomly selected for two treatment groups and control groups for each group; 1) patients treated with tacrolimus (Tac group) and 2) a placebo group (placebo group) with stratification by using a renin angiotensin system blocker. The Tac group was treated up to 16 weeks and then stopped administration of tacrolimus at the final visit (trial phase). We tracked patients at 12-, 24-, 52-, and 240-week (observational phase). The primary outcome was the percentage change of time-averaged proteinuria (TA-proteinuria; g/g cr) and estimated glomerular filtration rate (eGFR) between the trial and observational phases. The TA-proteinuria was defined as the average of urine protein to creatinine ratio (UPCR) measured every three month during the two phases.

Results: Significant reduction of UPCR was observed in the Tac group compared to its control group at 4-week and 8-week visits during the trial phase (p=0.023 and p=0.003, respectively). The difference between Tac and its control group was not evident at the other periods, estimated by repeated measured ANOVA. The percent change of TA-proteinuria in the Tac group was more than the control group (116 ± 96 % vs. 63 ± 239 %, p=0.004). Therefore the TA-proteinuria during the observational phase was not significantly different between the Tac and control groups (1.150 ± 0.733 g/g cr vs. 1.455 ± 2.017 g/g cr, p=0.775). The levels of eGFR throughout the observational phase were not significantly different between the two groups. Furthermore, the mean rate of eGFR change during the whole phase was -6.4 ml/min/1.73 m2/year in the control group and -5.4 ml/min/1.73 m2/year in the Tac group (p=0.988).

Conclusions: The anti-proteinuric effect of tacrolimus was promptly reversed 3 months after discontinuing the drug. The use of tacrolimus for a short period of time for the patients with IgA nephropathy temporarily reduces proteinuria, but ultimately, there is no long-term efficacy such as reduction of proteinuria and improvement of renal function.

SA-PO273

The Effects of Renin Angiotensin Aldosterone System Inhibitors (RASI) for IgA Nephropathy (IgAN) Patients with Oxford T1/2 Lesions Takahiro Kamiyama,[2] Takahito Moriyama,[3] Marie Nakano,[4] Kazunori Karasawa,[1] Kosaku Nitta.[3] *[1]Department medicine, Kidney Center, Tokyo Women's Medical University, Tokyo, Japan; [2]Tokyo Women's Medical University, Tokyo-to, Japan; [3]Tokyo Women's Medical University, Tokyo, Japan; [4]Tokyo Women's Medical University Hospital, Tokyo, Japan.*

Background: IgAN has been recognized as a not a benign disease and 40% of patients developed to end-stage renal disease (ESRD) within 20 years. Severe histological findings have been reported as risk factors of IgAN. Global sclerosis was one of the risk factors, and in Oxford classification, it was recognized as same as tubulointerstitial (T) lesions according to their correlation. Therefore, in IgAN patients with T lesions, the glomerular hyperfiltration and hypertension were seemed to be occurred, and, RASI might be effective to decrease them and prevent progressing to ESRD. However, these beneficial effects of RASI on patients with T lesions haven't been previously reported.

Methods: In this retrospective cohort study, from 697 biopsy proven IgAN patients in our institution between 1990 and 2010, we divided 87 patients withT1/2 lesions into two groups: RASI group (n=47, treated with RASI) and control groups treated with antiplatelet agents (APA group, n=40). We analyzed the clinical and histological background, the serial change of blood pressure and the amount of urinary protein (U-Prot), progression to ESRD, and the risk factors for progression after adjusting by propensity score matching.

Results: After adjusting clinical findings with significant difference at base line, 22 cases from each group were selected, and clinical and histological characteristics were similar between both groups The mean eGFR 58.5 vs.57.1 ml/min/1.73^2, and median U-Prot 1.14 vs. 0.95 g/day in RASI and APA group, respectively. Serial change of blood pressure during two years after treatment was significantly decreased in RASI group (p=0.0029), but not in APA group. The serial change of U-prot was tended to decrease in RASI group, though it was not significant (1.14 to 0.47 g/gCre), but it was similar in APA group (0.95 to 0.85 g/gCre). The renal survival rate in Kaplan Meyer Analysis was 60%/20 years in RASI group and 20%/20 years in APA group (p=0.0119). In multivariate Cox regression analysis, RASI was an independent factor to prevent from progression to ESRD (HR 5.91, 95% CI: 1.53-22.8).

Conclusions: RASI has shown significant beneficial effect on histologically advanced IgAN patients with Oxford T1/2 lesions, who were suspected to have glomerular hypertension and hyperfiltration according to severe global sclerosis.

SA-PO274

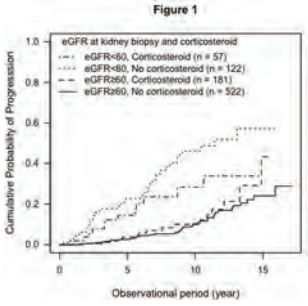
Efficacy of Steroid Therapy for IgA Nephropathy Yasuyuki Nagasawa,[1] Ryohei Yamamoto,[6] Maki Shinzawa,[6] Tatsuya Shoji,[4] Katsuyuki Nagatoya,[5] Terumasa Hayashi,[4] Yukiko Hasuike,[1] Takahiro Kuragano,[3] Atsushi Yamauchi,[5] Toshiki Moriyama,[7] Yoshitaka Isaka,[6] Takeshi Nakanishi.[2] *[1]Hyogo College of Medicine, Nishinomiya, Japan; [2]Hyogo College of Mediicne, Nishinomiya, Japan; [3]Internal Medicine Division of Kidney and Dialysis, Nishinomiya, Japan; [4]Osaka General Medical Center, Osaka, Japan; [5]Osaka Rosai Hospital, Sakai-city, Japan; [6]Osaka University Graduate School of Medicine, Suita, Japan; [7]Osaka University Health Care Center, Toyonaka, Japan.*

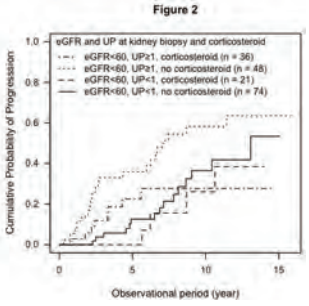
Background: IgA Nephropathy is most common primary glomerular nephritis not only in Asian, but also in Caucasians. Steroid therapy had been established as standard therapy for IgA nephropathy. But, IgA nephropathy patients with low proteinuria and with normal kidney function were known to have good prognosis. In this point, it is not clear that how much proteinuria and how worse eGFR in IgA nephropathy patients required for the steroid therapy. The aim in this study is to evaluate the relationship between eGFR, proteinuria and efficacy of steroid therapy for IgA nephropathy

Methods: Study design. Retrospective cohort study, 882. IgA nephropathy patients at the age more than 18, whose eGFR was more than 15mL/min/1.73m2, who were diagnosed by renal biopsy. Ethical committee in these three hospitals approved for this study. Exposures were eGFR at the renal biopsy, steroid therapy within one year after renal biops. 1.5 time increase of serum creatinine was treated as outcome.

Results: Multiple Poisson model analysis revealed proteinuria (per 1g/day, IRR 1.40 [95%CI 1.26-1.56]), eGFR (per 10 mL/min/1.73m2, 0.72 [0.63-0.83]), steroid therapy(0.15 [0.03-0.66]) were identified as renal progression factors, and there was significant interaction between steroid therapy*eGFR (interaction P=0.035). There was stronger suppression effect upon renal progression by steroid therapy in the IgA patients whose eGFR were less than 60mL/min/1.73m2, than in the IgA patients whose eGFR were more than 60(mL/min/1.73m2 (Figure 1). There was favorable effect by steroid upon renal progression in the IgA patient whose proteinuria was more than 60mL/min/1.73m2 (Figure 2)

Conclusions: There was no significant effect of steroid therapy in IgA nephropathy patients with less than 60 eGFR and more than 0.5g/day proteinuria at least during observation periods (5.6 years). Steroid therapy is effective for IgA nephropathy patients whose eGFR were less than 60 and proteinuria were more than 0.5g/day.





SA-PO275

Renal CD141+ Dendritic Cell Infiltration in IgA Nephropathy Titi Chen,[6,7] Qi Cao,[1] Padmashree Rao,[5,3] Guoping Zheng,[4,1] Yiping Wang,[2] David C. Harris.[3,7] *[1]Centre for Transplant and Renal Research, Westmead Millennium Institute, University of Sydney, Sydney, NSW, Australia; [2]Centre for Transplantation and Renal Research, Westmead Millennium Institute, The University of Sydney, Westmead, NSW, NSW, Australia; [3]Sydney Medical School - University of Sydney, Terrey Hills, NSW, Australia; [4]The University of Sydney, Sydney, NSW, Australia; [5]Westmead Millenium Institute for Medical Research, Parramatta, NSW, Australia; [6]School of Medicine, University of Sydney, Westmead, NSW, Australia; [7]Centre for Transplant and Renal Research, The Westmead Institute for Medical Research, Westmead, NSW, Australia.*

Background: Previous studies have shown that the severity of interstitial inflammatory infiltrates, which include myeloid dendritic cells (DCs), correlates with progression of IgA nephropathy. CD141+ DCs have recently been identified as a unique myeloid DC subset that plays a significant role in the induction and regulation of immunity. This DC subset has been studied in mouse models, but studies in humans are lacking. We aim to investigate the relationship between CD141+ DC infiltration and clinicopathologic features in IgA nephropathy.

Methods: Thirty adult patients with a sole diagnosis of IgA nephropathy were included in this study. Patients were excluded if they had received glucocorticoids or immunosuppressant therapy before renal biopsy. The histological classification was scored according to the Oxford classification. CD141+ DCs were identified through immunofluorescence staining and visualised using confocal microscopy.

Results: In normal human kidney, CD141+DCs were rarely present. Patients with IgA nephropathy had significantly higher number of CD141+ DCs than normal control (P=0.021) and CD141+DCs were mainly present in the interstitium. Higher CD141+ DC density was significantly associated with worse serum creatinine (r=0.81, P=0.015) and proteinuria (r=0.75, P=0.049). Higher CD141+ DC density was also associated with increased severity of tubular atrophy/interstitial fibrosis (P=0.025), but not with mesangial hypercellularity, endocapillary hypercellularity, segmental glomerulosclerosis, or number of crescents.

Conclusions: Our data highlight the close correlation between the density of CD141+ DCs and clinicopathologic features of IgA nephropathy progression. Further studies will be conducted in human samples and murine models to investigate whether CD141+ DCs mediate kidney injury, and the possible mechanisms involved.

SA-PO276

Improvement of Clinical Outcome in Kidney Diseases via the On-line Thai Glomerular Disease Registry: IgA Nephropathy Warangkana Pichaiwong,[3] Ratana Chawanasuntorapoj,[5] Ngoentra Tantranont,[6] Veerapatr Nimkietkajorn,[1] Suchin Worawichawong,[4] Chagriya Kitiyakara.[2] *[1]Buddhachinaraj hospital, Phitsanulok, Thailand; [2]Bangkok, Thailand; [3]RAJAVITHI HOSPITAL, Bangkok, Thailand; [4]Ramathibodi Hospital, Bangkok, Thailand; [5]Medicine, Siriraj Hospital, Bangkok, Thailand; [6]Siriraj Hospital, Mahidol University, Bangkok, Thailand. Group/Team: Thai Glomerular Disease Collaborative Network (TGCN).*

Background: IgA nephroathy (IgAN) is the most common primary glomerular disease leading the end stage renal disease in Thailand. The data on epidemiology of IgA nephropathy (IgAN) in Thailand are limited. The available data came from few medical schools, which might not represent the entire Thai population. The Thai Glomerular Disease Collaborative Network (TGCN) was established to determine the prevalence, clinical characteristics, outcomes and prognosis in Thai glomerular disease patients.

Methods: The data collected prospectively from TGCN included adult patients with biopsy-proven glomerular disease from institutes in Thailand participating in TGCN from July 2014 to March 2017. The clinical and renal pathology characteristics, treatment regimens at the time of renal biopsy were obtained via online data collection forms.

Results: Among 1,556 patients, the most common renal pathology finding in primary glomerular disease was IgAN with prevalence of 13.5%. At baseline, 44.3% of IgAN patients were male, the mean age was 39.4±13 years, median serum creatinine (sCr) was 1.76 mg/dL (0.56-13.2), median urine protein creatinine ratio (UPCR) was 2.63 g/g. Cr (0.02-21.56), and mean serum albumin (sAlb) was 3.6±0.7 g/dL. Nephritis was the most common presentation account for 48.1%. Most of the patients had high initial sCr at the time of biopsy (sCr ≥ 1.2 mg/dL, 77.5%). Clinically, both systolic and diastolic blood pressure at time of biopsy had the significantly high in patients who had serum creatinine ≥ 3 mg/dL compare to < 3 mg/dL (147±18/88±14 *vs*. 136±16/84±12 mmHg, p = 0.001 and p= 0.048). Histologically, an analysis of The Oxford Classification of IgAN, interstitial fibrosis/tubular atrophy (T) > 50% had significantly high in patients who had serum creatinine ≥ 3 mg/dL.

Conclusions: Conclusions: The prevalence of IgAN in our study was 13.5%. Two independent factors of severe manifestation at the time of biopsy were high blood pressure and high score of tubulointerstitial involvement. Further follow-up of clinical outcomes is being investigated.

Funding: Private Foundation Support

SA-PO277

The Beneficial Effect of Tonsillectomy Combined with Steroid Pulse Therapy on IgA Nephropathy Patients with Impaired Renal Function Saeko Kumon,[3] Takahito Moriyama,[2] Takahiro Kamiyama,[1] Marie Nakano,[3] Kosaku Nitta.[2] *[1]Tokyo Women's Medical University, Tokyo-to, Japan; [2]Tokyo Women's Medical University, Tokyo, Japan; [3]Tokyo Women's Medical University Hospital, Tokyo, Japan.*

Background: Tonsilectomy combined with steroid pulse therapy (TSP) has been reported to have beneficial effects on IgA nephropathy (IgAN), and has become a major treatment in Japan. However, it is still controversial whether TSP is effective for IgAN with impaired renal function or not, though the impaired renal function at the time of renal biopsy is still recognized as one of the severe risk factor of IgAN. Therefore, we analyzed the efficacy of TSP in IgAN with impaired renal function.

Methods: In this retrospective analysis, IgAN patients who was diagnosed from January 2006 to May 2015 in our institution, age≧16, >0.5g/day proteinuria and estimated glomerular filtration rate(eGFR) < 60 ml/min/1.73m^2 were divided into the two groups : the patients treated with TSP (TSP group; n=25) and the patients treated with oral prednisolone (oPSL group; n=41). We compared the clinical and histological findings at base line, renal survival rate until 25 % decline of eGFR from base line and progression to end stage renal disease (ESRD), and clinical remission(CR) rate defined as <0.3 g/day proteinuria and <5 urinary red blood cells per high-powered field (HPF) between both groups.

Results: There was no significant difference in clinical and histological findings between both groups (mean eGFR: 44.6 vs. 44.3 mL/min/1.73m^2; p=0.875, median proteinuria: 1.78 vs. 1.37 g/g creatinine; p=0.247, distribution of the amount of hematuria: 2, 11, 1, 13 vs. 3, 13, 5, 4 (<5, 5-20, 21-50, >51/HPF; p=0.097). The renal survival rate, until 25 % reduction from baseline eGFR, and until progression to ESRD was significantly higher in TSP than oPSL group (79.7% vs. 40.4%/9 years; p=0.009, 100.0% vs. 65.4%/9years; p=0.0495, respectively). The remission rate of hematuria was significantly higher in TSP than oPSL group (92.9% vs. 47.1%/4.5years; p<0.0001), though the remission rate of proteinuria was similar between both groups. TSP was the only independent factor to decrease hematuria according to the multivariate Cox regression analysis (OR: 3.10, 95% CI: 1.40-6.77, p=0.006).

Conclusions: TSP was effective for remission of hematuria and long term renal prognosis in IgAN patients with impaired renal function.

SA-PO278

Maintenance of Remission Following Completion of OMS721 Treatment in Patients with IgA Nephropathy (IGAN) Geoffrey A. Block,[1] Steve Whitaker.[2] *[1]Denver Nephrology, Denver, CO; [2]Omeros Corporation, SEATTLE, WA.*

Background: The lectin pathway of complement has been implicated in the pathogenesis of several glomerulopathies including IgAN. OMS721 is a fully human monoclonal antibody that inhibits mannan-associated lectin-binding serine protease-2 (MASP-2), the effector enzyme of the lectin pathway. In a clinical trial, all OMS721-treated patients with IgAN achieved partial remission. These patients were followed after the trial. The duration of remission after OMS721 treatment was assessed.

Methods: The 4 IgAN patients are from an ongoing OMS721 Phase 2 clinical trial. All completed the trial. For inclusion, patients demonstrated 1) biopsy-diagnosed IgAN, 2) uACR > 0.6 g/g, 3) eGFR ≥ 30 mL/min/1.73 m^2, 4) controlled BP on stable ACEI/ARB treatment, and 5) a stable steroid dose ≥ 10 mg prednisone. All patients received OMS721 IV once weekly for 12 weeks. After OMS721 treatment, patients were followed for 6 more weeks in the trial. After trial completion patients have been followed by the investigator. In the trial endpoints were uACR and 24-hour proteinuria. In post-trial follow-up, uPCR was measured. Each uPCR value was converted to uACR by multiplying by 0.64. (Zhao, Clin J Am Soc Nephrol 2016;11:947-55)

Results: All patients achieved partial remission following OMS721 treatment. The mean age of the 3 females and 1 male was 42 years, 3 are Caucasian and one is Asian, the mean eGFR was 41 mL/min/1.73 m^2, and the mean entry steroid dose was 55 mg. Follow-up ranged from 2-9 months after the last OMS721 dose. During the trial the mean uACR decreased 77% (p = 0.026). Three patients maintained partial remission during available follow-up (54%, 79%, and 88% uACR decreases at 12, 12, and 5 months, respectively). One patient had 90% of baseline uACR at 7 months. Three patients also demonstrated improved eGFR by 7, 13, and 7 ml/min/1.73 m^2 during follow-up. The fourth patient's eGFR was stable. All patients discontinued steroids. OMS721 was well tolerated. All adverse events were mild with headache and sinus congestion considered possibly related by the investigator.

Conclusions: Proteinuria significantly decreased in patients with IgAN during the 12-week treatment with OMS721. This reduction in proteinuria was maintained for up to

9 months after treatment completion. These data suggest that OMS721 may be efficacious in the treatment of IgAN and further study is warranted.

SA-PO279

Natural History of IgA Nephropathy and Henoch-Schönlein Purpura Nephritis Benjamin L. Spector, Jason Misurac. *University of Iowa, Iowa City, IA.*

Background: Though histopathologically identical, Henoch-Schönlein purpura nephritis (HSPN) and IgA nephropathy (IgAN) are thought to follow markedly different courses. Despite their relatively high prevalence, limited data exist describing their natural histories.

Methods: This retrospective analysis examines all biopsy-confirmed cases of HSPN (n=22) and IgAN (n=19) at our institution from January 1989 to May 2016 through 1-year of follow-up. Inclusion criteria were diagnosis before age 18 years, minimum 1-year of follow-up, and absence of pre-existing renal disease. We compared demographics, clinical biomarkers, and treatments.

Results: Both cohorts show male predominance. In HSPN, age at diagnosis was younger and renal biopsies showed higher rates of glomerular crescents and endocapillary proliferation. The IgAN cohort presented more often with gross hematuria (31.8% vs 63.2%, p= 0.06), hypertension (HTN), and lower estimated glomerular filtration rate (eGFR). Urine protein/creatinine ratio (UPC) and overall hematuria rates were equivalent between groups. At 1-year follow-up, there were no differences in clinical features or immunosuppressant use.

Conclusions: In HSPN, patients had younger presentation and higher prevalence of crescents and endocapillary proliferation on biopsy. IgAN was more likely to present with HTN, gross hematuria, and lower eGFR. There were no significant differences in clinical biomarkers at 1-year follow-up.

Demographics and clinical features

Item	HSPN	IgAN	P
Median			
Age at diagnosis (years)	8.4	12.4	0.09
eGFR at diagnosis (mL/min)	106	82	0.01
eGFR at 1 year (mL/min)	95	101	0.61
UPC at diagnosis	1.8	1.1	0.58
UPC at 1 year	0.2	0.2	0.75
Proportion (%)			
Male	68.1	89.4	0.14
Hypertension at diagnosis	45.5	26.3	0.33
Hypertension at 1 year	9.1	10.5	1.00
Hematuria at diagnosis	86.4	94.7	0.61
Hematuria at 1 year	36.4	36.8	1.00
Biopsy results (%)			
Mesangial proliferation	81.0	94.7	0.35
Endocapillary proliferation	36.3	5.3	0.02
Segmental sclerosis	52.4	68.4	0.35
Interstitial fibrosis/tubular atrophy	33.3	26.3	0.74
Glomerular crescents	45.5	15.8	0.05

SA-PO280

Is MEST Score a Risk Predictor in Pediatric Henoch-Schönlein Purpura Nephritis? Ashton Chen,[2,1] Dan P. Goldstein,[2] Marcia Voigt,[2] Andrew M. South,[2] Jen-Jar Lin.[3] *[1]Wake Forest Baptist Health, Winston Salem, NC; [2]Wake Forest School of Medicine, Winston Salem, NC; [3]Wake Forest University School of Medicine, Winston-Salem, NC.*

Background: Oxford Classification of IgA nephropathy (IgAN) includes the histologic components: mesangial (M) and endocapillary (E) hypercellularity, segmental sclerosis (S) and interstitial fibrosis or tubular atrophy (T). These have been utilized as the MEST score to predict renal outcome in IgAN. Pathological findings on renal biopsy in IgAN are identical to Henoch-Schönlein purpura nephritis (HSPN), but MEST score has not been validated in HSPN.

Methods: A retrospective chart review was performed from April 1, 2004 to May 31, 2017 at our center, identifying all children referred for HSPN who underwent renal biopsy. Blood pressure (BP), glomerular filtration rate (GFR), and degree of proteinuria were recorded at time of biopsy and compared at last follow-up. Biopsy reports were reviewed and assessed for crescents and MEST score. Treatment with steroids, immunosuppression, and ACEI/ARB was assessed.

Results: Of 49 patients referred for HSPN, n=29 underwent renal biopsy. Of 29 patients, all had spot urine protein/creatinine (u p/c) >0.2, 15 of whom had nephrotic-level proteinuria (u p/c>2.0). All had normal GFR at time of biopsy and 9/29 (31%) had hypertension (HTN). Overall biopsy results showed: crescents (69%), MEST M1 (66%), E1 (69%), S1 (28%), T1 (23%), and T2 (0%). Of patients with HTN: crescents (78%), M1 (78%), E1 (78%), S1 (11%), and T1 (22%). Those with nephrotic-level proteinuria had crescents (73%), M1 (73%), E1 (86%), S1 (13%), and T1 (13%). Patients with 10% or more crescents had higher rate of HTN at presentation (37% vs 20%, p=NS) and nephrotic proteinuria (58% vs 50%, p=NS). Median follow-up was 3.1 years. Patients with M1 vs M0 were more likely to have higher urine p/c at follow-up (p=0.14). Of patients with >10% crescents, 92% received steroids and 79% received immunosuppression. At last follow-up 1 patient had GFR <100mL/min/1.73m2, 2 had pre-HTN, and 5 had proteinuria.

Conclusions: After treatment, renal outcome in pediatric HSPN is favorable even with significant proteinuria and hypertension at presentation. Crescents and MEST score of M1 may be associated with HTN and nephrotic proteinuria at presentation in children. Further studies are needed to validate use of MEST score in pediatric HSPN.

SA-PO281

Long-Term Outcome of Pneumococcal Haemolytic Uraemic Syndrome Aoife Waters.[1,2] *[1]UCL Great Ormond Street Institute of Child Health, LONDON, United Kingdom; [2]Nephrology, Great Ormond Street Hospital NHS Foundation Trust, London, United Kingdom. Group/Team: UK P-HUS Study Group.*

Background: Haemolytic uraemic syndrome [HUS] is defined by microangiopathic haemolytic anaemia [MAHA], thrombocytopaenia and oliguria/elevated creatinine for age clinically manifesting from endothelial cell injury and microvascular thrombosis. Occurring as a rare complication of pneumococcal infection, P-HUS accounts for 5-15% of HUS cases in young children and is characterised by a more severe disease course compared to Shiga-toxin associated HUS[1]. We determined the long-term renal outcome of P-HUS[1] and serotype profile of P-HUS following the introduction of the pneumococcal conjugate vaccines (PCV7 and PCV13) in the UK.

Methods: A case note review of P-HUS was undertaken in 5 participating UK centres. P-HUS was defined as reported [1] and cases were included if followed for at least 5 years' duration. Data pertaining to duration of dialysis at presentation, duration of follow up, estimated GFR at follow up, proteinuria, blood pressure percentile, dialysis requirement and transplantation was collected. Additional information pertaining to mortality and co-morbidties were also collected. Information on pneumococcal serotype in post 2007 cases [following PCV vaccine introduction in UK] was also collected. Research protocols were approved by regional governance teams.

Results: Long-term outcome data was available for 16 of 38 patients who were previously reported[1]. All patients presented with P-HUS between April 1999 and February 2010: Median age at presentation: 10 months (IQR: 8,17), M:F 6:10, (0.6). Median duration of hospitalisation: 37 days (IQR: 23,75 days). Median eGFR 54 mls/min/1.73m^2 (IQR: 25,81) with median duration of follow-up: 10 years (IQR: 8,12). At time of follow up, none were on dialysis but three patients [18%] had received renal transplants without recurrence. Nine patients [56%] patients were on anti-hypertensive treatment at follow up, 7 of whom are on monotherapy [ACEI(5)] and 2 on dual therapy [ACEI with other]. Three patients had persistent proteinuria. Individual data will be presented. Following PCV7 introduction in 2010, the predominant serotype was 3 [previously 19A] and after PCV13 introduction, no cases of P-HUS have been observed since 2012.

Conclusions: Over 60% of P-HUS patients under follow up have chronic kidney disease. Ongoing analysis involving more UK centres is underway including those discharged from care. Reference: 1. Waters et al, J Pediatr. 2007 Aug;151(2):140-4

SA-PO282

Renal Outcomes in Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits Ramnika I. Gumber,[3] Jordana B. Cohen,[3] Matthew Palmer,[2] Laura M. Dember,[3] Brendan M. Weiss,[1] Jonathan J. Hogan.[3] *[1]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [2]Pathology, University of Pennsylvania, Philadelphia, PA; [3]Nephrology, University of Pennsylvania, Philadelphia, PA.*

Background: The natural history and response to therapy of proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is poorly characterized.

Methods: We retrospectively analyzed renal responses of 20 patients with PGNMID evaluated at our center from 2011 though 2016. Patients were stratified by treatment approach: targeted to detected clonal cell type or non-targeted. Renal response was defined as: 1. complete response (CR) if proteinuria decreased to <0.5 grams (per 24h urine collection or urine protein:creatinine ratio<0.5) with return to baseline of serum creatinine (SCr) 2. partial response (PR) if there was ≥50% decrease in proteinuria (and at least <3 grams) with stabilization of SCr.

Results: Median eGFR at presentation was 37 (interquartile range (IQR) 22-56) ml/min/1.73m^2, median proteinuria was 3.7 (IQR 2.5-8.1) grams. A paraprotein was detected in serum or urine in 8 patients and an underlying clone was detected in 7 patients (B cell n=2, plasma cell n=3, lymphoplasmacytic cell n=2); 5 of these patients received clone-directed therapy. All patients with clone-directed therapy had a renal response (CR in 60%); 54% of patients not receiving clone directed therapy had a renal response (CR in 27%). All patients receiving bortezomib-based therapy (n=4) had renal response (CR in 75%); 67% of patients not receiving bortezomib-based therapy (n=12) had renal response (CR in 25%). Among those who responded, median time to any renal response was 98 days in bortezomib-treated patients vs. 190 days in non-bortezomib-treated patients.

Conclusions: All patients with PGNMID who received clone-directed therapy had a renal response. Future studies should explore more sensitive methods for detecting an underlying pathogenic clone to direct treatment. Bortezomib appears promising for these conditions and should be explored further.

Renal response stratified by treatment approach

	Clone-Directed Therapy (N=5)	Non-Clone Directed Therapy (N=11)	No Therapy (N=4)
Complete Response	3 (60%)	3 (27%)	0 (0%)
Partial Response	2 (40%)	3 (27%)	0 (0%)
No Response	0 (0%)	5 (45%)	4 (100%)

SA-PO283

Diversity of Biopsy-Proven Kidney Diseases in Thai Diabetic Patients: Analysis of Thai Glomerular Disease Collaborative Network (TGCN) Veerapatr Nimkietkajorn,[3] Ratana Chawanasuntorapoj,[4] Ngoentra Tantranont,[5] Pornpen Sangthawan,[2] Warangkana Pichaiwong.[1] *[1]Medicine, RAJAVITHI HOSPITAL, Bangkok, Thailand; [2]Medicine, Prince of Songkla University Hospital, Songkhla, Thailand; [3]Medicine, Buddhachinaraj hospital, Phitsanulok, Thailand; [4]Medicine, Siriraj Hospital, Bangkok, Thailand; [5]Pathology, Siriraj Hospital, Mahidol University, Bangkok, Thailand. Group/ Team: Thai Glomerular Disease Collaborative Network (TGCN).*

Background: Diabetic nephropathy (DN) is the leading cause of chronic kidney disease worldwide including Thailand. However, there is also increasing recognized diagnosis of non-diabetic renal diseases (NDRD) in diabetic patients, which may influence in the different treatments and outcomes. This study reported the spectrum and clinical characteristics of NDRD and NDRD superimposed DN in Thai diabetic population.

Methods: Clinical data of the diabetic patients with aged > 18 years undergone kidney biopsy were collected via the nationwide web-based Thai glomerular diseases registry from TGCN during 2014-2017. These data including the demographic data and laboratory data together with kidney biopsy pathological findings.

Results: The 276 from 1,556 patients were recruited in this study; 123 cases were male (44.6%). The mean age was 51.8±years, and the median serum creatinine was 1.99 mg/dL (0.42-13.2). The 114 cases (41.3%) were diagnosed NDRD, while 23 cases (8.3%) were diagnosed NDRD superimposed DN. The rest of the patients were diagnosed isolated diabetic nephropathy; DN (50.4%). FSGS was either the most prevalent glomerular disease in both NDRD (23.7%) and NDRD superimposed DN (34.8%). The second and third kidney biopsy findings in NDRD were lupus nephritis (21.9%), IgA nephropathy (13.2%), respectively. In NDRD superimposed DN, membranous nephropathy (26.1%), and post-infectious glomerulonephritis (21.7%) were the second and third pathological findings. Nephritis was the clinical presentation of NDRD and NDRD superimposed DN approximately 15.8% and 13%, whereas it was not found in DN. Nephrotic syndrome was more common in DN and NDRD superimposed DN than in NDRD (80.6%, 73.9%, and 37.7%, respectively, $p<0.05$). Moreover, the quantity of proteinuria was found to be higher in DN and NDRD superimposed DN than in NDRD (6.4, 6.5, and 3.7 g/day, respectively, $p<0.05$).

Conclusions: This report disclosed the diversity and prevalence of NDRD that was diagnosed in more than one-third of Thai diabetic patients. Presence of nephritis was the more suggestive diagnosis of NDRD or NDRD superimposed DN. However, kidney biopsy is still the important means for the definite diagnosis of glomerular disease in diabetic patients.

Funding: Private Foundation Support

SA-PO284

Distribution of Glomerular Diseases in Taiwan: Preliminary Report of National Renal Biopsy Registry – Report on Behalf of Taiwan Society of Nephrology Hsien-Fu Chiu,[1] Kuo-cheng Lu,[2] Hung-Chun Chen,[3] Kuo-hsiung Shu.[4] *[1]Taichung Veteran General Hospital, Taichung, Taiwan; [2]Division of Nephrology, Department of Medicine, Cardinal Tien Hospital, School of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan; [3]Kaohsiung Medical Univ, Taiwan, Taiwan; [4]Lin Shin Hospital, Taichung, Taiwan.*

Background: Despite the development of biomarkers and noninvasive imaging tools, biopsy remains the only method for correctly diagnosing patients with unexplained hematuria, proteinuria and renal failure. Renal biopsy has been performed for several decades in Taiwan; however, a national data registry is still lacking until 2013.

Methods: The Renal Biopsy Registry Committee was established within the Taiwan Society of Nephrology in January 2013. A biopsy registry format, including basic demographic data, baseline clinical features, laboratory data, and clinical and pathological diagnosis was developed. Approval from the local institutional review board was obtained in each participating medical center.

Results: From January 2014 to September 2016, 1445 renal biopsies were identified from 17 medical centers. 53.8% cases were reported in men. The mean age at biopsy was 48.4±16.6 years. The median serum creatinine was 1.6 (IQR 0.9–3.3) mg/dL. The median daily urine protein was 2.7 (IQR 0.7–6.8) g/day, whereas 57.3% patients had hematuria. Primary glomerulonephritis (GN), secondary GN, tubulointerstitial diseases, and post-renal transplantation accounted for 40.7%, 33.6%, 10.3%, and 15.3%, respectively. Among primary GN, IgA nephropathy (26.0%), focal segmental glomerulosclerosis (FSGS) (21.6%), and membranous nephropathy (MGN) (20.6%) were most frequently diagnosed. Diabetic nephropathy (22.4%) and lupus nephritis (21.8%) were the most common among secondary GN. Patients with minimal change disease (MCD) and MGN had heavier proteinuria than those with FSGS and IgA nephropathy. The most common cause of nephrotic syndrome in primary glomerular disease was MGN (28.8%), followed by MCD (28.2%). IgA nephropathy was the leading cause of chronic nephritic syndrome, acute nephritic syndrome, and persistent hematuria. The incidence was 0.55, 0.47, 0.45, and 0.41 in 100,000/year for IgA nephropathy, FSGS, MGN, and MCD, respectively. The incidence of primary GN was 2.19 in 100,000/year.

Conclusions: This is the first report of the National Renal Biopsy Registry in Taiwan. IgA nephropathy is the most common primary GN, while MGN is the most common cause of nephrotic syndrome. Primary GN distribution in Taiwan is slightly different from that in other Asian countries.

SA-PO285

The Spectrum of Biopsy Proven Glomerular Disease among Children in China Sheng Nie. *National Clinical Research Center for Kidney Disease, State Key Laboratory of Organ Failure Research, Nanfang Hospital, Southern Medical University, Guangzhou, China.*

Background: Children with glomerular disease comprise an important part of pediatric patients worldwide, especially in developing countries. Nationwide epidemiological data on the spectrum of biopsy-proven glomerular diseases in children is currently limited in China.

Methods: We previously conducted a nationwide renal biopsy survey including 71,151 patients from 938 hospitals spanning 282 cities across China, over an 11-year period from January 2004 to December 2014. A total of 8547 pediatric patients (≤ 18 years old) were selected from the survey for current analysis. The demographic and clinical variables were extracted from referral records and pathological reports.

Results: We found nephrotic syndrome (49.5%) and proteinuria coexisted with hematuria (26.1%) were frequent indications of renal biopsy in children. Minimal change disease (MCD) was the most common primary glomerular disease (27.9%), followed by IgA nephropathy (IgAN) (17.0%) and mesangial proliferative glomerulonephritis (10.1%). Henoch-Schonlein purpura nephritis (13.2%) and lupus nephritis (LN) (8.8%) were two most common secondary glomerular diseases. Compare with male patients, female tended to be less frequently diagnosed as MCD (Odds Ratio [OR] 0.26, 95% CI 0.23-0.30) and Alport nephropathy (OR 0.38, 95% CI 0.21-0.69), while membraneous nephropathy (MN) (OR 2.91, 95% CI 2.41-3.51) and LN (OR 10.91, 95% CI 8.92-13.33) were more frequent in female patients, adjusting for age, region, indications of biopsy and hospital levels. Moreover, MCD (30.7%) was the most common glomerulopathy in adolescent (11-18 years old), while purpura nephritis (22.7%) was the major pathological diagnosis in younger children (0-10 years old). The frequency of MN and LN were varied greatly among different geographic regions of China.

Conclusions: In conclusion, we provided comprehensive information on the composition of pediatric glomerular diseases in China. The spectrum and clinicopathological correlations of pediatric glomerular diseases varied greatly across genders and age groups.

Funding: Government Support - Non-U.S.

SA-PO286

Diabetic and Non-Diabetic Kidney Disease in Patients with Diabetes Mellitus (DM) Youngho Kim, Caroline J. Poulton, Yichun Hu, Susan L. Hogan, Amy K. Mottl, Ronald J. Falk, J. Charles Jennette, Patrick H. Nachman. *UNC Kidney Center, University of North Carolina, Chapel Hill, NC.*

Background: Glomerular and interstitial diseases occur in patients with DM, with or without concurrent diabetic nephropathy (DN). Limited data exists on the impact of DM and DN on the treatment and outcomes of patients with non-diabetic kidney disease (NDKD). We explored the characteristics, treatments and outcomes in a large cohort of patients with DM.

Methods: We reviewed medical records and kidney biopsy reports of patients with DM from the Glomerular Disease Collaborative Network and University of North Carolina. We grouped the patients into 3 categories based on pathologic diagnosis: DN alone, NDKD alone and concurrent DN+NDKD.

Results: 382 patients with DM and kidney biopsy were identified: 53% male, 47% White, 40% Black, median age 55 years [IQR 46-64], BMI 30.9 kg/m² [26.8-36], eGFR 28 ml/min/1.73m² [16-49] and urine protein-creatinine ratio (UPCR) 5.5g/g [2.8-10.0]. Of these, 112 had DN, 180 had NDKD, and 90 DN+NDKD. Table 1 summarizes significant differences between these 3 groups. The DN+NDKD and NDKD groups differed significantly with respect to the distribution of glomerular and interstitial diseases (P=0.002). Lesions of FSGS were the most common in both groups (44% of DN+NDKD and 30% of NDKD). Interstitial nephritis was significantly more common in DN+NDKD (12% vs. 3%; P=0.007) and ANCA-GN more common in NDKD (7% vs 1%; P=0.04). Patients with NDKD received immunosuppressive therapy more frequently (64% vs 43%) and had more frequent remission (69% vs 33%) compared to DN+NDKD.

Conclusions: The concurrence of NDKD and DN affect the likelihood of immunosuppressive therapy and of remission. Given the high prevalence of DM in the general U.S. population, an in-depth analysis of treatment, adverse effects and outcomes of patients with DM and NDKD is warranted.

		DN	DN+NDKD	NDKD	P*
N		112	90	180	
Race	White	34%	54%	51%	0.002
	Black	54%	28%	37%	
	Other	12%	18%	12%	
Blood Pressure (mmHg)		N=99	N=73	N=147	
	Systolic	146 [135-160]	151 [134-166]	140 [128-150]	0.0004
	Diastolic	82 [73-93]	81 [72-90]	78 [70-89]	0.078
BMI		N=88	N=48	N=112	
		29.4[25.2-33.4]	30.2 [26.6-35.6]	32 [28.5-38.7]	0.003
Type I diabetes		N=112	N=90	N= 180	
		12%	10%	4%	0.025
Retinopathy		N=90	N=56	N= 123	
		24%	27%	1%	<0.0001
Diabetes treatment		N=83	N=55	N=110	
	Insulin	50%	56%	16%	<0.0001
	Oral agents	30%	24%	47%	
	Insulin+oral agents	18%	14%	13%	
	Diet control	3%	6%	26%	
eGFR (ml/min/1.73m^2)		25.4 [18.6-46.6]	23.1[14.4-43.4]	33.9[16.0-58.2]	0.054
UPCR (g/g)		N=87	N=66	N=131	
		6.3 [3.5-10.0]	8.7 [4.53-14.91]	4.6 [2.0-7.8]	<0.0001
Hemoglobin A1c %		7.1 [6.1-8.2]	7.4 [6.4-9.9]	6.6 [5.9-7.5]	0.008

Unless otherwise noted, data reported as median [IQR]. P values calculated using Fisher Exact test for categorical and Kruskal-Wallis test for continuous variables

SA-PO287

Very Low Levels of Microscopic Hematuria in Potential Living Kidney Donors Is Associated with Pathology That Precludes Donation Vineeta Kumar,[3] Manish K. Saha,[1] Bruce A. Julian,[2] Jayme E. Locke,[2] Robert S. Gaston.[2] *[1]UNC Kidney Center, Chapel Hill, NC; [2]University of Alabama at Birmingham, Birmingham, AL; [3]University of Alabama at Birmingham, Birmingham, AL.*

Background: A threshold of ≥3 rbc/hpf (red blood cells/high power field) or higher prompts additional testing when evaluating potential living kidney donors at most centers in the United States. In our experience, a lower degree of hematuria has yielded pathology that precluded kidney donation and here in we present the results of a single center experience.

Methods: We prospectively identified isolated asymptomatic microscopic hematuria in 19 out of 1124 potential living kidney donors. Microscopic hematuria was defined as presence of ≥1 rbc/hpf and persistent by presence on ≥2 separate urinalysis. Isolated was defined as presence of microscopic hematuria and with preserved GFR, absence of proteinuria, microalbuminuria or hypertension and no identifiable anatomical cause on native kidney imaging. Donors expressing continued interest had an evaluation with a cystoscopy. If unrevealing, they underwent a native kidney biopsy analyzed by a single pathologist using light, immunofluorescence and electron microscopy.

Results: There were no biopsy related complications. Degree of hematuria was modest ranging from 0-2 upto 3-10 rbc/hpf. Higher degree of hematuria was not isolated. 3/19 had IgA nephropathy and were not approved for kidney donation. All of these donors were related to their recipients. 1/19 had arteriosclerosis. Thin basement membrane disease (GBM) diagnosed after ruling out Alports was the most common finding in 11/19 patients and 4/19 had possible thin GBM based on segemental thinning only. These 15/19 were given a choice to donate after extensive counseling. One and two year follow up data have no worsening of hematuria or any of the renal parameters since donation.

Conclusions: Persistent asymptomatic microscopic hematuria of very minor degree in potential kidney donors with a biologically related recipient can be associated with pathologic findings that preclude kidney donation. A higher threshold of rbc/hpf on urine analysis as currently used can lead to a missed diagnosis and alter long term prognosis. At our center we have lowered our definition to ≥1 rbc/hpf after the results of this analysis.

SA-PO288

IgA Nephropathy with Positive Anti-Neutrophil Cytoplasm Antibody – A Case Series Amy Kang,[2] H. Terence Cook,[3] Charles D. Pusey.[1] *[1]Imperial College London, London, United Kingdom; [2]Imperial College Renal and Transplant Centre, London, United Kingdom; [3]Imperial College of London, London, United Kingdom.*

Background: IgA nephropathy (IgAN) with positive anti-neutrophil cytoplasm antibody (ANCA) is rare and may have different clinical characteristics from isolated IgAN.

Methods: We describe seven biopsy-proven IgAN patients (3% of our cohort) with positive ANCA (age 25 -66 years, 5 male and 2 female, median Cr 57mmol/L, eGFR 51mL/min/1.73m^2). Two initially ANCA negative patients developed worsening renal function and ANCA seropositivity. One recovered renal function with immunosuppression; the other was not immunosuppressed and progressed to dialysis. Five patients were ANCA positive from presentation. Two patients, with features of systemic vasculitis, received immunosuppression; one recovered renal function and the other progressed to dialysis. Two out of three patients with renal-limited disease had stable renal function on mycophenolate mofetil, and one was lost to follow-up. On biopsy, three out of the seven patients had segmental necrosis and crescents on a background of IgAN. Of the remaining four patients, one had features of endocapillary proliferation and the other three did not. IgAN can be associated with both PR3 and MPO – ANCA, but MPO-ANCA was more frequent in our cases (5 out of 7).

Results:

Conclusions: ANCA status can change in patients with IgAN and should be considered as a cause of rapid deterioration in renal function, as shown here. The patients in this series received a variety of treatment regimens. Four out of five patients who were selected to receive immunosuppressive therapy had improved or stable renal function at the end of follow up. IgAN with positive ANCA may represent an overlap syndrome between IgAN and ANCA vasculitis, and hence be more responsive to immunosuppressive treatment. We suggest that ANCA are tested in patients with IgAN, especially if renal function deteriorates rapidly, and that immunosuppressive treatment is considered if ANCA is detected.

SA-PO289

Anti-Ro Antibodies: A Novel Scleroderma Renal Crisis Biomarker Sarah M. Gordon, Stephen W. Olson. *Nephrology, Walter Reed National Military Medical Center, Bethesda, MD.*

Background: Autoimmunity is thought to play a significant role in the pathogenesis of scleroderma renal crisis (SRC). Anti- RNA polymerase III (RNAPOL3-Ab) is associated with SRC but only present in 20—50% of cases. Therefore, additional autoimmune risk factors for SRC are likely. Anti-Ro antibodies (Ro-Ab) are known to be associated with systemic sclerosis (SSc), but have not been studied at or before SRC diagnosis.

Methods: We queried the military electronic medical record for ICD9 code 701.1 (SSc) between 2005 and 2016. By individual chart review we identified 54 SRC cases and 407 SSc without SRC disease controls. Background data was collected to include presence of Ro-Ab. Department of Defense Serum Repository (DoDSR) provided up to 3 longitudinal prediagnostic serum samples for 16 SRC cases and 30 age, sex, race, and age of serum matched SSc without SRC disease controls. Ro-Ab levels were measured at the NIH using an established luciferase technique. We first compared presence of Ro-Ab among the 54 SRC cases to the 407 SSc without SRC controls at SSc diagnosis. We then compared longitudinal pre-diagnostic Ro-Ab levels in 16 SRC cases to that of 30 SSc matched disease controls. The non-white group was predominantly Black or 'Other.'

Results: More SRC cases had Ro-Ab at diagnosis than SSc without SRC disease controls (27% vs.13%, p=0.03). Ro-Ab were only associated with SRC in the non-White subgroup (38% vs.17%, p=0.04) versus the White subgroup (15% vs. 10%, p=0.69). More non-White SRC cases had persistent significantly elevated prediagnostic Ro-Ab than non-White SSc without SRC controls (40% vs.6%, p=0.01). In each SRC case, the Ro-Ab was greater than 30 times normal in the earliest available index sample up to 26.1 years before clinical presentation. No White cases had an elevated prediagnostic Ro-Ab level. Prediagnostic Ro-Ab and RNAPOL3-Ab were not present in the same cases.

Conclusions: We report for the first time that Ro-Ab are elevated both at and before SRC diagnosis, making it a potential predictive biomarker in non-Whites. Elevated serial prediagnostic Ro-Ab levels found decades before clinical SRC suggest a 'multi-hit' mechanism of disease that requires a second insult to manifest clinical disease. Our results also suggest that the subclinical pathophysiology of SRC may vary by race, similar to known clinical and serologic heterogeneity in SSc.

Funding: Other NIH Support - Labs were run at the NIH

SA-PO290

Activated Farnesoid X Receptor by GW4064 Protects against Renal Fibrosis through Regulation of Hippo Pathway Donghyun Kim,[1] Eun Hui Bae,[1] Seong Kwon Ma,[2] Soo Wan Kim.[2] *[1]Chonnam National University Hospital, Gwangju, Republic of Korea; [2]Chonnam National University Medical School, Gwangju, Republic of Korea.*

Background: Renal fibrosis is the common pathway of chronic kidney disease progression. transforming growth factor-β(TGF-β) induced SMAD2/3 is a critical event in progressive chronic kidney disease. However, the role of non-SMAD signaling in fibrotic progress and its underlying molecular mechanisms remain unexplored. The nuclear receptor farnesoid X receptor (FXR), a ligand-activated transcriptional factor, may play a pivotal role in renal fibrosis.

Methods: We tested whether activated-FXR by GW4064 protects against renal fibrosis through non-SMAD signaling. To explore anti-fibrotic effects of FXR, we investigated the effects of GW4064 in TGF-β induced renal fibrosis in human proximal tubular epithelial (HK-2) cells. We also examined the phosphorylation level of epidermal growth factor receptor (EGFR), Src kinase and Hippo pathway to identify the anti-fibrotic signals. To explore the anti-fibrotic effects of FXR agonist in the kidney of unilateral ureteral obstruction (UUO) mouse model, we treated with vehicle or GW4064 (30mg/kg) for 5 days, and checked the fibrosis markers.

Results: TGF-β-induced Src kinase and EGFR phosphorylations were decreased by the treatment of FXR synthetic agonist GW4064, while those phosphorylations were not altered by the treatment of chenodoxycholic acid (CDCA), FXR agonist. TGF-β-induced fibronectin, connective tissue growth factor and α-smooth muscle actin expressions were markedly decreased by GW4064 treatment. Phosphorylations of yes-associated protein (YAP), Mst1/2, and Lats1 were increased by GW4064 treatment, which facilitates blocked YAP nuclear accumulation and protects against renal fibrosis. The in vivo experiments showed that FXR agonist GW4064 protected against renal fibrosis in UUO mice.

Conclusions: These results suggested that activated nuclear receptor FXR by GW4064 has anti-fibrotic effects through regulation of Hippo pathway by inhibition of Src kinase phosphorylation. FXR-Src-Hippo pathway may be a novel target for the treatment of renal fibrosis.

Funding: Government Support - Non-U.S.

SA-PO291

Inability to Increase Fatty Acid Oxidation Following Renal Injury Worsens Renal Fibrosis Mardiana Lee,[1,2] Peter F. Mount,[1] Marina Katerelos,[1] Kurt Gleich,[1] David A. Power.[1,2] *[1]Austin Health, Melbourne, VIC, Australia; [2]Medicine, University of Melbourne, Melbourne, VIC, Australia.*

Background: Recent studies have reported reduced expression of genes regulating fatty acid metabolism in fibrotic kidneys. However, the exact role of fatty acid metabolism in renal fibrosis is still unclear. To answer this question, we used mice with knock-in mutations of the regulatory S79 and S212 phosphorylation sites in acetyl CoA carboxylase 1 and 2 (ACC 1/2 KI) which have reduced ability to increase fatty acid oxidation when stressed. We aimed to determine whether reduced fatty acid oxidation contributes to renal fibrosis.

Methods: The folic acid nephropathy (FAN) and unilateral ureteric obstruction (UUO) models were induced in male ACC1/2KI mice and wild type (WT) controls. Mice were sacrificed at 14 and 7 days, respectively. Samples were studied by histomorphometry, Western blot and qRT-PCR.

Results: There was no difference in the appearance or function of ACC1/2KI kidneys at 8-10 weeks of age compared with WT. Reduced expression of genes controlling fatty acid oxidation was confirmed in the FAN model. In both FAN and UUO models there was increased accumulation of lipid by Oil Red O staining in ACC1/2KI mice ($p<0.05$ and $p<0.01$, respectively). Sirius red staining demonstrated increased fibrosis in ACC1/2KI mice in both models ($p<0.05$ and $p<0.001$)(Fig. 1). This was associated with increased expression of α-smooth muscle actin by Western blot ($p<0.05$) and qRT-PCR ($p<0.01$). In the FAN model, ACC1/2KI mice also had increased mRNA transcripts for Collagen I ($P<0.05$) by qRT-PCR compared with WT.

Conclusions: These data indicate that a reduced ability to regulate fatty acid oxidation in response to renal injury contributes to the development of renal fibrosis, and is not simply a consequence of injury. Regulation of fatty acid oxidation may be a potential therapeutic target in renal fibrosis.

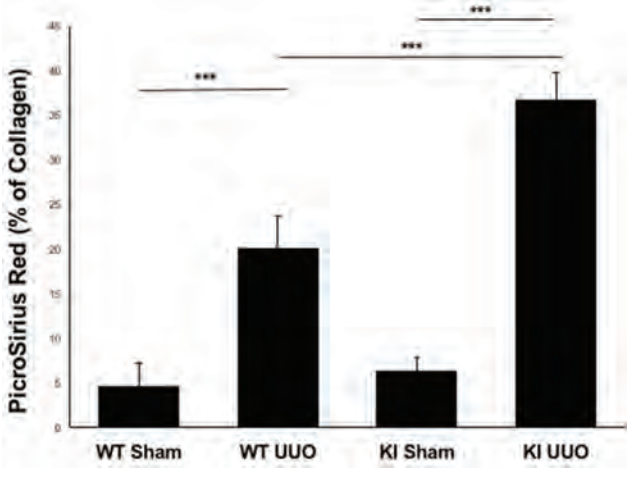


Figure 1. Quantification of PicroSirius Red stained kidney sections analysis showing increased Collagen in KI UUO compared to WT UUO (***P<0.001).

SA-PO292

Lipoxins Attenuate Diabetic Complications in the ApoE-/- Mouse Eoin P. Brennan,[2] Muthukumar Mohan,[1] Monica De gaetano,[2] Chris Tikellis,[1] Mariam Marai,[2] Mark Ziemann,[1] Orina Belton,[3] Assam El-Osta,[1] Karin Jandeleit-Dahm,[1] Mark E. Cooper,[1] Phillip Kantharidis,[1] Catherine Godson.[2] *[1]Department of Diabetes, and Central Clinical School, Monash University, Melbourne, VIC, Australia; [2]Diabetes Complications Research Centre, UCD Conway Institute & School of Medicine UCD, University College Dublin, Dublin, Ireland; [3]School of Biomolecular and Biomedical Science, University College Dublin, Belfield, Dublin, Ireland.*

Background: Targeting both inflammation and fibrosis in diabetes-related complications has proven elusive. Endogenous lipid mediators including Lipoxins (LXs) actively promote the resolution of inflammatory responses. We investigated the potential of Lipoxin A4 (LXA_4), an endogenously produced mediator that promotes the resolution of inflammation, and a synthetic lipoxin 15(R)-Benzo-LXA_4 as experimental therapeutics in the streptozotocin-induced diabetic $ApoE^{-/-}$ mouse, a model of diabetic complications.

Methods: Diabetes was induced with low-dose streptozotocin (55mg/kg). Following 10 weeks of diabetes progression, mice were administered either vehicle (0.1% ethanol), LXA_4 (5ug/kg), or Benzo-LXA_4 analogue (1.7ug/kg) for 6 additional weeks.

Results: LXs attenuated kidney disease, with evidence of reduced albuminuria (Diabetes+Vehicle: 25.1±2.1 μg/24h vs Diabetic+LXA_4: 17.3±2.4 μg/24h), glomerular expansion, and collagen deposition. RNA-Seq transcriptome profiling identified the diabetic renal gene signature (725 genes) and subsets regulated by LXs. Pathway analysis identified established (TGF-β1, PDGF, TNF-α, NF-κB) and novel (EGR-1) networks regulated by LXs. LXs also reduced aortic atherosclerotic plaque development and pro-inflammatory signaling pathways in vascular tissue. LXs attenuated vascular smooth muscle cell proliferation and migration, and inhibited monocyte-endothelial cell adhesion. Treatment of human carotid plaques *ex vivo* with LXA_4 attenuated secretion of pro-inflammatory cytokines including IFN-γ, IL-1β and TNF-α, thereby highlighting the potential clinical relevance of LX-based therapeutics. Finally, we have previously identified the let-7 miRNA family as important mediators of renal fibrosis, and here we demonstrate that restoration of let-7 levels in aortic vascular tissues could provide a new target for an anti-inflammatory approach in diabetic vascular disease.

Conclusions: In conclusion, these data support a novel pro-resolution therapeutic approach for treating and preventing concomitantly multiple vascular complications of diabetes.

Funding: Government Support - Non-U.S.

SA-PO293

TGF-β1 Promotes Fibrotic Gene Expression through Induction of Histone Variant H3.3 and Histone Chaperone HIRA Toshihiro Shindo, Shigehiro Doi, Kensuke Sasaki, Ayumu Nakashima, Takao Masaki. *Hiroshima university, Hiroshima city, Japan.*

Background: Recent studies show that histone variants and their chaperones serve as epigenetic marks that regulate transcriptional activity. In this study, we investigated transforming growth factor (TGF)-β1-induced histone variant H3.3 and its histone chaperone, HIRA, on fibrotic genes *in vivo* and *in vitro*.

Methods: Male C57BL/6J mice underwent unilateral ureteral obstruction (UUO) and were sacrificed on day 7. In UUO mice, expression of H3.3, HIRA, and α-smooth muscle actin (αSMA) were evaluated by western blotting (WB) and immunohistochemistry (IHC) with or without administration of a TGF-β1-neutralizing antibody. For *in vitro* experiments, rat renal tubular cells (NRK52E) and rat kidney fibroblasts (NRK49F) were used. TGF-β1-iduced expression of H3.3, HIRA and αSMA was assessed by WB with pretreatment of Smad3 or HIRA siRNAs. Furthermore, chromatin immunoprecipitation (ChIP) assays were carried out using primers for fibrotic genes, which were designed to include in a Smad-binding element, in TGF-β1-stimulated NRK52E cells.

Results: Expression of H3.3 and HIRA was increased in UUO mice, and the TGF-β1 -neutralizing antibody suppressed their expression. Smad3 siRNA treatment inhibited expression of H3.3 and HIRA in TGF-β1-stimulated NRK52E cells. HIRA siRNA treatment attenuated expression of H3.3 and αSMA in TGF-β1-stimulated NRK52E cells. In ChIP assays, TGF-β1 increased promoter activities of collagen 1 (Col1a1), connective tissue growth factor (CTGF), and plasminogen activator inhibitor-1 (PAI-1) in NRK-52E cells, which were colocalized with H3.3 and suppressed by the TGF-β1 neutralizing antibody.

Conclusions: TGF-β1-induced H3.3 and HIRA play an important role in expression of fibrotic genes.

SA-PO294

Galectin-1 Is a New Renal Fibrosis Gene Upregulated in Type I and Type II Diabetes Samy L. Habib. *UTHSCSA, San Antonio, TX.*

Background: Chronic exposure of tubular renal cells to elevated blood glucose contributes to tubulointerstitial changes seen in diabetic nephropathy. Tubular cells are primary targets of hyperglycemia, and chronic exposure to elevated blood glucose levels contributes to the tubulointerstitial changes seen in overt diabetic nephropathy.

Methods: Kidney tissues from wild type and diabetic mice from both type 1 DM (Akita) and type 2 (db/db) groups at age of 4, 6, 8 months old were used. RNA sequence and analysis of Gal-mRNA were performed in RNA extracted from kidney tissues. Proximal tubular epithelial renal cells treated with high glucose and/or HG+Insulin for different time points were used to measure promoter activity and protein expression of Gal-1. Gal-1 was cloned and transcription factor AP4 was i immunoprecipitated to identify the binding of Ap4 to Gal-1 promoter. siRNA of Gal-1, AP4 and tuberin as well as Gal-1 inhibitor and Akt inhibitor were used to test the effect of its downregulation on Gal-1 expression and promoter activity.

Results: In the present study, we identified a new fibrosis gene called Galectin-1 (Gal-1) that highly expressed in tubular cells in kidney of type I and type II mouse models of diabetes. Gal-1 protein and RNA expression showed significant Increased in kidney cortex of Akita and db/db mice compared to wild type mice. Mouse proximal tubular exposed to high glucose (HG) and HG+Insulin showed significant increase in phosphorylation of Akt that associated with significant increase in expression of Gal-1. We identified that AP4 binds to Gal-1 promoter to upregulates its function. The mutated binding sites of Ap4 to Gal-1 promoter showed decease in protein and function activity of Gal-1. Inhibition of Gal-1 by OTX-008 showed significant decrease in phosphorylation of Akt and expression of AP4 and Gal-1 protein/promoter activity. In addition, downregulation of Ap4 by siRNA resulted in significant decrease in protein expression and promoter activity of Gal-1.

Conclusions: In summery, our data showed that Gal-1 is highly expressed in kidney of type 1 and II diabetic mouse and Ap4 is a major transcription factor that activates Gal-1 under hyperglycemia through activation of Akt. Inhibition of Gal-1 by OTX-008 blocks activation of Akt and prevent accumulation of Gal-1 suggest a novel role of Gal-1 inhibitor as possible therapeutic target to treat renal fibrosis in diabetes.

Funding: Veterans Affairs Support

SA-PO295

Knockdown of Peroxiredoxin V (Prdx V) Exacerbates Unilateral Ureteral Obstruction-Induced Renal Fibrosis Hoon In Choi,[2] Tae-Hoon Lee,[1] Jung Sun Park,[2] Donghyun Kim,[2] Eun Hui Bae,[2] Seong Kwon Ma,[2] Soo Wan Kim.[2] *[1]School of Dentistry, Chonnam National University, Gwangju, Republic of Korea; [2]Chonnam National University Medical School, Gwangju, Republic of Korea.*

Background: Renal fibrosis is closely associated with chronic inflammation. Peroxiredoxin V (Prdx V), an atypical 2-Cys member of the Prdxs family, functions as anti-inflammatory effector as well as a thiol-dependent peroxidase in its catalytic cysteine-dependent manner. Recently, we demonstrated that overexpression of Prdx V attenuate TGF-β induced fibrosis in NRK49F cells. However, the relevance of Prdx V to renal pathobiology has not been fully characterized and the underlying mechanism remains poorly understood.

Methods: To investigate the role of Prdx V in renal fibrosis, we used a transgenic mouse model with PrdxV siRNA expression controlled by U6 promoter (C57BL/6J-Tg(U6-PrdxVsi)1Thlee/Krb; Prdx V^{si} mice). For in vivo experiments, both Prdx V^{wt} and Prdx V^{si} mice were divided to each two groups (Control vs UUO group, each n = 8). The UUO groups were subjected to unilateral ureteral obstruction (UUO) by ligation of the left ureter for seven days. The control groups were performed to the same treatment for seven days, with the exception of the ligature.

Results: Consistent with our previous data, the protein expression of Prdx V was less in UUO group kidney than the control group kidney. Compared with UUO-induced Prdx V^{wt} mouse kidney, UUO-induced Prdx V^{si} mouse kidney had more stained by TGF-β and α-SMA which is gradually increased by fibrosis progression. Knockdown of Prdx V in kidney exacerbated the UUO-induced increase in fibrotic marker expression, such as TGF-β, α-SMA, and vimentin, and also, augmented the reduction of E-cadherin, an epithelial marker as well as the increase in oxidative stress, such as nitrotyrosine and lipid peroxidation. Furthermore, we observed the activation of canonical and non-canonical TGF- β signal pathway, resulting in renal fibrosis progression. In canonical TGF- β signals, the increase of Smad4 that plays a critical role in nucleocytoplasmic shuttling of Smad2/3 is remarkable in UUO-induced Prdx V^{si} mouse kidney. In non-canonical TGF-β signals, phosphorylation of Stat3 is accentuated in UUO-induced Prdx V^{si} mouse kidney consistent with our earlier in vitro data.

Conclusions: Prdx V is an anti-fibrotic effector that sustains renal physiology. Negative regulation mechanism of TGF-β signaling by Prdx V could be a therapeutic target to protect renal fibrosis.

SA-PO296

The Kidneys and the Lungs in the Rat Show Different Vascular and Fibrotic Changes in an Acute Model of Fat Embolism in the Presence or Absence of the Renin Inhibitor Aliskiren Hisham Elsherbiny,[4] Farnaz Khalafi,[1] Vaishnavi L. Vaidyanathan,[3] Alan Poisner,[2] Dauod Arif,[3] Ahsan Siddiqi,[3] Agostino Molteni.[1] *[1]University of Missouri at Kansas City, Kansas City, MO; [2]Univ of Kansas Medical Center, Overland Park, KS; [3]University of Missouri-Kansas City, Kansas City, MO; [4]Internal Medicine, University of Missouri at Kansas CIty, Kansas City, MO.*

Background: In a rat model of fat embolism (FE) induced by injection of triolein (T), a severe inflammatory reaction leads to vasculitis and pulmonary fibrosis that was mitigated by drugs interfering with the renin angiotensin system (RAS): a renin inhibitor aliskiren (ALI). We extended the study to the kidneys by evaluating the renal arterial response to T treatment in this FE model and the effect of ALI.

Methods: 22 Sprague Dawley rats received T (0.2 ml IV, n=18) or saline (n=4). The T-treated rats were divided into three groups of 6 rats each and injected IP one hour later, with saline, ALI 50mg/kg or ALI 100mg/kg. Four controls received saline. Rats were killed 48 hours later; the organs fixed and stained with H&E, trichrome and smooth muscle actin (SMA). The vascular evaluation included lumen patency (LP) and media adventitia ratio (MAR), a marker of edema. Photos at 400 X and 100 X were taken on each slide by two pathologists unaware of the slide identity. Alpha SMA and trichrome-stained slides were digitally analyzed by image J software (NIH) to quantify the amount of myofibroblasts and collagen present in each slide.

Results: Rats injected with T + saline showed the expected severe pulmonary vascular inflammation markedly reduced by both ALI doses but no significant inflammatory response was observed in the kidneys. T + ALI 50 showed a significant ($p<0.01$) increase in pulmonary lumen patency vs the T + saline group which revealed only a trend in reduction vs the controls. No differences in lumen patency were seen for renal arteries. The pulmonary MAR measurements were similar in the four groups whereas there was a significant effect in the kidneys ($p<0.0007$) with a slightly larger ratio for the T +saline and T + ALI groups. Image J determination revealed other organ differences with ALI reducing alpha SMA and trichrome in lungs but not in kidneys. An opposite trend was seen in the MAR where T +ALI showed a return toward control values vs the T + saline induced increase while no difference among treatments were observed in lungs.

Conclusions: MAR differences suggest that FE has some renal vascular effects in this acute model mediated by the RAS, albeit different from that in the lungs.

Funding: Private Foundation Support

SA-PO297

Reduced Proteoglycans in the Kidney Causes Both Tubule and Glomerular Abnormalities Nabin Poudel,[1] Maria C. Munteanu,[1] Robert Silasi-Mansat,[2] Florea Lupu,[2] Myron Hinsdale.[1,3] *[1]Physiological Sciences, Oklahoma State University, Stillwater, OK; [2]Program of Cardiovascular Biology Research, Oklahoma Medical Research Foundation, Oklahoma City, OK; [3]Department of Cell Biology, University of Oklahoma, Oklahoma City, OK.*

Background: Most cells produce some form of proteoglycan(s). The initial assembly of glycosaminoglycan (GAG) on the core protein of proteoglycans(PG) requires the transfer of a xylose to a designated serine. The enzyme responsible for this is xylosyltransferase and it exists in two isoforms as xylosyltransferase 1(XylT1) and 2 (XylT2). The latter is ubiquitously expressed in many organs suggesting a significant biochemical role of XylT2 dependent proteoglycans in these organs. In our XylT2 knock-out mice (*Xylt2-/-* mice), substantial XylT activity remains in the kidney due to the remaining XylT1 activity. However, considerable renal abnormalities still occur including glomerular basement membrane changes, fibrosis, and tubule dilation. Our previous findings in *Xylt2-/-* mice established that proteoglycans are important in cyst development in the liver. Considering our findings in the *Xylt2-/-* mice and that reduced proteoglycans occurs in many different diseases affecting the kidney (e.g. polycystic kidney disease, PKD), we hypothesize that GAG levels have a modifying role in kidney function. Notably, PKD patients can develop proteinuria indicating a much poorer long-term prognosis.

Methods: Blood Urea Nitrogen (BUN) was measured from *Xylt2-/-* mice. Western blotting was performed on urine of *Xylt2-/-* mice to detect proteinuria. Transmission Electron Microscopy (TEM) was used to evaluate the structural changes in glomerular basement membrane and kidney tubule. In addition, TEM was performed on kidneys from mice injected with polyethylenemine (PEI) to measure anionic sites in the GBM.

Results: *Xylt2-/-* mice have increased BUN, proteinuria, and, in aged mice, renal failure. Investigations also show that additional changes occur ultrastructurally in the glomerular basement membrane including decreases in anionic charge. Furthermore, tubule structure is also impacted indicating tubule dysfunction.

Conclusions: The findings in the XylT2 deficient kidneys indicates that XylT2-dependent glycosaminoglycan (GAG) assembly onto core proteins is important in nephron homeostasis. Our analyses suggest that one source of the proteinuria could be reduced renal proteoglycans.

Funding: NIDDK Support, Other NIH Support - P20GM103648, DK087989, Private Foundation Support

SA-PO298

Serelaxin Improves Cardiac and Renal Function in a DOCA-Salt Model of Cardiorenal Syndrome in Rats Dong Wang,[5] Yuhuan Luo,[1] Komuraiah Myakala,[1] Xiaoxin Wang,[3] David J. Orlicky,[2] Evgenia Dobrinskikh,[4] Moshe Levi.[3] *[1]University of Colorado, Aurora, CO; [2]University of Colorado Anschutz Medical Campus, Aurora, CO; [3]University of Colorado Denver, Aurora, CO; [4]University of Colorado, Denver, Aurora, CO; [5]medicine, Uc denver, Aurora, CO.*

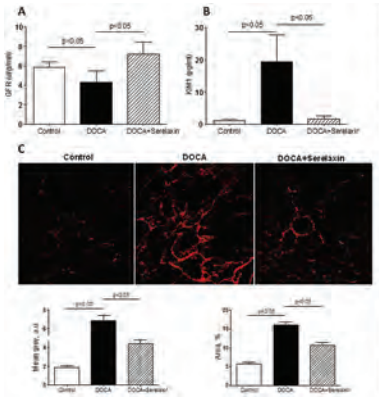
Background: Serelaxin, a recombinant form of the naturally occurring peptide hormone relaxin-2, is a pleiotropic vasodilating hormone that has been studied in patients with acute heart failure. In this study, the effects of serelaxin on cardiac and renal function, fibrosis, inflammation and lipid accumulation were studied in DOCA-salt treated rats.

Methods: Uninephrectomized rats were assigned to two groups: controls provided with normal drinking water and DOCA provided with DOCA pellets and sodium chloride drinking water. After 4 weeks, the DOCA-salt rats were randomly selected and implanted with osmotic minipumps delivering vehicle or serelaxin for another 4 weeks.

Results: Treatment with serelaxin prevented cardiac and renal dysfunction in DOCA-salt rats. Serelaxin prevented cardiac and renal fibrosis, as determined by Picrosirius Red staining and Second Harmonic Generation (SHG) Microscopy. Treatment of DOCA-salt rats with serelaxin decreased renal inflammation, including the expression of TGF-β, NFκB, MCP-1, interleukin-1, interleukin-6, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1) and CD68 macrophages. Serelaxin also decreased lipid accumulation in kidney in part by decreasing SREBP-1c, SREBP-2, ChREBP, FATP1, HMGCoAR, and LDL receptor, that mediate fatty acid and cholesterol synthesis and uptake, and increasing Acox1 and ABCA1, that mediate fatty acid oxidation and cholesterol efflux.

Conclusions: In conclusion, serelaxin reversed DOCA-salt induced cardiac and renal dysfunction by modulating inflammation, lipid metabolism, and fibrosis.

Funding: NIDDK Support, Commercial Support - Novartis



Serelaxin improves renal function of DOCA-salt rats. (A) DOCA induced a decrease in glomerular filtration rate and treatment with serelaxin reversed the decrease in glomerular filtration rate. **(B)** DOCA induced a marked increase in urinary KIM1 excretion and treatment with serelaxin significantly decreased and normalized KIM1 excretion. **(C)** Second Harmonic Generation Microscopy shows DOCA induces a marked increase in tubulointerstitial fibrosis and treatment with serelaxin markedly decreased the fibrosis.

SA-PO299

The RNA Binding Protein Staufen2 Is Required to Maintain Integrity of the Golgi Apparatus and Podocyte Cell-Matrix Adhesion Jessica J. Harris,[1] Valerie A. Schumacher.[2] [1]*Boston Childrens Hospital, Boston, MA;* [2]*Childrens Hospital Boston, Boston, MA.*

Background: Proper adhesion of podocytes to the glomerular basement membrane is necessary to withstand high transcapillary filtration pressure and to prevent glomerulosclerosis. Our preliminary data shows that the RNA binding protein Staufen2, known to mediate mRNA transport and local translation in neurons, is required for podocyte-matrix adhesion. In addition, we demonstrate that mice deficient in Staufen1 and 2 are more susceptible to glomerular disease, suggesting a role for local translation in the maintenance of the glomerular filtration barrier. The present study aims at determining the molecular mechanisms by which Staufen2 regulates cell-matrix adhesion.

Methods: A cell biological and biochemical approach was used to study the role of Staufen2 in the maintenance of cell-matrix adhesion.

Results: The most critical cell-matrix adhesion receptor in podocytes is a3b1 integrin, which bridges laminin 521 in the GBM to the intracellular actin cytoskeleton. We show that glycosylation of integrin β1 is altered in Staufen2 knockdown immortalized podocytes and that there is decreased phosphorylation of the b1 integrin effectors Src tyrosine kinase and focal adhesion kinase (FAK). Specifically, complex-type *N*-glycans added to b1 integrin in the Golgi apparatus by glucosaminyltransferases Gnt-III and V were decreased in Staufen2 knockdown cells. Both corresponding mRNAs were found to be bound and stabilized by Staufen2, suggesting a role for Staufen2 in regulating complex-type glycosylation. In addition, the Golgi apparatus was severely fragmented in Staufen2 knockdown podocytes, especially following mechanical stretch. This coincided with an increase in F-actin, known to cause Golgi fragmentation.

Conclusions: Staufen2 mediated morphological and functional integrity of the Golgi apparatus may represent a novel mechanism by which podocyte-matrix adhesion is maintained.

Funding: NIDDK Support

SA-PO300

The Role of Plekha7 in Renal Fibrosis Michael M. Yeboah,[1] Marla A. Chesnik.[2] [1]*Medicine, Medical College of Wisconsin, Milwaukee, WI;* [2]*Medicine, Medical College of Wisconsin, Milwaukee, WI.*

Background: Chronic kidney disease (CKD) affects about 12% of all adults in the United States and is associated with significant morbidity, including but not limited to progression to end-stage kidney failure, and increased cardiovascular death. The associated healthcare costs are enormous and continues to increase. Progressive tubule-interstitial fibrosis (TIF) is the hallmark of CKD irrespective of the underlying kidney disease. TIF results from excessive deposition and accumulation of extracellular matrix in the renal interstitium by myofibroblasts which may originate from tubular epithelial cells through a process called epithelial-mesenchymal transition (EMT). The pleckstrin homology domain containing family A member 7 (Plekha7) is a novel protein that is localized at the adherens junction of epithelial cells in association with E-cadherin which is involved with intercellular contacts. Plekha7 is also linked to signaling molecules (including β-catenin) and the cellular cytoskeleton. A SNP in Plekha7 has been associated with hypertension in multiple genome-wide association studies, and mutation of Plekha7 in rats leads to a reduction in salt-sensitive hypertension. In this study, we examined a possible role of Plekha7 in modulating EMT and development of renal fibrosis.

Methods: In vivo, plekha7 mutant and wild type rats underwent unilateral ureteral obstruction (UUO), an established model of kidney fibrosis. The animals were euthanized after 2 weeks and the kidneys were retrieved for analysis of fibrosis markers. In vitro, plekha7 was stably knocked down or overexpressed in HK-2 cells via lentiviral transduction.

Results: Plekha7 mutation resulted in increased TGF-beta expression, macrophage recruitment, and fibrosis in rat kidneys after UUO. In HK-2 cells, plekha7 knockdown reduced E-cadherin and increased alpha-smooth muscle actin and collagen 1A1 expression, while plekha7 overexpression in the cells was associated with increased E-cadherin and reduced fibronectin and collagen 1A1 expression.

Conclusions: Mutation of Plekha7 results in increased renal fibrosis in rats. Knockdown of plekha7 promotes EMT in HK-2 cells, while plekha7 overexpression restores the epithelial phenotype and reduces TGF-β-induced EMT.

Funding: Clinical Revenue Support

SA-PO301

Characterization of a Synthetic Adeno-Associated Virus (AAV-2/Anc80) That Targets Kidney Stroma and Validation through Gli2 Deletion in Fibrosis Yoichiro Ikeda,[4] Ru Xiao,[1] Luk Vandenberghe,[1] Zhao Sun,[3] Benjamin D. Humphreys.[2] [1]*Schepens Eye Research Institute, Harvard Medical School, Boston, MA;* [2]*Washington University School of Medicine, Clayton, MO;* [3]*Washington University in St Louis, Saint Louis, MO;* [4]*Washington University, School of Medicine, St. Louis, MO.*

Background: AAV is a non-integrating virus currently in human clinical trials for gene therapy. There are no reports of AAV with tropism to kidney, limiting our ability to deliver genetic material to that organ. We characterized the kidney tropism for a panel of AAV serotypes to set the stage for future use in human clinical trials.

Methods: Pseudotyped AAV with various capsid proteins and promoters were prepared and tested to validate the efficacy of transduction in mouse kidney. Initial studies utilized GFP reporters and later studies used AAV viruses that express Cre recombinase. To establish whether an AAV-based approach could efficiently delete floxed genes in kidney pericytes, we injected AAV-2/Anc80-CASI-Cre (3x10^11 GC/mouse) into Gli2(f/f);R26(tdTomato) mice or control. After three weeks, we performed UUO surgery, then kidneys were analyzed. Human iPSC kidney organoids and primary human kidney fibroblasts from patients were exposed to AAV-GFP and analyzed with fluorescent microscopy.

Results: Of all serotypes of AAV analyzed, AAV-2/Anc80-CASI most efficiently transduced kidney cell types. When AAV-2/Anc80-CASI-Cre was injected into R26(tdTomato) reporter mice, 58.9±3.5% (mean±SEM) of all pericytes became TdTomato positive. Other reporter positive cells were mesangial cells and juxtaglomerular cells. AAV-Cre injected Gli2(f/f); R26(tdTomato) mice had reduced fibrosis including 30 – 60% reduction in aSMA, fibronectin, collagen1a1, collagen3a1 mRNA and protein levels after UUO compared to control, which is consistent to immunofluorescent stainings of aSMA and collagen1. There were 40% fewer myofibroblasts in the Gli2flox compared to control kidneys after UUO. There was no toxicity to extrarenal organs with this dose, though higher dose (10^12 GC/mouse) of AAV-2/8-CASI did cause hepatitis. AAV-2/Anc80-CASI-GFP drove GFP specifically in stromal cells of human iPSC kidney organoids (30% of total Meis1 positive cells) and primary human kidney fibroblasts.

Conclusions: We demonstrate that AAV-Cre targets kidney pericytes and efficiently deleted Gli2 leading to an antifibrotic effect. AAV strategies will be useful both in preclinical models but also in human clinical trials.

Funding: NIDDK Support

SA-PO302

Adult Renal Stem/Progenitor Cells Can Revert LPS-Induced Endothelial-to-Mesenchymal Transition of Endothelial Cells Fabio Sallustio, Alessandra Stasi, Claudia Curci, Rossana Franzin, Chiara Divella, Paola Laghetti, Giuseppe De Palma, Angela Picerno, Monica Rutigliano, G. Lucarelli, Michele Battaglia, Giuseppe Castellano, Loreto Gesualdo. *DETO, University of Bari, Bari, Italy*.

Background: Acute Kidney Injury (AKI) is the major complication encountered in sepsis. Lipopolysaccharides (LPS) are frequently involved in the pathogenesis of AKI, that is mainly characterized by endothelial cell (EC) dysfunction. EC acquire a myo-fibroblast phenotype, by endothelial-to-mesenchymal transition (EndMT), contributing to the renal fibrosis. Resident adult renal stem/progenitor cells (ARPCs) enhance tubular regenerative mechanism during AKI, but little is known about their effects on endothelial compartment. The aim of this study is to investigate the effects of ARPCs on endothelial dysfunction.

Methods: Endothelial cells were stimulated in vitro with LPS for 48h and co-cultured with ARPCs for 24h. MTT cell viability assay was used to analyze the EC proliferation rate following LPS stimulation and in co-culture with ARPCs. FACs analysis was used to study the expression of myofibroblast markers. Gene expression profiles of ARPCs and EC were generated using Agilent Microarrays.

Results: We observed a significant increase of EC proliferation after stimulation with LPS. ARPCs in co-culture with EC normalized their proliferation rate and decrease the cell growth rate, even in presence of LPS. Moreover, LPS induced a significant decrease of EC markers, CD31 and VE-cadherin and a significant increase of EC dysfunction markers, Collagen I and Vimentin. ARPCs in co-culture with EC abrogated the LPS-induced EndMT by restoring the high expression of CD31 (95% vs 66%) and VE-cadherin (96% vs 31%) and limiting Collagen I (18% vs 73%) and Vimentin (35 % vs 50.86%) expression. Microarray analysis showed that LPS induced the upregulation of 305 genes and the down regulation of 694 genes in ARPCs (Q value < 0,05 and Fold change >2). Gene Set Enrichement Analysis and pathway analysis identified 27 genes specifically involved in prevention and recovery from infections caused by external agents.

Conclusions: Our data demonstrate that ARPCs could preserve EC phenotype by regulating LPS-induced EndMT. Interestingly, LPS induces the expression of a specific gene set in ARPCs able to prevent EC dysfunction.

SA-PO303

Alpha-Actinin-4 Is Required for Shp2 Activation in Podocytes Hsiao-Hui Lee. *Department of Life Sciences and Institute of Genome Sciences, National Yang-Ming University, Taipei, Taiwan.*

Background: Integrins mediate cell-matrix interaction and form focal adhesion (FA) to connect with cytoskeleton in adherent cells. Previously, we found that Shp2 promotes ROCKII activation that facilitates FA maturation and stress fibers orientation to optimize cellular tension in response to the increase of matrix rigidity.

Methods:

Results: In this study, we identified that α-actinin-4 interacts with Shp2 at FAs in mouse embryonic fibroblasts by an in vitro pull-down assay with recombinant Shp2 N-SH2 domain. This interaction between endogenous Shp2 and α-actinin-4 at FAs was confirmed by co-immunoprecipitation and proximity ligation assay. Since α-actinin-4 plays an important role in podocytes adhesion, we then used a mouse temperature-inducible podocyte line and found that differentiated podocytes exhibited distinct FAs and stress fibers with the hyperactivation of Shp2 and ROCKII. Knockout of ACTN4, which encodes α-actinin-4, by CRISPR/Cas9 reduced Shp2 activation significantly in podocytes. Furthermore, inhibition of Shp2 reduced ROCKII activation, FAs, stress fibers, and BSA-filtration ability of podocytes.

Conclusions: Taken together, our results suggest the essential role of α-actinin-4 in Shp2 activation that is crucial for the cell adhesion and filtration function in podocytes.

Funding: Government Support - Non-U.S.

SA-PO304

Expression of APOL1 Risk Alleles (G1 and G2) Compromises Spreading of Podocytes by Down Regulation of β3 Integrin Ali Hussain,[2] Rukhsana Aslam,[1] Vinod Kumar,[5] Ashwani Malhotra,[5] Karl Skorecki,[4] Pravin C. Singhal.[3] *[1]Feinstein Institute for medical research, Glenoaks, NY; [2]Feinstein Institute of Medical Research, New York, NY; [3]North Shore LIJ Health System, Great Neck, NY; [4]Rambam Health Care Campus, Haifa, Israel; [5]Immunolgy and Inflammation, Feinstein Inst.Med research and NSLIJ, Manhasset, NY.*

Background: Genetic epidemiology indicated that Africans Americans are at four fold higher risk for the development of focal segmental glomerulosclerosis when compared to European Americans. This disparity amongst African American has been attributed to carrying APOL1 risk alleles (G1 and G2). Expression of APOL1 G1 and G2 by podocytes has been reported to promote cell death both *in vitro* and *in vivo* studies. However, the role of APOL1G0 (wild- type) in podocytes is far from clear. Podocytes are normally detached and excreted in the urine in a normal physiological state. However, adjacent podocytes are able to maintain the integrity of the glomerular filtration barrier by spreading over the naked basement membrane caused by detachment of podocytes. We hypothesize that APOL1 risk alleles (G1 and G2) could be affecting the spread of podocytes compromising integrity of glomerular filtration barrier.

Methods: Cultured immortalized human podocytes proliferate at 33°C and differentiate at 37°C. Podocytes stably expressing vector, APOL1G0, APOL1G1, and APOL1G2 grown on coverslips (collagen coated) were incubated in media for 12 and 24 hours at 37°C (n=4). Subsequently, podocytes were labeled with α-actinin antibody and examined under a confocal microscope. Average size of podocytes determined at 8 random fields using J Image program. Proteins extracted from the cells treated under similar conditions, were probed for β3 integrin and α-actinin expession and reprobed for actin.

Results: Podocytes expressing APOL1 G1 and G2 displayed decreased ($P<0.01$) spreading when compared to podocytes expressing vector (V) or APOLO1G0 (Mean podocyte size at 12 hours: V, 74.3 ± 18.6; APOLO1G0, 87.8 ± 15.3; APOL1G1, 42.5 ± 12.2; APOL1G2, 35.2 ± 9.7 μM and at 24 hours: V, 118.1 ± 15.7; APOL1G0, 130.6 ± 17.5; APOL1G1, 65.1 ± 18.0; APOL1G2, 79.7 ± 16.4 μM) both at 12 h and 24 h. Podocytes expressing APOL1G0 displayed increased ($P<0.05$) spreading when compared to Vector. Western blot analysis demonstrated 2- 5 fold decreased expression of β3 integrin and α-actinin in podoctyes expressing APOL1G1 and G2 when compared to podocytes expressing vector and APOL1G0.

Conclusions: Expression of APOL1 risk alleles (G1 and G2) compromised podocyte spreading by down regulation of β3 intergrin α-actinin expressions.

Funding: NIDDK Support

SA-PO305

Inhibiting Post-Translational Core Fucosylation Protects against Albumin-Induced Proximal Tubular Epithelial Cell Injury Wang Dapeng. *The First Affiliated Hospital of Dalian Medical University, Dalian, China.*

Background: Albuminuria is an independent risk factor for renal interstitial fibrosis (RIF). Glomerular-filtered albumin may cause injury to proximal tubular epithelial cells (PTECs) in endocytic and non-endocytic pathways via megalin and TGFβRII respectively. As megalin and TGFβRII are both modified by post-translational core fucosylation which plays a critical role in RIF, we identified whether or not core fucosylation is a potential target for reducing albumin-induced injury to PTECs.

Methods: We constructed a human PTEC-derived cell line of HK-2 cells and a bovine serum albumin (BSA) injury model *in vitro*. RNAi was used to inhibit expression of megalin, TGFβRII and FUT8. Western blotting, immunostaining, enzyme-linked immunosorbent assay, lectin blotting and fluorescence-activated cell sorting were used to determine BSA-induced endocytic and non-endocytic damages in HK-2 cells. FUT8 is a core fucosylation-related gene, the expression of FUT8 was significantly increased after incubation with BSA in HK-2 cells.

Results: FUT8siRNA significantly reduced core fucosyaltion of megalin and TGFβRII. Meanwhile, it could also inhibit activation of the TGFβ/TGFβRII/Smad2/3 signaling pathway. Furthermore, FUT8siRNA could reduce monocyte chemotactic protein-1; reactive oxygen species and apoptosis; and significantly decrease fibronectin and collagen I levels in BSA-overloaded HK-2 cells. Notably, inhibiting core fucosylation is more effective than either inhibiting megalin or inhibiting TGFβRII in the prevention of albumin-induced injury to PTECs.

Conclusions: Inhibition of core fucosylation could effectively alleviate albumin-induced endocytic and non-endocytic injury to PTECs, our study provides a potential therapeutic target in albuminuria-induced injury.

Funding: Government Support - Non-U.S.

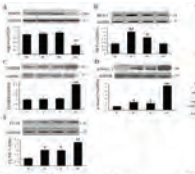


Fig. 1. BSA activates injury pathways and increases level of FUT8

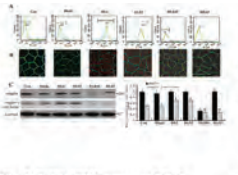


Fig. 2. FUT8 siRNA suppressed BSA endocytosis

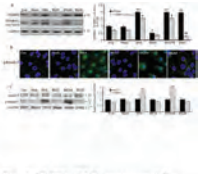


Fig. 3. FUT8 siRNA suppressed the activation of the TGFβ/TGFβRII/Smad2/3 signaling pathway

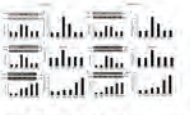


Fig. 4. FUT8 siRNA inhibits albumin-induced inflammation and oxidative stress

Fig. 5. FUT8 siRNA inhibited upregulation of Fibronectin and Collagen I

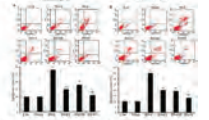


Fig. 6. FUT8 siRNA decreased cellular apoptosis

SA-PO306

Binding of Anti-dsDNA Antibodies to Major Vault Protein of Proximal Renal Tubular Epithelial Cells Resulted in Increased Fibronectin Expression and MCP-1 Secretion Susan Yung, Shirli S. Ho, Abel Chun, Kin Yi Au, Kwok Fan Cheung, Mel Chau, Daniel Tak Mao Chan. *Department of Medicine, The University of Hong Kong, Hong Kong SAR, Hong Kong.*

Background: Anti-dsDNA antibodies deposit in the kidney parenchyma in lupus nephritis. In addition to complement activation by immune complexes and activation of downstream pro-inflammatory mechanisms, whether these antibodies could directly induce organ damage remains controversial. We investigated the binding of human anti-dsDNA antibodies to proximal renal tubular epithelial cells (PTEC) and the downstream impact on cell functions.

Methods: Human polyclonal anti-dsDNA antibodies were isolated from the sera of lupus nephritis patients using affinity chromatography and those with high binding affinity to PTEC were selected for further studies. PTEC membrane, cytosolic and nuclear proteins were isolated and immunoprecipitated with anti-dsDNA antibodies to identify cross-reactive antigens using liquid chromatography-mass spectrometry (*LC-MS*).

Results: Anti-dsDNA antibodies bound to a 100 kDa protein, identified as major vault protein (MVP), which was present in the cytosolic and nuclear fractions, but not in the plasma membrane fraction. Incubation of PTEC with anti-dsDNA antibodies increased MVP expression, as determined by Western blot analysis, in a time-dependent manner ($P<0.001$, for 24h), and accompanied by increased fibronectin expression ($P<0.01$) and MCP-1 secretion ($P<0.05$) compared to cells incubated with IgG from healthy controls. Immunohistochemical studies showed predominantly perinuclear localization of MVP and weak intracellular expression of fibronectin under basal conditions. MVP overexpression in PTEC, by transfection with MVP plasmid, resulted in clustering of MVP in the cytoplasm, which was accompanied by fibronectin accumulation in the extracellular matrix and increased MCP-1 secretion ($P<0.01$). MVP gene silencing using RNAi resulted in 40% reduction in fibronectin expression and 53% reduction in MCP-1 secretion. Kidney biopsies from lupus nephritis patients showed markedly increased MVP expression, predominantly on proximal tubular epithelial cells.

Conclusions: Our data showed that anti-dsDNA antibody binding to MVP in PTEC was associated with downstream inflammatory and fibrogenic processes.

Funding: Government Support - Non-U.S.

SA-PO307

Module IV-Defected Mutant CCN2 Knock-In Transgenic Mice Grow and Develop Normally, but Fibrotic Properties Are Attenuated in a Number of Kidney Diseases Tsutomu Inoue, Ono Atsushi, Hirokazu Okada. *Saitama Medical University, Iruma-gun, Saitama, Japan.*

Background: CCN2 has been considered as important therapeutic target for CKD. It also plays a part in wound healing and metabolism in hard tissues, thus inhibition of the overall function of CCN2 is not practical as a treatment. Therefore, we are focusing on the modules that are responsible for fibrosis in the kidney.

Methods: As previously reported, we found that module IV-defective CCN2 expressed in tubular epithelial cells did not induce fibronectin synthesis in other cells. A CCN2 knockout mouse is potentially lethal. We next generated exon 5-deleted CCN2 gene knock-in mice (CCN2Ex5-/-), in which mutant CCN2 was expressed under the same control as the wild type. This experimental strategy allows us to investigate the fibrotic properties of CCN2 in detail. Unilateral ureter obstruction (UUO), subtotal nephrectomy (5/6Nx) and ischemic reperfusion (IRI) models were employed.

Results: In the UUO model, interstitial fibrosis was progressed at 8 and 24 hours, and 7 days in a time-dependent manner. The fibrotic area detected by Masson trichrome staining was significantly reduced in CCN2Ex5-/- mice. Expression of mutant CCN2 was elevated in CCN2Ex5-/- mice in comparison to CCN2Ex5+/+ mice. On the other hand, the expression of type I collagen (0.86 ± 0.28 vs. 0.52 ± 0.18), TGF-β1 (0.35 ± 0.07 vs. 0.23 ± 0.06), PAI-1 (0.13 ± 0.05 vs. 0.06 ± 0.04) were significantly decreased in CCN2Ex5-/- mice ($p<0.05$, Mann-Whitney U test). In the IRI model, although there was no significant difference in fibrosis or cytokine expression in the acute phase (at 3 days), both the progression of fibrosis and expression of related cytokines were significantly suppressed in CCN2Ex5-/- mice in the chronic phase (2 weeks). The same results were obtained with the 5/6Nx model. Western blot analysis using UUO 24-hour whole kidney samples revealed that there were no significant differences in signaling alterations in previously-reported cascades, including MAPK (ERK, p38, JNK) and Wnt/β-cat, between CCN2Ex5+/+ and CCN2Ex5-/-.

Conclusions: As module IV-defective CCN2 probably acts in a dominant-negative manner, the progression of interstitial fibrosis was suppressed in our transgenic mice. Also, this study indicates that module IV specifically contributes to the progression of CKD regardless of the type of primary disease process.

Funding: Government Support - Non-U.S.

SA-PO308

Sexual Dimorphism in the AKI to CKD Transition in the Rat Ixchel Q. Lima Posada,[3] Cinthya giovanna Portas cortés,[3] Rosalba Pérez-villalva,[2] Francesco Fontana,[4] Andrea Sanchez-Navarro,[3] Roxana Rodríguez Romo,[3] Gerardo Gamba,[1] Elena Zambrano,[1] Norma Bobadilla.[2] *[1]Instituto Nacional de Ciencias Medicas y Nutricion SZ, Mexico City, Mexico; [2]Molecular Physiology Unit, México, Mexico; [3]UNAM, Ciudad de México, Mexico; [4]Università degli studi di Modena e Reggio Emilia, Modena, Italy.*

Background: Recent epidemiological and experimental evidence has shown that after an episode of AKI, patients are at risk for developing CKD. In addition, it has been shown that the progression of chronic kidney disease is greater in men than in women before menopause, suggesting the involvement of sex hormones. This study evaluated if there is sexual dimorphism in the acute kidney injury to CKD transition, as well as the time course of the mechanisms involved in this potential dimorphic response.

Methods: Thirty nine female (F) and 39 male (M) rats were included. The rats were divided into two groups: sham operated and rats underwent 45 min bilateral renal ischemia (F+IR, and M+IR). All groups were studied and sacrificed at: 24 h, 1, 2, 4, and 4-months post-ischemia. Also, 41 oophorectomized rats were included and divided into sham or IR groups (Op and Op+IR). At the end of each experimental period, physiological, histopathological, and molecular studies were performed.

Results: We found a sexual dimorphic response in the AKI to CKD transition. After 24 h, I/R induced a similar functional and structural extent of renal injury in females and males, but female rats exhibited less oxidative stress and increased renal GSH content. After 4 months and despite similar renal injuries, the M+IR group developed CKD characterized by progressive proteinuria, renal dysfunction, tubulo-interstitial fibrosis and glomerular hypertrophy. Most of these alterations were observed since the 3rd month after IR and were associated with increased oxidative stress and a significant reduction in HIF1α, VEGF and endothelin receptor B mRNA levels since the 1st month. Interestingly, F+IR group did not develop CKD. Moreover, this group exhibited a significant increase in eNOS, TGFβ and Hif1α mRNA levels, since the 1st month after IR. Supporting this sexual dimorphism, Of+IR rats developed CKD similar to that observed in M+IR group.

Conclusions: We found a sexual dimorphic response in the AKI to CKD transition. Early antioxidant defense and higher TGFβ, HIF1α and eNOS mRNA levels were among the renoprotective mechanisms that the F+IR group demonstrated.

Funding: Government Support - Non-U.S.

SA-PO309

Kidney-Resident Macrophages (KRM) Upregulate Pro-Angiogenic Response in Chronic Ischemic Kidney Injury Amrutesh Puranik,[2] Irina A. Leaf,[1] Ahmed Saad,[2] Joseph P. Grande,[2] Stephen C. Textor,[2] Amir Lerman,[2] Jeremy S. Duffield,[3] Lilach O. Lerman.[2] *[1]Biogen, Cambridge, MA; [2]Mayo Clinic, Rochester, MN; [3]Vertex Pharmaceuticals, Boston, MA.*

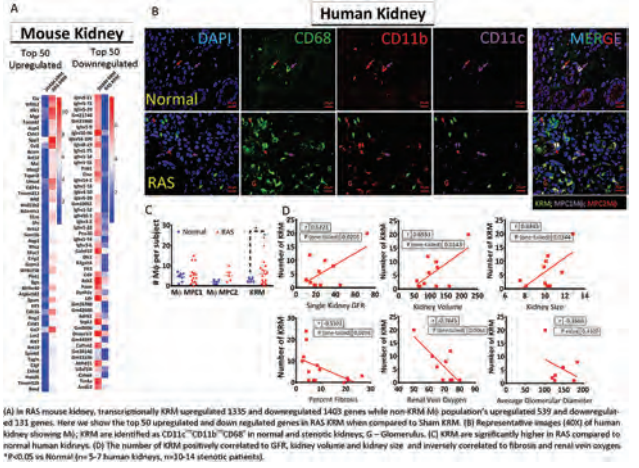
Background: Macrophages (Mϕ) play important roles in regulating progression & resolution of renal injury in renal artery stenosis (RAS). We have recently found that murine kidney Mϕ expressing $CD64^+F4/80^+FCRIV^+CD11b^{int}CD11c^{int}$ are anti-fibrotic and reparative. We hypothesized that these are KRM & expand in mouse and human renal ischemic disease

Methods: Using $CX3CR1^{creER}$:$Rosa26^{tdTomato}$ mice we fate-mapped the KRM and studied their kinetics in RAS. To dissect molecular mechanisms potentially underlying their protective properties in RAS, we compared KRM transcriptional profiles to non-KRM Mϕ by RNA Sequencing (Fig A). Furthermore, we identified $CD11b^{int}CD11c^{int}CD68^+$ KRM in human kidney biopsies of normal and RAS patient kidneys and correlated their number with kidney function (Fig B).

Results: Fate-mapping studies identified $CD64^+F4/80^+CD11b^{int}CD11c^{int}$ as KRM. BrdU labeling show KRM expand in RAS. KRM showed a more robust response to RAS compared to Sham KRM and non-KRM Mϕ (Fig A). RAS KRM were transcriptionally heterogeneous, containing both pro- and anti-inflammatory pathways. Angiogenic Pathway was the greatest functionally enriched in RAS-KRM. Further, while both KRM and non-KRM upregulated immune pathways, only KRM downregulated immune genes including Irf5, a molecular switch to pro-inflammatory states. Finally, KRM number significantly (Fig C) increased in human stenotic kidney biopsies compared to normal and correlated with better kidney function and lower fibrosis (Fig D).

Conclusions: Thus, murine $CD64^+F4/80^+FCRIV^+CD11b^{int}CD11c^{int}$ Mϕ are KRM, and can also be identified in human kidneys. KRM show a more robust response to chronic ischemic kidney injury compared to non-KRM Mϕ, upregulating a pro-angiogenic and reparative gene profile. These observations may have important prognostic and therapeutic implications in chronic kidney injury.

Funding: NIDDK Support



(A) In RAS mouse kidney, transcriptionally KRM upregulated 1335 and downregulated 1403 genes while non-KRM Mϕ population's upregulated 539 and downregulated 131 genes. Here we show the top 50 upregulated and down regulated genes in RAS KRM when compared to Sham KRM. (B) Representative images (40X) of human kidney showing Mϕ; KRM are identified as $CD11c^{+}CD11b^{int}CD68^{+}$ in normal and stenotic kidneys; G – Glomerulus. (C) KRM are significantly higher in RAS compared to normal human kidneys. (D) The number of KRM positively correlated to GFR, kidney volume and kidney size and inversely correlated to fibrosis and renal vein oxygen. *P<0.05 vs Normal (n= 5-7 human kidneys, n=10-14 stenotic patients).

SA-PO310

Hypoxia-Induced Proteins as Novel Biomarkers of Early Stage Kidney Disease Leah M. Ewart,[1] Karen A. Creevey,[1] Caitriona M. McEvoy,[1] Debra F. Higgins.[1,2] *[1]UCD Conway Institute, Dublin, Ireland; [2]School of Medicine, University College Dublin, Dublin, Ireland.*

Background: In the kidney, hypoxia (low oxygen) promotes fibrogenesis through stabilisation of hypoxia inducible transcription factors (HIFs), induction of pro-fibrogenic and pro-inflammatory gene expression, and modulation of the extracellular matrix. Inhibiting HIF-1 function attenuates renal fibrosis in vivo. As hypoxia is an early pathological feature of kidney injury, hypoxia-induced proteins may represent novel urinary biomarkers for detection of early stage renal injury.

Methods: Hypoxia-induced gene and protein expression was analysed in two pre-clinical models of kidney injury; reverse-unilateral ureteral obstruction (R-UUO) and gentamicin-sulphate-induced (GS) renal disease (40 or 120 mg/kg/day for 9 days), and in two independent kidney transplant biopsy collections from the GoCAR (Genomics of Chronic Allograft Nephropathy, United States) and the North Dublin Renal Biobank (Ireland) studies.

Results: A number of hypoxia-responsive genes were significantly increased in UUO and down-regulated with resolution of injury. Expression analysis of these genes revealed positive correlation with degree of injury and negative correlation with eGFR in the two independent renal transplant collections. Furthermore, urinary levels of the encoded hypoxia-responsive proteins correlated with injury in the gentamicin model and inhibition of their function protected the kidney from disease.

Conclusions: We conclude that hypoxia-responsive proteins are up-regulated during kidney injury, can be exploited as urinary biomarkers for early stage kidney disease and have potential as novel therapeutic targets for CKD.

Funding: Government Support - Non-U.S.

SA-PO311

Hypoxia-Inducible Factors-1α Driving a Metabolic Shift in Tubular Epithelial Cells Promotes Renal Fibrosis Qi Yuan,[1] Junwei Yang.[2] *[1]Nanjing Medical University, Jiangsu Nanjing, China; [2]Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.*

Background: Hypoxia promotes fibrosis in various renal disease models. Hypoxia-inducible factor 1 (HIF-1), a transcriptional factor, is a master regulator of gene expressions under hypoxic conditions. Fatty acids are used to fuel oxidative phosphorylation (OXPHOS) to produce ATP in normal tubular epithelial cells. Hypoxia can drive glycolysis, as an oxygen deficit results in limited OXPHOS. Recent studies have established that besides glycolysis, several aspects of lipid metabolism including lipid droplets and β-oxidation play key roles in adaptation to low oxygen conditions. Therefore, we hypothesize that the HIF pathway may provide a switch through which metabolic phenotypes can be amended during the process of renal fibrosis.

Methods: Western blot and qPCR analysis were performed to examine the levels of lipid catabolism enzymes, glycolytic enzymes and HIF-1α in folic acid (FA) induced renal fibrotic mice. Then, FA mice were administered with control or dinitrophenol (DNP), which causes kidney hypoxia and activates HIF-1α, to determine whether HIF-1α affects metabolic switch. Further mechanism was searched in tubular epithelial cells in vitro.

Results: We identified significant lipid accumulation and higher expression of glycolytic enzymes accompanied with up-regulated HIF-1α in renal tissues of FA mice. DNP treatment decreased fatty acid oxidation and increased glycolysis, which served to maintain sustained ATP and promote fibroblast proliferation and ECM production in mice kidney. In tubular epithelial cells, TGF-βaccumulated higher amount of lipids through a combination of metabolic alterations including fatty acid uptake, decreased fatty acid oxidation, and activated glycolysis enzymes, while increased the markers of collagen fibrils. Transfection with siRNA to HIF-1α reversed the effect in vitro.

Conclusions: It can be concluded that HIF-1α plays a major role in the metabolic reprogramming of renal fibrosis. Targeting the HIF pathway may provide novel therapeutic approach of kidney fibrosis.

Funding: Government Support - Non-U.S.

SA-PO312

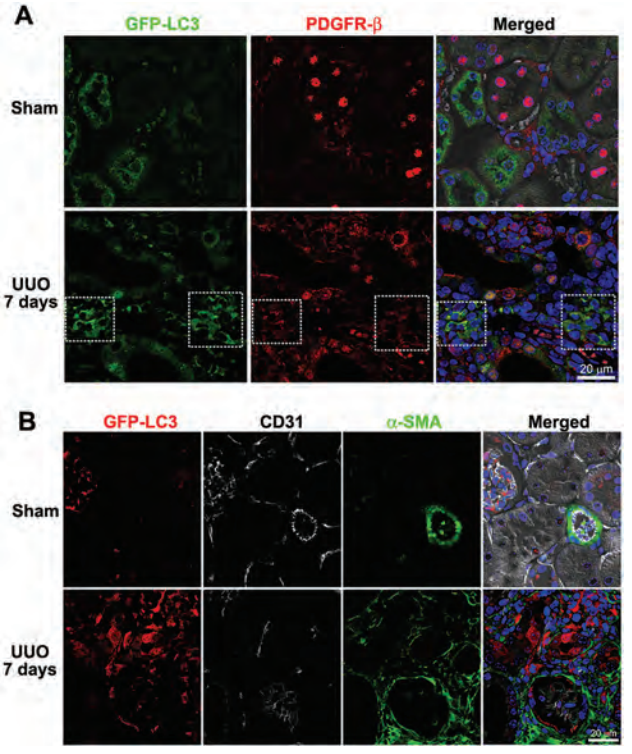
Autophagy in FOXD1 Stroma-Derived Cells Plays a Critical Role in Renal Tubulointerstitial Fibrosis Yong Kyun Kim,[3,4] Sun-ah Nam,[2] Chul Woo Yang,[1] Jin Kim.[2] *[1]Seoul St. Mary's Hospital, Seoul, Republic of Korea; [2]The Catholic University of Korea, Seoul, Republic of Korea; [3]Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea; [4]Cell Death Disease Research Center, College of Medicine, The Catholic University of Korea, Seoul, Republic of Korea.*

Background: Autophagy is a cellular process of degradation of damaged cytoplasmic components and regulates cell death and proliferation. It remians unclear whether the induction of autophagy has positive impact or negative impact in renal tubulointerstitial fibrosis (TIF). FOXD1 lineage pericyte has been recognized to plays a critical role in renal TIF. Here, we hypothesized that autophagy in FOXD1 lineage stromal cell may have pivotal role in renal TIF.

Methods: To examine the distribution of cells where autophagy was induced, we used GFP-LC3 transgenic mice. We also generated conditional knockout mice in which Atg7 is genetically ablated specifically in FOXD1-cells ($Atg7^{f/f}$;FOXD1-Cre^{+}).

Results: Punctate distribution of GFP-LC3 was was highly expressed in not only renal tubular epithelial cells but interstitial cells after UUO, which were colocalized with PDGFR-β positive cells. Tubulointerstitial fibrosis was enhanced in $Atg7^{f/f}$;FOXD1-Cre^{+} after UUO through Smad dependent TGF-β signaling compared with wild type (WT) mice. In $Atg7^{f/f}$;FOXD1-Cre^{+}, the accumulation of interstitial myofibroblasts was increased and the differentiation of pericyte into myofibroblasts was enhanced compared with WT mice after UUO. The peritubular capillary rarefaction and the apoptosis of interstitial cells were accelerated in $Atg7^{f/f}$;FOXD1-Cre^{+} after UUO.

Conclusions: Our data showed that autophagy in FOXD1 stroma-derived cells play a protective role in development of renal TIF, which may be a new therapeutic target for renal TIF.



A. After UUO, GFP-LC3 puncta was highly expressed in not only renal tubular epithelial cells but also interstitial cells, which were colocalized with PDGFR-β positive cells.B. GFP-LC3 puncta were rarely colocalized with a-SMA–positive interstitial cells or CD31-positive cells.

SA-PO313

Autophagy Is Induced via HIF-1 to Facilitate Renal Interstitial Fibrosis during Unilateral Ureteral Obstruction in Mice and Hypoxia in Tubular Cells Jing Liu,[1,2] Man J. Livingston,[2] Qingqing Wei,[2] Zheng Dong.[2,1] *[1]Department of Nephrology, The Second Xiangya Hospital, Central South University, Changsha, China; [2]Augusta University Medical College of Georgia, Augusta, GA.*

Background: Autophagy, a fundamental cellular catabolic process, has recently been implicated in renal fibrosis. However, it is unclear how autophagy is activated under this condition. Hypoxia-inducible factors (HIF) are master regulators of hypoxia responsive genes and may contribute to renal fibrosis. Whether HIF is involved in autophagy activation during renal fibrosis is largely unknown.

Methods: In vivo, renal fibrosis was induced by unilateral urethral obstruction in mice. In vitro, renal proximal tubular cells were exposed to hypoxia to induce fibrotic changes. YC-1 was used to inhibit HIF pharmacologically. Kidney proximal tubule-specific HIF-1 knockout (PT-HIF-1 KO) mice were also examined.

Results: UUO induced HIF-1 and autophagy, which was accompanied by renal interstitial fibrosis. Pharmacological inhibition of HIF with YC-1 attenuated autophagy activation and renal interstitial fibrosis during UUO. Moreover, compared with wild-type mice, PT-HIF-1 KO mice showed significantly lower autophagy during UUO. These mice also had lower levels of renal fibrosis as shown by the decreased expression of fibronectin, collagen I, α-SMA and vimentin. In cultured proximal tubular cells, hypoxia induced HIF-1, autophagy, and the accumulation of fibronectin, which were suppressed by the HIF inhibitor YC-1. In addition, knockdown HIF-1 in these cells attenuated autophagy activation and fibronectin accumulation during hypoxia exposure.

Conclusions: The results suggest that in renal fibrosis, HIF-1 may activate autophagy in renal tubular cells to facilitate the development of renal interstitial fibrosis.

Funding: NIDDK Support, Veterans Affairs Support, Government Support - Non-U.S.

SA-PO314

Screening Fibroblasts for Novel Therapeutic Targets in CKD Ian Logan,[3] Neil S. Sheerin,[1] Victoria G. Shuttleworth.[2] *[1]Newcastle University, Newcastle upon Tyne, United Kingdom; [2]Newcastle University, UK, Newcastle Upon Tyne, United Kingdom; [3]newcastle hospitals, Newcastle----, United Kingdom.*

Background: The most significant problem in nephrology is the progression of Chronic Kidney Disease (CKD) to End Stage Renal Disease (ESRD), which requires either dialysis or transplantation to sustain life. Despite an our knowledge that ESRD is caused by accumulation of fibrotic scar tissue leading to organ failure, no treatments are

available to treat fibrosis. Targeting disease-causing renal fibroblasts may hold the key to new drugs to treat CKD.

Methods: Drug screening: Human renal fibroblasts were isolated under ethical approval from the normal poles of 3 nephrectomy specimens and expanded by outgrowth. They were cultured in the presence of TGF B-1 and 181 drugs targetting human epigenetic enzymes prior to WST-1 proliferation assays. Flow cytometry: Cell cycle profiles were evaluated by propidium iodide staining fixed cells, whereas apoptosis was analysed using Annexin V staining in live cells. Animal studies: Black 6 mice underwent unilateral ureteric obstruction (UUO) by ligation, under ethical approval and licencing, then treated with Aurora kinase inhibitors from day zero. Animals were sacrificed on day 10. Immunohistochemistry for alpha-SMA was performed on kidney tissue and analysed by automated microscopy. Values were subject to T-test statistical analysis.

Results: 1. Drug screening revealed that 15 Aurora kinase inhibitors were effective at inhibiting proliferation of primary renal fibroblasts to more than 85%. Counterscreening showed these had no such impact on primary tubular cells. 2. Flow cytometry demonstrated that fibroblast cell cycle profiles were relatively unchanged upon Aurora kinase inhibitor treatment, but we observed a large enrichment in apoptosis to > 85% upon drug treatment. 3. We observed a 75% reduction in alpha-SMA staining upon treatment with Aurora kinase A inhibitor in injured kidneys compared to vehicle-treated animals.

Conclusions: 1. Primary renal fibroblasts can be propagated and used as a model of CKD in target identification studies. 2. Targeting Aurora kinases with small molecule inhibitors causes selective apoptosis in fibroblasts but not tubular cells. 3. UUO mice demonstrate reduced fibroblast accumulation, by alpha-SMA expression, upon Aurora kinase A inhibition. Overall, our data suggest that Aurora kinase inhibitors may have therapeutic utility in slowing progression of CKD to ESRD.

SA-PO315

Mechanisms of GLP-1 Receptor Independent Renoprotective and Anti-Fibrotic Effects of DPP-4 Inhibitor Linagliptin in GLP-1 Receptor Knockout Mice with 5/6 Nephrectomy Berthold Hocher,[3] Ahmed A. Hasan,[3] Karoline von Websky,[3] Christoph Reichetzeder,[3] Oleg Tsuprykov,[3] Jingli Guo,[2] Denis Delic,[1] Thomas Klein.[1] *[1]Boehringer Ingelheim, Biberach, Germany; [2]Charité-Universitätsmedizin, Berlin, Germany; [3]University of Potsdam, Potsdam, Germany*.

Background: Dipeptidyl peptidase (DPP)-4 inhibitors were reported to have beneficial effects in experimental chronic kidney disease models. The underlying mechanisms are not clearly understood. Many studies suggested that these renoprotective effects are mediated via the glucagon like peptide-1 (GLP-1)/GLP-1 receptor pathway. To challenge this hypothesis we investigated the renal effects of the DPP-4 inhibitor linagliptin (LIN) in GLP-1r$^{-/-}$ mice with 5/6 nephrectomy (5/6 Nx)

Methods: The mice were allocated to the following groups: sham + wild-type + placebo (PBO); 5/6 Nx + wild-type + PBO; 5/6 Nx + wild-type + LIN; sham + GLP-1r$^{-/-}$ + PBO; 5/6 Nx + GLP-1r$^{-/-}$ + PBO and 5/6 Nx + GLP-1r$^{-/-}$ + LIN and the treatment period was 12 weeks

Results: 5/6 Nx led to the development of renal interstitial fibrosis and glomerulosclerosis, increased plasma cystatin C levels and suppressed renal gelatinase/collagenase activity and these effects were counteracted by LIN treatment. In addition, proteins were separated from kidney tissues and subjected to LC-MALDI mass spectrometry. LIN treatment significantly up-regulated 4 peptides derived from collagen Iα1, thymosin β4, α-enolase and heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1) and significantly down-regulated one peptide derived from Yb-1 (Nuclease-sensitive element-binding protein 1)

Conclusions: HNRNPA1 phosphorylation plays a major role in the downstream nuclear signaling of atrial natriuretic peptide (ANP) through cGMP and cGMP-dependent protein kinase. In the kidney, a disturbance of ANP-mediated cGMP synthesis is known to be a trigger of fibrosis. Also, Yb-1, α-enolase and thymosin β4 were reported to be involved in renal fibrosis through controlling TGFβ-1, PAI-1, and extracellular matrix degradation. In conclusion, the beneficial renal effects of LIN in mice with 5/6 nephrectomy cannot solely be attributed to the GLP-1/GLP-1 receptor pathway, highlighting the importance of other novel signaling pathways influenced by DPP-4 inhibition such as collagen I homeostasis, the ANP/cGMP/HNRNPA1 pathway, Yb-1, α-enolase and thymosin β4

Funding: Commercial Support - Boehringer Ingelheim

SA-PO316

The Atypical Chemokine Receptor 2 Limits Fibrotic Remodelling after Ischemia-Reperfusion Injury of the Kidney Moritz X. Lux, Andrei Bideak, Alexander Blaut, Nuru Eltrich, Volker Vielhauer. *Nephrologisches Zentrum, Medizinische Klinik und Poliklinik IV, Ludwig-Maximilians-University Munich, Munich, Germany*.

Background: Acute kidney injury (AKI) is a risk factor for the development of chronic kidney disease (CKD). After ischemia-reperfusion-injury (IRI), a major aetiology of human AKI, resolution of renal inflammation allows tubular regeneration, whereas ongoing inflammatory injury mediated by infiltrating leukocytes leads to nephron loss and renal fibrosis, typical hallmarks of CKD. The atypical chemokine receptor 2 (ACKR2) is a chemokine decoy receptor, which scavenges inflammatory CC-chemokines and reduces local leukocyte accumulation and inflammation.

Methods: Here, we hypothesized that ACKR2 limits leukocyte infiltration, inflammation and fibrotic tissue remodelling after renal IRI, thus preventing progression to CKD after AKI. We tested this hypothesis by subjecting wild-type (WT) and Ackr2-deficient mice to IRI induced by transient renal pedicle clamping. In addition, in vitro experiments were performed with tubulointerstitial tissue isolated form wild-type and Ackr2-/- mice.

Results: Compared to WT control Ackr2 deficiency lead to significantly increased CCL2 levels in TNF-stimulated tubulointerstitial tissue in vitro. In vivo, Ackr2 deficiency did not affect renal dysfunction and tubular injury in early IRI one day after bilateral or 5 days after unilateral pedicle clamping, although accumulation of mononuclear phagocytes increased in postischemic Ackr2-/- kidneys. Regarding long-term outcomes, postischemic Ackr2-/- kidneys displayed significantly more tubular injury 5 weeks after unilateral IRI, which was associated with persistent increases in mononuclear phagocyte and T cell infiltrates compared to WT. Moreover, Ackr2 deficiency resulted in more severe inflammation in postischemic kidneys, with increased expression of proinflammatory chemokines and M1 macrophage markers, and enhanced accumulation of Ly6C^{high} inflammatory macrophages. This was associated with aggravated renal fibrosis in Ackr2-/- kidneys 5 weeks after IRI, as revealed by increased expression of matrix molecules, renal accumulation of αSMA+ myofibroblasts and enhanced renal infiltration of bone marrow-derived fibrocytes.

Conclusions: These data suggest that the chemokine decoy receptor ACKR2 plays an important role in limiting persistent inflammation, tubular loss, and renal fibrosis after ischemic AKI, and thus prevents subsequent progression to CKD.

Funding: Government Support - Non-U.S.

SA-PO317

Loss of the Protein Cystathionine β-Synthase during Kidney Injury Promotes Renal Tubulointerstitial Fibrosis Qiongjing Yuan. *Xiangya Hospital, Central South University, Changsha, China*.

Background: Renal tubulointerstitial fibrosis (TIF) is the common pathway of progressive chronic kidney disease. Inflammation has been widely accepted as the major driving force of TIF. Cystathionine β-synthase (CBS) is the first and rate-limiting enzyme in the transsulfuration pathway. The purpose of this study was to investigate the potential role and mechanism of CBS in renal inflammation and TIF.

Methods: Renal function, tubulointerstitium damage index score, extracellular matrix (ECM) deposition, and the expressions of CD3, CD68, IL-1β, TNF-α were measured in sham operation and UUO rats. Proteomics and gene array analysis were performed to screen differentially expressed molecules in the development of renal inflammation and TIF in UUO rats. The expression of CBS was detected in patients with obstructive nephropathy and UUO rats. We confirmed the expression of CBS using western blot and real-time PCR in HK-2 cells. Overexpression plasmid and siRNA were transfected specifically to study the possible function of CBS in HK-2 cells.

Results: Abundant expression of CBS, localized in renal tubular epithelial cells, was revealed in human and rat renal tissue, which correlated negatively with the progression of fibrotic disease. Expression of CBS was dramatically decreased in the obstructed kidney from UUO rats as compared with the sham group. In addition, knocking down CBS exacerbated ECM deposition, whereas CBS overexpression attenuated TGF-β1-induced ECM deposition in vitro. Inflammatory and chemotactic factors were also increased in CBS knockdown HK-2 cells stimulated by IL-1β.

Conclusions: These findings establish CBS as a novel inhibitor in renal fibrosis and as a new therapeutic target in patients with chronic kidney disease.

Funding: Government Support - Non-U.S.

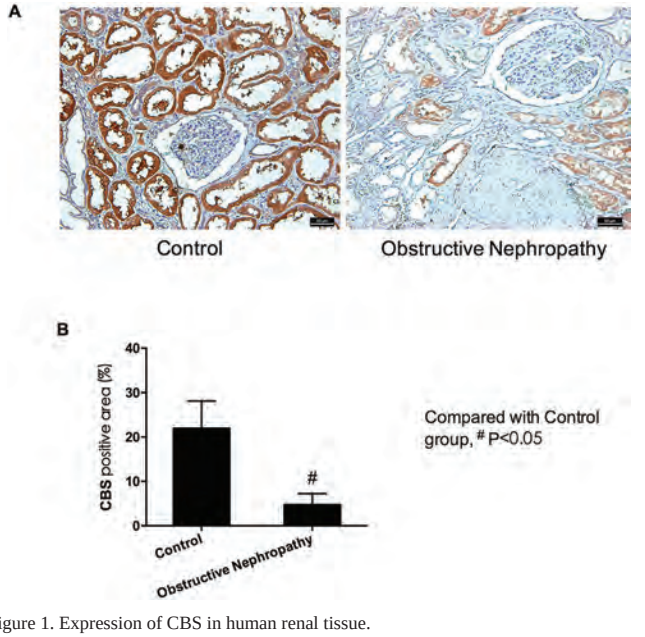


Figure 1. Expression of CBS in human renal tissue.

SA-PO318

Paraquat-Induced CKD in Experimental Animals: Relevance to CKD of Unknown Origin (CKDu) Fan Lei,[3] Qingtian Li,[1] Yi Tang,[4,1] Luping Huang,[1] Luan D. Truong,[2] David Sheikh-Hamad.[1] *[1]Baylor College of Medicine, Houston, TX; [2]The Methodist Hospital, Houston, TX; [3]Baylor College of Medcine, Houston, TX; [4]West China Hospital of Sichuan University, Chengdu, China*.

Background: CKDu is typically encountered in farm workers from different regions of the world, and kidney biopsies from representative patients display tubulointerstitial injury and inflammation. Survey of patients with chronic kidney disease of unknown etiology (CKDu) encountered at a safety net hospital in Houston, identified the herbicide Gramoxone (paraquat-based) as a possible etiologic factor for CKDu in migrant workers originally engaged in agricultural/farm work before their immigration to the US. These subjects described repeated and chronic (years) skin exposure to Gramoxone, as protective gear is not ordinarily used during preparation and spray work. We tested the hypothesis that repetitive exposure of mice to paraquat will lead to chronic kidney disease; as such, repetitive exposure to Gramoxone might produce CKD in humans.

Methods: Mice were given 10 i.p. injections of 20 mg/kg paraquat, given weekly, and allowed free access to food and water. This dose was based on titration experiments where a single dose produces no functional or histological changes in the kidney. At the end of week 10, 24h urine was collected and blood samples were obtained for measurement of creatinine clearance. Mice were euthanized and kidneys were subjected to PAS and Trichome stains and immunostain for T cells (CD3) and macrophages (F4/80); parallel examination of lung, liver and spleen was carried out to determine the effects on other organs.

Results: Paraquat-treated mice displayed doubling of serum creatinine, 50% reduction in creatinine clearance, three-fold increase in T-cells and macrophage infiltration, and increased trichrome staining. There were no changes in the morphology or macrophage infiltration in the liver and lung; however, the spleen showed increased macrophage infiltration.

Conclusions: Repetitive exposure of mice to paraquat given i.p. to simulate exposure of farm workers to paraquat (Gramoxone), produced CKD characterized by tubulointerstitial injury and inflammation, reminiscent of the pathological picture observed in patients with CKDu. Our data suggest that chronic exposure to the herbicide Gramoxone by farm workers in different regions of the world should be considered as a possible etiologic factor for CKDu.

Funding: Veterans Affairs Support, Private Foundation Support

SA-PO319

Development of a Refined Subtotal Nephrectomy Mouse Model to Study Progressive Renal Disease James O'Sullivan, Sarah L. Finnie, Laura Denby. *University of Edinburgh, Edinburgh, United Kingdom*.

Background: Chronic Kidney Disease (CKD) is characterised as the decline of renal function over time. Metabolomics data has elucidated new metabolites, including citrulline, to be associated with human CKD indicating alterations in metabolic pathways being involved in CKD [Rhee EP et al, 2013]. Furthermore, defective fatty acid oxidation has been found to be involved in tubulointerstitial fibrosis [Kang HM et al, 2015]. The rat subtotal nephrectomy (STNx) model is a commonly used model of progressive renal disease and replicates many aspects of human CKD. However, a consistent mouse model of STNx which mimics most of the typical features of CKD would be advantageous to elucidate the pathophysiology.

Methods: Inbred 129S2/SvHsd mice were randomised to sham or one-step subtotal nephrectomy (STNx) surgery and sacrificed after 6 (n=6/gp) or 10-weeks (n=8-9/group). The one-step STNx involves flank incision nephrectomy followed by flank incision removal of upper and lower poles of the remaining kidney. At sacrifice, tissue was taken for RNA, protein and histological analyses. At baseline, 6 weeks and 9 weeks animals had urine collected and echocardiography performed. Blood pressure (BP) was measured by tail cuff plethysmography (baseline and 9 weeks). Gene expression was determined via qRT-PCR and normalised to 18S/PPIA. Fibrosis scoring was conducted using picrosirius red staining for total collagen, quantified in ImageJ.

Results: This refined STNx model had a survival rate of 95%. At 10 weeks post surgery STNx animals had significantly increased systolic BP (Sham: 110+/7.8 vs STNx: 153.1+/-13.8 mmHg), significantly increased urinary albumin:creatinine ratio ($p<0.01$; 16.37 vs 2028.5 mg/g; sham vs STNx) and developed left ventricular hypertrophy (LVH) (1.4-fold increase STNX vs SHAM). Histological analysis revealed a significant increase in renal and cardiac fibrosis in STNx mice vs sham which was reflected by 2-fold increase in collagen gene expression ($p<0.01$ vs sham). Additionally, gene expression of metabolic pathways was downregulated in STNx kidneys and heart ($p<0.05$ vs sham).

Conclusions: Our refined STNx model is a robust model of progressive renal disease that develops significant hypertension, proteinuria, renal and cardiac fibrosis, LVH and alterations in cellular metabolism indicating this model reflects the cardio-renal dysfunction observed in human CKD.

SA-PO321

Elucidation of the Gene Regulatory Networks That Control Diabetes-Induced Kidney Damage Bo Wang,[2] Haroon Naeem,[2] Guanyu Ji,[1] Phillip Kantharidis,[2] Sharon D. Ricardo.[2] *[1]E-gene co.ltd, ShenZhen, China; [2]Monash University, Melbourne, NSW, Australia*.

Background: Diabetes mellitus is an epidemic of the 21st century and is now the leading cause of chronic kidney disease (CKD) that results in the development of fibrosis. TGF-b1 is of the major drivers in the progression of diabetic nephropathy We use advanced next-generation sequencing (NGS) technology to identify genomic sequences and signatures unique to TGF-b1 to provide a global approach for interrogating TGF-β1-induced kidney damage. The discovery of new therapeutic targets was coupled with complementary functional analyses to identify and validate novel regulators of kidney injury and fibrosis.

Methods: Mesangial cells were treated with TGF-β1 at 10ng/ml for 72 hours, followed by NGS to determine miRNA, mRNA, DNA methylation and H3K27me3 levels. Integrative and complementary functional analyses were employed to identify potential regulators and qPCR and luciferase assay used for validation.

Results: A genetic and epigenetic library as established and includes miRNA, RNA, DNA methylation and histone (H3K27me3) modification. Our data showed that the hyper-methylation of DNA methylation was induced by TGF-β1. H3K27me3 expression was inhibited by TGF-β1 treatment together with the regulation of NRARP and TnxB identified as new targets in the development of fibrosis. The negative and positive expression pattern of miRNA and mRNA were quantified in response to TGF-β1. A novel regulator, miR-378, was also found to be a pivotal regulator of the TGF-β/Smad pathway, confirmed using NRK52E cells co-transfected with the SMAD3 CAGA reporter and miR-378 in the presence of TGF-β1 for 3 days of culture and STZ-induced diabetic kidney samples. Moreover, miR-378 was found to regulate MAPK signalling through repression of the MAPK1 pathway.

Conclusions: TGF-b1 mediates genetic and epigenetic interactions in kidney mesangial cells within a complicated network of gene expression and DNA modification. DNA methylation and H3K27me3 modification were found to be involved in TGF-β1 regulated pathogenesis of mesangial cells. We established a multi-omics library to demonstrate the gene expression regulated by miRNA and epigenetic changes. We report a protective regulator of miR-378 through mediating MAPK pathway, in the downstream induction of kidney cell fibrosis and mesangial hypertrophy. Moreover, H3K27me3 was indicated as a novel regulator using NGS technology.

Funding: Government Support - Non-U.S.

SA-PO322

Modulation of Upregulated Transcriptional Signaling Pathways in Rodent Diabetic Nephropathy after Treatment with a Novel Anti-Fibrotic Agent FT011: Correlates with Human Diabetic Kidney Disease Robyn G. Langham,[3] Sebastian Martini,[1] Felix H. Eichinger,[2] Viji Nair,[2] Matthias Kretzler,[2] Darren J. Kelly.[1] *[1]Ludwig Maximilian University Munich, Munich, Germany; [2]University of Michigan, Ann Arbor, MI; [3]Monash University, Melbourne, VIC, Australia*.

Background: Transcriptomic analysis of diabetic nephropathy (DN) biopsy tissue has provided valuable insights into the regulatory networks that may drive progressive disease. In this study, we undertook a transcriptomic analysis associated with demonstrated improved histological and clinical effects of a new anti-fibrotic, FT011, in a rodent model of DN. We also aimed to compare the animal findings with that already understood to be involved in human DN, a means of predicting utility of FT011 in humans.

Methods: Control and diabetic Ren(2) rats were treated with either FT-011(200mg/kg/day) or vehicle for 16 weeks(Early), or for the last 2 days of the study(Late). Total RNA was isolated from renal cortex, reverse transcribed, linearly amplified, and hybridized on Affymetrix microarrays. The Ingenuity® Pathway Analysis Software Suite was used for gene analysis.

Results: Gene expression data in diabetic rats showed early findings in keeping with Type 1 diabetes, early suppression of lymphocyte genes, and an increase in known diabetes-related genes. Short term FT011-treatment of rats with established DN showed acute up-regulation of Fatty acid oxidation pathways, while the longer term treatment showed a suppression of activated inflammatory pathways, and suppression of drivers of fibrosis (*TGFß*) and of transcriptional regulators known to be involved in progressive forms of DN (*STAT1*). Short-term late treatment with FT011 showed a reduced inhibitory effect on inflammatory pathways. Comparison with the transcriptome from human DN demonstrated several overlapping key features and pathways of the human disease to be recapitulated in the animal model used, with a significant z-score of 6.4.

Conclusions: Analysis of transcriptional changes mediated by treatment with FT011 has shown an early up-regulation of fatty acid oxidation, and a later, more sustained anti-inflammatory and anti-fibrotic action. Similarity of the changes seen in the animal model to the human transcriptional data set highlights the close alignment of this model to the human disease. As well, the ability of FT011 to modulate key signaling pathways identified as important in the pathogenesis of human DN further supports its potential utility as a new therapy for DN.

SA-PO323

Melatonin Ameliorates Intrarenal Renin-Angiotensin System in a 5/6 Nephrectomy Rat Model Sayaka Ishigaki, Naro Ohashi, Takashi Matsuyama, Shinsuke Isobe, Naoko Tsuji, Tomoyuki Fujikura, Takayuki Tsuji, Akihiko Kato, Hideo Yasuda. *Hamamatsu University School of Medicine, Hamamatsu, Japan.*

Background: Activation of the intrarenal renin-angiotensin system (RAS) plays a critical role in the pathophysiology of chronic kidney disease (CKD) and hypertension. Reactive oxygen species (ROS) are important components of intrarenal RAS activation and there has been great interest in developing strategies that target the ROS-RAS axis in the treatment of CKD. Melatonin is recognized as a powerful antioxidant, and we recently reported that impaired nighttime melatonin secretion correlates negatively with urinary angiotensinogen excretion, the surrogate marker of intrarenal RAS activity in patients with CKD. However, whether melatonin supplementation ameliorates the augmentation of intrarenal RAS in CKD has remained unknown. We aimed to clarify whether exogenous melatonin ameliorates intrarenal RAS activation via the reduction of ROS production.

Methods: 5/6 nephrectomized (Nx) rats were used as a chronic progressive CKD model and compared with sham-operated control rats. The Nx rats were divided into untreated Nx rats and melatonin-treated Nx rats. The levels of intrarenal RAS, ROS components, and renal injury were evaluated after 4 weeks of treatment.

Results: Compared with the control rats, the untreated Nx rats exhibited significant increases in intrarenal RAS (angiotensinogen, angiotensin II type 1 receptors, and angiotensin II), accompanied by elevated blood pressure, higher oxidative stress (8-hydroxy-2'–deoxyguanosine), lower antioxidant (superoxide dismutase) activity, and increased markers of interstitial fibrosis (α-smooth muscle actin and type I collagen) in the remnant kidneys. Treatment with melatonin significantly reversed intrarenal RAS and ROS activation (angiotensin II positive area (%); Nx: 5.54 ± 0.44 vs. Nx+MEL: 2.99 ± 0.33, p<0.01 and superoxide dismutase (U/g tissue); Nx: 27.4 ± 3.0 vs. Nx+MEL: 42.4 ± 3.2, p=0.011), decreased blood pressure (systolic blood pressure (mmHg); Nx: 203.5±8.7 vs. Nx+MEL: 173.0 ± 8.7, p=0.049), and ameliorated interstitial fibrosis (α-smooth muscle actin (%); Nx: 2.76 ± 0.37 vs. Nx+MEL: 1.51 ± 0.21, p=0.033).

Conclusions: Antioxidant treatment with melatonin was shown to ameliorate intrarenal RAS and ROS activation and renal injury in a 5/6 Nx rat model.

SA-PO324

Targeting Src Attenuates Peritoneal Fibrosis and Inhibits Epithelial to Mesenchymal Transition of Peritoneal Mesothelial Cells Jun Wang,[2] Liuqing Xu,[3] Na Liu,[2] Shougang Zhuang.[1] *[1]Rhode Island Hospital, Alpert Medical School of Brown University, Providence, RI; [2]Department of Nephrology, Shanghai East Hospital, Tongji University, Shanghai, China; [3]Department of Nephrology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China.*

Background: Src mediates tissue fibrosis in several organs, but its role in peritoneal fibrosis remains unknown.

Methods: We evaluated the therapeutic effect of a highly selective Src inhibitor KX2-391, on development of chlorhexidine gluconate (CG)-induced peritoneal fibrosis in a rat model.

Results: Daily intraperitoneal CG injections induced peritoneal fibrosis, indicated by submesothelial collagen fibril accumulation and myofibroblast activation, accompanied by time-dependent Src phosphorylation at tyrosine 416. KX2-391 attenuated peritoneal fibrosis, abrogating increased phosphorylation of Src and multiple signaling molecules associated with tissue fibrosis, including epidermal growth factor receptor, Akt, Signal transducer and activator of transcription 3 and nuclear factor-κ*B* in the injured peritoneum. KX2-391 inhibited proinflammatory cytokine production and macrophage infiltration of injured peritoneum. Src inhibition by KX2-391 or siRNA in cultured human peritoneal mesothelial cells led to decreased expression of α-smooth muscle actin, fibronectin and collagen I, markers of epithelial to mesenchymal transition.

Conclusions: Src may be a critical mediator of epithelial to mesenchymal transition, fibroblast activation and peritoneal fibrosis. Src could be a potential therapeutic target for treating peritoneal fibrosis.

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SA-PO325

Renal Iron Trafficking – Potential Role for Endothelin System Malgorzata Kasztan, Kelly A. Hyndman, David M. Pollock. *University of Alabama at Birmingham, Birmingham, AL.*

Background: Elevated endothelin-1 (ET-1) levels reported in sickle cell disease correlate with microalbuminuria, linking ET-1, renal iron deposition and early sickle nephropathy. In humanized sickle cell mice (HbSS), long-term ET_A receptor antagonism provides robust protection from diverse renal pathologies, including significant attenuation of renal tubular iron deposition in proximal tubules (PT). We hypothesize that ET-1 regulates renal iron trafficking in iron overload-associated sickle nephropathy.

Methods: We first determined the time and concentration-dependent effect of ET-1 on the expression of iron trafficking mediators in mouse primary PT epithelial cells.

Results: Expression of the iron import transporter transferrin receptor 1, TfR-1, and the iron storage protein, H-ferritin, were increased in concentration-dependent manner by ET-1. The ET-1-induced decrease in iron exporter ferroportin-1, FPN-1 (65% reduction), was associated with a doubling in expression of hepcidin, HAMP, a key regulator of FPN-1 and iron removal from the cell. Exposure of PT cell to plasma from HbSS mice, increased cellular iron uptake compared to plasma from control HbAA mice (0.098±0.017 vs. 0.004±0.001 ng/μl). The ET_A antagonist, BQ123, completely prevented ET-1-induced alterations in all iron mediators, suggesting involvement of ET_A receptor in iron trafficking mechanisms. Neither selective ET_B nor combined (ET_A+ET_B) antagonism affected ET-1-induced changes in iron trafficking mediators. Cortical tissues of HbSS mice showed increased expression of TfR-1, H-ferritin and decreased expression of FPN-1 compared to HbAA mice.

Conclusions: These results reveal a novel role for ET-1 in PT iron trafficking and provide rational for the use of selective ET_A receptor blockade as a potential therapeutic approach in iron overload-associated sickle nephropathy.

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SA-PO326

Enteral Iron Therapy and Renal Autophagy in Juvenile Mice with Adenine-Induced CKD Oleh M. Akchurin,[3] Edwin A. Patino,[3] Divya Bhatia,[3] Vidhi Dalal,[4] Sureshbabu Angara,[2] Stefano Rivella,[1] Mary E. Choi.[3] *[1]Children's Hospital of Philadelphia, Philadelphia, PA; [2]Weill Cornell Medicine, New York City, NY; [3]Weill Cornell Medical College, NEW YORK, NY; [4]NYP Cornell, Cornell, NY.*

Background: Autophagy has been implicated in the pathophysiology of chronic renal injury and fibrosis. Iron therapy is common in patients with chronic kidney disease (CKD) and non-hematologic effects of iron therapy in CKD are of great interest. Iron-induced oxidative stress can damage cellular proteins and organells, which then need to be recycled by autophagy. However, the effect of iron on renal autophagy has not been elucidated.

Methods: Autophagy proteins Beclin 1 and LC3b were evaluated by western blot in the whole kidney lysates of juvenile C57Bl/6 male mice fed the following four diets from age 3 to 11 weeks: (1) physiologic diet, (2) 0.2% adenine diet (CKD), (3) 0.5% carbonyl iron diet (iron therapy), (4) 0.2% adenine + 0.5% carbonyl iron diet. Mice were euthanized after 8 weeks of experimental diet. Data were analyzed with ANOVA followed by Tukey post-hoc test.

Results: Adenine-induced CKD, as expected, was characterized by elevated serum hepcidin, low serum iron, and low hemoglobin. Iron therapy normalized serum iron and improved anemia in mice with CKD, while further elevating serum hepcidin. Iron therapy led to elevated non-heme iron content in the kidneys of mice with and without CKD. mRNA expression of iron exporter ferroportin was induced by high iron diet in control mice but not in mice with CKD, while kidney ferroportin protein expression was reduced in CKD, irrespective of iron therapy. Iron therapy led to higher expression of autophagy proteins Beclin 1 and LC3b in the kidneys of mice with CKD, as compared to mice with CKD not treated with iron. In contrast, expression of NCOA4, a marker of ferritinophagy, was reduced in mice with CKD, without significant influence of systemic iron status.

Conclusions: To our knowledge, this is the first study that demonstrated induction of renal autophagy by iron therapy in CKD. This effect was not specific to ferritinophagy, as ferritin cargo receptor NCOA4, which mediates its autophagy, was not induced by iron therapy in this model. In our ongoing experiments, we are evaluating mechanistic relationship between iron-mediated autophagy and renal fibrosis in CKD.

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SA-PO327

Role of Hepcidin and Iron Homeostasis in the Progression of AKI to CKD Ewa U. Mandziak,[3] Yogesh M. Scindia,[2] Valentina Loi,[1] Saleh Mohammad,[3] Sundararaman Swaminathan.[3] *[1]AO Brotzu Cagliari, Cagliari, Italy; [2]Univerisity of Virginia, Charlottesville, VA; [3]University of Virginia, Charlottesville, VA.*

Background: Maladaptive repair and fibrosis after acute kidney injury (AKI) contributes to progressive loss of kidney function. Systemic iron depletion strategies using iron chelators or diet-induced iron deficiency are known to reduce renal fibrosis. Splenic red pulp macrophages are one of the primary storage sites for iron. Hepcidin (*Hamp*), the master regulator of iron homeostasis, plays an important role in anemia of chronic kidney disease (CKD) through its effects on hepatic and splenic macrophages. We hypothesized that hepcidin dependent changes in systemic iron homeostasis may modulate renal fibrosis.

Methods: To induce CKD, Folic Acid (FA) 250 mg/kg (i.p.) was administered to WT, *Hamp KO* and *Hamp Het* mice (all on C57BL/6J background). BUN was measured to monitor AKI on day 2. In some experiments *Hamp Het* mice were reconstituted with exogenous hepcidin (50 μg, i.p) after the onset of AKI. Renal function and fibrosis related parameters were examined 19 days later.

Results: Compared to WT mice, AKI and mortality were reduced in *Hamp het* and *Hamp KO* mice. This initial worse AKI translated to more severe fibrosis on day 19 in WT, as indicated by collagen and α smooth muscle actin content. Both these parameters were significantly lower in *Hamp* deficient mice. There was a large infiltration of F4/80$^+$ macrophages in the fibrotic kidneys of the WT and *Hamp KO* mice, that was not seen in *Hamp* Het mice. Compared to WT kidneys, there was a significant reduction in both NOS-2 and Arginase-1 gene expression in *Hamp* Het kidneys. Arginase-1 showed a downward trend in *Hamp KO* kidneys also. Hepcidin reconstitution exacerbated renal fibrosis in *Hamp Het* mice.

Conclusions: Our studies reveal a novel protective role of hepcidin deficiency in progression of AKI to CKD. This protection was associated with reduction in splenic iron content and renal M2 macrophage infiltration.

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SA-PO328

Copper and Copper Transporter 1 Promote Renal Interstitial Fibrosis by Regulating Intracellular and Extracellular Transport of Copper Ions Niu Yangyang, Chen Yu. *Shanghai Tongji Hospital, SHANGHAI, China.*

Background: Copper is an essential trace element required for many biological processes. Some studies have demonstrated that copper accumulating was related to liver fibrosis, but the underlying mechanism is not very clear. Copper is the essential unit of lysyl oxidase (LOXs), which are the key enzymes of crosslinking of extracellular matrix. Copper transporter 1 (CTR1) is the most important factor responding to copper transport.

Methods: Sprague-Dawley rats were divided into the sham group, unilateral ureteral obstruction (UUO) operated group and UUO treated with copper chelating agents tetrathiomolybdate (TM). Rat kidney fibroblast cells (NRK-49F) were used in vitro. The concentration of copper, the LOXs activity and the degree of cross-linking of extracellular collagen were detected in vivo and vitro.

Results: (1) The copper concentration in serum, urine and kidney of rats increased significantly at 7 days after UUO surgery; After treatment of TGF-β1, the intracellular copper concentration was increased significantly in cells; (2) The expression of CTR1 was upregulated in the kidneys of UUO rats; The level of CTR1 was increased significantly by TGF-β1 in vitro; (3) Blockage of Smad2/3 suppresses TGF-β1-induced expression of CTR1; (4) Downregulation of CTR1 significantly inhibited the intracellular copper concentration; (5) The activity of LOXs was increased significantly after TGF-β1 treatment; (6) Downregulation of CTR1 significantly inhibited the activity of LOXs and the cross-linking of extracellular collagen induced by TGF-β1 in vitro; (7) The concentration of copper, the degree of collagen cross-linking and the deposition of collagen were decreased in the kidney tissue of UUO rats after treatment with TM. The concentration of intracellular copper, the activity of LOXs and the degree of collagen cross-linking were attenuated with treatment of TM in vitro.

Conclusions: We firstly found that the intracellular copper accumulating was closely to renal fibrosis. The underlying mechanism was related with the increasing expression of CTR1 and activity of LOXs. Treatment with TM ameliorated the renal fibrosis. This study presented a novel treatment target.

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SA-PO329

NLRP3 Inflammasome Inhibition Ameliorates Tubulointerstitial Injury in the Remnant Kidney Model Orestes Foresto-Neto, Victor F. Avila, Simone C. Arias, Fernanda F. Zambom, Lisienny C. Rempel, Flavia G. Machado, Camilla Fanelli, Claudia R. Sena, Vivian L. Viana, Denise M. Malheiros, Hugo Abensur, Niels O. Camara, Roberto Zatz, Clarice K. Fujihara. *University of Sao Paulo, Sao Paulo, Brazil.*

Background: We showed previously that NF-κB signaling inhibition attenuates renal injury and inflammation in the 5/6 renal ablation (Nx) model (AJPRenal, 2007). We subsequently showed that the NLRP3 inflammasome, another innate immunity pathway, is also activated in Nx (SciRep, 2017). There is evidence that the xanthine oxidase (XO) inhibitor allopurinol (ALLO) inhibits NLRP3 activation. We investigated whether NLRP3 inhibition by ALLO exerts renoprotection in Nx.

Methods: Munich-Wistar rats (N=33) underwent Nx or sham operation (**S**, N=16). Nx rats were divided in: **Nx**, untreated, and **Nx+ALLO**, given ALLO 36 mg/kg/day vo. On day 60, tail-cuff pressure (TCP, mmHg), urinary NGAL (uNGAL, mg/24h), interstitial collagen 1 (COL, %) and macrophages (MΦ, cells/mm^2), renal XO activity (rXO, μU/mg), renal uric acid (rUA, mg/g) and renal content of heme oxygenase 1 (HO-1), superoxide dismutase 2 (SOD2), caspase 1 (CASP1) and nuclear p65 (NF-κB) (fold increase x C), IL-1β (pg/mg), and interstitial NLRP3 (cells/ mm^2) were assessed.

Results: ALLO normalized rXO activity and prevented rUA and oxidative stress enhancement in Nx. ALLO also attenuated hypertension and promoted selective tubulointerstitial protection, reducing uNGAL, COL and MΦ. ALLO reduced the renal content of the inflammasome components (NLRP3, CASP1 and IL-1β), but not the NF-κB activation.

Conclusions: In view of its antiinflammatory, antioxidant and renoprotective effects, ALLO may help to prevent the progression of CKD. FAPESP/CNPq

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	S	Nx	Nx+ALLO
TCP	134±2	212±8^a	191±6^{ab}
uNGAL	29±4	48±5^a	32±3^b
COL	2±0	9±1^a	5±1^{ab}
MΦ	22±2	187±26^a	130±20^{ab}
rXO	70±5	116±7^a	69±5^b
rUA	1.3±0.1	2.3±0.1^a	1.3±0.2^b
HO-1	1.0±0.6	5.4±1.2^a	2.9±0.5^b
SOD2	1.0±0.1	0.7±0.1^a	1.1±0.2^b
NLRP3	0.7±0.4	5.0±0.4^a	2.8±0.5^{ab}
CASP1	1.0±0.1	2.5±0.2^a	1.8±0.3^{ab}
IL-1β	1.6±0.1	4.7±0.6^a	2.3±0.3^b
NF-κB	1.0±0.1	3.2±0.4^a	3.7±0.6^a

Mean±SE. ^{a}p<0.05 vs S, ^{b}p<0.05 vs Nx+ALLO.

SA-PO330

Protective Effect of DNA Methyltransferase Inhibitor against Progressive Renal Tubulointerstitial Inflammation and Fibrosis Eun Sil Koh,[1] Soojeong Kim,[2] Seok Joon Shin,[1] Cheol Whee Park,[1] Chul Woo Yang,[1] Yong-Soo Kim,[1] Sungjin Chung.[1,3] *[1]Department of Internal Medicine, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea; [2]Department of Biochemistry, The Catholic University of Korea College of Medicine, Seoul, Republic of Korea; [3]Division of Nephrology and Hypertension, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN.*

Background: Renal fibrosis is the final common pathway of virtually all progressive kidney diseases and correlates with the aggravation of renal function. However, the contributon of DNA methylation to the process of renal fibrosis is not clarified. The current study examined the impact of DNA methyltransferase inhibitor on the progression of inflammation and fibrosis in kidneys of mice with unilateral ureteral obstruction (UUO).

Methods: Zebularine (225 mg/kg/day), a DNA methytrasferase inhibitor, or vehicle was administred to male C57BL/6 mice intraperitoneally for 3 or 7 days after UUO operation.

Results: Administration of zebularine significantly attenuated renal tubulointerstitial fibrosis and inflammation as assessed by trichrome, α-smooth muscle actin, collgen IV, transforming growth factor-β1 staining both at 3 and 7 days after UUO. Zebularine downregulated mRNA expression levels of matric metalloproteinase (MMP) 2, MMP9 and fibronectin, and it also suppressed nuclear factor-κB (NF-κB) and pro-finlammatory cytokines such as tumor necrosis factor-α, interleukin (IL) – 1β and IL-6 in obstructed kidneys. Furthermore, zebularine treatment upregulated the nuclear expression of nuclear factor erythroid-derived 2 like factors 2 (Nrf2) and its subsequent antioxidant downstreams such as heme oxygenase-1, catalase, superoxide dismutase 1 and NAD(P) H: quinone oxidoreduates-1 in UUO kidneys.

Conclusions: Our findings suggest that inhibition of DNA methylation could restore the disrupted balance in pro-inflammatory pathway and antioxidant defence mechanism and alleviate renal fibrosis.

SA-PO331

Renal Release of Ac-SDKP Is Part of an Antifibrotic Peptidergic System in the Kidney Cesar A. Romero,[3] Nitin Kumar,[1] Oscar A. Carretero.[2] *[1]Henry Ford Health System, Detroit, MI; [2]Henry Ford Hospital, Detroit, MI; [3]Hypertension and Vascular research Division, Henry Ford Hospital, Detroit, MI.*

Background: Ac-SDKP is a natural peptide with anti-fibrotic and anti-inflammatory properties in vascular, myocardial and kidney diseases. Ac-SDKP is present in urine and increases under angiotensin converting enzyme inhibitors (ACEi). Ac-SDKP is released from Thymosin B4 (Tβ4) by two step enzymatic reactions by meprin-α and the prolyl oligopeptidase enzymes (POP) and degraded by angiotensin converting enzyme (ACE). Tβ4, Meprin-α and POP enzymes has been reported in kidney. *We hypothesized that Ac-SDKP is produced in the kidney.*

Methods: We evaluated the presence of Tβ4, Meprin-α and POP mRNA by analyzing the trascriptome in each segment of the nephron using the public access NHI database ESBL. We confirmed kidney expression of Meprin-α and POP by immunofluorescence and enzyme activity measurements. The *Stop Flow Pressure* technique was used to evaluate the Ac-SDKP formation in different segments of the nephron, in normal condition, under POP inhibition (POPi) and ACEi. All experiments were performed in Sprague-Dawley rats.

Results: Tβ4 mRNA was present in all the nephron segments, however Meprin-α mRNA was only expressed in proximal tubule (s3 region), and POP mRNA was present in proximal tubule, loop of Henle (inner medulla) and distal nephron (distal, connecting and collecting tubules). We confirmed the expression of Meprin-α by immunofluorescence in proximal tubules and the POP was found in the distal convoluted tubule in cortex and in higher amounts in the medullary region. POP activity was also high in kidney medulla (Cortex 613.8±352.1 vs. Medulla 1162.2±408.5 pmol/min/mg prot; P<0.01). The Stop flow technique showed the high Ac-SDKP/Inulin ratio in the distal nephron: 10.5±0.8 vs. 4.2±0.1 in the proximal segments (p<0.01). POPi infusion into the kidney decreased Ac-SDKP/Inulin in comparison to the vehicle group in distal (10.5±0.8 vs 5.6±0.8, p<0.01) and proximal nephron segments (4.22±0.1 vs. 2.1±0.2, p<0.01). ACEi increased the Ac-SDKP content in all nephron segments, mainly in the distal part. Chronic infusion of POP inhibitor increase kidney medullary interstitial fibrosis and that was prevented by Ac-SDKP (Fibrotic area in %: Vehicle 1.84±0.8, POPi 3.3±1*, POPi+Ac-SDKP 1.37±0.58; **p<0.001POPi vs. Vehicle and POPi+Ac-SDKP*).

Conclusions: We conclude that Ac-SDKP is released by the nephron and has an important antifibrotic effect in the kidney.

Funding: Other NIH Support - NHLBI

SA-PO332

Epstein-Barr Virus Induced Epithelial Mesenchymal Transition in HK2 Cells Sang Youb Han,[1] Seok ju Park,[1] Daeyoung Hur.[2] *[1]Inje University, GoYang, Republic of Korea; [2]Inje University College of medicine, Busan, Republic of Korea.*

Background: Epithelial mesenchymal transition (EMT) represents conversion of epithelial cells into mesenchymal phenotype. It is an important mechanism in tissue

fibrosis including kidney. Epstein-Barr virus (EBV), which is well known cause of acute febrile illness and lymphoproliferative diseases, is reported to induce tissue fibrosis such as lung, skin, and liver. However, it is not reported its association with renal fibrosis. We tested whether EBV could induce EMT in renal epithelial cells.

Methods: HK2 cells were incubated with EBV. HK2 cells changed their shape from cobble stone appearance into spindle shape. After confirmation of mesenchymal changes of HK2 cells, we evaluated E-cadherin, ZO-1, and beta-catenin for epithelial marker, N-cadherin, vimentin, TGF-beta for mesenchymal marker, MCP-1, IL8, TNF-alpha, IL18 for inflammatory changes, and Slug, Snail, V-Set And Immunoglobulin Domain Containing 4 (VSIG4) and pSTAT3 for EMT marker. All markers were tested using real-time PCR for mRNA or western blotting for protein expression.

Results: The expressions of E-cadherin, ZO-1, and beta-catenin were decreased and N-cadherin, vimentin, TGF-beta mesenchymal markers were increased after EBV exposure. And expressions of Slug, Snail, and pSTAT3 were also increased. And inflammatory markers such as MCP-1, IL8, TNF-alpha, IL18 were increased. To confirm whether these changes were due to EBV transfection or secretory proteins from EBV, the HK2 cells were stimulated with latent membrane protein 1 (LMP-1), which is representative EBV-related protein. LMP-1 downregulated the expression of E-cadherin, and upregulated those of vimentin and VSIG4. These findings suggested that EMT was induced by LMP-1 alone. To test VSIG4 involvement in LMP1-induced EMT, VSIG4 siRNA were treated in LMP1-stimulated HK2. The expression of E-cadherin and vimentin were reversed. The expression of E-cadherin was increased and that of vimentin was decreased.

Conclusions: In conclusion, EMT was induced by EBV-associated protein, LMP1, not by EBV in itself. The LMP1-induced EMT was related with VSIG4 changes. This result provided the possibility of EBV-related EMT in renal fibrosis.

SA-PO333

Novel Role of IL-20 Subfamily in the Pathogenesis of CKD Domonkos Pap,[1,2] Rita Lippai,[1] Apor Veres-Székely,[1] Réka Rokonay,[1] István M. Takács,[1] Erna Sziksz,[1,2] Beáta Szebeni,[1,2] Andrea Fekete,[1,3] Attila J. Szabo,[1,2] Ádám Vannay.[1,2] *[1]Semmelweis University, 1st Department of Pediatrics, Budapest, Hungary; [2]MTA-SE, Pediatrics and Nephrology Research Group, Budapest, Hungary; [3]MTA-SE, Lendület Diabetes Research Group, Budapest, Hungary.*

Background: Regardless of the etiology kidney fibrosis is a common outcome of progressive kidney diseases. Our recent study showed that levels of interleukin (IL)-20 subfamily members, including IL-19 and IL-24 significantly increased in newborn rat kidneys underwent unilateral ureteral obstruction (UUO). However, their precise role in the pathomechanism of renal fibrosis has not been investigated.

Methods: To study the role of IL-20 cytokine subfamily we applied a mouse model of UUO induced kidney fibrosis on wild type and IL-20 receptor beta gene knockout (IL-20Rβ KO) mice. Masson's trichrome and Picro-Sirius Red staining, real-time RT-PCR and western blot method were used to investigate the expression of fibrosis associated genes at mRNA and protein level between the two strains. We also investigated the *in vitro* effect of IL-24 treatment on transforming growth factor beta (TGF-β) and platelet derived growth factor B (PDGF-B) expression of human proximal tubular epithelial (HK-2) cells by real-time RT-PCR and flow cytometry.

Results: We found elevated level of IL-19, IL-24 and IL-20Rβ in the fibrotic kidneys. Lack of IL-20Rβ in KO mice was associated with decreased level of the pro-fibrotic marker alpha smooth muscle actin, TGF-β and PDGF-B expression and also with reduced amount of extracellular matrix deposition in the obstructed kidneys. Treatment of renal epithelial cells with IL-24 increased their TGF-β and PDGF-B production.

Conclusions: Increased expression of IL-19, IL-24 and IL-20Rβ in the fibrotic kidney suggest their role in the pathomechanism of obstructive nephropathy. IL-24 may promote tissue remodeling shifted toward an excessive deposition of extracellular matrix components via increased production of pro-fibrotic factors. Our data suggest that inhibition of IL-24 may have significant anti-fibrotic effect.

SA-PO334

Noninvasive Evaluation of Microcirculation Disorder, Tubular Injury, and Kidney Fibrosis Using Functional Magnetic Resonance Imaging Jiong Zhang,[1] Xiong Tang,[1] Ming-chao Zhang,[1] Long jiang Zhang,[2] Zhi-Hong Liu.[1] *[1]National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing China, Nanjing, China; [2]Medical Imaging, Department of Medical Imaging, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China.*

Background: The key contributors to the progression of nearly all forms of CKD are reduced microvascular blood flow, tubular injury and fibrosis. Despite theirs importance, clinicians currently have no means of noninvasively assessing these factors, except historically relied on percutaneous renal biopsy. Recent advances in imaging technology have raised the exciting possibility of MRI. The aim of this study was to evaluate the feasibility of functional MRI for functional assessment of renal morphology and diffusion, tubular injury, also fibrosis burden in CKD.

Methods: Seventy CKD patients were studied. The feasibility of three fRMI sequences, which were diffusion-wighted-imageing (DWI), aquaporins (AQP), and magnetic resonance elastography (MRE) were evaluated to assess kindey microcirculation disorder, tubular injury and scarring burden. Capillary situation was assessed by peritubular capillaries number, which was showed by CD34 staining. Tubular injury was measured by AQP1 staining. Cortex fibrosis was measured by kidney sections stainded with Masson's trichrome, which were scanned with an Aperio ScanScope system and analyzed using ImageScope.

Results: Functional MRI sequence DWI-ADC showed negative correlation with glomerulosclerosis and cortex fibrosis burden, R^2=0.128 and 0.167 respectively, P<0.01. Apparent DWI-ADC cortex values were significantly increased in CKD stage 3 and 4, which were higher than CKD stage 1 (P=0.02). There were no significant relationships with PTCs number per x400 image. AQP1 staining, which stands for AQP in tubular cells, was significantly decreased in later stages (P<0.01). Although, the fMRI-AQP value did not show statistical correlation with renal AQP staining changings in cortex (P=0.796), AQP sequence showed positive correlation with cortex fibrosis burden (R^2=0.071, P=0.028). Apparently, MRE60e Hz had negative correlation with glomerulosclerosis and cortex scarring burden in these patients (R^2=0.115 and 0.026 respectively, P=0.040 and 0.052). Interestingly, it was showed that MRE values were significantly lower in serious renal fibrosis subgroup than mild group or normal.

Conclusions: In this pioneer study, DWI, AQP and MRE sequence from functional MRI appear to serve as noninvasive evaluation method for evaluating renal microcirculation, tubular injury and fibrosis.

SA-PO335

A Broad-Spectrum Protein-Tyrosine-Kinase Inhibitor Prevents Upregulation of Inflammation/Fibrosis-Related Genes Induced by IgA1-Containing Immune Complexes in a Passive Mouse Model of IgA Nephropathy Zhi qiang Huang,[6] Colin Reily,[1] Nuo Xu,[7] Zina Moldoveanu,[4] Lea Novak,[5] Stacy D. Hall,[3] Rhubell T. Brown,[6] Terry L. Lewis,[6] Casey T. Weaver,[5] Bruce A. Julian,[6] Christopher D. Willey,[2] Jan Novak.[6] *[1]None, Birmingham, AL; [2]The University of Alabama at Birmingham, Birmingham, AL; [3]UAB, Birmingham, AL; [4]Univ of Alabama at Birmingham, Birmingham, AL; [5]University of Alabama at Birmingham, Birmingham, AL; [6]University of Alabama at Birmingham, Birmingham, AL; [7]university of alabama at birmingham, Birmingham, AL.*

Background: To identify potential therapeutic targets in IgA nephropathy (IgAN), we developed two systems: cultured primary human mesangial cells (MC) and a passive mouse model. Both systems use engineered immune complexes (EIC) consisting of galactose-deficient IgA1 bound by IgG autoantibody. EIC activate MC through multiple signaling pathways, leading to cellular proliferation. These events are blocked by dasatinib, a broad-spectrum protein-tyrosine-kinase inhibitor. These findings have been validated in a passive mouse model of IgAN and dasatinib prevented pathologic changes induced by EIC. To further study the effects of dasatinib, we assessed the kidney transcriptome in this IgAN mouse model.

Methods: SCID mice were injected every other day for three doses of EIC, EIC+dasatinib, or only IgA1. Kidneys were removed 1 day after last injection and snap-frozen in liquid nitrogen for RNAseq studies or fixed and processed for histopathology.

Results: Mice injected with EIC exhibited mesangial hypercellularity compared to control (51.6±8.0 *vs.* 39.4±6.5 nuclei x10^{-5}/um^2). This effect was blocked by dasatinib (39.0±5.3 nuclei x10^{-5}/um^2). RNAseq data revealed that most genes with expression altered by EIC were expressed at normal levels when dasatinib was used. Moreover, several genes that were upregulated by EICs are upregulated in human IgAN biopsy specimens (data from public databases). Among those genes, 10 were upregulated in glomeruli and 5 in tubuli. Among these genes, 7 are associated with inflammation, 4 with tissue fibrosis, and 2 with glycogen-storage disease. In mice treated with EIC and dasatinib, no upregulation of these genes was observed. SDS-PAGE-Western blotting and tissue staining for selected targets indicated that protein expression followed the pattern of mRNA expression.

Conclusions: Pathogenic EIC upregulated expression of inflammation/fibrosis-related genes. These changes were prevented by dasatinib. Use of signaling inhibitors may thus represent a rational therapeutic approach for IgAN.

Funding: NIDDK Support

SA-PO336

Previous Resistance Training Impact in CKD Leading to Improvements in Proteinuria, Creatinine Clearance, and Mortality Rate Reduction in Rats Alexandre Saud,[2] Rafael Luiz,[2] Natalia Reinecke,[2] Wesley Silva,[4] Samuel T. Filho,[4] Rodolfo R. Rampaso,[1] Nestor Schor.[3] *[1]None, São Paulo, Brazil; [2]UNIFESP, São Paulo, Brazil; [3]Universidade Federal de Sao Paulo/ Escola Paulista de Medicina, Sao Paulo, Brazil; [4]Universidade Federal de São Paulo, Sao Paulo [SP], Brazil.*

Background: The resistance training is applied to improve and increase muscle mass, however, how resistance exercise improves renal function is not fully understood. The aim of this study was to evaluate the EXE effects on renal function and mortality rate in rats with 5/6Nx

Methods: Adult Wistar rats were divided in four groups (n=8): Previous Exercise + Nx 5/6 + post surgery Exercise (ENE), Previous Exercise + Nx 5/6 + post surgery Sedentary (ENS), Sedentary + Nx 5/6 + post surgery Exercise (SNE) and Sedentary + Nx5/6 + post surgery Sedentary (SNS). We evaluated mean arterial pressure (MAP), creatinine clearance (CrCl), proteinuria (uProt), blood urea nitrogen (BUN), maximal load test (MLT), well as mortality rate. EXE was performed as follows: 6 to 12 climbs/day, 5 days a week, during 8 weeks, 40 to 60% of maximal load test

Results: Exercise in ENE group prevented the increase in proteinuria rate (45,7±3,6 mg/24h, p<0.05) vs SNS, Creatinine Clearance(1,3±0,1ml/min p<0,05) vs all and mean BUN(33,3±2,7 mg/dL p<0,05) was lower compared with the SNS and ENS groups. A

gain of strength was observed in ENE vs all (556±35 g p<0,05). A lower mortality rate was observed in ENE(0%) vs SNS(62%). Results suggested that the EXE minimize the impact of 5/6Nx, with lower proteinuria(35%), Clearance of creatinine(40%), lower increase in BUN(35%) and gain of strength(30%)

Conclusions: Results suggested that the EXE minimize the impact of 5/6Nx, with lower proteinuria (35%), Clearance of creatinine (40%), lower increase in BUN (35%) and gain of strength (30%). These parameters indicate that exercise could have a protective effect, especially under this experimental protocol. Thus, this study suggests that the exercise plays a preventive role in mortality and could be an additional strategy to be employed in CKD.

Funding: Government Support - Non-U.S.

	SNS	SNE	ENS	ENE
Weight (g)	337±13	345±15	370±7	369±15
MLT (g)	390±22	411±33	390±34	556±35$
uProt (mg/24hrs)	133±14$	66.8±13	87.3±7.4	45.7±3.6&
CrCl (ml/min)	0.5±0.1	0.7±0.1	0.7±0.1	1.3±0.1$
BUN (mg/dL)	52.3±5	43.1±4	50.1±3.5	33.3±2.7* &
Mortality Rate (%)	62%	11%	27%	0$
MAP (mmHg)	216±6#	176±13	217±4.7#	207±8.2

$ vs all; * vs SNS, # vs. SNE, & vs ENS.

SA-PO337

Four Weeks of Resistance Training (RT) Improves Physical Capacity, Creatinine Clearance, and Glomerulosclerosis and Decreases Mortality Rate in Rats with CKD Rafael Luiz, Alexandre Saud, Wesley Silva, Maria A. Gloria, Rodolfo R. Rampaso, Edson A. Pessoa, Nestor Schor. *NEPHROLOGY, UNIFESP, SAO PAULO, Brazil*.

Background: The aim of this study was to evaluate if 4 weeks of RT improves physical capacity (strength gain and VO_{2peak}), renal function, glomerulosclerosis and mortality in rats with CKD by nephrectomy 5/6 (Nx5/6).

Methods: Adult Wistar rats were divided in four groups (n=8): Sedentary (S) Exercise (E), Nx 5/6 + Sedentary (NSR), Nx 5/6 + Exercise (NER). We evaluated creatinine clearance (CrCl), proteinuria (uProt), blood urea nitrogen (BUN), glomerulosclerosis, mean arterial pressure (MAP) as well mortality rate. EXE periods were as follows: 6 to 12 climbs/day, 5 days a week, during 4 weeks, 40 to 60% of maximal load test (MLT). The physical capacity was performed with maximal load test (MLT), ergoespirometry test (Vo_{2peak}) and maximal exercise test (MEtest).

Results: The CrCl was improve in NER (43%) vs NS group, (p<0.05). Proteinuria was different in NSR and NER vs S and R groups but not in NSR vs NER. BUN was higher in NSR and NER vs S and R. Glomerulosclerosis was different in NSR vs NER (p<0.05). The MAP was lower in NER vs NSR group (p<0.05). Physical Capacity (MLT, VO_{2peak} and Mtest) was increased in NER vs NSR. A higher mortality rate was observed in NS (30%).

Conclusions: Results suggested that the 4 weeks of RT minimize the impact of 5/6Nx by increase in physical capacity (MLT, VO_{2peak} and Mtest), reduce the impact on CrCl (43%) and improve in glomerulosclerosis (44%). These parameters indicate that exercise could have a protective effect, especially under this experimental protocol. Thus, this study suggests that the exercise plays a preventive role in mortality and could be an additional strategy to be employed in CKD.

	S	R	NSR	NER
Weight (g)	363±14	346±8	312±13	325±17
CrCl (ml/min)	1.6±0.1	2.2±0.2	0.3±0.1*#	0.7±0.2*#
uProt (mg/24hrs)	6.8±0.9	6.8±0.5	38.1±3.0	37.6±3.4
BUN (mg/dL)	42.6±2.7	42.2±2.6	158.5±20.1	130.7±13.5
Glomerulosclerosis (%)	0	0	2.8±0.4 &	1.6±0.4 *#
MAP (mmHg)	132±3	126±2	213±5 &	180±10
Vo2 peak (ml/kg/min)	33.8±0.9	40.0±1.5 *	30.9±0.2 #	40.7±0.6 * %
MLT/Weight (g)	1.3±0.1	1.7±0.1 *	1.2±0.0 #	1.5±0.6 %
Mtest (m/min)	37±2	43±1	33±2 &	38±1
Mortality Rate (%)	0	0	30	10

* vs S; # vs R; % vs NSR and & vs all.

SA-PO338

Kidney Injury Induces HER3 Pathway Activation Bruno Seva Pessoa,[2] Eirini Kefalogianni,[1] Andreas Herrlich.[3] *[1]Washington University School of Medicine, St. Louis, MO; [2]Washington University St Louis, St. Louis, MO; [3]Washington University in St. Louis, St. Louis, MO*.

Background: Activation of epidermal growth factor receptor (EGFR or HER1) by specific soluble HER1 ligands drives injury-induced kidney fibrosis, and HER1 inhibition or deletion significantly protects against these effects. Another member of the HER family, HER3 has also been linked to fibrosis in lung and liver. HER1 function requires dimerization either with itself or with other HER receptors (HER2, HER3 or HER4). Whether HER3 and its ligands, soluble NRG1 and NRG2, are involved in injury-induced fibrosis and whether it acts in concert with HER1 or independently is unknown.

Methods: We performed bilateral ischemia-reperfusion injury (IRI) (30min of ischemia) or unilateral-ureteral-obstruction (UUO) (7 days) in wild-type mice. HER2, HER3, HER4 activation and their respective ligands were analyzed in mouse kidney samples by qPCR, Western blot and Immunofluorescence. Human biopsies were analyzed by Immunofluorescence.

Results: We show that kidney injury by IRI or UUO induces very significant transcriptional upregulation of HER3 and its ligands pro-NRG1 and pro-NRG2. Moreover, production of soluble active NRG1 was induced by IRI and HER3 phosphorylation could be detected in tubular cells and glomeruli. Similarly, fibrotic chronic kidney disease (CKD) biopsies also showed strong HER3 phosphorylation in tubular and glomerular compartments, suggesting that HER3 has an important function in these cellular compartments in mice and humans. To further study the HER3 pathway, we generated and validated proximal tubular- or podocyte-specific HER3 KO mice to test the role of HER3 in mouse models of kidney disease.

Conclusions: NRG1/HER3 pathway is activated by severe pro-fibrotic kidney injury, suggesting a potential role for NRG1/HER3 in this process.

Funding: NIDDK Support

SA-PO341

RIPK3 Blockade Ameliorates Renal Fibrosis in Diabetic Model of eNOS Knockout Mice Ying Shi,[2] Yongli Zhao,[2,1] Chunling Huang,[2] Xinming Chen,[2] Carol A. Pollock.[2] *[1]The Second Hospital of Dalian Medical University, Dalian, China; [2]kolling institute, the University of Sydney, Sydney, NSW, Australia*.

Background: Current therapies for renal fibrosis are largely ineffective. Therefore, identification of novel therapeutic targets is essential. RIPK3 is identified as a crucial regulator of necrosis, apoptosis and inflammation, which have been well recognised to be involved in renal fibrogenesis. To date, the role of RIPK3 in renal fibrosis has not been reported.

Methods: Endothelial nitric oxide synthase (eNOS) knockout mice were used in the study. STZ (55 mg/kg/day) was administrated to induce diabetic model by i.p. for 5 consecutive days. Dabrafenib (RIPK3 inhibitor) or vehicle were used as treatment on diabetic mice. After 24 weeks treatment, mice were sacrificed and kidney function was measured by 24 hour of urinary albumin excretion and urinary albumin creatinine ratio (UACR) by ELISAs. Kidney histological change and ECM deposition was assessed by PAS, Masson's trichrome, picrosirius red staining and immunohistochemistry. TGF-β expression level was detected by quantitative RT-PCR analysis.

Results: RIPK3 inhibition reduced 24 hours urinary albumin excretion and UACR compared to the increased level of vehicle diabetic group. Histological detections demonstrated the vehicle diabetic group had more renal fibrosis and ECM deposition compared to Dabrafenib treated mice. Immunohistochemistry showed consistent results on type III and type IV collagen expression on above groups. Moreover, quantitative RT-PCR exhibited Dabrafenib treated mice had lower expression level of TGF-β.

Conclusions: These results suggest that RIPK3 blockade may be a potential novel target in renal fibrosis.

Funding: Government Support - Non-U.S.

SA-PO342

BET Bromodomains Regulate Tubular EMT Program during Renal Fibrogenesis Bjoern Tampe, Desiree Tampe, Gerhard A. Mueller, Michael Zeisberg. *University Medical Center Goettingen, Goettingen, Germany*.

Background: Kidney fibrosis is associated with loss of functional parenchyma, directly linked to compromised kidney function. Intratubular EMT program of TECs has been shown to contribute to impaired tubular function and correlates with disease progression. In this context, TWIST is considered as a master regulator of EMT. Transcriptional activation is associated with local N-ε-acetylation of lysine side chains towards amino-terminal tails of histone proteins. Members of the bromodomain and dextraterminal (BET) family of bromodomain-containing epigenetic readers associate with acetylated chromatin structures promoting chromatin remodeling, recruitment of proteins involved in transcriptional initiation and activation. It has recently been shown that BRD4 interacts with di-acetylated TWIST to faciliate its recruitment to target gene promoters, initiating EMT program. Because genetically inhibition of TWIST-mediated EMT program in TECs has been shown to faciliate protection of functional parenchyma, we hypothesized that phamacological BET inhibition equally blocks TEC-EMT program.

Methods: In an *in vitro* system of TEC-EMT, BET inhibition was performed using specific siRNAs and small compounds i-BET151, RVX-208, PFI-1 and (+)-JQ1. Using mice challenged with UUO, the impact of (+)-JQ-1 administration was analyzed by immunostaining and qRT-PCR with regard of renal fibrosis and solute/solvent transporters of functional parenchyma.

Results: Here, we provide evidence that TWIST-induced EMT in TECs requires BRD4. EMT inhibition by targeting BET bromodomains with (+)-JQ1 blocks BRD4/TWIST-mediated transcriptional EMT program, restores altered solute and solvent transporter expression, ultimately associated with attenuation of experimental kidney fibrogenesis. This mechanism is not limited to rodents, we provide evidence that EMT program is also driven by BRD4/TWIST in human cells. Based on existing transcriptional profiling datasets among CKD patients, induction of BRD4/TWIST is associated with intrarenal EMT program (reflected by *TWIST1*, *SNAI1*, *SNAI2*) and kidney fibrosis (reflected by *COL1A2* and *ACTA2*), suggesting that pre-requisits for therapeutical intervention by targeting BRD4/TWIST (e.g. through administration of (+)-JQ1) are also present in humans in principle.

Conclusions: In summary, inhibition of BET bromodomains in the context of EMT represents a potential anti-fibrotic therapy.

SA-PO343

Wnt/β-Catenin-Promoted Macrophage Proliferation, Migration, and Alternative Activation Contribute to Kidney Fibrosis Ye Feng, Chunsun Dai. *Nanjing medical university, Nanjing, China.*

Background: The Wnt/β-catenin pathway initiates a signaling cascade that is crucial in both normal development and throughout life. However, the role and mechanisms for Wnt/β-catenin in regulating macrophage activation and its contribution to kidney fibrosis remain to be determined.

Methods: A mouse model with with tamoxifen-inducible deletion of β-catenin in macrophages was created.

Results: Here we found that in addition to promoting macrophage proliferation and migration, Wnt/β-catenin could exacerbate IL4 or TGFβ1-induced macrophage M2 polarization via activating STAT3 molecule. This observation was further confirmed in a mouse model with inducible deletion of β-catenin in macrophages. In that model, kidney fibrosis, macrophage accumulation, proliferation and M2 polarization were all diminished in the fibrotic kidneys compared to their control littermates.

Conclusions: This study demonstrated that Wntb-catenin signaling activation promotes kidney fibrosis may be ascribed to stimulating macrophage proliferation, migration, and M2 polarization.

Funding: Government Support - Non-U.S.

SA-PO344

Therapeutic Activity of the Novel Kinase Inhibitor ANG3070 in Models of Renal Scarring Accompanied by Co-Morbidities Prakash Narayan,[1] Bin Duan,[1] Ping Zhou,[1] Latha Paka,[1] Michael A. Yamin,[2] Itzhak D. Goldberg.[2] *[1]Angion Biomedica Corp, Uniondale, NY; [2]Angion Biomedica Corp., Uniondale, NY.*

Background: Chronic kidney disease (CKD), characterized by extracellular matrix deposition in the renal interstitium, is driven, in part by aberrant receptor tyrosine kinase signaling. We investigated the effects of a novel small molecule receptor tyrosine kinase inhibitor, ANG3070, in clinically relevant models of CKD accompanied by co-morbidities.

Methods: Approximately 18 month old male Fischer 344 rats were subjected to 5/6 nephrectomy (or sham surgery) to model CKD in middle-aged patients. Following onset of renal disease, animals were randomized to vehicle or ANG3070 (various doses, PO, BID). In order to model CKD in the setting of metabolic syndrome, ~8 week old, obese, male, ZSF1 rats were subjected to 5/6 nephrectomy, and following onset of renal disease, randomized to vehicle or ANG3070 (various doses, PO, BID). In both models, after 8 weeks of drug treatment, a comprehensive panel of renal functional and histological endpoints was evaluated to assess the effects of ANG3070.

Results: Intervention with ANG3070 in aged rats with CKD, reduced albuminuria and attenuated several indices of renal scarring including kidney hydroxyproline content, α-smooth muscle actin expression and collagen (picosirius red staining). Intervention with ANG3070 in the rat model of metabolic syndrome and CKD was associated with reduced kidney hydroxyproline content, α-smooth muscle actin expression and collagen (Masson's trichrome and picosirius red staining).

Conclusions: In clinically relevant models of renal scarring, intervention with the novel receptor tyrosine kinase inhibitor ANG3070 is beneficial.

Funding: Other U.S. Government Support

SA-PO345

Inhibition of NF-κB Signaling in Neural Crest-Derived Fibroblasts Attenuates Renal Fibrosis Tadashi Yoshida,[3] Maho Yamashita,[1] Matsuhiko Hayashi.[2] *[1]Apheresis and Dialysis Center, Keio University School of Medicine, Tokyo, Japan; [2]Apheresis and Dialysis Center, Keio University School of Medicine, Tokyo, Japan; [3]Apheresis and Dialysis Center, Keio University School of Medicine, Tokyo, Japan.*

Background: It has been recently reported that renal fibroblasts are derived from neural crest and phenotypic conversion of fibroblasts into myofibroblasts contributes to renal fibrosis in chronic kidney disease. The aim of the present study was to determine whether the NF-κB signaling in neural crest-derived fibroblasts was involved in renal fibrosis in a mouse unilateral ureteral obstruction (UUO) model.

Methods: Transgenic (P0-Cre/IκBΔN) mice, in which truncated IκB was expressed and the NF-κB signaling was inhibited selectively in neural crest-derived cells, were generated. Renal fibrosis and infiltration of inflammatory cells were examined in P0-Cre/IκBΔN and control mice following UUO.

Results: In response to UUO, renal fibrosis was developed in P0-Cre/IκBΔN and control mice, as determined by Masson trichrome staining and SM α-actin staining. However, of importance, renal fibrosis was significantly attenuated in P0-Cre/IκBΔN mice, as compared to control mice 14 days after UUO. By contrast, renal infiltration of inflammatory cells, including neutrophils, F4/80-positive macrophages, and CD3-positive lymphocytes, was not different between P0-Cre/IκBΔN and control mice.

Conclusions: Results suggest that the NF-κB signaling in fibroblasts originated from neural crest plays an important role in renal fibrosis in chronic kidney disease.

Funding: Private Foundation Support

SA-PO346

Potential Impact of Adenine (P0) Receptors on Urinary Albumin/Creatinine Ratio in CKD Yue Zhang,[2] Christa E. Müller,[4] Tao Liu,[5] Anna U. Brandes,[1] Bellamkonda K. Kishore.[3] *[1]Univ. of Utah & VA Medical Center, Salt Lake City, UT; [2]Univ. of Utah & VA Medical Center, Salt Lake City, UT; [3]Univ. of Utah and VA Medical Center, Salt Lake City, UT; [4]University of Bonn, Bonn, Germany; [5]Univ. of Utah & VA Medical Center, Salt Lake City, UT.*

Background: P0 is a G protein-coupled receptor (R), which binds adenine with high affinity, but not adenosine, AMP/ADP/ATP. Blood levels of adenine are markedly elevated in chronic kidney disease (CKD), and positively correlate with the duration or severity of CKD. We observed that P0-R is expressed in all regions of the mouse kidney, and hypothesized that blocking it in CKD will have significant effects.

Methods: 5/6[th] nephrectomized (Nx) CD-1 mice were divided into 2 groups. One group was infused with PSB-08162, a selective antagonist of P0-R, through osmotic minipumps to attain steady state plasma concentration ~30 μM. Controls were sham-operated. After 4 weeks of infusion, urine and blood samples were collected, and the mice were euthanized.

Results: The results of analysis (mean ± se) of terminal urine and serum samples are shown in the Table. Despite no significant differences in serum creatinine (CR) between Nx and Nx+PSB groups, the latter showed marked increase in urinary albumin/CR ratio (UACR), apparently due to low urinary CR excretion. In parallel the serum levels of 3-hydroxybutyrate, a ketone body, were significantly elevated.

Conclusions: Our results suggest that blocking the P0-R in CKD may elevate UACR by reducing urinary excretion of CR, probably by decreasing its secretion by the kidney. The elevated keto acid may also contribute to reduction in CR secretion in the kidney. Conversely, the elevated adenine levels in CKD may increase CR secretion in the kidney, and thus may decrease UACR values.

Funding: Veterans Affairs Support, Private Foundation Support

Terminal Urine and Serum Parameters

	Sham	Nx	Nx + PSB
	N = 4	N 5 or 6	N = 5 or 6
Urine Output (ml/24 h)	1.07 ± 0.16	3.54 ± 0.14*	3.15 ± 0.29*
Urine Osmolality (mOsm/Kg H2O)	1817 ± 341	855 ± 33*	765 ± 101*
Urine Albumin (μg/24 h)	20.0 ± 4.1	304.5 ± 109*	326.0 ± 99.0
Urine CR (mg/24 h)	0.98 ± 0.23	10.8 ± 3.5*	3.36 ± 1.3**
Urine CR (mg/dl)	101.1 ± 27.1	303.8 ± 102.4	66.2 ± 23.2**
UACR (Urine Alb/CR Ratio)‡	24.8 ± 8.2	47.3 ± 27.5*	158.7 ± 43.0**
Serum CR (mg/dl)#	0.163 ± 0.022	0.222 ± 0.011	0.244 ± 0.065
Serum CR (AUC)†	0.483 ± 0.165	0.690 ± 0.083	0.960 ± 0.417
Serum Urea (AUC)†	3993 ± 721	8233 ± 352*	8743 ± 318*
Serum 3-hydroxybutyrate (AUC)†	25.79 ± 3.61	33.40 ± 4.03	56.96 ± 8.07**

All statistics by ANOVA; #determined by enzymatic method; †determined by HPLC-MS (Area Under Curve); ‡calculated as albumin μg/L / creatinine mg/L; *significantly different from Sham; **significantly different from Nx group.

SA-PO347

Omega 3 Fatty Acid Attenuates Kidney Fibrosis in Ureteral Obstructed Mice via Enhancement of Autophagy Flux Dae Eun Choi,[1] Yoon-Kyung Chang,[2] Hyunsu Choi,[3] Chang hun Song,[1] Jiwon M. Lee,[4] Kiryang Na,[1] Kang Wook Lee,[1] Hong jin Bae,[1] Youngrok Ham.[1] *[1]Nephrology, School of Medicine, Chungnam National University, Daejeon, Republic of Korea; [2]Nephrology, School of Medicine, The Catholic University of Korea, Daejeon, Republic of Korea; [3]Clinical Institute of Medicine, Daejeon St. Mary's Hospital, Daejeon, Republic of Korea; [4]Pediatrics, School of Medicine, Chungnam National University, Daejeon, Republic of Korea.*

Background: It has been known that unilateral ureteral obstruction (UUO) induces autophagic activation in obstructed kidney. Inhibition of autophagy aggravates renal injury in UUO mice. Recently, it is reported that Omega 3 fatty acid regulate the autophagy. we evaluated whether ω3-PUFA may attenuate renal fbrosis in UUO mice, and evaluated associating mechanism.

Methods: 10-week-old male C57Bl/6 mice were divided into 4 groups; sham, Omega 3 + sham, vehicle (normal saline, same volume to Omega 3 + UUO, Omega 3 + UUO. Omega 3 and vehicle were administered orally using an NG tube (Omega 3 100mg/kg/day) from pre-operation day to 7 days after operation. Mice were sacrifced at 7 days after surgery and kidney tissue were collected. Real time RT-PCR, western blot and immunohistochemistry for molecular study and H&E stain and PAS stain for histologic examination were performed.

Results: Omega 3 treated UUO mice showed improvement of renal cell survival, renal function, and pathologic damage compared to vehicle treated UUO mice. Also omega-3 treatment reduced the renal expression of MCP-1, collagen IV, and TGF-ß in UUO kidney. UUO mice kidney showed that higher amounts of LC3, Beclin-1, Atg7 and p62 compared to sham mice. Omega 3 treated UUO kidney showed higher amounts of LC3, Beclin-1 and Atg7 and lower amounts of p62 compared to vehicle treated UUO kidney. Moreover, renal cathepsin D and ATP6E were also increased in Omega 3 treated UUO mice compared to vehicle treated UUO mice mice.

Conclusions: Omega 3 fatty acid ameliorate renal fbrosis in UUO kidney via enhancement of autophagy fux.

Funding: Government Support - Non-U.S.

SA-PO348

The Effect of Hirudin on PAR-1, TGF-β1, α-SMA of Renal Interstitial Tissue in Rats with Unilateral Ureteral Obstruction Dai Lu,[2] Yang Kang,[1] Pei Ming,[2] Ren Tong,[2] Shouci Hu,[1] Lijuan Wei,[1] Bo Yang,[2] Lin Yan,[2] Hongtao Yang.[2] *[1]Tianjin University of Chinese Traditional Medicine, Tianjin, China; [2]Division of Nephrology, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, China.*

Background: In the process of renal interstitial fibrosis, hirudin may reduce the expression of proteins and genes of PAR-1, TGF-β1 and α-SMA in the renal interstitial, We explored the intervention effect of hirudin by establishing a unilateral ureteral obstruction model.

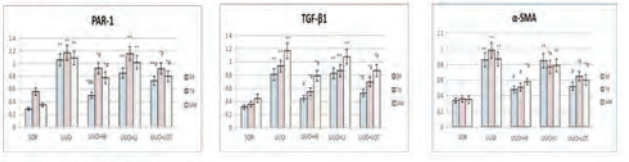
Methods: The 90 healthy Sprague-Dawley (SD) male rats, with the average weight of 180±20g, were randomly divided into Sham-operation group(SOR, n=18), unilateral ureteral obstruction model group(UUO, n=18), UUO with high dose Hirudin treatment group(UUO+HI, n=18), UUO with low dose Hirudin treatment group(UUO+LI, n=18), UUO with Lotensin treatment group(UUO+LOT, n=18). On 3rd, 7th, 14th days after the operation, 6 rats from each group were randomly sacrificed, the obstructive side of kidneys were storaged for RT-PCR and Western Blot tests to detected the expression of proteins and genes of PAR-1, TGF-β1, α-SMA with drug intervention.

Results: 1 Western Blot test: Compared with UUO group, the expression of PAR-1, TGF-β1 and α-SMA at each time point in UUO+LOT and UUO+HI groups were significantly reduced (P<0.05). **2 RT-PCR test:** Compared with UUO group, the expression of PAR-1 and α-SMA at each time points in each intervention groups were reduced (P<0.05). Compared with UUO group, the expression of TGF-β1 at different time points in UUO+HI group, on the 14th day in UUO+LI and UUO+LOT groups were decreased(P<0.05).

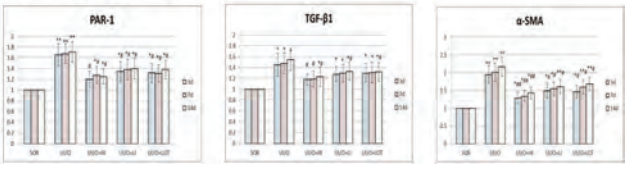
Conclusions: High dose of hirudin can significantly reduce the protein expression of PAR-1, TGF-β1 and α-SMA in renal interstitial of UUO rat model. Both high dose and low dose of hirudin can reduce the mRNA expression of PAR-1, TGF-β1, α-SMA in different degrees. Compared with UUO+LI group, UUO+HI group has a better effect on the down-regulation of the protein and mRNA expression of PAR-1, TGF-β1, α-SMA, the difference between two groups may be related to the mechanism of the best drug effective dose.

Funding: Government Support - Non-U.S.

The chart of Western Blot result:



The chart of RT-PCR result:



SA-PO349

Impact of Intrarenal and Circulating APOL1 Expression Levels on Phenotypes in Nephrotic Syndrome K Yasutake,[4] Anders H. Berg,[3] Khuloud Shukha,[1] Martin R. Pollak,[2] Matt G. Sampson.[4] *[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA; [3]Boston, MA; [4]University of Michigan, Ann Arbor, MI. Group/Team: NEPTUNE.*

Background: Although high-risk (HR) *APOL1* genotypes are associated with FSGS development & worse outcomes in patients with nephrotic syndrome (NS), less is known about the relationship between *APOL1* expression & clinical parameters. While in population & CKD cohorts, circulating *APOL1* levels are not CKD-associated, this relationship has not been studied in NS. Intrarenal *APOL1* expression level is not associated with HR genotype in NS patients. But higher *APOL1* expression, even the wildtype form, is associated with cytotoxicity & FSGS in model systems. Does increased *APOL1* expression contribute to poor outcomes in NS across races? To assess this, we characterized associations of intrarenal & circulating *APOL1* expression levels with clinical & histological phenotypes in black & non-black patients in the Nephrotic Syndrome Study Network (NEPTUNE).

Methods: NEPTUNE is a prospective study of NS patients of all ages receiving a clinically indicated biopsy. We identified *APOL1* genotyped patients with baseline & longitudinal clinical data and intrarenal mRNA expression profiling of microdissected glomeruli (GLOM) (n=160) or tubulointerstitium (TI) (n=193). 95 also had circulating *APOL1* protein levels measured with ELISA. Non-blacks made up 29% of patients with intrarenal & 68% with circulating expression. As a function of baseline GLOM, TI, or circulating *APOL1* expression, we modeled baseline eGFR, interstitial fibrosis (IF) on biopsy, complete remission (CR), & a composite endpoint. We also did analyses stratified by race & risk genotype.

Results: In multivariable analyses of black patients, higher TI expression of *APOL1* was significantly associated with lower eGFR (-9.8ml/min per doubling of *APOL1* expression; p=0.02) and increased IF(p=0.01), independent of *APOL1* risk genotype. These associations were not observed with TI *APOL1* expression in non-black or GLOM in black & non-black patients. There were no significant association of circulating *APOL1* levels with clinical or histologic parameters, across races & risk genotypes.

Conclusions: In black patients with NS, elevated TI *APOL1* expression, independent of risk genotype, was associated with lower eGFR & more fibrosis. It may be worth investigating whether decreasing intrarenal *APOL1* level is beneficial in any black NS patient. Further inquiry in larger cohorts of non-blacks with NS is also warranted.

Funding: NIDDK Support

SA-PO350

Apolipoprotein L1 Variants and the Prevalence of JC Polyoma Virus in Black South Africans with Hypertensive CKD Nolubabalo U. Nqebelele, Caroline Dickens, Therese Dix-peek, Raquel Duarte, Saraladevi Naicker. *University of the Witwatersrand, Gardenview, South Africa.*

Background: Variants in the apolipoprotein 1 (*APOL1*) gene associate with higher rates of nondiabetic nephropathy in black patients. First-degree relatives of African Americans with nondiabetic nephropathy with two *APOL1* risk variants had lower rates of kidney disease if they also had JC viruria. We aimed to determine the association of *APOL1* risk variants with renal traits and the prevalence of polyomavirus infection in black South Africans with hypertensive chronic kidney disease (CKD).

Methods: Black South Africans with hypertensive CKD (CKD patients) and their first-degree relatives were recruited. Controls were healthy black South Africans. Informed consent was obtained in 166 participants. Using restriction fragment length polymorphism, custom designed primers were used to genotype G1: rs60910145 and rs73885319 and G2: rs71785313 *APOL1* risk variants. Viral DNA was extracted from urine using Maxwell® system protocols. Viral-loads were determined by quantitative qPCR using genesig® JCV and BKV standard kits.

Results: CKD patients had advanced kidney disease with a median eGFR of 7 IQR (4-13), both controls and relatives had normal renal function; median eGFR of 121 (98-130) and 124 (93-144) respectively, with eGFR measured in mL/min/1.73m^2. *APOL1* high-risk alleles were absent in 50% of CKD patients, 41% of controls and 52% of relatives. Two *APOL1* risk alleles were present in 10% of CKD patients, 8.6% of controls and in 6**%** of relatives. In CKD patients, there was no difference in blood pressure, eGFR, proteinuria based on any allele combination. The overall prevalence of JCV was 21% compared to 6% for BKV, with coinfection present in four participants. JCV was present in only 3% CKD patients compared to 39% of controls and 21% of relatives; P < 0.0001, Fisher's exact test. None of the CKD patients had evidence of BKV. There was no difference in mean $\log_{10}$ viral load JCV between CKD patients and controls (P = 0.2644), between CKD patients and their relatives (P = 0.3074) or between controls and relatives (P= 0.7073), *t* test.

Conclusions: Apolipoproprotein L1 risk variants are infrequent in black South Africans with hypertensive CKD. There was a higher prevalence of JCV infection in black South Africans with normal renal function. JC virus seems to protect against development of kidney disease.

SA-PO351

Distribution of APOL1 Renal Risk Variants in General Population from Central Africa (Democratic Republic of Congo) Pepe M. Ekulu,[1,3] Michel N. Aloni,[1] François B. Lepira,[2] Elena N. Levtchenko.[3] *[1]Pediatrics, University of Kinshasa, Kinshasa, Congo (the Democratic Republic of the); [2]Nephrology Internal Medicine, University of Kinshasa, Kinshasa, Congo (the Democratic Republic of the); [3]Pediatric Nephrology, KU Leuven, Leuven, Belgium.*

Background: The susceptibility in chronic kidney disease among sub-Saharan African descent has been attributed to apolipoprotein-L1 (*APOL1*) genetic variants G1 and G2. However, in Africa, data related to the geographical distribution of *APOL1* risk variants are limited, and there is no reliable data from Democratic Republic of Congo (DRC). We aimed to describe the frequencies of *APOL1* risk variants in a large population from Central Africa and to assess the association with the early kidney damage in children.

Methods: A total of 465 participants from four large districts in Kinshasa were enrolled. *APOL1* high-risk genotype was defined by the presence of 2 high-risk variants (G1/G1, G2/G2, G1/G2) and low risk genotype if 0 or 1 risk variants were present. Albumin-to-creatinine ratio (ACR) was assessed in a fresh morning urine sample in children only, and elevated ACR was defined as ACR>30mg/g.

Results: From 465 subjects enrolled, 453 were successfully genotyped, of whom 388 children and 65 adults. APOL1 sequence analysis revealed 201 (44%) participants carrying at least one APOL1 risk variant, 36 (8%) 2 risk variants. Concerning the frequency of *APOL1* risk alleles, 14 % of all chromosomes carried G1 whilst 13% carried G2. Thus, the burden of *APOL1* risk allele was 27%. Of 388 children, 39 (10%) had elevated ACR. Compared to those carrying low-risk genotype, children with *APOL1* high-risk genotype had a higher prevalence of microalbuminuria (OR 1.48, 95% CI 0.41-4.84).

Conclusions: The burden of *APOL1* renal risk variants is high in DRC. However, no strong statistical association has been found between the high-risk genotype and the early kidney damage in general population of children

Funding: Government Support - Non-U.S.

SA-PO352

Houston Encounters of CKD of Uncertain Origin (CKDu): Lack of Major Etiologic Factor, except for Exposure to Herbicide Ilse M. Espina,[1] Edlyn G. Bustamante,[2] Maria E. Maldonado,[1] Joniqua N. Ceasar,[1] Jose R. Dominguez,[1] David Sheikh-Hamad.[1] *[1]Baylor College of Medicine, Houston, TX; [2]Harris Health, Houston, TX.*

Background: CKDu (aka MesoAmerican Nephropathy) is encountered globally. Proposed etiologies for CKDu include dehydration, toxic exposure and infection. To identify possible etiology for CKDu among patients encountered at a safety net hospital in Houston, we carried out chart review of CKD5 patients matching the inclusion criteria for the study.

Methods: Thirty patients were identified based on history consistent with CKDu – young, migrant worker, otherwise healthy who presents in renal failure. Patients were included in the study if 1) laboratory studies are consistent with CKD5 (BUN, serum creatinine, Ca/PO4, iPTH and anemia), 2) kidney ultrasound showing small kidneys, 3) urine studies without significant proteinuria or urine sediment, and 4) negative studies for viral hepatitis, syphilis, HIV, ANA, ANCA, SPEP, UPEP. Exclusion criteria: history of diabetes, known primary or secondary renal disease.

Results: 10 patients were available for interview. 9/10 male, 1/10 female; 6/10 from Mexico, 3/10 from El Salvador, 1/10 from Honduras. Only one had knowledge of kidney disease upon presentation, 3 had family history of CKD, 4/10 had occasional intake of Tylenol. Mean age at presentation 32.8 years (median: 33, range 25-43). Mean stay in the US before CKD5 diagnosis 9.2 years (median 8, range 1-15). Before immigrating to the US, 7/10 lived in a village/farm, 3/10 lived a city. 8/10 lived in hot climate zones (6/10 mountains, 2 valleys, 2 close to ocean); 4/10 worked in agriculture/farming (8-15 years). While in the US, 6/10 worked in construction, 3/10 in landscaping, 0/10 in farming. Of the 4 farm workers, 2/10 cultivated cane, 2/10 cotton, 3/10 corn, and 2/10 had exposure to animal stock; 3 had chronic intermittent exposure to Gramaxone (paraquat-based herbicide), while 1/10 had exposure to bug killer and fertilizers. 4/10 drank well water, the rest consumed bottled water, and only 2/10 consumed sweetened drinks; uric acid levels were normal (available on 3/10).

Conclusions: Patients with CKDu encountered are migrant workers, male, young, originally from a farm/village, living in hot mountainous regions. Hydration solution consisted of water. We found no clear identifiable risk factors for CKDu except for chronic exposure to Gramaxone/paraquat in farm workers.

Funding: Private Foundation Support

SA-PO353

CKDu in Mexican Children: The Case of Poncitlan, Jalisco Guillermo Garcia-Garcia, Ricardo Rubio, Melina D. Amador, Margarita Ibarra-Hernández, Librado De la Torre-Campos, Alexia C. Romero, Guillermo Navarro blackaller, Francisco gonzalo Rodríguez garcía. *Hospital Civil De Guadalajara, University of Guadalajara, Guadalajara, Mexico.*

Background: An elevated prevalence of CKD of unspecified cause (CKDu) has been documented in various developing countries. It has been reported by the media a high prevalence of CKDu among children in towns located by Chapala Lake, particularly within the municipality of Poncitlan, Jalisco. Environmental facros have been blamed as the probable cause of the pandemia.

Methods: Since 2006, we pioneered screening people at risk for the presence of CKD using mobile units that travel to rural and urban communities of Jalisco. Trained personnel collected demographic and clinical data, and obtained blood and urine for serum chemistry and dipstick urinalysis. Those individuals who were aware they had kidney disease were not assessed; all others were eligible to participate. GFR was estimated with the Schwartz equation. CKD was defined as an eGFR < 60 ml/min/1.73m^2. HTN, malnutrition, and obesity were defined by gender, age, and height specific normative values.

Results: Between 2007-2016, 659 children were screened in the mobile units, 144 of them in the municipality of Poncitlan. Results were compared with those of all other Jalisco municipalities (Table 1)

Conclusions: The prevalence of proteinuria and malnutrition was higher in Poncitlan as compared to other Jalisco municipalities. Undergoing studies will provide information on the posible causes of this high prevalence. Screening programs should be linked to community- and individual-level interventions to reduce the risk of chronic kidney disease in adulthood.

Funding: Private Foundation Support

Results

	All n=650	Poncitlan n=144	Other municipalities n= 505	p
Age, y	13.63±3.92	8.78±3.97	15.03±2.57	0.000
Male, %	41.4	50.0	38.8	0.01
Known DM, %	2.9	0.0	3.8	
Known HTN, %	1.5	0.0	2.0	
% with SBP or DBP ≥ 95th percentile	18.6	11.4	19.1	0.368
% with IMC < 5th percentile	6.7	15.6	4.2	0.000
% with IMC > 95th percentile	17.3	9.9	19.4	0.000
% with eGFR < 60 ml/min/1.73 m2	2.8	0.7	3.4	0.136
% with dipstick + proteinuria	16.5	44.4	4.8	0.000

SA-PO354

Prevalence and Risk Factors of CKD among Workers in the Brick Making Industry of La Paz Centro, Nicaragua Lyanne E. Gallo,[6] Komal Basra,[2] Mauricio E. Sánchez-Delgado,[6] Tania M. Gamez,[3] Caryn M. Sennett,[1] Rebecca L. Laws,[2] Juan J. Amador,[1] Damaris A. Lopez pilarte,[1] Yorghos Tripodis,[2] Michael Mcclean,[2] Joseph Kupferman,[1] David J. Friedman,[4] Marvin A. Gonzalez,[5] Madeleine K. Scammell,[2] Ana G. García,[1] Daniel R. Brooks,[2] Aurora Aragon.[1] *[1]Boston University, Boston, MA; [2]Boston University School of Public Health, Boston, AL; [3]MINSA, Chinandega, Nicaragua; [4]None, Brookline, MA; [5]Research Center on Health, Work and Environment at National Autonomous University of Nicaragua, Leon, León, Nicaragua; [6]UNAN.León, León, Nicaragua.*

Background: Western Nicaragua is a hotspot for Chronic Kidney Disease (CKD) of non-traditional etiology, also called Mesoamerican Nephropathy. This disease has killed tens of thousands of economically active individuals; primarily agricultural workers at sea level. The aim of this study is to establish the prevalence of CKD among workers in the artisanal brick and tile industry, and explore associations between risk factors of interest and changes in kidney function over time.

Methods: In 2016, 257 workers in small brick and tile making industries in the La Paz Centro region of Nicaragua were recruited for a prospective cohort study. Of those, 224 (93.5%) participated in follow-up four months later. At both baseline and follow-up, serum creatinine was measured using the Jaffe methods at the biochemical laboratory at the Medical Faculty of UNAN-León and used to estimate glomerular filtration rate (eGFR) using the CKD-EPI equation. CKD was defined as two measurements of eGFR<60 ml/min/1.73m^2 at least 3 months apart.

Results: 14.8% of participants had eGFR<60 at baseline. Virtually all were confirmed at follow-up for a prevalence of CKD of 14.3%; 97% of cases were male, 25% were less than 35 years of age, and 28% had stage 5 CKD (eGFR<15.) The mean difference in eGFR measured between baseline and follow-up was -4.1 (standard deviation=20.4), suggesting a decrease in mean kidney function in this brickmaking population over the study period. Linear mixed effects models indicate predictors include a job task that entails loading or operating the oven, age, sex, education, smoking status, water intake and having an immediate family member with CKD.

Conclusions: CKD prevalence among the workers in La Paz Centro was similar to prevalence reported in cross sectional studies conducted in the sugarcane growing region of Nicaragua, and slightly slower than prevalence among low-land agricultural workers in El Salvador.

Funding: Commercial Support - Funding was provided by Los Azucareros Del Istmo Centroamericano (AICA), and was managed by the CDC Foundation. Donors had no prior review of these results nor influence on content of abstract.

SA-PO355

Association between Obesity and Prevalence of CKD in Patients with Type 2 Diabetes Mellitus and/or Arterial Hypertension Laura Cortes-Sanabria,[2] Rafael A. Ayala cortes,[5] Clementina E. Calderon Garcia,[3] Enrique Rojas-Campos,[1] Alfonso M. Cueto-Manzano.[4] *[1]INSTITUTO MEXICANO DEL SEGURO SOCIAL, GUADALAJARA, Mexico; [2]Instituto Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico; [3]Mexican Social Security Institute, Guadalajara, Mexico; [4]None, Zapopan, Jalisco, Mexico; [5]Unidad de Investigación Médica en Enfermedades Renales, Guadalajara, Jalisco, Mexico.*

Background: Obesity, directly or through several comorbidities such as diabetes mellitus, high blood pressure, metabolic syndrome or cardiovascular disease, increase the risk for development and progression of CKD. It is noteworthy, however, the lack of information in this regard in settings with high prevalence of risk factors for CKD, such as Latin America, and particularly Mexico. *Aim*: To determine the association between obesity and CKD in patients recently diagnosed with only type 2 diabetes mellitus (DM2), arterial hypertension (AHT) without DM2, and DM2+AHT.

Methods: Cross-sectional study. Patients with transient causes of albuminuria were excluded. All patients had a medical history and clinical examination; glomerular filtration rate was estimated (eGFR) by the CKD-EPI formula and albuminuria/creatininuria was determined by nephelometry. Obesity was classified according with WHO criteria and CKD according with KDIGO guidelines.

Results: 2123 patients (DM2 = n 676; DM2+AHT = n 877, and AHT = n 570) were studied. Mean age was 60±12 yrs, 62% women, DM2 vintage 9 (4-15) yrs and AHT vintage 7 (3-14) yrs. Prevalence of obesity was lower in DM2 (35%) compared to DM2+AHT (45%) and AHT (46%) (p<0.0001). Comparing patients with obesity *vs* normal weight, prevalence of CKD were lower in DM2 (31% *vs* 42%, respectively, p= 0.01), but it was higher in DM2+AHT (38% *vs* 20%, p=0.02) and AHT (40% *vs* 16%, p= 0.01) patients. Results of multivariate analysis are shown in the Table

Conclusions: Frequency of obesity was significantly higher in patients with DM2+AHT. The risk to present CKD is higher in DM2+AHT than in isolated DM2 or AHT. It is necessary to advice for modification of negative lifestyle habits, especially in patients with diabetes and hypertension in order to prevent development and progression of kidney damage.

Logistic regression model of variables predicting CKD

	DM2			DM2+AHT			AHT		
Variable	OR	CI 95%	p	OR	CI 95%	p	OR	CI 95%	p
Age	0,97	0,95-0,98	<0,01	0,97	0,95-0,98	<0,01	0,94	0,92-0,97	<0,01
Male gender	1,56	1,1-2,22	<0,03	1,75	1,29-2,43	<0,01	1,67	1,05-2,67	0,06
DM Vintage	1,08	1,05-1,09	<0,001	1,07	1,05-1,09	<0,001	---	---	---
Systolic blood pressure	0,99	0,98-1,00	0,09	0,99	0,98-1,01	0,86	0,99	0,98-0,99	0,05
Overweight/Obesity	1,5	1,0-2,61	0,09	1,36	1,03-1,8	0,06	1,13	0,59-2,14	0,07

SA-PO356

Progression of CKD and Outcomes in Thailand: Thai-SEEK Project Amnart Chaiprasert,[4] Kraiwiporn Kiattisunthorn,[2] Warangkana Pichaiwong,[1] Vuddhidej Ophascharoensuk,[3] Thananda Trakarnvanich,[5] Dhawee Sirivong,[7] Atiporn Ingsathit.[6] *[1]RAJAVITHI HOSPITAL, Bangkok, Thailand; [2]Siriraj Medical School, Mahidol University, Bangkok, Thailand; [3]Chiang Mai University, Chiang Mai, Thailand; [4]Phramongkutklao Hospital, Pathumthani, Thailand; [5]Vajira Hospital, Bangkok, Thailand; [6]Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [7]Faculty of Medicine Khon Kaen University, Khon Kaen, Thailand. Group/Team: Thai-SEEK Steering Committee, Nephrology Society of Thailand.*

Background: Chronic kidney disease (CKD) is one of the major public health problems, however, the data of CKD in Thai population including prevalence and progression, also its outcomes are limited. In 2008, Thai-SEEK (Screening and Early Evaluation of Kidney Disease) study, a community-based cross-sectional study using stratified-cluster sampling method, was initiated which found prevalence of CKD for 17.5%. Therefore, the study was conducted to evaluate the progression and outcomes as well as predicting factors of CKD in Thailand.

Methods: A prospective cohort study was run from June 16, 2015 to December 15, 2016 by using subjects of the first survey. Data from history taking and physical examination, serum creatinine, urinalysis, and urine albumin creatinine ratio were done in 2,396 subjects (70%) who gave responses for participating follow up program, and death certificates were used to identify causes of death. Four hundred and eight subjects (68% of those diagnosed CKD in the first survey) were analyzed for CKD progression and outcomes. Serum creatinine standardized with SRM967a (National Institute of Standards and Technology, MD, USA) was put in GFR calculation using CKD-EPI formula. Staging of CKD was based on KDIGO 2012 criteria, and rapid CKD progression was defined as a change in CKD staging plus a decline in GFR >25% or >5 ml/min/1.73m^2/year or renal replacement therapy was initiated.

Results: Mean age was 54.6±13.7 years and 41% was male. Median follow-up time was 7.9 years (min, max 7.7, 9.1). Incidence of CKD progression was 0.23 (95% CI: 0.19, 0.28) with a decline in GFR 1.40±1.13, 1.95±1.66, 1.59±1.25, 1.66±1.18 and 1.60 ±0.77 ml./min/1.73 m^2/year in CKD stage G1, G2, G3a, G3b and G4, respectively. Predictors of progression were diabetes mellitus (RR 1.39; 95% CI: 0.09, 2.14) and hyperuricemia (RR 1.70; 95% CI: 1.17, 2.47). Mortality rate was 6% per year and associated severity of CKD staging at diagnosis. The most common cause of death was cancer (22%), following by cardiovascular disease (19.8%) and infection (12.8%).

Conclusions: During 8-year follow up, risk of CKD progression was 23%. Diabetes mellitus and hyperuricemia were the strong predictors of progression. The population based cohort would be a significant contributor in national policy making for slow CKD progression in Thailand.

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SA-PO357

Vascular Access Creation Decelerates Renal Function Decline and Its Determinant Factors Ming-Tso Yan,[2] Shih-Hua P. Lin.[1] *[1]Tri-Service General Hospital, Neihu, Taiwan; [2]Cathay General Hospital, Taipei, Taiwan.*

Background: Vascular access (VA) creation before hemodialysis (HD) initiation has been suggested to decelerate estimated glomerular filtration rate (eGFR) decline but it remains uncertain which factors contributing to the renal benefit of VA creation.

Methods: One hundred and nine patientswith chronic kidney disease (CKD) (aged 65.3 years, Male:Female=58:51) transitioning to hemodialysis during January 2009 to December 2015 were recruited in this retrospectively single-center study and all had at least 3 estimated glomerular filtration rate (eGFR) measurements either before or after VA creation. The correlation between ratio of pre-/post-VA creation eGFR declined rate and other factors was examined through logistic regression.

Results: VA was created at mean age of 67.7 ± 11.8 and HD was initiated at 68.1 ± 11.8 years, respectively. Fifty one (46.8%) patients had decelerated eGFR declined rate after VA creation and were characterized by faster eGFR declined rate before VA creation (1.00 ± 1.41 vs 0.29 ± 0.23 ml/min per month, P < 0.001), regardless of age, gender and history of diabetes mellitus (DM) and hypertension. Biochemical surveys at the time of VA creation showed that lower serum creatinine level (3.57 ± 1.50 vs 4.49 ± 1.68 mg/dl, p = 0.003), lower serum albumin (3.50 ± 0.46 vs 3.72 ± 0.62 g/L, p = 0.02) and higher eGFR (19.04 ± 11.08 vs 14.57 ± 8.51 ml/min, p = 0.02) in patients with decelerated eGFR declined rate. Serum albumin level at VA creation showed reversely linear correlation with ratio of pre-/post-VA creation eGFR declined rate. A positive correlation between ratio of pre-/post-VA creation eGFR declined rate and HbA1c level at VA creation was disclosed in patients with DM.

Conclusions: It may be better to create VA earlier to postpone initiation of dialysis especially in patients with poor baseline conditions such as faster eGFR declined rate, low serum albumin level and, if patients with DM, higher HbA1c level.

SA-PO358

Renal Biopsy Results from Patients with Multiple Myeloma – Data from a Comprehensive National Cancer Institute: A 10 Year MD Anderson Experience Laila S. Lakhani,[3] Umut Selamet,[1] Ali Ziaolhagh,[4] William F. Glass,[6] Amanda Tchakarov,[5] Ala Abudayyeh.[2] *[1]MD Anderson Cancer Center, Houston, TX; [2]The University of Texas MD Anderson Cancer Center, Houston, TX; [3]UT Houston, Houston, TX; [4]University of Texas, Housotn, TX; [5]University of Texas Medical School at Houston, Houston, TX; [6]University of Texas – Houston Medical School, Houston, TX.*

Background: Around 50% of patients with Multiple Myeloma (MM) have renal involvement at presentation. Renal lesions in MM is both heterogeneous and multifactorial. We set out to study the spectrum of these deposits and electron micrographic lesions, to determine their extent and correlation with biochemical paraproteinemia, clinically significant proteinuria and the other systemic findings in this population.

Methods: Data is extracted from the retrospective chart review of all patients at MD Anderson Cancer Center who received a renal biopsy between Jan 2008 – June 2017

Results: Out of 193 patients who underwent renal biopsy during this period, 39 had the diagnosis of Multiple Myeloma at the time of biopsy, with 14/39 (36%) on active chemotherapy and 11/39 s/p stem cell transplant. An equal gender distribution was noted (19 females, 20 males) with an average age of 62.5 years. The co-existing medical conditions included HTN (69%), DM (31%), and rarely other malignancies (8%). The most common indication for renal biopsy was AKI -85%, followed by proteinuria in 67% patients - (28% had nephrotic range proteinuria). 2/39 were inadequate biopsy samples. From the remaining 37 biopsies, 13/37 (35%) had glomerulopathy and tubulopathy from cast deposition, 4/37 (11%) had AL Amyloidosis and 1 patient had granulomatous TIN (AFB/fungal stains negative). Interestingly 19/37 (51%) had no evidence of 'myeloma kidney'; the most common findings in these patients were focal global glomerulosclerosis, hypertensive arterial and arteriolar glomerulosclerosis and diabetic nodular glomerulosclerosis.

Conclusions: The severity of renal involvement confers worse prognosis in patients with Multiple Myeloma. The biopsy findings helps us to predict outcomes and tailor our clinical approach and treatment regimens to minimize morbidity and mortality in patients with Multiple Myeloma.

Funding: Clinical Revenue Support

SA-PO359

TGF Beta Pathway Enriched as Candidate Plasma Severity Biomarkers in CKD Jennifer E. Van eyk,[1] Lesley Inker,[4] Josef Coresh,[5] Paul L. Kimmel,[2] Adrienne Tin.[3] *[1]Cedars Sinai Medical Center, Los Angeles, CA; [2]National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; [3]Baltimore, MD; [4]Tufts Medical Center, Boston, MA; [5]Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD. Group/Team: Biocon 1.*

Background: Our hypothesis is that in-depth proteomics discovery could identify novel plasma biomarkers that could be useful for the prognosis for development of chronic kidney disease (CKD) and to monitor progression (severity) of CKD. Furthermore, that as subset of markers would be related to key signaling pathways underlying the disease.

Methods: A four group design in which 64 plasma samples collected at two time points (T0 and T1) for 16 cases and 16 controls were analyzed. Cases were individuals with GFR slope >5ml/min/year and a total decline of at least 30 ml/min/year follow-up of at least 3 years while the controls had <1 ml/min/year for at least 3 years matched by age, sex, race, diabetes, hypertension, GR at T0, ACR. Each sample was depleted of the top 14 abundant plasma proteins, fractionated using reversed phase HPLC, digested, analyzed by mass spectrometry and batched searched. Proteins were ranked based on *p* values for prognosis (protein differences between cases and controls at T=0) and severity (cases between T0 &T1 / controls between T0 & T1) and deteremined pathways between the various candidate markers.

Results: Across all plasma samples, 1151 nonredundant protiens were identified with a protein and peptide probability of <0.1% (with >625,000 spectral counts). There were 3 and 43 candidate prognostic markers that were found to have p<0.01 and p<0.05, respectively. Within in this top group of severity markers were APO II, APO CIII, Haptoglobin and APOL1 which were ranked 4th (p=0.0058), #6 (p=0.011),13th (p=0.018) and 19th (p=0.021), respectively for prognosis. There were 2 and 66 candidate severity markers with p<0.01 and p<0.05, respectively. Of these CRP, Cystatin C and beta trace protein were ranked 6th (p=0.004), 7th (p=0.006) and 18th (P=0.04), respectively, as severity markers. Interestingly, the TGF beta pathway proteins was enriched in the candidate severity proteins (p<0.05) based on over 15 protein linkages. Although TGF beta 1 was identified in this data set, 90% of the data was missing.

Conclusions: This study indicates that *de novo* proteomic analysis of plasma can confirm changes of known biomarkers and identify potential new biomarkers. That different plasma proteins are aligned with prognosis versus severity. Proteins in the TGF beta pathway are particularly enriched as candidate severity biomarkers.

Funding: NIDDK Support

SA-PO360

The Role of Renal Vascular Endothelial-Mesenchymal Transition in Systemic Lupus Erythematosus Associated Thrombotic Microangiopathy Weixin Hu, Ying Zhou, Ying-hua Chen, Ming-chao Zhang, Shao-shan Liang, Fan Yang, Zheng-zhao Liu, Zhi-Hong Liu. *National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing China, Nanjing, China.*

Background: To investigate the phenotypic changes of renal vascular endothelial cells and its relationship with the vascular injury and renal interstitial fibrosis in patients with SLE associated thrombotic microangiopathy (SLE-TMA).

Methods: Biopsies from 30 SLE patients which showed lupus nephritis and renal vascular TMA were included in this study. TMA was divided into acute and chronic TMA groups according to the histology. The expression of vascular endothelial CD31, vessel endothelial cadherin (VE-cadherin), α-smooth muscle actin (α-SMA) and transforming growth factor-β (TGF-β) were stained with immunofluorescence and immune histochemical assays, the intensity of endothelial marker expression recorded as the mean density (integral optical density/ area of vascular endothelial layer) and the extent of renal interstitial fibrosis were quantitatively analyzed with Image-Pro-Plus 6.0 and ImageScope (Aperio) respectively.

Results: Confocal immunofluorescence microscopy demonstrated no α-SMA expression in endothelial cells in normal renal vessels but markedly higher endothelial α-SMA expression in renal vessels showing TMA. Compared with the normal group, the intensity of endothelial CD31 and VE-cadherin expression was significantly lower ($P<0.05$), and α-SMA expression was much higher ($P<0.001$) in acute TMA group. The endothelial CD31, VE-cadherin and TGF-β expression were significantly lower, while the α-SMA expression significantly higher in chronic TMA group than that in acute TMA group and normal group ($P<0.001$). The intensity of endothelial α-SMA expression was positively correlated with the extent of renal interstitial fibrosis ($r=0.439$, $P<0.05$), while the endothelial CD31 expression was negatively correlated with renal interstitial fibrosis ($r=-0.458$,$P<0.05$). Furthermore, endothelial α-SMA expression was also an independent risk factor for the poor treatment response in patients with SLE-TMA.

Conclusions: In SLE-TMA, the lower expression of normal endothelial cell markers and higher α-SMA expression indicated a pathogenetic process of vascular endothelial to mesenchymal transition, which was related with renal interstitial fibrosis and poor treatment response.

SA-PO361

Cystinosis Is Associated with Abnormal Bone Microarchitecture and Sarcopenia in Children and Adults Candice Sheldon,[1] Paul C. Grimm,[4] Jessica R. Whalen,[3] Kyla Kent,[2] Jin Long,[3] Maira Simas,[3] Mary B. Leonard.[2] *[1]Stanford, Palo Alto, CA; [2]Stanford School of Medicine, Palo Alto, CA; [3]Stanford University, Palo Alto, CA; [4]Stanford University Medical Center, Stanford, CA.*

Background: Cystinosis is associated with multiple risk factors for abnormal bone metabolism, including phosphate wasting, metabolic acidosis, malnutrition, chronic kidney disease, hypothyroidism, myopathy, delayed puberty and male hypogonadism. Prior bone studies are limited to case reports and a case series. Muscle mass has not been quantified.

Methods: Regional and whole body DXA scans were obtained in 37 cystinosis patients, age 6-49 yr. High-resolution quantitative CT (QCT) tibia scans were obtained in cystinosis patients and 61 matched controls. DXA results were converted to sex, race and age-specific Z-scores using robust population-based reference data in children and adults. Linear regression was used to assess group differences in QCT results, adjusted for age, sex and tibia length.

Results: Total Hip (mean ± SD: -0.96 ± 1.22), femoral neck (-1.23 ± 1.14), and 1/3rd radius (-1.02 ± 1.48) bone mineral density (BMD) Z-scores were reduced compared with reference data (all $p<0.001$) and were comparable in children and adults. Appendicular lean mass Z-scores were reduced in children (-0.93 ± 1.27, $p<0.01$) and adults (-1.80 ± 1.32, $p<0.0001$), and were positively associated with DXA BMD Z-scores at all sites (R 0.46-0.50, $p<0.01$). Median (interquartile range) eGFR was 58 (32-76) ml/min/1.73m^2. DXA Z-scores were not associated with eGFR. Tibia diaphysis cortical thickness and BMD ($p<0.02$), metaphysis trabecular bone volume fraction, thickness and number ($p<0.01$) and finite element estimates of failure load in the diaphysis and distal tibia ($p<0.0001$) were lower in cystinosis vs. controls in multivariate analyses. Appendicular mass was highly associated with failure load ($p<0.001$) independent of age, sex and tibia length. Adjustment for lean mass eliminated group differences in cortical thickness and failure load in the diaphysis ($p>0.20$) and attenuated differences in failure load in the distal tibia ($p=0.06$). In contrast, trabecular deficits persisted.

Conclusions: Cystinosis is associated with severe musculoskeletal deficits in children and adults. Bone deficits were correlated with sarcopenia suggesting a role of decreased biomechanical loading. Studies are needed to identify interventions to improve bone strength and muscle mass in cystinosis.

Funding: Private Foundation Support

SA-PO362

Plasma 25-Hydroxyvitamin D Levels and Renal Function Decline in African Americans Joseph Lunyera,[1] Clemontina A. Davenport,[1] Clarissa J. Diamantidis,[1] Nrupen A. Bhavsar,[1] Mario Sims,[2] Myles S. Wolf,[1] Jane F. Pendergast,[1] L. Ebony Boulware,[1] Julia J. Scialla.[1] *[1]Duke University School of Medicine, Durham, NC; [2]University of Mississippi Medical Center, Jackson, MS.*

Background: 25-hydroxyvitamin D [25(OH)D] deficiency is highly prevalent among African Americans and may contribute to their disproportionate risk of adverse chronic kidney disease (CKD) outcomes. We examined the association between plasma 25(OH)D levels and adverse CKD outcomes in the Jackson Heart Study (JHS).

Methods: We adjusted plasma 25(OH)D3 levels measured at baseline for monthly variation in sunlight exposure by using the residuals from the regression of 25(OH)D3 on the month of blood draw plus the overall mean. We examined the associations between baseline adjusted 25(OH)D3 and (a) annual estimated glomerular filtration rate (eGFR) decline and (b) incident CKD during follow-up using generalized linear models adjusted for demographics, behavioral factors, and comorbidity. Incident CKD was defined as either eGFR <60 mL/min/1.73m^{2}and a 25% decline in eGFR between baseline and follow-up, or albumin-to-creatinine ratio ≥30 mg/g at follow up among those without CKD at baseline.

Results: Among 5164 participants with non-missing 25(OH)D3 (97% of JHS cohort), the median [IQR] adjusted 25(OH)D3 was 12.0 [8.71-16.56] ng/mL, and mean ±SD eGFR was 94.11 ±21.98 mL/min/1.73m^2 at baseline. Over a median of 8 years, the mean ±SD annual eGFR decline was 1.27 ±1.96 mL/min/1.73m^2 per year, and 249 participants (12% of those whose CKD status could be determined) developed incident CKD. After adjusting for demographics, behavioral factors and comorbidity, each 10 ng/mL lower adjusted 25(OH)D3 was associated with 0.19 (95% CI 0.05-0.33) mL/min/1.73m^2 per year faster eGFR decline. However, the association did not persist after additional adjustment for baseline eGFR ($p=0.146$). 25(OH)D3 was not associated with incident CKD (OR [95% CI] per 10 ng/mL lower 25(OH)D3 1.12 [0.85,1.47]).

Conclusions: Plasma 25(OH)D3 was not associated with risk of kidney function decline in African Americans after adjustment for baseline eGFR and other covariates. Despite low levels at baseline, our data do not support a role of supplementation in preventing or slowing CKD in African Americans

Funding: NIDDK Support

SA-PO363

Soluble Urokinase Plasminogen Activation Receptor (suPAR) in the German Chronic Kidney Disease (GCKD) Study Claudia Sommerer,[3] Nicole G. Metzendorf,[1] Matthias Schmid,[5] Kai-Uwe Eckardt,[4] Jochen Reiser,[2] Martin G. Zeier.[3] *[1]Kidney Center Heidelberg, Heidelberg, Germany; [2]Rush University Medical Center, Chicago, IL; [3]University Hospital of Heidelberg, HEIDELBERG, Germany; [4]University of Erlangen-Nuremberg, Erlangen, Germany; [5]Institute of Biometry, University of Bonn, Bonn, Germany. Group/ Team: On behalf of GCKD investigators.*

Background: Soluble urokinase plasminogen activation receptor (suPAR) is an emerging biomarker for prediction and progression of kidney disease and cardiovascular events. The value of suPAR as a biomarker was evaluated in the large prospective observational German Chronic Kidney Disease (GCKD) study.

Methods: Chronic kidney disease (CKD) patients aged 18-76 years with an estimated glomerular filtration rate (eGFR) of 30 - <60 mL/min/1.73 m^2 or eGFR≥60 and overt proteinuria were enrolled in the GCKD study. suPAR was measured in baseline samples of participants and categorized in quintiles for investigation of the underlying disease, age and renal function.

Results: A total of 4994 CKD patients were studied (60.09 % males, mean age 60.08 ±11.98 years). Mean eGFR was 49.47 ± 18.29 mL/min/1.73 m^2 and median (IQR) albumin/creatinine ratio was 50.85 (25% quantile: 9.61, 75% quantile 387.17) mg/g. Mean suPAR level was 2184±1952 pg/mL with a range from 221 to 45433 (median 1771, 25% quantile: 1446.9, 75% quantile: 2254.1). Prevalence of patients with cardiovascular diseases, diabetic nephropathy, systemic diseases and smoking showed an upwards trend from suPAR quintile 1 to quintile 5. Median suPAR concentration increased with worsening renal function (CKD stage 1 to CKD stage 4, $p<0.0001$) and age ($p<0.0001$). Within CKD categories, suPAR rised with increase of albuminuria.

Conclusions: suPAR was evaluated in one of the worldwide largest CKD cohorts. In this study cohort, suPAR was associated with underlying cardiovascular disease, diabetic nephropathy as well as systemic disease involving the kidney. suPAR depended on renal function, proteinuria and age. The predictive value of suPAR on development of renal function and cardiovascular disease will be evaluated in this prospective study.

SA-PO364

The Relationship between Intrarenal Dopamine and Intrarenal Renin-Angiotensin System in CKD Patients Is Dependent on Renal Function Takashi Matsuyama,[4] Naro Ohashi,[4] Sayaka Ishigaki,[4] Shinsuke Isobe,[4] Naoko Tsuji,[2] Tomoyuki Fujikura,[3] Takayuki Tsuji,[4] Akihiko Kato,[1] Hideo Yasuda.[4] *[1]Hamamatsu University Hospital, Hamamatsu, Japan; [2]Hamamatsu University School of Medicine, Hamamatsu, Japan; [3]Hamamatsu university school of medicine, Munich, Germany; [4]Hamamatsu University School of Medicine, Numazu, Japan.*

Background: The mechanisms to activate intrarenal renin-angiotensin system (RAS) depend on the conditions of kidney diseases. In the angiotensin II (AngII) infusion models, the circulating AngII is filtered into renal tubular lumens and activates intrarenal RAS. Intrarenal dopamine system activation was shown to reduce angiotensinogen (AGT) expression in the proximal tubules and suppress intrarenal RAS activity. In the chronic kidney disease (CKD) models where filtered plasma AGT into the tubular lumens due to glomerular injury activates intrarenal RAS, the relationship between intrarenal dopamine system and intrarenal RAS in CKD models has not been clarified. Therefore, we performed this study to determine the mutual relationship in CKD patients.

Methods: We recruited 46 CKD patients (age: 51.1 ± 20.0 years old, 16 males, causes of CKD: chronic glomerulonephritis; 34, diabetic nephropathy; 2, nephrosclerosis; 4, or others; 6) without undergoing dialysis or taking RAS blockers. The urinary dopamine (U-DOPA) excretion as an indicator of intrarenal dopamine activity and the urinary AGT (U-AGT) excretion as a surrogate marker of intrarenal RAS activity were measured, and the relationships were investigated.

Results: U-DOPA excretion levels in patients with CKD stage 5 were significantly lower than those in patients with other CKD stages, and U-DOPA excretion levels tended to decrease as the CKD stages progressed. Conversely, U-AGT excretion levels in patients with CKD stage 5 were significantly higher than those in patients with CKD stages 1 to 3, and tended to increase as the CKD stages progressed. U-DOPA excretion levels were significantly and negatively correlated with U-AGT excretion levels ($r=-0.42$, $p<0.01$) and significantly and positively correlated with estimated glomerular filtration rate (eGFR) ($r=0.64$, $p<0.01$). Multiple regression analysis revealed that U-DOPA excretion levels were associated with U-AGT excretion levels after adjustment of age, sex, and body mass index ($\beta=-0.34$, $p=0.025$). However, the correlation disappeared when eGFR was additionally adjusted ($\beta=-0.057$, $p=0.70$).

Conclusions: The negative correlation between intrarenal dopamine system and intrarenal RAS system in CKD patients is affected by renal function.

SA-PO365

Impact of Bariatric Surgery on Prognosis of CKD Allon N. Friedman,[1] Abdus S. Wahed,[7] Junyao Wang,[7] Anita Courcoulas,[8] Gregory Dakin,[10] Paul L. Kimmel,[3] James E. Mitchell,[2] Jonathan Q. Purnell,[5] Carel W. Le roux,[6] Richard C. Thirlby,[9] Bruce M. Wolfe.[4] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]NRI, CHASKA, MN; [3]National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; [4]Oregon Health & Science University, Portland, OR; [5]Oregon Health and Science University, Portland, OR; [6]University College Dublin, University College Dublin, Ireland; [7]University of Pittsburgh, Pittsburgh, PA; [8]University of Pittsburgh Medical Center, Pittsburgh, PA; [9]Virginia Mason, Seattle, WA; [10]Weill Cornell Medical College, New York, NY.*

Background: Obesity is linked to the development and progression of chronic kidney disease (CKD) but whether weight reduction through bariatric surgery protects against CKD is poorly understood. Our goal was to assess if bariatric surgery influences the prognostic risk for CKD.

Methods: We studied the patient cohort from Longitudinal Assessment of Bariatric Surgery 2 (LABS-2), which included 2458 adults who underwent bariatric surgery from March 2006 to April 2009 at 10 US hospitals in 6 geographically diverse clinical centers. Participants underwent Roux-en-Y gastric bypass (n=1530), laparoscopic adjustable band (n=523), sleeve gastrectomy (n=52), banded gastric bypass (n=22), or biliopancreatic diversion with duodenal switch (n=17). The primary outcome was prognostic risk for CKD as measured by the Kidney Disease Improving Global Outcomes (KDIG) consortium criteria.

Results: Patients were 79% female and 87% white with a median age of 46 years. Using the KDIGO criteria 41% and 22% of the group classified at moderate prognostic risk for CKD before surgery (n=254, 11.9% of total cohort) had improvement in their risk category at 1 year and 7 years, respectively. In patients with high prognostic risk at baseline (n=73, 3.4% of total cohort) 56% and 29% improved their risk category at 1 and 7 years, respectively. In patients with very high prognostic risk at baseline (n=29, 1.4% of total cohort) 35% and 7% improved their risk category at 1 and 7 years, respectively. The proportion of patients whose prognostic risk category for CKD worsened was minimal (<5%) and only 5 patients developed end stage renal disease during the follow-up period. When year 1 was used as baseline in order to minimize the effect of weight loss on serum creatinine (and thereby influencing CKD prognostic risk), the magnitude of the benefits was reduced though results were qualitatively similar.

Conclusions: Treatment with bariatric surgery was associated with a reduction in the prognostic risk for CKD in a large proportion of patients for up to 7 years, especially in those with high risk at baseline. These findings support the consideration and further study of bariatric surgery as a treatment for CKD in obese patients.

Funding: NIDDK Support

SA-PO366

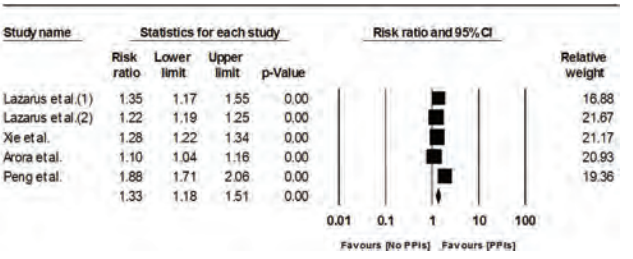
Proton Pump Inhibitors and Risk of CKD: A Meta-analysis Karn Wijarnpreecha,[2] Wisit Cheungpasitporn,[5] Supavit Chesdachai,[4] Panadeekarn Panjawatanan,[3] Charat Thongprayoon.[1] *[1]Bassett Medical Center, Cooperstown, NY; [2]Medicine, Bassett Medical Center, Cooperstown, NY; [3]Chiang Mai University, Chiangmai, Thailand; [4]Mahidol University, Bangkok, Thailand; [5]Mayo Clinic, Rochester, MN.*

Background: Proton pump inhibitors (PPIs) are one of the most commonly prescribed medications worldwide. Recent studies have raised a concern over increased risk of chronic kidney disease (CKD) or end-stage renal disease (ESRD) among PPIs users but the results of those studies were inconsistent. This meta-analysis was conducted to summarize all available data and to estimate this potential association.

Methods: A comprehensive literature review was conducted using MEDLINE and EMBASE database through March 2017 to identify all studies that reported the risk of CKD or ESRD among PPIs users compared with non-PPI users were included. Adjusted point estimates from each study were combined by the generic inverse variance method of DerSimonian and Laird.

Results: Of 8,950 studies, five studies (three cohort studies and two case-control studies) with 536,902 participants met the eligibility criteria and were included in the meta-analysis. We found that individuals with PPIs use had significantly increased the risk of CKD or ESRD when compared with non-PPIs users (pooled RR of 1.33, 95% CI, 1.18-1.51). There was no publication bias of overall included studies assessed by the funnel plots.

Conclusions: This study demonstrated an increased risk of CKD or ESRD among PPIs users. Whether this association is causal requires further investigations.



Forest plot

SA-PO367

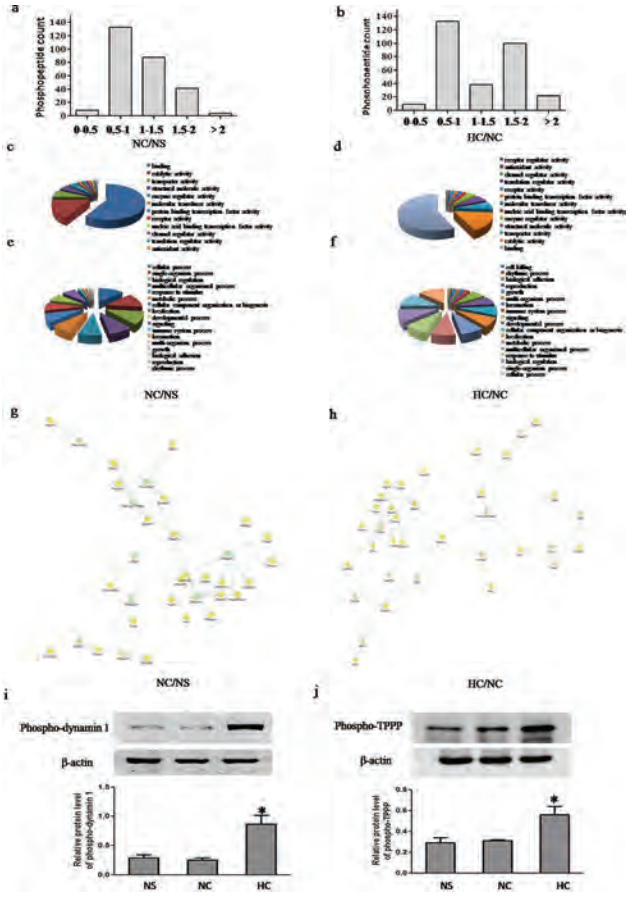
Salt-Induced Phosphoproteomic Changes in the Hypothalamic Paraventricular Nucleus in Rats with Chronic Renal Failure Aiqing Li, Lanying Li, Jiawen Li, Lishan Tan, Minzi Qiu. *Nanfang Hospital, Southern Medical University, Guangzhou, China.*

Background: Hypothalamic paraventricular nucleus (PVN) is a cardiovascular regulating center within the brain,which plays a critical role in high salt-induced progression of chronic renal failure (CRF). However, the phosphoproteomic changes in the PVN caused by CRF remain unclear. This study aimed to perform large-scale phosphoproteomic analysis of PVN induced by CRF and high salt intake.

Methods: Eight weeks post 5/6 nephrectomy (CRF model) or sham operation, Sprague–Dawley rats were fed a high-salt (4%) or normal-salt (0.4%) diet for 3 weeks. TiO_2 enrichment, iTRAQ labeling, and liquid chromatography tandem mass spectrometry were applied for phosphoproteomic profiling of PVN.

Results: A total of 3723 unique phosphopeptides corresponding to 1530 phosphoproteins were identified. Compared with sham group, 133 upregulated and 141 downregulated phosphopeptides were identified in CRF group during normal-salt feeding. However, with a high-salt diet, 160 phosphopeptides were upregulated and 142 downregulated in the CRF group. Gene Ontology analysis revealed that these phosphoproteins were involved in binding, catalytic, transporter, and other molecular functions. Search Tool for the Retrieval of Interacting Genes protein–protein analysis showed direct or indirect functional links among 25 differentially expressed phosphoproteins in CRF rats compared with sham group. However, 24 differentially phosphorylated proteins induced by high salt intake were functionally linked in CRF animals. The altered phosphorylation levels of dynamin 1 and TPPP were validated.

Conclusions: Phosphoproteomic changes of PVN triggered by CRF and high salt-load have been investigated. It will provide new insight into pathogenetic mechanisms of development of chronic kidney disease and salt sensitivity.



SA-PO368

Allopurinol and/or Bicarbonate Therapy Improves the Renal Damage Induced by Recurrent Thermal Dehydration (TD) and Cyclic Episodes of Rhabdomyolysis (CR) in Rats Fernando E. García-arroyo,[1] Guillermo Gonzaga,[1] Monica G. Blas-Marron,[1] Octaviano Silverio,[1] Edilia Tapia,[1] Ilana Weiss,[2] Jason R. Glaser,[4] Richard J. Johnson,[5] L. Gabriela Sanchez-Lozada.[3] *[1]INC Ignacio Chavez, Mexico City, Mexico; [2]La Isla Network, Ada, MI; [3]Nephrology, INCICh, Mexico City, DF, Mexico; [4]La Isla Foundation, INC., Ada, MI; [5]University of Colorado Denver, Aurora, CO.*

Background: Mesoamerican nephropathy (MeN) pathophysiology is poorly understood, but ↓CrCl, mild Uprot and hyperuricemia are observed. The aims of this study were to develop an experimental model and to test therapeutic alternatives.

Methods: TD was induced by exposure to 37°C, 1 h. CR was induced by IM glycerol dosed at day 1, 9, 18, 25 and 32. Hepatic uricase was also inhibited with oxonic acid (OA, 750 mg/K/d). The following groups were included: TD-CR, TD-CR-Allopurinol (AP, 150 mg/L), TD-CR+Bicarbonate (BC, 160 mM), and TD-CR+AP+BC. We also included Normal and OA groups as references. Cr, uric acid, osmolality, creatine kinase (CK), copeptin, NAG, and pH were measured in plasma and/or urine. In renal tissue, markers for oxidative stress, and the expression of the enzymes of polyo-fructokinase pathway were evaluated.

Results: The rodent model for MeN reproduced some of the characteristics of the disease (Table). Also, increased plasma CK, copeptin and NAG in urine, as well as increased oxidative stress and the overexpression of polyol-fructokinase enzymes in renal tissue, were found. BC raised urine pH. AP and BC treatments partially prevented muscle damage, hyperuricemia, overexpression of polyol-fructokinase pathway and renal damage, but only AP significantly prevented the fall in CrCl. Co-treatment with AP+BC did not provide further benefit.

Conclusions: In conclusion, a model for MeN was developed in rats. As AP and BC provided similar benefit and the cotreatment did not have a synergistic effect, those data suggest that both treatments might act by blocking pathophysiological pathways that converge in similar outcomes.

Funding: Private Foundation Support

Group	CrCl (mL/min)	PlasmaUA (mg/dL)	Uprot (mg/d)
Normal	1.2±.11	1.0±.2	11±2
OA	1.1±.25	2.8±.19	17±1
TD-CR	0.6±.09	3.6±.24	50±2
TD-CR+AP	0.9±.1a,b	1.7±.10a	35±1a
TD-CR+BC	0.7±.2	1.8±.22a	33±1a
TD-CR+AP+BC	0.9±.12a,b	1.5±.21a,b	31±1a

a=p<0.05 vs TD-CR; b=p<0.05 vs TD-CR+BC

SA-PO369

Kidney Produces Fibroblast Growth Factor 23 in Rat CKD Model Hidekazu Sugiura,[3] Nobuo Nagano,[1] Kosaku Nitta,[2] Ken Tsuchiya.[2] *[1]Hidaka-kai, Takasaki-shi, Japan; [2]Tokyo Women's Medical University, Shinjuku-ku, Japan; [3]Department of Nephrology, Division of Medicine, Saiseikai Kurihashi Hospital, Saitama, Japan.*

Background: Fibroblast growth factor 23 (FGF23) is a hormone secreted from the bone, and involved in phosphorus metabolism. FGF23 mainly bounds to the fibroblast growth factor receptor, which is accompanied by αKlotho expressed in the kidney or parathyroid, and regulates the expression of phosphate co-transporter, production of 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$), and secretion of parathyroid hormone (PTH). In chronic kidney disease (CKD), blood FGF23 level rises, which is believed to associated with cardiac hypertrophy and mortality.

Methods: In this study, we chose unilateral nephrectomy rat fed with high-phosphorus diet, 5/6 nephrectomy rat and doxorubicin renal failure rat as CKD model animals, and analyzed expression of renal FGF23 in each CKD model animal by real-time PCR and Western blot analysis.

Results: All model rats showed renal dysfunction and increased level of blood phosphorus. In both unilateral nephrectomy rat fed with high-phosphorus diet and 5/6 nephrectomy rat, blood FGF23 and PTH level were increased. However, level of $1,25(OH)_2D_3$ was increased in unilateral nephrectomy rat fed with high-phosphorus diet and decreased in 5/6 nephrectomy rat. In all three model animals, mRNA expression *of αKlotho, Na-dependent phosphate co-transporter type IIa and type IIc* were decreased in kidneys. *FGF23* mRNA was also measured in kidney. While *FGF23* mRNA expression in kidney was barely detectable in control groups, it was detectable in CKD model groups. The difference between two groups was statistically significant. In unilateral nephrectomy rat fed with high-phosphorus diet and 5/6nephrectomy rat, Western blot showed the level of renal FGF23 protein was increased.

Conclusions: This result suggests that FGF23 is expressed in kidney of the CKD model rat. FGF23 produced in kidney is suggested to affect the phosphorus metabolism in the kidney. We demonstrated in this study that FGF23 is produced in the kidney in CKD model rats.

Funding: Government Support - Non-U.S.

SA-PO370

Phosphorus Is an Exacerbation Factor in the Progression of CKD Model by the Accumulation of Small Kidney Injury in Klotho Deficit Mice Ken Tsuchiya,[1] Hidekazu Sugiura,[2] Norio Hanafusa,[1] Kosaku Nitta.[3] *[1]Department of Blood Purification, Tokyo Women's Medical University, Shinjuku-ku, Japan; [2]Department of Nephrology, Saiseikai Kurihashi Hospital, Kuki, Japan; [3]Department of Medicine IV, Tokyo Women's Medical University, Shinjuku-ku, Japan.*

Background: It has been established that klotho protein is a key molecule in the axis of Ca/P metabolism in CKD-MBD, on the other hand, klotho is speculated to be implicated in the mechanism of preceding the CKD, in which klotho suppression is likely to be a result and a cause of CKD. Previously, we reported that repeated minor kidney injury results in more reduction of klotho and cause of CKD in klotho deficit mice. In this study with this model, we investigated several factors which may be involved in making worse or improving the progression of CKD.

Methods: Short time clamping of renal artery for 20 minutes was performed and repeated once a week for 3 weeks in the klotho gene heterozygous mice (*kl(-/+)*). Renal function, the score of tissue damage and altered expression factors were monitored with immunohistochemistry and RT-PCR for mRNA expression. Then, klotho expression was modified by erythropoietin treatment or diet therapy assuming clinical matter. Practically, 200 μ/kg BW of recombinant erythropoietin (ESA) was injected subcutaneously 3 times per week. Since phosphorus is an old and new aggravating factor for CKD which has been drawing attention, stepwise dose of phosphorus was fed in diet in whole experimental period for dietary modification.

Results: Repeated ischemia reduced the renal function and worsen tissue score in *kl (-/+)* mice than in wild type mice. These changes were attenuated by ESA treatment. Klotho mRNA slightly recovered and the expression of fibrotic factors were reduced. Phosphorus is an aggravating factor that stands out than the other factors. Klotho deficit mice treated with repeated minor kidney injury were more sensitive to high phosphorus (2%) loading than control, resulting in more severely reducing the expression of klotho and accelerating renal damage (ATN scores 2.4 folds vs. control).

Conclusions: Repetitions of mild kidney injury possibly initiate or accelerate CKD in reduced klotho expression. Phosphorus loading damaged the kidney much more in these *kl(-/+)* mice, which may suggest that phosphorus restriction (reflecting low protein diet) is likely to be meaningful for the attenuation of the progression of CKD, indicating the importance of re-estimating of the significance of low protein diet (namely, low phosphorus) in clinical practice.

Funding: Government Support - Non-U.S.

SA-PO371

Vitamin D Deficiency Impairs the Renal Expression of M2 Macrophages in Rats Submitted to 5/6 Nephrectomy Rildo A. Volpini, Daniele Canale, Janaina G. Gonçalves, Maria H. Shimizu, Antonio C. Seguro, Ana Carolina de Braganca. *Faculty of Medicine - University of Sao Paulo, São Paulo, Brazil.*

Background: 5/6 nephrectomy (Nx) is a classical experimental model of chronic kidney disease (CKD). Many studies have shown a pivotal role of macrophages (MØ) in the progression of CKD. Broadly, two main groups of MØ are designated: M1 (proinflammatory MØ) and M2 (tissue repair MØ). Moreover, recent investigations have been linking Vitamin D Deficiency (VDD) to inflammatory process and predisposition to fibrosis formation.

Methods: For 90 days, male Wistar rats were fed a standard [Sham and Nx groups] or a vitamin D-free (VDD and VDD+Nx) diets. On day 30, Nx and VDD+Nx rats were submitted to Nx surgery. On day 90, we measured serum levels of 25(OH)D and PTH by ELISA, inulin clearance (Cin), mean arterial pressure (MAP), immunoblotted for TGF-β and performed IHC for MØ type 1 (ED1) and 2 (Mannose Receptor). Also, we estimated the interstitium enlargement by fraction interstitial area (FIA).

Results: As described in Table 1, VDD were associated with MAP elevation and decreased Cin in VDD+Nx group. Moreover, we observed higher expression of M1 macrophages and TGF-β as well as larger FIA in the renal cortex of those animals. Interestingly, we found a lower expression of M2 macrophages in VDD+Nx rats, indicating an important role of Vitamin D in the tissue repair and maintenance of inflammatory process.

Conclusions: Our study suggests that VDD is involved in tissue repair and fibrosis formation after Nx, reinforcing the role of VDD as an aggravating factor for CKD progression. (Financial Support: FAPESP 2015/05513-1)

Funding: Government Support - Non-U.S.

Table 1

Parameters	Sham	VDD	Nx	VDD+Nx
Cin (mL/min/100g BW)	0.65±0.01	0.58±0.03	0.48±0.03 af	0.39±0.03 adi
MAP (mmHg)	115.0±5.71	135.9±4.20 c	147.6±6.04 b	167.1±5.2 aei
25(OH)D (ng/mL)	49.49±2.87	<0.44 (undectable) a	42.26±3.97 d	<0.44 (undectable) ag
PTH (pg/mL)	311.2±44.20	899.8±167.6	1,023±334.3	901.7±184.3
M1 (% positive area)	0.20±0.02	0.25±0.04	0.52±0.08 cf	0.87±0.09 adh
M2 (% positive area)	0.18±0.02	0.12±0.01	0.29±0.07 f	0.11±0.02 i
TGF-β (%)	100.1±8.96	89.5±9.82	142.5±34.53	208.5±41.51 cf
FIA (%)	7.55±0.26	14.48±0.20 a	19.42±1.25 ad	23.74±1.26 adh

Data are expressed as mean±SEM. BW: Body weight. a p<0.001 vs Sham; b p<0.01 vs Sham; c p<0.05 vs Sham; d p<0.001 vs VDD; e p<0.01 vs VDD; f p<0.05 vs VDD; g p<0.001 vs Nx; h p<0.01 vs Nx; i p<0.05 vs Nx.

SA-PO372

Tubular Matrix Gla Protein Expression Increases Progressively with CKD Kana N. Miyata,[1] Pei Zhang,[1,2] Tiane Dai,[1] Cynthia C. Nast,[3] Ramanath B. Dukkipati,[1] Janine A. La page,[1] Jonathan P. Troost,[4] Leon J. Schurgers,[5] Sharon G. Adler.[1] *[1]LA Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA; [2]The First Affiliated Hospital of Anhui Medical University, He Fei, China; [3]Cedars-Sinai Medical Center, Los Angeles, CA; [4]University of Michigan, Ann Arbor, MI; [5]Maastricht University, Maastricht, Netherlands.*

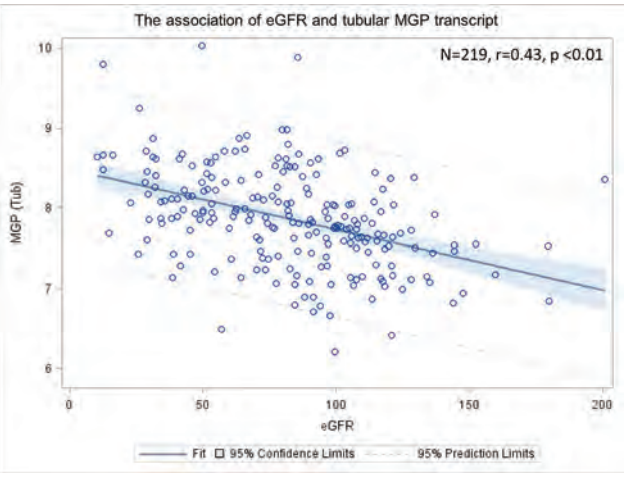
Background: Experimental data indicate that renal tubule dedifferentiation may contribute to CKD progression. A vitamin K–dependent protein, Matrix Gla Protein (MGP), is a potent in vivo inhibitor of arterial calcification. Little is known about de novo MGP expression and function in kidney.

Methods: We performed 5/6 nephrectomy (Nx) in rats, sacrificed them at 2 days, 2 weeks, and 4 weeks, and measured gene expression by microarray. Altered expression was noted for many proteins involved in vascular calcification. We focused on MGP and localized carboxylated MGP (cMGP) in kidneys from patients with CKD. Then, we analyzed the association between eGFR at biopsy and the MGP transcript levels of patients in the Nephrotic Syndrome Study Network (NEPTUNE) cohort.

Results: Renal MGP expression was significantly increased in 5/6Nx rats: 2.16-fold (2 days, p=0.002), 3.27-fold (2 weeks, p=0.0002), and 3.31-fold (4 weeks, p=0.0002). There was a trend for patients with advanced CKD (n=8) to have greater tubulointerstitial (TI) cMGP staining vs controls (NS). In NEPTUNE samples, there was an inverse relationship between eGFR and the TI MGP transcript. The TI MGP transcript correlated positively with interstitial fibrosis (r=0.47, p<0.01) and tubular atrophy (r=0.45, p<0.01), even after adjustment for eGFR, and was significantly higher in kidneys with acute tubular injury(p<0.01).

Conclusions: Our experiments demonstrate increased TI MGP expression in CKD in experimental animals and patients. TI MGP transcript levels increased progressively with CKD progression and was associated with interstitial fibrosis, tubular atrophy, and acute tubular injury. In published microarrays, TI MGP expression is also increased in patients with diabetic kidney disease and in ageing rats. Additional studies are needed to determine if the de novo expression of MGP represents tubular dedifferentiation or an adaptation to injury.

Funding: Other NIH Support - The Nephrotic Syndrome Study Network Consortium (NEPTUNE), U54-DK-083912, is a part of the National Institutes of Health (NIH) Rare Disease Clinical Research Network (RDCRN), supported through a collaboration between the Office of Rare Diseases Research (ORDR), NCATS, and the National Institute of Diabetes, Digestive, and Kidney Diseases. Additional funding and/or programmatic support for this project has also been provided by the University of Michigan, the NephCure Kidney International and the Halpin Foundation.



SA-PO373

Heat-Induced Renal Damage (HRD) Is Dose-Dependently Worsened by Fructose (F) Concentration in Rehydration Fluid L. Gabriela Sanchez-Lozada,[2] Fernando E. García-arroyo,[2] Guillermo Gonzaga,[2] Monica G. Blas-Marron,[2] Octaviano Silverio,[2] Itzel Muñoz,[1] Edilia Tapia,[2] Richard J. Johnson.[3] *[1]Government, México City, Mexico; [2]INC Ignacio Chavez, Mexico City, Mexico; [3]University of Colorado Denver, Aurora, CO.*

Background: Recurrent episodes of heat exposure result in HRD that is aggravated when F containing beverages are provided as rehydration fluid. The purpose of this study was to explore the effect of different concentrations of F in the rehydration fluid and correlate them with parameters of kidney damage.

Methods: Male Wistar rats were exposed to heat from Monday to Friday at 37°C, 1 h. Rats were allowed to rehydrate only at night with fluids containing the following F concentrations: 0, 2.5, 5, 7.5 and 10%. A group of the normal non-dehydrated rats was included as a reference. At 4 weeks, blood samples and urine were collected. Cr, uric acid (UA), osmolality (plasma and urine), vasopressin (plasma copeptin), and NAG were measured. Proximal and distal nephron segments were isolated, and the expression of aquaporin-2 (Aqp2) and cAMP concentrations were evaluated.

Results: Aqp2 expression and cAMP concentrations in distal segments were increased by repeated heat exposure and further by F rehydration, but there were no differences among the increasing F concentrations.

Conclusions: F rehydration aggravated the HRD in a dose-dependent fashion. F further increased UOsm and Aqp2 expression, despite there was not an additive effect caused by the increased F concentrations. These data suggest that the higher concentrations of vasopressin and hyperuricemia may contribute to exacerbating renal alterations in HDR. The fact that UOsm, Aqp2 expression and [cAMP] reached a threshold after the lower F concentration suggests that F might damage distal portions of the nephron affecting the urinary concentration capacity.

Funding: Other U.S. Government Support

Results

[F]/Group	CrC (mg/min)	PUA (mg/dL)	PCopeptin (ng/mL)	UNAG (uM PNP/min/d)	UOsm (mOsm/Kg)
Control	1.2±.08	1.0±.02	.01±.001	0	1358±225
0%	1.1±.13	1.4±.2	3±.004	0.5±.02	1176±328
2.5%	1.0±.10	1.7±.12	10±.83	0.6±.04	1856±345
5%	0.9±.07	1.7±.10	22±1.1	1.1±.13	1848±367
7.5%	0.76±.03	2.5±.22	32±1.8	1.4±.09	1825±209
10%	0.72±.02	3.4±.14	49±1.6	1.9±.02	1610±150
Linear trend	r2=0.72 P<0001	r2=0.86 P<0001	r2=0.97 P<0001	r2=0.97 P<0001	r2=0.17 P<0002

SA-PO374

A Recessive K572Q Mutation in Gamma-Adducin Plays a Causal Role in Impaired Renal Vascular Reactivity in FHH and MNS Rats Chao Zhang,[1,2] Ying Ge,[1] Tongyu Zhu,[2] Paige N. Mims,[1] Fan Fan,[1] Richard J. Roman.[1] *[1]University of Mississippi Medical Center, Jackson, MS; [2]Zhongshan Hospital, Fudan University, Shanghai, China.*

Background: The Fawn-Hooded hypertensive (FHH) rat is a genetic model for studying hypertension induced renal disease, however the causal genes involved are

unclear. We previously reported that the transfer of a small region in Chr. 1 of Brown-Norway (BN) rats which contains 15 genes, including gamma-Adducin (Add3), into the FHH background could restore the impaired renal microvascular function in FHH rats. Our further work identified a K572Q mutation in Add3 in FHH rats as a potential candidate variant in the pathogenesis of renal disease.

Methods: The present study examined the role of the K572Q mutation of Add3 in the autoregulation of renal blood flow (RBF) and the myogenic response of renal afferent arteriole (af-art) by using Add3 transgenic and knockout (KO) rats.

Results: RBF increased by 21.5 ± 3.0% in SD. Add3 KO rats (n=7) when mean arterial pressure (MAP) was increased from 100 to 150 mmHg. In contrast, RBF only increased by 3.5 ± 0.9% in wildtype (wt) SD rats (n=13). The diameter of the renal af-art decreased by 13 ± 0.8% in SD rats when perfusion pressure was increased from 60 to 120 mmHg, but it increased in by 5.0 ± 0.6% in the SD.Add3 KO rats. The myogenic response of af-arts in FHH rats was markedly impaired and increased by 8 ± 1.2% when the pressure was increased by from 60 to 120 mmHg. The myogenic response was restored, and the diameter of Af-art decreased by 12 ± 0.7% and 7 ± 1.0% in FHH. 1^{BN} congenic rats (n=27) and Add3 transgenic FHH rats that express wt-Add3. RBF increased by 35.1 ± 3.0% when MAP was increased from 100 to 150 mmHg in FHH rats (n=15) versus only 7.5 ± 1.7% and 6.0+ 1.3% in FHH.1^{BN} or a F1 cross of FHH and FHH.1^{BN} rats (n=8) and in Add3 transgenic FHH rats that express the wt-Add3 gene. The myogenic response of Af-art and autoregulation of RBF were also impaired in MNS rats (n=6) that carry the same K572Q mutation in Add3 as FHH rats. These phenotypes were complemented in an F1 of cross of FHH and MNS rats (n=7), but the myogenic response and autoregulation of RBF were restored in an F1 cross of FHH and FHH.1^{BN} rats with one copy of wt-Add3.

Conclusions: There results suggest that the recessive K572Q mutation of Add3 in FHH and MNS rats plays a causal role in renal microvascular dysfunction that may contribute to the development of proteinuria and chronic kidney disease in these models.

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SA-PO375

MDM2 Subcellular Trafficking Is Involved in the AKD to CKD Progression Induced by Repeated Cisplatin Exposure Hua Su. *Huazhong Science and Technology University, Wuhan, China.*

Background: Repeated cisplatin (CP) administration frequently leads to the development from acute kidney disease (AKD) to chronic kidney disease (CKD). During above pathogenic process the tubular epithelial cell (TEC) damage is the cardinal event. MDM2 is an E3 ligase and participates in multiple pathophysiologic responses. Previously our studies revealed that MDM2 not only involves in AKD but also accounts for CKD by promoting fibroblast activation. However, the role of MDM2 in repeated CP exposure induced AKD to CKD transition is unclear.

Methods: AKD to CKD mice model was established by intraperitoneal injection of CP (8mg/Kg) once a week. The mice were grouped into 1CP, 2CP, 3CP and 4CP according to the times of CP administration. 7 days after the final injection the mice were sacrificed and kidney cortex was collected. Immunostaining and sucrose gradient ultracentrifugation were utilized to label or isolate subcellular organelles. Immunoprecipitation was employed to examine the interaction between MDM2 with p53 or NHERF1, as well as the ubiquitination of p53 and NHERF1.

Results: We successfully established the CP-induced AKD to CKD mice model which was proved by the increased NAGL and KIM-1 expression in 2 CP group with later upregulated α-SMA, Collagen 3 and serum creatinine in 3CP and 4CP groups. Our data shown in physiological state MDM2 predominantly distributes in nuclei and binds with p53, however after first time of CP administration MDM2 moves from nuclei to cytoplasm along with decreased interaction of p53 and upregulated p53 expression. Furthermore, after 3 and 4 times of CP injection, we found cytoplasmic MDM2 further transports to cell membrane and interacts with NHERF1, a negative regulator of PDGF-BB/PDGFR-β axis, and which leads to the enhanced ubiquitination of NHERF1. Consequently, the abundance of NHERF1 minimized with the activation of PDGF-BB/PDGFR-β signaling, a well-known cytokine pathway involved in CKD development via autocrine as well as paracrine manner.

Conclusions: Repeated CP administration initiates the MDM2 trafficking form nuclei to cytoplasm, and eventually move to the cell membrane where MDM2 binds with and ubiquitinates NHERF1. Consequently, NHERF1 is degraded and PDGF-BB/PDGFR-β signaling is activated.

Funding: Government Support - Non-U.S.

SA-PO376

Adaptive and Pathologic Mechanisms in Diabetic Kidney Disease: A Modeling Analysis Hari shankar Mahato,[3] Christine Ahlström,[2] Rasmus Jansson-Lofmark,[2] Gabriel Helmlinger,[1] Melissa Hallow.[3] *[1]AstraZeneca Pharmaceuticals, Waltham, MA; [2]AstraZeneca R&D, Mölndal, Sweden; [3]University of Georgia, Athens, GA.*

Background: Translation from preclinical animal models to human diabetic kidney disease is challenging due to species differences in disease processes and timecourses. Quantitative systems models are helpful in understanding disease mechanisms and interspecies differences. We aimed to adapt a physiological model of human renal function to mice, to incorporate adaptive and pathologic mechanisms of diabetes and nephrectomy observed in the db/db uninephrectomized (UNX) mouse model, and to explore the response to clinically renoprotective drugs.

Methods: Some renal structural/functional characteristics are preserved across species (e.g. pressures, single nephron flow rates), while others differ markedly (e.g. nephron number, tubular lengths). We reparameterized a systems model of human renal hemodynamics to represent mice, and ensured appropriate phenotypic behavior (e.g. glomerular filtration rate [GFR], blood pressure). To model the adaptive and pathologic renal effects in kidney disease, we assumed that elevated glomerular capillary pressure causes 1) glomerular capillary hypertrophy, up to a limit, 2) podocyte damage and increased protein filtration, and 3) glomerulosclerosis. The renal consequences of 1) UNX, 2) increased blood glucose (and associated increased proximal reabsorption via SGLT) and sodium intake in db/db mice, and 3) the combination, was then simulated using experimental data to inform the model.

Results: The model implicitly reproduced the GFR rise (hyperfiltration) observed in db/db mice when glucose and Na+ intake increased, as well as the compensatory increase in single nephron GFR to keep total GFR stableafter UNX. In both cases, glomerular hypertrophy normalized glomerular pressure, so that proteinuria was minimal, as observed experimentally. However, combining UNX with diabetes increased glomerular pressure beyond the adaptive capacity and caused overt progressive proteinuria. The model also reproduced the proteinuria reduction observed in with enalapril, eplerenone and dapagliflozin.

Conclusions: The systems model provides insight into adaptive and pathologic renal processes in db/db UNX mice. By simulating responses to therapies for which preclinical and clinical data is available, it may aid benchmarking for clinical translation.

Funding: Commercial Support - AstraZeneca

SA-PO377

Experimental Heat Stress Nephropathy Is Improved by Allopurinol Carlos A. Roncal-jimenez,[4] Tamara Milagres,[4] Miguel A. Lanaspa,[4] Ana Andres-hernando,[4] Masanari Kuwabara,[4] Yuka Sato,[4] Thomas Jensen,[4] Gabriela E. Garcia,[4] L. Gabriela Sanchez-Lozada,[3] Ramon Garcia-Trabanino,[1] Emmanuel Jarquin,[1] Jason R. Glaser,[2] Richard J. Johnson.[4] *[1]Hospital Nacional Rosales, San Salvador, El Salvador; [2]La Isla Foundation, INC., Ada, MI; [3]NoneInst. Nal Cardiol. Ignacio Chavez, Mexico City, DF, Mexico; [4]University of Colorado Denver, Aurora, CO.*

Background: Mesoamerican nephropathy (MN) is a disease of unknown cause observed primarily in sugarcane workers with recurrent dehydration that affect to the kidney chronically (CKD). Some evidence suggests hyperuricemia may be involved; to test that hypothesis we evaluated the role of uric acid (UA) in an animal model of heat stress and dehydration.

Methods: Mice exposed to heat 39.5 °C x 30 min, 8x daily for 5 weeks, with water provided at night with allopurinol 32mg/Kg/d in drinking water, Group 4 (**Heat +AP**) or without allopurinol Group 3 (**Heat**), as well as **contro**l groups that were normal mice receiving water or water with allopurinol Groups 1 (**Control**) and 2 (**AP**), respectively n=7 per group

Results:

Conclusions: Allopurinol lowered serum uric acid in animals with heat stress and this was associated with less fibrosis, less proximal tubular injury (preserved ACE staining) and improved renal function. Interestingly, lowering serum uric acid was also associated with an increase in serum vasopressin and lower serum osmolarity in Heat animals; and with higher copeptin, lower urine osmolarity in normal mice. *p value** shows the value by Bonferroni's post hoc analysis between Heat and Heat+AP.

Funding: Other U.S. Government Support

	Control	AP	Heat*	Heat +AP*	ANOVA p value	p value*
Serum Osmo (mOsm)	324	324	344	336	<0.0001	0.015
Urine Osmo (mOsm)	2228	1554	3006	2893	<0.0001	NS
Serum UA (mg/dl)	4.4	3.5	4.6	3.6	<0.0001	0.0003
Serum Copeptin (pg/ml)	56	85	126	141	<0.0001	NS
Serum Cortisol (pg/ml)	231	399	417	428	0.0223	NS
Serum Cr (ug/ml)	0.86	0.80	0.97	0.77	0.0268	0.041
Fructose Ctx (mM/µg prot)	9.2	11.1	16.5	11.8	0.0100	0.078
Sorbitol Ctx (µmol/mg prot)	4.26	3.66	4.48	3.83	NS	NS
Urine NGAL (ng/ml)	34.0	28.7	60.1	60.8	<0.0001	NS
Coll-II (% positive area)	0.91	1.63	3.25	1.79	<0.0001	0.016
HSP-70 (% positive area)	20.4	24.9	32.3	26.0	<0.0001	0.019
AQP-2 phos (% positive area)	0.10	0.10	0.29	0.26	0.0028	NS
ACE (% positive area)	5.4	5.0	3.3	5.7	<0.0001	<0.0001

SA-PO378

Domain-Specific Antibodies Reveal the Membrane Topology of ApoL1 Nidhi Gupta,[1] Xinhua Wang,[1] Ann De Maziere,[2] George Posthuma,[2] Paul Moran,[1] Michael T. Lipari,[1] Daniel Kirchhofer,[1] Judith Klumperman,[2] Randall J. Brezski,[1] Andrew S. Peterson,[1] Suzie J. Scales.[1] *[1]Genentech, Inc., South San Francisco, CA; [2]UMC Utrecht, Utrecht, Netherlands.*

Background: ApoL1 (Apolipoprotein L1) is a component of the trypanolytic factor that circulates on HDL3b particles and protects against *Trypanosoma brucei brucei* infection. Two common African variants in ApoL1 (G1 and G2) additionally protect against *Trypanosoma brucei rhodesiense*, but also confer a greater risk of chronic kidney disease in homozygotes. ApoL1 contains three domains named for their roles in trypanolysis – a pore forming domain that forms ion channels leading to lysis; a membrane addressing domain responsible for HDL binding and lysosomal membrane insertion; and an SRA-interacting domain that binds to the serum resistance factor of *T.b. rhodesiense*. However, little is known about ApoL1 topology i.e. which domains are exposed on HDL particles and kidney podocytes, the susceptible cell type in chronic kidney disease.

Methods: We generated >100 monoclonal antibodies to ApoL1 to better understand its topology, localization and roles in kidney disease and trypanolysis. We probed ApoL1 membrane topology in cell lines using immunofluorescence on differentially permeabilized cells, electron microscopy and flow cytometry. ApoL1 domain accessibility in human serum was mapped by the ability of the antibodies to block trypanolysis.

Results: We obtained specific (non ApoL2 cross-reactive) antibodies to all three domains of ApoL1. ApoL1 localized to the endoplasmic reticulum in overexpressing kidney cells, with all three domains sequestered within the lumen, topologically equivalent to the cell surface. By contrast, ApoL2 (which lacks a signal sequence) localized to the cytoplasmic face of the endoplasmic reticulum. We found portions of all three domains of ApoL1 are exposed in serum, as judged by pull-down and inhibition of trypanolysis assays. However, on the podocyte cell surface, the membrane addressing domain of ApoL1 is not exposed.

Conclusions: ApoL1 topology differs between serum and kidney cells.

Funding: Commercial Support - Genentech

SA-PO379

Modulation of Podocyte (PD) Homeostasis by Mesenchymal Stromal Bone Marrow Cells (MS-BMC) in the Adriamycin Two and Single Kidney Injury Models Rukhsana Aslam,[1] Ali Hussain,[2] Seyedeh Shadafarin Marashi Shoshtari,[5] Abheepsa Mishra,[3] Vinod Kumar,[6] Ashwani Malhotra,[7] Pravin C. Singhal.[4] *[1]Feinstein Institute for medical research, Glenoaks, NY; [2]Feinstein Institute of Medical Research, New York, NY; [3]Feinstein Institute of Medical Research, Northwell Health, MANHASSET, NY; [4]North Shore LIJ Health System, Great Neck, NY; [5]The Feinstein Institute for Medical Research, Manhasset, NY; [6]Immunolgy and Inflammation, Fienstine Institute for Medical Research, New York, NY; [7]Immunolgy and Inflammation, Feinstein Inst.Med research and NSLIJ, Manhasset, NY.*

Background: Adriamycin has been demonstrated to induce focal segmental glomerulosclerosis (FSGS). Mesenchymal stromal bone marrow cells (MS-BMCs) have been demonstrated to provide cytoprotection by the modulation of cytokine production in several nephrotoxic models. Recently, parietal epithelial cells (PECS) have been considered as progenitor cells to manage podocyte homeostasis; however, PECs may also act as profibrotic cells in adverse milieus. In the present study, we evaluated the effect of MS-BMCs on modulation of the role of parietal epithelial cells in mananging the podocyte homeostasis in adriamycin-induced podocyte injury in two and single kidney injury models.

Methods: MS-BMCs were harvested from bone marrows of mice and their profile was characterized. Mice in groups of six were administered either buffer (group A), intracapsular instillation of MS-BMCs in left kidney (group B), or intraperitoneal MS-BMCs administration (Group C) 24 hours prior to Adriamycin (150 mg/Kg, subcutaneously) administration. Additional six mice administered normal saline were used as controls. All mice were euthanized after 4 weeks; urine and blood samples were collected for BUN and albumin: creatinine ratio. Kidneys were harvested for histology, immuno-staining for p57 and co-labeling for CD44 and phospho-ERK. Immunoblots were prepared and probed for podocin and WT1 and reprobed for actin.

Results: Group B and C mice displayed a decrease ($P<0.05$) in albumin: creatinine ratio vs. Group A mice. Immunoblotting studies revealed decreased ($P<0.01$) podocin, WT1, and p57 expressions in renal tissues of group C when compared to renal tissues of group A. On the other hand, renal tissues of the left kidneys from Group B displayed increased ($P<0.01$) protein expression of podocin, WT1, and p57 when compared to contralateral kidneys. Kidneys from the group C and right kidneys from the group B displayed increased ($P<0.05$) number of profibrotic cells (colabeled for phos-ERK and CD44) but a decreased ($P<0.05$) number of p57 +ve cells.

Conclusions: These findings indicate that MS-BMCs provide protection from injurious effect of adriamycin by decreasing the number of pro-fibrotic PECs and increasin the number of progentor cells.

Funding: NIDDK Support

SA-PO380

The Impact of Canagliflozin on the Gut Microbiota of Non-Diabetic CKD Rats and Its Effect on Cardiovascular System Ayumi Matsui,[4] Ayumi Yoshifuji,[1] Junichiro Irie,[3] Takaya Tajima,[4] Kiyotaka Uchiyama,[5] Tomoaki Ito,[2] Shu Wakino,[2] Hiroshi Itoh.[3] *[1]KEIO UNIVERSITY, Tokyo, Japan; [2]Keio University, Tokyo-to, Japan; [3]Keio University School of Medicine, Tokyo, Japan; [4]Keio University school of medicine, Tokyo, Japan; [5]Keio University, School of Medicine, Tokyo, Japan.*

Background: The gut is responsible for the production of some uremic toxins by microbiota which induces the tissue damages in chronic kidney disease (CKD). Gut microbiota population was reported to be aberrated in CKD. Novel anti-diabetic reagent sodium glucose cotransporter (SGLT)2 inhibitor, canagliflozin(Cana) harbors a marginal inhibitory potential to gut-type SGLT1, which is hypothesized to affect the dysbiosis in CKD. We investigated the impact of Cana on the microbiota and on cardiovascular and renal tissues in non-diabetic CKD rats.

Methods: 6-week-old male spontaneously-hypertensive rats (SHRs) were randomly assigned to three experimental groups; sham operated SHR (Sham), 5/6 nephrectomized SHR (Nx), and 5/6 nephrectomized SHR treated with Cana (0.024% mixed in standard chow) (Nx+C). After 12weeks, microbiota population was examined by T-RFLP and following PCR. The tissue findings and molecular changes of kidney, cardiovascular systems and intestine were also investigated.

Results: Proteinuria, serum creatinine and BUN levels were significantly elevated in Nx group, although Cana failed to improve the impaired renal function. Serum concentrations of gut-derived uremic toxins such as indoxyl sulfate and hippuric acid were significantly elevated in Nx rats, which were lowered by Cana. The population of gut microbiota was changed in Nx rats, which were restored by Cana. Quantitative analysis of *Lactobacillus* species confirmed a significant decrease of *Lactobacillus* by Nx, which was also reversed by Cana. Immunoblotting analysis of the tight junction proteins of colonic tissue confirmed that Cana restored claudin-1, occludin, and Zo1 expression which were downregulated in Nx rats. Nx rats showed significantly increased wall thickness of the thoracic aorta and cardiac intestinal fibrosis. CTGF and TGFβ1 mRNA expression in cardiac tissues were significantly increased by Nx. These changes were ameliorated by Cana.

Conclusions: Cana successfully reduced serum indoxyl sulfate and hippuric acid levels by restoring dysbiosis in non-diabetic CKD rats, which might have favorable effects on cardiovascular systems in CKD condition.

SA-PO381

DESI-MSI Based Spatial Metabolomics Reveals Altered Metabolome and Increased Pseudouridine in Renal Proximal Tubules of Mice with Diabetic Kidney Disease Guanshi Zhang,[1] Jialing Zhang,[2] Rachel J. Dehoog,[2] Manjula Darshi,[1,3] Benjamin F. Van espen,[1,3] Subramaniam Pennathur,[4] Vighnesh Walavalkar,[5] Theodore Alexandrov,[6,7] Livia S. Eberlin,[2] Kumar Sharma.[1,3] *[1]Center for Renal Translational Medicine, Division of Nephrology-Hypertension, Institute of Metabolomic Medicine, University of California San Diego, La Jolla, CA; [2]Department of Chemistry, The University of Texas at Austin, Austin, TX; [3]Division of Nephrology-Hypertension, Veterans Affairs San Diego Healthcare System, La Jolla, CA; [4]Division of Nephrology Department of Internal Medicine, University of Michigan, Ann Arbor, MI; [5]Department of Pathology, University of California San Diego, La Jolla, CA; [6]Structural and Computational Biology Unit, European Molecular Biology Laboratory, Heidelberg, Germany; [7]Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California San Diego, La Jolla, CA.*

Background: Diabetic kidney disease (DKD) is the most prevalent complication in diabetic patients, which contributes to high morbidity and mortality. Urine and plasma metabolomics studies have reported that both blood and urinary metabolites to provide valuable insights for DKD. Spatial distributions of metabolites in kidney tissues would link circulating metabolites to actual kidney compartments but the techniques are challenging. We employed an ambient desorption electrospray ionization – mass spectrometry imaging (DESI-MSI) approach to characterize the metabolome in a mouse model of DKD coupled to a novel bioinformatics platform (METASPACE).

Methods: DESI-MSI was performed for spatial untargeted metabolomics analysis in kidneys of mouse models (F1 C57BL/6J-*Ins2*^{Akita} male mice at 17 weeks of age) of type 1 diabetes (T1D, n = 5) and heathy controls (n = 6). Metabolite annotations from MSI were conducted using METASPACE and further validated by collision induced dissociation or higher-energy collisional dissociation tandem MS analysis. MetaboAnalyst 3.0 was employed for statistical analyses.

Results: Multivariate analyses (i.e., PCA and PLS-DA (a 2000 permutation test: $P < 0.001$)) showed clearly separated clusters for the two groups of mice on the basis of 878 measured *m/z*'s in kidney cortical tissues. Specifically, mice with T1D had increased relative abundances of pseudouridine (*m/z* 279.039), fatty acids (FA) (e.g., FA (18:2), *m/z* 279.233), and glycerophosphoglycerols (PG) (e.g., PG (36:1), *m/z* 775.548) in cortical proximal tubules when compared with healthy controls.

Conclusions: Results from the current study further support a role for pseudouridine in DKD and the data suggests that pseudouridine accumulation might originate from cortical proximal tubules. Lipid data indicate disordered fatty acid metabolism (e.g., enhanced FA synthesis and altered FA oxidation) and glycerophospholipid metabolism in DKD mice. DESI-MSI technology is a powerful approach to shed new light on fundamental pathways in disease states.

Funding: NIDDK Support

SA-PO382

Investigating Endoplasmic Reticulum Stress in the Development of Lupus Nephritis Mathilde L. Bonnemaison, Erika I. Boesen. *University of Nebraska Medical Center, Omaha, NE.*

Background: Lupus nephritis is a common complication of the autoimmune disease systemic lupus erythematosus (SLE) and is associated with glomerular and tubular injury. Although albumin uptake has been shown to induce endoplasmic reticulum (ER) stress in proximal tubule cells *in vitro*, it is unknown whether ER stress occurs in and contributes to the development of renal injury in SLE.

Methods:

Results: To investigate this, the current study used a well-established model of lupus nephritis, the NZBWF1 mouse (female only). Mice were randomized to receive either vehicle (normal drinking water) or the ER stress blocker 4-phenylbutyric acid (4-PBA, 20 mM) in drinking water starting from 12 weeks of age until 34 weeks of age or the onset of albuminuria, whichever came first. In a pilot study, this treatment protocol significantly reduced mRNA expression of the ER stress marker CHOP in both 20 and 34 week old NZBWF1 mice ($P_{treatment}=0.02$). Mice were sacrificed at the onset of albuminuria (≥100mg/dL by dipstick) or at 34 weeks of age, whichever came first. The relative risk of the 4-PBA mice progressing to albuminuria before 34 weeks of age was 0.83 (95% confidence interval of 0.56-1.3, P=0.2 by Chi-square test). Blood urea

nitrogen was significantly elevated in mice that developed albuminuria before 34 weeks of age (P<0.0001), but was not different between vehicle and 4-PBA groups. Plasma creatinine levels were unchanged over time in both groups. CHOP mRNA expression in the renal cortex was compared between untreated 20 week old mice (prior to SLE development) and vehicle-treated albuminuric and non-albuminuric 34 week old mice. Surprisingly, mRNA levels of the ER stress marker CHOP were significantly reduced in the renal cortex of albuminuric mice compared to the 20 week old mice (P<0.05), which had similar CHOP expression to 34 week old non-albuminuric mice. A similar trend was observed for GRP94, but this did not reach statistical significance.

Conclusions: Together, these findings do not support a major role for ER stress in the early stages of the development of renal injury in SLE, as defined by onset of albuminuria. Whether ER stress contributes to the further progression of renal injury in lupus nephritis once albuminuria has developed remains to be investigated.

Funding: Private Foundation Support

SA-PO383

Effect of Pioglitazone on the Shedding of Urinary Angiotensin Converting Enzyme (ACE) 2 and Neprilysin (NEP) in db/db Mice and Their Role as Urinary Biomarkers for Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is one of the major causes of end-stage renal disease. Angiotensin (Ang) II is the major biological active peptide of the renin angiotensin system. Elevated levels of Ang II contribute to initiation and progression of DKD. The actions of Ang II could be antagonized by its conversion to the vasodilator Ang (1-7), partly generated by the action of ACE2 and NEP. Although there is an emergence of some urinary biomarkers such as angiotensinogen, kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL), there is still a need for new early biomarkers for DKD. The aim is to investigate the effect of hyperglycemia on urinary albuminuria, ACE2, NEP and KIM-1 and to test the hypothesis that ACE2 and NEP can be used as early biomarkers for DKD.

Methods: 8 weeks old control and *db/db* diabetic mice were subjected to pioglitazone treatment (20 mg/kg/day) for 10 weeks. Metabolic and renal parameters were measured. Urine was collected for the evaluation of ACE2, NEP, KIM-1 protein expression and RAS activity.

Results: At 7 weeks old, there was no significant difference in urinary albumin, NEP and KIM-1 between *db*/*db* and control mice. However, western blot showed a significant increased shedding of urinary ACE2 fragment (60KDa and 70kDa immunoreactive bands) in *db*/*db* mice compared to controls. Although there was a prominent immunoreactive band for NEP in control mice at 9 weeks, there was no detectable immunoreactive band for ACE2. After the development of albuminuria in older *db*/*db* mice (9-17week), there was a significant increase of full length (95KDa) and fragment of ACE2, NEP (90kDa) and KIM-1 (75KDa) compared to control mice. Urinary NEP and ACE2 activities significantly increased in 17 weeks *db*/*db* mice compared to controls. Pioglitazone normalized hyperglycemia and attenuated urinary albumin, glucose and ACE2 shedding. However, it has no effect on urinary NEP and KIM-1.

Conclusions: In *db*/*db* diabetic mice, increased shedding of enzymatically active ACE2 precedes albuminuria. Depletion of tubular renal ACE2, NEP, could lead to accumulation of Ang II, with concomitant development of microalbuminuria. Urinary ACE2 and NEP could be used as biomarkers for DKD.

SA-PO384

Angiotensin II Induces Cholesterol Accumulation and Injury in Podocytes

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Background: Angiotensin Ⅱ (AngⅡ) is a risk factor for the initiation and progression of chronic kidney disease (CKD), elevated AngⅡ levels can lead to podocyte injury. Cholesterol is major component of lipid droplet (LD), cholesterol homeostasis exerts an important role in podocyte physiology. However, there are no studies on the role of AngⅡ in cholesterol metabolism or on the podocyte injury caused by cholesterol metabolism disorder.

Methods: In *vivo*, Oil red O and Nile red staining were evaluated LD deposition in glomeruli of AngⅡ-infused rats. The expression of LD marker ADRP and WT-1 by double immunolabeling was evaluated LD distribution in podocytes. In *vitro*, human podocytes were exposed to AngⅡ (10^{-7}M) for 24 h. LD was observed by Oil red O and Nile red staining. The expression of ADRP was determined by immunofluorescence and Western blot. Cholesterol content was tested by cholesterol quantitation kit. The expression of cholesterol metabolism-related molecules was determined by Real-time PCR and Western blot. Cholesterol efflux inducer methyl-β-cyclodextrin (CD) and cholesterol synthesis enzyme antagonist simvastatin were respectively pretreated to podocytes. Podocyte apoptosis was assessed by flow cytometry.

Results: In vivo, Oil red O and Nile red staining indicated that LD accumulated in glomeruli of AngⅡ-infused rats. Double immunolabeling of ADRP and WT-1 showed that LD deposited in podocytes. In *vitro*, LD was detected in podocyte exposed to AngⅡ but little in controls. The expression of ADRP was upregulated by AngⅡ. Cholesterol content was also increased, which was accompanied by decreased expression of cholesterol efflux-related molecule ABCA1 and increased expression of the cholesterol uptake-related molecule LDLR and cholesterol synthesis-related molecules SREBP-1, SREBP-2 and HMGCR. Treatment of AngⅡ-stimulated podocytes with CD showed that CD could decrease AngⅡ-induced cholesterol accumulation and reduce AngⅡ-induced podocyte apoptosis. Treatment of AngⅡ-treated podocytes with simvastatin indicated that simvastatin did not improve AngⅡ-induced cholesterol accumulation and podocyte apoptosis.

Conclusions: The present study suggests that AngⅡ induces podocyte cholesterol accumulation by regulating the expression of cholesterol metabolism related-molecules. Excess cholesterol induces podocyte injury.

SA-PO385

Phosphate Niclosamide Mitigates Renal Fibrosis through Inhibiting HIPK2 Expression

Xin Zhen, Xiaoyan Chang. *Nanfang Hospital Southern Medical University, Guangzhou, China.*

Background: Renal fibrosis is the final common pathway of all kinds of progressive chronic kidney disease (CKD). However, there are no effective therapies to prevent or slow the progression of renal fibrosis. Recently, homeodomain interacting protein kinase 2 (HIPK2) has been identified as a key regulator in kidney fibrosis and idiopathic pulmonary fibrosis (IPF) that acts upstream of several major pro-fibrotic and pro-inflammatory pathways including TGF-β/Smad, Wnt/β-catenin, Notch pathway and NF-κB pathway, indicating that HIPK2 might be a potential target for anti-fibrosis therapy. Niclosamide is a Food and Drug Administration (FDA) approved oral antihelminthic drug used for treating most tapeworm infections. It has been shown that P-NICLO exerts antitumor function by targeting multiple signaling pathways including NF-κB, Wnt/β-catenin, and Notch pathway. Given the critical role of the above pathways in the pathogenesis of renal fibrosis, the aim of the present study is to explore the potential therapeutic effect of P-NICLO on renal fibrosis.

Methods: In vivo, male BALB/C mice were injected with ADR(12mg/kg). P-NICLO (30mg/kg/d) was injected 2 weeks after ADR for 3 weeks. UUO mice received intraperitoneal injection of P-NICLO (30mg/kg/d) from day 7 after operation for 7 days. In vitro, NRK-52E or HK-2 cells reached approximately 60% confluence, pre-incubated with indicated amount of P-NICLO for 1 h followed by con-incubation with recombinant TGF-β1. WT-HIPK2 construct was transfected into HK-2 cells by using Lipofectamin 2000 Reagent 24 h after TGF-β1 (10ng/ml) and P-NICLO (0.4 μM) treatment.

Results: 1.P-NICLO attenuates glomerular injury and interstitial fibrosis induced by ADR. 2.P-NICLO ameliorates established renal fibrosis and interstitial inflammation induced by UUO 3.P-NICLO inhibits multiple profibrotic signaling pathways include TGF-β/Smads, Wnt/β-catenin, NF-κB and Notch pathways in vitro and in vivo 4.P-NICLO inhibits HIPK2 transcription through interfering the binding of Smad3 to the promoter region of HIPK2 gene to inhibit the expression of pro-fibrosis markers

Conclusions: In summary, we have shown here that P-NICLO is effective in slowing the progression of renal fibrosis. Mechanistically, P-NICLO directly attenuated the activation of multiple pro-inflammatory and profibrotic signalings through suppressing TGF-β1-induced HIPK2 expression

SA-PO386

FGF23 Promotes Progression of CKD by Directly Activating Pro-Inflammatory Signaling in Renal Epithelial Cells

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Background: There is solid evidence from several clinical and epidemiological studies that fibroblast growth factor 23 (FGF23) is a strong predictor of disease progression and adverse outcomes in patients with chronic kidney disease (CKD). However, the mechanisms underlying the association between FGF23 and CKD progression are unclear.

Methods: To gain more insight into the signaling mechanisms induced by FGF23 in renal epithelial cells, we treated 3-month-old wild-type (WT) mice, $Fgf23^{-/-}$/VDR (Fgf23/VDR; VDR, vitamin D receptor), and $Klotho^{-/-}$/VDR (Klotho/VDR) compound mutant mice with recombinant FGF23 (rFGF23), harvested proximal and distal renal tubules by laser capture microdissection 2 and 8 hours after treatment, and performed mRNA expression profiling by next generation sequencing (RNA-Seq).

Results: RNA-Seq analysis revealed that rFGF23 treatment led to strong activation of the Janus kinase/signal transducer and activator of transcription (Jak/STAT) pathway in proximal and distal renal epithelium in a Klotho independent fashion. This unexpected and striking finding was confirmed by qRT-PCR and immunohistochemical analysis of the Jak/STAT pathway. *In vitro* experiments using murine primary renal epithelial cells revealed that rFGF23 rapidly and Klotho-independently activates Jak/STAT signaling in a largely FGF receptor-3 dependent fashion. To analyze the role of FGF23-induced pro-inflammatory signaling in CKD pathology, we used 5/6-nephrectomized (5/6-Nx) mice as a disease model. CKD mice were characterized by high circulating concentrations of intact Fgf23, activation of renal Jak/STAT signaling, and renal interstitial fibrosis, 8 weeks after 5/6-Nx. Treatment of CKD mice with low doses of neutralizing anti-Fgf23 antibody (50 μg per mouse, two times per week) over 8 weeks largely prevented CKD progression, and profoundly reduced the Jak/STAT-mediated pro-inflammatory and pro-fibrotic pathways in a Klotho independent manner.

Conclusions: In conclusion, our study identified excessive FGF23 signaling as a pro-inflammatory factor, directly acting on renal epithelial cells to promote inflammation and fibrosis in the diseased kidney.

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SA-PO387

The Effects of Sevelamer on Renal Klotho Expression and Serum Levels of Klotho, FGF23, and sTWEAK in Adenine Induced CKD Rats Hassan Argani. *Modares Hospital, Tehran, Islamic Republic of Iran.*

Background: Klotho down-regulation may be induced by specific cytokines such as tumour necrosis factor-α or TWEAK through the canonical activation of the inflammatory transcription factor nuclear factor kappa B (NFκB) and, specifically RelA. Klotho itself has antioxidant and anti-inflammatory properties and the canonical NFκB component RelA is one of its targets. Klotho is a key regulator of phosphate balance and phosphate play a role in ageing. Recent studies demonstrate soluble tumor necrosis factor (TNF) weak inducer of apoptosis (sTWEAK) levels follow declining of renal function, as a marker of cardiovascular events in nondialyzed chronic kidney disease patients were reduced, On the other hand high FGF23and low Klotho were reported in CKD patients. Over last few years, several studies have noted a direct correlation of inflammatory markers such as Tumor Necrosis Factor-α (TNF) with circulating FGF23 in patients with CKD. The present study is aim at evaluating the sevelamer (phosphate binder) effect in renal Klotho expression and Serum levels of FGF23, s TWEAK, Klotho in rat model of adenine induced renal failure.

Methods: Adenine 3mg/kg was used to induce CKD in 60 male wistar rats. These divided into 6 groups based on the dose administration of sevelamer for 4 weeks. Group 1 (n = 10) control group was given 0% adenine, 0% Sev, Group2 (n = 10) 0% Sev in Aenine group, Adeine contol group, Group 3(n = 10) 1% Sev in Aenine group, Group 4(n = 10) 2% Sev in Aenine group, Group 5 (n = 10) 3% Sev in Aenine group and group 6 (n = 10) 2% Sev in the normal diet. Serum stweak, Klotho levels were measured by enzyme-linked immunosorbent assay. Real-time polymerase chain reaction and Western blotting were used to evaluate Renal Klotho expression in each group.

Results: Induced renal failure was induced by adenin, FGF23 levels could be manipulated through the control of serum phosphorus levels by sevelamer treatment. Treatment with sevelamer controlled sTWEAK and KLotho downregulated in CKD rats. Sevelamer treatment also improved reduced renal expression and serum levels of Klotho and deteriorated renal function and could alleviate adenine -induced renal histological changes.

Conclusions: Treatment with sevelamer might lead to ameliorat renal Klotho and downregulation sTWEAK in CKD and suppressed FGF23 increases through the control of serum phosphorus levels in CKD patients.

Funding: Government Support - Non-U.S.

SA-PO388

suPAR Induces Proteinuria in Solitary Functioning Kidney Models Xuexiang Wang,[1] Michael R. Garrett,[2] David C. Wei,[1] Jochen Reiser.[1] *[1]Rush University Medical Center, Chicago, IL; [2]University of Mississippi Medical Center, Jackson, MS.*

Background: Single functioning kidney (SFK) is expected in one out of 1500 births, and it causes renal injury before adulthood in over 50% of those affected. Similarly, kidney donors may have increased risk for future CKD. The underlying mechanisms and related biomarkers are still lacking. The soluble urokinase receptor (suPAR) is a circulating factor implicated in FSGS and is also a potent biomarker for predicting CKD incidence and progression. In this study, we explore the effect of elevated circulating suPAR on proteinuria development in three different rodent models of SFK.

Methods: Uninephrectomy and sham surgeries were performed on C57B/6 (B/6) mice, suPAR transgenic models or littermate controls. Minipumps with three different concentrations of LPS were implanted subcutaneously in B/6 mice only. Proteinuria and/or suPAR were followed weekly for 4 weeks. In the HSRA spontaneous one-kidney rat model, the recombinant human suPAR protein was injected intravenously into HSRA single kidney rats (HSRA-S) and two-kidney controls (HSRA-C). Proteinuria was measured 24 hours after. The activity of beta3 integrin in podocytes was determined by AP5 immunostaining.

Results: In B/6 mice, all three concentrations of LPS infusion resulted in increased level of serum and urine suPAR. Interestingly, nephrectomy resulted in higher serum suPAR and proteinuria, compared to the sham two-kidney groups. In contrast, uPAR deficient SFK mice are protected from LPS induced proteinuria. Nephrectomized suPAR transgenic mice demonstrated slowly increased proteinuria over 4 weeks of time, while the littermate control mice with nephrectomy showed no change in the urinary protein. HSRA-S rats revealed an increase of proteinuria compared to HSRA-C after the recombinant human suPAR injection. Moreover, the activity of the suPAR receptor beta3 integrin was significantly increased in the kidney of HSRA-S rats following administration of suPAR.

Conclusions: Increased circulating suPAR levels, either induced by LPS, or from suPAR transgenic models or extrinsically injected, induce proteinuria in uninephrectomized mice or rats with unilateral kidney agenesis, when compared to their two-kidney controls. These findings suggest an important role of suPAR in SFK kidney, possibly in kidney donors. Monitoring circulating suPAR levels might be important in understanding the pathogenesis and risk-control for patients with SFK.

Funding: NIDDK Support

SA-PO389

Essential Role of Endothelial HIF-1a in Light-Induced Hypertensive CKD Renna Luo. *The First Affiliated Hospital of Dalian Medical University, Dalian, China.*

Background: Hypertensive chronic kidney disease (CKD) is one of the most prevalent medical conditions with high morbidity and mortality in the United States and worldwide. Emerging evidence indicates that increased inflammatory response is involved in hypertensive CKD. Supporting this notion, recent study show that infusion of cytokine to mice leads to chronic hypertension, such as LIGHT, a TNF-a superfamily member. To determine the general significance of persistently elevated endothelial HIF-1 in hypertensive CKD, we used LIGHT-infused hypertensive CKD mouse model.

Methods: We obtained *VE-cadherin cre*$^{+}$ mice and *Hif-1α*$^{f/f}$*VE-cadherin cre*$^{+}$ mice from Dr. Holger Eltzchig's laboratory in University of Colorado at Denver. Six to twelve mice for each group were infused with LIGHT by minipump(4ng/day). Control mice were infused with PBS. We collected urine and measured blood pressure at 0,3,7,10,14 day. After treatment for 14-days, mice were sacrificed.

Results: We first found that LIGHT infusion induced persistently elevated HIF-1a protein levels in endothelial cells of capillary lumen of glomeruli in the control HIF-1a$^{f/f}$ mice. Then we identified that LIGHT-induced HIF-1a gene expression is crucial for prolonged accumulation of HIF-1a in the endothelial cells in hypertensive CKD by inducing a series of potent vasoactive components. As such, we further found that LIGHT-induced hypertension, proteinuria, decreased urinary osmotic pressure and renal fibrosis. Next, we found that endothelial HIF-1a gene expression was induced by LIGHT in a NF-kB-dependent manner. Finally, we discovered reciprocal positive transcriptional regulation of endothelial *Hif-1α* and *Nf-κb* genes is a key driving force for their persistent activation and disease progression. Overall, our findings revealed that the stimulation of HIF-1α in endothelial cells is detrimental to induce kidney injury, hypertension and disease progression.

Conclusions: Our findings highlight early diagnostic opportunities and therapeutic approaches for hypertensive CKD.

SA-PO390

Blocking the Phosphorylation of Ribosomal Protein S6 Inhibits Focal Segmental Glomerulosclerosis Fang Li,[6,1] Caihong Dai,[2] Qiyuan Zhuang,[5] Jian-Kang Chen,[4] Huijuan Wu.[3] *[1]2. Departments of Cellular Biology & Anatomy and Medicine, AUGUSTA UNIVERSITY, AUGUSTA, GA; [2]Augusta University, Augusta, GA; [3]Department of Pathology, School of Basic Medical Sciences, Fudan University, Shanghai, China; [4]None, Evans, GA; [5]Shanghai Medical College, Fudan University, Shanghai, China; [6]Department of pathology, Fudan University, Shanghai, China.*

Background: The pathogenic mechanism of focal segmental glomerulosclerosis (FSGS) remains poorly understood. Renal hypertrophy is largely mediated by phosphorylated rpS6 (p-rpS6), a downstream effector of the mTORC1-S6K1 pathway.

Methods: We detected p-rpS6 levels in kidney biopsy specimens from patients with FSGS. By crossing *Tsc1*-floxed mice with podocin-Cre mice, we generated podocyte-specific Tsc1 knockout (TSC1^{pdKO}) mice with or without rapamycin treatment. We also compared Adriamycin (ADR)-induced FSGS, a widely used mouse model of FSGS, in *rpS6* knockin mice expressing nonphosphorylatable rpS6 (rpS6$^{P-/-}$) and in gender-matched wild type littermates.

Results: p-rpS6 was markedly increased in the renal glomeruli of both FSGS patients and ADR-induced FSGS mice. Podocyte specific rpS6 hyper-phosphorylation induced by genetic deletion of Tsc1, an upstream negative regulator of mTORC1, induced striking hypertrophy of surviving podocytes and recapitulated many features of human FSGS, including podocyte loss and segmental glomerulosclerosis, which were blunted by low-dose rapamycin treatment (0.5 or 1 mg/kg). Similarly, treatment with the phosphatase inhibitor, Tautomycin, also increased p-rpS6 and significantly promoted podocyte hypertrophy, leading to exacerbated FSGS. Conversely, completely blocking rpS6 phosphorylation by generating congenic rpS6 knockin mice expressing non-phosphorylatable rpS6 significantly blunted podocyte hypertrophy and podocyte loss (20% podocytes were lost in rpS6 knockin mice vs. 46% podocytes loss seen in wild type mice) in the ADR-induced mouse model of FSGS. Moreover, pharmacologic inhibition of S6K1 signaling to rpS6 phosphorylation using the S6K1 inhibitor, PF- 4708671, markedly blunted podocyte hypertrophy and attenuated FSGS.

Conclusions: rpS6 hyperphosphorylation plays a key role in adaptive podocyte hypertrophy and progressive podocyte loss in response to initial podocyte injury during the development and progression of FSGS.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO391

Acute Renal Venous Pressure-Induced Renal Vasoconstriction Is Not Mediated by Increased Renal Sympathetic Nerve Activity and Is Abolished by High Salt Diet in Rats Shereen M. Hamza,[1,2] Xiaohua Huang,[1] Wenqing Zhuang,[1] William A. Cupples,[3] Branko Braam.[1,2] *[1]Medicine, University of Alberta, Edmonton, AB, Canada; [2]Physiology, University of Alberta, Edmonton, AB, Canada; [3]Simon Fraser University, Burnaby, BC, Canada.*

Background: Combined cardiac/renal dysfunction may be perpetuated by elevated renal venous pressure (RVP). We demonstrated that renal nerves modulate the increase

in renal vascular resistance (RVR) in response to mild but not severe RVP elevation. This suggests additional non-neural mechanisms. We hypothesized that mild RVP elevation would increase renal sympathetic nerve activity (RSNA) and that severe RVP elevation leads to vasoconstriction and diminished GFR via activation of the RAS. **Objectives:** (1) Measure renal sympathetic nerve activity in response to RVP elevation. (2) Evaluate RVP-induced modulation of renal hemodynamics following RAS suppression by high salt diet.

Methods: Blood pressure, RVP and RSNA were measured in anesthetized rats (300-400g, n=25). Separately, renal arterial blood flow (RBF) and GFR were assessed in rats (n=11) supplemented with 6% NaCl (2 weeks). In all rats, following baseline, RVP was increased to 10 or 20 mmHg by partial occlusion of the left renal vein for 120 min.

Results: RSNA was maintained in response to RVP 10 mmHg (frequency: 12.3±12.4%; amplitude: 0.06±0.2μV). RVP 20 mmHg induced a significant and sustained reduction in RSNA (-50.3±11.3%, $p<0.05$) and spike amplitude (-0.68±0.2μV, $p<0.05$). After high salt diet, RVP 10 or 20 mmHg did not elicit a change in RBF (RVP 10: -0.8±0.4ml/min; RVP 20: -1.0±0.4ml/min) and completely abolished the increase in RVR (RVP 10: -1.3±1.3mmHg.ml^{-1}.min; RVP 20: -1.7±2.0mmHg.ml^{-1}.min). High salt did not alter GFR response to RVP increase (RVP 10 GFR: -0.09±0.26ml/min; RVP 20 GFR: -1.11±0.28ml/min).

Conclusions: Mild RVP elevation sustains RSNA while severe RVP elevation supresses RSNA and reduces recruitment of nerve fibres. High salt-suppression of the RAS abolishes RVP-induced modulation of renal hemodynamics, indicating that the RAS, rather than RSNA mediates the renal response to acute RVP elevation.

SA-PO392

RNA-Sequencing Based Approach to Identify Novel Pathways Regulating Atrophic and Hypertrophic Renal Remodeling Mark Paterson,[1] Alison J. Kriegel.[1,2] *[1]Department of Physiology, Medical College of Wisconsin, Milwaukee, WI; [2]Center of Systems Molecular Medicine, Medical College of Wisconsin, Milwaukee, WI.*

Background: There is a great need to understand the mechanisms that regulate renal survival to preserve tubular function in patients with various forms of renal disease. In previous studies in Sprague Dawley rats we observed that excision of 2/3 of the left kidney resulted in atrophy of the remnant kidney, while excisions of both 2/3 of the left kidney and the entire right kidney resulted a robust hypertrophy of the remnant kidney from 5 to 7 weeks after surgery. The sole difference between these models is the presence or absence of the right kidney, providing a well-controlled opportunity to explore mechanisms that promote survival and senescence. The goal of this study was to identify molecular pathways that regulate renal hypertrophy and atrophy by the contrasting mRNA expression changes within each model. We hypothesized that transcript analysis would reveal unique expression profiles, highlighting the distinct stress response in each state.

Methods: We collected remnant kidneys from the atrophic and hypertrophic models (n=6/group), as well as the left kidney in sham operated controls 6 weeks after respective surgery (n=5). Next-generation RNA sequencing of these samples was performed, and subsequent statistical and Ingenuity Pathway Analysis (IPA) was completed.

Results: Comparison of RNA expression in atrophic and hypertrophic remnant kidneys against sham control kidneys identified 1112 and 867 differentially expressed transcripts (DET; adjusted p-value <0.05), respectively. In the atrophic kidney nearly 1/3 of the DET were downregulated (32.4%). IPA revealed an enrichment of numerous downregulated transcripts encoding proteins within electron transport chain and amino acid synthesis pathways, among others, consistent with changes expected in senescent tissue. The transcripts altered in the hypertrophic kidney were overwhelmingly upregulated (98.5%), enriched in pathways related to hypertrophic growth and many others. This analysis also revealed novel upstream pathways enriched with differentially expressed transcripts that will be explored to nominate therapeutic targets for functional evaluation in these models.

Conclusions: Together our data suggest that these remnant kidney models will allow us to appropriately model processes relevant to renal hypertrophy and renal atrophy and indentify molecular pathways involved with morphological and functional changes.

SA-PO393

MicroRNA-451 as an Early Predictor of and Protector against Diabetic Nephropathy (DN) Maurice Fluitt, Narayan Shivapurkar, Lijun Li, Carolyn M. Ecelbarger. *Georgetown University, Washington, DC.*

Background: MicroRNAs (MiRs) play a role in affecting transcription of a number of genes involved in DN progression, and are an attractive target as biomarkers and therapeutics. Recent studies report an early elevation in urine exosomal (UE) miR-451 with developing DN, but that overall higher renal expression was relatively protective. The current study aimed to determine whether UE miR-451 is an early predictor of albuminuria and the effect of miR-451 antagonism on DN progression in mice prone to type 2 diabetes.

Methods: Male TALLYHO/Jng mice were divided into 2 treatment groups. Mice received weekly intraperitoneal injections of locked nucleic acid (LNA)-miR-451-inhibitor or LNA-scrambled compound (2mg/kg bw; n = 8/ treatment) for 8 weeks. All mice were fed a high-fat diet (60% kCal). Urine (24-hr) was collected every 2 weeks. Mice were humanely euthanized after 8 weeks and kidneys, livers, abdominal adipose tissue, and pancreas were collected for analysis. UE were prepared by high-speed centrifugation (200,000xg). MiR-451 was quantified by qRT-PCR.

Results: UE miR451 levels were reduced 97% in antagonist-treated mice by week 2. Urine albumin levels at week 8 were positively correlated to UE miR-451 at week 2 showing potential predictive power (r=0.45). MiR-451 antagonist did not significantly affect final body or kidney weights. Fasting blood glucose (18-hr) did increase in in the inhibitor treated group at week 3, but decreased at 6 weeks. Inhibitor treated mice also presented with greater variability in blood glucose, with some mice becoming hypoglycemic at 6 weeks (blood glucose <65 mg/dl). Blood collected at euthanasia was analyzed by iSTAT. Serum sodium was significantly higher (2.4%) in the LNA-inhibitor treated group (when compared to the scramble-treated group). In addition, BUN and base excess (extracellular fluid) were 16% and 67% lower, respectively, in the LNA-inhibitor treated group. No other blood chemistry parameters were significantly different. Masson's trichrome-stained were scored for collagen deposition and showed an increase in increased glomerular injury and collagen deposition in the LNA-inhibitor treated group (scores 2.00 versus 2.95, $p < 0.001$).

Conclusions: Overall, we find that miR-451 may hold promise as an early biomarker for DN in mice, and that therapy to enhance renal expression may be beneficial.

Funding: Clinical Revenue Support

SA-PO394

Alterations in Notch Signaling Pathway Activity and Its Potential Role in Kidney Damage in Carriers of APOL1 Risk Alleles Marianinha Joanes,[1] Shi Yang,[3] Chris Andry,[1] Adam Gower,[2] Joel M. Henderson.[3] *[1]Boston Medical Center, Boston, MA; [2]Boston University, Boston, MA; [3]Boston University Medical Center, Boston, MA.*

Background: The association between apolipoprotein L1 (*APOL1*) gene variations and the increased incidence of chronic kidney disease (CKD) in individuals of African ancestry has been well established. Despite their importance, little is known about how these variants contribute to renal dysfunction, and better understanding of this mechanism could yield new diagnostic and treatment options.

Methods: To address this shortcoming, we studied kidney tissue obtained before the development of parenchymal damage in order to identify any pathway alterations that create a milieu that promotes the later development of kidney injury. We focused on glomerular changes, given the association of *APOL1* variations with several glomerular disease phenotypes. Kidney samples were stratified according to *APOL1* genotype, including zero risk alleles (G0G0), one risk allele (G0G1, G0G2) and two risk alleles (G1G2). Gene expression profiling was performed using Affymetrix microarrays with RNA extracted from laser capture micro-dissected glomeruli, and biological pathways that are coordinately regulated between the G0G0 and G1G2 groups were identified using Gene Set Enrichment Analysis (GSEA).

Results: Our data shows that gene sets related to the Notch signaling pathway (NSP) are significantly coordinately upregulated in the G1G2 group compared to the G0G0 group (FDR $q < 0.25$).

Conclusions: Given that the NSP is already implicated in other glomerular diseases, the altered NSP activity in carriers of *APOL1* risk alleles may be a precursor to future disease before overt kidney injury is apparent. This also suggests that genetic variation in *APOL1* may have indirect effects on other genes relevant to glomerular function.

SA-PO395

Albuminuria and Podocytopathy Induced by Podocyte-Specific Deletion of Acid Ceramidase α Subunit Guangbi Li,[1] Krishna M. Boini,[1] Todd W. Gehr,[4] Pin-lan Li.[1] *[1]Department of Pharmacology and Toxicology, School of Medicine, Virginia Commonwealth University, Richmond, VA; [4]Devision of Nephrology, School of Medicine, Virginia Commonwealth University, Richmond, VA.*

Background: Acid ceramidase (AC) as a lysosomal enzyme has been shown to be critical for the metabolism of sphingolipid, ceramide, which regulate lysosome function and related cellular activities such as autophagy and vesicle or molecular trafficking. It remains unknown whether AC is involved in the control of podocyte function and in the development of glomerular disease. In the present study, we generated a mouse line with podocyte-specific deletion of α subunit in Asah1 gene (AC gene code in mouse), a main subunit for its activity in lysosomes using Cre-Lox recombination technology. This AC flox/podocyte Cre (Asah1fl/fl/podoCre) mouse colony was characterized by several genetic, molecular and biochemical approaches. By PCR genotyping, detection of both homozygous floxed gene Asah1 and Cre recombinase gene was considered as homozygous mice with Cre expression. If neither floxed Asah1 gene nor Cre recombinase gene was detected, mice are wild type (WT/WT). If only floxed Asah1 gene was detected without Cre recombinase gene, the mice were Asah1 flox control without podocyte specific deletion (Asah1fl/fl/WT). Immunofluorescent staining and immunohistochemistry showed that ACα was not detactable in podocytes in glomeruli of Asah1fl/fl/podoCre mice, compared to Asah1fl/fl/WT and WT/WT mice. Although Periodic acid-Schiff staining showed no significant increase in glomerular damage index in Asah1fl/fl/podoCre mice compared with other two types of mice, there were severe proteinuria and albuminuria found in Asah1fl/fl/podoCre mice even started at 6 weeks old. Correspondingly, compared Asah1fl/fl/WT and WT/WT mice at the same ages, hypoalbuminemia and edema were observed in Asah1fl/fl/podoCre mice when they grew to 12 weeks old. Under electron microscope, Asah1fl/fl/podoCre mice were found to have foot process effacement, vacuolation, and microvillus formation in podocytes. In cultured mouse podocytes, we also found that inhibition of AC activity by carmofur, a selective AC inhibitor, remarkably decreased the expression of podocin. These results suggest that AC and associated metabolism of ceramide are essential for the maintenance of podocyte structural and functional integrity and that the defect or deficiency of AC expression and function may result in podocytopathy and related glomerular disease such as minimal change disease.

Methods:

Results:

Conclusions:

Funding: NIDDK Support

SA-PO396

Sex Differences in the Exacerbating Effects of Chronic Nicotine on Angiotensin II-Induced Renal Injury Rodrigo Maranon,[2] Kiran B. Chandrashekar,[1] Luis A. Juncos.[2] *[1]UMMC, Brandon, MS; [2]University of Mississippi Medical Center, Jackson, MS.*

Background: Chronic Nicotine (Ch-Nic) worsens angiotensin II (AngII)-induced renal injury in male rodents via various mechanisms that alter heme oxygenase and oxidant stress. Because females may regulate these factors differently, and also metabolize nicotine than males, we tested whether Ch-Nic exacerbates AngII-induced renal injury in females to the same extent as in males. For this, we tested male and female Sprague Dawley rats for 60 days with Ch-Nic (12.5µg/ml) or vehicle in water, and then randomized into 4 groups each, which received either AngII (200ng/kg/min) or vehicle via SQ osmotic minipumps for an additional 28 days. Systolic blood pressure (SBP) was measured by tail-cuff plethysmography twice weekly and parameters of renal function and injury were assessed at the end of the experiments. See Table below.

Methods:

Results:

Conclusions: Cotinine excretion rates were 5 times higher in females than males, suggesting that females metabolize nicotine much faster and thus may be protected against the deleterious effects of Ch-Nic. Despite this, Ch-Nic exacerbated AngII-induced renal injury in both males and females, albeit with some differences. Males developed proteinuria earlier than females, and sustained higher levels of proteinuria throughout the study. Despite less proteinuria, NGAl and inflammation (TNF), females appeared to lose more GFR, as suggested by the more pronounced increase in serum creatinine levels. Our data indicate that despite the rapid metabolism of nicotine in females, Ch-Nic still induces renal injury in them. The differences in the pattern of injury and lack of inflammation, raise the possibility that the mechanisms of renal injury are different between the sexes.

Funding: NIDDK Support, Private Foundation Support

	Cotinine (ng/ml)	SBP (mmHg)	Proteinuria (mg/24 hrs)	Creatinine (mg/dl)	NGAL (pg/ml)	TNF-alpa (pg/ml)
Females						
Control	4±0.24	131±2	18±4	0.39±0.01	7.7±1	4.5±2
Ch-Nic	572±25*	149±1*	11±4	0.48±0.06	11.7±3	6.1±3
AngII	3±0.38	160±2*†	117±12*†	1.42±0.22*†	46.1±9*†	26.1±4*†
AngII + Ch-Nic	541±30*	172±5*†*	165±23*†*	2.16±0.01*†*	98.7±13*†*	31.1±5*†
Males						
Control	0.2±0.04	121±0.8	18±2	0.37±0.04	14.5±2	7.1±1
Ch-Nic	104±3*	122±3	25±6	0.53±0.09	23.6±6	20.8±4*
AngII	0.2±0.05†	145±2*†	125±46*†*	1.51±0.12*	85.9±15*	44.4±8*
AngII + Ch-Nic	112±7*#†	157±3*#†	229±47*†*	1.88±0.15*†*	153.3±41*†*	76.7±14*#†

* p<0.05 vs Control † p<0.05 vs Ch-Nic; # p<0.05 vs AngII

SA-PO397

Heterogeneity and Clinical Relevance of Tertiary Lymphoid Tissue in Murine and Human Kidneys Yuki Sato,[1,2] Peter Boor,[3] Jürgen Floege,[4] Motoko Yanagita.[2] *[1]Medical Innovation Center TMKP, Graduate School of Medicine, Kyoto University, Kyoto, Japan; [2]Department of Nephrology, Graduate School of Medicine, Kyoto University, Kyoto, Japan; [3]Institute of Pathology, RWTH University of Aachen, Aachen, Germany; [4]Department of Nephrology, RWTH University of Aachen, Aachen, Germany*.

Background: Unlike reversible AKI in the young, AKI in the elderly often leads to end-stage renal disease. We previously demonstrated that after AKI aged but not young mice developed multiple renal tertiary lymphoid tissues (TLTs), which comprised mainly lymphocytes and fibroblasts. These promoted aberrant inflammation and underlied the "AKI to CKD sequence". We also showed that aged (> 60 yrs old) but not young (40 yrs old >) humans exhibited renal TLTs (*Sato Y et al. JCI insight 2016*). Although TLTs are closely involved in the pathophysiology of various chronic inflammatory diseases in human, the developmental stages and clinical relevance remain ill defined.

Methods: Utilizing surgically removed human kidney samples as well as the mouse TLT model, which we have recently established, we investigated the developmental stages and potential clinical relevance of renal TLTs. Human kidney samples were derived from 2 independent patient groups: Japanese aged patients and German pyelonephritis patients.

Results: Kidneys from patients with chronic pyelonephritis exhibited multiple heterogeneous TLTs, which appeared to represent various developmental stage of TLTs. The same cellular and molecular components such as CXCL13 and p75NTR in fibroblasts were detectable both in pyelonephritis-induced TLTs and age-dependent TLTs and proved indistinguishable, suggesting that TLT formation is a uniform response to injury irrespective of the etiology in human kidney. Furthermore, we classified TLTs into 3 groups based on their presumed developmental stages and found that the TLT-stage was closely associated with the severity of kidney injury in mice, raising the possibility that the presence and developmental stage of TLTs can be a predictor of kidney disease progression. In humans, the kidneys of aged patients with CKD exhibited more frequent and advanced TLT-stages than those without CKD, whereas in chronic pyelonephritic kidneys TLTs in advanced stages clustered in destroyed areas.

Conclusions: TLT-formation in murine and human kidneys appears to be a relatively uniform process that proceeds through several stages. Stratification using the TLT-stages may offer a novel strategy to evaluate the CKD patients and potentially improve their therapeutic approaches.

Funding: Commercial Support - Mitsubishi tanabe pharma corporation, Government Support - Non-U.S.

SA-PO398

Chronic Nicotine Mediated Accentuation of Angiotensin-II-Induced Renal Injury Is Prevented but Not Readily Reversed by Sildenafil Kiran B. Chandrashekar,[3] Rodrigo Maranon,[4] Arnaldo F. Lopez-Ruiz,[2] Istvan Arany,[1] Luis A. Juncos.[4] *[1]Dept. Pediatrics, Dv. Pediatric Nephrology, UMC, Jackson, MS; [2]None, Rochester, MN; [3]UMMC, Brandon, MS; [4]University of Mississippi Medical Center, Jackson, MS.*

Background: Chronic Nicotine (Ch-Nic) exacerbates angiotensin II (AngII)-induced renal dysfunction. Because sildenafil can preserve cGMP levels and increase heme oxygenase 1, both of which are protective against renal injury, we tested whether early administration of sildenafil prevents Ch-Nic-mediated exacerbation of AngII-induced renal injury. We also tested whether late administration sildenafil, after there is established renal injury, halts or reverses the progression of renal dysfunction

Methods: Sprague Dawley rats received nicotine (12 g/ml in their drinking water) with or without SP-AngII (200ng/kg/min via SQ infusion for 22 days). Separate groups were also concomitantly treated with sildenafil from either day 0 (Early sildenafil) or day 14 (Late sildenafil). Systolic blood pressure (SBP) was measured throughout and renal vascular resistance (OM-RVR) calculated. Renal function (plasma creatinine), pro-inflammatory (TNF-alfa), renal injury (NGAL), pro-apoptotic (cyt-c) and pro-fibrotic (TGF-beta) markers were assessed by ELISA. HO activity was evaluated based on the amount of bilirubin generated.

Results: p≤ 0.05: * vs. Control; # vs. Ang-II; Ω vs. AngII+ NIC. Early sildenafil treatment was very effective at decreasing Ch-Nic mediated exacerbation of AngII-induced renal dysfunction, inflammation, injury, and pro-apoptotic and pro-fibrotic signaling while increasing HO activity. In contrast, late sildenafil decreased blood pressure, but was much less effective at improving renal parameters of injury

Conclusions: Our data indicates early SIL therapy may ameliorate the exacerbating effects of NIC in a SP-AngII hypertensive model, but longer term studies are necessary to determine whether it can prevent progression or cause reversal of injury.

Funding: NIDDK Support, Private Foundation Support

	SBP (mmHg)	OM-RVR TPU/mmH g	PL.Creat (mg/dl)	TNFα (pg/µg protein)	NGAL (UI/mg creat)	Cytochrome c (ng/ µg protein)	TGF-beta (ng/µg protein)	HO-Activity (nMol bil/mg)
Vehicle	107 ± 6	4.5 ±0.15	0.5 ± 0.04	1.4 ±0.05	0.32 ± 0.03	8.3 ± 0.4	14.2 ± 0.7	0.42 ± 0.02
Vehicle+ NIC	108 ± 5	4.7 ± 0.1	0.53 ± 0.03	1.4 ± 0.05	0.3 ± 0.02	16 ± 1*	23.4 ± 1.2 *	0.55 ± 0.04
AngII	156 ± 4*	6.6 ± 0.3*	1.47 ± 0.1*	11.8 ± 0.4*	4.2 ± 0.2*	30 ± 1.5*	36.5 ± 1*	3.6 ± 0.1*
AngII+ Early Sildenafil	126 ± 3#	5.5 ± 0.2#	0.8 ± 0.03#	5.2 ± 0.3#	2.1 ± 0.06#	18.4 ± 0.7#	21.8 ± 0.6#	3 ± 0.04#
AngII+ Late Sildenafil	145 ± 5#	6.15 ± 0.3#	1.3 ± 0.05	10.3 ± 0.6	3.9 ± 0.2	26.6 ± 1.2	33 ± 0.7	1.5 ± 0.04#
AngII+ NIC	170 ± 2*#	9.5 ± 0.4#	2.5 ± 0.04#	14.2 ± 0.7#	8.0 ± 0.3#	72.6 ± 3.4#	41 ± 1.2#	2 ± 0.14#
AngII+NIC + Early Sildenafil	130 ± 3 Ω	6.2 ± 0.1Ω	1.3 ± 0.03 Ω	6.0 ± 0.4 Ω	3.8 ± 0.1 Ω	39.2 ± 1.2 Ω	22.4 ± 0.7 Ω	3 ± 0.03 Ω
AngII+NIC + Late Sildenafil	146 ± 2 Ω	6.9 ± 0.1 Ω	2.25 ± 0.1	13.0 ± 0.6	7.1 ± 0.1	62 ± 5.6	36.8 ± 0.6	2.3 ± 0.06

* p≤ 0.05 vs. Control; #: vs. AngII; Ω: vs. AngII+ NIC

SA-PO399

Fludrocortisone Time-Dependently Up-Regulates Erythropoietin (Epo) mRNA Expression via HIF2α Pathway in Rat Kidney Hiroshi Nonoguchi,[4] Yukiko Yasuoka,[1] Yuichiro Izumi,[5] Yushi Nakayama,[5] Hideki Inoue,[5] Takanori Nagai,[2] Masayoshi Nanami,[2] Takeshi Nakanishi,[2] Masashi Mukoyama,[5] Yuichi Sato,[3] Katsumasa Kawahara.[1] *[1]Dept of Physiol, Kitasato Univ School of Med, Sagamihara, Japan; [2]Hyogo College of Medicine, Nishinomiya, Japan; [3]Kitasato University, Sagamihara, Japan; [4]Kitasato University Medical Center, Kitamoto, Japan; [5]Kumamoto University Graduate School of Medical Sciences, Kumamoto, Japan*.

Background: Epo is produced by the kidney in response to hypoxia and anemia via stimulation of hypoxia-inducible factor 2α (HIF2α). Although renin-angiotensin-aldosterone system (RAS) blocker-induced renal anemia strongly suggests the participation of RAS on Epo production, no hormonal studies of Epo production have been conducted. Therefore, we investigated the effects of fludrocortisone, an analogue of aldosterone, on Epo mRNA expression in the rat kidney.

Methods: Male SD rats were given intraperitoneal injection of fludrocortisone 2.5 mg/100 g BW/day. At 2, 4, 6 and 72 hr, the kidney was removed and RNA was extracted for real time PCR. We also used tubule suspensions of renal cortex to test the direct effects of aldosterone (10^{-9} and 10^{-6} M) on Epo mRNA expression. Tubule suspensions were incubated w/ or w/o aldosterone in 2 hr. Plasma Epo concentration was also measured using CLEIA.

Results: In kidney cortex, the Epo mRNA expression was increased by 3-fold at 4 hr and decreased to very low level at 72 hr after the injection of fludrocortisone. The levels of HIF2α, HIF1α and PHD2 mRNA expressions also changed in the same time course. In tubule suspension, the Epo and HIF2α mRNA expression levels became nearly zero after 3 hr-incubation. It was restored by 2-hr incubation with aldosterone, together with the increase of HIF2 α, HIF1α, mineralocorticoid receptor, GATA2 and GATA3 mRNA expressions. Plasma Epo concentrations were increased from 1.10 ± 0.4 to 2.22 ± 0.17

mIU/ml (n=5, p<0.05) at 6 hr after the injection of fludrocortisone, but was decreased to 1.62 ± 0.43 U/ml (n=10, p>0.05) at 72 hr.

Conclusions: Aldosterone may regulate Epo production by the nephron via stimulation of a HIF2α pathway. HIF2α is regulated not only by hypoxia but also by RAS.

Funding: Commercial Support - Takeda Research Support, Government Support - Non-U.S.

SA-PO400

Current Nephrology Practices for Slowing CKD Progression – The Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) Benedicte Stengel,[1,2] Charlotte Tu,[3] Celine Lange,[4] Lindsay Zepel,[3] Danilo Fliser,[6] Roberto Pecoits-Filho,[5] Ziad Massy,[7,1] Bruce M. Robinson.[3] *[1]Inserm-CESP, Villejuif, France; [2]Univ Paris-Saclay, Villejuif, France; [3]Arbor Research Collaborative for Health, Ann Arbor, MI; [4]Biomedicine Agency, La Plaine Saint-Denis, France; [5]Pontificia Universidade Catolica do Parana, Curitiba, Brazil; [6]Saarland University Medical Centre, Homburg/Saar, Germany; [7]Ambroise Pare University Hospital, Boulogne Billancourt/ Paris cedex, France. Group/Team: CKD-REIN and CKDopps.*

Background: The 2012 KDIGO guideline for the management of CKD recommends several measures for preventing CKD progression, including blood pressure (BP) control, use of renin-angiotensin system inhibitors (RASi), and dietary advice. Whether these recommendations are followed in current nephrology practice is unknown.

Methods: We used baseline data from CKDopps (2013-17), a prospective cohort study of adult patients (pts) with eGFR < 60 ml/min/1.73m^2 from national samples of nephrology clinics in Brazil (BR), France (FR), Germany (GER), and the United States (US) to describe success rates in achieving recommended measures by albuminuria category (using either spot or 24-hour urinary albumin or protein equivalent) or eGFR, and by country

Results: Median age ranged from 67 yrs in BR to 77 yrs in GE. Albuminuria or proteinuria was routinely measured in 42%, 44%, 43% of pts in BR, GER, and the US, respectively, and 89% in FR (where this was requested per study protocol). Proteinuria was more commonly measured than albuminuria in all countries. Percentages of pts with BP <140/90 were lower at higher UAP, and higher in the US and GER than in BR and FR. RASi use did not vary by albuminuria level, but was lower at lower eGFR in BR, GER, and the US. Receiving dietary advices was slightly more common in pts with low eGFR, and better for salt than protein intake, but dietician visit was not common practice.

Conclusions: Monitoring albuminuria as recommended is not a standard practice in nephrology. BP control and RASi use vary substantially by country, and expert dietary advice remains poor across participating countries. The effects on clinical outcomes, and reported variation in incidence of kidney failure by country, will be evaluated during follow-up.

Funding: Commercial Support - CKDopps Brazil supported by AbbVie, CKDopps US by Keryx, and CKD-REIN by Amgen, Baxter, GSK, Fresenius, Lilly, MSD, Otsuka, Government Support - Non-U.S.

Table: Prevalence of RASi use, dietary advice, and blood pressure (BP) target achievement by eGFR or albuminuria category and country

	France		Brazil		Germany		US	
eGFR(mL/min/1.73m²)	≥30	<30	≥30	<30	≥30	<30	≥30	<30
N pts (%)	1657 (55%)	1347 (45%)	269 (31%)	586 (69%)	474 (26%)	1355 (74%)	359 (31%)	786 (69%)
RASi[a] use	78%	74%	75%	60%	81%	77%	66%	46%
Pts reporting to have received advice to reduce:								
Salt intake	66%	73%	77%	80%	-	-	48%	59%
Protein intake	32%	39%	43%	51%	-	-	13%	24%
Pts with at least 1 dietician visit past year								
	23%	27%	33%	39%	-	-	21%	32%
Albuminuria categories (or equivalent)[b]	Normal to mildly increased	Moderately/ severely increased	Normal to mildly increased	Moderately/ severely increased	Normal to mildly increased	Moderately/ severely increased	Normal to mildly increased	Moderately/ severely increased
N pts (%)	692 (27%)	1835 (73%)	273 (46%)	323 (54%)	77 (22%)	276 (78%)	219 (32%)	456 (68%)
BP < 140/90 mmHg	55%	43%	61%	44%	64%	57%	66%	53%
BP < 130/80 mmHg	33%	23%	25%	17%	31%	20%	39%	30%
RASi use	74%	82%	64%	69%	86%	81%	58%	52%

[a]RASi :Renin angiotensin system inhibitor.
[b]Urinary albuminuria excretion or equivalent < 30 mg/g: normal to mildly increased; ≥30 mg/g: moderately/ severely increased

SA-PO401

Nomograms for Evaluating the Long-Term Prognostic Risk of IgA Nephropathy Xiangmei Chen. *Chinese PLA General Hospital, Beijing, China.*

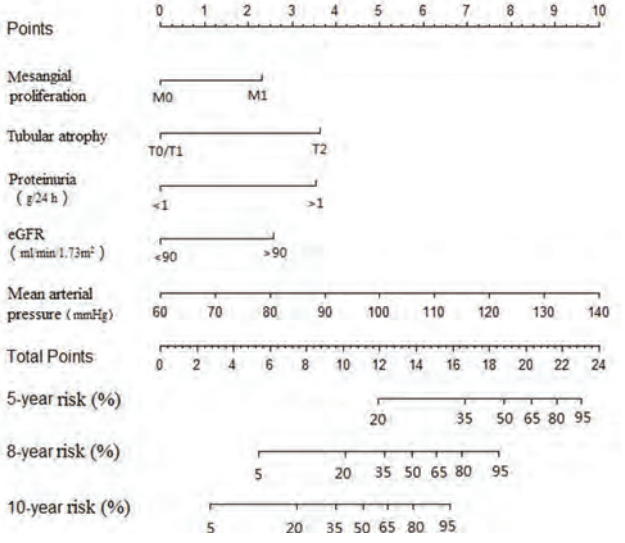
Background: IgA nephropathy(IgAN) shows strong heterogeneity between individuals. The prognosis of IgAN is associated with lesions of Oxford classification and many clinical indicators. However, simple tools for evaluating the prognosis for clinician remains limited. Our objective was to develop an intuitive estimation tool for predicting the prognosis of IgAN.

Methods: Patients with IgAN diagnosed by renal biopsy at Chinese PLA General Hospital were retrospectively analyzed. The endpoint was a decrease in estimate Glomerular filtration rate (eGFR)≥50% or progression to end-stage renal disease(ESRD). Multivariate COX proportional hazards model with backward stepwise were performed. Using COX regression coefficients, nomograms was developed to predict the risk of endpoint events.

Results: In the modeling cohort, 48 among 274 patients developed into endpoints during 81 months followed- up. Nomograms was established, of which mesangial lesions, tubulointerstitial lesions as well as baseline 24h urinary protein content>1g, baseline eGFR<90ml/min/1.73m^2 and baseline mean arterial pressure were included. Additional 117 IgAN patients were retrospectively followed as validation cohort at a mean of 79 months.[s1] The nomograms showed good discrimination and goodness of fit in the modeling cohort (C-index=0.86,r^2=0.75) and in the validation cohort (C-index=0.89,r^2=0.72) respectively.

Conclusions: The nomograms involving clinical and pathological parameters can predict the prognosis of IgAN effectively and intuitively

Funding: Government Support - Non-U.S.



nomograms for risk of endpoints

SA-PO402

Impact of Inter-Laboratory Variability of Serum Creatinine Assays on KFRE Risk Scores Divyanshi Jalan,[1] Elizabeth S. Lee,[2] Christine P. Collier,[3] Ayub Akbari,[4] Christine A. White.[3] *[1]Queen's University School of Medicine, Kingston, ON, Canada; [2]University of British Columbia, Vancouver, BC, Canada; [3]Queen's University, Kingston, ON, Canada; [4]University of Ottawa, Ottawa, ON, Canada.*

Background: Inter-laboratory variation in creatinine (Cr) measurement exist and result in inter-laboratory variability in eGFR-EPI and chronic kidney disease (CKD) diagnosis. We aim to examine the impact of inter-laboratory variability in Cr measurement on the Kidney Function Risk Equation (KFRE).

Methods: Split serum samples from 33 patients with eGFR-EPI between 10 and 60 ml/min/1.73m^2 were sent to 12 laboratories for Cr measurement. For each patient and laboratory we calculated the 5 year risk of ESKD using the KFRE equation (KFRE-5) assuming 65 year old non-African American woman and three ACR levels (27, 266, 885 mg/g). For each patient and ACR value we calculated the KFRE-5 all method mean (AMM), coefficient of variation (CV_a) and range. For the cohort, we determined the mean KFRE-5 range, CV_a and the mean ratio of minimum and maximum KFRE-5 scores.

Results: Figure 1 shows individual patients' mean, minimum and maximum KFRE-5 scores (ACR 266 mg/g). There is substantial variability in KFRE scores which are more pronounced with higher albuminuria and when KFRE values are between 5% and 80% [Table 1, Figure 1].

Conclusions: Inter-laboratory variability of serum Cr measurement results in variability in KFRE scores which is more pronounced when eGFR is moderately-severely reduced and ACR is high. This needs to be considered when using KFRE cut-offs for referrals, clinic discharge, vascular access placement and suitability for CKD funding. Manufacturers need to improve assay specificity in order to reduce KFRE variability between laboratories.

Funding: Private Foundation Support

Table 1: Mean ± SD KFRE-5 range and max/min ratios

	ACR 27 mg/g	ACR 266 mg/g	ACR 885 mg/g
KFRE-5 range (mean ± SD) (%)	2.9 ± 2.4	6.3 ± 4.5	8.4 ± 5.7
KFRE-5 CVa (mean ± SD) (%)	20.8 ± 11.3	19.9 ± 11.6	19.0 ± 12.0
KFRE-5 max/min (mean ± SD)	2.4 ± 1.2	2.3 ± 1.2	2.3 ± 1.2

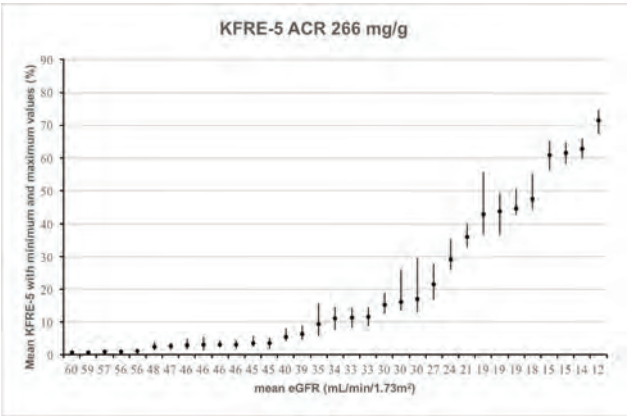


Figure 1: Individual patients' mean, minimum and maximum KFRE-5 scores (ACR 266 mg/g)

SA-PO403

GFR Measurement Method: A Critical Determinant in Estimation Equation Assessment Céline M. Allen,[1] Ayub Akbari,[2] Greg A. Knoll,[2] Christine P. Collier,[1] Christine A. White.[1] *[1]Queen's University, Kingston, ON, Canada; [2]University of Ottawa, Ottawa, ON, Canada.*

Background: Multiple equations exist to translate various serum analyte concentrations into estimates of the glomerular filtration rate (eGFR). Validation studies of these estimates often yield differing results. This is likely the result of differing patient populations and characteristics, analyte assay manufacturer biases, and GFR measurement protocols. This study was designed to examine the impact of GFR measurement methodology on the performance of the creatinine CKD-EPI equation (eGFRCr-EPI).

Methods: Cr was measured and eGFRCr-EPI calculated in 85 research subjects. GFR was measured (mGFR) simultaneously using different methodologies: renal inulin clearance, plasma ^{99m}Tc-DTPA clearance (2-4 hour sampling), plasma iohexol clearance (2-4 hour sampling) and plasma iohexol clearance (2-10 hour sampling). For each method, bias (eGFR - mGFR), precision (standard deviation of mean bias) and accuracy (P30-the percent of all eGFRCr-EPI within 30% of the mGFR) were determined. Bias and accuracies were compared using paired t-tests and McNemar's test respectively.

Results: Mean age 60 ± 14 yrs, mean BSA 1.98 ± 0.30 m^2, 95% non-black and 40% female sex. Mean inulin GFR 39.3 ± 28.8 ml/min/1.73m^2 while mean eGFRCr-EPI was 38.7 ± 28.5 ml/min/1.73m^2. Performance results are shown in Table 1.

Conclusions: eGFRCr-EPI performance results differ significantly depending on how GFR is measured (tracer, clearance strategy and sample timing). Short plasma-based strategies yield the highest biases and worse accuracies for the eGFRcr-EPI equation. These discrepancies need to be considered when interpreting validation data and designing validation studies.

Funding: Government Support - Non-U.S.

Table 1: eGFRCr-EPI performance by GFR methodology

	Mean Bias (ml/min/1.73m^2)	Precision (IQR) (ml/min/1.73m^2)	Accuracy: P30 (%)
mGFR-renal inulin	-0.5	8.8	79
mGFR-plasma DTPA (2-4 hour)	-8.3 *	13.6	57 $^{\beta}$
mGFR-plasma iohexol (2-4 hour)	-5.5 *	11.8	59 $^{\delta}$
mGFR-plasma iohexol (2-10 hour)	-2.1 **	9.6	79

* p = 0.0001 compared to inulin, ** p = 0.08 (NS) compared to inulin, $^{\beta}$ p = 0.0012 compared to inulin, $^{\delta}$ p = 0.006 compared to inulin

SA-PO404

The Spectrum of CKD in China: A National Study Based on 64.7 Million Hospitalized Patients from 2010 to 2015 Yu-ming Huang,[3] Damin Xu,[3] Jianyan Long,[1] Ying Shi,[1] Luxia Zhang,[3] Haibo Wang,[1] Adeera Levin,[2] Ming Hui Zhao.[3] *[1]China Standard Medical Information Research Center, Shenzhen, China; [2]St. Paul's Hospital and University of British Columbia, Vancouver, BC, Canada; [3]Renal Division, Peking University First Hospital, Beijing, China.*

Background: Chronic kidney disease (CKD) is a significant public health burden worldwide. Previous studies demonstrate that diabetes exceeded glomerulonephritis and became the leading cause of CKD in China, but the transition of other causes was still unclear.

Methods: We utilized a national in-patients database covering 878 class 3 hospitals (which provide primary, secondary and tertiary care to nationwide patients) and involving 64.7 million adult patients from 2010 to 2015. The specific causes of CKD were extracted from International Classification of Diseases-10 codes of discharge diagnoses.

Results: Altogether 4.5% of hospitalized patients (1.8 million) were identified as having CKD, with an increased percentage from 2010 (3.7%) to 2015 (4.7%). Increasing trends of diabetic kidney disease and hypertensive kidney damage were observed from 2010 to 2015, especially for northern urban areas. The percentage of obstructive nephropathy also increased gradually and constituted an important cause of CKD for southern rural residents.

Conclusions: The spectrum of etiologies of CKD is changing in China, and varies over time and geographic regions.

Funding: Other NIH Support - the World Health Organization (WHO Reference 2014/435380-0); the National Key Technology R&D Program of the Ministry of Science and Technology (2011BAI10B01); the Beijing Science and Technology Committee (D131100004713007); and the University of Michigan Health System-Peking University Health Science Center Joint Institute for Translational and Clinical Research (BMU20140479), Government Support - Non-U.S.

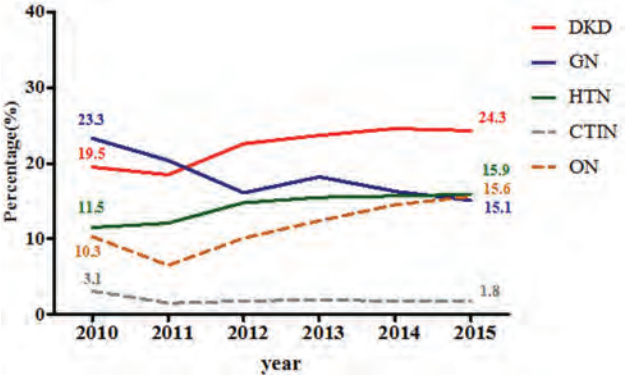


Figure 1. Trend of subgroups among hospitalized patients with CKD from 2010 to 2015

Note: DKD, chronic kidney disease with diabetes; GN, CKD due to glomerulonephritis; HTN, hypertensive kidney damage; CTIN, chronic tubulo-interstitial nephritis; ON, obstructive nephropathy.

Figure 2. Prevalence of subgroups among hospitalized patients with CKD by geographic regions in 2015

SA-PO405

Regional Differences in Prevalence and Determinants of CKD among Individuals with Hypertension in Rural Communities in South Asia Liang Feng, Tazeen H. Jafar. *Duke-NUS Medical School, Singapore, Singapore.*

Background: The objectives of the study were to determine the regional burden and differences in prevalence and determinants of chronic kidney disease (CKD) in rural Bangladesh, Pakistan, and Sri Lanka.

Methods: We conducted a cross-sectional study on 2349 participants aged ≥ 40 years with hypertension in 30 randomly selected rural communities, 10 each in Bangladesh, Pakistan, and Sri Lanka. The primary outcome was CKD defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 estimated by CKD Epidemiology Collaboration (CKD-EPI) or urinary albumin to creatinine ratio ≥ 30 mg/g

Results: The mean (SD) age of participants was 58.8 (11.3) years, and 36% were men, 27% had diabetes, and 10% were current smokers. The age-standardized prevalence (95% CI) of primary outcome of CKD was 38.4% (34.1 to 42.8%) in Bangladesh, 19.1% (15.7 to 22.5%) in Pakistan, and 49.8% (45.1 to 54.6%) in Sri Lanka. The factors independently associated with CKD were older age (OR=1.06,95%CI(1.05,1.07) for every 1 year increase), diabetes (OR=2.03,95%CI(1.63,2.52)), elevated systolic blood pressure (OR=1.06,95%CI(1.04,1.09), per 5 mm Hg increase), current vs non-smoker

(OR=1.42,95%CI(1.01,2.00)), and country (OR=0.57,95%CI(0.40,0.80) for Bangladesh vs Sri Lanka, and OR=0.18,95%CI(0.12,0.26) for Pakistan vs Sri Lanka). A significant interaction with p<0.001 was detected between age and country indicating that the association between older age and higher prevalence of CKD was stronger in Sri Lanka compared to the other two countries.

Conclusions: CKD is common among individuals with hypertension in rural South Asia with alarmingly high rates of reduced kidney function in Sri Lanka. Our findings underscore the urgency of addressing the key determinants of CKD, and establishing CKD detection and management programs as a public health priority in the South Asian region.

Funding: Government Support - Non-U.S.

Table 1. Crude prevalence of CKD (n=2349)

CKD n (%, 95% CI)	Total N=2349	Bangladesh N=818	Pakistan N=685	Sri Lanka N=796
CKD (eGFR <60 ml/min/1.73m2 or UACR≥30mg/g)	908 (38.6. (36.7,40.7))	316(36.4 (33.2,39.7))	127 (18.5 (15.6,21.5))	465 (58.4(54.9,61.9))
eGFR <60 ml/min/1.73m2 only	519 (22.1,(20.4,23.8))	102 (11.8 (9.6,14.0)	34 (5.0 (3.3,6.7))	383 (48.1 (44.6,51.7))
UACR≥30 mg/g only	573 (24.4,(22.6,26.2)	257 (29.6 (26.5,32.7))	110 (16.1 (13.2,18.9))	206 (25.9 (22.8,29.0))

SA-PO406

Prevalence of CKD in the Healthy Elderly Using the Aspirin in Reducing Events in the Elderly (ASPREE) Study Cohort Kevan Polkinghorne,[4] Rory Wolfe,[1] Robyn L. Woods,[1] John J. Mcneil,[1] Mark Nelson,[3] Christopher M. Reid,[1] Anne M. Murray.[2] *[1]Monash University, Melbourne, VIC, Australia; [2]Hennepin County Medical Center, Minneapolis, MN; [3]University Of Tasmania, Hobart, NSW, Australia; [4]Monash Medical Centre and Monash University, Melbourne, VIC, Australia. Group/Team: ASPREE investigators.*

Background: The diagnosis & definition of CKD in the elderly is controversial. GFR declines with age such that reduced eGFR is common in the elderly but may not reflect true underlying kidney related disease. The ASPREE study is an international (Australia, US) RCT designed to assess whether daily treatment with aspirin extends the duration of life free of dementia & physical disability in healthy elderly participants who are free of diagnosed cardiovascular disease or disability. Subjects with diabetes &/or hypertension (unless poorly controlled) were included. We assessed prevalence & predictors of CKD in this cohort using the MDRD and CKD-Epi eGFR equations as well as the elderly specific Berlin Initiative Study equation 1 (BIS1).

Methods: A cross sectional analysis of the ASPREE cohort at randomisation was performed. eGFR was estimated using all 3 equations. CKD was defined as eGFR<60 ml/min with or without albuminuria. CKD prevalence was calculated using each equation and compared. Predictors of CKD were assessed by logistic regression.

Results: 17,931 subjects (15,588 Australia, 2,343 USA) had complete data from urine and blood testing. Mean age was 75 years (SD 4.6), 56% were female, 76% had hypertension and 9% diabetes mellitus. Median UACR was 0.8 (IQR 0.5, 1.6) mg/mmol. Mean eGFR by CKD-Epi was 72.8 (SD 14.3) ml/min. CKD prevalence was similar by the MDRD and CKD-Epi equations (19 and 18% respectively) but substantially higher by the BIS1 equation (41%). This difference was predominantly driven by reclassification of individuals from stage 2 CKD to stage 3a without albuminuria. 69% of those with CKD by CKD-Epi had stage 3a without albuminuria compared to 75% of those using the BIS1 equation. An increased risk of CKD was related to participants being older, female, diabetic, or having higher BMI.

Conclusions: The prevalence of CKD in this healthy elderly population was 19% (CKD-Epi) and lower than previously described in the US (47% by CKD-Epi). The elderly-specific GFR equation BIS1 doubled the prevalence of CKD with the majority reclassified from stage 2 to stage 3a CKD.

Funding: Other NIH Support - National Institute on Aging and National Cancer Institute

SA-PO407

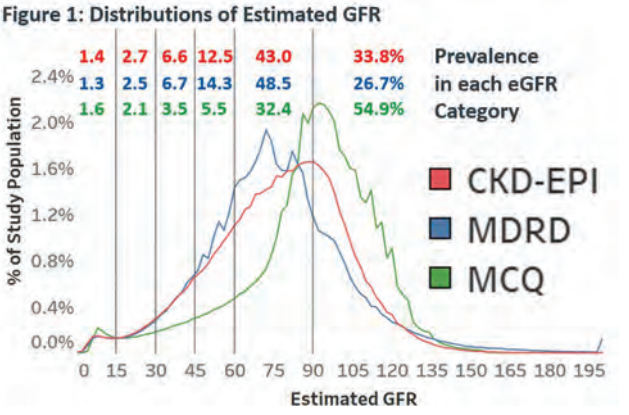
A Comparison of Different Equations for Estimating GFR in 29 US Health Care Organizations Nikita Stempniewicz,[1,2] Shoshana Ballew,[2,3] Elizabeth Ciemins,[1] Morgan Grams,[3,4] Kunihiro Matsushita,[2,3] Jerry Penso,[1] Josef Coresh.[2,3] *[1]AMGA, Alexandria, VA; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [3]Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; [4]Johns Hopkins School of Medicine, Baltimore, MD.*

Background: The KDIGO 2012 guidelines recommend reporting eGFRcreat in adults using the 2009 CKD-EPI creatinine equation to diagnose and stages CKD with known risk relationships. Some health care organizations use different equations, with common alternatives being the MDRD and Mayo Clinic Quadratic (MCQ). Electronic heath record (EHR) data provide the opportunity to estimate the impact of using these three common equations to estimate GFR to a health care organization and its patient population.

Methods: This study uses EHR data from 29 AMGA member organizations who are using the Optum One population health analytics platform. Data from 2.3 million patients age 18-99, with a history of hyperglycemia, at least 1 ambulatory office visit, and a serum creatinine recorded between 01/01/2013 and 12/31/2016 were included. Estimated GFR was calculated for each patient using the CKD-EPI, MDRD, and MCQ equations.

Results: The 2.3 million patients had mean age 62.3 years, were 52.8% female, 10.7% black race, and 51.1% had a diagnosis of type 2 diabetes (on a claim or the patients problem list in the EHR). The average (standard deviation) eGFR from the CKD-EPI, MDRD, and MCQ equations were 77.4 (25.4), 76.3 (28.9), and 88.8 (25.4) mL/min/1.73 m^2, respectively. Distributions of eGFR for the three equations differed markedly (Figure 1). In the CKD G3+ range (<60 ml/min/1.73m^2) the MCQ estimates gave a much lower prevalence compared to the CKD-EPI and MDRD equations (23.2 and 24.8 vs. 12.7%, summing the prevalence in range below 60 in Figure 1). Only 48.7% of patients were classified in the same CKD GFR categories with all three equations.

Conclusions: Compared to the CKD-EPI equation which is currently recommended and stages CKD with a known relationship to risk, the MDRD equation produces similar results at low eGFR, while the MCQ equation yields a dramatically lower prevalence of CKD.



SA-PO408

Creatinine versus Cystatin C: Is There Any Benefit in Using a Cystatin C Based Equation for Assessment of CKD in Older Adults? Shahrzad Zonoozi,[2] Sheena E. Ramsay,[1] Olia Papacosta,[2] Peter Whincup,[3] Sasiwarang G. Wannamethee.[2] *[1]Newcastle University, Newcastle Upon Tyne, United Kingdom; [2]University College London, London, United Kingdom; [3]SGUL, London, United Kingdom.*

Background: Chronic kidney disease (CKD) is associated with excess cardiovascular disease (CVD) mortality and morbidity. CKD diagnosis relies on calculation of the estimated glomerular filtration rate (eGFR) commonly based on serum creatinine which may lead to inaccurate estimations of GFR in the older population. Cystatin C is an alternative GFR marker less influenced by exogenous factors and the CKD Epidemiology Collaboration (CKD-EPI) has developed an equation for estimating GFR using this marker (CKD-EPI$_{Cys}$). Whether this is a better indicator of CVD risk and mortality in older adults than the CKD-EPI creatinine-based equation (CKD-EPI$_{Cr}$) is unclear. We have investigated the association between CKD classification, using CKD-EPI$_{Cr}$ and CKD-EPI$_{Cys}$, and cardiovascular risk markers and CVD mortality in older adults.

Methods: Prospective and cross-sectional analysis of 1722 men aged 71-92 examined in 2010-2012 across 24 British towns, from the British Regional Heart Study initiated in 1978-1980, followed up for a median of 5 years for CVD and all-cause mortality. Participants completed a questionnaire, underwent a physical examination and had blood samples taken.

Results: The prevalence of CKD stages 1, 4 and 5 was increased in our population using CKD-EPI$_{Cys}$ versus CKD-EPI$_{Cr}$ to calculate eGFR. Both CKD equations were significantly associated with markers of inflammation (C-reactive protein), endothelial function (von Willebrand factor) and cardiac function (N-terminal pro brain natriuretic peptide). The hazard ratio (HR) for all CVD mortality in those with CKD stages 4 and 5 versus those with CKD stages 1 and 2 was 3.05 (95% CI, 1.63-5.70) and 3.62 (95% CI, 2.08-6.30) using CKD-EPI$_{Cr}$ and CKD-EPI$_{Cys}$ respectively. For all-cause mortality the HR was 2.30 (95% CI, 1.60-3.32) and 2.57 (95% CI, 1.87-3.54) using CKD-EPI$_{Cr}$ and CKD-EPI$_{Cys}$ respectively.

Conclusions: Estimating GFR using CKD-EPI$_{Cys}$ leads to reclassification of CKD staging and increased prevalence of CKD stages 1, 4 and 5 compared to CKD-EPI$_{Cr}$. Our study shows that compared to CKD-EPI$_{Cr}$, CKD-EPI$_{Cys}$ shows no improvement in the prediction of all-cause and CVD mortality in older British men. In view of the drive to use cystatin-c based equations in clinical practice, this may have important cost implications.

Funding: Private Foundation Support

SA-PO409

Comparison of eGFR with Creatinine and Cystatin C by eCKD-EPI in CKD Patients with and without Hypoalbuminemia Carlos Federico Varela,[1] Graciela Jimenez,[1] Griselda Bratti,[1] Maria L. Ocampo,[2] Gustavo Greloni,[1] Guillermo Rosa Diez.[1] *[1]Nephrology, Hospital Italiano de Buenos Aires, CABA, Argentina; [2]Nephrology, Hospital Italiano Buenos Aires, CABA, Argentina.*

Background: Serum cystatine C (CysC) could be a better predictor than serum creatinine (Crea) in comorbid patients with CKD. Differences between CysC and Crea eGFR in patients with and without hypoalbuminemia (hypoA) were poorly understood/studied. We compare average differences between eGFR based on CysC and Crea in patients with and without hypoalbuminemia.

Methods: We estimated GFR by the new CKD-EPI equations based on CysC and Crea The CKD stage was determined by the Crea-based eGFR. HypoA was defining by serum albumin ≤ 3.5 gr/L. In each CKD stage, differences between average of CysC and Crea-based equation and concordance to assign to the same CKD stage were calculated. We performed the same analysis in patients with and without hypoA.

Results: We included 1954 patients, (46.5% female) aging 63±18 years. 50.9% were elderly. Mean Crea, CysC and serum albumin in total group were 1.6 ± 1.2 mg/dl, 2.1±1.1 mg/dl and 3.5±0.6 gr/L respectively. Mean of eGFR of Crea was 54.8± 28 and CysC was 38.9±25 ml/min/1.73. Mean differences between eGFR of Crea and CysC were 34.9, 21.5, 14.2, 10.1, 5.5, -0.9 ml/min/1.73 for stage 1 to 5 respectively in total group. Serum albumin was 2.8±0.4 and 3.9±0.3 gr/L in patients with and without hypoA. Patients with hypoA had significantly differences between mean eGFR of Crea and CysC compared with those without hypoA, showing 48 vs 17 in stage1, 31 vs 15 in stage 2, 19 vs 11 in stage 3A, 13 vs 8 in stage 3B, 6 vs 4 in stage 4 and -0.9 vs -0.8 in stage 5. All differences except stage 5 were significant.

Conclusions: Differences between eGFR in CysC and Crea-based equation could be affected in the setting of low serum albumin values. Patients with hypoA show highest differences.

Table: 1. Characteristics of the study population.

CKD stage	1	2	3A	3B	4	5
Serum Creatinine	0.72 (0.17)	0.96 (0.20)	1.26 (0.21)	1.66 (0.33)	2.62 (0.66)	5.46 (1.73)
Serum Cystatine C	1.23 (0.46)	1.45 (0.48)	1.82 (0.61)	2.29 (0.72)	3.29 (0.95)	4.48 (1.01)
CKD-EPI-Crea	105.2 (14.1)	73.1 (8.8)	51.8 (4.3)	37.5 (4.2)	22.5 (4.5)	10.1 (2.8)
CKD-EPI-CysC	70.3 (28.8)	51.6 (21.3)	37.6 (14.8)	27.4 (10.7)	16.9 (6.1)	11.1 (3.5)
Concordance Crea vs CysC	38.8 %	46.7 %	68.9 %	80.1 %	49.1 %	44.8 %
Diff hypoalbuminemia	48 (±23)	31 (±16)	19 (±12)	13 (1±0)	6 (±6)	-0.9 (±3)
Diff without hypoalbuminemia	17 (±23) °°	15 (±20) °°	11 (±14) °°	8 (±9) °°	4 (±5) °	-0.8 (±3)

References:. °°; p value < 0.001 and °; p value < 0.05 between patients with and without hypoA.

SA-PO410

Estimated Glomerular Filtration Rate by Serum Creatinine Lacks Accuracy and Precision in Older Adults with and without Type 1 Diabetes: Results from the Canadian Study of Longevity in Type 1 Diabetes Daniel Scarr,[3] Leif E. Lovblom,[3] Petter Bjornstad,[1] Julie A. Lovshin,[4] Mohammed A. Farooqi,[3] Genevieve Boulet,[3] Andrej Orszag,[3] Yuliya Lytvyn,[4] Alanna Weisman,[3] Hillary A. Keenan,[2] Michael Brent,[4] Narinder Paul,[4] Vera Bril,[4] David Cherney,[4] Bruce A. Perkins.[4] *[1]Children's Hospital Colorado, Aurora, CO; [2]Joslin Diabetes Center, Boston, MA; [3]Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, ON, Canada; [4]University of Toronto, Toronto, ON, Canada.*

Background: Estimates of glomerular filtration rate (eGFR) by serum creatinine are routinely used for clinical assessment of kidney function, however eGFR is considered inaccurate until GFR <60mL/min/1.73m². Accurate ascertainment of eGFR is important to identify kidney disease. We aimed to evaluate the performance of creatinine-based equations compared to GFR by inulin clearance in older adults with and without type 1 diabetes (T1D).

Methods: Sixty-six adults with ≥50yr T1D duration and 73 non-diabetic controls from age/sex-matched subgroups (65±8yr and 77[55%] were female) underwent measurement of GFR by inulin clearance (mGFR) and eGFR was calculated by serum creatinine using the MDRD ($eGFR_{MDRD}$) and CKD-EPI ($eGFR_{CKD-EPI}$) equations. In T1D, eGFR and mGFR were measured under clamped euglycemia (4-6mmol/L). Equation performance was evaluated using bias (mean difference), precision (SD), and accuracy (inaccuracy defined as the proportion of eGFR that differed by >20% of mGFR) metrics.

Results: In the 139 participants mean mGFR was 104±18mL/min/1.73m² (range: 70-154mL/min/1.73m²) and was not different between T1D (103±17mL/min/1.73m²) and controls (105±19mL/min/1.73m², p=0.39). Both equations significantly underestimated mGFR with bias –14.9mL/min/1.73m² (p<0.001) for $eGFR_{MDRD}$ and –15.9mL/min/1.73m² for $eGFR_{CKD-EPI}$ (p<0.001); bias was similar between equations (p=0.15). Precision was similar between $eGFR_{MDRD}$ (SD 17.2mL/min/1.73m²) and $eGFR_{CKD-EPI}$ (SD 16.5mL/min/1.73m², p=0.63). Inaccuracy was similar between $eGFR_{MDRD}$ (32.4%) and $eGFR_{CKD-EPI}$ (37.4%, p=0.13). Both equations demonstrated greater bias and were less accurate across higher ranges of mGFR (60-89, 90-119, and ≥120mL/min/1.73m², p<0.001 for all comparisons). Results were similar between T1D and controls.

Conclusions: Creatinine-based eGFR substantially underestimated mGFR, lacked precision and accuracy, and had lower performance at higher ranges of mGFR. Better measures of kidney function in older adults are needed for research and clinical practice.

SA-PO411

Prediction of Mortality in Elderly Patients with CKD – The Role of Cystatin C and Other GFR Markers Sebastjan Bevc,[1,3] Nina Hojs,[1,3] Masa Knehtl,[1,3] Robert Ekart,[2,3] Radovan Hojs.[1,3] *[1]Department of Nephrology, University Clinical Centre Maribor, Maribor, Slovenia; [2]Department of Dialysis, UKC Maribor, Maribor, Slovenia; [3]Faculty of Medicine, University of Maribor, Maribor, Slovenia.*

Background: The prevalence of chronic kidney disease (CKD) in the elderly is high. Serum cystatin C is accurate marker of kidney function and has also prognostic utility in CKD patients. The aim of our study was to determine the prediction of cystatin C and other markers of kidney function on long-term survival in elderly CKD patients.

Methods: 58 adult Caucasian patients, older than 65 years (50% women; mean age 73 years; range from 65 to 85 years), were included. Patients with known malignancy, on steroid therapy and/or thyroid disease were not enrolled in the study. In each patient ^{51}CrEDTA clearance, serum creatinine (IDMS traceable method), serum cystatin C (immunonephelometric method) and eGFR using three formulas (CKD-EPI creatinine, BIS2 and FAS) were determined on the same day and patients were then followed for 11 years or until their death.

Results: The means: ^{51}CrEDTA clearance 53.3±17.4 ml/min/1.73m², serum creatinine 143.4±44 μmol/l, serum cystatin C 1.79±0.5 mg/l, CKD-EPI creatinine 40.3±14.2, BIS2 39.3±10.9, FAS 31±10.4 ml/min/1.73m², respectively. In the follow up period of 11 years 47 (81%) of our elderly CKD patients (23 women and 24 men) died. Cox regression analysis showed different hazard ratios (HR) for death: for ^{51}CrEDTA clearance HR 0.978 (95% CI 0.960-0.996; P=0.015), serum creatinine HR 1.013 (95% CI 1.006-1.019; P<0.001), serum cystatin C HR 2.028 (95% CI 1.269-3.241; P=0.003), CKD-EPI creatinine HR 0.953 (95% CI 0.928-0.980; P=0.001), BIS2 HR 0.947 (95% CI 0.918-0.977; P=0.001), FAS HR 0.946 (95% CI 0.914-0.979; P=0.002).

Conclusions: Our results showed the highest hazard ratio for serum cystatin C values among the markers of kidney function for prediction of the outcome in elderly CKD patients.

SA-PO412

Metabolites Associated to Renal Function in the CKD and General Population Silvia M. Titan,[1] Gabriela Venturini,[4] Kallyandra Padilha,[4] Gesiane F. Tavares,[1] Isabela M. Bensenor,[3] Paulo Lotufo,[3] Eugene P. Rhee,[2] Ravi I. Thadhani,[2] Alexandre C. Pereira.[4] *[1]Nephrology Division, Faculty of Medicine, Sao Paulo University, Sao Paulo, Brazil; [2]Nephrology Division, Massachusetts General Hospital, Boston, MA; [3]Clinical Research Center, Universitary Hospital, Sao Paulo University, Sao Paulo, Brazil; [4]Laboratório de Cardiologia Molecular, Incor, Hospital das Clínicas, Faculty of Medicine, University of Sao Paulo, Sao Paulo, Brazil.*

Background: Metabolomics is a novel tool to identify biomarkers and pathways involved in diseases. In CKD, there is a growing interest in metabolites that are related to renal function that could be used for assessing GFR. However, data is scarce and diverse. **Objective:** To evaluate metabolites related to eGFR in a CKD Study. Replication was tested in 2 other studies using the same metabolomics platform.

Methods: Derivation study was the Progredir Study (PS; n=454 class 3 and 4 CKD). Validation studies were Diabetic Nephropathy Study (DNS; n=56 macroalbuminuric DN) and the Baependi Study (BS; n=1145p from the general population). Metabolomics was performed by GC and Mass Spectrometry. Metabolites were identified using Agilent Fiehn GC/MS Metabolomics and NIST libraries (Agilent MassHunter Work-station Quantitative Analysis, version B.06.00). Adjusted linear regression models on eGFR-CKDEPI were built. FDR<0,05 was used in the derivation study.

Results: In the PS, 135 metabolites where related to eGFR, after adjustments for batch, sex, age, DM, smoking and SBP. Of those, 24 were also related to eGFR in the BS and 17 in the DNS. However, only 6 metabolites were significantly related to eGFR in all 3 studies: D-threitol, myo-inositol, ribitol, 4-deoxierythronic acid, galactonic acid and galacturonic acid. While correlation to eGFR was high in the 2 CKD studies, it was moderate in the general population (Table 1).

Conclusions: Our results demonstrate that metabolites are potential markers of renal function. Further investigation is needed to determine their performance against otherwise gold-standard methods, most notably among those with normal eGFR.

Funding: Government Support - Non-U.S.

Table 1. Spearman's correlation coefficients and p values for metabolites and eGFR in the 3 studies.

Metabolite (log2)	PS	DNS	BS
Replicated in the 3 studies			
D-threitol	-0.71 / 8.7E-70	-0.80 / 9.6E-14	-0.28 / 1.6E-21
Myo-inositol	-0.70 / 4.9E-66	-0.81 / 5.4E-14	-0.19 / 2.0E-11
Galactonic acid	-0.61 / 5.7E-19	-0.47 / 2.8E-04	-0.23 / 2.8E-05
Galacturonic acid	-0.47 / 6.1E-15	-0.58 / 9.3E-06	-0.23 / 9.0E-11
4-Deoxyerythronic acid	-0.38 / 7.9E-17	-0.56 / 2.5E-05	-0.02 / 0.51
Ribitol	-0.36 / 3.0E-8	-0.81 / 7.7E-13	-0.28 / 8.0E-22
Replicated only in the CKD studies			
Pseudo uridine	-0.71 / 1.26E-65	-0.86 / 3.8E-17	-0.08 / 0.01
Butyric acid	-0.67 / 8.26E-53	-0.60 / 1.6E-05	-

SA-PO413

A Novel Equation Using Low-Invasive Test Items to Estimate the Severity of Interstitial Fibrosis in IgA Nephropathy Keita Inui,[1] Kosuke Yamaka,[1] Yosuke Yamada,[1] Yuji Kamijo.[2] *[1]Shinshu University, Matsumoto, Japan; [2]Shinshu University School of Medicine, Matsumoto, Japan.*

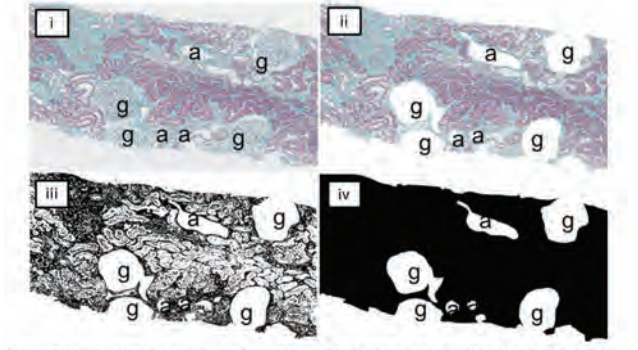
Background: In IgA nephropathy, tubulointerstitial fibrosis is said to be very important in predicting whether or not renal dysfunction is progressive. Until now, however, invasive renal biopsy has been the primary means of determining the severity of fibrosis in IgA nephropathy. A formula to estimate tubulointerstitial fibrosis severity using such low-invasive parameters as physical findings, serology, and urinalysis is therefore needed.

Methods: Masson Trichrome-stained renal biopsy specimens of 51 patients diagnosed as having IgA nephropathy at Shinshu University Hospital were collected. The severity of interstitial fibrosis as calculated by the percentage of area stained blue in the cortex tubulointerstitium (Fib%) was quantitatively measured by ImageJ analysis software (Figure) and its correlation with various factors was examined. A formula for estimating interstitial fibrosis was then derived by multiple regression analysis using parameters whose correlation with Fib% was strong.

Results: Fib% increased proportionally to Oxford classification T-score ($P<0.001$) and accurately reflected the severity of interstitial fibrosis. Fib% also correlated strongly with serum creatinine (sCre) (mg/dL) (correlation coefficient [R]: 0.61; $P<0.01$), urinary N-acetyl-β-D-glucosaminidase (uNAG) (U/gCre) (R: 0.44; $P<0.01$), and body mass index (BMI) (kg/m^2) (R: 0.44; $P<0.01$). The estimation formula of Fib% from these 3 parameters was determined as: Fib% = 16.84 + 17.71(sCre) + 0.51(BMI) + 0.59(uNAG) (coefficient of determination: 0.53; $P<0.01$).

Conclusions: Interstitial fibrosis in IgA nephropathy can be estimated using data obtained from low-invasive tests. A prospective study is being planned to validate our novel formula.

Figure



i) a, artery; g, glomerulus. ii) Parts containing arteries and glomeruli are removed. iii) Parts of blue-stained areas were detected and area was calculated. iv) The area of all tubulointerstitial parts was calculated. Fib% = area iii/area iv × 100%

SA-PO414

Prediction of Urinary Creatinine Excretion and of Renal Function in CKD Patients from Body Composition Analysis Carlo Donadio. *University of Pisa, Pisa, Italy.*

Background: The utility of creatinine clearance (CCr) to measure renal function is greatly reduced by its low accuracy and by the need for a timed collection of urine. Different formulas have been proposed to predict CCr or GFR from serum creatinine (PCr) and anthropometric data. However, the inaccuracy in the estimate of urinary creatinine excretion (UCr) is probably the major cause of error of prediction formulas. The aim of this study was to evaluate the possibility to obtain a more accurate prediction of UCr, and hence of CCr from the measure of body cell mass (BCM). BCM is the body compartment which contains muscle mass, where creatinine is generated.

Methods: Two-hundred and eleven CKD patients (115 women), aged 17-81 years, PCr 0.5-14.4 mg/dL. Glomerular filtration rate (GFR) was measured in all patients as the renal clearance of 99mTc-DTPA. The other examined parameters were: PCr; UCr (urine collection 24 hrs); CCr measured as UCr x V / PCr (m-CCr); CCr predicted by Cockcroft and Gault formula (C&G-CCr). BCM was measured using a single frequency tetrapolar impedance analyzer.

Results: GFR was 1.3-147 mL/min (mean 55.1), mCCr 3.7-135 mL/min (mean 61.2), 24h-UCr 416-2102 mg (mean 1075), BCM 12.2-45.2 kg (mean 23.7). A strict linear correlation was found between 24h-UCr and BCM (r=0.780), which was closer than that between 24h-UCr and BW (r=0.626). Multiple linear regression (MR) modeling for urinary creatinine excretion indicated that UCr was determined positively by BCM, body weight, male gender and height, and negatively by age and PCr. The most relevant determinants of UCr were BCM, age, and PCr. UCr predicted from MR equation (MR-UCr) ranged 378-1856 mg (mean 1075) quite similar to measured 24h-UCr. MR-BCM-CCr, that is CCr predicted from MR-UCr and PCr, was very similar to measured CCr (61.5±32.0 VS 61.2±32.1 mL/min, NS), with a closer correlation than C&G CCr (r= 0.940 VS 0.857) and a lower prediction error (11.1 VS 13.0 mL/min). The concordance between MR-BCM-CCr and mCCr was better than that of C&G CCr.

Conclusions: In CKD patients at the different stages of GFR impairment, urinary creatinine excretion can be more accurately estimated, and creatinine clearance can be predicted from the value of body cell mass combined with other anthropometric data and with serum creatinine.

Funding: Government Support - Non-U.S.

SA-PO415

Usefulness of Repeated Measurement of Casual Urine Sodium-to-Potassium Ratio in Patients with CKD Yuka Okuyama,[2] Haruhito A. Uchida,[1] Toshiyuki Iwahori,[4] Hidemi Takeuchi,[2] Nozomu Otaka,[2] Masashi Kitagawa,[3] Hitoshi Sugiyama,[3] Katsuyuki Miura,[4] Hirotsugu Ueshima and EPOCH-JAPAN Group,[4] Jun Wada.[1] *[1]Okayama Univeristy, Okayama, Japan; [2]Okayama University, Okayama, Japan; [3]Okayama University Graduate School, Okayama, Japan; [4]Shiga University of Medical Science, Otsu, Shiga, Japan.*

Background: Lowering sodium-to-potassium ratio has been reported to benefit people for hypertension prevention and control in epidemiological studies. Four to seven repeated measurements of casual urine sodium-to-potassium ratio is known to provide high correlation and good agreement quality with less bias to estimate 7-day 24-hour urinary Na/K ratio in normotensive and hypertensive individuals. However, little is known about urinary Na/K ratio in patients with chronic kidney disease (CKD). The aim of this study was to clarify the relationship of the repeated measurement of casual and 24-hour urinary sodium-to-potassium ratio in patients with CKD.

Methods: A total of 61 inpatients with CKD, 31 in stage 1-3 (eGFR ≥ 30 ml/min/1.73m^2) and 30 in stage 4-5 (eGFR < 30 ml/min/1.73m^2), aged 20 to 85 under low-sodium diet (NaCl 6 g/day) were recruited in Okayama University hospital. Na/K ratio in casual urine at 4 points/day (first void after rising, each urine after breakfast, lunch or dinner) for 2 days and 2-day 24-hr urine at the same day were measured. Correlation and the quality of agreement by Bland and Altman between casual urine and 24-hour urine samples were analyzed.

Results: Mean 24-hour Na and K excretion was lower in participants in stage 4-5 (Na: 87.5 mmol/24h, K: 18.8 mmol/24h) than in participants in stage 1-3 (Na: 99.0 mmol/24h, K: 26.1 mmol/24h), whereas mean 24-hour urine Na/K ratio was higher in participants in stage 4-5 (5.1) than in participants in stage 1-3 (4.1). Casual urine Na/K ratio was strongly correlated with 2-day 24-hour urinary Na/K ratio by sampling 2 casual urine specimens per day for 2 days in participants in stage 1-3 (r = 0.69-0.78), but not in stage 4-5 (r = 0.12-0.19). The bias for mean Na/K ratio between 2-day 24-hour urine and sampling 2 casual urine per day for 2 days in participants in stage 1-3 ranged from -0.86 to 0.16, and the quality of agreement for the mean of this casual urine sampling was similar to that of all 8 points of casual urine samples for estimating 2-day 24-hour values.

Conclusions: Repeated casual urine Na/K ratio measurement is useful to estimate 24-hour urine Na/K ratio in stage 1-3 CKD patients as well as normotensive and hypertensive people; however, not in stage 4-5 CKD patients.

SA-PO416

Metabolic Syndrome, Inflammation, and Risk of Developing CKD in Rheumatoid Arthritis Masako Kochi, Kentaro Kohagura, Yusuke Ohya. *University of the Ryukyus, Nishihara-cho, Japan.*

Background: Inflammation is a risk factor for progression of CKD in patients with rheumatoid arthritis (RA) as well as general population. High incidence of metabolic syndrome (MetS) has been reported in RA. MetS is associated with both inflammation and developing CKD. However, the combined effects of MetS and inflammation on the risk of developing CKD are not known in RA. This study aims to examine the relationship between MetS, C-reactive protein (CRP; a marker of inflammation), and the incidence of CKD in RA patients.

Methods: We retrospectively examined a total of 345 RA patients. The outcome of interest was incidence of CKD which was defined as an eGFR<60 mL/min/1.73 m^2 and/or positive dipstick testing for proteinuria for ≥3 months. MetS was defined as the presence of ≥3 of the following criteria: obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol, high blood pressure, and high fasting glucose level. CRP was used as an inflammation marker, and a high CRP was defined as persistently CRP value of >3 mg/L during the first 6 months of follow-up. Patients were categorized into four subgroups by the presence of MetS and high CRP at baseline: non-MetS with low CRP, non-MetS with high CRP, MetS with low CRP, and MetS with high CRP.

Results: Mean baseline patient age was 57 years, and mean eGFR was 87 ml/minute/1.73 m^2. Over a median follow-up of 8 years, 47 (14%) patients developed CKD. MetS and high CRP were independently associated with the incidence of CKD,respectively. Subgroup analysis showed that the cumulative incidence of CKD was the highest in patients with MetS / high CRP group compared with all other groups ($P < 0.0001$, log-rank test). In a multivariate analysis, MetS / high CRP group was significantly associated with increased risk for incident CKD (adjusted HR, 5.35; 95% confidence interval, 2.27–12.71; $P = 0.0002$) independent of age, eGFR, and anti-RA drug uses.

Conclusions: Independent of confounding risk factors, MetS had an inflammation-augmented association with increased risk of incident CKD in patients with RA.

SA-PO417

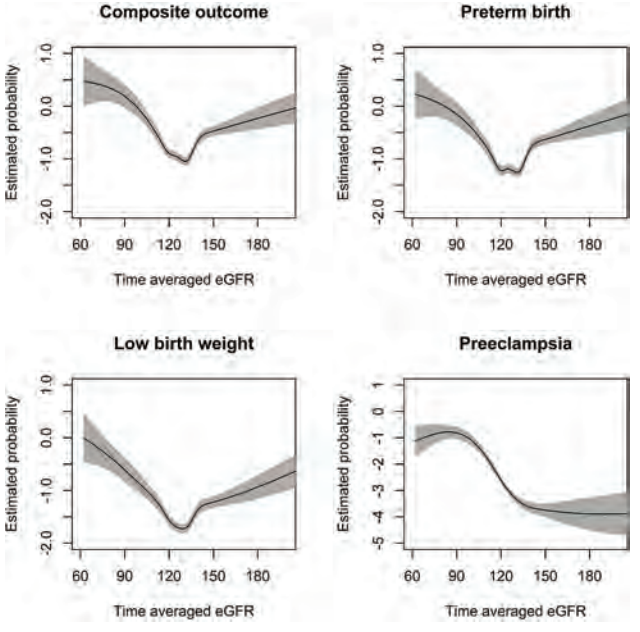
Association of Estimated Glomerular Filtration Rate and Gestational Complications Sehoon Park,[2] Ho Jun Chin,[1] Ki Young Na,[1] Dong Ki Kim,[2] Yon Su Kim,[2] Hajeong Lee.[2] *[1]Seoul National University Bundang Hospital, Seong nam, Republic of Korea; [2]Seoul National University Hospital, Jongno-gu, SEOUL, Republic of Korea.*

Background: Glomerular filtration rate elevation represents the intrarenal hemodynamic changes in pregnant women, yet, estimated glomerular filtration rate (eGFR) during gestation and its association with pregnancy outcomes remains to be investigated.

Methods: We collected pregnancy cases in two tertiary teaching hospitals in Korea from 2001 to 2015. With eGFR during pregnancy, estimated by CKD-EPI method, we calculated time-averaged eGFR considering the value as a time-dependent variable. Adverse pregnancy outcome was composition of preterm birth, low birth weight and preeclampsia.

Results: Among total of 12,900 mothers, a number of 4,028 (31.2%) mothers experienced composite adverse pregnancy outcomes. Gestational eGFR showed a non-linear U-shaped association with the risk of gestational complication, which was most prominent with the midterm eGFR values. The adjusted odds ratio (aOR) and associated 95% confidence interval of an adverse pregnancy outcome for eGFR levels below and above the reference level of 120–150 mL/min/1.73 m^2 were as follows: ≥150 mL/min/1.73 m^2, aOR 1.86 (1.56-2.22), *P*<0.001; 90–120 mL/min/1.73 m^2, aOR 1.18 (1.06-1.31), *P*=0.003; and 60–90 mL/min/1.73 m^2, aOR 1.72 (1.12-2.65), *P*=0.014. Moreover, gestational eGFR additively elevated power to predict gestational complications [AUROC with eGFR 0.733 (0.717-0.740). vs AUROC without eGFR 0.728 (0.722-0.744), *P* for AUROC comparison = 0.006].

Conclusions: We demonstrated a non-linear, U-shaped relationship between eGFR during gestation and the risk of adverse pregnancy outcome. Appropriate interpretation of eGFR values in pregnancy might be helpful for risk prediction of gestational complications.



SA-PO418

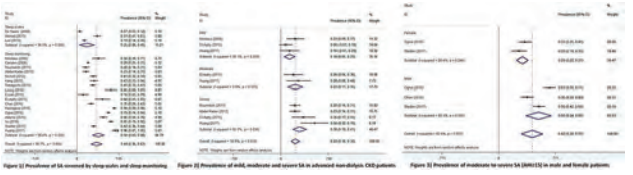
The Prevalence of Sleep Apnea in Non-Dialysis CKD Patients: A Systematic Review and Meta-Analysis Zhuo Huang, Xi Tang, Ping Fu. *Kidney Research Institute, Division of Nephrology, West China Hospital, Sichuan University, Chengdu 610041, China.*

Background: The prevalence of sleep apnea (SA) is diverse across preceding studies in chronic kidney disease (CKD) patients.

Methods: A systematic review and meta-analysis was conducted to estimate the aggregated prevalence of SA in adults with non-dialysis CKD. We searched Medline and Embase (up to April 2017) for relevant studies. The pooled prevalence of SA was calculated. Subgroup analyses based on varied means of identifying SA, different stages of CKD and gender were conducted as well. Random-effects model was employed in our meta-analysis.

Results: 20 out of 2553 studies involving 2,790 participants were included. The pooled prevalence of SA positive varied between different tools. The prevalence of SA positive screened by sleep rating scales was 25%, while the prevalence of SA diagnosed by sleep monitoring like polysomnography was 54%, which was significantly higher than that in sleep questionnaires subgroup (P for subgroup analysis=0.018; Figure 1). Besides, in studies utilizing polysomnography patients with advanced CKD may have a greater chance of suffering from severe SA (P for subgroup difference=0.082; Figure 2). In addition, subgroup analysis based on gender showed that male participants were more likely to be affected by moderate to severe SA than female participants (50% vs. 29%, P for subgroup difference =0.02: Figure 3).

Conclusions: SA is a common comorbidity in about half of non-dialysis CKD patients. Sleep rating scales underestimates the presence of SA compared with sleep monitoring. The risk of SA increases with the stages of CKD. Moreover, Male CKD patients have a higher risk for SA than female patients. It is necessary to routinely screen SA in non-dialysis CKD patients, and randomized trials using standard diagnostic criteria to identify SA are needed. More studies about effects of interventions against SA on the progression of CKD are required.



Figures for subgroup analyses

SA-PO419

Oral Iron Therapy and Serum Hepcidin in Children with CKD Ameneh Amini,[2] Richa Gautam,[2] Eduardo M. Perelstein,[2] Stefano Rivella,[1] Mary E. Choi,[2] Juhi Kumar,[2] Oleh M. Akchurin.[2] *[1]Children's Hospital of Philadelphia, Philadelphia, PA; [2]Weill Cornell College of Medicine, New York, NY.*

Background: Hepatic peptide hepcidin, a major regulator of iron homeostasis, is up-regulated in adults and children with chronic kidney disease (CKD). Hepcidin blockade ameliorates renal anemia in experimental CKD. Iron and inflammation contribute to hepcidin over-production in animal models and in adult patients with CKD. However, the relationship between oral iron therapy and hepcidin in children with CKD has not been characterized.

Methods: Cross-sectional single center study. Serum hepcidin was measured by ELISA (Intrinsic Lifesciences, USA). Clinical data were abstracted from medical records of children with stages 2-5 CKD. Platelet-to-lymphocyte ratio (PLR) was used as a marker of inflammation. Glomerular filtration rate (GFR) was estimated using bedside Schwartz formula. Normally distributed data are shown as mean±SD. T-test and linear regression were used for data analysis.

Results: Hepcidin was measured in 36 childern (60% males, median age 12.5). Hepcidin strongly correlated with serum ferritin (r=0.64, p<0.005) and modestly with total iron binding capacity (TIBC; r=-0.43, p=0.02), and GFR (r=-0.34, p=0.04). There was a trend toward correlation between hepcidin and hemoglobin (r=-0.29, nondirectional p=0.09, directional p=0.04). No significant correlation was observed between serum hepcidin and PLR (r=0.1). Oral iron therapy was prescribed to 14 children (Fe+ group) and not prescribed to 22 (Fe-). GFR was 34.6 and 47.4 mL/min/1.73m^2 in the Fe+ and Fe- groups, respectively (p=0.03). Fe+ group had lower hemoglobin compared to Fe- group (11.7±1.5 vs. 13.0±2.0, p=0.04), but similar serum iron, ferritin, TIBC, and transferrin saturation. Serum hepcidin was higher in the Fe+ group than in Fe- group (94.6±41 ng/mL vs. 44±78, p=0.015). This difference remained significant after adjusting for age, sex, CKD etiology (glomerular vs. non-glomerular) and PLR (adjusted p=0.017), and was attenuated after additional adjustment for GFR (adjusted p=0.05).

Conclusions: In this pediatric CKD cohort, serum hepcidin was associated with iron therapy status, independently of PLR. Additional analyses of inflammatory markers in this cohort are ongoing. Further investigations of the impact of iron-mediated hepcidin elevation on clinically relevant outcomes in childern with CKD are warranted.

SA-PO420

Assessment of Renal Impairment on the Prognosis of Newly Diagnosed Multiple Myeloma Veronica T. Costa e Silva,[7] Elerson Costalonga,[3] Marcella M. Frediani,[1] Renato A. Caires,[7] Fernanda O. Coelho,[2] Emmanuel A. Burdmann,[6] Antonio A. Portela Neto,[5] Adriel G. Silva.[4] *[1]HC-FMUSP, Sao Paulo, Brazil; [2]None, São Paulo, Brazil; [3]School of Medicine, University of Sao Paulo, São Paulo, Brazil; [4]USP, São Paulo, Brazil; [5]University State of São Paulo, São Paulo, Brazil; [6]University of Sao Paulo Medical School, Sao Paulo, Brazil; [7]University of Sao Paulo School of Medicine, Sao Paulo, Brazil.*

Background: Severe Renal Impairment (RI) is associated with early death in patients (pts) with multiple myeloma (MM). The new criteria from the International Myeloma Working Group (IMWG) defined RI as serum creatinine (SCr) > 2.0 mg/dL or estimated glomerular filtration rate (eGFR) < 40 ml/min/1.73 m^2. If these definitions are associated to overall survival (OS) is still debatable.

Methods: All pts with newly diagnosed MM (up to three months) admitted for treatment at the Hematology Outpatient Service from the Sao Paulo State Cancer Institute, between February 2012 and January 2014, were prospectively followed. Exclusion criteria were: age < 18 years; pts on maintenance dialysis; follow up < 3 months. Chronic Kidney Disease (CKD) was diagnosed as eGFR < 60 ml/min/1.73 m^2. GFR was estimated by the CKD Epidemiology Collaboration formula. International Staging System (ISS) relyed on serum albumin (Alb) and ß$_2$ microglobulin (B2M).

Results: One hundred twenty pts were enrolled. Pts characteristics were age 62.02 ± 11.2 years, 56.2% male. MM type was IgG Kappa in 59% of cases and 21% of pts had light chain MM. The clinical stages included Durie-Salmon stage III (DS-III) in 81% and ISS stage III (ISS-III) in 30% of pts. Serum exams were: 43% hemoglobin (Hb) < 10 g/dL; 14.3% total calcium (CaT) > 11 mg/dL; 39.2% SAlb < 3.5 g/dL; 54.5% B2M > 3.5 mg/L; 18.3% lactate dehydrogenase (LDH) > normal value. At the moment of enrollment, SCr was 1.05 (0.74 – 1.43) mg/dL and eGFR was 69.8 (42.7 – 97.1) ml/min/1.73 m^2. Thirteen percent of pts had RI with SCr > 2.0 mg/dL; CKD stage 3 was detected in 43% pts. Overall survival (OS) was 3.70 (1.97 – 4.44) years. No pts characteristics, CaT, Hb or DS-III were related to reduced OS. Neither was SCr > 2.0 mg/dL (P=0.425) or eGFR < 40 ml/min/1.73 m^2(P=0.189). Conversely, CKD stage 3 was associated to reduced OS (3.26 [1.56 – 4.41] vs 3.72 (2.69 – 4.96) years, P=0.032) as well as ISS-III (P=0.022). On Cox regression model, only B2M > 3.5 mg/L (Hazard Ratio : 2.14 [1.03 – 4.42]) and LDH > normal value (Hazard Ratio: 2.74 [1.45 – 5.18]) were associated with lower OS.

Conclusions: Currently used KDIGO CKD definitions seem to be superior than the new IMWG criteria to assess the impact of RI on the prognosis of newly diagnosed MM pts.

SA-PO421

Results from the Cross-Sectional Evaluation of Clinical Symptoms and Epidemiologic Parameters in Patients with TMA, Differentiated by Laboratory Parameters Study (CESAR) Ulf Schoenermarck,[3] Wolfgang Ries,[2] Bernd Schroppel,[4] Michael Jeglitsch.[1] *[1]Alexion, Munich, Germany; [2]Diako Flensburg, Flensburg, Germany; [3]University Hospital Munich-Grosshadern, D-81377 Muenchen, Germany; [4]University of Ulm, Ulm, Germany.*

Background: Atypical hemolytic uremic syndrome (aHUS), thrombotic thrombocytopenic purpura (TTP) and HUS caused by Shiga toxin-producing *Escherichia coli* (STEC-HUS) are diseases with thrombotic microangiopathy (TMA) and similar clinical presentations. Epidemiological data on TTP and aHUS in Germany are lacking.

Methods: CESAR is a German prospective, multicenter, cross-sectional, epidemiological study of the relative incidences (RI) of aHUS, TTP and STEC-HUS in patients (pts) presenting with TMA. ADAMTS13 activity and presence of STEC were tested. Treating clinicians diagnosed pts as either aHUS, TTP, STEC-HUS or "other".

Results: From 04/2014 to 03/2017, 232 pts were enrolled in 22 German centers. RIs and clinical data are shown in the table. 104 (74%) pts with aHUS had at least one complement-amplifying condition.

Conclusions: aHUS was the most common diagnosis in pts with clinical TMA. Less frequent differential diagnoses including TTP should be rapidly ruled out through specific diagnostic tests. Pts with aHUS or STEC-HUS were less thrombocytopenic and experienced more severe acute kidney injury than pts with TTP.

Funding: Commercial Support - Alexion Pharma Germany GmbH

Table 1. Relative incidences, demographic and clinical characteristics of patients presenting with TMA

Characteristic	aHUS (n=141)	TTP (n=31)	STEC-HUS (n=14)	Other (n=46)
Relative incidence	61%	13%	6%	20%
Age at enrolment (years), mean (SD)	55.4 (20.3)	50.5 (16.7)	24.3 (29.9)	57.5 (20.7)
Gender, female, n (%)	79 (56)	21 (68)	8 (57)	17 (37)
Presenting symptoms, n (%)				
Renal	131 (93)	22 (71)	14 (100)	43 (93)
Gastrointestinal	71 (50)	11 (35)	12 (86)	23 (50)
Neurological	57 (40)	18 (58)	4 (29)	10 (22)
Cardiovascular	51 (36)	7 (23)	2 (14)	4 (9)
Pulmonary	48 (34)	4 (13)	0 (0)	5 (11)
Other	44 (31)	10 (32)	2 (14)	21 (46)
Platelets ($10^3/\mu L$), median (IQR)	98.5 (46.8–123.3)	26.0 (12.0–57.0)	53.0 (34.8–103.8)	61.0 (29.0–83.0)
Hemoglobin reduced below LLN, n (%)	134 (95)	25 (81)	13 (93)	40 (87)
Serum creatinine (mg/dL), median (IQR)	2.1 (1.3–3.7)	1.1 (0.9–1.4)	4.5 (3.1–5.3)	2.2 (1.3–3.8)
Bilirubin (mg/dL), median (IQR)	1.0 (0.6–2.0)	2.1 (1.9–2.7)	2.2 (1.0–3.0)	1.4 (0.7–3.2)

aHUS, atypical hemolytic uremic syndrome; IQR, interquartile range; LLN, lower limit of normal; SD, standard deviation; STEC-HUS, Shiga toxin-producing *Escherichia coli*-HUS; TTP, thrombotic thrombocytopenic purpura.

SA-PO422

Nephrologist-Reported Symptoms and Their Impacts on Patients with Anemia Associated with CKD Tony Okoro,[1] Kirsten L. Johansen,[3] Susan Mathias,[2] Hilary H. Colwell,[2] Steven I. Blum,[1] Vanja Sikirica.[1] *[1]GlaxoSmithKline, Collegeville, PA; [2]Health Outcomes Solutions, Winter Park, FL; [3]University of California, San Franicsco, San Francisco, CA.*

Background: To explore the relevant symptoms and their impacts on patients with anemia associated with chronic kidney disease (aCKD) as reported by nephrologists.

Methods: Double-blind (sponsor and nephrologist) qualitative telephone interviews using a semi-structured interview guide were conducted with a random sample of practicing nephrologists in the United States. Nephrologists were asked about symptoms and their impacts reported by their patients, as well as which symptoms they ask their patients about during clinic visits. Symptoms and impacts reported both spontaneously and with probing were included. Interviews were audio-recorded, transcribed, and analyzed using MAXQDA software. Verbal consent was obtained.

Results: Nephrologists (n=29) had been in practice for ~19 years; most were in freestanding (66%), for-profit (69%), and nonacademic (69%) institutions. Nephrologists reported (spontaneously or after being probed) a range of symptoms that their patients with aCKD experience (**Table**). Nephrologists reported that 48% of their patients are negatively affected by aCKD symptoms in the area of physical functioning, 50% in their ability to carry out daily activities, and 37% in emotional functioning. Symptoms that bother patients the most are fatigue (93%), dyspnea (41%), and difficulty sleeping (22%). The symptoms that clinicians most commonly ask their patients about are fatigue (83%), dyspnea (57%), and loss of appetite (43%).

Conclusions: In general, clinicians reported that their patients with aCKD experience a variety of symptoms and related impacts. Fatigue and dyspnea are frequently and spontaneously reported by clinicians and routinely assessed. Nephrologists may not commonly ask about other symptoms such as difficulty remembering things or concentrating, which may be relevant to their patients.

Funding: Commercial Support - GlaxoSmithKline

Symptom	Any Mention, n (%) (n=29)	Spontaneous, n	Probed, n
Fatigue	29 (100)	29	None
Dyspnea	28 (97)	24	4
Gastrointestinal symptoms	26 (90)	2	24
Difficulty sleeping	26 (90)	9	17
Difficulty remembering	22 (76)	5	17
Difficulty concentrating	23 (79)	5	18

SA-PO423

Evolution of HIV-Associated Glomerulopathy with Treatment and Time: A Study of Serial Biopsies Rachel Hung,[2] Viyaasan Mahalingasivam,[1] John Connolly,[2] John W. Booth.[2] *[1]Mid Essex Hospitals NHS Trust, Harrow, United Kingdom; [2]Royal Free Hospital, London, London, United Kingdom.*

Background: While the spectrum of HIV-associated glomerular disease is well described, the impact of treatment on evolution of these diseases, both clinically and histologically, is less clear. In the era of widespread antiretroviral therapy (ART) use, many patients with renal disease will be identified and investigated after a period of suppressed viral replication, potentially complicating interpretation of the renal biopsy. Serial biopsies are rarely performed so histological progression is as yet not well understood. Our aim was to examine the histologic evolution of HIV-associated glomerular disease with time and/or treatment through study of patients who had undergone serial kidney biopsies.

Methods: Patients with HIV and serial biopsies were identified through local database searches in two UK renal units. Patients whose first biopsy was considered non-diagnostic (n=2) were excluded. Histology data was obtained from structured departmental reports; all repeat biopsies had been reported with reference to the initial biopsy. Clinical data and drug treatments were obtained by review of notes and pathology databases.

Results: 13 patients with glomerular disease and serial biopsies were identified (n; HIV-associated nephropathy (HIVAN)=3, immune complex kidney disease (ICKD)=6, IgA nephropathy=4). Typical collapsing glomerulopathy was not identified on the second biopsy of any patient with HIVAN, all of whom had received ART in the intervening period. 3 patients with ICKD had cellular segmental lesions with crescents in their index biopsy; all had resolved on serial biopsy leaving segmental scleroses (n=2, both received ART) or mesangial hyperplasia (n=1, received steroids). Glomerular appearances showed no improvement on serial biopsy in IgA patients; 1 patient with crescentic IgA showed no improvement on 2 serial biopsies despite robust control of viral replication

Conclusions: In this small and unique study, it was demonstrated that the morphology of established HIV-associated glomerular disease can change with treatment and time. 'Healed' segmental proliferative lesions in ICKD may simulate 'primary' FSGS, while typical collapsing glomerulopathy in HIVAN may be reversed, or obscured by glomerular obsolescence. On the other hand, viral control did not impact on histological activity of HIV-associated IgA.

SA-PO424

Performance of a Pure Metabolite Panel Estimate of GFR (accuGFR) Josef Coresh,[1] Lesley Inker,[2] Jingsha Chen,[1] Gudny Eiriksdottir,[3] Vilmundur Gudnason,[3] Vicente E. Torres,[4] Lisa Ford,[5] Maria Oyaski,[5] Regis Perichon,[5] Andrew S. Levey.[2] *[1]Johns Hopkins Medical Institutions, Baltimore, MD; [2]Tufts Medical Center, Boston, MA; [3]Icelandic Heart Association, Kopavogur, Iceland; [4]Mayo Clinic, Rochester, MN; [5]Metabolon, Inc., RTP, NC.*

Background: We showed that panels of metabolites can provide an accurate estimate of glomerular filtration rate (GFR) without creatinine and demographic characteristics. We present a Laboratory Developed Test (LDT) to estimate GFR (accuGFR) and estimate its performance in subgroups where eGFRcr is less accurate. **Study Population:** GFR measurements (mGFR) on 3,236 individuals in the AASK, MDRD, AGES and the CRISP studies were divided randomly into a development sample (50%) and validation samples (25% complete, 25% unused backup).

Methods: Laboratory Methods: Stored (-70°C) serum specimens were subjected to targeted UPLC-mass spectrometry assays for 4 metabolites and serum creatinine (CV <5%). **Data Analysis:** accuGFR estimated using linear regression of log mGFR on log metabolites in the development sample. Performance measured using large errors (1-P30

and 1-P20, the percentage of estimates deviating from the mGFR by >30% and >20%). We compared the accuGFR to eGFR by CKD-EPI equations.

Results: mGFR spanned a wide range (mean 55, SD 26 ml/min/1.73m^2). accuGFR based on 4 metabolites without demographics had substantially better accuracy than eGFRcr and eGFRcys but similar performance to eGFRcr-cys in the accuGFR development and validation samples. In subgroups where there is concern that eGFRcr may be inaccurate, accuGFR often outperformed even eGFRcr-cys, particularly for 1-P20.

Conclusions: accuGFR based on four metabolites without serum creatinine or demographics nearly halved the rate of large errors compared to eGFRcr and appears to be robust across a range of relevant subgroups. The utility of the accuGFR test based on a single blood draw should be tested in diverse clinical and research populations.

Table 1. Improved performance by accuGFR vs. CKD-EPI eGFRcr, eGFRcys and eGFRcr-cys

1-P30	accuGFR Development (n=1612)	accuGFR Validation (n=806)	All accuGFR Age ≥75 (n=526)	All accuGFR BMI ≥35 (n=333)	All accuGFR Poor eGFRcr (n=380)
eGFRcr	16.4%***	14.4%**	10.6%***	**19.8%***	100%***
eGFRcys	16.9%***	20.7%***	6.7%	17.7%**	32.4%
eGFRcr-cys	10.0%	9.9%	4.0%	11.7%	42.6%***
accuGFR (reference)	10.0%	10.0%	4.2%	10.2%	26.6%
%improvement vs eGFRcr	*39%***	*31%**	*60%***	*48%***	*73%***
1- P20	**accuGFR Development (n=1612)**	**accuGFR Validation (n=806)**	**All accuGFR Age ≥75 (n=526)**	**All accuGFR BMI ≥35 (n=333)**	**All accuGFR Poor eGFRcr (n=380)**
eGFRcr	37.9%***	34.7%***	40%***	41%***	100%***
eGFRcys	34.1%***	35.4%***	20%***	39%***	51.8%
eGFRcr-cys	26.5%**	26.1%	20%**	33%**	72.4%***
accuGFR (reference)	22.8%	22.5%	13%	24%	48.4%
%improvement vs eGFRcr	*40%***	*35%***	*68%***	*41%***	*52%***

accuGFR sample: MDRD, AASK, AGES and CRISP (sampled 50% for development and 25% for validation); "all accuGFR" samples include 2/3 used for algorithm development, plus 1/3 validation samples not used in algorithm development

* p<0.05, ** p<0.01, ***p<0.001 vs. accuGFR, Poor eGFRcr performance defined as errors from mGFR > 30%

SA-PO425

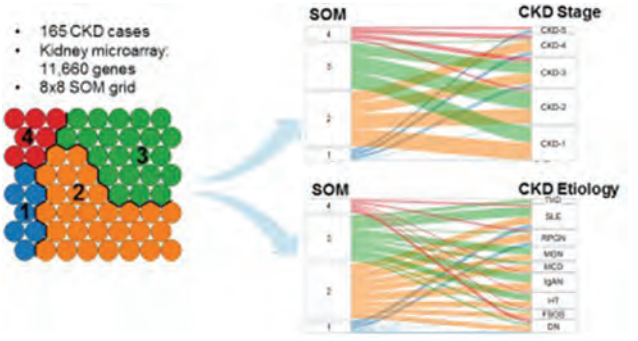
Molecular Re-Classification of CKD Based on Kidney Transcriptomics Profiles Anna Reznichenko,[1] Viji Nair,[5] Sean Eddy,[5] Tao Wei,[2] Tim Slidel,[6] Wenjun Ju,[5] James Conway,[7] Shawn S. Badal,[3] Johnna D. Wesley,[4] John T. Liles,[3] Uptal D. Patel,[3] Matthew D. Breyer,[2] Kevin L. Duffin,[2] Carol P. Moreno Quinn,[6] Maria chiara Magnone,[1] Matthias Kretzler.[5] *[1]AstraZeneca, Gothenburg, Sweden; [2]Eli Lilly and Company, Indianapolis, IN; [3]Gilead Sciences, Inc., Foster City, CA; [4]Novo Nordisk Research Center, Seattle, Seattle, WA; [5]University of Michigan, Ann Arbor, MI; [6]MedImmune, Cambridge, United Kingdom; [7]MedImmune, Gaithersburg, MD. Group/Team: Renal Precompetitive Consortium (RPC2).*

Background: The CKD population is highly heterogeneous and includes a wide range of etiologies with a multitude of underlying molecular processes in the kidney. Current clinical classification of CKD into five stages based on GFR and albuminuria is agnostic to the disease heterogeneity and intrarenal biology, and thus is antithetical to the personalized medicine (PM) concept. We re-classified a CKD patient population based on the kidney molecular profiles, consistent with PM initiatives.

Methods: From clinically indicated renal biopsies in 165 ERCB cohort participants, transcriptomics profiles were generated using Affymetrix U133 platforms. Self-Organizing Maps (SOM), an unsupervised neural network machine learning algorithm, was used to stratify CKD population by clustering cases with similar transcriptomics profiles. Gene Ontology, pathway, and Gene Set Enrichment analyses were performed to identify key molecular mechanisms per SOM cluster.

Results: Using SOM, we identified four distinct patient clusters within the topological map of renal transcriptomics data structure. Relating these molecular clusters back to the current classification revealed the lack of overlap with CKD stages, thus demonstrating that SOM clusters represent a novel characterization beyond clinical classification. The SOM clusters were also not explained by CKD etiology, confirming the hypothesis of disease heterogeneity at the molecular level. Enrichment analyses showed that the SOM clusters differed in terms of biological pathways in the kidney including inflammation, metabolism, cell signaling and apoptosis.

Conclusions: Molecular re-classification may help realize the potential of PM for CKD. Elucidation of the molecular drivers of population clustering can lead to new biological hypotheses, therapeutic targets, and cluster-specific biomarkers that would enable PM-based regimens.



CKD molecular re-classification

SA-PO426

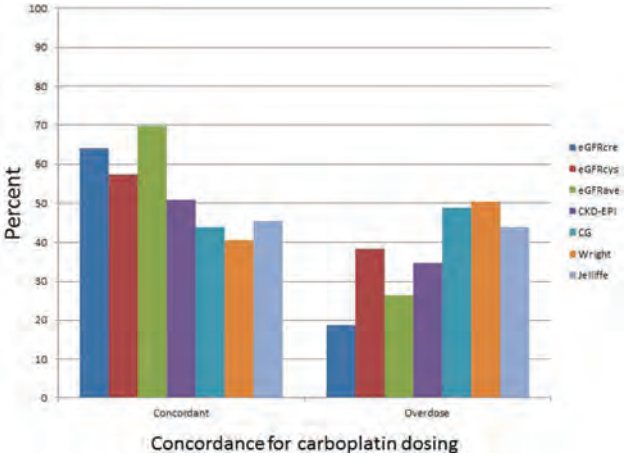
Quest for Simple and Accurate Estimate of Kidney Function for Chemotherapy Dosing: A Comparison of Commonly Used GFR Estimates and Inulin Clearance Fumiaki Tanemoto,[1] Taisuke Ishii,[1] Eriko Nakano,[2] Yasuhiro Komatsu.[1] *[1]Nephrology, St.Luke's International Hospital, Tokyo, Japan; [2]Medical oncology, St.Luke's International Hospital, Tokyo, Japan.*

Background: The increase in the number of oncology patients with renal impairment demands the accurate estimate of kidney function to avoid unnecessary adverse effects caused by overdose of chemotherapy. However, dose accuracy after renal function assessment calculated using eGFR equations based on creatinine measured by enzymatic assay and/or cystatin C remains unclear.

Methods: In this single-center study, we collected data from all adult patients whose inulin clearance was measured between January 2009 and March 2017. Renal function and consequent dose of renally-excreted chemotherapy, including carboplatin, were calculated by estimated creatinine-based GFR (eGFRcre) developed by the Japanese Society of Nephrology (JSN), estimated cystatin C-based GFR (eGFRcys) developed by JSN, averaged value of eGFRcre and eGFRcys (eGFRave), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Cockcroft-Gault (CG), Wright, and Jelliffe formulae. Logistic regression analysis was conducted to determine factors associated with overdose.

Results: The concordance of renal function estimates according to the CKD classification with measured inulin clearance (67±32 ml/min/1.73m^2) in 187 adults (age 52±16, 58.3% men) for eGFRcre, eGFRcys, eGFRave, CKD-EPI, CG, Wright, and Jelliffe formulae was 53.5%, 56.6%, 58.5%, 52.9%, 49.2%, 52.4%, and 52.9%, respectively. Concordance for recommended dosage of chemotherapy using each respective formulae was 71.1%, 64.8%, 74.8%, 68.9%, 65.2%, 67.9%, and 67.4%. Especially concordance for carboplatin was 64.2%, 57.2%, 69.8%, 57.2%, 43.9%, 40.6%, and 47.6%, respectively. Hypoalbuminemia was an independent factor for overdose (OR 3.14, 95% CI 1.75-5.61).

Conclusions: For accurate chemotherapy dosing, eGFRave appears to be the most appropriate estimate of renal function. Patients with hypoalbuminemia may need actual measurement of inulin clearance.



SA-PO427

Serum Creatinine from 29 US Health Care Organizations: The Case of Imprecise Measurement Nikita Stempniewicz,[1,2] Shoshana Ballew,[2,3] Elizabeth Ciemins,[1] Morgan Grams,[3,4] Kunihiro Matsushita,[2,3] Jerry Penso,[1] Josef Coresh.[2,3] *[1]AMGA, Alexandria, VA; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [3]Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; [4]Johns Hopkins School of Medicine, Baltimore, MD.*

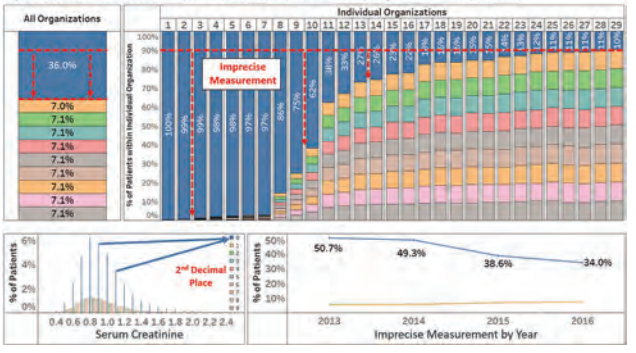
Background: For precise measurement of estimated GFR (eGFR), KDIGO 2012 guidelines recommend clinical laboratories report serum creatinine to the nearest 0.01 mg/dl. Rounding serum creatinine measurements to 0.1 mg/dl reduces the precision of eGFR, e.g., a female with a serum creatinine of 1.0 mg/dl, and ages of 60, 70, or 80 would represent eGFR (CKD-EPI) in the ranges of 58-64, 54-60, and 51-56 mL/min/1.73 m^2, respectively. However, many laboratories still round to 0.1 mg/dl.

Methods: We analyzed 2.3 million patients with serum creatinine measurements from the electronic health record (EHR) data of 29 AMGA member organizations who use the Optum One population health analytics platform. We used the most recent serum creatinine recorded between 01/01/2013 and 12/31/2016 for patients age 18-99, with a history of hyperglycemia, and at least one ambulatory office visit. Imprecision in serum creatinine reporting was quantified using the proportion of values with a 0 in the second place after the decimal (e.g., 0.90, 1.00). With precise measurement we expect ~10% of patients to end in each digit including 0.

Results: Overall, 36% of serum creatinine measurements had 0 for the second decimal place (e.g. X.X0, blue in Figure 1). This proportion varied among organizations, ranging from 10%-100%. Over the last 4 years the proportion with 0 in the second place after the decimal decreased from 51% (2013) to 34% (2016).

Conclusions: Imprecise measurement of serum creatinine by clinical laboratories in the US is improving but is still a prevalent practice which should be eliminated to meet with guidelines and improve the quality of health care.

Figure 1: Differences in Precise Serum Creatinine Measurement, by Organization and Over Time



SA-PO428

Existing Creatinine Based Estimating Equations Overestimate GFR in Indian Subjects Vivek Kumar,[5] Ashok K. Yadav,[5] Yoshinari Yasuda,[3] Vinod Kumar,[6] Krishan Lal L. Gupta,[4] Masaru Horio,[2] Vivekanand Jha.[1] *[1]George Institute for Global Health, New Delhi, India; [2]Osaka University Graduate School of Medicine, Ashiya, Japan; [3]Nagoya University Post Graduate School of Medicine, Nagoya, Japan; [4]Postgraduate Institute of Medical Education & Research, Chandigarh, India; [5]Postgraduate Institute of Medical Education and Research, Chandigarh, India; [6]Fienstine Institute for Medical Research, New York, NY.*

Background: Ethnic differences, predominantly vegetarian diet and poor representation in derivation and validation cohorts for eGFR equations call for assessment of accuracy of current eGFR equations in Indian population.

Methods: This study was done at PGIMER, Chandigarh, India. Stable adult prospective living renal donors or subjects with CKD were eligible for enrolment. GFR was measured (mGFR) by urinary clearance of inulin. eGFR were calculated using CKD-EPI$_{Cr}$, Japanese coefficient-modified CKD-EPI, MDRD and CKD-EPI Pakistan equation. Bias (mGFR-eGFR), 95% limits of agreement, precision (95% CI of mGFR-eGFR) and accuracy (RMSE of mGFR-eGFR, and % of subjects with eGFR within ±30% of mGFR i.e. P_{30}] were calculated.

Results: After excluding 5 subjects with incomplete data, 130 subjects were included for final analyses (63 prospective donors and 67 subjects with previously diagnosed CKD). 50% were strict vegetarian and average meat intake among meat eaters was only 3.8 times/month. The average creatinine (Cr) excretion was 14.7 mg/kg/day (95% CI: 13.5 to 15.9 mg/kg/day) and 12.4 mg/kg/day (95% CI: 11.2 to 13.6 mg/kg/day) in males and females, respectively. The average daily protein intake based on 24-hour urea nitrogen excretion was 46.1 g/day (95% CI: 43.2 to 48.8 g/day), respectively. Bias, precision and accuracy of eGFR equations are shown in table 1. All Cr based eGFR equations overestimated GFR with CKD-EPI$_{Cr}$ and MDRD being the poorest.

Conclusions: Cr based eGFR equations significantly overestimate GFR in the predominantly vegetarian Indian population. Lower Cr excretion suggest that this overestimation is likely linked to lower muscle mass. There is need of an appropriately powered study to develop either a correction factor or a new equation for accurate assessment of kidney function in Indian population.

Funding: Private Foundation Support

Table 1: Performance of GFR estimating equations as compared to measured GFR by urinary inulin clearance

eGFR equation	Bias (mGFR-eGFR) (ml/min/1.73m2)	95% Limits of agreement (ml/min/1.73m2)	Precision (95% CI) (ml/min/1.73m2)	Accuracy RMSE (ml/min/1.73m2)	Accuracy P30 (%)
CKD-EPICr	-24.92±17.17	-58.57 to 8.73	-27.90 to -21.95	30.22	22.3
CKD-EPI (PK)	-16.84±15.39	-47.00 to 13.32	-19.52 to -14.17	47.72	39.2
CKD-EPI (JAP)	-10.62±13.07	-47.00 to 13.32	-12.87 to -8.33	16.79	51.5
MDRD	-31.01±25.33	-80.60 to 18.59	-35.41 to -26.62	39.98	16.2

SA-PO429

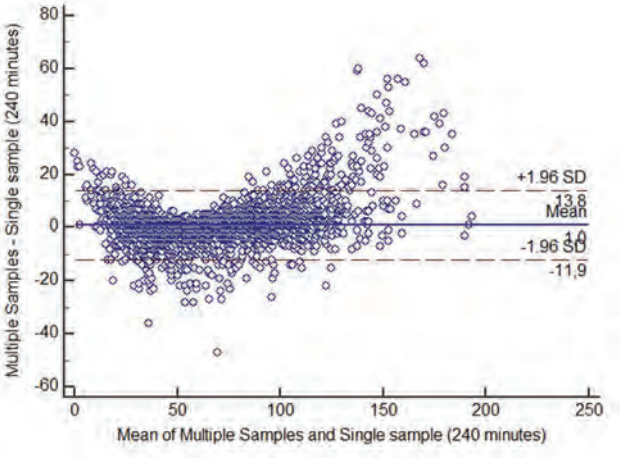
Measuring Plasma Clearance for Exact Assessment of GFR: Multi versus Single Sampling Natalie Ebert,[3] Elke Schaeffner,[2] Hans Pottel,[4] Etienne Cavalier,[5] Laurence Dubourg,[7] Martin Flamant,[1] Pierre Delanaye.[6] *[1]APHP, Paris, France; [2]Charite, Berlin, Germany; [3]Charite University Hospital, Belgrade, Serbia; [4]KULeuven, Kortrijk, Belgium; [5]University of Liege, CHU Sart-Tilman, Liege, Belgium; [6]University of Liège, Liège, Belgium; [7]hospices civils de Lyon -Université Claude Bernard Lyon 1-INSERM U 820, LYON, France.*

Background: Measurement of plasma clearance (PC) of iohexol or 51Cr-EDTA are both recognized as gold standard for exact GFR assessment. However, there are different protocols for PC measurement in terms of a varying number of plasma samples. We compare GFR results obtained from multi sample (MS) versus single sample (SS) PC measurement.

Methods: We used data from 4 European cohorts including indiv. with PC of iohexol (Liège, Lyon, Berlin) or 51Cr-EDTA (Paris). MS clearance was calculated using a one compartment model with 3 or 4 samples at 120, 180, 240 and 300 min (or longer) after injection and Bröchner-Mortensen correction. The SS PC was calculated using the Jacobsson method based on the preexisting estimated GFR. We studied concordance between both methods within ±10%.

Results: N=5,106 were included into the analysis with PC results based on 3 sampling points (120, 180 and 240 min) for slope calculation. Out of 5,106 indiv 657 had GFR results based on a 300 min (or longer) sampling period. In total 43% were females, mean age (SD) was 54 (±17) yrs, BMI 25.9 (±5.5) kg/sqm, mean GFR 65±26 mL/min (4-195 mL/min). Overall GFR results with SS at 120, 180 and 240 min had a concordance of ±10% with MS of 67, 84 and 91%, respectively. In the 657 individuals, highest concordance was observed with the 300 min sample if GFR <50 ml/min and with 240 min sample if GFR ≥50 ml/min (concordance within 10% was 96%, within 5% was 85%). Smallest concordance was found in individuals with very low GFR, at old age and with extreme BMI.

Conclusions: GFR results obtained from PC measurement with SS showed a high concordance with values from MS technique. This applies all the more if the timing for SS method was adjusted to estimated GFR. In conclusion, we found that in certain circumstances, i.e. epidemiological studies, SS iohexol PC measurement is an acceptable alternative to MS method.



SA-PO430

Prevalence of Hyperkalemia in Medicare Patients Keith Betts,[1] J. Michael Woolley,[2] Fan Mu,[1] Wenxi Tang,[1] Yao Wang,[1] Eric Wu.[1] *[1]Analysis Group, Inc., Los Angeles, CA; [2]ZS Pharma Inc., San Mateo, CA.*

Background: The objective of this study was to estimate the prevalence of hyperkalemia in the Medicare patient population.

Methods: Adults with at least one medical service were selected from the 5% random Medicare sample (01/01/2010-12/31/2014). Patients with at least one calendar year of data with continuous enrollment throughout the year were included. Hyperkalemia was

defined as having at least one diagnosis code of hyperkalemia (ICD-9, 276.7). Prevalence of hyperkalemia for each calendar year (2010-2014) was calculated as the number of patients with hyperkalemia divided by the total number of eligible patients within the year. Additionally, prevalence of hyperkalemia was also estimated among comorbidity subgroups defined by chronic kidney disease (CKD), CKD stage, heart failure (HF) and dialysis. CKD, CKD stage, and HF were identified via ICD-9 codes, and dialysis was identified via procedure codes. Hyperkalemia prevalence standardized to the US elderly population was calculated using hyperkalemia prevalence stratified by age and gender among patients aged 65 and above in the 5% Medicare sample and the corresponding US census population distribution.

Results: A total of 1,964,905 patients were included in the analysis (2010-2014). The prevalence of hyperkalemia in the overall population ranged from 2.6%-2.7% across calendar years. The prevalence of hyperkalemia was 10.8%-12.4% among CKD patients, 8.6%-9.4% among HF patients, 8.9%-9.3% among patients with CKD and/or HF, and 50.2%-52.8% among patients that underwent dialysis. The prevalence of hyperkalemia was 9.4%-11.1% for CKD stage 3 patients, 19.5%-20.7% for CKD stage 4 patients, and 17.8%-20.2% for CKD stage 5 patients. The standardized prevalence of hyperkalemia ranged between 1.0 and 1.1 million (2.5%-2.6%) from 2010-2014 in the US elderly population.

Conclusions: This study estimated that the prevalence of hyperkalemia among Medicare beneficiaries is 2.6%-2.7%. The prevalence of hyperkalemia is much higher among CKD patients, HF patients, CKD and/or HF patients, and patients that underwent dialysis, as compared to the general Medicare population. Annually, approximately 1 million of US population aged 65 and above are estimated to have hyperkalemia.

SA-PO431

Economic Burden of Hyperkalemia in the Medicare System Keith Betts,[1] J. Michael Woolley,[2] Fan Mu,[1] Cheryl Q. Xiang,[1] Akanksha Dua,[1] Eric Wu.[1] *[1]Analysis Group, Inc., Boston, MA; [2]ZS Pharma Inc., San Mateo, CA.*

Background: The objective of this study was to estimate the economic burden associated with hyperkalemia in the Medicare population.

Methods: Adult patients with and without hyperkalemia (cases vs. controls), were selected from the Medicare Claims Database (5% random sample) (1/1/2010-12/31/2014). Hyperkalemia was defined as having at least one diagnosis code of hyperkalemia (ICD-9-CM 276.7). The index date was a randomly selected claim date with hyperkalemia diagnosis for cases and a randomly selected claim date for controls. Continuous enrollment for at least 6 months before the index date (baseline period) and 12 months after the index date (study period) was required. Controls were exactly matched one-to-one to cases on age group, chronic kidney disease (CKD) stage, dialysis and heart failure (HF). 30-day and 1-year resource utilization and total costs (2016 USD) were compared between cases and controls.

Results: A total of 90,814 patients with hyperkalemia were matched to 90,814 patients without hyperkalemia. Cases had higher rates of inpatient admissions (30-day: 0.48 vs. 0.06; 1 year: 1.28 vs. 0.44), outpatient visits (30-day: 3.11 vs. 3.04; 1-year: 30.48 vs. 23.88), emergency department (ED) visits (30-day: 0.27 vs. 0.14; 1-year: 2.01 vs. 1.17) and skilled nursing facility (NF) admissions (30-day: 0.15 vs. 0.02; 1-year: 0.36 vs. 0.11) (all p<0.001). Cases also had more inpatient days (30-day: 3.79 vs. 0.34; 1-year: 10.54 vs. 3.04) and skilled NF days (30-day: 2.46 vs. 0.39; 1-year: 14.78 vs. 4.84) compared to controls (all p<0.001). Cases incurred $7,208 higher 30-day costs ($8,894 vs. $1,685) and $19,348 higher 1-year costs ($34,362 vs. $15,013) than controls (both p<0.001). Among the 41,271 matched pairs of patients with CKD and/or HF, the 30-day and 1-year total cost differences were $7,726 ($9,906 vs. $2,180) and $21,577 ($41,416 vs. $19,839), respectively (both p<0.001).

Conclusions: Patients with hyperkalemia were more likely to have inpatient, ED and skilled NF admissions, and had longer stays in inpatient and skilled NF compared to their matched patients without hyperkalemia. These data indicate that hyperkalemia is associated with a significant economic burden to Medicare.

SA-PO432

Post-Discharge Economic Burden of Hyperkalemia-Related Hospitalizations Keith Betts,[1] J. Michael Woolley,[2] Fan Mu,[1] Sneha S. Kelkar,[1] Cheryl Q. Xiang,[1] Yao Wang,[1] Eric Wu.[1] *[1]Analysis Group, Inc., Boston, MA; [2]ZS Pharma Inc., San Mateo, CA.*

Background: The objective of this study was to estimate healthcare resource use and costs post hyperkalemia-related hospitalization discharge.

Methods: Adults with potassium lab results available were selected from a large US commercial claims database (1/1/2010-12/31/2014). Patients with at least one hospitalization with a hyperkalemia diagnosis (ICD-9 276.7) during the inpatient stay were selected as cases. Patients with at least one hospitalization and with normal potassium lab results (≤5.0 mEq/L), no hyperkalemia diagnoses, and no sodium polystyrene sulfonate prescriptions were selected as controls. The first hyperkalemia-related hospitalization was defined as the index hospitalization for cases and a randomly selected eligible hospitalization was identified as the index hospitalization for controls. Continuous enrollment from 6 months prior to index hospitalization admission (baseline period) to 12 months post discharge (study period) was required. The day after index hospitalization discharge was defined as the index date. Controls were matched 1:1 to cases exactly on age group, chronic kidney disease (CKD) stage, receiving dialysis, heart failure, Renin-Angiotensin-Aldosterone-System inhibitor use, major diagnostic categories, and selected diagnosis-related groups. Resource use and total costs (2016 USD) were compared between cases and controls.

Results: A total of 4,418 matched cases and controls were included in the analysis. Cases had higher rates of inpatient admissions (1.00 vs. 0.41), emergency department visits (1.98 vs. 1.13), and outpatient visits (49.60 vs. 38.93) compared to controls in the 1-year study period (all p<0.001). Cases incurred $33,120 higher 1-year total all-cause costs ($71,322 vs. $38,203), and higher costs within each quarter (Q1: $23,615 vs. $12,041; Q2: $16,466 vs. $9,241; Q3: $16,630 vs. $8,560; Q4: $14,611 vs. $8,361) compared to controls (all p<0.001). Among patients with CKD and/or heart failure, cases had $33,827 higher 1-year total costs than controls ($76,971 vs. $43,143; p<0.001).

Conclusions: The results indicate that hyperkalemia-related hospitalizations are associated with significant economic burden during the 1-year post-discharge period.

SA-PO433

Development of a Predictive Model for Hyperkalemia Keith Betts,[1] J. Michael Woolley,[2] Fan Mu,[1] Iryna Bocharova,[1] Arielle G. Bensimon,[1] Eric Wu.[1] *[1]Analysis Group, Inc., Boston, MA; [2]ZS Pharma Inc., San Mateo, CA.*

Background: The objective of this study was to develop and validate a predictive model for the risk of hyperkalemia (HK) in US adults.

Methods: Adults were selected from a large US commercial claims database (2013-2014) if they were continuously enrolled from 7/1/13-12/31/13 (baseline) and 1/1/14-12/31/14 (follow-up) and had at least one serum potassium (K+) lab result during follow-up. The resulting sample was partitioned into two subsamples to train (60%) and validate (40%) the model. HK was defined as having in 2014: two elevated K+ values (>5.0 mEq/L); or one diagnosis for HK (ICD-9=276.7); or one prescription fill of sodium polystyrene sulfonate. In the training sample, multivariate logistic regression was used to develop a model estimating the 1-year probability of HK as a function of baseline covariates. Receiver operating characteristic (ROC) curve analysis of the validation sample was used to assess the predictive performance of the model.

Results: HK was identified in 4,815 (1.6%) of 295,511 adult patients in the training sample. Some important baseline predictors of HK included: CKD stages 3-5 (e.g., odds ratio [OR] for stage 5 without dialysis= 8.11; 95% CI: 6.51-10.11); each additional year in age (OR=1.028; 1.025-1.030); history of HK (e.g., number of HK-related hospitalizations OR=1.65; 1.20-2.26); type II diabetes (OR=1.65; 1.53-1.77); and use of renin-angiotensin-aldosterone system inhibitors (RAASi, OR=1.38; 1.29-1.47). ROC curve analysis in the validation sample showed good predictive accuracy (area under the curve=0.78). The figure shows the probability of HK for a RAASi patient as a function of CKD stage, age, and history of hyperkalemia.

Conclusions: This study developed a HK prediction model with the most important predictors being CKD stage, age, and history of HK. More frequent K+ monitoring may be warranted for patients at elevated risk.

Probability of Hyperkalemia in RAASi Patient

No History of Hyperkalemia				History of Hyperkalemia		
Age				Age		
50	65	80	CKD	50	65	80
1%	2%	3%	None	6%	8%	12%
3%	4%	6%	Stage 3	14%	19%	26%
7%	10%	14%	Stage 4	27%	36%	46%
9%	12%	18%	Stage 5	33%	43%	53%

SA-PO434

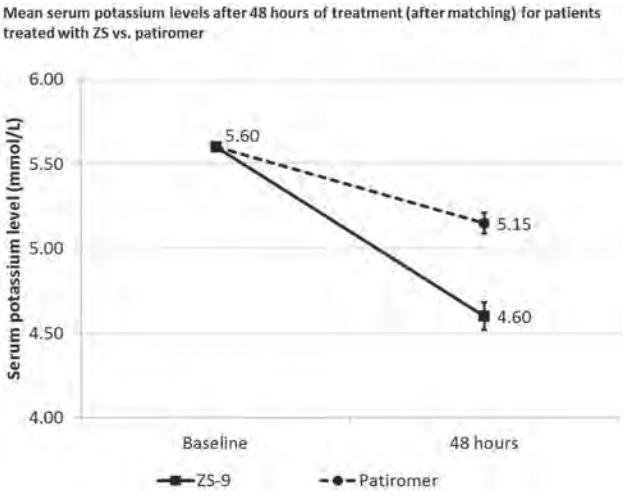
Indirect Comparison of Sodium Zirconium Cyclosilicate versus Patiromer in the Treatment of Hyperkalemia through 48 Hours Keith Betts,[1] J. Michael Woolley,[2] Yan Song,[1] Wei Gao,[1] Eric Wu.[1] *[1]Analysis Group, Inc., Boston, MA; [2]ZS Pharma Inc., San Mateo, CA.*

Background: Two agents have completed phase 3 trials for treatment of hyperkalemia; patiromer which was approved by US FDA in 2015 and sodium zirconium cyclosilicate (ZS) which is an investigational medication. An indirect treatment comparison was conducted to compare efficacy of ZS and patiromer in lowering serum potassium [K^+] after 48 hours of treatment.

Methods: To compare mean [K^+] after 48 hours of treatment, a matching-adjusted indirect comparison (MAIC) was conducted using patient-level data for patients treated with 10g ZS from the ZS-003 and ZS-004 trials and published aggregate data of patiromer from the OPAL-HK trial. Inclusion/exclusion criteria of the OPAL-HK trial were applied to ZS trials to derive a subset of patients comparable to those in the OPAL-HK trial. To adjust for cross-trial differences, patients from ZS trials were reweighted using the method of moments to exactly match baseline characteristics reported in OPAL-HK.

Results: Applying inclusion/exclusion criteria of OPAL-HK, 253 ZS treated and 243 patiromer treated patients were included in the analysis. After matching, all baseline characteristics were balanced between the two treatments. The mean baseline [K^+]of both sets of patients was 5.60 mmol/L, and, after 48 hours of treatment, the mean [K^+] achieved by ZS treated patients was significantly lower than those treated with patiromer (4.60 vs. 5.15 mmol/L; difference = –0.55 mmol/L; p-value <0.01; Figure 1). As a sensitivity analyses, the exclusion criteria were varied and the results remained consistent.

Conclusions: After adjusting for baseline differences, at 48 hours after the initiation of treatment, patients treated with ZS had a statistically significantly lower mean [K^+] than those treated with patiromer.



SA-PO435

Management of Hyperkalemia in Veterans with Advanced CKD Enrica Fung,[1] I-Chun Thomas,[1] Manjula Kurella Tamura.[1,2] *[1]Stanford University, Palo Alto, CA; [2]Veteran Affairs Palo Alto Health Care System, Palo Alto, CA.*

Background: Hyperkalemia is a serious complication among patients with advanced chronic kidney disease. The frequency and success of hyperkalemia management strategies are not well described.

Methods: We assembled a national cohort of veterans with advanced CKD not on dialysis, defined by an outpatient eGFR ≤30 ml/min/1.73m^2 and at least one episode of hyperkalemia (potassium ≥5.5meq/L), using administrative, laboratory and medication data from the Department of Veterans Health Affairs.

Results: Among 76,021 veterans with advanced CKD, 25,227 (33.2%) had at least one episode of hyperkalemia during 5 years of follow-up. The majority of patients (57.3%) were on at least one medication that can potentiate hyperkalemia, and 18.1% were on two or more potentiating medications. Of these patients, 74.1% had drug discontinuation after the hyperkalemic episode, including 59.0% on RAAS blockade. Initiation of potassium lowering medications occurred in 30.6% of patients, with diuretic initiation being most common (23.7%), while 3% of patients received acute dialysis. Recurrence of hyperkalemia within 90 days occurred in 5.5% of the cohort, with those prescribed fludrocortisone, sodium polystyrene sulfonate, and those who discontinued NSAIDs having the highest frequency of recurrence (**Table**).

Conclusions: Among patients with advanced CKD and hyperkalemia, discontinuation of RAAS blockers and initiation of diuretics are the most common strategies employed to manage hyperkalemia. Recurrence of hyperkalemia is infrequent, but may occur more commonly with certain management strategies.

Funding: NIDDK Support, Veterans Affairs Support

Management strategies and recurrence of hyperkalemia within 90 days (n, %)

Medications	*Total cohort*	*No recurrence*	*Recurrence to K 5.5-6.5 meq/L*	*Recurrence to K>6.5 meq/L*
Initiation of				
Diuretics	*5968 (23.7%)*	*5567 (93.3%)*	*373 (6.3%)*	*28 (0.5%)*
Sodium bicarbonate	*1137 (4.5%)*	*1060 (93.2%)*	*71 (6.2%)*	*6 (0.5%)*
Fludrocortisone	*87 (0.3%)*	*74 (85.1%)*	*12 (13.8%)*	*1 (1.1%)*
Sodium polystyrene sulfonate	*2940 (11.7%)*	*2636 (89.7%)*	*284 (9.7%)*	*20 (0.7%)*
Initiation of any K lowering drug	*7727 (30.6%)*	*7148 (92.5%)*	*543 (7.0%)*	*36 (0.5%)*
Discontinuation of				
RAAS blockade	*5505 (59.0%)*	*5057 (91.9%)*	*426 (7.7%)*	*22 (0.4%)*
K sparing diuretics	*1990 (68.7%)*	*1853 (93.1%)*	*130 (6.5%)*	*7(0.4%)*
NSAIDs	*1538 (79.5%)*	*1394 (90.6%)*	*134 (8.7%)*	*10 (0.7%)*
K supplements	*4770 (81.5%)*	*4408 (92.4%)*	*339 (7.1%)*	*23 (0.5%)*
Discontinuation of any potentiating drug	*10719 (74.1%)*	*9929 (92.6%)*	*740 (6.9%)*	*50 (0.5%)*
Any medication change	*14358 (56.9%)*	*13360 (93.0%)*	*937 (6.5%)*	*61 (0.4%)*
No medication changes	*10869 (43.1%)*	*10486 (96.3%)*	*368 (3.4%)*	*15 (0.1%)*

SA-PO436

Beta Blockers as the Cause of Hyperkalemia in Near-End Stage Renal Disease Patients: A Cross-Sectional Study Kazuhiro Okamura,[1] Sho Sasaki,[1,2] Masahide Furusho,[1] Makoto Hirakawa.[1] *[1]Iizuka Hospital, Iizuka-city, Japan; [2]Department of Healthcare Epidemiology, Kyoto University Graduate School of Public Health, Kyoto city, Japan. Group/Team: JOINT-KD.*

Background: Although there are several case reports on hyperkalemia caused by beta blockers so far, few studies have verified its causal relationship based on epidemiological methods. The objectives of this study were to assess the association between beta blocker use and risk of hyperkalemia among patients with near end-stage renal failure (ESRD).

Methods: Design and participants: We performed a cross-sectional study at seven Japanese teaching hospitals. Consecutive adult patients with eGFR <15 ml/min/1.73m2 that visited outpatient departments from April 1 to June 30, 2013, were enrolled. Patients with dialysis, post-transplantation, or hospitalization within 30 days were excluded. **Exposure**: We set the usage of beta blockers as the exposure to be tested. **Outcomes**: Serum K^+ concentration was taken as the outcome. **Statistical analysis**: Descriptive analysis was done. Next, multivariate analysis adjusted for age, sex, eGFR, presence of diabetes mellitus, RAAS inhibitor use, K-sparing diuretics use, loop diuretics use, and K absorption drugs use was conducted. In addition, analysis stratified by age (cut off: 75 yo) and RAAS inhibitor use was performed.

Results: Of 517 patients (56.9% male) who were at a median age of 72 (interquartile range, 63 to 80), with median eGFR 11.1 ml/min/1.73m2 (interquartile range, 9.2 to 13.1) included, 239 (46.2%) had diabetes mellitus, 305 (59%) used RAAS inhibitors, and 148 (28.6%) used beta blockers. In the results of the multivariate analysis adjusted for possible confounders, there was no significant difference in the serum K^+ value between the group using the beta blockers and the group not using the beta blockers (+0.07mEq/L, 95% Confidence Interval [CI] -0.067 to - 0.211, p=0.3). An additional analysis stratified for age showed that beta blocker use in participants with an age of 75 yo or older results in significantly higher serum K^+ levels (+0.24 mEq/L, 95%CI 0.012 to 0.470, p= 0.04) compared with participants without beta blockers. Further, the combined use of RAAS inhibitors and beta blockers resulted in higher serum K^+ levels (+0.42mEq/L, 95% CI 0.14 - 0.71, p<0.01) compared with participants who used neither in the subgroup of 75 yo or older.

Conclusions: In patients with near ESRD who were 75 years of age or older, it was suggested that the use of beta blockers may raise the serum K^+ value.

SA-PO437

Medication Discrepancies in Late Stage CKD Jamil Ibrahim,[1] Azzour Hazzan,[1] Vipulbhai Sakhiya,[1] Meng Zhang,[2] Candice Halinski,[1] Steven Fishbane.[1] *[1]Nephrology, Hofstra Northwell Health School of Medicine, Great Neck, NY; [2]Biostatistics, Northwell Health, Manhasset, NY.*

Background: Late stage chronic kidney disease (LS-CKD) is defined by glomerular filtration rate (GFR) 0- 30 ml/min in patients not yet on dialysis. It is a period at high risk for medication discrepancies for multiple reasons. In this study we sought to characterize medication discrepancies in LS-CKD.

Methods: We analyzed patients enrolled in Northwell Health's Healthy Transitions in Late Stage CKD program from its inception in 2011. All patients had eGFR 0-30 ml/min. Medications were reviewed by a nurse care manager at a home visit, at the first program contact with the patient. The patient presented their medication bottles, with careful review for which medications were actually being used and how they were being taken. The patient's medication usage and practice were compared to the nephrologist's electronic health record medication list. We defined high risk discrepancies (HRD) as mismatches in dose or frequency or medications not being taken, excluding laxatives, vitamins and herbals.

Results: All 716 patients were reviewed. The mean age was 67.5±16.5 years, 56% were men, 25% were black, 54% were white, 9% were Hispanic, 51% were diabetic, 93% had hypertension. There were 395 (55.1%) patients with medication discrepancies, 3.2±2.8 (range 1-18) per patient. HRD occurred in 285 patients (39.8% of all patients) *with a total of 553 HRD*. The most common medications for HRD were antibiotics, cardiovascular medications, analgesics and treatments for renal mineral and bone disorder. By univariate analysis, male gender (p=0.02), hypertension (p=0.047) and CHF (p<0.0001) were predictors of HRD. By multivariable logistic regression only CHF remained a significant predictor of HRD, (odds ratio=1.83, 95% CI 1.28 to 2.59, p= 0.0008).

Conclusions: Medication discrepancies are common in LS-CKD. The presence of CHF is a key predictor of high risk discrepancies. Further research should be directed at systems of care to improve medication safety in LS-CKD.

Funding: Other U.S. Government Support

Effect	Odds Ratio Point Estimates	95% Confidence Intervals		P Value
Age	1.003	0.99	1.01	0.58
Gender: Male vs Female	1.3	0.95	1.77	0.09
CHF	1.825	1.28	2.59	0.0008
Hypertension	1.768	0.91	3.41	0.09

SA-PO438

End-of-Life Care in Advanced Kidney Disease Treated and Not Treated with Maintenance Dialysis Susan P. Wong,[2] Margaret K. Yu,[3] Chuan-fen Liu,[2] Paul L. Hebert,[1] Ann M. O'Hare.[2] *[1]VA HSR&D Puget Sound Healthcare System, Seattle, WA; [2]VA Puget Sound Health Care System, HSR&D, Seattle, WA; [3]Stanford Univerity, Stanford, CA.*

Background: Little is known about the clinical course of patients with chronic kidney disease (CKD) who do not receive maintenance dialysis.

Methods: We followed a national cohort of 28,568 patients receiving care in the US Department of Veterans Affairs (VA) from the date of their second estimated glomerular filtration rate <15 ml/min per 1.73m^2 occurring between 2000-2009 through October 1, 2011. We used a combination of national registry data on dialysis, VA and Medicare files, and medical record review to identify a subset of 18,051 patients who were treated with dialysis, 851 patients in whom there was a decision not to pursue dialysis, and 640 patients

who were preparing for but had not started dialysis during follow-up. We compared survival, hospitalization and receipt of an intensive procedure during the final month of life, in-hospital death, palliative care consultation and hospice enrollment during follow-up across treatment groups.

Results: Median survival was 47.4 months for patients who received dialysis, 6.3 months for those who did not pursue dialysis (HR 2.17, 95% CI 2.94-3.42) and 10.7 months for those who were preparing for dialysis (HR 2.39, 95% CI 2.19-2.62). Hospitalization (57.3% vs. 76.8%; OR 0.40, 95% CI 0.34-0.46), receipt of an intensive procedure (3.5% vs. 24.6%; OR 0.15, 95% CI 0.10-0.22) and in-hospital death (41.4% vs. 57.3%; OR 0.78, 95% CI 0.74-0.82) were less common and palliative care consultation (52.6% vs. 21.6%; OR 4.19, 95% CI 3.58-4.90) and hospice enrollment (38.7% vs. 18.2%; OR 3.32, 95% CI 2.83-3.89) more common among patients who did not pursue dialysis than in those who received dialysis. For patients who were preparing for dialysis, hospitalization, receipt of an intensive procedure, and in-hospital death were less common but palliative care consultation and hospice referral similar as compared with patients treated with dialysis.

Conclusions: Patients with advanced CKD not treated with dialysis had more limited survival and received less intensive end-of-life care than those treated with dialysis.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO439

Ethnic Differences in Mortality among Veterans with Kidney Disease: A 13-Year National Longitudinal Cohort Study Mukoso N. Ozieh,[2,4] Mulugeta Gebregziabher,[1,6] Ralph Ward,[6] David J. Taber,[1,6] Leonard Egede.[3,5]
[1]Medical University of South Carolina, Charleston, SC; [2]Nephrology, Medical College of Wisconsin, Milwaukee, WI; [3]Internal Medicine, Medical College of Wisconsin, Milwaukee, WI; [4]Nephrology, Zablocki VAMC, Milwaukee, WI; [5]Center for Patient Care and Outcomes Research (PCOR), Medical College of Wisconsin, Milwaukee, WI; [6]Health Equity and Rural Outreach Innovation Center, Ralph H. Johnson VAMC, Charleston, WI.

Background: To assess the association between ethnic differences and mortality among Veterans with chronic kidney disease (CKD) over a 13-year period.

Methods: We examined all-cause mortality among Veterans with CKD from Jan 2000 to Dec 2012, including 3,015,318 Veterans using a unique algorithm to identify CKD; which was defined as estimated glomerular filtration rate (eGFR) of >60ml/min/1.73m^2 and presence of proteinuria for >3 months for stage 1 and 2 CKD or eGFR <60 ml/min/1.73m^2 for >3 months for stage 3 CKD or higher. Cox proportional hazards models were used to assess the relationship between mortality and racial/ethnic groups, and the models were developed in a sequential fashion. Hazard ratios (HR) and corresponding 95% CI were reported overall. All analyses were performed in SAS 9.4.

Results: The mean age for the cohort was 76.7 ± 11 years, which varied by ethnicity: 70.8 ± 12 years in Non-Hispanic blacks (NHB); 74.5 ± 11.7 years in Hispanics and 78.0 ± 10.3 years in non-Hispanic whites (NHW)]. The unadjusted all-cause mortality rate was 52.0% in NHW, 42.7% in NHB and 41.3% in Hispanics. After adjusting for demographic variables, NHBs and Hispanics had statistically significant lower CKD mortality risk relative to NHW (HR 0.92; 95% CI, 0.91 - 0.92) and (HR: 0.73, 95% CI, 0.72 - 0.74) respectively. In the fully adjusted model (adjusting for CKD stage and comorbidities in addition to other relevant covariates), NHB and Hispanics maintained this survival advantage compared to NHW, [NHB (HR: 0.85, 95% CI, 0.84 - 0.85) and Hispanic (HR: 0.74, 95% CI, 0.73 - 0.74)].

Conclusions: This is the first national longitudinal cohort study among Veterans which uses a robust algorithm to identify CKD. Non-Hispanic blacks and Hispanic Veterans with CKD have a survival advantage relative to NHW after adjusting for demographics, CKD stage and comorbidities.

SA-PO440

Treatment of Depression Symptoms Is Associated with Attenuated Risk of All-Cause Mortality among Patients with CKD Delphine S. Tuot,[3] Keith C. Norris,[2] Jennifer J. Gassman,[1] Elaine Ku.[3] *[1]Cleveland Clinic, Cleveland, OH; [2]UCLA, Marina Del Rey, CA; [3]University of California, San Francisco, San Francisco, CA.*

Background: Depression is common, under-recognized, and undertreated among patients with CKD, especially among racial/ethnic minorities. We examined whether the relationship between depressive affect and mortality differs by antidepressant use or race/ethnicity among patients with CKD.

Methods: We assessed the presence of depressive symptoms among Chronic Renal Insufficient Cohort (CRIC) participants, defined by a Beck Depression Inventory II (BDI) score of ≥14 at baseline enrollment. Cox regression was used to associate baseline depressive symptoms with risk of all-cause mortality (before or after ESRD) adjusted for socioeconomic factors, baseline CKD severity, time-updated comorbid conditions including ESRD status, and baseline anti-depressant use. We tested for the presence of interaction between race/ethnicity and depressive symptoms. Confirmatory analyses were performed using long-term follow-up data from the African American Study of Kidney Disease and Hypertension Cohort (AASK).

Results: Among 3725 CRIC participants, 23.3% had a baseline BDI of ≥14 with 17.0% prevalence of anti-depressant use. Crude mortality rate was 3.37/100-person years (PY) during 6.7 years of median follow-up. Baseline BDI ≥14 was associated with higher risk of all-cause mortality, attenuated by antidepressant use (Table). Differences in the relationship between BDI score and mortality were noted by race/ethnicity ($P_{interaction}$= 0.04, Table). Results were consistent among 652 AASK study participants, among whom 30.3% had BDI ≥14 with a crude mortality rate of 6.8/100-PY. Baseline BDI ≥14 in AASK was not associated with greater risk of mortality during 5.1 years of median follow-up (aHR=0.84; 0.61-1.18).

Conclusions: Treatment of depressive symptoms was associated with attenuated risk of mortality among individuals with CKD. Further investigation is needed to better understand differences in mortality risk by depressive symptoms among racial/ethnic subgroups.

Funding: NIDDK Support

CRIC participants	Baseline BDI >= 14	Baseline antidepressant use	Number of deaths	Crude mortality rate (per 100 person years)	Association between baseline BDI >=14 and all-cause mortality			
					unadjusted HR	Model 1	Model 2	+ baseline antidepressant use
Overall	23.3%	17.0%	753	3.37	1.93 (1.66-2.24)	1.41 (1.21-1.70)	1.21 (1.01-1.45)	1.17 (0.97-1.40)
Whites	13.6%	23.0%	286	2.78	1.61 (1.20-2.17)	1.58 (1.15-2.16)	1.52 (1.10-2.09)	1.35 (0.97-1.88)
Blacks	20.7%	14.0%	387	3.88	1.34 (1.06-1.70)	1.24 (0.98-1.59)	1.06 (0.82-1.37)	1.01 (0.78-1.31)
Overall cohort includes Whites, Blacks and Hispanics								
Model 1 adjusted for age, gender, income, education, insurance, marital status and employment								
Model 2 adjusted for model 1 + Body Mass Index, hypertension, coronary artery disease, congestive heart failure, cardiovascular disease, diabetes, cancer, tobacco use, alcohol use, baseline eGFR, baseline proteinuria, ESRD								
BDI = Beck Depression Inventory								

SA-PO441

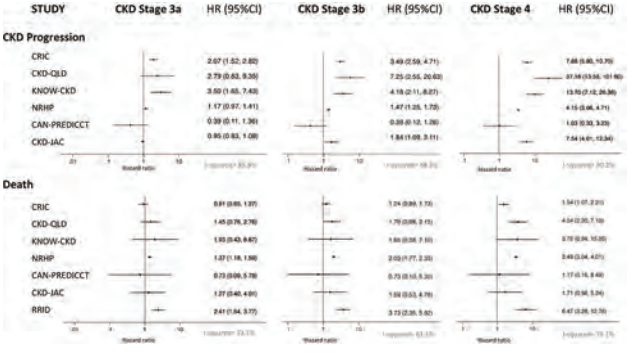
Global Variation in Rates of ESRD and Death among the ISN's International Network of CKD Cohort Studies (iNET-CKD) Paula F. Orlandi,[2] Adam Shardlow,[6] Adeera Levin,[8] Curie Ahn,[7] Helen G. Healy,[5] Kook-Hwan Oh,[7] Laura Sola,[3] Lisa C. Nessel,[11] Maarten W. Taal,[5] Masafumi Fukagawa,[10] Naohiko Fujii,[4] Ognjenka Djurdjev,[1] Pablo Rios,[12] Wei Yang,[11] Wendy E. Hoy,[9] Harold I. Feldman.[11] *[1]BC Renal Agency, Vancouver, AB, Canada; [2]University of Pennsylvania, Philadelphia, PA; [3]CASMU-IAMPP, Montevideo, Uruguay; [4]Hyogo Prefectural Nishinomiya Hospital, Nishinomiya, Japan; [5]None, Philadelphia, PA; [6]Royal Derby Hospital, Derby, United Kingdom; [7]Seoul National University Hospital, Seoul, Republic of Korea; [8]St. Paul's Hospital and University of British Columbia, Vancouver, BC, Canada; [9]The University of Queensland, Brisbane, QLD, Australia; [10]Tokai University School of Medicine, Isehara, Japan; [11]University of Pennsylvania, Philadelphia, PA; [12]National Fund of Resources, Montevideo, Uruguay.*

Background: Little is known about the variability in rates of CKD progression and death among CKD populations across the globe. The aim of this study was to assess this variability among cohorts that are members of iNET-CKD.

Methods: Group-level analysis comparing rates of CKD progression and death among 7 iNET-CKD cohorts. A total of 34,466 participants with eGFR < 90 ml/min/1.73m2 were included. Crude incidence rates were calculated overall and stratified by CKD stage. Cox regression models were performed to compare relative rates of CKD progression and death adjusted for age, sex, education, history of diabetes, cardiovascular disease, systolic blood pressure, BMI, smoking status, and proteinuria.

Results: Overall, crude rates (100 p-y) varied from 3.1 (95%CI: 3.0-3.3) to 9.2 (95%CI: 8.6-10.0) (100 p-y) for CKD progression and from 0.8 (95%CI: 0.6-1.1) to 6.0 (95%CI: 5.6-6.6) for death. Rates of CKD progression among participants with CKD stage 4 varied from 0 to 19.2 (95%CI: 17.7-20.8) and for death varied from 1.0 (95%CI:0.7-1.4) to 11.2 (95%CI: 9.9-12.7). The contrast among study rates remained significant after adjustment for baseline characteristics **(figure).**

Conclusions: Crude rates and adjusted relative rates of CKD progression and death vary extensively among iNET-CKD cohorts. Both findings suggest that factors that mediate CKD progression and death vary across countries and represent opportunities for future research.



Adjusted hazard ratios for CKD progression and death across CKD stages for each cohort study (reference group: CKD stage 2)

SA-PO442

Body Mass Index, Waist Circumference, and Risk of Kidney Function Decline in a Global Consortium Alex R. Chang. *CKD Prognosis Consortium, Baltimore, MD.*

Background: Limited data exist on the association between body mass index (BMI) or waist circumference (WC) with kidney function decline.

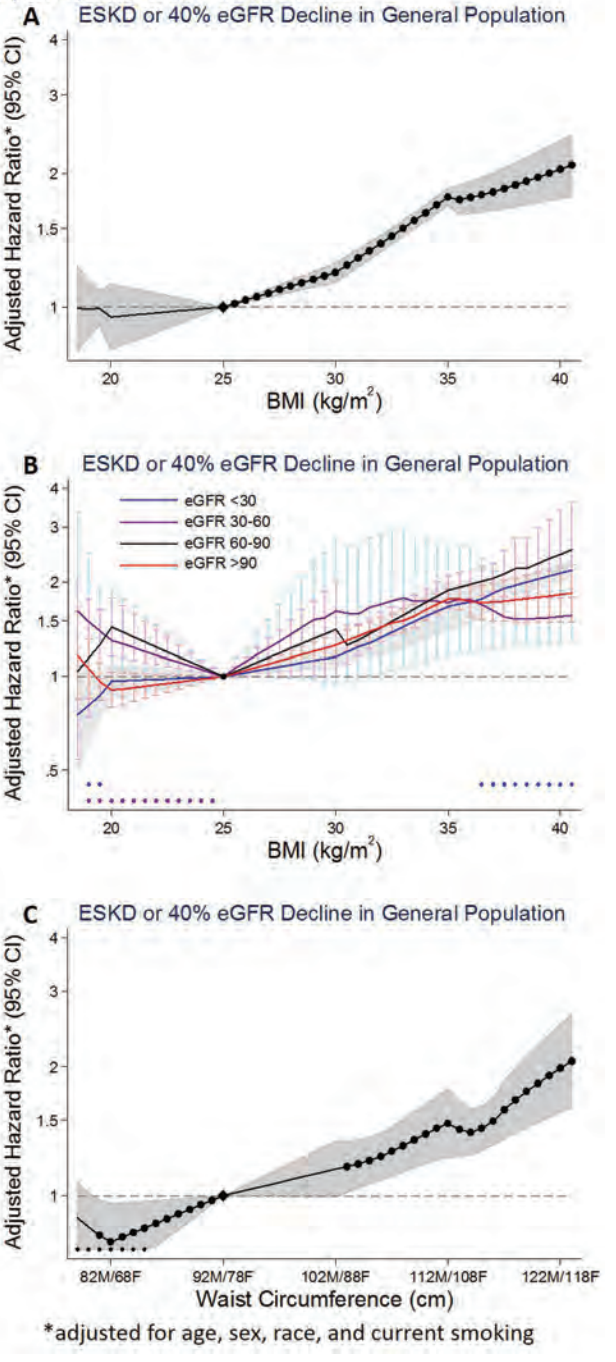
Methods: We performed collaborative meta-analyses to examine the association between BMI and WC with kidney function decline (ESKD or eGFR decline ≥40%) in 26 general population (GP) (n=712748) cohorts, of which 17 (n=238210) cohorts had WC data. Secondary meta-analyses were done in 12 CKD cohorts (n=22587), and in 6 high-risk population cohorts (n=135054). References were set at BMI 25 kg/m^2 and sex-specific WC values of 92 cm (men) and 78 cm (women).

Results: In GP cohorts, mean values for BMI, eGFR, and sex-specific WC were 27.8 (6.3) kg/m^2, 90.1 (22.5) ml/min/1.73m^2, and 92.2 (11.5) cm for men and 84.3 (13.2) cm for women, respectively. Within the 26 cohorts, 26,424 individuals developed kidney function decline over a mean follow-up of 6.9 (4.2) years. In analyses adjusted for age, sex, race, and current smoking, a BMI of 30 kg/m^2 vs. 25 kg/m^2 was associated with a hazard ratio (HR) of 1.20 (95% CI: 1.14-1.26) for kidney function decline **(Figure).** For the same outcome, WHO-recommended cut-points of waist circumference of 102 cm (men) and 88 cm (women) were associated with an HR of 1.15 (95% CI: 0.99-1.34) relative to the sex-specific references. The relationship between BMI and kidney function decline did not significantly differ by age, gender, diabetes, or baseline eGFR category. Associations were attenuated in high-risk and CKD cohorts, and when models were additionally adjusted for baseline diabetes, cardiovascular disease, hypertension, and eGFR.

Conclusions: Elevated BMI and WC are risk factors for ESKD and eGFR decline ≥40% in individuals with normal and reduced eGFR.

Funding: NIDDK Support, Private Foundation Support

Figure. Adjusted hazard ratios for kidney function decline according to (A) BMI overall, (B) BMI by level of eGFR, and (C) sex-specific waist circumference



SA-PO443

Why Select Conservative Management? A Qualitative Study of Patient-Identified Factors and Influences Contributing to Advanced Kidney Disease Patients' Decisions to Choose Non-Dialysis Care Emily Lu,[1] Jeffrey I. Silberzweig,[2] Anna M. Hennon,[3] Nathaniel E. Berman,[2] Ronald D. Adelman,[3] Megan J. Shen,[3] Katherine Lampa,[3] Manney C. Reid.[3] *[1]Nephrology and Hypertension, Weill Cornell Medicine/New York Presbyterian Hospital, New York, NY; [2]The Rogosin Institute, New York, NY; [3]Geriatrics and Palliative Medicine, Weill Cornell Medicine/New York Presbyterian Hospital, New York, NY.*

Background: Conservative management (CM) of advanced chronic kidney disease (CKD) continues to be an area of growing interest. However, in the United States, little is known about why and how patients decide to pursue CM. The purpose of this study is to

better understand why American patients with advanced CKD select CM and to identify factors or influences important to them in this decision-making process.

Methods: Patients with estimated glomerular filtration rate (eGFR) <30 ml/min who had previously made the decision to select CM—non-dialysis care—for their CKD were recruited. Semi-structured interviews of 15 patients were conducted, audiotaped, and transcribed. Data were analyzed inductively using grounded theory to identify common themes in patients' narratives.

Results: Four emerging themes were identified: 1) Choice of CM remains ultimately fluid, provisional, or circumstance-dependent (patients would consider dialysis if specific situation(s) developed, e.g. imminent danger/death, nephrologist recommendation, no longer felt well); 2) Importance of quality of life (negative impact of time required for dialysis, wish to live without restriction/limitation); 3) Currently feeling well (selected CM because does not feel sick); 4) Gaps in knowledge of and/or discussion with nephrologist regarding CKD care options (lack of recollection of discussion or content, difficulty describing anticipated symptoms of CKD progression).

Conclusions: Understanding how advanced CKD patients select CM as a treatment option for their CKD provides insight regarding the values/beliefs, motivations, and concerns they take into account during the decision-making process. Further interviews will be conducted to reach thematic saturation. The identified themes will inform a future longitudinal study of treatment decision-making in advanced CKD.

SA-PO444

Polycystic Kidney Disease Is Significantly Associated with Alzheimer Dementia RiskPropensity Score Matched Analysis of a Nationwide, Population-Base Cohort Tung-Min Yu, Ya-Wen Chuang, Misaki Moriishi, Shinichiro Tsuchiya. *Taichung Veterans General Hospital, Taichung ---, Taiwan.*

Background: Data on the risk of neurodegenerative diseases, including Alzheimer disease and Parkinson disease, in patients with polycystic kidney disease (PKD) are lacking.

Methods: A total of 4229 patients who were aged ≥20 years and had received a diagnosis of PKD were included in the PKD cohort. For each PKD case identified, 1 participant aged ≥20 years without a history of PKD, dementia, or PD was selected from the comparison cohort. For each patient with PKD, the corresponding controls were selected 1:1 on the basis of the nearest propensity score calculated using logistic regression.

Results: The incidence density rates of dementia were 4.31 and 2.50 per 1000 person-years in the PKD and control cohorts, respectively. A 2.04-fold higher risk of dementia was observed in patients with PKD than in controls (adjusted hazard ratio [aHR] = 2.04; 95% confidence interval [CI] = 1.46–2.85). Regarding the risk of different dementia subtypes including AD and vascular dementia (VD), the aHR for AD and pre-senile dementia was 2.71 (95% CI = 1.08–6.75) and that for VD was 0.90 (95% CI = 0.43–1.87) in patients with PKD compared with controls, after adjustment for age, sex, and comorbidities. Compared with controls, the risk of PD increased by 1.78-fold (95% CI = 1.14–2.79) in patients with PKD.

Conclusions: In clinical practice, health care professions should be aware of the risk of these neurodegenerative diseases in patients with PKD.

SA-PO445

Cognitive Function and Hyponatremia: Baseline Data from the SPRINT Trial Daniel E. Weiner,[4] S. Gaussoin,[8] Manjula Kurella Tamura,[3] Alfred K. Cheung,[6] William C. Cushman,[2] Anthony A. Killeen,[5] Mahboob Rahman,[1] Barry M. Wall,[2] Jamie P. Dwyer,[7] Kausik Umanath.[9] *[1]Case Western Reserve University, Cleveland, OH; [2]Memphis VA Medical Center, Memphis, TN; [3]Stanford University, Palo Alto, CA; [4]Tufts Medical Center, Boston, MA; [5]University of Minnesota, Minneapolis, MN; [6]University of Utah, Salt Lake City, UT; [7]Vanderbilt University Medical Center, Nashville, TN; [8]Wake Forest, Winston-Salem, NC; [9]Henry Ford, Derroit, MI.*

Background: Hyponatremia is stated as a reversible cause of cognitive impairment despite very limited data exploring this association.

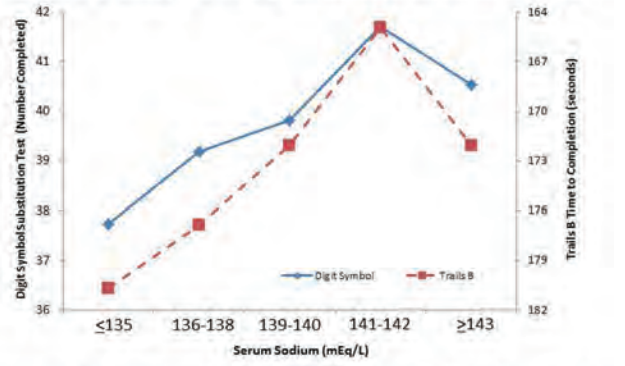
Methods: To explore the relationship between serum sodium concentration and cognitive function, we evaluated baseline data from the Systolic Blood Pressure INTervention (SPRINT) cognition substudy, SPRINT-MIND. Five cognitive domains were defined from 11 cognitive tests using z-scores, and the association of serum sodium with cognitive performance and brain abnormal white matter volume quantified by MRI were evaluated using linear and quantile regression, respectively.

Results: Among 9361 SPRINT-MIND participants, 2853 were administered an expanded cognitive battery at baseline, 664 of whom had brain MRI. Mean age was 68 years; 20% had known CVD and 29% eGFR <60 ml/min/1.73m^2. There were 120 participants with serum sodium ≤135 mEq/L, 485 with sodium 136-138, 983 with 139-140, 891 with 141-142, and 374 with ≥143 mEq/L. In analyses adjusted for age, sex, SPRINT network, education, race, diabetes, CVD, BMI, smoking, ACEi/ARB use, systolic and diastolic BP, lipids, eGFR, and albuminuria, lower serum sodium was associated with significantly worse executive function (p=0.002) and a trend to worse attention (p=0.08) and global cognitive function (p=0.12). Associations were unchanged following adjustment for thiazide and anti-depressant use. When examining thresholds, participants with Na ≥143 mEq/L also demonstrated worse cognitive test performance in most domains, consistent with a 'J'-shape relationship between sodium and cognition. In the MRI subgroup, sodium was not associated with brain abnormal white matter volume in adjusted analyses (p=0.77).

Conclusions: In older adults with hypertension, lower serum sodium is associated with worse cognitive function, particularly executive function. This does not appear to reflect structural brain disease.

Funding: NIDDK Support, Other NIH Support - NIA, NHLBI, NINDS, NCATS, Veterans Affairs Support

Figure. Adjusted least squares means for performance on Trailmaking Test Part B (p=0.005) and the Digit Symbol Substitution Test (p<0.001)



Adjusted for age, network, education, race, sex, diabetes, cardiovascular disease, BMI, use of ACE inhibitors or angiotensin receptor blockers, thiazide diuretics, loop diuretics, antidepressant medication use, SBP, DBP, Total cholesterol, HDL, LDL, eGFR, and albuminuria. For the Digit Symbol Substitution Test, a higher score is better while, for Trails B, a lower time is better.

SA-PO446

Atrial Fibrillation and Risk of Decline in Cognitive Function in CKD Mark D. Mccauley,[9,13] Jesse Y. Hsu,[12] Ana C. Ricardo,[9] Dawood Darbar,[10] Mayank Kansal,[9] Alan S. Go,[3] Manjula Kurella Tamura,[5] Harold I. Feldman,[12] John W. Kusek,[4] Jonathan J. Taliercio,[1] Panduranga S. Rao,[11] Tariq Shafi,[2] Jiang He,[6] Xue Wang,[8] Kristine Yaffe,[7] James P. Lash.[9] *[1]Glickman Urological and Kidney Institute, Cleveland, OH; [2]Johns Hopkins University School of Medicine, Baltimore, MD; [3]Kaiser Permanente Northern California, Oakland, CA; [4]NIDDK, Bethesda, MD; [5]Stanford University, Palo Alto, CA; [6]Tulane School of Public Health and Tropical Medicine, New Orleans, LA; [7]UCSF, San Francisco, CA; [8]UNIVERSITY OF PENNSYLVANIA, Philadelphia, PA; [9]University of Illinois at Chicago, Chicago, IL; [10]University of Illinois at Chicago, Chicago, USA, Chicago, IL; [11]University of Michigan Health System, Ann Arbor, MI; [12]University of Pennsylvania, Philadelphia, PA; [13]Medicine/Cardiology, Jesse Brown VA Medical Center, Chicago, IL.*

Background: Studies in the general population suggest that atrial fibrillation (AF) is an independent risk factor for decline in cognitive function, however this relationship has not been examined in persons with chronic kidney disease. We investigated the association between AF and changes in cognitive function over time in men and women enrolled in the Chronic Renal Insufficiency Cohort Study.

Methods: AF status was determined annually using 12-lead electrocardiogram and/or participant self-report. Global cognitive function was assessed biannually with the Modified Mini-Mental State Exam (3MS). Linear mixed effect regression was used to compare the association between time-updated AF status and longitudinal change in 3MS.

Results: Compared to individuals without AF (n= 3120) at baseline, individuals with AF (n=673) were older, had lower socioeconomic status, increased prevalence of cardiovascular disease, and lower estimated glomerular filtration rate. Baseline 3MS scores were similar (90.6 vs 91.3) in AF and non-AF groups. Median follow-up time was 5.8 years. Table below summarizes multivariable analyses.

Conclusions: Despite a greater burden of cardiovascular disease at baseline in individuals with AF, there was no independent association between AF and longitudinal changes in cognitive function.

Funding: NIDDK Support, Other NIH Support - National Heart Lung and Blood Institute (NHLBI, NIH)

	AF			No AF			Parameter Estimate, AF vs. No AF		
MODEL	ß coefficient	SE	P	ß coefficient	SE	P	ß coefficient	SE	P
Model 1	0.21	(0.02)	<0.0001	0.15	(0.04)	<0.0001	-0.057	(0.04)	0.16
Model 2	0.23	(0.02)	<0.0001	0.20	(0.04)	<0.0001	-0.03	(0.04)	0.41
Model 3	0.27	(0.03)	<0.0001	0.29	(0.05)	<0.0001	0.02	(0.05)	0.75

Model 1: Adjusted for site, age, sex, race/ethnicity, education
Model 2: Adjusted for factors in model 1 and systolic BP, diabetes, peripheral arterial disease, stroke, alcohol use, antiplatelet agents, anticoagulants, statin
Model 3: Adjusted for factors in models 1 and 2 and baseline eGFR, proteinuria

SA-PO447

Metabolomics Study Identifies Several Metabolites Associated with Uremic Symptoms in Advanced CKD Jiun-Ruey Hu,[1,5] Andrew S. Levey,[3] Josef Coresh,[1,4] Morgan Grams,[1,4] Eugene P. Rhee,[2] Tariq Shafi.[1,4] *[1]Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD; [2]Massachusetts General Hospital, Boston, MA; [3]Tufts Medical Center, Boston, MA; [4]Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University, Baltimore, MD; [5]Vanderbilt University School of Medicine, Nashville, TN.*

Background: Uremic symptoms are common in patients with advanced CKD, but the toxins that cause these symptoms are unknown.

Methods: We measured metabolites in participants of the Modification of Diet in Renal Disease (MDRD) with measured GFR < 20 ml/min/1.73 m^2 (N=216), using an untargeted LC/MS/MS platform. We determined the association of 667 metabolites with uremic symptom scores using linear regression adjusting for clinical factors and accounting for multiple comparisons.

Results: The mean age of the participants was 52 years and 81% were white. Uremic symptoms were common. 80% of participants had at least 1 uremic symptom. Metabolites associated with uremic symptoms are presented in the accompanying table.

Conclusions: We identified several metabolites associated with uremic toxins. Metabolomics has the potential to identify toxins that cause uremic symptoms.

Metabolite	Beta	p
Altered taste		
4-acetamidobutanoate	6.7	0.00038
3-methylglutarylcarnitine	4.4	0.00033
tauroursodeoxycholate	3.5	0.00039
bilirubin	-3.5	0.00044
N-delta-acetylornithine	-4.4	0.00041
cortisol	-5.5	0.00028
N-acetylcarnosine	-7.1	0.00019
deoxycarnitine	-7.6	0.00004
Vomiting		
N-formylmethionine	3.7	0.00005
N2,N5-diacetylornithine	-1.6	0.000002
bilirubin	-1.9	0.000002
Lack of energy		
N-acetylserine	13.5	0.00044
N6-carbamoylthreonyladenosine	12.8	0.00037
S-adenosylhomocysteine	12.1	0.00030
4-acetamidobutanoate	11.1	0.00001
homovanillate	9.6	0.00005
indoleacetylglutamine	5.1	0.00002
p-cresol-glucuronide	4.1	0.00003
Weakness		
4-acetamidobutanoate	11.7	0.00003
5-methylthioadenosine	11.3	0.00005
homovanillate	9.5	0.00036
hydantoin-5-propionic acid	6.3	0.00003
malonylcarnitine	-7.6	0.00032

Metabolite association with uremic symptoms

SA-PO448

Near-Infrared Spectroscopy Measured Muscle Haemoglobin O2 Saturation Kinetics and Physical Performance in CKD Thomas J. Wilkinson,[2] Alice e. White,[2] Daniel Nixon,[2] Douglas W. Gould,[2] Emma L. Watson,[2] Alice C. Smith.[1] *[1]John Walls Renal Unit, Leicester General Hospital, Leicester, United Kingdom; [2]University of Leicester, Leicester, United Kingdom.*

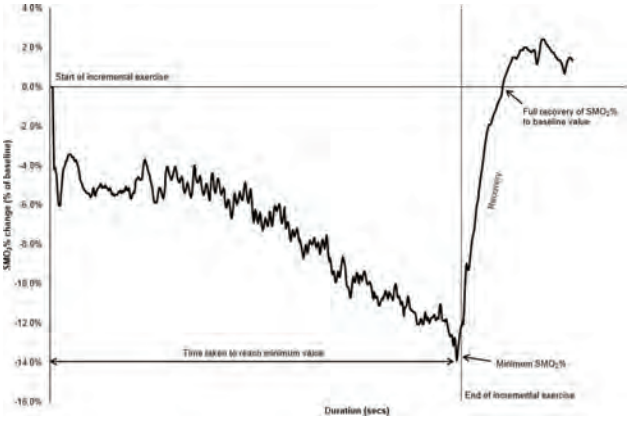
Background: CKD patients have poor exercise capacity. A possible factor may be an imbalance in muscle oxygen (O_2) supply and utilisation, moderated by mitochondrial and endothelial dysfunction. Near-infrared spectroscopy (NIRS) can be used to measure *in vivo* muscle oxidative metabolism. Using NIRS we investigated gastrocnemius skeletal muscle O_2 kinetics in non-dialysis CKD patients during exercise.

Methods: 30 patients (59±16 yrs; 11 female; eGFR: 54±26 mL/min/kg/1.73m^2) completed the incremental shuttle walk test. NIRS measured light attenuation in the near-infrared spectrum and determined chromophores, primarily % of oxygenated haemoglobin present in the muscle (SMO_2%). SMO_2% was assessed before, during, and after (recovery) exercise. Resting cardiac parameters were assessed, along with habitual physical activity (PA). Patients were divided into aerobic capacity tertiles to determine SMO_2% differences.

Results: From baseline, SMO_2% declined by 12±7% during exercise before rapidly recovering upon cessation (Fig 1). Controlled for age, sex and eGFR, patients with higher aerobic capacity took 258 (56-461) secs (55%) longer (P=.016) to reach minimum SMO_2%, and recovered 49 (2-96) secs (75%) quicker (P=.040) than those with lower aerobic capacity. Better SMO_2% kinetics were associated with higher stroke volume and PA levels, and lower peripheral resistance.

Conclusions: Superior SMO_2% kinetics (i.e. slower deoxygenation rate, quicker recovery) are associated with greater exercise capacity, better vasculature, and higher PA in CKD. The dysfunctional kinetics observed may indicate endothelial dysfunction and an inability of mitochondria to efficiently carry out oxidative phosphorylation. Accordingly, NIRS is a low-cost and non-invasive means to evaluate O_2 kinetics and could be a useful tool to measure oxidative metabolism mechanisms in CKD.

Funding: Private Foundation Support



SA-PO449

Exercise Improves Self-Reported Physical Symptom Burden and Fatigue in Non-Dialysis CKD Thomas J. Wilkinson,[3] Soteris Xenophontos,[3] Douglas W. Gould,[3] Amy L. Clarke,[3] Barbara P. Vogt,[2] Joao L. Viana,[4] Emma L. Watson,[3] Alice C. Smith.[1] *[1]John Walls Renal Unit, Leicester General Hospital, Leicester, United Kingdom; [2]Universidade Estadual Paulista UNESP, Botucatu, Brazil; [3]University of Leicester, Leicester, United Kingdom; [4]University Institute of Maia, Porto, Portugal.*

Background: CKD patients suffer from a variety of physical symptoms due to the disease and its treatments. Symptoms include fatigue, muscle weakness, pain, and sleep disruption, and these can negatively affect quality of life (QoL) and discourage physical activity. Whilst intradialytic exercise may help ameliorate some symptoms in dialysis patients, research on whether exercise can reduce symptom burden in non-dialysis patients is lacking.

Methods: 36 patients (62±12 yrs; 22 female; eGFR: 26±8 mL/min/kg/1.73m^2) completed supervised aerobic exercise (AE) (n=18) or combined aerobic plus resistance exercise (A+RE) (n=18) 3x/week for 12 weeks. Self-reported symptom burden and fatigue measures were taken pre- and post-exercise. The Leicester Uraemic Symptom Scale (LUSS) measured the frequency and intrusiveness of 11 symptoms. Fatigue was measured using the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F); the total FACIT-F score and Trial Outcome Index (TOI) were used.

Results: AE reduced the total mean number of symptoms from 6.3 to 5.4 (14% P=.014) and the frequency of itching by 35% (P=.004). AE also reduced the intrusiveness of sleep disturbance by 14% (P=.001) and experience of muscle spasm/stiffness by 29% (P=.021). In the A+RE group, only a reduction in the frequency (41% P=.001) and intrusiveness (39% P<.001) of a feeling in loss of muscular strength/power was seen. Exercise improved fatigue; total FACIT-F score was improved in the AE and A+RE groups by 9% (P=.028) and 23% (P=.068) respectively, whilst the TOI was improved by 10% (P=.067) and 27% (P=.048).

Conclusions: Exercise can significantly reduce physical symptom burden and fatigue in non-dialysis CKD. Patients performing AE experienced less symptoms overall, with itching, sleep disturbance, and muscle stiffness symptoms improving specifically. Unsurprisingly, patients performing additional strength training felt stronger. Fatigue was improved following both exercise modalities. Symptom burden contributes to physical inactivity and a reduction in QoL, and as such exercise should be encouraged to help improve patient's health status.

Funding: Private Foundation Support

SA-PO450

"It's Opened Up My Eyes to How Much I Can Actually Do": A Mixed Methods Study Exploring the Feasibility of a Physical Activity Education Programme in CKD Amy L. Clarke, Heather J. Mackinnon, James Burton, Alice C. Smith. *University of Leicester, Leicester, United Kingdom.*

Background: Physical activity (PA) can improve the quality of life (QoL) and health of patients with chronic kidney disease (CKD). However, patients exhibit minimal PA, and currently, no specific pathways exist to target physical inactivity in CKD. "PACT" is a 3.5-hour structured group education programme designed to initiate PA by eliciting illness perceptions, providing basic disease education, highlighting health risks, and promoting the benefits of PA and self-regulation.

Methods: A mixed methods 'before and after' feasibility study of the PACT intervention to explore recruitment, retention and engagement; and patient acceptability of intervention and outcome measures. Semi-structured interviews were conducted to gain an understanding of patient experience.

Results: Overall, 75 non-dialysis CKD patients were approached and 19 (25%) were consented. 17 (90%) attended the group session, and 4 withdrew due to unrelated reasons, resulting in a 68% completion rate. Engagement with step monitoring was good during the 8 weeks of walking;11 returned PA diaries completed at a rate of 61-100%. There was a mean (CI 95%) increase in daily steps from pre-to post-intervention of 1947(-445, 4349) which produced a small-moderate effect *(d=0.47)*. Positive changes were observed for: physical function, QoL, activation and knowledge. Our qualitative analysis found that participants enjoyed the interactive session and would recommended it; outcome assessments were for the most acceptable, and self-monitoring steps enhanced engagement. However, some participants felt that real time monitoring on a mobile app, further guidance for exercise intensity, and a greater emphasis on psychological strategies related to disease adjustment and PA motivation could improve the intervention.

Conclusions: The purpose of this trial was to determine acceptability of and engagement with the PACT protocol. Findings were positive, with some areas for refinement indicated. The trial was not powered to assess efficacy, but demonstrated potential to improve PA, and domains related to QoL. This approach to lifestyle management has great promise in CKD and deserves further attention.

SA-PO451

Prevalent Depression and Associated Factors in a Disadvantaged CKD Population Carl P. Walther, Jingbo Niu, Sai Kaumudi Saridey, Wolfgang C. Winkelmayer, Sankar D. Navaneethan. *Baylor College of Medicine, Houston, TX.*

Background: Depression is common among individuals with CKD and associated with adverse outcomes. In the US population, prevalence is lower in older persons and varies with race/ethnicity. We studied factors associated with depression in a diverse non-dialysis CKD cohort, which could help to identify high-risk patients and disparities.

Methods: We identified adults with eGFR <60 for ≥90 days who received care through a safety-net health system from 2006-16. Depression was determined from ICD codes prior to or within 2 weeks of cohort entry. Comorbidities were identified using a similar method. We categorized CKD into stages 3A, 3B, 4, and 5. Race/ethnicity was recorded in 5 mutually-exclusive categories. We used multivariate logistic regression to analyze associations with demographics, comorbidities, and CKD stage, and calculated predicted probabilities and 95% CIs.

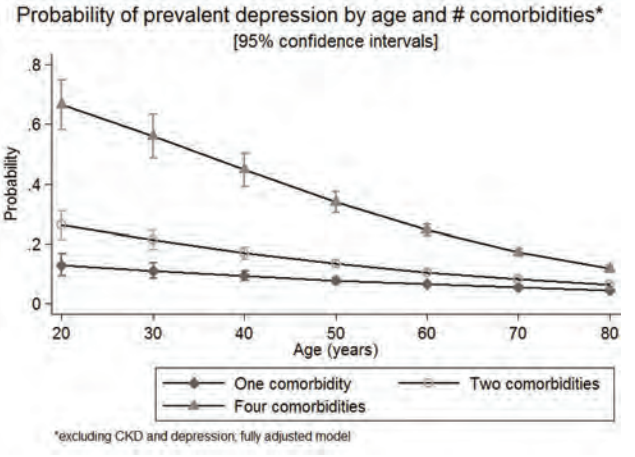
Results: We included 13678 CKD patients of whom 39.4% were Hispanic, 40.9% black, 11.5% white, 5.9% Asian/Pacific Islander, and 2.2% other/unknown race. Depression prevalence was 11.6% overall, and 23.9% among whites, 11.1% among blacks, 9.8% among Hispanics, and 5.3% among Asians/PIs. Interactions between age and race/ethnicity, and between age and number of comorbidities were observed.

Conclusions: Depression prevalence varied with race/ethnicity, age, and comorbidities. Depression decreased markedly with age in blacks and whites, but not Hispanics. The association of comorbidities with depression decreased with age.

Stratified Odds Ratios [95% CIs] for Depression*

Age category (years)	Hispanic (versus black or white)†	One additional comorbidity‡
18 to 34	0.30 (0.11-0.87)	2.63 (1.56-4.43)
35 to 49	0.50 (0.36-0.69)	1.70 (1.49-1.93)
50 to 64	0.76 (0.65-0.89)	1.59 (1.50-1.68)
65 to 79	0.87 (0.68-1.11)	1.59 (1.56-1.73)
80 or older	1.61 (0.94-2.77)	1.23 (1.03-1.46)

*Adjusted for CKD stage, sex, cohort year, continuous age, and either †comorbidity count or ‡race/ethnicity



SA-PO452

Prevalence and Associated Factors of Depressive Symptoms among Predialysis CKD Patients in China: Results from the Chinese Cohort Study of CKD (C-STRIDE) Lei Pu,[2] Li Wang,[2] Guisen Li.[1] *[1]Renal Division and Institute of Nephrology, Sichuan Academy of Medical Sciences and Sichuan Provincial People?s Hospital, Chengdu, China; [2]Sichuan Provincial People's Hospital, Chengdu, China. Group/Team: C-STRIDE study group.*

Background: Depression was reported to be the most common mental disorder in patients with chronic kidney disease (CKD). Previous studies found that depression could accelerate the progression of CKD disease, and was an independent risk factor of hospitalization and death among patients with CKD. The objective of this study is to investigate the prevalence of depression in Chinese patients with predialysis CKD, and to identify factors associated with depression.

Methods: Baseline data of a multicenter prospective cohort study, Chinese cohort study of chronic kidney disease(C-STRIDE)study were used. Altogether 2995 participants with CKD stage 1 to 4 who completed a survey of depressive symptoms were included. The depressive symptoms were assessed by Zung Self-Rating Depression Scale (ZSDS). ZSDS≥50 was used as thecutoff score of the presence of depressive symptoms. MultivariableLogistic regression models were used to identify factors associated with depression.

Results: Mean eGFR level was 51.59±29.49ml/min/1.73m2. The prevalence of depressive symptoms was 37.8% and increased significantly with advanced CKD stages. Female, higher education level, low income, larger economic impact of disease cost, comorbid cardiovascular disease, anemia, lower physical activity ability were independently associated with depressive symptoms.

Conclusions: Our study revealed that depressive symptoms were common among Chinese predialysis CKD population. Socioeconomic factors andclinical characteristics of severity of disease were strongly associated with the depressive symptoms.

SA-PO453

The Impact of CKD on Disability and Health-Related Quality of Life (HR-QOL) of Children and Adolescents Anna Francis,[1] Madeleine Didsbury,[2] Anita Van zwieten,[1] Kerry Chen,[7] Laura J. James,[7] Siah Kim,[6] Tonya Kara,[5] Natasha Nassar,[1] Allison Tong,[7] Steven Mctaggart,[9] David W. Johnson,[4] Jonathan C. Craig,[8] Kirsten Howard,[1] Germaine Wong.[3] *[1]University of Sydney, Sydney, NSW, Australia; [2]Centre for Kidney Research, Westmead, NSW, Australia; [3]None, Auambie, NSW, Australia; [4]Princess Alexandra Hospital, Brisbane, QLD, Australia; [5]Starship Children's Hosptial, Auckland, New Zealand; [6]Sydney Children's Hospital, Newtown, NSW, Australia; [7]The University of Sydney, Westmead, NSW, Australia; [8]University of Sydney/ Children's Hospital, Sydney, NSW, Australia; [9]Children's Health Queensland, Brisbane, QLD, Australia.*

Background: Children with CKD suffer from reduced HR-QOL. The extent of impairment and risk factors for poorer HR-QOL and disability are under-studied. The study aimed to compare overall HR-QOL and severity of disability in children and adolescents with different stages of CKD and to determine factors associated with lower HR-QOL scores.

Methods: HR-QOL data were collected from children and adolescents (age 6-18 years) across five paediatric units in Australia and New Zealand. The Health Utilities Index 3 survey was used to measure overall utility based HR-QOL (where 0 represents being dead and 1 represents full health). A score of 1.00 represents no disability, 0.89-0.99 represents mild disability, 0.70-0.88 represents moderate disability and less than 0.70 represents severe disability. HR-QOL scores and disability stages were compared between CKD stages using the Mann-Whitney-U test. Multivariable linear regression assessed factors associated with decline in HR-QOL.

Results: There were 377 children with CKD (median age 12.6 years). The median unadjusted HR-QOL score for those with CKD stages 1-4 was 0.88 (interquartile range

[IQR] 0.61-0.97), higher than those on dialysis (0.67, IQR 0.39-0.91, p<0.001), but similar to kidney transplant recipients (0.83, IQR 0.59-0.97, p=0.4). Severe disability was more common in dialysis patients (20/35, 57%), compared to transplant recipients (37/114, 33%) or those with CKD stages 1-4 (57/176, 32%) (c2=8.4, p=0.02) (table 1). The factors associated with decrements in HR-QOL were being on dialysis (compared to CKD stages 1-4: reduction by 0.13, 95%CI 0.02-0.24) and lowest quartile family income (compared to highest income quartile: reduction by 0.10, 95%CI 0.01-0.20), when adjusted for age and gender.

Conclusions: HR-QOL children with CKD was significantly related to stage of disease and family income, with children on dialysis and those the lowest family income having significant lower HR QOL.

Funding: Private Foundation Support

Disability in children with CKD

	None to mild disability	Moderate disability	Severe disability
Whole CKD cohort (n, %)	138 (43)	73 (22)	114 (35)
Dialysis (n, %)	10 (29)	5 (14)	20 (57)
Transplant (n, %)	46 (40)	31 (27)	37 (33)
CKD 1-4 (n, %)	82 (47)	37 (21)	57 (32)

SA-PO454

Posttraumatic Stress Disorder and Outcomes among US Veterans Who Transition to Renal Replacement Therapy: A Transition of Care in CKD Study Vanessa A. Ravel,[1] Elani Streja,[1] Connie Rhee,[1] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh.[1] [1]*UC Irvine, Orange, CA;* [2]*University of Tennessee Health Science Center, Memphis, TN*.

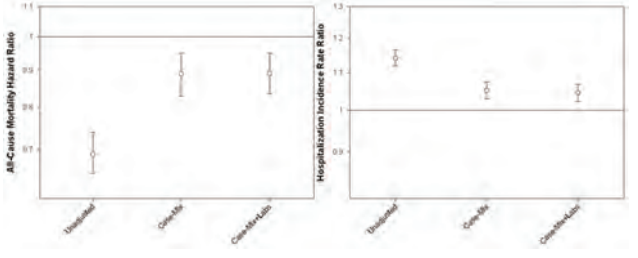
Background: End stage renal disease (ESRD) patients starting dialysis treatment often experience worse mental health and quality of life. While poor mental health has been associated with a higher risk of mortality and hospitalization in studies of veteran patients, there is a dearth of research specifically evaluating the association of posttraumatic stress disorder (PTSD) and these outcomes in veterans transitioning to dialysis.

Methods: From a nationwide contemporary cohort of 79,331 US veterans transitioning to dialysis between 10/2007 and 3/2014, we identified 5,464 (6.9%) veterans with a PTSD diagnosis prior to transition. The association between pre-ESRD (prelude) PTSD and 1-year all-cause mortality was examined via adjusted Cox regression, and Poisson regression was used to evaluate the association between PTSD and 1-year hospitalization rate. Models were hierarchically adjusted for case-mix and laboratory covariates.

Results: Patients were 71±12 years old and included 5% women, 24% African-Americans, 61% diabetics and 9% were homeless. Patient with prelude PTSD had a higher a risk of 1-year all-cause mortality [aHR: 0.89 (0.84-0.95)], but a lower 1-year hospitalization incident rate ratio [aIRR: 1.05 (1.02-1.07)] in fully adjusted models.

Conclusions: While prelude PTSD is associated with reduced risk of post-ESRD mortality in veterans transitioning to dialysis, it is also associated with a higher hospitalization rate. Studies are warranted to examine the role of psychosocial factors between prelude PTSD and post-ESRD outcomes, and whether an increased hospitalization rate mediates better survival for veterans with PTSD transitioning to ESRD.

Funding: NIDDK Support



SA-PO455

Impact of Multimorbidity on Patient-Reported Quality of Life – Analysis of a Real World CKD Patient Population James Jackson,[1] Anna Hadfield,[2] Rebecca Moon.[1] [1]*Adelphi Group, Macclesfield, United Kingdom;* [2]*Adelphi Real World, Macclesfield, United Kingdom*.

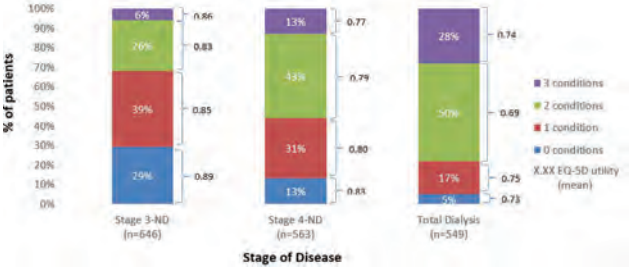
Background: It is widely accepted that the prevalence of anemia, secondary hyperparathyroidism (SHPT) and hyperkalemia amongst chronic kidney disease (CKD) patients increases as CKD worsens. The objective of this analysis was to determine whether an increase in the number of CKD related comorbidities has an impact on patient quality of life (QoL).

Methods: Data were drawn from the Adelphi CKD Disease Specific Programme (DSP), a real-world, cross-sectional survey of consulting non-dialysis (ND) and dialysis CKD patients across 5EU and USA. Patients were segmented according to the number of physician-reported, CKD-related comorbidities (anemia, SHPT and/or hyperkalemia) experienced and patient-reported QoL was assessed using EuroQol-5D-3L (EQ-5D).

Results: Results from 1758 CKD patients showed that as CKD worsened, patients were more likely to experience multiple comorbid conditions (Figure 1). An increase in multimorbidity at Stage 3-ND and Stage 4-ND was associated with a decrease in patient-reported QoL. For Stage 4-ND patients, a significant reduction was observed in the mean EQ-5D score for patients with 3 conditions compared with those who have 0 conditions (Figure 1). Although a similar trend was not observed amongst the Dialysis population, the QoL scores were lower overall than those patients at an earlier stage (Figure 1).

Conclusions: Multimorbidity increases as CKD progresses. Increased multimorbidity is associated with a poorer quality of life for CKD patients. Slowing disease progression could help prevent the onset of anemia, SHPT and/or hyperkalemia leading to maintenance of better QoL for longer.

Figure 1: Proportion of patients with 0, 1, 2 or 3 comorbidities commonly associated with CKD and related EQ-5D utility scores



SA-PO456

Association between Peer Mentoring and Quality of Life among Patients with CKD Hafiz Z. Mahmood, Awais Ammar, Emily J. Wasserman, Tara Liaghat, Umar Farooq, Nasrollah Ghahramani. *Penn State College of Medicine, Hershey, PA.*

Background: Health related quality of life (HRQOL) has been increasingly recognized as an important medical outcome in patients with chronic kidney disease (CKD). Peer mentoring (PM) has been proposed as an effective model for active patient engagement and subsequent improvement in HRQOL. This study evaluates the preliminary effects of face-to-face peer mentoring on HRQOL among patients with chronic kidney disease.

Methods: Sixty-one patients with CKD were assigned to trained peer mentors with whom they had weekly phone contact and at least monthly face-to-face contact for a six month period. All participants completed a baseline Short Form Kidney Disease Quality of Life (KDQOL) instrument, developed as a self-report, health-related QOL tool designed specifically for patients with CKD. Currently, 25 patients have also completed the 12-month assessment. The Wilcoxon Signed Rank Test was used to evaluate paired differences in patient outcome measures for patients receiving face-to-face mentorship between the baseline and 12-month assessments (Change = Difference of 12-month assessment minus baseline assessment). All reported p-values are two-sided with a significance level of 0.05.

Results: There was a significant difference in the 'Symptoms/Problems' subscale (p=0.003; Median Change =6.25, IQR = 20.83, N=25) and the 'Effects of Kidney Disease' subscale (p=0.01; Median Change=12.50, IQR=25.00, N=25) of the KDQOL between the baseline and 12-month assessments. No significant differences were noted in the Burden of Kidney Disease (p=0.73, N=25), Physical Component Summary (p=0.89, N=15) and Mental Component Summary (p=0.30, N=15).

Conclusions: Face-to-face peer mentoring is associated with improved symptoms and problems subscale, as well as the effects of kidney disease subscale of the KDQOL instrument.

Funding: Other NIH Support - Patient-Centered Outcomes Research Institute

SA-PO457

Depression, Anxiety, and Stress – Before and After Dialysis Initiation: A Pilot Study Cicero I. Bezerra, Bruno C. Silva, Rosilene M. Elias. *Universidade de Sao Paulo, Sao Paulo, Brazil*.

Background: Chronic kidney disease (CKD) affects psychological and emotional aspects that are particularly critical while choosing the renal replacement therapy (RRT) modality. Anxiety, depression and stress are common yet frequently overlooked among these patients. We have examined the behavior of these emotional components pre- and post-RRT, and hypothesized that there will be an improvement of symptoms after starting dialysis, regardless of chosen modality.

Methods: This is a prospective observational study in which patients were approached in two moments: while attending the structured Pre-Dialysis Education Program, and after starting RRT (within the first 3 months). Scales of anxiety, depression and stress (Hospital Anxiety and Depression Scale and Perceived Stress Scale, respectively) were applied. Demographic and clinical characteristics were also assessed.

Results: Out of 67 patients, 16 have already started RRT by April 2017 (50% men, age 56 ± 15 years, 58% Caucasian, 42% diabetic). Scores of depression, anxiety and stress reduced significantly from pre to post RRT initiation (Table 1), with no difference between patients who chose peritoneal dialysis or hemodialysis. Before RRT, anxiety scores correlated significantly with depression (r=0.75) and stress scores (r=0.79); after RRT initiation, anxiety scores correlated significantly with depression (r=0.59) and stress scores (r=0.62).

Conclusions: Although decision-making on RRT is a process associated with high scores of depression, anxiety and stress, these symptoms are attenuated at the end of this process, with patients already on dialysis. This finding identifies the importance of targeting psychological symptoms on RRT modality choosing process, and highlights that an improvement might occur after RRT initiation.

Table 1 - Anxiety, Depression and Stress scores before and after RRT initiation

	Before starting RRT	After starting RRT	p
Anxiety scores	6.1 ± 3.3	1.9 ± 1.8	<0.0001
Depression scores	7.8 ± 4.0	4.2 ± 2.8	<0.0001
Stress scores	29.4 ± 7.5	11.1 ± 6.4	<0.0001

SA-PO458

Enhanced Evaluation of Human Renal Biopsies Using Multicolor Flow Cytometry and Cytokine Analysis: A Focus on Transplanted Kidneys Kimberly A. Muczynski, Nicolae Leca, Susan K. Anderson. *Medicine-Nephrology, University of Washington, Seattle, WA.*

Background: Virtually all renal disease is due to an immune response. Examination of renal biopsies with light, immunofluorescence and electron microscopy provide limited information about immune mechanisms causing kidney injury and disease activity. In adddition, information is often insufficient to direct therapy with specific agents, which becomes a frustration with new immune modulating agents being developed.

Methods: To enhance the information available from a biopsy we developed a technique for reducing a fraction of a renal biopsy to single cells for multicolor flow cytometry and for capture and quantitation of secreted cytokines present within the biopsy. As proof of concept, after evaluation of over 400 biopsies, we use our technique to suggest new criteria for evaluating rejection and renal inflammation that are clinically useful for directing therapy.

Results: A ratio of CD8+ to CD4+ lymphocytes of greater than 1.2 within the biopsy of transplanted kidneys is associated with rejection, even before it is apparent by microscopy. Elevated numbers of CD45 leukocytes and higher levels of IL-6, IL-8 and IL-10 within the kidney indicate more severe injury. Antibody binding to renal microvascular endothelial cells can be measured and corresponds to antibody-mediated forms of allograft rejection. Eculizumab binding to endothelial cells suggests complement activation, which may be independent of bound antibody. A comparison of intrarenal leukocyte subsets and their activation states to those of peripheral blood from the same donor at the time of biopsy identify significant differences supporting the need to develop techniques which interrogate the immune system within the kidney.

Conclusions: Our use of cytometry to assess intrarenal leukocyte subsets, microvascular endothelial cell properties and secreted cytokines from a fragment of a standard renal biopsy provide useful information about the immune processes in the kidney. After evaluation of over 400 biopsies we find results reliable indicators of disease activity. This information is not available from peripheral blood. While we have focused on biopsies from transplanted kidneys (due to their availability), our techniques are equally applicable to native kidneys. Cytometry can enhance renal biopsy evaluation in a clinically significant manner.

Funding: Private Foundation Support

SA-PO459

Outcomes of Kidney Transplant Recipients with G3 Glomerulitis Fahad Aziz,[2] Sandesh Parajuli,[5] Weixiong Zhong,[4] Didier A. Mandelbrot,[3] Arjang Djamali.[1] *[1]School of Medicine and Public Health, Madison, WI; [2]University of Wisconsin, Madison, WI; [3]U of Wisconsin Hospital, Madison, WI; [4]University of Wisconsin Madison, Madison, WI; [5]UW Health, Middleton, WI.*

Background: Glomerulitis is one of the pathological features of AMR. However, the natural history of kidney allografts with g3 lesions (glomerulitis in >75% of glomeruli) is poorly defined.

Methods: We sought to determine the concomitant immunopathological findings and outcomes in a case series of kidney transplant recipients with g3 lesions.

Results: Thirty seven consecutive kidney transplant recipients with g3 lesions in diagnostic biopsies performed 6.2 ± 6.7 years after transplant were included. At the time of biopsy, mean age was 45.5 years and all patients were on triple therapy with CNI, MPA, and prednisone. The majority were Caucasian (80%), male (60%), and had transplant glomerulopathy (68%). Kidney function and immunopathological findings (mean values) at the time of biopsy are displayed in table 1. Treatment after the biopsy included pulse steroids/IVIG (70%), Rituximab (50%), and plasma exchange (10%). Patients were followed up for a mean of 1.6±1.1 years. The incidence of graft loss and death was 11 (30%) and 3 (10%), respectively. Univariate regression analyses including demographic, functional, and immunohistological variables determined that t score (HR = 2.7, 95%CI: 1.3 to 5.8), ct score (HR = 2.1, 95%Cl: 1.009 to 4.7), Scr (HR = 1.6, 95%CI: 1.1 to 2.2), and live donor status (HR = 0.18, 95%Cl: 0.3 to 0.9) were significantly associated with graft loss. Multivariate stepwise Cox regression analyses only retained Scr (HR = 1.8, 95%Cl: 1.2 to 2.7) and live donor status (HR = 0.14, 95%Cl: 0.02 to 0.8). Notably, C4d staining and DSA were not retained as significant predictors.

Conclusions: In this largest case series of patients with g3 lesions, 30% of the grafts were lost with in 2 years. Scr and live donor status were the most important variables associated with graft loss. Future studies are needed to determine preventive and treatment stratagies to improve outcomes in patients with g3 lesions.

Table 1. Kidney function and immunopathological characteristics of 37 patients with G3 lesions

Serum Creatinine	eGFR	UPC	DSA +	Sum MFI	i	t	v	g	mvi	C4d	ci	ct	cv	cg	Sum Chronicity
2.3	42	1.6	40%	11000	0.4	0.3	0.4	3	4	0.6	1.1	1.2	0.9	1.4	4.7

SA-PO460

Eosinophil-Rich Inflammation in Allograft Renal Biopsies: An Analysis of Clinical Significance and Correlation with Rejection Payaswini Vasanth, Carla L. Ellis. *Emory University, Atlanta, GA.*

Background: In this study we investigate the significance of interstitial eosinophilic inflammation in renal allograft and its association with rejection, response to treatment, risk of subsequent rejections, and allograft outcome.

Methods: We studied 26 kidney transplant pts between 2012-17 with AKI who underwent biopsies. The biopsies showed clusters of interstitial eosinophils histologically, with or without evidence of ACR, AMR, or both. Allograft function at the time of the biopsy was assessed by SCr and by its change from baseline. After initial treatment, pts were categorized as, - Complete Responders (CR): SCr returned to baseline - Partial Responders (PR): SCr decreased to a level that was greater than 50% of SCr at the time of biopsy, but never returned to baseline. - Non Responders (NR): SCr remained at or above SCr at the time of biopsy.

Results: 22 out of the 26 biopsies with eosinophils had rejection [Borderline 10(45%), 1A 1 (5%),1B 5(23%), 2A 1(5%), 2B 2(9%), AMR+ACR 3(14%)]. Allograft response to treatment of underlying and incidents of subsequent rejection is shown in Table 1. 13 of 22 pts with eosinophilia and rejection had subsequent rejections. 7 (4 NR, 3 PR) pts progressed to needing RRT, of which 4 lost allograft within 2 yrs. 22%(5) of pts with eosinophilic rejection had h/o BK viremia, 22%(5) had h/o CMV viremia, of which 75% were NR. 50%(11) of the pts who had eosinophilic rejection had history of recurrent UTIs. One pt with HIV had severe rejection with plasma cells and allograft loss within a year of transplantation. 61% (16) pts were on drugs that are shown to be associated with AIN especially PPIs. Only 3%(1) pts had peripheral eosinophilia.

Conclusions: Of the 26 pts with eosinophilic inflammation in their allograft biopsy we note a higher incidence of ongoing rejection and risk of developing subsequent rejection and allograft loss. Pts with history of infection (UTIs, BK, CMV) had higher incidence of underlying rejection with eosinophilic infiltrates.

Table 1: Allograft response to treatment of underlying and incidents of subsequent rejection

	With Rejection		Subsequent Rejection	
	# of Pts	% of total pts	# of Pts	% of total pts
CR	6	27%	3	21%
PR	8	36%	5	43%
NR	8	36%	5	36%
Total Pts:	22		13	

SA-PO461

Angiotensin-2 Expression Is Increased in Macrophages during Acute Cellular Rejection of Human Allografts Ping L. Zhang. *Anatomic Pathology, Beaumont Laboratory, Beaumont Health System, Royal Oak, MI.*

Background: The renin-angiotensin system (RAS) is well known to involve in hemodynamic changes in the kidney, but recent in vivo studies imply immunologic effects of RAS to cause damages in kidneys, partially through stimulating Interleukin-1 production by macrophages. We previously demonstrated that macrophages are one of dominantly cellular components in prominent acute cellular rejection (ACR). This study was to investigate whether there was an expression of angiotensin-2 (Ang2), the effector molecule in RAS, in macrophages involving ACR.

Methods: The study included 3 groups. The group 1, as the negative controls, was composed of 15 normal parenchyma sections away from renal cell carcinoma in nephrectomy specimens. The group 2, as the study group, consisted of 20 human allograft explant cases with ongoing ACR. As Ang2 is a small 8-peptid molecule being difficult for targeted staining, we selected 20 sarcoidosis cases (composed of aggregated and fused macrophages into giant cells), mostly known to have elevated serum angiotensin-converting enzymes, as the positive controls (4 in kidneys, and others in tonsil, liver and hilar lymph nodes). All paraffin embedded sections were stained for Ang2 by immunohistochemical staining method and cytoplasmic staining of Ang2 was graded 0 to 3+ (0 - no staining, 1+ - weak fine granular staining, 2+ - moderate granular staining and 3+ - strong granular staining).

Results: All negative controls (group 1) stained negatively for Ang2, as no or minimal inflammatory cells were present. All sarcoid granulomatous cells (macrophages and giant cells) in positive controls demonstrated moderate to prominent (2+ to 3+) positive staining for Ang2 in the cytoplasm. In macrophages involved in ACR of group 2, there was diffuse granular expression of Ang2 in macrophages with intensity ranging from 1+ to 3+. In the group 2, lymphocytes with scant cytoplasm appeared to stain weakly for Ang2 as well.

Conclusions: Using sarcoid granulomas as positive controls for Ang2 expression, the data indicate that Ang2 expression can be highly present in the activated macrophages involving in ACR of human allografts, implying Ang2 as a potential therapeutic target against ACR. In addition, the results from human specimens also support a notion that the RAS may affect some immunologic activities in the kidneys, based on previously in vitro and in vivo experiments.

SA-PO462

Peritubular Capillary Loss in the First Month after Kidney Transplantation Is More Pronounced in Patients with Rejection Compared to Delayed Graft Function Anke Keijbeck,[1] Floortje Steegh,[1] Marielle Gelens,[2] Maarten H. Christiaans,[2] Carine Peutz-Kootstra.[1] [1]*Pathology, MUMC, Maastricht, Netherlands;* [2]*Internal Medicine, MUMC, Maastricht, Netherlands.*

Background: Loss of peritubular capillaries (PTC) in patients with chronic transplant dysfunction is associated with worse outcome. We have shown previously that PTC loss occurs in the first three months after transplantation and precedes renal function decline (Steegh *et al.* JASN 2011). PTC density in the first weeks after transplantation has not yet been studied.

Methods: A cohort of 205 patients, who had a kidney transplantation between August 2003 and December 2009 at the Maastricht University Medical Centre and of whom representative protocol biopsies were taken at transplantation, and 3 and 12 months posttransplant, was analysed. In 102 of these patients an indication biopsy was taken in the first month after transplantation because of delayed graft function (DGF) or rise of creatinine. PTC numbers were studied as described earlier (Steegh *et al.* JASN 2011).

Results: Recipients who underwent an indication biopsy more often received a DCD graft. Consequently the ischemia times were higher than in the recipients who did not have an indication biopsy. Furthermore, patients with an indication biopsy developed more IF/TA 1 year after transplantation (p=0.04). In patients with indication biopsies, a significant loss of PTC density occurs already in the first month after transplantation (Figure 1 panel A) (p<0.01). This PTC loss is more pronounced in patients suffering from rejection than patients with DGF (Figure 1 panel B). However, in the rejection group there is a stabilisation of the PTC loss between 1 and three months, while in the DGF group there is further loss of PTCs (p<0.01).

Conclusions: We found that PTC loss occurs in the first weeks after transplantation. The pattern of PTC loss in the first 3 months after transplantation differs between patients with rejection and DGF. Prevention of microvascular damage during and early after transplantation may be crucial to prevent chronic transplant dysfunction.

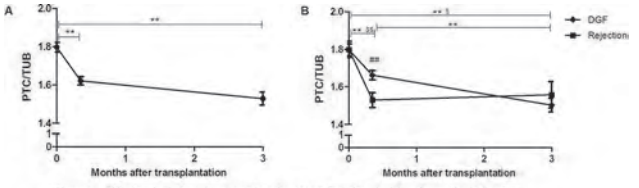


Figure 1. PTC density in first three months after transplantation. A) All patients with indication biopsy. B) Per indication; DGF and rejection.
Results shown as mean ± SEM.
A) ** p<0.01
B) ## p<0.01 DGF vs. rejection, ** p<0.01 DGF, $ p<0.05 rejection, $$ p<0.01 rejection

SA-PO463

Molecular Diagnosis of Rejection in Formalin Fixed Paraffin Embedded Kidney Transplant Biopsies Is Feasible but Extensively Compromises the RNA Konrad S. Famulski, Jeff Reeve, Philip F. Halloran. *University of Alberta, Edmonton, AB, AB, Canada.*

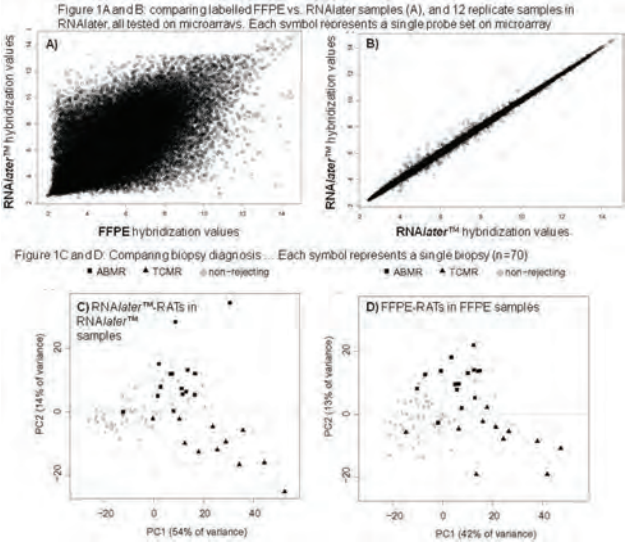
Background: While molecular assessment of transplant biopsies is usually performed on biopsies immediately frozen or stabilized in RNA*later*™, there would be advantages to analyze the FFPE biopsies already prepared for routine histology. We undertook a systematic characterization of microarray gene expression performance with degraded RNA from FFPE compared to intact RNA from RNA*later*™ specimens from the same kidney transplant biopsies.

Methods: We compared selected paired 70 FFPE and RNA*later*™ samples from 67 patients representing T cell-mediated rejection (n=11), antibody-mediated rejection (n=16) and no rejection in the Molecular Microscope system. The RNA performance was evaluated by quality matrices, rejection-associated transcripts (RATs) obtained from each method and diagnostic classifiers were developed.

Results: The FFPE samples yielded less RNA, and showed massive deterioration in RNA quality compared to RNA*later*™, causing false positive and false negative hybridization with the microarray probe sets (Figure 1A, B). Most RNA*later*™-RATs were not detectable in FFPE specimens and vice versa, and their association strength (p-value) with rejection was stronger than FFPE-RATs. RNA*later*™-RATs and FFPE-RATs distributed rejection phenotypes in Principal Component Analysis similarly, only when tested in their originating material (Figure 1C, D). FFPE classifier of rejection performed in FFPE samples with lower accuracy (71%) compared to RNA*later*™ classifier in RNAlater samples (80%).

Conclusions: Molecular system for assessing FFPE samples is possible when RNA*later*™ material is not available, but with disadvantages of smaller RNA yields (potential sampling error) and increase in diagnostic errors. Rejection associated transcript sets or classifiers developed with RNA*later*™ samples cannot be used for FFPE samples: they must be developed in FFPE samples.

Funding: Government Support - Non-U.S.



SA-PO464

Mapping Potential Errors in Histology by Comparison with Molecular Phenotyping in 1208 Kidney Transplant Biopsies Philip F. Halloran, Jeff Reeve. *University of Alberta, Edmonton, AB, Canada. Group/Team: MMDx-Kidney study group.*

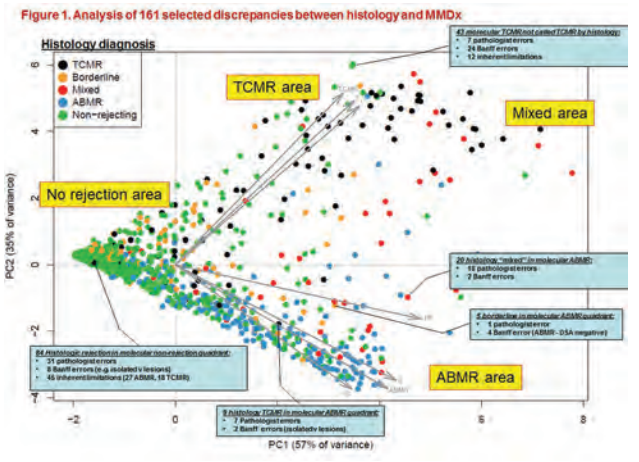
Background: Histologic interpretation of biopsies is empirical because there has been no external standard for comparison. For kidney transplants, the emergence of a centralized molecular diagnostic system for kidney transplant biopsies, the Molecular Microscope™ system (MMDx) (Nature Reviews Nephrology 12:534, 2016) provides an external standard for assessing the accuracy of histologic diagnoses.

Methods: In 1208 prospective indication biopsies, we compared diagnoses of rejection (Banff criteria) assigned by local standard-of-care histology in 13 experienced international centers to the MMDx assessments by microarrays (Clinicaltrials.gov NCT01299168).

Results: MMDx used archetype scores derived from 84 classifier equations to assign diagnoses of antibody-mediated rejection (ABMR) (subclassified early-stage, fully-developed and late-stage) and T cell-mediated rejection (TCMR) (J. Reeve et al. *JCI Insight* 2017 (In Press). Disagreement with histology was 39%: 16% in biopsies with no histologic rejection, but 72% in biopsies with histologic rejection. Discrepancies were particularly common in TCMR, early-stage ABMR, and mixed rejection. Analyzing 161 selected discrepancies in detail (figure 1) revealed 3 classes of discrepancies: errors by pathologists applying complex Banff rules (N=59/161); previously flagged errors in Banff rules e.g. isolated v lesions (N=42/161); or inherent limitations (non-specificity) of histology lesions (N=60/161). For example, tubulitis occurs in many renal inflammatory diseases, including ABMR, and is not exclusive to TCMR.

Conclusions: There is a high rate of errors in standard–of-care histology assessments in experienced centers, particularly in rejection-related conditions. Potential solutions include simplifying and correcting rules; using probabilistic regression equations (AJT 16: 1183, 2016); and incorporating molecular assessments. Supported by Canada Foundation for Innovation and Transcriptome Sciences Inc.

Funding: Commercial Support - We gratefully acknowledge the support of the Industrial Research Assistance Program. This research has been supported by funding and/or resources from University Hospital Foundation at the University of Alberta. Dr. Philip Halloran held a Canada Research Chair in Transplant Immunology until 2008 and currently holds the Muttart Chair in Clinical Immunology. P F Halloran holds shares in Transcriptome Sciences Inc., a company with an interest in molecular diagnostics. The other authors have declared no conflict of interest exists.



SA-PO465

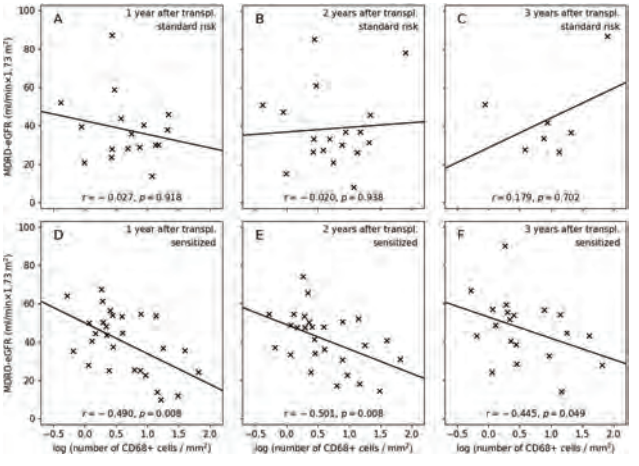
The Predictive Value of the Tissue Expression of CD68 in the Occurrence of Antibody Mediated Rejection, Graft Dysfunction, and Loss in Both Standard-Risk and Sensitized Kidney Transplant Recipients Luis E. Becker, Anne-Sophie Nick, Martin G. Zeier, Christian Morath. *Nephrology, University of Heidelberg, Heidelberg, Germany*.

Background: Tissue analysis of intragraft immunological processes remains an essential, but often underestimated tool as an early prognostic determinant of humoral changes and graft loss in kidney transplantation. This is particularly true for the growing population of sensitized recipients with an increased risk of immunological graft loss.

Methods: We retrospectively studied all eligible 213 allograft biopsies from 104 standard-risk and sensitized patients transplanted between 2006 and 2012, obtained in the first year after transplantation. We compared the effect of macrophage infiltration on long-term-allograft function and death-censored graft loss in both risk populations, analyzing the impact on the development of acute and chronic changes.

Results: Organ recipients from deceased donors had a higher CD68-positive cell infiltration one month after transplantation compared to living donor ones. Strong CD68 positivity in the first month after transplantation was associated with the occurrence of delayed graft function in sensitized patients. High number of CD68 positive cells one month after transplantation was a valid predictor of death censored graft loss in standard-risk patients. In sensitized patients, the number of tissue infiltrating CD68-positive cells in biopsies obtained between day 90 and 360 of transplantation was inversely correlated with the kidney function 1, 2 and 3 years after transplantation. Moreover, each CD68-positive cell increased the risk in 1.024 for the further development of antibody mediated rejection in this collective.

Conclusions: Macrophage tissue infiltration represents a potential additional tool for the analysis of kidney transplant biopsies and may predict worse outcomes especially in sensitized patients, irrespective of the histological diagnosis.



SA-PO466

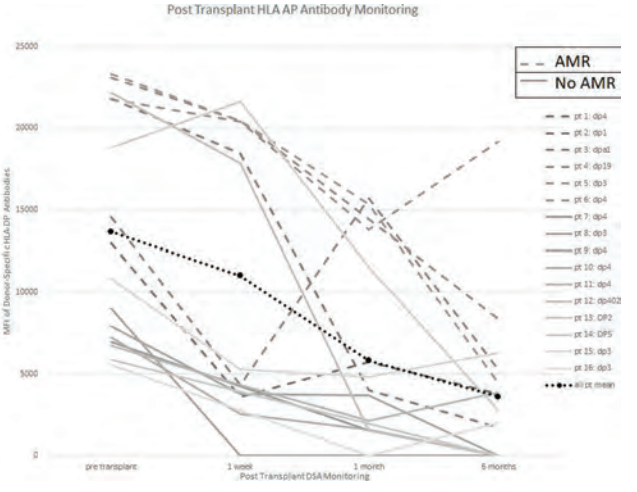
Kidney Transplantation across Strong Donor-Specific HLA-DP Antibodies Patrick Ahearn,[1] Allison B. Webber,[1] Kelly J. Cunniffe,[2] David Gae,[2] Matthew M. Tavakol,[3] Garrett Roll,[3] Gilberto Da Gente,[2] Ryutaro Hirose,[3] John Roberts,[3] Rajalingam Raja.[2] [1]*Nephrology, UCSF, San Francisco, CA;* [2]*Immunogenetics Laboratory, UCSF, San Francisco, CA;* [3]*Surgery, UCSF, San Francisco, CA.*

Background: Patients (pts) awaiting kidney transplant (ktx) with pre-formed donor specific anti-HLA antibodies (DSA) have been subjected to aggressive desensitization or long wait times for a compatible donor. Anti-DP DSA may represent a unique situation amenable to ktx without desensitization. Since 2014, we have done 16 ktx with isolated pre-formed anti-DP DSA with Mean Fluorescence Intensity (MFI) >5000 without desensitization.

Methods: We performed a chart review to assess the incidence of antibody mediated rejection (AMR) and graft survival at 6 months post ktx in this pt population.

Results: 16 pts with DP DSA >5,000 MFI and cPRA ranging from 75-100% underwent ktx. All pts have completed 6 month follow up. Virtual crossmatch was used in all pts; 8 had a positive B cell flow crossmatch. All pts received 2 g/kg IVIG in the immediate post- ktx period. There was a significant decrease in DP DSA MFI (figure). During six month follow up period, 14 pts had allograft biopsy. Six pts were diagnosed with AMR. There was no graft loss. Mean eGFR (MDRD equation) at 6 months was (63.9 ml/min). eGFR for the 10 patients without AMR was 71.5 ml/min versus 43.1 ml/min in those patients with AMR (P=0.02). There was no difference between those with AMR vs no AMR wrt sex (P=0.12), race (P=0.28), cPRA (P= 0.65), or positive flow x match (P=1). Pts with AMR were younger (P=0.03) and displayed a trend toward higher pre-ktx DP DSA MFI compared to those without AMR (16897 vs 11719, P= 0.16).

Conclusions: We have been successfully transplanting pts with high levels of DP DSA (even with positive FXM) without aggressive desensitization. At 6 months, 10 out of 16 patients with anti DP DSA MFI >5000 experienced no AMR and there was no graft loss. Further investigation is needed to identify definitive risk factors for AMR in ktx with anti-DP DSA. Higher MFI pre-ktx may be a risk factor for AMR in this population and should be further investigated.



SA-PO467

An Integrative Approach of Assessing Peritubular Capillaritis Extent and Score in Microvascular Inflammation Is Superior in Predicting Transplant Glomerulopathy and Graft Loss Zeljko Kikic,[1] Farsad A. Eskandary,[1] Gregor Bond,[2] Georg Bohmig,[1] Nicolas Kozakowski.[1] [1]*Medical University Vienna, Vienna, Austria;* [2]*None, Vienna, Austria.*

Background: Banff Classification accepts two histomorphological features as surrogates of HLA Antibody-Antigen interaction on renal endothelium: C4d staining and microvascular inflammation scores (MVI sum score:ptc+g≥2) which are strong predictors of transplant glomerulopathy (TG) and subsequent graft loss. However, increasing evidence questions the ability of the ptc score to solely mirror all diagnostic and prognostic aspects of ptc morphology. More recently we observed a highly significant relationship of diffuse extent of ptc (inflammation of >50% the renal cortex) with graft loss and significantly higher DSA levels suggesting potential inclusion of diffuse ptc as an additional surrogate of antibody-antigen interaction.

Methods: We included 616 patients (Tx 1999-2006) with adequate material for interpretation of MVI and C4d staining in first indication biopsies. Alternatively we assessed MVI with an integrated view of ptc morphology including both results of ptc score and ptc extent: additionally to MVI scores, cases with a ptc score of 1 but diffuse extent of ptc (ptc $1_{diffuse}$, n=25) and no glomerulitis were added as a surrogate of antigen-antibody interaction. Outcomes measured were prediction of any TG in all indication biopsies (n=1619) and death-censored graft loss until 01.01.2017.

Results: Linear C4d in PTCs and MVI scores ≥2 were observed in 11% and 19% of the specimens. TG (cg score>0) in one or more biopsies was found in 13% of patients. The incorporation of ptc $1_{diffuse}$ in addition to the MVI score≥2 significantly increased the

receiver operating characteristic curve for TG [AUC: 0.605 (95%CI 0.53-0.68), p=0.003] compared to the Banff MVI score ≥2 [AUC: 0.571 (95%CI 0.49-0.64), p=0.046] or C4d + [AUC: 0.540 (95%CI 0.47-0.61), p=0.26]. After adjusting for multiple confounders, including C4d or cellular rejection, ptc $1_{diffuse}$ remained independently related to TG [OR 2.13 (CI: 1.22-3.72), p=0.008]. Ptc $1_{diffuse}$ and MVI score ≥2 subjects had similar graft survival (44%) compared to patients with ptc 1_{focal} or without MVI with best overall survival (70% and 68%) after a mean follow-up of 9 years.

Conclusions: An integrated view of ptc morphology including diffuse ptc in assessing MVI is superior for TG and subsequent graft loss risk prediction

SA-PO468

Differential Outcomes in Patients with De Novo Donor-Specific Antibodies (DSA) Compared to Patients with Preformed DSAs Maria Ajaimy,[1] Adriana Colovai,[1] Nicole A. Hayde,[3] Enver Akalin.[2] *[1]Montefiore Medical Center, Bronx, NY; [2]Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY; [3]None, Bronx, NY.*

Background: We aimed to investigate the prevalence and dynamic changes of preformed and de novo DSAs after kidney transplantation and its association with clinical outcomes

Methods: This is a prospective study including 664 non-HLA-identical patients who received a kidney transplant between January 2009 and December 2014. Protocol testing for DSA via LABScreen single antigen beads was done before and at 1, 3, 12 months, and then annually. Patients with preformed DSAs received a transplant with anti-thymocyte globulin and IVIG induction treatment if CDC cross-match was negative and MFI value was < 5,000 for HLA-A, B, DR and < 10,000 for HLA-C, DQ and DP.

Results: 108 (16%) patients had preformed DSA before transplantation. During a median 3.8 (2.4-5.3) years of follow-up, de novo DSA developed in 95 patients (17%) at a mean of 20.3±13.3 months after transplantation. Those patients were compared to 461 patients without any DSA. There was no difference between incidences of acute antibody(AMR) or T cell mediated rejection(ACR), chronic rejection, transplant glomerulopathy(TG), serum creatinine levels, graft and patient survival when preformed DSA patients compared to no DSA patients. While there was no significant difference in patient survival, de novo DSA group had lower graft survival (64.1% vs. 92.7%), higher AMR (17.3% vs. 1.6%), ACR (14.1 vs. 4.3%) and TG/CAMR (16.3% vs. 3.3%). Of the 108 patients with preformed DSA, 67 patients lost DSA and 41 showed persistent DSA. Persistent DSA patients had more class II antibodies (56% vs. 36%) and higher MFI values (4608+/-4150 vs. 2325+/-1283). For de novo DSA patients, 49% had persistent DSA, 40% lost their DSA and 11% had their DSA MFI decreased by more than 50%. The mean sum MFI of de novo DSA in the persistent group (9562.8±9409.1) was higher than the patients who lost their DSAs (4063.9±3487) or DSA MFI decreased by more than 50% (8768.7±4854.5).

Conclusions: 17% of our transplant recipients develop de novo DSA after kidney transplantation and associated with significantly higher acute and chronic rejection and lower allograft survival. Low leveL pre-tx DSA does not increase the risk of graft loss in patients who receive thymoglobulin/IVIG induction therapy

SA-PO469

The Natural History of De Novo Donor Specific Antibody (dn DSA): Results from Systemic Monitoring of DSA at ECMC Shirley S. Chang,[1] Cindy S. Yip,[1] Sunil Patel,[2] Aijaz A. Gundroo,[1] Mareena S. Zachariah.[1] *[1]Internal Medicine, SUNY Buffalo, Buffalo, NY; [2]Surgery, SUNY Buffalo, Buffalo, NY.*

Background: Dn DSA development has shown to adversely affect long-term allograft survival, but it's natural history is not well studied.

Methods: Systemic screening DSA post-transplant at ECMC prospectively was performed from Jan 2012 to Sept 2016 on kidney (K) transplant (tx) recipients at 1 month (m), 2 m, 3 m, 6 m, & yearly interval, more frequently if DSA+. Management of dn DSA+ includes Tx K Bx if MFI>3000, and treatment depends on the bx findings. ACR is treated with steroid bolus, acute AMR with steroid bolus±Thymo & Plasmapheresis/IVIG, and those without rejection were treated with IVIG until MFI<1500 (negative).

Results: 49 recipients developed DSA, & 330 did not. Of those with dn DSA, 27% developed HLA I DSA (median onset 40 days post-tx), 88% HLA II DSA (median onset 180 days, p<0.05), 12% had HLA I & II DSA. Causes of dn DSA were due to infection [N=12 (8 had BKN, 1 BK viremia, 1 BK viremia & CMV viremia, 1 recurrent UTI, 1 Hep C], rejection [N=11 (3 with prior ACR, 3 prior AMR, 1 prior ACR+AMR; 4 with current ACR, 1 with current AMR], elevated cPRA/prior Tx [N=9 (4 due to cPRA>80%, 5 with prior K Tx with elevated cPRA), nonadherence (N=8), unknown etiology (N=7), and long CIT >39 hours with DGF (N=2). Patient with dn DSA were grouped into **Transient DSA** (N=19, with 10 had minimal intervention, & 9 had intervention such as PE+IVIG or Rituximab or IVIG alone), **Persistent DSA** (N=30, 7 had MFI<3000, 8 had MFI between 3000-6000, and 15 had MFI>6000). Of those dn DSA who had K Bx (N=48), 36% developed concomitant rejections at initial dn DSA presence; 3 with borderline, 4 Banff 1A, 3 Banff 1B, 3 Banff 2B, and 3 with acute AMR rejections. None of the recipients with transient DSA lost their graft. There was one graft failure in the persistent dn DSA with MFI<3000, 3 graft failure in the MFI 3000-6000 range, & 5 graft failures including 2 patient death in the MFI>6000 group.

Conclusions: 12.9 % K Tx recipients develop dn DSA, with HLA I occurs earlier than HLA II. Causes for dn DSA include infection (25%), rejection (22 %, with 12% occurs after prior rejection episodes, & 10% with active rejection concomitantly), highly sensitization (18%), nonadherence (16%), unknown cause (14%), & prolonged CIT/DGF (4%). Recipients with persistent DSA especially Class II and higher MFI levels are risk factors for graft failure.

Funding: Clinical Revenue Support

SA-PO470

De Novo Donor Specific Antibody (dnDSA) and Biopsy Proven Acute Rejection (BPAR) Are Associated with Higher Intrapatient Variability (IPV) in Tacrolimus Trough Levels Following Renal Transplant Petra M. Goldsmith. *Royal Liverpool Hospital, Lymm, United Kingdom. Group/ Team: UK Transplant Audit Collaborative.*

Background: High IPV in Tacrolimus trough levels has been associated with poorer kidney transplant outcomes, including the occurrence of BPAR. However, there is a paucity of information in the published literature about any association between high IPV and the development of dnDSA.

Methods: We performed a single centre retrospective cohort study with the hypothesis that patients identified as having BPAR or dnDSA at any timepoint would have a greater mean IPV than those who did not. Patients transplanted in our centre between 2009-2014 and receiving standard preparation Tacrolimus based immunosuppression were included. Patients receiving other primary immunosuppression, who were in receipt of organs other than kidneys and who did not have a functioning transplant at 2 years were excluded. One hundred and seventy one patients were identified with IPV data collected at 2 predetermined time points: 6-12 months post-transplant (T1) and the most recent 12 months (T2).

Results: IPV values were compared using Mann Whitney U tests between patients developing a) BPAR and b) dnDSA with those who did not, at both T1 and T2. The results are shown in table 1. There is a clear association between BPAR and high IPV at T1 (p=0.01) which reverses at T2 but fails to reach statistical significance. For dnDSA, we observe a higher IPV for both T1 and T2 although in both cases it is not statistically significant.

Conclusions: As most episodes of BPAR occur early post-transplant, it is possible that the observed reversal in IPV at T2 reflects more precise monitoring and control of Tacrolimus exposure in these patients following rejection. In respect of the observation of higher IPV at both T1 and T2 for dnDSA, the small sample size who developed antibodies may have contributed to the failure to reach significance and it is anticipated that this analysis will be expanded to a multicentre cohort in the future.

Table 1: Mann Whitney U Test to compare BPAR and DnDSA

	Mean Rank T1	T1 P Value	Mean Rank T2	T2 P Value
BPAR (N=24) No BPAR (N=147)	108.3 82.4	0.01	71 88.5	0.05
DnDSA (N=16) No dnDSA (N=155)	84.6 99.3	0.13	84.8 97.2	0.17

SA-PO471

Anti-HLA Antibody-Mediated Rejection in ABO-Incompatible (ABOI) Living Donor Kidney Transplant (KT) Patients Hyuk yong Kwon, Jin M. Kong. *Nephrology, BHS-Hanseo hospital, Busan, Republic of Korea.*

Background: Antibody-mediated rejection(AMR) in ABOi KT patients can either be due to donor-specific antiHLA antibody(DSA) or anti-blood group antibody(anti-ABO). The relative frequency and possible differential clinical features of these two types of AMR in ABOi KT patients has not been investigated.

Methods: Among 91 ABOi KT patients between 2007 and 2016 in our center, 11(12.1%) patients developed clinical acute AMR. Since there is no histologic distinction between DSA- and anti-ABO-induced AMR, we assumed the causative antibody in each case based on anti-ABO level and DSA, measured in serum collected at the time of AMR. DSA was determined by luminex single antigen beads assay.

Results: Of these 11 cases of AMR, 5 were attributable to anti-ABO since anti-ABO titer was 16 or higher and DSA was undetectable at the time of rejection. Three cases were attributable to DSA since DSA was detectable and anti-ABO was low (≤ 8) during rejection. Another 2 cases with low (2) anti-ABO titer and undetectable DSA were assumed to be DSA-induced, since this low level of anti-ABO is unlikely to cause rejection and DSA can be undetectable in DSA-induced AMR by adsorption of Ab on graft, as frequently seen in ABO-compatible patient. One case with anti-ABO 8 and no detectable DSA was regarded as undetermined. The onset of AMR was within 2 weeks in all cases and comparable between two types of AMR. Initial anti-ABO titer was also not statistically different, median(range) 256(64-4096) in ABO-AMR and 64(16-256) in DSA-AMR. All the 5 patients with ABO-AMR had negative PRA before KT, whereas 4 of 5 patients with DSA-AMR had positive PRA before KT, and one DSA-AMR patient had persistent DSA before KT and at the time of AMR. All the AMR were recovered by treatment and no graft was lost to rejection.

Conclusions: We conclude that a significant proportion of AMR in ABOi KT are caused by DSA, and clinical features and possible differential therapeutic approach of these 2 types of AMR needs to be explored by further studies.

SA-PO472

Altered Kynurinine 3-Monooxidase May Mediate Rejection and Tubular Cell Injury in Pig Kidney Transplants Youli Wang,[1] Xuexiu Fang,[1] Daniel T. Kleven,[1] Chak-Sum Ho,[2] N. Stanley Nahman,[3,4] Todd D. Merchen.[3] *[1]Augusta University, Evans, Colombia; [2]Gift of Life Michigan, Ann Arbor, MI; [3]Medical College of Georgia at Augusta University, Augusta, GA; [4]Norwood VAMC, Augusta, GA.*

Background: The indoleamine 2,3-dioxygenase (IDO) transprotein prevents rejection (RJX) in rodent solid organ transplantation, including kidney transplant (KTx). Thus, the increase in IDO activity in RJX seen in our pig KTx model (JASN 27:723A) and in KTx patients (KI 77:60) is paradoxical. Kynurinine (KYN) 3-monooxidase (KMO) is a downstream enzyme of IDO generating 3-OH-KYN which is both pro-tolerant and cytoprotective. On this basis, we theorized that RJX would blunt KMO activity from rejecting pig kidneys, and in particular, silence tubular epithelial cell (TEC) KMO expression.

Methods: Pigs underwent allogeneic (Allo) (n=9) or auto renal transplants (Auto) (n=10 and as a control for ischemia), as we described (Trans Immunol, in press). For Allo, pairs of mismatched pigs were operated simultaneously with L kidneys exchanged. All Autos were also the L kidney. All pigs then had right nephrectomy (control tissue = RNx) prior to closure, and left Nx at sacrifice after 72 hrs. No immunosuppression was used. In all kidneys, RJX was assessed using Banff criteria; IDO and KMO gene expressions quantitated with qPCR; tissue IDO activity measured by HPLC, and tissue KMO localized and quantitated with immunohistochemistry (IHC).

Results: Postop creatinine was higher in Allo vs Auto (8.12±1.50 vs 2.83±0.60 mg/dL respectively, P=0.006). Auto had mild tubular injury, and no changes in IDO mRNA or activity vs RNx (n=16). Allo showed acute rejection (Banff 1 to 3), with a 6 fold (X) increase in allograft IDO mRNA, and 19.5X increase in tissue IDO activity vs Auto. KMO showed a 2X reduction in Auto, and 5X decrease in Allo RJX kidneys. By IHC KMO activity was constituent in Auto and RNx TEC, but silent in TEC from rejecting Allo.

Conclusions: KMO gene activity and TEC expression are blunted in KTx rejection. KMO may be an important downstream mediator of IDO activity and function in a protolerant and cytoprotective capacity. This may help explain the paradoxical increase in IDO activity seen in KTx rejection.

SA-PO473

Association of HLA-DR and DQ Mismatches and Acute Rejection in Living Donor Kidney Transplant Recipients Daniel Onete,[3] Qingyong Xu,[1] Rita Suri,[2] Lakshman Gunaratnam.[1] *[1]London Health Sciences Centre, Oakville, ON, Canada; [2]Université de Montréal, Montreal, QC, Canada; [3]Physiology and Pharmacology, Western University of Canada, London, ON, Canada.*

Background: Previous studies show that HLA incompatibility is associated with greater risk of graft failure in deceased-donor kidney transplant patients. However, whether HLA-mismatches are important in low-risk recipients of living donor kidneys in the era of modern immunosuppression is unclear. Given that de novo, donor specific antibodies against Class II HLA (DQ or DR) are associated with poor long-term outcomes in deceased donor transplant recipients, we hypothesized that having 3-4 (vs. 0-2) HLA DQ/DR mismatches would be associated with acute rejection in low-risk, living donor kidney transplant recipients.

Methods: We conducted a retrospective cohort study of all cross-match negative, transplant-naive, living donor kidney transplant recipients at our center from 2006-2016. Electronic charts were reviewed for demographics, comorbidities, HLA genotype and outcomes. HLA genotyping was performed using molecular typing. The primary outcome was acute rejection within 1-year post-transplant, and was defined as either: definitive biopsy-proven T-cell mediated rejection (TCMR) (Banff criteria), or as borderline TCMR on biopsy that was treated with pulse steroids and/or anti-thymocyte globulin. The secondary outcome was serum creatinine at 1 year post-transplant. Outcomes were compared between patients with 0-2 vs. 3-4 HLA-DR/DQ mismatches.

Results: Of the 178 recipients transplanted with living donor kidneys from 2006-2016, 6 were excluded due to incomplete follow-up data. In total, 124 (72%) and 48 (28%) received 0–2 and 3–4 HLA-DR/DQ mismatched kidneys, respectively. We observed 27 definitive rejections and 25 treated borderline rejections within 1-year post-transplant. Patients with 3–4 HLA-DQ/DR mismatched kidneys had a statistically significant greater risk of acute rejection (odds ratio = 3.43 [95% CI 1.69-6.94]; p=0.0008). This association persisted when we limited the primary outcome to definitive rejection (odds ratio = 3.39 [95% CI 1.45-7.89]; p=0.0053). There was no significant difference between groups in the mean 1-year serum creatinine (122.4 ± 5.889 vs. 117.0 ± 4.035; p=0.59).

Conclusions: In this single center study, we found that greater HLA-DR and DQ mismatches were associated with increased risk of acute rejection at 1-year after living donor kidney transplant.

Funding: Government Support - Non-U.S.

SA-PO474

Highly Sensitized Patients at Miami Transplant Institute: An Update Camilo Cortesi,[2] Mai Sedki,[2] Giselle Guerra,[3] Gabriel Contreras,[1] Adela D. Mattiazzi.[2] *[1]University of Miami, Miami, FL; [2]University of Miami/Jackson Memorial Hospital, Miami, FL; [3]University of Miami/Miller School of Medicine, Miami, FL.*

Background: Highly sensitized (HS) patients are defined as transplant candidates sensitized against human leukocyte antigen (HLA) antibodies with a panel reactive antibody (PRA) greater than 80%. This has been a major obstacle to kidney transplantation (KT). Major causes are blood transfusions, pregnancy and prior transplants. HS patients have an increased risk of rejection, worse graft survival, and less annual transplant rates. There are different strategies available for desensitization including intravenous immunoglobulin (IVIG), plasmapheresis (PE), and Rituximab (R). We provide an update of our experience comparing patients undergoing desensitization.

Methods: This is a retrospective analysis of 50 HS KT recipients categorized into 2 groups based on induction immunosuppression received at transplantation. The control group (CG), 12 HS KTs, received standard induction. The Rituximab group (RG), 38 HS KTs, received standard induction as well as R ± IVIg ± PE based on the immunological risk stratification model. The primary outcomes were defined as rejection rate, allograft failure, and death. Secondary outcomes assessed graft function via serum creatinine at various times post-transplant.

Results: The number of HLA mismatches was not statistically different between the 2 groups. In the CG, 75% had prior transplants compared to 53% in the RG. Mean waiting time for KT was 7.6 years and 5.4 years for the CG and RG, respectively (p=0.007). The cumulative proportion of patients who remained free of death or allograft failure was significantly higher in the RG (87%) compared to the CG (60%)(p=0.039). The probability of rejection was similar in both groups (p=0.36). The mean serum creatinine at 1 year was 1.35 ± 0.54 and 1.36 ± 0.64 mg/dL for the CG and RG, respectively.

Conclusions: Desensitization strategies are fundamental for the management of the HS population. Our study confirms that the addition of R continues to improve allograft survival and decrease death rates.

	Control Group	Rituximab Group
Age, (years) mean ± SE	52 ± 18.5	49 ± 15
Gender, n (%)	6 (50) male, 6 (50) female	12 (32) male, 26 (68) female
Patients with Prior Transplantation, n (%)	9 (75)	20 (53)
Total HLA mismatch level, n (%)		
6	3 (25)	5 (13)
5	4 (33)	20 (52)
4	4 (33)	9 (24)
3	0	4 (11)
2	0	0
1	0	0
0	1 (9)	0
DR HLA mismatch level, n (%)		
2	5 (41)	23 (61)
1	6 (50)	13 (34)
0	1 (9)	2 (5)
PRA at IVIg Treatment, mean ± SE	96.9 ± 5.2	91 ± 22.6
PRA at Transplant, mean ± SE	84 ± 20.4	87 ± 15
Time to Transplantation in days, median (95% confidence interval)	2346 (1914 – 3648)	1553 (1539 – 2425)
High Risk Level [1, 2, 3], n (%)	9 (75), 2 (16), 1(9)	18 (47), 14 (37), 6 (16)
Delayed Graft Function, n (%)	2 (16)	7 (18)
Plasmapheresis, n (%)	0	8 (21)
Rejection, n (%)	3 (25)	10 (26)
Allograft Failure, n (%)	2 (17)	2 (5)
Death, n (%)	2 (17)	2 (5)

SA-PO475

Magnitude of Pre-Biopsy Decline in Renal Function and Its Association with Allograft Rejection Santhi Voora, Patrick Ahearn, Matthew M. Tavakol, Kirsten L. Johansen, Elaine Ku. *UCSF, San Francisco, CA.*

Background: Acute rejection is a significant cause of morbidity, and transplant biopsy remains the gold standard for the diagnosis of rejection. Guidelines published by KDIGO recommend biopsy for "persistent, unexplained increase in serum creatinine." To our knowledge there have been few studies defining the magnitude of decline in renal function that should trigger a biopsy to rule out rejection.

Methods: We performed a retrospective analysis of patients at a single center who underwent diagnostic transplant biopsy (excluding surveillance biopsies) between 2006-2016 at least three months post-transplant. We evaluated for association between pre-biopsy decline in renal function (mean of renal function measured between 6 months prior to biopsy and day of biopsy) and pathologic findings of rejection using logistic regression models (adjusted for age, race, sex, diabetes, donor type and transplant year). Absolute rise in serum creatinine and percent change in estimated glomerular filtration rate (eGFR) by CKD-EPI equation were examined as predictors of the outcome of rejection (cellular or antibody-mediated).

Results: 1,224 biopsies were included for analysis. Mean age was 46.3 years. 58.3% were men, and 18% were black. Overall, 53.5% of biopsies demonstrated evidence of rejection. Declines in eGFR of ≥20% were associated with higher odds of rejection in both unadjusted and adjusted analyses compared to a <5% decline in eGFR [Table]. Rises in absolute serum creatinine by ≥0.3 mg/dL also corresponded with a higher risk of rejection compared to rises in creatinine by <0.3 mg/dL.

Conclusions: In this single-center study, decline in eGFR ≥20% or rise in serum creatinine by ≥0.3 mg/dL were associated with higher risk of rejection. Changes in renal function of this magnitude may warrant prompt arrangement of biopsy given the high risk of rejection.

Funding: NIDDK Support, Other NIH Support - NHILB

Thresholds of decline in renal function and risk of rejection

Percent Change in eGFR	Number of biopsies	Unadjusted Odds Ratio (95% CI)	P Value	Adjusted Odds Ratio (95% CI)	P Value
<5%	230	1.0	ref	1.0	ref
5-<20%	249	0.91 (0.63-1.32)	0.61	0.93 (0.64-1.35)	0.70
20-40%	202	1.55 (1.08-2.22)	0.02	1.65 (1.14-2.39)	0.02
≥40%	543	2.43 (1.73-3.42)	<0.001	2.33 (1.64-3.29)	<0.001
Absolute rise in serum creatinine (mg/dL)	**Number of biopsies**	**Unadjusted Odds Ratio (95% CI)**	**P Value**	**Adjusted Odds Ratio (95% CI)**	**P Value**
<0.3	437	1.0	ref	1.0	ref
0.3-<0.6	201	1.68 (1.19-2.36)	0.003	1.67 (1.19-2.37)	0.003
≥0.6	584	2.70 (2.09-3.50)	<0.001	2.55 (1.96-3.32)	<0.001

SA-PO476

Ultrasound and CT Guided Kidney Transplant Biopsies: Evaluating Complications Camilo Cortesi,[4] Karla G. Carias martinez,[1] Mai Sedki,[4] Giselle Guerra,[5] David Roth,[3] Adela D. Mattiazzi.[2] *[1]Jackson Health System, Miami, FL; [2]None, Miami, FL; [3]University of Miami Miller School of Medicine, Miami, FL; [4]University of Miami/Jackson Memorial Hospital, Miami, FL; [5]University of Miami/Miller School of Medicine, Miami, FL.*

Background: Kidney transplant (KT) rejection is one of the main indications for KT biopsy (KTb). The ultrasound (US)-guided approach is the preferred method however the computed tomography (CT)-guided approach offers an excellent alternative when the yield is low. We sought to evaluate the incidence of complications in both techniques.

Methods: We identified 646 KTb performed to rule out rejection, 32 of those were CT-guided and the rest US-guided. Retrospective chart review was performed. Complications were divided into moderate and severe where moderate complications included: hematoma, hydronephrosis, arteriovenous fistula, hemoglobin drop >2 g/dL, and need for blood transfusions; severe included the former events associated with a kidney dysfunction, Page kidney or the need for nephrectomy. Descriptive analysis was used for the CT-KTb and a logistic regression was conducted for the US-KTb.

Results: The logistic regression was statistically significant, indicating that the predictors as a set did reliably predict complication occurrence (chi square=51.044, p<0.05, df=34). Prediction success overall was 91.2%. The Wald criterion demonstrated that blood pressure control, BUN, and use of anticoagulants prior to biopsy had a statistically significant impact in predicting complications (p=0.015, p=0.001, p=0.027, respectively). Patients on anticoagulants prior to biopsy were 4 times as likely to have complications (odds ratio 4.167). In CT-KTb only one patient had complications. This patient had uncontrolled blood pressure, BMI > 35, platelet count of 93K/uL and INR was 1.21 at the time of biopsy.

Conclusions: Our data shows that uncontrolled blood pressure, defined as >160/90, uremia, and anticoagulant use were the main predictors of negative outcomes. The presence of these risk factors, particularly in combination, could be of great value in weighing the necessity of a procedure. Additionally, CT-KTb was shown to be a safe alternative for obtaining renal tissue. We highlight the need to achieve adequate control of blood pressure prior to KTb.

Demographics

	US-KTb	CT-KTb
Age	52.7 ± 15	57 ± 15.8
Gender n (%)	273 (40%) female	13 (41%) female
Uncontrolled HTN n (%)	163 (24%)	8 (25%)
Anticoagulation n (%)	40 (6%)	14 (44%)
BUN - mg/dL	38 ± 22	54 ± 25
Creatinine - mg/dL	2.71 ± 2.03	3.66 ± 2.84
Platelets - K/uL	215 ± 83	200 ± 100
INR	0.99 ± 0.12	1 ± 0.25
Complications n (%)	78 (12%) moderate 11 (2%) major	2 (6%) moderate 1 (3%) major
Time between biopsy and complication in days	11.1 ± 38.4	2

Format is mean ± SE unless otherwise specified

SA-PO477

Evaluation of C1q status and Titre of Donor Specific Antibodies as Predictors of Allograft Survival Osama Attia,[2,1] Emma White,[3] Delordson Kallon,[3] Arun Gupta,[3] Neil Ashman,[1] Muhammad M. Yaqoob.[4,1] *[1]renal unit, Royal London hospital, London, United Kingdom; [2]Renal Unit, Zagazig university hospital, Zagazig, Egypt; [3]Royal London Hospital, London, United Kingdom; [4]William Harvey Research Institute, London, United Kingdom.*

Background: Donor-specific antibodies (DSA) either developed as de-novo or formed before renal transplantation are independent predictors of allograft loss. However, it is unknown if DSA and DSA C1q status post transplantation can independently predict allograft loss. Serologically emergence of de-novo or rising titres of preformed DSA is used as surrogate markers of impending graft dysfunction and rejection. However sensitivity and specificity of this approach is not robust enough to escalate immunosuppression. However recent evidence suggests that complement binding DSA may identify clinically relevant anti-allograft antibodies

Methods: 600 patients received either a deceased or live donor kidney transplant between January 2008 and June 2015 after negative CDC cross match. All patients received standard immunosuppression as per departmental protocol. 42 patients with either persistent or de-novo DSA between 3-28 months post transplantation were studied retrospectively. C1q fixing DSA were studied using single Ag luminex technique with MFI more than 5000 was detected as positive.

Results: 19 patients were positive for C1q status. 60% graft developed rejection and 43% of the grafts were lost in the entire cohort predominantly within the two years of positivity. C1q positive status compared to negative did not differentiate between rate and type of rejection (68% vs 52% p=1.14). Rejection within three months of C1q positivity were significantly higher (63% vs 33% p=0.034). However, significantly greater grafts were lost with C1q positivity compared to C1q negative (63% vs 35% p < 0.05) despite receiving similar antirejection therapy.

Conclusions: We conclude that C1q binding DSA post transplantation is associated with rejection if tested within three months of biopsy for graft dysfunction. More importantly It is also associated with poor graft survival. C1q status may help clinician in the identification of patients who may be at high of losing graft following rejection and help in optimization of immusuppression therapy.

Funding: Government Support - Non-U.S.

SA-PO478

Genome-Wide Association Meta-Analysis for Acute Rejection of Kidney Transplants Ajay K. Israni,[3,11] Pamala A. Jacobson,[11] Weihua Guan,[11] Casey R. Dorr,[4,11] Martin H. De Borst,[7] Caragh P. Stapleton,[5] Paul J. Phelan,[15] Peter J. Conlon,[1] Kelly A. Birdwell,[13] Stephan J. Bakker,[7] Gianpiero Cavalleri,[5] William S. Oetting,[11] David P. Schladt,[4] Jessica Van setten,[6] Pui-Yan Kwok,[2] Michael Eikmans,[14] Harold Snieder,[7] Baolin Wu,[11] Laia Bassaganyas,[9] Jianxin Yang,[14] Peter J. Van der most,[10] Folkert W. Asselbergs,[8] Brendan Keating.[12] *[1]Beaumont Hospital, Dublin 9, Co Dublin, Ireland; [2]UCSF, San Francisco, CA; [3]Hennepin County Medical Center, Minneapolis, MN; [4]Minneapolis Medical Research Foundation, Minneapolis, MN; [5]RCSI, Dublin, Italy; [6]UMC Utrecht, Utrecht, Netherlands; [7]University Medical Center Groningen, Roden, Netherlands; [8]University Medical Center Utrecht, Utrecht, Netherlands; [9]University of California, San Francisco, San Francisco, CA; [10]University of Groningen, Groningen, Netherlands; [11]University of Minnesota, Minneapolis, MN; [12]University of Pennsylvania, Philadelphia, PA; [13]Vanderbilt University, Nashville, TN; [14]Leiden University, Leiden, Netherlands; [15]NHS Lothien, Edinburgh, United Kingdom. Group/Team: Kidney Group of iGeneTRAiN.*

Background: Acute rejection (AR) is associated with worse kidney allograft survival.
Methods: We performed a genome-wide association study (GWAS) meta-analysis of AR in recipients and donors after kidney transplantation using the Affymetrix exome plus chip. AR was defined by treating physician at anytime post-transplant. Genotype imputation was carried out based on the 1000 Genomes project and Genomes of The Netherlands reference datasets. The analysis was adjusted for age, sex, living versus deceased donors, and population stratification using principal components.

Results: The interim meta-analysis of 5 GWAS cohorts participating in iGeneTRAiN included 4,437 Caucasian kidney transplant recipients with 999 (23%) AR events (Table 1). Twenty-five recipient single-nucleotide polymorphisms (SNPs) reached GWAS significance ($p \leq 1E-7$) for their association with AR. The top four recipient SNPs with strongest AR association include two located in introns of *MANSC1* rs12578158 (p =1.53E-9) and rs12580693 (p = 1.75E-9). Another is located 7.5 kb upstream of *UGT2B10* rs294768 (p = 1.24E-8). The fourth SNP is located in the 3'UTR of *NUB1* rs544144806 (p = 4.81E-8). Furthermore, 14 of the 25 top recipient SNPs are located in or near *UGT2B10*, including rs2942857, which is an mRNA splice acceptor. The donor analysis identified 66 SNPs reaching GWAS significance for their association with AR. The top two of these SNPs are rs8180830 (p = 2.90E-9) and rs77439859 (p = 3.69E-9) which are 79 kb and 58 kb upstream, respectively, of *HERPUD2*. Another donor SNP associated with AR is rs79865478 (p = 4.62E-8), located in an intron of *SOX5*.

Conclusions: We identified several novel susceptibility loci associated with AR, which can be validated by independent cohorts.

Funding: Other NIH Support - AI U19 AI070119

Kidney Genome-Wide Association Studies Included in the Meta-Analysis

Study Name	N	% Living Donors	AR Events
TransplantLines, Netherlands	1106	23	369
Ireland Cohort	315	0	130
DeKAF Genomics, USA, Canada	2329	60	390
Liden	277	42	45
Scripps	410	76	65

SA-PO479

Bortezomib in Late Antibody-Mediated Kidney Transplant Rejection – A Double-Blind Randomized Placebo-Controlled Trial (BORTEJECT Study) Farsad A. Eskandary,[1] Heinz Regele,[2] Gregor Bond,[1] Nicolas Kozakowski,[2] Markus Wahrmann,[1] Luis G. Hidalgo,[5] Helmuth Haslacher,[4] Christopher Kaltenecker,[1] Bernadette Aretin,[6] Rainer Oberbauer,[1] Jeff Reeve,[3] Philip F. Halloran,[3] Georg Bohmig.[1] *[1]Nephrology and Dialysis, Medical University Vienna, Vienna, Austria; [2]Clinical Pathology, Medical University Vienna, Vienna, Austria; [3]Alberta Transplant Applied Genomics Centre, University of Alberta, Edmonton, AB, Canada; [4]Laboratory Medicine, Medical University Vienna, Vienna, Austria; [5]Laboratory Medicine and Pathology, University of Alberta, Edmonton, AB, Canada; [6]Pharmacy, AKH-Wien, Vienna, Austria.*

Background: Antibody-mediated rejection (ABMR) is a leading cause of long-term kidney transplant loss. Optimal treatment of late ABMR is unclear, and our current knowledge is mostly based on uncontrolled studies.

Methods: In this randomized, double-blind, placebo-controlled, single-center phase 2 trial (NCT01873157), we investigated whether two cycles of the proteasome inhibitor bortezomib (each cycle: 1.3 mg/m2 on days 1, 4, 8 and 11) are able to halt the progression of late ABMR, using eGFR slope (Over 0, 3, 6, 12, 18 and 24 months) as primary endpoint (44 patients; 1:1 randomization). Secondary outcomes were mGFR at 24 months, donor-specific antibody (DSA) course and morphological/molecular results of 24-month follow-up biopsies.

Results: Upon systematic cross-sectional HLA antibody screening of 741 recipients [inclusion criteria: age >18a, eGFR >20 ml/min/1.73 m2 at ≥180 days post-transplantation] we identified 111 recipients with DSA. Forty-four DSA+ recipients with morphological evidence of ABMR were included in the trial. Twenty-one patients were allocated to receive bortezomib, and 23 placebo. Despite a trend in reduction of DSA levels, bortezomib neither affected eGFR decline (bortezomib vs. placebo: -4.6 ± 2.7 vs. -4.8 ± 2.5 ml/min/1.73 m2/year), nor median mGFR at 24 months [33mL (IQR: 28-40) vs. 43mL (26-51), p=0.2]. There were also no differences regarding two-year overall graft survival (81% vs. 96%, p=0.1) and morphological (ABMR category, g+ptc score, IFTA score, C4d) and molecular results (Molecular-ABMR score, MMDx) of 24-month follow-up biopsies. Bortezomib treatment was associated with a higher rate of GI adverse events (diarrhea: 67% vs. 22%, p=0.005) and thrombo- and leukocytopenia.

Conclusions: The BORTEJECT trial demonstrates that proteasome inhibition does not ameliorate the two-year course of late ABMR. Our results underscore the need for randomized trials to dissect the efficiency and safety of new treatment strategies in this context.

Funding: Government Support - Non-U.S.

SA-PO480

Rituximab in Antibody Mediated Rejection: Delayed Benefit for Graft Survival? Sandesh Parajuli,[3] Didier A. Mandelbrot,[2] Brenda L. Muth,[4] Maha A. Mohamed,[6] Robert R. Redfield,[4] Weixiong Zhong,[5] Brad C. Astor,[4] Arjang Djamali.[1] *[1]School of Medicine and Public Health, Madison, WI; [2]U of Wisconsin Hospital, Madison, WI; [3]UW Health, Middleton, WI; [4]University of Wisconsin, Madison, WI; [5]University of Wisconsin Madison, Madison, WI; [6]University of Wisconsin School of Medicine and Public Health, Madison, WI.*

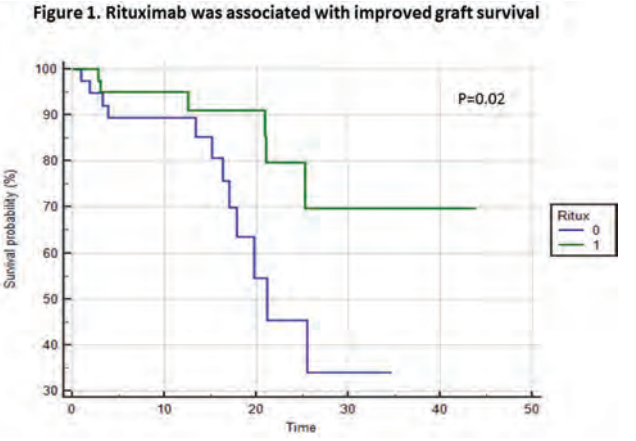
Background: There is limited information on the role of monitoring biopsies and treatment strategies in late antibody mediated rejection (ABMR) after kidney transplantation.

Methods: Seventy-eight patients diagnosed with late ABMR were treated with standard of care (SOC) steroids/IVIG (n=38) ± rituximab (n=40). All patients underwent a follow-up biopsy and DSA monitoring within 3-12 weeks. Patients were followed for 15.9 ± 9.6 months.

Results: Both treatment strategies were associated with a significant decline in DSA, microcirculation inflammation (ptc+g), and C4d Banff scores. In univariate regression analyses, rituximab, eGFR, Banff i, t, v, and chronicity (ci+ct+cv+cg) scores on the first biopsy, and eGFR and Banff v score on the follow-up biopsy were associated with graft loss. Mulltivariate analyses retained only rituximab (HR 0.23, 95% CI 0.06 to 0.84, p=0.03) and eGFR at follow-up biopsy (0.84, 95% CI 0.76 to 0.92, p<0.001) as significant predictors of graft loss. Kaplan-Meier analyses demonstrated that the benefit associated with rituximab was apparent after one year (15% vs. 32% graft loss, p=0.01) (Figure 1).

Conclusions: In conclusion, treatment of late ABMR with steroids/IVIG + rituximab was effective in reducing DSA, microcirculation inflammation, and graft loss. Follow-up biopsies could be considered in the management of acute rejection to monitor the effect of therapy.

Figure 1. Rituximab was associated with improved graft survival



SA-PO481

Hospitalization Trends for CMV Disease in Kidney Transplant Recipients in the United States, 2004–2014 Neetika Garg,[7] Nilay Kumar,[7] Sandesh Parajuli,[4] Tripti Singh,[1] Fahad Aziz,[5] Maha A. Mohamed,[6] Brenda L. Muth,[5] Arjang Djamali,[2] Didier A. Mandelbrot.[3] *[1]None, Madison, WI; [2]School of Medicine and Public Health, Madison, WI; [3]U of Wisconsin Hospital, Madison, WI; [4]UW Health, Middleton, WI; [5]University of Wisconsin, Madison, WI; [6]University of Wisconsin School of Medicine and Public Health, Madison, WI; [7]University of Wisconsin, Madison, Madison, WI.*

Background: CMV infection is a frequent complication of kidney transplantation, especially with increasing use of more aggressive immunosuppressive regimens. How the burden of inpatient hospitalization related to this diagnosis has changed over time in the United States is not known.

Methods: We used the National Inpatient Sample 2004 – 2014 to identify hospitalizations with primary or secondary diagnosis of CMV disease (ICD-9 code: 078.5) in the setting of known history of kidney transplantation. Survey analysis techniques were used to generate national estimates. Data regarding prevalent kidney transplant recipient population was obtained from OPTN/SRTR. Linear and logistic regressions were used to test trends in hospitalization rate, acute kidney injury (AKI), dialysis-requiring AKI, length of stay (LOS) and cost.

Results: 2,126 hospitalizations over the 11-year study period were representative of 10,215 hospitalizations for CMV disease nationally. Mean age was 52 years; 44.3% were women. Rate of hospitalization remained stable during the study period (6.3 to 5.3 per thousand prevalent recipient population, p-trend=0.75). However, a trend towards increasing in-hospital mortality (1.8% to 2.9%, p-trend=0.07) along with significant increases in rates of AKI, dialysis-requiring AKI, LOS and cost were noted (Table 1). This was accompanied by an increase in comorbidity burden as measured by Mean Charlson Comorbidity Index (0.80 to 2.02, p<0.001) during the study period.

Conclusions: Our study findings may reflect a shift towards outpatient management of CMV disease with hospitalization only for the sickest patients in the United States. Patient outcomes were worse and resource utilization (duration and cost of hospitalization) was higher for those admitted in more recent years.

Table 1

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	p-trend
Hospitalization rate (per 1000 prevalent kidney transplant recipients)	6.29	5.76	4.84	4.85	6.54	7.35	6.01	5.31	5.09	6.01	5.30	0.75
In-hospital mortality (%)	1.8	0.5	2.2	1.9	1.8	3.5	1.9	5.6	3.7	1.8	2.9	0.07
AKI (%)	9.5	13.0	7.0	18.7	21.3	21.2	27.2	27.6	33.2	31.6	32.7	<0.001
Dialysis-requiring AKI (%)	0.6	1.1	0.7	1.3	2.2	1.7	0.5	3.7	2.7	2.6	2.9	0.02
LOS (days, mean)	7.7	7.3	6.9	8.1	8.2	8.8	8.9	9.9	9.6	8.4	8.5	0.01
Inflation-adjusted cost ($, mean)	16,323	16,213	16,690	21,968	25,420	26,845	25,709	29,604	25,249	22,216	29,723	<0.001

SA-PO482

Long-Term Outcomes of Valganciclovir versus Valacyclovir for Cytomegalovirus Prophylaxis in Renal Transplantation: A Parallel Group, Open-Label Randomized Controlled Trial Tomas Reischig,[1] Martin Kacer,[1] Petra Hruba,[2] Daniel Lysak,[1] Pavel Jindra,[1] Ondrej Hes,[1] Mirko Bouda.[1] *[1]Charles Univ. Medical School and Teaching Hospital, Pilsen, Czech Republic; [2]Institute for Clinical and Experimental Medicine, Prague, Czech Republic.*

Background: Both valganciclovir and high-dose valacyclovir are recommended for cytomegalovirus (CMV) prophylaxis after renal transplantation. Less early acute rejection was observed with valganciclovir, however long-term comparison is lacking.

Methods: In a randomized, open-label, single-center trial, renal transplant recipients (recipient or donor CMV seropositive) were randomly allocated (1:1) to 3-month prophylaxis with valganciclovir (900mg daily) or valacyclovir (2g four times daily). The

primary outcome was moderate to severe interstitial fibrosis and tubular atrophy (IFTA) assessed by protocol biopsy at 3 years. Analysis was by intention-to-treat.

Results: A total of 119 patients were assigned to valganciclovir (n=60) or valacyclovir prophylaxis (n=59). At 3 years, the incidence of CMV DNAemia (36% vs 42%, P=0.272) and CMV disease (9% vs 2%, P=0.199) were comparable in both groups. Among the 101 patients with a protocol biopsy specimen available, 11 (22%) of the 51 patients in the valganciclovir group and 17 (34%) of the 50 patients in the valacyclovir group had moderate to severe IFTA. The risk of moderate to severe IFTA was significantly lower with valganciclovir after adjusting for baseline recipient and donor characteristics (adjusted odds ratio [aOR], 0.22; 95% confidence interval [CI], 0.07–0.70; P=0.011). A trend toward less acute rejection (24% vs 32%, adjusted hazard ratio [aHR], 0.53; 95% CI, 0.25-1.10; P=0.087) and more polyoma BK virus viremia (42% vs 26%; aHR, 1.91; 95% CI, 0.95–3.82; P=0.069) at 3 years was observed in the valganciclovir group. 4-year patient and graft survival was not significantly different between groups.

Conclusions: Valganciclovir prophylaxis compared to high-dose valacyclovir is associated with reduced risk of moderate to severe IFTA in late protocol biopsies in renal transplant recipients. (Trial registered at Australian New Zealand Clinical Trials Registry: ACTRN1260000016033)

Funding: Government Support - Non-U.S.

SA-PO483

Use of Body Surface Area Corrected GFR results in Inappropriate Valganciclovir Dosing in Kidney Transplant Recipients Rohan S. Paul, Chethan M. Puttarajappa, Sundaram Hariharan. *University of Pittsburgh Medical Center, Starzl Transplant Institute, Pittsburgh, PA.*

Background: Clinicians generally use the MDRD or CKD-EPI equations to gauge renal function, which normalize GFR to a body surface area (BSA) of 1.73 m^2. We hypothesized that since absolute GFR is rarely measured and used, prophylactic valganciclovir is being dosed inappropriately in certain renal transplant recipients which may predispose to leukopenia and/or CMV infection.

Methods: This cross-sectional study included 225 renal transplant recipients from UPMC who were transplanted from January 1, 2013 to December 31, 2015. MDRD reported GFR was converted to absolute GFR. Patients were categorized into BSA tertiles (low BSA < 1.73 m^2; middle BSA: 1.73-2.09 m^2; high BSA > 2.09 m^2). The appropriateness of valganciclovir dose among these groups at three months post-transplantation was determined and compared using Chi-squared test. The point prevalence of leukopenia (WBC < 3500 × $10^3/mm^3$) among the dosing categories was analyzed using One-way ANOVA. The incidence of PCR confirmed CMV infection was compared using Chi-squared test.

Results: The study population consisted of 138 (61%) males and 87 (39%) females. Analysis of valganciclovir dosing across the BSA tertiles found no significant difference based on normalized GFR (P = 0.811), but a significant difference based on absolute GFR, with a trend towards overdosing with low BSA and underdosing with high BSA (P < 0.001). There was no difference in the point prevalence of leukopenia across the dosing categories (P = 0.819). There was no difference in the incidence of CMV infection within 100 days post-transplantion as there were zero infections in this period. There was a signficant difference in the incidence of CMV infection 100-400 days post-transplantation with a higher rate seen with higher BSA (P = 0.0468).

Conclusions: We conclude that normalized GFR leads to inappopriate valganciclovir dosing in a large subset of kidney transplant recipients. This did not translate into a higher point prevalence of leukopenia in those receiving supratherapeutic doses. However there was a higher incidence CMV infection in the 100-400 days post-transplantation in patients with a higher BSA. The observed valganciclovir underdosing in this BSA group is suspected to be at play. We therefore propose that absolute GFR be routinely used for valganciclovir dosing in kidney transplant recipients.

SA-PO484

Significantly Less CMV- and BKV-Events with Everolimus-Based versus Tacrolimus-MPA Regimen in De Novo Renal Transplant Recipients: 12 Months Data on Infections from the Athena Study Ingeborg A. Hauser,[2] Claudia Sommerer,[11] Barbara M. Suwelack,[4] Duska Dragun,[10] Peter Schenker,[5] Oliver Witzke,[8] Christian Hugo,[12] Nassim Kamar,[3] Pierre Merville,[7] Martina Junge,[6] Friedrich Thaiss,[9] Björn Nashan.[1] *[1]Bundesärztekammer, Hamburg, Germany; [2]University Clinic Frankfurt (UKF), Frankfurt Main, Germany; [3]Toulouse University Hospital, Toulouse, France; [4]Muenster, Germany; [5]Ruhr-University Bochum, Bochum, Germany; [6]Novartis Pharma GmbH Germany, Nuremberg, Germany; [7]PELLEGRIN HOSPITAL, Bordeaux, France; [8]University Duisburg-Essen, Essen, Germany; [9]University Hospital, Hamburg, Germany; [10]University Hospital Charite, Campus Virchow, Berlin, Germany; [11]University Hospital of Heidelberg, HEIDELBERG, Germany; [12]University of Dresden, Dresden, Germany, Dresden, Germany. Group/Team: Athena Study Group.*

Background: The ATHENA trial was designed to compare everolimus [EVR] in combination with tacrolimus [TAC] or cyclosporine A [CyA] vs. a standard of mycophenolic acid [MPA] and TAC in de novo kidney transplant [KTx] recipients.

Methods: In this 12 months [M], prospective, open-label, randomized study with 15 German and 12 French sites, 612 patients [pts] were randomized 1:1:1 at time of Tx to either EVR (3-8ng/ml M1-M12) +TAC (4-8ng/ml M1-M3; 3-5ng/ml M3-M12), or EVR (3-8ng/ml M1-M12) + CyA (75-125ng/ml M1-M3; 50-100ng/ml M3-M12) or to control TAC regimen (4-8ng/ml M1-M3; 3-5ng/ml M3-M12) with MPA. All pts continued on steroids. Herein we report M12 outcomes on infections and CMV events from ITT with 208 EVR+TAC pts, 199 EVR+CyA pts and 205 TAC+MPA pts.

Results: From randomization to M12 total incidences of infections were 73% in EVR+TAC and 72% in EVR+CyA treated pts vs 82% in TAC+MPA pts. Whilst incidences of bacterial infections were similar between the three treatment groups (44% EVR+TAC, 43% EVR+CyA, 42% TAC+MPA) major differences were seen for viral infections with incidences of 41% in TAC+MPA vs only 26% in EVR+TAC and 12% in EVR+CyA groups. Incidence of BKV events was 23% in TAC+MPA vs 17% in EVR+TAC vs 9% in EVR+CyA pts (p<0.01). CMV events occurred two thirds less in EVR treated pts compared to TAC+MPA control group with an incidence of 21% in TAC+MPA vs 6% for EVR+TAC and 3% for EVR+CyA treatment pts (p<0.001).

Conclusions: ATHENA as largest European KTx study confirmed comparable efficacy and safety together with less viral infections for EVR-based treatment groups compared to TAC+MPA group. A significant, protective effect of EVR-based regimens vs CMV/BKV events was robustly confirmed.

Funding: Commercial Support - Novartis Pharma GmbH, Germany, Government Support - Non-U.S.

SA-PO485

Peptide Vaccination against Cytomegalovirus (CMV) Induces Cellular Immune Responses in CMV Seronegative ESRD Patients Claudia Sommerer,[2] Anita Schmitt,[3] Paul Schnitzler,[1] Martin G. Zeier,[2] Michael Schmitt.[3] *[1]Virology, University Hospital Heidelberg, Heidelberg, Germany; [2]Nephrology, University Hospital Heidelberg, Heidelberg, Germany; [3]Internal Medicine V, University Hospital Heidelberg, Heidelberg, Germany.*

Background: Cytomegalovirus (CMV) reactivation occurs particularly in patients after solid organ transplantation (SOT) from seropositive donors. CMV reactivation is associated with a high risk of disease and mortality. The nonamer peptide NLVPMVATV derived from CMV phosphoprotein 65(CMVpp65) is highly immunogenic. Here we report on a clinical phase I peptide vaccination trial with this peptide in a water-in-oil emulsion (Montanide™) plus administration of or imiquimod (Aldara™) as adjuvant.

Methods: Four vaccines were administered subcutaneously at a biweekly interval to ten CMV seronegative endstage renal disease patients waiting for kidney transplantation. The clinical course, CMVpp65 antigenemia and CMV replication were monitored. CMV-specific CD8+ T cells were characterized by multi-color flow cytometry and Enzyme Linked Immuno Spot Assay (ELISPOT) and correlated it to clinical parameters.

Results: Peptide vaccination was well tolerated and no drug-related serious adverse events were detected except from local skin reactions. In four patients, specific CD8+ T cell responses against CMV could be elicited by prophylactic vaccinations. In responders an increase of CMV-tetramer positive CD8+ T cells and interferon gamma secretion was detected. Interestingly a shift from CCR7+CD45+ naïve T cells towards CCR7-CD45RA+ effector T cells could be observed suggesting an effective immune response against the virus.

Conclusions: In ten CMV seronegative endstage renal disease patients on the waiting-list for kidney transplantation we demonstrated that administration of CMVpp65 peptide vaccination was safe, well tolerated and clinically encouraging. Imiquimod can serve as an adjuvant with a similar efficacy.

SA-PO486

Intensive BK Virus Screening Protocol – A Single Center Experience Anshul Bhalla, Nitender Goyal, Ronald D. Perrone. *Tufts Medical Center, BOSTON, MA.*

Background: Polyoma virus associated nephropathy (PyVAN) caused by BK virus (BKV) occurs in 1-10% of kidney transplant recipients (KTR). Due to lack of effective treatment, screening for BKV replication is the most important tool to improve outcomes. Proposed screening strategies are based on consensus guidelines but protocols vary across centers. Increased frequency of BKV monitoring can allow for early detection and guide management. We report 1 year outcomes in a single center with an intensive BKV screening protocol.

Methods: We performed a retrospective analysis of KTR between January 2014 and March 2016. BKV screening protocol included monthly plasma BKV DNA quantitative PCR for the first 12 months. BK Viremia >3-log copies/mL was considered positive. Since management was based on confirmation of the positive value, only patients (PTS) with 2 or more positive results within a 4-week period were considered to have presumptive PyVAN (PP). Information regarding incidence, treatment and outcomes of PyVAN, rejection episodes and graft and patient survival was collected.

Results: Among 77 KTR, 70 underwent screening. Median age was 51 years (range 24-75), 61% male, 66% white and 40% had a deceased-donor transplant. 15% underwent desensitization with IVIG and 93% received Thymoglobulin for Induction. Maintenance immunosuppression (IS) regimen included Tacrolimus in 93%, Mycophenolate in 84% and Steroids in 37% PTS. Delayed graft function, defined as the need for dialysis in first week, was noted in 20%. 6 PTS (9%) had biopsy proven cellular rejection in the first 12 months. PP was noted in 19 patients (27%) during the screening period. Median time from transplant to detection of BK viremia was 81 days (range 37-265). Almost all PTS (18/19, 95%) were managed with reduction of IS (most commonly, calcineurin inhibitor followed by anti-proliferative agent and steroids). IVIG was used in 3/19 patients (16%). 8 PTS (42%) underwent allograft biopsy of which 3 had BK nephropathy. 14 out of 19 PTS (74%) had resolution of BK viremia during follow up period. Graft and PTS survival was 100% at 12 months.

Conclusions: Intensive BKV screening in the 1st year post kidney transplant allows for early intervention to guide IS management with excellent graft outcomes. This strategy reduces risk of over-treatment or risk of acute rejection. Larger trials are needed to determine the optimum frequency of BKV monitoring.

SA-PO487

Targeted Sequencing of BKPyV in Urothelial Carcinomas in Transplant Recipients Evan A. Farkash, Edward S. Harake. *University of Michigan, Ann Arbor, MI.*

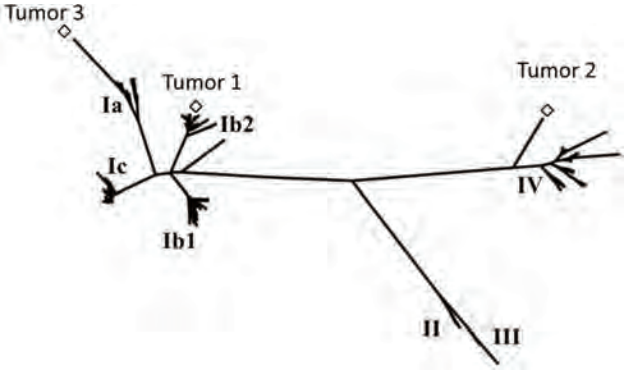
Background: Some urothelial carcinomas arising in transplant recipients show strong, universal expression of BKPyV Large T antigen (LTA). BKPyV is closely related to known oncoviruses SV40 and MCPyV; we hypothesize that BKPyV acts as oncovirus in immunosuppressed transplant reciepients. Determining the genomic structure of BKPyV in urothelial tumors may provide clues to the mechanism of oncogenesis.

Methods: We designed 26 sets of fully nested 5' and 3' primers using the BKPyV DIK strain and validated on a DIK isolate. DNA was extracted from paraffin blocks of 2 urothelial carcinomas with diffuse LTA expression (QIAMP FFPE). The BKPyV genome was amplified by 2x overlapping nested PCRs and Sanger sequenced. Sequences were aligned and compared to 312 full length BKPyV sequences from the NCBI database, as well as 1 tumor previously sequenced by a different method (Megalign, Figtree).

Results: Tumor 1 (fatal) arising 9.7 years after transplant in 59 year old male harbors a clade Ib1 virus (84.8% sequenced). Tumor 2 (nonfatal) arising 8.9 years after transplant in a 68 year old female harbors a clade IV virus (31.2% sequenced). Tumor 3 (previous work) contains a clade 1a virus. Clade I has a worldwide distribution, and clade IV is enriched in Asian and Japanese regions.

Conclusions: A targeted amplification strategy was partially successful at sequencing BKPyV from urothelial carcinoma tumors from FFPE tissue. Identification of viruses from clades Ia, Ib1 and IV provides evidence that potential oncogenecity from BKPyV in transplant recipients is not restricted to a single clade. No viral integration sites or flanking DNA were identified, and a linker DNA technique is likely needed to map potential integration sites.

Funding: Other NIH Support - NIAID, Clinical Revenue Support



Phylogenetic analysis of BKPyV from 3 urothelial carcinomas and 312 full length BKPyV sequences. Roman numerals indicate viral clade.

SA-PO488

Shotgun Cellfree DNA Sequencing to Evaluate Renal Allograft Damage in Recipients with BKVN Darshana Dadhania,[2] Philip Burnham,[1] John R. Lee,[2] Catherine Snopkowski,[3] Carol Y. Li,[2] Hua Yang,[2] Thangamani Muthukumar,[2] Manikkam Suthanthiran,[2] Iwijn De Vlaminck.[1] *[1]Cornell University, Ithaca, NY; [2]Weill Cornell Medical College, New York, NY; [3]Weill Medical College of Cornell University, New York, NY.*

Background: BKV replication is frequent and is associated with graft loss in 20-50% of cases. Existing non-invasive assays to detect BKV replication fail to correlate with the extent of renal allograft damage. Advances in the measurement of cellfree (cf) DNA in allograft recipients may be useful to identify allograft damage associated with BKVN.

Methods: In 16 recpients with stored urine supernatants, we studied cf DNA of BK virus DNA & donor DNA fractions. Analysis was performed in sex-mismatched individuals with normal protocol biopsy (n=4) & biopsy proven BKVN diagnosis (n=12). We performed shotgun metagenomic sequencing on an Illumina NextSeq (2 x 75 bp) using a single-stranded library preparation. In patients who received organs from the opposite sex, a comparison of the depth of sequencing coverage of the sex chromosomes was used to determine the cf donor DNA fraction and associated with graft injury.

Results: Urine cellfree BKV DNA correlated with urine cell pellet BKV VP1 copies (Fig 1) and Figure 2 demonstrates the correlation between serum creatinine at the time of biopsy and cf donor DNA fraction. Female recipients (n=4) receiving a male donor kidney had significantly lower cf DNA fraction compared to male recipients (n=12) receiving female kidney (Fig 3a). Among the male recipients, those with BKVN diagnosis had significantly higher urine cf donor DNA fraction compared to those with normal protocol biopsy and stable graft function (Fig 3b).

Conclusions: Our data on sex mismatched allograft recipients demonstrates that urinary cf DNA measurement in recipients offers a noninvasive measure of the burden of viral disease & allograft damage. Additional studies are needed to apply this technology to study the dynamic changes in cf donor DNA fraction with increasing/decreasing allograft damage & changes in renal function.

Figure 1.

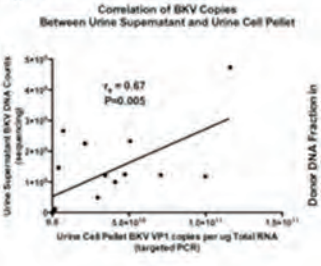


Figure 2.

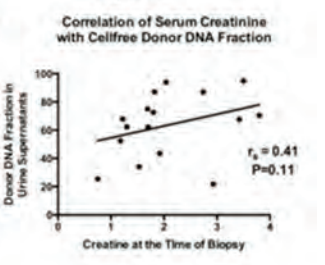


Figure 3a.

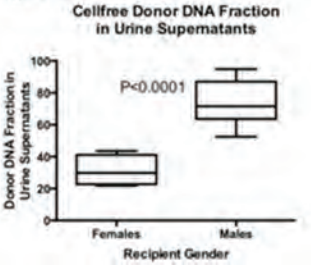
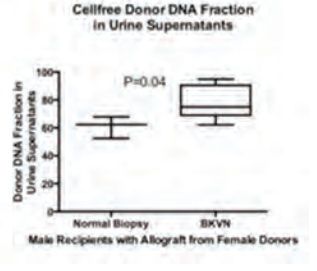


Figure 3b.



SA-PO489

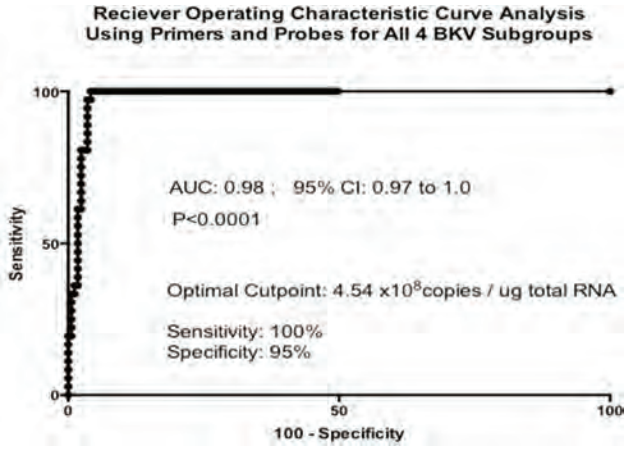
A Universal Real Time Quantitative Multiplex PCR Assay for the Non-Invasive Diagnosis of BK Polyomavirus Associated Nephropathy Darshana Dadhania,[1] Catherine Snopkowski,[2] Carol Y. Li,[1] Liana S. Perry,[1] Hua Yang,[1] John R. Lee,[1] Thangamani Muthukumar,[1] Manikkam Suthanthiran.[1] *[1]Weill Cornell Medical College, New York, NY; [2]Weill Medical College of Cornell University, New York, NY.*

Background: BK Polyomavirus associated nephropathy (BKVN) is an important cause of kidney allograft failure. Early detection & reduction of immunosuppression is the best strategy for mitigating BKVN associated graft dysfunction. Use of sensitivity DNA PCR and neighbor-joining method, a phylogenetic tree of BKV has been developed & population specific prevalence of BK has been emphasized. Existing BKV PCR assays fail to account for BKV subtypes, we designed & developed a multiplex quantitative PCR assay for detection of clinically significant subtypes.

Methods: We designed 3 sense & 3 antisense primers and 3 TaqMan probes, which in combination, amplified 7 BKV subtypes- BKV Dunlop, Ia, IC, III, 1v, V, and VI. Total RNA was isolated from 205 biopsy matched urine specimens reverse transcribed to cDNA and real-time quantitative multiplex PCR assays were established. All biopsies were stained for SV40: 36 were SV40 positive & classified as BKVN biopsies; remaining 169 were SV40 negative & classified as acute rejection (n=56); Normal (n=53); acute tubular injury (n=50); Other (n=10). Receiver-operating- characteristic curve analysis was used to calculate area under the curve (ROC-AUC), sensitivity and specificity for distinguishing BKVN biopsies from all other biopsy diagnoses.

Results: Analysis involving ROC curve demonstrated that BKVN diagnosis can be predicted with a sensitivity of 100% & a specificity of 95% with the use 4.54×10^8 copies of BKV mRNA per microgram of RNA as the cutpoint (ROC-AUC=0.98, 95% CI, 0.97 to 1.0, P<0.0001). (Figure 1)

Conclusions: We have designed and developed real time quantitative multiplex PCR assays for the detection of major subtypes of BKV and demonstrate its utility for the noninvasive diagnosis of BKVN. In view of population specific prevalence of BKV subtypes, the newly developed assay should have universal appeal.



SA-PO490

Predictive Value of the Combination of Peripheral Blood Lymphocyte Count and Urinary Cytology in the Diagnosis of Polyomavirus BK Nephropathy Kosuke Masutani,[2] Akihiro Tsuchimoto,[2] Yuta Matsukuma,[2] Yasuhiro Okabe,[3] Kazuhiko Tsuruya,[4] Takanari Kitazono.[1] *[1]Department of Medicine and Clinical Science, Fukuoka, Japan; [2]Kyushu University, Fukuoka, Japan; [3]Kyushu University Hospital, Fukuoka, Japan; [4]None, Fukuoka, Japan.*

Background: Screening of Polyomavirus BK (BKV) infection is recommended for kidney transplant (KT) patients. Graft biopsy is the gold standard for the diagnosis of BKV nephropathy (BKVN), and polymerase chain reaction for viral DNA is the most specific screening technique. However, the identification of non-invasive, and cost-effective marker is still important and can improve monitoring. Thus we investigated the predictive value of the peripheral blood lymphocyte (PBL) count and urinary cytology for the diagnosis of BKVN.

Methods: From July 2008 through May 2014, 492 adult patients received KT at Kyushu University Hospital. We investigated the PBL count and cytology results at graft biopsy in the patients with BKVN (BKVN group, n=21), acute T-cell mediated rejection (TCMR group, n=79), and no evidence of rejection (NoAR group, n=149). We performed univariate and multivariate logistic regression and receiver operating characteristics analyses to compare the test performance of PBL count alone, cytology alone, and their combination in the diagnosis of BKVN.

Results: PBL count (mean ± SD) at graft biopsy was significantly lower in BKVN group than those in TCMR and NoAR groups (959 ± 290, 1433 ± 673, and 1531 ± 549 /μL, respectively, p<0.01). PBL count increased after the treatment of BKVN (at diagnosis, after 1, 2, and 3 months were 959 ± 290, 1123 ± 377, 1238 ± 419, and 1292 ± 491, respectively, p<0.05). On univariate logistic regression analysis, the area under the curve for prediction of BKVN was significantly higher in the combined model than those in PBL alone and cytology alone (0.930, 0.797 and 0.875, respectively, p<0.01). The improvement of predictive performance in the combined model remained significant after adjustment for the classical risk factors of BKVN (0.972, 0.844, and 0.928, respectively, p<0.01).

Conclusions: Decreased PBL count was found in the patients with BKVN. Although PBL count alone showed moderate accuracy, the predictive performance of the combination of PBL count and urinary cytology is significantly enhanced in the diagnosis of BKVN.

SA-PO491

Urinary Exosomal Viral miRNA as a Marker of BK Virus Nephropathy after Kidney Transplantation Sang-Ho Lee,[3] Yu ho Lee,[3] Seo Jung-Woo,[3] Jin sug Kim,[4] Yang gyun Kim,[1] Kyung-hwan Jeong,[5] Ju young Moon,[8] Chun-Gyoo Ihm,[6] Tae won Lee,[2] Byung ha Chung.[7] *[1]Division of Nephrology Department of internal medicine Kyung Hee University College of Medicine, Seoul, Republic of Korea; [2]Kyung Hee Universitiy School of Medicine, Seoul, Republic of Korea; [3]Kyung Hee University Hospital at Gangdong, Seoul, Korea, Seoul, Republic of Korea; [4]Kyung Hee University Medical Center, Seoul, Republic of Korea; [5]Kyung Hee University, School of Medicine, Seoul, Republic of Korea; [6]None, Seoul, Republic of Korea; [7]Seoul St. Mary's Hospital, Seoul, Republic of Korea; [8]University of Southern California, Los Angeles, AL.*

Background: Recently, bkv-miR-B1-5p, one of the miRNAs encoded by BK virus, was reported to be elevated in the blood among the patients with BK virus nephropathy (BKVN). Urinary exosome was suggested to be a possible source of biomarker for kidney diseases, but it was unknown whether it could contain viral miRNA as well as human miRNAs.

Methods: In a cross sectional, observational study, we evaluated the prevalence of biopsy proven BKVN among 458 graft biopsies from 385 kidney transplant recipients at five transplantation centers from August 2013 to July 2015. For patients with BKVN (n=13) and 67 age, sex-matched renal transplant recipients, we measured BK viral miRNA B1-5p, 3p and human miRNA-16 in urinary exosomal fraction and compared the diagnostic value with viral DNA in plasma and urine.

Results: Pathology proven BKVN was diagnosed in 13 patients (2.8%). The prevalence of BKVN was significantly higher in patients who underwent indication biopsy than in patients who underwent protocol biopsy (4.8% vs. 0.5%). High levels of bkv-miR-B1-5p and bkv-miR-B1-3p were shown in all patients with BKVN. Plasma viral DNA assay (cut-off value of $1x10^4$ copies/mL) showed false negative in 3 cases and urinary viral DNA assay (cut-off value of $1x10^7$ copies/mL) showed false negative in 1 case among these 13 patients. When compared to 67 propensity score matching patients with other pathologic classification, the receiver operator characteristics (ROC) curve analysis for bkv-miR-B1-5p and bkv-miR-B1-5p/miR-16 showed excellent values of area under curve (AUC) for the diagnosis of BKVN.

Conclusions: This study suggests that urinary exosomal bkv-miR-B1-5p and bkv-miR-B1-5p/miR-16 also could be surrogate markers for the diagnosis of BKVN.

Funding: Government Support - Non-U.S.

SA-PO492

Clinical Outcomes of Patients with BK Viremia in ABO-Incompatible Kidney Transplantation and Comparison with ABO-Compatible Kidney Transplantation Jung a Yoon, Chung Hee Baek, Su-Kil Park, Hyosang Kim. *Nephrology, Asan Medical Center, University of Ulsan College of Medicine, SEOUL, Republic of Korea.*

Background: ABO-incompatible kidney transplantation (ABOiKT) recipients may have an increased risk of BK virus allograft nephropathy (BKVAN), a major cause of renal dysfunction and allograft loss. We investigated BK viremia and BKVAN in ABOiKT recipients compared to those receiving ABO compatible kidney transplantation (ABOcKT).

Methods: This study analyzed a total of 1111 kidney transplant recipients between January 2012 and December 2015 (n= 217 ABOiKT and n= 894 ABOcKT) at Asan Medical Center. High viremia was defined as serum BK viral load with peak ≥ 10,000 copies/mL more than once after transplantation and low viremia was defined as serum BK viral load with peak < 10,000 copies/mL. BKVAN was confirmed by biopsy.

Results: The incidence of high viremia was 12.0% (n= 26/217) in ABOiKT and 8.4% (n= 75/894) in ABOcKT (p= 0.067). BKVAN was diagnosed in 4.6% (n= 10/217) ABOiKT recipients and 1.6% (n = 14/894) ABOcKT recipients (p= 0.015). In ABOiKT, graft survival was not significantly different among the groups according to degree of BK viral loads (p= 0.092), but graft functions of patients with high viremia were worse than that of patients with aviremia, especially at 6 months and 12 months (p= 0.020 and p=0.006, respectively). Among patients with high viremia, 38.5% (10/26) patients in ABOiKT were diagnosed BKVAN compared with only 18.7% (14/75) patients in ABOcKT (p= 0.041). BKV was first detected within 6 months after transplantation in both groups (p=0.304). In patients with high viremia, graft functions of ABOiKT patients were worse than that of ABOcKT patients at 6 months after transplantation. There was no significant difference in the incidence of graft failure, but graft failure was caused by BKVAN in ABOiKT with high viremia and by acute rejection in ABOcKT with high viremia. However, there was no significant difference in graft survival between ABOiKT and ABOcKT.

Conclusions: ABOiKT recipients have a greater risk for BK viremia and BK allograft nephropathy compared to ABOcKT. In ABOiKT, high BK viremia was associated with worse graft function although it did not affect graft survival.

SA-PO493

Variable Presentation and Histologic Findings in JC Nephropathy Brian K. Lee,[3] Kuang-Yu Jen,[2] Zoltan G. Laszik.[1] *[1]Pathology, University of California San Francisco, San Francisco, CA; [2]Pathology, University of California, Davis, Sacramento, CA; [3]Nephrology, University of California San Francisco, San Francisco, CA.*

Background: Polyomaviruses commonly infect healthy individuals and remain latent. However, immunosuppression (IMMS) can result in reactivation. With renal tropism BK virus is the most common cause of virus associated nephropathy (VAN) in kidney allografts while JC VAN is a rare complication with only a handful of JC VAN cases reported previously.

Methods: From 01/2007 to 12/2014, 3 cases of JC VAN in renal transplant patients were detected at our institution. Here, we report on the variable presentation and histologic findings for JC VAN in these patients. Two patients had an acute rise in serum creatinine which prompted allograft biopsy (bx), while the other underwent a surveillance bx. The time at bx ranged from 6 to 75 months post-transplant. Only one case displayed viral cytopathic changes, but two showed inflammation and tubulitis. All exhibited polyoma VAN with positive SV40 stains. However, plasma BK viral loads were undetectable, which prompted further testing for JC virus. All subsequently showed JC viremia. Recent acute cellular rejection was seen in two cases, which resulted in intensified IMMS.

Results:

Conclusions: JC VAN can present sub-clinically with low/transient viral replication. Presence of viral cytopathic changes is variable, making histologic diagnosis challenging. Previous reports suggest that the onset of JC VAN lagged behind that of BK virus. One of our cases presented early at 6 months post-transplant, arguing that a higher index of suspicion even in those with stable graft function undergoing protocol bx is crucial in capturing this condition. Routine SV40 stains may help catch some cases. Reduction in IMMS remains the mainstay of treatment. Caution with treating accompanying

inflammation as rejection activity should be exercised, as intensified IMMS likely contributes to JC VAN.

Cases	1	2	3
Age	62	62	46
Sex	F	M	M
Cause of ESRD	Hypertension	Diabetes Type 2	Diabetes Type 1
Donor Source	Deceased	Deceased	Living Unrelated
Serum Creatinine (mg/dl)			
At bx	3.06	1.90	2.05
18 mos post-bx	2.28	1.99	2.02
Time at Bx (months post-tx)	75	6	24
Tacrolimus Trough at Bx (mcg/L)	8.7	12.6	10.1
JC Viremia (copies/ml)			
Peak titer	204,000	8591	Detected (not quantified)
Last visit	19,200	<500	Not done
Interstitial Fibrosis & Tubular Atrophy	30-40%	0%	20%
Tubulitis Score	t0	t2	t2
Interstitial Inflammation Score	i0	i2	i1
Preceding ACR (within 6 months of bx)	No	ACR 2A	ACR 1A
Treatment for JC VAN	Lowered IMMS	Lowered IMMS	Lowered IMMS IV Cidofovir

Fig 1.

SA-PO494

Incidence of Hepatitis B Virus Reactivation after Kidney Transplantation with Low-Dose Rituximab Administration Kosuke Masutani,[2] Kazuya Omoto,[4] Masayoshi Okumi,[4] Yasuhiro Okabe,[3] Tomokazu Shimizu,[4] Kazuhiko Tsuruya,[2] Takanari Kitazono,[1] Hideki Ishida,[4] Kazunari Tanabe.[4] *[1]Department of Medicine and Clinical Science, Fukuoka, Japan; [2]Kyushu University, Fukuoka, Japan; [3]Kyushu University Hospital, Fukuoka, Japan; [4]Tokyo Women's Medical University, Tokyo, Japan. Group/Team: Japan Academic Consortium of Kidney Transplantation (JACK) Investigators.*

Background: In patients with hematological malignancy who are intended to receive rituximab, hepatitis B virus (HBV) serology screening and viral reactivation monitoring are recommended. However, the effect of single-dose rituximab on HBV reactivation in kidney transplant (KT) patients with previous HBV infection is still unclear.

Methods: In this retrospective cohort study of 1,294 KT patients, we identified 76 who were negative for preoperative hepatitis B surface antigen and HBV DNA, and positive for hepatitis B core antibody. A rituximab dose of 200 mg/body was administered to 48 patients; 46 of whom did not receive prophylaxis (rituximab + group). Twenty-eight patients received neither rituximab nor prophylaxis (rituximab – group). We monitored HBV DNA by polymerase chain reaction every 1–3 months, and HBV reactivation was defined as detectable HBV DNA.

Results: HBV reactivation was found in one patient in the rituximab + group (2.2%) and one in the rituximab – group (3.6%) at 6 weeks and 5.5 years post-KT, respectively, but it was spontaneously cleared. Both patients were positive for hepatitis B surface antibody (anti-HBs) preoperatively. HBV reactivation was not found in six patients lacking anti-HBs preoperatively.

Conclusions: Low-dose rituximab administration in KT patients without prophylaxis is associated with a low incidence of HBV reactivation. However, the sequential monitoring is necessary for many years to detect viral reactivation and prevent de novo hepatitis.

SA-PO495

Comparison of Renal Safety and Efficacy of Tenofovir and Entecavir Treatment in Chronic Hepatitis B Patients with Kidney Transplantation Seonghoon Kim, Hyosang Kim, Soo Ya Bae. *Asan Medical Center, University of Ulsan College of Medicine, SEOUL, Republic of Korea.*

Background: Nucleotide reverse transcriptase inhibitor is used for the treatment of chronic hepatitis B (CHB). Preemptive antiviral therapy can improve the survival of HBsAg-positive renal allograft recipients. But there are concerns about the potential risk of nephrotoxicity with long-term use. This study aims to assess the nephrotoxicity and efficacy of tenofovir and entecavir in kidney transplant recipients.

Methods: We performed a single center based, retrospective study of 55 patients with CHB treated with tenofovir (n=34) and entecavir (n=21) after kidney transplantation. Patients with a decrease <20% in eGFR were recorded, calculated using the Modification of Diet in Renal Disease. Treatment efficacy was assessed by HBV DNA levels and virological breakthrough.

Results: Tenofovir was associated with a decrease in eGFR at 1 year from treatment (unadjusted odds ratio, 10.313; 95% CI, 1.111-95.762; p=0.026; patients with decreased GFR, 5/21 vs. 1/34). Mean eGFR at 1 year was 55.6 ml/min/1.73m^2 and 64.0 ml/min/1.73m^2 at tenofovir and entecavir group. Delta eGFR at 1 year was -2.82 ml/min/1.73m^2 in entecavir group and 0.10 ml/min/1.73m^2 in tenofovir group. There was no significant change in eGFR between the entecavir group and the tenofovir group after a mean of 45 months (Mean eGFR, 56.5 ml/min/1.73m^2 vs. 62.7 ml/min/1.73m^2). There was no difference in rate of virological breakthrough between two groups at the end of treatment (patients with virological breakthrough, 5/21 vs. 6/34; p=0.731). By multivariate analysis, the significant factor associated with a decrease in eGFR at 1 year from treatment were tenofovir (adjusted odds ratio, 18.477; 95% CI, 1.123-275.953; p=0.034).

Conclusions: Patients who received KT and treated with tenofovir were likely to have decline in renal function than patients who treated with entecavir at 1 year from treatment. Tenofovir was independently associated with decrease in eGFR at 1 year from treatment. There was no significant difference in an efficacy between tenofovir and entecavir group at the end of treatment.

SA-PO496

MAGELLAN-2: Glecaprevir/Pibrentasvir for 12 Weeks in Renal Transplant Patients With Chronic Hepatitis C Virus Genotypes 1–6 Nancy Reau,[4] Paul Kwo,[5] Susan Rhee,[1] Martin Prieto,[2] Edward Gane,[7] Parvez Mantry,[6] Abhishek Gulati,[1] Preethi Krishnan,[1] Emily Dumas,[1] Nancy Shulman,[1] Xavier Forns.[3] *[1]AbbVie Inc., North Chicago, IL; [2]Hospital Universitario y Politécnico La Fe and CIBERehd, Valencia, Spain; [3]Liver Unit, Hospital Clinic, CIBEREHD, IDIBAPS, Barcelona, Spain; [4]Rush University Medical Center, Chicago, IL; [5]Stanford University School of Medicine, Stanford, CA; [6]The Liver Institute at Methodist Dallas, Dallas, TX; [7]University of Auckland, Auckland, New Zealand.*

Background: Chronic HCV infection is associated with poor long-term patient and allograft survival following renal transplant. Treatment is challenging and limited data exist on the use of IFN-free direct-acting antiviral (DAA) therapies in these patients. This study evaluated the safety and efficacy of glecaprevir/pibrentasvir (G/P) in renal transplant patients with chronic HCV infection.

Methods: MAGELLAN-2 was a Phase 3, single-arm, open-label trial. Renal transplant patients infected with chronic HCV genotypes (GT) 1–6, who were treatment-naïve or -experienced (IFN- or SOF-based) and non-cirrhotic, received 12 weeks of G/P 300/120 mg once daily. Safety data and the percentage of patients achieving sustained virologic response (HCV RNA <LLOQ) at post-treatment Week 12 (SVR12) were assessed.

Results: Overall, 20 patients were enrolled: the majority were male (55%), white (55%), and treatment-naïve (80%); 30% had HCV GT1a, 55% had GT1b, 10% had GT3, and 5% had GT4 infection; 90% had F0–F1 and 10% had F3 fibrosis. Most patients had a baseline eGFR <60 mL/min/1.73 m^2 (55%), and baseline immunosuppressants (IS) were cyclosporine (20%), tacrolimus (55%), or other (25%); adjustments in IS dosing were minor. SVR12 was 100%. AEs were mostly mild; fatigue, nausea, and upper respiratory tract infection were most common (20% each). One patient had decreased creatinine clearance (<30 mL/min) during treatment 2 days after the last G/P dose, which was not related to the DAA. There were no DAA-related serious AEs and no graft rejections.

Conclusions: G/P for 12 weeks is highly efficacious for renal transplant patients infected with chronic HCV GT1–6, with a 100% SVR12 rate. G/P was well tolerated, with no discontinuations.

Funding: Commercial Support - AbbVie

SA-PO497

Effectiveness of Direct-Acting Antiviral Regimens in the Treatment of Hepatitis C Virus (HCV) in Kidney Transplant Recipients Karolyn S. Horn,[1] Maya Campara,[2] Michelle T. Martin,[2] Ignatius Y. Tang.[1] *[1]University of Illinois Hospital and Health Sciences System, Chicago, IL; [2]University of Illinois Hospital and Health Sciences System / University of Illinois at Chicago College of Pharmacy, Chicago, IL.*

Background: The AASLD Hepatitis C virus (HCV) guidance document does not offer recommendations for the treatment of kidney transplant recipients. Real-world data are needed to evaluate the effectiveness of direct-acting antivirals (DAAs) in this underrepresented population.

Methods: Authors performed a retrospective chart review of kidney transplant recipients (KTRs) who were treated for HCV at an urban medical center from January 1, 2014 to December 1, 2016. This reports[M1] our single-center, retrospective analysis of the efficacy and safety of DAA-based regimens in kidney (K), kidney-liver (KL), and kidney-pancreas (KP) transplant patients.

Results: 28 KTRs were treated for HCV; 54% were K, 32% KL, and 14% KP. Patients had a mean age of 60 (±7) years, 50% were male, 71% were treatment naïve, 25% had cirrhosis, and all GT 1. Pre-treatment and end-of-treatment levels did not differ for serum creatinine (n=22 patients, 1.5mg/dL vs 1.7mg/dL, p=0.4); or urine microalbumin to creatinine ratio (n=15 patients, 337.3 vs 111, p=0.3). 18% had dose changes in immunosuppression (IMS) levels during and after HCV treatment, but the mean daily tacrolimus levels did not differ from baseline and 12 weeks after treatment completion (4.6 mg vs 4.8 mg, respectively, p>0.05). The overall SVR rate was 86%. SVR did not differ by regimen; 50% with sofosbuvir+ribavirin, 90.9% with sofosbuvir+simeprevir, 90% with ledipasvir/sofosbuvir, 75% ledipasvir/sofosbuvir + ribavirin, and 100% with elbasvir/grazoprevir achieved SVR (p=0.55). SVR did not differ by type of transplant (92.9% K vs 80% KL vs 75% KP, p = 0.54). SVR also did not differ by genotype, gender, ethnicity, BMI, baby-boomer status, cirrhosis, treatment history, adherence, or diabetes (p>0.05). SVR did differ by primary IMS agent, SVR rates were 100% for mycophenolate mofetil (n=1), 91.7% for tacrolimus (n=24), 100% for sirolimus (n=1), and 85.7% for cyclosporine (n=2) (p=0.005).

Conclusions: DAA regimens were highly effective in treating HCV in KTRs. Renal allograft function was stable throughout and 12 weeks after DAA therapy. Comparison

across groups was limited due to small numbers. IMS levels should be monitored closely during HCV treatment as many patients required dose adjustments.

SA-PO498

Impact of Early Ureteric Stent Removal on Urinary Tract Infection and Ureteric Complication after Kidney Transplantation – A Single Centre Experience Stephanie Chong,[3] Viyaasan Mahalingasivam,[2] Sajeda Youssouf,[1] Mark Blunden.[3] *[1]Barts Health NHS Trust, London, United Kingdom; [2]Mid Essex Hospitals NHS Trust, Harrow, United Kingdom; [3]Royal London Hospital, London, United Kingdom.*

Background: Recurrent urinary tract infection (UTI) is a common cause of renal allograft dysfunction as well as a burden on patient quality of life and the health economy.

Methods: We performed a retrospective study of consecutive deceased donor transplants undertaken at our centre between January 2012 and June 2016 to determine the effectiveness of strategies which had been established to reduce rates of UTI in our patient cohort. These included changing pre-operative antibiotic prophylaxis from co-amoxiclav to meropenem in January 2014, whilst a cohort of patients underwent the intra-operative tying of ureteric stents to indwelling urinary catheters, in order to allow for early concurrent removal on day 5. The remaining patients continued to undergo standard cystoscopic stent removal after six weeks. Our aim was to determine the difference these changes made to the incidence of UTI in the first three months after transplantation. 555 adult deceased donor transplants were studied of which 23 were excluded due to early explantation. 115 underwent early stent removal whilst 418 underwent later cystoscopic removal.

Results: There was no difference in the number of patients with at least one UTI between with groups (37.0% with early stent removal, 38.3% with later stent removal, p=0.83) or with more than two UTIs (15.6% vs 14.8%, p=0.83). There was no difference in the average number of UTIs per patient (1.02 vs 1.05, p=0.43). There was also no difference in the incidence of extended-spectrum beta-lactamases (ESBL) (6.09% vs 7.42%, p=0.58) or hospital admission (10.5% vs. 6.09%, p=0.15). There was no difference in the rate of ureteric complication (6.9% vs 5.7%, p=0.85). There was however, an increase in the rate of UTI per patient after the antibiotic protocol was switched from co-amoxiclav to meropenem (0.68 to 1.33, p<0.05). The rate of ESBL was similar (5.49% vs 8.36%, p=0.20) in both groups.

Conclusions: Early ureteric stent removal does not appear to reduce the incidence or frequency of UTI and there was no significant difference in ureteric complication rates in our patient cohort. These findings suggest that early stent removal is a potentially viable and cost effective surgical strategy in renal transplantation but further prospective randomised controlled trials are needed for validation.

SA-PO499

Gut Microbiota Disturbances and Post-Transplant Diarrhea in Kidney Allograft Recipients John R. Lee,[2] Matthew Magruder,[2] Lisa T. Zhang,[2] Thangamani Muthukumar,[2] Darshana Dadhania,[2] Lars Westblade,[2] Michael Satlin,[2] Lilan Ling,[1] Eric Pamer,[1] Manikkam Suthanthiran.[2] *[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Weill Cornell Medicine, New York, NY.*

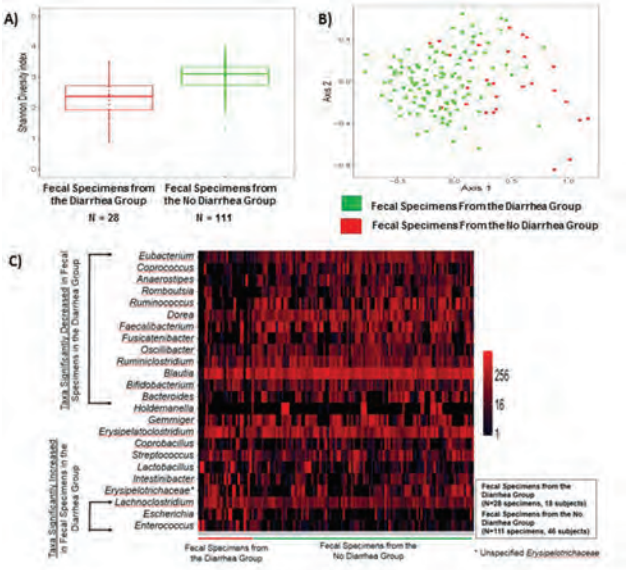
Background: Diarrhea is a common complication in kidney transplant recipients, but its etiology is unknown. In a prior gut microbiota profiling study, we reported lower abundance of commensal bacterial taxa (*Ruminococcus, Dorea, Corpococcus,* and *Bacteroides*) in kidney transplant recipients with post-transplant diarrhea.

Methods: Herein, we perform a validation study using an independent cohort of 71 kidney transplant recipients. We collected 199 serial fecal specimens from this population in the first 3 months of transplantation and profiled their microbiota using 16S rRNA deep sequencing of the V4-V5 hypervariable region. 24 subjects developed post-transplant diarrhea and 47 did not. We compared 28 diarrheal fecal specimens from the Diarrhea Group to 111 fecal specimens from the No Diarrhea Group.

Results: Microbial diversity was significantly lower in the diarrheal fecal specimens from the Diarrhea Group than in the fecal specimens from the No Diarrhea Group (P < 0.001, Wilcoxon rank sum) (Fig A) and non-metric dimensional scaling using Bray-Curtis dissimilarity separated the two groups (Fig B). Thirteen genera including the 4 reported in the prior study were significantly lower in the diarrheal fecal specimens from the Diarrhea Group than in the fecal specimens from the No Diarrhea Group (q value<0.15, Benjamini-Hochberg correction) (Fig C). PCR array for common diarrhea-associated pathogens (Biofire GI Film Array) was negative in 26 of 28 diarrhea fecal specimens.

Conclusions: We have identified decreased commensal bacterial taxa in the kidney transplant recipients with post-transplant diarrhea, which supports future studies using prebiotics and/or probiotics to prevent and/or treat this common complication.

Funding: Other NIH Support - NIAID K23 AI 124464



A) Box and whisker plots of Shannon Diversity index of the fecal specimens from the Diarrhea Group and of those from the No Diarrhea Group. **B)** NMDS scaling of the fecal specimens in the Diarrhea Group and No Diarrhea Group by color **C)** Heatmap with the relative abundance of the top 24 genera with fecal specimens from the Diarrhea Group (left) and fecal specimens from the No Diarrhea Group (right). The top 13 taxa were significantly lower in the fecal specimens form the Diarrhea Group than in those from the No Diarrhea Group

SA-PO500

Gut Microbiota Disturbances and Urinary Tract Infections in Kidney Transplant Recipients John R. Lee,[2] Matthew Magruder,[2] Lisa T. Zhang,[2] Darshana Dadhania,[2] Thangamani Muthukumar,[2] Lilan Ling,[1] Eric Pamer,[1] Manikkam Suthanthiran.[2] *[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Weill Cornell Medicine, New York, NY.*

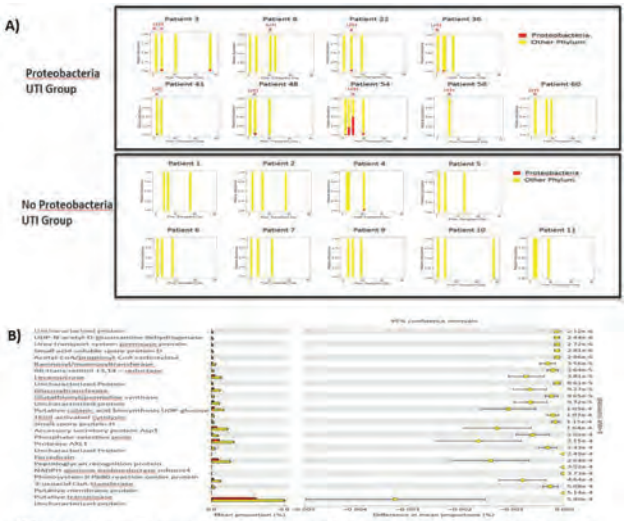
Background: Disturbances in the gut microbiota has been linked to infectious complications beyond *C. difficile.* In a pilot gut microbial profiling study, we found a link between the abundance of pathogenic gut microbiota and urinary tract infections (UTI) in kidney transplant recipients.

Methods: Herein, we perform a validation study using an independent cohort of 71 kidney transplant recipients. We collected 199 serial fecal specimens from this population in the first 3 months of transplantation and profiled their gut microbiota using 16S rRNA deep sequencing of the V4-V5 hypervariable region. Among the 71 subjects, 13 developed Proteobacteria UTIs and 58 subjects did not. We compared the gut microbial profiles in the 11 fecal specimens collected at the time of Proteobacteria UTI (Proteobacteria UTI Group) to the gut microbial profiles of 135 fecal specimens collected at the same time urine cultures were negative for Proteobacteria UTI (No Proteobacteria UTI Group).

Results: The fecal abundance of Proteobacteria, the phylum that contains gram negative pathogens like *Escherichia,* was significantly higher in the 11 fecal specimens from the Proteobacteria UTI Group than in the 135 fecal specimens from the No Proteobacteria UTI Group (1.3% vs. 0.2%, P=0.03, Wilcoxon rank sum) (Fig A). Predicted bacterial genes based on the 16S rRNA data (using PICRUSt) revealed lower metabolism related genes in the fecal specimens in the Proteobacteria UTI Group than in those in the No Proteobacteria UTI Group (Fig B).

Conclusions: Our identification of a gut microbiota-urinary tract infection relationship in kidney transplant recipients suggest that correction of gut dysbiosis may help prevent and/or treat UTIs, especially recurrent and multi-drug resistant UTIs.

Funding: Other NIH Support - K23 AI 124464



A) Each set of bar graphs represent a subject. On the x axis is the post-transplant day and on the y axis is the relative abundance of different phyla with Proteobacteria in red and other phyla in yellow. The top 9 graphs are representative patients from the Proteobacteria UTI Group and the bottom 9 are representative patients from the No Proteobacteria UTI Group. Abundance of Proteobacteria is associated with the timing of UTI. **B)** The top 27 genes that were significantly different between the fecal specimens from the Proteobacteria UTI Group and the fecal specimens from the No Proteobacteria Group are shown. On the left are the relative mean abundances of the different genes by group and on the right are the differences in mean proportions between the two groups. Q value is represented on the far right.

SA-PO501

Cell-Free DNA Sequencing of Urine Supernatants: A Novel Approach to Characterize the Urine Microbiome, Bacterial Growth Dynamics, and Antibiotic Resistomes in Kidney Transplantation John R. Lee,[1] Philip Burnham,[2] Darshana Dadhania,[1] Thangamani Muthukumar,[1] Manikkam Suthanthiran,[1] Iwijn De Vlaminck.[2] *[1]Weill Cornell Medicine-, New York, NY; [2]Cornell University, New York, NY.*

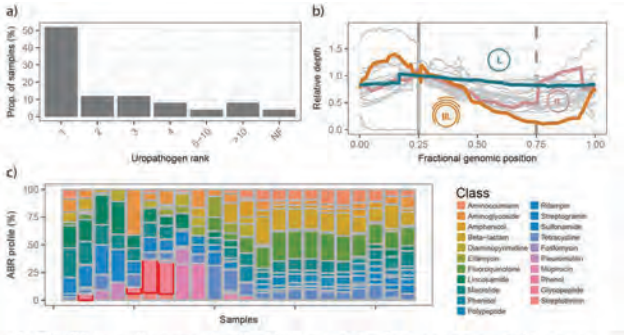
Background: Cell-free DNA sequencing can provide an all-inclusive method to profile the microbiome, bacterial growth dynamics, and antibiotic resistant patterns. Herein, we utilize cell-free DNA sequencing of urine supernatants to test its utility in a cohort of kidney transplant recipients with and without urinary tract infections (UTI).

Methods: We collected serial urine supernatants from kidney transplant recipients with UTI (N=25 urine samples from 18 subjects) and without UTI (N= 20 samples from 7 subjects). We performed single-stranded library preparation and shotgun sequencing on all of the 45 urine supernatants (Illumina Next Seq, 75 bp by 75 bp). Microbial identification was performed using the Grammy pipeline.

Results: In 24 of the 25 UTI samples, cfDNA identified the pathogen confirmed by bacterial culture (Fig. A) but also identified other pathogens in the same sample that were not detected by conventional urine culture. Uneven coverage over the origin of replication has been shown to reflect bacterial growth rates (Korem et al., Science 2015). We therefore utilized this novel principal and detected active growth rates in the pathogens causing UTIs (Fig. B). The antibiotic resistome profiles derived from cfDNA, shown in Fig. C, demonstrate the additional layer of information captured by cfDNA sequencing.

Conclusions: In this first-in-kind study, we report urinary cfDNA sequencing as an all-inclusive method to detect co-infections, bacterial growth rates, and antibiotic resistomes, which may be particularly useful in measuring the response to treatment in recurrent UTI in kidney transplantation.

Funding: Other NIH Support - K23 AI 124464



A) The 25 uropathogens identified by bacterial culture are presented by rank found in the cfDNA, indicating co-pathogens identified in the urine not detected by bacterial culture. B) Relative coverage of cfDNA (y-axis) based on fractional genomic position (x-axis) with origin region (25% fractional genomic position) and terminus region (75% fractional genomic position) with pathogen I) low growth, II) medium growth, and III) high growth. C) antibiotic resistant genes by relative abundance for each of the 25 cfDNA profiles associated with UTIs.

SA-PO502

Prevalence and Clinical Outcomes in Kidney Transplant Patients with Viral and Fungal Opportunistic Infections and Malignancies Michelle L. Lubetzky,[2] Nicole A. Hayde,[5] Layla Kamal,[3] Maria Ajaimy,[3] Puneet Bedi,[1] Enver Akalin.[4] *[1]Brookdale University Hospital Medical Center, Brooklyn, NY; [2]Transplantation, Montefiore Medical Center, New York, NY; [3]Montefiore Medical Center, Bronx, NY; [4]Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY; [5]None, Bronx, NY.*

Background: Opportunistic infections (OI) and malignancy after kidney transplant (KTX) are associated with increased morbidity and mortality. We aimed to assess clinical outcomes in patients with these complications.

Methods: We performed a single-center retrospective review of KTX patients from January 2009 until December 2014. Patients with opportunistic viral infections (BK virus or cytomegalovirus (CMV)), fungal infections, or malignancies were reviewed and compared to patients without these complications.

Results: During a median follow-up of 3.8 years (2.4-5.3), out of a total 677 patients, 222 developed OI or malignancy (32.8%); 19.2% had BK viremia, 1.5% BK nephropathy, 9.5% CMV viremia, 2.1% invasive CMV infection, 2.5% fungal infection, and 5.6% had malignancies. There was no difference between the groups in terms of age, race, gender, induction type, or etiology of kidney disease (Table). One year and most recent serum creatinine levels were significantly higher in the OI/Malignancy group ($p<0.01$). There were significantly higher rates of acute rejection in the OI/Malignancy group ($p<0.01$). There was significantly more graft loss (22.5%) in the OI/malignancy group compared to only 4.2% in the non OI group ($p<0.01$). Additionally patient survival was lower in the OI/malignancy group ($p=0.05$). Graft loss in the OI/malignancy group was more likely to be due to chronic rejection (58% vs. 31.6% $p=0.06$); in most cases rejection occurred in the setting of reduced immunosuppression.

Conclusions: Opportunistic infections and malignancies develop in 33% of kidney transplant recipients, and are associated with lower graft and patient survival and increased risk of acute rejection.

Characteristic	Opportunistic infections/malignancy (N=222) %	Opportunistic infections/malignancy (n=455) %	P Value
Recipient Age	53.6±13.5	53.2±13.2	0.73
Recipient Gender (Male)	63.9%	57.1%	0.10
Race (African-American)	42.6%	39.6 %	0.11
Etiology of Kidney disease (Diabetes Mellitus)	24.23%	26.2%	0.24
Transplant Type (Deceased-donor)	78.4%	76.2%	0.56
Induction (Thymoglobulin)	59.2%	55.5%	0.42
Acute Rejection	21.2%	5.9%	<0.01
1 year creatinine mg/dl	1.85+/-1.3	1.44+/-0.7	<0.01
Most recent creatinine mg/dl	1.6+/-0.75	1.5+/-1.1	<0.01
Graft Survival	77.5%	95.8%	<0.01
Patient Survival	89.2%	93.2%	0.05

SA-PO503

A Randomized Controlled Trial Comparing Belatacept to Tacrolimus in De Novo Kidney Transplantation Gretchen N. De Graav, Carla Baan, Marian Clahsen - van Groningen, Jan H. Von der thüsen, Monique Cadogan, Jacqueline Van De Wetering, Joost van Rosmalen, Willem Weimar, Dennis A. Hesselink. *Erasmus MC, Rotterdam, Netherlands.*

Background: Belatacept (bela) allows for calcineurin-inhibitor-free immunosuppressive therapy after kidney transplantation but is associated with a higher acute rejection risk than ciclosporin. We compared clinical outcomes in a randomized-controlled trial comparing bela to tacrolimus (tac) in *de novo* kidney transplantation.

Methods: Forty kidney transplant recipients were 1:1 randomized to a bela- or tac-based immunosuppressive regimen combined with basiliximab, mycophenolate, and prednisolone. One-year graft- and biopsy-proven acute rejection (BPAR)-free survival were assessed, as well as the development of *de novo* donor-specific anti-HLA antibodies (DSA), the incidence of adverse events (AEs) and eGFR (in mL/min/1.73m^2).

Results: Three graft losses occurred on days 12, 59, and 161 after transplantation, resulting in a 1-year death-censored graft survival of 85% in the belatacept group *vs.* 100% in the tacrolimus group ($p=0.08$). All were the result of glucocorticoid-resistant

rejection. The incidence of BPAR was higher in the bela-treated than in the tac-treated patients, n=11 (55%) *vs.* n=2 (10%), p=0.006, respectively, and rejections were of a more severe grade. In the first year, 2 patients, of which 1 rejected, developed DSA, both in the bela group. Total AEs were similar between groups; means of 10.3 and 11.9 per patient in the bela- and tac-groups, respectively, p=0.41. Post-transplant diabetes mellitus occurred more often in the tacrolimus group; n=7 *vs.* n=1 in the belatacept group, p=0.04. eGFR, excluding graft losses, was not different between bela-treated and tac-treated patients on month 12: 54 (28–89) and 50 (33–84) mL/min, respectively; p=0.57. However, graft-loss censored eGFR in bela-treated rejectors (n=8) was 36 (28-76) mL/min at month 12, which was lower than the eGFR of 58 (37-84) mL/min in the bela-treated non-rejectors, p=0.001.

Conclusions: Bela-based immunosuppressive therapy results in a higher rejection rate and severity compared to standard, tac-based therapy, and shows similar graft function 1 year after transplantation.

SA-PO504

Single-Dose (SD) Pharmacokinetics (PK), Pharmacodynamics (PD), and Safety of Belatacept (Bela) in Adolescent Kidney Transplant Recipients (KTRs) Asha Moudgil,[3] Vikas R. Dharnidharka,[1] Daniel Feig,[4] Barry L. Warshaw,[5] Vidya Perera,[2] Bindu Murthy,[2] Martin Polinsky,[2] Robert B. Ettenger.[6] *[1]Washington University, St Louis, MO; [2]Bristol-Myers Squibb, Princeton, NJ; [3]Children's National Medical Center, Washington, DC; [4]University of Alabama, Birmingham, AL; [5]Emory University & Children's Healthcare of Atlanta, Atlanta, GA; [6]University of California, Los Angeles, CA.*

Background: Bela blocks CD86-CD28 co-stimulation between antigen presenting cells and T-cells. It is approved for rejection prophylaxis in KTR >18 yrs old. A phase I trial of adolescent KTR assessed SD bela PK and its PD effect, measured by % CD86 receptor occupancy (%CD86RO).

Methods: 9 EBV-positive KTR aged 13–17 yrs (mean 15.1 yrs) on CNI-based immunosuppression for >6 months post-KT received one IV bela infusion (7.5 mg/kg, 30 min). Blood was collected for PK serially over Days 1–57 and for %CD86RO on Days 1, 29, and 57. Adverse events (AEs) were recorded to Day 57 and serious AEs (SAEs) to Month 6.

Results: All 9 completed the study. Mean half-life ($t_{1/2}$), volume of distribution (V_{ss}), and systemic clearance (CL) in adolescent KTR were comparable to values from healthy adult volunteers (HV) and adult KTR (Table), indicating consistency across adolescent and adult populations. Mean %CD86RO increased with increasing bela concentration, indicating a direct PK/PD relationship (Figure). Three had 7 AEs, with 4 SAEs; all SAEs were considered unrelated to bela.

Conclusions: In adolescent KTR, the range of PK values was similar to those seen in HV and adult KTR. The PK/PD relationship between %CD86RO and bela concentration was similar to that seen in adults, providing a basis for dose selection in future adolescent studies. SD bela was well tolerated in the 9 adolescent KTR.

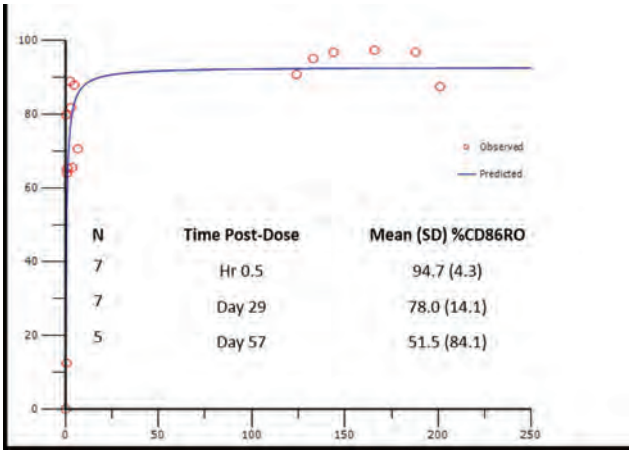
Funding: Commercial Support - Bristol-Myers Squibb

	Adolescent KTR (SD 7.5 mg/kg)	HV (SD 10 mg/kg)	Adult KTR (multiple doses 5 mg/kg)
C_{max}, µg/mL	151 (20)	300 (25.7)	139 (20.1)
$t_{½}$, h	173 (46.8)	235 (28.5)	196.8 (29.2)
CL, mL/h/kg	0.48 (27)	0.39 (17.9)	0.51 (27.4)
V_{ss}, L/kg	0.09 (30)	0.09 (22.2)	0.12 (25.0)
AUC, µg•h/mL	15407 (25)*	26398 (19.6)*	14090 (27.3)†

Data are mean (coefficient of variation as a %)

*AUC_{0-inf}

†AUC_{0-tau}, where tau=4 wks



SA-PO505

Induction Immunosuppressive Therapy with One versus Two Basiliximab Dosage in Kidney Transplant Patients with Low Immunological Risk: Preliminary Report Diana A. Aguirre Campos, Luis A. Mariscal, Jesus Arellano. *Hospital General Dr. Miguel Silva, Morelia, Mexico.*

Background: The two basiliximab dosage is supported by phase III studies which established the optimal prescription with two 20 mg intravenous dose on day 0 and 4 of renal transplant. More recent studies have shown that one single doses(20mg) achieve adequate T cell suppression with similar clinical outcomes. There is no information about this topic on Mexican population The objective of the study is to compare one single 20mg dosage of basiliximab versus standard two dosage in patients with low immunological risk.

Methods: Single center, prospective, randomized 2:1 study that included kidney transplant patients between August 2012 and February 2016 with low immunological risk. Low immunological risk was defined as live donor with antibody reactive panel I and II less than 5%. Patients were randomized to receive one (1D) versus two basiliximab dosage (2D). Renal biopsies were indicated or by protocol at 6 months and one year after renal transplantation. Statistical analysis was performed using chi-squared test and Mann-Withney U test; the rejection-free survival curve was performed by Kaplan-Meier method. A preliminary report is presented

Results: At this moment 33 patients have been included, 23 men (69.7%), with a median age of 25 [21-34] years old and follow-up of 498 [304-722] days. There were 20 patients in the 1D group versus 13 patients on 2D group. No differences were found between demographic and clinical baseline data in both groups; the basal function of the graft was similar in both groups (creatinine 1.12 [0.8-1.3] vs 1.1 [0.9-1.2] mg/dL and GFR 85 [67-98] vs 89 [64-98] mL / min, p=NS, 1D vs 2D group, respectively), with no difference in delayed graft function, slow graft function or maintenance calcineurin inhibitor. The graft function at the end of follow-up was similar in both groups (creatinine 1.3 [1.1-1.5] vs 1.1 [0.9-1.4] mg/dL and GFR 77 [63-86] vs 79[54-102] mL/min, p=NS, 1D and 2D group respectively). Rejection-free survival was similar in both groups (Log rank=NS)

Conclusions: This preliminary report suggests that there is no difference in rejection-free survival and graft function at the end of follow-up with the 20 mg dose of basiliximab compared to 40 mg in patients with renal transplantation and low immunological risk. Should confirm this results with a large number of patients

SA-PO506

Induction Therapy with Low Dose Thymoglobulin versus Standard Therapy with Basiliximab: A Comparative Study of Safety and Effectiveness in Marginal Donor Kidney Transplant Recipients Giorgia Comai, Olga Baraldi, Vania Cuna, Matteo Ravaioli, Maria Cappuccilli, Gaetano La Manna. *University of Bologna, Bologna, Italy.*

Background: In renal transplant the most commonly administered induction immunosupprive therapy is based on Basiliximab, a chimeric non depleting anti-IL2-receptor monoclonal antibody, or Thymoglobulin, a polyclonal depleting agent. The use of Thymoglobulin in the recipients of marginal kidney transplants is an attractive opportunity, since besides the known anti-rejection effect, it has a protective potential against ischemia/reperfusion injury and the subsequent delayed graft function (DGF), thus allowing the reduction of maintenance therapy.

Methods: We retrospectively analyzed 71 patients who received a kidney transplant from marginal donors in the period 2013-2015 to assess the safety (incidence of infections, new onset diabetes after transplantation-NODAT, cardiovascular events) and efficacy (rejection rate, graft survival, DGF, graft function) of two different induction regimens during the 2-year follow-up period: Basiliximab (n=39) vs Thymoglobuline (n=32) at a very low dose (with a cumulative dose of 2 mg/kg).

Results: The two groups were similar for donor and recipient age, but there were different frequencies of double renal transplants: 4/39 (10.3%) in Basiliximab group and 18/32 (56.2%) in Thymoglobulin group (p<0.01). Likewise, ischemia interval and Karpinski score were higher in the Thymoglobulin group (p<0.05). The safety of the two induction regimens was comparable, as no significant differences were found in the incidence of infections, NODAT and cardiovascular events. Concerning the parameters used to evaluate efficacy, rejection rate, graft survival and DGF did not differ significantly between the groups, while serum creatinine (sCreat) and proteinuria were higher in Basiliximab group that in Thymoglobulin group (sCreat: 1.8 ± 0.3 vs 1.6 ± 0.4 mg/dL; p=0.019; urine protein levels: 37 ± 21 vs 17 ± 18 mg /dL; p<0.01).

Conclusions: Induction therapy with low dose thymoglobulin has been shown to have a comparable efficacy with Basiliximab, also showing an excellent safety profile. This finding appears to be promising, also in view of unfavourable characteristics of the transplanted patients included in the Thymoglobulin group, namely double kidney transplant, longer cold ischemia time and higher Karpinski score.

SA-PO507

Basiliximab versus Thymoglobulin Induction for Pancreas Transplant: A Retrospective Comparative Study of Graft and Patient Outcomes Yvonne El Kassis, Ziad S. Zaky, Emilio D. Poggio. *Cleveland Clinic, Cleveland, OH.*

Background: Induction therapy is common practice following pancreas transplant (PTx). According to the International Pancreas Transplant Registry, ≥90% of PTx recipients treated with induction receive depleting agents (Thymoglobulin aka ATG)

whereas <10% get IL2-receptor blockade (Basiliximab). Our center has historically used ATG induction but has more recently favored Basiliximab for simultaneous pancreas kidney transplants (SPK). We sought to retrospectively compare the graft and patient outcomes of SPK and pancreas transplant alone (PTA) recipients treated with either ATG or Basiliximab induction.

Methods: We reviewed all 242 cases of PTx at out institution between 2003 and 2014. Patients who received a pancreas after kidney (51) and those who did not receive induction (15) were excluded. From the remaining 176 patients, 105 received ATG induction at 4.5 mg/kg and 71 got Basiliximab 20mg on POD 0 and 4. Outcomes included 1 and 3-year graft survival, patients' survival, incidence of rejection episodes, time to first rejection episode, viral infections (CMV, BK, and EBV viremias), and malignancies.

Results: Mean duration of follow up was 81.6 ± 3.8 months (m) for the ATG group and 63.6 ± 3.4 for Basiliximab (p<0.01). All patients in the Basiliximab group had received an SPK whereas 44% of those who received ATG induction had a PTA (p<0.01). Maintenance immunosuppression was similar in both groups. Graft survival at 1 and 3 years were 96 and 88% for Basiliximab and 90 and 81% for the ATG group (p 0.05). Patients' mean survival was not different between both groups (121 ± 6 m for Basiliximab and 142 ± 5 for ATG, p=0.7). There was no statistically significant difference in the incidence of rejection, infections, or malignancies (Table 1).

Conclusions: Basiliximab appears to be a reasonable alternative for induction following SPK, and does not seem to be associated with a higher incidence of rejection, graft failure, or viral infections.

	Thymoglobulin	Basiliximab	p value
Rejection	25 (24%)	19 (27%)	0.65
Time to first rejection episode (months)	23.4 ± 7.6	13.2 ± 3.9	0.24
Infections (%)	33 (31%)	28 (39%)	0.27
CMV viremia (%)	17 (16%)	15 (21%)	0.40
BK viremia (%)	13 (12%)	12 (17%)	0.39
EBV viremia (%)	10 (10%)	6 (8%)	0.8
Malignancy (%)	9 (9%)	7 (10%)	0.77

SA-PO508

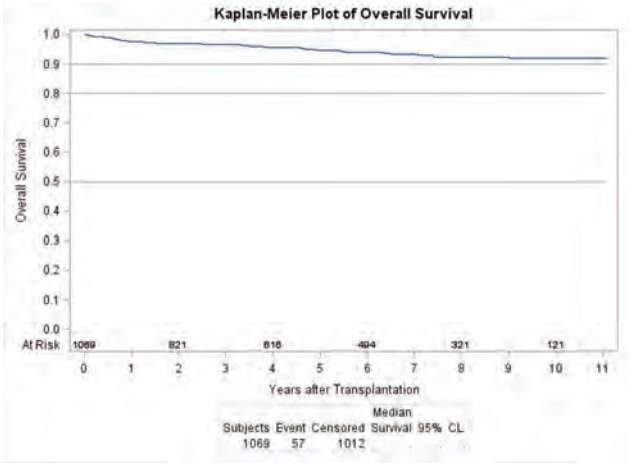
Low Dose Rituximab and Thymoglobulin Induction in a Steroid Free Protocol Involving Protocol Biopsies Improves Patient and Graft Survival at 11 Years after Kidney Transplantation Vivek Pathak. *Nephrology, Kovai Medical Center and Hospitals, Coimbatore, India.*

Background: The purpose of this study is to document long term patient and graft survival in a steroid free regime with a different induction protocol.

Methods: 1069 patients, who underwent renal transplantation at our institute in eleven years since July 2005 till Jan 2017 were studied. Thymoglobulin was used for induction at a dose of 1.5mg/kgm 3 doses in the first 5 days. Rituximab 200 mg was given to those patients who were considered to be at high risk for rejection and approximately 60 to 65% of the cohort received it. Maintenance immunosuppression was Tacrolimus and Mycophenolate mofetil. Prednisolone was rapidly discontinued by fifth post operative day. All patients underwent protocol biopsies at 3 months, 1 year, 5 years and 10 years indicated biopsies were done whenever required.

Results: The Patient and graft survival rates at 11 years were 92% and 85.4 % respectively. Biopsy proven acute rejection free graft survival was 78.1% at 11 years including subclinical rejections. The cumulative incidence of graft loss was 8.07%. The incidence of death was 5.3%. This is an improvement over the data published by Rizarri et al(CJASN 2012) where patient and graft survival rates were 70% and 61% repsectively at 10 years. The OPTN data in AJT December 2016 showed all cause graft failure >35% at 10 years whereas our all cause graft failure is 14.6% at 11 years. 79.07% patients were prednisolone free at 11 years.

Conclusions: The reasons for the improved patient and graft survival in our study in comparison to published literature could have been the addition of low dose pre-operative Rituximab, steroid withdrawal and aggressive cardiovascular screening resulting in low post transplant mortality due to ischemic heart disease, decreased incidence of BK virus induced graft loss, reduced death due to malignancy and reduction in fatal infections.



SA-PO509

Reassessing Thymoglobulin Induction in Kidney Transplantation (RETHINK): An Analysis of the Scientific Registry of Transplant Recipients (SRTR) Isa Ashoor,[1] Robbie A. Beyl,[2] Vikas R. Dharnidharka.[3] *[1]Pediatrics, LSU Health Sciences Center, New Orleans, LA; [2]Pennington Biomedical Research Center, Baton Rouge, LA; [3]Washington University School of Medicine, St Louis, MO.*

Background: Recent single center studies suggest lower dose Thymoglobulin (TMG) for induction in kidney transplant (KT) provides effective rejection prophylaxis comparable to higher dose TMG with less infectious morbidity. We sought to determine whether less TMG exposure is effective in a large national cohort of KT recipients.

Methods: All first time KT only recipients in SRTR on MMF and tacrolimus based immunosuppression who received TMG induction were analyzed. Recipients of expanded criteria donor kidneys or with delayed graft function were excluded. TMG exposure days were analyzed. Primary outcome was graft failure due to acute rejection or infection by 12 mo post KT. Logistic regression was used to identify covariates affecting primary outcome.

Results: 27,808 KT recipients met inclusion criteria (56% male, 52% Whites, 39% Living donor source). Most were adults (92% >21 years old) and transplanted in past 10 years since 2007 (70%). Recipients received a median of 4 days of TMG with 45% receiving 3 days or less. Low (≤3 days) and high (>3 days) TMG exposures differed in gender, transplant year, peak PRA, and HLA mismatch (**Table**). The primary outcome of graft failure due to acute rejection or infection within 12 mo post KT was seen in 197 recipients. Logistic regression identified worst odds of graft failure in relation to non-white race (OR 2.2), younger age ≤21 years (OR 3.7), and older transplant era prior to 2007 (OR 2) all with p-value <0.0001. Low TMG exposure was not detrimental to graft outcome and just missed significance for benefit (OR 0.76, p-value 0.06).

Conclusions: In this large cohort of first time KT recipients on contemporary immunosuppression with TMG induction, graft failure due to acute rejection or infection within 1 year was rare, and not influenced by TMG exposure days. Further studies are needed to confirm results using granular dosage information.

Funding: Other NIH Support - "Supported in part by 1 U54 GM104940 from the National Institute of General Medical Sciences of the National Institutes of Health, which funds the Louisiana Clinical and Translational Science Center. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.", Clinical Revenue Support

Comparison of Low and High Thymoglobulin Exposure Groups

Baseline Characteristic N = 27,808	Sub-category	Low Thymoglobulin Exposure (≤ 3 days) n (column %)	High Thymoglobulin Exposure (> 3 days) n, (column %)	P-value
Gender	Male Female	7181 (58%) 5216 (42%)	8470 (55%) 6941 (45%)	< 0.0001
Race	White Non-White	6414 (52%) 5983 (48%)	8054 (52%) 7357 (48%)	0.385
Age	% 21 years old > 21 years old	972 (8%) 11425 (92%)	1296 (8%) 14115 (92%)	0.0849
Donor Type	Living Donor Deceased Donor	4720 (38%) 7677 (62%)	5928 (38%) 9483 (62%)	0.5
Peak PRA	<20 20-80 >80	9309 (75%) 2215 (18%) 873 (7%)	10691 (69%) 3081 (20%) 1639 (11%)	< 0.0001
HLA Mismatch (MM)	0-2 3-4 5-6	2360 (19%) 5010 (40%) 5027 (41%)	3071 (20%) 6336 (41%) 6004 (39%)	0.0183
Transplant era	Before Jan 1st, 2007 On or after Jan 1st, 2007	3093 (25%) 9304 (75%)	5221 (34%) 10190 (66%)	<0.0001

SA-PO510

Everolimus [EVR]-Based versus Tacrolimus [TAC]-MPA Regimen in De Novo Kidney Transplant Recipients: 12 Months Safety and Efficacy Data from the Athena Study Duska Dragun,[10] Claudia Sommerer,[11] Ingeborg A. Hauser,[2] Barbara M. Suwelack,[3] Peter Schenker,[6] Oliver Witzke,[8] Christian Hugo,[12] Nassim Kamar,[7] Pierre Merville,[5] Martina Junge,[4] Björn Nashan,[1] Friedrich Thaiss.[9] *[1]Bundesärztekammer, Hamburg, Germany; [2]University Clinic Frankfurt (UKF), Frankfurt Main, Germany; [3]Muenster, Germany; [4]Novartis Pharma GmbH Germany, Nuremberg, Germany; [5]PELLEGRIN HOSPITAL, Bordeaux, France; [6]Ruhr-University Bochum, Bochum, Germany; [7]Toulouse University Hospital, Toulouse, France; [8]University Duisburg-Essen, Essen, Germany; [9]University Hospital, Hamburg, Germany; [10]University Hospital Charite, Campus Virchow, Berlin, Germany; [11]University Hospital of Heidelberg, HEIDELBERG, Germany; [12]University of Dresden, Dresden, Germany, Dresden, Germany. Group/ Team: Athena Study Group.*

Background: The ATHENA study was set up to compare EVR combined with TAC or cyclosporine A [CyA] vs. mycophenolic acid [MPA] combined with TAC in de novo kidney transplant [KTx] recipients.

Methods: In this 12 months [M] prospective, open-label, multi-center study 612 patients [pts] were randomized 1:1:1 at time of Tx to either EVR (3-8ng/ml M1-M12) + TAC(4-8ng/ml M1-M3; 3-5ng/ml M3-M12), or EVR (3-8ng/ml M1-M12) + CyA (75-125ng/ml M1-M3; 50-100ng/ml M3-M12) or TAC(4-8ng/ml M1-M3; 3-5ng/ml M3-M12) + MPA, all with steroids. Here we report M12 efficacy and safety (208 EVR +TAC, 199 EVR+CyA, 205 TAC+MPA pts).

Results: M12 Kaplan Meier estimates for treated BPAR were 6.7% in EVR+TAC, 17.6% in EVR+CyA and 3.9% in TAC+MPA group, with most events graded BANFF IA (1.9%; 9%; 1.5%), few (1.5%, 2% vs 0.5%) BANFF IIB/III. 5 pts in EVR+TAC, 5 in EVR+CyA and 6 in TAC+MPA died. Few graft losses occured: 10 pts (4.8%) in EVR+TAC, 13 (6.5%) in EVR+CyA, 6 (2.9%) in TAC+MPA arm, including 5 primary non-functioning grafts in each EVR-group and 1 in TAC+MPA arm. Safety profiles were comparable, incidences of AEs/infections leading to study drug discontinuation or dose adjustment/interruption were 56.7% in EVR+TAC, 55.5% in EVR+CyA vs 61.3% in TAC+MPA arm. Main reasons for changes were infections (7.1%EVR+TAC, 4.5%EVR+CyA, 23.5%TAC control) and lympho-/leucopenia (3.3%, 3.5%, 13.2%). No differences in AEs on wound complications were seen (sum-incidences: 41.9% EVR+TAC, 38.9% EVR+CyA, 43.2% TAC+MPA).

Conclusions: ATHENA as largest European KTx study confirmed good efficacy and event rates within international standards for all 3 groups with no unexpected safety events for this pts population. There were no differences in reported AEs wound healing and less leucopenia with EVR-based regimens.

Funding: Commercial Support - Novartis Pharma GmbH, Germany

SA-PO511

Randomized Controlled Trial Assessing the Impact of Conversion to Everolimus with Ultra-Low Tacrolimus Exposure on Graft Outcomes in Kidney Transplant Recipients David J. Taber,[3] Avudaiappan Chokkalingam,[2] Zemin Su,[3] Titte Srinivas.[1] *[1]Intermountain Medical Center, Murray, UT; [2]Mayo Clinic, Rochester, MN; [3]Medical University of South Carolina, Charleston, SC.*

Background: Despite low rate of acute rejection, the triple regimen of tacrolimus (FK), mycophenolate (MMF) and prednisone can increase the risk of late graft loss due to nephrotoxicity and opportunistic infections.

Methods: Single-center, randomized, controlled trial assessing the impact of a three month conversion to EVR with ultra-low FK exposure, compared to the regimen of full exposure FK with MMF (NCT 02096107). Adult, solitary kidney transplant recipients with a functioning graft at 3 months were eligible for inclusion. Goal trough levels in the intervention arm were 2-5 ng/mL for FK and 3-8 ng/mL for EVR, while FK was maintained at 5-12 ng/mL in the control arm.

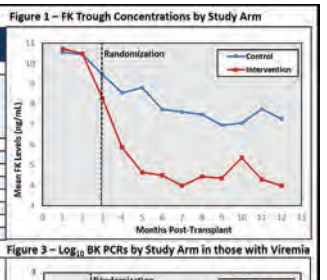
Results: 60 patients were randomized (30 in each arm). Groups were well matched at baseline (3 months post-transplant), except there were fewer females in the intervention arm. FK levels were significantly lower in the EVR arm (Figure 1). At 12-months post-transplant, acute rejection rates (7% FK/MMF vs. 3% FK/EVR, p=0.554, Table 1) and graft function (mean eGFR FK/MMF 56±15 vs FK/EVR 59±14 mL/min/1.73 m^2, p=0.465; Figure 2) were similar between arms. The EVR/ultra-low FK arm had significantly lower rates of CMV infection, severe BK infection and improved BK viral clearance kinetics (Figure 3). All safety measures, including immunosuppression discontinuation, hospitalizations, and graft and patient loss were similar between arms (Table 1).

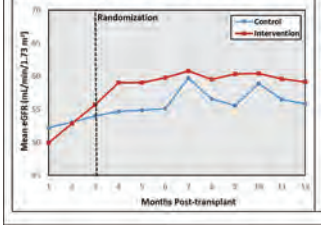
Conclusions: An immunosuppression conversion regimen of EVR with ultra-low exposure FK provides equally sufficient immunosuppression prophylaxis efficacy as compared to standard exposure FK and MMF, with the potential advantage of significantly lower rates of opportunistic viral infections, including BK and CMV.

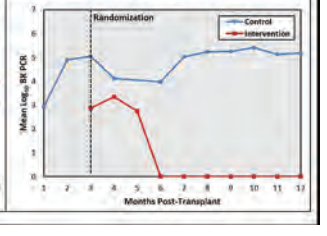
Funding: Commercial Support - Novartis Pharmaceuticals

Table 1 – Clinical Outcomes by Study Arm

Outcome	Control FK/MMF	Intervention FK/EVR	p-value
Acute Rejection	7%	3%	0.554
BK Infection	13%	7%	0.389
Mild BK (<2,000 copies/mL)	0%	3%	0.313
Mod BK (2-10,000 copies/mL)	0%	3%	0.313
Severe BK (>10,000 copies/mL)	13%	0%	0.088
BK Nephropathy	7%	0%	0.150
CMV Infection	17%	0%	0.020
Other Infection	10%	13%	0.688
Any Infection	30%	17%	0.222
Hospitalization After Randomization	20%	27%	0.542
Immunosuppression Held or D/C'd	20%	37%	0.152
de novo DSA	7%	3%	0.554
Graft Loss	0%	0%	1.000
Death	0%	0%	1.000







SA-PO512

Median Intrapatient Tacrolimus Variability Is Comparable between Renal Transplant Centres: A Multicentre UK Retrospective Study Matthew J. Bottomley. *Oxford Kidney Unit, Churchill Hospital, Oxford, United Kingdom. Group/Team: UK Transplant Audit Collaborative.*

Background: Tacrolimus is an immunosuppressant with a narrow therapeutic window and regular serum trough level monitoring is necessary. Increased intrapatient variability (IPV) in these levels has been identified as a risk factor for graft rejection and loss after renal transplant. Previous reports have been from single centre studies with varying methodologies: thus it is unclear how comparable tacrolimus levels and hence IPV are between centres and studies.

Methods: A retrospective study was undertaken in five UK transplant centres using a unified methodology. Renal databases in all centres were interrogated to provide demographic details and laboratory results for all renal transplant recipients (RTR) between 1 January 2009 and 31 December 2014 who received tacrolimus therapy. RTR were excluded if they received dual-organ transplants or if death or graft loss occurred within two years of transplantation, or if their immunosuppression regimens included modified release tacrolimus. IPV was calculated from trough levels taken during the 6-12 month post-transplant period (T1) and the last 12 months of follow-up (T2).

Results: A total of 1070 eligible RTR across the five centres were included (Table 1). Despite variation in ethnic make-up and median age across centres, median tacrolimus IPV at both T1 and T2 was similar at around 14-16%. Across all centres male gender and non-Caucasian ethnicity were not associated with increased IPV. Increasing age did not correlate with IPV. There was no correlation between duration of transplant follow-up and T2 IPV.

Conclusions: In the first national retrospective study of this kind, we report that despite variation in population demographics between centres, median tacrolimus IPV is remarkably consistent. Increased IPV does not appear to be associated with age or ethnicity. This data will be pooled to enable formulation of a 'national standard' IPV, which will allow further study to assess whether RTR with an above median IPV have poorer transplant outcomes.

Funding: Commercial Support - Astellas Educational Grant

Table 1: Tacrolimus IPV in UK Transplant Centres

	Oxford (n=284)	King's London (n=134)	Liverpool (n=171)	Glasgow (n=168)	Manchester (n=313)
% Male	60.6%	76.1%	61.4%	63.8%	63.9%
Median (IQR) age at transplant	53 (42 - 61)	51 (40 - 59)	51 (39 - 60)	50 (39 - 56)	46 (37 - 57)
%Caucasian	80.6%	47.0%	88.9%	91.1%	71.9%
Median (IQR) T1 Tacrolimus IPV	15.4% (10.4 - 22.1)	14.8% (10.1 - 20.4)	16.4% (12.2 - 23.0)	15.6% (12.3 - 23.2)	15.9% (11.8 - 22.3)
Median (IQR) T2 Tacrolimus IPV	16.0% (10.3 - 24.0)	14.8% (9.8 - 23.9)	14.9% (8.9 - 21.1)	14.0% (9.4 - 19.5)	14.9% (10.6 - 23.7)

SA-PO513

Is There a Relationship Between HLA Mismatch and Intra-Patient Tacrolimus Variability in Kidney Transplant Patients? A Comparative Multi-Centre Retrospective Study Stavros Papachristos,[1] Bence Forgacs,[4] Anju john John velvet,[3] Okechukwu O. Okidi.[2] *[1]Transplantation Surgery, Central Manchester Foundation Trust, Manchester, United Kingdom; [2]Central Manchester NHS Foundation Trust UK, Manchester, United Kingdom; [3]Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom; [4]Manchester Royal In irmasry, Manchester, United Kingdom. Group/Team: UK Tacrolimus Audit Collaborative.*

Background: Tacrolimus (Tac) is a critical component of immunosuppressive therapy after kidney transplantation (tx). It has been previously reported that high Tac Intrapatient Variability (IPV) (patient's trough level variability over time) is associated with higher rejection episodes and poor long term outcome after kidney tx. The relationship between HLA mismatch (MM) and Tac IPV has not been previously evaluated.

Methods: 1068 kidney transplant recipients in 5 UK centres between 2009-2014 and who were taking standard release Tac preparations were included in the study. IPV data was retrospectively collected from 2 time points – 6-12months post-transplant (T1) and the last 12 months of follow up (T2). Patients were divided into a high immunological risk HLA MM (HLA MM 4-6) and a low risk HLA MM group (HLA MM 0-3). Association between HLA MM and IPV was evaluated for each centre.

Results: Table 1 demonstrates the results of 1068 patients included from 5 UK centres. When comparing IPV≤20% and IPV>20%, there was no significant correlation with the high risk HLA MM group or the low risk HLA MM group (p>0.1 for all comparisons). The relation between HLA mismatch and Tacrolimus IPV did not reach significance in T1 and T2 periods in all centres.

Conclusions: This study represents the first and largest population based evaluation of relation between HLA mismatch and IPV. Our results demonstrate a clear evidence that HLA mismatch does not affect Tac IPV in either early or late post operative periods. This finding is consistent between 5 UK tx centres. Therefore, HLA mismatch should not be considered as a factor that affects Tac IPV for kidney transplant patients.

Funding: Commercial Support - Astellas Pharma LTD, Government Support - Non-U.S.

Table 1. Relation between HLA MM and Tac IPV for periods T1 and T2

		HLA MM 0-3 (Low Risk)		HLA MM 4-6 (High Risk)	
		IPV≤20%	IPV>20%	IPV≤20%	IPV>20%
Manchester (n=311)	T1	66.6%	33.3 %	67.5%	32.5 %
	T2	65.4 %	34.6 %	67.5 %	32.5 %
Glasgow (n=168)	T1	68 %	32 %	66.6%	33.3 %
	T2	76.6%	23.4%	77.7 %	22.3 %
Liverpool (n=171)	T1	65.5%	34.5%	67.3%	32.7 %
	T2	71.3%	28.7 %	67.3%	32.7%
Oxford (n=284)	T1	71.6 %	28.4 %	65.5%	34.4 %
	T2	63.4%	36.6%	75.5%	24.5%
King's College Hospital (n=134)	T1	70.8%	28.2%	68.4%	31.6%
	T2	65.6%	32.4%	65.8%	34.2%

SA-PO514

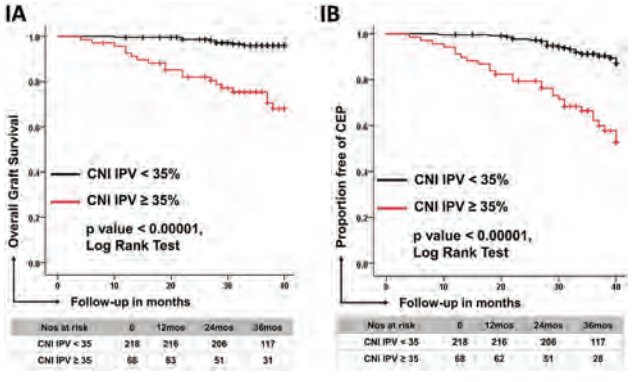
High Calcineurin Inhibitor (CNI) Intra Patient Variability (IPV) Is Associated with Early Renal Allograft Inflammation, Chronicity, and Loss Akhil Sharma,[3] Aravind Cherukuri,[1] Rajil B. Mehta,[1] Puneet Sood,[2] Sundaram Hariharan.[2] *[1]UNIVERSITY OF PITTSBURGH, Pittsburgh, PA; [2]University of Pittsburgh Medical Center, Pittsburgh, PA; [3]University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA.*

Background: High CNI IPV has been associated with poor kidney allograft outcomes, albeit in small limited studies.

Methods: We evaluated effect of CNI IPV *(the degree of fluctuation of CNI levels in all patients over 2-12M post-transplant)* on early allograft inflammation, subsequent chronicity, graft loss (GL) and a composite end-point (CEP) of GL and impending GL (GLi defined as eGFR<30ml/min & 30% decline). 286 patients transplanted between 01/13-11/14 were enrolled with 2 Protocol Bx and any For-Cause Bx. The mean CNI values tested per patient was 37±15. The trough level < 6 ng/ml was considered as sub-therapeutic.

Results: CNI-IPV: The mean CNI-IPV was 28.5% and 1/4 of them had IPV≥35% (High IPV). High IPV was associated with more sub-therapeutic CNI levels (29% vs.11%, p<0.0001). Baseline demographic differences between those with high IPV and acceptable IPV were similar with a trend towards more non-Caucasian patients in the high IPV group. **Allograft Histology:** High IPV was associated with a higher incidence of subclinical & clinical acute rejection (AR) at 3mos (40.9% vs. 19.5%, p<0.0001), more persistent/recurrent AR at 1yr (18.2% vs 6.2%, p 0.002) and high-grade AR (≥Banff 1B, 27.5% vs 7.3%, p < 0.0001). Patients with *denovo* DSA & high IPV had more AR (24.6% vs. 9.1%, p=0.001). High IPV was associated with worse IFTA (p= 0.005) and IF+'i' (p < 0.0001) on 1yr protocol Bx. **Graft Outcomes**: High CNI-IPV was associated with increased GL (Fig1A) and GLi (Fig1B). Sub-analysis of patients with DGF and *denovo* DSA revealed that high IPV was associated with worse GLi. In a multivariate Cox Proportional Hazards Model, high CNI IPV was independently associated with GLi (HR 3.1, p=0.0005).

Conclusions: High CNI-IPV within 1 year post-transplant is associated with worse allograft outcomes including more severe acute rejection, allograft chronicity, GL, and GLi. Thus, this represents an early simple modifiable risk factor for allograft loss.



SA-PO515

Low Post-Transplant 1-Year Tacrolimus Level Is Associated with Poor Renal Allograft Survival in Kidney Transplant Patients Jung-hwa Ryu, Tai yeon Koo, Kyungok Min, Jaeseok Yang. *Seoul National University Hospital, Seoul, Republic of Korea.*

Background: Symphony study demonstrated that low-dose tacrolimus therapy with trough level between 3 to 7 ng/ml can achieve the best short-term renal allograft outcomes. However, it is still controversial that low tacrolimus exposure has good impact on long-term graft outcomes. Here, we investigated the association of tacrolimus trough-level at 1 year after kidney transplantation and graft survival rate.

Methods: This retrospective observation study included patients older than 18 year who underwent kidney transplantation under tacrolimus-based regimens in the Seoul university hospital between April 30, 1997 and June 8, 2016. Kaplan-Meier survival analysis and multivariate Cox regression analysis were performed according to tacrolimus trough-levels within 1 month and at 1 year after kidney transplantation.

Results: A total of 865 kidney transplant patients were included and 46 grafts failed during the study period. Tacrolimus levels < 7 ng/mL at 1 year after transplantation were associated with worse death-censored graft survival (Figure, P = 0.017). In multivariate analysis, tacrolimus < 7 ng/mL was an independent risk factor for poor graft survival (HR 0.469: 95% C.I. 0.235-0.936, P = 0.032). Furthermore, tacrolimus level < 7 ng/mL within 1 month was also associated with worse 10-year graft survival (P=0.007). However, there was no significant association between post-transplant 1-year tacrolimus levels and patient survival rate.

Conclusions: Keeping sufficient tacrolimus level (≥ 7 ng/mL) at 1 year after transplantation is beneficial for good long-term allograft survival.

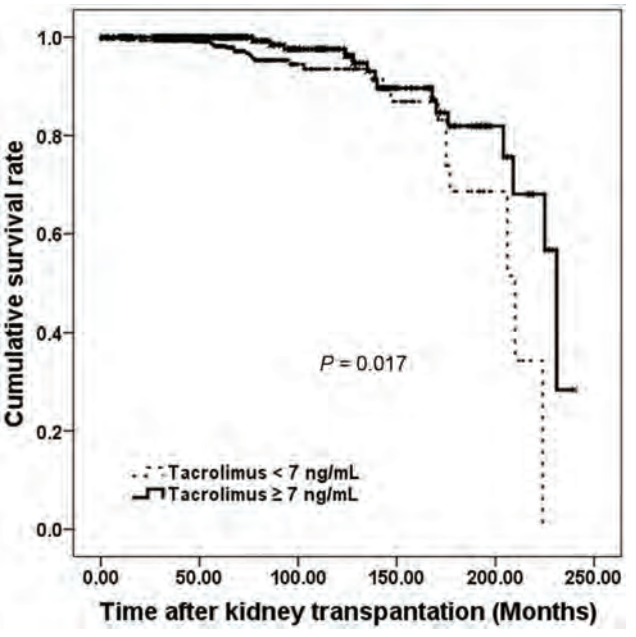


Figure. Renal allograft survival rates according to tacrolimus level of 7 ng/mL at 1 year after transplantation.

SA-PO516

Immunoadsorption and Rituximab Therapy Induces Sustained Reduction of Anti-Pneumococcal IgG in ABO Incompatible Kidney Transplantation Sian E. Faustini,[1,2] Andrew J. Bentall,[3,2] Nadezhda Wall,[1] Shazia Shabir,[2] Alex Richter,[1,2] Simon T. Ball.[2] *[1]University of Birmingham, Birmingham, United Kingdom; [2]University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom; [3]Mayo Clinic, Rochester, MN.*

Background: Patients with chronic kidney disease (CKD) have a higher infectious burden than the general population. Immunosuppression in kidney transplantation increases infection risk further. In addition to conventional immunosuppression, ABO incompatible transplantation (ABOi) requires modulation of the recipient antibody (Ab) pool to reduce anti-donor blood group Ab, which may also reduce protective Ab.

Methods: This study measures specific-IgG against protein and polysaccharide vaccine antigens in 14 ABOi patients, who undergo immunoadsorption therapy and rituximab (IAR), and 37 patients who undergo ABO compatible (ABOc) transplant with conventional immunosuppression. Plasma samples were analysed for IgG directed against tetanus toxoid (TT) and 12 pneumococcal polysaccharides (PnPs), using a luminex bead based assay, at baseline and 12 months post-transplant for both cohorts and in addition, post-IA/rituximab for ABOi and 3 months post transplant for ABOc patients.

Results: At baseline, the ABOi and ABOc cohorts did not differ significantly in age or proportion of individuals with IgG titres above protective thresholds for TT (79 v 92%) or ≥ 8 Pneumococcal serotypes (50% v 65%). For ABOi, there was a significant reduction in anti-TT and 11/12 anti-PnPs titres from baseline to post-IAR (median reduction in titre of 17% and 27% respectively). For ABOc, there was significant reduction in anti-PnPs IgG titre for 8/12 serotypes tested at 3 months, but anti-TT IgG remained stable. At 12 months, the ABOc cohort had recovered anti-PnPs IgG titres to 10/12 Pneumococcal serotypes. In contrast, anti-PnPs IgG had only recovered for 2 serotypes in the ABOi group, despite anti-TT titres recovering to pre-transplant levels.

Conclusions: Both transplant cohorts had relatively low Pneumococcal, but good TT coverage pre-transplantation. Conditioning with IAR reduced specific IgG directed against non-blood group polysaccharide antigens such as PnPs. The ABOi cohort shower

a greater reduction in Pneumococcal IgG coverage than the ABOc group and this did not recover at 12 months. Our findings reveal the impact of IAR on protective antibodies and suggest an opportunity to revisit the timing of vaccination schedules.

Funding: Private Foundation Support

SA-PO517

Weaning Immunosuppression in Patients with Failing Kidney Grafts: When and How? Hyunjin Ryu, Yong Chul Kim, Mi-yeon Yu, Yon Su Kim, Hajeong Lee. *Seoul National University Hospital, JongNo-Gu, Seoul, Republic of Korea.*

Background: Immunosuppressant (ISA) weaning protocol in failing allograft has not been established. Maintaining ISA would preserve residual renal function (RRF) and prevent graft intolerance syndrome (GIS) and sensitization, although it would increase risk of infection, malignancy and cardiovascular disease. However, there is no optimal ISA weaning protocol after GF.

Methods: We retrospectively reviewed graft failure (GF) cases after kidney transplantation (KT) in a single center. After excluding 424 patients with age under 19, death within 6 month after KT or 1 month after GF, and lost follow-up, a total of 131 GF patients were analyzed. Maintaining ISA was defined as either ≥10 mg of prednisolone (Pd) or combination treatment including Pd with calcineurin inhibitors or antimetabolites at 6 month after GF. ISA weaning was defined as either all ISA discontinuation or using < 10mg of Pd at 6 month after GF. Duration of low dose steroid usage after GF, which is < 10mg of Pd, were also reviewed. Outcomes were infection-related hospitalization, death, GIS, nephrectomy, and RRF represented as duration of diuretics usage.

Results: Among 131 cases, 34 (26%) were female and mean age at GF was 44.9±11.1 years. At the time of GF, 72 (55%) patients were maintaining ISA but 6 month after, only 22 (16.8%) patients were maintaining ISA. With low dose steroid usage, 60 (45.8%) and 33 (25.2%) patients maintained Pd at 6 and 12 months after GF. There were total 68 events of infection related hospitalization, 11 GIS, 20 graft nephrectomy (9 GIS, and 3 graft kidney cancers), and 17 deaths (8 Cardiovascular disease, 5 infection, 2 malignancy and 1 unknown) during median 216 months (range; 15-375 months) follow up. ISA maintaining significantly lowered patient survival rate (log rank P=0.027) than weaning. Moreover, it was an independent risk factor for mortality even after adjustment (odds ratio of 3.36, 95% CI 1.06-10.64, P=0.04). Infection related hospitalization, GIS and nephrectomy was not affected by ISA weaning protocol. However, low dose steroid maintaining at 6 and 12 months after GF, was protective in RRF preservation (P=0.002 and P<0.001, respectively).

Conclusions: In this study, we suggested that ISA should be maintained less than 6month after GF due to elevated mortality risk. However, lower dose steroid continuation up to 1 year after GF could be advantageous for preserving RRF.

SA-PO518

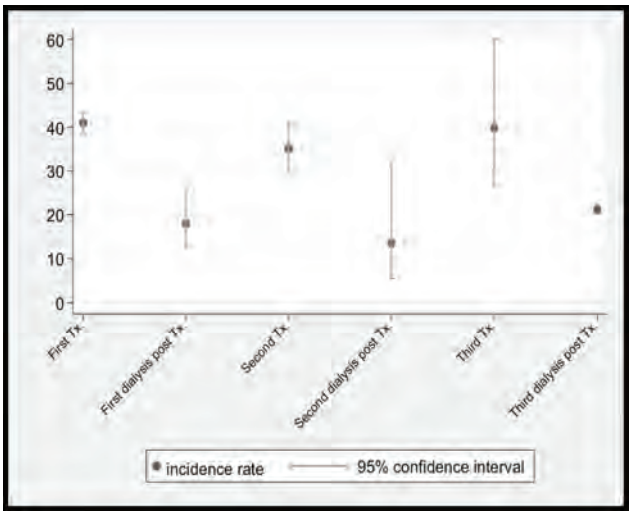
Non Melanoma Skin Cancer Risk Following Graft Failure in Renal Transplant Recipients in Ireland, 1994-2015: Does the Hazard Vary during Periods of Dialysis? Donal J. Sexton,[3,1] Patrick O'kelly,[4] Sandra Deady,[2] Peter J. Conlon.[1] *[1]Beaumont Hospital, Dublin 9, Co Dublin, Ireland; [2]National Cancer Registry, Ireland, Cork, Ireland; [3]The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin., Dublin, Ireland; [4]Beaumont Hospital, Dublin, Ireland.*

Background: Non melanoma skin cancer (NMSC) is common after renal transplant. Whether the risk of skin cancer development varies as treatment for ESKD varies is not well described. We evaluated whether this risk is attenuated during periods of graft loss with a return to dialysis.

Methods: The National Kidney Transplant Service (NKTS) database was accessed for the years 1994-2015 and all recipients with available data were included in the analysis. This data was linked with the national Irish Cancer Registry (NCRI) to capture episodes of malignancy over follow up. In our analysis we considered end stage kidney disease (ESKD) treatment modality as a time varying covariate and calculated incidence rates, which may fluctuate between transplant and dialysis over follow up. Limitations include: difficulty in capturing the lag between exposure and diagnosis, which may vary by treatment period.

Results: 3,672 deceased and living donor adult kidney transplants were assessed comprising 2,310 (62.9%) male and 1,362 (37.1%) female recipients. Periods of treatment with functioning transplant had a higher incidence of skin cancer diagnosis [adjusted incidence rate ratio IRR 2.41 (1.72, 3.38), P<0.001]. Other risk factors for skin cancer included male sex, the number of transplants, and episodes of acute rejection. Tacrolimus was associated with a lower risk compared to cyclosporin however this may be due to a period effect, with longer follow up and ascertainment with ciclosporin.

Conclusions: The incidence of skin cancer was higher during periods defined by a functioning renal transplant and lower during subsequent periods of dialysis following graft failure. It is likely that periods defined by graft failure lead to lower overall immunosuppressive burden over follow up.



Non-Melanoma skin cancer incidence with ESKD treatment modality as a time-varying covariate.

SA-PO519

The Incidence and Predictors of Post-Transplant Lymphoproliferative Disease (PTLD) after Kidney Transplantation Anna Francis,[4] David W. Johnson,[2] Jonathan C. Craig,[3] Germaine Wong.[1] *[1]Auambie, NSW, Australia; [2]Princess Alexandra Hospital, Brisbane, QLD, Australia; [3]University of Sydney/Children's Hospital, Sydney, NSW, Australia; [4]University of Sydney, Sydney, NSW, Australia.*

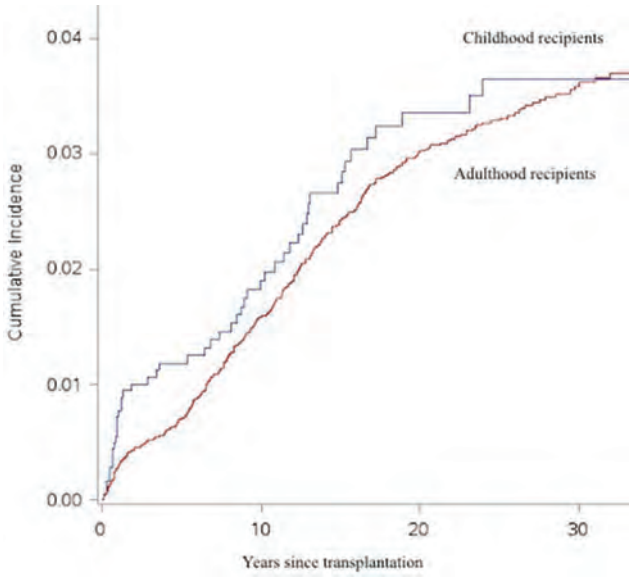
Background: PTLD is well described, but the long-term incidences and risk factors for PTLD for adult and paediatric renal transplant recipients remain unclear.

Methods: Using data from the Australian and New Zealand Dialysis and Transplant Registry (1963-2015), the cumulative incidence of PTLD in all kidney transplant recipients was calculated using a competing risk of death model and compared with age-matched population-based data using standardized incidence ratios (SIR). Risk factors for PTLD in the modern era of immunosuppression (from year 2000) were assessed using competing risk Cox regression.

Results: Among 23, 477 patients (92% adult, 60% male) followed for a median time of 8.5 years, 505 developed PTLD with 50/505 occurring in childhood (age at transplant under 20 years) recipients. The 25-year cumulative incidence of PTLD was 3.3% (95%CI 2.9-3.6%) for adult recipients and 3.6% (95%CI 2.7-4.8%) for child recipients (figure 1). Childhood transplant recipients had a 30-fold increased risk of developing lymphoma compared to the general population (SIR 29.5, 95%CI 21.9-38.8), higher than for adult transplant recipients (SIR 8.4, 95%CI 7.7-9.2). EBV negative recipient serology (adjusted hazard ratio [aHR] 2.85, 95%CI 1.69-4.81), year of transplantation (aHR 0.89 for each year after the year 2000, 95%CI 0.82-0.95) and having diabetes (aHR 2.53, 95%CI 1.37-4.67) were independently associated with PTLD, when adjusted for race, gender, age group and induction agent.

Conclusions: Lymphoproliferative disease in transplant recipients occurs at higher rates than in the general population, particularly in paediatric recipients. EBV-negative patients and those with diabetes are at increased risk of PTLD, however PTLD rates have been decreasing over the last 15 years.

Funding: Private Foundation Support



Cumulative incidence of PTLD post kidney transplantation

SA-PO520

Kidney Cancer after Renal Transplant: 9 Year Review Dennis Hu,[1] Suresh K. Rijhwani,[3,1] Harlan C. Rust,[3,1] Usama T. Hussein,[2,1] Sandeep Magoon,[4,1] Thomas R. McCune.[3,1] *[1]Eastern Virginia Medical School, Norfolk, VA; [2]Nephrology associates of tidewater, Virginia Beach, VA; [3]Renal Transplantation, Sentara Norfolk General Hospital, Norfolk, VA; [4]Nephrology, Nephrology Associates of Tidewater, Virginia Beach, VA.*

Background: Renal transplant patients are at increased risk of renal cell carcinoma (RCC). The overall incidence of RCC following renal transplantation from 1987-2010 is 5.68 times higher than in the general population. Possible explanations include immunosuppression leading to DNA repair interference, decreased host immune surveillance with resulting unchecked tumor development, and increased oncogenic viral infections. Due to the rapid growth and metastasis of RCC, renal ultrasounds (US) have been used as a screening tool; however, there is no guideline on the frequency of US after renal transplantation.

Methods: Retrospective chart review of 543 renal transplant recipients (age 21-75 at transplant) at Sentara Norfolk General Hospital from 1/1/07-10/31/16 was performed. All patients received similar immunosuppression regimens and serial routine post transplant renal ultrasounds. Patient characteristics including gender, race, age at transplant, underlying cause of ESRD, and US at 1, 3, 5, 7, and 9 years post-transplant were collected. If renal malignancy was found, tumor characteristics including timing of development, mass location, pathology, staging, and outcome was assessed. RCC incidence was calculated based on timing of US post-transplant.

Results: RCC incidence was 2.2% and found in 92% males and 8% females. RCC was found in patients aged 30-40 (16%), 40-50 (25%), 50-60 (16%), and 60-70 (41%) years old at transplant. Incidence on 0-1, 1-3, 3-5, 5-7, and 7-9 year ultrasounds post-transplant were 0.18%, 0.73%, 1.29%, 0%, and 0%, respectively. Median time of RCC diagnosis was 3 years post-transplant. Tumor characteristics were clear cell (33%), papillary (33%), oncocytoma (13%), tubulocystic (6%), and unclassified (13%). Staging was T1aNxMx (73%), T1bNxMx (20%), and T3aNxMx. (6.7%). 3 patients had different RCC in the same kidney. 1 patient had RCC 4.5 years after previous RCC. All patients had radical nephrectomies. Etiology of ESRD was HTN (33%), Diabetes (50%), and unspecified glomerulonephritis (16%).

Conclusions: US at 1,3,5 and 7 years post-transplant identified all RCCs and remained localized within the kidney. Men are at increased risk of RCC. PCKD is not associated with developing RCC. Multicentric development of RCC suggests that follow-up of remaining kidney after nephrectomy is required.

SA-PO521

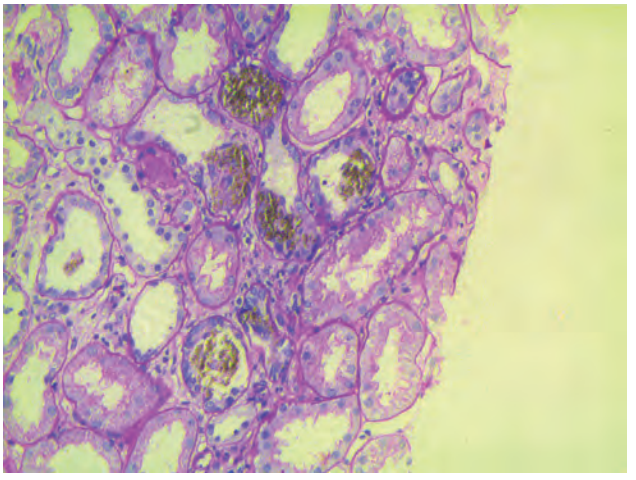
Recurrent 2,8 DHA Nephropathy Reversal in a Renal Allograft Recipient Vivek Pathak. *Nephrology, Kovai Medical Center and Hospital, Coimbatore, India.*

Background: APRT deficiency is a rare autosomal recessive inherited disorder of purine metabolism. In the absence of APRT, adenine is oxidized to 2,8 DHA and forms crystals resulting in nephrolithiasis and progressing to ESRD.This disease can cause recurrent renal allograft failure in post transplant patients. DHA stones are radiolucent and misdiagnosed as uric acid stones.

Methods: A 44 year old male was suffering from end stage kidney failure without any calculi. There was no family history of renal calculus disease. He underwent dialysis for 3 months and received kidney from his mother. He received triple immunosuppression. He had non-oliguric AKI post operatively and then renal function started worsening 4 weeks later A renal biopsy was done and it showed brown crystals favoring 2,8 DHA crystals. He was started on haemodialysis. Primary hyperoxaluria work up was negative. He was started on tab. Febuxostat 80mg a day due to suspicion of recurrent DHA nephropathy. A blood spot test showed very low level of APRT (courtesy Dr. Dawn Milliner, mayo Clinic) and a DNA analysis showed mutation of APRT gene. Patient gradually became better and creatinine came down from 7.8mg% to 2.7mg% in 4 months and is stable two-and-half years later.

Results:

Conclusions: This patient illustrates the importance of recurrent crystalline nephropathy in a post transplant patient. 2,8 DHA is an under-recognized cause of ESRD and can be prevented by correct diagnosis. This patient's diagnosis was not recognized pre-operatively. A repeat renal biopsy gave the first clue for the diagnosis. The diagnosis was confirmed by measurment of APRT activity in red blood cells and DNA analysis showed mutation consistent with APRT deficiency. This patient responded well perhaps due to early start of therapy with Febuxostat even before confirming the diagnosis. The disease must be considered in the differential diagnosis of crystalline nephropathy even in the absence of history of nephrolithiasis(Nasr et al NDT 2010).



SA-PO522

Association of Pre-Transplant Anti-LG3 Autoantibodies and Delayed Graft Function in Kidney Transplant Recipients Habib Mawad,[1] Julie Boucquemont,[3] Bethany J. Foster,[2] Heloise Cardinal.[1] *[1]Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; [2]McGill University Health Center, Montreal, QC, Canada; [3]Research Institute McGill Univ. Health Centre, Montreal, QC, Canada.*

Background: Pre-transplant antibodies to the LG3 fragment of perlecan (anti-LG3) are associated with an increased risk of delayed graft function (DGF) in kidney transplant recipients (KTR). Factors that increase susceptibility of the allograft to the deleterious effects of pre-transplant anti-LG3 antibodies have not been characterized. The aims of this study were to validate the association between pre-transplant anti-LG3 titers and DGF and to assess if this relationship is modified by longer ischemia or donor type.

Methods: We performed a retrospective cohort study in 2 Canadian adult kidney transplant centers. All consecutive KTR were recruited between June 1st, 2008 and July 20th, 2014. The primary outcome was DGF, defined as the need for dialysis within the first week after transplantation, failure of serum creatinine to decrease by more than 10% on the first 3 post-operative days, or serum creatinine >250 umol/L on post-operative day 5 in the presence of scintigraphic evidence of acute tubular necrosis. The main independent variable was pre-transplant anti-LG3 titers, measured with a locally-developed ELISA. Anti-LG3 >225 U/mL were considered positive. The interaction variables were ischemic time and donor type. Total ischemic time was dichotomized at the top quartile (15h). Donor type was classified as extended-criteria or deceased after cardiac-arrest vs. all other donor types.

Results: Among the 442 study subjects, 163 (37%) developed DGF. In multivariate analyses adjusted for donor type and ischemic time, positive anti-LG3 titers were associated with the occurrence of DGF (odds ratio (OR) 1.90, 95% confidence interval (CI) 1.18-3.07). The point estimates for the association between anti-LG3 and DGF were higher when total ischemic time was >15h (OR 2.51, 95% CI 0.89-7.78) vs. ≤15h (OR 1.80, 95% CI 1.07-3.00), but the interaction was not statistically significant. Similarly, the OR was higher for transplants from extended-criteria donors/donors after cardiac-arrest (OR 2.25, 95% CI 0.97-5.61) vs. other recipients (OR 1.60, 95% CI 0.90-2.78), but the interaction was not significant.

Conclusions: These results confirm that anti-LG3 are independently associated with DGF. Larger studies are needed to determine if ischemia and extended criteria donors/donors after cardiac arrest enhance the association between anti-LG3 and DGF.

SA-PO523

Frequent Histologic Recurrence of Lupus Nephritis after Kidney Transplantation M. Lourdes Gonzalez Suarez, Andrea G. Kattah, Fernando G. Cosio, Lynn D. Cornell, Mariam P. Alexander. *Mayo Clinic, Rochester, MN.*

Background: Recurrent lupus nephritis (RLN) has been described as uncommon after kidney transplantation (KTx), though reported incidences vary from 0 to 44%. RLN may be subclinical and therefore missed in some patients (pts) without protocol kidney biopsies (KBx). We aimed to assess the incidence and characteristics of histologic subclinical recurrence of lupus nephritis (SRLN) by protocol KBx.

Methods: A multicenter review of medical records of pts with lupus nephritis (LN) who underwent a KTx (January 1998-December 2012) was conducted. Baseline demographics, proteinuria, hematuria, LN class and KBx findings, graft and patient survival by Kaplan Meir were reviewed. A cohort of 60 pts with polycystic kidney disease (PKD) that had received a KTx in the same period was randomly selected as controls.

Results: We found 51 pts with LN who received a KTx in the participating centers. Population was predominantly female (66%); median age at time of KTx was 37±7. RLN, including SRLN and clinical RLN (CRLN) was seen in 29 pts (57%). Median time to any recurrence was 33.1 months. KBx was clinically indicated due to rising creatinine and/or BK viremia in 18 of 29 pts, and due to suspicion of RLN in 2 pts who had systemic flares. SRLN was found in 10 pts (34%). One of SRLN pts had concomitant acute rejection; 4 CRLN pts also had rejection. Among SRLN pts, hematuria was seen in 4 and mean proteinuria was 295 mg/24h (range 45-1433) vs. 9 of 18 CRLN pts had hematuria, and mean proteinuria was 1098 mg/24hr (range 100-4000) (p=0.1). Two CRLN pts had low complements (one had low C3 and C4, the other one only low C4); the rest of the CLRN pts and SRLN pts had normal complements. Graft loss occurred in 3 SRLN pts and 4 CRLN pts (30% vs. 22% accordingly). No difference was found in graft survival among SRLN, CRLN and PKD groups. Mean time to graft loss was 10.3±1.2 years in SRLN, and 7.6±0.7 years in CRLN (p=0.8). Patient survival was similar among SRLN, CRLN and PKD groups, with a median of 10 years (until time of follow up) (p=0.7).

Conclusions: RLN was found in more than half of our study population. There was clinical suspicion of recurrence in 2 cases. SRLN was found on 1/3 of protocol KBx. Our study showed that SRLN is common and can remain subclinical overtime, though did not impact graft loss or survival as compared to controls in this study population.

SA-PO524

Fate of Mesangial IgA Deposits in Donated Kidney after Transplantation Faiza N. Khan. *Sugar Land, TX.*

Background: IgA nephropathy is a primary cause of glomerulonephritis in the world with a recognized progression to ESRD and a known recurrence in transplanted kidney. However, the clinical significance of mesangial IgA deposits in healthy individuals and donor kidneys is unclear. Although, IgA deposits are often considered to be a precursor lesion to IgA nephropathy, the two entities likely have a distinct pathogenesis. Whereas IgA nephropathy results because of an aberrant IgA protein which activates the immune system causing mesangial damage, mesangial IgA deposits result from a high circulating load of normal IgA protein which deposit in mesangium due to filtration. Prior studies regarding mesangial IgA arise from eastern hemisphere where IgA nephropathy is common. We examined the frequency, clinical significance and histological fate of mesangial IgA deposits in our heterogenous population.

Methods: Donor baseline biopsies obtained at Houston Methodist Hospital during 2009-2016 were examined for IgA deposits noted with immunofluorescence. Subsequent biopsies of recipients of IgA positive deposits were examined for outcome of these deposits. Clinical data was obtained and two tailed T test was used to compare categorical variables.

Results: 958 baseline biopsies were examined. 94 biopsies had positive IgA deposits as the dominant or co-dominant immunoglobulin. An overall incidence rate of mesangial IgA deposits of 9.8% was noted with an incidence rate of 12.2% in deceased donor population and a rate of 6.3% in living donors. Of the 94 positive baseline biopsies, 43 recipients had adequate subsequent biopsies. During the first post-transplant year, 65% of the recipients showed complete resolution of IgA deposits and 12% with decreased IgA deposits. Mean time to resolution of IgA deposits in all re-biopsies was noted to be 295 days. Kaplan- Meier analysis (KM)of patient survival at 5 years showed 90% patient survival in IgA positive recipients vs 88% in recipients without IgA deposits. KM analaysis of graft survival at 5 years showed 88% graft survival in IgA positive donors vs 80% in donors without IgA deposits.

Conclusions: A higher incidence of mesangial IgA deposits were noted in deceased donors than living donors which may be secondary to systemic illnesses present in our deceased donors. Donor kidneys with IgA deposits have a higher incidence of delayed graft function but similar rate of patient and graft survival.

SA-PO525

Incidence and Treatment of Recurrent FSGS Following Kidney Transplantation in Patients with Pre-Emptive Plasmapheresis Meredith Harris, David K. Hooper. *Cincinnati Children's Hospital Medical Center, Cincinnati, OH.*

Background: Focal Segmental Glomerulosclerosis (FSGS) is a leading cause of end stage renal disease (ESRD) in children. Unfortunately, it reoccurs in up to half of patients following kidney transplantation. Pre-emptive therapeutic plasma exchange (TPE) has been suggested as a way to prevent recurrent FSGS, although few studies have evaluated its' efficacy. Once FSGS does recur, therapies such as rituximab and cyclosporine have been tried in combination with TPE to induce remission, but few studies report the efficacy of these therapies.

Methods: We performed retrospective chart review of 258 patients transplanted at CCHMC from May 2003 through November 2016 and identified patients with FSGS as the primary diagnosis. We then identified all patients who received at least one TPE treatment prior to kidney transplantation and evaluated the risk of FSGS recurrence. FSGS recurrence was compared between patients with 1 TPE treatment vs. ≥ 3 treatments. For patients with recurrent FSGS, we compared treatment in patients with early vs. late remission.

Results: 35/258 (14%) transplants had FSGS as the primary diagnosis, 20 of which received pre-emptive TPE. 11/20 (55%) patients with pre-emptive TPE experienced FSGS recurrence at a median of 3 days (range 1-90) post-transplant. 2/5 patients (40%) who received 1 pre-emptive TPE had recurrent disease compared 9/15 (60%) patients who received ≥ 3 TPE treatments (p =0.62). Of the 11 patients with FSGS recurrence, 10 (90%) achieved remission within a median of 9 months (range 1 – 24 mos). 8/11 patients received rituximab, 9/11 were switched from tacrolimus to cyclosporine, and all patients remained on TPE until remission was achieved. 5 patients experienced early remission (<3 months) whereas 6 had late (> 3 months) or no remission. Of 5 patients with early remission 100% switched to cyclosporine within 5 days of recurrent disease, compared to only 1/6 (17%) patients with late or no remission (p=0.015). 4/5 patients with early remission received rituximab compared to 4/6 patients with late remission (p=1).

Conclusions: Preemptive TPE does not prevent FSGS recurrence regardless of the number of treatments. Rapid switch to cyclosporine was associated with faster time to remission.

SA-PO526

Evolution of Post-Transplant Atypical Hemolytic Uremic Syndrome (aHUS) Silvana Maria C. Miranda,[1] Pedro Augusto M. Souza,[2] Gerson M. Pereira jr,[3] Carlos rafael A. Felipe,[3] Vanessa B. Souza,[1] Izabela L. Piana,[2] Andre S. Alvarenga,[3] Cláudia Ribeiro.[1] *[1]Hospital Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; [2]None, Belo Horizonte, Brazil; [3]Santa Casa de Belo Horizonte, Belo Horizonte, Brazil.*

Background: The incidence of post-transplant thrombotic microangiopathy (PT-TMA) ranges from 1-5% and causes reduction of graft survival. Nevertheless, diagnosis of aHUS is difficult due to multiple potential triggers. Timely treatment of aHUS with eculizumab may improve prognosis.

Methods: Retrospective cohort review of 306 kidney transplant recipients (KTR) from September 2012 to September 2016 at a single brazilian center. PT-TMA was diagnosed by graft biopsy or thrombotic microangiopathic syndrome.

Results: The incidence of PT-TMA was 3.9% (n = 12). Of these, two were diagnosed with acute antibody-mediated rejection, one tacrolimus induced and nine with aHUS by excluding secundary causes. The etiology of renal disease was unknown in six patients of aHUS group. The other three cases were attributed to diabetic nephropathy, malignant arterial hypertension and membranous nephropathy. Fifty five percent of aHUS patients received prednisone, tacrolimus (TAC) and mycophenolate while the remaining received prednisone, tacrolimus and everolimus. Six had TAC trough levels greater than 10 ng/mL, two greater than 20 ng/ml and none had everolimus trough levels greater than 6 ng/mL. All nine patients received eculizumab, two of which received plasmapheresis with no response. Median time from transplant to aHUS diagnosis was 81 (35.5 – 134.5) days. Median time from diagnosis to eculizumab treatment was 17 (4.5 – 134) days and was not different between those whose grafts survived or not. After eculizumab creatinine improved in five patients, three remain on dialysis and one suffered sudden death after two doses. Two of those who improved renal function, died, one from gastrointestinal bleeding and one from sepsis of cutaneous infection. Death censored graft survival was 55.6% in six months versus 83.5% in those who did not have aHUS. No graft failed after 6 months in aHUS group.

Conclusions: aHUS occurred until 6 months PT-TMA and was related to tacrolimus trough levels above 10 ng/mL in 66% of patients. aHUS has a great impact in graft survival leading to very poor prognosis. Time from diagnosis to treatment with eculizumab did not correlate to better graft survival, but the small sample size should be considered when interpreting these results.

SA-PO527

Monoclonal IgG Deposits on Tubular Basement Membrane in Renal Allograft: Is This Significant for Chronic Allograft Injury? Anri Sawada,[3,5] Kunio Kawanishi,[4] Sekiko Taneda,[3] Masayoshi Okumi,[3] Kazuya Omoto,[3] Tomokazu Shimizu,[3] Hideki Ishida,[3] Kazuho Honda,[1] Shohei Fuchinoue,[3] Motoshi Hattori,[3] Kazunari Tanabe,[3] Junki Koike,[2] Yoji Nagashima,[3] Kosaku Nitta.[3] *[1]Showa University School of Medicine, Shinagawa-ku, Tokyo, Japan; [2]St.Marianna University, Kawasaki, Kanagawa, Japan; [3]Tokyo Women's Medical University, Shinjuku-ku, Japan; [4]University of California, San Diego, La Jolla, CA; [5]Nippion Medical School, Tokyo, Japan.*

Background: In renal allografts, tubular basement membrane immune deposit (TBMID) has often been observed. Such deposits are usually found in association with BK virus nephropathy and immune complex glomerulonephritis; however, their significance is not well-understood. In recent years, monoclonal immunoglobulin (Ig) G deposition in the glomeruli has been reported. However, monoclonal IgG TBMID has not been studied until now. Therefore, we conducted a retrospective clinicopathological study on monoclonal IgG TBMID.

Methods: In total, 7177 biopsy specimens obtained in our institution from 2007 to 2015 were studied. Conventional light and electron microscopic studies and indirect fluorescence immunostaining for Ig heavy and light chains and complements C1q and C3c were performed. Monoclonal IgG TBMID was diagnosed if an IgG subclass or light-chain restriction was present and all other antibodies were absent in TBMID.

Results: Ten patients showed monoclonal IgG TBMID. Of these, seven showed monoclonal IgG1κ TBMID and three showed monoclonal IgG2κ, IgG2λ, and IgG3κ TBMID, respectively. In all patients with monoclonal IgG1κ TBMID, abundant and large granular electron-dense deposits (EDD) were detected in the tubular basement membrane (TBM). EDD was absent in TBM in patients with monoclonal IgG2κ, IgG2λ, and IgG3κ TBMID. On the other hand, eight patients showed polyclonal IgG TBMID. Progression of interstitial fibrosis and tubular atrophy (IFTA) was significantly higher in patients with monoclonal IgG and IgG1κ TBMID compared with that in those with polyclonal IgG TBMID ($P < 0.05$). There were no significant differences in the other clinical parameters between monoclonal IgG and IgG1κ and polyclonal IgG TBMID.

Conclusions: This is the first study on patients with monoclonal IgG TBMID in renal allografts. We found that monoclonal IgG1κ TBMID was associated with EDD formation in TBM and the progression of IFTA.

SA-PO528

Allograft Crescent Predicts Graft Failure in Recurrent IgA Nephropathy Patients Sehoon Park, Hyunjeong Cho, Mi-yeon Yu, Yaerim Kim, Yon Su Kim, Hajeong Lee. *Seoul National University Hospital, SEOUL, Republic of Korea.*

Background: Recent studies demonstrated the predictive value of crescent in IgA nephropathy (IgAN) prognosis. However, it remains unclear whether allograft crescent is associated with worse graft prognosis in patients with recurrent IgAN.

Methods: We reviewed 376 IgAN patients who received kidney transplantation from 1979-2016 in a university hospital in Korea. Allograft biopsies were performed when patients had a significant proteinuria, hematuria, or a progressive deterioration of renal function. Clinical and pathologic characteristics at the time of biopsy were collected in recurrent IgAN cases. The degree of the crescent formation was classified into prominent (> 10%), mild (0-10%), and none (0%). The renal outcome was death-censored graft failure (DCGF).

Results: During the follow-up duration of 7.0 (3.7-14.3) years, 122 (32.3%) patients were diagnosed as recurrent IgAN by allograft biopsy. Median time to recurrence was 4.1 (1.9-8.1) years. Recipients who recurred their IgAN were younger. They were donated allograft from younger donor and received less induction immunosuppressive treatment. Among the recurred IgAN patients, 36 (29.5%) reached graft failure after 9.3 (5.7-12.2) years from their transplantation. Moreover, IgAN recurrence itself was a strong time-dependent risk factor for DCGF (adjusted HR 2.703, 95% CI 1.608-4.545, P<0.001). Regarding the pathologic findings, crescent was identified in 20 patients with recurrent IgAN, in those with relatively old graft age, decreased renal function at the time of IgAN recurrence, and higher MEST scores. All five patients with prominent (>10%) crescent formation in their allograft biopsies progressed to consequent DCGF within from 0.4 to 4.6 years after the IgAN recurrence. Also, the presence of prominent (>10%) crescent in transplanted kidney was a strong risk factor for DCGF when compared with other recurrent IgAN patients without crescent formation (adjusted HR 6.313, 95% CI 1.699-23.458, P=0.006), even after adjustment of MEST scores and coexisting rejection.

Conclusions: Despite its rarity, a prominent allograft crescent (>10%) was demonstrated to attribute to rapid renal deterioration in recurrent IgAN patients. Treatment strategies for those patients should be investigated.

SA-PO529

When Post-Transplant IgA Deposition Is Not Recurrence Claire Kennedy,[5,6] Darren McMahon,[4] Orna Waldron,[7] Andrea M. Fitzmaurice,[1] Patrick O'kelly,[1] Megan R. Finan,[3] Brendan Doyle,[1] Anthony M. Dorman,[1] Peter J. Conlon.[2] *[1]Beaumont Hospital, Dublin 9, Ireland; [2]Beaumont Hospital, Dublin 9, Co Dublin, Ireland; [3]Beaumont hospital, Dublin 1, Ireland; [4]University College Dublin, Monaghan, Ireland; [5]Department of Nephrology, Beaumont Hospital, Dublin, Ireland; [6]Royal College of Surgeons Ireland, Dublin, Ireland; [7]Royal College of Surgeons in Ireland, Dublin, Ireland.*

Background: Immunoglobulin A (IgA) deposition in the post-transplant setting usually represents disease recurrence but can occasionally represent donor-related or *de novo* disease. We aimed to examine post-transplant outcomes in the setting of donor-related or *de novo* IgA deposition and compare patient and graft outcomes in these cohorts to those in all other Irish renal transplant recipients during a similar time period.

Methods: All renal biopsy records from 1/1/1995 to 31/12/2012 (n=7296) were reviewed to identify those with post-transplant IgA deposition. Detailed chart review was performed to identify those in whom the IgA deposition was deemed donor-related (<6 months post-transplant) or *de novo* (>6 months post-transplant) as opposed to recurrent. A retrospective research MEST score (0-7) was assigned to each biopsy. The National Kidney Transplant Service database was accessed to facilitate a comparison of patient and graft outcomes in these cohorts and all other renal transplant recipients.

Results: Fifteen cases of post-transplant IgA deposition were deemed to be donor-related (fourteen deceased donors) and had a mean research MEST score of 1.65 (range 0.32-3.03). Serial biopsies in seven of these cases showed resolution of the deposits over time. Eight cases were deemed to represent *de novo* IgA deposition. The mean research MEST score, which is less specific in this setting, was 2.60 (range 1-4). There were no differences in patient and graft survival rates in these groups compared to all other transplants performed during a similar time period. Cox regression multivariate analysis did not identify either donor-related or *de novo* IgA deposition as a contributing factor to patient or graft survival.

Conclusions: Cases of donor-related or *de novo* IgA deposition were infrequently encountered in our review of 'for-cause' biopsies. Neither condition, when histologically mild-moderate, was found to impact on patient or graft survival rates. These results cannot be extrapolated to the setting of living donation. This information is important for prognostication and counselling purposes in selected future cases.

SA-PO530

Long-Term Prognosis of Kidney Transplant Patients with Rapidly Progressive Glomerulonephritis (RPGN) Talar Kharadjian,[2] Brad C. Astor,[1] Sarah E. Panzer,[2] Tripti Singh.[2] *[1]University of Wisconsin, Madison, WI; [2]School of Medicine and Public Health, University of Wisconsin, Madison, WI.*

Background: ANCA associated vasculitis (AAV) and anti-GBM are the leading cause of ESRD due to RPGN. We report our institution's experience with renal transplant patients in patients with ESRD due to RPGN.

Methods: We compared the outcomes for patients with ESRD due biopsy-proven AAV and anti-GBM with patients with ESRD due to IgA nephropthy (IgAN) and autosomal dominant polycystic kidney disease (ADPKD) who underwent kidney transplant between 1994 to 2013.

Results: 72 patients with biopsy proven RPGN (AAV N=46, anti-GBM N=26) underwent kidney transplant between 1994-2013. The mean follow up time was 7.2 years (± 4.7 years). The incidence of graft loss was 2.9/100 person years for AAV and 5.2/100 persons year for anti-GBM. The incidence of patient death was 3.8/100 person years for AAV and 3.2/100 person years for anti-GBM. The risks of graft loss and patient death were similar to those for IgAN (2.8 and 2.2/100 person years) in multivariable analysis (Table 1). 10-year death censored graft survival for AAV and anti-GBM was similar to IgAN and ADPKD (Fig1).

Conclusions: Long-term patient and graft survival for patients with ESRD due to AVV and anti-GBM after kidney transplant was good and similar to ESRD due to IgAN and ADPKD post transplantation.

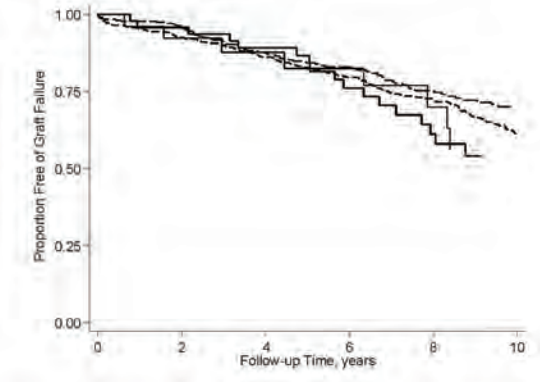


Fig 1. Kaplan-Meier curve of allograft survival in transplant recipients with GPA (thin black line), anti-GBM (bold black line), IgAN (thin dashed line), ADPKD (bold dashed line)

		Glomerular disease diagnosis		
		AAV	Anti-GBM	IgAN
Death-censored graft loss	Incidence Rate (per 100 person-years)	2.9 (p=.87)	5.2 (p=.06)	2.8 (Reference)
	Adjusted relative HR*	1.09 (.49, 2.47) p=.83	1.31 (.52, 3.33) p=.57	1.0 (Reference)
Death	Incidence Rate (per 100 person-years)	3.8 (p=.06)	3.5 (p=.25)	2.2 (Reference)
	Adjusted relative HR*	1.18 (.53, 2.66) p=.69	0.55 (.17, 1.79) p=.32	1.0 (Reference)

* Adjusted for age, sex, race, dialysis pre-transplant, duration of dialysis, HLA mismatch, PRA, donor status, prior transplant, DGF, cold ischemia time, induction agent, CNI use

Table 1. Death-censored graft loss and patient death with relative hazard (HR, 95% confidence interval), by diagnosis

SA-PO531

PLA2R De Novo Membranous Nephropathy and Antibody Mediated Rejection in a Renal Allograft Marika Manolopoulou,[1] Kathy L. Jabs,[1] Mark Lusco,[2] Paisit Paueksakon.[1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Vanderbilt University School of Medicine, Nashville, TN.*

Background: The pathophysiology of de novo membranous nephropathy (dnMN) is not clearly understood but may be associated with antibody-mediated rejection (AMR) in the allograft. The presence of phospholipase A2 receptor (PLA2R) antibodies usually indicates recurrent MN or dnMN not associated with AMR. We present a case of PLA2R positive dnMN in the presence of AMR and its resolution by histologic evidence upon rejection targeted treatment.

Methods: Our patient is a 19-year old male with end stage renal disease due to obstructive uropathy who received a deceased donor kidney transplant in 6/2015.

His immunosuppression included anti-thymocyte globulin (ATG) induction therapy, and maintenance with prednisone, mycophenolate mofetil, and tacrolimus. Post-transplant his serum creatinine (sCr) was stable at 0.99 mg/dl. Fourteen months post-transplant he presented with with a creatinine of 2.2 mg/dl in the setting of likely medication nonadherence. A renal transplant biopsy revealed acute cellular rejection (ACR), AMR (peritubular capillaritis with C4d positivity in >50% of capillaries) and serum donor specific antibody (DSA) positivity. There was also PLA2R positive membranous nephropathy. His infectious workup was negative. He was treated with pulse methylprednisolone, ATG, plasma exchange, intravenous immunoglobulin (IVIG) and rituximab. His sCr decreased to 1.03 mg/dl at hospital discharge. His interval follow up demonstrated stable renal function. At nineteen months post-transplant his sCr was 1.57 mg/dl, he had negative DSA and undetectable tacrolimus trough level. He was next seen 3 months later with allograft pain and a sCr of 7.0 mg/dl. Renal biopsy was consistent with ACR, microcirculation inflammation suspicious for AMR (negative C4d, positive DSA) and no evidence of membranous nephropathy. He was treated with ATG, methylprednisolone, rituximab, plasma exchange, and IVIG and his sCr decreased to 3.7 mg/dl.

Results:

Conclusions: While the pathophysiology of dnMN remains to be elucidated, this disease entity is currently viewed as an alloimmune disease mediated by chronic AMR. In contrast to idiopathic MN, dnMN associated with AMR has not been found to be PLA2R positive. Although rare, the presence of PLA2R positive dnMN should be considered in the setting of AMR. Further study and long term follow up of these patients will help us gain a better understanding.

SA-PO532

Characteristics of Donor Transmitted Membranous Nephropathy in Kidney Transplantation Yasuhiro Otsuka, Yoshihiko Watarai, Asami Takeda. *Nagoya Daini Red Cross Hospital, Nagoya, Japan.*

Background: Donor transmitted membranous nephropathy (MN) is unique entity that shows histological features of MN even though donor urinalysis is negative for protein before kidney transplantation (KTx). Donor transmitted MN is rarely seen in KTx, but its prognosis and histological changes are unclear.

Methods: Retrospective data were collected from 2002 to 2016. Out of 1113 KTx cases, eight patients were diagnosed with donor transmitted MN by 1 hour biopsy. All eight cases were living KTx, and posttransplant renal function and urinary protein of both donor and recipient were analyzed. Protocol renal allograft biopsies were performed one hour, three weeks, and one year after KTx, and light microscopy, immunofluorescent study for IgG, C3, C4d, and IgG subclass, and electron microscopy were performed.

Results: Donor age was 61.1 ± 13.1 years, and four were male. Urinalysis was negative for protein in all eight donors. Donor eGFR and urinary albumin creatinine ratio (UACR) before KTx was 83.0 ± 11.2 ml/min/1.73m^2 and 38.0 ± 38.7 mg/g. Donor eGFR and UACR one year after KTx was 51.5 ± 9.1 ml/min/1.73m^2 and 3.5 ± 0.9 mg/g. Donor follow up period was 43.1 ± 43.9 months, latest eGFR and urinary protein was 50.6 ± 10.1 ml/min/1.73m^2 and 0.08 ± 0.12 g/day. Recipient age was 38.6 ± 7.0 years, five were male, and all eight cases were ABO compatible KTx. Recipient eGFR and urinary protein one year after KTx was 41.6 ± 11.9 ml/min/1.73m^2 and 0.14 ± 0.08 g/g. Recipient follow up period was 52.0 ± 43.0 months, latest eGFR and urinary protein was 37.5 ± 6.8 ml/min/1.73m^2 and 0.11 ± 0.20 g/day. In immunofluorescence study for IgG, one case out of five cases was negative at three weeks biopsy and five out of six was negative at one year biopsy. Four out of five were positive for C4d on capillary wall at one year biopsy. IgG subclass stain revealed that one case was negative for IgG4. By light microscopy, bubbling appearance was observed at one hour and one year biopsy in all available cases. By electron microscopy, stage did not change at one year biopsy except one case from Ehrenreich–Churg stage III to stage IV.

Conclusions: This study suggest that deposition of IgG in donor transmitted MN decreases within one year after KTx. Clinical data showed a good renal function and urinary protein within normal limit at latest follow-up in both donor and recipient.

SA-PO533

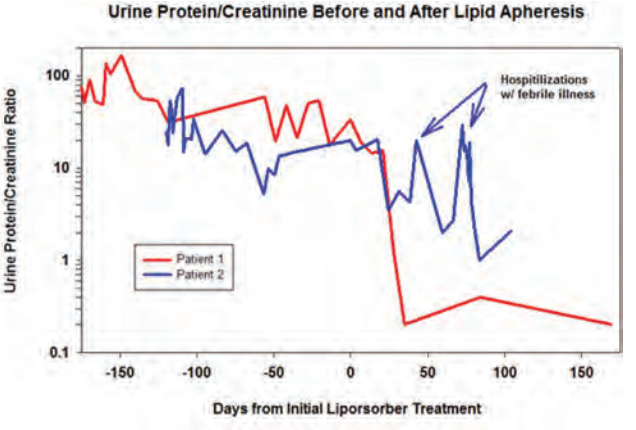
Successful Remission of Recurrent FSGS Following Lipid Apheresis in Renal Transplant Recipients Lokesh N. Shah,[8,9] Christopher J. LaRosa,[7] Justine Speckhals,[2] Carolyn Tait,[1] Kimberly A. Lasalvia,[6] Kyla Clark-Freeman,[4] Divya G. Moodalbail,[3] Joshua Zaritsky.[5] *[1]Nemours A.I. duPont Hospital for Children, Wilmington, DE; [2]Nemours/ Alfred I. DuPont Hospital for children, Avondale, PA; [3]Nemours/ Alfred I. duPont Hospital for Children, Wilmington, DE; [4]Nemours/Alfred I DuPont Hospital for Children, Wilmington, DE; [5]Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE; [6]Nemours/ duPont Hospital for Children, Wilmington, DE; [7]None, Wilmington, DE; [8]Thomas Jefferson University, Philadelphia, PA; [9]Alfred I duPont Hospital for Children, Wilmington, DE.*

Background: The Liposorber® LA-15, a lipoprotein apheresis device, has been used as a rescue therapy in patients with recurrent primary focal segmental glomerulosclerosis (FSGS). Using a protocol of weekly lipid apheresis in combination with IV methylprednisolone, we describe the remission of recurrent FSGS in two pediatric kidney transplant recipients.

Methods: Both patients were diagnosed with steroid-resistant biopsy-proven FSGS at age 2. They failed to respond to multiple interventions (high dose steroids, high dose calcineurin inhibition, mycophenolate, and rituximab). They eventually underwent renal transplantation due to ensuing ESRD. Both post-transplantation courses were complicated by immediate recurrence of FSGS with urine protein/creatinine (Up/cr) ratios > 50. Again, both failed to respond to high dose steroid and calcinuerin inhibition; nor did they respond to 3 months of thrice weekly standard plasmapheresis. As a rescue therapy both patients underwent weekly lipid apheresis using the Liposorber® LA-15 system with a treatment volume of 60 mL/kg along with a 10 mg/kg dose of IV methylprednisolone. The final cycle of lipid apheresis occurred approximately 80 days after its initiation in both patients. In both cases there was a dramatic decrease in the urine protein to creatinine ratios (FIGURE). After stopping lipid apheresis both patients have remained in clinical remission without further treatment.

Results:

Conclusions: Lipid apheresis has shown promise in the treatment of both primary and recurrent FSGS; however, experience with this modality is limited. Our successful use of lipid apheresis in combination with methylprednisolone to induce remission in treatment resistant recurrent FSGS provides a protocol for future studies, and provides a better understanding of the ill-defined pathophysiology of hyperlipidemia and nephrotic syndrome.



SA-PO534

Recurrent FSGS in Renal Transplantation: A Single Centre Experience Marilina Antonelou,[1] Omid sadeghi-alavijeh,[1] Daniel P. Gale,[1] Gareth L. Jones,[2] Alan D. Salama.[1] *[1]University College London, Centre For Nephrology, London, United Kingdom; [2]Royal Free London NHS Trust, London, United Kingdom.*

Background: Renal transplantation in patients with Focal segmental glomerulosclerosis (FSGS) is often complicated by disease recurrence which is associated with poor outcome. There are no reliable tests to predict recurrence of FSGS after transplantation. The aim of this study was to evaluate if clinical criteria can identify patients at high risk for recurrent disease.

Methods: Retrospective review of patients diagnosed with FSGS who received a renal transplant in our centre between 1995 and 2017. The diagnosis of primary FSGS was based on a native renal biopsy or unexplained proteinuria and a family history of kidney disease. Recurrence of FSGS was defined as the occurrence of proteinuria, greater than 100 mg/mmol after transplantation with histological evidence of FSGS.

Results: We identified 99 patients with FSGS who received a kidney transplant. Twenty five (25.2%) had biopsy proven recurrent FSGS. The median interval from transplantation to onset of proteinuria was 3.1(1-28)months. A comparison of baseline and follow-up data is shown in Table 1. The median interval between onset of proteinuria and a renal biopsy confirming the diagnosis of recurrent FSGS was 2.7(1.1-4.3) months. Nine patients did not have histological evidence of FSGS on their initial biopsy. None of the 25 patients with recurrent FSGS had a family history of kidney disease. Seven patients had a previous failed transplant, four following FSGS recurrence.

Conclusions: Our data suggest that primary, as opposed to secondary FSGS is a reliable marker of increased recurrence risk in patients with FSGS undergoing renal transplantation. The family history is a useful tool for risk stratification. Close monitoring for proteinuria is important for the initiation of treatment as histological changes might not be present at the early disease stage.

	Recurrence (n=25)	No recurrence (n=74)	p value
Gender (male,%)	14(56)	45(60.8)	0.81
Age of onset of disease (years)	26(16-43)	37(30-47)	0.14
Primary FSGS (n,%)	24(96)	57(77)	0.03
Family history of kidney disease (n,%)	0	9(12.2)	0.10
Live donor (n,%)	8(32)	22(29.7)	0.80
Cadaveric donor (n,%)	17(68)	52(70.3)	
Patients with ≥1 failed transplant (n,%)	7(28)	5(6.8)	0.001
Interval from transplantation to last follow-up (LTFU) (years)	2.9(1.5-15.4)	8.1(3.1-15.3)	0.09
Creatinine at LTFU (mmol/L)	167(123-347)	139(108-188)	0.19
RRT dependent at LTFU (n,%)	10(40)	6(8.1)	<0.001
Death (n,%)	5(20)	8(10.8)	0.30

SA-PO535

Clinical Findings, Pathology, Treatment, and Outcomes of PGNMID after Kidney Transplantation Hassan A. Salameh, Hatem Amer, Ladan Zand, Fernando C. Fervenza, Nelson Leung. *Mayo Clinic, Rochester, MN.*

Background: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a rare form of glomerular disease caused by monoclonal immunoglobulin (Ig) deposition localized to the glomeruli. The outcome of recurrent PGNMID in renal allografts is not well known and to our knowledge has been reported in only 12 patients. We describe a single centers' experience with PGNMID after kidney transplantation (KTx).

Methods: Between 2000 and 2016 we identified 20 patients with PGNMID who underwent KTx. We describe their clinical findings, labratory data, recurrence rates, biopsy findings, treatment and outcomes during the study period.

Results: The median age at the time of native kidney biopsy-proven PGNMID was 54 (range 23-74) years. Median time between the initial kidney biopsy to ESRD (KTx or dialysis) was 36 (range 2-146) months. Post-transplant, PGNMID recurred in 18 out of 20 patients (90%). The median time to recurrence in the kidney biopsy was 4 (range 1-48) months (Figure 1). Four patients did not receive targeted treatment for the PGNMID recurrence and no graft loss was noted with median follow-up of 48.5 months. Three patients were treated with additional immunosuppressive agents including steroids and cyclophosphamide and 33% (n=1) had graft loss in this group. Seven patients received B-cell targeted therapy with Rituximab with graft loss rate of 28% (n=2). Four patients received plasmapheresis in addition to immunosuppressive therapy; graft lost in 75% (n=3); however; only 25% (n=1) was attributed to PGNMID with the other two loses due to rejection.

Conclusions: In our experience, PGNMID was associated with a very high rate of recurrence in allografts reaching 90%. Graft loss occurred in 33% of recurrent cases. The median time to graft loss was 67 (range 31-132) months. Graft loss incidence due to PGNMID was similar between the immunosuppression, Rituximab and plasmapheresis groups; however, the plasmapheresis group had more aggressive disease that lacked response to other treatment options.

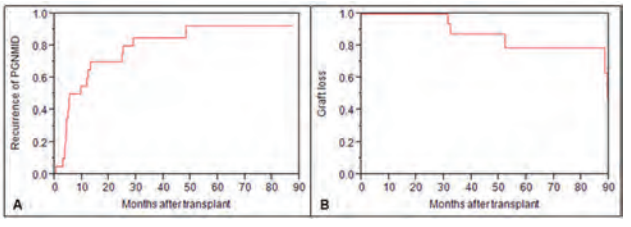


Figure 1. Kaplan-Meier plots of (**A**) Cumulative incidence of PGNMID recurrence in grafts and (**B**) Graft loss in recurrent PGNMID.

SA-PO536

Determinants of Renal Progenitor Cell Responsiveness to the Inductive Wnt9b Signal from the Ureteric Bud Kyle Dickinson,[2] Thomas J. Carroll,[3] Paul R. Goodyer.[1] *[1]McGill University, Montreal, QC, Canada; [2]McGill University, Montreal, QC, Canada; [3]UTSW Medical Center, Dallas, TX.*

Background: The canonical Wnt-signalling pathway is essential for kidney development as fully primed renal progenitor cells (RPC) appear in the metanephric mesenchyme. RPCs receive inductive Wnt9b signals from the adjacent ureteric bud to initiate a proliferative program. Specificity of Wnt ligand binding is determined by the co-receptor complex, consisting of a Frizzled (Fzd1-10) and Lipoprotein related receptor protein (Lrp5/6), however, the specific molecular components conferring responsiveness in RPCs have yet to be identified. The receptor complex is stabilized by R-spondin1 and R-spondin3 (Rspo1 and Rspo3), amplifying the Wnt signal.

Methods: We obtained M15 cells, derived form E10.5 mesonephric mesenchyme (Hastie et al, 1999) and systematically analyzed Wnt receptor/signalling components required for a canonical Wnt response. To measure activation of the canonical Wnt pathway, we transfected our M15 cells with reporter plasmid 8X TOPFlash and measured luciferase activity using a luminometer. RNA was analyzed by qRT-PCR.

Results: Exposing M15 cells to external Wnt9b resulted in minimal luciferase activity suggesting a signalling component is missing. We analyzed M15 cells for components of the β-catenin/TCF pathway and found mRNA expression of Fzd1-6, Lrp6 but neither Rspo1/3. To ascertain whether absence of R-spondin accounts for the lack of response, we transfected M15/TOPFlash cells with Wnt9b and added recombinant Rspo1 or Rspo3 and observed a 4.8-fold and 7.8-fold increase in luciferase activity, respectively. In the presence of Rspo1, we transfected the cells with Fzd1-10 and observed an additional 5-fold increase in the presence of Fzd5 but not the other Fzds. Knockdown of Lrp6 with siRNA (60% reduction in mRNA level) resulted in a 60% reduction in luciferase activity which was not rescued by Lrp5.

Conclusions: Our results suggest that early RPCs must acquire a specific receptor complex consisting of Fzd5, Lrp6 and Rspo1/3 before they can transduce an optimal β-catenin/TCF signal in response to Wnt9b during nephrogenesis. We speculate that putative RPCs lacking these components are incompetent for primary nephrogenesis and/or regeneration of damaged adult kidneys.

Funding: Government Support - Non-U.S.

SA-PO537

DNMT1-Dependent Cytosine Methylation Is Essential for the Control of Progenitor Cell Differentiation in Early Nephron Development Szu-Yuan Li,[1,2] Jihwan Park,[1] Rojesh Shrestha,[1] Katalin Susztak.[1] *[1]University of Pennsylvania, Philadelphia, PA; [2]Medicine, Taipei Veterans General Hospital and Yang-Ming University, Taipei, Taiwan.*

Background: The basic functional units of the mammalian kidney, nephrons, are generated repetitively during kidney organogenesis. Six2 positive cells represent a multipotent nephron progenitor population within cap mesenchyme and give rise to all epithelial cells in the kidney. Cytosine methylation changes play a key role in gene expression regulation; however, the role of cytosine methylation changes in kidney development has not been studied. Cytosine methylations are established by DNA methyltransferases (Dnmt) and are further modified by Tet eleven hydroxylase (TETs). Dnmts function as methylation writers and maintainers, and Tets act as methylation erasers.

Methods: To examine the role of cytosine methylation in renal epithelial cells, we crossed mice with DNMT1, 3a, 3b, Tet1 or Tet2 conditional allele (flox) with Six2cre mice. To understand the role of cytosine methylation in differentiated epithelial cells, we crossed Dnmt1, 3a, 3b and Tet1,2 mice with podocin Cre mice. Genome wide transcript level and cytosine methylation changes were analyzed by RNA sequencing and reduced representation bisulfate sequencing (RRBS).

Results: DNMT1, 3a, 3b and Tet1 are highly expressed in embryonic kidneys, and their expression levels decrease remarkably after kidney organogenesis is completed. Mice with podocyte-specific ablation of Dnmt1, 3a, 3b, Tet1 or Tet2 did not show functional or structural changes. We have induced glomerular disease in these animals by Adriamycin injection and found no differences in injury response when compared to controls, indicating the dispensable role for these enzymes. On the contrary, Six2 cre DNMT1 f/f mice died on day1 after birth; their kidneys were small and their bladders void of urine. Histological analysis revealed that although the progenitor cell population was maintained in absence of DNMT1, nephron maturation stopped in early stages (renal vesicle/ C-shape body). Expression of the cap mesenchymal genes including Gdnf were increased while nephron maturation genes including Fgf8 and Lhx1 were decreased.

Conclusions: DNMTs and TETs expression are dynamic during kidney development. Dnmt1 dependent DNA methylation is essential to complete nephron maturation.

Funding: NIDDK Support

SA-PO538

HIF Prolyl-4-Hydroxylation in FOXD1 Lineage Cells Is Essential for Normal Kidney Development Hanako Kobayashi,[1] Volker H. Haase.[2] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]Vanderbilt University Medical Center, Nashville, TN.*

Background: Hypoxia in the embryo is a frequent cause of intra-uterine growth retardation, low birth weight and multiple organ defects. In the kidney this can lead to low nephron endowment predisposing to chronic kidney disease and arterial hypertension. A key component in cellular adaptation to hypoxia is the hypoxia-inducible factor (HIF) pathway, which is regulated by prolyl-4-hydroxylase domain (PHD) dioxygenases PHD1, PHD2 and PHD3. In the adult kidney, PHDs function as oxygen-sensors, are differentially expressed in a cell type-dependent manner and control the production of erythropoietin in interstitial cells. The role of interstitial cell PHDs in renal development, however, has not been examined.

Methods: In order to examine the role of interstitial HIF oxygen sensing in renal development and homeostasis, we used the Cre-loxP system to target all 3 HIF-PHDs in conjunction with HIF-1α or HIF-2α in FOXD1-expressing stromal cells.

Results: PHD2 and PHD3 are essential for normal kidney development as the combined inactivation of stromal PHD2 and PHD3 resulted in renal failure that was associated with reduced kidney size, decreased numbers of glomeruli and abnormal postnatal nephron formation. In contrast, nephrogenesis was normal in animals with individual PHD inactivation. We furthermore demonstrate that the defect in nephron formation in PHD2/PHD3 double mutants required intact HIF-2 signaling and was dependent on the extent of stromal HIF activation.

Conclusions: The ability to regulate HIF prolyl-4-hydroxylation in FOXD1 stroma-derived cells is essential for normal nephron formation. Our data have implications for the therapeutic use of HIF prolyl-4-hydroxylase inhibitors, which are currently in phase 3 clinical development for renal anemia.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO539

Hedgehog-TGFβ Signaling in Foxd1+ Stromal Cells Controls Stromal Patterning and Nephron Formation Christopher Rowan, Norman D. Rosenblum. *The Hospital for Sick Children, Toronto, ON, Canada.*

Background: In the embryonic mammalian kidney, signals from *Foxd1+* stromal cells are critical in establishing a full complement of nephrons. Yet, the molecular mechanisms that control stromal-nephrogenic cell interactions are largely unknown. Previously, we demonstrated that homozygous deficiency of SMO, a cell surface Hedgehog signaling effector, in the stromal lineage (*Smo-null*^{stroma}) results in a 42% decrease in nephron number. Remarkably, low nephron number is preceded by expansion of SIX2+ nephron progenitors and a relative block of mesenchymal to epithlial conversion [ASN 2014]. Here, we identify molecular mechanisms that control nephrogenesis in *Smo-null*^{stroma} mice.

Methods: RNA expression was assayed by RNASeq, quantitative (q)PCR, and *in situ* hybridization. Functional assays were performed in cultured mouse embryonic kidney explants using neutralizing antibodies and vivo-morpholinos (MO). TGFβ receptor II deficiency was generated in a CRE-dependent manner under the control of cell-specific promoters.

Results: RNASeq of wild type and *Smo-null*^{stroma} E13.5 kidney tissue demonstrated decreased expression of *Tgfb2* in mutant tissue. qPCR showed a 30% decrease in *Tgfb2* in *Smo-null*^{stroma} mutant kidney tissue and in FACS-isolated mutant *Foxd1+* stromal cells. *In situ* hybridization demonstrated decreased *Tgfb2* expression, and immunostaining demonstrated decreased expression of the TGFβ intracellular effector pSMAD2/3 in *Smo-null*^{stroma} mutant kidneys. Treatment of wild type embryonic kidney explants with neutralizing antibody or MO specific to TGFβ2 resulted in 65% (P=0.017) and 35% (P=0.003) fewer nephrons, respectively (n=3 per group). CRE-dependent deletion of TGFβ receptor II (*Tgfbr2*, specific to TGFβ ligands) within *Foxd1+* stromal cells (*Tgfbr2-null*^{stroma}) caused a 1.3-fold increase in SIX2+ nephron progenitors (P=0.01, n=8/genotype), as observed in *Smo-null*^{stroma} mice, and mispatterning of stromal cells *in vivo*. *Tgfbr2* deficiency targeted to either ureteric or SIX2+ nephron progenitor cells, alone, caused neither of these pathologic effects (n=3/genotype). However, *Tgfbr2* deficiency in both *Foxd1+* and *Six2+* cells concurrently caused hypoplasia in addition to defects observed in *Tgfbr2-null*^{stroma} mice.

Conclusions: We conclude that HH-TGFβ signaling exerts both cell autonomous and non-cell autonomous effects to control nephron formation and stromal patterning.

Funding: Government Support - Non-U.S.

SA-PO540

Stromal Progenitor-Derived Netrin-1 Signals Are Required for Proper Kidney Development Lori L. O'Brien, Deanna M. Hardesty, Shamus L. Cooper. *University of North Carolina at Chapel Hill, Chapel Hill, NC.*

Background: Kidney morphogenesis is driven by reciprocal signaling between progenitor populations. However, novel signaling pathways may remain unknown. We recently uncovered targets of Six2/SIX2 in the nephron progenitors of mouse and human kidneys through a combination of ChIP-seq and RNA-seq. We analyzed these lists to identify novel signaling pathways acting in the developing kidney.

Methods: We identified *Unc5C/UNC5C* as a common target expressed within nephron progenitors. Unc5c is a receptor for the ligand Netrin-1 (Ntn1) which has roles in axon guidance as well as vascular, lung, and mammary gland development. *In situ* analyses show that *Ntn1* expression is restricted to the stromal progenitors. Other receptors for Ntn1 such as *Unc5b* are expressed in the vascular endothelium and medullary collecting ducts. Therefore, we focused on assessing the knockout phenotype of their common ligand Ntn1. We utilized the *Foxd1*^{GC} line to conditionally ablate *Ntn1* in the stromal progenitors.

Results: *Ntn1* mutant kidneys are hypoplastic. At E15.5, immunostaining for Six2, cytokeratin, and Wt1 reveals relatively normal nephron progenitor and ureteric tree organization with developing nephrons and glomeruli present despite kidneys being smaller. Since Ntn1 has roles in vascular development and axon guidance, we also stained kidneys for CD31 (endothelium) and Tuj1 (neuron). Mutant kidneys often had additional endothelial and neuronal projections extending over the outer cortex. Subsets of P0 mutant collecting ducts showed extensive dilation. Numbers of each genotype were assessed at P14 and indicate that most conditional *Ntn1* mutants die postnatally.

Conclusions: We have identified a novel signaling pathway acting in the embryonic kidney. Stromal progenitor-derived Ntn1 may play several roles including regulating the nephron progenitor population through Unc5c as well as guiding vascular and neuronal cell networks. Current studies are underway to assess cell and tip numbers, proliferation, and any consequences to ureteric, vascular, and neuronal networks. Additionally, we are analyzing Unc5c mutant kidneys. Our studies will help shed light onto new signaling pathways controlling mammalian kidney development and may have implications on vascularization and innervation of the kidney where much less in known about their development and regulation during morphogenesis.

SA-PO541

Study on Morphogenesis of Renal Vasculature Architecture Based on Computer-Assisted 3D Reconstruction Jie Zhang,[1] Jie Yang,[1] Shi-Jie Chang,[2] Ling Gu,[1] Kaiyue Wang,[1] Jesper S. Thomsen,[3] Arne A. Andreasen,[3] Erik I. Christensen,[3] Xiao-Yue Zhai.[1] *[1]Department of Histology and Embryology, China Medical University, Shenyang, China; [2]Department of Biomedical Engineering, China Medical University, Shenyang, China; [3]Department of Biomedicine-Anatomy, Aarhus University, Aarhus, Denmark.*

Background: The architecture of the renal vasculature (RV) is formed so that the renal function is highly efficient. However, a relationship has been suggested between the morphogenesis of RV and the progression of renal fibrosis in CKD, due to the close proximity of peritubular capillaries and tubules. Present study demonstrates the transformation of RV trees from young to adult kidneys based on histological serial sections, and provides a quantitative reference with establishment of microcirculation, aiming at better understanding the morphogenic processes, meanwhile the progression of the nephron pathophysiology.

Methods: Serial paraffin and epoxy sections from E14.5, E17.5, P5, and adult kidneys were prepared for vessel tracing on aligned micrographs, using custom-made computer software. In addition, glomerular and medullary capillaries volume densities were measured on sections immunostained for CD34, from 3 mouse kidneys of each of 11 developing days.

Results: At E14.5, the RV trees consisted of six main arteries running between cortex and medulla and dozens of lateral branches along them. These smaller branches further divide in even smaller branches connecting to the earliest formed immature glomeruli. Soon after, with rapidly increasing number of nephrons, a burst branching network of RV formed with tremendous lateral and bifid branching until P5. After that, with expansion of especially the medullary volume, the RV tree remodeled into the typical spatial arrangement, including main, arcuate, and interlobular arteries, as well as afferent and efferent arterioles (AA and EA). The typical medullary vascular bundles (VB) originated from the EAs of earlier born nephrons intimately accompanying with Henle's ascending limb, and gradually formed by branching of the EA accompanied by more thin limbs and vessels when penetrating into the deep medulla. Consistently, the volume density of medullary microcirculation increased with the VB formed.

Conclusions: A large number of RV branches are completed by cessation of nephrogenesis. The RV is not only formed by iterative branching, but also by lateral and sprouting branches. In addition, the RV trees undergo remodeling corresponding to an increasing volume density, driven by the spatial arrangement of the neighboring tubules during the postnatal life.

Funding: Government Support - Non-U.S.

SA-PO542

Hypoxia-Regulated MicroRNA-210 Expression and Role in Nephrogenesis Shelby L. Hemker,[2,3] Andrew S. Clugston,[2,3] Yu Leng Phua,[2,3] Jacqueline Ho,[2,3] Dennis Kostka.[1,4] *[1]Developmental Biology, University of Pittsburgh, Pittsburgh, PA; [2]Rangos Research Center, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA; [3]Pediatrics, Division of Nephrology, University of Pittsburgh, Pittsburgh, PA; [4]Computational & Systems Biology, University of Pittsburgh, Pittsburgh, PA.*

Background: Placental insufficiency causes fetal hypoxia, reduced blood flow to the kidneys, and is the main cause of intrauterine growth restriction (IUGR). IUGR and fetal hypoxia adversely affects kidney development, resulting in decreased nephron number and increased chance of congenital anomalies of the kidney and urinary tract (CAKUT), the leading cause of kidney failure in children. Furthermore, IUGR puts affected individuals at an increased risk for developing hypertension and chronic kidney disease. We hypothesize that key regulators of normal kidney development are responsive to changes in oxygen tension. *microRNA-210* (*miR-210*) is the most consistently induced miRNA in hypoxia and is directly regulated by the Hypoxia Inducible Factor (HIF) transcription factor family. microRNAs (miRNAs) are ~22nt small noncoding RNAs that fine-tune gene expression through post-transcriptional regulation of specific target mRNAs and are essential for proper mammalian development.

Methods: First, we defined *miR-210* expression throughout murine kidney development using small RNA sequencing and *in situ* hybridization. Then, we cultured *ex vivo* kidney explants in different oxygen levels and examined the effect on both miRNA and mRNA expression through RNA sequencing. Furthermore, we investigated the effect of a global *miR-210* mouse knockout on kidney development using real time RT-qPCR and histological analyses.

Results: We found that *miR-210* is broadly expressed in the developing kidney, including in nephron progenitors (cells that differentiate to form the nephron) and ureteric bud epithelium (cells that form the collecting duct system). Our transcriptomic studies found that *miR-210* is upregulated in hypoxia, while several of its target mRNAs are down-regulated. Most interstingly, the *miR-210* knockout mouse has altered expression of key genes in nephron progenitors, ureteric bud, and endothelial cells during kidney development.

Conclusions: Together, our data suggests that *miR-210* plays a role in normal kidney development.

Funding: NIDDK Support

SA-PO543

Understanding Normal and Hoxa9,10,11-/-; Hoxd9,10,11-/- Kidney Development Through Single Cell RNA-Seq Bliss Magella,[2] Robert Mahoney,[5] Meenakshi Venkatasubramanian,[1] Nathan Salomonis,[3] Steven Potter.[4] *[1]Cincinnati Children's Hospital, Cincinnati, OH; [2]Cincinnati Children's Hospital Medical Center, Sharonville, OH; [3]Cincinnati Children's Hospital Medical Research Center, Cincinnati, OH; [4]Cincinnati Children's Hospital, Cincinnati, OH; [5]Cincinnati Childrens, Fairfield, OH.*

Background: The kidney is a complex organ that is made of many different cell types. In an effort to better understand the cell diversity within the developing kidney we have performed single cell RNA-seq on embryonic day 14.5 mouse kidneys. Of particular interest is the apparent lack of a Hox code within the developing kidney. Previous studies have determined that Hox 10 and 11 paralogous groups are functioning within kidney development. Interestingly, thirty-six of the thirty-nine mammalian Hox genes are expressed during kidney development.

Methods: Analysis of wild type and mutant E14.5 kidneys was performed using data obtained through Drop-seq. Additional data sets were gathered using Fluidigm and Chromium In-Drop for wild type validation. Hoxa9,10,11; Hoxd9,10,11 mutants were used to determine the functional role of the Hox genes during kidney development. Altanalyze and Seurat based analyses are being used to determine the normal and mutant expression profiles.

Results: Sixteen cell groups were identified in the wild type data set; medullary collecting duct, cortical collecting duct, ureteric bud tip, loop of Henle, distal comma shaped body, podocyte, mid S-shaped body, early proximal tubule, pre-tubular aggregate, three cap mesenchyme groups, endothelium, nephrogenic zone stroma, cortical stroma,

and medullary stroma. In addition to the known identifier genes, novel specific gene associations were also discovered during analysis. One such example is the discovery of *Gdnf* expression from within the stromal population, which was previously thought of as being exclusively expressed from the cap mesenchyme. Morphological analysis of the Hox mutants shows alterations in mature nephron segment identity, medullary zone specification, and the formation of a pelvic opening.

Conclusions: Obtaining a comprehensive data set allows for the visualization of the expression profile of many genes within the wild type developing kidney. These data can then be used as an atlas for comparing mutant data sets. By combining the Hox mutant morphological phenotypes with the single cell expression profiles we can better understand the molecular regulation of kidney development. This greater understanding provides necessary information for future studies looking to make kidneys through organoid cultures.

Funding: NIDDK Support

SA-PO544

Chemical Genetic Screen Reveals Novel Role for PPAR Signaling in Renal Progenitor Development Joseph M. Chambers, Rebecca A. Wingert. *University of Notre Dame, Notre Dame, IN.*

Background: The genetic and molecular mechanisms directing nephron segmentation during kidney development are not well understood. Deregulation of genes involved in kidney development result in a variety of diseases broadly categorized as Congenital Anomalies of the Kidney and Urinary Tract (CAKUT). Embryonic zebrafish have a simplified kidney, the pronephros, comprised of proximal and distal segments that display conservation with mammalian nephrons, including humans, thus enabling CAKUT modeling.

Methods: Through a novel chemical genetic screen, we discovered that peroxisome proliferator-activated receptor (PPAR) signaling is essential for normal nephron segment development. PPARs are a group of nuclear receptor proteins that are activated by ligands such as fatty acids and act as transcription factors by heterodimerization with retinoid X receptor (RXR) to regulate cell differentiation and perform diverse roles in metabolism. We found that treatment with the PPAR agonist bezafibrate during nephrogenesis alters the balance of proximal and distal cells. Interestingly, *pparg* co-activator, *ppargc1a*, which binds to activated PPARs to regulate transcription of target genes, is dynamically expressed in renal progenitors.

Results: To test the functional role of this co-activator during nephron segmentation, we examined nephron development in *ppargc1a*^{sa13186} mutants, where a lesion in exon 8 with a TàA substitution results in a premature STOP codon and an anticipated loss of the RNA processing domain. *ppargc1a*^{sa13186} mutants have an abrogated distal tubule and increased proximal tubule domain, which was recapitulated in subsequent knockdown studies as well. Further, *ppargc1a* knockout and knockdown models development renal cysts, a hallmark of dysplastic CAKUT. Interestingly, there is a decrease in cilia within the nephrons of mutant and knockdown examples. Assessment of essential nephron regulators revealed that *ppargc1a* acts to inhibit *irx3b* and promote *tbx2b*.

Conclusions: Taken together, our studies suggest a novel mechanism by which PPAR signaling coordinates lineage choices during nephrogenesis. These findings may lead to a better understanding of the therapeutic value of PPARs in relation to renal birth defects and cystic disease conditions as well.

Funding: NIDDK Support

SA-PO545

Genetic Mechanisms of Multiciliated Cell Development during Renal Ontogeny Amanda N. Marra, Rebecca A. Wingert. *University of Notre Dame, Notre Dame, IN.*

Background: Multiciliated cells (MCCs) are found in a wide variety of species and tissues, ranging from the embryonic kidney of frogs and fish to the reproductive and respiratory systems of mammals. Differentiation of MCCs has become an increasingly attractive area of research due to their association with fluid flow and disease. There is evidence for a core, conserved pathway of MCC development that includes the Notch signaling pathway as a negative regulator of MCC fate.

Methods: The embryonic zebrafish kidney, or pronephros, has emerged as a useful tool to study MCC genesis *in vivo*, where the transcription factor *mecom* acts upstream of Notch to restrict MCC development while Retinoic Acid (RA) signaling promotes MCC fate by inhibiting *mecom* and promoting expression of the ETS transcription factor *etv5a*.

Results: Here, we report phenotype analysis of the *etv5a*^{sa16031} allele, which encodes a nonsense mutation in the conserved ETS DNA-binding domain of *etv5a*. Embryos with one copy of this allele display decreased expression of MCCs, suggesting that *etv5a* is a haploinsufficient gene. Next, we found that *mecom* inhibits *etv5a* expression in the kidney, as knockdown of *mecom* caused an expansion of the *etv5a* domain. Additionally, we have identified a role for the transcription factor *irx2a* in MCC development, where knockdown of *irx2a* results in a loss of MCCs similar to that seen in *etv5a*-deficient embryos. Lastly, we have uncovered a role for prostaglandin (Pg) signaling in MCC development through a large-scale chemical screen. Inhibition of the Pg pathway via Indomethacin or concomitant knockdown of the Pg biosynthesis enzymes Cox1 and 2 significantly reduced MCC number. Interestingly, Pg inhibition did not produce a detectable change in the *etv5a* pronephros domain, suggesting that Pg signaling promotes MCC development separate from *etv5a*.

Conclusions: In conclusion, we have discovered a novel relationship between *etv5a* and *mecom* during MCC development, established *irx2a* as a MCC fate factor, and have identified an essential role for Pg signaling in MCC genesis.

Funding: NIDDK Support

SA-PO546

Silencing of cep104 in Zebrafish Embryos Gives Rise to a Ciliopathy Phenotype Elisa Molinari, Simon Ramsbottom, John Sayer. *University of Newcastle, Newcastle upon Tyne, United Kingdom.*

Background: Joubert syndrome (JBTS) is a rare autosomal recessive ciliopathy characterized by a cerebellar hypoplasia which may be accompanied by additional symptoms including developmental delay, ataxia, intellectual disabilities, retinal dystrophy and juvenile cystic renal disease (nephronophthisis, NPHP). To date, JBTS-causing mutations have been identified in 28 genes (JBTS1-JBTS28). JBTS25 is associated with the *CEP104* gene. Of note, the cilia phenotype of *CEP104* mutation carriers has not yet been reported nor has genetic silencing been tested in vertebrate models. Our results demonstrate for the first time *in vivo* a function for *cep104* in zebrafish development.

Methods: Using antisense morpholino oligonucleotide (MO) technology, we silenced *cep104* in *Danio rerio* (zebrafish). To assess specific phenotypes, we used wild type zebrafish *golden* and AB strains, alongside the transgenic *islet-1*:GFP strain which expresses GFP in cranial motor neurons under the control of *islet1* promoter and the *cmlc2*:GFP transgenic strain, expressing the GFP gene under the control of the *cmcl2* promoter.

Results: *cep104* MO-injected zebrafish embryos at 48 hpf displayed cardiac phenotypes, tail curvature and microophthalmia, which can be rescued by co-injection of a human *CEP104* mRNA, confirming the specificity of the MO. Analysis of Kupffer's vesicle, a ciliated organelle important for left-right axis formation, showed a ciliary defect, with a reduction in ciliary length. Morphant embryos display *situs inversus*, with reversed cardiac looping. Most relevant in respect to JBTS, characteristic developmental defects were observed within the brains of *cep104* zebrafish morphants, with a major involvement of oculomotor neurons. These specific defects were also rescued by co-administration of *CEP104* mRNA.

Conclusions: These data reveal that *cep104* morphant phenotypes are highly consistent with a ciliopathy syndrome, and suggest a role for cep104 in cilia formation within Kupffer's vesicle as well as development of the heart and cranial nerves.

Funding: Private Foundation Support

SA-PO547

Morphological and Morphometrical Analyses of Renal Tubules in Danio rerio Regarding Nephrogenesis Jasmin Hochstuhl, Markus Islinger, Marlies Elger. *Heidelberg University, Medical Faculty Mannheim, Mannheim, Germany.*

Background: Recent studies indentified functional markers for individual segments of the zebrafish pronephros and the definitive kidney. However, those studies largely lack direct correlations of segment markers with the substructure of the respective segment.

Methods: The pronephric kidney and the definitive kidney were studied in zebrafish, Danio rerio. We investigated larvae (72h), juveniles (26d) and adults (sexually mature fish). By using light and transmission electron microscopy as well as fluorescence labeled lectins, we established criteria for identification of nephron segments, cell types and their substructure.

Results: The pronephric kidney consists of six segments: neck segment (NS), first proximal tubule (PI), second proximal tubule (PII), early distal tubule (EDT) and late distal tubule (LDT), followed by a short collecting tubule. The nephrons of the definitive kidney showed the same sequence of segments as found in the pronephric kidney. However, in fully developed nephrons the second proximal tubule (PII) could be subdivided into two parts (PIIa and PIIb). For every segment, distinct morphological and morphometrical criteria could be identified. Based on segment location and cellular substructure, in most cases the major function of the segments could be assumed by comparison with physiological data of the respective segments in fish and mammals. Measurements of segment length and epithelial height allowed to classify different developmental stages of the entire nephron and of individual nephron segments. Nephron anlagen of different developmental stages were found exclusively apposed to the pronephric duct and the collecting duct. In all cases the prospective distal end of the anlagen invaded the pronephric duct or the collecting duct, respectively.

Conclusions: This study presents comprehensive morphological data of the tubular substructure of the pronephros and the definite kidney and may serve as a structural basis for the investigations dealing with transport mechanisms and renal disorders in this established model organism.

SA-PO548

Generation of Interspecies Chimeric Nephrons from Nephron Progenitor Cells by Conditional Elimination and Replacement Shuichiro Yamanaka,[1] Kei Matsumoto,[1] Susumu Tajiri,[1] Toshinari Fujimoto,[1] Shohei Fukunaga,[1,2] Takashi Yokoo.[1] *[1]Division of Nephrology and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, Minato, Japan; [2]Shimane University, Izumo, Japan.*

Background: The animal embryonic organ niche may have applications in the generation of regenerative organs, and progenitor cells may be an appropriate cell source for this purpose because of their safety and availability. Therefore, we established a combination method through which donor cells could be precisely injected into the nephrogenic zone and native nephron progenitor cells (NPCs) be eliminated in a time- and tissue-specific manner. We successfully removed Six2+ NPCs within the nephrogenic niche and replaced transplanted NPCs. The transplanted cells differentiated into

neo-nephrons. Furthermore, we generated rat neo-nephrons in the mouse nephrogenic zone by conditional elimination and replacement.

Methods: We used Cre-LoxP technology in combination with diphtheria toxin receptor-loxP (DTR-loxP) and Six2-Cre mice for Diphtheria Toxin (DT)-mediated NPC elimination. Metanephros (MN) was isolated from the Six2/DTR +/+ mouse embryos. Wild-type rat NPCs were transplanted into the Six2/DTR +/+ mouse nephrogenic zone and simultaneously administered DT, followed by co-culture in an organ culture dish for seven days. We examined donor NPCs differentiation into neo nephrons by immunostaining of nephron markers (WT1, PAX8, GATA3, Cytokeratin8, E-cadherin, LTL).

Results: Donor rat NPCs were observed in the broad engraftment in host mouse cap mesenchyme, which eliminated native mouse NPCs on DT administration. The interspecies chimeric nephrons expressed glomerular and tubular markers. We also observed a connection between host collecting ducts and the neo-nephrons.

Conclusions: Using progenitor cells conditional elimination system, we demonstrated that donor rat NPCs replaced host mouse NPCs in the mouse nephrogenic zone, and that generation of neo-nephrons is possible by other species. Thus, this technique enables the differentiation of progenitor cells into nephrons, providing insight into the nephrogenesis and organ regeneration processes. We believe that this technique could effectively be used to evaluate the differentiation of NPCs from pluripotent stem cells (PSCs).

Funding: Other NIH Support - Grants-in-Aid for Scientific Research, Grant-in-Aid for Young Scientists (B)

SA-PO549

Regeneration of Rat Nephrons in the Mouse Metanephros: In Vivo Regeneration of Nephrons between Different Species under the Administration of Optimal Immunosuppressive Agents Toshinari Fujimoto, Shuichiro Yamanaka, Susumu Tajiri, Kei Matsumoto, Shohei Fukunaga, Takashi Yokoo. *Division of Nephrology and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan.*

Background: The transplant of exogenous nephron progenitor cells(NPCs)to a nephrogenic niche has demonstrated very low engraftment efficiency, possibly due to the competition with existing native host NPCs occupying the niche. Previously, we generated a transgenic mouse model with ablation of NPCs by using a drug for induction. We demonstrated that host mouse NPCs were replaced with donor mouse NPCs by eliminating existing native host NPCs, and that donor cells regenerate neo nephrons that connect with host collecting ducts. In the future, we aim to regenerate human nephrons in different species using the NPCs elimination and replacement system, and apply this novel strategy to the treatment of kidney failure. As a first step, we needed to examine the possibility of interspecies regeneration of nephrons. We already succeeded in regenerating rat nephrons in the mouse metanephros(MN)on an organ culture dish using this system. In this work, we verified the in vivo regeneration of nephrons between rat and mouse models.

Methods: In the transgenic mouse, diphtheria toxin receptor is specifically expressed on Six2-positive NPCs. The MN was isolated from the E13 embryo, following which donor rat NPCs that were not affected by the diphtheria toxin were transplanted into the MN. Diphtheria toxin was simultaneously added to the MN for the elimination of native NPCs only. Subsequently, the mouse MN-implanted rat NPCs were transplanted into the abdominal para-aortic area of an adult rat under the administration of tacrolimus and Mycophenolate mofetil. After 3 weeks, regeneration of rat nephrons in the transplanted mouse MN was examined through immunohistological analysis.

Results: Donor rat NPCs were noted engraftment in the host mouse cap mesenchyme, which ablated native NPCs using diphtheria toxin. Additionally, donor rat NPCs differentiated into neo nephrons in the host mouse metanephros transplanted into the adult rat.

Conclusions: We demonstrated interspecies regeneration of nephrons within a living organism under the administration of optimal immunosuppressive agents by using the NPCs elimination and replacement system. This novel strategy is considered an effective method for kidney regeneration.

SA-PO550

Maintenance of Mature Collecting Duct Principal Cells Is Dependent on Notch Signaling Malini Mukherjee,[1] Jennifer DeRiso,[1] Kameswaran Surendran.[1,2] *[1]Sanford Research, Sioux Falls, SD; [2]Pediatrics, University of South Dakota, Sioux Falls, SD.*

Background: During kidney development Notch signaling endows the collecting ducts with proper urine concentrating capacity by ensuring that a sufficient number of collecting duct cells differentiate into mature principal cells instead of selecting intercalated cell fates. Based on the continued expression of Notch ligands in intercalated cells adjacent to mature principal cells we tested the hypothesis that Notch signaling is required for the maintenance of the mature principal cell state.

Methods: Three different mouse models were generated to study the role of Notch signaling in the mature mouse collecting ducts: (i) ectopic expression of dominant-negative mastermind like-1 (dnMaml), a known inhibitor of Notch/RBPJ-mediated transcriptional activation, in mature mouse kidney epithelial cells, (ii) conditional genetic inactivation of Notch1 and Notch2 in the mature kidney epithelial cells of mice starting at three weeks of age, and (iii) conditional genetic inactivation of the down-stream Notch-signaling target Hes1 in the renal epithelium starting at three weeks of age.

Results: Inhibition of Notch signaling in the adult mouse kidneys resulted in a significantly decreased urine concentrating capacity when compared with that of control littermates in all three mouse models. Induction of dnMaml expression in the renal epithelia of three week old mice for three days reduced expression of *Nrarp*, a gene known to be transcriptionally regulated by Notch signaling, along with principal cell specific genes such as *Aqp2* and *Avpr2*, while expression of intercalated cell specific genes, *Foxi1* and *Slc4a9*, were increased. Genetic inactivation of Notch1 and Notch2 or Hes1 in the mature epithelial cells of the mouse kidneys resulted in reduced number of principal cells and increased number of intercalated-like cells as determined by immunohistochemistry.

Conclusions: Notch signaling is required for maintaining mature principal cells in a functional state by ensuring continued expression of critical principal cell specific genes, and repressing essential intercalated cell specific genes. Lineage tracing of principal cells during kidney development revealed that inhibition of Notch signaling causes principal into intercalated-like cell transdifferentiation. Similarly, Notch signaling appears to prevent transdifferentiation of mature principal cells in the adult mouse kidneys.

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SA-PO551

Human Missense Variants in Integrin-Linked Kinase Abrogate Renal Branching Morphogenesis by Disrupting MAPK Signaling Dana Kablawi,[1] Kirsten Y. Renkema,[2] Nine V. Knoers,[2] Norman D. Rosenblum.[1] *[1]The Hospital for Sick Children, Toronto, ON, Canada; [2]University Medical Center Utrecht, Utrecht, Netherlands.*

Background: Integrin-linked kinase (ILK) is required for murine renal branching morphogenesis and acts via p38MAPK/ATF2 signaling. Yet, its contribution to human congenital kidney-urinary tract anomalies (CAKUT) is undefined. The objective of these studies is to identify *ILK* variants in CAKUT and define their functional consequences.

Methods: Patients with CAKUT were analyzed by exome sequencing. Variants were verified by Sanger sequencing. Cells stably expressing human *ILK* variants were generated by lentivirus transduction and clonal selection. Signaling pathway activity and transcription factor activation were analyzed using immunoblotting. Subcellular localization of transcription factors was imaged by immunofluorescence. Gene expression and pathway enrichment were assayed using whole genome microarray and quantitative (q) PCR. *Ex vivo* assays were conducted using lentivirus-based transduction of mouse embryonic kidney explants.

Results: Exome sequencing of 208 CAKUT candidate genes in 453 probands with CAKUT identified ILK^{T173I} (1 proband) and ILK^{N22S} (4 probands), both of which are missense variants in ILK ankyrin repeat domains. Stimulation of mIMCD3 cells stably expressing ILK^{T173I} (versus ILK^{WT}) with EGF (15 minutes) revealed increased phosphorylation of each of JNK, C-Jun and AKT ($P<0.05$, n=3), as well as increased nuclear translocation of P-C-Jun ($P<0.05$, n=3). *c-Jun* RNA, a JNK signaling target, was increased 2.6-fold ($P<0.05$, n=6, qPCR). Pathway enrichment analysis of genome-wide RNA expression after 1 hour of EGF stimulation revealed dysregulation of AKT/MTOR target genes (n=3). In contrast to ILK^{T173I}, EGF mediated stimulation of mIMCD3 cells expressing ILK^{N22S} increased ERK phosphorylation ($P<0.05$, n=3). Treatment of E12.5 kidney explants with lentivirus expressing ILK^{T173I} resulted in hypoplasia with a 45% decrease in ureteric bud (UB) tip number ($P< 0.025$, n=9 kidneys). Treatment with lentivirus expressing ILK^{N22S} generated a spectrum of phenotypes including reduced number of UB tips (n=6 kidneys, $P<0.009$), increased (1.5-fold) number of UB tips (n=6 kidneys, $P<0.048$), and ectopic branching of the main ureter (n=3 kidneys).

Conclusions: ILK ankyrin-repeat domain missense variants associated with human CAKUT cause distinct abnormalities in MAPK signaling and variable patterns of disrupted kidney explant development.

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SA-PO552

Loss of Zeb2 in Ureteric Mesenchymal Cells Causes CAKUT Phenotype in Mice Sudhir Kumar, Richa Sharma, Xueping Fan, Weining Lu. *Boston University Medical Center, Boston, MA.*

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are major causes of renal failure in children. ZEB2 is a SMAD-interacting transcriptional factor that causes Mowat-Wilson Syndrome (MWS), a congenital disorder with an increased risk for CAKUT phenotype including hydroureter and hydronephrosis. However, no defined underlying cellular and molecular mechanisms for hydroureter and hydronephrosis in MWS have been established.

Methods: We generated *Zeb2* ureteric mesenchyme-specific conditional knockout mice (*Zeb2* cKO) by crossing *Zeb2* flox mice with *Tbx18Cre* mice. Urinary tract phenotypes in *Zeb2* cKO mice and their wild-type littermate controls were analyzed by gross and histological examination. ZEB2 expression in developing ureter was analyzed by immunofluorescence staining. Ureteral cellular and molecular phenotypes were studied using cell specific markers, apoptosis assay, and anti-SMAD antibodies.

Results: We found that ZEB2 is highly expressed in the ureteric mesenchymal cells and is co-localized with TBX18 in developing mouse ureter at E14.5. Deletion of *Zeb2* flox allele using *Tbx18Cre* mice leads to hydroureter and hydronephrosis phenotype in E18.5 embryos. At E16.5, *Zeb2* cKO mice showed reduced ureteral smooth muscle cells as well as abnormal urothelium morphology compared to wildtype littermates. Immunohistochemical analysis further revealed a downregulation of TBX18 expression in the ureteric mesenchyme in E14.5 *Zeb2* cKO mice, indicating abnormal ureteric mesenchyme development. We also found increased apoptosis and upregulation of pSMAD1/5/8 expression in ureteric mesenchyme cells in E14.5 *Zeb2* cKO, suggesting loss of ureteric mesenchymal cells and abnormal SMAD signaling in developing ureter.

Conclusions: ZEB2 is required for normal ureteric mesenchymal cell development. Loss of *Zeb2* in ureteric mesenchymal cells leads to reduced TBX18+ mesenchymal cells

and abnormal ureteral smooth muscle formation due to aberrant SMAD signaling, which eventually causes hydroureter and hydronephrosis in *Zeb2* cKO mice.

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SA-PO553

A Morphogenetic Study of Murine Renal Collecting System Based on 3D Visualization Ling Gu,[1] Jie Zhang,[1] Shi-Jie Chang,[2] Kaiyue Wang,[1] Jesper S. Thomsen,[3] Arne A. Andreasen,[3] Erik I. Christensen,[3] Xiao-Yue Zhai.[1] *[1]Department of Histology and Embryology, China Medical University, Shenyang, China; [2]Department of Biomedical Engineering, China Medical University, Shenyang, China; [3]Department of Biomedicine – Anatomy, Aarhus University, Aarhus, Denmark.*

Background: The iterative bifid branching of ureteric bud (UB) lays basis for formation of the collecting system (CS), and for generation of nephrons as the tip of the UB induces nephrogenesis at the nephrogenic zone (NZ). A low nephron number is associated with adult defect, such as hypertension. Therefore, a full knowledge of the morphogenesis and the connections of CS with nephrons is crucial to understand the development of such adult defects. The present study provides a spatial morphologic transformation of UB branching into adult CS based on 3D reconstruction.

Methods: Serial paraffin and epoxy sections of 3 mouse kidneys from each of different embryonic (E) and postnatal (P) days were prepared. The branching paths of UB at E14.5, E17.5, and CS from P7 and adult kidneys were traced on aligned micrographs using custom-made software. The architecture of adult CS was first established for comparison of UB branching trees.

Results: 1) The morphology of cortical CS was asymmetric. One ICT rapidly bended down into the juxta-medullary cortex from the main CD at the middle to superficial cortex forming an abrupt arcade. The other ICT went straight outwards to the superficial cortex and ran a certain distance beneath the renal capsule. 2) The connection of nephrons with CS in a specific temporospatial order. The earlier formed nephrons connected with the arcade in distal to proximal order along the trunk, while the later formed nephrons, connected with the ICT in proximal to distal order. 3) The association of UB branching morphogenesis with nephrogenesis was established. By E14.5 when the first mature nephrons appeared, the UB bifurcations reached up to 7 to 10 cycles, laying basis for adult CD formation. With time until P3, the tips at NZ increased in number, consistently inducing nephrogenesis instead of branching.

Conclusions: The CS is formed by more than one type of branching: 1) the traditional bifurcation for formation of CD; 2) lateral branching along the arcade for formation of the ICT and connecting segments; and 3) sprouting for formation of the CNT connecting directly with individual nephrons. This suggests that the number of the nephrons is closely associated not only to the iterative branching, but also to the formation of lateral and sprouting branches, the latter mainly occurred near NZ.

Funding: Government Support - Non-U.S.

SA-PO554

Loss of the Planar Cell Polarity Gene Fuzzy Leads to Defective Branching Morphogenesis and Cystogenesis in Embryonic Kidneys Yanran Wang,[1,2] Elena Torban.[1,2] *[1]Division of Experimental Medicine, Department of Medicine, McGill University, Montreal, QC, Canada; [2]McGill University Health Centre, Montreal, QC, Canada.*

Background: The PCP effector gene Fuzzy is essential for organogenesis. In Drosophila, it is critical for establishing planar cell polarity via controlling the actin cytoskeleton. In vertebrates, the role of Fuzzy is less clear, but it appears to control some aspects of trafficking protein cargos to the basal body. Fuzzy has been designated as a Ciliogenesis and PCP effector (CPLANE) gene. Disruption of Fuzzy in mice results in severe malformations, including neural tube defects, polydactyly, facial defects andetc, suggesting its participation in various signaling pathways.

Methods: To study kidney development, homozygous E14.5 and E16.5 embryos carrying a gene-trap Fuzzy mutation and wildtype littermates were harvested for immunofluorescense and in situ hybridization (ISH) studies.

Results: Fuzzy$^{-/-}$ mutants exhibited profound renal hypoplasia at E14.5. Although Six2-positive progenitor cells and their differentiation into early nephron structures were unaffected, the number of the ureteric buds was decreased to 50% of control. This was accompanied by a ~ 50% reduction in the number of glomeruli without a decrease in the number of podocytes per glomerulus. ISH studies indicated that GDNF expression was unaffected, but c-Ret expression was upregulated in Fuzzy$^{-/-}$ mutants. The expression of the Hippo kinase pathway effector Yap was decreased significantly in ureteric buds. At E16.5, Fuzzy$^{-/-}$ mutants exhibited glomerular cysts in the medullary layer, manifested by the dilation of Bowman's capsule. E16.5 Fuzzy$^{-/-}$ mutants also developed proximal tubular cysts but collecting ducts remained intact.

Conclusions: Impaired UB branching is a major cause of renal hypoplasia in E14.5 Fuzzy$^{-/-}$ mice and is associated with increased Ret signaling and a decrease in Yap expression in the UBs. This phenotype is reminiscent of the phenotype of Yap mutants, suggesting that Fuzzy may participate in Hippo signaling pathway. The mechanisms of glomerular and proximal tubular cysts formation are being investigated.

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SA-PO555

Robo2 Mediated Raldh2 Signaling in Bladder Mesenchyme Is Crucial for Ureter Development Qinggang Li,[2] Xiangmei Chen.[1] *[1]Chinese PLA General Hospital, Beijing, China; [2]Chinese PLA general Hospital, Beijing, China.*

Background: Congenital anomalies of urinary-tract are a significant cause of morbidity in infancy, many of the congenital anomalies are linked to ureter development. Despite the frequent occurrence of the ureter abnormalities, little is known about their cause that normally control ureter-bladder development. Robo2 loss can cause congenital abnormalities of the urinary-tract, with ureter defect and vesicoureteral reflux. While mechanistic aspects of this pathway are increasingly well defined, it remains unclear how Robo2 modulation impacts ureter development.

Methods: We performed in immunofluorescence on mouse embryonic whole mount kidney and section with E-cadherin, and Co-IP and Mass spectrometry analysis on mouse embryonic kidneys and urogenital tracts with a specific ROBO2 polyclonal antibody. Laser scanning confocal microscopy and real time RT-PCR were used to observe expression of Robo2 in frozen section and urogenital tract samples. Kidney explants dissected from E12.5 embryo were cultured in DMEM/10%FCS.

Results: Robo2 is expressed in common nephric duct (CND) and primitive bladder, and interact with Raldh2. Moreover, the ureter elongation is depend on signaling in bladder, not kidney morphogenesis, reveals how Robo2 impact ureter cell fate decisions. Delayed apoptosis due to failure of CND fusion with primitive bladder in Robo2$^{-/-}$embryo, resulting in the abnormal ureter remain connected to CND. Analysis of Robo2$^{-/-}$ mice reveals hydronephrosis and defective ureter development by the CND remodeling defects and delayed fusion with primitive bladder. Using retinoic acid rescued ureter anomalies in Robo2$^{-/-}$embryo.

Conclusions: We found Robo2 impacts CND migration and fusion with primitive bladder via its novel protein partner Raldh2 signaling, this may have relevance for diverse disease conditions, associated with altered signaling from primitive bladder.

Funding: Government Support - Non-U.S.

SA-PO556

Tubular Immaturity Underlies Erythropoietin-Deficiency Anemia of Prematurity Nariaki Asada. *Keio University School of Medicine, Tokyo, Japan.*

Background: Kidneys are physiologically hypoxic and produce erythropoietin (EPO) after birth by sensitively detecting oxygen levels. Preterm neonates, especially those less than 32 weeks of gestation, develop EPO-deficiency anemia, known as anemia of prematurity (AOP). In AOP, immature kidneys cannot produce sufficient EPO in response to anemia even when renal injuries are absent. It remains unclear how kidneys start to produce EPO after birth.

Methods: Neonatal mice were used as AOP model since they are physiologically born premature. To confirm factors associated with AOP in human, correlation of hemoglobin levels with fraction excretion of sodium (FENa), urinary creatinine to beta 2-microglobulin ratio (uCr/uβ2MG), serum creatinine, birth weight, or gestational age were evaluated in prospective observational study of 18 preterm patients at age 14 days and 21 days.

Results: Mice at postnatal day 14 (P14) showed physiological anemia and elevated renal EPO production. Mice at P7, however, showed AOP-like deficient renal EPO production regardless of the same degree of anemia. Pimonidazole staining showed that kidneys at P14 were more hypoxic than those at P7. There were no difference in the expression of αSMA or the density of peritubular capillaries. The expression of transporters NHE3, NKCC2, NCC, αENaC, and Megalin were significantly low at P7 compared to P14. Suppression of tubular reabsorption by losartan or short-term use of diuretics decreased EPO, pimonidazole-positive area, and hematocrit at P14. Upregulating reabsorption by long-term use of diuretics increased the expression of sodium transporters, EPO production, pimonidazole-positive hypoxic area, and hematocrit at P7, suggesting that low tubular oxygen consumption for reabsorption is a cause of deficient EPO production at P7. Prolyl hydroxyrase inhibitor (PHDi) also ameliorated AOP. In preterm patients, hemoglobin levels were correlated with FENa and uCr/uβ2MG, but not with serum creatinine, birth weight, or gestational age.

Conclusions: AOP is caused by insufficient hypoxic environment due to low oxygen consumption by immature tubules. Kidneys start to produce EPO as tubules mature and renal oxygen levels decrease. PHDi can be a therapeutic option for AOP in preterm patients.

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SA-PO557

DNA Hydroxymethylation Is Altered by Maternal Nutrient Restriction in Rat Kidney Mariko Hida,[1] Mayumi Oda,[2] Midori Awazu.[1] *[1]Department of Pediatrics, Keio University School of Medicine, Tokyo, Japan; [2]Department of Systems Medicine, Keio University School of Medicine, Tokyo, Japan.*

Background: DNA hydroxymethylation is an epigenetic modification that oxidizes 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC). Increasing evidence suggests that the role of DNA hydroxymethylation is different from DNA methylation in various organs but that in the kidney is unclear. We previously showed that the global DNA methylation was reduced and the gene-specific DNA methylation was altered in kidney of rat embryos from nutrient-restricted mothers. In the present study, we investigated DNA hydroxymethylation in the same model.

Methods: The kidneys of embryonic day 18 fetuses (E18) from dams given food ad libitum (CON) and those subjected to 50% food restriction throughout pregnancy (NR) were examined (n=3 litters for each group). Global hydroxymethylation levels were assessed by ELISA. The local 5hmC detection by hMe-Seal method followed by high throughput sequencing (5hmC-seq) was used to analyze the changes in hydroxymethylation patterns by NR. 5hmC enriched regions (5hmC peaks) were identified using a peak finding algorithm (MACS1.4) and then annotated to the nearest genes.

Results: Global hydroxymethylation levels in E18 metanephroi was significantly increased in NR vs CON (0.31±0.02% vs 0.20±0.03%). On the other hand, the number of 5hmC peaks detected by 5hmC-seq analysis was smaller in NR; 582 peaks in CON only and169 peaks in NR only. There were 362 peaks common in CON and NR. Annotated genes present in these regions were 581 and 169 in CON and NR, respectively. Most of the identified 5hmC sites reside in intergenic regions, followed by introns, while the sites near the transcriptional start sites were few. Among genes with CON-specific hydroxymethylated peaks, some genes were related to the kidney development (Amph1, Glcci, Gli3, Igfbp3, Cdh11, FGF10, Ihh, and Agtr1a, in descending order of peak score). Genes with NR-specific hydroxymethylated peaks also had a few kidney development genes (Edn2, Igfbp3, and Fst). Protein expression of Amph1 and Cdh11 was upregulated in NR. The transcript level of Agtr1a assessed by PCR was not different between CON and NR.

Conclusions: Maternal nutrient restriction increased the global DNA hydroxymethylation and changed the local hydroxymethylation in genes involved in kidney development.

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SA-PO558

Intrauterine Growth Restriction (IUGR) by Maternal Protein Undernutrition Disrupts the Transcriptional Networks of Energy Metabolism in Nephron Progenitors Francesca Edgington-Giordano, Hongbing Liu, Sylvia Hilliard, Jiao Liu, Yuwen Li, Renfang Song, Zubaida R. Saifudeen, Samir S. El-Dahr. *Tulane University School of Medicine, New Orleans, LA.*

Background: Fetal IUGR from maternal undernutrition is linked to reduced nephron endowment, resulting in suboptimal renal function and a predisposition towards hypertension and chronic kidney disease. Using an established protein-deficiency mouse model of IUGR, we examined the impact of maternal undernutrition on nephron progenitor cell (NPC) maintenance and gene expression.

Methods: CD1 mice were fed isocaloric low-protein (6%) or control (20% protein) diets 3 weeks prior to timed mating. Kidneys were harvested at P0 to assess NPC pool size (Six2, NCAM) and differentiating nephrons (NCAM, Lhx1, WT1) by IF. RNA-Seq was performed on RNA isolated from native NPC of P0 kidneys (n=3), and data analyzed by IPA and GO-Panther. Bonferroni correction was applied.

Results: Significantly reduced ($p<0.0001$) P0 body and kidney weight were observed. However, kidney/body weight ratios are not significantly changed in 6% vs 20% pups. 6% pups show diminished nephrogenic zone, a smaller Six2+ NPC pool and nascent nephron deficit ($p<0.0001$, n=4). Increased immunostaining for p53, phospho-p38 and phospho-ATF2 indicate activation of fetal cellular response to maternal nutritional stress. Mitosis marker phospho-histone H3 staining in the NPC is decreased. RNASeq data show 1,694 upregulated and 2,114 down-regulated genes (1.5-fold cut-off). Top gene enrichment in Biological Processes include RNA splicing/metabolism, cellular metabolic process and cellular component biogenesis. Highest enrichment of genes in Cellular Component was observed for ribonucleoprotein complex and mitochondrion. Energy metabolism categories (EIF2 signaling, Glycolysis, mTOR, eIF4/p70S6K) top the canonical pathways. Expression of renewing NPC markers Cited1, Six2 and Meox are unchanged. Differentiation/induction marker Wnt4 expression was unchanged, however Lhx1 and Jag1 expression decreased more than 2-fold. ISH show decrease in Bmp7, Wnt11 and Wnt9b mRNA.

Conclusions: Pups from undernourished moms demonstrate decreased NPC pool and nascent nephrons. Cellular processes and metabolism are the profoundly altered at the transcriptional level in the NPC. For the long-term, this mouse is an excellent model to analyze how maternal undernutrition impacts offspring kidney development and function.

Funding: NIDDK Support

SA-PO559

The Quantitative and Qualitative Characteristics of Glomerular Basement Membrane in Rat Kidney Development and Glomerulonephritis Liang Fei,[1,2] Dedong Kang,[2] Ping Lan,[3,2] Shinya Nagasaka,[2] Akira Shimizu.[2] *[1]Department of Histology and Embryology, China medical university, Shenyang, China; [2]Department of Analytic Human Pathology, Nippon Medical School, Tokyo, Japan; [3]First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.*

Background: The renal glomerulus is filtrate function of primary urine through glomerular tuft, which consists of podocytes, glomerular basement membrane (GBM) and endothelial cells. Mature GBM is mainly composed of α3/α4/α5 chain of type IV collagen (IV).

Methods: In order to clarify the maturation process of renal glomerular tuft during renal development, and injured and recovery of glomerular tuft from injuries in glomerulonephritis (GN), we evaluated the pathology and α chains (IV) of GBM and glomerular capillaries of 1-day-old and 10-week-old rat kidneys, as well as experimental Thy-1 GN on day 7 and 10 (n=3) and clinical biopsy cases of membranoprolferative GN (n=7).

Results: In the development, glomerular capillaries with endothelial cells migrated from interstitium into the cleft of S-shape body to form the glomerulus. The basement membrane (BM) of S-shape nephron and glomerular capillaries formed GBM, which were mainly composed by α1/α1/α2 chain (IV) in S-shape stage. In the early capillary loop stage of glomerulus, the cleft of the S-shaped body was occupied by a primitive capillary network. GBM was consisted of two BMs, such as continuous GBM of primitive podocytes with α3/α4/α5 chain (IV) and discontinuous capillary BM with α1/α1/α2 chain (IV). At late capillary loop stage of glomerulus, two layers of GBM such as continuous podocytes'BM and discontinuous or continuous capillary BM change to one layer of GBM with only α3/α4/α5 chain (IV). In early to late capillary stage, formation of foot processes and fenestrated structures was found in podocytes and endothelial cells, respectively. In experimental and biopsy cases of GN, injured glomerular tuft showed double contour of GBM, α3/α4/α5 chain (IV) of podocytes'GBM and α1/α1/α2 chain (IV) of capillary BM, with irregular effacement of foot processes of podocytes and irregular loss of fenestra of endothelial cells, resembling the pathology of glomerular tuft of early capillary stage. However, after recovery, glomerular tuft showed one layer of GBM with α3/α4/α5 chain (IV) and mature podocytes and endothelial cells.

Conclusions: Our findings suggest that injured glomerular tuft was accompanied by quantitative and qualitative alterations of GBM in GN, and recovery of glomerular tuft after injuries may be following similar processes in the development of glomerular tuft.

SA-PO560

RP-103 Controls WBC Cystine Levels and Promotes Growth in Treatment-Naive Patients ≤6 Years with Nephropathic Cystinosis Craig B. Langman,[3] Juliana C. Ferreira,[1] Kyleen Young,[2] Maria Helena Vaisbich.[4] *[1]Instituto da Criança do HCFMUSP, São Paulo, Brazil; [2]Lurie Children's Hospital Chicago, Chicago, IL; [3]Feinberg School of Medicine, Northwestern Univ., Chicago, IL; [4]Nephrology, Sao Paulo University Medical School, Sao Paulo, Brazil.*

Background: Nephropathic Cystinosis (NC) is a recessive disease in which the lysosomal cystine exporter is deficient, intralysomal cystine accumulates, and the biomarker, WBC ½ cystine/mg protein is > 1 nmol. Cysteamine bitartrate (Cys-Bi), is used to lower levels to <1 nmol. Previous trials of RP-103 have converted patients from an every 6h form of Cys-bi to this every 12h formulation.

Methods: We conducted a long-term, prospective, controlled, open-label study of RP-103 in 17 Cys-Bi naive patients with NC in the US & Brazil. The RP103 starting dose was gradually escalated (10%, every 2 weeks) until the WBC ½ cystine level was <1 nmol. We evaluated height and weight at each visit, and safety (incidence of TEAEs and SAEs). Data reported (mean±SD) below will be for 15/17 subjects ≤ 6y of age.

Results: Age was 2.2±0.9y, range 1.04–4.53y. Ten were ♂. Prior to RP-103, the WBC cystine concentration was 3.1± 2.9 nmol ½ cystine/mg protein. At each subsequent time, the mean concentration was < than at Day 1: 2.2±3, Week(wk) 2; 1.1 ±1.3 wk 12; 0.73±0.64, Month(m) 18. By end of study, 76.9% of subjects had a WBC cystine <1nmol. On Day 1, standing height was in the 2.59 ± 4.00 %ile of the reference population, and increased to 3.27±5.69 at wk 2, 6.95±10.88 at wk 12, and 55.36±43.88 %ile at m18. Z-scores for height were –3.16±1.55 at Day 1 and increased to 0.11±1.96 at study end. On Day 1, weight was in the 3.46 ±11.13 %ile and increased at study exit to 32.85±35.58 %ile. All 17 subjects in the Safety Population had at least 1 TEAE, and 8 had at least 1 TEAE considered related to the study drug. Twelve had an SAE, 5 (29.4%) had a TEAE ≥ Grade 3, and 1 (5.9%) died (unrelated to study drug). No TEAEs led to permanent discontinuation of study drug.

Conclusions: RP-103 safely and effectively lowered the biomarker to target (<1 nmol) in young Cys-Bi naive patients with NC. Linear Growth and body mass increased into the normal range for age (z-score) for those ≤ 6y. Thus, Cys-Bi naive patients ≤ 6y with nephropathic cystinosis may safely and efficiently be started on cystine-reduction therapy with RP-103 (Procysbi).

Funding: Commercial Support - Horizon Pharmaceuticals; Raptor Pharmaceuticals

SA-PO561

ATP-Binding Cassette A–13 (ABCA13) Is a Candidate Gene for Familial FSGS Gentzon Hall,[3,5] Megan Chryst-ladd,[1] Liming Wang,[3] Gina E. Kovalik,[2] Guanghong Wu,[4] Brandon M. Lane,[2] Eugene C. Kovalik,[3] Robert F. Spurney,[3] Rasheed A. Gbadegesin.[3] *[1]Duke Molecular Physiology Institute, Durham, NC; [2]Duke University, Durham, NC; [3]Duke University Medical Center, Durham, NC; [4]Duke university, Durham, NC; [5]Duke Molecular Physiology Institute, Durham, NC.*

Background: FSGS is a major cause of ESKD that is characterized by steroid-resistant nephrotic syndrome, rapid progression to ESKD, focal scarring of the glomerular capillary tuft and effacement of podocyte foot processes. Characteristic features of FSGS-associated podocytopathy include 1.) dysregulation of actin cytoskeletal dynamics and dysmotility, 2.) inappropriate cell cycle re-entry and hyperproliferation, and 3.) apoptosis. We carried out whole exome sequencing (WES) on a family with FSGS. Three variants segregated with disease in the family. Of the three variants, only the change in *ABCA13* (p.2330fsX2354) is a novel, loss-of-function (truncating) variant. *ABCA13* is the largest member of a family of 13 transport proteins involved in cellular drug and lipid efflux. Given the established role of *ABCA1* deficiency in cholesterol-induced podocyte injury in diabetic nephropathy, we hypothesized that *ABCA13* knockdown (KD) in immortalized human podocytes may induce dysfunction via a mechanism that involves impaired

cholesterol efflux. Futher, given the known role of cholesterol as an activator of Rac1 signaling, we postulated that *ABCA13* KD may induce inappropriate activation of Rac1 and promote podocyte dysmotility through the Rac1-mediated upregulation of JNK/paxillin signaling.

Methods: Whole-exome sequencing, direct sequencing, lentivirus-mediated siRNA gene silencing, scratch wound healing assays, and immunoblotting.

Results: *ABCA13* KD induced an upregulation of JNK activation ($p < 0.01$) and an increase in Rac1 membrane recruitment in podocytes. Additionally, cell migration in *ABCA13* KD podocytes was significantly increased ($p < 0.01$) relative to scramble siRNA controls. This enhanced podocyte motility was significantly attenuated by the cholesterol extracting agent methyl-b-cyclodextrin ($p = 0.03$) and the JNK inhibitor tanzasertib ($p < 0.01$). Additionally, *ABCA13* KD enhanced paxillin phosphorylation at the JNK target site Ser178 in podocytes.

Conclusions: *ABCA13* KD enhances podocyte motility possibly through the dysregulation of Rac1/JNK/Paxillin signaling axis. These data suggest that: 1. Rac1/JNK/Paxillin signaling may play an important role in the pathogenesis of FSGS, and that 2. targeting this signaling pathway may be a novel therapeutic approach for the treatment of FSGS.

Funding: NIDDK Support, Private Foundation Support

SA-PO562

A Homozygous Missense Mutation in VWA2, Encoding an Interactor of the Fraser-Complex, as a Likely Cause of Vesico-Ureteral Reflux Shirlee Shril,[1] Amelie van der Ven,[1] Birgit Kobbe,[2] Stefan Kohl,[1] Hans-Martin Pogoda,[2] Hadas Ityel,[1] Jing Chen,[1] Daw-yang Hwang,[1] Eugen Widmeier,[1] Dervla M. Connaughton,[1] Nina Mann,[1] Matthias Hammerschmidt,[2] Raimund Wagener,[2] Friedhelm Hildebrandt.[1] *[1]Boston Children's Hospital, Boston, MA; [2]University of Cologne, Cologne, Germany.*

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) are the most common cause of chronic kidney disease in the first 3 decades of life. About 38 monogenic causes of CAKUT are known so far, explaining <20% of CAKUT cases.

Methods: To identify additional monogenic causes of CAKUT, we performed whole exome sequencing in a consanguineous patient with CAKUT from Indian origin.

Results: We identified a homozygous missense mutation (c.1336C>T, p.Arg446Cys) in the gene *Von Willebrand factor A domain containing 2 (VWA2)*. By immunohistochemistry on kidneys of newborn mice, we show that Vwa2 and Fraser extracellular matrix complex subunit 1 (Fras1) co-localize in the nephrogenic zone of the renal cortex. There was pronounced staining for Vwa2 in the basement membrane of the UB and derivatives of the MM (comma-shaped and S-shaped bodies). By applying cell-based protein expression studies, we demonstrate that the Arg446Cys mutation decreases secretion of the VWA2 protein into the extracellular space *in vitro*: Lack of secretion is most likely due to increased intracellular aggregate formation of VWA2 secondary to the additional, unpaired cysteine residue in the mutated protein. Recombinant mutant VWA2 additionally forms disulfide-linked higher aggregates *in vitro*.

Conclusions: VWA2 is a known, direct interactor of FRAS1 of the Fraser-Complex (FC). FC-encoding genes *FRAS1*, *FREM1*, *FREM2* and interacting proteins GRIP1 and ITGA8 have previously been implicated in the pathogenesis of syndromic and isolated CAKUT phenotypes in humans (Kohl *JASN* 25, 2014). The results from *in vitro* experiments indicate a dose-dependent, gain-of-function effect of the Arg446Cys homozygous mutation in *VWA2*. *VWA2* therefore constitutes a very strong candidate in the search for novel CAKUT-causing genes.

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SA-PO563

Mutations of GAPVD1 and ANKFY1 Are Novel Causes of Nephrotic Syndrome Tobias F. Hermle,[1] Ronen Schneider,[1] David Schapiro,[1] Sherif M. El desoky,[2] Jameela A. Kari,[2] Daniela A. Braun,[1] Friedhelm Hildebrandt.[1] *[1]Boston Children's Hospital/Harvard Medical School, Boston, MA; [2]King Abdul Aziz University Hospital, Jeddah, Saudi Arabia.*

Background: Steroid resistant nephrotic syndrome (SRNS) is a frequent cause of end-stage renal disease within the first 3 decades of life. The discovery of more than 50 different monogenic causes has helped to elucidate the pathogenesis of SRNS.

Methods: To identify novel monogenic causes of SRNS we performed homozygosity mapping and whole exome sequencing (WES) in a worldwide cohort of ~600 individuals with nephrotic syndrome. Co-immunoprecipitation using HEK cells was employed to analyze protein interaction.

Results: By WES we identified two homozygous missense mutations of *GAPVD1 (*c.1240C>G, p.L414V and c.2810G>A, p.R937Q) in two patients from unrelated families with early-onset nephrotic syndrome. Both mutated amino acids are conserved to *C. intestinalis.* One patient did not respond to steroids while the other showed the unusual combination of congenital nephrotic syndrome and spontaneous remission. This has previously been observed in few alleles of *NPHS1*. The histology in both cases was characterized by mesangial hypercellularity while electron microscopy revealed podocyte foot process effacement. *GAPVD1* is a known regulator of endosomal trafficking and interacts with *RAB5*. *GAPVD1* harbors both, a GTPase activating and an inactivating domain. We further identified a mutation of *ANKFY1* (c.284G>T, p.R95L, conserved to *D. melanogaster*) in a patient with SRNS and FSGS with an affected sibling sharing the mutation. *ANKFY1* is also an interaction partner of *RAB5* and serves as a *RAB5*-effector. Western blotting revealed expression of *GAPVD1* and *ANKFY1* in a human podocyte cell line. Using co-immunoprecipation we observed physical interaction between both proteins. We further found interaction of *GAPVD1* and the slit diaphragm protein *NPHS1*. Mapping experiments suggest that both functional domains of *GAPVD1* bind to *NPHS1*.

Conclusions: We discover mutations of *GAPVD1* and *ANKFY1* as novel monogenic causes of nephrotic syndrome. Interestingly, both proteins interact with each other and *RAB5*. *GAPVD1* further interacts with *NPHS1,* mutations in which cause SRNS.

Funding: Other NIH Support - DK076683, Government Support - Non-U.S.

SA-PO564

Whole Exome Sequencing Identifies a Monogenic Cause in ~43% of Families with Hypertension from Midaortic Syndrome Jillian K. Warejko,[1] Markus Schueler,[1] Asaf Vivante,[1] Jennifer A. Lawson,[1] Weizhen Tan,[1] Ankana Daga,[1] Shirlee Shril,[1] Shrikant M. Mane,[2] Deborah R. Stein,[1] Michael A. Ferguson,[1] Friedhelm Hildebrandt.[1] *[1]Boston Children's Hospital, Boston, MA; [2]Genetics, Yale University, New Haven, CT.*

Background: Midaortic syndrome (MAS) is a cause of severe hypertension in children with narrowing of the abdominal aorta. It involves the renal vessels in >80% of cases (*Ped Nephrol* 24:2225, 2009). Treatment requires antihypertensive medications and operative or endovascular interventions. Morbidity is high with hypertensive encephalopathy, stroke, heart failure and renal dysfunction. MAS may occur as part of a genetic syndrome, such as neurofibromatosis 1. However, most cases have been considered idiopathic until now.

Methods: We hypothesized that in patients with MAS, a monogenic cause of disease may be detected in one of 38 candidate genes of syndromic or non-syndromic vasculopathies. We studied 36 individuals from 35 different families by whole exome sequencing (WES).

Results: Patients were recruited at Boston Children's Hospital from 1/2014 to 12/2016. Individuals were included in WES if MAS was diagnosed before age <25 years with evidence of narrowing of the abdominal aorta on imaging. We examined WES data for mutations in all 38 candidate genes. In 15/35 families (42.9%), we identified a causative dominant or recessive mutation. Mutations were identified in five candidate genes: *NF1* (6/15 families), *JAG1* (4/15), *ELN* (3/15), and one each for *GATA6* and *RNF213*. A total of 15 different mutations were detected, 10 of which were novel. In 2/6 families with *NF1* mutation and 1/4 families with *JAG1* mutation the appropriate diagnosis of NF or Alagille syndrome respectively, had not yet been made by clinical criteria.

Conclusions: We demonstrate that WES in combination with an *a priori* candidate gene approach can provide a conclusive molecular genetic diagnosis in a high fraction of individuals with syndromic or isolated MAS. We present data that there may be genotype/phenotype correlations between the severity of the mutation and the phenotype observed.

Funding: Other NIH Support - DK076683, DK007726-31A1

SA-PO565

New Interaction between Galectin-3 and Cystinosin Reveals a Role of Inflammation in Kidney Pathogenesis in Cystinosis Tatiana V. Lobry,[5] Roy Miller,[5] Nathalie Nevo,[2] Celine Rocca,[5] Marie-Claire Gubler,[4] Tristan Y. Montier,[1] Corinne Antignac,[3] Stephanie Cherqui.[6] *[1]Faculté de médecine de Brest, Brest, France; [2]INSERM, Paris, France; [3]Imagine Institute, Paris, France; [4]None, Paris, France; [5]UCSD, San Diego, CA; [6]University of California, San Diego, La Jolla, CA.*

Background: Cystinosis is a lysosomal storage disorder caused by mutations in the *CTNS* gene, encoding a lysosomal cystine transporter, leading to cystine accumulation. Affected individuals typically present with proximal tubulopathy, end-stage renal disease and multi-organ failure. Cystinosin has now been shown to have other cellular functions and an unbiased screen revealed a direct interaction of cystinosin with a member of the galectin's family, galectin-3. This protein is implicated in different biological processes like cell death, cell cycle and inflammation.

Methods: We generated a murine model deficient for both cystinosin and galectin-3, the $Ctns^{-/-}Gal3^{-/-}$ mice.

Results: We showed that cystinosin enhances galectin-3 lysosomal localization and degradation. In the $Ctns^{-/-}$ mouse model, expression of galectin-3 was increased compared to wild-type. Moreover, absence of galectin-3 in cystinotic mice led to a better renal function and preservation of kidney morphology. Less inflammatory cell infiltration was observed in kidney of $Ctns^{-/-}Gal3^{-/-}$ mice compared to $Ctns^{-/-}$ mice, suggesting that galectin-3 mediated inflammation is involved in progression of the kidney disease in cystinosis.

Conclusions: We are currently investigating the mechanism by which galectin-3 induces recruitment of inflammatory cells in the kidney of cystinosis and we already found an interaction between galectin-3 and a chemokine implicated in the recruitment of monocytes/macrophages. This work brings new insights on the pathogenesis of the kidney disease in cystinosis and may lead to the identification of new drug targets to delay its progression to renal failure.

Funding: NIDDK Support, Private Foundation Support

SA-PO566

Whole Exome Sequencing Identifies the Causative Mutation in 50% of Families with Adult-Onset CKD Dervla M. Connaughton,[1,2] Claire Kennedy,[2] Shirlee Shril,[1] Amelie van der Ven,[1] Hadas Ityel,[1] Nina Mann,[1] Shrikant M. Mane,[3] Mark A. Little,[4] Peter J. Conlon,[2,5] Friedhelm Hildebrandt.[1] *[1]Boston Children's Hospital, Boston, MA; [2]Department of Nephrology, Beaumont Hospital, Dublin 9, Ireland; [3]Department of Genetics, Yale University School of Medicine, New Haven, MA; [4]Trinity Health Kidney Centre, Tallaght Hospital, Dublin, Ireland; [5]Department of Medicine, Royal College of Surgeons in Ireland, Dublin 2, Ireland.*

Background: Over 250 monogenic causes of chronic kidney disease (CKD) have been identified (Nat Rev Nephrol 12:133, 2016), mostly in pediatric populations. However, the frequency of monogenic causation in adult-onset CKD has not been extensively studied.

Methods: We conducted whole exome sequencing (WES) in 16 Irish families (27 cases) with CKD. Selection criteria were: A positive family history of CKD (n=12 families) and/or history of extra-renal disease manifestations (n=8 families). Individuals with autosomal dominant polycystic kidney disease or Alport's syndrome were excluded.

Results: WES identified a causative mutation in one of 250 known monogenic CKD genes in 50% of families (n=8/16 families, 12 individuals). Six of the 8 families had no prior diagnosis of the cause of CKD. The 8 families in whom a causative mutation was identified included nephronophthisis (n=4, *IFT140, NPHP1, BBS9, DYNC2H1*), autosomal recessive polycystic kidney disease (n=1, *PKHD1*), congenital abnormalities of the kidneys and urinary tract (n=1, *PAX2*), Lowe's syndrome (n=1, *OCRL*) and interstitial nephritis (n=1, *FAN1*). In 3 families, in whom known CKD genes were excluded, 3 different potential novel candidate genes were identified.

Conclusions: This study establish that WES can detect specific causative mutations in 50% of families with adult-onset CKD. Furthermore, WES allows the identification of novel candidate genes. WES is therefore an important diagnostic tool to establish an etiologic diagnosis in an adult-onset CKD.

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SA-PO567

The ANLNR431C FSGS Mutation Alters AKT and Rac1 Activation in Podocytes Brandon M. Lane,[1] Gentzon Hall,[2] Robert F. Spurney,[2] Megan Chryst-ladd,[1] Guanghong Wu,[1] Rasheed A. Gbadegesin.[1] *[1]Department of Pediatrics and Duke Molecular Physiology Institute, Duke University School of Medicine, Durham, NC; [2]Department of Medicine, Duke University School of Medicine, Durham, NC.*

Background: We previously reported that a heterozygous missense mutation (*R431C*) in *ANLN* caused focal and segmental glomerulosclerosis (FSGS) in a kindred with familial FSGS. Anillin has been shown to play a significant role in the regulation of cell motility and survival signaling through the phosphoinositide 3-kinase (PI-3K)/AKT pathway. We hypothesized that the *ANLN R431C* mutation may exert its pathogenic effects in FSGS by inducing aberrant PI3K/AKT pathway signaling.

Methods: Immortalized human podocyte cell lines were stably transfected with tGFP vector control, tGFP-tagged WT (ANLNWT) or mutant (ANLNR431C) constructs using a lentiviral gene delivery system. We examined the effect of the R431C mutation on cell migration, cell proliferation and apoptosis. Pharmacologic inhibitors were used to determine the role of PI3K/AKT signaling pathways in the observed podocyte phenotypes.

Results: Overexpression of $ANLN_{R431C}$ increased cell migration (p=0.002), proliferation (p=0.003), and apoptosis (p=0.0015) compared to cells overexpressing equivalent levels of $ANLN_{WT}$. Western blot analyses and Rac1 activity pulldown assays showed an increase in AKT and Rac1 activation in the $ANLN_{R431C}$-overexpressing podocytes relative to $ANLN_{WT}$-overexpressing podocytes. The increase in podocyte motility was attenuated by the mTor inhibitor rapamycin and the selective Rac1 inhibitor NSC-23766.

Conclusions: The $ANLN_{R431C}$ mutation causes dysregulation of podocyte motility and survival signaling through enhanced activation of PI3K/AKT and Rac1. Targeting PI3K/AKT and Rac1 signaling may have a role in the treatment of FSGS.

Funding: NIDDK Support

SA-PO568

Whole Exome Sequencing Identifies a Monogenic Cause of ESRD in 33% of Pediatric Kidney Transplant Patients Nina Mann,[1] Shirlee Shril,[1] Daniela A. Braun,[1] Weizhen Tan,[1] Amelie van der Ven,[1] Hadas Ityel,[1] Dervla M. Connaughton,[1] Shrikant M. Mane,[2] Kassaundra Amann,[1] Leslie D. Spaneas,[1] Khashayar Vakili,[1] Heung B. Kim,[1] Michael J. Somers,[1] Nancy M. Rodig,[1] Friedhelm Hildebrandt.[1] *[1]Boston Children's Hospital, Boston, MA; [2]Yale University, New Haven, CT.*

Background: Renal transplantation is the treatment of choice for children with end-stage renal disease (ESRD). Living donation is preferred as it leads to longer graft survival. However, it has been suggested that living related donors (LRDs) are at a higher relative risk for ESRD (Poggio, *JASN*, advance online publication, 2017). We hypothesized that LRDs may have increased genetic susceptibility to kidney disease and aimed to determine the percentage of pediatric kidney transplant patients in whom a genetic cause of ESRD can be identified.

Methods: Patients who underwent kidney transplantation at Boston Children's Hospital from 2010 to 2016 were recruited. We performed targeted gene sequencing in 11 individuals and whole exome sequencing (WES) in 49 individuals. When WES was performed, data were analyzed for variants in known and candidate ESRD genes.

Results: 60 individuals from 58 families were recruited. 37/60 (62%) patients had congenital anomalies of the kidney and urinary tract (CAKUT), 11/60 (18%) had nephrotic syndrome (NS), and 12/60 (20%) had nephronophthisis (NPHP). We identified a monogenic cause of ESRD in 19/58 (33%) families. Pathogenic mutations were identified in 16% of families with CAKUT, 60% of families with NS, and 64% of families with NPHP. One individual developed insulin-dependent diabetes post-transplantation, which was attributed to steroid use. However, we identified a heterozygous *WFS1* mutation in this patient, which can cause impaired glucose regulation and may better explain his clinical picture.

Conclusions: We detected a cause of ESRD in 33% of pediatric patients who undergo renal transplantation. Knowledge of this genetic information can have implications in decision-making for living related donor transplant ascertainment, and may also help to guide future management of transplant patients.

Funding: Other NIH Support - NIH DK088767, NIH DK086306, and NIH DK076683 to F.H.

SA-PO569

Follow Up of Patients with ADCK4 Associated Glomerulopathy and the CoQ10 Treatment Jia Rao,[4] Xiaoxiang Song,[2] Qian Shen,[3] Hong Xu.[1] *[1]Children's Hospital of Fudan university, Shanghai, China; [2]Children's hospital of Suzhou university, Suzhou, China; [3]Children's Hospital of Fudan University, Shanghai, China; [4]Renal department, Children's Hospital of Fudan university, Shanghai, China.*

Background: ADCK4 related glomerulopathy is an important differential diagnosis in adolescents with steroid resistant nephrotic syndrome (SRNS) and/or chronic kidney disease (CKD) of unknown origin. ADCK4 interacts with components of the coenzyme Q10 (CoQ10) biosynthesis pathway.

Methods: The incidence and phenotypes of patients with ADCK4 mutations were investigated in a cohort of Chinese pediatric patients with SRNS non-nephrotic proteinuria, or CKD.

Results: We identified 12 patients from 11 families with bi-allelic mutations of ADCK4. Patients with ADCK4 mutations showed a largely renal-limited phenotype, with three subjects exhibiting occasional seizures, two subject exhibiting mild mental retardation, and one subject exhibiting retinitis pigmentosa. ADCK4 nephropathy presented during adolescence (median age, 7.6 years) with nephrotic-range proteinuria in 58.3% of patients and advanced CKD in 63.6% of patients at time of diagnosis. Renal biopsy specimens uniformly showed FSGS. ESRD occurred almost after age of 6 in patients with ADCK4 nephropathy. CoQ10 supplementation was administered following genetic diagnosis. Median estimated glomerular filtration rate (eGFR) just before CoQ10 administration was 120.4 (IQR 69.5-135.9) ml/min/1.73m^2, proteinuria was evaluated by the ratio of urinary protein and creatinine (Up/cre) showing 3.9 (IQR 2.4-6.0). After a median follow-up of 21 (range 12–24) months following CoQ10 administration, proteinuria was significantly decreased (median Up/cre 2.2, IQR 1.5-2.5),whereas the eGFR was preserved (median eGFR 128.0 ml/min/1.73m^2, IQR 68.2-137.4).

Conclusions: ADCK4 mutations are one of the most common causes of adolescent-onset albuminuria and/or CKD of unknownetiology in China. CoQ10 supplementation appears efficacious at reducing proteinuria, and may thereby be renoprotective.

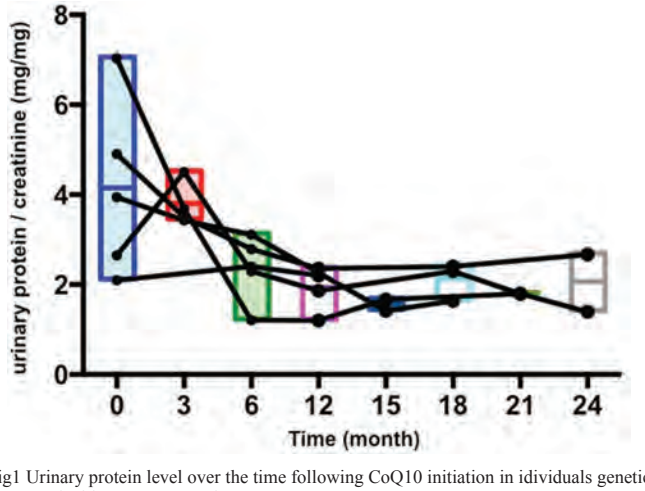


Fig1 Urinary protein level over the time following CoQ10 initiation in idividuals genetic diagnosed with ADCK4 mutation.

SA-PO570

Recessive Mutation in CD2AP Causes Focal Segmental Glomerulosclerosis in Humans and in Mice Tomoko Takano,[1] Lamine Aoudjit,[1] Cindy Baldwin,[1] Jasmine El andalousi,[2] Lina Muhtadie,[3] Indra R. Gupta.[2] *[1]Medicine, McGill University Health Centre, Montreal, QC, Canada; [2]Pediatrics, Montreal Children's Hospital, Montreal, QC, Canada; [3]Medicine, Lakeshore General Hospital, Montreal, QC, Canada.*

Background: CD2-associated protein (CD2AP) is an adaptor protein expressed in podocytes. Cd2ap$^{-/-}$ mice develop early-onset severe nephrotic syndrome and die at 6 weeks old, while Cd2ap$^{+/-}$ mice show susceptibility to insults and glomerulosclerosis at 9 months old. However, only a few patients have been described with mutations in *CD2AP*.

Methods: Whole exome sequencing (WES) was performed on genomic DNA. C57B6 mouse-derived ES cells were electroporated with Cas9, two guide sequences and a donor oligo to allow CRISPR-mediated insertion of 4 base-pairs into the *Cd2ap* gene. One ES clone with the desired insertion was used to generate chimeric mice that were crossed to C57B6 mice for germline transmission.

Results: Three siblings (2 males and 1 female) born of consanguineous parents developed FSGS in their teens and progressed to ESRD by 20 years of age. WES identified an insertion of 4 nucleotides in the *CD2AP* gene, causing a frame shift at Ser198, resulting in a stop codon (p.Ser198fs). All three siblings were homozygous for the mutation, while the unaffected father was heterozygous. Mother's DNA was not available. When heterozygous mice carrying the insertion were bred, wild-type (WT), heterozygous, and homozygous mice were born at the expected Mendelian frequency. By 2-3 weeks, homozygous mice showed heavy albuminuria, glomerulosclerosis, tubular atrophy, and interstitial leukocyte infiltration. By 4-6 weeks, histological changes worsened and were accompanied by elevated serum creatinine and BUN and hypoalbuminemia. These changes were not seen in heterozygotes or WT. Homozygous mice died at 7-8 weeks, likely from kidney failure.

Conclusions: CRISPR/Cas9 gene editing has been utilized to generate a mouse model with a recessive mutation in *Cd2ap*, p.Ser198fs that results in FSGS, nephrotic syndrome, and kidney failure in mice. The results prove that this recessive mutation in *CD2AP* is causal in human FSGS.

Funding: Government Support - Non-U.S.

SA-PO571

Acute Regulation of the Proximal Tubule Endocytic Pathway in Cell Culture and Ex-Vivo Kidney Slices Catherine J. Baty,[1] Kimberly R. Long,[2] Ora A. Weisz.[1] *[1]University of Pittsburgh, Pittsburgh, PA; [2]University of Pittsburgh School of Medicine, Pittsburgh, PA.*

Background: The proximal tubule (PT) of the kidney is highly specialized for apical endocytosis of megalin/cubilin ligands that pass through the glomerular filtration barrier into the tubule lumen. Impaired uptake of these ligands results in tubular proteinuria, which is observed in genetic diseases such as Lowe syndrome, Dent disease, and sickle cell disease. Despite the critical role of endocytosis for PT function, we know little about how the apical endocytic pathway is regulated in these cells. Studies in PT cells demonstrate that endocytosis of megalin/cubilin ligands is rapidly responsive to changes in fluid shear stress (FSS). However, currently available PT cell culture models lack many key features needed for PT function. Additionally, it is not known whether cells lining the PT *in vivo* also respond endocytically to changes in FSS.

Methods: We have established an OK cell culture system that dramatically enhances cell differentiation and more closely recapitulates the morphology and robust apical endocytic capacity of PT cells *in vivo*. We used fluorescence-based assays and confocal imaging to visualize endocytic uptake in PT cells exposed to variable levels of FSS. As a complementary approach, we optimized conditions to study endocytic uptake in *ex vivo* ultra-thin (<150 mm) murine kidney slices. C57Bl/6J mice (Jackson Laboratory) were anesthetized with isoflurane and kidneys were perfused, surgically harvested and immediately sectioned for culture and functional assays to visualize endocytosis.

Results: Our cell culture model demonstrates dramatically increased apical endocytic capacity compared with OK cells cultured under standard conditions. Additionally, endocytosis of megalin/cubilin ligands is rapidly and reversibly modulated by changes in FSS. Consistent with our studies in cell culture, endocytic uptake was enhanced in slices exposed to shear stress. Studies are in progress to assess the mechanism of FSS-mediated uptake in PT cells and whether this is impaired in diseases that result in tubular proteinuria.

Conclusions: Together, these complementary models offer a useful approach to dissect the effect of physiologically-relevant stimuli on the PT apical endocytic pathway and its disruption in genetic and other diseases that result in tubular proteinuria

Funding: NIDDK Support

SA-PO572

OXGR1 Mutations Present a Novel Cause of Nephrolithiasis Amar J. Majmundar,[1] Ankana Daga,[1] Daniela A. Braun,[1] Heon Yung Gee,[5] Shirlee Shril,[1] Jan Halbritter,[2] Shrikant M. Mane,[6] John A. Sayer,[4] Hanan Fathy,[3] Michelle A. Baum,[1] Friedhelm Hildebrandt.[1] *[1]Medicine, Div Nephrology, Boston Children's Hospital, Boston, MA; [2]University Clinic Leipzig, Leipzig, Germany; [3]El Shatty Children's Hospital, Alexandria, Egypt; [4]Newcastle University, Newcastle, United Kingdom; [5]Yonsei University College of Medicine, Boston, Republic of Korea; [6]Yale University School of Medicine, Yale Center For Mendelian Genomics, New Haven, CT.*

Background: Nephrolithiasis (NL) affects 1 in 11 individuals worldwide and causes significant morbidity and cost including surgical intervention. There are >30 genes, for which causative mutations have been identified in 11% of adult and 17-20% of pediatric NL cases (Halbritter *JASN* 26:543, 2015; Braun c*JASN* 11:664, 2016). Identifying novel NL genes can reveal new pathogenic mechanisms.

Methods: We employed whole exome sequencing (WES) to identify novel genes in familial NL cases.

Results: By WES, we identified a heterozygous missense variant (c.371T>G, p.L124R) in the gene *OXGR1* that segregated in 4 affected children and 1 affected mother from an Egyptian family with an autosomal dominant inheritance pattern of calcium oxalate containing NL and/or nephrocalcinosis (NC). *OXGR1* encodes oxoglutarate receptor 1, a G-protein coupled receptor (GPCR) that is expressed in the distal nephron and promotes urinary alkalinization (Tokonami *JCI* 123:3166, 2013). The affected amino acid residue is conserved through vertebrate orthologues and in 72% of 300 human GPCR sequences. The predicted protein change showed strong SIFT and PolyPhen-2 scores. In the ExAC Exome Database, the allele is not found in the homozygous state and found once heterozygously in 60,632 individuals. Targeted sequencing of *OXGR1* in 599 additional families with calcium oxalate containing NL and/or NC identified 3 additional alleles (c.649T>C, p.C217R; c.697A>C, p.S233R; c.860C>T, p.S287F) in 4 additional families (0.8% of cohort).

Conclusions: We identified *OXGR1* mutations as novel monogenic cause of NL. As *OXGR1* is implicated in urine alkalinization, further study of the disease mechanisms may provide insight into novel therapeutic options for NL.

Funding: NIDDK Support, Other NIH Support - NIH DK086306, NIH T32-AR053461-04

SA-PO573

TBC1D8B Mutations Are a Novel Cause of Nephrotic Syndrome Ronen Schneider,[4] Tobias F. Hermle,[3] David Schapiro,[1] Afig Berdeli,[5] Reyner F. Loza,[6] Daniela A. Braun,[2] Friedhelm Hildebrandt.[1] *[1]Boston Children's Hospital, Brookline, MA; [2]Boston Children's Hospital, HMS, Boston, MA; [3]Boston Children's Hospital/Harvard Medical School, Boston, MA; [4]Nephrology, Boston Childrens Hospital, Boston, MA; [5]Ege University Medical Faculty, Izmir, Turkey; [6]Cayetano Heredia Hospital, Los Olivos, Peru.*

Background: Nephrotic Syndrome (NS) is the second most frequent cause of end-stage renal disease in the first 3 decades of life. RAB proteins are regulators of endocytosis, which is an important feature of podocyte function. Identification of 50 monogenic genes that if mutated cause NS, has rendered first insights into disease mechanisms of NS. To date no monogenic mutations affecting RAB proteins or related proteins have been implicated in the pathomechanism of NS.

Methods: To identify novel monogenic causes of NS we combined homozygosity mapping with whole exome sequencing (WES) in a worldwide cohort of ~600 individuals with NS.

Results: In patient B931 with steroid resistant NS (SRNS) and FSGS, who presented at the age of 9 years, we detected a hemizygous mutation in the X-chromosomal gene *TBC1D8B* (c.2338A>T; p.Thr780Ser). Thr780 is conserved since *D. Rerio*. In patient A2563 who presented with steroid sensitive NS (SSNS) at the age of 7 years, and had minimal change disease on renal biopsy, we detected a hemizygous *TBC1D8B* mutation (c.190C>T; p.Arg64Cys). Arg64 is highly conserved since *S. Cerevisiae*. Both *TBC1D8B* mutations are predicted to be disease causing by SIFT, MutaTaster and PolyPhen2 software programs. Both variants are not present hemizygously in the ExAC database. The yeast orthologue for *TBC1D8B*, *Msb3*, has GTPase Activating Protein (GAP) activity for RAB proteins, which play a role in the endocytic pathway (Lachmann, Mol Biol Cell, 23: 2516, 2012). By Western blot and gene specific siRNA knockdown we show that TBC1D8B is expressed in a human podocyte cell line. By Co-IP studies we show that RAB5, a key regulator of endocytic trafficking, interacts with TBC1D8B protein when overexpressed in human HEK cells. TBC1D8B also interacts with endogenous RAB5. In human podocytes TBC1D8B localizes to vesicles but does not co-localize with RAB5, RAB7, or RAB11.

Conclusions: We here identify recessive mutations of *TBC1D8B* as a likely novel monogenic cause of nephrotic syndrome. Interaction with RAB5 without co-localization of both proteins suggests that another RAB protein may be the primary target of TBC1D8B. Further functional studies will shed light on the pathomechanism of TBC1D8B loss-of-function in NS.

Funding: Other NIH Support - NIH DK076683 to Friedhelm Hildebrandt

SA-PO574

A Rare Kidney Disease Family with CCDC114 Mutation and Cilia Xiangmei Chen. *PLA Genaral Hospital, Beijing, China.*

Background: Ciliopathies is a group of diseases characteriaed by dysfunction of cilia and patients with ciliapathies have a variety of developmental and degenerative disorders.

Methods: We present the case of a 15-year-old child with dysplasia and multiple organ damage who was initially diagnosed as nephrotic syndrome. Her parents and sister are in good health. Physical examination shows normal blood pressure;edema of face and lower limb;sensorineural deafness and hypopsia. She also has dysplasia including congenital heart disease and duplex kidney. The patient also has intermittent cough. Laboratory investigation shows creatinine is 1.88 mg/dl;eGFR is 39.12 mL/min/1.73 m^2;proteinuria is 3.42g/24h;albumin is 23.1g/L;hemoglobin is 88g/L;decreased thyroid function. The brain MRI shows abnormal signal in bilateral parietal lobe of the brain groove in FLAIR sequence which indicates decreased cerebrospinal fluid flow rate. Renal biopsy shows focal segmental glomerular sclerosis. The patient progressed to renal failure and received hemodialysis 10 months after renal biopsy. The patient's clinical manifestations are consistent with cilioapathies, very similar to Alström syndrome. Cilia immunofluorescence of renal tissue showed a decrease number of cilium of the patient compared to normal kidney. Then WES shows a site mutation in *CCDC114*(NM_144577 exon7 c.596C>T p.Ala199Val)in patient. We found that CCDC114 located in centrosome and knock down *CCDC114* could affect the occurrence of cilia in hRPE1 cells.

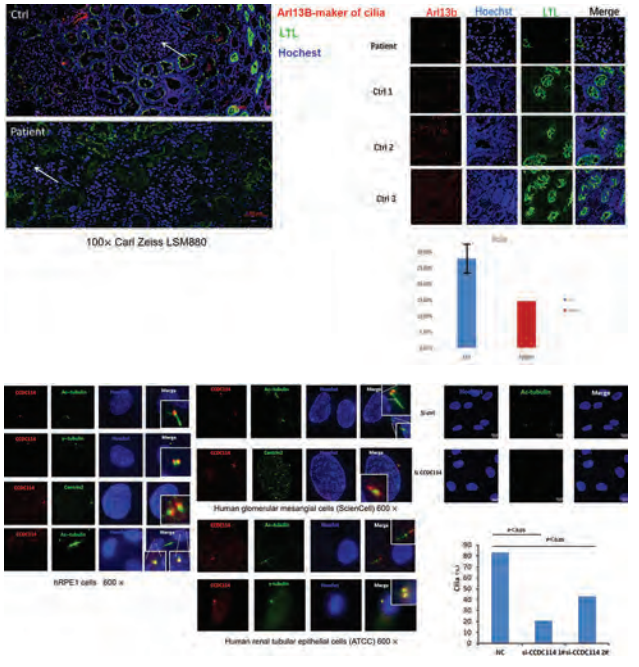
Results:

Conclusions: We found a decrease in the number of cilium in the kidney of patient with ciliapathies and identified *CCDC114* as the main target gene by WES. We found that CCDC114 affected primary cilia formation in hRPE1 cells.

Funding: Government Support - Non-U.S.

Genotype of the family

Gene	Ref	Alt	Case	Father	Mother	Sister
CCDC114	G	A	A/A	G/A	G/A	G/A



SA-PO575

NOS1AP Mutations Cause Steroid-Resistant Nephrotic Syndrome Amar J. Majmundar,[1] Daniela A. Braun,[1] Eugen Widmeier,[1] Shirlee Shril,[1] Shrikant M. Mane,[4] Neveen Soliman,[3] Christoph Aufricht,[2] Friedhelm Hildebrandt.[1] *[1]Medicine, Div Nephrology, Boston Children's Hospital, Boston, MA; [2]Medical University of Vienna, Vienna, Austria; [3]Pediatrics, Cairo University, Cairo, Egypt; [4]Genetics, Yale University, New Haven, CT.*

Background: Steroid resistant nephrotic syndrome (SRNS) is the second leading cause of chronic kidney disease in the first three decades of life. Mutations in >39 genes provide a monogenic cause in 29.5% of SRNS cases (Sadowski *JASN* 26:1279, 2015) and have defined patho-mechanisms (Lovric *NDT* 31:1802, 2016).

Methods: We performed whole exome sequencing (WES). Live cell imaging was performed following wild-type and mutated cDNA construct expression in immortalized human podocytes.

Results: By WES, we identified homozygous recessive mutations in 2 unrelated individuals with SRNS in the gene *NOS1AP* (c.428G>A; p.C143Y in subject A1018 and c.345-3T>G; p.I116Afs*4 in subject A5016). *NOS1AP* encodes an adaptor protein that interacts with nitric oxide synthase (NOS) and with NOS effectors through its phosphotyrosine binding domain (PTB) (Fang *Neuron* 28:183, 2000). The C143 residue within the PTB is conserved through invertebrate orthologues and in 85% of 101 human PTB sequences. The p.C143Y change registered strong SIFT and PolyPhen-2 scores. The c.345-3T>G coding change is predicted to reduce splicing of the acceptor site of intron 4. Skipping of adjacent exon 5 results in the truncating coding change p.I116Afs*4. Neither mutation is observed in the ExAC Exome Database. NOS1AP is expressed in podocytes but not endothelial or mesangial cells of rat kidney glomeruli. Transfection of wild-type NOS1AP induced filopodia in 58% of immortalized human podocytes versus only 1% of mock GFP transfected cells. Podocytes transfected with mutated NOS1AP p.C143Y and NOS1AP p.I116Afs*4, which we detected in the SRNS subjects, lacked filopodia formation, demonstrating loss of NOS1AP function.

Conclusions: We identified mutations in *NOS1AP* in 2 unrelated families with SRNS, revealing a novel monogenic cause of glomerular disease. These findings highlight a new pathogenic mechanism related to nitric oxide signaling and a potential therapeutic target for nephrotic syndrome.

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SA-PO576

Whole Exome Sequencing Identifies Causative Mutations in 16% and Novel Candidate Genes in 24% of Individuals with a Diagnosis of CAKUT Dervla M. Connaughton,[1] Amelie van der Ven,[1] Hadas Ityel,[1] Shirlee Shril,[1] Nina Mann,[1] Makiko Nakayama,[1] Jing Chen,[1] Asaf Vivante,[1] Daw-yang Hwang,[1] Eugen Widmeier,[1] Julian J. Schulz,[1] Velibor Tasic,[2] Shrikant M. Mane,[3] Friedhelm Hildebrandt.[1] *[1]Boston Children's Hospital, Harvard Medical School, Boston, MA; [2]University Children's Hospital, Skopje, Macedonia (the former Yugoslav Republic of); [3]Genetics, Yale University, New Haven, CT.*

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) cause 50% of chronic kidney disease in children. Several lines of evidence support the hypothesis that CAKUT has a monogenic origin: i) congenital nature, ii) monogenic multi-organ syndromes with CAKUT, iii) familial occurrence, iv) monogenic mouse models and v) the complex genetics underlying renal morphogenesis. About 40 monogenic causes of CAKUT are known so far, explaining ~17% of cases.

Methods: We applied whole exome sequencing (WES) to 135 individuals from 76 families with CAKUT. WES data were evaluated for mutations in known causes of CAKUT in humans (~40 genes), and novel candidate genes for syndromic (~200 genes) or murine CAKUT (~180 genes). In consanguineous or multiplex families, we also performed a search for novel recessive CAKUT genes (14/76) or trio analysis (24/76), respectively.

Results: In 9/76 (12%) families, a causative mutation in a known gene for isolated or syndromic CAKUT was identified that sufficiently explained the respective patients phenotype. In 3/76 (4%) of families, a mutation was identified in a gene causing a kidney disease that may represent a phenocopy of CAKUT (e.g. small kidneys). When evaluating candidate genes for human syndromic CAKUT, we detected deleterious mutations in 5/76 (7%) families with isolated CAKUT. In 1 family, mutations in a mouse candidate gene was identified. In 14/76 consanguineous and 24/76 non-consanguineous families we additionally applied a targeted search for homozygously mutated genes or trio analysis, respectively, and identified 12 potential novel candidate genes for CAKUT.

Conclusions: By WES, we detected causative mutations in 16% of cases with a diagnosis of CAKUT and identified 12 potential novel CAKUT genes. We show that syndromic and murine candidate genes are useful to identify genetic causes of isolated human CAKUT.

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SA-PO577

Precision in CAKUT: The Italian Study Group on the Genetics of Congenital Anomalies of the Kidney and Urinary Tract Monica Bodria,[8] Isabella Pisani,[4] Claudio La scola,[16] Davide Meneghesso,[13] Francesca Taroni,[20] Ilaria Luongo,[17] Stefano Guarino,[18] Milena Brugnara,[19] Mario Giordano,[9] Vinicio Goj,[3] Pasquale Esposito,[5] Pasquale Zamboli,[12] Licia Peruzzi,[11] Giuseppe Masnata,[1] Giovanni Conti,[7] Domenico Santoro,[10] Loreto Gesualdo,[14] Ali G. Gharavi,[2] Francesco Scolari,[15] Simone Sanna-Cherchi,[2] Gian Marco Ghiggeri.[6] *[1]Azienda Ospedale G. Brotzu, Cagliari, Italy; [2]Columbia University, New York, NY; [3]Fatebenefratelli Hospital, Milan, Italy; [4]University of Parma, Parma, Italy; [5]Fondazione IRCCS Policlinico "San Matteo", Pavia, Italy; [6]G. Gaslini Children Hospital, Genoa, Italy; [7]G. Martino Hospital, Messina, Italy; [8]G. Gaslini Children Hospital, Genoa, Italy; [9]Pediatric Hospital Giovanni XXIII, Bari, Italy; [10]Policlinico G Martino, Messina, Italy; [11]Regina Margherita Children's Hospital; Citta della Salute e della Scienza, Turin, Italy; [12]Second University of Naples, Naples, Italy; [13]University Hospital of Padua, Italy, Padua, Italy; [14]University of Bari, Altamura, Italy; [15]University of Brescia, Montichiari (Brescia), Italy; [16]Nephrology and Dialysis Unit, Department of Pediatrics, Azienda Ospedaliero Universitaria Sant'Orsola-Malpighi, Bologna, Bologna, Italy; [17]Santobono Hospital, Naples, Italy; [18]Azienda Ospedaliero-Universitaria "Luigi Vanvitelli", Napoli, Italy; [19]Universitary Pediatric Clinic, Verona, Italy; [20]UOC Nefrologia Dialisi e Trapianto Pediatrico, Fondazione IRCCS Ca Granda Policlinico, Milano, Italy. Group/Team: Precision In CAKUT Italian Study Group.*

Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) are a leading cause of end stage renal disease. Pathogenetic mechanisms behind CAKUT are mostly unknown. Point mutations and copy number variations (CNVs) account for 10-30% of the cases. Genetic tests are often not performed, thus limiting prognosis and management.

Methods: We present a multi-institutional Italian study group on CAKUT, composed of adult and pediatric nephrology and urology investigators. The group aims at recruiting and charactering CAKUT patients to a) conduct clinical characterization and prospective studies b) perform research DNA microarrays and whole exome sequencing (WES) c) perform clinically certified CLIA confirmation of results d) implement genetic results into clinical practice and e) devise novel precision medicine approaches.

Results: 30 Italian centers have recruited and characterized 1,482 index cases. 658 of them have been subjected to DNA microarrays for GWAS and CNVs, and 393 have been subjected to WES. The most commonly identified CNVs were the deletion at the loci 17q12, 22q11.2, 1q21 and 16p11.2, while the most commonly point mutations were in *PAX2*, *EYA1*, *HNF1B*, *SIX5*, *GATA3*. Most of these genetic lesions predispose to extra-renal diseases and would benefit for early intervention strategies. The remaining samples are undergoing DNA microarrays/WES.

Conclusions: We plan to enroll 5,000 patients. The deep clinical and phenotypic characterization will allow precise anatomical classification of disease. Genetic data will be used to guide deep phenotyping. The longitudinal design will allow identification of genetic and non-genetic prognostic factors in order to improve renal and overall patient outcome.

SA-PO578

Development of DCR-PHXC, an Optimal Treatment Approach for Primary Hyperoxalurias Chengjung Lai,[1] Natalie Pursell,[1] Wei Zhou,[1] Michael D. Dills,[1] Chaitali Dutta,[1] Utsav H. Saxena,[1] Girish R. Chopda,[1] Martin L. Koser,[1] Rebecca Lescarbeau,[1] Naim Nazef,[1] Boyoung Kim,[1] Rachel A. Storr,[1] Weimin Wang,[1] Marc Abrams,[1] Hank Dudek,[1] Eduardo C. Salido,[2] Bob D. Brown.[1] *[1]Dicerna Pharmaceuticals, Inc., Cambridge, MA; [2]Hospital Universitario Canarias, La Laguna, Tenerife, Spain.*

Background: Primary hyperoxalurias (PHs) are autosomal recessive disorders caused by the overproduction of oxalate leading to calcium oxalate precipitation in the kidney and eventually to end stage renal disease. Currently, the only treatment effective in reducing oxalate production in patients who do not respond to high-dose vitamin B6 therapy is a combined liver and kidney transplant. We have previously demonstrated that a potential strategy to treat PH Type I (PH1), the most severe form of PH, is to reduce the hepatic production of oxalate using an RNA interference (RNAi) approach targeting *hydroxyacid oxidase 1*, which encodes glycolate oxidase (GO). Reduction of GO in the livers of mice and non-human primates blocks the conversion of glycolate to glyoxylate, the main precursor to oxalate in the liver. Alternatively, reducing the amount of hepatic lactate dehydrogenase (LDH) expression, the key enzyme responsible for converting glyoxylate to oxalate, should more effectively prevent the accumulation of oxalate in PH1, as well as PH Type 2, PH Type 3, and Idiopathic PH, patients.

Methods: Here we report the development of DCR-PHXC, an investigative RNAi therapeutic targeting hepatic LDH, for the treatment of PHs. DCR-PHXC was administered via subcutaneous injection to genetically engineered and chemically-induced mouse and non-human primate models of multiple PHs.

Results: We demonstrate that reduction of hepatic LDH achieves more effective and durable oxalate reduction than suppression of GO in mouse and non-human primate models of PHs. Continued repression of hepatic LDH in mice and non-human primates showed no adverse effects.

Conclusions: The results presented here support the further development of hepatic-specific inhibition of LDH as a highly efficient therapeutic approach to treat all types of primary hyperoxaluria.

SA-PO579

PRDM15 Mutations Cause Steroid-Resistant Nephrotic Syndrome with Microcephaly, Polydactyly, and Heart Defects Shazia Ashraf,[1] Denny Schanze,[4] Amelie van der Ven,[1] Shasha Shi,[3] Svjetlana Lovric,[1] Neveen Soliman,[2] Mohamad A. Jairajpuri,[5] Jan Kadlec,[3] Martin Zenker,[4] Friedhelm Hildebrandt.[1] *[1]Boston Childrens Hospital, Harvard Medical School, Boston, MA; [2]Cairo University, Cairo, Egypt; [3]INSERM, Grenoble, France; [4]Institute of Human Genetics, Magdeburg, Germany; [5]Jamia Millia Islamia University, New-Delhi, India.*

Background: Steroid-resistant nephrotic syndrome (SRNS) causes 15% of chronic kidney disease in children and young adults. First insights into the pathogenesis of SRNS came from identification of >50 single-gene causes. PRDM proteins contain SET domain and multiple zinc fingers domains, and are involved in transcriptional regulation.

Methods: We performed whole exome sequencing (WES) to identify novel monogenic causes of SRNS in >1,000 individuals with SRNS.

Results: We identified 3 different recessive mutations in *PRDM15* (PR domain containing 15) (p.M483K, E519K and C1173Y) in 6 unrelated families. Interestingly, 4 affected individuals with the C1173Y mutated allele exhibited SRNS (childhood-onset) with microcephaly, polydactyly, and heart defects, while the 2 mutations in the SET domain of PRDM15 only caused isolated SRNS. C1173 is a critical "cysteine" residue at the "knuckle" of the Cys-x-x-Cys sequence necessary to complex the zinc ion. We tested the stability of wild type (WT) protein *versus* two mutations (M483K and E519K) in the SET domain of PRDM15, using thermal stability assay by tryptophan absorption. We demonstrate that the M483K mutant was significantly less stable than WT, while the E519K mutant was insoluble. Further, we show that stable knockdown of *PRDM15* results in decreased cell migration and severe proliferation defects in cultured human podocytes. WT, but not 3 mutant, constructs rescue the migration defects in podocytes, confirming deleteriousness of the mutations that we identified in SRNS patients. By immunofluorescence studies, we find that PRDM15 colocalizes with fibrillarin at nucleoli of human podocytes.

Conclusions: We have identified *PRDM15* mutations as a novel cause of childhood-onset SRNS with microcephaly, polydactyly and heart defects. Our findings may implicate a defect in a transcriptional program as a new cause of SRNS.

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SA-PO580

Defects in All Components of the t6A Biosynthesis Pathway Lead to Galloway-Mowat Syndrome Geraldine Mollet,[1] Bruno Collinet,[2] Dominique Liger,[2] Christelle Arrondel,[1] Laurine Buscara,[1] Gaelle Martin,[1] Olivier Gribouval,[1] Olivia Boyer,[1] Daniela A. Braun,[3] Anne-Claire Boschat,[4] Sylvia Sanquer,[5] Daniella Magen,[6] Audrey Laurent,[7] Friedhelm Hildebrandt,[3] Herman Van tilbeurgh,[2] Corinne Antignac.[1] *[1]Laboratory of Hereditary Kidney Diseases, Inserm UMR1163-Imagine Institute-Paris Descartes University, Paris, France; [2]Institut de Biologie Intégrative de la Cellule, Université Paris Sud CNRS UMR9198, Orsay, France; [3]Boston Children's Hospital, Boston, MA; [4]Mass spectrometry Facility, Inserm U1163 Imagine Institute, Paris, France; [5]Metabolomic and proteomic Biochemistry Department-Necker Hospital, AP-HP, Paris, France; [6]Pediatric Nephrology Institute-Rambam Health Care Campus-Technion Faculty of Medicine, Haifa, Israel; [7]Service de Néphrologie, Rhumatologie et Dermatologie pédiatriques, Hospices Civils de Lyon-Hôpital Femme-Mère-Enfant, Bron, France.*

Background: The universal threonylcarbamoyladenosine (t6A) modification on tRNAs, essential for translation initiation and translational efficiency, is catalyzed by two enzymes, YRDC and OSGEP, the last one being part of the highly conserved multiprotein complex KEOPS composed of 5 subunits (C14ORF142, LAGE3, OSGEP, TP53RK and TPRKB). Lately, we identified mutations in all 5 subunits of KEOPS in patients with Galloway-Mowat Syndrome (GAMOS, OMIM 251300) associating steroid-resistant nephrotic syndrome with microcephaly and neurological impairment. However, the role of the newly identified C14ORF142 (C14) subunit is still unclear.

Methods: To identify new genes of GAMOS and better understand the role of C14, we performed whole exome sequencing, measured t6A modification by mass-spectrometry and performed western blot and qRT-PCR of KEOPS subunits in lymphoblastoid cell lines (LCLs) from GAMOS patients.

Results: We identified compound heterozygous missense mutations in the *YRDC/Sua5* gene in one patient with an extremely severe GAMOS phenotype. Interestingly, primary fibroblasts from this patient present growth defects likely due to t6A deficiency. By contrast, we did neither observe any growth defects in C14-null fibroblasts, nor any change in the t6A level in C14-mutated LCLs. Nevertheless, we demonstrated that the absence of C14 leads to a decreased expression level of the four other KEOPS subunits, likely through the shortening of the half-life of KEOPS subunits since without any effect on mRNA levels.

Conclusions: We identified mutations in an additional gene known to be involved in the biosynthesis of the t6A modification that confirms the crucial role of this modification in the pathogenesis of GAMOS. The differences in the clinical phenotypes between YRDC and C14 patients can be explained by the different role of these proteins in t6A

modification, YRDC being directly involved in its biosynthesis, whereas C14 would stabilize the KEOPS complex to modulate its function(s).

Funding: Government Support - Non-U.S.

SA-PO581

Visualization of Force Dynamics and Actin Remodeling in ACTN4 Mutant Podocytes Subjected to Stretch Di Feng,[1] Ava Benjamin,[1] Jacob Notbohm,[2] Minxian Wang,[1] Ramaswamy Krishnan,[3] Martin R. Pollak.[1] *[1]Nephrology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA; [2]University of Wisconsin-Madison, Madison, WI; [3]Emergency Medicine, BIDMC/ Harvard Medical School, Boston, MA.*

Background: Alpha-actinin-4 gene (ACTN4) mutations cause a rare form of familial focal segmental glomerulosclerosis (FSGS) and podocyte injury in humans. Our study aimed to better understand the mechanism by which mutant ACTN4 contributes to podocyte dysfunction by assessing the effect of the mutation on a podocyte's response to transient stretch.

Methods: We used primary podocytes isolated from Actn4 K256E Knock in mutant mice (n=3) and WT littermates (n=3) as a cellular model. Measurements were performed in isolated single cells and data were pooled across multiple mice. We used traction force microscopy to quantify contractile forces exerted by podocytes on their underlying substrate in response to transient stretch. We used live cell imaging to examine the distribution of actin.

Results: Compared to WT, mutant ACTN4 podocytes bear more actin stress fibers bundles and exert greater contractility before stretch. After the first transient stretch, WT and mutant podocytes demonstrated similar reductions in their contractile forces. During the recovery period, WT podocytes demonstrated recovery of their contractile forces close to pre-stretch baseline values, whereas the majority of mutant podocytes showed impaired recovery. After a total of 3 transient stretches, WT podocytes on average recovered 79% of their baseline contractile forces, whereas the majority of mutant podocytes (10/15) recovered less than 50% of their baseline, with 7 failing entirely (completely losing their ability to generate contraction forces). Additionally, representative WT podocytes demonstrated cracks in their cytoskeletons after the first stretch that were subsequently repaired during the recovery period, whereas representative mutant podocytes whose contractile forces failed demonstrated cracks that persisted during the recovery period.

Conclusions: Our findings provide the first direct evidence of a mutant ACTN4 podocyte's inability to maintain its structure and function in response to mechanical stress, suggesting a clearer path through which mutant ACTN4 leads to podocyte detachment and kidney injury.

Funding: NIDDK Support

SA-PO582

MicroRNA Content in Cells Is Globally Disrupted by the Nephrotic Syndrome-Related Point Mutation in XPO5 Devorah Gur-Wahnon, Iddo Z. Ben-Dov. *Nephrology and Hypertension, Hadassah - Hebrew University Medical Center, Jerusalem, Israel.*

Background: MicroRNA (miRNA) are small noncoding RNA that regulate gene expression. Mature miRNA are crucial for the development and homeostasis of podocytes. Maturation of miRNA entails a multistage process that involves several proteins. Recently, steroid-resistant nephrotic syndrome (SRNS) in a child was attributed to a point mutation in Exportin-5 (*XPO5*), a protein that exports miRNA precursors from the nucleus to the cytoplasm (Braun DA 2016). However, whether or not the mutation affects the miRNA-related function of Exportin-5 is not known. We hypothesized that the V552I mutation impedes miRNA maturation, and that the association with SRNS may shed light on the roles of specific miRNA in podocytes.

Methods: We transfected XPO5-knockout (*XPO5*$^{-/-}$) HCT116 cells with plasmids encoding either wt *XPO5* or *XPO5*[V552I] and compared global miRNA content with non-rescued *XPO5*$^{-/-}$ cells and parental cells via small RNA sequencing.

Results: miRNA quantification confirmed global depletion of mature miRNA in *XPO5*$^{-/-}$ compared to parental cells. Transfection experiments showed partial rescue of miRNA content with wt XPO5. Transfection of a plasmid encoding XPO5 harboring the V552I mutation did not rescue miRNA maturation (Figure). Conversely, mapping of small RNA reads to mRNA and rRNA was relatively higher in *XPO5*$^{-/-}$ cells and mutant XPO5-transfected *XPO5*$^{-/-}$ cells compared to parental and wt XPO5-transfected *XPO5*$^{-/-}$ cells.

Conclusions: Together with predictions of disrupting impact of the V552I mutation, our experiments show that the SRNS-related *XPO5* mutation may cause global reduction of mature miRNA. Further experiments should pinpoint specific miRNA and miRNA targets responsible for the podocyte phenotype.

Funding: Government Support - Non-U.S.

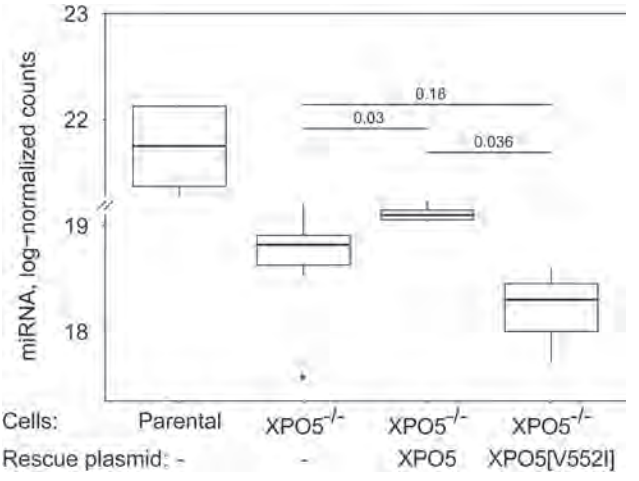


Figure: Log-normalized global miRNA counts in HCT116 cells, XPO5$^{-/-}$ HCT116 cells, XPO5$^{-/-}$ HCT116 cells transfected with wildtype XPO5-encoding plasmid and XPO5$^{-/-}$ HCT116 cells transfected with mutant (V552I) XPO5-encoding plasmid

SA-PO583

Primary Genetic Mechanism with Secondary Focal Segmental Glomerulosclerosis Is the Prevalent Cause of Early-Onset Proteinuria Resistant to Treatment Francesca Becherucci,[2] Benedetta Mazzinghi,[2] Samuela Landini,[1] Rosa maria Roperto,[2] Fiammetta Ravaglia,[1] Giulia Sansavini,[2] Marco Allinovi,[1] Sabrina Giglio,[1] Paola Romagnani.[1,2] *[1]University of Florence, Florence, Italy; [2]Nephrology and dialysis Unit, Meyer Children's Hospital, Florence, Italy.*

Background: Proteinuria is a hallmark of kidney diseases and represents an important determinant to the progression toward chronic kidney disease (CKD), especially in children and young adults. The importance of genetic causes is clearly emerging and has already been reported in about 30% of patients with steroid-resistant nephrotic syndrome (SRNS) and in 25% of patients with early-onset CKD.

Methods: To assess the role of genetic variants in the pathogenesis of proteinuria and CKD we applied whole-exome sequencing (WES) followed by bioinformatic filtering for 308 genes reported as even rare causes of CKD to 107 patients with different types of proteinuric diseases and an age at onset younger than 20 yeras, excluding immuno- and complement-mediated forms.

Results: This strategy allowed us to find a prevalence of potentially pathogenic genetic variants as high as 71.7% in patients presenting with SRNS and severe proteinuria, whereas no genetic defect was present in patients with steroid-sensitive nephrotic syndrome. These variants occurred in podocyte genes in 48.8% of cases and in *COL4A* genes associated with variants in modifier genes in 20.9% of cases. Among patients with mutations, the most frequent pathologic finding was focal segmental glomerulosclerosis, irrespectively of the different genetic causes, whereas the clinical phenotype at onset mirrored the type of gene involved. In addition, the presence of pathogenic variants was associated with the lack of response to immunosuppressive treatments and complete remission of the disease could only be observed in the group of negative patients. Finally, progression toward CKD was significantly higher in patients with pathogenic variants than in negative patients, suggesting that the presence of genetic defects is highly predictive of the clinical outcome of these patients.

Conclusions: These results suggest that genetic abnormalities are key elements in the pathogenesis of proteinuric diseases and are predictive of specific phenotypic features, such as the response to therapies and the outcome of the disease, thus supporting the opportunity of including WES in the diagnostic flow-chart of these disorders, especially in patients with an early onset of the disease.

SA-PO584

Rare GREB1L Mutations Contribute to the Genetic Heterogeneity of Congenital Kidney Malformations Simone Sanna-Cherchi,[2] Kamal Khan,[4] Rik Westland,[11] Priya Krithivasan,[2] Hila Milo Rasouly,[2] Iuliana Ionita-Laza,[2] David Fasel,[3] Krzysztof Kiryluk,[2] Monica Bodria,[5] Edgar A. Otto,[10] Matt G. Sampson,[10] C. Gillies,[10] Adele Mitrotti,[2] Loreto Gesualdo,[8] Friedhelm Hildebrandt,[1] Joanna Van Wijk,[11] Marijan Saraga,[7] Francesco Scolari,[9] Velibor Tasic,[6] Gian Marco Ghiggeri,[5] Anna Materna-Kiryluk,[12] David B. Goldstein,[2] Nicholas Katsanis,[4] Erica Davis,[13] Ali G. Gharavi.[2] *[1]Boston Children's Hospital, Boston, MA; [2]Columbia University, New York, NY; [3]Columbia University Medical Center, New York, NY; [4]Duke University, Durham, NC; [5]G. Gaslini Children Hospital, Genoa, Italy; [6]University Children's Hospital, Skopje, Macedonia (the former Yugoslav Republic of); [7]University Hospital in Split, Split, Croatia; [8]University of Bari, Altamura, Italy; [9]University of Brescia, Montichiari (Brescia), Italy; [10]University of Michigan, Ann Arbor, MI; [11]VU University Medical Center, Amsterdam, Netherlands; [12]Poznan University of Medical Sciences, Poznan, Poland; [13]Duke University Medical Center, Durham, NC.*

Background: Renal agenesis and hypodysplasia (RHD) are a major cause of pediatric end-stage renal disease.

Methods: We conducted whole exome sequencing in 203 patients with RHD and identified diagnostic pathogenic mutations in 8/203 patients. In another 6 patients, we found non-recurrent novel loss-of-function (LOF) variants in genes associated with rare syndromes that include kidney defects (*SETBP1, WNT5A*), or in genes whose inactivation results in kidney malformations in the mouse (*SLIT3, HSPA4L, T, SCTR*).

Results: To define novel genetic drivers in the remaining cohort of 195 patients, we compared their LOF burden with 6,905 controls. We identified rare LOF variants in *GREB1L* (P=2.04x10^{-5}), a gene ubiquitously expressed in the developing mouse kidney. Expansion of our model with novel deleterious missense variants resulted in exome-wide significance for *GREB1L* (P=4.08x10^{-6}). Three mutations (2 LOF and 1 missense) segregated in an autosomal dominant fashion and one predicted deleterious missense was *de novo* (joint value for burden, inheritance and *de novo* occurrence: P<1.0x10^{-8}). In a replication cohort of 410 RHD cases, we identified 8 more qualifying LOF/missense variants in *GREB1L*. To directly test our genetic findings, we generated a *greb1l* zebrafish model. Knockdown and CRISPR/Cas9 deletion of *greb1l* in zebrafish showed specific pronephric defects that could be rescued by introduction of wild-type human mRNA. Randomized testing of missense alleles by *in vivo* complementation showed that 4/4 alleles found exclusively in patients were unable to rescue the phenotype.

Conclusions: Taken together, our study provides new insight into the genetic landscape of renal malformations and identifies *GREB1L* as a novel susceptibility gene for RHD.

Funding: NIDDK Support, Other U.S. Government Support, Government Support - Non-U.S.

SA-PO585

The Novel, Non-Toxic Nonsense Suppressor Drug, ELX-02, Is Effective in Cystinosis Emma J. Brasell,[2] Lee lee Chu,[3] Iris Alroy,[1] Idit Eshkar-Oren,[1] Michal Shavit,[1] Meytal Shohat,[1] Pedro Huertas,[1] Yojiro Yamanaka,[2] Paul R. Goodyer.[2] *[1]Eloxx Pharmaceuticals, Rehovot, Israel; [2]McGill University, Montreal, QC, Canada; [3]RI-MUHC, Montreal, AB, Canada.*

Background: Cystinosis is caused by mutations in the cystinosin (*CTNS)* gene, encoding a lysosomal membrane transporter responsible for the efflux of cystine. Intralysosomal cystine accumulation drives progressive organ dysfunction in cystinosis. In Quebec, about 50% of patients harbor a W138X nonsense mutation, causing a premature termination codon (PTC) in exon 7. PTCs cause nonsense-mediated decay (NMD) of mutant transcripts and inhibit protein translation. Aminoglycosides have nonsense suppressor activity, which permits translational read-through of PTCs, but are too toxic to be used for therapy. In contrast, the novel compound ELX-02 was safe and generally well-tolerated in humans up to 5mg/kg.

Methods: To test the efficacy of ELX-02, we treated human fibroblasts harboring the W138X mutation and examined *CTNS* expression and intracellular cystine levels. Using zinc finger nuclease technology, we generated a *Ctns*$^{Y226X/Y226X}$ mouse and replicated the in vitro experiments in mouse fibroblasts. Mice were then injected with ELX-02 (10mg/kg s/c X2/week for 22days). Half-cystine levels were assessed in kidneys and pharmacokinetics (PK) studied in plasma and kidney tissue.

Results: After treatment with ELX-02, *CTNS* mRNA transcript levels in *CTNS*$^{W138X/W138X}$ fibroblasts increased to normal levels and intracellular cystine was reduced. These results suggest that ELX-02 reduces NMD of *CTNS*^{W138X} transcript and allows production of functional CTNS protein. In addition, ELX-02 had a similar therapeutic effect on the Y226X mutation in mouse fibroblasts. In ELX-02 treated mice, pathologic half-cystine was reduced to 55% of untreated levels. ELX-02 in plasma had similar Cmax (15ug/ml at 15 min), AUC and elimination half-life (~30 min) following single and repeated administration. ELX-02 was more concentrated in kidney (Cmax 40ug/g), with sustained levels of 15ug/g for > 8 hrs.

Conclusions: These data demonstrate read-through activity of ELX-02 on h*CTNS* W138X and m*Ctns* Y226X mutations, producing sufficient CTNS protein for cystine efflux from lysosomes. Thus, ELX-02 may be an effective therapy for cystinosis caused by PTCs.

Funding: Commercial Support - Eloxx Pharmaceuticals, Private Foundation Support

SA-PO586

Identifying Modifier Genes of X-Linked Alport Syndrome Using a Novel Multi-Parent Mouse Model Ron Korstanje, Daniel M. Gatti, Yuka Takemon. *The Jackson Laboratory, Bar Harbor, ME.*

Background: A major goal for precision medicine in genetic diseases is the identification of modifier genes as potential therapeutic targets. Using X-linked Alport Syndrome (XAS) as a model for heritable kidney diseases, we have developed a novel approach to identify modifier genes that modulate disease severity outcomes. To identify modifiers for XAS, we introduced a *Col4a5* mutation into the genetically heterogeneous Diversity Outbred (DO) mice and conducted high-resolution mapping for several renal phenotypes.

Methods: The DO mice are an ideal population for high-precision genetic mapping, containing 45 million SNPs originating from 8 founder strains. The diversity captured in the DO emulates the variation in the human genome. To introduce XAS into the DO population, we crossed female C57BL/6J-*Col4a5*$^{+/-}$ mice with 100 unique male DO mice. From each mating we selected one *Col4a5*$^{-/Y}$ male and one *Col4a5*$^{+/-}$ female F1 offspring to create a cohort of 200 mice. We measured albuminuria (ACR) at 6, 10, and 15 weeks, and glomerular function (GFR) at 14 weeks of age. We genotyped each animal, reconstructed haplotypes, and mapped loci associated with variation in ACR and GFR.

Results: There was large variation in GFR and ACR in our cohort. Similar to human XAS patients, males had increased severity with elevated ACR and reduced GFR relative to females. High-resolution linkage and association mapping revealed several loci as narrow as 1Mbp harboring genes responsible for driving variation in ACR and GFR. The most significant GFR locus contains only 5 annotated genes, including a transcription factor regulating microtubule network related protein expression. Similarly, a locus for ACR contains a gene associated with actin filament formation. Both candidates suggest an affect on the structure and therefore the function of podocyte foot processes, critical for kidney health.

Conclusions: Our study successfully identified several novel candidate genes implicated in modifying XAS disease severity outcomes. These candidates are prime therapeutic targets for XAS. This work demonstrates the power of high-resolution genetic mapping in the DO mice, an approach that can be applied to other forms for heritable renal diseases such as polycystic kidney disease.

Funding: Other NIH Support - NIH GM076468

SA-PO587

Clinical Overview and Long-Term Prognosis of Dent Disease and Lowe Syndrome in Japan Ken-ichiro Miura,[1] Yutaka Harita,[2] Kiyonobu Ishizuka,[1] Tomoo Yabuuchi,[1] Naoto Kaneko,[1] Shoichiro Kanda,[2,1] Atsushi Sato,[2] Tsuyoshi Isojima,[2] Takashi Igarashi,[3] Motoshi Hattori.[1] *[1]Tokyo Women's Medical University School of Medicine, Tokyo, Japan, Tokyo, Japan; [2]Department of Pediatrics, University of Tokyo, Tokyo, Japan; [3]National Center for Child Health and Development, Tokyo, Japan.*

Background: Epidemiologic data of Dent disease (DD) and Lowe syndrome (LS) are lacking, and long-term prognosis of LS has not been surveyed. The aim of this study was to investigate the prevalence and long-term prognosis of patients with DD and LS in Japan.

Methods: Questionnaire was distributed to 1,814 departments of pediatrics, nephrology, endocrinology and internal medicine of major hospitals in Japan. Data of the patients who visited the hospitals in 3 years (between 2013 and 2015) were collected. This study was approved by the Ethics Committee of Tokyo Women's Medical University (IRB No.3916) and was supported by Health and Welfare Labour Sciences Research Grants.

Results: The response rate was 49% and 83% in the primary and the secondary survey, respectively. Clinical and laboratory data were obtained from 110 patients with DD and 67 patients with LS. A low response rate and small sample sizes did not allow estimation of patient numbers. The majority of patients with DD were diagnosed asymptomatically by annual urinary screening test at median age of 3 years. Prominent low molecular weight proteinuria (LMWP), hypercalciuria and nephrocalcinosis were noted in 100%, 49% and 37% of patients, respectively. Only 3 (19%) out of 16 adult patients developed CKD stages 3 or 4 in their 20s and 30s. Genetic analyses were performed in 37% and mutations in the CLCN5 and the OCRL genes were documented in 68% and 11%, respectively, the proportion of which was similar to the previous reports. Most patients with LS were diagnosed in infancy. All patients presented with prominent LMWP, cataract and mental retardation. Estimated GFR negatively correlated with age and indicated that most patients developed end stage renal disease in their 30s and 40s. OCRL mutations were documented in 21 (96%) out of 22 patients analyzed.

Conclusions: The prognosis of DD in Japan might be better than that in Europe and USA probably due to detection of individuals with milder phenotypes by annual urinary screening test. It might be suggested that the only required item for the diagnosis of DD is prominent LMWP in Japan. In addition, we described long-term renal prognosis of LS for the first time, which would contribute to treatment strategy and genetic counseling.

Funding: Government Support - Non-U.S.

SA-PO588

Genetic Findings in Adults with Sporadic Steroid-Resistant Nephrotic Syndrome Aude Servais,[1,2] Olivier Gribouval,[2] Olivia Boyer,[1,2] Aurelie Hummel,[1] Jacques Dantal,[3] Marie-Josèphe Tête,[2] Corinne Antignac.[2,1] *[1]Necker University Hospital, Paris, France; [2]Inserm U1163, Imagine Institute, Paris Descartes University, Paris, France; [3]Institut de Transplantation Urologie Néphrologie, Nantes, France.*

Background: In recent years, proposals for genetic screening paradigms in Steroid-Resistant Nephrotic Syndrome (SRNS) preferentially addressed congenital, infantile onset and familial cases. Sporadic SRNS/FSGS adult patients are currently only tested for the *NPHS2* nonneutral p.R229Q polymorphism. To uncover the distribution of disease-causing gene mutations in an adult sporadic FSGS/SRNS population, we used a NGS panel in a cohort of adult patients.

Methods: We selected adult patients (age at onset of proteinuria above 18 years), with non syndromic biopsy proven FSGS and/or SRNS, without known family history. We used strict clinical criteria including no response to glucocorticoids but also to cyclosporine and no relapse after renal transplantation. We applied a NGS panel covering 37 genes to 135 unrelated patients.

Results: Mean age at onset of proteinuria was 30.1 (18.1-84.0) years. Eighteen (13.3%) presented with mutation (15/135, 11.1%) or variant of unknown significance (VOUS) (3/135, 2.2%) in known monogenic SRNS genes and 14 (10.4%) with *APOL1* high risk allele. We identified 11 novel mutations including mutations in *PAX2, INF2, NPHS2, MYO1E,* and *CD2AP* genes. Collagen mutations represented 38.8% of all mutations. Mean age at onset of proteinuria was lower in the group with mutations than in patients with no mutation or *APOL1* risk variant (24.9±7.9 vs 30.9±11.7, p=0.01). Mutations in non collagen genes were all found in patients younger than 30 years of age, whereas mutations in collagen genes were also identified in older patients until 50 years of age. Patients with mutations presented with lower eGFR at diagnosis (43.6±31.8 vs 87.4± 34.8 ml/min/1.73m2, p=0.006), reflecting a more severe disease. Age at ESRD was higher in patients with mutations in collagen genes than in patients with mutations in other genes (47.5±1.6 vs 26.6±4.6 years, p=0.01).

Conclusions: We identified a mutation or a VOUS in known monogenic SRNS genes in 13.3% of patients and *APOL1* high risk allele in 10.4%. Collagen mutations causing Alport Disease were the more frequent identified mutations.

Funding: Government Support - Non-U.S.

SA-PO589

Cobalamin C Deficiency Induces a Specific Histopathological Pattern Associating Renal Thrombotic Microangiopathy and Characteristic Glomerular Lesions Dominique Guerrot,[5] Mathilde Lemoine,[5] Steven Grange,[5] Marion Rabant,[4] Valerie Chatelet Pouliquen,[5] Emilie Cornec-Le Gall,[3] Damien AMBROSETTI,[1] Georges Deschênes,[2] Arnaud Francois.[5] *[1]CHU Nice, Nice, France; [2]Hospital Robert Debre, Paris, France; [3]Mayo Clinic, Rochester, AL; [4]NECKER Hospital, PARIS, France; [5]Rouen University Hospital, Rouen, France.*

Background: CblC deficiency is the most common inborn error of vitamin B12 metabolism. CblC deficiency most frequently presents as failure to thrive, neurologic deterioration, and hematologic abnormalities during the first year of life. Renal failure attributed to thrombotic microangiopathy (TMA) has occasionally been described, in the rarer late-onset presentation of CblC deficiency, in children and young adults. Due to the rarity of the disease and of available kidney biopsies, kidney lesions associated with CblC deficiency remain poorly defined. This study aims to describe the characteristics of kidney disease in cblC deficiency, and to provide a comparative histological analysis with cblC-independent renal TMA.

Methods: We performed a multicenter retrospective study including 7 patients with cblC deficiency and available kidney biopsy, and 16 matched controls with cblC-independent TMA. The histological characteristics were established by a systematic centralized review.

Results: The patients included were aged 6 to 26 years at the time of the first manifestations. All patients presented with acute renal failure, proteinuria and hemolysis. Five required dialysis. The histological study revealed arteriolar and glomerular TMA in all patients. After comparison with the cblC-independent TMA control group, a vacuolated aspect of the glomerular basement membrane (GBM) (86% *vs* 7% cases, $p<0.001$) and the intensity of glomerular parietal IgM deposits (score 1.8±0.8 *vs* 0.4±0.5, $p<0.01$) were more present in cblC deficiency patients than in controls. Six patients were treated by hydroxycobalamin. All of them improved with disappearance of hemolysis and 3 of the 4 patients requiring renal replacement therapy were weaned off dialysis.

Conclusions: This study provides the first demonstration of characteristic kidney pathology in CblC deficiency, combining lesions of glomerular and arteriolar TMA, a vacuolated aspect of the GBM and glomerular IgM deposits. Due to major therapeutical implications, we suggest patients with renal TMA be screened for CblC deficiency regardless of age, particularly when the kidney biopsy shows a vacuolated aspect of the GBM and glomerular parietal IgM deposition.

SA-PO590

The Minor rs4293393 SNP Variant Is Associated with a Delayed Age of ESRD in Uromodulin Kidney Disease Anthony J. Bleyer,[9] Kendrah O. Kidd,[9] Petr Vyletal,[1] Jorge Reis Almeida,[7] Joaquim T. Calado,[9] Rosa J. Torres,[6] Sofia C. Jorge,[8] Catarina S. Silveira,[4] Eric G. Olinger,[3] Olivier Devuyst,[2] Stanislav Kmoch.[5] *[1]First Faculty of Medicine, Institute of Inherited Metabolic Disorders, Charles University, Prague, Czech Republic; [2]University of Zurich, Zurich, Switzerland; [3]University of Zürich, Zürich, Switzerland; [4]GenoMed, Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal; [5]Institute of Inherited Metabolic Disorders, Prague, Czech Republic; [6]La Paz University Hospital, IdiPaz, Madrid, Spain; [7]Vanderbilt University, Nashville, TN; [8]Portuguese Society of Nepghrology, Lisbon, Portugal; [9]Wake Forest School of Medicine, Winston-Salem, NC.*

Background: Uromodulin kidney disease (UKD) is a form of autosomal dominant tubulo-interstitial kidney disease (ADTKD) caused by mutations in the *UMOD* gene encoding uromodulin. UKD is characterized by slowly progressive kidney failure. The minor variant of rs4293393 in the *UMOD* promoter is associated with 50% decreased uromodulin production. We hypothesized that if this minor variant is found in the mutated *UMOD* gene promoter in individuals with UKD, there will be decreased mutant *UMOD* production and a later ESRD onset.

Methods: Genotyping of the rs4293393 snp was performed in 365 individuals from 149 families. Association with the mutated UMOD gene was determined. Age of ESRD was determined.

Results: Hardy Weinberg equilibrium was not met, with only 8/149 (5%) families linked to the minor variant vs. 15% expected (p-value < 0.0001). The mean age of end stage renal disease (ESRD) for individuals linked to the minor variant was 59.5+/- 11.1 (n=6) vs. 45.3+/- 10.5 years for individuals linked to the major variant (n=139) (p=0.0008). No individual linked to the minor variant reached ESRD before age 45 as opposed to 71 individuals (51%) linked to the major variant (Figure 1).

Conclusions: The rs4299393 minor variant, previously linked to decreased uromodulin production has a significant protective effect on age of ESRD if it is found in the promoter of the mutant *UMOD* gene in individuals with UKD. The deviation from expected allele and genotype frequencies could be due to the preservation of kidney function such that families linked to the minor variant are not being diagnosed at the same rate as other UKD families. These findings identify a prognostic factor in age of ESRD in UKD and suggest that decreasing mutant uromodulin production will improve renal survival.

Funding: NIDDK Support

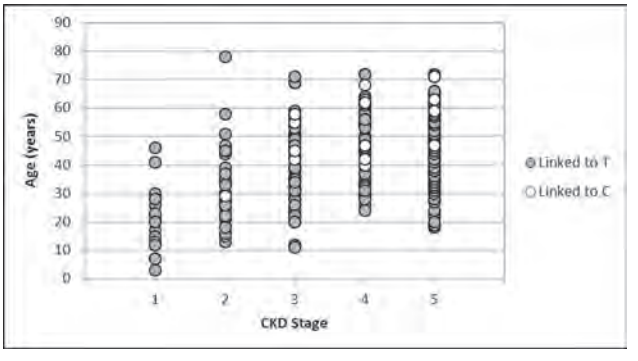


Figure 1: Association of CKD with rs4293393 linkage. The rs4293393 minor variant is C and the ancestral variant is T. CKD stages are based upon NKF KDOQI guidelines.

SA-PO591

Collagen IV Receptor Blockade as Add-On Therapy in Alport Syndrome Diana Rubel, Rainer Girgert, Gerhard A. Mueller, Oliver Gross. *University Medicine Goettingen, Goettingen, Germany.*

Background: Alport Syndrome (AS) is caused by a lack or misfolding of collagen IV alpha 3, 4 and 5 due to a mutation in one of these genes. Podocytes sense this abnormal glomerular basement membrane (GBM) by collagen receptors such as discoidin domain receptor 1 and Integrin $\alpha 2$. In our present study, we evaluated the nephron-protective effect of knocking-out both receptors in AS (TripleKO) with and without standard ACE-inhibition (ACEi). We hypothesized that the loss of collagen-receptors could inhibit recognition of the altered GBM in AS and improve the renal phenotype. ACEi as the standard off-label therapy delays renal failure until aldosterone escape. Therefore, it is important to evaluate new therapies on top of ACEi.

Methods: Here, we analyze the effect of ACEi and collagen receptor blockade as possible new therapy in wildtype (WT), mice with AS, TripleKO and ACEi treated mice. Mode of action was characterized by real-time PCR, light and electron microscopy with immunogold reactions.

Results: TripleKO mice showed a significant longer survival, less matrix accumulation and fibrosis compared to Alport mice. Additionally, the foot processes were preserved until later stages of disease and splitting of the GBM was considerably less. The relative expression of podocin in Alport mice was significant reduced compared to WT. In contrast, the TripleKO mice showed a podocin expression which was comparable

to WT. Nephrin expression was slightly reduced in TripleKO mice compared to WT, but significant elevated in ACEi treated mice. In Alport mice, the immunogold reactions revealed a podocin accumulation in the areas of podocyte effacement in an age-dependent manner. TripleKO mice showed the same ultrastructural changes, but at a later stage of disease. Nephrin aggregated in TripleKO mice in areas where footprocesses were still preserved.

Conclusions: ACEi and loss of collagen receptors both delay progression of AS in a similar manner, but have different ways of action. In contrast to ACEi therapy for example, podocin expression in TripleKO mice seemed to be maintained, but the protein was mislocated. This confirms a different mode of action resulting in a considerable add-on effect on delaying renal failure. Thus, these additive effects of collagen receptor blockade on top of ACEi should be in the focus of further studies.

Funding: Private Foundation Support

SA-PO592

Deleterious Impact of a Novel CFH Splice Site Mutation in Atypical Hemolytic Uremic Syndrome Anna Seidel,[2] Ria Schönauer,[2] Carsten Bergmann,[1] Maik Grohmann,[1] Tom H. Lindner,[2] Jan Halbritter.[2] *[1]Bioscientia, Ingelheim, Germany; [2]University Clinic Leipzig, Leipzig, Germany*.

Background: Atypical hemolytic uremic syndrome (aHUS) is a rare disease typically based upon uncontrolled activation of the alternative complement pathway (ACP). Clinical signs and symptoms comprise microangiopathic haemolytic anemia (MAHA), thrombocytopenia, and acute kidney failure (AKI). Mutations in ACP regulating genes such as *C3*, *CFI*, *CFH*, and *MCP*/*CD46* are found in around 50% of patients.

Methods: A 27 year-old female without prior past medical history presented with nausea, confusion, petechial bleeding, and anuric AKI necessitating initiation of dialysis. Laboratory examination revealed MAHA with schistocytes but normal ADAMTS13-levels. Kidney biopsy showed glomerulary thrombotic microangiopathy (TMA), which was treated with steroids, plasmapheresis, and eculizumab (induction/maintenance), leading to complete hematological and clinical remission, as well as significant recovery of kidney function within 2 months. Targeted next generation sequencing for aHUS-associated genes identified a paternally transmitted novel heterozygous mutation in the *CFH* gene (c.3134-2A>G). *CFH* encodes complement factor H, a key inhibitory protein of the ACP. The mutation is located in the obligatory splice acceptor site of intron 19. Sanger sequencing of patient cDNA indicated that as a consequence of the mutation, alternative splicing results in a deletion of the first 27 base pairs of exon 20. On the protein level, CFH consists of 20 similar structural conserved Sushi domains, where each has four conserved cysteines forming two disulfide bonds. This in-frame deletion leads to a partial loss of the Sushi domain 18 (p.Asp1045_Thr1053del) including a cysteine (p.Cys1048). As this cysteine is thought to be essential for proper protein folding, its loss may consequently result in a defective protein structure, impairing binding to C3.

Results:

Conclusions: In summary, we detected a new *CFH* splice site mutation in a patient with aHUS, which probably leads to an incorrect protein structure impairing inhibitory control of C3 and thereby ACP activity. Incomplete penetrance demonstrated by the clinically asymptomatic father underlines the necessity of an additional disease trigger for aHUS manifestation.

SA-PO593

HLA Alleles Confer Risk to Primary Idiopathic Nephrotic Syndrome in Individuals of Caucasian Ancestry Dina Ahram,[6] C. Gillies,[15] Adele Mitrotti,[6] Priya Krithivasan,[6] Monica Bodria,[8] Paola Pontrelli,[12] Loreto Gesualdo,[11] Marida Martino,[9] Mario Giordano,[10] Maddalena Gigante,[14] Isabella Pisani,[16] Antonio Amoroso,[3] Vivette D. D'Agati,[5] Gerald B. Appel,[5] Andrew S. Bomback,[4] Francesco Scolari,[13] Riccardo Magistroni,[17] Y. Caliskan,[7] Ali G. Gharavi,[6] Krzysztof Kiryluk,[6] Gian Marco Ghiggeri,[2] Friedhelm Hildebrandt,[1] Matt G. Sampson,[15] Simone Sanna-Cherchi.[6] *[1]Boston Children's Hospital, Boston, MA; [2]G. Gaslini Children Hospital, Genoa, Italy; [3]University of Torino, Torino, Italy; [4]Columbia University, New York, NY; [5]Columbia University College of Physicians and Surgeons, New York, NY; [6]Columbia University Medical Center, New York City, NY; [7]Division of Nephrology, Department of Internal Medicine, Istanbul Faculty of Medicine, Istanbul, Turkey; [8]None, Langhirano, Italy; [9]Pediatric Hospital "Giovanni XXIII" Bari-Italy, Modugno (BA), Italy; [10]Pediatric Hospital Giovanni XXIII, Bari, Italy; [11]University of Bari, Altamura, Italy; [12]University of Bari-Dept. of Emergency and Organ Transplantation, Bari, Italy; [13]University of Brescia, Montichiari (Brescia), Italy; [14]University of Foggia, Foggia, Italy; [15]University of Michigan, Ann Arbor, MI; [16]University of Parma, Bozzolo (Mantova), Italy; [17]Università di Modena e Reggio Emilia, Modena, Italy*.

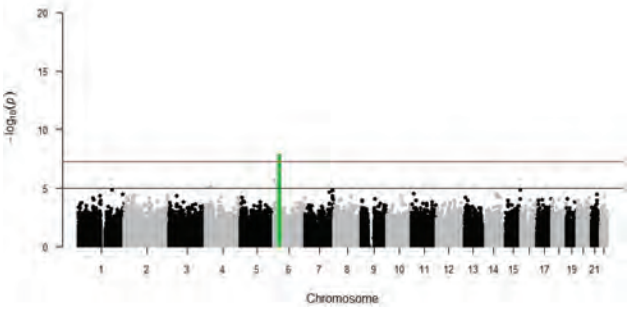
Background: Primary idiopathic nephrotic syndrome (NS) caused by focal segmental glomerulosclerosis (FSGS) or minimal change disease (MCD) is a frequent cause of end-stage renal disease (ESRD). Despite the identification of several genetic causes, the etiology of NS remains to be fully understood. We investigated the genetic basis of FSGS in a population of Caucasian descent.

Methods: We recruited a heterogeneous population of Caucasian descent (1,153 cases) ascertained for FSGS (88% of the cases) and MCD (12%). A set of independent and meta-analyzed case-control, genome-wide association studies (GWAS) were performed using an additive model with covariate-correction for population stratification in the three Caucasian cohorts (Western European: 301, Italian: 754, Turkish: 98), matched genetically with 2,393 controls. Quality control assessment was carried out according to standard practices.

Results: In a Meta-analysis of three, combined Caucasian cohorts (1153 cases, 2393 controls), a significant association was found for the SNP rs28383303 (OR=1.57, 95%CI: 1.29-1.67, P= 1.48×10^{-8}) (Figure 1). All three cohorts contributed to the signal without evidence for heterogeneity. The variant was identified in a 50kb haploblock on chromosome 6p21, which contains the gene encoding the HLA complex class II HLA-DQ alpha chain 1 (*HLA-DQA1*).

Conclusions: In line with previously reported findings implicating the HLA system in childhood-onset nephrotic syndrome and membranous nephropathy, our results indicate the association of HLA risk alleles with NS in individuals of Caucasian descent. Our findings allude to a role for HLA in modulating adaptive immunity and suggest a basis for understanding the complex genetic mechanisms of FSGS.

Funding: Other U.S. Government Support



SA-PO594

A Bioinformatics Analysis of Gene Expression in Experimental Alport Syndrome Reveals an Fstl1 Signature in the Kidney Nicholas Maksimowski,[1] Xuewen Song,[2] Eun Hui Bae,[3] York P. Pei,[2] James W. Scholey.[1,2] *[1]University of Toronto, Toronto, ON, Canada; [2]University Health Network and University of Toronto, Toronto, ON, Canada; [3]Chonnam National University Hospital, Gwangju, Republic of Korea*.

Background: Alport syndrome (AS) is a rare inherited form of chronic kidney disease characterized by progressive nephropathy and the development of end stage renal disease. It is caused by mutations in the Col4a3, Col4a4, and Col4a5 genes. The goal of my studies is to better understand the pathogenesis of AS in the kidney.

Methods: We performed studies using a well-characterized experimental murine model of AS. Global gene expression profiling of renal cortical mRNA samples was performed in male Col4a3-/- mice and Col4a3+/+ control mice at 4 and 7 weeks of age to identify early differentially expressed genes. We performed a cluster analysis and constructed a heat map on the microarray studies at 4 and 7 weeks of age. Finally, studies using HK2 cells were conducted to analyze inflammation and apoptosis related to a protein of interest and its cognate receptor.

Results: The microarray analysis revealed that only 5 genes were differentially expressed in the kidneys of male Col4a3-/- mice at 4 weeks of age compared to Col4a3+/+. Amongst these genes was Follistatin-related protein 1 (FSTL1). We used search tool for the retrieval of interacting genes/proteins to predict protein-protein interactions (PPIs) thereby identifying a functional protein association network for FSTL1. The network included 39 proteins. Cluster analysis of the cognate genes from the FSTL1 protein network showed marked upregulation of gene expression at 7 weeks of age. FSTL1 increased NFκB mediated luciferase activity, caspase 3 activation and PARP cleavage in HK2 cells. These effects were due, at least in part to TLR4 receptor activation.

Conclusions: Our microarray and bioinformatics analyses identified early upregulation of FSTL1 in the kidneys of Col4a3-/- mice. A FSTL1 gene signature, based on predicted PPIs, emerged in the kidneys by 7 weeks of age. FSTL1 elicited an inflammatory response and activated apoptosis in HK2 cells. These findings support the hypothesis that FSTL1 may be a novel determinate of kidney injury in mice with experimental AS.

SA-PO595

Modelling Alport Syndrome in Zebrafish Richard W. Naylor, Saule N. Gasiunas, Rachel Lennon. *University of Manchester, Manchester, United Kingdom*.

Background: Alport syndrome is a hereditary renal disorder that manifests in early childhood with haematuria followed by proteinuria and ultimate progression to end stage renal disease. Genetic analysis has shown that patients with Alport syndrome carry mutations in genes encoding three isomers of collagen type IV: *COL4A3*, *COL4A4* and *COL4A5*. Type IV collagens are the most abundant collagens in basement membranes and exist as three different trimeric protomers, α1α1α2(IV), α3α4α5(IV) and α5α5α6(IV). In the glomerulus, podocytes deposit the α3α4α5(IV) trimer and the endothelium deposits the α1α1α2(IV) trimer. The fusion of these two extracellular matrices forms the glomerular basement membrane (GBM). In Alport syndrome, mutations in either *COL4A3*, *COL4A4* and *COL4A5* lead to depletion of the α3α4α5(IV) trimer in the

GBM. This loss of α3α4α5(IV) initially creates a thinner GBM that at later stages of the disease develops a 'basket-weave' appearance. Treatment of Alport syndrome is limited to angiotensin converting enzyme inhibitors but the mechanism of their action on the glomerulus has not been fully elucidated.

Methods: To improve our understanding of disease and treatment mechanisms we aimed to generate a zebrafish model of Alport syndrome. The zebrafish is a highly tractable system that has become a premier organism for disease modelling. Many of the cellular components of the glomerular filter are conserved between zebrafish and humans. We have used *in situ* hybridisation with RNA probes and immunofluorescence with collagen type IV antibodies to observe if the molecular components of the glomerular filter are also conserved. In addition, we have used the CRISPR/Cas9 system to generate *col4a3*, *col4a4* and *col4a5* knockout mutant lines.

Results: We find zebrafish podocytes express *col4a3*, *col4a4* and *col4a5* and have also identified collagen type IV isoforms in the zebrafish GBM. We have also found phenotypes in the glomerulus of our knockout lines and have performed functional and ultrastructural analyses.

Conclusions: We have demonstrated expression of the α3α4α5(IV) network in the zebrafish GBM and have created a new *in vivo* model for Alport syndrome. This model will allow the use of new approaches to investigate disease mechanisms in Alport syndrome and will facilitate high throughput compound screening for drug discovery.

Funding: Government Support - Non-U.S.

SA-PO596

Genetically Affected Individuals with UMOD and MUC1 Mutations Who Donate a Kidney Have Surprisingly Good Renal Outcomes Anthony J. Bleyer,[5] Kendrah O. Kidd,[6] Peter J. Conlon,[1] Peter J. Lavin,[7] Claire Kennedy,[4] Anna Greka,[2,8] Stanislav Kmoch.[3] *[1]Beaumont Hospital, Dublin 9, Co Dublin, Ireland; [2]Harvard Medical School, Boston, MA; [3]Institute of Inherited Metabolic Disorders, Prague, Czech Republic; [4]Beaumont Hospital, Dublin, Ireland; [5]Wake Forest University School of Medicine, Winston-Salem, NC; [6]Wake Forest School of Medicine, Winston-Salem, NC; [7]Trinity Health Kidney Centre, Dublin, Ireland; [8]Broad Institute, Cambridge, MA.*

Background: Some individuals with UMOD and MUC1 mutations who were mildly affected donated kidneys prior to genotyping being available. The outcome of these individuals has not been studied.

Methods: We studied renal outcomes in 4 individuals with UMOD mutations and 3 individuals with MUC1 mutations.

Results: All donors donated to family members with the same mutation. One donor had a cerebral hemorrhage with donation immediately prior to death. The eGFR post-donation was lower than seen in health donors, with a mean egfr of 46.5± 5.3 ml/min. However, kidney function remained stable, and no donors required renal replacement therapy at a mean follow up of 10.2 5± 6.6 (range 3-18) years follow up. Likewise recipients have done well with all allografts functioning 12.9± 9.6 (range 3-18) years post-transplant.

Conclusions: Some individuals with MUC1 or UMOD mutations are mildly affected, and their eGFR and that of their donors remains surprisingly stable in most instances after donation. However, at this time individuals with these mutations should not yet be considered as kidney donors until more data is available.

Funding: NIDDK Support, Private Foundation Support

Genetically Affected Donors

Donor	Mutation	Donor Age	Current Age	Current eGFR
1	MUC1	34	52	53
2	MUC1	39	44	43
3	MUC1	52	55	42
4	MUC1	36	Deceased	
5	UMOD	25	34	44
6	UMOD	No data		
7	UMOD	42	58	52

SA-PO597

Possible Link Between Aging Nephropathy and DHTKD1 in C57BL/6J Mice Nathan D. Susnik,[1] Ron Korstanje,[2] Laura Reinholdt,[2] Nils Hanke,[1] Jan Hegermann,[1] Christoph Wrede,[1] Heike Bähre,[1] Hermann G. Haller,[1] Mario Schiffer,[1] Roland Schmitt.[1] *[1]Hannover Medical School, Hannover, Germany; [2]The Jackson Laboratory, Bar Harbor, ME.*

Background: During renal aging experiments, we found a spontaneous phenotype in a cohort of 18-22 month old C57BL/6J mice. Old mice developed pronounced glomerulosclerosis, amyloidosis, and renal dysfunction with proteinuria (GARD). Here, we tested the assumption that the GARD phenotype was due to a spontaneous mutation.

Methods: Whole exome sequencing data from a GARD mouse was compared to publicly available C57BL/6J reference sequence (GRCm38). C57BL/6J and C57BL/6JRJ mice purchased from different suppliers were sequenced for mutations in DHTKD1. Cellular localization of DHTKD1 was examined in murine and human kidneys and in renal cells. *DHTKD1* expression was manipulated with Crispr-Cas9 and siRNA in cell lines and morpholino in zebrafish.

Results: Whole exome sequencing revealed that GARD mice had a single nucleotide polymorphism leading to an amino acid substitution (A335T) in the thiamine-binding motif of dehydrogenase E1 and transketolase domain containing 1 (*DHTKD1*). All C57BL/6J mice in the GARD cohort were homozygous for the *Dhtdk1* mutation (*Dhtkd1*$^{A335T/A335T}$) while C57BL/6JRJ mice with normal renal aging carried the reference allele (*Dhtkd1*$^{+/+}$). *DHTKD1* was expressed in podocytes, proximal tubules, and distal tubules. Contrary to previously reported data, knockout (KO) of *DHTKD1* left mitochondrial morphology, genes associated with mitochondrial function, and ATP production unchanged. Flow cytometry, however, revealed more MTC02 in *DHTKD1* KO cells. KO cells also had more 2-aminoadipic- and 2-oxoadipic acid, metabolites of lysine degradation. siRNA in human podocytes changed some mitochondria-associated genes, but made no difference in ATP production. Knockdown of *Dhtkd1* in zebrafish larvae led to proteinuria and podocyte foot process effacement. While these changes indicate a functional role for DHTKD1 in renal maintenance, C57BL/6J *Dhtkd1*$^{A335T/A335T}$ mice aged at our own facilities did not develop GARD.

Conclusions: Overall, knockdown of *DHTKD1* causes structural and functional changes in cells and zebrafish; however, the GARD phenotype in *Dhtkd1*$^{A335T/A335T}$ mice was not fully penetrant, suggesting that other variables like diet or housing are involved. .

Funding: Other NIH Support - National Cancer Institute

SA-PO598

A Novel Deletion in ACTN4 in a Patient with Renal FSGS and Concomitant TMA Johannes Muench,[4] Ralph Wendt,[3] Ria Schönauer,[4] Maik Grohmann,[1] Joachim H. Beige,[3] Thorsten Wiech,[2] Tom H. Lindner,[4] Carsten Bergmann,[1] Jan Halbritter.[4] *[1]Bioscientia, Ingelheim, Germany; [2]Department of Pathology, University Hospital Hamburg Eppendorf, Hamburg, Germany; [3]Hospital St. Georg, Leipzig, Germany; [4]Division of Nephrology, University Clinic Leipzig, Leipzig, Germany.*

Background: Thrombotic microangiopathy (TMA) of the kidney leading to renal failure is associated with genetic susceptibility due to variants of genes encoding complement components in the majority of cases. Recently, Challis et al (*JASN 2016*) reported two families with biopsy proven TMA who inherited mutations of *INF2*, a gene that is known to cause familial FSGS. As inverted formin 2 (INF2) is essential for podocytic cytoskeleton integrity by regulating the actin-polymerization and –depolymerization process, it is reasonable to assume, that genetically determined functional deficiency of further podocytic structural proteins might provoke renal TMA-phenotypes as well.

Methods: A 30-year old male patient presented with acute kidney failure and proteinuria (eGFR 11 ml/min, proteinuria 3563 mg/g creatinine). At the time of presentation, laboratory findings showed no signs of hemolytic anemia. Kidney biopsy revealed advanced glomerulosclerosis and TMA in preglomerular arterioles and glomeruli. Genetic testing regarding mutations of known aHUS-genes showed no pathogenic variants but the risk polymorphisms *MCP-H2* and *CFHR1*B.* However, a novel heterozygous three-base deletion in exon 8 of *ACTN4* was detected, leading to loss of lysine at amino acid residue 255 (c.763_765delAAG; p.Lys255del). A therapeutic approach with eculizumab was unsuccessful as control biopsy after four months revealed progressive glomerular and tubulointerstitial scarring.

Results:

Conclusions: *ACTN4*-mutations are known to cause autosomal dominant FSGS and most disease-causing mutations are located within the protein's actin-binding domain. The pathogenicity of the *ACTN4* mutation in our patient is assumable, as functional alterations upon amino acid substitution at the same position (C.763A>G; p.Lys255Glu) have been demonstrated previously (Feng et al, *PLoS One* 2015). However, *ACTN4* mutations have not been associated with renal TMA yet, although this phenotype was already reported in other forms of familial FSGS (Benz et al, *Pediatr Nephrol* 2007). We therefore propose that pathogenic variants in *ACTN4* may account for renal TMA, which adds to the clinical pleiotropy of mutated *ACTN4*. Hence, mutated *ACTN4* should be considered in patients with renal TMA, especially in those with an eculizumab-resistant progress and unremarkable complement genetics.

Funding: Private Foundation Support

SA-PO599

Comprehensive Analysis of the Renal and Systemic Phenotypes Associated with Familial Deficiency of Lecithin-Cholesterol Acyltransferase: a Case Series Carlos T. Sampaio,[1] Bruno E. Balbo,[1] Leonardo C. Saraiva,[1] Henrique R. Nakano,[1] Andressa G. Amaral,[1] Eliene Costa,[1] Elieser H. Watanabe,[1] Precil D. Neves,[1] Ana P. Chacra,[2] Raul Maranhao,[2] Antonio A. Guerra,[3] Ricardo M. Braga,[4] Ruth M. Santo,[4] Leonardo A. Testagrossa,[5] Marlene A. Reis,[6] Junior A. Silva,[7] Henrique Carrascossi,[8] Luiz F. Onuchic.[1] *[1]Nephrology and Molecular Medicine, University of Sao Paulo, Sao Paulo, Brazil; [2]Cardiopneumology, University of Sao Paulo, Sao Paulo, Brazil; [3]Hematology, University of Sao Paulo, Sao Paulo, Brazil; [4]Ophtalmology, University of Sao Paulo, Sao Paulo, Brazil; [5]Pathology, University of Sao Paulo, Sao Paulo, Brazil; [6]Pathology, Federal University of Triangulo Mineiro, Uberaba, Brazil; [7]Piaui Municipal Service, Sao Francisco, Brazil; [8]Araraquara Municipal Service, Araraquara, Brazil.*

Background: Lecithin cholesterol acyltransferase (LCAT) is involved in cholesterol metabolism. Familial LCAT deficiency (FLD) is a recessive disease associated with systemic lipid deposition, often resulting in CKD and fish-eye opacities.

Methods: Retrospective study, comprising clinical, laboratory and molecular genetic analyses of FLD patients.

Results: Twenty males and 18 females were diagnosed with FLD at an age of 38.6±16.4 yrs. Three pathogenic mutations in *LCAT* were identified: p.R268H, p.T298I and p.I227F, corresponding to distinct disease clusters. All patients had HDL-c ≤10mg/dL, ApoAI was 0.45±0.10g/L and ApoB 0.41±0.19g/L. Corneal opacities were seen in 36 cases; Scheimpflug densitometry revealed high corneal density in all 3 evaluated individuals. Anemia was present in 25 cases (Hb of 10.7±2.2g/dL) and hemolysis in 27. Increased resistance of red blood cells to osmotic stress was observed in all 5 evaluated patients. Estimated glomerular filtration rate (eGFR) displayed high intra- and interfamilial variability; 7 patients developed ESKD at an age of 38.3±14.2 yrs. Protein/creatinine ratio was 0.54g/g (p25-p75: 0.12-1.77) in nondialytic cases; 9 of 21 had hematuria. C3 was low in 1 patient while C4 was normal in all. Hypertension, present in most cases, was associated with age>30 yrs and eGFR<83mL/min/1.73m^2 (OR 15.5). Coronary artery calcium score was zero in the 2 evaluated patients. Kidney biopsy revealed glomerular deposits (8/8 patients), glomerular sclerosis (7/8), endocapillary proliferation (4/8), glomerular basement membrane splitting (4/8), and interstitial fibrosis (<5-60%). Thrombotic microangiopathy (TMA) was detected in 3 cases and dominance/codominance of C3 mesangial deposits in all. Treatment included RAS inhibitors and statins.

Conclusions: The renal phenotypic variability suggests that environmental and/or genetic factors may modify CKD progression in FLD. Our findings suggest that, in addition to cholesterol deposition, TMA and C3 mesangial deposits may also contribute to renal injury, supporting a pathogenic role for activation of the alternative complement pathway.

Funding: Government Support - Non-U.S.

SA-PO600

Clinical Characterization of Families with Mutations in the MUC-1 Gene Anthony J. Bleyer,[8] Constantinos Deltas,[7] Gregory Papagregoriou,[7] Stanislav Kmoch,[4] Kendrah O. Kidd,[8] Seth L. Alper,[2] Peter J. Lavin,[9] Daniel P. Gale,[6] Peter J. Conlon,[1] Peter C. Harris,[5] Anna Greka.[3] *[1]Beaumont Hospital, Dublin 9, Co Dublin, Ireland; [2]Beth Israel Deaconess Medical Center, Boston, MA; [3]Harvard Medical School, Boston, MA; [4]Institute of Inherited Metabolic Disorders, Prague, Czech Republic; [5]Mayo Clinic, Rochester, MN; [6]University College London, London, United Kingdom; [7]University of Cyprus, Nicosia, Cyprus; [8]Wake Forest University School of Medicine, Winston-Salem, NC; [9]Trinity Health Kidney Centre, Dublin, Ireland.*

Background: Autosomal dominant tubulo-interstitial kidney disease (ADTKD) due to MUC1 mutations is caused most commonly by a single cytosine insertion within the variable number of tandem repeat (VNTR) region of the MUC1 gene. ~ 30 families have been reported with this condition to date, with considerable variation in the observed age of onset of end stage renal disease (ESRD). We have reevaluated these clinical findings in a larger cohort of families.

Methods: MUC1 mutational analysis was carried out through an assay designed by and offered at no cost to patients or providers at Broad Institute of MIT and Harvard on families with a history of ADTKD. Family histories and pedigrees were clinically characterized. We also included historic data for patients with presumed ADTKD-MUC1 (defined as deceased family members who reached ESRD, and from whom DNA samples were unavailable for mutational analysis).

Results: We identified a *MUC1* mutation in 129 families. The mean age of ESRD among individuals was 44.0 ± 13.7 years, with substantial inter- and intrafamilial variation. The mean age of ESRD onset for all families was 41.5 ± 11.5, with a range from 25 to 73.5 years. The mean age of ESRD for families with more than 20 affected members was 50.9 ± 13.0, vs a mean age of ESRD of 41.4 ± 13.1 for families with fewer than 20 affecteds ($p < 0.0001$). Figure 1 shows the mean age of ESRD onset for 23 largest families, with significant variation in age of ESRD within families.

Conclusions: The mean age of ESRD varies substantially within and among families with ADTKD-MUC1. Larger families have a later mean age of onset of ESRD, likely reflecting milder kidney disease resulting in larger ascertained family size. Further work will aim to identify risk factors for disease severity.

Funding: Private Foundation Support

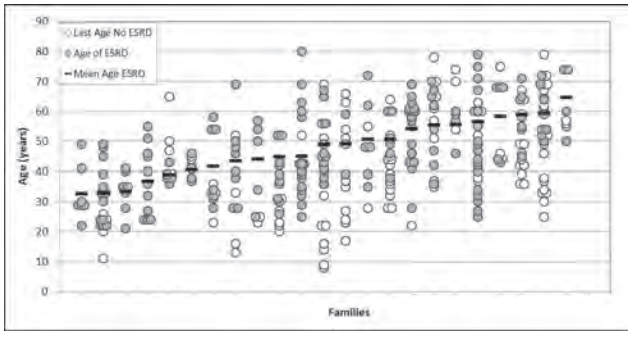


Figure 1. Age of ESRD in individuals according to *MUC1* family. Each column represents one of our 23 largest MKD families.

SA-PO601

Kidney Outcome in Primary Hyperoxaluria Type 3 Mary I. McIntosh,[1] Peter C. Harris,[1] Ramila A. Mehta,[2] Julie B. Olson,[1] Barbara M. Seide,[1] Felicity T. Enders,[1] David J. Sas,[1] John C. Lieske,[1] Dawn S. Milliner.[1] *[1]Mayo Clinic, Rochester, MN; [2]Mayo Clinic, Rochester, MN, Rochester, MN. Group/Team: Rare Kidney Stone Consortium.*

Background: Primary hyperoxaluria type 3 (PH3) is caused by *HOGA1* gene mutations. Little is known of the mechanism of hyperoxaluria, long term outcome, or genotype effects.

Methods: PH3 patients were identified (n=47) from the Rare Kidney Stone Consortium (RKSC) PH Registry and categorized by *HOGA1* mutations. In addition to demographics and baseline laboratory data, eGFR and urine oxalate (Uox) were compared at diagnosis (dx) and last followup (f/u). Comparisons between groups were by Chi-square test for categorical variables and Kruskal-Wallis test for continuous variables.

Results: Most frequent mutations were the splicing change p.Leu233_Gly234ins17, n=10 homozygotes (Leu233), and the inframe deletion p.Glu315del, n=9 homozygotes (Glu315). Comparisons were made between these and all other combinations (n = 28). Among PH3 overall, eGFR declined with age (r^2=.30, p= .0001). Among patients < 20 yrs of age, median eGFR at dx for Leu233 was 125.3 ml/min/1.73m^2 vs. 115.7 in Glu315 and 86.3 among all others (p=0.057). There were no significant differences among genotype groups for age at dx or f/u yrs [median 4.5(1.1,11.7)]. There was a trend toward lower Uox and higher eGFR in the Leu233 group at dx and at f/u, though statistically significant only for Uox at f/u (p=0.02) and eGFR at dx (p=0.047). Urine HOG did not correlate with urine glycerate in PH3 overall (r=.39, p=0.12).

Conclusions: PH3 patients show decreasing eGFR over time. Lower Uox and higher eGFR trends were seen in Leu233 homozygotes, though patient numbers were small. HOG suppression of GRHPR as a mechanism for the hyperoxaluria, predicted to elevate d-glycerate, is not supported by this data. Further study is needed to understand genotype effects and outcome of PH3.

Funding: NIDDK Support, Other NIH Support - NCATS, Private Foundation Support

PH3 Patient Characteristics

	Total (n=47)	Leu233 (n=10)	Glu315 (n=9)	Others (n=28)	P
Age at diagnosis (dx), yrs	5.8(2.3,19.8)	3.8(2.1,4.8)	3.2(1.4,46.8)	6.9(4.2,27.1)	0.15
Uox at dx [1]	1.1(0.9,1.4)	1.05(0.91,1.33)	1.03(0.85,1.12)	1.18(0.94,1.44)	0.49
UHOG, mg/gm creat [2]	76.4(39.7,108.0)	102.4(99.2,108.0)	42.4(38.6,100.6)	44.3(27.7,150.3)	0.41
Uglycerate, mg/gm creat [3]	3.0(0.83,13.17)	23.1(10.3,44.0)	3.8(0.66,3.9)	1.3(0.15,7.9)	0.09
eGFR at dx	93.9(67.1,107.4)	101.0(94.6,134.6)	102.2(74.1,104.2)	77.9(62.9,95.0)	0.047
Uox at f/u	0.98(0.7,1.3)	0.62(0.53,0.96)	1.06(0.82,1.16)	1.13(0.81,1.35)	0.03
eGFR at f/u	95.1(69.7,109.2)	98.0(85.4,133.3)	96.6(65.5,104.1)	86.2(68.1,108.8)	0.40

Values are median(Q1,Q3); [1]Uox, mm/BSA/day, normal < 0.45; [2]Urine HOG, normal < 5 mg/gm creat; [3]Urine glycerate, normal < 55 mg/gm creat <10 yrs of age then <25

SA-PO602

KEOPS Complex Dysfunction Causes Nephrotic Syndrome by Impairing Protein Biosynthesis and by Inducing ER Stress Daniela A. Braun,[1] Jia Rao,[1] Geraldine Mollet,[3] David Schapiro,[1] Weizhen Tan,[1] Jennifer Hu,[4] Peter Dedon,[5] Herman Van tilbeurgh,[7] Martin Zenker,[6] Corinne Antignac,[2] Friedhelm Hildebrandt.[1] *[1]Boston Children's Hospital, HMS, Boston, MA; [2]Imagine Institute, Paris, France; [3]Inserm U1163, Paris, France; [4]MIT, Cambridge, MA; [5]Massachusetts Institute of Technology, Cambridge, MA; [6]University Hospital Magdeburg, Magdeburg, Germany; [7]Université Paris Sud CNRS UMR9198, Orsay, France.*

Background: Steroid resistant nephrotic syndrome (SRNS), a disease of glomerular podocytes, is a frequent cause of end-stage renal disease in children and young adults. Identification of single-gene causes of SRNS has contributed to a better understanding of podocyte biology. In 32 unrelated families, we recently identified mutations in genes encoding the evolutionarily highly conserved KEOPS complex (*LAGE3, OSGEP, TP53RK,* and *TPRKB)* as novel monogenic cause of SRNS and microcephaly. The KEOPS complex catalyzes an essential posttranscriptional modification of tRNA.

Methods: To characterize the pathogenesis of the four newly recognized human disease genes, we measured tRNA modifications by mass-spectrometry, assessed protein biosynthesis *in vitro*, and performed immunoblotting of ER stress marker proteins.

Results: We show that shRNA knockdown of *OSGEP* or *TPRKB* in human podocytes reduced the cellular content of t6A, a specific posttranscriptional modification of tRNA. Using a yeast system, we demonstrate that human mutations of *OSGEP,* identified in patients with SRNS, alter the t6A-related catalytic activity of the encoded protein. We furthermore found that knockdown of *OSGEP, TP53RK,* or *TPRKB* inhibited *de novo* protein biosynthesis and activated the unfolded protein response in human podocytes, thus indicating the presence of ER stress. Knockdown of either of the three genes induced apoptosis in human podocytes, suggesting a central role in the pathogenesis of SRNS in patients with mutations in KEOPS complex genes.

Conclusions: Studying the pathogenesis of four newly recognized monogenic causes of SRNS, we generate evidence that altered function of the KEOPS complex results in podocyte damage by impairing the rate and the accuracy of *de novo* protein biosynthesis.

Funding: NIDDK Support, Government Support - Non-U.S.

SA-PO603

Analysis of 24 Genes Reveals a Monogenic Cause in 11% of Cases with Steroid Resistant Nephrotic Syndrome at a Single Center Weizhen Tan,[1] Svjetlana Lovric,[1,2] Shazia Ashraf,[1] Jia Rao,[1] David Schapiro,[1] Merlin Airik,[1,3] Shirlee Shril,[1] Heon Yung Gee,[1] Michelle A. Baum,[1] Ghaleb H. Daouk,[1] Michael A. Ferguson,[1] Nancy M. Rodig,[1] Michael J. Somers,[1] Deborah R. Stein,[1] Asaf Vivante,[1] Jillian K. Warejko,[1] Eugen Widmeier,[1] Friedhelm Hildebrandt.[1] *[1]Boston Children's Hospital, Boston, MA; [2]Hannover Medical School, Hannover, Germany; [3]University of Pittsburgh, Pittsburgh, PA.*

Background: Background: Steroid resistant nephrotic syndrome (SRNS) is the second most frequent cause of end stage renal disease (ESRD) among patients manifesting <25 years of age. We performed mutation analysis using a high-throughput PCR-based microfluidic technology in 24 single-gene causes of SRNS in a cohort of 72 families, who manifested with steroid resistant nephrotic syndrome before the age of 25 years.

Methods: Methods: Within an 18 month interval, we obtained DNA samples, pedigree information, and clinical information from 77 consecutive children with SRNS from 72 different families seen at Boston Children's Hospital (BCH). Mutation analysis was completed by combining high-throughput multiplex PCR with next-generation exon sequencing. We analyzed the sequences of 18 recessive and 6 dominant genes of SRNS in all 72 families for disease causing variants.

Results: Results: We identified the disease causing mutation in 8 of 72 (11.1%) families. Mutations were detected in the 6 genes: *NPHS1* (2/72), *WT1* (2/72), and in *NPHS2, MYO1E, TRPC6,* and *INF2.* Median age of onset was 4.1 years in patients without a mutation (range 0.5-18.8), and 3.2 years in those where the causative mutation was detected (range 0.1-14.3). Mutations in dominant genes presented with a median onset of 4.5 years (range 3.2-14.3). Mutations in recessive genes presented with a median onset of 0.5 years (range 0.1-3.2).

Conclusions: Conclusion: Our molecular genetic diagnostic study identified the underlying monogenic cause of steroid-resistant nephrotic syndrome in ~11% of patients with SRNS using a cost effective technique. We delineated some of the therapeutic, diagnostic, or prognostic implications. Our study confirms that genetic testing is indicated in pediatric patients with SRNS.

Funding: NIDDK Support, Private Foundation Support, Government Support - Non-U.S.

SA-PO604

Clinical and Molecular Analysis of 17 Families with a Heterozygous Mutation in COL4A3 or COL4A4 Ilse M. Rood, Sander Groen in 't Woud, Jeroen Schoots, Jack F. Wetzels, Dorien Lugtenberg, Jeroen Deegens, Ernie M. Bongers. *Radboudumc, Nijmegen, Netherlands.*

Background: Heterozygous mutations in *COL4A3* and *COL4A4 (COL4A3/4)* have been described as a cause of Alport syndrome and benign familial hematuria. Recently, these mutations were associated with focal segmental glomerulosclerosis (FSGS) and renal function deterioration as well. The aims of this study are 1) further delineation of the phenotypic spectrum of heterozygous *COL4A3/4* variants, and 2) to investigate whether variants in *NPHS2* (R229Q/ R138Q) and *NEPH3* (V353M) modify the phenotypic expression of *COL4A3/4* mutations.

Methods: Patients with a heterozygous mutation in *COL4A3/4,* detected by diagnostic exome sequencing (ES) using a renal gene panel between 2013 and 2016, were included.

Results: Of 72 patients analyzed because of a familial glomerular disease, a heterozygous mutation in *COL4A3/4* was found in 17 (24%). All patients had microscopic hematuria at clinical presentation and 14 had (micro)albuminuria, including two patients within nephrotic range (3,7 and 6gr/24h). Median age at clinical presentation was 43 years (range 4-55). Renal biopsy in ten index patients showed FSGS (n=3), TBMN (n=1) and MCN (n=1), and in one patient electron microscopy (EM) was compatible with Alport syndrome. In four patients, LM and IF was inconclusive, and EM showed segmental thinning of the GBM. No correlation was found between renal biopsy and clinical status. Segregation analyses in 13 families revealed 24 additional patients with a heterozygous *COL4A3/4* variant. At end of follow up (median age 53 years, range 13-81), 14/41 patients (35%) had renal function deterioration (MDRD4 < 60ml/min), of whom six had ESRD (mean age at ESRD 51 years). Hearing loss and visual impairment was present in 1/41 patients. The R229Q / R138Q variants in *NPHS2* were not detected. Variant V353M in *NEPH3* was found homozygous in one patient and heterozygous in another patient.

Conclusions: This study broadens the phenotypic spectrum: 1) clinical presentation and course of disease is highly variable and not limited to benign hematuria, 2) renal pathology is not limited to FSGS or TBMN. The heterogeneity could not fully be explained by modifier variants in *NPHS2* and *NEPH3.*

SA-PO605

APOL1 Glomerular Transcriptional Networks in Non-Black FSGS Patients D Fermin, K Yasutake, Matt G. Sampson. *University of Michigan, Ann Arbor, MI. Group/Team: NEPTUNE.*

Background: The "G1" & "G2" alleles of *APOL1* are common in African-Americans and confer greatly increased risk for the development of FSGS. While these risk variants are essentially absent in non-blacks, *APOL1* is substantially expressed in kidney tissue across races. Furthermore, experimental models have shown that increased expression of wild-type *APOL1* is also associated with renal toxicity. Thus, we hypothesized that even when not harboring G1 & G2, glomerular *APOL1* may have a role in NS pathogenesis. To pursue this, we contextualized *APOL1* expression within glomerular transcriptional networks derived from whites with FSGS enrolled in the Nephrotic Syndrome Study Network (NEPTUNE).

Methods: Transcriptomic data was available from microdissected glomeruli of 18 white NEPTUNE participants with FSGS (100% wild-type *APOL1*). We measured *APOL1* expression & then used "**W**eighted **G**ene **C**o-expression **N**etwork **A**nalysis" (WCGNA) to identify genesets significantly correlated with its expression. To identify biologic processes associated with these genesets, we use gene-ontology term based enrichment analysis. To idenity key genes in these biologic processes, we constructed interaction networks.

Results: *APOL1* was in the top 15th percentile of expression of the 18,000 glomerular genes analyzed. There were 5 co-expression networks significantly correlated with *APOL1*. The most significant (r=-0.65, p=0.004) was enriched for GO terms related to anion transmembrane transport & metabolic processes. The 2nd most correlated network (r=0.64, p=0.004) was enriched for development processes, particularly vascular & epithelial development. Viral responses & Type 1 Interferon signaling pathways, previously implicated in intrarenal transcriptomic studies of black NS patients with a HR *APOL1* genotype, were enriched in the 5th most correlated network (r=0.50, p=0.04). *CD4* was a central hub in this network.

Conclusions: Our study of *APOL1* in the glomeruli of white FSGS patients identified similarities to black patients with *APOL1*-attributed NS, both in expression level & co-regulated networks. But we also discovered highly correlated glomerular networks enriched for non-immune related biology. Some of these processes have been implicated in previous studies of *APOL1*, while others are novel. Further study of *APOL1* glomerular transcriptional networks across races may help us discover the biologic mechanisms driving *APOL1*-attributed NS.

Funding: NIDDK Support, Private Foundation Support

SA-PO606

Clinical Gout Separates ADTKD-UMOD from ADTKD-MUC1 in a Large International Registry Eric G. Olinger,[3] Kendrah O. Kidd,[4] Anna Greka,[1] Stanislav Kmoch,[2] Anthony J. Bleyer,[4] Olivier Devuyst.[3] *[1]Harvard Medical School, Boston, MA; [2]Institute of Inherited Metabolic Disorders, Prague, Czech Republic; [3]University of Zurich, Zurich, Switzerland; [4]Wake Forest University School of Medicine, Winston-Salem, NC.*

Background: Autosomal dominant tubulointerstitial kidney diseases (ADTKD) comprise a group of rare disorders characterized by progressive CKD with interstitial fibrosis and tubular atrophy. ADTKD is genetically heterogeneous: mutations in *UMO*D are mainly involved but *MUC1*, *HNF1B* and *REN* have also been associated. Despite a recent gene-based disease ontology, clinical characteristics and diagnostic criteria of various ADTKD subgroups remain to be defined.

Methods: In an international effort, 463 families diagnosed with ADTKD were included in a comprehensive registry. Index cases were screened for *UMOD* mutations, followed by *MUC1*, *HNF1B* and *REN* mutations in *UMOD*-negative families.

Results: We detected mutations in *UMOD* in 181 families (39.1%). Among the *UMOD*-negative families, 20.3% screened positive for *MUC1*, 12.5% positive for *HNF1B* and 1.8% positive for *REN* mutations. 107 mutations were detected in *UMOD,* all missense except 7 small indels, with 90% clustering in exon 3 and 56% involving cysteine residues. All *MUC1* families displayed cytosine insertion in the VNTR region. Point mutations, small indels and large genomic rearrangements were reported in *HNF1B*. Clinical gout was more prevalent in ADTKD-*UMOD* cases compared *to* ADTKD-*MUC1* (58% vs. 17% of cases respectively, p<0.0001; PPV: 0.86) with an earlier age of onset (29.0±12.7 vs. 43.3±14.2 years; p<0.0001). A family history (FH) of CKD and gout was reported in 66% of ADTKD-*UMOD* cases contrasting with a predominant FH of isolated CKD in 84% of ADTKD-*MUC1*. FH of CKD with gout separates ADTKD-*UMOD* from ADTKD-*MUC1* (p<0.0001; PPV: 0.92) in this cohort.

Conclusions: Mutations in *UMOD* and *MUC1* are the leading genetic causes for ADTKD. Personal or familial history of clinical gout and early age of gout onset are specifically associated with ADTKD-*UMOD* inside this group of disorders. This international registry will help to identify modifying genes and biomarkers in ADTKD subgroups and to test future interventions.

SA-PO607

Identification of a New Mutation Mapping in the Renin Mature Protein Associated with Autosomal Dominant Tubulo-Interstitial Kidney Disease Celine Schaeffer,[1] Claudia Izzi,[2] Gianfranco Savoldi,[2] Elena Pasqualetto,[1] Gianluca Caridi,[3] Antonio Amoroso,[4] Luca Rampoldi,[1] Francesco Scolari.[2] *[1]San Raffaele Scientific Institute, MILAN, Italy; [2]Montichiari Hospital, ASST, Montichiari (Brescia), Italy; [3]Gaslini Institute, Genova, Italy; [4]University of Torino, Torino, Italy.*

Background: Autosomal dominant tubulo-interstitial kidney diseases (ADTKD) is a renal disorder characterised by interstitial fibrosis, tubular atrophy and dilation, and thickening and lamellation of tubular basal membranes. Known responsible genes are *UMOD* (uromodulin), *MUC1* (mucin 1), *HNF1B* (HNF1beta), *REN* (renin) and *SEC61A1* (Sec 61 translocon alpha 1 subunit). ADTKD-*REN* is usually characterised by early onset, anaemia during childhood, hyperkaelemia and mild hypotension. All ADTKD mutations in renin so far reported are localised in the leader peptide of the protein (aa 1-23; exon 1), affecting its co-translational insertion in the endoplasmic reticulum (ER).

Methods: Whole exome sequencing was performed on 3 sibs (2 affected and 1 healthy) of a pedigree with suspected ADTKD of unknown origin that tested negative for

UMOD, *HNF1B* and *REN* (exon1). A variant was found in *REN* (exon 10) and confirmed by Sanger sequencing. The effect of such variant was studied by expression in cell lines.

Results: We identified a unique *REN* mutation (p.L381P) that is associated with ADTKD. This variant co-segregates with renal disease following an autosomal dominant way on inheritance. It was found in all tested affected individuals (3) and absent in healthy subject (1). The p.L381P variant is not found in sequence databases from disease-specific and population genetic studies (ExAC, gnomAD). Interestingly this variant maps in mature renin and is predicted to be damaging (Polyphen, SIFT, SDM). Functional studies in HEK293 and AtT20 cell lines showed that L381P renin is fully retained in the ER and it is absent from the culturing medium. This effect is likely due to mutant protein misfolding. ER retention induces ER stress. Co-expression of mutant protein with wild type renin does not interfere with wild type protein trafficking and secretion.

Conclusions: These results suggest that the spectrum of *REN* mutations associated with ADTKD is broader and that screening of the *REN* gene in patients compatible with ADTKD diagnosis should not be limited to exon 1. Interestingly, the possible mechanism of pathogenesis associated with the p.L381P mutation, i.e. ER stress and reduced secretion, is likely similar to the one proposed for already described mutations in the leader peptide.

SA-PO608

Diet-Dependent Development of CKD in a Mouse Model of Cystinuria Type I Lauren E. Woodard,[1,3] Rick C. Welch,[3] Ruth A. Veach,[2] Thomas M. Beckermann,[3] Feng Sha,[3] Talat Alp Ikizler,[1,3] Jay A. Tischfield,[4] Amrik Sahota,[4] Matthew H. Wilson.[1,3] *[1]Veterans Affairs, Tennessee Valley Healthcare System, Nashville, TN; [2]Vanderbilt University Medical Center, Nashville, TN; [3]Medicine, Division of Nephrology, Vanderbilt University Medical Center, Nashville, TN; [4]Genetics, Rutgers University, Piscataway, NJ.*

Background: Cystinuria type I results from mutation of *SLC3A1* and is a disorder of renal amino acid transport, resulting in recurrent nephrolithiasis and significant morbidity. It is one of the most common autosomal recessive genetic disorders in humans with an incidence in the United States of 1 in 15000. Using two diets, we compared the rate of stone and chronic kidney development in *Slc3a1* knockout mice.

Methods: In a mouse model of cystinuria type I, mice lacking the gene had increased basic amino acids in their urine and developed cystine stones. Mice were supplied with either a normal or breeder chow diet and allowed to age for approximately one year. Blood and tissue samples were obtained to assess development of chronic kidney disease in each group. We also evaluated cystine levels in the blood and glutathione (GSH) levels in the liver.

Results: When placed on a normal diet, aged *Slc3a1* knockout mice had an elevated blood urea nitrogen (BUN) and normal serum creatinine. *Slc3a1* knockout mice that were aged on a breeder diet containing higher levels of cystine had more severe chronic kidney disease as indicated by both elevated BUN and serum creatinine. Histologic analysis also revealed a greater degree of kidney and bladder injury in aged mice maintained on a breeder diet than in those maintained on a normal diet. Additionally, we observed lower levels of cystine in the blood of knockout animals. The availability of cysteine, which forms cystine when two molecules are joined together, is a major determinant of the regulation of GSH synthesis. We found that glutathione levels in the liver were reduced in the *Slc3a1* knockout animals.

Conclusions: These results suggest that diet can modulate the severity of kidney disease that developed over time in an animal model of cystinuria and may have implications for the potential to modulate disease severity in cystinuric patients. Additionally, lack of *Slc3a1* function results in lower blood cystine and tissue glutathione levels indicating a metabolic phenotype beyond just kidney stone formation in cystinuria.

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SA-PO609

Macrophage Enzyme Chitotriosidase Reflects Long-Term Cystine Accumulation in Cystinosis Mohamed A. Elmonem,[2,5] Koenraad Veys,[3] Maria Van dyck,[4] Mirian C. Janssen,[6] Elisabeth A. Cornelissen,[1] Elena N. Levtchenko.[3] *[1]Radboud University Medical Centre, Nijmegen, Netherlands; [2]Laboratory of Pediatric nephrology, University Hospital Leuven, KU Leuven, Leuven, Belgium; [3]University Hospitals Leuven, Leuven, Belgium; [4]university hospitals Leuven, Leuven, Belgium; [5]Clinical and Chemical Pathology, Faculty of Medicine, Cairo University, Cairo, Egypt; [6]Radboudumc university Medical centre, NIJMEGEN, Netherlands.*

Background: Cystinosis is an autosomal recessive lysosomal storage disorder characterized by early renal damage. Strict compliance to the cystine depleting agent cysteamine is necessary for more efficient treatment. Leucocyte cystine is the current therapeutic monitor. Although highly specific, its use is hindered by many technical difficulties and its availability in only few laboratories. Recent evidence suggests that inflammatory cells play a major role in the pathogenesis of cystinosis and its rapid progression to ESRD. Macrophage activation markers, such as chitotriosidase and several cytokines have been linked to disease severity and response to cysteamine therapy in cross-sectional studies. We aim to assess the longitudinal clinical value of these markers as potential therapeutic monitors in a large cohort of cystinosis patients.

Methods: Fifty four patients (19 children and 35 adults) were recruited from the cystinosis clinics in Leuven (Belgium), Nijmegen (Netherlands) and Traunstein (Germany). Patients were followed-up for two years during which, clinical and laboratory data were regularly collected from hospital records. Every three months, plasma samples were obtained to analyze chitotriosidase and other cytokines. These markers were correlated with leucocyte cystine concentration and with other parameters of renal disease such as, serum creatinine and urinary albumin/creatinine ratio.

Results: Cystinosis patients showed large variation in compliance/response to cysteamine therapy. Average leucocyte cystine concentrations over two years ranged from 0.65 to 5.8 nmol ½ cystine/mg protein. During the first year of the study, plasma chitotriosidase activities ranged from 2 to 834 nmol/ml plasma/h in cystinosis patients (reference range <55 nmol/ml plasma/h). Chitotriosidase activities correlated with individual cystine measurements ($r=0.432$, $P=0.002$). More importantly, the correlation was stronger with the average cystine values ($r=0.582$, $P<0.001$).

Conclusions: Chitotriosidase activity correlates with long-term cystine concentrations and can be used for the therapeutic monitoring of cysteamine therapy in nephropathic cystinosis.

Funding: Commercial Support - Raptor pharmaceuticals

SA-PO610

Cell Non-Autonomous Origin of Renal Fibroblasts in Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD) Annie Shao, Siu Chiu Chan, Alan Mickelson, Peter Igarashi. *University of Minnesota, Minneapolis, MN.*

Background: Autosomal dominant tubulointerstitial kidney disease (ADTKD) is an uncommon disorder that is characterized by slowly progressive CKD and autosomal dominant inheritance. Renal histology shows tubular cysts and interstitial fibrosis. ADTKD is genetically heterogeneous and can arise from mutations in at least four different genes. ADTKD-HNF1B is caused by mutations of the transcription factor hepatocyte nuclear factor-1β (HNF-1β). The mechanism whereby mutations of HNF-1β, an epithelial-specific protein, produce renal interstitial fibrosis is not known. Here, we performed lineage analysis to determine whether renal fibroblasts originate from HNF-1β-deficient tubular epithelial cells or via a cell non-autonomous process.

Methods: Ksp/Cre;$Hnf1b^{F/F}$ mice were generated to specifically ablate HNF-1β in renal tubular cells. These mice were crossed with RYFP mice to introduce an EYFP reporter gene that is permanently activated upon Cre/loxP recombination, thereby enabling us to follow the fate of HNF-1β mutant cells. Kidneys were harvested from Ksp/Cre;$Hnf1b^{F/F}$;RYFP (HNF-1β KO) mice at P16 and P28. $Hnf1b^{F/+}$;RYFP littermates were used as negative controls.

Results: Histological staining with trichrome, PAS, and H&E showed that HNF-1β KO kidneys developed cysts and had increased extracellular matrix compared to control kidneys at P16. Costaining of HNF-1β KO kidney sections with antibodies against HNF-1β and EYFP showed that HNF-1β was absent in EYFP-positive cyst epithelial cells, confirming that expression of EYFP marks HNF-1β mutant cells. Costaining of HNF-1β KO kidney sections at P28 with antibodies against EYFP and entactin revealed that HNF-1β mutant cells remained on the luminal side of the tubular basement membrane. Costaining of HNF-1β KO kidney sections with antibodies against EYFP and smooth muscle α-actin revealed that myofibroblasts accumulated in the renal interstitium but did not express EYFP.

Conclusions: We conclude that HNF-1β-deficient kidneys develop fibrosis as early as P16. Lineage tracing demonstrates that HNF-1β mutant epithelial cells do not migrate out of renal tubules. Fibroblasts in the interstitium are not of tubular origin, indicating that fibrosis in ADTKD-HNF1B is due to a cell non-autonomous mechanism.

Funding: NIDDK Support

SA-PO611

Leveraging Statistical Natural Language Processing (NLP) to Surface Clinically Relevant Biomarkers in Pediatric Nephrotic Syndrome Friedhelm Hildebrandt,[1] Svjetlana Lovric,[1] Shirlee Shril,[1] Patrick Mcneillie,[3] Irene Dankwa-Mullan,[3] Evan Leibovitz,[2] Kevin J. Scanlan.[3] *[1]Boston Children's Hospital, Boston, MA; [2]IBM, Cambridge, MA; [3]IBM Watson Health, Bethesda, MD.*

Background: The majority of pediatric idiopathic nephrotic syndrome (NS) have minimal change disease, which is generally responsive to steroid therapy. Patients with genetic forms of steroid-resistant nephrotic syndrome (SRNS) are unresponsive to steroid therapy. Thus, therapeutic decisions are based on the underlying etiology, renal histology and genetic screening. While mechanisms of NS are not well understood, recent advances in molecular genetics have shown that single gene defects are responsible for a 25-33% of all cases of isolated and syndromic SRNS. Biomarkers represent significant value to the clinical domain, offering information on disease diagnosis, prognosis, risk-assessment, and treatment efficacy. However, the process of extracting biomarkers from unstructured literature is time consuming and requires domain expertise. This study evaluates the potential for NLP and cognitive analytics to facilitate a review of SRNS to accelerate discovery of potential biomarkers.

Methods: Boston Children's Hospital (BCH) and IBM collaborated to train a machine learning model to identify appropriate entities and relationships across literature articles focused on SRNS. The team identified and labeled 11 entity types and 50 relationship types across 180 literature articles. The trained model was tested against the unstructured text of articles and outputs were analyzed for accuracy and precision.

Results: Comparing the expert output and the trained model showed 100% precision (23/23) and 92.0% sensitivity (23/25). One false-negatives was due to lack of co-reference, which links the lexical subject across multiple sentences. The other false-negative was due to the gene not being identified as relevant. The model took less than 30 seconds to identify the relevant biomarkers and provided passage level references to enable seamless follow up by the researcher.

Conclusions: The machine learning model provided rapid and accurate extraction of potential molecular biomarkers for NS. With additional training this model could

be expanded to other rare diseases, accelerating mutational analysis for therapeutic interventions.

Funding: Commercial Support - IBM

SA-PO612

Pharmacologic Chaperone Responsiveness in Canadian Patients with Fabry Disease Michael L. West,[1] Daniel G. Bichet,[2] Sandra Sirrs.[3] *[1]Dalhousie University, Halifax, NS, Canada; [2]University of Montreal, Montreal, QC, Canada; [3]Vancouver General Hospital, Vancouver, AB, Canada. Group/Team: Canadian Fabry Disease Initiative Research Group.*

Background: Fabry disease (FD) is an X-linked lysosomal storage disease due to deficiency of the enzyme α-galactosidase. This results in premature death from renal failure, hypertrophic cardiomyopathy and strokes. Treatment with intravenous enzyme replacement therapy (ERT) is expensive and not curative. Pharmacologic chaperone therapy (PCT) with Migalastat, an oral iminosugar, increases residual enzyme activity by stabilizing the molecule and delivering more enzyme to the lysosome. Recent data suggests that some patients on ERT may derive additional benefit from PCT. We report the prevalence of chaperone responsiveness in Canadian Fabry disease patients as a guide to planning future therapy.

Methods: The Canadian Fabry Disease Initiative (CFDI) is a registry of 466 FD patients followed for up to 10 years. All known GLA gene mutations in CFDI patients were evaluated using a published library of chaperone responsive mutations based on a good laboratory practice-validated HEK cell assay (Benjamin et al Genetics in Medicine 2017;19:430-8).

Results: The majority of Canadian patients with FD are enrolled in the CFDI with ascertainment of 92%. Over 95% have been genotyped. We evaluated 404 FD patients with 143 males, 261 females, mean age 45.0±17.8 (sd), range 8-86 years. ERT use under Canadian Fabry Treatment Guidelines was 50%. Chaperone responsiveness mutations (n=23) were noted in 86 patients (21.3%); missense 95.6%; half were receiving ERT. Non-responsive mutations (n=67) were found in 318 patients (78.7%); missense 53%, deletion/insertion 26%, stop codon 13%, duplication 3%, intronic 3%, frame shift 2%. Patients with chaperone responsive mutations had classic FD phenotype in 72.1%, vs. variant (24.4%) or indeterminate (3.5%) phenotypes. Chaperone responsive mutations varied by region with a maximum prevalence of 48.1% in Alberta (n=25) vs. a low of 2.2% in Nova Scotia (n=2). This is explained in part by the presence of a large Nova Scotia kindred with a chaperone non-responsive A143P mutation.

Conclusions: Oral PCT could be currently used in about one fifth of the Canadian FD population. Only half of those patients meet the current Canadian FD treatment guidelines for ERT suggesting that introduction of chaperone therapy would potentially only offer a change of treatment in a maximum of 40 (10%) FD patients in Canada. These data will help plan future therapy.

Funding: Commercial Support - Amicus, Shire

SA-PO613

We Propose a Single Heterozygous Mutation in ATP6V0A4 as a Novel Genetic Cause of dRTA Takayasu Mori,[1] Motoko Chiga,[1] Takuya Fujimaru,[1] Shintaro Mandai,[1] Shota Watanabe,[2] Yasuhisa Nakamura,[2] Takehiro Morishita,[2] Osamu Uemura,[4] Eri Imai,[3] Shuzo Kaneko,[3] Yusuke Tsukamoto,[3] Eisei Sohara,[1] Tatemitsu Rai,[1] Shinichi Uchida.[1] *[1]Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Tokyo, Japan; [2]Ichinomiya Municipal Hospital, Ichinomiya, Japan; [3]Itabashi Chuo Medical Center, Itabashi-Ku, Japan; [4]Aichi Children's Health and Medical Center, Obu, Aichi, Japan.*

Background: We have recently reported the development of a comprehensive diagnostic panel using next-generation sequencing (NGS) for 166 genes responsible for various inherited kidney diseases such as Gitelman syndrome, nephrogenic diabetes insipidus, Alport syndrome, renal tubular acidosis (RTA), etc., named SPEEDI-KID. Of the 137 families with inherited kidney diseases analyzed so far, three distal RTA (dRTA) families carrying only a single heterozygous variant in the known pathogenic gene, *ATP6V0A4*, were included. All the cases showed hypokalemic metabolic acidosis with nephrocalcinosis and high urine pH (>6.5). Interestingly, two cases showed late-onset of the disease (40 and 12 y.o., respectively), indicating that the phenotypes of the individuals are relatively milder than the previously reported cases. Genetic diagnosis revealed that each of the three families carried a single heterozygous missense variant in *ATP6V0A4* (p.P393L, p.S544L, and p.G822S, respectively), even though autosomal recessive is the known inheritance mode. In all the cases, no other variants in known genes for RTA were detected. Relatively large genomic rearrangement in the alternative allele was excluded by using the NGS data. One family had two affected siblings carrying the same variant. In the other family, possibly affected father and an affected child had the same variant. The variants are extremely rare in general populations (ExAC, 1000G, and ToMMo2K) and *in silico* prediction scores (SIFT, PolyPhen2, and CADD) are consistent with the concept that these variants are disease-causative. Considering that heterozygous knockout mouse of *ATP6V0A4* was reported to present metabolic acidosis under the condition of acid administration, these heterozygous variants could be responsible for the disease.

Methods:

Results:

Conclusions: We propose single heterozygous mutations in ATP6V0A4 can be responsible for dRTA. dRTA with late-onset and mild phenotype caused by heterozygous variants in *ATP6V0A4* may be more commonly present.

Funding: Government Support - Non-U.S.

SA-PO614

Whole Exome Sequencing Frequently Detects a Monogenic Cause in Early Onset Nephrolithiasis and Nephrocalcinosis Ankana Daga,[7] Amar J. Majmundar,[2] Jennifer A. Lawson,[6] Shirlee Shril,[5] Daniela A. Braun,[4] Michelle A. Baum,[1] Friedhelm Hildebrandt.[3] *[1]Boston Children Hospital, Boston, MA; [2]Boston Children's Hospital, Somerville, MA; [3]Boston Children's Hospital, Boston, MA; [4]Boston Children's Hospital, HMS, Boston, MA; [5]Boston Childrens Hospital, Boston, MA; [6]University of Connecticut School of Medicine, Farmington, CT; [7]Nephrology, Boston Children's Hospital, Boston, MA.*

Background: The incidence of Nephrolithiasis (NL) continues to rise. We previously detected a monogenic cause of NL in 20% of patients manifesting before the age of 25 years, and recently confirmed this high rate of monogenic causation (17%) in a pediatric cohort of patients by using a gene panel sequencing approach containing 30 known NL genes. We here employ whole exome sequencing (WES) rather than panel sequencing to identify monogenic causes of NL and/or nephrocalcinosis (NC).

Methods: Patients who had a history or renal ultrasound finding of at least one renal stone (NL) or NC before age 25 years were enrolled between 1/2014 to 12/2015. WES was performed on 51 families (65 affected individuals), and evaluated for causative mutations in 30 NL/NC genes. Deleteriousness of mutations was evaluated by pathogenicity prediction scores, evolutionary conservation, and prior reporting status of mutations.

Results: 63% were males, and the median age at presentation was 6 years (Range: 1 mo – 24 years). Of the 65 individuals, 32 had isolated NL, 22 had isolated NC, and 11 had both NL and NC. We detected a causative mutation in 15 out of 51 (29.4%) families. We detected a mutation in 7 recessive genes (*AGXT, ATP6V1B1, CLDN16, CLDN19, GRHPR, SLC3A1, SLC12A1*), in 1 dominant gene (*SLC9A3R1*), and in 1 gene (*SLC34A1*) with both recessive and dominant inheritance. 7 of the 19 different mutations were not previously described as disease causing. Median age of onset was significantly lower in patients in whom we detected a monogenic cause of NL/NC (3 yrs) vs. those without mutation detection (7 yrs) ($p < 0.05$). In one family we detected a causative mutation in one of 117 genes (*CTNS*) that represent phenocopies of NL-causing genes. Several factors that correlated with higher detection rate were younger age of onset of NL/NC (58%), presence of multiple affected in a family (41%), and presence of consanguinity (75%). In 9 of 15 families the genetic diagnosis led to specific implications for future clinical management and prevention of stone recurrence.

Conclusions: Thus, we established WES as an efficient approach towards a molecular genetic diagnosis in individuals with NL/NC who manifest before 25 years. Specific genetic diagnosis holds potential for personalization of the treatment plan.

SA-PO615

Mutational Burden in Monogenic Glomerular Kidney Disease Genes in Adult CKD Patients Matthias Wuttke,[2] Anselm Hoppmann,[2] Ulla T. Schultheiss,[2] Kai-Uwe Eckardt,[4] Beata S. Lipska-Zietkiewicz,[1] Franz S. Schaefer,[3] Anna Kottgen.[2] *[1]University of Gdansk, Gdansk, Poland; [2]University of Freiburg, Freiburg, Germany; [3]University of Heidelberg, Heidelberg, Germany; [4]Charité University Medicine Berlin, Berlin, Germany.*

Background: Monogenic kidney diseases often show severe manifestations in childhood (recessive) or mid-age (dominant traits). Conversely, moderate chronic kidney disease (CKD) in adults is often regarded a complex disease with a genetic predisposition. The contribution of mutations in monogenic kidney disease genes in adult CKD patients and the combined effects of rare variants and common susceptibility alleles are understudied.

Methods: 341 participants of the German Chronic Kidney Disease study (inclusion criteria CKD stages G1-G3 or A3 with biopsy-proven primary glomerular disease) underwent next-generation gene panel sequencing (Illumina MiSeq) of 37 glomerulopathy-associated monogenic traits. Read alignment and variant calling followed GATK best practices and incorporated consensus calling. Variants were annotated using VEP/SNPeff and filtered using GEMINI based on frequency, predicted impact and presence in clinical mutation databases to obtain putative deleterious mutations.

Results: At present, data are available for 202 patients. Definite pathogenic mutations were identified for 12 patients (median age 44 yr, eGFR 49 ml/min/1.73m2, UACR 357 mg/g, 67% FSGS) in genes with dominant inheritance mode (4 in *COL4A5*, 2 in *PAX2*, and 1 each in *GLA, INF2* and *WT1*) and 3 compound heterozygotes in *NPHS2*. In addition, 21 individuals carried plausible pathogenic variants (in *ACTN4, ANLN, ARHGAP24, COL4A5, CRB2, GLA, LMX1B, PAX2, TRPC6, TTC21B* and *WT1*). Within the next weeks, sequencing and evaluation of atypical presentations and extra-renal manifestations as well as integration with common susceptibility alleles from GWAS will be completed.

Conclusions: About 5% of adult patients selected for CKD stages G1-G3 or A3 and with presumed primary glomerular etiology carry pathogenic mutations in monogenic glomerular disease genes. Another 10% carry plausible pathogenic variants. Evaluating rare mutations together with common CKD susceptibility variants may provide further insights into their combined impact and contribution to atypical presentations and a mild disease course.

SA-PO616

The Comprehensive Gene Screening for Congenital, Infantile, and Steroid Resistant Nephrotic Syndrome in Japan Keita Nakanishi,[4] Kandai Nozu,[3] Junya Fujimura,[4] Shogo Minamikawa,[4] Tomohiko Yamamura,[4] Hiroshi Kaito,[5] Yuko Shima,[6] Koichi Nakanishi,[2] Kazumoto Iijima.[1] *[1]Dept. of Pediatrics, Kobe Univ. Graduate School of Medicine, Kobe, Japan; [2]Graduate School of Medicine, University of the Ryukyus, Nishihara-cho, Japan; [3]Kobe University, Kobe, Japan; [4]Kobe University Graduate School of Medicine, Kobe, Japan; [5]None, Kobe, Japan; [6]Wakayama Medical University, Wakayama City, Japan.*

Background: Cases with congenital nephrotic syndrome (CNS), infantile nephrotic syndrome (INS) or steroid-resistant nephrotic syndrome (SRNS) frequently progress to end stage renal disease (ESRD). It has been reported that about thirty percent of CNS/INS/SRNS patients possessed single causative gene variants in podocyte related genes that were detected by next generation sequencing. It has been revealed CNS/INS/SRNS patients with gene defects show severe renal prognosis; however, those patients seldom show recurrence of nephrotic syndrome after kidney transplantation. Thus, we established a gene screening system for CNS/INS/SRNS patients in their early stages, to suggest their clinical courses.

Methods: The gene screening system by targeted sequencing for 45 podocyte related genes that have been reported as causative genes for CNS/INS/SRNS was established. Newly diagnosed patients as CNS/INS/SRNS were recruited between January in 2016 and May in 2017.

Results: In total, 84 patients from 42 hospitals in Japan were screened. We detected causative genes in 25 patients (30%). The most frequent gene was WT1 (4 patients), and other genes were LAMB2 (3 patients), ADCK4, TRPC6, LMX1B, INF2, NUP107 (2 patients each), and so on. None of our cases possessed NPHS2 gene variants, which is most common causative gene in European countries. Seven out of 25 patients progressed to ESRD, and only one patient who had TRPC6 variant had kidney transplantation and showed no recurrence of nephrotic syndrome. The cost of gene screening for one sample was about 250.00 (USD).

Conclusions: We have established a comprehensive gene screening system for CNS/INS/SRNS cases in their early disease stages in Japan and detected a single causative gene in 30% in our cohort. The variation of causative genes in Japan was different from those in other countries. The screening results will be used in deciding treatment and thereby help to improve the quality of life for patients.

SA-PO617

Quantifying Mendelian Genetic Disease in the Pediatric Renal Clinic Yadhavan Upendran,[2] Fiona Mackie,[1] Rebecca A. Spicer,[1] Siah Kim,[1] Sean E. Kennedy,[1,2] Hugh J. Mccarthy.[1,2] *[1]Sydney Children's Hospital, Randwick, NSW, Australia; [2]University of New South Wales, Sydney, NSW, Australia.*

Background: With the advent of new sequencing technology, gene tests are more readily available to the nephrologist and increasingly cost effective. Planning is required to provide the same level of counseling for those now undergoing testing in the renal clinic compared to the clinical genetic clinic. The aim of this study was to determine the prevalence of disease with a likely genetic aetiology within the paediatric renal clinic.

Methods: An algorithm was configured to determine those with a possible Mendelian genetic aetiology to disease who could be offered gene testing. A retrospective review was then undertaken of new referrals to the renal clinic at a tertiary children's hospital from 2012-2015 to determine the number of patients who would have then required genetic counseling.

Results: The algorithm identified risk as Inherited Glomerular (including steroid resistant or congenital nephrotic syndrome and Alport's syndrome); Tubular or Metabolic disorders; Complement mediated disorders, Nephrocalcinosis/lithiasis; Cystic Kidney Disease; Syndromic Congenital Anomalies of Kidney and Urinary Tract (CAKUT); other including familial not otherwise specified. Simple CAKUT was excluded due to low rate of identifiable genetic aetiology. In the total cohort, the mean age at presentation was 5.25 years and male to female ratio was 1.52. 173/751 (23%) patients so far analysed have a possible genetic aetiology to their renal disease and could have been offered genetic counseling +/- testing.

Conclusions: Gene testing is becoming a routine component of clinical practice within nephrology either to direct management; aid diagnostic dilemmas; inform for family planning or living donation. The number of patients who would benefit justifies establishing a separate renal genetic service to run concurrently with the routine service in order to ensure optimal counseling for patients and their families.

Sub-category split of genetic at risk cohort

	Number n=173 (%)
Glomerular	39 (22.5)
CAKUT	58 (33.5)
Cystic	17 (9.8)
Tubular/Metabolic	10 (5.8)
Nephrocalcinosis/Lithiasis	23 (13.3)
Complement Mediated	4 (2.3)
Other	22 (12.7)

SA-PO618

Integrative Analysis of Genome-Wide Transcriptome Data Sets Reveals Shared Biology Between Lupus and its Co-Morbidities Thomas Oates, Alan D. Salama. *University College London, London, United Kingdom.*

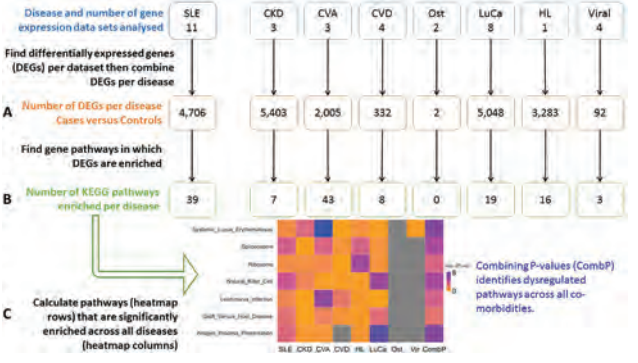
Background: The autoimmune disease Systemic Lupus Erythematosus (SLE) is frequently complicated by co-morbidities such as cardiovascular disease and stroke. The biology of these disease associations are largely unknown but increased understanding may result from transcriptomic analysis of SLE and its co-morbidities.

Methods: 7 major co-morbidities of SLE were identified for analysis: chronic kidney disease, stroke, cardiovascular disease, osteoporosis, lung cancer, Hodgkin lymphoma, and viral infections. Transcriptomic datasets for these diseases available via the Gene Expression Omnibus were screened and those with over 30 subjects in a case-control design were retained for analysis. Previously described methods were used to explore SLE and the chosen co-morbidities at gene, pathway and disease level (PMID: 27842596). The methods used are statistically robust to the multiple-test corrections required in genome-wide experiments and the combination of results from several independent tests.

Results: 36 microarray datasets passed the filter criteria above. These contained expression data from 4,776 individuals (3,320 cases, 1,456 controls). Differentially expressed genes (DEGs) between cases and controls were calculated for each dataset and combined for all datasets per disease (see Figure row A). Next, enrichment of the DEGs per disease was examined in multiple reference pathways including the Kyoto Encyclopedia of Genes and Genomes (KEGG) (Figure row B). Combining P-values across the 8 studied diseases (Figure row C) delineated pathways that retained statistical significance for dysregulation in SLE and all co-morbidities (Figure Heatmap & blue text).

Conclusions: The significant enrichment of pathway gene sets across SLE and its co-morbidities suggest that these diseases may share an underlying molecular architecture. Further analysis of these data may be able to guide treatment decisions when SLE is complicated by co-morbidities, or delineate gene expression signatures that could prompt focused screening of patients with SLE for relevant co-morbidities.

Funding: Government Support - Non-U.S.



SA-PO619

Genetic Alterations in DMBT Confer Urinary Tract Infection Risk in Children and Mice Andrew L. Schwaderer,[2] David S. Hains,[4] John Ketz,[1] Ed Hollox.[3] *[1]Nationwide Children's Hospital, Columbus, OH; [2]The Ohio State University, Westerville, OH; [3]University of Leicester, Leicester, United Kingdom; [4]Riley Children's Hospital, Indianapolis, IN.*

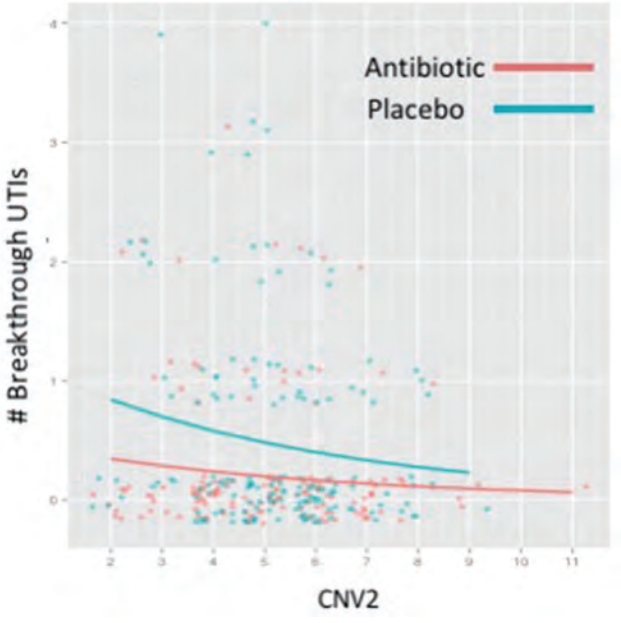
Background: The deleted in malignant brain tumor 1 (DMBT1) gene is prone to copy number variation (CNV) that alters the number of bacteria-binding domains in 2 distinct gene regions (CNV1 and CNV2). DMBT1's role in urinary tract functions (UTI) has not been previously evaluated

Methods: RIVUR study children with UTI and vesicoureteral reflux treated with antibiotics vs. placebo were studied. Copy number estimates for CNV1 and CNV2 were determined using a paralogue ratio test (PRT). Experimental UTI was induced by transurethral inoculation of uropathogenic E.coli (UPEC) into *Dmbt1*$^{-/-}$ vs wild-type mice. DMBT1-UPEC aggregation was evaluated by evaluating differential GFP expressing UPEC aggregation in the bottom of wells coated with DMBT versus control.

Results: DNA samples from 314 Caucasian children (159 in antibiotic prophylaxis group and 155 in the placebo group) were typed for DMBT1 CNV1 and CNV2. Higher copy number of CNV2 (but not CNV1) was associated with fewer infections (p=.007), particularly in the prophylaxis group (Figure). Compared to wild type mice, *Dmbt1*$^{-/-}$ mice had 5-fold higher bladder bacterial burdens (cfu/bladder) at 6 hrs following following low (10^7UPEC) inoculum and a 2.4-fold higher UPEC bladder burden at 6 hrs following a high (10^8 UPEC) inoculum; p values were 0.04 and 0.01 respectively. Kidney UPEC burdens were not different between *Dmbt1*$^{-/-}$ and wild-type mice. Additionally, DMBT protein, but not control resulted in bacterial clumping in our bacterial agglutination assay.

Conclusions: Our results indicate that children with low copy number of DMBT1 CNV2 would benefit from antibiotic prophylaxis. Increased murine bladder bacterial burdens in *Dmbt1*$^{-/-}$ mice compared to wild type and increased UPEC agglutination with DMBT demonstrates it's functional relevance in the innate immune defense against UTI.

Funding: NIDDK Support



SA-PO620

Congenic Substitution to Uncover the Genetic Pathway of Hypertensive Renal Injury Peter A. Doris,[2] Michael C. Braun,[1] John Hicks,[4] Isha Dhande.[3] *[1]TCH/ BCM, Houston, TX; [2]UNIVERSITY OF TEXAS HOUSTON, Houston, TX; [3]University of Texas Health Science Center at Houston, Houston, TX; [4]Pathology, Texas Children's Hospital, Houston, TX.*

Background: The SHR-A3 line of the spontaneously hypertensive rat experienes progressive renal injury (RI). Susceptibility arises from natural gnetic variaiton and contrasts with injury resistant SHR-B2. These two lines are 87% genetically identical. SHR-A3 has higher blood pressure (BP) than SHR-B2. We have mapped a locus responsible to an 8MB block on chr17. Here we assess whether a congenic line (CL) in which this block is transferred from SHR-B2 into SHR-A3 experiences different levels of BP and RI than SHR-A3. The SHR-A3 and SHR-B2 genomes are most divergent in the immunoglobulin heavy chain (IgH). We created a CL substituting the SHR-B2 IgH locus into SHR-A3 and assesssed the effect on BP and RI. Finally we have created a bicongenic (2CL) line containing both these SHR-B2 loci within the SHR-A3 background.

Methods: CLs were created by backcrossing using genetic markers to identify those regions of the genome at which SHR-A3 and SHR-B2 differ. Blood pressure was measured by telemetry. Renal injury was assessed histologically in paraffin-embedded tissue stained with Periodic acid-Schiffs stain.

Results: Congenic substitution of the chr17 locus was associated with a reduction in blood pressure to a level that was significantly below SHR-A3, but not different from SHR-B2. At 40wks of age, glomerular injury (GI) was indistinguishable in this CL from SHR-B2. Tubulointerstital injury (TI) in the CL was intermediate, but significantly below SHR-A3. Congenic substituion of the IgH locus from SHR-B2 into the SHR-A3 background had no effect on BP. At 40wks, this CL also had GI indistinguishable from SHR-B2 and TI intermediate between SHR-A3 and SHR-B2. In the 2CL, GI and TI were both reduced to the SHR-B2 level.

Conclusions: RI in SHR-A3 appears to result from at least two genetic loci. One is an 8Mbase block on chromosome 17 that results in hgiher blood pressure in SHR-A3 than SHR-B2. The other is the immunoglobulin heavy chain, indicating that genetic variation in germ-line antibody sequences may contribue to the pathogenesis of renal injury in this model. The combined effect of these loci eliminates histologically assessed RI, resulting in animals that are 99.5% geneticall identical to SHR-A3, but resistant to renal injury.

Funding: NIDDK Support, Private Foundation Support

SA-PO621

COL4A3 Gene Variants Exacerbate Diabetic Kidney Disease: Genetic Investigation from Nine MODY Families Yiting Wang,[1] Junlin Zhang,[2] Fang Liu.[2] *[1]Division of Nephrology, West China Hospital of Sichuan University, Chengdu, China; [2]West China Hospital of Sichuan University, Chengdu, China.*

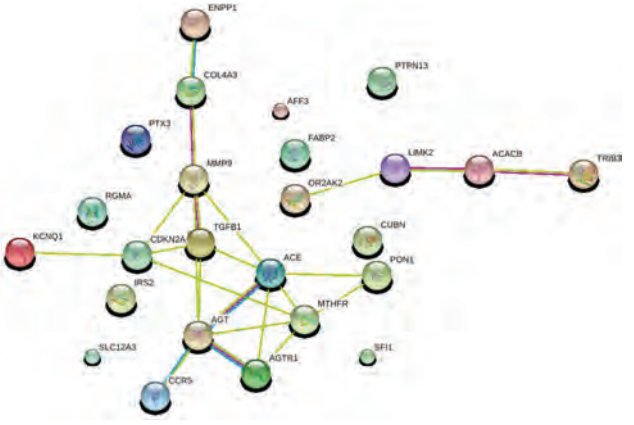
Background: Despite the advances in the identification of genetic factors of diabetic kidney disease (DKD), much of the heritability for the clinical heterogeneity of DKD remains unexplained. In the study, DKD of nine probands who were suspected maturity-onset diabetes of the young (MODY) were proven by renal biopasy. Notably, three of the probands has processed to ESRD and other four with overt proteinuria or albuminuria, however, their parents remained almost normal renal function or denied any discomforts or clinical symptoms of DKD, despite they have suffered longer duration of DM. The present study aimed to explore the genetic factor in clinical heterogeneity of DKD.

Methods: The whole-exome sequencing (WES) was performed for the nine probands and their families. The susceptibility genes of DKD were reviewed and analyzed with Gene Ontology enrichment. The variants which have been reported to be associated with DKD, or MAF<0.05 and predicted to be pathogenic by software in susceptibility genes of DKD were selected.

Results: HNF1B-MODY, CEL-MODY, PAX4-MODY, and WFS1-MODY were diagnosed among nine families. There were 174 selected variants of 25 susceptibility genes among all participants, quantity of selected variants in genes related to DKD were identified more in offspring, moreover, pathogenic variants in COL4A3 genes were only identified in four probands but their MODY parents. Combined with analysis of gene function and Protein-Protein interaction network, we speculated the cumulative effect of susceptibility genes on the severity of DKD and indentified the potential pathogenesis of COL4A3 gene variants in aggravating the progression of DKD.

Conclusions: Pathogenic variants of COL4A3 gene and cumulative effect of susceptibility genes exacerbate DKD.

Funding: Government Support - Non-U.S.



Protein-Protein interaction pathway

SA-PO622

Collagen VI Associates with Basement Membrane Defects in Alport Syndrome Michael J. Randles,[1] Franziska Lausecker,[1] Paul K. Potter,[2] Sara Falcone,[2] Hani Suleiman,[3] Jeffrey H. Miner,[4] Rachel Lennon.[1] *[1]University of Manchester, Manchester, United Kingdom; [2]Medical Research Council, Harwell, United Kingdom; [3]Washington University, Saint Louis, MO; [4]Washington University School of Medicine, St. Louis, MO.*

Background: Alport Syndrome is caused by genetic defects in *COL4A3, COL4A4* or *COL4A5*, leading to inadequate assembly of the type IV collagen α3, α4, α5 network in basement membranes. In the glomerulus this causes irregularities in glomerular basement membrane (GBM) width and a characteristic basket weave appearance. We aimed to build our basic understanding about the glomerular extracellular matrix (ECM) in Alport syndrome and performed global analysis of composition and ultrastructural imaging in the both the *Col4a3-/-* and *Col4a5-/-* Alport mouse models.

Methods: Cellular and ECM fractions from wild type and Alport glomeruli at 6-8 and 16-18 weeks of age were analysed by mass spectrometry (MS)- based proteomics. Imaging included serial block face-scanning electron microscopy (SBF-SEM) and stochastic optical reconstruction microscopy (STORM).

Results: MS analysis revealed moderate changes in the composition of glomerular ECM at 6-8 weeks, even prior to the onset of glomerular barrier dysfunction. These changes included complete absence of type IV collagen α3, α4, α5 in both mouse models and an upregulation of type IV collagen α1, α2, α6 and the interstitial type VI collagen. At 16-18 weeks more dramatic changes were detected including elevated type IV collagen α1, α2, fibronectin, type I collagen, laminin α2 and fibrinogen chains. Global and pathway analysis of cellular fractions indicated changes in actin regulating proteins at 6 weeks and mitochondrial dysfunction at 16 weeks. SBFSEM demonstrated thickened and irregular GBM with evidence of invading podocyte protrusions. Interestingly, STORM localised type VI collagen to GBM defects in Alport mice whereas collagen VI was absent from wild type controls.

Conclusions: Our data demonstrate that Alport syndrome progresses with distinct early changes in ECM followed by more profound ECM accumulation, disruption and a marked increase in type VI collagen in the GBM. Enhanced understanding about the pathways that control matrix deposition in glomerular disease may ultimately inform targeted strategies to correct or repair glomerular barrier dysfunction.

SA-PO623

Impact of High-Risk APOL1 Variants in Kidney Disease in South America Cristian Riella,[1] Tobias A. Siemens,[3] Rodrigo P. Campos,[5] Thyago P. Moraes,[4] David J. Friedman,[1] Miguel C. Riella,[3] Martin R. Pollak.[2] *[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA; [3]Hospital Universitário Evangélico de Curitiba, Curitiba, Brazil; [4]Pontificia Universidade Catolica do Parana, Curitiba, Brazil; [5]Nephrology, Federal University of Alagoas, Maceio, Brazil.*

Background: The presence of apolipoprotein L-1 (APOL1) mutations is associated with increased risk of end-stage renal disease (ESRD) in African Americans. This effect has not been investigated in South Americans of African descent. In this study we analyzed APOL1 variants in dialysis patients and healthy controls with African descent in Brazil.

Methods: Inclusion criteria: dialysis patients 18 years of age or older who reportedly had African ancestry, first degree relatives were selected as controls. **Exclusion criteria**: individuals below the age of 18, history of obstructive uropathy, polycystic kidney disease, and known SLE or other vasculitic etiologies. After informed consent was obtained, clinical data along with blood samples for DNA extraction were collected. Genotyping was performed with a TaqMan RT-PCR assay for the wild type allele G0, and G1 and G2 risk alleles.

Results: 440 individuals were included in the study (271 patients and 169 controls). The frequency of high risk variants (G1,G2) was higher in dialysis patients than controls: one risk variant frequency was **17.7%(48) vs. 10.6%(18);** two risk variants: **12.2%(33) vs. 1.2%(2),** respectively. In a multivariate logistic regression model, the presence of one risk variant was associated with a 4-fold increase in risk of ESRD (OR=3.95, p=0.002, CI=1.68-9.27); while carriers of **two risk variants had a 21-fold increase in risk of ESRD** (OR=21.66, p<0.0001, 95% CI= 4.13-113.51). After adjusting for comorbidities and other variables, patients with two risk alleles started dialysis 7.5 years earlier (Coef.=-7.53856, p=0.007) in a multivariate linear regression model. The analyses were adjusted for gender, comorbidities, smoking status, income and education level.

Conclusions: APOL1 mutations are a significant risk factor for the development of ESRD in South American individuals of African descent. The presence of two APOL1 risk alleles conferred up to 21-fold higher risk of ESRD and was associated with younger age at the start of dialysis.

SA-PO624

APOL1 Nephropathy Risk Variants and Incident Cardiovascular Disease Events in Community-Dwelling Black Adults Orlando M. Gutierrez,[9] Marguerite Irvin,[8] Ninad S. Chaudhary,[10] Mary Cushman,[11] Neil A. Zakai,[11] Sophie Limou,[5] Nathalie Pamir,[6] Alex Reiner,[14] Rakhi Naik,[2] Michele Sale,[12] George W. Nelson,[7] Monika M. Safford,[13] Hyacinth I. Hacinth,[1] Suzanne E. Judd,[8] Jeffrey B. Kopp,[4] Cheryl A. Winkler.[3] *[1]Aflac Cancer and Blood Disorder Center, of Children?s Healthcare of Atlanta, Atlanta, GA; [2]Johns Hopkins, Baltimore, MD; [3]NCI, NIH, Frederick National Laboratory, Frederick, MD; [4]NIDDK, NIH, Bethesda, MD; [5]NIH, Leidos Biomedical Research Inc, Nantes, France; [6]Oregon Health and Science University, Portland, OR; [7]SAIC-Frederick/FNLCR, Frederick, MD; [8]UAB, Birmingham, AL; [9]UAB School of Medicine, Birmingham, AL; [10]University of Alabama at Birmingham, Birimingham, AL; [11]University of Vermont, Colchester, VT; [12]University of Virginia, Charlottesville, VA; [13]Weill Cornell Medicine, New York, NY; [14]University of Washington, Seattle, WA.*

Background: *APOL1* nephropathy risk variants are strongly associated with chronic kidney disease progression in Black adults, but associations with incident cardiovascular disease (CVD) are uncertain.

Methods: We examined associations of *APOL1* risk variants with incident coronary heart disease (CHD,n=323), stroke (n=331), and a combined CVD end point (n=500) in 10,605 Black participants of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. Main analyses compared those with *APOL1* high-risk nephropathy genotypes (2 risk variants) to *APOL1* low-risk genotypes (0/1 risk variant) in Cox models adjusted for CVD risk factors and ancestry principle components.

Results: *APOL1 h*igh-risk participants were younger and more likely to have albuminuria than *APOL1* low-risk participants. The risk of incident stroke, CHD or the composite CVD endpoint did not significantly differ by *APOL1* genotype in multivariable models. However, the association of *APOL1* genotype with the composite CVD outcome differed by diabetes status (P<0.01). In those without diabetes, high-risk genotypes were associated with higher risk of incident composite CVD than low-risk genotypes in fully adjusted models [table]. This association appeared to be driven by incident stroke risk. In contrast, the *APOL1* high-risk genotype was associated with a trend towards lower risk of CVD in diabetics.

Conclusions: *APOL1* high-risk genotypes are associated with higher incidence of CVD events in individuals without diabetes, whereas the association appeared to be opposite among individuals with diabetes.

Funding: NIDDK Support, Other NIH Support - NINDS

Hazard ratio (95% confidence interval) of incident CVD in APOL1 high- vs. low-risk genotypes

	N events/N at risk	Model
No diabetes		
Stroke	197/6621	2.32(1.33,4.07)
Coronary heart disease	174/6173	1.31(0.81,2.10)
Composite Events	297/5755	1.67(1.12,2.47)
Diabetes		
Stroke	131/2660	0.55(0.22,1.37)
Coronary Heart Disease	148/2329	0.53(0.24,1.14)
Composite Events	200/2072	0.52(0.26,1.03)

Model adjusted for age, sex, smoking, medications, and principal components ancestry

SA-PO625

Clinician Attitudes Toward Use of APOL1 Genetic Testing in Clinical Practice Ebele Umeukeje,[1] Wylie Burke,[2] Kerri L. Cavanaugh,[1] Stephanie M. Fullerton,[2] James G. Wilson,[3] Bessie A. Young.[4] *[1]Nephrology, Vanderbilt University Medical Center, Vanderbilt Center for Kidney Disease, Nashville, TN; [2]Bioethics and Humanities, University of Washington, Seattle, WA; [3]Physiology & Biophysics and Medicine, University of Mississippi Medical Center, Jackson, MS; [4]Nephrology, University of Washington, VA Puget Sound Health Care System, Kidney Research Institute, Seattle, WA.*

Background: Apolipoprotein L1 (*APOL1*) high-risk variants are common among African Americans (AA) and are associated with a 7-10 fold higher risk of non-diabetic endstage renal disease (ESRD). However, there are gaps in knowledge regarding the clinical implication of *APOL1* variants in part because associated effects on risk in combination with co-morbidities or environmental exposures are not fully established. The objective of this study is to describe clinicians' views of *APOL1* genetic testing in clinical practice.

Methods: As part of an ongoing study of stakeholder views regarding *APOL1* genetic testing in AA, we conducted key informant interviews with primary care (N=13) and nephrology (N=14) clinicians in Seattle WA, Nashville TN, and Jackson MS. Interviews assessed clinicians' views about the use of *APOL1* genetic testing in clinical care.

Results: Clinicians were recruited from different practice settings (63% in Academic centers; 26% in private practice; and 11% in the VA and other settings), and 78% of them provide care to a significant proportion of AA patients (≥ 25%). Dominant themes included possible increased monitoring and motivation of patients with risk factors (e.g. hypertension, family history) vs. possible over or under treatment, increased cost, stigmatization and increased psychological stress. Exemplar quotes: "In terms of getting people to change their lifestyles, for some people, having this risk might help that. It might just freak them out. I don't really know. I think those are all – I think we're in uncharted territory clinically, actually"; "We want to make sure we're following the data and not jumping to conclusions about when to apply something that may still be in the phase of further interpretation in the science."

Conclusions: Our results suggest that clinicians hold uncertain views on the use of *APOL1* testing to guide clinical practice. Further research is needed to determine the impact of testing on clinical outcomes especially in patients with ESRD risk factors.

Funding: Other NIH Support - NIH / National Human Genome Research Institute (NHGRI): 1R01HG007879-01A1

SA-PO626

Nephrologists Treating C3 Glomerulopathy Patients Report Highest Clinical Utility by Using Gene Sequencing to Confirm a Diagnosis of C3G in Departure from C3G Consensus Report Bjorn Stromsness. *Machaon Diagnostics, Oakland, CA.*

Background: C3 glomerulopathy (C3G) is a recent renaming of a group of diseases and applies to MPGN Type II and III as well as C3 Glomerulonephritis [2]. In 2013, a C3 glomerulopathy consensus report was published with testing guidelines [1, 3]. We were curious about the degree to which physicians followed these guidelines and their impressions of the tests recommended in that report.

Methods: An anonymous survey titled "C3 glomerulopathy testing: A questionnaire for nephrologists" was sent via email to approximately 4,000 nephrologists.

Results: The C3 glomerulopathy consensus report recommended all suspected C3G patients receive testing for C3 Levels, C4 Levels, C3 Nephritic Factor, CFH Level, Serum paraprotein detection and screening for a CFHR5 mutation. Of the physicians who complete the first detailed section of the survey, 97% reported ordering C3 Levels, 93% had ordered C4 Levels, 69% had ordered CFH Levels and 76% had ordered C3 Nephritic Factor testing. For the self-identified experts, there were five tests seen as having "High Utility in C3G." Those tests were C3 Level (67%), C4 Level (67%), C3 Nephritic Factor (67%), CFH Antibody (67%) and Genetic Sequencing (83%).

Conclusions: The clinical value of genetic sequencing (CFH, CFI, CD46, C3, CFB, DGKE, CFHR5), C3 Nephritic Factor and CFH antibody testing appears greater than the consensus report indicated. The importance of serum paraprotein detection (Serum Protein Electrophoresis, or SPEP) and the CFHR5 mutation screen may need to be further demonstrated to the field. Additionally, in a search for performing laboratories, we could not find a test which explicitly targeted the CFHR5 duplication referenced in the consensus report and so physician may not actually be screening for that specific mutation.

Funding: Clinical Revenue Support

All Nephrologists Treating C3G Patients

Testing Options	Have ordered	Highly likely in C3G
C3 Level*	87%	71%
C4 Level*	93%	43%
CFH Level*	69%	39%
Serum paraprotein detection*	52%	25%
C3 Nephritic Factor*	78%	61%
CFHR5 Mutation Screen (Cypriot)*	55%	29%
C4 Nephritic Factor	21%	11%
CFB Level	59%	25%
C5 Level	41%	18%
C3d	21%	7%
C3c	17%	7%
soluble C5b-9	45%	32%
CFH Antibody	59%	46%
CFB Antibody	48%	36%
Genetic Sequencing (C3, CFH, CFI, CFB, CD46, CFHR5, DGKE)	69%	57%

*recommended for all C3G patients in C3G consensus report

Nephrologists with self-reported expertise in C3G testing

Testing Options	Have ordered	Highly likely in C3G
C3 Level*	100%	67%
C4 Level*	100%	67%
CFH Level*	83%	33%
Serum paraprotein detection*	33%	0%
C3 Nephritic Factor*	100%	67%
CFHR5 Mutation Screen (Cypriot)*	83%	33%
C4 Nephritic Factor	17%	17%
CFB Level	50%	17%
C5 Level	67%	17%
C3d	50%	17%
C3c	33%	17%
soluble C5b-9	50%	33%
CFH Antibody	67%	67%
CFB Antibody	67%	33%
Genetic Sequencing (C3, CFH, CFI, CFB, CD46, CFHR5, DGKE)	100%	83%

*recommended for all C3G patients in C3G consensus report

SA-PO627

Attitudes towards Biosample Collection and Genetic Testing in a Racially Diverse CKD Population in Cleveland, OH Jessica N. Cooke Bailey,[2] Dana C. Crawford,[1] Julie A. Pencak,[3] Marleen Schachere,[1] William S. Bush,[1] John R. Sedor,[3] John F. O'Toole.[1] *[1]Case Western Reserve University, Cleveland, OH; [2]Case Western Reserve University, Cleveland, OH; [3]MetroHealth Medical Center, Cleveland, OH.*

Background: The NIH All of Us Research Program (AURP) is an ambitious national effort to longitudinally collect health data and biospecimens from a million Americans for storage, processing, and analysis in a government-funded data repository. Previous studies have suggested minority populations would be reluctant to share personal data and samples with the Federal government. We tested this premise in a population of chronic kidney disease (CKD) patients in Cleveland, OH.

Methods: Patients in a CKD clinic were approached prior to standard of care visit, asked to complete a structured 5 question bioethics and IRB-approved survey, and to provide blood sample for future genetic analysis.

Results: Most (86%) participants in the genetic study took the survey; 50% African American, 54% female, average age 61.5. Responses from 111 individuals indicate the majority would participate in the AURP and were willing to send biosamples to a national repository and share de-identified data, but <50% of respondents were willing to install a phone app to track personal data. Most wanted results returned and 96% of those who did wanted personal (health or genetic) data returned; 41% wanted *at least* summary data about the PMI-CP cohort, 4% *only* summary data about the overall group, 76% *at least* personal health data, and 4% *only* personal health data. Genetic data was priority; 89% wanted *at least* personal genetic data while 19% wanted *only* personal genetic data. 10% did not want any results returned. We found no significant difference between responses when comparing African American and White individuals.

Conclusions: Attitudes of CKD patients in a diverse health care environment towards the AURP are varied but, in contrast to published data, did not differ across self-reported race (African Americans and Whites) in this sample. Willingness to participate in some aspect of a AURP-like project was high. Of those agreeing to the survey, almost all wanted return of genetic results. Given this demand, efficient processes should be developed to provide subjects with appropriate education and context for results return. Other chronic disease populations and healthy subjects need to be studied to determine if health status, race or ethnicity modifies willingness to join the AURP.

SA-PO628

Renal Biopsy Findings Precede Clinical Evidence of Renal Disease in Female Patients with Fabry Disease Luiz A. Moura,[3] Maria Eugenia F. Canziani,[2] Hugo Abensur,[6] Valeria Veloso,[7] Simone M. Lima,[8] Marlene A. Reis,[9] Nayze L. Aldeman,[1] David G. Warnock,[4] Agnes B. Fogo.[5] *[1]FEDERAL UNIVERSITY OF PIAUI, TERESINA, Brazil; [2]Federal University of Sao Paulo, Sao Paulo, Brazil; [3]Hospital do Rim e Hipertensao, Sao Paulo, Brazil; [4]UAB, Birmingham, AL; [5]Vanderbilt University Medical Center, Nashville, TN; [6]Universidade de Sao Paulo, Sao Paulo, Brazil; [7]universidade Federal de Goias, Goiania, Brazil; [8]Medical Affairs, Sanofi Genzyme, São Paulo, Brazil; [9]Federal University of Triangulo Mineiro - UFTM, Uberaba, Brazil.*

Background: Fabry nephropathy results from mutations in the GLA gene causing a deficiency in alpha-galactosidase and the accumulation of glycosphingolipids in kidney cells, proteinuria and progressive loss of kidney function. The aim of this study was to describe renal biopsy findings in a Brazilian cohort of Fabry patients according to the ISGFN Fabry renal pathology scoring system and correlate these findings to clinical and laboratory data.

Methods: Kidney biopsies, indicated based upon a family screening program, were analyzed by light microscopy from paraffin embedded sections stained by PAS and semi-thin sections from plastic embedded sections stained by toluidine blue. Clinical data were retrieved from patient medical records.

Results: A total of 27 (14 male and 13 female) kidney biopsies from Fabry patients were analyzed. None of the patients had previously initiated enzyme replacement therapy. Males and females were the same age (34.7±10.8 vs. 36.8±18.4 yo) and predominantly in CKD stage 1 (59%) and 2 (22%). Proteinuria was significantly more pronounced in males compared to females ($p<0.05$). Renal biopsies in female patients showed histological alterations, particularly podocyte inclusions, even with proteinuria less than 200mg/24h and GFR greater than 60 ml/min/1.73 m2. There was no difference males vs females in vacuolization or inclusions in podocytes. More women had biopsies without glomerular sclerosis ($p<0.05$) while men had 5 times more scarring than age-matched women. Males had significantly more interstitial fibrosis than females (26.1±30.9% vs. 5.0±2.89; $p=0.007$). Interstitial fibrosis correlated with eGFR ($p<0.001$) in males but not in females ($p=0.501$). Interstitial inflammation was present in 93% of biopsies from males vs. 23% of females ($p<0.001$).

Conclusions: Males with Fabry disease, even in early stage of CKD, showed substantially more interstitial fibrosis and inflammation than females. Females had better preserved renal function than males, but still histological lesions, mainly podocyte inclusions, even though renal function was nearly normal. Renal histologic findings may be important factors to be considered when making therapeutic decisions for patients with Fabry disease.

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SA-PO629

Fabry Disease Prevalence in Kidney Transplant Patients: A Multicenter Study S. F. Yalin,[8] N Eren,[15] A. Sinangil,[14] A. Ucar,[9] V. T. Yilmaz,[2] O Can,[17] A Gurkan,[5] D TAYMEZ,[10] S. Ecder,[12] S. Gulcicek,[6] M. Mese,[11] K. Turkmen,[3] N. Arik,[1] Z Bicik,[7] M. B. Ogutmen,[16] H. Kocak,[4] Y. Caliskan,[8] T. Ecder,[13] N. Seyahi.[8] *[1]Ondokuz Mayis Univ., Samsun, Turkey; [2]Akdeniz Univ., Antalya, Turkey; [3]Necmettin Erbakan Univ., Konya, Turkey; [4]Akdeniz Univ., Antalya, Turkey; [5]Medicana C. Hosp., Istanbul, Turkey; [6]Istanbul T.R.Hosp., Istanbul, Turkey; [7]Kartal T.R.Hosp., Istanbul, Turkey; [8]Istanbul Univ., Istanbul, Turkey; [9]Istanbul Univ., Istanbul, Turkey; [10]Kocaeli S. Hosp., Kocaeli, Turkey; [11]Kartal T.R.Hosp., Istanbul, Turkey; [12]Istanbul Medeniyet Univ., Istanbul, Turkey; [13]Istanbul Bilim Univ., Istanbul, Turkey; [14]Istanbul Bilim Univ., Istanbul, Turkey; [15]Kocaeli Univ., Kocaeli, Turkey; [16]Haydarpasa Numune Hosp., Istanbul, Turkey; [17]Haydarpasa Numune Hosp., Istanbul, Turkey.*

Background: Higher prevalence of Fabry disease was reported in specific patient populations. To the best of knowledge, a formal prevalence study was not conducted in kidney transplant (TX) recipients. We aimed to investigate the prevalence of Fabry disease in transplant recipients.

Methods: We performed a multicenter cross-sectional study in transplant centers. We also screened dialysis (D) patients to have comparative data. All adult patients were screened regardless of primary disease. Blood was collected for the measurement of alpha-galactosidase enzyme activity in males and for the screening of genetic mutations in females. Additionally, a genetic screening was performed in males with low alpha-galactosidase enzyme activity.

Results: We screened 2206 TX and 1442 D patients for a total of 3648 cases (mean age 48,9±15,7; 63,1%male). Data regarding study population are shown in Table 1. In the whole population, a total of 12 unique mutation were detected in 23 patients (0,63%) (15 with TX, 8 with D).

Conclusions: Our results have important implication regarding TX activity. First, in countries where living donation is common, donors are generally relatives of the patients. Therefore in those cases, screening for the genetic diseases that can lead to kidney failure is important. Second, recurrence can be prevented with timely initiation of enzyme replacement therapy and patients might have better survival.

	Tx	Dialysis	P
Age	46,6±14,7	52,4±16,4	0,000
Male (%)	68,9	54,1	0,000
Etiology Diabetes (%)	7,7	31,3	0,000
Etiology Unknown (%)	38	24,4	0,000
Etiology Other (%)	54,3	44,3	0,000
Patients with low α-gal (%)	6,1	9,3	0,000
Patients with mutation (%)	0,67	0,55	0,640

SA-PO630

Fabry's Disease within Dialysis Patients in Madeira Island: An Unexpected Surprise Maria N. Pestana, José M. Durães, Ana F. Gomes da silva, Miguel Goncalves, Pedro M. Vieira, Luís Resende, Jose N. Guimaraes Rosa, José Teixeira, Gil Silva. *Nephrology, Hospital Central do Funchal, Funchal, Portugal.*

Background: Fabry's Anderson disease (FAD) is a rare disorder that is highly undiagnosed worldwide. This entity is caused by alpha-galactosidase A gene (GLA) mutations. FAD, being a rare cause of end-stage renal disease (ESRD), accounts for less than 0,02% of all causes. The prevalence of FAD in Portugal is expected to be 1 in 833,000. Considering Madeira Island's (MI) population of about 250.000, one would not ponder more than one case, but little is known about FAD. Nevertheless, preliminary studies taking course point out to an increased genetic pool.

Methods: Screening of FAD is being performed among dialysis patients in MI. Alpha galactosidase A (AGAL) activity is obtained by a blood spot test. Male patients with decreased AGAL activity are tested for genetic mutations. Female patients are tested for genetic mutations regardless of AGAL activity. The diagnosis is confirmed by the presence of the mutations in the GLA gene. These patients also have lyso-Gb3 measurements. The pathogenicity is determined according to Annual Clinical Meeting Genetics (ACMG).

Results: Among 72 patients tested, we found 4 different mutations in 4 different families, all with distinctive pathogenicity. Following studies in those families revealed 10 additional cases and we are still testing other members. Two of these families have

a previously described pathogenic mutation, c.937G>T (pAsp313Tyr) in family 1 with 2 affected females and c.870G>C (pMet290Ile) in family 2 with 1 affected male and 5 affected females. Family 3 has a c.352C>T (pArg118Cys) mutation labelled as pathogenic although with conflicting reports in several studies. Curiously, we discovered a novel mutation in family 4 never reported before, referring to exon 4 of GLA gene, c.580A>G (p.Thr194Ala). Further evaluations of clinical findings suggest this mutation to be pathogenic.

Conclusions: Testing in dialysis patients and other members of identified families in MI will probably result in higher prevalence of FAD. These results are clearly above what would be expected from published previous studies. The reasons are unknown and further prompt investigation is required. Additional evaluation of affected patients will help understand the pathogenic implications.

Funding: Commercial Support - Shire

SA-PO631

A Potential Novel Mutation of CYP24A1 Leading to Hypercalcemia and Hypercalciuria Pace Romney,[3] Robert H. Yenchek,[1] Josephine Abraham.[2] *[1]Salt Lake City, UT; [2]University of Utah, Holladay, UT; [3]University of Utah Medical Center, Salt Lake City, UT.*

Background: Mutations of CYP24A1 can lead to a deficiency of vitamin D 24-hydroxylase and can lead to hypercalcemia due to dysregulation of vitamin D 1,25-OH. New mutations are continuing to be discovered.

Methods: A 29 year old man with history of prior nephrolithiasis sustained a traumatic pelvic fracture and he was incidentally discovered to have CT findings consistent with severe bilateral medullary nephrocalcinosis, hypercalcemia, and elevated creatinine. Prior to the trauma, the patient was well and had no complaints. He had 24 hour urine collections done and was found to have hypercacliuria. Parathyroid hormone was low, vitamin D 25-OH and vitamin D 1,25-OH levels were both within normal limits. Given his long history of nephrocalcinosis and nephrolithiasis at a young age, a genetic mutation of CYP24A1 was suspected and so he was started on empiric low dose of fluconazole to control his hypercalcemia. He subsequently underwent genetic sequencing for nephrocalcinosis. The results of the genetic test were positive for three mutations; heterozygous for a c.62del (p.Pro21Argfs*8) in CYP24A1, homozygous for c.1219T>A (p.Tyr407Asn) in CYP24A1, and heterozygous for c.374C>G (p.Thr125Arg) in SLC2A9. The heterozygous mutation for CYP24A1 is reported as a recessive mutation for idiopathic infantile hypercalcemia. The heterozygous mutation of SLC2A9 was felt not to fit his clinical picture. The homozygous mutation of CYP24A1 has not been previously reported in literature and modeling predicted this mutation to have probable deleterious effects. Since starting fluconazole, the patient's calcium level has normalized.

Results:

Conclusions: Idiopathic hypercalcemia is often caused by genetic mutations of CYP24A1 which encodes for the enzyme 24-hydroxylase. This enzyme promotes the conversion of 25-OHD to 24,25-(OH)2D instead of 1,25-(OH)2D and also promotes the conversion of 1,25-$(OH)_2$D to 1. With a deficiency of this enzyme, various phenotypes of hypercalcemia and nephrocalcinosis have been described. This patient has been found to have a newly discovered mutation of the CYP24A1 gene which is suspected to be causing hypercalcemia and nephrocalcinosis.

SA-PO632

Undiagnosed Genomic Disorders in Adult with CKD Miguel Verbitsky,[1] Priya Krithivasan,[1] Maddalena Marasa,[1] Junying Zhang,[1] Yifu Li,[1] Wei Yang,[2] Simone Sanna-Cherchi,[1] Krzysztof Kiryluk,[1] Harold I. Feldman,[2] Ali G. Gharavi.[1] *[1]Columbia University, New York, NY; [2]University of Pennsylvania, Philadelphia, PA.*

Background: Genomic Disorders (GDs) are caused by pathogenic deletions or duplications of large genomic regions of the genome. GDs are associated with many multiorgan developmental disorders and are enriched in children with chronic kidney disease (CKD), associating with poorer neurocognitive scores.

Methods: We studied the prevalence of GDs in adults with all-cause CKD enrolled in the Chronic Renal Insufficiency Cohort (CRIC, N= 3,375) and in the Columbia University CKD cohort (CU-CKD, N= 1,146) and compared them to 21,498 population controls. All samples were genotyped on Illumina microarrays and screened for deletions and duplications that are diagnostic of 131 known GDs.

Results: We detected GDs in 58/4,521 (1.3%) renal patients compared to 134/21,498 (0.6%) population controls (OR = 2.1, p = 1.3 x 10^{-5}). Known GDs in the CKD cohorts included 1q21.1 and 4p16.3 deletions and the 15q13.3, 16p13.11, 17p12, 17q12, 22q11.2 deletions/duplications. These GDs were all undiagnosed in the CU-CKD cohort, while diagnosis data were not available in CRIC. Analysis of available baseline clinical data in CRIC participants demonstrated that GDs are associated with significantly lower serum Mg (p = $7x10^{-4}$) and lower educational achievement (p = $8x10^{-3}$). We also detected known phenotypic associations for specific syndromes. For example, the 17q12 deletion/duplication syndrome (renal cyst and diabetes syndrome) was detected in 9 CRIC participants and was associated with diabetes (8/9 carriers) and insulin therapy (7/9 carriers) despite normal BMI, as well as hypomagnesemia (7/9 carriers).

Conclusions: GDs are undiagnosed and significantly enriched in adults with CKD, providing a molecular explanation for poorer neurocognition and specific metabolic defects in mutation carriers. Systematic detection of GDs can enable a precise genetic diagnosis and reconcile seemingly disparate clinical findings in patients. Risk stratification with GDs can also remove confounders in ongoing clinical studies, offering an opportunity to better explore causal relationships between CKD and outcomes.

Funding: NIDDK Support, Other NIH Support - NHGRI

SA-PO633

Plasma Biomarkers and Renal Outcome in African Americans with High-Risk APOL1 Variants and Preserved Renal Function Girish N. Nadkarni,[1] Kinsuk Chauhan,[1] Divya A. Verghese,[1] Chirag R. Parikh,[2] Ron Do,[1] Carol Horowitz,[1] Erwin P. Bottinger,[1] Steven G. Coca.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Yale University and VAMC, New Haven, CT.*

Background: Variants in Apolipoprotein L1 (*APOL1*) gene are associated with end stage renal disease (ESRD) in African Americans (AAs). However, risk stratification in AA's with high risk *APOL1* genotype (G1/G1; G2/G2 or G1/G2) is poor. We assessed the association between plasma biomarkers and renal outcomes in AAs with high-risk *APOL1* genotype.

Methods: We genotyped AA Bio*Me* Biobank participants for high-risk *APOL1* genotype. We measured soluble tumor necrosis factor receptor 1/2 (sTNFR1/2) and kidney injury molecule-1 (KIM1) in plasma specimens *via* MesoScale Discovery multiplex assay and determined their association with a composite renal outcome of ESRD or 40% sustained decline in eGFR. We assessed improvement in area under curve (AUC) with addition of biomarkers from a baseline model using kidney failure risk equation (KFRE) with age, sex and eGFR.

Results: Among 498 *APOL1* high-risk participants, median age was 56 years, 68% were female and baseline eGFR was 83 ml/min. 80 (16%) experienced the composite renal outcome over median of 6.9 years. After adjusting for age, sex and baseline eGFR, sTNFR1, sTNFR2, and KIM1 were independently associated with the renal outcome when expressed continuously or in tertiles, and in sensitivity analyses adjusting for baseline proteinuria in those with available measurements (n=209). (**Table**) AUC improved from 0.57 with the KFRE model to 0.74 with a biomarker-enhanced model. The event rate for participants with all 3 biomarkers in the top tertile was 40%, compared to 7% and 19% with 0 or 1 biomarker elevated, respectively (p < 0.001).

Conclusions: sTNFR1/2 and KIM1 are independently associated with renal outcome in AA's with high-risk *APOL1* genotype and improve risk discrimination. These markers can be valuable for risk stratification in AA's with *APOL1* high risk.

Funding: NIDDK Support

Associations and Discrimination for plasma biomarkers with Renal Outcome in AA's with High Risk APOL1 Genotype

Biomarker	Unit of Analysis	Adjusted HR (95% CI)	AUC for clinical model plus biomarker
sTNFR1	Per log2 increment	1.7 (1.3 - 2.2)	0.69
	3rd vs. 1st tertile	4.0 (1.9 - 8.5)	
sTNFR2	Per log2 increment	2.6 (1.6 - 4.1)	0.66
	3rd vs. 1st tertile	2.6 (1.3 - 5.2)	
KIM1	Per log2 increment	1.8 (1.3 - 2.4)	0.72
	3rd vs. 1st tertile	3.8 (1.7 - 8.2)	
All three biomarkers		NA	0.74

HR- hazard ratio; AUC- area under curve

SA-PO634

African and European Ancestry Proportions Are Associated with eGFR Measures in Over 270,000 Participants from the Million Veterans Program (MVP) Digna R. Velez edwards,[4] Ayush Giri,[4] Eric S. Torstenson,[4] Jacklyn N. Hellwege,[4] Csaba P. Kovesdy,[3] Christopher J. O'Donnell,[1] Todd L. Edwards,[2] Adriana Hung.[4,5] *[1]Boston Veterans Administration, Boston, MA; [2]Vanderbilt University Medical Center, Nashville, TN; [3]University of Tennessee Health Science Center, Memphis, TN; [4]Vanderbilt University, Nashville, TN; [5]VA TVHS, Nashville, TN. Group/Team: On behalf of VA Million Veteran Program.*

Background: Current methods estimate glomerular filtration rate (eGFR) using a creatinine based equation. Because African Americans have higher muscle mass and creatinine generation, current eGFR equations incorporate a dichotomous indicator for race (black/not black). It is unclear if this measure appropriately accounts for eGFR variability due to genetic ancestry.

Methods: To determine whether ancestry proportions influence eGFR, we evaluated associations between genetically inferred proportions of ancestry relative to 5 reference populations (GBR, PEL, YRI, CHB, and LWK) and eGFR in 56,237 self-reported blacks and 216,528 self-reported whites from the MVP. Traits were modeled using linear regression against each ancestry proportion variable adjusted for important covariates to report estimates per 10% increase for a given inferred ancestry percentage in whites and blacks separately.

Results: In self-reported blacks, every 10% increase in GBR ancestry was associated with 1.1 unit increase in eGFR levels (p-value = $5x10^{-76}$), while 10% increase in Yoruban ancestry was inversely associated with eGFR (beta: -1.1; p-value = $1x10^{-88}$). The virtually identical magnitude of effect estimates is consistent with the known two-way European/African admixture observed in blacks from the United States. Interestingly, despite the small contribution of Native American (estimated using Peruvian (PEL)) admixture to this group, PEL ancestry was positively associated with eGFR (beta: 2.16; p-value = $1.2x10^{-9}$); with the largest effect estimates observed in non-diabetic blacks. Neither CHB nor LWK ancestry was associated with eGFR in blacks (p-values >0.05). In Whites, PEL ancestry was positively associated with eGFR (beta = 0.63; p-value = $2.5x10^{-21}$), while both African ancestry proportions were inversely associated (YRI beta = -0.86, p-value = $8x10^{-29}$; LWK beta = -3.10, p-value = $8x10^{-39}$).

Conclusions: Overall, Yoruban ancestry strongly associates with decreased eGFR in both whites and blacks, after accounting for dichotomous race in the eGFR equation. Since

eGFR is a strong predictor of end stage renal disease, our results suggest incorporating ancestry proportion information into eGFR calculations may provide a better predictor for future disease risk.

Funding: Veterans Affairs Support

SA-PO635

Sparsentan Pharmacokinetics and Pharmacodynamics as the Basis of Dose Selection for Primary Focal Segmental Glomerular Sclerosis (FSGS) Michael Karol, Xin-Ru Pan-Zhou, Sarah E. Tuller, Radko Komers. *Retrophin, Inc., Cambridge, MA.*

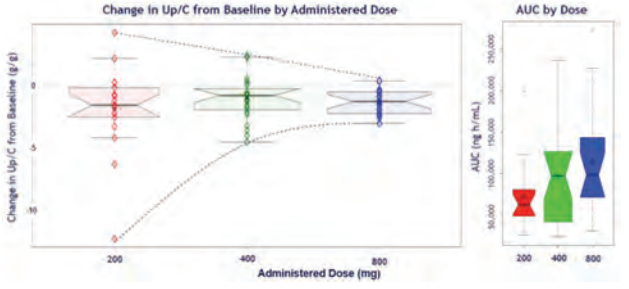
Background: Sparsentan's dual action is being studied for potential use in the treatment of primary FSGS. This analysis was performed to assess the dose/pharmacokinetic (PK)/pharmacodynamic (PD) relationship of sparsentan in FSGS patients enrolled in the DUET trial, to guide future dose selection.

Methods: The DUET trial determined the sparsentan-induced changes in urine protein/creatinine ratio (Up/C), (baseline to Week 8) in patients assigned to 200 (n=13), 400 (n=21), or 800 (n=30) mg/day. The relationship between sparsentan dose or area under the curve (AUC), and change in Up/C was assessed. PK/PD analyses were based on actual doses received, accounting for dose reductions resulting in PK/PD sample sizes of 17, 23, and 22 for 200, 400, and 800 mg/day, respectively.

Results: Due to small sample sizes, antiproteinuric effects across sparsentan doses were not statistically distinguishable; however, likelihood of a patient having drug exposures resulting in a decrease in Up/C was greater for the 800 mg dose. For the three dose groups, the percentages of patients with a decrease in Up/C were 76%, 74%, and 91%, respectively, as shown in the Figure. Of the 30 patients assigned to the 800 mg dose, 18% experienced hypotension. In general, sparsentan was safe and well tolerated with no clinically significant changes in vital signs or major clinically significant abnormalities in laboratory tests.

Conclusions: Initial daily dosing at 400 mg, followed by escalation to 800 mg for those that tolerate 400 mg, increases the likelihood of antiproteinuric effect while maximizing safety. Both the therapeutic effect vs dose or AUC and AUC distribution analyses each led to the same conclusion.

Funding: Commercial Support - Retrophin Inc.



SA-PO636

Exploring population Pharmacokinetics of Vancomycin While Using Different Anticoagulant Modalities during Continuous Venovenous Haemodiafiltration (CVVHDF) Hannah M. O'Keeffe,[3] Reema M. Munshi,[2] Mary Coyle,[1] Evelyn Deasy,[1] Maria B. Donnelly,[1] Gerard J. Fitzpatrick,[1] Peter J. Lavin,[3] Deirdre M. D'Arcy.[2] *[1]Tallaght Hospital, Dublin, Ireland; [2]Trinity College Dublin, Dublin, Ireland; [3]Trinity Health Kidney Centre, Tallaght Hospital, Dublin, Ireland.*

Background: Uncertainty remains concerning pharmacokinetics (PK) of antimicrobials in critically ill patients due to the scarcity of data and the heterogeneity of the patient cohort. Our aim was to describe the population PK estimates and the influence of patient covariates and anticoagulant modality on PK of vancomycin, following intermittent infusion in intensive care patients receiving CVVHDF.

Methods: Vancomycin dose and concentration data (peak, trough) were collected retrospectively from the electronic health records of 31 critically ill patients (n = 280 levels). A one-compartment model was used to describe the vancomycin concentration-time profiles using Pmetrics software. For brevity, only R^2 values are presented here, from observed vs. population predicted concentration plots. Dosing intervals were classified according to the dialysis modality for the majority of the dosing interval i.e. 1) dialysis with citrate anticoagulation (60 levels) 2) dialysis with non-citrate anticoagulation (120 levels) or 3) not on dialysis (44 levels). Continuous covariates were: cumulative fluid balance, effluent flow rate, blood flow rate, body weight, albumin concentration and age.

Results: An acceptable base model was produced using the Elimination Rate Constant (Ke) and Volume of Distribution (V) (R 2 0.51). The mean ± SD of vancomycin PK estimates were: V 80.65 ± 22.65 L; Ke 0.03 ± 0.01 h -1. The best population predicted models included cumulative fluid balance and albumin concentration as covariates (R^2 = 0.59 for both). The concentrations in the citrate group correlated best with the population predicted models as compared to the non-citrate dialysis and not on dialysis cohorts, with R^2 of 0.86, 0.58 and 0.28, respectively.

Conclusions: Cumulative fluid balance and albumin concentration data along with citrate anticoagulation status are suggested as covariates for further analysis with richer data, to optimise covariate PK modelling of vancomycin in ICU patients on CVVHDF, and support dose optimisation. Interestingly, the less variable PK estimates in the citrate group model suggest that the anticoagulant modality used might be associated with observed PK variability

SA-PO638

Pharmacokinetics and Intra-Renal Accumulation of the Drug Delivery Biopolymer Elastin-Like Polypeptide Is Dependent on its Molecular Weight Marija Kuna,[1] Jeremy W. Mcgowan,[2] Fakhri Mahdi,[2] Gene L. Bidwell.[2,1] *[1]Biochemistry, University of Mississippi Medical Center, Jackson, MS; [2]Neurology, University of Mississippi Medical Center, Jackson, MS.*

Background: The number of patients suffering from chronic kidney disease (CKD) and end-stage renal disease (ESRD) is rising, highlighting the need to identify novel therapies to slow down, stop or possibly reverse progression of the disease. Our lab focuses on the development of a drug delivery system based on a bioengineered protein polymer called elastin-like polypeptide (ELP) and on development of ELP-fusion proteins for renal therapy. Considering our interest in the development of ELP for kidney-targeted drug delivery, the aim of this study is to investigate how the physical characteristics of ELP, particularly its molecular weight (MW), affect its plasma clearance, biodistribution, kidney accumulation, and intra-renal distribution.

Methods: ELP proteins were synthesized, purified and characterized by SDS-PAGE, DLS and turbidity assays. Fluorescently labeled ELPs were used to assess *in vitro* degradation and in chronic and acute mice studies to define the pharmacokinetics and biodistribution.

Results: Our data show that increasing the ELP MW from 25 kDa to 86 kDa resulted in an increase of the hydrodynamic radius from 4 to almost 7 nm. Degradation studies demonstrated that the proteins are stable for 10 days with negligible degradation at 4°C in both plasma and PBS. The proteins were also stable at 37°C in PBS, but showed time-dependent degradation in plasma at 37°C. After 24 hours, 12-15% degradation was present, and these levels increased to 50% for ELPb-63 (25 kDa) and 24% for ELPb-191 (74 kDa) over the 10-day experiment. However, these degradation rates were slow compared to the plasma clearance rate. ELP plasma half-life increased from 0.84 to 7.05 h with an increase in MW from 25 to 74 kDa. As expected, ELPs accumulated predominantly in the kidneys, with ELPb-63 levels significantly different from the larger proteins. ELPb-63 accumulated mostly in the cortex, while increasing MW resulted in more ELP deposition in the medulla.

Conclusions:

Funding: Other NIH Support - NIH NHLBI Grant R01HL121527 (GLB)

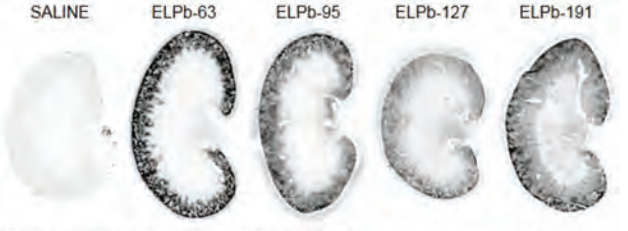


Figure 1. Intrarenal Distribution of ELPb Constructs. Four hours after intravenous injection of fluorescently labeled ELPbs, mice kidneys were rapidly frozen and cut into 14 µm sections. Slides were scanned using a fluorescence slide scanner.

SA-PO639

Safety, Tolerability, and Pharmacokinetics of the Selective Mineralocorticoid Receptor Antagonist KBP-5074 in Hemodialysis and Non-Hemodialysis Patients with Severe CKD Jeffrey J. Connaire,[1,2] Mark A. Bush,[5,2] Vincent Benn,[3] Y. Fred Yang,[2] Jon L. Ruckle,[4,2] Xiaojuan Tan.[2] *[1]Davita Clinical Research, Minneapolis, MN; [2]KBP Biosciences Co., Ltd., Princeton, NJ; [3]KBP Biosciences USA Inc, Princeton, NJ; [4]Pacific Pharma Group, LLC, Tacoma, WA; [5]Wingate University School of Pharmacy, Wingate, NC.*

Background: Background: Chronic kidney disease (CKD) is a leading cause of morbidity/mortality in the US. Mineralocorticoid receptor antagonism (MRA) has been shown to benefit in heart failure/hypertension but not in advanced CKD patients due to safety concerns, e.g., hyperkalemia. KBP-5074 is a novel, non-steroidal, highly-selective MRA being developed for patients with hypertension and advanced CKD.

Methods: Methods: This was a Phase 1, open-label study to evaluate the safety, tolerability, and pharmacokinetics (PK) of KBP-5074 following single oral administration to subjects with severe CKD, comparing Stage 5 subjects receiving hemodialysis (HD) with Stage 4 subjects not receiving hemodialysis (non-HD). Eleven subjects (6 HD and 5 non-HD) were enrolled and received a single 0.5 mg dose of KBP-5074. HD subjects were dosed immediately following a dialysis session. All subjects were followed for 13 days post-dose. In HD subjects, PK samples were collected before, during, and after the first HD session.

Results: Results: The mean age of the study subjects was 53.5 years; 54.5% were male. KBP-5074 was well tolerated: 6 TEAEs (mostly mild) were reported in 4/11 subjects. Plasma exposure of KBP-5074 in HD subjects was statistically significantly lower than in non-HD subjects: C_{max} (7.34 ng/ml vs 10.6 ng/ml)/AUC (669 hr*ng/ml

vs. 1310 hr*ng/ml), and $T_{1/2}$ was shorter in HD subjects (64.2 hrs vs. 87.9 hrs). HD was associated with minimal alterations in KBP-5074 plasma concentrations and outflow dialysate concentrations of KBP-5074 were undetectable, indicating negligible clearance of KBP-5074 via HD. Plasma aldosterone and serum potassium values were generally comparable between HD and non-HD subjects.

Conclusions: Conclusions: KBP-5074 at a dose of 0.5 mg was safe and well tolerated in all study subjects. Plasma exposures of KBP-5074 in HD subjects were significantly lower than in non-HD subjects. Hemodialysis had a negligible effect on plasma concentrations of KBP-5074. These data support further evaluation of KBP-5074 in patients with advanced CKD.

Funding: Commercial Support - KBP Biosciences

SA-PO640

The Effect of Tacrolimus Exposure on CYP3A5 and P-gp Expression in a Model of Human Proximal Tubule Cells for Studying the Role of Pharmacogenetic Variation in Renal Drug Metabolism and Toxicity

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Background: Tacrolimus (Tac) constitutes the mainstay of immunosuppressive therapy and is metabolized through the interplay between CYP3A enzymes and the P-gp transporter (*ABCB1*). Clinical and fundamental studies have demonstrated the importance of genetic variation for the expression of corresponding proteins in relation to drug metabolism and toxicity. The effect of Tac on their expression in renal cells with a variable pharmacogenetic background common in the general population is unknown.

Methods: Human immortalized proximal tubule cells (PTC) with 4 combinations of *CYP3A5(rs776746)* and *ABCB1(rs1045642)* were selected. Tac exposure during experiments was based on WST-1 assay and *in vivo* data on tissue levels in allograft recipients, i.e. vehicle, 50 ng/ml and 300 ng/ml for 24 and 72hrs. Quantitative and functional expression was assessed by RT-PCR, WB, midazolam (MDZ) hydroxylation (for CYP3A5) and calcein efflux (P-gp).

Results: Only very high Tac concentrations (45,000ng/ml) resulted in cell death. Baseline *mRNA*, protein and functional expression of CYP3A5 was higher in ciPTC with the **1* versus **3/*3 allele.* Increasing Tac conc. within the range of tissue levels had no effect on CYP3A5 mRNA or protein expression but resulted in decreasing 1'OH MDZ hydroxylation ($p<0.001$). Quantitative expression of ABCB1mRNA and Pgp was similar between variants of *ABCB1 3435C>T,* but calcein-AM efflux was higher in *TT* vs. *CC/CT* (delta fluorescence: 45.3% vs. 27.1%; $p= 0.001$). Tac conc. did not affect quantitative ABCB1/P-gp expression but resulted in decreasing calcein efflux ($p<0.001$) in both variants.

Conclusions: Tacrolimus exposure associated with in vivo tissue levels are not lethal and have no direct effect on the regulation of gene/protein expression for CYP3A5 and P-gp in PTC with a variable pharmacogenetic background. However, these concentrations do result in decreasing functional expression of both actors involved in Tac metabolism on top of the differences associated with the genetic background. The potential nephrotoxic effect ascribed to Tac might therefore be the result of basal variation in functional expression due to underlying genotype for *CYP3A5* or *ABCB1,* and/or in combination with the inhibitory effect of tacrolimus on the enzyme and pump function.

SA-PO641

Age Influences on Tacrolimus Pharmacokinetics Post-Transplant

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Background: Minimal data is available describing the influence of age on tacrolimus (TAC) pharmacokinetics (PK) in African American (AA) and Caucasian (C) renal transplant recipients (RTR) in spite of increased renal transplantation in the elderly. This sub-study investigated the impact of age on TAC PK in stable AA and C RTR.

Methods: The 12-hour PK study of TAC was investigated in 35 AA and 32 C RTR receiving enteric coated MPA and tacrolimus. Cumulative adverse effects (CAE) were assessed including gastrointestinal, neurologic and aesthetic manifestations. Patents were categorized by age as follows: Young: >21 & ≤ 40 years; Middle Age: >40 &≤ 60 years and Elderly>60 years. Apparent clearance (CL), BMI normalized CL (CL/BMI), Area Under the Concentration-time curve 0-12h (AUC12), dose-normalized AUC12 (AUC*), 12 hour troughs (C-12h) and dose normalized C-12hr(C-12h/Dose) with CAE were determined and analyzed with univariate ANOVA.

Results: Table summarizes the results. All group means were within the therapeutic AUC12 guide of 120-200 mg.hr/ml for TAC. The elderly received the lowest TAC dose and achieved comparable, therapeutic C-12h troughs and AUC12 to other groups. The elderly had a higher dose normalized trough and AUC* with slower CL and more CAE compared to younger patients.

Conclusions: These findings suggest that TAC dosing regimens need be individualized based upon adult ages and time post transplant. Further investigations into age-related changes in TAC exposure and relation to clinical responses(i.e. adverse effects) remain important for safe and efficacious immunosuppression.

Funding: NIDDK Support, Commercial Support - ASTELLAS

Endpoints	Young(n=16)	Middle Age(n=38)	Elderly(n=13)	P Value
e-GFR	57.06 (16.04)	52.97(14.26)	59.40 (19.26)	0.390
TAC Dose(mg)	3.3(1.4)	3.6(1.9)	2.7 (1.6)	0.257
MPA Dose (mg)	641.3 (185.5)	630.0(176.3)	595.4(135.2)	0.757
C-12h (ng/ml)	7.0(1.5)	7.1(2.0)	7.6(1.9)	0.715
C-12h/Dose	2.4(1.0)	2.6(1.6)	3.4(1.5)	0.011*
AUC12 (ng.hr/ml)	126.0(31.1)	124.6(33.8)	126.7(31.4)	0.976
AUC*	41.2(14.2)	44.3(25.0)	56.2(23.3)	0.037*
CL (L/hr)	28.1(11.9)	29.1(14.6)	21.8(11.1)	0.034*
CL/BMI	1.01 (0.51)	1.01(0.51)	0.68(0.38)	0.043+
CAE Score	0.13 (0.09)	0.14 (0.08)	0.15 (0.05)	0.064*

* Time Post-Transplant Adjusted Analysis

SA-PO642

Antibiotics: A Novel Factor Associated with Tacrolimus Trough Variability in Kidney Transplantation

John R. Lee,[2] Yuanpu Zheng,[1] Michael P. Wagner,[1] Darshana Dadhania,[2] Thangamani Muthukumar,[2] Manikkam Suthanthiran.[2] *[1]New York Presbyterian Hospital, New York, NY; [2]Weill Cornell Medicine-, New York, NY.*

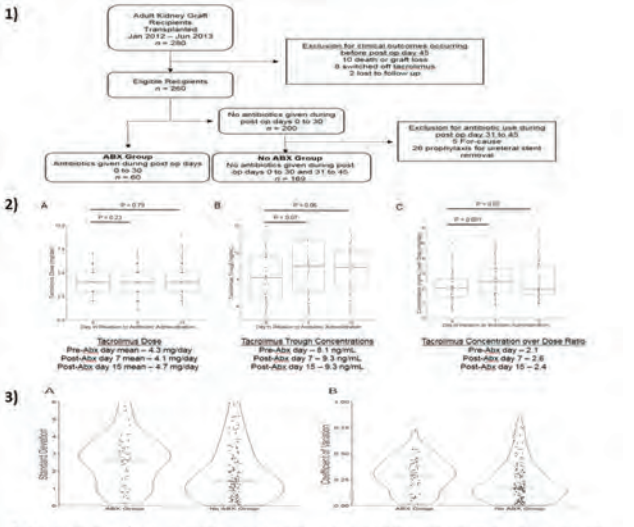
Background: We previously reported a relationship of the gut microbiota to tacrolimus dosing requirements. Based upon this data, we hypothesize that antibiotics, which are known to alter the gut microbiota, is associated with tacrolimus trough variability.

Methods: We performed a retrospective chart review of subjects who received a kidney transplantation at our institution from 2012 to 2013. We divided the population into subjects who received antibiotics during the first month of transplantation (Abx Group, N=60) and subjects who did not (No Abx Group, N=169) (Fig A). We evaluated whether antibiotics increase tacrolimus trough levels and tacrolimus trough level over dosing (C/D) in the Abx Group and whether antibiotics increase tacrolimus trough variability as measured by standard deviation (SD) and coefficient of variation (CV) between post op days 31 to 45.

Results: In the Abx Group, 48 subjects had a tacrolimus trough level measured prior to antibiotic administration and these subjects had increased tacrolimus trough levels and increased tacrolimus C/D, 7 and 15 days after antibiotic administration (Fig 2B, 2C). Subgroup analysis of type of antibiotics suggested increasing C/D after 7 days after antibiotic administration in penicillin type antibiotics and cephalosporin type antibiotics (P=0.08, 0.09, respectively). Tacrolimus trough variability as measured by SD and CV between post op days 31 to 45 was significantly different between the Abx Group and the No Abx Group (SD median 2.6 vs 1.6, P=0.03; CV median 0.29 vs. 0.18, P=0.02, Wilcoxon rank sum test) (Fig 3).

Conclusions: Our identification of antibiotics' association with tacrolimus trough variability highlights the need to measure tacrolimus trough levels after antibiotic administration.

Funding: Other NIH Support - NIAID K23 AI 124464



1) Cohort selection. **2)** Box and whisker plots with days after antibiotic administration on the x axis and tacrolimus dose (A), tacrolimus trough (B), and tacrolimus C/D (C) on the y axis. Tacrolimus trough and tacrolimus C/D increases after antibiotic administration (P values calculated using one-way anova with repeated measures using contrasts and are above each group comparison). **3)** Violin plots analyzing tacrolimus trough levels between post op day 31 to 45. On the x axis is the ABX Group and the No ABX Group and on the y axis is the standard deviation of tacrolimus trough levels for each subject (Left) and the coefficient of variation of tacrolimus trough levels for each subject (right). The line represents the median value in each group.

SA-PO643

Intrapatient Tacrolimus Variability Has Similar Outcomes on Kidney Allograft Function between UK Transplant Centers Ryan Ghita. *NHS Greater Glasgow and Clyde, Glasgow, United Kingdom. Group/Team: UK Transplant Audit Collaborative.*

Background: Tacrolimus based immunosuppression regimes are the mainstay of treatment for transplant patients in the United Kingdom. High intrapatient variability (IPV) of tacrolimus levels has been associated with poorer kidney allograft function. A retrospective study looked at the effects of high IPV on eGFR in five transplant centers across the UK (Glasgow, Oxford, King's London, Liverpool, Manchester).

Methods: Data was collected from patients who received a kidney transplant between 2009 and 2014 in one of the 5 UK centers. Tacrolimus trough levels were recorded at two time points - 6-12 months post transplant (T1) and most recent 12 months (T2). Exclusion criteria included patients that received dual-organ transplants or if death or graft loss occurred within two years of transplantation, or if their immunosuppression regimens included modified release tacrolimus. For each transplant center, patients that fell into the highest and lowest IPV quartiles were identified and their MDRD eGFR were compared using a Mann-Whitney U-test. The results are in table1.

Results: Three of the comparisons between the high and low variability groups had a U-value lower than the critical value suggesting a significant difference in MDRD eGFR. In all other groups the median eGFR was lower in the high IPV group however this was not found to be statistically significant.

Conclusions: The results suggest a correlation between high IPV and worse allograft function, as determined by eGFR, throughout the UK transplant centers. However the small patient cohort in each center limits analysis. Further analysis will be performed merging the data from all centers which to the best of our knowledge will be the largest study looking at IPV with over 1000 patients.

Table 1: eGFR comparison between patients with high and low tacrolimus variability in UK Transplant Centers

	Glasgow (n=168)	Oxford (n=284)	Liverpool (n=171)	Manchester (n=313)	King's London (n=134)
T1 MEDIAN (IQR) eGFR of low IPV patients	62 (49-77)	54 (45-64)	51.5 (38-57.3)	49 (38.5-61)	56 (48.3-73.3)
T1 MEDIAN (IQR) eGFR of high IPV patients	46 (34.3-58.6)	50 (35.5-58)	44 (36-52)	48.5 (39.3-59.3)	55 (43-67)
P – value	0.001	0.02	0.19	0.59	0.52
T2 MEDIAN (IQR) eGFR of low IPV patients	55 (47-73)	52 (39-65)	50 (36-56)	48 (38-56.5)	58.5 (48-73.8)
T2 MEDIAN (IQR) eGFR of high IPV patients	53.5 (28-64.8)	47 (37.5-64)	46 (33.5-58)	44 (30-60.6)	51 (28.8-63.8)
P – value	0.13	0.26	0.47	0.69	0.03

SA-PO644

Drug Dosing During AKI Michael E. Brier,[2] George Aronoff,[1] Adam E. Gaweda.[2] *[1]DaVita, Inc., Naples, FL; [2]University of Louisville, Louisville, KY.*

Background: When renal function is rapidly changing during acute kidney injury (AKI), determining the proper dosage for drugs that are renally eliminated becomes difficult. We tested the hypothesis that estimating the creatinine production rate (CPR) combined with measured serum creatinine (Scr) allows us to determine the level of renal function as the estimated glomerular filtration rate (eGFR) to guide in drug dosing.

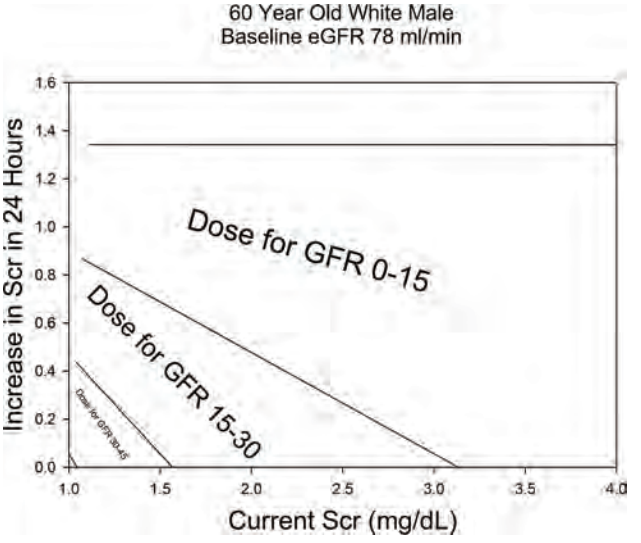
Methods: Baseline creatinine production was determined by rearrainging the CKD-EPI equation and solving for creatinine generation using the principle that at steady-state the rate of elimination = rate of production. We calculated creatinine production over a range of baseline serum creatinine concentrations for white males, white females, black males, and black females at different ages. Using the change in Scr in 24 hours we are able to determine the integrated eGFR. We then simulated the hourly change in Scr using the estimated CPR and actual GFR to determine delta Scr/24 hours and developed a graphical representation.

Results: The results are shown in the table for CPR (mg/hr) for a 60 year old white male. Dosing information for this patient is shown in the figure with recommendations to dose at a GFR of 0-15, 15-30, and 30-45. Maximum increase in Scr for this patient at no renal function is 1.34 mg/dL/day.

Conclusions: Complex processes occur during AKI that complicate drug dosing. However, estimation of renal function can still occur using routinely obtained Scr measurements that can help in determining drug dosage adjustments. CKD-EPI shows that CPR is decreased in the population as baseline Scr increases.

Creatinine Production Rate (mg/hr)

Baseline Scr	White/Male	White/Female	Black/Male	Black/Female
1.0	47	32	54	37
2.0	30	21	35	24
3.0	24	16	27	19
4.0	20	13	23	16
5.0	17	12	20	14



Example dosing nomogram.

SA-PO645

Proteinuric Renal Disease Alters the Biodistribution of Antisense Oligonucleotides Allowing Reduction in Dose for Kidney Targets Anna Granqvist,[1] Lena William-Olsson,[1] Barbro Basta,[1] Thomas Bell,[3] Patrik Andersson,[2] Magnus Soderberg,[2] Mark J. Anderton,[2] Christine Ahlström.[1] *[1]Innovative Medicines & Early Development Cardiovascular & Metabolic Disease, AstraZeneca R&D, Gothenburg, Sweden; [2]Drug Safety & Metabolism, AstraZeneca R&D, Gothenburg, Sweden; [3]Ionis Pharmaceuticals, Carlsbad, CA.*

Background: An increasing number of oligonucleotide therapeutics are used in clinical trials today. Antisense oligonucleotides (ASOs) are predominantly taken up by the liver and kidneys, which makes them a desirable modality for the treatment of renal disease. However, there is a concern regarding potential clinical safety risks such as thrombocytopenia, injection site reactions and renal/liver toxicity at higher doses. The biodistribution of ASOs to different tissues is assisted by plasma protein binding that delays urinary excretion and it was therefore hypothesized that distribution of ASOs with phosphorothioate backbone is altered in proteinuric renal disease.

Methods: We investigated the tissue exposure and distribution of a phosphorothioate cEt gapmer ASO in the obese diabetic BTBR ob/ob mouse. This is a suitable model as it mimics key features of human diabetic nephropathy, including progressive proteinuria and glomerulopathy. Mice were subcutaneously administered weekly doses of 3, 10, 30 or 100 mg/kg ASO in saline and followed for 2-12 weeks.

Results: In all animals tissue exposure and significant knock down of the target gene in kidney was achieved (between 45-75% decreased expression, $p \leq 0.001$). In the diabetic BTBR ob/ob mice a shift in the distribution of ASO towards the kidney was observed in comparison to healthy mice, leading to a lower exposure in liver. Similar exposure and knock down in the kidney was achieved in the diseased animals with a 30 mg/kg dose compared with a 100 mg/kg dose in healthy animals. There were no nephrotoxic effects of the ASO treatment (determined by biomarker analysis and histology).

Conclusions: These results suggest that in a model of proteinuric renal disease similar level of kidney mRNA knockdown is observed at lower ASO dose levels compared to healthy mice. If such observations translate to patients with kidney disease, this may reduce the risk of toxicities in other organs and tissues.

SA-PO646

Targeted C4 Inhibition by Affinity Purified Immunoglobulins Elena Volokhina,[3] Thea J. Van der velden,[1] Marloes Michels,[4] Nicole Van De Kar,[2] Marcin Okroj,[5] Bert Van den heuvel.[4] *[1]Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; [2]UMC St. Radboud Nymegen, Nijmegen, Netherlands; [3]Radboud university medical center, Nijmegen, Netherlands; [4]Radboudumc, Nijmegen, Netherlands; [5]Medical University Gdansk, Gdansk, Poland.*

Background: Immunoglobulins (Igs) can activate complement when bound to their antigens. Moreover, they may inhibit complement activation and in clinical practice intravenous Igs are widely used to treat immunodeficiencies as well as inflammatory conditions. Complement inhibitory properties of Igs are poorly understood, which limits their use for targeted complement modulation in renal disorders. In this study we describe immunoglobulin preparations with specific complement inhibiting properties.

Methods: Igs from healthy donors were purified using Protein L or Protein A/G affinity chromatography. Classical (CP) and alternative pathway (AP) activation was assessed using hemolytic assays. Activation of C1q, C4b, C3b and C5b-9 in CP was assessed by ELISA. Purified fractions were analyzed by SDS-PAGE and silver staining.

Results: Igs purified from serum using Protein L, but not Protein A/G inhibited CP in normal human serum (NHS) to below 10% of normal activity when added at 13 mg/mL. Igs from lepirudin, citrate and heparin plasma showed similar inhibiting results, while those isolated from EDTA plasma had no effect. None of the fractions had effect on AP. CP ELISA revealed normal deposition of C1q, and strongly decreased deposition of C4b, C3b and C5b-9. All fractions showed same band pattern in SDS-PAGE. All purified Igs retained ability to activate CP when heat-aggregated. Moreover, Igs isolated from serum spiked with 100 μg/mL eculizumab were still able to fully block AP when added to NHS.

Conclusions: Thus, Igs purified using Protein L chromatography block complement in NHS at the stage of C4. These findings have important therapeutic potential for the inhibition of classical complement pathway in the future in such conditions as antibody-mediated renal graft rejection, lupus nephritis and antiphospholipid syndrome.

SA-PO647

Effect of the Microbiota-Derived Uremic Toxin Indoxyl Sulfate on FMO Expression and TMAO Formation: A Pilot Study Alexander J. Prokopienko, Anand Joshi, Raman Venkataramanan, Thomas D. Nolin. *School of Pharmacy, Center for Clinical Pharmaceutical Sciences, University of Pittsburgh, Pittsburgh, PA.*

Background: Cardiovascular disease (CVD) is the leading cause of death in kidney disease. Microbiota-derived uremic toxins likely contribute to CVD progression and may be modifiable risk factors. The microbiota-derived uremic toxins indoxyl sulfate and trimethylamine-N-oxide (TMAO) are associated with poor CVD outcomes. Indoxyl sulfate activates the aryl hydrocarbon receptor (AhR) transcription factor, which partially regulates flavin-containing monooxygenase (FMO) expression. FMOs are an important class of hepatic enzymes that oxidize trimethylamine to TMAO. We hypothesize that indoxyl sulfate induces hepatic FMO expression and activity, thereby increasing TMAO formation. The aim of this pilot study was to assess the effect of indoxyl sulfate on the expression and activity of FMO.

Methods: Primary cultures of human hepatocytes (n=1 donor) were pre-treated with 0.1% dimethylsulfoxide (vehicle control), rifampin (induction control), PCB-77 (AhR agonist) and indoxyl sulfate (1, 25, 100 and 250 μM) for 72 hours. All treatments were run in duplicate. Hepatocytes were then incubated for 3 hours with trimethylamine and formation rate of TMAO was used as an indicator of hepatic FMO activity. TMAO was measured via LC-MS. Gene expression was determined by RT-qPCR using specific Taqman® probes and master mix. All data was analyzed using one-way ANOVA.

Results: FMO3 mRNA expression increased by 2.4-fold, 2.1-fold, 2.9-fold and 5.1-fold compared to vehicle control with indoxyl sulfate 1, 25, 100 and 250 μM, respectively ($p<0.0055$). CYP1A2 mRNA expression increased by 2.7-fold, 16-fold, 96-fold and 254-fold compared to vehicle control with indoxyl sulfate 1, 25, 100 and 250 μM, respectively ($p<0.0003$). AhR mRNA expression was not significantly changed compared to control. Indoxyl sulfate 1, 25, 100 and 250 μM increased TMAO formation by 1.2-fold, 1.6-fold, 1-fold, and 3-fold compared to vehicle control, respectively ($p<0.0049$).

Conclusions: These results suggest that indoxyl sulfate induces FMO3 mRNA expression and activity, leading to increased FMO-mediated TMAO formation. This novel metabolic interaction may contribute to dramatically increased systemic exposure of TMAO and CVD progression in kidney disease patients.

Funding: NIDDK Support, Other NIH Support - NCATS

SA-PO648

Genetics of Serum Urate Concentrations and Gout in a High-Risk Population, Patients with CKD Ulla T. Schultheiss,[4] Jiaojiao Jing,[9] Arif Ekici,[8] Thomas Sitter,[5] Kai-Uwe Eckardt,[7] Elke Schaeffner,[1] Yong Li,[3] Florian Kronenberg,[2] Anna Kottgen.[6] *[1]Charite, Berlin, Germany; [2]Innsbruck Medical University, Innsbruck, Austria; [3]University Hospital Freiburg, Freiburg, Germany; [4]University Hospital Freiburg, Freiburg, Germany; [5]Medizinische Klinik, Munich, Germany; [6]University Hospital Freiburg, Freiburg, Germany; [7]University of Erlangen-Nuremberg, Erlangen, Germany; [8]University of Erlangen-Nuremberg, Erlangen, Germany; [9]University of Freiburg, Freiburg, Germany.*

Background: Gout is the most common inflammatory arthritis in many countries with a strong genetic component. Individuals with chronic kidney disease (CKD) represent a high-risk population for gout. Genetic risk factors for gout and their interactions with clinical factors in CKD are understudied.

Methods: Genome-wide association studies of serum urate and gout were performed in 4941 CKD patients (1217 with gout) in the German Chronic Kidney Disease study. Effect sizes of 26 known serum urate-associated SNPs from population-based studies were examined. Interactions of urate-associated variants with serum urate-altering medications and clinical characteristics of gout were evaluated.

Results: Genome-wide significant associations ($p<5E-08$) with serum urate and gout were identified for the known loci *SLC2A9* and *ABCG2*, encoding urate transporters. Effects of 26 known SNPs were of similar magnitude in CKD patients and population-based studies (**Figure 1**). Gene-medication interactions implicated interactions (e.g. *ABCG2* rs2231142 and loop diuretics) but were not significant when accounting for multiple testing. Effects of *ABCG2* rs2231142 on serum urate were higher in those with lower eGFR, consistent with the transporters role in urate excretion. Associations with gout in specific joints were strongest for *SLC2A9* rs12498742 in elbows and wrists, and *ABCG2* rs2231142 in knees and ankle joints.

Conclusions: Known genetic variants in *SLC2A9* and *ABCG2* were associated with serum urate and gout in a CKD cohort with effect sizes similar to population-based studies. Studying pharmacogenomic interactions is challenging in the setting of polypharmacy in CKD. CKD patients are at high risk of gout due to reduced kidney function, diuretics intake and genetic predisposition.

Funding: Commercial Support - Astra Zeneca, Grünenthal, Private Foundation Support, Government Support - Non-U.S.

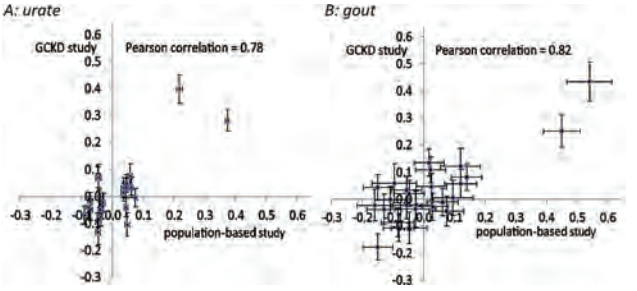


Figure 1: Effect size comparison of SNPs on serum urate in population-based studies (X) vs. CKD patients (Y) for urate (panel A) and gout (panel B, log odds ratio).

SA-PO649

Targeting Stat3 Activity Blocks Muscle Wasting in CKD Liping Zhang,[2] William E. Mitch.[1] *[1]Baylor College of Medicine, Houston, TX; [2]Nephrology, Baylor College of Medicine, Houston, TX.*

Background: Muscle wasting with morbidity and mortality is common in patients with chronic kidney disease (CKD) but there are no regularly effective treatments. We find there is activation of a p-Stat3/CEBPδ/myostatin signaling pathway in muscles of patients or mice with CKD and inhibition of myostatin or p-Stat3 blocked muscle loss in mice with CKD. We also find that C188-9, a small-molecule inhibitor of Stat3 increases muscle mass and improves muscle function despite CKD. To extend these results, we examined optimal dosing, frequency and route of administration of C188-9 to rats with CKD

Methods: CKD (subtotal nephrectomy) was created in male Sprague-Dawley rats. C188-9 was administered by gavage feeding or i.p. injection; plasma levels of C188-9 were measured by LC/MS

Results: For pharmacokinetics, we administered C188-9 (doses 0, 10, 30, 100 mg/kg) once to 2 groups of rats: A) sham-operated, control rats; and B) rats with CKD, pair fed with control rats. Plasma was collected at 0, 0.25, 0.5 1, 2, 4, 8 and 24 hr following C188-9 treatment. We found: 1) plasma C188-9 concentrations were linear with the administered dose in control and CKD rats. 2) C188-9 plasma concentrations in mg/ml were similar in CKD vs. control rats at different doses: 10 (CKD, 2.5 vs control, 2.4); 30 (8.4 vs. 8.3) and 100 mg/kg, (13 vs. 9.8). 3). Time to maximal C188-9 blood level was 1h for all doses of control and CKD rats. 4) In CKD rats, the C188-9 half-life was greater vs. results in control rats. 5) At 3 days after C188-9 dosing, we measured C188-9 in muscle lysates; levels of C188-9 in muscle were similar in sham and CKD rats. 6) Notably, C188-9 suppressed muscle p-Stat3 levels in CKD rats vs. controls (no C188-9) and the p-Stat3 level was inversely correlated with the C188-9 in muscle. 7). C188-9 was tolerated in CKD rats even at 100 mg C188-9/kg/day for 7 days

Conclusions: 1) the optimal C188-9 dose is 30mg/kg which blocks p-Stat3 effectively in muscle of rats with CKD and it has a half-life similar to that of 100 mg/kg. 2) From this half-life, C188-9 could be dosed every 4 hrs to CKD rats. 3) C188-9 has a potential for developing oral dosing as results with gavage feeding were similar to those of i.p. injection. 4) The drug remains in muscles, inhibiting p-Stat3 effectively. 5) C188-9 exhibits minimal short-term toxicity. Thus, C188-9 has a potential for combating muscle wasting in patients with CKD.

Funding: NIDDK Support, Commercial Support - Atara Biotherapeutics, Private Foundation Support

SA-PO650

Apabetalone (RVX-208) Impacts Key Markers and Pathways Associated with CKD in Patients with Severe Renal Impairment Ewelina Kulikowski,[3] Sylwia Wasiak,[3] Laura Tsujikawa,[3] Christopher Halliday,[3] Stephanie Stotz,[3] Dean Gilham,[2] Ravi Jahagirdar,[3] Kamyar Kalantar-Zadeh,[5] Richard A. Robson,[1] Michael Sweeney,[6] Jan O. Johansson,[4] Norman C. Wong.[4] *[1]CHristchurch Clinical Studies Trust, Christchurch, New Zealand; [2]Resverlogix, Calgary, AB, Canada; [3]Resverlogix Corp, Calgary, AB, Canada; [4]Resverlogix Corp., San Francisco, CA; [5]University of California Irvine, School of Medicine, Orange, CA; [6]Resverlogix Inc, San Francisco, CA.*

Background: Chronic kidney disease (CKD) is associated with a progressive loss of renal function and a high risk of cardiovascular disease (CVD). Apabetalone is an orally active BET protein inhibitor that decreased major adverse cardiac events (MACE) in CVD patients in phase 2 clinical trials. Thus, a phase 1, open-label, parallel group study of patients with impaired kidney function was conducted to determine the effect of apabetalone on plasma proteins associated with CVD complications in CKD.

Methods: 8 subjects with stage 4 CKD not on dialysis (mean eGFR=20 ml/min/1.73m²) and 8 matched controls (mean eGFR=78.5 ml/min/1.73m²) received a single 100 mg dose of apabetalone. Plasma was collected over 48h for PK analysis and at 12h post dose for proteomics analysis using the SOMAscan® platform (1305 proteins). Data

were analysed with Ingenuity® Pathway Analysis (IPA®) to identify pathways regulated by apabetalone.

Results: PK parameters were similar in CKD patients and controls. Plasma proteomics in CKD patients showed that after 12h apabetalone altered levels of 261 proteins by 10-58% ($p<0.05$), versus baseline. 257/261 proteins were downregulated, consistent with inhibition of BET sensitive genes. IPA® revealed a robust effect of apabetalone on pathways involved in immunity and inflammation, acute phase response, diabetes, endothelial dysfunction, vascular calcification, fibrosis, and hypertension. Apabetalone also reduced circulating CKD and CVD markers, including IL-6, TNFα, IL-1, ICAM-1, VCAM-1, CRP, PAI-1, L-selectin, E-selectin, MMP-3, MMP-10, fibronectin and SPP1 ($p<0.05$).

Conclusions: In stage 4 CKD patients, apabetalone rapidly downregulates plasma markers and molecular pathways linked to renal disease and CVD complications. The long term impact of apabetalone is currently being studied in a subpopulation with impaired kidney function of the phase 3 BETonMACE CVD outcomes trial.

SA-PO651

Personalized Levetiracetam Dosing Adjustments for Patients Undergoing Continuous Venovenous Hemofiltration Shamir Kalaria,[2] Paul J. Mccarthy,[2] Miguel Franquiz,[2] Michael Armahizer,[3] Mathangi Gopalakrishnan.[1] *[1]School of Pharmacy, University of Maryland, Baltimore, Baltimore, MD; [2]University of Maryland, Baltimore, MD; [3]University of Maryland Medical Center, Baltiomre, MD.*

Background: Few clinical data exist on the effect of continuous renal replacement therapy (CRRT) methods on medication pharmacokinetics (PK). Appropriately designed PK studies could potentially optimize dosing recommendations in patients undergoing CRRT. This clinical study in critically ill patients receiving levetiracetam aims to understand the (1) methodology of conducting an appropriate CRRT study to characterize PK, (2) potential barriers that exist with an observational CRRT study, and (3) derivation of individualized dosing recommendations.

Methods: Five patients receiving oral or intravenous levetiracetam and continuous venovenous hemofiltration (CVVH) in a neurocritical care unit were sampled to investigate the need for dosing adjustments. Pre-filter, post-filter, and ultrafiltrate samples were taken before dosing, after the completion of a 15 minute infusion, and at 4-5 additional time points post-infusion. Plasma concentrations were determined using a validated HPLC-UV bioanalytical method. Blood and effluent flow rates and laboratory parameters were also collected at the time of sampling. Non-compartmental analysis was conducted using Phoenix WinNonlin® 7.1 (Pharsight Corporation).

Results: The average sieving coefficient (ratio of ultrafiltrate concentrations to prefilter plasma concentrations) was 0.90 ± 0.1 and the average volume of distribution was 52.7 ± 7.6 liters. Three out of the five patients experienced concentrations outside the reported therapeutic range (12-46 mg/L) of levetiracetam. Average total drug clearance for patients taking 750 mg, 1000 mg, and 2000 mg were 3.10, 5.14, and 3.46 L/hr respectively, indicating that differences in clearance can be attributed to differences in ultrafiltration flow rates.

Conclusions: Preset ultrafiltrate rates were different amongst patients and need to be taken into consideration when determining an appropriate dose. Patients with higher ultrafiltrate rates will have increased drug clearance and therefore will require higher doses in order to match exposures seen in patients with normal renal function. Therefore, individualized dosing recommendations should be based on CRRT flow parameters and drug specific sieving coefficients.

Funding: Private Foundation Support

SA-PO652

Effect of CKD on Expression of Cyp3a11, Cyp2c37, Cyp2d22, and Oatp1b2 in C57BL/6 Mice Nicholas Tonial,[3] Emily D. Hartjes,[3] Jean-Francois Thibodeau,[2] Chet E. Holterman,[1] Eldjonai Kamto,[1] Lyne Gagnon,[2] Brad Urquhart.[3] *[1]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [2]ProMetic BioSciences Inc., Laval, QC, Canada; [3]Western University, London, ON, Canada.*

Background: Drug disposition can be severely altered in patients with chronic kidney disease (CKD) due to the multitude of physiological changes that occur. Cytochrome P450s and membrane transporters are major contributors to overall drug disposition, and have been extensively studied in rodent models of CKD. Induction of CKD in rat models by 5/6 nephrectomy or dietary treatment with adenine have shown decreased expression of CYPs such as CYP3A2 and CYP2C11. CKD mouse models using 3/4 nephrectomy have also shown a reduced expression of Cyp3a11. However, the use of adenine to induce CKD in mice for the purpose of evaluating drug response has not been studied. This study investigated the effects of adenine-induced CKD in C57BL/6 mice on the expression of Cyp3a11, Cyp2c37, Cyp2d22, and Oatp1b2. It was hypothesized that CKD would decrease the expression of these genes.

Methods: C57BL/6 mice were fed standard chow (n=4) or standard chow supplemented with 0.25% adenine (n=6) for 4 weeks. Mice were sacrificed, organs collected and RNA was isolated and analyzed by RT-qPCR for Cyp3a11, Cyp2c37, Cyp2d22, and Oatp1b2 with expression levels normalized to beta actin using the $\Delta\Delta C_T$ method.

Results: Plasma urea and creatinine were significantly elevated ($p<0.05$, $p<0.01$ respectively), and creatinine clearance was significantly reduced ($p<0.01$) in adenine-fed mice compared to controls. No differences were found between the two groups for the four genes analyzed ($p>0.05$), however a trend was observed for increased Cyp2c37 expression in CKD mice compared to control mice (143.5% increase; $p=0.0967$).

Conclusions: CKD did not alter expression levels of Cyp3a11, Cyp2c37, Cyp2d22, and Oatp1b2 in C57BL/6 mice. Although not a statistically significant increase, Cyp2c37 expression remains of interest for future studies to better elucidate this change. Analysis of protein expression and functional activity remain to be determined to better understand the impact of CKD on drug metabolism and distribution in this mouse model.

SA-PO653

Comparative Effectiveness of Allopurinol, Febuxostat, and Benzbromarone on Renal Function in CKD Patients with Hyperuricemia: A 13 Year Cohort Study Ching-Wei Tsai,[1,2] Chin-Chi Kuo.[1,2] *[1]Internal Medicine and Big Data Center, China Medical University Hospital, Taichung, Taiwan; [2]China Medical University, Taichung, Taiwan.*

Background: Direct comparisons of the effectiveness of allopurinol with that of other urate-lowering agents in chronic kidney disease (CKD) populations, as well as guideline recommendations for clinical practice, are lacking.

Methods: We constructed a pharmacoepidemiology cohort study by using patients from Taiwan's long-term integrated CKD care program to compare the effectiveness among allopurinol, febuxostat, and benzbromarone in reducing the risk of progression to dialysis. A total of 874 patients with hyperuricemia who were newly treated with allopurinol, febuxostat, or benzbromarone were included. The primary and secondary outcomes were incident ESRD and the serum uric acid (SUA) changes from baseline, respectively. The results were analyzed using multiple Cox proportional models adjusted for multinomial propensity scores.

Results: Compared with allopurinol, benzbromarone therapy was associated with a reduced risk of progression to dialysis, the adjusted hazard ratio (aHR) was 0.50 (95% CI, 0.25–0.99). Patients who received allopurinol or febuxostat exhibited a comparable risk of end-stage renal disease [aHR, 0.99 (0.40–2.44)]. Febuxostat was significantly more potent than was allopurinol or benzbromarone in lowering SUA levels in the fully adjusted model. Among patients who reached the therapeutic target, those with febuxostat and benzbromarone initiation had a significantly lower risk of ESRD.

Conclusions: In conclusion, compared with conventional allopurinol, febuxostat and benzbromarone are more effective in reducing the risk of progression to dialysis and in lowering SUA levels in CKD populations.

Effect of serum uric acid and eGFR associated with allopurinol, febuxostat, and benzbromarone

Study drugs	N	Change from baseline (mg/dL)	Percentage change from baseline (%)
		Adjusted†	Adjusted†
		LSM (95% CI)	LSM (95% CI)
Serum uric acid			
Allopurinol	308	-1.49 (-1.82, -1.16)	-13.70 (-16.90, -10.60)
Febuxostat	133	-3.71 (-4.18, -3.23)	-36.70 (-41.30, -32.20)
Benzbromarone	366	-2.76 (-3.03, -2.49)	-26.90 (-29.50, -24.30)
eGFR			
Allopurinol	247	-4.68 (-6.44, -2.92)	-16.92 (-24.81, -9.03)
Febuxostat	95	-2.22 (-4.91, 0.47)	-10.64 (-22.70, 1.42)
Benzbromarone	313	-2.17 (-3.60, -0.74)	-10.73 (-17.14, -4.31)

†Adjusted for propensity score and time since the index date to the last SUA measurement

SA-PO654

Single Ascending Dose Study of Intraperitoneal Triferic® (Ferric Pyrophosphate Citrate) in Patients on Chronic Peritoneal Dialysis Raymond D. Pratt,[2] Sarah L. Grimberg,[1] Ajay Gupta.[2] *[1]Rockwell Medical, Inc., Mission Viejo, CA; [2]Rockwell Medical Inc, Wixom, MI.*

Background: The inconvenience of giving intravenous (IV) iron as an outpatient has limited its use in peritoneal dialysis patients (PD). Ferric pyrophosphate citrate (FPC) is a complex, water soluble iron salt approved to maintain iron balance and hemoglobin in patients receiving chronic hemodialysis. FPC donates iron to transferrin, bypassing the reticuloendothelial block to iron metabolism in patients with chronic kidney disease. We postulated that FPC could be administered in peritoneal dialysis fluid (PDF) to replace and/or maintain iron stores.

Methods: Thirty (30) PD patients were enrolled in an open-label, randomized, two-period, single ascending dose study of FPC administered in PDF in 5 cohorts. All patients received FPC in either Dianeal® (1.5% or 2.5% dextrose) 2 L or Extraneal® (Icodextrin 7.5%) 1.5 L for a 12 hour dwell. FPC was added to the PDF at iron concentrations of 2.5, 5.0 (2 cohorts), 7.5, or 12.5 mg Fe/L. At another session, 6.6 mg FPC was administered IV over 4 hours. A serum iron profile (sFe) was obtained at defined time points to characterize the PK of absorbed iron.

Results: Iron absorption from PDF was dose dependent with peak sFe values at approximately 6 hours. Clearance of PD administered iron followed the time course of IV FPC administration. Serum iron levels exhibited an initial rapid rise followed by a slower increase. Estimates of iron absorption ranged from 0.8 mg with the 2.5 mg Fe/L dose to 7.3 mg Fe with the 12.5 mg Fe/L dose. Triferic was generally well tolerated. Two patients (7%) experienced moderate abdominal discomfort and cramping upon infusion of the 12.5 and 7.5 mg dose. One subject in the 12.5 mg dose group withdrew due to the event the other event resolved. Transient nausea and vomiting were experienced by 2 patients (7%) upon infusion of PDF. No changes in PDF cell counts or differential were observed at any dose level.

Conclusions: Ferric pyrophosphate citrate (Triferic®) iron is bioavailable via peritoneal dialysis. The adverse effects were mild to moderate in severity and appeared to be dose dependent. Iron absorbed from PDF to the systemic circulation was rapidly cleared with a time course similar to IV FPC. FPC added to PDF may be an effective and simple iron replacement therapy for PD patients.

Funding: Commercial Support - Rockwell Medical Inc.

SA-PO655

Parathyroid Hormone Contributes to the Down-Regulation of Cytochrome P450 3A through the cAMP/PI3K/Akt Signaling Pathway in Secondary Hyperparathyroidism Hiroshi Watanabe,[1] Ryusei Sugimoto,[1] Masafumi Fukagawa,[2] Toru Maruyama.[1] *[1]Department of Biopharmaceutics, School of Pharmacy, Kumamoto University, Kumamoto, Japan; [2]Tokai University School of Medicine, Isehara, Japan.*

Background: Although it is reported that humoral factors, such as uremic toxins, may contribute to the change of extra-renal drug clearance observed in CKD, the details have not been clarified. We investigated the role of parathyroid hormone (PTH) in the change of extra-renal clearance.

Methods: Secondary hyperparathyroidism (SHPT) model rats were created by feeding a high phosphorus diet to the 5/6 renal nephrectomy rats. In vitro experiments were performed using rat primary hepatocyte and Caco-2 cells.

Results: In rats with SHPT, hepatic and intestinal expression of CYP3A was down-regulated. Pharmacokinetic study using midazolam, a probe of CYP3A metabolism, showed that area under the curve (AUC) after oral administration increased about 8 times in the SHPT group compared to the sham group. These changes were suppressed by the administration of cinacalcet, a calcimimetic PTH suppressor, suggesting PTH contributes to the down-regulation of CYP3A. Using rat primary hepatocytes and Caco-2 cells, PTH (1-34) treatment decreased the expression of CYP3A proteins. The data supported the results obtained from SHPT rats. In Caco-2 cells, PTH (1-34) down-regulated mRNA expression of CYP3A but inactive PTH derivative (13-34) did not, suggesting that the action of PTH (1-34) occurs via PTH receptor. In addition, 8-Br-cAMP significantly reduced mRNA expression of CYP3A. Inhibitors of PI3K, NF-κB, PKC and PKA reversed the PTH-induced CYP3A down-regulation.

Conclusions: PTH down-regulates hepatic and intestinal CYP3A expression through cAMP/PI3K/Akt pathways, following the elevation of intracellular cAMP via PTH receptor. Such effects of PTH can be prevented by a cinacalcet treatment.

SA-PO656

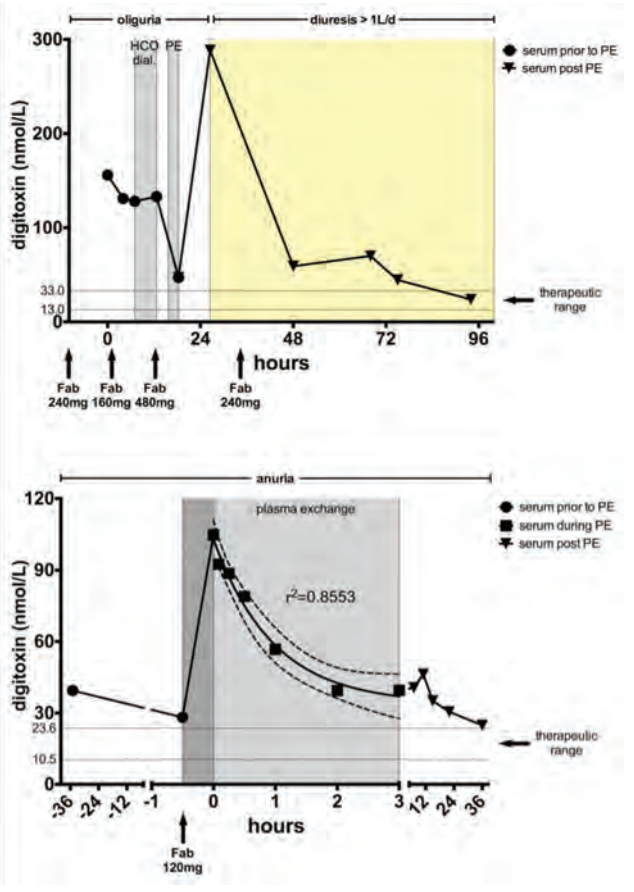
Time for a(n Ex)Change: Treatment of Acute Cardiac Glycoside Intoxication with Extracorporeal Fab-Glycoside Removal in the Setting of Oliguria or Anuria: Experience from Two Cases Treated with TPE Michael S. Balzer, Klaus Stahl, Susanne V. Fleig, Sascha David, Hermann G. Haller. *Hannover Medical School, Hannover, Germany.*

Background: Anti-cardiac glycoside-antibody-fragments (Fab) (46kDa) are the only approved treatment for severe digitoxin intoxication. Simplified binding of the Fab to the glycoside inhibits its therapeutic effects and facilitates its renal excretion. Therefore, sustaining effectiveness of this detoxification strategy requires a certain glomerular filtration rate. It becomes obvious that in acute kidney injury (AKI) or chronic kidney disease (CKD) scenarios this elimination efficacy might be negatively affected. Removal of the Fab-glycoside complex by conventional hemodialysis is not efficient.

Methods: We here report 1 case of a patient with oliguric AKI and 1 case of an anuric patient with CKD stage 5D, both with symptomatic digitoxin intoxication. Treatment with Fab was complemented by subsequent elimination of the Fab-glycoside complex using either therapeutic plasma exchange (TPE) alone or a combination of TPE and high cut-off (HCO) dialysis. Digitoxin serum levels prior to, during and after the different treatment regimens are presented in Figure 1 and include a kinetic time course during TPE for the anuric patient.

Results:

Conclusions: TPE appeared to be much more efficient in reducing digitoxin serum levels than HCO dialysis. This was most likely due to the high extent of plasma protein binding of digitoxin. As demonstrated by these 2 cases, we suggest to consider extracorporal Fab-glycoside removal to prevent rebound toxicity following Fab treatment in severe cardiac glycoside intoxication in oliguric or anuric patients. While it has still to be demonstrated that HCO dialysis is efficient in digoxin intoxication, TPE might be the preferred treatment modality in digitoxin intoxication.



SA-PO657

Mortality after Continuous Renal Replacement Therapy (CRRT) in Maintenance Hemodialysis Patients: A Scoring System of Short-Term Mortality Risk after CRRT Toma Hamada, Masahide Mizobuchi, Yasuto Shikida, Takanori Shibata. *Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan.*

Background: Critically ill patients, suffering from serious diseases such as acute heart failure, acute kidney injury, septic shock, and so on, often require continuous renal replacement therapy (CRRT). Little is known about the outcome of CRRT in maintenance hemodialysis (MHD) patients, and what clinical parameters are risk factors of short-term mortality after CRRT. The objective was to investigate whether MHD patients are at high risk of the short term mortality after CRRT and to determine a scoring system relating to the mortality.

Methods: In this study, 308 patients who required CRRT in our facility from April 2013 to March 2015 were retrospectively analyzed. We excluded patients who were indicated HD within 7 days before CRRT, transferred to other hospital, and lost to follow. Patients were stratified by two groups, MHD group and Non-MHD (control) group. Analyses were performed using JMP.

Results: Two hundred fifty eight patients are included in the study. Sixty five % of them were male, mean age was 71 years. Cumulative incidence of death for MHD group versus control group was 60.4 % versus 46.0 % at 30 days (p=0.09), respectively. Kaplan-Meier analysis revealed that MHD group (log-rank test: p=0.02), intubated patients (log-rank test: $p < 0.0001$) had significant lower cumulative survival rate at 30-days after CRRT. Logistic regression analysis revealed that MHD patients were likely to die within 30-days after CRRT but did not reach statistically significance (unadjusted odds ratio 1.79; 95 % CI 0.92 – 3.54). After adjustment for elderly (age over 65 years), catecholamine administration, intubation, and MHD, MHD was an independent risk factor for 30-days mortality after CRRT (adjusted odds ratio 2.75; 95 % CI 1.31 – 5.94; p = 0.0067). We formulated a scoring system. The scoring system, MEIC score, was derived as follows: (MHD×5) +(Elderly(Age>65 y)×3)+(Intubation×7) + (Catecholamine×5). The area under the ROC curve was 0.73 for the MEIC score.

Conclusions: These results suggested that MHD, intubation, elderly, catecholamine administration were independent risk factors of 30-days mortality after CRRT. The MEIC score could be a useful scoring system for the short-term mortality.

SA-PO658

Impact of Early Initiation of Continuous Renal Replacement Therapy in Critically Ill Patients with AKI Jihyun Yang,[1] Taeyeon Hwang,[1] Sung Yoon Lim,[1] Woori C. Cho,[1] Yoon kyung Choi,[1] Myung-gyu Kim,[2] Sang-Kyung Jo,[1] Won-Yong Cho.[1] *[1]Korea University Medical Center, Sungbuk-Gu, Seoul, Republic of Korea; [2]National Institutes of Health, North Bethesda, MD.*

Background: The overall incidence of acute kidney injury (AKI) in ICU patients range from 20% to 50% and AKI represents a significant risk factor for mortality ICU patients with AKI ≥ 50%. CRRT (Continuous renal replacement therapy) widely used in ICU because of slower solute clearance and removal of fluid (better hemodynamic tolerance). However the optimal timing for initiation of CRRT in critically ill patients with AKI remains controversial. The purpose of this study is to investigate the outcomes of patients who received CRRT without any of these indications (Non-classic) with patients with one or more of these indications (Classic).

Methods: This is a retrospective single center cohort study enrolling patients who underwent CRRT in Korea University Anam Hospital. CRRT is run by the specialized CRRT team composed of two specialized nephrologists, an Intensivist, and two CRRT specialized nurses. The primary clinical outcome variables were 90-day Mortality and Renal recovery. Renal recovery was defined by creatinine clearance (≥15 mL/minute) with no need of renal replacement therapy at 90 days.

Results: At 90 days after CRRT, the mortality rate in the Classic group was 79.4% and that in the Non-classic group was 57.1%. Delayed initiation of CRRT was independently associated with greater odds of 90 day mortality. The classic group had lower renal recovery than the non-classic group. Delayed initiation of CRRT was independently associated with greater odds of non renal recovery.

Conclusions: In conclusion, initiating CRRT in critically ill patients with AKI should not be delayed until fulfillment of classic indications.

SA-PO659

Females Receive Continuous Dialysis Modalities Less Often Than Their Male ICU Counterparts Neelja D. Kumar, Ladan Golestaneh. *Albert Einstein College of Medicine; Montefiore Medical Center, Bronx, NY.*

Background: Acute kidney injury (AKI) carries significant mortality with rates as high as 50-70% reported in the Intensive Care Unit (ICU). Standard clinical parameters for hemodialysis (HD) in AKI include azotemia, hyperkalemia, acidosis, and volume overload. Continuous renal replacement therapy (CRRT) is used in hemodynamically unstable patients or those with massive volume overload requiring prolonged ultrafiltration. Initiation of CRRT involves dedicated ICU nursing and is generally more expensive than HD. Race and initiation of dialysis has been evaluated though data remains conflicted. Gender also influences delivery of care as some studies suggest that males with AKI receive initiation of dialysis less often, while others suggest that women receive less aggressive critical care and dialysis. We hypothesize that certain non-clinical factors like race, socioeconomic status (SES), gender, or location affect the decision to pursue CRRT versus HD.

Methods: We used a clinical database "Clinical Looking Glass" (CLG) to retrospectively analyze 1,519 patients in the ICU between 2012-2015. AKI was defined as creatinine >3.0 mg /dL with pre-admission creatinine < 2.0 mg/dL. Endpoints included: CRRT, HD, Palliative Care or no intervention. Variables evaluated included age, gender, SES, race, vasopressor use, laboratory parameters before RRT initiation, and the type of ICU. We did bivariate analyses examining demographic and clinical variables with treatment assignment. We then built a logistic regression model to test our hypothesis.

Results: A total of 370 subjects (24.4%) received CRRT, 307(20.2%) received HD, 264(17.4%) received palliative care and 578(38%) received no intervention. In the cohort, 46.7% were female, 32.8% were black and 18.3% were white; with a mean age of 63.3 years. Our logistic regression model included 408 subjects and showed a significant association between gender and type of RRT received, with females having a significantly lower odds of receiving CRRT(odds ratio: 0.58, CI(0.37-0.89), as compared to HD, after adjusting for other variables. Other variables significantly associated with use of CRRT were vasopressor use, lower pH, lower creatinine, type of ICU, and hospital location.

Conclusions: Female patients were less likely to receive CRRT than males. Other factors including race and SES did not significantly affect the decision to start CRRT versus HD.

SA-PO660

Thrombocytopenia among Critically Ill Patients Receiving CRRT in the Medical ICU: Is it AKI or CRRT? Ghassan Bandak,[1] Ankit Sakhuja,[1] Kianoush Banaei-Kashani.[1,2] *[1]Pulmonary and Critical Care, Mayo Clinic, Rochester, MN; [2]Nephrology and Hypertension, Mayo Clinic, Rochester, MN.*

Background: Thrombocytopenia has been reported as a side effect of hemodialysis in ESRD patients. It has also been reported in critically ill patients receiving CRRT. CRRT is commonly used in patients requiring RRT who are hemodynamically unstable in the ICU for both patients with AKI and ESRD. However, these populations are different in multiple aspects. There are various patient and treatment-related factors that are proposed to be contributing to thrombocytopenia. Furthermore, thrombocytopenia has been linked to increased mortality among patients receiving CRRT. We hypothesized that the rates of thrombocytopenia will be higher among patients with AKI in comparison with ESRD patients given their severe inflammatory state, new exposure to extracorporeal membranes and uremic milieu.

Methods: We performed a retrospective analysis of all patients receiving CRRT in our institution between Jan 1, 2007, to Oct 31, 2015. Data was electronically abstracted from the electronic medical chart. We included patients in medical ICUs and excluded patients in surgical and cardiovascular ICUs. We identified ESRD patients using ICD 9 and 10 codes. New thrombocytopenia was defined as a 50% drop in platelets count after CRRT initiation. We performed a chi-square test to compare rates of decline in platelets among ESRD and AKI patients. A P-value of 0.05 was considered to be statistically significant. Data analysis was done using STATA 14.0. We provide a standard CVVH prescription with regional citrate anticoagulation for all patients in our ICUs

Results: We identified a total of 673 unique patients who received CRRT in medical ICUs. A total of 94 patients (13.9%) had a diagnosis of ESRD. 54.4% were males. Median (IQR) age was 60 years (51-68). The rate of new thrombocytopenia after CRRT initiation was 55.4%. Median platelet count prior to CRRT was 107 and median lowest platelet count after CRRT initiation was 45. The incidence of drop of platelets amongst patients with ESRD was 53.8% vs. 55.6% amongst those without ESRD (P=0.7)

Conclusions: Both ESRD patients and AKI patients requiring CRRT are at significant risk of developing thrombocytopenia. The risk is not different between the two patient populations and is possibly influenced by CRRT treatment-related factors in the setting of critical illness.

SA-PO661

Propofol Induced CRRT Failure Mohammad Y. Alsawah, David B. Butcher, Lamia Aljundi, Rachel E. Wilson. *Nephrology, St John Hospital and Medical Center, Detroit, MI.*

Background: Severe hypertriglyceridemia (TG level >1000 mg/dL) is a known complication of prolonged (>48 hours) propofol infusion Serial monitoring of serum triglycerides (TG) level is recommended in these cases. Continuous renal replacement therapy (CRRT) is the hemodialysis modality of choice in hemodynamically unstable patients. The CRRT machine cartridge can clot during the dialysis procedure. Anticoagulation with citrate or heparin can decrease clotting. There are a few case reports describing CRRT cartridge clotting in association with hypertriglyceridemia in patients treated with TPN. We describe a case of severe hypertriglyceridemia associated with propofol infusion resulting in clotting of the CRRT cartridge.

Methods: .**Case report** A 42 year old African American male with newly diagnosed stage 4 Hodgkin's lymphoma was admitted to the intensive care unit with septic shock and respiratory failure that developed after receiving the first cycle of chemotherapy. Sedation was provided with propofol infusion at a rate of 5 mcg/kg/min. He developed acute renal failure and was started on continuous renal replacement therapy (CRRT). Local circuit anticoagulation was not used due to severe thrombocytopenia and liver disease. CRRT was interrupted 48 hours after initiation due to cartridge failure. This was associated with a yellow discoloration of the blood in the dialyzer tubing. The serum triglyceride (TG) level was elevated at 1,552 mg/dL (reference range 30-149 mg/dL). Propofol was discontinued and follow up serum TG decreased to less than 500 mg/dL. CRRT was successfully restarted within 48 hours of stopping propofol infusion

Results:

Conclusions: Critically ill patients receiving propofol sedation are at risk of developing hypertriglyceridemia. Elevated triglyceride (TG) levels can promote a procoagulant state, potentially inducing cartridge clotting. CRRT cartridge failure due to hypertriglyceridemia was previously described in association with TPN infusion. Our case illustrates the important of frequent monitoring of triglyceride levels with prolonged propofol use.

SA-PO662

A Mystery Case of Blood Leak Alarm Triggering Rhyan Maditz. *Beaumont Health - Royal Oak, Royal Oak, MI.*

Background: The mandatory blood leak detector (BLD) in a hemodialysis machine protects patients from harm by automatically shutting down the instrument if a leak is detected. Mechanical issues such as air bubbles or grease depositis may falsely activate the BLD alarm. Hemolysis has also been shown to activate the BLD. Hydroxocobalmin is known to interfere with the blood leak detector, causing a false alarm, which leads to the inability to perform dialysis.

Methods: A 68-year-old male with end stage renal disease on intermittent hemodialysis was admitted to the hospital after presenting with weakness and fatigue. He was previously scheduled to have outpatient coronary artery bypass grafting due to severe coronary artery disease. Patient was found to have aortic valve infective endocarditis and underwent urgent aortic valve replacement along with coronary artery bypass grafting. His postoperative course was complicated by hypotension, resulting in acute kidney injury requiring hemodialysis. He initially received intermittent hemodialysis with a 2008K Fresenius dialyzer instruments with adequate tolerance. On post-operative day 10, BLD interrupted dialysis as the dialysate effluent became read in color. Work up for hemolysis returned negative. Hemoglobin remained stable. Hemodialysis was attempted twice again using different 2008K Fresenius dialyzer instruments and the BLD alarm interrupted dialysis on each occasion. We bypassed the BLD alarms by testing the dialysate fluid for leaks every 15 minutes and by continuously resetting the alarm. Review of administered medications revealed that the patient received 5 mg of hydroxocobalmin (Vitamin B12A) intravenously on the day preceding the first blood leak alarm for vasoplegia syndrome. Rifampin was included in the patient's antibiotic regimen for infective endocarditis and is known to cause reddish discoloration of bodily fluids. Rifampin was discontinued but did not resolve the issue. The BLD no longer alarmed two days following discontinuation of hydroxocobalmin. Rifampin was restarted without any additional blood leak alarms.

Results:

Conclusions: This case highlights the importance of recognizing other etiologies of BLD alarms, especially when mechanical issues and hemolysis have been ruled out. It is important to recognize hydroxocobalmin as a cause for BLD false alarms. Fleishman issued a black box warning several months after our case.

SA-PO663

Efficacy and Safety of a Citrate Anticoagulation Protocol for Slow Extended Dialysis in AKI Cancer Patients Using Path Batch Hemodialysis: A Case Control Study Antonio A. Portela Neto,[3] Renato A. Caires,[2] Marcella M. Frediani,[3] Elerson Costalonga,[2] Fernanda O. Coelho,[3] Emmanuel A. Burdmann,[3] Etienne Macedo,[1] Veronica T. Costa e Silva.[3] *[1]UCSD, San Diego, CA; [2]University State of São Paulo, São Paulo, Brazil; [3]University of Sao Paulo Medical School, Sao Paulo, Brazil.*

Background: Few reports have addressed citrate anticoagulation (CA) for hybrid dialysis therapies using Path Batch Hemodialysis (PBH).

Methods: Slow extended dialysis (SLED) procedures with a PBH system in adult critically ill AKI cancer patients in the Sao Paulo State Cancer Institute, from January 7 to April 7, 2015, were prospectively followed. Procedures performed with regional CA (4% sodium citrate and dialysate containing calcium at 5 mg/dL) were compared with those using continuous normal saline (NS) as anticoagulation.

Results: Twenty four CA and 27 NS sessions were performed in 11 patients. Baseline patient characteristics were similar, whereas duration, ultrafiltration (UF) and flow prescription were different within CA and NS groups (Table). At the end of CA-SLED, median citrate flow was 310 (280 320) mL/h and systemic ionized calcium (SCai) was 4.20 (3.92 – 4.47) mg/dL. During the SLED procedure, hypocalcemia (SCai < 3.6 mg/dL) and metabolic alkalosis (serum bicarbonate > 30 mEq/L) rates were 8.0% and 4%, respectively (N=96). Interruption of PBH by clotting was recorded in only three (12.5%) of CA-SLED sessions and in six (22.2%) of NS procedures (P=0.363). Filter[V-W1] life was 8.0 (6.0 – 8.0) and 4.0 (2.75 – 5.00)h in the CA and NS groups (P<0.0001), respectively. Hypotension rate (mean blood pressure <70 mmHg) was similar in both groups (12.5% in CA-SLED vs 14.8% in NS group, P=0.811). No major bleeding, arrhythmia or relevant clinical events were observed in neither groups. PBH provided a satisfactory metabolic control in both groups (data not shown)

Conclusions: A CA protocol can be safely and efficiently used in PBH SLED in critically ill cancer patients with AKI. Larger sample size studies including control pcts are needed to establish the benefit of citrate based anticoagulation for PBH SLED procedures.

Characteristics of PBH procedures

	CA-SLED (N=11)	NS (N=11)	P
Blood/Dialysate flow (ml/min)	180 (180 – 195)	250 (200 - 250)	< 0.001
Prescribed dialysis duration (DD)(hrs)	8.0 (6.5 – 8.0)	4.0 (4.0 – 5.0)	< 0.001
Prescribed UF (L)	2.0 (1.5 – 2.5)	1.0 (0 – 1.5)	0.001
Prescribed/Achieved UF (%)	94.3 ± 12.3	85.8 ± 26.2	0.461
Prescribed/Achieved DD (%)	94.7 ± 11.7	89.5 ± 15.9	0.321

SA-PO664

Concurrent Hemoperfusion and Hemodialysis in Patients with Acute Pesticide Intoxication Hyo-Wook Gil. *Soonchunhyang university Cheonan Hospital, Cheonan, ChungcheongNam-do, Republic of Korea.*

Background: Water soluble and insoluble chemicals in the pesticide formulation may be eliminated more effectively in time if hemodialysis (HD) and hemoperfusion (HP) are performed concurrently. This study is aimed at evaluating the efficacy of concurrent HP and HD in patients with acute pesticide intoxication.

Methods: Between January 2011 and December 2012, we used HP and HD consecutively (HP-HD group, 347 cases), and then during the next 2 years (January 2013 to December 2014), we used concurrent HP and HD (HPD group, 383 cases). We compared the clinical outcomes between the 2 groups. For HP, we used an Absroba 300C HP membrane and for HD, we used a Polyflux 170H HD dialyzer (Baxter).

Results: The mortality was higher in the HP-HD group than in the HPD group: (48.1 vs. 20.9%) for the overall mortality and (81.8 vs. 57.9%) for the paraquat (bipyridylium) mortality ($p < 0.001$). In multiple logistic analyses, age ($p = 0.013$), ingested volume ($p < 0.001$), and HP-HD ($p = 0.014$) were significant risk factors for mortality in the paraquat ingested group.

Conclusions: Concurrent HP and HD would be an effective and safe treatment for patients with acute pesticide intoxication, in particular, paraquat intoxication.

Funding: Government Support - Non-U.S.

SA-PO665

Single-Pass Albumin Dialysis with Continuous Renal Replacement Therapy in Patients with Liver Failure Vimal Chadha,[2] Darcy K. Weidemann,[2] Nathan T. Beins,[4] Uttam Garg,[3] Rebecca M. Greene,[1] Brooke English,[1] Marita Thompson.[5] *[1]Children's Mercy Hospital, Kansas City, MO; [2]Children's Mercy Hospital, Kansas City, MO; [3]Children's Mercy Hospitals and Clinics, Knasas City, MO; [4]None, Kansas City, MO; [5]University of Missouri Kansas City, Children's Mercy Hospital, Kansas City, MO.*

Background: Multiple organ dysfunction syndrome is not uncommon in critically ill children. While many of these children receive CRRT for management of AKI, there is no standard approach available for managing liver failure in which several metabolites that are highly protein bound accumulate, and thus are not cleared with conventional CRRT. Molecular Adsorbent Recycling System (MARS) has been successfully used in these situations, but is unavailable in most centers. Modification of CRRT with Single-Pass Albumin Dialysis (SPAD) has been reported previously.

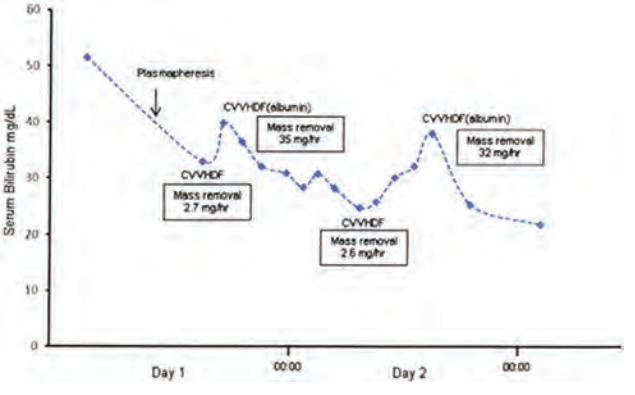
Methods: We report our experience in four children who were treated with SPAD-CRRT. All patients received CRRT (CVVHDF) with a clearance of 2 L/hr/1.73m2. For SPAD, 400 mL of 25% albumin was added to the 5 L dialysate (PrismaSol®) bag to give final albumin concentration of 1.85%. Serum bilirubin was used as a surrogate marker of efficacy of SPAD. Serum and dialysate bilirubin concentrations were monitored to calculate the mass bilirubin removal.

Results: The findings are briefly summarized in the Table.

Conclusions: Our experience shows >10-fold increase in bilirubin clearance with SPAD-CRRT. While SPAD-CRRT is effective in decreasing serum bilirubin and other toxins, its impact on removal of nutrients and medications is currently unknown, Further studies are needed to see if SPAD-CRRT can improve patient outcomes.

Case	Age (yrs)	Sex	Diagnosis	Max. Bilirubin (mg/dL)	SPAD duration (hrs)	% reduction in bilirubin with SPAD	Outcome
1	0.6	M	Hemophagocytic histiolymphocytosis with liver failure.	52	35	56%	Expired
2	7	M	Cystic fibrosis, sepsis, acute on chronic liver failure.	33	96	42%	Recovered, expired 3 weeks later
3	5	M	Fulminant acute liver failure.	24	26	21%	Received liver transplant
4	3	M	Neuroblastoma, post-HCT, VOD, and liver failure.	32	240	73%	Recovered, expired 1.5 yrs later

While severe hyperbilirubinemia was the main reason for using SPAD in patients 1, 2, and 4, it was used as a bridge to liver transplant in patient #3.



SA-PO666

24-Hour Urine Volume May Be a Practical and Convenient Method of Monitoring Change in Native Kidney Function in Patients on In-Center HD Kevin D. Marquez,[2] Andrew I. Chin.[1,3] *[1]University of California Davis, Sacramento, CA; [2]University of California Davis Medical Center, Sacramento, CA; [3]Internal Medicine, VA Health Care Northern California, Mather Field, CA.*

Background: Nephrologists are caring for more in-center HD patients with Acute Kidney Injury on Dialysis (AKI-D). Identifying renal recovery is important. In non-HD patients, change in serum creatinine is commonly used to determine change in renal function. In HD patients, the best indictor of a change in renal function is not known. We examined incident HD patients to determine which factors best correlated to the longitudinal change in residual kidney urea clearance (Kru).

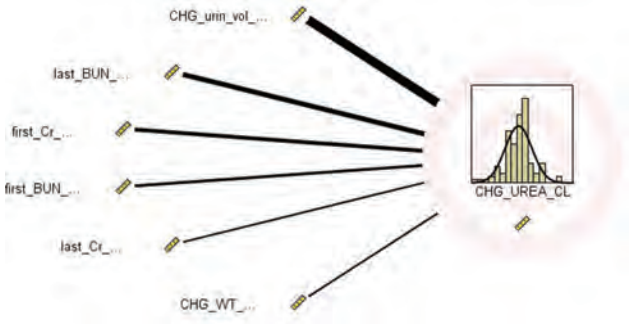
Methods: Retrospective study of incident HD patients with 2 timed, 24-hour urine collections within a 6 month period. Demographic, laboratory, dialysis parameters, and urine data were analyzed to determine the best model to predict change of Kru.

Results: 106 incident HD patients were included, mean age of 57 ± 17 years, 35% female and 40% diabetic. Mean time between paired 24 hour urine collections was 106 ± 34 days. Kru increased in 36% of the patients between urine collections. We modeled the change in Kru using: demographic data; post-HD body weight and fluid gain; change in body weight and fluid gain between the 2 urine collections; pre-dialysis BUN, creatinine and albumin; change in these blood tests between the 2 urine collections. The change in 24

hour urine volume was heavily weighted in best predicting the change in Kru (Figure 1). Increase or decrease of pre-dialysis serum creatinine poorly predicted the change in Kru.

Conclusions: While other factors were included in the model, change in 24 hour urine volume was most important in the correlation with kidney function urea clearance change in patients undergoing in-center HD. Pre-dialysis serum creatinine poorly correlated with change in Kru. Extrapolating these findings to AKI-D patients, formal urine collection and clearance calculation is the best method of gauging renal recovery, but serial measure of timed urine volume may be a convenient and appropriate way for weekly, frequent monitoring.

Funding: Clinical Revenue Support



Urine volume contributes most to predicting change in kidney urea clearance.

SA-PO667

Calculation of Weekly Standard Kt/V by Urea Mass Removed During Hemodialysis Results in a Simple Equation J. Ken Leypoldt, Edward F. Vonesh. *San Clemente, CA.*

Background: Accurate calculation of weekly urea standard Kt/V (stdKt/V) during hemodialysis (HD) requires first calculating sequentially single-pool and equilibrated Kt/V (Daugirdas et al, Kidney Int 2010), but this approach can be intimidating to clinicians. We explored whether an alternative approach to calculating stdKt/V based on urea mass removed would lead to a simple equation with approximately equivalent accuracy for both conventional and more frequent HD.

Methods: Theoretical consideration of urea mass balance during HD treatments derived the following equation for stdKt/V, namely stdKt/V = N * (URR + UFV/V)/(1 - N * t / 10080) where N is number of treatments per week, URR is urea reduction ratio per treatment, UFV is ultrafiltration volume per treatment, V is post-dialysis urea distribution volume and t is treatment time in minutes. The URR requires correction for post-dialysis rebound (Tattersall et al, Kidney Int 1996). The numerator of this equation represents the fractional urea mass removed from V, and the denominator corrects for intradialytic urea generation. We compared the accuracy of this novel equation for calculating stdKt/V with the conventional approach (Daugirdas et al, Kidney Int 2010) by simulations using a two-compartment model of urea kinetics. Model simulations were performed for patients with V of 20-50 L, weekly UFV of 0-14 L, treatment times of 2-8 hours, 5 different dialyzer urea clearances; this generated 350 different treatment conditions for HD performed 3, 4, 5 and 6 times per week.

Results: Results are tabulated as the absolute value of differences between approximation equations and the numerically simulated stdKt/V.

Conclusions: The urea mass removed and Daugirdas et al equations compute values of stdKt/V that are clinically equivalent. This work provides a novel, simple equation for calculating stdKt/V during HD and strengthens the theoretical understanding of stdKt/V.

Treatments per week	Statistic	Daugirdas et al equations	Urea mass removed equation
3	Mean ± SD	0.019 ± 0.016	0.014 ± 0.017
	Median (IQR)	0.017 (0.009-0.023)	0.008 (0.003-0.018)
4	Mean ± SD	0.024 ± 0.022	0.072 ± 0.029
	Median (IQR)	0.020 (0.011-0.030)	0.069 (0.051-0.090)
5	Mean ± SD	0.080 ± 0.049	0.076 ± 0.082
	Median (IQR)	0.075 (0.047-0.105)	0.041 (0.015-0.110)
6	Mean ± SD	0.086 ± 0.054	0.022 ± 0.028
	Median (IQR)	0.080 (0.049-0.113)	0.014 (0.008-0.022)

SD = standard deviation; IQR = interquartile range

SA-PO668

Volume of Urea Cleared as a Therapy Dosing Guide for More Frequent Hemodialysis J. Ken Leypoldt,[2] Allan J. Collins.[1] [1]*Chronic Disease Research Group, Minneapolis, MN;* [2]*None, San Clemente, CA.*

Background: Prescribing more frequent hemodialysis (HD) based on conventional thrice weekly HD therapy normalized to a weekly dose is challenging. Urea kinetic modeling based on the normalized urea distribution volume (V) has been shown to be suboptimal for smaller and female patients. Alternatively, prescribing the volume of urea cleared (Kt) to patient body surface area (BSA) has recently been shown to be promising (Maduell et al, Kidney Int 2016; Sridharan et al, Am J Kidney Dis 2017). Prescribing more frequent HD (5 or 6 times-per-week) to BSA has not been adequately explored.

Methods: We compared modeled Kt to the nearest L required to achieve a minimal dose of therapy based on BSA as defined by Lowrie et al (Kidney Int 2005) with that recommended by KDOQI Clinical Practice Guideline for Hemodialysis Adequacy Update based on patient V, i.e. weekly stdKt/V=2.1 (NKF, Am J Kidney Dis 2015). Estimates of Kt were calculated for conventional, thrice weekly HD (treatment time=240 min) and 5 and 6 times-per-week HD (treatment times=180 min). Results were compared for patients with different anthropometric estimates of total body water (Vw). BSA was assumed proportional to V to the power of 0.7, and residual kidney function was assumed negligible.

Results: Modeled Kt (L) for the therapies are tabulated. As during conventional thrice weekly HD, minimal Kt for more frequent HD based on BSA is higher for patients with small Vw and lower for patients with large Vw than based on weekly stdKt/V=2.1. Simple Kt prescriptions for 5 times-a-week HD based on the principles from Lowrie et al in L are equal to 20+0.4×(Vw-35). For 6 times-a-week HD, Kt prescriptions in L are equal to 16+0.3×(Vw-35). Such prescriptions require careful consideration of dialyzer type, blood flow rate, and dialysate flow rate (or total dialysate volume).

Conclusions: Prescribing more frequent HD based on BSA as extrapolated from Lowrie et al suggests the minimal dose of Kt is higher for small patients and lower for large patients than based on a weekly stdKt/V=2.1. Other aspects of dialysis adequacy require additional consideration.

Funding: Commercial Support - NxStage Medical

Modeled Kt (L) versus Patient Vw (L)

	3 Times-per-week HD		5 Times-per-week HD		6 Times-per-week HD	
Patient Vw (L)	Lowrie et al	KDOQI	Lowrie et al	KDOQI	Lowrie et al	KDOQI
25	38	34	16	14	13	11
35	45	47	20	20	16	16
45	51	61	24	26	19	20
55	55	74	27	31	21	25

SA-PO669

The Cost of Dialysis in Canada: A Contemporary Cost Minimization Analysis Thomas W. Ferguson,[2] Sandi M. Dumanski,[1] Alain Beaudry,[3] Navdeep Tangri,[1] Claudio Rigatto,[1] Paul Komenda.[3] [1]*Winnipeg, MB, Canada;* [2]*Seven Oaks General Hospital, Winnipeg, MB, Canada;* [3]*University of Manitoba, Winnipeg, MB, Canada.*

Background: Over 5,000 patients experience renal failure in Canada every year. Most of these patients will be unable to secure a transplant and will require life-saving hemodialysis or peritoneal dialysis. These therapies are expensive and require a substantial investment from the Canadian public health care system, with over 1.8 billion dollars spent annually. In this study, we aimed to describe the costs of dialysis modalities, including facility hemodialysis, home peritoneal dialysis (PD), and home hemodialysis (HHD) (both for conventional home hemodialysis and with the NxStage System One).

Methods: We determined costs from the perspective of the Canadian public health payer; namely, human resource expenses, medical and surgical supplies, dialysis-related drugs, equipment, utilities, and capital costs. Cost estimates were sourced from hospital statements of operations, product suppliers, established utility rates, and activity-based dialysis workload estimates. Human resource time estimates are based on a review of literature, yielding mean direct and indirect resource consumption.

Results: The model outputs provide accurate estimates of expenditures for dialysis delivery over time. From this, we can generates clear thresholds for life expectancy, below and above which the most cost-effective dialysis modality may be identified. Annual maintenance expense totaled $64,214 for facility dialysis, $38,658 for PD, $39,236 for HHD, and $43,817 for HHD using the NxStage System One. Substantial cost drivers were human resources in facility dialysis (68% of total cost including benefits) compared with 12% for PD and 16 – 18% for home hemodialysis. Medical and surgical supplies accounted for 72% of PD costs compared with 13% for facility dialysis and 40 – 45% for home hemodialysis.

Conclusions: Beyond a model-defined threshold of treatment duration, home-based renal replacement therapy is less expensive than facility-based hemodialysis. When treatment and quality of life outcomes are similar between both treatments, these therapies should be recommended in patients who are capable of self-care. Ease of administering home modality should also be considered in its relation to patient uptake rates. Assisted home dialysis programs should be evaluated in more complex cases.

Funding: Commercial Support - NxStage Medical Inc.

SA-PO670

Technique Failure in a Multicenter Canadian Home Hemodialysis Cohort Robert P. Pauly,[1] Iram Usman,[1] Rhonda J. Rosychuk,[1] Frances D. Reintjes,[2] Maliha Muneer,[2] Christopher T. Chan,[3] Michael A. Copland,[4] Robert M. Lindsay,[5] Jennifer M. MacRae,[6] Gihad E. Nesrallah,[7] Andreas Pierratos,[8] Deborah Lynn Zimmerman,[9] Paul Komenda.[10] *[1]University of Alberta, Edmonton, AB, Canada; [2]Alberta Health Services, Edmonton, AB, Canada; [3]Toronto General Hospital, Toronto, ON, Canada; [4]University of British Columbia, Vancouver, BC, Canada; [5]London Health Sciences Centre, London, ON, Canada; [6]University of Calgary, Calgary, AB, Canada; [7]The University of Western Ontario, Toronto, ON, Canada; [8]University of Toronto, Toronto, ON, Canada; [9]University of Ottawa, Ottawa, ON, Canada; [10]University of Manitoba, Winnipeg, MB, Canada.*

Background: Increasing uptake of home hemodialysis (HD) has led to interest in characteristics that predict modality failure. Recent reports of practice pattern variability led us to hypothesize there are patient- and center-specific factors that influence outcomes in home HD.

Methods: We assembled a retrospective cohort of incident home HD patients from 7 centers in Canada from 2000 to 2010 to evaluate case-mix and process of care characteristics on technique failure and mortality. Care characteristics included intervals of follow up/blood work/vascular access monitoring, nursing and physician models of care, patient-to-nurse ratio, and presence/absence of routine home visits and technique audits among others.

Results: The cohort consisted of 579 patients. Mean age was 49.9±14.1 years, 74% were Caucasian, with a median dialysis vintage of 1.9 years (IQR 0.6, 5.2); 68% used an AVF or AVG. Mean duration of dialysis 31.2±12.6 hrs/wk. Unadjusted 1 and 2 year technique survival (censored for death and transplantation) and overall survival was 90% and 83%, and 94% and 86%, respectively. Treating center was a strong predictor of adverse outcomes (Table). With baseline adjustment for center effect, few patient-specific variables remained significant predictors of either study outcome; we did not identify significant program-specific characteristics of care processes to explain the center effect.

Conclusions: The home HD treating center has a significant impact on technique failure and patient mortality. We did not identify specific components of programmatic care to explain this observation. The relationship between process of care and patient outcomes is critical and requires further investigation.

Funding: Private Foundation Support

Technique Failure			
Center	**HR**	**95% CI**	**p-value**
1	1.00	Reference	-
2	1.48	0.40-5.53	0.56
3	3.57	1.15-11.08	0.03
4	2.69	0.95-7.63	0.06
5	4.34	1.49-12.67	0.007
6	13.73	4.75-39.74	<0.001
7	3.68	1.25-10.89	0.02
Mortality			
1	1.00	Reference	-
2	0.62	0.23-1.67	0.35
3	0.11	0.01-0.82	0.03
4	0.61	0.30-1.24	0.17
5	1.41	0.69-2.90	0.35
6	5.31	2.59-10.91	<0.001
7	1.43	0.70-2.92	0.33

Technique Failure and Mortality According to Treatment Center

SA-PO671

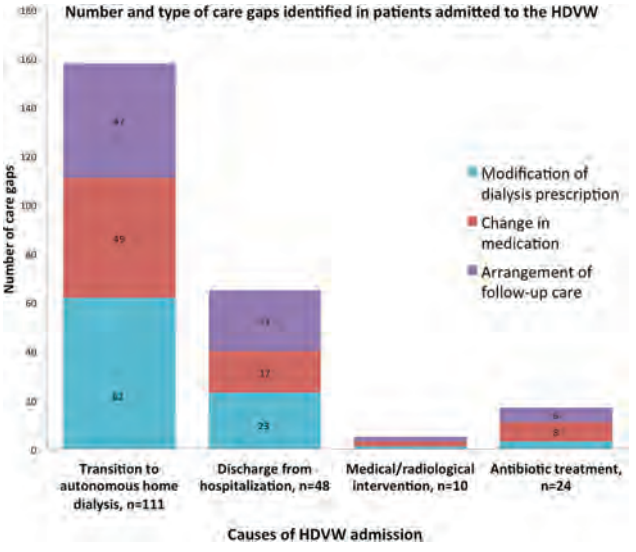
Predictors of Care Gaps in the Home Dialysis Virtual Ward Annie-Claire Nadeau-Fredette,[3] Karthik K. Tennankore,[7] Joanne M. Bargman,[9] Michael A. Copland,[6] Deborah Lynn Zimmerman,[2] Matthew J. Oliver,[5] Nikhil A. Shah,[4] Simon N. Finkle,[1] Robert P. Pauly,[4] Jeffrey Perl,[8] Christopher T. Chan.[9] *[1]Dalhousie University, Hammonds Plains, NS, Canada; [2]The Ottawa Hospital, Ottawa, ON, Canada; [3]Hopital Maisonneuve-Rosemont, Montreal, QC, Canada; [4]University of Alberta, Edmonton, AB, Canada; [5]Sunnybrook Health Sciences Center, Toronto, ON, Canada; [6]University of British Columbia, Vancouver, BC, Canada; [7]Dalhousie/Nova Scotia Health, Halifax, NS, Canada; [8]St. Michael's Hospital, Toronto, ON, Canada; [9]Toronto General Hospital, Toronto, ON, Canada.*

Background: Despite the benefits of home dialysis, home dialysis patients are prone to medical complications, especially at time of a transition/change in care. The home dialysis virtual ward (HDVW) initiative aimed to describe gaps in care following these transition periods.

Methods: The HDVW is a multicenter Canadian study conducted between January 2014 and December 2015. Patients admitted to the HDVW experienced a transition event defined as one of: (1) transition from peritoneal dialysis (PD) or home hemodialysis (HHD) training to autonomous home dialysis (2) a discharge from hospitalization, (3) receipt of a medical/radiological procedure and (4) treatment with antibiotics. HDVW admission consisted of a maximum of 14 days of follow-up using repeated clinician-led telephone interviews. Gaps of care were identified when a change of management was required in any of these 3 domains: dialysis prescription, medication and follow-up care. Predictors of the care gaps were assessed in an adjusted ordinal logistic regression.

Results: Ninety HHD and 103 PD patients were included. Overall, 245 care gaps were identified in 135 patients. (Figure 1) Higher age > 65 years (odds ratio [OR] 2.92, 95% confidence interval [CI] 1.15-7.42, p=0.02) and female (OR 1.73, 95% CI 1.18-2.52, p=0.005) were associated with an increased risk in care gaps while medical procedure as a cause for HDVW admission (OR 0.22, 95% CI 0.09-0.54, p=0.001) or antibiotic-treatment (OR 0.35, 95% CI 0.14-0.87, p=0.03) had lower risk of care gaps compared to post hospital discharge HDVW admissions.

Conclusions: Gaps in care are frequent in the home dialysis population particularly following hospital discharge. Efforts should be directed toward improvement of transitional care especially among older individuals.



SA-PO672

A Single Center Cross-Sectional Study of Health Literacy Levels in Pre-Dialysis, Home Dialysis, and In-Center Hemodialysis Patients Fabrice Mac-Way,[3] Yannick Bégin,[4] Mathieu Rousseau-Gagnon,[2] Mohsen Agharazii.[1] *[1]CHUQ-HDQ, Quebec City, AB, Canada; [2]CHUQ-Hôtel-Dieu-de-Québec, Lac-Beauport, QC, Canada; [3]None, Quebec, QC, Canada; [4]Université Laval, Québec, QC, Canada.*

Background: Health literacy is the ability to obtain, understand and use healthcare information to make appropriate health decisions. Recent studies have suggested that chronic kidney disease (CKD) patients may have low levels of health literacy. We aimed to evaluate and compare the health literacy levels in pre-dialysis and dialysis patients.

Methods: This is a cross-sectional single-center study conducted at CHU de Québec-Laval University. Adult patients attending pre-dialysis clinic, and ongoing home hemodialysis, peritoneal dialysis and in-center HD completed a French Canadian version of the Health Literacy Questionnaire (HLQ), a validated questionnaire. Cronbach's Alpha analysis was used. The HLQ measures nine specific domains of health literacy: feeling understood and supported (D1), having sufficient information (D2), actively managing health (D3), social support (D4), appraising information (D5), engaging with health providers (D6), navigating the health care system (D7), finding good information (D8) and understanding information (D9). Each domain is composed of 4 to 6 questions.

Results: A total of 353 patients (152 pre-dialysis, 157 in-center hemodialysis, 38 peritoneal dialysis (PD) and 16 home hemodialsysis (HHD)) completed the HLQ. There was a high level of agreement within each domain's questions with a Cronbach's Alpha of at least 0.75. Patients on HHD and PD were more likely to feel understood and supported (D1 p<0.001). HHD patients were more likely to understand and appraise health information (D5 and D9 p<0.001). There was a nonsignificant tendency for them to feel like they had sufficient information (D2 p=0.06), that they could actively manage their health (D3 p=0.07) and that they had a good social support (D4 p=0.09). However, we did not find any difference between the CKD groups regarding the ability to actively engage with healthcare providers (D6), to navigate through the healthcare system (D7) or to find good health information (D8).

Conclusions: This study reports for the first time detailed health literacy levels in pre-dialysis, home dialysis and in-center hemodialysis patients. Our findings will be useful in implementing strategies that take into account these nine domains of health literacy in order to improve CKD patient outcomes and quality of life.

SA-PO673

Nephrologist/Patient Conversations About Renal Replacement Meg Wise,[3] Dorian R. Schatell,[1] Betty Chewning,[2] Micah R. Chan.[3] *[1]Medical Education Institute, Madison, WI; [2]University of Wisconsin, Madison, WI; [3]University of Wisconsin-Madison, Madison, WI.*

Background: Patient-centered, valued-based decision-making is the gold standard for choosing complex medical treatments.

Methods: We conducted a mixed-method conversation study to understand how nephrologists and patients communicate about renal replacement therapy (RRT), with 8 nephrologists from 3 clinics and 61 of their patients with eGFR ≤25. Analysis of verbatim transcripts of audio-recorded clinic visits assessed word ratios and discussion of RRT options. Surveys collected demographics and RRT preferences.

Results: Nephrologists established rapport with patients and worked to delay dialysis. RRT was the most uncomfortable part of the conversation for both nephrologists and patients: clinicians spoke ~3.25 times more in the whole visit, but ~8 times more about RRT, suggesting that patients shut down. In-center hemodialysis (HD), peritoneal dialysis (PD), and transplant (despite non-eligibility) were most often discussed; home HD was hardly discussed. Nephrologists' used scripted didactic (teaching) versus dialogic (two-way) communication about RRT, perhaps overwhelming patients. Nephrologists may have inadvertently discouraged PD by emphasizing a need for a care partner (vs. optional), a sterile home (vs. just the dialysis room), and extensive training (vs. easy to learn). Home vs. center-borne infections, or that the "professionals" administering HD are largely technicians were not cited. Nephrologists did not talk about end-of-life or address patients' emotional or existential concerns. They did not directly elicit patients' values or tailor information-giving to those values even when patients inserted them. All but one nephrologist said they would use tools to help communicate more easily with their patients about RRT options.

Conclusions: A patient-centered values-based dialysis decision aid might serve as an ice-breaker, include the patients' values into the RRT conversation, and increase patients' participation in the RRT conversation and preferences for home dialysis.

Funding: Commercial Support - Amgen, Inc.

Participant Demographics

NEPHROLOGISTS	n=8
Age, mean (range)	39.43 (37-44)
Years of practice, mean (range)	7 (2-10)
PATIENTS	n=61
eGFR, mean (SD)	20.62 (4.08)
Age, mean (SD), range	68.82 (12.78) 25-94
Female	36 (60%)
< College degree	40 (65%)

SA-PO674

Higher Likelihood of Home Hemodialysis Training Graduation in Patients Using Nx2me Connected Health Technology Eric D. Weinhandl,[1,2] Allan J. Collins.[1,2] *[1]NxStage Medical, Inc., Victoria, MN; [2]University of Minnesota, Minneapolis, MN.*

Background: In the United States, approximately 1 in 6 patients who initiate home hemodialysis (HHD) training fail to complete training. Strategies that increase the likelihood of training graduation would permit more patients to dialyze at home and improve the economics of home dialysis programs. Digital tools that are introduced during HHD training and that "go home" may accelerate development of patient understanding about HHD equipment and procedures. We assessed whether introduction of the Nx2me iPad app during HHD training was associated with higher likelihood of training graduation.

Methods: We ascertained HHD patients that initiated use of Nx2me during the first 2 weeks of HHD training with the NxStage System One. For each Nx2me user who was prescribed *q* treatments per week and had accumulated *t* training days with the System One at first use of Nx2me, we identified potential controls who were prescribed *q* treatments per week and had accumulated at least *t* training days (without use of Nx2me), and we randomly selected 3. We followed Nx2me users and their respective matched controls from *t* days after training initiation until either HHD training graduation or training dropout. We used Cox regression to model incidence of training graduation, with stratification by matched cluster and adjustment for age, race, sex, vascular access modality, and center-level metrics of training activity and success (number of trainees during the past 12 months, probability of graduation among trainees, and mean duration of training among graduates).

Results: We identified 94 Nx2me users. The mean number of days between HHD training initiation and Nx2me introduction was 7.2. In Nx2me users (matched controls, but without adjustment), the cumulative incidence of training graduation was 5.3% (5.5%) after 1 week of follow-up, 23.1% (18.0%) after 2 weeks, 46.9% (34.9%) after 3 weeks, 71.6% (49.8%) after 4 weeks, 88.0% (66.0%) after 6 weeks, and 93.6% (71.9%) after 8 weeks. The adjusted hazard ratio of training graduation for Nx2me users versus matched controls was 1.53 (95% confidence interval, 1.02-2.29).

Conclusions: Introduction of the Nx2me iPad app during the first 2 weeks of HHD training is associated with significantly higher likelihood of training graduation, even after adjustment for center-level performance metrics.

SA-PO675

Effects of a System-Wide Application of a Comprehensive Pre-Dialysis Education Program on Home Dialysis Therapies Colin A. Hinkamp,[3] Emma R. Segal,[3] Teri B. Martinez,[3] Michelle Thomas,[1] Shahab Bozorgmehri,[2] Tezcan Ozrazgat-baslanti,[3] Ashutosh M. Shukla.[3] *[1]Dialysis Clinic, Inc., Gainesville, FL; [2]None, Newberry, FL; [3]University of Florida, Gainesville, FL.*

Background: The efficacy of comprehensive pre-dialysis education (CPE) with respect to its ability to improve home dialysis (HoD) choice and utilization, across the unselected, spectrum of prevalent US advanced CKD patients has not been examined.

Methods: We present a retrospective analysis of the first 20 months of our CPE program to show the impact of implementing a new CPE program across the entire spectrum of CKD, in a university CKD population with respect to its impact on HoD choice and utilization. Details of our CPE protocol has been prior published.

Results: Over the first 20 months, 200 patients were referred for CPE, of which 32% (n=63) patients chose not to participate in the awareness effort. Of the 137 patients enrolled, the majority (91%) chose to participate in only one session of CPE whereas 8% and 1% attended 2 and 3 sessions, respectively. At the end of the CPE, 72% chose HoD (69% peritoneal dialysis (PD) and 3% home HD (HHD)) whereas 11% chose in-center HD (IHD) with 17% remaining undecided. Over the 20 months of follow-up, 25% needed initiation of renal replacement therapy therapies. Amongst these, 73% were initiated on HoD. Univariate and multivariate analyses showed that age, gender, race, insurance status, marital status, smoking status, body mass index and comorbidity status (Diabetes/CHF), had no impact on the individual choice of HoD. The institution of CPE program led to an overall 66% (p trend<0.001) increase in utilization of HoD over the first 20 months with HoD representing 32% of all prevalent dialysis subjects.

Conclusions: The results validate that institution of CPE program leads to increase to HoD choice and utilization. We further show that benefits of CPE are not limited to only those with socio-economic privilege.

SA-PO676

Feasibility and Effectiveness of an Online Portal for Delivery of Care to Home Dialysis Patients Karthik K. Tennankore,[1] James Kiberd,[1] Kenneth A. West,[1] Christopher T. Chan,[2] Steven D. Soroka.[1] *[1]Dalhousie University, Halifax, NS, Canada; [2]Toronto General Hospital, Toronto, ON, Canada.*

Background: Home dialysis has a number of advantages over in-center hemodialysis. However, there is the potential for improvement in patient communication and experience. The purpose of this study was to determine if an online portal improved patient experience and quality of life (QoL) for home dialysis patients.

Methods: We conducted a pilot interventional study of home dialysis patients. Consecutive patients were enrolled over a four-month period and asked to join the portal via email. The portal (RelayHealth®) consisted of an online messaging platform that permitted asynchronous communication between patients and home dialysis staff. The Consumer Quality Index (CQI, a tool to measure patient experience) and EQ-5D QoL index were recorded at baseline, six and 12 months after enrollment. Satisfaction with the portal was evaluated at the end of follow-up using a Likert scale.

Results: 63 patients were approached, 41 patients consented to participate and 27 (66%) joined the online portal. Mean age was 57.1± 1.9 years and 48% were female. Monthly messaging frequency is noted in Figure 1. 25% of patient-initiated messages were sent for health-related issues. Sixteen and 10 patients completed follow-up at six and 12 months, respectively. Patients had a positive experience with their care at baseline, and there was no improvement in mean CQI during follow-up. EQ-5D QoL also did not differ significantly during follow-up. Overall, patients' were satisfied with the portal (mean Likert score 6.5 ±0.6; 1 completely dissatisfied-10 completely satisfied), felt it was easy to use and did perceive it to be helpful in some aspects of their care.

Conclusions: While feasible, we found no significant improvement in patient experience or QoL after using the portal. Participants were generally satisfied with the portal and it did improve some aspects of their dialysis care.

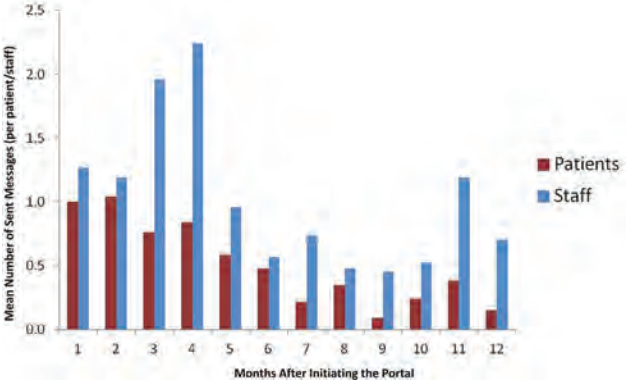


Figure 1. Patient Portal Mean Messaging Frequency (Patients/Staff)

SA-PO677

Quality of Life in Caregivers Compared with Dialysis Recipients: The CO-ACTIVE Substudy of the ACTIVE Dialysis Trial Nicholas A. Gray,[4] Daqing Hong,[3] Brendan Smyth,[2] Min Jun,[6] Kirsten Howard,[8] Kris Rogers,[7] Vlado Perkovic,[7] Li Zuo,[1] Meg J. Jardine.[5] *[1]Peking University People's Hospital, Beijing, China; [2]Newtown, NSW, Australia; [3]Sichuan Provincial People's Hospital, CHENGDU, China; [4]Sunshine Coast University Hospital, Birtinya, NSW, Australia; [5]The George Institute for Global Health, UNSW, Newtown, NSW, Australia; [6]The George Institute for Global Health, UNSW Sydney, Newtown, NSW, Australia; [7]The George Institute for Global Health, Sydney, NSW, Australia; [8]University of Sydney, Sydney, NSW, Australia. Group/Team: ACTIVE Dialysis Steering Committee.*

Background: The support of people living with chronic illness may be dependent on voluntary caregivers whose well-being is critical for patient management.

Methods: A subgroup of participants in the ACTIVE Dialysis study and their nominated caregivers completed quality of life (QOL) questionnaires including the EQ5D, SF-36 physical composite score (PCS) and mental composite score (MCS) as well as the Personal Wellbeing Index. Data was collected at baseline (prior randomisation to standard or extended hour dialysis) and every quarter until study end at 12 months. Baseline caregiver QOL was compared with dialysis patient QOL using paired t test for continuous variables, while predictors of baseline caregiver QOL were determined using multivariable regression.

Results: There were 54 patient and caregiver pairs, predominantly from China. Caregivers had a mean (SD) age of 53.4 (11.3) years and 56% were female. Most (89%) were married or lived with a partner and 24% were in paid employment. Half were educated to secondary school and 33% to university level. Caregivers mostly cared for their spouse/partner (67%) or child (11%), while 20% reported admission to hospital in the preceding year. At baseline, caregivers had a better physical but similar mental QOL compared with dialysis patients (PCS: 46.9±8.7 vs 40.4±10.2, P<0.001); MCS: 47.8±9.7 vs 49.6±12.0, P=0.84). Chinese SF-36 population norms are 77.5 for PCS and 73.6 for MCS. EQ5D for caregivers was 0.9 (0.2) compared with 0.8 (0.2) for dialysis patients (P=0.054). The Chinese EQ5D norm is 0.92. Personal Wellbeing Index was 43.7±15.5 for caregivers (Chinese norm 60-70). Higher SF-36 scores among caregivers was predicted by university education but not age, gender or daily hours spent caring.

Conclusions: Caregivers have a higher physical QOL and equivalent mental QOL to dialysis patients but poorer physical QOL, mental QOL and personal wellbeing than the general Chinese population. University education predicts better QOL and may be a surrogate for current financial resources or other socioeconomic factors.(NCT00649298)

Funding: Private Foundation Support

SA-PO678

Patient Satisfaction with a Home Dialysis Virtual Ward Karthik K. Tennankore,[1] Annie-Claire Nadeau-Fredette,[2] Joanne M. Bargman,[6] Michael A. Copland,[7] Simon N. Finkle,[1] Matthew J. Oliver,[5] Robert P. Pauly,[3] Jeffrey Perl,[4] Nikhil A. Shah,[3] Deborah Lynn Zimmerman,[3] Christopher T. Chan.[6] *[1]Dalhousie/Nova Scotia Health, Halifax, NS, Canada; [2]Hopital Maisonneuve-Rosemont, Montreal, QC, Canada; [3]None, Edmonton, AB, Canada; [4]St. Michael's Hospital, Toronto, ON, Canada; [5]Sunnybrook Health Sciences Center, Toronto, ON, Canada; [6]Toronto General Hospital, Toronto, ON, Canada; [7]University of British Columbia, Vancouver, BC, Canada.*

Background: The home dialysis virtual ward (HDVW) initiative aimed to address gaps in care after periods of patient transition. The purpose of this study was to assess patient satisfaction with the HDVW.

Methods: The HDVW was a multicenter Canadian trial of home dialysis patients conducted from January 2014-December 2015. The intervention consisted of 5-6 clinician-led telephone interviews over 14 days using a standardized questionnaire to identify and address gaps in care (including medication discrepancies and dialysis prescription changes). The intervention occurred after four care transition events: graduation from home dialysis training, discharge from hospital, following a medical procedure and after treatment with antibiotics. Satisfaction with the HDVW including perceived impact on several care domains was assessed following the intervention using a visual analogue scale (VAS; 1 not satisfied to 10 completely satisfied).

Results: Fifty-five percent (106/193) of patients completed satisfaction surveys and most transitioned to the HDVW after completion of home dialysis training (65%). The mean age of responders was 55+/- 15 years and 51% were female. 58% of patients were performing peritoneal dialysis and most patients (87%) were independent in performing their dialysis. Overall, patients were satisfied with the HDVW (median VAS 8, IQR 2). Patients perceived that the HDVW had a positive impact on their overall health, understanding of medications and access to a nephrologist. In contrast, patients perceived a neutral impact on their chance of needing readmission or travel for dialysis care (Figure 1).

Conclusions: Patients enrolled in the HDVW were highly satisfied with their care. This intervention may be valuable in supporting home dialysis patients during care transitions.

Funding: Commercial Support - Baxter: Investigator Initiated High Dose Hemodialysis Grant

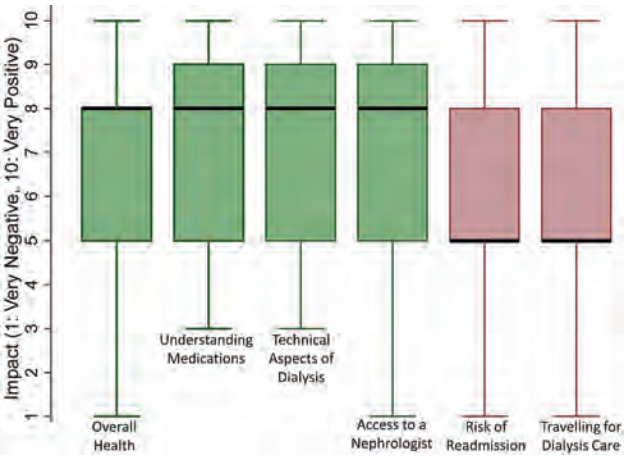


Figure 1. Patient perceived impact of the HDVW on several domains of care

SA-PO679

Use of an NxStage Machine at Home for Vegetative, Disabled, and Home Bound Dialysis Patients: A Preliminary Result of a Unique Experience Bassam O. Bernieh,[2] Fredric Calaud,[1] Musa Ahmed,[1] Bienmelyn L. Hernandez.[1] *[1]Al Ain Life, Abu Dhabi, United Arab Emirates; [2]The Heart Medical Center, Al Ain-Abu Dhabi, United Arab Emirates.*

Background: Home hemodialysis (HHD) was invented to treat active, autonomous, and relatively, healthy dialysis patients. The number of dialysis patients, who are vegetative, debilitated, bed and home bound is steadily increasing, creating a major burden on the health care system. We are presenting our new and unique experience of treating these highly co-morbid and disabled dialysis patients, with nursing assisted home hemodialysis (NAHHD). The purpose of this modality is to decrease risks, financial, and emotional burdens, of the patients, their families, and of the health care providers.

Methods: Hemodialysis patients who were fulfilling the National Insurance Company criteria for HHD were accepted in the NAHHD program. These criteria include mainly bed and home bound patients. NxStage System One is used to deliver the hemodialysis at home or at long term care facility with a hemodialysis nurse. Duration of session, weekly number of session and volume of fluid are calculated by dose calculator given by NxStage Company, with a target standardized KT/V of 2.

Results: Nineteen dialysis patients on NxStage machine at home or in a long term care facility were included in this preliminary study. 7(36.8%) males and 12 (63.2%) females. Median age 73 year (42-88). Median duration on NAHHD was 3 months (2-8). Etiology of end stage renal disease was DM 13(68.5%), HTN 5 (26.5%), and familial nephropathy 1(5%). Indications of NAHHD were: vegetative status 1, bed and home bound 17, and 1 HIV case. Vascular access: AVF 8 (42%), AVG 1(5%), and tunneled catheter 10(53%). Average dialysate volume was 25 L. Number of session per week was 4, and average duration of session 3:10 hours. Pre-dialysis BP 131.2±30.5/66±9.3, post dialysis BP 136.6±36.7/ 64.4±5 (p=NS).). The average of the standardized KT/V was 1.94. There was a positive impact of the NAHHD on the patients' quality of life, as measured by time of recovery of 13.75 minutes, average sleeping of 6 hours, and satisfaction of 7.5/10.

Conclusions: NAHHD by using NxStage machine is a very promising modality for treating vegetative, debilitated, bed and home bound dialysis patients, providing a good quality of care, managing the sufferance of the patients, and of their families, and decreasing the risks and the cost of special transportation.

SA-PO680

Correlation between Changes in Body Mass Index and Mortality in Patients Undergoing Long Intermittent Hemodialysis without Dietary Restriction Manabu Hishida,[1] Takahiro Imaizumi,[1] Sawako Kato,[1] Toshiro Nishiyama,[3] Hiroshi Kaneda,[2] Shoichi Maruyama.[1] *[1]Nagoya University Graduate School of Medicine, Nagoya, Japan; [2]Nephrology, kamome clinic, Yokohama, Japan; [3]Nephrology, kamome clinic, Kitaibaraki, Japan.*

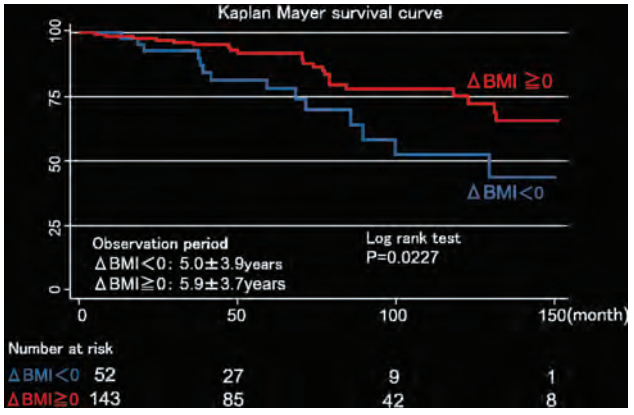
Background: Poor nutritional status is a known mortality risk in chronic kidney disease (CKD) patients. Patients undergoing long intermittent hemodialysis (LIH) without dietary restriction are generally well nourished. We aimed to study whether body mass index (BMI) in patients undergoing this therapy is maintained better and longer than those in conventional hemodialysis (CH), and to understand the association between BMI changes and mortality.

Methods: We examined patients undergoing LIH without dietary restriction with at least one-month dialysis vintage at Kamome Hitachi Clinic (KHC) between January 2002 and April 2016. BMI was calculated based on dry weight. Longitudinal BMI changes were monitored in these patients, and compared to those in CH patients, obtained from previous reports. Using the Cox proportional hazard model, we evaluated mortality risk associated with decrease in BMI.

Results: We enrolled 195 patients, with a mean observation period of 5.7 ± 3.7 years. The baseline BMI at the onset of LIH without dietary restriction was 23.36 ± 3.81. The

mean BMI increased for 3 years after initiation of this therapy, similar to the pattern in CH patients. However, BMI in this study population remained stable longer than that in CH patients. BMI in 52/195 patients decreased from the third to 12th month after initiation of this therapy. The hazard ratio (HR) of mortality was 3.004 [95% confidence interval (CI); 1.415-6.374].

Conclusions: We showed that patients undergoing LIH without dietary restriction maintain BMI for a longer period. Additionally, we found that decreased BMI was associated with an increased mortality risk, suggesting that preserving a good nutritional status in these patients contributes to a better prognosis. In conclusion, although further studies are needed, non restricted dietary therapy in LIH maintains good nutritional status and lowers mortality risk in CKD patients.



SA-PO681

Change in Blood Pressure and Body Weight in Incremental Hemodialysis Patients Inkyong Hur,[1] Yoshitsugu Obi,[1] Elani Streja,[1] Melissa Soohoo,[1] Connie Rhee,[1] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine, Orange, CA; [2]University of Tennessee Health Science Center, Memphis, TN.*

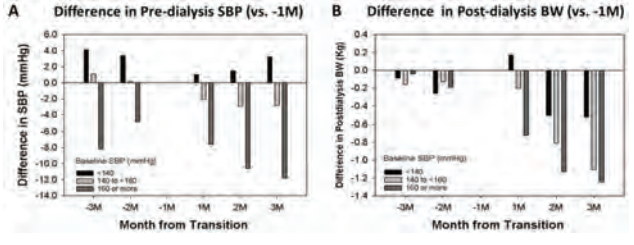
Background: Fluid status is expected to improve by increasing hemodialysis (HD) frequency from twice-weekly to thrice-weekly (i.e., incremental HD), but there are scarce data about how much improvement in blood pressure that can be achieved in such patients.

Methods: We retrospectively examined 569 HD patients who transitioned from twice-weekly to thrice-weekly HD within 3 months (M). We compared the pre-dialysis systolic BP (SBP) and post-dialysis body weight (BW) before and after the transition (i.e., -3M to 3M). Data at -1M served as the reference and SBP was categorized into three groups (i.e., <140 [27%], 140-<160 [42%], and ≥160 mmHg [31%]).

Results: The mean±SD age of the cohort was 66±14 years and included 46% women. SBP was increased up to -1M. Patients with the highest baseline SBP showed the greatest improvement in SBP after transition (-7.6±13.1, -10.4±15.8, and -11.9±15.9 mmHg at 1M, 2M, 3M, respectively; $p<0.001$) while patients with the lowest showed slightly increased (0.9±10.2, 1.4±12.0, 3.3±12.9 mmHg at 1M, 2M, 3M, respectively; $p=0.022$). Decreasing trends in post-dialysis BW after transition was consistently observed across the three groups, but was greater in higher baseline SBP patients (-0.7±1.8, -1.0±2.7, and -1.2±3.0 Kg at 1M. 2M, 3M, respectively; $p<0.001$) [Figure].

Conclusions: The transition from twice-weekly to thrice-weekly frequency resulted in an improvement in pre-dialysis blood pressure control especially in patients with higher baseline SBP, which coincided with decreasing trends in post-HD body weight.

Funding: NIDDK Support



SA-PO682

Seven Days a Week Dialysis Service to Achieve an Effective In-Center Short Daily Hemodialysis Program Pedro Pascoal, Adolfo Simon, Kelia Xavier, Vilber Bello, Juliane Lauar, Istenio Pascoal. *Centro Brasiliense de Nefrologia & Dialise, Brasilia, Brazil.*

Background: In-center hemodialysis programs usually operate Monday through Saturday, encompassing two conventional thrice-weekly schedules: Mon-Wed-Fri or Tue-Thu-Sat. On Sundays, in the midst of the long 72-hour Fri-Mon or Sat-Tue interval, dialysis centers are regularly closed and patient care relies on emergency rooms. After setting up a 6 days a week in-center short daily hemodialysis program, we started to provide dialysis treatments also on Sundays. We have now examined the 10-year impact of the seven-day availability on patient schedule and compliance as well as on hospitalization and survival rates.

Methods: We assessed the conversion rate from 6 to 7 times a week, the prevalence of absences from hemodialysis treatments (no shows), the hospitalization rate and the actuarial survival curve of 160 private-insured patients (98M/62F; mean age at dialysis initiation 57.3±8.2 yrs, range 8-92) receiving in-center short daily hemodialysis treatments (6-7 times/week; lasting 118±18.7 min, range 90-180; ultrapure dialysate and single-use highflux dialyzer). To accommodate all patient needs, our hemodialysis schedule encircles five 2-hour duration shifts on weekdays, 3 shifts on Saturdays and 2 shifts on Sundays.

Results: From June 2007 to May 2017, 24 out 160 (15%) of our cumulative short daily hemodialysis patients extended their schedule from 6 to 7 treatments per week, 9 (6%) chose Saturdays as their regular day-off, and the remained 127 (79%) have ocasionally dialysed on Sundays to replace most of the missed treatment occurring in their original track. Over the 10-year study period, the average missed treatment rate was 1.47% or 4.5 days per patient-year and the hospitalization rate was 0.4 admissions per patient-year. In parallel, the 5-year cumulative patient survival rates were 98%, 92%, 82%, 69% and 60% at 12, 24, 36, 48 and 60 mo, respectively. Sunday dialysis additional costs have been offset by favoring low missed treatment rate and very low hospitalization rate.

Conclusions: Historically all but a few dialysis centers have provided treatments and care for patients Monday to Saturday, leading to concerns of higher mortality over weekends. To sustain a short daily hemodialysis program and to overcome its compliance and economic challenges, our dialysis center has successfully established a regular seven days a week schedule.

SA-PO683

Quasi-Frequent Hemodialysis Affects Hospitalization for Cardiovascular Disease and Cardiac Function in ESRD Patients with Severe Heart Failure Masataka Banshodani, Hideki Kawanishi, Misaki Moriishi, Sadanori Shintaku, Shinichiro Tsuchiya. *Tsuchiya General Hospital, Hiroshima, Japan.*

Background: Previous reports indicated that frequent hemodialysis (FHD) maintained cardiac function. However, no reports have evaluated the impact of quasi-FHD (q-FHD) on hospitalization for cardiovascular diseases (CVDs) and cardiac function in end-stage renal disease (ESRD) patients with severe heart failure.

Methods: This is a retrospective observational study that evaluated hospitalizations for the period from 1 year before to 1 year after q-FHD initiation (≥4 times a week) and ejection fraction (EF) by using echocardiography in ESRD patients with severe heart failure (New York Heart Association Functional Classification III or IV) at a single center between 1995 and 2014.

Results: Of 1,955 hemodialysis (HD) patients, 60 (3.1%; 42 men; mean age, 65.4 years; mean dialysis vintage, 80.0 months) started q-FHD (mean, 4.3 ± 0.7 times a week) and 52 continuously received q-FHD (4.6 ± 0.8 times a week) 1 year later. The 1-year mortality rate after q-FHD initiation was 13.3%. The mean EF decreased from 61.8% at dialysis initiation to 50.6% at q-FHD initiation ($P < 0.001$) but did not change 1 year later (49.4%; $P = 0.7$). All-cause hospitalization rates (per person-year) were similar between before and after q-FHD initiation (1.79 [102 hospitalizations] vs 2.07 [115 hospitalizations]; $P = 0.2$). On the other hand, the emergency hospitalization rate for CVDs significantly decreased from 0.73 to 0.37 after q-FHD initiation ($P = 0.002$). However, the emergency hospitalization rates for infectious diseases, including vascular access-related infection, were similar between before and after q-FHD initiation (0.12 vs 0.16; $P = 0.5$).

Conclusions: The hospitalization rate for CVDs significantly decreased after the q-FHD initiation in the ESRD patients with severe heart failure. Moreover, q-FHD maintained cardiac function in these patients. Further multicenter studies are needed to evaluate these findings.

SA-PO684

Change in Ultrafiltration Volume in Incremental Hemodialysis Inkyong Hur,[1] Yoshitsugu Obi,[1] Elani Streja,[1] Connie Rhee,[1] Csaba P. Kovesdy,[2] Kamyar Kalantar-Zadeh.[1] *[1]UC Irvine, Orange, CA; [2]University of Tennessee Health Science Center, Memphis, TN.*

Background: Incremental hemodialysis (HD) is a strategy of the gradual increase from twice-weekly to thrice-weekly HD in incident ESRD patients. While it is expected that augmentation of dialysis frequency leads to improvement in patients' health status, there are scarce data about changes in ultrafiltration in such patients.

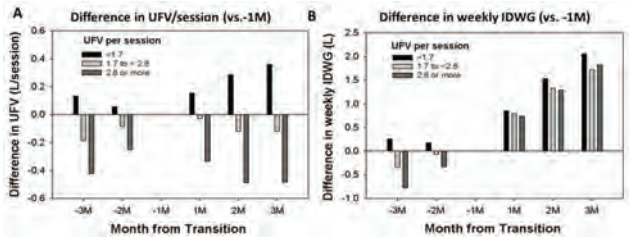
Methods: We retrospectively examined 569 HD patients who underwent incremental HD between 2007 and 2011. We compared the ultrafiltration volume (UFV) per session and weekly interdialytic weight gain (IDWG) before and after the transition (i.e., -3 months (M) to 3M). Ultrafiltration (UF) at -1M served as the reference and was categorized into tertiles (<1.7, 1.7 to <2.8, and ≥2.8 L/session).

Results: The mean±SD age of the cohort was 66±14 years, and included 46% women. Patients with the highest baseline UFV showed a decreasing trend in UFV/session after transition (-0.3±0.7,-0.5±0.7, and -0.5±0.7 L at 1M, 2M, 3M, respectively; $p<0.001$), but patients with the lowest baseline UFV paradoxically showed an increasing trend (0.1±0.6, 0.3±0.7, and 0.4±0.7 L at 1M, 2M, 3M, respectively; $p<0.001$). Increases in weekly IDWG after the transition were consistently observed across UFV tertiles, but were greater among patients with lower baseline UFV (2.8±1.8, 3.5±1.9, and 4.1±2.2 L at 1M, 2M, 3M, respectively; $p<0.001$) [Figure].

Conclusions: Transitioning from twice-weekly to thrice-weekly HD resulted in less UFV/session among patients with higher baseline UFV, but paradoxically resulted

in increased UFV/session among patients with the lowest baseline UFV. Weekly IDWG increased irrespective of baseline UFV.

Funding: NIDDK Support



Figure

SA-PO685

Calcium (Ca) and Phosphate (P) Balance in Short Daily Hemodialysis (SDHD) with the NxStage System One Cycler (NSO): Comparison with Standard Bicarbonate Dialysis (BHD) Chiara Carla Maria Brunati,[1] Roberto Corciulo,[3] Francesca Gervasi,[5] Costanza Casati,[5] Simone Corciulo,[2] Loreto Gesualdo,[4] Giacomo Colussi.[1] *[1]ASST Niguarda, Milano, Italy; [2]University of Foggia, Foggia, Italy; [3]Azienda Ospedaliera Policlinico Bari, Bari, Italy; [4]University of Bari, Altamura, Italy; [5]University of Milan Bicocca, Milan, Italy.*

Background: SDHD with NSO has gained popularity as home HD prescription. Short HD sessions, as in use with NSO, might not allow adequate removal of P, which benefits from time to optimize removal.

Methods: We compared single run and weekly balances of P and Ca, and changes in plasma levels, in 25 pts treated with NSO in 2 centers with different prescription: 14 pts (Milan) were prescribed 6 runs/week (dialysate 22.7±3.8L/run, time 154±23min/run), 11 pts (Bari) 4 or 5 runs/week (mean 4,8±0,48, dialysate 24,1±3,5, time 194±24). Data were compared to those in 14 pts treated with BHD (3/week, 4 hours, dialysate 500ml/min).

Results: Are shown in table 1.

Conclusions: Despite lower P removal per run in NSO, weekly removal was equal (Bari) or higher (Milan) than in BHD. More frequent NSO runs (6) are more efficient than less frequent runs (4/5). Plasma P decrease was quantitatively similar in NSO and BHD, despite lower run duration. P removal was directly correlated with pre-HD plasma levels in both NSO and BHD. Plasma Ca level increased less in NSO than in BHD, yet PTH fell along the run; Ca balance was correlated to basal Ca levels and net UF; at observed UF, it was negative at plasma Ca>8.5mg/dL. Our data show that SDHD with NSO, despite lower run time and dialysate volume, allows similar P removal as compared to BHD; plasma Ca changes and balance do not substantially differ in NSO and BHD.

Table 1. P and Ca

	NSO-Milan	NSO-Bari	BHD	p
Plasma P, start (mg/dl)	5.1+1.4	5.2+0.9	4.5+2.8	n.s.°
Plasma P, end (mg/dl)	2.7+0.8*	2.6+0.7*	2.2+0.5**	0.02°
Net decrease (mg/dl)	2.4+1.0	2.5+0.6	2.6+3.0	n.s.°
Net removal (mg/session)	-581.4+196.8	-581.1+160.1	-878.1+292.6	0.0006°
Weekly removal (mg)	-3488+1181	-2690+726.8	-2634+878	0.0037$
Plasma Ca, start (mg/dl)	8.7±0.7	8.9+0.3	9.0±0.5	n.s.°
Plasma Ca, end (mg/dl)	9.4±0.6*	9.3+0.4**	10.0±0.5*	0.0002°
Net increase (mg/dl)	0.7±0.3	0.5±0.1	1.0±0.6	0.05°
Net balance (mg/session)	-43.8±106.1	-17.7±258.6	-110.3±233.3	n.s.°
Weekly balance (mg)	-262.8±236.7	-78.6±643.7	-331.0±589.1	n.s.°

Vs start: *p<0.0001, **p<0.006; °: vs NSO-Milan and Bari; $:vs NSO-Milan

SA-PO686

Cardiovascular Assessment in Patients on Nxstage System One (NxO) Chiara Carla Maria Brunati,[1] Francesca Gervasi,[2] Costanza Casati,[2] Giacomo Colussi.[1] *[1]ASST Niguarda, Milano, Italy; [2]University of Milan Bicocca, Milan, Italy.*

Background: Left ventricular hypertrophy (LVH) is an independent risk factor for mortality in patients on conventional hemodialysis (HD). According to the Frequent Haemodialysis Network daily trial, increased frequency of conventional in-centre HD is associated with a reduction in antihypertensive therapy, extracellular fluid (ECW) and left ventricular mass. Little data exists with the non-conventional daily dialysis system, NxO.

Methods: From May 2011 to December 2016, we enrolled 12 patients (median age 49yrs, from 25yrs - 66yrs) on a NxO home program, follow up of 22 months (variation 3 to 68months, 6runs a week, QD 22±4L, duration of session 144±25min StKt/V 2,4±0,2). Treatment effects of volume parameters were evaluated monthly in all patients in the interdialytic period, according to BIA parameters (BIA impedentiometry Frisenius) including the proBNP levels. In 6 patients with 12 months of follow up, an echocardiography was also performed in order to evaluate the cardiac mass and compare with data at baseline. We compared BIA evaluation, measurements of the cava diameter and of the presence of lung comets in NxO patients, a total 134 tests, with those of 30 patients on traditional HDB treatment who were evaluated directly post session, as normohydratate. ProBNP was evaluated in both groups.

Results: We observed a reduction of mean blood pressure (from 97±17 to 81±5mmHg) and this even despite a reduction in antihypertensive drug units (median of –2UD from 0 to – 15UD). In 7 patients with 12 months of follow up, a significant reduction in cardiac mass was recorded (148±44 gr/m^2 to 120±35gr/m^2 p≤0.05). The BIA evaluation evidences an overhydratation state in only 10% of measurements. In comparison with normohydratate HBD patients, no difference in ECW/TBW values were recorded. NxO patients had higher levels of ICW/TBW values, indicating a more physiological distribution of volume as reflected by lower levels of proBNP.

Conclusions: According to our results, daily HD sessions using NxO improves certain cardiovascular parameters. Although no reduction in extra-cellular volume was seen, we can hypothesize excellent volume control due to the interdialytic measurements.

	Nr pz	Nr tests	SBP (mmHg)	MBP (mmHg)	ECW/TBW	ICW/TBW	proBNP (ng/L)
HDB	30	30	133 ± 20	94 ± 11	0.45 ± 0.003	0.54 ± 0.030	8508 ± 11579
NXT	12	134	117 ± 18	82 ± 21	0.45 ± 0.038	0.56 ± 0.034	2591 ± 4068
p			≤ 0.001	n.s.	n.s.	≤ 0.005	≤ 0.001

SA-PO687

Successful Home Hemodialysis in a Patient with an LVAD (Left Ventricular Assist Device) Shubha Ananthakrishnan,[1] Munir Janmohamed.[2] *[1]UC Davis, Sacramento, CA; [2]Cardiology, UCSF, San Francisco, CA.*

Background: LVADs for end-stage heart failure are on the rise as a bridge to transplant, including in patients on dialysis. There are many technical and logistic challenges faced by patients with an LVAD, who dialyze at a dialysis center. Here we describe successful home hemodialysis by a patient with an LVAD, awaiting a combined heart-kidney transplant.

Methods: The patient is a 39 yr old African American male, with ESKD due to FSGS, formerly on peritoneal dialysis for 6 years, who started home hemodialysis in 2015. He also has a h/o non-ischemic cardiomyopathy with EF around 18%. Given cardiac status and pulmonary hypertension, a decision was made to implant a HeartWare® LVAD in March 2016 as a bridge to transplant, with a flow of 5L/min, speed 2400 RPM, pulsatility of 7. The patient continued on home hemodialysis after the LVAD insertion, caring for the LVAD equipment, drive line dressing changes, as well as performing home hemodialysis without a partner. Home hemodialysis was performed using the NxStage® platform, Qb 400 ml/min, Flow fraction 35%, 1K, 3Ca bath, 5 days a week, using a L forearm AV fistula. BPs were controlled to goal SBP < 100 mm Hg targeting optimal dry weight and medication use. The patient had palpable radial pulses and was able to record blood pressures at home using a standard BP cuff and monitor. Warfarin anticoagulation was used for VAD patency, with goal INR 2-2.5. The patient did not require ESA therapy and was able to maintain Hb around 10 – 12 with intermittent iron alone. Other labs of interest: standard Kt/V 2.11, Albumin 4.3, Ca 9.3, Phos 4.9, PTH 655. He had one episode of bacteremia that was successfully treated with antibiotics. The patient continues to dialyze at home and is closely cared for by the home hemodialysis team and the LVAD team.

Results:

Conclusions: Hemodialysis in LVAD patients has been reported in center-based dialysis setting. However, due to several logistic challenges including training and familiarity of dialysis center staff to care for these patients, there are only a handful of hemodialysis centers that are able to accept patients with LVAD. Home hemodialysis in LVAD patients is feasible and overcomes these challenges of in-center dialysis. Very close communication and coordination between the LVAD team and HHD team is crucial.

SA-PO688

Case Report: Patient with a Total Artificial Heart Maintained on Outpatient Dialysis While Listed for Combined Organ Transplant: A Single Center Experience Ramy M. Hanna,[2] Huma S. Hasnain,[3,2] Mohammad Kamgar,[1,2] Raffi R. Minasian,[1] James Wilson.[1,2] *[1]Manhattan Beach, CA; [2]UCLA Health, Rolling Hills Estates, CA; [3]UCLA Nephrology, Los Angeles, CA.*

Background: Advanced mechanical circulatory support is increasingly being used with more sophisticated devices that can deliver pulsatile rather than continuous flow. These devices are more portable as well, allowing patients to await cardiac transplantation in an outpatient setting. It is known that patients with renal failure are at increased risk for developing worsening acute kidney injury during implantation of a ventricular assist device (VAD) or more advanced modalities like a total artificial heart (TAH).

Methods: Dealing with patients who have an implanted TAH who develop renal failure has been a challenge with the majority of such patients having to await a combined cardiac and renal transplant prior to transition to outpatient care. Protocols do exist for VAD implanted patients to be transitioned to outpatient dialysis care, but there are no reported cases of TAH patients with ESRD being successfully transitioned to outpatient dialysis care.

Results: In this report, we identify a patient with a TAH and ESRD transitioned successfully to outpatient Hemodialysis (HD) and maintained for more than two years, though he did not survive to transplant

Conclusions: It is hoped that this report will raise awareness of this possibility, and assist in the development of protocols for similar patients to be successfully transitioned to outpatient dialysis care.

SA-PO689

In Vitro Mast Cell Degranulation Assay to Assess Hemodialysis Sorbent Cartridges Stephen Merchant,[4] Mark Costanzo,[4] Claudy Mullon,[4] Mayuri Thakuria,[3] Amparo L. Figueroa,[1] Robert J. Kossmann.[2] *[1]Fresenius, Boston, MA; [2]Fresenius Medical Care North America, Waltham, MA; [3]Fresenius Medical Care, North America, Waltham, MA; [4]Fresenius Medical Care, Oklahoma City, OK.*

Background: Hemodialysis (HD) sorbent cartridges aimed at dialysate regeneration contain urease to hydrolyze urea into bicarbonate and ammonium. Urease may come from sources that can cause allergic reactions. Here, we compared in vitro, two sorbents in their propensity to cause allergic reaction.

Methods: In vitro mast cell degranulation method was used to examine dialysate samples from an FDA cleared sorbent cartridge (REDY) and a new cartridge (PAK). Both sorbent cartridges were primed with typical hemodialysis dialysate and recirculated for 30 minutes. Samples for analysis were taken from the recirculated dialysate in the reservoir at 10, 20, and 30 minutes. Diluted (50 µl) concanavalin A (Con A) standards in complete RPMI plus IL-3 medium (positive controls), culture medium (negative control), or sorbent cartridge effluent test articles were added to 200 µL of culturing medium containing ~0.3 million MC/9 cells, in duplicate. Cells were incubated for 24 hours at 37 degrees C under 5% CO_2. Histamine levels in each cell culture supernatant sample were determined using Histamine ELISA Cell Culture Kit. To evaluate the responsiveness of the method, various concentrations of Con A were used as positive controls.

Results: There was no significant difference (p=NS) in the histamine concentrations between both the PAK and REDY sorbent dialysates vs. negative control at 10, 20, and 30 minutes. At Con A concentration of 0.1 – 0.8 µg/ml, positive correlation was observed with histamine release, r=0.95, p<0.001. At con A concentration of 0.1 – 0.8 µg/ml, the mean histamine release was between 17.76 -94.52 ng/ml. On the other hand, the negative control had a mean histamine release of 17.68 ng/ml.

Conclusions: In this proof of concept study, we report the first ever in vitro histamine release testing of sorbent cartridge dialysates incubated in the presence of mast cells. The findings demonstrate that the histamine release from the dialysate generated by the PAK sorbent is not significantly different to that of the negative control culture medium and the dialysate generated by the REDY sorbent.

Funding: Commercial Support - Fresenius Medical Care

SA-PO690

Natural History of Thyroidal Functional Disease in Peritoneal Dialysis Jean-christophe Szelag,[1] Carlos Cardozo,[1] Myriam Pastural,[1] Maurice Laville.[1,2] *[1]AURAL, LYON, France; [2]Université de Lyon, Pierre-Bénite, France.*

Background: Thyroidal functional disease (TFD) is frequent in chronic kidney disease. The main reported abnormalities are hypothyroidism, especially in its subclinical pattern (SCH), and low circulating triiodothyronine (low T3 syndrome). Recent data has established a link between TFD and mortality in stage V CKD, however, little is known about the natural evolution of TFD in end stage renal disease patients, especially treated with peritoneal dialysis.

Methods: We studied a cohort of 114 incident peritoneal dialysis patients (mean follow up, 23 +/- 19 months; men: 59,6%, diabetes: 25%, 61,7+/-16.6 years old) tested for thyroid function on a quarterly basis. THS above the highest normal lab value (4.2 mIU/L) with normal fT4 defined SCH, an isolated fT3 below the lowest normal lab value (2,5 pmol/L) defined low T3 syndrome, in untreated patients.

Results: At baseline, 96 patients were euthyroid, 17 (14,9%) displayed a SCH and only one a low fT3 condition (0,8%). Low fT3 corrected in less than three months. Thyroid function corrected in all but two SCH patients along an average period of 9 +/- 7,7 months. A late recurrence was observed in one patient. Multivariate analysis didn't suspect any predictive variable associated with baseline SCH (age, sex, diabetes, hemodialysis before PD, cardio-renal syndrome, nutrition status, inflammation status) while two previous stories of thyroiditis and one exposition to amiodarone were found in three patients with persistent/recurrent SCH. Eight patients (8,3%) with normal thyroidal status at baseline subsequently evolved to SCH (4) or low fT3 syndrome (4) after a mean follow up of 6,2 +/-5,9 and 7,1+/-6,9 months, respectively. Diabetes (SCH, *p= 0,02*) and albuminemia (low fT3, *p=0,043*) were the only factors associated with the occurrence of a thyroid disturbance in baseline euthyroid patients. Of interest, low fT3 was always transient and disappeared spontaneously while SCH became a constant disorder in all but one patient (75%), No patient developed overt hypothyroidism over the follow-up.

Conclusions: SCH is highly prevalent in patients starting PD but disappeared within the first year in the absence of previous thyroid disease. Its signification could be different when occurring in initially euthyroid individuals. Low fT3 syndrome is less common and seems to be a transient condition associated with albumin variations.

SA-PO691

Dialysis Modality in PD Patients Undergoing Laparoscopic Surgery Janis Cho,[5] Jennifer L. Waller,[5] Mufaddal F. Kheda,[5] Stephanie L. Baer,[1] Rhonda E. Colombo,[5] Lu Huber,[2] John J. White,[5] Troy J. Plumb,[4] N. Stanley Nahman.[3,1] *[1]Augusta VA Medical Center, Augusta, GA; [2]Avera Medical Group Nephrology, Sioux Falls, SD; [3]Medical College of Georgia at Augusta University, Augusta, GA; [4]University of Nebraska Medical Center, Omaha, NE; [5]Augusta University, Augusta, GA.*

Background: Historically, PD patients requiring abdominal surgery required a change to hemodialysis (HD). Laparoscopic surgery (LPS) has been used for many abdominal procedures, but it is unclear if PD patients can undergo LPS and continue with PD. To address patterns of dialysis modality change in PD patients undergoing LPS, we queried the USRDS.

Methods: Incident PD patients from 2004 – 2011 (n=56,192) who underwent LPS were studied. Groups included: no interruption of PD(P); planned temporary (PT) HD then back to PD($_{PT}$HD-P); permanent switch (PS) to HD($_{PS}$HD); urgent temporary (UT) HD then back to PD($_{UT}$HD-PD); or urgent(U) HD with PS to HD($_{U}$HD-$_{PS}$HD). Demographics and outcomes were determined. The relative risk (RR) of complications versus no interruption of PD (P) up to 3 months post-op were estimated.

Results: 7298 PD patients had LPS, 45% women, 74% White, with mean±SD age 55±3 years, and time on dialysis of 16.6±1.9 months. Outcomes and group comparisons are shown in the table. Continuing PD was the most common form of dialysis in PD patients undergoing LPS, had the lowest complication rate, and may represent the lowest-risk cohort for LPS. Planned switches to HD were better than urgent switches, and were likely applied to higher risk patients. Urgent switches that returned to PD had the highest complication rates for peritonitis, bacteremia, and wound infection, and may indicate cohorts of patients developing complications with or during LPS.

Conclusions: Continuing PD during laparoscopic surgery is common and appears safe. The need for urgent HD is uncommon, but if PD is resumed, it is associated with a higher risk of post-op complications. Risk stratification may help predict whether to switch dialysis modality in PD patients prior to LPS.

Dialysis Modalities Among PD Patients Undergoing LPS

Variable	$_{PT}$HD-P	$_{PS}$HD	$_{UT}$HD-P	$_{U}$HD-$_{PS}$HD	P	p Value
N (%)	2801 (27)	1465 (19)	250 (3.3)	159 (2.1)	3529 (47)	NA
Final logistic regression model comparing switches to P (RR (95% CI))						
Level	Peritonitis		Bacteremia		Wound Infection	
$_{PT}$HD-P vs P	1.98 (1.41 – 2.79)		5.76 (4.44 – 7.47)		2.72 (1.50 – 4.95)	
$_{PS}$HD vs P	0.44 (0.24 – 0.81)		1.48 (1.03 – 2.12)		2.24 (1.14 – 4.42)	
$_{UT}$HD-P vs P	5.64 (0.35 – 9.24)		6.37 (4.15 – 9.79)		6.05 (2.57 – 14.22)	
$_{U}$HD-$_{PS}$HD vs P	1.79 (0.71 – 4.53)		4.50 (2.48 – 8.18)		5.32 (1.76 – 16.03)	

SA-PO692

Comparison of Two Different Neutral Peritoneal Dialysis Fluids in Japan, Bicarbonate/Lactate-Buffered Fluid versus Lactate-Buffered Fluid Yudo Tanno, Nanae Matsuo, Yukio Maruyama, Ichiro Ohkido, Keitaro Yokoyama, Takashi Yokoo. *Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan.*

Background: Recently, new neutral peritoneal dialysis fluid (PDF) contained bicarbonate 25mEq/L and lactate 10mEq/L (Bic/Lac PDF), instead of lactate 40mEq/L contained neutral fluid (Lac PDF), was available in Japan. Bic/Lac PDF is expected to achieve better biocompatibility and to compensate overcorrection of metabolic acidosis by reducing total alkaline buffer. However, there are few reports comparing Bic/Lac PDF and neutral Lac PDF. Therefore, we conducted a prospective study to clarify the effect of Bic/Lac PDF on clinical status including acid-base disturbance.

Methods: Sixty-three stable PD patients were included (60±12 y/o, male 76%, PD duration 43.6±30.2 months). All PDF contained 40 mEq/L of lactate before changing to Bic/Lac PDF, and the daily volume of PDF was not changed until the end of the examination period. The patient's existing medications were not changed during the study period. The patients' data (bicarbonate, pH, ionized calcium, carbon dioxide and Lactate levels) were obtained before and 3 months after the induction of Bic/Lac PDF. We also investigated the change in effluent drain volume, D/P creatinine ratio from the 4-hour peritoneal equilibration test and residual renal function.

Results: After switching PDF, bicarbonate and carbon dioxide were decreased significantly (26.5±2.8 vs. 24.4±2.6 mEq/L; P<0.01, 46.6±6.4 vs. 43.2±5.8 mmHg; P<0.01, respectively). Patients treated with low dose PDF (3.3±0.5 L/day) demonstrated insufficient correction of metabolic acidosis (bicarbonate 24.0±2.7 vs. 21.9±3.8 mEq/L; P<0.01) as compared with middle dose PDF (5.6±0.6 L/day, bicarbonate 26.7±2.2 vs. 23.9±2.0 mEq/L; P<0.01) and high dose PDF (7.5±1.0 L/day, bicarbonate 29.7±2.5 vs. 26.8±1.6 mEq/L; P<0.01). Whereas, other parameters did not change significantly between before and after induction of Bic/Lac PDF.

Conclusions: The new Bic/Lac PDF is effective for overcorrection of metabolic acidosis in PD patients, although it must be carefully managed in such a patient who is treated with low dose PDF.

Funding: Commercial Support - Baxter

SA-PO693

Association of Gender with the Utilization of Peritoneal Dialysis Savannah Vogel,[2] Brad C. Astor,[1] Sana Waheed.[1] *[1]University of Wisconsin, Madison, WI; [2]University of Wisconsin - Madison, Madison, WI.*

Background: Peritoneal dialysis (PD) is underutilized in the United States compared to other countries. We analyzed data from the USRDS and US census to assess the association between gender and initial dialysis modality to determine whether gender might impact PD utilization. We also investigated gender-specific associations of age, race/ethnicity, median household income and employment status on the incidence of PD.

Methods: We estimated the proportion of USRDS patients utilizing PD as their initial modality between 2000-2014, adjusting estimates to the mean value of all covariates (age, race, ethnicity, cause of ESRD, comorbidities, incidence year, income and employment status) and compared these estimates for women and men.

Results: 108,022 patients (45% women) initiated PD and 1,375,825 patients (44% women) initiated hemodialysis during this time period. Women were more likely than men (OR: 1.16, 95% CI 1.15-1.18) to utilize PD as their initial dialysis modality. Women were more likely than men to initiate PD for age <67. However, this relationship was reversed for those ≥68 years [Fig. 1]. Other factors influencing the likelihood of being on PD included black race (OR: 0.56), median household income (OR for each $10K higher: 1.03), and being employed (OR: 2.49) [Table 1].

Conclusions: Our results indicate that women in the US were more likely than men to utilize PD as their initial modality, but this association varies with age. This study emphasizes the role gender may play in medical decision making and highlights the need to further investigate the factors that influence patients of each gender to choose PD.

Table 1. Gender, race, income and employment influence the likelihood on being on PD.

	Odds Ratio	95%CI
Women/Men	1.16	1.15-1.18
Black/White	0.56	0.55-0.57
Each $10K higher in median household income	1.03	1.02-1.04
Part or full-time employed/unemployed	2.49	2.45-2.53

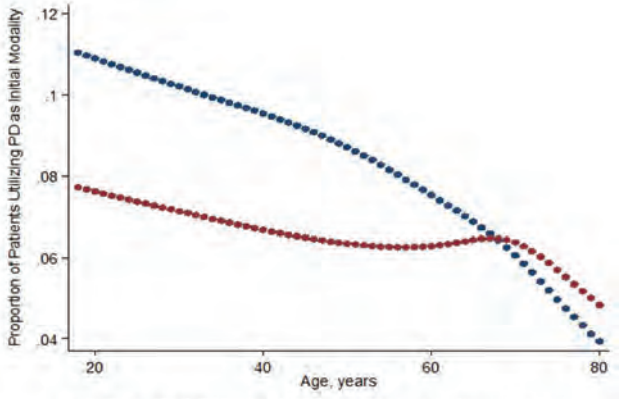


Figure 1. Incidence of PD decreases with age. Men are more likely than women to utilize PD after age 67.

SA-PO694

Engaging Stakeholders in Protocol Development for Qualitative Research on Remote Management for Peritoneal Dialysis Lalita Subramanian,[1] Rosalind H. Kirk,[2] Rachel Perlman,[3] Therese T. Adamowski,[3] Margie D. Mccall,[4] Erica E. Perry,[5] Kathy A. Restovic,[5] Lisa M. Fitzpatrick,[6] Nicole E. Bryant,[7] Rachel Tocco,[1] Kimberly Fox,[1] James A. Sloand,[8] Jeffrey Perl,[9] Ronald L. Pisoni.[1] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]Independent Qualitative Research Consultant, Edinburgh, United Kingdom; [3]University of Michigan Health Center, Ann Arbor, MI; [4]Greenfield Health Systems, Detroit, MI; [5]Stakeholder Group, Arbor Research Collaborative for Health, Ann Arbor, MI; [6]McLaren Northern Michigan, Harbor Springs, MI; [7]National Kidney Foundation-Michigan, Ypsilanti, MI; [8]Baxter Healthcare Corporation, Deerfield, IL; [9]St. Michael's Hospital, Toronto, ON, Canada.*

Background: Remote management (RM) involves various technologies designed to remotely monitor and manage a range of health conditions in order to alert healthcare professionals (HCPs) of any changes that might need follow-up. In this study, patients, social workers, nurses and nephrologists, together with researchers, developed interview and focus group guides for qualitative data collection on factors important to different stakeholders in considering RM technology for patients on peritoneal dialysis (PD).

Methods: Researchers introduced concepts and shared information on current RM technology for PD before proceeding with four brainstorming sessions with the stakeholder group on positives and negatives of RM for patients, care partners and HCPs in turn. Interviews of five HCP teams in the United Kingdom, United States and Canada using or transitioning to RM use for PD care provided insight on current technology. Concepts derived from all these sessions were categorized and mapped to domains in the COM-B framework (Figure 1).

Results: Literature, stakeholder and RM user perspectives, and a theoretical framework to explore the role of RM in modifying behavioral factors influencing PD and RM use informed the semi-structured interview and focus group guides for collecting data from patients, care partners and HCPs, as well as the study protocol.

Conclusions: This stakeholder-engaged process will increase the relevance of questions to participants and improve the quality of data collected, without the limitations of researchers' pre-conceived views on RM. Data from this study will provide deeper understanding of factors related to skill, access and motivation in PD and RM use which will inform HCPs and technology developers leading to improved care for patients.

Funding: Commercial Support - Baxter Healthcare Corporation

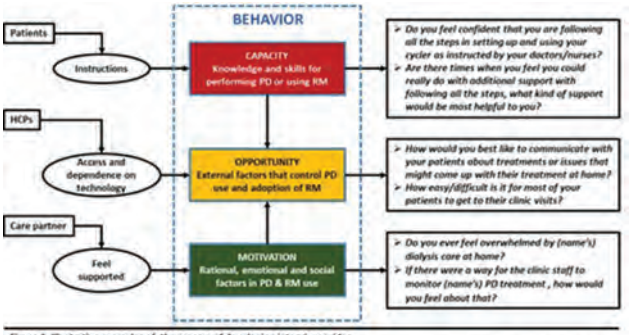


Figure 1. Illustrative examples of the process of developing interview guides.
Concepts (ovals) relevant to each stakeholder group involved in RM and PD were mapped to domains (colored boxes) of the COM-B* framework to drive questions on the respective interview guides.
*Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci 2011;6:42.

SA-PO695

Ribonucleases Defend the Peritoneum from Invading Pathogens During Chronic Peritoneal Dialysis Neha Dhingra,[1] Hanna H. Cortado,[1] Sudipti Gupta,[2] Birong Li,[1] Ashley R. Jackson,[1] Ariel Cohen,[1] Christina B. Ching,[2] John D. Spencer,[1] Rose M. Ayoob,[1] Brian Becknell.[1] *[1]Nephrology, Nationwide Children's Hospital, Columbus, OH; [2]Urology, Nationwide Childrens Hospital, Columbus, OH.*

Background: Peritonitis is a rare but serious complication in ESRD patients undergoing chronic peritoneal dialysis (PD). Improvements in standardized technique have reduced but not eliminated the incidence of peritonitis, which remains the leading cause of PD failure and change in dialysis modality. The RNase A superfamily encodes cationic antimicrobial peptides (AMPs) with broad spectrum activity against pathogens implicated in peritonitis in the PD population. Here, we evaluated the expression of these AMPs in the baseline PD effluents of pediatric ESRD patients undergoing chronic PD, in the absence of peritonitis.

Methods: PD effluent was collected from seven pediatric patients undergoing chronic cycling PD, prior to starting nightly dialysis. We also collected ascites fluid from patients with acute kidney injury undergoing paracentesis or acute PD. RNases were analyzed by immunocytochemistry, qRT-PCR Western blotting, and ELISA. RNase localization within omentum was analyzed by immunofluorescence microscopy. RNase bactericidal activity was evaluated by incubation with *Staphylococcus epidermidis*, followed by plating and colony enumeration.

Results: Viable cells recovered from PD effluent express RNase3, RNase6, and RNase7 mRNA and protein. These AMPs are present in cell-free supernatants from ascites and PD effluent, and RNase7 levels are the most abundant. Immunocytochemistry identifies RNase3+ eosinophils, RNase6+ macrophages, and RNase7+ mesothelial cells as sources of these AMPs. These RNases are distributed similarly in omentum, and RNase7 expression is detected in immortalized mesothelial cells. Functionally, recombinant peptides derived from RNase 3, 6, and 7 exhibit potent bactericidal activity toward *S. epidermidis.*

Conclusions: Multiple AMPs in the RNase A superfamily are present in peritoneal fluid of patients with ESRD undergoing PD. These AMPs have distinct cellular sources and exhibit antimicrobial activity toward *S. epidermidis*. The omentum is a source of multiple AMP producing cells, a finding with potential clinical implications given the practice of omentectomy at PD catheter insertion. Strategies aimed at preserving or enhancing RNase levels and antimicrobial activity may comprise a formidable approach to peritonitis prevention and treatment.

SA-PO696

Activation of mTORC1 Disrupted LDL Receptor Pathway: A Potential New Mechanism for the Progression of Peritoneal Fibrosis by High-Glucose PDS Liu Jing. *Institute of Nephrology, Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China., Nanjing, China.*

Background: High-glucose peritoneal dialysis solution (PDS) play important roles in the peritoneal fibrosis. Recent studies demonstrated that high glucose could promote the intracellular accumulation of cholesterol via low density lipoprotein receptor (LDLr) in peritoneal mesothelial cell (PMC), which induce the expression of extracellular

matrix protein in PMC. This study aimed to explore the potential mechanisms of the dysregulation of LDLr under the stimulation of high-glucose PDS.

Methods: Human PMCs (HMrSV5) was stimulated by high-glucose PDS. Oil red O and filipin staining were used to examine lipid accumulation. The expression of LDLr regulation, mammalian target of rapamycin complex1 (mTORC1) pathway and extracellular matrix proteins were assessed by real-time PCR and western blot.

Results: Results demonstrated that high-glucose PDS increased lipid accumulation in PMCs. These effects were correlated with an increase in LDLr transcription, which was mediated through the up-regulation of sterol regulatory element-binding protein (SREBP) cleavage-activating protein (SCAP), SREBP-2, and through enhanced translocation of the SCAP/SREBP-2 complex from endoplasmic reticulum (ER) to Golgi. In addition, our data indicated that there was a parallel increase in the expression of extracellular matrix proteins such as fibroblast specific protein-1, a-smooth muscle actin and collagen I. Further analysis showed that high-glucose PDS enhanced the protein phosphorylation of mTOR, eukaryotic initiation factor 4E-binding protein 1, and p70 S6 kinase. Interestingly, blocking mTORC1 activity inhibited the gene transcription of LDLr and decreased extracellular matrix deposition.

Conclusions: Our findings demonstrated that increased mTORC1 activity exacerbated peritoneal fibrosis by disrupting LDLr transcriptional regulation.

Funding: Government Support - Non-U.S.

SA-PO697

Effect of Lipo-PGE1 on Peritoneal Transport Function and Micro-Inflammatory State in Peritoneal Dialysis Patients Hao Zhang,[1] Jianwen Wang.[2] *[1]The Third Xiangya Hospital of Central South University, Changsha, China; [2]The third Xiangya Hospital of Central South University, Changsha, China.*

Background: Besides the low molecular weight(LMW) solutes, macromolecule such as proteins can also be transported from plasma to peritoneal cavityin peritoneal dialysis(PD). Prostaglandin E1 incorporated in lipid microspheres (Lipo-PGE1) is a potent vasodilator. It was shown to protect vascular endothelial cellsand inhibit the infiltration of inflammatory cells. The aim of this study was to investigate the effect of Lipo-PGE1 on peritoneal transport function and micro-inflammatory state in PD patients.

Methods: We recruiteda total of 89 CAPD patients in the Third Xiangya Hospital from January 2015 to January 2017. Patients were divided into 2 groups, namely the experimental group (Lipo-PGE1 group, n=46) and the control group (not treated with Lipo-PGE1, n=43). The MTACs of urea and creatinine were regarded astheindexes for the transport of LMW solutes. Peritoneal clearances of β2-microglobulin, cystatin C, and albumin were taken asthe indexes to evaluate peritoneal macromolecule transport. IL-6 appearance rate(AR)in the PD effluent, serumIL-6, and hs-CRP were the inflammatory indicators.

Results: The results in the same group before and after2-week treatment showed that: in the experimental group, peritoneal clearances of β2-microglobulin,cystatin C and albumin increased significantly(P<0.05); IL-6 AR, serum IL-6 and hs-CRP level decreased obviously (P<0.05); The MTACs of urea and creatininehave no statistical significance (P>0.05). In the control group, after 2-week treatment, all above indexes have no statistical significance (P>0.05). Thecomparison between two groups showed that: in the experimental group, peritoneal clearance of β2-microglobulin and cystatin C are significantly higher than that in the control group (P<0.05). Peritoneal clearance of albumin, MTAC urea,and MTAC creatinine are also higher than that in the control group, but with no statistically significant difference (P>0.05). IL-6 AR are obviously lower than that in the control group (P<0.05); Serum IL-6 and hs-CRP are also lower than that in the control group, but with no significant difference (P>0.05).

Conclusions: Lipo-PGE1 significantly increases peritoneal transport of macromolecules. Lipo-PGE1 can decrease inflammatory cytokines IL-6 concentration, and reduce micro-inflammatory state in CAPD patients, especially peritoneal cavity local inflammation response.

Funding: Government Support - Non-U.S.

SA-PO698

Comparison of Mesenchymal Stem Cells (MSCs) and Extracellular Vesicles (EVs) in the Treatment of Experimental Peritoneal Fibrosis Priscila Q. Gouveia, Cleonice Silva, Irene L. Noronha. *Cellular and Molecular Nephrology Lab, University of São Paulo, São Paulo, Brazil.*

Background: Long-term peritoneal dialysis is associated with the development of structural and functional changes in the peritoneal membrane, leading to fibrosis and ultrafiltration failure. Infusion of MSCs represents a potential strategy to treat fibrotic processes, due to paracrine effects. EVs released by MSCs are responsible for cell-cell interactions and possibly for the therapeutic effects of MSCs on tissue regeneration. Our aim was to compare the effects of MSCs with EV in an experimental model of peritoneal fibrosis (PF).

Methods: PF was induced in male Wistar rats by intraperitoneal (IP) injections of 0.1% chlorhexidine gluconate (CG), on alternate days for 30 days. MSCs obtained from adipose tissue were isolated and characterized by flow cytometry and *in vitro* differentiation. EVs obtained from MSCs supernatants were isolated by differential ultracentrifugation and characterized by Bradford assay, Zetasizer Nano and scanning electron microscopy. MSCs or EVs were administrated IP on days 3 and 10 after PF induction. The study groups consisted of: **Control** (n=6), normal rats receiving only vehicle (saline); **PF** (n=9), rats receiving CG injections to develop PF; **PF+MSC** (n=7), PF rats treated with $2x10^6$ MSCs and **PF+EV** (n=7), PF rats treated with 30μg EVs.

Results: Administration of MSCs or EVs prevented peritoneal thickening and ameliorated ultrafiltration. Both treatments significantly decreased the expression of genes associated with fibrosis (TGF-β, FSP-1 and SMAD3). In addition, both treatments reduced the inflammatory infiltrate and the expression of TNF-α and VEGF.

Conclusions: We conclude that MSCs and EVs are equally efficient in blocking the PF process in this experimental model of PF.

Funding: Government Support - Non-U.S.

	Control	PF	PF+MSC	PF+VE
Peritoneal Thickness(μm)	26±0	64±14 *	23±2 #	26±6 #
Ultrafiltration(mL)	13±1	3±1 *	5±1 * #	6±1 * # §
TGF-β(mRNA)	1±1	12±1 *	3±1 #	1±0 #
FSP-1(mRNA)	1±1	18±1 *	1±0 #	1±0 #
Smad-3(mRNA)	1±0	8±1 *	1±0 #	1±1 #
Macrophages(cells/mm ^{2})	106±35	404±122 *	263±49 * #	147±17 #
T-cells(cell/mm ^{2})	4±1	87±31 *	7±3 #	11±4 #
VEGF(mRNA)	1±1	21±2 *	4±3 #	2±1 #
TNF-α(mRNA)	1±1	14±1 *	1±1 #	1±1 #

*p<0.05vsControl;#p<0.05vsPF;§<0.05vsFP+MSC

SA-PO699

Patient On Line (POL) Software as Useful Tool in Assessing Nutritional Status of Peritoneal Dialysis Patients Ewa Suchowierska,[1] Beata Naumnik.[2] *[1]I Department of Nephrology and Transplantation with Dialysis Unit, Medical University of Bialystok, Poland, Bialystok, Poland; [2]Medical University of Bialystok, Bialystok, Poland.*

Background: Moderate to severe malnutrition is associated with increased risk of death in peritoneal dialysis (PD) patients. Serum albumin concentration below 3,8 g/dl is a biochemical surrogate for malnutrition. Protein loss into dialysate and urine contributes to malnutrition problems. The nPCR (normalized Protein Catabolic Rate), mentioned as protein equivalent of nitrogen appearance, is useful in assessing protein intake. Patient on Line (POL) software, calculating the adequacy parameters, is widely used to adjust therapy to patient's needs. This method involves direct measurement of 24 hour dialysate and urea appearance rate to which a value for estimated dialysate and urine protein loss is added.

Methods: We compared classical measurements such as Kt/V, CCr and nPCR (by Randerson formula) with values calculated with POL software created by Fresenius Medical Care (Bad Homburg, Germany). 20 PD patients (mean age 49 +/-14.5 yrs) were included. Measurements were done at the same time using two methods (classical and POL). LTM (Lean Tissue Mass), % LTM, FAT and % FAT were assessed by Fresenius Body Composition Monitor. Total protein, albumin, calcium and phosphate levels as well as mean dialysate and urea protein loss were assessed by routine tests. SATISTICA 10.0 was used for data analysis.

Results: Kt/V was lower than Kt/V POL (p=0.0001), CCr was higher than CCr POL (p=0.0045) and nPCR was higher than nPCR POL (p=0.0001). We observed a strong positive correlations between total protein level and Kt/V POL (r=0.69, p<0.05), CCr (r=0.56, p<0.05), CCr POL (r=0.55, p<0.05) as well as between blood urea level and nPCR calculated classically (r=0.77, p<0.05) and with POL formula (r=0.69, p<0.05). Phosphatemia was negatively correlated with Kt/V (r=-0.51, p<0.05), Kt/V POL (r=-0.62, p<0.05), CCr (r=-0.61, p<0,05) and CCr POL (r=-0.65, p<0.05).

Conclusions: POL software seems to be a better tool in assessing PD patients' nutritional status than Randerson formula, because it takes into account dialysate and urine protein loss. Kt/V POL, but not Kt/V values, positively correlated with total protein level. Phosphatemia and urea concentration were strong predictors of adequacy and nutritional parameters in PD patients.

SA-PO700

Are Peritoneal Protein Losses Related to Peritonitis Risk in Patients on Peritoneal Dialysis? Sara S. Rodrigues, Clara Santos, Ana Marta Gomes, Joao C. Fernandes. *Centro Hospitalar Vila Nova de Gaia-Espinho, Vila Nova de Gaia, Portugal.*

Background: Peritoneal protein losses (PPL) are an inevitable process on peritoneal dialysis (PD). Few studies have supported a positive correlation between PPL and infections or general morbility and mortality. The aim of this study was to investigate whether baseline PPL (bPPL) was a risk factor of peritonitis in PD patients.

Methods: We retrospectively studied all incident PD patients in our center during the last 9 years. bPPL, serum hemoglobine (Hb) and albumin (alb) and other relevant analytic and clinical data were recorded at baseline. Number and timing of peritonitis episodes were registered. Patients were distributed by 3 groups of bPPL (group 1: <4,5 gr/day, group 2: 4,5-9gr/day and group 3: >9gr/day) in order to compare their peritonitis risk.

Results: 104 patients were included, 54% male, median age: 57 years, median follow-up: 29 months. Group 3 patients had lower baseline hb and alb (p=0.03 and p 0.02). Higher bPPL patientes had a greater chance of having at least one peritonitis (group 3:72%, group 2:69%, group 1:39%, p=0.02) and removal of the PD catheter by PD related infection was higher (group 3:74%, group 2:47%, group 1:19%, p=0.01). bPPL was shown to be an independent predictor after adjustment for age, sex and diabetes (p=0.02). Time until the first peritonitis was shorter in higher bPPL groups (p=0.02) and, after adjustment for covariates, group 3 maintained a significant higher risk of peritonitis over group 1 (*HR* 2.38, p=0.04). bPPL and age significantly increased the absolute number

of peritonitis during the follow-up (p=0.03 and p=0.02). No difference was observed in mortality as well as in the occurrence of severe non-PD related infections between groups.

Conclusions: Higher bPPL were able to independently predict risk for peritonitis, reflecting its impact on the morbidity of PD patients. The association between higher bPPL with lower basal serum alb and hb may highlights the hypothesis that bPPL can be a marker of disease severity at the onset of PD, possibly being related to a malnutrition and pro-inflammatory state. It would be useful to explore these effects prospectively and understand the underlying mechanisms in future. This could include a better characterization of the type of protein loss and its quantification of immunoglobulins, which could theoretically explain the higher infectious risk.

SA-PO701

Effect of Peritoneal Dialysis on Cardiac Functional Parameters in Patients with Congestive Heart Failure Andreas Bozikas,[1] Panagiotis Pangidis,[1] Fotini Lazaridou,[2] Eleni Kitoukidi,[1] Iliana Kiriakoutzik,[1] Theotokis Kaltzidis,[2] Pinelopi Pisanidou,[1] Stella Vakiani,[1] Antigoni Martika,[1] Nikolaos Georgilas,[1] Ioannis Tsounos,[2] Sofia Spaia.[1] *[1]Nephrology, General Hospital of Thessaloniki "Agios Pavlos", Thessaloniki, Greece; [2]Cardiology, General Hospital of Thessaloniki "Agios Pavlos", Thessaloniki, Greece.*

Background: Limited data support that peritoneal dialysis (PD) applied in patients (pts) with congestive heart failure (CHF), resistant to diuretic therapy, results in significant improvement of their status. We examined the long term effect of PD, as a continuous ultrafiltration treatment to pts with CHF, NYHA stage IV & Renal Disease stage > IIIb on cardiac functional parameters. We have applied a detailed Cardiac Echo (CE) examination in an effort to identify markers to distinguish population that might benefit of early PD application.

Methods: We enrolled 18 pts (mean age 80.3 years) in PD. Inclusion criteria were NYHA IV class symptoms & deterioration of renal function. Monthly complete biochemical workup & assessment of the cardiac function by (CE) on initiation of PD & 6-12 months later. We recorded the Ejection Fraction (LVEF), Relative Wall Thickness (RWT), Left Ventricular Mass Index (LV), E/E', Left Atrium Volume Index (LA), Pulmonary Artery Systolic Pressure (PASP), Tricuspid Annular Plane Systolic Excursion (TAPSE).

Results: Mean time on the method was 10.1 (6-12) months. We observed body weight decrease (p=0.0083), improved eGFR (p=0.026), decrease of bilirubin levels (p=0.0475), substantial decrease of diuretics, as well as elimination of hospitalizations due to CHF decompensation & remarkable improvement of NYHA class. Significant reductions of LA and LV (p<0.05) were noted in every patient. The rest of the parameters remained unaffected. LVEF showed equivocal changes. One pts died on the 8th month of therapy due to sudden death.

Conclusions: All pts demonstrated clinical improvement of their living status, as a result of the gradual & continuous removal of excess fluid. Therefore, dramatically diminishing hospitalizations, due to cardiac events, & restoring pts autonomy. Furthermore, there was an improvement of left cardiac function. However, markers of right cardiac function did not change, probably due to technical or individualized causes. For the same reasons interpretation of LVEF changes is ambiguous & cannot be used as an objective marker to identify this population. The results of this prospective, but small sized, study encourage the application of PD in selected pts with CHF.

SA-PO702

Glucose Metabolism as Part of Metabolic Syndrome in Non-Diabetic PD Patients: Results from PD-CRAFT Mark Lambie,[1,2] Simon J. Davies.[1,2] *[1]Keele University, Crewe, United Kingdom; [2]University Hospital of North Midlands, Stoke-on-Trent, United Kingdom.*

Background: Dialysate glucose loading has been associated with an increase in metabolic syndrome in ethnically Chinese patients however the impact on other populations is not clear, and neither is the impact on systemic glucose metabolism.

Methods: This was a cohort study of prevalent patients on peritoneal dialysis in 39 centres in the UK. Whole blood samples were stored in the BioCentre and transferred to a central laboratory for glycated haemoglobin assays. Waist circumference was measured with dialysate in situ, and other demographic and clinical measures were stored in a bespoke database (PDDB). Adjusted analysis was by linear regression models, with backwards selection of variables.

Results: 628 non-diabetic patients were included but 26 patients with values >8.0% were excluded from further modelling. There was a median glycated haemoglobin of 5.7% (IQR 5.4-6.0). There was no significant correlation between glycated haemoglobin and dialysate glucose load (-0.08). Correlations with individual components of metabolic syndrome were absent/weak (body mass index 0.05, triglycerides 0.09, HDL cholesterol -0.06) apart from waist circumference (0.17). Results for random plasma glucose levels were similar to glycated haemoglobin. In multivariable modelling there was strong evidence for an effect of age, and decreasing strength of evidence for an association with triglycerides, waist circumference and ischaemic heart disease with no evidence for other variables including dialysate glucose load. The multivariable model had an adjusted R-squared value of 0.18. Waist circumference provided a better model than body mass index (Δ-2LL=3.58).

Conclusions: There does not appear to be any significant association between glycated haemoglobin and dialysate glucose load in non-diabetic PD patients. This could be partly because the variability in glycated haemoglobin is poorly explained by other aspects of metabolic syndrome.

SA-PO703

Determinants of Carnitine and Acetylcarnitine in Peritoneal Dialysis Patients: Results from PD-CRAFT Mark Lambie,[1,2] Simon J. Davies.[1,2] *[1]Keele University, Crewe, United Kingdom; [2]University Hospital of North Midlands, Stoke-on-Trent, United Kingdom.*

Background: In haemodialysis (HD) patients carnitine metabolism plays an important role in lipid metabolism and oleoylcarnitine levels independently predicted death. The role of carnitine in peritoneal dialysis patients is less clear.

Methods: PD-CRAFT is a cross-sectional observational study of 1349 UK prevalent PD patients. A substudy of 961 patients included blood samples taken at the time of data collection assayed for carnitine (C0) and acetylcarnitine (C2) levels with mass spectroscopy. Linear mixed modelling accounting for clustering by centre with backwards variable selection was used in multivariable modelling of log-transformed C0 and square root transformed C2 levels.

Results: The population was representative of the UK PD population (mean age 59.2 years, 65% male, 27% diabetic and median duration of PD 9 months). C0 and C2 had median levels of 23.7 (IQR 26.4-32.1) and 15.5 (IQR 9.7-22.5) respectively. Higher C0 levels were associated with male gender (0.17, 95%CI 0.04, 0.31), lower LDL-cholesterol (-0.07, 95%CI -0.12, -0.01) and not using Icodextrin (0.23, 95%CI 0.09, 0.37). Higher C2 levels were associated with male gender (0.19, 95%CI 0.005, 0.38), lower plasma albumin levels (-0.030, 95%CI -0.049, -0.011), higher BMI (0.030, 95%CI 0.014, 0.047), use of APD (0.22, 95%CI 0.02, 0.42) and not using Icodextrin (0.31, 95%CI 0.10, 0.51). The associations with Icodextrin and use of APD persisted when adjusted for dialysate glucose load and peritoneal solute transport.

Conclusions: Higher carnitine levels were associated with reductions in LDL-cholesterol in PD patients. The gender difference in carnitine levels described previously in the general population persists in PD. The association between C2 and use of APD replicates a previous smaller study, whilst the consistent and robust association between both C0/C2 and Icodextrin could reflect either a direct effect or indirect via reduced dialysate glucose loading over a prolonged period.

SA-PO704

Candida glabrata Fungal Peritonitis in a Peritoneal Dialysis Patient: A Case Report Sina Emami,[2] Susie Q. Lew.[1] *[1]George Washington University Medical Center, Washington, DC; [2]George Washington university, MClean, VA.*

Background: Fungal peritonitis is a rare but serious complication in patients undergoing peritoneal dialysis (PD), and is associated with high morbidity and mortality. Fungal peritonitis accounts for 3% - 6% of all PD-associated peritonitis episodes. The most common cause of the disease is Candida, predominately C. albicans, and C. parapsilosis. C. glabrata peritonitis has not been reported in the United States. The main factors associated with the development of fungal peritonitis include previous antibiotic therapy (particularly for bacterial peritonitis), fungal overgrowth in the gastrointestinal track, and declining peritoneal defenses because of peritonitis. A major obstacle in C. glabrata infection treatment is their innate resistance to azole antimycotic therapy, which is very effective in eradicating infections caused by other Candida species.

Methods: A 74-year-old female with a history of diabetes, hypertension and end stage renal disease on peritoneal dialysis with multiple previous episodes of bacterial peritonitis presented with signs and symptoms typical of peritonitis. Empiric antibiotic therapy with intraperitoneal ceftriaxone and vancomycin was initiated to treat peritonitis. Following identification of yeast on the Gram stain, oral fluconazole therapy was started. The culture was identified as Candida glabrata resistant to fluconazole, itraconazole and voriconazole. Oral fluconazole was switched to micafungin and the PD catheter was removed. Micafungin 100 mg IV every 24h was administered for a total 15 days. She transitioned to in-center HD. Although she wanted to return to PD, the team thought she was not a good candidate due to her age and home situation.

Results:

Conclusions: The approach to fungal peritonitis has changed considerably in recent years. The conventional antifungal regimens include fluconazole, amphotericin B, and flucytosine alone or in combination, optimally based on fungal sensitivities. Anti-fungal agents generally continue for at least 2 weeks after catheter removal. Observational studies suggest that prompt catheter removal probably improves outcome and reduces mortality. The newer agents such as caspofungin, micafungin and voriconazole have the potential to alter treatment strategies for fungal peritonitis, but further studies are required to clarify the precise role of these agents in this patient cohort.

SA-PO705

Right versus Left Insertion of Peritoneal Dialysis Catheters in ESRD Patients by Open Surgical Technique Jin ho Lee,[3,4] Seon Deok Hwang,[4,5] Hee yeoun Kim,[3] Dongyeol Lee,[3] Joon Seok Oh,[2] Yong hun Sin,[1] Joong Kyung Kim.[2] *[1]Bong Seng Hospital, Busan, Republic of Korea; [2]Bong Seng Hospital, Korea, Dong-gu, BUSAN, Republic of Korea; [3]Bong Seng Memorial Hospital, Busan, Republic of Korea; [4]None, Pusan, Republic of Korea; [5]Inha University College of Medicine, Incheon, Republic of Korea.*

Background: The open surgical technique is a traditional and old method of peritoneal dialysis catheter(PDC) insertion. Left-sided insertion is the same direction as peristalsis, thus reducing the frequency of malposition. However, if surgery is not possible to the left side or suspected adhesion due to previous major surgery, it can be inserted to

the right side. In this study, we compared left-side and right-side insertions of peritoneal catheter by surgical technique.

Methods: We retrospectively compared the right approach for PDC insertion by open surgical technique with the left approach. From June 2013 to September 2016, 69 of the catheters were successfully inserted Rt. side and 79 of catheters were inserted Lt. side. Primary outcome was catheter survival. Secondary outcome were peritonitis free survival and exit site infection free survival.

Results: The mean(±SD) age of patients was 63 ± 12 years, the ratio of male to female is 42.6% vs. 57.4%. Of all patients, 55.1% of patients have diabetes and 70.7% have hypertension. The repositioning operation due to malposition was 2 of 66(3%) in Rt. side insertion(RSI) and 3 of 76(3.8%) in Lt. side insertion(LSI)(p=0.30). Exit infection was 6 of 66(9.1%) in RSI and 4 of 76(5.1%) in LSI(p=0.513). Peritonitis was 15 of 66(22.7%) in RSI and 13 of 76(16.5%) in LSI (p=0.401). The catheter survival was not statistically significant for RSI compared to LSI(p=0.126). Catheter survival(Fig.1) and exit site infection free survival were not different between two groups(p=0.432). However, peritonitis free survival of RSI was significantly higher than LSI(p=0.020)(Fig.2).

Conclusions: When the peritoneal dialysis catheter was inserted by open surgical technique, catheter survival was not inferior to the left side insertion on the right side insertion. In addition, peritonitis free survival showed statistically superior results in the right side insertion.

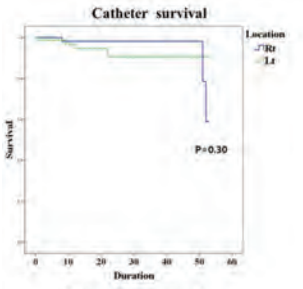


Fig.1 Catheter survival

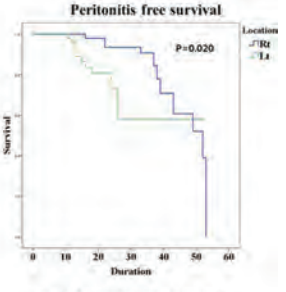


Fig.2 Peritonitis free survival

SA-PO706

The Choice of Urgent-Start Peritoneal Dialysis versus Hemodialysis through a Tunneled Central Venous Catheter: A Single Center Experience in the United States Delin Wang, Eric S. Kerns, Jonah Licht, Susie L. Hu. *Division of Kidney Disease and Hypertension, Brown University, Providence, RI.*

Background: Peritoneal dialysis (PD) has been underutilized for patients with unplanned need for initiation of renal replacement therapy compared to hemodialysis (HD) through a tunneled central venous catheter (CVC) in the United States.

Methods: We examined outcomes related to urgent start PD versus HD (with a tunneled CVC) in a retrospective cohort of 47 adults who required urgent dialysis initiation from January 2015 to December 2016. Those who are unstable with critical illness were excluded. In addition to baseline demographics and comorbidities, we compared dialysis access related complications and total number of procedures required related to dialysis modality selection. Comparisons were performed using t-test for linear variables, and chi-square test for categorical variables.

Results: 28 patients had tunneled CVC placed for HD and 19 patients had PD catheter placed. Mean follow-up was 60 months for HD patients and 46 months for PD patients. The PD group was significantly younger, with less heart failure, more hypertension, and higher pre-dialysis serum creatinine (Table). 75% of patients who underwent HD with a tunneled CVC versus 47% who performed urgent start PD had any access related procedures.

Conclusions: The complication rate related to dialysis modality choice between urgent start PD and HD with a tunneled CVC is similar. There was a trend towards fewer procedures required for urgent start PD and should be more commonly considered for those requiring dialysis urgently.

Comparisons between urgent start PD and HD

	HD	PD	P-value
Age (years)	60 ± 15	46 ± 17	0.007
Follow-up duration (months)	60	46	0.85
Potassium (mEq/L)	4.8 ± 0.9	4.3 ± 0.7	0.05
HCO3 (mEq/L)	19 ± 4	18 ± 4	0.64
BUN (mg/dL)	97 ± 41	111 ± 38	0.25
Creatinine (mg/dL)	8.1 ± 4.7	12.0 ± 6.1	0.01
Coronary artery disease (%)	39	16	0.08
Congestive heart failure (%)	43	5	0.005
Hypertension (%)	89	95	0.01
Diabetes mellitus (%)	57	21	0.51
Access-related procedures (%)	75	47	0.05

SA-PO707

Impact of Medicare Bundled Payment on Provision of Peritoneal Dialysis among Existing versus New Dialysis Providers Virginia Wang,[1,2] Cynthia Coffman,[1,2] Linda L. Sanders,[1] Richard A. Hirth,[3] Shoou-Yih D. Lee,[4] Matthew L. Maciejewski.[1,2] *[1]Duke Univ, Durham, NC; [2]Durham VAMC, Durham, NC; [3]U of Michigan, Ann Arbor, MI; [4]UNC-Chapel Hill, Chapel Hill, NC.*

Background: One of the goals of Medicare's 2011 implementation of ESRD bundled payment is to encourage greater peritoneal dialysis (PD) provision among providers. Service strategies may differ between facilities operating prior to bundled payment proposals in 2005 versus new entrants in the dialysis market. We examine the differential response to dialysis payment reform on PD service availability among existing versus new dialysis providers.

Methods: We used the USRDS and Medicare data to construct a longitudinal cohort of US outpatient dialysis facilities in 2006-2013 and identified facilities operating before 2005 (existing) and opening after 2005 (new). Our outcome of interest was facility-level offering of PD service. We applied generalized estimating equations to examine whether the 2011 policy effect on PD services differed between existing and new facilities, adjusting for facility and regional ESRD and general demographic characteristics.

Results: Of 6,194 dialysis facilities operating in 2006-2013, 70.5% were in operation before 2005 and 29.5% were new facilities. Over time PD provision modestly increased from 37% of facilities with PD in 2006 to 42% in 2013. Similar rates of existing and new facilities offered PD (38.6% vs. 39.8%), but there was a greater presence of new facilities exclusively offering home-based dialysis (1.9% of existing vs. 7.4% of new). In adjusted analysis, PD provision was greater after bundled payment ($p<0.001$), but there were no pre-post policy differences between existing and new facilities ($p=0.67$). PD services differed for new vs. existing by urban location: PD in existing facilities was similar but new, urban facilities offered PD at higher rates than new, non-urban facilities ($p<0.001$). Existing and new facilities differed in their relationship between facility size and PD provision, with a slower rate of PD provision by increasing facility size for new facilities ($p=0.009$).

Conclusions: Existing and relatively new entrants to the US dialysis market differ in their service strategies when it comes to PD services. However, existing and new dialysis providers responded similarly to the 2011 bundled payment reform.

Funding: NIDDK Support

SA-PO708

Peritoneal Dialysis Modality Is Independently Associated with Salty Taste Impairment in Patients with ESRD Miki Torigoe,[1] Yoko Obata,[1] Kenta Torigoe,[1] Takashi Harada,[2] Satoshi Funakoshi,[2] Tomoya Nishino.[1] *[1]Department of Nephrology, Nagasaki University Hospital, Nagasaki, Japan; [2]Nagasaki Renal Center, Nagasaki, Japan.*

Background: In chronic kidney disease (CKD) patients, it is reported that the gustatory threshold for salty taste is increased, and its increase is associated with excessive oral salt intake and result in high blood pressure or volume overload. However, little is known about the relationship between the patients with end-stage renal disease (ESRD) requiring renal replacement therapy and the gustatory threshold for salty taste. The aim of this study was to assess the gustatory threshold for salty taste and clarify relevant factors in ESRD patients.

Methods: In this cross-sectional study, we enrolled 29 healthy volunteers and 79 dialysis patients (22 peritoneal dialysis (PD) patients, 57 hemodialysis (HD) patients) in Nagasaki University Hospital and Nagasaki Kidney Center in Japan. For the assessment of gustatory threshold for salty taste, we used a salt-impregnated taste strip, Salsave® (Advantech Tokyo Co, Tokyo, Japan) which are impregnated various salt concentrations (0.6, 0.8, 1.0, 1.2, 1.4 and 1.6 mg/cm^2). The clinical data were collected from electronic medical records and we analyzed risk factors of salty taste impairment.

Results: Compared with healthy volunteer, prevalence of salty taste impairment (recognition threshold of salt at ≧1.0 mg/cm^2 concentration) was higher in ESRD patients (3% vs 58% $p<0.001$). Among ESRD patients, rate of PD modality was higher in salty taste impaired group (37.0% vs 15.6% $p=0.04$). Moreover, in multiple logistic regression adjusting for age, gender, sex, duration of dialysis, serum zinc, C-reactive protein and KT/V, PD modality was independently associated with salty taste impairment (Odds ratio 8.0, 95% confidence intervals 1.1 – 57.4, $p=0.04$). Among PD patients, the gustatory threshold for salty taste was positively correlated with serum creatinine ($\rho=0.44$, $p=0.04$), serum β_2-microglobulin ($\rho=0.63$, $p=0.002$) and transferrin saturation ($\rho=0.50$, $p=0.02$), negatively correlated with 24-hour urine volume ($\rho=-0.50$, $p=0.02$) and residual renal KT/V ($\rho=-0.55$ $p=0.01$).

Conclusions: This study demonstrated that prevalence of salty taste impairment was higher in ESRD patients, and PD modality was independently high risk of salty taste impairment. Moreover, the gustatory threshold for salty taste was negatively correlated with residual renal function in PD patients.

SA-PO709

Non-Infectious Peritoneal Dialysis Exit Site Rash: Unusual Case Report and Review of Literature Srilakshmi Ravula,[3] Mohammed M. Siddiqui,[1] Omar Rabadi,[4] Manisha Singh.[2] *[1]Little Rock, AR; [2]University of Arkansas For Medical Sciences, Little Rock, AR; [3]University of Arkansas Medical Center, Little Rock, AR; [4]University of Arkansas for Medical Sciences, Little Rock, AR.*

Background: Peritonitis is one of the leading causes of morbidity in patients on peritoneal dialysis(PD). Exit site infections(ESI) can cause six-fold increase in the risk of peritonitis. Exit site infection is characterized by purulent drainage, erythema, pain and swelling at PD catheter site. On review of literature case reports of non-infectious exit site rash are found to be rare, hence we are reporting this case of PD exit site non-infectious rash that was finally diagnosed as granuloma gluteal adultorum.

Methods: A 74-year-old white man with ESRD from diabetes on CCPD(continuous cycler assisted PD) presented with localized area of redness, itching and serous drainage around PD catheter site measuring 1x1cm. The lesion was noticed week ago that progressively worsened. He denied trauma to catheter site, pain, fever or cloudy effluent. He was compliant with exit site care instructions and was using mupirocin ointment as part of catheter care regimen, denied changes in medications or povidone iodine use. On exam, abdomen was soft and no purulent drainage was expressed from exit site. PD fluid cell count ruled out peritonitis. Exit site cultures were obtained & keflex was started. On follow up exam, it was noted that areas of skin desquamation had gotten worse with increased itching. Dermatology was consulted and shave skin biopsy was done. Histopathological findings were consistent with spongiotic dermatitis with eosinophils, diagnosis of granuloma gluteale adultorum was made. Topical zinc oxide was prescribed in addition to continuing topical antibiotic therapy. Patient had significant improvement in one week. As discussed, erythema with pain and purulent discharge are hallmarks of ESI. There have been very few case reports published reviewing non-infectious PD site dermatitis.

Results:

Conclusions: ESI is a differential for catheter site erythema, pain and discharge. Empiric treatment with antibiotics is warranted. Prompt dermatological assessment and skin biopsy should be considered if there is no resolution of symptoms.

Review of Case Reports

Authors et al	Agent Identified	Description of Rash	Management
Elvira O. Gosmanova	Gentamicin-induced contact dermatitis	Ovoid crusted plaque with peripheral rim of erythema	Stopped gentamicin cream and switch to Mupirocin
Yavascan O	Povidone Iodine	Patchy, linear erythema	Daily Application of Normal Saline
Chasset F	Povidone Iodine	Bullous Eruption	Switch betadine to chlorhexidine
Roland Schmitt	Octenisept	Expanding erythematous rash	Avoid allergen
Satoshi Kurihara	Silicone Rubber	Eczematous skin rash	Antihistaminic ointment

SA-PO710

Metformin Ameliorates the Phenotype Transition of Peritoneal Mesothelial Cells and Peritoneal Fibrosis via a Modulation of Oxidative Stress Duk-Hee Kang,[1] Hyun-Jung Kang,[4] Eun sun Ryu,[3] Dal-ah Kim.[2] *[1]Ewha University College of Medicine, Seoul, Republic of Korea; [2]Ewha Womans University Medical Center, Seoul, seoul, Republic of Korea; [3]Ewha Womans University School of Medicine, Seoul, Republic of Korea; [4]Ewha Womans University, Seoul, Republic of Korea.*

Background: Phenotype transition of peritoneum is an early mechanism of peritoneal fibrosis. Metformin, 5'-adenosine monophosphate-activated protein kinase (AMPK) activator, has recently received a new attention due to its preventive effect on organ fibrosis and cancer metastasis by inhibiting epithelial-to-mesenchymal transition (EMT)

Methods: EMT was evaluated by morphological changes of human peritoneal mesothelial cells (HPMCs) and the expressions of E-cadherin and α-SMA by real time PCR, WB and ICC. ROS generation was assessed by DCF-DA staining, NOX activity, NOX mRNA expressions, and MitoSox^{R} staining. Activation of Smad2/3, MAPK, GSK-3β phosphorylation, nuclear translocation of β-catenin and snail expression were assessed. The effect of AMPK gene silencing or AMPK inhibitor on peritoneal EMT was evaluated. Animal model of peritoneal dialysis was established by daily infusion of 4.25% glucose-based dialysate for 8 weeks via intraperitoneal catheter. Effects of metformin (50 mg/kg/day, ip) on EMT, peritoneal thickening and an expression of markers of oxidative stress were investigated.

Results: TGFβ1 (1 ng/mL)-induced EMT in HPMC was ameliorated by metformin. Metformin (1 ng/mL) alleviated NOX - and mitochondria-mediated ROS production with an increase in superoxide dismutase (SOD) activity and SOD2 expression. Metformin inhibited the activation of Smad2/3 and MAPK, GSK-3β phosphorylation, nuclear translocalization of β-catenin and Snail. Effect of metformin on TGFβ1-induced EMT was ameliorated by either Compound C (20 μg/mL) or AMPK gene silencing. Another AMPK agonist, 5-amino-1-β-D-ribofuranosyl-imidazole-4-carboxamide (10 μM) partially blocked TGF-β1-induced EMT. In animal model of PD, intraperitoneal metformin decreased the peritoneal thickness and EMT with an increase in ratio of reduced to oxidized glutathione and the expression of SOD whereas it decreased the expression of nitrotyrosine and 8-hydroxy-2'-deoxyguanosine

Conclusions: A modulation of AMPK in peritoneum can be a novel tool to prevent peritoneal fibrosis by providing a favorable oxidant/anti-oxidant milieu in peritoneal cavity and ameliorating phenotype transition of peritoneal mesothelial cells

SA-PO711

Novel Score to Predict the Risk of Loss of Technique at 3 Months in Patients with Peritonitis Associated with Peritoneal Dialysis Monica C. Jimenez cornejo,[1] Daniel Murillo brambila,[1] Jonathan Chavez,[1] Karina Renoirte,[1] Gabriela J. Abundis Mora,[1] Ricardo Rubio,[1] Hernando Amezcua,[2] Guillermo Garcia-Garcia.[1] *[1]Hospital Civil De Guadalajara, University of Guadalajara, Guadalajara, Mexico; [2]IMSS, Zapopan, Mexico.*

Background: CKD is a major public health problem in Mexico, the incidence of CKD G5 reach 377 patients pmh, the most frequent modality of RRT is PD. Peritonitis is the most frequent cause of technique failure.

Methods: A descriptive, prospective study of 116 PD patients with peritonitis, we determinate by multivariate analysis the risk factors associated with loss of peritoneal technique at 3 months of onset of peritonitis Data are shown in numbers, percentages, mean, standard deviation, chi square, according the magnitude of the OR we develop a numeric scale, a ROC curve was done to determinate the AUC of the best cut-off point to predict loss of peritoneal technique at 3 months of the onset of peritonitis.

Results: A total of 116 episodes of peritonitis were recorded, fifty-two (45%) of them resulted in technique failure. Factors independently associated with increased risk were: diarrhea (OR =3.0, P = 0.023), >1000 white cells in PD fluid (OR =1.98, P = 0.006), turbid DP fluid (OR = 5.0, P = 0.032), time in PD (OR=3.6 P=0.014) and first episode of peritonitis (OR =4, P = 0.002). Severity score was set as low risk (≤ 5 points) and high risk (≥6 points). The incidence of technique failure in the first 3 months occurs more often in high-risk patients (OR 7.2 IC95% 1.2 to 2.3, P <0.001), the AUROC was 0.686, sensitivity 70% and specificity 32%

Conclusions: In patients with peritonitis associated with PD, a simple score including clinical and laboratory data available on admission may predict the risk of technique failure in the next 3 months; this finding may assist clinician to ensure a close follow-up of the patient at high-risk and anticipate possible outcomes.

Funding: Other U.S. Government Support, Government Support - Non-U.S.

Table 1: Baseline characteristic

	Total n=116	No technique failure < 3 meses (gruop A) n= 63	Technique failure < 3meses (gruop B) n=53	A vs B P
Male. (%)	74(63.8)	43(68.3)	31(58.5)	0.27
Age (a)				0.88
18 - 30 (a). (%)	55(47.4)	29(46)	26(49.1)	0.74
31 - 60 (a). (%)	40(34.5)	23(36.5)	17(32.1)	0.61
> 60 (a). (%)	21(18.1)	11(17.5)	10(18.9)	0.84
Diabetes. (%)	42(36.2)	20(31.7)	22(41.5)	0.27
Hypertension. (%)	89 (76.7)	48 (76.2)	41(77)	0.88
Fever				0.66
37.5 (%)	55(47.4)	33(52.4)	22(41.5)	0.24
37.6-38.5 (%)	46(39.7)	26(41.3)	20(37.7)	0.69
>38.5 (%)	15(12.9)	4(6.3)	11(20.8)	**0.021**
Pain scale > 7 (%)	56(48.3)	28(44.4)	28(52.8)	0.36
Diarrhea (%)	80(69)	37(58.7)	43(81.1)	**0.009**
Episode of peritonitis				**0.001**
first(%)	46(39.7)	34(54)	12(22.6)	**0.001**
Second. (%)	42(36.2)	20(31.7)	22(41.5)	0.27
Third (%)	28(24.1)	9(14.3)	19(35.8)	**0.007**
Turbid DP fluid. (%)	72(62.1)	29/46	43(81.1)	**<0.001**
Time in DP > 6 months. (%)	77(66.4)	34(54)	43(81.1)	**0.002**
DPCA	25 (21.6)	16 (25.4)	9 (16.9)	0.27
White cells in DP fluid (%)				**0.001**
250.(%)	9(7.8)	9(14.3)	0	**0.004**
250-500.(%)	20(17.2)	15(23.8)	5(9.4)	0.041
500-1000.(%)	27(23.3)	15(23.8)	12(22.6)	0.88
>1000.(%)	60(51.7)	24(38.1)	36(67.9)	**0.001**

SA-PO712

JAK1/2 Inhibitor and/or Losartan Preserved Long-Term Peritoneal Membrane Structure/Function during Intraperitoneal Instillation of Dialysate in Polycystic Rats Pei Zhang,[1,2] Kana N. Miyata,[1] Sharon G. Adler,[1] Janine A. La page,[1] Cynthia C. Nast,[3] Tiane Dai.[1] *[1]Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA; [2]The First Affiliated Hospital of Anhui Medical University, He Fei, China; [3]Cedars-Sinai Medical Center, Los Angeles, CA.*

Background: Peritoneal dialysis (PD) is limited by reduced efficacy over time. Early peritoneal membrane (PM) injury is characterized by inflammation which progresses to hypervascularity and fibrosis. JAK/STAT signaling mediates inflammatory pathways, including angiotensin signaling. We test whether a JAK1/2 inhibitor (JAK1/2i) and/or an ARB maintains PM structure/function in rats with polycystic kidneys (PCK) chronically infused with 4.25% Dianeal x 16 wks.

Methods: PCK rats were used. Dialysate infusions were performed BID via an implanted subcutaneous port in the neck tunneled to the intraperitoneal cavity. The following treatments were administered: **(1)** No surgery/infusions; **(2)** 0.9% Saline; **(3)** 4.25% Dianeal; **(4)** 4.25% Dianeal + JAK1/2i (5mg/kg BID); **(5)** 4.25% Dianeal +

Losartan (5mg/kg BID); and **(6)** 4.25% Dianeal + Losartan +JAK1/2i (5mg/kg BID each). Peritoneal equilibration testing (PET) measured peritoneal function by calculating initial dialysate glucose at time 0 (D_0) and measuring it 90 minutes after dialysate infusion (D). Parietal peritoneum submesothelial compact zone (SMCZ) width was morphometrically measured in ≥ 60 sections/rat. Data were analyzed by one-way-ANOVA followed by Tukey test. Results are mean±SEM.

Results: Widened SMCZ in Gps 1-3 was due to fibrosis. Fibrosis was reduced in all 3 treatment groups, with the greatest effect in the JAK1/2i group. D/D_0 glucose measurements showed functional impairment in rats receiving Dianeal, with function maintained in all 3 treatment groups similarly (Table). *P<0.05, #P<0.01.

Conclusions: Summary. Treatment with JAK1/2i, losartan, and both preserved peritoneal structure/function during long-term 4.25% Dianeal exposure. Morphologic protection was superior in the JAK1/2i alone group. **Conclusion.**Long-term JAK1/2i and/or losartan intraperitoneal treatment preserves peritoneal integrity by limiting peritoneal fibrosis and functional decline. Angiotensin inhibition is advocated to maintain residual renal function. These data show that ARBs also protect peritoneal structure/function.

Funding: Other NIH Support - NIH/National Center for Advancing Translational Science (NCATS) UCLA CTSI Grant Number UL1TR000124; Renal Research Institute Grant Number 31197, Private Foundation Support

	Control (n=3 rats)	Normal Saline (n=3 rats)	4.25% Dianeal (n=4 rats)	4.25% Dianeal +JAK1/2i (n=4 rats)	4.25% Dianeal +losartan (n=4 rats)	4.25% Dianeal +JAK1/2i+losartan (n=4 rats)	p
SMCZ thickness [µm]	57.63±14.40	54.46±17.51	88.17±33.18	35.80±13.83	54.37±12.31	49.81±13.77	<0.05
D/Do glucose	0.33±0.02	0.31±0.03	0.24±0.05	0.35±0.03	0.33±0.00	0.33±0.00	0.002

SA-PO713

Protein Kinase C Isoforms Alpha and Beta Are Differentially Regulated in Glucose-Mediated In Vivo and In Vitro Peritoneal Dialysis Michael S. Balzer,[1] Sibylle Von Vietinghoff,[1] Yulia Kiyan,[1] Hermann G. Haller,[1] Nelli Shushakova.[2] *[1]Hannover Medical School, Hannover, Germany; [2]Nephrology and Hypertensiology, 30625 Hannover, Germany*.

Background: Damage to the peritoneal membrane (PM) during peritoneal dialysis (PD) comprises inflammatory, neoangiogenetic and fibrotic processes. In a PD mouse model, we have previously demonstrated glucose-mediated pro-inflammatory, pro-fibrotic and pro-angiogenic properties of protein kinase C (PKC)-alpha, which is the dominant mesothelial PKC isoform. Preliminary data suggest regulation of PKC-alpha by PKC-beta at the PM. The specific role of PKC-beta and especially its main source in glucose-mediated PM damage are not clear.

Methods: For in vivo PD, PKC-beta KO and WT mice were subjected to a catheter-delivered, high glucose-mediated PM damage model (once daily with 4.25% glucose for 5 weeks) and analyzed for structural and functional PM changes. Peritoneal effluents were analyzed for cellular and cytokine composition. PKC-beta expression was analyzed in omentum, mesothelial cells and macrophages of WT animals. For in vitro PD, both immortalized mouse peritoneal mesothelial cells (MPMC) and primary mouse peritoneal macrophages were stimulated with different glucose concentrations and studied for cytokine and PKC expression.

Results: In comparison to WT mice, PKC-beta KO mice undergoing PD demonstrated a stronger fibrotic and angiogenetic phenotype with higher peritoneal TGF-beta production, larger fibrotic areas and increased peritoneal VEGF and CD31 expression. PKC-beta deficiency in vivo increased peritoneal IL-6, TNF-alpha, MCP-1 and MIP-2 levels as well as PM inflammatory cell influx. In contrast to mesothelium, PKC-beta is the predominant conventional PKC isoform in peritoneal macrophages, which was further up-regulated by high glucose. After LPS stimulation PKC-beta KO peritoneal macrophages demonstrated increased production of pro-inflammatory cytokines IL-6, TNF-alpha and MCP-1and drastically decreased production of anti-inflammatory cytokine IL-10 compared to WT cells.

Conclusions: PKC-beta, the dominant mesothelial PKC isoform in peritoneal macrophages, is up-regulated and exerts peritoneal anti-inflammatory effects during PD through regulation of the dominant mesothelial PKC isoform PKC-alpha. PKC-beta deficient animals present a macrophage phenotype in response to in vivo PD.

Funding: Veterans Affairs Support, Government Support - Non-U.S.

SA-PO714

Protein Kinase C Isoforms Alpha and Beta Are Differentially Regulated in Glucose-Mediated In Vivo and In Vitro Peritoneal Dialysis Michael S. Balzer, Sibylle Von Vietinghoff, Yulia Kiyan, Hermann G. Haller, Nelli Shushakova. *Hannover Medical School, Hannover, Germany*.

Background: Damage to the peritoneal membrane (PM) during peritoneal dialysis (PD) comprises inflammatory, neoangiogenetic and fibrotic processes. In a PD mouse model, we have previously demonstrated glucose-mediated pro-inflammatory, pro-fibrotic and pro-angiogenic properties of protein kinase C (PKC)-alpha, which is the dominant mesothelial PKC isoform. Preliminary data suggest regulation of PKC-alpha by PKC-beta at the PM. The specific role of PKC-beta and especially its main source in glucose-mediated PM damage are not clear.

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Conclusions: PKC-beta, the dominant mesothelial PKC isoform in peritoneal macrophages, is up-regulated and exerts peritoneal anti-inflammatory effects during PD through regulation of the dominant mesothelial PKC isoform PKC-alpha. PKC-beta deficient animals present a macrophage phenotype in response to in vivo PD.

SA-PO715

Effect of TonEBP on TGF-β1-induced Phenotype Transition of Mesothelial Cells via Modulation of NLRP3 Inflammasome Duk-Hee Kang,[1] Eun sun Ryu,[3] Dal-ah Kim,[2] Hyun-Jung Kang.[4] *[1]Ewha University College of Medicine, Seoul, Republic of Korea; [2]Ewha Womans University Medical Center, Seoul, seoul, Republic of Korea; [3]Ewha Womans University School of Medicine, Seoul, Republic of Korea; [4]Ewha Womans University, Seoul, Republic of Korea*.

Background: Phenotype transition of mesothelial cells(MC) such as epithelial-to-mesenchymal transition(EMT) is known as an early mechanism of peritoneal fibrosis in peritoneal dialysis(PD). Nod-like receptor 3(NLRP3) inflammasome is comprised of the NLRP3, the adapter ASC and pro-caspase-1, which promotes the maturation of IL-1β and IL-18. Tonicity-responsive enhancer binding protein(TonEBP) is a transcriptional enhancer that enables cellular adaptation to hypertonic stress by promoting expression of specific genes. The aim of this study is to investigate whether TonEBP plays a role on phenotype transition via a modulation of NLRP3 inflammasome in peritoneal MCs isolated from omentum and dialysate effluents from patients on PD

Methods: The expressions of TonEBP and components of NLRP3 inflammasome, nuclear translocation of TonEBP and snail were evaluated by western blotting. E-cadherin promoter activity was confirmed by luciferase assay. Effect of either TonEBP or NLRP3 gene silencing on EMT was examined using siRNA technique. MCs were also isolated from overnight dwell dialysates from 9 clinically stable PD patients (MC-DE) to assess the expression of TonEBP and NLRP3 inflammasome, and to clarify the association with the markers of EMT

Results: TGFβ1 enhanced TonEBP expression with an increased nuclear translocation in MC, which was followed by an altered expression of epithelial and mesenshymal cell markers. TGFβ1 also activated the expression of NLRP3, ASC and procaspase-1 with an increased production of IL-1β and IL-18. TGFβ1-induced EMT was ameliorated by either siTonEBP or siNLRP3, which was associated with a decrease in snail expression and an increase in E-cadherin promotor activity. TonEBP gene silencing also alleviated TGFβ1-induced activation of NLRP3 inflammasome pathway. The expressions of TonEBP and NLRP3 were higher in MC-DE compared to MC never been exposed to dialysate, which were significantly correlated with the degree of EMT assessed by an altered expression of E-cadherin and α-SMA

Conclusions: This data suggest TonEBP plays a key role in peritoneal EMT via tonicity-independent mechanism by either an inhibition of E-cadherin transcription or an activation of the NLRP3 inflammasome. Modulation of TonEBP in MCs could be a novel approach to protect the peritoneum from the development of EMT and peritoneal fibrosis in PD patients

SA-PO716

A Strategy for the Simultaneous Preservation of Residual Renal Function and Peritoneal Structure/Function Kana N. Miyata,[1] Pei Zhang,[1,2] Sharon G. Adler,[1] Janine A. La page,[1] Tiane Dai.[1] *[1]Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA; [2]The First Affiliated Hospital of Anhui Medical University, He Fei, China*.

Background: Residual renal function (RRF) preservation is key to maintaining peritoneal dialysis (PD) long-term. In a separate abstract, we showed that in rats with polycystic kidneys (PCK), the peritoneal fibrosis and functional decline due to 16 wks of dialysate infusion with 4.25% Dianeal was attenuated by the intraperitoneal administration of Losartan and/or Ruxolitinib (JAK1/2 inhibitor). Here, we investigated their effects on renal function.

Methods: Tunneled PD catheters were placed in PCK rats who received BID infusions of normal saline, 4.25% Dianeal, 4.25% Dianeal + Ruxolitinib (5mg/kg), 4.25% Dianeal + Losartan (5mg/kg), or 4.25% Dianeal + Losartan + Ruxolitinib for 16 weeks. Control group did not receive a catheter or PD fluid. We measured tail cuff mean arterial pressure (MAP), BUN, 24h urine protein-to-creatinine ratio (UPCR), urine albumin-to-creatinine ratio (UACR), and total kidney/body weight ratio(KW/BW). Results were evaluated by one-way ANOVA followed by the Tukey test. Values were expressed as mean± SEM.

Results: PCK rats (fibrocystin mutation) develop proteinuria, albuminuria, cystic tubulointerstitial disease, and progressive GFR decline. UPCR, UACR, and MAP were significantly lower in groups given Losartan compared to those without Losartan. BUN rise was lowest in the Dianeal alone and Losartan groups. Ruxolitinib did not significantly affect measured parameters. None of the interventions altered KW/BW ratio. Summary: In PCK rats, Dianeal intraperitoneal infusions alone or with Losartan attenuated a rise in BUN. Losartan also reduced UPCR, UACR, and MAP, but not KW/BW. Ruxolitinib did not significantly alter renal parameters.

Conclusions: Taken together with our work on peritoneal structure/function in this PCK model, Losartan alone, or Losartan in combination with Ruxolitinib, offer the possibility of maintaining peritoneal structure and function and RRF while reducing proteinuria. Strategies that maintain both peritoneal and renal structure and function may enhance PD technique survival.

Funding: Other NIH Support - NIH/National Center for Advancing Translational Science (NCATS) UCLA CTSI Grant Number UL1TR000124. Renal Research Institute Grant Number 31197., Private Foundation Support

	Control (n=3)	Normal Saline (n=3)	4.25% Dianeal (n=4)	4.25% Dianeal + Ruxolitinib (n=3)	4.25% Dianeal + Losartan (n=4)	4.25% Dianeal + Losartan + Ruxolitinib (n=4)	p
MAP [mmHg] (16 week)	147 (n=1)	136 (n=1)	139 (n=2)	150 (n=2)	132 (n=2)	108 (n=2)	<0.01 ***
BUN [mg/dL] (16 week)	34.0 ± 4.2	26.0 ± 3.1	22.3 ± 1.0	27.0 ± 2.1	22.5 ± 1.0	24.0 ± 0.0	0.011
UPCR [g/g] (12 week)	25.1 ± 1.4	20.3 ± 2.4	17.1 ± 3.1	20.5 ± 2.2	4.8 ± 1.0	7.6 ± 2.0	<0.0001
UACR [mcg/mg] (12 week)	5356 ± 1062	4628 ± 720	4042 ± 891	3743 ± 1720	1137 ± 253	1808 ± 438	0.024
Total Kidney/body weight ratio [%] (16 week)	1.82± 0.14	1.63 ± 0.35	1.42 ± 0.18	2.07 ± 0.23	1.38 ± 0.11	1.41 ± 0.10	0.127

* p<0.01, **<0.05, *** with vs without Losartan

SA-PO717

Lithium-Mediated Protection of Mesothelial Cells during Peritoneal Dialysis Rebecca Herzog,[2,3] Katarzyna Bialas,[2] Christoph Aufricht,[1] Klaus Kratochwill.[2,1] *[1]Pediatric Nephrology, Medical University of Vienna, Vienna, Austria; [2]Christian Doppler Laboratory of Molecular Stress Research in Peritoneal Dialysis, Medical University of Vienna, Vienna, Austria; [3]Research, Zytoprotec, Vienna, Austria.*

Background: Peritoneal mesothelial cells (MC) are harmed by peritoneal dialysis fluids (PDF), at least in part caused by inadequate cellular stress responses. In immortalized MC, we have shown that addition of lithium chloride (LiCl) restored heat shock protein expression. Lithium salts could therefore be a promising group of molecules to be used as cytoprotective additives to PDF. Here, we analyzed the protective potential of LiCl in human primary MC (HPMC) on the gene and protein expression level in a multi-omics approach and *in-vivo* in a chronic mouse model of PD.

Methods: HPMC of 5 individual donors were exposed to PDF (Extraneal, Baxter) without or with 2.5 or 10mM LiCl 30 min and allowed to recover for 4 or 16 h. Cell death was analyzed by LDH-release. mRNA levels were analyzed by gene expression microarrays and significantly altered biological processes were identified using the PANTHER database. Changes of the proteome were analyzed with a 2D difference gel electrophoresis (DiGE) based approach. C57/B6 mice (n=32) were treated with PDF without or with 5mM LiCl for four weeks via an implanted catheter. The parietal peritoneum was analyzed for thickening/fibrosis and effluent cells were characterized following a 30 min dwell by FACS.

Results: PDF-induced cell injury was associated with significantly differential expression of 601 genes compared to control. Six biological pathways (oxidative stress response, VEGF signaling, PDGF signaling, angiogenesis, CCKR signaling, GNRHR pathway) were significantly overrepresented. Added LiCl led to significantly decreased cell death and significantly altered the expression of 1003 genes, of which 62 showed an abolishment of the PDF-effects. These genes are regarded as markers of LiCl-mediated cytoprotection. *In-vivo* LiCl lead to a decrease of PDF-induced peritoneal membrane thickening and increased Treg/IL-17 ratio of the effluent cells.

Conclusions: The cytoprotective effects of added LiCl, combined with the modulation of the cellular stress response, fibrosis and inflammation suggests a therapeutic potential of this intervention. Future studies including pharmacokinetics following once daily exposure to LiCl added to Extraneal are needed to further translate these findings into the clinical setting of PD.

Funding: Commercial Support - Zytoprotec GmbH

SA-PO718

Impact of Liver Cirrhosis on the Outcome of Peritoneal Dialysis Young Lee Jung,[1] Jae Yoon Park,[2] Hyunjin Ryu,[1] Yaerim Kim,[1] Jae shin Choi,[1] Dong Ki Kim,[1] Chun Soo Lim,[3] Yon Su Kim,[1] Kook-Hwan Oh,[1] Seung Seok Han.[1] *[1]Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [2]Dongguk University Ilsan Hospital, Gyeonggido, Republic of Korea; [3]Seoul National University Boramae Medical Center, Seoul, Republic of Korea.*

Background: Peritoneal dialysis(PD) is popular treatment modality for ESRD. However, its application to liver cirrhosis(LC) and subsequent outcomes have not been thoroughly evaluated yet.

Methods: We retrospectively reviewed 1,366 patients(≥18 yrs old) who started PD at Seoul National University Hospital between January 2000 and December 2015. Radiologic evaluation was applied to define LC at the time of PD initiation. 33 patients were assigned to LC, and their outcomes were compared with non-LC(n=35), which was selected based on the propensity score matching by age, sex, and diabetes mellitus. Primary outcome was the technical failure;secondary outcomes were peritonitis, exit site infection, and all-cause mortality.

Results: Patients were followed for a mean duration of 42.9±35.8 months. During that period, 6 patients with LC encountered technical failures, but this rate was not different from that of non-LC[Figure 1]. This difference did not alter despite adjusting several covariates, such as comorbidities and lab findings. When evaluating infection, common causes for peritonitis and exit site infection were E.coli(5.8%) and S.aureus(19.3%); these rates were not different from those of non-LC. Overall mortality were similar between LC and non-LC. All of these outcomes were not dependent on severity of LC, which was quantitatively determined by Child-Pugh and MELD score. LC with hepatocellular carcinoma(n=6) did not have inferior outcomes including mortality to counterpart group without carcinoma.

Conclusions: The presence of LC and its severity did not affect subsequent outcomes in patients starting PD. Based on the fact that trials with randomization of dialysis modality are not feasible, the present observational results may provide reassurance to the LC starting PD.

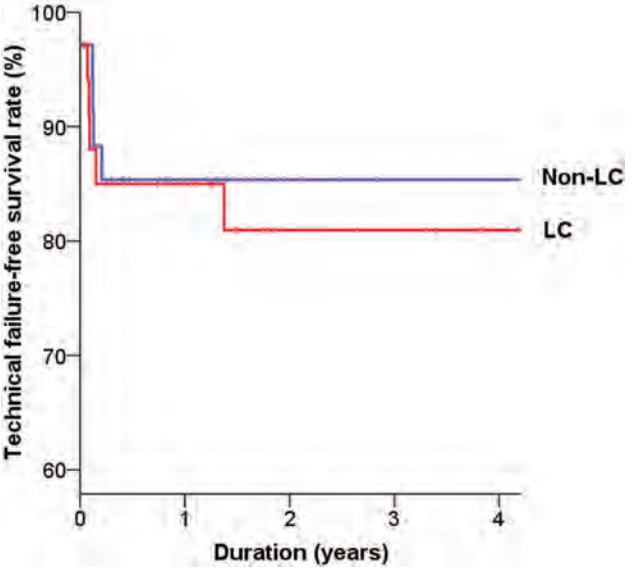

Figure 1. Technical failure-free survival curves between LC and non-LC patients

SA-PO719

Staphylococcal Peritonitis in Chronic Peritoneal Dialysis Patients: A Seven-Year Review Tiago J. Carvalho, Patricia Q. Branco, Ana Rita M. Martins, Domingos S. Machado, Maria augusta C. Gaspar. *Nephrology, Santa Cruz Hospital, Carnaxide, Portugal.*

Background: Staphylococcal peritonitis (SP) is a serious complication of chronic peritoneal dialysis (CPD). The aim of this study was to examine the frequency, predictors and clinical outcomes of SP.

Methods: We reviewed all consecutive cases of SP in a CPD unit from 2010 to 2016. The mean number of patients treated per year was 87±14. There were 300 episodes of peritonitis, of which 109 (36.3%) were SP, affecting 59 patients, aged 52±15 years. Peritonitis rates varied from a minimum of 0.32 to a maximum of 0.52 episodes/patient/year. The unit's empirical antibiotic protocol was intraperitoneal cefazolin and ceftazidime.

Results: Among SP affected patients, 30 had one episode, 17 had two episodes and 12 had three or more. There were 63 cases (57.8%) of coagulase-negative SP and 46 (42.2%) of *Staphylococcus aureus* peritonitis, 4 of which were methicillin-resistant. Caucasians had a higher risk of *S. aureus* peritonitis (Odds Ratio (OR) 22.71, 95% Confidence Interval (CI) 5.06-101.85, p<0.001). Overall primary response to treatment was 75.2%.

When compared to coagulase-negative SP, *S. aureus* peritonitis were associated with a higher risk of catheter substitution/removal in a multivariate Cox regression adjusted for age, diabetes *mellitus* and previous exit-site infection (Hazard Ratio (HR) 2.81, 95% CI 1.08-7.29, p=0.033). There was also a trend towards increased hospitalization (OR 2.27, 95% CI 0.95-5.43, p=0.066). There were no differences in relapse rate (34.8% vs 33.3%) or permanent transfer to hemodialysis (0.02% vs 0.07%). No deaths occurred. Other factors associated with a higher risk of catheter substitution/removal were previous exit-site infection (OR 6.68, 95% IC 1.57-28.48, p=0.010) and relapse or repeat episode (OR 11.30, 95% IC 2.93-43.57, p<0.001).

Conclusions: SP remains an important clinical problem in CPD patients. Caucasian patients have a higher risk of *S. aureus* peritonitis. Previous exit-site infection, *S. aureus* peritonitis and relapse or repeat peritonitis episodes are associated with an increased risk of catheter substitution/removal. However, permanent transfer to hemodialysis remained low.

SA-PO720

Alanyl-Glutamine in Peritoneal Dialysis Fluids Restores Cytoprotective Responses of Endothelial Cells Klaus Kratochwill,[3,1] Silvia Tarantino,[1] Rebecca Herzog,[3,1] Maria Bartosova,[2] Claus P. Schmitt,[2] Christoph Aufricht.[1] *[1]Pediatric Nephrology, Medical University of Vienna, Vienna, Austria; [2]Center for Pediatric and Adolescent Medicine, University of Heidelberg, Heidelberg, Germany; [3]Christian Doppler Laboratory of Molecular Stress Research in Peritoneal Dialysis, Medical University of Vienna, Vienna, Austria.*

Background: Peritoneal vascular changes manifested as vasculopathy and increased angiogenesis are major factors causing ultrafiltration failure in patients undergoing peritoneal dialysis (PD). Hyperglycemic conditions created during PD fluid (PDF) exposure are similar to those responsible for cellular pathomechanisms relevant in diabetic retinopathy and nephropathy. This study focused on characterizing endothelial cell (EC) injury and stress responses after exposure to PDF with/without cytoprotective intervention with alanyl-glutamine dipeptide (AlaGln).

Methods: Human umbilical vein ECs (HUVECs) exposed to PDF were subjected to a combined proteomic and bioinformatics approach using 2D-DIGE and fluorescent cyanine dyes. Cellular injury was associated with a molecular landscape of a set of enriched biological processes that characterize PDF cytotoxicity and counteracting cellular repair processes. These include "glucose catabolic process", "cell redox homeostasis", "RNA metabolic process", "protein folding", "regulation of cell death", and of "actin cytoskeleton reorganization".

Results: Supplementation of PDF with AlaGln preserved EC viability and restored control levels of proteins in PDF perturbed processes, especially enhancing protein folding capacity and response to stress. The direct comparison revealed a set of 55 differentially abundant spots of which 58.2% were restored with AlaGln. In support to the findings in our model, cross-comparison with transcriptomic data obtained from human peritoneal biopsies from children on PD showed changes in 12 potential marker genes of PDF cytotoxicity, of which 5 genes were restored to control levels following addition of AlaGln to the PD fluid.

Conclusions: This combined proteomics and bioinformatics approach shows that PDF harms endothelial cells and leads to drastic changes of the cellular process landscape. Cell damage and proteome changes were effectively counteracted by AlaGln. In summary, this study elucidates potential mechanisms by which AlaGln exerts cytoprotective effects in endothelial cells, offering therapeutic targets to reduce side effects of PD.

SA-PO721

Peritonitis and Predictors of Treatment Failure in Peritoneal Dialysis Patients: An Experience of 902 Consecutive Episodes in Thai Centers Chayutthaphong Chaisai,[4,5] surapon nochaiwong,[4,5] Chidchanok Ruengorn,[3,5] Kiatkriangkrai Koyratkoson,[4,5] Kajohnsak Noppakun,[6] Ratanaporn -. Awiphan,[2,5] Wilaiwan -. Chongruksut,[7,5] Sirisak Nanta.[1,5] *[1]Maesai District Hospital, Chiang Rai, Thailand, Chiang Rai, Thailand; [2]Chiangmai University, Chiangmai, Thailand; [3]Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand; [4]Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand; [5]Pharmacoepidemiology and Statistics Research Center (PESC), Chiang Mai University, Chiang Mai, Thailand; [6]Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand; [7]Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. Group/Team: Thai Renal Outcomes Research (THOR) Investigators.*

Background: Peritonitis is a common cause of peritoneal dialysis (PD) technique failure as well as a major contributing cause of death in PD patients. Early prediction of treatment outcomes can be major potential subsequent management for PD-related peritonitis. To date, existing evidences regarding the prognostic factors for treatment failure are scarce. We therefore determine factors predicted treatment failure among PD-related peritonitis.

Methods: A multicenter, retrospective observational study was based on the PD registry database of patients aged ≥ 18 from three PD center in Thailand. Baseline sociodemographics and laboratory examination characteristics were collected between January 2006 and December 2016. Treatment failure was defined as catheter removal or peritonitis-associated death. Predictors related to treatment failure were investigated by univariable and multivariable logistic regression.

Results: A total of 902 PD-related peritonitis episodes were included, 224 (24.8%) of which had treatment failure. Of those, 157 (17.4%) required Teckhoff catheter removal and 67 (7.4) had peritonitis-associated death.

Conclusions: In order to make a decision, four key predictors from this study may potentially help to identify patients at risk of treatment failure. Early establishment of the severity of PD-related peritonitis may offer opportunities to improve treatment outcomes.

Funding: Government Support - Non-U.S.

Factors Predicted Treatment Failure among PD-Related Peritonitis by Multivariable Logistic Regression Analysis

Factors PD with assistance	Adjusted OR (95% CI)	P Value	Factors Causative organisms	Adjusted OR (95% CI)	P Value
• Alone	Reference		Gram-positive only (excluding MRSA)	Reference	
• With family	1.39 (0.80 – 2.39)	0.238	MRSA	0.95 (0.06 – 16.16)	0.969
• With others	15.42 (4.74 – 50.15)	< 0.001	Gram-negative only (excluding *Acinetobacter spp.* and *Pseudomonas spp.*)	2.29 (0.75 – 6.97)	0.144
Systolic blood pressure, mmHg			*Acinetobacter spp.*	11.97 (3.05 – 46.98)	< 0.001
• < 90	5.15 (1.42 – 18.69)	0.013	*Pseudomonas spp.*	3.72 (1.02 – 13.56)	0.046
• 90-140	Reference		Fungi	48.37 (4.52 – 518.12)	0.001
• > 140	1.75 (1.01 – 3.04)	0.046	Mycobacterial	4.17 (0.58 – 30.03	0.156
Peritoneal dialysate white count on day 5 > 100/mm^3			Polymicrobial	7.51 (3.42 – 16.52)	< 0.001
• No	Reference		Culture negative	1.22 (0.66 – 2.25)	0.523
• Yes	70.66 (34.94 – 142.92)	< 0.001			

CI, confidence interval; Methicillin-resistant *Staphylococcus aureus,* OR, odds ratio

SA-PO722

The Influence of Duration of Peritoneal Dialysis on the Proteomic and Metabolomic Profiles of Plasma and Peritoneal Fluid Magdalena Luczak,[1] Dorota Formanowicz,[2] Joanna Tracz,[1] Elzbieta Pawliczak,[2] Krzysztof Schwermer,[2] Maria Wanic-Kossowska.[2] *[1]Polish Academy of Sciences, Pozna?, Poland; [2]Poznan University of Medical Sciences, Pozna?, Poland.*

Background: Long-term peritoneal dialysis (PD) is associated with changes of the peritoneal membrane. The major goal of this study was investigation of the effect of PD duration on metabolomic and proteomic profiles of peritoneal fluid (PF) and plasma in order to identify molecular changes occurring through long PD duration.

Methods: Plasma and PF samples were obtained from 35 diabetes and non-diabetes PD recipients in four time-points: at the time of initiation of PD (T1) and after 3 (T2), 6 (T3) and 12 months (T4) of PD. Collected 280 samples were analyzed using LC-ESI-MS/MS and GC-EI-MS/MS. Qualitative and quantitative differences in the accumulation of the individual proteins and metabolites were determined.

Results: One hundred forty-two ANOVA significant differential molecules were identified in plasma and PF samples when time T1 and T4 were compared. For example increased accumulation of CD59 glycoprotein, proliferation-inducing protein 33, insulin-like growth factor-binding protein 4 and 6 were revealed in PF of T4 diabetic samples compared to their T1. The same proteins did not differed T1 and T4 PF samples if derived from non-diabetes. One of the most interesting result concerned monocyte antigen CD14 and lipopolysaccharide-binding protein. Both proteins differentiated T1 and T4 plasma and PF samples obtained from non-diabetes and diabetes but in completely different way. The abundance of CD14 antigen was increased in PF of T4 non-diabetic patients (fold change 3.5; p = 0.004) compared with T1 and in plasma of diabetes (fold change 2.4; p = 0.02). In turn, accumulation of CD14 was 3.4 times lower in PF of T4 diabetic (p = 0.02) and 3.2 times lower (p = 0.005) in T4 plasma of non-diabetes.

Conclusions: Obtained data indicate that PD duration is strongly associated with alterations in proteomic and metabolomic profiles of plasma and PF. Patients starting PDs differed considerably in abundance of many molecules compared to the same patients after 1 year of PD. However large differences in accumulation of proteins between diabetes and non-diabetes may suggest that in these patients molecular mechanisms related to these variations are differ. Especially interesting are differences concerning CD14, a key pattern recognition receptor of the innate immune system.

SA-PO723

Peritoneal Dialysis in Sichuan Province of China—Report from the Chinese National Renal Data System Daqing Hong. *Sichuan Provincial People's Hospital, CHENGDU, China.*

Background: The Chinese National Renal Data System (CNRDS) was established in 2010 to collect data from patients undergoing Peritoneal Dialysis in renal department of China. In this study, we aimed to study the patients of Sichuan province in the registry and analysis total characteristics and treatment effect and to examine whether or not the based clinical statistics effected the outcome of peritoneal dialysis, exploring the risk factors for peritoneal dialysis patients.

Methods: This study included 2654 patients undergoing peritoneal dialysis between January 2010 and December 2016. All data were conducted statistical analysis using SPSS 21.0.

Results: Primary glomerular disease, secondary glomerular disease and hereditary nephritis were the first three causes (Figure 2). From 2010 to 2016, the number of patients was on the rise, while patients who died or dropped out were decreasing. All

drugs including Erythropoietin, antihypertensive drugs, iron, calcium agents, phophorus lowering medicine and Vitamin D were beneficial for patients technical survival ($P<0.01$), in which the percentage of using erythropoietin, iron and antihypertensive agents were higher than other drugs. There was no significant association between based clinical variable and outcome of patients, except that ALB had a beneficial effect ($P<0.05$) for technical survival.

Conclusions: Our registry results, representing the first largest report of PD in the Southwest of China, indicate that peritoneal dialysis patients are increasing, which will require more and more medical cost to improve their outcome.

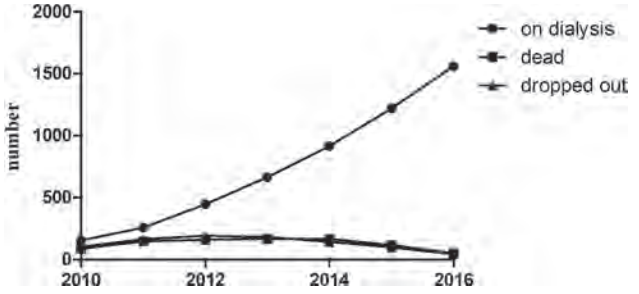

Figure 1 Prevalence of peritoneal dialysis patients.

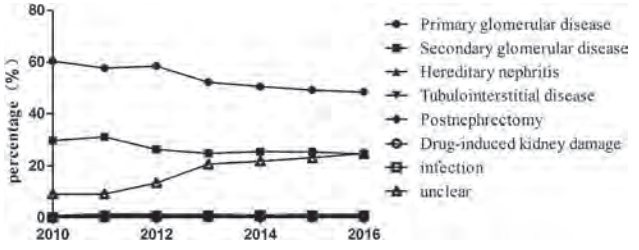

Figure 2 Cause of end-stage renal disease of peritoneal dialysis patients

SA-PO724

Optimal Dwell Time for Maximal Small Solute Clearances in Peritoneal Dialysis Patients

Suchai Sritippayawan. *Division of Nephrology, Internal Medicine, Siriraj Hospital, Bangkok, Thailand.*

Background: The adequacy of peritoneal dialysis was assessed by urea and creatinine clearances which depend on daily dialysate volume and dwell time. The objective of this study was to identify the optimal dwell time producing maximal small solute clearances in peritoneal dialysis patients.

Methods: Prospective cohort study was performed in chronic peritoneal dialysis patients at Siriraj hospital. We compared small solute clearances at 9 dwell time periods (0, 5, 10, 15, 20, 30, 40, 50 and 60 minutes). Weekly KT/V urea and weekly nCCr were obtained to identify the optimal dwell time which produced maximal small solute clearances. We also compared rate of glucose absorption, ultrafiltration and other small solute removals such as sodium, potassium, calcium, phosphorus and uric acid at each dwell time period.

Results: Twenty-two peritoneal dialysis patients were enrolled. The 20 minutes of dwell time had maximal weekly KT/V urea (5.01; $p < 0.001$), weekly nCCr (104.95 L/1.73m^2; p 0.018) and potassium removal (78.17 mEq/day; p 0.002). Maximal sodium removal was observed at 0 minutes (394.56 mEq/day; p 0.005). There were no significance different of glucose absorption, ultrafiltration rate and other small solute removal (phosphorus, uric acid and calcium) at any periods of dwell time. Small solute clearances, ultrafiltration and solute removals were not associated with the peritoneal membrane transport types.

Conclusions: 20-minutes dwell time had the highest weekly KT/V urea and weekly nCCr in chronic peritoneal dialysis patients. Small solute clearances were not associated with the peritoneal membrane transport types in each short dwell time period.

Funding: Government Support - Non-U.S.

SA-PO725

Use of Composite Endpoint to Improve Feasibility of Clinical Trials in Peritoneal Dialysis

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Background: Peritoneal dialysis (PD) is frequently complicated by PD–related adverse events, such as peritoneal membrane damage and/or peritonitis. Currently used PD fluids likely contribute to pathological mechanisms responsible for these complications. Low feasibility to recruit PD populations for adequately powered trials may impair clinical development of improved PD fluids. In trials in which more than one outcome is thought to be affected by the treatment, the use of composite endpoint can be recommended. Here, we test the effect of introducing clinically relevant composite PD outcomes on clinical trial design in PD.

Methods: The composite outcome "Major Adverse Peritoneal Events (MAPE)" was designed based on incidence rates of 3 individual endpoints obtained from published clinical trials: ultrafiltration (component 1), peritoneal transport characteristics (2), and peritonitis rate (3). Taking into account that some patients could experience more than one event, several degrees of overlaps of events were investigated. Sample size calculations were carried out using a chi-square test for a parallel group design in binary composite endpoint MAPE with two-sided significance level of 5% to achieve power of 80%.

Results: Based on previously reported clinical trials, event rates of 33% were assumed for each individual component (1,2,3) for the control group. In a scenario with reduction of adverse events by 25%, adequately powered studies would need a sample of more than 1000 patients to test effects on ultrafiltration, peritoneal transport characteristics or peritonitis rate, when studied individually. Combining 2 of these outcome variables reduces the required sample by approximately half, whereas the composite outcome MAPE may reduce the needed sample size to 256 patients.

Conclusions: Introduction of the composite outcome MAPE, covering 3 major PD outcomes, increases power of future clinical trials in PD, thereby improving feasibility. This results in the need for significantly lower sample sizes for assessing clinically relevant effects on PD-related complications.

SA-PO726

Peritoneal Dialysis as a Treatment for Diuretic Resistant, Refractory Heart Failure in Patients with CKD: A Single Centre Experience

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Background: To assess the role and feasibility of peritoneal dialysis (PD) on clinical outcomes in patients with diuretic resistant refractory heart failure (HF) and Chronic Kidney Disease (CKD).

Methods: Retrospective data and case-note review of 20 patients with HF and CKD started on PD for fluid management. Setting: UK PD unit with an established assisted APD programme. The period of the study was between November 2010 and January 2017. Patients with eGFR <15ml/min were only included if believed to have decline in eGFR as a result of decompensating heart failure (cardio-renal syndrome).

Results: Mean age was 72±9 years, 18 (90%) aged 65 year or older, 85% male. Mean eGFR at PD initiation was 23.9±12.47 and 6 (30%) patients had eGFR of ≤15 ml/min at start of treatment. The aetiology of heart failure was ischaemic in 17 patients (85%). All patients had NYHA class III or IV, and diuretic resistance. Recent estimated ejection fraction (EF) before starting PD was available in 15 patients (EF 10%-60%), 46.6%: EF≤35%, 33.3%: EF 35-45% and 20%: EF >45%. All PD catheters were inserted using Seldinger technique and had a patency rate of 95%. The median duration of PD was 9.35 months (IQR 3.41-16.08). During the study period 14 patients (70%) died, 30% (6 patients) died within the first year, and overall the median survival was 14.8 months (IQR 4.81-24.89). Among those who has lasted on PD for at least 12 months the mean number of hospital visits (days per year) for HF or PD related issues in the year before starting PD (52.43±27.8) was significantly higher than the year after starting PD (6.86±5.87) *{p=0.007}*. The median eGFR has shown a rise by 0.5 ml/min/month over the first 3 months and a decline by 0.83 ml/min/month at 6 months.

Conclusions: Peritoneal dialysis could serve as a feasible therapeutic intervention to reduce hospital admissions in fluid management in heart failure patients where symptom control with conventional medical treatment becomes a challenge.

SA-PO727

Carbamylated Albumin Predicts Mortality in Peritoneal Dialysis (PD) Patients

Yang Li,[1] Dongyang Liu,[2] Lanping Jiang,[1] Jie Liu,[2] Zijuan Zhou,[1] Haiyun Wang,[1] Ying Wang,[1] Xuemei Li,[1] Pei Hu,[2] Sahir Kalim,[3] Limeng Chen.[1] *[1]Department of Nephrology, Chinese Academy of Medical Sciences, Peking Union Medical College Hospital, Beijing, China; [2]Clinical Pharmacology Research Center, Chinese Academy of Medical Sciences, Peking Union Medical College Hospital, Beijing, China; [3]Renal Division, Massachusetts General Hospital, Boston, MA.*

Background: Carbamylation is a posttranslational protein modification mediated by cyanate, the dissociation product of urea, which increases in patients with kidney dysfunction. Recently, carbamylated albumin (C-Alb) was reported to be independently associated with mortality in maintenance hemodialysis patients, but its value in peritoneal dialysis populations has not been studied yet. We employed high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) to measure C-Alb levels and analyze its association with mortality in PD patients.

Methods: We collected serum samples from 114 maintenance adult PD patients at a single university medical center between July 2010 and January 2011, following them until December 2016 (mean length of follow up was 39.6 ± 25.6 months). C-Alb levels were natural log-transformed, and then divided into two groups (high and low levels) according to the cut-off value with highest Youden Index in ROC curve for death. Multifactor Cox regression models were used to analyze the association between C-Alb and death.

Results: The average age of the PD cohort was 63.6±13.3 years, 51% were female, and the average dialysis vintage at baseline was 37.4±29.8 months. The primary causes of ESRD were diabetic nephropathy (DN, 31.6%), hypertensive nephrosclerosis (30.7%) and chronic glomerulonephritis (20.2%). After 6 years follow up, 66 patients died (57.9%), mainly due to cardiovascular events (50.0%). Those who died were older (69.6±10.3 vs. 55.3±12.6, P<0.001), had a higher proportion of DN (40.9% vs. 18.8%, P=0.012), cardiovasular comorbidities (27.3% vs. 6.2%, P=0.004) and hypoalbuminema (Alb<35g/L) rate (63.6% vs. 43.8%, P=0.035). The Kaplan-Meier analysis showed a worse survival rate for PD patients with higher C-Alb level (Log-Rank Test: P=0.017). The univariate Cox regression analysis showed that higher C-Alb levels were associated with death. After adjusting for other important or significant mortality predictors in this cohort including age, gender, DN and cardiovascular comorbidities, higher C-Alb levels (HR=1.763, 95% CI 1.032-3.014, P=0.038) remained an independent risk factor for death in PD patients.

Conclusions: For the first time, we report higher C-Alb level was an independent risk factor for mortality in PD patients confirming similar observations in hemodialysis cohorts.

SA-PO728

Higher Serum Magnesium Is Associated with Lower Abdominal Aortic Calcification Burden in Peritoneal Dialysis (PD) Patients Kostas Stylianou,[4] Dimitra Bacharaki,[1] Olga Balafa,[5] Dimitra Lygerou,[4] Eleftheria-Kleio Dermitzaki,[4] Anastasia K. Georgoulidou,[3] George I. Tsirpanlis,[6] Marios Theodoridis,[7] Konstantinos S. Mavromatidis,[3] Periklis P. Kyriazis,[2] Ploumis Passadakis,[7] Dimitrios V. Vlahakos.[1] *[1]Attikon University Hospital, Athens, Greece; [2]Beth israel Deaconess Medical Center, Brookline, MA; [3]GENERAL HOSPITAL OF KOMOTINI, Komotini, Greece; [4]University Hospital of Heraklion, Heraklion, Greece; [5]University Hispital of Ioannina, Ioannins, Greece; [6]Nephrology, "G.Gennimatas" General Hospital, Athens, Greece; [7]University Hospital of Alexandroupolis, Alexandroupolis, Greece.*

Background: To identify factors potentially capable of preventing the progression of abdominal aortic calcification (AAC), a surrogate of cardiovascular risk in PD patients

Methods: 95 stable PD patients were studied (52 men), with a mean age of 62±15 years and a median dialysis vintage of 43 (IQR 28-71) months. The AAC was evaluated with Leena Kauppila (LK) score (range 0-24) on plain lateral abdominal radiographs. Patients were divided in a Low calcification score (CS) group: (LK score 0-4) and a High CS group: (LK score 5-24,), each comprising 38 (40%) and 57(60%) patients, respectively. Univariate and multivariate regression analysis were used to determine factors associated with a High CS.

Results: Mean CS in the whole group was 6.95±6.3. Patients with a High CS (10.8±5.1) were older, had a higher prevalence of diabetes (38.6 vs. 17.6%; p=0.04) and peripheral vascular disease (PVD) (29.8 vs. 10.5%; p=0.02), higher pulse pressure (PP) (57±14 vs. 51±15 mmHg; p=0.037) and malnutrition inflammation score (MIS) (5.12±3.1 vs. 3.8 ±2.7; p=0.039, lower serum magnesium (sMg) levels (2.12±0.36; vs. 2.37±0.54; p=0.008) and less use of cinacalcet (19.3 vs. 39.5%; p<0.03). In a multivariate analysis every 1mg/dl increase in sMg was associated with 74% lower odds of having a High CS (Table 1). MIS also emerged as a significant predictor of a high CS (Table 1). sMg was significantly (r=0.31; p=0.002) correlated with dialysate Mg concentration (0.50/0.25 mmol/L)

Conclusions: Our data indicate that sustaining higher sMg levels, as by using higher Mg dialysate concentration, and correcting the malnutrition and inflammation complex syndrome may potentially lower the AAC burden and, thus, improve cardiovascular risk in PD patients

Funding: Clinical Revenue Support

Table 1

	UNIVARIATE		MULTIVARIATE	
	OR (95%CI)	P	OR (95%CI)	P
Age (↑1 yr)	1.08 (1.04–1.1)	<0.001	1.055 (1.009–1.1)	0.018
Diabetes	2.9 (1.007–8.5)	0.048		
PVD	3.6 (1.1–11.7)	0.033		
PP (↑1 mmHg)	1.03 (1001-1.06)	0.04		
MIS (↑1 point)	1.18 (1.004–1.37)	0.04	1.25 (1.02–1.52)	0.027
sMg (↑1mg/dl)	0.28 (0.103–0.74)	0.01	0.26 (0.07-0.94)	0.04
Cinacalcet	0.36 (0.14–0.92)	0.04		

SA-PO729

The Influence of Alanyl-Glutamine on the Peritoneal Proteome in a Chronic Model of Peritoneal Dialysis Michael Boehm,[1] Rebecca Herzog,[2] Christoph Aufricht,[1] Klaus Kratochwill.[2] *[1]Pediatric Nephrology and Gastroenterology, Medical University Vienna, Vienna, Austria; [2]Christian Doppler Laboratory for Molecular Stress Research in Peritoneal Dialysis, Medical University Vienna, Vienna, Austria.*

Background: Peritoneal dialysis (PD) fluids exert cytotoxic properties towards peritoneal mesothelial cells. Recent studies showed that alanyl-glutamine (Ala-Gln) modulates the cellular stress response, improves survival of mesothelial cells and reduced submesothelial thickening in experimental models of PD, and improved PD effluent cell function with regards to stress and immune responses in clinical studies. However, the mechanism of Ala-Gln-mediated membrane protection is not yet fully understood. Here, we apply a novel proteomics approach in a clinically relevant in vivo model.

Methods: Following experimental PD for 5 weeks, using PD fluid with or without supplementation of Ala-Gln, or sham treatment as control, mesothelial cells from rat peritoneum were directly harvested by detergent extraction and subjected to proteomic analysis based on difference gel electrophoresis (DiGE) and subsequent protein identification by mass spectrometry. Submesothelial thickening was measured in parallel by microscopy of peritoneal tissue sections.

Results: From a total protein spot pattern of 744 spots, in 500 spots proteins were identified, linking to 233 unique protein IDs. Using database information from UniProt, proteins were assigned either to the group of high abundance plasma proteins (serum-type) or to the group of cellular proteins (cell-type). Following statistical analysis of mixed effects of PD fluid and Ala-Gln, pathway analysis allowed further assignment of candidate proteins to specific roles in the stress response and membrane preservation, observed by decreased submesothelial thickening.

Conclusions: This study shows that by combination of proteomics and bioinformatics the separation of residual plasma proteins and cellular proteins of various origin in PD effluent is feasible. Thereby, the peritoneal mesothelial cell stress proteome can be assessed after exposure to different PD fluids. Identified biological processes might allow linking molecular mechanisms of membrane protection in the in vivo model to protective effects observed in vitro and in clinical PD.

SA-PO730

Prospective, Randomized, Multi-Center, Double-Blind, Controlled, Two-Period, Two-Treatment, Crossover, Phase II Trial to Evaluate the Safety and Efficacy of Alanyl-Glutamine in Peritoneal Dialysis Andreas Vychytil,[1] Klaus Kratochwill,[2] Rebecca Herzog,[2] Christoph Aufricht.[3] *[1]Medicine III, Nephrology and Dialysis, Medical University of Vienna, Vienna, Austria; [2]Christian Doppler Laboratory for Molecular Stress Research in Peritoneal Dialysis, Medical University Vienna, Vienna, Austria; [3]Pediatric Nephrology and Gastroenterology, Medical University Vienna, Vienna, Austria.*

Background: Peritonitis and membrane failure remain serious complications of peritoneal dialysis (PD). In early clinical testing, addition of alanyl-glutamine (AlaGln) to a single dwell of glucose-based PD fluids restored peritoneal cellular stress responses and leukocyte function. This study tests effects of a novel AlaGln supplemented PD fluid on relevant biomarkers in a nation-wide trial.

Methods: In a prospective, double-blinded, cross-over design (EudraCT-2013-000400-42) stable PD outpatients were enrolled to undergo 16 weeks of treatment, 8 weeks with standard PD fluid (Physioneal 40, Baxter, US) and 8 weeks with AlaGln supplemented standard PD fluid (Physioneal 40 and Dipetiven (Fresenius-Kabi, Bad Homburg, Germany) in a randomized order. Cancer-antigen 125 (CA-125) appearance rate as marker of peritoneal cell mass and ex-vivo stimulated interleukin 6 (IL-6) release as marker of peritoneal immune competence were assessed in effluents of standard peritoneal equilibration tests (PET) at 1 h (IL-6 release) and 4 h (CA-125). Secondary outcome parameters were peritoneal and systemic markers of inflammation, amino acid metabolism and transport kinetics.

Results: Out of 54 enrolled PD patients in eight Austrian centers, 50 patients were randomized. In the full analysis set (n=41), addition of AlaGln met both primary outcome parameters with significantly increased CA-125 appearance rate and ex-vivo stimulated IL-6 release. No adverse events or safety signals were observed with PD fluid with added AlaGln, all peritonitis episodes in the safety population (n=47) occurred in the control group with standard PD fluid treatment.

Conclusions: We conclude that a novel AlaGln-supplemented glucose-based PD fluid improves biomarkers of mesothelial cell status and peritoneal immune competence compared to treatment with a standard dual-chamber PD fluid. Future clinical trials are needed to translate these findings into reduction of major PD-related clinical adverse events.

Funding: Commercial Support - Zytoprotec GmbH

SA-PO731

Clinical Outcomes of Patients Receiving Long-Term Continuous Ambulatory Peritoneal Dialysis for More Than 10 Years Seong Sik Kang,[1,2] Hayeon Park,[1] Sang Mok Yeo,[1] Woo Yeong Park,[1,2] Kyubok Jin,[1,2] Sung Bae Park,[1,2] Seungyeup Han.[1,2] *[1]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Republic of Korea; [2]Keimyung University Kidney Institute, Daegu, Republic of Korea.*

Background: The penetration of peritoneal dialysis (PD) is decreasing lately as it is difficult to keep it stable for a long time due to infectious or non-infectious complications. However, PD is still an important and physiologic modality of dialysis for end-stage renal disease. Our objective is to analyze the characteristics of patients who are safely maintaining PD for long period.

Methods: We retrospectively investigated 78 patients who had performed PD over 10 years. We analyzed the characteristics of patients, the episodes of PD peritonitis, the change of laboratory findings between the beginning of PD and 10 years after PD, and patient survival.

Results: The mean duration of PD was 152 ± 26.6 months. The mean age at which dialysis began was 46 ± 12 years. The mean number of peritonitis episodes was 0.228 times/patient/year. The mean time from the beginning of PD to first episode of PD peritonitis was 57 ± 51.9 months. Patient survival was 100% at 10 year, 63.7% at 15 year, 45.2% at 20 year, and the leading cause of death was infection (16.7%), followed by cardiovascular disease (3.8%). There were no changes of level of serum albumin, TG, LDL, HDL, and CRP between basal and 10 year follow-up result. Nutritional status,

inflammation markers, and chronic kidney disease-mineral bone disease were well maintained compared with overall PD population.

Conclusions: In the long-term PD patients, the mean age at which dialysis began was younger and the mean time to occur first peritonitis was longer, compared with the previous reported studies. It means long-term PD patients had attack of PD peritonitis less and late and maintained good nutrition status and iron, calcium and phosphorus balance for long time. We should pay more attention to maintain good nutritional status and low incidence of PD peritonitis for maintenance of long-term PD.

SA-PO732

Does Intraperitoneal Pressure Vary in Peritoneal Dialysis Patients According to the Moment of Measurement? Fabio Procaccini, Amir Shabaka, Fernando Tornero. *Hospital Clinico San Carlos - Madrid, Madrid, Spain.*

Background: Elevated intraperitoneal pressure (IPP) in peritoneal dialysis patients (PD) is linked to alterations in peritoneal transport. IPP is commonly measured at the start of volume infusion and a maximum IPP of 18 mmHg has been recommended which corresponds to 1400ml/m2 of volume infusion. Nevertheless, there may be an adaptation of the peritoneal cavity that could cause IPP to decrease during peritoneal dwell time. Our aim was to study the hypothesis of peritoneal cavity adaptation, and analyze the relationship between IPP and dialysis infusion and drainage volumes.

Methods: We determined IPP in 17 patients in the PD program at our center by measuring the fluid column of solution in the drainage tube at the beginning and end of the peritoneal equilibration test (PET). No patient presented peritonitis or abdominal complications within 4 weeks prior to measurement. Demographic, anthropometric and PET data were collected.

Results: Out of the 17 patients studied, 12 were men (70.6%); 12 were on CAPD (70.6%) and 5 on APD (29.4%), mean age 61.87±17.8 years, mean body mass index (BMI) was 29.01±5.48 kg/m2, mean body surface area was 1.82±0.23 m2, median time in PD was 499 days (IQR 142-880.5). The mean IPP was 14.47±4.34 cmH2O after infusion and 15±4.64 cmH2O at drainage. Mean ultrafiltration was 516.12±269.5 mL with a mean weekly Kt/V of 2±0.45. We observed a decrease in IPP/volume ratio of 7.97±3.68 cmH2O/mL (p= 0.019) at drainage compared to the initial infusion value. IPP/intraperitoneal volume ratio (at both infusion and drainage) showed strong correlation with volume/BSA ratio (at infusion; r= -0.624, p= 0.007 and at drainage; r= -0.703, p= 0.002). There was a significant correlation between infused volume/initial IPP and final IPP, so that the final IPP= 21.114 - [0.041x (Infused Volume/initial IPP)] (r= 0.578, p= 0.015). There was a correlation between final IPP/BSA and infusion volume so that Volume Infused= 2355.201 - [52.727 * (final IPP/BSA)] (r= 0.630, p = 0.007).

Conclusions: The lower IPP/volume ratio at drainage confirms the adaptation of the abdominal cavity during dwell time, rendering it more important to measure IPP at the end of the exchange. We have determined an equation to predict the final IPP at drainage by measuring IPP at infusion based on infusion volume and BSA. In addition, IPP showed stronger correlation to BSA than to weight.

SA-PO733

Changes in Dialysis Prescription Affect the Time Course of Solute Transport in Peritoneal Dialysis Irene Brenna,[1,2] Emma H. Elphick,[1,2] Mark Lambie,[1,2] Simon J. Davies.[1,2] *[1]Keele University, Stoke on Trent, United Kingdom; [2]University Hospital of North Midlands, Stoke-on-Trent, United Kingdom.*

Background: Long term peritoneal dialysis (PD) is associated with increased peritoneal solute transport rate (PSTR), which correlates with hard outcomes. Whether different clinical approaches affect PSTR rate of increase is unclear.

Methods: This is a single centre retrospective longitudinal analysis, collecting data from 01/01/1990 to 31/12/2016 from PETs routinely performed twice a year in all PD patients at the Royal Stoke University Hospital. Using a linear mixed model approach, 3889 PETs from 865 patients were analysed, follow-up being up to 12.7 years, median 1.6. A random intercept/slope model was fit to assess whether the exposure to different clinical practice patterns (PD type, average glucose exposure, long dwell strategy) had an effect on the PSTR rate of increase, adjusting for patients' demographics, comorbidities, residual renal function (RRF) and peritonitis episodes.

Results: Mean predicted PSTR at PD start was 0.723, average increase 0.012 per year. Average glucose exposure affected PSTR absolute value, but not its rate of increase. The use of icodextrin was associated with higher PSTR at PD start (+ 0.055, 95%CI 0.040/0.070) and slower increase over time (0.005 per year, p=0.002). A dry long dwell resulted in lower PSTR at PD start (- 0.090, 95%CI -0.114/-0.067), but faster increase (0.029 per year, p<0.0001). The pattern of PSTR changed with starting-period too (p<0.001), the starting PSTR being lower in 1990-95 (0.723) and rising until 2005-2010 (0.824), and lower starting values were associated with greater increases over time. The change with starting-period was only partially explained by changes in practice pattern.

Conclusions: Both the initial PSTR and the subsequent change over time are associated with different PD prescription strategies.

SA-PO734

Are We Worried about Early Complications in Urgent-Start Peritoneal Dialysis? Jiri Vlasak. *Dialysis center, Fresenius Medical Care, Sokolov, Czech Republic.*

Background: Urgent-start peritoneal dialysis is defined as initiation of peritoneal dialysis (PD) in patients with newly diagnosed end-stage renal disease (ESRD) who are not yet on dialysis and who require dialysis initiation less than two weeks after PD catheter placement, but do not require urgent hemodialysis. Theoretically, an increase in the incidence of peritoneal leaks could be assumed.

Methods: Since 2011 in our dialysis center eighty-nine patients have started peritoneal dialysis (PD) with laparoscopically introduced PD catheter. Fifteen of them have initiated urgent-start PD and peritoneal dialysis treatment was initiated with lower volumes of exchange. Seventy four of them started with PD conventional (routinly 3-4 weeks after PD catheter placement). We compared retrospectively these groups focusing on early complications - infections, leaks and catheter migration, both following catheter insertion and PD commencement (within 4 weeks).

Results: Urgent-start patiens were more likely to be referred late, some of them were under the control of a nephrologist, but they experienced unexpected impairment of renal function. We did not record leaks in either group and only three patients from conventional started PD had early catheter migration. There were no infectious complications in either group.

Conclusions: Urgent-start peritoneal dialysis appears to be as safe as conventional (planned) peritoneal dialysis.

SA-PO735

An Effective Chronic Peritoneal Dialysis Model in Uremic Rats Jenny C. Nystrom, Kerstin Ebefors, Borje Haraldsson. *University of Gothenburg, Goteborg, Sweden.*

Background: Thousands of patients undergo chronic peritoneal dialysis (PD) every day but it has been remarkably difficult to establish experimental models of chronic PD in uremic animals. Such models are needed for tests of new dialysis fluids, new medications and techniques in order to further improve treatment of patients with PD. For that purpose, we have developed a new system for chronic automated PD (APD) in uremic rats.

Methods: Rats were made uremic using the nephrotoxin orellanine, a mushroom toxin known to induce uremia through selective destruction of the tubular epithelial cells with no other effects on other organs acutely or chronically, as previously investigated by us both in patients and animal models. The uremic rats and a control group of saline treated rats subsequently underwent APD for three weeks in an automated PD system; one additional set of control rats did not undergo dialysis (n=8 in each group). Each day five exchanges of 15 ml of dialysis fluid (Gambrosol® trio 10) were performed in the APD-system. At the end of the experiment, dialysate, serum and peritoneal tissue were collected for further analysis.

Results: APD worked equally well in both groups of rats. Peritoneal dialysis *per se* induced elevated expression levels of the growth factors TGF-ß and VEGF in the peritoneal fluid and tissue compared to rats that did not undergo APD. Orellanine treatment did not affect the rats negatively part from the induced uremia. Anuric rats did well on dialysis and continued to grow, albeit at slower pace compared to healthy rats with APD.

Conclusions: This study shows that it is possible to maintain uremic rats for at least three weeks in peritoneal dialysis. The elevated levels of levels of TGF-ß and VEGF in the peritoneal fluid and tissues were found to be due to APD itself, and uremia did not affect these biomarkers significantly. The use of orellanine to induce uremia in rats is an effective option without the side effects commonly seen in surgical models of uremia. We believe that the APD model shown here is a new, effective and reliable model for the testing of new dialysis fluids or new therapeutic targets in uremic animals. We hope this will improve dialysis treatment of patients in the future.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO736

Sclerosing Encapsulating Peritonitis Developing Two Years after Peritoneal Dialysis Cessation Rhyan Maditz. *Beaumont Health - Royal Oak, Royal Oak, MI.*

Background: Sclerosing encapsulating peritonitis (SEP) is a rare chronic inflammatory condition of the peritoneum believed to result from recurrent low grade peritonitis. The condition occurs when loops of bowel are encased within the peritoneal cavity by a membrane, leading to intestinal obstruction. Long peritoneal dialysis (PD) duration, acetate-buffered or hypertonic solutions and recurrent episodes of peritonitis may contribute to the development of SEP.

Methods: 46 yo male with PMHx of ESRD secondary to FSGS and loculated sclerosing peritonitis presented with fatigue of one-week duration. He was previously on PD for years but switched to HD two years prior to presentation because he was unable to achieve adequate clearance. He missed two HD sessions prior to arrival due to fatigue. CT performed on admission revealed a large amount of complicated/complex ascites, thickening of the peritoneum and nonspecific colitis and enteritis. Soon after admission, the patient became altered, hypotensive, and was transferred to the medical intensive care unit. Patient was anorexic during the hospitalization, unable to tolerate oral intake. PEG tube insertion was determined to be too risky given his comorbidities and a dobhoff tube was inserted. Methylprednisolone 500 mg daily for three days was trialed, which did not lead to clinical improvement. Further immunosuppression with Imuran/calcineurin

inhibitors was determined to be too high risk. Enterolysis was discussed, however, patient was deemed too high risk for surgery given his debilitated state. Despite the best efforts of a corroboration of medical specialties, the patient unfortunately expired after a one-month hospital stay.

Results:

Conclusions: Clinicians must be aware of SEP as a rare, but dangerous complication of prolonged PD. Patients with SEP secondary to PD progress rapidly and treatment should be immediately initiated after diagnosis. Our patient may have benefited from total parenteral nutrition (TPN), however volume status is difficult to control after TPN initiation. The patient was trialed on a short course of Solumedrol without success. Enterolysis, a last resort treatment modality for SEP, is reported to improve outcomes. Our patient was a poor surgical candidate and likely would have not survived the procedure; therefore, enterolysis was not attempted. Earlier recognition of SEP may have resulted in a better outcome for our patient.

SA-PO737

Trehalose Ameliorates Peritoneal Fibrosis through the Induction of Autophagy and the Downregulation of Snail Protein in Peritoneal Mesothelial Cells Taito Miyake,[1] Norihiko Sakai,[1] Yasutaka Kamikawa,[1] Shinji Kitajima,[1] Tadashi Toyama,[1] Akinori Hara,[1] Yasunori Iwata,[1] Miho Shimizu,[1] Kengo Furuichi,[1] Takashi Wada.[1,2] *[1]Division of Nephrology, Kanazawa University Hospital, Kanazawa, Japan; [2]Department of Nephrology and Laboratory Medicine, Kanazawa University, Kanazawa, Japan.*

Background: Peritoneal fibrosis is a severe complication of peritoneal dialysis, but there are few effective therapies to treat and/or provide for it. Trehalose is a non-reducing disaccharide and can be an osmolyte of peritoneal dialysis solution. Recent studies reveal new biological effects of trehalose as an autophagy inducer and it can be considered to be a hopeful candidate of therapeutic reagent for some diseases. But there are few reports about therapeutic effects of trehalose on fibrotic diseases. We therefore examined if trehalose has anti-fibrotic effects on the peritoneal fibrosis.

Methods: Peritoneal fibrosis was induced by intraperitoneal injection of chlorhexidine gluconate (CG). 5% trehalose or vehicle (normal saline) was administered by intraperitoneal injection to mice every other day. For in vitro study, we isolated primary mouse peritoneal mesothelial cells to investigate the ability of trehalose to attenuate the profibrotic responses.

Results: CG-induced increases in peritoneal thickness, type I pro-collagen mRNA expression and hydroxyproline content were significantly attenuated in trehalose-treated mice (n=4-9). In addition, CG challenges induced a marked peritoneal accumulation of α smooth muscle actin (αSMA)+ fibroblasts that was significantly reduced by trehalose. To specifically identify αSMA+ fibroblasts originated from peritoneal mesothelial cells, dual immunostainings of peritoneal sections were performed using anti-Wilms' tumor 1(WT1) antibody and anti-αSMA antibody. The number of WT1/αSMA dual positive cells in the peritoneum after CG challenges was significantly suppressed by trehalose (n=4). In primary peritoneal mesothelial cells, trehalose attenuates the increase of αSMA and type I pro-collagen mRNA expression induced by TGF-β1, through the induction of autophagy and the downregulation of Snail protein.

Conclusions: Our results suggest that trehalose might be a novel therapeutic reagent for peritoneal fibrosis through the induction of autophagy and the downregulation of Snail protein in peritoneal mesothelial cells.

SA-PO738

Adherence to Mediterranean Diet Predicts the Presence of Left Ventricular Hypertrophy (LVH) and Patterns of LV Remodeling in Peritoneal Dialysis (PD) Patients Dimitra Bacharaki,[2] Ignatios Ikonomidis,[5] Eleftheria-Kleio Dermitzaki,[7] Dimitra Lygerou,[7] Marios Theodoridis,[8] Kostas Stylianou,[7] Ourania Tsotsorou,[2] Anastasia K. Georgoulidou,[4] Olga Balafa,[1] Spiros Katsoudas,[2] Anastasia Korovesi,[6] Dimitra Chatzivasili,[6] Anastasia Markaki,[6] Konstantinos S. Mavromatidis,[4] Periklis P. Kyriazis,[3] Ploumis Passadakis,[8] Dimitrios V. Vlahakos.[2] *[1]University Hospital of Ioannina, Ioannina, Greece; [2]ATTIKON UNIVERSITY HOSPITAL, Athens, Greece; [3]Beth israel Deaconess Medical Center, Brookline, MA; [4]GENERAL HOSPITAL OF KOMOTINI, Komotini, Greece; [5]National and Kapodistrian University of Athens, ATHENS, Greece; [6]Technological Educational Institute of Crete, Heraklion, Crete, Greece; [7]University Hospital of Heraklion, Heraklion, Greece; [8]University Hospital of Alexandroupolis, Alexandroupolis, Greece.*

Background: To examine the impact of adherence to a Mediterranean Diet (MD) on LVH and cardiac geometry in PD patients

Methods: 53 PD patients (27 men) with a mean age of 62±14 years were studied. A MD adherence score (MDS) (range 0-55, 55 representing maximal adherence) was estimated according to a previously reported method (Panagiotakos 2007). Echocardiographic LVH was defined by LV mass index (LVMI) >95g/m^2 in women and >115g/m^2 in men. Based on LVMI and relative wall thickness (RWT), four LV geometric patterns were defined: normal (normal LVMI and RWT), concentric remodeling (normal LVMI and increased RWT>0.42), eccentric LVH (increased LVMI and normal RWT) and concentric LVH (increased LVMI and RWT)

Results: Patients with LVH (n=29) as compared to patients with no LVH (n=24) were older in age (p<0.01), had lower MDS (24.3±2.4 vs. 26.5±2.8; p<0.01) and higher malnutrition inflammation score (p<0.05), pulse pressure (p<0.05) and body mass index (p<0.01). In a multivariate logistic regression analysis adjusted for all factors mentioned above, each 1-point greater MDS was associated with 25% (OR= 0.75, 95%CI:0.57-0.93; *p*<0.05) lower odds of having LVH. The area under the ROC curve for predicting the development of LVH was 0.726 (p=0.005). At an optimal MDS cutoff of 25.5 the sensitivity and specificity of MDS in predicting the occurrence of LVH were 63% and 76%, respectively. Considering LV geometry, there was a progressive decrease in MDS from the normal group (26.4±3.2) to concentric remodeling (26.5±2.7), eccentric (24.7±2.3) and then to concentric LVH (24.1±2.4) group (p=0.038 for the trend). Finally, the MDS was associated positively with serum magnesium (Mg) (rho=0.34; p<0.05) and negatively with serum calcium (Ca) (rho=-0.28; p<0.05)

Conclusions: Greater adherence to a MD is associated with decreased LV mass, an important CVD risk factor and can confer protection against future cardiac dysfunction in PD patients. Whether these associations are partly mediated through opposite changes in serum Mg and Ca levels warrant further investigation

Funding: Clinical Revenue Support

SA-PO739

Immunophenotypic Abnormalities of Uremic Patients Undergoing Peritoneal Dialysis Maria Molina, Claudia Yuste, Enrique Morales, Manuel Praga. *Nephrology Department., Hospital Universitario 12 de Octubre, Madrid, Spain.*

Background: Chronic kidney disease (CKD) is usually associated with various immunologic abnormalities. However, there is a scarcely data regarding the impact of peritoneal dialysis (PD) on these abnormalities.

Methods: We presented a descriptive transversal study analysing lymphocyte absolute counts and subpopulations (CD3+, CD4+, CD8+, CD56+, CD19+, and CD4+/CD8+) in patients undergoing PD. Those patients where compared with a similar cohort of haemodialysis (HD) patients.

Results: Nineteen PD patients were studied (mean time on PD 7.6 ± 6.57 [3-20] months, age 48.4 ±18.7 [22,80] years, 57.9% women, 10 % diabetics, mean weekly KTV 2.52 ± 0.43 [2.24, 2.82]). Fourteen patients started PD after a follow up in low clearance clinic, whereas 4 where transferred from HD (mean time on HD 5.5 ±4.1 [2,14] months) and one patient had a previous kidney transplant. Eleven patients (57.9%) presented absolute lymphopenia (<1200 cells/mm^3), where 63.2% had a low CD3+ account (<850 cells /mm^3), 42.1% low CD4+ (<500 cells/mm^3), 15.8% low CD8+ (<160 cells /mm^3), 21.1% low CD56+ (<60 cells /mm^3) and 36.8% low CD19+ (<100 cells /mm^3). Patients on continuous ambulatory PD (n=6) seem to have lower lymphocyte absolute counts compared with patients on automated PD (n=13) (1163 [927-1498] cells /mm^3 vs 1074 [859-1271] cells /mm^3 respectively], secondary to a lower lymphocyte subpopulations. Lymphopenia seem to be more frequent in patients with longer mean time on PD (mean time on PD on lymphopenics 7 [1-19] months vs 4 [3-7.2] non-lymphopenic, NS). When we compared PD with HD patients, PD patients presented a non-significant trend to low lymphocyte account secondary to CD3+, CD4+ and CD8+. However, PD patients could present less changes on CD19+, known for its atherogenic role.

Conclusions: PD patients presented several changes on them immune mediators that could be different from the observed alterations on HD patients that should be studied with larger studies. The different immunological profile could explain the best survival on PD patients.

SA-PO740

Urgent-Start Peritoneal Dialysis in the Outpatient Setting in an Underserved Urban Area Andres Serrano, Melby Philip. *Mount Sinai Hospital, Chicago, IL.*

Background: Despite an increase in End-Stage Renal Disease (ESRD) incident cases selecting Peritoneal Dialysis (PD), the proportion of patients on PD remains below historical levels achieved in the 80s. There is an increased interest in urgent-start PD, as a way of increasing the number of patients on PD, and decreasing the number of patients initiating hemodialysis (HD) through a central venous catheter. However, implementing these programs could be challenging in a community hospital with scarce resources. Also, there is a great level of concern regarding complications at the moment dialysis is initiated. We are presenting our experience with a group of patients who had urgent-start PD.

Methods:

Results: During a period of 8 years, a total of 81 patients initiated PD. Forty-three patients (53%) had an indication for urgent dialysis initiation, and they either decided in advance for PD or after education regarding RRT then decided for PD. The patients underwent laparoscopic PD catheter insertion, and within 14 days they initiated PD training at the dialysis clinic. During the time in training, they received low volume PD. Of the 43 patients, 21 patients (49%) presented through the ER with no history of kidney disease. The average age was 47.9 years, and the majority of patients were Hispanics (67%). In fourteen patients (33%) the etiology of ESRD was unknown. The average estimated GFR at dialysis initiation was 6 ml/min, and the average number of days between PD catheter insertion and PD initiation was 8 days. Seven patients required in-hospital temporary HD because of impending complications related to uremia, but once stable, they had the PD catheter placed and they initiated PD training as outpatient. Two patients started PD immediately in the hospital after the catheter was placed because of emergent dialysis needs and no HD access. In terms of complications, there were 2 mechanical complications (1 pericatheter leakage, 1 poor catheter flow) and one PD related peritonitis, compared to 0 mechanical complications and 3 PD related peritonitis in patients who started PD the traditional way.

Conclusions: Our experience shows that urgent-start PD is a safe alternative to initiate renal replacement therapy avoiding the use of long term central venous catheters. We also demonstrated that urgent-start PD can be done successfully in the outpatient setting.

SA-PO741

Peritoneal Dialysis Modalities Portend Distinct Decongestive Properties Abhilash Koratala, Olanrewaju A. Olaoye, Amir Kazory. *University of Florida, Gainesville, FL.*

Background: Previous studies have established the adverse impact of lingering fluid overload on the outcomes of patients with ESRD treated with peritoneal dialysis (PD). There is mounting evidence that decongestion, if not associated with significant sodium removal, does not improve the outcomes in specific subsets of patients such as those with heart failure. We sought to explore available evidence on the ability of the two main modalities of PD (i.e. continuous ambulatory PD [CAPD] and automated PD [APD]) with regard to sodium removal.

Methods: Articles cited in PubMed database from January 2000 to March 2017 using key words "peritoneal dialysis", "sodium removal", and "ultrafiltration" were searched. Articles evaluating sodium extraction and ultrafiltration (UF) were reviewed. Clinical trials on comparative impacts of CAPD and APD were selected. Relevant data including urine volume, UF volume, and sodium removal were extracted and compared. Using Pearson product-moment correlation, the degree of linear dependence between sodium removal and UF was determined.

Results: A total of 76 citations were reviewed and 7 studies with 654 participants were included. The mean age was 55.7 years and 55.9% were men. The mean PD sodium removal was 142±44 and 87±23 mmol/day for CAPD and APD respectively (p=0.006). There was no difference between urine sodium excretion between the two groups (42.4±25 and 39.9±21 mmol/day for CAPD and APD respectively, p=0.42). The mean UF volume was 1133±331 and 931±210 mmol/day for CAPD and APD (p=0.09). There was a strong correlation observed between PD sodium removal and UF volume for CAPD (r=0.99, p=0.0) while it was only modest for APD (r=0.6, p=0.15).

Conclusions: Currently available evidence suggests that fluid removal is comparable for CAPD and APD. However, CAPD is associated with significantly greater sodium extraction compared to APD, with strong correlation between UF volume and the amount of sodium removal. Therefore, it is conceivable that CAPD would be advantageous in clinical settings such as heart failure where sodium removal *per se* is of utmost importance. Future prospective studies are needed to explore whether the advantageous sodium extraction by CAPD would translate into improved outcomes in these patients.

SA-PO742

Intradialytic Blood Pressure Stability during Hemodialysis with a Novel Hemodialysis Device Luis Alvarez,[2,3] Paul Chen,[4] Dean Hu,[4] Sarah S. Prichard.[1] *[1]Advisor, Ouset Medical Inc, San Jose, CA; [2]Nephrology, Palo Alto Medeical Foundation, Palo Alto, CA; [3]Outset Medical Inc, San Jose, CA; [4]Outset Medical, San Jose, CA.*

Background: Intradialytic hypotension (IDH) is a common event. The literature suggests that up to 20% of dialysis patients have IDH that requires intervention, over 70% of patients have a decrease of systolic BP (SBP) of 20mmHg and up to 27% have a decrease of of 40mmHg. Patients with frequent IDH have worse outcomes. The Tablo™ Hemodialysis System is a novel technology designed to be simple for both patients and staff to use, which enables self-care hemodialysis in a variety of clinical settings. This study reports on the intradialytic BP of patients dialyzed using Tablo.

Methods: 2012 dialysis treatments using Tablo were assessed in the outpatient setting at 10 dialysis units. Tablo automatically takes and records BP at preset intervals during dialysis as prescribed by the physician and transmits them wirelessly in real time. The percent of patients with a change in SBP of 20 mmHg or 40mmHg, a change in mean arterial pressure of 10mmHg, or a SPB < 90mmHg (with a diastolic BP of <60) were calculated. UF and pre/post weights were also collected.

Results: Results are shown in Table 1

Conclusions: Patients dialyzed with Tablo have less IDH compared to that reported in the literature. The reason for this difference may relate to differences in the patient populations or unique features of Tablo. This important clinical observation needs further study to determine if the use of Tablo could favorably influence outcomes.

Funding: Commercial Support - Outset Medical Inc

Table 1

PARAMETER Sample size (n)	Number (%) 2012
Δ Systolic BP > 20mmHg	765(30%)
Δ Systolic BP > 40mmHg	0 (0%)
Δ MAP > 10mmHg	919 (45.6%)
< 90 Sys BP & < 60 Dia BP	130 (6.5%)
Pre-dialysis weight	81.2 + 20.8 kg (45.1-147.2kg)
Post-dialysis weight	78.5 + 20.6 kg (41.0-145.2kg)
Avg ultrafiltration	2486 + 1094 mL (0-6000ml)
Avg UF rate	8.7 + 3.7 mL/kg/h (0-25.2 ml/kg/hr)

SA-PO743

Achieving Dry Weight, Intradialytic Hypotension, and Outcomes in Patients Undergoing Hemodialysis Salim Bou Slaiman, Nabil Zeineddine. *staten island university hospital, Staten Island, NY.*

Background: Patients with end stage renal disease (ESRD) are known to have high rate of hospitalizations and increased mortality compared to the general population. These morbidities might be related to a set of complications that occur during hemodialysis (HD) sessions, such as hypotensive episodes. On the other hand, reaching the dry weight (DW) during a HD session was also linked to improved outcomes.

Methods: This is a retrospective study with patients recruited in a dialysis center in Staten Island, NY; 36 HD sessions per patient in 3 months duration, with the rate of hypotensive episodes (as defined by KDOQI), and whether a DW was achieved or not, will be collected. Hospitalization rate and complications (cardiovascular and fistula-related) will be recorded for the following 12 months.

Results: 49 patients with a mean age of 60.42 (±14.6) years and their 1729 HD session were analyzed so far. They were 50% males and 50% females. Results didn't show any significant difference in hospitalization or complications in patients who had more episodes of hypotension (p=0.25), however a statistically significant difference was found between patients who achieved DW and those who didn't in terms of having a clotted arteriovenous (AV) access (p=0.048). There was a statistically significant negative correlation between hypotension and achieving DW (R= -0.136; p= 0.022). Also female gender was strongly associated with more hypotensive episodes on one hand, and failure to achieve DW during HD sessions on the other hand (p=0.0001 for both differences).

Conclusions: The results seen so far didn't appreciate any significant effect of hypotension or achieving DW during HD sessions on morbidity and complications in the following year except for a slightly significant difference in having a clotted AV access seen more in patients who achieved their DW; this might be secondary to a more aggressive ultrafiltration for attaining the target weight. The strong negative correlation between achieving DW and hypotensive episodes indicates that the main reason for not achieving DW is hypotension. On the other hand, females were more prone for intradialytic complications such as hypotension and failure to achieve DW. A larger population is needed for a better analysis and to further investigate any relation between intradialytic complications and morbidity and mortality in patients with ESRD.

SA-PO744

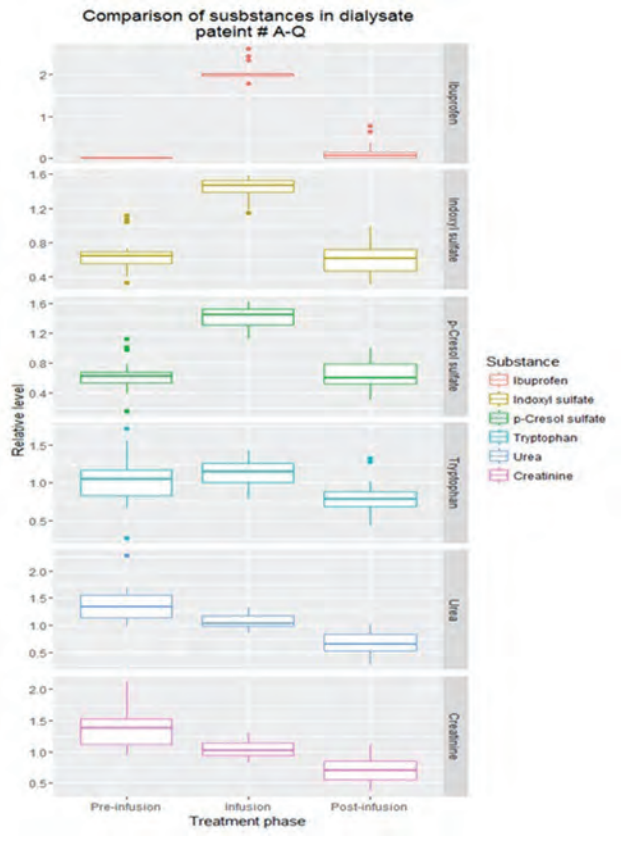
Displacer-Enhanced Dialytic Removal of Protein-Bound Uremic Toxins during Hemodialysis Karla B. Cano Escobar,[1] Xia Tao,[3] Israel Campos,[3] Vaibhav Maheshwari,[2] Jillian Brown,[4] Garry J. Handelman,[4] Stephan Thijssen,[3] Peter Kotanko,[2] BEATRIZ E. CORNEJO MEDELLIN,[1] Magdalena Madero.[1] *[1]INCIC, Mexico, Mexico; [2]Renal Research Insitute, New York, NY; [3]Renal Research Institute, New York, NY; [4]University of Massachusetts, Lowell, MA.*

Background: Hemodialysis(HD) has limited efficiency on protein-bound uremic toxins(PBUTs) removal due to their high albumin binding. Binding competitors to PBUTs("displacers") such as ibuprofen(IBF) can increase the free concentration of PBUTs and enhance dialytic removal. We investigated if infusion of IBF improves the dialytic removal of p-cresyl sulfate(pCS) and indoxyl sulfate(IS)

Methods: Chronic HD patients(National Institute of Cardiology, Mexico City) were studied during a mid-week HD on their standard prescriptions(Q_b300 mL/min;Q_d500 mL/min). IBF(800 mg) was infused at a constant rate into the arterial line, from 20 to 40 minutes into the treatment. Dialysate levels of IS, pCS, IBF, tryptophan(TRP) were measured by HPLC. Concentration data were normalized to the respective patient mean levels, which are reported as mean±SD and were compared before, during and after IBF infusion

Results: Seventeen patients were included(10 females, mean age 36±11 years;HD vintage 24 (3-111) months). IBF infusion was well tolerated. Mean of relative levels in the dialysate outlet before, during and after IBF infusion were 0.67±0.23,1.42±0.14, and 0.61±0.19 for IS, 0.63±0.24,1.42±0.15, and 0.64±0.19 for pCS, respectively, indicating a marked increase of dialytic PBUT removal during IBF infusion. Creatinine and urea, non-protein bound control solutes, continued to decline during the IBF infusion, while TRP, a moderately protein bound molecule, increased non-significantly(Fig.1)

Conclusions: This first-in-man study shows that IBF as a displacer during HD significantly enhanced the dialytic removal of PBUTs. These results should stimulate the search for safe and effective molecules that may be used as displacers during HD



SA-PO745

Assessment of the Impact of Fluid Removal Rate on Central Arterial Waveform Analysis Michael E. Brier,[2] Alfred A. Jacobs,[2] George Aronoff.[1] *[1]DaVita, Inc., Naples, FL; [2]University of Louisville, Louisville, KY.*

Background: Rapid fluid removal during dialysis is associated with poor cardiac outcomes when rates exceed 10 ml/h/kg. We tested the hypothesis that measuring central arterial pressure and waveform analysis including measures of vascular stiffness would help identity those patients at risk.

Methods: Nineteen subjects at the University of Louisville were enrolled in a prospective study measuring central blood pressure and waveform analysis using the SphygmoCor device. Subjects were studied following informed consent on the first and last dialysis treatment of the same week. Measurements were obtained prior to dialysis and at 30 minute intervals. Measurement data were summarized using regression analysis and the resulting slope and intercept were tested against fluid removal rate. We compared central arterial pressures (systolic, diastolic, mean, augmentation), augmentation index, and reflection magnitude. All analyses were performed in SPSS using linear regression.

Results: Subject predialysis weight ranged from 53 to 167 kg. Four subjects were female. Fluid removal rates ranged from 4.1 to 30.8 ml/h/kg and were significanlty related to predialysis weight (p=0.003). The results of the analysis comparing fluid removal rate to measured parameters are shown in the following table.

Conclusions: Comparison of central pressures and vascular stiffness with fluid removal rate demonstrated a significant relationship between central diastolic pressure and central mean pressure. The relationship demonstrated an increase in these measures for those subjects with the greatest fluid removal rate which may be a contributing factor in the observed morbidity and mortality of these patients. This observation is confounded by predialysis weight where the largest fluid removal rates were associated with the smallest patients. Three measures of vascular stiff were not found to be related to fluid removal rates.

Parameter	Regression Estimate	p value
Central systolic pressure	15.2	0.119
Central diastolic pressure	54.6	0.002
Central mean pressure	36.0	0.011
Augmentation pressure	-28.8	0.227
Augmentation Index	-19.2	0.099
Reflection magnitude	-30.8	0.112

Comparison of individual regression slope results to fluid removal rate.

SA-PO746

Routine Hemodialysis Does Not Result in Optimal Plasma Magnesium Concentrations Niki H. Leenders,[2] Tiny Hoekstra,[2] Frans J. van Ittersum,[2] Joost Hoenderop,[1] Marc G. Vervloet.[2] *[1]Radboud university medical center, Nijmegen, Netherlands; [2]VU University Medical Center, Amsterdam, Netherlands.*

Background: Lower plasma magnesium (Mg) concentrations have been associated with a higher overall and cardiovascular mortality in hemodialysis patients. The optimal level of plasma Mg in hemodialysis patients appears to be above the reference range for the healthy population (typically 0.70-1.00 mmol/L). Plasma Mg is not routinely measured after hemodialysis. Aim of this study was to determine the effect of standard hemodialysis treatment on plasma Mg.

Methods: Plasma Mg was measured in duplicate before (Mg_{pre}) and after (Mg_{post}) 6 consecutive dialysis sessions in 34 patients on a regular 3 times weekly hemodialysis schedule with a standard 0.50 mmol/L dialysate magnesium concentration.

Results: Mean Mg_{pre} was 0.88 mmol/L (SD 0.14), 76% of patients had a mean Mg_{pre} below 1.00 and the coefficient of intra-individual biological variation was 5.6%. Post-dialysis, mean Mg was decreased to 0.78 (SD 0.06, p<0.001). Univariate linear regression showed that mean Mg_{pre} and Mg_{post} in an individual were positively correlated (p<0.001) and the regression line indicated that Mg was stable during dialysis at a Mg_{pre} of 0.73, decreased at a Mg_{pre} above 0.73 and increased at a Mg_{pre} below 0.73. In an analysis with linear mixed models a 0.10 mmol/L higher Mg_{pre} was associated with a 0.03 mmol/L higher Mg_{post} (95%-CI 0.024-0.037, p<0.001). If added to the model, baseline factors including gender, age, serum albumin, height and weight; and dialysis characteristics including vascular access type, dialysis duration, ultrafiltration volume, blood flow and dialysis efficiency did not change this association.

Conclusions: In the majority of the hemodialysis patients Mg_{pre} is suboptimal. Routine hemodialysis further declines magnesium in the majority of patients. Current dialysate magnesium concentrations may be too low.

Funding: Private Foundation Support

SA-PO747

Enhanced Phosphate Clearance of Dialyzers by Membrane Inner Surface Structure Optimization Tiancheng Xu,[2] Chunyao Zhang,[2] Xingya Wang,[2] Changjun Mu.[1] *[1]WEGO blood purification products Co., Ltd, Weihai, China; [2]Wego Blood Purification Products Co., Ltd., Weihai, China.*

Background: Elevated phosphate levels increased morbidity and mortality among dialysis patients, so the control of serum phosphate concentration is a considerable clinical approach. To enhance the phosphate clearance of dialyzers, hemodialysis membranes with different properties of inner surface structure have been specially developed and researched.

Methods: Firstly, SEM, dextran retention method (DRM), SurPASS and liquid-liquid displacement porometry (LLDP) were used to characterize the zeta potential, mean flow pore diameter of membranes respectively in MF13 and F6HPS dialyzers. In addition, a case-control study including 105 chronic kidney diseases patients (55 males, 50 females, mean age 56 years) enrolled at two hospitals in China who had been undergone stable hemodialysis for at least three months was conducted in 2016. Polysulphone dialyzers (Fresenius F6HPS or Wego MF13) were applied to each hemodialysis treatment. Finally, the SPSS PASW (statistical package of social science) Statistics v18.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the patient data.

Results: When pH=7.0 (close to the blood pH of the hemodialysis patient), the membrane inner surface zeta potential of MF13 (-17.1 mv) was slightly lower than F6HPS (-15.0 mv), but the mean flow pore diameter of membrane of MF13 (28.3 nm) was much larger than F6HPS (22.2 nm). A thinner inner surface and higher inner surface porosity were obtained in the membrane of MF13. According to the tortuous capillary pore diffusion model, the increase of k_M followed by the r_p has been concluded, which leads the prediction of the removal of phosphate in MF13 being superior to F6HPS theoretically. In fact, the clinical datas with significant differences between MF13 and F6HPS for total 105 HD patients being randomly divided into two groups were presented in Table 1.

Conclusions: The mean flow pore diameter, surface thickness and porosity are the determinant factors of phosphate clearance when the other characteristics of membrane inner surface structure were same, such as membrane surface materials and surface zeta potential.

Funding: Other NIH Support - China Association for Medical Devices Industry (CAMDI)

Outcome	Phosphorus clearance		Phosphorus decrease	
	F6HPS	MF13	F6HPS	MF13
N	53	52	53	52
Mean	152.2	170.3	52.3	57.6
SD	34.6	25.4	12.4	11.6
MSD	4.8	3.5	1.7	1.6
P	P=0.003<0.05		P=0.025<0.05	

SA-PO748

Study of Lung Ultrasound as a Sensitive Tool for Evaluating Fluid Status in Chronic Hemodialysis Patients Hala S. Elwakil. *U of Alexandria - Faculty of Medicine, Alexandria, Egypt. Group/Team: Hemodialysis lung comets group.*

Background: Control of fluid status is an important constituent of adequate and efficient hemodialysis treatment. Dry weight is usually assessed clinically, and several methods have been developed to assess the hydration status in chronic hemodialysis patients. Ultrasonographic lung comets evaluates extravascular lung water while the diameter of inferior vena cava (IVC) estimates central venous pressure, so ultrasound is considered as a useful tool to evaluate the hydration status of hemodialysis patients. The present study was designed to use lung ultrasound to assess lung congestion before and after a dialysis session in correlation to clinical signs and symptoms and the achieved dry weight as well as IVC diameter in hemodialysis patients.

Methods: The present study included 25 patients on maintenance hemodialysis in Alexandria University Hospitals. All the patients were subjected to thorough history taking with special concern on grade of dyspnea and ultrafiltration volume, as well as clinical examination for signs of hypervolemia. Radiological examination including ultrasound lung comets score and diameter of hepatic portion of inferior vena cava (IVC) before and after dialysis session.

Results: The mean lung comets score before dialysis was 54.72±28.47 and decreased significantly after dialysis to 28.52±19.88 (p=0.000). There was a significant positive correlation between ultrafiltration volume and the absolute change of lung comets score (p=0.003) while there was no significant correlation between the ultrafiltration volume and the absolute change of IVC diameter (p=0.219). There was a significant correlation between lung comets score and grade of dyspnea before and after dialysis (p=0.037, 0.001 respectively). Furthermore lung comets were found in asymptomatic patients especially after dialysis. There was a significant positive correlation between the grade of lung comets and IVC diameter both before and after dialysis (p=0.004, 0.003) respectively.

Conclusions: Ultrasound lung comets score is a sensitive marker of lung congestion and even may precede the development of symptoms of lung congestion in hemodialysis patients. Moreover, lung comets score is highly correlated with ultrafiltration volume, thus, it could be used as a good marker for achieving dry weight in hemodialysis patients with more superiority over IVC diameter assessment.

Funding: Government Support - Non-U.S.

SA-PO749

Dietary Sodium Intake and Clinical Outcomes in Hemodialysis Patients Antonio R. Morales,[2] Carlos alberto López lozano,[1] Sandra L. Báez lópez,[1] Anel V. Barbarín vázquez,[1] Javier Soto-Vargas,[2] Jorge fernando Topete reyes.[2] *[1]Clinical Nutrition, University of Guadalajara, Guadalajara, Mexico; [2]Regional General Hosptial 46, Mexican Institute of Social Security, Guadalajara, Mexico, Guadalajara, Mexico.*

Background: Dietary sodium is thought to play a major role in the pathogenesis of hypertension, hypervolemia and mortality in hemodialysis patients. The evidence supporting daily dietary sodium intake of 2 g on hemodialysis is not strong. Our objective was to assess the relation between sodium intake and interdialytic weight gain, hyper and hypotension in hemodialysis sessions, and hospitalizations.

Methods: We included 70 patients receiving thrice-weekly hemodialysis treatment in this prospective observational study. The median follow up was 32.4 months (IQR 24.8-34.3). Available data included demographics, laboratory and clinical measures and details of the dialysis prescription. We examined the dietary sodium intake in a hemodialysis and inter dialytic day with 2-day diet diary-assisted recalls.

Results: There was a male predominance (62.9%). The mean age was 45 years (IQR 29-60.0). The median sodium intake in a hemodialysis day was 1144.5 mg (IQR 576.0-1905.5) and in no HD day of 1499.5 mg (IQR 877-2098.2). The dry weight assessed by impedance was 60.0 kg (IQR 50.4-66.5) the post HD weight was 62.5 kg (IQR 52.0-68.4), with a median ultrafiltration of 2.5 liters (IQR 2.0-3.5), only 24 (34.3%) of the patients were in theirs dry weight. 40 (57%) patients were hypertensive previous to the HD session, and 15 (21.4%) developed hypotension during HD session. There were a weak correlation between sodium intake on HD day and no HD day, with the average ultrafiltration (R2 0.362 and 0.261, p= 0.002 and 0.041 respectively), but no with the systolic or diastolic pressures before and after HD session. There were an inverse association between the amount of sodium intake and hospitalizations (p=0.026). There were no association between sodium intake and the difference of actual weight and dry weight, or the development of hypotension or hypertension.

Conclusions: We find an inverse association between the amount of sodium intake and the number of hospitalizations; however there were no association with interdialytic weight gain, hypertension or hypotension in this cohort of HD patients.

SA-PO750

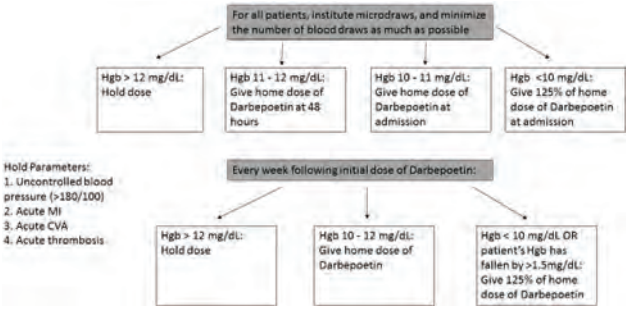
Increasing Erythropoietin-Stimulating Agent (ESA) Administration in Hospitalized ESRD Patients Benjamin Griffin,[3] Elizabeth Flanigan,[1] Cara A. Chao,[5] Diana I. Jalal,[4] John M. Carson.[2] *[1]Memorial Health System, Colorado Springs, CO; [2]None, Aurora, CO; [3]University of Colorado, Aurora, CO; [4]University of Colorado Denver Health Science Center, Aurora, CO; [5]University of Colorado School of Medicine, Aurora, CO.*

Background: Anemia is a common complication in patients with ESRD due to decreased production of erythropoietin in the diseased kidneys. ESAs have been developed to combat anemia in ESRD, and now are widely used to maintain hemoglobin levels in the range of 10 - 11 in ESRD outpatients. ESRD patients who are hospitalized are at greater risk to develop anemia than their outpatient counterparts. Despite this, ESA use rates in the hospital for patients with ESRD patients are exceedingly low. Our magnitude assessment shows that only 30% of patients received their ESA while an inpatient at UCH.

Methods: Given the known harms associated with anemia in the ESRD population, the high rates of anemia following hospitalization, and the low use of ESAs in the inpatient setting, we set out in this QI project to increase inpatient ESA administration from 30% to 60%. Our intervention was to implement a standardized ESA dosing protocol for all ESRD patients based on their outpatient dose and inpatient hemoglobin values (Figure 1). Hold parameters included blood pressure > 180/100, and active myocardial infarct (MI), stroke, or thrombosis. The hemodialysis template was also modified to prompt the provider to include ESA administration information.

Results: Since implementation of the ESA administration interventions in April 2017, 92 ESRD patients have been hospitalized a total of 138 times. During these hospitalizations, the rate of ESA administration, defined as receiving one or more doses of an ESA as an inpatient, was 70%. The rates of thrombosis, cardiac events, and strokes has remained constant since implementation. Hemoglobin values at 3 months from discharge are being collected, but are not yet available for the majority of our patients.

Conclusions: The implementation of an ESA dosing algorithm results in higher rates of inpatient ESA administration without an increase in complications.



SA-PO751

Comparison of Stroke Volume Measurements during Hemodialysis Using Bioimpedance Cardiography and Echocardiography Michael J. Germain,[4] Jyovani W. Joubert,[1] Brian H. Nathanson,[3] Yossi Chait,[5] Nathan W. Levin.[2] *[1]Kidney Care and Transplant Services of New England, Agawam, MA; [2]None, New York, NY; [3]OptiStatim, LLC, Longmeadow, MA; [4]Renal and Transplant Assoc of New England, Hampden, MA; [5]University of Massachusetts, Amherst, MA.*

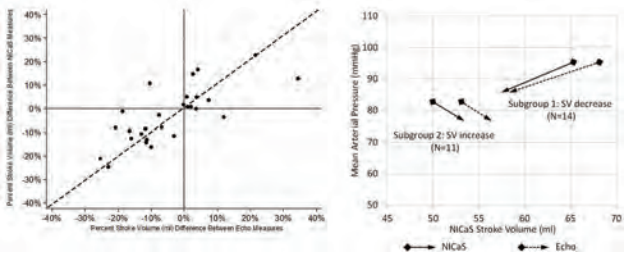
Background: Inadequate fluid management during hemodialysis (HD) has serious morbidity and mortality consequences. Intradialytic fluid management is typically guided by blood pressure, an indirect measure of hemodynamics status. Direct measurements of hemodynamic parameters may improve cardiovascular outcomes by providing empirical bases for intervention. We compare stroke volume (SV) measurements using a non-invasive, regional biompedance cardiography device (NiCaS) with Doppler echocardiography (Echo) in an HD setting.

Methods: Stroke volumes were simultaneously measured using the devices in 17 patients receiving maintenance HD. Measurements were made during two weekly HD treatments, and twice within each HD treatment during the first and last hourd, for a total of 64 SV measurements. Agreement between devices was assessed using linear regression, Pearson's correlation coefficient, a Bland Altman plot, and 4-Quadrant plot each adjusted for repeated measures within patients.

Results: Echo and NiCaS SV mean and 95% CIs were 58.0 (50.1, 65.8) and 56.7 (49.4, 64.0) ml, respectively. NiCaS SV correlated strongly with Echo SV during the first and last hours of treatments ($r = 0.93$, $p<0.001$ and $r = 0.92$, $p<0.001$, respectively). Linear regression of NiCaS on Echo showed a slope of 0.97, 95% CI (0.91, 1.02) which did not differ from 1, $p = 0.20$. A Bland-Altman plot and 4-Quadrant plot (Figure, left) indicated the two methods produced comparable measurements. Mean arterial pressure (MAP) changes during first and last hours of treatments did not correlate with SV changes during the same periods (Figure, right).

Conclusions: NiCaS SV measurements correlate with and are similar to Echo SV measurements. Thus, noninvasive NiCaS technology may be a practical method for measuring SV during HD.

Funding: Commercial Support - New NI Medical



(left) A 4-qaudrant plot showing percent change in SV from the first measurement of both Echo and NiCaS devices; (right) Hemodynamic changes between first and last hours of treatments (means of 2 subgroups) showing lack of correlation between changes in MAP and changes in SV.

SA-PO752

Characteristics of ESRD Patients Admitted for Inpatient Dialysis and Its Contribution to Cost of Care Madhuri Ramakrishnan,[1] Siva sagar Taduru,[1] Reem Mustafa.[2] *[1]University of Missouri Kansas City, Kansas CIty, MO; [2]Nephrology, Kansas University Medical Center, Kansas City, KS.*

Background: The United States Renal Data System (USRDS) 2010 report shows that Medicare spent $29 billion, or almost 6% of its annual budget in 2009, on patients with end stage renal disease (ESRD). This covers a variety of expenditure, including hospital admissions. These admissions can be for complications that require emergent dialysis. We aim to present data on admissions of patients with ESRD for complications including hyperkalemia, acidosis and pulmonary edema requiring inpatient dialysis.

Methods: We identified ESRD patients who were admitted with indications of emergent dialysis, and with a length of stay (LOS) < 2 days, and therefore had conceivably no further indication for continued admission. We searched the National Inpatient Sample (NIS) from 2008 – 2014 using International Classification of Diseases Clinical Modification (ICD-9-CM) codes to identify patients with ESRD on long-term dialysis, who were admitted with a primary diagnosis of hyperkalemia, acidosis, or pulmonary edema. We then identified those patients who received dialysis while inpatient, and those whose LOS was < 2 days. We describe categorical variables as proportions and continuous variables as means.

Results: We identified total of 30,918 admissions between 2008 – 2014 for patients with ESRD, who were admitted with indications for emergent dialysis, and had a LOS < 2 days. These represented 1.03% of all-cause admissions in ESRD patients. The patients' mean age was 52.0 ± 15.6 years and 54% were males. Of these patients, 32.2% were Caucasians, 31.3% African-Americans, and 25.8% Hispanics. Hyperkalemia was the primary indication in 79.2% of cases, pulmonary edema in 12.3%, ESRD in 8%, and acidosis in only 0.5% of cases. 63.6% patients were insured by Medicare, 18.8% by Medicaid, 9.1% by private insurance, and 5.8% were uninsured. 55.9% of these admissions were seen in urban teaching hospitals. The mean total charges were $13,141 ± 9,522 per admission, which amounts to a mean annual charge of $58,041,920.

Conclusions: Our study reports on admissions of ESRD patients with indications for emergent dialysis. We hypothesize that a proportion of which could represent preventable admissions, incurring higher costs than outpatient dialysis. Further studies are needed to identify factors associated with such admissions, and form strategies to prevent them.

SA-PO753

A Twelve Month Retrospective Analysis of Corrected Serum Calcium (CSC) and Parathyroid Hormone (iPTH) in Patients Hemodialyzed with Citrate Acidified Dialysate (CD) Linda H. Ficociello,[1] Ludmila Anderson,[1] Paul Balter,[2] Alice Topping,[2] Claudy Mullon,[1] Robert J. Kossmann.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Renal Research Institute, New York, NY.*

Background: CD contains citric acid (citrate) as the acidifying agent. In the blood, citrate binds to calcium (Ca); however, citrate is quickly metabolized by the liver releasing and restoring Ca levels. The objective of this database analysis was to assess potential effects of CD on CSC and iPTH in chronic hemodialysis (HD) patients who converted from acetate acidified dialysate (AD) to CD.

Methods: HD patients with 3 mos. of AD treatment data (baseline [BL]) followed by 12 mos. of CD treatment data were analyzed. Mean pre-HD CSC and iPTH laboratory values for AD and CD treatment periods were compared by quarters (Q1-Q4) and overall. Subanalyses were carried out by iPTH ranges (<130, 130-600, >600 pg/ml) during BL. Changes in concomitant medications (Ca-based phosphate binders [CaPB], cinacalcet, in-center vitamin D [VitD]) were explored. Paired t-test, chi^2, α=.05 were used.

Results: Non-significant changes in CSC were observed after the CD conversion. Increases in iPTH during Q1 leveled off during Q2-Q4, with the exception of the BL iPTH > 600 pg/ml group where a steady iPTH decrease occurred (BL: 1,095.4 vs. Q4: 905.1 pg/ml, p<.001) (Table). From BL to Q4, the proportion of patients treated with CaPB remained the same (18% vs. 22%), cinacalcet use increased from 22% to 31% (p=.01), and in-center VitD use from 81% to 88% (p<.001).

Conclusions: No changes in CSC, and clinically modest changes in iPTH, followed the conversion from AD to CD. Variability was observed according to the BL iPTH range. Limitations include the observational nature of the assessment and inability to account for wide-ranging clinical practices. Future analyses should incorporate ionized Ca.

Funding: Commercial Support - Fresenius Medical Care North America

iPTH (pg/ml)	BL	Q1	Q2	Q3	Q4	BL-Q4 Change p-value
All Patients n=483 Change from prior quarter	635.5	667.1 +31.6	695.2 +28.1*	686.5 -8.7	639.1 -47.4*	0.9
BL iPTH < 130 n = 31 Change from prior quarter	77.3	241.8 +164.5*	336.2 +94.4*	351.0 +14.9	364.5 +13.5	<001
BL iPTH 130-600 n = 262 Change from prior quarter	368.0	464.1 +96.1*	502.1 +38.0*	515.9 +13.8	478.8 -37.2*	<001
BL iPTH > 600 n = 190 Change from prior quarter	1,095.4	1,016.4 -79.0*	1,020.1 +3.6	976.5 -43.6	905.1 -71.3*	<001

* p-value < .05 for the change

SA-PO754

Control of Uremic Solute Levels in Smaller Pediatric Hemodialysis Patients Frank J. O Brien,[1] Enrica Fung,[1] Natalie Plummer,[1] Timothy W. Meyer,[1] Paul R. Brakeman,[2] Scott M. Sutherland,[3] Tammy L. Sirich.[1] *[1]Stanford University/VAMC Nephrology, Palo Alto, AL; [2]UCSF, San Francisco, CA; [3]Stanford University, Palo Alto, CA.*

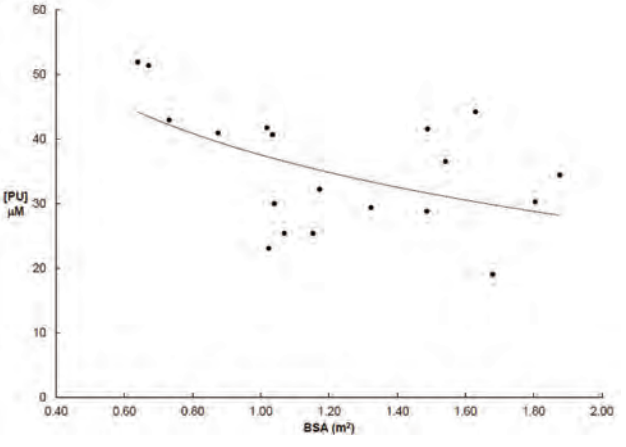
Background: Current guidelines for hemodialysis (HD) in pediatric patients are adapted from those for adults, and dialysis is prescribed proportional to urea's distribution volume to achieve a target Kt/V_{urea}. Dosing HD proportional to volume in smaller patients, however, has been questioned. Uremic waste solutes may be produced in proportion to metabolic rate, may be more nearly proportional to body surface area (BSA) than volume. As body size decreases, the ratio of BSA to volume increases. Plasma levels of uremic solutes may thus remain higher in smaller patients when dialysis is prescribed proportional to volume. We tested this hypothesis by measuring plasma levels of pseudouridine (PU), a uremic waste solute whose generation is proportional to BSA, in pediatric dialysis patients.

Methods: PU and urea nitrogen (UN) were measured in plasma and dialysate obtained at the midweek session in 19 pediatric patients with BSA from 0.64 to 1.88 m^2 receiving thrice weekly HD.

Results: The dialytic clearance (K_d) of PU was proportional to that of UN (K_{dPU}/K_{dUN} 0.83±0.06, R^2 0.95, p<0.001). As expected, the generation of PU assessed by PU recovery in the dialysate was proportional to BSA (189±45 μmol/day/m^2, R^2 0.70, p <0.001). spKt/V was well maintained averaging 1.55±0.24 and did not vary over the range of BSA values. As shown in the figure, however, the pre-treatment plasma PU level was significantly higher in the patients with lower BSA (p <0.05).

Conclusions: Dosing HD by volume may leave uremic solutes at higher levels in smaller pediatric patients. Further studies are needed to determine whether prescription of HD based on BSA provides clinical benefit.

Funding: Veterans Affairs Support



Pre treatment pseudouridine levels vs. Body Surface Area

SA-PO755

Impact of Thrice-Weekly In-Centre Nocturnal Hemodialysis on Health-Related Quality of Life Chance S. Dumaine, Kelvin C. Leung, Jennifer M. MacRae. *University of Calgary, Calgary, AB, Canada.*

Background: Home hemodialysis is associated with improved health-related quality of life (HRQoL); however, few studies have examined the impact of in-centre nocturnal hemodialysis (ICNHD) on HRQoL or on dialysis-related symptoms. We sought to determine whether conversion from conventional hemodialysis to ICNHD (8 hours, thrice weekly) improves HRQoL or reduces the burden of dialysis-related symptoms.

Methods: Prospective cohort study of conventional in-centre HD patients transitioned to ICNHD between October, 2013, and January, 2016. Health-related quality of life and

symptoms associated with dialysis were assessed at baseline using the Kidney Disease Quality of Life-36 (KDQOL-36) survey. Follow-up surveys were completed at 12 months and differences from baseline were assessed using paired t-testing.

Results: Thirty-six patients were enrolled in ICNHD during the study period (69% male, mean age 54). Mean time on dialysis prior to enrollment was 31 months and mean Charlson Comorbidity Index score was 2.19 (range 0-4). Twenty-four patients (67%) were included in final analyses. Table 1 shows changes in the domains of the KDQOL-36. Significant improvements were seen in the "Effects of Kidney Disease" and "Mental Health Composite" domains (increase of 17% and 16%, respectively). Analyses yet to be conducted include an assessment of individual symptoms, as well as a sub-analysis using baseline KDQOL-36 scores to divide the cohort into tertiles.

Conclusions: In-centre nocturnal hemodialysis results in improved HRQoL. Previous studies have shown that patients with the lowest HRQoL at baseline derive the most benefit from home hemodialysis; further analyses will examine whether the same is true for ICNHD. Further studies are needed to determine whether improved HRQoL with ICNHD is associated with improved patient survival.

Table 1: Change in Health-Related Quality of Life

	Baseline Mean (SD)	12-Month Follow-up Mean (SD)	p-value
Symptoms/Problems	73.4 (11.9)	77.0 (12.6)	0.09
Effects of Kidney Disease	48.2 (23.1)	56.4 (22.3)	0.046
Burden of Kidney Disease	29.7 (25.2)	31.8 (23.1)	0.33
Physical Health Composite	34.7 (7.3)	36.4 (10.7)	0.24
Mental Health Composite	43.9 (12.1)	51.0 (10.5)	0.003

Table 1: Mean and standard deviations for each of the 5 domains of the KDQOL-36. Each domain scored on a scale of 1 to 100, with higher values representing superior HRQoL.

SA-PO756

Using Intradialytic Blood Pressure Slopes to Assess Extracellular Volume in Hemodialysis Patients Peter N. Van Buren,[2] Hao Liu,[1] Mark T. Sonderman,[1] Shani Shastri.[2] *[1]Internal Medicine, Nephrology, UT Southwestern Medical Center, Dallas, TX; [2]UT Southwestern, Dallas, TX.*

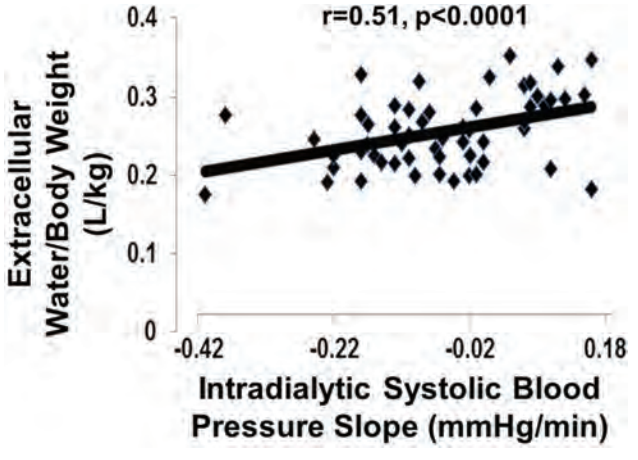
Background: Extracellular volume (ECV) overload increases mortality risk in hemodialysis (HD) patients, but there is no standardized clinical method to assess ECV in them. We evaluated the association between slopes of multiple intradialytic blood pressure (BP) measurements with bioimpedance spectrscopy (BIS)-determined measurements of ECV overload as a novel method to assess ECV using routine clinical data.

Methods: We measured systolic BP every 30 minutes in a mid-week HD treatment. Using multifrequency BIS, we measured pre and post HD extracellular water (ECW), total body water (TBW), ECW/TBW and ECW/weight. Using Pearson correlation and mixed linear regression we compared associations between post-HD ECV overload with multiple peridialytic BP metrics.

Results: Mean intradialytic BP slope (n=58) was -0.06 mmHg/min (±0.1). The correlation between this slope and post-HD ECW/body weight was 0.4 (p=0.003) in all subjects and 0.51 (p<0.0001) in those with post-HD hypertension (SBP>130 mmHg, n=45)(figure 1). This significant association persisted after controlling for age, gender and ultrafiltration rate (β=1.9, p<0.001) and was stronger than associations wtih slope and other ECV metrics. ECW/body weight had a stronger association with intradialyltic BP slope than with pre-HD (r=-0.2, p=0.3), post-HD (r=0.2, p=0.1), or delta SBP (r=0.2, p=0.09).

Conclusions: There is a significant correlation between intradialytic BP slopes and BIS based measurements of ECV overload in hypertensive HD patients. The slope of multiple intradialytic BP measurements better assesses ECV than pre, post or delta SBP. Determining intradialytic blood pressure slope is an innovative way to objectively assess ECV in HD patients.

Funding: NIDDK Support



Among HD patients with post-HD SBP>130, the correlation coefficient for Intradialytic Blood Pressure Slope (mmHg/min) and post-HD ECW/body weight is 0.51 (p<0.0001).

SA-PO757

Impact of High Convective Volumes on Metabolic Profile and Body Composition of Diabetic Patients on Online Hemodiafiltration Nicolás Macías,[4] Tania Linares,[3] Almudena Vega,[6] Esther Torres aguilera,[4] Alba Santos,[1] Marian Goicoechea,[2] Eduardo Verde,[2] Soraya Abad.[5] *[1]Gregorio Mara?on Hospital, Madrid, Spain; [2]Hospital General Universitario Gregorio Marañon, Madrid, Spain; [3]H.G.U. Gregorio Marañon, Madrid, Spain; [4]HGUGM, Madrid, Spain; [5]HOSPITAL GREGORIO MARAÑON, MADRID, Spain; [6]Hospital Gregorio Marañón., Madrid, Spain.*

Background: OL-HDF with high convective volumes improves patient survival compared with high-flux hemodialysis. It has been proposed to limit the amount of convective transport in patients with diabetes mellitus, due to glucose load that is administered with replacement fluid. The aim of this study is to analyze the influence of substitution volume(SV) in the evolution of metabolic profile of diabetic patients incident on OL-HDF.

Methods: Prospective observational study in 29 diabetic patients incident on postdilution OL-HDF, three 4-hours sessions weekly. Baseline data included clinical, demographic, laboratory and body composition(BIS) parameters. Laboratory and SV were collected every four months, and in 23 patients another BIS was performed after a minimum follow-up of one year. Variations of glycosylated hemoglobin(HbA1c), triglycerides(TG), total cholesterol, LDL-c, HDL-c, albumin, prealbumin and C-reactive protein(CRP) were calculated at one-two-three years, and at the end of follow-up. Also quarterly and annual variations were calculated, as well as changes in body composition. Variations were collected to evaluate the influence of SV in these changes.

Results: Age at baseline was 69.7±13.6years, 62.1%male, with 48(35.5 – 76)months on dialysis, 72.3±13.9Kg weight, 27.1±5.4kg/m2 BMI, 1.78±0.16m^2 BSA. 81.5%received insulin, 7.4%antidiabetic drugs and 51.9%statins. Mean SV was 26.9±2.9L per session and follow-up(time on OL-HDF) was 40.4±26months. We found significant correlation between SV and final changes in HDL-c(0.385,p0.039), prealbumin(0.404,p0.003) and CRP(-0.498,p0.007). Also convective dose adjusted with BSA was related with changes in HDL-c(0.393,p0.035) and inversely correlated with changes in TG(-0.423,p0.022) and CRP(-0.573,p0.007) since the second year of follow up. Quarterly comparisons(n 271) showed that quarterly SV correlated with variations in HbA1c(-0.146,p0.021). No correlation was observed between SV and changes in weight, body water, lean or fat tissue in the period between BIS measurements.

Conclusions: Higher convective dose is associated with a slight improvement in metabolic profile in diabetic patients in OL-HDF. There is not evidence to restrict the convective transport in diabetic patients due to the glucose content of the replacement fluid.

SA-PO758

In-Vitro Dialysate Regeneration Using Dharma, the EasyDial Portable Hemodialysis Machine Osman S. Khawar,[1] Timothy R. Mcnamara,[2] Sarah L. Foster.[2] *[1]Balboa Nephrology Medical Group, Escondido, CA; [2]EasyDial, Irvine, CA.*

Background: Dharme is a unique, fully portable dialysis machine, which uses only 5 Liters of dialysate per treatment. In order to achieve this limited dialysate volume, dialysate is regenerated using a chemical filter through which dialysate in recirculated continuously during dialysis, while electrolyes are supplied via an infusion into the dialysate reservior.

Methods: Bovine blood was tested during a 2 hour dialysis, using a 70 mL concentrated mixture of calcium, potassium, and magnesium administered continuously during into 5 Liters of dialysate using an ambIT peristalitc pump. Samples of dialysate were collected every 15 minutes and analyzed for electrolyte concentrations.

Results: The electrolytes were continuously present at acceptable concentations, indicating that dialyate was regenerated during the dialysis. Concentrations are provided in table 1. Baseline and 2 hour concentrations for each ion were: Calcium 37.06 ppm 36.67ppm, Magnesium 10.63ppm and 13.58ppm, potassium 71.03ppm and 5.15ppm.

Conclusions: These results verify that continuous infusion of key electrolytes into the dialysate during dialysis with Dharma maintains electrolyte concentrations in regenerated dialysate. Dharma offers the unique features of portability (18 lbs), no fixed water connection (5L dialysate) and the possilbiity for significantly reducing dialysis treatment times.

Funding: Commercial Support - EasyDial Inc

Electrolyte Concentrations in Dialysate

Time	Calcium ppm	Magnesium ppm	Potassium ppm
0	37.96	10.63	71.03
15	31.65	9.29	53.2
30	47.07	15.42	42.02
60	60.44	17.82	9.49
75	41.15	14.38	5.26
90	35.47	13.21	3.13
105	36.03	13.45	3.1
120	36.67	13.58	5.15

SA-PO759

Quality Improvement Empowerment: Dialysis Clinic Staff Lead Projects for Change Laura J. Maursetter. *University of Wisconsin School of Medicine and Public Health, Madison, WI.*

Background: Quality improvement provides an avenue for delivering healthcare that meets the best practices standards across medicine. Dialysis centers strive to provide the optimal care but in the era of dialysis center ratings measures of care delivery become even more impactful. There are many centers that have provided examples where quality improvement projects have improved the delivery of care. There are none that have created a system where all staff are educated about quality improvement and encouraged to lead their own project.

Methods: In the fall of each year, a portion of the staff meeting is dedicated to quality improvement (QI). The dialysis director talks about the differences between quality improvement and research, noticing gaps in care, methods of analyzing and measuring a problem and thinking of interventions. Each staff member is encouraged to develop a indea and there is a simple QI curriculum available to assist in facilitating the project. Periodically the dialysis direct and charge nurse discuss the projects with each leader and the results of the projects were brought to the hospital administration at the end of the year.

Results: After this program was started, there have been 12 projects initiated. In the first year of the program 80% of the staff developed a project. All types of staff led projects: these included the dietician, the social worker, 75% of the nurses, and 100% of the dialysis technicians. The project topics included improved patient knowledge of emergencies, improved knowledge of dialysis treatment options, discussions with patients about the importance of dialysis adequacy and maintaining the prescribed dialysis schedule, improvement in the time the staff spend with each patient, increase fun activities for patients during dialysis, improved referrals for positive depression screening, and improvement in the albumin level.

Conclusions: Creating an environment and formalized QI program that empowers employees to notice problems and create solutions was able to make an impact on the quality of care provided in this small dialysis center. This simple curriculum could be translated into larger dialysis units to improve the quality of care and satisfaction of the patients or employees of the unit.

SA-PO760

UK Clinical Experiences of a New Expanded Hemodialysis Therapy with a Novel Medium Cut-Off Dialyzer Jyoti B. Baharani,[1] Bernard Barrios,[1] Debbie Hopkins,[2] Wyn Passmore.[2] *[1]Heart of England NHS Foundation Trust, Birmingham, United Kingdom; [2]Morriston Hospital, Swansea, United Kingdom.*

Background: Middle molecules are associated with the pathology of uremia, and their removal is enhanced by increased convection with hemodiafiltration (HDF) therapy. However, HDF therapy may not be suitable for, or available to, all patients. A newly developed medium cut-off (MCO) membrane allows hemodialysis (HD) to be expanded in terms of middle molecule removal (HDx therapy) using conventional HD infrastructure. Here, we describe the experience of two UK clinics trialing HDx therapy.

Methods: At Heartlands Hospital (HH), the patient demographic (n=8) was: 48–90 years of age, mixed ethnicities, and 1–14 years of HD experience. Patients (treated thrice weekly) were switched from high-flux HD with a polysulfone dialyzer (FX60 or FX80, Fresenius) to HDx therapy with the MCO membrane (Theranova 400, Baxter). At Morriston Hospital (MH), patients (n=18) were 25–91 years of age with 2–16 years of HD experience. Patients who had failed to tolerate (n=14) or tolerated (n=4) HDF therapy were switched to HDx therapy with the MCO membrane. Reduction ratios (RRs) of beta-2-microglobulin (β2M) and albumin loss were assessed; data are based on averages of 3 dialysis sessions (HH) or 1 dialysis session (MH).

Results: At HH, average β2M RRs (post- vs pre-dialysis level) with HDx therapy were 69.3% (Week 1) and 69.4% (Week 9) vs 48.8% with high-flux HD. At Week 9, serum albumin levels increased during dialysis by 0.8 g/L. Following 9 weeks of HDx therapy, pre-dialysis levels of β2M were reduced by 11.7%, and no difference in albumin level was seen. At MH, average β2M RRs with HDx therapy were 71.0% (Week 1) and 73.9% (Week 9). For patients who tolerated HDF, at Week 1 β2M RRs were 72.2% and 73.9% with HDx and HDF therapy, respectively. Based on serum albumin levels, albumin loss in both groups was minimal.[a] No adverse events were noted; 1 patient with arthritis did not experience any arthritic flare-ups during HDx therapy.

Conclusions: HDx therapy was convenient, simple to implement, and achieved high β2M RRs with low albumin loss. It offers opportunity for achieving the clearance of middle molecules delivered by HDF, when patient factors exist or HDF is not available.
[a]Based on 2 of 4 HDF patients and all 14 HDx patients.

SA-PO761

Comparison of Albumin Binding Capacity and Uremic Toxins in Hemodiafiltration versus Novel Dialysis Membrane Sebastian Koball,[4] Christina Westphal,[1] Silvius Frimmel,[2] Michael Hinz,[5] Sebastian Klammt,[3] Steffen R. Mitzner.[4] *[1]Fraunhofer Institiut for Cell Therapy and Immunology, Rostock, Germany; [2]Rostock University Medical Center, Rostock, Germany; [3]University Rostock, Rostock, Germany; [4]University of Rostock, Rostock, Germany; [5]Universität Rostock, Rostock, Germany.*

Background: Albumin is an important transport protein for non-water-soluble protein-bound drugs and uremic toxins. A decreased transport capacity may lead to endogenous intoxication and worsening of uremic symptoms. It is known that the albumin binding capacity (ABiC) is reduced in patients with advanced stages of chronic kidney disease. Moreover, ABiC is an important marker of the detoxification capacity of extracorporeal treatments. It is presumed that open-pored filters remove high molecular substances more efficiently than conventional treatment, thereby increasing the detoxification capacity. The Baxter-Theranova (HDx) filter is the first approved filter which could meet these requirements. The study aim was to evaluate the effectiveness of the HDx dialyzer with regard to the improvement of ABiC and the removal of uremic toxins (e.g.hippuric acid, paracresylglucoronid, indoxylsulfate, paracresylsulfate, indolacetic acid), phosphate, urea, albumin concentration during standard hemodialysis/ hemodiafiltration treatment.

Methods: The efficacy of HDx was assessed by comparing Baxter Theranova 500 filters with the standard Fresenius FX80 filters (HDF). We included 32 patients with dialysis-dependent chronic kidney disease (stage 5d); above age 18 who provided written informed consent. Key exclusion criteria were acute infectious diseases, bleeding and a hospital stay within the last 14 days. All patients were first treated with HDF for 14 days (3 times a week) and blood samples were drawn (15ml) before and after treatment at study entry, before and after first HDx treatment and before/after 6 HDx treatments, to determine ABiC and other clinically relevant parameters. Alteration of ABiC and other relevant parameters was assessed by using Wilcoxon matched-pairs signed-rank test.

Results: ABiC improved significantly in both therapies (HDx/HDF), however, no significant differences were found between the two therapies. The same was true for phosphate, indoxylsulfate, urea, creatinine, and uric acid. A reduction of albumin concentration during HDx treatment was not observed, neither during single treatment nor over the 14 days period.

Conclusions: Expanded hemodialysis enabled by Theranova demonstrates equal effects on ABIC and uremic toxins in comparison to OL-HDF.

Funding: Commercial Support - Baxter Healthcare

SA-PO762

Influence of Dialysis Membranes on Bisphenol A Serum Levels in Online Hemodiafiltration Sebastian Mas,[3] Enrique Bosch,[1] Alberto Ruiz,[1] Esther Civantos,[1] Jesus Egido,[2] Alberto Ortiz,[2] Emilio E. Gonzalez-parra.[2] *[1]IIS- FJD, Madrid, Spain; [2]Fundacion Jimenez Diaz, Madrid, Spain; [3]IIS-FJD, Madrid, Spain.*

Background: In uremia, the environmental toxin Bisphenol A (BPA) accumulates bound to proteins. BPA-containing dialyzers contribute to increase plasma BPA concentration in conventional hemodialysis patients. Online hemodiafiltration (OL-HDF) more efficiently clears high molecular weight molecules, and this may improve BPA clearance. However, OL-HDF requires high infusion volumes of replacement fluid generated online by using BPA-containing membranes and, thus, can be a source of BPA load. Objectives:To assess plasma BPA levels in OL-HDF patients using BPA-free or BPA-containing dialyzers.

Methods: In a prospective study, plasma BPA was assessed at baseline and 3 months after switching from baseline BPA-free polynephron to BPA-containing polysulfone (n=31) dialyzers, or from baseline polysulfone to polynephron (n=27) dialyzers in OL-HDF patients. Results were compared to a prior study on conventional hemodialysis.

Results: OL-HDF patients had lower plasma BPA than those in conventional hemodialysis (12.12±15.91 vs. 64.55±93.8 ng/mL) and both were several fold higher than healthy controls (<2 ng/ml). However, this was influenced by the dialysis membrane. Thus, baseline BPA was 8.79±7.97 ng/ml in patients dialyzed ≥6 months with polynephron versus 23.42±20.38 ng/mL with polysulfone. During the first single OL-HDF session with the switch membrane, BPA decreased in the polysulfone-to-polynephron group (pre-dialysis 23.42±20.38 ng/ml to post-dialysis 6.44±10.77 ng/mL, $p < 0.01$), but remained unchanged in polynephron-to-polysulfone patients. After 3 months on polysulfone, BPA levels rose non-significantly from 8.79±7.97 to 11.02±16.17 ng/mL in the polynephron-to-polysulfone group, while they decreased 51% in the polysulfone-to-polynephron group ($p<0.01$).

Conclusions: Optimal reduction in BPA levels is achieved by using OL-HDF with BPA-free dialyzer membranes. Attempts at optimizing net BPA clearance in OL-HDF are justified by the residual higher plasma BPA levels when compared to healthy controls.

Funding: Commercial Support - Nipro corporation

SA-PO763

Dialyzer Reuse in Prevalent Hemodialysis Patients: Mortality and Clinical Outcomes Daniel Murillo brambila,[1,2] Monica C. Jimenez cornejo,[1,2] Karina Renoirte,[1,2] Gabriela J. Abundis Mora,[1,2] Guillermo Garcia-Garcia.[1] *[1]Hospital Civil De Guadalajara, University of Guadalajara, Guadalajara, Mexico; [2]Nephrology, PISA SANEFRO, Jalisco, Mexico.*

Background: Dialyzers reuse has been a common practice in the US. In Mexico, economical restrains related to CKD have forced to seek cheaper options to provide RRT among ESRD patients. Thus, dyalizer reuse has become a common practice in most of the hemodialysis clinics across the country. It is regulated by the Ministry of Health. Previous studies have reported no difference in mortality among patients with dialyzer reuse versus one single use. The aim of this study was to evaluate the clinical implications of dialyzer reuse in prevalent HD patients from Jalisco, Mexico

Methods: A cross-sectional, multicenter study in prevalent hemodialysis patients in Jalisco. 2561 insured and uninsured patients conformed the national data base. Only patients who had a Kt/V ≥1.2 were included for analysis. Mortality, vascular access, clinical variables and laboratory values were compared among patients with reusable dialyzers and those with single use dialyzers.

Results: 2561 patients were evaluated for analysis. Only 597 patients (23.3%) had a kt/v ≥ 1.2. Reuse of dialyzer was performed in 482 of them (80.7%). Average reuse was 5.5 times per dialyzer (range 1-12). Serum electrolite, creatinine, uric acid, albumine, PTH, iron kinetics, urea pre/post did not differ among both patients who underwent reuse of dialyzer vs those with one single use dialyzer.

Conclusions: Serum electrolite, creatinine, uric acid, albumine, PTH and iron kinetics did not differ among patients who underwent reuse of dialyzer vs those with one single use dialyzer. Hemoglobine, urea pre and post values were statistically better for patients with dialyzer reuse. Time to death and mortality did not differ among both groups. Dialyzer reuse continues to be a controversial practice, but according these findings, it appears to be a safe. Further studies are needed to asses the long term clinical impact of this practice, since the financial panorama of CKD points to an urgent and generalized need to optimize economical resources in order to provide safe treatments to more patients at lower costs.

Multivariate analysis	*p*	OR	CI 95%
# of vascular acceses	<0.01	1.2	1.1-1.4
Fistulae	0.038	1.6	(1.02-2.5)
Hemoglobin	0.58	0.9	0.6-1.2
Hematocrite	0.83	0.98	0.86-1.1
Urea Pre	0.48	1	(0.9-1)
Urea Post	0.69	1	0.9-1)
Weekly iron	0.16	1	1-1.09
Heparine bolus	0.23	1	(0.99-1)
Intradialitic heparine	0.65	1	0.99-1)
Multivariate analysis with binary logistic regression			

SA-PO764

Acute Effects of Hemodialysis on Circulating Microparticle Levels Fengxia Xiao,[3] Hussein Abujrad,[4] Teik C. Ooi,[4] Alexander Sorisky,[3] Marcel Ruzicka,[2] Dylan Burger.[1] *[1]Kidney Research Centre, Ottawa, ON, Canada; [2]None, Ottawa, ON, Canada; [3]Ottawa Hospital Research Institute, Ottawa, AB, Canada; [4]University of Ottawa, Ottawa, ON, Canada.*

Background: Individuals with end stage kidney disease (ESKD) are at increased risk of cardiovascular complications. Previous studies have shown that levels of circulating microparticles are increased in ESKD and that an increase in circulating endothelial microparticles is a predictor of cardiovascular morbidity and mortality (Amabile, 2012). The purpose of this study was to examine the effect of a single hemodialysis session on levels of circulating microparticles in patients with ESKD.

Methods: We studied 23 patients (age 58±3 years, 12 M/11F) undergoing a single hemodialysis session. Levels of circulating total, endothelial, leukocyte, and platelet microparticles were assessed by flow cytometry immediately prior to, and at the completion of, hemodialysis (3 times weekly, 4 hour sessions).

Results: Participants had been treated by hemodialysis for 50±8 (mean±SEM) months prior to enrollment. The mean ultrafiltration volume on the day of study was 2.06 ±0.17 L. The level of total microparticles was significantly reduced by ~55% following hemodialysis ($5.15x10^7$±1.1 $x10^7$ [Pre] vs $2.32x10^7$±$4.27x10^6$ [Post], P<0.05). Similarly, the level of platelet microparticles was significantly reduced by ~75% following hemodialysis ($4.33x10^7$±1.06 $x10^7$ [Pre] vs $1.06x10^7$±$3.8x10^6$ [Post], P<0.05). In contrast, the level of leukocyte microparticles was not altered by hemodialysis ($2.65x10^6$±3.19 $x10^5$ [Pre] vs $2.15x10^6$±$3.2x10^5$ [Post], P=n.s). The level of endothelial microparticles also remained the same before and after hemodialysis ($2.09x10^6$±4.85 $x10^5$ [Pre] vs $1.39x10^6$±$2.94x10^5$ [Post], P=n.s). There was no correlation between the degree of ultrafiltration and the reduction in platelet, leukocyte, or endothelial microparticles.

Conclusions: Hemodialysis is associated with reductions in circulating total and platelet microparticles with no impact on circulating endothelial or leukocyte microparticles. These results suggest that dialytic clearance selectively influences the levels of circulating microparticle subpopulations in ESKD patients undergoing hemodialysis. Consideration should therefore be given to the timing of sampling for circulating microparticles in any study involving hemodialysis patients.

Funding: Government Support - Non-U.S.

SA-PO765

Cognitive Impairment and Depression among Hispanic Hemodialysis Patients in Puerto Rico Neysha J. Sanchez,[2] Angel F. Delgado garrastegui.[1] *[1]Internal Medicine, University of Puerto Rico, Medical science campus, San Juan, PR; [2]University of Puerto Rico, San Juan, PR.*

Background: Cognitive Impairment and Depression are prevalent in patients with End Stage Renal Disease on hemodialysis (HD). Studies have shown as many as two thirds of these patients suffer cognitive impairment, which is higher than in the age matched population. Cognitive Impairment in HD patients is an important public health problem given the increasing age and prevalence of comorbidities, such as diabetes and vascular disease. Similarly, depression with prevalence of 40% in these patients has significant effects on individual patient well-being and delivery of medical care. The prevalence of cognitive impairment and depression is unknown in our Hispanic population.

Methods: The population is 43 of 55 patients receiving ambulatory HD at The University Hospital in PR three times per week. Exclusion criteria included patients suffering from dementia or prior cerebrovascular accident. The instrument included The Beck Depression Inventory and The General Practitioner assessment of Cognition. Statistical Analysis was summarized using descriptive statistics for continuous variables and frequency distributions for categorical variables. Chi-square (X 2) test and Fisher's test were conducted to evaluate the associations between cognitive impairment and depression.

Results: The prevalence of depression was 26.30% and of cognitive impairment 88%. There was no statistically significant association between age, gender, education status, income or dialysis vintage and depression. Most of the subjects who screened positively for depression were active smokers (p-value < 0.05). There was no statistically significant association between age, gender, smoking status, education status, income or dialysis vintage and cognitive impairment.

Conclusions: There were no statistical significant associations between gender, age, education, income and dialysis vintage with the presence of cognitive impairment and depression. Subjects who screened positively for depression reported more smoking. As found in others studies, cognitive impairment was common and undiagnosed in HD patients. Further studies are needed to determine whether dialysis exacerbates the cognitive impairment attributable to underlying disease. Contrary to the findings in our study, depression and education levels were shown to be independent predictors for cognitive impairment in multivariate analysis of other studies.

SA-PO766

Effect Modification by Age and Pulse Pressure (PP) on the Association Between Mediterranean Diet (MD) and Telomere Length (TL) in Hemodialysis (HD) Patients Anastasia Markaki,[3] Dimitra Lygerou,[4] Eleftheria-Kleio Dermitzaki,[4] Periklis P. Kyriazis,[2] Andriana Pilarinou,[3] Kalliopi K. Gkouskou,[5] Aikaterini Charonitaki,[3] Konstantina Kyriakidi,[3] Argyro Gioume,[3] Dimitra Bacharaki,[1] Kostas Stylianou.[4] *[1]ATTIKON UNIVERSITY HOSPITAL, Athens, Greece; [2]Beth israel Deaconess Medical Center, Brookline, MA; [3]Technological Educational Institute of Crete, Greece, Siteia, Greece; [4]University Hospital of Heraklion, Heraklion, Greece; [5]Embiodiagnostics, Athens, Greece.*

Background: TL is considered to be a biological marker for aging. Telomere shortening is associated with age-related health outcomes and risk of death. Here, we investigated whether the associations of greater adherence to a MD with longer TL depend on age and pulse pressure in HD patients

Methods: 46 HD patients, (28 men) were studied. A MD adherence score (MDS range 0-55, 55 representing maximal adherence) was estimated using a previously reported method (Panagiotakos 2007). TL was measured from leukocyte DNA using a realtime PCR to measure T/S ratio, the ratio of telomere (T) to single copy gene (S) sequence. TL was analyzed as a dichotomous variable: above (High TL group) and below (Low TL group) the median value of T/S ratio (1.13)

Results: Patients in the high TL group were younger in age (56±14 vs. 70±9 years; p<0.001), had higher MDS (30±4 vs. 28±3; P=0.037) and lower PP (58±14 vs.68±14 mmHg; p=0.02), prevalence of diabetes mellitus (DM)(8.7 vs. 34.8 %; p=0.032) and peripheral vascular disease (PVD) (30.4 vs. 65.2%; p=0.018). Logistic regression analysis, after adjusting for age, PP, DM and PVD, showed that MDS was associated with longer TL (OR=1.6, 95%CI: 1.13-2.28; p=0.009). An interaction effect between MDS and age was significant (p=0.014), after controlling for the main effects, CVD, DM and PP. The same was true for the interaction between MDS and PP (p=0.006). Stratifying by age (above and below the median= 65 years), we found a significant association between MDS and TL in the younger age group (OR=2.269, 95%CI: 1.021-5.042; p=0.044), but not in the older patients. Also, stratifying by PP tertiles (first <56 mmHg vs. second and third), a significant association between MDS and TL was detected in the high PP group (OR=1.49, 95%CI: 1.051-2.13; p=0.025). Similar results were obtained when TL was examined as a continuous variable.

Conclusions: Our results show that adherence to a MD is associated with longer TL in patients under the age of 65 and in patients with increased arterial stiffness (PP>56 mmHg), indicating that adoption of a MD may have beneficial effects in these specific subgroups of HD patients.

Funding: Clinical Revenue Support

SA-PO767

Variability of Pre-Dialysis Serum Sodium and Its Association with Survival in Hemodialysis Patients: Results of the MONDO Consortium

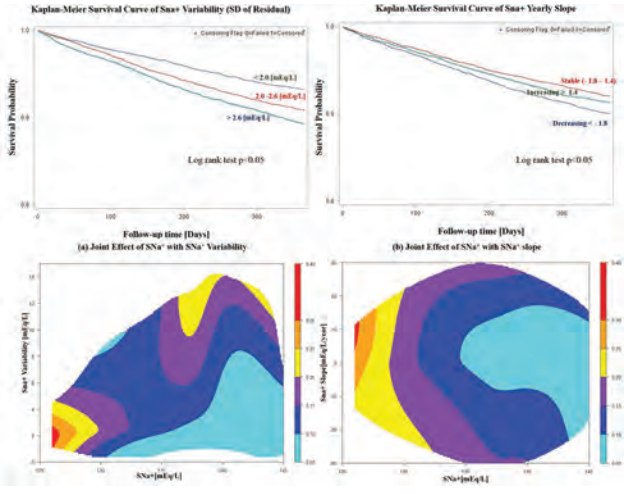
Xiaoling Ye,[8] Jeroen Kooman,[6] Bernard J. Canaud,[1] Nathan W. Levin,[7] Cristina Marelli,[2] Albert J. Power,[9] Frank van der Sande,[5] Stephan Thijssen,[8] Xiaoqi Xu,[3] Len A. Usvyat,[4] Yuedong Wang,[10] Peter Kotanko,[8,11] Jochen G. Raimann.[8] *[1]FMC Deutschland GmbH, Bad Homburg, Germany; [2]Fresenius Medical Care Argentina, buenos Aires, Argentina; [3]Fresenius Medical Care Asia Pacific, Hong Kong, China; [4]Fresenius Medical Care North America, Melrose, MA; [5]Maastricht University Medical Centre, Maastricht, Netherlands; [6]Maastricht University Medical Centre, Maastricht, Netherlands; [7]New York, NY; [8]Renal Research Institute, New York, NY; [9]Richard Bright Renal Unit, Bristol, United Kingdom; [10]University of California - Santa Barbara, Santa Barbara, CA; [11]Icahn School of Medicine at Mount Sinai, New York, NY. Group/Team: MONDO initiative.*

Background: Pre-dialysis serum sodium (SNa^+) is the main determinant of plasma osmolality. Whereas hyponatremia is associated with adverse outcomes in hemodialysis (HD) patients (pts), variations swings in SNa^+ may lead to fluid shifts between the extracellular and intracellular spaces and cell volume changes. The aim of the study was to explore the relationship between SNa^+, the rate of change (slope), and the SD of the residual (variability) of SNa+ with all cause of death.

Methods: All incident and prevalent pts from the MONDO initiative with at least 6 SNa+ measurements during baseline (1st year in HD) were selected. Follow-up defined as 2nd year on HD. Survival analysis were applied to study the effect of SNa+, slope and variability on event. Smoothing spline logistic regression models were used to explore the joint effect of (a) SNa^+ with variability, and (b) SNa^+ with slope on event. Additionally, time to event analysis were used to delineate the association of various demographic and clinical parameters with event.

Results: 15, 335 HD pts (63.2 years, 59% males, 24% diabetics) from Europe (10,907), West Asia (1,991), South America (283) and US (2,154) were included. Lower SNa^+, positive and negative slope, and higher variability associated with an increased the risk of event. Increased risk of death with higher variability and slopes appeared to be present at all levels of SNa^+, with apparently stronger effects for variability than slope (Figure 1). However, the relation between SNa+ variability and slopes with outcome lost significance after adjusted for confounders.

Conclusions: Our findings suggest that SNa^+ variability may constitute a novel prognostic indicator. Underlying pathological conditions may explain the relation between SNa^+ and outcome.



SA-PO768

Modified Compression Bioimpedance in Edema Quantification in Patients on Hemodialysis

Amit P. Singh,[2] John J. Pitre,[1] Joseph L. Bull,[1] Leo Koziol,[2] William Weitzel,[3,2] Panduranga S. Rao.[2] *[1]Tulane University, New Orleans, LA; [2]University of Michigan Health System, Ann Arbor, MI; [3]VA Ann Arbor Health System, Ann Arbor, MI.*

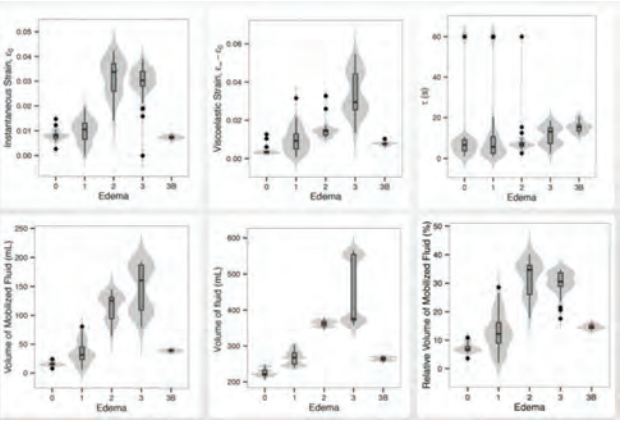
Background: Quantification of edema in dialysis patients is subjective and problematic. Given the importance of fluid overload, objective measures are necessary.

Methods: We conducted a clinical study using bioimpedance and circumferential strain apparatus for quantification of lower extremity edema in hemodialysis patients. Eleven stable hemodialysis patients, 18-85 years of age, with varying grades of clinical edema participated. During their usual hemodialysis session, a series of compression cycles (30 seconds, 50mm Hg) were applied above one ankle using a blood pressure cuff. Bioimpedance and strain data were collected using the bioimpedance meter and plethysmograph, respectively. This procedure was repeated until the completion of the dialysis session.

Results: Using the strain data we calculated the volume of mobilized fluid during compression. Using the bioimpedance data we calculated the total volume of fluid underneath the cuff. The median volume of fluid estimate for each subject was used to normalize the volume of mobilized fluid obtained from the strain measurements. These data, along with the fit parameters for the strain data, were plotted as a function of the edema grades. Of the three strain fitting parameters (ε_0, $\varepsilon_\infty - \varepsilon_0$ *and* τ), the ANOVA revealed significant differences among edema grades for both the instantaneous strain ε_0 ($p < 2\times10^{-16}$) and the viscoelastic strain $\varepsilon_\infty - \varepsilon_0$ ($p < 2\times10^{-16}$). ANOVA also revealed significant differences among edema grades for the strain-based estimate of the volume of mobilized fluid V_f^m ($p < 2\times10^{-16}$); bioimpedance based total fluid volume ($p = < 2\times10^{-16}$) and relative volume of mobilized fluid ($p < 2\times10^{-16}$).

Conclusions: Using this novel technique in dialysis patients we demonstrated the potential to quantify mechanical characteristics of edema, ε_0, $\varepsilon_\infty - \varepsilon_0$ *and* τ, to better characterize peripheral edema.

Funding: Private Foundation Support



Violin plots of strain fit parameters and estimates of volume parameters.

SA-PO769

Effect of Fluid Status on the Fat Mass Estimated by Bioimpedance in Hemodialysis Patients

Samer R. Abbas,[3] Stephan Thijssen,[3] Erik L. Penne,[1] Jochen G. Raimann,[3] Nathan W. Levin,[2] Peter Kotanko,[3,4] Fansan Zhu.[3] *[1]Medical Center Alkmaar, Alkmaar, Netherlands; [2]None, New York, NY; [3]Renal Research Institute, New York, NY; [4]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: This prospective study utilizes calf bioimpedance spectroscopy (cBIS) to guide the attainment of dry weight (DW_{cBIS}) in chronic hemodialysis (HD) patients. In the present research we evaluate whether fat mass is altered when DW_{cBIS} is attained.

Methods: Target post-HD weight was gradually reduced from baseline (BL) until DW_{cBIS} was achieved. DW_{cBIS} was defined as the presence of both flattening of the curve of extracellular resistance during HD and the attainment calf normalized resistivity (CNR) in the normal range (Zhu, Physiol Mea 2008). Extracellular (ECV), intracellular (ICV) volume and total body water (TBW) were measured using whole body bioimpedance spectroscopy (Hydra 4200). Fluid overload (FO), lean body mass (LBM), and fat mass (FM) were calculated according to a body composition model (Chamney, Am J Clin Nutr 2007).

Results: Twenty-eight patients (13 females; 7 diabetic; age 53.7±12 years) achieved DW_{cBIS} over a period of 43.8±30.1 days. On average 16±10 measurements per patient were required to attain DW_{cBIS}. Although significant decreases in body weight, CNR and ECV pre and post HD were observed, LBM and FM at DWcBIS did not differ significantly from BL (Table 1). ECV/TBW and FO were non-significantly higher at BL compared to DW_{cBIS} (Table 1).

Conclusions: This study showed that attainment of DW_{cBIS} did not affect fat mass.

Table 1

	Wt (kg)	CNR	ECV (L)	ECV/TBW	FO (kg)	LBM (kg)	Fat (kg)
Pre HD BL	78±15.8	14.2±2	16.9±2.6	0.48±0.05	1.8±3.2	34.7±15.5	31.2±16.3
DWcBIS	76±15.7	16.2±2.1	16.0±2.7	0.47±0.04	1.7±2.3	35.5±9.4	28.8±12.5
p value	<0.0001	<0.0001	<0.001	0.2	0.077	0.23	0.79
Post HD BL	75.4±15.6	17.9±2.5	14.4±2.2	0.43±0.05			
Post HD DWcBIS	73.5±15.6	20.5±2.4	13.7±2.2	0.42±0.05			
p value	<0.0001	<0.0001	<0.001	0.1			

SA-PO770

Lower Blood Flow Rate in the Last Quarter of Hemodialysis May Protect Against Hypotension Rebecca Backenroth,[1,2] Dvora Rubinger,[1] Tasneem Kab,[3] Irit Mor yosef levi,[4] Dan Sapoznikov.[1] *[1]Hadassah U Med Center, Jerusalem, Israel; [2]Barzilai U Med Center, Ashkelon, Israel; [3]Hadassah u med center, Jerusalem, Israel; [4]Nephrology, Hadassah, Jerusalem, Israel.*

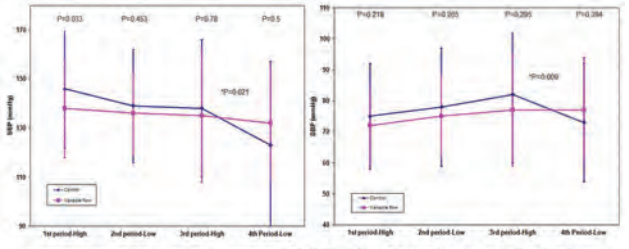
Background: In hemodialysis (HD), high blood flow rate (BFR) increases clearances and decreases clotting of the extracorporeal circuit. However, possible adverse effects are not well delineated.

Methods: A prospective crossover study compared the effects of higher vs lower BFR, with patients serving as their own controls. Consenting stable adults on chronic HD were studied for 2 sessions in random order usually a week apart. The control session, with 'high' constant BFR, 300-450 cc/min, and the variable flow session, alternating high then low, 250 cc/min BFR in 4 equal periods of the session. Continuous beat to beat BP and pulse were monitored noninvasively by Finometer ™, O2 saturation by pulse oximeter, and subjective wellbeing by questionnaires.

Results: Twelve patients in 24 HD sessions were studied. Baseline weight, pulse, interdialytic weight gain and UF rates were similar in the sessions but intial systolic BP (SBP) was higher in the control HD. In the control HD, SBP declined while the diastolic BP (DBP) declined only in the 4th quarter. The variable flow HD was similar until the last quarter, when lower BFR was associated with significant reversal of the decline of SBP and DBP, and a rise in DBP. Pulse increased insignificantly during both sessions. Autonomic parameters were similar except LFα (index of baroreflex sensitivity) which increased in the control, but decreased in the 4th, lower BFR period (p=0.03). Total peripheral resistance also differed only in the 4th period, when it decreased in the control, but increased in the variable BFR group. Stroke volume was significantly higher in the 1st period of low BFR, and cardiac output decreased in both sessions. SBP did not correlate with cardiac output. Subjective feelings and O2 sat were similar in both sessions.

Conclusions: Low BFR during the last quarter of HD seems to attenuate decreases in both SBP and DBP.

Funding: Clinical Revenue Support



Mean systolic and diastolic blood pressures (SBP) (DBP) ±SD. "High" and "Low" refer to the blood flow rate in the variable flow session. p - difference in means. *p - difference in slope between periods.

SA-PO771

Prediction of Residual Renal Function (RRF) in Hemodialysis (HD) and Hemodiafiltration (HDF) Maria-Eleni Roumelioti,[2] Christos Argyropoulos,[2] Mark L. Unruh,[2] V. Shane Pankratz.[1] *[1]UNM Health Sciences Center, Albuquerque, NM; [2]University of New Mexico, Albuquerque, NM.*

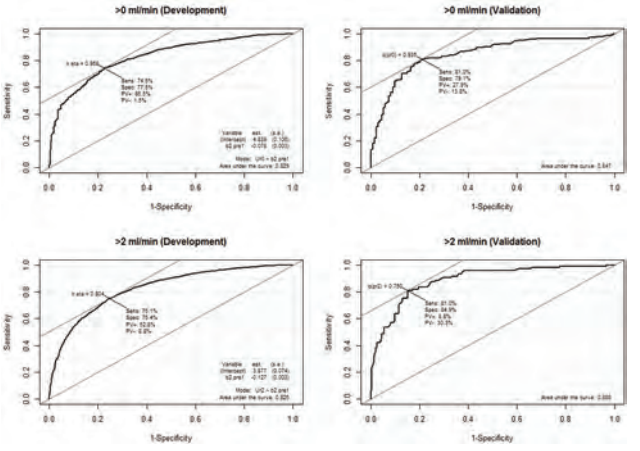
Background: RRF is associated with improved survival in HD patients but requires cumbersome urinary collections to measure. Beta-2 microglobulin, (B2M) has been proposed as measures of RRF, without the need for such collections. We validate the predialysis B2M from the first session of the week, as a predictor of RRF in pts receiving HD or HDF.

Methods: We simulated the distribution of the predialysis B2M concentration in a mixed cohort of pts (N=10,000) receiving HD or HDF at different levels of RRF using a recently described population kinetic (PopK) model for B2M (PLoS ONE10(6):e0129575). Logistic regression models were used to derive cutoffs of B2M predicting the RRF in this **development cohort (Dev)**. These models were then used to predict the Urea Clearance (as a measure of RRF) in a **validation cohort (Val)** of 350 actual patients receiving either HF or HDF (PLoS ONE 10(12): e0143813) in whom B2M had been measured. Characteristics of the Dev cohort were deliberately chosen to differ from the Val cohort to assess generalizability.

Results: Median (IQR) RRF in ml/min was 5 (2.5-7.5) in Dev & 0.61 (0.0-2.3 ml/min Urea Cr) in the Val. Median (IQR) B2M in ml/L was 18.9 (11.6-23.2) in Dev & 25.5 (19.5-32.1) in Val. **Sensitivity** (Sens), **Specificity** (Spec) were > 75%, while **AUCs** were >0.83 in both the Dev and Val cohorts [figure]. Median (IQR) of the optimal (AUC maximizing) B2M (in mg/L) cutoffs for RRF > 0ml/min & > 2 ml/min were 22.1 (20.0-23.2) & 19.5 (19.2-20.3) respectively in the Dev cohort. Sens/Spec of these cutoffs were 0.53/0.93 & 0.60/0.90 in the Val cohort.

Conclusions: PopK derived cutoffs of B2M predict with high accuracy RRF in pts on HD or HDF. These cutoff values are nearly identical to the values previously estimated in actual pts, attesting to the validity of the PopK model. Such cutoffs may have utility when implementing the KDOQI incremental dialysis guideline & as enrollment criterion in ESRD studies.

Funding: Clinical Revenue Support



SA-PO772

Bedside BNP as a Marker of Overhydration in Hemodialysis Patients Jan Melin,[3] Magnus Lindberg,[2] Jenny Stenberg,[3] Hans Furuland.[1] *[1]University Hospital, Uppsala, Uppsala, Sweden; [2]University of Gävle, Gävle, Sweden; [3]University Hospital Uppsala, Uppsala, Sweden.*

Background: Management of hydration status in dialysis patients is a great challenge to nephrologists, and new tools to understand the hydration status (HS) are needed. The aim of this study was to investigate the usefulness of brain natriuretic peptide (BNP), analyzed bedside, as a marker of overhydration (OH) in hemodialysis (HD) patients.

Methods: We investigated the distribution of BNP, measured by Alere Triage® BNP Test, and analyzed the correlation between BNP and HS, defined by bioimpedance spectroscopy (BIS) in 64 HD patients. We assumed there would be a difference in HS between patients with high levels of BNP (h-BNP) and low levels of BNP (l-BNP) and choose an arbitrary cut off of 500 ng/ml, and then differences between the groups were tested for significance. HS, blood pressure (BP) and heart rate was measured, and BNP analyzed, before one mid-week dialysis session. Blood samples were also drawn for analysis of NT-proBNP and inflammatory markers. Demographic data, comorbidities, lab values and nutritional status were collected from medical records.

Results: A positive correlation was found between BNP and OH (r = 0.4), although many severely overhydrated patients had normal or just slightly elevated BNP. BNP levels were above 500 in 38 % (n=24) of the participants. The level of OH before dialysis was higher in the h-BNP group than in the l-BNP group. There was no difference in BP before or after dialysis, but patients in the h-BNP group were older, had lower muscle strength and lower Hemoglobin and Albumin levels compared to the l-BNP group.

Conclusions: A normal BNP does not rule out OH as defined by BIS in HD patients, on the other hand euvolemia was rare in patients with elevated BNP. This suggests that BNP might serve as a marker of OH in a subgroup of old and frail patients. In a further study we aim to investigate if the relationship between BNP, when elevated, and OH is reproducible at an individual level.

Funding: Private Foundation Support, Government Support - Non-U.S.

Difference between groups, high and low BNP

Variables	BNP < 500 (n = 40)	BNP > 500 (n = 24)	Level of significance
Age (years)	65 ± 2.1	77 ± 2.0	P < 0.001
BMI	27.8 ± 0.9	25.5 ± 0.9	NS
Handgrip (kg)	30 ± 2.0	23 ± 1.8	P < 0.05
Albumin (g/L)	31.9 ± 0.6	27.7 ± 0.9	P < 0.001
CRP (mg/L)	12.0 ± 2.7	30.5 ± 13.2	NS
Hemoglobin (g/L)	113.7 ± 1.9	101.8 ± 2.4	P < 0.001
Overhydration (L)	1.8 ± 0.2	2.8 ± 0.3	P < 0.05

Values presented as mean ± SEM

SA-PO773

Government Support in the Development of Hemodialysis in County Level Hospitals in China Hua Liu,[2] Hongli Jiang.[1] *[1]Dialysis Center of First Affiliated Hospital of Medicine School, Xi?an Jiaotong University, Xi'an, Shaanxi, China; [2]First Affiliated Hospital of Medical College of Xi'an Jiaotong University, Xi'an, China.*

Background: In 2013, there were 88 hemodialysis center in Shaanxi province in China and all equipment and medical personnel could only meet the demand of about 22% ESRD patients. This paper will explore the role of government decision-making and financial support in the construction of hemodialysis center projects in county level hospitals in Shaanxi province in China after increasing investment in health care reform.

Methods: After 2013, the hemodialysis room construction project in county hospitals in Shaanxi province was carried out. Under the support of the government, we prepared the blood purification training materials and recorded teaching physicians and nurses in blood purification standard operating procedures, arranged 150 hours courses and 135 days clinical practice stage from 2013 to 2015 in four times. The effect of the training

course of the projects and the status of the hemodialysis center in the county hospital of Shaanxi province were analyzed retrospectively.

Results: From the May 14, 2013 to June 30, 2015, we held four consecutive training classes, training a total of 827 doctors, nurses and technicians. After the implementation of this project, the number of dialysis rooms increased by leaps and boundsin Shaanxi provinc. By the end of December 31, 2016, there were 66 new county hospital hemodialysis room throughout 57 counties, and there were 2068 new dialysis patients registered in national dialysis registration system, far higher than the previous year increasing level (more than 30%), also higher than increasing ratio of the world's new hemodialysis patients.

Conclusions: The project construction of the hospital hemodialysis room at the county level is the policy of the provincial government to improve the level of medical treatment in patients with chronic kidney disease. The government give a strong financial support in the purchase of equipment, personnel training and other aspects, which is convenient for patients with end-stage renal disease to obtain renal replacement therapy, improve the ability of hospital hemodialysis services and comprehensive treatment.

Patiens and hemodialysis room development by hemodialysis network reported in China from 2014 to 2016

	In 2014	In 2015	In 2016
numbers of hemodialysis patients	6350	6856	9170
the new MHD patients	833	770	2068
hemodialysis room in county hospital	30	40	89

SA-PO774

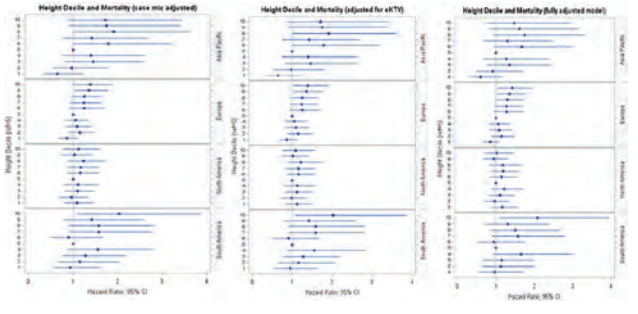
Heights of Hemodialysis Patients Are Associated with Outcomes: Results From the Monitoring Dialysis Outcomes (Mondo) Initiative Samir D. Patel,[10] Alice Topping,[10] Xiaoling Ye,[10] Bernard J. Canaud,[1] Cristina Marelli,[6] Adrian M. Guinsburg,[2] Xiaoqi Xu,[3] Albert J. Power,[4] Neill D. Duncan,[8] Jeroen Kooman,[9] Frank van der Sande,[9] Len A. Usvyat,[7] Yuedong Wang,[5] Peter Kotanko,[10] Jochen G. Raimann,[10] Paola Carioni.[1] *[1]FMC Deutschland GmbH, Bad Homburg, Germany; [2]Fresenius Medical Care, Moron, Argentina; [3]Fresenius Medical Care Asia Pacific, Hong Kong, China; [4]Richard Bright Renal Unit, Bristol, United Kingdom; [5]University of California - Santa Barbara, Santa Barbara, CA; [6]Fresenius Medical Care Argentina, buenos Aires, Argentina; [7]Fresenius Medical Care North America, Melrose, MA; [8]Imperial College Renal and Transplant Centre, London, United Kingdom; [9]Maastricht University Medical Centre, Maastricht, Netherlands; [10]Renal Research Institute, New York, NY.*

Background: In the general population taller people have better metabolic profiles and cardiovascular outcomes (Nelson NEJM 2015), a finding reversed in hemodialysis (HD) patients (pts) (Shapiro CJASN 2015, Elsayed JASN 2015). We studied this relationship in incident HD pts in the international MONDO database.

Methods: In this retrospective cohort study, we included incident HD pts commencing treatment between 01/01/2006 and 12/31/2010, and noted their outcome over 2.5 years following a 6 months baseline. Patients were stratified into deciles of their respective database population, [Asia-Pacific (AP), North (NA) and South America (SA), Europe (EU)], and by gender. Analysis was done using Cox regression with height decile 5 as reference. We constructed 3 different models: a simple case-mix adjusted model for age, gender, post-dialysis weight (Figure 1); the second model additionally including eKt/V (Figure 2); and a fully adjusted model further including albumin, interdialytic weight gain, phosphorus, and pre dialysis systolic blood pressure (Figure 3).

Results: We studied 23,353 pts (62 ± 15 years old, 42% females, body mass index 26 ±6 kg/m^2, 165 ± 10 cm tall). In the fully adjusted models, for SA we found a trend of increasing hazard ratio (HR) without significance among deciles > 5. In EU, deciles 8-10 had significantly increased HR. We observed no significant trend in AP and NA (Figure 3). The result remains materially identical in adjusted models.

Conclusions: Taller height associates with poorer outcomes for reasons yet to be elucidated. Trends we observed were not consistent between continents. Additional studies including body composition analysis may provide additional insight.



Forrest plots of height decile and mortality. Figure 1, Figure 2, Figure 3.

SA-PO775

Dry Mouth with Hemodialysis Patients Results in Hypogeusia Miho Suzuki,[2] Ikuto Masakane.[1] *[1]Honcho-Yabuki Clinic, Yamagata, Japan; [2]Yabuki hospital, Yamagata, Japan.*

Background: Dry mouth is one of the causes of taste disorder and affects excessive intake of salt or decreased appetite. Dry mouth often occurs in hemodialysis (HD) patients. However, there have been few reports about dry mouth associated with taste disorder in HD patients. In this study, we examined salivation secretion and taste sensitivity in Maintenance HD patients.

Methods: Inclusion criteria were 46 HD patients who complained of dry mouth by symptomatic investigation and were recognized to have low taste sensitivity from the taste test results. 17 individuals (mean age; 67.9±9.1 yr, 10 men) agreed to enroll in the study. The subjects were divided by unstimulated whole salivation into Low Salivation (LS; 7 patients) and Normal Salivation (NS; 10 patients) groups. Taste sensitivity was determined by the filter paper disc method. Taste sensitivity of sweet, salt, sour and bitter tastes were evaluated. The sample with each taste has five levels of concentration. Low Taste Sensitivity was determined when patients were not able to recognize level three. Salt intake was determined by a 3-day food diary. These results were compared between the two groups by using a Student t-test or Mann-Whitney's U test.

Results: Of the low taste sensitivity patients 7 were categorized as LS and 9 were categorized as NS. Of the subjects that complained of taste disorder symptoms; 4 in the LS group complained of hypogeusia; and 6 in the NS group complained of hypogeusia, pantogeusia, heterogeusia and hemigeusia. Between the LS and NS groups respectively, the ages were (70.9 ± 7.3 vs 65.8 ± 10.1 yr p = 0.275), and the dialysis vintage was (114.9 ± 96.7 vs 75.8 ± 78.3 mth p = 0.353). The taste sensitivity of the four tastes showed no significant difference. But salt taste sensitivity (5.0 ± 1.8 vs 3.2 ± 1.7 points p = 0.088) tended to be lower in the LS group than the NS group. Salt intake showed no significant difference (6.3 g ± 2.0 vs 8.1 ± 2.1 g p = 0.096).

Conclusions: There are many causes & symptoms of taste disorders. Dry mouth tends to result in hypogeusia, especially in patients with less salt taste sensitivity. However, salt intake showed no significant difference between the LS and NS groups. Therefore, it cannot be determined that dry mouth results in a taste disorder which then results in an excessive intake of salt.

SA-PO776

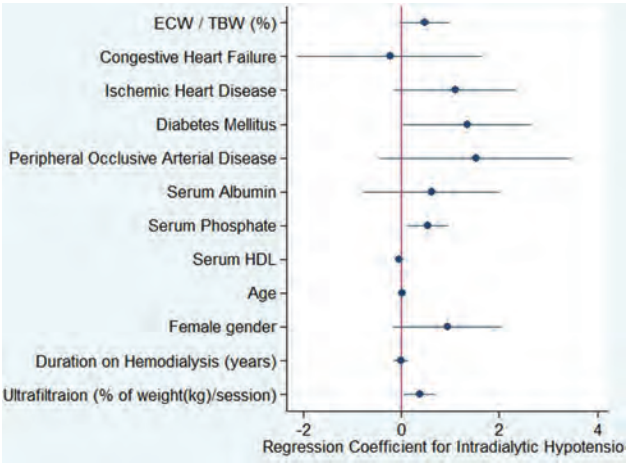
Muscle Mass Measured by Multi-Frequency Bioimpedance and Intradialytic Hypotension among Hemodialysis Patients Jong Cheol Jeong,[1] YOUNG-IL Choi,[2] Myoung-sung Kim,[3] MinJeong Lee,[1] Inwhee Park,[1] Gyu Tae Shin,[1] Heungsoo Kim.[1] *[1]Ajou University School of Medicine, Suwon, Republic of Korea; [2]Dr.Choi's Medical Clinc, SEOUL, Republic of Korea; [3]Myoung clinic, Ansan, Republic of Korea.*

Background: With the introduction of bio-impedance devices, more relevant and reproducible assessment have become possible. To find optimal bio-impedance indices to predict clinical outcomes, more data are needed.

Methods: Prevalent hemodialysis patients (duration of dialysis more than 3 months) were enrolled in three dialysis units. At baseline, clinical indices, physical assessment of volume status, arthropometry examination, NT-proBNP and cardiac indicies by chest PA were collected. At follow up, cardiac indices and clinical events including intradialytic hypotension, cardiovascular events, pulmonary edema were collected. Segmental bio-impedance assessments were performed at every assessment.

Results: Total 150 patients were enrolled. Mean age was 58.5 ± 14.1 years old. Female were 75 (50%). Modified Charlson comorbidity score, Tilburg frailty score, and PG-SGA were 3.9 ± 1.8, 3.3 ± 2.3, and 3.2 ± 4.2, respectively. Body mass index was 22.6 ± 3.3 kg/m^2. ECW/TBW was significantly correlated with cardiac index in positive direction. (spearman's rho 0.351, $p < 0.001$) ECW/TBW also showed significant correlation with NT-proBNP. (spearman's rho 0.384, $p < 0.001$). However, higher ECW/TBW was reported to be associated with intradialytic hypotension in the multivariable logistic regression models. (Odds ratio (OR) 1.627, 95% confidence interval (C.I.) 0.985 – 2.687, $p = 0.058$) (Figure 1). Skeletal muscle index was negatively associated with ECW/TBW. (spearman's rho -0.416, $p < 0.001$) Skeletal muscle index was better predictor for intradialytic hypotension than NT-proBNP (AUC comparison of NT-proBNP vs. skeletal muscle index; 0.721 vs. 0.506, $p = 0.003$).

Conclusions: Reduced skeletal muscle mass was associated with frequent intradialytic hypotension. Optimal values of ECW/TBW, as other than index as inversed reflection of muscle mass, still need to be validated with clinical outcomes.



SA-PO777

Psychological Distress in Dialysis-Dependent CKD Syed S. Zaidi,[1] Andrew Nixon,[1,2] Judi M. Todd,[1] Dawn Brannigan,[1] John Anderton,[1] Mark Brady,[1] Ajay P. Dhaygude.[1] *[1]Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom; [2]University of Manchester, Manchester, United Kingdom.*

Background: The burden of chronic kidney disease (CKD) and renal replacement therapy results in a high prevalence of psychological distress. It is not routine practice to screen for psychological distress in patients with CKD. The Distress Thermometer (DT) is a screening tool for psychological distress that has been validated in the renal population. Our aims were to establish healthcare provider ability to perceive patient psychological distress and to assess factors that are associated with psychological distress in those with dialysis-dependent CKD.

Methods: One-hundred patients with dialysis-dependent CKD were recruited. Patient age-modified Charlson Comorbidity Index (CCI) and WHO performance status were assessed. Dialysis unit nursing staff assessed patient psychological distress using the DT. Patients completed the DT on the same day as the nurse assessment. A DT cut off score of ≥7 was used to define severe levels of psychological distress. The correlation between nurse and patient DT scores was assessed using Pearson's correlation coefficient. Linear regression was performed to assess the magnitude of associations. A p value of <0.05 was considered statistically significant.

Results: Mean age was 63.19 years (SD: 14.18) with 58 male patients. Median time on haemodialysis was 38 months (IQR 16.25 to 66.75). Mean CCI score was 5.56 (SD: 1.97). The prevalence of WHO score ≥3 was 37%. The prevalence of severe psychological distress was 29%. Mean nurse DT score was 4.34 (SD: 2.69) and mean patient DT score was 4.32 (SD: 3.37). There was a weak to moderate correlation between the nurse and patient DT scores (r=0.50, p= 0.00, 95% CI 0.32-0.65). After adjusting for age, gender, dialysis vintage and CCI, only WHO score was associated with patient DT score. Each 1 point increase in WHO score was associated with an increase in patient DT score by 0.91 (p=0.01, 95% CI 0.27-1.55).

Conclusions: Psychological distress is highly prevalent in those with dialysis-dependent CKD. Psychological distress is associated with performance status; however, it is not associated with multimorbidity. Healthcare provider perceptions of patient psychological distress do not correlate strongly with patient reported psychological distress. Therefore, patients should be offered the opportunity to complete a psychological distress screening tool, such as the DT.

SA-PO778

The Association Between Tobacco Use and Intradialytic Hemodynamics in Hemodialysis Mark T. Sonderman, Peter N. Van Buren. *UT Southwestern Medical Center, Dallas, TX.*

Background: Extreme changes in intradialytic blood pressure are associated with poor outcomes in hemodialysis patients, but the overall effect of traditional cardiovascular risk factors on these outcomes is poorly understood. We sought to explore the effect of lifetime tobacco use on vascular hemodynamics during dialysis.

Methods: We determined smoking status among a group of hypertensive hemodialysis (HD) patients concurrently enrolled in a cross-sectional study. We compared differences in pre, post, and intradialytic change in systolic blood pressure (SBP), total peripheral resistance index (TPRI), and cardiac index (CI) in subjects defined as never smokers or smokers (current or former) using unpaired t-tests and multivariable linear regression controlling for ultrafiltration rate, diabetes, baseline hemodynamics, and other baseline characteristics.

Results: The pre and post dialysis hemodynamics are shown in Table 1. The ΔTPRI was -582 dynes/sec/cm2/m2 in smokers and 102 dynes/sec/cm2/m2 in non-smokers (p-value = 0.003). The ΔCI was 0.249 L/min/m2 in smokers and -0.063 L/min/m2 in non-smokers (p-value = 0.02). The ΔSBP was -14.5 mmHg in smokers and -10.3 mmHg in non-smokers (p-value = 0.63). In multivariable linear regression, there was an independent association between smoking and ΔTPRI (p=0.012) with an average reduction of 522 dynes/sec/cm2/m2 in ΔTPRI in HD patients with a history of tobacco use.

Conclusions: Hemodialysis patients with a smoking history have reductions in intradialytic TPRI compared to non-smokers although overall BP changes were not different. Further research needs to be done to identify the role of smoking and smoking cessation on intradialytic hemodynamics.

Funding: NIDDK Support

Hemodynamic Values Before and After Dialysis

	Smokers			Never Smokers			
Variable	Pre	Post	Delta	Pre	Post	Delta	p-value
SBP	153 (21.0)	139 (23.0)	-14.5 (29.1)	158 (17.7)	147 (21.7)	-10.3 (31.5)	0.63
TPRI	3320 (972)	2740 (640)	-582 (799)	2920 (703)	3030 (1010)	102 (834)	0.003
Cardiac Index	2.91 (0.647)	3.16 (0.521)	0.249 (0.459)	3.05 (0.577)	2.99 (0.702)	-0.063 (0.486)	0.02

The p-value compares the delta between the two groups.

The data are presented as box plots which indicate the 5th, 25th, 50th, 75th, and 95th percentiles.

SA-PO779

Patient Characteristics Associated with the In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems (ICH CAHPS) Scores Taimur Dad,[2] Hocine Tighiouart,[2] Megan Grobert,[1] Eduardo K. Lacson,[2,1] Klemens B. Meyer,[2] Dana Miskulin,[2] Daniel E. Weiner,[2] Michelle M. Richardson.[2] *[1]Dialysis Clinic Inc, Boston, MA; [2]Tufts Medical Center, Boston, MA.*

Background: The In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems (ICH CAHPS) Survey is a mandatory assessment of patient experience of ICH patients. To better understand performance on this quality metric, we evaluated patient characteristics associated with high ICH CAHPS scores.

Methods: Cross-sectional analysis of ICH CAHPS scores in 2012 to all ICH patients in Dialysis Clinic, Inc (DCI) facilities. Eligibility criteria determined by AHRQ included ≥ 18 years old and received dialysis at the current facility for ≥ 3 months. Measures include patient-level demographic, clinical, laboratory, and functional characteristics. Outcomes include "top box" scores for the three global rating scores for the nephrologist, dialysis facility staff, and dialysis facility and three composite scores 'Nephrologists' Communication and Caring' (Comm), 'Quality of Dialysis Center Care and Operations' (Qual), and 'Providing Information to Patients' (Info). "Top box" was defined by AHRQ as ≥8 for global rating scores (scale 0-10 with 10 being the best) and either "Always" (from Always, Usually, Sometimes, Never) or "Yes" (from Yes, No) answer choice to questions within each composite.

Results: Among 11,055 eligible patients, 4,514 (41%) returned the survey or completed it by phone. In random intercept multivariable logistic models which accounted for dialysis facility effect, older age and lower education were consistently associated with higher odds of top box scores for all three global ratings. Among composite outcomes, higher Kt/V (Comm), lower education (Qual), and being active on the transplant list (Info) were associated with higher odds of top box scores. Shortened treatments were associated with lower odds for a top box score for all global ratings and the Comm composite. Results were similar after imputing missing predictor data.

Conclusions: Older age and lower educational level were associated with higher global rating scores while higher Kt/V, lower educational level, and being active on the kidney transplant list were associated with higher composite scores. Our findings raise concern about dialysis facility scores being influenced by patient case-mix with associated expectations of care experience.

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SA-PO780

The Standardised Outcomes in Nephrology-Haemodialysis (SONG-HD) Consensus Workshop on Establishing a Core Outcome Measure for Fatigue in Patients on Haemodialysis Angela Ju,[3] Mark L. Unruh,[2] Jonathan C. Craig,[4] Allison Tong.[1] *[1]The University of Sydney, Sydney, NSW, Australia; [2]University of New Mexico, Los Ranchos, NM; [3]University of Sydney, Sydney, NSW, Australia; [4]University of Sydney/Children's Hospital, Sydney, NSW, Australia.*

Background: Fatigue is a critically important outcome for patients on haemodialysis but is infrequently and inconsistently reported across trials and observational studies, which probably reflects the lack of suitable measures that are feasible and psychometrically robust to use in this setting.

Methods: At an international consensus workshop, 56 (15 patients/caregivers; 42 health professionals) participated from nine different countries in six facilitated breakout groups. All discussions were transcribed and analysed thematically

Results: Four themes were identified. *Drawing attention to a distinct and all-encompassing symptom* was explicitly recognising fatigue as a multifaceted symptom that is unique to haemodialysis. *Emphasising the pervasive impact of fatigue on life participation* confirmed the importance of addressing patient concerns about consequences of fatigue such as being limited in their ability to do usual activities such as work and hobbies, and justified the focus on assessing this restriction. *Ensuring meaningfulness* of the measure was advocated to facilitate treatment decision-making for both patients and clinicians. *Minimising burden of administration* meant that the measure should be simple, short, without imposing additional burden given the high level of fatigue in the haemodialysis population. These support a proposed core outcome measure that asks patients about the extent to which fatigue limits participation in usual activities.

Conclusions: Patients, caregivers and health professionals supported the need for a simple, short, and meaningful core outcome measure that focuses on the impact of fatigue on life participation to be used in haemodialysis trials.

Funding: Government Support - Non-U.S.

SA-PO781

Measurement of Fluid Shifts during 15 Minutes of Standing Using Bioimpedance in Hemodialysis Patients and Healthy Subjects Xia Tao,[1] Fansan Zhu,[1] Ohnmar Thwin,[1] Priscila Preciado,[1] Laura Rosales,[1] Stephan Thijssen,[1] Peter Kotanko.[1,2] *[1]Renal Research Institute, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: The InBody 770 bioimpedance device allows measurements of fluid status and body composition. Due to gravity, body fluid can shift from the trunk to the legs while standing. The aim of this study was to investigate if gravity-induced fluid shifts produce detectable changes in fluid distribution and if the magnitude of fluid shifts differs between hemodialysis (HD) patients and healthy subjects (HS).

Methods: We studied ten HD patients (7 males, age 58.1±12 years), pre and post HD, and 12 HS (7 females, age 33.3±5.6 years). Two measurements were performed 15 minutes apart in a standing position with the InBody 770 (InBody USA, Cerritos, CA, USA). Extracellular (ECW), intracellular (ICW), and total body water (TBW), ECW in the right and left leg (ECW_{RL}; ECW_{LL}) and the trunk (ECW_T) were recorded. ECW/TBW ratio was calculated with measurements at the start of observation period. Repeated measurements were compared by paired t-test. Unpaired t-test was used to compare patients to HS for ECW/TBW ratio.

Results: During the 15-minute observation period, no significant change in TBW, ICW, or total and trunk ECW occurred. Leg ECW increased significantly for both patients and healthy subjects. In HD patients, the observations above were true both pre and post HD (average fluid removal on HD: 2.2 kg). Pre-HD ECW/TBW differed significantly from post-HD in patients and from HS.

Conclusions: Fifteen minutes of standing did not produce measurable changes in whole body ECW or TBW. However, leg ECW did increase significantly over this period, and this was true in healthy subjects, HD patients before dialysis, and HD patients after fluid removal.

Funding: Commercial Support - Fresenius medical care/ Renal Research Institute LLC

Table 1: The differences (Δ) were calculated as the respective fluid compartment changes over a period of 15 minutes.

Studies	ΔTBW (L)	ΔICW (L)	ΔECW (L)	ΔECWRL (L)	ΔECWLL (L)	ΔECWT (L)	ECW/TBW
Pre-HD	0.300±0.478	0.180±0.329	0.120±0.162	0.036±0.035*	0.038±0.035*	0.030±0.082	0.393±0.013
Post-HD	-0.060±0.272	-0.080±0.187	0.020±0.092	0.029±0.020*	0.036±0.017*	0.000±0.067	0.385±0.012**†
Healthy subjects	0.000±0.186	-0.025±0.160	0.025±0.062	0.031±0.024*	0.035±0.017*	0.008±0.079	0.378±0.006**‡

*p<0.01, data compared for the 15-minute interval. ** p<0.01, compared to pre-HD results.

SA-PO782

Osteocytic Perilacunar/Canalicular Turnover in Dialysis Patients with High and Low Serum PTH Levels Aiji Yajima,[1] Ken Tsuchiya,[2] Kosaku Nitta.[2] *[1]Indiana University, Indianapolis, IN; [2]Tokyo Women's Medical University, Shinjuku-ku, Japan.*

Background: Osteocytic perilacunar/canalicular turnover in hemodialysis (HD) patients has not yet been reported, despite its particular relationship to bone and mineral metabolism in these patients. Under these circumstances, we were prompted to investigate osteocytic perilacunar/canalicular turnover in CKD patients.

Methods: Osteocyte lacunae in lamellar bone and woven bone were classified as eroded surface-, osteoid surface-, and quiescent surface-predominant osteocyte lacunae (ES-Lc, OS-Lc, QS-Lc, respectively) in HD patients with high or low parathyroid hormone (PTH) levels and control subjects without CKD.

Results: While the number of ES-Lc per unit bone volume (N.ES-Lc/B.Ar) was higher than N.OS-Lc/B.Ar in all groups [high-PTH (P<0.001) -, low-PTH (P=0.002) -, and control (P<0.001)], N.ES-Lc/B.Ar was higher in the high-PTH group than in the low-PTH (P<0.001) and control groups (P<0.001). The total volume of ES-Lc per unit bone volume (ES-Lc.Ar/B.Ar) was greater than OS-Lc.Ar/B.Ar in the high PTH (1.2 ± 0.4 vs. 0.5 ± 1.0 %, P<0.001) and the low-PTH groups (0.6 ± 0.3 vs. 0.1 ± 0.2 %, P<0.001). N.ES-Lc/B.Ar was higher in woven bone than in lamellar bone (P<0.001). MS/BS obtained from both groups were greater than that in the control group (1.15 ± 1.19 vs. 0.51 ± 0.38 %, P=0.039 and 0.92 ± 0.43 vs. 0.51 ± 0.38 %, P=0.016, respectively). Moreover, we could validate the shapes of the lacunar walls by backscattered electron microscopy.

Conclusions: Osteocytic perilacunar/canalicular turnover depends, at least in parts, on serum PTH level. Thus, attention should be paid to bone loss from the viewpoint of osteocytic parilacunar/canalicular turnover in HD patients. **Acknowledgment-**We acknowledge Professor David B. Burr for analyses of the bone histomorphometric parameters and capturing of the images of osteocyte lacunae under the backscattered electron microscope. And we also acknowledge Dr. Keith W. Condon for his excellent technique to make bone samples for the observation by electron microscopy.

SA-PO783

Sleep Disorders in ESRD Claire Kennedy,[3,4] Thomas Kane,[2] Peter J. Conlon.[1] *[1]Beaumont Hospital, Dublin 9, Co Dublin, Ireland; [2]Department of Respiratory and Sleep Medicine, Beaumont Hospital, Dublin 9, Dublin 9, Ireland; [3]Department of Nephrology, Beaumont Hospital, Dublin, Ireland; [4]Royal College of Surgeons in Ireland, Dublin, Ireland.*

Background: Sleep disturbance may be overlooked in patients with ESRD due to competing medical issues, as well as a perception that it is difficult to study and frustrating to manage. We aimed to study sleep quality in an ESRD cohort using subjective and objective tools, and to assess the impact of renal replacement therapy (RRT) modality change on sleep disturbance.

Methods: A detailed assessment of sleep quality was performed in an unselected cohort of dialysis patients using several validated subjective tools as well as unattended home polysomnography (PSG) and/or wrist actigraphy. Repeat assessment was performed in those that switched RRT modality.

Results: Baseline interviews were performed in 33 patients. The majority reported poor sleep quality (54.5%, n=18), troublesome restless legs syndrome (RLS; 54.5%; n=18) and reduced quality of life (QOL) most marked in the fatigue and general health perception domains. Screening for depression identified one patient with possible mild depression. PSG (n=19) and actigraphy (n=14) confirmed high rates of sleep fragmentation and disordered sleep architecture across all dialysis modalities. PSG identified periodic limb movement (PLM) disorder in 42% (n=8) and sleep apnoea (apnea-hypopnea index >5) in 58% (n=11). Four patients were medicated for severe PLM with good effect; CPAP was initiated in one patient with severe obstructive sleep apnoea with marked clinical improvement. There were six RRT modality changes. Three were transplanted with improved self-reported sleep quality, fatigue and RLS at 6 months; serial PSG (n=2) showed reduced sleep apnea and PLM, with increased sleep efficiency. Three switched from conventional to nocturnal home hemodialysis (NHHD); again this led to better self-reported sleep quality and fatigue scores. Repeat PSG (performed on and off NHHD at one and six months) demonstrated reduced PLM and increased sleep efficiency, with the improvement most marked on the on-dialysis nights.

Conclusions: This cohort of dialysis patients had poor sleep quality and reduced quality of life without features of depression. Simple therapeutic interventions, made on the basis of home PSG, made a big clinical difference. NHHD and transplantation improved sleep quality. Unattended home PSG and actigraphy were well tolerated, including by those on nocturnal dialysis.

SA-PO784

Quality of Sexual Life Is More Associated with Mental Aspect of Quality of Life Rather Than Physical among ESRD Patients Nien-Chen Li,[1] Norma J. Ofsthun,[2] Franklin W. Maddux,[1] Nwamaka D. Eneanya.[3] *[1]Fresenius Medical Care, Waltham, MA; [2]Fresenius Medical Care North America, Waltham, MA; [3]Massachusetts General Hospital, Boston, MA.*

Background: In the Kidney Disease Quality of Life Short Form (KDQOL-SF) survey, there is an item that specifically investigates quality of sexual life (QSL). Few studies have demonstrated associations of QSL with different subscales featured in the KDQOL-SF. We sought to elucidate the relationship of QSL with overall QOL among ESRD patients.

Methods: Between 1/1/2014 and 8/31/2016, we administered KDQOL surveys to 184,986 patients aged between 18 to 85 with ESRD. QSL was ascertained by analyzing the item "How much does kidney disease bother you in your sex life?" with responses ranging from "Not at all" to "Extremely bothered". To investigate the associations between QSL and overall QOL, two methods were used: 1) correlational analysis between the QSL item and all other items in KDQOL, and 2) correlational analysis between the QSL item and all 5 composite subscales derived from KDQOL.

Results: Among the sample cohort, the mean age at the time of survey was 60.8 (±14.0) years. Fifty-seven percent were male, 60% white race, and 41% married. Thirty-four percent of all patients indicated that their kidney disease bothered their sex life. QSL was more correlated with "emotional" or "mental" rather than "physical" items. For example, r=0.27 for "I feel frustrated dealing with my kidney disease", but r=0.13 for "moderate activities" For composite subscales, sex life was correlated with the effects of kidney disease subscale (after removing the sex item) by 0.48, followed by the symptom subscale (0.34), burden of kidney disease subscale (0.33), mental component summary (0.30), and physical component summary (0.19). All correlations had a p value <.001.

Conclusions: We demonstrated that QSL was more associated with mental (rather than physical) well-being among dialysis patients. To improve QSL among patients with ESRD, psychological evaluations and treatments should be prioritized.

Funding: Commercial Support - three authors are employees of Fresenius Medical Care, Private Foundation Support

SA-PO785

Intradialytic Laughter Therapy: A Qualitative Study Paul N. Bennett, Brigitte Schiller, Christine Kalife, John H. Vo. *Satellite Healthcare, San Jose, CA.*

Background: Hemodialysis patients experience poor physical function and increased anxiety and depression. Intradialytic Laughter Therapy is a group therapy that can be performed while patients are on hemodialysis. Laughter Therapy combines elements of physical activity, intentional laughter, controlled deep breathing and meditation. Laughter Therapy has been shown to increase exercise in the facial, chest, abdominal and skeletal muscles, reduce stress, reduce anxiety and counteract depressive symptoms in non-dialysis patients. The aim of this study was to explore patients' and staff perceptions of an Intradialytic Laughter Therapy program.

Methods: Intradialytic Laughter Therapy was delivered in two separate regional US hemodialysis clinics consisting of 30 minute sessions during dialysis, once per week for 3 months. Patients and clinical hemodialysis staff from the two clinics were surveyed and then interviewed using semi-structured interviews immediately following the 3 month program of Intradialytic Laughter Therapy. Content analysis of survey free text and interview transcript data identified coded items that were categorized into themes.

Results: 58 patients and 25 clinical hemodialysis staff were surveyed and interviewed. The four major themes emerging from the survey interview data were: (1) dialysis is boring and depressing, (2) laughter improved mood, health and wellbeing, (3) improved connections and community and (4) not for everyone. Laughter therapy made people feel happy, and helped them forget about their problems and the boredom of dialysis. Laughter therapy brought people together and establish comradery improving the rapport between staff and patients. Although Laughter Therapy was embraced by most patients those patients who felt indifferent still recommended continuing laughter therapy for the benefit of other patients and staff who they knew enjoyed the Laughter Therapy.

Conclusions: Intradialytic Laughter Therapy is a safe, complementary therapy that can be used during hemodialysis to improve interpersonal interaction, help build group identity, solidarity, and cohesiveness and increase intradialytic physical activity. Laughter Therapy has been shown to be a positive therapy and can be seen as an important element to improve patient and staff experience in US hemodialysis clinics.

SA-PO786

Quality of Sexual Life in ESRD Patients Nien-Chen Li,[1] Norma J. Ofsthun,[2] Franklin W. Maddux,[1] Nwamaka D. Eneanya.[3] *[1]Fresenius Medical Care, Waltham, MA; [2]Fresenius Medical Care North America, Waltham, MA; [3]Massachusetts General Hospital, Boston, MA.*

Background: Sexual dysfunction is a highly prevalent problem for patients (pts) undergoing dialysis. This study investigated associations of QSL with quality of life (QOL) for different ESRD modalities.

Methods: In Jan14-Aug16, we administered KDQOL surveys to ascertain the effect of kidney disease on quality of sexual life (QSL) (scaled from "not at all bothered" to "extremely bothered") among a national cohort of dialysis patients, The sample consisted of 184,986 prevalent pts aged 18-85. Logistic model was used to derive odds ratios (ORs) of bothered sexual life (SexL) for age, gender, race, marital status, dialysis modality (PD vs. HD), QOL (physical component summary [PCS] and mental component summary [MCS]). Since demographics were not matched between PD and HD pts, the model was weighted by propensity scores.

Results: Mean age at survey was 60.8 (±14.0) yr; 57% males; 60% Whites; and 41% married. Pts aged 30-64 were most bothered in SexL with OR=1.32 (95% CL 1.23-1.41, p<.001) and 1.95 (1.90-1.99, p<.001) when compared to those aged 18-29 and 65-85, respectively. Males had 2.5X higher odds of having bothersome SexL than women (p<.001). Married pts were 60% more likely to have bothersome SexL than unmarried (p<.001). PD pts were 46% more likely to be bothered in SexL than HD pts (p<.001). For every 1 SD reduction in PCS and MCS, the odds of having bothered SexL increased by 39% and 72%.

Conclusions: We demonstrated that PD pts were more subject to lower QSL than HD pts. Lower QSL was associated with lower QOL physically and mentally. Male middle-aged, and married pts had the most bothersome QSL. Sexual educational programs and interventions should be developed to improve QSL for ESRD pts.

Funding: Commercial Support - 3 authors are employees of Fresenius Medical Care, Private Foundation Support

SA-PO787

A Six Month Program of Intradialytic Exercise Is Effective in Reducing Length of Hospital Stay in Hemodialysis Patients Daniel S. March,[1] Charlotte E. Grantham,[1] Matthew P. Graham-Brown,[2] Hannah M. Young,[2] Nicola Cooper,[1] James Burton.[1] *[1]University of Leicester, Leicester, United Kingdom; [2]University of Leicester and University Hospitals of Leicester NHS Trust, Leicester, United Kingdom.*

Background: Hemodialysis (HD) patients have a greater risk for hospital admission than the general population with a longer length of in-patient stay (LOS). Intradialytic exercise (IDE) programs have shown improvements in patient related outcomes but there is little evidence regarding the utilisation of health services or cost effectiveness of such programs.

Methods: We performed a retrospective analysis on a subset of 35 patients enrolled in a randomised controlled trial investigating the effect of IDE on cardiac structure and function. The IDE group (n=14) performed 6 months of cycling exercise during HD for 30 mins thrice weekly. Usual care was continued for the control group (n=21). In addition to demographic data, hospital admissions (elective and non-elective stay), and LOS were collected from patient's medical records for 6 months (6M) pre (baseline), 6M during and 6M post IDE.

Results: Hospital admissions in the exercise group stayed the same over the length of the study, there was a small reduction in hospital admissions in the control group for 6M during and 6M post IDE (Table 1). There was a small reduction (11%) in LOS for the control group during the 6M IDE period compared to 6M pre. However, for the exercise group there was a 73% reduction in LOS (3.3 days) during the 6M IDE, which regressed towards baseline for the 6M post period.

Conclusions: We have shown a 3 d reduction in LOS in HD patients while participating in a program of IDE. Based on the current estimates, an additional day of in-patient care costs the UK NHS around £373. An annual reduction of in-hospital care of 3 d for each of the 23,000 UK HD patients would amount to a cost saving of ~£25.7m for the UK health economy.

Total Hospital admissions and length of stays for patients

	6M pre	6M during	6M post
	Hospital Admissions		
Control	1.5 ± 1.5	1.0 ± 1.4 (-33%)	1.3 ± 1.8 (-13%)
IDE	0.6 ± 0.9	0.6 ± 0.9 (0%)	0.6 ± 0.9 (0%)
	Length of Stay		
Control	8.0 ± 17.1	7.1 ± 18.4 (-11%)	7.8 ± 12.0 (-2%)
IDE	4.5 ± 8.9	1.2 ± 1.7 (-73%)	3.4 ± 6.7 (-24%)

Mean ± SD (% change from 6M pre)

SA-PO788

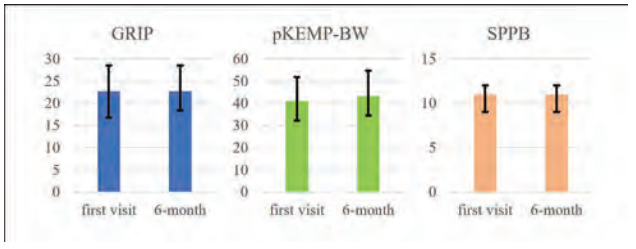
Resistance Training Improves Muscle Strength and Maintained Physical Performance in Patients with Maintenance Hemodialysis Yoshifumi Moriiyama,[2] Sae Aratani,[3] Masahiko Hara,[4] Hideaki Ishikawa.[1] *[1]Konan Kosei Hospital, Konan, Japan; [2]Nagoya kyoritsu hospital, Nagoya, Japan; [3]Nippon Medical School Hospital, Tokyo, Japan; [4]Osaka City University Graduate School of Medicine, Osaka, Japan.*

Background: It is reported that reduced muscle strength and physical performance are prevalent conditions in patients with maintenance hemodialysis, and deleterious changes in these parameters are associated with elevated mortality.

Methods: We provided 306 patients with 6-month resistance training program during hemodialysis. Primary outcome measures included muscle strength measured by handgrip (mean of right and left), percent knee extension muscle power to body weight (pKEMP-BW; mean of right and left), and physical performance measured by short physical performance battery (SPPB). Differences of these variables during 6-month were compared using Wilcoxon signed rank test.

Results: Median age was 71 (quartile 64-77) years old, 160 patients (52.2%) were men, and median dry weight was 54.5 (47.5-62.0) kg. During the 6-month, handgrip showed a slight increase in lower quartile from 22.8 (16.8-28.5) kg to 22.8 (18.3-28.5) kg (p<0.001), pKEMP-BW showed significant increase from 41.0 (32.0-51.8) % to 43.1 (34.4-54.7) % (p<0.001), and SPPB did not change the median and quartile values from 11.0 (9.0-12.0) to 11.0 (9.0-12.0) (Figure).

Conclusions: Resistance training improved muscle strength and maintained physical performance in patients with maintenance hemodialysis. We speculate that resistance training has a potential to prevent progression of sarcopenia and frailty in patients with maintenance hemodialysis.



SA-PO789

Multicenter, Prospective, Randomized, Crossover Trial to Demonstrate the Benefits of Hemodialysis without Acetate (with Citrate): ABC-Treat Study Patricia De Sequera,[1] Rafael Perez-Garcia,[1] Manuel Molina.[2] *[1]Hospital Infanta Leonor, Madrid, Spain; [2]H Santa Lucia, Murcia, Spain. Group/Team: Spanish ABC-treat group study.*

Background: Dialysis fluid, essential element in hemodialysis, is manufactured in situ by the monitors mixing 3 basic components: treated water, bicarbonate concentrate and acid concentrate. We have 2 types of acid concentrate: acetate (A) and citrate (C). **Objective:** To evaluate the impact of HD with C on calcium metabolism, acid base status, inflammation, coagulation and hemodynamic stability compared to HD with A.

Methods: Multicenter, prospective, randomized and crossover study, 32 weeks, 16 with 3mmol/l A (SoftPac®) and 16 with 1mmol/l C (Select BagCitrate®). Inclusion criteria: adults in HD for at least 3 months by arteriovenous fistula, and sign informed consent. Exclusion criteria: allergy or intolerance to citrate, intercurrent inflammatory diseases, significant cognitive impairment. Epidemiological, dialysis, and biochemical data were collected. Visual clotting scores of the dialyser and venous chambers were quantified.

Results: 53 patients were included, 44(83%) males, average age:64(16,5) years, dialysis technique HD/HDF: 18(34%)/35(66%). Mean values of the dialysis parameters: Blood flow: 392,8(48,2) ml/min; kt: 53,5(8,2) L, infusion volume in HDF: 26,9(3,7) L, dialysate bicarbonate concentrations: 31,5(1,6) mmol/l. Results Of the 32 patients who completed the study on 03/31/2017 in table. Coagulation scores from either chambers and dialyser, as well as the number of hypotension episodes recorded during the sessions were lower with the C (p=0.00). We did not find differences neither in the inflammatory parameters measured with C-reactive protein and IL-6, nor in the preHD bicarbonate values.

Conclusions: Dialysis with C modifies most phosphocalcic metabolism parameters, not only acutely as previously described, but also in the long term, and decreases/avoids postdialysis alkalaemia. We have found lower coagulation scores and arterial hypotension episodes with C.

Funding: Commercial Support - Baxter

	Acetate	Citrate	Significance
PreHD Ca++ (mmol/L)	1,12 (0,0)	1,10 (0,0)	0,02
PreHD P (mg/dl)	4,0 (1,1)	4,4 (1,2)	0,04
PreHD Mg (mg/dl)	2,2 (0,3)	2,0 (0,0)	0,00
PreHD PTH (pg/ml)	301,1 (217)	367,6 (215)	0,04
PostHD Ca++ (mmol/L)	1,2 (0,1)	1,1 (0,0)	0,00
PostHD Mg (mg/dl)	1,9 (0,1)	1,8 (0,1)	0,02
PostHD PTH (pg/ml)	204,6 (168)	300 (231)	0,00
PostHD Bicarbonate (mmol/L)	28,3 (2,3)	26,5 (1,9)	0,02

SA-PO790

Risks and Benefits of Novel Oral Anticoagulants across the Spectrum of CKD among Patients with Atrial Fibrillation Jung-Im Shin,[1] Alex Secora,[1] Josef Coresh,[1] Alex R. Chang,[2] Morgan Grams.[1] *[1]Johns Hopkins University, Baltimore, MD; [2]Geisinger Medical Center, Danville, PA.*

Background: The relative safety of novel oral anticoagulants (NOACs) vs. warfarin for treatment of atrial fibrillation (AF) in patients with chronic kidney disease (CKD) in real-world settings is unknown. The objective of the study was to evaluate risks and benefits of NOACs in comparison with warfarin across a range of estimated glomerular filtration rate (eGFR).

Methods: We analyzed a cohort of 3,206 patients with AF who used NOACs (Apixaban, Rivaroxaban, or Dabigatran) and a 1:1 propensity-score matched cohort of 3,206 warfarin users between October 2010 and January 2017 in the Geisinger Health System. We estimated the incidence rates of bleeding and ischemic stroke, stratified by G-stage of CKD.

Results: Mean baseline age of the study population was 73.3 years, 46.6% were women, and mean eGFR was 68.5 ml/min/1.73 m^2. There were 1,181 bleeding events, 466 ischemic strokes, and 310 deaths among 6,412 patients with 7,391 person-years (PYs) of follow-up. The incidence rates of bleeding (NOACs vs. warfarin) were 17.4 vs. 16.9 per 100 PYs among those with eGFR≥60, 25.2 vs. 19.0 among those with eGFR 30-59, and 38.1 vs. 30.4 for eGFR<30 ml/min/1.73 m^2, respectively (Figure 1). The incidence rates of ischemic stroke were 6.0 vs. 6.0, 8.8 vs. 7.5, and 9.2 vs. 10.6 for those with eGFR≥60, eGFR 30-59, and eGFR<30 ml/min/1.73 m^2, respectively. Similar findings were observed when each drug was analyzed individually. Among the 122 NOACs users with eGFR<30, 27.8% were not prescribed with renal dose adjustment.

Conclusions: In real-world settings, patients with CKD on NOACs for treatment of AF appeared to experience bleeding events more frequently than those on warfarin. Further large-scale studies are warranted to confirm our descriptive findings.

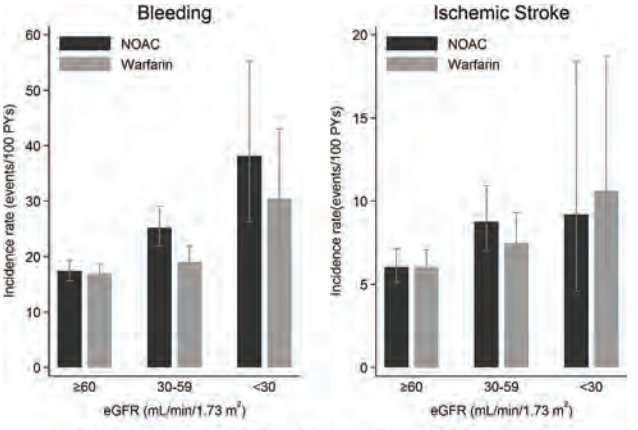


Figure 1. Incidence Rate of Outcomes by eGFR Category

SA-PO791

Cardiac Output Changes Relate to Ultrafiltration Volume during Intermittent Hemodialysis and to Pre-HD Intravascular Volume Assessed by Inferior Vena Cava Ultrasound Collapsibility in ICU Patients Matthew Kaptein,[2,3] Christopher Nguyen,[1] John Kaptein,[3] Elaine Kaptein.[3] *[1]Keck School of Medicine of USC, Los Angeles, CA; [2]Loma Linda University Medical Center, Loma Linda, CA; [3]LAC+USC Medical Center, Los Angeles, CA.*

Background: The goal of volume management is to optimize intravascular volume and maximize cardiac output (CO). CO tends to increase after volume administration in volume depleted patients[1], to increase with UF in volume overloaded ESRD patients[2,3], and to decrease with UF in ESRD patients prone to intradialytic hypotension[4].

Methods: We retrospectively studied 12 ICU patients in 29 intermittent HD (IHD) encounters who had relative intravascular volume assessed by respiratory changes in inferior vena cava diameter within 24 hours prior to IHD/UF, and CO assessed by thermodilution before and after IHD/UF. IVC Collapsibility Index (CI) = (IVCmax-IVCmin)/IVCmax *100%. CO change >10% was considered significant.

Results: For encounters with IVC CI <10% (volume overload), UF -1.6 to -2.6L was associated with increased CO (+14 to +66%) [A]. Larger (-3.0 to -3.2L) [B] or minimal (-0.75 to +0.2L) [C] UF was associated with decreased CO (-15 to -22%). With IVC CI >30% (volume depleted) volume given during IHD may increase CO [D], while UF (-2.4 to -3.0L) may decrease CO (-28 to -44%) [E]. With IVC CI of 10 to 30%, volume removal (-1.4 to -2.8L) may decrease CO (-4 to -20%) [F].

Conclusions: Changes in CO with respect to IVC CI and net volume change with IHD/UF (Fig 1a) may be consistent with changes in position along the Frank Starling curve (Fig 1b), assuming that relative intravascular volume is a primary determinant of IVC CI and CO. These data are consistent with IVC CI being an indicator of relative intravascular volume, and provide empiric evidence that “appropriate” volume removal can improve CO in ICU patients. Reference PMID: 1) 28261499, 2) 8420299, 3) 12059009, 4) 27539225

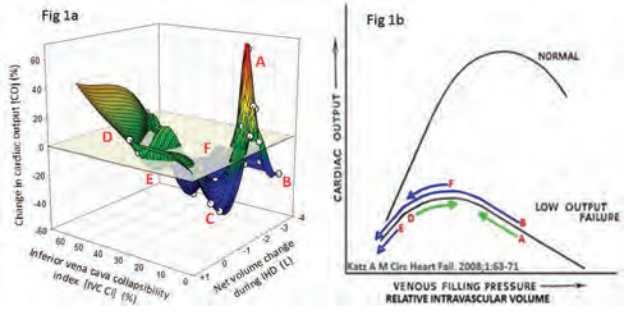


Fig 1a: 3D mesh plot of relationships among change in CO with IHD/UF, intravascular volume assessed by IVC CI before IHD, and volume change during IHD. (O) - individual encounters. Letters indicate different response patterns. Fig 1b: Frank Starling curve with response patterns.

SA-PO792

Individual-Level Changes in Interdialytic Weight Gain and Blood Pressure before Dialysis Treatment Are Associated with Same-Day Extreme Heat Events within Northeastern US Cities Alice Topping,[3] Richard V. Remigio,[4] Jochen G. Raimann,[3] Peter Kotanko,[3] Franklin W. Maddux,[2] Patrick Kinney.[1] *[1]Boston University School of Public Health, Boston, MA; [2]Fresenius Medical Care, Waltham, MA; [3]Renal Research Institute, New York, NY; [4]University of Maryland, College Park, Washington, DC.*

Background: In previous work, we have observed the effect of seasonal changes on interdialytic weight gain (IDWG) and pre-treatment blood pressure among hemodialysis (HD) patients. We sought to understand this seasonal effect at a finer temporal resolution by joining averaged daily ambient weather data with individual-level patient data. We focused on patients residing within northeastern United States cities.

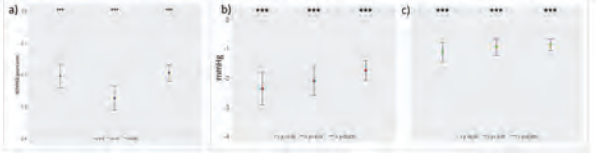
Methods: Clinical data were extracted from Fresenius Medical Care-North America (FMC-NA) database for HD patients in Boston (N=1439), New York (N=2241), and Philadelphia (N=3762) between 2001 and 2012. Using weather data from the National Oceanic and Atmospheric Agency (NOAA), we defined a heat wave event as average ambient air temprature in the 99th percentile for each city. We applied linear mixed-effects regression modeling to estimate the effect of same-day heat wave event exposures on IDWG and, systolic blood pressure (pre-SBP), and diastolic blood pressure (pre-DBP) for patients in each city.

Results: All three cities demonstrated associations between same-day heat wave events and IDWG percentage. When compared to non-heat wave events, individual-level IDWG percentage can decrease up to 0.34 % on average (Figure 1a). Same-day heat wave effects on blood pressure demonstrated associations for all three cities. When compared to non-heat events, pre-SBP and pre-DBP can decrease up to 3.28 mmHg and 1.45 mmHg on average, respectively (Figure 1b,c).

Conclusions: Same-day heat wave exposures demonstrated a consistent effect on IDWG percentage and blood pressure among individual patients in the northeastern region of the USA. Our preliminary findings demonstrate a potential relationship between outdoor heat events and important clinical measures in hemodialysis patients. Further work is needed to account for possible regional-specific variation related to these clinical measures.

Funding: Commercial Support - Renal Research Institute

Figure 1: IDWG percentage (a) and pre-treatment SBP (b) and DBP (c) for heat wave events compared to non-heat wave events



SA-PO793

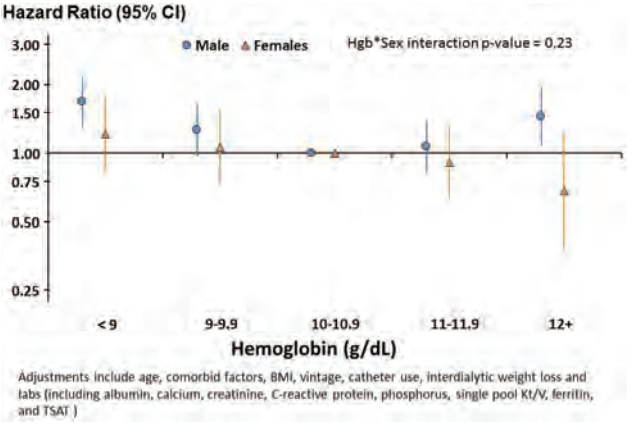
Evaluation of Gender Differences in the Association between Hemoglobin and Mortality Among Hemodialysed Patients in the JDOPPS Norio Hanafusa,[1,5] Charlotte Tu,[2] Keith McCullough,[2] Brian Bieber,[2] Ronald L. Pisoni,[2] Bruce M. Robinson,[2] Takeshi Hasegawa,[3,5] Masaomi Nangaku.[4,5] *[1]Department of Blood Purification, Tokyo Women's Medical University, Tokyo, Japan; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]Division of Nephrology, Department of Medicine, Showa University Fujigaoka Hospital, Yokohama, Japan; [4]Division of Nephrology and Endocrinology, the University of Tokyo School of Medicine, Tokyo, Japan; [5]Anemia Working Group, the Japan Dialysis Outcomes and Practice Patterns Study, Tokyo, Japan.*

Background: Lower hemoglobin (Hb) levels can be permissible among female patients without kidney diseases. Little is known about the gender-specific anemia management in hemodialysis (HD) patients.

Methods: We studied the gender differences in the association between baseline or time-varying Hb values in five categories and all-cause mortality on 6,891 patients in phases 3-5 (2005-2015) of Japan Dialysis Outcomes and Practice Patterns Study (JDOPPS). The associations were investigated by Cox proportional hazard models, with different levels of adjustment. The interaction between gender and hemoglobin's effect on mortality was analyzed using likelihood ratio tests. Several sensitivity analyses were performed, including time-dependent 0-90-day-lagged models and models stratified by vintage and by patient age.

Results: During the median follow-up of 2.58 years, 781 patients died. In the baseline Hb models without lag, a "U-shaped" association (Figure) was observed only in male patients (sex*Hb interaction p=0.23). Similar associations were seen in the lagged time-dependent models. Stratified analyses showed that patients with vintage >1 year or age <75 years exhibited trends similar to the entire population.

Conclusions: The association between Hb and survival might differ between genders in Japanese HD patients. Only male patients showed a "U-shaped" association between Hb and survival, while a moderate linear relationship was observed in females. The detailed investigations in the male patients with higher hemoglobin levels might lead to better understanding of the gender differences in anemia management and of anemia management in whole dialysis population as well.



Adjusted hazard ratio of all-cause mortality, by baseline hemoglobin and gender

SA-PO794

Endogenous Erythropoietin and Requirement of Erythropoietin Supplementation in Hemodialysis Patients Laura Sola, Susana B. Gonzalez, Juan C. Diaz, Veronica Miranda, Laura C. Fajardo, Ricardo A. Hermo. *CASMU-IAMPP, Montevideo, Uruguay.*

Background: Anemia is frequent in hemodialysis (HD) patients (Pts) and is associated to increased morbidity and mortality, being the main cause decreased erythropoietin (EPO) production. The objective of this study is to measure endogenous EPO (EPOe), and asses its relationship with hemoglobin (Hb) and required dose of erythropoietin supplementation (EPOsup) in HD Pts.

Methods: EPOe was measured in HD Pts older than 18 years on treatment in the HD Unit of CASMU on February 2017. Were excluded Pts with evident bleeding, neoplasia, acute infection or hospitalization in the previous month. Data was registered regarding gender, age, and residual renal function (RRF) (creatinine clearance when diuresis ≥300 ml/day) EPOe and Hb were measured after 1 week without EPOsup, in midweek HD, with Advia 2010, Siemens. EPOe was considered low when <4.3, normal value 4.3 to 29 and high >29 mUI/ml. EPO dose was considered as UI/Kg/week, and its response as Hb/EPO dose Quantitative data was expressed as mean and standard deviation or median and interquartile range (IQ), and compared by t test or ANOVA, and categorical measures expressed by percentage and compared by chi square. Significant differences were considered with p values <0.05.

Results: We studied 134 Pts, 83 men (61.9%), median age 70 (IQ 60-79) years, 44 diabetics (32.8%), HD vintage 28 months (IQ 14-49). Diuresis in 54 Pts was 800 (IQ 500-1350) ml/day, with RRF 6,4 (IQ 2,8-9,3) ml/min. Median EPOe was 9.4 (6.6-13.7) mUI/ml. Low EPOe in 10 (7.5%), normal in 116 (86.5%), and high in 8 Pts (6.0%). Pts who did not received EPOsup (19) not differ regarding mean age, HD vintage or EPOe with those with EPOsup. Hb levels were significantly higher in those Pts without EPOsup (12.4±1.1 vs 11.1±1.1 g/dL). EPO categories did not differ regarding age, gender, diabetes, Hb levels or EPO dose. Higher EPOe levels were significantly associated to higher vintage (low EPOe 36.7 ± 23.5, normal EPOe 35.7 ± 41.4 and high EPOe 77.6 ± 70.6 months).

Conclusions: Unexpectedly only 7.5% of the Pts had low EPOe, even though normal levels are inadequate in anemic Pts. Higher EPOe in Pts with longer dialysis vintage may suggest others sources for EPOe besides kidneys in these Pts.

Funding: Clinical Revenue Support

SA-PO795

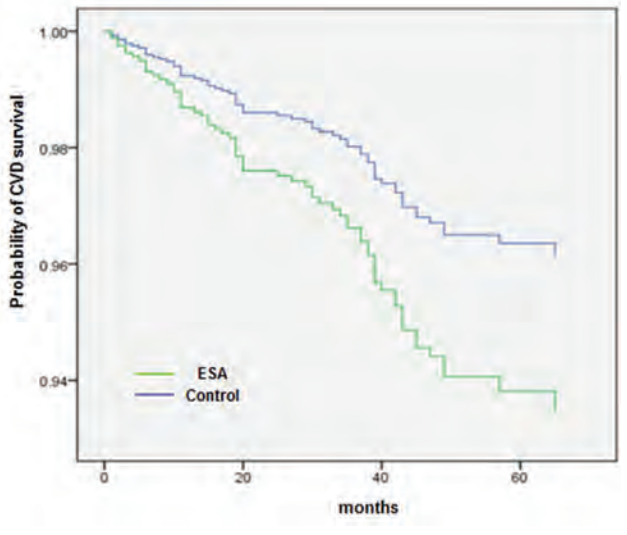
Safety of Erythropoietin Administration among ESRD Patients Jong hoon Lee,[1] Byung ha Chung,[1] Cheol Whee Park,[4] Chul Woo Yang,[3] Yong-Soo Kim,[5] Bumsoon Choi.[2] *[1]Seoul St. Mary hospital, Seoul, Republic of Korea; [2]Division of Nephrology, Department of Internal Medicine, Seoul, Republic of Korea; [3]Seoul St. Mary's Hospital, Seoul, Republic of Korea; [4]The Catholic University of Korea, Seoul, Republic of Korea; [5]The Catholic University of Korea College of Medicine, Seoul, Republic of Korea.*

Background: Erythropoietin (EPO) has been used to care for anemia in CKD patients. Concerns about the administration of EPO include CVD events and tumor progression, but definite associations were not fully identified. We performed the study to validate safety of EPO administration among ESRD patients.

Methods: 3432 ESRD patients were included to a prospective observational study in Clinical Research Center for ESRD registry. The patients were divided into HD group and PD group by dialysis methods. A dose of EPO, IV iron administration and serum Hb levels, CVD and cancer mortality were collected in the registry. Analyses were conducted to estimate hazard ratio(HR) for the EPO administration, dose of EPO and Hb levels with mortality of CVD and cancer.

Results: The mortality rate of CVD was 1.71% in HD group and 1.94% in PD group. CVD mortality was increased by EPO administration in PD group (HR 1.72, p=0.04). But the mortality has no correlation with EPO dose and Hb level. Any factor did not relate to CVD mortality in HD group. The mortality rate of cancer in ESRD patients was 0.94% in HD group and 0.78% in PD group. Hb level, EPO administration and dose were not associated with cancer mortality in both groups. In multivariate risk factor analysis, the mortality of CVD was associated to diabetes (p<0.01) and age (p<0.01) in both groups. However, the mortality of cancer was not associated with any factor.

Conclusions: EPO administration was associated with an increase of CVD mortality in PD patients. Diabetes and age were independent risk factors of CVD mortality. On the other hand, the mortality of cancer in ESRD patients was not associated with EPO administration.



Cardiovascular disease survival among peritoneal dialysis patients

SA-PO796

The Impact of Dose of ESA and Iron on the Risk of Adverse Events in Hemodialysis Patients Takahiro Kuragano,[2] Takeshi Nakanishi.[1] *[1]Hyogo College of Mediicne, Nishinomiya, Japan; [2]Internal Medicine Division of Kidney and Dialysis, Nishinomiya, Japan.*

Background: Anemia treatment with higher doses of ESA in patients with maintenance hemodialysis(MHD) might increase the risk of cardiovascular disease(CVD). On the other hand, higher doses of iron might cause iron overload, which can induce oxidative stress and CVD. The effects of the dosage balance of ESA and iron on the adverse events of MHD patients have not been well established.

Methods: This work was a prospective observational multicenter study over a period of 3 years in 1095 patients on MHD. The patients were divided into 4 groups according to the dose of ESA (high ESA (≥3000 IU/week), low ESA) and intravenous iron (high iron (≥15 mg/week), and low iron). Furthermore, in another analysis, the patients were divided into 4 groups according to the dose of ESA and iron storage (high ferritin (≥50 ng/mL), and low ferritin). A time-dependent Cox hazard model was applied to evaluate the association between patient groups and adverse events.

Results: *Doses of ESA and iron:* There was no significant difference in CVD risk between low ESA/low iron and high ESA/low iron. However, the CVD risks for high ESA/high iron (HR: 2.6, P=0.03) and low ESA/high iron (HR: 3.1, P=0.01) were significantly higher than that for low ESA/low iron. The risk of death for high ESA/high iron was significantly (HR: 2.8, P=0.04) higher than for low ESA/low iron. *Dose of ESA according to iron storage:* There was no significant difference in CVD risk between low ESA/low ferritin and high ESA/low ferritin. However, the CVD risks for low ESA/high ferritin (HR: 3.3, P=0.01) and high ESA/high ferritin (HR: 3.3, P=0.01) were significantly higher than that for low ESA/low ferritin. The risk of death for high ESA/high ferritin was significantly (HR: 3.1, P=0.01) higher than that for low ESA/low ferritin.

Conclusions: We found that high doses of ESA and iron were significantly associated with higher risks of CVD and death. Regardless of ESA dose, a higher dose of iron was significantly associated with a higher risk of CVD. Interestingly, patients with iron deficiency treated with a high dose of ESA were not necessarily at high risk of CVD. We concluded that a higher dose of iron for improving the responsiveness to ESA did not necessarily attenuate this risk of CVD and death.

SA-PO797

Association between Resistance to Erythropoiesis-Stimulating Agents and Carnitine Profile in Patients on Maintenance Hemodialysis Daigo Kamei,[2] Ken Tsuchiya,[1] Kosaku Nitta.[1] *[1]Blood Purification, Tokyo Women's Medical University, Shinjuku-ku, Japan; [2]Blood purification, Tokyo Women's University, Tokyo, Japan.*

Background: Patients on dialysis are in a chronic carnitine-deficient state. This condition may be associated with abnormalities in fatty acid and organic acid metabolism; however, the details are unknown. We investigated the association between carnitine profiles before and after dialysis and the erythropoiesis-stimulating agent (ESA) resistance index (ERI), which is a significant prognostic factor in patients on maintenance hemodialysis.

Methods: cross-sectional study. We measured the carnitine profile of 79 patients on maintenance hemodialysis before and after dialysis using liquid chromatography-tandem mass spectrometry (LC-MS/MS). The associations between the ERI and pre-dialysis carnitine profile, removal rate of various carnitines, and previously-reported ERI-related factors were investigated. Significant factors were determined with stepwise multiple regression analysis and validated with the bootstrap method. SPSS version 22.0 was used for analysis, and P<0.05 was considered statistically significant.

Results: The removal rate of long-chain acylcarnitine with dialysis was lower than that of short-chain or medium-chain acylcarnitines. Stepwise multiple regression analysis (n=79) demonstrated that 3-hydroxy isovalerylcarnitine (C5-OH, P<0.001, β= -0.469) and stearoylcarnitine (C18, P<0.001, β= 0.390) were independent significant factors (R^2= 0.239) of ERI. The bootstrap method similarly indicated these two to be significant factors.

Conclusions: ERI was positively correlated with long-chain C18 acylcarnitine and was negatively correlated with short-chain C5-OH acylcarnitine. C5-OH and C18 acylcarnitines at baseline might be contributing factors in distinguishing responders from nonresponders after L-carnitine administration.

SA-PO798

Hemoglobin Level and Dose of Erythropoietin Stimulating Agent Depending on Hemoglobin Measurement Day Soo Ya Bae, Chung Hee Baek, Su-Kil Park, Hyosang Kim. *Asan Medical Center, University of Ulsan College of Medicine, SEOUL, Republic of Korea.*

Background: Hemoglobin (Hb) variability is frequently observed in end stage renal disease (ESRD) patients. There have been many discussions over true functional Hb in ESRD patients without any confirmative conclusion. Optimal dosing of Erythropoietin Stimulating Agent (ESA) based on true Hb level is important, because high dose ESA is known to be related to poor outcomes with increased health care expenditure. We investigated changes in Hb level and erythropoietin stimulating agent (ESA) dose depending on the change of Hb measurement day in maintenance hemodialysis (HD) patients

Methods: The day for predialysis Hb measurement was changed from days after long interdialytic period (Monday or Tuesday) to midweek days (Wednesday or Thursday) in Asan Medical Center in September 2013. We reviewed baseline clinical characteristics, laboratory data including Hb, dose of ESA, dose of intravenous (IV) iron, and parameters related to HD for two years before and after the change of Hb measurement day in 92 patients receiving maintenance HD.

Results: Mean age of patients was 61.6 ± 12.1, and diabetes mellitus was the leading cause of ESRD (52.2 %). Mean Hb level was 10.71 ± 0.06 g/dL a year before the change of Hb measurement day, 10.78 ± 0.47 g/dL a year after the change (p=0.105). Mean ESA dose was 175.36 ± 72.47 μg darbepoietin alfa per month, 163.65 ± 83.95 μg per month, before and after the change, respectively (p=0.022). Mean IV iron dose was 6.32 ± 4.89 ample (100 mg Fe3+/1 ample) iron hydroxide sucrose per year, 4.47 ± 5.02 ample per year, before and after the change, respectively (p<0.001). Mean interdialytic weight gain was 2.81 ± 0.82 kg and 1.99 ± 0.61 kg, before and after the change, respectively (p<0.001). The number of patients without achievement of target Hb requiring higher dose of ESA was decreased from 8 to 2, before and after the change respectively.

Conclusions: Significant decrease in the ESA and IV iron dose was observed without change in Hb level after midweek predialysis Hb measurement. Midweek predialysis Hb level would be better criterion for ESA dosing.

SA-PO799

Association of Predialysis ESA Anemia Treatment with Mortality after Dialysis Initiation James B. Wetmore,[5] Suying Li,[4] Heng Yan,[4] Hairong Xu,[2] Marvin V. Sinsakul,[1] Yi Peng,[4] Jiannong Liu,[3] David T. Gilbertson.[4] *[1]AstraZeneca, Bethesda, MD; [2]Astrazeneca, Westlake Village, CA; [3]Minneapolis Medical Research Foundation, Minneapolis, MN; [4]Chronic Disease Research Group, Minneapolis, MN; [5]Hennepin County Medical Center, Minneapolis, MN.*

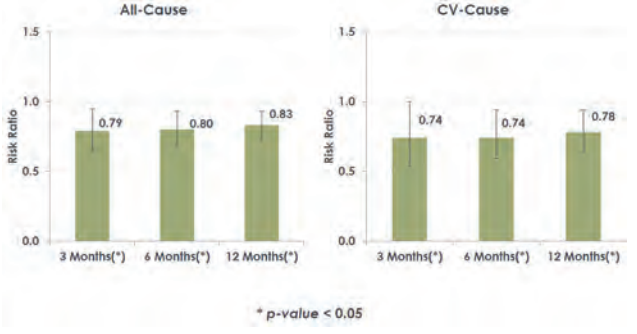
Background: Whether treatment of anemia in the setting of CKD prior to hemodialysis (HD) initiation may reduce post-initiation mortality is unknown.

Methods: Patients who initiated HD between April 1, 2012 and June 30, 2013 were identified from USRDS end-stage renal disease (ESRD) and pre-ESRD files. Hemoglobin (Hb) measurements at HD initiation and at least one other measurement in the subsequent 3-months, in the absence of transfusion, were required. Patients who either never had anemia (defined as Hb ≥ 9.0 g/dL) in the absence of treatment or those who had persistent post-initiation anemia despite treatment were eliminated. Patients who were consistently well-treated (Hb ≥ 9.0 g/dL) with ESAs were retained and compared with patients who appeared to have untreated or ineffectively-treated anemia prior to HD initiation, provided the latter responded to ESAs after initiation. Cox PH models, adjusted for patients' demographics and comorbidities, were used to calculate the hazard ratio of all-cause and cardiovascular (CV) mortality after HD initiation.

Results: The study sample was comprised of 3662 consistently well-treated patients and 4461 patients in the compared group. Adjusted risks of outcomes are shown in the Figure. All-cause mortality was significantly less for the consistently well-treated patients at 3 (HR 0.79, 95% CIs 0.65-0.95), 6 (HR 0.80, 95% CIs 0.69-0.93), and 12 (HR 0.83, 0.73 – 0.93) months. A similar pattern was observed for CV mortality at 3 (HR 0.74, 95% CIs 0.54-1.00), 6 (HR 0.74, 95% CIs, 0.59-0.94) and 12 (HR 0.78, 95% CIs 0.64-0.94) months.

Conclusions: Failure to achieve Hb ≥ 9.0 g/dL through lack of treatment in the predialysis period may represent missed treatment opportunity to reduce mortality after HD initiation.

Funding: Commercial Support - AstraZeneca



Risk of all-cause and cardiovascular mortality in patients with consistently well-treated predialysis anemia (Hb at least 9.0 g/dL) compared to those patients who were not adequately treated but who later proved to be treatable after dialysis initiation.

SA-PO800

Anemia Management in Hemodialysis Patients – Is Six-Weekly Monitoring of Hemoglobin Sufficient? Abdullah A. Alaryni, M. Khaled Shamseddin, Frances Macleod, Eduard A. Iliescu. *Kingston General Hospital, Kingston, ON, Canada.*

Background: The KDIGO guidelines recommend monitoring of hemoglobin (Hb) in hemodialysis patients (HD pts.) at least monthly (not graded). Canadian HD programs vary from every 4 to 6-weeks and protocols exist for both schedules. Our centre changed from monthly to every 6 weeks in March, 2014. The objective of this QI report is to examine the volume of CBC measurements, costs, and proportion of pts. with Hb on target before and after the change.

Methods: This is a retrospective study of prevalent HD pts. in South-Eastern Ontario including all in-centre, satellite and home HD. The primary variables were the number of CBCs performed (obtained from EMR) during the 252 days before and 252 days after Mar. 24, 2014 and the associated costs (CDN $ 8.27/CBC Ontario Provincial Fee Schedule). The 252 day equal periods represent exactly 8 complete monthly cycles and 6 complete 6-weekly cycles before and after the change. The proportion of pts. with Hb on target (100 – 120 g/L) was assessed for a longer period of 2 yrs. before and after the change to assess long term outcomes.

Results: The profile of HD pts. is 430 - 440 total, 46 % in-centre, 43 % satellite, 11 % home HD, majority Caucasian, mean age 66 yr., 44 % female, 46 % DM, and 45 % with CVC. The CBC numbers and costs decreased overall but more in satellite than in in-centre pts (Table 1). The proportion of patients with Hb on target 2 years before and after were similar, 60 and 60.5 % respectively.

Conclusions: The results of this study suggest that anemia management in HD pts. results in similar outcomes with CBC measured every 6 weeks as with monthly with reduced cost. The reduction in CBCs was lower in in-centre pts. who had more CBCs measured between the routine bloodwork likely due to higher acuity and overall this is rational use of more frequent testing in sicker pts. The results of this study provide a regional perspective as this is the only HD program in the region, but may not be generalizable to HD programs with different population characteristics.

Table 1.

	Monthly Cycles	6-Weekly Cycles	Reduction/Savings
In-Centre (# CBC)	2194	1995	199
Satellites (# CBC)	1605	1275	330
Total (# CBC)	3799	3270	529
Cost (CDN $)	31,417.73	27,042.90	4,374.83

SA-PO801

Definition and Validation of a Novel Metric to Assess Erythropoiesis Stimulating Agent Response in Hemodialysis Patients Calvin J. Meaney,[4] Spinel Karas,[2] Ben Robinson,[4] Jamie L. Gaesser,[3] Alan Forrest,[6] Wojciech Krzyzanski,[3] Mandip Panesar,[1] Gauri G. Rao.[5] *[1]Williamsville, NY; [2]The University of North Carolina, Durham, NC; [3]University at Buffalo, Glen Mills, PA; [4]University at Buffalo School of Pharmacy and Pharmaceutical Sciences, Buffalo, NY; [5]University of North Carolina, Chapel Hill, NC; [6]University of North Carolina Eshelman School of Pharmacy, Chapel Hill, NC.*

Background: Erythropoiesis stimulating agents (ESA) are the primary treatment of anemia in end-stage renal disease (ESRD) patients. Hemoglobin variability in and out of a narrow target range is common and associated with higher mortality and/or morbidity. More robust metrics of ESA response are needed to define optimal dosing and association to clinical outcomes.

Methods: In this cross-sectional, single-center, retrospective study, 49 ESRD patients on hemodialysis were followed for 12 months. To quantify the excursion of hemoglobin outside the target range (10-12g/dl), the area-under-the-curve of hemoglobin versus time over a 12-month period (AUC-HGB) was calculated using the trapezoidal rule. Patients were categorized into 4 responder groups based on AUC-HGB quartiles. Comparative analysis of demographic and clinical characteristics between responder groups was performed using Chi-square and Kruskal Wallis tests as appropriate. Spearman correlations between AUC-HGB, erythropoietin resistance index (ERI) and time within therapeutic range (TTR) were performed.

Results: There were no significant differences in demographics, laboratory, or dialysis parameters between responder groups except hemoglobin and ESA dose. The mean age was 58.0±13.1 years, 59% were male and 69% were African-American. Mean hemoglobin was 10.4±0.58g/dl (range 6.0-13.6g/dl). The median (range) AUC-HGBs for each group were: 4.45 (0-20) g x year/dL in the excellent responder group; 48.2 (26-65) g x year/dL in the good responder group; 101 (76-109) g x year/dL in the fair responder group; and 201 (123-528) g x year/dL in the poor responder group. There was a negative correlation with AUC-HGB and TTR (r=-0.93, p<0.001) and hemoglobin concentration (r=-0.85, p<0.01), while there was a positive correlation with AUC-HGB and ERI (r=0.70, p<0.001). The poor response group received higher median ESA dose (160 U/kg/week) compared to the excellent response group (68.8 U/kg/week, p<0.001) with a similar number of ESA dose changes between the groups. Over 2 years of follow-up, 5 patients died, of which 3 were in the poor response group.

Conclusions: AUC-HGB is a valid metric of ESA response in the hemodialysis population and may serve as a better marker of ESA response compared to conventional metrics.

SA-PO802

GX-E2 versus CERA for Anemia in Patients Receiving Maintenance Peritoneal Dialysis: A Phase 2, Randomized, Multi-Center, Active-Comparator, Dose-Finding Safety and Efficacy Study E un jeong Ko,[1] Byung ha Chung,[1] Sug kyun Shin,[2] Hyung Wook Kim,[3] Byung chul Shin,[4] Seok Joon Shin,[5] Hyeong cheon Park,[6] Young Sun Kang,[7] Sang-Ho Lee,[8] Ho Cheol Song,[5] Su Hyun Kim,[9] Ki Young Na,[10] Young-Il Jo,[11] Won Kim,[12] Eun Young Seong,[13] Yong-Lim Kim,[14] Minkyu Heo,[15] Jungwon Woo,[15] Chul Woo Yang.[1] *[1]Seoul St. Mary's Hospital, Seoul, Republic of Korea; [2]Ilsan Hospital NHIS, Gyeonggi, Republic of Korea; [3]St. Vincent's Hospital, Gyeonggi, Republic of Korea; [4]Chosun University, Gwangju, Republic of Korea; [5]Incheon St. Mary's Hospital, Gyeonggi, Republic of Korea; [6]Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea; [7]Korea University Medical College Ansan Hospital, Gyeonggi, Republic of Korea; [8]Kyung Hee University Hospital, Seoul, Republic of Korea; [9]Chung-Ang University Hospital, Seoul, Republic of Korea; [10]Seoul National University Bundang Hospital, Gyeonggi, Republic of Korea; [11]Konkuk University Hospital, Seoul, Republic of Korea; [12]Chobuk National Univeristy Medical School, Jeonju, Republic of Korea; [13]Pusan National University Hospital, Busan, Republic of Korea; [14]Kyungpook National University Hospital, Daegu, Republic of Korea; [15]Genexine, Inc., Seongnam-si, Republic of Korea.*

Background: GX-E2 is hybrid Fc (hyFc)-fused long-acting recombinant human erythropoietin. We conducted a phase 2, randomized, active-comparator, safety and efficacy study in patients with anemia receiving maintenance peritoneal dialysis.

Methods: Patients with a stable end-stage renal disease treated with peritoneal dialysis were included. In Part A, a dose-finding study was conducted in 60 subjects with 4-week treatment of six different dosage of GX-E2. In Part B, 12-week treatment was conducted in 72 individuals with two selected doses of GX-E2 based on the Part A results, and with methoxy polyethylene glycol-epoetin β (CERA) (0.6 μg/kg bi-weekly). Primary endpoint was mean hemoglobin change from baseline to the end of treatment.

Results: In Part A, mean Hb level was significantly increased after 4 weeks GX-E2 administration and mean Hb changes from baseline were 0.6±1.3 g/dL in 3 μg/kg, 1.3±1.1 g/dL in 5 μg/kg, and 1.4±1.0 g/dL in 8 μg/kg bi-weekly. In Part B, participants were randomly assigned to 3 groups, treated bi-weekly with 5 μg/kg, 8 μg/kg of GX-E2 and 0.6 μg/kg of CERA. Mean Hb level changes after 12 weeks GX-E2 administration were 2.2±1.3 g/dL in 5 μg/kg, 3.1±1.1 g/dL in 8 μg/kg, and 1.7±1.4 g/dL in CERA, GX-E2 showed comparable or better outcome compared to CERA (p-values for each 0.233, <0.001). No safety issues were observed.

Conclusions: In this phase 2 study of anemia treatment in patients with end-stage renal disease on maintenance peritoneal dialysis, GX-E2 was well-tolerated and effectively maintained Hb levels.(grant number: HI14C1038)

Funding: Commercial Support - Genexine, Government Support - Non-U.S.

SA-PO803

Epoetin Alfa and Darbepoetin Alfa: A Cross-Sectional Study Comparing Doses According to Administration Intervals Marie-Eve Dupuis,[5] Caroline Lamarche,[4] Robert Z. Bell,[1] Katherine Desforges,[3] Laurence Lepage,[2] Vincent Pichette,[5] Jean-Philippe Lafrance,[4] Michel Vallee.[4] *[1]Centre de recherche Hopital Maisonneuve-Rosemont, St. Lambert, QC, Canada; [2]Hopital Maisonneuve Rosemont, Montreal, QC, Canada; [3]Maisonneuve-Rosemont Hospital, Montréal, QC, Canada; [4]None, Montreal, QC, Canada; [5]Université de Montréal, Montréal, QC, Canada.*

Background: Anemia is a common problem among patients with chronic kidney disease. Erythropoiesis stimulating agents (ESA) are frequently used to maintain haemoglobin between 95-115 g/L. Multiple studies suggest that longer intervals than those recommended in the product monographs of these ESA can be effective. Most of these studies were done in non dialysis patients. Fewer studies were done with population in hemodialysis, peritoneal dialysis and in transplanted patients.

Methods: In this retrospective, single center, cross-sectional study, we compared the dose, reported in IU/kg/week, between groups defined by the interval at which patients received ESA (more than once a week (G0), once a week (G1), once every other week (G2), once every three weeks (G3), once every 4 weeks (G4) and once every more than 4 weeks (G5). Charts of all patients receiving an ASE at a stable dose for at least three months and followed in either the pre-dialysis, hemodialysis, peritoneal dialysis and transplant clinic were reviewed.

Results: Five hundred and ninety four patients were included. One hundred and twenty-two patients (22%) were on epoetin alfa and 462 (78%) were on darbepoetin alfa. The mean dose/kg/week was less when a longer interval was used: the mean dose/kg/week) was 247 in G0, 195 in G1, 82 in G3, 67 in G3, 33 in G4 and 28 in G5 ($p<0.0001$). In the epoetin subgroup, the mean dose/kg/week was 256 in G0, 124 in G1, 52 in G2, 37 in G3, 19 in G4, 17 in G6 ($p<0.0001$). In the darbepoetin subgroup, the mean dose/kg/week was 162 in G0, 228 in G1, 86 in G2, 71 in G3, 35 in G4, 33 in G5 ($P>0.0001$).

Conclusions: Doses were significantly lower in the longer interval groups, suggesting that longer intervals are efficient to maintain haemoglobin in the desired target in a large population of patients with chronic kidney disease. The mean dose remained smaller in the longer intervals when comparing both ESA types, however, the mean dose was generally less in the epoetin group compared to the darbepoetin group. A selection bias might explain some of the differences between groups. Nonetheless, using longer intervals seem possible in a significant number of patients. Since longer intervals are more acceptable to patients and are more cost effective, this approach might be favourable.

Funding: Clinical Revenue Support

SA-PO804

Conversion from Epoetin Alfa to Darbepoetin Alfa in HD: Optimized Dose Conversion Algorithm and Hb Stability Dongyang Shang,[1] Alex Yang,[1] Shijie Chen,[1] Steven Chang,[1] Sheila Doss-McQuitty,[1] Brigitte Schiller.[1,2] *[1]Satellite Healthcare, San Jose, CA; [2]Stanford University, Palo Alto, CA, CA.*

Background: Previous conversion experiences from thrice weekly epoetin to once weekly darbepoetin resulted in inconsistent outcomes when using the conversion table in the prescribing information (PI). This study tested an improved conversion algorithm and assessed the accuracy through achieved target hemoglobin (Hb), Hb stability and speed to reach Hb stability.

Methods: This is a prospective, controlled, open-label, multi-center interventional trial. Data from 5643 in-center HD patients from 54 dialysis centers from January 2016 to May 2017 are presented. Conversion occurred from June 2016 to February 2017. Doses were adjusted monthly to achieve a target Hb of 10 to 11.4 g/dL. Hb values were measured monthly for the 4 months before conversion, 1 month during the conversion, and up to 4 months after conversion. Hb consistency was defined as an increase or decrease of ≤ 3% in the percentage of patients in each Hb category.

Results: The improved conversion table increases the number of dose categories, resulting in doses that overall are 8.8 times more closely aligned with the optimal dosing curve than the current PI. The distribution of patients (n=4634) treated with darbepoetin for 4 months reaching the target Hb 10.0-11.4 g/dL is clinically and statistically similar to pre-conversion. Within 2 months of conversion 54% of patients reached target Hb, similar to the month prior to conversion.

Conclusions: In this real-world dosing conversion study switching from epoetin to darbepoetin, the improved conversion table reduces the risk of initial under-dosing and shortens the duration of time before patients achieve stable Hb. Appropriate therapeutic conversion provides more accurate darbepoetin dosing based on patients' ESA needs.

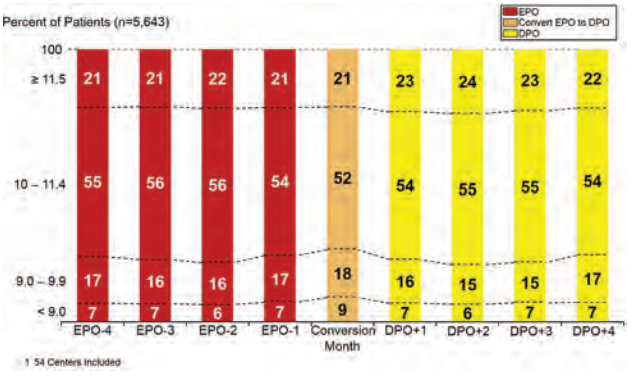


Figure: Hb Stability During Darbepotin Conversion[1] – Proportion of Converted Patients by Hb Ranges from January 2016 to May 2017

SA-PO805

Levels of the EPO-Responsive Hormone Erythroferrone in Mice and Humans with CKD Mark R. Hanudel,[1] Maxime Rappaport,[1] Victoria R. Gabayan,[2] Isidro B. Salusky,[1] Tomas Ganz,[2] Elizabeta Nemeth.[2] *[1]Department of Pediatrics, David Geffen School of Medicine at UCLA, Los Angeles, CA; [2]Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA.*

Background: We previously demonstrated that, in mice with normal kidney function, erythropoietin (EPO) stimulates erythroblasts to secrete the hormone erythroferrone (ERFE), which acts to suppress production of the iron-regulatory hormone hepcidin. ERFE-mediated hepcidin suppression increases iron availability for RBC production. ERFE has not been assessed in humans or in the setting of CKD.

Methods: We measured serum ERFE levels in wild type mice, with and without adenine diet-induced CKD, after administration of a single EPO dose. We also measured serum ERFE in adults with normal kidney function after EPO treatment, as well as in 161 adult and pediatric healthy controls, 82 adult and pediatric non-dialysis CKD patients, and 101 adult and pediatric dialysis patients.

Results: In mice with normal kidney function, serum ERFE levels, undetectable at baseline, increased in response to EPO, peaking 6h post-injection. In mice with CKD, serum ERFE levels increased to a similar degree, but peaked later, at 24h post-injection. In both groups, serum hepcidin was decreased at 48h. In four adults with normal kidney function injected with a single EPO dose, serum ERFE increased 2.2-fold from baseline by 48-72h post injection. Concurrently, serum hepcidin levels decreased 2.3-fold from baseline by 48-72h hours post injection. Median serum ERFE did not differ between non-dialysis CKD and control patients (6.1 vs. 7.8 ng/ml), but was significantly elevated in dialysis patients (15.7 ng/ml, $p<0.05$). In the non-dialysis CKD patients, serum EPO correlated positively with ERFE (Spearman $r=0.59$, $p<0.001$), but ERFE did not correlate with hepcidin. Hepcidin correlated with TSAT (Spearman $r=0.34$, $p=0.004$), but not with CRP or eGFR. Similarly, in the dialysis patients, rhEPO dose correlated positively with ERFE (Spearman $r=0.44$, $p<0.001$), but ERFE did not significantly correlate with hepcidin. Hepcidin did not correlate with TSAT or CRP.

Conclusions: In humans with normal kidney function, EPO administration increases ERFE and suppresses hepcidin. In CKD patients, ERFE correlates with serum EPO or rhEPO dose, but not hepcidin. These data suggest that ERFE is responsive to EPO in humans and mice regardless of kidney function, but that regulation of hepcidin in CKD is multifactorial, masking the hepcidin suppressive effects of ERFE.

Funding: NIDDK Support, Other NIH Support - NIH Loan Repayment Program

SA-PO806

Impact of Intra-Venous Ferric-Sucrose Hydroxide on Mortality in HD: MEDIAL Iron Cohort ECHO (MICE Study) Victorio Menoyo,[2] Malik Touam,[4] Pierre-Yves Durand,[1] A. Testa.[3] *[1]ECHO, VANNES, France; 2HEMODIALYSiS, ECHO, NANTES, France; 3ECHO NANTES, NANTES, France; 4Necker Hospital, Paris, France. Group/Team: MEDIAL STUDY GROUP.*

Background: Intraveinous iron is the main complement to Erythropoiesis Stimulant Agent (ESA) treatment for HD patients. Ferric Sucrose Hydroxide (HFS) is one of this. Previous retrospective studies have shown the potential toxicity of HSF, and have report increased mortality above some monthly dose. We aimed to study the toxicity of HSF, and to precize its relationship with this markers.

Methods: Medical Iron Cohort ECHO is a multicenter cohort of HD patients coming from 49 HD french centers. All incident patients were included from year 2005 to 2015. Data were retrospectively analyzed. Iron injections, ESA, hemoglobin and other biological data were recorded in a single database : MEDIAL. Statistical analysis used

a non-parametric test for exceedances of the Ferritin, TSAT and CRP standards as well as kt/V <1.3. We considered the usual demographics and diabetes. We have defined 4 subgroups according to the dose of HFS: A: <100 mg / month; B: 100-200 mg / month; C: 200-300 mg / month; D: 300-400 mg / month; E:> 400 mg / month. The proportional risk regression survival analysis (Cox model) was performed using the STATISTICA software.

Results: 1,370 patients were included. The average follow-up was 41.5 months. 481 deaths occured during the study period. It was a very strong relationship between mortality and HFS dose above 200 mg / month. (P <0.0000) The stratified analysis showed that this relationship was dose-dependent and the effect appears above a dose of 100 mg / month of HFS. Although there was no significant difference between subgroups A, B, C, there was a trend towards it. There was no significant relationship between mortality and Ferritin or TSAT blood levels. There was no significant difference between the 5 groups regarding the received ESA dose or hemoglobin. Gender and diabetes were not linked to mortality, while other independent factors appeared to be significant: age at onset of dialysis, albuminemia, CRP and kt/V <1.3.

Conclusions: This study suggests that intraveinous HFS in HD patients could be toxic, probably for doses considered to be low toxicity to date. Ferritin and TSAT blood levels are not good markers for HSF toxicity. Advanced age at the start of ESRD, undernutrition, inflammatory status, or poor dialysis dose are significant markers linked to mortality. Further prospective studies are required to confirm these results.

SA-PO807

Serum Concentration of Non-Transferrin Bound Iron in Hemodialysis Patients Is Increased after Oral Iron Administration Noriko Saito,[4] Kazuhide Saito,[6] Tetsuo Morioka,[3] Hisaki Shimada,[4] Kozo Ikarashi,[3] Yutaka Tsubata,[5] Taiji Sasagawa,[3] Katsuya Ikuta,[1] Yutaka Kohgo,[2] Shigeru Miyazaki.[3] *[1]Asahikawa Medical University, Asahikawa, Japan; [2]International University of Health and Welfare, Nasushiobara, Japan; [3]Shinraku-en Hospital, Niigata, Japan; [4]Shinraku-en hospital, Niigata, Japan; [5]Shinrakuen hospital, Niigata city, Japan; [6]Niigata University, Niigata, Japan.*

Background: Non-transferrin bound iron (NTBI), which appears in serum in iron overload, is thought to cause organ damage through free radical production. We reported NTBI was increased after intravenous iron administration (IVIA) in hemodialysis (HD) patients (ASN2016), on the other hand, their kinetics after oral iron administration(OIA) is unknown. Aim of this study is to assess the kinetics of NTBI concentration after OIA in HD patients.

Methods: 16 HD patients without any iron load within 4 weeks, whose Hb<12g/dl, ferritin<100ng/ml and CRP<1.0mg/dl, were enrolled. They received oral ferrous sulfate 105mg at the start of HD session. We evaluated the following markers before and at 1,2,3,4 and 48 hours(hr) after OIA : NTBI, Hepcidin-25(HPC), high sensitive CRP(hsCRP), 8-oxo-2'-dehydroguanosin, serum iron, transferrin saturation(TSAT), transferrin(Tf), ferritin, soluble Tf receptor and standard hematological parameters. NTBI was measured by recently described reliable method(Clin Chim Acta437:129-135, 2014). 4 HD patients without OIA were also enrolled as control.

Results: 1. Fe before OIA was 30(24-49)μg/dl and significantly increased to 45(27-57)μg/dl at 1hr and reached the peak level of 272(104-320)μg/dl at 4hr and then decreased to 52(34-81)μg/dl at 48hr (Medians(interquartile range)). 2. TSAT before OIA was 12(7-17)%, significantly increased to 24(17-39)% at 2hr, reached the peak level of 70(34-80)% at 4hr and decreased to 17(14-26)% at 48hr. 3. NTBI before OIA was 0.02(0-0.10) μM and significantly increased to 0.15(0.03-0.56)μM at 4hr and decreased to 0.02(0-0.07) at 48hr. 4. NTBI at 4hr after OIA correlated with TSAT at 4hr(r=0.894,p<0.001). 5. The predictor of NTBI 4hr after OIA was percentage of hypochromic red cells (%HypoHe) before OIA by stepwise analysis (β=0.548, p=0.028, R2=0.3) 6. Ferritin before OIA was 16(15-29) ng/ml and significantly increased to 35(19-48)ng/ml at 48hr. HPC was unchanged during 48hr. 7. In control patients TSAT, NTBI and ferritin were not changed during 48hr.

Conclusions: TSAT and NTBI significantly increased at 2hr and 4hr after OIA, respectively and both peaked at 4hr. %HypoHe before OIA was negative predictor of NTBI at 4hr. Clinical significance of NTBI increment after OIA should be further examined.

Funding: Private Foundation Support

SA-PO808

Evaluating Iron Overload in Haemodialysis Patients with MRI T2* Benjamin Elyan,[1] Kenneth Mangion,[1,2] Samantha F. Cockburn,[1] Patrick B. Mark,[1] Elaine Rutherford.[1,2] *[1]Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, United Kingdom; [2]Cardiology and Imaging Group, British Heart Foundation Glasgow Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom.*

Background: Intravenous iron is commonly prescribed to hemodialysis (HD) patients but optimal dosing is not established and iron overload is a clinical concern. MRI derived non-contrast T2* time is used to screen for cardiac and liver iron overload in other clinical groups, such as thalassemia - the lower the T2* time, the greater the degree of iron overload. T2* has not been studied in HD patients. We hypothesised that T2* in HD patients would differ from matched healthy volunteers (HVs) and that T2* in HD patients may correlate with their total cumulative intravenous iron doses.

Methods: 22 incident HD patients and 26 age and sex matched HVs were enrolled. Participants underwent a 3.0T MRI scan (Siemens Verio). T2* images were blindly analysed offline using Medis analysis software (QMaps) placing regions of interest in the myocardial septum and the liver. Statistical analysis was done using SPSS (version 22).

Results: Liver and myocardial septal T2* times were higher in HD patients (Table 1). Septal T2* times in HD patients negatively correlated with cumulative iron dose (R^2 = -0.49 p= 0.017) (Figure 1). Liver T2* times also negatively correlated with cumulative iron dose (R^2 = -0.46 p 0.028).

Conclusions: T2* times in septal and liver tissues are higher in incident HD patients compared with HVs, suggesting that HD patients do not have overt signs of iron overload early on. However, greater cumulative iron doses correlated with lower T2* times in HD patients. Imaging signs of iron overload may develop in patients established on HD for longer. Further research should explore the longitudinal affects of cumulative iron dose on T2 * times.

Funding: Private Foundation Support

Table 1: Median septal & mean liver T2* times

	HD Patients n=22	Healthy Volunteers n=26	p-value
T2* septum (ms) (Interquartile Range)	31.0 (5.5)	23.0 (6.5)	<0.001
T2* liver (ms) (95% Confidence Interval)	27.5 (24.9, 30.1)	19.6 (18.1, 21.0)	<0.001

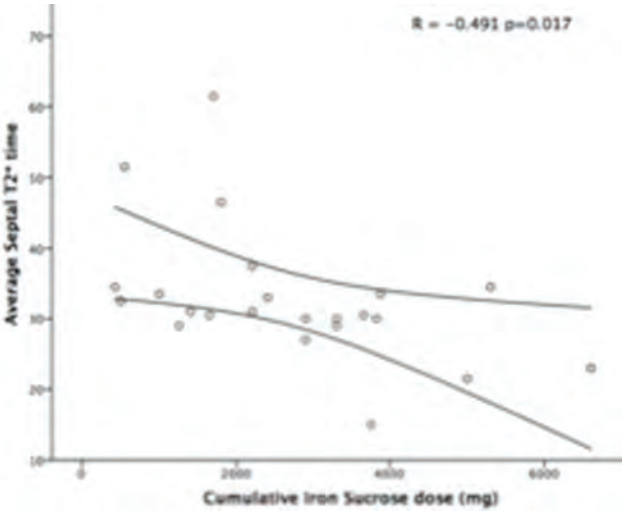


Figure 1: Correlation of average septal T2* time (ms) to cumulative Iron Sucrose dose (mg)

SA-PO809

Effects of Adult Erythropoietin Dosing Regimens on Pediatric Dosing Practice: Findings from North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) Sarah A. Twichell,[3] Elizabeth A. Hunt,[3] Karen Martz,[2] Michael J. Somers.[1] *[1]Boston Children's Hospital, Boston, MA; [2]NAPRTCS, Rockville, MD; [3]University of Vermont Children's Hospital, Burlington, VT.*

Background: Development of recombinant erythropoietin (epo) led to declines in anemia among hemodialysis (HD) patients, but studies showed more morbidity in adult HD patients with a 'normal' hemoglobin (hgb) level, so 2008 adult guidelines recommended target hgb <11.5 gm/dL. Adult guidelines are often applied to pediatric dialysis patients, though increased morbidity with higher hgb levels has not been demonstrated in children. We evaluated transfusions and anemia among pediatric HD patients before and after adult anemia guideline implementation.

Methods: We performed a retrospective analysis of children in the NAPRTCS database, a voluntary, prospective registry of children with end stage renal disease. We assessed transfusions, anemia, epo dosing, and hospitalizations in 3 time periods: baseline (2003-2007), implementation (2008-2011) and post-implementation (2012-2016). Children were included once in the earliest period enrolled.

Results: 1,199 children enrolled in the NAPRTCS HD registry during the study period (54.7% male, median age 13.4 years). Children in post-implementation were significantly younger than children in baseline and implementation. 12.8% of patients had transfusions in baseline, 19.6% in implementation (p=0.008 vs. baseline), and 17.4% in post-implementation (p=0.08 vs. baseline). Mean hgb 6 months after HD start was 11.8 gm/dL in baseline, 11.1 gm/dL in implementation (p<0.001 compared with baseline) and 11 gm/dL in post-implementation (p<0.02 compared with baseline). Median epo dosing 6 months after starting HD was 211 u/kg/week in baseline, 131 u/kg/week in implementation, and 142 u/kg/week in post-implementation. 6 months after starting dialysis, 42.7% of children were hospitalized in baseline, 43.4% in implementation, and 46.5% in post-implementation. The rate of anemia (hgb <10) 6 months after starting dialysis was 17.4% in baseline, 23.5% in implementation, and 23.8% in post-implementation.

Conclusions: With implementation of adult epo dosing guidelines, epo dosing was lower, anemia rate increased, transfusion rate increased, and mean hgb levels decreased among NAPRTCS participants. There was no significant difference in hospitalization rates before and after guidelines. Further study of safe target hgb levels among pediatric HD patients is warranted.

SA-PO810

Iron Supplementation for Hemodialysis Patients: Less Oxidative Stress by Oral Ferric Citrate Hydrate as Compared to Intravenous Saccharated Ferric Oxide Masaaki Nakayama,[6] Yoshihiro Tani,[4] Wan-Jun Zhu,[6] Keitaro Yokoyama,[1] Masafumi Fukagawa,[7] Takashi Akiba,[5] Myles S. Wolf,[2] Hideki N. Hirakata.[3] *[1]Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan; [2]Duke University, Durham, NC; [3]Fukuoka Renal Clinic, Fukuoka City, Japan; [4]Fukushima Medical University, Fukushima, Japan; [5]Sekikawa Hospital, Tokyo, Japan; [6]Tohoku University, Tohoku University Hospital, Sendai City, Japan; [7]Tokai University School of Medicine, Isehara, Japan.*

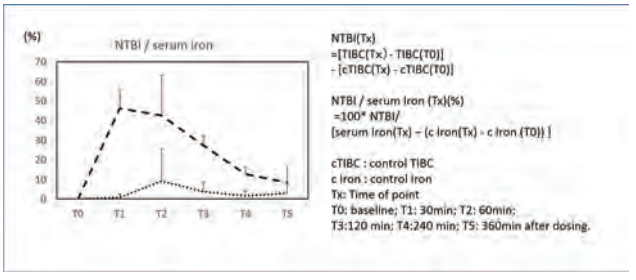
Background: Orally dosed ferric citrate hydrate (FC) corrects renal anemia in patients on hemodialysis (HD), suggesting a need for exploration of the biological differences in effects of iron supplementation using different routes of administration. To address this issue, the present study compared oral FC with intravenous saccharated ferric oxide (FO) in stable HD patients.

Methods: Six patients received 3 consecutive protocols in the first HD session of the week in a fasting state: nothing given, as control (C); oral load of FC (480 mg iron), and 5 minutes of intravenous FO (40 mg iron). Iron dynamics and biological impact on redox-inflammation status during the study (6 hours) were examined.

Results: Significant increases in serum iron and transferrin saturation (TSAT) were seen with both FC and FO. Regarding total iron-binding capacity, no changes were found in FC, whereas significant increases were seen in FO, despite the lower serum iron levels in FO, suggesting appearance of nontransferrin-binding iron (NTBI). This is suggested by the significant changes of NTBI/serum Iron ratio (%) in FO, but not in FC (Fig). Compared to C, increases were seen in serum myeloperoxidase (oxidative marker) with accompanying significant decreases in thioredoxin (anti-oxidant) in FO, whereas no changes were found in FC. While ratio of intact- to c-terminal FGF23 at 4 hours after starting HD were significantly higher with FO, as compared with C or FC.

Conclusions: Oral FC differs from intravenous FO in areas such as transferrin-binding capacity, NTBI generation, induction of oxidative stress, and FGF23 metabolism. Oral FC may have benefits in terms of iron supplementation for anemia associated with chronic kidney disease.

Funding: Commercial Support - Japan Tobacco, Government Support - Non-U.S.



SA-PO811

A 29-Day Safety, Efficacy, and Pharmacodynamic Study of a Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitor, Daprodustat, Administered TIW in Anemic Subjects on Hemodialysis (HD) Christine K. Bailey,[2] Stephen Caltabiano,[2] Alexander R. Cobitz,[2] Chun Huang,[2] Kelly M. Mahar,[2] Vickas Patel,[2] Steven Zeig.[1] *[1]Pines Clinical Research, Inc., Hollywood, FL; [2]GlaxoSmithKline, Collegeville, PA.*

Background: This randomized, double-blind, placebo (PBO)-controlled study (funded by GSK) examined the relationship between daprodustat TIW dosing and hemoglobin (Hgb) level and safety over 29 days in 103 subjects on HD ≥ 3 times weekly and who were previously receiving a stable dose of an erythropoiesis-stimulating agent (ESA).

Methods: Subjects with baseline Hgb of 9.0–11.5 g/dL discontinued ESAs and were randomized to receive daprodustat 10, 15, 25, or 30 mg TIW or PBO.

Results: Mean baseline Hgb was 10.6 g/dL for all randomized subjects. Switching from an ESA to daprodustat produced dose-dependent mean changes in Hgb (g/dL) from baseline and maximum EPO after 29 days (**Table**). Day 29 pre-dose EPO levels were near or below baseline values, indicating no accumulation of EPO after daprodustat TIW treatment. At Day 29, mean hepcidin levels were reduced from baseline in a dose-dependent manner by an overall mean of 11.7% in subjects in the combined daprodustat group compared with a mean increase of 27.8% in the PBO group. Daprodustat was generally well tolerated, with an adverse event profile consistent with the HD population. No new safety concerns were identified. Based on the TIW dose-response relationship in this study and the QD dose-response relationship in the prior study PHI113633, each characterized by a Bayesian Emax model, the dose conversion ratio between QD to TIW dosing of daprodustat was ~ 2.0 across the dose range.

Conclusions: These data inform the Hgb dose-response relationship of daprodustat in anemic HD subjects who were switched from a stable dose of ESA and treated with daprodustat TIW for 29 days. Daprodustat TIW treatment reduced hepcidin levels and increased plasma EPO levels in a dose-dependent manner. These data support future longer-term clinical studies in patients on HD to further explore daprodustat TIW to treat anemia of CKD.

Funding: Commercial Support - GlaxoSmithKline

	PBO	Daprodustat (mg)			
		10	15	25	30
Mean change from baseline in Hgb (g/dL)	−0.61	−0.19	−0.13	0.64	0.55
Median maximum observed plasma EPO levels (IU/L)	13.1	30.9	56.7	191.7	455.1

SA-PO812

Intravenous Regular Administration of 40mg Iron a Month Might Reduce Hemoglobin Variability of Hemodialysis Patients in Japan Tatsuo Tsukamoto. *Kitano Hospital, The Tazuke Kofukai Medical Research Institute, Osaka, Japan.*

Background: Japanese hemodialysis patients show relatively lower ferritin level than that of other countries, although their TSATs (transferrin saturation) are more than 20%. I have measured iron loss by iron contents of residual blood in the blood tubing set and dialyzer, and estimated that 500mg of iron would be lost by routine hemodialysis procedure in Japan (Am J Nephrol 2016,43,32-38). In this study, I show here the stable iron status as well as hemoglobin (Hb) level by regular administration of 40mg iron a month. Moreover, I demonstrate the reduction of Hb variability by the supplementary protocol.

Methods: 157 patients of Otowa Memorial Hospital were enrolled after informed consent. Men were consisted in 64.7%, and the mean age was 69.2±13.5 (m±SD). 40.4% was diabetic. 40mg of iron (saccharated ferric oxide) was intravenously administered once a month after hemodialysis session. Hb, TSAT, and ferritin were monitored every month before and after the regular iron supplementation. Hb variability was counted in each patient by the Fishbane's method described in the previous paper (Kidney International 2005,68, 1337-1343). ERI (erythropoiesis resistance index) was also calculated with human recombinant erythropoietin (rHuEPO) dose in a month divided by Hb and body weight (dry weight). Erythropoiesis-stimulating agents (ESAs) used in this study were rHuEPO, darbepoetin-a (DA), and continuous erythropoietin receptor activator (CERA). DA was converted to 200U, and CERA was 240U of rHuEPO, respectively. The dose of ESA was determined by an attending physician along the Japanese guideline for renal anemia in chronic kidney disease 2008.

Results: Hb levels kept from 11.2±1.0g/dL at the beginning to 10.9±1.0g/dL after 12 months. TSAT and ferritin did not change from 26.3±12.2% and 88.9±86ng/mL to 25.7±9.9% and 77.6±94.6ng/mL, respectively. ERI changed from 40.5±36.1 to 39.6±32.6. Although iron status and ERI did not changed significantly, Hb variability reduced from 120 times per 6 months before the regular iron administration to 98 times after 6 months and 81 times after 1 year.

Conclusions: Intravenous regular administration of 40mg iron a month might reduce hemoglobin variability of hemodialysis patients without significant change of iron status In Japan.

Funding: Private Foundation Support

SA-PO813

Pharmacokinetics of Ferric Pyrophosphate Citrate (Triferic®) in Pediatric CKD-5HD Patients Raymond D. Pratt, Ajay Gupta. *Rockwell Medical Inc, Wixom, MI. Group/Team: RMFPC-11 Study Group.*

Background: Triferic (FPC) is a carbohydrate-free complex iron salt with a MW ~1300 Daltons. FPC is approved as an iron replacement product to maintain hemoglobin in adult patients receiving chronic hemodialysis. Triferic rapidly transfers across the dialyzer membrane, donates iron directly to transferrin, and is cleared from the circulation with a half-life of 2 to 4 hr. The current study examined the pharmacokinetics (PK) of Triferic administered via dialysate and intravenously (IV) to pediatric hemodialysis patients.

Methods: This was an open-label, two period single dose study conducted in 22 CKD-5HD patients between ages 1 and 17 years. Each patient received 2 treatments in sequential order. Blood was drawn for serum iron profile at defined times for PK analysis. The treatments were Triferic 0.07 mg Fe/kg IV into the post-dialyzer blood line (FPC-IV) and Triferic 2 mM (110 mg Fe/L) via HD (FPC-HD). HD was conducted for 3-4 hours and IV infusions were administered during HD. An estimate of iron delivered at the dialysis session was calculated by using partial AUC based on the IV dose.

Results: A total of 22 subjects, age range 1-17 years were enrolled. PK data are available on 21 subjects. There was greater inter-individual variability and lower peak iron levels in the younger age group patients. FPC-HD showed a similar intradialytic and post-dialysis iron profile as FPC-IV in all age groups. The results of mean intradialytic change in serum Fe with HD and IV, and average dose administered via HD (Fe HD) are presented below: Non-compartmental analysis showed that FPC was rapidly cleared with a t½ of approximately 2 hr. FPC was well tolerated with no drug related adverse effects noted.

Conclusions: This study shows that FPC iron can be delivered to pediatric CKD5HD patients either intravenously when using solid bicarbonate cartridge or bag system, or via the dialysate. FPC was well tolerated. The results suggest that IV administration in patients below age 12 be started at 0.1 mg Fe/kg and increased as needed to achieve a post HD target TSAT of around 75%.

Funding: Commercial Support - Rockwell Medical Inc.

Iron Parameters after FPC via Dialysate or IV

Age yr.	N	ΔsFe HD µg/dL (SD)	ΔTSAT %	$TSAT_{Max}$ %	Fe HD Dose mg	Fe HD Dose mg/kg	$TSAT_{max}$ IV
1-5	3	55.5 (26.2)	17.3	34.3	1.47	0.08	34.7
6-11	2	73.5 (9.2)	25.3	52.5	1.67	0.06	43.8
12-17	16	189.9 (58.5)	59.1	87.3	4.97	0.09	61.6

SA-PO814

Labile Plasma Iron for the Early Detection of Iron Overload in ESRD Alon Benaya,[4] Itzchak N. Slotki,[3] Linda Shavit,[2] Jolanta Malyszko.[1] *[1]Medical University, Bialystok, Poland; [2]Shaare Zedek Medical Center, Jerusalem, Israel; [3]Share Zedek Medical Center, Jerusalem, Israel; [4]shaare zedek, Jerusalem, Israel.*

Background: The increased usage of intravenous iron (IVI) in hemodialysis patients during recent years has led to increasing concern over the potential development of iron overload (IO). Current methods for detecting iron overload, transferrin saturation (TSAT) and serum ferritin are neither sensitive nor specific. Labile plasma iron (LPI) represents a component of non-transferrin bound iron that is both redox active and chelatable and may be a more accurate indicator of impending iron overload. We studied whether LPI measured using the FeROS LPI detecting system (Aferrix) can serve as an early indicator of impending IO in hemodialysis patients.

Methods: Chronic hemodialysis patients from two medical centers in Israel and Poland who received IVI were included. Demographic data, cause of ESRD, comorbidities, medications and the following laboratory parameters were recorded: Hb, serum iron, transferrin, TSAT, ferritin. LPI was measured before and 48 hours after a single IV administration of either iron sucrose 100 mg, iron gluconate 62.5 mg, iron (III)-hydroxide dextran complex 100 mg. A test result of 0.6 units of LPI or more indicated a potential for iron-mediated production of reactive oxygen species in the sample.

Results: 111 hemodialysis patients, aged 64 ± 15, were included in the study. 90 patients received iron sucrose, 14 iron gluconate and 7 iron dextran at mean monthly doses of 233 ± 133 mg; LPI was negative in all patients prior to IVI, but became positive post administration in 4 patients, all of whom received iron sucrose. Three of these were diabetic, had TSAT <30% and ferritin <360 ng/ml and received monthly iron doses of 400-500 mg.

Conclusions: Doses of IVI routinely used in chronic hemodialysis patients appear to be safe. However, higher monthly doses may be associated with detectable LPI post administration, even in the absence of currently used laboratory parameters of IO.

SA-PO815

Low-Dose Iron Treatment and Erythropoiesis Efficiency in Hemodialysis Patients with Anemia Treated by Erythropoiesis-Stimulating Agents Tadashi Kuji,[1] Shota Suzuki,[2] Tetsuya Fujikawa.[3] *[1]Yokodai Central Clinic, Yokohama, Kanagawa, Japan; [2]Yokohama City University, Yokohama, Kanagawa, Japan; [3]Yokohama National University, Yokohama, Kanagawa, Japan.*

Background: Anemia is a common comorbidity and is a major cause of morbidity and mortality among hemodialysis (HD) patients. Iron deficiency is a major cause of resistance to erythropoiesis-stimulating agents (ESA) therapy; however, excessive iron has toxic effects including oxidative stress. Even standard-dose parental iron supplementation causes oxidative stress due to free iron in the blood, therefore low-dose iron is desirable to reduce the free iron release for optimal prognosis. We aimed to investigate whether low-dose iron supplementation is as effective for erythropoiesis as standard-dose iron supplementation.

Methods: A randomized, controlled, parallel-group study was performed for six months. One hundred and two patients were randomized to receive 20mg intravenous elemental iron per week (Low-dose iron group: n = 53) or 40 mg intravenous elemental iron doses per week (Standard-dose iron group: n = 49). Ferritin and transferrin saturation were measured at two-month intervals. Iron was administered for two months when HD patients showed iron deficiency (transferrin saturation < 20% and ferritin < 100ng/ml). ESA resistance index was defined as the weekly weight-adjusted dose of ESA divided by hemoglobin concentration.

Results: No significant differences in baseline characteristics except systolic blood pressure were evident between the two groups. The mean numbers of two-month long iron supplementation were 0.74 ± 0.83 in low-dose iron group and 0.49 ± 0.56 in standard-dose iron group. Mean Hb levels during the evaluation period of 6 months were 10.5 ± 0.4 g/dL in the low-dose iron group and 10.4 ± 0.4 g/dL in the standard-dose iron group (p = 0.315). There was a tendency toward low ESA dose in the low-dose iron group compared to the standard-dose iron group (4116.1 ± 2170.4 IU/week vs. 4935.1 ± 1792.8 IU/week, p = 0.079). There was a trend towards decrease in ferritin levels in low-dose iron group compared with the standard-dose iron group (-36.4±50.5 ng/mL vs. -11.8 ± 65.2 ng/mL, p = 0.073). Reticulocyte hemoglobin levels (newly synthesized hemoglobin) and ESA resistance index were not significantly different between the two groups.

Conclusions: Low-dose iron treatment suppresses ferritin levels, but does not decrease hemoglobin levels and reticulocyte hemoglobin levels or does not increase required ESA dose.

SA-PO816

Link between Iron Deficiency and Thrombocytosis in Dialysis Patients – Are ADPKD Patients Different? Felix Nadrowitz,[1] Klaus Stahl,[2] Bernhard M. Schmidt,[1] Gero D. von Gersdorff,[4] Katherine Rascher,[4] Hermann G. Haller,[1] Roland Schmitt.[3] *[1]Hannover Medical School, Hannover, Germany; [2]MHH, Hannover, Germany; [3]Medizinische Hochschule Hannover, Hannover, Germany; [4]University Hospital Cologne, Cologne, Germany.*

Background: Secondary thrombocytosis has been reported in iron deficiency (ID) anemia. Maintenance hemodialysis (MHD) patients with adult polycystic kidney disease (ADPKD) often receive low iron supplementation due to their spontaneously high hemoglobin levels. We analyzed a possible correlation between ID and platelet count in MHD ADPKD and non-ADPKD patients.

Methods: We conducted a multi-center cohort study with 2387 ADPKD and 30923 non-ADPKD patients. Data between 2008 and 2015 were extracted from over 190 outpatient hemodialysis centers from the institutional KfH quality registry. Multivariable correlation as well as multivariable linear regression analysis with thrombocyte count and parameters of iron status were performed. To correct for inflammation dependent changes laboratory measurements were only included when CRP was in the normal range.

Results: While mean transferrin saturation (TSAT) in ADPKD patients indicated ID (16.6 ± 7.4 %), mean ferritin was not in the ID range (544.8 ± 416.9 ng/ml). Mean absolute thrombocyte count in the ADPKD cohort was 202.2 ± 65.0 $x10^3/\mu l$. A correlation coefficient of -0.12859 implicated a statistically significant, but minor negative correlation of thrombocytes with TSAT. In non-ADPKD MHD patients mean TSAT was 17.9 ± 9.6 % and mean ferritin was 631.6 ± 446.2 ng/ml. Mean platelet count was 216.5 ± 73.7 $x10^3/\mu l$ with a likewise significant, but small negative correlation coefficient to TSAT (-0.11974). Only an extremely low TSAT (< 2%) was associated with platelet counts above the upper limit of normal.

Conclusions: In MHD patients with ADPKD we could not find a relevant correlation of TSAT and platelet count. This was not different from non-ADPKD patients. Our study demonstrates that common degrees of ID in ADPKD and non-ADPKD patients on MHD do not result in thrombocytosis.

SA-PO817

Efficient Hemoglobin Maintenance Levels Are Achieved by Relatively Lower Levels of Serum Ferritin and Moderate Transferrin Saturation in Hemodialysis Patients Chie Ogawa,[2] Ken Tsuchiya,[1] Fumiyoshi Kanda,[2] Kunimi Maeda.[2] *[1]Department of Blood Purification, Tokyo Women's Medical University, Shinjuku-ku, Japan; [2]Maeda Institute of Renal Research, Kawasaki, Japan.*

Background: The optimal iron levels for patients on hemodialysis (HD) are currently unknown. However, excessive iron intake can lead to oxidative stress or impair the efficiency of its use. To identify the optimal iron content for patients on HD, we investigated the relationship between hemoglobin (Hb) level and iron status in patients on HD.

Methods: 208 HD-outpatients treated with recombinant human erythropoietin (rHuEPO) were followed up from July 2006 to June 2007. The doses of rHuEPO and low-dose iron supplement were adjusted to maintain a Hb level of 10–11 g/dL, according to the Japanese guidelines. Hepcidin 25 (Hep 25) was measured at baseline measured using LC-MS/MS assay. Using the mean values for a 1-year period, the relationships among Hb, s-ft levels, and TSAT levels were investigated based on a receiver operating characteristic curve (ROC) and a logistic regression model. In addition, the correlations among s-ft, TSAT, and Hep25 levels were analyzed by Pearson product–moment correlation coefficient.

Results: By ROC, the cutoff point of s-ft and TSAT levels with a Hb ≥10 g/dL showed <90 ng/mL and ≥20%. Upon logistic regression model analysis with a Hb ≥ 10 g/dL set as the endpoint, the odds ratios relative to a group with s-ft ≥ 90 ng/mL and TSAT < 20% revealed that the group with s-ft < 90 ng/mL and TSAT ≥ 20% had the highest ratio: 46.75 (95% CI: 10.89–200.70, p < 0.001). Hep 25 exhibited a strong positive correlation with s-ft [r = 0.78 (95% CI: 0.72–0.83, p < 0.001)] and a weak positive correlation with TSAT [r = 0.18 (95% CI: 0.04–0.31, p = 0.010)].

Conclusions: In this study, the iron status showing s-ft < 90 ng/mL and TSAT ≥ 20% was optimal in HD patients receiving rHuEPO for anemia therapy. This result indicates that the threshold values for the optimal iron status may be lower than those currently recommended in the guidelines for iron level management.

SA-PO818

A Prospective Study Examining the Contribution to Renal Anemia Treatment of Ferric Citrate Hydrate, an Iron-Based Oral Phosphate Binder, in Hemodialysis Patients with Hyperphosphatemia: ASTRIO Study Keitaro Yokoyama,[1] Masafumi Fukagawa,[6] Takashi Akiba,[4] Masaaki Nakayama,[5] Koji Hanaki,[3] Ito Kyoko,[7] Hideki N. Hirakata.[2] *[1]Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan; [2]Fukuoka Renal Clinic, Fukuoka City, Japan; [3]JAPAN TOBACCO INC., Tokyo, Japan; [4]Sekikawa Hospital, Tokyo, Japan; [5]Tohoku University, Tohoku University Hospital, Sendai City, Japan; [6]Tokai University School of Medicine, Isehara, Japan; [7]Torii Pharmaceutical Co., Ltd, Tokyo, Japan.*

Background: We conducted a prospective study examining the contribution to renal anemia treatment of Ferric citrate hydrate (FC) compared with non-iron-based oral phosphate binders (Control), in HD patients with hyperphosphatemia undergoing ESA therapy.

Methods: The study was designed as a multicenter, open-label, active-controlled, randomized, parallel-arm comparison study. HD patients who had been used non-iron-based oral phosphate binders were randomized to FC group (n=45) or Control group (n=48). In FC group, previous treatment was discontinued at registration and switched to FC, and continued for 24 weeks. In Control group, previous treatment was continued. Serum P and Hb were controlled in the target ranges of 3.5 to 6.0 mg/dL and 10.0 to 12.0 g/dL, respectively. We have evaluated the doses of ESA and IV iron.

Results: Mean changes in ESA dose (IU/week) from baseline to end of treatment (EOT) were –1211.8±3609.5 in FC group and 1195.5±6662.8 in Control group. It was significantly lower in FC group than Control group (p=0.0386). Cumulative dose of IV iron from baseline to Week 24 was also significantly lower in FC group than Control group (p=0.0065). Other parameters are shown in the table.

Conclusions: We confirmed that FC decreased doses of ESA and IV iron. We also confirmed the differences of ERI, MCV, RDW and FGF23 between FC group and Control group. It was considered iron supplementation by FC was done in functional manner. FC is expected to contribute to renal anemia treatment and hematopoietic.

Parameter	FC group (N=40) Change (from baseline to EOT)	Control group (N=42) Change (from baseline to EOT)	Adjusted Mean Difference (FC minus Control)	p-value
Serum P (mg/dL)	0.24	-0.17	0.55	0.0643
Hb (g/dL)	0.45	0.34	0.17	0.5065
TSAT (%)	8.6	0.5	9.0	0.0005
Serum ferritin (ng/mL)	79.0	2.9	79.5	<0.0001
ERI	-2.43	2.62	-5.12	0.0246
MCV (fL)	1.2	-2.6	3.9	<0.0001
RDW (%)	0.19	0.83	-0.83	0.0379
i-FGF23 (pg/mL)	-716.5	152.0	0.8	0.3305
c-FGF23(pg/mL)	-67.0	25.7	0.7	0.0418

SA-PO819

Predictive Hierarchical Modeling of Determinants of Outcomes of Anemia Management with Binocrit®, a Biosimilar Epoetin Alfa, in the Hemodialysis Setting (MONITOR-CKD5 Study) Frank Dellanna,[1] David Goldsmith,[2] Johannes F. Mann,[3] Philippe Zaoui,[4] Christian Combe,[5] Andriy Krendyukov,[6] Ivo Abraham,[7] Karen Macdonald.[8] *[1]MVZ DaVita Rhein-Ruhr GmbH, Duesseldorf, Germany; [2]Guy's & St. Thomas' NHS Foundation Trust, Great Maze Pond, United Kingdom; [3]KfH Nierenzentrum, München, Germany; [4]Clinic of Nephrology Chu Grenoble, Grenoble, France; [5]CHU de Bordeaux, Bordeaux, France; [6]Sandoz Biopharmaceuticals, Holzkirchen, Germany; [7]University of Arizona, Tucson, AZ; [8]Matrix 45, Tucson, AZ.*

Background: The European observational MONITOR-CKD5 study demonstrated the real-world effectiveness of Binocrit® in renal anaemia. Patients treated for up to 24 months showed stable dosing patterns and stable hemoglobin (Hb) outcomes. Predictive hierarchical modeling was applied to identify determinants of outcomes of interest.

Methods: A subset of 484 patients with complete 24-month data was used to investigate pre-specified potential determinants of the following outcomes: (1) mean Hb of last 4 visits, estimated using Wald test (hierarchical linear regression); risk for (2) chronic hyporesponsiveness, (3) overnight hospitalization, (4) thromboembolic events (TEE), (5) mortality. Risks were estimated using adjusted odds ratios (OR; hierarchical logistic regression). The intraclass correlation coefficient (ICC) quantified the proportion of variance in outcome attributable to a center class effect.

Results: The following determinants were retained for each outcome of interest at p<0.05. For mean Hb of last 4 visits (ICC=0.0477): age (+0.0067g/dL per 1 year over mean); chronic infection or inflammatory disease at baseline (-0.3395g/dL if present); Kt/V≥1.2 at baseline (+0.3181g/dL if present). For risk of chronic hyporesponsiveness (ICC=0.1599): chronic infection or inflammatory disease at baseline (OR=3.055). For risk of hospitalization (ICC=0.2349): no determinants retained despite ICC. For TEE risk (ICC=0.0550): serum albumin ≥3g/dL (OR=0.396); Kt/V≥1.2 at baseline (OR=0.455); age (per 1 year of age over mean, OR=1.021). For overall mortality (ICC=0.1156): deficient iron status (OR=2.354); Kt/V≥1.2 at baseline (OR=0.316); age (per 1 year over mean, OR=1.064).

Conclusions: In hemodialysis patients receiving Binocrit® for 2 years, determinants of positive Hb outcome included Kt/V≥1.2 and serum albumin ≥3g/dL. The presence of chronic infection or inflammatory disease and deficient iron status were predictive of poorer Hb outcomes. Age was associated positively with Hb levels, but negatively with TEE and mortality risk. Consistent with findings from the DOPPS and ESAM observational studies, all determinants except for age are clinically modifiable or manageable.

Funding: Commercial Support - Sandoz

SA-PO820

Development and Validation of a Transfusion Risk Score David T. Gilbertson,[3] Heng Yan,[3] Hairong Xu,[2] Marvin V. Sinsakul,[1] Yi Peng,[3] James B. Wetmore,[5] Jiannong Liu,[4] Suying Li.[3] *[1]AstraZeneca, Bethesda, MD; [2]Astrazeneca, Westlake Village, CA; [3]Chronic Disease Research Group, Minneapolis, MN; [4]Minneapolis Medical Research Foundation, Minneapolis, MN; [5]Hennepin County Medical Center, Minneapolis, MN.*

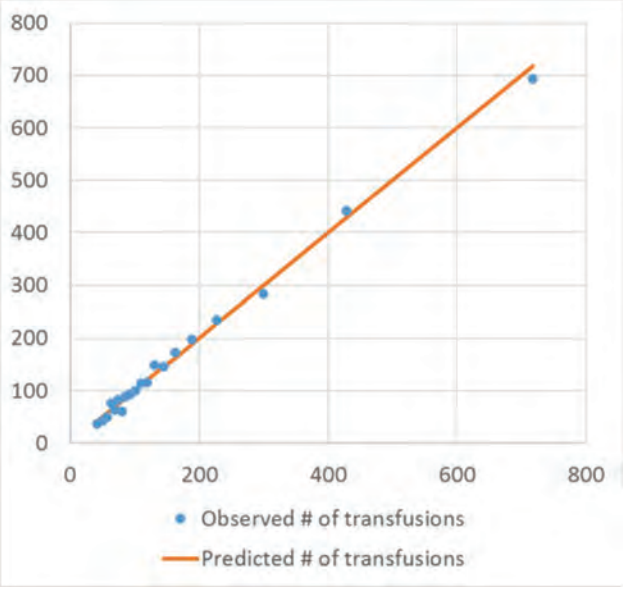
Background: Following changes to CMS payment for dialysis services in Jan 2011 and the ESA label revision 6 months later, a decline in hemoglobin (Hb) levels and an increase in transfusions were observed in dialysis patients. Transfusions have decreased from their 2012 peak, and transfusion avoidance is the preferable option in dialysis patients. We sought to develop a predictive model for transfusions using comorbidity, markers of inflammation, previous transfusion, vitamin D use, IV iron use, ESA dose, Hb, ferritin and TSAT.

Methods: USRDS/Crownweb data from 2012-13 were used for model development. Point prevalent hemodialysis (HD) patients on 11/1/12 with ≥ 6 months Medicare A/B coverage and mean Hb < 10 g/dL were included. Aug-Oct were used to assess anemia-related variables (Hb, ESA, TSAT, ferritin, IV iron use, vitamin D, and transfusion), and May-Oct were used to assess comorbidity from claims. Logistic regression with Lasso for variable selection was used to predict transfusion during the next 3 months. For model validation, similar cohort construction was used, with point prevalent HD patients on 8/1/13.

Results: Variables retained in the final model included Hb, ESA dose, ferritin, TSAT, IV iron, vitamin D, prior transfusion, and interactions of these variables. In the validation dataset, a calibration plot showed good agreement between observed/predicted transfusions (Figure): *c*-statistic = 0.74.

Conclusions: The addition of ferritin and TSAT, along with inflammatory comorbidities, aided in prediction of transfusions in patients with Hb levels < 10 g/dL. Optimal anemia management strategies involve balancing CV risk on the high end of Hb and ESA exposure with transfusion risk on the low end. The ability to identify patients at risk for transfusion may lead to improved anemia management and outcomes.

Funding: Commercial Support - AstraZeneca



SA-PO821

Association of Hepcidin with Anemia Parameters in Incident Dialysis Patients: Difference between Dialysis Modalities Jeong hoon Lim,[1] Jong-Hak Lee,[2] Man-hoon Han,[1] Kyu Yeun Kim,[1] Hee-Yeon Jung,[1] Ji-Young Choi,[1] Jang-Hee Cho,[1] Chan-Duck Kim,[1] Sun-Hee Park,[1] Yong-Lim Kim.[1] *[1]Kyungpook National University Hospital, Daegu, Republic of Korea; [2]Daegu Fatima Hospital, Daegu, Republic of Korea.*

Background: Hepcidin has been considered to be a key regulator of iron homeostasis in recent years. However, its relationships to other variables are not well understood. This study aimed to evaluate association of serum hepcidin level with iron parameters and other clinical parameters, especially according to dialysis modality, in end-stage renal disease (ESRD) patients.

Methods: A total of 110 incident dialysis patients, 68 on peritoneal dialysis (PD) and 42 on hemodialysis (HD), were prospectively followed up for 6 months. Serum hepcidin level was measured by a commercial ELISA kit (DRG Instruments, Marburg, Germany) at baseline and 6 months after initiation of dialysis. The relationship of hepcidin to clinical parameters was investigated using linear regression models.

Results: Serum hepcidin levels significantly increased in initial 6 month after start of dialysis. PD group showed higher hemoglobin after 6 months dialysis than HD group, in spite of less use of erythropoiesis-stimulating agents during study period. In multivariate regression model, independent predictors of serum hepcidin were aspartate transaminase (ß=21.359, *p*=0.003), ferritin (ß=0.056, *p*=0.008), transferrin saturation (ß=0.644, *p*=0.009), and phosphate (ß=6.946, *p*=0.001) in incident ESRD patients. At 6 month after initiating dialysis, serum hepcidin was independently predicted by urine volume (ß=–0.008, *p*=0.043), alanine transaminase (ß=12.091, *p*=0.008), ferritin (ß=0.051, *p*<0.001), and total iron binding capacity (TIBC) (ß=–0.191, *p*=0.002) in all patients, whereas by ferritin (ß=0.056, *p*<0.001) and TIBC (ß=–0.184, *p*=0.023) in PD patients, and urine volume (ß=–0.021, *p*=0.004), ferritin (ß=0.048, *p*=0.095), and TIBC (ß=–0.225, *p*=0.015) in HD patients.

Conclusions: Serum hepcidin was differentially associated with anemia parameter between PD and HD patients. Urine volume was an independent predictor of hepcidin in incident HD patients. It suggests preservation of urine volume may be important to reduce hepcidin concentration in incident HD patients.

Funding: Commercial Support - Roche Pharma AG, Fresenius Medical Care North America

SA-PO822

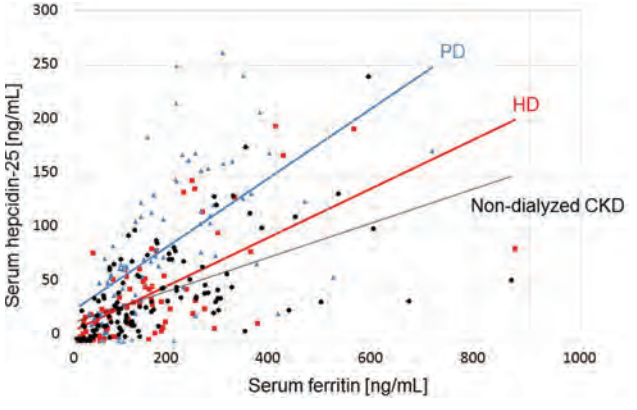
Difference in the Hepcidin/Ferritin Ratio among Non-Dialyzed CKD Patients, and Patients on Hemodialysis and Peritoneal Dialysis Takahito Niikura,[1] Yukio Maruyama,[1] Satomi Nakashima,[1] Nanae Matsuo,[1] Yudo Tanno,[1] Ichiro Ohkido,[1] Keitaro Yokoyama,[1] Hiroyasu Yamamoto,[1,2] Takashi Yokoo.[1] *[1]Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan; [2]Department of Internal Medicine, Atsugi City Hospital, Atsugi, Japan.*

Background: The level of hepcidin, a key mediator of iron homeostasis, generally increases in patients with chronic kidney disease (CKD), attributable to inflammation or a decline in the glomerular filtration rate (GFR). Although the hepcidin/ferritin ratio is used in hepatic disorders (e.g., viral and autoimmune hepatitis) and hematological disease (e.g., hereditary hemochromatosis and thalassemia), its role in renal patients have never been investigated. We evaluated the hepcidin/ferritin ratio in non-dialyzed CKD patients, and in those undergoing hemodialysis (HD) or peritoneal dialysis (PD); we also used this ratio to explore iron homeostasis in CKD patients.

Methods: We recruited 285 CKD patients (117 non-dialyzed CKD patients, 80 HD patients, and 88 PD patients) and measured the levels of serum hepcidin-25, ferritin and markers of kidney disease. Serum hepcidin-25 levels were assessed via liquid chromatography/tandem mass spectrometry.

Results: The serum hepcidin-25 level was elevated in all CKD patients, and was significantly higher in PD than non-dialyzed CKD and HD patients (68.6 [0.4–262] vs. 32.8 [0.7–240] vs. 25.9 [0.4–196] ng/mL, p < 0.01). The serum hepcidin-25 level correlated positively with that of serum ferritin in all CKD patients, whereas the hepcidin/ferritin ratio was higher in PD patients than in other CKD patients.

Conclusions: PD patients exhibited a higher serum hepcidin-25 level and the hepcidin/ferritin ratio than did non-dialyzed CKD and HD patients. Several factors unique to PD patients, such as continuous peritoneal stimulus by the dialysate, and subclinical inflammation and infection, may explain the high hepcidin/ferritin ratio in such patients.



SA-PO823

Determinants of Hepcidin/Ferritin Ratio in Patients Undergoing Maintenance Hemodialysis Takahiro Kuragano, Takeshi Nakanishi. *Hyogo College of Mediicne, Nishinomiya, Japan.*

Background: Hepcidin is the key regulator of iron absorption. Although low serum levels of hepcidin allow iron uptake in patients with iron deficiency, an imbalance of hepcidin and iron storage might be associated with iron overload. As iron containing phosphate binder has expanded the clinical use in chronic kidney disease patients, intestinal iron absorption should be properly evaluated.

Methods: Study design: Cross sectional study. Subjects: 317 patients undergoing maintenance hemodialysis (MHD). We measured the blood levels of Hb, ferritin, transferrin saturation (TSAT), body mass index (BMI), total protein, albumin, high-sensitivity (h) CRP, int-PTH, creatinine (Cr), urea nitrogen (UN), β 2-microglobulin (β2MG), and hepcidin-25. The Mann-Whitney U test and least absolute shrinkage and selection operator (LASSO) analysis were applied to evaluate the association between the hepcidin/ferritin ratio and the clinical parameters.

Results: According to the Mann-Whitney U test, the hepcidin-25/ferritin ratio in patients with diabetes (0.34± 0.33) was significantly (P<0.05) higher than in patients without diabetes (0.27± 0.3). In LASSO analysis, higher albumin (0.06), higher int-PTH (0.03), higher Cr (0.03), higher dose of intravenous iron administration (0.01) and diabetes (0.09) were identified as significant determinants of a higher hepcidin-25/ferritin ratio. In the patients with higher CRP levels (≥0.3 mg/dL), higher ferritin (19.64), higher int-PTH (1.76), and male (0.36) were selected as the significant predictors of higher serum levels of hepcidin-25, male sex (0.11), diabetes (0.13), lower TSAT (-0.01), and lower BMI (-0.03) were selected as significant predictors of a higher hepcidin-25/ferritin ratio.

Conclusions: In this study, we found that in MHD patients, the hepcidin/ferritin ratio is significantly associated with patient characteristics such as nutritional condition, diabetes, sex, and hyperparathyroidism. Furthermore, in MHD patients with inflammation, iron dysutilization (low TSAT), malnutrition (low BMI), and diabetes are significantly associated with the higher hepcidin-25/ferritin ratio. The imbalance of hepcidin and ferritin might cause increased iron absorption and iron overload, and thus iron supplementation for these patients should be performed carefully.

SA-PO824

Randomised Controlled Trial of Intravenous Iron versus Increased Erythropoietin in Haemodialysis Anaemia Sarah Hildebrand, Neill D. Duncan, Frederick W. Tam, Damien Ashby. *Imperial College Renal and Transplant Centre, London, United Kingdom.*

Background: Anaemia in haemodialysis patients is treated with both erythropoietin and intravenous iron, but response rates are suboptimal, and treatment thresholds remain controversial. Despite poor reliability, traditional iron indices such as ferritin are usually used to guide treatment choices, whilst the relative effectiveness of the two available treatments has never been compared in a randomised trial.

Methods: Stable haemodialysis patients who became moderately anaemic (Hb 90-104g/l) on routine testing with non-extreme ferritin (100-800ng/l) were randomly allocated to treatment with either intravenous iron (1g divided over 5 consecutive sessions, IVFE group) or increased erythropoietin (starting 3000unit/week or median increase 50%, EPO group). No further treatment was given for 2 months.

Results: In 194 patients followed for up to 18 months (2438 patient-months observed), there were 160 anaemia episodes with completed randomisation and follow-up (mean age 63, 71% male). Intravenous iron and increased erythropoietin were equally effective: a positive haemoglobin response (increase by at least 5g/l by 2 months) was observed in 54/76 IVFE patients, and 62/84 EPO patients (71.1 vs 73.8%, p=0.7). Factors predictive of treatment response were assessed in both groups. In the IVFE group, compared to non-responders, those achieving Hb response had lower hepcidin (101 vs 143ng/ml, p=0.031), lower mean cell volume (90.6 vs 94.5, p=0.034) and lower reticulocyte Hb (33.8 vs 35.5, p=0.047). In the EPO group only low CRP was predictive of a positive response (13.5 vs 28.6, p=0.038). Ferritin was not predictive of response in either group (p=0.9 and 0.2 respectively). Weaker associations with response were found for gender, B12 levels, previous erythropoietin dose and warfarin use.

Conclusions: Intravenous iron and erythropoietin are equally effective in the majority of haemodialysis patients who become anaemic. Ferritin does not predict treatment response, but hepcidin and several established biomarkers do: in combination they could be used in an evidence-based protocol with improved response rates.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO825

The Effect of Ferric Citrate on IV Iron, ESA Utilization, and Laboratory Parameters in Real-World Dialysis Practice Csaba P. Kovesdy,[3] Christopher G. Rowan,[1] Bryce Foote,[2] Luke S. Acree,[2] Leslie A. Meltzer,[2] Robin Lewinter.[2] *[1]COHRDATA, Santa Monica, CA; [2]Keryx Biopharmaceuticals, Boston, MA; [3]University of Tennessee Health Science Center, Memphis, TN.*

Background: Ferric Citrate (FC) is an iron-based phosphate (P) binder approved for control of serum P in patients (pts) with CKD on dialysis. We retrospectively evaluated changes in healthcare resource utilization (HRU) and laboratory parameters before and after FC initiation in typical dialysis practice.

Methods: FC users were identified between 1/2015-7/2016 from a large U.S. dialysis provider. HRU and lab data were ascertained for continuous FC users in 4 sequential periods (1 pre and 3 post-FC initiation; 3 months each). We determined mean change and mean % change for each post-FC period vs. pre-FC (baseline). Mean change was analyzed using Students t-test for paired data.

Results: 2,395 FC initiators were included (mean age 54 years, 50% female, 43% black race). Median dialysis vintage was 3.5 years (mean 4.6 years) and 9% were phosphate binder naive. Mean follow-up for continuous FC users was 104 days. At baseline, P management in these patients was suboptimal as only 25% of pts had P <5.5 mg/dL. P significantly decreased within 1 month (mean change -0.26 mg/dL, *P*<0.001), and 40% had P <5.5 mg/dL by 6 months. At 3, 6 and 9 months post-FC (compared to pre-FC),

we observed small but statistically significant mean increases in hemoglobin, transferrin saturation (TSAT) and ferritin despite decreases in cumulative IV iron and ESA dose (all $P<0.05$). At 3-6 months post-FC (vs. pre-FC), the mean reduction in cumulative IV iron and ESA administration was -130 mg ($P<0.001$) and -17,127 IU ($P<0.001$), respectively. The Figure depicts mean % change for each HRU and lab parameter.

Conclusions: Despite significant reductions in IV iron and ESA utilization, hemoglobin and iron parameters improved within 3 months of FC initiation in pts on dialysis. Additionally, serum P control improved significantly in this patient population.

Funding: Commercial Support - Keryx Biopharmaceuticals Inc.

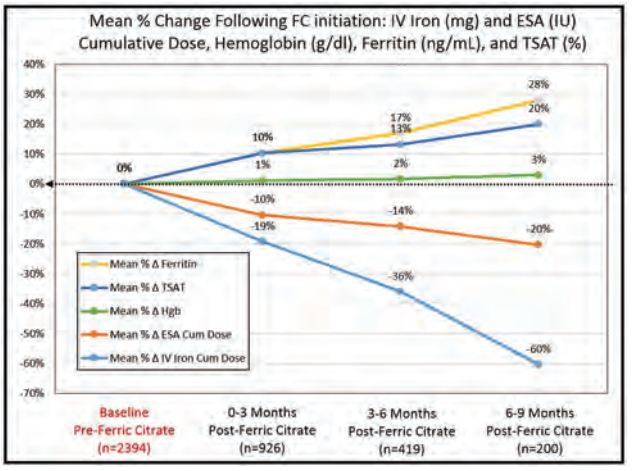


Figure: HRU and Lab Mean Percent Change

SA-PO826

Patterns of Anemia Management and Response in the Predialysis Period James B. Wetmore,[4] Heng Yan,[3] David T. Gilbertson,[3] Hairong Xu,[2] Marvin V. Sinsakul,[1] Yi Peng,[3] Jiannong Liu,[5] Suying Li.[3] *[1]AstraZeneca, Bethesda, MD; [2]Astrazeneca, Westlake Village, CA; [3]Chronic Disease Research Group, Minneapolis, MN; [4]Hennepin County Medical Center, Minneapolis, MN; [5]Minneapolis Medical Research Foundation, Minneapolis, MN.*

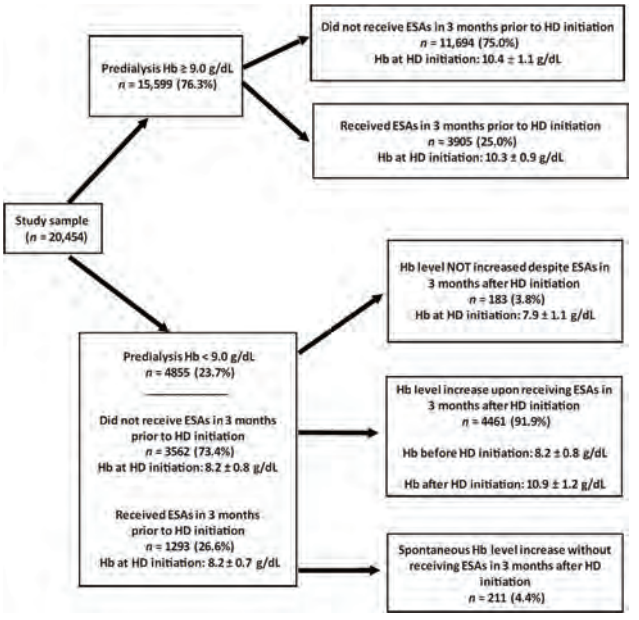
Background: The management of anemia in the predialysis period has not been fully described.

Methods: We used USRDS ESRD and pre-ESRD files to study patients initiating hemodialysis (HD) between April 1, 2012 and June 30, 2013. Patients had to have a hemoglobin (Hb) measurement at HD initiation and at least one other measurement in the 3 months after, in the absence of a blood transfusion. Patients were divided into those with predialysis Hb ≥ 9.0 g/dL and those <9.0 g/dL. Percent of patients receiving ESAs and associated Hb levels before and after dialysis initiation were reported.

Results: Of 20,454 patients, 15,599 (76%) had predialysis Hb ≥ 9.0 g/dL. Of those with Hb ≥ 9.0 g/dL, 11,694 (75%) did not require ESAs; mean predialysis Hb was 10.4 ± 1.1 g/dL. The remaining 25% required ESAs, attaining a predialysis Hb level of 10.3 ± 0.9 g/dL. Of 4855 (24% of the total) who had predialysis Hb <9.0 g/dL, only 1293 of these (27%) received ESAs; mean predialysis Hb was 8.2 ± 0.7 g/dL; the remainder (73%) with Hb < 9.0 g/dL did not receive ESAs and had a predialysis Hb level of 8.2 ± 0.8 g/dL. Only 183 (4%) proved poorly responsive to ESAs after initiation, with Hb increasing from 7.9 ± 1.1 g/dL (predialysis) to only 8.5 ± 0.7 g/dL (postinititiation). Of the 4461 (92%) who responded to ESAs after initiation, Hb increased markedly from 8.2 g/dL (predialysis) to 10.9 ± 1.2 g/dL (postinitiation).

Conclusions: One quarter of patients had predialysis Hb < 9.0 g/dL, of whom only one-quarter received ESAs. Since only 1 in 20 patients with Hb < 9.0 g/dL subsequently proved to be poorly responsive to ESAs after initiation, the vast majority of patients with predialysis Hb <9.0 g/dL appear to have been "rescuable" from anemia, suggesting that opportunities to effectively treat predialysis anemia are being missed.

Funding: Commercial Support - AstraZeneca



SA-PO827

Roxadustat Treatment of CKD Anemia Is Not Influenced by Inflammation Lynda Szczech,[3] Anatole Besarab,[4] Khalil G. Saikali,[1] Lona Poole,[5] Gopal Saha,[2] Thomas B. Neff.[3] *[1]FibroGen, Inc., San Francisco, CA; [2]FibroGen Inc, San Francisco, CA; [3]FibroGen, Inc., San Francisco, CA; [4]FibroGen, Inc., San Francisco, CA; [5]Fibrogen, Inc, San Francisco, CA.*

Background: The efficacy of ESAs in the treatment of anemia is diminished in inflammation. The hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat is being developed for treatment of CKD anemia. This analysis of Phase 2 studies was undertaken to explore the efficacy of roxadustat in non-dialysis-dependent (NDD) and dialysis-dependent (DD) CKD patients with and without inflammation.

Methods: Data from five completed Phase 2 studies in NDD- and DD-CKD patients in both anemia correction and conversion of patients already treated for anemia were analyzed in this *post hoc* analysis. Among studies, roxadustat doses, study duration, and comparator (placebo or epoetin alfa) varied. Baseline (BL) hemoglobin (Hb) and change from BL (CFB) were summarized in the efficacy-evaluable populations among patient subgroups with BL CRP ≤ and > ULN (4.9 mg/L).

Results: A total of 234 NDD-CKD and 262 DD-CKD subjects were treated in these studies. Mean CFB in Hb with roxadustat versus comparator was summarized by study and inflammatory state. Roxadustat-driven erythropoiesis, at similar doses, is clinically similar in inflamed versus non-inflamed NDD-CKD and DD-CKD subjects. In all studies, BL CRP correlated with hepcidin and roxadustat significantly reduced hepcidin in a dose-dependent fashion.

Conclusions: Roxadustat corrected and maintained Hb similarly in NDD-CKD and DD-CKD subjects both with and without inflammation, in contrast to ESA comparators, for which inflamed subjects had a less robust response. Phase 3 trials are currently underway to further establish the efficacy and safety of roxadustat.

Funding: Commercial Support - FibroGen

Hemoglobin CFB among subgroups defined by inflammatory status

Study	Treatment (N)	Baseline CRP(mg/L)	Baseline Hb(g/dL)	Change from Baseline in Hb noninflamed subgroup	Change from Baseline in Hb inflamed subgroup
041	Roxadustat (N=143)	7.45 (±12.69)	9.72 (± 0.67)	1.70 (±0.12)	1.54 (±0.18)
047	Roxadustat (N=61)	2.92 (± 9.33)	8.81 (± 0.92)	2.04 (±0.18)	2.45 (±0.67)
	Placebo (N=30)	1.48 (± 2.19)	8.90 (± 0.82)	0.37 (±0.18)	-0.30 (±0.95)
040	Roxadustat (N=94)	8.85 (±12.13)	11.21 (± 0.67)	-0.29 (±0.23)	0.39 (±0.23)
	Epoetin (N=31)	7.37 (± 9.68)	11.29 (± 0.84)	-0.42 (±0.27)	-0.60 (±0.34)
048	Roxadustat (N=60)	4.16 (± 7.00)	10.76 (± 0.73)	0.89 (±0.18)	0.91 (±0.33)
	Epoetin (N=22)	3.00 (± 4.70)	10.59 (± 0.96)	0.16 (±0.23)	0.17 (±0.58)
053	Roxadustat (N=55)	6.74 (± 9.71)	8.34 (± 1.03)	2.74 (±0.24)	2.09 (±0.33)

Noninflamed subgroup = Baseline CRP <= ULN. Inflamed subgroup = Baseline CRP > ULN.

Mean±SD for baseline CRP and Hb. LSmean±SE for Hb CFB.

SA-PO828

Relationship between History of Coronary Heart Disease at Dialysis Initiation and Onset of Events Associated with Heart Disease: A Propensity-Matched Analysis of a Prospective Cohort Study Daijo Inaguma,[3] Shigehisa Koide,[2] Kazuo Takahashi,[1] Hiroki Hayashi,[1] Midori Hasegawa,[2] Yukio Yuzawa.[2] *[1]Fujita Health University School of Medicine, Toyoake, Japan; [2]Fujita Health University School of Medicine, Aichi, Japan; [3]Nephrology, Fujita Health University School of Medicine, Toyoake, Japan.*

Background: Few studies have reported serial observations during dialysis initiation and maintenance. Therefore, we examined whether the incidence of heart disease events during maintenance dialysis differed between CKD patients with and without a history of coronary heart disease (CHD) at dialysis initiation.

Methods: The subjects were patients in the 17 centers participating in the Aichi Cohort Study of Prognosis in Patients Newly Initiated into Dialysis (AICOPP) from October 2011 to September 2013. We excluded 9 patients whose outcomes were unknown, as determined by a survey conducted at the end of March 2015. Thus, we enrolled 1,515 subjects into the study. We classified patients into 2 groups according to the history of CHD (i.e., a CHD group and a non-CHD group). Propensity scores (PS) represented the probability of being assigned to a group with or without a history of CHD. Onset of heart disease events and associated mortality and all-cause mortality were compared in PS-matched patients by using the log-rank test for Kaplan-Meier curves. Factors contributing to heart disease events were examined using stepwise multivariate Cox proportional hazards analysis.

Results: There were 254 patients in each group after PS-matching. During observation, heart disease events occurred in 85 patients (33.5%) in the CHD group and 48 (18.9%) patients in the non-CHD group. The incidence was significantly higher in the CHD group ($p < 0.001$). Heart disease-related death occurred in 27 patients (18.9%) in the CHD group and 12 (10.6%) in the non-CHD group ($p = 0.014$). All-cause death occurred in 70 patients (27.6%) in the CHD group and 47 (18.5%) in the non-CHD group ($p = 0.026$). The CHD group was associated with higher incidence of heart disease events (vs. the non-CHD group, HR = 1.75, 95% CI = 1.16-2.64). In addition, comorbidities such as diabetes mellitus (HR = 1.77), low body mass index (HR = 0.92), and low serum high-density lipoprotein cholesterol (/ 10mg/dL, HR = 0.86), were associated with higher incidence of events.

Conclusions: History of CHD at dialysis initiation was associated with a higher incidence of heart disease events and mortality and all-cause mortality.

SA-PO829

Trends and Outcomes of Surgical versus Transcatheter Aortic Valve Replacement in Patients on Maintenance Dialysis Priti Poojary,[1] Aparna Saha,[1] Shanti N. Patel,[2] Neha Debnath,[1] Kinsuk Chauhan,[1] Steven G. Coca,[1] Girish N. Nadkarni,[1] Lili Chan.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Maimonides Medical Center, New York, NY.*

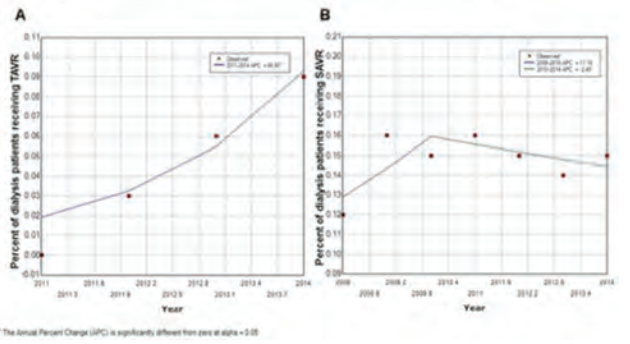
Background: The prevalence of aortic stenosis in maintenance dialysis patients is high (28-55%). Dialysis patients generally have high operative risk for surgical aortic valve replacement (SAVR). While transcatheter aortic valve replacement (TAVR) in high-risk patients is associated with better survival in clinical trials, dialysis patients are generally excluded from these studies. We sought to assess outcomes and trends of SAVR vs. TAVR in dialysis patients from a nationally representative database

Methods: Utilizing the National Inpatient Sample from 2008 – 2014, hospitalizations in dialysis patients for SAVR and TAVR were identified utilizing ICD-9-CM codes. TAVR patients were propensity matched with SAVR patients on demographics, hospital type, primary payer type, income, and Charlson comorbidity index

Results: The proportion of dialysis patients receiving SAVR procedures increased from 2008–2010 (annual percentage change(APC) of 11), then declined from 2010-2014(APC of -2). The proportion of dialysis patients receiving TAVR has significantly increased over time (APC of 69) (Figure 1). Prior to propensity matching, patients in the TAVR group were older(75 vs. 63 years, P<0.001), more likely to be white(67% vs 40%, P<0.001), and more likely to be female(40% vs. 31%, P<0.001). After matching, SAVR was associated with a longer length of stay (18 vs. 10 days, P<.001) and higher cost (76,450 vs. 67,510, P=0.05). TAVR was associated with lower odds for in-hospital mortality [OR 0.46 (95% CI 0.24-0.91)]

Conclusions: TAVR in dialysis patients is increasing and is associated with lower in-hospital mortality. The decreasing trend in SAVR suggests that these patients are now getting TAVRs instead. Patients who are getting TAVRs have different demographics from those getting SAVR. Further investigation is needed to identify reasons for gender and racial differences and evaluation of long-term outcomes between SAVR and TAVR

Figure 1: Trends in proportion of dialysis patients receiving (A) TAVR and (B) SAVR



SA-PO830

Effect of Sodium Thiosulfate on Arterial Stiffness in ESRD Patients Undergoing Chronic Hemodialysis: A Randomized Controlled Trial Donlawat Saengpanit,[1] Monchai Siribumrungwong,[2] Paweena Susantitaphong,[1] Pisut Katavetin,[1] Somchai Eiam-Ong,[1] Kriang Tungsanga,[1] Visith Sitprija,[3] Kearkiat Praditpornsilpa.[1] *[1]King Chulalongkorn Memorial Hospital, Thai Red Cross Society and Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand; [2]Lerdsin Hospital, Bangkok, Thailand; [3]Queen Saovabha Memorial Institute, Bangkok, Thailand.*

Background: End-stage renal disease (ESRD) patients undergoing chronic hemodialysis (HD) have an extremely poor cardiovascular outcome. Arterial stiffness (AS), a strong independent predictor of survival in HD patients, is related to vascular calcification (VC). Intravenous (IV) sodium thiosulfate (STS) can prevent VC in animal studies and delay progression of VC in HD patients, likely by cationic chelating and antioxidant properties. The effect of STS on AS has not been assessed in this patient population. This study is the first to evaluate the efficacy of STS on AS in HD patients.

Methods: We enrolled 50 HD patients with AS measured by Cardio-Ankle Vascular Index (CAVI ≥ 8) into an open-label, randomized controlled trial. Patients were allocated to receive IV STS 12.5 gram during the last hour of HD twice weekly for 24 weeks (n=24) or usual care (control; n=26). CAVI, hemodynamics, and biochemical parameters were determined at baseline, 12 weeks and after 24 weeks. (Thai Clinical Trials Registry ID: 20160814001)

Results: All baseline parameters including CAVI (IV STS, 9.33 ± 0.87 vs. control, 9.34 ± 0.94) were comparable. Twenty-four weeks of twice weekly IV STS slightly lowered AS but insignificantly when compared with the control group (mean difference of the change of CAVI between STS and control was -0.53; 95% CI -1.07, 0.02; P = 0.17). Significant improvement of AS was observed in those without diabetes mellitus (DM) (P<0.05). There were no significant changes in hemodynamic parameters in both groups. No significant changes in serum calcium, phosphate, calcium-phosphate product, intact parathyroid hormone, and 25-OH vitamin D levels at baseline and after 24 weeks in both groups were observed. High-sensitivity C-reactive protein was slightly but not significantly decreased in IV STS treated group than the control group. After STS treatment, anion gap significantly increased from baseline (P<0.05).

Conclusions: Intradialytic STS treatment has a trend toward improvement in AS measured by CAVI in HD patients. The subgroup results which demonstrated that ESRD patients without DM are affected differently by STS treatment are interesting and require further study for confirmation.

Funding: Government Support - Non-U.S.

SA-PO831

The Effect of Far Infrared Therapy on Peripheral Artery Disease in Hemodialysis Patients Chih-Ching Lin.[1,2] *[1]Division of Nephrology, Department of Medicine, Taipei Veterans General Hospital, Taipei City, Taiwan; [2]School of Medicine, National Yang Ming University, Taipei, Taiwan.*

Background: In hemodialysis (HD) patients, peripheral artery disease (PAD) remains a critical cardiovascular complication which is usually diagnosed by ankle brachial index (ABI). Far infrared therapy improves access flow of vascular access but the effect on PAD in HD patients is still unknown.

Methods: We enrolled 198 maintenance HD patients in this study. PAD was defined as ABI ≤ 0.90. Only PAD patients received WS TY101 FIR emitter (Firapy) for 40 minutes during each HD session, three times weekly for six months. The ABI was measured for bilateral lower extremities for 4 times [pre-dialytic timing (0 minute) and 40 minutes after the initiation of HD session at both day 0 and 6 months after the FIR therapy].

Results: Fifty-one out of 198 patients had PAD. In comparison with the period without FIR therapy in the 51 PAD patients, 6 months of FIR therapy significantly improved the ABI of right/ left side for 0 minute (from 0.77±0.19 to 0.81±0.20, P=0.027/0.79±0.20 to 0.81±0.17, P=0.049), 40 minutes during HD (from 0.73±0.23 to 0.83±0.19, P<0.001/ from 0.77±0.21 to 0.83±0.18, P<0.001) and incremental change between 0 and 40 minutes (from -0.04±0.14 to 0.02±0.13, P= 0.007/ from -0.02±0.13 to 0.02±0.14, P=0.012) respectively.

Conclusions: We demonstrate 40 minutes of FIR therapy three times weekly for 6 months improved ABI of both lower extremities, thus providing a new strategy for the treatment of PAD in HD patients.

Funding: Government Support - Non-U.S.

SA-PO832

Effect of Physical Training on Echocardiographic Parameters during Hemodialysis: A Randomized Clinical Trial Gabriela J. Abundis Mora,[3] Guillermo Garcia-Garcia,[1] Daniel Murillo brambila,[1] Monica C. Jimenez cornejo,[3] Karina Renoirte,[2] Jonathan Chavez.[2] *[1]Hospital Civil De Guadalajara, University of Guadalajara, Guadalajara, Mexico; [2]Hospital Civil de Guadalajara, Guadalajara, Mexico; [3]Hospital Civil de Guadalajara "Fray Antonio Alcalde", Guadalajara, Mexico.*

Background: Patients on HD reduce their motor capacity over the time. It has been shown that physical training programs in HD are a safe intervention that positively impacts patients quality of life with positive effects on peak oxygen consumption, endothelial function and arterial stiffness index. Our objective was to evaluate the effect of a physical activity program with ergonomic bicycle during HD on the echocardiographic parameters of patients with conventional HD

Methods: Randomized, controled, unblinded clinical trial in prevalent HD patients, from september 2015 to may 2016, ≧18 years old. Patients with amputation of lower limbs, motor sequelae of cerebral vascular event and patients with vascular accesses in the lower extremities were excluded. Pre-dialysis biochemical test and echocardiographic parameters were taken at 0, 4 and 8 months. The intervention group included 14 pts who performed 135 min per week of moderate intensity exercise with ergonomic bicycle for a period of 35 weeks. SPSS software version 2.0 was used.

Results: 28 pts, average age 41 years, male (64%), HD vintage of 26 months. No difference was found in gender distribution, hereditary history, BMI, HbA1c, progression of CKD or hemodialysis time between the 2 groups. In the intervention group there was an increase in deceleration time with a baseline value of 157 ms to 220 ms at 8 months, with a statistically significant result which was not observed in the control group. In the control group, there was an increase in PSAP with an initial value of 35 mmHg, which increased to 44.5 mmHg, with a statistically significant result. Comparisons of biochemical level did not show statistically significant changes between both groups at 8 months of follow-up

Conclusions: HD pts with physical activity with an ergonomic bicycle for an 8-month period, compared against patients who did not perform physical activity, increased the deceleration time and did not increase PSAP. Intradialytic aerobic exercise is a feasible way to improve the myocardial function of HD pts, however, the design of new studies is required to further explore the impact of this intervention on other vascular function markers and to determine whether or not it reduces cardiovascular morbidity and mortality observed in patients with CKD.

SA-PO833

Dietary N-3 Polyunsaturated Fatty Acids (PUFA) Intake and Mortality in Adults on Hemodialysis: The DIET-HD Multinational Cohort Study Valeria M. Saglimbene,[1,4] Germaine Wong,[1,5] Jonathan C. Craig,[2] Jorgen B. Hegbrant,[3] Giovanni F. Strippoli.[6,3] *[1]Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia; [2]University of Sydney/ Children's Hospital, Sydney, NSW, Australia; [3]Diaverum Medical-Scientific Office, Lund, Sweden; [4]Diaverum Medical-Scientific Office, Lund, Sweden; [5]Centre for Kidney Research, Children's Hospital at Westmead, Sydney, NSW, Australia; [6]University of Bari, Bari, Italy. Group/Team: For DIET-HD investigators.*

Background: N-3 PUFA are protective factors for cardiovascular risk in the general population. However their role in hemodialysis patients, in whom the pathogenesis of cardiovascular disease is different, is uncertain.

Methods: The DIET-HD study is a prospective cohort study (January 2014-January 2016) in 9757 adults treated with hemodialysis in Europe and South America. The dietary N-3 PUFA intake was measured at baseline using the validated GA²LEN Food Frequency Questionnaire. Adjusted cox regression analyses clustered by country were conducted to evaluate the association between dietary N-3 PUFA intake and cardiovascular and all-cause mortality.

Results: During a median follow up of 1.5 years (8108 person-years), there were 1214 deaths of which 515 were attributable to cardiovascular causes. Compared to patients with the lowest dietary N-3 PUFA intake (<0.37 g/wk), the hazard ratios (95% confidence intervals) for cardiovascular mortality among patients in the middle (0.37 to <1.8 g/wk) and highest (≥1.8 g/wk) tertiles of N-3 PUFA were 0.80 (0.64 to 1.00) and 1.13 (0.88 to 1.45), respectively; the hazard ratios for all-cause mortality were 0.95 (0.82 to 1.09) and 1.08 (0.92 to 1.28), respectively. Only one third of the study population consumed sufficient N-3 PUFA (at least 1.75 g/wk) as recommended for primary cardiovascular prevention, and less than 10% as recommended for secondary prevention (7-14 g/wk).

Conclusions: Dietary N-3 PUFA intake was not associated with cardiovascular or all-cause mortality in patients on hemodialysis. The possibility that higher dose N-3 PUFA, reached from supplementation, might mitigate cardiovascular risk has not been excluded.

SA-PO834

Initiation of Hemodialysis Is Associated with Altered Protein Composition of High-Density Lipoprotein Ke Wang,[2] Cassianne Robinson-Cohen,[2] Andrew N. Hoofnagle,[2] Bryan R. Kestenbaum,[2] The HFM Study Group.[1] *[1]NIDDK, Bethesda, MD; [2]University of Washington, Seattle, WA.*

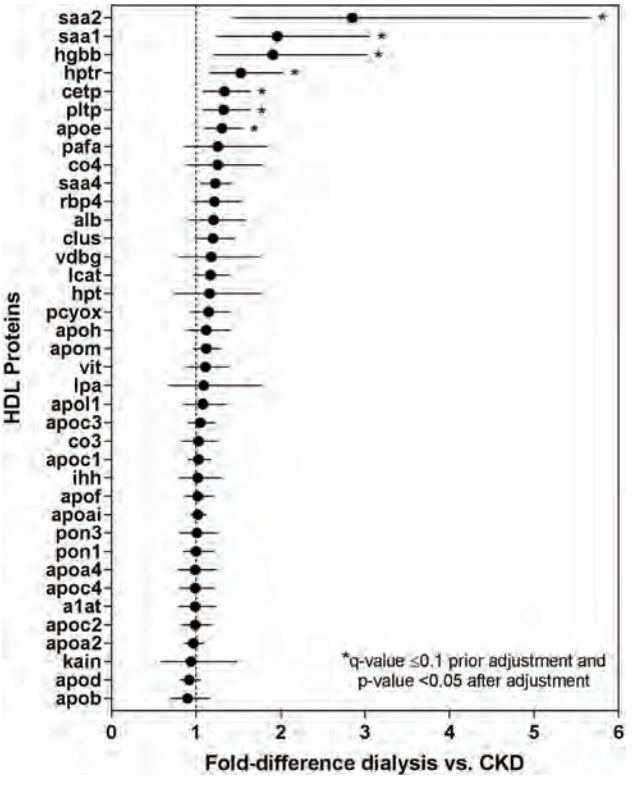
Background: High-density lipoprotein cholesterol (HDL-C) is composed of lipids and proteins that play important roles in cardiovascular disease development. The protein composition of HDL-C is altered in chronic dialysis patients compared to healthy controls. However, such differences conflate potential effects of kidney disease with those of dialysis procedures. We compared HDL-C associated proteins in patients recently initiating hemodialysis to those of patients with advanced chronic kidney disease (CKD).

Methods: We used liquid chromatography-mass spectrometry to quantify 38 HDL-C proteins in participants from the Hemodialysis Fistula Maturation (HFM) Study. We used linear regression to compare differences in log-transformed HDL-C proteins between 110 CKD patients awaiting dialysis (mean estimated GFR 12.8 ml/min/1.73m²) to 143 patients who initiated dialysis within the previous year. We used a q-value false discovery rate threshold of ≤0.1 to select candidate proteins that differed by dialysis status. We adjusted for age, race, gender, diabetes, body mass, smoking, prior cardiovascular disease, and statin use.

Results: Eight HDL-C associated proteins met the specified false discovery rate threshold for statistical significance (Figure). After covariate adjustment, seven of these proteins remained statistically significant at the p<0.05 level with minimal changes in effect sizes.

Conclusions: HDL-C associated proteins in pathways of inflammation and thrombosis are higher among recently initiated hemodialysis patients compared to those with late stage CKD. These findings suggest that the hemodialysis procedure itself may provoke adverse metabolic changes.

Funding: NIDDK Support



Differences in HDL-C proteins by dialysis status.

SA-PO835

Increased Risk of Mortality, Major Cardiovascular Adverse Events, and Major Bleeding Outcomes Associated with Non-Steroidal Anti-Inflammatory Drugs in Patients with ESRD Hyung Ah Jo,[3] Seokwoo Park,[1] Hajeong Lee,[2] Dong Ki Kim.[3] *[1]SEOUL, SEoul, Republic of Korea; [2]Seoul National University College of Medicine, Seoul, Republic of Korea; [3]Seoul National University Hospital, Jong ro Gu, SEoul, Republic of Korea.*

Background: Many epidemiologic and randomized controlled studies have shown that non-steroidal anti-inflammatory drugs (NSAIDs) had cardiovascular risk and bleeding adverse events. Many dialysis patients complaint various causes of pain, and need of NSAIDs is considerable. However, there was no known study about the effect of NSAIDs on patients with end-stage renal disease (ESRD) receiving dialysis. Therefore, a nationwide epidemiologic study to evaluate the effect of NSAIDs on dialysis patients

should be considered. We investigated the risk of mortality, major cardiovascular adverse events (MACE), major bleeding events associated with NSAIDs.

Methods: A retrospective case-cross over designed nationwide epidemiologic study was conducted by analyzing Korean National Health Insurance (NIH) database. Inclusion criteria was patients older than 20 years with maintenance dialysis between January, 2008 and April, 2015. We excluded the patients who could not maintain dialysis at least 90 days from the date of dialysis initiation. For each included dialysis patients, we defined a case period as 1 to 30 days before the index date and control period as 60 to 90 days and 91 days to 120 days before the index date.

Results: A total of 9,417 patients with mortality, 3,313 patients with MACE and 4,923 patients with major bleeding events were included. For mortality, increased risk more obvious in non-selective NSAIDs such as diclofenac and aceclofenac than selective NSAIDs. Non-selective NSAIDs showed increased risk of MACE, and selective NSAIDs did not increase MACE. In regarding to major bleeding events, both selective (OR: 1.684. CI: 1.310-2.165) and non-selective NSAIDs (OR: 1.945, CI: 1.813-2.087) showed increased risk in dialysis patients.

Conclusions: Use of NSAIDs increased mortality, MACE and major bleeding events in dialysis patients. Increased risk of non-selective NSAIDs was more evident in MACE than selective NSAIDs and both non-selective and selective NSAIDs increased risk of major bleeding events.

SA-PO836

The Association of Comorbidity and Nephrology Care with Mortality in Incident Dialysis Patients: A Population-Based Study Yiwen Chiu,[1,2] Ming-Yen Lin,[1,2] Feng-Xuan Jian,[1,2] Ping-hsun Wu,[1,2] Shang-Jyh Hwang.[1,2] *[1]Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [2]Kaohsiung Medical University, Kaohsiung, Taiwan.*

Background: Nephrology care in late CKD can improve the survival after dialysis, how the morbidity affects this effectiveness remains unclear.

Methods: We conducted a retrospective cohort study to include incident patient with dialysis ≥ 3 months by using Taiwan National Health Insurance Research Databases from 2004 through 2012. Incident patients were included from 2007 through 2011 and their comorbidities were identified within three years before dialysis start. Nephrology care was evaluated by cumulative care (total nephrology visits in 3 years before dialysis), critical period care (at least one nephrology visit in 6 months before dialysis), and consistent critical period care (nephrology visits more than 3 in the 6 months before dialysis). One-year mortality risks after dialysis start were evaluated in all study subjects as well as cohorts stratified by comorbidity number by various nephrology cares in late CKD.

Results: We included total 44,698 (mean age 63.3±14.2, male 51.9%) and identified 9,600 (21.5%, mean age 67.8±11.4, male 47.6%) patients with multi-morbidity(≥ 3 diseases). 5428 patients(12.1%, mean age 61.2±16.2, male 56.1%) had no any nephrology visit, and only one half had nephrology visits more than ten times in 3 years before dialysis. After adjusted age, sex, socioeconomic status, living area, urbanization and comorbidity number, higher cumulative care (> 10 times), having critical period care, and consistent critical period care were associated with a lower mortality risk. Regular care in other specialties didn't have such association. In addition, the increase of comorbidities didn't change the pattern of significant association. (Table1)

Conclusions: Regular nephrology care should be highlighted in late CKD no matter how the burden of comorbidities is.

Funding: Government Support - Non-U.S.

Table1

Expressed as: Adjusted HR(95%CI)	All N=44,698	1 comorbidity N=15,431	2 comorbidity N=12,118	≥ 3 comorbidity N=9,600
cumulative care (>10 times vs. 0)	**0.67(0.59-0.78)**	**0.72(0.56-0.94)**	**0.68(0.52-0.89)**	**0.74(0.58-0.96)**
critical period care (yes vs. no)	**0.88(0.78-0.99)**	0.92(0.74-1.14)	0.83(0.67-1.04)	0.85(0.69-1.03)
consistent critical period care (yes vs. no)	**0.75(0.69-0.82)**	**0.74(0.63-0.87)**	**0.79(0.67-0.93)**	**0.72(0.62-0.85)**

p<0.05 shown in bold

SA-PO837

Health Literacy Improves Medication Adherence and Clinical Outcomes Sreejith M. Velliyattikuzhi, Dipesh Maan, Swathi Lavudi, Richard J. Marcus, Barbara A. Clark. *Allegheny General Hospital, Pittsburgh, PA.*

Background: Poor medication adherence (MA) remains an important issue in end stage renal disease (ESRD) making blood pressure (BP) and phosphorous (P) control a challenge. We speculated the root cause for poor MA as lack of health literacy (HL) and designed a study to measure the extent of MA in ESRD and to determine if HL education improves MA in turn improving clinical outcomes.

Methods: 35 dialysis patients at a single center underwent a baseline interview which included open ended questions to assess MA (good MA defined as self-reported missed medication ≤ twice per week) and HL (knowledge of implications of BP and P control and awareness of anti-hypertensives and P binders). Medications were reconciled with the patient's pharmacy and an updated medication list along with verbal and written education materials were provided. In six weeks, a follow up interview was performed to re-assess MA and HL. Average systolic and diastolic BP and P levels were measured before and after the study.

Results: MA at baseline was 54%. Only 66% and 29% understood implications of BP and P control respectively. 56% were not aware of their P binders. Post intervention showed significant improvement in MA (86%, p=0.002), awareness of antihypertensive medications (p=0.01) and P binders (p<0.001). Systolic BP after intervention showed significant improvement (p<0.001). There was a trend towards improvement in diastolic BP, but did not reach statistical significance. No significant difference was observed with P levels and with number of missed hemodialysis sessions after intervention. Refer to table.

Conclusions: MA and HL in ESRD is poor. Open ended questioning identifies gaps in HL and directed education improves MA, HL and clinical outcomes.

Variable		Pre	Post	p-value
Medication Adherence(%)		54	86	0.002
Understand importance of BP control(%)		66	83	0.034
Understand importance of Phosphorus control(%)		29	63	0.001
Systolic BP-2 week average pre dialysis in mmhg(mean±SD)		147±21	139±18	<0.001
Diastolic BP-2 week average pre dialysis in mmhg(mean±SD)		83±15	80±14	0.198
Phosphorus Level in mg/dL (mean±SD)		6.4±1.9	6.2±1.8	0.311
Awareness of anti-hypertensive medications(%)	None	20	9	0.011
	Some	60	60	
	Good	20	31	
Awareness of phosphate binders(%)	None	56	9	<0.001
	Some	27	67	
	Good	17	24	
No: of missed HD days (mean±SD)		0.88±1.15	0.74±1.33	0.431

SA-PO838

Application of Extended Home Hemodialysis with the NxStage System One Eric D. Weinhandl,[2,3] J. Ken Leypoldt,[1] Allan J. Collins.[2,3] *[1]San Clemente, CA; [2]NxStage Medical, Inc., Victoria, MN; [3]University of Minnesota, Minneapolis, MN.*

Background: Extended hemodialysis, which is characterized by session duration beyond the usual interval of 3 to 5 hours, facilitates the removal of large fluid volumes at slow rates, likely resulting in fewer intradialytic hypotensive episodes and lower interdialytic blood pressure. There are few data about applications of extended hemodialysis with a low volume of dialysate per session. We used a telehealth platform to collect data about home hemodialysis (HHD) patients using the NxStage System One for extended hemodialysis.

Methods: We collected treatment factors and intermediate outcomes in HHD patients using the NxStage System One in tandem with the Nx2me Connected Health platform. We analyzed digital flowsheets collected from US patients between Nx2me product launch and March 31, 2016, and retained those patient-weeks with prescription of at least 3 sessions and receipt of at least 3 flowsheets with session duration ≥6 hours. We used descriptive analysis to summarize collected data.

Results: We identified 1932 patient-weeks of extended hemodialysis among 56 patients. Percentages of patient-weeks with 3.5, 4, and 5 prescribed sessions per week were 5%, 30%, and 65%, respectively. The mean number of delivered sessions per week was 4.22 (adherence, 90%). Mean session duration was 421 minutes, with 5th and 95th percentiles of 353 and 481 minutes, respectively; the mean number of cumulative treatment hours per week was 29.3. Sixty liters of dialysate were prescribed for 67% of sessions and the median blood flow rate was 300 mL/minute. Mean ultrafiltration volume was 2.1 L, with 5th and 95th percentiles of 0.6 and 3.9 L. In patient-weeks of extended hemodialysis, we identified 7429 digital flowsheets with complete data. Mean (standard deviation [SD]) ultrafiltration rate (UFR) was 2.97 (1.37) mL/hour/kg; 99.9% of sessions had UFR < 10 mL/hour/kg. Before treatment, mean (SD) systolic blood pressure (SBP) was 127 (24) mmHg and mean (SD) diastolic blood pressure (DBP) was 72 (12) mmHg. After treatment, mean (SD) SBP was 122 (23) mmHg and mean (SD) DBP was 72 (12) mmHg. The percentages of sessions with predialysis and postdialysis blood pressure in KDOQI target ranges were 67% and 56%, respectively.

Conclusions: Extended HHD on the NxStage System One delivered almost 30 hours of treatment each week, partially due to excellent adherence. UFR was very low and BP control was generally very good.

SA-PO839

Lymphopenia CD19+, a New Cardiovascular Risk Factor in Hemodialysis Patients Maria Molina, Enrique Morales, Claudia Yuste, Manuel Praga. *Nephrology Department, Hospital Universitario 12 de Octubre, Madrid, Spain.*

Background: Cardiovascular disease (CVD) is one of the most important causes of mortality in hemodialysis patients (HD). Traditional factors for CVD aren't good predictors of events. On the other hand, uraemia in HD induce have a proinflamatory environment that facilitate atheromatous lesions. Recently, the role of CD19+ lymphocytes in atheromatosis process has been described in non-uremic patients. The role of CD19+ lymphocytes in CVD in HD patients is unknown. **Aim:** To evaluate the role of lymphocytes CD19+ in cardiovascular deaths in HD patients.

Methods: A single centre prospective cohort study was started in 2011. We measured the lymphocytes CD19+ in 104 patients on HD and we followed them for 5 years, until a change in renal replacement therapy (kidney transplantation or peritoneal dialysis).

We studied the influence of lymphocytes CD19+ in CDV mortality; other causes of death were censored.

Results: The mean age was 64.8±15 y, 51% were male. Cardiovascular risk factors as arterial hypertension, diabetes mellitus and dyslipidaemia were found in 76%, 29.8% and 51.9%, respectively. 62 (60%) patients had previous CVD: 28% (29) ischemic heart disease, 14.5% (15) stroke and 25% (26) peripheral vascular disease. The follow up were 18 (7-47) months and 55 patients died. 22 patients (40% of all deaths) died for CVD. Multivariable analysis showed the variables associated with CDV mortality: age (HR: 1.04 (95% IC 1.006-1.1), p=0.02), Charlson index (HR: 1.16 (95% IC 1.02-1.3), p=0.02), previous ischemic heart disease (HR: 3.5 (95% IC 1.4-9), p=0.008), lymphocyte CD19+ < 100 cells/μL (HR: 4.1 (95% IC 1.18-14.6), p=0.02) and previous immunosuppression therapy (HR: 0.17 (95% IC 0.06-0.5), p=0.001).

Conclusions: Low CD19+ lymphocyte could be a new cardiovascular risk factor as important as ischemic heart disease in HD patients. To improve the immunological knowledge could decrease the CVD deaths of the HD patients. It is mandatory to performed more studies about the role of CD19+ lymphocyte in CVD in uremic patients.

SA-PO840

Aggravated Aging-Related Immune Changes Are Associated with Inflammation and Cardiovascular Diseases in ESRD Patients: Baseline Findings from the iESRD Study Kai-Hsiang Shu,[3,4] Yu-sen Peng,[2] Yen-Ling Chiu.[1] *[1]Far Eastern Memorial Hospital, Banciao, New Taipei City, Taiwan; [2]Far Eastern memorial hospital, Taipei, Taiwan; [3]Division of Nephrology, Far Eastern Memorial Hospital, New Taipei City, Taiwan; [4]Graduate Institute of Immunology, National Taiwan University, Taipei, Taiwan.*

Background: Patients with end-stage renal disease (ESRD) exhibit accelerated aging of the immune system and increased risk for cardiovascular diseases, but the overall contribution of "immune system aging", or "immunosenescence" to cardiovascular disease is not clear.

Methods: We performed a comprehensive lymphocyte and monocyte immunophenotyping in 412 ESRD patients on maintenance hemodialysis and age-matched 57 healthy individuals. Peripheral bloods were sampled before hemodialysis session and processed immediately for mononuclear cell isolation and staining. Using multicolor flow cytometry, lymphocytes were separated into subpopulations including naive T cells (CCR7+CD45RA+, T_{Naive}), central memory (CCR7+CD45RA-, T_{CM}), effector memory (CCR7-CD45RA-, T_{EM}), terminally differentiated (CCR7-CD45RA+, T_{EMRA}) and memory stem cells (naive cells with high CD28 andCD95, T_{SCM}). Monocytes were separated into classical (CD14++CD16-), intermediate (CD14++CD16+) and non-classical monocytes (CD14+CD16+).

Results: Compared to healthy individuals, ESRD patients showed decreased levels of naive CD4+ and CD8+ T cells, increased levels of terminally differentiated T_{EMRA} cells and intermediate monocytes (CD14++CD16+), and these changes not only significantly correlated with age but also enhanced by increasing dialysis vintage. Lymphocyte and monocyte aging also correlated with other established cardiovascular risk factors, including hemoglobin and high-sensitivity C-reactive protein. In multivariate-adjusted logistic regression models, a high terminally differentiated CD8+ T_{EMRA} cell level in combination with a high intermediate monocyte level was independently associated with the existence of coronary artery disease (OR=2.29, 95% CI=1.2~4.5, p=0.016) as well as cardiovascular diseases including stroke and peripheral arterial occlusive disease (OR=2.32, 95% CI=1.2~4.4, p=0.008).

Conclusions: Aging-related changes in the immune system are significantly aggravated in ESRD. Cardiovascular disease burden in the ESRD population might be enhanced by the presence of accelerated aging-related immune changes.

SA-PO841

The Modification Effects of Age, Inflammation, and Acyl-Ghrelin on the Relationship between Obestatin Levels and Clinical Outcomes in Maintenance Hemodialysis Patients Ilia Beberashvili,[5] Anna Katkov,[3] Inna Sinuani,[6] Ada Azar,[7] Gregory Shapiro,[4] Leonid Feldman,[1] Shai Efrati.[2] *[1]Nephrology division, Assaf Harofeh Medical Center, Zerifin, Israel; [2]None, Zerifin, Israel; [3]Nephrology division, Assaf Harofeh Medical Center, Zerifin, Israel; [4]Nephrology Division Assaf Harofeh Medical Center, Zerifin, Israel; [5]Nephrology division, Assaf Harofeh Medical Center, Zerifin, Israel; [6]Pathology department, Assaf Harofeh Medical Center, Zerifin, Israel; [7]Nutrition department, Assaf Harofeh Medical Center, Zerifin, Israel.*

Background: Obestatin, an anorexigen, was proposed as a physiological opponent of acyl-ghrelin (AG). While obestatin failed to reproduce the anorexigenic property in further studies, experimental evidence has accumulated suggesting protective cardiovascular effects of obestatin.

Methods: To examine the hypothesis that obestatin interactions with age, AG and inflammatory markers predict outcomes of maintenance hemodialysis (MHD) population, we investigated the associations between the obestatin, acyl-ghrelin, IL-6, TNF-α, and mortality in a prospective cohort of 261 MHD patients with 6 years of follow-up. During this period 160 patients died in total, with 74 because of cardiovascular causes.

Results: For each ng/ml increase in baseline obestatin level, in fully adjusted models (including malnutrition-inflammation score, IL-6 and AG) the hazard for death from all causes was 0.90 (95% CI, 0.81 to 0.99) and for cardiovascular death 0.85 (95% CI, 0.73 to 0.99). However, these associations were more robust in subgroup of patients aged above 71 years. An interactions between high IL-6 (above median) and low obestatin (below median) levels for increased risk of all-cause mortality (synergy index 5.14, p=0.001) and cardiovascular mortality (synergy index 4.81, p=0.02) emerged in multivariable adjusted models. Interactions were observed also between obestatin, TNF-α and AG, which were associated with mortality risk. High AG and high obestatin interaction was negative (synergy index 0.76, p=0.03) in predicting lower risk for all-cause mortality and cardiovascular mortality (synergy index 0.80, p=0.008).

Conclusions: The prognostic ability of obestatin is modified by age being very prominent in patients older than 71 years. In addition, we report on novel interactions between obestatin, inflammatory mediators and AG associated with mortality risk in the study population.

SA-PO842

Inflammatory and Angiogenic Factors Associated with Microvascular Changes over a 6-Month Period in a Cohort of Hemodialysis Patients Nicos Mitsides,[2] Tom Cornelis,[1] Natascha Broers,[3] Nanda Diederen,[3] Paul E. Brenchley,[2] Frank van der Sande,[3] Casper Schalkwijk,[3] Jeroen Kooman,[3] Sandip Mitra.[2] *[1]Jessa General Hospital, Hasselt, Belgium; [2]Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom; [3]Maastricht University Medical Centre, Maastricht, Netherlands.*

Background: Cardiovascular (CV) disease is a major contributor to poor outcomes in haemodialysis (HD). Comorbidity & oxidative stress are confounding factors to this phenomenon. High Dose HD (HDHD) regimes have been linked with a CV benefit compared to Conventional HD (CHD). We investigate the relationship between HD intensity, pro-inflammatory & endothelial mediators and micro- & macrocirculatory parameters over a 6-month period.

Methods: We report the findings of the 6-month analysis of participants to the study of Uremic Toxins, Cardiovascular Effects & Physical Activity in Intensive Haemodialysis (INTHEMO); a 2yr multicentre study investigating the effects of HDHD on CV parameters. Macrocirculation was assessed with pulse wave velocity & 24hr ambulatory blood pressure measurements. Microcirculation was assessed using sublingual dark field capillaroscopy. A panel of pro-inflammatory & endothelial biomarkers added to the assessment of vascular health. Hydration state was assessed by means of multifrequency bio-impedance.

Results: Of the 47 followed up at over a 6-month period, 21 were performing HDHD (>12hr of haemodialysis per week) & 26 CHD. CHD participant were older (63.5±14.2 v 53.7±12.6yr; p=0.02), with a smaller dialysis vintage (median vintage 23, max-min 6-106 v 61, max-min 10-432 months; p<0.01) & better-preserved residual renal function (61.5% v 9.5%;p<0.01). HD intensity did not correlate to any changes to CV measurements over a 6-month period. Higher serum levels of IL 8 (median 14.3pg/ml, min-max 3.5-185.7) measured at baseline independently predicted increase in the Perfused Boundary Region (5-25μm) of the endothelial glycocalyx (β=0.408, p<0.01) while higher levels of soluble Flt-1 (median 253pg/ml, min-max 139-1434) had a significant inverse effect (β=0.408, p<0.01) in an adjusted multivariate linear regression model.

Conclusions: HD intensity did not predict any changes in either macro- or microvascular parameters in HD patients. Micro-inflammation mediated through the TNF-alpha & IL-8 pathway was a predictor of microvascular injury while Flt-1, a potential marker of angiogenesis & endothelial repair might have a significant protective role. Further exploration into the pathophysiological effects of these pathways is required.

Funding: Clinical Revenue Support

SA-PO843

Monocyte/Lymphocyte Ratio Is a Better Predictor Than Neutrophil/ Lymphocyte Ratio for Cardiovascular Events in Incident Dialysis Patients Sawako Kato,[1] Bengt Lindholm,[2] Yukio Yuzawa,[3] Yoshinari Tsuruta,[4] Shoichi Maruyama.[1] *[1]Nagoya University Graduate School of Medicine, Nagoya, Aichi, Japan; [2]Baxter Novum & Renal Medicine Karolinska Institute, Stockholm, Sweden; [3]Fujita Health University School of Medicine, Toyoake, Japan; [4]Meiyo Clinic, Toyohashi, Japan.*

Background: A higher neutrophil/ lymphocyte ratio (NLR) may indicate increased risk of cardiovascular disease (CVD) in incident dialysis patients (pts). However, recent studies suggest that monocyte/lymphocyte ratio (MLR) might a more sensitive predictor of CVD events than NLR, because the monocyte, a multifunctional immune professional cell and an ancestor of lipid-laden macrophages, may directly contribute to the progression of atherosclerosis. Here we explored the mortality predictive capacity of MLR among incident dialysis pts.

Methods: In an ongoing prospective cohort study, 132 incident Japanese dialysis pts (91 males, age 59 ±12 years) were enrolled and followed for a median of 48.7 months (range 1-113 months). Laboratory biomarkers including white blood cell count (WBC) - and its differential count - were determined at baseline.

Results: Median MLR was 0.35 (range 0.46-0.27). The duration from start of dialysis therapy to the first CVD event was shorter in pts with higher MLR (Log rank 5.60, P=0.018). The number of CVD events per year was higher in pts with high MLR (18.6 events per 100 person-years) than in pts with low MLR (11.1 events per 100 person-years). In Cox hazard model, after adjustments for age, gender, smoking habits, and presence of diabetes, the pts with high MLR and high monocyte count – treated as continuous variables - had a significantly increased relative risk of CVD (5.64, 95% CI; 1.1-24.8, P = 0.028; and 7.17, 95% CI; 1.1-43.5, P = 0.037, respectively). However, the relations of CVD events to NLR or to neutrophil and lymphocyte counts were not significant.

Conclusions: In Japanese incident dialysis pts, a higher MLR and higher monocyte count associated with increased long-term risk of CVD events. These results may suggest

that an increased circulating number of monocytes might play a role in the development of atherosclerosis in chronic kidney disease pts, possibly through differentiation of monocytes into macrophages in plaques, or by other mechanisms.

Funding: Government Support - Non-U.S.

SA-PO844

Significant Association between Serum Magnesium and the Elevation of Troponin T in Maintenance Hemodialysis Patients Eiji Ishimura,[1] Shinya Nakatani,[2] Akihiro Tsuda,[2] Nobuyuki Kuwamura,[1] Ryusuke Kakiya,[1] Jiro Miyawaki,[3] Senji Okuno,[3] Tomoyuki Yamakawa,[3] Shigeichi Shoji,[3] Masaaki Inaba.[2] *[1]Meijibashi Hospital, Osaka, Japan; [2]Osaka City University Graduate School of Medicine, Osaka, Japan; [3]Shirasagi Hospital, Osaka, Japan.*

Background: Serum magnesium (Mg) levels is well known to be closely associated with cardiovascular disease in the general population. Troponin T has been reported to be a cardiac contractility modulating protein, and is measured as a biomarker for diagnosing myocardial injury. In hemodialysis patients, serum troponin T is elevated, and elevated serum troponin T has been reported to be a risk of death from all-cause mortality and cardiovascular disease. We hypothesized that serum Mg would be associated with the elevation of troponin T in hemodialysis patients.

Methods: A total of 432 stable maintenacne hemodialysis patients were examined (age: 64.0±11.3 years, hemodialysis duration: 8.0±6.9 years, 63.7% men, and 37.5% diabetics). Troponin T was measured twice in one year interval. Patients were divided into two groups; the group with elevation of serum troponin T in a year (98 patients) and the group with its non-elevation (334 patients).

Results: The group of elevation of serum troponin T showed significant older age, compared to the group of no-elevation of serum troponin T (67± 10 vs. 63 ± 12 vs. years, p = 0.0006). Cardia thoracic ratio (CTR) was significantly larger in the former than in the latter (50.5 ± 4.7 vs. 49.3 ± 4.4 %, p = 0.0260). Body mass index or duration of hemodialysis did not significantly differ between the two groups. Serum magnesium concentrations were significantly lower in the group of elevation of serum troponin T in a year, compared to the group of no elevation of serum troponin T in a year (2.6 ± 0.3 vs. 2.8 ± 0.4 mg/dL, p = 0.0015), although there were no significant differences in serum calcium, phosphate or intact PTH between the two groups. In a multivariate logistic analysis, serum Mg levels (OR = 0.394; 95% CI, 0.177 to 0.877; p = 0.0224) were significantly and independently associated with the elevation of troponin T, in addition to other significant factors of age, hemodialysis duration, and smoking (R^2=0.097, p < 0.0001), after adjustment of several clinical factors.

Conclusions: These results demonstrated that lower serum Mg concentration was significantly associated with the elevation of troponin T in hemodialysis patients, possibly suggesting that significant association of lower serum Mg and higher cardiac injury.

SA-PO845

Level of Anti-Cytomegalovirus Antibody Positively Correlates with Coronary Artery Disease and Cardiovascular Diseases in ESRD Patients Feng-Jung Yang,[1,3] Kai-Hsiang Shu,[2,4] Yen-Ling Chiu.[2,1] *[1]Graduate Institute of Medicine, College of Medicine, National Taiwan University, Taipei, Taiwan; [2]Far Eastern Memorial Hospital, Banciao, New Taipei City, Taiwan; [3]Internal Medicine Department, National Taiwan University Hospital Yunlin Branch, Douliu, Taiwan; [4]Internal Medicine Department, National Taiwan University Hospital, Taipei, Taiwan.*

Background: Accumulating evidence indicates cytomegalovirus (CMV) infection is associated with several health-related adverse outcomes including atherosclerosis and premature mortality in individuals with normal renal function. Patients with end-stage renal disease (ESRD) exhibit impaired immune function and may face higher risk of CMV-related adverse outcomes. Whether level of anti-CMV immune response may associate with the prognosis of hemodialysis patients is unknown.

Methods: The immunity in ESRD study (iESRD) recruited 412 hemodialysis patients from both northern and southern Taiwan. By history taking and detailed chart reviews, baseline co-morbidities were recorded. Peripheral blood was sampled before hemodialysis session and processed immediately. Plasma levels of CMV-IgG and high-sensitivity C reactive protein were determined by ELISA. Peripheral blood monocyte and T cell differentiation subsets were determined by multicolor flow cytometry.

Results: Among these patients, 99% were CMV-seropositive. In the univariate analysis, log level of anti-CMV IgG was independently associated with the existence of coronary artery disease (OR=1.944, 95% CI=1.2~3.0, p=0.004) as well as cardiovascular diseases including stroke and peripheral arterial occlusive disease (OR=1.53, 95% CI=1.03~2.276, p=0.034). In a multivariate-adjusted logistic regression model, log level of anti-CMV IgG was independently associated with the existence of coronary artery disease (OR=1.944, 95% CI=1.2~10.4, p=0.019) as well as cardiovascular diseases including stroke and peripheral arterial occlusive disease (OR=3.98, 95% CI=1.5~10.8, p=0.007) after adjusting for age, gender, dialysis vintage, hemoglobin, DM, and hs-CRP. Level of anti-CMV IgG positively correlated with both percentage and absolute number of terminally differentiated CD8+CD45RA+CCR7- TEMRA cells, indicating the accumulation of these cells participate in the progression of atherosclerosis.

Conclusions: Anti-CMV humoral immune response positively correlates with the existence of coronary artery disease and cardiovascular diseases in ESRD patients. Role of CMV and the associated immune response should be further investigated in the pathogenesis of atherosclerosis in this patient population.

Funding: Government Support - Non-U.S.

SA-PO846

Serum Sclerostin Level Is an Independent Predictor of Short-Term Mortality in Maintenance Hemodialysis Patients Kosaku Nitta, Ken Tsuchiya. *Tokyo Women's Medical University, Shinjuku-ku, Japan.*

Background: Sclerostin has recently been recognized as a novel marker of bone remodeling and vascular calcification. However, whether a high circulating sclerostin level is also a risk factor for death has not been clearly established. The aim of this study was to determine whether there is an association between the serum sclerostin levels and their mortality of maintenance hemodialysis (MHD) patients.

Methods: We measured the serum sclerostin levels in a Japanese MHD cohort, and followed over a 4-year period, and classified the patients into tertiles according to their serum sclerostin levels. We then assessed their short-term mortality (16 months) and long-term mortality (42 months) according to their serum sclerostin levels. Cox regression analyses were performed to test for associations between their serum sclerostin levels and both all-causemortality and cardiovascular disease (CVD)-related mortality. Kaplan-Meier curves were used to perform the survival analyses.

Results: The cohort consisted of 389 MHD patients aged 42.3 ± 18.8 years (55% males, 15% diabetics). There were 75 deaths during the follow-up period of 38.2 ± 9.3 months, 75 patients died. The main cause of death was CVD (n = 31), and was followed by infection (n = 30). The results of the multivariate logistic regression adjusted for confounders showed that history of CVD (HR 3.34, 95% CI 1.219 – 8.255, P = 0.0209) was the only significant predictor of all-cause mortality, but the serum tryglyceride level (HR 0.002, 95% CI 0.002 – 0.594, P = 0.0305) and being in the 1st tertile of sclerostin levels (HR 8.791, 95% CI 1.574 – 164.808, P = 0.0098) were significant predictors of CVD-related mortality during the 16 month-follow-up period. Kaplan-Meier analyses showed no significant differences in CVD-related mortality between tertiles during 16 month-follow-up period, but higher mortality in the 1st tertile (P = 0.0274). There were no significant differences in all-cause or CVD-related mortality tertiles during the 42 month-follow-up period.

Conclusions: The serum sclerostin level is an independent predictor of short-term mortality in MHD patients, but whether clinical interventions to modulate their serum sclerostin levels would improve their survival remains to be determined.

SA-PO847

Residual Urine Volume in Hemodialysis Patients: International Trends, Predictors, and Outcomes in the DOPPS Manfred Hecking,[3] Keith McCullough,[1] Friedrich K. Port,[1] Hiroyasu Yamamoto,[2] Michel Y. Jadoul,[5] Loreto Gesualdo,[4] Michelle M. Wong,[1] Bruce M. Robinson.[1] *[1]Arbor Research Collaborative for Health, Ann Arbor, AL; [2]Division of Nephrology and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan; [3]Medical University of Vienna, Nephrology & Dialysis, Vienna, Austria; [4]University of Bari, Altamura, Italy; [5]University of Louvain Medical School, Brussels, Belgium.*

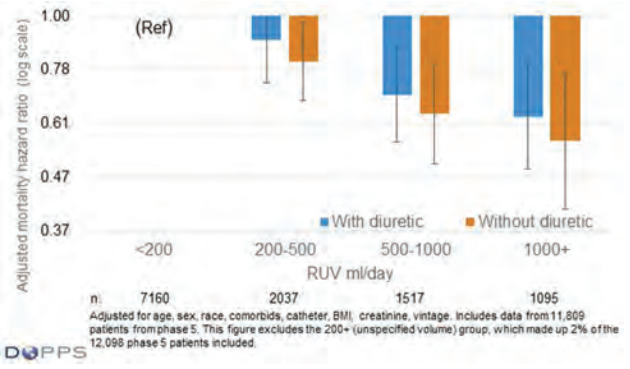
Background: Residual urine volume (RUV) decline after hemodialysis initiation has received limited attention in hemodialysis, and preventive actions are matter of debate. We determined international trends in RUV and analyzed the effect of potentially modifiable predictors on the association between RUV and mortality.

Methods: Among n=21,199 patients from 12 countries in DOPPS phases 2-5 (2002-2015), RUV was self-reported as ≥200mL versus <200mL and was measured or estimated in categories (in DOPPS phase 5, 2012-2015). Statistical methods included Cox regression models with adjustment for demographics, vintage, country and comorbidities.

Results: In prevalent patients with median vintage of 3.5 years, 31% reported RUV ≥200mL, at a wide geographical range (19% in Japan to 58% Germany), without a substantial time trend identified over DOPPS phases. RUV ≥200 was reported for 59% of patients on dialysis less than 1 year, decreasing to 45%, 36% and 17% of patients on dialysis 1-1.9 years, 2-2.9 years, and 3+ years, respectively. Prevalent patients who reported RUV <200mL had higher adjusted mortality than patients with RUV ≥200mL. In line, higher RUV was predictive of better survival in a dose-dependent fashion (Figure). The mortality risk associated with RUV did not differ among patients who were prescribed (versus not prescribed) diuretics (p-value for interaction =0.32).

Conclusions: Maintenance of RUV differs by region and vintage, but has remained relatively stable in the DOPPS since 2002. The fact that >17% of patients on dialysis at 2 and 3 years have RUV may previously have been underrecognized. Our survival model among prevalent patients confirms the dose-dependent importance of RUV as a predictor of survival. Although diuretics did not modify RUV-associated mortality risk, high-dose diuretics and other means to potentially preserve RUV deserve more focused investigation.

Funding: Commercial Support - Amgen, AstraZeneca, Baxter Healthcare, Kyowa Hakko Kirin, Hexal AG, Janssen, Keryx, Proteon, Relypsa, Roche, Vifor Fresenius Medical Care Renal Pharma, ERA-EDTA, Japanese Society for PD, Association of German Nephrology Centres, Societies for Nephrology in Germany, Italy, & Spain., Government Support - Non-U.S.



SA-PO848

Differences between Home and In-Center BP Readings in Dialysis Patients Dana Miskulin,[1] Ambreen Gul,[2] R. Schrader,[2] Jennifer J. Gassman,[4] Antonia Harford,[3] Philip Zager.[2] *[1]Tufts Medical Center, Sommerville, MA; [2]DCI, Albuquerque, NM; [3]UNM, Albuquerque, NM; [4]Cleveland Clinic, Cleveland, OH. Group/Team: For BID Study Investigators.*

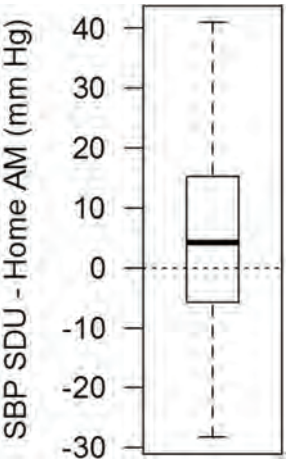
Background: Critics argue that 'in-center' pre-dialysis BP readings in hemodialysis patients are not reflective of 'true BP' because patients are at the extremes of fluid balance, are more anxious than usual and staff do not follow AHA guidelines for measurement. Few studies have compared home with in-center readings, and those that have, have been limited to 1-2 weeks of home readings. The BID was a pilot RCT in which 126 thrice weekly hemodialysis patients were randomized to 12 months of treatment to a pre-dialysis standardized dialysis unit (SDU) systolic blood pressure (BP) 110-140 or 155-165 mm Hg. Patients measured BP at home on the day following the mid-week treatment for one year.

Methods: The difference between the mid-week pre-dialysis SDU and home systolic BP the next morning was modeled using linear mixed regression with cubic splines.

Results: Systolic BP at home was a mean (SD) 6.1 (0.7) mm Hg lower than the pre-dialysis SDU (Figure 1) though, the range of the difference was wide and for 25% of the population, home was less than SDU by more than 15 mm Hg. The 'within patient' variability in systolic BP was slightly higher for home (16.9 mm Hg) as compared with. pre-dialysis SDU (14.3) readings. Results were not different when SDU was compared with the average of the morning and evening home BPs.

Conclusions: The average difference between systolic BP taken pre-dialysis using a standardized protocol vs. at home of ~6 mm Hg is surprisingly consistent with the difference between office and home BP in the general population. However, for some patients, it is much larger, and the differences are likely to be even greater with routine (as opposed to standardized) in-center BP measurement. Obtaining home BP readings in dialysis patients may reduce 'overtreating' hypertension, which would be especially important in elderly patients and those prone to falls.

Funding: NIDDK Support, Other NIH Support - Dialysis Clinic Inc.



Difference between Home and Standardized Pre-Dialysis Systolic BP

SA-PO849

Effect of Spironolactone on Left Ventricular Mass in Hemodialysis Patients: The MiREnDa Study – A Randomized Controlled Trial Christoph Wanner,[5,12] Uwe Malzahn,[7] Julian Donhauser,[6] Christoph Betz,[13] Clemens Grupp,[2] Thomas Döltz,[4] Nils Pollak,[3] Sören Grebe,[10] Esther Murillo,[1] Severin Bausch,[6] Tobias G. Hauser,[11] Monika Mehling,[6] Kirsten Hofmann,[6] Christian O. Ritter,[9] Vera Krane,[10] Fabian Hammer.[8,12] *[1]University Hosptial Würzburg, Würzburg, Germany; [2]Department of Nephrology, Bamberg, Germany; [3]Hospital of the university of Würzburg, Würzburg, Germany; [4]KfH, Germany, Bamberg, Germany; [5]University Hospital, Wuerzburg, Germany; [6]University Hospital Wuerzburg, Wuerzburg, Germany; [7]University Hospital Würzburg, Würzburg, Germany; [8]University Medicine Greifswald, Greifswald, Germany; [9]University Medicine of Goettingen, Goettingen, Germany; [10]University of Wuerzburg, Wuerzburg, Germany; [11]University of Würzburg, Würzburg, Germany; [12]Comprehensive Heart Failure Centre, University Würzburg, Würzburg, Germany; [13]Medicine, University Hospital Frankfurt, Frankfurt, Germany.*

Background: Hemodialysis (HD) patients are characterized by an extraordinary high cardiovascular (CV) morbidity and mortality but effective medical treatment is lacking. Left ventricular mass (LVM) constitutes an independent predictor of all-cause and CV mortality risk. We here evaluated the effect of spironolactone on LVM in HD patients.

Methods: We enrolled 118 HD patients of which 97 patients (female: 22.9%; mean age: 60.3±13.3 years; mean body mass index: 27.6±5.0 kg/m2; median duration of dialysis: 42.0 (16.6-76.0) months) were randomized 1:1 to spironolactone 50mg once daily (N=50) or placebo (N=47). The primary efficacy end point was the change in the LVM index as determined by cardiac magnet resonance imaging before and at the end of the 40 week treatment period. Secondary outcomes included the effect on 24h ambulatory blood pressure and the development of severe hyperkalemia (potassium≥6.5mmol/l).

Results: Treatment with spironolactone compared to placebo did not result in a significant change of the LVM index (spironolactone vs. placebo: -2.86±11.87 vs. 0.41±10.84 g/m2, p=0.337, ANCOVA). Likewise treatment with spironolactone did not change mean 24h systolic (0.0±11.6 vs. 2.1±15.4 mmHg, p=0.433) or diastolic (-1.3±7.9 vs. 0.1±9.0 mmHg, p=0.505) ambulatory blood pressure. The incidence of severe hyperkalemia was not different between the two groups.

Conclusions: Treatment of HD patients with 50mg spironolactone had no effect on LVM or blood pressure and did not increase the risk of severe hyperkalemia.

Funding: Government Support - Non-U.S.

SA-PO850

ECW/TBW Determined by Three Bioimpedance Devices: A Comparative Study in Hemodialysis Patients and Healthy Subjects Priscila Preciado, Fansan Zhu, Ohnmar Thwin, Xia Tao, Laura Rosales, Jochen G. Raimann, Stephan Thijssen, Peter Kotanko. *Renal Research Institute, New York, NY.*

Background: The ratio of extracellular (ECW) to total body water (TBW) is a widely accepted indicator of fluid status. However, ECW/TBW may differ between bioimpedance devices. We compared three commercially available bioimpedance devices in hemodialysis (HD) patients and health subjects (HS)

Methods: Ten patients (8 males, age 58.1±12 years) and 12 healthy subjects (7 females, age 33.3±5.6 years) were studied using two eight-point bioimpedance devices, InBody 770 (InBody USA, Cerritos, CA), Seca mBCA 514 (Seca North America, Chino, CA) and Hydra 4200 (Xitron Technologies, San Diego, CA). Measurements were performed pre and post HD in patients and once in HS.ECW, intracellular water (ICW), TBW, and ECW/TBW reported by the devices were compared between pre and post HD, and between patients and HS

Results: ECW and ICW were significantly lower in InBody compared to Seca and Hydra (**Table 1**). Peridialytic changes of ECW (ΔECW), ICW (ΔICW), and TBW (ΔTBW) did not differ. Peridialytic weight loss (ΔWt; 2.58±0.51 kg) did not differ from ΔTBW reported by InBody and Hydra. ΔECW reported by InBody and Hydra was significantly lower than ΔWt. Seca measurements of ΔTBW was higher than ΔWt. In HD patients and HS InBody measurements of ECW/TBW were lower compared to Seca and Hydra, respectively(**Fig.1**). Pre and post HD ECW/TBW measured with InBody and Hydra did not differ(**Fig.2**)

Conclusions: This pilot study indicates that ECW/TBW measurements differ between bioimpedance devices. InBody reports significantly lower ECW/TBW values compared to Seca and Hydra

Device	Pre HD ECW (L)	Pre HD ICW(L)	Pre HD TBW (L)	ΔECW (L)	ΔICW (L)	ΔTBW (L)	Post HD ECW/TBW
InBody	15.5±2.6	24.0±4.4	39.6±6.9	1.1±0.4	0.9±0.5	2.0±0.8	0.39±0.01
Seca	17.7±2.7	21.0±4.5	38.7±6.8	2.3±1.7	1.5±2.5	3.8±4.2	0.44±0.03
Hydra	17.5±2.8	20.0±5.5	37.5±7.3	1.5±0.9	1.1±2.2	2.6±2.0	0.45±0.05
p1-2	<0.01	<0.0001	ns	0.06	ns	ns	<0.0001
p1-3	<0.01	<0.01	ns	ns	ns	ns	<0.001

p1-2 indicates paired t test between InBody and Seca; p1-3 indicates paired t test between InBody and Hydra.ΔECW, ΔICW and ΔTBW represent the differences between pre HD and post HD

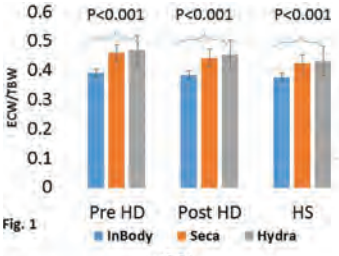


Fig. 1

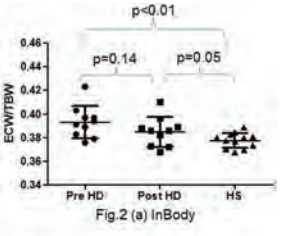


Fig.2 (a) InBody

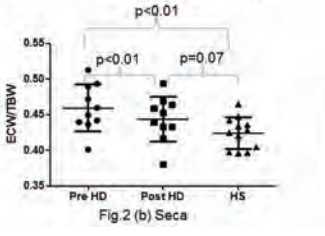


Fig.2 (b) Seca

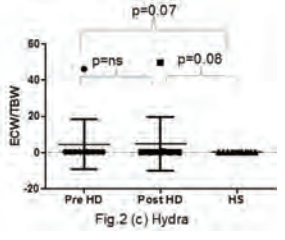


Fig.2 (c) Hydra

SA-PO851

Magnesium Prevents Vascular Calcification by Inhibition of Hydroxyapatite Crystal Formation Jeroen H. De Baaij, Anique D. Ter braake, René J. Bindels, Joost Hoenderop. *Radboud University Medical Center, Nijmegen, Netherlands.*

Background: Mg^{2+} has been shown to effectively prevent vascular calcification in multiple experimental calcification models. Vascular calcification is common in chronic kidney disease and contributes to increased mortality. Mg^{2+} has been hypothesized to prevent the upregulation of osteoblastic gene expression that drive calcification. However, extracellular effects of Mg^{2+} on Ca^{2+}-Pi crystal formation have been largely neglected. This study aimed to investigate the effects of Mg^{2+} on both intracellular changes associated with vascular calcification as well as effects on crystal formation in the extracellular space.

Methods: Bovine vascular smooth muscle cells (bVSMC) were calcified using β-glycerophosphate (BGP). Transdifferentiation was assessed by transcriptional analysis, cellular alkaline phosphatase (ALP) activity and development of apoptosis. X-ray powder diffraction, scanning electron microscopy and energy dispersive spectroscopy on crystals isolated from cell culture supernatants were used to map extracellular effects of Mg^{2+} on crystal formation and crystal composition.

Results: Mg^{2+} effectively prevented BGP-induced calcification in bVSMC. BGP did not cause changes in mRNA expression of the osteogenic genes BMP2, RUNX2 or ALP. Moreover, alkaline phosphatase activity was stable and apoptosis was only detected after calcification independent of Mg^{2+}. In addition, blocking of the Mg^{2+} channel TRPM7 using 2-ABP did not abrogate the protective effects of Mg^{2+}, indicating that intracellular Mg^{2+} is not involved in BGP-induced calcification of bVSMCs. Extracellular Mg^{2+} prevented the formation of hydroxyapatite crystals, which formed extensively after BGP treatment. Further analysis of the composition of the hydroxyapatite crystals showed that Mg^{2+} supplementation resulted in reduced Ca^{2+} and Pi fractions of 68% and 41%, respectively, without increasing the fraction of Mg^{2+}.

Conclusions: This study demonstrates that Mg^{2+} inhibits bVSMC mineralization through inhibition of Ca^{2+}-apatite formation in the extracellular space, independent of VSMC transdifferentiation. These results emphasize the need for randomized-controlled clinical trials assessing the effects of Mg^{2+} supplementation on vascular calcification.

Funding: Government Support - Non-U.S.

SA-PO852

Bone Turnover in Patients with Calcific Uremic Arteriolopathy Sagar U. Nigwekar,[2] Jeffrey L. Hymes,[1] Diane M. Rondeau,[1] Franklin W. Maddux,[1] Ravi I. Thadhani.[2] *[1]Fresenius Medical Care, Waltham, MA; [2]Massachusetts General Hospital, Boston, MA.*

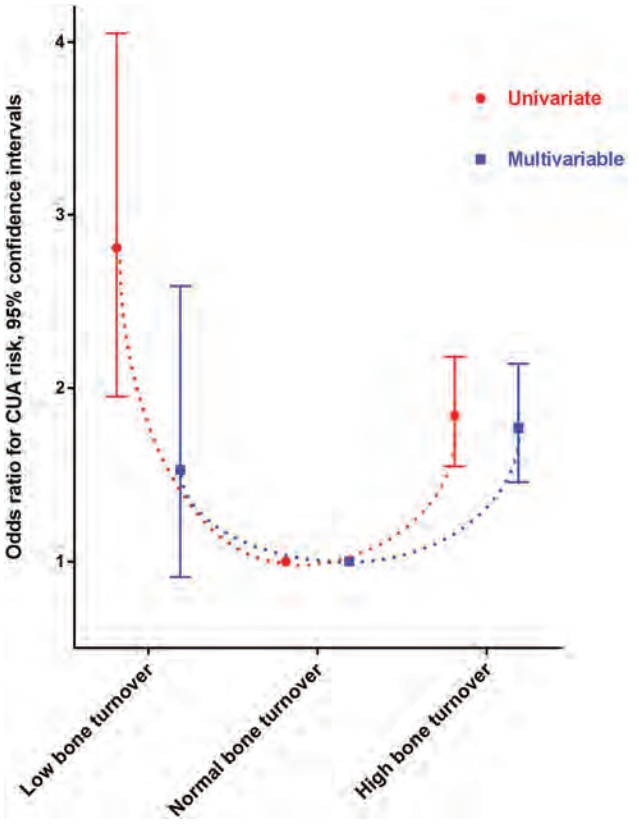
Background: Calcific uremic arteriolopathy (CUA) is an arteriolar calcification disorder with no effective treatment. Investigation of links between bone and vascular health in ESRD has largely focused on arterial calcifications; however the relationship between bone turnover and CUA is not well studied.

Methods: We examined the prevalence of bone turnover categories at hemodialysis (HD) initiation in patients who subsequently developed CUA. Bone turnover categories were defined by intact parathyroid hormone (iPTH) and alkaline phosphatase (ALK): high turnover if iPTH is >323 pg/mL and ALK>80 U/L; low turnover if iPTH is <103 pg/mL and ALK <25 U/L. We compared the prevalence of bone turnover categories between CUA patients and age, sex, and race matched controls. Univariate and multivariable logistic regression analyses were performed.

Results: We analyzed data from 1,030 CUA cases and 2,060 controls. High bone turnover at HD initiation was present in 8% of patients and low turnover in 9% of patients who subsequently developed CUA. Among controls, the prevalence of high bone turnover was 3% and of low turnover was 4%, both lower than in CUA patients (p<0.001). Both high and low bone turnover at HD initiation were associated with increased odds of subsequent CUA development in univariate and multivariable analyses adjusted for diabetes mellitus, obesity, and warfarin [figure].

Conclusions: The association between bone turnover at HD initiation and subsequent CUA development is U-shaped. Confirmation in future studies that apply bone biopsies will pave the way for targeted therapeutics to prevent/treat CUA (e.g. bisphosphonates, RANKL inhibitors for high turnover and teriparatide for low turnover).

Funding: Private Foundation Support



Risk of subsequent CUA development is increased in patients with low and high bone turnover at dialysis initiation

SA-PO853

The Specificity of Histologic Findings in Calciphylaxis W. Charles O'Neill. *Emory University, Atlanta, GA.*

Background: The diagnosis of calciphylaxis, also known as calcific uremic arteriolopathy (CUA), usually depends on a skin biopsy but data on the specificity of histopathologic criteria are limited. To assess this, histolology was compared in skin biopsies performed for a suspicion of CUA and in skin obtained from healthy margins of amputations in ESRD patients without CUA.

Methods: Skin biopsies in 38 patients with a clinical suspicion of CUA and 43 amputations from ESRD patients without CUA were identified retrospectively. Patients with skin biopsies were assigned a low (16), moderate (6), or high (16) suspicion for CUA based on review of the medical record by a nephrologist unaware of the biopsy results. This determination was based largely on the impression of the consulting dermatologist. Hematoxylin and eosin and von Kossa stains were examined for medial calcification, intimal hyperplasia, or thrombosis of small arteries or arterioles, and for extravascular soft tissue calcification by a pathologist unaware of the clinical information.

Results: Lesions in small arteries or arterioles were present in 35% of amputation specimens and 55% of skin biopsies, but in 87% of skin biopsies from patients with a high suspicion of CUA. Comparison of amputations and high-suspicion skin biopsies is shown in the table. The combination of vessel calcification and thrombosis showed the greatest difference, being 6-fold more prevalent in high-suspicion skin biopsies. The combination of vessel calcification and intimal hyperplasia was not seen in any specimen. There were no significant differences between the findings in amputations and those in the skin biopsies from patients without a high clinical suspicion for CUA.

Conclusions: Histopathologic findings historically associated with calciphylaxis also occur in viable tissue from unaffected ESRD patients. This calls into question the specificity of individual histologic findings for calciphylaxis. However, the combination of vessel calcification and thrombosis may provide more specificity.

Funding: Clinical Revenue Support

	Skin biopsies (%)	Amputations (%)	p
Vessel calcification	63	21	0.004
Thrombosis	47	14	0.013
Intimal hyperplasia	13	12	
Calcif + thrombosis	31	5	0.013
Calcif + intimal hyperplasia	0	0	
Non-vasc calcif	19	40	
Vessel + non-vasc calcif	13	9	

SA-PO854

Protein Carbamylation Exacerbates Vascular Calcification Daisuke Mori,[1] Isao Matsui,[1] Nobuhiro Hashimoto,[1] Ayumi Matsumoto,[1] Karin Shimada,[1] Satoshi Yamaguchi,[1] Tatsufumi Oka,[1] Keiichi Kubota,[1] Sayoko Yonemoto,[1] Yusuke Sakaguchi,[2] Takayuki Hamano,[2] Yoshitaka Isaka.[1] *[1]Osaka University Graduate School of Medicine, Suita, Japan; [2]Department of Comprehensive Kidney Disease Research, Osaka University Graduate School of Medicine, Osaka, Japan.*

Background: Protein carbamylation is an irreversible posttranslational modification that can occur non-enzymatically in the presence of urea. Although carbamylation is recognized as a prognostic biomarker, the effects of protein carbamylation on organ dysfunction remain uncertain.

Methods: Using *in vitro, ex vivo, in vivo* models, we investigated the effects of carbamylation on vascular calcification (VC), a life-threatening pathological condition that is common under carbamylation-prone situations.

Results: Protein carbamylation exacerbated the calcification of human vascular smooth muscle cells (hVSMCs) by suppressing the expression of ectonucleotide pyrophosphate/phosphodiesterase 1 (ENPP1), a key enzyme in the generation of pyrophosphate. By using immunoprecipitation in combination with mass spectrometry, we determined that several mitochondrial proteins, including ATP synthase subunits α and β, were carbamylated, although ENPP1 itself was not identified as a carbamylated protein. Rather, protein carbamylation reduced mitochondrial membrane potential and exaggerated mitochondria-derived oxidative stress, which downregulated ENPP1. The effects of carbamylation on ectopic calcification were abolished in mitochondrial-DNA-depleted hVSMCs and in hVSMCs treated with Mito-TEMPO, which indicated that mitochondria played essential roles in carbamylation-mediated effects. We also evaluated the carbamylation effects by using *ex vivo* and *in vivo* models: Protein carbamylation suppressed enzymatic histochemical staining for cytochrome c oxidase and succinate dehydrogenase in rat aortae, exacerbated calcifying-medium-induced VC in aortic ring cultures, and exacerbated warfarin/vitamin-D-induced VC in rats.

Conclusions: Protein carbamylation exacerbates VC by exaggerating mitochondria-derived oxidative stress and the resultant suppression of ENPP1.

SA-PO855

Direct Inhibition of Phosphate-Induced Vascular Smooth Muscle Cell Calcification via Suppression of PiT2 Expression by 25-Hydroxyvitamin D Masanori Tokumoto,[2] Shunsuke Yamada,[1] Kazuhiko Tsuruya,[3] Takanari Kitazono,[1] Hiroaki Ooboshi.[2] *[1]Department of Medicine and Clinical Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [2]Department of Medicine, Fukuoka Dental College, Fukuoka, Japan; [3]Department of Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.*

Background: Inverse association between 25-hydroxyvitamin D (25(OH)D) level and cardiovascular (CV) risk has been reported. Recently, the low serum 25(OH)D levels, which are frequently recognized in chronic kidney disease, has been also connected with vascular calcification, but the mechanism remains fully unknown. In the present study, we examined whether 25(OH)D directly reduce phosphate (P)-induced vascular smooth muscle cell (VSMC) calcification and its mechanism.

Methods: Human VSMCs were cultured in high P media with the additional P load of 2.0mM to induce calcification and treated with 25(OH)D of 10^{-10} ~ 10^{-6} M for a week. The degree of calcification and the expression of intrinsic calcification inhibitors and osteogenic differentiation markers were examined at Day 1 and 7. The degree of calcification was expressed as the calcium (Ca) content precipitated on the human VSMCs, and the content of calciprotein particle (CPP) was expressed as the Ca content in the precipitation of media, centrifuged by 16,000g for 2 hours at room temperature.

Results: Megalin and 1-hydroxylase were expressed in human VSMCs, and P-induced calcification was decreased with 25(OH)D of 10^{-10} ~ 10^{-7} M ($p<0.01$) at Day 7. The PiT1 expression was not altered by administration of 25(OH)D, but the PiT2 expression was decreased with 25(OH)D of 10^{-10} ~ 10^{-6} M at Day 1 and 7 ($p<0.01$). The Ca contents at Day 7 were correlated with the PiT2 expression at Day 1 and 7 ($p<0.01$, $r=0.66$ and 0.57, respectively). Furthermore, the CPP content and the SOX9 expression were correlated with the PiT2 expression at Day 1 ($p<0.01$, $r=0.55$, and $p<0.05$, $r=0.49$, respectively). Our results indicate that 25(OH)D ameliorates P-induced calcification via the inhibition of PiT2 expression in human VSMCs.

Conclusions: Our results indicate that 25(OH)D ameliorates P-induced calcification via the inhibition of PiT2 expression in human VSMCs.

Funding: Government Support - Non-U.S.

SA-PO856

Source of Matrix Vesicles (MV) Differentially Affect Cell Signaling and Calcification in Co-Cultures with Recipient Vascular Smooth Muscle Cells (VSMC) Neal X. Chen,[1] Kalisha O'Neill,[1] Sharon M. Moe.[1,2] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Roduebush Veterans Affairs Medical Center, Indianapolis, IN.*

Background: In patients with CKD the major risk factor for progression of arterial calcification is the presence of existing (baseline) calcification. VSMC from CKD rats produce MV; vesicles isolated from cell lysate (cellular) induce calcification in co-cultures with recipient normal rat VMSC whereas those from media do not. We hypothesized that

the induction of different signaling pathways by recipient normal VSMC explains the differential effect on calcification.

Methods: Cellular and Media derived MV from VSMC were examined for structure and content by transmission electron microscopy (TEM) and Western blots. Both types of MV were co-cultured with recipient VSMC and alteration of oxidative stress (ROS production), intracellular calcium ($[Ca]_i$), gene expression and calcification were determined by biochemical assay or real time PCR.

Results: TEM showed both types of MV are around 100 mm diameter membrane–bound vesicles of similar structure. By Western blot, both media and cellular MVs contain the exosomal tetraspanins CD63 and CD81. Media MV contain significantly greater fetuin-A and lower annexins than cellular MV. The addition of media MV to recipient normal VSMC increased ROS production but had no effect on intracellular Ca ($[Ca^{2+}]_i$). In contrast, the addition of cellular MV to normal VSMC had no effect on ROS but significantly increased $[Ca^{2+}]_i$ despite evidence that both are similarly endocytosed. Both media and cellular MV increased gene expression of NOX1 but cellular MV also increased the expression of anti-oxidant superoxide dismutase-2 (SOD2) by 94% whereas media MV had no effect. Blockade of NOX1 activity with GKT137831 reduced media MV-induced ROS production by 25% in recipient VSMC and blocked cellular MV-induced calcification in recipient VSMC.

Conclusions: Cellular and media derived MV from CKD rats have different components and induce distinct cell signaling, gene expression and calcification in recipient normal VMSC. Cellular derived MV, as compared to media MV, do not induce ROS presumably due to a favorable oxidant/anti-oxidant ratio suggesting the ultimate cellular fate of the two MV types may be different.

Funding: Veterans Affairs Support

SA-PO857

CKD Patients with Calciphylaxis and Sodium Thiosulfate Treatment: A Systematic Review and Meta-Analysis Suwasin Udomkarnjananun, Paweena Susantitaphong, Somchai Eiam-Ong, Kearkiat Praditpornsilpa. *Chulalongkorn University, Bangkok, Thailand.*

Background: Chronic kidney disease (CKD) patients with calcific uremic arteriolopathy (CUA, calciphylaxis) are at high cardiovascular and mortality risks. Sodium thiosulfate (STS) is currently the most common treatment for CUA but the outcome is still unclear. Our objective is to systematically explore the outcome of CUA treatment with STS in CKD patients.

Methods: We searched MEDLINE, Scopus, and Cochrane Central Register of Controlled Trials from 1960 to April 2017 to identify case-control, cohort, and randomized controlled trials reporting the mortality rate of CKD patients with CUA and the outcomes after treated with STS. Only human studies published in English language were included.

Results: From 1,071 articles searched, 24 cohort and case-control studies reporting mortality rate of CKD patients with CUA were included into a systematic review. Ten of them were specified on STS treatment outcomes and had enough details for data analysis. No randomized controlled trial were found. There were total 284 patients receiving STS,27.1(22.2-32.7)% were male and 53.1(47.2-58.9)% had diabetes mellitus. The CUA lesions were mainly in the lower extremities (87.3%,63.2-96.5%). Mean accumulated STS dosages were 796±276 grams and mean duration of treatment were 10±2 weeks. After treatment with STS the wound completely resolved in 34.8 (22.6-49.55)% and partially resolved in 35.5 (24.6-48.2)%. The overall mortality rate of CUA patients receiving STS was 57.8 (45.7-68.9)%, as high as the pooled mortality rate from general 1,707 CUA patients (57.2%,49.3-64.8%). The odds ratio for mortality showed no statistical significance between the patients who had received STS and who had not (odds ratio 0.62,95%CI 0.27-1.42).

Conclusions: This is the first systematic review and meta-analysis of STS treatment in CKD patients with CUA. Although about 70% of CUA patients had wound improvement, the mortality was not lowered with STS treatment compared to the general CUA patients. Lacking of controlled trials may limit the evidence of the true efficacy of STS.

Study details

First author, year	Baldwin,2011 (Canada 2007-2010)	Nouredd,2011 (US 2003-2008)	Sood,2011 (Canada 2006-2008)	Malabu,2012 (Australia 2006-2011)	Nigwekar,2012 (US 2006-2009)	Zitt,2013 (Austria 2004-2010)	Lee,2015 (Singapore 2012-2013)	Bourgeois,2016 (Belgium 2009-2014)	McCarthy,2016 (US 1999-2014)	Zhang,2016 (US 2001-2015)
Patients number	7 patients received STS	14 patients received STS	6 patients received STS	3 patients received STS 3 patients did not received STS	172 patients received STS	27 patients received STS	11 patients received STS 1 patients did not received STS	6 patients received STS	34 patients received STS 67 patients did not received STS	4 patients received STS 3 patients did not received STS
Patients characteristics	HD 14% PD 72% CKD 14%	HD 57% PD 43%	HD 33% PD 67%	HD 100%	HD 100%	HD 85% PD 15%	HD 58% PD 33% Kidney transplantation 8%	HD 33% PD 17% Kidney transplantation 50%	Dialysis 59% CKD 41%	PD 100%
STS dosages and duration	Dose not described Duration 8±3.7 weeks	Dose 850±1648 g Duration not described	Dose 771±253 g Duration 10.8±3.7 weeks	Total dosages and duration not described	Dose 950 g (IQR 425,1975) Duration 13 weeks	Dose 1268±1555 g Duration 13.4 weeks (IQR 7.7,19)	Total dosages and duration not described	Dose 413±255 g Duration 5.6±3.9 weeks	Total dosages and duration not described	Dose not described Duration 12 weeks (IQR 11.2,20.4)
Wound outcome	Completely resolved 86% Partially resolved 14%	Completely resolved 36% Partially resolved 36%	Completely resolved 33% Partially resolved 33%	Resolved 50% in patients with STS treatment Resolved 100% in patients without STS treatment	Completely resolved 26% Partially resolved 47%	Completely resolved 52% Partially resolved 19%	Resolved 65% in patients with STS treatment Resolved 0% in patients without STS treatment	Completely resolved 33% Partially resolved 33%	Not described	Not described
Death	29%	71%	50%	100% in patients with STS treatment 67% in patients without STS treatment	42%	52%	82% in patients with STS treatment 100% in patients without STS treatment	67%	64.7% in patients with STS treatment 79.1% in patients without STS treatment	75% in patients with STS treatment 67% in patients without STS treatment

SA-PO858

Combined Therapy of Menaquinone-7 and Omega-3 Fatty Acid Prevents Progression of Aortic Calcification in Adenine and Low Protein Diet Induced Rat Model Su mi Lee,[1] Hyuck jae Choi,[1] Kitae Kim,[2] Sung Hyun Son,[2] Young ki Son,[1] Seong Eun Kim,[1] Won Suk An.[1] *[1]Department of Internal Medicine, Dong-A University, Busan, Not Applicable, Republic of Korea; [2]BHS Han Seo Hospital, Busan, Republic of Korea.*

Background: Vascular calcification is common and progressing in chronic kidney disease and dialysis patients. Diet with high-dose menaquinone-7 (MK-7) (100 ug/g diet) inhibited the development of cardiovascular calcification in 5/6 nephrectomy rat combined with high phosphate diet. Eicosapentaenoic acid (1g/kg/day), one of omega-3 fatty acid (FA), attenuates arterial medial calcification induced by warfarin. We evaluated whether the effect of omega-3 FA and MK-7 on aortic calcification in adenine and low protein diet induced vascular calcification rat model.

Methods: Male Sprague Dawley rats were fed the diets containing 0.75% adenine and 2.5% protein for 3 weeks. After 3 weeks, 4 rats were sacrificed for calcification evaluation of thoracic aorta. Thirty two rats were randomly divided into four groups, which were treated and fed the diets containing 2.5% protein for 4 weeks: adenine control (0.9% saline), adenine control treated with omega-3 FA (300 mg/kg/day by gastric gavage), adenine control treated with MK-7 (50 ug/kg/day by gastric gavage), adenine control treated with omega-3 FA and MK-7. Normal control rats were fed the diets containing 2.5% protein for 7 weeks. For quantitative assessment of aortic calcification, von Kossa stain of aorta was done and calcium contents were measured with calcium colorimetric kit.

Results: Serum creatinine of adenine control group treated with omega-3 FA and MK-7 was lower than adenine control group without treatment. Serum calcium and BUN levels were not significantly different between adenine control group with treatment and without treatment. Two rats among 4 rats showed aortic calcification at 3 weeks. After 4 weeks, aortic calcification was progressed in adenine control group without treatment on von Kossa stain and calcium contents analysis of aorta. Aortic calcification on von Kossa stain and calcium contents was the least progressed in adenine control group treated with combination of omega-3 FA and MK-7 compared to omega-3 FA or MK-7 single therapy.

Conclusions: Combined treatment with omega-3 FA and MK-7 definitely prevents progression of aortic calcification compared to rat without treatment in adenine and low protein diet induced vascular calcification rat model.

SA-PO859

Nrf-2 Attenuates Vascular Calcification in CKD-MBD by Suppression of Oxidative Stress Yi Li,[3] Daqing Hong,[2] Guisen Li,[1] Li Wang.[2] *[1]Renal Division and Institute of Nephrology, Sichuan Academy of Medical Sciences and Sichuan Provincial People?s Hospital, Chengdu, China; [2]Sichuan Provincial People's Hospital, CHENGDU, China; [3]University of Electronic Science and Technology, Chengdu, China.*

Background: Under pathological conditions in vascular calcication, uncontrolled production of ROS induced increased oxidase activities and impaired cellular antioxidant systems. NF-E2 p45-related factor-2 (Nrf-2) is a powerful factor to regulate oxidative stress. In our study, we aimed to validate the effect and mechanism of Nrf-2 on vascular calcification of ESRD involving oxidative stress.

Methods: We selected 36 patients admitted at the Department of Nephrology in Sichuan Provincial's Hospital between 2011 and 2012. 14 cases of age and sex matched biopsy-proven non-calcification were selected as negative control and 7 healthy volunteers as normal control. To mimick vascular calcification in ESRD, we used β-glyceophosphate to stimulate the rat vascular smooth muscle cells (RASMCs). 24 rats were randomly assigned to 4 groups: normal control group, vascular calcification group, vascular calcification with DMF treatment group and DMF treated alone group. The rattus CKD-MBD vascular calcification was induced by injection of Vitamin D3 and gavage nicotine.

Results: The blood phosphorus and iPTH in ESRD patients with vascular calcification was significantly increased. Nrf-2 expression was negaitvely correlated with vascular calcification in ESRD patients indicating by Alizarin-red S staining and immunohistological staining. To further elucidate the role of Nrf-2 in vascular calcification of CKD-MBD, we had knockdown or pharmacological blockaded Nrf-2 in rat aortic smooth cells (RASMCs) followed by hyperphosphate treatment. Then we observed that knockdown or pharmacological blockade Nrf-2 could induce vascular calcification in CKD-MBD. Nrf-2 agonist treatment showed that activation Nrf-2 could ameliorate vascular calcification in RASMCs. Then ROS inhibitor NAC pretreatment increased the level of Nrf-2 and ameliorated vascular calcification in RASMCs. Activation of Nrf-2 inhibited oxidative stress and attenuated mitochondria injury in RASMCs upon vascular calcification. Pathological examination reaveled that Nrf-2 agonist could suppress vascular calcification in rat CKD aortas. Immunohistological staining about Nrf-2 indicated that calcified rat aortas decreased the expression of Nrf-2. However, DMF increased the expression of Nrf-2 in vascular calcification rat aortas.

Conclusions: These resluts might indicate Nrf-2 attenuates vascular calcification in CKD-MBD by suppression of oxidative stress.

SA-PO860

BMP7 Ameliorates Procalcific Gene Expression Patterns in the Calcified Uremic Aorta Eva Gravesen,[3] Maria L. Mace,[1] Anders Nordholm,[1] Jacob Hofman-Bang,[3] Keith A. Hruska,[2] Klaus Olgaard,[3] Ewa Lewin.[1] *[1]Herlev Hospital, Copenhagen, Denmark; [2]Washington University St. Louis, St. Louis, MO; [3]Rigshospitalet, University of Copenhagen, Copenhagen, Denmark.*

Background: Hyperphosphatemia and vascular calcification(VC) are frequent complications of chronic renal failure(CRF). BMP7 has been shown to protect against development of VC in uremia. Thus the potential reversibility of established VC was examined in two experimental models; 1. by studying if BMP7 treatment could reduce the degree of VC in uremia and 2. by isogenic transplantation(ATx) of the calcified aorta from uremic rats to healthy littermates.

Methods: CRF and VC was induced in adult DA-rats by 5/6 nephrectomy, high phosphate(P) diet and alfacalcidol treatment. After 14 wks, severe VC was present. In model 1, CRF rats were allocated either to 250µg/kg of BMP7 ip once weekly or vehicle for 8 wks. In model 2, the abdominal aorta was transplanted orthotopically from CRF rats to healthy littermates. Ctrl group had normal to normal ATx. Rats were sacrificed 4 wks after ATx.

Results: BMP7 treatment resulted in a significant reduction of plasma P from 2.06±0.14 to 1.56±0.07mmol/L, p<0.01, despite persistent uremia. Uremia induced increase in aortic expression of fibronectin 1.15±0.11, periostin 1.31±0.14 and activin-A 1.34±0.06, and BMP7 treatment resulted in a significant decrease; Fn1 0.82±0.09, Postn 0.91±0.09, Inhiba 0.97±0.11, p<0.05. In the BMP7 study Ca content was significantly increased in the uremic vehicle treated rats both in the distal abdominal aorta 1.9±0.2µg/mg and in the proximal thoracic aorta 71±11µg/mg, and similar levels were seen in the BMP7 treated rats; 2.2±0.2µg/mg in the distal abdominal aorta and 54±7µg/mg in the proximal thoracic aorta. In the ATx study Ca content of the aorta from uremic rats was significantly elevated to 17.0±0.2µg/mg in the proximal abdominal aorta and similarly increased in the transplanted uremic aorta 15.9±0.6µg/mg, confirming that established uremic VC is not reversible despite removal of the uremic milieu.

Conclusions: BMP7 treatment resulted in a significant decrease in the expression of procalcific genes and a siginificant decrease in plasma P. Despite these favorable changes no effect on aortic Ca content was seen. These results were confirmed in the ATx study, where complete reversal of the uremic mileu neither reversed established uremic VC.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO861

Maintenance of Vascular Microrna-145 Levels Effectively Attenuates Uremia- and High Phosphate-Induced Aortic Calcification Sara Panizo,[1] Natalia Carrillo-Lopez,[1] M. Vittoria Arcidiacono,[2,3] Sandra De la fuente,[3] Anabel Castro,[3] Manuel Naves,[1] Isabel Rodriguez,[1] Jorge B. Cannata-Andia,[1,4] Adriana S. Dusso.[1] *[1]Bone and Mineral Research Unit, Hospital Universitario Central de Asturias, Instituto Reina Sofía de Investigación, REDinREN del ISCIII, Oviedo, Spain; [2]Department of Morphology, Surgery and Experimental Medicine and LTTA Centre, University of Ferrara, Ferrara, Italy; [3]Division of Experimental Nephrology, IRB Lleida, Lleida, Spain; [4]Department of Medicine, Faculty of Medicine, University of Oviedo, Oviedo, Spain.*

Background: In CKD, the control of vascular calcification (VC) is essential to reduce the risk of cardiovascular mortality. Herein, maintenance of mature microRNA-145 (miR-145) was examined as an anti-calcifying strategy because: a) miR-145 is the prevalent miR in vascular smooth muscle cells (VSMC) and essential to maintain their contractile phenotype; b) miR-145 targets osteogenic Osterix in osteoblasts; c) high phosphate (P) reduces normal VSMC miR-145 levels supporting a link between high P, miR-145 reductions, increased Osterix and VC.

Methods: Aortic calcium (Ca), pri-miR-145, miR-145 content and mRNA levels of vascular/osteogenic markers (a-actin and Osterix) were measured in: a) A7r5 cells (rat aorta VSMC), with or without miR-145 over-expression or silencing, and exposed to calcifying (2mM Ca; 3mM P) or non calcifying (1mM Ca; 1mM P) conditions for 4 days; b) Aortas from either 5/6 nephrectomized (NX) rats fed high dietary P for a month or from 3/4NX mice fed normal dietary P for 3½ months.

Results: In A7r5 cells, the exposure to calcifying media (CM) significantly reduced miR-145 levels in part through a 30% downregulation of pri-miR-145 (p<0.04) which supports the inhibition of miR-145 gene expression. Also, while miR-145 silencing further exacerbated the osteogenic differentiation (reduced α-actin and increased Osterix mRNAs) and Ca deposition induced by the CM, miR-145 overexpression markedly attenuated both. Importantly, miR-145 silencing also reduced α-actin and increased Osterix under non-CM. Accordingly, in 5/6NX rats fed high P, an inflexion point value was found for aortic miR-145 that accurately discriminated aortas with higher than normal Ca content (miR-145 levels below the threshold) from those with normal Ca content (aortic miR-145 above the threshold) (p<0.005, n=24). Also, in the mouse model mimicking slow human CKD progression with no hyperphosphatemia, an 85% reduction of aortic miR-145 concurred with an 80% reduction in aortic α-actin but no significant increases in Osterix or Ca content.

Conclusions: Maintaining vascular miR-145 levels should attenuate the vascular phenotype switch prompting osteogenic differentiation and calcification from early CKD stages and regardless of serum P.

Funding: Government Support - Non-U.S.

SA-PO862

Change in EXTL2, a Novel Factor Related to Vascular Calcification, in Hemodialysis Patients Shunsuke Goto,[1] Hideki Fujii,[1] Satomi Nadanaka,[2] Kentaro Watanabe,[1] Shuhei Watanabe,[1] Keiji Kono,[1] Shohei Nakanishi,[3] Jong-Il Kim,[3] Hiroshi Kitagawa,[2] Shinichi Nishi.[1] *[1]Kobe University Graduate School of Medicine, Kobe, Japan; [2]Kobe Pharmaceutical University, Kobe, Japan; [3]Chibune General Hospital, Osaka, Japan.*

Background: Vascular calcification is an important risk factor in hemodialysis patients. Although various factors are associated with vascular calcification, the mechanisms are not fully understood. Recent experimental study has reported that knockout of glycosaminoglycan-related enzyme exostosin-like 2 (EXTL2) was associated with vascular calcification in 5/6 nephrectomized mice. However, there are only a few clinical papers on it and EXTL2 has not been investigated in hemodialysis patients yet. The aim of our study was to investigate EXTL2 in hemodialysis patients.

Methods: We included 15 stable hemodialysis patients and 12 healthy control subjects in this study. We measured mRNA expressions of EXTL2, other glycosaminoglycan-related enzyme chondroitin 4-O-sulfotransferase 1 (C4ST1), xylosyltransferase 2 (XYLT2), and family with sequence similarity 20 member B (Fam20B) in blood. These mRNAs expressions were compared between hemodialysis patients and controls.

Results: mRNA expression levels of EXTL2 were 0.15 (0.10-0.24) in hemodialysis patients, and those were significantly lower compared to the control subjects (0.45 (0.27-0.55), p < 0.05), while, mRNA expression levels of C4ST1, XYTL2, and Fam20B were comparable between the two groups.

Conclusions: Our data suggested that EXTL2 levels decreased in hemodialysis patient compared to general population. Further study is needed to elucidate whether the decrease in EXTL2 is associated with the progression of vascular calcification in hemodialysis patients.

Funding: Private Foundation Support

SA-PO863

Relationship between Abdominal Aortic Calcifications by a Plain Lateral Lumbar X-Ray and Coronary Artery Calcifications by a CT-Based X-ray in CKD Patients Kittisak Thanwirunroj, Pongsathorn Gojaseni, Anutra Chittinandana. *Department of Medicine, Bhumibol Adulyadej Hospital, Royal Thai Air Force, Bangkok, Thailand.*

Background: The presence and severity of cardiovascular calcifications strongly predict cardiovascular mortality in patients with chronic kidney disease (CKD). Most studies examining calcifications in CKD patients use computed tomographic (CT)-based techniques which are relatively expensive to detect coronary artery calcifications (CAC). This study focuses on testing whether lateral abdominal radiographs, which are widely available and less costly, could be used instead of CT imaging.

Methods: A cross-sectional study was done in patients diagnosed as pre-dialysis CKD stage 3-5. All participants were detected CAC scores by a CT-based technique and abdominal aortic calcification (AAC) by a lateral plain film of the lumbosacral (LS) region within 3 months after enrollment. Medical data were collected from patients and medical records.

Results: A total of 70 patients (44 males, 26 females), aged 70.59 ± 10.16 years were enrolled in this study. There was a significant association between CT-based Agatston CAC scores and plain film-based AAC scores. The correlation coefficient (r) between CAC scores and 4-scale AAC, 8-scale AAC and 24-scale AAC were 0.399 (p = 0.001), 0.364 (p = 0.002) and 0.385 (p = 0.001), respectively. From ROC analysis, it was shown that AAC scores had strong correlation with CAC scores ≥ 400, which is considered to be a good predictor of cardiovascular mortality [figure 1].

Conclusions: Abdominal aortic calcification detected by lateral abdominal radiographs could be used instead of CT-based coronary calcification scores. Prognostic value of the abdominal aortic calcification in this population should be determined in large scale, prospective cohort studies.

Funding: Government Support - Non-U.S.

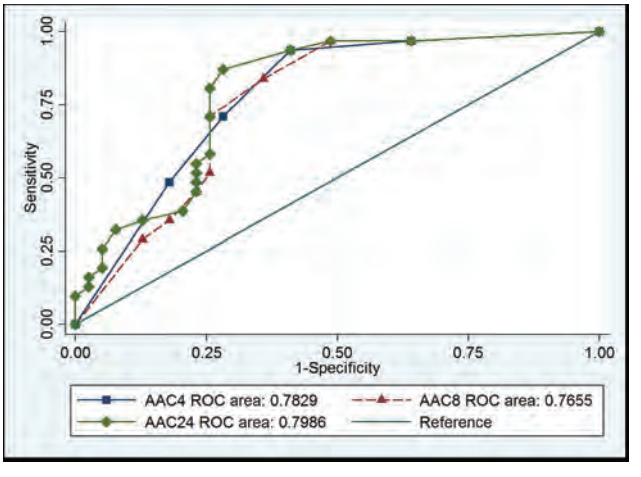


Figure 1: ROC curve of various AAC scores to predict CAC scores ≥ 400 Agatston

SA-PO864

Do Hemodialysis and Peritoneal Dialysis Differ Regarding Their Effect on Coronary Calcification? Thijs T. Jansz,[2] Franka E. Van reekum,[2] Akin Ozyilmaz,[1,5] Marianne C. Verhaar,[2] Brigit C. van Jaarsveld.[3,4] *[1]University Medical Center Groningen, Groningen, Netherlands; [2]University Medical Center Utrecht, Amsterdam, Netherlands; [3]VU medical center, Amsterdam, Netherlands; [4]Diapriva Dialysis Center, Amsterdam, Netherlands; [5]Dialysis Center Groningen, Groningen, Netherlands. Group/Team: NOCTx investigators*.

Background: Identifying modifiable risk factors of vascular calcification in end-stage renal disease is crucial in light of the associated high cardiovascular morbidity and mortality. In this cross-sectional study, we compared coronary artery calcification and levels of biomarkers associated with vascular calcification in pts treated with hemodialysis (HD) and peritoneal dialysis (PD), respectively.

Methods: We assessed coronary artery calcification using multi-slice computed tomography in 121 pts treated with HD (≤ 16 hrs/wk) and 46 pts treated with PD, who were included in the NOCTx study (NCT00950573). Biomarker measurements were performed in a subset of 55 HD and 33 PD pts using enzyme-linking immuno-assays and multiplex assays. We adjusted for age, sex, dialysis vintage, diabetes mellitus, use of vitamin K antagonists, smoking and residual diuresis in multivariate analyses.

Results: Pts treated with HD were somewhat older (53.1 ± 12.2 versus 49.8 ± 15.1 years) and had been on dialysis longer (26, IQR 12 – 57 versus 14, IQR 7 – 33 months). In univariate and multivariate analyses, coronary artery calcification in HD pts (median score 208, IQR 1 – 809) was not significantly different from PD pts (median score 84, IQR 0 – 1066). In HD pts, phosphate levels tended to be higher compared with PD pts (1.68 ± 0.39 versus 1.59 ± 0.35 mmol/L). Osteoprotegerin was evidently lower in HD pts (2.95 ± 1.33 versus 3.43 ± 1.81 µg/L, $p < 0.01$), while inactive matrix Gla protein (dp-ucMGP) levels did not differ significantly between HD and PD pts. Only dp-ucMGP was independently associated with extent of coronary artery calcification. Inflammatory markers C-reactive protein, interleukin-1β and interleukin-6 did not differ significantly between HD and PD pts. Probably due to intermittent fluid overload in HD, NT-proBNP was significantly higher in HD pts (2217 ± 1817 versus 1045 ± 1372 pmol/l, $p = 0.01$).

Conclusions: Uremia per se is detrimental for the coronary vasculature, seemingly irrespective of treatment with HD or PD. Whether coronary artery calcification and its progression are affected by other renal replacement therapies needs further evaluation.

Funding: Commercial Support - The NOCTx study is performed with minor grants from: Baxter Nederland BV; Roche Nederland BV; Amgen Nederland BV; Fresenius Medical Care Nederland; Shire Pharmaceuticals Benelux; Novartis BV; and the "Wellerdieck-de Goede" Foundation with mediation of Stichting Vrienden UMC Utrecht., Private Foundation Support

SA-PO865

Iron Stimulation Enhanced Calcification Along with TNF-Alpha in Human Vascular Smooth Muscle Cells Yasuyuki Nagasawa,[1,5] Sayuri Kawada,[1,5] Mutsuki Kawabe,[1] Aritoshi Kida,[1,5] Masayoshi Nanami,[5] Takahiro Kuragano,[4] Yukiko Hasuike,[1,5] Keiji Nakasho,[3] Hiromitsu Kishimoto,[1,5] Takeshi Nakanishi.[2,5] *[1]Hyogo College of Medicine, Nishinomiya, Japan; [2]Hyogo College of Mediicne, Nishinomiya, Japan; [3]Hyogo college of medicine, Nishinomiya, Japan; [4]Internal Medicine Division of Kidney and Dialysis, Nishinomiya, Japan; [5]Internal Medicine, Division of Kidney and Dialysis, Nishinomiya, Japan.*

Background: In CKD patients, atherosclerosis is one of important key factors which determine their prognosis. It was reported the calcification induced by TNF-alpha was related with iron in HUVEC cells by our group. The feature of the atherosclerosis in CKD patients was called as Moenckeberg's arteriosclerosis which was seen in vascular media, but the relationship between iron and calcification in vascular smooth muscle cell remained unclear. To reveal the relationship between calcification in vascular media and iron stimulation using cultured vascular smooth muscle cells.

Methods: The aorta smooth muscle cells were cultured for three weeks. At day 0, we changed the usual culture medium to calcification medium, and TNF-alpha and iron were added to the calcification medium. Calcification in each condition was confirmed by Alizarin staining. And to reveal early mechanism to enhance the calcification by iron and TNF-alpha stimulation, we compared the gene expression profile between each condition in day 1 and day 3 using microarray analyses. We confirmed gene expression of cytokine which had increased in microarray analysis in time course.

Results: We confirmed both iron and TNF-alpha stimulation enhanced calcification by Alizarin Staining. Moreover, both iron and TNF-alpha stimulation at the same time enhanced calcification more strongly than single stimulation. We picked up a cytokine which had increased with both iron and TNF-alpha stimulation in the microarray analysis as similar as the Alizarin Staining result had shown. Also, we confirmed gene expression of this cytokine by real-time PCR. Gene expression was increased at day1 by stimulation of iron(5.8±3.0 fold change vs control), TNF-alpha (7.8±1.9 fold change vs control), and both stimulation(53.1±27.1fold change vs control), synergistically(shown below). At day 3, gene expression showed as same increase as at day 1. The time course of this cytokine was confirmed in mRNA level and in protein levell.

Conclusions: Iron stimulation enhanced calcification in vascular smooth muscle cells along with TNF-alpha stimulation. The possibility was suggested that iron stimulation along with inflammatory induced cytokine expression changes in early stage, which continued during calcification process.

SA-PO866

Relationship between Bone Sialoprotein and Vascular Calcification in Maintenance Hemodialysis Patients Hongwei Wu, Fanna Liu. *The First Affiliated Hospital of Jinan Universtiy, Guangzhou, China*.

Background: Recent studies shown that vascular calcification was a osteoblast-like process involving multiple factors. Bone sialoprotein, a recently discovered protein, participated in the metabolism of bone-vascular axis and expressed in the medial layer of calcified vessel in uremia patients. The mechanism of vascular calcification that influenced by bone sialoprotein was not clear. This study was to evaluate the potential association of bone sialoprotein with the development of abdominal aortic calcification (AAC)in maintenance hemodialysis (MHD) patients.

Methods: Seventy-five patients who were on MHD between May 2016 and Feb 2017 in the dialysis center were enrolled. Serum bone sialoprotein was tested. AAC was measured by abdomen lateral plain. Kauppila score was used to assess the degree of CAC. Referring to CORD segmentation method, patients was divided into three groups: no or mild calcification group, moderate calcification group and severe group. Logistic regression analysis was used to determine the risk factor of AAC in MHD patients. The diagnostic value of serum bone sialoprotein for AAC was assessed using receiver operator characteristic curve (ROC).

Results: AAC(AACs>4) was present in 49.3% (37/75) patients, the median AAC score was 4(0,24). The median of serum bone sialoprotein was 20.12(18.63,24.21)ng/mL. The serum bone sialoprotein levels were significantly elevated in moderate calcification group and severe group compared to no or mild calcification group [22.43(19.58,26.84) ng/L and 21.99(19.87,26.18)vs 19.16(17.3,23.3)g/L, $P<0.05$]. Multivariate logistic regression analysis showed that serum bone sialoprotein level was independent risk factor for AAC (OR=1.175,95%CI 1.004~1.375, $P<0.05$). The area under the ROC curve of serum sclerostin for AAC was 0.718 (95%CI 0.604~0.833,P=0.001), sensitivity was 0.711, and specificity was 0.595 for a cutoff value of 21.51 ng/L.

Conclusions: Serum bone sialoprotein level is associated with AAC. Serum bone sialoprotein level may have a diagnostic value for AAC in MHD patients.

Funding: Private Foundation Support, Clinical Revenue Support

SA-PO867

Endothelial Hyperpermeability Induced by Mineral Stress Is Involved in the Development of Medial Layer Vascular Calcification Yasuto Shikida,[1] Masahide Mizobuchi,[1] Hiroaki Ogata,[2] Fumihiko Koiwa,[3] Takanori Shibata.[1] *[1]Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan; [2]Department of Internal Medicine, Showa University Northern Yokohama Hospital, Yokohama, Japan; [3]Division of Nephrology, Department of Medicine, Showa University Fujigaoka Hospital, Yokohama, Japan.*

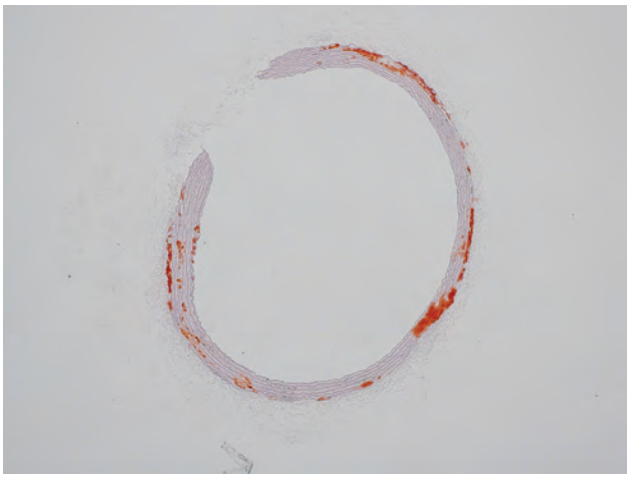
Background: Mineral stress such as high calcium and/or phosphate induces vascular calcification (VC) in chronic kidney disease. Although investigations regarding VC are growing, the precise mechanisms underlying the development of VC by the mineral stress remain to be studied. We investigated the role of vascular endothelial cell (EC) function in medial layer VC.

Methods: Human Umbilical Endothelial Cells (HUVEC) and aortic rings from normal and 5/6 nephrectomized uremic rats were used. Mineral stress was induced by a high calcium (3.6 mM) and phosphate (2.2 mM) media to HUVEC and aortic rings. Thereafter permeability and EC markers (CD31, VE-cadherin, and ZO-1) of HUVEC, and calcium contents and EC markers of aortic rings were studied. Alizarin red staining was also performed to evaluate the localization of mineral deposition in the rings. Regular media was utilized as control groups in each experiment.

Results: The mineral stress significantly increased permeability of HUVEC (2.5-fold to control, $p<0.05$) in conjunction with a significant decrease in mRNA levels of EC markers (CD31:0.5-fold to control, $p<0.01$, VE-cadherin: 0.7-fold to control, $p<0.05$, and ZO-1: 0.7-fold to control, $p<0.05$). The mineral stress also significantly increased calcium content in the aortic rings of normal ($p<0.05$ vs control) and uremic rats ($p<0.05$ vs control), respectively. A similar tendency was observed for EC markers in the rings of normal and uremic rats, respectively. Alizarin red staining showed medial layer mineral deposition of the aortic rings. (Figure: the ring of a uremic rat with the mineral stress).

Conclusions: Hyperpermeability of vascular ECs was induced by mineral stress indicating that loss of barrier function of ECs might have a crucial role in the development of medial layer VC.

Funding: Private Foundation Support



SA-PO868

Vitamin K and Vascular Health: A Systematic Review and Meta-Analysis Jennifer S. Lees,[2,1] Fiona A. Chapman,[1] Patrick B. Mark.[2,1] *[1]NHS Greater Glasgow and Clyde, Glasgow, United Kingdom; [2]University of Glasgow, Glasgow, United Kingdom.*

Background: Vitamin K deficiency is prevalent among patients with chronic kidney disease. Matrix Gla protein, an important regulator of vascular calcification, is dependent on adequate vitamin K intake. We conducted a systematic review and meta-analysis of effect of vitamin K supplementation on vascular health, and assessed evidence that level of desphospho-uncarboxylated Matrix Gla protein (dpucMGP) is associated with incident cardiovascular disease (CVD) or mortality.

Methods: Two authors searched Medline, Embase, Cochrane and Google for: i) adult human studies of vitamin K supplementation versus control which measured effect on vascular calcification, vascular stiffness or dpucMGP, and ii) prospective observational studies assessing effect of baseline dpucMGP on incident CVD or mortality. Random effects meta-analysis was conducted using *meta* and *metafor* packages for R statistical software package. Egger regression and Trim and Fill were used to assess for publication bias.

Results: Electronic searching identified i) 5095 and ii) 1850 references of which i) 8 and ii) 12 met our pre-specified inclusion criteria. In groups treated with vitamin K, there was a meaningful change in vascular calcification (see Figure, p=0.038) and dpucMGP (n=6, -235.5 (-292.1; -178.8) pmol/l, p<0.001), and a trend towards improvement in vascular stiffness (n=3, -3.70 (-7.77; 0.37) %, p=0.075). Over a median follow up period of 7.8 years (IQR 4.9-11.3), stepwise increase in dpucMGP was not associated with fatal or non-fatal CVD (log HR 0.06 (-0.1; 0.23), p=0.48) or mortality (log HR 0.02 (-0.11; 0.16), p=0.74). Egger regression and Trim and Fill analyes suggest a degree of publication bias in favour of positive results.

Conclusions: Vitamin K supplementation significantly reduces dpucMGP level, though dpucMGP is not associated with incident CVD or mortality. Supplementation appears to reduce progression of vascular calcification, with a trend towards improvement in vascular stiffness, though there are limited data available. Further clinical trials of the effect of vitamin K supplementation on vascular health are warranted.

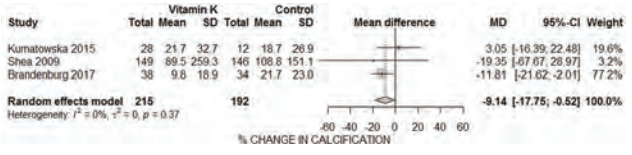


Figure: Forest plot of random effcts meta-analysis: % change in calcification with vitamin K supplementation versus control

SA-PO869

Mortality Prediction of Abdominal Aortic and Pelvic Calcification on Plain X-Ray in CKD, Hemodialysis, and Kidney Transplant Patients Sinee Disthabanchong. *Division of Nephrology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand.*

Background: Vascular calcification (VC) is highly prevalent in CKD and predicts poor outcomes. Both cardiovascular and CKD related risk factors participate in the development of VC. The gold standard for evaluation of VC is computed tomography but plain x-rays offer a less costly and less radiation exposure alternative. Lateral abdominal and pelvic x-rays have been utilized to evaluate the calcification of abdominal aorta, iliac and femoral arteries which was found to be highly correlated with abdominal aortic calcification (AAC) and CAC obtained by CT. The data regarding the predictability of AAC and pelvic arterial calcification (PAC) on patient outcomes are limited.

Methods: Four hundred and nineteen CKD stages 2-5 (CKD 2-5), maintenance HD (HD) and long-term KT (KT) patients were included. Only KT recipients who had been transplanted for at least 1 year were enrolled in order to allow the time for stabilization of mineral metabolism. AAC score as described by Kauppila et al and PAC score as described by Adragao et al were applied to determine the severity of AAC and PAC on lateral abdominal and pelvic x-rays respectively. The median follow-up time was 62.7 months for CKD 2-5, 52 months for HD and 62.5 months for KT.

Results: AAC and PAC scores correlated well with the correlation coefficients (*r*) >0.4 in all 3 populations (p<0.001). Patients with AAC score >6 or PAC score >1 were older, had higher prevalence of DM, serum PO_4 and PTH but lower serum albumin and eGFR. Increased KT duration was associated with a more severe degree of AAC, whereas prolonged dialysis vintage was associated with a more severe degree of PAC. Kaplan-meier survival curves revealed AAC score >6 as a significant predictor for all-cause mortality in CKD 2-5 but not in HD or KT, whereas PAC score >1 was a significant predictor of mortality in all 3 populations. After an adjustment for age, the predictability of AAC in CKD 2-5 was lost, whereas PAC >1 remained an independent predictor of mortality in all 3 populations. Further adjustments for age, sex, BMI, serum albumin, calcium and PO_4 revealed the predictability of PAC for mortality in CKD 2-5 patients and KT recipients but not in HD patients.

Conclusions: PAC was a better predictor of mortality than AAC in all 3 populations of CKD and should be considered in the evaluation of VC in CKD and KT patients.

SA-PO870

The Mechanism of Sodium-Dependent Phosphate Cotransporter Pit-1 in Phosphate-Induced Vascular Calcification in HASMCs Minwen Ding, Xinxin Jiang, Mengjing Wang, Minmin Zhang, Jing Chen. *Huashan Hosopital, Fudan Univeristy, Shanghai, China.*

Background: Vascular calcification (VC) is an important risk factor for cardiovascular disease in maintenance hemodialysis (MHD) patients. Hyperphosphatemia and micro-inflammatory state are known to be the prevalent conditions in MHD patients, which contribute greatly to the development of VC. The aims of this study were to explore the effects of hyperphosphate on peripheral blood mononuclear cells (PBMCs) and then the direct effects of hyperphosphate and TNF-αon human aortic smooth muscle cells (HASMCs).

Methods: Low concentration TNF-α(10pg/ml) and supernatants of monocytes (isolated from healthy donors' PBMCs) were used to evaluate the effects of micro-inflammatory on HASMCs. Cells were divided into five groups: NP, HP, TNF-α, supernatants and PFA group. The antagonist of Pit-1 (PFA) was used to explore the possible effects of Pit-1 on monocytes and the further effects on HASMCs. We used Alizarin red staining to determine the vascular calcification extent. The gene expressions of TNF-α, Pit-1 and osteochondrogenic factors (OCF) were tested by Realtime PCR. The excretion of TNF-α in monocytes was evaluated by ELISA. The protein expression of Pit-1 was tested by Western Blot.

Results: 1. After exposure of human monocytes to HP (4M), the concentration and mRNA expression of TNF-α was increased (p<0.05 vs. NP). HP also increased the protein and mRNA expression of Pit-1 (p<0.05 vs. NP). Incubation in the presence of PFA (2M) partially prevented the effects of HP (p<0.05 *vs.* HP). 2. The presence of low concentration TNF-α(10pg/ml) alone or supernatants of monocytes alone had no effect of OCF gene expression or mineralization (p>0.05 vs.NP) on HASMCs. HP increased the mRNA and protein expression of OPN and Runx2 (p<0.05 *vs.* NP) and caused mineralization in HASMCs. 3. After exposure to both HP(4M) and TNF-α(10pg/ml) or supernatants, the mineralization and OCF gene expression were markedly increased in HASMCs (p<0.05 vs.HP). Incubation in the presence of PFA (2M) also partially prevented the aforementioned effects (p<0.05 vs.HP) in HASMCs.

Conclusions: We conclude that via Pit-1, hyperphosphate could increase the synthesis and secretion of TNF-α in human monocytes, furthermore accelerating the vascular calcification in HASMCs, which may be the therapeutic target in preventing vascular calcification in MHD patients.

SA-PO871

Fibroblast Growth Factor-23 and Vascular Calcification in Human Atherosclerosis Juan F. Navarro-Gonzalez, Javier Donate, Ernesto Martín-Núñez, Carla M. Ferri, Angel López-Castillo, Alejandro Delgado-Molinos, Nayra Pérez-Delgado, Carolina Hernández-Carballo, Victoria Castro López-Tarruella, Carmen Mora. *Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain.*

Background: Fibroblast growth factor 23 (FGF23) is a phosphaturic hormone implicated in disorders of serum phosphorus concentration and vitamin D, as well as in cardiovascular disease. Vascular calcification (VC) is a significant component of vascular disease and atherosclerosis in chronic kidney disease, with important clinical and outcome implications. However, the role of FGF23 in VC remains controversial. In this study we investigate the relationship between FGF23 and VC in patients with clinical atherosclerotic disease.

Methods: Eighty-six patients (mean age, 69.7±10.3 years; 76% males) undergoing an elective open vascular surgery procedure affecting different vascular territories (carotid, aorta, femoral) were included in this study. Serum intact and C-terminal FGF-23 were measured by ELISA. A rabbit polyclonal anti-FGF-23 antibody (1:250 dilution) was used for immunohistochemistry. Transcripts encoding for FGF-23, RunX-2 and GAPDH (housekeeping gene) were measured by TaqMan real-time quantitative PCR.

Results: VC was present in 35 patients (41%). Serum concentrations of FGF-23, both the intact form and the C-terminal, were significantly higher in patients with VC: 24.2

(12-44) vs. 16.8 (10-26) pg/mL; and 36 (27-93) vs. 31.7 (19-52) RU/mL, respectively (P<0.01). We also determined the expression levels of FGF-23 and RunX-2 genes in vascular samples. Expression levels of both genes were significantly higher in samples with VC (P<0.05). Correlation analysis showed a significant association between vascular expression levels of FGF-23 and RunX-2 (r = 0.74, P<0.01). Finally, FGF-23 immunoreactivity was present in 90% of artery samples obtained from subjects with VC, but only in 56% of samples recovered from patients without VC (P<0.05). In all the samples with positive immunoreactivity for FGF-23, the signal for this factor was detected both intra- and extra-cellularly.

Conclusions: In conclusion, FGF-23 is related to VC in patients with clinical atherosclerosis. These findings suggest that transformation of vascular smooth muscle cells (the main cell type involved in VC process in the renal patient) towards an osteogenic phenotype is associated with the capability of these cells to produce FGF-23.

Funding: Government Support - Non-U.S.

SA-PO872

Premature Vascular Smooth Muscle Cell Ageing Drives Inflammation and Calcification in Children on Dialysis Catherine M. Shanahan,[1] Pilar Sanchis,[1] Yiwen Liu,[1] Chin Yee Ho,[1] Leilani Beltran,[1] David A. Long,[3] Rukshana Shroff.[2] *[1]Cardiovascular Division, King's College London, London, United Kingdom; [2]Nephrology Unit, Great Ormond Street Hospital, London, United Kingdom; [3]University College London, London, United Kingdom.*

Background: Children on dialysis have a cardiovascular mortality risk equivalent to the very elderly in the general population. Medial vascular calcification, an age-associated pathology, is prevalent in these children therefore we investigated whether premature vascular smooth muscle cell (VSMC) ageing might play a role in driving calcification.

Methods: Vessels from children with CKD and controls were harvested at time of surgery and subjected to histological analysis for parameters of ageing. VSMCs grown from these vessels were also phenotyped for calcification propensity and ageing markers including growth capacity, DNA damage, senescence and inflammation. Children with CKD were subjected to vascular phenotyping including pulse wave velocity and spiral CT and these measures were correlated with serum markers of inflammation.

Results: Vessels from children on dialysis showed oxidative DNA damage as well as increased expression of the senescence markers p16 and p21. *In vitro* VSMCs from dialysis patients showed elevated levels of DNA damage, grew poorly and senesced early compared with control VSMCs. DNA damage correlated with increased expression of the osteogenic markers Runx2 and BMP2, and increased calcification in response to elevated levels of calcium (Ca) and phosphate (P). Ca and P treatment induced oxidative DNA damage in CKD vessel rings *ex vivo*, and accelerated VSMC senescence *in vitro*. Cytokine array analysis showed that VSMCs from CKD patients displayed a proinflammatory, senescence associated secretory phenotype (SASP) *in vitro*, and blockade of ATM-mediated DNA damage signalling reduced inflammation. Clinically, children on dialysis showed elevated circulating levels of SASP factors including BMP2, OPG and IL6 and these correlated with increased vascular stiffening and calcification *in vivo*.

Conclusions: Taken together, these data suggest that dysregulated mineral metabolism accelerates VSMC ageing by inducing oxidative DNA damage and premature senescence. In turn, the paracrine SASP promotes osteogenic differentiation, vascular calcification and systemic inflammation suggesting drugs that target DNA damage signalling or senolytics may be therapeutic agents for vascular calcification.

Funding: Private Foundation Support

SA-PO873

Activation of the mTORC1 Pathway by Inflammation Contributes to Vascular Calcification in Patients with ESRD Liu Jing. *Institute of Nephrology, Affiliated Drum Tower Hospital, Medical School of Nanjing University, Nanjing, China.*

Background: Chronic inflammation plays an important role in the progression of vascular calcification (VC). This study was designed to explore the effects and underlying mechanisms of inflammation on VC in the radial arteries of patients with end-stage renal disease (ESRD) with arteriovenostomy.

Methods: Forty-eight ESRD patients were divided into control (n=25) and inflamed groups (n=23) according to plasma C-reactive protein (CRP) level. Surgically removed tissues from the radial arteries of patients receiving arteriovenostomy were used in this study. Alizarin Red S staining was used to examine calcium deposition. The expression of inflammation markers, bone structure-associated proteins and mammalian target of rapamycin complex1 (mTORC1) pathway-related proteins were assessed by immunohistochemical staining.

Results: The expression of tumor necrosis factor-α (TNF-α) and monocyte chemotactic protein-1 (MCP-1) was increased in the radial arteries of the inflammation group. Additionally, Alizarin Red S staining revealed an obvious increase in calcium deposition in the inflammation group compared to that in the control group. Further analysis by immunohistochemical staining demonstrated that the deposition was correlated with the increased expression of bone-associated proteins such as bone morphogenetic proteins-2 (BMP-2) and osteocalcin and collagen I, which suggested that inflammation induces osteogenic differentiation in vascular tissues and that osteogenic cells are the main cellular components involved in VC. Interestingly, there was a parallel increase in the expression of phosphorylated mTOR (p-mTOR) and p-ribosomal protein S6 kinase 1 (p-S6K1) in the inflammation group. Furthermore, mTORC1 pathway-related proteins were significantly associated with the enhanced expression of bone formation biomarkers.

Conclusions: Inflammation contributed to VC in the radial arteries of ESRD patients via the induction of osteogenic differentiation in vessel walls, which could be regulated by the activation of the mTORC1 pathway.

Funding: Government Support - Non-U.S.

SA-PO874

Loss of Secreted Frizzled-Related Protein 5 Contributes to Vascular Calcification in CKD by Activating Non-Canonical WNT Pathway Ji Yong Jung, Ae jin Kim, Han Ro, Jae Hyun Chang, Hyun Hee Lee, Wookyung Chung. *Gachon University Gil Medical Center, Incheon, Republic of Korea.*

Background: Vascular calcification (VC) is frequently accompanied with bone loss in patients with chronic kidney disease (CKD). WNT regulates osteoblast activation through canonical (β-catenin dependent) and non-canonical (-independent) signaling pathways, but a common pathophysiology between the pathways during VC and bone loss still remained a conundrum. Therefore, we hypothesized that VC results from phenotypic conversion of vascular smooth muscle cell (VSMC) into an osteoblast-like cell involves induction of an osteoblast transcriptional program via a non-canonical WNT pathway, while bone loss is mainly regulated by canonical WNT pathway.

Methods: Adenine-induced CKD animal model with VC was induced in male Sprague Dawley rats fed 0.75% adenine (2.5% protein, 0.92% phosphate) and intraperitoneal calcitriol (0.08 μl/kg/day) injection for 4 weeks. In an angiotensin II (3μM)-induced VC in high phosphate milieu (3mM) through its effect on VSMC, the effect of WNT signaling on VC was determined by expression of osteoblastic transcriptional factor (RUNX2), Von Kossa stain and WNT downstream signaling factors.

Results: In mRNA profiler PCR assay of WNT signaling pathway from animal model, secreted frizzled-related protein 4 (sFRP4) were increased, while sFRP5 was decreased than those of control group fed with normal rat chow (0.62% phosphate). From the in vitro study, the protective effect of sFRP5 on VSMC differentiation was mediated through the inhibition of Rho/ROCK and JNK pathways. Moreover, the effect of Rho/ROCK and JNK pathways on sFRP5 repression through VSMC differentiation were aggravated by anisomycin (JNK activator), whereas recovered with SP600125 (JNK inhibitor). Those expressions of RUNX2 and WNT signaling factors in adenine-induced CKD animal model with VC showed in the similar patterns.

Conclusions: Our study suggests that loss of sFRP5 was associated with VC in CKD environment by activating non-canonical WNT pathway, which indicate that sFRP5 may be a new therapeutic target in VC in CKD environment.

SA-PO875

Association between Circulating Osteogenic Precursors and Vascular Calcification in CKD Patients Janaina d. Ramalho,[2] Brygida Bisikirska,[1] Michael T. Yin,[1] Stavroula Kousteni,[1] Rosa M. Moyses,[2] Thomas Nickolas.[1] *[1]Columbia University Medical Center, New York, NY; [2]University of São Paulo, São Paulo, Brazil.*

Background: Vascular calcification (VC) is highly prevalent in CKD patients and is an independent predictor of cardiovascular morbidity and mortality. It has been recognized as an active process mediated by trans-differentiated vascular smooth muscle cells. Previously we found and association between higher frequency of circulating osteogenic precursors (COPS) among peripheral blood mononuclear cells (PBMCs), defined as lineage (LIN)-CD34-osteocalcin(OCN)+RUNX2+ cells, and higher bone strength (stiffness) measured by high-resolution peripheral quantitative computed tomography (HR-pQCT). We aimed to investigate the relationship of COP cells with prevalence and severity of VC in CKD.

Methods: In 53 CKD patients from Columbia University, USA, we compared the distribution of COP cells between those with or without lower leg arterial calcification (LLAC) and wrist arterial calcification (WAC) as assessed by HR-pQCT. LLAC and WAC presence were defined as measurements ≥ 1 mgHA. We evaluated Spearman correlations between COPs (LIN-CD34-OCN+RUNX2+, LIN-CD34-OCN+RUNX2-) and CD34- and endothelial precursor cells (LIN-CD34+KDR+CD133+) and severity of VC.

Results: Mean age was 48 ± 13 years, 71% male. Of 53 with LLAC measurement, 36% had LLAC, and of 49 with WAC measurement, 24,5% had WAC. Percentage of LIN-CD34-OCN+RUNX2- cells among LIN- parental cells was significantly higher in those with than without LLAC (p = 0.04) and WAC (p=0.02). Percentage of LIN-CD34-OCN+RUNX2+ was negatively correlated with WAC (rho = -0.55, p = 0.04). We did not find significant association between endothelial precursor cells and vascular calcification.

Conclusions: Osteocalcin+ COP cells are associated with the presence and severity of vascular calcification assessed by HR-pQCT in CKD patients. The role of COP cells and its association with bone versus vascular disease should be focus of future studies.

SA-PO876

RIPK-Independent Necroptosis Plays Significant Roles in the Progression of Vascular Calcification In Vitro Yu-Chun Chang,[1] Yan Ding,[3] Langjing Zhu,[4] Qinghua Liu,[1] Li-Li Hsiao.[2] *[1]Brigham and Women's Hospital, Boston, MA; [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [3]None, Newton, MA; [4]The Eighth Affiliated Hospital, Sun Yat-sen University, Roxbury Xing, MA.*

Background: Vascular calcification (VC) is a major complication in individuals with chronic kidney disease. A constant inflammatory state remains a key characteristic in the

development of VC. Necroptosis is a programmed form of cell death that results in an inflammatory phenotype. Early descriptions of necroptosis involve phosphorylation of Mlkl by RIPK1/3 signaling. Many studies have shown that necroptosis is a key contributor in various inflammatory diseases, but none in VC. In this study we aim to examine the roles of necroptosis in a model of VC *in vitro.*

Methods: We establish VC by utilizing Human Aortic Smooth Muscle Cells (HA-SMCs) treated with 5mM $CaCl_2$ and β-glycerolphosphate for 7, 14, 21 days. VC was confirmed by Arsenazo III and Alizarin Red Staining and by expression of Klotho and Runx2. Necroptosis is assessed through the expression of Mlkl, phospho-Mlkl, RIPK1, RIPK3 using Western Blot. Pan-caspase inhibitor Z-VAD.fmk (10mM), RIPK inhibitor necrostatin-1 (20mM, 40mM), and Mlkl inhibitor necrosulfonamide (0.5mM, 1mM), were used to assess the effects of necroptosis inhibition.

Results: The VC was confirmed by down regulation of Klotho and up regulation of Runx2. RIPK1 and RIPK3 expression were down regulated in a time-dependent manner in our VC model. The opposite was seen in Mlkl and phospho-Mlkl, indicating the presence of necroptosis in VC. Furthermore, treatment with Mlkl inhibitor, necrosulfonamide, alone displayed a dose-dependent reduction of calcification. Neither Z-VAD.fmk (Pan-caspase inhibitor) nor necrostatin-1 (RIPK inhibitor) resulted in significant changes in calcification.

Conclusions: Calcification of HA-SMCs highlight increased activity of Mlkl, but not RIPK1/3. Inhibition of Mlkl resulted in significant decrease of total degree of calcification, an effect not seen with treatment with necrostatin-1 or Z-VAD.fmk. Our results indicate that RIPK-independent activation of Mlkl may play a significant role in the development of VC. These findings suggest a novel pathway of necroptosis whose inhibition may be a target in the treatment of vascular calcification.

Funding: Private Foundation Support

SA-PO877

OPA1 Disruption Is Involved in the Development of Arterial Calcification in CKD Fengying Guan,[1,2] Junnan Li,[1] Kenneth Lim,[3] Linjing Feng,[1] Yali Zhao,[1] Fei Teng,[1] Li-lun Ho,[2] Thomas F. Hiemstra,[4] Tzongshi Lu,[2] Li Chen.[1] *[1]College of Basic Medical Sciences, Jilin University, , Changchun, China; [2]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [3]Massachusetts General Hospital, Boston, MA; [4]University of Cambridge, Cambridge, United Kingdom.*

Background: Arterial calcification is a significant contributor to cardiovascular disease in patients with Chronic Kidney Disease (CKD). OPA1 is a GTPase of the dynamin family that functions in the mitochondrial inner membrane. It is involved in 1) maintenance of the respiratory chain and membrane potential; 2) cristae organization and control of apoptosis; and 3) stabilization of mitochondrial DNA. OPA1 protect cells from mitochondrial dysfunction by blocking intramitochondrial cytochrome c redistribution, which proceeds remodeling of the cristae in the presence of mitofusin 1 (MFN1). Our preliminary data has shown that OPA1 mediated disruption of mitochondrial dynamics may be involved in β-cell damage in type 2 diabetes. In this study, we investigated the role of OPA1 in human arteries from healthy and CKD patients.

Methods: Human arteries were collected from healthy (n=15) and CKD (n=15) patients. Arterial calcification was analyzed qualitatively by Alizarin Red. Total RNA from human arteries was extracted using the Nucleospin RNA isolation kit. cDNA was synthesized and fragmented using SMART-seq2 and Nextera XT (Illumina), respectively to generate libraries for sequencing on Hi-seq 2000 (Illumina). Five million single-ended raw reads from each sample were mapped to the human reference genome consortium GRCh38 by Burrows-Wheeler Aligner (BWA). Gene analysis were performed by the combinations of fold-changes on log 2 ratio, and p value < 0.05.

Results: Human arteries from CKD patients had extensive medial calcification while arteries from healthy controls did not develop significant calcification. RNA sequencing analysis revealed that OPA1 was significantly downregulated (Fold changes, FC, 2.33) in CKD arteries compared to arteries from healthy patients. CKD arteries had also reduced MFN1 (FC=1.83) and the downstream anti-apoptotic Bcl2 gene (FC=4.52). Both caspase 3 (FC=2.6) and cytochrome c (FC=2.29) expression were significantly increased in CKD arteries compared to control.

Conclusions: Mitochondrial OPA1 and MFN1 dysfunction may be involved in the pathogenesis of accelerated arterial calcification in CKD. Further investigation into the molecular mechanisms are needed.

Funding: Private Foundation Support

SA-PO878

Immune Cell Subsets Related to Vascular Calcification in Hemodialysis Patients Javier Rodriguez-Carrio,[1,2] Mariana Seijo,[1] Catalina Ulloa,[3] Natalia Carrillo-Lopez,[1] Minerva Rodriguez,[3] Ana Suarez,[2] Jorge B. Cannata-Andia,[1,4] Adriana S. Dusso.[1] *[1]Bone and Mineral Research Unit, Hospital Universitario Central de Asturias, Instituto Reina Sofía de Investigación, REDinREN del ISCIII, Oviedo, Spain; [2]Area of Immunology, Department of Functional Biology, Faculty of Medicine, University of Oviedo, Oviedo, Spain; [3]Division of Nephrology, Hospital Universitario Central de Asturias, Oviedo, Spain; [4]Department of Medicine, Faculty of Medicine, University of Oviedo, Oviedo, Spain.*

Background: In CKD patients, inflammation contributes to the disproportionally high incidence of vascular calcification (VC) through immune mechanisms that remain incompletely understood. This study aims to characterize different immune cell subsets related to VC in the context of CKD.

Methods: A group of individuals with normal renal function (n=5) and non-diabetic hemodialysis (HD) patients (n=17), matched by CKD etiology, age and gender but with either none, moderate or severe arterial calcification (Kauppila and Lumbar Spine indexes) were studied for inflammatory and aging markers (flow cytometry) and biochemical parameters of bone and mineral homeostasis.

Results: HD patients exhibited an increased frequency of the senescent $CD4^+CD28^{null}$T-cell subset (p=0.030), which were associated with the degree of VC and negatively correlated with 25-hydroxyvitamin D levels (r=-0.594, p=0.025). Angiogenic T cells ($CD3^+CD31^+CD184^+$), related to vascular homeostasis, were decreased in HD patients (p=0.024), regardless of their degree of VC. The frequency of regulatory T cells (Treg, $CD4^+CD25^{high}CD127^{low/neg}FOXP3^+$) did not differ between HD patients and healthy controls, although they were slightly reduced in patients without VC (p=0.022) compared to those with VC (moderate and severe groups). However, the analysis of cytokine expression may point to a non-regulatory phenotype of Treg in the latter. Additionally, ACE expression was higher in monocytes from HD patients (p=0.020) compared to healthy counterparts. This increase was restricted to intermediate monocytes ($CD14^+CD16^+$), strongly increased in patients (p<0.001), and was found even in patients without VC. ACE expression on intermediate monocytes was negatively associated with vitamin D (r=-0.499, p=0.060) and positively with PTH (r=0.578, p=0.030). Finally, a higher percentage of low-density granulocytes ($CD14^{low}CD15^+$) was observed in CKD (p<0.001).

Conclusions: Several immune cell subsets related to inflammation, immunosenescence and vascular homeostasis are altered in CKD, even in the early stages of VC. Impaired vitamin D levels may be associated with this abnormal immune profile. This study paves the ground for the identification of early biomarkers to identify patients at higher risk of developing VC.

Funding: Government Support - Non-U.S.

SA-PO879

Bone Phenotype in ADPKD Patients with ESRD Pieter Evenepoel,[5] Kathleen Claes,[4] Bert Bammens,[5] Etienne Cavalier,[6] Bjorn Meijers,[5] Peter Stenvinkel,[1] Magdalena Jankowska,[2] Patrick C. D'Haese.[3] *[1]Karolinska University Hospital Huddinge, Stockholm, Sweden; [2]Medical University of Gdansk, Gdansk, Poland; [3]University Antwerp, Edegem, Belgium; [4]University Hospitals Leuven, Leuven, Belgium; [5]University Hospitals Leuven, Leuven, Belgium; [6]University of Liege, CHU Sart-Tilman, Liege, Belgium.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is among the most common hereditary nephropathies and arises as the consequence of mutations in one of two genes, pkd1 or pkd2. PKD1 and PKD2 proteins form a complex on the primary cilium and are thought to play a role in mechanosensation in various cells including osteocytes. Preliminary data showed increased sclerostin levels suggesting impaired mechanosensation in ADPKD patients with end stage renal disease (ESRD). A bone phenotype of reduced bone mass and turnover has been reported in mice with targeted disruption of pkd1 and normal kidney function. The aim of the present post-hoc analysis was to compare the bone phenotype between ADPKD patients with ESRD to non-ADPKD controls.

Methods: Laboratory parameters of mineral metabolism including FGF23 (Kainos) and sclerostin (Tecomedical), bone turnover markers (all IDS iSYS) and bone mineral density (BMD, by dual energy x-ray absorptiometry, DXA) were assessed in 518 renal transplant candidates (ADPKD, n=99), with also bone biopsy data available in a subset of patients (n=71).

Results: Circulating sclerostin levels were significantly higher in ADPKD patients (2.20 vs 1.84 ng/L, p=0.001). Circulating levels of bone alkaline phosphatase (17.4 vs 22.6 ng/mL, p<0.0001) and tartrate-resistant acid phosphatase 5b (4.65 vs 5.46 U/L, p=0.006) were significantly lower in ADPKD, as were histomorphometric parameters of bone formation (e.g. Ob.Pm/T.Pm p=0.04). Associations remained after adjustment for classical determinants (e.g. PTH, age, gender …) in regression analysis. Histomorphometric parameters of bone mineralization were numerically higher in ADPKD (e.g. O.Pm/B. Pm, p=0.06). DXA showed better preserved BMD in skeletal sites rich in cortical bone (Z-score radius 1/3 -0.04 vs -0.14, p<0.0001; femoral neck -0.72 vs -1.02, p=0.01).

Conclusions: Our data confirm a distinct bone phenotype in ADPKD patients with ESRD, characterized by high sclerostin levels, depressed bone turnover and preserved areal bone mineral density in skeletal sites rich in cortical bone.

SA-PO880

Bone Disease Characterization in a Portuguese Predialysis Cohort Ricardo Neto,[2,1] Luciano Pereira,[2,1] João Frazão.[2,1] *[1]Nephrology and Infectious Diseases Research and Development Group, INEB-(I3S), Porto, Portugal; [2]Centro Hospitalar São João, Porto, Portugal, Porto, Portugal.*

Background: Renal osteodystrophy (ROD) is an early and common complication of chronic kidney disease (CKD). Histomorphometry is the gold-standard diagnostic tool for ROD, but there is little data on bone histological changes in pre-dialysis patients. Most studies are old and results are inconsistent. We report the results of bone biopsies performed on a cohort of Portuguese pre-dialysis patients.

Methods: Transiliac bone biopsy after double tetracycline labelling was performed on 35 consecutive patients enrolled in our pre-dialysis clinic. Inclusion criteria were age between 18 and 80 years old and glomerular filtration rate between 15 and 60 mL/min/1.73 m^2. Patients were excluded if they were on calcium salts, any form of vitamin D, steroids or bisphosphonates. KDIGO TMV classification was used to characterize biopsy results. Clinical and biochemical data were recorded at the time of biopsy.

Results: Four patients (11.4%) were excluded due to inadequate bone sample. Thirty-one biopsies were therefore analyzed. Twenty-two patients (70.9%) were male. Mean age was 67.3 ± 8.1 years. Mean serum creatinine and glomerular filtration rate were 2.2 ± 0.4 mg/dL and 27.6 ± 7.0 mL/min/1.73 m2, respectively. Mean serum calcium, phosphorus, intact parathyroid hormone (iPTH) and native vitamin D (VD) levels were 9.0 ± 0.5 mg/dL, 3.5 ± 0.6 mg/dL, 140.6 ± 130.2 pg/mL and 17.8 ± 11.9 ng/mL, respectively. Twenty-four patients (77.4%) had normal bone histology, 3 (9.7%) had adynamic disease, 3 (9.7%) had mild hyperparathyroid disease and one (3.2%) had mixed uremic osteodystrophy. No cases of osteomalacia were found. Except for mineralization lag time and bone volume, histomorphometric parameters did not significantly differ between histological classes. Despite a trend for higher iPTH with rising bone formation rate, levels did not significantly differ between groups.

Conclusions: In a contemporary Portuguese pre-dialysis cohort, roughly 3/4 of the patients had normal bone histology, one tenth had adynamic bone disease and another tenth had mild hyperparathyroid disease. There was one case of mixed disease and none of osteomalacia. Our results also suggest that biochemical testing are not predictive of histological findings, thus highlighting the importance of bone biopsy as the gold-standard tool to evaluate ROD. Further histomorphometric studies are needed to enlighten the spectrum of ROD in pre-dialysis CKD.

SA-PO881

HIV/AIDS Is Associated with Bone Histomorphometric Abnormalities before Antiretroviral Therapy Janaina d. Ramalho,[2] Carolina S. Martins,[3] Juliana C. Galvão,[4] Rosa M. Pereira,[2] Thomas Nickolas,[1] Michael T. Yin,[1] Luciene dos Reis,[2] Vanda Jorgetti,[3] Rosa M. Moyses.[2,4] *[1]Columbia University Medical Center, New York, NY; [2]Faculdade de Medicina da Universidade de Sao Paulo, Sao Paulo, Brazil; [3]Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil; [4]Universidade Nove de Julho, São Paulo, Brazil.*

Background: The reduction in bone mineral density (BMD) is a known metabolic complication of antiretroviral therapy (ART), especially tenofovir, which may cause tubular dysfunction, excess phosphaturia and osteomalacia. Low BMD and increased fracture risk, however, has been recognized in patients with HIV/AIDS even before treatment initiation. We aimed to identify and describe abnormalities in bone histomorphometry in ART-naïve HIV patients.

Methods: In 20 male patients with HIV infection, ART-naïve, we evaluated bone structure, turnover and mineralization by iliac crest bone biopsy with histomorphometry. Main exclusion criteria were eGFR < 60ml/min/1,73m², metabolic bone disease, cirrhosis, diabetes, and medications affecting bone metabolism. HIV viral load and CD4+ T cell count (CD4) were determined. Serum 25 vitamin D (25vitD), PTH and RANKL levels were measured. BMD was assessed by DXA.

Results: Mean age was 29.6 ± 5.5 years, mean BMI was 24.7 ± 2.4, median time since diagnosis of HIV infection was 87 (71 – 231) days, with median viral load of 29,945 (IQR 5,485 – 53,118) copies/mL and mean CD4 of 375 ± 200 cells. Mean 25vitD was 22.3 ± 7.9 ng/ml and PTH was within reference range in all patients. RANKL levels correlated positively with HIV viral load (r = 0.48, p = 0.04) and negatively with CD4 (r -0.65, p =0.003). Three patients (15%) had low BMD (Z score ≤ -2) at any site. By histomorphometry, 20% had low bone trabecular volume and 25% had decreased cortical thickness, whereas cortical porosity was normal in all of them. Decreased bone formation rate was seen in 80% and abnormal mineralization was detected in 60%. Increased osteoclastic and eroded surface were seen in 40 and 30%, respectively.

Conclusions: Abnormalities in bone volume, turnover and mineralization are common among HIV-infected persons, especially decreased formation and mineralization, even before ART exposure. Immune dysregulation, mediated by abnormalities in RANKL levels, may contribute. Further study is necessary to determine which factors (immunologic, hormonal or others) predict greater bone loss with ART initiation.

Funding: Government Support - Non-U.S.

SA-PO882

The Trabecular Bone Score as a Tool to Assess Bone Microarchitecture in CKD Janaina d. Ramalho,[3] Igor Marques,[6] Vanda Jorgetti,[5] Rosa M. Moyses,[4] Didier Hans,[2] Thomas Nickolas.[1] *[1]Columbia University Medical Center, New York, NY; [2]Lausanne University Hospital - CHUV, Lausanne, Switzerland; [3]None, Sao Paulo, Brazil; [4]Universidade Nove de Julho, São Paulo, Brazil; [5]Universidade de Sao Paulo, Sao Paulo, Brazil; [6]University of Sao Paulo School of Medicine, Sao Paulo, Brazil.*

Background: Recent studies have demonstrated that low bone mineral density (BMD) by dual energy X-ray absorptiometry (DXA) predicts fractures in CKD patients. However, as bone strength reflects the integration of both BMD and bone quality, BMD only partially describes fracture risk. The Trabecular Bone Score (TBS) is a novel clinical tool that uses grayscale variograms of the lumbar spine image from DXA to assess bone quality and fracture risk. Its ability to assess trabecular (Tb) bone quality has been validated against bone biopsy in the general population but not in CKD. We hypothesized that TBS would reflect Tb bone quality at the iliac crest in CKD patients.

Methods: In 52 CKD patients from Columbia University, USA and University of Sao Paulo, Brazil, we determined Spearman correlations controlling for age between TBS and bone microarchitecture assessed by both high-resolution peripheral quantitative computed tomography (HR-pQCT) at the radius and tibia and iliac crest bone histomorphometry.

Results: Mean age was 50.4 ± 15.5 years, 35 (67%) were on dialysis; 25%, 18% and 13% had T-Scores ≤ -2.5 at spine, femoral neck and total hip respectively. Mean TBS was 1.29±0.13 (normal TBS ≥1.35). Correlations between TBS and microarchitectural parameters are shown in Table.

Conclusions: TBS reflects Tb microarchitecture from bone biopsy and Ct and Tb microarchitecture from HR-pQCT. TBS may be a useful tool in the clinic to assess bone quality and fracture risk in CKD patients.

Funding: Other NIH Support - K23DK080139, Government Support - Non-U.S.

Partial Spearman Correlations

Histomorphometry	
BV/TV	0.55 (p < 0.001)
TbWidth	0.53 (p < 0.001)
TbN	0.18 (p = 0.24)
TbSp	-0.21 (p = 0.17)
CtWidth	-0.16 (p = 0.30)
CtPo	-0.21 (p = 0.18)
Radius HR-pQCT	
Total density	0.37 (p = 0.01)
Ct density	0.18 (p = 0.24)
Tb density	0.43 (p = 0.003)
CtTh	0.31 (p = 0.04)
TbN	0.13 (p = 0.40)
TbTh	0.43 (p < 0.004)
TbSp	-0.17 (p = 0.28)
Tibia HR-pQCT	
Total density	0.18 (p = 0.23)
Ct density	0.19 (p = 0.21)
Tb density	0.29 (p = 0.05)
CtTh	0.26 (p = 0.08)
TbN	0.28 (p = 0.06)
TbTh	0.14 (p = 0.36)
TbSp	-0.29 (p = 0.05)

BV/TV trabecular bone volume, Th thickness, N number, Sp separation, Po porosity

SA-PO883

Clinical Characteristics of Susceptible Factors and Nutritional Status in 576 Secondary Hyperparathyroidism Patients Undergoing Parathyroidectomy Ningning Wang,[1] Yao Jiang,[3] Guang Yang,[1] Chang Ying Xing,[2] Xiaoming Zha.[4] *[1]Department of Nephrology, The First Affiliated Hospital with Nanjing Medical University, Nanjing, China; [2]First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [3]Nanjing Medical University, Nanjing, China; [4]First Af?liated Hospital with Nanjing Medical University, Nanjing, China.*

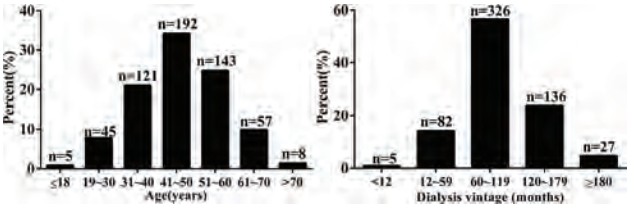
Background: Secondary hyperparathyroidism(SHPT) is a common complication of chronic kidney disease-mineral and bone disorder(CKD-MBD). Parathyroidectomy(PTX) is the prior therapy for severe SHPT, however, few large samples studies on predisposing factors and nutritional status of severe SHPT were explored. We aim to analyze the characteristics of high risk group and summarize the nutritional status of CKD patients with PTX.

Methods: Clinical data of 576 PTX patients were collected and grouped according to the age and dialysis vintage.

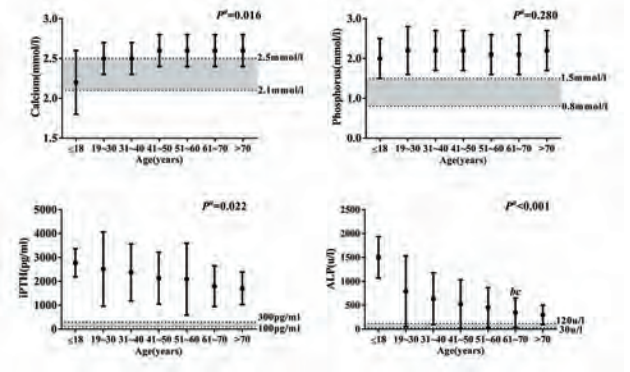
Results: There were 55.9% males and the mean age of all PTX patients were (46.4±11.3) years. The major cause of CKD was chronic glomerulonephritis (91.5%). Severe SHPT was more common in middle aged patients with long hemodialysis vintage (Fig 1). Levels of serum intact parathyroid hormone(iPTH) were gradually reduced from young age group to old age group(Fig2). The levels of BMI were (21.9±3.5) kg/m², which was negative correlated with serum iPTH levels. Serum albumin in each age group was lower than the reference range, and in age groups of ≤18 and >70 years old were lower than the other groups.

Conclusions: Susceptible factors of severe SHPT include middle age, chronic glomerulonephritis and long hemodialysis vintage. Focused surveillance and timely treatment for mild or moderate SHPT patients with risk factors are suggested. The elderly and juveniles severe SHPT patients may have more serious malnutrition and higher operation risk. We recommend personalized diagnosis and treatment strategy for CKD-MBD patients.

Funding: Government Support - Non-U.S.



PTX patients were grouped according to the age and dialysis vintage.



Characteristics of blood bone metabolic indices in different age groups.

SA-PO884

Parathyroidectomy (PTX), KDOQI Targets, PTH Lowering Therapies, and Mortality in a Cohort of Italian Dialysis (D) Patients: A Multicenter Observational Study Sandro Mazzaferro. *Sapienza University of Rome, Rome, Italy. Group/Team: On behalf of Italian Study Group of Mineral Metabolism*.

Background: PTX might improve survival by improving biochemical control.

Methods: We prospectively collected data of 528 prevalent PTX cases (age: 57.63 ±12.52 y.o; D time: 14.63±8.37 y; M/F: 44/56%) from 149 D units in Italy, out of 12515 patients on D (=4,2%) and evaluated KDOQI targets, therapies and survival. Control cases (n=418, nested case-control selection) were balanced for sex (45/55%) but not age (60.30±14.36 y.o, p<.01) or D duration (11.2±7.3 y; p<.001).

Results: PTX cases were at lower KDOQI targets for Ca (50 vs 57 %; p<.05) and PTH (19 vs 37%; p<.001) and received more calcitriol and Ca-based phosphate binders and less calcimimetic than controls. Also PTX cases included in the follow-up were less frequently at target for PTH and were confirmed to receive more calcitriol and Ca-based phosphate binders and less calcimimetic than controls (table 1). Univariate analysis adjusted for D age, showed lower HR of mortality for PTX (0.556, CI:0.387-0.800, p=.002), albumin (0.327; CI:0.249-0.555, p=.000) and hemoglobin (0.672, CI:0.558-0.810, p=.000). Multivariate analysis confirmed PTX (HR 0.679, CI:0.465-0.970, p<.05), age (HR 1.043, CI 1.014-1.055, p<.001) and D duration (HR 1.034, CI 1028-1059, p<.001) as independent predictors of mortality. Albumin inclusion in the model excluded PTX (p=0.065). Indeed, PTX cases had higher albumin levels than controls (3.8±0.4 vs 3.6±0.4; p<.01).

Conclusions: PTX associates with lower risk of mortality regardless of PTH control and despite "more risky" therapy. As a toxin, PTH could negatively affects serum albumin.

Funding: Commercial Support - Amgen

Table. 1 Prevalences of therapies during follow-up

		PTX	Control group	P
1° year	n.	257	418	
	Ca based phosphate binders	65.7%	36.0%	<.001
	Calcitriol	58.0%	44.3%	<.05
	Calcimimetic	14.0%	34.0%	<.001
2° year	n.	221	295	
	Ca based phosphate binders	67.0%	40.7 %	<.001
	Calcitriol	57.0%	28.8 %	<.001
	Calcimimetic	22.0%	39 %	<.001
3° year	n.	183	230	
	Ca based phosphate binders	68.0%	38.0%	<.001
	Calcitriol	57.0%	25%	<.001
	Calcimimetic	16.0%	41.0%	<.001
4° year	n.	132	144	
	Ca based phosphate binders	62.0%	33.0%	<.001
	Calcitriol	61.0%	20.8%	<.001
	Calcimimetic	19.0%	39.0%	<.001

Table 1

SA-PO885

Effects of Vitamin D Supplementation on Markers of Bone and Mineral Metabolism in Pediatric Patients with Early and Late CKD Dieter Haffner,[2] Christian Lerch,[2] Franz S. Schaefer,[3] Rukshana Shroff.[1] *[1]Renal Unit, Great Ormond Street Hospital for Children, London, United Kingdom; [2]Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School Children's Hospital, Hannover, Germany; [3]Division of Pediatric Nephrology, University Children's Hospital Heidelberg, Heidelberg, Germany. Group/Team: ESPN CKD-MBD working group and 4C Study consortium*.

Background: Recent research findings suggest that vitamin D may have PTH independent effects on the regulation of bone and mineral metabolism. We investigated the effects of vitamin D supplementation on circulating fibroblast growth factor 23 (FGF23), Klotho, and sclerostin levels in two pediatric cohorts with early and late CKD.

Methods: Eighty vitamin D deficient children were selected: 40 with early CKD from the ERGO Study, a randomized placebo-controlled trial of ergocalciferol supplementation in children (mean eGFR 55 ml/min/1.73m^2), and 40 with advanced CKD from the observational 4C Study (eGFR 24 ml/min/1.73m^2, p<0.01). In each study 20 children received vitamin D supplementation, and 20 age and eGFR-matched children not on vitamin D served as controls. Z-scores (SDS) were calculated for serum levels of Klotho, FGF23, and sclerostin, at baseline and after a median period of 8 months.

Results: Untreated patients in the ERGO study had normal FGF23 (0.31 SDS) but decreased levels of klotho (-0.77 SDS) and sclerostin (-1.04 SDS), whereas untreated children in the 4C cohort had increased FGF23 (3.87 SDS) and sclerostin (0.76 SDS), but normal klotho (-0.27 SDS) levels. Vitamin D supplementation further increased FGF23 levels in 4C but not in ERGO patients. Serum klotho and sclerostin normalized during vitamin D supplementation in ERGO but remained unaffected in 4C patients. In the whole cohort significant differences between vitamin D treated patients and controls were noted for Klotho at eGFR 40-70 ml/min/1.73 m^2 and for sclerostin at eGFR 60-70 ml/min/1.73 m^2. 25-hydroxyvitamin D levels >75nMol/L was independently associated with the changes in Klotho and sclerostin levels.

Conclusions: Vitamin D supplementation normalizes Klotho and sclerostin levels in vitamin D deficient children with early CKD, but further increases FGF23 levels in vitamin D deficient children with advanced CKD.

SA-PO886

Bone Disease Post Kidney Transplantation – Beyond Bone Mineral Density Ashish K. Sharma,[1,3] Nigel D. Toussaint,[1,3] Stephen G. Holt,[1,3] Grahame J. Elder,[1,1] Paul A. Baldock,[1] Kiara Honma,[2] Chamith S. Rajapakse,[2] Rosemary Masterson.[1,3] *[1]The Royal Melbourne Hospital, Parkville, VIC, Australia; [2]University of Pennsylvania, Philadelphia, PA; [3]Department of Medicine (RMH), University of Melbourne, Parkville, VIC, Australia*.

Background: Post-transplant bone disease in kidney transplant recipients (KTRs) is traditionally characterised by severe loss of bone mineral density (BMD) and increased fracture risk. Recent studies have shown less dramatic decrease in BMD at various skeletal sites. Bone microarchitecture changes post-transplant are not well defined and cannot be accurately evaluated with bone biomarkers and dual energy x-ray absorptiometry (DXA). Bone biopsy is invasive and infrequently performed. We longitudinally evaluated changes in BMD, microarchitecture and biomarkers post kidney transplantation, using high-resolution magnetic resonance imaging (MRI, distal tibia), peripheral quantitative computed tomography (pQCT, radius), DXA and biomarkers of mineral metabolism.

Methods: Twelve adult live donor KTRs (mean age 49+/-10.96, 66% M) underwent MRI, pQCT and DXA (hip, spine) at baseline and 12 months post transplantation. Laboratory testing was performed at baseline, 6 and 12 months.

Results: Compared with baseline, 12-month MRI (tibia) showed deterioration in indices of trabecular network integrity - surface to curve ratio (S/C, -15%, p=0.042) and erosion index (EI, +19%, p=0.005). Changes were also seen in cortical thickness (+4.6%, p=0.0269) and cortical area (+11.5%, p=0.03). Numerical changes in areal BMD and volumetric BMD were not statistically significant. Interval changes in S/C and EI correlated with total hip T-score (DS/C; r= 0.70, p=0.01 & EI; r=-71, p=0.009) and trabecular vBMD at radius (DS/C; r= -0.68, p=0.015 & DEI; r=71, p=0.009). There was no significant difference in serum calcium, but PTH and phosphate levels decreased after 12 months (-80.5%, p=0.03 & -49.3%, p<0.001 respectively). Changes in PTH were inversely predictive of BMD at the lumbar spine (r=-0.58, p=0.04) and femoral neck (r=-0.69, p=0.014) but were unrelated to cortical parameters.

Conclusions: Post-transplantation, there was deterioration in trabecular bone quality and network without significant changes in trabecular volume, structural parameters and BMD at central or peripheral sites. The preservation of cortical structure in our cohort is differs from recent studies and highlights the heterogeneous nature of histologic changes and multifactorial pathology of post-transplant bone disease.

Funding: Commercial Support - AMGEN

SA-PO887

Deterioration of Cortical Bone Microarchitecture in Renal Osteodystrophy – Under-Represented in the "Turnover Mineralisation Volume" (TMV) Classification? Ashish K. Sharma,[1,3] Nigel D. Toussaint,[1,3] Stephen G. Holt,[1,3] Alyssa J. Johncola,[2] Chamith S. Rajapakse,[2] Rosemary Masterson,[1,3] Grahame J. Elder,[1,5] Paul A. Baldock.[5] *[1]The Royal Melbourne Hospital, Parkville, VIC, Australia; [2]University of Pennsylvania, Philadelphia, PA; [3]Department of Meidicne (RMH), University of Melbourne, Parkville, VIC, Australia; [5]Garvan Institute of Medical Research, Darlinghurst, NSW, Australia*.

Background: Cortical bone contributes significantly to mechanical strength of bone and its deterioration is associated with non-vertebral fractures. Recent imaging and histomorphometric studies demonstrate prevalence of thin cortices and increased cortical porosity in CKD which may have diagnostic and therapeutic implications. Changes in bone microarchitecture as measured by TMV classification do not completely reflect deterioration in cortical parameters. We evaluated trabecular and cortical bone microarchitecture in patients with chronic kidney disease (CKD) by classical histomorphometry and microcomputed tomography (mCT) of iliac crest biopsies

Methods: Iliac crest bone biopsies were performed in 14 patients undergoing kidney transplantation (n=12) and parathyroidectomy (n=2). Trabecular structural parameters

were analyzed by histomorphometry and 3D mCT and included trabecular bone volume, thickness, number and separation. Cortical thickness (CtTh) and porosity (CtPo) were measured by 3D mCT. Bone mineral density (BMD) was measured by peripheral quantitative CT (radius) and dual energy x-ray absorptiometry. Associations were determined by analysis with Spearman's rank correlation coefficients.

Results: Trabecular parameters from bone biopsy were within normally accepted ranges in most patients. In contrast, all patients showed decreased CtTh (mean thickness; 30 +/- 40 μm) and significantly increased CtPo (60.31 +/- 22.53%) at the iliac crest. CtPo was unrelated to turnover status but demonstrated positive relationship with PTH levels (r=0.62; p=0.021) and was inversely related to trabecular thickness (r=-0.60; p=0.024) at the iliac crest and cortical area (r=-0.59; p=0.045) at the radius. CtTh was also associated with lumbar spine (r=-0.72; p=0.013) and femoral neck BMD (r=-0.55; p=0.07)

Conclusions: Marked deterioration of cortical microarchitecture in the setting of relatively normal trabecular parameters in our cohort reinforces the importance of comprehensive cortical bone evaluation in CKD.

Funding: Commercial Support - AMGEN

SA-PO888

FRAX® Predicts Fracture Risk in Patients with CKD Reid Whitlock,[2] William Leslie,[1] James A. Shaw,[2] Claudio Rigatto,[2] Paul Komenda,[2] David T. Collister,[2] Navdeep Tangri.[2] *[1]St Boniface General Hospital, Winnipeg, MB, Canada; [2]University of Manitoba, Winnipeg, MB, Canada.*

Background: FRAX® was developed to predict fracture risk in the general population but its applicability to patients with chronic kidney disease (CKD) is unknown.

Methods: Using the Manitoba Bone Mineral Density (BMD) Database, we identified adults not receiving dialysis services with serum creatinine measurements and bone densitometry within 1 year between 2005-2010. Estimated glomerular filtration rate (eGFR) was calculated using the *Chronic Kidney Disease* Epidemiology Collaboration equation. Incident major osteoporotic fractures (MOF) and hip fractures were ascertained from population-based healthcare databases. The performance of FRAX, derived without and with BMD, was studied in relation to CKD stage.

Results: We studied N=10,099 subjects (mean age 64 ± 13 y), including N=2154 with GFR 30-60 mL/min/1.73 m^2 (CKD stage 3) and N=590 with GFR <30 mL/min/1.73 m^2 (CKD stages 4-5). During a 5 year observation period, there were 772 individuals with an incident MOF and 226 with incident hip fractures. In Cox proportional hazards models, FRAX predicted risk for MOF and hip fracture in all eGFR strata. For every standard deviation increase in FRAX score derived with BMD, the HR for hip fracture was 4.54 (95% CI 3.57-5.77) in those with eGFR ≥ 60 mL/min/1.73m2, 4.52 (95% CI 3.15-6.49) in individuals with eGFR 30-60 mL/min/1.73m2, and 3.10 (95% CI 1.80-5.33) in individuals with eGFR <30 mL/min/1.73m2. HRs for MOF were lower than the equivalent hip fracture HRs in all eGFR categories, but greater for MOF in those with moderate and severe reductions in eGFR (FRAX*eGFR interaction P≤0.001)

Conclusions: FRAX stratifies fracture risk in patients with moderate to severe CKD as well as in those with preserved eGFR. These findings support the use of the FRAX score to risk stratify patients with CKD for hip and major osteoporotic fractures.

Funding: Government Support - Non-U.S.

SA-PO889

Relationships between Vitamin D and Bone Formation and Mineralization in Adults and Children with Pre-Dialysis CKD Thomas Nickolas,[1] Renata C. Pereira,[7] Maria Coco,[4] Joachim H. Ix,[6] Michel Chonchol,[8] James M. Pullman,[3] Stuart M. Sprague,[5] Isidro B. Salusky.[2] *[1]Columbia University Medical Center, New York, NY; [2]Mattel Children's Hospital, Los Angeles, CA; [3]Montefiore Medical Center, Bronx, NY; [4]Montefiore Medical Center, Bronx, NY; [5]NorthShore University HealthSystem University of Chicago Pritzker School of Medicine, Chicago, IL; [6]UCSD, San Diego, CA; [7]University of California, Los Angeles, CA; [8]University of Colorado, Aurora, CO. Group/Team: Kidney Disease Bone Biopsy Working Group.*

Background: The Institute of Medicine (IOM) recommends levels of 25-hydroxyvitamin D (25D) >20ng/mL to optimize bone quality for the general population. In contrast, optimal 25D levels in adults and children with pre-dialysis CKD have not been established. We used bone-tissue level data to investigate the 25D level that is associated with optimal turnover and mineralization in adult and pediatric patients with pre-dialysis CKD.

Methods: From Columbia University, Montefiore Medical Center, NorthShore University and UCLA, we pooled iliac crest bone biopsies with tetracycline double labeling and quantified relationships between 25D and 1,25-dihydroxyvitamin D (1,25D) and histomorphometry in 25 adults and 31 children with CKD. Spearmen correlations were adjusted for kidney function (CKD-EPI in adults; Schwartz Formula in children). To determine 25D levels that optimized bone formation and mineralization we used receiver operator curve (ROC) analysis and defined high turnover renal osteodystrophy (ROD) as bone formation or mineralization in the upper tertile of respective adult and pediatric populations.

Results: In adults, mean±SD age and GFR were 63±14yrs and 27±18mL/min, respectively, and levels of 25D and 1,25D were 28±17ng/mL and 34±20pg/mL, respectively. 25D was inversely correlated with bone formation rate (BFR; r -0.47, p0.02) and mineralizing surface (r -0.48, p0.02), and 1,25D was inversely correlated with osteoid surface (r -0.54, p0.006). In ROC analysis, 25D levels ≥35ng/mL provided 100% specificity of both non-high turnover and normal mineralization rates and no patient had high turnover ROD. In contrast, >60% of patients with 25D <35ng/mL had high turnover ROD. In children, age and GFR were 14±4yrs and 50±21mL/min respectively and levels of 25D and 1,25D were 27±7ng/mL and 33±14pg/mL, respectively. 25D did not correlate with histomorphometry, but 1,25D was positively correlated with BFR (r 0.41, p0.02) and mineral apposition rate (r 0.46, p0.01).

Conclusions: Relationships between 25D and 1,25D and bone differ in adult and pediatric CKD patients. In adults, 25D levels that are greater than the IOM recommendations may be needed to optimize bone quality. In children, 1,25D may have more of an effect on bone quality than 25D. Larger studies will further explore these findings.

Funding: NIDDK Support

SA-PO890

Risk Factors of Fractures in Patients with Stage 3 CKD: Analysis of CARTaGENE Louis-Charles Desbiens,[1] Remi Goupil,[2] Francois Madore,[2] Aboubacar Sidibé,[1] Fabrice Mac-Way.[1] *[1]CHU de Québec Research Center, Faculty of Medicine, Laval University, Quebec City, QC, Canada; [2]Hopital du Sacre-Coeur de Montreal, Montreal, QC, Canada.*

Background: The association between end-stage renal disease and increased fracture risk is well described. However, whether mild chronic kidney disease (CKD) is also associated with higher fracture risk is poorly known. We aimed to determine if mild CKD increases fracture risk vs general population. Secondary objectives were to evaluate whether bone mineral density (BMD) is associated with fracture and to compare the risk factors of fractures in mild CKD vs general population.

Methods: Cross-sectional, retrospective study of the CARTaGENE cohort, a large health population-based survey of 40 to 69 years old individuals from province of Quebec (Canada). Patients with CKD stage 3 (eGFR between 30 and 60 ml/min/1,73m^2) were compared to controls (eGFR > 60 ml/min/1,73m^2). Self-reported fractures were classified as osteoporotic (femur, hip, rib, vertebra, wrist, pelvis, sacrum) or total fractures. Fracture risk was adjusted for baseline demographic, clinical, pharmacological and biochemistry parameters using multivariate logistic regression. Stepwise multivariate regressions stratified for CKD were performed to evaluate risk factors of fractures.

Results: 17,614 patients without anti-resorptive therapy had available data on fractures and BMD (656 CKD and 16,958 controls). CKD patients (mean eGFR 53±6 ml/min/1,73m^2) were older, had more diabetes, cardiovascular disease, hypertension, smokers and a lower BMD t-score. Total but not osteoporotic fracture risk was higher in CKD patients, but remained similar when stratified by age group and after adjustments for covariables. In multivariate stepwise models, BMD t-score and use of benzodiazepines were associated with total fracture in both groups. Total cholesterol levels and mean blood pressure were associated with fracture in CKD while age, smoking and body mass index were associated with fracture in control group.

Conclusions: Stage 3 CKD patients have a similar fracture risk but different risk factors for fracture vs general population. Our results suggest that bone pathology in CKD is different from the general population even at early stages of CKD.

Funding: Government Support - Non-U.S.

SA-PO891

Relation of Dietary Acid Load to Bone Mineral Density (BMD) and Osteoporosis in Early CKD Tanushree Banerjee,[5] Chi-yuan Hsu,[4] Austin G. Stack,[2] Nilka Rios Burrows,[1] Rajiv Saran,[6] Neil R. Powe.[3] *[1]Centers for Disease Control and Prevention, Atlanta, GA; [2]Graduate Entry Medical School, University of Limerick, Limerick, Ireland; [3]Priscilla Chan and Mark Zuckerberg San Francisco General Hospital & University of California SF, San Francisco, CA; [4]University of California San Francisco, San Francisco, CA; [5]University of California, San Francisco, San Francisco, CA; [6]University of Michigan, Ann Arbor, MI.*

Background: Acidosis is buffered by bone leading to the release of calcium and bone resorption. High dietary acid load (DAL) may contribute to low BMD with studies in the general population showing inconsistent results. Inconsistencies may be due to lack of consideration of protein intake in the etiology of bone loss. Further, it has not been explored whether high DAL is associated with a decrease in bone turnover in chronic kidney disease (CKD). We investigated the association between DAL and BMD/osteoporosis by gender in early CKD and explored whether higher protein intake modifies these associations.

Methods: We studied 1,580 participants aged>=20 years with early CKD (stages 1 and 2) from 1999-2006 National Health and Nutrition Examination Survey. Nutrient intake from 24-hour recall was used to calculate net endogenous acid production (NEAP) and potential renal acid load (PRAL) (mEq/d). BMD measurements were made at the lumbar spine or pelvis and osteoporosis was defined as a T-score≤−2.5 standard deviation. Linear and logistic regression analyses explored associations between energy-adjusted NEAP or PRAL and BMD (including osteoporosis) after adjustment for demographics, weight, height, physical activity, smoking, alcohol, estrogen use, total calories, dietary magnesium and calcium, eGFR, and protein intake.

Results: Mean age in men and women was 52.5±0.7 and 49.7±0.8 yrs. Among men, a statistically significant inverse association was observed between PRAL with either pelvis or lumbar BMD (β[95% CI]:-0.03[-0.05,-0.01],-0.12[-0.14,-0.09], respectively) as well as with NEAP (-0.03[-0.06,-0.003],-0.13[-0.15,-0.10], respectively). When adjusted for protein intake, the association was positively modified between PRAL or NEAP with BMD (all p>0.05). In women, PRAL was positively associated with pelvis BMD (0.03[0.01-0.06]) but not with lumbar BMD. NEAP was positively associated with both pelvis and lumbar BMD and was inversely modified by protein intake. Neither PRAL

nor NEAP associated with osteoporosis and further adjustment for protein intake did not modify these null associations.

Conclusions: DAL was associated with reduced BMD in men and was positively associated with BMD in women. Protein intake modified the association in both genders. Additional studies could help explain the reasons underpinning these gender differences.

Funding: NIDDK Support, Other U.S. Government Support

SA-PO892

Advanced Glycation End-Products (AGEs) Is Associated with Vascular Calcification and Osteoporosis in CKD Patients

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Background: Chronic kidney disease (CKD) is associated with mineral and bone disorder (MBD) and cardiovascular disease (CVD). Advanced glycation end-products (AGEs) contribute to these complications and their tissue accumulation can be indirectly measured through skin autofluorescence (sAF) by AGE-Reader™.

Methods: To investigate the relations between AGEs intake, tissue and serum AGEs levels with CVD and MBD parameters in CKD patients stages 3-4 and in peritoneal dialysis (PD), clinical and observational study with healthy subjects (N=37) and patients distributed in 2 groups: CKD stages 3-4 (N=20) and PD (N=28). Clinical and laboratorial parameters, ankle-brachial index (ABI), AGEs-sAF levels and AGEs intake were analyzed. In addition, CKD patients performed hip, hands and lateral abdomen radiographs for investigation of vascular calcification (VC), echocardiogram, bone densitometry and serum carboxymethyllysine (CML) levels assay.

Results: AGEs-sAF was increased in CKD 3-4 and PD patients compared to the healthy subjects (3.05±0.6 *vs.* 2.4±0.4; p<0.05), despite similar AGEs intake (10.118±4.760 *vs.* 11.942±5.581; p>0.05). There are no differences in AGEs-sAF levels between CKD3-4 and PD patients (3.04±0.6 *vs.* 3.06±0.7; p=0.9); AGEs-sAF levels were positively correlated with interventricular septum (R=0.36; p=0.02), age (R=0.56; p=0.0001) and negatively correlated with the T *score* from bone densitometry (R=-0.36; p=0.03). In addition, AGEs-sAF levels were higher in patients with VC [N=14 (31%)] (3.4±0.5 *vs.* 2.8±0.5; p=0.01) and among patients with osteoporosis (3.2±0.8 *vs.* 2.6±0.4; p=0.04).

Conclusions: CKD stages 3-4 and PD patients have increased AGEs-sAF levels, which can be measured non-invasively with the AGE-Reader™. AGEs tissue accumulation might play a role on development of VC and osteoporosis in CKD patients.

SA-PO893

Association of Pre-ESRD Mineral and Bone Disorder Parameters with Post-ESRD Hospitalization for Fractures

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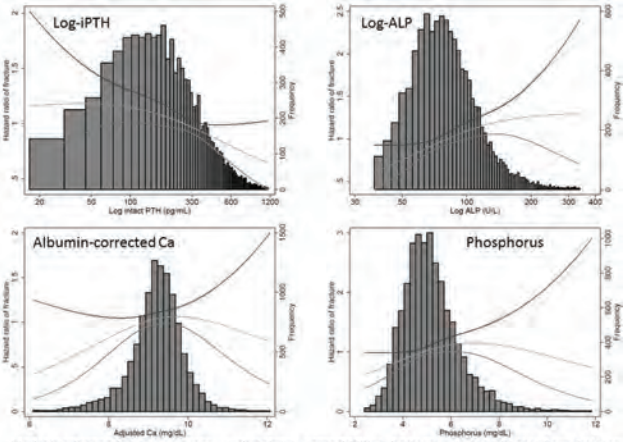
Background: Mineral and bone disorder (MBD) is associated with fractures both in CKD and ESRD. However, the association of MBD parameters in advanced CKD with fracture risk after dialysis is unknown.

Methods: We identified 10,942 US veterans starting dialysis between 10/2007-3/2014 with measurements of serum intact parathyroid hormone [iPTH], alkaline phosphatase [ALP], albumin-corrected calcium, and phosphorus within six months prior to dialysis start. MBD parameters were examined using splines and were also categorized into 3 groups with the reference group defined using guideline-based ranges, except for ALP which was categorized into tertiles. Associations of each MBD parameter with post-ESRD fracture-related hospitalization were examined in multivariable adjusted Cox regressions.

Results: 478 events occurred over a median follow-up of 1.8 years. Higher ALP was associated with higher fracture risk (adjusted hazard ratio [HR] [95% CI] for the highest [vs. lowest] tertile: 1.43 [1.11-1.85]). Both higher iPTH and lower calcium were associated with lower fracture risk (0.76 [0.59-0.98] and 0.64 [0.43-0.94], vs. referent). No association was seen between phosphorus and fracture risk (Figure).

Conclusions: Derangements of distinct pre-ESRD MBD parameters are associated with fracture risk after dialysis start. Further studies are needed to determine if correction of ALP, iPTH and calcium could prevent fractures.

Funding: NIDDK Support



SA-PO894

Comparison of the Prevalence of Mineral and Bone Disorders in Elderly and Non-Elderly Dialysis Population

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Background: Disorders in mineral and bone metabolism are common in patients with chronic kidney disease (CKD). These disturbs is a set of clinical-laboratory changes that cause negative effects on the various outcomes of chronic renal failure patients. International consensuses, like KDOQI and KDIGO were intended to assist the practitioner caring for adults and children with CKD stages 3-5, on chronic dialysis therapy, or with a kidney transplant. But there are no specific recommendations for analysis and management of elderly patients.

Methods: The study included a population of hemodialysis patients from a in-hospital service in the city of Maceió, Brazil. We performed a cross - sectional study of patients on hemodialysis for at least 3 months. We observed the socio-demographic, clinical data and the annual average of the laboratory analyzes. The data were then compared between Group 1 patients > 60 years and Group 2 patientes < 55 years.

Results: 168 patients were evaluated, 41 of Group 1 and 147 of Group 2. Group 1: age 68.5 years (± 5.81); 68% men; diabetic nephropathy as the main underlying disease (51%); weakness as the most reported complaint (50%); PTH 183 ± 23.86 pg / ml; alkaline phosphatase 104 ± 9.07 U / L; serum calcium 9 ± 0.11 mg / dL; serum phosphorus 4.56 ± 0.13 mg / dl. Group 2: age 39.5 years (± 14.9); 54% men; hypertensive nephrosclerosis as the main underlying disease; PTH 368.20 ± 29.78pg/ml; alkaline phosphatase 148.60 UI ± 9.61; serum calcium: 8.93 ± 0.05 mg/dL; serum phosphorus: 5.51 ± 0.10 mg/dL. Group 1 exibited PTH and alkaline phosphatase values lower than Group 2, especially in females (p <0.0001). There were differences in serum phosphorus levels - being higher in Group 1 (p <0.001). The comparison between elderly women and men showed no siguinificative differences. It is inferred that sex is probably not a determining factor in the pattern of alterations in the parameters of mineral disorders but age was an independent factor in the profile of this population.

Conclusions: Differences in the pattern of prevalence of the main bone and mineral disorders among the elderly and non-elderly can be observed. Studies with a greater number of patients may corroborate the need to establish specific guidelines for the mineral and bone disorders of elderly patients with chronic kidney disease.

SA-PO895

Efficacy of Denosumab for Dialysis Patients with Osteoporosis

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Background: Osteoporosis is a major complication in patients on hemodialysis (HD) because therapeutic drugs for it are limited. Recently, the superior efficacy of denosumab—human monoclonal antibody to RANKL—in non-HD patients was reported, but evidence of its effect in HD patients remained very limited. Accordingly, we studied the safety and efficacy of denosumab in these patients.

Methods: We prospectively enrolled HD and non-HD patients who started denosumab between June 2013 to October 2015 in our hospitals, and followed them for a year. Changes in bone mineral density (BMD), serum calcium, and bone metabolic markers before and after the treatment were analyzed.

Results: In this study, 192 patients (65 HD patients, 127 non-HD patients) were enrolled. Increase of BMD in the lumbar spine among HD patients was similar to that of non-HD patients (7.1±10.7 vs 6.2±6.8 %, p=0.73), and also similar in the femoral neck (4.8±6.5 vs 3.3±7.8). On the other hand, prevalence of hypocalcemia (<8.5mg/dL) was significantly higher in HD patients than non-HD patients (32% vs 4%, p<0.001). The median duration of appearance of hypocalcemia after injection was 6 days, and change of serum calcium at day 7 was significantly lower in HD patients than in non-HD patients

(-0.7±1.0 vs -0.3±0.4, p=0.03). Changes of bone metabolic markers were similar in both groups.

Conclusions: Our study suggests that denosumab was effective in HD patients, much as it was in non-HD patients. However, careful monitoring of blood tests—at least for a week—is recommended for HD patients.

Funding: Private Foundation Support

SA-PO896

Cinacalcet Attenuates Bone Loss in CKD through Preventing the Endothelial to Adipocyte Transition Li-Hua Ni,[1] rining tang,[1] Kaiyun Song,[1] Bi-Cheng Liu.[2] *[1]Institute of Nephrology, Zhongda Hospital, Southeast University School of Medicine, Nanjing, China, Nanjing, China; [2]Zhong Da Hospital, Southeast University Medical School, Nanjing, China.*

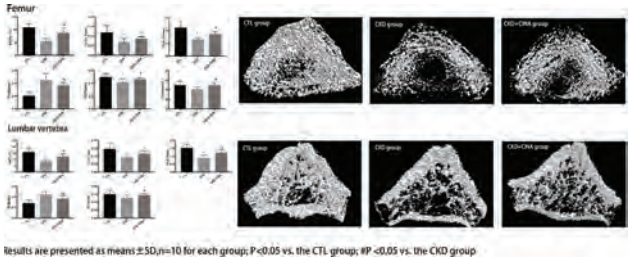
Background: Recently, cinacalcet (CINA) has been proved to be beneficial to bone lose in chronic kidney disease (CKD), while the exact mechanism is largely unknown. Emerging studies have shown that the conversion into mesenchymal stem cells (MSCs) via the endothelial-to-mesenchymal transition (EndMT) could be trigger into adipocytes. In this study, we hypothesized whether CINA could attenuate bone loss in CKD rats by inhibition the endothelium to adipocytes transformation.

Methods: Eight-week male Sprague Dawley rats were divided into three groups: a control group (CTL), vehicle-treated CKD group (CKD) and a cinacalcet-treated CKD group (CKD+CINA). CKD was induced by a 0.75% adenine diet. After adenine withdrawal, all rats were maintained on high phosphate diets. We performed blood analysis, emission computed tomography (ECT), bone mechanical properties tests, dual energy X-ray absorptiometry (DEXA) and micro-computed tomography (micro-CT), bone histomorphometry assessments in rats at the age of 42 weeks. The bone marrow expression of EndMT- and adipocyte-markers were also examined.

Results: In CKD rats, CINA treatment significantly decreased the serum PTH, phosphate (P), and Ca (Calcium) × P product ($P < 0.05$). The ECT images of the parathyroid glands indicated hyperparathyroidism in CKD rats but normal parathyroid function in CTL rats and CKD+CINA rats. Bone mineral density, trabecular BV/TV, trabecular number, cortical area, cortical thickness, force and stiffness were decreased in the CKD group, which were alleviated in the CKD+CINA group ($P < 0.05$). The expression of endothelial marker (CD31) was significantly down-regulated in CKD rats, whereas the expression of mesenchymal marker (FSP1), mesenchymal stem cell markers (STRO-1, CD44, CD10), adipocyte-markers (PPAR-γ and LPL) were markedly up-regulated. These changes were inhibited by CINA treatment ($P<0.05$).

Conclusions: This study firstly demonstrated that CINA exerted a beneficial effect on bone loss in CKD through a novel mechanism of preventing bone marrow endothelial-to-adipocyte transition.

Funding: Clinical Revenue Support, Government Support - Non-U.S.



Results are presented as means ±SD,n=10 for each group; P<0.05 vs. the CTL group; #P <0.05 vs. the CKD group

SA-PO897

Bisphosphonate Skeletal Accumulation Is Increased in Early and Mid-Stage CKD Mohammad W. Aref,[1] Elizabeth A. Swallow,[1] Neal X. Chen,[1] Sharon M. Moe,[1,2] Matthew R. Allen.[1,2] *[1]Indiana University School of Medicine, Indianapolis, IN; [2]Roudebush VA, Indianapolis, IN.*

Background: Bisphosphonates represent the gold standard pharmacological treatment for skeletal disease. Despite limited data, this class of drugs is contraindicated in patients with chronic kidney disease (CKD) due to concerns of compromised excretion and thus increased skeletal accumulation. The goal of this study was to use an animal model of progressive chronic kidney disease (Cy/+ rat) to study bisphosphonate distribution in the setting of reduced kidney function.

Methods: At 25 weeks of age, CKD and normal (NL) animals were administered a single bolus of fluorescently labelled zoledronic acid (Fam-ZOL). Animals were euthanized either 24 hours or 5 weeks later (30 weeks of age) and radius/ulna, distal femur, tibia, and 3rd lumbar vertebra (L3) were collected. Bulk levels of FAM-ZOL accumulation were estimated using whole bone fluorescence imaging (NightOwl LB981). Skeletal perfusion, to estimate blood flow and thus FAM-ZOL delivery, was measured prior to euthanasia via intra-cardiac injection of fluorescent microspheres.

Results: CKD animals had blood urea nitrogen (BUN) levels 2x higher than NL. At 24-hours post-dose, total bone fluorescence was higher in CKD radius (+134%, $p<0.05$), distal femur (+105%, NS), L3 body (+26%, NS) and tibia (+51%, $p<0.05$) compared to NL. Five-weeks post-dose, levels of drug in bone were significantly higher in all four bone sites of CKD animals relative to NL. Levels of drug in the bone at 5 weeks were indistinguishable from levels at 24-hrs post dose in both treatment groups. Skeletal perfusion was non-significantly higher in CKD relative to NL at 25 weeks of age. By 30 weeks (~20% NL GFR), perfusion was higher in CKD humeri (+155%, $p<0.05$), distal femur (+138%, NS) and L4 body (+142%, NS) compared to NL.

Conclusions: Based on these data we conclude that animals with reduced kidney function have altered dynamics of zoledronate accumulation in the skeleton, but such accumulation might be driven by factors other than compromised kidney excretion and may be due to altered blood flow.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO898

VS-605, a Mg+2-gum Arabic complex, Is a Non-Absorbed, Calcium- and Aluminum-Free, Highly Effective Phosphate Binder J. Ruth Wu-Wong, Yung-wu Chen, Jerry Wessale. *Vidasym, Chicago, IL.*

Background: Inadequate control of serum phosphate (Pi) in chronic kidney disease can lead to pathologies of clinical importance. Effectiveness of on-market phosphate binders is limited by safety concerns and low compliance due to large pill size/burden and gastrointestinal (GI) discomfort.

Methods: VS-605, a novel phosphate binder, is a polymer consisting of only Mg^{+2} and gum Arabic (a fiber component commonly used in food), with ~30% Mg^{+2} tightly complexed to gum Arabic (by X-ray photoelectron spectroscopy). VS-605 was evaluated for its efficacy and potential side effects in various pre-clinical studies including dosing 5/6 nephrectomized (NX) uremic SD rats with either VS-605 or sevelamer for 1 month.

Results: VS-605 has a high density at 1.89 g/cm^3 (vs. 1.27 g/cm^3 for sevelamer) as determined by helium pycnometer. When exposed to simulated gastric fluid, VS-605 exhibited a low swell volume at 0.3 cm^3/ml/0.1 g (vs. 4 cm^3/ml/0.1 g for sevelamer). After incubating with a phosphate buffer or in simulated gastric fluid for 24 hr at 37°C, VS-605 released <2% of Mg^{+2} into solution. In 5/6 NX uremic SD rats fed a high-phosphate diet, increasing dietary Pi led to an increase in serum Pi, which was prevented in rats treated with VS-605 or sevelamer (0.2 - 5% in food). Urinary Pi increased from 71 ± 19 at Week 0 to 785 ± 58 μmol/24 hr at Week 4 ($p<0.001$) in the vehicle-treated group; treatment with VS-605 or sevelamer (0.2 - 5% in food) reduced urinary phosphate in a dose-dependent manner (to 100 ± 28 and 102 ± 42 μmol/24 hr for 3% VS-605 and 5% sevelamer at Week 4, respectively). Concurrently, VS-605 or sevelamer increased fecal Pi in a dose-dependent manner. The high Pi diet also increased serum FGF-23 and parathyroid hormone in 5/6 NX rats, which was prevented by VS-605 or sevelamer. More aortic calcification was observed in the 5/6 NX rats treated with 5% sevelamer; neither VS-605 nor sevelamer exhibited any significant effects on intestine histology and intestinal sodium-dependent phosphate cotransporter gene expression.

Conclusions: These results support the conclusion that VS-605 effectively controls Pi imbalance in uremic rats by adsorbing dietary Pi in the GI tract. The minimal swell volume and high density of VS-605 may result in a potential advantage for a small pill size and reduced GI discomfort.

SA-PO899

Roles for Type III Sodium-Dependent Phosphate Transporter, PiT-2, in Bone Development and Growth in Mice with Normal and Impaired Kidney Function Shunsuke Yamada, Mary C. Wallingford, Timothy C. Cox, Cecilia M. Giachelli. *University of Washington, Seattle, WA.*

Background: Phosphate (Pi) is an essential component of bone and involved in normal bone development, growth, and homeostasis. The type III sodium-dependent phosphate transporters, PiT-1 and PiT-2, are expressed in bone but their exact functions remain unclear. In this study, the role of PiT-2 in bone homeostasis in normal and chronic kidney disease (CKD) mice was evaluated.

Methods: Global PiT-2 knockout (KO) and wild type (WT) male mice with intact kidneys were euthanized at 10 weeks of age and subjected to serum biochemical determination and micro CT analyses, which included measurement of bone length and bone mineral density (BMD) and calculation of static bone parameters. Furthermore, to determine the impact of PiT-2 deficiency on renal Pi handling, 10-week-old WT and PiT-2 heterozygous knockout (HET) female mice were subjected to 24-hour urine collection and serum measurement, followed by kidney collection. WT and PiT-2 HET mice also underwent two-step 5/6th nephrectomy and were subjected to micro CT analyses at 3 weeks after CKD induction.

Results: Bone length in PiT-2 KO mice was significantly shorter in femur, tibia, and vertebral column than the WT mice. BMD in systemic bones including mandibles and both trabecular and cortical bone of femurs were significantly lowered in the PiT-2 KO mice than the WT mice. When femurs were analyzed by micro CT, both cortical and trabecular bone thickness were decreased in the PiT-2 KO mice compared with the WT mice. No significant differences were observed in bone mineral density, serum calcium and Pi levels, kidney function, renal mRNA expression of SLC34A1 and SLC34A3, and fractional excretion of Pi between the WT and PiT-2 HET mice. However, in the setting of CKD and high Pi diet feeding, PiT-2 haploinsufficiency decreased trabecular bone volume and thickness but did not change cortical bone volume and had no effect on serum levels of creatinine, calcium, and Pi.

Conclusions: PiT-2 is required for bone development and growth under both normal kidney function and CKD, and enhancing its activity might provide benefits in CKD patients with bone disorders.

Funding: NIDDK Support

SA-PO900

Bone Expression of HIF-1 in Osteocytes Is Decreased in CKD Rats

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Background: Different studies, including our own, have shown that hypoxia-inducible factor-1 (HIF-1) enhances vascular calcification. However, HIF-1's role in chronic kidney disease (CKD)-related bone disease is currently unknown. The aim of this study is to determine bone HIF-1 expression in chronic kidney disease (CKD) rats with vascular calcification.

Methods: CKD was induced by 5/6 nephrectomy and vascular calcification by a supplement of calcium, phosphorus and 1,25-dihydroxyvitamin D3 (Ca/P/VitD). Three groups were studied: control (n=8), CKD (n=14) and CKD + Ca/P/VitD (n=12). At 2 months, tibia bone and thoracic aorta were harvested for micro-CT, histomorphometry and vascular calcification quantification. HIF-1α expression, the essential HIF-1 subunit, was assessed in the tibia by immunohistochemistry and quantified using ImageJ.

Results: Vascular calcification occurred only in CKD + Ca/P/VitD rats. Compared to controls, CKD and CKD + Ca/P/VitD rats presented with a lower bone volume and bone mineral content, while trabecular thickness and separation were significantly increased in the CKD+Ca/P/vitD group. Osteoid volume and surface were also increased in CKD + Ca/P/VitD rats, which is compatible with a mineralisation defect (low turnover and mineralisation parameters). HIF-1α was expressed in osteocytes. Interestingly, the proportion of positive osteocytes for HIF-1α was decreased in CKD and CKD+Ca/P/vitD rats as compared to the controls (respectively 63.01 ± 16.78% vs 60.91 ± 23.17% vs 89.31 ± 5.87% in controls, p<0.01)

Conclusions: Our study is the first to describe HIF-1 expression in bone from CKD rats with vascular calcification. Since HIF-1 was previously suggested to play a role in bone formation, these results suggest that lower osteocyte HIF-1 expression could be involved in the development of bone anomalies during CKD.

Funding: Government Support - Non-U.S.

SA-PO901

Leptin Signaling Blockade Ameliorates Muscle Wasting, Bone Disease, and Growth Failure in CKD

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Background: We showed that aberrant leptin signaling is important in the pathophysiology of CKD-associated wasting (Cheung W et al JCI 115:1659-65, 2005 & JASN 25:119-28, 2014). As muscle and bone health are related, we investigated whether leptin signaling blockade affects bone disease and growth failure in CKD.

Methods: We performed 5/6 nephrectomy (CKD) or sham-operation (S) in 8 week old c57BL/6J wild-type (WT), leptin-deficient (ob/ob) and leptin receptor deficient (db/db) mice. Then, WT-CKD mice were treated with a pegylated leptin antagonist (PLA) (7 mg/kg/day) or vehicle (V) for 4 weeks. Secondary hyperparathyroidism was restricted with low phosphorus diets. WT-CKD mice were fed ad libitum while all other mice were pair-fed to that of WT-CKD. Body composition was determined by EchoMRI. Whole body and femoral mineral content (BMC) and bone mineral density (BMD) were assessed by dual-energy x-ray absorptiometry. Femoral bone strength and bone architecture were assessed by 3-point failure load test and X-ray microtomographic scanning (μCT), respectively.

Results: WT-CKD, ob/ob-CKD, db/db-CKD, WT-CKD+PLA and WT-CKD+V mice had significantly higher blood urea nitrogen and serum creatinine than WT-S, ob/ob-S, db/db-S, WT-S+PLA and WT-S+V mice. Bone disease in WT-CKD mice was characterized by decreased whole body BMC, BMD as well as decreased femoral length, BMC, BMD, cortical area, thickness and failure load. μCT confirmed that femoral bone volume, cortical area and thickness were significantly reduced in WT-CKD. Uremic bone phenotype was significantly improved in ob/ob-CKD and db/db-CKD compared to WTCKD mice. Weight gain, lean mass and muscle function were normalized in WTCKD+PLA relative to WT-S+V mice. Increased expressions of muscle inflammatory cytokines (IL-1α, IL-1β, IL-6 and TNF-α) were normalized in WT-CKD+PLA relative to WT-S+V mice. Uremic bone disease was prevented in WT-CKD+PLA mice. Whole body BMC, BMD as well as femoral length BMD, BMC, and failure load were normalized in WT-CKD+PLA relative to WT-S+V mice.

Conclusions: Aberrant leptin signaling may play an important role in the pathogenesis of muscle wasting, osteodystrophy and growth failure in CKD. Its blockade may represent a novel therapeutic strategy.

Funding: Clinical Revenue Support

SA-PO902

Increased Bone FGF23 expression Is Linked to Impaired Osteocyte Maturation in CKD

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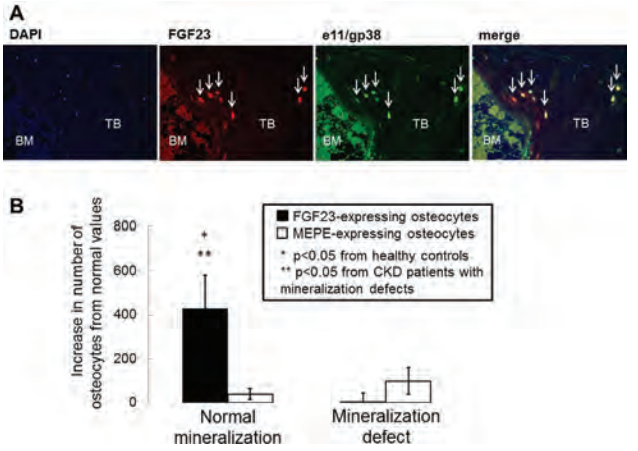
Background: Increased FGF23 expression and skeletal mineralization defects characterize bone in CKD. FGF23-expressing osteocytes are located in clusters at the trabecular periphery. Since young osteocytes are also at the trabecular periphery, we hypothesized that FGF23 is a marker of young osteocytes. We also hypothesized that increased numbers of young, FGF23-expressing, osteocytes reflect an adaptive response to impaired osteocyte maturation, the consequence of which is defective skeletal mineralization, in CKD.

Methods: We evaluated bone from 32 pediatric CKD patients (stages 2-4: n=12; stage 5: n=20). Patients were dichotomized based on the presence (n=13) or absence (n=19) of skeletal mineralization defects, defined by increased osteoid volume along with prolonged osteoid maturation time. Co-expression of FGF23 (FGF23(225-244); Quidel) with markers of osteocyte maturity (early osteocytes: e11/gp38 (ab25, Abcam); late osteocytes: MEPE(ab108073, Abcam)) was evaluated by immunofluorescence. Numbers of FGF23 and MEPE expressing osteocytes were evaluated by immunohistochemistry.

Results: FGF23 co-localized with e11/gp38 but did not co-localize with MEPE. Normal skeletal mineralization indices were associated with a 429 ± 153% increase in numbers of FGF23-expressing osteocytes (p<0.05 from control values; p<0.05 from patients with skeletal mineralization defects). Numbers of MEPE-expressing osteocytes did not differ between groups or between CKD patients and controls.

Conclusions: FGF23 is a marker of young osteocytes. Normal mineralization indices in CKD are associated with a robust increase in young osteocytes. Impaired osteocyte maturation may precede and contribute to the development of skeletal mineralization defects and secondary hyperparathyroidism in CKD.

Funding: NIDDK Support, Private Foundation Support



A) Colocalization of FGF23 and e11 in iliac crest. B) Increased numbers of FGF23-expressing osteocytes, but not MEPE-expressing osteocytes, in CKD patients with normal mineralization indices.

SA-PO903

Relationship between Sarcopenia and Bone Mineral Density in Hemodialysis (HD) Patients

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Background: Little is known about the relationship between sarcopenia and bone mass in HD patients. Moreover, definition of sarcopenia was made only in considering the muscle mass in most of the previous studies. The purpose of this study was to strictly assess sarcopenia by both muscle mass and muscle strength in HD patients, and was to compare bone mineral density (BMD) between HD patients with and without sarcopenia.

Methods: A total of 287 patients on maintenance HD were examined. BMD at the 1/3 distal radius and appendicular skeletal muscle mass were measured by dual energy X-ray absorptiometry (DXA). Low muscle mass was defined as skeletal muscle mass index (SMI) of < 6.87 kg/m² for males and < 5.46 kg/m² for females. Low muscle strength was defined as hand grip strength of < 26 kg for males and < 18 kg for females, according to the criteria of Asian Working Group for Sarcopenia. Sarcopenia was defined as decline in both hand SMI and grip strength.

Results: There were no significant differences in HD duration or in prevalence of diabetes between patients with and without sarcopenia in both genders. Age was significantly higher in patients with sarcopenia than those without sarcopenia in both genders (62.2 ± 12.7 *vs.* 53.3 ± 10.4 years, p < 0.0001 in males; and 65.3 ± 8.6 *vs.* 55.3 ± 11.2 years, p < 0.0001 in females). BMD of the 1/3 distal radius in patients with sarcopenia was significantly lower than that of patients without sarcopenia in both genders (0.62 ± 0.12 *vs.* 0.69 ± 0.09 g/cm², p < 0.0001 in males; and 0.44 ± 0.09 vs. 0.53 ± 0.09 g/cm², p < 0.0001 in females). In a multiple linear regression analysis, presence of sarcopenia (β = - 0.196, p = 0.0075 in males; β = - 0.188, p = 0.0340 in females) was significantly, independenly associated with BMD of the 1/3 distal radius after adjustment with age, HD duration, presence of diabetes, body mass index, and serum parathyroid hormone levels in both genders (R^2 = 0.320, p < 0.0001 in males; and R^2 = 0.448, p < 0.0001 in females).

Conclusions: These results clearly demonstrate that sarcopenia, which was strictly assessed by muscle mass and strength, is significantly associated with decrease in BMD in HD patients, suggesting that sarcopenia should be regarded as a significant risk factor for either osteoporosis or renal osteodystrophy in these patients.

SA-PO904

Bone Mineral Density by Quantitative Computed Tomography Can Predict Fractures in Kidney Transplantation Candidates

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Background: Fracture risk is increased in chronic kidney disease (CKD), but the role of bone mineral density (BMD) in assessing bone fragility is still controversial. This study investigates if BMD can predict incident fractures in late stage CKD.

Methods: Adult kidney transplantation candidates were included. Volumetric BMD of spine and hip was analyzed from computed tomography (CT) scans. Low trauma fractures were recorded from patient interviews and records.

Results: During a median follow-up of 3.7 years, 19 out of 157 patients (12%) sustained a clinical fragility fracture. Patients with fracture had reduced BMD at the hip, but not at the spine (Table 1). Type 1 diabetes ($p < 0.001$), bone specific alkaline phosphatase ($p = 0.03$), and hip *T*- and *Z*-scores ($p < 0.05$) were identified as predictors of fracture by univariate cox regression. Thus, patients with total hip or femoral neck *T*-scores≤-2.5 were at increased risk (Figure 1). A 1 unit decrease in total hip *Z*-score was associated with a 2-fold increase in the risk of fracture (HR 2.01, CI 1.24 to 3.24, p<0.01) after adjusting for dialysis therapy at baseline and kidney transplantation during follow-up.

Conclusions: Hip BMD by CT may predict fractures in adult kidney transplantation candidates with severe CKD.

Funding: Private Foundation Support

Table 1 Bone density in patients with and without fracture

		Fracture (n=19)	No fracture (n=136)	p
Lumbar spine	vBMD	123±40	122±39	0.86
	Z-score	-0.54±1.30	-0.43±1.38	0.75
	T-score	-1.83±1.53	-1.93±1.46	0.79
Total hip	vBMD	210±45	232±44	0.04
	Z-score	-1.82±1.12	-1.15±1.07	0.01
	T-score	-2.47±1.04	-1.89±1.07	0.03

Data are mean±SD with p values by Student's t-test

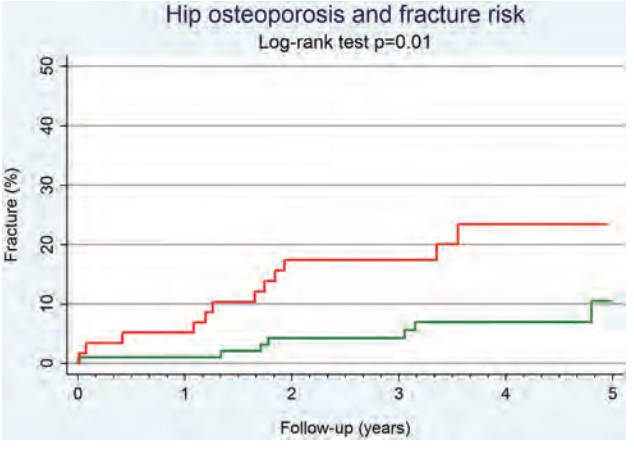

Figure 1 Risk of incident fracture in kidney transplantation candidates, red line=total hip or femoral neck *T*-score≤-2.5 (n=58), green line=hip *T*-scores>-2.5 (n=99)

SA-PO905

Risk of Fracture in Glomerular Disease: A Population-Based Cohort Study Using the Health Improvement Network

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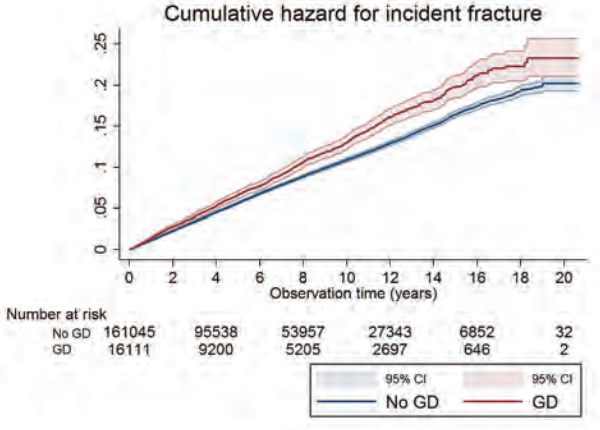
Background: Current understanding of skeletal complications in glomerular disease (GD) is limited. To our knowledge, there have been no studies in children or adults addressing the risk of fracture associated with GD independent of kidney function.

Methods: We performed a population-based retrospective cohort study using The Health Improvement Network. The median calendar year at the start of observation was 2005 (1994-2015). We identified 16,111 patients with ≥1 of 155 diagnostic codes for primary GD and 161,045 randomly selected age, sex, and practice-matched individuals. Exclusion criteria included age ≥90 years, systemic lupus or vasculitis, multiple myeloma, amyloidosis, inflammatory bowel disease, celiac disease, HIV, hepatitis B or C, malignancy, and non-renal solid organ transplant. Cox regression was used to estimate the hazard ratio (HR) for first fracture.

Results: Median age was 42 years, and 57% were male. Over a median observation period of 5 years, 1328 incident fractures (132 per 10,000 person-years) occurred in participants with GD versus 11,423 in those without GD (110 per 10,000 person-years). In multivariable analysis adjusted for age, sex, and diabetes and chronic kidney disease (stage 3-5D and/or renal transplant) as time-varying covariates, GD was associated with an increased risk of fracture (HR 1.13; 95% CI: 1.06, 1.19, p<0.001). The adjusted HR for first incident vertebral fracture was 1.47 (95% CI: 1.10, 1.95, p=0.009). The adjusted HR for first incident hip/femur fracture was 1.46 (95%CI: 1.21, 1.75, p<0.001), and the increased risk associated with GD was more pronounced in younger individuals (HR 2.65 for those <40 years old vs. 1.42 for those ≥40 years, interaction p=0.03).

Conclusions: In this large-population based cohort study, GD was associated with an increased risk of incident fracture, particularly at the hip and spine, independent of impaired kidney function.

Funding: NIDDK Support



SA-PO906

Effects of Parathyroidectomy on Blood Bone Markers and Heart Rate Variability in CKD Patients

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Background: Lower heart rate variability (HRV) in chronic kidney disease (CKD) patients is associated with increased risk of cardiovascular disease (CVD). We aimed to evaluate the relationships between blood bone markers and HRV in stage 5 CKD patients, longitudinal changes in severe secondary hyperparathyroidism (SHPT) subgroup with parathyroidectomy (PTX) were also explored.

Methods: This cross-sectional study included 134 CKD patients, 100 controls, and a prospective study in PTX group(n=45) with median follow-up time of 6.7 months. Bone parameters included (1) intact parathyroid hormone (iPTH), as classic bone remodeling regulators; (2) bone-specific alkaline phosphatase (BAP), representing bone formation; (3) tartrate-resistant acid phosphatase (TRACP-5b), indicating bone resorption; (4) bone-derived hormone, fibroblast growth factor 23 (FGF23). HRV were measured by 24h Holter.

Results: Circulating bone markers of the participants were shown in Table 1. Baseline iPTH, BAP and lnFGF23 levels were independently associated with decreased HRV in CKD patients. Elevated blood iPTH, BAP, TRACP-5b, FGF23 levels and attenuated HRV were ameliorated after PTX, furthermore, improved HRV were associated with reduced iPTH, TRACP-5b and FGF23 levels(Fig1).

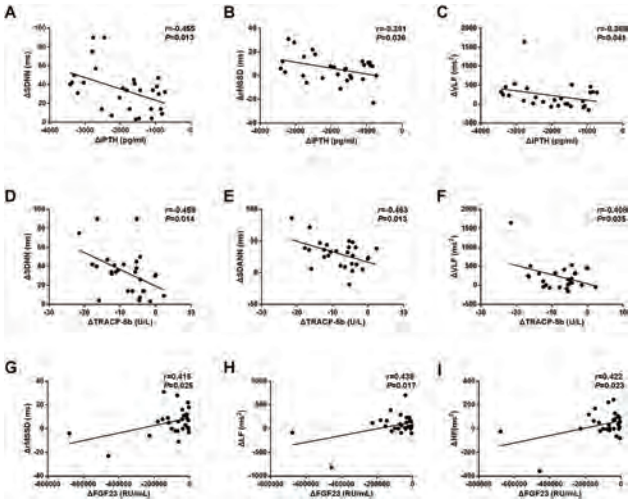
Conclusions: In CKD patients, circulating iPTH and FGF23 levels may play important roles in imbalances of cardiovascular autonomic nervous system while the roles of bone resorption/formation need more research.

Funding: Government Support - Non-U.S.

Circulating Bone Markers of Different Participants

Variable	Controls (n=100)	Stage 5 CKD Patients (n=134)	Stage 5 CKD patients(n=134) Non-PTX(n=89)	PTX(n=45)
iPTH(pg/mL)	35.6(27.4-49.0)	495.7(193.5-1466.0)*	252.0(108.1-495.7)	1776.7(1147.2-2796.7)**
BAP(μg/L)	16.3(13.2-19.6)	22.1(13.7-76.0)*	16.1(12.5-24.2)	131.0(51.3-327.7)**
TRACP-5b(U/L)	2.0(1.4-2.5)	5.8(3.7-9.9)*	4.8(3.0-7.8)	10.5(6.1-17.9)**
FGF23(RU/mL)	62.7(51.2-78.4)	6390.9(1041.7-39476.2)*	1477.6(682.4-6848.7)	52636.1(17316.4-121101.2)**
LnFGF23	4.1±0.3	8.8±2.1*	7.8±1.6	10.9±1.2**

*,compared with controls, P<0.001; **, compared with CKD with Non-PTX, P<0.001



Improved HRV were associated with reduced blood bone markers in PTX group

SA-PO907

Kidney Stones Associate with Increased Risk for Fracture in Patients with CKD Dong Ho Shin,[1] Jung-woo Noh,[2] Jeonghwan Lee.[3] *[1]College of Medicine, Hallym University, Seoul, Republic of Korea; [2]Hallym University, Seoul, Republic of Korea; [3]Hallym University Hangang Sacred Heart Hospital, Seoul, Republic of Korea.*

Background: Most of kidney stones may result from renal hypercalciuria, which is a systemic dysregulation of calcium homeostasis. Accordingly, fractures related with this dysregulation occur more frequently in patients with nephrolithiasis than in the general population. However, little is known about the potential influence of kidney stones on bone health status in patients with chronic kidney disease (CKD).

Methods: A total of 2284 patients with stage 3 – 4 CKD, who were treated at Kandong Scared Heart Hospital were included. Patients were divided into 2 groups according to the presence and absence of kidney stones, and clinical and laboratory data were compared between groups. The association of fractures with kidney stones analyzed using Cox proportional hazards analysis.

Results: Patients with kidney stones and without kidney stones were 502 and 1782, respectively. Among these patients, 172 (7.4 %) were diagnosed with fractures. Hip, pelvis, vertebra, proximal humerus or distal forearm fractures were 43, 31, 50, and 48, respectively. Compared to patients without kidney stone, patients with kidney stones had a significantly higher proportion of fractures (12.4 % vs 6.2 %, P = 0.02). In particular, Cox proportional hazard analysis revealed that kidney stones were a significant independent predictor of vertebral fracture even after adjusting for other factors in patient with CKD stage 3-4 (HR, 1.81, 95% CI 1.12 – 1.81, P = 0.04).

Conclusions: Kidney stones are at increased risk for fractures. Especially, kidney stones are independently associated with higher risk of vertebral fracture in patients with CKD.

SA-PO908

Effects of Primary Kidney Disease on Bone Histomorphometry in Pediatric Dialysis Patients Ornatcha Sirimongkolchaiyakul,[1] Katherine Wesseling-Perry,[1] Barbara Gales,[3] Georgina Chow,[4] Renata C. Pereira,[5] Isidro B. Salusky.[2] *[1]David Geffen School of Medicine at UCLA, Los Angeles, CA; [2]Mattel Children's Hospital, Los Angeles, CA; [3]None, Calabasas, CA; [4]UCLA, Murrieta, AL; [5]University of California, Los Angeles, CA.*

Background: Little is known as to the effect of primary kidney disease on renal osteodystrophy. The current study was thus designed to assess the association between CKD etiology, mineral metabolism and bone histromorphometry in pediatric ESKD.

Methods: Demographic, biochemical and bone histomorphometric data were analyzed from 207 patients (aged 12.7 ± 5.6 years) with ESKD who underwent double tetracycline labeled bone biopsy at UCLA. Patients were divided into 2 groups according to CKD etiology: inflammatory (n = 85) v. non-inflammatory (n=122) disease. Non-inflammatory disease was further divided into CAKUT (n = 87) v. non-CAKUT (n = 35). Serum Ca, P, ALP, PTH, 25D, and C-term FGF23 levels were measured at the time of biopsy.

Results: Serum Ca, P, PTH and 25D did not differ between groups. Serum ALP levels were higher, and cFGF23 levels were lower, in patients with CAKUT (Table). Bone turnover and volume did not differ between groups. Osteoid volume (OV/BV), osteoid surface (OS/BS), osteoid thickness (O.Th) and osteoid maturation time (OMT) were increased in patients with CAKUT. As previously reported, multiple regression analysis demonstrated that Ca, P, ALP and PTH were independent predictors of OV/BV and O.Th. ALP and PTH were an independent factors affecting BFR/BS. Disease etiology was not an independent predictor of any histomorphometric variable.

Conclusions: After controlling for biochemical variables, ESKD etiology did not affect bone histomorphometric parameters of turnover, mineralization, or volume.

Funding: NIDDK Support, Private Foundation Support

Table: Biochemical and bone histomorphometry results

Parameters	Non-inflammation		Inflammation (N= 85)	p-value	Normal range
	CAKUT (N = 87)	Non-CAKUT (N = 35)			
Biochemical variables					
Serum Ca (mg/dl)	9.1 ± 0.9	9.2 ± 0.9	9.0 ± 1.1	0.67	
Serum P(mg/dl)	5.9 ± 1.3	6.4 ± 1.7	6.4 ± 1.5	0.13	
Serum ALP (IU/L)	315 (204, 571)	210 (132, 322)[a]	201 (122, 386)[c]	<0.01	
Serum PTH (pg/ml)	409 (170, 919)	364 (185, 720)	414 (143, 844)	0.81	
Serum 25(OH)D (ng/ml)	18.7 (12.7, 27.2)	19.0 (11.4, 27.0)	15.4 (9.4, 23.9)	0.33	
Plasma cFGF23 (RU/ml)	194 (83, 788)	883 (606, 2058)[a]	1869 (407, 11287)[c]	<0.01	
Bone histomorphometry					
Turnover					
BRF/BS ($\mu m^3/\mu m^3$/year)	77.6 (26.7, 118.2)	63.2 (27.1, 110.7)	59.9 (16.0, 94.5)	0.52	8.0-73.4
ES/BS (%)	7.6 (4.3, 11.3)	7.5 (5.8, 10.8)	7.4 (4.0, 12.0)	0.99	0.5-4.3
Mineralization					
OV/BV (%)	8.5 (4.9, 13.6)	4.9 (2.3, 8.0)[a]	6.9 (3.9, 11.3)[a]	<0.01	0.2-5.8
OS/BS (%)	47.1 ± 17.7	33.4 ± 18.1[a]	43.5 ± 18.4[a]	<0.01	4.3-31.7
O.Th (µm)	12.9 (9.4, 20.1)	10.7 (8.7, 14.9)[a]	11.4 (9.1, 14.8)[c]	0.02	2.0-13.2
OMT (day)	13.4 (9.1, 23.6)	11.5 (8.5, 13.7)	11.2 (8.2, 15.2)[c]	0.03	1.2-11.5
MLT (day)	40.4 (23.0, 82.7)	25.1 (13.3, 49.2)[a]	31.5 (20.2, 82.6)	0.05	2.3-63.8
Volume					
BV/TV (%)	28.8 (24.8, 35.3)	28.2 (25.8, 36.3)	26.4 (22.0, 34.7)	0.31	8.9-34.4

a: p < 0.05 versus CAKUT
b: p < 0.05 versus non-inflammatory other
c: p < 0.05 versus CAKUT

SA-PO909

PPI Use Is Associated with Higher Prevalence of Bone Fractures and Mortality in Young Hemodialysis Patients Maria Fusaro,[5] Maurizio Gallieni,[6] Graziella D'arrigo,[3] Annalisa Pitino,[4] Andrea Aghi,[7] Bruce M. Robinson,[1] Brian Bieber,[1] Keith McCullough,[1] Francesca Tentori,[8] Giovanni Tripepi.[2] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]CNR-IBIM, Reggio Calabria, Italy; [3]Clin. Epid. and Physiopath. of Renal Dis. and Hypertens., CNR-IBIM, Reggio Calabria, Italy; [4]Consiglio nazionale delle ricerche (CNR), Rome, Italy; [5]National Research Council (CNR) e Institute of Clinical Physiology (IFC), Pisa, Italy, Padua, Italy; [6]Ospedale San Carlo Borromeo - ASST Santi Paolo e Carlo - University of Milano, Milano, Italy; [7]Department of Medicine, University of Padua, Padua, Italy; [8]DaVita Clinical Research, Minneapolis, MN.*

Background: Proton pump inhibitors (PPIs) are extensively used in the general population and even more in dialysis patients. The aim of this observational study was to evaluate the association between use of PPIs and bone fractures (BFs) in hemodialysis (HD) patients enrolled in the Dialysis Outcomes and Practice Patterns Study (DOPPS) study.

Methods: Among 49564 (58% male) hemodialysis patients from the DOPPS dataset, 39,9% of patients received PPI treatment, aged 63.8±14.3 years, median (IQ range) dialysis duration 19 (4-55) months, BMI 25.5±5.8 Kg/m2, median follow-up time 19 months (IQR 9-27).

Results: In the whole study cohort, 12567 patients experienced the combined endpoint BFs/death and 7.538 patients, with available data on hip fractures (HFs) had the HFs/death outcome. A significant (P≤0.002) and inverse effect modification by age on the relationship between PPI treatment and the incidence rate of BFs and HFs was found, the effect of PPI being progressively lower from 35 years of age onwards (Fig. 1). Both crude and adjusted effect modification analyses considering the competitive risks of mortality fully confirmed these results, the effect of PPI on the combined outcomes BFs/D and HFs/D being closely and inversely dependent on age (Fig. 1).

Conclusions: In this study, the association between PPI use and bone fracture risk was clearly confirmed in the dialysis population especially in younger patients. In addition, we could demonstrate a combined increased risk of bone fractures and death, again higher in younger patient, indicating a remarkable and avoidable adverse effect of PPIs in this population.

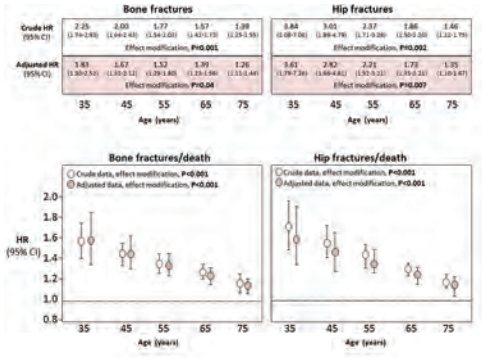


Fig. 3

Effect modification by age on PPI use

SA-PO910

The Regina CKD-MBD Study Bhanu Prasad,[2] Shelley Giebel,[3] Thomas Nickolas.[1] *[1]Columbia University Medical Center, New York, NY; [2]None, Regina, SK, Canada; [3]Regina QuAppelle Health Region, Regina, SK, Canada*.

Background: Recent studies have demonstrated that measurement of areal bone mineral density (BMD) by dual energy X-ray absorptiometry predicts fractures in patients with chronic kidney disease (CKD). However, whether fracture risk prediction by BMD is enhanced by assessment of biochemical markers of CKD-mineral and bone disease or clinical risk factors is not clear. We hypothesized that in a selected cohort of patients managed in a CKD clinic, that combining T scores with biochemical markers would optimize fracture discrimination than using DXA alone.

Methods: We conducted a retrospective review of 374 consecutive patients who underwent mandatory DXA imaging at the point of entry into our multidisciplinary CKD program. BMD measurements were obtained from DXA scan reports from the Nuclear Medicine Department. BMD data were collected at four sites: the lumbar spine, total hip, mean of left and right femoral neck, and the 1/3- radius. We collected data on demographic, lab markers of mineral metabolism and fractures (identified through self-reported questionnaires, hospital electronic medical records and physician billing records.

Results: In our cohort, 14.3% of stage 3 CKD, 15.7% of stage 4 CKD and 19.7% of stage 5 CKD experienced a clinical fracture during the study period. In an unadjusted model, each standard deviation decrease in total hip T-Score was associated with a 47% higher odds of fracture (OR=1.47, 95%CI: 1.18-1.82, p=0.0006). After adjustment for clinical risk factors (age, sex, BMI and diabetes) the odds of fracture remained unchanged (OR=1.47, 95%CI: 1.14-1.89, p=0.0028), and after adjustment for clinical risk factors and markers of CKD-MBD, BMD remained a significant predictor of fracture (OR=1.52, 95%CI: 1.17-1.99, p=0.0018). In the final model, additional adjustment for eGFR did alter the relationship between total hip T-Score and fracture (OR=1.53, 95%CI: 1.17-1.99, p=0.0017). Neither clinical risk factors nor markers of CKD-MBD were related to fracture in multivariate models and there was no interaction between total hip T-score and eGFR (p=0.5).

Conclusions: We conclude that measurement of BMD by DXA scans predicts fractures in stages 3-5. However, fracture risk prediction was not further enhanced by the addition of biochemical markers of CKD-MBD.

SA-PO911

Risk Factors of Fragility Fracture in Patients with CKD Mark A. Kleman,[2] Waleed Zafar,[1] Alex R. Chang.[3] *[1]Geisinger, Dnville, PA; [2]Geisinger Health System, Danville, PA; [3]Geisinger Medical Center, Danville, PA*.

Background: Management of chronic kidney disease-mineral and bone disorder (CKD-MBD) focuses mainly on parathyroid hormone (PTH), phosphorus, and calcium. However, little is known about fragility fracture risk factors in CKD patients.

Methods: The study population included 5,733 patients in the Geisinger Health System with CKD [estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2, or urine albumin/creatinine ratio >=30 mg/g], intact PTH measurements, and no prior history of fragility fracture or use of osteoporosis medications. Fragility fracture was defined by ICD-9 codes for wrist, humerus, hip, and clinical spine fracture.

Results: Over a median follow-up of 5.0 (3.4-7.5) years, 609 (10.6%) CKD patients experienced an incident fragility fracture. Median (interquartile range) values for age, eGFR, intact PTH, alkaline phosphatase (ALP) were 70 (60-78) y, 43 (31-54) ml/min/1.73m^2, 57 (37-90) pg/ml, and 77 (63-97) IU/L. and 68.0 y, 52.7% were female, 98.1% were white, mean eGFR was 44.8 (22.1) mL/min/1.73m^2, and median Elevated alkaline phosphatase (ALP) >= 100 IU/L was associated with increased risk of incident fragility fracture; intact PTH, 25-hydroxyvitamin D, serum phosphorus and bicarbonate levels were not. Other significant risk factors included older age, female gender, body mass index (BMI) < 20 kg/m^2, serum albumin < 4 g/dl, and history of non-fragility fracture **(Table)**.

Conclusions: Several routinely collected clinical factors are associated with increased risk of fragility fracture in patients with CKD. Future clinical trials aimed at improving bone health and reducing fracture risk may consider using clinical factors to identify CKD patients at high risk of fragility fracture.

	HR	P value
Age (per 1-y increase)	1.04 (1.03-1.05)	<0.001
Female	1.36 (1.12-1.67)	0.002
White	2.47 (0.79-7.71)	0.1
Current smoker	1.16 (0.82-1.64)	0.4
BMI <20 kg/m2	2.23 (1.42-3.50)	0.001
Hx Stroke	1.18 (0.95-1.47)	0.1
Hx non-fragility fracture	1.56 (1.21-2.01)	0.001
ALP >= 100 IU/L	1.31 (1.05-1.60)	0.02
Intact PTH >= 130 pg/ml	1.19 (0.89-1.60)	0.2
Serum albumin < 4 g/dl	1.55 (1.26-1.91)	<0.001
Estrogen medications	0.52 (0.26-1.06)	0.07
DBP <60 mmHg	1.34 (1.00-1.79)	0.05
C Statistic	0.68	

SA-PO912

Influence of Vitamin D Receptor Polymorphisms on Biochemical Markers of Mineral Bone Disorders in South African Patients with CKD Bala Waziri,[2] Saraladevi Naicker.[1] *[1]University of the Witwatersrand, Johannesburg, South Africa; [2]Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa*.

Background: It remains unclear whether genetic factors may explain the reported variation in the levels of biochemical markers of chronic kidney disease mineral and bone disorders (CKD- MBD) across ethnic groups. Therefore, the aim of this study was to examine the influence of VDR polymorphisms on secondary hyperparathyroidism and its association with vitamin D levels in black and white South African study participants.

Methods: This was a cross sectional study involving 272 CKD stage 3- 5D patients and 90 healthy controls. The four common VDR polymorphisms (*Bsm 1, Fok 1, Taq 1, and Taq 1*) were genotyped using the polymerase chain reaction- restriction fragment length polymorphism (PCR –RFLP) method. In addition, the biochemical markers of CKD-MBD were measured to determine their associations with the four VDR polymorphisms.

Results: With the exception of *Taq I* polymorphism, the distribution of the VDR polymorphisms differs significantly between blacks and whites. In hemodialysis patients, the Bb genotype was significantly associated with moderate secondary hyperparathyroidism (OR, 0.3.12; 95 CI 1.11-8.83, p=0.03) and severe hyperparathyroidism (OR, 2.55; 95 CI 1.19-5.47, p=0.02). This was consistent with the observed higher levels of median PTH and mean phosphate in patients with Bb genotype. This candidate risk genotype (Bb) was over represented in blacks compared to whites (71.0 % versus 55.6 %, p <0.0001). In an unadjusted regression model, *Fok Ff* genotype was found to be significantly associated with the risk of developing severe vitamin D deficiency < 15ng/ml (OR, 1.89; 95 CI 1.17-3.07, p=0.01).

Conclusions: The VDR Bb genotype is an independent predictor of developing secondary hyperparathyroidism in patients with end stage renal disease. In addition, study participants with the *Fok Ff* genotype are at increased of developing severe 25(OH) D deficiency

SA-PO913

Integrative Point-of-Care Ultrasound (POCUS) Curriculum Imparts Diagnostic Skills Relevant to Nephrology Surekha U. Mullangi, Stephen M. Sozio, Steven Menez, Tariq Shafi. *Johns Hopkins University School of Medicine, Baltimore, MD*.

Background: The utility of POCUS has been expanding as a multipurpose diagnostic tool for nephrologists. However, a clear, nephrology-specific, curriculum has not been established. We have developed and implemented a POCUS curriculum that teaches focused skills to nephrology fellows. The goal of our study is to describe our initial experience with this innovative program.

Methods: The Johns Hopkins Renal Fellowship POCUS curriculum is a two-week elective that provides focused training to assess the following: heart (ejection fraction, pericardial effusion, chamber size), lungs (pulmonary edema, effusion, pneumothorax), inferior vena cava (diameter, collapsibility), kidney (size, echogenicity, hydronephrosis), bladder (volume), and fistula (depth, diameter). We teach these skills using a combination of didactic lectures, guided scanning, and independent scanning. We grade both image interpretation skills using a Qualtrics-based test and image acquisition skills using an POCUS-Objective Structured Clinical Examination (OSCE). Pre-tests and post-tests were administrated prior to and after completion of the program. Comfort with ultrasound skills was gauged using a 5-point Likert scale.

Results: 12 fellows and trainees have so far started the course; 4 have completed all modules and the remaining are continuing training. Of the 4 who completed training, fellows were mean (sd) 7.3 (2.2) years after graduation from medical school. 25% of fellows had used POCUS before for diagnostic purposes, but none were formally trained in use. The fellows that completed the course reported significant improvement ($p < 0.05$) in assessing kidney pathology, bladder volume, ejection fraction, and pericardial effusion. Comparing pre-test to post-test scores, fellows felt significantly more comfortable identifying and assessing pathology across all domains following the course (2.40 (0.87) to 4.20 (0.65), $p < 0.001$). At the end of the course, 100% of fellows agreed or strongly

agreed that POCUS was easy to obtain, improved assessment of patients, should be a part of the fellowship, and that other nephrology colleagues and faculty should be trained.

Conclusions: A 2-week nephrology-specific P OCUS c urriculum i s f easible and enhances fellows' learning experience.

SA-PO914

Nephrology Practice and Training in the Intensive Care Unit: Results of a United States Survey Paul J. Mccarthy,[2] kemsha Z. Huslin,[1] Farhan Ali.[1] *[1]Smithsburg, MD; [2]University of Maryland, Baltimore, MD.*

Background: Renal pathology is common in the intensive care unit (ICU). Understanding of the entire ICU patient is optimal. We completed a survey looking at opinions of intensivists and nephrologists regarding renal replacement. There was agreement on many issues and disparity in some areas. We completed a second survey on ICU nephrology to identify potential areas for future study and imrpovements in our training program.

Methods: A survey on renal replacement was emailed to training program directors in critical care medicine and nephrology and to nephrologists from a department database. A second survey was emailed to program directors in nephrology and nephrologists from a department database with questions on practices and nephrology training related to the ICU. Questions in the second survey were the result of responses from the first survey.

Results: Respondents were from both academic and non-academic settings, large and small centers and were from all parts of the country. The 1st survey showed agreement among nephrologists and intensivists on indications to start renal replacement and dosing for CRRT. There were differences based on specialty in volume assessment and rounding patterns. Half of responding to the second survey stated that up to 50% of their patients are in the ICU. Most respondents report that they place dialysis catheters, manage hemodialysis, CRRT and half prescribe pheresis. 75% have not participated in a continuing medical education (CME) activity specific to ICU nephrology in the last year. Rarely respondents round on patients at night. For training programs, less than half reported a minimal of proctored CRRT cases are required. 40% of training programs give renal fellows specific training in hemodynamic monitoring and 15% or less of programs report training fellows in ultrasound, mechanical ventilation or require a formal rotation as part of an ICU team.

Conclusions: Nephrologists spend a good portion of time seeing ICU patients. Most place dialysis catheters, manage hemodialysis, CRRT and many manage pheresis. 75% have not participated in a CME specific to ICU nephrology in the last year. Most nephrology training programs have no minimum requirement of proctored CRRT cases and most programs do not train fellows in hemodynamic monitoring, ultrasound, mechanical ventilation or require dedicated time as an ICU team member.

SA-PO915

Assessing Teaching Practices in Percutaneous Kidney Biopsy among Pediatric Nephrology Training Programs Shamir Tuchman,[1] John D. Mahan.[2] *[1]Children's National Medical Center, Washington, DC; [2]Nationwide Children's Hospital, Columbus, OH.*

Background: Standardized approaches for teaching kidney biopsies in pediatric nephrology fellowship training have not been established. To date, there has not been a comprehensive assessment of kidney biopsy teaching practices among pediatric nephrology training programs. The purpose of this study was to determine common practice patterns for teaching kidney biopsies for pediatric nephrology trainees.

Methods: An online survey was piloted and administered to training program directors (TPD's) at 40 ACGME accredited pediatric nephrology training programs in the United States.

Results: 28 (70%) of TPD's completed the survey. Trainees performed the majority of all kidney biopsies at 73% of the institutions with the majority (63%) of kidney biopsies performed by 1st year trainees. A supervising attending nephrologist was uniformly in attendance in the procedure area. Less than 50% of programs used didactic instruction or simulations in teaching obtaining consent and performing kidney biopsies. "Observation" was uniformly employed (100%) as the primary teaching modality for these purposes. All institutions used ultrasound localization for kidney biopsies. In 22% of the institutions, the trainee performing the biopsy was responsible for ultrasound guidance of the biopsy needle. 86% of the programs that have the nephrologist performing simultaneous ultrasound provided formal instruction in ultrasonography to their trainees. There was a broad range in the number of kidney biopsies performed by each trainee through training ranging from 10 to 150 biopsies with 10-80% of these performed in renal allografts. Among TPD's, the minimum number of kidney biopsies felt to be sufficient to attain competency for independent practice was 10 with the majority (57%) of TPD's feeling that 20-40 biopsies were necessary for a trainee to achieve competence. 92% of training programs provide teaching in the interpretation of kidney biopsies using a combination of didactic instruction (73%), renal pathology conferences (93%), and formal rotations with pathology within or outside their institutions (63%).

Conclusions: Despite a lack of formalized guidance or national standards, pediatric nephrology training programs employ common practices in teaching pediatric nephrology trainees to competently perform kidney biopsies in children and adolescents.

SA-PO916

Virtual Patient Simulation Improves Clinical Decisions for Hyperkalemia Treatment in Patients with Heart Failure Susan Gitzinger, Donald Blatherwick, Douglas Blevins. *Medscape, Lexington, KY.*

Background: This study was conducted to determine if an online, virtual patient simulation-based continuing medical education (CME) intervention could improve performance of nephrologists and cardiologists in the management of patients with heart failure and hyperkalemia.

Methods: The CME intervention comprised 2 cases presented in a virtual patient simulation (VPS) platform, allowing learners to choose from lab tests, diagnoses, and treatments matching the scope and depth of actual practice. Learner clinical decisions, entered using open field entries, were analyzed using a sophisticated decision engine; tailored clinical guidance (CG) was provided based on current evidence and expert recommendation. Decisions were collected post-CG and compared with each user's pre-CG data using a 2-tailed paired t-test to determine *P* values. Data is reflective of learners who participated in the assessment from 2/23/17 to 4/21/17.

Results: Significant improvements include: *Case 1 (n=86 nephrologists, n=126 cardiologists):* Nephrologists and cardiologists demonstrated statistically significant changes from pre-CG to post CG in (all P<0.001): Diagnosis of hyperkalemia (3% vs 37% of nephrologists; 0% vs 45% of cardiologists) Orders for patiromer (1% vs 29% of nephrologists; 1% vs 36% of cardiologists) Orders for a preferred beta-blocker (12% vs 51% of nephrologists; 26% vs 56% of cardiologists) Orders for an ACEi (12% vs 40% of nephrologists; 30% vs 56% of cardiologists) Orders for influenza vaccination (0% vs 35% of nephrologists; 0% vs 36% of cardiologists) *Case 2 (n=68 nephrologists, n=102 cardiologists):* Nephrologists and cardiologists demonstrated statistically significant changes from pre-CG to post CG in (all P<0.001): Orders for patiromer (35% vs 68% of nephrologists; 21% vs 63% of cardiologists) Orders for sacubitril/valsartan (10% vs 46% of nephrologists; 19% vs 59% of cardiologists) Orders for influenza vaccination (0% vs 46% of nephrologists; 0% vs 40% of cardiologists) Orders for pneumococcal vaccination (0% vs 49% of nephrologists; 0% vs 43% of cardiologists)

Conclusions: This study demonstrated the success of online, VPS-based education that engages nephrologists and cardiologists for an authentic and practical learning experience that can improve evidence-based clinical decisions in the management of hyperkalemia in patients with heart failure.

Funding: Commercial Support - Relypsa

SA-PO917

CKD-Related Hyperkalemia: Effectiveness of Online Medical Education on Clinical Decision-Making Susan Gitzinger,[1] Karen Badal,[2] Donald Blatherwick.[1] *[1]Medscape, Lexington, KY; [2]WebMD, New York, NY.*

Background: Inhibition of the renin-angiotensin-aldosterone system (RAAS) has become a cornerstone of evidence-based therapies in chronic kidney disease (CKD), diabetes, and heart failure. Despite this, RAAS inhibitors remain widely underutilized in current clinical practice. We sought to determine if participating in a case-based online educational intervention related to CKD management improves clinical decision-making of nephrologists and cardiologists in the United States.

Methods: An interactive, case-based, online CME activity was developed. The educational effects were assessed using a repeated pairs pre-assessment/post-assessment study design. For all questions combined, the McNemar's chi-squared test assessed whether the mean post-assessment score differed from the mean pre-assessment score. P values are shown as a measure of significance; P values <.05 are statistically significant. Cramer's V was used to calculate the effect size (0.06-0.15 is a small effect, 0.16-0.30 medium, and >0.30 large). The activity launched on December 19, 2016, and data were collected through January 24, 2017.

Results: Improved clinical-decision making was seen among nephrologists (n = 130) and cardiologists (n = 107) pre- to post-assessment in (all *P*<.001): Causes of CKD progression in individual patients (nephrologists: 73% to 92%, V=0.242; cardiologists: 53% to 81%, V=0.299) Optimization of RAAS inhibitors in CKD (nephrologists: 55% to 87%, V=0.355; cardiologists: 55% to 79%, V=0.259) Alternative options for management of hyperkalemia and safe polypharmacy in patients requiring maximization of RAAS inhibition (nephrologists: 64% to 83%, V=0.218; cardiologists: 43% to 68%, V=0.254)

Conclusions: Participation in this interactive, case-based, online CME activity resulted in improved clinical decision-making by nephrologists and cardiologists in the management of patients with CKD particularly in regard to safe and appropriate maximization of RAAS inhibition. Significant improvements were seen in considering causes for CKD progression, the importance of effective RAAS inhibition and RAAS inhibitor maximization, and alternative management strategies in patients with hyperkalemia.

Funding: Commercial Support - Relypsa

SA-PO918

Success of CME at Improving Physicians' Knowledge of Diagnosis and Treatment of Hepatorenal Syndrome Susan Gitzinger,[1] Donald Blatherwick,[1] Julia A. Muino.[2] *[1]Medscape, Lexington, KY; [2]Medscape, LLC, New York, NY.*

Background: Timely diagnosis and intervention are critical for improving outcomes for patients with hepatorenal syndrome (HRS), yet most specialists are not fully confident in their ability to identify and classify HRS, or to select appropriate pretransplant

therapies. We sought to determine if continuing medical education (CME) improves physician knowledge of the diagnosis and treatment of HRS.

Methods: The CME activity consisted of an online video roundtable discussion among leading experts in HRS. Participants completed a 4-question survey before and after the activity to identify changes to knowledge, competence or confidence in relation to a specific clinical situation. A repeated pairs pre-assessment/post-assessment study design was used. The analysis included: - A paired, 2-tailed t-test to assess differences between mean pre- to post-assessment scores - McNemar's chi-square test assessed differences from pre- to post-assessment; P values <.05 are statistically significant - Cramer's V to determine effect size Survey data were collected from March 29, 2017 through May 2, 2017.

Results: In total, nephrologists (n=127) and gastroenterologists (n=139) improved their understanding and competence in several specific topic areas including (data expressed as % correct pre-assessment vs % correct post-assessment; all $P<.001$): - The link between HRS and ascites (88% vs 99% of nephrologists and 85% vs 96% of gastroenterologists) - Characteristics of type 1 HRS (72% vs 98% of nephrologists and 69% vs 93% of gastroenterologists) - Appropriate first-line therapies for patients with type 1 HRS awaiting liver transplantation (52% vs 80% of nephrologists and 60% vs 84% of gastroenterologists) Overall, the educational effect size was medium, indicating a noticeable effect on participants' ability to choose correct responses (nephrologists: V=0.285; gastroenterologists: V=0.251). In addition to these gains in clinical knowledge. 46% of nephrologists and 52% of gastroenterologists indicated that they felt more confident in their ability to properly diagnose HRS after participation in this education.

Conclusions: This study demonstrates that a well-designed online CME initiative can have a positive effect on both nephrologists and gastroenterologists, resulting in significant improvements ($P<.05$) in clinical knowledge and competence seen in both audiences on all topics presented.

Funding: Commercial Support - Mallinckrodt

SA-PO919

Best Practices in Social Media Xavier F. Parada, Miguel A. Cota, Arvind Conjeevaram, Basu Gopal, Fernanda Arce, Jose E. Lopez-Almaraz, Krishnam R. Penmatsa, Rolando Claure-Del Granado, Sonia Rodriguez, Tejas P. Desai. *@ISNeducation, Brussels, Belgium.*

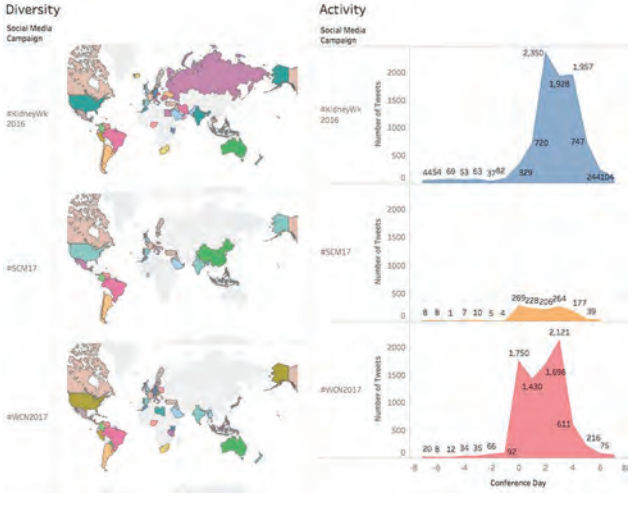
Background: Nephrology societies have begun to use social media (SoMe) during meetings. However live coverage is limited, decentralised & disorganised

Methods: We compare 3 SoMe operations to identify successes & flaws. The NKF & ISN deployed vanguard SoMe strategies: The NKF's Social Media Ambassador Program asked volunteers to participate in #SCM17 campaign if they agreed to 6 stipulations. The ISN's Social Media Task Force assigned specific tasks to members giving full support to broadcast the #WCN2017 campaign. These were compared to the #KidneyWk 2016 campaign that employed no known strategy, analyzing the Activity, Diversity, & Vibrancy using NOD Analytics

Results: #KidneyWk contained 8032 tweets but had a 1-day greater duration. It's 5-day-best activity was only 1% greater than #WCN2017. Participants in #WCN2017 & #KidneyWk came from 55 nations. #WCN2017 represented Latin American, Caribbean, & African nations the best. #SCM17 & #KidneyWk represented the Middle East the best. Nearly 45% of tweets in #SCM17 were vibrant. #WCN2017 followed closely w/43% & #KidneyWk w/38% vibrant tweets

Conclusions: A strategy of assigned tasks and organizational support offers the best balance of activity, diversity, and vibrancy. #WCN2017 earned a high global reach (55 nations) and vibrancy (43% of tweets) while not sacrificing activity (-1% from the top campaign)

Funding: Private Foundation Support



Tweet diversity & activity

SA-PO920

Improvement in Self-Perceived Clinical Competence among Indiana University Nephrology Fellows after Intersession Ayman Hallab, Michael T. Eadon, Ranjani N. Moorthi, Brian S. Decker. *Indiana University School of Medicine, Indianapolis, IN.*

Background: The first year of Nephrology fellowship training is a clinically intensive experience in the USA. Our Nephrology fellowship program introduced an Intersession for first-year fellows during the academic year 2016-2017. We hypothesized that an intersession will improve fellows' self-perceived competence in core nephrology disciplines.

Methods: A 2-week intersession included hands-on training in home hemodialysis, peritoneal dialysis, and temporary catheter placement. Instruction in acute kidney injury management, hypo/hypernatremia, acid-base disorders and resistant hypertension was conducted via didactics, independent readings, and case-based discussions. Small-group workshops emphasized consultant professionalism. Fellows were exempt from clinical duties with the exception of their once weekly continuity clinic. An anonymous survey of 8 questions was conducted before and two weeks after the intersession to rate self-perceived competence. A scale of 1 to 5 was used to assess self-competence.

Results: All five first-year fellows participated in the Intersession. Five pre-surveys and 4 post-surveys were collected. One pre-survey was not adequately filled and excluded from the analysis. The average competence pre- and post-intersessions are shown in table 1. There was an increase in competence in AKI, acid-base, hypertension, and home hemodialysis management ($p<0.05$ for all). There was an increase in overall competence ($p<0.05$).

Conclusions: An intersession for first-year nephrology fellows significantly improves self-reported competence. It is expected that intersessions will be continued in the following years in the Nephrology fellowship program and longer term outcomes will be available.

Table 1- Self-reported competence pre- and post-intersession

	Pre	Post	p-value
Acute Kidney Injury	3.25	4.33	0.045
Hypo/hypernatremia	3.25	3.75	0.390
Acid-base disorders	2.75	3.75	0.030
Temporary catheter insertion	3.50	4.50	0.356
Hypertension	2.50	4.25	0.004
Home hemodialysis	1.75	3.00	0.002
Peritoneal Dialysis	2.75	3.25	0.207
Consultant Professionalism	4.25	4.75	0.207
Overall Competency	3.00	3.95	0.010

SA-PO921

Comparison of Five Methods of Measuring Specific Gravity in Mock Urine Solutions Heidi Saxton,[3] Nirupama Ramkumar,[2] Martin C. Gregory.[1] *[1]Salt Lake City, UT; [2]University of Utah, Salt Lake City, UT; [3]University of Utah School of Medicine, Salt Lake City, UT.*

Background: Urine specific gravity (SG) is commonly used as an indicator of urine concentration in the clinical nephrology setting. SG measurements can aid in distinguishing pre-renal etiologies from acute tubular necrosis, although the accuracy of these measurements by different methods remains unknown. Our main objective in this study was to compare five methods of measuring SG in solutions that resemble normal and pathologic urine specimens.

Methods: We measured the SG and osmolality of solutions with varying concentrations of salts, glucose, urea, albumin, and intravenous contrast using the methods of hydrometry (urinometer), refractometry, reagent strips, and pycnometry. Samples were also sent to the hospital clinical laboratory for measurement by automated refractometry. Slope of SG versus osmolality and Pearson's correlation coefficient was calculated for each method.

Results: Slopes of SG by hydrometry correlated most closely with slope of specific gravity by pycnometry across all solutions (r value of 0.996). Slopes of SG by refractometry and clinical laboratory methods correlated moderately well (r values of 0.950 and 0.927, respectively), while slopes of SG by reagent strip correlated very poorly (r value of -0.434).

Conclusions: As mock urine solutions become more concentrated, the method of hydrometry correlates most closely with pycnometry. Refractometry manually and by clinical laboratory have moderate accuracy, while the method of reagent strip performs very poorly. This latter method may have poor clinical utility, especially in pathologic urine from patients with kidney disease.

Correlation of slope of specific gravity against calculated osmolality with pycnometry slope

	Refractometry	Reagent strip	Hydrometry	Clinical laboratory
All solutions	0.9499	-0.4341	0.9963	0.9265
NaCl, Urea, Albumin/urea, Glucose/urea	0.9701	-0.1686	0.9984	0.9494

SA-PO922

Patient Impressions of Hemodialysis and Peritoneal Dialysis
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Background: It is established that the more a patient knows about peritoneal dialysis (PD), the more likely he is to select it. At our center, patients with advanced chronic kidney disease (CKD) are referred to a dialysis options visit with a nurse educator to learn about PD and hemodialysis (HD). In the current project, we spoke to CKD patients to collect feedback about the visit.

Methods: Patients with stage 4 or 5 chronic kidney disease (CKD) were invited to a semi-structured interview immediately following their education visit. The interviews were recorded and transcribed. Qualitative content analysis was conducted by two staff members using NVivo 11 software. Basic demographics were collected.

Results: The mean age of the 10 CKD patients interviewed was 62 years (SD = 9.4). 60% were female, 40% were married, and 40% were Caucasian. 40% were not educated beyond high school, 60% reported an annual income of < $20,000. Most patients did research before their education appointment. This typically involved an internet search (n=7), however others also spoke to dialysis patients, talked with their doctors/nurses, and one patient visited a unit. Only three patients said they knew nothing about dialysis before the visit. The patients interviewed displayed a preference for HD because of the perceived ease of therapy. The major advantages described were the schedule (with days off) and the fact that the therapy was delivered by others (the notion of just needing to show up). Only a minority of patients identified shortcomings of HD. One patient described the time commitment as a disadvantage and a few patients voiced concerns about the need for a fistula and needles. PD in contrast was overwhelmingly viewed as a burdensome therapy. Patients were dismayed by the need to store supplies at home, to complete dialysis daily on their own, and the potential for infection. A couple of patients did not want the nurse to explain PD. Only two patients seemed to be considering PD as an option.

Conclusions: The patients interviewed displayed little confidence they would be able to successfully complete PD and were left with a negative impression. In contrast, there was little perceived downside to HD. These results may reflect the shortcomings of our current model of education. Further research is needed to determine different styles of education can overcome these barriers and improve utilization of PD.

Funding: Commercial Support - Baxter

SA-PO923

Developing Partnerships to Advance Renal Care and Ameliorate "Brain-Drain" in Haiti
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Background: Immediately following the earthquake in Haiti (Jan 2010), BR provided acute hemodialysis (HD) for several patients with acute kidney injury (AKI). This involved major support and equipment from the Dartmouth community and Partners in Health/Zanmi Lasante. Once the earthquake crisis ended, we recognized that it would require a concerted effort and multiple partnerships to bring ongoing renal care to Haiti. Furthermore, despite Haiti investing years of free training of health care professionals, over 80% leave the country creating a "brain-drain" due to lack of jobs, low pay, little ongoing medical education and few resources to provide adequate patient care.

Methods: Two academic institutions, DHMC and BIDMC, have established partnerships with Bridge of Life, Sustainable Care Kidney Foundation, Partners in Health and Zanmi Lasante and our new charity, TORCH, along with NxStage Medical, Inc, to initiate treatment of AKI with HD at HUM. We have effectively used teleconferencing between DHMC and HUM to provide education, biomedical support, train staff, and build relationships. We subsequently have developed a "mini" fellowship program inviting Haitian physicians and nurses to DHMC and BIDMC for short (2 week) training venues to provide specific skill development and ongoing mentoring.

Results: With the help of our partners, nurses and residents came from HUM to the USA for specific training in HD, central line placement, urinalysis, AKI diagnosis, echocardiography, and peritoneal dialysis treatment and complications. Teleconferencing has been used to provide ongoing contact and reinforce training. Since 2014, 41 patients with AKI have been treated with HD at HUM with 25 patients surviving.

Conclusions: The development of industry/academic/NGO partnerships was able to build a successful program for treating AKI. Long-term relationships with nurses and residents at HUM via teleconferencing and "mini" fellowships has advanced renal patient care, supported the physicians and nurses at HUM, and may provide a partial answer to the problem of "brain-drain" that impairs Haitian medical care.

Funding: Private Foundation Support

SA-PO924

Conflicts of Interest in Nephrology Clinical Practice Guidelines
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Background: Clinical practice guidelines (CPG) are evidence-based guidelines, which serve as a standard of care in practice, quality improvement and reimbursement. The extent of conflicts of Interest (COI) in Nephrology CPG's has not been well studied. Our study evaluated the extent of COI in the Kidney Disease Improving Global Outcomes (KDIGO) practice guidelines. We also attempted to correlate this to the level of evidence and strength of recommendations outlined in KDIGO guidelines.

Methods: We examined 9 of the most recent KDIGO's CPG which developed between 2008 and 2013. Using disclosure lists, we catalogued COIs for participants in each CPG work group. The categories included : Advisor/ consultant, Honoraria, Travel stipend, Grant/ Research support, Speaker, Equity interest, Employee, Board of trustees, Royalties, Board of Directors, Employment, Ownership interests, Data monitoring committee, Expert testimony and Development of education materials. We reviewed COIs for members of the evidence review team (ERT) as well. We cataloged the companies/ institutions involved in each disclosure. Episode describes 1 instance of participation of an individual in 1 company in 1 category of each guideline. "Company" describes a commercial, industry or institute affiliation reported by an individual in each episode. We correlated this data to a previously published article: A systematic review of evidence underlying KDIGO guidelines (Am J Kidney Dis.2016 Mar; 67(3):417-22)

Results: 93 (65.9%) of a total of 141 individuals reported COIs. A total of 758 episodes were disclosed. Being a consultant/ advisor was the most common category (31%) followed by Grant/ research support (29%). The % of episodes varied between CPGs (6.3%-19.5%). A total of 127 companies were associated with COI disclosure. 1 company was the most frequently reported company involving 82 (10.8%) of the 758 episodes. Only 1 member in the ERT reported 1 COI. The guideline with the maximum episodes (19.5%) had 3% recommendations as Category 1A and 33% as 2C. Guideline with lowest number of episodes (6.33%) had the highest number of recommendations category 1A (19%)

Conclusions: COIs are prevalent in KDIGO guidelines with up to 2/3rd of participants disclosing COI. The ERT however had only one COI to report. We were not able to clearly correlate the strength of recommendations in each guideline with COI in the same guideline.

SA-PO925

Knowledge and Practice Patterns in the Diagnosis, Evaluation, and Management of Mineral Bone Disease in CKD among Primary Care Physicians and Nephrologists
Brittany L. Schreiber, Flor Espinoza, Omar A. Aleter, Hania Kassem. *University of Texas Medical Branch, Galveston, TX.*

Background: Mineral bone disease in chronic kidney disease (CKD-MBD) is a systemic disorder encompassing mineral, bone, and calcific cardiovascular abnormalities that develop as a complication of CKD and contribute to morbidity and mortality in these patients. Despite the availability of guidelines, there continues to be a disparity in practice patterns contributing to therapeutic inertia. Our aim was to identify gaps in knowledge and variations in clinical practice among primary care providers in comparison to nephrologists regarding the diagnosis, evaluation and management of CKD-MBD especially in earlier stages of CKD when patients might not be followed by a nephrologist.

Methods: This study was conducted using a questionnaire which was distributed to residents, fellows and faculty in primary care specialties and nephrology. Questions were derived from the 2009 practice guidelines from the Kidney Disease Improving Global Outcomes work group and the 2003 National Kidney Foundation's Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease.

Results: Nephrologists scored higher than primary care physicians in all areas tested including pathophysiology of the disease, screening parameters and intervals, target levels and treatment strategies. The difference in score was statistically significant in the majority of those areas. Overall, primary care specialists (n of 51) scored an average of 31.7 % while nephrologists (n of 11) scored an average of 80.3 % (p-value <0.01).

Conclusions: Our investigation showed there is a significant discrepancy in knowledge between primary care physicians and nephrologists regarding diagnosis and management of CKD-MBD. It is necessary to improve primary care physicians' knowledge and practice in this field to provide high quality of care to patients. Our next steps include physician education and creation of best practice advisory alerts using the electronic medical record system which will include criteria for appropriate nephrology referral for this subset of patients.

SA-PO926

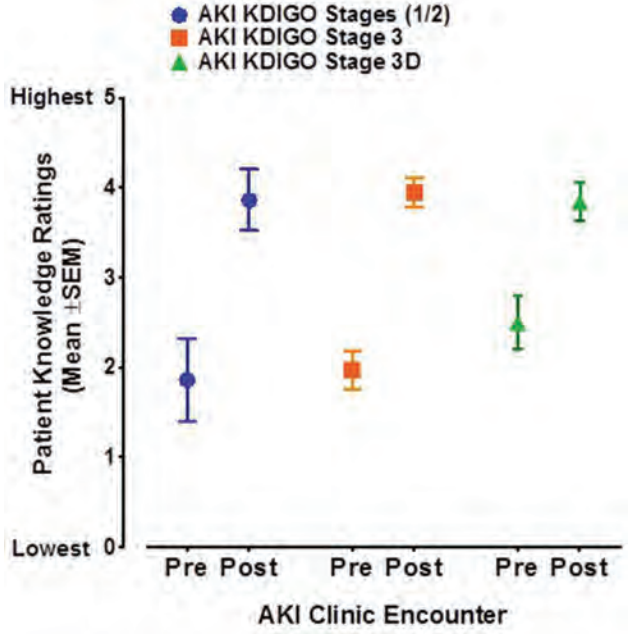
Examining Patients' Knowledge about AKI in Hospital Survivors Followed in a Dedicated AKI Clinic
Victor M. Ortiz-Soriano,[1] Joseph L. Alcorn,[1] Fabiola G. Gianella,[1] Brian S. Armentrout, MS, PA-C,[1] Taha Ayach,[1] B. Peter E. Sawaya,[2] Hartmut H. Malluche,[1] Javier A. Neyra.[2] *[1]University of Kentucky, Lexington, KY; [2]University of Kentucky Medical Center, Lexington, KY.*

Background: Acute kidney injury (AKI) survivors are at high risk of adverse outcomes. There are few clinics dedicated to improving the care of AKI survivors. Specialized post-discharge nephrology care may improve AKI literacy and prevent renal and non-renal complications. We examined self-rated AKI knowledge in AKI survivors followed in a specialized AKI Clinic.

Methods: This is a prospective study of 62 non-dialysis dependent AKI survivors. Patients self-rated the level of knowledge about their AKI diagnosis and the level of severity of their AKI at two time-points: pre and post their first clinic encounter. AKI was defined by KDIGO criteria. Patients' ratings (scale: 1 lowest to 5 highest) were compared by KDIGO stages and by the occurrence of renal recovery (ratio of the first clinic encounter serum creatinine (SCr)/baseline SCr ≤1.5). Mixed-model ANOVAs were utilized.

Results: Mean (SD) age was 54 (14.7) years; 51.6% were males and 87.1% whites. Patients' ratings of their knowledge about AKI significantly increased following the clinic encounter (p=0.001 for each KDIGO stage [**Figure 1**] and each renal recovery group). Patients with AKI KDIGO Stages 1 and 2 rated their AKI as less severe than patients with AKI Stage 3 (p=0.049) and Stage 3D (p=0.002). There were no differences in the level of severity of AKI ratings by renal recovery status.

Conclusions: Post-discharge specialized nephrology care increased patients' self-assessed knowledge about their AKI diagnosis. Patients with higher KDIGO stages rated the severity of their AKI as more severe than those with lower KDIGO stages, indicating that the survey has face validity. Future studies should examine the impact of patients' AKI literacy on patient-centered outcomes.



SA-PO927

Talking Animated Videos to Educate Patients with Kidney Disease Jonathan Slater. *Longmeadow, MA.*

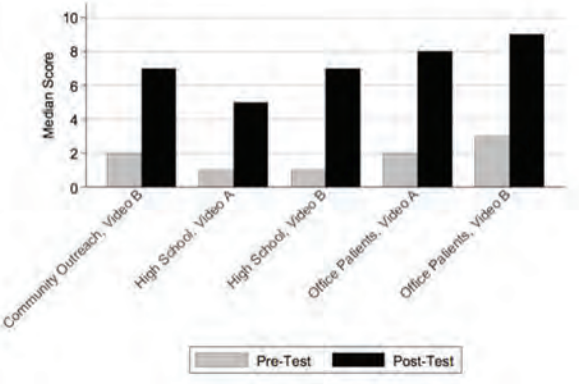
Background: Improved patient understanding of their disease state promotes engagement and facilitates partnership and shared decision making. Digital Health education utilizing animated videos (AV) are gradually being incorporated into EMRs (e.g. EMMI, EPOCH, etc.) to help fill this need; however, there is very limited data on their effectiveness in educating both low and high healthcare literate patients. Kidneyman (KM) had its beginngs 7 years ago with a mission for patient education. It has now created a library of AV for patient kidney education. This study provides a preliminary assessment of the efffectiveness of these AV in educating different sub-populations.

Methods: The following AVs from the library of KM were used for this study: Understandig Chronic Kidney Disease (A) and Treamnt Options for patients with ESRD (B). The AVs, which are 5-7 minutes in length, were shown to different sub-population incuding: high-schoolers heath class ; attendees to communty outreach Kidney Program and indivdual patients being seen in Nephrologists outpatient office. Viewers of the videos were given the same specific questionaire, designed for that particluar AV, before and after watching the videos and the results were culminated and analyzed. Videos can be watched by going to kdneyman.co

Results: The results for the Outreach to the Community participants for Video B, the high-schoolers for Video A and B as well as the office patients for both videos all showed significant improvement in number of correct answers after watching the video (see Table and Graph).

Conclusions: The results from this study do support these AVs as being effective in educating 3 different sub-group of populations. The style and format of all the AVs in the Kidneyman library have been specifically desinged to reach both low and high healthcare literate people and further testing to validate this is ongoing.

Group	Pre-test Median [25th, 75th percentile]	Post Test Median [25th, 75th percentile]	p-value from the Wilcoxon matched-pairs signed-rank
Outreach to community; Video B; N = 25	2 [1,3]	7 [4,9]	<0.001
High School; Video A; N = 15	1 [1,2]	5 [4, 8]	<0.001
High School; Video B; N = 28	1 [1, 2]	7 [6, 8]	<0.001
Office Patients; Video A; N= 5	2 [2,2]	8 [7, 9]	0.04
Office Patients; Video B; N = 5	3 [3, 4]	9 [9,10]	0.04



SA-PO928

Enhancing Learning and Interest in Nephrology among United States Medical Students Hitesh H. Shah, Nupur N. Uppal, Kenar D. Jhaveri. *Hofstra Northwell School of Medicine, Great Neck, NY.*

Background: Interest in nephrology careers remains low among United States (US) medical graduates. The type of nephrology elective that US medical students experience may play an important role in creating and enhancing interest in nephrology career.

Methods: A redesigned 4-week nephrology elective was created at our institution for US medical students. Our redesigned elective included both 2-week inpatient (IP) and 2-week outpatient (OP) nephrology experiences. The OP rotation included 10 half-days of various nephrology clinic experiences, 2 half-days of immediate post-transplant clinic, 1 half-day of kidney donor evaluation clinic, 2 half-days of PD clinic and 3 half-days of outpatient HD rounding. Our redesigned elective also included educational conferences. To evaluate the elective experience, all medical students were asked to complete an on-line survey following the completion of their rotation.

Results: From July 2012 to April 2017, nineteen 4th year medical students (from 14 different US medical schools) completed our redesigned elective. All students responded to our survey. All reported adequate OP nephrology experience during their elective. 84% of the students had worked with 1 or 2 faculty members during the IP setting. In comparison, 90% were exposed to at least 4 different faculty members during the OP experiences. All students had interacted with at least 3 fellows. All reported that the elective experience enhanced their exposure and knowledge in nephrology. They also thought that this elective structure provided them with a better insight into what nephrologists do in practice. 84% of the students reported that this elective experience created an interest in nephrology career. Majority (68%) of the students responded that they would consider nephrology as one of their 3 top career choices as a result of this elective experience.

Conclusions: Measures to enhance learning and interest in nephrology among medical students are needed. We believe that the restructured elective provides the medical student with a much needed and realistic exposure to nephrology careers. Based on our experience, we recommend nephrology training programs to consider this elective structure for medical students.

SA-PO929

CKD Patient and Provider Feedback Surrounding Dialysis Modality Education Kristin M. Corapi,[1] Warissara Sorat,[3] Ishir Bhan.[2] *[1]Massachusetts General Hospital, Boston, MA; [2]None, West Newton, MA; [3]university of Massachusetts Lowell, Lowell, MA.*

Background: Both hemodialysis and peritoneal dialysis impact patients' lifestyles. In an effort to help patients make an informed choice, the nephrology community is

encouraged to provide education about dialysis options. At our hospital, this involves a one on one visit with a nurse educator. In the current project, we talked with patients and providers to get feedback on our dialysis education.

Methods: Patients with chronic kidney disease (CKD) stage 4/5 and providers were invited for semi-structured interviews. The interviews were recorded and transcribed. Qualitative content analysis was conducted by two staff members using NVivo 11. Basic demographics were collected.

Results: The mean age of the ten CKD patients enrolled was 62 years (SD = 9.4). 60% were female and 40% were Caucasian. 40% were not educated beyond high school and 60% reported an annual income of < $20,000. The providers interviewed (n=11) were 5 MD's, 4 RN's, 1 social worker, and 1 one dietician. The mean age of providers was 49 years (SD= 13.1) with an average of 18 years in practice (SD = 9.1). 64% were Caucasian and 64% were female. Following the visit, half of the patients reported feeling scared, confused or disappointed to learn they might need dialysis. Similarly, staff depicted patients as in denial, resigned, overwhelmed, and stressed. The majority of patients felt that the single visit provided all of the information needed to choose a modality. The remaining patients (n=4) asked for additional information about diet, lifestyle changes, and how to slow further CKD progression. Staff agreed that diet and lifestyle changes are difficult for patients to understand and might be topics that would benefit from more explanation. Patients recommended the use of videos, written material, emails, and talking to peers as strategies to help improve their understanding. Staff agreed that the addition of a patient network would be beneficial. Staff also suggested having more than one visit, group classes, multi-disciplinary involvement, and introducing dialysis earlier in the CKD trajectory would help patients choose a dialysis modality.

Conclusions: The referral to dialysis education is stressful to patients as they begin to accept the severity of their disease. Employing various educational styles, venues, and peer support may help ease these emotions and help patients to choose the modality best for them.

Funding: Commercial Support - Baxter

SA-PO930

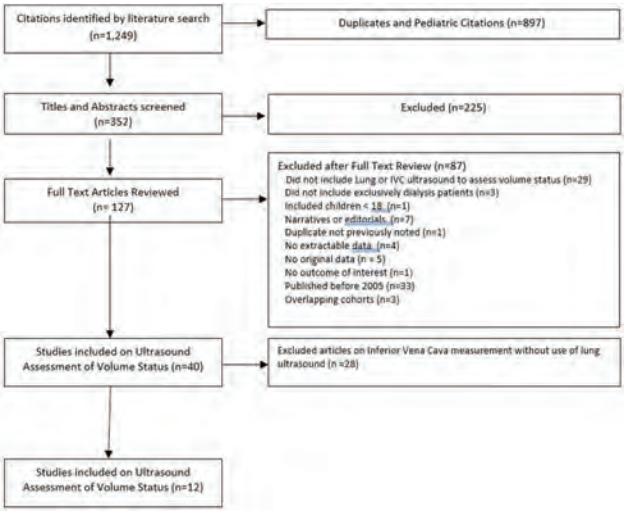
Lung Ultrasound in ESRD: Moving from Evidence to Practice Daniel W. Ross,[5] Mohammed Abbasi,[2] Kenar D. Jhaveri,[1] Mala Sachdeva,[3] Richard L. Barnett,[3] Mangala Narasimhan,[6] Anna Mathew.[4] *[1]Hofstra Northwell School of Medicine- Northwell health system, Great neck, NY; [2]Montefiore Medical Center, Bronx, NY; [3]None, Great Neck, NY; [4]North Shore-LIJ Health System, Great Neck, NY; [5]Medicine, Division of Nephrology, Hofstra Northwell School of Medicine, Great Neck, NY; [6]Northwell, Sleepy Hollow, NY.*

Background: Lung ultrasound (US) allows for enhanced ability to detect extravascular lung water compared to traditional physical exam or standard chest XRay. This is extremely important for our CKD and ESRD patients to assess volume status. Training in using point of care US that includes lung US is vital in this era for our fellows and faculty. We conducted a review of lung US use in dialysis patients and assessed how it was taught to researchers.

Methods: We conducted a strategic search in Medline, Embase, Cochrane, and Web of Science. Eligibility criteria for included studies were: (1) 5 or more adults (age ≥ 18) with ESRD on chronic dialysis; (2) measured and reported lung US findings; and (3) reported another comparator outcome measure of volume status. Articles that looked at only IVC and not lung US were excluded. Titles and abstracts were screened by a single reviewer and the remaining full texts were reviewed independently by two reviewers. Discrepancies were resolved by a third reviewer.

Results: We identified 1,249 articles of potential interest. After title and abstract screening, we reviewed 352 full-text articles. We identified 12 studies where lung US was used to detect extravascular lung water in dialysis patients. In two studies nephrologists were trained but in most studies residents were trained. Reported training time varied from 2 to 3 hours. Time to perform lung US ranged from 6 to 15 minutes. All studies reported high concordance between novice and expert sonographers.

Conclusions: Lung US can be reliably taught to learners in a short 2 to 3-hour training course. Teaching lung US to our nephrology trainees is an important step to improve care collaboration with our critical care and emergency medicine colleagues and improving volume assessment in our CKD and ESRD patients.



SA-PO931

Patient Engagement in ESRD: Do Patients Know Who Their Nephrologist Is? Arjun Sekar,[1] Leslie P. Wong.[2] *[1]Cleveland Clinic Foundation, University Heights, OH; [2]Cleveland Clinic, Solon, OH.*

Background: Patient engagement describes how involved patients are in their care. We observed that some hospitalized dialysis patients are unable to describe their care, including who their nephrologist is. We hypothesize that patients unaware of these basic details may not actively participate in their care. We performed a survey to assess perceptions of the patient-doctor relationship and dialysis care.

Methods: We included hospitalized adult ESRD patients requiring hemodialysis. Intensive care, peritoneal dialysis and non-English speaking patients were excluded. Subjects completed a questionnaire about routine aspects of their dialysis care. We did a descriptive analysis of their responses and attempted to identify trends based on whether or not they knew their nephrologist's name.

Results: Of 66 patients approached, 44 completed the survey. Over one-fifth (23%) did not know their attending nephrologist and 54% said a different nephrologist also rounded on them at dialysis. 74% felt their nephrologist answered their concerns promptly; 44% raised their health concerns with the nephrologist all the time. Only 24% were aware of palliative options. While 93% felt maintaining their dry weight was important to their health, only 60% knew their dry weight. Though 90% thought fluid restriction was important, only 60% stated they were compliant. Most (86%) thought controlling phosphorus was necessary but fewer (64%) were aware of its adverse effects. Sub-analysis of responses (Table) was done based on whether or not patients knew their attending nephrologist.

Conclusions: This study aimed at assessing patient engagement in ESRD. A number of patients reported disjointed perceptions of their dialysis care, including an inconsistent relationship with an attending nephrologist. This might impact discussions about palliative care and willingness of patients to follow advice. Better awareness and focus on the patient- nephrologist relationship in dialysis is needed.

RESPONSES BASED ON WHETHER PATIENTS KNEW THEIR NEPHROLOGIST

	YES=34	NO=10
DIFFERENT NEPHROLOGISTS ROUNDING ON THEM	58%	40%
LIKELY TO FOLLOW NEPHROLOGISTS ADVICE	86%	56%
AWARE OF PALLIATIVE CARE	28%	10%
KNOW THEIR DRY WEIGHT	66%	33%
COMPLIANT WITH FLUID RESTRICTION	91%	88%
AWARE OF ADVERSE EFFECTS OF PHOSPHORUS	74%	30%
THINK DIALYSIS IMPROVES QUALITY OF LIFE	74%	71%

SA-PO932

Penile Calciphylaxis: Suspicion Is the Key Olanrewaju A. Olaoye,[2] Abhilash Koratala.[1] *[1]Gainesville, FL; [2]University of Florida, Division of Nephrology, Gainesville, FL.*

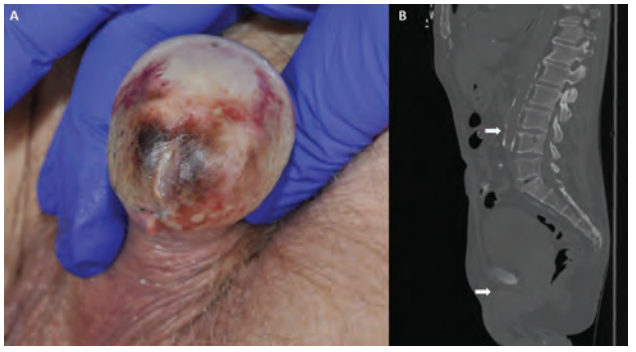
Background: Calciphylaxis or calcific uremic arteriolopathy (CUA) is a rare and potentially fatal condition that presents with skin ischemia and necrosis, typically seen in end stage renal disease (ESRD) patients on dialysis. Histologically, it is characterized by medial calcification of dermal arterioles. CUA commonly involves legs, abdomen and gluteal region. Herein, we present a case of CUA of the glans penis.

Methods: An 81-year old white man with history of hypertension and CKD stage 5 was admitted to the hospital for uremic symptoms necessitating initiation of haemodialysis. He complained of pain and redness of the glans penis that first appeared 3 weeks ago. At that time, he was treated for possible balanitis with antibiotics and had partial relief. He denied having any fever, chills, difficulty urinating or discharge from the urethra. On examination, he had purpuric patches, erosions and superficial necrosis of penile glans with minimal tenderness [Figure 1A]. His labs were significant for serum

creatinine of 12.7 mg/dl, phosphate 8.4 mg/dl, calcium 9.8 mg/dl, albumin 2.6 g/dl, and parathyroid hormone 1131 pg/ml. CT scan of the abdomen showed extensive calcification of the aorta and pudendal vessels [Figure 1B]. Based on the clinical features and imaging evidence of vascular calcification, we diagnosed him with CUA of the penis

Results:

Conclusions: While the definitive diagnosis of CUA requires skin biopsy, it is not routinely recommended for penile lesions because of the risk for progression of necrosis. Risk factors for CUA include White race, CKD-MBD axis abnormalities, obesity, hypercoagulable conditions including protein C and S deficiency, diabetes mellitus, hypoalbuminemia, warfarin use and longer dialysis vintage of over 6-7 years. Management includes intensification of dialysis regimen, phosphate and PTH lowering therapy, and intravenous sodium thiosulfate therapy. Clinicians should be aware of rare presentations of CUA for prompt diagnosis and appropriate treatment



SA-PO933

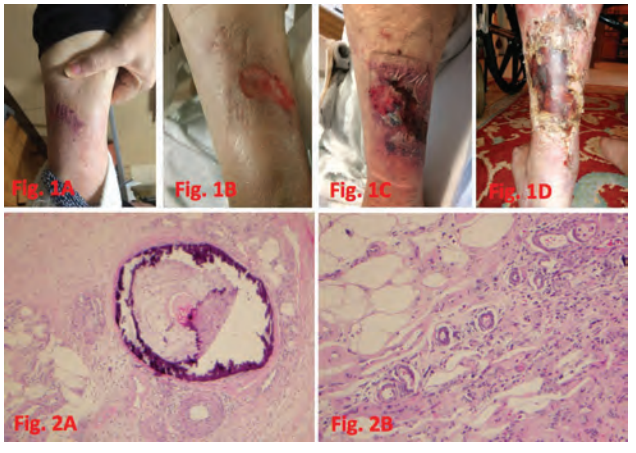
A Wolf in Sheep's Clothing: Calciphylaxis, Innocuous at First Glance Stefan C. Hemmings, Derek M. Fine. *Johns Hopkins University School of Medicine, Baltimore, MD.*

Background: Calciphylaxis is a debilitating skin condition with high mortality seen in patients on dialysis who are at particular risk due to disordered calcium and phosphorus metabolism. Its early features are unfamiliar to many clinicians.

Methods: A 61 year old woman with diabetes on peritoneal dialysis for 5 years with adequate clearance by Kt/V was noted to have an erythematous painful lesion on the left leg (fig. 1A), which was diagnosed as shingles by her primary physician. She presented 2 days later to hospital for complaints of abdominal pain and was noted to have shallow ulceration of the lesion (fig.1B). She was evaluated by dermatology who felt that is was most consistent with venous stasis. Labs results: Calcium 10mg/dL, Phosphorus 6.4mg/dL, Cal-Phos product 58, iPTH 244pg/dL and 25-hydroxy vit D 47.5ng/mL. She was on 30mg cinacalcet for hyperparathyroidism. She followed up in dermatology clinic a few days after discharge and the ulceration had deteriorated as shown in fig. 1C. Concern for its progression prompted a skin punch biopsy that confirmed the diagnosis of calciphylaxis with histopathological features of vascular medial calcification (figs. 2A and 2B). She was readmitted and transitioned to hemodialysis for aggressive therapy with sodium thiosulfate. Despite this, the area of involvement progressed extensively in the left leg and new lesions on the fingers developed. After 10 weeks of treatment the leg lesion appeared to stabilize with eschar formation and healing skin at the borders (fig. 1D).

Results:

Conclusions: Nephrologists and internists alike need to be aware of the initial innocuous presentations of calciphylaxis that may not raise clinical suspicion. The classic eschar is oftentimes a late feature. Early recognition can prevent the morbidity and mortality related to infections and amputations associated with delayed treatment, as the condition can progress rapidly. High vigilance for painful skin lesions is required in patients on dialysis.



SA-PO934

A Rare Case of a Large Calcified Mass in a Calciphylaxis Patient Raju A. Patil,[3] Jason Cobb,[4] Peter Daring,[1] Carol A. Gray,[2] William Mckinnon.[5] *[1]Colorado College, Decatur, GA; [2]Emory Healthcare, Atlanta, GA; [3]Emory University, Decatur, GA; [4]Emory University School of Medicine, Atlanta, GA; [5]Peachtree Vascular Surgery, Atlanta, GA.*

Background: Calciphylaxis is a rare clinical disorder in patients with ESRD and is characterized by painful skin ulcerations due to ischemia and necrosis of the skin and subcutaneous adipose tissue. The disorder carries a mortality rate of 80% in the first year, and death is often due to recurrent infections leading to sepsis. The pathogenic mechanism is not clearly understood and therapeutic options are limited. We present a rare case of a calcified tumor from a patient suffering from calciphylaxis measuring 23.0 x 22.0 x 6.5 cm and 27 x 26 x7.5 cm on the medial aspect of the thigh.

Methods:

Results: A 58 year old black female with ESRD due to a collapsing glomerulopathy, diabetes, developed symptoms of pain and skin ulcerations over her bilateral lower extremities and abdomen. A tissue biopsy of the lesions revealed necrotic ulcerations of the epidermal and dermal layers, and focal calcium deposition in the subcutaneous adipose tissue. She presented to the hospital with symptoms of fever, weakness and pain, with large areas of induration and skin ulcerations (the largest measuring 20 cm) over the inner aspects of the thigh bilaterally. Examination revealed a large area of induration and skin ulcerations with a large firm mass. Lab levels included PTH <100 pg/ml (she presented on cinacalcet), serum phosphorus within normal limits, and unfortunately she had been on long-term warfarin due to chronic dialysis access thrombosis. She was transferred to our hospital for further management of calciphylaxis which included wound care, surgery debridement, and hyperbaric oxygen therapy. Vascular surgery excised 27 x 26 x 7.5 cm and 23.0 x 22.0 x 6.5 cm masses from the right and left inner thigh. Histopathology examination confirmed vascular calcifications, fat necrosis with fibrosis, inflammation, and subcutaneous calcification classically described in calciphylaxis. Approximately one month after surgery the patient subsequently succumbed to sepsis.

Conclusions: Although calciphylaxis most commonly presents with skin ulcerations and calcified deposition under the skin, this is an unusual case of calciphylaxis which manifested in the form of a large calcified mass. This is rarely described in the literature and one of the first cases of an excised mass with a pathological diagnosis. The pathogenesis of this proliferation of tissue in calciphylaxis needs to be further identified and studied.

SA-PO935

Acute Esophageal Necrosis (Black Esophagus) Complicating Calcific Uremic Arteriolopathy Jawed Akhtar,[1] Vijaya Kumar Gorantla,[1] Barry M. Wall.[2,1] *[1]UTHSC, Memphi, TN; [2]Veterans Affairs Medical Center, Memphis, TN.*

Background: Calcific uremic arteriopathy (CUA) is associated with medial arterial calcification with vascular thrombosis and necrosis. While skin manifestations predominate, CUA rarely involves the gastrointestinal tract.

Methods: A 76-year-old male receiving chronic hemodialysis for 7 years presented with severe penile pain with ulceration due to phimosis and balanitis, requiring surgical debridement. Pathology confirmed medial artery calcification and tissue necrosis, consistent with CUA. He later developed nausea and melena. Endoscopy revealed black, friable mucosa of nearly the entire esophagus with a clear transition to viable tissue at the gastroesophageal junction. Pathology confirmed necrosis and the diagnosis of acute esophageal necrosis was made. He was placed on IV proton-pump inhibitors (PPI) and TPN. Workup for vasculitides was negative. HIV, fungal, HSV-2, and CMV tests were also negative. Calcium (11.4 mg/dL) and parathyroid hormone (PTH; 525.6 pg/mL) were noted to be elevated. Parathyroid scan confirmed tertiary hyperparathyroidism. Patient received non calcium phosphate binders, pamidronate and sodium thiosulfate with dialysis. Patient declined daily dialysis or parathyroidectomy. Cinacalcet was started when oral intake improved. Follow up: PTH improved to 390 pg/ml, calcium 9.0 mg/dl an PO4 3.5 mg/dl. Repeat endoscopy revealed significant improvement with persistent severe esophagitis in the distal and middle third of the esophagus with a normal proximal third. He was started on a clear liquid diet and transitioned to oral PPI. TPN was discontinued 5 days later. He was discharged to a rehabilitation center, receiving oral liquid nutritional supplement (1800 cal/day) with no further gastrointestinal symptoms or bleeding.

Results:

Conclusions: Gastrointestinal manifestations of CUA include mucosal edema, diffuse ulcer formation, and bowel perforation arising from bowel infarction. Gastrointestinal bleeding is a common presentation. Acute esophageal necrosis, a rare cause of upper gastrointestinal bleeding is found in patients with significant morbidities and is associated with high mortality. To our knowledge, there have been no prior reports involving coexistence of these conditions.

Funding: Other U.S. Government Support

SA-PO936

Native Kidney Osseous Metaplasia – Incidental Finding or a Disease to Treat Gyongyi Okechuku,[1] Saed Shawar,[1] Jingyin Yan.[2] *[1]Baylor College of Medicine, Houston, TX; [2]None, Houston, TX.*

Background: Osseous metaplasia is an atypical phenomenon involving the formation of the bone tissue outside the skeletal system. This pathologic process may occur in sites such as the skin, subcutaneous tissue, and skeletal muscle, occasionally seen in visceral

organ like intra-abdominal sites. We describe a case of osseous metaplasia in a native kidney.

Methods: We present a 26 year old African American woman with biopsy proven minimal change disease (MCD) at age of 5. Her disease course is significant for been steroid dependent initially with multiple relapses upon steroid taper and partial remissions. She had 3 renal biopsies in childhood. All 3 were consistent with minimal change disease. Her treatment regimen consisted of steroids, cellcept, started after she had side effect from cyclosporine and Lisinopril. She presented to our Nephrology clinic with worsening SOB, orthopnea and PND. Physical examination was significant for fine crackles in lungs, and 3+ bilateral pitting pedal edema. Labs showed serum calcium 8.2, phosphorus 4.1, vitamin D 34, and bicarbonate of 28, BUN of 15 and creatinine of 0.6. Her white cell count was 6.8, with hemoglobin 6.6, Platelets were 113. Her urinalysis was notable for 2+ proteinuria. C3 and C4 were normal. Negative RF; negative ANA; normal serum protein electrophoresis and light chain assay, dsDNA, ANCA were negative. A renal sonogram was unremarkable. A repeat renal biopsy was done findings suggested Minimal change disease. However, we found unmineralized osteoblast within 1 glomerulus.

Results: Osseous metaplasia (OM) pathophysiology is not well known, but many factors have been incriminated including chronic ischemia, trauma, and chronic inflammation. The pathphyisology of this finding is not well understood. Osseous metaplasia has been described in some transplant allograft, and associated with malignacies affecting the kidney, some leukemias and basal cell carcinoma. Ectopic calcifications are different entities. OM is asymptomatic and probably often confounded with ectopic calcifications since their radiological aspects are identical. Treatment usually is watchful waiting approach.

Conclusions:

SA-PO937

Perioperative Acute Systolic Cardiac Dysfunction as Complication of Parathyroidectomy Itunu O. Owoyemi,[3] Angie G. Nishio-Lucar,[4] Sundararaman Swaminathan,[3] Karen M. Warburton,[1] Gayle M. Vranic,[2] Peter I. Lobo,[3] Alden M. Doyle.[1] *[1]Charlottesvilee, VA; [2]University of Virginia Health System, Charlottesville, VA; [3]University of Virginia, Charlottesville, VA; [4]University of Virginia HS, Charlottesville, VA.*

Background: Several factors including hypocalcemia have been incriminated in the pathogenesis of abnormal cardiac function in End Stage Kidney Disease (ESKD).

Methods: We report a case of a 57 yo woman with ESKD due to hypertension, failed kidney transplant graft from BK nephropathy 8 years ago referred for management of severely elevated parathyroid hormone levels (PTH). Patient had undergone subtotal parathyroidectomy 5 years prior. Despite intensive therapy with calcitriol and cinacalcet, her PTH levels had remained around 2000 pg/mL. She had stress test done 2 months prior to operation that showed no evidence of inducible myocardial ischemia and preserved ejection fraction. Her evaluation included a sestamibi scan with showed activity within the mediastinum prompting the decision for resection and auto-transplantation. A day prior to surgery, she recieved IV calcitriol during dialysis and was down to her target weight. Cinacalcet was discontinued. Her surgery was uncomplicated. She received 1 g of IV calcium chloride. She was extubated quickly in the recovery room and initially did well. Over the next hour, she developed acute shortness of breath with hypercapneic respiratory failure. A stat chest X-ray revealed left pleural effusion and mild cardiomegaly, which were new findings compared to chest X-ray done a day before surgery. Pertinent laboratory findings prior to this episode include hemoglobin 10.7mg/dL, ionized calcium 3.9 mg/dL, and phosphorus 7.7 mg/dL. PTH was 190 pg/mL, down from 1399 pg/mL at beginning of surgery, troponin – 0.03 with no EKG changes. An Echocardiogram done showed decreased left ventricular systolic global function and small pericardial effusion adjacent to the right ventricle. A protocol for prevention of hypocalcemia was immediately embarked upon to prevent further episodes of hypocalcemia which resulted in good control of serum calcium and phosphorus levels. Her cardiac dysfunction resolved prior to discharge and she has done well since.

Conclusions: Modifications of myocellular calcium interactions or sensitivity which may alter relaxation and contribute to cardiac dysfunction. Patients with severe hyperparathyroidism are at risk in the early post-operative period and should be monitored closely for hypocalcemia and, less commonly, acute cardiac dysfunction.

SA-PO938

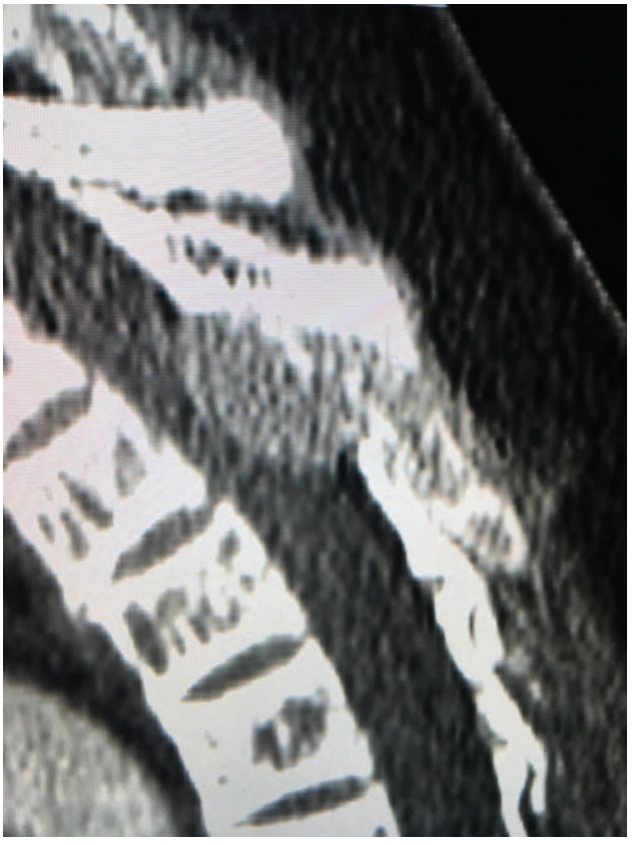
Acute Neurological Syndrome Complicating Secondary Hyperparathyroidism Ravina Patel,[1,3] Michael R. Wiederkehr.[2] *[1]Baylor University Medical Center, Dallas, TX; [2]Dallas Nephrology Associates, Dallas, TX; [3]Methodist Dallas Medical Center, Dallas, TX.*

Background: Long-term severe secondary hyperparathyroidism in dialysis patients can lead to formation of "brown tumors," a benign but locally aggressive neoplasm of predominantly osteoclast-like giant cells in a fibrous stroma. They present as single or multiple lesions and are locally destructive by their lytic and expansive properties. Parathyroidectomy is preferred over medical management. Here we describe a case of acute cord compression caused by a brown tumor.

Methods: A 33-year-old Hispanic female, dialysis dependent for 9 years, presents with progressive lower extremity weakness and back pain. She had many years of uncontrolled hyperparathyroidism. Levels of iPTH were consistently above 2000, but recently up to 5500. Addition of cinacalcet improved PTH but it remained above 3000. Hypercalcemia indicated development of tertiary hyperparathyroidism. Imaging now revealed numerous lytic lesions through the spine, ribs, and sternum, and two expansive masses at T3 and T12 with severe spinal cord compression at T3 with associated cord edema (see image), moderate spinal canal stenosis at T12. She underwent emergent T2-T4 laminectomy with resection of the tumor, followed by subtotal parathyroidectomy one week later. Intraoperative PTH dropped from 2358 to 268, and to 11 the following day.

Results:

Conclusions: Spinal cord compression by a brown tumor is a rare complication of secondary or tertiary hyperparathyroidism and poses a treatment dilemma as regression of brown tumor after parathyroidectomy has been well described. Given her acute presentation with cord edema at T3 we decided on neurosurgical intervention. The brown tumor at T12 caused spinal stenosis but no cord compression. We are now following expectantly as we monitor the T12 mass and lytic bone lesions in anticipation of resolution post parathyroidectomy.



SA-PO939

Nephrocalcinosis and Nephrolithiasis in Renal Allograft during Cinacalcet Treatment for Severe Hyperparathyroidism Anshul Bhalla, Marwa El-Sabbahy, Monika Pilichowska, Nitender Goyal. *Tufts Medical Center, BOSTON, MA.*

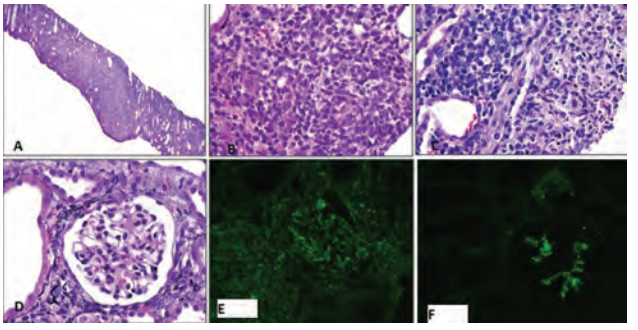
Background: Hyperparathyroidism (HPT) is commonly associated with ESRD and resolves with kidney transplant (KTx). Elevated parathyroid hormone (PTH) levels may persist post-KTx causing hypercalcemia. Cinacalcet use is common in these patients, but reportedly increases the risk of nephrocalcinosis (NC) and nephrolithiasis (NL), due to hypercalciuria.

Methods: A 61 year old female with lupus nephritis causing ESRD, on dialysis for 8 years, underwent deceased donor KTx with immediate graft function. Basiliximab was used for induction and Tacrolimus, Mycophenolate and Prednisone for maintenance immunosuppression (IS). Hypercalcemia early after transplant prompted Cinacalcet initiation and its persistence required dose up-titration on follow up. A 3.5 gland parathyroidectomy (PTX) performed 4 months after KTx was complicated by post-op acute kidney injury, with moderate hydronephrosis and distal ureter obstructing calculus seen on allograft imaging. Impacted stones in the ureteral orifice were partially removed by cystoscopy, but stent placement was unsuccessful requiring percutaneous nephrostomy. Serum creatinine (SCr) improved. Kidney biopsy was performed 6 months post-KTx for elevated SCr, BK Viremia and de-novo donor specific antibody to DR14 and DR52 HLA antigens. Morphologic examination revealed acute tubular epithelial cell injury in addition to luminal depositions of calcium phosphate, consistent with NC, with no evidence of rejection or BK nephropathy. Allograft function stabilized after percutaneous nephrolithotripsy and nephrouretral catheter placement. Stone analysis revealed calcium oxalate (20%) and calcium apatite (80%).

Results:

Conclusions: Resorption of soft tissue calcification, higher allograft Vitamin D production, severe HPT and Cinacalcet use cause renal calcium loading, increasing the risk of NC and NL, which are otherwise rare post KTx. We postulate that a combination of these factors contributed to kidney stones in our patient. Early PTX in KTx recipients with persistently high PTH levels and hypercalcemia might prevent this complication.

Laboratory Data Pre and Post Kidney Transplant						
	Calcium (mg/dL)	Albumin (g/dL)	iPTH (pg/mL)	Phosphorus (mg/dL)	Creatinine (mg/dL)	Dose of Cinacalcet (mg)
Before Transplant	9.8	3.9	1090	5.7	7.5	90 daily
After Transplant						
1 week	11.1	3.8	1475	2.3	0.9	60 daily
2 months	11.8	4.1	NA	1.6	1.2	90 BID
3 months (Hospital admission for AKI, hypercalcemia)	12.3	4.1	1172	1.8	2.3	60 BID
4 months (Pre-parathyroidectomy) (Post-parathyroidectomy)	10.7 8.2	4.1 3.4	1504 23	2.4 3	1.5 2.3	60 BID NA
6 months	8.1	4.1	343	3.7	1.7	NA



A-massive infiltrate B-Plasma cells C- Plasma cells D-Glomerulus E-IF IgG F-IF IgG

SA-PO940

Disseminated Bartonellosis Masquerading as PTLD in a Renal Transplant Recipient Srijan Tandukar, Christine Wu. *University of Pittsburgh Medical Center, Pittsburgh, PA.*

Background: A solid organ transplant recipient is at high risk for infections due to immunosuppression. We report a case of a renal transplant recipient presenting with diffuse lymphadenopathy concerning for PTLD who was found to have disseminated bartonellosis.

Methods: A 32 year old male presented 11 months following his renal transplant (CMV +/-, EBV +/+) with complaints of malaise, drenching night sweats and fever to 101.8 F while on tacrolimus and mycophenolate mofetil. Review of systems was positive for a cat scratch on his knee several months back. He was hemodynamically stable on presentation. On exam, he had tender right inguinal lymphadenopathy. Urinalysis, chest x-ray and blood cultures were negative. His WBC count was 6,700/mm^3 and creatinine was 1.6 mg/dl (baseline 1.2 mg/dl). CT scans showed left supraclavicular, axillary, retroperitoneal and iliofemoral lymphadenopathy with hypodense lesions in the liver, spleen and renal allograft. PCR showed 110 copies/ml EBV and no CMV. Serologies for Bartonella henselae were positive for IgG (1:512) and IgM (1:80). Lymph node biopsy showed necrotic areas, neutrophilic abscesses with focal positivity for Bartonella and large abnormal cells that were EBV positive. He was treated with azithromycin and doxycycline for 8 weeks. His symptoms, along with lymphadenopathy, splenic and liver lesions on repeat CT scan resolved completely. His creatinine stabilized at 1.5-1.7 mg/dl.

Results:

Conclusions: PTLD is characterized by lymphoid proliferation of B cells that may be monoclonal or polyclonal in origin and affects up to 1-2% of kidney transplant patients. As in our case, patients with PTLD often present with fever, malaise and lymphadenopathy. Bartonella henselae is a bacterium that is transmitted from cats to humans from a scratch or bite. Infected patients often present with fever, lymphadenopathy and night sweats. Dermatologic and neurologic findings may also be present. In an immunocompromised patient, the features may be more severe, with dissemination to other organs. In our patient, complete resolution of symptoms and CT findings following antibiotic treatment confirmed the diagnosis of bartonellosis. Disseminated bartonellosis should be considered in transplant patients presenting with fever and lymphadenopathy.

SA-PO941

Rapid Onset Donor Cell Transformation into Plasmacytoid Post-Transplant Lymphoproliferative Disorder (PTLD) in a Kidney Transplant Recipient Mahmoud A. Mahmoud,[1] Barry M. Wall,[2] Manish Talwar.[1] *[1]University of Teneessee Health Science Center, Memphis, TN; [2]Veterans Affairs Medical Center, Memphis, TN.*

Background: Post-transplant lymphoproliferative disorder (PTLD) is a complication of both solid organ transplant and allogeneic bone marrow or stem cell transplants. PTLD is most often of recipient B cell lineage and is typically associated with Epstein-Barr Virus (EBV) infection.

Methods: A 56-year-old AA male with ESRD secondary to hypertension received a kidney transplant from a 9 year-old deceased female donor. Donor and recipient EBV IgG was positive. He received induction with thymoglobulin and maintenance therapy with mycophenylate, tacrolimus, and prednisone. Hospital discharge serum creatinine was 4.9 mg/dl and 1.8 mg/dl on post-op day 15. Allograft biopsy (Figure1), performed on post-op day 48 due to rising creatinine and fever, revealed a massive plasma cell infiltrate which was negative for EBV, but strongly CD138 positive with monotypic lambda light chain expression by in situ hybridization, consistent with PTLD. Recepient EBV IgM and early D antigen were negative posttransplant, and EBV serum PCR was <500. There was no evidence for cellular or vascular rejection. FISH studies revealed a female cell population comprising the plasmacytoid infiltrate. Recipient bone marrow examination was negative for PTLD. Immunosuppression was withheld and treatment was attempted with bortezomib and cyclophosphamide; however, renal function declined and he resumed hemodialysis. Allograft nephrectomy showed diffuse hemorrhagic necrosis of parenchyma with presistent plasma cell infiltrates.

Results:

Conclusions: FISH studies performed on the preserved kidney tissue showed a predominant female cell population comprising the atypical plasmacytoid infiltrate, confirming that PTLD was donor derived. There has been no evidence of persistent PTLD in the patient during 10 months of followup. Recipients of other organs from the same donor have not developed PTLD after 10 months of followup.

SA-PO942

A Rare PTLD Presenting as Autonomic Dystonia: Who Would Have Thought Sathish Karmegam,[2] Kosunarty Fa,[2,1] Jose A. Castillo-Lugo.[2,1] *[1]Dallas Nephrology Associates, Dallas, TX; [2]Nephrology, Methodist Dallas Medical Center, Dallas, TX.*

Background: Introduction: Post Transplant Lymphoproliferative Disorders (PTLD) are life threatening complications of transplantation. Chronic use of immunosuppressive agents to prevent allograft rejection increases the long-term risk of malignancy. This is a report of a rare case of Diffuse Large B Cell Lymphoma presenting with autonomic dysfunction as a paraneoplastic syndrome.

Methods: Case Description: A 40 y/o Caucasian man with PMH of Living Unrelated Kidney Transplant (about 15 months ago), acute vascular rejection 2B (within 6 months of transplant), and HTN presented with fatigue and bloody diarrhea. His medications were tacrolimus, MMF, prednisone and lisinopril. He had severe orthostatic hypotension with recurrent syncopal episodes on admission. Hgb and chemistries were normal. Lisinopril was discontinued. He received aggressive volume expansion, oral fludrocortisone, and midodrine. Infectious stool work up was negative. CMV viral load was weakly positive. He was started on IV ganciclovir empirically. His adrenal axis, cardiac function and CT of abdomen were normal. CMV adrenalitis was ruled out and ganciclovir discontinued. His EBV PCR turned out to be strongly positive. IV acyclovir was started. Chest CT showed no central lymphadenopathy but small left axillary lymphadenopathy. A colonoscopy showed 'multiple shallow ulcers throughout the colon with heaped up margins'. Biopsy was negative for CMV inclusion bodies. Colonic mucosa showed atypical large cell lymphoid infiltrate in the lamina propria consistent with 'Diffuse large B-Cell Lymphoma' (DLBC). Axillary lymph node excision biopsy was consistent with 'Diffuse large B-cell lymphoma and T-lymphocytes with positive CD-20. MRI of the brain was negative. MMF was discontinued and tacrolimus dose was decreased. Hematology service recommended R-CHOP chemotherapy. His autonomic dysfunction improved with treatment.

Results:

Conclusions: Discussion: Lymphomas are among the most common complications of transplantation and many are related to EBV infection. The incidence is highest in the first post-transplant year due to high immunosuppression. Autodystonia is a well-known paraneoplastic syndrome of CNS and Hodgkin's lymphomas. High level of suspicion is required to make diagnosis and initiate treatment early. DLBC lymphoma presenting with autodystonia is extremely rare and no other cases have been reported until now.

SA-PO943

Familial Anti-GBM Disease in Zero Human Leukocyte Antigen Mismatch Siblings Nicola Lepori,[1,2] Andrea Angioi,[1,2] Wisit Cheungpasitporn,[1] Sanjeev Sethi,[3] An S. De Vriese,[4] Fernando C. Fervenza.[1] *[1]Nephrology and Hypertension, Mayo Clinic, Rochester, MN; [2]Division of Nephrology, Ospedale Brotzu, Cagliari, Italy; [3]Anatomic Pathology, Mayo Clinic, Rochester, MN; [4]Division of Nephrology, AZ Sint-Jan, Bruges, Belgium.*

Background: Familial anti-GBM disease is extremely rare. The single gene mutations that may play a role in the development of familial anti-GBM disease are currently unidentified.

Methods: A 65-year-old woman presented to our institution with hemoptysis, gross hematuria and oliguria. Physical examination revealed bilateral diffuse wheezes and edema of the lower extremities. The patient was a smoker and had a family history positive for serologic and renal biopsy-proven anti-GBM disease in 2 of her 15 siblings; morover she had been exposed to kerosene during her childhood. Laboratory testing showed hemoglobin (Hb) of 10.2 mg/dL and serum creatinine (sCr) of 12.0 mg/dL. Urinalysis showed 1+proteinuria and hematuria. Serology demonstrated positive anti-GBM IgG antibody test at 2.1 units and negative ANCA. Kidney biopsy showed a crescentic and necrotizing glomerulonephritis, with linear staining of IgG (3+) along the glomerular basement membranes on the IF, consistent with anti-GBM disease. Patient was started on IV metilprednisolone and daily plasmapheresis sessions, followed by oral cyclophosphamide plus prednisone. Nevertheless, due to uremic symptoms, hemodialysis was started. 3 weeks after treatment, anti-GBM IgG antibody became negative and at 3-month follow-up visit renal function had improved and hemodialysis was discontinued. The patient continued to do well with negative anti-GBM antibodies at 15-month follow-up visit with sCr of 1.4 mg/dL without significant proteinuria. HLA typing from the

patient and one of her affected brothers showed they had identical HLA typing (0 of 6 HLA mismatch) and were homozygous for HLA-DR15.

Results:

Conclusions: HLA-DR15 is associated with an increased risk of anti-GBM disease, but HLA types in familial anti-GBM disease cases have never been reported. We present the first case of familial anti-GBM disease involving 3 siblings in the same family with a potential link of HLA-DR15 in the development of familial anti-GBM disease.

SA-PO944

One Drug's Promise Leads to an Unavoidable Complication Andrew Kowalski,[2] Daniel Fantus,[1] John J. Friedewald.[2] *[1]Comprehensive Transplant Center, Northwestern University, Chicago, IL; [2]Northwestern University, Lombard, IL.*

Background: CMV is a major pathogen for immunocompromised patients, especially including solid organ transplant recipients resulting in a broad range of syndromes and inducing organ rejection. This case study examins the course of denovo CMV infection in the setting of immunosupression with belatacept.

Methods: 48 yo male, with a history of CKD stage V due to IgA nephropathy who underwent a successful living related kidney transplant in 7/2015. Due to his HLA status he received a steroid protocol induction and then transitioned to mycophenolate mofetil and tacrolimus. In the next few months he was transitioned to belatacept and off tacrolimus based on a study protocol. A year later he presented with complaints of vague abdominal pain and diarrhea. He was found to have a CMV viral load of 439,804 IU/mL, and placed on ganciclovir. His viral load decreased and then rose to 55,678 IU/mL the following month despite continued ganciclovir. He complained of worsening gastrointestinal symptoms and his viral load was 152,305 IU/mL. Belatacept was stopped and tacrolimus was restarted. His creatinine was at baseline and foscarnet was started. He presented with complaints dyspnea, new onset hematuria and fevers. His creatinine was 4.45mg/dL and urine analysis had a large amount of blood and protein. Foscarnet was then held. He underwent a renal biopsy that was consistent with foscarnet induced renal toxicity. Creatinine remained stable at 4.7mg/dL, repeated CMV viral loads were undetectable and foscarnet was discontinued. His creatinine had then peaked at 10mg/dL. His abdominal symptoms returned and his CMV viral load had increased to 41,332 IU/mL. He was readmitted for cidofovir. His creatinine had risen to 13.9mg/dL. Mycophenolate was discontinued to boost his white cell count and his CMV viral load decreased to 7000 IU/mL, but his creatinine increased to 17. He was then started on dialysis.

Results:

Conclusions: Belatacept binds to CD80 and CD86 receptors and blocks the required CD28 mediated interaction between APCs and T cells needed to activate T lymphocytes. The nature of belatacept prohibits the body to mount a response against EBV leading to an increase in PTLD. We recommend that this concern be extended to CMV negative patiens as this case shows that the use of belatacept hinders the ability of the body to mount a response leading to uncontrolled infection and nessecitating the use of nephrotoxic medications.

SA-PO945

Disseminated Adenoviral Infection with Nephropathy in a Kidney/Pancreas Transplant Recipient Natalie Nesmith, Meghan E. Kapp, Agnes B. Fogo, Paisit Paueksakon, Gowri Satyanarayana, Heidi M. Schaefer, J.H. Helderman, Beatrice P. Concepcion. *Vanderbilt University Medical Center, Nashville, TN.*

Background: Adenovirus (AV) is a commonly encountered viral pathogen with self-limited infection in immunocompetent hosts. In immunocompromised hosts more serious complications can occur. We report a kidney/pancreas (KP) transplant recipient who developed disseminated adenoviral infection with nephropathy which was successfully treated with cidofovir.

Methods: A 32 year old man with Type I Diabetes Mellitus with diabetic nephropathy, retinopathy, and peripheral vascular disease underwent simultaneous KP transplant in 10/2016. He was induced with solumedrol and alemtuzumab. Maintenance therapy included three drug regimen with tacrolimus, prednisone and mycophenolate mofetil. Two months later he developed gross hematuria, high-grade fevers, and acute kidney injury (sCr 1.46 mg/dL vs baseline sCr 0.8 mg/dL). Amylase/lipase were normal. Serum (>2million copies/mL) and urine AV PCR were positive with positive AV nasal swab. He underwent transplant biopsy which showed multifocal tubulocentric necrotizing granulomas with viral cytopathic nuclear changes in tubular epithelial cells and podocytes, the latter associated with a cellular crescent with fibrinoid necrosis and apoptotic debris. Electron microscopy demonstrated focal crystalline viral particles in tubules. Immunohistochemical stains were diffusely positive for AV and negative for SV40. There was no evidence of concomitant acute cellular rejection and no diagnostic evidence of antibody-mediated rejection with negative C4d by immunofluorescence. He was started on cidofovir/probenecid with resolution of fevers after two doses and ultimately received eight doses. Four months later, serum AV PCR was negative and sCr was 1.5 mg/dL.

Results:

Conclusions: While disseminated adenovirus is rare amongst KP transplant recipients, it can cause serious complications including multi-organ dysfunction, graft loss, and death. Severe disease including AV nephropathy warrants treatment with cidofovir despite its nephrotoxicity.

SA-PO946

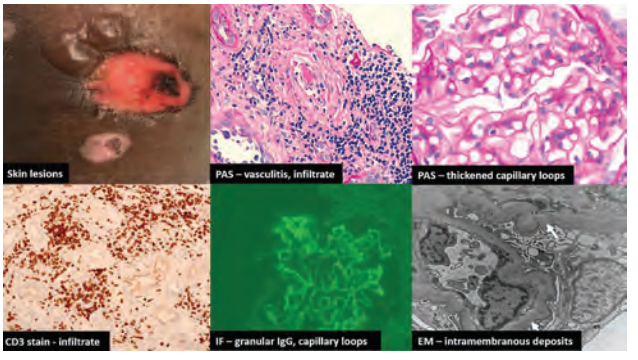
Bullous Pemphigoid and Renal Transplant Rejection: More Than a Mere Coincidence? Abhilash Koratala,[2] William L. Clapp,[2] Olanrewaju A. Olaoye,[1] Alfonso Santos.[2] *[1]University of Florida, Division of Nephrology, Gainesville, FL; [2]University of Florida, Gainesville, FL.*

Background: Bullous pemphigoid (BP) is an autoimmune blistering disease characterized by subepithelial blister formation and deposition of immunoglobulins and complement in the epidermal and/or mucosal basement membrane zone. There are few case reports on the association between BP and allograft rejection, and membranous nephropathy (MN). We report a unique case of BP associated with both acute cellular rejection (ACR) and de novo MN in a renal transplant recipient.

Methods: A 63-year-old man with a history of ESRD secondary to MN, status post living related kidney transplant 5 years ago who has been compliant with his immunosuppressant regimen was admitted for worsening skin rash that started 3 weeks ago and acute kidney injury. Skin exam revealed multiple scattered bullae with clear fluid and erosions with a collarette of scale on the neck, chest, back and limbs. His serum creatinine (Scr) was 7.3 mg/dL at presentation (baseline ~1.5). Urine exam showed 45/hpf RBC, 1/hpf WBC and an albumin-creatinine ratio of ~0.5 g/g. BK virus, CMV, Herpes simplex and Varicella zoster serologies were negative. Skin biopsy revealed BP. His Scr minimally improved with supportive measures and allograft biopsy showed Banff 2A ACR with de novo MN and ~50% interstitial fibrosis and tubular atrophy (IFTA). He was treated with pulse corticosteroid and antithymocyte globulin but his Scr remained unimproved after 1 month. Further immunosuppression was not attempted due to the severity of IFTA on repeat biopsy. His skin lesions eventually improved with high-dose steroid therapy.

Results:

Conclusions: Though the possibility of multiple distinct autoimmune processes cannot be excluded, allograft rejection-induced immune stimulation or anti-basement-zone antibody interactions are possible unifying mechanisms for the simultaneous skin and renal involvement. Whether the diagnosis of BP in a renal transplant recipient warrants kidney biopsy remains unanswered.



SA-PO947

Long-Term Outcome after Treatment of Plasma Cell-Rich Rejection of the Kidney in Simultaneous Kidney and Pancreas and Kidney and Liver Transplant Recipients Ksenija Vucur,[2] Zeljka Jurekovic,[2] Branislav Cingel,[2] Danica G. Ljubanovic,[1] Mladen Knotek.[2] *[1]University of Zagreb School of Medicine, Clinical Hospital Dubrava, Zagreb, Croatia; [2]Department of Nephrology, University of Zagreb School of Medicine and University Hospital Merkur, Zagreb, Croatia.*

Background: Although plasma cells (PC) participate in the kidney graft rejection, their major involvement (i.e. plasma cell rich rejection - PCRR) is rare. We identified three cases with PCRR among simultaneous kidney-pancreas (SPKT) and liver-kidney (SLKT) recipients in our center.

Methods: Case I: A 35-yr old Caucasian male who had SPKT in 2006 presented three mths posttx with renal dysfunction. Kidney biopsy (bx) showed acute cellular rejection (ACR) IB with infiltrate consisting of 17% of PC. Donor-specific antibodies (DSA) were negative. After treatment with steroid boluses there was only a mild decrease in serum creatinine, and the second bx revealed again PCAR. Treatment with high-dose (2 g/kg) IVIG and boluses of steroids led to normalization of renal function. On a follow-up bx at 1 yr, there were no signs of rejection. Eleven yrs later, both graft function is excellent. **Case II:** A 55-yr old Caucasian male who received SLKT in 2006 presented two yrs after tx with renal dysfunction. Kidney bx revealed ACR IB. The infiltrate consisted of 27% PC. After treatment with high-dose IVIG and steroid boluses, a repeat bx showed no signs of acute rejection. Subsequently, the patient had persistent stable renal dysfunction. He died in 2012 from sepsis. **Case III:** A 36-yr old Caucasian male presented in 2009, four yrs after SPKT with worsening of renal function. Kidney bx revealed acute PCRR with microvascular injury (MVI) that was treated with steroid boluses. At that time he had DSA against DQ and DR. Subsequent two bx showed persistent ACR and the treatment included high-dose IVIG. Afterwards renal function improved, but five yrs later serum creatinine increased again, and on biopsy PCRR with MVI was again diagnosed. It was treated with bolus of steroids and high-dose IVIG and was followed by creatinine decrease. On the last visit in 2017 patient had both graft function stable with creatinine 155 μmol/L.

Results:

Conclusions: We showed that in SPKT or SLKT PCRR may affect only kidney function and was only partially associated with DSA and MVI. Combined treatment with high-dose IVIG and pulse steroids may be effective in treatment of PCRR resulting in a good long-term graft survival. To our knowledge, this is also the first report of PCRR in a patient with SLKT.

SA-PO948

AKI Post Kidney Transplant Associated with Macroscopic Glomerular Hematuria Secondary to Rivaroxaban Magdi H. Abdelrahman,[2,1] Muhammad R. Mustafa,[2,1] Praveen N. Chander.[1] *[1]New York Medical College, Valhalla, NY; [2]Westchester Medical Center, West Harrison, NY.*

Background: Reversible AKI secondary to macroscopic glomerular hematuria (MGH) has been described in IgA nephropathy, Anticoagulant-related nephropathy (ARN) and rarely in Thin GBM disease in the native kidneys. Acute tubular damage and widespread intraluminal obstructive RBC casts are salient histologic features. ARN is classically caused by warfarin; however other anticoagulants have been reported to cause it. We report a case of reversible AKI associated with rivaroxaban post heart and kidney transplantation.

Methods: A 51 yo male with a history of non-ischemic cardiomyopathy and ESRD due to ANCA-associated vasculitis underwent combined heart and kidney transplantation from a deceased donor. He received Induction with basiliximab and methylprednisolone. Post-operative course was complicated by the development of catheter-related intra-jugular vein thrombosis and he was started on intravenous heparin. His maintenance immunosuppression was prednisone, Tacrolimus and Mycophenolate mofetil. He was switched to rivaroxaban when his serum creatinine (SCr) improved to 1.5 mg/dl. Two weeks after his transplant, his SCr increased to 2.8 mg/dl. Tacrolimus level was 11.6; ANCA titer was 1:640. Large numbers of RBCs were detected on urinalysis. A transplant kidney biopsy showed a small segmental epithelial crescent in 1/11 glomeruli and numerous RBCs in the Bowman's space of another, without any necrotizing or other significant lesions. Widespread intraluminal obstructive casts were present in tubules. The degree of renal impairment and tubular RBC casts were disproportionately greater than the glomerular disease suggesting coexistent ARN. Rivaroxaban was stopped; the patient was treated with rituximab, and pulse steroids. SCr dropped to 1.6 mg/dl in 2 weeks.

Results:

Conclusions: Common etiologies of renal dysfunction in the early period post-transplantation are acute rejection, recurrent primary disease, or calcineurin inhibitor nephrotoxicity. To our knowledge, this is the first case of AKI post combined heart and kidney transplantation due to ARN (rivaroxaban). In conclusion, MGH of any etiology obstructing renal tubules should be considered in the differential diagnosis of early post-transplant acute kidney injury especially in patients on anticoagulants. Renal histology can be of help in evaluating such cases.

SA-PO949

A Case of Kaposi's Sarcoma Developed during the Intensive Immunosuppression Therapy against T Cell-Mediated Rejection, but Resolved Rapidly after Adding mTOR Inhibitor Kosuke Sako,[1] Yosuke Nakagawa,[1] Yudai Isozaki,[1] Chiaki Kawabata,[1] Naoto Hamano,[1] Hiroaki Ishida,[2] Masahiro Koizumi,[1] Go Ogura,[3] Takehiko Wada,[1] Masafumi Fukagawa,[1] Michio Nakamura.[2] *[1]Division of Nephrology, Endocrinology and Metabolism, Tokai University School of Medicine, Isehara, Japan; [2]Department of Transplantation Surgery, Tokai University School of Medicine, Isehara, Japan; [3]Department of Pathology, Tokai University School of Medicine, Isehara, Japan.*

Background: Incident renal allograft rejections have been decreasing in number due to dramatic advance in immunosuppression therapies for kidney transplantation (KT). In contrast, infections and *de novo* neoplasms associated with those therapies have become an important issue. Here, we report a case of Kaposi's sarcoma developed during the intensive immunosuppression therapy against T cell-mediated rejection, but resolved rapidly after adding mTOR inhibitor, everolimus.

Methods: A 44-year old Mongolian woman, who had been on hemodialysis for 4 years with end stage renal disease due to autosomal dominant polycystic kidney disease, received a kidney transplant from her husband. Because of ABO-incompatible KT, she had received rituximab 100 mg twice, double filtration plasmapheresis and intravenous immunoglobulin as pre-transplantation conditioning. Initial immunosuppression consisted of tacrolimus, mycophenolate mofetil, basiliximab and steroids. Her serum creatinine level was decreased to 1.26 mg/dL at minimum, however, it was elevated to 1.69 mg/dL again at 2 months after KT. The findings of a graft biopsy were compatible with T cell-mediated rejection, which was successfully treated with steroid pulse therapy and gusperimus hydrochloride. Immunosuppression therapy was intensified by increasing the dose of tacrolimus and her serum creatinine levels persisted 1.6-1.8 mg/dL thereafter. However, there appeared aggregated dark reddish nodules on her skin at nose and between eyebrows at 6 months after KT. They did not resolve with topical corticosteroid and tacrolimus but rather grew gradually. Skin biopsy demonstrated monomorphic spindled cells with HHV-8-positive nuclei and capillary proliferation, which provided the diagnosis of Kaposi's sarcoma. Everolimus was added to immunosuppression therapy regimen and then the sarcoma was significantly reduced.

Results:

Conclusions: Kidney transplant patients with Kaposi's sarcoma are supposed to increase in number with the progress of immunosuppression therapies. Everolimus, which is expected to have an anti-angiogenic effect, may be one of therapeutic options for Kaposi's sarcoma associated with immunosuppression therapies.

SA-PO950

The "Conn" Artist: An Unlikely Cause of Post-Kidney Transplantation Hypertension Laila S. Lakhani,[2] Angelina Edwards.[1] *[1]University of Texas at Houston Health Science Center, Houston, TX; [2]Internal Medicine, University of Texas Health Science Center at Houston, Houston, TX.*

Background: Hypertension among the post-renal transplant population is largely due to pre-existent essential hypertension in end stage renal disease (ESRD). Other transplant-specific causes of hypertension include the use of Calcineurin inhibitors and Corticosteroids, Renal artery stenosis or Graft Versus Host Disease. Secondary causes of hypertension are rarely reported in the literature. We report an interesting case of a patient with a non-secretory adrenal adenoma pre-transplant, which became functional post-transplant, leading to resistant hypertension and metabolic derangements.

Methods: 60 year old female with ESRD secondary to hypertension and diabetes mellitus type 2, underwent evaluation for transplant at our Center. Abdominal imaging revealed a 8 mm left adrenal nodule, however biochemical evidence for a secretory adenoma was negative. She underwent a deceased donor renal transplant, with basiliximab induction and maintenance immunosuppression with cyclosporine, mycophenolate mofetil and prednisone. She had excellent allograft function with nadir creatinine of 1.4 mg/dL but was noted to have uncontrolled blood pressures, despite maximum doses of 5 antihypertensive agents. Laboratory parameters were significant for hypokalemia and metabolic alkalosis. A workup for secondary causes of hypertension was pursued (Table 1). Repeat abdominal imaging at this time showed an enlarged left adrenal adenoma, 1.3x1.9 cm. Labs showed elevated aldosterone levels and adrenal vein sampling localized the secretion to the left adrenal gland (Left: 979ng/dL vs Right: 18 ng/dL). She was started on an aldosterone antagonist with only mild improvement of her blood pressure, subsequently requiring a left adrenalectomy. Post- surgery, she had complete resolution of hypokalemia and stability of her blood pressure, requiring minimal antihypertensive therapy.

Results:

Conclusions: Hypokalemia and resistant hypertension from primary hyperaldosteronism can be easily masked in the ESRD population. Although it remains a common problem, medically refractory hypertension post renal transplant should prompt a work up for secondary causes, including hyperaldosteronism.

Table 1: Laboratory findings pre and post-Transplant.

	Pre-Transplant	Post-Transplant
Aldosterone/PRA ratio	22	310
Metanephrines	39	2085
Cortisol	11.7	13.9

SA-PO951

Nocardiosis in a Renal Transplant Patient: A Case Report and Review of Literature Mohit Gupta,[1] Irtsam Shahid,[2] Rupesh Raina.[2] *[1]Internal Medicine, Cleveland Clinic Akron General, Akron, OH; [2]Internal Medicine, Cleveland Clinic Akron General, Akron, OH.*

Background: Nocardiosis is a rare and systemic disease that occurs in up to 5% of renal transplant recipients. Amongst patients with Nocardiosis, Central Nervous System involvement is seen in approximately 50% of cases. We report a patient with remote history of renal transplantation who was found to have multiple brain abscesses consistent with Nocardia infection.

Methods: A 66 year-old male with prior history of living donor renal transplant approximately 4 years ago presented for evaluation of progressive dizziness, nausea and vomiting. MRI revealed the presence of a peripherally enhancing lesion in the medial right cerebellum in addition to 2 smaller lesions in the right frontal lobe. CT Scan of the Chest done also revealed the presence of several small pulmonary nodules in both lungs. With the use of Mycophenolate Mofetil and Tacrolimus, there was a concern for brain abscess versus malignancy. The patient was started on IV Trimethoprim – Sulfomethaxozole in addition to Vancomycin and Ceftazidime with plan for aspiration and culture. Immunosuppression was modified due to concern for worsening kidney function thought to be due to calcineurin toxicity. However, false elevation in Creatinine secondary to Trimethoprim was also considered. Aspirate of the culture revealed the presence of branching gram positive organisms consistent with Nocardia. Vancomycin was switched to Linezolid and Ceftazidime to Imipenem with a plan to continue IV antibiotics for 6 weeks.

Results:

Conclusions: Nocardiosis is an opportunistic infection that occurs in up to 5 % of renal transplant recipients. It is seen commonly in the intense immunosuppression period after renal transplantation (which is 1-6 months) or after high dose therapy is used to treat rejection. The primary site of involvement is the pulmonary system, but spread to the CNS can also occur. Risk factors for development of Nocardia include multiple rejection episodes, worsening kidney function as well as high dose immunosuppression. Empiric antimicrobial therapy is often recommended as it is very slow growing. Trimethoprim-Sulfomethaxozole is first line therapy for management of Nocardia brain abscess due to good penetration of sulfonamides. The mortality rate in immunosuppressed patients has been reported to be up to 50%. Hence, a high degree of clinical suspicion is necessary when such CNS findings are observed in renal transplant recipients.

SA-PO952

Hidden, Donor-Derived Malignancy: A Tale of Two Kidneys Amaleswari Pamarthy,[2] Pradeep Vaitla.[1] *[1]Madison, MS; [2]UMMC, Madison, MS.*

Background: PTLD (Post-transplant lymphoproliferative disorder) is a relatively common malignancy but rarely donor derived. PTLD includes clinical syndromes ranging from uncomplicated post-transplant infectious mononucleosis to true malignancies that contain clonal chromosomal abnormalities which may or may not be associated with EBV infection. Most cases occur in the first year. Mortality is as high 50-80% in monoclonal form. High index of suspicion and clinical vigilance is critical since patients can present with nonspecific symptoms & signs. Pathophysiology is not well understood. Hence anticipation and prevention of PTLD remains a challenge.

Methods: Mate kidneys obtained from EBV and CMV IgG negative donor were transplanted to 69-year-old male and 68-year-old female who were positive for EBV IgG and CMV IgG. Kidney and spleen biopsies were done at procurement. Both patients received induction with Anti-thymocyte globulin and maintained on Tacrolimus, Mycophenolate mofetil, Prednisone. Kidney biopsies at the time of transplant did not show any evidence of disease process. Post-transplantation, pathology of donor's spleen revealed plasmacytoma. Hence both recipients called in for further work. SPEP was unremarkable, serum free light chains showed a mild increase in lambda light chains, which were followed regularly. One patient developed abdominal pain 4 months post transplant and imaging revealed 10cm mass arising from transplant kidney, the biopsy confirmed plasmacytoma. The second patient presented with urinary retention and imaging revealed a large para-aortic lymph nodal mass. Biopsy confirmed plasmacytoma as well. Both patients were started on chemotherapy and doing fairly well now.

Results:

Conclusions: Despite having a normal kidney biopsy at the time of transplant, donor-derived malignancy can be transmitted through lymphatics of the donor organs. If suspicion for PTLD is high, more aggressive screening and high clinical vigilance is indicated. Negative bonemarrow biopsies might not preclude from having PTLD. If high suspicion for EBV-related PTLD present, prophylactic therapies, including antiviral agents and immunoglobulins were proposed but need to be tested in randomized, placebo-controlled trials to determine their true efficacy. Decreasing the immunosuppression is the cornerstone and might help with regression of the PTLD, sometimes aggressive chemotherapy is indicated as presented above.

SA-PO953

An Unusual Case of Renal Cell Carcinoma (RCC) with Sarcomatoid Changes in a Renal Transplant Allograft Muhammad O. Saleem, Laura L. Mulloy, Carlos F. Zayas, Rajan Kapoor. *Augusta University, Medical College of Georgia, Augusta, GA.*

Background: Renal transplant recipients are at a higher risk of developing RCC than general population. RCC in renal transplant allograft is unusual. We present a rare case of highly agressive RCC with sarcomatoid changes in an allograft.

Methods: A 69-year Caucasian female with CKD stage 5 due to Autosomal Dominant Polycystic Kidney Disease (ADPKD) received a preemptive deceased donor kidney transplant. She presented 2 years post transplant with persistent hematuria. CT scan revealed 3.4 x 2.9 x 2.3 cm hypo-enhancing structure concerning for malignancy in the transplant allograft in addition to multiple simple and hemorrhagic cysts in both native ADPKD kidneys. She underwent a percutaneous biopsy of suspicious renal allograft mass, which was negative for malignancy and revealed only bland myofibroblastic proliferation. A repeat biopsy, which was also negative for malignancy was done 2 weeks later to confirm pathological findings and to eliminate any sampling error. A plausible diagnosis of persistent hematuria from her native polycystic kidney ruptured cysts was made. She presented about a year later with significant weight loss of 25 lbs and anorexia for two months duration. Repeat CT showed significant increase in the size of renal transplant mass. A MAG3 scan showed a fistula formation from the allograft mass to ileum. Patient underwent an exploratory laparotomy and an en bloc resection including transplant allograft nephrectomy and ileo-cecectomy was performed. Histopathology showed poorly differentiated RCC with sarcomatoid changes of allograft invading into the bowel wall. Staging CT showed multiple pulmonary metastases as well.

Results:

Conclusions: Renal transplant patients are at increased risk of developing RCC of the native kidneys. RCC can occur in transplant allograft as well but incidence is extremely low. A tumor registry reported incidence as low as <0.01% in allograft. RCC with sarcomatoid changes is extremely rare and only a few cases have been reported. Patients with ADPKD have higher incidence of sarcomatoid changes in RCC (33% vs 1 to 5%) as compared to general population. Our case is an unusual scenario due to findings of extremely rare and highly aggressive form of RCC with sarcomatoid features in a transplant allograft. We suggest an aggressive approach to diagnose renal allograft mass particularly in patients with ADPKD.

SA-PO954

Transitional Cell Carcinoma Involving Graft Kidney in a Kidney Transplant Recipient: A Case Report Seong il Jo, Yoon-Kyung Chang, Suk young Kim, Yu ah Hong. *College of Medicine, The Catholic University of Korea, Seoul, Korea, Daejeon, Republic of Korea.*

Background: Kidney transplantation (KT) is the treatment option for patients with end stage renal disease (ESRD) to prolong survival and improve quality of life. Although the use of potent immunosuppressive agents increases graft survival in kidney transplantation recipients (KTRs), it may lead to the development of malignancy, including transitional cell carcinoma (TCC). TCC developing in the pelvis of graft kidney is very rare in KTRs

Methods:

Results: A 40-year-old male visited hospital with complaints of nausea, vomiting and gross hematuria. Eleven years ago, he was diagnosed ESRD of unknown origin, and received a living related KT from his father one year later. Radiologic findings showed a huge polypoid mass in the pelvis of graft kidney with pelvo-calyceal dilation and a 3.3 cm-sized nodule in aortocaval chain and a 2.5 cm-sized nodule in right external iliac chain. Sonography-guided percutaneous needle biopsy of pelvis mass in the graft kidney revealed a low grade urothelial cell carcinoma. Radical graft nephroureterectomy was performed and histopathological diagnosis confirmed as a low grade urothelial carcinoma of graft pelvis and ureter lumen, which invaded to perirenal fat and renal parenchyma with lymphovascular presence (pT3N0M0). The patient started with adjuvant concurrent chemo-radiation therapy and returned to regular hemodialysis.

Conclusions: We report a rare case of TCC in the pelvis of graft kidney with already advanced disease at diagnosis in a young KTR. For the early diagnosis of TCC in KTRs, exposure history to Chinese herb or analgesics should be investigated before KT and high risk population in KTRs should be tightly performed regular postoperative surveillance for TCC and considered of less calcineurin inhibitor-based immunosuppressant protocol.

SA-PO955

Successful Kidney Transplantation and Chronic Lymphocytic Leukemia: A Case Report Mohammed Nazmul,[2] Clifford D. Miles,[2] Vamsi Krishna Chilluru,[1] Ryan Mullane,[2] Scott G. Westphal.[1] *[1]Omaha, NE; [2]University of Nebraska Medical Center, Omaha, NE.*

Background: Active malignancies are typically considered as contraindication to kidney transplantation. Chronic lymphocytic leukemia (CLL) has variable prognosis; many have indolent course, with median survival up to 10 years, and some centers are considering the role of kidney transplantation in patients with active CLL who develop advanced kidney disease. Concerns related to transplantation include influence of immunosuppression on disease progression, possibility for leukemic infiltration of the allograft and increased risk of infectious complications. Few cases of kidney transplantation into patients with CLL have been described, however allograft and patient outcomes have been discouraging with high rate of graft failure and mortality. We report a patient with CLL treated with Bruton Tyrosine Kinase inhibitor, ibrutinib, underwent successful renal transplantation with relatively uncomplicated post-transplant course.

Methods: A 50-year-old man was diagnosed with CLL/small lymphocytic lymphoma Rai stage 0 with favorable cytogenetics. He was managed conservatively initially, but later treated with cyclophosphamide and maintenance rituximab due to declining renal function. Kidney biopsy revealed IgA nephropathy with CLL renal involvement characterized by lymphocytic interstitial infiltrate. He progressed to end-stage kidney disease requiring hemodialysis. He completed two years of rituximab and was later transitioned to maintenance therapy with ibrutinib which controlled his CLL with stable WBC counts and no infections. Given clinical stability and favorable prognosis, he was approved for kidney transplantation and received a deceased donor kidney transplant (KDPI 67%) with basiliximab induction followed by maintenance immunosuppression including tacrolimus, mycophenolate sodium and prednisone. He is now 1.5 years out from his transplant and had a successful allograft outcome with serum creatinine 1.0 mg/dl (eGFR 76 ml/min) at last check. There have been no infectious complications. He has maintained a persistent lymphocytosis, but has not had adverse allograft injury related to his CLL.

Results:

Conclusions: Patients with CLL have often been excluded for consideration for kidney transplantation, newer therapies and improved understanding of favorable prognostic markers may allow for safe kidney transplantation in carefully selected patients.

SA-PO956

Long Term Function of Pediatric En Bloc Kidneys: A Single Center Study Amr Habbach, Kalathil K. Sureshkumar. *Westpenn Allegheny Health Network, Pittsburgh, PA.*

Background: Pediatric en bloc kidneys are considered "marginal" and many transplant centers are reluctant to use them. However, these kidneys double the number of nephrons and previous studies have shown that when exposed to adult hemodynamics these kdineys grow to adult size within first year. We aimed to compare extended long term function of pediatric en bloc kidneys to living donor kidneys performed at our institution.

Methods: This is a single center restrospective study of pediatirc en bloc and living donor kidney transplants performed at our center between January 1990 and December 2001 who had functiong graft beyond 5 years. Graft survival, yearly serum creatinine and

estimated GFR using modified MDRD equation were calculated and compared between en bloc and living donor kidney recipients.

Results: There were 72 patients in the en bloc and 75 in the living donor group who were transplanted during the study period. Maximum available follow up for serum creatinine value was 17 years following transplantation. Kaplan-Meier survival analysis showed no difference in graft survival between the groups over 27 years of follow up (long rank p 0.78). However on regression analysis, allograft function was found to be superior for en bloc vs. living donor kidney recipients longitudinally as evidenced by higher estimated GFR (33.0 ± 7.8 ml/min, p<0.0001) as shown in figure.

Conclusions: Our single center study showed simlar graft survival but superior long term graft function as measured by estimated GFR among pediatric en bloc kidneys compared to living donor kidneys. This could be related to increased "nephron dose" among en bloc kidneys which could likely make them less susceptible to hyperfiltration injury in the long term. Our study encourages more widespread use of en bloc kidneys which can alleviate organ shortage while providing excellent long-term function. Strengths of our study include relatively large number of study patients and extended available follow up.

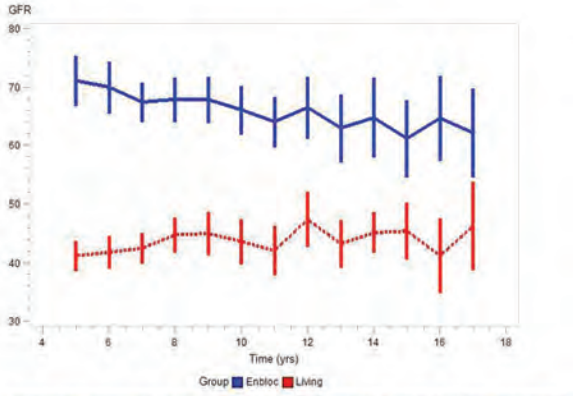


Figure 1: Plot Means with Standard Error Bars for GFR stratified by Pediatric En Bloc Renal Transplant vs Living Donor transplant

SA-PO957

Experience with Interleukin-1 Blockade in Three Renal Transplant Patients with Severe Gout Arthritis Vega Goedecke,[1] Gunilla Einecke,[2] Hermann G. Haller,[1] Annette D. Wagner.[3] *[1]Hannover Medical School, Hannover, Germany; [2]Medical School Hannover, Hannover, Germany; [3]Medizinische Hochschule Hannover, Hannover, Germany.*

Background: Hyperuricemia and gout are common comorbid conditions experienced by up to 28% of kidney transplant recipients. Reasons include reduced excretory renal function, intake of diuretic medication as well as side-effects of immunosuppressant drugs such as calcineurin-inhibitors. Treatment of gout in these patients remains a challenge, as uricostatic drugs such as allopurinol have a narrow therapeutic range in patients with impaired renal function whereas uricosuric medications such as benzbromarone are less effective due to reduced excretory renal function. Allopurinol and febuxostat are contraindicated when azathioprine is given, as they can cause severe drug interactions. Also, allopurinol therapy may increase cyclosporine plasma levels. Interleukin 1 (IL-1) plays a crucial role in gout arthritis and its blockade with selective IL-1 inhibitors such as canakinumab or anakinra has shown promising results in the treatment of gout. Canakinumab was shown to be effective in preventing gout attacks in patients who had contraindications or were unresponsive to colchicine and/or non-steroidal inflammatory drugs. Data on the use of IL-1 blockade as treatment for gout in renal transplant patients are limited, therefore we present our experience with interleukin 1 blockade in 3 patients after renal transplantation. All of them had refractory gout arthritis despite various treatment regimens prior to starting IL-1 blockade therapy.

Methods: We present our clinical experience with anti-interleukin-1-antibody treatment in three renal transplant patients with gout arthritis. All of them had refractory gout arthritis despite various treatment regimens prior to starting IL-1 blockade therapy. Two patients improved significantly and have had no gout symptoms since starting IL-1 blocking therapy. One patient suffered from pneumonia 1 month after starting therapy. Therefore, IL-1 blocking therapy was discontinued and the patient was started on rasburicase therapy.

Results:

Conclusions: Overall, therapy was well tolerated and symptoms improved in 2/3 patients. Therefore, Il-1 blocking therapy with canakinumab or anakinra is an option for treating refractory gout arthritis in renal transplant patients, even with chronic kidney disease stage 4. Infection was the main complication of therapy observed in our patients, therefore, close monitoring is recommended.

SA-PO958

Renal Allograft Malakoplakia: A Rare Cause of Allograft Failure Payaswini Vasanth,[1] Jeffy Kenny Thomas,[1] Thomas E. Rogers,[2] Sharon M. Graves.[1] *[1]Nephrology, Emory Univeristy, Atlanta, GA; [2]Emory University, Atlanta, GA.*

Background: Malakoplakia is an unusual granulomatous inflammatory disorder associated with diminished bactericidal action of leukocytes. Cases of renal allograft malakoplakia are rare and are generally associated with a poor graft and patient survival. We present a case of renal allograft malakoplakia triggered by repeated UTIs in the setting of recent increase in immunosuppression.

Methods: 50-year-old female with history of pediatric en bloc kidney transplant with baseline allograft function ranging between 2-2.5mg/dl on immunosuppression regimen of low dose Tacrolimus (trough between 3-5), low dose MMF due to history of UTIs and BK viremia and prednisone. Her post transplant was complicated by recurrent *E.coli* UTIs and mesangioproliferative-type glomerulopathy, with prominent staining for IgM and C3 which is a variant of focal segmental glomerulosclerosis (FSGS), and hence her immunosuppression was increased to high dose prednisone with prolonged taper. Soon after she developed *E.coli* UTI and acute kidney injury, her creatinine increased to 9.5mg/dl. She was treated with IV Antibiotic rocephin and transitioned to oral Levoquin for 3 weeks. Her creatinine trended down to 4.2mg/dl and a biopsy was performed that showed epithelioid histiocytes with basophilic inclusions called Michaelis-Gutmann bodies suggestive of malakoplakia with severe IFTA. Her creatinine remained at 4mg/dl and we maintained her on low immunosuppression in the setting of malakoplakia.

Results:

Conclusions: Renal parenchymal malakoplakia is a rare cause of renal allograft failure. Currently, malakoplakia is thought to be associated with infection, *E.coli* is the most common. Therefore, agents targeting Gram negative bacteria with high bioavailability in macrophages are most commonly chosen, such as quinolones and sulfamido groups. In malakoplakia, macrophage dysfunction and persistent antigens within cells cause progressive delivery of cytokines, resulting in renal inflammation and further injury. If the early interstitial injury is not controlled, renal injury continues to deteriorate and even progresses to interstitial fibrosis even when bacteria is removed and is associated with poor graft outcome, as demonstrated in this case.

SA-PO959

Pazopanib (Votrient) Induced Podocytopathy in a Transplant Kidney Massini Merzkani,[2] Kenar D. Jhaveri,[2] James M. Pullman,[1] Rimda Wanchoo.[2] *[1]Pathology, Montefiore Medical Center, Bronx, NY; [2]Nephrology, Hofstra Northwell School of Medicine, Great Neck, NY.*

Background: Glomerular endothelial cell injury and podocyte damage, resulting in glomerular disease including thrombotic microangiopathy(TMA) and focal segmental glomerulosclerosis, are well recognized complications of tyrosine kinase inhibitors(TKI) used in targeted therapy for cancers. TKI use in kidney transplant recipients is not well described. We report a case of nephrotic syndrome in a kidney transplant recipient with metastatic renal cell cancer treated with the TKI- pazopanib(Votrient).

Methods: A 58 year old male with a living unrelated renal transplant 15 years ago was diagnosed with metastatic renal cell cancer (RCC). Immunosuppression was changed to minimal dose mycophenolate mofetil, tacrolimus was replaced with sirolimus, and low dose prednisone was continued. Renal function was normal without proteinuria. The TKI pazopanib was started to treat the metastatic RCC. Within three months of starting treatment, he developed worsening hypertension, edema and nephrotic range proteinuria (7 gms/day) with low serum albumin (3.4g/dl). A kidney biopsy revealed podocytopathy and early glomerular endothelial damage. There was no evidence of T- cell or antibody mediated rejection. Proteinuria improved with discontinuation of sirolimus and pazopanib but worsened again with re-initiation of pazopanib alone. We therefore conclude that pazopanib caused the podocytopathy as well as the endothelial injury. Without other options for RCC treatment, pazopanib was continued with conservative management of proteinuria by angiotensin receptor blockade and blood pressure control.

Results:

Conclusions: We report the first case of biopsy proven podocytopathy with endothelial injury secondary to the TKI pazopanib in a kidney transplant recipient. Nephrologists, transplant physicians and oncologists need to be aware of complications of this and other targeted therapies in transplant recipients.

SA-PO960

Transplant Associated Thrombotic Microangiopathy (TA-TMA) in a Child with Neuroblastoma and Complement Factor Deletion: A Novel Association Amirtha Chinnadurai,[2] Ali Y. Suliman,[3] Michael Kent,[1] Alda Tufro.[4] *[1]Yale University, New Haven, CT; [2]Pediatric Nephrology, Yale University School of Medicine, New Haven, CT; [3]Yale univeristy School of medicine, Hamden, CT; [4]Yale University School of Medicine, New Haven, CT.*

Background: TA-TMA is an increasingly recognized morbidity following stem cell transplantation. It is uncommon in autologous stem cell transplantation (auto-SCT). Risk factors for TA-TMA following auto-SCT include specific malignancies such as neuroblastoma, platinum based chemotherapy, total body irradiation and infections. To our knowledge, there are no previous reports of genetic predisposition as a cause of TMA in neuroblastoma following auto-SCT.

Methods: A 3-year-old hispanic boy with stage IV poorly differentiated neuroblastoma, received 6 cycles of high dose chemotherapy, primary tumor resection

and underwent auto-SCT two months later. His post-stem cell transplant course was complicated with septic shock with multi-organ dysfunction including respiratory failure, recurrent supraventricular tachycardia and acute kidney failure requiring continuous renal replacement therapy, which subsequently resolved and the neuroblastoma remained in remission. Two months after auto-SCT, he developed refractory hypertension on multiple anti-hypertensive therapy, seizures associated to acute posterior reversible leukoencephalopathy syndrome, recurrent acute kidney injury and severe thrombocytopenia and anemia, dependent on daily transfusions. The diagnosis of TMA was then established with the presence of schistocytes, low serum haptoglobulin, elevated lactate dehydrogenase, negative Coombs, normal ADAMTS13, marked decrease in CH50 and complement component 5 activity. Complement gene panel revealed homozygous deletion of CFHR1 gene. He received weekly eculizumab for two months leading to normalized renal function, eGFR of more than 100ml/min/1.73m2 (modified schwartz), resolved hypertension, proteinuria, anemia and thrombocytopenia. Eculizumab therapy was tapered as all TMA signs resolved, and remains in remission to date (23 months from onset), while receiving Eculizumab every two months.

Results:

Conclusions: We report for the first time a case of TMA in a child with neuroblastoma harboring a complement genetic mutation known to cause TMA or atypical hemolytic uremic syndrome. It resolved upon Eculizumab and remains in remission after extending the therapy interval to 8 weeks. We hypothesize that complement genetic variants may constitute a risk factor for sporadic TA-TMA.

SA-PO961

Kidney Transplantation in a Patient with Severe Pulmonary Hypertension on Macitentan Therapy Sandhya L. Kommana,[1] Erik L. Lum.[2] *[1]Harbor ULCA MEDICAL CENTER, Harbor City, CA; [2]UCLA Ronald Reagan Medical Center, Westwood, CA.*

Background: Pulmonary Hypertension (PH) is associated with a significant reduction in patient survival and graft function following kidney transplantation. Patients with severe pulmonary hypertension, defined as a 6 minute walk test < 300 meters or ventricular systolic pressure (RVSP) > 55 mmHg, are at increased risk for peri-operative complications and is considered a contraindication to kidney transplantation. Here we report a case with severe PH on maintenance Macitentan (Endothelin receptor antagonist) therapy who underwent successful kidney transplantation.

Methods: A 65-year-old male with ESRD secondary to autoimmune vasculitis was evaluated for kidney transplantation. His past medical history was notable for dermatomyositis, interstitial lung disease, pulmonary hypertension, and coronary artery disease. Two years prior to evaluation he was noted to have increasing dyspnea. A CT scan of the chest revealed pulmonary fibrosis. Pulmonary function tests revealed restrictive lung disease with FEV1 75% predicted, FEV1/FVC 57% and significant DLCO impairment of 28%. An Echocardiogram showed RVSP of 70 mmHg and was started on nocturnal oxygen therapy. His symptoms continued to worsen and was started on Macitentan, with improvement in his pulmonary pressures (32 mmHg) and nocturnal oxygen was discontinued. One year prior to transplantation he developed worsening dyspnea as a result of pulmonary edema in association with progression of his renal disease and was initiated on hemodialysis. His symptoms improved and he was cleared for kidney transplantation. The patient underwent living unrelated kidney transplantation without complications. His Macitentan was continued during the perioperative period. We used caution not to use Diltiazem or Fluconazole postoperatively due to drug interaction with Macitentan. He is currently 3 months post kidney transplantation and has good allograft function with S Cr of 1.2 mg/dl.

Results:

Conclusions: The prevalence of pulmonary hypertension in ESRD patients has been estimated between 9-15% and when severe may preclude patients from getting kidney transplantation. However, the recent development of effective pharmaceutical therapies for PH may improve these outcomes. To our knowledge, this is the first reported case where kidney transplantation was performed in a patient with pulmonary hypertension on drug therapy.

SA-PO962

Acyclovir Neurotoxicity Occurring in Two Patients on Peritoneal Dialysis with Varicella-Zoster Virus Encephalitis Xunxi S. Guo,[1] Vesh Srivatana.[2] *[1]NYP/Cornell, New York, NY; [2]The Rogosin Institute, New York, NY.*

Background: Acyclovir neurotoxicity which can have varying symptoms including agitation, delirium, myoclonus, and coma are known to appear more commonly in end-stage renal disease (ESRD) patients. The kidney is the major route for acyclovir elimination and in ESRD patients, hemodialysis (HD) eliminates an estimated 45% of the drug during a 3-hour treatment, however in continuous ambulatory peritoneal dialysis (CAPD) clearance is 22 times lower compared to HD. We report 2 cases of acyclovir neurotoxicity in peritoneal dialysis (PD) patients with varicella-zoster virus (VZV) encephalitis with improved mental status after transitioning to HD.

Methods: Case 1: A 56 year-old female with ESRD on CAPD for 3 months, recently started on valacyclovir for 2 days for herpes zoster opthalmicus presents with acute onset of confusion. She was started on IV Acyclovir upon admission. Cerebrospinal fluid (CSF) analysis showed 3,500 Varicella DNA copies/mL. Her encephalopathy worsened and neurological evaluation with EEG and MRI/MRA was unrevealing. On hospital day 4, she underwent HD with subsequent improved mental status. Acyclovir level was 3.1 mcg/mL pre-HD and none detected post-HD. She was treated with 2 weeks of IV Acyclovir and intermittent HD with return to normal mental status and transitioned back to CAPD at discharge. **Case 2:** A 50 year-old female with ESRD on automated PD for 6 years presents with worsening mental status in setting of zoster ophthalmicus and superimposed cellulitis. She had been on valacyclovir for 2 days and continued on IV Acyclovir. Her mental status quickly deteriorated, only grimacing to pain. CSF analysis showed 81,700 Varicella DNA copies/mL. Acyclovir level was 8.1 mcg/mL. On hospital day 3, she was started on HD. Her course was complicated by troponinemia, hypotension, and reduced ejection fraction attributed to VZV myocarditis and was briefly on continuous renal replacement therapy. Her mental status returned to baseline 5 days after start of HD. She completed a course of acyclovir and was transitioned back to PD at discharge.

Results:

Conclusions: We present two unique cases of acyclovir neurotoxicity in PD patients with VZV encephalitis. They highlight that acyclovir even at appropriate dosing can lead to toxic levels and neuropsychiatric effects in the PD population due to no appreciable clearance.

SA-PO963

A Unique Case of Valganciclovir Associated Reversible Azoospermia in a Renal Transplant Patient Al J. Lee, Myriam C. Vela-Ortiz, Karthik M. Ranganna, Sandeep Aggarwal. *Drexel University College of Medicine, Philadelphia, PA.*

Background: Azospermia with secondary infertility has not been reported as an adverse effect associated with valgancyclovir. We present a case of reversible azospermia in a renal transplant patient associated with valgancyclovir therapy.

Methods: 30y/o male with past medical history of surgically corrected Tetralogy of Fallot whom developed dialysis dependent renal failure post cardiac surgery and required renal transplant 11 years ago. Patient presented for routine outpatient transplant appointment with complaints of inability to conceive. He denied genitourinary trauma, ED dysfunction, family history of infertility, or exogenous use of androgens. He was a well-nourished, well developed male who appeared as stated age and had an unremarkable physical exam. Referral was made to fertility clinic. The patient's semen analysis results are: semen volume 3.8mL and no sperm identified. Diagnosis of primary male infertility secondary to azopsermia was made. At this time the patient was on stable immunosuppression with tacrolimus 1mg BID and prednisone 5mg daily and valgancyclovir 900mg BID (for 3 years)secondary to persistent EBV viremia. Autoimmune, hormonal, and radiological workup for infertility was negative. In an attempt to uncover medication related azospermia, valgancyclovir was stopped. 1 month later repeat semen analysis results were: semen volume 2.9mL, sperm concentration 21mil/mL, total sperm number 60.9mil/ejac, progressive motility 41%, total motility 63%, vitality N/P, sperm morphology 3%, pH 8, leukocyte <1. There were no further other medication changes. Patient was able to conceive a child and had semen cryopreserved. Patient currently not on valgancyclovir with stable EBV PCR of 7272 copies/mL; unchanged since initial stoppage of valgancyclovir 10 months prior.

Results:

Conclusions: In animal studies gancyclovir has been a potent inhibitor of spermatogenesis but to our knowledge this is the first h uman r eported c ase of valgancyclovir associated azospermia. Further studies needed including careful post-marketing analysis to confirm this association.

SA-PO964

Rapidly Growing Mycobacteria (RGM) – An Unusual Cause of Peritoneal-Dialysis Associated Mycobacterial Peritonitis Nasir Khan,[2] Valerie Jorge Cabrera,[2] Neera K. Dahl.[1] *[1]Madison, CT; [2]Yale School of Medicine, New Haven, CT.*

Background: Non-tuberculous mycobacteria are a rare but serious cause of peritoneal dialysis-related peritonitis. *M.chelonae*, a member of the rapidly growing non-tuberculous mycobacteria (RGM) group, is an atypical organism mostly found in soil and water and known to cause skin and soft tissue infections. We present a case of *M.chelonae* infection manifested with chronic skin lesions and peritonitis in a diabetic peritoneal dialysis patient.

Methods: A 54 year old African American male developed 2 nodular lesions on the mid abdominal area. His past medical history included diabetes, hypertension and end-stage renal disease due to diabetic nephropathy. He had been started on peritoneal dialysis (PD) around 2 years ago. Over the course of 7 months these nodular skin lesions developed intermittent purulent discharge. Wound cultures, including fungal and acid-fast bacilli (AFB) cultures were repeatedly negative. Several days prior to admission, his peritoneal effluent became cloudy without any systemic symptoms. Two ulcerated nodules with purulent drainage were noted on the mid abdominal area. Peritoneal fluid cell count showed 4256 nucleated cells. Computed tomography (CT) of the abdomen confirmed the lesions to be interconnecting. A discrete 1.5 x 2.5 cm collection was also reported along the peritoneal catheter track. Four days later preliminary peritoneal fluid cultures revealed gram-positive acid fast bacilli, later identified as *M.chelonae*. The PD catheter was surgically removed and the patient was transitioned to hemodialysis. Deep wound cultures obtained in the operating room also confirmed the diagnosis. He was started on a 4-month course of Tigecycline and Amikacin based on culture sensitivities.

Results:

Conclusions: *M.chelonae* characteristically causes chronic nodular lesions with a purple discoloration. Very few cases of *M.chelonae* peritoneal dialysis-related peritonitis have been reported. Mainstay of treatment is removal of the source as well as antibiotics. A high level of suspicion for organisms such as fungi and non-tuberculous mycobacteria should be maintained in peritoneal dialysis patients with routine negative dialysate cultures who are unresponsive to standard empirical antibiotics.

SA-PO965

Peritonitis Following Fecal Microbiota Transplantation (*2) via Colonoscopy in a Peritoneal Dialysis Patient Shree R. Mulay, Sana Waheed. *University of Wisconsin, Madision, Madison, WI.*

Background: Fecal microbiota transplantation (FMT) is commonly utilized in the treatment of recurrent Clostridium difficile (C. diff) infection. However, there is no consensus on how best to manage these patients who are on peritoneal dialysis (PD) regarding administration of prophylactic antibiotics prior to FMT. We share our experience with one such case requiring an FMT who subsequently developed peritonitis.

Methods: A 50-year-old female on peritoneal dialysis for end stage renal disease secondary to ANCA vasculitis and recurrent C. diff infection was admitted with abdominal pain and severe diarrhea. She was found to have another C. diff infection and since she had already failed treatment with oral vancomycin and fidaxomicin a decision was made to proceed with FMT via colonoscopy. Given the concern that she may not have a successful FMT if given prophylactic antibiotics, she was not given any antimicrobial prophylaxis and all antibiotics were held 48 hours prior to the procedure. She resumed peritoneal dialysis after the procedure and her fluid remained clear. However, 2 days later her diarrhea and abdominal pain recurred. She had an extensive GI work up and no alternative explanation could be found for her abdominal pain and her C. diff remained positive. She underwent another FMT considering the fact that there could be a 5-10% failure rate with the procedure. Again, she was not given prophylactic antibiotics. Her PD fluid turned cloudy the next day and she had low grade fever and her PD fluid cell count showed a total of 404 nucleated cells with 29% polymorphic neutrophils. Her PD culture grew Enterococcus faecalis and she was treated with intraperitoneal daptomycin daily for a total of 3 weeks. Her abdominal pain and diarrhea have not recurred since the second FMT.

Results:

Conclusions: FMT can be used to successfully treat patients on peritoneal dialysis with recurrent C. diff. However, our patient developed peritonitis as a result of the procedure which can be a risk if prophylactic antibiotics are not administered. We suspect she developed peritonitis from the second FMT because it was associated with a more thorough diagnostic (exploratory) colonoscopy. We recommend that the risk of peritonitis be discussed in detail with patients who are on peritoneal dialysis undergoing FMT.

SA-PO966

Klebsiella pneumonia Renal Abscess and Peritonitis in a Peritoneal Dialysis Patient: A Novel Route of Infection Miten Dhruve,[2] Joanne M. Bargman.[1] [1]*Toronto General Hospital, Toronto, ON, Canada;* [2]*Nephrology, University Health Network, Toronto, ON, Canada.*

Background: We present a route of bacterial translocation leading to peritoneal dialysis (PD) peritonitis never before reported in the literature.

Methods: A 60 year old patient with newly-diagnosed CKD of uncertain cause underwent a kidney biopsy inadvertently performed during an episode of Klebsiella urosepsis. The biopsy was consistent with advanced diabetic nephropathy and after appropriate education and preparation, a PD catheter was placed and training commenced. The patient presented soon thereafter with abdominal pain and cloudy effluent consistent with PD peritonitis. Imaging revealed a renal abscess at the biopsy site. Microbiology from the PD effluent and from needle drainage of the renal abscess were both positive for *Klebsiella pneumoniae*.

Results:

Conclusions: We propose that the PD peritonitis was the result of seeding of the peritoneal cavity across the retroperitoneum with bacteria from the renal abscess. Successful treatment was achieved through drainage of the abscess and intraperitoneal antibiotics. The patient's course is consistent with a novel route of bacterial entry into the peritoneal cavity culminating in PD peritonitis.

SA-PO967

Atypical Presentation of Acute Type A Aortic Dissection in a Peritoneal Dialysis Patient – A Case Report Waqas J. Siddiqui,[1] Muhammad Aslam,[2] Abu Bakar,[2] Hasan Arif,[1] Sandeep Aggarwal,[1] Ellie Kelepouris.[1] [1]*Division of Nephrology and Hypertension, Drexel University College of Medicine, Philadelphia, PA;* [2]*Dow University of Health Sciences, Karachi, Pakistan.*

Background: Clinical presentation in dialysis patients if often atypical. A commonly encountered clinical sign of dyspnea in dialysis patients is often secondary to fluid overload, but this generalization can often times lead to delay in diagnosis of important underlying causes. We present a case of acute aortic dissection (AoD) in a peritoneal dialysis (CCPD) patient with dyspnea refractory to fluid removal as the only presenting clinical symptom.

Methods: 53 year old man with a history of HIV, ESRD on CCPD awaiting renal transplant, hypertension, cardiomyopathy and recent culture negative peritonitis presented with 3 days of exertional dyspnea and orthopnea. He is compliant with his CCPD exchanges and medications, having recently started Furosemide 40 mg orally for better volume control. His vitals at presentation were: BP = 140/80 mmHg, heart rate = 100/minute (min), temperature = 98.0 °F orally, respiratory rate = 18/min and O_2 saturation on room air = 98%. His EKG showed prolonged QTc = 530 milliseconds. Remaining EKG and blood workup were unremarkable. Chest x-ray revealed mild congestion. The patient was misdiagnosed with fluid overload likely due to CCPD failure. Later he desaturated to 90% on room air requiring high flow O_2 at 6L/min. He was transferred to MICU and started on PD for 4 hours with Dianeal 4.25% solution resulting in net ultrafiltration of 1.2L. His SBP peaked at 158 mmHg. Next morning on cardiac auscultation, loud III/IV diastolic murmur was heard at a left parasternal border. Urgent echo and CT chest with contrast confirmed severe aortic regurgitation with Type-A AoD. An emergent surgical repair was done. Post operatively he received Continuous Veno-venous Hemodialysis, later on, transitioned to intermittent hemodialysis and subsequently discharged.

Results:

Conclusions: Acute AoD is a rare but potentially life-threatening vascular catastrophe with a high associated mortality. This case reminds us that dialysis patients can have an atypical presentation of acute AoD and should be considered if a patient is not improving with conventional treatment. Patients at risk of acute AoD include patients with T2DM, advanced age, atherosclerosis, high BUN, connective tissue diseases and uncontrolled hypertension.

SA-PO968

Successful Placement and Follow Up of ESRD Patient on Peritoneal Dialysis with an LVAD Valerie S. Barta, Kenar D. Jhaveri, Rimda Wanchoo. *Nephrology, Hofstra Northwell School of Medicine, GREAT NECK, NY.*

Background: Left ventricular assist devices(LVAD)s have been shown to improve cardiac function in patients with advanced congestive heart failure(CHF) that are refractory to medical therapy. LVADs are contraindicated in patients with end stage renal disease(ESRD) on hemodialysis(HD). Peritoneal dialysis(PD) is widely considered a contraindication as well, given the close proximity of the peritoneal catheter to the device as well as risk of systemic infections. We report a successful placement of LVAD in an ESRD patient on PD with short and long term follow up.

Methods: A 52 year old Caucasian male with ESRD secondary to chronic heart failure on PD for five years got evaluated for a heart-kidney transplantation. Due to the patient's worsening heart failure and significant symptom burden, he underwent LVAD (HeartWare) placement while continuing PD. He tolerated the procedure well and there were no infectious complications related to his PD catheter. Post LVAD follow up his PD prescription has not required adjustment and his mean arterial pressures(MAP) have remained > 60 mm hg. As blood pressure monitoring is not possible in LVAD patients, MAP values using arterial Doppler ultrasound are used to assess volume status. His fluid management was adjusted using these MAP values in combination with physical exam. Nine months following the LVAD, the patient remains stable on PD awaiting heart-kidney transplantation.

Results:

Conclusions: Our case highlights that PD can be safely performed in LVAD patients. There were no complications with volume management, interrupted LVAD function or peritonitis in our patient. PD should not be a contraindication for placement of LVADs. Additionally, it is our recommendation that in cases of acute kidney injury requiring initiation of dialysis post LVAD, the option of PD should be offered.

SA-PO969

Can Ferric Citrate Lead to Iron Overload in Peritoneal Dialysis Patients? Luke M. Basdeo, Maulik C. Govani, Nabeel Aslam. *Mayo Clinic Florida, Jacksonville, FL.*

Background: Ferric citrate (FC), a novel oral phosphorus binder, is FDA approved for treatment of hyperphosphatemia in patients receiving dialysis. FC binds to dietary phosphate in GI tract producing ferric phosphate and is excreted in feces. However, small quantity of iron is systemically absorbed. There is limited data about the safety of ferric citrate among peritoneal dialysis (PD) patients. Iron overload with FC in PD patients has not been previously reported. We present a series of three PD patients who developed iron overload while receiving FC.

Methods: Patient 1- 65-years old man with ESRD due to IgA nephropathy, status post failed kidney transplant, on CCPD for 3 years with adequate clearance, started on ferric citrate in 1/2016, dose adjusted to 3 tablets tid with meals and 1 with snack; max total dose of 11 tablets/day resulting in acceptable phosphorus control. No IV iron or transfusion during subsequent 12 months. Iron studies summarized in table. FC discontinued at 12 months. Hematology work up consistent with acquired hemosiderosis. **Patient 2**-51-years old woman with ESRD due to systemic sclerosis, on CCPD for 7 years with good clearance, started on ferric citrate in 1/2016, dose titrated up to maximum of 12 tabs/day with good phosphorus control. No IV iron or blood transfusion during the subsequent 12 months. Iron studies summarized in table. FC discontinued at 12 months. **Patient 3**-72-years old man with ESRD due to AL amyloidosis, on CCPD for 1.5 years with adequate clearance, started on ferric citrate in 10/2016, dose titrated up to max of 11 tab/day with acceptable phos control. No IV iron or transfusion after FC initiation. Iron studies summarized in table. FC discontinued at 6 months

Results:

Conclusions: PD patients may be more prone to developing iron overload with the use of ferric citrate. This may be due to less iron loses in PD patients as compared to HD patients. These cases highlight the importance of close monitoring of iron studies in PD patients while receiving ferric citrate as phosphate binder. Further studies are needed to assess the safety of maximum approved dose of ferric citrate among PD patients.

Funding: Clinical Revenue Support

Iron Studies

	Prior to Start	Prior to Start	3 Months	3 Months	6 Months	6 Months	9 Months	9 Months	12 Months	12 Months
	Ferritin	%Sat	Ferritin	%Sat	Ferritin	%Sat	Ferritin	%Sat	Ferritin	%Sat
Patient1	475	24	2998	n/a	2161	51	2028	59	4023	77
Patient2	553	17	1237	47	1486	44	2544	33	1972	76
Patient3	118	39	266	34	943	65				

SA-PO970

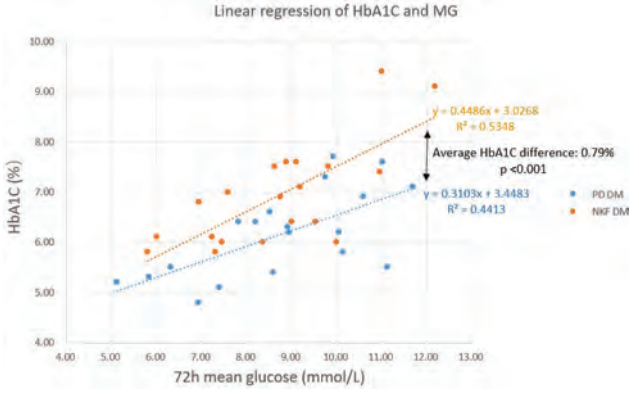
HbA1c Underestimated Glucose Level in Diabetic PD Patients Compared to Normal Kidney Function Diabetic Patients Hua Zheng. *Peking Union Medical College, Beijing, China.*

Background: HbA1C is widely used as glycemic marker for general DM patients. However, its accuracy has been questioned in ESRD patients for potential effect of renal anemia, EPO usage and uremia on glycation physiology. Most research relevant to the topic was done in hemodialysis. Yet, reports on whether HbA1C underestimated glucose level in PD patients were contradictory. This research aimed to compare HbA1C value adjusted with mean glucose in PD DM and DM patients with normal kidney function (NKF) and the potential cause of the difference.

Methods: Twenty DM PD patients were enrolled in this single-centered prospective research for 72-hour Continuous Glucose Monitoring (CGM). PD patients were matched with twenty DM NKF patients based on 72-hour mean glucose (MG), age and gender who underwent CGM during the same period.

Results: One PD patient was discarded for incomplete data. No significant gender and age difference was detected between PD and NKF patients. For PD patients, mean EPO dose for previous three months was 8002 IU per week. Mean Hgb was 106.8g/L. PD and NKF patients had negligible MG (8.8±1.9 vs 8.7±1.7 mmol/L, p=0.868) with significantly different HbA1C value (6.17%±0.87% vs 6.93%±1.02%, p=0.043). PD patients also had worse linear correlation than NKF patients. Significant different regression formula was found between PD and NKF patients (p for intercept=0.02). PD patients had 0.79% lowered absolute value than NKF patients for HbA1C (6.15% vs 6.94%, $p < 0.001$) at pooled mean MG (8.74mmol/L). Further analysis on regression residuals or residuals over estimated HbA1C found that this difference could not be explained by EPO dose (p=0.733), hemoglobin (p=0.727), urea (p=0.934), creatinine (p=0.648), albumin (p=0.582), residual GFR (p=0.767) or nPCR (p=0.408).

Conclusions: HbA1C significantly underestimated glucose level in diabetic PD patients compared to normal kidney function diabetic patients. The difference might not be simply explained by hemoglobin, EPO injection dose, uremia, residual GFR, albumin, or nPCR.



SA-PO971

Hematuria in a Chronic Hemodialysis Patient Anuradha Konkesa,[3] Srikanth Thiruvarudsothy,[4] Neeraj Sharma,[7] Aravindan V. Jeyarajasingam,[1] Sushma Munugoti,[6] Alluru S. Reddi,[5] Farah Piracha.[2] *[1]Swedesboro, NJ; [2]Rutgers NJ Medical School, Staten Island, NY; [3]Rutgers, Morrisplains, NJ; [4]Rutgers NJMS, Belleville, NJ; [5]Rutgers New Jersey Medical School, Newark, NJ; [6]Rutgers UNIVERSITY, Montclair, NJ; [7]Rutgers University, Bloomfield, NJ.*

Background: Spontaneous gross hematuria in a chronic hemodialysis patient is an uncommon finding which can be a consequence of renal cyst rupture, renal cell carcinoma, angiomyolipoma, stones, or vascular diseases. We recently treated a patient on chronic hemodialysis for spontaneous gross hematuria who was found to have renal cysts and renal cell carcinoma.

Methods: A 47-year-old African American man with past medical history of AIDS, hypertension, and ESRD on HD due to HIVAN since 2002 was evaluated for gross hematuria (1 to 2 ml). Hematuria was not associated with flank pain, weight loss, dysuria, or trauma. A CT scan of the abdomen and Pelvis with contrast showed a 6.3x6.2x5.1 cm mass in the mid to upper pole of right Kidney. There were bilateral renal cysts and both kidneys were atrophic. He underwent a right laparoscopic nephrectomy. Histology revealed clear cell renal carcinoma.

Results:

Conclusions: Acquired cystic kidney disease (ACKD) is recognized as a disease of consequence affecting patients on long-term hemodialysis (≥3 years), and the prevalence of ACKD increases linearly with duration of dialysis. Approximately 1- 4% of patients with ACKD develop renal cell carcinoma (RCC), and the development of cysts and their degeneration into carcinoma is poorly understood. The range of patients affected by ACKD-RCC is very narrow. Compared to the general population, the risk of developing RCC in ACKD is increased by more than 100-fold. In general, RCC associated with ACKD is considered to be less aggressive than sporadically occurring RCC. A CT scan should be performed to rule out other causes of spontaneous renal rupture. Recommendation to screen patients with ESRD for ACKD and renal cell cancer has not been uniform because of their limited life expectancy; however we believe screening will be valuable for patients in good general health with a good life expectancy.

SA-PO972

Successful Fecal Microbiota Transplant in an ESRD Patient Jeffy Kenny Thomas,[2] Jason Cobb,[2] Jung W. Suh.[1] *[1]Atlanta Gastroenterology Associates, Atalnta, GA; [2]Emory University School of Medicine, Atlanta, GA.*

Background: The incidence of clostridium difficile (c. difficile) colitis is increasing and there are reports of 10-25% of patients treated with medical therapy (metronidazole or vancomycin) having relapse of colitis despite medical therapy. A treatment option in these refractory or recurring c. difficile colitis cases is fecal microbiota transplant (FMT). There is a paucity of data of c. difficile colitis in patients with kidney disease. We present a case of an ESRD patient with refractory c. difficile colitis that underwent a successful FMT.

Methods:

Results: 60 year-old African-American female with ESRD requiring hemodialysis for 3 years. Her ESRD is due to diabetic nephropathy. She was admitted to an outside hospital in March 2017 for coronary artery disease and atrial fibrillation, and was transferred to our hospital for further cardiac care. She received intravenous antibiotics at the outside hospital for 1 day. Upon presentation to our hospital, she had severe diarrhea which required the placement of a fecal management system. Her stool was positive for c. difficile and due to the severity of her disease oral vancomycin was initiated. Despite treatment for 12 days with oral vancomycin, intravenous metronidazole was added. She continued to have persisting diarrhea despite treatment. She received bezlotoxumab (human monoclonal antibody for the treatment of c. difficile infections) but continued to have severe watery diarrhea. Gastroenterology was consulted and a decision was made to perform a FMT. The patient received a FMT on April 14th and April 25th, 2017. It was performed per colonoscope with 60 ml syringes of fecal material being injected in the terminal ilium and cecum for a total of 240 ml each time. At the time of discharge (14 days after initial FMT) the patient was off antibiotics, off probiotics, and having only one semi-formed stool each day.

Conclusions: This is the first case of an ESRD patient undergoing a FMT and shows that it is a safe treatment option in ESRD patients with refractory or relapsing c. difficile colitis.

SA-PO973

Clinical Picture: Central Venous Catheter-Related Occlusive Disease Jin Wen,[1,3] Yang Yu,[2] Tianlei Cui.[2] *[1]Nephrology and Rheumatology Department, Yongchuan Hospital of Chongqing Medical University, Chongqing, China; [2]Nephrology Department, West China Hospital & Sichuan University, Chengdu, China; [3]Nephrology Department, West China Hospital & Sichuan University, Chengdu, China.*

Background: The central venous catheter (CVC)-related occlusive disease is a major and serious complication of central venous cannulation, posing a huge challenge to end-stage renal disease (ESRD) patients, especially for the growing group of hemodialysis patients when CVC becomes the only available form of access. Herein, we report a successful case of multiple central venous occlusion and thrombosis by percutaneous superior vena cava (SVC) cannulation technique under cross-located fluoroscopy.

Methods: A 50-year-old male with ESRD for 7 years presented with 3 weeks of hemodialysis catheter dysfunction. Before transferred to our hospital, he had undergone a maintenance hemodialysis via a tunneled right femoral vein catheter for 6 months, when other possible vascular accesses had been tried but failed, unfortunately. Physical examination showed collateral tortuous veins in the right chest wall. CT venography of the chest demonstrated chronic occlusion of the entire right brachiocephalic vein (BCV), left BCV and the distal end of SVC. Meanwhile, venography revealed inferior vena cava (IVC) long segment total occlusion with thrombosis (Fig1). Under this situation, we successfully implanted a new tunneled catheter by percutaneous SVC cannulation technique under cross-located fluoroscopy (Fig2), and then removed the previous malfunctioned catheter. The patient discharged 2 days after the new functional catheter establishment.

Results:

Conclusions: The CVC-related occlusive disease is usually so troublesome that leads to increasing mortality of ESRD patients, especially for those who suffer from exhausting hemodialysis vascular access. Although many patients are asymptomatic, some can present with symptoms of venous hypertension, such as edema of upper extremity and collaterals of the chest or abdominal wall, which require our more attention and supervision. However, it remains challenging to deal with such severe CVC-related occlusion when almost all the principal venous are occlusive. Notably, we implanted a new tunneled catheter by percutaneous SVC cannulation technique under cross-located fluoroscopy. Our successful case manifests that this technique may light a new lamp in combating the CVC-related occlusive disease.

Funding: Other NIH Support - No.

SA-PO974

Long-Term Clinical Spectrum and Circulating RAS Evaluation of Anephric Patients on Hemodialysis: A Series of 4 Cases and Literature Review Lin Liu,[2] Yumei Zhang,[1] Fangting Fu,[2] Wenge Li.[1] *[1]China-Japan Friendship Hospital, Beijing, China; [2]Department of Nephrology, China-Japan Friendship Hospital, Beijing, China.*

Background: Blood pressure decline is one of the short-term complications of bilateral nephrectomy mainly due to sharp change of circulating renin-angiotensin system (RAS), but data about long-term outcome of clinical status and the development of circulating RAS of these patients is limited.

Methods: We enrolled 4 Chinese cases with both their kidneys removed for 2, 6, 8 and 8 years, respectively, from 304 patients on maintenance hemodialysis in December 2016 in our center. The blood samples for RAS tests were drawn after the subjects seated for 30 minutes immediately before hemodialysis was started. Radioimmunoassay was performed to assess their circulating RAS. Their ages ranged from 49 to 80, and 3 out of 4 were female. The reasons of nephrectomy included polycystic kidney disease (n=1), cancer (n=2), and hydronephrosis (n=1). Hypotension after surgery occurred in 2 patients, and mostly happened during dialysis. They suffered embolism of arteriovenous fistula, but not any life-threatening complications happened. At present, the SBPs in 24 hours of the 4 subjects were all above 90mmHg,and the lowest SBP of 90mmHg and DBP of 46mmHg occurred during dialysis and at midnight, respectively. Only one patient developed severe hypertension again since 4 years after surgery, whose BP now was not well-controlled despite 6 kinds of antihypertensive drugs including ACEI and ARB. The average hemoglobin level was 103.3±12.3g/L. Two of them complicated with hemorrhage of digestive tract, resulting in the need of high erythropoietin (EPO) dosages. The other two patients without hemorrhage received intravenous EPO of only 4500-8000iu/week. The 3 patients receiving blood tests all presented with extremely low plasma renin activity (PRA) of 0.08±0.03ng/ml, compared with normal range of 0.93-6.56ng/ml. Surprisingly, plasma Angǁ concentration of 71.37±8.28 pg/ml and aldosterone level of 0.17±0.02 ng/ml were within normal limits.

Results:

Conclusions: In conclusion, in 2 to 8 years after surgery, the 4 anephric cases did not suffer life-threatening complications with their hypotension gradually recovered and EPO dosage relatively small. Although their PRA was extremely low, they produced normal Angǁ and aldosterone in plasma, indicating the kidney-independent mechanism of Angǁ production compensated well in 2 years after removement of kidneys.

Funding: Government Support - Non-U.S.

SA-PO975

Acute Pancreatitis Related to Hemolysis During Hemodialysis Due to Defective or Kinked Blood Tubing Muataz Yaziji, Sobia N. Khan, Leonard A. Arbeit, Kyung Ho Kim, Nand K. Wadhwa. *Stony Brook Medicine/University Hospital, Stony Brook, NY.*

Background: Hemolysis during hemodialysis (HD) may be related to dialysate, extracorporeal circuit or patients' disease. Extracorporeal hemolysis may result from blood pump occlusion, miss-size needle and partial occlusion of catheter in relation to high BFR, and kinked or faulty tubing. We report a case with massive hemolysis during HD related to faulty or kinked blood tubing presenting as acute pancreatitis.

Methods: A 32-year-old man with ESRD due to obstructive uropathy has been on HD since 2014. On his HD day, he started HD at 5:37 AM at BFR 400 ml/min with a 14 gauze needle using right brachiocephalic AV fistula. At 6:08 AM, arterial pressure increased from -80 to -10 mmHg and venous pressure dropped from 170 to 50 mmHg at a BFR of 360 ml/min. He continued HD until 6:43 AM with repeated alarms. He was moved to another HD machine and completed HD for 3.45 hrs with no issues. He presented to ER the next morning with gradual, progressive worsening abdominal and back pain, nausea and vomiting since HD yesterday. On departure, the patient felt well but staff noted that his color had changed to dark red. On way home, he began to feel unwell and progressed until presented to the ER where labs were repeatedly reported hemolyzed. Physical exam: Alert and oriented, BP 122/88 mmHg, HR 98 bpm, RR 18/min, Temp 36.7°c. He was jaundiced with a soft abdomen and mild tenderness. Rest of the exam was normal. Lab data: WBC 6.78 K/uL, Hgb 7.7 g/dl (10.5 g/dL on 2 week prior), hcts 21.6%, platelets 138 K/UL with no schistocytes, Na 135 mmol/L, K 4.3 mmol/L, BUN 69 mg/dL, Cr 9.5 mg/dL, amylase 525 IU/L, lipase 1260 IU/L, T Bili 2.4 mg/dL, D Bili 0.4 mg/dL, LDH 2300 IU/L, haptoglobin 10.3 mg/dl and negative Coombs test. MRI abdomen: Dilated common bile duct with no luminal defect. HIDA Scan: No acute cholecystitis. He received 1 unit of PRBC during HD the next day. He continued to improve in the hospital. He was discharged home on third day to outpatient HD with no further issues.

Results:

Conclusions: Our patient developed severe mechanical hemolysis during HD likely related to blood tubing in view of temporal relation to out-patient HD with repeated alarms. This was supported by a sudden change in his skin color to dark red after HD. His abdominal and back pain were due to acute pancreatitis likely related to toxic effect of free hemoglobin in his blood.

SA-PO976

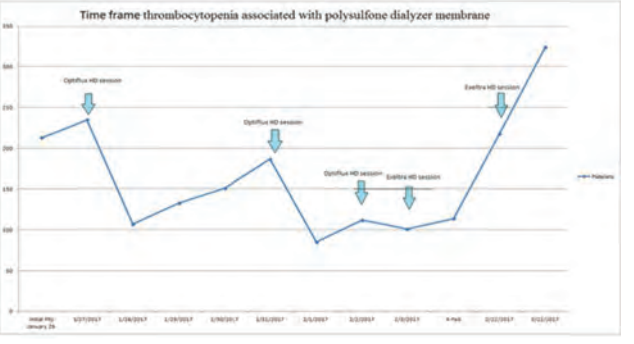
Thrombocytopenia Associated with Polysulfone Dialyzer Membrane Massini Merzkani,[1] Nishita Parikh,[1] Kenar D. Jhaveri.[2] *[1]Northwell Health, New Hyde Park, NY; [2]Hofstra Northwell School of Medicine- Northwell health system, Great Neck, NY.*

Background: Heparin and other drug induced thrombocytopenia are the most common cause of thrombocytopenia in patients with end stage renal disease (ESRD). Dialysis membrane associated thrombocytopenia is extremely rare.

Methods: A 44 year old male with history of ESRD on hemodialysis (HD) was admitted for presumed tunneled HD catheter infection. Over 2 days, the patient grew pseudomonas aeruginosa at the exit site and received piperacilin-tazobactam, vancomycin and eventually cefepime followed by catheter removal. Prior to the first treatment of heparin freeHD (Optiflux 180) on the 1/27/2017 the platelets were $235x10^3/\mu L$. The day after platelets drop $107x10^3/\mu L$. Prior the second HD session (Optiflux 180) was on 1/31/2017, the serum platelets were $187x10^3/\mu L$. The day after HD, the serum platelets dropped to $85x10^3/\mu L$. A presumption of heparin induced antibody was made due to prior use of heparin for deep venous thrombosis prophylaxis and argatroban drip was commenced. Serum heparin induced thrombocytopenia antibodies and serotonin release assay were negative and argotroban was discontinued. Patient was having hemodialysis in the hospital with a dialyzer Polysulfone based (Optiflux 180). Assuming the thrombocytopenia was related to the polysulfone dialyzer given the see-saw effect noted pre and post dialysis (Figure), dialysis was changed to a cellulose base dialyzer (Exeltra 210). Thrombocytopenia resolved as a result of this switch. Following this, the platelets remained to improved and continued in the normal range.

Results:

Conclusions: There have been rare reports of thrombocytopenia associated with dialyzer membranes. As per literature review one of the causes for thrombocytopenic effect of the polysulfone dialyzers is the use of electron beam sterilization. The electron beam modifies the property of polysulfone membranes, increasing their hydrophilicity. Given only monthly blood draws, this entity might not be evident or perhaps, overlooked in the outpatient ESRD units. Our case highlights an important under-recognized cause of asymptomatic thrombocytopenia in the HD patient.



SA-PO977

Dialysis Related Pacemaker Failure Chinonye C. Ogbonnaya-Odor,[3] Dia R. Waguespack,[1] Ali Ziaolhagh.[2] *[1]UTHealth, Houston, TX; [2]University of Texas, Housotn, TX; [3]University of Texas Houston, Houston, TX.*

Background: Dialysis is used in the treatment of electrolyte disorders. Electronic pacemakers are used in the management of arrhythmia's. Failure to capture is a term describing electronic pacemaker pacing, without desired cardiac response. We present a case of unstable bradyarrhythmia due to pacemaker failure to capture, resulting from transient electrolyte changes during hemodialysis.

Methods: An 87-year-old man with CKD III, bradycardia requiring pacemaker placement, and severe hypercalcemia related to left parathyroid adenoma, presented with altered mental status, constipation, and acute kidney injury. He was treated with calcitonin, crystalloids, cinacalcet and hemodialysis. On day 7 parathyroidectomy was performed. Post-surgery, Intact parathyroid (iPTH) trended down rapidly, ionized (iCa) levels gradually decreased, but Creatinine (Scr) increased, and patient became anuric. Labs showed Sodium (Na): 139 mEq/L Potassium (K): 3.9 meq/L Chloride (Cl):102, Bicarbonate (CO2): 21 q/L, iCa of 1.50 mmol/L, Magnesium (Mg):2.4 Mg/dL, Phosphorus: 4.1 Mg/dL. Hemodialysis (HD) was performed with dialysate containing Na: 140 Meq, K: 2.0 Meq, Ca: 1.5 mEq, CO2: 35 mEq. Vitals were stable. After 2 hours of dialysis, patients' heart rate decreased to 20-30 bpm, pacemaker failure to capture was noted on telemetry. Blood pressure (BP) decreased to 75/54, and he became less responsive. HD was discontinued. He was treated with intravenous albumin, crystalloid bolus and atropine with poor response in BP and HR. Transcutaneous pacing was initiated, with appropriate response. Labs revealed iCa: 1.20 mmol/L, K: 3.1 mEq/L, Mg: 1.1 mEq/L, hematocrit: 27%, glucose of 127mg/dL. Pacemaker was interrogated. Findings revealed an acute increase in cardiac pacing threshold during event, which normalized within the next 2 hours. Mg was replaced with intravenous magnesium sulfate.

Results:

Conclusions: Hypocalcemia affects cardiac conduction by increasing phase 2 of cardiac repolarization. The effects are bradycardia and prolonged QTc. Hypomagnesemia can produce similar effects. In this patient, electrolyte flux during dialysis led to pacemaker malfunction. Appropriate treatment for this patient included electrolyte

replacement and changing pacemaker to asynchronous pacing, by placing a magnet on the pacemaker engine.

SA-PO978

Utility of Lung Ultrasound B-Lines in Volume Assessment of ESRD Patients on Hemodialysis Muhammad O. Saleem, Jung Hee Chae, Ahmad A. Kabbani, Jennifer L. Waller, John J. White, N. Stanley Nahman. *Augusta University, Medical College of Georgia, Augusta, GA.*

Background: Volume assessment in end stage renal disease (ESRD) patients on hemodialysis (HD) can be sometimes challenging. Lung ultrasound to look for B-lines, which indicate interstitial edema, is an emerging tool in assessing bedside volume status, and may assist in setting ultrafiltration (UF) goals for dialysis. We performed a quality assurance project to assess the utility of lung ultrasound in determining UF goals.

Methods: ESRD patients were studied before and after HD. Clinical parameters of volume status including systolic blood pressure (SBP) and presence of edema were recorded pre-dialysis, and target UF was set accordingly. We counted the number of B-lines pre and post HD using two portable ultrasound machines, GE V-scan and GE Sonosite. For each patient, the ultrasound probe was placed at the same mid-axillary or mid-clavicular intercostal space to visualize B-lines pre and post HD. Linear regression or ANOVA was used to examine the association between the number of B-lines and fluid removed by UF.

Results: 24 ESRD patients were studied for the number of lung B-lines pre and post HD. B-lines were categorized as 0, 1-2, and 3 or more. For all patients, UF removed trended with the number of B-lines, but there was no significant association. There was a non-significant decrease in the number of B-lines with UF from 3.4±2.1 to 0.7±1.0 (p=0.53). Patients with ≥3 B-lines tended to get more volume removal with mean UF volume of 2.4±0.9L. Mean UF removal in patients with 1-2 B-lines was 1.3±0.9L, and with 0 B-lines was 1.4±0.6L. Interestingly, four patients who did not have any B-lines could not tolerate target UF set pre-HD on the basis of SBP and edema.

Conclusions: Lung ultrasound may be a useful tool for bedside volume assessment of hemodialysis patients and help in deciding UF goals to achieve dry weight. Our pilot project shows a trend that higher number of B-lines may correlate with higher UF tolerance but the data is non-significant. A larger sample size and more sophisticated portable ultrasound machines may give a better idea of any association between B-lines and the determination of UF goals in HD.

SA-PO979

Myoclonus and Altered Mental Status Due to Gabapentin Neurotoxicity in a Patient with Acute on CKD Margaret Ivanov, Ummerubab Syeda, Rakesh Gulati. *Thomas Jefferson University Hospital, Philadelphia, PA.*

Background: Gabapentin neurotoxicity in patients with renal dysfunction continues to be underrecognized in clinical practice, and has been found to be initially suspected in fewer than half of all presenting cases[1].

Methods: A 72-year-old male with a medical history significant for chronic kidney disease stage 4 and non-insulin dependent diabetes mellitus type 2 with severe diabetic polyneuropathy, was admitted to the hospital with septic shock from a urinary tract infection and cellulitis, and acute kidney injury (creatinine 4.2 mg/dL, baseline 1.8 mg/dL). On hospital day 7 despite improvement in his overall condition from a hemodynamic and infectious standpoint, the patient developed agitation and confusion, and was noted on exam to have asterixis and multifocal myoclonus. Of note, his renal function had been steadily declining throughout the hospitalization, with labwork at the time of his deterioration notable for BUN 98 mg/dL, SCr 5.4 mg/dL, and GFR 10 mL/min/1.73m^2. The Nephrology service was consulted with concern for uremic encephalopathy. In reviewing the chart, it was noted the patient had been receiving gabapentin 600mg daily throughout the hospitalization. Although the dose had been reduced from 600mg t.i.d. on admission, it was inappropriately high for his creatinine clearance at the time of his deterioration, and he was found to have a serum gabapentin level of 45.8 mcg/mL (reference range 4.0-8.5 mcg/mL). The patient was started on continuous venovenous hemodialysis filtration with improvement in his mental status and myoclonus by the following morning, and complete resolution of symptoms after 48 hours on CVVHD, with a repeat gabapentin level of 8.6 mcg/mL.

Results:

Conclusions: Due to the occurrence of mental status changes and myoclonus in uremia, the role of neurotoxic medications in patients with renal dysfunction may be overlooked. This case adds to the recent growing body of literature recognizing signs of gabapentin neurotoxicity, and underscores the importance of attentive prescribing of renally cleared medications in patients with fluctuating renal function. [1]Zand L, McKian KP, Qian Q. Gabapentin toxicity in patients with chronic kidney disease: A preventable cause of morbidity. American Journal of Medicine 2010;123:367-373

SA-PO980

Gabapentin Toxicity in a Patient with AKI Lukasz Kiljanek, Al J. Lee, Hasan Arif, Sandeep Aggarwal, Rebecca K. Seshasai. *Drexel University College of Medicine, Philadelphia, PA.*

Background: Gabapentin is a commonly used therapy for the treatment of chronic and neuropathic pain and requires dose adjustment in patients with renal insufficiency. Its toxicity can present as myoclonus and can be managed with hemodialysis.

Methods: 81 year old woman with CKD, baseline creatinine one week prior to admission of 2.4 mg/dl, also hypertension, type 2 diabetes and congestive heart failure admitted after a fall to the trauma service. The patient reports that she fell due to "body jerks" causing loss of balance. As per protocol, she received CT scans with intravenous contrast to rule out acute trauma, all were negative. Creatinine on admission 4.24 mg/dl and rose to 7.27 mg/dl on day 4, at time of nephrology consultation. Patient hemodynamically stable, no episodes of hypotension. On exam she had what appeared almost like dyskinesia, unable to hold her arms, legs or torso steady, as well as myoclonus although mental status was intact. She was diagnosed with contrast induced nephropathy. BMP showed sodium 132 mmol/l, potassium 5.4 mmol/l, bicarbonate 22 mmol/l, glucose 44 mg/dl. Urinalysis unremarkable. She was making < 500 cc urine/day. Renal ultrasound unremarkable. Medication list notable for gabapentin 2200 mg daily, furosemide and losartan. Serum gabapentin level 78 mcg/ml (reference 4-16 mcg/ml). Gabapentin, furosemide, losartan all discontinued. She received two sessions of hemodialysis with full resolution of body movements and myoclonus and recovered from her AKI with a discharge creatinine of 3.09.

Results:

Conclusions: Gabapentin, a 3-cyclohexyl-GABA, is an analogue of GABA able to activate its receptors. Hypoglycemia, myoclonus, and altered mental status have been previously reported as symptoms of gabapentin toxicity. This drug can easily accumulate in patients with impaired renal function. In patients with ESRD on non-HD days elimination half-life of gabapentin is 132 hours, while in the general population it is 5-7 hours. Levels of above 15 μg/mL are considered toxic. Gabapentin can be effectively cleared by hemodialysis. Given its relatively frequent use in patients with renal insufficiency, it is important to remain mindful of potential gabapentin toxicity in patients with neurological symptoms.

SA-PO981

Acquired Erythropoietin (EPO) Deficiency Following Microwave Ablation of Papillary Renal Cell Carcinoma in a Renal Transplant Myriam C. Vela-Ortiz,[2] Joseph H. Brezin,[1] Brian A. Bianco.[3] *[1]Clinical Nephrology VA Associates, LTD, Philadelphia, PA; [2]Drexel University, Philadelphia, PA; [3]Hahnemann University Hospital, Drexel University College of Medicine, Philadelphia, PA.*

Background: Percutaneous microwave ablation of renal malignancies is a novel nephron sparing option for patients who are poor candidates for surgical resection. We present the development of acquired EPO deficiency following microwave ablation of papillary renal cell cancer in a renal allograft.

Methods: A 48-year-old Caucasian female with a PMH of acute post streptococcal glomerulonephritis developed progressive CKD over the next 8 years. She was dependent on recombinant EPO for anemia of CKD for one year prior to renal transplantation in 1995. She received an HLA identical renal transplant from her brother. Her hemoglobin over the next 21 years was normal (12.5-14 gm/dL) without further EPO. The patient was maintained on immunosuppression with cyclosporine, mycophenolate mofetil, and prednisone. Her serum creatinine was 1.5 to 1.7 mg/dl in the first half of 2016. During a work up for resistant hypertension, a 2 x 1.6 cm contrast enhancing mass was found in the lower pole of her kidney transplant. Needle biopsy revealed a low grade papillary renal cell carcinoma. The lesion was treated with microwave ablation as renal sparing therapy. Concurrently the patient was found to have a 7 cm mass of the left native kidney that was treated with laparoscopic radical nephrectomy, also a papillary renal cell carcinoma. Imaging studies 6 months later showed a defect in the lower pole of the renal allograft with no blood flow or contrast enhancement. She developed a normocytic anemia with normal iron studies over the next 3 months and was hospitalized for symptomatic anemia: hemoglobin 6.9 g/dL, WBC 7.3 mm3, platelet count 252, and reticulocyte count 1.4 %. The EPO level was exceedingly low at 7 mlU/L. The bone marrow was hypo cellular on biopsy. She was treated with a blood transfusion followed by judicious recombinant EPO supplementation to avoid further transfusions. Her current hemoglobin is 9.5 gm/dL and her serum creatinine is 1.97 mg/dL.

Results:

Conclusions: Herein we present the case of a patient with papillary renal cell carcinoma of her renal transplant that was successfully treated with microwave ablation. However, she subsequently developed EPO deficiency with severe anemia. We suggest that this may represent a heat related injury to a single functioning kidney that attenuated the production of erythropoietin.

SA-PO1000

Warburg Effect – Unusual Cause of Lactic Acidosis in Cancer Patients Nasir Khan,[1] Lloyd G. Cantley.[2] *[1]Yale School of Medicine, New Haven, CT; [2]Yale University School of Medicine, New Haven, CT.*

Background: Lactic acidosis is the most common cause of anion gap metabolic acidosis in critically ill patients and is associated with significant mortality. While most cases of severe lactic acidosis are from either decreased tissue perfusion or oxygenation (type-A lactic acidosis), other causes should be considered in the differential diagnosis, especially in cancer patients. We present a case of repeated episodes of lactic acidosis, first from tumor lysis syndrome (TLS) and then from anaerobic tumor metabolism in a critically ill patient with Non-Hodgkin Lymphoma (NHL).

Methods: A 75 year old woman with widespread Diffuse Large B-Cell Lymphoma diagnosed three years previously, complicated by severe TLS during induction chemotherapy requiring renal replacement therapy in the past, was admitted with severe metabolic acidemia from lactic acidosis (serum lactate peaked at 30 mmol/L) in the setting of another severe TLS episode triggered by ibrutinib chemotherapy. She was treated with rasburicase and intravenous fluids as well as temporary renal replacement therapy. Her clinical and laboratory parameters improved quickly with resolution of her

lactic acidosis, and she was taken off of renal replacement therapy with return of her renal function to normal. One week later she developed persistent hypoglycemia (glucose values in the 50 mg/dl range despite D10W infusion) followed rapidly by severe lactic acidosis with arterial pH below 7 and serum lactate peak of 29 mmol/L. She remained hemodynamically stable with normal liver and renal function, and her labs did not support TLS: her LDH was only moderately elevated, with normal serum uric acid, calcium and phosphate. Based on her lab findings of persistent hypoglycemia as well as severe lactic acidosis, and CT scan showing progression of her lymphoma, we attributed her lactic acidosis to anaerobic metabolism by her rapidly growing tumor.

Results:

Conclusions: The Warburg Effect, described by Dr *Otto Heinrich Warburg* in 1924, is the metabolic shift of malignant cells to anaerobic glycolysis for ATP production, especially during phases of rapid tumor growth. The resultant inefficient utilization of glucose and generation of large amounts of lactate can lead to clinically significant hypoglycemia and severe lactic acidosis.

SA-PO1001

An Atypical Presentation of Gitelman's Syndrome: Unmasking with Vomiting and Diarrhea

Eric Chang, Jeffrey M. Turner. *Yale University, New Haven, CT.*

Background: Hypokalemia is frequently encountered in the daily practice of nephrology. There are a variety of reasons for hypokalemia, commonly hypomagnesemia, diarrhea or diuretics. Genetic entities such as a salt-wasting tubulopathy like Gitelman syndrome, are rarer etiologies. We report a case of Gitelman syndrome unmasked by vomiting and diarrhea from small bowel overgrowth syndrome.

Methods: A 22-year-old male was referred for persistent severe hypokalemia and hypomagnesemia. He presented with the following electrolyte levels: potassium 2.4-3.4 mmol/L, magnesium 1.2-1.4 mmol/L, and calcium 10.5-10.7 mmol/L. His hypokalemia was noted to occur after acute onset of nausea, vomiting, and diarrhea. His electrolyte abnormalities persisted despite oral potassium and magnesium repletion as well as treatment of small bowel overgrowth syndrome with improved gastrointestinal symptoms. After obtaining additional historical labs, it was noted that he had mild to moderate hypokalemia dating back years prior to his onset of nausea, vomiting, and diarrhea. Our workup revealed a potassium fractional excretion of 11%, magnesium fractional excretion of 7%, aldosterone level of 4, plasma renin activity level of 11.9 (aldo/PRA 0.33). Genetics panel demonstrated compound heterozygous mutations in the SLC12A3 gene. He is now maintained on high dose oral potassium and magnesium supplementation daily with weekly intravenous infusions as well. Adjunctive therapy has been intermittently tolerated due to perceived worsening of his gastrointestinal symptoms. This has included a potassium sparing diuretic, angiotensin receptor blocker, mineralocorticoid receptor antagonist, and NSAIDs.

Results:

Conclusions: Gitelman syndrome is a rare autosomal recessive disorder afflicting 1:40,000 people. Specifically, mutations in the SLC12A3 lead to defective NCC channels in the distal tubules, creating a thiazide-like effect leading to hypokalemia and hypomagnesemia. This case presented a diagnostic challenge as his electrolyte abnormalities initially presented in the setting of severe gastrointestinal illness, which were thought to be the source of his potassium and magnesium losses. This case highlights the critical role of routinely screening for renal wasting of electrolytes even when alternative causes are present.

SA-PO1002

Severe Metabolic Alkalosis After Cystogastrostomy in a Patient with Chronic Necrotizing Pancreatitis

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Background: Hospital acquired metabolic alkalosis occurs in the setting of diuresis or other volume depleting conditions. Correction of volume depletion, hypochloremia and hypokalemia results in resolution of alkalosis. We present a case of severe metabolic alkalosis that was an unexpected complication of cystogastrostomy, a common procedure utilized in chronic pancreatitis.

Methods: A 68 year old man was hospitalized for chronic necrotizing pancreatitis managed with abscess drains and cystogastrostomy tube. On hospital day 154, he required restenting of cystogastrostomy tube. Following this, gastric output was 15 L in 5 days with an average net negative balance of 900 ml/day. Physical examination revealed blood pressure of 86/61 mmHg, heart rate at 88/min and normal mental status. Over 5 days, serum bicarbonate rose from 20 to >45 mmol/L and chloride decreased from 118 to 94 mmol/L. Serum creatinine rose from 1.0 to 1.4 mg/dL. Arterial blood gas revealed pH 7.61 pCO2 55 mmHg, pO2 71 mmHg and calculated bicarbonate at 55 mmol/L. Pertinent medications included fludrocortisone 50 mcg for chronic orthostatic hypotension. In addition to his obligate intake of ~4L/day it took aggressive chloride replacement with normal saline (15 L in 3 days) and potassium replacement with 430 mEq over 3 days to resolve the alkalosis.

Results:

Conclusions: Cystogastrostomy is a common procedure that is used to manage walled-off pancreatic fluid collections. Gastric irritation and excessive vomiting are not an expected complication of this procedure. This patient's volume assessment was a challenge due to chronic hypotension with chronic orthostasis. It was not anticipated that he would require an extraordinary amount of isotonic sodium chloride to reverse the alkalemia. Direct chloride loss, volume depletion, hypokalemia and fludrocortisone therapy were likely mechanisms leading to such severe metabolic alkalosis. Neither acetazolamide nor HCl therapy was utilized given excellent response to aggressive fluid resuscitation. This case highlights the need to recognize and correct precipitating and maintenance factors in metabolic alkalosis in order to avoid hypercapnia and respiratory failure.

SA-PO1003

Pseudohyponatremia Secondary to Lipid Infusion

Ankur Shah,[2] Michael Kitchens,[1] Sidney M. Kobrin.[1] *[1]University of Pennsylvania, Philadelphia, PA; [2]Nephrology, University of Pennsylvania, Philadelphia, PA.*

Background: We present the case of a 26 y/o male with a history of bipolar disorder admitted with acute seroquel intoxication (approximately 18000mg) treated with lipid emulsion infusion who developed pseudohyponatremia.

Methods: A 26 year old male with a history of bipolar disorder presented to the emergency department after he called his partner and admitted to taking a full bottle of seroquel pills (calculated to be approximately 18000mg). During his initial evaluation he was noted to be having seizure like activity and thusly he was intubated and started on vasopressors to maintain a MAP > 65. After consultation with poison control he was given an IV lipid emulsion bolus and infusion, 20% in concentration. The total dose of lipid infusion was 720 ml. Prior to infusion his serum sodium was within the normal range. Shortly after infusion he developed hyponatremia with a sodium that nadired at 124. The critical care service attempted to treat this with fludrocortisone and salt tabs prior to consultation with nephrology. Workup revealed normal serum osmolarity at the time of hyponatremia, revealing the diagnosis to be pseudohyponatremia. Fludrocortisone and salt tabs were discontinued.

Results:

Conclusions: It is oft quoted that the most frequently searched topic on uptodate is hyponatremia, here we present a new presentation of a classic disorder. The first step in the workup of hyponatremia is to evaluate the serum osmolarity to confirm that the hyponatremia is truly hypo-osmolar. Common causes of "pseudohyponatremia" include glycine infusion, hyperlipidemia, hyperglycemia, and hyperparaproteinemia. To our knowledge, this is the first reported case of iatrogenic pseudohyponatremia from a lipid emulsion infusion in an adult without an unintentional overdose. As lipid effusion grows as a treatment modality for lipophilic drug intoxication we will likely be seeing more of this entity and the course of treatment of this patient highlights the importance of increasing awareness.

Lab Values

Date	4/7/2017 18:34	4/7/2017 18:35	4/7/2017 20:57	4/7/2017 20:00	4/7/2017 21:08	4/7/2017 21:12	4/7/2017 23:42	4/8/2017 02:59
Sodium/Event	138	140	139	Lipid Infusion	139	139	138	135
Serum Osm								
Date	4/8/2017 07:40	4/8/2017 08:47	4/8/2017 11:15	4/8/2017 16:12	4/8/2017 18:11	4/8/2017 21:18	4/9/2017 02:47	4/9/2017 03:00
Sodium	132	133	131	127	127	128	124	132
Serum Osm								282

SA-PO1004

Is Urea Effective in the Management of Oxcarbazepine-Induced Hyponatremia?

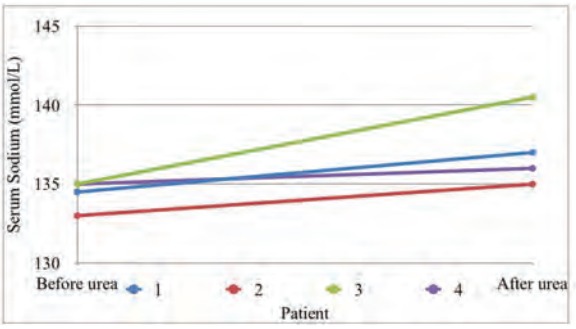
Selasie Goka,[3] Christopher J. LaRosa,[2] Joshua Zaritsky,[2] Divya G. Moodalbail.[1] *[1]Nemours/ Alfred I. duPont Hospital for Children, Wilmington, DE; [2]Nemours/Alfred I. duPont Hospital for Children, Wilmington, DE; [3]Thomas Jefferson University/A.I.Dupont Hospital for Children, Wilmington, DE.*

Background: Oxcarbazepine and carbamazepine, anticonvulsants used to manage partial seizures, are a known cause of hyponatremia largely due to increased tubular sensitivity to ADH. Common ways of addressing this include fluid restriction and sodium chloride (NaCl) supplementation. These can increase the risk of developing nephrocalcinosis/nephrolithiasis in medically complex patients with epilepsy who are largely sedentary. As an alternative, we sought to determine if urea, by osmotic increase in free water excretion, was effective in safely correcting hyponatremia. We present 4 patients whose hyponatremia resolved with the use of urea in place of NaCl.

Methods: The patients, ages 6 to 17 years, were found to have hyponatremia with a nadir between 122 and 131(Figure 1 shows median values) after starting oxcarbazepine. Despite supplementation with NaCl (1-4mEq/kg/day) with some doing fluid restriction; sodium levels remained in the low 130s. The patients were then started on enteral urea (g-tube, j-tube or orally) at 15g to 30g (250-500 mosm) daily. Serum sodium levels normalized within 1-2 weeks of starting urea. Three of the four patients have been successfully weaned off NaCl supplementation with plans to wean the fourth as well.

Results:

Conclusions: Our results show that urea is effective in treating oxcarbazepine-induced hyponatremia. It works to increase urine osmolarity and the excretion of electrolyte-free water. It has been suggested in an animal model to also have neuroprotective effects minimizing risk of osmotic demyelination resulting from rapid correction of chronic hyponatremia. Urea does not potentiate the formation of stones, and as it allows for an electrolyte free-water diuresis it may enable less fluid restriction, help reduce urinary solute concentration and increase urine flow, thereby contributing to stone prevention. It is easy to administer, is not nephrotoxic and can be obtained from retail pharmacies. Given these results, urea may also be a useful alternative for symptomatic hyponatremia in place of hypertonic saline or vaptans.



SA-PO1005

Severe Hyponatremia: A Rapid Correction with Potassium Repletion in a Patient with Lithium-Induced Nephrogenic Diabetes Insipidus Sobia N. Khan, Reena Baharani, Dorothy Rodenbeck, Terence Choy, Muataz Yaziji, Nand K. Wadhwa. *Stony Brook Medicine/ University Hospital, Stony Brook, NY.*

Background: Severe hyponatremia is rare in patients with lithium-induced nephrogenic diabetes insipidus (NDI). This can result from a decreased osmoles intake and acute compulsive water drinking exceeding the capacity of the kidney to excrete free water. Rapid over correction of hyponatremia can occur with potassium repletion. We report a case with bipolar 1 disorder (BD1) with NDI who developed severe hyponatremia with compulsive water drinking on a weight loss diet.

Methods: A 51-year-old woman with BD1, HTN and hypothyroidism presented to the ER with altered mental status, tonic-clonic seizure, lethargy and slurred speech. In the ER, she received IV lorazepam and was intubated for airway protection. Physical exam: Wt 76.4 kg, Temp 35.6ºC, BP 166/92 mmHg, HR 71 bpm. Heart, lungs and abdomen were normal. Six months ago, her serum Na was 140 mmol/L. Lab data: WBC 10.48 K/UL, Hct 30.1%, platelets 232 K/UL, serum Na 105 mmol/L, K 2.1 mmol/L, Cl 65 mmol/L, BUN 7 mg/dL, Cr 0.78 mg/dL, Ca 7.5 mg/dL, Mg 1.3 mg/dL, PO_4 3.1 mg/dL, osmolality 239 mOsm/kg, cortisol 33.2 UG/dL and TSH 2.82 UIU/ml. Urine: Na 48 mmol/L, K 6.0 mmol/L, osmolality 130 mOsm/kg. She received KCl 160 mmol IV and 180 mmol oral, and $MgSO_4$ 4 g IV in first 24 hrs. She received a total dose of DDAVP 16 mcg IV in 24 hours to prevent rapid correction of serum Na. She passed 6600 mL of urine in the first 24 hrs. In the first 12 hrs, her serum Na increased to 117 mmol/L without receiving NaCl solution. With IV infusion of D5W, this rapid increase was reversed and maintained on a serum Na rise of 6-8 mmol/L in 24 hrs. She was extubated the next day. No response to DDAVP was a clue to the diagnosis of NDI. Further history revealed lithium use for 10 years 20 years prior. Her serum Na slowly increased to 133 mmol/L by hospital day 4. She was instructed to eat a regular diet and to drink to thirst with close nephrology and psychiatry follow up. Over a 6 month follow up, her serum Na remained in normal range.

Results:

Conclusions: Hyponatremia is typically not seen in NDI. Our patient was able to maintain normal serum sodium until she began decreasing her oral food intake due to obsessive thoughts about her weight along with compulsive water drinking. In addition, in this case rapid overcorrection of hyponatremia resulted from potassium repletion.

SA-PO1006

Water on the Brain—A Case Report on Crystal Meth-Induced Primary Polydipsia Reema Palankar,[1] Roberto L. Collazo-Maldonado.[2] *[1]UNTHSC Texas College of Osteopathic Medicine, Irving, TX; [2]Dallas Nephrology Associates, Dallas, TX.*

Background: Symptomatic and potentially fatal hyponatremia has been described after ingestion of the designer amphetamine, Ecstasy (MDMA). Along with polydipsia, some studies propose additional mechanisms of MDMA hyponatremia, including induction of an SIADH state and increased activity of aquaporin channels in the medullary collecting duct. Primary polydipsia associated with pure methamphetamine, differing by a methylenedioxy moiety from MDMA, is extremely rare.

Methods: A 36-year-old Hispanic woman with no previous history of systemic illness presented to the ED after suffering an acute-onset seizure that lasted 15 minutes. She was somnolent, disoriented with unintelligible speech. She required intubation on arrival for airway protection. History obtained from her partner revealed crystal meth use earlier that day, after which she drank 10-15 pint sized bottles of water because of "excessive desire to drink water as she was very thirsty." He denied previous history of ongoing excessive water intake, use of ecstasy, or neuropsychiatry conditions. Vitals were stable at admission and she was euvolemic. Workup revealed severe hypotonic hyponatremia (Na 107mmol/L, serum Osm 223 mOsm/kg) with urine Na 79 mmol/L, urine Cl 58 mmol/L, and urine osmolality of 121 mOsm/kg, which was consistent with hyponatremia from primary polydipsia. Head CT revealed diffuse cerebral edema with slit-like ventricles without evidence of herniation. For the symptomatic severe hyponatremia, she received 100 mL hypertonic saline bolus. In addition, she was placed on free water restriction. Repeat CT showed improvement of cerebral edema, which resulted in improvement of mental status and Na levels. She was discharged four days later without any neurological sequelae.

Results:

Conclusions: Cases of methamphetamine-induced primary polydipsia are very rare and probably underreported. It is important to shed light on the prevalence of amphetamine abuse in the teenage/young adult population and the complications of Amphetamine use, including severe hyponatremia, coma and death.

SA-PO1007

Double Trouble with Small Cell Lung Cancer: A Case of Simultaneous Production of Two Ectopic Hormones from a Common Lung Primary Krishna A. Agarwal. *UMMS-Baystate, Chicopee, MA.*

Background: The association of small cell lung cancers (SCLC) with syndrome of inappropriate antidiuretic hormone secretion (SIADH) is well known. Upto 15% cases with SCLC exhibit SIADH but only 1% of patients with SCLC have ectopic ACTH production.

Methods: A 55-year-old cachectic woman with recurrent hospitalizations for weakness, nausea and vomiting was seen in the nephrology office for hyponatremia. SIADH was diagnosed on bloodwork and CT scan of her chest revealed a new hilar mass. Bronchoscopic biopsy and metastatic workup confirmed a small cell type lung cancer with metastasis to her liver, right femur and ribs. Her hyponatremia was treated with water restriction and salt tablets. Two weeks later, she was admitted with right lung collapse and found to have persistent hypertension, metabolic alkalosis, hyponatremia and hypokalemia alongwith elevated ACTH and cortisol. A high-dose overnight dexamethasone suppression test revealed an ectopic non-suppressible source of ACTH and imaging studies ruled out a pituitary or adrenal source of hypercortisolemia. Repeat chest CT showed extensive local infiltration of the lung cancer and widespread hepatic metastasis. Palliative chemotherapy and ketoconazole were trialed in the hopes of reducing tumor burden and improving hypercortisolemia but her clinical status continued to deteriorate and she passed away peacefully.

Results: Case studies have shown that upto 15% of SCLC patients have SIADH and management of hyponatremia improves mortality and therefore palliative chemotherapy is recommended even for extensive disease. Our patient had a unique presentation with both hyponatremia and hypercortisolemia. The median survival time of patients with extensive SCLC is 6-12 months, but it decreases to 7.1 months with concomitant hyponatremia and to 5.5-6.2 months with ectopic ACTH production.

Conclusions: There have only been rare case reports of multiple ectopic hormones being produced from a single primary SCLC. Due to the poor prognosis associated with extensive lung cancer disease and significant worsening with paraneoplastic phenomena like SIADH and ACTH, it is important to diagnose these conditions early and initiate aggressive treatment. Especially, chemotherapy and treatment of hyponatremia because these have been shown to improve performance status and mortality.

SA-PO1008

A Suspected Case of Glycolic Acid Poisoning Daniel Edmonston, Dinushika Mohottige, Jessica D. Morris, Niraj R. Kothari. *Nephrology, Duke University Hospital, Durham, NC.*

Background: The diagnosis of ethylene glycol and other toxic alcohol poisoning is often challenging. Metabolism by alcohol dehydrogenase may result in undetectable ethylene glycol levels in serum. Similarly, the elevation in osmolal gap may not be present once ethylene glycol is metabolized to its charged metabolites. One of the most toxic of these metabolites is glycolic acid. We report a case of suspected recurrent glycolic acid poisoning.

Methods: Our patient was a 38-year-old woman with a history of ethanol abuse and an 8-month span of recurrent admissions for altered mental status in the setting of severe lactic acidosis and acute kidney injury. Investigations including urine toxicology screen, ethanol levels, and volatile acid levels including ethylene glycol, methanol, and isopropyl alcohol were negative during each admission. The patient and family denied any availability of antifreeze and other toxins in the home. Metabolic evaluation for a mitochondrial disorder was negative. She was admitted for nine days for severe lactic acidosis with negative evaluation, which improved with supportive treatment of acidemia. On the day of discharge, her serum bicarbonate was 25 mmol/L. The next day, she became altered again after returning home from the drug store. Her bicarbonate was now 5 mmol/L with arterial pH of 7.13. Her osmolal gap was 5. Again, screening for toxic ingestions was negative. Given high suspicion, she was empirically started on fomepizole and continuous renal replacement therapy was initiated. She remained on pressor support with progressive acidemia, and ultimately died despite aggressive renal replacement therapy. Her autopsy was notable for extensive intravascular and perivascular oxalate crystals in the brain and kidneys. She was also noted to have a transmural acute myocardial infarction of the left ventricle.

Results:

Conclusions: Glycolic acid is found in a myriad of cosmetic products and can be toxic in lethal doses. Unfortunately, the presentation may be difficult to diagnose as the osmolal gap may be normal, lactate markedly elevated (glycolic acid can interfere with certain lab assays for lactate), and ethylene glycol level negative. Even in cases of ethylene glycol poisoning, the glycolic acid level is often a more reliable marker of toxicity. This case highlights the importance of assessment of glycolic acid level in suspected toxic alcohol poisoning.

SA-PO1009

A Known Complication from an Unlikely Source: Propylene Glycol Toxicity Fatima B. Cintron-Rosa, Jannice M. Arroyo, Hector Diaz, Ileana E. Ocasio Melendez. *Nephrology, University of Puerto Rico, San Juan, PR.*

Background: High anion gap metabolic acidosis (HAGMA) in a critically ill patient on vasopressor support could be attributed to the presence of shock. However, this is not specific and additional causes must be investigated. We present an unusual cause of HAGMA and hyperosmolarity in a patient with septic shock and acute kidney injury (AKI), a propylene glycol intoxication.

Methods: A 40-year-old man was admitted due to multiple body trauma secondary to a motor vehicle accident. He required surgery due to bladder rupture with extraperitoneal leakage. Prolonged hospital course complicated with septic shock secondary to multiple nosocomial infections and AKI and was consulted to Nephrology service. Evaluation demonstrated a critically ill patient on mechanical ventilation and vasopressor support, sedated with an intravenous (IV) infusion of lorazepam. Lorazepam was infused at a dose exceeding 0.1 mg/kg/hr. Physical examination revealed fluid overload without oliguria. Laboratory tests supported the clinical impression of AKI and pure HAGMA and acidemia, with a serum bicarbonate concentration of 14.4 mEq/L, an arterial pH 7.214 and a calculated anion gap 27.6. Serum lactic acid level was 39.9 mg/dL. An osmolal gap was present and calculated to be 68 mOsm/kg. Stopping lorazepam IV infusion had no improvement in metabolic acidosis. Patient sedation was changed to an IV midazolam infusion, which is not diluted in propylene glycol. Hemodialysis was initiated and patient showed a rapid improvement in AKI, HAGMA and osmolal gap with withdrawal of hemodialysis therapy after only two sessions.

Results:

Conclusions: This clinical features are classic of propylene glycol toxicity in a patient receiving high doses of lorazepam. Propylene glycol is the diluent used in parenteral formulations of lorazepam and diazepam, which are commonly used sedative medications. This active ingredient is metabolized by alcohol and aldehyde dehydrogenase to D and L-lactic acid, which accounts for the HAGMA with associated elevated osmolal gap not explained by septic shock. Toxicity of propylene glycol is associated to hyperosmolarity, HAGMA, high osmolal gap and AKI and can progress to multisystemic organ failure if severe. Treatment consists of removal of offending agent and dialysis if without improvement, which resulted favorably in our patient.

SA-PO1010

A Preventable Poisoning in Renal Failure Krystahl Z. Andujar, Ileana E. Ocasio Melendez, Fatima B. Cintron-Rosa, Jannice M. Arroyo, Enrique O. Ortiz-Kidd. *Nephrology, University of Puerto Rico, Medical Sciences Campus, San Juan, PR.*

Background: Metformin has become a drug of choice for the treatment of type 2 diabetes mellitus. It has multiple benefits, which include decreasing fasting and post-prandial blood glucose, decreasing body weight and improving lipid profile. However, its use is not without complications and one of the most common toxicities from metformin use is lactic acidosis.

Methods: A 61-year-old man with diabetes mellitus type 2 and arterial hypertension presented to the emergency department after sustaining head trauma. He referred dizziness, nausea and vomiting. Outpatient medications included metformin 1g twice daily. Vital signs revealed hypotension, tachycardia and tachypnea. He appeared uncomfortable, was somnolent but arousable and oriented to person and place. Lungs were clear and extremities without edema. Laboratories showed a creatinine of 13 mg/dL, blood urea nitrogen of 103 mg/dL, bicarbonate of 2.7 mEq/L, glucose of 30 mg/dL and arterial pH of 6.8. Anion gap was 55.3, consistent with a high anion gap metabolic acidosis. Lactic acid levels were elevated at 104 mg/dL. Patient was placed on mechanical ventilation, started on vasopressors and transferred to intensive care unit. A bicarbonate drip was started until hemodialysis was instituted. After hemodialysis, his mental status improved considerably, metabolic abnormalities began to normalize and vasopressors were discontinued.

Results:

Conclusions: Biguanides can lead to the accumulation of lactate by reducing gluconeogenesis and glycogenolysis, inhibiting oxygen consumption and impairing mitochondrial function. This patient had a high risk of metformin accumulation given renal disease. He had a profound acidemia with high anion gap metabolic acidosis and elevated serum lactate levels, consistent with the unusual metformin-associated lactic acidosis (MALA). A case series comparing MALA with other types of lactic acidosis, described only metformin associated with a mean blood pH below 7.0, as in this patient. In patients with severe metformin poisoning, hemodialysis is the preferred approach, which in our patient established hemodynamic stability promptly. However, given the common use of this drug, kidney function and metabolic disturbances should be closely monitored.

SA-PO1011

An Unusual Case of Extensive Brain Infarction and Metabolic Acidosis George Vasquez-Rios, Hani Alkhankan, B. Peter E. Sawaya, Javier A. Neyra. *Nephrology, Bone and Mineral Metabolism, University of Kentucky Medical Center, Lexington, KY.*

Background: Extensive CNS compromise is a rare complication of methanol intoxication that needs prompt recognition.

Methods: A 24-year-old man presented to the ED with a 2-day history of progressive lethargy, diffuse muscular rigidity, and fever. His medical history was relevant for schizophrenia, substance abuse, and essential hypertension. On arrival, his vitals were BP: 169/133 mmHg, HR: 123 beats/min, RR: 25 respirations/min, SatO2: 98% (FiO2: 50%) and T: 38.3 C. Neurological findings included GCS:7, bilateral mydriasis and symmetrical hypoactive reflexes. Laboratory studies revealed severe high anion gap metabolic acidosis (arterial pH 7.21, pO2 100 mmHg, pCO2 8 mmHg and $HC03^-$: 5 mEq/L; anion gap: 36), leukocytosis, mild hyperkalemia, and elevated serum creatinine at 1.36 mg/dl (baseline: 0.96 mg/dl). Calculated and measured serum osmolality were: 302 mOsm/Kg and 297 mOsm/Kg respectively (osmolar gap: 5). After initial workup, sepsis, medication overdose, illicit substance abuse and toxic environmental exposure were excluded. Head CT scan showed extensive bilateral infarctions affecting the lenticular nuclei with hemorrhagic conversion on the right side, along with occipital lobe and cerebellar infarction. Ultimately, his serum methanol level was found to be 40 mg/dL confirming the diagnosis of acute methanol intoxication. Initially, he was aggressively treated with isotonic fluid resuscitation and bicarbonate replacement with mild improvement of his overall clinical status. A 4-hour hemodialysis treatment was administered (delivered single-pool Kt/V: 1.32) to enhance acid/toxic byproduct removal. Intravenous fomepizole (600 mg) and leucovorin (4 doses) were also administered. He was transitioned to continuous venous-venous hemofiltration (CVVH) with an effluent dose of 35 ml/kg/hr to prevent a potential rebound effect. Following 18-hour CVVH therapy, his serum methanol levels were down to 11 mg/dL. His clinical status progressively improved although residual visual impairment and motor deficits were noted upon discharge.

Results:

Conclusions: Extensive cerebral infarction is an unusual presentation of methanol intoxication and may cause a delay in reaching the final diagnosis in a patient with decreased mental status. Rapid recognition and treatment of methanol intoxication are pivotal for survival and attenuation of sequelae.

SA-PO1012

Amantadine Toxicity: An Unexpected Case of Metabolic Acidosis Divya Sharma, Ramapriya Sinnakirouchenan. *Medical College of Wisconsin, Milwaukee, WI.*

Background: Propylene glycol is a solvent used to dissolve a variety of medications and can become toxic when administered in large doses. We present a case of severe metabolic acidosis in a patient taking toxic doses of amantadine, which in some formulations contain the carrier propylene glycol.

Methods: A 66-year-old woman with a history of multiple sclerosis (MS) and end stage renal disease (ESRD) was admitted from Neurology clinic with concerns for MS flare. Her last dialysis was the day prior to admission. Labs revealed BUN 36 mg/dL, Cr 5.81 mg/dL, and bicarbonate 16 mmol/L. That evening she developed severe respiratory distress requiring transfer to the intensive care unit where she was urgently intubated. Arterial blood gas showed pH 6.98, pCO2 <20 mmHg, pO2 104 mmHg, and bicarbonate 3 mmol/L. Basic metabolic panel revealed BUN 59 mg/dL, Cr 7.32 mg/dL, and bicarbonate 4 mmol/L. Other significant labs included lactic acid 20 mmol/L and serum osmolality 322 mOsm/kg. She had an elevated anion gap of 44 mmol/L and an osmolar gap of 18 mOsm/kg. A toxicology screen, including aspirin, acetaminophen, acetone, ethanol, isopropanol, and methanol was negative. The patient underwent emergent hemodialysis for severe acidosis and was extubated the next day.

Results:

Conclusions: It was subsequently found that our patient was started on amantadine 3 weeks prior for MS related fatigue. She was prescribed 100 mg oral twice daily, instead of the recommended dose for ESRD of 200 mg oral weekly. Upon further investigation, we noted that some dosage forms of amantadine contain propylene glycol, which in large amounts can be potentially toxic and be associated with hyperosmolality, lactic acidosis, increased anion gap metabolic acidosis, and respiratory depression. As no other etiology for her acidosis was identified, propylene glycol toxicity was presumed to be the etiology as she was essentially receiving 7 times the dose recommended for her level of renal function. Amantadine was discontinued immediately, and she had no further recurrences of acidosis. This case illustrates the importance of obtaining a thorough history from our patients, including all medications. Not only must we be especially vigilant to dose medications for level of renal function, but to recognize solvents such as propylene glycol that are carriers for a variety of medications and the widespread and potentially harmful effects they may have.

SA-PO1013

Severe Metabolic Acidosis Secondary to Metastatic Melanoma Reoccurrence: The Warburg Effect Sylvester Barnes,[1] Vinod K. Bansal.[2] *[1]Loyola University, Wheaton, IL; [2]Loyola University Medical Center, Maywood, IL.*

Background: The Warburg effect is a phenomenon where a high rate of glycolysis occurs in tumor cells and it uncoupled from aerobic respiration. To keep up with the metabolic demands of the cell, glycolysis increases at the expense of significant glucose utilization and a resultant elevated lactate levels as oxidative phosphorylation does not occur in this process. It is believed this process allows the cell to export various carbohydrate components from the Krebs Cycle to instead promote cell growth.

Methods: The patient is a 85 year old man with CKD stage 3 who presented to the hospital after being seen by his PCP for increasing dyspnea for 6 weeks. The patient has a history of malignant melanoma first diagnosed in 1964 and no sign of recurrence since 2011. Labs were remarkable for a creatinine of 1.54mg/dl, a serum bicarbonate level of 8mmol/L, albumin of 2.9g/dl, alkaline phosphate 538 IU/L, AST 101 IU/L and

ALT of 64 IU/L. His INR and bilirubin were normal. An ABG showed a pH of 7.28, pCO2 of 21mmHg, and calculated bicarb of 9mmol/L. Serum lactic acid was measured at 18 mmol/L. CT scan was obtained showing numerous hypervascular liver lesions, and biopsy confirming melanoma reoccurrence. Nephrology was consulted to help with his metabolic acidosis. When examined the patient was noted to be resting comfortably with only mild tachypnea. Thiamine along with bicarbonate 1300mg three times a day was tried for the patient with no improvement in bicarbonate levels. The patient remained fairly asymptomatic and was discharged home. Four days post discharge the patient presented again to the hospital with increased dyspnea along and altered mental status. Serum bicarbonate was measured at less than 5mmol/L and lactate level obtained was 22mmol/L. An ABG showed a pH of 6.9, pCO2 8mmHg and calculated serum bicarbonate of 2mmol/L. It was decided a focus on comfort would be more appropriate than treatment and the patient ultimately passed away later during the day.

Results:

Conclusions: The patient's persistent lactic acidosis was initially fairly asymptomatic leading to only mild tachypnea and compensatory respiratory alkalosis. It was believed that the majority of his lactate generation was due to his melanoma using primary glycolytic pathways, the Warburg effect. Unfortunately, this is generally seen as a poor prognostic indicator, as was the case for our patient.

SA-PO1014

Thiamine Deficiency Leading to Severe Lactic Acidosis Jamil Ibrahim,[3] Daniel W. Ross,[2] Kenar D. Jhaveri,[1] Richard L. Barnett.[2] *[1]Hofstra Northwell School of Medicine- Northwell health system, Great neck, NY; [2]None, Great Neck, NY; [3]Northwell, Mineola, NY.*

Background: Sepsis and drug induced lactic acidosis are encountered commonly in clinical practice. Lactic acidosis is a rare side effect of thiamine deficiency. Here we will describe a confounding case of Type B lactic acidosis rapidly reversed by thiamine infusion.

Methods: An 88 year old Chinese woman with heart failure on furosemide, tricuspid regurgitation, hypertension, right hand nerve palsy, chronic anemia secondary to beta thalassemia intermedia presented with worsening shortness of breath. She was noted to have a poor diet that featured mainly porridge and polished white rice. Early in her admission she exhibited a lactic acid of 10.8 mmol/L without signs of infection or impending hemodynamic collapse; no complaints apart from shortness of breath. Her elevated lactic acid raised concerns for a major ischemic compromise; clinical stability and absent lab and imaging findings of any end organ damage suggested an alternate cause of her lactic acidosis. Her lactic acid rose to19 mmol/L two days after admission. She was started on an intravenous bicarbonate infusion in order to mitigate further worsening acidosis without success. Her anion gap increased to39 mmol/L, while serum bicarbonate declined to less than 10 mmol/L. Given her dietary history, diuretic use and ethnicity, a diagnosis of thiamine deficiency was made and empirically received 1 dose of thiamine 100 mg intravenously. Her lactic acid level plummeted within hours to 2.7 mmol/L her anion gap closed and serum bicarbonate increased to 32; this alkalosis likely resulted from the HCO3 infusion concurrent with rapid lactate metabolism.

Results:

Conclusions: Thiamine deficiency can lead to wet and dry beri beri, usually seen in alcoholics with/without poor nutrition, weight loss surgery and parenteral therapy if adequate thiamine is not provided. Studies have suggested that subclinical thiamine deficiency is common among hospitalized patients with heart failure, especially if they are treated with loop diuretics but lactic acidosis is uncommon. Nonetheless it should be considered in susceptible individuals such as our patient. The bicarbonate drip further accelerated the rise in lactic acid by creating a low intracellular [H+] environment that stimulates phosphofructokinase activity and hence glycolysis. The extremely rapid disposal of lactic acid consequent to thiamine mediated stimulation of pyruvate dehydrogenase was diagnostic.

SA-PO1015

Pseudo-Anion-Gap Metabolic Acidosis from Severe Hypertriglyceridemia Corrected by Plasma Exchange: A Case Series John T. Ludwig,[1] Charissa Marie R. Carag,[1] Venkata R. Behara,[2] Pravir V. Baxi,[1] Casey N. Gashti.[1] *[1]Rush University Medical Center, Chicago, IL; [2]NANI (Nephrology Associates of Northern Illinois), Mt. Prospect, IL.*

Background: A link between severe hypertriglyceridemia (H-TG) and falsely low or even unmeasurable serum bicarbonate ([HCO3]), known as pseudo-hypobicarbonatemia, has been reported. This is believed to be due to interference by serum triglycerides (TG) - typically >1000 mg/dL - when the commonly used enzymatic assay is utilized for [HCO3] measurement. When the [HCO3] is calculated using an ABG machine, the value is near normal. Chloride measurements are not affected by the TG level. This could lead to the misdiagnosis of a severe anion-gap metabolic acidosis, resulting in an extensive work-up that would typically include expensive toxicology screening.

Methods: We report a series of 4 pts with pseudo-hypobicarbonatemia associated with severe H-TG (Tab. 1). All TG values were >2000 mg/dl and each pt had lipemic serum. All pts had a measured serum [HCO3] of ≤ 6 mmol/L and an elevated anion gap (AG). The calculated [HCO3] from a simultaneous blood sample run using a blood gas machine was 15-27 mmol/L with a pH in the normal range. 3 of the 4 pts presented with acute pancreatitis from H-TG and received 1-3 membrane based therapeutic plasma exchange (TPE) treatments with immediate improvement in TG levels. The 4th pt had discontinuation of PEG-L-asparaginase, known to cause H-TG, and did not require TPE. In each case the serum [HCO3] normalized after lowering of H-TG with a simultaneous resolution of the elevated AG.

Results:

Conclusions: Pseudo-anion-gap metabolic acidosis is a laboratory phenomenon seen when severe H-TG interferes with the normal enzymatic measurement of the [HCO3]. The calculated [HCO3] is not affected when determined using a blood gas analysis machine. While this phenomenon has been previously described, this is the first report to demonstrate immediate resolution of the pseudo-anion-gap metabolic acidosis following aggressive lowering of the TG levels with TPE. Recognition of lipemic serum in the setting of an otherwise unexplained AG metabolic acidosis should prompt the clinician to get an ABG sample for true determination of the acid-base status. Doing so may avoid an extensive and expensive metabolic work-up.

Pt	TG[I]	TG[P]	HCO3[I]	HCO3[P]	AG[I]	AG[P]	HCO3[ABG]	# of TPE
1	4807	303	<5	24	18	8	19	2
2a	8000	341	6	27	19	9	15	3
2b*	5680	653	<5	28	21	12	21	N/A
3	2068	307	<5	24	37	12	27	1
4	2980	332	5	25	29	8	24	N/A

I = initial value, P=post TPE, ABG =arterial blood gas measurement
*Pt 2, second admission

Table 1

SA-PO1016

Total CO2 Assay Interference Induced by Hypertriglyceridemia Diego A. Beltran Melgarejo, Gautam B. Bhave, Anna M. Burgner. *Division of Nephrology, Vanderbilt University Medical Center, Nashville, TN.*

Background: Measurement of CO_2 is a key component of acid base assessment. Although modern laboratory instruments provide high accuracy and reliability, assays are still prone to error. We present a case where interference in CO_2 measurement lead to significant disparities between total CO_2, calculated CO_2, and clinical findings.

Methods: A 55-year-old female with type 1 diabetes mellitus and alcohol abuse, presented with 1 day of dyspnea, palpitations, vomiting and abdominal pain. She reported recent binge drinking, poor dietary intake and missing insulin doses. Physical exam revealed sinus tachycardia and no other abnormalities. Workup indicated acute liver failure, anuric acute kidney failure, and a high anion gap metabolic acidosis initially attributed to ketoacidosis. There was a discordance on labs with total CO_2 (TCO_2) measuring 13mmol/L and venous blood gases (VBG) showing a pH of 7.33, pCO_2 of 33 mmHg, and calculated HCO_3 ($cHCO_3$) 17mmol/L. On follow up labs, tCO_2 dropped to <5 mmol/L, while VBG continued to show pH>7.33, and cHCO3 >18mmol/L. Discrepancies amongst tCO_2, $cHCO_3$, and clinical findings suggested a falsely low tCO_2 result. There was no hemolysis or significant hyperbilirubinemia, which commonly interfere with the tCO_2 assay, however triglycerides (TG) were 1712mg/dL, and the serum sample was markedly lipemic on visual inspection. She was treated with normal saline, insulin drip, and continuous renal replacement therapy. The discrepancy between tCO_2 and $cHCO_2$ resolved as TG improved. Hepatic and renal failure resolved.

Results:

Conclusions: Measurement of tCO_2 can be achieved by electrode-based assay or as in this case by spectrophotometry. Lipemia might interfere with the latter, as large lipid particles like VLDL and chylomicrons absorb or disperse light, leading to erroneous results. Although manufacturers report minimal error with TG of 1000-2000mg/dL, this error is estimated using a lipid emulsion (Intralipid) that does not match the large size of TG particles. Mixing experiments by Wiencek et al, demonstrated a greater negative CO_2 error when estimates are based on TG dilutions instead of Intralipid testing. This case illustrates that accurate acid base assessment requires a careful clinical interpretation of tCO_2/$cHCO_3$ and patient's clinical condition.

SA-PO1017

A Case of Perioperative Euglycemic Ketoacidosis and Concomitant Non-Anion Gap Metabolic Acidosis and AKI Associated with Canagliflozin Manuel E. Gonzalez, Juan Carlos Q. Velez. *Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA.*

Background: Oral inhibitors of the renal sodium-glucose cotransporter SGLT2 ("-gliflozins") are now available for the management of type 2 diabetes mellitus. Reports of euglycemic ketoacidosis caused by these drugs have emerged. However, concomitant acute kidney injury (AKI) and non-anion gap (NAG) metabolic acidosis are not usually present in those cases. We report a case suggestive of euglycemic ketoacidosis due to the SGLT2 inhibitor canagliflozin that was confounded by concomitant AKI and NAG metabolic acidosis.

Methods: A 65 year-old Caucasian woman with type 2 diabetes mellitus, hypertension and obesity was evaluated for profound weakness and vomiting on post-operative day 1 after a laparoscopic sleeve gastrectomy indicated for weight loss. Her home medications included dulaglutide, metformin, and canaglifozin. Dulaglutide was stopped 1 week prior to the procedure, and metformin and canaglifozin were stopped 1 day prior her surgery. Upon evaluation, her blood pressure was 131/64 mmHg, her pulse was 94/min and her body mass index was 36 kg/m^2. Examination was remarkable for obesity and a mildly tender abdomen with a dressed abdominal incision. Serum studies revealed: sodium 135 mEq/L, chloride 113 mEq/L, total CO_2 < 5 mEq/L, potassium 4.8 mEq/L, glucose 128 mg/dL, urea nitrogen 12 mg/dL and a creatinine 1.0 mg/dL (up from a baseline of 0.6 mg/dL). The serum anion gap (AG) was 17 mEq/L. An arterial blood gas revealed a pH 7.1 and a pCO_2 20.8 mmHg. She had a normal lactate of 0.9 mmol/L but a positive

beta-hydroxybutyrate of 5.1 mmol/L. Urinalysis showed 2+ ketones. The delta AG / delta bicarbonate was 0.3, suggesting co-existence of AG and NAG metabolic acidosis, caused by ketoacidosis and AKI, respectively. She was treated with intravenous isotonic sodium bicarbonate solution, followed by normal saline, insulin infusion with dextrose drip until the AG normalized and her kidney function returned to baseline.

Results:

Conclusions: This case illustrates that SGLT2-induced euglycemic ketoacidosis with concomitant AKI can occur as a serious disorder in diabetics. The combination of fasting, volume depletion and deficiency of insulin appear to trigger this relatively novel syndrome. We call for caution in preoperative care of patients taking "-gliflozins".

SA-PO1018

Caffeine Overdose: Case Report Andrew Hipp, Keith E. Eidman. *Hennepin County Medical Center, Minneapolis, MN.*

Background: Caffeine is a ubiquitous stimulant in today's society. Massive caffeine ingestion, although rare, is associated with life threatening complications. This case involves a patient presenting after intentional caffeine overdose of approximately 20g(LD50 for patient is 6g). Previous case reports have demonstrated hemodialysis as an effective treatment. Dialysis treatment directed by hemodynamic parameters was used in this case and proved helpful in guiding repeat dialysis treatments as caffeine levels were not readily available.

Methods: The patient was brought in following an intentional overdose of caffeine pills. Patient presented with hypotension, tachycardia, hypokalemia, and depressed mental status. Patient was treated with IVF, sedation, intubation, and blood pressure support with phenylephrine. Hemodialysis was started in the setting of massive ingestion and ongoing hemodynamic instability. Patient underwent hemodialysis using a high flux dialyzer with improvement in both tachycardia and blood pressure. Patient required a second run of hemodialysis after decompensating after cessation of the first run and required placement back on phenylephrine. Following the completion of a second run, the patient remained hemodynamically stable and off vasopressor support. Caffeine levels prior to HD eventually returned at 187.5 mcg/ml. Post first HD run caffeine levels improved to 57 mcg/ml and subsequently to 6.0 mcg/ml after second run of HD.

Results:

Conclusions: Caffeine and it numerous metabolites including theophylline, theobromine, and paraxanthine can cause life threatening hemodynamic instability. The mechanism of caffeine and its metabolites actions are through adenosine antagonism, catecholamine release, and phosphodiesterase inhibition. Caffeine is a suitable target for removal with Vd of 0.6 L/kg, small molecular weight, and only 25-36% protein bound. This case demonstrates acute hemodialysis is indicated in massive caffeine ingestion and treatment can be directed by hemodynamic parameters.

SA-PO1019

Acute Hypocalcemia in Patients on Denosumab Therapy Following Transfusion Warda Zaman, Komal Patel. *Northwell Health Lenox Hill Hospital, New York, NY.*

Background: We present two patients on denosumab therapy with acute hypocalcemia following pRBC transfusion.

Methods: An 84-year old man with CKD III presented with fatigue 12 days after denosumab therapy to treat bone metastases from carcinoid tumor. Initial labs showed Ca 7.9mg/dL, albumin 2.5g/mL, Cr 1.57mg/dL, and eGFR 40mL/min. He received 1 unit pRBC and developed muscle cramps 2 hours post transfusion. Repeat blood work revealed Ca< 5.0mg/dL, ionized Ca 0.77mmol/L, albumin 2.5g/mL, Cr 1.46mg/dL, eGFR 40mL/min, 25-OH Vitamin D 4ng/mL, 1,25-di(OH) Vitamin D 41.6pg/mL and PTH 340pg/mL. He required calcium infusion for 4 days, and maintained his calcium level above 8.0 mg/dL with oral supplementation. A 77-year old man with CKD IV and metastatic prostate cancer who had received denosumab 4 weeks prior presented with a right pathologic femoral neck fracture. Labs revealed Ca 7.7mg/dL, albumin 2.7g/mL, Cr 2.57mg/dL, and eGFR 23mL/min. On hospital day 9, after a second pRBC transfusion, Ca level was < 5.0mg/dL from 6.1mg/dL, ionized Ca 0.83mmol/L, albumin 2.0g/mL, Cr 2.73mg/dL, eGFR 21mL/min, 25-OH Vitamin D 21.4ng/mL, 1,25-di(OH) Vitamin D 112pg/mL and PTH 1321pg/mL. He reported lethargy with perioral paresthesia without Chvostek sign or carpopedal spasm. He required calcium infusion for 24 hours, along with oral supplementation and subsequently maintained a calcium level of 8.3 mg/dL.

Results:

Conclusions: Denosumab, a monoclonal antibody to RANK ligand, inhibits osteoclast formation decreasing bone resorption and increasing bone mineral density. It is not metabolized or excreted renally. Hypocalcemia post-denosumab is reported in 5.5% to 20.8% of patients. It is known to cause a nadir in calcium 10 days after administration, with effects lasting up to twelve months. Renal insufficiency results in activated vitamin D deficiency and secondary hyperparathyroidism increasing risk of hypocalcemia with denosumab. Symptomatic hypocalcemia with citrated blood is rare unless citrate metabolism is impaired in hepatic or renal failure. Our case report demonstrates the need for providers to adhere to guidelines advising against blood transfusion with Hgb >7.0g/dl. Furthermore, providers should maintain a high degree of suspicion for hypocalcemia and closely monitor Vitamin D and calcium levels when using denosumab in CKD patients.

SA-PO1020

Acute Myeloid Leukemia Presenting as Nephrotic Syndrome Maryam K. Saeed. *University of Illinois- Urbana Champaign, Urbana, IL.*

Background: Nephrotic syndrome(NS) is characterized by heavy proteinuria, hypoalbuminemia and peripheral edema. Acute Myeloid Leukemia(AML) has been rarely reported in association with NS.

Methods: 73 year old white male presented with lower extremity edema and dyspnea for the last 3 weeks. He denied chest pain, palpitations, fevers, or recent immobilization. History was significant for non-insulin dependent type II diabetes mellitus with neuropathy without retinopathy and hypertension. On examination his blood pressure was 160/80mm Hg with + 2 pitting peripheral edema. Basic labs showed hemoglobin of 12.7g/dL, Creatinine 0.8 mg/dL, total serum protein 6.8mg/dL, albumin 3.6g/dL with 24 hour urine protein of 5.9 grams and no hematuria. Echocardiogram and renal ultrasound were unremarkable. Furosemide was initiated for suspected diabetic nephropathy. However, patient's edema significantly worsened with development of ascites. Repeat labs showed proteinuria(5.6g/24 hours)and hypoalbuminemia(2.9g/dL). Serum complement levels, hepatitis panel, antinuclear antibody levels were unremarkable. A renal biopsy was scheduled for possible secondary causes of NS.Labs prior to biopsy showed a decreased white cell count of 3.1 x10^3/uL, hemoglobin of 8.9 g/dl, MCV of 67.6 fL and normal platelet count. Peripheral smear revealed neutropenia with left shift and frequent blasts. The patient was referred for urgent bone marrow biopsy and flow cytometry with results consistent with AML.Azacitadine chemotherapy was subsequently started. Renal biopsy revealed features consistent with renal involvement by extramedullary myeloid neoplasm, diffuse glomerular mesangial sclerosis and changes suggestive of chronic thrombotic microangiopathy. Despite chemotherapy, the patient's condition worsened with development of healthcare associated pneumonia, refractory ascites and multiple hospital readmissions. Eventually the patient decided to opt for comfort care measures

Results:

Conclusions: Hematological malignancies associated with NS are mainly Hodgkin's and non-Hodgkin's lymphomas and chronic lymphocytic leukemia. The onset of NS in patients with AML is reported after development of leukemia, during chemotherapy or at presentation. In our patient NS preceded AML with evidence of renal extramedullary hematopoiesis, rarely described with myeloproliferative neoplasms.

SA-PO1021

A Rare Case of Renal Oncocytosis with Agent Orange Exposure Amit Reddy,[1] Mary T. Sessums,[1] John C. Henegan,[2] Varsha Manucha.[1] *[1]Pathology, University of Mississippi Medical Center, Jackson, MS; [2]Hematology/Oncology, University of Mississippi Medical Center, Jackson, MS.*

Background: During the Vietnam War, more than 3 million veterans were exposed to Agent Orange, an herbicide containing dioxin that has been linked to increased cancer risk. There is sufficient evidence for an association between Agent Orange and hematological disorders, but only a few cases have been reported in relation to renal neoplasms. Here we present a case of bilateral renal masses with right sided renal oncocytosis and Agent Orange exposure in a patient with chronic kidney disease (CKD).

Methods: A 68-year-old Caucasian male with hypertension, CKD, and previous Agent Orange exposure was noted to have an elevated serum creatinine of 1.9mg/dL and blood urea nitrogen of 36mg/dL which triggered further evaluation. He had no recent hematuria, flank pain, or weight loss. A renal ultrasound showed multiple renal masses, and magnetic resonance imaging confirmed these to be concerning for renal cell carcinoma with one mass in the upper pole of the right kidney measuring up to 3.3cm and a second mass in the interpolar region of the left kidney measuring 2.3cm. All nodules were completely confined to the kidney. Preoperative germline testing of a panel of genes in which variants are associated with hereditary renal carcinoma syndromes revealed no pathogenic mutations. Right partial nephrectomy was performed which noted multiple oncocytic nodules ranging in size from a microscopic collection of a few cells to large, grossly visible nodules. Immunostains were negative for AMACR and CK7 and positive for CAM5.2 and CD117, consistent with a diagnosis of renal oncocytosis.

Results:

Conclusions: Renal oncocytosis is an extremely rare disorder with multiple oncocytic nodules of the renal parenchyma and is associated with CKD and Birt-Hogg-Dube Syndrome. The incidence is about 4.3% of all solid renal masses. According to literature, there have been only 4 similar cases reported of oncocytosis with Agent Orange exposure but there has been no definitive link. The diagnosis of renal oncocytosis remains a challenge due to the difficulty in distinguishing between benign and malignant lesions with imaging. As with this case, partial nephrectomy allowed for a definitive diagnosis. Renal oncocytosis in this case could be related to CKD and any link to previous exposure to Agent Orange will require further follow-up of patients with this history to determine if it is a risk factor for renal oncocytosis.

SA-PO1022

A Report on Multifocal Bilateral Renal Oncocytomas Leading to Interstitial Nephritis Divyanshu Malhotra,[1] Randy L. Luciano.[2,1] *[1]Yale New Haven Hospital, New Haven, CT; [2]Yale University School of Medicine, New Haven, CT.*

Background: Renal oncocytomas are benign tumors originating from the intercalated cells of the collecting duct. They are rare, with an incidence of up to 7% of all renal

tumors. The majority of tumors are solitary, but up to 12% can be multifocal with 4-12% being bilateral. These are often found incidentally, but on occasion flank pain or hematuria are presenting signs. Less is known about the nature of multifocal bilateral oncocytomas and their renal complications. Here we present two patients with multifocal bilateral oncocytomas with associated interstitial nephritis.

Methods: The first patient is a 44 year old gentleman with no significant medical history who was found to have multifocal renal tumors on CT scan that was performed after the discovery of hematuria. Biopsy showed multiple oncocytomas with a surrounding dense interstitial infiltrate. Clinically the patient had a serum creatinine of 1.5 mg/dL with no underlying medications or co-morbid conditions that could be attributed to the interstitial inflammation. The second patient is a 72 year old gentleman with a history of treated prostate cancer and well controlled hypertension who had multifocal kidney lesions identified on CT scan when he was diagnosed with prostate cancer. Biopsy revealed a dense interstitial infiltrate in tissue adjacent and away from the encapsulated lesions. No medications or disease could explain the interstitial nephritis. Clinically his creatinine has increased steadily from 1.8 mg/dL to 2.7 mg/dL over the last five years.

Results: Renal oncocytomas are rare but potentially important tumors. Diagnosis through histology is important because they can appear similar to malignant renal tumors. Pathological examination reveals a well-circumscribed collection of oncocytes with a central scar, devoid of necrosis or vascular inflammation. Treatment usually consists of radical or partial nephrectomy versus observation, and prognosis is excellent. Both of these patients demonstrate the importance of diagnosing renal involvement in patients with multifocal oncocytomas. Since surgery is not possible for these multifocal and bilateral kidney lesions, it is necessary to monitor these patients closely with the possibility of medically treating the underlying inflammation if unexplained rises in creatinine ensue.

Conclusions:

SA-PO1023

Erythropoietin Producing Glioblastoma Multiforme in a Patient with ESRD Min Naing,[1] Farhanah Yousaf,[1] Andres A. Urrutia,[2] Volker H. Haase,[2] Alla Goldberg,[1] Bruce S. Spinowitz.[1] *[1]Nephrology, New York Presbyterian Queens, Flushing, NY; [2]Vanderbilt University Medical Center, Nashville, TN.*

Background: Elevated hemoglobin (Hgb) is rare in patients undergoing hemodialysis and may be associated with malignancy, polycythemia vera, nephroangiosclerosis, lung or liver disease or acquired cystic kidney disease. We report a rare case of elevated Hgb associated with glioblastoma multiforme (GBM).

Methods: A 66-year-old, white, non-Hispanic male with history of hypertension, diabetes mellitus type 2, dyslipidemia, secondary hyperparathyroidism on maintenance hemodialysis since March 2010 presented to our center in May 2015 with elevated Hgb. Physical exam was unremarkable. Patient's erythropoietin (EPO) level was elevated to 42.7 mIU/mL during 2014 but evaluation for erythrocytosis did not reveal any suspicious lesion on abdominal ultrasound. The EPO level continued to rise to 116 mIU/mL with Hgb 18 g/dL and JAK-2 V617F mutation analysis was negative by July 2015. An EPO producing tumor seemed likely but only splenomegaly was evident on CT abdomen and pelvis. On March 2016, transferrin saturation had fallen to 17% and ferritin was 60 ng/mL with a resultant Hgb drop (10 g/dL) and received 2 doses of 300 mg of IV iron sucrose which increased Hgb to 11.4 g/dL. Leukocytes and platelets remained in the normal range. In April 2016, patient was evaluated for depression and memory problems. All the tests were unremarkable except elevated thyroid stimulating hormone. CT head revealed a right frontal GBM which was resected and he underwent radiation therapy. Hgb fell and he received multiple blood transfusions while ESAs were contraindicated. Two months post resection, EPO level was 9.4 mIU/mL. He expired in Oct 2016 after withdrawing from hemodialysis. GBM tissue sample slides were analyzed using EPO mRNA fluorescent in situ hybridization which showed low levels of EPO mRNA throughout the GBM tissue sample except in necrotic areas.

Results:

Conclusions: This is the first case report of an EPO producing GBM. The expression of EPO mRNA in the GBM tissue and the temporal relationship of changes in EPO and Hgb levels with respect to the GBM resection strongly support GBM as the ectopic EPO production site.

SA-PO1024

Autoantibodies: Novel Biomarkers for Diagnosing Malignancy? Divyanshu Malhotra,[1] Maryam Gondal,[1] Randy L. Luciano.[2] *[1]Yale New Haven Hospital, New Haven, CT; [2]Yale University School of Medicine, New Haven, CT.*

Background: ANA and related autoantibodies can be detected with a variable frequency in patients with Lymphoma. However, a majority of these patients do not display features of any underlying autoimmune disease. The exact patho-physiological significance of these is not well defined at this time. Here we present a case of positive autoantibodies in a patient with T-cell Lymphoma and membranous nephropathy which initially posed a diagnostic dilemma.

Methods: 37 year old male with an unremarkable past medical history was admitted for fatigue, lethargy, anorexia and weight loss. He had been experiencing shortness of breath with exertion and also noted that his urine was foamy. He was taking naproxen infrequently for generalized pain. Physical exam was remarkable for significant peripheral edema. Labs revealed a BUN 48 mg/dl, Cr 3.2 mg/dl, phosphorus 5.8 mg/dl, Hgb 7.1g/dl, Platelet count 30000, Albumin 2.2 g/dl and Urine Pr/Cr 5 g/g. Urine analysis showed a mix of isomorphic and dysmorphic RBCs however no casts were noted. Autoimmune work up was positive for ANA, AntidsDNA, AntiSm, AntiSm/RNP and Anti SS-B. However he did not meet the criteria for SLE and did not have any clinical features consistent with other autoimmune conditions. Thus a further work up was planned. Renal US was remarkable for echogenic right and left kidney measuring 12.7 cm and 13.8 cm respectively. Renal Biopsy was consistent with membranous nephropathy with negative immunofluorescence. Bone Marrow biopsy was performed and was consistent with T-cell lymphoma and this prompted initiation of chemotherapy. Unfortunately, despite therapy his disease progressed with multi-organ involvement and patient was transitioned to hospice care.

Results:

Conclusions: A wide spectrum of renal lesions can be observed in patients with T-Cell Lymphoma including glomerulonephritis, acute kidney injury and parenchymal infiltration. This case is unique, as the autoimmune markers were not related to the glomerulonephritis but independently associated with the T-Cell Lymphoma. In small retrospective analyses it is interesting to note that these autoantibodies were generally not assocaited with underlying auto-immune conditions, were seen more commonly in men and did not appear to have any significant prognositc significance. Thus it is important to recognize this entity and look for underlying malignancies when the clinical features do not corelate.

SA-PO1025

Resistant Edema – Management of Chronic Systemic Capillary Leak Syndrome with IVIG Ryan Mullane, Eric D. Langewisch, Troy J. Plumb. *University of Nebraska Medical Center, Omaha, NE.*

Background: Systemic capillary leak syndrome (SCLS) is a rare, poorly understood disorder characterized by increased vascular permeability. It presents with intermittent acute episodes of profound capillary leak that may result in hypotension/shock. There are few reported cases of chronic SCLS, which is characterized by persistent refractory edema and pleural effusions. We present a case of chronic SCLS where ongoing treatment with intravenous immunoglobulin (IVIG) has resulted in a marked and sustained improvement in the signs and symptoms of the capillary leak syndrome.

Methods: A 54-year-old man presented with new onset lower extremity edema, which initially responded to oral diuretics. However, his edema later worsened with the development of upper extremity edema, bilateral pleural effusions and a total fluid weight gain of 20 kg which was refractory to diuretics. He required ultrafiltration for fluid removal in addition to recurrent thoracentesis for his pleural effusions. Evaluation revealed hypoalbuminemia and an IgG kappa monoclonal gammopathy, but bone marrow biopsy was normal. Cardiac, renal, hepatic and lymphatic evaluations failed to disclose an etiology for his edema. Initial therapy with theophylline was discontinued due to significant chest discomfort. Initiation of IVIG 1 g/kg every 4 weeks for a period of 4 months and then maintenance therapy every 6 weeks has resulted in a significant and persistent improvement over the past 18 months.

Results:

Conclusions: Systemic capillary leak syndrome presents with recurrent episodes of generalized edema, hypotension and hypoalbuminemia. Although the pathogenesis is unknown, IVIG decreases the occurrence of episodes in the acute form of SCLS. Few cases of the chronic form of SCLS are reported in the literature with prior treatments including theophylline, terbutaline and steroids. There have been no prior reports of IVIG therapy for chronic SCLS. Our patient had significant and durable improvement of refractory edema related to chronic systemic capillary leak syndrome with IVIG. This case demonstrates that IVIG may be an effective treatment modality for the chronic form of this disorder.

SA-PO982

Canagliflozin Associated Fanconi Syndrome Don H. Esprit,[1] Abhilash Koratala.[2] *[1]University of Florida, Gainesville, FL; [2]University of Florida, Gainesville, FL.*

Background: Sodium-glucose cotransporter-2 (SGLT2) inhibitors have gained popularity due to convenient, once-daily oral dosing and their association with weight loss, lower blood pressure, and a low risk of hypoglycemia as well as lower cardiovascular mortality as with empagliflozin. However, with the increasing use of these drugs, there have been increased reports of adverse effects as well. Herein, we present the case of a diabetic patient on canagliflozin who presented with EuDKA and found to have proximal renal tubular acidosis with Fanconi syndrome that was attributable to the drug. To the best of our knowledge, this is the second such case in the literature.

Methods: A 54-year-old Caucasian woman with a past medical history of type 2 diabetes mellitus, hypertension, coronary artery disease, and hyperlipidemia has originally presented with chest pain and found to have EuDKA. Her blood glucose was 175 mg/dL but had anion gap metabolic acidosis with a serum bicarbonate of 9 mmol/L (22-28) and elevated beta-hydroxybutyrate. Serum lactate was 0.65 mmol/L (0.3-1.5). Her medications consisted of canagliflozin 300 mg daily, metformin 500 mg twice daily, lisinopril 10 mg daily and atorvastatin 20 mg daily. She was treated with insulin until the anion gap closed and then was switched to oral medications. However, she was noted to have persistent non-anion gap metabolic acidosis and hypophosphatemia. Urinalysis was significant for glycosuria, which is expected with SGLT2 inhibitor use. Interestingly, she was found to have phosphaturia with a fractional excretion of phosphate of 23% (normal <5) with a serum phosphate of 1.8 mg/dL (2.7-4.5) and generalized aminoaciduria with prominent excretion of glycine suggesting impaired renal tubular function. On reviewing her old labs, she was found to have some degree of persistent non-anion gap metabolic acidosis for the past 2 years, which temporally correlates with canagliflozin therapy. We discontinued this medication in favor of home insulin therapy. Her renal function remained normal during this period.

Results:

Conclusions: While we do not have follow up data on whether the patient's laboratory abnormalities resolved after discontinuation of the drug, we recommend that clinicians be aware of the emerging side effects of SGLT2 inhibitors and closely monitor the metabolic profile of these patients.

SA-PO983

Severe Partial Fanconi Syndrome with Nephrogenic Diabetes Insipidus After Initiation of the Newer "Non-Nephrotoxic" Tenofovir Alafenamide Fumarate Connor Deal, Daniel C. Andreoli, Roger A. Rodby. *Rush University Medical Center, Chicago, IL.*

Background: Tenofovir disoproxil fumarate (TDF) is one of the more commonly used antiretroviral agents and is a well-established cause of renal tubular toxicity which may manifest as partial or complete Fanconi syndrome, AKI, CKD and rarely nephrogenic diabetes insipidus (NDI). Tenofovir Alafenamide Fumarate (TAF), a prodrug of tenofovir (FDA approved in 11/16), has a larger volume of distribution requiring a lower dose to achieve the same antiviral effect and thus has yet to demonstrate the nephrotoxicity associated with TDF. We describe a patient receiving TAF who developed severe hypokalemia (K), hypophosphatemia (PO4) leading to rhabdomyolysis, in addition to NDI, all of which resolved with cessation of the TAF.

Methods: A 35-year-old male with HIV presented with 2-days of proximal muscle weakness and tenderness. He had been started on Genvoya (elvitegravir, cobicistat, emtricitabine, TAF) 2-weeks prior. On presentation, his serum creatinine was normal at 0.8 mg/dL, PO4 < 0.7 mg/dL and K 2.0 mmol/L, with rhabdomyolysis (CPK 10,769 U/L). The serum HCO3 was normal and glycosuria was not present. He did not develop AKI. Initial urine studies showed K and PO4 wasting (see Table). The patient was polyuric with 24-hour urine of 6.1 L/d. A random urine osmolality was 179 mosm/kg with a serum Na of 147 mmol/L. 16 units of ADH were administered IV and a Uosm was 165 mosm/kg at 2 hours, confirming a diagnosis of partial NDI. The TAF was discontinued upon admission and after aggressive K and PO4 repletion, these values normalized and remained normal without further need for supplementation. His polyuria similarly resolved with a urine output of 1-2 L/d.

Results:

Conclusions: TAF is a newer form of tenofovir felt to have minimal nephrotoxicity. This patient developed both proximal and distal tubular defects following the initiation of TAF that were identical to that described with TDF. The timing of the presentation relative to starting TAF, and the complete resolution after TAF discontinuation suggests a direct causative effect.

Initial Blood and Urine tests

Serum PO4 (mg/dl)	<0.7
Fractional excretion of PO4 (%)	38
Serum K (mmol/l)	2.0
Fractional excretion of K (%)	8.2
Urine K/creatinine ratio (meq/g)	33

SA-PO984

A "Paint"ed Picture of RTA Amaleswari Pamarthy, Juan A. Medaura. *UMMC, Madison, MS.*

Background: Toluene is by far the most commonly inhaled volatile drug. It is used in various ubiquitous products such as paints, paint thinners, glues, adhesives and cleaning products. It is easily accessible and of low cost. It is hard to control or regulate as well. Acute toluene toxicity causes neurological changes as well as various metabolic alterations and almost all organs suffer from some form of alteration. Case reports from 1950's described it as "sudden sniffing death" which could be due to malignant ventricular arrhythmias. Hypokalemic paralysis and renal failure are other life-threatening complications. Neurological sequelae including memory and learning deficits can persists for years.

Methods: 44year old female presented with 1week history of nausea, vomiting and diarrhea. In ER, She was found to be drowsy and lethargic, got intubated for airway protection. She was afebrile with blood pressure of 152/73mm of hg. EKG showed ventricular bigeminy and prolonged QTc interval. Labs showed mild AKI, severe hypokalemia (<2mmol/L), severe non-anion gap metabolic acidosis(<7). Drug and volatile screen positive for benzodiazepines only. No serum osmolar gap noted. Etiology was not clear but initially was thought to be secondary to diarrhea. She was started on aggressive bicarbonate and potassium repletion. Positive urine anion gap and clinical picture suggested distal RTA. Further history was available from patient's family. Reportedly patient is addicted to inhalant paint and might have snuffed the paint in a trip a week ago. After 2 days she became more awake but could not move which was thought to be secondary to hypokalemic periodic paralysis. With all the supportive management patient recovered well without any focal deficits.

Results:

Conclusions: Inhalant abuse can result in a wide array of pathology on most of organ systems. Inhalant drugs are notoriously difficult to capture on laboratory testing. A detailed history is the key to diagnosis. Meticulous clinical assessment not to miss any underlying causes of RTA is critical. The most important role of laboratory testing is to assess the effects of inhalants on other organ systems which can be the clue to diagnosis. Studies indicate there is clearly overproduction of hippuric acid and overt reduction of excretion of net acid (NH4+) excretion in urine, hence checking them in urine might be of value.

SA-PO985

Ibuprofen Induced Renal Tubular Acidosis Muhammad Y. Jan,[3] Mirza M. Baig,[1] Tarek M. El-Achkar.[2] *[1]Nephrology, Indiana University, Indianapolis, IN; [2]Nephrology, Indiana University, Indianapolis, IN; [3]Internal Medicine, Indiana University School of Medicine, Indianapolis, IN.*

Background: Ibuprofen is a widely available over the counter analgesic. We report a rare but potentially fatal case of renal tubular acidosis (RTA) from ibuprofen overuse.

Methods: A 58 year old African American male with no past medical history presented to the emergency department with complaints of generalized upper and lower extremity weakness 2 weeks after undergoing dental extraction. This was associated with poor oral intake. He reported taking up to 60 pills of 200mg Ibuprofen daily for 10 days (up to 12 grams/day) for pain. He denied diarrhea or vomiting. Physical exam showed normal vital signs and generalized weakness in all extremities, with preserved reflexes and sensation. History was negative for autoimmune diseases and any other medication use. Lab results showed serum potassium of 1.8mmol/l (3.5-5.5), creatinine of 2.79mg/dl (0.6-1.1), bicarbonate of 10mmol/l (21-32), chloride of 110mmol/l (98-106), blood urea nitrogen of 69 mg/dl (7-18), phosphorus of 2.3mg/dl (2.5-4.9 mg/dl) and normal sodium level. Venous blood gas showed a pH of 7.10 (7.35-7.45) and pCO2 of 33 mm Hg (35-48). Urine pH was 6.0(5-8) with a positive urine anion gap. Serum alcohol, acetone, isopropyl alcohol, methanol, salicylate, acetaminophen levels and urine drug screen was negative. Thyroid stimulating hormone level and kidney ultrasound were normal. Given the severe non anion gap metabolic acidosis, he was diagnosed with distal renal tubular acidosis due to ibuprofen overuse, in the absence of other identifiable etiology. He was admitted to the intensive care unit for monitoring due to severe acidosis and wide QRS interval on electrocardiogram. He was managed with intravenous fluids and potassium repletion, followed by sodium bicarbonate infusion and oral citrate. His motor strength gradually improved over 4 days and he was discharged home, after correction of the metabolic acidosis and normalization of kidney function.

Results:

Conclusions: Ibuprofen is known to inhibit carbonic anhydrase enzyme in the renal proximal tubule as well as the collecting ducts and can cause proximal as well as distal RTA. Timely repletion of potassium prior to correction of acidosis is vital in preventing fatal arrhythmias. Ibuprofen toxicity should be considered in the differential diagnosis of patients who present with severe hypokalemia and metabolic acidosis.

SA-PO986

An Unusual Cause of Delirium: Ibuprofen Induced Renal Tubular Acidosis Roulan Abu hwij, Dima Jaradat, Aziz Bakhous. *cleveland clinic-akron general, Akron, OH.*

Background: Ibuprofen is one of the easily accessible over the counter (OTC) medication, general population perceive it as nonharmful. Few cases in the literature reported ibuprofen as a cause of distal renal tubular acidosis (dRTA) associated life-threatening hypokalemia. It is hypothesized that carbonic anhydrase (CA) inhibition may play a role in the pathogenesis of ibuprofen-induced dRTA.

Methods: Our 65-year-old female patient presented to the ER with altered mental status, she has a history of fibromyalgia, chronic pain syndrome and hypertension. laboratory workup showed K of 2.2, HCO3 9, BUN 18, Cr 0.69, AG 12, Mg 2. Urine studies showed K of 13, Na 63, CL 71, urinary anion gap 5, urine PH 6.5 and her VBG revealed PH of 7.179. Serologic studies including ANA, C3, C4, RF, anti-ccp and urine protein electrophoresis were all unremarkable. Patient was managed supportively with bicarbonate infusion and potassium replacement. We discontinued iboprofen. Her mental status improved gradually. Our patient was diagnosed with RTA type 1. Ibuprofen is the presumed underlying culprit as she had more than 6 months of daily use of ibuprofen 800 mg bid. After ibuprofen was stopped and with supportive management her symptoms as well as her labs improved. No other etiologies were identified including auto-immune diseases (Rheumatoid arthritis, Sjogren's syndrome, Multiple myeloma). No family history of dRTA was identified.

Results:

Conclusions: This case highlights the association between ibuprofen use and dRTA. We hope to raise awareness among the general population and physicians regarding the need for more strict NSAID use "an OTC drug".

SA-PO987

Simultaneous Renal Tubular Acidosis and Nephrogenic Diabetes Insipidus in a Patient with Sjogren's Syndrome Mohamad A. Hanouneh, Steven Menez, Jose M. Monroy-Trujillo. *Department of Medicine, Division of Nephrology, Johns Hopkins University, Baltimore, MD.*

Background: There are several renal manifestations of Sjogren's Disease. Among them are distal and proximal renal tubular acidosis, diabetes insipidus, tubulointerstitial nephritis. However, it is unusual to find multiple manifestations simultaneously.

Methods: 39 year old woman with medical history significant for anorexia nervosa (BMI 17 kg/m2) was transferred to psychiatric unit for management of eating disorder. She additionally had nausea, vomiting, polyuria and polydipsia. She complained of longstanding dry eyes and mouth. She described prolonged history of joint pain and

recurrent nephrolithiasis. She was only taking Sertraline 100 mg twice a day. Vitals were normal. Mucous membranes were significantly dry. She had significant digital clubbing. Cardiac, pulmonary, and neurological exams were normal. Urine output was 4-5 L/daily. Workup revealed non-anion gap metabolic acidosis with hypokalemia (serum sodium 138 mmol/L, serum potassium 3.0 mmol/L, sodium HCO3 20 mmol/L, serum chloride 108 mmol/L). Serum creatinine was 1.1 mg/dL which was stable over the prior year. Urine anion gap had a positive value. (Urine sodium 20 mmol/L, urine potassium 10 mmol/L, urine chloride 21 mmol/L) and urine osmolality 130 mosm/kg. CT abdomen showed bilateral nephrocalcinosis with no hydronephrosis. She was diagnosed with distal renal tubular acidosis. Regarding polyuria and polydipsia, diabetes insipidus was suspected given development of hypernatremia (her serum Na trended up to 145 mmol/L) and low urine osmolality (Urine Osmolality was 150 mosm/kg at that time). Patient received desmopressin with no significant change in urine volume and urine osmolality. Anti-nuclear antibodies (ANA) and Ro antibodies were strongly positive. Schirmer's test confirmed the finding of dry eyes. She was diagnosed with Sjogren's syndrome based on The American College of Rheumatology (ACR) criteria. Patient was treated symptomatically with eye drops, recommended to continue oral hydration driven by thirst and to have water available at all times. She was also started on hydroxychloroquine 200 mg PO daily. She did not tolerate potassium citrate given GI symptoms.

Results:

Conclusions: Distal RTA with nephrocalcinosis and nephrogenic DI are known renal manifestations of Sjogren 's syndrome. However, it is unusual to find both manifestations simultaneously.

SA-PO988

Sweet and Salty: A Rare Case of Concomitant Nephrogenic Diabetes Insipidus and Fanconi Syndrome Induced by Tenofovir Mario J. Robles-Franceschini,[3] Hashim K. Mohmand,[4] Lisa M. Sebastian,[3] Elena Chen,[2] Andrew Coppola.[1] *[1]Baylor Family Medicine Residency at Garland, Garland, TX; [2]Texas A&M College of Medicine, Plano, TX; [3]Nephrology Division, Methodist Dallas Medical Center, Dallas, TX; [4]Nephrology, Dallas Nephrology Associates, Garland, TX.*

Background: Tenofovir is widely used in combination with other antivirals for treatment of patients with HIV. It has been well reported to be nephrotoxic, but reports of hypernatremia are rare. This case is unusual in having concomitant presentation of Fanconi Syndrome and Nephrogenic Diabetes Insipidus.

Methods: A 21 year old female with history of cerebral palsy, seizures, and HIV was brought to ER with one week history of decreased oral intake, decreased responsiveness, and higher than usual urine output despite poor oral intake. Home medications included Divalproex, Baclofen, Tenofovir disoproxil combined with Elvitegravir/Cobicistat/Emtricitabine. Physical examination was remarkable for cachexia, hypotension, and tachycardia. Initial labs showed Na 162 mmol/L, K 2.0 mmol/L, CL 131 mmol/L, CO2 19 mmol/L, Phos 2.0 mg/dL, BUN 25 mg/dL, and Cr 1.4 mg/dL (baseline creatinine was 0.5 mg/dL). Hypernatremia did not correct after appropriate volume expansion and free water administration. She continued with significant polyuria (4L urine/d) and low urine osmolality (158 mOsm/kg), consistent with diabetes insipidus. She did not respond to conventional dosing of DDAVP therapy. Further testing revealed aminoaciduria, glycosuria with normoglycemia, hypophosphatemia with inappropriate phosphaturia, consistent with Fanconi Syndrome. Management consisted of discontinuation of Tenofovir, administration of free water through PEG tube, and bicarbonate, potassium, and phosphorus replacement. The patient's electrolytes normalized with treatment and was discharged.

Results:

Conclusions: The most common renal complications of Tenofovir are glycosuria and AKI. The simultaneous presentation of Nephrogenic Diabetes insipidus and Fanconi Syndrome is a rare complication of Tenofovir. It is important to recognize that Tenofovir nephrotoxicity is not limited to the proximal tubule, but that can also affect other segments of the nephron. Nephrologists should be suspicious of this potential complication in patients who take Tenofovir and present with hypernatremia.

SA-PO989

Double Trouble: Severe Hypernatremia Secondary to Central Diabetes Insipidus (DI) Complicated by Hypercalcemic Nephrogenic DI: A Case Report Waqas J. Siddiqui,[1] Muhammad abdullah Yousaf,[2] Zehra Tauqir,[2] Sandeep Aggarwal.[1] *[1]Drexel University College of Medicine, Levittown, PA; [2]Rawalpindi Medical University, LANSDALE, PA.*

Background: Patients with advanced malignancies often have electrolyte abnormalities. We present a case of patient with central DI secondary to metastatic pituitary invasion complicated by hypercalcemic nephrogenic DI.

Methods: 40 year old female with history of stage IV Breast Ca including skeletal and leptomeningeal metastasis with compression of optic chiasm and pituitary with central DI, baseline labs shown in table 1, was admitted with confusion. Patient's husband stated that she had been constantly thirsty, drinking "gallons" of water in the recent past and making a lot of urine. Pertinent vitals and physical exam showed: BP = 134/76 mmHg and heart rate = 130/minute, patient was confused, sunken eyes, flat neck veins, and tachycardia and reduced skin turgor. Patient was found to have severe hypercalcemia and profound hypernatremia (Electrolytes and urine output are summarized in table 1). Other relevant labs: PTH = 24 pg/mL, PTH-rp = 2.4 pmol/L and 25-OH Vitamin D = 25.9ng/mL. Patient received 5% dextrose for rehydration, one dose of Intravenous (IV) Pamidronate 90 mg, one dose of IV Desmopressin 2mcg and 4 days of subcutaneous Calcitonin 200 International Units Q12H was given. Initially Patient's urine output in the hospital was in the range of 350 – 400 mL/hour which responded well to one dose of DDAVP. In the subsequent days, patient's serum sodium and calcium normalized but she died because of the extensive malignancy.

Results:

Conclusions: Our case emphasizes the importance of identification of causes and complications of electrolyte abnormalities associated with metastatic cancers. These electrolyte abnormalities can be primary or paraneoplastic and should be actively pursued and treated in such cases.

Table 1: Urine and serum electrolyte and Urine output trends

Timeline/Trends	Serum Na meq/L	Serum Osmolality msom/kg	Urine Na mmol/L	Urine Osmolality msom/kg	Serum Ca mg/dL	Urine output ml/hour
Baseline - Prior to admission	151	334	20	115	8.8	N/A
At admission – Day 0	167	347	72	185	16.5	350 - 450
Day 1 (DDAVP + Calcitonin + Pamidtronate)	158	N/A	189	451	12.2	100 - 150
Day 2	158	N/A	N/A	N/A	11.5	50 - 150
Day 3	148	303	151	455	9.3	75 - 150

Na = Sodium; Ca = Calcium; N/A = Not available; DDAVP = Desmopressin; msom = milliosmoles; kg= Kilogram; mmol = millimoles; mg = milligrams; dL = deciliter; L = liters; mL = milliliters

SA-PO990

A Case of Hypophosphatemia Due to Ferric Carboxymaltose Induced Renal Phosphate Wasting Tramanh Phan, Scott E. Liebman. *University of Rochester Medical Center, Rochester, NY.*

Background: Hypophosphatemia due to renal phosphate wasting typically results from either hyperparathyroidism or as part of global proximal tubular dysfunction as in Fanconi syndrome. Isolated renal phosphate wasting is rare, but has been described with ferric carboxymaltose (FCM). Here we report a case of transient, but symptomatic hypophosphatemia due to renal phosphate wasting in the setting of FCM infusion.

Methods: A 26-year-old male with a past medical history of ulcerative colitis status post total colectomy and J pouch creation three years prior presented for evaluation of hypophosphatemia. He initially saw his primary care physician complaining of diffuse bone pain. Laboratory studies at that time showed a phosphorus level of 1.5 mg/dL. He did not note any gastrointestinal symptoms, and noted his ostomy output was unchanged from baseline. He did not have any prior history of hypophosphatemia except immediately post-operative following his colectomy. He was not taking any medications known to cause hypophosphatemia, but review of his past medical history showed that he had iron deficiency and had received FCM two days prior to symptom onset. His physical examination was benign and did not show any musculoskeletal abnormalities. Further work up revealed a fractional excretion of phosphate (FE_{PO4}) of 25.5%, normal calcium, parathyroid hormone and 25-OH vitamin D levels, and the absence of glucose in the urine indicating a primary, isolated renal phosphate wasting disorder, suspected due to receipt of FCM. FGF-23 levels were not obtained. He was started on an oral phosphate supplement with subsequent normalization of serum phosphorus and resolution of the bone pain within several days. His phosphorus remained normal and oral phosphate supplements were discontinued six weeks later. Two weeks thereafter, his phosphorus level was maintained off supplementation and his FE_{PO4} was 9.3%.

Results:

Conclusions: FCM is a convenient treatment option for iron deficiency as it only requires a single infusion. Clinicians should be aware of the association between FCM and hypophosphatemia, and consider this diagnosis in patients who present with symptoms consistent with hypophosphatemia after infusion.

SA-PO991

Refractory Hypokalemia Secondary to Intestinal Pseudo-Obstruction Vijaya Kumar Gorantla,[1] Geeta G. Gyamlani,[2] Barry M. Wall.[2] *[1]Nephrology, University of Tennessee Health Science Center, Memphis, TN; [2]Veterans Affairs Medical Center, Memphis, TN.*

Background: Intestinal pseudo-obstruction, a functional obstruction of the bowel seen in multiple medical and surgical conditions, is likely due to autonomic imbalance. Water and electrolytes can be sequestrated in dilated intestinal loops resulting in profuse watery diarrhea and hypokalemia. This is likely mediated by upregulation of BK channels in colonic mucosa, which are thought to be responsible for hypersecretion of potassium, which drives the osmotic diarrhea. Stool potassium concentrations are significantly elevated.

Methods: A 64-year old male with hypertension, GERD, muscular weakness and alcoholism was admitted for evaluation of hypotension and electrolyte abnormalities: serum potassium 1.4mEq/L, magnesium 1.3mg/dL and calcium 7.2mg/dL for which oral and intravenous replacement was initiated. Due to persistent hypokalemia (<2.5mEq/L) Nephrology was consulted. On initial examination, he was afebrile, normotensive, appeared thin built with soft, distended abdomen with hyperactive bowel sounds and poor muscle tone. Abdominal X-ray showed adynamic ileus. After evaluation, proton pump inhibitor intake and alcoholism were thought to be the cause and were discontinued and potassium replacement was continued. Renin (<0.15ng/ml/hr), aldosterone(<1ng/dL), random urine potassium (7 meq/L), creatinine, osmolality were measured to calculate fractional excretion of potassium (2%) and transtubular potassium gradient (TTKG) (<2) suggesting extrarenal potassium losses. He continued to have abdominal distention with intermittent profuse watery diarrhea. Infectious and GI workup, including colonic

mucosal biopsies were negative. He had recurrent admissions for abdominal distention, diarrhea and hypokalemia. Abdominal imaging continued to show dilated loops of small bowel and colon (>13cm). Stool electrolytes were measured as sodium (<20mEq/L) and potassium (162mEq/L). This pattern was consistent with intestinal pseudo-obstruction causing extrarenal potassium loss.

Results:

Conclusions: Clinicians should be aware of this unusual etiology for extrarenal potassium wasting and the need for aggressive potassium replacement until the pseudo obstruction resolves. Measurement of stool electrolytes are necessary to confirm the etiology of the refractory hypokalemia.

SA-PO992

Hypokalemia in Pregnancy: A Case of Maternal Bartter Syndrome Savannah Vogel,[1] Daniel Guerra Rodas,[2] Sana Waheed.[1] *[1]University of Wisconsin - Madison, Madison, WI; [2]University of Wisconsin Hospital and Clinics, Middleton, WI.*

Background: Bartter Syndrome (BS) type 3, a rare autosomal recessive renal tubular disorder caused by a mutation in the CIC-Kb chloride channel in the ascending loop of Henle, is characterized by a post-natal presentation of hypokalemia, metabolic alkalosis, hypomagnesemia and failure to thrive. Here, we report a case of the management of BS during pregnancy.

Methods: A 22-year-old G1P0 female presented to us at 19w0d gestation for management of BS diagnosed at 6 months of age. Prior to her pregnancy, she was managed with indomethacin 50mg QD, spironolactone 25mg BID and potassium chloride (KCl) 30mEq BID. Due to the risk of fetal complications, these medications were discontinued, amiloride was added at 10mg QD and KCl supplementation was increased. Potassium levels stabilized after an eight-week titration period up to 10mg BID amiloride and 400mEq QD potassium. Her potassium levels remained stable between 3.2-3.7 mEq/L for the remainder of the pregnancy. The patient delivered a healthy male infant with Apgar scores of 9 at 1 and 5 minutes by spontaneous vaginal delivery at 38w5d. Amiloride was discontinued at the start of labor and the patient was given potassium and magnesium supplementation throughout labor, delivery and her postpartum hospital stay. Following delivery, as patient was breastfeeding, indomethacin was restarted at 50 mg QD and potassium supplementation was titrated down to 30mEq BID. Postpartum potassium levels stabilized in the range of 3.4-3.6 mEq/L.

Results:

Conclusions: Patients with Bartter Syndrome often experience severe metabolic disturbances without treatment. NSAIDs, aldosterone antagonists and ACE inhibitors are considered the mainstay of treatment, however, these drugs have documented fetal side effects and thus cannot be safely used during pregnancy. Management of BS in pregnancy is further complicated by increased potassium needs due to increased volume of distribution. In our patient, we successfully used amiloride, a class B drug during pregnancy, along with increased KCl supplementation to maintain serum potassium levels. She was able to tolerate the high dose of KCl 400mEq QD without any complications. Due to concerns for its safety in breastfeeding, amiloride was discontinued at the initiation of labor and replaced with indomethacin and patient's post-partum potassium levels were again stabilized.

SA-PO993

Hypokalemic Periodic Paralysis Possibly Precipitated by Amphetamine Abuse Rashna Shetty,[4] Liang Wang,[1] Justin Hoskin,[5] Saisridhar Boddupalli,[2] Ibrahim Qaqish.[3] *[1]Barrow Neurological Institute, Phoenix, AZ; [2]Dignity Health, Scottsdale, AZ; [3]Mayo Clinic, Scottsdale, AZ; [4]ST. JOSEPH'S HOSPITAL AND MEDICAL CENTER, PHOENIX, AR; [5]Barrow Neurological Society, Phoenix, AZ.*

Background: We describe a rare case of acute hypokalemic paralysis associated with the abuse of methamphetamine.

Methods: A 28-year year old Caucasian male with a history of polysubstance abuse presented to the emergency department with a chief complaint of painless bilateral lower extremity paralysis that developed over several hours. He denies vomiting, diarrhea, diuretic use or previous similar episodes. He denied any trauma to the back or heavy carbohydrate diet preceding this event. Physical exam revealed normal vital signs and bilateral lower extremity muscle weakness; proximal greater than distal with hyporeflexia. Cranial nerves were intact. Initial serum potassium was 2.4mmol/L. Urine drug screen was positive for amphetamine and random urine potassium was 14 mmol/L. Serum magnesium and TSH were within normal limits. Electrocardiogram revealed no QT interval changes or U wave. Patient was started on careful supplementation with 30mEq of intravenous and 40 mEq of oral potassium chloride that increased the level to 4.9 mmol/L. This lead to slow but complete resolution of the paralysis causing the patient to be able to walk after six hours.

Results:

Conclusions: Hypokalemic periodic paralysis (HPP) is neuromuscular disorder characterized by episodes of painless muscle weakness. Most cases are hereditary from calcium channel mutations but acquired cases have been described. Usually there is an increased release of epinephrine or insulin causing potassium to shift into cells. Methamphetamine is an indirect sympathomimetic amine, although it lacks direct adrenergic stimulation, it inhibits presynaptic epinephrine and dopamine reuptake mediated adenosine triphosphate dependent (ATP) channels resulting and surge of both alpha and beta adrenergic effects. The main steps in the management include exclusion of other causes of hypokalemia, potassium replacement, close monitoring of the cardiac rhythm and serum potassium levels. While the mechanism of action of amphetamine explains the physiology of HPP, no cases have ever been reported of amphetamine induced HPP in literature.

SA-PO994

Unusual Case of Severe Hypokalemia, Metabolic Alkalosis, and Starvation Ketosis Nihar Jani, Iris J. Lee, Duncan B. Johnstone, Swati Rao. *Temple University School of Medicine, Philadelphia, PA.*

Background: Severe hypokalemia is a life threating emergency and requires prompt therapeutic and diagnostic intervention. Causes of inappropriate renal potassium (K) loss are traditionally divided into conditions based on concomitant acidosis or alkalosis. We present a case of severe hypokalemia with combined metabolic alkalosis and acidosis.

Methods: A 59 y/o African American male presented with 2 weeks of decreased oral intake due to severe food paranoia. He appeared malnourished and hypovolemic with BP 107/56mmHg. Laboratory data revealed K of 1.3 mEq/L, glucose of 134mg/dl, bicarbonate of 40 mEq/L, anion gap (AG) of 23, lactate 3.6mmol/l, arterial pH 7.56 and ketonuria. With aggressive K repletion (920 mEq oral and IV), K improved from 1.3 to 2.2mg/dl. Urine studies were consistent with renal K wasting: high urine K (27mEq/L), high TTKG (9.9) and high FeK (21%). Over the next few days, the patient increased his oral intake and starvation resolved along with normalization of patient's electrolyte derangements. Renal K handling normalized and the patient remained normokalemic with acid-base equilibrium.

Results:

Conclusions: In our case, identifying a unifying diagnosis of hypovolemia, renal K wasting with combined severe metabolic alkalosis and acidosis was challenging. Genetic (Bartter, Gittleman) and pathological (diuretic abuse) causes were considered given low blood pressure, K wasting and alkalosis. The AG acidosis however, remained unexplained and unaccounted for by the level of lactate. In our patient, a prolonged duration of starvation ketoacidosis addressed all metabolic findings. Starvation resulted in renal excretion of non-absorbable anions (ketones) along with increased obligatory loss of cations (such as K). Ensuing hypokalemia and hypovolemia caused and sustained a metabolic alkalosis, due to distal tubular exchange of K with hydrogen (H) via H-K ATPase and activation of H-ATPase. Normalization of severe electrolyte and acid-base disturbances as well as renal K handling after adequate nutrition, confirmed a transient reversible defect in renal K handling. Although ketone body production from starvation is commonly associated with metabolic acidosis, our case instead presented with alkalosis and alkalemia. We believe this is a rare presentation of severe hypokalemia and metabolic alkalosis due to starvation ketosis overwhelming renal tubular handling capacity.

SA-PO995

Watch What You Eat: An Unusual Cause of Hypercalcemia Muhannad Leghrouz, Abhilash Koratala, Jogiraju V. Tantravahi. *University of Florida, Gainesville, FL.*

Background: Primary hyperparathyroidism and malignancy are by far the most common causes of hypercalcemia, though the differential diagnosis is usually broad. Determining the etiology of hypercalcemia is the cornerstone of its management. Herein, we describe an interesting case of a patient who developed severe hypercalcemia as a result of "pica", which in turn was secondary to iron deficiency anemia.

Methods: A 66-year-old man with history of hypertension and diabetes mellitus type 2 has presented with fatigue, diarrhea, polyuria and hand tremors for 3 days. His vitals were stable. Laboratory values demonstrated acute kidney injury with a serum creatinine of 2.2 mg/dL (baseline ~1), hypercalcemia with serum calcium 14.8 mg/dL, and metabolic alkalosis with a bicarbonate level of 39 mmol/L. His hemoglobin was 10.7 g/dL. Patient denied taking any antacids, calcium or vitamin D supplements. His serum PTH was 15 pg/mL, PTH-related peptide and vitamin D level were not elevated. Protein electrophoresis was negative for paraproteinemia and age-appropriate cancer screening was apparently negative. He was found to be iron deficient with an iron saturation of 6% and on detailed questioning, he admitted to having an irresistible urge to eat small white stones from his backyard, which are found to be chalks, i.e., calcium carbonate [Figure 1]. This is the most likely cause for both his hypercalcemia and metabolic alkalosis. The patient was managed with counselling and further work up for his iron deficiency has been negative so far.

Results:

Conclusions: Pica is characterized by an appetite for substances that are largely non-nutritive, such as ice, paper, metal, paint, stones etc. It has been linked to iron deficiency and mental disorders of obsessive–compulsive spectrum. In our patient, pica has turned out to be the cause for hypercalcemia. Through this case report, we would like to emphasize the importance of "most inexpensive" investigation in the evaluation of hypercalcemia, i.e., "careful history taking".

SA-PO996

Hypercalcemia: Lung Nodules with a Pathological Fracture Are Not Always Indicative of Malignancy Omer Alrawi,[2] Ravi K. Thimmisetty,[2] Nehal Altaie,[1] Walid Ibrahim,[4] Yahya M. Osman Malik,[3] Nashat B. Imran.[2] *[1]Detroit medical center, Detroit, MI; [2]Wayne State University, Detroit, MI; [3]Wayne State University Medical School, Detroit, MI; [4]Wayne State University/ DMC, Dearborn, MI.*

Background: Hypercalcemia is a relatively common clinical problem. The initial goal of the laboratory evaluation is to differentiate parathyroid hormone (PTH)-mediated hypercalcemia from non-PTH mediated hypercalcemia. Although malignancy is the most common cause of non-PTH mediated hypercalcemia, other differentail should be considered specially in immunocompromised patients.

Methods: A 60-year old Asian female with past medical history inclusive for diabetes type 2, hypertension, chronic kidney disease stage 3, hepatitis B on treatment, myasthenia gravis on immunosuppressive treatment (prednisone, mycophenolate mofetil), and osteoporosis presented following a fall. Her x-ray showed a fracture of the left forearm and an incidental small left upper lobe lesion adjacent to the aorta. Chest CT scan confirmed the lesion and PET scan was suspicious for malignancy. Initial workup was remarkable for hypercalcemia at 11 mg/dl with inappropriate normal PTH (due to CKD 3). Left lobectomy with excision of 11 lymph nodes was done. Final report revealed giant cell granulomas and fungus consistent with cryptococcal infection. All lymph nodes were negative for malignancy and were sterile for anaerobic, aerobic, TB and other fungal culture. A serum cryptococcal antigen was positive at 1:4 titer. Brain imaging and CSF exam were negative for cryptococcal involvement. HIV testing was negative. Other workup showed High 1,25 Vitamin D at 148 pg/ml (normal range 15-75 pg/ml) with normal Vitamin D 25 at 42 ng/ml that is consistent with granulomatous process. She was started on fluconazole. Consequently, her calcium and cryptococcal antigen were normalized following 9 months of therapy.

Results:

Conclusions: This case demonstrates the importance of considering all differential diagnoses of non-PTH mediated hypercalcemia, which include granulomatous disorders, vitamin D intoxication, and malignancy. Before committing the patient to unnecessary procedures; it is imperative to have a tissue diagnosis to guide further surgical and medical management, especially in immunocompromised patients were infection is more common.

SA-PO997

The Great Masquerader: Persistent Hypercalcemia in a Multiple Myeloma Patient Kayla Shirley, Sean Verma, Claude Bassil. *University of South Florida, Tampa, FL.*

Background: Hypercalcemia is a commonly encountered electrolyte abnormality in multiple myeloma patients. We present a case of persistent hypercalcemia which was not fully explained by underlying multiple myeloma and did not respond to initial treatment, thus, alerting a concomitant disease process and new diagnosis.

Methods: A 60-year-old woman with lambda light chain multiple myeloma, CKD secondary to biopsy proven chronic tubular injury secondary to lambda light chain proximal tubulopathy, type 2 diabetes mellitus, and hypertension was found to have acute on chronic renal failure with creatinine of 3.5 mg/dl (baseline 2.8 mg/dl) and hypercalcemia with corrected calcium of 13.3 mg/dl on routine labs. The patient was previously treated with bortezomib, dexamethasone, and cyclophosphamide, followed by autologous hematopoietic stem cell transplant with appropriate response and was not currently receiving chemotherapy. Hypercalcemia was previously attributed to underlying multiple myeloma and tertiary hyperparathyroidism, however, responded incompletely to treatment with intravenous fluids and pamidronate. She underwent additional workup, with intact parathyroid hormone of 319.5 pg/ml, 25-hydroxy vitamin D of 10.8 ng/ml, and elevated 1, 25-dihydroxy vitamin D level of 109 pg/m. Parathyroid hormone related peptide was within normal limits. PET/CT revealed hypermetabolic supraclavicular, mediastinal, and hilar lymphadenopathy. Left supraclavicular lymph nodes were biopsied, revealing rare small lymphocytes, rare epithelioid cells and multinucleated giant cells, suggesting a granulomatous process. Angiotensin converting enzyme was 46 U/L. The patient was diagnosed with sarcoidosis and treated with prednisone with improvement in hypercalcemia and creatinine.

Results:

Conclusions: Hypercalcemia in patients with granulomatous disorders is driven primarily by elevated calcitriol concentrations, which serve to increase calcium absorption from the gut and resorption from bone. Treatment of hypercalcemia in this setting involves not only treating the underlying disease process, but reducing dietary calcium and vitamin D supplementation. While in multiple myeloma patients, hypercalcemia is likely related to underlying disease, the nephrologist should rule out less common etiologies in cases poorly responsive to traditional therapy.

SA-PO998

A Rare Case of De Novo Claudin 19 Mutation Nhi Tan, Aalia Akber, Sijie Zheng. *Kaiser Oakland Medical Center, OAKLAND, CA.*

Background: Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is an autosomal recessive disorder caused by mutations in the tight junction proteins claudins. Claudins play a key role in regulating paracellular transport of ions in the thick ascending loop of Henle. Mutations lead to decreased cell membrane permeability, limiting reabsorption of magnesium and calcium. FHHNC may present as nephrocalcinosis, vision defects, and renal failure in childhood. First described in 1972, more than 120 cases have been reported, though exact prevalence is unknown. Most cases are found within family clusters. We present a rare case of de novo claudin-19 mutation.

Methods: A 17-year-old Hispanic woman presented with 15 lb weight loss over 6 months, polyuria, and polydipsia. She had alwasy been a "picky eater" and shorter and thinner than her siblings. Past medical history noted macular dystrophy at age 3, and short stature less than fifth percentile and less than mid-parental height. Family history was unremarkable. Labs were notable for end stage renal disease with a creatinine of 7.3 mg/dl, secondary hyperparathyroidism, hyperphosphatemia of 6 mg/dl, hypocalcemia of 7.4 mg/dl, normocytic anemia of 8.9 g/dl, but surprisingly hypomagnesemia of 1.2 mg/dl and mild metabolic acidosis for the degree of renal failure. Ultrasound showed atrophic kidneys with nephrolithiasis. Peritoneal dialysis was initiated. Genetic testing revealed homozygous variant in CLDN 19 gene, NM_148960.2:c.59G>A(p.Gly20Asp). The variant p.Gly20Asp has been reported in heterozygous and homozygous individuals with FHHNC with ocular involvement and is the founder pathogenic variant in the Spanish and French population.

Results:

Conclusions: Treatment options are limited. Oral magnesium may be used to supplement tubular magnesium wasting. Amiloride can exert magnesium sparing effects. Thiazides increase calcium reabsorption in the distal tubule. None have significant effect and patients eventually progress to end stage renal disease. The only curative treatment is transplant, where calcium and magnesium excretion is normalized following transplant and there is no recurrence of the disease. In young patients who present with early ocular deficits, FHHNC should be evaluated. Given the limits of supportive care, and no recurrence of FHHNC with renal replacement, early transplant should be considered.

SA-PO999

12 Years of Intraperitoneal Magnesium Infusions for Gitelman Patient with Normal GFR Nasir Khan,[1] David Geller,[1,2] Margaret J. Bia.[1] *[1]Nephrology, Yale University School of Medicine, New Haven, CT; [2]Nephrology, West Haven VA Hospital, West Haven, CT.*

Background: Gitelman's Syndrome is an autosomal recessive salt-wasting renal tubular disorder characterized by hypokalemic metabolic alkalosis with hypomagnesemia that can be potentially life threatening. We report a case of Gitelman's Syndrome with use of peritoneal infusions in the setting of preserved renal function to manage these severe electrolyte complications.

Methods: A 57-year-old Caucasian female with longstanding history of muscle weakness and twitching, paresthesias and palpitations manifested at the time of her pregnancy at age 24 years when she was found to have severe hypomagnesemia and hypokalemia. She was presumptively diagnosed with Gitelman's Syndrome, a diagnosis confirmed genetically years later. She did not tolerate oral magnesium(Mg) replenishment due to severe gastrointestinal side effects. Intramuscular Mg replenishment was also attempted but this was complicated by recurrent boils at injection sites. She was diagnosed with idiopathic cardiomyopathy and heart block, both attributed to her electrolyte derangements, and a permanent pacemaker was placed. A Hickman catheter was placed to allow parenteral electrolyte repletion, but this led to multiple bouts of septicemia over a period of several years, caused by gram-positive, gram-negative and fungal infections. In addition she had several pacemaker lead changes, resorting to epicardial leads at times to avoid transvenous leads. Given her significant disease burden and electrolyte derangements, a peritoneal catheter was placed to attempt intraperitoneal(IP) infusion as a method to replenish Mg and potassium(K). Although she did not tolerate intraperitoneal K infusions (abdominal pain), she has now infused IP Mg for 12 years with relatively few complications and a significant improvement in her health and quality of life.

Results:

Conclusions: Gitelman's Syndrome is a hereditary cause of potentially severe hypokalemia and hypomagnesemia. Management of these electrolyte complications is challenging, and patients often suffer significant morbidity from both the electrolyte derangements and the efforts to control these derangements. We describe the successful use of IP infusions to manage a particularly challenging case of hypomagnesemia. We believe the unique characteristics of the peritoneal membrane make this modality an excellent option in patients in whom parenteral electrolyte repletion is considered necessary.

SA-PO1026

Furosemide Increases Green Fluorescent Protein-Arginine Vasopressin Expression in the Hypothalamus in Transgenic Rats Hiromichi Ueno,[1] Tetsu Miyamoto,[1] Kenichiro Bando,[2] Yutaka Otsuji,[2] Masahito Tamura,[1] Yoichi Ueta.[2] *[1]University of Occupational & Environmental Health, Kitakyushu, Japan; [2]University of Occupational and Environmental Health, Kitakyushu, Japan.*

Background: Furosemide is an essential medication for fluid overload by inhibiting sodium reabsorption in the Henle's loop, however, furosemide resistance is often observed in patients with kidney disease. Arginine vasopressin (AVP) is synthesized in the paraventricular nucleus (PVN) and the supraoptic nucleus (SON) of the hypothalamus, and increases water reabsorption in the collecting duct. Although previous studies have reported that furosemide activates the neurohumoral factors, AVP synthesis in the hypothalamus after peripheral administration of furosemide remains unclear.

Methods: Measurement of serum AVP levels is difficult because of its short half life (4-20 min). We therefore generated transgenic rats carrying a novel enhanced green fluorescent protein (eGFP)-AVP fusion gene. We examined AVP expression in the hypothalamus by observing fluorescence after intraperitoneal administration of furosemide in transgenic rats. We also investigated AVP gene expression using in situ hybridization histochemistry. Neuronal activity in the hypothalamus was examined by immunohistochemistry for Fos.

Results: After peripheral administration of furosemide in the transgenic rats, the fluorescence intensities in the SON and the magnocellular divisions of PVN (mPVN) were significantly increased. eGFP expressions in the SON and the mPVN were accompanied by Fos expression. Furthermore, AVP hnRNA levels in the SON and the mPVN were significantly increased after administration of furosemide.

Conclusions: We observed increased neuronal activity and AVP expression in the hypothalamus after peripheral administration of furosemide in eGFP-AVP transgenic rats. These results might account for one of the cause of furosemide resistance.

SA-PO1027

Fludrocortisone-Induced Production of Erythropoietin (Epo) in Mouse Kidney Nephron Yukiko Yasuoka,[2] Tomomi Oshima,[2] Yuichi Sato,[2] Hiroshi Nonoguchi,[3] Katsumasa Kawahara.[1] *[1]Dept of Physiol, Kitasato Univ School of Med, Sagamihara, Japan; [2]Kitasato University, Sagamihara, Japan; [3]Kitasato University Medical Center, Kitamoto, Japan.*

Background: Under normal conditions, Epo mRNA expression was small but clearly detected in kidney tubules, such as proximal convoluted tubule (PCT), medullary thick ascending limb (MTAL), distal convoluted tubule (DCT) and collecting ducts (CDs). The expression in the peritubular cells was observed only in hypoxic condition (7% O2, 4 hr). (Nagai, Yasuoka, et al, 2014). We investigated the effect of fludrocortisone (an aldosterone receptor agonist) on Epo mRNA in the mouse kidney.

Methods: Fludrocortisone of 2.5 mg/100 g BW was once applied to mice (C57BL/6J, male, 10 weeks) at time 0. Then, Epo, hypoxia-inducible factor 2α (HIF2α) and prolylhydroxylase 2 (PHD2) mRNAs expressions were evaluated at 2, 4, 6 and 72 hr using tyramide-ISH technique.

Results: After the injection, Epo mRNA expression was slightly increased in MTAL, and strongly increased in CCD and outer medullary CD (OMCD). However, it was never detected in the peritubular interstitial cells. The HIF2α mRNA was increased in glomerulus, PCT, TAL, DCT, CCD and OMCD as well as the peritubular cells of both kidney cortex and medulla. The PHD2 mRNA expression was also increased in PCT, TAL, DCT, CCD and OMCD. Epo, HIF2α and PHD2 mRNA expressions were increased in parallel at 4 hr after injection, and decreased to the original level at 72 hr.

Conclusions: Epo mRNA expression is increased only at renal tubule cells by stimulation of fludrocortisone. The regulation of the Epo expression by fludrocortisone is different from that by hypoxic stimulation.

SA-PO1028

Endoplasmic Reticulum Stress Induces Aminoaciduria Moeko Koga, Ayaka Kato, Hiroko Sonoda, Sayaka Oshikawa, Masahiro Ikeda. *Department of Veterinary Pharmacology, University of Miyazaki, Miyazaki, Japan.*

Background: Endoplasmic reticulum (ER) stress is caused by accumulation of misfolded proteins in the ER. ER stress is known to activate intracellular signaling pathway, named unfolded protein response (UPR). UPR has been reported to be involved in kidney disease, including acute kidney injury and diabetic nephropathy. However, the effect of ER stress on the renal physiological function is largely unknown. The purpose of this study is to clarify the effect of ER stress on the function, focusing on renal handling of amino acids.

Methods: Tunicamycin (TM), a ER stress inducer, was administered to rats by subrenal capsule injection. Urine samples were collected at 18-24 hours after injection. The composition of urinary amino acids was investigated by HPLC. Total RNA was extracted from the kidney 24 hours after administration.

Results: Real-time PCR and microarray analyses showed that GRP78 (known to be a marker for activation of the UPR) mRNA level dramatically increased in the treatment group. Urinary amino acid analysis showed that TM increased excretion of threonine, serine, glutamine, glycine, and alanine. Gene expression analyses showed that the mRNA levels of glutamine transporter (Slc38a3) and glycine transporters (Slc6a18 and Slc6a20) were significantly decreased in the TM group. Microarray analysis also showed the decrease in 7 genes out of 12 known causal genes for Fanconi syndrome.

Conclusions: These results suggest that ER stress lowers the expression levels of glutamine and glycine transporter genes, resulting in aminoaciduria. Also, it is considered that ER stress is a common mechanism of pathogenesis of aminoaciduria in Fanconi syndrome.

SA-PO1029

Bioimpedance Vector Analysis (BIA) in Patients with Systemic AL Amyloidosis Tamer Rezk,[2,3] Andrew Davenport,[1] Christianne Guillotte,[3] Helen J. Lachmann,[3] Ashutosh Wechalekar,[3] Philip N. Hawkins,[3] Julian D. Gillmore.[3] *[1]Royal Free Hospital, London, United Kingdom; [2]Center for Nephrology, UCL Division of Medicine, London, United Kingdom; [3]National Amyloidosis Centre, London, United Kingdom.*

Background: Systemic AL amyloidosis is a progressive and fatal disease affecting the heart and kidneys in 50% and 70% of patients respectively. Fluid retention and sarcopenia from heart failure may be exacerbated by systemic chemotherapy(Sattianayagam. 2013) and influence management and prognosis. BIA has been validated in patients with CKD and cardiovascular disease(Davenport. 2012). We hypothesize that BIA is a superior method of detecting fluid retention and sarcopenia among patients with systemic AL amyloidosis than absolute change in weight.

Methods: All newly diagnosed patients with systemic AL amyloidosis attending the UK National Amyloidosis Centre from April 2016 to April 2017 who were enrolled into the ALCHEMY prospective observational study underwent body composition assessment via BIA using InBody 770 at baseline (n=193) and first follow up (n=58) in conjunction with routine clinical, biochemical and scintigraphy assessments.

Results: Median age was 68yr, M:F ratio 1:1. Median serum creatinine 98μmol/L, eGFR 62ml/min and NT-proBNP 2389ng/L. At baseline; median ECW/TBW ratio was 0.411 (normal range 0.36-0.39); 183/193 (95%) patients had ECW/TBW ratio above the normal range. SMM/h^2 revealed severe sarcopenia in 0 (0%), moderate sarcopenia in 33 (17%) and normal muscle mass in 159 patients (87%) respectively (NHANES III). There was a correlation between baseline plasma NT-proBNP and ECW/TBW ratio (Pearson correlation 0.337 $p<0.001$). Follow up BIA revealed median weight loss of 3kg (4%), ECW/TBW ratio increase of 0.008 (2%) and SMM loss of 1kg (2%). Follow up SMM/h^2 revealed severe sarcopenia in 1 (2%), moderate sarcopenia in 14 (24%) and normal muscle mass in 43 (74%) patients respectively. Again, there was a correlation between percentage change in ECW/TBW ratio and percentage change in Log NT-proBNP at 6 months (Pearson correlation 0.4673, $p<0.008$).

Conclusions: BIA is a non-invasive method of assessing fluid excess and sarcopenia in patients with systemic AL amyloidosis at baseline and follow up. Significant fluid retention and sarcopenia were present in 93% and 17% at baseline and both worsened during or shortly after systemic chemotherapy. Since sarcopenia is increasingly recognised to be an independent risk factor for treatment intolerance, BIA may help minimise treatment toxicity in systemic AL amyloidosis.

SA-PO1030

The Role of Desmopressin in the Management of Severe Hypovolemic Hyponatremia Frank Ward,[1] David M. Naimark.[2] *[1]Nephrology, Sunnybrook Health Science Centre, Toronto, ON, Canada; [2]Sunnybrook Health Science Centre, Toronto, ON, Canada.*

Background: The role of desmopressin (DDAVP) to prevent or treat rapid serum sodium concentration ([Na]s) correction during hyponatremia management remains unclear. The study aim was to assess DDAVP use during the first 48-hours of severe, hypovolemic hyponatremia management. The primary study hypothesis was that the use of DDAVP would slow the rate of [Na]s correction compared to those not receiving DDAVP.

Methods: A retrospective, observational study was conducted in a single, tertiary centre of all patients managed for severe, hypovolemic hyponatremia over a 12-month period. Inclusion criteria were [Na]s <125mmol/l at referral, serum osmolality <275mOsm/kg, urine sodium <30mmol/l and urine osmolality >100mOsm/kg. Patients with signs of extra-cellular fluid compartment overload were excluded. The primary outcome measure was $[Na]_s$ correction during the first 48-hours, compared between patients who did or did not receive DDAVP using linear regression.

Results: Twenty-eight patients were identified, with baseline mean [Na]s of 112.7±6.6mmol/l vs 117±4.3mmol/l ($p=0.06$) in those who received (n=16) and did not receive DDAVP (n=12), respectively. The DDAVP group had a more rapid [Na]s correction on the first day compared to those who did not receive DDAVP, 7.7±3.8mmol/l/day vs 5.1±2.0mmol/l/day ($p=0.04$). On the second day, there was a similar rate of [Na]s correction for those receiving DDAVP and those who did not, 1.3±4.3mmol/l/day vs 2.6±3.2mmol/l/day ($p=0.39$). Overall, there was no difference in [Na]s correction after 48-hours between those who received DDAVP and those who did not, 121.7±7.5mmol/l vs 124.8±5.7mmol/l ($p=0.24$). Patients who had experienced an over-correction were successfully treated with DDAVP (n=5), so that no patient had an ongoing over-correction by 48-hours. The final [Na]s for patients who received a single dose of DDAVP (n=7) was similar to those who received multiple doses (n=9), 123.8±5.8mmol/l vs 120±8.5mmol/l, $p=0.32$.

Conclusions: DDAVP appears safe and effective in the management of severe, hypovolemic hyponatremia, associated with similar [Na]s correction to those who did not receive DDAVP after 48-hours, despite an initial more rapid correction. A single dose of DDAVP may be as effective as multiple doses. A randomized trial should examine what benefit DDAVP confers in addition to standard care in the management of severe, hypovolemic hyponatremia.

SA-PO1031

Neonatal Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) Associated with Hypothalamic Malformation in a Patient with Chromosome 1q21.1 Deletion Syndrome Bakri Alzarka,[1] Rachel L. Usala,[2] Sun-Young Ahn.[1] *[1]Children's National Medical Center, Washington, DC; [2]MedStar Georgetown University Hospital, Washington DC, DC.*

Background: Chromosome 1q21.1 deletion syndrome (OMIM 612474) is associated with a wide range of clinical abnormalities including mental retardation, microcephaly, autism, cardiac abnormalities, and cataracts. SIADH, caused by impaired water excretion, can develop from various conditions including tumors, central nervous system disorders, medications, pulmonary disease, hypothyroidism, and glucocorticoid deficiency. To our knowledge, it has not yet been reported in association with chromosome 1q21.1 deletion syndrome.

Methods: A 6 week-old, former 34-week gestational age, female was noted to have hyponatremia (serum sodium 128 mmol/L) shortly after birth. Clinical evaluation showed a low serum osmolality, relatively high urine osmolality and urine sodium, and a significantly elevated plasma arginine vasopressin (AVP) level (32.7 pg/ml, normal 1-11). With the absence of any clinical evidence of volume depletion or any other cause of hyponatremia including renal, thyroid or adrenal dysfunction, these findings were consistent with a diagnosis of SIADH. Her exam also showed microcephaly and situs inversus with dextrocardia. Microarray results were consistent with chromosome 1q21.1 deletion syndrome. Her brain MRI revealed multiple anomalies, including posterior/inferior hypothalamic malformation with hypoplastic mammillary bodies and a markedly diminutive posterior pituitary hyperintensity on T1-weighted images, which may reflect abnormal release of AVP from the posterior pituitary gland. The patient had a partial response to fluid restriction, furosemide, and sodium supplementation. However, tolvaptan initiation resulted in effective normalization of the patient's serum sodium level.

Results:

Conclusions: We report an unusual case of congenital SIADH associated with hypothalamic malformation in a neonate with chromosome 1q21.1 deletion syndrome. Our findings suggest that congenital hypothalamic/pituitary malformations should be considered as a cause of SIADH in patients with phenotypic findings consistent with chromosome 1q21.1 deletion syndrome. In addition, tolvaptan may provide an effective therapeutic option for infants with SIADH.

SA-PO1032

Gene Expression Changes in Vasopressin-Sensitive mpkCCD Cells after CRISPR/Cas9-Deletion of cAMP-Dependent Protein Kinase (PKA) Hyun Jun Jung, Kiyoshi Isobe, Chin-Rang Yang, Maurice B. Burg, Viswanathan Raghuram, Mark A. Knepper. *NHLBI/NIH, Bethesda, MD.*

Background: Vasopressin regulates collecting duct water permeability in part through stimulation of transcription of the aquaporin-2 gene, *Aqp2*. Vasopressin signaling occurs via several mediators including β-arrestin, Epac (RapGEF3/4), and cAMP-dependent protein kinase (PKA).

Methods: To address the role of PKA in gene expression in the renal collecting duct, we used genome editing (CRISPR-Cas9) to ablate expression of both PKA catalytic subunits in mouse mpkCCD cells. We carried out transcriptomics (RNA-Seq) and quantitative proteomics (SILAC-based quantitative LC-MS/MS) of in three pairs of PKA-KO vs. control clones. Deletion was confirmed using newly developed isoform-specific PKA antibodies. Cells were grown on permeable supports in the presence of 0.1 nM dDAVP.

Results: The PKA-KO cells were viable and maintained polarity. In RNA-Seq, only 68 out of 10,190 transcripts showed significant abundance decreases based on dual criteria (FDR-corrected $P < 0.05$ and $\log_2$(PKA-KO/Control) < -1). These included several transcripts previously found to be upregulated by vasopressin (Aqp2, Adh1, Akr1b3, Bcat1, Cyfip2, Gsdmc2, Gsdmc4, Gsta4, Pde4b, Tmem45b and Tmprss4). Quantitative proteomics confirmed the deletion of both PKA isoforms, showed that AQP2 protein was undetectable in the PKA-KO cells (confirmed by immunoblotting), and showed decreases in protein abundances of Tmprss4, Baiap2l2, Prom1, C3, Upk1a and Muc4, in parallel with mRNA changes. When either PKA catalytic subunit was transfected into the PKA-KO cells, AQP2 protein expression was rescued (immunofluorescence microscopy and immunoblotting).

Conclusions: We conclude that transcription of the *Aqp2* gene requires PKA. PKA-dependent gene transcription is highly selective, involving less than 1% of expressed genes in collecting duct cells.

Funding: Other NIH Support - NHLBI

SA-PO1033

Comparative Analysis of Vasopressin V1a Receptor Distribution in Rodent and Human Kidneys Torsten Giesecke,[1] Taka-aki Koshimizu,[4] Katsumasa Kawahara,[3] Nina Himmerkus,[2] Julian Isermann,[2] Markus Bleich,[2] Alina Smorodchenko,[1] Sebastian Bachmann,[1] Kerim Mutig.[1] *[1]Charité Universitätsmedizin Berlin, Berlin, Germany; [2]Christian Albrechts Universität Kiel, Kiel, Germany; [3]Dept of Physiol, Kitasato Univ School of Med, Sagamihara, Japan; [4]Jichi Medical University, Shimostuke, Tochigi, Japan.*

Background: Selective antagonists of V1a vasopressin receptor (V1aR) have been discussed as an emerging therapeutic strategy for retardation of chronic kidney disorders. Therefore, detailed knowledge of renal V1aR distribution is fundamental. This work provides comparative analysis of segmental and cellular localization of the receptor in mouse, rat, and human kidney supported by functional studies.

Methods: Immunofluorescence and high-resolution immunocytochemistry using own antibody to V1aR were performed for localization studies. Functional experiments with a V1aR agonist (AO-4-67) were conducted in vivo cultured cells and isolated, perfused renal tubules.

Results: Incubation of mouse kidney sections with the anti-V1aR antibody produced basolateral signal in macula densa cells and in type-A intercalated cells of connecting tubules and collecting ducts, whereas type-B intercalated cells showed punctate perinuclear and apical V1aR signal. In the rat and human kidneys, both types of intercalated cells exhibited chiefly diffused intracellular or apical V1aR signal patterns, whereas macula densa cells did not show any significant V1aR immunoreactivity. Administration of AO-4-67 to vasopressin-deficient Brattleboro rats for 4h induced luminal trafficking of V-ATPase in type-A intercalated cells suggesting increased proton secretion. Accordingly, treatment of isolated mouse collecting ducts with vasopressin or AO-4-67 decreased the luminal pH. Cultured mouse macula densa cells responded to the agonist with rise of intracellular calcium, which verified the V1aR presence in this cell type in mice.

Conclusions: In summary, these results suggest that activation of V1aR modulates function of intercalated cells across the studied species, whereas effects in macula densa cells may be restricted to the mouse species.

SA-PO1034

Quantification of Single and Multi-Site AQP2 Phosphorylation Naofumi Yui, Shinichi Uchida. *Tokyo Medical and Dental University, Sagamihara-shi, Kanagawa-ken, Japan.*

Background: Vasopressin regulates AQP2 phosphorylation at several serine residues. However, the amounts of the singly and multiply phosphorylated forms in the whole AQP2 population are unclear.

Methods: In this study, we developed an immunoprecipitation-based quantification of AQP2 phosphorylation. MDCK cells expressing FLAG-tagged human-AQP2 were grown to confluence, lysed, and precipitated with an anti-pS261 antibody, and then blotted and probed with anti-pS256, anti-pS261, and anti-FLAG-M2 antibodies. The signal intensity of the precipitated pS261-positive AQP2 (IP-pS261; consisting of pS261-single form and pS256-pS261-double form) was normalized to the whole pS261 signal in the lysate (IP-pS261/whole-pS261), and the ratio was used as the control. The ratios of the IP-pS261 signal intensity to the whole pS256 signal intensity (IP-pS261/whole-pS256), and to the whole AQP2 signal intensity (IP-pS261/whole-AQP2) were compared with the control ratio. pS256-positive AQP2 was analyzed in the same way.

Results: pS261-positive AQP2 constituted 21% of the whole AQP2 population under basal condition, this declined to 10% after FK (20 μM, 60 min) treatment. pS256-positive AQP2 constituted 48% of the whole AQP2 population under basal condition, this was at 51% after FK treatment. In the pS256-positive AQP2 population, pS261-positive AQP2 (pS256-pS261-double form) constituted a major part of the pS256-positive AQP2 population at 59% under basal condition, this declined to 27% in the population after FK treatment. IP-pS256/whole-pS256 did not differ significantly from IP-pS256/whole-pS261 with or without FK treatment.

Conclusions: Ser-256 is most highly phosphorylated in the cell; pS256-positive AQP2 constantly constitutes around 50% of the whole AQP2 population with or without FK treatment. Most pS261-positive AQP2 is the pS256-pS261 doubly phosphorylated form. This double phospho-form constitutes about a half population in the pS256-positive AQP2, and decreased by 50% after FK treatment in the population. To the contrary, the pS261-single form may constitute a minor component. This study suggests that relative quantification of pS261 signal may be a good biomarker of vasopressin action on pS256-positive AQP2, and will contribute to develop inspective assays of renal vasopressin action in animal and human samples.

Funding: Other U.S. Government Support

SA-PO1035

A Transcriptional Network Controlling Epithelial Barrier Function in the Collecting Duct Is Necessary to Maintain Renal Medullary Osmolality Christian Hinze,[5,2] Janett Ruffert,[2,3] Katharina Walentin,[2] Kerim Mutig,[4] Sebastian Bachmann,[4] Michael Schumann,[6] Nina Himmerkus,[1] Markus Bleich,[1] Kai M. Schmidt-Ott.[5,2] *[1]Institute of Physiology, CAU, Kiel, Germany; [2]Max Delbrueck Center for Molecular Medicine, Berlin, Germany; [3]Urological Research Laboratory, Charité-Universitätsmedizin, Berlin, Germany; [4]Anatomy, Charité, Berlin, Germany; [5]Nephrology, Charité, Berlin, Germany; [6]Gastroenterology, Charité, Berlin, Germany.*

Background: Osmolytes are accumulated in the renal medulla generating a gradient between the hypertonic interstitial medullary tissue and the urine to facilitate urinary concentration. The transcription factor grainyhead-like 2 (GRHL2) is highly expressed in renal collecting ducts. We previously showed that mice with collecting duct-specific GRHL2 deficiency show a decreased urine concentrating ability and a predisposition for prerenal acute kidney injury. We also demonstrated a loss of barrier function in GRHL2-deficient collecting ducts, as shown by a reduced transepithelial resistance in freshly isolated collecting ducts from the inner stripe of the outer medulla. However, the functional consequences of the epithelial barrier loss remained unclear.

Methods: We generated collecting duct-specific GRHL2 knockout mice (Hoxb7/Cre; $Grhl2^{flox/-}$, further referred to as $GRHL2^{CD-/-}$) and measured tissue osmolalities in the cortex, the inner stripe of the outer medulla (ISOM) and the inner medulla (IM) in control and $GRHL2^{CD-/-}$ mice. We used inner medullary collecting duct (IMCD-3) cells with a

CRISPR/Cas9-induced Grhl2 knockout and wildtype control cells for functional analyses. GRHL2 target genes were identified by microarray gene expression analyses from control and GRHL2$^{CD-/-}$ kidneys and by Grhl2 chromatin immunoprecipitation followed by next generation sequencing (ChIP-seq) from wildtype kidneys.

Results: Our data show a significantly decreased tissue osmolality in ISOM and IM of GRHL2$^{CD-/-}$ kidneys compared to control kidneys. GRHL2 knockout IMCD-3 cells when compared with wildtype cells showed a significantly reduced transepithelial resistance and an increased paracellular flux of sodium and chloride. Integration of microarray and ChIP-seq data indicated that Grhl2 target genes were involved in tight junction assembly.

Conclusions: These data functionally link collecting duct epithelial barrier function with urinary concentrating ability for the first time. We identify a transcriptional network regulated by the transcription factor GRHL2, which is necessary to maintain tight epithelial barriers across the collecting duct epithelium, thereby preventing leakage of sodium and chloride into the urine and preserving a high medullary osmolarity.

SA-PO1036

SLC26A6 Mediates Enteric Oxalate Secretion in CKD Laura I. Neumeier,[1,3] Robert B. Thomson,[3] Kai-Uwe Eckardt,[2] Peter S. Aronson,[3] Felix Knauf.[2,3] *[1]Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; [2]University Hospital Charite Berlin, Berlin, Germany; [3]Yale University School of Medicine, New Haven, CT.*

Background: A state of oxalate equilibrium is maintained in patients with healthy kidney function. However, as GFR declines plasma oxalate levels start to rise. Upregulation of oxalate secretion in the colon of rats with CKD has been described in the past, yet the molecular identification of the oxalate transporter(s) involved has yet to be defined. Hence, we examined whether oxalate transporter SLC26A6 contributes to the extrarenal clearance of oxalate via the gut in CKD.

Methods: CKD was induced by injecting age- and gender-matched 129S6 (wild-type) and Slc26a6$^{-/-}$ mice with aristolochic acid. Renal function was monitored by changes in plasma creatinine sampled retro-orbitally. Intestinal SLC26A6 was assessed by qPCR and western blot analysis. Mice were maintained on an oxalate-free diet and plasma and fecal oxalate levels were measured enzymatically using an oxalate oxidase assay.

Results: SLC26A6 mRNA and protein expression were greatly increased in colon of mice with CKD. However, expression levels of glucose (SGLT-1) and amino acid transporters (CAT-1), other representative intestinal transport processes, did not differ in colon of CKD mice. In line with these findings, fecal oxalate excretion was increased in mice with CKD. In contrast, fecal oxalate excretion was reduced and plasma oxalate levels significantly increased in Slc26a6$^{-/-}$ mice as compared with wild-type mice.

Conclusions: In summary, we demonstrate that SLC26A6-mediated enteric oxalate secretion is critical in decreasing the body burden of oxalate in CKD.

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SA-PO1037

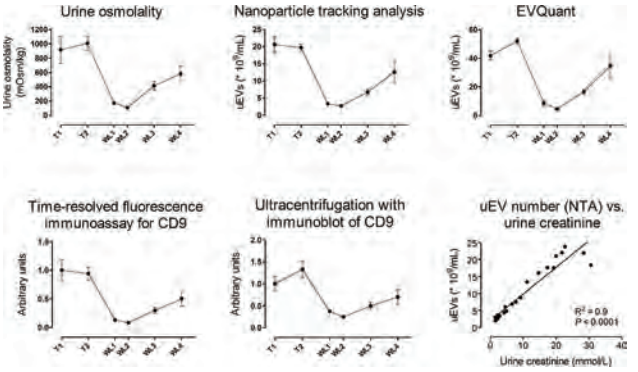
Quantification of Urinary Extracellular Vesicles Charles J. Blijdorp, Thomas Hartjes, Martin E. Van royen, Robert Zietse, Ewout J. Hoorn. *Erasmus Medical Center, Rotterdam, Netherlands.*

Background: Urinary extracellular vesicles (uEVs) have emerged as a powerful non-invasive tool to study renal epithelial transport in humans. However, the optimal method to quantify and normalize uEVs remains unclear, especially for spot urines.

Methods: Four healthy subjects were subjected to overnight thirsting (10 pm-noon) followed by water loading (20 ml/kg in 30 min). Spot urines were collected during thirsting (T1-2) and after water loading (WL1-4, noon-7 pm). Subsequently, 4 uEV quantification techniques were compared: (1) nanoparticle tracking analysis (NTA), (2) uEV isolation by ultracentrifugation followed by immunoblotting of CD9, CD63, CD81, ALIX, and TSG101, (3) a time-resolved fluorescence immunoassay (TRFIA) that captures CD9+ uEVs, and (4) EVQuant, a novel technique which counts individual fluorescently labeled EVs after immobilization in a matrix. A Bland-Altman analysis was used to compare methods using NTA as reference.

Results: As expected, urine osmolality was near-maximal during thirsting, decreased after water loading and then increased again (Figure). The results of the 4 uEV quantification methods showed similar dynamics as urine osmolality suggesting that uEV number changes in proportion to urinary concentration (Figure). Of interest, EVQuant identified 2.4 ± 0.6 times more uEVs than NTA. Using NTA as reference, the Bland-Altman analysis showed that EVQuant had the lowest bias (% difference 6 ± 27) followed by TRFIA (10 ± 21). Of the uEV-markers, CD9 agreed best with NTA (-12 ± 34). uEV number correlated strongly with urine creatinine (Figure) and osmolality (r^2 for both 0.9, P<0.0001).

Conclusions: uEV number is proportional to urinary concentration and both urine creatinine and osmolality can be used to normalize spot urines for uEV number. EVQuant is a promising alternative to NTA and appears more sensitive for uEV detection. These uEV quantification methods can be used to analyze if changes in a uEV protein of interest are the result of more protein per uEV or the excretion of more uEVs containing this protein.



SA-PO1038

WNK4 Deletion Inhibits Adipogenesis In Vitro and In Vivo Daiei Takahashi,[4,6] Takayasu Mori,[4] Eisei Sohara,[4] Miyako Tanaka,[2] Yuichi Inoue,[5] Naohiro Nomura,[4] Motoko Chiga,[1] Moko Zeniya,[4] Takayoshi Suganami,[2] Tatemitsu Rai,[3] Shinichi Uchida.[4] *[1]Department of Nephrology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Bunkyo-ku, Tokyo, Japan; [2]Nagoya University, Nagoya, Japan; [3]TOKYO MEDICAL & DENTAL UNIV, TOKYO, Japan; [4]Tokyo Medical and Dental University, Tokyo, Japan; [5]Tokyo medical and dental university, Tokyo, Japan; [6]Internal medicine, Tokyo Metropolitan Ohtsuka Hospital, Tokyo, Japan.*

Background: The *with-no-lysine kinase (WNK) 1 and WNK4* genes are responsible for pseudohypoaldosteronism type II (PHAII), a hereditary hypertensive disease. We have demonstrated the importance of the WNK4–OSR1/SPAK–NCC signaling cascade in the kidney for blood pressure regulation, however, the extrarenal roles of WNK4 is not clear. We previously presented WNK4 is induced in the early phase of 3T3-L1 adipocyte differentiation and is expressed in mouse mature adipose tissues. In this study, we evaluated *WNK4*'s contribution to the adipogenesis *in vitro* and *in vivo*.

Methods: We used mouse primary preadipocytes, 3T3-L1 fibroblasts, and human mesenchymal stem cells (hMSC-AT) to elucidate potential roles of WNK4 in adipose tissue. The functions of WNK4 in these cells was examined by siRNA specific to WNK4 (si-WNK4). We also generated WNK4 knock-down 3T3-L1 cell lines using TALEN. We fed WNK4$^{-/-}$ mice a high-fat diet and examined their metabolic functions.

Results: In mouse primary preadipocytes, WNK4 was predominantly expressed in the mature adipocyte, and WNK4 in the stromal vascular fraction was induced by the differentiation stimuli. WNK4 expression preceded the expression of key transcriptional factors PPARγ and C/EBPα. Si-WNK4-transfected 3T3-L1 cells and hMSC-AT cells showed reduced expression of PPARγ and C/EBPα and decreased lipid accumulation. WNK4 knocked-down 3T3-L1 cells also showed reduced PPARγ expression. In the WNK4$^{-/-}$ mice, PPARγ and C/EBPα expression were decreased in adipose tissues, and the mice exhibited partial resistance to high-fat diet-induced adiposity.

Conclusions: WNK4 is a key molecule of adipocyte differentiation and is involved in diet-induced adiposity. Thus, WNK4 would be a novel target molecule for the treatment of metabolic syndrome.

Funding: Government Support - Non-U.S.

SA-PO1039

Decreased Protein Expression of KLHL3 Is Involved in the Pathogenesis of PHAII Caused by CUL3 Mutation In Vivo Sayaka Yoshida, Yuya Araki, Takayasu Mori, Emi Sasaki, Yuri Kasagi, Kiyoshi Isobe, Koichiro Susa, Yuichi Inoue, Tatemitsu Rai, Shinichi Uchida, Eisei Sohara. *Department of Nephrology, Tokyo Medical and Dental University, Bunkyo-ku, Japan.*

Background: Pseudohypoaldosteronism type II (PHAII) is a hereditary hypertensive disease. PHAII is caused by mutations in four genes: WNK1, WNK4, KLHL3 and Cullin3 (Cul3). Recently it was revealed that Cul3-KLHL3 E3 ligase complex ubiquitinate WNK1 and WNK4, leading to their degradation, and that one of the common pathogenesis of PHAII is the defective degradation of WNKs by Cul3-KLHL3 E3 ligase complex. PHAII-causing Cul3 mutations result in the skipping of exon 9, leading to a CUL3 protein with a 57-amino acid deletion(Δ403-459). However, the pathogenesis of PHAII caused by CUL3Δ403–459 *in vivo* is still unclear.

Methods: We generated and analyzed CUL3$^{WT/Δ403-459}$ PHAII model mice.

Results: CUL3 $^{WT / Δ 403-459}$ mice were successfully generated, and they exhibited hyperkalemia, metabolic acidosis and hypertension, indicating that they are good mouse model of PHAII. Protein levels of WNK kinases were increased, resulting in increased phosphorylation of OSR1, SPAK, and NCC, the downstream components of the WNK signal. In CUL3$^{WT/Δ403-459}$ mice, the abundance of KLHL3 protein was decreased in kidney and brain. On the other hand, the protein levels of the other KLHL family proteins, KLHL2 and Keap1, which also form ubiquitin ligase complexes with CUL3, were comparable between CUL3$^{WT/WT}$ and CUL3$^{WT/Δ403–459}$.

Conclusions: In CUL3 $^{WT / Δ 403-459}$ mice, expression levels of KLHL3 were decreased. Considering that heterogygous knockout of CUL3 expression alone in mice which we

published previously was not sufficient to develop PHAII, the decreased protein expression of KLHL3 observed in CUL3$^{WT/\Delta 403-459}$ mice could be involved in the mechanism of PHAII caused by the CUL3 mutation *in vivo*. As KLHL2 and Keap1 were not decreased in CUL3 $^{WT/\Delta 403-459}$mice, it might be a specific phenomenon in KLHL3.

Funding: Government Support - Non-U.S.

SA-PO1040

KS-WNK1: An Aldosterone-Induced Inhibitor of ENaC? Maria Chavez-Canales,[1] Peng Wu,[2] Shaohu Sheng,[1] Jingxin Chen,[3] Bettina Serbin,[1] Nikita Radionov,[1] Christelle Soukaseum,[1] WenHui Wang,[2] Thomas R. Kleyman,[3] Juliette Hadchouel.[1] *[1]INSERM, Paris, France; [2]New York Medical College, Valhalla, NY; [3]University of Pittsburgh, Pittsburgh, PA.*

Background: Mutations in the gene encoding the serine threonine kinase WNK1 [With No lysine (K)] result in an increased expression of the catalytic isoform, thus causing Familial Hyperkalemic Hypertension, a rare form of human hypertension. Another isoform, KS-WNK1, is also produced from the *WNK1* gene. Devoid of kinase activity, it is expressed specifically in the distal nephron. *In vitro* data suggest that KS-WNK1 inhibits the activity of other WNK kinases. We previously showed that the inactivation of KS-WNK1 in mice leads to an increased expression of the Na-Cl cotransporter NCC, which could result from an increased activity of WNK1 and/or WNK4. However, aldosterone secretion is decreased in *KS-WNK1*$^{-/-}$ mice while renin is not, suggesting that potassium balance is impaired, which could also explain the increased NCC expression.

Methods: KS-WNK1 is expressed in the distal convoluted tubule but also in the connecting tubule (CNT) and cortical collecting duct (CCD). In order to characterize its role in potassium balance independently from the DCT, we generated a mouse model of KS-WNK1 inactivation specifically in the CNT-CCD (*WNK1*$^{AQP2/AQP2}$ mice).

Results: As in *KS-WNK1*$^{-/-}$ mice, the secretion of aldosterone, but not renin, is decreased in *WNK1*$^{AQP2/AQP2}$ mice. An increase in aldosterone, by chronic infusion or potassium load, as well as a sodium load provoke a significant decrease in plasma potassium in *WNK1*$^{AQP2/AQP2}$ mice, suggesting that the activity of the Na channel ENaC is increased. Using patch-clamp on isolated tubules, we confirmed that ENaC activity is increased in the CNT of *WNK1*$^{AQP2/AQP2}$ mice. Accordingly, overexpression of KS-WNK1 in *Xenopus laevis* oocytes decreases the activity of the sodium channel.

Conclusions: Taken together, these data suggest that KS-WNK1 is an inhibitor of ENaC in a Nedd4-2 independent manner. Since the expression of KS-WNK1 is induced by aldosterone infusion or potassium load, KS-WNK1 could therefore be an aldosterone-induced inhibitor of ENaC.

Funding: NIDDK Support, Government Support - Non-U.S.

SA-PO1041

Depletion of Kidney-Specific WNK1 (KS-WNK1) Abolishes the Effect of High Dietary K Intake (HK) on ROMK Channel in the Distal Convoluted Tubule (DCT) WenHui Wang,[2] Peng Wu,[2] Xiao-Tong Su,[2] Andrew Terker,[3] Zhongxiuzi Gao,[2] David H. Ellison,[4] Juliette Hadchouel,[1] Jacques Teulon.[5] *[1]INSERM, Paris, France; [2]New York Medical College, Valhalla, NY; [3]OHSU, Portland, OR; [4]Oregon Health & Science University, Portland, OR; [5]University Pierre et Marie Curie-UPMC, Paris, France.*

Background: Previous studies have shown that with-no-lysine kinases (WNK) regulate ROMK (Kir1.1) channel, a K secretory channel expressed in the apical membrane of aldosterone-sensitive distal nephron (ASDN). While WNK4 and full-length WNK1 (L-WNK1) inhibit ROMK cannel activity by facilitating endocytosis, KS-WNK has been shown to inhibit L-WNK1 thereby stimulating ROMK.

Methods: Since KS-WNK1 is mainly expressed in the DCT, we now performed the whole-cell patch-clamp recording to measure TPNQ (ROMK inhibitor)-sensitive K currents in the isolated split-open DCT of WT and WNK4 knockout (KO) or KS-WNK1 KO mice.

Results: TPNQ-sensitive K currents in DCT2 of KS-WNK1 KO (450±40 pA) and WNK4 KO mice (370±50 pA) were significantly smaller than that of WT mice (1060±120 pA). Moreover, WNK4 KO mice were hypokalemic (3.2±0.05 mM) while KS-WNK1 KO mice had normal plasma K level (4.5±0.3 mM). Thus, it is possible that diminished ROMK cannel activity in WNK4 KO mice may be the result of hypokalemia. HK intake (7 days) significantly increased K currents in DCT2 to 1600±80 pA (WT) and to 1090±40 pA (WNK4 KO), suggesting that lack of WNK4 did not compromise the effect of HK intake on ROMK in DCT2. In contrast, HK intake fails to stimulate ROMK channels in DCT of KS-WNK1 KO mice because TPNQ-sensitive K currents were not significantly increased (540±30 pA) in DCT2 of KS-WNK1 KO mice. However, plasma K level in KS-WNK1 KO mice on HK was even lower (3.9±0.1 mM) than that of WT mice (4.4±0.1 mM), suggesting that defective regulation of ROMK by HK in DCT2 did not decrease net renal K excretion in KS-WNK1 KO mice. This notion is supported by the observation that HK intake actually stimulates TPNQ-sensitive K currents in the CCD from 1090±90 pA to 2400±140 pA in KS-WNK1 KO mice.

Conclusions: In summary, ROMK cannel activity is decreased in DCT2 of WNK4 KO and KS-WNK1 KO mice. However, only the depletion of KS-WNK1 but not WNK4 abolished the stimulatory effect of HK intake on ROMK in DCT2. However, HK intake is still able to activate ROMK in the CCD of KS-WNK1 KO mice. We conclude that KS-WNK1 plays a role in mediating the stimulatory effect of HK intake on ROMK in the DCT2 but not in the CCD.

Funding: NIDDK Support

SA-PO1042

WNK4 Acts on Thick Ascending Limbs In Vivo as Well as Distal Convoluted Tubules Andrew Terker,[3] Kayla J. Erspamer,[4] Lauren N. Miller,[5] Mohammed Z. Ferdaus,[4] WenHui Wang,[2] Xiao-Tong Su,[2] Ryan J. Cornelius,[5] James A. McCormick,[4] Gerardo Gamba,[1] Chao-Ling Yang,[5] David H. Ellison.[4] *[1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Tlalpan, Mexico City, Mexico; [2]New York Medical College, Valhalla, NY; [3]OHSU, Portland, OR; [4]Oregon Health & Science University, Portland, OR; [5]Oregon Health and Science University, Portland, OR.*

Background: WNK4 mutations increase thiazide-sensitive NaCl cotransporter (NCC) activity in the distal convoluted tubule (DCT) and cause familial hyperkalemic hypertension (FHHt). Conversely, WNK4 knockout (KO) in mice leads to a 'Gitelman-like' phenotype', similar to loss of NCC function. Even though the WNK/SPAK-OxSR1 pathway can modulate the Na-K-2Cl cotransporter (NKCC2) in vitro, effects of WNK4 KO on NKCC2 were not noted in mice. Yet WNK4 knockout mice are not hypocalciuric, a cardinal feature of NCC dysfunction, suggesting a mixed phenotype. To test this, we revisited the phenotypes of WNK4 KO and WNK4 activation (WNK4Q562E) in mice.

Methods: Plasma and urine electrolyte concentrations from WNK4 KO and WNK4Q562E mice were determined. Western blots determined protein abundance. Modified diets were reported previously. NKCC2 and NCC activity were assessed with furosemide (25mg/kg IP) and hydrochlorothiazide (25mg/kg IP).

Results: As reported previously, plasma potassium and chloride were significantly lower in WNK4 KO mice than in controls, but urine calcium excretion was normal. A high salt/high K^+ diet increased urine calcium in control mice, compared with high salt/normal K^+, but not in WNK4 KO (interaction p=0.0183). WNK4 KO mice exhibited low total and phosphorylated NCC, compared with controls, as expected, but also exhibited low phosphorylated NKCC2 (total NKCC2 was normal). In contrast, WNK4Q562E mice had more phosphorylated NKCC2 than controls. The response to furosemide, an index of NKCC2 function, was similar in WNK4 KO and control, but we reasoned that this may have reflected compensatory NCC activation in controls. When compensatory DCT transport was inhibited with thiazide, however, the response to furosemide was significantly lower in WNK4 KO mice than in controls, consistent with reduced NKCC2 activity.

Conclusions: While WNK4 clearly has predominant effects on NCC, it also modulates NKCC2 in vivo. Thus, although WNK4 deficiency has been suggested to cause a mild 'Gitelman-like phenotype', it much more closely mimics Bartter syndrome type III, with a mixed thick ascending limb and DCT phenotype. WNK4-mediated FHHt likely also involves activation of both NCC and NKCC2, accounting for variable reports of furosemide action in some cases.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO1043

Differential Regulation of L-WNK1 and KS-WNK1 by the Ubiquitin Ligases Nedd4-2 and Kelch-CUL3 Complex Mauricio Ostrosky-Frid,[1,3] Eduardo R. Argaiz,[1] Fabiola Gallardo,[1] Maria Chavez-Canales,[4] Norma H. Vázquez,[4] David H. Ellison,[2] Gerardo Gamba.[1,4] *[1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Tlalpan, Mexico City, Mexico; [2]Oregon Health & Science University, Portland, OR; [3]Programa de Estudios Combinados en Medicina, UNAM, Mexico City, Mexico; [4]Instituto de Investigaciones Biomédicas, UNAM, Mexico City, Mexico.*

Background: It has been suggested that the full-length form of WNK1 kinase (L-WNK1) is a target for ubiquitylation by the Nedd4-2 and the Kelch-Cul3 ubiquitin ligases. The major transcript of WNK1 gene in the renal tissue is KS-WNK1, the truncated kidney-specific isoform that is almost exclusively expressed in the distal convoluted tubule, where its transcript is 80 times more abundant than L-WNK1. The higher transcript expression could be due to a different sensibility to the ubiquitin-induced degradation. The effect of ubiquitin ligases in the KS-WNK1 variant, however, is not known.

Methods: The effect of Nedd4-2 and Kelch3-CUL3 complex upon L-WNK1 and KS-WNK1 was assessed by western blot and immunoprecipitation (IP) two days after microinjection of *Xenopus* oocytes with Myc-tagged KS-WNK1-Δ11 and/or L-WNK1-Δ11 cRNA, in the absence or presence of Flag-tagged Nedd4-2 or Flag-tagged-Kelch3 cRNA. The NCC activity was measured by functional expression in the oocytes using tracer $^{22}Na^+$ uptake. We used the variants lacking the exon 11 (Δ11) because this is the most abundant form in the kidney. Immunoprecipitation between WNK1 variants and Nedd4-2 or Kelch3 was corroborated using a c-myc precipitation kit.

Results: We observed that KS-WNK1-Δ11, was completely degraded by Kelch-CUL3 complex (N=10). In contrast, only about 20% of the L-WNK1-Δ11 was degraded in the presence of Kelch3. The IP confirmed that the Kelch-CUL3 complex is co-precipitated with KS-WNK1, but not with L-WNK1-Δ11 (N=3). Functionally, the positive effect of KS-WNK1-Δ11, but not that of L-WNK1-Δ11, on NCC was prevented by the coinjection with Kelch3 (n=3). Interestingly, the effect of Nedd4-2 was the opposite. Nedd4-2 induced degradation of L-WNK-Δ11 and reduced its effect on NCC, while it had no effect on KS-WNK1-Δ11. Using the same expression system, we observed that WNK4 was also highly sensitive to Kelch3.

Conclusions: Although KS-WNK1 and L-WNK1 exhibit the same interaction site for ubiquitin ligases, KS-WNK1-Δ11 is sensitive to Kelch3, but not to Nedd4-2, while L-WNK1-Δ11 is sensitive to Nedd4-2, but not to Kelch3. Given the differential expression of KS-WNK1 and L-WNK1 along the distal nephron, modulation of these

kinases abundance by Nedd4-2 and Kelch3 could have an implication in the fine tune modulation of ion transport.

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SA-PO1044

Role of WNK Aggregate Formation in Activating Na-Cl Cotransport Catherina A. Cuevas,[3] Lauren N. Miller,[4] Kerim Mutig,[1] Sebastian Bachmann,[2] Chao-Ling Yang,[4] David H. Ellison.[3] *[1]Charite-Universitaetsmedizin Berlin, Berlin, Germany; [2]Charité Universitätsmedizin Berlin, Berlin, Germany; [3]Oregon Health & Science University, Portland, OR; [4]Oregon Health and Science University, Portland, OR.*

Background: Activation of the thiazide-sensitive Na-Cl cotransporter (NCC) is essential to retain K^+ in response to dietary K^+ restriction and hypokalemia. Formation of WNK4/SPAK-OSR1 aggregates in distal convoluted tubule (DCT) cells is a common event that occurs when dietary K^+ is low and NCC activity is high. While these aggegates bring together key signaling proteins required to activate NCC, it has not been clear whether WNK4 aggregate formation facilitates NCC activation or whether these represent stress features, or even autophagosomes.

Methods: Here, we fed C57/BL6 mice normal (NK, 0.8% K^+) or potassium-deficient (LK, 0% K^+) diets for 12 to 72 hours. Some mice were switched to high potssium diet (HK, 5%). Plasma electrolytes were determined with iSTAT. Protein aggregates containing WNK4, SPAK and ATG5 (autophagy marker) was assessed by light and electron microscopy.

Results: Plasma [K^+] decreased with LK (3.3±0.3 vs 4.0±0.1 mmol/l); The abundance of phospho-NCC (T53) reached a maximum after only 12h of LK, with a striking increase in phospho SPAK-Ser373/OSR1-Ser325 at the apical membrane of DCT1 segments (identified with parvalbumin). Increased phospho NCC abundance at this time also correlated with appearance of phospho SPAK-Ser373/OSR1-Ser325 containing aggregates, but these aggregates did not contain WNK4, which appeared unaffected. WNK4 and ATG5, however, were clearly associated with aggregates in DCT seegments after 24h of LK diet and increased in a time-dependent fashion. By electron microscopy, the aggregates were not surrounded by membranes typical of autophagosomes. Potassium replenishment protocol (LK diet for 2 days followed by 2 additional days in HK) increased plasma [K^+] (5.2± 0.1 mmol/l), as expected, and reduced phospho-NCC protein abundance. WNK4, SPAK and ATG5 aggregates were no longer detected in the DCT after this brief K^+ replenishment. Basolateral K^+ channels (Kir4.1) mediate [K^+] sensing in DCT. In LK Kir4.1 KO mice, only occasional cells retaining Kir4.1 developed WNK4 aggregates.

Conclusions: WNK4-ATG5 aggregates are atypical, membraneless, dynamic structures that form after NCC is activated in response to LK, which require sensing through Kir4.1. WNK4 aggregate formation thus is not required for early NCC activation by LK, but these structures also are not typical autophagosomes.

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SA-PO1045

Generation and Analysis of KLHL2 Knockout Mice Yuri Kasagi,[1] Daiei Takahashi,[1] Tomomi Aida,[2,3] Hidenori Nishida,[1] Naohiro Nomura,[1] Moko Zeniya,[1] Takayasu Mori,[1] Emi Sasaki,[1] Fumiaki Ando,[1] Tatemitsu Rai,[1] Shinichi Uchida,[1] Eisei Sohara.[1] *[1]Department of Nephrology, Tokyo Medical and Dental University, Bunkyo-ku, Japan; [2]Laboratory of Molecular Neuroscience, Medical Research Institute (MRI), Tokyo Medical and Dental University, Bunkyo-ku, Japan; [3]Laboratory of Recombinant Animals, MRI, Tokyo Medical and Dental University, Chiyoda-ku, Japan.*

Background: Mutations in the with-no-lysine kinase 1 (*WNK1*), *WNK4,* Kelch-like 3 (*KLHL3*), and Cullin3 (*CUL3*) genes were identified as being responsible for hereditary hypertensive disease pseudohypoaldosteronism type II (PHAII). KLHL3/CUL3 ubiquitin ligase complex regulates degradation of WNK kinases via their degradtion. In PHAII, the loss of interaction between KLHL3 and WNK4 increases levels of WNKs because of impaired ubiquitination, leading to abnormal over-activation of the WNK-OSR1/SPAK-NCC cascade in the kidney's distal convoluted tubules (DCT). KLHL2 is highly homologous to KLHL3, especially in kelch-repeat domain (WNK-binding domain). We previously reported KLHL2 ubiquitinated and degraded WNKs *in vitro*. However, the physiological role of KLHL2 *in vivo* is still unclear.

Methods: We generated KLHL2$^{-/-}$ mice using CRISPR/cas9 system and evaluated the phenotype.

Results: KLHL2 expressed abundantly in the brain, stomach, and kidneys. However, we found that the expression of WNK4 was increased only in the KLHL2$^{-/-}$ mice kidneys. KLHL2$^{-/-}$ mice did not exhibit increased phosphorylation of the OSR1/SPAK-NCC cascade in the kidneys and PHAII-like phenotype. KLHL2 was predominantly expressed in the kidney medulla compared with the cortex. Accordingly, medullary WNK4 protein levels were significantly increased in the kidneys of KLHL2$^{-/-}$ mice.

Conclusions: KLHL2 is indeed a physiological regulator of WNK4 *in vivo*; however, WNK protein levels in KLHL2-expressing tissues may not be solely governed by KLHL2, except in kidney medulla.

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SA-PO1046

The Sensibility of WNK3 and WNK4 for Intracellular Chloride Concentration and Cell Volume Is Opposite Diego L. Carrillo Perez,[1] Karla Leyva-Rios,[3] Adriana P. Mercado,[2] Elisa Hernandez Mercado,[2] Erika Moreno,[1] Norma H. Vázquez,[4] Diana Pacheco-Alvarez,[3] Gerardo Gamba.[1,4] *[1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Tlalpan, Mexico City, Mexico; [2]Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico; [3]Universidad Panamericana, Mexico City, Mexico; [4]Instituto de Investigaciones Biomédicas, UNAM, Mexico City, Mexico.*

Background: The activity of the electroneutral chloride cotransporters (CCCs) such as the Na-K-2Cl and the K-Cl cotransporters is modulated by intracellular chloride concentration $[Cl^-]_i$ and cell volume. Depletion of $[Cl^-]_i$ and cell shrinkage induce phosphorylation of CCCs, while increase of $[Cl^-]_i$ and cell swelling induces dephosphorylation. However, cell shrinkage increases $[Cl^-]_i$ and cell swelling decreases $[Cl^-]_i$. It is known that the effect of $[Cl^-]_i$ towards CCCs is traduced by the WNK1 or WNK4 kinases. Thus, the effect of cell volume towards CCCs must be traduced by a different kinase. Because WNK3 bypasses the tonicity requirements for regulation of the CCCs (PNAS 2005 and 2006), we tested the hypothesis that WNK3 is sensitive to cell volume, rather than to the $[Cl^-]_i$.

Methods: Xenopus oocytes were microinjected with N(K)CCs or KCCs cRNA alone or together with WNK3 wild type or mutants in which catalytic activity and/or the chloride binding site has been eliminated (WNK3-DA; WNK3 L295/297F; WNK3-DA-LLFF). The effect of $[Cl^-]_i$ or extracellular tonicity on WNKs was assessed. WNKs phosphorylation at the activating serine of the T-loop with specific antibodies was analyzed as a surrogate of WNKs activity.

Results: Depletion of $[Cl^-]_i$ increases the activity of WNK1 and WNK4 and thus increases the NCC activity, while it had not effect on the WNK3 and its effect towards NCC. In contrast to what we previously observed for WNK1 and WNK4, elimination of the chloride-binding site in WNK3 had no effect on the activity of the kinase. WNK3, but not WNK4, phosphorylation was sensitive to changes in cell volume. Compared to isotonic condition, WNK3 phosphorylation significantly diminished or increased by 50% in hypotonic or hypertonic conditions, respectively. The phosphorylation of WNK4 was not affected by similar changes in tonicity.

Conclusions: Our data show that WNK3 is not sensitive to changes of the $[Cl^-]_i$, but is modulated by changes in cell volume in the expected direction according to the effect of WNK3 wild type and the catalytically inactive WNK3 on the CCCs. We propose that WNK3 is a volume sensitive kinase modulating the effect of cell volume changes in CCCs.

Funding: Government Support - Non-U.S.

SA-PO1047

Cushing's Syndrome Increases Renal Sodium Transporters in Urinary Extracellular Vesicles Dominique M. Bovee, Mahdi Salih, Alexander H. Danser, Robert Zietse, Richard Feelders, Ewout J. Hoorn. *Erasmus Medical Center, Rotterdam, Netherlands.*

Background: Increased renal sodium (Na^+) reabsorption contributes to hypertension in Cushing's syndrome (CS). Renal Na^+ transporters can be analyzed non-invasively in urinary extracellular vesicles (uEVs). The aim of this study was to analyze renal Na^+ transporters in uEVs of patients with newly diagnosed CS.

Methods: uEVs were isolated by ultracentrifugation and analyzed by immunoblotting in 10 CS patients and 7 age-matched healthy subjects. The majority had an ACTH-producing pituitary adenoma (n=8). In 3 CS patients uEVs were analyzed before and after treatment (unilateral adrenalectomy or ketoconazole). uEVs were isolated without interfering medication (renin-angiotensin system inhibitors or diuretics).

Results: The 10 patients with CS were hypertensive (144 ± 14 / 92 ± 17 mmHg) and had a 2-fold higher abundance of the Na^+/H^+exchanger type 3 (NHE3) in uEVs compared to healthy controls ($p<0.05$). CS patients were subsequently divided in those with a suppressed and non-suppressed renin-angiotensin-aldosterone system (RAAS, n=5/group). CS patients with suppressed vs. non-suppressed RAAS had similar blood pressure but significantly lower serum K^+ (3.9 ± 0.2 vs. 4.4 ± 0.3 mmol/l, p=0.04). Furthermore, only those with suppressed RAAS had 3- to 4-fold higher phosphorylated Na^+-K^+-Cl^-cotransporter type 2 (pNKCC2) and higher total and phosphorylated Na^+-Cl^- cotransporter (NCC) in uEVs. Serum K^+ but not urinary free cortisol correlated with pNKCC2, pNCC, and NCC in uEVs (r = -0.9, -0.8, and -0.7, respectively; $p<0.05$ for all). In the 3 CS patients with uEV-analysis before and after treatment, pNKCC2, pNCC, and NCC abundances normalized after treatment in parallel with serum K^+. No changes were observed in other uEV proteins of interest, including prostasin (a regulator of the epithelial sodium channel), Rac1 (which reflects mineralocorticoid activity), and aquaporin-2.

Conclusions: CS increases renal Na^+ transporter abundance in uEVs especially in patients with suppressed RAAS. In addition to a mineralocorticoid effect of excess glucocorticoids, low serum K^+ may also contribute to increased renal Na^+ reabsorption and hypertension in CS. Our findings recapitulate previously characterized effects of glucocorticoids on NHE3, NKCC2, and NCC in experimental animals and of mineralocorticoids in patients with primary aldosteronism.

SA-PO1048

High K Intake Modulates Thiazide Sensitive Na-Cl Cotransporter Mediated Na and K Transport: Effects of Gender and Angiotensin II Type 1a (AT1a) Receptor Jing Li,[1] Shuhua Xu,[1] Claire J. Wang,[1] Haiyan Hu,[1] Alan M. Weinstein,[2] Lawrence G. Palmer,[2] Tong Wang.[1] *[1]Yale University, New Haven, CT; [2]Weill Medical College of Cornell, New York, NY.*

Background: The thiazide-sensitive Na-Cl cotransporter (NCC) plays a key role in controlling NaCl absorption in the distal tubule, and also modulates salt and fluid delivery to downstream portions of the nephron, thus regulating K secretion. Previously we reported that higher NCC expression correlates with activity in female WT, and that gender-specific differences were absent in AT1a receptor knockout (KO) mice. We have now studied the gender difference in response to high K intake in WT and AT1a receptor KO animals.

Methods: Renal clearance experiments were performed on male WT and KO mice treated with normal and high K (5% KCl, 7 days) diets. Urine volume (UV), glomerular filtration rate (GFR), absolute (ENa, EK) and fractional (FENa, FEK) Na and K excretion were measured and compared at peak changes after a bolus iv injection of hydrochlorothiazide (HCTZ; 30mg/kg). Total NCC (tNCC) and Na/H-exchanger isoform 3 (NHE3) expressions in the kidney were examined by Western blotting.

Results: In WT mice, HK reduced tNCC abundance by 70% in females and by 60% in males. In KO mice HK produced more reduction of tNCC in male (60%) than female (33%). Functional measurements showed that in WT, K loading diminished HCTZ-dependent FENa by 53% in females and 42% in males. FENa was not reduced by high-K diet in KO mice. High-K intake significantly increased HCTZ-induced kaliuresis (EK) by 129% in WT male, but reduced EK in WT female (68%), KO male (51%) and KO female (55%). NHE3 expression was significantly reduced with high-K diet in all groups. There was no hyperkalemia in any group.

Conclusions: These results suggest that i) NCC activity decreases in response to a high-K diet, in part through decreased protein expression; ii) these responses depend on gender as well as on the presence of the AT1a receptor; iii) Proximal tubule function is also regulated by chronic high-K intake.

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SA-PO1049

Signaling through the Angiotensin-II Type 2 Receptor (AT2R) Suppresses AT1R-Induced SGK1 Phosphorylation and NHE3 Activity Vikram Suri,[2] David Pearce.[1] *[1]University of California San Francisco, San Francisco, CA; [2]University of California- San Francisco, San Francisco, CA.*

Background: Activation of the Angiotensin Type 1 Receptor (AT1R) by Angiotensin-II has been shown to enhance proximal tubular sodium reabsorption via induction of NHE3, as well as distal sodium reabsorption via ENAC. Evidence from the literature supports a role for SGK1 as a critical signaling intermediate in the activation of both transporter systems. The Angiotensin Type 2 Receptor (AT2R) is a well-described receptor that has been shown to exert beneficial effects on blood pressure and natriuresis, and these effects are hypothesized to occur through antagonism of AT1R. In this study, we hypothesized that AT2R suppresses Angiotensin-II-mediated induction of SGK1 activation by AT1R.

Methods: HEK293 cells were transfected with constructs expressing AT1R, AT2R, or both, and stimulated with Angiotensin-II. In order to correlate suppression of SGK1 phosphorylation with transporter activity, we measured the Na-dependent recovery from an acid load, as a marker of NHE3 activity (using Bafilomycin A1 and 1uM EIPA to inhibit the v-H^+-ATPase and NHE1, respectively). MDCK-2 cells were transfected with constructs expressing AT1R, AT2R, or both, loaded with the pH-sensitive dye BCECF-AM, stimulated with Angiotensin-II, and subjected to an acute acid load. Cytosolic pH was measured using ratiometric fluorescence measurements and calibration with Nigericin clamp.

Results: In these experiments, AT2R consistently suppressed AT1R-mediated SGK1 phosphorylation (at S422) by approximately 50% at 30 minutes (as measured by immunoblot). In addition, our data suggests that this suppression may occur through delayed kinetics of SGK1 phosphorylation. In response to an acute acid load, MDCK-2 cells that co-express AT1R and AT2R showed diminished/delayed recovery from an acid load (dpHi/dt), as compared to cells that express either AT1R or AT2R alone.

Conclusions: We conclude from these data that co-expression and activation of AT2R suppresses AT1R-mediated SGK1 phosphorylation and downstream NHE3 activation, and these effects may underlie the observed natriuretic effect of AT2R agonists.

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SA-PO1050

Probenecid Downregulates Pendrin and Enhances Hydrochlorothiazide–Induced Diuresis Sharon L. Barone,[1,2] Jie Xu,[1] Kamyar A. Zahedi,[1,2] Marybeth Brooks,[1] Manoocher Soleimani.[1,2] *[1]University of Cincinnati, Cincinnati, OH; [2]Research Services, Veterans Administration, Cincinnati, OH.*

Background: The inactivation or inhibition of NCC or pendrin does not cause any overt salt wasting under baseline conditions. However, double deletion or inactivation of NCC and pendrin causes severe salt wasting in rodents, indicating an important role for pendrin in compensatory salt absorption in the setting of NCC inhibition. Probenecid is a uricosuric agent that inhibits the organic anion transporters (OAT) in the proximal tubule and is used in the treatment of hyperuricemia and gout. In addition, probenecid inhibits the ATP transporter Pannexin 1 in the proximal tubule (PT) and the collecting duct, downregulates pendrin in mammary gland cells and possesses a positive ionotropic effect in the heart. We hypothesized that pretreatment with probenecid will downregulate pendrin, and consequently enhances hydrochlorothiazide (HCTZ) diuresis.

Methods: Male Sprague Dawley rats were treated with probenecid i.p. at 250 or 100 mg/kg/day for 6 days and then received HCTZ daily for 4 days while being maintained on probenecid. Balance studies were performed and expression levels of pendrin and AQP-2 in the kidney were estimated using double immunofluorescence labeling.

Results: Urine output increased from 9.8 at baseline to 15.9 ml/24 hrs after 10 days of Probenecid at 250 mg/kg ($p<0.02$, n=5). Treatment with HCTZ alone for 4 days caused a mild diuresis, with urine output increasing to 13.8 ml/24 hrs ($p>0.05$, vs. baseline, n=5). However, rats pretreated with Probenecid for 6 days exhibited a profound diuresis when HCTZ was added for 4 additional days, with urine output increasing to 42.9 ml/day, a more than 300% increase vs. rats treated with either Probenecid or HCTZ ($p<0.003$ vs. both groups, n = 5). In the absence of pretreatment with Probenecid, the diuresis caused by concurrent Probencid plus HCTZ treatment was similar to HCTZ alone ($p>0.05$). Immunofluorescent labeling and/or Western hybridization studies demonstrated a significant reduction in the expression of pendrin and AQP2 in the kidney cortical collecting duct/cortex of probenecid treated rats.

Conclusions: Probenecid pretreatment downregulates pendrin and AQP2 and robustly enhances diuresis by HCTZ-mediated NCC inhibition in the distal nephron. We propose that Probenecid followed by HCTZ is a strong diuretic regimen for fluid overloaded states and also prevents the hyperuricemia that is caused by HCTZ.

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SA-PO1051

Furosemide Is a Potassium-Sparing Diuretic in Mice on a Low Sodium High Potassium Diet Bangchen Wang, Donghai Wen, Jun Wang-France, Steven C. Sansom. *University of Nebraska Medical Center, Omaha, NE.*

Background: Because of its cardio-protective benefits, a low Na, high K diet (LNaHK) is often warranted in conjunction with diuretics for hypertensive patients. However, it is necessary to understand the renal handling of such diets in order to choose the best diuretic. As previously shown by our lab, furosemide, a K-wasting diuretic, decreased renal K clearance (CL_K) in mice on LNaHK by inhibiting the net K^+ secretion in the thick ascending limb (TAL). Given that furosemide acidifies the urine by increasing acid secretion from TAL and that distal K^+ secretion is affected by urine pH, we hypothesized that furosemide reduces distal K^+ secretion via the large conductance, Ca-activated K channel (BK).

Methods: Wild-type (WT) and BK-β4 knockout mice (KO) were kept on LNaHK (0.01% Na, 5% K) for 7 days. After intraperitoneal injections of vehicle, furosemide (furo; 15 mg/kg), amiloride (amil; 5 mg/kg), or amil + furo, mice were placed into metabolic cages to collect urine for 12 hours. Another group of WT were kept on LNaHK for 7 days and placed into metabolic cages to collect urine for 24 hours with access to either regular water or alkaline furosemide water (0.1 mg/mL, pH 8.8). The mice were then sacrificed and the [K^+] and pH were measured from blood and urine samples. Fluorescence immunohistochemistry (FIHC) was performed on paraffin-embedded kidney sections stained for BK-α.

Results: In WT, the furo group exhibited lower urine pH and lower CL_K than vehicle. In KO, the furo group exhibited a lower urine pH but a similar CL_K compared to vehicle. The amil + furo group had a lower CL_K than the amil group of both WT and KO. There is a positive linear association between CL_K and urine pH in WT but not BK-β4 KO on LNaHK. FIHC showed that BK-α was localized in the apical membrane of connecting tubule cells (CNT) in WT vehicle group. However, BK-α was localized in the cytoplasm of CNT in the WT furo group and both groups of KO. Urine pH and CL_K were not different between WT on LNaHK with regular water and alkaline furosemide water.

Conclusions: These results suggest that in mice on LNaHK, in addition to suppressing net K^+ secretion in TAL, furosemide inhibits BK-αβ4-mediated K^+ secretion in the distal nephron by acidifying the urine. These actions together make furosemide a K-sparing diuretic in the setting of LNaHK.

Funding: NIDDK Support

SA-PO1052

RNA-Seq Reveals the Transcriptome Changes of Mouse Collecting Duct Cells in Response to Urinary Flow and Primary Cilia Sensing Sami G. Mohammed,[1] Francisco J. Arjona,[1] Zeineb Z. Bakey,[2] Wynand Alkema,[4] Sacha Van hijum,[4] Miriam Schmidts,[3,2] René J. Bindels,[1] Joost Hoenderop.[1] *[1]Physiology, Radboud University Medical Center, Nijmegen, Netherlands; [2]Human Genetics, Radboud University Medical Center, Nijmegen, Netherlands; [3]University College London (UCL), London, United Kingdom; [4]Centre for Molecular and Biomolecular Informatics, Radboud University Medical Center, Nijmegen, Netherlands.*

Background: External cues such as mechanical forces generated by fluid flow play a crucial role in renal physiology. Studies have shown that renal tubular cells respond to mechanical stimuli generated by urinary flow, to regulate the activity and abundance of electrolyte transporters including ion channels. The aim of this study is to reveal the transcriptome changes of tubular epithelia in response to fluid flow and determine the role of primary cilia in this process.

Methods: IMCD3 (inner-medullary collecting duct) cells without cilia were generated using CRISPR/Cas9 technology. Cells were seeded onto μ-slide ibidi chambers and subjected to either static or physiologically relevant fluid flow (~0.7 dyne/cm^2) for 3 h at 37 ^{0}C. RNA was isolated and prepared for RNA-seq by next generation sequencer.

Differentially expressed genes with fluid flow between ciliated and unciliated cells were identified by applying statistical models and validated by RT-qPCR.

Results: The absence of cilia in two independent knockout IMCD3 cell lines (*Ift140* KO or *Dync2h1* KO) and the presence of cilia in one control cell line was confirmed by immunocytochemistry for the cilia marker ARL13b. RNA-seq analysis of ciliated cells subjected to fluid flow showed upregulation of 1379 genes and repression of 1294 genes compared to static control cells (adjusted $p < 0.05$). Several known flow-sensitive genes, such as *Ptgs2* and *Ccl2* were significantly upregulated with fluid flow. Interestingly, fluid flow sensing by primary cilia triggers a transcriptomic response of only 54 genes including genes linked to the regulation of the activity of the epithelial Na^+ channel ENaC, the activity of aquaporins, tight junction permeability, iron transport, phosphate transport, and bicarbonate handling.

Conclusions: Fluid flow elicits a transcriptomic response in the collecting duct of the kidney. The role of primary cilia in this response is restricted to 54 genes, of which 16 are involved in the primary function of the collecting duct, namely ion (principally Na^+) and water (re)absorption.

Funding: Government Support - Non-U.S.

SA-PO1053

A Truncation Mutant Targets Wild-Type NKCC1 to the Apical Membrane of Epithelia Rainelli Koumangoye,[2] Salma Omer,[1] Eric J. Delpire.[3] *[1]Anesthesiology, Vanderbilt University Medical Center, Nashville, TN; [2]Anesthesiology, Vanderbilt University Medical Center, Nashville, TN; [3]Anesthesiology, Vanderbilt University Medical Center, Nashville, TN.*

Background: We recently reported the case of a 13-year old patient with complete gastrointestinal and bladder shut-downs; thyroid-, parathyroid-, and pancreatic-insufficiencies; and orthostatic intolerance. The patient carries a *de novo* mutation in SLC12A2, the gene encoding the Na-K-2Cl cotransporter-1 or NKCC1. The 11 bp deletion resulted in a *non-functional* transporter with a shorter cytosolic COOH-terminal tail. Presence of the mutant transporter was shown to increase the amount of dimer, indicating the possibility that the mutant transporter exerts dominant-negative effects on wild-type transporter. No dominant-negative effects were observed in *Xenopus laevis* oocytes.

Methods: In this study, we used fluorescent-tagged wild-type and mutant NKCC1 transporter cDNAs transfected in HEK293 and MDCK cells to examine cell membrane trafficking. HEK293 cells were grown on glass coverslips, whereas MDCK cells were grown on glass coverslips, permeabilized support, and matrigel.

Results: Cells transfected with mutant NKCC1 showed rounding and disruption of well-organized honeycomb-like structures. The overall NKCC1 signal was markedly reduced, indicating that the mutant transporter significantly affected expression of the wild-type transporter. In polarized MDCK cells, most of the mutant transporter signal was observed on the apical membrane. The mutant transporter also affected the formation of MDCK cysts in 3-D cultures, as we observed the presence of multiple lumens per cyst. To test whether mutant NKCC1 affected the trafficking of the wild-type cotransporter, co-transfection experiments with tdTomato- and EGFP-tagged transporters were performed. We demonstrated that the mutant transporter caused trafficking of wild-type cotransporter to the apical membrane. The NKCC1 mutant transporter, however, did not affect the overall polarity of the cells, as the alpha subunit of the Na^+/K^+-ATPase was still observed on the basolateral membrane.

Conclusions: Our data demonstrate that expression of a truncated Na-K-2Cl cotransporter in epithelia causes targeting of the wild-type cotransporters to the wrong membrane and also affects proper lumen formation in MDCK cysts. These observations may explain the multisystem dysfunction that is observed in the patient.

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SA-PO1054

Cathepsin B Mediated ENaC Activation in Nephrotic Syndrome Alexey Larionov,[1] Abdel A. Alli,[2] Geraldine Mollet,[3] Franziska Theilig.[1] *[1]University of Fribourg, Fribourg, Switzerland; [2]University of FL, Gainesville, FL; [3]Inserm U1163, Paris, France.*

Background: Patients with nephrotic syndrome (NS) often present symptoms of volume retention, such as edema formation or hypertension. The primary dysregulation was localized to the renal cortical collecting duct and involves an inappropriate activation of the epithelial sodium channel, ENaC. Plasma proteases passing the leaky glomerular filter were made responsible; however clinical observations demonstrate volume retention before the onset of proteinuria.

Methods: To elucidate its relationship and the underlying mechanisms, inducible podocyte-specific^{Cre}; Nphs2$^{fl/fl}$ developing FSGS with NS was used.

Results: Analysis of renal functional parameters from NS mice revealed sodium retention between day 4 – 7, hypertension and proteinuria starting at day 10 and 12 after FSGS induction. Morphological and biochemical analysis of NS mice kidneys demonstrated at 5 and 9 days increased full-length α- and γENaC expression and proteolytical cleavage of αENaC, and at 17 days increased full-length ENaC and cleaved subunit expression. Aldosterone and vasopressin levels remained unaltered. Urine analysis from NS mice revealed proteolytic activity starting at day 2 after FSGS induction which increased over the time. Urine from day 2 – 9 of NS mice was separated by HPLC and proteases of proteolytic fractions were identified by mass spectrometry. From the identified proteases cathepsin B cleaved αENaC and cathepsin D and legumain cleaved γENaC and all of them resulted in increased ENaC activity.

Conclusions: We identified cathepsin B induced proteolytical activation of αENaC as a new mechanism of volume retention in NS early in FSGS development. Cathepsin D and legumain are new γENaC cleaving proteases; their role needs to be further clarified.

Funding: Government Support - Non-U.S.

SA-PO1055

A High Salt Diet Suppressed CXCL9 and CXCL10 in Proximal Tubules through the IFNγ-JAK1-STAT1 Signaling Pathway Yohei Arai,[1] Daiei Takahashi,[1] Kenichi Asano,[3] Masato Tanaka,[3] Mayumi Oda,[2] Shigeru B. Ko,[2] Minoru S. Ko,[2] Shintaro Mandai,[1] Naohiro Nomura,[1] Tatemitsu Rai,[1] Shinichi Uchida,[1] Eisei Sohara.[1] *[1]Department of Nephrology, Graduate School of Medicine, Tokyo Medical and Dental University, Bunkyo-ku, Japan; [2]Department of Systems Medicine, Keio University School of Medicine, Shinjuku-ku, Japan; [3]Laboratory of Immune regulation, School of Life Science, Tokyo University of Pharmacy and Life Sciences, Hachioji-shi, Japan.*

Background: The mechanisms of immunosuppression by salt remain unknown, despite the existence of many clinical evidences indicating that salt loading protects proximal tubules from injury. Therefore, we investigated the mechanisms of immunosuppression by salt in proximal tubules *in vitro* and *in vivo*.

Methods: We focused on cytokine-related gene expression profiles suppressed in kidneys of mice fed a high salt diet using microarray analysis and quantitative RT-PCR. We investigated the mechanism of these cytokine suppressions by salt using a cultured line of human proximal tubular epithelial cells (HK2) *in vitro*. Then, we confirmed this mechanism could apply equally to kidneys of mice fed a high salt diet *in vivo*.

Results: We found that IFNγ inducible chemokine ligands, CXCL9 and CXCL10, and a specific receptor, CXCR3, were suppressed in kidneys of mice fed a high salt diet using microarray analysis and quantitative RT-PCR. Then, we revealed that a high salt concentration suppressed these CXCLs induced by IFNγ in HK2 cells using ELISA. We demonstrated that a high salt concentration decreased IFNGR1 expression in the basolateral membrane of HK2 cells using biotinylation assay, leading to decreased phosphorylation of activation sites of JAK1 and STAT1, activators of CXCLs. JAK inhibitor canceled the effect of a high salt concentration on STAT1 and CXCLs, indicating that the JAK1-STAT1 signaling pathway is essential for this mechanism. Furthermore, we confirmed that the induction of CXCL9 and CXCL10 by IFNγ was suppressed in kidneys of mice fed a high salt diet using immunoblotting. Moreover, the phosphorylation of JAK1 was decreased in kidneys of mice fed a high salt diet.

Conclusions: A high salt diet suppresses the IFNγ-JAK1-STAT1 signaling pathway and the induction of chemokines in proximal tubules in vivo. This finding may explain how salt ameliorates certain kinds of proximal tubular injury and offer a new insight into the linkage between salt and immunity.

Funding: Government Support - Non-U.S.

SA-PO1056

Characterization of Kidney-Specific, C-Terminally Truncated Forms of WNK4 Kinase Adrian R. Murillo-de-Ozores,[3,4] Silvana Bazua-Valenti,[3,1] Alejandro Rodriguez-Gama,[3,1] Karla Leyva-Rios,[3] Norma H. Vázquez,[3,1] Chao-Ling Yang,[2] Johannes Loffing,[5] David H. Ellison,[2] Gerardo Gamba,[3,1] Maria Castañeda-Bueno.[3,4] *[1]Instituto de Investigaciones Biomedicas, UNAM, CDMX, Mexico; [2]Oregon Health & Science University, Portland, OR; [3]Molecular Physiology Unit, INCMNSZ, CDMX, Mexico; [4]Facultad de Medicina, UNAM, CDMX, Mexico; [5]Institute of Anatomy, UZH, Zurich, Switzerland.*

Background: The kinase WNK4 is an important regulator of renal salt handling. Mutations in this gene cause Familial Hyperkalemic Hypertension, mainly due to overactivation of the renal NaCl cotransporter, NCC. In addition to the full-length WNK4, we have observed shorter forms of this kinase in kidney lysates.

Methods: Western Blot, LC-MS/MS, immunoprecipitation, site-directed mutagenesis, transfection in HEK293 cells, and *in vitro* proteolytic assays were performed to characterize the short forms of WNK4.

Results: In Western blot assays, using WNK4$^{-/-}$ mice as control and two different N-terminal WNK4 antibodies, we observed lower bands (between 130 and 95 kDa) corresponding to WNK4 fragments in renal lysates of WNK4$^{+/+}$ mice. These bands were not observed in other tissue lysates. LC-MS/MS confirmed that these bands correspond to WNK4 fragments that lack a C-terminal segment. One of these WNK4 forms may be produced by proteolytic cleavage, as we found that recombinant WNK4 is cleaved when incubated with kidney lysate. This process was prevented by a Zn^{2+} chelator. In HEK293 cells, we observed that truncation of WNK4's C-terminus at several positions increases kinase's activity towards SPAK, unless the truncated segment is large enough to include the SPAK binding site. This gain of function is caused by the loss of a protein phosphatase 1 (PP1) binding site. Cotransfection of PP1 causes dephosphorylation of WNK4, while this effect is abrogated in the WNK4-PP1 binding site mutant. Biochemical evidence suggests that the WNK4 short forms detected *in vivo* may lack the SPAK binding site and thus may not behave as constitutively active kinases.

Conclusions: We show the identification of short, C-terminally truncated, and kidney-specific WNK4 forms, at least one of which may be product of proteolysis. Moreover, this work allowed us to identify a *bona fide* PP1 binding site in the C-terminal region of WNK4 that modulates its activity towards SPAK-NCC.

Funding: Government Support - Non-U.S.

SA-PO1057

Functional Human Epithelial Na+ Channel Variants in the Extracellular Beta-Ball Domain Shaohu Sheng, Jingxin Chen, Thomas R. Kleyman. *Medicine, University of Pittsburgh, Pittsburgh, PA.*

Background: Epithelial Na^+ channels (ENaC) have a key role in the regulation of extracellular fluid volume, extracellular K^+ concentration and blood pressure. Recent human genome sequencing has revealed a large number of ENaC variants. However, the functional consequences of the vast majority of human ENaC variants are unknown. In this study, we investigated several non-synonymous ENaC variants located at a beta strand within a core beta-ball structure of the extracellular domain for their functional roles.

Methods: Point mutations corresponding to the selected variants were introduced into human alpha ENaC cDNA by site-directed mutagenesis. Wild type (WT) and mutant alpha subunits, together with WT beta and gamma subunits of human ENaC were expressed in *Xenopus* oocytes by cRNA injections. Channel activities were examined by two-electrode voltage clamp. Channel densities in plasma membranes were examined by a luminescence assay using a FLAG epitope tag inserted into the extracellular domain of beta subunit. Na^+ self-inhibition was determined by measuring the decrease in current from the peak to the steady state elicited by a rapid increase in extracellular Na^+ concentration from 1 to 110 mM at -100 mV.

Results: We examined three ENaC variants located at the beta strand 7, one of the five beta-ball strands at the extracellular domain core. Oocytes expressing the R350W ENaCs showed two-fold greater amiloride-sensitive currents than cells expressing WT channels ($p < 0.001$). The variation did not significantly alter channel surface expression. The mutant channels showed a diminished Na^+ self-inhibition, which correlates to an increased open probability. The V351A mutant had a reduced current (55% of WT, $p < 0.001$), whereas G355R showed an increased current (1.6-fold of WT, $p < 0.01$).

Conclusions: R350W and G355R are gain-of-function ENaC variants, and V351A is a loss-of-function variant. R350W is an ENaC gating modifier via suppressing Na^+ self-inhibition. Our results suggest that the core beta strand containing these variants and residing at a subunit interface has an important role in the regulation of ENaC gating.

Funding: NIDDK Support, Commercial Support - Dialysis Clinic, Inc.

SA-PO1058

The Different Modulations of NCC by ERK 1 and ERK 2 Signaling Pathway Xiuyan Feng,[1] Shan Chen,[1] Jia Xiao,[1] Xinxin Chen,[1] Hui Cai.[1,2] *[1]Emory University School of Medicine, Atlanta, GA; [2]Nephrology, Atlanta VA Medical Center, Decatur, GA.*

Background: In our previous studies we found that ERK 1/2 knock-down increased NCC expression in cell experiments. Staub group previously reported that total NCC abundance was siginificantly decreased in the nephron-specific *Nedd4L* knockout (KO) mice. ERK1 and ERK2 are presumed to be functionally redundant given their 84% sequence homology, shared upstream activators, and similar substrate specificity. Our preliminary data indicated that ERK 1 and ERK 2 have different roles in NCC modulation *in vivo*. However, the relationship between ERK 1/2 and Nedd4-2 as well as the effects of unique ERK 1 and ERK 2 on NCC remain not entirely clear. In this study, we investigated the different roles of ERK 1 and ERK 2 in NCC modulation in cells and in both ERK1 KO mice and Pax8+cre+ERK2$^{flox/flox}$ mice.

Methods: Cell culture, western blot analysis, siRNA knock-down experiments, ERK 1 global KO and Pax8+cre+ERK2$^{flox/flox}$ mice were used in this study.

Results: Firstly, we knocked down ERK1 or ERK2 expression separately in Cos-7 cells cotransfected with NCC. We found that ERK1 knock down increased NCC expression while ERK 2 knock down decreased NCC expression. To further explored the different roles of ERK 1 and ERK 2 on NCC. We generated the inducible nephron-specific ERK 2 KO (ERK 2 KO) mice by feeding Pax8+cre+ERK2$^{flox/flox}$ mice with doxycycline 1g/L for 14 days. Western blot results showed that the NCC expression in ERK1 global KO mice increased by 27.7%, whereas in ERK 2 KO mice NCC decreased to 62.1% compared to those in WT mice. We also found that total Nedd4-2, phospho-S448-Nedd4-2 and phospho-S328-Nedd4-2 were decreased to 50.4%, 52.5% and 76.8% respectively in ERK1 KO mice, while they were increased by 1.46, 1.5 and 3.11 folds in ERK 2 KO mice. We further tested the effects of low salt diet (LSD) on NCC abundance in ERK 2 KO mice fed with LSD for 14 days. We found that NCC abundance decreased to 68.8% while 14-3-3 gamma expression increased by 2.07 folds and total NEDD4-2 increased by 2.47 folds compared with that in WT mice.

Conclusions: All data suggested that ERK 1 and ERK 2 signalings have different role in regulationg NCC likely through modulating Nedd4-2 and 14-3-3 gamma. However, the interactions among MAPK- ERK1/2 signaling pathway, Nedd4-2 and 14-3-3 gamma need to be further investigated in the future studies.

Funding: Veterans Affairs Support

SA-PO1059

A Novel Molecule, Gephyrin, Functionally Associates with ClC-5 Chloride Channel in Response to Metabolic Acidosis in the Mouse Kidney Miyuki Ogawa,[1] Hisato Sakamoto,[3] Makoto Itakura.[2] *[1]Nephrology, Kitasato University, SAGAMIHARA, Japan; [2]Biochemistry, Kitasato University, SAGAMIHARA, Japan; [3]Nephrology, Graduate School of Medical Science, Kitasato University, SAKAMIHARA, Japan.*

Background: ClC-5 channel is co-localized with the V-ATPase in subapical endosomes of renal proximal tubule (PT) and α-intercalated cells. ClC-5 may play a crucial role in regulating both endocytosis and sorting of the acid transporters. However the regulatory molecule associated with ClC-5 has not been elucidated. This study aimed to identify the associated molecule and to examine its physiological roles in the regulation of intracellular sorting of ClC-5 in response to metabolic acidosis.

Methods: Following to immunoisolation of ClC-5-bearing vesicles using the magnetic beads coated with originally generated specific antibody (Ab), we identified specific binding molecules using the analysis by LC-MS and immunoprecipitation assays. To examine the physiological role of the molecule, we prepared the fractions enriched for plasma membrane (P1) and endosomal membrane (P2) using differential centrifugation under conditions with or without NH_4Cl-induced acidosis. The protein abundances of transporters and associated molecule were assessed by Western blot. The co-localization of CLC-5 and associated proteins were also imaged using confocal microscopy.

Results: We identified gephyrin as a specific associated molecule with ClC-5 by LC-MS. Immunohistochemistry showed the predominant expression of gephyrin and its co-localized with ClC-5 in the apical membrane of PT compared with that of distal tubule. In addition, gephyrin was co-immunoprecipitated with specific Ab against ClC-5 using crude homogenates of mouse kidney. Mice given NH_4Cl in drinking water developed metabolic acidosis within 2 days of acid intake. ClC-5 protein abundance was relatively decreased in P1 and increased in P2 after 6 days of acid loading. In contrast the protein abundances of gephyrin were increased by 230% in P1 and 120% in P2 under the same condition of acid loading.

Conclusions: ClC-5 might be functionally anchored by gephyrin in the apical membrane of PT. Furthermore, gephyrin may implicate in the self-assemble into a scaffold to reconstruct and strengthen plasticity following to the sorting of ClC-5 from plasma membrane to intracellular vesicles after acid loading.

Funding: Commercial Support - Pfizer

SA-PO1060

Low Chloride Increased NCC Expression through Modulating Both ERK1/2 and SPAK Signaling Pathways Jia Xiao,[1] Xiuyan Feng,[1] Xinxin Chen,[1] Shan Chen,[1] Hui Cai.[1,2] *[1]Emory University School of Medicine, Atlanta, GA; [2]Nephrology, Atlanta VA Medical Center, Decatur, GA.*

Background: Previous studies have showed that low chloride concentration activates NCC activity via WNK-SPAK signaling pathway. We also found that ERK1/2 signal pathway plays an important role in regulating NCC. We previously showed that ERK 1/2 phosphorylation increased in SPAK KO mice, suggesting that SPAK signaling affects ERK 1/2 signaling pathway. Therefore, we investigated whether low chloride concentration affects NCC expression through modulating interaction between ERK1/2 and SPAK signaling pathways.

Methods: Cell culture, transfection, siRNA knock-down, and western blot analysis were used in this study.

Results: We first treated the Cos-7 Cells transfected with NCC with different low chloride concentrations (chloride concentrations decreased from 142 to 7 mEq/L) for 12 hours. The western blot analysis showed that NCC protein expression increased with the decrease in chloride ion concentration in a dose-dependent manner while ERK1/2 phosphorylation decreased and S373-SPAK phosphorylation increased. To further confirm the role of MAPK-EKR1/2 signaling pathway in modulating NCC in response to low chloride concentration, we knocked down the ERK1/2 expression in Cos-7 cells using ERK1/2 siRNA and treated the cells with the low chloride solution. The western blot analysis showed that the basal NCC expression increased in the ERK1/2 siRNA knocked down group compared with the control group transfected with the scramble siRNA as expected. However, NCC expressions further increased with lowering chloride concentration while ERK 1/2 phosphorylation was also further decreased. We also found that SPAK phosphorylation increased with the ERK1/2 siRNA knocked down. To investigated the interation role of SPAK signal pathway with ERK 1/2 signaling, we knocked down SPAK expression in Cos-7 cells using SPAK siRNA and treated the cells with some chloride solutions. We found that the increase in NCC expression was partially reversed by SPAK Knocked down while the ERK1/2 phosphorylation increased.

Conclusions: These data suggested that both MAPK-ERK1/2 and SPAK signaling pathways are involved in the regulation of NCC in response to low chloride stimulation.

Funding: Veterans Affairs Support

SA-PO1061

High Cholesterol Diet (HCD) Downregulates BK Channels in the Rabbit Cortical Collecting Duct (CCD) Rolando Carrisoza-Gaytan,[1] Daniel A. Flores,[2] Lisa M. Satlin.[1] *[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Mount Sinai School Of Medicine, New York, NY.*

Background: The apical BK channel in the CCD mediates flow-induced K secretion (FIKS) and adaptation to K loading. Preliminary results had shown that 4-5 wks HCD increases plasma membrane cholesterol content in the CCD, blunts flow-stimulated but not basal net Na absorption (JNa), and inhibits FIKS (~37%) in rabbit CCDs. As studies in endothelial cells and osteoblasts identify genomic effects of a HCD (Physiol Genomics, 2012; Acta Pharm Sinica, 2011), we speculated that a HCD may reduce abundance of BK channels in the CCD.

Methods: NZW rabbits were randomized after weaning to receive either a standard (Base Diet; BD) or a cholesterol enriched diet (HCD; 0.3%) for 4-5 wks, at which time the animals were sacrificed. Kidneys were removed and CCDs microdissected for (i) microperfusion to measure JNa and net K secretion (JK), (ii) quantitative PCR to assess abundance of mRNA encoding Slo1 and (iii) immunoperfusion with anti-BKα Ab to examine plasma membrane expression.

Results: In 6 HCD CCDs, JNa increased from 13.3±6.6 to 30.1±8.5 pmol/min.mm (P≤0.01) in response to an increase in flow rate from 1 to 5 nl/min.mm; this flow-stimulated increase in JNa was less than observed in BD (25.9±4.3 to 73.3±7.0; n= 4; P≤0.01). In the same 6 HCD CCDs, a 5-fold increase in flow rate increased JK from -4.9±1.3 to -11.5±2.2 pmol/min.mm (P≤0.04), transport rates half those observed in BD (-11.3±4.0 to -21.2±1.6; n= 4; P≤0.03). Slo1 mRNA expression in HCD CCDs (n=6 samples; 10-20 mm total tubular length/sample) tended to be less than in BD CCDs (n=3 samples; 13-25 mm/sample; p=0.07). The relative apical/whole-cell expression of BKα was less in HCD principal (Δ=27±0.7%) and intercalated (Δ=24±1.0 %) cells than in BD cells (n=4 rabbits per diet; P≤0.001).

Conclusions: Our results suggest that HCD downregulates the transcription and apical expression of BKα and thus inhibits FIKS in the rabbit CCD. Whether HCD also reduces expression of other channels necessary for K secretion, including ENaC, ROMK and Ca2+ channels, remains to be explored.

Funding: NIDDK Support

SA-PO1062

14-3-3 γ Inhibits BK Activity by Enhancing Its Degradation through a Lysosomal Pathway via an ERK1/2 Signaling-Dependent Mechanism Shan Chen,[1] Xiuyan Feng,[1] Jia Xiao,[1] Xinxin Chen,[1] Hui Cai.[1,2] *[1]Emory University School of Medicine, Atlanta, GA; [2]Nephrology, Atlanta VA Medical Center, Decatur, GA.*

Background: 14-3-3 γ belongs to a family of multifunction regulatory proteins that mainly bind to phosphorylated Ser/Thr residues in the target proteins. Our previous data showed that 14-3-3 γ inhibits Big K (BK) channel activity and its protein expression through altering ERK1/2 signaling pathway. Thus, we hypothesized that 14-3-3 γ inhibits BK protein expression by altering BK protein degradation via ERK1/2 signaling.

Methods: Cell culture, transfection, western blot analysis, immunoprecipitation, and WT mice were used in this study.

Results: To determine the inhbitory effects of 14-3-3 on BK channel expression, we first did transfection experiments in Cos-7 cells. We found that overexpression of 14-3-3 γ significantly decreased BK protein expression, and knockdown of 14-3-3 γ expression obviously increased BK protein expression. To confirm that 14-3-3 γ modulates BK protein expression through an ERK1/2 signaling pathway, we performed ERK1/2 inhibition experiments. Cos-7 cells were cotransfected with Flag-14-3-3 γ and myc-BK for 48 hours with or without ERK1/2 inhibitior U0126 treatment. We found that inhibition of ERK1/2 phosphorylation abolished 14-3-3 γ-mediated inhibitory effects of BK protein expression. To explore whether overexpression of 14-3-3γ decreased BK protein expression through a lysosomal degradation pathway, we determined the effects of lysosomal inhibitor, bafilomycin A1 (Baf A1) on BK protein expression in Cos-7 cells. We found that Baf A1 treatments reversed the inhibitory effects of 14-3-3 γ on BK protein expression. We further investigated whether 14-3-3 γ involved in BK protein ubiquitination in HEK 293 stably expressing BK cells transiently transfected with 14-3-3 γ plasmid. We found that overexpression of 14-3-3 γ increased BK protein ubiquitination while increasing ERK 1/2 phosphorylation.

Conclusions: These data suggested that 14-3-3 γ inhibits BK protein expression by increasing BK ubiquitination, leading to enhanced BK degradation through a lysosomal pathway via an ERK1/2 signaling-dependent mechanism.

Funding: Veterans Affairs Support

SA-PO1063

Differential Sodium Ion Distribution in Muscle and Skin and Its Relationship to Hydration Status in Advanced CKD Nicos Mitsides,[1] Damien J. Mchugh,[2] Jane Alderdice,[1] Agnieszka Swiecicka,[2] Paul E. Brenchley,[1] Geoff J. Parker,[2] Sandip Mitra.[1] *[1]Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom; [2]The University of Manchester, Manchester, United Kingdom.*

Background: Body sodium (Na) excess is an important determinant of cardiovascular risk in chronic kidney disease(CKD). Its effect is mediated, predominantly, through extracellular fluid (ECW) expansion. Although ECW is assumed to be a homogenous isotonic compartment, the relative proportions of water & Na ions in different tissue is unclear in CKD. We aim to quantify Na concentration in muscle(M) and subcutaneous(SC) tissue in relation to hydration states in advanced CKD.

Methods: Na ionic concentration was measured using a 3T MRI scanner & a dual-tuned $^{1}H/^{23}Na$ coil. The lower leg of 8 healthy controls(HC) & 20 CKD stage 5 patients(eGFR<15 ml/min, not on dialysis) was imaged & the M & SC Na concentration derived using saline calibration phantoms. Overhydration index(OH), ECW, intracellular(ICW) & total body water(TBW) was assessed using multifrequency bioimpedance spectroscopy(BIS). Blood Pressure(BP) was assessed by 24hr ambulatory monitoring & Na balance calculated using 3 day food diary & 24 hr urine Na measurements.

Results: The HC & CKD cohorts were similar in age(HC: 50±14.3yr;CKD 53±9.3yr;p=0.60) & sex(50% male) but the CKD cohort had significantly higher comorbidity (Charlson Index:HC 1.0 v CKD 3.0;p<0.01). The MR derived M Na concentrations were not different between the 2 groups (CKD 24.9±5.5mmol/L;HC 23.1±2.7mmo/L,p=0.38). However, CKD participants had higher SC Na concentration than HC(CKD 25.8±10.2mmol/L;HC 19.5±5.0mmol/L,p=0.04). M Na was strongly correlated to BIS measured ECW volume(ECW/TBW:r=0.502,p=0.01). Higher M Na was also associated with increased ECW/ICW ratio(r=0.533,p<0.01) & higher systolic BP(r=0.449,p=0.02). Both M & SC Na correlated with OH(M: r=0.536,p< 0.01;SC:r=0.452,p=0.02). Baseline Na intake was 94.9±32.3mmol/24hr for CKD & 113.1±46.9mmol/24hr for HC(p=0.23) while urine Na excretion was 109.5±41.7 & 171.3±170.5 mmol/24hr respectively(p=0.98).

Conclusions: The distribution of Na ions appears to be heterogenous in body tissues. In M, Na appears to be accompanied by water (osmotically active) & closely linked to ECW expansion. On the other hand, the higher SC Na concentration seen in CKD is dissociated from ECW content & BP, implying an alternative pathophysiology, unrelated to volume homoeostasis, & possibly linked to CKD & higher comorbidity.

Funding: Clinical Revenue Support

SA-PO1064

Reduced Secretion of PTH and Hypocalcemia in Systemic Heterozygous ATP2B1 Null Mice Yosuke Ehara,[1] Nobuhito Hirawa,[2] Akira Fujiwara,[2] Kouichi Tamura.[1] *[1]Yokohama City University Graduate School of Medicine, Yokohama-shi, Kanagawa, Japan; [2]Yokohama City University Medical Center, Yokohama, Japan.*

Background: We reported the association between high blood pressure and ATP2B1 gene in Japanese population through Millennium Genome Project. ATP2B1 is a gene encoding plasma membrane calcium ATPase 1 (PMCA1), which is known to be expressed throughout the body. PMCA1 plays a role of discharging Ca ions from the inside of the cell to the outside of the cell, and strictly adjusts the intracellular Ca concentration. In subsequent studies we reported that systemic heterozygous ATP2B1 deficient mice exhibited hypertension and reduced eNOS activity, NO production was involved. In addition, it was confirmed that the mouse exhibited hypocalcemia. Therefore, in order to investigate the mechanism of hypocalcemia, we studied bone, small intestine, kidney and parathyroid gland, which are important organs related to Ca metabolism.

Methods: Blood test, urinalysis, bone formation, bone resorption marker, bone density, bone tissue, and the expression levels of Ca regulatory protein in the small intestine in the Systemic heterozygous ATP2B1 deficient mice ($ATP2B1^{+/-}$) and the control mice ($ATP2B1^{+/+}$) were compared.

Results: In the $ATP2B1^{+/-}$ mice, bone mineral density ($ATP2B1^{+/-}$ versus $ATP2B1^{+/+}$: 689.0 ± 12.9 versus 645.2 ±9.2 ; P<0.05), bone mass and urinary calcium excretion (0.769 ± 0.117 versus 0.330 ± 0.082 ; P<0.05) were increased, serum intact PTH (153.6 ± 41.0 versus 324.4 ± 41.4 ; P<0.05) and ATP2B1 expression of intestine (0.56 ± 0.092 versus 1.00 ± 0.117 ; P<0.05) were decreased, compared with control mice. In the intestine, no significant change was observed in the expression levels of various Ca regulatory proteins other than ATP2B1.

Conclusions: Systemic heterozygous ATP2B1 deficient mice exhibited hypocalcemia, and increased bone density and decreased PTH secretion. ATP2B1 might play important roles in bone metabolism.

SA-PO1065

ApoL1 Confers pH-Switchable Ion Permeability to Phospholipid Vesicles John C. Edwards. *St. Louis University, Saint Louis, MO.*

Background: Variants in ApoL1 confer risk of certain chronic kidney diseases. ApoL1 is thought to function as an ion channel but reports vary substantially. We sought to characterize ApoL1 ion permease activity with the hope that it may provide insight into ApoL1-associated kidney disease.

Methods: Recombinant His-tagged ApoL1 was purified by Ni-affinity and gel filtration. Ion permeability was assessed using vesicle-based, voltage dependent Cl and K efflux assays using ion selective electrodes. ApoL1 membrane association was measured by mixing protein with lipid, Na_2CO_3 extraction to remove peripherally-associated protein, and isolation of the remaining integral membrane protein by floating the vesicles through a sucrose cushion.

Results: Addition of Apol1 to vesicles yields robust Cl selective permeability. The activity is dependent on pH at which protein and membranes interact, with a sharp drop above pH 6.0. K permeability is minimal at any pH when protein and vesicles are mixed and assayed at the same pH. However, K permeability is detected when protein and vesicles are allowed to interact at low pH and then shifted to neutral pH for efflux assay. K permeability is greatest if protein and vesicles are mixed at pH 5.5-6.0 and then assayed at pH 7.5. pH switch not only activates the K permeability but also partially inactivates the Cl permeability. Both Cl and K permease activities are linearly dependent on mass of protein, and are dependent on lipid composition, requiring the presence of negatively charged phospholipids. The K permeability requires the presence of Ca ion. Membrane association assays demonstrate pH-sensitive membrane insertion which occurs at low pH, requires the presence of negatively charged phospholipids, and is stable when pH is shifted back to neutral after insertion takes place.

Conclusions: ApoL1 inserts into vesicles at low pH and confers Cl-selective permeability if pH remains low, or switches to K-selective permeability if the pH is neutralized. The data suggest a model in which ApoL1 in the acidic and low Ca environment of the endocytic pathway could insert into membranes and confer Cl selective permeability, and if subsequently targetted to the plasma membrane where it would be exposed to neutral pH and Ca, switch to K permeability. This model might account for the variety of ApoL1 effects that have been reported in both trypanosomes and cultured mammalian cells.

SA-PO1066

MRI Spatial and Temporal Characterization of Acute and Chronic Hypotonic Brain Edema Marta Tejedor,[2] Giovanna Martín,[3] Ángel Nava,[3] Clara Usón,[3] Javier Soto,[3] Alberto Tejedor jorge.[1] *[1]Fundación para la Investigación Biomédica del Hospital General Universitario Gregorio Marañón, Madrid, Spain; [2]Hospital Infanta Elena, Valdemoro, Madrid, Spain; [3]Universidad Complutense de Madrid, Madrid, Spain.*

Background: Hypotonic brain edema has not been studied in depth with imaging techniques such as MRI. **Aims:** to assess spatial and temporal responses within different areas of the brain to hypotonicity, and differences between acute and chronic hyponatremia.

Methods: Chronic hyponatremia was induced in Wistar rats by intraperitoneal (ip) injection of desmopressin (0.4 ug/kg/d), hyposodic liquid diet and free access to water for 7 days (G1). A group of control normonatremic animals was fed with pellet based diet (G2). Brain edema was studied with MRI at baseline and after ip injection of either 10% of body weight in water (both G1 and G2) or 2 mL of NaCl3% for every 100 grams of body weight (G1) over 120 minutes. ADC (apparent diffusion coefficient) assessed the degree of brain edema in different regions of interest: cortex, hypothalamus, nervous fibers, extra-pyramidal system.

Results: Baseline [Na] were 147±7mmol/L (G2) and 136±7mmol/L (G1); after acute water load: 112±5mmol/L and 119±5mmol/L respectively. Baseline ADC values were lower in G1, indicating relevant brain edema. After acute water load, a further drop in the ADC levels was observed in both groups. A transient period of cellular defense where water was actively pumped outside the cells was observed, being more efficient in G1, becoming the ADC levels similar in both groups at 60 min, but worsening again at 90 and 120 min. Lateral hypothalamus was the first region to become edematous, followed by the cortex, and then, at different time points, by the extra-pyramidal system and myelinated fibers. Response to edema appeared with different time delays from the maximum degree of edema, but it seemed to follow a structural order: hypothalamus, cortex, extra-pyramidal system and fibers. Treatment of G1 with hypertonic saline (NaCl3%) induced a correction of the edema that was three times faster than the spontaneous one. Sodium concentrations went from 136±7mmol/L to 140±7mmol/L.

Conclusions: Brain response to hypotonicity is not homogeneous, and edema develops at different time points in different regions. The time course of the response to that edema is not homogeneous either. The different speed in the response to brain edema in adjacent areas suggests that damage leading to central pontine myelinolysis could be earlier than observed in clinical practice.

SA-PO1067

MT-3995, a Novel Non-Steroidal Mineralocorticoid Receptor Antagonist, Has Pharmacological Profiles Differentiated from Eplerenone and Spironolactone Kohei Kikkawa,[2] Naritoshi Shirata,[2] Misae Takakuwa,[2] Akito Nishi,[2] Taku Iguchi,[2] Hitomi Munakata,[2] Tomoko Ikeda,[3] Naomi Koyama,[2] Hidetoshi Shimizu,[2] Yoshinori Watanabe,[2] Masashi Nishio,[2] Makoto Katoh.[1] *[1]Medical Science, Mitsubishi Tanabe Pharma Corporation, Tokyo, Japan; [2]Innovative Medical Science, Mitsubishi Tanabe Pharma Corporation, Toda, Japan; [3]Discovery Technology, Mitsubishi Tanabe Pharma Corporation, Toda, Japan.*

Background: MR antagonists such as eplerenone (Epl) and spironolactone (Spi) improve outcomes in patients with heart failure. However, their use is limited because of steroid-related adverse effects and hyperkalemia risk. MT-3995 is a novel non-steroidal MR antagonist, and the clinical studies are ongoing in patients with diabetic nephropathy (P2b). This study was planned to clarify the pharmacological profiles of MT-3995, comparing with Epl and Spi.

Methods: MR selectivity was evaluated in steroid receptor binding assays. The effect on transcriptional activity was evaluated in cultured CHO cells expressing "Gain-of-function" type mutant MR (S810L). The organ protective effect was evaluated by histopathological finding in salt-loaded SHR/NDmcr-cp, measuring blood pressure via radiotelemetry, 24-hr urinary albumin excretion, mRNA levels in the kidney, and plasma drug concentrations.

Results: MT-3995 had a highly selective MR antagonistic activity with Ki value of 104 nmol/L (Epl: 84.9 nmol/L). MT-3995 (10,000 nmol/L) had almost no binding affinities for other steroid receptors (GR, PR, AR, ER). Spi and Epl enhanced the transcriptional activity in the mutant MR at therapeutic concentrations. While, MT-3995 (10,000 nmol/L or less) had no effect in the mutant MR. Chronic oral MT-3995 (1, 3, 10 mg/kg, for 4 weeks) prevented the progression of cardiorenal damage with a mild anti-hypertensive effect and suppression of pro-inflammatory and pro-fibrosis mRNA levels in the kidney (osteopontin, MCP-1, TGFb1, Col type1). The renal protective effect at 1mg/kg MT-3995 was equivalent to that of 100mg/kg Epl. The pharmacokinetic data indicated that the renal protective effect of MT-3995 was associated with the long-acting MR blockade around the Ki value all day.

Conclusions: MT-3995 is a highly specific MR antagonist, suggesting no risk of steroid-related adverse effects. MT-3995 has renal protective effect with a long-acting MR blockade around the Ki value, indicating that the avoidance of redundant Cmax elevation would be a strategy to minimize hyperkalemia risk in DN patients.

Funding: Commercial Support - Mitsubishi Tanabe Pharma Corporation

SA-PO1068

Mineralocorticoids Modulate the Expression of the Beta-3 Subunit of the Na +, K + - ATPase in the Renal Collecting Duct Macarena Rojas,[3] Pablo A. Leon,[1] Victor M. Barrientos,[3] Rodrigo Alzamora,[2] Luis F. Michea.[3] *[1]Universidad de Chile, Santiago, Chile; [2]University of Chile, Santiago, Chile; [3]Millennium Institute on Immunology and Immunotherapy, ICBM, Facultad de Medicina Universidad de Chile, Santiago, Chile.*

Background: Renal sodium reabsorption depends on the activity of the Na^+,K^+-ATPase (NKA) a/b heterodimer. Four a (a_{1-4}) and three b subunit isoforms (b_{1-3}) had been described. It is accepted that renal tubule cells express a_1/b_1. Aldosterone stimulates NKA se activity and may modulate a_1/b_1 expression. However, some studies suggested the presence of β3 in the kidney. We hypothesized that the β_3 isoform of the NKA is expressed by tubular cells of the distal nephron and is modulated by mineralocorticoids.

Methods: We studied kidney from rats (male SD) and mice (male C57BL/6). β_3 mRNA distribution was determined by qRT-PCR and *in situ* hybridization (ISH). We compared the abundance of renal β_3 mRNA to the abundance in other tissues known to express β_3 mRNA (testis, lung, liver). β_3 protein was analyzed by western blot. In addition, convoluted proximal tubules (CPT), cortical collecting ducts (CCD) and inner medullary collecting ducts (IMCD) were isolated for qRT-PCR studies. The MR-dependence of β_3 expression was studied in adrenalectomized (ADX) rodents with or without MR replacement therapy (DOCA; 7.6 mg/100 g b.w.; 5 days). We also tested the effect of the pharmacological MR blockade (Sprinololactone, SPIRO, 25 mg/kg/day)

Results: Kidney tissue express β_3 mRNA, with higher relative abundance in medulla (12.2±0.2- vs. 1.0±0.2 in cortex; n=3, $p<0.05$). ISH studies showed the preferential expression of β_3 mRNA in collecting duct principal cells of cortex and medulla. IMCD presented 4-fold higher abundance of β_3 mRNA as compared to CPT (n=4, $p<0.05$). ADX rodents showed increased β_3 mRNA and protein abundance by 3-fold and 2-fold respectively (n=4, $p<0.05$). The increase of β_3 was prevented by DOCA. SPIRO increased medullary β_3 mRNA (4-fold) and protein (2-fold, n=4, $p<0.05$). No changes in the abundance of β_1 (cortical/medullar) β_3 (cortical) were detected after ADX or Spiro.

Conclusions: We show that the β_3 isoform of the Na^+,K^+-ATPase is mainly expressed in collecting duct principal cells of renal under the modulation of mineralocorticoids. FONDECYT 1130550, FONDECYT 1171869, FONDECYT 1151423; IMII P09-016-F

Funding: Government Support - Non-U.S.

SA-PO1069

A Dual COX2-sEH Inhibitor Prevents Sorafenib-Induced Renal Injury John D. Imig,[1] Abdul Hye Khan,[1] Sung hee Wang,[2] Bruce Hammock.[2] *[1]Medical College of Wisconsin, Milwaukee, WI; [2]UC Davis, Davis, CA.*

Background: Anti-cancer drugs, vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFRi) can cause hypertension and severe glomerular injury that compromises their effective and safe use. Glomerular cells generate arachidonic acid metabolites with actions that can cause glomerular injury. Therefore, we hypothesized that a novel dual cyclooxygenase-2 and soluble epoxide hydrolase (COX-2/sEH) inhibitor, PTUPB, would decrease deleterious arachidonic acid metabolites, lower blood pressure, and prevent glomerular injury caused by the VEGFRi, sorafenib.

Methods: Sprague-Dawley male rats were administered sorafenib (20 mg/kg/d p.o.) alone or in combination with PTUPB (10 mg/kg/d i.p.) for 4 weeks. Blood pressure was measured weekly and urine and renal tissues were collected from rats after the treatment period.

Results: Sorafenib administration increased blood pressure and this elevated blood pressure reached a plateau by day 14. PTUPB treatment slowed the progression of hypertension (control = 126 ± 7 mmHg; sorafenib = 162 ± 5 mmHg; sorafenib & PTUPB = 148 ± 4 mmHg, $P<0.05$). Sorafenib-induced renal injury was significantly reduced by PTUPB treatment. Albumin to creatinine ratio in sorafenib rats was significantly elevated compared to controls (sorafenib = 18.4 ± 3.5 μg/mg; control = 1.2 ± 0.3 μg/mg). PTUPB treatment decreased albuminuria by 70% (sorafenib & PTUPB = 6.3 ± 0.7 μg/mg, $P<0.05$). Kidney histological analysis determined that glomerular injury as well as medullary fibrosis and tubular cast formation were decreased in rats administered sorafenib and treated with PTUPB.

Conclusions: In conclusion, PTUPB slows the progression of hypertension and significantly decreases glomerular and renal injury in rats administered the VEGFRi, sorafenib. These findings indicate that a novel dual COX-2/sEH inhibitor, PTUPB combats the detrimental side effects of hypertension and severe glomerular injury that compromises the effective and safe use of anti-cancer VEGFRi therapies.

Funding: NIDDK Support

SA-PO1070

Chronic ASA Administration Exacerbates Renal Damage in Hypertensive Rats Chris R. Kennedy,[1] Jean-Francois Thibodeau,[1,3] Chet E. Holterman,[2] Anthony Carter,[1] Greg O. Cron,[4] Rafael Glikstein.[5] *[1]Kidney Research Centre, Ottawa, ON, Canada; [2]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [3]ProMetic BioSciences Inc., Laval, QC, Canada; [4]The Ottawa Hospital, Ottawa, ON, Canada; [5]The ottawa Hospital, U of Ottawa, Ottawa, ON, Canada.*

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs, e.g. (Aspirin (ASA), ibuprofen, naproxen) inhibit cyclooxygenases whose eicosanoid products buffer renal vasoconstriction in hypertension (HTN) but are contraindicated in hypertensive

individuals as they increase risk for renal injury via decreased renal blood flow and GFR. However, there is little *in vivo* evidence of this phenomenon. We showed that in mice with HTN, vascular-specific deletion of the EP4 receptor (mimicking some of the downstream effects of NSAIDs) significantly reduced renal perfusion and exacerbated injury. The present study was undertaken to test the hypothesis that hypertensive renal injury would be more severe with chronic ASA administration.

Methods: Male Sprague-Dawley rats (n=5 per group) were implanted with Model 2002 Alzet osmotic minipumps loaded with vehicle or Angiotensin II (AngII) to deliver a dose of 400 ng/kg/min for 4 weeks. ASA was administered concurrently via drinking water (0.067 mg/ml) to yield a dose of 10mg/kg/day. Renal function was assessed by plasma creatinine using HPLC. Renal histology was assessed on Masson trichrome and PAS-stained kidney sections. At 0, 2, and 4 weeks, dynamic contrast-enhanced (DCE) MRI was performed using a 7T GE/Agilent MR901 and data analyzed with a two compartment filtration model (PMI, S. Sourbron) to estimate renal blood volume.

Results: After 4 weeks of AngII infusion, rats given daily ASA had significantly decreased bodyweight and appeared dehydrated. Surprisingly, despite comparable ASA dosing, this combination was associated with a 60% survival rate compared to 100% in all other groups. AngII/ASA decreased renal function vs all other groups as indicated by a doubling of plasma creatinine. Renal hypertrophy was similar in both AngII-treated groups. AngII treatment alone led to modest tubulointerstitial injury, characterized by increased tubulointerstitial fibrosis, tubular flattening/dilation and proteinaceous casts. However, the combination of ASA and AngII significantly increased the severity of tubular and glomerular injury, while DCE-MRI revealed profound loss of renal blood volume (P<0.006 vs all other groups).

Conclusions: The combination of AngII-mediated hypertension and chronic ASA intake accelerates renal function decline and injury.

SA-PO1071

Paternal Factors Contribute to Development of Superimposed Preeclampsia in the Stroke-Prone Spontaneously Hypertensive Rat (SHRSP)

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Background: We have recently demonstrated that the SHRSP strain represents a spontaneous model of superimposed PE, characterized by defective trophoblast-dependent arterial remodeling and placental insufficiency. In the present study we have evaluated the contribution of paternal genotype to the placental pathology associated with the development of superimposed PE in this model.

Methods: A paternal effect model was established by mating normotensive Wistar Kyoto females to SHRSP males (WKYxSHRSP), and compared with control (WKYxWKY) and preeclamptic (SHRSPxSHRSP) pregnancies. Maternal blood pressure (BP) was determined pre-mating and on the morning of gestation day (GD)1, 7, 9, 13, 17 and 19. On the selected dates, 24 h urine and blood samples were collected. Animals were euthanized and implantation sites isolated for morphological analyses. Fetal and placental weights were recorded on GD18 and GD20

Results: Pregnancies sired by SHRSP males displayed decreased numbers of implantation units versus control (WKYxWKY) pregnancies (Fig. 1A). Maternal SBP rose suddenly in WKYxSHRSP pregnancies, peaking on GD9 and returning to pre-pregnancy levels at term (GD19, Fig 1B). WKYxSHRSP dams displayed a significant increase in proteinuria on GD14 (Fig 1C) versus controls, consistent with glomerular damage. Pregnancies sired by SHRSP males showed signs of placental insufficiency and fetal growth restriction (FGR) on GD18 and 20 (Fig. 1D). At mid pregnancy (GD14), morphological alterations were evident in the placenta, including an expansion of the labyrinth layer and thickened walls of the uterine spiral arteries.

Conclusions: Hypertension as a paternal factor influences the kinetics of maternal blood pressure during pregnancy and compromised fetal growth, as a result of placental dysfunction. Identification of placental factors contributed by the paternal genotype may improve the understanding of disease mechanisms in hypertensive disorders of pregnancy.

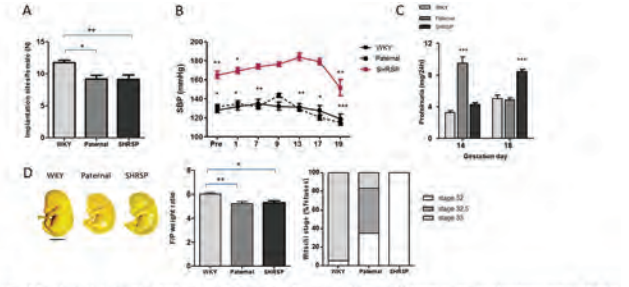

Figure 1. Hypertension as a paternal factor influences maternal physiology and compromises fetal growth A) Females pregnant from hypertensive males (WKYxSHRSP matings, Paternal model) showed an impaired fertility, as noted by decreased number of implantation sites respect to controls (WKY matings). **B)** Analysis of systolic blood pressures (SBP) registered by the tail-cuff method in the different mating models. WKYxSHRSP dams showed a sudden, significant increase in SBP (>140 mmHg, systolic hypertension) on GD9 compared to controls **C)** Urinary protein levels (mg/24 h) in the different models. **D)** Placental dysfunction and fetal growth restriction in WKYxSHRSP pregnancies. Left panel: Representative examples of GD18 fetuses recovered from the different models. Scale bar: 5 mm. Fetuses sired by SHRSP males showed signs of FGR (i.e., reduced length) and placental insufficiency (e.g.: significant reduction of F:P ratios, middle panel) on GD20. FGR in WKYxSHRSP matings was also evident as a maturation delay according to the Witschi Scale for fetal development (i.e.: open eyelids and divergence of the anterior fingers, features consistent with a Witschi stage 32, left). In all panels, *p<0.05, ** p< 0.01 and *** p<0.001 assessed by two-way ANOVA.

SA-PO1072

Preeclamptic Pregnancy Exacerbates Renal Injury in Dahl Salt Sensitive (S) Rats

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Background: Preeclampsia results in increased susceptibility to stroke, heart attack, hypertension, and chronic kidney disease postpartum. Despite increased cardiorenal disease risk, recommendations for prevention in these patients have not been established due to a lack of evidence for the mechanisms responsible for disease progression or evaluation of optimal therapeutic regimens. The purpose of this study was to test the hypothesis that preeclampsia accelerates the progression of chronic kidney disease and is associated with changes in the nitric oxide (NO):endothelin-1 (ET-1) balance.

Methods: Dahl S rats on a 0.3% salt diet (previously characterized model of superimposed preeclampsia) who experienced 2 pregnancies (12 and 17 weeks of age) and virgin littermate controls were aged to 6 months. Rats were implanted with telemetry transmitters (DSI), mean arterial pressure (MAP) was recorded, and rats were placed in metabolic cages for 24 hour urine collection prior to tissue harvest.

Results: Prior pregnancy did not result in a further increase in MAP at 6 months in the already hypertensive Dahl S females (virgin:185±6.9 mm Hg, prior pregnancy:184.6±6.6 mm Hg, n=8-10). Despite similar BP, rats who experienced prior preeclamptic pregnancy had greater renal injury compared to virgin littermates. Urinary excretion of protein (96±20 vs 195±45 mg/day), nephrin (0.6±0.4 vs 3.1±1.2 µg/day), and podocalyxin (4.9±1.0 vs 21.0±7.6 µg/day) was higher compared to littermate controls (p<0.05, Bradford assay, Exocell ELISA). These measures of renal injury were corroborated by histological examination as kidneys from rats that experienced preeclampsia demonstrated greater glomerular sclerosis (2.9±0.3) compared to virgin littermates (2.5±0.3, p=0.05). Analysis of urine from Dahl S rats following 2 consecutive pregnancies indicated decreased NO bioavailability (13.0±5.0 vs 5.2±1.6 µmol/day, Cayman Chemical NOx Assay) and increased renal production of ET-1 (4.6±1.5 vs 11.9±3.5 pg/day, with no change in plasma levels of ET-1, R&D Systems Quantiglo ELISA) suggesting that there may be an imbalance in the NO and ET-1 systems following preeclamptic pregnancy.

Conclusions: These data support the hypothesis that alterations in the NO/ET-1 balance in the kidney could link the maternal syndrome of preeclampsia to the increased postpartum risk of cardiovascular and renal disease.

Funding: NIDDK Support, Other NIH Support - NHLBI, Private Foundation Support

SA-PO1073

Impairment of Key Sphingolipid Metabolism Enzymes in Placenta and Kidneys of Reduced Uterine Perfusion Mouse Model

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Background: Preeclampsia (PE), is a pregnancy disorder characterized in the early gestation by placental ischemia, hypertension, and proteinuria. These complications may lead to the development of chronic kidney disease. Bioactive sphingolipids ceramide and sphingosine-1-phosphate (S1P) function as key regulators of cellular homeostasis such as angiogenesis, inflammation and endothelial permeability. Ceramide and S1P levels are altered in preeclamptic women, and sphingolipid pathway has been reported to involve in renal injury. Ceramidase hydrolyzes ceramide to produce sphingosine. Sphingosine can then be phosphorylated by sphingosine kinase (Sphk) 1 and 2 to form S1P. In the present study, we tested the hypothesis that placental ischemia alters the acid ceramidase 1 (ASAH1), Sphk1 and Sphk2 enzymes expression in placenta and kidneys of reduced uterine perfusion (RUP) mouse model.

Methods: C57bl/6J mice underwent sham or RUP surgeries at day 13 of gestation. Mice were instrumented with a carotid arterial catheter for measurement of mean arterial pressure (MAP) at E18 in the conscious state. Placenta and kidneys were harvested after MAP measurement and subjected to western blot analysis.

Results: MAP was significantly elevated in RUP (N=8) versus sham (N=5) (122±2 vs. 105±3 mmHg, $P<0.01$; respectively). ASAH1 were significantly($P<0.01$) lower in the kidneys (50%) and placenta (40%) of RUP (N=4) compared to sham (N=4). Sphk 1 and Sphk 2 were significantly decreased in the placenta of RUP compared to sham (30 % decrease in Sphk1 and 55 % decrease in Sphk2). However, Sphk1 and sphk2 were significantly increased in kidneys of RUP (N=4) compared to sham (N=4) (100 % increase in Sphk1 and 75 % increase in Sphk2).

Conclusions: Taken together, this study suggests the reduced uterine perfusion in mice alters keys sphingolipid metabolism enzymes in placenta and kidneys and may play an important role in the pathogenesis of PE.

Funding: Private Foundation Support

SA-PO1074

Uncoupled Endothelial Nitric Oxide Synthase (eNOS) in the Kidney Correlates with Increased Blood Pressure (BP) in Insulin-Infused Mice

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Background: Insulin stimulates NO production in the kidney via activation of eNOS which may lower BP; however, whether and how insulin resistance alters this relationship is unclear.

Methods: We tested whether insulin infusion into insulin-sensitive (C57Bl/6, "C57") versus insulin-resistant (TALLYHO, "TH") mice resulted in differential BP responses and renal eNOS regulation. Male mice (4-6 months old) were infused with insulin (50 U/

kg●bw/d) by osmotic minipump for 14 days (some mice were maintained as untreated). One-half of the infused mice in each strain were switched from a normal NaCl diet (NSD, 1%) to a high-NaCl diet (HSD, 4%) at day 7 of the infusion (n = 6-8/group).

Results: Mean arterial BP (MAP), measured by radiotelemetry, was 10-15 mm Hg lower in C57 mice (relative to TH) at baseline, fell days 2-5 of infusion, then rose days 7-14, so that by day 14, it was no longer different from TH. Pulse pressure (PP) was constant. In TH, MAP was relatively resistant to insulin, while PP fell (~40%). Light-to-dark ratio of MAP (indicator of diurnal rhythm) was elevated in TH in the baseline and increased in both strains with HSD. Urine was measured for nitrites plus nitrates (NOx) at baseline and days 1, 7, and 14 of the infusion. Mean urine NOx increased in both strains (30-40%) between baseline and day 1, but fell to ~55% of baseline by day 14. Plasma NOx concentration was significantly higher in untreated TH (relative to C57), but fell ~40% with insulin infusion (with either NSD or HSD). In contrast, plasma NOx rose in C57 with insulin infusion (13%) and an additional 23% with insulin plus HSD. NOS activity (per mg tissue) was increased by insulin infusion in renal cortex (CTX) in both strains, but in the medulla the increase was restricted to the C57. Western blotting of kidney revealed that coupled (150 KDa) and uncoupled (120 KDa) eNOS band densities were higher in TH, and insulin plus HSD substantially increased the uncoupled band especially in TH.

Conclusions: In summary, insulin infusion for 14 days abrogates BP differences between C57 and TH mice suggesting hyperinsulinemia may primarily underlie the modest hypertension in TH mice. Furthermore, progressive renal eNOS uncoupling and impaired NO production may play a role in the development of hypertension associated with insulin resistance.

Funding: Clinical Revenue Support

SA-PO1075

Renal Oxygenation during Chronic Nitric Oxide Synthase Inhibition as Recorded by Telemetry Tonja Emans,[2,1] Jaap A. Joles,[1] C.T.P. (Paul) Krediet.[2] *[1]Nephrology & Hypertension, UMC Utrecht, Utrecht, Netherlands; [2]Internal Medicine-Nephrology, AMC-UvA, Amsterdam, Netherlands.*

Background: Renal hypoxia has been advanced as a crucial factor in the vicious circle of disease progression leading to kidney failure. Nitric oxide (NO) is involved in renal vascular regulation. NO synthase (NOS)-inhibition leads to hypertension while decreasing renal blood flow and thus oxygen delivery. Furthermore, NO inhibits mitochondrial oxygen consumption. Therefore, we hypothesized that NOS inhibition would induce renal hypoxia. We now report telemetrically monitored mean arterial pressure and oxygen pressure (pO_2) in renal cortex and medulla in conscious rats during chronic NOS inhibition.

Methods: Oxygen sensitive electrodes were implanted in either renal cortex (n=6) or medulla (n=7) in healthy rats. After recovery and stabilization, baseline pO_2 was recorded for one week. Then, to inhibit NOS, L-NNA (40mg/kg/day) was administered via drinking water for two weeks. A separate group of rats (n=6), instrumented with blood pressure recording telemeters, followed the same protocol. Terminal glomerular filtration rate (GFR), renal blood flow (RBF), renal oxygen extraction and natriuresis were assessed under isoflurane anesthesia in all L-NNA rats (n=19) and in untreated controls (n=6).

Results: NOS inhibition rapidly induced hypertension (164 ± 6 vs. 108 ± 3 mmHg, p<0.001) and progressive proteinuria (82 ± 13 vs. 17 ± 2 mg/day, p<0.01). After an initial dip, cortical oxygenation returned to baseline. In contrast, medullary oxygenation decreased progressively (up to -23 ± 8% vs. baseline; p<0.05). Terminal GFR (1334 ± 74 vs. 2036 ± 166 µl/min) and RBF (4840 ± 343 vs. 8986 ± 938 µl/min) were reduced vs. control (both p<0.01). Terminal sodium reabsorption efficiency (TNa/QO2) also decreased (12.7 ± 1.1 vs. 22.8 ± 2.2 µmol/µmol, p<0.01).

Conclusions: Chronic NOS inhibition induced temporal changes in renal pO_2. Cortical pO_2 was not persistently altered, despite reduced RBF and therefore oxygen supply. In contrast, medullary pO_2 decreased progressively. Chronic NO deficiency leads to decreased renal perfusion and reabsorption efficiency (possibly of mitochondria) resulting in progressive medullary hypoxia. This suggests that juxtamedullary nephrons are particularly sensitive to chronic NO depletion. Supported by: Netherlands Organisation for Health Research (ZonMW, 40007039712461)

Funding: Government Support - Non-U.S.

SA-PO1076

The Role of Plasma Cells in Autoimmune Associated Hypertension Erin Taylor,[2] Michelle T. Barati,[3] David W. Powell,[3] Michael J. Ryan.[1] *[1]Univeristy of Mississippi Medical Center, Jackson, MS; [2]University of Mississippi Medical Center, Jackson, MS; [3]University of Louisville, Louisville, KY.*

Background: Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that is characterized by the loss of immune tolerance leading to the production of pathogenic autoantibodies, and is associated with prevalent hypertension, renal injury, and cardiovascular disease. Because long-lived plasma cells produce the majority of serum immunoglobulins (Ig) and are the primary source of autoantibodies in SLE, we hypothesized that depletion of plasma cells using the proteasome inhibitor bortezomib would lower autoantibody production and attenuate hypertension.

Methods: Thirty week old female NZBWF1 and control (NZW) mice were injected i.v. with vehicle (0.9% saline) or bortezomib (0.75 mg/kg) twice weekly for four weeks.

Results: Percentages of $CD138^+$ intracellular-κ $light\ chain^+$ plasma cells in the bone marrow were lower in bortezomib treated SLE mice compared to vehicle-treated SLE mice (1.7±0.19% vs. 0.95±0.18%, p<0.05), as assessed by flow cytometry. Circulating B and T cells were not altered after bortezomib treatment. Total plasma IgG was higher in SLE mice as compared to control mice (5.02±1.2 vs. 2.88±0.78 mg/mL, p<0.05), and were lower in SLE mice treated with bortezomib (1.5±0.5 mg/mL, p<0.05 vs. SLE-vehicle). In addition, bortezomib treatment reduced circulating anti-dsDNA IgG levels in SLE mice (1.36±0.25 vs. 0.44±0.11 OD450, p<0.01). This was associated with reduced glomerular IgG deposition in bortezomib treated SLE mice compared to vehicle treated SLE mice (1752±402 vs 916±57 fluoresence/µm², n=5-6, p<0.05) Urinary albumin excretion was increased in SLE mice as compared to controls (16.8±10.1 vs. 0.015±0.002 mg/day, p<0.05) and was lower in bortezomib treated SLE mice (0.24±00.16 mg/day, p<0.05 vs. SLE-vehicle). Mean arterial pressure (MAP; mmHg) measured in conscious mice by carotid artery catheter was higher in SLE mice than in control mice (142±5 vs. 118±3, p<0.001). MAP was significantly lower in SLE mice treated with bortezomib when compared to vehicle treated mice (119±4 vs. 142±5, p<0.001).

Conclusions: These data suggest that production of autoantibodies by plasma cells in SLE mechanistically contribute to the pathogenesis of hypertension.

Funding: Other NIH Support - NHLBI, Veterans Affairs Support

SA-PO1077

Renal Dendritic Cells from Hypertensive Mice Transferred Hypertension and Modified Renal Sodium Handling Patricio A. Araos,[4,1] Carolina E. Prado,[2] Edison S. Salas-Huenuleo,[3,5] Marcelo Kogan,[3,5] Rodrigo Pacheco,[2] Luis F. Michea.[4,1] *[1]ICBM, Facultad de Medicina, Universidad de Chile, Santiago, Chile; [2]Fundacion Ciencia y Vida, Santiago, Chile; [3]Depto. de Química toxicológica y Farmacológica, Facultad de Cs. Químicas y Farmacéuticas, Universidad de Chile, Santiago, Chile; [4]Millennium Institute on Immunology and Immunotherapy, Santiago, Chile; [5]Advanced Center for Chronic Diseases ACCDiS, Santiago, Chile.*

Background: High Angiotensin II (AngII) induce hypertension (HT). Previously, using genetically modified mice that allowed the systemic ablation of Dendritic Cells (DCs), we observed that DCs are necessary for the development of HT.The kidney is a tissue rich in DCs, which are present in the interstitial space. We hypothesized that renal DCs have pro-hypertensive properties that are acquired after HT.

Methods: In this study, we evaluated if renal DCs from hypertensive mice (AngII infusion, osmotic minipump, 1.042 µg/Kg/min, 14d) can transfer HT. We compared the transfer of renal DCs and splenic DCs from control (WT) and hypertensive mice ($CD11c^+$ cells, magnetic beads isolation). Isolated DCs from control and hypertensive mice were characterized (CD86, CD80, MHC-II and CX_3CR_1, flow cytometry). We monitoring blood pressure (BP, tail cuff method), and tracked DCs location after transferring (tail vein injection) by labeling DCs with a DiR dye (In vivo FX Pro system, Bruker). To evaluate the effect of DCs transferring on renal Na^+ handling, we challenged recipient mice with the injection of isotonic saline solution (saline test, 10% of BW, i.p. injection) and measured 4h-natriuresis 24h post-DCs transfer.

Results: Renal DCs obtained from hypertensive mice showed increased abundance of CD80, CD86, MHC-II, and CX_3CR_1 (MFI fold of induction: 1.6±0.2; 1.6±0.4; 1.4±0.3 and 3.2±0.8 respectively p<0.05 vs control; n=4-8). Transfer of renal DCs from hypertensive mice transiently increased BP (basal=102.5±4.4; day 1=123.3±4.4; mmHg; n=5, p< 0,001 vs basal). In contrast, transfer of splenic DCs did not modify BP. Renal DCs showed renal-preferential location 24 hours post injection, irrespective of the origin (control or hypertensive kidney). Recipients of hypertensive renal DCs showed decreased renal sodium excretion (basal urinary Na^+ excretion=10.2±1.9 vs. 8.2±0.8 µEq/BW/4h 1 day after transfer; p<0,05 n=5).

Conclusions: Renal, but not splenic, hypertensive DCs presented a preferential homing to kidney, transferred hypertension and transiently reduced natriuresis. These results suggest that renal DCs have a pro-hypertensive phenotype, acquired after the development of hypertension, which confers the ability of modulating sodium renal handling. FONDECYT1130550 and 1171869, IMII P09-016-F, BECA CONICYT 21130482

Funding: Government Support - Non-U.S.

SA-PO1078

Leukocyte Angiotensin II Type 1 Receptor-Associated Protein as a Surrogate Marker and Inhibitory Factor of Inflammation Kotaro Haruhara,[1,3] Hiromichi Wakui,[1] Ryu Kobayashi,[1] Daisuke Kurotaki,[2] Nobuo Tsuboi,[3] Takashi Yokoo,[3] Kouichi Tamura.[1] *[1]Department of Medical Science and Cardiorenal Medicine, Yokohama City University Graduate School of Medicine, Yokohama, Japan; [2]Department of Immunology, Yokohama City University Graduate School of Medicine, Yokohama, Japan; [3]Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan.*

Background: Previous studies have shown that the leukocyte gene expression of the renin-angiotensin system, particularly type1 angiotensin II receptor (AT1R), is involved in the pathogenesis of non-communicable diseases (NCD) and its target organ diseases. We found that AT1R-associated protein (ATRAP) is a novel molecule that specifically binds to AT1R and promotes internalization of AT1R along with the suppression of activated AT1R signal in animal models of NCD. The aim of this study was to determine the factors that may regulate the gene expression of ATRAP in leukocytes.

Methods: Blood samples were obtained from healthy volunteers and NCD patients. We examined the relationships between leukocyte ATRAP mRNA and clinical variables. Bone marrow ATRAP-deficient chimeric mice and bone marrow wild-type mice as control were generated by a procedure of bone marrow transplantation. After injection

of low-dose lipopolysaccharide, these mice were sacrificed and measured inflammatory cytokines mRNA expression in leukocytes.

Results: ATRAP was expressed predominantly in granulocytes and monocytes from healthy volunteers. In blood samples from 86 patients (mean age 63 years, hypertension in 95%, dyslipidemia in 76%, chronic kidney disease in 63%), the ATRAP mRNA was positively correlated with the age, neutrophil count, monocyte count, and serum CRP. These associations remained significant after adjustment for age, sex, estimated glomerular filtration rate, and urinary albumin excretion. Furthermore, the ATRAP mRNA was positively correlated with the IL-1β, TNF-α and MCP-1 mRNA in leukocytes. In addition, these cytokines were upregulated in bone marrow ATRAP-deficient chimeric mice in comparison to control mice after injection of low-dose lipopolysaccharide.

Conclusions: These results suggest that leukocyte ATRAP expression is associated with systemic and leukocyte inflammatory status and increases to compensate for inflammation.

SA-PO1079

Macrophage COX-2 Deletion Activates Renal T Cells and Transporter Activity in Response to High Salt Intake Ming-Zhi Zhang, Zhilian Li, Sungjin Chung, Yinqiu Wang, Aolei Niu, Xiaofeng Fan, Raymond C. Harris. *Vanderbilt University Medical Center, Nashville, TN.*

Background: Chronic use of non-selective NSAIDs or selective cyclooxygenase-2 (COX-2) inhibitors leads to increases in blood pressure. Recently, the immune system has been shown to play an important role in the pathogenesis of hypertension. Both interleukin-17 (IL-17) and interferon γ (IFNγ) production by aberrantly activated effector T cells contribute to angiotensin II-mediated and DOCA/salt-induced hypertension. Bone marrow-derived cells are known to be a rich source of prostaglandins and COX-2-derived prostaglandins modulate and affect both macrophage and T cell function. We recently reported that bone marrow cell COX-2 promotes non-inflammatory, alternatively activated M2 phenotypes in renal macrophages, and bone marrow cell COX-2 deletion led to salt-sensitive hypertension. In the current studies we investigated the potential activation of renal T lymphocytes in response to high salt intake when macrophage COX-2 is deleted.

Methods: Male COX-$2^{f/f}$ (WT) and CD-11b Cre; COX-$2^{f/f}$ (macrophage COX-2-/-) mice (FVB background) were fed a high salt diet (8% NaCl) for 5 weeks. Renal macrophages and T lymphocytes were isolated with CD11b and CD90.1 microbeads, respectively.

Results: Renal macrophage COX-2 mRNA was efficiently deleted in macrophage COX-2-/-. Renal macrophages from high salt-treated macrophage COX-2-/- mice expressed increased IL-23, known to activate Th17 cells. In kidneys from high salt-treated macrophage COX-2-/- mice, there were increased CD4-positive T cells, which expressed increased IFNγ and IL-17, but there were decreased regulatory T cells (Tregs). Cleaved epithelial sodium channel (ENaC) levels, an indicator of its activation, were much higher in high salt treated macrophage COX-2-/- mice.

Conclusions: These results suggest that deletion of macrophage COX-2 leads to aberrant activation of T lymphocytes, with subsequent increased production of IL-17 and IFNγ and activation of sodium transporters in response to chronic salt intake and may contribute to salt-sensitive hypertension.

Funding: NIDDK Support

SA-PO1080

β-Catenin Activity Is Dependent on Mouse Strain in Angiotensin II Induced Renal Hypertensive Injury Priyantha S. Kulatilake, Elena Wolodimeroff, Helen Williams, Sarah Higgins, Carl J. May, Gavin I. Welsh, Sarah J. George. *University of Bristol, Bristol, United Kingdom.*

Background: Hypertensive kidney injury has been well established; however, little is known about the involvement of Wnt/β-catenin signalling in this process. Here, we induced hypertension with Angiotensin II (AngII) infusion in two strains of mice to determine the effect on β-catenin activity and renal physiology.

Methods: DBA2/J (DBA) mice and mice crossed on a C57/Bl6x129S1/SvImJ background (129/Bl6) were implanted with subcutaneous osmotic pumps containing AngII for 28 days. Blood pressures (BP) were measured and kidneys were excised and processed for RNA, protein and histological analysis.

Results: At baseline DBA mice were significantly more proteinuric than 129/Bl6 mice (n=8 $p<0.05$). However, AngII infusion increased mean arterial BP and albuminuria in both strains of mice (n=8 $p<0.01$). This confirmed AngII induced hypertensive kidney injury. We observed significant changes in renovascular remodelling in both strains with AngII infusion. Increased renovascular fibrosis was induced with AngII in DBA mice (n=8 $p<0.05$); however, it was reduced 129/Bl6 mice (n=8 $p<0.05$). Interestingly, only 129/Bl6 mice developed generalised renal cortical fibrosis with AngII infusion (n=8 $p<0.05$). Levels of active β-catenin only significantly increased in DBA mice that received AngII (n=8 $p<0.01$) and immunohistochemistry showed a renal tubular distribution of β-catenin in kidney paraffin sections. A Wnt focused microarray showed increased β-catenin pathway signalling with altered downstream cell cycling markers. *In vitro* work showed that β-catenin blockade with 25μM iCRT resulted in decreased proliferation (n=3 $p<0.05$) and increased permeability (n=3 $p<0.05$) of HK-2 cells (proximal tubular).

Conclusions: Firstly; these results suggest β-catenin activity in renal hypertension is strain dependent. Secondly; that β-catenin plays an important role in proximal tubular cell proliferation and permeability; therefore β-catenin activity could prove to be a mechanism by which proteinuria develops in DBA mice with AngII induced hypertension.

SA-PO1081

Mocetinostat Attenuates Renal Injury and Dysfunction via the Inhibition of HDAC in Npr1 Gene-Targeted Mutant Mouse Models Prerna Kumar, Christian Nguyen, Venkateswara R. Gogulamudi, Ramachandran Samivel, Kailash N. Pandey. *Tulane University Health Sciences Center and School of Medicine, New Orleans, LA.*

Background: Mice lacking functional guanylyl cyclase/natriuretic peptide receptor-A (GC-A/NPRA) gene (*Npr1*) exhibit hypertension and heart failure. The objective of the present study was to elucidate the effect of class I histone deacetylase (HDAC) inhibitor, mocetinostat (MGCD) on the regulation of *Npr1* expression and repair of renal injury and dysfunction in *Npr1* heterozygous mutant mice.

Methods: Male *Npr1* gene-disrupted heterozygous (1-copy; $Npr1^{+/-}$), wild-type (2-copy; $Npr1^{+/+}$) and gene-duplicated (3-copy; $Npr1^{++/+}$) mice were injected intraperitonealy with MGCD (2 mg/kg) at alternate days for 2-weeks.

Results: The treatment with MGCD significantly increased renal NPRA protein and cGMP levels in all three mice genotypes ($Npr1^{+/-}$, $Npr1^{+/+}$, and $Npr1^{++/+}$) compared with vehicle-treated controls. The $Npr1^{+/-}$ mice exhibited significantly increased renal HDAC activity and HDAC1/2 protein levels compared with $Npr1^{+/+}$ and $Npr1^{++/+}$ mice. MGCD treatment attenuated HDAC activity by 48% and HDAC1/2 protein levels by 42% in $Npr1^{+/-}$ mice compared with wild-type mice. Heterozygous $Npr1^{+/-}$ mice exhibited higher systolic blood pressure (SBP, mm Hg) (130 ± 6 vs. $Npr1^{+/+}$, 102 ± 3 and $Npr1^{++/+}$ mice, 93 ± 3) and lower creatinine clearance (μl/min) (51 ± 10 vs. $Npr1^{+/+}$ mice, 130 ± 14; $p < 0.05$). MGCD-treated $Npr1^{+/-}$ mice showed significantly reduced SBP (106 ± 3; $p < 0.001$) and increased creatinine clearance (105 ± 13; $p < 0.05$) compared with vehicle-treated $Npr1^{+/-}$ mice. Higher urinary total protein and albumin to creatinine ratios were also detected in $Npr1^{+/-}$ mutant mice compared with $Npr1^{+/+}$; however, both of these parameters were dramatically reversed after MGCD treatment.

Conclusions: The present results demonstrate that HDAC inhibitor, MGCD upregulates *Npr1* expression *in vivo* and repairs renal injury in $Npr1^{+/-}$ mice. These findings will have important implications in the treatment and prevention of hypertension and renal injury and dysfunction in humans.

Funding: Other NIH Support - National Heart Lung and Blood Institute

SA-PO1082

Chronic Hypoxia Attenuated Hypertension and Renal Injury in an L-NAME Model Lisienny C. Rempel, Amanda H. Albino, Karin C. Oliveira, Fernanda F. Zambom, Simone C. Arias, Victor F. Avila, Camilla Fanelli, Claudia R. Sena, Vivian L. Viana, Denise M. Malheiros, Niels O. Camara, Clarice K. Fujihara, Roberto Zatz. *Univ of Sao Paulo, Sao Paulo, Brazil.*

Background: Tissue hypoxia has been postulated as a central factor in the pathogenesis of Chronic Kidney Disease (CKD). We showed recently that, rather than worsening renal injury, chronic hypoxia promoted renoprotection in the remannt kidney model. Here we investigated whether chronic hypoxia promotes similar renoprotection in the chronic NO inhibition model

Methods: Male Munich-Wistar rats received Nω-nitroarginine methylester (NAME) in drinking water (80 mg/Kg/day). Sixteen C (Cnor) and 13 NAME rats (NAMEnor) remained in normoxia (21% O2), while 16 C (Chyp) and 16 NAME rats (NAMEhyp) were kept in a normobaric hypoxia chamber (12% O2). After 4 weeks, we assessed: body weight (BW, g), hemoglobin (Hb, g/dL), tail-cuff pressure (TCP, mmHg), urine albumin/creatinine (Ualb/Ucr), glomerulosclerosis (GS, %), ischemic glomeruli (IG, **%),** cortical interstitium (INT, %), interstitial macrophages (MΦ, cells/mm2) and Angiotensin II positive cell (AngII, cells/mm2) as well as nuclear p65 content (NF-kB, x Cnor). Renal hypoxia was confirmed by pimonidazole immunohistochemistry.

Results: Hypoxia was confined to the outer medulla in Cnor and spread to the cortical area in Chyp. In NAMEnor, hypoxia also extended to the cortical area, a process that was intensified in NAMEhyp. In agreement with our findings in the remnant kidney model, hypoxia attenuated hypertension, inflammation and renal injury, in association with decreased infiltration by Ang II+ cells.

Conclusions: As in the remnant kidny model, chronic hypoxia limited inflammation as well as glomerular and interstitial injury in the chronic NO inhibition model, suggesting that this may be a universal effect. FAPESP/CNPq

Funding: Government Support - Non-U.S.

	BW	Hb	TCP	Ualb/UCr	GS	IG	INT	MΦ	AngII	NF-κB
Cnor	286±4	14±1	141±3	0.1±0.1	0.1±0.1	0.5±0.3	0.1±0.1	30±4	1.6±0.4	1.0±0.3
NAMEnor	249±8[a]	14±1	202±5[a]	4.3±0.8[a]	1.1±0.3[a]	6.9±0.9[a]	1.3±0.3[a]	114±14[a]	4.6±0.8[a]	2.4±0.5[a]
Chyp	268±4[b]	16±1[b]	137±3	0.3±0.1	0.1±0.3	0.4±0.3	0.1±0.1	32±3	1.7±0.6	1.0±0.2
NAMEhyp	251±5	17±1[b]	161±3[ab]	0.6±0.2[b]	0.1±0.1[b]	0.4±0.1[b]	0.1±0.1[b]	46±6[b]	1.7±0.4[b]	1.3±0.2

SA-PO1083

Podocyte Injury Enhances Intrarenal Angiotensin II Generation and Sodium Retention Dependently on Megalin Masahiro Koizumi,[3] Fumio Niimura,[3] Akira Nishiyama,[1] Motoko Yanagita,[2] Masafumi Fukagawa,[3] Taiji Matsusaka.[3] *[1]Kagawa University Medical School, Kita-Gun, Japan; [2]Kyoto University Graduate School of Medicine, Kyoto, Japan; [3]Tokai University School of Medicine, Isehara, Japan.*

Background: We have previously shown that podocyte injury enhances glomerular filtration of liver-derived angiotensinogen (Agt) and intrarenal angiotensin (A) II

generation (*KI* 2014) and that filtered Agt is reabsorbed by proximal tubular cells dependently on megalin (*JASN* 2012). In the present study, we aimed to study the role of megalin in generation of renal AII and sodium handling during nephrotic syndrome.

Methods: We generated proximal tubule-specific megalin knock out (KO) mice by crossing megalin-loxP, Ndrg-Cre, and Kap-Cre mice. Furthermore, to induce podocyte injury, we crossed these megalin KO mice and NEP25 mice, in which podocyte-specific injury can be induced by injection with immunotoxin.

Results: At baseline without podocyte injury, renal Agt staining was markedly diminished, with increase in urinary Agt in KO mice. However, renal AII levels were similar between KO (n=12) and control (n=16) mice (108 ± 11 vs. 101 ± 17 fmol/g tissue). We next tested the effect of megalin KO on AII generation in the kidney with abnormally increased filtered load of Agt in mice with podocyte-specific injury. Control NEP25 mice (n=10) showed markedly intense renal Agt staining and enhanced renal AII levels (450 ± 61 fmol/g tissue) 7 days after the induction of podocyte injury. Megalin KO/NEP25 mice (n=12) showed diminished renal Agt staining and significantly attenuated renal AII levels (119 ± 23 fmol/g tissue, $p < 0.01$). Compared with control NEP25 mice, megalin KO/NEP25 mice excreted more sodium in urine (U-Na/Cr: 2.06 ± 0.83 vs. 0.58 ± 0.26, $p < 0.001$). Four days after the induction of podocyte injury, when tubulointerstitial damage is milder, the result was comparable. Blood pressure levels were similar between the two groups. Quantitative RT-PCR showed that *NKCC2* mRNA in megalin KO/NEP25 mice were 70.6% to that of control ($p < 0.01$).

Conclusions: These indicate that, in podocyte injury, abnormally increased filtered load of Agt is reabsorbed via megalin by proximal tubular cells and induces the inappropriate activation of intrarenal renin-angiotensin system, which may contribute to sodium retention and edema formation.

Funding: Government Support - Non-U.S.

SA-PO1084

Relationship between Blood Pressure and Estimated Glomerular Filtrating Ratio or Proteinuria without a Life-Related Disease Masatoshi Kawashima,[2] Akihiro Kuma,[1] Kazuhiko Enta.[3] *[1]Shizuoka Office, Health Care Center, Central Japan Railway Inc., Shizuoka, Japan; [2]Tokyo Office, Health Care Center, Central Japan Railway Company, Tokyo, Japan; [3]Health Care Center, Central Japan Railway Company, Nagoya, Japan.*

Background: Both estimated glomerular filtrating ratio (eGFR) and proteinuria influences to systolic and diastolic blood presure. We examined the relationship between blood pressure and estimated glomerular filtrating ratio or proteinuria in the absence of a life-related disease.

Methods: We collected the yearly medical examination data from 2008 to 2015 of workers in a railway company in Japan. The data of individuals without a life-related disease, such as hypertension, diabetes mellitus, dyslipidemia, and hyperuricemia, were selected. The selected individuals were classified into 3 categories by average eGFR from 2008 to 2015. Categories I, II, and III were ≥90, 60–90, and <60 ml/min/1.73m^2, respectively. The individuals were next classified into 3 categories by the number of proteinuria reports from 2008 to 2015. Categories 0, 1, and 2 were 0, 1, and ≥2 reports, respectively. Category I–III and Category 0–2 were then combined to form 9 categories (Category I0-III2) and their relationship to systolic and diastolic blood pressure in 2014 examined using ANCOVA with adjusted age and gender.

Results: The selected group of workers included 7,042 (female 336) workers of 24–64 years old in 2015. For systolic blood pressure, significant differences showed in 2 combinations (II0 and II2 P=0.029, and II1 and II2 P<0.001) in association with the proteinuria category. For diastolic blood pressure, a significant difference showed in 2 combinations (II0 and II2 P=0.027, and II1 and II2 P=0.003) in association with the proteinuria category. There were no significant differences detected in comparisons of the eGFR categories with systolic and diastolic blood pressures.

Conclusions: A relationship was detected between proteinuria and blood pressure, which appeared to be a stronger relationship than the relationship between eGFR and blood pressure.

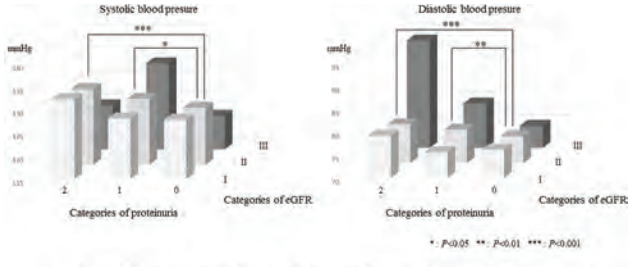


Figure 1. Blood pressure of combined of estimated glomerular filtrating ratio and proteinuria

SA-PO1085

A Critical Role of Angiotensin II Type 1 Receptor Binding Molecule in Hypertension in a CKD Model Ryu Kobayashi,[3] Hiromichi Wakui,[3] Kazushi Uneda,[3] Kotaro Haruhara,[3] Akira Nishiyama,[1] Katsuyuki Tanabe,[2] Yohei Maeshima,[2] Kouichi Tamura.[3] *[1]Kagawa University Medical School, Kita-Gun, Japan; [2]Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science, Okayama, Japan; [3]Yokohama City University Graduate School of Medicine, Kanazawa-Ku, Japan.*

Background: The renin-angiotensin system plays a key role in the maintenance of cardiovascular and renal homeostasis, principally via appropriate activation of Ang II type 1 receptor (AT1R). We previously identified an AT1R-associated protein (ATRAP/Agtrap), which promotes AT1R internalization along with suppression of hyperactivation of tissue AT1R signaling. We hypothesized that dysregulation of renal ATRAP expression and subsequent AT1R hyperactivation contributes to development of hypertension that occurs as a complication of the remnant kidney CKD model.

Methods: We compared changes in endogenous ATRAP expression and blood pressure between 129/Sv and C57BL/6 mice using the remnant kidney model after 5/6 nephrectomy. We also examined the effect of ATRAP deficiency in C57BL/6 mice (with a hypertension-resistant strain background) on blood pressure regulation after 5/6 nephrectomy. To more directly examine the mechanism of hypertension, ATRAP-knockout (KO) mice were treated with the soluble TNF-α receptor, etanercept, or with vehicle after 5/6 nephrectomy.

Results: We first examined the effect of 5/6 nephrectomy on endogenous ATRAP expression in the kidney of C57BL/6 and 129/Sv mice. While 129/Sv mice that underwent 5/6 nephrectomy showed decreased renal ATRAP expression and developed hypertension, C57BL/6 mice exhibited increased renal ATRAP expression and resistance to progressive hypertension. Consequently, we hypothesized that downregulation of renal ATRAP expression is involved in pathogenesis of remnant kidney CKD model-related hypertension. To investigate this, we performed 5/6 nephrectomy in ATRAP-knockout (KO) mice on the hypertension-resistant C57BL/6 background. ATRAP-KO mice that underwent 5/6 nephrectomy showed hypertension with increased plasma volume. Moreover, in ATRAP-KO mice compared with wild-type C57BL/6 mice after 5/6 nephrectomy, renal expression of the epithelial sodium channel α-subunit and tumor necrosis factor-α was significantly enhanced, concomitant with increased plasma membrane AT1R in the kidneys.

Conclusions: These results indicate that renal ATRAP downregulation is involved in onset and progression of blood pressure elevation caused by renal mass reduction, and implicates ATRAP as a therapeutic target for hypertension in CKD.

SA-PO1086

The Effect of Serine Protease Inhibition on Glomerular Injuries in Salt-Sensitive Hypertension Yasunobu Iwata,[1] Yutaka Kakizoe,[1] Terumasa Nakagawa,[1] Yuichiro Izumi,[1] Takashige Kuwabara,[1] Masataka Adachi,[1] Kenichiro Kitamura,[2] Masashi Mukoyama.[1] *[1]Department of Nephrology, Kumamoto university graduate school of medical sciences, Kumamoto, Japan; [2]Internal Medicine III, University of Yamanashi Faculty of Medicine, Chuou, Japan.*

Background: We previously reported that a synthetic serine protease (SP) inhibitor, camostat mesylate (CM), suppressed epithelial sodium channel (ENaC) activation by SPs and exerted an antihypertensive effect in Dahl salt-sensitive (DS) rats. Furthermore, CM significantly attenuated proteinuria even before it exerted BP lowering effect, suggesting that some SPs are involved in glomerular injuries independently of BP. Recently, it was reported that plasminogen filtered through damaged glomeruli was activated to plasmin by tPA expressed on the surface of podocytes, and that plasmin could directly cause podocyte injuries. We conducted this study to identify SPs which could be associated with glomerular injuries and to explore therapeutic effects of SP inhibition on glomerular injuries in salt-sensitive hypertension.

Methods: Four-week-old male DS rats were divided into following three groups: control group (0.3% NaCl), high-salt (HS) group (8% NaCl diet), and HS+CM group (HS+0.1%CM diet). After systolic BP measurement and 24h urine collection were performed, rats were sacrificed at day 7. SP activities were evaluated by zymography.

Results: HS group did not develop hypertension but displayed significant proteinuria at day 7, which was attenuated in HS+CM (Urinary TP (mg/day); control 4.09±1.17, HS 42.01±3.72, HS+CM 14.31±7.63). CM did not mitigate glomerular hyperfiltration reflected by increased creatinine clearance (Ccr) with salt loading (Ccr (mL/h); control 0.3±0.1, HS 0.8±0.1, HS+CM 0.8±0.2). Urinary plasmin activation was induced by HS, which was substantially inhibited by HS+CM. Furthermore, CM also suppressed albuminuria as early as at day 1-2 even when any apparent activation of SPs was not detected in urine.

Conclusions: Our current study indicates that plasmin and other unknown SPs would be involved in the pathogenesis of glomerular injuries, suggesting that SP inhibition could be a new strategy for the treatment of renal injuries in salt-sensitive hypertension.

SA-PO1087

PGE2 EP1 Receptors Contribute to Hypertensive Injury in Mouse Kidney Jamie Ghossein, Rania Nasrallah, Alex Gutsol, Richard L. Hebert. *University of Ottawa, Ottawa, ON, Canada.*

Background: Prostaglandin E2 (PGE2) derived from COX-2 is upregulated in hypertension and diabetes, and we previously reported that the PGE2 EP1 receptor is involved in glomerular injury and proteinuria in the diabetic mouse. We hypothesize that EP1 contributes to renal injury in hypertension.

Methods: Using a genetic model of hypertension, where TTRhRen mice overexpress renin (Htn), we studied the effects of EP1 deletion using 4 mouse groups at 24 weeks of age: wildtype (WT), EP1-/-, Htn, and HtnEP1-/-. All male mice were placed in metabolic cages, and 24 hour urine was collected. Urine osmolality was determined by freezing point depression and albumin levels were measured by ELISA. Glomerular filtration rate was determined by FITC-Inulin clearance, and systolic blood pressure was measured by tail-cuff plethysmography. Kidneys were fixed and PAS stained for pathological analysis of glomerular, mesangial, and capillary areas using ImageJ photo analysis software.

Results: Urine osmolality was decreased by 33% in Htn mice compared to WT mice, and further decreased by 17% in HtnEP1-/- mice compared to Htn mice. Urine albumin was elevated by 10 fold in Htn mice compared to WT mice, and further increased in HtnEP1-/- mice by 2.5 fold compared to Htn mice. Blood pressures were elevated by 25mmHg in Htn mice compared to WT mice, but this hypertensive state was unaffected by EP1 deletion. FITC-inulin clearance was unchanged in Htn mice, but reduced by 50% in HtnEP1-/- mice compared to WT. Pathological analysis revealed that mesangial cell numbers were unchanged in Htn mice, but stimulated 1.5 fold in both groups lacking EP1 receptors compared to WT. Glomerular and mesangial volume were increased by 1.25 fold and 1.5 fold in Htn mice compared to WT respectively, and mesangial volume was significantly higher in HtnEP1-/- mice compared to Htn mice, reaching 1.95 fold of WT. In contrast, capillary volumes were unchanged in Htn mice, but significantly reduced by 50% in EP1-/- and HtnEP1-/- mice compared to WT mice.

Conclusions: Taken together, the data suggest that the EP1 receptor maintains glomerular permeability and prevents hypertension induced glomerular injury, independent of effects on blood pressure.

Funding: Government Support - Non-U.S.

SA-PO1088

PGE2 EP1 Receptor Regulates Renal Aquaporin and Sodium Transporter Expression and Inhibits AVP-Dependent Water Reabsorption and Sodium Transport in Mouse Collecting Duct Rania Nasrallah,[1,3] Joe A. Zimpelmann,[1,3] Jamie Ghossein,[1,3] Chris R. Kennedy,[1] Kevin D. Burns,[2,1] Richard L. Hebert.[1,3] *[1]Kidney Research Centre, Ottawa, ON, Canada; [2]The Ottawa Hospital - Riverside Campus, Ottawa, ON, Canada; [3]University of Ottawa, Ottawa, ON, Canada.*

Background: Prostaglandin E2 (PGE2) regulates glomerular hemodynamics, renin secretion, and tubular transport. The purpose of this study was to determine the contribution of PGE2 EP1 receptors to salt and water homeostasis, given that we previously reported no effect on blood pressure in mice lacking EP1.

Methods: Male FVB EP1-/- mice were bred with hypertensive TTRhRen mice (Htn) to evaluate kidney aquaporins, sodium transporters, and transport function at 8 wks of age in 4 groups: wild-type (WT), EP1-/-, Htn, HtnEP1-/-. Total RNA was isolated from renal cortex and medulla, and microdissected proximal tubules (PT), thick ascending limb (TAL), and cortical (CCD) and inner medullary collecting ducts (IMCD) for quantitative PCR analysis. CCD and IMCD were microdissected for in vitro perfusions to determine tubular fluid reabsorption in response to PGE2 and vasopressin (AVP), and transepithelial voltage in CCD stimulated with PGE2. CCD were also pre-treated with amiloride (ENaC inhibitor) or hydrochlorothiazide (pendrin inhibitor) prior to PGE2 stimulation.

Results: Cyclooxygenase (COX)-1 and microsomal PGE2 synthase mRNA were increased and COX2 was decreased in mice lacking EP1, along with increases in EP3 and reductions in EP2 and EP4 mRNA throughout the nephron. PT sglt1, NHE3, and AQP1 were increased in HtnEP1-/-, but sglt2 was increased in EP1-/- mice. TAL NKCC2 was reduced in the cortex but increased in the medulla. IMCD AQP1 and ENaC were increased, but AVP V2 receptor and urea transporter-1 were reduced in all mouse groups compared to WT. In WT and Htn mice, PGE2 inhibited AVP-stimulated water transport in the IMCD, but not in EP1-/- or HtnEP1-/- mice. Similarly, PGE2 depolarized the transepithelial voltage (inhibited sodium transport) in mouse CCD via EP1 in WT and Htn mice, but not in in mice lacking EP1; both amiloride and hydrochlorothiazide attenuated the inhibitory response of PGE2.

Conclusions: Taken together, the data suggest that EP1 regulates renal aquaporins and sodium transporters, and EP1 plays a major role in attenuating AVP-mediated water transport and inhibiting sodium transport in the mouse collecting duct. The inhibition of sodium transport in response to PGE2 is mediated by both ENaC and pendrin-dependent pathways.

Funding: Government Support - Non-U.S.

SA-PO1089

Previous Aerobic Exercise Increases Vo2 Peak in Rats with Kidney Chronic Disease Wesley Silva,[2] Rafael Luiz,[1] Alexandre Saud,[1] Natalia Reinecke,[1] Samuel T. Filho,[1] Kleiton A. Silva,[3] Rodolfo R. Rampaso,[1] Luciana Jorge,[1] Nestor Schor.[1] *[1]Universidade Federal de São Paulo, São Paulo, Brazil; [2]Universidade Federal de São Paulo, Sao Paulo [SP], Brazil; [3]University of Missouri, Columbia, AL.*

Background: Chronic Kidney Disease (CKD) contributes to harm the renal and cardiovascular function. The Aerobic exercise training have been used widely to modulation of renal and cardiovascular environment, reducing cardiovascular risk-associated diseases. **Aim**: To evaluate the effects of the previous exercise training (PET) on oxygen consumption peak (VO2 peak) and renal function of rats submitted to nephrectomy 5/6

Methods: Wistar rats (n=5), were randomically divided in four groups: Exercise + NX + exercise (ENXE), exercise + NX + sedentary (ENXS), sedentary + NX + sedentary (SNXS). Treadmill exercise was performed at 40 to 60% of VO2 peak for 8 weeks. NX surgery was perfomed on 4th week of exercise training protocol

Results: The VO2 peak and exercise capacity were improved in NXES and NXEE groups compared to NXSS. Exercise training decreased proteinuria, although, it was not observed changes in creatinine clearance, serum creatinine and urinary volume. Systolic arterial pressure decreased in NXEE when compared to NXSS and NXES

Conclusions: The data suggest that exercise training may be applied to patients with CKD, especially when performed previous onset of the disease. Thus it demonstrated that exercise were effective to prevent death in NXES and NXEE and could be an addition strategy to treatment of CKD patients

	NXSS	NXES	NXEE
Proteinuria (mg/24)	196.4 ± 16.4	193.6 ± 12.6	132.2 ± 14.9 *#
Creatinine serum (mg/dL)	1.2 ± 0.1	1.4 ± 0.1	1.4 ± 0.1
Creatinine Clearance (ml/min)	0.4 ± 0.1	0.8 ± 0.2	0.6 ± 0.1
Blood pressure (mm/Hg)	250 ± 5	249 ± 2	225 ± 1 *#
Urinary volume (ml/24h)	46.2 ± 4	32 ± 9	37 ± 1
VO2 peak (ml/kg/min)	20.6 ± 0.4	27.5 ± 2.1 *	37.8 ± 1.4 *#
Maximum load test (m/min)	28 ± 2	30 ± 1	40 ± 1 *#

* vs NXSS; # vs NXES; p<0,05

SA-PO1090

Chronic Treatment with Tadalafil Prevented Renal Dysfunction and Hypertension Caused by High Salt Intake and Preserved Serum SDF-1α Levels in Dahl Salt-Sensitive Rats Natsumi Tomita,[1] Yuji Hotta,[1] Aya Naiki-Ito,[2] Tomoya Kataoka,[3] Yasuhiro Maeda,[1] Satoru Takahashi,[2] Kazunori Kimura.[1,3] *[1]Hospital Pharmacy, Graduate School of Pharmaceutical Sciences, Nagoya City University, Nagoya, Japan; [2]Experimental Pathology and Tumor Biology, Graduate School of Medical Sciences, Nagoya City University, Nagoya, Japan; [3]Clinical Pharmaceutics, Graduate School of Medical Sciences, Nagoya City University, Nagoya, Japan.*

Background: Phosphodiesterase inhibitors (PDE5is) are reported to prevent renal damage and/or blood pressure (BP) elevation in an ischemic-reperfusion model. It is uncertain whether PDE5is are effective against salt sensitive hypertension; thus, we investigated the effects of a PDE5i, tadalafil, on hypertension and renal dysfunction induced by high salt intake using an animal model.

Methods: Eight-week-old male Dahl salt-sensitive rats were divided into three groups (n=6); normal salt (NS), high salt (8% NaCl-included diet; HS), and high salt and tadalafil treatment (10 mg/kg/day, p.o; Tad). Blood urea nitrogen, serum creatinine (SCre), proteinuria, and BP were evaluated at 0, 4, and 8 weeks. The kidney was extracted at 8 weeks and PAS staining was performed. Serum stromal cell-derived factor 1 (SDF-1)-α level, which is associated with the repair of vascular endothelial injury, was also evaluated at the 8 week timepoint.

Results: BP and proteinuria significantly increased in the HS group (P<0.01), while tadalafil treatment attenuated proteinuria and BP elevation at 8 weeks (P<0.01 vs. HS) (Fig.1). While SCre did not increase in the Tad group, it increased in the HS group (P<0.05) at 8 weeks. Glomerulosclerosis and atherosclerosis in the kidney also increased in the HS group (P<0.01), although they were suppressed in the Tad group (P<0.01 vs. HS). Serum SDF-1α level significantly decreased (P<0.01) in the HS group and normalized in the Tad group (P<0.05 vs. HS).

Conclusions: Tadalafil may be an effective treatment for salt-sensitive hypertension, atherosclerosis, and renal dysfunction and maintains SDF-1α level.

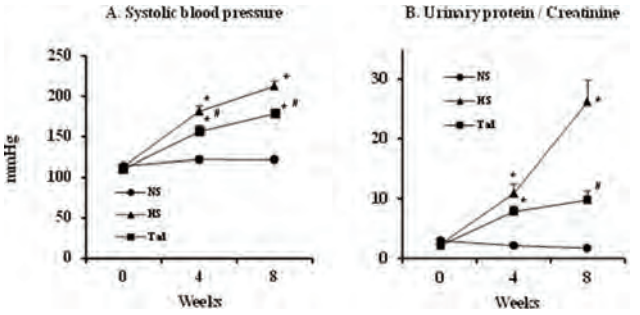


Fig.1 Variations in systolic blood pressure (A) and urinary protein to creatinine ratio (B) in each group (n=6). ANOVA and Bonferroni-type multiple *t*-test. * P<0.01 vs. NS, # P<0.01 vs. HS

SA-PO1091

Urinary L-Type Fatty Acid-Binding Protein Is Useful for Evaluation of the Renoprotective Effect of Bardoxolone Methyl, a Nuclear Factor Erythroid 2-Related Factor 2 Activator Mikako Hisamichi,[1] Takeshi Sugaya,[1] Kenjiro Kimura,[2] Yugo Shibagaki,[1] Atsuko Ikemori.[1] *[1]Division of Nephrology and Hypertension, St Marianna University Hospital, Kawasaki, Japan; [2]Tokyo Takanawa Hospital, Tokyo, Japan.*

Background: Nuclear 1 factor related factor 2 (Nrf2) activator has an anti-oxidant effect and is expected to be a new strategy for chronic kidney disease. Urinary tubular marker, L-type fatty acid-binding protein (L-FABP), is known to accurately reflect tubular damage in a variety of renal stress, especially in oxidative stress. The aim of this study is to reveal the utility of urinary L-FABP as an indicator of the renoprotective effect of bardoxolne metyl (BM), a Nrf2 activator, in renal injury model due to oxidative stress.

Methods: We used an aldosterone (Ald)- and salt-induced renal injury model, in which oxidative stress is strongly associated with onset of tubulointerstitial damage. Tubulointerstitial damage with urinary L-FABP was evaluated using human L-FABP chromosomal transgenic (L-FABP$^{+/-}$) male mice. Male L-FABP$^{+/-}$ mice were divided into three groups: The Ald group received systemic aldosterone infusions via an osmotic minipump and were given 1% NaCl water for 35 days. The Ald-Nrf2 group was given BM intraperitoneally in addition to an injection of aldosterone and salt. The dose of the Nrf2 activator was gradually increased every 7 days, reaching 10mg/kg/daily and continued for 14 days. The control group was only given a vehicle.

Results: The administration of BM significantly increased renal expression of the Nrf2 target antioxidant gene. Tubulointerstitial damage was significantly ameliorated in the Ald-BM group compared to the Ald group. The increase in reactive oxygen species in the kidneys of the Ald group was significantly prevented in the Ald-BM group. The upregulation of human L-FABP expression induced in the kidneys and the increase in urinary L-FABP in the Ald group were significantly suppressed by BM administration. The dynamics of L-FABP were significantly and strongly correlated with the prevention of the tubular damage (r=0.63), inflammatory infiltration(r=0.68) and fibrosis (r=0.72) by the administration of BM.

Conclusions: Urinary L-FABP is a useful marker reflecting the therapeutic efficacy of BM in Ald- and salt-induced renal injury.

Funding: NIDDK Support

SA-PO1092

Metformin Treatment Downregulates Intrarenal Renin-Angiotensin System in Angiotensin II Infused Mice Rodrigo Alzamora,[3,5] Victor M. Barrientos,[4] Pablo A. Leon,[2] Luis F. Michea.[1] *[1]Facultad de Medicina, U de Chile, Santiago, Chile; [2]Universidad de Chile, Santiago, Chile; [3]Instituto de Ciencias Biomédicas, Facultad de Medicina, Universidad de Chile, Santiago, Chile; [4]University of Chile, Santiago, Chile; [5]The Millennium Nucleus of Ion Channels-Associated Diseases (MiNICAD), Santiago, Chile.*

Background: Activation of an intrarenal renin-angiotensin system (irRAS) is a characteristic of angiotensin II (AngII) induced hypertension. The irRAS contributes to the development and progression of hypertension, by increasing tubular sodium reabsorption, and promotes kidney tissue damage. Recent data have suggested an antihypertensive effect of metformin in several animal models of hypertension. Metformin activates the AMP-activated protein kinase (AMPK), which has been reported to downregulates the activity of renal sodium channels and transporters. We evaluated the effect of metformin treatment on blood pressure (BP) and the expression of components of the irRAS.

Methods: Changes in BP and expressions of angiotensinogen (AGT), renin, AngII type-1 receptor (AT1R) and angiotensin converting enzyme (ACE) were measured in kidney tissue from AngII-infused C57/BL6 mice with or without metformin treatment.

Results: Metformin-treatment prevented the AngII-induced increase in SBP compared to control mice (AngII 153±6 vs. AngII+Met 105±5 mmHg, *P*>0.05, n=4) and decreased renal expressions of renin, ACE and AT1R but did not modified the induction of AGT. As compared to control mice, phosphorylation of AMPK (T172) was decreased in AngII-infused mice (52% reduction, *P*>0.05, n=4) but restored by metformin-treatment. Additionally, metformin-treatment prevented the induction of Na^+-H^+-exchanger-3 (NHE3) expression in kidney cortex from Ang-II infused mice. In contrast, metformin-treatment had no effect on BP, irRAS components and NHE3 expression in control mice.

Conclusions: Metformin has protective effects, by preventing AngII-induced increase in BP, the induction of irRAS and the upregulation of NHE3 caused by AngII infusion. Supported by FONDECYT 1151423 and 1130550, The Millennium Nucleus of Ion Channels-Associated Diseases (MiNICAD). The Millennium Institute on Immunology and Immunotherapy (MIII) P09/016-F (ICM).

Funding: Government Support - Non-U.S.

SA-PO1093

Effects of Neurogenic CGRP on Renal Afferent Peptidergic Neurons Kristina Rodionova,[1,2] Giulia Raschke,[1] Tilmann Ditting,[1,2] Martin Hindermann,[1,3] Chrstian Ott,[1,2] Roland E. Schmieder,[1] Kerstin U. Amann,[3] Roland Veelken.[1,2] *[1]Dept. of Nephrology, Friedrich-Alexander-University Erlangen, Erlangen, Germany; [2]Paracelsus Medical University Nuremberg, Nuremberg, Germany; [3]Department of Nephropathology, Friedrich-Alexander Universität Erlangen, Erlangen, Germany.*

Background: Although release of the proinflammatory vasodilator CGRP from peptidergic afferent nerves is generally unquestioned the matter is far less investigated with respect to afferent renal innervation that is said to be involved in sympathetic control and blood pressure regulation. Furthermore, it is not known in how far released neurogenic CGRP will affect renal afferent innervation in return. Hence we wanted to test the hypothesis that CGRP elicits action potential production related to TRPV1 receptor stimulation in cultured neurons with afferent projections from the kidney in vivo.

Methods: Cultured dorsal root ganglion neurons (Th11-L2) of rats with renal afferents in vivo were investigated in current clamp mode to asses action potential generation or in voltage clamp mode to investigate inward currents during stimulation of TRPV1 receptors with acid of pH 6 (-80mV holding voltage) and/or administration of CGRP (0,5 µmol). Furthermore, renal slices were incubated during baseline, experimental stimulation period and recovery to study CGRP release due to TRPV1 receptor stimulation (capsaicin 10^{-6} M, increased proton concentrations). CGRP concentrations in the organ bath were assessed with a commercial kit. Capsazepine was used for TRPV1 receptor blockade

Results: More than 90 DRG neurons with renal afferents were tested. Addition of CGRP did not change action potential generation nor inward currents. Proton stimulation (ph 6) of TRPV1 markedly increased long-term inward currents (baseline -361,7 +/- 89,6 pA vs. -1393,3+/-337,3 pA, p<0,05, mean +/- SEM). The co-stimulation of renal neurons with protons (pH 6) and CGRP led to an impairment of sustained inward current as compared to proton stimulation alone (baseline -478,2 +/-54,4 pA vs. -767,6+/-89,6 pA, p<0,05, mean +/- SEM). Baseline CGRP release of renal slices (2.5 to 6 pg/ml) increased significantly after TRPV1 receptor stimulation (on average: 21+4 pg/ml CGRP).

Conclusions: In contrast to our hypothesis CGRP could not elicit action potentials in afferent neurons related to the kidney but even impaired electric currents in general after TRPV1 receptor stimulation. Hence, renal CGRP secretion from peptidergic afferent nerves might decrease further neuronal CGRP release.

Funding: Government Support - Non-U.S.

SA-PO1094

Voluntary Exercise Decreases Blood Pressure, Angiotensin II, and Aldosterone without Changing Glomerular Filtration Rate in Two-Kidney One-Clip Hypertensive Rats Brian M. Waldman,[1] Robert A. Augustyniak,[1] Haiping Chen,[1] Noreen F. Rossi.[1,2] *[1]Wayne State University, Detroit, MI; [2]John D. Dingell VAMC, Detroit, MI.*

Background: Voluntary dynamic exercise promotes sympathoinhibition and decreases blood pressure in two-kidney one-clip (2K1C) rats, a model of renovascular hypertension. Renal sympathetic nerves increase renin secretion and tubular sodium (Na^+) reabsorption. We hypothesized that daily spontaneous wheel running exercise by 2K1C rats will decrease mean arterial pressure (MAP), plasma angiotensin II (Ang II) and aldosterone (Aldo), and normalize urinary Na^+ and potassium (K^+) excretion independent of glomerular filtration rate (GFR).

Methods: Five week-old male Sprague Dawley rats underwent sham clipping (Sham) or right renal artery clipping (2K1C). Rats were randomly assigned to standard caging (SED) or cages with access to running wheels (EX). After 12 weeks, rats were assigned to 1) collection of aortic blood for measurement of Ang II and Aldo or 2) assessment of inulin clearances and excretory function.

Results: Running distances were comparable in both EX groups. MAP was lower in 2K1C EX vs 2K1C SED rats (191±4 vs 169±2 mmHg; *P*<0.05). Elevated plasma Ang II in 2K1C SED rats (187.4±43.6 fmol/ml) was lower in 2K1C EX rats (48.9±7.5 fmol/ml; *P*<0.05) which did not differ from Sham SED or Sham EX rats (29.3±8.1 and 47.3±7.1 fmol/ml). Aldo levels paralleled those of Ang II. Clipped kidney weights were significantly lower in both 2K1C groups (*P*<0.05), but GFR and urine flow rates were no different from right and left kidneys among the four groups. Total and fractional Na^+ excretion from the unclipped kidney of 2K1C SED rats was higher vs either Sham group (*P*<0.05). Values in 2K1C EX rats were similar to the Sham groups. Total and fractional K^+ excretion was higher from the unclipped kidney of 2K1C SED rats (*P*<0.05); results of exercise paralleled those of Na^+ excretion.

Conclusions: These findings show that voluntary dynamic exercise, known to promote renal sympathoinhibition, lowers blood pressure and decreases plasma Ang II and Aldo levels in the 2K1C model of renovascular hypertension without deleterious effects on GFR. The effects on Na^+ excretion underscore the impact of pressure natriuresis

despite elevated plasma Ang II and Aldo in sedentary 2K1C rats. In contrast, K^+ excretion appears to be primarily regulated by circulating Aldo levels and distal Na^+ delivery.

Funding: Veterans Affairs Support

SA-PO1095

Phosphoinositide-3 Kinase γ Regulates Inflammation and Renal Fibrosis in Angiotensin II-Induced Hypertension Changlong An,[1,2] Sandhya S. Thomas,[1,2] Zhaoyong Hu,[1] William E. Mitch,[1] Yanlin Wang.[1,2] *[1]Baylor College of Medicine, Houston, TX; [2]Michael E. DaBakey VA Medical Center, Houston, TX.*

Background: We have recently shown that CXCL16/CXCR6 axis plays a critical role in recruiting inflammatory cells and bone marrow-derived fibroblasts into the kidney resulting in renal injury and fibrosis. However, the underlying signaling mechanisms are not known. In the present study, we examined the role of phosphoinositide-3 kinase γ (PI3Kγ) in recruitment of inflammatory cells and bone marrow-derived fibroblasts into the kidney and development of renal injury and fibrosis in an experimental model of hypertension.

Methods: Wild-type (WT) and PI3Kγ knockout (KO) mice were treated with angiotensin II via subcutaneous osmotic minipumps at 1500 ng/kg/min for 4 weeks following uninephrectomy. All the mice were given 1% NaCl in drinking water ad lib. Blood pressure, kidney function, proteinuria, and renal histology were evaluated. Immunostaining was performed to examine the number of inflammation cells and myeloid fibroblasts in the kidney. Proinflammatroy molecule expression was assessed by rela-time RT-PCR. Renal fibrosis and extracellular matrix protein production were determined by sirius red staining, immunostaining and Western blot. Transwell migration assay was performed to determine the role of PI3Kγ in the regulation of cell migration in vitro.

Results: WT and PI3Kγ KO mice had virtually identical blood pressure at baseline. Angiotensin II treatment led to an increase in blood pressure that is similar between WT and PI3Kγ KO mice. Compared with WT mice, PI3Kγ KO mice were protected from angiotensin II-induced renal dysfunction and injury and developed less proteinuria. PI3Kγ deficiency suppressed bone marrow-derived fibroblast accumulation and myofibroblast formation in the kidney and inhibited total collagen deposition and ECM protein production in the kidney in response to angiotensin II. PI3Kγ deficiency inhibited infiltration of $F4/80^+$ macrophages and $CD3^+$ T cells into the kidney and reduced gene expression levels of proinflammatory cytokines in the kidney following angiotensin II treatment. Inhibition of PI3Kγ with AS605240 suppressed CXCL16-induced Akt activation and monocyte migration in vitro.

Conclusions: Our results indicate that PI3Kγ plays a pivotal role in the development of hypertensive kidney injury and fibrosis through regulation of macrophage and T cell infiltration and bone marrow-derived fibroblast accumulation.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO1096

A Novel Approach for Evaluation of Cleavage of Angiotensin Peptides by Their Angiotensinase Partners Jan Wysocki, Tilman Müller, Pan Liu, Jing Jin, Daniel Batlle. *Division of Nephrology and Hypertension, The Feinberg School of Medicine, Northwestern University, Chicago, IL.*

Background: Angiotensin (1-7) formation from AngII (1-8) occurs via a release of a single c-terminal phenylalanine (Phe). ACE2 and prolylendopeptidase (PEP) are angiotensinases known to cleave Phe from Ang II to form Ang1-7. To capture physiologically important enzymatic conversion of other biologically active angiotensins, such as Ang III (2-8), we used a new quantitative fluorimetric assay which detects the cleaved c-terminal Phe. Since Phe is relatively stable in tissue lysis conditions, this method should provide new insights into specific angiotensinase activities involving Phe cleavage in complex biological samples, such as the kidney, an organ rich in angiotensins and angiotensinases.

Methods: An assay detecting the release of Phe from Ang Peptides in a reaction with the Phe ammonia lyase was used in vitro with recombinant (r) angiotensinases (ACE2, PEP) and ex vivo using kidneys from C57bl/6 mice.

Results: *In vitro*, rACE2 and rPEP caused Phe release from Ang II to form Ang 1-7, as anticipated. Ex vivo incubation of kidney lysates with Ang II and Ang III (10^{-3}M) resulted in a marked generation of Phe. Of note, *Ex vivo* Phe generation from Ang II was significantly higher than that of Ang III (2373±98 vs. 1820±153 RFU/ug prot, n=5, $p<0.05$, respectively). Aminopeptidase A (APA), which is abundant in the kidney, converts Ang II to Ang III (2-8) and the subsequent cleavage of Ang III to Ang (2-7) could generate Phe as well. Consistent with this, an APA inhibitor amastatin (10^{-5}M) reduced significantly Phe cleavage from Ang II in kidney lysates (2373±98 vs. 1906±101, n=5, $p<0.01$, respectively). In addition, purified rACE2 and rPEP caused Phe release from Ang III showing that both enzymes convert Ang III to Ang 2-7. This shows that a substantial portion of Phe formation within kidney during Ang II exposure occurs downstream of this main peptide and that Ang III (2-8), an active metabolite, is also efficiently degraded by endogenous angiotensinases such as ACE2 and PEP.

Conclusions: The new assay detects c-terminal Phe cleavage from Ang II(1-8) but also other Ang peptides, such as Ang III, by ACE2 and PEP, angiotensinases not previously known to cleave this important peptide. This method provides a new tool in evaluating kidney enzyme activities involving cleavage of Phe from bioactive peptides that have this amino acid in c-terminal position.

SA-PO1097

Renin-Independent Blood Pressure Development in Dahl Salt-Sensitive Rats Daria Ilatovskaya,[2] Vladislav Levchenko,[2] Denisha R. Spires,[2] Tengis S. Pavlov,[1] Alexander Staruschenko.[2] *[1]Henry Ford Health System, Detroit, MI; [2]Medical College of Wisconsin, Milwaukee, WI.*

Background: RAAS is considered to be the central regulator of water and salt homeostasis; angiotensin receptors' and/or ACE inhibitors are widely employed to control blood pressure (BP) in humans. Here we used renin knockout ($Ren^{-/-}$) rats created on the Dahl Salt-Sensitive (SS) rat background to study renin-independent BP development; these rats exhibit polyuria, reduced weight and lower mean arterial pressure (MAP) compared to wild type controls.

Methods: To test the involvement of renin in the BP regulation of the Dahl SS rats, 9 week old $Ren^{-/-}$ rats and their wild type littermates were kept on 0.4% NaCl diet since weaning (normal salt, NS), and then challenged with sodium deficient (SD, 0.01%) or high salt (HS, 4% NaCl) diets for 11 days. BP was recorded via telemetry, and kidney function and tissue damage were assessed.

Results: On NS diet $Ren^{-/-}$ rats have a significantly lower MAP compared to littermates (65.9 ± 2.1 vs 121.9 ± 1.9 mmHg). After a HS diet was introduced, we observed a very fast raise in MAP in the $Ren^{-/-}$ rats (ΔMAP was 60.4 ± 7.1 mmHg over a 5 day period, compared to 5 ± 0.4 mmHg in the littermates). In the $Ren^{-/-}$ group HS diet caused mortality within 8 days, which was not observed in the littermates. SD diet did not affect BP and survival rates in either group. 24 hr urinary output was increased in the wild type littermates on HS (not measured in the $Ren^{-/-}$ group due to mortality). However, in all SD diet fed groups urinary output was reduced (15.7 ± 1.7 vs 2.5 ± 0.2 ml/100g before diet switch, and 1.9 ± 0.7 vs 4.8 ± 0.9 ml/100g on SD diet ($Ren^{-/-}$ vs littermates)). On NS diet GFR was found to be lower in the $Ren^{-/-}$ rats (0.18 ± 0.03 ml/min/100g vs 0.54 ± 0.04 in littermates), and HS diet induced an increase in GFR in the littermates on day 10, whereas SD diet did not affect GFR in either group. No difference was found in electrolyte excretion between groups fed a SD diet. Histological analysis revealed exacerbated damage to the hearts and kidneys of the $Ren^{-/-}$ rats fed a SD diet compared to wild type littermates.

Conclusions: BP in the $Ren^{-/-}$ Dahl SS rat increases in response to salt intake, which suggests an involvement of the non-renin components in this mechanism; however, $Ren^{-/-}$ animals are able maintain homeostasis when challenged a SD diet. These data open new avenues to understanding the role of RAAS in SS hypertension.

Funding: NIDDK Support, Other NIH Support - NHLBI

SA-PO1098

Thymosin β4 Deficiency Accelerates Renal Fibrosis and Damage in Angiotensin-II Hypertension Nitin Kumar, Tang-Dong Liao, Cesar A. Romero, Mani Maheshwari, Oscar A. Carretero. *Henry Ford Hospital, Detroit, MI.*

Background: Angiotensin-II (Ang-II)-induced hypertension is associated with renal fibrosis and damage. Thymosin β4 (Tβ4) regulates cell morphology, inflammation and fibrosis in several organs and administration of exogenous Tβ4 is protective in diabetic nephropathy. However, role of endogenous Tβ4 in hypertension-induced renal damage is unknown. We *hypothesize* that, loss of Tβ4 accelerates renal fibrosis and damage in Ang-II hypertension.

Methods: Tβ4 knockout (Tβ4 KO) and wild-type (WT) C57BL/6 mice (n=6-14) were infused continuously for six-weeks with either Ang-II (980 ng/kg/min) or vehicle via osmotic minipumps. Blood-pressure was measured weekly by non-invasive tail-cuff method. Urinary albumin (24 hours urine collection) and renal cortex collagen were measured by ELISA and hydroxyproline assay, respectively. Renal cortex expressions of nephrin and α-smooth muscle actin (α-SMA) were evaluated by western blot.

Results: All the results are presented in table 1. In Ang-II infusion, systolic blood-pressure was not different between WT and Tβ4 KO mice (Table 1). Interestingly, urinary albuminuria was significantly higher in Tβ4 KO mice compared to WT mice by Ang-II infusion. Tβ4 is highly expressed in the glomeruli along with the high expression of nephrin, an important protein in the filtration barrier of the kidney. In Ang-II infusion, nephrin protein expression was greatly reduced in mice deficient of Tβ4, suggesting that loss of nephrin is one of the mechanisms for elevated urinary albumin in Tβ4 KO mice. Additionally, renal fibrosis in the cortex was higher in Tβ4 KO mice and this was accompanied by elevated profibrotic α-SMA protein expression. Susceptibility to Ang-II induced kidney damage in Tβ4 KO mice may be associated with the observed high mortality rate in these mice.

Conclusions: These data indicate that, in Ang-II hypertension, loss of endogenous Tβ4 caused significant renal fibrosis, damage and mortality, suggesting renal protective role of Tβ4.

Funding: Other NIH Support - NHLBI

Table 1

Parameters	WT-Vehicle	Tβ4 KO-Vehicle	WT-Ang-II	Tβ4 KO-Ang-II
Systolic Blood-Pressure (mmHg)	103±4	113±8	164±11‡	159±7°
Urinary Albumin (μg/24hrs)	37±3	50±8	312±35‡	9143±1267*†
Nephrin Protein Expression (Arbitrary Units)	1.23±0.12	1.15±0.05	0.89±0.07‡	0.59±0.08*†
Total Collagen in Kidney (μg/mg dry kidney weight)	10.7±0.73	13.9±1.3	15.24±0.3‡	17.91±0.65*†
Renal α-SMA Protein (Arbitrary Units)	0.11±0.07	0.20±0.02	0.66±0.06‡	0.89±0.04*†
Survival Rate (%)	100	100	100	57#

‡ P<0.005 WT-Vehicle versus WT-Ang-II. * P<0.005. # P<0.05 Tβ4 KO-Vehicle versus Tβ4 KO-Ang-II. † P<0.005 WT-Ang-II versus Tβ4 KO-Ang-II.

SA-PO1099

Aldosterone Breakthough Does Not Affect Central Hemodynamics Andrew Beenken,[2] Andrew S. Bomback.[1] *[1]Columbia University, New York, NY; [2]New York Presbyterian/Columbia University, New York CIty, NY.*

Background: Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) are widely used in patients with congestive heart failure (CHF) and chronic kidney disease (CKD), but up to 40% of patients on these agents experience aldosterone breakthrough, with aldosterone levels rising above pre-treatment levels after 6-12 months of RAAS blockade. Aldosterone breakthrough has been associated with worsening CHF and CKD, yet the pathophysiology remains unclear. While aldosterone breakthrough has not been associated with elevated peripheral blood pressure (PBP), no studies have yet evaluated the effect of breakthrough on central blood pressure (CBP).

Methods: In this cross-sectional study, 19 subjects with well-controlled PBP (<140/90), on stable doses of ACEi/ARB for >1 year, had aldosterone levels checked and CBP parameters measured using the SphygmoCor® system. The CBP parameters of subjects with or without breakthrough, defined as serum aldosterone >15 ng/dL, were compared.

Results: Of 19 subjects, 6 had breakthrough with a mean aldosterone level of 33.8 ng/dL, and 13 were without breakthrough with a mean level of 7.1 ng/dL. There was no significant difference between subjects with and without breakthrough in any of the CBP parameters (mmHg), including CBP (92 ± 16 vs. 95 ± 8, p=0.5), central pulse pressure (40 ± 10 vs. 34 ± 11, p=0.2), augmentation pressure (10 ± 5 vs. 7 ± 6, p=0.3), and augmentation index (16 ± 8 vs. 16 ± 12, p=0.4).

Conclusions: We found no correlation between aldosterone breakthrough and CBP. Accordingly, the clinical impact of aldosterone breakthrough on CKD and CHF likely depends on its non-genomic, pro-fibrotic, and pro-inflammatory effects rather than its regulation of extracellular volume.

SA-PO1100

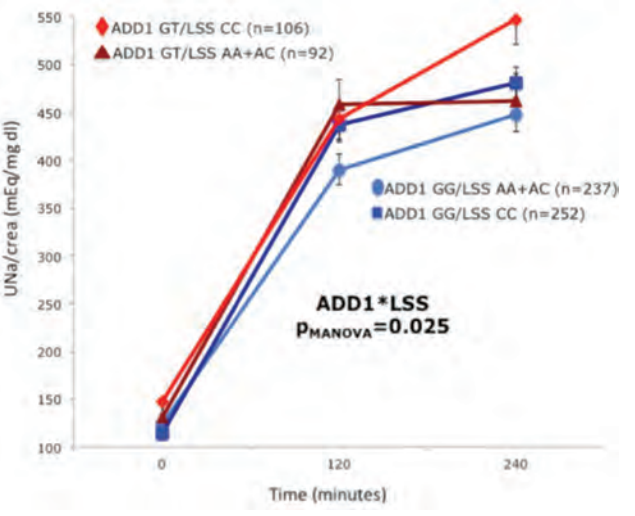
Alfa-Adducin and Lanosterol Synthase Interaction Cause Renal Impairment in Salt Sensitive Hypertension Chiara Lanzani,[4] Simone Fontana,[7] Chiara Maggioni,[4] Laura Zagato,[2] Elisabetta Messaggio,[6] Lorena Citterio,[8] Marco Simonini,[4] Elena Brioni,[9] Simona Delli carpini,[3] John Hamlyn,[5] Paolo Manunta.[1] *[1]HSR-Nefrologia, Milano, Italy; [2]Ospedale San Raffaele, Milano, Italy; [3]San Raffaele Hospital, Milano, Italy; [4]San Raffaele Scientific Institute, Milan, Italy; [5]University of Maryland, Baltimore, Baltimore, MD; [6]Università San Raffaele, Milano, Italy; [7]Università Vita Salute San Raffaele, Milan, Italy; [8]Università Vita-Salute - Ospedale San Raffaele, Milano, Italy; [9]ospedale San Raffaele, Milan, Italy.*

Background: The study of genes involved in the development of renal damage and salt sensitive hypertension (SSH) are still unknown. Impaired renal function is considered the major determinant of salt sensitive hypertension. To explore the role of alpha-adducin (ADD1) and lanosterol synthase (LSS) genes coding for two structural proteins of cell membrane, we studied their genetic interactions that regulate renal function and arterial pressure after saline loading in naïve hypertensive patients (NHP).

Methods: Acute saline load (NaCl 308 mEq/2 h e.v.) was performed in 701 NHP (age 44.95 ± 9.61 years, male 568, female 133), where functional and hormone renal parameters were tested.

Results: Under baseline conditions NHP carriers of the genotype LSS AA (n = 57, 114.8±3.8 ml/min) have a significantly reduced GFR (p = 0.039) compared to homozygous LSS CC subjects (126.08 ± 1.6 ml /m). After acute saline test both are able to increase the filtrate. Carriers of the LSS AA genotype show a slight increase in EO from 231 ± 29 to 242 ± 35, compared to LSS CC, where instead a significant (p=0.05) reduction is observed from 252 to 220 ± 15 pMol/L. The analysis of gene*gene interactions demonstrates that NHPs carrying mutated GT ADD1 and homozygous for LSS C variants excreted the sodium load more rapidly than their wild type ADD1*LSS polymorphism counterparts (Fig 1).

Conclusions: The results of this work demonstrate: First, patients with LSS AA genotype have a reduced glomerular filtrate under basal conditions; second, LSSAA should be define EO non modulator, since the are not able to decrease EO; third, the ADD1*LSS interaction may identify those NHPs with exaggerate natriuresis after saline load.



SA-PO1101

Combination of High Fructose and High Salt Increases Renal Sodium Reabsorption and Blood Pressure That Is Dependent on Ketohexokinase Takahiro Hayasaki,[1] Takuji Ishimoto,[1] Tomohito Doke,[1] Tomoki Kosugi,[1] Miguel A. Lanaspa,[2] Naotake Tsuboi,[1] Richard J. Johnson,[2] Shoichi Maruyama.[1] *[1]Nagoya University Graduate School of Medicine, Nagoya-shi, Japan; [2]University of Colorado Denver, Aurora, CO.*

Background: High fructose intake has been reported to induce metabolic syndrome in laboratory animals and humans. Although it has been also reported that fructose intake enhances sodium reabsorption and causes the elevation of blood pressure (BP), its mechanism is unclear. Here, we examined whether fructose metabolism by the primary enzyme of fructose, ketohexokinase (KHK) regulates sodium reabsorption and BP by using KHK deficient mice (lacking both isoform A and C, KHK-KO).

Methods: Male, C57BL/6, wild-type mice (WT) and KHK KO were used. Study 1; WT and KHK KO were fed with control diet (CD) or 4% high salt diet (HSD), and 10% fructose water (Fr) or tap water (Wa). BP was measured every week (tail cuff), and samples were collected at 5 weeks. Pathological analysis was done, and renal and jejunal KHKs and NHE3 (sodium-hydrogen exchanger 3) expressions were assessed. Study 2; To investigate the effect of fructose intake on renal sodium reabsorption without intestinal absorption, control WT and KHK KO mice and those fed CD and Fr for 5 weeks were administered intraperitoneally with 1.5 ml of normal saline, then urine was collected 6 hours later.

Results: Study 1; KHK was colocarized immunohistochemically with NHE3 in proximal tubular cells in WT. Combination of HSD and Fr for 5 weeks induced the elevation of BP with the decrease of urinary sodium excretion and the increase of renal expression of KHK-C and NHE3 in WT, but not in KHK KO. WT fed HSD without Fr did not show the elevation of BP nevertheless of higher amount of sodium intake than WT fed HSD and Fr. Jejunal NHE3 was tend to increase in WT fed HSD and Fr than KHK KO. Study 2; Urinary sodium excretion after intraperitoneal sodium loading was reduced in WT given Fr compared with that of the control WT. In KHK KO, that reduction was not observed, and renal NHE3 expression was lower than WT.

Conclusions: These results suggest that fructose metabolism by KHK is involved in the development of salt-sensitive hypertension through increases of renal sodium reabsorption by NHE3.

SA-PO1102

Na/K-ATPase Signaling as an Amplifier of Oxidative Stress Contributes to the Increased Salt Sensitivity of Obese Hypertension Yanling Yan, Muhammad A. Chaudhry, Ying Nie, Jung Han Kim, Zi-jian Xie, Joseph I. Shapiro, Jiang Liu. *Marshall University School of Medicine, Huntington, WV.*

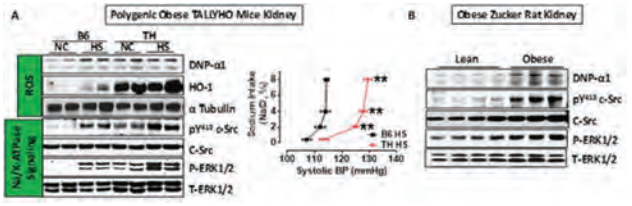
Background: Na/K-ATPase acts as a receptor for reactive oxygen species (ROS) and amplifies ROS signaling, regulating renal sodium excretion (JBC, 2011&2013; JAHA, 2016). Whether or not these pathways are involved in the pathogenesis of obese hypertension due to impaired Na/K-ATPase signaling has not been investigated.

Methods: Blood pressures were measured using the tail-cuff method. Na/K-ATPase signaling activation was assessed in the kidney cortex from high fat (HF)-induced obese C57BL/6J (B6) mice, polygenic obese TALLYHO/JngJ (TH) mice and obese Zucker rats by measuring the phosphorylation of c-Src and ERK1/2 by Western blot. Protein carbonylation (DNP) and heme oxygenase 1 (HO-1) as a commonly used marker for oxidative stress were used to measure the levels of ROS. Renal function curve was constructed with high salt diets (HS, 2, 4, and 8% NaCl).

Results: In the kidney cortex tissue, the Na/K-ATPase signaling (c-Src and ERK1/2 phosphorylation) and oxidative stress (protein carbonylation and HO-1) were activated and were not stimulated by HS diets in obese TH mice (comparing to B6 mice, Figure

A, left panel). Moreover, in salt-loading experiments (with 2, 4, and 8% NaCl), we demonstrated that obese TH mice exhibited an increased salt sensitivity of blood pressure, characterized by a right-shifted, reduced slope in renal function curve (Figure A, right panel, p<0.01). We also observed had a higher baseline oxidative stress and Na/K-ATPase activation in Obese Zucker rats (comparing to lean Zucker rats, Figure B) and high fat-induced obese B6 mice.

Conclusions: Na/K-ATPase signaling activation as a commonly featured characteristic in obese mice and rat was implicated in the increased salt sensitivity of obese hypertension. Further studies targeting Na/K-ATPase signaling will explore the potential nodes for therapeutic intervention and precise target localization to render the required pharmacologic therapy more effective, minimizing the need for medications.



SA-PO1103

Loss of Urine Concentration and Subsequent Dehydration Characterizes Hypertension in Rats with Chronic Renal Failure Johannes J. Kovarik,[11] Kento Kitada,[5] Adriana Marton,[9] Steffen Daub,[1] Yahua Zhang,[9] Tetyana Pedchenko,[10] Yan Zhao,[10] Janet D. Klein,[2] James L. Bailey,[4] Nada Cordasic,[7] Karl F. Hilgers,[8] Jeff M. Sands,[3] Akira Nishiyama,[6] Jens Titze.[9] *[1]Department of Clinical Pharmacology, Vanderbilt University Medial Center, Nashville, TN; [2]Emory University, Atlanta, GA; [3]Emory University Renal Division, Atlanta, GA; [4]Emory University School of Medicine, Atlanta, GA; [5]Kagawa University, Kagawa, Japan; [6]Kagawa University Medical School, Kita-Gun, Japan; [7]University Hospital of Erlangen, Erlangen, Germany; [8]University of Erlangen, Erlangen, Germany; [9]Vanderbilt University, Nashville, Romania; [10]Vanderbilt University Medical Center, Nashville, TN; [11]Division of Clinical Pharmacology, Vanderbilt University, Nashville, TN.*

Background: The pressure-natriuresis concept suggests that blood pressure-driven increase in renal salt excretion in parallel normalizes the extracellular volume (ECV). In contrast to this traditional view, we have recently shown, that the biological principle of renal salt excretion is urea-driven ECV control by the renal concentration mechanism. We tested the hypothesis, whether hypertension in rats with experimental renal failure (5/6Nx) is characterized by body water loss due to an inability to concentrate the urine.

Methods: We investigated urine flow, osmolyte excretion, urine concentration, arterial blood pressure, and hepatic and extrahepatic urea generation in 5/6Nx (n=23; renal mass ablation) and sham-operated (n=19) Sprague-Dawley rats.

Results: 7 weeks after renal mass ablation, 5/6Nx rats increased their arterial blood pressure by 24.4±20.1 mmHg (P<0.05). Hypertensive 5/6Nx rats showed dehydration with a 13.8±7.0 mOsm/kg increase in plasma osmolality (P<0.001) and reduced ability to concentrate the urine (urine osmolality reduced by -771±590 mOsm/kg; P<0.001). In anesthetized animals, we found a direct relationship between 2Na+2K+Urea osmolyte excretion and urine flow (y=1.24x-3.3; R^2=0.75), indicating osmotic diuresis. 5/6Nx rats showed pronounced 2Na+2K+Urea osmolyte loss (+13.2±5.1 mmol/d) with predominant urea loss (+13.4±4.9 mmol/d) which increased the urine volume by +19.5±7.4 ml/d (all P<0.001) and was paralleled by only discrete Na^+ loss and K^+ retention. In conscious 5/6Nx rats, the urea-driven loss of the renal concentration ability was coupled with a +37.9±15.1 ml/d increase in free-water clearance, indicating renal water loss. The renal urea leak resulted in compensatory increases in urea osmolyte generation in skeletal muscle (arginase activity: +8.7±6.7 units/L/kg, P<0.05; urea content: +1.9±1.2, P<0.01) in 5/6Nx rats.

Conclusions: Hypertension in a rat model of chronic renal failure is characterized by urea-driven loss of the renal concentration mechanism, which leads to increased renal water loss and extracellular volume contraction. Our findings indicate that sodium retention with subsequent volume overload is not the underlying cause of blood pressure increase in 5/6Nx rats.

SA-PO1104

Intrarenal High Salt Administration Causes Tonic Inhibition of Renal Sympathetic Nerve Activity (RSNA) Martin Hindermann,[1,3] Kristina Rodionova,[1,2] Amelie Dietz,[1] Tilmann Ditting,[1] Chrstian Ott,[1,2] Roland E. Schmieder,[1] Kerstin U. Amann,[3] Roland Veelken.[1,2] *[1]Dept. of Nephrology, Friedrich-Alexander-University Erlangen, Erlangen, Germany; [2]Paracelsus Medical University Nuremberg, Nuremberg, Germany; [3]Dept. of Nephropathology, Friedrich-Alexander-University Erlangen, Erlangen, Germany.*

Background: Afferent renal nerve fibers from the kidney likely counterregulate salt sensitive blood pressure increases by decreasing renal sympathetic nerve activity. We recently reported on a long-lasting tonic sympatho-inhibition due to intrarenal afferent renal nerve stimulation eliciting a TRPV1 dependent neuro-humoral pathway. We wanted to test the hypothesis that sodium influences this afferent sympatho-depressory mechanism.

Methods: Groups of anesthetized SD rats (n=8) were equipped with femoral catheters (blood pressure (BP) & heart rate (HR) recording, drug application), a renal arterial catheter for intrarenal administration (IRA) of high salt (10 % NaCl, 10 µl) or Capsaicin (CAP 3.3, 6.6, 10, $33*10^{-7}$ M, 10 µl) and a bipolar electrode for RSNA recordings; eventually an intravenous (iv) bolus of the NK_1-receptor blocker RP67580 ($10*10^{-3}$M, 15 µl) was given. Cultured dorsal root ganglion neurons (Th11-L2) of rats with renal afferents were investigated in current clamp mode to assess action potential generation or in voltage clamp mode to investigate inward currents during 10 sec exposure to 4.5 % NaCl or equi-osmotic 20% mannitol. Results are given in mean±SEM.

Results: IRA high salt and IRA CAP decreased RSNA from baseline 4.1±0.6 µV*sec to 2.2±0.8 µV*sec (10% NaCl, p<0.05) and 3.9±0.5 µV*sec to 0.9±0.2 µV*sec (CAP, p<0.01). Suppressed RSNA in high salt groups and CAP could be unmasked by systemic (i.v.) administration of the NK_1-blocker (2.7±1.8 µV*sec to 5.8±2.2 µV*sec; p<0.05 (10% NaCl); 1.0±0.2 µV*sec to 6.1±1.5 µV*sec; p<0.01 (CAP)). Cultured renal neurons exhibited production of action potentials (3.5±0.8*, from baseline, p<0.05) and increased sustained inward currents from baseline during exposure to NaCl 4.5 % (-10708.8±3546.5 pA*, from baseline, p<0.05). No responses to mannitol 20%.

Conclusions: Increased intrarenal sodium concentrations might induce long-lasting sympatho-depression via a neuro-humoral TRPV1 dependent and tachykinin mediated afferent nerve pathway from the kidney. Impairment of this sympatho-depressory mechanism could be involved in salt sensitive hypertension.

SA-PO1105

Identification of an miRNA That Regulates Sodium-Hydrogen Antiporter 1 Expression in the Medullary Thick Ascending Limb of a High Sodium Induced Hypertension Rat Model Patrizia Lombari,[4] Massimo Mallardo,[6] Joseph amruthraj Nagoth,[7] Oriana Patrazzuolo,[3] Giuseppe Fiume,[2] Sara Damiano,[3] Diego Ingrosso,[5] Anna Iervolino,[1] Giovambattista Capasso.[1] *[1]University of Campania Luigi Vanvitelli, Napoli, Italy; [2]Università degli Studi di Catanzaro ?Magna Graecia?, Catanzaro, Italy; [3]Università degli studi della Campania, Naples, Italy; [4]Department of Cardio-Vascular Medicine, Università degli studi della Campania, Naples, Italy; [5]Università degli studi della Campania "L. Vanvitelli", Naples, Italy; [6]Università degli studi di Napoli "Federico II", Naples, Italy; [7]Department of Cardio-Vascular Medicine, Università degli studi della Campania, Naples, Italy.*

Background: The kidney is one of the principle candidate organs involved in the etiology of essential hypertension. In particular, the medullary thick ascending limb (MTAL) of kidney is important in maintaining acid-base balance by reabsorbing most of the filtered bicarbonate, which is not reabsorbed by the proximal tubule. Microarray expression profiling studies in human revealed different expression profiles of microRNAs in hypertensive vs normotensive patients. In this study, we analyzed miRNA expression profiles in isolated MTAL taken from high sodium intake induced hypertensive rats (HSD) versus their normotensive counter parts (NSD).

Methods: Male Sprague Dawley rats weighing about 185-298 g (Charles river) were allowed free access to standard rodent chow (NIH 31 diet, Ziegler Bros., Gardeners, PA) and drinking solution up to the time of experiments. Control rats were fed with normal drinking water (NSD) and rats on HS-in were fed with 0.28 M NaCl in drinking water (HSD) for 15 days. Renal tubule isolation was performed following method described on Hofmeister, M. V. et al (Am J Physiol Renal Physiol 2009; **296**:F194-203) and the total RNAs was analyzed by genome-wide miRNAs expression profile in MTAL dissected from rats upon HSD or NSD

Results: We have identified seven miRNAs, involved in the onset of salt sensitive hypertension, among them one was the most strongly down-regulated. We identified the sodium-hydrogen antiporter 1 (NHE1) mRNA as a putative target of this miRNA, by in silico analysis. Our data showed that this miRNA is downregulated in the MTAL of HSD rats while NHE1 is upregulated, we also checked whether the levels of protein NHE1 could be lowered by overexpression of the identified miRNA. To verify this hypothesis we overexpressed this miRNA in MTAL cell line, by retroviral infection, and observed a downregulation of NHE1 protein.

Conclusions: Our result indicate NHE1 as a target of the identified miRNA and that the expression of this miRNA is influenced by high sodium intake in thick ascending limbs of rats.

SA-PO1106

Reciprocal Regulation between the Renal Endothelin and Circadian Rhythm Systems Michelle L. Gumz,[1,2] Lauren G. Douma,[1] I. Jeanette Lynch,[1] Kristen Solocinski,[1] Kit-yan Cheng,[1] Brian D. Cain,[1] Charles S. Wingo.[1,2] *[1]University of Florida, Gainesville, FL; [2]NF/SG Veterans Health System, Gainesville, FL.*

Background: Mice lacking the circadian rhythm gene Per1 exhibit non-dipping hypertension in response to a high salt diet plus mineralocorticoid treatment (HS/DOCP). We hypothesized that Per1 knockout (KO) mice have a renal Na handling defect involving ET-1 that contributes to non-dipping hypertension. ET-1 can mediate renal injury in salt-sensitive hypertension.

Methods: Twelve hour urine collections were made in metabolic cages to determine the night:day ratio of urine Na excretion in WT vs. Per1 KO mice in response to HS/DOCP. We assessed Per1 transcriptional activity using quantitative real time RT-PCR.

Kidney cortex RNA was collected from WT and Per1 KO mice on control or HS/DOCP treatment at noon, the time when BP dips in WT mice but remains high in Per1 KO mice.

Results: WT mice exhibited a high night:day ratio of Na excretion but, Per1 KO had a significant reduction in the night:day Na excretion ratio (WT:6, KO:2, P<0.05). To explore the molecular mechanisms underlying this phenotype, we examined expression of *Edn1* which encodes the peptide hormone endothelin-1 (ET-1). ET-1 mRNA levels did not change in WT in response to HS/DOCP. In contrast, Per1 KO mice exhibited increased expression of ET-1 mRNA in the renal cortex (40% increase, p<0.01). To test the hypothesis that there is reciprocal regulation between ET-1 and the molecular clock, we measured Per1 mRNA expression in the kidneys of collecting duct-specific ET-1 KO mice compared to WT controls after HS/DOCP treatment. Per1 expression was reduced by 50% in the renal medulla of CD ET-1 KO mice relative to WT mice (p<0.01).

Conclusions: The reduced night:day ratio in urine Na excretion suggest that a renal Na handling defect may contribute to non-dipping hypertension in Per1 KO mice. Per1 appears to be a negative regulator of ET-1 expression during HS/DOCP, whereas ET-1 may play a role in the positive regulation of Per1 expression. These data indicate that reciprocal regulation between renal ET-1 and the molecular clock, specifically Per1, occurs and may constitute a new feedback loop in mineralocorticoid-sensitive renal Na handling.

Funding: NIDDK Support, Private Foundation Support

SA-PO1107

Dietary Sodium-Induced Changes in the Microcirculatory System of the Skin Are Associated with Blood Pressure Response in Healthy Males Eliane F. Wenstedt, Rik H. Olde Engberink, Nienke M. Rorije, Bert-jan Van den born, Jan Aten, Liffert Vogt. *Academic Medical Center, Amsterdam, Netherlands.*

Background: Studies indicate that not only the kidney but also the skin microcirculation might be pivotal for a sodium-sensitive blood pressure (BP) response. While high sodium diet (HSD) is associated with reduced density of blood capillaries, animal studies showed an increment of skin lymphatic capillaries in both amount and size. We investigated sodium-induced changes in both lymphatic and blood skin microcirculation of healthy males in relation to blood pressure (BP).

Methods: We performed a randomized crossover study in healthy males. All subjects pursued an 8-day low sodium diet (LSD: <50 mmol Na+/day) and HSD (>200 mmol Na+/day). Diet order was randomized and time in-between diets was 1-2 weeks. After each diet, BP measurements and skin biopsies were obtained. Endothelia of blood (CD31) and lymphatic capillaries (D2-40) were identified through immunohistochemistry.

Results: Overall (n=12, mean age 22 years), there was no BP increase after HSD vs. LSD (mean arterial pressure (SD): 78 (5) vs. 78 (5), p=0.66). HSD increased lymphatic cross sectional surface area (p=0.01). No differences in lymphatic or blood capillary density were observed. There was a correlation between lymphatic and blood capillary density after LSD but not after HSD (fig 1a). Differences in mean arterial pressure between LSD and HSD correlated with changes in blood capillary density (fig 1b), but not with lymphatic capillary density or cross sectional surface area.

Conclusions: HSD is associated with skin lymphangiogenesis and a loss of correlation between the lymphatic and blood microcirculation. Blood microcirculatory changes correlate with BP response, possibly playing a role in sodium-sensitive hypertension development.

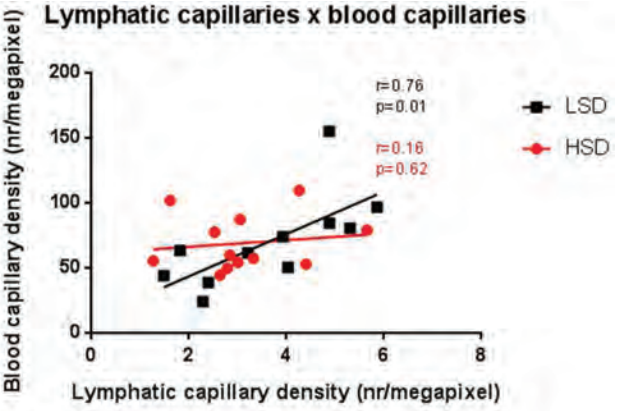


Fig 1A. Correlation between lymphatic capillary density and blood capillary density after low sodium diet (LSD) and high sodium diet (HSD). Densities are expressed as the number of lymphatic/blood capillaries per megapixel (= 1.000.000 pixels).

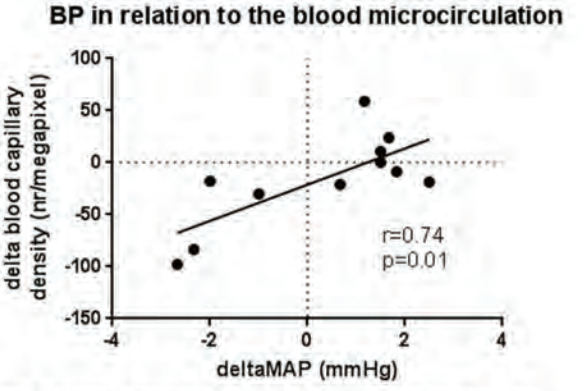


Fig 1B. Absolute differences in mean arterial pressure (MAP) between high sodium diet (HSD) and low sodium diet (LSD) in relation to absolute differences in blood capillary density between HSD and LSD.

SA-PO1108

Changes in Phosphorylation and Expression of Sodium Transporters in Pre-Eclampsia Detected in Urinary Exosomes Peter F. Mount,[1,4] CHIH-CHIANG Hu,[5] Marina Katerelos,[1,5] Suet-Wan Choy,[1,3] Natasha Cook,[1] Amy A. Crosthwaite,[1,3] Gabrielle L. Pell,[3] Kathy Paizis,[2,3] Susan P. Walker,[3,4] David A. Power.[1,4] *[1]Austin Health, Melbourne, VIC, Australia; [2]Austin health, Heidelberg, NSW, Australia; [3]Mercy Health, Melbourne, Vic, NSW, Australia; [4]University of Melbourne, Melbourne, VIC, Australia; [5]Kidney Laboratory, Institute for Breathing and Sleep, Melbourne, VIC, Australia.*

Background: PE (pre-eclampsia) is characterized by hypertension, vasoconstriction, proteinuria and renal sodium retention. It is unknown whether expression or phosphorylation of the distal renal tubular sodium transporters (NKCC2, NCC and EnaC) changes in women with PE.

Methods: A cross-sectional study of 18 PE patients, 22 normotensive pregnant women (NP) and 20 normal women (NC) was performed. Exosomes were isolated from urine by ultracentrifugation. Expression of sodium transporters was analysed by Western Blot corrected for expression of the exosome marker CD9. Statistical comparisons were made by ANOVA and a post-hoc test.

Results: Expression of NKCC2 was increased 1.6-fold in PE (ANOVA p=0.046, post-hoc=ns). Phosphorylation on the SPAK/OSR1 activation site T101/105 was reduced 1.9-fold (ANOVA p=0.030; PE vs NP p<0.05) while phosphorylation of the activating PKA S130 site was increased 2.8-fold (ANOVA p<0.001; PE vs NP p<0.01) in PE compared to NP. There was no difference in expression of NCC but phosphorylation of the SPAK/OSR1 site T60 was reduced 2.5-fold (ANOVA p=0.008; PE vs NP p<0.05). Expression of the alpha (ANOVA p<0.001; PE vs NP p<0.01) and full-length gamma ANOVA (p<0.001; PE vs NP p<0.05) subunits of ENaC was increased 6.0-fold and 2.7-fold, respectively, in PE compared to NP. There was a non-significant trend to increased expression of the cleaved 50 kD form of gamma ENaC in PE (ANOVA p=0.06).

Conclusions: These data suggest a role for increased activity of ENaC and NKCC2 in mediating sodium-retention in PE, occurring despite reduced signalling through the WNK/SPAK/OSR1 pathway.

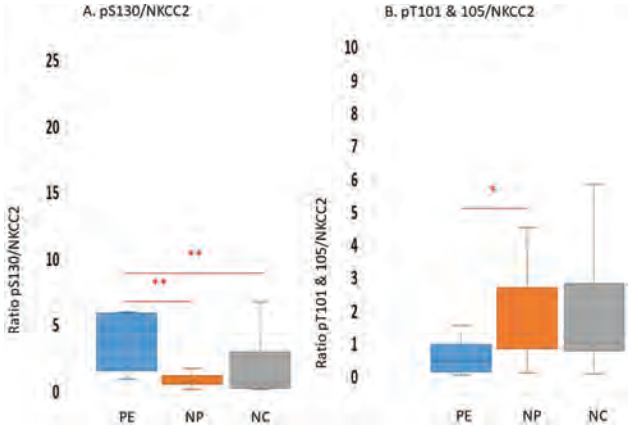


Fig. 1: Phosphorylation of NKCC2 on S130 and T101/105. S130 is a PKA and AMPK phosphosite. T101 and 105 are SPAK/OSR1 phosphosites. (A) pS130/NKCC2: ANOVA p<0.001. PE vs NP, p<0.01; PE vs NC p<0.01. (B) pT101&105/NKCC2: ANOVA p=0.03. PE vs NP, p<0.05.

SA-PO1109

In Obese ZSF1 Rats, Females Show Increased Salt-Sensitivity Compared to Males Isabel T. Nguyen, Bart Boermans, Jaap A. Joles, Marianne C. Verhaar. *Nephrology & Hypertension, UMCU, Utrecht, Netherlands.*

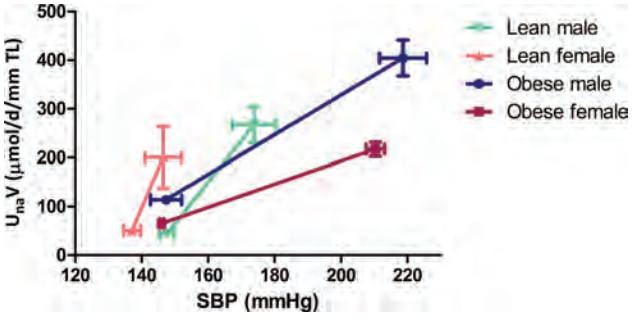
Background: The obese Zucker fatty/spontaneously hypertensive heart failure F1 hybrid (ZSF1) rat has been proposed as a viable animal model to study the metabolic cardiorenal syndrome as these rats spontaneously develop diastolic heart failure and chronic kidney disease in the presence of obesity, hyperglycemia and hypertension. Risk factors associated with the metabolic syndrome correlate strongly with salt-sensitivity of blood pressure. We investigated the interaction of obesity and sex on salt-sensitivity in obese and lean ZSF1 rats. We hypothesized that obesity and male sex would both promote salt-sensitive hypertension.

Methods: Male and female ZSF1 rats, lean as well as obese (n=6/subgroup), were either implanted with a deoxycorticosterone acetate (DOCA) pellet and fed a high salt diet (6% NaCl) or a placebo pellet and fed a normal salt diet from 19 weeks of age. Every two weeks, from 18 (i.e. prior to pellet implantation) to 26 weeks of age, systolic blood pressure (SBP, tail-cuff) and 24-hour natriuresis were measured.

Results: SBP was higher in both obese compared to lean DOCA+6% salt groups (p<0.0001). Natriuresis was higher in male obese vs. lean DOCA +6% salt groups (p<0.05). The SBP response to high salt intake occurred in a stepwise manner in all four DOCA+6% salt groups (with constant SBP from 22 to 24 weeks). Comparison of slopes of the natriuresis-pressure relations using 18 and 26-week data (figure) showed differences between male obese and lean (p=0.01) and female obese and lean (p=0.02) ZSF1 rats, suggesting that obesity promotes salt-sensitivity. Additionally, the slopes between obese males and females differed (p=0.02) suggesting that salt-sensitivity was most marked in female obese ZSF1 rats.

Conclusions: Our results in ZSF1 rats indicate i) a phased blood pressure response to high salt intake, ii) an adverse effect of obesity on salt-sensitivity, and iii) a further increased salt-sensitivity in obese females vs. obese males.

Funding: Private Foundation Support



Natriuresis-pressure relations in ZSF1 rats corrected for mm tibia length (TL).

SA-PO1110

Influence of Dietary K on Angiotensin II Hypertension in Females Luciana C. Veiras,[1] Jessica E. Prescott,[1] Donna Ralph,[2] Alicia A. McDonough.[1] [1]*Keck School of Medicine of USC, Los Angeles, CA;* [2]*University of Southern California, Los Angeles, CA.*

Background: Male Sprague Dawley rats (SDR) infused with angiotensin II, "AngII HTN" (400 ng/kg/min, 14 days) exhibit increased Na^+ transporter activation by phosphorylation (p) or cleavage (cl) in cortical TAL (NKCC2), DCT (NCC), CNT/CD (ENaC) and increased SPAK kinase. Doubling dietary K^+ during AngII HTN prevents NCC, NCCp activation, attributed to ENaC driven K loss. Female SDR at baseline, compared to males, exhibit lower PT transporter activity, higher volume flow from PT (estimated with lithium clearance, CLi), and more abundant NCC, NCCp and ENaC-cl.

Methods: This study aimed to determine the effect of doubling dietary K (1% to 2%) on female SDR at baseline (1K vs 2K) and during AngII HTN (as above, 1KAngII, 2KAngII), n=6/group.

Results: In 2K vs.1K fed female SDR: plasma [Na] and [K] were unchanged and [aldosterone] doubled; in overnight urine: UV was unchanged, UK doubled, UNa increased 1.5 fold (p=0.02); CLi increased 1.7 fold (p=0.02). 2K vs. 1K diet had no effect on NHE3, NKCC2, NCC, ENaC or SPAK abundance or activation assessed by quantitative immunoblot. AngII treatment in female SDR raised BP to 193 ± 8 mmHg, not different in 2K vs 1K. UV increased 1.7 (1KAngII) and 1.8 fold (2KAngII) (both p<0.02). UNaV and UKV were not further changed by AngII in either group. CLi increased in 2KAngII vs 2K by 1.7 fold (p=0.04). In PT paracellular Cldn2 increased 2.2 fold (1KAngII) and 3.8 fold (2KAngII) (p<0.006), AngII increased NHE3 1.4 fold in both 1K and 2 K fed, and increased NHE3p (an inactivation indicator) 1.4 fold in 1KAngII alone. Cortex (not medulla) NKCC2 and NKCC2p were increased 2.2 and 1.8 fold (p=0.002) in the 1KAngII, and the effect was blunted in 2KAngII (to 1.6 and 1.3 fold, p > 0.1). NCCp was borderline increased in 1KAngII (1.4 fold, p = 0.06) and suppressed 50% in 2KAngII vs 1KAngII (p=0.007). Cortex (not medulla) SPAK, was increased 3 fold in both groups. Alpha ENaC was activated in cortex and medulla (>2 fold, p < 0.01) in both groups. Cldn7 increased 25 (1KAngII) and 50% (2KAng).

Conclusions: The results indicate that in female SDR: 1) doubling K intake reduces apparent PT reabsorption (CLi) independent of abundance of PT transporters or plasma [K] associated with natriuresis and the expected kaliuresis. 2) 2K diet during AngII HTN further increases CLi as well as Cldn2, Cldn7 and blunts the effect of AngII on NKCC, NKCCp and NCCp activation.

Funding: NIDDK Support, Private Foundation Support

SA-PO1111

Urinary Sodium-to-Potassium Ratio Associated with Normal Blood Pressure Tanushree Banerjee,[3] Anthony Sebastian,[1] Lynda A. Frassetto.[2] [1]*San Francisco, CA;* [2]*University of California San Francisco, San Francisco, CA;* [3]*University of California, San Francisco, San Francisco, CA.*

Background: Higher levels of sodium intake are reported to be associated with higher blood pressure (BP). Whether this relationship is stronger with urinary sodium to potassium ratio (U[Na/K]) and in those with diagnosed and pre hypertension is not well determined.

Methods: We studied 188 older healthy patients randomized to potassium bicarbonate 30, 60, or 90 mmol/d (KBC treatment) or placebo, for up to 36 months. The 24-hour urine and arterialized blood collections were done at baseline and then at the subsequent follow-up visits. The simple Pearson correlation coefficients (r) between urinary sodium, potassium and U[Na/K], urine pH and systolic and diastolic BP levels were calculated at baseline. The correlation coefficients were also calculated for the dietary equations estimating acid load described as net endogenous acid production (NEAP) by Frassetto, and potential renal acid load (PRAL) by Remer and Manz with urine pH. The association of U[Na/K] and arterial BP was investigated using mixed-effects model, with adjustment for age, weight, height, creatinine clearance, and treatment.

Results: Correlation analyses results are shown in Table 1. Mean arterial BP increased significantly with an increase in the urinary Na/K ratio (β [95% CI]: 0.28 [0.17-0.44]). There was effect modification by treatment (p interaction=0.02). Stratified models by treatment showed a significant association between U[Na/K] and mean arterial BP in those receiving KBC (0.32 [0.20-0.47]) while no significant association was observed in case of placebo (0.24 [-0.02-0.51]). In case of diagnosed and pre hypertension, we did not find a significant association between U[Na/K] and arterial BP (0.05 [-0.22-0.18] in diagnosed and 0.02 [-0.31-0.24] in undiagnosed hypertension). However, in normotensives a significant association was noted (0.31 [0.18-0.49]).

Conclusions: The ratio of urinary Na/K was independently associated with arterial BP even after adjustment for potential confounders, and this association may be more pronounced in normotensives.

Funding: Private Foundation Support

	Systolic BP	Diastolic BP	Urine pH
Urine Na	0.04	-0.07	-0.07
Urine K	-0.03	-0.05	0.09
Urine Na/K ratio	-0.06	-0.08	-0.19 (p=0.007)
NEAP			-0.25 (p=0.008)
PRAL with sodium chloride			-0.37 (p<0.0001)
PRAL without sodium chloride			-0.36 (p<0.0001)

PUB001

Urinary Retinal Binding Protein (uRBP) in Systemic AL Amyloidosis: A Pilot Study Tamer Rezk,[3,5] Rabya H. Sayed,[4] Helen J. Lachmann,[5] Philip N. Hawkins,[5] Christianne Guillotte,[5] Sharon Shreeves,[6] Simon D. Packer,[1] Julian D. Gillmore,[5] Stephen B. Walsh.[2] *[1]BBI Solutions Ltd, Sittingbourne, United Kingdom; [2]UCL, London, United Kingdom; [3]Center for Nephrology, UCL Division of Medicine, London, United Kingdom; [4]University College London, London, United Kingdom; [5]National Amyloidosis Centre, London, United Kingdom; [6]BBI Solutions, Kent, United Kingdom.*

Background: Renal involvement causing progressive proteinuric CKD is present in 70% of patients with systemic AL amyloidosis at diagnosis. Prolonged patient survival, renal survival and preservation of renal function are associated with free light chain (FLC) suppression by chemotherapy. uRBP, an indicator of renal tubular injury, has been used to detect early renal involvement in multiple myeloma. FLCs are known to be toxic to proximal tubules causing cast nephropathy and Fanconi's syndrome. Systemic chemotherapy (proteasome inhibitor based) to suppress FLC production can itself be associated with AKI. We hypothesized that a significant number of patients with systemic AL amyloidosis have proximal tubular dysfunction at baseline and that this may predict renal outcomes.

Methods: All patients with newly diagnosed systemic AL amyloidosis who attended the National Amyloidosis Centre from September 2016 to April 2017 and were enrolled into the ALchemy prospective observational study underwent uRBP analysis along with routine clinical, biochemical and scintigraphy assessments.

Results: Median age was 68yr, eGFR 67ml/min/1.73m^2, and urinary protein creatinine ratio (uPCR) was 311mg/mmol. Median uRBP was 282µg/L (normal range 0–16mg/mmol). There was a significant correlation between uRBP and serum creatinine (Pearson correlation p<0.0001, R 0.6129) and uRBP and uPCR (Pearson correlation p<0.0001, R 0.5323). There was a strong positive correlation between altered fractional excretion of both phosphate and urate with uRBP (Pearson correlation, p<0.0001, R 0.6524).

Conclusions: A significant proportion of patients with systemic AL amyloidosis have both preserved renal excretory function and absence of significant proteinuria but elevated uRBP levels. There is a significant correlation between low molecular weight proteinuria indicating proximal tubular dysfunction with serum creatinine and uPCR. The association between uRBP and fractional excretion of both phosphate and urate indicates genuine proximal tubular dysfunction as opposed to simply 'overflow' from heavy unselective glomerular proteinuria in patients with untreated systemic AL amyloidosis. uRBP excretion may be a novel biomarker of renal involvement in systemic AL amyloidosis and may predict long term renal outcomes in this disease.

PUB002

Modulation of HO-1 Potentiates CI-AKI in Diabetic Rats via NO Sheila M. Fernandes,[1] Cassiane D. da Fonseca,[1] Maria De Fatima Vattimo,[1] Mirian Watanabe,[1] Fernanda T. Borges,[2] Edson A. Pessoa,[2] Luciana soares C. Santos.[1] *[1]School of Nursing, University of São Paulo, Carapicuíba, Brazil; [2]Universidade Federal de São Paulo, São Paulo, Brazil.*

Background: CI-AKI is a toxic nephropathy with generation of oxygen species (ROS). Diabetes Mellitus (DM) preexisting has been described as a risk factor for CI-AKI. HO-1 has a renoprotective effect in renal disease models, but its potential action in diabetic nephropathy has not been concluded. This study evaluated the role of HO-1 and NO in CI-AKI in diabetic rats.

Methods: Adult male Wistar rats were randomized in 5 groups. Physiological parameters; renal function (inulin clearance); renal hemodynamics; oxidative injury (urinary peroxides-UP, tiobarbituric acid reactive substances–TBARS, urinary nitric oxide-NO and thiols in renal tissue); gene expression and protein syntesis of HO-1 and iNOS and kidney histological analysis were evaluated.

Results: DM+IC+ZnPP group showed reduced renal function and increased renal vascular resistance. Also, ZnPP in DM+IC group elevated urinary peroxides, NO and TBARS and reduced thiols in renal tissue compared that DM+IC. ZnPP administration induced elevation on gene expression and protein syntesis of HO-1 and iNOS. Renal histology showed cell flattening and hyalinization in renal tissue.

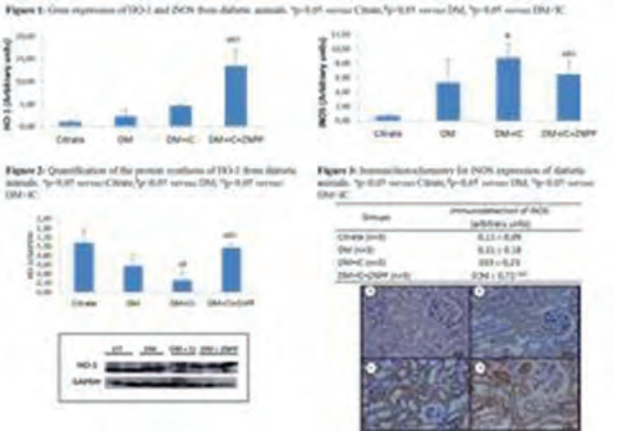
Conclusions: The data highlighted that modulation of HO-1 potentiates CI-AKI in diabetic rats confirmed by reduced function, renal hemodynamic changes and oxidative damage, possibly due to NO participation.

Funding: Government Support - Non-U.S.

Renal function, renal heminam and oxidative profile

Groups	Inulin clearance 100g (ml/min)	Renal blood flow (ml/min)	Renal vascular resistance (mmHg / ml/min)	Urinary peroxides (nmol/g creatinine)	Urinary thiobarbituric acid-reactive substances (nmol/g creatinine)	Renal tissue thiols (nmol/g protein)	Nitric oxide (nmol/g creatinine)
Citrate (n=10)	0.78±0.09	6.8±1.04	14±3	1.2±0.7	0.2±0.1	22.7±4.9	22.3±7.2
IC (n=10)	0.81±0.14	6.1±0.4	17±2	1.5±0.2	0.1±0.1	21.6±4.2	26.2±8.2
DM (n=10)	0.52±0.08 $^{\alpha\beta}$	4.8±1.6 $^{\alpha\beta}$	25±7 $^{\alpha\beta}$	12.4±4.7 $^{\alpha\beta}$	14.3±4.9 $^{\alpha\beta}$	15.0±3.0 $^{\alpha\beta}$	55.2±15.2 $^{\alpha\beta}$
DM+IC (n=10)	0.19±0.02 $^{\alpha\beta\Omega}$	3,03±0.87 $^{\alpha\beta\Omega}$	36±12 $^{\alpha\beta\Omega}$	18.7±7.1 $^{\alpha\beta\Omega}$	21.9±6.1 $^{\alpha\beta\Omega}$	11.1±1,94 $^{\alpha\beta\Omega}$	78.1±63.1 $^{\alpha\beta\Omega}$
DM+IC+ZnPP (n=10)	0.08±0.05 $^{\alpha\beta\Omega\delta}$	2.0±0.5 $^{\alpha\beta\Omega\delta}$	49±14 $^{\alpha\beta\Omega\delta}$	22.8±10.8 $^{\alpha\beta\Omega\delta}$	29.3±7.6 $^{\alpha\beta\Omega\delta}$	5.1±1.5 $^{\alpha\beta\Omega\delta}$	91.0±8.9 $^{\alpha\beta\Omega}$

αp<0,05 versus Citrate; βp<0,05 versus IC; Ωp<0,05 versus DM; δp<0,05 versus DM+IC.



PUB003

Heme Oxygenase-1 Role in Contrast-Induced AKI in CKD Rats Cassiane D. da Fonseca,[2] Maria De Fatima Vattimo,[2] Sheila M. Fernandes,[2] Daniel M. Martins,[2] Mirian Watanabe,[2] Fernanda T. Borges,[4] Edson A. Pessoa,[5] Luciana soares C. Santos,[3] Natalia A. Oliveira.[1] *[1]Organization University of São Paulo, São Paulo, Brazil; [2]Experimental of Laboratory of Animals Models, School of Nursing, Sao Paulo, Brazil; [3]Universidade de São Paulo, SÃO PAULO, Brazil; [4]UNIFESP, São Paulo, Brazil; [5]Universidade Federal de São Paulo, São Paulo, Brazil. Group/Team: Research Group on Acute Kidney Injury-GERA.*

Background: Contrast Induced -acute kidney injury (CI-AKI) is the third cause of hospital acquired AKI, specially in the presence of CKD. Heme oxygenase-1 (HO-1) is part of a cytoprotective system that is involved with nitric oxide (NO) syntesis and modulates renal dysfunctions and oxidative damage in AKI models. This study evaluated the role of the HO-1 inhibitior, zinc protoporphyrin (ZnPP), in CI-AKI rats with CKD.

Methods: Adult male Wistar rats were randomized in 4 groups. Sham (control group), Nx5/6 (CKD group), Nx5/6+IC (CKD+iodinated contrast group), Nx5/6+IC +ZnPP. Renal function (inulin clearance); renal hemodynamics; oxidative injury (urinary peroxides-UP, tiobarbituric acid reactive substances–TBARS, urinary nitric oxide-NO and thiols in renal tissue); gene expression and protein syntesis of HO-1 and iNOS and kidney histological analysis were evaluated.

Results: Inulin clearance was reduced due to an elevation on renal vascular resistance, while urinary NO levels were increased in Nx5/6+IC+ZnPP group when compared to the Nx5/6+IC group. Gene expression and protein syntesis of HO-1 and iNOS were elavated in Nx5/6+IC+ZnPP group. Kidney histology showed tubular cells vacuolization and edema in IC animals.

Conclusions: These data highlight that the heme oxygenase -1 inhibitor mitigates CI-AKI in the presence of CKD risk factor most likely via NO.

Funding: Government Support - Non-U.S.

Table 1. Global renal function and oxidative metabolites

Groups (n)	Inulin Clearance (mL/min/100g)	Renal Vascular Resistance (mmHg/mL/min)	Urinary Peroxides (nmol/g creatinine)	TBARS (nmol/g creatinine)	Thiols (nmol/mg protein)	Urinary nitric oxide (µmol/g creatinine)
Sham (8)	0.72 ± 0.06	9.5 ± 4.0	10 ± 6	0.007 ± 0.002	17.4 ± 5.5	17 ± 9
Nx5/6 (8)	0.30 ± 0.07 $^{\alpha}$	15.0 ± 4.1 $^{\alpha}$	9 ± 4	0.012 ± 0.003	10.8 ± 1.7 $^{\alpha}$	17 ± 5
Nx5/6+IC (10)	0.16 ± 0.06 $^{\alpha\beta}$	24.6 ± 4.5 $^{\alpha\beta}$	31 ± 16 $^{\alpha\beta}$	0.030 ± 0.016 $^{\alpha\beta}$	5.2 ± 2.6 $^{\alpha\beta}$	60 ± 9 $^{\alpha\beta}$
Nx5/6+IC+ZnPP (5)	0.08 ± 0.07 $^{\alpha\beta\delta}$	39.1 ± 7.1 $^{\alpha\beta\delta}$	19 ± 12	0.016 ± 0.005 $^{\delta}$	21.4 ± 3.8 $^{\alpha\beta\delta}$	83 ± 9 $^{\alpha\beta\delta}$

α p<0.05 vs Sham; β p<0.05 vs Nx5/6; δ p<0.05 vs Nx5/6+IC. Data are show as mean ± SD. TBARS: tiobarbituric acid reactive substances, Nx5/6: uninephrectomy 5/6, IC: iodinated contrast.

PUB004

AKI Due to Antibiotic Spacer Kamron Saleem, Benjamin K. Sarsah, Amy N. Sussman, Bijin Thajudeen. *University of Arizona, Tucson, AZ.*

Background: This is a case of a 58 y.o. woman who underwent right total hip arthroplasty 4months prior to admission. Intraoperatively 10 mL of RapidCure loaded with 2 g of vancomycin and 2.4 g of tobramycin were placed in deep layers around the hip as prophylaxis and she was discharged with 1 week of oral antibiotics. She returned after 2 months with an infection involving the right hip. 11 days later, she went to the OR for exploration, placement of antibiotic spacer containing 4g vancomycin, 3g cefuroxime and 2.4g tobramycin. In addition, 20 mL of Rapid Cure containing 4g vancomycin and 4.8g tobramycin was placed into the deep tissue layers around the hip. Admission renal function was normal with sCr of 0.7mg/dl and on the day of surgical explantation, renal function remained normal. Intraop hypotension occurred, treated with volume resuscitation. On postop day 2, Vancomycin trough and tobramycin levels increased markedly. sCr increased 1.2 mg/dL and continued to worsen. Due to concern

for tobramycin and vancomycin toxicity, orthopedic surgery was asked to remove the spacer. Removal was deemed high risk and nephrology was asked to medically manage her renal dysfunction. Due to concern for continuous release of tobramycin from the spacer, hemodialysis was initiated for tobramycin clearance. She remained nonoliguric throughout. Roughly 1 million joint arthroplasties are performed each year in the USA. Between 1% and 2% result in a prosthetic joint infection. Two-stage arthroplasty is the current treatment of choice for infected hip and knee joint prostheses. Aminoglycosides and vancomycin are the most commonly used. The high local antibiotic level exceeds the MIC of many potential organisms. Data on spacer induced AKI is limited. No standard of care is available to determine the amount of antibiotics to be placed in a spacer. We propose a multidisciplinary approach between the Orthopedic, Nephrology, Infectious Diseases, and Pharmacology communities to formulate a standard criteria for antibiotic dosing in antibiotic-impregnated cement spacers. It would be helpful to re-analyze existing data using a more standardized definition of AKI per KDIGO. Further studies are needed to evaluate long-term prognosis in this group of patients.

Methods:

Results:

Conclusions:

PUB005

Protective Effect of Sulforaphane in Maleic Acid-Induced Nephropathy Alfredo Briones-Herrera,[2] Sabino H. Avila Rojas,[2] Omar E. Aparicio-Trejo,[2] Magdalena Cristobal,[1] L. Gabriela Sanchez-Lozada,[1] Edilia Tapia,[1] José Pedraza-chaverri.[2] *[1]INC Ignacio Chavez, Mexico City, Mexico; [2]National Autonomous University of Mexico, Mexico City, Mexico.*

Background: Sulforaphane (SF) is able to activate the antioxidant response by inducing the Nrf2 transcriptional factor; it has been observed that it has protective effects by improving the mitochondrial function. Maleic acid (MA) injection induces a nephropathy characterized of impaired urine acidification and by proteinuria, phosphaturia and glycosuria, inhibition of the Krebs cycle, induction of oxidative stress and alterations in mitochondrial function. The objective of this work was to study if SF diminishes the oxidative stress and renal damage provided by MA.

Methods: Male Wistar rat (230-260 g) were used and divided in four experimental groups, Control (CT) group that received vehicle, MA-treated group received a single dose of MA (400 mg/kg, ip), MA-SF group received a pretreatment of 1 mg/kg/day ip of SF four days and the MA dose in the fourth day, and SF group received the pretreatment with SF for four days. Twenty-four h after the MA injection proteinuria, urinary N-acetyl-β-D-glucosaminidase (NAG) activity, plasma creatinine and glutathione peroxidase (GPx) activity were measured. Glomerular filtration rate (GFR), renal blood flow (RBF), renal perfusion and oxygenation (pO_2) were also measured by dissecting the left kidney; then rats were sacrificed. Mitochondrial bioenergetics were determined in isolated mitochondria from renal cortex and oxidative stress parameters were measured in renal cortex homogenates.

Results: Twenty-four h after MA injection proteinuria and urinary NAG raised up. MA decreased plasma GPx, RBF, renal cortex pO_2 and perfusion. MA impaired mitochondrial bioenergetics associated to the complex I (O_2 consumption, mitochondrial membrane potential and respiratory control index) and increased the mitochondrial production of reactive oxygen species, augmented the oxidized proteins and lipid peroxidation and decreased the content of thiol groups. SF prevented all these alterations.

Conclusions: MA nephropathy was diminished by the pretreatment with SF by preserving mitochondrial bioenergetics, ameliorating oxidative stress and improving pO_2 in renal cortex.

Funding: Government Support - Non-U.S.

PUB006

Curcumin Prevents Kidney Potassium Dichromate-Induced Renal Hypoxia Sabino H. Avila Rojas,[2] Alfredo Briones-Herrera,[2] Omar E. Aparicio-Trejo,[2] Edilia Tapia,[1] L. Gabriela Sanchez-Lozada,[1] José Pedraza-chaverri.[2] *[1]INC Ignacio Chavez, Mexico City, Mexico; [2]National Autonomous University of Mexico, Mexico City, Mexico.*

Background: Curcumin is a polyphenolic compound, a bifunctional antioxidant that exhibits various therapeutics properties. $K_2Cr_2O_7$-induced nephropathy has been associated with oxidative stress ROS production affects renal oxygenation and it has been proposed that this as a causal agent of the progression of renal damage. However, it has not been explored if the $K_2Cr_2O_7$ induces this alteration.

Methods: Male Wistar rats (290-320 g) were used. Rats were treated with a daily intragastric dose of curcumin (400 mg/Kg) for 10 days prior to receive an injection of $K_2Cr_2O_7$ (12.5 mg/Kg, s.c). Animals continued to receive treatment with curcumin for 48 h following $K_2Cr_2O_7$ administration. At the end treatment, renal function (Uprot, Pcreat, BUN and GFR), hemodynamics parameters (RBF, MAP, RVR and FF), $O_2^{\bullet-}$ production by NADPH oxidase (NOX) and nitric oxide synthase (NOS) in renal cortex, renal perfusion (cortex and medulla) and renal oxygen tension (cortex and medulla renal) were evaluated. In addition, studies were carried out on isolated mitochondria from renal cortex (mitochondrial membrane potential and mitochondrial H_2O_2 production).

Results: $K_2Cr_2O_7$-induced renal damage showed an increase of proteinuria, plasma creatinine, BUN, MAP, RVR, $O_2^{\bullet-}$ production by NOX and NOS, and mitochondrial H_2O_2 production compared to control. In the same way, $K_2Cr_2O_7$ administration decreased GFR, RBF, RPF, mitochondrial membrane potential, as well as renal perfusion and renal oxygen tension in both the renal cortex and renal medulla. Renal oxygen tension positively correlated with the fall in the renal perfusion. All the above-described alterations were prevented with the curcumin pretreatment.

Conclusions: Curcumin treatment prevented $K_2Cr_2O_7$-induced renal damage. The protective effect of curcumin was associated with its ability to prevent the increase in the O_2 consumption ($O_2^{\bullet-}$ production), as well as the reduction in the O_2 supply (RBF, renal perfusion and renal tension oxygen)

Funding: Government Support - Non-U.S.

PUB007

ANCA and IgA Glomerulonephritis All in One: Prevalence, Prognosis, and Complications Pitchaphon Nissaisorakarn,[3] Kisra Anis,[3] Vivette D. D'Agati,[2] Belinda Jim.[1] *[1]Albert Einstein College of Medicine, New Hyde Park, NY; [2]Columbia University College of Physicians and Surgeons, New York, NY; [3]Jacobi Medical Center, Bronx, NY.*

Background: Co-existing IgA nephropathy and pauci-immune ANCA-associated crescentic glomerulonephritis has rarely been reported. Both entities are prevalent separately but their co-existence is less common with a reported prevalence of 0.2-2%.

Methods: A 75 year-old Hispanic woman with PMH of DM, HTN, HLD and CKD stage III presented to the ED for abdominal pain with nausea, vomiting and hematuria for 3 days. She had been treated for pneumonia with azithromycin 1 month prior. On physical exam, she was afebrile, BP 155/71 mmHg, HR 78; exam was normal except for right CVA tenderness. She was found to have acute kidney injury and nephrotic range proteinuria with positive myeloperoxidase antibody and required HD. A renal biopsy revealed IgA nephropathy with superimposed pauci-immune ANCA-associated crescentic glomerulonephritis. She was subsequently treated with pulse intravenous methylprednisolone, cyclophosphamide IV and plasmapheresis. Unfortunately, her renal function did not improve and she continued to require HD. One week after administering her 2nd dose of cyclophosphamide, the patient was re-admitted to the ICU for infectious complications of herpes zoster on her right trunk, influenza A virus, bacteremia secondary to the pansensitive Rothia species, and C. difficile negative diarrhea. She required a prolonged course of IV antibiotics and was subsequently able to be discharged home on HD.

Results:

Conclusions: The co-existence of ANCAs and IgA may be a coincidence or may be pathogenic. One possibility is that patients may have pre-existing IgA deposits in the mesangium, which are then further complicated by the presence of ANCAs. On the other hand, patients with crescentic IgA could have coincident ANCA autoantibodies with no additional pathogenic potential. Some case series, however, have found a distinctive clinical and histologic picture of IgA and ANCA positivity, suggesting pathogenicity. The cornerstone for treatment is aggressive therapy with immunosuppressive agents. Current literature suggests that reduced dose immunosuppression for the elderly have been shown to have similar efficacy and might have a more favorable safety profile.

PUB008

Vitamin D and FGF 23 Prognostic Indicators of the Severity of AKI Joseph Saabiye,[1] Jeanne Kamal,[1,2] Firas Safa,[1] Julie Zaidan,[1] Rania El Mais,[1] Christine Boumitri,[1,3] Patricia Nasr,[1,4] Suzanne E. El Sayegh,[1,5] Elie El-Charabaty.[1,5] *[1]Internal Medicine, Staten Island University Hospital, Staten Island, NY; [2]Nephrology, NYULMC, New York, NY; [3]Gastroenterology, University of Missouri, Columbia, MO; [4]Nephrology, Tufts University, Boston, MA; [5]Nephrology, Staten Island University Hospital, Staten Island, NY.*

Background: Vitamin D (VD) and Fibroblast Growth Factor 23 (FGF 23) are two molecules that have been correlated with different diseases including kidney dysfunction. Acute kidney Injury (AKI) is a common and serious complication occurring in hospitalized patients. Markers helping early recognition of patients at risk and predicting recovery are still lacking. This raises the interest of studying VD and FGF 23 as new markers for AKI progression.

Methods: Patients with normal kidney function at baseline (Glomerular filtration rate (GFR) >60) admitted with the diagnosis of AKI based on the KDOQI criteria were included in the study. VD, FGF 23 levels and Serum creatinine (SCr) were collected within 24h of admission (D1). Daily VD intake was estimated using a Food Frequency Questionnaire (FFQ). Patients were divided into 2 groups based on SCr at day 3 (D3) : AKI recovery (return to baseline GFR or 50% decrease in SCr D3) vs AKI progression. VD levels were collected at D3 for patients who failed to recover.

Results: 102 patients were enrolled, 69.7% were men, mean age was 65.7, mean BMI was 31.3. 64.6% recovered from AKI. D1 1,25-dihydroxy VD (1,25 VD) levels correlated negatively with SCr on D1, D3 and peak SCr levels (r -0.38 p 0.0001; r -0.35 p 0.0007; r -0.39 p 0.0001 respectively). D1 1,25 VD levels were significantly higher in patients whom kidney function improved (40.5 vs 25.2 p 0.0002). Moreover D3 1,25 VD correlated negatively with SCr D3(r -0.55, p 0.01). FGF 23 had a negative correlation with D1 1,25 VD (r -0.57 p 0.0001) and Scr D3 (r -0.43 p 0.001). Per FFQ analysis, 25-Hydroxy VD levels correlated with daily VD consumption (r 0.32 p 0.001) and a cut off of 663.7 units/ day of VD intake was needed for sufficient levels.

Conclusions: FGF 23 lowers 1,25 VD levels in patients with chronic kidney disease. In our study, patients with AKI with normal kidney function at baseline had elevated levels of FGF 23. Those whom kidney function did not improve had lower levels of 1,25 VD and higher levels of FGF 23 at presentation. Could these molecules be used as prognostic markers and eventually new targets for therapies in patients with AKI?

PUB009

Deficiency of Proangiogenic Factor Vasohibin-2 Exacerbates AKI via Impaired Renal Tubular Cell Survival Katsuyuki Tanabe, Hiromasa Miyake, Kana Masuda, Satoshi Tanimura, Hitoshi Sugiyama, Jun Wada. *Okayama university Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.*

Background: A number of mediators including angiogenesis-related factors have known to be involved in the progression of acute kidney injury (AKI). Understanding the role of such mediators in AKI may lead to development of novel therapeutic strategies. Vasohibin-2 (VASH2) is a proangiogenic factor secreted by tumor cells and its expression has been associated with higher grade of the malignancies. However, its physiological and pathogenic roles in kidney has not been elucidated yet. In the present study, we examined the effects of endogenous VASH2 deficiency on renal function and histology in murine AKI model.

Methods: Ischemic-reperfusion (I/R) injury was induced by clumping bilateral renal pedicles for 25 min in eight to nine-week-old C57BL6/J wild type (WT) and VASH2 knockout ($VASH2^{LacZ/LacZ}$) mice (n=6 in each group). Blood samples were collected and kidneys were harvested 24 hours after the reperfusion. Cultured human tubular epithelial cells (HK-2) was transfected with human VASH2 using adenoviral vectors and treated with 500 μM of hydrogen peroxide (H_2O_2) for 12 hours.

Results: Increase serum creatinine and blood urea nitrogen caused by I/R in WT were significantly accelerated in $VASH2^{LacZ/LacZ}$ mice. Histologically, ATN score and number of TUNEL-positive nuclei following I/R in $VASH2^{LacZ/LacZ}$ mice was significantly exuberated compared with WT mice. Increased accumulation of malondialdehyde and 4-hidroxynonenal was more prominent in $VASH2^{LacZ/LacZ}$ I/R mice. Whereas decreased number of peritubular capillaries after I/R was greater in $VASH2^{LacZ/LacZ}$ mice, decreased VEGF mRNA was comparable between WT and $VASH2^{LacZ/LacZ}$ I/R mice. Renal VASH2 mRNA was markedly elevated after I/R and immunostaining revealed that the increased VASH2 expression was localized in renal tubular cells. Adenoviral overexpression of VASH2 in HK-2 led to prominent Akt phosphorylation. H_2O_2-induced upregulation of pro-apoptotic factor Bax was prevented by VASH2 overexpression.

Conclusions: These results suggested that endogenous VASH2 was upregulated in renal tubular cells in I/R injury to improve renal tubular cell survival.

Funding: Government Support - Non-U.S.

PUB010

Necrostatin-1 Attenuates Sepsis Associated AKI through Promoting Autophagosome Elimination of Renal Tubular Epithelial Cells Wei Dong, Xinling Liang. *Division of Nephrology, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhoou, China.*

Background: The aim of the present study was to investigate the protective effect of necrostatin-1 (Nec-1) in sepsis associated AKI (SA-AKI).

Methods: The SA-AKI mice model was established by intraperitoneal injection of lipopolysaccharide (LPS). Nec-1 was delivered to SA-AKI mice. Renal function and histology changes were observed. LC3-II and p62, the markers for autophagy flux, were detected. Autophagosome and autolysosome of renal tubular epithelial cells were identified using electron microscopy.

Results: Pretreatment with Nec-1 could reverse increased blood urea nitrogen (BUN) (LPS+Nec-1 vs. LPS group, 15±4.14 mmol/l vs 32.54±5.46 mmol/l, P<0.001) or serum creatinine (SCr) (11.50±1.67 μmol/l vs. 30.08±4.18 μmol/l, P<0.001) induced by LPS. There were no significant differences in tubular epithelial cell necrosis between the groups. Protein analysis showed LC3-II and p62 were increased while transcription analysis showed neither LC3-II nor p62 mRNA was increased. Massive autophagosomes and paucity of autolysosome were observed using electron microscope. When mice were pretreated with Nec-1, LC3-II and p62 decreased and a large number of autolysosomes were observed using electron microscope. These results indicate Nec-1 improved autophagosome elimination of renal tubular epithelial cells impaired by LPS.

Conclusions: In conclusion, Nec-1 could prevent sepsis-associated acute kidney injury through promoting autophagosome elimination in renal tubular epithelial cells.

Funding: Government Support - Non-U.S.

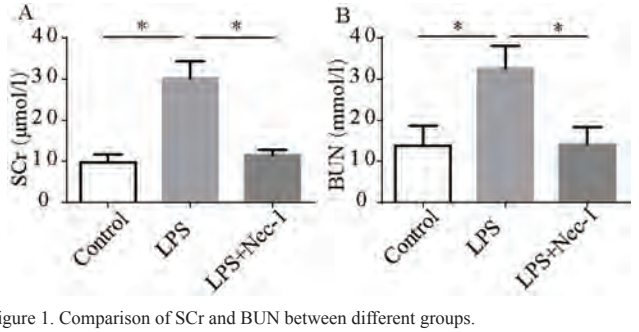


Figure 1. Comparison of SCr and BUN between different groups.

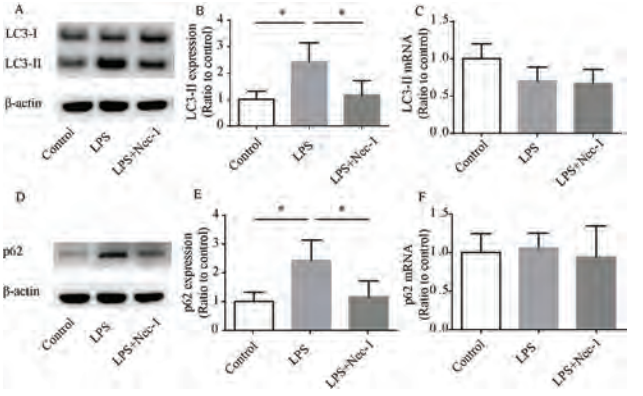


Figure 2. Transcription and expression levels of LC3-II and p62 in renal tissues of different groups.

PUB011

The Role of Growth Arrest and DNA Damage-45γ in Cyclosporine A-Induced Renal Tubular Cell Death Gyu Tae Shin,[1] Jieun Park,[1] Seung-Jung Kim.[2] *[1]Ajou University School of Medicine, Suwon, Republic of Korea; [2]Ewha Womans University, Seoul, Republic of Korea.*

Background: Nephrotoxicity is the major adverse effect of cyclosporine A (CsA) and it has been shown that CsA directly damages renal tubular cells. Growth Arrest and DNA Damage-45γ (GADD45γ) is a stress-responsive molecule, and our previous studies showed GADD45γ might contribute to the progression of chronic kidney disease [Kidney Int. 2008, Am J Nephrol. 2009]. In the present study, we investigated the role of GADD45γ in CsA-induced renal tubular cell death.

Methods: Human renal epithelial (HRE) cells that are of kidney tubular origin were incubated with CsA 25 ug/ml for 48 hours in the presence or absence of zVAD, necrostatin-1 or ferrostatin-1. To knockdown GADD45γ expression, stable cell lines expressing GADD45γ shRNA were generated. The recombinant adenovirus containing the GADD45γ gene was synthesized to overexpress GADD45γ protein. The degree of apoptosis and necrosis were evaluated using flow cytometry after staining with Annexin V and propidium iodide.

Results: We found that CsA significantly induced GADD45γ expression by HRE cells. Treatment of CsA provoked HRE cell death by inducing apoptosis and necrosis. Inhibition of caspases by zVAD significantly decreased CsA-induced apoptosis as well as necrosis, which is considered to be secondary to apoptosis, leading to a significantly increased cell survival. Inhibition of receptor-interacting serine/threonine-protein kinase 1 by necrostatin-1 reduced necrosis but not apoptosis, leading to an increased overall cell survival but to a lesser degree than zVAD. This result suggests that CsA induces cell death by mainly apoptosis as well as by necroptosis (primary necrosis). Inhibition of ferroptosis by ferrostatin-1 was ineffective in preventing cell death. GADD45γ overexpression augmented CsA-induced apoptosis while decreasing necrosis without affecting overall cell survival, indicating the switch of the mode of cell death from necrosis to apoptosis. Accordingly, GADD45γ overexpression activated apoptosis-related caspases but not necroptosis-related mixed lineage kinase domain like protein. GADD45γ knockdown cell lines showed significantly decreased CsA-induced apoptosis as well as necrosis, and the rescue of GADD45γ expression restored CsA-induced apoptosis.

Conclusions: GADD45γ knockdown prevents CsA-induced renal tubular cell death by blocking apoptosis and secondary necrosis.

PUB012

Effect of Physical Preconditioning in AKI Induced by Renal Ischemia-Reperfusion in Rats Frederico Fazan,[1] Lucas F. Almeida,[1] Heloisa D. Francescato,[1] Natany G. Reis,[1] Cleonice Silva,[1] Fernando S. Ramalho,[2] Terezila M. Coimbra.[1] *[1]Physiology, Ribeirao Preto Medical School, Ribeirao Preto, Brazil; [2]Pathology, Ribeirao Preto Medical School, Ribeirao Preto, Brazil.*

Background: Acute kidney injury (AKI) is one of the most common kidney illnesses. Manny factors can cause AKI including ischemia-reperfusion (I/R). An increasing number of evidence show that ischemia-reperfusion of the kidneys can provoke renal lesions through inflammatory pathways and endothelial dysfunction. Several studies show a relation between physical exercise and healthy vascular function with imunomodulatory roles. The objective of this study was to evaluate the effect of previous physical exercise in the AKI induced by renal ischemia-reperfusion in rats.

Methods: Male Wistar rats were divided into four groups: 1-Sedentary Sham; 2-Sedentary I/R; 3-Trained Sham; 4-Trained I/R. The trained animals were subjected to mild intensity treadmill training 5 days a week during 9 weeks. After the training, the animals underwent surgical procedure of bilateral renal artery occlusion for 45 minutes. After that, the clamps were removed and 48 hours after the urine and blood samples were collected for renal function evaluation and the kidneys were removed for histological and immunohistochemical examination.

Results: The trained group presented, after I/R induced injury, a small reduction of renal function and structure when compared to sedentary group. They showed plasmatic creatinine levels of 2.03±1.24 mg%, fractional sodium excretion of 2.97±4.66% and plasma osmolality of 317.9±15.5 mOsm/Kg H2O, when in the sedentary animals the plasma creatinine level was 6.89±2.02 mg%; fractional sodium excretion 29.3±19.6% and plasma osmolality 367.8±13.0 mOsm/Kg H2O. The structural lesions were also reduced as the sedentary animals kidneys, avaliated by scores, ranging from 0 to 4 (smallest to widest extension of lesion) was 3.5±0.3 in the sedentary animals and 2.4±0.9 in trained animals. The inflammation was also reduced in the trained animals as the group showed a smaller number of macrophage cells in the renal cortex and outer medulla, 17.11±1.52 cells/0.45mm2 for the trained animals and 36.35±1.7 cells/0.45mm2 for the sedentary animals, $p<0.05$.

Conclusions: Physical preconditioning attenuated the decrease in renal function and structure. These disturbances were associated with inflammation that was also less intense in the kidneys of the animals of the training group.

Funding: Government Support - Non-U.S.

PUB013

The Role of XBP1 in AKI to CKD Progression through G2/M Arrest and Fibrotic Induction Chia-Hsien Wu,[1,4] Yuan-Siao Chen,[1] Jia-Rong Jheng,[3] Chih-Kang Chiang,[1,2] Shing-Hwa Liu.[1] *[1]Graduate Institute of Toxicology, National Taiwan University, College of Medicine, Taipei, Taiwan; [2]Department of Integrated Diagnostics & Therapeutics, National Taiwan University Hospital, Taipei, Taiwan; [3]Department of Internal Medicine, National Taiwan University, College of Medicine, Taipei, Taiwan; [4]Division of Endocrinology and Nephrology, University of Tokyo, Graduate School of Medicine and Faculty of Medicine, Tokyo, Japan.*

Background: X-box binding protein 1 (XBP1), one of the key molecules of unfolded protein responses (UPRs), is responsible for induction of UPR signaling. Studied have revealed UPRs associated with various kidney diseases. However, there is no report discussed about the role of UPRs during the transition from acute kidney injury (AKI) to chronic kidney disease (CKD).

Methods: C57BL/6 mice was clamped by micro-clips on left renal pedicle for 30 mins, then complete reperfused to generate unilateral ischemia/reperfusion injury (UIRI) model. Mice were sacrificed after 1, 3, 5, 11, 15 days after surgery. Serum BUN and Cr were analyzed, and tissue histology, including H&E, Periodic Acid-Schiff and Masson's trichrome were evaluated. Furthermore, UPRs-related initiators were evaluated by Western blot and qPCR. In vitro, the proliferation and cell cycle analysis of XBP1-deficient HK2 cells was analyzed by MTS assay, Western blot and flow cytometry, respectively.

Results: The expression level of UPRs initiators PERK, IRE1α are relatively higher in UIRI group than in sham group, however, expression of both spliced and unspliced XBP1are decreased during CKD progression. Besides, XBP1 expression level has a negative correlation with fibrosis progression. Recently, renal tubular epithelial cells arrest in G2/M contributes to renal fibrosis progression through releasing fibrogenesis factors and obstructing the repairing process has been reported. Here we then hypothesis that losing XBP1 in epithelial cells may result in cell cycle arrest and contribute to the fibrosis progression after AKI. In the following experiments, knock-down XBP1 in cell line derived from human proximal epithelial cells cause cell cycle arrest in G2/M, and the cell growth is retard. Wee1 expression and the ratio of cyclin B1 to cyclin D1 are higher after knockdown of XBP1, indicate the G2/M arrest of cells. Expression level of the DNA damage marker, phospho-H2AX is also higher after knockdown of XBP1. Furthermore, it induced a higher expression of profibrotic factor CTGF and COL4A1, and secreted a higher level of TGF-β in culture medium after knockdown of XBP1.

Conclusions: In conclusion, these results indicate that XBP1 plays a role in maintaining DNA repair process and losing XBP1 cause renal tubular epithelial cells cell cycle arrest in G2/M, following worsen the fibrosis after AKI.

Funding: Government Support - Non-U.S.

PUB014

Development of a Novel Model of Contrast-Induced AKI in Mice Atsushi Uchida,[1] Kengo Kidokoro,[2] Hajime Nagasu,[1] Minoru Satoh,[1] Tamaki Sasaki,[3] Naoki Kashihara.[1] *[1]Kawasaki Medical School, Kurashiki, Japan; [2]Kawasaki Medical school, Kurashiki Okayama, Japan; [3]None, Kurashiki, Japan.*

Background: Contrast-induced acute kidney injury (CI-AKI) is characterized by the abrupt loss of kidney function following the intravascular administration of iodinated contrast media. CI-AKI has been found to be strongly associated with morbidity and mortality of the patients. CI-AKI may be caused by sustained contrast-induced renal arteriolar vasoconstriction, outer medullary and tubular hypoxia or direct cytotoxicity due to ischemia-mediated oxidative stress. However, the mechanism of CI-AKI has not been completely elucidated. One of the seasons is lack of established CI-AKI model. The purpose of this study is to create a clinically relevant and functionally obvious CI-AKI mouse model corresponding to the risk factors of CI-AKI, which provides feasibility for the mechanism study of CI-AKI.

Methods: Dehydration and higher dose of the contrast medium are known as risk factors for CI-AKI. So, in all experiments, contrast medium or saline (Control) was injected from tail vein with water deprivation from 24 hr before injection to 24 hr after injection (total 48 hr). Dose of the contrast medium is three times as much as the previous reports (iohexol:18 ml/kg). Underlying renal insufficiency and diabetes are also known as risk factors for CI-AKI. So, (1) Adenine induced renal failure model mice and (2) Akita diabetic model mice were used. Oxidative stress and endothelial dysfunction are thought to contribute CI-AKI development. So, (3) Nrf2 knockout mice as high sensitivity to oxidative stress model and (4) eNOS knockout mice as endothelial dysfunction model were used. In experiment (1), adenine containing diet was given for 14 days before contrast injection. In experiment (2-4), mice were subjected to left kidney nephrectomy 7 days before contrast injection. These mice were euthanized 48h after contrast injection, and the blood samples were collected.

Results: In all experiments, serum creatinine and blood urea nitrogen were not elevated by contrast injection compared to Control. AKI was not induced by contrast medium in murine.

Conclusions: In the murine, it is hard to establish AKI model caused by contrast media. As the injection of contrast media alone does not cause overt AKI in mice, multiple insults are necessary for inducing histopathological and functional decline.

PUB015

Endothelial Prostacyclin Protects the Kidney from Ischemia-Reperfusion Injury Cao Ying, Chuan-Ming Hao. *Huashan Hosp., Shanghai, China.*

Background: Ischemia-reperfusion injury (IRI) is one of the most common causes of AKI. Prostacyclin, or PGI_2, is one of metabolites of arachidonic acid via cyclooxygenase and PGI synthase (PGIS). In the kidney, PGI_2 is reported to play an important role in maintaining the renal blood flow. This study explores the role of endothelium derived prostayclin in IRI.

Methods: To genetically suppress the expression of PGI_2, we generated a mouse line whose PGIS gene was specifically deleted in endothelial cells (TEK-CRE $PGIS^{fl/fl}$). The IRI animal model was established by right nephrectomy and left renal pedicle clamping for 25 minutes. Animals were sacrificed at different time point after reperfusion, and blood and renal samples were collected for further analyses. Nephrotoxic AKI was induced by folic acid (250mg/Kg by ip). Kidney damage was assessed by BUN, kidney histology and TUNEL assay.

Results: The kidney PGIS protein expression markedly increased following IRI in the wild mice but not in the TEK-CRE $PGIS^{fl/fl}$ mice. TEK-CRE $PGIS^{fl/fl}$ mice had a significantly more severe acute kidney injury following IRI than wild type mice (at 24 hours, BUN 162.5 ± 4.747 VS 57.61 ± 5.083mg/dl,$P<0.001$). Histologic changes were consistent with BUN changes. No blood pressure difference was observed between wild type mice and endothelial PGIS deletion mice (108.3 ± 2.361 vs 102.2 ± 2.942). Iloprost, an analogue of PGI_2, administrated (0.05mg/Kg by ip) 30 minutes before the IRI, markedly attenuated renal damage induced by IRI in both wild type mice (BUN 57.61 ± 5.083 VS 33.66 ± 5.847 mg/dl,$P<0.001$) and TEK-CRE $PGIS^{fl/fl}$ mice (BUN 162.5 ± 4.747 VS 88.94 ± 6.214 mg/dl,$P<0.001$). Further studies show that kidney p-PKA expression significantly increased after IRI in wild type mice but not in the PGIS deletion mice, suggesting that the protective effect of PGIS is IP receptor dependent. Folic acid also induced marked kidney injury, however endothelial PGIS deletion did not worsen kidney injury compared with wild type mice (BUN 117.3 ± 13.32 VS 99.04 ± 12.08, mg/dl,$P>0.05$).

Conclusions: In conclusion: PGIS derived PGI2 can protect the kidney from acute injury caused by ischemic reperfusion and could be a potential intervention target for AKI. The protective effect of PGI_2 was not observed in the nephrotoxic AKI model induced by folic acid.

PUB016

Community Acquired AKI in a Mexican Emergency Department Julio A. Gutierrez, Denisse Arellano, Javier Soto-Vargas, Perla T. Figueroa-Gonzalez, Hugo E. Chavez. *Mexican Institute of Social Security, Regional General Hospital 46, Guadalajara, Mexico.*

Background: Acute kidney injury (AKI) is a common and serious medical condition associated with increases in morbidity, mortality, and cost of care. As the main 2nd level hospital in Mexico for the Mexican Institute of Social Security with more than 1.5 million afilliated beneficiaries and more than 600 beds our purpose was to identify the prevalence of community acquired acute kidney injury (CA-AKI) in an Emergency Department (ED) in one month regardless of the consultation to the nephrologist, and to describe its prognosis at 120 days.

Methods: A prospective-observational study in which the serum creatinine (SCr) of all adult patients admitted to the ED in the period of December 1-31, 2016, were analyzed at 24-48 hours of stay in the ED to identify AKI by SCr criteria from the AKI KDIGO guidelines. We investigated the prevalence, neprhology consultation, and the 120-days mortality of patients with CA-AKI.

Results: A total of 1244 patients were treated in the ED in the study period. For the analysis only 944 patients who had complete information were included. The prevalence of CA-AKI was 5.5% (52 patients), of whom 57.7% were KDIGO 1, 17.3% KDIGO 2, and 21.2% KDIGO 3. Nephrology consultation was only requested in 9.6% (5/52 patients) of CA-AKI cases and only 4 of 11 cases of AKI KDIGO 3. 19 (36.5%) patients had follow-up at 30 days, 9 (17.3%) at 60 days, and only 6 (11.5%) at 120 days. The 120-days mortality according to our electronic medical records was 34.5% (20/52 patients with CA-AKI) and according to the severity of AKI was 22.2%, 55.6% and 81.8%, in AKI KDIGO 1, 2 and 3, respectively (Figure 1).

Conclusions: The division of nephrology of our hospital urgently needs to implement an AKI rapid response team. The prevalence in our population is similar to previous reports, but have a great impact on mortality at day 120, the lack of nephrology consultations could represent lack of awareness of this entity and its impact on outcomes.

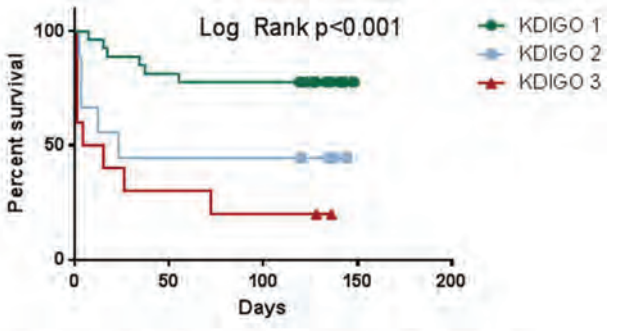


Figure 1. Survival curves of 120-day mortality according to AKI severity.

PUB017

Mechanistic Toxicity Testing of Old and New Polycationic Polypeptide Antibiotics Using a Kidney Proximal Tubule "Organ-on-a-Chip" Elijah Weber,[1] Martti Vaara,[5] Timo Vaara,[5] Thomas Neumann,[3] Maria beatriz Monteiro,[4] Jonathan Himmelfarb,[2] Edward J. Kelly.[1] *[1]University of Washington, Seattle, WA; [2]Kidney Research Institute, Seattle, WA; [3]Nortis, Inc., Seattle, WA; [4]Harvard Medical School, Boston, MA; [5]Northern Antibiotics Ltd., Espoo, Finland.*

Background: The renal proximal tubule is susceptible to drug-induced injury, which can be attributed to concentrative transport processes. Our lab has developed a microphysiological system (MPS) using proximal tubule epithelial cells (PTECs) in a three-dimensional flow-mediated culture which recapitulates both the functional and structural aspects of the proximal tubule. The purpose of this study is to define the mechanism(s) of drug-induced injury using the kidney MPS. The polymyxin class of antibiotics contains polycationic polypeptides with high biological efficiency. However, polymyxin use has been associated with a high incidence of acute kidney injury and the precise mechanisms remain unclear. The safety of Polymyxin B (PMB) to next generation polymyxins (NAB739 and NAB741) was evaluated.

Methods: PTECs are cultured for ~1 week (reaching maximum confluency) before being treated with 0uM PMB (ctrl), 50uM of PMB, or 50uM NAB739/741. Treatment duration was 48 hours with effluent collection in 24 hour intervals and analyzed for both kidney injury molecule-1 (KIM-1) and miRNA content. Nephrotoxicity was determined by evaluating urinary injury response (KIM-1, miRNA), cell-associated injury (via the induction of heme-oxygenase-1, HO-1), and transcriptional response via RNA-seq technologies.

Results: We observed consistent polymyxin-induced toxicity as measured by cell-associated HO-1 induction and both effluent KIM-1 and miRNAs (miR-155-5p and -200c-3p). Transcriptional analysis revealed significant differences between the treated (50uM PMB) and control group lending evidence toward polymyxin-induced apoptosis via the induction of tumor necrosis factor alpha (TNF-α) as well as induction of the cholesterol biosynthesis pathway. Furthermore, polymyxin-analogues (NAB739/741) were shown to have increased safety by demonstrating injury profiles similar to that of the control group. The transcriptional response to NAB-exposure is currently being evaluated.

Conclusions: Using the kidney MPS, we have shown that new structural variants of PMB are less cytotoxic with a predicted improved safety profile. Additionally, we have made advances towards clarifying the previously unknown mechanisms of polymyxin-induced nephrotoxicity by observing the transcriptional response to PMB exposure.

Funding: Other NIH Support - NCATS-UH3, NIEHS-EDGE, Other U.S. Government Support

PUB018

A Risk Prediction Score for AKI in Amazon Intensive Care Units Fernando de Assis F. Melo,[6,3] Ana Caroline F. Bezerra,[7] Emmanuel A. Burdmann,[4] Dirce M. Zanetta,[5] Ravindra L. Mehta,[2] Etienne Macedo.[1] *[1]UCSD, San Diego, CA; [2]University of California San Diego Medical Center, San Diego, CA; [3]University of Sao Paulo, Rio Branco, Brazil; [4]University of Sao Paulo Medical School, Sao Paulo, Brazil; [5]University of São Paulo, S Paulo, Brazil; [6]Acre Federal University, Rio Branco, Brazil; [7]SESACRE, Rio Branco, Brazil.*

Background: In Amazon Intensive Care Units (ICU) AKI is a common complication, associated with increased morbidity and mortality. In resource-constrained areas, early identification of high-risk patients is a fundamental step to improve patient care and outcomes. In this study, we aim to validate a risk score for AKI development in a cohort of ICU patients in the Amazon region.

Methods: All patients admitted to three Intensive Care Units (ICU's) from Feb 2014 to Feb 2016 were screened. We applied a risk score for AKI development based on chronic diseases and acute risk factors (Table 1) within 48 h of ICU admission. The discriminative ability of the risk model was assessed by the area under the receiver operating characteristic curve (AUROC)

Results: Of 1073 screened patients, 52% developed AKI and 31.8% were classified as high risk for AKI. The score had a good calibration and discrimination, with an AUROC of 0.78 [95% confidence interval (CI) 0.74–0.83]. Sensitivity, specificity, positive predictive value, negative predictive value for patients with score ≥ 5 points were 89.2%, 41.5%, 62.3%, 78%, respectively. Mortality rate were significantly higher (38.6% vs 23.1% ; $p = 0.017$) in the high risk group

Conclusions: AKI is common in ICU patients in the western Brazilian Amazon. A simple risk score integrating chronic comorbidities and acute events at ICU admission can identify patients at high risk to develop AKI. In resource constrain areas, the application of this risk assessment tool could help clinicians to stratify patients for more active renal function surveillance, and early drug adjustment and therapeutic interventions to improve care and outcomes of ICU patients

Funding: Government Support - Non-U.S.

Figure 1: Area under curve of risk model for prediction of acute kidney injury.

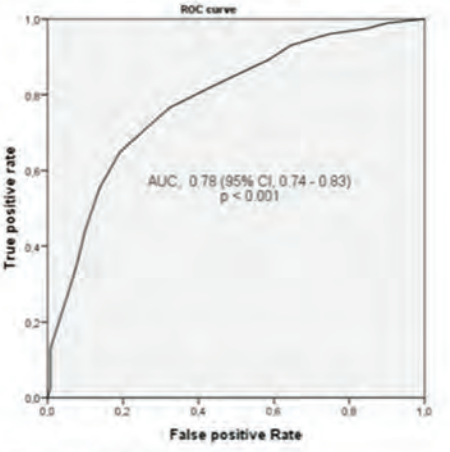


Table 1. AKI risk prediction score.

	Risk factor	Points
Chronic	Chronic kidney disease	2
	Chronic liver disease	2
	Congestive heart failure	2
	hypertension	2
	Atherosclerotic coronary vascular disease	2
Acute	ph ≤ 7.30	3
	Nephrotoxin exposure	3
	Severe infection/ sepsis	2
	Mechanical ventilation	2
	Anemia	1

Minimum total score, 0; maximum total score, 21.

PUB019

Morphology of Bevacizumab Associated Glomerulopathy Fermin J. Person,[5,9] Silke R. Brix,[8,9] Sonia Wulf,[5] Maria de las Mercedes Noriega,[6] Oliver M. Steinmetz,[7,9] Jessica Schmitz,[2] Peter F. Zipfel,[3,10] Jan H. Braesen,[4] Thorsten Wiech.[1,9] *[1]Department of Pathology, University Hospital Hamburg Eppendorf, Hamburg, Germany; [2]Hannover Medical School, Hannover, Germany; [3]Leibniz Institute for Natural Product Research and Infection Biology, Jena, Germany; [4]Medizinische Hochschule Hannover, Hannover, Germany; [5]UKE, Hamburg, Germany; [6]Universitaetsklinikum Hamburg - Eppendorf, Hamburg, Germany; [7]University Hospital Hamburg Eppendorf, Hamburg, Germany; [8]University Hospital Hamburg-Eppendorf, Hamburg, Germany; [9]SFB 1192, Hamburg, Germany; [10]University Jena, Jena, Germany.*

Background: Bevacizumab as a chemotherapeutic agent is a humanized monoclonal IgG1 antibody neutralizing vascular endothelial growth factor (VEGF). It is used for the treatment of different cancer types and of age-related macular degeneration (AMD). As a known side effect it can lead to nephrotic syndrome. Aim of our study was to determine the morphologic correlate in comparison to thrombotic microangiopathy (TMA) and cryoglobulinemic glomerulonephritis (GN).

Methods: We analyzed 13 renal biopsies of patients with nephrotic syndrome after Bevacizumab therapy and compared them to 7 cases of cryoglobulinemic glomerulonephritis, some of them associated with hepatitis C or monoclonal gammopathy and 5 cases of thrombotic microangiopathy (aHUS). First we determined the morphologic pattern in PAS staining. In addition to standard diagnostic immunohistochemical markers (IgA, IgG, IgM, C1q, C3, and fibrin) we stained for IgG1-4, CD61, CD34 and compared electron microscopic features.

Results: All 13 Bevacizumab cases revealed an MPGN like immune complex glomerulopathy with hyaline pseudothrombi, some of them being strongly PAS positive and others being nearly PAS negative in a patchy pattern. Another striking feature was a marked dilatation of the glomerular capillaries filled with these pseudothrombi. Double

contours of the peripheral basement membrane were found in other areas. In contrast to that the thrombi in cryoglobulinemic GN were consistently strongly PAS positive and in TMA cases only weakly positive. In the latter groups dilatation of the capillaries was almost absent. The pseudothrombi were mostly positive for IgG1-3 and only rarely positive for IgG4 with no obvious difference compared to cryoglobulinemic GN. In contrast to TMA cases no CD61 positive thrombi were found. Like TMA cases and to lesser extent also cryoglobulinemic GN cases the pseudothrombi in Bevacizumab cases were frequently accompanied by a loss of surrounding CD34+ endothelial cells.

Conclusions: Bevacizumab associated glomerulopathy often exhibits a unique histomorphologic pattern with a patchy pattern of PAS positive and nearly negative hyaline pseudothrombi in markedly dilated glomerular capillaries with loss of endothelial cells. Recognizing this pattern can be important for differential diagnosis in cancer patients with nephrotic syndrome.

PUB020

Timing for Initiation of Sequential Continuous Renal Replacement Therapy in Patients with Extracorporeal Membrane Oxygenation: A Propensity Score Analysis Anna Lee. *SNUBH, Gyeonggi-do, Democratic People's Republic of Korea.*

Background: Extracorporeal membrane oxygenation (ECMO) is a lifesaving therapy used in critically ill patients with severe cardiopulmonary dysfunction. Continuous renal replacement therapy (CRRT) is added to treat fluid overload, acute kidney injury and electrolyte disturbances during ECMO. However, it is not well defined when to initiate CRRT. We performed this study to identify the optimal timing for CRRT on ECMO.

Methods: We conducted a multicenter retrospective cohort study of 296 patients who received CRRT during ECMO in Seoul National University Bundang Hospital, Yonsei University Hospital and Seoul National University Hospital between 2005 and 2016. We assigned the patients to either an early or late CRRT group depending on the initiation time of CRRT. We considered "early CRRT" to be CRRT instituted within 72 hours of ECMO initiation.

Results: Among 296 patients, 212 patients (71.6%) received early CRRT. After using a method, Ninety-four patients were included in a propensity score matching analysis. No difference in patients' mortality between early and late CRRT groups was found (59.6 vs. 57.4%, $P = 0.834$, respectively). Time from ECMO initiation to CRRT initiation was 1.1 ± 0.9 days in the early CRRT group and 14.6 ± 18.6 days in the late CRRT group. After adjusting all covariables, early CRRT group did not have worse survival than late CRRT group (HR, 0.697; 95% CI, 0.410-1.184; $P = 0.182$). In patients with baseline creatinine levels < 1.3 mg/dL, the late CRRT group showed better patient survival than the early CRRT group (HR, 0.438; 95% CI, 0.196-0.982; $P = 0.045$).

Conclusions: This study showed that early CRRT treatment may not be superior to late CRRT treatment in ECMO patients, and patients with better baseline renal function may allow to delay the initiation of CRRT. Clinical trials may be needed on timing to initiate subsequent CRRT in ECMO patients.

PUB021

The Additive Value of Serum Anion Gap and pH for Mortality in Patients Receiving Concomitant Continuous Renal Replacement Therapy and Extracorporeal Membrane Oxygenation Anna Lee. *SNUBH, Gyeonggi-do, Democratic People's Republic of Korea.*

Background: The anion gap is an easily calculated marker based on analytes typically available from routine chemistry analysis. An increased serum anion gap is known as a risk factor for hypertension, decreased renal function and mortality in critical illness. This study aimed to investigate whether serum anion gap and pH might be predictive of mortality in patients receiving continuous renal replacement therapy (CRRT) and extracorporeal membrane oxygenation (ECMO).

Methods: Patients who received CRRT and ECMO in Seoul National University Bundang Hospital, Yonsei University Hospital and Seoul National University Hospital between 2005 and 2016 were included. The albumin and blood urea nitrogen-adjusted anion gap (AGc) was calculated using this formula : AGc (mmol/L) = serum sodium (mmol/L) – (serum chloride (mmol/L) + serum bicarbonate (mmol/L)) + ([4 – serum albumin (g/dL)] x 2.5) – ([blood urea nitrogen (mg/dL) – 15] ÷ 7)

Results: Among 307 patients, 204 patients died (66.4%). According to the receiver operating characteristic curve analysis, the optimal threshold of AGc and pH for mortality were 14.75 mmol/L (sensitivity 0.782 and specificity 0.434) and 7.34 (sensitivity 0.718 and specificity 0.491). Multivariate analysis showed that patients with AGc above 14.75 mmol/L had 1.5 times higher risk of mortality (HR, 1.533; 95% CI, 1.047-2.244; $P = 0.028$) and patients with pH below 7.34 had 1.9 times higher risk of mortality (HR, 1.869; 95% CI, 1.308-2.670; $P = 0.001$). Patients with AGc ≥ 14.75 and pH < 7.34 increased the risk of mortality than patients with AGc < 14.75 and pH ≥ 7.34 (HR, 3.367; 95% CI, 2.094-5.412; $P < 0.001$). Whereas, albumin-adjusted anion gap did not show any significant predictive value for mortality.

Conclusions: This study showed that AGc and pH may have independent prognostic values and additive effects on mortality in patients receiving CRRT during ECMO.

PUB022

Tenofovir Nephrotoxicity in a Patient With Sepsis Youngjun Park,[3] Prince Singh,[2] Nawsheen Chowdhury,[3] Ismail O. Jimada,[1] James Drakakis,[3] Shayan Shirazian,[3] Minesh Khatri.[3] *[1]Department of Medicine, Division of Infectious Disease, NYU-Winthrop Hospital, Mineola, NY; [2]Department of Medicine, NYU-Winthrop Hospital, Mineola, NY; [3]Department of Medicine, Division of Nephrology, NYU-Winthrop Hospital, Mineola, NY.*

Background: Tenofovir disoproxil fumarate (TDF) is a commonly prescribed antiretroviral medication. We present a case of a HIV+ patient who presented with septic shock and acute kidney injury (AKI) and was found to have TDF nephrotoxicity on renal biopsy.

Methods: A 50-year-old African-American female with HIV infection for the past 15 years presented with one week of altered mental status and fevers. She had been on TDF for HIV viral load suppression for the past 7 years. Other medications include atazanavir, ritonavir, and Bactrim (starting one week prior to admission for CD4 count of 170 cells/mm^3). On initial presentation, she was noted to have altered mental status and was presumed to be in septic shock from multifocal pneumonia with labs significant for lactate of 5.8mmol/L, Cr 5.2mg/dL, albumin 2.3gm/dL, and serum glucose 194mg/dL. Urine studies revealed spot urine protein of 3 gm/gm, glycosuria, and hematuria. Serologies for glomerulonephritis were negative. She was initiated on dialysis for oliguric renal failure. Given the unclear etiology of her renal failure and lack of renal recovery despite hemodynamic improvement, a renal biopsy was done which revealed diffuse and severe proximal tubular interstitial changes, diffuse interstitial edema with scattered rounded eosinophilic intracytoplasmic inclusions in the proximal tubular epithelial cells, as well as enlarged dysmorphic mitochondria on electron microscopy. TDF was discontinued on admission but she remained without renal recovery three weeks later and was discharged on hemodialysis.

Results:

Conclusions: TDF has been shown to cause proximal tubular dysfunction, chronic kidney disease (CKD) and AKI. Other risks factors for TDF nephrotoxicity include advanced age, decreased CD4 count, baseline CKD, concurrent use of protease inhibitors, and genetic defects in renal drug transporter proteins. AKI from TDF nephrotoxicity can occur in isolated settings but can be potentiated by the presence of other nephrotoxins. In this case we largely attributed the patient's AKI to septic shock but believe that this predisposed the patient to TDF nephrotoxicity, which in turn further amplified the renal insult. This case also emphasizes that TDF nephrotoxicity can develop at any time, even after years of uneventful treatment.

PUB023

Abstract Withdrawn

PUB024

Dynamic Changes of Properdin in Mouse Renal Ischemia Reperfusion Injury and Repair Hui Wang,[1] Yuanyuan Wu,[2,3] Aifen Liu,[2] Yufang Zhang,[2] Qian Wang,[1] Wenting Li,[1] Yaping Fan,[1] Bin Yang.[3,1] *[1]Affiliated Hospital of Nantong University, Nantong, China; [2]Nantong University, Nantong, China; [3]University of Leicester, Leicester, United Kingdom.*

Background: Properdin, released predominantly from neutrophils, is an only known positive regulator of alternative pathway of complement activation via stabilizing C3bBb. Our pilot studies revealed that renal ischemia reperfusion (IR) injury at 72 h was significantly aggregated by properdin deficiency in mice. This study, aimed to explore the dynamic changes and effects of properdin *in vivo*.

Methods: IR-related injury was established in mouse kidneys subjected to 30-min ischemia followed by 6-72 h, 1 week reperfusion *in vivo*. Then the expression of properdin and complement activation related protein C3b was investigated, and the changes of renal function, inflammation, apoptosis were also measured. In addition, we make the correlation analysis between properdin and some renal damage markers.

Results: In mouse IR kidneys, serum creatinine (SCr) was significantly increased after 24-h reperfusion and reached the peak at 48 h. The expression of properdin protein was increased in a time-dependent manner and reached the peak at 24 h, while there was no significant change in C3b protein. immunohistochemistry staining results showed that the properdin protein is mainly distributed in the renal tubular area. In addition, the inflammation related protein HMGB-1 and the apoptosis related protein caspase-3 was also increased in a time-dependent manner and reached the peak at 24 h and 12 h, respectively. Furthermore, the protein expression of properdin was significantly positively correlated with HMGB-1 and caspase-3.

Conclusions: Properdin plays an important role in renal IR-related injury and repair. However, whether enhanced properdin could be beneficial in injury repair/recovery and its underlying mechanisms are worthy to be further investigated.

Funding: Government Support - Non-U.S.

PUB025

GUT Derived Endotoxin Contributes to the Inflammation of Ischemia-Reperfused Kidney Tao J. Li,[1,2] Chen Yu.[1,3] *[1]Shanghai Tongji Hospital, SHANGHAI, China; [2]TONGJI UNIVERSITY SCHOOL OF MEDICINE, SHANGHAI, China; [3]TONGJI UNIVERSITY SCHOOL OF MEDICINE, SHANGHAI, China.*

Background: Endotoxins from gut are presumed to play an important role that augment organ inflammation in critical ill condition. In the present study, we studied the effects of endotoxins in renal inflammation in renal ischemia-reperfusion rats(IR).

Methods: Sprague-Dawley rats were divided into 4 groups (n=5 per group): Sham+saline, Sham+norfloxacin, IR+saline and IR+norfloxacin. Rats were treated with oral norfloxacin 20 mg/kg/day or saline for 4 weeks before IR operation. For IR induction, the bilateral kidneys experienced a 60 min of ischemia plus 24h reperfusion. The protein expressions of TLR4, NFκBp65 and cytokines of the kidney homogenate were measured. The kidney tissue were stained for TLR4 and NFκB. Endotoxemia was measured using Limulus amoebocyte lysate (LAL) assays. Rat kidney epithelioid cells (NRK-52E) were treated with 20% serum from rats (sham or renal IR group) with or without polymyxin B (PMB), a LPS inhibitor. Cytokines was analyzed by real-time polymerase chain reaction and TLR4-NFκBp65 protein was identified with Western-blotting.

Results: Endotoxemia was alleviated in norfloxacin treated rats. The IR rats with norfloxacin showed significant attenuation of the increased IL-6 and MCP-1 in renal tissue. The upregulations of TLR4 and NFκBp65 were decreased significantly in the norfloxacin treated rats(Figure 1A-I). Norfloxacin failed to improve renal function and tubular injury(Data are not shown). IL-6, MCP-1, TLR4 and NF-κB p65 expressions were increased in the NRK-52E stimulating with **s**erum of renal IR. PMB inhibited IL-6, MCP-1 TLR4 and NF-κB p65 expressions (Figure 2A-B).

Conclusions: Endotoxin contributes to IR induced renal inflammation. Improvement of intestinal barrier dysfunction and inactivation of endotoxins may be novel targets for intervention.

Funding: Government Support - Non-U.S.

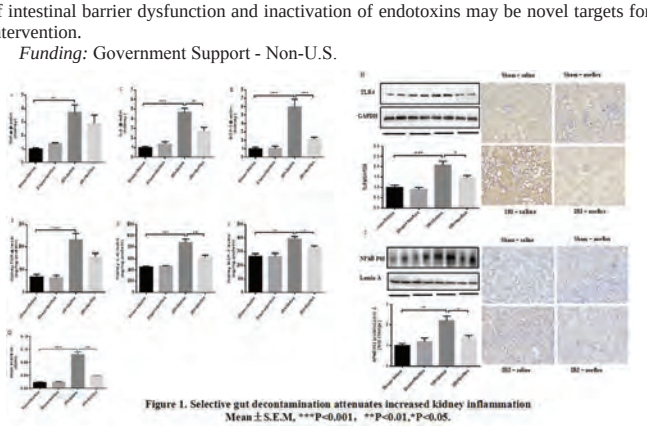


Figure 1. Selective gut decontamination attenuates increased kidney inflammation
Mean ± S.E.M, ***P<0.001, **P<0.01,*P<0.05.

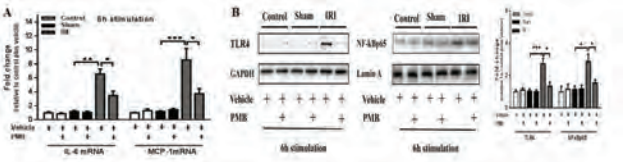


Figure 2. PMB inhibited IR serum induced cytokines gene activation,TLR4 and NF-κB p65 protein expressions. NRK-52E cells were treated with 20% serum and PMB (50μg/ml) or vehicle for 6h.
Mean ± S.E.M, ***P<0.001,*P<0.05.

PUB026

AKI Recovery in Hemodialysis-Dependent Hospital Survivors Discharged to an Acute Rehabilitation Facility Meredith Mcadams,[1] George Vasquez-Rios,[1] Fabiola G. Gianella,[1] B. Peter E. Sawaya,[2] Javier A. Neyra.[2] *[1]University of Kentucky, Lexington, KY; [2]University of Kentucky Medical Center, Lexington, KY.*

Background: Acute kidney injury-requiring dialysis (AKI-D) occurs in about 5% of hospitalized patients and is associated with adverse outcome. Little is known about the incidence of AKI-D recovery post-discharge. We examined AKI-D recovery in hospital survivors that were discharged to an acute rehabilitation facility with the need of acute hemodialysis (HD) therapy.

Methods: Retrospective cohort study of 43 acute rehabilitation facility residents that required nephrology consultation from 8/2015 to 12/2016. Among these, 24 patients were identified that nephrology was consulted on for AKI-D management as they were HD-dependent at the time of discharge from the University of Kentucky Hospitals. AKI-D recovery was defined as the patient no longer requiring HD therapy for AKI. The observation period ended at the time of acute rehabilitation facility discharge.

Results: Mean (SD) age was 61.5 (10.2) years; 70.8% were males and 87.5% whites. AKI-D recovery post-discharge occurred in 14/24 (58.3%) patients. A total of 3/24 (12.5%) patients died during the rehabilitation facility stay, 2/3 (66.7%) without AKI-D recovery. Patients without AKI-D recovery post-discharge had lower baseline eGFR: 45.9 (16.9) vs 78.1 (12.0), p<0.001 and tended to have longer hospitalization days: median (25th-75th percentile) 44 (28–55) vs 33 (21–43) days, p=0.25. Importantly, hospital HD vintage days were significantly higher in those without AKI-D recovery: 54.5 (37.3–96.5) vs 33.0 (20.3–39.0), p=0.04. Similarly, total intradialytic hypotension episodes were more frequent in patients without AKI-D recovery: 10.0 (4.0–15.0) vs 2.5 (1.0–3.3), p=0.07. Critical illness and comorbidity scores were not significantly different among those with vs without AKI-D recovery post-discharge.

Conclusions: At least 1 out of 2 patients discharged to an acute rehabilitation facility with AKI-D diagnosis recovered kidney function no longer requiring HD therapy for AKI. HD-specific characteristics may play a central role in the development of risk-stratification tools for the prediction of AKI-D recovery post-discharge.

PUB027

Oxcarbazepine Induced Rhabdomyolysis Nuray Can usta, Sara Yavuz. *Trabzon Kanuni Training and Research Hospital, Trabzon, Turkey.*

Background: Rhabdomyolysis is a damage of muscle cells and an involvement of systemic circulation of cellular elements. In addition to the direct toxic effect of myoglobulin, the tubular obstruction of direct iron ions also plays a role in the pathogenesis of acute renal failure. We would like to remind the rhabdomyolysis, side effect of oxcarbazepine which is an antiepileptic agent used in the treatment of trigeminal neuralgia due to mortal consequences as acute renal failure.

Methods: 70 year old female patient applied to the clinic with the complaint of pain that affected her right side of her face. Her history contained diabetes mellitus, hypertension, bronchial asthma and hyperthyroidism. Her neurological examination was normal. Laboratory investigation detected only slightly elevated blood glucose. The patient was diagnosed with trigeminal neuralgia and treated with Oxcarbazepine 150mg 2x1. On the third day of the treatment, drowsiness and decreased amount of urine was observed. Patient's serum creatinine levels were 4.0mg/dl. Serum myoglobin and creatin phosphokinase were 1000ng /ml and 765 U/L respectively. Myglobin level of urine was 1700 ng/ml. Acute renal failure caused by rhabdomyolysis was considered. Oxcarbazepine was discontinued. Hydration and support aids were administered. In the follow-ups, it was noted that the apathy state of the patient was mended, there was no need for renal replacement therapy, serum creatinine levels had decreased to 1.2 mg/dl and she was discharged.

Results:

Conclusions: Trigeminal neuralgia is a sharp, intermittent and superficial pain, limited to nerve traces and is caused by demyelination of cranial nerves caused by various factors. Anticonvulsants must be used first. Rhabdomyolysis occurs when muscle cells are damaged and intracellular elements enter systemic circulation. Non-physical causes include alcohol hyperphosphatemia, hyperpotassemia, infections and drug usage such as statins, amphetamines, tricyclic antidepressants, amphotheresin B, antimalarial drugs, cocain, colchicine, corticosteroids, diuretics and central nervous system depressants. Increase in the plasma myoglobin levels is the most reliable test. Creatinine phosphokinase levels 5 or more times higher than the laboratory upper limit is generally enough to make the diagnosis of rhabdomyolysis. Treatment is suitable hydration and bicarbonate infusion and renal plasma treatment must be applied when it is needed.

PUB028

Human Epithelial C5aR1 Signalling Enhances Bacterial Adhesion to Renal Tubular Epithelial Cells through Upregulation of the Expression of Mannosyl Residues (the Ligand for Type I Fimbrae) Ke Li,[2] Wuding Zhou.[1] *[1]King's College London, London, United Kingdom; [2]Xi'an Jiaotong University, Xi'an, China.*

Background: Our recent work has shown that C5aR1 participates in the pathogensis of renal infection in a murine model of ascending urinary tract infection through C5aR1 singalling-mediated upregulation of mannosyl residue (the ligand for type 1 fimbrae) expression on renal tubular epithelial cells which enhances bacterial adhesion and colonization of renal tubular epithelium. However, the relevance of these findings to human is unknown. In the present study, we investigated whether human C5aR1 plays the same roles as mouse C5aR1 in enhancement of bacterial adhesion to renal tubular epithelial cells.

Methods: Normal human kidney tissues were used for detection of C5aR1 (by immunohistochemical staining) and a-mannosyl residue expression (by lectin staining using fluorescence GNL). Parimarry cultures of human renal tubular epithelial cells (RTEC) were used for assessment of bacteria adhesion/uptake, mannosyle residue expression, inflammatory cytokine production and activation of intracellular signaling pathways in response to human C5a stimulation. RT-qPCR and flow cytometry bead array were used for measuring cytokine production. GNL staining was used for detection of a-mannosyl residue expression on the cell surface. CFU assay was used for measuring bacterial binding and uptake. α

Results: C5aR1 and α-mannosyl residues were clearly detected in renal tubules, predominantly localised at the cortical-medullar junction. C5aR1 and) a-mannosyl residues were also detected in RTEC. C5a (10nM) stimulation of RTEC resulted in significant up-regulation of: i) a-mannosyl residue expression, ii) ERK and NF-kB phosphorylation, iii) pro-inflammatory cytokine production (i.e. TNF-a, IL-1β, IL-6) under infection conditions (in the presence of LPS or killed E coli), iv) bacterial binding/ uptake and epithelial barrier damage. C5aR1 blockade using C5aR1 antagonist (PMX53 5mM) effectively inhibited the effect of C5a-mediated up-regualtion of bacterial binding/ uptake in RTEC.

Conclusions: Our findings demonstrate an important role for human C5aR1 in enhancement of bacterial adhesion to renal tubular epithelial cells which has implications for the pathogenesis of human renal infection.

Funding: Government Support - Non-U.S.

PUB029

Imbalance between Vasoactive Factors during the Development of Experimental Aristolochic Acid Nephropathy Inès Jadot,[4] Blanche Martin,[4] Olivia Botton,[3] Joelle L. Nortier,[1] Anne-Emilie Decleves,[2] Nathalie Caron.[5] *[1]Hospital Erasme, Brussels, Belgium; [2]Laboratory of Molecular Biology, University of Mons, Belgium, NIMY (MONS), Belgium; [3]UNamur, Namur, Belgium; [4]University of Namur, Namur, Belgium; [5]University of Namur - FUNDP, Namur, Belgium.*

Background: Aristolochic Acid (AA) nephropathy (AAN) is a pertinent example of tubulo-interstitial nephritis characterized by an early phase of acute kidney injury (AKI) leading to progressive fibrosis and chronic kidney disease (CKD). It is now greatly recognized that endothelial cell activation as well as imbalance between vasoactive substances widely contributes to the transition from AKI to CKD. Therefore, in the present study, we aimed to characterize the potential imbalance between vasoactive substances such as nitric oxide (NO), endothelin-1 (ET-1), angiotensin II (Ang II) and urotensin II (UT II) in the successive phases of AAN.

Methods: C57BL/6J male mice were randomly subjected to daily i.p. injection of vehicle or AAI (3,5mg/kg) for 4 days. Mice were euthanized, 5, 10 and 20 days after the beginning of AAI injections.

Results: AA-treated mice developed marked renal injury and histopathological features of AAN were reproduced. Early phase of AKI observed at day 5 was characterized by necrosis of proximal tubular epithelial cells and proteinuria. Later phase of CKD developed at day 20 as attested by tubular atrophy and massive interstitial fibrosis. Oxidative stress and inflammatory cell infiltration were also characterized concomitantly to the progression from AKI to CKD. Regarding the vasoactive factors, our results revealed that AA-intoxicated mice presented: (1) Reduced urinary NO and cGMP levels throughout the protocol whereas renal mRNA expression of *NO synthases* (*eNOS, nNOS, iNOS*) remained unchanged. (2) Reduced renal mRNA expression of *angiotensinogen* (*AGT*), *angiotensin II converting enzyme* (*ACE*) and *angiotensin II receptors* (AT_1 and AT_2) throughout the protocol. (3) Increased urinary and plasma ET-1 levels and increased renal mRNA expression of *ET-1* and its *receptor A* (ET_A) whereas renal mRNA expression of *receptor B* (ET_B) was strongly downregulated. (4) Increased renal mRNA expression of *UT II* and *UT receptor*.

Conclusions: Our findings demonstrated that imbalance between vasoactive substances occurs during AAN progression and could contribute to the transition from AKI to CKD.

Funding: Government Support - Non-U.S.

PUB030

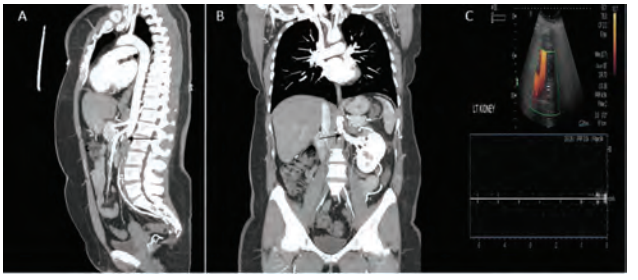
Takayasu Arteritis Causing Complete Occlusion of the Infrarenal Abdominal Aorta and Left Renal Artery Stenosis Don H. Esprit, Volodymyr Chornyy, Vikrampal Bhatti, S. Irfan Qadri. *UF Department of Nephrology, Gainesville, FL.*

Background: Takayasu Arteritis is classified as a large-vessel vasculitis which primary affects the aorta and its branches. The renal arteries are of no exception. We present a case of a female patient with complete infrarenal abdominal aorta occlusion and severe left renal artery stenosis.

Methods: The patient was a 50 year old caucasian female with a past medical history significant but not limited to Takayasu arteritis, right renal nephrectomy secondary to right renal artery occlusion when she was 35 years old as a consequence of Takayasu arteritis. She presented with frontal headache and was found to have elevated blood pressure and acute kidney injury with oliguria. CTA of the abdomen and chest showed complete occlusion of the infrarenal abdominal aorta with associated mesenteric collateral consistent with chronic occlusion. [IMAGE A]. The right renal artery was absent and the left renal artery revealed high grade proximal stenosis. [image B]. However a Doppler ultrasound did not reveal any significant flow to the left kidney. [image C]. She was taken to the operating room and underwent aortobifemoral bypass with a 14x7 Hemashield graft and left aortorenal bypass with 6mm Hemashield graft. Luckily she escaped renal replacement therapy.

Results:

Conclusions: Takayasu Arteritis(TAK) is a rare granulomatous vasculitis affecting women of childbearing age. TAK should be suspected based upon clinical findings and specific imaging findings of the aorta and its branches. There are no diagnostic laboratory test for TAK. Erythrocyte sedimentation rate and C-reactive proteins may provide some support for the systemic inflammatory process but normal values should not exclude the diagnosis. Clinicans, nurses, and other clinical staff need to be cognizant of this rare pathology especially in patients who presents with hypertension at a young age. Early diagnosis is vital in order to prevent major complications or even death.



PUB031

Collagen Type III Degradation Increases Following Ischemia Reperfusion Injury in Rats Signe Holm Nielsen,[2,4] Daniel Guldager Kring Rasmussen,[2,3] Federica Genovese,[2] Morten A. Karsdal,[2] Rikke Norregaard.[1] *[1]Aarhus University, AARHUS N, Denmark; [2]Nordic Bioscience, Herlev, Denmark; [3]Institute of Molecular Medicine, Cardiovascular and Renal Research, University of Southern Denmark, Odense, Denmark; [4]Department of Biomedicine and Biotechnology, Technical University of Denmark, Kgs. Lyngby, Denmark.*

Background: Survival of patients receiving a kidney allograft has increased significantly over the years. However, maintenance of kidney function in allograft kidneys remains challenging, and most allografts develop significant fibrosis within a few years after surgery. It is therefore important to understand and monitor the mechanisms that cause fibrosis at early stages to prevent allograft loss and to be able to identify the most susceptible patients for treatment. Ischemia reperfusion injury (IRI) promotes the development of kidney fibrosis in the allograft. Upon IR, changes in the extracellular matrix (ECM) protein turnover occur, causing tissue remodeling. Collagen type I (COL I) and III (COL III) are the most abundant collagens in the kidney ECM.

Methods: We quantified the degradation of COL III by measuring a neo-epitope of COL III generated by MMP-9 with the uC3M ELISA in urine samples from rats subjected to unilateral nephrectomy (NTx) followed by ischemia reperfusion (NTxIRI). Control rats were subjected to NTx but not to IRI. The correlation between levels of uC3M and levels of plasma creatinine, blood urea nitrogen (BUN), mRNA of markers of kidney injury (KIM-1 and NGAL), and mRNA of markers involved in tissue repair and fibrosis (TNFα, αSMA, fibronectin, TGFβ, and the alpha-1 chain of type I collagen (COL 1a1)) was investigated.

Results: Levels of uC3M did not increase following NTx, but were significantly elevated seven days after ischemia reperfusion injury in NTxIRI compared to animals only receiving NTx. Levels of uC3M correlated with NGAL mRNA (R2=0.82, p=0.0019), but not KIM-1 mRNA in NTxIRI animals (R2=0.25, p=0.21). uC3M correlated with plasma creatinine and BUN in NTxIRI animals, but there was no correlation between uC3M and mRNA of TNFα, αSMA, fibronectin, TGFβ, or Col1a1.

Conclusions: In conclusion, levels of uC3M increased following ischemia reperfusion injury, and correlated with kidney function and NGAL mRNA. This marker may be useful to non-invasively assess the changes in renal tissue remodeling as a consequence of kidney injury.

Funding: Private Foundation Support

PUB032

Angiogenic or Anti-Inflammatory Factor Secreting-Genome Engineered Mesenchymal Stem Cells for the Treatment of AKI Hye-Jeong Park, jeong-in Cho, Eui-Jung Park, Hyo-Jung Choi, Tae-Hwan Kwon. *Kyungpook National University, Taegu, Republic of Korea.*

Background: Acute kidney injury (AKI) is defined as an abrupt reduction of kidney function which is accompanied by renal tubular necrosis, vascular injury and inflammation. AKI is associated with high morbidity and mortality and hence, new strategies directed to reduce renal injury and improve renal function are greatly needed. Stem cell-based therapy with genome engineering has been proposed as a potential strategy. Here, we aimed to generate genome-engineered mesenchymal stem cells (MSCs) to secrete angiogenic factors, VEGF and angiopoietin1 (ANG1), or anti-inflammatory factors, erythropoietin (EPO) and a-melanocyte stimulating hormone (a-MSH), respectively, for therapeutic application.

Methods: To integrate each gene expression cassette into a safe harbor locus, AAVS1, of the human umbilical cord-derived MSCs (hUCMSCs) chromosome, AAVS1-targeting Zinc Finger Nuclease (ZFN) or AAVS1-targeting CRISPR/Cas9 system was used.

Results: ZFN- or CRISPR/Cas9-aided targeted integration was achieved in hUCMSCs which were confirmed by flow cytometry and junction PCR analysis. Genome-engineered hUCMSCs were confirmed to maintain their characteristics of stem cells. Each protein product released from genome-engineered hUCMSCs with AAVS1-targeting ZFN or CRISPR/Cas9 was measured in conditioned media by each protein-specific ELISA (VEGF-hUCMSCs: 12 or 7 ng; ANG1-hUCMSC: 11 or 10 ng; EPO-hUCMSCs: 32 or 5 IU, and α-MSH-hUCMSCs: 0.2 ng per 10^6 cells for 24 h (ZFN only). Then, we made the scaffold-free cell sheet system based on temperature-responsive polymer (poly(N-isopropylacrylamide) to enable transplanted hUCMSCs to be engrafted for a long time to maximize the therapeutic effects.

Conclusions: Taken together, cell sheet system of hUCMSCs secreting angiogenic or anti-inflammatory factors is successfully established. This is to be examined in animal models of AKI to demonstrate the therapeutic effects of stem cell-based regenerative strategy against AKI.

Funding: Government Support - Non-U.S.

PUB033

Reprogramming of Mitochondrial Metabolism Induces Tubulointerstitial Fibrosis after Ischemic AKI Yang Zhou,[2] Nan Qin,[1] Junwei Yang.[2] *[1]Nanjing Medical University, Nanjing, China; [2]Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.*

Background: Acute kidney injury (AKI) is a global public health concern associated with hospitalizations and is especially common in critically ill patients (up to 40% at ICU admission and 60% during admission). The transition of AKI to consequence chronic kidney disease (CKD) has major clinical significance; however, the pathophysiology of AKI-to-CKD remains largely unknown. Reclaim of fluid, sodium and many solutes from glomerular filtrate by tubule is an energy consumption process relies mainly on mitochondrial metabolism. Whether energy metabolism contributes to the progression of AKI-to-CKD is unknown.

Methods: We generated AKI-to-CKD model using ischemia-reperfusion injury (I/R) and examined alternations of mitochondrial morphology and critical enzymes that govern fatty acid oxidation and glycolysis.

Results: Impairment of renal function and remarkable accumulation of extracellular matrix in the tubulointerstitial spaces were quite evident several weeks after I/R injury. Mitochondria reduction and swellings, as well as lipid droplets deposition suggested metabolic abnormalities of fatty acid. However, increased glycolytic enzyme expression and inhibitory phosphorylation of pyruvate dehydrogenase were exhibited indicating a switch to glycolysis. Furthermore, renal expression of hypoxia-inducible factor 1 a (HIF-1a) was increased and mTOR was activated, which suggested that the glycolytic phenotype may be regulated by mTOR signaling through enhancing HIF-1a activity.

Conclusions: Reprogramming of mitochondrial metabolism from fatty acid oxidation to glycolysis in the context of active mTOR signaling and hypoxia may contribute to pathogenesis of AKI-to-CKD.

Funding: Government Support - Non-U.S.

PUB034

Udenafil Attenuates Renal Injury through Inhibition of Thrombospondin-1 after Unilateral Ischemia-Reperfusion Injury Jong-Hwan Jung,[2] Seon-Ho Ahn.[1] *[1]Iksan, Jeollabuk-Do, Republic of Korea; [2]Wonkwang University Hospital, Iksan, Republic of Korea.*

Background: Thrombospondin-1 (TSP-1) is a ligand of CD36, transmembrane receptor. TSP-1 shows antiangiogenic effect and plays as an endogenous activator of TGF-ß concerning of renal fibrosis. Udenafil, a cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 inhibitor is well-known as vasodilator with anti-oxidant effect. Udenafil shows a protective effect through nitric oxide (NO)/cGMP pathway in ischemic kidney, particularly. Herein, we newly investigated a role of udenafil related with TSP-1 in unilateral ischemia-reperfusion injury (IRI).

Methods: Unilateral IRI surgery was performed on male Spraque-Dawley rats with various weights of 200~250 g. All rats, including control (n=6), saline injection (n=7), and udenafil injection (n=8) were at 7 weeks of age. We performed a flank approach to induce IRI. The renal ischemia was induced by vascular clamps over the pedicles for 45 minutes. The udenafil of 20 mg/kg in only udenafil group (n=8) was administrated intraperitoneally with volume of each 5 mg/ml at 24 hours and 0 hour before IRI surgery with volume of 5 mg/ml. At 24 hours after the IRI, kidneys were harvested and fixed in paraformaldehyde for pathological studies.

Results: On western blotting, unilateral IRI increased molecules, such as TSP-1, fibronectin, and P-smad 2/3 compared to control. Pretreatment of udenafil in rats with unilateral IRI also attenuated expression of TSP-1 and fibronectin compared to saline + unilateral IRI rats. There was unfortunately no difference of expression of P-smad 2/3 between udnenafil + IRI and saline + IRI group. There was pathologic findings, including renal tubular epithelial dilatation and severe interstitial inflammation on IRI rats, however, histologic improvement was not shown in rats with udnenafil + IRI compared to rats with saline + IRI.

Conclusions: Generally, udenafil shows anti-angiogenic effect through the activation of NO/cGMP pathway. Thus, udenafil showed beneficial effect in the kidney with renovascular stenosis or ischemia. To date, there were unfortunately rare data for relationship between udenafil and renal fibrosis induced by IRI. Although there was no a histological improvement in udenafil + IRI rats due to severe IRI for 45 minutes, significant change of molecules, such as TSP-1 and fibronectin, supports that udenafil might have a protective or anti-fibrotic effect after IRI.

PUB035

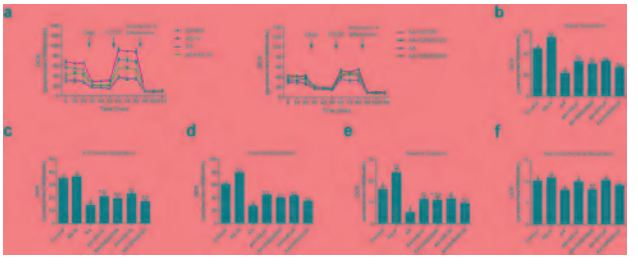
Astragaloside IV Ameliorates Aristolochic Acid-Induced AKI Associated with Antiapoptosis and Reduction of Mitochondrial Injury Xinghua Shao,[1] Shan Mou,[2] Lei Tian,[1] Zhaohui Ni.[1] *[1]Ren Ji Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, China; [2]Renji Hospital, Shanghai, China.*

Background: Aritstolochic acid nephropathy (AAN) is characterized by AKI subsequently followed by interstitial fibrosis. Apoptosis and mitochondrial injury play a critical role.Astrogaloside IV (AS-IV) has been shown to exert renal protection in many mouse models of AKI, but its role in preventing AA-induced AKI still remain obscure.

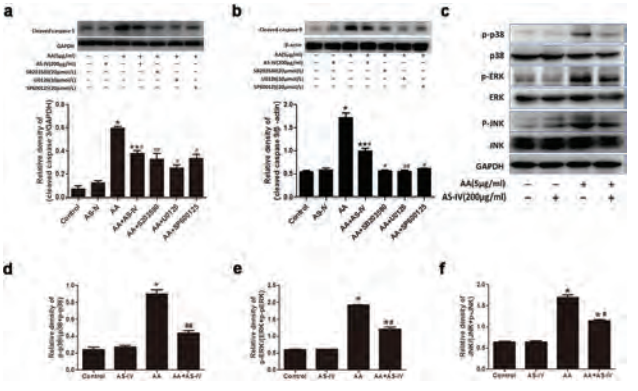
Methods: HK-2 cells induced by AA were used to investigate the protective role of AS-IV in antiapoptosis and reduction of mitochondrial injury. In vivo, mice subjected to AA injection were administered AS-IV by intraperitoneal injection. TUNEL assay, immunofluorescence staining, electron microscopic examination and Immunoblot analysis were ultilized to dectect the protective role of AS-IV in antiapoptosis. Extracellular flux analysis were carried out by Seahorse XF24 analyzer to examine the protective role of AS-IV in reduction of mitochondrial injury.

Results: Results in vivo showed that AS-IV provided morphologic and functional renoprotection against AA-induced AKI via inhibiting apoptosis and reducing mitochondrial morphological change. Further, data in vitro suggested treatment with AS-IV ameliorated mitochondrial respiration damage induced by AA, and inhibition of MAPKs pathways protected apoptosis and mitochondrial respiration.

Conclusions: All these findings indicated a promising effect of AS-IV in protection against AA-induced AKI via anti-apoptosis and reduction of mitochondrial injury, and inhibition of MAPKs pathways might be involved in this process.



AS-IV ameliorated mitochondrial respiration damage induced by AA in HK-2 cells.



Effects of AS-IV on cell apoptosis and activation of MAPKs pathways in HK-2 cells 24 hr after AA incubation.

PUB036

Nesfatin-1 Improves Contrast-Induced Nephropathy in Rats Mehmet Koc,[2,3] Abdullah Shbair,[2] Seda Kutlug Agackiran,[2] Zarife Ozdemir,[3] Ozlem Tugce Cilingir Kaya,[1] Naziye Ozkan,[1] Sule Cetinel,[1] Berrak Yegen.[3] *[1]Marmara University Medical Faculty, Department of Histology, Istanbul, Turkey; [2]Marmara University Medical Faculty, Department of Internal Medicine, Istanbul, Turkey; [3]Marmara University Medical Faculty, Department of Physiology, Istanbul, Turkey.*

Background: Contrast-induced nephropathy (CIN) is the third common cause of acute kidney injury (AKI). Mechanisms of CIN include renal medullar hypoxia, endothelial injury, oxidative stress and direct tubular toxicity of contrast agents. Nesfatin-1 (NS-1) is reported to have anti-inflammatory and antiapoptotic actions in several experimental models. However, the role of NS-1 in the development of CIN has not yet been elucidated. In this study, we aimed to demonstrate the effects of NS-1 on CIN.

Methods: Male Sprague-Dawley rats were injected intraperitoneally with only saline (control group, n=9), while CIN groups were treated with either saline (SL, n=10) or NS-1 (10 mcg/kg/day, n=8) at 0, 24 and 48 hours of the experiment. CIN was established by intravenously injecting indomethacin (10 mg/kg), L-NAME (10 mg/kg) and a high-osmolar contrast agent (Urografin 76%, 6 ml/kg) at 24th h of the experiment. On the 72nd h, kidneys were removed for the assessment of histopathological changes and the determination of glutathione levels and myeloperoxidase activity. Data were analyzed using ANOVA and Student's t-test.

Results: Serum creatinine levels in SL-treated and NS-1-treated CIN groups were elevated as compared to control group ($p<0.05$), while the increase in NS-1-treated group was relatively lower but not significant ($p>0.05$). In contrast to depressed 24-h creatinine clearance in SL-treated CIN group ($p<0.05$), clearance in NS-1-treated group was not different than that of the control group. CIN-induced increase in renal myeloperoxidase activity ($p<0.05$) in SL-treated group was abolished in NS1-treated group ($p>0.05$), Renal glutathione content which was reduced in SL-treated CIN group, was elevated by NS-1 treatment back to the levels observed in control group. Histopathological damage scores obtained by light microscopic examination were significantly increased in the SL-treated CIN group compared to control group ($p<0.05$), while treatment with NS-1 decreased the score ($p<0.001$).

Conclusions: The present data demonstrate that CIN is ameliorated by NS-1, which appears to act by inhibiting the infiltration of neutrophils and preventing the oxidative stress. These data suggest that NS-1 may have a regulatory role in protecting against CIN.

Funding: Government Support - Non-U.S.

PUB037

Patient with Ethylene Glycol Poisoning and Need for Following Renal Replacement Therapy Erika Székelyová. *FMC, Velká Hledsebe, Czech Republic.*

Background: Ethylene glycol poisoning causes fatal intoxications, even relatively small ingestions of thise alcohol can produce significant toxicity. Rapid recognition and early treatment, including alcohol dehydrogenase inhibition, are crucial. To provide proper management, clinicians must understand the metabolic activation of ethylene glycol to their toxic acid metabolites, the limitations of available laboratory tests, and the indications for treatment with antidotes, with or without hemodialysis.

Methods: A 46-year-old man was admitted to the hospital on the 30 November 2011 with suicidal ethylene glycol poisoning. It was a severe intoxication with serum ethylen glycol concentration above 10 g/l. Initial haemodialysis was urgently started followed by continual veno-venosus haemodialysis (CVVHD). Intravenous ethanol was continuously administered as a competitive inhibitor of alcohol dehydrogenase (ADH). After 48 hours, when serum ethylen glycol concentration was zero, CVVHD had finished, but the patient needed renal replacement therapy because of ongoing kidney failure. The last haemodiafiltration was done on the 10 January 2012, after there had been renal function partially repaired to glomerular filtration (GF) on grade 3a-b, and since the year 2013, glomerular filtraton is on grade 2. On the 12 April 2017, the patient was admitted to the hospital again with suicidal ethylene glycol poisoning (he ingested demonstrably 1l automotive antifreeze), and the initial serum ethylen glycol concentration was 4,7 g/l. Initial haemodiafiltration was started (befor we known serum ethylen glycol concentration), followed by continual veno-venosus haemodiafiltration (CVVHDF) and intravenous ethanol was continuously administered. Metabolic acidosis was not serious, and spontaneous diuresis had been maintained. The next haemodiafiltration was done on the 13 April, followed on the 15 April by continual veno-venosus haemodiadiafiltration (CVVHDF), when the serum ethylen glycol concentration was zero. The patient did not develop a progression of chronic kidney disease, and the last glomerular filtration was 1,4 ml/s (measured GF) or 1,21 ml/s (GF- MDRD).

Results:

Conclusions: According to our experience, early comprehensive treatment of severe ethylene glycol poisoning saves not only the life of the patient, but also, in the optimum case, it may also enable the repair of renal function.

PUB038

Unraveling the Role of BUN as a Marker of Renal Function or Maladaptive Neurohormonal Activity in Patients with Acute Heart Failure Abhilash Koratala,[2] Muhannad Leghrouz,[2] Amir Kazory.[1] *[1]University of Florida, Gainesville, FL; [2]University of Florida, Gainesville, FL.*

Background: It has been proposed that blood urea nitrogen (BUN) could be a marker of exacerbated neurohormonal activity (NA) above and beyond its role in determination of renal function in the setting of acute heart failure (AHF). Changes in weight and daily fluid balance are commonly used to monitor decongestive therapy in these patients; ultrafiltration (UF) has emerged as an option for more efficient fluid removal and alleviation of NA. We sought to determine whether decongestion by UF is correlated with a decrease in BUN as a surrogate for maladaptive NA.

Methods: Articles cited in PubMed database from January 2000 to March 2017 using variable combinations of key words "ultrafiltration", "heart failure", and "decongestion". Original clinical articles evaluating the role of UF in AHF were reviewed and selected. Relevant data including primary outcomes, and decongestion markers were extracted and compared. Using Spearman's rank correlation analysis, the degree of dependence and correlation between weight reduction and fluid removal with changes in BUN was determined

Results: A total of 348 patients in 8 studies were included. The mean age was 65 years and 68% were male. There existed substantial variation across studies in the reporting of surrogates of decongestion. Weight loss ranged from 2.6 to 9.7 Kg (mean 6.2±2.05 Kg) and fluid removal ranged from 2.6 to 12.1 L (mean 8.5±3.0 L). Changes in BUN ranged from +0.8 to +12.54 mg/dl (median +8.5 ± 4.5 mg/dl). There was a negative correlation between changes in BUN and reduction in weight (R= -0.47, 95%, CI of Correlation -0.89-0.35, p=0.24) and with the amount of fluid removal (R= -0.53, 95%, CI of Correlation -0.9-0.27, p=0.17).

Conclusions: Based on the currently available evidence, decongestion by UF is correlated with a rise in BUN level in patients with AHF. Therefore, although BUN could reflect NA in this setting, it can still be used as a marker of renal function that is affected by intravascular volume changes. Since the goal of therapy in AHF is optimal decongestion without overzealous fluid removal, future studies are needed to explore whether combining BUN with clinical markers of decongestion could more precisely guide the process of fluid extraction.

PUB039

Liraglutide-Induced Acute Tubular Necrosis Paris Barkan, Avrum Gillespie. *Temple University Hospital, Philadelphia, PA.*

Background: Liraglutide, a GLP-1 agonist used to treat Diabetes Mellitus, has known gastrointestinal and thyroid side effects, but only few reports of renal toxicity. Given insufficient evidence, Liraglutide can be overlooked as the culprit in a patient presenting with acute renal failure, thereby delaying the diagnosis and decreasing the likelihood of renal recovery.

Methods: A 48 year-old female with a past medical history of CKD III, HIV (CD4 1395), Type II Diabetes Mellitus, and HTN presented to the hospital with one week of progressive dyspnea and lower extremity swelling. Of note the patient was started on liraglutide 1 month prior to admission. Her creatinine on presentation was 6.92 mg/dl from a baseline of 1.5 mg/dl. Her UA was significant for 300 mg/dl protein and urine sediment revealed only rare granular casts. HBV, HCV, C3/C4 were within normal limits. Her HIV RNA viral load was undetectable. A SPEP showed a polyclonal gammopathy and UPEP quantified 460 mg/dl protein of mixed tubular/glomerular origin. ANA was positive in a 1:320 speckled pattern. A renal ultrasound was unremarkable. A renal biopsy revealed moderate to severe acute tubular necrosis in the background of diabetic changes. Immunofluorescence (IF) was negative. Given the finding of ATN and interval work-up, drug reaction to liraglutide was noted as the primary insult. Upon review of her medication list, liraglutide was her only new medication and the only medication that could have induced ATN. Liraglutide was discontinued on admission and she improved with aggressive IV diuresis. Her creatinine 5 weeks after discharge came down to 3.39 from a peak of 7.8.

Results:

Conclusions: This case illustrates the importance of a medication history in identifying a temporal relationship between new drug initiation and the onset of renal failure. This patient had multiple risk factors for renal dysfunction including Diabetes Mellitus, HTN, HIV and morbid obesity. Although rarely reported, Liraglutide-induced AKI should be considered in the differential of a diabetic patient presenting with renal dysfunction when more common etiologies have been excluded. It is particularly important to monitor and recognize this adverse event early as withdrawing the offending agent can prevent progression to End Stage Renal Disease.

PUB040

Atypical Hemolytic Syndrome Post-Transplant Liza Cholin, Jordan Burlen, Hitarth S. Dave, Susan C. Coventry. *University of Louisville, Louisville, KY.*

Background: Introduction: Hemolytic Uremic Syndrome (HUS) is a type of Thrombotic Microangiopathy (TMA); it presents with thrombocytopenia, anemia, and acute renal failure. Atypical HUS (aHUS) accounts for 10% of all HUS cases, and occurs due to defective alternate complement pathway regulation, resulting in injury to endothelial cell lining of small blood vessels. When compared to Shiga-toxin producing Escherichia coli HUS, aHUS has a much poorer prognosis with death and end-stage kidney disease (ESKD) occurring in 53% of patients at three years. **Case Description:**

A 37 year old female with ESKD status post pancreas-kidney transplant presented with gastroenteritis-like symptoms. Laboratory evaluation showed a creatinine of 2.59 (baseline 0.55), hemoglobin of 10.9, platelets of 38, with schistocytes and polychromasis on peripheral smear. Further testing included a low C3 level, low normal C4, elevated lactate dehydrogenase, normal haptoglobin, negative cultures (blood, urine, stool), normal ADAMTS13 activity, and negative Shiga toxin. Renal biopsy revealed thrombi in rare glomerular capillary loops and acute tubular necrosis, with no signs of acute T-cell mediated or antibody mediated rejection. Genetic testing was negative for a specific quantitative or genetic factor leading to complement dysregulation. Patient was treated with hemodialysis and eculizumab. Renal function improved, and she no longer required dialysis at time of discharge.

Methods:

Results:

Conclusions: Discussion: Initial presentation of aHUS can be indistinguishable from other types of TMAs. Once, you have excluded shiga toxin-producing bacterial infection, ADAMTS13 deficiency, and other systemic diseases, then an aHUS diagnosis can be made. Genetic testing is also helpful to determine if it is a familial or sporadic form. Renal biopsy is typically not necessary; however, it can be beneficial if patient is post-transplant to rule out rejection. Treatment includes therapeutic plasma exchange, steroids, eculizumab, and transplantation (MCP-aHUS only). This case was rare, in that the patient had sporadic aHUS precipitated by a viral gastroenteritis.

PUB041

The Impact of Syndrome of Rapid Onset ESRD on Renal Allograft Survival: A 13-Year Mayo Clinic ESRD Cohort Investigation Macaulay A. Onuigbo,[2] Nneoma Agbasi.[1] *[1]NHS, ILFORD, United Kingdom; [2]Mayo Clinic, Rochester, Eau Claire, WI.*

Background: We first described the syndrome of rapid onset end stage renal disease (SORO-ESRD), acute irreversible renal failure, in 2010. The impact on renal allograft survival is unknown.

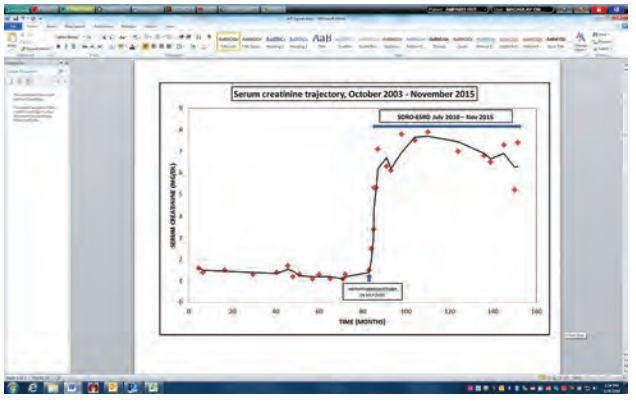
Methods: A retrospective study of individual patient-level serum creatinine trajectories of ESRD patients on maintenance hemodialysis at Mayo Clinic Rochester for >90 days, 2001-2013.

Results: 149/1461 ESRD patients had SORO-ESRD: 13 RTRs - 4M:9F, 12 white, age 45 (18-83) years. Serum creatinine was 1.4 (0.8 – 1.7) mg/dL the year before dialysis. Initial access in all was a catheter. AKI causing SORO-ESRD was from acute rejection (4), postoperative (2), tubulointerstitial nephritis (2), unknown (2), infection (1), contrast nephropathy (1), BKV nephropathy (1), and cardio-renal syndrome (1). Renal allograft survival - 1469 (277-4939) days. Acute rejection and ATN were common (Table). Time on dialysis - 856 (129-1630) days. 5/13 died - 3 following cardiac arrest; 2 after stopping dialysis. 4/13 were re-transplanted.

Conclusions: SORO-ESRD contributed significantly to late renal allograft loss and return to hemodialysis. Potentially preventable causes of AKI leading to SORO-ESRD were identified. Larger studies are warranted.

BIOPSY DATA

PATIENT	ACUTE REJECTION	CHRONIC TRANS GLOM	ACUTE TUBULAR NECROSIS	OTHER PATHOLOGY	NO BIOPSY
1					X
2	X (Banff Type I)				
3					X
4		X	X	Focal Segmental Glomerulosclerosis	
5		X		Acute Thrombotic Microangiopathy	
6	X (Banff Type IB)			Recurrent Membranous Glomerulopathy	
7	X	X			
8				Chronic Polyoma Virus Infection	
9					X
10			X	Cholesterol Embolization	
11					X
12			X		
13	X	X			



SORO-ESRD CREATININE TRAJECTORY

PUB042

AKI and Renal Replacement Therapy after Implantation of Left Ventricular Assist Device Abhilash Koratala,[2] Olanrewaju A. Olaoye,[1] Amir Kazory.[2] *[1]University of Florida, Gainesville, FL; [2]University of Florida, Gainesville, FL.*

Background: Implantable left ventricular assist devices (LVADs) are increasingly used for long-term management of patients with advanced heart failure (AHF) due to their established salutary impact on survival. Renal dysfunction is common in the setting of AHF and is associated with worse outcomes. We sought to explore the available evidence on the incidence of acute kidney injury (AKI) and need for renal replacement therapy (RRT) in AHF patients treated with LVAD.

Methods: Articles cited in PubMed database from January 2000 to April 2017 using key words "left ventricular assist device" and "heart failure" were searched. Articles evaluating LVAD in management of AHF were reviewed. Clinical trials that used continuous flow and contained data on renal parameters were selected. Pertinent data including baseline renal function, definition of AKI, and incidence of AKI were extracted and recorded.

Results: A total of 138 citations were reviewed and after exclusion of duplicate studies or those exclusively evaluating pulsatile flow LVADs, 23 clinical trials with 7733 participants were included. The mean age was 54.8 years, and 76.3% were men. The mean ejection fraction was 17.5%. There existed substantial variation across studies in the degree of baseline renal function and the definition of AKI. The baseline serum creatinine level was 1.46 mg/dl ± 0.16. The incidence of AKI was reported in 16 studies and was between 4 to 45.2% (mean 15.8% ±10.5). The incidence of need for RRT, reported in 12 studies, was between 2 to 38.1% (mean 15.8% ±11).

Conclusions: With the exponential growth of LVAD use, the number of patients with AHF receiving these devices as "destination therapy" is increasing, hence the need for evaluation of long-term impact on end-organ function. We found that renal dysfunction is prevalent in patients referred for LVAD therapy. Moreover, these data suggest that despite treatment of circulatory failure by LVAD and consequent improvement in renal function, a small subset of patients with AHF develop AKI, and a similar proportion require RRT post-operatively. Future studies are needed to identify the population at risk for renal complications after LVAD implantation, and to explore treatment strategies aiming at preservation of renal function in these patients.

PUB043

Tenofovir Induced AKI: A Single Centre Experience Umesh L. *Nephrology, institute of nephrourology, Bangalore, India.*

Background: Tenofovir has been widely prescribed in various first line antiretroviral regimen. It is infrequently associated with renal failure and biopsy findings of proximal tubular injury. We studied the clinical and histopathological findings in 27 patients having tenofovir induced nephrotoxicity

Methods: An observational study over a period of two and half years(from August 2014 to March 2017) in a State run government hospital which included all patients who were seropostive for HIV with renal dysfunction. Renal biopsy was performed whenever indicated.

Results: A total of 27 cases of tubular injury in the setting of tenofovir use were identified. There were 19 men and 8 women with a mean age of 45.03±12.95. Ten of twenty seven patient required hemodialysis. Mean creatitine at the time of biopsy was 5.78±2.71 mg/dl with mean protienuria of 1643.96±1056.44mg/dl. Time duration from TDF use to the time of biopsy ranged from 7 weeks to 13 months with a mean of 7.7 ±5.5months. Glycosuria detected in ten patients (all with normoglycemia), eight of them had phosphaturia. RENAL biopsy showed toxic proximal tubular injury with interstial inflammation which was mild and localized in 14 patients, moderate to severe, and diffuse in remaining 13 patients. Twenty two patients were available for follow up once tenofovir was discontinued and 77.27% of them had complete recovery of renal function at the end of 6 months

Conclusions: This study shows that tenofovir nephrotoxicity is a largely reversible form of toxic acute tubular necrosis which targets the proximal tubules accompanied by interstial inflammation. Hence renal parameters should be closely monitored in these patients.

PUB044

Serum Procalcitonin Level May Predict AKI in ICU Patients with Sepsis Mahmoud H. Imam,[1] Enas Elsebaey ahmed,[3] Amr Marzouk,[2] Amira Mohamady,[3] Rizk sayad rizk Sarhan,[3] Ahmed W. Elshourbagy.[4] *[1]Internal Medicine Department, Benha University, Benha, Egypt; [2]Anesthesia Department, Ain Shams University, Cairo, Egypt; [3]Benha University, Benha, Egypt; [4]banha faculty of medicine, Benha, Egypt.*

Background: Sepsis still has a high incidence even in developed countries. Acute kidney injury (AKI) frequently occurs in significant percentage of septic ICU critically ill patients with decimal prognosis. Early prediction of AKI and early interventions may improve outcome. The aim of this study is to examine if procalcitonin (PCT) can be used for early prediction of AKI septic patients in ICU.

Methods: 67 patients with sepsis were enrolled in this study. On admission, PCT was measured together with serum creatinine, urea, and other inflammatory markers. qSOFA was calculated at the emergency department. Patients were classified into two groups: AKI and non-AKI groups.

Results: PCT had a significantly higher value among patients who developed AKI than non-AKI group (67.04±20.59 ng/ml vs. 36.84±18.36 ng/ml); $p < 0.001$. Also, PCT exhibited a good predictive role for AKI with the ROC area under the curve was. 0859 ($p < 0.001$).

Conclusions: PCT may help in the early prediction of AKI among septic ICU patients.

PUB045

Successful Treatment of Renovascular Hypertension in Takayasu's Arteritis via Stenting: A Two Year Outcome Aparna Natarajan,[1] Julia Schneider,[1] Ivie O. Okundaye.[2] *[1]LUMC, Westmont, IL; [2]Loyola University Medical Center, NEENAH, WI.*

Background: A 31 year -old woman with no prior medical history presents to an outside to the ER for abdominal pain. Physical exam was notable for blood pressure of 190/96 mm Hg and diffuse tenderness to palpation of the abdomen. ESR 88, amylase 146 and lipase 834, UA negative for blood and protein. Patient was started empirically on steroids for autoimmune pancreatitis. Subsequent MRI showed infrarenal aortic wall thickening with extension into left renal artery concerning for aortitis. Upon initiation of lisinopril creatinine doubled to 2.05 mg/dL. A CT angiogram of abdomen revealed duplicated right renal artery, moderate to severe occlusion of bilateral renal arteries and thus suspicion of bilateral renal artery stenosis was confirmed. In addition, CT also showed inflammation around infra- renal aorta, findings suggestive of Takayasu's arteritis. Other possible causes of large vessel vasculitis or infection were ruled out.

Methods: While the patient was started on prednisone and mycophenolic acid to treat vasculitis, she continued to be profoundly hypertensive with little response to antihypertensive agents in three different classes plus diuretics. Renal duplex showed 8.9 cm R and L 11 cm without hydronephrosis. Given complete occlusion of the two right renal arteries and small right kidney size, a decision was made to perform Left renal artery stent placement. Renin levels at the time of the angiogram were 24 ng/mL/hr. In follow up of six weeks after drug-eluting stent placement, she had improvement in blood pressure readings, improvement in inflammatory markers and was able to discontinue most of the antihypertensive agents. Subsequent renal duplex studies demonstrated improved renal velocities (1.7m/sec from 2.6m/sec of left renal artery) which are maintained two years post procedure. Patient is now on maintenance steroid, ace-inhibitor, cellcept 1500mg BID and clopidogrel.

Results:

Conclusions: Takayasu's Arteritis is a rare cause of renal artery stenosis. Endovascular stenting and immunosuppression haves been proposed treatments in prior studies.This case report demonstrates efficacy of this combined approach two years post stent placement for treatment of hypertension and preservation of renal function.

PUB046

Long-Term Clinical Impacts of Cumulative Fluid Balance in Continuous Renal Replacement Therapy Chun Soo Lim, Jung Nam An, Jung Pyo Lee, Yun Kyu Oh. *Seoul National University Boramae Medical Center, Seoul, Republic of Korea.*

Background: Renal functional assessment at 3 months after continuous renal replacement therapy (CRRT) initiation can be useful in predicting long-term mortality and progression to ESRD.

Methods: We investigated the association between fluid balance before and after CRRT initiation and long-term outcomes after acute kidney injury (AKI) episode requiring CRRT. Among 1764 adult AKI patients started on CRRT from 2009 to 2013 in intensive care units in four tertiary academic hospitals in Korea, 331 survivors at 3 months after CRRT initiation were enrolled. Chronic kidney disease (CKD) progression was defined as a worsening renal status assessed at 3 months after CRRT initiation, comprising RRT continuation, an increase in serum creatinine of more than 50%, and a decrease in the estimated glomerular filtration rate of 35% or more than the baseline values.

Results: Cumulative fluid balance during 5 days after CRRT initiation was not associated with CKD progression. However, a positive fluid balance during 24 hours before CRRT initiation had the protective effect for CKD progression [Odds ratio 0.46 (0.23-0.91); $P = 0.026$]. This result was significant after adjustment for gender, age, and baseline serum creatinine. During the median 20.4 (7.5-39.7) months of follow-up, fluid balance was not associated with the long-term mortality.

Conclusions: Cumulative fluid balance after CRRT initiation was not associated with the long-term clinical outcomes. However, positive fluid balance during 24 hours before CRRT initiation was a favorable factor for CKD progression. The monitoring and management of fluid balance before CRRT initiation could be important.

PUB047

Clinical Analysis of Cardiac Surgery Patients with AKI shuqin hu, Hongli Jiang. *Dialysis Center of First Affiliated Hospital of Medicine School, Xi?an Jiaotong University, Xi'an, Shaanxi, China.*

Background: AKI is one of the severe clinical syndromes with the high morbidity and mortality. Due to the difference of geographical and disease distribution, the risk factors of postoperative AKI are still controversial. This research retrospectively analyzes the mortality, morbidity, risk factors and clinical features of Postoperative AKI. Analysis the risk factors in mortality and severity of AKI for improving prognosis and treatment. In order to reduce the morbidity and mortality of AKI after cardiac surgery, it is necessary to identify and intervene the risk factors.

Methods: 575 underwent cardiac surgery in the first affiliated hospital of Xi'an JiaoTong University from July 2015 to June 2016. The definition of AKI was based on the KDIGO clinical practice guideline for AKI. Screening patients with AKI or not who met the inclusion criteria and had complete case histories. We investigated clinical features, general information, laboratory data, basic diseases and prognosis. Logistic regression analysis was used to investigate the risk factors in morbidity and severity of AKI

Results: Results Of the 575 patients, AKI developed in 177(31.78%) patients, whereas (4.17%)had renal replacement therapy. Patients with AKI had higher mortality than patients without AKI (10.17%VS0.5%, P<0.001). AKI occurred mainly the first day after the cardiac surgery, and most of them are stage The highest diagnostic rate (80.23%) of AKI is the first day after the operation. The incidence of AKI at stage 2 and stage 3 is higher in the second day after operation than the first day. Multivariate logistic regression analysis showed that cardiopulmonary bypass, the advanced age, the high level of preoperative blood CystatinC, perioperative infection, intraoperative cardiopulmonary bypass time, were the independent risk factors of AKI after cardiac surgery. Left ventricular ejection fraction (LVEF) <40%, perioperative infection and postoperative arrhythmia were risk factors influencing the severity of AKI

Conclusions: Cardiac surgery induces high morbidity of AKI and mortality and poor prognosis which closely associated with many risk factors. Perioperative infection is not only an independent risk factor for the occurrence of AKI, but also an independent risk factor for the severity of AKI

PUB048

Causes, Clinical Features, and Treatment of Rhabdomyolysis: A Retrospective Analysis Yu Zongchao,[1] Fanna Liu.[2] *[1]nephropathy, The First Affiliated Hospital of Jinan University, Guangzhou, China; [2]The First Affiliated Hospital of Jinan Universtiy, Guangzhou, China.*

Background: RM is a condition of skeletal muscle breakdown where muscle injury causes a release of myoglobin and the muscle enzymes creatine phosphokinase (CPK), lactate dehydrogenase (LDH), and the transaminases. The classic presentation of this condition is muscle aches, weakness, and tea-colored urine. RM is commonly associated with myoglobinuria, and if sufficiently severe, this can result in AKI. Since a systematic review of RM is currently lacking in the literature, we undertook this study of the causes, clinical features, and treatments of RM.

Methods: We retrospectively reviewed the medical charts of patients with confirmed diagnoses of RM from June 2012 to August 2016, who had received care at the First Affiliated Hospital of Ji'nan University, Guangzhou, China.

Results: A total of 48 patients were included in this study (36 males and 12 females). The most common causes of RM among these patients were strenuous exercise (50%) and infection (25%). Muscular weakness (72.92%) and muscular pain (64.58%) were the most common presenting symptoms, followed by fever, dark urine, emesis, and oliguria or anuria. Among the patients, 42 received intravenous (IV) fluid therapy, and none developed acute kidney injury (AKI). The other six patients accepted continuous renal replacement therapy (CRRT), five of whom had an alleviation of their symptoms. One patient was transferred to another hospital for further treatment since the primary disease was dermatomyositis and it was non-responsive to immunotherapy.

Conclusions: RM is a complex condition with non-specific symptoms that can develop from various causes. The syndrome is treatable and has good outcomes. Early and aggressive fluid has been the main intervention for preventing and treating AKI. Renal replacement methods can also play a supportive role, though they are not the first line of treatment for RM-induced AKI. Our results indicate that the most effective treatments are early diagnosis, comprehensive therapy, active prevention, and the timely elimination of complications.

PUB049

Sofa Coagulation Score and Patient Outcomes in Severe AKI: Analysis from the Randomised Evaluation of Normal versus Augmented Level (RENAL) Study Jin Lin,[1,4] Ying Wang,[1] Rinaldo Bellomo,[2] Meili Duan,[3] Martin P. Gallagher.[1] *[1]George Institute for Global Health, Sydney, NSW, Australia; [2]Austin Health, Melbourne, NSW, Australia; [3]Intensive care unit, Beijing Friendship Hospital, Beijing, China; [4]Intensive care unit, Beijing Friendship Hospital, Beijing, China.*

Background: A decline in platelet count is common in critically ill patients with severe AKI. However, there is relatively little data assessing the association of SOFA coagulation scores and clinical outcomes in severe AKI patients receiving continuous RRT.

Methods: We performed a secondary analysis from the Randomised Evaluation of Normal versus Augmented Level of RRT (RENAL) study. The primary endpoint was all-cause mortality at 90 days after randomisation. The secondary outcomes were the length of intensive care unit (ICU) and hospital stay. The association between the SOFA coagulation scores and these outcomes were analysed using multivariate Cox model adjusted for baseline variables.

Results: Among 1465 patients in the RENAL study, the complete SOFA coagulation score data were available in 1280 patients. Among them, 579 patients had high SOFA coagulation scores (defined as ≥1), while 701 patients had normal SOFA coagulation scores (<1). The univariate analysis showed that high SOFA coagulation scores were associated with higher mortality at day 90 (49% versus 38.5%, p=0.0002). There was no significant difference in the length of ICU and hospital stay between these two groups.

In multivariate analysis, the association between high SOFA coagulation scores and increased mortality rate at 90 days remained significant.

Conclusions: In the RENAL study, an approximately 50% of patients had an increase in SOFA coagulation scores during their ICU admission. High SOFA coagulation scores were associated with increased mortality at 90 days.

PUB050

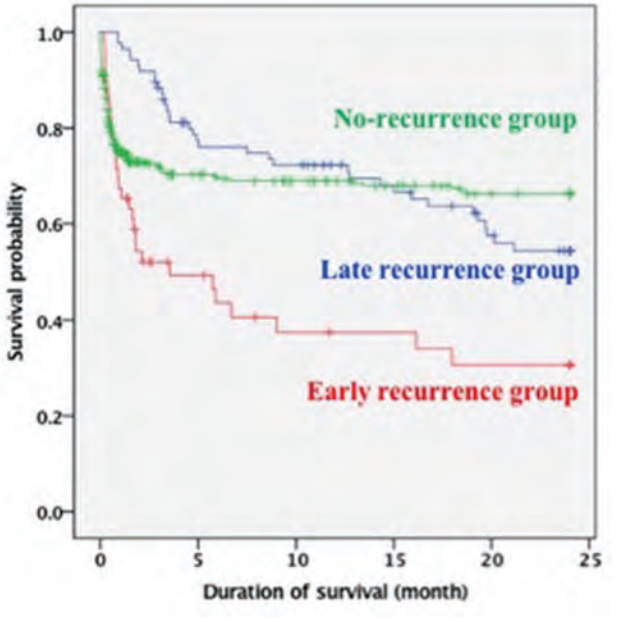
Early Recurrence of AKI Is a Prognostic Factor for All-Cause Mortality Keisuke Sako, Kengo Furuichi, Yasuyuki Shinozaki, Tadashi Toyama, Shinji Kitajima, Akinori Hara, Yasunori Iwata, Norihiko Sakai, Miho Shimizu, Takashi Wada. *Kanazawa university hospital, Tonami, Japan.*

Background: Recurrent acute kidney injury (AKI) is associated to a risk factor for mortality. However, it is unclear whether the period until AKI recurrence may influence mortality. We set up a hypothesis that early recurrence is higher mortality and evaluated the prognosis of recurrent AKI cases by setting 21 days as the cut-off period of AKI recurrence.

Methods: All of the cases were admitted and followed-up at the Kanazawa University Hospital in Japan from November 1, 2006 to October 31, 2007. A total of 21,939 cases were evaluated retrospectively. The primary endpoint was death. The observation time was two years. Recurrent AKI was defined as the re-increase of serum creatinine after the previous AKI episode. Cases developed AKI recurrence less than 21 days were defined as the early recurrence group, and the other cases were defined as the late recurrence group.

Results: Four hundred sixty adult cases (2.1%) developed AKI in two years. One hundred thirty-five cases developed recurrent AKI among them. The number of early recurrence group was 49, and the number of late recurrence group was 86. The rates of all-cause mortality were higher in the early recurrence group (p=0.001; log-rank test; the early recurrence group, 105.5 deaths per 100 person-years; the late recurrence group, 32.7 deaths per 100 person-years; No-recurrence group, 34.4 deaths per 100 person-years).

Conclusions: Patients with recurrent AKI less than 21 days showed poor prognosis. Careful follow-up for at least 21 days after AKI is necessary detect the recurrence of AKI to predict prognosis after AKI.



PUB051

You Only Diagnose What You Think Of – A Case of IgG-4 Related Kidney Disease Mubasshar Rehman,[2] George C. Bonifant,[2] Karim El Hachem,[2] Steven D. Smith,[1] Ira S. Meisels,[3] Purva D. Sharma.[3] *[1]Icahn School of Medicine at Mount Sinai/St Luke's-Roosevelt Hospital Center, New York, NY; [2]Nephrology, Mount Sinai St Luke's Hospital, New York, NY; [3]None, New York, NY.*

Background: IgG4-related disease affects multiple organs and is characterized by fibrosis and a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells. Renal involvement is observed in 15% of cases with tubulointerestitial nephritis being the predominant pathologic finding.

Methods: A 55 year old man with history of hypertension presented for several months of diarrhea, abdominal pain and recent perioral numbness. A non contrast Computed Tomorgraphy of the abdomen revealed normal sized kidneys with mild bilateral pelvic fullness and findings consistent with pancreatitis. His laboratory work up showed a creatinine of 8.7mg/dL, calcium of 6.0 mg/dL, IgG4 of 1470 mg/dL, and a low C3 (33 mg/dL). His creatinine failed to improve with hydration. The urinary sediment was bland. He underwent a kidney biopsy revealing diffuse, severe interstitial and glomerular scarring with marked mononuclear interstitial inflammation including plasma cells, many of which stained positively for IgG4. The patient did not respond to steroids and was started on hemodialysis for uremic symptoms. 6 months prior, he had presented for dry mouth, unintentional weight loss, and chronic diarrhea with negative EGD and colonoscopy. His creatinine was 1.68 mg/dL with 230 mg of albumin/gram of creatinine, findings that were deemed to be hypertension related. No additional work up had been done at that time.

Results:

Conclusions: IgG4- related kidney disease can present with kidney dysfunction, minimal proteinuria and a bland urine sediment. In the right clinical context, we suggest obtaining IgG4 and complement levels with a low threshold for a kidney biopsy. Early recognition and tissue diagnosis can lead to prompt treatment with steroids with or without Rituximab and avoidance of progression to ESRD.

	Reference	First presentation	Current presentation
Serum Creatinine (mg/dL)	0.5-1.2	1.68	8.76
Urinalysis		Trace protein, no blood	Trace protein, no blood
ACR (mg/gm creatinine)	<30	230	456
C3 (mg/dL)	90-180	--	33
C4 (mg/dL)	10-40	--	39
IgG4 subclass (mg/dL)	1-123	--	1470
Total IgG (mg/dL)	700-1600	--	2620
ANA	<1:40	--	<1:40

Table1. Summary of laboratory findings

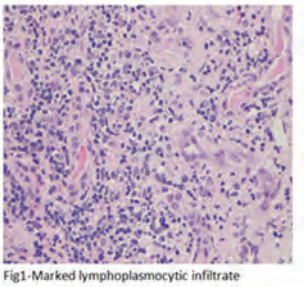


Fig1-Marked lymphoplasmocytic infiltrate

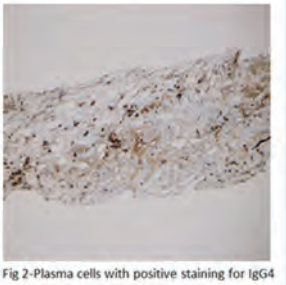


Fig 2-Plasma cells with positive staining for IgG4

PUB052

Integrated Endovascular Approach to Treatment of Acute Renal Vein Thrombosis Manifested as Primary Membranous Glomerulopathy Natalia Plotskaya. *Capital Health RMC, Trenton, NJ.*

Background: Renal vein thrombosis (RVT) is a very common complication of nephrotic syndrome, it can be symptomatic and chronic asymptomatic. It is associated with imbalance between procoagulant and anticoagulant factors, endothelial dysfunction. Multiple modality treatment might be required in symptomatic RVT with extension to inferior vena cava.

Methods: A 51 year old male with a long history of hypertension and 4 months lower extremity edema presented with severe sharp left flank pain with radiation to low back for 4 days. He had similar pain in the right flank 2 months ago. Physical examination revealed elevated BP of 190/110 mmHg, left lower abdominal tenderness and moderate lower extremities edema. No family history of kidney disease or hematologic disorders was identified. Laboratory date shown increased creatinine of 1.35 mg/dL for 2 months, decreased albumin of 2.6 g/dL. CT scan of abdomen with intravenous contrast detected left renal vein thrombosis extending into the suprarenal inferior vena cava, also possible extension of thrombus into the left gonadal vein, enlarged and heterogeneous left kidney. Immediately patient was started on heparin drip. Despite of tPA infusion at rate 3 mg/hr for 6.5 hrs follow up left renal venogram still shown large clot. Decision was made to proceed with AngioJet thrombolysis and mechanical removal of residual clot which finally lead to its resolution confirmed by venogram. Next day creatinine decreased to 1.19 mg/dL. On day 5 after intervention nuclear renal scan demonstrated symmetric flow to both kidneys, no evidence of hydronephrosis. Hypercoagulability work up was unremarkable. Isolated elevation of homocysteine 12.5 umol/L and protein S antigen > 200% were noted. Urinalysis shown severe proteinuria of 11. 6 g/24hours. For this reason on day 7 patient underwent successful left kidney biopsy which shown membranous glomerulopathy (MGN) stage1-2. Indirect immunofluorescence staining was positive for phospholipase A2 receptor (PLA2R) which supported primary MGN.

Results:

Conclusions: Acute RVT should be highly suspected in symptomatic patients with acute kidney injury associated with lower extremity edema, sudden flank pain. Timely diagnosis with CT angiography is necessary to access extension of thrombosis and initiate combined intervention to preserve renal function and prevent further thromboembolic event.

PUB053

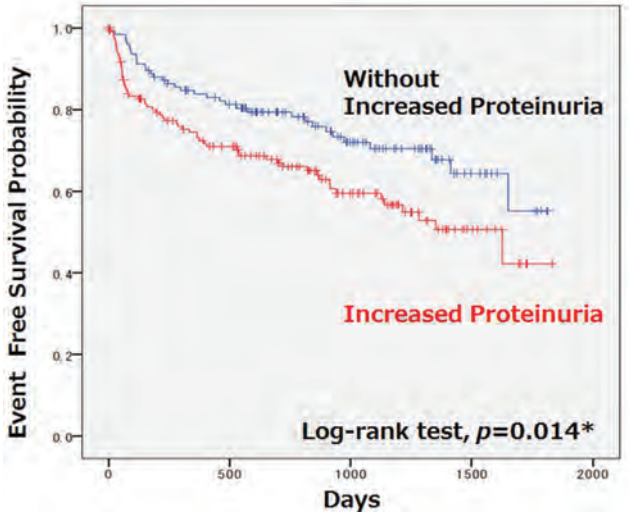
Isolated Increased Proteinuria Predicts Poor Long-Term Outcomes in CKD Patients without Contrast-Induced Nephropathy Raku Son, Takuya Fujimaru, Masahiko Nagahama, Yasuhiro Komatsu. *Nephrology, St. Luke's International Hospital, Tokyo, Japan.*

Background: Contrast-induced nephropathy (CIN) is associated with long-term adverse events. Although CIN is defined only by increased serum creatinine, previous studies have shown that contrast media exposure induces transient proteinuria. However, no study has evaluated the association of isolated increased proteinuria without CIN and clinical outcomes.

Methods: In this single-center, retrospective cohort study, we collected data of chronic kidney disease (CKD) patients who underwent contrast-enhanced CT and received CIN prevention protocol from April 2012 to March 2016 at outpatient clinic. Patients who developed CIN were excluded. Increased proteinuria was defined as post to pre urine protein creatinine (P/C) ratio more than 1. The primary end point was the composite of certain adverse events, including death, stroke, myocardial infarction, end-stage kidney disease, coronary artery intervention and others. Log-rank test and Cox proportional hazard analysis were performed.

Results: Of 291 patients who received CIN prevention protocol, 4 patients were excluded due to CIN. In the rest patients (n=287, age 73.3±10.2, 67.2% of males), 161 patients (56.1%) had increased urine P/C ratio. During the follow-up (1250±46.8 days), 97 patients (33.8%) had adverse events. In Kaplan-Meier survival curves, patients with increased proteinuria showed significantly poor outcomes compared to those without increased proteinuria (p=0.014) (Figure). After adjusting for age, sex, baseline eGFR and urine P/C ratio, hypertension, diabetes mellitus and cardiovascular diseases, increased proteinuria significantly associated with poor long-term outcomes (Hazard ratio 2.00, 95% confidence interval 1.29-3.09).

Conclusions: Isolated increased proteinuria after contrast-enhanced CT predicts poor clinical outcomes in CKD patients even without CIN.



PUB054

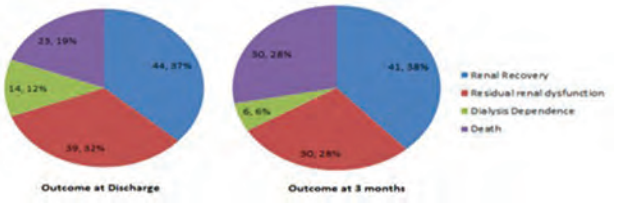
AKI in Intensive Care Unit: A Clinical and Outcome Study Prof narinder P. Singh, Danish Kathuria, Neeru Aggarwal, Anish Gupta. *MAX SUPER SPECIALITY HOSPITAL, DELHI, India.*

Background: Acute kidney injury has both short term as well as long term consequences in critically ill patients. Our study was aim to document the evolving epidemiology of AKI in India.

Methods: A longitudinal study was performed in a tertiary care center in North India among 120 patients with AKI. We enrolled patients who were either admitted in ICU with AKI i.e. community acquired (CA-AKI) or developed AKI during their ICU stay i.e. hospital acquired (HA-AKI). Diagnosis, staging, risk factors assessment and management of enrolled patients was done as prescribed by the KDIGO clinical guidelines for AKI. The outcome was assessed at discharge and at 3 months and classified as favourable (renal recovery) and adverse (residual renal dysfunction, dialysis dependence and death). A statistical analysis was performed, using a Pearson's Chi-square test and paired 't' test.

Results: Out of 120 patients, 87(73%) had de novo AKI while 33 (27%) had acute on CKD. Out of all patients, 55 % had CA-AKI while 45 % developed HA-AKI. Almost half of the subjects (47.5%) had stage I AKI, 27.5% had stage II and remaining quarter of subjects had stage III AKI. Sepsis (60.8 %), circulatory shock (53.3%), age > 65 years (58.3%) were the most prevalent risk factors which were significantly associated with poor outcome (p <0.05). Severity of AKI showed a linear trend with adverse outcome at discharge, which was significant (p 0.025). Clinical outcome at the time of discharge and at 3 months are demonstrated in figure 1. Almost 50 % of the stage I AKI showed complete renal recovery at 3 months as compared to only 25% and 29.6% for stage II and III respectively. Different stages of AKI also showed a graded increase in mortality at 3 months - 19.2% for stage I compared to 35.7% for stage II and 37 % for stage III.

Conclusions: This study demonstrated increasing prevalence of adverse outcome in a linear fashion with increase in the severity of AKI. The epidemiology of AKI in critical care in India has started to resemble high income group countries, in terms of both age distribution as well as etiology.



PUB055

A Case of AKI from Hemophagocytic Lymphohistiocytosis Induced by Ehrlichiosis Olanrewaju A. Olaoye, Saraswathi Gopal. *University of Florida, Division of Nephrology, Gainesville, FL.*

Background: Hemophagocytic Lymphohistiocytosis (HLH) is an aggressive life-threatening syndrome of excessive immune activation occurring from either inherited or acquired defect in cytotoxic T lymphocytes and natural killer cells. Cytokine mediated acute kidney injury has been described to be strongly associated with HLH. Here we present a rare case of HLH associated with severe renal failure due to Erlichiosis chaffeensis

Methods: A 70-year-old African American male with history of diabetes mellitus, benign prostatic hypertrophy and hepatitis C successfully treated with Harvoni presented with generalized weakness, nausea vomiting and abdominal discomfort. Eleven days prior to his hospitalization, he was treated for right forearm cellulitis. On admission, vital signs were significant for a temperature of 39.5oC, pulse rate of 126/min. His labs showed WBC of 2,500/mm^3, hemoglobin of 10.4 g/dL, platelet of 39,000/mm^3, ALT 406 IU/L, AST 1,501 IU/L, ALP 110 IU/L, total bilirubin 0.9 mg/dL, ferritin 27,889 ng/ml and serum creatinine of 6.37 mg/dL (recent baseline was 1.1-1.2 mg/dL). Chest radiograph and pan-culture were not suggestive of an infection. Peripheral smear was unremarkable for schistocytes. Patient developed respiratory and renal failure requiring mechanical ventilation and hemodialysis. Given persistent pancytopenia, a bone marrow biopsy was done which showed hemophagocytic macrophages containing predominantly RBCs and neutrophils. A diagnosis of HLH was made; patient was started on Etoposide and Dexamethasone therapy for immunosuppression. Ehrlichia chaffeensis serology was also obtained, considering recent history of forearm cellulitis., the titers resulted as positive (IgG 1:1204 & IgM <1:16). Patient was treated with Doxycycline for 2 weeks. During the course of doxycycline therapy patient started to recover renal function, hemodialysis was stopped. Three weeks after initiation of doxycycline, he was discharged with a serum creatinine of 1.26 mg/dL

Results:

Conclusions: HLH is a syndrome of cytokine storm leading to multi-organ dysfunction including the kidneys. Early identification is crucial, as immunomodulatory therapy is required to diminish the hyperinflammatory response. Moreover, identifying the underlying cause and initiating specific therapy is imperative as it can reduce the mortality associated with HLH, which is around 50%.

PUB056

Potential Hydralazine-Induced False Positive ANCA Specific for Proteinase 3 (PR3) as a Sentinel Event Mimicking of Granulomatosis with Polyangiitis (GPA) in a Case of Focal Acute Tubular Injury Nader S. Bahri. *Meharry Medical College, Brentwood, TN.*

Background: Rapid declining of renal function accompanied by proteinuria and hematuria in a hypertensive and diabetic individual on hydralazine with work- up showed Positive ANCA serology activity required diagnostic renal biopsy with no evidence of GPA vasculitis with a rare reported presentation.

Methods: A 45 year-old female with a past medical history of hypertension on multiple medications recently on hydralazine, DMT2 with Hb A1C of 7.6, a known case of CKD 3 with the baseline of creatinine 1.29 mg/dl presented in December 2016 with rapid onset shortness of breath with coughing that produced minimal amounts of blood, orthopnea, and swelling. She had a similar presentation back in November 2016 where a CT of her chest was performed that showed scattered alveolar opacities consistent with pneumonitis (Infections versus idiopathic). She subsequently developed rapid declining of renal function (serum creatinine 3.08 mg/dl), Non- nephrotic range proteinuria (protein/creatinine ratio 3.3 g/g) and hematuria which raised diagnosis of pulmonary-renal syndrome and immediate therapy with high dose corticosteroids were initiated. During the work-up ANCA serology activity was positive 1:20 titer confirmed by enzyme immunoassay to confirm ANCA specific for PR3;all other serological analyses were negative and patient was initiated on cyclophosphamide with thinking of granulomatosis and polyangiitis (Wegner's granulomatosis) as main diagnosis. Afterward kidney biopsy demonstrated moderate arterionephrosclerosis with features of accelerated hypertension-related vascular injury, moderate diabetic nephropathy and foal acute tubular injury. These findings didn't support the diagnosis of granulomatosis and polyangiitis(GPA). Hydralazine were suggested as potential cause for False Positive ANCA testing. All previous treatments has stopped and ANCA activity turns negative after withdrawal of

hydralazine. Patient treated for her pneumonia and acute tubular injury with improving condition.

Results:

Conclusions: This case highlights the presentation of false positive testing induced by medications. Hydralazine is a known agent causing of sporadic Pauci-immune Glomerulonephritis via ANCA activity, however in this case the false positive ANCA serology specific for PR3 didn't revealed any pathologic evidence of vasculitis.

PUB057

AKI, Its Risk Factors, and Mortality in Chronic Obstructive Pulmonary Disease Patients Tae won Lee,[2] Ha nee Jang,[5] Hee jung Park,[5] Hyun Seop Cho,[5,6] Eunjin Bae,[1] Se-Ho Chang,[5,6] Hyun-Jung Kim,[4] Dong Jun Park.[3,6] *[1]Gyeongsang National University Changwon Hospita, Changwon, SEOUL, Republic of Korea; [2]Department of Internal Medicine, Gyeongsang National University Changwon Hospital, Changwon-si, Gyeongsangnam-do, Republic of Korea; [3]Gyeongsang National University Hospital, JINJU, Republic of Korea; [4]School of Medicine, Gyeongsang National University, Jinju, Republic of Korea; [5]Department of Internal Medicine, Gyeongsang National University Hospital, Jinju, Gyeongsangnam-do, Republic of Korea; [6]Gyeongsang National University, Institute of Health Sciences, Jinju--si, Gyeongsangnam-do, Republic of Korea.*

Background: Chronic obstructive pulmonary disease (COPD) is an inflammatory airway disease and a major cause of illness and death throughout the world. Inflammation is known to play a major role in the pathophysiology of AKI. We evaluate the impact of acute kidney injury (AKI) on mortality and risk factors in patients with COPD.

Methods: We retrospectively enrolled patients who hospitalized due to COPD acute exacerbation between January 2011 and April 2014. We categorized patients into two groups: with AKI and without AKI. We evaluated factors associated with AKI and effect of AKI on all-cause mortality.

Results: Among the 177 patients, 41 patients (23.2%) had AKI and 30 patients (16.9%) died during follow up period. Patients with AKI tend to lower blood pressure, lower estimated glomerular filtration rate (eGFR) and received invasive mechanical ventilation (MV) at the time of admission. Older age, lower BMI, lower eGFR level, diabetes and AKI were significantly associated with all-cause mortality. In addition, lower eGFR level, diabetes, invasive MV and presence of pneumonia were significantly associated with AKI.

Conclusions: The prevalence of AKI is relatively high in COPD patients and AKI is independent factor of the all-cause mortality. Thus, close monitoring and prevention for AKI is important in COPD patients.

PUB058

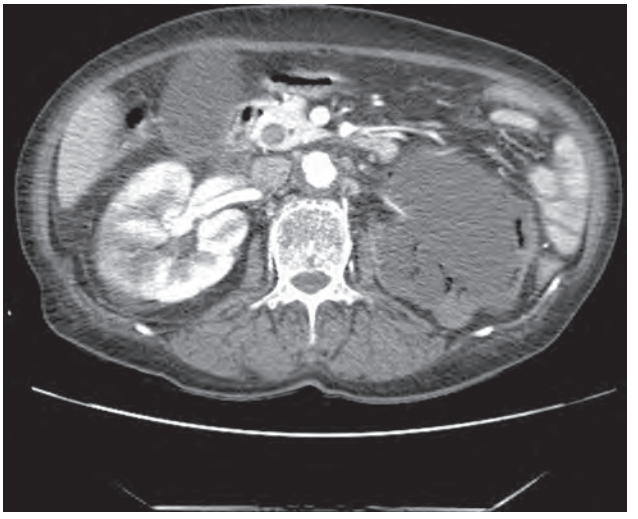
A Case of Urinary Tract Infection: One Kidney Is EPN and the Other Is Simple Pyelonephritis Heeryong Lee, Woochul Lee, Jeong gun Kim. *Good Samsun Hospital, Busan, Busan, Republic of Korea.*

Background: Emphysematous pyelonephritis(EPN) is an acute necrotizing parenchymal and perirenal infection caused by gas-forming organism. EPN is commonly associated with diabetes mellitus, urinary tract obstruction and immunosuppression. In comparison with simple pyelonephritis, EPN is an acute severe necrotizing infection with a mortality rate of up to 25%. The most common pathogens are *Escherichia coli (E. coli)* and *Klebsiella pneumonia*. We report a case of a 78-year-old woman who developed EPN in one kidney and simple pyelonephritis in the other.

Methods: A 78-year-old woman presented to the emergency department with fever, chills, and both flank pain. Her medical history was significant for diabetes mellitus, hypertension. Spot urine reveal pyuria. Abdominal radiography revealed gas collection. And computed tomography (CT) revealed gas collection in the parenchyma and huge hydronephrosis of the left kidney and wedge-shape low attenuation of the right kidney (Panel A). The patient received a diagnosis of emphysematous pyelonephritis of the left kidney and simple pyelonephritis of the right kidney. The patient was started on intravenous piperacillin/tazobactam on arrival. This was then switched to meropenem as blood cultures collected on two separated days grew *E.coli*. After the CT results were confirmed, the percutaneous nephrostomy catheter was inserted. Here she was noted to have pus and air. Antibiotics were maintained for 2 weeks and symptoms and laboratory findings improved. Control abdominal CT revealed more improving state of emphysematous pyelonephritis and hydronephrosis. So she was discharged after catheter removal.

Results:

Conclusions: EPN is caused by gas-forming organism, most commonly *E. coli*. But, Even if the infection is caused by the same organism, it can be expressed as another type of infection in same organ.



PUB059

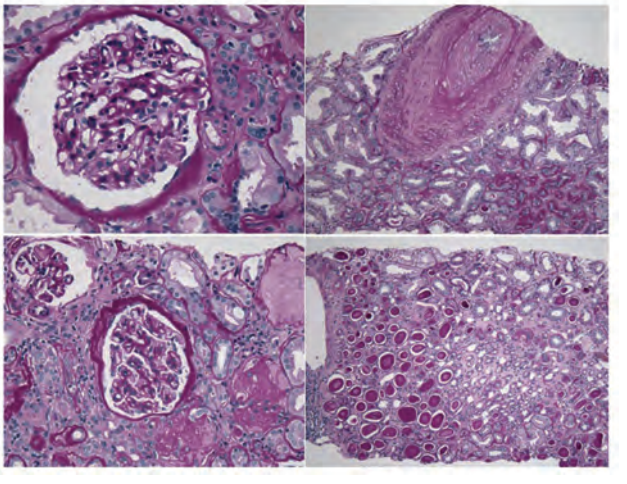
Methylphenidate Associated Antiphospholipid Antibody Syndrome Mediated AKI Neal B. Shah,[4] Helmut G. Rennke,[1] Juan Pablo Domecq Garces,[3] Peter G. Czarnecki,[1] Yanli Ding,[2] David B. Mount.[1] *[1]Brigham and Women's Hospital, West Roxbury, MA; [2]Brigham and Womens Hospital, Boston, MA; [3]Brigham's Women Hospital, Boston, MA; [4]Nephrology, Brigham and Womens Hospital, Boston, MA.*

Background: 70 year Caucasian female admitted for elevated creatinine levels found on routine blood testing.

Methods: 70 y/o F with history of hypertension, CAD and normal pressure hydrocephalus (recent VP shunt placement) was admitted for elevated creatinine 2.3mg/dl. Methylphenidate had been started 1 month prior to admission, for slow mentation; it was held on admission. Physical exam significant for 3/6 systolic murmur radiating to carotid and mild suprapubic tenderness. No edema, anasarca or skin rash. Creatinine remained elevated despite IV saline. She was non-oliguric. Hospital course significant for labile hypertension and two episodes of acute pulmonary edema with systolic BP 200s. Labs remarkable for Hb 9g/dL (previously 12g/dL), BUN was 44mg/dL, Cr 2.3mg/dL. PTT elevated at 49s. Low haptoglobin of 8mg/dl and mild LDH elevation of 329U/L. Peripheral smear had few schistocytes. Urinalysis showed 0-2 RBCs, 3-5WBCs with bacteria, 2+ proteinuria. Urine culture tested positive for E Coli UTI, treated with fosfomycin. Protein creatinine ratio was 3.2. Renal US showed bilateral 9.5cm kidneys and normal echogenicity. Initial serologic workup was unremarkable. Kidney biopsy showed severe arterial and arteriolar sclerosis, marked hypoperfusion, no evidence of deposition disease. Anticardiolipin IgG was elevated at 35.7 CU (normal 0-19); was 19 CU two months prior. She was diagnosed with antiphospholipid syndrome, treatment included IV methylprednisolone followed by 6 week oral prednisone taper, plasmapheresis, and rituximab. BP was well controlled on captopril. Creatinine improved from peak of 2.7 to 1.3mg/dl, with drop in anticardiolipin titer to 8 CU. Haptoglobin and LDH levels normalized.

Results:

Conclusions: Methylphenidate initiation may have been the second hit causing worsening of antiphospholipid syndrome and precipitation of AKI.



Cortex with global glomerulosclerosis, hypoperfused glomeruli & sclerosis of interlobular artery. Outer medulla shows tubular atrophy, cast formation.

PUB060

Low Doses of Perioperative Flurbiprofen Protect Individuals Suffering from AKI Hao Zhang,[1] Qin Liao,[2] Jianwen Wang,[2] Shi-kun Yang.[3] *[1]The Third Xiangya Hospital of Central South University, Changsha, China; [2]The third Xiangya Hospital of Central South University, Changsha, China; [3]The third Xiangya Hospital, Central South University, Changsha, China.*

Background: Flurbiprofen is a new nonsteroidal anti-inflammatory and analgesic drug, it may be associated with AKI but the thoroughly effects are unclear. In this study, we attempt to explore the association between the perioperative using of flurbiprofen and AKI after operation.

Methods: We obtained data from a database of 141467 patients, who underwent operations in the Third Xiangya Hospital of Central South University January 2012 to July 2016, 10774 patients were enrolled for this retrospective study. Acute kidney injury (AKI) was defined as KDIGO guideline. Chi-square test, univariate analysis and Logistic regression analysis were used to determine the risk factors for AKI and evaluate the effects of different does of flurbiprofen on AKI.

Results: There were 2656 cases who used flurbiprofen perioperatively in 10774 cases, the prevalence of postoperative AKI was 6.94% in 10774 cases, the prevalence rate of AKI was5.8% and 7.3% in subjects using flurbiprofen and subjects without using flurbiprofen, respectively. After the does stratification of flurbiprofen, the incidence of AKI in patients with a low dose of flurbiprofen (5.2%) was significantly lower than that of patients without using of flurbiprofen (7.3%) ($P<0.01$), while the incidence of AKI in patients with a high dose of flurbiprofen (11.2%) was significantly higher than that of patients without using of flurbiprofen (7.3%) ($P<0.05$). Multivariate logistic regression analysis showed that the ASA classification, preoperative estimated glomerular filtration rate, excessive bleeding and emergency surgery were independent risk factors for AKI in total patients (OR= 2.4, 4.7, 1.6, 2.1 respectively, $P<0.01$), while using of low dose lurbiprofen (≤150mg) was a protective factor for AKI (OR= 0.4, $P<0.01$). On the other hand, in 2656 patients who used flurbiprofen, multivariate logistic regression analysis showed that the large dose of lurbiprofen, ASA classification, preoperative estimated glomerular filtration rate, excessive bleeding and emergency surgery were independent risk factors for AKI. (OR= 2.9, 3.1, 1.8, 2.4 respectively, $P<0.01$).

Conclusions: Large dose of perioperative flurbiprofen (≥200mg) was an independent risk factors for AKI. Using of low dose lurbiprofen(≤150mg) perioperatively could effectively reduce the incidence of AKI, while a large dose of flurbiprofen could aggravate the incidence of AKI.

PUB061

Incidence of AKI in Acute Decompensated Heart Failure Oisin O Corragain,[3] Avrum Gillespie,[2] Mark G. Weiner.[1] *[1]Lewis Katz School of Medicine at Temple University, Philadelphia, PA; [2]None, Philadelphia, PA; [3]Temple University Hospital, Philadelphia, PA.*

Background: Acute Kidney Injury (AKI) is a significant cause of morbidity and mortality, affecting 27-40% of all patients hospitalized for acute decompensated heart failure (ADHF) in previous literature. Rising creatinine levels in ADHF is often thought to be secondary to Cardio-renal syndrome (CRS), however it is often difficult to differentiate increased creatinine due to CRS from other causes of AKI, mainly tubular damage and acute tubular necrosis (ATN). There is conflicting evidence on outcomes of AKI in ADHF, some showing worse outcomes, while several previous studies have noted a mortality benefit with increased creatinine during diuresis. Early recognition of tubular damage and ATN may prevent progression to AKI Stage 3, need for renal replacement therapy, ICU admission and mortality. The purpose of this study is to characterize the incidence of AKI in patients admitted with ADHF. The specific objectives are to try to predict AKI not due to CRS, assess outcomes with worsened severity of AKI and to identify patients at higher risk of AKI

Methods: We performed a retrospective review of existing data on patients hospitalized with ADHF, involving all patients admitted to Temple University Hospital with a primary or secondary discharge diagnosis of ADHF between August 5th, 2016 (The date of the transition to inpatient Epic Electronic Medical Record from the preceding largely paper based inpatient medical record system) and April 4th 2017.

Results: 230 individual patients with an inpatient diagnosis of ADHF without a diagnosis of End Stage Renal Disease were identified; with a total of 425 admissions identified. 56.9% were male; the average age was 64.7 with a range of 28 to 101. The incidence of AKI based on KDIGO criteria was 50.8% (N=117) for patients, with AKI noted in 55.5% (N=236) of all admissions. Of those with AKI, 84.7% (N=200) had AKI Stage 1, 13.5% (N=32) had Stage 2 and 1.6% (N=4) had Stage 3. 58% (N=138) of admissions with AKI had not resolved by last day of admission.

Conclusions: Not all elevation in creatinine is CRS in ADHF. Future studies will better characterize these patients, identify risk factors for incidence of AKI, and explore the association of discharge AKI with likelihood of readmission.

PUB062

Hidden Beneath the Surface: A Case of Chronic Lymphocytic Leukemia Manifesting as AKI and Pancytopenia Khurram Mehtabdin,[2] Anam Siddiqui,[3] Kenar D. Jhaveri.[1] *[1]Hofstra Northwell School of Medicine-Northwell health system, Great neck, NY; [2]North Shore-LIJ Healthsystem, Great Neck, NY; [3]Northwell, Elmhurst, NY.*

Background: Chronic lymphocytic leukemia is a neoplastic disease of B cells, usually involving hematopoietic organs such as the bone marrow, blood, lymph nodes and spleen. There are rare instances where extra-hematopoietic manifestations can occur. This is a case of a patient with AKI and pancytopenia treated for presumed lupus nephritis despite negative serologies with pulse steroids and subsequently develops worsening leukocytosis.

Methods: A 55 year old female with no past medical history presents with recurrent fevers, polyarthritis and diarrhea. Labs reveal pancytopenia, AKI with peak Cr 5.26mg/dl, hematuria, subnephrotic proteinuria of 1.8 on spot ratio and hypocomplementemia. Chest radiography demonstrated slight left lower lobe pulmonary infiltrates and mediastinal lymphadenopathy. ANA was 1:80 and all other secondary serological testing was negative, (ANCA, anti-GBM, cryoglobulins, hepatitis, HIV). The patient was started on pulse steroids (1gm for 3 days) for presumptive seronegative lupus nephritis with rapid improvement in renal function and resolution of pancytopenia within days. A kidney biopsy was performed during the resolution phase of the AKI. After steroids were started, the patient developed leukocytosis (up to 60 K/uL), with significant lymphocytosis and smudge cells noted on smear. Flow cytometry was consistent with small lymphocytic leukemia, a form of CLL. The bone marrow testing confirmed 20-30% involvement with CLL. The kidney biopsy confirmed resolving interstitial nephritis and tubular damage but was negative for any infiltrative malignant CLL cells.

Results:

Conclusions: This patient's case demonstrates the various manifestations, including both renal and rheumatologic complications of chronic lymphocytic leukemia. Interstitial nephritis has been reported with CLL and can respond to steroids alone albeit treatment of CLL. It is presumed to be a reactive inflammatory process from small pockets of malignant cells. Autoimmune processes have also been reported with CLL. The pancytopenia and clinical manifestation might have been a paraneoplastic autoimmune process seen with CLL. The patient's kidney function is now normal and steroids are being tapered. The physician should be aware of renal insufficiency present in 7.5% of patients at the time of CLL diagnosis and in an additional 16.2% during the course of the disease.

PUB063

Study of Renal Morphological and Structural Changes at Different Ischemic Times and Types of Renal Vascular Pedicle Clamping Angela Mazzeo,[1,2] Miguel A Goes.[1,2] *[1]Hospital Israelita Albert Einstein, Sao Paulo, Brazil; [2]Division of Nephrology, Federal University of São Paulo, São Paulo, Brazil.*

Background: Clinical manifestation of acute renal injury is often seen in patients who underwent interventions such as partial nephrectomies, and renal transplantation during the post-surgical period. Additional factors that may potentiate this condition, such as the severity of the installed condition, the complexity of the surgical procedure and comorbidities, should be considered. Objective: To study renal morphological and structural changes in relation to different ischemic times and types of renal vascular pedicle clamping

Methods: We performed simulating this procedure in which 16 pigs were ramdomized in two groups containing 8 animals each: Group AV; unilateral left clamping of the renal artery and vein with contralateral kidney used as control and Group A - unilateral left renal artery clamping only, with the contralateral kidney also used as control. Serial biopsies of the renal parenchyma were performed at times 0, 10, 20, 30, 40, 50, 60, 70, 80, and 90 minutes after clamping. The tissues were submitted to histopathological analysis to identify structural and morphological alterations

Results: : We observed higher vascular congestion and edema in A group after 10 min, 20 min, 30 min, 40 min and 60 min post ischaemia ($p<0.001$, $p=0.001$, $p=0.02$, $p=0.001$, $p=0.001$; respectively). We observed higher frequency of lesions in Group A for all cellular alterations found (interstitial inflammatory infiltrate, interstitial hemorrhage and cell degeneration) in all times of clamping except for the formation of pigmented cylinders that were only found in the AV Group

Conclusions: the number of lesions derived from ischemia is associated with the duration of the insult. In addition, the AV Group presented a lower frequency of injuries than Group A (it presented a higher number of injuries in a shorter time interval of ischemia)

PUB064

Prevalence and In-Hospital Outcomes of AKI in a University Hospital in Argentina Carlos Federico Varela,[2] Luciana Rubin,[2] Michelangelo Hernan,[2] Maria L. Ocampo,[1] Gustavo Greloni,[2] Daniel Luna,[2] Guillermo Rosa Diez.[2] *[1]Hospital Italiano Buenos Aires, CABA, Argentina; [2]Hospital Italiano de Buenos Aires, CABA, Argentina.*

Background: Comprehensive epidemiologic data on AKI in Argentina has not been written. The aim of our study is to evaluate the epidemiology and clinical outcomes of AKI among hospitalized adults.

Methods: Patients admitted between June 1, 2014 and May 31, 2015 were studied. Inclusion criteria were age above 18 years, the presence of two serum creatinine (Crea) during or 2 month before hospitalization and having stayed hospitalized more than one day. We excluded patients with chronic dialysis requirement and renal transplantation. We used hospital laboratory, admission and discharge databases. AKI was defined and staged according to KDIGO Crea criteria. Using Crea at discharge, we evaluated renal recovery.

Results: We studied 19930 in-hospital episodes. The mean age of patients included was 64±19, 52% were female, median of length of stay (days, LOS) was 4.5 and mortality was 5.6%. AKI prevalence was 11.6% and mortality in this group was 19.8%. AKI patients were older and average of days between first and highest Crea was 2 days. KDIGO stage 1 occurred in 9.2%, stage 2 in 1.6% and stage 3 in 0.8% with a stepwise increase in mortality with increasing AKI severity. ICU patients were 4631(23% of total group) of these had AKI 26%, while ward patients suffering AKI in 7.2%. Contrast media were

administered in 22% vs 9.4% of patients with and without AKI respectively. AKI occurred in 10.1% of patients who undergo cardiac surgery. LOS 9.8 vs 4.1 in patients with and without AKI respectively. In survivors, 73% have recovery of baseline renal function and 27% have partial recovery. In the last group 89.3% have a eGFR under 60ml/min/1.73m2.

Conclusions: As described in literature, AKI is common in hospitalized adults and is associated with significantly higher in-hospital mortality and CKD.

Table: 1. Clinical and demographical data

	All patients 19930 (100%)	AKI 2310 (11.6%)	No AKI 17620 (88.4%)	p value
Age (years)	64.16 ± 19,33	70,4±17	63,3±19	0.001
Gender female %	52.20%	45.60%	53,00%	0.001
LOS (days)	4.5	9.8	4.1	0.001
Mortality %	5.6%	19.80%	3.80%	0.0001
ICU patients %	23.2%	52,2%	19,2%	0.0001
Contrast media %	10.9%	22%	9,40%	0.0001
Cardiac surgery %	2.20%	10.10%	1.20%	0.0001

PUB065

Preexisting AKI Could Be Reversed in a Portion of Patients after Cardiac Surgery Xin Wan,[2] Jing Li,[1] Changchun Cao.[3] *[1]Nanjing First Hospital, Nanjing Medical University, Nanjing, China; [2]Nanjing Hospital Affiliated to Nanjing Medical University (Nanjing First Hospital), Nanjing, China; [3]Sir Run Run Hospital Affiliated to Nanjing Medical University, Nanjing, China.*

Background: Acute kidney injury (AKI) is a common complication after heart surgery. However, in clinical practice, preexisting AKI could also be reversed in some occasions after cardiac surgery, especially in patients with higher level of preoperative creatinine level. In this article, the occurrence, short-term prognosis and influential factors were discussed.

Methods: Five years of retrospective data (2008-2012, n=2832) were collected in the Division of Thoracic and Cardiovascular Surgery, Nanjing First Hospital, Nanjing Medical University. Observation of a decrease of 26.5μmol/L in serum creatinine in patients without renal replacement treatment was seen as the case of released preexisting AKI. Statistical description and binary logistic regression(backward stepwise: Wald)was applied in the study.

Results: After excluding the cases of patients with end-stage renal disease (ESRD) and missing data, 2383 cases were included in the study. Among which, 137 cases (5.7%) of patients were observed with released preexisting AKI. In patients with lower level of preoperative eGFR, the occurrence increased dramatically (from 1.4% to 50%). Compared with the postoperative acute, patients with reversed preexisting AKI suffered from lower mortality (1.5% vs. 2.6%). In the model of logistic regression, male (OR 1.794, 95% CI 1.201 to 2.681), lower level of preoperative eGFR (OR 6.438, 95% CI 4.808 to 8.620), previous cardiac surgery (OR 2.918, 95% CI 1.241 to 6.902) and preoperative use of IABP (OR 5.710, 95% CI 2.103 to 15.102) were the factors prompting the phenomenon. While patients with older age (OR 0.516, 95% CI 0.342 to 0.777), hypertension (OR 0.621, 95% CI 0.396 to 0.974), diabetes (OR 0.399, 95% CI 0.166 to 0.959) and peripheral vascular diseases(OR 0.253, 95% CI 0.135 to 0.471) were harder to reverse from the preexisting AKI. The area under the receiver operating characteristic curve was 0.842 (95% CI 0.826 to 0.856).

Conclusions: Preexisting AKI could be reversed in some occasions after cardiac surgery. Preoperative creatinine is influential but not decisive in postoperative renal prospective. Combination of preoperative state could predict the releasable preexisting AKI accurately, which may provide objective evaluation for the patients with higher level of preoperative serum creatinine.

PUB066

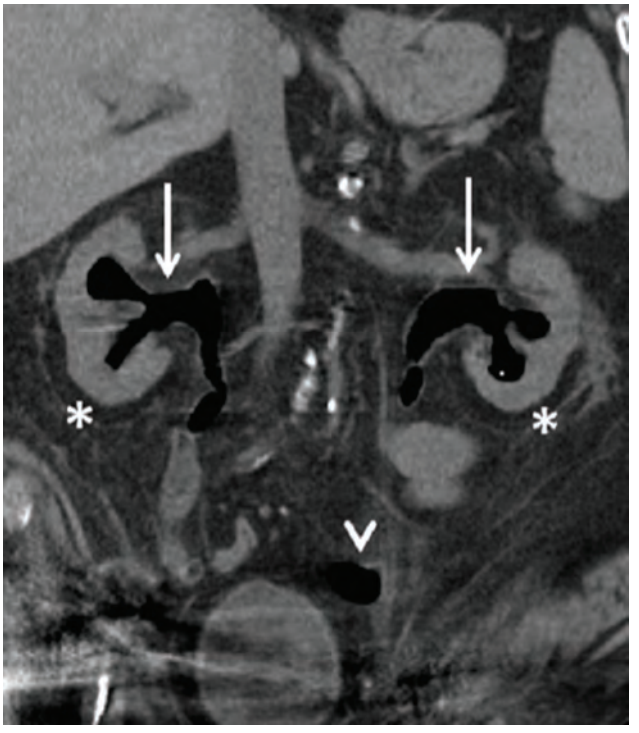
Foley Folleys: Emphysematous Pyelitis from Instrumentation in Obstructive AKI Anna S. Gutman,[1] Shimshon Wiesel,[1] Jonah E. Abraham,[2] Militza K. Kiroycheva.[1] *[1]Staten Island University Hospital, Staten island, NY; [2]Anesthesia, University of Pittsburgh Medical Center, Pittsburgh, PA.*

Background: Emphysematous pyelitis (EP) is a subclass of the life threatening infection, ephysematous pyelonephritis (EPN). We report a case of an 81-year old man, who developed EP after urinary tract (UT) manipulation.

Methods: An 81-year-old man with chronic obstructive nephropathy due to benign prostatic hyperplasia presented to our hospital with worsening kidney function. He was asymptomatic, afebrile, and had stable vital signs. His serum creatinine was 3.1 mg/dL, up from 1.5 mg/dL, and he had mild hematuria, pyuria, and proteinuria. Renal ultrasound showed bilateral hydroureteronephrosis with high post void residual volume, for which a urinary catheter was placed. Repeat ultrasound showed bilateral renal collecting shadowing echogenic foci, and a CT abdomen/pelvis showed air throughout the collecting systems and ureters. He was treated with antibiotics despite a negative urine culture, and a repeat CT showed resolution of the EP.

Results:

Conclusions: EPN is divided into: Class 1 (EP) – gas in the collecting system Class 2 – gas in the renal parenchyma Class 3A – gas/abscess extension to the renal fascia Class 3B – gas/abscess extension to adjacent tissues Class 4 – bilateral EPN or a solitary kidney with EPN Treatment for EPN is individualized, with general guidelines: Class I and II – antibiotics and percutaneous drainage (PCD) if the UT remains obstructed Class III and IV – antibiotics, PCD, and nephrectomy if no improvement For all classes: relief of the UT obstruction Our patient had asymptomatic, class I EPN, likely due to UT manipulation, obstruction, or infection. He improved with antibiotics, and did not require surgical intervention.



CT: air in the renal pelvises extended into the ureters (arrows). Fat-stranding of the bilateral kidneys (asterisks). Air at the left uretero-vesicular junction (arrowhead)

PUB067

Association of the Severity and Recurrence of AKI with Incident CKD in Head and Neck Cancer Patients with High-Dose Cisplatin-Based Chemo-Radiotherapy Akihiko Kato,[2] Naoko Tsuji,[2] Takayuki Tsuji,[1] Naro Ohashi,[1] Hideo Yasuda.[1] *[1]Hamamatsu University School of Medicine, Hamamatsu, Japan; [2]Hamamatsu University Hospital, Hamamatsu, Japan.*

Background: Acute kidney injury (AKI) is a serious complication of cisplatin (CDDP)-based chemotherapy. However, its impact of long-term renal outcome is not clear. We aimed this study to examine the impact of AKI severity and recurrence on renal outcome in head and neck cancer patients with CDDP treatment.

Methods: We identified 52 head and neck cancer patients whose basal estimated glomerular filtration (eGFR) was higher than 60 ml/min/1.73m^2, and who had underwent chemo-radiotherapy including 66-70 Gy with repeated infusion of CDDP of 80 mg/m^2 on days 1, 22, and 43 (age: 60±10 years old, male/female=48/4, basal eGFR: 87±18 (60-143) mL/min/1.73m^2).

Results: Of 52 patients, 24 (46.2%) developed AKI; 14 (26.9%) developed stage 1, 8 (26.9%) developed stage 2, and 2 (3.8%) did stage 3. There were 18 patients who complicated of one episode of AKI, 7 patients who did of 2 episodes, and 1 patient who did of 3 episodes during the chemotherapy. During the 4-month follow-up after the treatment, mean eGFR was decreased to 67±25 (32-182) mL/min/1.73m^2. There were 23 patients (44.2%) who developed incident chronic kidney disease (CKD), 19 of stage G3a and 4 of stage G3b. A multiple regression analysis revealed that basal eGFR was a significant determinant of incident CKD (β=-0.41, $p<0.01$). Especially, of 20 patients whose basal eGFR was lower than 80 mL/min/1.73m^2, 14 (70.0%) patients developed CKD after CDDP treatment. In contrast, AKI stage, number of AKI episode, and timing of AKI onset during the chemotherapy did not relate to the onset of CKD.

Conclusions: The findings suggest that the severity and recurrence of AKI episode during the CDDP-based chemotherapy did not relate to subsequent CKD progression. Rather, a lower basal eGFR (< 80 ml/min/1.73m^2) was a potent risk factor of incident CKD after the CDDP-based chemotherapy.

PUB068

The Jaffe Reaction Is Not Affected by Acetylcysteine James S. Cain,[2,3] Jack E. Sherman.[1] *[1]Roanoke Valley Governor's School, Roanoke, VA; [2]Nephrology, Carilion Virginia Tech School of Medicine, Roanoke, VA; [3]Valley Nephrology Associates, Roanoke, VA.*

Background: Alkaline picrate creatinine determinations (the Jaffe reaction) are used to measure urine and serum creatinine levels, alternative methods have been proposed to resolve the multiple problems with this venerable technique. A common alternative (Trinder reaction) is subject to negative interference by acetylcysteine (NAc.) NAc is used

to offer nephroprotection from IV contrast and is the subject of numerous investigations. We found no literature clearing the Jaffe reaction from this interference. As researchers rely upon this assay, we studied the effect of NAc on this test.

Methods: Serial dilutions of known concentrations of creatinine were prepared. The samples were analyzed with a negative control using manual and automated kinetic alkaline picrate procedures. Samples with creatinine concentrations of 15, 30, 60, and 120 mg/dl were assayed with added Nac of 0, 200, 100, 50, 25 and 12.5 mg/dl.

Results: In no case did the addition of NAc significantly alter the optical density of the "spiked" test samples compared to their non spiked counterparts, this was confirmed by ANOVA testing

Conclusions: The Jaffe reaction appears to be free of negative or positive interference from NAc. Conclusions drawn from creatinine assays under these conditions can be trusted. This affirms the use of the Jaffe reaction in both clinical and research venues involving NAc in both kinetic and non kinetic assays. The assay has numerous other known interfering substances which need to be considered.

PUB069

Systolic Blood Pressure Predicted One Year Mortality of Patients with Type-3 Cardio-Renal Syndrome Ying Zhou, Chen Yu. *Department of Nephrology, Department of Nephrology, Tongji Hospital, Tongji University School of Medicine, Shanghai, China., Shanghai, China.*

Background: Cardiorenal syndrome (CRS) is the clinical syndrome with heart failure and kidney damage, there is a complex interaction between them. The aim of this study was to investigate the clinical features of acute renocardiac syndrome (cardiorenal syndrome type 3) and prognostic factors in a tertiary referral hospital in Shanghai of China.

Methods: There were 1011 out of 19361 subjects (5.22%) admitted to our internal medicine ward (from January 2015 to December 2015), diagnosed with CRS. There were 33 cases which were diagnosed as type 3 CRS. This was a retrospectively cohort and we analyzed the anthropometric, history, clinical, biochemical and mortality characteristics of them.

Results: During 1-year follow-up, 9(27.3%) patients died. Mean age of these 33 patients was 75.33±11.82 years, 16 (48.4%) were males, 5 (15.2%) were smokers, 8 (24.2%) were diabetic, 25(75.8%) had a history of hypertension, 11 (33.3%) had coronary heart disease, 9 (27.3%) were affected by stroke. They were divided into 2 groups: survival group and dead group. Systolic blood pressure (154.46±30.71 vs 126.78±21.42), hemoglobin [(75.8, 109.0) vs (58.5, 90.0)] and Glutamyl transpeptidase [(18, 40) vs (9.8, 26.5)]levels were higher in survival group than in dead group ($P<0.05$). However, PCT levels were higher in dead group(1.02, 17.10) than in survival group(0.19, 0.66) ($P<0.05$). Multivariate logistic regression analysis suggested that systolic blood pressure independently predicted one year mortality (odds ratio: 0.947; 95% confidence interval [CI]: 0.901 to 0.99; $p = 0.033$).

Conclusions: CRS is common, and one year mortality of patients with type-3 CRS was high. Systolic blood pressure can help predicted one year mortality of patients with type-3 CRS.

Funding: Government Support - Non-U.S.

PUB070

Elderly versus Younger Patients in Vasculitis: A Single Centre Experience Vasantha M. Muthuppalaniappan,[2] Philip Davis,[3] Abhishek Dattani,[2] Saurabh Chaudhri.[1] *[1]Stratford, United Kingdom; [2]Barts Health NHS Trust, London, United Kingdom; [3]NHS, London, United Kingdom.*

Background: ANCA associated vasculitis (AAV) is a multi-systemic autoimmune disease primarily of older adults with a peak age between 65 & 74 years old. Without treatment AAV leads to considerable morbidity & mortality. The potential adverse effects of immunosuppressive therapy can be daunting when considering treatment in elderly. Our aim was to evaluate the clinical features & outcomes in elderly patients with AAV in comparison to younger patients at our unit.

Methods: We performed a single centre, retrospective study, observing 1 year survival outcomes & relapse rates in any patient diagnosed with AAV who presented to our renal unit, between Jan 2014-Dec 2015. Patients were divided into elderly group (EG) (≥70 years) and younger group (YG) (<70 years). Data on clinical features, treatment, survival and renal outcome were analysed.

Results: A total of 31 patients (17 male) aged 31-82 (mean age 61.7±14.9) were identified. The EG of 12 patients were compared to the YG of 19 patients.(Table 1) Overall 1 year survival in the YG was 93.8% & 50% in the EG. Mortality increased with age (R^2=.230, p=0.006) & C-reactive protein (R^2 .268, p=0.003). Mortality was raised in the EG with non-standard immunosuppression but large SD affected the p value. 33.3% of patients in the YG and 20% of patients in the EG had at least 1 relapse episode in a year. 26.7% of the younger patients required an average of 1 hospital admission. Each elderly patient had at least 1 hospital admission. Among patients who survived at 1-year, 20% of elderly patients and 13.3% of younger patients required dialysis.

Conclusions: Elderly patients with AAV had a higher mortality rate in comparison to the younger group. Relapses were more frequent in the younger group. Hospitalisations were more frequent in the elderly patients. Age at presentation in the whole group significantly affected survival outcomes.

Table 1

	Young AAV Group <70 years (n=19)	Elderly AAV Group ≥70 years (n=12)
Age at diagnosis mean	53 ± 12	75.8 ± 4.8
Mean BVAS score	21.1 ± 6.5	17.3 ± 6.6
MPO	42.1% (8)	50% (6)
PR3	57.9% (11)	25% (3)
GBM	0	8.3% (1)
Double positivity	0	16.7% (2)
HD at presentation	15.8% (3)	41.7% (5)
Standard immunosuppression	94.7% (18)	50% (6)
Non standard immunosuppression	5.3% (1)	50% (6)

PUB071

Digoxin Toxicity in a Patient with Liver Failure and AKI: Role for CRRT versus Plasmapheresis Aravindan V. Jeyarajasingam,[6] Srikanth Thiruvarudsothy,[3] Anuradha Konkesa,[2] Sushma Munugoti,[5] Smita Mahendrakar,[1] Alluru S. Reddi.[4] *[1]Swedesboro, NJ; [2]Rutgers, Morrisplains, NJ; [3]Rutgers NJMS, Belleville, NJ; [4]Rutgers New Jersey Medical School, Newark, NJ; [5]Rutgers UNIVERSITY, Montclair, NJ; [6]Nephrology, Rutgers NJMS, Newark, NJ.*

Background: Introduction: Digoxin has been used for management of atrial fibrillation (AF) and congestive heart failure (CHF). One of the concerns of digoxin use is its toxicity, particularly in patients with renal failure. We present a patient with AF, decompensated liver failure, superimposed on alcoholic cirrhosis and acute kidney injury (AKI), who was successfully treated with CVVHDF and plasmapheresis for AKI and digoxin toxicity.

Methods: Case Description: A 62-year-old man with past medical history of alcoholic cirrhosis and recently diagnosed AF and CHF was admitted for fatigue and weakness. He was on digoxin, furosemide and spironolactone. On admission, the patient was found to have bradycardia with heart rate of 33 beats/min and digoxin level of 3.6 ng/ml which peaked to 6.2 ng/ml. Serum creatinine was 3.4 mg/dl, which continued to rise, and the patient became anuric. Patient received Digibind and CVVHDF. His heart rate improved to 70s and subsequently dropped to 40s on days 4 and 5. Second episode of digoxin toxicity was suspected with likely digoxin-digibind complex deconjugation, as repeat digoxin level was 1.9 ng/ml. Patient received another dose of digibind on day 6 of the admission and followed by one cycle of plasmapheresis to remove the digoxin – digibind complex. Patient's vitals improved significantly after the plasmapheresis and remained stable during rest of the hospital stay.

Results:

Conclusions: Discussion: Digoxin is a cardiac glycoside that has very narrow therapeutic window; therefore, toxicity is common. It is excreted through kidneys. Owing to large molecular weight of digoxin and digoxin-digibind complex, CVVHDF that was initiated for anuric AKI failed to eliminate this complex. Deconjugation of digoxin-digibind circulating complex in the blood likely caused the second episode of digoxin toxicity with increase in digoxin levels as well as bradycardia. This case suggests that digoxin toxicity can be improved by 1-2 treatments of plasmapheresis when digibind fails to improve digoxin toxicity in patients with AKI and/or CKD.

PUB072

Clinical Characteristics of Sepsis Patients Who Were Treated with Continuous Renal Replacement Therapy A young Cho, In O Sun. *Presbyterian Medical Center, Jeonju, Korea, Jeonju, Republic of Korea.*

Background: Soluble inflammatory mediators are known to exacerbate sepsis-induced acute kidney injury (AKI). Despite the frequent use of continuous renal replacement therapy (CRRT) in the management of sepsis-induced AKI, predictor of mortality remain unclear.

Methods: We enrolled 337 patients who were treated with CRRT due to sepsis at the Presbyterian Medical Center intensive care unit from 2010 to 2014 in the study. We divided these patients into two groups (survivors vs non-survivors) according to 28-day all-cause mortality, compared their clinical characteristics, and analyzed the predictors of survival.

Results: The study included 212 men and 125 women, with a mean age of 67 years (range, 21-92 years). When we compared clinical characteristics of survivors (n=212) and non-survivors (n=125), no differences were identified, with the exception of age, total bilirubin, platelet count, and red blood cell distribution width (RDW). Survivors were younger (64 ± 14 vs 69 ± 12 year, P=0.001) and had high platelet count (180×10^3/ mL vs 134×10^3/ mL, $p<0.01$) than non-survivors. However, survivors had low RDW (14.99 ± 2.1 vs 16.17 ± 3.3, $p<0.01$) and low total bilirubin (1.04 ± 1.45 vs 2.7 ± 6.13, $p<0.01$) than non-survivors. In multivariate logistic regression analysis, age, platelet count and RDW were assessed as prognostic factors to predict 28-day all-cause mortality in sepsis patient who needed CRRT.

Conclusions: Age, platelet count and RDW could be predictors for 28-day all-cause mortality in sepsis patients with CRRT.

PUB073

Use of Point of Care Creatinine Testing to Identify AKI in the Community Setting Joshua Storrar,[1] James Ritchie,[2] Dimitrios J. Poulikakos.[1] *[1]Salford Hospital, Manchester, United Kingdom; [2]Salford Royal Hospital, Manchester, United Kingdom.*

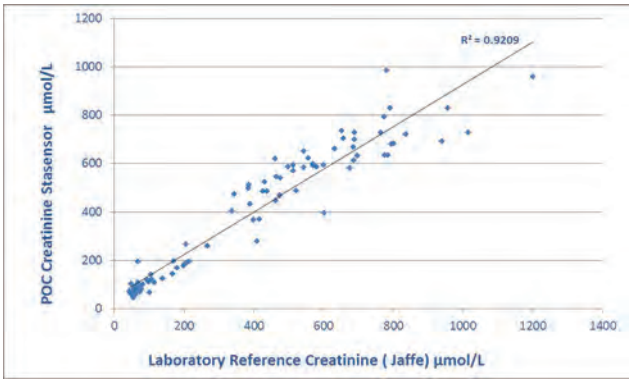
Background: Two thirds of Acute Kidney Injury (AKI) cases detected in hospital are community acquired. Point of care renal function testing in primary care may assist early identification and management of community acquired AKI to improve outcomes. Point of care (POC) creatinine testing has been developed but has not been used in the community routinely. In this study we aimed to evaluate existing creatinine POC testing against our standard laboratory method in order to support its use in the community.

Methods: We obtained POC creatinine (venous or capillary) values with StatSensor (NOVA) and serum creatinine values with Siemens Advia 2400 Jaffe for 89 patients in the hospital setting (either in the Emergency Department, outpatient clinic, ward environment or haemodialysis units). Of the POC samples, 28 were capillary blood and 61 were venous blood. POC samples were obtained at the same time as laboratory samples. We measured the percentage difference in values with the two different methods and performed correlation analysis.

Results: POC creatinine values ranged from 44µmol/L to 985µmol/L and laboratory creatinine values ranged from 43µmol/L to 1201µmol/L. There was a good correlation between POC and laboratory creatinine values (R^2 0.92, p value 0.006), Figure 1. The average percentage difference between POC creatinine and laboratory creatinine was -10%.

Conclusions: We have demonstrated a correlation between POC and laboratory creatinine results. POC testing overall tends to overestimate creatinine values. POC has reasonable agreement with laboratory assays to detect normal and abnormal values. Since AKI is defined based on change in creatinine values caution should be exercised when using POC testing and baseline laboratory values particularly for small fluctuations.

Funding: Commercial Support - NOVA- provided point of care creatinine devices, Government Support - Non-U.S.



Correlation of point of care creatinine values with laboratory creatinine values

PUB074

The Clinical Implication of Computed Tomography in Predicting Severity of Acute Pyelonephritis Associated AKI A young Cho, In O Sun. *Presbyterian Medical Center, Jeonju, Korea, Jeonju, Republic of Korea.*

Background: The aim of this study is to investigate the incidence and clinical characteristics of acute kidney injury (AKI) in patients with acute pyelonephritis (APN) and evaluate the efficacy of contrast-enhanced computed tomography (CECT).

Methods: From May 2007 to December 2009, we included 541 patients with APN who underwent a CECT examination. We investigated the incidence and clinical characteristics of APN associated AKI using the RIFLE criteria. In addition, we divided these patients into four groups according to renal parenchymal involvement in CT (group 1; less than 25% involvement, group 2; 25% or greater involvement but less than 50% involvement, group 3; 50% or greater involvement but less than 75% involvement, group 4; greater than 75%), and compared their clinical characteristics, incidence of AKI.

Results: The patients included 33 males and 508 females with a mean age of 55 years (range, 18 to 92). The incidence of AKI was 14.4%; of which, 8.0%, 5.4% and 1.0% were classified as Risk, Injury and Failure, respectively. When we compared clinical characteristics among groups, there were no differences except hospital stay. The patients in group 4 have longer hospital stay than other groups (grade 1; 9±5, grade 2; 9±4, grade 3; 9±4, grade 4; 10±5, p=0.008). There was no difference in baseline renal function (70±27 vs 76±27 vs 74±23 vs 74±23, p=0.87) and incidence of AKI among groups (G1: 9.4%, G2: 9.3%, G3: 7.2%, G4: 11.3%).

Conclusions: The incidence of APN-associated AKI was 14.4%. Although CECT is useful to detect severe APN, it seems to be less helpful to predict the AKI in patients with APN.

PUB075

Intravenous Immunoglobulin Associated Nephrotoxicity Umair S. Ahmed. *Lavale, MD.*

Background: Intravenous immunoglobulins (IVIg) are an effective treatment of multiple conditions and are usually well tolerated. We present 3 cases of IVIg associated acute kidney injury (AKI)

Methods: Case 1 56-year-old female, admitted with asymptomatic thrombocytopenia on routine testing. Platelet count on admission was 11,000. Patient was started on prednisone 100 mg daily and received 2 doses of sucrose containing IVIg, 1gm/kg. Serum creatinine on the day of administration of IVIg was 1.0, increasing progressively to 1.60, 2.50 and 2.60 over the next 3 days. No other nephrotoxic insults were identified. Urine evaluation was unremarkable. Serum creatinine 2 weeks later was 1.0 Case 2 53 years old male, admitted with back pain and bilateral lower extremity weakness. Serum creatinine on admission was 0.90. Patient was diagnosed with Guillain-Barre syndrome. A total of 2 g/kg of sucrose containing IVIg was administered over 5 days. Serum creatinine on day of initial IVIg administration was 0.80, increasing 2 days later to 2.0 and peaking at 2.20. Serum creatinine decreased to 1.20 three days after IVIg was completed. No other nephrotoxic insults were identified. Urine evaluation was unremarkable. Case 3 83 years old male, history of chronic kidney disease stage III and diffuse large B-cell lymphoma who presented with asymptomatic thrombocytopenia noted on routine investigations. Serum creatinine on the day of IVIg administration was 1.80 which was his baseline. Serum creatinine increased the day after IVIg infusion to 3.0 and continued to worsen. Patient started manifesting symptoms of uremia and was started on hemodialysis. Renal functions recovered to his baseline function after 4 sessions of hemodialysis.

Results:

Conclusions: Stabilizers are used in IVIg preparations to prevent formation of dimers and polymers, which may result in many of the adverse effects. Stabilizers include sucrose, glucose and sorbitol. Incidence of IVIg related AKI is approximately 6%, and higher with with sucrose-stabilized products. Sucrose administered intravenously enters tubular epithelial cells, causing swelling and cytoplasmic vacuolization of the proximal tubule and osmotic nephrosis. IVIg-associated AKI mostly occurs in patients at increased risk for AKI such as chronic kidney disease, diabetes mellitus, age > 65 years old, volume depletion or concomitant use of nephrotoxic agents.

PUB076

A Case of Oxalate Nephropathy in the Setting of Esophagogastrectomy and High Dietary Oxalate Intake Nawsheen Chowdhury,[2] Margaret O'Shea,[1] Youngjun Park,[3] Shayan Shirazian,[1] Naveed N. Masani.[1] *[1]Winthrop University Hospital, Mineola, NY; [2]Winthrop university hospital, Mineola, NY; [3]Winthrop-University Hospital, Mineola, NY.*

Background: Oxalate nephropathy has been defined as acute kidney injury (AKI) or chronic kidney disease (CKD) that results from tubular deposition of calcium oxalate. It is mostly reported in patients with primary hyperoxaluria, short bowel syndrome, ethylene glycol and high dose vitamin C intake. We present a case of Oxalate induced nephropathy secondary to high oxalate dietary supplement in the setting of esophagogactrectomy.

Methods: A 71-year-old Caucasian male with a history of type 2 diabetes mellitus for 17 years, esophageal cancer, status post gastroesophagectomy three years ago, nephrolithiasis, and stage 3 CKD with a baseline creatinine of 1.4 mg/dL presented to clinic with AKI and creatinine of 4.1 mg/dL. His urinalysis revealed a bland sediment with no protein. Despite discontinuation of his PPI and ACEi his renal failure worsened to a creatinine of 4.5 mg/dL and he was initiated on hemodialysis. The patient underwent renal biopsy that revealed acute tubular injury associated with multiple intratubular crystalline inclusions which are optically clear and produced strong birefringence under polarized light, most consistent with calcium oxalate. After a thorough investigation the patient admits to taking a vegetable supplement that includes Spinach, yams, carrots, broccoli, celery, and kale. After restriction of high oxalate dietary supplement, the patient was able to come off dialysis and now has stable creatinine of 2.9 mg/dL. A random oxalate:creatinine ratio was high at 86.7 mg oxalate/gm creatinine.

Results:

Conclusions: Excessive dietary oxalate intake has been shown to cause oxalate nephropathy. Risk factors for dietary induced oxalate nephropathy include primary hyperoxaluria, ethylene glycol poisoning, secondary hyperoxaluria due to bariatric surgery, inflammatory bowel disease, Orlistat therapy, high dose Vitamin C. In our case it appears that high oxalate supplement in the setting of esophagogastrectomy led to hyperoxaluria and calcium oxalate deposition in the renal tubules. As with other cases of oxalate nephropathy the renal dysfunction improved with removal of the offending agent; our patient is left with significant residual chronic kidney disease, stage IV.

PUB077

AKI Diagnosed by KDIGO Criteria Is an Independent Risk Factor for Mortality in Critically Ill Burned Patients Judith Martins. *HOSPITAL UNIVERSITARIO DE GETAFE, MADRID, Spain.*

Background: INTRODUCTION AND AIMS: Acute kidney injury (AKI) has been associated with increased morbidity and mortality in critically ill patients. However, the impact of AKI in outcomes in critically ill burned patients has not been extensively studied. The aim of our study was to assess the relationship between the diagnosis of AKI and different outcomes in this patient population. .

Methods: MATERIAL AND METHODS: We performed a retrospective analysis of patients admitted to the Intensive Care Burn Unit (ICBU) of our hospital from 1992 to

2012 (n=1635). We included patients with length of UCBU stay ≥ 3 days. We assessed the relationship between the presence of AKI (KDIGO criteria) during the first 7 days of ICBU admission and different outcomes (mortality, infection rate and requirement of renal replacement therapy [RRT]) using a stimative multivariate logistic regression model. The strength of the association was measured by the odds ratio (OR) and the 95% confidence interval. Data are percent or median and interquartile range. A p value < 0.05 was considered statistically significant

Results: RESULTS: A total of 840 patients were evaluated (age 44 [31-61] years; male 601 [72%]; total surface area burned 24% [15%-40%]; non survivors 109 [13%]; RRT 34 patients [4%]). Comorbidities associated were: hypertension 102 (12.2%), diabetes mellitus 35 (4.2%), chronic kidney disease 1 (0.1%). AKI developed in 466 (55.5%) patients. Mortality of patients with AKI versus patients without AKI was 17% and 8%, respectively (p<0.001). In the multivariate analysis, after adjustment for 12 covariates (hypertension, diabetes, chronic kidney disease, heart failure, age, sex, SAPS score, SOFA score for the cardiovascular, coagulation and respiratory components at admission, deep burn surface area and requirement of mechanical ventilation in the first 72 hours) AKI was associated with an increased risk of death (OR 2.22 [1.21-4.08], p=0.010), infection rate (OR 1.36 [1.01-1.84], p=0.044) and requirement of RRT (2.37 [0.99-5.65], p=0.051).

Conclusions: CONCLUSIONS: In our study AKI is common and is independently associated with poor outcomes, including a higher mortality rate, among critically ill burned patients.

PUB078

Hospital Acquired Kidney Injury in Critically Ill Patients Judith Martins. *HOSPITAL UNIVERSITARIO DE GETAFE, MADRID, Spain.*

Background: INTRODUCTION AND AIMS: Hospital acquired acute kidney injury (AKI) is common and is a risk factor for all-cause mortality and chronic kidney disease. Early detection of AKI is important to prevent the progression of AKI and to improve clinical outcomes. The aim of this study was to examine AKI acquired during the stage in the intensive care unit (ICU).

Methods: METHODS: We performed a retrospective cohort study of patients admitted ato the Intensive Care Unit (ICU) between January 2010 and December 2015. We included patients diagnosed AKI using KDIGO criteria during their hospital ICU stay and were evaluated by the nephrology department. Exclusion criteria were: Previous renal function unknown, AKI diagnosed at admission.

Results: RESULTS: We studied 50 patient: mean age was 67,22 years (±11.62), 35 (70%) were male, mean SPAS score was 59,1 (±5,3). The median length of hospital stay was 35.66 ± 27.03 days and ICU stay was 14,62 (± 14.4)days. Comorbidities associated were: hypertension (58%), Diabetes Mellitus (46%) and previous chronic kidney disease (60%). The main causes of the AKI were:40% hypovolemia (volume depletion, arterial hypotension), 22 % sepsis and 20 % of the cases were caused by multifactorial risk factors. 39 patients (78%) patients need renal replacement therapy(RRT). The majority of RRT procedures were with a continuous modality (CRRT). The principal cause to iniciate RRT was fluid overload and the median duration was 4,7 (±8.4)days. 2% of patients required RRT at hospital discharge. Independent risk factors for RRT were: SPAS score >59 and SOFA cardiovascular 4. Kidney function at ICU discharge with estimated glomerular filtration was 50.01 ± 27.1 ml/min and at hospital discharge was 47 ± 23 ml/min. The in-ICU mortality rate was 42.6%. Independent risk factors for hospital mortality were: previous chronic kidney disease, female and SPAPS score >59,17.

Conclusions: CONCLUSIONS: AKI hospital acquired is a frequent complication in critically ill patients. The diagnosis its associated with a high rate of mortality and need of RRT.

PUB079

Outcomes after Hospital Discharge for Dialysis Dependent AKI Patients with End Stage Liver Disease Victoria T. Vo, Roberto Pisoni, Ruth C. Campbell. *Medical University of South Carolina, Charleston, SC.*

Background: Acute kidney injury (AKI) in the setting of end stage liver disease (ESLD) has a high morbidity and mortality. There is little data on outcomes of ESLD patients who develop AKI requiring hemodialysis (AKI-D) who survive to discharge and how many ultimately survive to transplantation. To investigate this further, we conducted a retrospective chart review of ESLD patients who developed AKI-D and required hemodialysis (HD) after hospital discharge.

Methods: Patients with ESLD and AKI-D were identified by ICD-9 codes for intermittent hemodialysis and by admitting service (ESLD service). Patients on HD before the index admission & patients with newly diagnosed end stage renal disease (ESRD) from progressive chronic kidney disease (CKD) were excluded. The protocol was approved by the MUSC IRB.

Results: 54 patients met criteria for analysis. 23 patients died during the index admission and 6 were discharged to hospice. 8 patients were discharged home without HD after recovery of renal function. 17 patients were discharged home on HD. Median age was 52 years (range 28-65 y), 9 (53%) were women. Causes of AKI were acute tubular injury 9 (53%) and hepato-renal syndrome 5 (29%). Causes of ELSD were hepatitis C 5 (29%), NASH 7 (41%), alcohol induced 4 (23%). At the time of analysis, 3 of the 17 (17.6%) patients had undergone liver-kidney transplant (at day 30, 60 and 210), 4 patients were on the kidney-liver transplant list (1 currently waiting, 2 lost to follow up, 1 died), 1 declined further evaluation, and 2 patients were too high risk for listing. 5 people were in the evaluation process and 2 patients were lost to follow up without listing status. Only 1 patient recovered renal function and stopped HD.

Conclusions: AKI-D in ESLD carries a poor prognosis. HD after discharge may serve as a bridge to liver-kidney transplantation in selected patients. Renal recovery was poor.

PUB080

Nursing Perceptions Towards the Care of Patients with Post-Operative AKI Neesh I. Pannu. *University of Alberta, Edmonton, AB, Canada.*

Background: Patients undergoing operative procedures have a high incidence of in-hospital acute kidney injury (AKI) that is often under recognized and associated with adverse outcomes. Surgical teams without nephrology involvement generally manage post surgical AKI. At present, the attitudes and proficiency towards AKI of non-nephrology care providers has not been explored. Our aim was to assess surgical nursing perceptions of post-operative AKI.

Methods: A 14-question survey was provided to registered nurses and licensed practical nurses working on two general surgery wards at the University of Alberta Hospital in Edmonton, AB, Canada. Admitted patient population included trauma patients, and post-operative patients from elective, urgent, or emergent general surgery or urologic operations. Participation in the survey was voluntary, and questions assessed: years of experience, experience in other care environments, comfort level caring for patients with post-operative AKI, agreement with statements concerning the epidemiology, diagnosis, management, and prognosis of post-operative AKI, and attitudes towards performing quality improvement and increasing education around post-operative AKI.

Results: 22 nurses participated, of which, 77% were registered nurses, and 68% had been in practice less than 15 years. Only 36% of nurses had previous care experience in internal medicine wards, the emergency room, or an intensive care unit. The majority of nurses (86%) felt comfortable caring for patients with post-operative AKI. Similarly, most nurses believed that post-operative AKI could lead to irreversible kidney damage (77%), was preventable (95%), and that patients at risk for post-operative AKI could be predicted (81%). Of interest, 68% of nurses felt that the care of post-operative AKI required the involvement of nephrology or medicine consultants. The majority of nurses felt that more could be done to prevent and treat post-operative AKI on their units, and wanted additional education on AKI (72% and 95% respectively).

Conclusions: Although nurses caring for patients with post-operative AKI have minimal exposure to nephrology, they are receptive to nephrologists providing education and guiding quality improvement regarding AKI.

PUB081

Unusual Cause for Acute Kidney Failure: T-Cell Lymphomatous Infiltration and Impingement D heeraj Kaul,[2] Okwudili Nnaji,[4] Gary R. Briefel,[1] Mary C. Mallappallil,[2] Moro O. Salifu,[3] Ian L. Provancha.[5]

[1]Kings County Hospital, Brooklyn, NY; [2]None, Brooklyn, NY; [3]SUNY Downstate Medical Center, Brooklyn, NY; [4]SUNY downstatemedicsl center, Brooklyn, NY; [5]SUNY Downstate Medical Center, Brooklyn, NY.

Background: Extra-nodal kidney infiltration is an unusual manifestation of T-cell lymphoma. Most patients with lymphoma presenting as extra-nodal disease have B-cell phenotype. Acute kidney injury (AKI) due to lymphomatous infiltration is rare, with the reported incidence of 0.05% in the literature. Lymphomatous infiltration of the kidney occurs late in the disease progress, being very unusual at presentation. We describe a unique case of T-cell lymphoma presenting with AKI with enlarged retroperitoneal lymph nodes causing hydronephrosis and encasement of one of the kidneys, consecutive lymph node biopsy showed T-cell lymphomatous infiltration.

Methods: A 79 year old Hispanic lady from Caribbean descent, with comorbidities such as hypertension, mixed hyperlipidemia, anxiety disorder and stage 3b chronic kidney disease came in for abdominal discomfort 2 weeks after screening colonoscopy and biopsies of colonic polyps. Physical exam showed hypertension of 178/73 mm Hg and normal physical findings. Laboratory studies showed AKI, serum creatinine 4.20, potassium 3.9, lactate dehydrogenase 989 and uric acid 10.4, presumed to be acute spontaneous tumor lysis syndrome. Staging work up with CT scan showed marked retroperitoneal lymphadenopathy, encasement of the right kidney and left kidney hydronephrosis with atrophic changes. Consequently, retroperitoneal lymph node biopsy showed T-cell lymphoma; CD3 positive, C20 and AE1/AE3 negative.

Results:

Conclusions: Review of PubMed Literature of published incidents of cell lymphoma presenting with AKI rendered 258 case reports in humans between 1975 and 2017. Reports described B-cell phenotype lymphoma (100%) the majority seen in immunosuppressed individuals with only a few (12) reports of T-cell lymphoma HTLV-related. Here we present a case of T-cell lymphoma (HTLV-negative) infiltrating and encasing both kidneys presenting as AKI. The unexpected lymphoma presentation warrants need to expand differential diagnosis of AKI.

PUB082

Acute Tumor Lysis Syndrome Caused by Palliative Radiotherapy in a Patient with Metastatic Prostate Cancer Umair S. Ahmed. *Lavale, MD.*

Background: Acute kidney injury as a result of tumor lysis syndrome has been reported in patient with hematological malignancies and can be spontaneous or treatment induced, usually secondary to chemotherapy. We present a case of a patient with

prostate cancer who developed tumor lysis syndrome secondary to radiation therapy and subsequently developed an acute kidney injury.

Methods: Patient is a 67 years old male with a past medical history significant for high grade metastatic prostate cancer who presented to the hospital with abdominal pain, nausea and generalized weakness. He was noted to be hemodynamically stable on admission. Serum creatinine was noted to be 4.80 on admission as compared to a normal baseline serum creatinine. Patient had a history of metastatic prostate cancer and had been treated with six cycles of Taxotere with minimal response. He had also undergone an orchiectomy. Due to severe back pain due to pelvic disease, patient was started one treatment with radium 223 which was 1 week prior to current hospital admission. He had not received prophylactic anti-uric acid treatment. Serum potassium was 6.0, phosphorus was 6.0 while serum uric acid was 35. Patient also had high anion gap metabolic acidosis and was subsequently started on a bicarbonate infusion. He also received 2 doses of IV rasburicase 9 mg. Peak serum creatinine was 6.20 and improved to 1.60. Electrolyte abnormalities resolved. Repeat serum uric acid level was undetectable.

Results:

Conclusions: Tumor lysis syndrome is uncommon after radiation therapy. This case highlights the importance to anticipate the possibility of developing acute kidney injury after radiation therapy which can be minimized by prophylactic administration of Allopurinol.

PUB083

Severity of AKI in Critically Ill Burned Patients Depends on the Diagnostic Criteria Used Judith Martins. *HOSPITAL UNIVERSITARIO DE GETAFE, MADRID, Spain.*

Background: INTRODUCTION AND AIMS: Acute Kidney injury (AKI) is a common and serious complication in burned patients The definition of AKI has been evolving for several years. The latest classification proposed by the Kidney Disease: Improving Global Outcomes (KDIGO) had the aim of unifying the definition of AKI. Following this definition, AKI is diagnosed according to a laboratory criterion (relative changes in serum creatinine [SCr]) and a urine output (UO) criterion. Patients are classified into three different stages. The aim of our study was to investigate the relationship between the criteria used for the diagnosis (laboratory [L], UO [U] or both [L+U]), and different outcomes (Intensive Care Burn Unit [ICBU] mortality and requirement of renal replacement therapy [RRT]) for each AKI stage.

Methods: MATERIAL AND METHODS: We performed a retrospective analysis of patients admitted to the ICBU of our hospital from 1992 to 2012 (n=1635). We included patients with length of UCBU stay ≥ 3 days. We assessed patients for the presence of AKI (KDIGO criteria) for the first 7 days of ICBU admission. We compared the relationship between each stage and different outcomes (mortality and RRT) depending on the criteria used for the diagnosis of AKI (L, U or L+U).

Results: RESULTS: A total of 840 patients were evaluated (age 44 [31-61] years; male 601 [72%]; total surface area burned 24% [15%-40%]; non survivors 109 [13%]; RRT 34 patients [4%]). Comorbidities associated were: hypertension 102 (12.2%), diabetes mellitus 35 (4.2%), chronic kidney disease 1 (0.1%). AKI developed in 458 (54.5%) patients. Patients presented AKI stage I (395 [84%], stage II 52 [11%], and stage III 19 [4%]). For patients diagnosed with L, U or L+U criteria, mortality was, respectively: All stages: 55 (17%), 18 (15%), 4 (24%) (p=0,601); Stage I: 48 (16%), 15 (16%), 1 (20%) (p=0.972); Stage II, 6 (43%), 2 (7%), 2 (20%) (p=0.022) ; and Stage III: 1 (17%), 1 (33%), 1 (50%) (p=0.632). For patients diagnosed with L, U or L+U criteria requirement of RRT was, respectively: All stages 11 (4%), 5 (4%),3 (18%) (p=0.017). Stage I: 8 (3%), 3 (3%),0 (0%) (p=0,891) and stage III: 1 (17%), 1 (33%), 1 (50%) (p=0,632).

Conclusions: CONCLUSIONS: KDIGO defines three stages of AKI of different severity. However, outcomes differ within each stage depending on the criterion met (laboratory versus urine output).

PUB084

Pre Transplant Predictors of Renal Recovery in Patients Undergoing Liver Transplant Sanjeev Gupta,[1] Anastasios Papanagnou,[1] Sharika G. Menon,[2] Savneek S. Chugh.[1] *[1]Westchester Medical Center, Valhalla, NY; [2]Westchester medical center, Valhalla, NY.*

Background: Hepato-Renal Syndrome (HRS) is a life threatening complication of liver cirrhosis. The activation of neurohormonal compensatory mechanisms can lead to intense renal vasoconstriction and resultant renal failure, needing dialysis at times. Liver transplantation was the first therapeutic option to change the prognosis of cirrhotic patients with HRS. Although not all patients post-transplant went into renal recovery. We are presenting a study looking at relationship of total bilirubin with renal recovery.

Methods: We did a retrospective analysis of 40 cirrhotic patients who underwent orthotropic liver transplant (OLT) from 1996 to 2014 with Acute Kidney Injury at our institution. Patients with impaired renal function were classified as having HRS based on the Ascites Club Criteria. The diagnosis of pre-renal azotemia and ATN were based on renal consult notes in the chart. Post-transplant renal function was assessed at day 30.

Results: Total patient population was 40 with mean age; MELD score, total bilirubin, and serum creatinine (SCr) at the time of transplant were 51, 32.4, 15 mg/dl, and 2.58 mg/dl respectively. Mean SCr at day 30 was 1.68 mg/dl with eGFR of 47.4 ml/min/1.73m2. Out of 40 patients, 76.3% were male and 23.7% were female. Patients with bilirubin level of more than 10mg/dl were associated with poor renal recovery with an Odd ratio of renal recovery as 0.5 (P: 0.33).

Conclusions: Renal non-recovery after liver transplantation can be 9-32% but only a limited number of studies have done to look for possible etiology. These studies have shown longer duration of renal dysfunction, repeat liver transplantation, type II DM and age at liver transplantation as predictors of renal non-recovery. In our study we concluded that total bilirubin level greater than 10mg/dl at the time of liver transplant in patients with HRS will have poor renal recovery post liver transplant.

PUB085

Diffuse Alveolar Hemorrhage in Pulmonary-Renal Vasculitides: Successful Resolution with Emergent Adjunctive Plasma Exchange Jan C. Hofmann. *California Pacific Medical Center, San Francisco, CA.*

Background: Antibody mediated diffuse alveolar hemorrhage (DAH) in pulmonary-renal vasculitides is an acute, often life-threatening condition. While high dose immunosuppressive (IS) therapy is paramount in controlling this condition, plasma exchange often proves to be critically important.

Methods: From 1/08-1/17, we evaluated 63 patients (pts) diagnosed with DAH. Of 154 pts with ANCA or anti-GBM antibody renal vasculitis (RV) treated with adjunctive plasma exchange during this 9-year period, 63 pts (41%) were diagnosed with DAH: 28/74 (38%) with MPO positive ANCA RV, 26/60 (43%) pts with Prot3 positive ANCA RV, and 9/20 (45%) pts with anti-GBM RV. Pts were defined as having DAH if the pt had progressive hemoptysis and/or evidence of DAH by bronchoscopy. Median pt age was 54 years (19-85 years old); 37 (59%) pts were female. Majority of pts presented with cough, dypsnea, and hemoptysis; hypoxemia; and diffuse bilateral alveolar opacities. 54/63 (86%) pts underwent bronchoscopy; 46 pts (73%) were intubated. All pts received the following IS regimen: high dose corticosteroids (CS), plasma exchange (PE), and cyclophosphamide (CP) or rituximab (RTM). Pts received CS (methylprednisolone 500-1000 mg IV X 3-5 days) followed by prednisone taper, and CP (500-750 mg/m^2 IV every 4 weeks, or 75-150 mg/day PO, for 3-6 months) or RTM (375 mg/m^2 weekly X 4 weeks). Pts received daily PE treatments (txs) using FFP replacement until DAH resolved.

Results: 55/63 (87%) pts had resolution of DAH ≤7 days after starting IS regimen. Resolution of DAH was defined as: complete or near complete resolution of alveolar bleeding or hemoptysis, and improvement in oxygenation (decrease in FI02 ≥0.30, or increase in SA02 ≥10%), with or without improvement in chest x-ray findings. Mean number of PE txs was 3.7 (2-8 txs). 41/46 (89%) of intubated pts were extubated. 52/63 (83%) pts had significant improvement in oxygenation; 46 (73%) pts had decreased pulmonary infiltrates. 7 (11%) pts died of complications of pneumonia and sepsis.

Conclusions: Diffuse alveolar hemorrhage is an uncommon, but potentially life-threatening complication of pulmonary-renal vasculitides. High dose corticosteroids, cyclophosphamide or rituximab, and plasma exchange are useful treatment modalities and, when initiated promptly, can be highly effective in providing rapid resolution of antibody mediated alveolar hemorrhage.

PUB086

AKI and Cast Nephropathy: Clinicalpathological Features and Associated Outcomes Fernando Manuel G. Pereira,[1] Afonso Santos,[3] Miguel Goncalves,[1] Pedro Pereira Campos,[1] Rita Theias Manso,[1] Karina Soto.[2] *[1]Hospital Fernando Fonseca EPE, Lisbon, Portugal; [2]Hospital Fernando Fonseca EPE and CEDOC Universidade Nova de Lisboa, Lisbon, Portugal; [3]Hospital Prof. Doutor Fernando da Fonseca, Lisbon, Portugal.*

Background: Cast nephropathy is the most common AKI presentation in Multiple Myeloma (MM). Combination of new generation chemotherapy with efficient removal of serum free light chains (FLC) was recently suggested to increase kidney and patient outcomes. Herein we present our experience with 18 patients, presented with AKI and diagnosed as myeloma cast nephropathy (MCN).

Methods: A retrospective analysis of MM patients with clinical and/or pathological diagnosis of MCN referred to Nephrology Department was done. Kidney response was defined by eGFR≥ 30 mL/min/1.73 m^2 and/or dialysis independence at 3 months.

Results: Eighteen patients were included, 62,5% male, mean age 71yo, with mean follow-up 17 mo. Most of them admitted with AKI III, median SCr 7.4mg/dL; proteinuria 4,82 g/d; ACR 0.33G/G at admission; 70% of cases with nephrotoxic agents; 81% needed RRT; 44% also treated with PE and 62,5% with HCO-HD. In 68,7% of patients MM was Lambda (median FLCs 4540), 25% Kappa (27100), one biclonal, and another with heavy and light chains. Mean BM plasma cells was 55%, and most with bone lytic lesions. All were treated with QT, 87,5% based on BTZ. After 1st QT cycle 50% non-recovered kidney function, at the end of follow-up 56% were ESRD. Kidney biopsy was performed in 68,75%. Of them, 82% had MCN confirmed, one case with interstitial nephritis and tubular FLC deposit and another with heavy and light MDD and rare casts. ESRD was related with higher percentage of tubules with casts. Of note, Lambda FLC was related with worse kidney outcome, as well as the high levels of FLC at admission. At the begining 75% had hematological response, with median FLC reduction of 55,30%. Best FLC reduction was 82% in 1,22 months, after 1st QT cycle. However, the frequency of relapses determined a global mortality of 70% in a mean period of 16,5 months, most related to MM (50%) and 25% sepsis-related.

Conclusions: Combined approach with BTZ-based chemotherapy and HCO-HD lead to significant and fast reduction of serum FLC, resulting in early kidney response. However, late MM diagnosis with high FLC levels were related with worse kidney and patient outcomes. Future large multicenter studies are still needed to confirm the benefits of HCO-HD. Severe chronic renal impairment strongly affects survival in patients with MM.

PUB087

Characterisation of Polymere Membranes by MALDI-Mass-Spectrometric Imaging Techniques Joachim Jankowski,[1] Vera Jankowski.[2] *[1]RWTH Aachen, Aachen, Germany; [2]University hospital RWTH Aachen, Aachen, Germany.*

Background: For physical and chemical characterisation of polymers a wide range of analytical methods is available. Techniques like NMR and x-ray are often combined for a detailed characterisation of polymers used in medical applications. Over the last few years, MALDI mass-spectrometry has been developed as a powerful tool for space-resolved analysis, not least because of its mass accuracy and high sensitivity. MALDI imaging techniques combine the potential of mass-spectrometric analysis with imaging as additional spatial information. MALDI imaging enables the visualisation of localisation and distribution of biomolecules, chemical compounds and other molecules on different surfaces.

Methods: In this study, surfaces of polymeric dialyzer membranes, consisting of polysulfone (PS) and polyvinylpyrrolidone (PVP) were investigated, regarding to chemical structure and compound's distribution. Flat membranes as well as hollow fibre membranes were analysed by MALDI imaging. In accordance with polymer's characteristics analysis parameters like laser intensity and laser raster step size were established firstly to optimize signal intensity and spatial resolution. Best signal quantity and quality and spatial resolution were achieved with settings of 60 µJ laser intensity and 50 µm laser raster step size. The mass spectrometric investigation of both polymers showed clear differences in ionisation behaviour.

Results: According to the manufacturing process luminal and abluminal membrane surfaces are characterised by differences in chemical composition and physical characteristics. The MALDI imaging demonstrated that the abluminal membrane surface is more consisting of polysulfone than polyvinylpyrrolidone, the luminal membrane surface displayed more PVP than PS. The addition of PVP as hydrophilic modifier to polysulfone-based membranes increases the biocompatibility of the dialysis membranes. The analysis of polymer distribution is a relevant feature for characterisation of dialysis membranes.

Conclusions: In conclusion, MALDI imaging is a powerful technique for polymer membrane analysis, regarding not only detection and identification of polymers but also localisation and distribution in membrane surfaces.

PUB088

Identifying Hub Genes Associated with Clinical Characteristics in IgA Nephropathy by WGCNA Yan Xu,[1] Chenyu Li.[2] *[1]Affiliated Hospital of Qingdao University, Qingdao, China; [2]Affiliated hospital of qingdao university, Qingdao, China.*

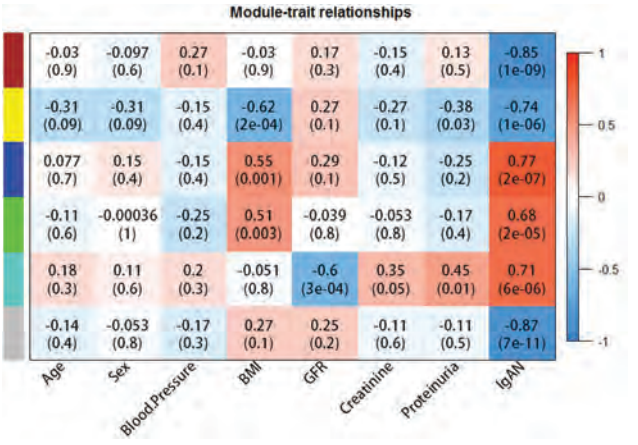
Background: Clinically, IgA nephropathy has a variety of symptoms including paroxysmal gross hematuria, nephritic syndrome and nephrotic syndrome. This study aimed at investigating hub gene and genes modular related to IgA nephropathy clinical characteristics.

Methods: We collected 32 human samples from the European Renal cDNA Bank, used the WGCNA to construct the gene co-expression network and identify the hub genes associated with clinical characteristics. GO and KEGG analysis for hub genes were performed by DAVID, and PPI information was acquired from STRING.

Results: For glomeruli, there were 1470 DEGs containing 10 hub genes associated with age, 8 hub genes associated with sex, and 48 hub genes associated with Bp enrichd in ERK1 and ERK2 cascade, 223 hub genes associated with BMI enrich in organic acid catabolic process, 136 hub genes associated GFR enriched in immune response, 82 hub genes associated with proteinuria enriched in extracellular matrix organization. In tubulointerstitium, there were 480 DEGs containing 6 hub genes associated with age, 15 hub genes associated with sex, and 35 hub genes associated with Bp enrichd in positive regulation of apoptotic process, 87 hub genes associated with GFR enriched in negative regulation of macromolecule metabolic process, 33 hub genes associated with proteinuria enriched in regulation of apoptotic process.

Conclusions: In conclusion, we made a preliminary investigation on molecular mechanisms of relationship between IgA nephropathy and clinical characteristics, and identified hub genes and pathways closely related with BMI, GFR and Proteinuria in IgA nephropathy by a series of bioinformatics analysis.

Funding: Government Support - Non-U.S.



Weighted gene co-expression network analysis in IgA nephropathy glomeruli Each column corresponds to a trait, row to a module eigengene. Each cell contains the corresponding correlation, with color-coded according to the color legend, and P-value.

PUB089

Novel Vascular Access Device for Hemodialysis Access Eduard Tsyrulnykov,[1] Anil K. Agarwal,[3] Aleksandr V. Obabko.[2] *[1]kenvelo, Mequon, WI; [2]Argonne National Laboratory, Lemont, IL; [3]Ohio State University, Columbus, OH.*

Background: The current methods of cannulation of dialysis access (2 needles) could be ineffective in access with challenging geometry. Proposed single needle cannulation device could be useful in situation where access can accomodate only 1 needle.

Methods: The device consists of a single needle with a dilator with side holes. One of the distinctive features of this device is the use of double dilator (combination of external (element 30) and removable with needle (element 40) internal dilator (elements 45,48 and 30 of image)). There are benefits of using double dilator : 1. Use cannulation needle of smal size. 2. Use of larger size of internal tube advanced into external dilator that will result in higher flow rates of blood through device. Pilot bench and animal studies using this novel VAD for HD were performed between 2005 and 2014. More than 1,200 cannulations were performed in dialysis fistulas in different stages of maturation in animals with medication induced kidney failure. Venous and arterial pressure, blood flow rates, blood recirculation rates, post-treatment bleeding time, and blood urea nitrogen (BUN) clearance were observed and recorded.

Results: The device provides blood flow rate 600 ml/min on radio cephalic fistula. Average post-treatment bleeding time is 3 minutes with applied pressure, blood loss is 3-5 ml. Without applied pressure, bleeding stopped after 10 min and blood loss is 5-10 ml. The decreased level of bleeding is likely due to using smaller size needles. The proposed device develops recirculation 20-30% for the flow rate of 600 ml/min http://www.mcs.anl.gov/~obabko/ed7_te4a.mpeg 2. When flow inside the device is decreased to 450 ml/min, the simulation predict that recirculation will go to zero. http://www.mcs.anl.gov/~obabko/ed8_te4.mpeg

Conclusions: The research presented in this paper suggests that this device could be safely used for dialysis accesses in animals. In the future this device may provide comfort and access for humans. The smaller needle size and increased flow rate will provide additional comfort to patients and possibly increase efficacy of dialysis.

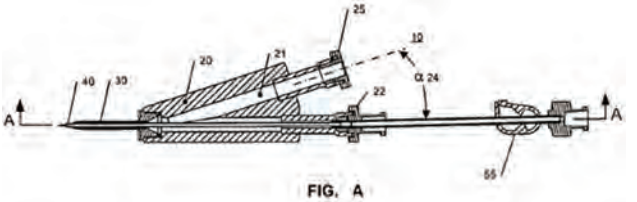
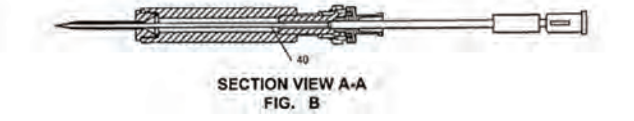


FIG. A



SECTION VIEW A-A
FIG. B

PUB090

Employing the Lotus Effect for Indwelling Medical Devices Jimmy Ni,[1] Jie Cui.[2] *[1]3J Technologies, Inc., San Diego, CA; [2]Massachusetts General Hospital, Boston, MA.*

Background: Central catheter is the most common hemodialysis access in ESRD patients and associated with increases hospitalization, mortality and healthcare-cost burden. There are many long-term problems of current tunneled catheters especially infection and thrombosis. Thrombotic occlusion occurs in 30-40% of patients, which can occur within 24 hours after insertion or after prolonged continuous successful usage (4, 5). Severe systemic infection occurs in 30% of central catheter-associated bacteremia. When catheter gets infected, patients will need to receive 6 weeks antibiotics[z1], catheter removal, temporary catheter placement and another tunneled catheter reinsertion and a chest X-ray. Center of Disease Control (CDC) estimates the cost of each central line associated infection at $16,550.

Methods: A new type of catheter has been investigated and fabricated, as desired to be efficacious for resolving these problems. We have investigated a cost-effective, long-term, bacteria-resistant, anti-thrombotic interventional medical device on our IP-protected Lotus technology.

Results: The Investigated medical device is based on *Lotus* technology, involving nano-engineered structure array (*Lotus* structure) on the inner surface by a cost-effective, long-lasting micro/nano fabrication method. The catheter is constructed of a monolithic polymer to efficiently carry a bio fluid through an inner surface of a tubular component having a nanostructure array configuration.

Conclusions: We have investigated a cost-effective, long-term, bacteria-resistive, anti-thrombosis interventional medical device on our IP-protected *Lotus* technology. The manufacture process enables it to reform when subject to mechanical molding applied by *Lotus* substrate.

Funding: Commercial Support - 3J Technologies, Inc.

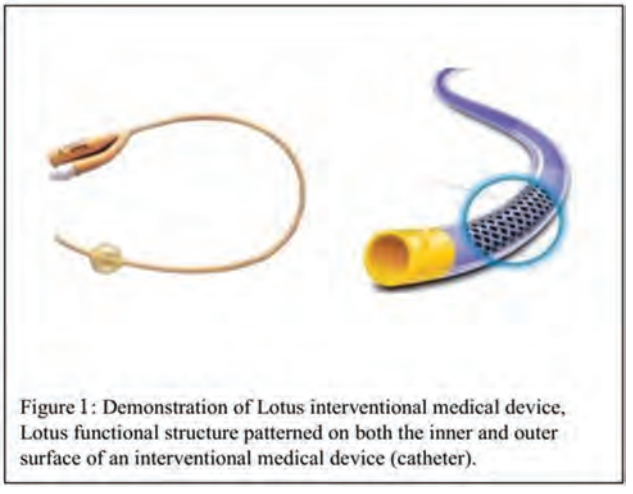


Figure 1: Demonstration of Lotus interventional medical device, Lotus functional structure patterned on both the inner and outer surface of an interventional medical device (catheter).

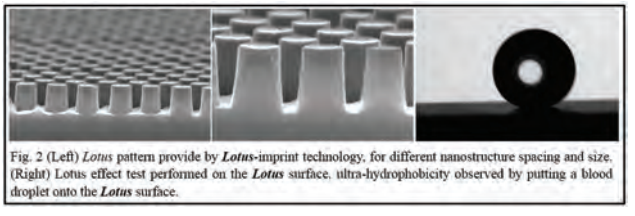


Fig. 2 (Left) *Lotus* pattern provide by ***Lotus***-imprint technology, for different nanostructure spacing and size. (Right) Lotus effect test performed on the ***Lotus*** surface, ultra-hydrophobicity observed by putting a blood droplet onto the ***Lotus*** surface.

PUB091

Estimation of Internal Filtration of Two New High Retention Onset Dialyzers Anna Lorenzin,[1] Mauro Neri,[1] Francesco Garzotto,[3] Alessandra Brendolan,[3] Federico Nalesso,[2] Monica Zanella,[3] Nicola Marchionna,[3] Claudio Ronco.[3] *[1]IRRIV, Vicenza, Italy; [2]S.Bortolo Hosp., Vicenza, Italy; [3]St. Bortolo Hospital, Vicenza, Italy.*

Background: During hemodialysis, one of the phenomena contributing to high convective volumes is the internal/backfiltration(IF/BF). In an era of highly permeable and more and more selective membranes, it becomes important to estimate IF/BF volumes for a specific dialyzer and in specific therapy settings. Aim of our study was to in vitro estimate IF volumes by a semiempirical method of two new high retention onset dialyzers in a simulating HD session setting.

Methods: 2 dialyzers were tested: The ranova 400 and 500(Baxter,US). Ultrafiltration coefficients were 48 and 59 ml/h/mmHg respectively. Test was set up in order to collect pressures at inlet and outletof dialyzer compartments in counter-current configuration. Test parameters were:blood flow=300ml/min, dialysate flow=500ml/min, net ultrafiltration=0. Human blood was used. 3 mathematical models were applied:simple linear, double linear and non-linear. The 3rd model considers the blood non-Newtonian and rheological behavior.

Results: Graphs of TMP vs dialyzer length, obtained from the 3 models, are summarized in figure 1. About Theranova400 (Theranova500), single linear model generates an IF volume of 2727ml/h(2906ml/h), but it largely overestimates the result and doesn't match the zero balance condition; double linear model generates 1591ml/h(1815ml/h); the third model, based on assumptions derived previous works in literature, is the most precise and the final volume is equal to 1620 ml/h(1865ml/h).

Conclusions: Geometrical and morphological characteristics of new-generations HD dialyzers and membranes, leading to high permeability and sharp sieving profiles, determine high convective volumes. The convective contribution to the total removal of renal toxins can be increased exploiting internal cross filtration.

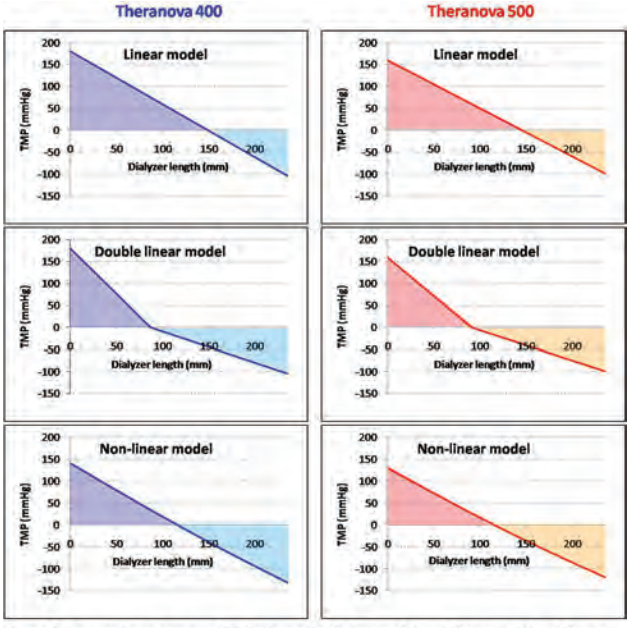


Figure 1. Transmembrane pressures (TMP) estimated inside the two dialyzers, Theranova 400 and Theranova 500, through three different models. The areas under the positive TMP represent the amount of internal filtration (IF), the areas under the negative TMP the amount of backfiltration (BF).

PUB092

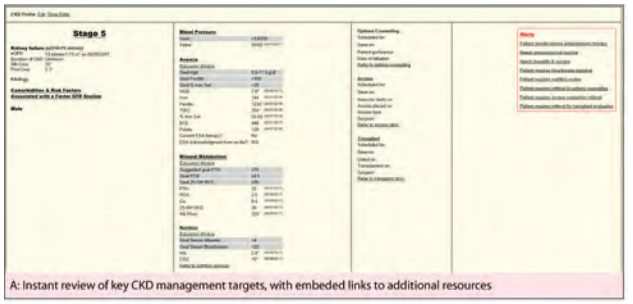
Development of a Digital Dashboard to Streamline CKD Management Nikhil Agrawal,[2] Krzysztof Wierzbicki,[4] Stewart H. Lecker,[2] Andrea Renken,[1] Julie Rockwell,[2] Martin R. Pollak,[3] Ali Poyan-Mehr.[5] *[1]BIDMC, Boston, MA; [2]Beth Israel Deaconess Medical Center, Brookline, MA; [3]Beth Israel Deaconess Medical Center/Harvard Medical School, Boston, MA; [4]Beth Isreal Deaconess Medical Center, Hyde Park, MA; [5]None, Boston, MA.*

Background: In spite of improved safety, and cost-effectiveness over conventional paper-based records, the ever-increasing complexities of electronic health records(EHR) applications and their poor user interface(UI) have been implicated as a major contributor to medical errors, and physician burnout. With the healthcare provider as the end user in mind, we created a streamlined EHR interface to support ambulatory CKD patients care.

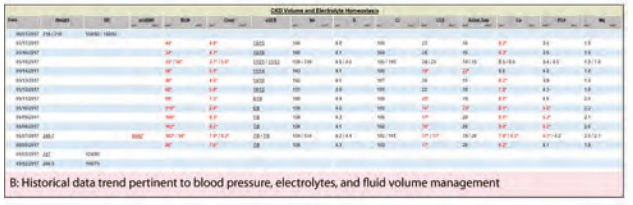
Methods: We formed a multidisciplinary team including an IT specialist, system engineer, nephrologist, nurse, and trainee to develop an electronic dashboard through an an iterative process of UI Design that included: Provider interview, clinical guideline review, definition of the unmet needs, design, prototyping, beta testing, and end user evaluation. Emphasis was placed on user experience and patient needs during the clinic visit.

Results: We have brought all elements pertinent to CKD management under one digital page, referred to as the "CKD Sheet". Provider can access a patient's current state of: Renal function, proteinuria, blood pressure, anemia, iron stores, mineral metabolism, nutritional state, options planning, and transplant evaluation. Each of these 9 categories has built-in educational tools and references. Patient materials (e.g. dietary guides) are readily accessible for print during the visit. Clinical decision support is provided by algorithm-driven alerts for values out of range based on current professional guidelines. Longitudinal data is displayed and grouped by disease systems (e.g. weight, blood pressure, and BNP trended together).

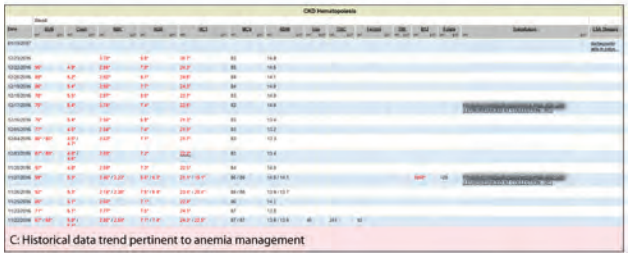
Conclusions: Through an iterative user interface design process and early involvement of end users we have created an EHR-based support tool for the management of patients with CKD.



A: Instant review of key CKD management targets, with embeded links to additional resources



B: Historical data trend pertinent to blood pressure, electrolytes, and fluid volume management



C: Historical data trend pertinent to anemia management

PUB093

Machine Learning Prediction Model of Combined End Point of AKI and New Onset Renal Replacement Therapy (RRT) in ICU Patients Lukasz Kiljanek, Sandeep Aggarwal. *Drexel University College of Medicine, Philadelphia, PA.*

Background: AKI and new onset RRT in ICU patients is associated with significant morbidity and mortality. Prediction of combined endpoint of AKI or need for RRT can potentially improve patient outcomes. To accomplish part of this use of biomarkers, scoring systems and machine learning, have been tried in the past. In our study we attempted the use Gradient Boosting Machine (GBM) - machine learning algorithm to create a AKI and new onset RRT prediction tool using MIMIC III (Medical Information Mart for Intensive Care III) database.

Methods: GBM algorithm from H2O.ai R project library was used to model 2008-2012 MIMIC 3 database. We defined 750 clinical and laboratory variables from first 24 hours after ICU admission. Patients in whom serum creatinine rose by 0.3 mg/dl or more within first 24 hours, with past medical history of dialysis or RRT related events charted within first 24 hours of ICU stay were excluded. Remaining 8893 patients were divided 20 times randomly into training (95% of patients) and testing (5% of patients) datasets. For all patients, minimal serum creatinine within first 24 hours after ICU admission was recorded as baseline. AKI within 24-72 hours after ICU admission was defined as observation of creatinine rise recorded between 24-72 hours by 0.3 mg/dl or more from baseline. New onset RRT was defined as presence of any dialysis related event between 24-72 hours of ICU stay. Average incidence of combined endpoint of AKI or RRT was 82.2 (18%) [95% CI 77.9 - 86.4] for 20 testing sets. Each training dataset was used to build GBM for predicting combined endpoint of AKI or RRT. Each such GBM model was validated on testing dataset. Area under curve (AUC) of receiver-operator characteristics curve (ROC) was recorded.

Results: For 20 testing datasets, AUC of ROC for GBM was 0.79 [95% CI 0.77 - 0.8]. Most important predictors, recorded within first 24 hours of ICU stay, from 1 of 20 runs, with their scaled importances (as per GBM) were : delta creatinine (1), number of pH checks on blood gasses (0.76), last recorded phosphorus (0.4).

Conclusions: In our analysis GBM model showed relatively good accuracy. Our approach can be employed to EMRs in hospitals as an AKI and new onset RRT combined endpoint prediction tool, but more research is warranted to assess clinical applicability and robustness of our methods.

PUB094

Calcitriol Mitigates IL-6 Induced Podocyte Hypermotility via STAT3/MLC Signaling Dian Bao,[2] Fang-Fang He,[4] Hua Su,[1] Chun Zhang.[3] *[1]Huazhong Science and Technology University, Wuhan, China; [2]Union Hospital, Wuhan, China; [3]Union Hospital, Huazhong University of Science and Technology, Wuhan Hubei Provicne, China; [4]Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei, China.*

Background: Podocyte motility contributes to the pathogenesis of foot process effacement and proteinuria during glomerular diseases. Interleukin-6 (IL-6) is a multifunctional inflammatory cytokine and frequently involves in cancer cells invasion and metastasis. It is well-known that calcitriol has anti-inflammatory and immunomodulatory effects besides its classic role in regulation of bone mineral metabolism. Here, we investigated the pathogenic role of IL-6 in podocyte motility as well as the therapeutic effect of calcitriol.

Methods: We cultured conditional immortalized human podocytes and detected podocyte motility by wound healing and transwell assay. Myosin light chain (MLC) or signal transducer and activator of transcription 3 (STAT3) shRNAs were transfected into podocytes by lentivirus transfection system. ML-7 and stattic were employed as inhibitors for the activation of MLC and STAT3 respectively. The expressions of phosphorylated MLC (pMLC), MLC, phosphorylated STAT3 (pSTAT3) and STAT3 were assessed by western blot. The architecture of actin cytoskeleton and focal adhesions were observed by immunofluorescence staining.

Results: We found that IL-6 promotes the expression of pMLC as well as the motility of podocyte in a time-dependent manner. Either genetic deletion or chemical inhibition the phosphorylation of MLC prevents the IL-6 induced podocyte hypermotility, also preserves actin cytoskeleton and focal adhesions of podocyte. Furthermore, our data confirmed that, in IL-6 treated podocyte, STAT3 is an upstream regulator for MLC phosphorylation, and interrupting STAT3 pathway can significantly minimize the hypermotility of podocyte. Calcitriol, widely applied in clinic, markedly attenuates IL-6 induced podocyte hypermotility via blocking STAT3/MLC signaling.

Conclusions: Our data indicated that IL-6 enhances podocyte motility via STAT3/MLC pathway. Whereas calcitriol exertes its protective role by inhibiting this signaling.

Funding: Government Support - Non-U.S.

PUB095

Cold Shock Proteins Interfere with TNFα Binding to Its Receptor and Modulate Progranulin-Mediated Inhibition of Signaling Jonathan A. Lindquist, Christopher L. Hessman, Antonia Bock, Sabine Brandt, Peter R. Mertens. *Otto-von-Guericke University, Magdeburg, Germany.*

Background: Inflammation and an influx of immune cells are common elements in the pathogenesis of many diseases including autoimmunity. Amongst the pro-inflammatory cytokines, tumor necrosis factor-α (TNF α) plays a central role due to its ability to amplify the cytokine network. Therefore TNF blocking agents have been developed and demonstrated effectiveness against a number of immune-mediated disorders (rheumatoid arthritis, ankylosing spondylitis, psoriasis). Progranulin (PGRN) is a growth factor that binds to TNF-receptors and interferes with TNFα-mediated signaling. Extracellular PGRN is proteolytically processed into granulins by proteases released from immune cells. PGRN exerts anti-inflammatory effects, whereas granulins are pro-inflammatory. The factors coordinating these ambivalent functions remain unclear.

Methods: We investigated the role of Y-box binding protein-1 (YB-1) as a potential candidate for this immune modulating activity. We identified an interaction between YB-1 and PGRN using a yeast-2-hybrid assay and verified the physical interaction by co-immunoprecipitation. Western blotting and gene expression analysis were used to investigate the influence of YB-1/PGRN on TNF-mediated signaling.

Results: Similar to PGRN, we demonstrate that YB-1 interferes with TNFα binding to its receptors in a dose-dependent manner. Using bone marrow-derived macrophages, we show that YB-1 in combination with PGRN inhibits TNFα-mediated signaling, supporting the functionality in vitro. Costimulation of macrophages with TNF, YB-1, and PGRN reduced MAPK activation as well as NFκB. Using YB-1-deficient cells, we show that NFκB activation was reduced after TNFα-stimulation, confirming that YB-1 is essential for NFκB activation. Recombinant YB-1 reconstitutes this effect, increasing NFκB phosphorylation after TNFα stimulation.

Conclusions: Taken together, we show that YB-1 displays immunomodulatory functions by affecting the binding of TNFα to its receptors and influencing TNFα-mediated signaling, thereby enhancing the anti-inflammatory effect of progranulin. The relevance for chronic kidney disease was already demonstrated, as anti-TNFα therapy significantly decreased disease activity. Given that we observe differential acetylated YB-1 bands in patient urine, we are investigating their relevance for disease activity.

Funding: Government Support - Non-U.S.

PUB096

Effect of Novel Phosphate Binder, Ferric Citrate, on Renal Function, Histology, Oxidative Stress, Inflammation and Fibrotic Pathway in Rats with CKD

Wanghui Jing,[1,2] Ane C. Nunes,[1] Mahyar Khazaeli,[1] Nosratola D. Vaziri.[1] *[1]University of California Irvine, Orange, CA; [2]School of Pharmacy, Xi'an Jiaotong University, Xi'an, China.*

Background: CKD commenly result in anemia. Ferric citrate (FC) is a novel phosphate binder which has been shown to increase hemoglobin, serum ferritin, and transferrin saturation. Scince iron overload can accelerate the CKD by promoting by oxidative stress and inflammation, this study was designed to determine the effect of FC administration on the structure and function of kidney in CKD rats.

Methods: Rats were randomized into 5/6 nephrectomized and sham groups. Each group was subdivided into 4% ferric citrate supplemented diet (CTL+FC, CKD+FC) and regular diet (CTL, CKD). After 6 weeks, blood pressue, kidney function, serum phosphorus, hemoglobin, serum iron and renal oxidative, inflammation and fabrosis markers were assessed.

Results: FC administration decreased SBP, BUN, as well as serum phosphate, and raised body weight, serum iron, and Hb. Kidney tissue in CKD rats showed activation of NF-κB, and upregulation of pro-inflammatory, pro-oxidant and pro-fibrotic molecules including MCP-1, iNOS, COX-2, gp91^{phox}, MPO, nitrotyrosine, PAI-1, TGF-β and α-SM actin; reduction in nuclear translocation of Nrf2 and down-regulation of its key target products. FC administration in CKD animals resulted in accumulation of iron in the proximal tubular epithelial cells, and significant attenuation of most molecular markers of oxidative stress, inflammation and fibrosis in renal tissue.

Conclusions: FC administration could improve the renal function in CKD rats, and mitigate CKD-associated upregulation of oxidative, inflammatory, and fibrotic in the remnant kidney. The salutary effect of FC on renal function and structure in CKD rats is presently unknown. However, it might be related to the protective effect of the citrate on proximal tubular epithelial cells.

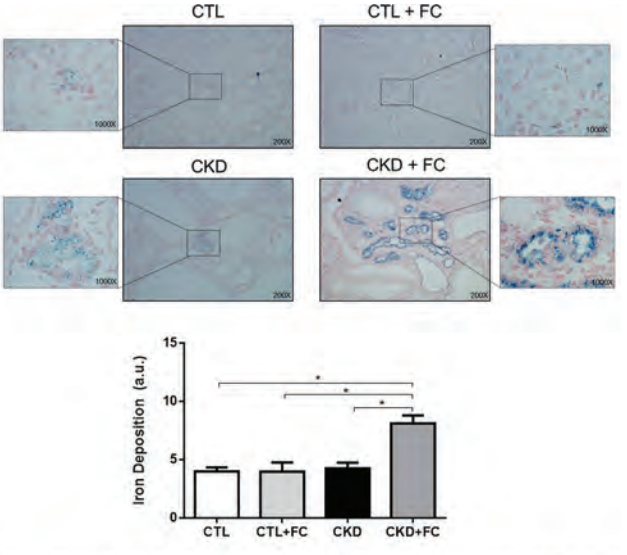


Figure 1. Representative photomicrographs of Prussian Blue stained kidney tissue from CTL (n=5), CTL+FC (n=6), CKD (n=4) and CKD+FC (n=6) treated animals. Data depicting the colon iron deposition in different groups. Data are mean ± SEM. *P<0.05.

PUB097

The Reactive Oxygen Species Production by Erythrocytes, but Not Cell Death, Is Associated with Anemia in Pre-Dialysis CKD Patients

Andrea N. Moreno-Amaral,[3] Gabriela F. Dias,[4] Natalia Borges Bonan,[1] Ana C. Gadotti,[2] Stephany Van der goot,[6] Alessandro A. Halama,[4] Peter Kotanko,[5] Roberto Pecoits-Filho.[3] *[1]PUC-PR, CURITIBA, Brazil; [2]PUCPR, Curitiba, Brazil; [3]Pontificia Universidade Catolica do Parana, Curitiba, Brazil; [4]Pontifícia Universidade Católica do Paraná, Pinhais, Brazil; [5]Renal Research Institute, New York, NY; [6]Pontificia Universidade Católica do Paraná, Curitiba, Brazil.*

Background: Increased oxidative stress is well-documented in uremic patients. Evaluation of redox status in red blood cells (RBC) has been used as a reliable method to evaluate oxidative stress in patients with chronic kidney disease (CKD). Our aim was to study the associations of RBC death (eryptosis), reactive oxygen species (ROS) generation by RBC, and anemia in pre-dialytic patients at various CKD stages.

Methods: We studied 20 CKD patients (8 CKD 3; 12 CKD 4/5). Pulse oximetry was used to determine arterial oxygen saturation. ROS generation and eryptosis were evaluated by flow cytometry using DCFH-DA probe and Annexin-V binding, respectively.

Results: While ROS production was increased in anemic compared to non-anemic patients, no association between eryptosis and anemia was observed. RBC ROS production or eryptosis were not associated to CKD stages or Oximetry (Table 1).

Conclusions: RBC ROS generation is increased in anemic pre-dialysis CKD patients, indicating its possible role in the pathogenesis of renal anemia.

Table 1

Parameters Analyzed	Anemia		CKD Stages				Oximetry		
	<12g/dL (n=10)	>/=12g/dL (n=10)	P	III (n=8)	IV/V (n=8/4)	P	<95 (n=7)	>/=95 (n=13)	P
ROS (MFI)	46.6±5.3	27.5±5	0.018*	35.8±6.4	37.2±5.2	0.866	44.9±6.4	32.2±4.7	0.133
Eryptosis (MFI)	9.8±1.5	6.8±1.4	0.176	8±1.7	8.1±1.3	0.988	10.5±1.6	6.7±1.2	0.083

Mean Fluorescence Intensity (MFI); *non-parametric t-Student statistic

PUB098

Follistatin Protects Against Thapsigargin-Induced Apoptosis in Mesangial Cells

Neel Mehta,[1] Agata Gava,[1] Joan C. Krepinsky.[2] *[1]McMaster University, Hamilton, ON, Canada; [2]McMaster University, St. Joseph's Hospital, Hamilton, ON, Canada.*

Background: In numerous glomerular diseases including diabetic nephropathy, glomerular mesangial cell (MC) apoptosis correlates with progressive glomerulosclerosis and albuminuria. Thapsigargin (TG), an endoplasmic reticulum Ca^{2+}-ATPase inhibitor, causes MC apoptosis through increasing $[Ca^{2+}]_i$ and reactive oxygen species (ROS). We have observed that while promoting MC apoptosis, TG also up-regulates the expression of follistatin (FST). FST is a secreted glycoprotein that neutralizes TGFβ super-family members, primarily activins. Since FST inhibits apoptosis and ROS production in numerous cell types, we determined whether FST is protective against TG-induced apoptosis in MC.

Methods: Studies were conducted on primary mouse MC using standard molecular biology techniques including immunoblotting, immunofluorescence and luciferase assays.

Results: TG caused apoptosis in MC that was characterized by elevated caspase 3 cleavage and caspase 3/7 enzymatic activity. TG-mediated apoptosis post-translationally stabilized and increased the expression of FST. Functionally, FST down-regulation augmented, while FST over-expression and exogenous FST pre-treatment protected against TG-induced apoptosis. FST did not exert its protective effects through mediating $[Ca^{2+}]_i$ flux. However, using ROS scavengers, TG-induced apoptosis was found to be dependent on the presence of ROS. Interestingly, while FST protected against TG-induced ROS production, it had no effect on superoxide production. FST is most potently active against Activin A, which has been shown to induce ROS production in other cell types. However, in MC, TG did not increase Activin A production nor did Activin A induce ROS production or apoptosis. Mechanistically, TG induced Smad3 transcriptional activity which was attenuated by FST and the ALK4/5/7 inhibitor SB431542. These data indicate that the protective effects of FST may be explained by its inhibition of activin B, which is being explored in current studies.

Conclusions: In MC, FST protects against TG-induced apoptosis through inhibiting the production of ROS. This is independent of activin A, but may depend on activin B. Future studies will determine whether FST can be used *in vivo* to protect against the progression of glomerular diseases involving MC apoptosis and ROS-mediated injury.

Funding: Government Support - Non-U.S.

PUB099

Rapamycin Enhances Repressed Autophagy and Attenuates Aggressive Progression in a Rat Model of IgA Nephropathy

Di Liu, Yexin Liu, Zheng Dong, Hong Liu. *The Second Xiangya Hospital, Central South University, Changsha, China.*

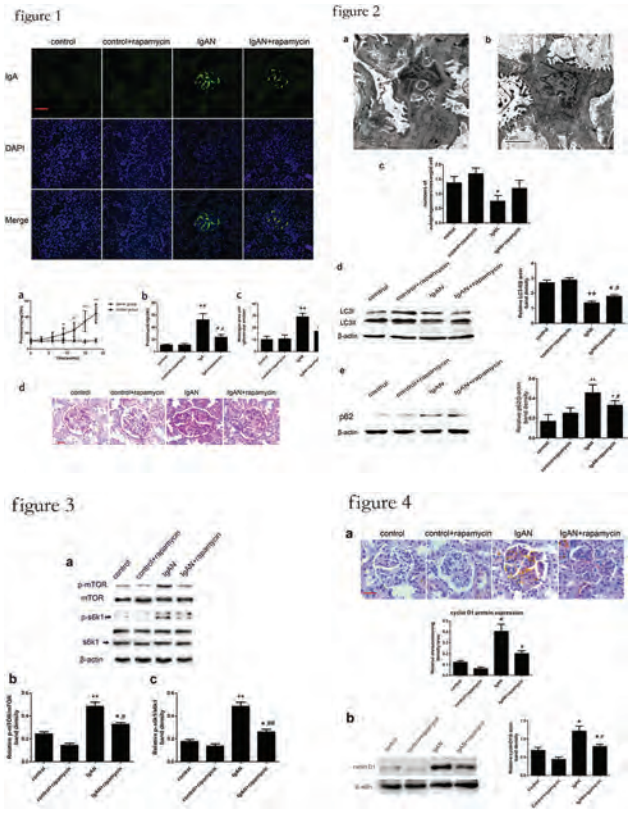
Background: IgA nephropathy (IgAN) has been considered as the most frequent form of primary glomerulonephritis wordwide with a variety of factors involved in the occurrence and development of it. The impact of autophagy in IgAN, however, remains partially unclear. The present study was designed to investigate effects of rapamycin in an IgAN model.

Methods: After establishing an IgAN rat model, SD rats were divided into four groups: control, control+rapamycin, IgAN, IgAN+rapamycin. Proteinuria and the pathological changes and the level of autophagy of kidney were texted. Identify the expression of phosphorylation and total mTOR and s6k1 as well as cyclin D1 in the kidney of rats through Western blot and immunohistochemistry.

Results: We observed a significant reduction in the progression of proteinuria as well as alleviation of pathological lesions in IgAN rats with rapamycin treatment. Besides, autophagy was inhibited while mTOR/S6k1 pathway was activated and expression of cyclin D1 was increased in IgAN. Rapamycin treatment increased autophagy and decreased the expression of cyclin D1.

Conclusions: These results may suggest that mTOR mediated autophagy inhibition may result in mesangial cell proliferation in IgAN. These results may suggest that mTOR mediated autophagy inhibition may result in mesangial cell proliferation in IgAN.

Funding: Government Support - Non-U.S.



PUB100

Cryptotanshinone Reduces Angiotensin II Induced Senescence and Autophagy through STAT3/mTOR Signaling in Human Glomerular Mesangial Cells Shuang Yang, Lining Wang, Dan Sun, Xiuying Wang. *The First Hospital of China Medical University, Shenyang, China.*

Background: Angiotensin II induces premature senescence of human glomerular mesangial cells and activation of STAT3. Cryptotanshinone, an active component isolated from Salvia miltiorrhiza Bunge, is an inhibitor of STAT3. The objective of this study is to investigate effect of cryptotanshinone on senescence in human mesangial cells and its mechanism.

Methods: Human glomerular mesangial cells were stimulated with Ang II,then S3I-201(an inhibitor of STAT3)or cryptotanshinone were added into human glomerular mesangial cells

Results: Angiotensin II increased expression of LC3 II and autophagosome formation, decreased expression of p62. Expression of STAT3/mTOR has changed which was correlated with development of cell senescence and autophagy. We also showed that blockage of STAT3 by S3I-201 or cryptotanshinone abrogated the effects of on cellular senescence, on autophagy, on STAT3/mTOR signaling with Angiotensin II.

Conclusions: Cryptotanshinone reduces angiotensin II induced autophagy and senescence, at least in part, by regulating STAT3/mTOR signaling in human glomerular mesangial cells.

Funding: Government Support - Non-U.S.

PUB101

STAT1 Mediates Cellular Senescence Induced by High Glucose in Human Glomerular Mesangial Cells via Regulation of Autophagy Activity Dan Sun, Lining Wang, Shuang Yang, Xiuying Wang. *The First Hospital of China Medical University, Shenyang, China.*

Background: The signal transducer and activator of transcription 1 (STAT1), which was the first discovered protein in the signal transducers and activators of transcription (STATs), is a latent transcription factor involved in a variety of signal transduction pathways, including cell proliferation, apoptosis, and differentiation. Here, we examined whether the process of senescence would be affected by STAT1 .

Methods: We passaged human mesangial cells (HMC) and induced HMC senescence by high glucose (30mmol/L) after 72h incubation. To explore the mechanism between STAT1 and autophagy that exerts on senescence-associated signal pathway.We inhibited STAT1 by pretreating cell with fludarabine and enhanced autophagy activity with rapamycin to observe the alternation of senescence.

Results: We observed that high glucose induced STAT1 activation, while the activity of autophagy was suppressed and the senescence-associated signal pathway was activated,then senescence expressed. We identify that the expression of p53/p21 pathway was suppressed and senescence was relieved through enhanced autophagy activity, while the senescence expression was relieved by the enhancement activity of autophagy through inhibiting STAT1 by incubation of fludarabine (50umol/L).

Conclusions: STAT1 might mediate cellular senescence induced by high glucose in human glomerular mesangial cells via regulation of autophagy activity.

Funding: Government Support - Non-U.S.

PUB102

Ferroptosis Is Involved in Renal Tubular Cell Death in Diabetic Nephropathy Meiyan Wu,[1] Sukyung Kang,[1] Boyoung Nam,[1] Arum Choi,[1] Tae-Hyun Yoo.[2] *[1]Department of Internal Medicine, College of Medicine, Severance Biomedical Science Institute, Brain Korea 21 PLUS, Yonsei University, Seoul, Republic of Korea; [2]Department of Internal Medicine, College of Medicine, Institute of Kidney Disease Research, Yonsei University, Seoul, Republic of Korea.*

Background: TGF-β1-induced cell death is known to contribute to the pathogenesis of diabetic nephropathy. Ferroptosis, a new atypical form of cell death, is an iron-dependent cell death that is distinct from apoptosis, necroptosis, and autophagy, and results from lipid peroxide accumulation. In this process, glutathione peroxidase 4 (GPX4) and glutamate/cystine antiporter (xCT) are surmised to be principally involved. Recently, ferroptosis has been reported to cause several kidney diseases. However, the impact of ferroptosis on tubular cell death under diabetic conditions has never been elucidated.

Methods: *In vitro*, rat proximal tubular epithelial cells (NRK-52Es) were cultured in DMEM media containing 5.6 mM glucose (normal glucose, NG) or NG + TGF-β1 (10 ng/ml) with or without ferroptosis inhibitors (Ferrostatin-1 and Liproxstatin-1) or iron chelator (Deferoxamine) for 12 hours. *In vivo*, 12 C57BL/6 mice were intraperitoneally injected with saline (Control, C) (N=6) or STZ (50 mg/kg/d) for 5 consecutive days (Diabetes, DM) (N=6), and were sacrificed after 6 weeks. The protein expression of GPX4, xCT, hypoxia-inducible factor (HIF)-1α, heme oxygenase-1 (HO-1), and nuclear factor erythroid 2-related factor 2 (Nrf2) were determined in cultured tubular epithelial cells and the mouse kidneys by western blot analysis. Cell viability and lipid peroxidation (MDA) were also evaluated in cultured tubular cells.

Results: Compared to NG cells, the protein expression of xCT was significantly decreased, while HIF-1α, HO-1, and Nrf2 protein expression were significantly increased in TGF-β1-stimulated renal tubular epithelial cells. In contrast, GPX4 expression was not changed in renal tubular cells exposed to TGF-β1. Moreover, MDA levels were significantly increased along with significantly decreased cell viability in TGF-β1-stimulated cells. These changes in cultured tubular cells exposed to TGF-β1 were significantly ameliorated by ferroptosis inhibitors or iron chelator treatment. A significant decrease in xCT protein expression was also observed in the kidney of DM mice compared to the C kidney.

Conclusions: These results suggest that ferroptosis is involved in renal tubular cell death under diabetic conditions and that ferroptosis inhibitor or iron chelator can be a promising therapeutic agent in patients with diabetic nephropathy.

PUB103

HIV Induces Ferroptosis in Human Podocytes Kamesh R. Ayasolla,[1] Vinod Kumar,[4] Abheepsa Mishra,[2] Ashwani Malhotra,[5] Pravin C. Singhal.[3] *[1]Feinstein Institute for Medical Research, Great Neck, NY; [2]Feinstein Institute of Medical Research, Northwell Health, MANHASSET, NY; [3]North Shore LIJ Health System, Great Neck, NY; [4]Immunolgy and Inflammation, Fienstine Institute for Medical Research, New York, NY; [5]Immunolgy and Inflammation, Feinstein Inst.Med research and NSLIJ, Manhasset, NY.*

Background: Loss of critical number of podocytes promotes the development of focal development of glomerulosclerosis. Occurrence of cell death in adverse milieus has been repoted to incur by multiple mechanisms including apoptosis, pyroptosis, ferroptosis and necroptosis. Occurrence of podocyte apoptosis and pyroptosis has been reported in HIV-associated nephropathy; however, the role of ferroptosis in HIV-induced podocyte injury has not been investigated to date. Ferroptosis is a programmed caspase independent cell death initiated by cellular non-chelated iron and driven by altered lipid environment (reduced glutathione and lipid alterations) and condensed mitochondrial structures. We investigated whether lipid alteration mediated ferroptosis contributes to the loss of podocytes in HIV-associated nephropathy (HIVAN). To elucidate this aspect, we studied the role of sphingomyelinase (SMase) in the induction of podocyte ferroptosis in HIV milieu, in vivo as well as in vitro.

Methods: SMase activities of renal tissues of control (FVB/N, n=5) and HIVAN (Tg26, n=6) mice and vector (V/HP) - and HIV-transduced human podocytes (HIV/HPs) were determined. To examine the effect of sphingomyelinase inhibitor (GW48), V/HPs and HIV/HPs were incubated in media containing either buffer or GW48 for 48 hours. At the end of experimental period, cells were evaluated for SMase activity and lipid peroxidation. V/HPs and HIV/HPs were evaluated for cell death with or without blockers of ferroptosis, caspase-1, and caspase-3 at different time periods. Additionally, role of PKC-ζ and NF-kB on SMase-induced HIV/HPs' downstream signaling was evaluated.

Results: Renal tissues of Tg26 mice and HIV/HPs displayed several fold increase in SMase activity. HIV/HP-induced SMase activity could be effectively blocked by GW48. Additionally, HIV/HPs displayed increase in lipid peroxidation that could be inhibited by GW48. A vast numbers of HIV/HPs succumbed to death during 96 hours. The relative cell survival using blockers of ferroptosis, Caspase-1, and Caspase 3 were 35%, 45%, and

20% respectively. HIV activated PKC-ζ and NF-kB and inhibitors of PKC-ζ and NF-kB prevented HIV induced ferroptotic cell death.

Conclusions: HIV induces ferroptosis in podocytes through the activation SMase activity and associated downstream signaling.

Funding: NIDDK Support

PUB104

Long Non-Coding RNA Expression Profile in Adult Renal Stem/Progenitor Cells: Role in Cell Proliferation and Differentiation Simona Simone,[1] Giuseppe De Palma,[1] Claudia Curci,[1] Alessandra Stasi,[1] Monica Rutigliano,[1] G. Lucarelli,[1] Paola Laghetti,[1] Rossana Franzin,[1] Michele Battaglia,[1] Giuseppe Grandaliano,[2] Loreto Gesualdo,[1] Giovanni B. Pertosa,[1] Fabio Sallustio.[1] *[1]University of Bari, Bari, Italy; [2]University of Foggia, Foggia, Italy*.

Background: Adult renal stem/progenitor cells (ARPC) are a cell population identified in the kidney potentially useful for the renal damage treatment. However, to fully exploit such potential it is necessary to study the conditions that regulate their behavior. Recently, long non-coding RNAs (lncRNAs) have emerged as a class of regulators of gene expression. Several lncRNAs regulate specific tissue stem cell renewal or differentiation, while others promote a differentiation program. Their functions are facilitated by protein partners that impair the ability to activate or repress gene expression or posttranscriptionally regulate other RNAs. The aim of this study was to determine the lncRNA expression profile in ARPC.

Methods: lncRNA expression profile was obtained by ARPC and renal proximal tubule epithelial cells (RPTEC) by using Agilent microarrays. Data were analyzed with GeneSpring and R software. lncRNA microarray data were validated by real time-PCR.

Results: We compared lncRNA expression in ARPC and RPTEC: 588 lncRNAs were differently modulated in ARPC compared to RPTEC (fold change >2; Q value <0.05). In particular, we found 51 upregulated lncRNAs and 53 downregulated lncRNAs. Classification analysis showed that most lncRNAs expressed in ARPC are involved in Wnt and BMP signaling pathways, activation of the immune cells and G protein-mediated signaling: processes involved in the response to cellular damage. Over-representation test demonstrated their involvement in the calcium signal transduction, cell cycle and protein glycosylation processes ($p < 0.005$). Among differentially modulated lncRNAs, LINC00263 was the most down-regulated in ARPC compared to RPTEC (fold change <3). LINC00263 is highly expressed in cerebral tissue and is involved in the differentiation inhibition and processes regulating maintenance of cytoskeleton structure, cellular adhesion, and membrane signaling. It may therefore be involved in maintaining ARPC in an undifferentiated state.

Conclusions: In conclusion, our results suggest that lncRNAs could play a role in response to cell damage and in ARPC differentiation and could represent a new therapeutic target in renal damage.

Funding: Government Support - Non-U.S.

PUB105

A Systems Biology Study of Pyroptosis Gene Signatures in HIV-Associated Nephropathy Kamesh R. Ayasolla,[1] Tânia Barata,[4] Abheepsa Mishra,[2] Ashwani Malhotra,[5] Pravin C. Singhal.[3] *[1]Feinstein Institute for Medical Research, Great Neck, NY; [2]Feinstein Institute of Medical Research, Northwell Health, MANHASSET, NY; [3]North Shore LIJ Health System, Great Neck, NY; [4]CNC/UC-Biotech, Cantanhede, Portugal; [5]Feinstein Inst.Med research and NSLIJ, Manhasset, NY*.

Background: Loss of podocytes play an important role in HIV-Associated Nephropathy (HIVAN). We have recently reported that HIV induces pyroptosis in podocytes both *in vitro* and *in vivo* studies (Am J Pathol 2016, 186). We carried out systems biology approach to analyze genes associated with pyroptosis genes which overlap in HIVAN.

Methods: We used a curated set of 62 genes which make up the NOD-like receptor signaling pathway (KEGG) database. Previously published expression data sets of HIVAN were obtained from gene chip arrays (GEO). We used GSEA software parameters to achieve following variables : 1. Ranking the genes according to those differential expressed values, (ii) identifying the rank positions, (iii) calculate an enrichment score (ES), and (iv) estimating the statistical significance. The pyroptosis activation signature genes were given as input to the UniHI database. To predict the upstream regulators, transcription factors (TFs) and kinases, of genes up-regulated in pyroptosis, we used the Expression2Kinases (X2K) software, Kinase Enrichment Analysis (KEA) software and the Fisher's exact test (to score the kinases).

Results: Gene Set Enrichment analysis showed activation of pyroptosis gene signature in HIVAN. Enrichment score for the pyroptosis gene set was positive in the two independent microarray studies, indicating an activation of the pyroptosis genes in both mouse models (Tg26 and Vpr transgenic) of HIVAN. Notably, genes activated in pyroptosis formed a densely connected network (UniHi); for example association with MAPK, Toll-like receptor signaling pathway, and apoptosis. Network analyses indicated regulation of pyroptosis genes by kinases with a known role in the development of HIVAN. Using X2K, we could identify upstream regulators of pyroptosis genes, which played an important role in pyroptosis.

Conclusions: We identified transcription factors (TFs) that were connected through a network of 'intermediate proteins' by using experimentally reported protein–protein interaction network related to pyroptosis in HIVAN. There are kinases (MAPK1, MAPK3, MAPK8, HIPK2, TGFBR1 and MAPK14) in common with the previously reported top-ten kinases, most enriched in HIVAN.

Funding: NIDDK Support

PUB106

Inhibition of RON Receptor Tyrosine Kinase Attenuated Epithelial Mesenchymal Transition and Fibrosis in Human Proximal Tubular Epithelial Cells Jung Sun Park,[3] Hoon In Choi,[4] Eun Hui Bae,[1] Seong Kwon Ma,[2] Soo Wan Kim.[2] *[1]Chonnam National University Hospital, Gwangju, Republic of Korea; [2]Chonnam National University Medical School, Gwangju, Republic of Korea; [3]Chonnam National University, GwangJu, Republic of Korea; [4]Chonnam National University, GwangJu, Republic of Korea*.

Background: Receptor tyrosine kinases plays an important role in the pathogenic processes of renal fibrosis. However, pathophysiological roles of recepteur d'origine nantais (RON), in kidney disease have not yet been identified. We investigated whether the activation of the RON and sequence-specific small interfering RNA (siRNA) induced suppression of the RON expression could regulate renal fibrosis, and examined its the underlying molecular mechanisms.

Methods: Stable cell lines for RON overexpression and the transfected cells of siRNA for RON inhibition were developed to understand the renal fibrosis and molecular mechanisms by RON in human renal proximal tubular epithelial (HK-2) cells. The protein expression of epithelial-mesenchymal transition (EMT)-related proteins, N-cadherin, E-cadherin, vimentin and fibrosis-related proteins TGF-β, α-smooth muscle actin (αSMA), fibronectin as well as Smad family and MAPK signal pathway was determined by semiquantitative immunoblotting. Staining of receptor tyrosine kinase family was evaluated using confocal laser microscopy.

Results: RON overexpression increased protein expression of EMT- and fibrosis-related proteins such as N-cadherin, E-cadherin, vimentin, TGF-β, αSMA, and fibronectin in HK-2 cells. Moreover, overexpression of RON increased phophorylation of Smad2/3 and smad-4, and Erk1/2, p38, and Jnk MAPK pathways. In contrast, RON inhibition by siRNA attenuated expression of EMT- and fibrosis-related proteins and decreased phosphorylation of Smad family and MAPK pathway. In addition, the siRNA silencing of RON attenuated expression of IGFR, VEGFR, and PDGFR.

Conclusions: Inhibition of RON may exert anti-fibrotic effect by suppression of EMT by controlling Smad and MAPK signal pathways in HK-2 cells.

Funding: Government Support - Non-U.S.

PUB107

Small Interfering RNA Targeting of Recepteur d'Origine Nantais Attenuates Platelet-Derived Growth Factors Receptor (PDGFR)-Mediated Renal Fibrosis in Human Proximal Tubular Epithelial Cells Jung Sun Park,[4] Hoon In Choi,[1] Eun Hui Bae,[2] Seong Kwon Ma,[3] Soo Wan Kim.[3] *[1]Chonnam National University, GwangJu, Republic of Korea; [2]Chonnam National University Hospital, Gwangju, Republic of Korea; [3]Chonnam National University Medical School, Gwangju, Republic of Korea; [4]Chonnam National University, GwangJu, Republic of Korea*.

Background: PDGFR-α and β are continuously expressed in various kidney cells and PDGFR signaling is associated with inflammatory responses and fibrosis leading to acute kidney disease and chronic kidney disease. This study examined whether the sequence-specific small interfering RNA (siRNA) suppression of the RON expression could attenuate PDGFR- mediated renal fibrosis, and investigated the involved molecular mechanisms.

Methods: In vivo experiments, mouse UUO models were subjected to unilateral ureteral obstruction (UUO) for 7 or 14 days. For the in vitro study, human proximal tubular (HK2) cells were Sequence-specific RON siRNA were transiently transfected in HK-2 cells. The protein and mRNA expression of RON, PDGFR, Collagen I, Collagen IV, CTGF, JAK/STAT, PI3K/AKT, and MAPK was determined by semiquantitative immunoblotting and RT-PCR. Staining of PDGFR a and b and RON was evaluated using confocal laser microscopy.

Results: Protein expression of PDGFR was increased in the kidney of UUO compared with control kidney. Sequence-specific siRNA effectively suppressed the PDGFR α and β expression at both the mRNA and protein levels. Silencing of the RON expression significantly inhibited fibrosis-related proteins such as collagen I, collagen IV, and CTGF. In addition, phosphorylation of JAK/STAT, PI3K/AKT, and MAPK signal pathways were inhibited by transfection of RON siRNA.

Conclusions: Inhibition of RON may exert anti-fibrotic effect by suppression of PDGFR by controlling JAK/STAT, PI3K/AKT, and MAPK signal pathways in HK-2 cells.

Funding: Government Support - Non-U.S.

PUB108

CKD in Patients Long-Term after Liver Transplantation Marcin Adamczak, Damian Gojowy, Henryk Karkoszka, Piotr Kubis, Magdalena Gorecka, Andrzej Wiecek. *Department of Nephrology, Transplantation and Internal Medicine, Medical University of Silesia, Katowice, Poland*.

Background: Liver transplantation (LTx) is the only effective method of treating the end-stage failure of this organ. Coexisting chronic kidney disease (CKD) may worsen

the prognosis of these patients. The aim of this retrospective, single center, observational study was to determine the prevalence and predisposing factors of CKD in patients long-term after LTx.

Methods: Medical records of 118 patients after LTx (age 47.5±12.2 years) who completed 24 months follow-up were studied. Patients were divided into groups depending on the etiology of end-stage liver disease and on immunosuppressive therapy used after transplantation. CKD was diagnosed in patients with eGFR below than 60 mL/min/1.73m^2 or with proteinuria at least for 3 months. Results are presented as means with standard deviation.

Results: CKD has been diagnosed in 33% patients in 12. month after LTx and in 34% patients in 24. month after LTx. One, 12 and 24 months after LTx eGFR were: 79.9±34.0mL/min; 79.5±31.4mL/min; 78.0±31.2 [mL/min/kg/1.73m^2], respectively. Prevalence of CKD was lower in patients that were transplanted due to autoimmune disease (10.8%) compared to viral (41.9%) and alcohol abuse (42.9%) etiology (chi-square: p<0.05; post hoc analyses: autoimmune vs viral; p=0.02; autoimmune vs alcohol abuse; p=0.02). A significant negative correlation was found between blood concentration of tacrolimus and eGFR in 24. month after LTx (p<0.05).

Conclusions: 1. The prevalence of chronic kidney disease in patients after liver transplantation seems to be higher than in the general population. 2. Patients with autoimmune etiology of the liver disease are characterized by better renal function. 3. Treatment with calcineurin inhibitors may have an adverse influence on renal function.

Funding: Government Support - Non-U.S.

PUB109

Urinary Phosphorous Excretion and Kidney Disease Progression – A Retrospective Cohort Study David Levy,[1] Matthew K. Abramowitz,[2] Rebeca D. Monk,[1] David A. Bushinsky,[1] Katherine Grzesik,[1] Emily Walters,[1] Matthew Taylor,[1] Susan Messing,[1] Wei Chen.[1] *[1]University of Rochester School of Medicine, Rochester, NY; [2]Albert Einstein College of Medicine, New York, NY.*

Background: High urinary phosphate excretion may lead to tubular damage and has been shown to be associated with progression of CKD. However, there is limited evidence to support this causal relationship. Thus, the goal of the study is to test the hypothesis that high urinary phosphate excretion per GFR predicts kidney disease progression.

Methods: In this retrospective cohort study, we performed a chart review of 143 adult patients who had 24 hour urine supersaturation studies done as a part of the work up for nephrolithiasis between 3/1/2011 and 2/28/2014. We estimated urinary phosphate excretion per GFR by dividing 24 hour urinary phosphate excretion by 24 hour urine creatinine clearance (phos/CrCl). We followed these patients for 2 years to monitor kidney disease progression, which was defined as the rate of eGFR decrease (ΔeGFR per year). We used linear regression to examine the association of urinary phos/CrCl with ΔeGFR per year, while adjusting for participant demographics, diabetes, hypertension and coronary artery disease (CAD) status.

Results: The mean age was 59 ±11years (47% female, 7% black). At baseline, the mean eGFR was 76±24 ml/min/1.73m^2, the median urinary phosphate excretion was 935 (IQR 699, 1207) mg/day and urinary phos/CrCl was 8.9± 3.6 mg/day per ml/min. The mean follow up duration was 24.6±1.8 months and the eGFR declined by 1.5±5.1 ml/min/1.73m^2 per year on average. Participants with higher urinary phos/CrCl were more likely to be older, male, hypertensive, have eGFR<60 ml/min/1.73m^2 and CAD at baseline compared to those with lower urinary phos/CrCl. In the fully adjusted model, with every 1 unit increase in phos/CrCl, the eGFR increased by 0.18 ml/min/1.73m^2 per year on average but this was not statistically significant (CI -0.09, 0.45, p=0.19).

Conclusions: Our findings did not support the hypothesis that urinary phosphate excretion per GFR is an independent predictor for kidney disease progression. The study was limited by small sample size, low severity of kidney disease and short duration of follow up.

PUB110

Abstract Withdrawn

PUB111

Systemic Redox Imbalance in ADPKD and IGAN Terje Apeland,[1] Ambreen Tariq,[1] Grete Jonsson,[1] Audun Slettan,[2] Chathuri P. Karunarathna weeraman,[2] Hans-Peter Marti,[3] Mohammad A. Mansoor.[2] *[1]Stavanger University Hospital, Stavanger, Norway; [2]University of Agder, Kristiansand, Norway; [3]University of Bergen, Bergen, Norway.*

Background: Oxidative stress and redox dysregulation are evident already at an early stage of chronic kidney disease (CKD). We wanted to study some redox biomarkers in autosomal dominant polycystic kidney disease (ADPKD) and IgA nephropathy (IGAN) in CKD stages 1–4.

Methods: Case-control study with two patient groups: ADPKD (n=54) and IGAN (n=58); compared to controls (n=86). Their male/female ratio were 18/36, 49/9 and 47/39, respectively (p<0.0001). Their mean age were 49.9, 49.0 and 46.1 yrs, respectively (p=0.14). Their eGFR were 61, 69 and 91 ml/min, respectively (p<0.0001). AOPP (advanced oxidation protein products, μmol/g protein), MDA (malone dialdehyde, μmol/L) and redox species of the major plasma aminothiols were analysed by HPLC. The Redox ratios were calculated as the ratio of free reduced /free oxidized (not protein bound) aminothiols (μM/μM). Hcy, i.e. homocysteine; CG, i.e. cysteinylglycine, Cys i.e. cysteine. DNA was analysed for single nucleotide polymorphisms (SNP) in ten redox related enzymes.

Results: The IGAN group had higher levels of the oxidation products AOPP and MDA (Table). Patients had lower Hcy and Cys Redox ratios than controls and this was most pronounced in the IGAN group (Table). In the patient group, there were inverse relationship between Cys redox ratio and both AOPP and MDA concentrations (simple regression, p= 0.005 and p= 0.04, respectively). The frequency of SNP *rs4880* of mitochondrial superoxide dismutase (SOD2) was significantly elevated in IGAN patients (data not shown).

Conclusions: Patients with ADPKD and IGAN had evidence of oxidative stress, and this was most pronounced in IGAN group – despite similar eGFR. Cys Redox ratio may be regarded as a measure of oxidant generation.

Funding: Clinical Revenue Support

Redox biomarkers

	ADPKD	IGAN	Controls	P
Hcy Redox ratio	0.38 ±0.44 #∞	0.16 ±0.44 †∞	0.62 ±0.67	<0.0001
CG Redox ratio	0.27 ±0.10	0.30 ±0.13	0.31 ±0.11	0.10
Cys Redox ratio	0.10 ±0.04 #∞	0.08 ±0.03 †ᵇ∞	0.12 ±0.05	<0.0001
p-AOPP	1.14 ±0.36	1.38 ±0.43 ᵃ§∞	1.11 ±0.39	0.0007
p-MDA	0.64 ±0.18	0.69 ±0.15 §	0.62 ±0.16	0.021

Patient group Vs. Controls: † p<0.0001; * p≤0.001; # p<0.01; § p≤0.017. IGAN Vs ADPKD: a p=0.003; b p=0.011. ∞ i.e. remained significant after correcting for age and gender.

PUB112

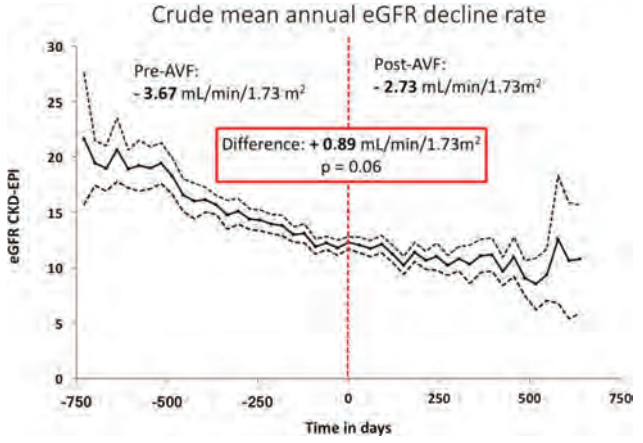
Impact of Arteriovenous Fistula Creation on Estimated Glomerular Filtration Rate Decline in Pre-Dialysis Patients Valerie Benard, Maude Pichette, Jean-Philippe Lafrance, Vincent Pichette, Naoual Elftouh, Louis-Philippe Laurin, Annie-Claire Nadeau-Fredette. *Hopital Maisonneuve-Rosemont, Montreal, QC, Canada.*

Background: Arteriovenous fistula (AVF) is the vascular access of choice for hemodialysis. Recent evidence suggests that AVF creation may slow estimated glomerular filtration rate (eGFR) decline. The study objective was to assess the impact of the AVF creation on eGFR decline, after controlling for key confounding factors.

Methods: This retrospective cohort study included adult patients followed in a single-center pre-dialysis clinic between 1999 and 2017. Patients with a functional AVF for a minimum of six months were followed up to two years pre- and post-AVF creation. Patients with other vascular access, renal transplant and follow-up time exceeding two years without initiation of dialysis were excluded. Estimated GFR trajectory was reported using linear mixed models adjusted for demographic characteristics, comorbidities and medication.

Results: A total of 110 patients were studied: 68.0 (60.0-74.6) years; 48% female; 86.4% Caucasians; 59.6% with diabetes. The median eGFR at time of AVF creation was 12.4 (11.0-13.7) mL/min/1.73m^2. The annual eGFR decline tended to be lower after AVF creation (-3.65 vs. -2.73 mL/min/1.73m^2; p=0.06) (Figure 1). In adjusted analysis, the predicted eGFR was higher after AVF creation compared to before (β 0.93, 95% CI 0.55-1.31, p<0.001) when taking into account the monthly adjusted decline (-0.36 mL/min/1.73m^2). There was also a significant interaction between time and AVF creation such that eGFR decline was attenuated more each month after AVF creation (β 0.17, 95% CI 0.12-0.21, p<0.001).

Conclusions: AVF creation was associated with a time-dependent reduction of eGFR decline in pre-dialysis patients, after adjustment for potential confounders. Further prospective studies should evaluate AVF as a potential strategy to prevent progression of chronic kidney disease.



PUB113

An Endogenous Na Pump Inhibitor, Marinobufagenin (MBG), Is a Marker of CKD Severity Kristen L. Nowak,[3] Michel Chonchol,[3] Mikaela R. Malaczewski,[3] Heather Farmer-Bailey,[3] Wen Wei,[2] Christopher H. Morrell,[1] Alexei Y. Bagrov,[2] Olga Fedorova.[2] *[1]Loyola University Maryland, Baltimore, MD; [2]National Institute on Aging, Baltimore, MD; [3]University of Colorado Anschutz Medical Center, Aurora, CO.*

Background: High levels of an endogenous steroidal Na pump inhibitor MBG have been reported in CKD. MBG is a pro-hypertensive, pro-fibrotic, and implicated in cardiovascular diseases. We hypothesized that higher circulating MBG levels are associated with vascular dysfunction and relate to CKD severity.

Methods: Plasma MBG (competitive immunoassay), alkaline phosphatase (ALP) and systolic blood pressure (SBP) were measured in 11 patients with stage 3/4 CKD (9M/2F; 63±11 yrs), 8 chronic hemodialysis patients (7M/1F; 59±11 yrs), and 10 healthy controls (6M/4F; 45±17 yrs). Brachial artery flow-mediated dilation (FMD_{BA}), aortic pulse-wave velocity (aPWV), carotid intimal medial thickness (cIMT), and carotid/peripheral SBP were assessed in stage 3/4 CKD patients and controls (Table).

Results: Plasma MBG levels increased in patients with stage 3/4 CKD and in hemodialysis compared to controls (Table). Plasma MBG correlated positively with carotid and peripheral SBP, aPWV, cIMT, and ALP and negatively with FMD_{BA}. After adjustment, plasma MBG remained significantly associated with higher ALP and SBP.

Conclusions: Elevated plasma MBG in CKD and dialysis patients is associated with higher ALP, a marker of a tissue destruction and fibrosis, and with progressive kidney function decline. As a pro-hypertensive and pro-fibrotic factor, MBG may independently contribute to cardiovascular risk, be useful as a marker of severity of CKD, and represent a CKD therapeutic target.

Funding: Other NIH Support - Intramural Research Program, NIA, Private Foundation Support

Clinical parameters in control, CKD, and dialysis (DIAL) patients

Variable	Control (n=10)	3/4 CKD (n=11)	DIAL (n=8)
pMBG (nmol/L)	0.50 ± 0.18	0.79 ± 0.19 *	1.27 ± 0.46 ** ##
ALP (IU/L)	47.7 ± 13.9	81.6 ± 16.9 **	90.0 ± 26.4 **
Peripheral SBP (mmHg)	121 ± 10	128 ± 16	-
eGFR (ml/min/1.73m^2)	95.4 ± 15.0	36.8 ± 9.3 ††	-
FMDBA (%)	6.94 ± 4.4	3.44 ± 2.37 †	-
aPWV (m/s)	6.93 ± 1.74	10.83 ± 3.47 ††	-
cIMT (mm)	0.50 ± 0.08	0.80 ± 0.26 ††	-
Carotid SBP (mmHg)	115 ± 19	134 ± 18 †	-

Values are mean ± SD. *P<0.05, **P<0.01 vs. control, #P<0.05, ##P<0.01 vs. III/IV CKD by 1-way ANOVA followed by Newman-Keuls test; †P<0.05, ††P<0.01 vs. III/IV CKD by t-test.

PUB114

The Effect of the Complement C3a on the Podocyte Epithelial Mesenchymal Transition and Its Mechanism with Adriamycin Nephropathy in Mice Yi Chen,[1] Jianxin Wan,[2] Jiong Cui.[2] *[1]Department of Nephrology, The First Affiliated Hospital of Fujian Medical University, FuZhou, China; [2]the First Affiliated Hospital of Fujian Medical University, FuZhou, China.*

Background: Podocyte EMT is the early reversible process of podocyte damage reaction. Podocyte have perfect C3a receptors, C3a can lead to podocyte damage, however there has been scarce research on the relationship between C3a and Podocyte EMT. we study the relationship between C3a and podocyte EMT in adriamycin nephropathy at mice.

Methods: 30 male BALB/c mice were randomized into control group, ariamycin nephrpathy group, ariamycin +3mg/kg C3a receptor antagonist (SB290157), ariamycin+10mg/kg SB290157, ariamycin +30mg/kg SB290157. On days 7, 14 and 21 after the intervene, 24-urine was collected to analyze the urine proteins. The renal tissues were obtained on 21 days to observe the podocyte using electron microscopy; the deposition of C3 on the podocyte were examined by double immunohistochemistry ;the expression of nephrin, podocin, α-SMA, FSP-1, ILK, snail were measured by immunohistochemistry, quantification of nephrin, α-SMA, snail protein was carried out by western blot.

Results: Compared with control group, in ADR group, the diffuse effacement of podocyte foot process was observed, the urine protein increased, the deposition of C3 on podocyte was increase, α-SMA, FSP-1, ILK, Snail, α-actinin-4 increased and nephrin, podocin significantly reduce, the α-SMA, snail proteins expression were increased and the nephrin podocin exprsssion reduced (P<0.05).10mg/kg SB290157 can relieve the injure of podocyte foot process and reduce 24-h urinary protein, the deposition of C3 and the expression of α-SMA, FSP-1, ILK, Snail and α-actinin-4 of podocyte and increase the expression of nephrin and podocin (P<0.05).

Conclusions: 1. There is the deposition of C3 on the podocyte in adriamycin nephropathy at mice, SB290157 can suppress the process of podocyte epithelial-mesenchymal transition in adriamycin nephropathy at mice, which indicate complement C3a can induce podocyte EMT in vivo. 2. The expression of ILK and snail were increased in adriamycin nephropathy at mice and SB290157 can reduce its expression, which indicate the important role of the ILK signing pathway in the process of complement C3a induce podocyte EMT.

Funding: Government Support - Non-U.S.

PUB115

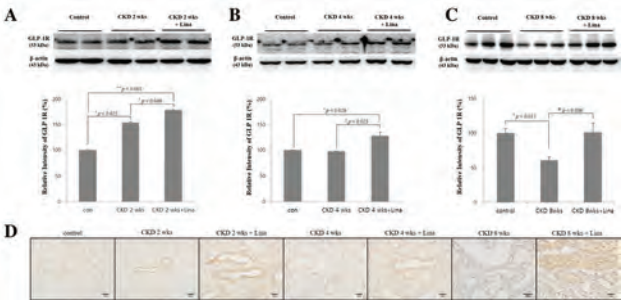
Proximal Tubular GLP-1 Receptor Activity Is Increased in CKD Rat with Myocardial Infarction Which Is Enhanced by Linagliptin Soon Kil Kwon, Hye-Young Kim, Sun Moon Kim. *Chungbuk National University Hospital, Cheongju, Republic of Korea.*

Background: Chronic kidney disease (CKD) is an important risk of ischemic heart disease. Glucagon like peptidase-1 (GLP-1) is an incretin hormone that enhances insulin secretion and GLP-1 agonist is used for glycemic control in patient with type 2 diabetes. Renal GLP-1 activity is increased in the chronic kidney disease, also GLP-1Receptor (GLP-1R) activation is related with vascular protection. We investigated difference of renal GLP-1 activity in the CKD rat with ischemic reperfusion and MI model and the change of GLP-1 receptor activity after DPP-4 inhibitor.

Methods: Sprague Dawley rat was used for CKD model with 5 each group with 5/6 nephrectomy and shame operation. For myocardial ischemia, left anterior descending coronary artery was ligated 2 weeks after 5/6 nephrectomy. 30 Minutes after ligation, we released ligated vessel for reperfusion and kept ligation for MI. CKD and MI rat were treated with oral linagliptin, renal cortical and myocardial GLP-1R was measured via IHC and Western blot (WB).

Results: Renal cortical GLP-1R activity was increased 2 wks after 5/6 nephrectomy; however, it decreased to control levels 4 wks and 8 wks after surgery. Linagliptin treatment enhanced GLP-1R expression in the renal cortex (Fig). Immunohistochemistry findings were similar with WB. Peak intensity was noted 2 weeks later, then decreased after 4 wks and 8 wks after surgery. GLP-1R in CKD with MI and CKD with ischemic reperfusion were significantly increased. WB of GLP-1R was increased in the ischemic reperfusion rats, but decreased in CKD-MI model. However, it was increased in infarcted area after linagliptin. The 5/6 nephrectomy with MI reperfusion lead to dephosporylation Akt, ERK1/2 and decreased Bcl-2, whereas linagliptin treatment reversd.

Conclusions: Expression of GLP-1R in kidney has a role in renal disease progression and GLP-1R activity may provide reno-protective effects independent of its hypoglycemic effects. Linagliptin can increase renal GLP-1R in CKD with MI rat model.



Expression of GLP-1R in the CKD rat.

PUB116

Association between Serum Na-Cl Level and Renal Function Decline in CKD Yuichi Maruta,[1,4] Takeshi Hasegawa,[1,5] Hiroki Nishiwaki,[1] Fumihiko Koiwa,[1] Enyu Imai,[2] Akira Hishida.[3] *[1]Division of Nephrology, Department of Medicine, Showa University Fujigaoka Hospital, Yokohama, Japan; [2]Nakayamadera Imai Clinic, Takarazuka, Japan; [3]Yaizu City Hospital, Yaizu, Japan; [4]Department of Medicine, Showa University Koto Toyosu Hospital, Tokyo, Japan; [5]Office for Promoting Medical Research, Showa University, Tokyo, Japan.*

Background: Metabolic acidosis, which reduces the serum bicarbonate level, contributes to the progression of chronic kidney disease (CKD). Total carbon dioxide (TCO_2) has spread as the direct and standard marker for the metabolic acidosis, but not popular in Japan. The difference between serum sodium and chloride (Na-Cl) may theoretically, predict serum bicarbonate levels. Therefore, the aim of our study was to evaluate Na-Cl level as a risk factor for a decline in renal function among patient in the Chronic Kidney Disease Japan Cohort (CKD-JAC) study.

Methods: The association between low Na-Cl concentration (<34 mmol/L) and renal function decline was evaluated among 1515 patients with a CKD stage G3a-4. Patients were free from malignancy and hypoalbuminemia at baseline. Predictive variables were identified using Cox regression analysis, with corresponding hazard ratios (HR) estimated after adjusting for the following covariates: age, sex, diabetes mellitus (DM), DM-associated nephropathy, cardiovascular disease, use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor antagonists (ARBs), cigarette smoking, body mass index, serum albumin, systolic blood pressure, urine albumin/creatinine ratio, and CKD stage. The primary endpoint was defined as a composite of initiation of any renal replacement therapy or a significant decline in eGFR (mL/min/1.73 m^2/year) from baseline. In addition, to assess which patients are more susceptible to Na-Cl, two of subgroup analyses were performed according to the CKD stages and hemoglobin concentration.

Results: A decline in renal function was identified in 289 patients. The risk for decline was higher among patients with a low serum Na-Cl level (HR, 1.428, adjusted for covariates). Subgroup analysis identified the effect of a low Na-Cl level to be stronger among patients with CKD stage G4 and those with anemia.

Conclusions: Na-Cl is easy to calculate and is an independent predictor of CKD progression, especially among patients with CKD stage G4 and those with anemia.

PUB117

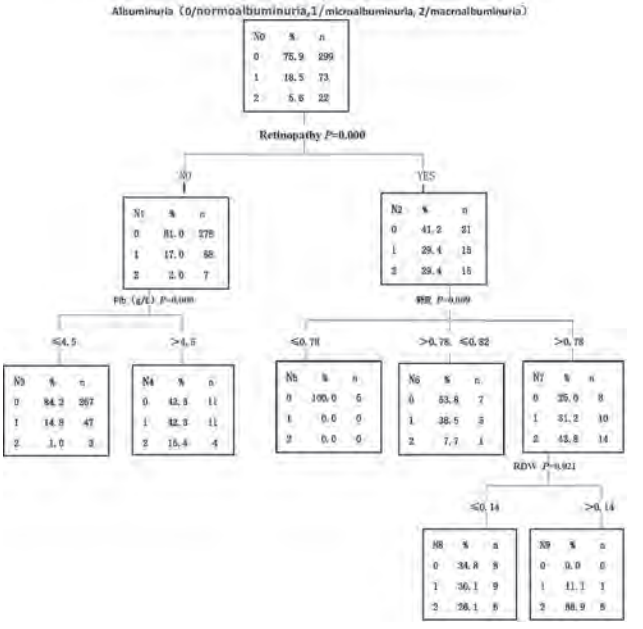
Classification Tree Model Analysis on Related Factors of Different Stages of Kidney in Type 1 Diabetic Patients Wenbo Zhao,[2] Hui-qun Li,[1] Lin Sun,[2] Cong Sun,[2] Wenhao Yang.[2] *[1]The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [2]the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.*

Background: To analyze the related factors of microalbuminuria and macroalbuminuria In type 1 diabetes mellitus (DM) by the classification tree model, and to screen the high risk population of Diabetic Kidney Disease.

Methods: A total of 394 patients with type 1 diabetes were enrolled in our hospital from 2008 to 2015. According to glomerular filtration rates and urine albumin quantification, the patients were divided into type 1 diabetes group (299 cases), microalbuminuria group (73 cases) and macroalbuminuria group (22 cases). The classification tree model was used to analyze the related factors to the different stages of proteinuria, and the high risk population was screened by node gain analysis.

Results: Four important explanatory variables were screened out by the classification tree model from the 23 candidate variables related to early renal damage, including retinopathy, fibrinogen waist-hip ratio (WHR), red blood cell distribution width (RDW). Retinopathy was an important factor of DKD. The probability of macroalbuminuria in retinopathy and WHR>0.82 group was 43.8%, and if at the same time RDW>0.14, the probability of macroalbuminuria was 88.9%.

Conclusions: The classification tree model can analyze the major influential factors of the different stages of proteinuria in type 1 diabetic patients effectively, to identify the characteristics of high-risk populations.



PUB118

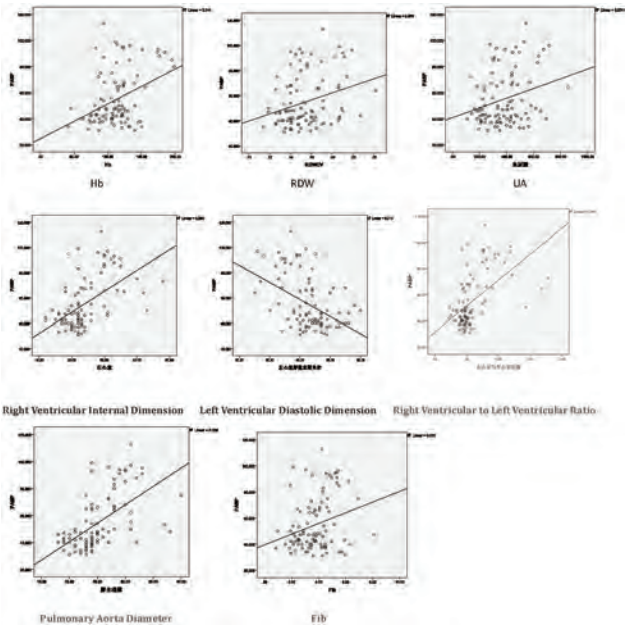
Clinical Features of Patients of Pulmonary Hypertension Associated with Lupus Glomerulonephritis Wenbo Zhao,[2] Hui-qun Li,[1] Wuyue Han,[2] Xiaomei Wu,[2] Cong Sun.[2] *[1]The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [2]the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.*

Background: The study was intended to analyze the clinical characters and relative factors referring to SLE related PAH in different stage.

Methods: We've studied 99 SLE patients combined with PAH and analyzed the results of hemoglobin level, platelet count, red cell distribution width (RDW), uric acid level, Fib, kidney function and cardiac ultrasonic examination, in order to understand the difference and relativity of these data among different degrees of PAH.

Results: Among all the 99 cases based on the grading scale of PAH, 58 patients had mild PAH, 20 had middle PAH and 21 had severe PAH. Result showed that Hb(r=0.379, P=0.000), RDW(r=0.294, P=0.003), Fib(r=0.265, P=0.008), blood uric acid(r=0.272, P=0.006), right ventricle internal dimension (RVID)(r=0.539, P=0.000), ratio of RVID to right ventricle internal dimension (LVID)(r=0.538, P=0.000) and pulmonary artery diameter(r=0.582, P=0.000) were positively related to the PASP level. LVID(r=-0.458, P=0.000) indicated the opposite result. Left atrial diameter(r=-0.160, P=0.114) and EF (r=-0.072, P=0.482)value were not related to the PASP level. There were significant differences in Fib (P=0.018)and PASP (P=0.011)of Logistic Analysis between the groups with or without renal damage.

Conclusions: Our study presented that the incidence of SLE combined with PAH was the highest. And higher level of Hb, RDW, blood uric acid, Fib, RVID and larger ratio of RVID to LVID and pulmonary artery diameter led to severer PAH. PASP was a related risk factor for lupus renal damage. PASP may be the main factor affecting the right ventricular function in patients with SLE. RDW, serum uric acid and Fib may be predictive factors of SLE related PAH and prognosis.



PUB119

Relationships of 24-Hour Urinary Phosphate Excretion and Serum Phosphate with Clinical Outcomes in CKD: From the Korean Cohort Study for Outcome in Patients with Chronic Kidney Disease (KNOW-CKD) Hong sang Choi,[3] Ha yeon Kim,[2] Chang Seong Kim,[1] Eun Hui Bae,[1] Seong Kwon Ma,[2] Kook-Hwan Oh,[4] Curie Ahn,[4] Soo Wan Kim.[2] *[1]Chonnam National University Hospital, Gwangju, Republic of Korea; [2]Chonnam National University Medical School, Gwangju, Republic of Korea; [3]Chonnam national university hospital, Gwang-ju, Republic of Korea; [4]Seoul National University Hospital, Seoul, Republic of Korea.*

Background: Recent studies suggest that dietary phosphate intake is only weakly linked to its serum concentration, and the relationship the phosphate intake and clinical outcomes is not yet well studied. We investigated the relationships of dietary phosphate intake and serum phosphate with clinical outcomes in chronic kidney disease(CKD) patients.

Methods: We collected the data of 2238 CKD stage 1-5 non-dialysis patients from a prospective cohort study (KNOW-CKD). A renal event is defined by a >50% decrease in estimated glomerular filtration rate (eGFR) from the baseline values, doubling of serum creatinine concentration, or end stage renal disease. Cardiovascular event is defined as myocardial infarction, coronary revascularization, stroke and new onset or aggravation of congestive heart failure. We used cox proportional hazards models to assess the associations between baseline 24-hour urine phosphate excretion (24h-UPE) and serum phosphate concentration with clinical outcomes.

Results: Among the 2238 participants in this study, the mean age was 53.68 ± 12.24 years (range 20–75), 61.2% were male. 24-UPE was not significantly correlated with serum phosphate concentrations (r=0.016, p=0.484). Models were adjusted for age, sex, primary renal disease, eGFR, 24-hour urine protein and nitrogen excretion, body mass index, smoking, use of phosphate binder, and medical history of diabetes, hypertension and coronary artery disease. The lowest quartile of 24h-UPE (11.4-400 mg/day) was associated with renal (hazard ratio [HR] 1.734, 95% confidence interval [CI] 1.191-2.524, p=0.004) and total event (HR 1.575, 95% CI 1.146-2.165, p=0.005) when compared with third quartile of 24h-UPE (579-745 mg/day) after adjustment for confounders. The highest quartile of serum phosphate (4.2-8.8 mg/dL) was associated with renal (HR 1.743, 95% CI 1.128-2.695, p=0.012) and total event (HR 1.949, 95% CI 1.355-2.804, p<0.001) after fully adjustment.

Conclusions: Low dietary phosphate intake assessed by 24h-UPE and high serum phosphate concentration was associated with poor clinical outcome in CKD patients. Low urinary phosphate excretion and high serum phosphate concentration should be considered as important prognostic factor in CKD.

PUB120

Higher Fluid Intake Is Associated with Improved Renal and Survival Outcomes in Hypertensive Kidney Disease Robert C. Hartley,[2] Elena A. Mylroie,[2] Kalani L. Raphael.[1,2] *[1]VA Salt Lake City Health Care System, Salt Lake City, UT; [2]University of Utah, Salt Lake City, UT.*

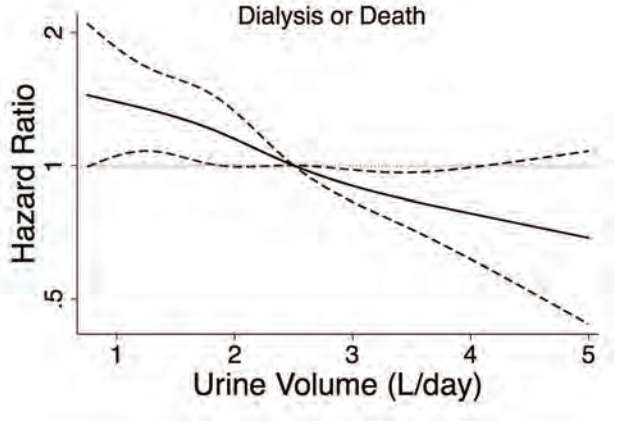
Background: Higher fluid intake reduces kidney injury in animal models of CKD. The relationship between fluid intake and outcomes in persons with CKD is unclear. We evaluated whether urine volume, as a marker of fluid intake, is associated with death or dialysis in the African American Study of Kidney Disease and Hypertension.

Methods: We performed Cox regressions in 1093 AASK participants who submitted 24-hr urine samples at baseline to determine the association between urine volume and the composite outcome of death or dialysis. Participants were categorized into <1.5 L, 1.5 to <2.5 L, and ≥2.5 L urine volume per day groups. Models were adjusted for age, gender, randomized group, BMI, SBP, measured GFR, proteinuria, diuretic and/or ACE-i use, heart disease, and urine osmolality. Those with the lowest urine volume served as the reference. We also evaluated the association between every 500 mL higher urine volume with the composite outcome and performed cubic spline regression models using similar adjustment.

Results: The mean age was 54 yrs, 61% male, mean GFR 46 mL/min/1.73m^2, mean proteinuria 326 mg/g, and 64% used diuretics. Mean urine volume was 2.2 L (SD 0.9), and 232, 500, and 361 had urine volume <1.5 L, 1.5 to <2.5 L, and ≥2.5 L, respectively. The hazard ratios of death or dialysis were 0.68 (95% CI, 0.51-0.91) and 0.88 (95% CI, 0.68-1.13) for those with urine volume ≥2.5 L and 1.5 to <2.5 L, respectively. Each 500 mL higher urine volume was associated with 9% lower risk of death or dialysis (95% CI, 0.85-0.96). Urine volume was linearly and inversely associated with these outcomes (Figure).

Conclusions: Higher 24-hour urine volume was associated with lower risk of mortality or dialysis among African Americans with hypertensive kidney disease. An interventional study to determine whether increasing fluid intake improves outcomes in hypertensive CKD should be considered.

Funding: Veterans Affairs Support



Solid line represents mean HR, dashed lines represent 95% CI.

PUB121

Stable Isotopic Surrogates with Urinary Proteomics for Assessing Renal Tissue Damage in CKD Andrew Z. Wei, Pan Liu, Tomokazu Souma, Ellen Brooks, Craig B. Langman, Jing Jin. *Feinberg School of Medicine, Northwestern University, Chicago, IL.*

Background: Pathologic proteinuria is the hallmark of most chronic kidney diseases (CKD), including congenital anomalies of the kidney and urinary track (CAKUT) and focal segmental glomerulosclerosis (FSGS). Often, functional kidney loss is evaluated in part by albuminuria. However, lab tests that can identify kidney-specific markers of ongoing tissue damage for the prediction of CKD progression remain unavailable. We report a novel urinary proteomic approach aimed at detecting urine proteins reflective of renal tissue damage by employing stable isotope labeling with amino acids in cell culture (SILAC, or SILAM when whole mouse serum is radiologically labelled) followed by qMS for substantiating and quantifying urine proteins.

Methods: Two CKD stage-matched urines from children with either CAKUT or FSGS were obtained with IRB approval. One patient had nephrotic syndrome secondary to biopsy proven FSGS, while the other had CAKUT associated with a neurogenic bladder. Both had significant proteinuria. To evaluate the differences in cell-derived vs. plasma-derived protein contents in CAKUT and FSGS urine, each was mixed with either 6/8 SILAC-labeled HEK293 lysate or 0/6 SILAM-labeled mouse serum. Following digestions with either trypsin or lys-C respectively, the resulting peptide fragments were analyzed by LC-MS/MS and mapped to the known human proteome.

Results: FSGS vs. CAKUT urines differed in the number overlapping proteins with the SILAC cell extract: 16 vs. 52 of cell-derived proteins, respectively, whereas serum-derived urinary proteins were more balanced (28 vs. 29 between FSGS and CAKUT). Cellular proteins that were detected in both FSGS and CAKUT urines were also markedly different in their concentrations even after being normalized against the SILAC standards. For instance, Actin that was identified in both had an abundance that was 40 times higher in CAKUT, consistent with the gross anatomical damage typically being worse in CAKUT at the late stages of CKD.

Conclusions: Our pilot using the SILAC methodology demonstrated important differences in tissue derived proteins in the urine of two subjects with CKD (FSGS vs. CAKUT). We hope that this pilot will eventually enhance the future detection of ongoing kidney tissue damage so to direct clinicians toward targeted therapeutics to treat category and tissue-specific mechanisms of CKD progression.

Funding: Private Foundation Support

PUB122

The Prediction of Systolic Blood Pressure at Representative Time-Points for 24 Hour Mean Systolic Blood Pressure on 1-Year Renal outcomes in Diabetic CKD Patients

Jiwon Ryu,[1] Sejoong Kim,[6] Ran-hui Cha,[4] Hajeong Lee,[7] Jung Pyo Lee,[5] Myung jin Choi,[2] Young rim Song,[3] Yon Su Kim.[7] *[1]Cheju Halla Hospital, Seoul, Republic of Korea; [2]Chuncheon Sacred Heart Hospital, Chuncheon, Republic of Korea; [3]Hallym Univ. Sacred Heart Hospital, Anyang, Republic of Korea; [4]National Medical Center, Seoul, Republic of Korea; [5]Seoul National University Boramae Medical Center, Seoul, Republic of Korea; [6]Seoul National University Bundang Hospital, Seongnam, GyeongGi-Do, Republic of Korea; [7]Seoul National University College of Medicine, Seoul, Republic of Korea.*

Background: Control of blood pressure(BP) in diabetic chronic kidney disease(CKD) patients is important in preventing target organ damage. 24-hour ambulatory BP measurement(ABPM) is the best known in BP monitoring, but it is not easy to use. APrODiTe study suggested systolic blood pressure(SBP) of specific time-points that can represent the 24-hour mean SBP(mSBP) were 7:00AM and 9:30PM in chronic kidney disease(CKD) patients. We followed the study 1 year later and evaluated whether SBPs at these time-points can predict renal outcomes after 1 year such as 24-hour mSBP in diabetic CKD patients.

Methods: We recruited 125 diabetic CKD patients with from 4 centers in Korea 1 year later. Baseline SBPs at 7:00AM and 9:30PM were evaluated whether they have predictive correlation for the change of renal function, proteinuria after 1 year compared with 24-hour mSBP. The renal outcomes were an increase in random urine protein/creatinine ratio than baseline value or estimated glomerular filtration rate(eGFR) deterioration which means a decrease in eGFR ≥ 5 (ml/min/1.73m²).

Results: The followed mSBPs at 7:00AM, 9:30PM and 24-hour mSBP were 135.4 ± 26.0 mmHg, 147.7 ± 131.8 mmHg and 132.9 ± 26.0 mmHg, they did not changed significantly from baseline mSBPs (paired t-test, p= 0.861; p= 0.537; p = 0.294). The SBP at 7:00AM correlated with eGFR deterioration in univariate analysis, after multivariate analysis, SBP at 7:00AM has significant association with eGFR deterioration (odds ratio: 1.026; 95% confidence interval (CI): 1.111-1.052; P = 0.046). In an association with proteinuria progression, SBP at 7:00AM has a correlation in univariate analysis, but in multivariate analysis, SBPs at any time-points has no association with proteinuria progression. In subgroup analysis, the association between SBP at 7:00AM and eGFR deterioration persisted in CKD stage 3-5 patients (odds ratio: 1.037; 95% CI: 1.005-1.070; P = 0.024).

Conclusions: These data suggested that the SBP at 7:00AM may have better prediction on 1-year eGFR deterioration in diabetic CKD patients, especially in subgroup of CKD stage 3-5 patients. Whereas SBPs at any time-points may not be correlated to 1-year proteinuria progression in diabetic CKD patients.

PUB123

Incidence of CKD and Risk Attributable to Cardiovascular Risk Factors in Two Asian Populations

Charumathi Sabanayagam,[2,3] Weng Kit Lye,[3] Kunihiro Matsushita,[1] Ecosse L. Lamoureux,[2,3] Ching-Yu Cheng,[2,3] Tien Yin Wong.[2,3] *[1]Johns Hopkins Bloomberg School of Public Health, Baltimore, AL; [2]Singapore Eye Research Institute, Singapore, Singapore; [3]Office of Clinical Sciences, Duke-NUS Medical School, Singapore, Singapore.*

Background: Prevalence of chronic kidney disease (CKD) is escalating in Asian populations due to ageing and increasing prevalence of diabetes and hypertension. CKD shares many of the cardiovascular risk factors. We compared the incidence, risk factors and impact of CKD in two Asian populations with high burden of diabetes.

Methods: We analysed data from two cohorts consisting of Malay (n=1517) and Indian (n=1743) adults aged 40-80 years and free of CKD at baseline: The Singapore Malay Eye Study (SiMES, 2004-06; SiMES-2, 2011-13); the Singapore Indian Eye study (SINDI, 2007-09; SINDI-2, 2013-15). Incident CKD was defined as an (estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m²+25% decrease in eGFR at follow-up. Risk factors assessed included age, sex, education, smoking, diabetes, hypertension, dyslipidemia, cardiovascular disease, overweight/obesity, antihypertensive medication use, systolic blood pressure, HbA1c, C-reactive protein, total and HDL cholesterol and baseline eGFR. Population-attributable risks (PAR) were computed for significant risk factors.

Results: The 6-year incidence of CKD was 6.8% in Malays and 3% in Indians. At baseline, 25% of Malays and 34.7% of Indians had diabetes; 59.7% and 53.9% had hypertension. In multivariable models, among the continuous predictors, age, systolic BP, HbA1c, and lower baseline eGFR in both populations, and lower total cholesterol in Malays were significantly associated with CKD. Among the categorical predictors, diabetes (hazard ratio [95% confidence interval] = 3.47 (1.82-6.63), hypertension (3.13 [1.17-8.4]), overweight/obesity (1.79 [1.05-3.11]) in Malays and diabetes alone in Indians (2.99 [1.27-7.02]) were associated with CKD. Hypertension was not associated with CKD in Indians (1.86 [0.55-14.94]). Diabetes (13%), hypertension (7%) and overweight/obesity (3%) contributed to 23% of PAR of CKD in Malays and diabetes contributed to 4.7% of CKD in Indians.

Conclusions: Incidence of CKD in Asian Malays and Indians were similar to that of Western populations. Although the prevalence of diabetes was higher in Indians, contribution of diabetes to CKD was higher in Malays compared to Indians.

PUB124

APOL1 Genotype, Serum Bicarbonate, and Clinical Outcomes in AASK

Man Li,[5] Michael S. Lipkowitz,[1] Cheryl A. Winkler,[3] Lawrence J. Appel,[2] Kalani L. Raphael.[4,5] *[1]Georgetown University Medical Center, Washington, DC; [2]Johns Hopkins Medical Institutions, Baltimore, MD; [3]NCI, NIH, Frederick National Laboratory, Frederick, MD; [4]VA Salt Lake City Health Care System, Salt Lake City, UT; [5]Internal Medicine, University of Utah School of Medicine, Salt Lake City, UT.*

Background: *APOL1* high-risk genotype and metabolic acidosis are individually associated with CKD progression in African Americans. *APOL1* is produced by proximal tubule cells (PTC), but its function in PTC is unclear. PTC are critically important in renal acid-base regulation. We evaluated whether the association between acidosis and outcomes in CKD is modified by *APOL1* high-risk genotypes.

Methods: We evaluated this in 639 African American Study of Kidney Disease and Hypertension (AASK) participants using multivariate Cox models (adjusted for demographics, measured GFR, proteinuria, BMI, net endogenous acid production, and percentage of European ancestry estimated by ancestry informative markers) with an interaction term and stratification by *APOL1* status. Serum bicarbonate groups were grouped as <22, 22-28 (referent), and >28 mEq/L and the primary outcome was the composite of doubling serum creatinine, dialysis, or death.

Results: Mean age was 53.5 years, 61% were women, mean GFR was 47.5 ml/min/1.73 m², mean bicarbonate was 25.2 mEq/L, 146 (22.8%) had *APOL1* high-risk genotype (two copies of the high-risk alleles). Over a mean follow-up of 4.1 years, 315 (39.7%) participants had doubling serum creatinine, dialysis, or death. The prevalence of low bicarbonate is 12.4% in *APOL1* low-risk group and 15.1% in *APOL1* high-risk group. Results of the association of baseline bicarbonate levels with the composite outcome stratified by *APOL1* status are shown in Table 1. The interaction between *APOL1* and low bicarbonate was not significant p=0.98.

Conclusions: The association between acidosis and poor outcomes in African Americans with hypertensive kidney disease is not modified by *APOL1* risk status.

Table 1. Association of baseline serum bicarbonate with the hazard of doubling serum creatinine, dialysis, or death by APOL1 status.

	APOL1 high-risk genotype (N=493)	APOL1 low-risk genotype (N=146)
Serum bicarbonate (mEq/L)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Normal: 22-28	REF	REF
Low: <22	1.46 (0.85, 2.51)	1.32 (0.90, 1.94)
High: >28	1.12 (0.52, 2.41)	1.31 (0.90, 1.92)

PUB125

Dyslipidemia and Renal Damage during Pregnancy in Women with Chronic Renal Disease

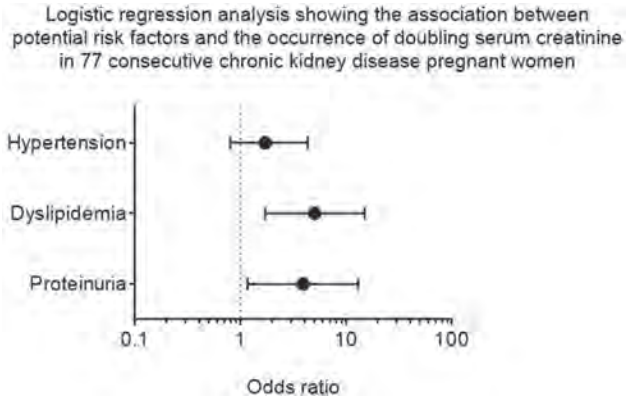
Amelia R. Bernasconi,[2] Liliana S. Voto,[1] Alicia M. Lapidus,[3] Rosa A. Waisman,[5] Ricardo M. Heguilen.[4] *[1]Obstetrics, Hospital Juan A Fernandez, Buenos Aires, Argentina; [2]Medicine, Hospital Juan A Fernandez, Buenos Aires, Argentina; [3]Obstetrics, Hospital J. A. Fernandez, Buenos Aires, Argentina; [4]Nephrology, Hospital Juan A Fernandez, Buenos Aires, Argentina; [5]Obstetrics, Juan A Fernandez, Buenos Aires, Argentina.*

Background: Cardiovascular disease (CVD) is the leading cause of death in women (W). The prevalence of hypertension (HTN) and dyslipidemia (DLP), is high among fertil W. HTN and proteinuria (Uprot) during pregnancy (P) are associated with adverse outcomes such as preeclampsia, low birth weight, etc. DLP may also have adverse effects on the fetus and mother. P W with renal disease (CKD) are at a higher risk of deterioration of GFR. The primary objective of this study was to evaluate the potential association of DLP and the occurrence of doubling serum creatinine (2xScr) from pre-P values.

Methods: Case-control study aimed at identifying risk factors worsening renal function in P W suffering from CKD. Uni and multivariate logistic regression was used to determine whether 2xScr was a dependent variable on the following potential covariates: HTN, overweight, the presence of pre-P conditions such as DLP, hyperuricemia, or Uprot, Odds ratios with the 2-sided 95% CI were reported. p values < 0.05 were considered statistically significant.

Results: Data from 77 consecutive CKD, P women recruited during a period of 3 ½ years were included in the analysis. 29 of them doubled Scr before delivery. Both groups were similar in age, BW, baseline Scr, estimated GFR; systolic or diastolic BP; uric acid levels and gestational age at the time of first visit but those who 2xScr had higher TGs levels (107.8 + 6.5 vs. 88.8 + 4.2 p< 0.01); total cholesterol (219.5 ± 8.6 vs 165.5 + 6.3 p< 0.01) and LDL levels (156.7 + 6,0 vs 115.9 + 3.1p< 0.01) or Uprot (0.7 ± 0.1 vs. 0.4 ± 0.1. Results from the logistic regression analysis is shown in Figure 1

Conclusions: DLP arise as a relevant factor associated with worsening renal function in P W with CKD. Given the health importance of identifying risk factors among CKD fertil W, DLP screening in this population is needed and aggressive treatment should be considered pre or during P in this population.



PUB126

The Efficacy of Hemodialysis in Preventing Contrast-Induced Nephropathy in Patients with Pre-Existing Renal Insufficiency: A Single Center Experience Panagiota E. Giannou,[2] Athanasia Kapota,[2] Nikolaos Magkas,[1] Feretou Katerina,[3] Aglaia Chalkia,[2] Dimitrios Petras.[2] *[1]1st Cardiology Clinic Hippokration Hospital, ATHENS, Greece; [2]Nephrology Department Hippokration Hospital, Athens, Greece; [3]Cardiology Department Hippokration Hospital, Athens, Greece.*

Background: Contrast-induced nephropathy (CIN) is defined as the impairment of renal function—measured as either a 25% increase in serum creatinine (sCr) from baseline or a 0.5 mg/dL (44 μmol/L) increase in absolute sCr value—within 48-72 hours of intravenous contrast administration. The reported incidence of CIN varies widely, largely depending upon the presence or absence of risk factors, primarily including underlying chronic kidney disease (CKD). The risk is also higher among patients with heart failure or hemodynamic instability. There are an increasing number of reports that CIN is associated with significant in-hospital and long-term mortality. The aim of the current study was to assess whether prophylactic immediate hemodialysis (HD), after intravascular contrast media administration in patients with pre existing renal insufficiency, could be used in order to preserve residual renal function.

Methods: 39 patients (30 men-9 women) who underwent procedures with administration of intravascular contrast media, were studied. Subjects had a mean value of eGFR 22.5 ml/min/1.73m^2, mean age 75.7 years and mean value daily diuresis 1.2 lt. In all patients a central venous catheter was placed and a 3hr Hemodialysis (HD) session was performed, 2 hours after contrast media administration. SerumCr levels were measured at the day of contrast media administration and 3 days after HD.

Results: None of the patients had any deterioration of their sCr value or of their daily diuresis, while no other complications were noticed during HD session.

Conclusions: In view of the limited benefit of prevention remedies such as hydration, bicarbonate and NAC, dialysis may be considered a solution. Scattered studies indicate that in patients with CKD who are undergoing coronary angiography, prophylactic HD can improve renal outcome. There are insufficient data to support the use of prophylactic HD following contrast exposure, so more multicenter, randomized studies on the subject are needed. Nevertheless a better collaboration of nephrologists and other physicians who refer patients for contrast procedures is a necessity.

PUB127

Urinary Peptide Biomarkers of CKD in Dogs Valerie Brunchault,[1] Lena Pelander,[2] Benedicte Buffin-Meyer,[1] Julie Klein,[1] Benjamin Breuil,[1] Petra Zürbig,[3] Pedro Magalhães,[3] William Mullen,[4] Joost Schanstra,[1] Jonathan Elliott,[6] Harriet M. Syme,[5] Jens Häggström,[2] Ingrid Ljungvall.[2] *[1]INSERM U1048, Toulouse, France; [2]Swedish University of Agricultural Sciences, Uppsala, Sweden; [3]Mosaiques Diagnostics GmbH, Hannover, Germany; [4]University of Glasgow, Glasgow, United Kingdom; [5]Royal Veterinary College, Hatfield, United Kingdom; [6]The Royal Veterinary College University of London, London, United Kingdom.*

Background: Chronic kidney disease (CKD) is a clinically important cause of morbidity and mortality in dogs. This heterogeneous disease is insidious in onset and often not recognized until late in the course of disease. Currently available tools lack sensitivity to identify CKD in dogs.

Methods: We have analyzed the urinary peptidome of dogs with CKD with the aim to evaluate if capillary electrophoresis coupled to mass spectrometry (CE-MS)-based urinary peptidome analysis can discriminate healthy dogs from dogs with CKD with high sensitivity and specificity.

Results: Analysis of the urinary peptidome with CE-MS demonstrated the presence of ~5400 peptides in dog urine. Comparison of 15 healthy and 15 dogs with CKD identified 133 differentially excreted peptides after correction for multiple testing. Sequence information was obtained for 35 peptides out of the 133, and included 33 collagen (I and IV) and 2 uromodulin fragments, urinary peptides that were also found to be differentially excreted in humans with CKD. The 133 and 35 sequenced peptides were combined in two support vector machine classifiers called 133P and 35P, respectively. These models were validated in an independent, cohort of 20 dogs where the analyst was masked to their classification. The 133P classifier predicted CKD with a sensitivity of 80% [95%confidence interval (CI), 44 to 97%], a specificity of 80% (95% CI, 44 to 97%) and an area under the curve (AUC) of 0.88 (95% CI, 0.72 to 1.04). The 35P classifier predicted CKD with a sensitivity of 80% [95%confidence interval (CI), 44 to 97%], a specificity of 90% (95% CI, 55 to 100%) and an area under the curve (AUC) of 0.89 (95% CI, 0.73 to 1.05).

Conclusions: In conclusion, this first study of the urinary peptidome of dogs with CKD identified peptides that predicted presence of CKD in dogs with high accuracy. Future studies should validate its usefulness for early CKD diagnosis and prediction of progression in a clinical setting. [equal contribution VB and LP].

Funding: Government Support - Non-U.S.

PUB128

Urinary Exosomes and the Loading of CCL2 mRNA as Biomarkers of IgA Nephropathy Patients Ye Feng, Linli Lv. *Institute of Nephrology, Zhong Da Hospital, Southeast University, Nanjing, China.*

Background: Proteinuria is the major clinical risk factor for progressive loss of renal function in immunoglobulin A nephropathy (IgAN) patients. Excessive amount of proteins enter the urinary tract which might be toxic to cells facing the urinary space and increases the exosome excretion in urine. Here we aimed to explore the role of urinary exosomes and the loading chemokine, CCL2 mRNA serving as biomarkers of IgAN.

Methods: We isolated exosomes from urine samples of IgAN patients(N=55) at the time of renal biopsy and healthy controls(N=24). Samples from 14 patients with average 19.5-month follow-up after treatment were also collected. Kidney histological damage of IgAN patients was scored according to the Oxford classification. The protein of urinary exosomes were quantified by Bradford Protein Assays and Western blotting (using Alix, CD63 as exosome markers). Exosomal RNA was extracted by miRNeasy micro kit (Qiagen) and CCL2 mRNA was quantified through RT-PCR.

Results: Interestingly, rarely exosome was detected in healthy controls through western blotting with exosomal markers including CD63 and Alix. Exosome excretion in urine was increased with increasing severity of proteinuria in IgAN patients. The level of urinary exosomal protein closely correlated with levels of proteinruria and tubular injury marker, NGAL. Follow-up studies showed significantly less exosome excretion with decreased levels of proteinuria. It indicated that overloaded protein could increased exosome excretion from tubular epithelial cells. Moreover, according to the Oxford classification of IgAN, patients with higher endocapillary hypercellularity showed remarkably larger amount of urinary exosomes. Besides, exosomal CCL2 mRNA was significantly upregulated in IgAN compared with controls, and correlated with the deterioration of renal function as determined by eGFR. Exosomal CCL2 mRNA also increased in patients with high scores of tubular atrophy and interstitial fibrosis.

Conclusions: Proteinruia is toxic to tubular epithelial cells and endocapillary damage may increase exosome excretion in urine in IgAN. Urinary exosomes production and the CCL2 mRNA might be the promising biomarkers of IgAN reflecting the deterioration of renal function and pathologic damage. Further studies are need to explore the potential role of exosomes in the progression of IgAN.

PUB129

Fibrinogen: A Possible Predictor of Microalbuminuria Stage in Type 1 Diabetic Nephropathy Wenbo Zhao,[2] Hui-qun Li.[1] *[1]The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [2]the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.*

Background: Analysis of the correlation of fibrinogen a nd different stages albuminuria in type 1 diabetic.

Methods: nephropathyAs a Cross-sectional study, we collected hospital clinical data of 394 cases for type 1 diabetes, without albuminuria group (299 cases), microalbuminuria group (73 cases) and macroalbuminuria group (22 cases), analying albuminuria progress related influence factors for multiple factors regression.

Results: The levels of fibrinogen was in the three groups respectively for(3.06±0.78) g/L, (3.566±1.79)g/L, (4.46±1.15)g/L(P=0.000). In the without albuminuria group and microalbuminuria group, the multi-factor Logistic regression analysis showed fibrinogen (Fib) (β= 0.408, P = 0.005, OR = 1.504), and retinopathy, UA, RDW into the model. In microalbuminuria group and macroalbuminuria group, the multi-factor Logistic regression analysis showed fibrinogen (Fib) was not into the model. But retinopathy, HDL, Waist-to-hip ratio into the model.

Conclusions: Fibrinogen associated with microalbuminuria stage in type 1 diabetic nephropathy, that could be independent predictors of early renal damage in type 1 diabetic nephropathy.

PUB130

Prevalence of Co-Morbidities by Ethnicity in a UK Primary Care CKD Cohort Rupert Major,[1,2] Gang Xu,[2,3] Laura Gray,[1] Nigel J. Brunskill.[2,3] *[1]Department of Health Sciences, University of Leicester, Leicester, United Kingdom; [2]University Hospitals of Leicester, Leicester, United Kingdom; [3]Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, United Kingdom. Group/Team: PSP-CKD Study.*

Background: Cardiovascular (CV) and endstage renal disease events in CKD are more common in non-white ethnicities compared to white ethnicities. The prevalence of

co-morbidities in CKD in Black and South Asian ethnicities outside of North America is poorly studies but may account for these higher renal and CV event rates.

Methods: We analysed cross-sectional data from the PSP-CKD study (ClinicalTrials.gov NCT01688141). Individuals were analysed if they had a baseline EPI eGFR <60 ml/min/1.73m^2 and an ethnicity code. The groups' baseline characteristics between ethnicities were compared using t-tests and Chi^2.

Results: 18,058 (78.1%) individuals out of 23,129 had ethnicity recorded. Of these, 17,264 (95.6%) were White, 263 (1.5%) Black and 243 (1.4%) were South Asian. Individuals of Black and South Asian ethnicities were more likely to be male and younger. Mean EPI eGFRs were similar across ethnicities but South Asians had higher mean ACR in both those with and without diabetes mellitus (DM). In Black individuals a diagnosis of hypertension (HTN) was less common but both systolic and diastolic blood pressures had higher mean values. DM was more prevalent in South Asians and HbA1c was higher too. Both Black and South Asian groups had lower rates of CV disease.

Conclusions: In South Asians with CKD, DM was present in more than 40% and glycaemic control was worse. A HTN diagnosis was less common in Black individuals but blood pressure was more poorly controlled. Both groups had lower rates of previous CV events. Targeted management of these co-morbidities in South Asian and Black populations with CKD may be warranted.

Cohort Characteristics by Ethnicity

Variable	White	South Asian	p-value	Black	p-value
n	17,264	243		263	
Female	62.9%	54.0%	0.01	55.1%	<0.01
Age	75.8 (11.1)	69.7 (11.4)	<0.001	64.5 (14.4)	<0.001
Mean EPI eGFR	50.6 (9.6)	49.9	0.23	50.6 (11.6)	0.97
ACR (mg/mmol)	6.8 (18.0)	13.3 (27.3)	0.03	12.5 (25.1)	0.10
CV Disease	17.4%	11.5%	0.02	10.7%	<0.001
HTN	91.0%	90.1%	0.65	84.8%	<0.001
Systolic BP	134.3 (16.3)	134.7 (18.9)	0.65	136.7 (18.2)	0.02
Diastolic BP	74.8 (10.0)	75.2 (10.7)	0.58	79.1 (11.3)	<0.001
DM	23.1%	44.0%	<0.001	29.3%	0.02
HbA1c % if DM	7.4 (1.4)	7.8 (1.6)	0.01	7.5 (1.5)	0.68

p-values refer to comparison to White ethnicity. For continuous variables values refer to means and figures in parentheses refer to standard deviations.

PUB131

A Retrospective Analysis of Positive Predictors for the Utility of Ultrasound in the Diagnosis and Management of CKD in an Outpatient Population Erin Dohaney,[1] Martin G. Mackinnon.[2] *[1]Dalhousie University School of Medicine, Rothesay, NB, Canada; [2]Horizon health, Quispamsis, NB, Canada*.

Background: Given the economic constraints of today's health care system, there is an increasing emphasis on cost-effectiveness and judicious use of resources. Choosing Wisely is a campaign that encourages health care providers in all aspects of medicine to look for ways to reduce the use of unnecessary tests while maintaining quality care for patients. The aim of this study is to add to the existing body of "diagnostic research" by assessing the diagnostic yield and clinical utility of ultrasound in the setting of chronic kidney disease.

Methods: A retrospective multi-variant analysis was performed using data collected from 2 hospitals in New Brunswick, Canada, involving patients presenting for initial outpatient nephrology consult between January 2012 and January 2015. Data on patient presenting history and symptoms at the time of initial nephrology consult were collected via chart review. Demographic, laboratory, imaging and procedural data ranging from one year prior up to and including one year following the initial nephrology consult date was collected via electronic data extraction. A focus group attended by nephrology and radiology staff was used to determine what ultrasound findings would represent a "positive" result that would effectively change diagnosis and management. Multivariate regression analysis is being used to analyze the relationship between patient characteristics and ultrasound results.

Results: At the time of submission, of the 357 patients collected in the initial chart review, 304 (85%) were captured within our data extraction and matched to patient database demographic information with an initial nephrology consult ID and date. 221 of 304 (73%) had matches to the laboratory dataset (≥1 lab result). A total of 26,602 labs records were extracted for those 221 patients. 48 of 221 patients (22%) had ultrasounds performed. 53 ultrasounds were performed on 48 patients with 5 patients having had 2 ultrasounds. 7 of 221 (3%) had matches to pathology reports, indicating that biopsy was performed. Ultrasound findings were as follows: normal study (43%), increased echogenicity and cortical thinning (17%), re-checks with abnormalities (15%), non-obstructing calculi (8%) simple renal cysts (7%), renal atrophy (6%) and de novo lesions (4%).

Conclusions:

Funding: Private Foundation Support

PUB132

Greater Acid Retention in Patients with More Advanced CKD Is Associated with Faster eGFR Decline Nimrit Goraya,[4,5] Jan Simoni,[3] Lauren N. Sager,[1] Donald E. Wesson.[2,4] *[1]Biostatistics, Baylor Scott & White, Temple, TX; [2]Diabetes Health and Wellness Institute, Dallas, TX; [3]Surgery, Texas Tech University Health Sciences Center, Lubbock, TX; [4]Internal Medicine, Baylor Scott and White Health, Temple, TX; [5]Internal Medicine, Texas A and M, Temple, TX*.

Background: Acid (H^+) retention measured by microdialysis causes progressive GFR decline in animal models of chronic kidney disease (CKD), even in the absence of metabolic acidosis by plasma acid-base parameters, it worsens with declining GFR, and greater H^+ retention causes faster GFR decline in these CKD models. Patients with reduced eGFR but no metabolic acidosis also have H^+ retention (Wesson, et al. AJP 300:F830) and eGFR decline rate was faster in the absence of dietary H^+ reduction in CKD patients with stage 3 (Goraya et al. KI 86:1031, 2014) compared to stage 2 (Mahajan, et al. KI 78:303, 2010) eGFR (4.3 vs. 2.4 ml/min/1.73m^2/year). We tested the hypothesis that faster eGFR decline in more advanced CKD stages is associated with greater H^+ retention.

Methods: Twenty-six CKD stage 1 (CKD 1), 40 CKD 2, and 36 CKD 3, macroalbuminuric, non-diabetic CKD subjects underwent measurement of H^+ retention by comparing the observed to the expected increase in plasma [HCO_3] in response to retained HCO_3 (dose-urine excretion) two hours after an oral $NaHCO_3$ bolus (0.5 meq/Kg bw), assuming 50% body weight HCO_3 space of distribution. Specifically, H^+ retention = [(retained HCO_3/0.5 x body weight) – observed increase in plasma [HCO_3]] x (0.5 x body weight). Cystatin C-based eGFR was measured at baseline and then yearly for five years.

Results: Baseline eGFR in ml/min/1.73m^2 was as follows: CKD 1=101±8, CKD2=76±6, and CKD 3=40±7. The yearly rate of eGFR decline, expressed as ml/min/1.73m^2/year, was faster in CKD 2 than CKD 1 (2.32±0.14 vs. 1.74±0.17, p<0.0001) and was faster in CKD 3 (3.77±0.15) than CKD 2 (p<0.0001). The Bonferroni correction required a p-value of < 0.0083 for significance among group comparisons for H^+ retention. Accordingly, H^+ retention was greater in CKD 2 vs. CKD 1 (17.4±8.9 vs. 3.0 ± 14.0 mmol, p<0.0001) and in CKD 3 (24.9±15.4 mmol) than CKD 2 (p=0.0079).

Conclusions: These data show that the faster rate of eGFR decline in CKD patients with lower initial eGFR was associated with greater H^+ retention which might mediate their more rapid progression. The data suggest that CKD patients with more advanced CKD and lower eGFR require more aggressive dietary H^+ reduction to better resolve underlying H^+ retention and thereby possibly optimize the kidney protective benefits of this therapy.

PUB133

Time-Average Proteinuria during Follow-Up and Renal Prognosis in Patients with Benign Nephrosclerosis Hoichi Amano,[5] Kentaro Koike,[2] Nobuo Tsuboi,[4] Kotaro Haruhara,[3] Makoto Ogura,[1] Takashi Yokoo.[4] *[1]Division of Kidney and Hypertension, The Jikei University School of Medicine, Tokyo, Japan; [2]Division of nephrology and hypertension, The Jikei university school of medicine, Tokyo, Japan; [3]The Jikei University School of Medcine, Tokyo, Japan; [4]The Jikei University School of Medicine, Setagaya-ku, Japan; [5]Division of Nephrology and Hypertension, The Jikei University School of Medicine., Tokyo, Japan*.

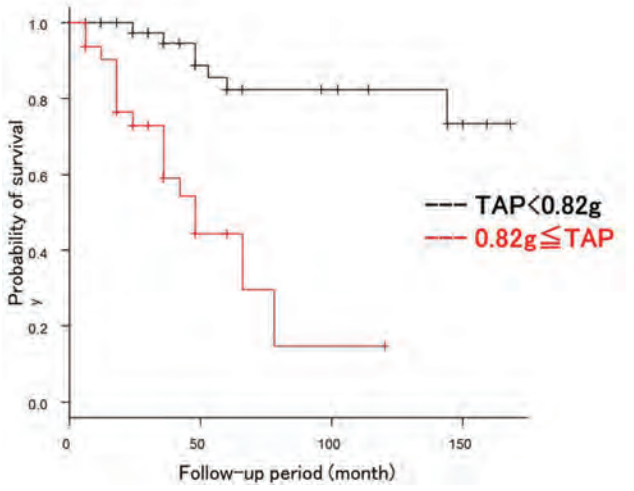
Background: Heavy proteinuria at the time of diagnostic renal biopsy has been reported as an independent risk factor for deteriorating renal function in benign nephrosclerosis (BNS). However, few studies have investigated the relationship between the amount of proteinuria during follow-up and long-term renal prognosis in BNS. The purpose of this study was to assess the relationship between time-average proteinuria (TAP) and renal prognosis in BNS.

Methods: Patients with biopsy-proven BNS from the Jikei University Hospital participated in this study. Multivariate analysis was used to investigate the effects of TAP and other clinicopathological findings on the risk for renal events (a 30% decline in eGFR from baseline or ESRD). Proteinuria was measured every 6 months, and the mean value was used as an indicator of TAP.

Results: This study included a total of 67 BNS patients [average 51±12years old, eGFR; 51 ± 24 ml/min, urine protein excretion at baseline; 0.78 g / g Cr (0.51 - 1.79)]. The rate of renal events in patients with higher TAP was significantly elevated as compared to the rate in those with lower TAP (Figure; Log-rank trend test, P < 0.001). The adjusted model indicated a significant association between TAP and renal events (HR: 3.84, CI: 2.00-7.51), which was independent of higher baseline proteinuria, glomerulosclerosis and tubulointerstitial damage. Figure

Conclusions: These results suggest that TAP is an independent risk factor for renal prognosis in patients with BNS, indicating the significance of urinary protein excretion during follow-up in the progression of BNS.

Figure.



PUB134

Angiotensin 2 and Innate and Adaptative Immunity in a Model of CKD Caused by Brief Treatment with L-NAME and Salt Overload Karin C. Oliveira, Fernanda F. Zambom, Lais Braga, Amanda H. Albino, Viviane D. Faustino, Victor F. Avila, Simone C. Arias, Camilla Fanelli, Claudia R. Sena, Vivian L. Viana, Denise M. Malheiros, Niels O. Camara, Clarice K. Fujihara, Roberto Zatz. *Univ Sao Paulo, SP, Brazil*.

Background: We showed previously (AJPRenal 2006) that short-term NO inhibition by L-NAME (N) and salt overload (HS) promotes severe hypertension and renal injury that regress after treatment is ceased, but progress slowly to chronic kidney disease (CKD) thereafter. Here we investigated whether Ang2, innate and adaptive immunity are involved in the pathogenesis of CKD in this late phase.

Methods: Male Munich-Wistar rats received HS (2.2% Na) and N (32 mg/Kg/d) for 1 mo. Control rats (C) received HS only. Four wks after all treatments had been ceased, tail-cuff pressure (TCP, mmHg), albuminuria (ALB, mg/d), glomerulosclerosis (GS, %), ischemic glomeruli (IG, %), interstitial collagen 1 (COLL, %), renal content of IL1β (pg/mg), as well as interstitial infiltration (cells/mm²) by macrophages (MΦ), lymphocytes (Ly), angiotensin 2+ (Ang2+) and NLRP3+ cells were assessed in 14 rats (Post-HS+N_4). All measurements were repeated in additional rats, followed for 24 wks while receiving either no treatment (Post-HS+N_{24}, n=15) or Losartan, 50 mg/kg/d (Post-HS+N+L_{24}, n=11).

Results: Mild hypertension and renal injury/inflammation, along with increased infiltration by Ang2+ cells and activation of the NLRP3 pathway, were observed in Post-HS+N_4. After 24 weeks, ALB, GS and COLL were aggravated in association with persistently high levels of MΦ, Ly, Ang2+ cells and NLRP3/IL1β. In addition, the IL1β levels correlated positively with GS, MΦ and Ang2+ cells. Losartan prevented the increase in TCP, ALB, COLL and GS, but aggravated IG. Likewise, MΦ, Ly, Ang2+and IL1β were attenuated, and IL1β correlated positively with ALB.

Conclusions: Continued activation of innate and adaptive immunity, even after the initial insult is ceased, may interact with Ang2 to mediate the development of inflammation and CKD in this model. FAPESP/CNPq

	TCP	ALB	GS	IG	COLL	MΦ	Ly	Ang2	NLRP3	IL1β
C	146±3	5±1	0±0	1±1	2±1	34±5	50±5	2±1	1±1	2±1
Post-HS+N_4	164±4^a	24±6^a	1±1^a	7±1^a	4±1^a	85±15^a	119±14^a	14±3^a	3±1^a	3±1^a
Post-HS+N_{24}	161±8^a	65±12^{ab}	7±2^{ab}	4±1^{ab}	5±1^{ab}	104±17^a	127±15^a	10±2^a	5±1^a	5±1^{ab}
Post-HS+N+L_{24}	122±4^{abc}	15±5^{ac}	1±1^{ac}	10±2^{ac}	2±1^{bc}	53±5^c	54±3^{bc}	4±1^{bc}	4±1^a	3±1^{ac}

Mean±SE; ^{a}p<0.05 vs. C, ^{b}p<0.05 vs Post-HS+N_4, ^{c}p<0.05 vs Post-HS+N_{24}

PUB135

Factors Related to Proteinuria Relapse in Childhood IgA Nephropathy Yuko Shima,[1] Koichi Nakanishi,[3] Taketsugu Hama,[1] Masashi Sato,[1] Yu Tanaka,[1] Hironobu Mukaiyama,[1] Hiroko Togawa,[1] Hiroshi Kaito,[2] Kandai Nozu,[2] Ryojiro Tanaka,[4] Kazumoto Iijima,[2] Hiroyuki Suzuki,[1] Norishige Yoshikawa.[5] *[1]Pediatrics, Wakayama Medical University, Wakayama City, Japan; [2]Dept. of Pediatrics, Kobe Univ. Graduate School of Medicine, Kobe, Japan; [3]Graduate School of Medicine, University of the Ryukyus, Nishihara-cho, Japan; [4]Pediatric nephrology, Hyogo prefectural Kobe children's hospital, Kobe, Japan; [5]Clinical Research Center, Wakayama Medical University, Wakayama, Japan.*

Background: Proteinuria remission is the most significant predictive factor for renal outcome in childhood IgA nephropathy (IgAN). Even if the proteinuria remission could be once obtained, some of the patients show proteinuria relapse during the long-time disease course. The purpose of this study is to clarify the incidence and factors related to proteinuria relapse in childhood IgAN.

Methods: Retrospective analysis of 309 cases with proteinuria remission among 538 consecutive biopsy-proven IgAN children from July 1976 to June 2013 to compare clinical and pathological findings between the patients with proteinuria relapse and others.

Results: Ninety patients (29.1%) showed proteinuria relapse during the observation period (median 7.0 [25%-75%: 4.0–11.0] years). Clinical findings showed significant differences (relapse vs non-relapse) in onset age (11.3±3.3 vs 9.9±2.8 years, p=.0005) and the duration from onset to proteinuria remission (3.0±1.9 vs 2.7±2.9, p=.01). As to the pathological findings, there were significant differences in the ratio of tubular atrophy/interstitial fibrosis present (65.4% vs. 47.4%, p=.005). The Kaplan-Meier analysis suggested that the patients with proteinuria relapse had significantly lower renal survival rates than the others at 16 years (91.9% [95%CI: 78.5-97.2] vs 99.5% [95%CI: 96.2-99.9], p<.04). Proteinuria relapse is the only significant factor for renal survival in the 309 cases that remission of proteinuria was once obtained (hazard risk 3.15e^9 [95%CI:2.8-2.8], p=.004).

Conclusions: About one third of the proteinuria remission patients showed proteinuria relapse again regardless of treatments. Tubular atrophy such as a chronic lesion was significantly related to the proteinuria relapse.

PUB136

Impact of Oral Sucrosomial Iron in Anemia of CKD Patients and Its Relation with Mineral Bone Disease Parameters Ioannis Griveas.[1,2] *[1]401 General Military Hospital of Athens, Athens, Greece; [2]RENAL CLINIC "ATHENS-NEPHROLOGY", ATHENS, Greece.*

Background: Iron deficiency is one of the main causes of anemia in patients with chronic kidney disease (CKD), and iron supplements constitute the basis of its therapy. Oral sucrosomial iron, a preparation of ferric diphosphate carried inside a phospholipidic membrane, is characterized by higher gastrointestinal absorption and bioavailability than other oral formulations, as well as lower incidence of side effects. Different biochemical abnormalities of metabolic bone disease have been associated with anemia of CKD. However, all of these abnormalities are closely inter-related and their individual effect on the development of anemia is uncertain. The study purpose was to assess the efficacy and tolerability of the treatment with sucrosomial iron in anemic patients with CKD and also to investigate the relationship between anemia, renal function and a set of metabolic bone disease biomarkers.

Methods: 30 patients (mean age 74.21years, range: 39-86 years) with CKD stage 3-5 (e GFR <60 mils/min, range: 12-48) and anemia along with iron depletion. All of the patients received oral sucrosomial iron once daily. Hematological profile, renal function and bone-mineral data were recorded at the beginning of the study and every 2 months until the end of the study protocol.

Results: We noticed that Hct levels increased from 33.3±1.87% at the beginning of the protocol to 36.61±2.72 in the end (p<0.05). Hemoglobin levels were 10.98±0.73 g/dl at the beginning of the study and ended to be 11.86±0.71 (p=NS). Ferritin levels also increased from 42.73±24.47 to 98.89±126.99 (p=NS). The above improvement of renal anemia profile drove the renal function (e GFR) of our patients to remain stable, during the 18th month period of the study. Correction of anemia helped PTH levels to decline over the study period from 359.05±447.24 pg/ml to 163.72±89.12 pg/ml (p=NS). Ca, K, Na levels remained stable without also significant changes. Oral iron was well tolerated and no significant adverse effects were recorded.

Conclusions: Oral sucrosomial iron seems to be a safe and efficacious alternative in managing CKD patients with anemia. Whether an association between PTH and hemoglobin also exists in patients with CKD is still unclear, yet in this study we noticed an association between PTH, e GFR and correction of anemia in CKD-patients.

PUB137

Clinical and Histopathological Characteristics in "Smoldering" ANCA Positive Vasculitis and Nephritis Over One Year before Burst of RPGN Eri Muso,[1,2] Youngna Kang,[2] Shuichiro Endo,[2] Yayoi Ogawa,[3] Hiroko Kakita,[1] Tomomi Endo,[1] Hiroyuki Suzuki,[1] Motoko Yanagita,[2] Tatsuo Tsukamoto.[1] *[1]Kitano Hospital, The Tazuke Kofukai Medical Research Institute, Osaka, Japan; [2]Kyoto University Graduate School of Medicine, Kyoto, Japan; [3]Hokkaido Renal Pathology Center, Sapporo, Japan.*

Background: RPGN is most frequent phenotype of renal involvement of AAV with typical pathology of crescentic GN accompanying necrotizing vasculitis. As in most cases RPGN is the start to investigate ANCA positivity and AAV, the clinical and especially pathological information in "smoldering " phase before the burst of RPGN is limited. Some ANCA positive patients, however, could be under histological analysis due to mild but apparent urinary abnormality. Previously, the comparing those who did not develop RPGN, those developed RPGN showed positive PTCitis and arteriolar wall thickening (Kang, Muso et al, 17th ANCA Wrokshop 2015). The clinic- pathological features of further accumulated cases were analyzed.

Methods: Cases received renal biopsy due to positive nephritic urine and serum ANCA were surveyed in three different hospitals in Japan. They did not complain any systemic symptoms of vasculitis nor rapidly progressive renal dysfunction. Among them, the clinical and histological features of those developed burst of rapidly progresive glomerulonephritis(RPGN) due to ANCA associated vasculitis later were analyzed.

Results: 6 cases (female:male: 2:4 age 17-82, average: 56.1 years)showed active hematuria and proteinuria. ANCA titers were 18-880EU, Cre : 0.8-1.45mg/dl. Histologically no necrotizing lesion nor vasculitis, however, wall thickening of arteriole

were noted. At that occasion, 2 cases were diagnosed as IgA nephropathy. After average of 1.7 years during when all cases did not receive steroid therapy except one, developed RPGN. All second biopsy of 5 of them showed crescentic GN with active and necrotizing vasculitis. Before burst of RPGN, ANCA were stably high or gradually elevated.

Conclusions: At least 10 months before the burst of RPGN, inflammatory swelling of arteriole might have started in ANCA positive patients showing nephritic hematuria and proteinuria even without systemic symptom of vasculitis. The accumulation of these cases of "smoldering" AAV which later developed RPGN should be performed to propose predictive clinical or histological parameters and appropriate therapeutic approach.

Funding: Private Foundation Support

PUB138

Urinary Angiotensinogen (uAOG) Levels Are Associated with Development of CKD in Type 1 Diabetes Daniel Batlle,[2] Alejandro Sanchez,[2] Sheeba H. Ba aqeel,[2] Jan Wysocki,[2] Minghao Ye,[2] Ahmed M. Khattab,[2] Alfred Rademaker,[2] Xiaoyu Gao,[1] Ionut Bebu,[1] Mark E. Molitch.[2] *[1]George Washington University, Rockville, MD; [2]Northwestern University Feinberg School of Medicine, Chicago, IL. Group/Team: For CKD Biomarkers Consortium and DCCT/EDIC Research Group.*

Background: uAOG has been reported to be increased in diabetic kidney disease (DKD) but its predictive value for DKD has not been demonstrated. Although AOG, like albumin, is filtered by a disrupted glomerular barrier, it is also produced intrarenally and thus any excess of AOG can activate the Renin Angiotensin System within the Kidney and trigger CKD progression. We examined if AOG was associated with the development of DKD using biosamples from participants in the Epidemiology of Diabetes Intervention and Complications (EDIC).

Methods: In a nested case-control design we performed a preliminary analysis of 34 cases from EDIC participants in whom GFR eventually fell to <60ml/min/1.73m^2 (Stage 3 CKD) as the study outcome. Controls were 51 EDIC subjects in whom eGFR remained well above 60ml/min/1.73m^2, followed over the same period and matched for age, gender, DM duration. Matching was done during the earliest EDIC visit where urine samples for AOG evaluation were available prior to development of CKD3 (average of ~2 yrs before CKD3, range 1-7). Analysis was by conditional logistic regression. Progressive Renal Decline (PRD, eGFR loss >3.5 ml/min/1.73m^2/yr) is an index used to predict ESRD. In a separate post-hoc exploratory analysis, uAOG levels were compared in a subset of the primary renal case/control group of 20 cases with PRD versus 53 without PRD, of whom 20 and 13 respectively were CKD3 cases. Analysis was by logistic regression with nominal p-values and AUC.

Results: The median uAOG in cases was higher than that of controls (13.9 vs 3.8µg/mg, p=0.027). uAOG was associated with the development of CKD3 after adjusting for eGFR (p=0.039) and HbA1c (p=0.043) but not for AER (p=0.50). The median uAOG in PRD decliners was higher than in non-decliners (29.8 vs 4.2µg/mg, nominal p=0.063). AOG was associated with eGFR decline after adjustment for HbA1C (p= 0.045) but not for eGFR (p=0.067) nor AER (p=0.13). The AUC for AOG was 0.77, a value not significantly better than that for AER 0.759

Conclusions: Urinary AOG is associated with the development of Stage 3 CKD. In addition, increased uAOG independently of eGFR or HbA1C is also associated with progressive renal decline, a strong index of progression to ESRD. uAOG is not significantly better than AER in predicting CKD or PRD.

Funding: NIDDK Support

PUB139

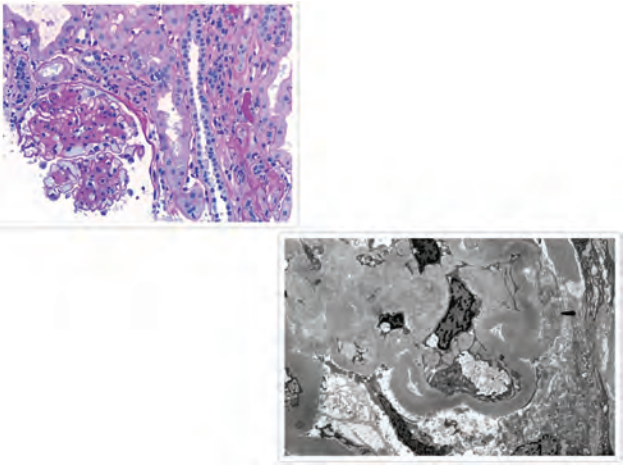
Idiopathic Nodular Glomerulosclerosis (ING) in an African American (AA) Male with Hepatitis C Nirmal K. Onteddu,[2] Anand C. Reddy,[2] Jayasri Duggirala.[3] *[2]Texas Tech University of Health Sciences, Odessa, TX; [3]Permian Research, Tampa, FL.*

Background: ING in non-diabetic patients is rare. We report this case to suggest the existence of yet unknown etiologies of ING other than previously known.

Methods: A 68-year-old AA male with BMI(22.5), hypertension and smoking presented with anasarca. His physical examination and laboratory workup showed -BP -156/96, 4+ pedal edema, hemogram was normal except for platelets117, creatinine 2.4, Urea 25, albumin 2.5, HbA1c of 5, 24hr urine protein 7.7gm, Hepatitis C antibody reactive, vasculitis workup was negative. On immunoelectrophoresis no free kappa light chains seen. Non specific increase in Alpha 2 globulins, monoclonal protein seen in gamma fraction of protein electrophoresis. Renal biopsy demonstrated nodular glomerulosclerosis. Congo red staining was negative. Immunofluorescence microscopy with human IgG, IgA, IgM, C1q, C3, albumin, fibrinogen, kappa and lambda immunoglobulin light chains was negative. No electron dense deposits.

Results:

Conclusions: Kimmelstiel and wilson described findings of nodular glomerulosis as a pathognomonic of diabetic nephropathy. Other causes of ING are diabetic nephropathy, amyloidosis, light chain disease, fibrillary and immunotactoid glomerulopathy, Collagen type 3 disease, nodular membranoproliferative glomerulonephritis and takayasu's arteritis. However our patient had a long history of smoking and hypertension, normal A1c and renal biopsy findings we diagnosed ING by exclusion. One cannot conclude that those risk factors alone caused his ING and ignore Hepatitis C antibody, MGUS as possible risk factors. He is currently treated with angiotensin converting enzyme inhibitors along with other anti hypertensive medications, smoking cessation. Long term follow up is needed to see if his renal function improve after treatment of hepatitis c and also with regular follow up on A1c as he may develop DM later.



1. Mesangial matrix expansion forming mesangial nodules with thickened and wrinkled glomerular basement membranes on EM

PUB140

The Factors Influenced on Change in Systolic Blood Pressure Variability in CKD Patients: The APrODiTe-2 1-Year Follow-Up Study Jiwon Ryu,[1] Sejoong Kim,[6] Ran-hui Cha,[4] Hajeong Lee,[7] Jung Pyo Lee,[5] Myung jin Choi,[2] Young rim Song,[3] Yon Su Kim.[7] *[1]Cheju Halla Hospital, Seoul, Republic of Korea; [2]Chuncheon Sacred Heart Hospital, Chuncheon, Republic of Korea; [3]Hallym Univ. Sacred Heart Hospital, Anyang, Republic of Korea; [4]National Medical Center, Seoul, Republic of Korea; [5]Seoul National University Boramae Medical Center, Seoul, Republic of Korea; [6]Seoul National University Bundang Hospital, Seongnam, GyeongGi-Do, Republic of Korea; [7]Seoul National University College of Medicine, Seoul, Republic of Korea.*

Background: The blood pressure variability (BPV) may be affected by several factors such as medication, underlying disease and others. We evaluated what factors may influenced change in the BPV in the APrODiTe study in chronic kidney disease(CKD) patients.

Methods: We recruited 378 hypertensive CKD patients with 1-year follow-up from 4 centers in Korea. The Systolic BPV (SBPV) was the mean value of the differences between systolic BP at every 30 minutes for 24 hours. The factors affecting BPV were considered such as anti-hypertensive drugs, diabetes mellitus (DM), smoking, alcohol, exercise, and CKD stages.

Results: After 1-year observation period, SBPV were increased by 2.9 mmHg (Initial SBPV, 20.8 ± 11.9 mmHg; final SBPV, 23.7 ± 10.7 mmHg; $P < 0.001$ by paired t-test). SBPV in patients treated with 2 different anti-hypertensive drugs (renin-angiotensin esterase inhibitor or angiotensin receptor blockers (RAAS blocker) and beta blockers (BB), BB + calcium channel blockers (CCB)) and 3 drugs (RAAS blocker, BB and CCB) sustained over 1-year observation ($P = 0.611$, $P = 0.588$ and $P = 0.481$ by paired t-test, respectively). The type of anti-hypertensive drugs such as RAAS blocker, BB and CCB did not influence on changes in SBPV. In diabetic patients, non-smokers and patients on early-stage CKD (stage 1-2), SBPV was not changed during the observation ($P = 0.072$, $P = 0.079$ and $P = 0.281$ by paired t-test, respectively).

Conclusions: We found that SBPV in CKD patients may be increased over times, and that multiple anti-hypertensive drug users may prevent the increase in SBPV, rather than the type of anti-hypertensive drugs.

PUB141

CKD in an Underserved Population with Cardiovascular Disease Hector Alvarado verduzco,[1] Carola A. Maraboto gonzalez,[3] Avantee V. Gokhale,[1] Tarek Rashid,[4] Anjali Acharya.[2] *[1]JACOBI MEDICAL CENTER, BRONX, NY; [2]Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY; [3]Jacobi Medical Center, BRONX, NY; [4]None, Fort Lee, NJ.*

Background: Chronic kidney disease (CKD) is a growing major health problem worldwide carrying a high morbidity and mortality as well as increased costs. Patients with underlying cardiovascular disease have a higher risk of CKD than the general population, however its prevalence in our diverse community hasn't been reported.

Methods: We conducted a retrospective review of our medical records to evaluate the prevalence of CKD in the Cardiology clinic during 6 months. Patients of age 18 years or older were included. Descriptive statistics were used and analysis was done using SPSS.

Results: A total of 498 patients were included: 192 (38.6%) Hispanic, 149 (29.9%) African-American, 14 (2.8%) Caucasians, 38 (7.6%) others, and 105 (21.1%) unclassified. Of this sample, 32% had CKD, which was defined according to an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 calculated from the MDRD equation.

Conclusions: CKD is highly prevalent in the Cardiology clinic in our unique population with high ethnic diversity, >75% of patients belonging to US minorities. These

results should help increase the awareness of this problem in the outpatient setting to promote early diagnosis and treatment of this condition, as well as prompt referral for specialized evaluation by Nephrology.

Parameter	
Age, years	62.0 +/- 13.8
Male	259 (52%)
Medical history	
Heart failure	189 (38%)
Coronary artery disease	225 (45%)
Hypertension	367 (74%)
Atrial fibrillation	83 (17%)
Diabetes	251 (50%)
Hyperlipidemia	265 (53%)
Laboratory values	
Creatinine, mg/dl	1 (0.8-1.3)
Left ventricular ejection fraction, %	60 (45-65)
Glomerular filtration rate	73 (53-89)
Chronic kidney disease (GFR <60)	161 (32%)
A1c, %	6.1 (5.6-7.6)
Medications	
Aspirin	341 (68.5%)
Beta-blocker	352 (71%)
Statin	364 (73%)
ACEi or ARB	275 (55%)

Continuous variable presented as mean +/- SD or median; categorical variables as N (%)

PUB142

Serum Myeloid-Related Protein 8 and 14 (MRP8/14) Are Increased in CKD Patients, Making It a Probable Novel Biomarker for Prognosis Tatsuki Matsumoto,[1] Yoshinori Taniguchi,[2] Daisuke Hashimoto,[2] Masami Ogasawara,[2] Tomohiro Eguchi,[2] Hirofumi Nishikawa,[2] Kazu H. Ode,[2] Yoshiko Shimamura,[2] Kosuke Inoue,[2] Taro Horino,[2] Yoshio Terada.[2] *[1]Kochi University, Nankoku, Japan, Japan; [2]Kochi university, Nankokushi, Japan.*

Background: Myeloid-Related Protein 8/14 complex (MRP8/14) is an endogenic ligand of toll-like receptor (TLR)-4, and is considered to be an inflammatory marker. Although it has been reported that MRP8/14 related to arteriosclerosis and coronary lesion in type 2 diabetes, there are no reports about the relationship between MRP8/14 and chronic kidney disease (CKD). We studied the association between MRP8/14 levels and renal function or the other parameter and renal prognosis in CKD.

Methods: A total of 432 patients (mean age 60±17) with CKD were enrolled. Serum samples were collected, and MRP8/14 levels were measured by using ELISA kit. Serum creatinine (Cr), blood urea nitrogen (BUN), uric acid (UA), urine protein/Cr ratio, and the other parameter of renal function were also measured. We follow up the prognosis of 250 patients for 3 years. This study was approved by Kochi Medical School review board. All patients provided written informed consent.

Results: MRP8/14 levels were positively associated with serum Cr (p=0.007, r=0.135), BUN (p<0.001, r=0.175), UA (p=0.011, r=0.127) levels, and urinary protein/Cr ratio (p<0.001, r=0.212), and Body Mass Index (BMI) (p<0.001, r=0.189). MRP8/14 levels were inversely associated with eGFR (p=0.006, r=-0.137). MRP8/14 levels significantly increased in CKD stage 5 (p<0.05; vs stage1-4). Moreover, MRP8/14 levels in CKD patients with diabetes and hypertension were significantly increased (p<0.05), compared to patients without diabetes and hypertension. Stepwise multiple regression analysis showed that MRP8/14 levels correlated well with BMI, Hb and urinary protein levels. The higher levels of MRP8/14 patients have a tendency of poor prognosis in 3 years.

Conclusions: Serum MRP8/14 significantly correlated with renal function and BMI in CKD patients, and might show that MRP8/14 is critical for disease progression and metabolic pathogenesis in CKD.

PUB143

A Parent-Child Case of Hyperlipoproteinemia and Early-Onset Obesity Complicating Obesity-Related Glomerulopathy Masanori Takaiwa,[1] Takayuki Miyai.[2] *[1]Matsuyama Red Cross Hospital, Matsuyama, Japan; [2]Okayama university, Okayama, Japan.*

Background: The relationship between the obesity-related glomerulopathy (ORG), typically characterized by proteinuria, glomerulomegaly and FSGS, and the high heritability of severe obesity is unknown. Hence, the accumulation of family cases of ORG is useful for searching the genetic factors of ORG. We report a parent-child cases of hyperlipoproteinemia with ORG combined.

Methods: Case 1: A 11-year-old Japanese boy was found to have obesity, progressive proteinuria and hematuria at the age of 3. At the time of the biopsy, he exhibited significant proteinuria (UP/CR ranging from 1.44 to 4.04). Serum albumin and eGFR were normal. CAKUT and congenital malformation syndromes were not found. He presented with obesity (BMI 33.2), hyperlipoproteinemia (triglyceride 234 mg/dl; total cholesterol 296 mg/dl). The biopsy detected glomerulomegaly and FSGS (perihilar variant). After the hospitalization receiving 2000 kCal diet, he lost weight and showed amelioration of UP/CR (from 0.61 to 1.28). He is diagnosed ORG and receiving valsartan and lisinopril. Case 2: A 46-year-old male, the father of the case 1, was diagnosed obesity, proteinuria and hematuria at the age of 14. Since renal biopsy performed at the age of 25 confirmed mild mesangial proliferation without positive immunostaining, no medication was initiated. At the age of 36, he was diagnosed obesity (BMI 26.0), hypertension, hyperlipoproteinemia (triglyceride 2225 mg/dl; total cholesterol 338 mg/dl), fatty liver, type 2 diabetes, significant proteinuria (dipstick 3+) and hematuria. He initiated exercise, nutritional guidance, glimepiride, amlodipine, telmisartan and fenofibrate. 5 years later, he maintained improved BMI (23.0), blood pressure, triglyceride (300 mg/dl), total cholesterol (138 mg/dl), and HbA1c (6.6%). In parallel, the urine dipstick analysis was normalized.

Results:

Conclusions: Although further investigation is required, this parent-child case may suggest the benefit to clarify the relationship between ORG and the genetic causes of hyperlipoproteinemia. A family history of hyperlipoproteinemia could be a potent indicator for diagnosing ORG and might avoid unnecessary use of steroids and immunosuppressants. *Vice versa,* early diagnosis of ORG might lead to a sufficiently early detection of hyperlipoproteinemia to prevent the cardiovascular complications.

PUB144

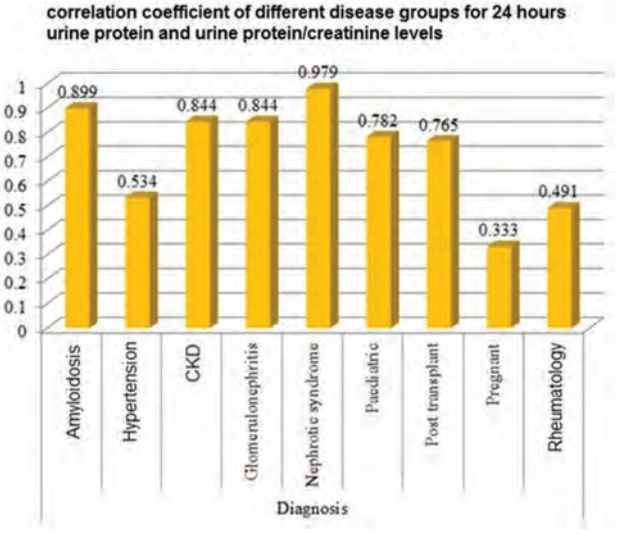
The Diagnostic Significance of Urine PR/CR Ratio and Its Replacement Capability of 24 Hours Urine Protein in Indian Non Diabetic Nephropathy Patients Hariharan R. Munganda,[1] Jitendra Kumar,[1] Punit Pruthi.[2] *[1]Asian institute of medical sciences, Faridabad, Haryana, India; [2]internal medicine, Asian Institute of Medical Sciences, FARIDABAD, India.*

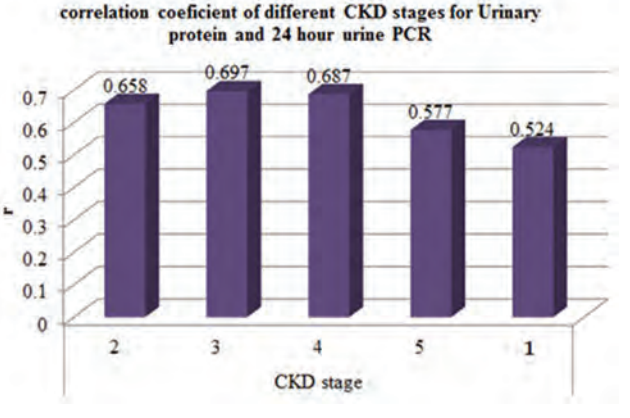
Background: The measurement of urinary protein excretion provides a sensitive marker of of kidney disease from early to advanced stages. U Pr/Cr ratio as a screening tool helps in categorisation of diseases and helps in early intervention and treatment strategy but 24 hrs urine protein still remains as a gold standard. It may be scientifically incorrect to use these tests interchangeably across all patient population.

Methods: Correlations between quantitative variables of 300 patients were evaluated using Pearson's Correlation coefficient. (SPSS) software version 15.0 was used for the statistical analysis. Diabetic nephropathy, ESRD patients on dialysis, Multiple myeloma patients were excluded

Results: Correlation between 24 hrs UP and U Pr/Cr is poor in patients with proteinuria range < 150 mg(r=0.119) and 150-300mg/24 hrs(r=0.143), this may be because the validation in international literature is mainly for albumin but in our study it was protein that was focussed, as it has varied sources. Moderate in >300 mg/24 hour (r=0.48). Best in 24 hrs UP range of 900-3000 mgs and U Pr/Cr ratio of 0.9-3.

Conclusions: U Pr/Cr ratio even in random fresh urine samples taken at any time of the day shows good correlation and seems to be an reliable alternative for 24 hrs UP. Advised 24 hours urine creatinine should be checked along with 24 hrs urine protein to know the adequacy of urination.





PUB145

In Search of Mesoamerican Nephropathy: Albuminuria as a Marker for Renal Damage in an Agricultural Community on Guatemala's Southern Coast Ever O. Cipriano,[3] Marcos Rothstein,[1] Vicente J. Sanchez polo.[2] *[1]Barnes-Jewish Dialysis Center, St. Louis, MO; [2]guatemalan social security institute, Guatemala City, Guatemala; [3]Nephrology, Instituto Guatemalteco de Seguridad Social, Guatemala, Guatemala.*

Background: In 2002, in El Salvador, a non traditional Nephropathy was described among young male adults, sugar cane workers, in the geographical region that includes Southeast Mexico, Guatemala, Belize, El Salvador, Honduras, Costa Rica and Panama. This Chronic Renal Disease of Non-Traditional Causes has claimed many lives at the Central American level and in Guatemala this entity has also been observed particularly in habitants of the coast of Pacific region of Guatemala.

Methods: OBJETIVES Identify kidney damage using albuminuria as a marker of renal damage in high risk population of southern coast in Guatemala. METHODS Cross-sectional, population-based prevalence study Conducted in the agricultural communities of El Terrero and La Gomera in Escuintla, Guatemala. All individuals ages 10 and older were included. Labs – All patients had a urinalysis. Serum glucose and creatinine was randomly checked in patients with + albuminuria on urinalysis.

Results: See the Pictures.

Conclusions: A high prevalence of albuminuria (as a marker of renal disease) was noted in the studied rural community along the Guatemalan coast. There was no observed relationship between sugar cane workers and prevalence albuminuria or hematuria. Majority of identified patients with CKD did not have diabetes.

	Patients > 10 years		Adult Patients
	N=54		N=192
CLINICAL EVALUATION			
Weight Kg X (DE)	41,08 (16,4)		68,31(34,31)
Height Cm X (DE)	144,3 (12,1)		163,43 (94,88)
Abdominal C. X (DE)	71,02 (11,19)		91,88 (12,88)
Systolic P. X (DE)	103,4 (6,8)		119,11 (12,83)
Diastolic P. X (DE)	65,7 (7,1)		74,49 (10,18)
Glycaemia X (DE)	97,8 (14,6)		136 (74)
Body Mass Index X (DE)	19,08 (6,3)		27,80 (14,82)
LABS			
Leukocytes (n/%)			
Negative	40 (74)		97 (51)
Positive	14 (26)		95 (49)
Blood (n/%)			
Negative	49 (90)		13(6,8)
Positive	5 (10)		179 (93,9)
Microalbumin Micraltest (n/%)			
Negative	33 (61)		68 (35)
Positive	21 (39)		124 (65)
eGFR (N: 80 Patients) ml/min MDRD			**50.69 (23.02)**

CHARACTERISTICS OF PATIENTS			
		Patients > 10 years	Adult Patients
	N=54		N=192
Age X (DE)		12,3 (2,3)	42,9 (17,7)
Gender (%)			
	Male	26 (48)	51 (26,6)
	Female	28 (52)	141 (73,4)
Place of Birth (n/%)			
	El Terrero	27 (50)	106 (55)
	La Gomera	20 (37)	29 (15)
	Other	7 (7)	57 (29)
Place of Residence (n/%)			
	El Terrero	53(98)	190 (99)
	Other	1 (2)	2 (1)
Work History (n/%)			
	Agricultural Work	-	41 (25)
	Housewife	-	130 (67)
	Sugar Cane Cut	-	46 (24)
	Other	-	24 (12)
Medical History			
Personal History (n/%)	Diabetes	-	24 (12)
	Hypertension	-	47 (24)
	CDK	-	7 (3,6)
	Hyperuricemia	-	29 (15)
	Dyslipidemia	-	14 (7,3)
Family History (n/%)	Diabetes	32 (59,3)	88 (45)
	Hypertension	18 (33)	62 (32)
	CDK	6 (11)	20 (10,4)
	Hyperuricemia	7 (13)	
Medicine Ingest (n/%)			
	Antibiotics	13(24)	15 (7,8)
	Analgesics	17 (31)	100 (52)
Urinary Infections (n/%)			
	< 3/Year	7 (13)	57 (29,7)
	3-5 /Year	21 (38)	57 (29,7)
	> 5 Year	12 (22)	29(26)
Habits (n/%)			
	Tobacco		17 (8,9)
	Alcoholic Beverages		47 (24)
	Carbonated drinks (Sodas)	**53 (98)**	**186 (96,9)**

PUB146

Performance of 8 Equations to Evaluate Baseline and Postoperative eGFR Changes in Patients with Morbid Obesity Undergoing Bariatric Surgery Ricardo E. Varela, Fabiola Gallardo, Diego L. Carrillo Perez, Ricardo Correa-Rotter, Luis E. Morales-Buenrostro. *Instituto Nacional de Ciencias Medicas y Nutrición Salvador Zubirán, Ciudad de México, Mexico.*

Background: Many current equations employed to estimate GFR do not take in account anthropometric variables. Gold standard measured GFR techniques show reduction in glomerular hyperfiltration in obese individuals after significant weight loss. The aim of this study was to evaluate the performance of 8 equations to detect eGFR changes after bariatric surgery.

Methods: We retrospectively analyzed a cohort of morbidly obese patients subjected to bariatric surgery between 2000-2014. We compared 8 eGFR equations before and 12 months after surgery. T test or Wilcoxon test were used for comparison of repeated measures.

Results: 168 patients were analyzed, mean age of 38.3 ± 9 years. All equations that included anthropometric measures showed a decrease in eGFR at 12 mo, in accordance to what has been shown with measured GFR, while all formulas that do not include anthropometric measures displayed an increase in eGFR (Table).

Conclusions: In this study, equations that included anthropometric variables demonstrated reduction in glomerular hyperfiltration, similarly to what has been reported in studies with gold-standard measured GFR. Other currently used equations standardized to a body surface of 1.73m^2 should not be employed in patients with morbid obesity. The only equation developed for obese individuals is the Salazar Corcoran, yet there is a need of eGFR concordance studies in obese individuals between measured GFR and estimation equations.

Equation	Basal eGFR Mean ± SD	12m eGFR Mean ± SD	p
CKD-EPI (ml/min/1.73m2)	102.3 ± 17.8	109.0 ± 14.7	< 0.001
CKD-EPI adjusted to BSA (ml/min/BSA)	145.2 ± 33.6	127.6 ± 26.5	< 0.001
MDRD (ml/min/1.73m2)	100.1 ± 23.1	110.3 ± 23.9	< 0.001
MDRD adjusted to BSA (ml/min/BSA)	140.9 ± 40.2	128.7 ± 34.2	< 0.001
CG-TBW* (ml/min)	191.6 ± 64.3	141.8 ± 46.9	< 0.001
CG-LBW** (ml/min)	88.9 ± 26.5	80.7 ± 24.4	< 0.001
CG-40%*** (ml/min)	125.7 ± 36.9	110.3 ± 30.1	< 0.001
Salazar Corcoran (ml/min)	138.6 ± 38.6	122.1 ± 32.2	< 0.001

* Cockcroft-Gault adjusted to total body weight, ** Cockcroft-Gault adjusted to lean body weight,

*** Cockcroft-Gault adjusted to 40% of total body weight. BSA: body surface area.

PUB147

Accurate eGFR Reporting in Children Independent of Height Emil Den bakker,[3] Isabelle Hubeek,[2] Joanna Van Wijk,[5] Reinoud R. Gemke,[4] Arend Bokenkamp.[1] *[1]VU Medical Center, Amsterdam, Netherlands; [2]VU university medical center, Amsterdam, Netherlands; [3]VUMC, Duivendrecht, Netherlands; [4]VUmc, Amsterdam, Netherlands; [5]Vrije Universiteit University Hospital Amsterdam, Amsterdam, Netherlands.*

Background: Background Reporting estimated GFR (eGFR) instead of serum creatinine (crea) leads to earlier recognition and more timely referral of patients with suspected kidney failure and has been implemented in current guidelines both for adults and children. Due to varying muscle mass, which is related to height, most creatinine-based equations for children require height, a patient characteristic not standard available in many settings. An approach using age-related creatinine reference data has been developed by Pottel et al (2008). Cystatin C (CysC), an alternative marker for GFR, is independent of muscle mass and CysC based eGFR equations do not require anthropometric data. Combining crea and CysC-based eGFR has been shown to significantly increase the accuracy of GFR estimation in children. <!--[endif]----> <!--[endif]----> **Aim** To study the accuracy of combining crea and CysC based *height-independent* equations for GFR estimation in children. <!--[endif]---->

Methods: Methods Single injection inulin clearance tests were done in a convenience sample of children on clinical grounds with a simultaneous serum crea and CysC measurement. GFR was estimated from crea using the CKid1<!--[endif]----> (Schwartz et al, 2012) (height-dependent) and Pottel (height-independent) equations and by the cysC-based CKid2 equation (Schwartz et al, 2012). The mean of pairs of the crea and CysC based equations was calculated and the bias and p30 accuracy analyzed.<!--[endif]---->

Results: Results A total of 459 measurements were done in 459 children (or 459 bloodsamples?) and adolescents aged 1 month to 19.5 years. Of the creatinine-based equations CKid1 (bias 4.7 ml/min/1.73m^2, p30 accuracy 82.1%) outperformed Pottel (bias -15.6, p30 accuracy 76.3%). CKiD2 (bias 14.3, p30 accuracy 80.8) performed similarly to CKid1. The combination of a crea and a CysC based equations markedly increased accuracy and decreased bias. The mean of Pottel and CKid2 (bias -0.6, p30 accuracy 87.8%), performed as well as the mean of CKid1 and CKid2 (bias 9.5, p30 accuracy 89.1%).

Conclusions: Conclusion Combining the Pottel creatinine and the CKid2 Cystatin C-based eGFR equations enables accurate allows for GFR estimation in children *independent of height* with good accuracy and which allows for direct can eGFR be reporting reported directly by the laboratory.

PUB148

CKD in HIV-Infected Patients: Relationship with Comorbidities Rosbel M. Brito,[2] Justine Johnson,[2] Eric J. Lai,[2] Rochelle E. Castro,[4] Edward A. Graviss,[3] Duc T. Nguyen,[3] Angelina Albert,[1] Ann S. Barnes,[4] Wadi N. Suki.[5] *[1]Houston Methodist, Houston, TX; [2]Houston Methodist Hospital, Houston, TX; [3]Houston Methodist Research Institute, Houston, TX; [4]Legacy Community Health, Pearland, TX; [5]None, Houston, TX.*

Background: Use of HAART has increased life expectancy in HIV-infected patients, but also is related to the development of traditional cardiovascular risk factors like HTN, dyslipidemia, and insulin resistance, among other conditions. Our aim, determine the association between HAART use, CKD, and various comorbidities frequently found in HIV-infected patients

Methods: Retrospective cohort study (2012-2016) in 3719 HIV-infected patients followed in a Federally-qualified community clinic. Prevalence of CKD (defined by the CKD-Epi Equation as eGFR<60 ml/min/1.73m^2) was determined, and its relationship with potential comorbidities examined

Results: A REDCap database was created with 3719 HIV-infected patients. CKD was present in 4.11% of the population. CKD patients were generally older, males, African American, and had HIV infection for longer. The association of different comorbidities with CKD compared with non-CKD patients was as follows:CKD patients had higher proportions of HTN (63.4% vs 27.0%,p<0.001), DM2 (15.0% vs 8.1%, p=0.003), hyperlipidemia (35.3% vs 23.3%,p=0.001), cardiovascular disease (9.2% vs 4.1%,p=0.002), cerebrovascular disease (6.5% vs 1.5%,p<0.001), HBV (9.2% vs 4.8%,p=0.02), oral candidiasis (13.7%vs8.4%,p=0.03), CMV infection (9.8%vs5.3%,p=0.02), HSV (20.9%vs15.8%, p=0.09), history of kidney stone (4.6%vs1.6%,p=0.01), and positive smoking status (40.5%vs47.4%,p=0.08). In all the 3714 patients, smoking, HTN, hyperlipidemia, and HSV infection were the most frequent comorbidities detected (47.5%, 28.5%, 23.8% and 16.0%, respectively). Other comorbidities were found in less than 10% of patients. In the CKD group, the most common comorbidity was hypertension, present in nearly two-third of the patients. On the other hand, smoking was the most common comorbidity in the non-CKD group with nearly all patients having ever smoked

Conclusions: Progressive loss of kidney function over a period of months or years, has become one of the leading causes of mortality among HIV-infected patients. HIV infection, and its treatment are often associated with comorbidities that adversely impact kidney function, such as diabetes mellitus, dyslipidemias, and hypertension. Early detection, a corrective treatment, and a meticulous follow-up of these conditions are the cornerstone of measures to decrease morbidity and mortality in HIV- infected patients

PUB149

Kidney Function in HIV-Infected Patients Seen in a Community Clinic: Characteristics and Natural History of the Disease Rosbel M. Brito,[2] Justine Johnson,[2] Eric J. Lai,[2] Rochelle E. Castro,[4] Edward A. Graviss,[3] Duc T. Nguyen,[3] Angelina Albert,[1] Ann S. Barnes,[4] Wadi N. Suki.[5] *[1]Houston Methodist, Houston, TX; [2]Houston Methodist Hospital, Houston, TX; [3]Houston Methodist Research Institute, Houston, TX; [4]Legacy Community Health, Pearland, TX; [5]None, Houston, TX.*

Background: The kidney plays a role in the metabolism and excretion of some antiretroviral drugs (ARV), and this makes it more vulnerable to various types of injury that can lead to blood and urinalysis abnormalities. Our aims were to identify patients with reduced renal function according to the KDIGO stages of kidney disease;to characterize the nature of the kidney disease encountered and to determine the rate of loss of renal function

Methods: Retrospective cohort study (2012-2016) in 3,719 HIV-infected patients seen in a Federally-Qualified community clinic. Blood and urine laboratory results were extracted from medical records. Changes in eGFR were derived from multiple serum creatinine values collected over time

Results: We measured GFR for each patient and staged patient's kidney function based on the KDIGO Clinical Practice Guideline Figure 1.153 patients (4.1%) had CKD. As compared to patients with better preserved kidney function patients with CKD were likely to have a lower level of HGB than non-CKD patients median 13.5 vs 14.4g/dl and lower level of albumin median 4.3 vs 4.4g/dL p<0.001 and higher levels of K^+ median 4.40 vs 4.30mEq/L in the non-CKD group p=0.01. Na^+ and CL^- were not significantly different between the two groups. $C0_2$ was 22mol-1 in the CKD patients vs 23mol-1 in non-CKD group p<0.001. The CKD patients also had a significantly greater decline in their eGFR, from first to the last follow-up reflecting a median percentage change of -26.5 versus 0 ml/min/1.73m^2 (IQR-9.2, 8.5) in non-CKD patients p<0.001. The median rate in eGFR changes per year was -4.0 vs -0.2 ml/min/1.73m^2/year in the non-CKD counterpart p<0.001. Data from urinalysis were insufficient for significant statistical analysis.

Conclusions: CKD was present in 4.1% of a population of HIV-patients. The disease did not appear to have any distinctive characteristics. However, in the affected patients the rate of loss of renal function appeared to be fairly rapid

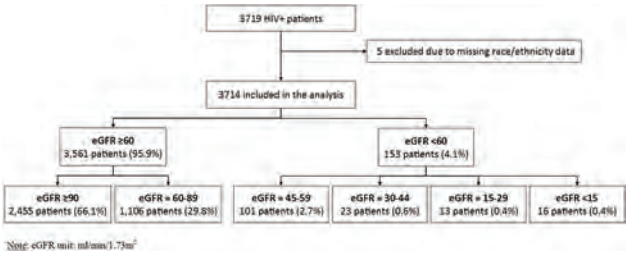


Figure1. Study flowchart to stablish cohort of patients with and without CKD

PUB150

Utility of Reticulocyte Haemoglobin Content as a Marker of Iron Deficiency Anaemia in Black CKD Patients in South Africa Aishatu M. Nalado,[1,3] Saraladevi Naicker.[2] *[1]Aminu Kano teaching hospital, Kano, Nigeria; [2]University of the Witwatersrand, Johannesburg, South Africa; [3]MEDICINE, Charlotte Maxeke Academic hospital, Johannersburg, South Africa.*

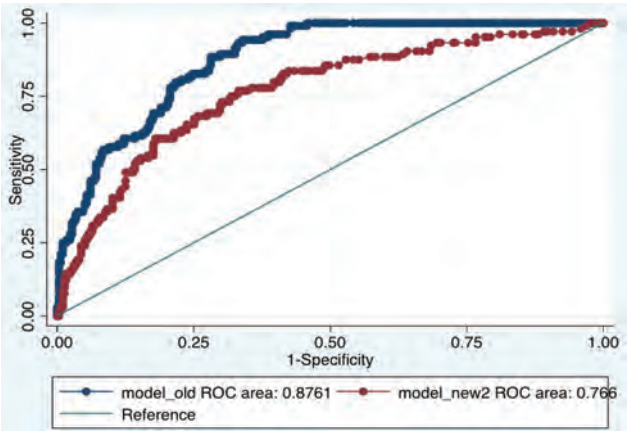
Background: : Anaemia is a common cause of morbidity and mortality among CKD patients. Early diagnosis of iron deficiency anaemia (IDA) is essential to initiate prompt treatment and improve prognosis. Various biochemical parameters are used to diagnose IDA with varying validity. We evaluated the ability of CHr to predict IDA in black pre-dialysis CKD patients.

Methods: : This was a cross- sectional study of 258 pre-dialysis CKD patients and 141 age- and sex-matched healthy controls at the renal outpatient clinic of Charlotte Maxeke Johannesburg Academic Hospital between 1 June 2016- 30 December 2016. Haematological and biochemical parameters were analysed, using standard laboratory methods. Univariate and multivariate logistic regression was conducted to determine the predictors of IDA. Receiver operator characteristic (ROC) curves were conducted on CHr, TSAT and Ferritin. Parametric ROC analysis was used to determine the validity of CHr in the diagnosis of IDA. The validity of CHr was compared with TSAT and Ferritin using the ROC curves.

Results: : Table 1 shows characteristics of the study population. The prevalence of IDA was 26% and the prevalence of functional IDA was 13-fold higher in CKD patients as compared to controls (18.6% vs 1.4%, P <0.001). The discriminating value of iron deficiency by CHr is fairly good (AUC=73%; sensitivity=71.2%; specificity=71.2%), but lower than that of the conventional parameter (TSAT and Ferritin) (0.88 vs 0.73; P=0.02).

Conclusions: Although the predictive value of CHr in diagnosing IDA among pre-dialysis CKD patients was lower than the conventional methods, CHr can still be proposed in our environment, when considering the trade off in terms of cost, accessibility and ease of performance.

Funding: Private Foundation Support



PUB151

Sacubitril/Valsartan in CKD: A Nephrologist Point of View Borja Quiroga,[2] Antonio De santos wilhelmi,[4] David S. Sapiencia Sanjines,[3] Yamila Saharaui,[1] Antonio manuel R. Gonzalez,[3] Vicente Álvarez.[1] *[1]Hospital Universitario de La Princesa, Madrid, Spain; [2]Nephrology, Hospital Universitario de La Princesa, Madrid, Spain; [3]Hospital de La Princesa, Madrid, Spain; [4]Spanish National Health Service, Madrid, Spain.*

Background: The angiotensin receptor neprilysin sacubitril/valsartan(SV) reduces cardiovascular morbidity and mortality in patients with systolic dysfunction(SD) as shown in the PARADIGM-HF study. Renal function in patients with chronic kidney disease(CKD) has not been evaluated as a hard endpoint in clinical trials. In this study, we include patients with CKD and SD in order to assess their renal function after initiating SV.

Methods: In this prospective study, we included 41 consecutive patients with CKD and SD. We included patients with NYHA class II to IV being receiving maximal tolerated doses of optimal medical therapy including angiotensing converting enzyme inhibitors (ACEi), beta-blockers and mineralcorticoid receptor antagonist if appropriate. At baseline, comorbidities and epidemiological data was collected and low doses of SV were initiated. At month 1 and 3, doses of sacubitril/valsartan were rise up to maximal doses. At each visit (baseline, 1 month and 3 month), we evaluated renal function, estimated glomerular filtration rate (GFR) with CKD-EPI, pro-brain natriuretic peptide and changes in body composition using bioimpedance spectroscopy (BIS).

Results: Of the 41, 30 patients(73.2%) were men, with a mean age of 76±13 years. Regarding comorbidities, 39 patients (95.1%) had hypertension, 20(48.8%) were diabetic, 30(73.2%) had dyslipidemia and 5(12.2%) had history of cerebrovascular disease. Thirty six patients(87.8%) had history of ischemic heart disease, with a mean left ventricular ejection fraction of 33±8. Creatinine at baseline was 1.55±0.52 mg/dL(GFR estimated by CKD-EPI 46±20 ml/min/1.73m^2). After one month of treatment GFR improved a mean of 2.6(0.1-5.1) ml/min/1.73m^2 (p=0.03). At fourth month, renal function was stable and no differences in GFR were observed respecting baseline (p= 0.47). Diuretics were diminished or eliminated in 30 patients(73.1%). However, no differences in overhydration (measured using BIS) during the study were observed.

Conclusions: SV is safe in CKD and offers a transient improvement in renal function. Long-term clinical trials are required to confirm this results.

PUB152

Length of Stay Implications of Anemia in Patients with Heart Failure Exacerbation in an Inner-City Hospital Avantee V. Gokhale,[1,3] Samuel Mon-Wei Yu,[2] Poonam Mahato,[2] Pitchaphon Nissaisorakarn,[2] Anjali Acharya.[3] *[1]JACOBI MEDICAL CENTER, BRONX, NY; [2]Jacobi Medical Center, Bronx, NY; [3]Jacobi Medical Center, Albert Einstein College of Medicine, Bronx, NY.*

Background: Anemia is a known risk factor for poor survival, frequent hospitalization, and impaired life quality in patients with heart failure. Severe anemia [hemoglobin (Hb) < 9] is associated with poor hospital and patient outcomes in heart failure patients with chronic kidney disease. However, this relationship in patients with mild-to-moderate anemia is unclear. Hence, we assessed the relationship of admission Hb to the length of stay (LOS) during a hospitalization in patients admitted with acute decompensated heart failure (ADHF) in an inner-city hospital catering mainly to a minority patient population.

Methods: 118 consecutive patients admitted between 01/01/15 to 06/30/16 with a diagnosis of ADHF were included. Retrospective chart review was performed to gather demographics, lab data on admission and LOS. The cohort was stratified based on the presence of mild-to-moderate anemia defined by Hb levels, <12 for women and <13 for men and a lower Hb cut-off level of 9. Statistical analyses included descriptive statistics and multivariable regression analyses.

Results: Of 118 patients (mean age=69), 69 (59%) had mild-to-moderate anemia. They were older (71±13 vs. 66±14, p=0.01), but had similar gender distribution (males: 54% vs. 59%) compared to those without anemia (n=49). More anemic patients were on beta-blockers (83% vs. 63%, p=0.02). Despite similar pro-BNP levels, anemic patients had a longer LOS [median (IQR): 8 (5-14) vs. 6 (5-8); p=0.03] and a higher fraction with LOS > 7 days (54% vs. 29%; p<0.001). LOS was inversely associated with Hb levels on admission (**beta**=-0.16, p=0.01) and the association persisted beyond demographics, history of chronic kidney disease, beta blocker use, ACEi/ARB use, diuretics and BUN/creatinine on admission (**beta**=-0.18, p=0.03). Finally, compared to anemic patients, patients with normal Hb levels had lower odds of prolonged LOS (>7 days) [OR (95% CI): 0.32 (0.16-0.64), p<0.001] after adjustment.

Conclusions: In conclusion, LOS is inversely associated with admission hemoglobin in ADHF patients. even among patients with mild-to-moderate anemia. These findings confirm results of STAMINA–HF. Hence, Hb could be a modifiable risk factor for decreasing LOS, however, larger prospective studies are needed to confirm our findings.

PUB153

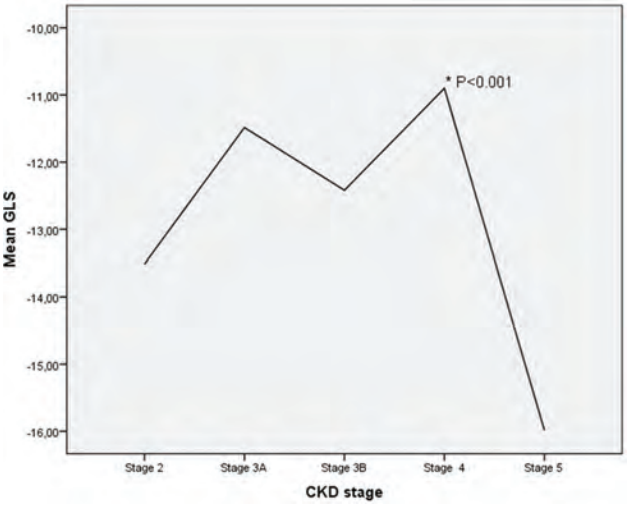
Global Longitudinal Strain (GLS) as Cardiac Imaging in Mid-Range Heart Failure (HF) (LVEF 40-49%) and CKD Stages 1-5ND Secundino Cigarran,[1] Jose Lomban,[2] Jesus Calvino,[3] Nicolas Menendez,[1] Ana maria Sanjurjo amado,[1] Juan Latorre,[1] Nuria C. López,[1] Lourdes Gonzalez tabares,[3] Belen Rodriguez delgado.[1] *[1]Nephrology, Eoxi Cervo-Lugo-Monforte, Burela, Spain; [2]Cardiology, Eoxi Cervo-Lugo-Monforte, Burela, Spain; [3]Nephrology, Eoxi Cervo-Lugo-Monforte, Lugo, Spain.*

Background: CKD carry a high CV risk and imaging plays a key role in assessing the severity and providing risk stratification. HF mid range LVEF 40–49% is considered that represent a grey area, most probably have primarily mild systolic dysfunction and features of diastolic dysfunction. A novel method is GLS tissue doppler imaging, which evaluate the degree of deformation in space and time of myocardial fibers during systole and diastole. The aim of this study is to assess GLS in CKD stages 1-5ND with mid range HF.

Methods: 105 pts (22.9% W, 50.5% DM2), median age 73 years. 21% CKD 1&2; 53.3% CKD 3A&3B; 25.7% CKD 4&5. All evaluated anthropometrically, and body composition was by BIVA (EFG, Akern, Fl, Ita). Anemia markers, bone metabolic disease, renal function (GFR CKD-EPI & ACR) were assessed. Peripheral arterial disease by ankle-arm-index (AAI) and carotid US and AGEs by skin autofluorescence and vascular age as well. Ecocardiography tisular doppler was performed by the same author (JAL) and derived measures were GLS, E/é, E/A & Vol LA (LAVI: VolLA/sc (m^2).

Results: Mean LVEF 45.15±2.6%. Mean GLS -12.6±3.8% (Normal: -20%). GLS was significantly higher with Charlson Index (r:.297; p=0.05), vitamin D (r:-.347; P=0.023), E/A (r: -373; p=0.039); Vol LA index (r: 268; p< 0.040). DM vs noDM (-11.80±3.5% vs -13.4±4.0; p=0.007); PAD vs NPAD (-10.2 ± 4.0% vs -13.4±3.56%; p= 0.024); atherosclerosis vs no atherosclerosis (NS).[Image1] shows GLS through CKD stages.

Conclusions: CKD from early stages, left ventricular becomes stiff and less contractile. HF mid range LVEF constitute a grey area poorly studied. In CKD may be an early mortality marker. The evolution of left ventricular functionality with GLS assess CV risk. Futher prospective studies are need to confirm these findings.



PUB154

Abstract Withdrawn

PUB155

CKD and Carotid Atherosclerosis Are Associated with Symptomatic Stroke Keiko Tanaka,[3] Haruhito A. Uchida,[2] Nobuo Kajitani,[5] Yuki Kakio,[3] Masashi Kitagawa,[4] Hitoshi Sugiyama,[4] Jun Wada.[1] *[1]Okayama, Japan; [2]Okayama Univeristy, Okayama, Japan; [3]Okayama University, Okayama, Japan; [4]Okayama University Graduate School, Okayama, Japan; [5]Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan.*

Background: Symptomatic stroke is the most prevalent cardiovascular and neurological diseases in Asia. However, the relationship between stroke, atherosclerosis and chronic kidney disease (CKD) has not been fully investigated. We aimed to investigate the relationship between CKD, symptomatic stroke, and carotid atherosclerosis.

Methods: We enrolled 455 subjects who underwent carotid ultrasonography in our hospital. Three hundred eleven patients were examined with carotid ultrasonography at the onset of symptomatic brain infarction, and 144 patients without any symptoms were examined. Carotid intima-media thickness (IMT), rate of internal carotid artery vasoconstriction, and maximal plaque size were measured using high-resolution B-mode ultrasonography.

Results: The mean age was 68.5 ± 11.0 years, and the mean estimated glomerular filtration rate (eGFR) was 68.8 ± 18.2 ml/min/1.73m^2. After adjustment for cardiovascular risk factors, the mean IMT in patients with CKD showed significant progression in comparison to those without CKD. Moreover, the IMT and eGFR were negatively correlated in patients with stroke (r = -0.169, p = 0.003). The mean IMT, plaque size, and vasoconstriction area were found to be significant determinants of symptomatic stroke after the adjustment of multivariate risk factors. The eGFR was found to be a negative determinant of stroke after adjusting for risk factors (OR (95%CI) = 0.877 (0.777-0.990), p = 0.034).

Conclusions: This study demonstrated that CKD could be associated with the progression of carotid atherosclerosis in patients with symptomatic stroke.

PUB156

The Role of Peritoneal Dialysis in Congestive Heart Failure: One Center Experience Panagiota E. Giannou,[2] Athanasia Kapota,[2] Aikaterini Damianaki,[2] Giorgos Bougatsos,[2] Christina Chrysohoou,[1] Dimitrios Petras.[2] *[1]Cardiology department, Hippokration Hospital, PIKERMI RAFINA, Greece; [2]Nephrology Department, Hippokration Hospital, ATHENS, Greece.*

Background: Peritoneal ultrafiltration (PUF) could be an effective strategy for the treatment of wastewater without compromising cardiac output and thus the renal function in patients with advanced congestive heart failure (CHF). The objective of this study is to determine the therapeutic role of PD in the management of patients with advanced CHF and renal dysfunction.

Methods: We studied retrospectively 15 patients who met the following inclusion criteria: (i) at least two nonscheduled hospitalizations for acute heart failure (AHF), the last episode in the last six months (ii) functional class NYHA III / IV (iii) persistent congestion despite optimal treatment with diuretics and (iv) the presence of renal dysfunction [estimated glomerular filtration rate (eGFR) <60 ml / min/1,73 m^2].

Results: After the first 6 months patients improved the stage of heart failure (from stage NYHA III / IV in II / III), dramatically reduced hospitalizations due to cardiac symptoms, improved quality of life, maintained satisfactory diuresis (>1000ml/day) thus maintained residual renal function (mean eGFR>35 ml/min/1,73 m2), preserved hemodynamic stability, improved lower limps edema and ascites.

Conclusions: All the data gathered to date from observational studies on the role of PUF as treatment adjuvant to standard pharmacotherapy, in patients with severe CHF refractory to optimal treatment, are encouraging and indicate their efficacy as well as safety. Given that the complications such as peritonitis or leaks are relatively rare, it seems that the benefits of the therapy far outweigh its risks. The possible mechanisms of clinical improvement in patients with CHF by PUF appear to be multifactorial. The reduction of preload and clearance of vasoactive-inflammatory agents seem to be the main factors. Only the results of multicenter, randomized trials may answer the question whether PUF could extend patient's lifespan. The close cooperation of cardiologists and nephrologists could identify patients with CHF who would benefit from PD, as the method is not widely used because it does not apply to all centers, but mainly because doctors are not familiar with the process and not advice it to patients as an alternative therapy.

PUB157

Resistin as a Predictor of Hospital Admission Due to Cardiovascular Events Filipa B. Mendes,[1] Luisa H. Pereira,[1] Ana P. Silva,[2] Pedro L. Neves.[3] *[1]Centro Hospitalar do Algarve, Faro, Portugal; [2]Hospital de Faro E.P.E, Faro, Portugal; [3]Centro Hospitalar Algarve, Faro, Portugal.*

Background: The hormone resistin appear to have a relevant role on several pathological pathways in complex illness such as diabetes, cardiovascular disease, liver disease, chronic kidney disease, auto-immune disease and several inflammatory conditions. More than that, high serum resistin levels have been associated with increased risk of cardiovascular disease in the general population. Diabetic and renal impaired patients seems to present with the biggest risk. The aim of this study is to determine the role of serum resistin levels as a predictor of hospital admissions triggered by cardiovascular episodes in type 2 diabetic patients with mild to moderate CKD.

Methods: An observational study enrolled 78 diabetic patients with mild to moderate CKD which were screened and selected in an outpatient diabetic nephropathy clinic and were followed from January 2008 to December 2016.

Results: Out of the total 78 patients included, 13 were admitted at the hospital and newly diagnosed with cardiovascular pathology. There was a statistically significant result for resistin as a predictor of cardiovascular related hospital admissions (p <0.05). Laboratory parameters such as creatinine clearance, albumin, HbA1c, phosphorous, PTH, insulin resistance, CRP, resistin and active vitamin D, were positively related to cardiovascular hospital admissions.

Conclusions: Serum resistin levels demonstrated to be a valuable instrument to predict cardiovascular hospital admissions in type 2 diabetic patients with mild to moderate CKD. Also, other factors often altered in type 2 diabetics and patients with renal impairment were associated with hospital admissions but didn't prove to have any potential in predicting hospital admissions in this group.

PUB158

The Role of Proteinuria on Vascular Function in Hypertensive Patients with CKD Vagner S. Meira, Claudio P. Loivos, Mario F. Neves, Carla C. Lemos, Márcia R. Klein, Maria Ines Barreto-Silva, Rachel Bregman. *State University of Rio de Janeiro, Rio de Janeiro, Brazil.*

Background: CKD is associated with cardiovascular disease (CVD), however the best marker for this alteration is not established. Proteinuria is a marker of progression of CKD and endothelial damage. Left ventricular mass index (LVMI) and arterial stiffness (AS) are related to target organ damage. Endothelial dysfunction (ED) is associated with CVD. We evaluated the association of proteinuria with CVD markers in CKD patients.

Methods: We evaluated 97 patients, eGFR: CKD-EPI (categories 3-4). Proteinuria evaluated in urine sample (mg/g). LVM evaluated by echocardiography and LVMI obtained by dividing it by the body surface area. AS evaluated by carotid-femoral (CF) pulse wave velocity (PWV). ED evaluated through the technique of flow-mediated dilation (FMD) of the brachial artery. We analyzed 4 subgroups according to age and proteinuria: Group1: age <65 years, proteinuria<300mg/g; Group2: age≥65 years, proteinuria<300mg/g; Group3: age <65 years, proteinuria≥300mg/g; Group4: age≥65 years, proteinuria≥300mg/g. All patients followed during 18 months. Statistical analysis: SPSS-20.

Results: Data for all patients: mean ± SD. Age 64 ± 10 years; 57% of males; eGFR: 30.6 ± 9.8ml/min/1.73 m^2; systolic blood pressure (SBP) : 151 ± 22mmHg; pulse pressure (PP): 70 ± 19mmHg; DMF: 10.3 ± 6.8%; CFPWV: 10.8 ± 3.4m/s; LVMI: 106.8 ± 43.5g/m^2. Median proteinuria: 320mg/g (43-4992). Proteinuria did not show association with LVMI nor FMD, and was associated with SBP after adjustment for age (p=0.0001), PP (p<0.0001) and CFPWV (p=0.001). CFPWV(m/s) values: Group1: 9.3 ± 1.6, Group2: 10.3 ± 2.6, Group3: 9.1 ± 1.9, Group4: 13.4 ± 3.6. Group 2 vs 4 p=0.03. eGFR showed a decrease >5ml/min/1.73m^2/year in 14% of the patients. Cardiovascular events: 6.2% (acute myocardial infarction or stroke); end-stage renal disease:5.2% and death:1%. All outcomes were observed in patients with higher proteinuria and CFPWV.

Conclusions: DMF was not different among the groups. AS was higher in those with higher proteinuria and independent of the eGFR. Therefore, proteinuria but not eGFR, neither age, may be associated with the AS and consequently with CVD in this population. We suggest that the simple evaluation of proteinuria, can be used as an early marker of cardiovascular disease in CKD, instead of more complex technics.

PUB159

Secondary Hyperparathyroidism Is Independently Associated with Left Ventricular Diastolic Dysfunction in Patients with CKD Il Young Kim,[2] In seong Park,[1] Min Jeong Kim,[2] Miyeun Han,[1] Harin Rhee,[1] Sang Heon Song,[1] Eun Young Seong,[1] Dong Won Lee,[2] Soo Bong Lee,[2] Ihm Soo Kwak.[1] *[1]Pusan National University Hospital, Busan, Republic of Korea; [2]Pusan National University Yangsan Hospital, Yangsan, Republic of Korea.*

Background: Cardiovascular disease (CVD) is the leading cause of death in patients with chronic kidney disease (CKD). Left ventricular diastolic dysfunction is known for the predictor of CVD in these patients. Secondary hyperparathyroidism (SHPT), a common complication of CKD, contribute to cardiac dysfunction. This study aimed to evaluate the association between SHPT and left ventricular diastolic dysfunction in patients with CKD.

Methods: This study included 332 pre-dialysis CKD patients (estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2). Two-dimensional echocardiography was performed to left ventricular ejection fraction (LVEF). Tissue Doppler imaging was used to measure the early mitral inflow velocity (E) and the peak early mitral annular velocity (E'). Diastolic function was estimated by the E' and the ratio of E to E' (E/E'). The associations of echocardiographic index with clinical and laboratory variables [age, sex, diabetes, hypertension, eGFR, albumin, uric acid, calcium, phosphate, total cholesterol, hemoglobin, C-reactive protein, and intact parathyroid hormone (PTH)] were investigated by univariate (Pearson's correlation, r) and multivariate analysis (multiple linear regression analysis, β).

Results: Of the 332 patients, 198 were in CKD stage 3, 84 in CKD stage 4, and 50 in CKD stage 5. The degree of diastolic dysfunction was more severe (lower E' and higher E/E') with increasing CKD stage. There were no significant differences between the three CKD groups in LVEF. In univariate analysis, the intact PTH levels correlated with E' (r = -0.321, P < 0.001) and E/E' (r = 0.297, P < 0.001). However, they did not correlated with index of systolic dysfunction (LVEF). In multivariate analysis, the intact PTH levels were significantly associated with E' (β = -0.349, P < 0.001), and E/E' (β = 0.322, P < 0.001) after adjustment for other confounding factors.

Conclusions: Increased intact PTH levels were independently associated with decreased E' and increased E/E' in patients with CKD, suggesting that SHPT are independent predictor of left ventricular diastolic dysfunction in these patients. Further studies are needed to determine whether the treatment for SHPT could prevent left ventricular diastolic dysfunction in CKD patients.

PUB160

Diagnosis of CKD, Thrombotic Cardiovascular Events, and Prescription Trends for Aspirin and Oral P2Y12 Inhibitors among Veterans with CKD Manisha Singh,[3,2] Deepa Raghavan,[4,2] Nithin Karakala,[3] James S. Williams,[1] Nishank Jain.[2] *[1]Department of Veterans Affairs, North Little Rock, AR; [2]Little Rock VA Hospital, Little Rock, AR; [3]University of Arkansas For Medical Sciences, Little Rock, AR; [4]University of Arkansas for Medical Sciences, Little Rock, AR.*

Background: Use of aspirin and P2Y12 inhibitors (P2Y12) is standard of care for patients experiencing thrombotic cardiovascular (CV) events. However, chronic kidney disease (CKD) patients have been excluded from these trials. We explored prevalence of CKD diagnosis among Veterans, proportion of thrombotic CV events occurring in Veterans with CKD and P2Y12 prescription-trends in this Veteran population.

Methods: Using the Corporate Warehouse data from fiscal year (FY)11-15, we determined the number of Veterans with a diagnosis of CKD and thrombotic CV events using validated ICD-9 codes. We used VA pharmacy drug codes and generic names of drugs to identify prescriptions for aspirin and P2Y12. We calculated % annual increase in the number of prescriptions for P2Y12- as the difference in the prescription counts between consecutive fiscal years.

Results: The point prevalence of CKD among Veterans increased by 49% from 2.30% to 3.42%. Of 226,982 total thrombotic CV events, 56.7% occurred in Veterans with CKD. Of the 378,233 Veterans with CKD, 66.7% were on aspirin and 25% received prescriptions for oral $P2Y_{12}$ inhibitors- 97% for clopidogrel, 1% for ticagrelor and 2% for prasugrel. Half of the total prescriptions for clopidogrel and prasugrel; and two-thirds of the ticagrelor prescriptions were associated with CKD diagnosis. Prescriptions for P2Y12 increased during the observation period, with the highest increase in ticagrelor.

Conclusions: CKD is a rapidly growing chronic disease among Veterans. Thrombotic CV events are common in Veterans with CKD. There is a dramatic rise in prescriptions for P2Y12 among Veterans with CKD. Optimal use of P2Y12 needs to be defined in Veterans with CKD in order to maximize benefits, minimize risks and justify healthcare-associated costs.

Funding: Private Foundation Support

PUB161

Association of Blood Pressure (BP) with Proteinuria among Children with CKD Tammy M. Brady,[3] Shang-En Chung,[3] Michelle N. Eakin,[3] Andrea C. Goodman,[3] Cozumel S. Pruette,[3] Barbara A. Fivush,[3] Shamir Tuchman,[1] Susan R. Mendley,[4] Kristin Riekert.[2] *[1]Children's National Medical Center, Washington, DC; [2]Johns Hopkins School of Medicine, Baltimore, MD; [3]Johns Hopkins University, Baltimore, MD; [4]University of Maryland, Baltimore, MD.*

Background: Hypertension and proteinuria are risk factors for CKD progression and often occur together. We aimed to determine how various methods of BP measurement associate with proteinuria among children with CKD.

Methods: Cross-sectional analysis of the baseline visit in the CKD: Hypertension Adherence in Teens (CHAT) study. Children were 11-19 yrs, had CKD, and were prescribed ≥1 BP medication. Children had a clinic BP, 3 consecutive standardized home oscillometric BPs, and 24-hr ambulatory BP (ABPM). BP index (BPi; measured BP/95th %ile BP; BP≥1 indicates hypertension) was calculated to standardize comparisons between BP measurements. Multiple logistic regression adjusting for age, sex, race, body mass index z-score, and estimated glomerular filtration rate was used to determine how each BP measurement associated with significant [urine protein:creatinine (Upr:cr)>0.2 but <2.0] and nephrotic (Upr:cr≥2.0) proteinuria.

Results: 116 children with baseline first am Upr:cr available were included. Mean age 15.6 +/-2.6 yrs, 53% African American, 55% male, 32% hypertensive, 39% with significant proteinuria, 10% with nephrotic proteinuria. CKD Stage: I 23%; II 38%; III 26%; IV 6.3%; V 7.3%. No BP measurements were associated with Upr:Cr >0.2 but <2.0 in adjusted models. SBPi by every measurement method was associated with an increased odds of nephrotic proteinuria. Clinic DBPi was the only method of DBPi measurement not associated with nephrotic proteinuria [Table].

Conclusions: SBP by every measurement method was associated with nephrotic proteinuria. Overall, BP by ABPM was most closely associated with nephrotic proteinuria, providing additional support for its value in monitoring hypertension in progressive, heavily proteinuric CKD.

Funding: NIDDK Support

	Nephrotic Proteinuria (UPr:cr ≥ 2)
Triage SBPi	4.68(1.40,15.7)*
Home 1st SBPi	2.65(1.19,5.89)*
Home mean SBPi	2.82(1.26,6.30)*
Mean awake SBPi	4.16(1.58,10.9)*
Triage DBPi	1.32(0.64,2.73)
Home 1st DBPi	2.13(1.24,3.66)*
Home mean DBPi	2.19(1.27,3.79)*
Mean awake DBPi	2.23(1.09,4.54)*

*p<0.05

PUB162

Assessment of Volume Status in Edematous CKD Patients: What to Choose Young Sun Kang,[4] Jin Joo Cha,[2] Ho jun Lee,[3] Dae R. Cha,[2] Hye sook Min.[1] *[1]Department of Internal Medicine, Wonkwang University Gunpo Hospital, Gunpo-si, Republic of Korea; [2]Korea University, Ansan, Republic of Korea; [3]Korea University Ansan Hospital, Ansan, Republic of Korea; [4]Korea University Medical College Ansan Hospital, Ansan city, Republic of Korea.*

Background: In the clinic, managements of volume overload are commonly determined by physical examination such as dyspnea and pitting edema and evaluation of signs of the disease, which could be inaccurate and lead to volume depletion. Therefore, more objective assessment of volume status is needed for management and optimization of volume status in clinically edematous patients.

Methods: We conducted a prospective observational study in patients with chronic kidney disease who visited hospital due to dyspnea and generalized edema. During hospitalization, volume status was evaluated using body composition monitor (BCM-Fresnius Medical Care) and 2D-echography. After 1 week and 1 month later, we reevaluated their volume status by BCM and 2D-echography.

Results: Of total 28 patients, mean age of the patients was 58.85±14.47. 14(50%) visited hospital due to dyspnea and 23(82.1%) due to pitting edema. Patients' edema was treated with diuretics (60.7%) and low salt diet or low salt diet only. Pitting edema, CKD stage, creatinine, NT-proBNP and UPCR(urine protein creatinine ratio) were significantly increased in relative overhydration(ROH>7%) group compared with non-relative overhydration group. 10(35.7%) patients had left ventricular hypertrophy, and 10(35.7%) patients had abnormally increased left atrial volume. At baseline and 1 week later, there were little correlations with overhyration value (OH, ECW, ECW/ICW) with ejection fraction, left atrial volume and end-diastolic left ventricle diameter. BCM value and 2D Echography were followed up after 1 month. Patients' symptoms were relieved during the treatment period with a significant weight difference (p value < 0.001). However, there were no significant differences in 2-D echo findings during 1 week nor 1 month. There were significant difference between the baseline and 1 month in overhydation value as well as body weight.

Conclusions: Current findings suggest that volume status may be more accurately assessed with bed side body composition monitor than echographic measurement.

Overhydration parameters on day 1 and 1month

Parameters	Baseline	1 Month	p value
OH (L)	4.57±4.12	3.34±2.95	0.018
Body weight (kg)	72.9±14.7	64.7±10.8	0.01
Extracellular water (ECW, L)	20.19±5.44	17.38±4.11	0.002
LAVI (ml/m2)	43.96±9.99	45.66±13.79	0.593
LVEDD (mm)	49.93±8.67	50.46±8.09	0.05

PUB163

Pathological Cardiac Remodeling Is Induced by Unilateral Urinary Obstruction (UUO) and Is Attenuated by Renin and Angiotensin Inhibition Onju Ham,[3] Lei Lei,[2] William Jin,[1] Hua A. Lu.[2] *[1]MGH, Wayland, MA; [2]Massachusetts General Hospital, Boston, MA; [3]Massachusetts General Hospital/Harvard medical school, Boston, MA.*

Background: Cardiac hypertrophy and fibrosis are frequently observed in patients with chronic kidney failure. The mortality of cardiac disease is nearly doubled in chronic kidney disease (CKD) patients. Reno-cardio syndrome, or cardiorenal syndrome (CRS) type 4, is used to define cardiac dysfunction associated with chronic kidney injury. Despite close interactions between kidney dysfunction and cardiovascular disease, as evidenced by large amounts of clinical data, the underlying cellular and molecular mechanisms of cardiorenal syndrome remain poorly understood. Here, we report a study of cardiac remodeling in the context of chronic kidney failure, induced by unilateral urinary obstruction (UUO) in mice. CKD is induced after ligation of the left urethra for 21 days, as evidenced by the doubling of serum creatinine in treated mice. Despite no significant changes in cardiac function, we observed significantly increased cardiac mass, and enlarged cardiac myocytes, in UUO-induced CKD mice. Further examination, by trichrome and immunofluorescence staining of collagen type 1 and fibronectin, revealed the presence of significant extracellular matrix deposition in the cardiac interstitium. Significantly increased expression of ECM genes was detected by quantitative real time PCR, immunostaining, and immunoblotting. Further analysis indicated increased expression of TGF-β and TGF-β receptor 2, and increased phosphorylation of Smad 2 and 3; these suggest activation of the canonical TGF-β signaling cascade. Finally, treating animals with an angiotensin converting enzyme inhibitor (ACE I), Enalapril, significantly attenuated activation of the TGF-β signaling pathway and UUO-induced cardiac fibrosis.

Methods:

Results:

Conclusions:

PUB164

Iron Therapy Is Associated with a Higher Incidence of CKD in Type 2 Diabetes Mellitus (DM2): A Retrospective Analysis of Veteran Patients in the VINCI Database Archana Goel,[5] Peter S. Wiegmann,[4] Mukut Sharma,[2] Vikas Singh,[3] Virginia J. Savin,[1] Ram Sharma,[3] Thomas Wiegmann.[6] *[1]KC VA Medical Center, Kansas City, AL; [2]KCVA Medical Center, Kansas City, MO; [3]Kansas City VA Medical Center, Kansas City, MO; [4]Midwest Biomedical Research Foundation, Kansas City, MO; [5]None, Leawood, KS; [6]VA Medical Center, Kansas City, KS.*

Background: Anemia is common with DM2 and iron therapy may exacerbate DM2. Iron is a key participant in both energy metabolism and oxidative stress with cellular damage. But it is not clear if standard iron therapy in DM2 produces a corresponding deleterious effect in the clinic. We undertook a retrospective study on the effect iron therapy on CKD progression veterans with DM2.

Methods: Data from a large cohort of veterans diagnosed with DM2 and Anemia by ICD (N=349,713) followed between 2002-2017 were used to determine the effect of iron therapy. Data from the Veterans Administration Informatics and Computing Infrastructure (VINCI) were analyzed using SQL and SAS. Patients were divided into those who did not receive iron therapy (No-Iron, N=185,272) and those who received iron therapy (Iron-Rx, N=164,441). Progression to ESRD was determined by an increase in creatinine values to above 1.5, 3.0 or 6.0 mg/dL). Groups were also compared for all-cause mortality, new onset CVA, MI and retinopathy. Significance was determined by Chi-square test.

Results: Results are outlined in the Table. Less than half of patients (47%) with anemia received iron therapy. The number of subject with creatinine values 3.0 and 6.0 were significantly higher in the Iron-Rx group (P<0.001). incidence of stroke (CVA), myocardial infarction (MI) and retinopathy was higher (P<0.001) in the Iron-Rx group. as was all-cause mortality (P<0.001).

Conclusions: Incidental or intentional iron therapy associates with significantly higher advance to ESRD and higher incidence of MI, CVA, and mortality, all consistent with advancing macro-vascular disease. Significant increased retinopath**y** signals concurrent micro-vascular disease.

	No Iron		Iron Rx					Totals	
Group	N	%	N	%	Diff	Diff %	p-value	N	%
All	185272	52.98	164441	47.02				349713	100.00
CVA	29092	15.70	33250	20.22	4.52	28.77	< 0.001	62342	17.83
MI	8878	4.79	12639	7.69	2.89	60.40	< 0.001	21517	6.15
Retinopathy	70577	38.09	77112	46.89	8.80	23.10	< 0.001	147689	42.23
Creat GE 1.5	81204	43.83	84699	51.51	7.68	17.52	< 0.001	165903	47.44
Creat GE 3.0	23871	12.88	37416	22.75	9.87	76.60	< 0.001	61287	17.52
Creat GE 6.0	10198	5.50	17174	10.44	4.94	89.74	< 0.001	27372	7.83
Death	61773	33.34	61084	37.15	3.80	11.41	< 0.001	122857	35.13
Depression	33550	18.11	26886	16.35	-1.76	-9.71	< 0.001	60436	17.28
Dementia	6765	3.65	7014	4.27	0.61	16.81	< 0.001	13779	3.94
PTSD	22706	12.26	28107	17.09	4.84	39.47	< 0.001	50813	14.53

PUB165

Early Evidence of Intramuscular Inflammation in CKD Patients Stage 3b-4 Douglas W. Gould,[2] Alice C. Smith,[1] Emma L. Watson.[2] *[1]John Walls Renal Unit, Leicester General Hospital, Leicester, United Kingdom; [2]University of Leicester, Leicester, United Kingdom.*

Background: Muscle wasting is a common feature of Chronic Kidney Disease (CKD), but the precise mechanisms are not yet fully defined. However, evidence from end stage renal disease indicates an increase in protein catabolism is central to this. Intramuscular inflammation plays an important role in initiating muscle loss, but its contribution to protein degradation and impaired muscle regeneration in earlier stages of non-dialysis CKD has not been studied. Therefore, we investigated skeletal muscle cytokine gene expression and the expression of proteins involved in protein degradation and myogenesis in CKD patients stage 3b-4, compared to matched healthy controls.

Methods: Vastus lateralis muscle biopsies were collected from 10 CKD patients stage 3b-4 (mean eGFR 26, range 15-35ml/min/1.73m^2; mean age 63, range 35-75 years) and 10 healthy controls (mean age 63, range 35-75 years). IL-6, MCP-1, TNF-α, MyoD, Myogenin, Pax7, Myf5, Myostatin, activin type 2B receptor (ACVR2B), MuRF-1 and MAFbx mRNA expression were analysed by real-time PCR with 18s as internal control. Relative expression was calculated by 2^{-DCT}

Results: No differences were seen between patients and controls in the expression of any protein except IL-6 and TNF-a, which were both significantly elevated in the skeletal muscle of CKD patients by 8.7-fold (P=0.04) and 11.9-fold (P=0.01) respectively. There was a trend for increased expression of the myostatin receptor, ACVR2B, by 6.7-fold, but this fell short of significance (P=0.07).

Conclusions: This work shows marked intramuscular inflammation in non-dialysis CKD (3b-4) with elevations in mRNA expression of IL-6 and TNF-a. No significant increases were seen in MuRF-1, MAFbx or myostatin mRNA, although these were all elevated by at least 4-fold compared to the control group. This suggests that intramuscular inflammation starts early in the disease process and may play an important role in initiating muscle loss, which is known to progress with declining renal function.

PUB166

Renal Function and Infections Caused by Multidrug-Resistant Organisms in Patients Hospitalized with Infections Guobin Su,[1] Hong Xu,[1] Emilia Riggi,[3] Zhiren He,[2] Liming Lu,[2] Bengt Lindholm,[1] Gaetano Marrone,[1] Zehuai Wen,[2] Xusheng Liu,[2] Juan J. Carrero,[1] Cecilia S. Lundborg.[1] *[1]Karolinska Institutet, Stockholm, Sweden; [2]The 2nd Affiliated Hospital, Guangzhou University of Chinese Medicine, Guanghzou, China; [3]University of Pavia, Pavia, Italy.*

Background: Antibiotic resistance is a major global health threat. High prevalence of colonization and infections with multi-drug resistance organisms (MDROs) have been reported in patients undergoing dialysis. It is unknown if this finding extends to patients with mild and moderate/severe kidney disease.

Methods: An observational study included adult (≥18 years) incident patients hospitalized with a discharge diagnosis of infection, the presence of serum creatinine measurement at admission, and with microbial culture results, excluding those undergoing renal replacement therapy between 2012 and 2015, in four hospitals in China. Four categories of eGFR: eGFR≥105, 60-104 (reference), 30-59, and <30 ml/min/1.73 m^2 were compared. The odds ratio of MDROs, defined as *Staphylococcus aureus, Enterococcus spp., Enterobacteriaceae, Pseudomonas aeruginosa* and *Acinetobacter spp.*, and resistance to three or more antibiotic classes, were calculated using multivariable logistic regression model across eGFR strata, adjusting for age, sex, Charlson comorbidity index, and types of hospitalizations.

Results: We selected 9,196 the first positive cultures out of 94,445 microbial culture records. Among them, 6,356 were potential MDROs. The odds of infections by MDROs was 16% and 31% higher in those with eGFR between 30-60 ml/min/1.73 m^2 (Adjusted odds ratio (AOR): 1.16, 95% CI 1.02-1.33, P= 0.027) and eGFR <30 ml/min/1.73 m^2 (AOR: 1.31, 95% CI 1.07-1.60, P= 0.01), respectively.

Conclusions: Patients with impaired renal function have a higher risk. Kidney dysfunction at admission may be an indicator for closer attention to microbial culture results and the need of a subsequent change of antibiotics.

Funding: Government Support - Non-U.S.

PUB167

Changes of Therapeutic Efficacy and Outcomes in Lupus Nephritis Patients from 1994 to 2010 in China Si-Jia Shao, Jin-Hua Hou, Cai-hong Zeng, Huixian Zhu, Ye Liu, Zhi-Hong Liu. *National Clinical Research Center of Kidney Diseases, Jinling Hospital, Nanjing University School of Medicine, Nanjing China, Nanjing, China.*

Background: With more therapeutic options emerging in the management of lupus nephritis (LN) in recent decades, whether the efforts made in treatment has translated into improvement of patient outcomes remains questionable in Chinese patients. To assess trends in treatment modalities, therapeutic effects and long-term outcome of biopsy-proven lupus nephritis patients over time.

Methods: All patients aged > 14 years with biopsy-proven LN at the National Clinical Research Center of Kidney Diseases, Jinling Hospital from January 1994 to December 2010 were included. Patient characteristics, treatment regimens (including induction therapies and non-immunosuppressive therapies), and follow-up data were collected. Patients were stratified in 3 groups according to the year of renal biopsy: 1994–1998, 1999–2004, and 2005–2010. The primary end point of the study was end stage renal disease (ESRD). The treatment response and renal relapse were assessed as secondary outcomes.

Results: A total of 1945 LN patients were included in our analysis (182 from 1994-1998, 584 from 1999-2004, 1179 from 2005-2010). Use of MMF and combined therapy increased with the decline of cyclophosphamide. The cumulative probability of overall response at 12 months increased from 49.1% (95% CI, 42.0%-59.7%) in 1994-1998 to 77.8% ((95% CI, 74.2%-81.1%) in 1999-2004 and to 89.8% (95% CI, 87.9%-91.5%) in 2005-2010 ($P < 0.001$). The probability of free of renal flare increased over time ($P = 0.007$). The 10-year renal survival rates were 81.7% (95% CI, 74.2%-87.2%) in 1994-1998, 86.2% (95% CI, 82.8%-89.0%) in 1999-2004 and 89.3% (95% CI, 84.0%-92.9%) in 2005-2010 ($P = 0.006$). Compared with 1999-2004, the unadjusted hazard ratios for ESRD was in 1.13 (95% CI, 1.04-1.23) in 1994-1998 and 0.81 (95% CI, 0.73-0.90) in 2005-2010. The risk of ESRD still decreased over time after adjustment.

Conclusions: Between 1994 and 2010, treatment of LN patients improved substantially with an increasing trend in response rates to induction therapies and reduction in rates of renal relapse. It is encouraging that the long-term renal survival of LN patients have also increased over time.

PUB168

Prevalence of Reduced Bone Density in Systemic Lupus Erythematosus Patients: A Single-Center Study and a Meta-Analysis Yi Yang,[3] Gang Xu,[2] Shuwang Ge.[1] *[1]Tongji Hospital, Huazhong University of Science and Technology, WUHAN, China; [2]Tongji Hospital, Tongji Medical College, Huazhong Univ of Science and Technology, WUHAN, China; [3]Tongji hospital affiliated to Tongji medical college, Huazhong University of Science and Technology, Wuhan, Hubei, China, Wuhan, China.*

Background: The reported frequency of reduced bone mineral density (BMD) in systemic lupus erythematosus (SLE) patients vary widely. The data in Chinese SLE patients undergo minimal study. Risk factors associated are still under debate from different countries. We aimed to (1) detect the frequency and possible risk factors of reduced BMD in patients with SLE in our single center, and (2) conduct a meta-analysis concerning the frequency of reduced BMD in SLE with evidence from published studies.

Methods: We aimed to (1) detect the frequency and possible risk factors of reduced BMD in patients with SLE in our single center, and (2) conduct a meta-analysis concerning the frequency of reduced BMD in SLE with evidence from published studies.

Results: In our single-center study, 91 female SLE patients were assessed. 52.7% of the patients had low BMD, 56.0% had osteopenia and 19.8% had osteoporosis. Prevalence of osteopenia was higher in post-menopausal patients compared with pre-menopausal patients at total hip and femoral neck. Body weight was positively associated with BMD in all measured sites and menopause duration was negatively associated with lumbar spine and total hip BMD. In the meta-analysis, 71 reports with 33527 SLE patients were included. Low BMD, osteopenia and osteoporosis at any site were presented, respectively in 45%, 38% and 13% of the SLE patients. The prevalence of osteoporosis increased with the advancing of age, while U-shaped associations between age and the prevalence of low BMD and osteopenia were found. Lumbar spine was indicated to have severer bone loss compared to total hip and femoral neck in both our cross-sectional study and meta-analysis.

Conclusions: SLE Patients showed a high prevalence of reduced BMD. Low body weight, menopause duration, old age and disease-related factors might be the possible associated risk factors of bone loss.

Funding: Government Support - Non-U.S.

PUB169

Effect of Intravenous Sodium Ferric Gluconate on Serial Platelet Counts in CKD Patients with Iron Deficiency Anemia Neville R. Dossabhoy,[1,2] Pallavi D. Shirsat,[1,2] Sangeeta Pal.[1,2] *[1]Medicine/Nephrology, VA Medical Center, Shreveport, LA; [2]LSU Health Shreveport School of Medicine, Shreveport, LA.*

Background: Iron deficiency often leads to reactive thrombocytosis; theoretically, its correction should lead to a lowering of the platelet count (PLT). Only a few studies have investigated this aspect, with some showing a reduction in PLT, whereas others did not. We investigated the effect of iron repletion with intravenous (IV) sodium ferric gluconate (SFG) on serial PLT counts in CKD patients with iron deficiency anemia (IDA).

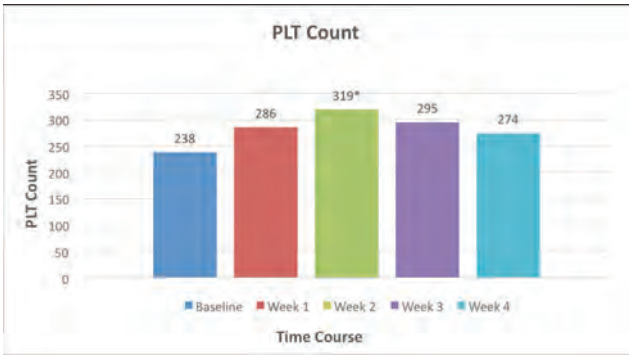
Methods: We conducted a retrospective chart review, including patients with CKD and IDA who were treated with IV SFG. Patient demographics were recorded, as were baseline laboratory values for creatinine, eGFR, Hgb, iron stores and PLT. Serial, post-dose PLT values were recorded weekly for 4 weeks.

Results: A total of 118 doses of IV SFG (mean ± SD = 199±63 mg) were studied in patients with age 53±15 years, Creatinine 4.3±4.1 mg/dL, Hgb 8.7±1.8 g/dL and T-sat 12±7%. All CKD stages were represented in the study sample. Hgb and Fe stores improved post-dose. The variation in post-dose PLT over time is depicted below. All the values upto 4 weeks were elevated compared to the baseline, with the 2-week count reaching significance (P = 0.007).

Conclusions: Correction of iron deficiency did not lower PLT in CKD patients with IDA who received IV SFG. In fact, PLT were elevated compared to baseline throughout the 4-week period of follow-up, reaching statistical significance at the 2-week mark. This finding stands in contrast to some previous evidence and current popular theories. It confirms the previous report that PLT counts were not significantly reduced with IV iron dextran used as total dose infusion. Our finding may raise the possibility that increased PLT in the short-term post-dose, may contribute to the thrombotic events noted in clinical trials of erythropoiesis stimulating agents in CKD patients.

Platetet Counts

	Baseline	Week 1	Week 2	Week 3	Week 4
Mean	238	286	319	295	274
SD	163	224	209	121	136
P-value vs Baseline		0.094	0.007	0.052	0.186



PUB170

Loop Diuretics Associate with Greater Risk of Sarcopenia in Non-Dialysis-Dependent CKD Patients Seiko Ishikawa,[1] Shotaro Naito,[1] Shintaro Mandai,[1] Soichiro Iimori,[1] Naohiro Nomura,[1] Eisei Sohara,[1] Eiichiro Kanda,[2] Tomokazu Okado,[1] Tatemitsu Rai,[1] Shinichi Uchida.[1] *[1]Tokyo Medical and Dental University, Tokyo, Japan; [2]Tokyo Kyosai Hospital, Meguro, Japan.*

Background: Sarcopenia is defined as progressive decline of skeletal muscle mass and function with age. Few studies have investigated the actual situation of sarcopenia in non-dialysis-dependent chronic kidney disease (NDD-CKD) patients.

Methods: We conducted a cross-sectional study comprised of 217 NDD-CKD patients over 65 years of age. Total body skeletal muscle mass was measured by dual-energy X-ray absorptiometry. Sarcopenia was diagnosed using the criteria of Asian Working Group for Sarcopenia. Adjusted odds ratios (aOR) for sarcopenia were estimated by using multivariate logistic models after stratifying the patients into 3 groups according to CKD stages.

Results: Mean age was 75.6±6.6 years, mean body mass index was 22.8±3.6 kg/m^2, and mean eGFR was 30.6±13.3 ml/min/1.73 m^2. 30.4% of the patients had diabetes mellitus (DM), 18.4% were treated with loop diuretics, and 25.3% were diagnosed as sarcopenia. Adjusted by age and gender (Model 1), the aOR in CKD5 group was 2.60 [95% confidence interval (CI) 1.04-6.50] compared to CKD 3 group. Adjusted by age, gender, and either DM (Model 2) or loop diuretics (Model 3), the aORs for CKD groups were statistically insignificant. On the other hand, each of DM and loop diuretics was associated with risk of sarcopenia [DM: aOR 2.02 (95%CI 1.01-4.07); Model 2]; [loop diuretics: aOR 3.07(95%CI 1.32-7.12); Model 3]. Furthermore, adjusted by age, gender, CKD groups, DM and loop diuretics (Model 4), the aOR for DM was statistically insignificant whereas the aOR for loop diuretics remained significant [loop diuretics: aOR 2.64(95%CI 1.10-6.33)]. In all models, age was an independent risk factor for sarcopenia.

Conclusions: Age and loop diuretics were independently associated with sarcopenia. In particular, loop diuretics were associated with increased risk of sarcopenia more than renal function and DM. Previous studies have shown that loop diuretics suppress skeletal muscle differentiation. This is the first study to show the risks of sarcopenia associated with usage of loop diuretics in a cohort of NDD-CKD patients. Since loop diuretics are commonly used in patients with advanced CKD treatment of volume overload, consideration for risk of sarcopenia may be necessary in such patients.

PUB171

The Endoscopic Findings of Double Balloon Enteroscopy in Patients with CKD and Obscure Gastrointestinal Bleeding Mohamad A. Hanouneh,[2] Steven Menez,[2] Diana S. Najjar,[2] Qiuyu Jin,[2] Ahmed El-Telbany.[1] *[1]Department of Medicine, Cleveland Clinic, Cleveland, OH; [2]Department of Medicine, Division of Nephrology, Johns Hopkins University, Baltimore, MD.*

Background: Obscure gastrointestinal bleeding is a common problem and associated with increase morbidity and mortality. Scarce data exist describing the small bowel characteristics of patients with chronic kidney disease (CKD) who present with obscure gastrointestinal (GI) bleeding. The **aim** of the study is to investigate the endoscopic findings of double balloon enteroscopy in patients with CKD who present with obscure GI bleeding.

Methods: We recruited 66 adult patients with CKD stages III-V who had obscure GI bleeding and underwent double balloon enteroscopy between 2002 and 2013. Stages of CKD were defined based on the glomerular filtration rate. Glomerular Filtration Rate (GFR) Estimate by Modification of Diet in Renal Disease (MDRD) Equation. Stage III for GFR 30-59, stage IV for GFR 15-29 and stage V for GFR <15. Obscure GI bleeding was defined as persistent or recurrent gastroentintestinal bleeding (hematemesis, melena, hematochezia or positive fecal occult blood test) with negative upper and lower endoscopies.

Results: A total of 66 patients were included in the study, of whom 37 patients had CKD stage III, 11 patients had CKD stage IV and 18 patients had CKD stage V. The median serum creatinine in the entire study population was 1.89 mg/dL [1.39, 3.28]. The source of bleeding was identified on 45 patients (68.2 %). The most common findings of double balloon enteroscopy were arteriovenous malformation (AVM) (n=30, 45.5%) of whom 18 patients had CKD stage III, 4 patients had CKD stage IV and 8 patients had CKD stage V. Overall, the most common locations of the AVM were the jejunum (73.3%). Other causes of obscure GI bleed include erosions (n=7, 10.6%) and ulcers (n=7, 10.6 %).

Conclusions: Arteriovenous malformation (AVM) is the most common finding of double balloon enteroscopy in patients with chronic kidney disease who have obscure GI bleeding.

PUB172

Correlation and Agreement between BIS-1 and CKD-EPI Equations to Estimate GFR in a Wide Cohort of Older Patients In Argentina Rosario Luxardo,[1] Maria L. Ocampo,[1] Griselda Bratti,[1] Carlos Federico Varela,[2] Alejandro Sengoku,[2] Nadia Satera,[2] Gustavo Greloni,[3] Guillermo Rosa Diez.[3] *[1]Hospital Italiano Buenos Aires, CABA, Argentina; [2]Hospital Italiano de Buenos Aires, CABA, Argentina; [3]None, Buenos Aires, Argentina.*

Background: Chronic kidney disease (CKD) is highly prevalent among older adults in Latin America. KDIGO proposes the use of Chronic kidney disease Epidemiology collaboration (CKD-EPI) equation, however this equation is not specific for patients aged over 70 years. Its application results on the inclusion of these patients on advanced stages of CKD increasing the burden on CKD programs. The Berlin Initiative Study (BIS-1) equation, compared to CKD-EPI equation, would improve the precision and accuracy of glomerular filtration rate estimation (GFRe) in patients aged over 70 years. There are limited reports of its use in Latin America and there is no data available for Argentina. Therefore, the aim of this study is to assess correlation and concordance betwween BIS-1 equation and CKD-EPI equations in a wide cohort of patients.

Methods: Plasma creatinine was measured on a cohort of 28.411 patients aged over 65 years under follow-up at Hospital Italiano of Buenos Aires. GFR was estimated with CKD-EPI and BIS-1 equations. The mean difference of GFR obtained with equations, correlation as well as the Bland-Altman analysis was calculated. The mean of GFRe was compared overall, by stages and by quartiles of age. The number of patients included on every stage was analyzed for both equations. $p<0.01$ was considered significative. A statistical analysis was performed with MedCalc Statistical Software version 16.8.4 (MedCalc Software bvba, Ostend)

Results: The mean age was 75±7 years. 65.7 % (n 18.678) female and 34.4% (n 9763) male. Mean GFR estimated by CKD-EPI was 68.3±17 ml/min/1.73m^2 and for BIS-1 was 60±15 ml/min/1.73m^2 ($p<0.01$) There was a significant correlation between both equations ($p<0.01$). BIS-1 included significative more patients on GFRe from 15 to 60 mil/min than CKD decreasing the number of patients on the rest of the stages (see Table 1). On graph 1 Bland-Altman graph showed that below 30 and above 60 mil/min the difference of the obtained results for both equations were outside the limits of concordance.

Conclusions: BIS-1 decreases the number of patients included in advanced stages of CKD (4 and 5) but, nevertheless, increases the number for stage 3B; without reducing the burden of patients on CKD programs.

PUB173

Sex, Age, and the Association of CKD with All-Cause Mortality in Buddhist Priests: A Retrospective Analysis of a Buddhist Priest Cohort in Korea Hyo Jin Kim,[1] Yunmi Kim,[1] Jae Yoon Park,[1] Sejoong Kim,[2] Ho Jun Chin,[2] Hajeong Lee,[1] Dong Ki Kim,[3] Kook-Hwan Oh,[3] Kwon Wook Joo,[3] Yon Su Kim,[3] Sung joon Shin,[1] Kyung Soo Kim,[1] Kyung Don Yoo.[1] *[1]Department of Internal Medicine, Dongguk University College of Medicine, Gyeongsangbuk-do, Republic of Korea; [2]Seoul National University Bundang Hospital, Seongnam, GyeongGi-Do, Republic of Korea; [3]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea.*

Background: Buddhist priests are one of the major religious groups in Asia. Their unique life style with practicing asceticism, especially in vegetarian diet, might be influence their mortality. We explored the mortality among Buddhist priests in Korea compared with general population.

Methods: The present study is a single-center, retrospective study. Patients with Buddhist priests from Dongguk University Gyeongju Hospital from Jan, 2000 to Dec, 2014, founded by the Jogye Order of Korean Buddhism were enrolled. Standardized mortality ratios (SMR) were computed for all causes of death by comparing with the general population using national statistics (accessed at Korean Statistical Informational Service; http://kosis.kr/) in Korea. A total of 3,639 patients, 724 patients were known for baseline lavatory test including renal function. In subgroup analysis, SMR between chronic kidney disease (CKD) and non-CKD patients were analyzed. CKD was defined as dipstick proteinuria ≥1 or an estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2.

Results: Among 3,639 Buddhist priests, mean age was 44.6±12.4 years old and 47.7% were male. During follow-up for 56.8±56.2 months, 152 (4.2%) patients died (102 [5.9%] in male, 50 [2.6%] in female). The SMR for all causes of death was 0.34 (95% CI, 0.29- 0.40). The SMR values for male (0.33; 95% CI, 0.27-0.40) and female (0.33; 95% CI, 0.25-0.44) were significantly smaller than general population. Among 724 patients, 74 (10.2%) patients had CKD and 3 (0.4%) patients developed end stage renal disease during follow-up period. The SMR value for non-CKD patients (0.76; 95% CI, 0.56-0.99) was significantly smaller than general population without CKD. Taking sex mortality differences into account, only female SMR value was significantly smaller (0.25; 95% CI, 0.08-0.57 *vs.* male; 0.81; 95% CI, 0.55-1.14). The SMR value for CKD patients was not significantly different comparing with general population (1.41; 95% CI, 0.85-2.21).

Conclusions: Buddhist priests showed significantly lower mortality compared with general population. Buddhist priests without CKD had significantly lower mortality, especially in female.

PUB174

Assessment of CKD Stage 3/4 Using Multiparametric Magnetic Resonance Imaging Huda Mahmoud,[3] Charlotte E. Buchanan,[1] Eleanor Cox,[1] Benjamin L. Prestwich,[2] Nicholas M. Selby,[2,3] Susan Francis,[1] Maarten W. Taal.[2,3] *[1]Sir Peter Mansfield Imaging Centre, Nottingham, United Kingdom; [2]University of Nottingham, Nottingham, United Kingdom; [3]Center for Kidney Research and Innovation, Derby, United Kingdom.*

Background: Progression of Chronic Kidney Disease(CKD) occurs secondary to inflammation and fibrosis independent of the underlying aetiology. Recent advances in Magnetic Resonance Imaging(MR) allow assessment of renal structure and function. We performed a multiparametric MR study to assess its utility and reproducibility in CKD patients.

Methods: 26 CKD Stage3-4 patients with kidney biopsies and 13 healthy volunteers(HV) had 2 multiparametric renal MR scans performed 7-14d apart on a 3T Philips Ingenia scanner. Structural assessments included renal volume, longitudinal-relaxation time(T_1) and Diffusion-Weighted Imaging(DWI) as markers of fibrosis and/or inflammation. Functional assessments included Arterial Spin Labelling(ASL) to measure renal perfusion and Blood Oxygenation Level Dependant Imaging(BOLD) as an indicator of renal oxygenation. The Coefficient of Variance(CoV) was calculated for each measure between the scans.

Results: CKD patients: mean 57±15yrs, eGFR 39±13mls/min/1.73m^3, uPCR 120±188mg/mmol. HVs were age-matched, had normal eGFR and no proteinuria. CKD cortical and medullary T_1 values were higher than HVs, 1580±92ms & 1739±78ms compared to 1396±64($p<0.0001$) & 1700±107($p<0.0001$) respectively, indicating more fibrosis/inflammation. CKDs had lower renal perfusion values($p=0.003$) and a trend for lower DWI values than HVs, no difference in volume and T_2*(BOLD) were found. Correlations were found between T_1 values and the extent of interstitial fibrosis observed on histology($p=0.02$). Reproducibility was excellent for cortical and medullary T_1(CoV 2.6% & 2.0% respectively), T_2*(CoV 2.6%), ADC(CoV 8.2%) and volumes(CV 3.0%).

Conclusions: This study demonstrates that mutiparameteric MR differentiates between HVs and CKD patients and is reproducible. The MR results reflect the known pathophysiological changes expected in CKD; reduced perfusion and the presence of fibrosis and/or inflammation, but interestingly did not demonstrate a difference in T_2* a potential marker of renal hypoxia. Further studies are required to build on this initial work to determine how best multiparametric MR can be used to assess whole kidney pathology and prognosis.

Funding: Private Foundation Support

PUB175

The Risk of Hip Fracture in Patients Suffering from Different Stages of CKD Ammar Qureshi,[2] Fernando R. Aguilar,[1] Nesreen Benhamed.[3] *[1]Georgetown University Hospital, Washington, DC; [2]Internal Medicine, Marshall University, Huntington, WV; [3]Internal Medicine, MUSOM, Barboursville, WV.*

Background: Patients with CKD are at an increased risk of hip fracture than the normal population, which is attributed to the resulting vitamin D deficiency caused by the failure of the kidney to activate vitamin D. Failure in the calcium-phosphate homeostasis also adds to the poor bone condition. The aim of our study is to analyze the correlation between the stage of CKD (determined by GFR) and incidence of hip fracture.

Methods: Data was extracted from the 2005'12 nationwide sample (NIS) registry. We stratified these patients based on the stages of CKD (Stage 1 GFR > 90 mL/min; Stage 2 GFR 60-89 mL/min; stage 3 GFR 30-59 mL/min; stage 4 GFR 15-29 mL/min ; stage 5 < 15 mL/min). The incidence of hip fracture was calculated in each stage of CKD. Patients with CKD were matched with those without CKD using propensity score matching to determine the all-cause mortality in patients with hip fracture and those without hip fracture in patients with CKD.

Results: A total of 2.85 million patients were diagnosed with chronic kidney disease including ESRD in the year between 2005 and 2012. When stratifying according to the stages of CKD, stages 3 (0.54 % p<0.007 OR 0.70) and ESRD (0.76% p<0.007 OR 1.15) had the highest rates of sustaining a hip fracture when compared to the other stages of CKD. 1.35 % of these patients suffering from chronic kidney disease and hip fractures died during their hospital stay. The odds of sustaining a hip fracture with a patient suffering from chronic renal disease were 1.3 times. The difference in rates of sustaining a hip fracture between those patients diagnosed with renal osteodystrophy and those who were not was not found to be significant (p= 0.93).

Conclusions: Our data showed that patients end stage renal stage disease had a significantly higher chance of sustaining a hip fracture than patients in other stages of the CKD. Hence a worsening GFR could be correlated with the odds of sustaining a hip fracture, which means that as the stage of CKD progressed, patients were more prone to hip fractures These patients also had a higher mortality risk, however this could be a confounding factor since patients who are inflicted with both CKD and hip fracture could be sicker patients. There was no difference in the incidence of hip fractures if the patient was diagnosed with renal osteodystrophy.

PUB176

Cyclosporine as Rescue Therapy for Focal Segmental Glomerulosclerosis Who Were Refractory to Steroid Combination with Tacrolimus Xiayu Li. *Kidney Disease Center, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, China.*

Background: A proportion of adults with focal segmental glomerulosclerosis (FSGS) are refractory to treatment of steroid combination with tacrolimus due to persistent severe hypoalbuminemia and proteinuria. It is a challenge to find rescue therapies that are effective and safe in treating such difficult patient. Cyclosporine may be a promising alternative to tacrolimus for such patients.

Methods: In this prospective observational study, nineteen patients with adult-onset FSGS who did not respond to treatment with steroid (daily prednisone 0.5 mg/kg per day) combination with tacrolimus (target level of 4-10 ng/ml) for 12 weeks were studied from January 2013 to September 2016. Oral cyclosporine was administered (target trough level of 200-250 ng/ml) for 24 weeks, and then with tapering cyclosporine was given (target trough level of 50-100 ng/ml) for another 24 weeks. Oral prednisone was started at 0.5 mg/kg per day. Primary outcome variables were remission. Secondary outcome variables were time to remission, relapse rate, changes in serum creatinine and estimated glomerular filtration rate.

Results: One patient discontinued cyclosporine because of reversible acute nephrotoxicity, and 18 patients completed at least 12 weeks of cyclosporine therapy. Five patients (27.8%) experienced complete remission and 7 patients (38.8%) experienced partial remission. Primary resistance to cyclosporine was seen in 6 patients (33.3%). The mean time to partial remission and complete remission was 6.2 ± 3.4 weeks and 12.6 ± 4.5 weeks, respectively. After a mean follow up of 28.3 months, 33.3% (4/12) of patients who had remission experienced relapses. Two patients who were resistant to cyclosporine therapy had a doubling of serum creatinine concentration during follow-up.

Conclusions: Cyclosporine may be a suitable therapeutic option for treatment of adult-onset refractory FSGS. However, controlled studies with more patients are needed to compare the efficacy and safety of cyclosporine with tacrolimus in treating FSGS.

PUB177

Relationship between Renalase and Kidney Disease in 72 Patients with Renal Biopsy Nan Hu,[2,3] Sha Y. Huang,[2,3] Chuan-Ming Hao,[1] Xin-zhou Zhang.[2,3] *[1]Huashan Hosp., Shanghai, China; [2]Department of Nephrology, Shenzhen People's Hospital, Shenzhen, China; [3]Key Renal Laboratory of Shenzhen, Shenzhen, China.*

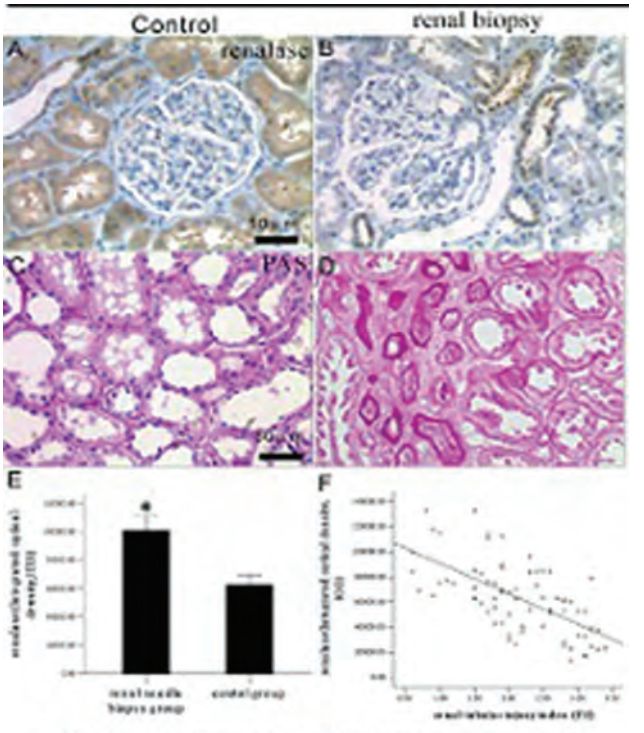
Background: Renalase is the only one amine oxidase that can be synthesized by a target organ. We evaluated the expression of renalase and explored the possible mechanism between renal tubular epithelial cells and renal cell apoptosis in 72 patients with renal biopsy.

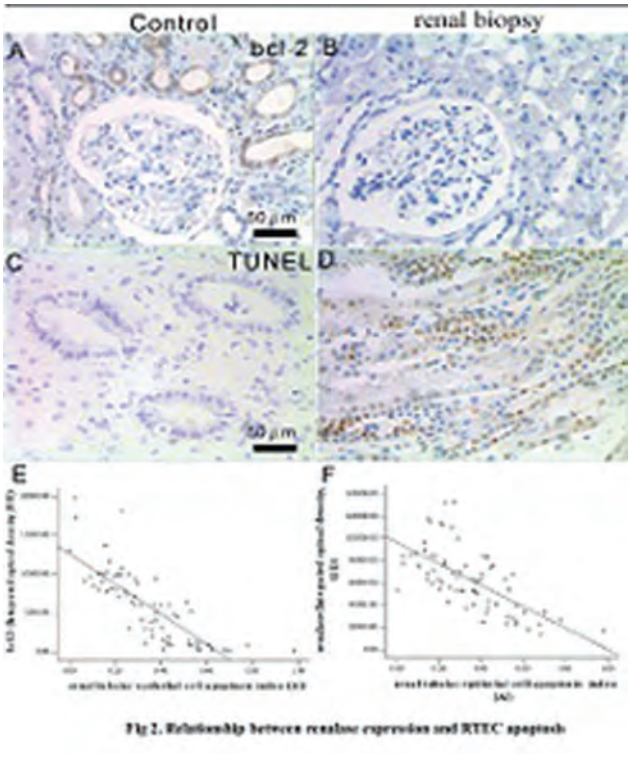
Methods: The study group consisted of a total of 72 patients undergoing renal biopsy. Patient profiles and renal function were collected. Concentrations of renalase and bcl-2were measured by the IHC method. The tubular injury was detected and calculated by PAS and renal tubular epithelial cell apoptosis was assessed with TUNEL stain.

Results: The expression of renalase in renal biopsy with significantly lower levels than in patients with renal cell carcinoma of normal kidney tissue(Fig 1). In patients undergoing renal puncture biopsy, renal tubule injury index, as well as tubular epithelial cell apoptosis index showed a negative linear correlation with renalase (Fig 2). The results showed that renalase probably increase the expression of bcl-2 protein.

Conclusions: The research proved that it may reduce the renal tubular injury and apoptosis of renal tubular epithelial cells through the mitochondrial apoptosis pathway, finally achieve the purpose of delaying the progress of renal failure.

Funding: Government Support - Non-U.S.





PUB178

Urine Liquid Biopsy of the Kidney Tadashi Yamamoto,[1,4] Keiko Yamamoto,[1] Yoshitoshi Hirao,[1] Bo Xu,[3] Shigeru Miyazaki.[2] *[1]Niigata University, Niigata, Japan; [2]Shinraku-en Hospital, Niigata, Japan; [3]niigata university, Niigata, Japan; [4]Shinrakuen Hospital, Niigata, Japan.*

Background: Many studies have been done to identify kidney disease biomarkers by proteomics of urine. However, urine biomarkers sufficient enough from scientific and practical views have not been identified yet. One of the reasons may come from the study designs. For example, to identify biomarkers for chronic kidney disease (CKD), urine samples collected from CKD patients with proteinuria were analyzed by proteomics, resulting that plasma proteins have mostly been identified. To overcome the problem and to identify biomarkers informing the sites of injury, we aimed to identify urine biomarkers for injury at each different tissue compartment in the kidney and to make a panel test (urine kidney biopsy), which may inform pathological changes as kidney biopsy.

Methods: Several kidney compartments (glomerulus, proximal tubule, distal tubule, collecting duct, kidney cortex and medulla) are laser-microdissected from formalin-fixed paraffin-embedded human kidney specimens and peptides digested with trypsin were collected by the on-site direct digestion (OSDD) method for mass spectrometry. These proteomes were compared each other and also with those of plasma and urine to select proteins, which were uniquely identified in each compartment and not found in the plasma but found in the urine as urine biomarker candidates for each kidney compartment injury. Then, some of these candidates (PRA2R1 and GPRC5C for glomerulus, NPR1 for proximal tubule and GGT5 for interstitium injury) were selected and quantitatively measured in urine samples from CKD patients (IgA nephropathy and diabetic nephropathy) by surface plasmon resonance method using antibodies against them (ProteOn, Bio-Rad).

Results: Concentrations of the proteins increased significantly in urine with the stage of CKD. PRA2R1 and GPRC5C excretion presumed to reflect the glomerular injury, especially, podocyte alterations, NPR1 the proximal tubule reactions and GGT5 the interstitial expansion, indicating that the urine liquid biopsy may provide more valuable information than the routine kidney function tests and more quantitative evaluation than the kidney biopsies.

Conclusions: By the urine liquid biopsy of a biomarker panel for kidney compartment events, injuries at different comartments in the kidney were individually and quantitatively evaluated by a non-invasive manner.

Funding: Private Foundation Support

PUB179

A Rare Case of Granulomatous Interstitial Nephritis Associated T Cell Lymphoma Miho Karube,[1] Shintaro Masuko,[1] Hideki Shimizu,[2] Hikaru Kukimoto,[1] Shinya Kaname.[1] *[1]Kyorin University School of Medicine, Tokyo, Japan; [2]Kyorin university, Tokyo, Japan.*

Background: Introduction: Although granulomatous interstitial nephritis is known to be associated with sarcoidosis and tuberculosis, it has been rarely reported in T cell lymphoma.

Methods:

Results: A 50-year-old woman was referred to our hospital because of abdominal lymphadenopathy two years ago. Open lymph node biopsy revealed granulomatous lymphadenitis. A year and a half later, renal dysfunction was recognized by increased levels of serum Cr 1.95 mg/dl and urine β2 microglobulin 17,621μg/l, and renal biopsy was performed, showing global glomerulosclerosis in 5 out of 21 glomeruli and advanced tubulointerstitial nephritis with a marked infiltration of CD3,4,5-positive/CD20-negative, small-sized T lymphocytes and granulomatous changes. No plasma cells or eosinophils were observed. The T cell clonality test for TCRG using the renal tissues revealed T-cell monoclonality signal, thus together with a serum increase in soluble IL-2 receptor levels (2,880 U/ml), she was diagnosed with T cell lymphoma. After glucocorticoid and standard chemotherapy, renal function slightly improved and re-biopsy of the kidney showed improved T-cell infiltrations, associated with advanced tubulointerstitial changes with fibrosis.

Conclusions: Discussion: We reported a rare case of granulomatous tubulointerstitial nephritis in a patient with T cell lymphoma. T cell lymphoma should be considered in tubulointerstitial nephritis of unknown origin.

PUB180

Efficacy of AST-120 in Patients with CKD: A Systematic Review and Meta-Analysis Mei-Yi Wu,[1] Ying-Chun Chen.[2] *[1]Department of Nephrology, Taipei Medical University-Shuang Ho Hospital, Taipei, Taiwan; [2]Taipei Medical University, Shuang Ho Hospital, Taipei, Taiwan.*

Background: AST-120 (Kremezin), which is an oral spherical carbonaceous adsorbent of the precursor of indoxyl sulfate (IS), has been reported to be potential for retarding disease progression in patients with chronic kidney disease (CKD). In the present study, we aimed to evaluate its efficacy in slowing disease progression in CKD patients.

Methods: We systematically searched for clinical trials published in PubMed, Medline, and Cochrane databases. Randomized controlled trials of AST-120 in CKD patients were selected. The primary outcomes were the composite of renal outcome and all-cause mortality. The secondary outcome was the changes in serum IS level.

Results: Eight studies providing data for 3320 patients were included in the meta-analysis. Among patients treated with AST-120, the summary RR of composite of renal outcome was 0.97 (95% CI 0.88-1.07) using a random effects model (heterogeneity I^2=0%). The summary RR of all-cause mortality was 0.94 (95% CI 0.73-1.2) using a random effects model (heterogeneity I^2=0%). Change of IS level from baseline to the end of the study was higher in patients treated with AST-120 (mean difference: -0.34 mg/dL; 95% CI, -0.48 to -0.2, 4 trials) compared with placebo.

Conclusions: This review provides evidence that AST-120 can effectively lower IS level but still controversy in slowing disease progression and all-cause mortality. Further studies are needed to assess which is the optimal CKD population to be treated by AST-120.

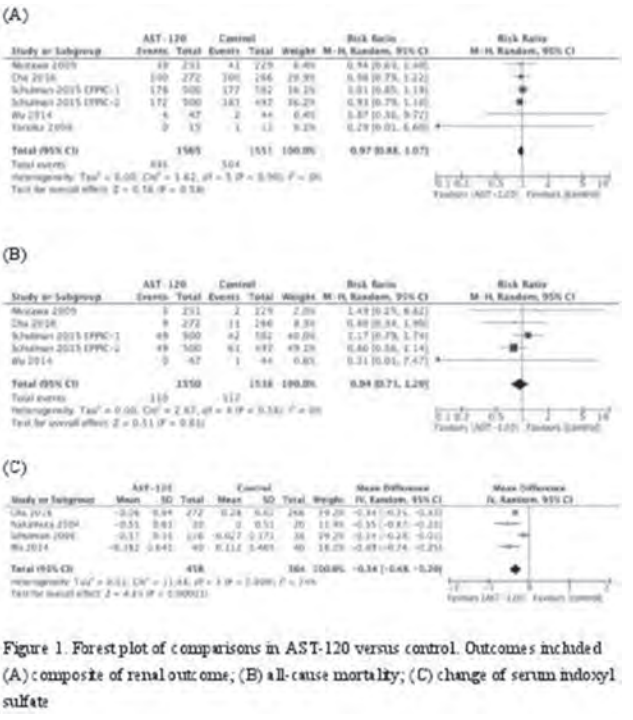


Figure 1. Forest plot of comparisons in AST-120 versus control. Outcomes included (A) composite of renal outcome; (B) all-cause mortality; (C) change of serum indoxyl sulfate

PUB181

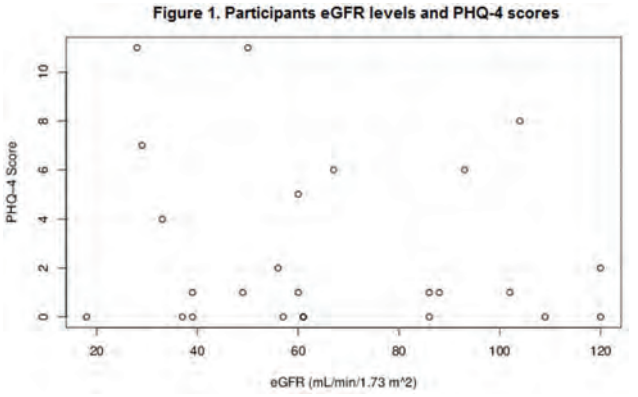
Anxiety in Patients with Autosomal Dominant Polycystic Kidney Disease Denghui Guo, Salpi S. Siyahian, Meyeon Park. *UCSF, San Francisco, CA.*

Background: The prevalence of depression and anxiety among patients with autosomal dominant polycystic disease (ADPKD) is high due to the disease's significant morbidity and uncertain prognosis. We investigated whether individuals with prognostic scores indicative of higher risk for ESRD onset and more impaired kidney function have higher levels of depression and anxiety.

Methods: We conducted a cross sectional study involving 30 individuals diagnosed with ADPKD. The PROPKD score is a prognostic tool that predicts the age of onset of ESRD for individuals with ADPKD. Participants were risk-stratified based on their PROPKD score and eGFR. We approximated the PKD mutation in the absence of genotyping using age of ESRD of a first-degree family member. The degrees of depression and anxiety symptoms were measured using the Patient Health Questionnaire 4 (PHQ-4). We calculated Spearman correlation coefficients to determine associations of PROPKD variables and eGFR with PHQ-4 scores.

Results: Median age was 52; 66.7% were male. 33.3% of study participants had mild to severe psychological distress (PHQ-4 ≥ 3). There was no significant correlation between PROPKD and PHQ-4 scores [r = -0.049, p = 0.795], or eGFR and PHQ-4 scores [r = -0.098, p = 0.642] (Figure). The two patients with the highest PHQ-4 scores both had eGFR < 60 ml/min/1.73m^2, while the patient with the lowest eGFR had a PHQ-4 score of 0 (no symptoms of depression or anxiety).

Conclusions: Symptoms of depression and anxiety are prevalent in patients with ADPKD. Neither PROPKD score nor the degree of kidney function impairment as determined by eGFR were significantly correlated with psychological distress as measured by PHQ-4 score. Understanding what contributes to anxiety in patients with ADPKD will be important to improving symptoms.



PUB182

Renadyl™: Improving GFR and Quality of Life: Results of 3rd Biannual Survey 2017 Natarajan Ranganathan,[1] Kevin M. Hanlon.[2] *[1]KIBOW BIOTECH INC, Newtown Square, PA; [2]Kibow Biotech, Newtown Square, PA.*

Background: Kibow Biotech's "Enteric Dialysis®" concept based off of the modulation of the gut microbiome to maintain healthy kidney function has proved to be helpful in many of those suffering from CKD. Kibow's product "Renadyl™" has been available since 2010 and is continually being studied to assess just how effective it is. A short survey given to 600 Renadyl customers was distributed to ascertain how their GFR changed, and the impact on their quality of life after adding the dietary supplement Renadyl™ into their standard care of therapy.

Methods: "Renadyl™," a synbiotic dietary supplement was assessed in its ability to maintain healthy kidney function (stabilize GFR), and ability to improve quality of life. A survey was distributed to 600 customers asking for GFR when they began taking Renadyl, and at their most recent doctors visit, as well as Age, Race, ethnicity, and if Renadyl™ had improved their overall quality of life or not. Statistical analyses were performed on the GFR data to estimate Renadyl's™ impact on GFR, and quality of life. Of the 600 surveys sent, 210 (35%) responses were received (116 male, 94 female).

Results: The average age of a Renadyl user was 69 years old. The average survey participant had been using Renadyl for 2.05 years. Of the surveys received, 140 contained complete information, including GFR. The lowest baseline GFR recorded was 4, the highest was 100 (ESRD to Healthy). The average baseline GFR of a survey participant was 29 (Stage IV). The most recent GFR reported varied from 5 to 102. The highest GFR impact was an increase of 65, and the largest decrease in GFR was -43. The average change in GFR for a survey participant was an increase of 2.39. Among the survey respondents, 88% reported that Renadyl™ improved their quality of life.

Conclusions: Chronic kidney disease is generally recognized as a degenerative process. However, with over 4,000 customers we sought feedback from 15% of them to assess the impact of Renadyl™ usage over an average of 2.05 years. The longest using participant used the product for 7 years, the shortest for 6 months. With the ability to stabilize and improve GFR, it may be possible to delay the progression of kidney failure at all stages. Improving quality of life in 88% of participants certainly signifies the advantages of using Renadyl™ in patients with compromised renal function worldwide.

Funding: Private Foundation Support

PUB183

Chemotherapy Induced Neuropathy in CKD Patients Biruh Workeneh,[2] Louie H. Morsy,[1] He Zhou,[1] Bijan Najafi.[1] *[1]Baylor College of Medicine, Houston, TX; [2]MD Anderson Cancer Center, Houston, TX.*

Background: Chemotherapy induced neuropathy (CIPN) is a prominent feature of traditional and targeted therapy for cancer, and contributes significantly to the frailty of cancer patients. Frailty and peripheral neuropathy are also features of chronic kidney disease (CKD), and we sought to determine the influence of CKD on the severity of CIPN. We studied patients with cancer who had clinically established CIPN and screened them for an objective measure of abnormal nerve conduction with vibration perception threshold (VPT) analysis, which has been shown to predict outcomes such as falls, foot ulceration and quality of life.

Methods: We recruited 17 subjects >50 years of age with cancer who had clinically established CIPN. VPT analysis was performed on each subjects and recorded at plantar foot sites: bilaterally: heel, 5th metatarsal and big toe. We defined the CKD group by an eGFR <60ml/min at the time of testing, and recorded demographics and comorbidities.

Results: A description of both CKD and non-CKD groups are listed in Table 1. VPT scores were recorded at the following plantar foot sites and results are shown in Figure 1. The CKD consistently had lower scores across VPT testing sites, and reached significance in the right big to region. Multivariate analysis suggested that diabetes diagnosis prior to chemotherapy may be independently associated with the development of neuropathy, but did not reach significance.

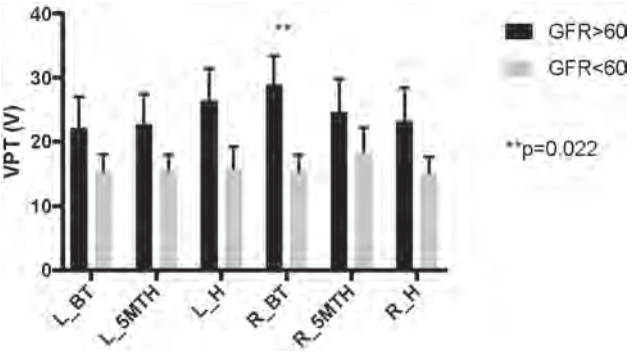
Conclusions: Although preliminary, our results show that the presence of CKD is associated with a decreased severity of neuropathy and that diabetes may be independently associated with more severe neuropathy related to cancer treatment.

Funding: Other NIH Support - NIH-R21

Demographics

Variable	CKD	non-CKD
N	8	9
Age (SD)	69 (8)	69 (8)
Sex (M/F)	6/2	4/5
DM	1	3

DM=diabetes mellitus



PUB184

Immunization: An Important Addition to Standard Care in Glomerulonephritis Patients Melissa Lan, Coleman Rotstein, Rory F. McQuillan, Daniel C. Cattran. *University Health Network, Toronto, ON, Canada.*

Background: Glomerulonephritis (GN) is a group of rare kidney diseases that can progress to end stage renal failure. GN patients are at increased risk for infection given nephrotic remission/relapse pattern, exposure to immunosuppressant therapy, and/or possible progression to chronic kidney disease. Thus our focus on guidelines indicating that hepatitis B, pneumococcus, influenza, and varicella are vaccine preventable infections.

Methods: Using the model for Quality Improvement (QI), a multifaceted GN immunization protocol (GNIP) was adopted after a needs assessment found that the first 20 patient charts had no documented immunization history. Patient (N=64) preference assessment for receipt of immunizations was by family physician (FP) 65.6%, primary nephrologist 10.9%, hospital clinic 6.3%, and walk-in clinic 4.7%. Investigation of options for vaccine administration helped construct a fish bone diagram and process map that further focused the GNIP. Physician and patient communication and documentation tools were created and the protocol initiated. The GNIP assessed/recommended hepatitis B, pneumococcus, tetanus-diphtheria-acellular pertussis, varicella, and herpes zoster immunizations plus annual administration of the inactivated influenza vaccine.

Results: Outcome measures at 4-months post-GNIP implementation: 1. 73% (92/126) of patients assessed for GNIP now have documented immunization history. 2. 63.5% (80/126) of patients assessed for GNIP have now received immunization recommendations. 3. 19.4% (90/465) of the recommended immunizations have now been administered. Additional findings: 3.1% (4/130) of patients refused to participate in the GNIP; major FP issue is the high-dose hepatitis B immunization requirement; most critical is the communication links between patient, FP, and GN clinic.

Conclusions: The GNIP fulfills an unmet medical need in GN care. This QI project highlights that need and indicates a developmental process for implementation of a solution. Early results indicate improved immunization documentation, an increase in immunization administration, and the potential for increased patient infection protection.

PUB185

Depression and CKD – A Deadly Combination with Insufficient Screening Haldane Porteous,[2] Stefan C. Hemmings,[1] Daphne H. Knicely.[3] *[1]Johns Hopkins Medicine, Baltimore, MD; [2]Johns Hopkins University, Baltimore, MD; [3]Johns Hopkins University School of Medicine, Baltimore, MD.*

Background: The prevalence of depression in the general population is approximately 7 percent but in patients with chronic kidney disease (CKD) depression rates are significantly higher, approximately 22 percent. There is a 30 percent increased risk of death in CKD patients with depression compared to CKD patients without depression. Additionally, the former are subjected to increased hospitalization rates, poorer treatment compliance, and decreased quality of life. Unfortunately, despite these known adverse associations, depression in CKD remains underdiagnosed and undertreated. Screening for depression via validated tools which are widley avialable could identify at risk patients and early intervention with pharmacological or non-pharmacological treatment could possibly improve patient outcomes.

Methods: A pre/post intervention quality improvement project involving CKD stage 3-5 patients using the validated Patient Health Questionnaire-2 (PHQ2) depression screening tool was conducted within the Nephrology Fellows' Continuity Clinic. From September 2016 to November 2016, 202 charts were audited to determine the depression screening rate of patients. The intervention phase consisted of clinician education on the importance of screening for depression as well as a built-in electronic smart phrase based on the PHQ2 tool. Between December 2016 and February 2017, 202 charts were audited

to determine the post intervention screening rate. From March 2017 and April 2017, 50 charts were audited to determine if the post-study result was sustained.

Results: Pre-intervention screening rate was 1.48 percent. Post-intervention screening rate increased to 10.45 percent. Post-study screening rate was 12.01 percent.

Conclusions: Depression is prevalent in CKD patients and is associated with increased mortality. This quality improvement project demonstrated that clinician education and an electronic smart phrase based on a validated screening tool are two metrics associated with a sustained improvement in depression screening. Research studies are needed to identify other metrics which can be used to improve depression screening so that CKD patients can receive early treatment which may reduce the risk of hospitalization and/or death.

PUB186

Advance Care Planning in the CKD Stages 3-5 Non-Dialysis Population 65 Years and Older Barbara M. Weis. *College of Nursing, University of Colorado, Aurora, CO.*

Background: In the chronic kidney disease (CKD) academic outpatient predialysis clinic, there were no identified protocols or procedures for advance care planning (ACP) for this chronic CKD stages 3-5 population 65 years and older. Research has indicated the value of ACP and the collection of advance directives in patients with chronic disease states. This quality improvement project addressed the identified gap of lack of evidence-based ACP interventions specific to this population.

Methods: The purpose of this quality improvement project was to (a) assess the effectiveness of an evidence-based educational intervention versus usual care in increasing completion of medical durable powers of attorney (MDPOAs) and advance directives by these select groups of CKD patients (b) determine the effect of independent variables on this CKD population education in completion of ACP for the purpose of tailoring an evidence-based ACP program. Pre-dialysis CKD stage 3-5 patients' (N = 60) response to an advance care planning intervention and the completion of advance directives and MDPOAs was studied. Data were analyzed using descriptive and inferential statistics (frequency distribution, Pearson's chi square planning test for independence and McNemars' test).

Results: Results indicated statistical significance ($p < .05$) in the increase in collection of advance directives in the educational versus the control group. The results also demonstrate statistical significance ($p < .05$) in the collection of MDPOAs in an outpatient CKD clinic in patients 65 years and older.

Conclusions: This quality improvement project has shown with the right resources, effective communication with staff and providers, an open clinical population, a cost effective and sustainable delivery system for ACP in an outpatient clinic in line with the organizational mission can be a reality. Ultimately, improving the process of educating patients about end-of-life care and collection of advance directives and MDPOS will improve end-of life care and decrease hospital costs related to end-of-life care as well as bring revenue to the practice.

PUB187

Provider Experience with Implementation of a Pragmatic Randomized Trial of CKD Screening in Primary Care: A Qualitative Report Martin J. Frigaard,[1] Leticia Rolon,[6] Lowell J. Lo,[2] Anna Rubinsky,[7] Delphine S. Tuot,[7] Neil R. Powe,[4] Michael Shlipak,[5] Carmen A. Peralta.[3] *[1]Kidney Health Research Collaborative, Oakland, CA; [2]None, San Francisco, CA; [3]University of California San Francisco/SFVAMC, San Francisco, CA; [4]Priscilla Chan and Mark Zuckerberg San Francisco General Hospital & University of California SF, San Francisco, CA; [5]San Francisco VA Medical Center, San Francisco, CA; [6]UCSF Medical Center, San Francisco, CA; [7]University of California, San Francisco, San Francisco, CA.*

Background: Provider burden from participation in pragmatic randomized clinical trials (RCT) is not well documented. To inform future research, we surveyed providers who had recently completed a pragmatic RCT of CKD screening in primary care. We characterized their insights and thoughts regarding perceived burden of the intervention and self-reported CKD knowledge at the end of the trial.

Methods: The protocol required participation in the RCT between February 2016 to March 2017. All primary care providers (PCPs) received education about the study and reviewed a list of eligible patients for exclusion. Additionally, PCPs randomized to intervention reviewed CKD results, co-signed notes with CKD-related recommendations, and discussed plan of care with patients. Clinical pharmacists provided hypertension medication management and CKD education. We sent a 5-question (three yes/no, two open-ended), anonymous web-based survey to all participating providers.

Results: Of 33 providers, 20 (61%) completed the questionnaire. Among respondents, 12 (60%) answered affirmatively to "I learned how to improve care for patients with CKD" and 12 (60%) answer yes to "I changed the plan of care of one or more patients" from participation in the program. The most frequently reported changes included better understanding of CKD testing strategies, more confidence to educate patients on CKD and safe NSAID use, and addition of ACE/ARB or diuretic for hypertension treatment. The majority 16 (80%) replied "no" to whether the program increased burden. The most frequent reason for increased burden was more time spent on patient counseling about study correspondence and CKD results.

Conclusions: Providers in a pragmatic CKD screening trial in primary care didn't report substantial increases in burden. Providers also reported perceived improvements in CKD knowledge and applying practice improvements.

Funding: NIDDK Support

PUB188

Assessment of Efficacy of a CKD Support Decision Making Application and Home Blood Pressure Measurement System in Patients with CKD: Study Protocol of a Randomized, Controlled Trial Shiho Kosaka,[2] Junichi Hoshino,[3] Masayuki Yamanouchi,[3] Akinari Sekine,[3] Yoshifumi Ubara.[1] *[1]Setagaya, Japan; [2]Tokyo Medical and Dental University, Tokyo, Japan; [3]Toranomon Hospital, Tokyo, Japan.*

Background: Disease management of patients with chronic kidney disease is complicated, and requires extensive time dedicated to decision making. Therefore, this study aimed to develop a support decision making application for patients with chronic kidney disease (CKD-SDM app), to prevent future disease progression and to support the decision making process regarding renal replacement therapy (RRT).

Methods: Inclusion criteria were: patient at the kidney internal medicine outpatient clinics, age over 20 years old, provision of informed consent, to be assure by doctor, RRT not yet selected, and eGFR<60. This study is a clinical, prospective, randomized, controlled trial with balanced randomization (1:1). The planned sample size is 68 participants. Participants in both groups will be followed up at 2 and 6 months after randomization. The intervention group will receive conventional care from the attending physician; the patient and physician will also be given a tablet equipped with the CKD-SDM app and an automated sphygmomanometer for home blood pressure monitoring for 2 months. The CKD-SDM app includes 61 items in three categories: "Let's study CKD", "What's about RRT?", and "Learn and consent of CKD". The control group will receive conventional care and only the automated sphygmomanometer for 2 months. The primary outcome measure is change in home blood pressure data from baseline. Secondary outcomes are renal function, spot urine test, self-efficacy for chronic illness, disease burden, knowledge level of self-management in CKD, and decision for RRT. Recruitment began in March 2017 with the last participant due to be continued.

Results:

Conclusions: This study will attempt to evaluate the effect of a self-management and support decision making intervention for chronic kidney disease. Outcome data will be used to clarify whether the new intervention prevents disease progression and improves quality of RRT selection. Trial Registration: This study is registered to UMIN Clinical Trial Registry (000025792)

Funding: Government Support - Non-U.S.

PUB189

Digital Tools for Complex Medication Regimens in CKD: Scoping Review Ginyoung Lee, Stephanie W. Ong. *University Health Network, Toronto, ON, Canada.*

Background: Despite advances in medical therapy, medication non-adherence remains to be a health threat causing poor clinical outcomes in patients with chronic kidney disease (CKD). Digital medication adherence tools (DMATs) may play a key role as advanced features and functionalities can be adapted to address known multifactorial barriers to medication adherence in CKD. This study examined features and functionalities of DMATs, how they specifically address barriers of medication adherence and explored currently available evidence.

Methods: A multi-step approach was undertaken including: literature search from January 2006 to 2017 using PubMed, Medline supplemented by reference lists, environmental scan using Google Search engine for available commercial DMATs and grey literature to include pre-market tools.

Results: Total of 17 studies were extracted which had distinct DMATs and met the inclusion criteria. Of these studies, DMATs ranged from digital pill systems, electronic medication container devices, electronic medication administrating devices and mobile applications. Each had unique and overlapping features and functionalities that address factors of medication non-adherence ranging from visual/auditory stimuli to act as reminders, addressing forgetfulness, organizing in Bluetooth capable dosette boxes up to allowing clinicians to remotely monitor and track medication intake. All of these factors are known barriers to medication adherence in CKD patients with complex medication regimens. It was found no single DMAT can address all factors. Evidence of use and efficacy in chronic disease are lacking at this point.

Conclusions: Available DMATs possess varying features and functionalities that address barriers of medication adherence. DMATs can play a role in promoting CKD medication taking practices if personalized and tailored use to target specific medication adherence barriers is identified. Their impact on medication adherence should be further explored in future studies.

PUB190

Cost Implications of Inappropriate Proton Pump Inhibitor (PPI) Use in Advanced CKD Amanda Chow,[1] Rory F. McQuillan,[2,1] Marisa Battistella,[1,2] Annemarie Cesta,[1] Stephanie W. Ong.[1] *[1]University Health Network, Toronto, ON, Canada; [2]University of Toronto, Toronto, ON, Canada.*

Background: PPIs ranked second highest drug use in Ontario, Canada. The long term use of PPIs in kidney disease has been associated with adverse clinical outcomes. Their continued use can also have impact on unnecessary drug cost burden on the patient. This study determined the proportion of advanced CKD patients who were taking PPI inappropriately and assessing this drug cost implication of inappropriate indications to the patient.

Methods: A cross sectional chart review was performed in May 2017 in outpatient renal clinics that oversee the care of patients with advanced CKD (stage 4 and 5). Data on PPI use was determined from clinic pharmacy records obtained by patient medication history. Indication for PPI use was then determined using medical charts. Indications were categorized as appropriate or inappropriate based on predetermined list of accepted long term PPI indication derived from accepted protocols. The cost of inappropriate use was then calculated from the drug list price of each PPI gathered from Ontario drug formulary list price.

Results: A total of 413 charts were reviewed. A total of 127 (31%) patients had current active documentation of PPI use. Examining the duration of PPI use, 124 patients of 127 (97.6%) had documentation of PPI use for more than 8 weeks. Seventy four (59%) patients were deemed to be using them for an inappropriate (e.g. asymptomatic GERD) or unknown indication. Cost estimates using the price per pill accounted for a total 30-day cost of $1,565.78 for these inappropriate indications. This results in a yearly cost of $18,789.37 and an average cost per patient of $147.95.

Conclusions: Inappropriate PPI use in advanced CKD not only has clinical implications but also an economic impact with respect to pill burden and associated costs incurred. PPI deprescribing protocols should be implemented to address inappropriate use and alleviate these unnecessary drug costs.

PUB191

The Expectation, Concern, and Experience of Patients towards Integrative Chinese-Western Medicine for Diabetic Kidney Disease: A Qualitative Study

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Background: Emerging data suggest that Chinese medicine could reduce the risk of end-stage renal kidney disease among chronic kidney disease patients by 59% in a six-year period. However, a recent cross-sectional study in Hong Kong found that only 20% of diabetic kidney disease (DKD) patients have consulted a Chinese medicine practitioner. The experience and concerns regarding integrative Chinese-western medicine management among DKD patients remains unknown and undocumented.

Methods: Focus group interviews with DKD patients were conducted to explore their experience and concerns. Patients with different age group, gender, stage of chronic kidney disease, comorbidity, knowledge and usage of western and Chinese medicine and history of herbal toxicity were purposively sampled. A trained moderator conducted the interview based on an adaptive semi-structured interview guide. Audiotaped interviews were transcribed verbatim and analysed by framework analysis by two independent researchers.

Results: The interview covered the scopes regarding 1) barrier towards integrative service, 2) motivation to seek alternative and complementary treatment, 3) experience in the use of Chinese medicine and 4) preferred mode of integrative service. Data saturation was observed at the third round of interview. Twenty-one patients with a wide spectrum of demographics were interviewed. Two to six key themes were identified under each scope with specific examples from DKD patients. Overall, patients with severe DKD tend to seek alternative options for disease management. However, the efficacy, safety, finance, convenience of access and lack of referral channels were key barriers in consulting integrative service. Organisational support from the government plays a critical role in enhancing patient's confidence in utilising integrative service.

Conclusions: Our findings document specific expectation and concerns from DKD patients over the access of integrative medicine for the future consideration of health service provision and research design. **Funding support:** The University of Hong Kong and Hong Kong Society of Nephrology Research Grant

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PUB192

Detection of Renal Fibrosis by CT Scanning: Results from a Primate Model

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Background: Early detection of fibrosis has a major impact on diagnosis and therapy. Renal fibrosis is a known sequel of total body irradiation (TBI).

Methods: 99 non-human-primates (NHP) have been under long term follow-up after TBI ranging from 0 to 8.5 Gy. They undergo serial follow-up with blood testing and CT scanning and a full necropsy at death. 19 died during follow-up, of which 4 were non-irradiated. Kidneys were stained for collagen with Masson trichrome, and scored twice in a masked fashion using 4 or more microscope fields at 100x. Renal cortical fibrosis was scored as absent (0), minimal (1, absent in most viewed fields), scattered (2, present in some fields), moderate (3, present in most fields), and severe (4, present in all fields). CT scanning was done by a 32 slice Toshiba Aquilion CT Scanner with parameters: 120 kV, 300mA, field of view = 320 mm, matrix = 512x512, and slice thickness = 0.5 mm. Cortex regions of interest (ROIs) were traced in three coronal slices and averaged for an average mean gray scale value for that kidney's cortex. For each ROI that was measured, the total cross sectional area of tissue penetrated was also measured to correct for x-ray beam hardening. ROIs were traced in fat, muscle, and achilles tendon for use as reference tissues to calibrate the conversion of gray scale to Hounsfield units (HU). The histological score was correlated to the HU of each kidney.

Results: There was a direct correlation of the histological fibrosis score to the CT HU of each kidney (r=0.6, p=0.003). CT HU was 90% specific and 83% sensitive for histologic fibrosis. The fibrosis scores for the irradiated NHP were significantly greater than those of the non-irradiated NHP (p=0.02). Computerized color-intensity scanning correlated with the human semi-quantitative scores. The five grades of fibrosis cannot be distinguished by analyzing the uncorrected CT images; the correction for beam hardening is required. The median BUN in the irradiated NHP was 24 and that of the non-irradiated NHP was 22 mg/dl (p=0.8).

Conclusions: Renal fibrosis can be detected by CT scanning, this requires correction for body size and beam hardening, and fibrosis can be detected before there is significant azotemia.

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PUB193

Proteomic Analysis of the Epithelial Secretome Implicates Jagged-1 in Tubule Dysfunction and Paracrine Communication

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Background: Tubulointersititial fibrosis (TIF) is a critical contributor to chronic disease strongly correlating with renal insufficiency. Persistent epithelial dysfunction is integral to TIF progression. The role of specific tubule-derived paracrine factors that crosstalk to fibroblasts is less understood.

Methods: Stable isotope labeling with amino acids in cell culture (SILAC) allowed incorporation of heavy or light amino acids into native proteins to measure their abundance in human renal proximal tubule epithelial cell (hRPTEC)-derived conditioned medium (determined from the relative mass spectrometry (MS) signal intensities). The bioinformatical program Genecodis analyzed the MS-based proteomics of the epithelial secretome in response to HB-EGF or TGF-β treatment (24h) compared to untreated cells. Biochemical approaches characterized Jagged-1 (Jag-1) as a novel tubule paracrine factor.

Results: SILAC/MS-based proteomics identified 157 and 181 secreted proteins that increased significantly in hRPTECs treated with HB-EGF or TGF-β, respectively. Genecodis analysis revealed 95 tubule paracrine factors similarly upregulated by HB-EGF and TGF-β related to signal transduction, adhesion, inflammation and negative regulation of cell proliferation pathways. Of interest, Jag-1, a ligand of the Notch pathway, was increased 15.123 and 8.2409-fold in the conditioned media of HB-EGF or TGF-β-stimulated epithelial cells, respectively. Gene silencing of Jag-1 in hRPTECs decreased HB-EGF and TGF-β-induced matrix protein CTGF and dedifferentiation regulator Snail compared to identically treated control siRNA-expressing hRPTECs. Pharmacological inhibition of γ-secretase (RO-4929097), necessary for the activation of canonical Notch signaling via NICD, also reduced TGF-β-dependent CTGF, Snail, and cell cycle regulator $p16^{INK}$ in hRPTECs. Conditioned media derived from Jag-1-depleted hRPTECs stimulated by HB-EGF or TGF-β had decreased fibroblast proliferation compared with fibroblasts incubated in conditioned media-derived from control counterparts.

Conclusions: These results suggest that activation of EGFR or TGF-β signaling in the proximal tubule promotes the secretion of paracrine factors driving epithelial dysfunction and fibroblast activation and identifies Jag-1-dependent Notch signaling as a potentially important mediator of these processes.

Funding: NIDDK Support, Veterans Affairs Support

PUB194

Ecdysone Elicits Chronic Renal Impairment via Mineralocorticoid-Like Pathogenic Activities

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Background: Ecdysteroids are steroidal insect molting hormones and also exist in herbs. Ecdysteroid-containing adaptogens have been popularly used for improving well-being and by bodybuilders for muscle growth. However, there is growing evidence suggesting that use of ecdysone is apparently associated with disturbed electrolyte and water balance that is manifested as water retention and body weight gain. The underlying pathogenic mechanism remains unknown and was examined in this study.

Methods: Virtual screening tools were employed to identify compounds homologous to ecdysone and putative ecdysone-interacting proteins. The kidney effect of ecdysone was examined *in vitro* and *in vivo* and compared with that of aldosterone.

Results: Computer-assisted molecular structure matching revealed that ecdysone is highly homologous to aldosterone. Moreover, virtual screening based on ccompound–protein interaction profiles identified mineralocorticoid receptor, the cognate receptor for aldosterone, as one of the top-ranking proteins with strong interaction with ecodysone. To validate the biological functionality, ecdysone was applied to inner medullar collecting duct cells, which are typical mineralocorticoid-sensitive effector cells, and induced cellular hypertrophy, accumulation of extracellular matrix, and epithelial to mesenchymal transition, marked by *de novo* expression of α-smooth muscle actin. In addition, ecdysone disrupted cellular tight junction and retarded cell motility, akin to the effect of aldosterone. *In vivo*, daily treatment of mice with ecdysone for 2 weeks resulted in body weight gain and reduced urinary sodium to potassium ratios. Moreover, increased cell apoptosis, as probed by TUNEL staining, and early signs of renal fibrogenesis, marked by deposition of collagen and fibronectin in tubulointerstitium, were noted in the kidney, reminiscent of the activity of aldosterone. The cellular and pathobiological effects of ecdysone were likely mediated by mineralocorticoid receptor as evidenced by remarkable nuclear translocation of mineralocorticoid receptor in renal tubular cells both *in vitro* and *in vivo*. Conversely, blockade of mineralocorticoid receptor by concomitant spironolactone treatment largely abolished the actions of ecdysone.

Conclusions: Our findings suggest that ecdysone possesses mineralocorticoid-like activities that impair renal function and elicit renal injury.

PUB195

Tamoxifen Attenuates Fibrosis by Suppressing PI3K/Akt and mTOR/p70S6K Pathways through Src Kinase in Obstructive Nephropathy in Rats Chang Seong Kim, Hong sang Choi, Ha yeon Kim, Eun Hui Bae, Seong Kwon Ma, Soo Wan Kim. *Chonnam National University Medical School, Gwangju, Republic of Korea.*

Background: Tubulointerstitial fibrosis is the final pathway of chronic progressive kidney diseases. Src kinase and mammalian target of rapamycin (mTOR) pathway play a critical role in the pathogenesis of renal fibrosis. Here we investigated the effects of tamoxifen on renal fibrosis and its' underlying molecular mechanisms in the obstructive nephropathy rat model.

Methods: Renal fibrosis was induced by unilateral ureteral obstruction (UUO) in male Sprague-Dawley rats for 14 days. Tamoxifen (10mg/kg) was given by oral gavage after UUO operation. We also treated human proximal tubular epithelial (HK-2) cells with tamoxifen (5 μM) in the presence or absence of tumor growth factor (TGF)-β1 (2 ng/mL), estrogen receptor (ER)-α antagonist ICI (5 μM), and ER-α receptor siRNA to examine the effects of tamoxifen treatment on TGF-β1-stimulated renal fibrosis via ER-α.

Results: Tamoxifen treatment ameliorated the UUO-induced renal fibrosis with decreased expression of α-smooth muscle actin (SMA), fibronectin and connective tissue growth factor (CTGF). Phosphorylation of Src (Tyr 416), PI3K/Akt and mTOR/p70S6K protein was also significantly decreased after tamoxifen-treated compared to vehicle-treated UUO kidneys. These renoprotective effects were not associated with inhibition of TGF-β1. In HK-2 cells, tamoxifen suppressed TGF-β1-induced protein expression of α-SMA and CTGF, and phosphorylation of Src, PI3K/Akt and mTOR/p70S6K, which was counteracted by the treatment with ICI and silencing ER-α with siRNA.

Conclusions: Tamoxifen treatment attenuates renal fibrosis in the obstructed kidney of rats with UUO. Tamoxifen-induced antifibrotic effect is associated with the suppression of Src kinase via ER-α followed by inhibition of phosphorylation of PI3K/Akt and mTOR/p70S6K signaling pathways in HK-2 cells.

PUB196

Interleukin (IL)-17 Production by Tubulointerstitial Human γ/δ T Cells in Renal Fibrosis and CKD Helen G. Healy,[1,2] Becker Meng-Po Law,[1,2] Xiangju Wang,[1,2] Katrina Kildey,[1,2] Melissa Rist,[1,2] Ray Wilkinson,[1,2] Andrew J. Kassianos.[1,2] *[1]Conjoint Kidney Laboratory, Pathology Queensland, Brisbane, QLD, Australia; [2]Kidney Health Service, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia.*

Background: γ/δ T cells are effector lymphocytes recognised as having important functional roles during chronic inflammatory processes. Mouse studies suggest a pathological role for γ/δ T cells in immune-mediated models of kidney disease. This study evaluates γ/δ T cells present in human fibrotic chronic kidney disease (CKD).

Methods: We extracted γ/δ T cells from healthy kidney tissue and diseased biopsies with and without fibrosis. γ/δ T cells were identified, enumerated and phenotyped by twelve-colour flow cytometry. Localisation and production of the pro-inflammatory cytokine IL-17 by γ/δ T cells was examined by multi-colour immunofluorescent microscopy.

Results: We detected significantly elevated numbers of γ/δ T cells ($CD45^+CD3^+\gamma/\delta^+$) in diseased biopsies with interstitial fibrosis compared with diseased biopsies without fibrosis and healthy kidney tissue. The increased numbers of γ/δ T cells correlated significantly with loss of kidney function (eGFR). Furthermore, expression levels of CD161, a marker of human IL-17-producing T cells, were increased on γ/δ T cells from fibrotic biopsies compared with non-fibrotic kidney tissue. Immunofluorescent analysis of fibrotic kidney tissue localised the accumulation of γ/δ T cells within the tubulointerstitial compartment, adjacent to proximal tubular epithelial cells (PTEC), defined as tubular cells expressing aquaporin-1. Notably, we identified these tubulointerstitial γ/δ T cells as a key source of pro-inflammatory cytokine IL-17.

Conclusions: The correlation of IL-17-producing γ/δ T cells with histologically and functionally more severe CKD suggests a pathological role. Further functional dissection of renal γ/δ T cells is now required for the development of therapeutics capable of blocking this previously untargeted immune cell population.

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PUB197

The Protective Role of Kallistatin in Tubulointerstitial Fibrosis Ye Li,[1] Wai Han Yiu,[1] Dickson W. Wong,[1] Kam wa Chan,[1] Bin Li,[1] Loretta Y.Y. Chan,[1] Joseph C K Leung,[1] Hui Y. Lan,[2] Kar Neng Lai,[1] Sydney C. Tang.[1] *[1]Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Hong Kong, China; [2]Department of Medicine and Therapeutics, and Li Ka Shing Institute of Health Sciences, The Chinese University of Hong Kong, Shatin, China.*

Background: Kallistatin, a tissue kallikrein binding protein, exerts renoprotective functions against renal fibrosis in various animal models of kidney disease. However, the underlying mechanisms remains poorly understood. Recent data suggest that kallistatin antagonizes Wnt/β-catenin signaling in cancer cells and that this signaling pathway plays a crucial role in the pathogenesis of renal fibrosis. Here, we investigated the effect of kallistatin on Wnt/β -catenin signaling and the pro-fibrotic process in renal proximal tubular epithelial cells.

Methods: Cultured human proximal tubular epithelial cells (HK-2) were transfected with kallistatin plasmid (0.5-4 μg/ml) prior to TGF-β stimulation (10 ng/ml) that is known to activate Wnt/β-catenin. The efficiency of kallistatin transfection was verified by ELISA. The induction of TGF-β-induced Wnt/β-catenin signaling and the expression of fibrotic molecules was detected by real-time qPCR and Western blotting.

Results: TGF-β activated β-catenin signaling in HK-2 cells as evidenced by increased phosphorylation of GSK3β and accumulation of β-catenin in both the cytosol and nucleus. Additionally, TGF-β significantly increased the expression of Wnt family members (Wnt5a, Wnt9a and Wnt3) and the Wnt antagonist DKK1 in HK-2 cells. Overexpression of kallistatin in HK-2 cells not only inhibited TGF-β induced phospho-GSK3β and β-catenin levels, but also decreased the expression of Wnt5a, Wnt 9a and DKK1 as well as numerous fibrosis-related genes such as TGF-β, Snail, PAI-1, Collagen I in a dose-dependent manner. Finally, the phosphorylation of Akt was increased by TGF-β, which was also abrogated by kallistatin.

Conclusions: Kallistatin attenuates the profibrotic effects of TGF-β via inhibition of Wnt/β-catenin and Akt signaling, thereby reducing the expression of fibrotic genes in tubular cells. These findings further support the renoprotective role of kallistatin and highlight its therapeutic potential in renal fibrosis. **Funding:** Research Grants Council of Hong Kong (GRF grant number 17151716)

Funding: Government Support - Non-U.S.

PUB198

Histone Deacetylase 6 Inhibition Counteracts Epithelial–Mesenchymal Transition of Peritoneal Mesothelial Cells and Prevents Peritoneal Fibrosis Liuqing Xu,[2] Na Liu,[2] Yingfeng Shi,[2] Shougang Zhuang.[1] *[1]Rhode Island Hospital, Alpert Medical School of Brown University, Providence, RI; [2]Department of Nephrology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China.*

Background: Peritoneal fibrosis is an important pathological remodeling feature in peritoneal dialysis patients. Little is known about epigenetic regulation of its development and progression.

Methods: We examined effects of HDAC6 inhibition on epithelial–mesenchymal transition (EMT) of cultured human peritoneal mesothelial cells (HPMCs) and development of peritoneal fibrosis in a rat model induced by high glucose dialysate.

Results: In cultured HPMCs, treatment with highly selective HDAC6 inhibitor tubastatin A, or HDAC6 silencing with siRNA inhibited transforming growth factor β1 (TGF-β1)-induced EMT, manifesting as increased α-SMA, fibronectin, and collagen I expression, decreased E-cadherin expression. In a rat model of peritoneal fibrosis induced by high glucose dialysate, HDAC6 prevented submesothelial thickening and decreased collagen I and a-SMA expression. Tubastatin A treatment inhibited TGF-β1 expression and Smad-3, epidermal growth factor receptor, STAT3, and NF-κBp65 phosphorylation. HDAC6 inhibition suppressed production of inflammatory cytokines/chemokines and reduced macrophage infiltration in injured peritoneum. Moreover, tubastatin A effectively inhibited peritoneal increase of CD31(+) blood vessels and expression of vascular endothelial growth factor after high glucose dialysate injection.

Conclusions: HDAC6 inhibition may attenuate peritoneal fibrosis by inhibiting multiple pro-fibrotic signaling pathways, EMT, inflammation and angiogenesis.

Funding: Government Support - Non-U.S.

PUB199

Meprin Metalloproteases and Meprin Targets Secreted in the Urine of African American Men with Diabetic Kidney Injury: Insights on Underlying Mechanisms Elimelda M. Ongeri, Lei Cao, Lisa M. Felton, Ava Boston. *Biology, North Carolina A&T State University, Greensboro, NC.*

Background: Minority ethnic groups are disproportionately affected by diabetic kidney disease (DKD). Susceptibility genes identified include meprins, zinc metatalloproteases of the astacin family, which are abundantly expressed in kidney epithelial cells. Meprins are also differentially expressed in podocytes and leukocytes (monocytes and macrophages). Meprins have been implicated in the pathology of DKD in humans and rodent models. Single nucleotide polymorphisms in the meprin β gene were associated with DKD in the Pima Indians, a US ethnic group with extremely high incidence of DKD. Decreased meprin expression and activity were demonstrated in rodents with diabetic kidney injury. We recently showed that meprin deficiency enhances kidney injury in mice with STZ-induced type 1 diabetes. However, the cellular and molecular mechanisms by which meprins modulate DKD are not understood. We have gained insights from identified meprin targets in the kidney, which include modulators of inflammation (e.g IL-1β, IL-6, pro-IL18, MCP-1) and extracellular matrix (ECM) proteins (e.g collagen IV, laminin, fibronectin, and nidogen-1).

Methods: Fasting urine samples were collected from three groups of African American men aged 18-65 years; 1) nondiabetic controls, 2) diabetics, and 3) diabetics with diagnosed kidney disease. ELISA assays were used to determine the levels of albumin, creatinine, and MCP-1. Western blot analysis was used to determine the levels of meprin A, meprin B, nidogen-1, fibronectin, and laminin.

Results: Meprins and meprin targets were not detectable in the urine of non-diabetic controls or diabetics with albumin to creatinine ratios (ACR)≤10. Diabetic patients with ACR≥30 had high levels of urinary meprins, fibronectin, laminin, and nidogen-1, with a ~3-fold increase in levels for patients with ACR≥200. For nidogen-1, we detected both full-length (~136 kDa) and a 55 kDa fragment.

Conclusions: The data suggest proteolytic processing of nidogen-1 by meprins in DKD which could trigger release of other ECM proteins from the basement membrane. More importantly, this could serve to reduce ECM buildup and thus reverse the fibrosis associated with DKD. The correlation between diabetic kidney injury and the levels of meprins and meprin targets in urine suggests that they could serve as diagnostic tools for DKD.

Funding: Other NIH Support - NIMHD, NIGMS

PUB200

Fibroblast Growth Factor 23 (FGF-23) Regulates HK-2 Cell Proliferation, Migration, and Response to TGF-β1 Jack S. Lawson, Harriet M. Syme, Caroline P. Wheeler-Jones, Jonathan Elliott. *Royal Veterinary College, London, United Kingdom.*

Background: Plasma FGF-23 concentration increases early in the course of chronic kidney disease (CKD), and rises progressively with deteriorating renal function. Elevated FGF-23 is associated with progression of CKD, and may play a direct role in the development of renal injury and tubulointerstitial fibrosis. The aims of this study were to investigate the effects of FGF-23 on proliferation, migration, viability and pro-fibrotic gene expression in a human tubular epithelial cell line (HK-2), and to determine whether FGF-23 modulates the transcriptional and functional effects of TGF-β1.

Methods: HK-2 cells were incubated with FGF-23 (0.1-100 ng/ml) ± 10 ng/ml TGF-β1 for 72 h. ERK1/2 phosphorylation was measured by immunoblotting. Expression of E-cadherin, N-cadherin, connective tissue growth factor (CTGF), collagen 1α1 (col1α1) and TGF-β1 was assessed by RT-qPCR (normalised to GAPDH/RPS7). Cell migration was measured using a scratch wound healing assay, and proliferation and viability monitored by cell counting, crystal violet staining and measurement of caspase 3/7 activity. The MEK inhibitor PD184352 (1 μM) and the FGF receptor 1 (FGFR1) antagonist SU5402 (10 μM) were used to investigate involvement of MEK-ERK signalling and FGFR activation, respectively.

Results: FGF-23 increased ERK phosphorylation and stimulated cell proliferation, which was completely attenuated by PD184352. Scratch wound closure was stimulated by FGF-23 in a concentration dependent manner, and this was blocked by SU5402. TGF-β1 decreased wound closure, and this was partially ameliorated by FGF-23. FGF-23 suppressed col1α1 expression, and at 100 ng/ml partially inhibited TGF-β1-driven increases in col1α1, N-cadherin, and CTGF expression. FGF-23 and TGF-β1 each inhibited E-cadherin expression, but there was no additive inhibitory effect. FGF-23 did not modify TGF-β1 mRNA expression or TGF-β1-mediated caspase 3/7 activation.

Conclusions: FGF-23 stimulates migration and proliferation of HK-2 cells most likely through engagement of FGFR1 and MEK-ERK pathway activation, and partially reverses pro-fibrotic and anti-repair responses to TGF-β1. These results suggest FGF-23 facilitates tubular repair and regeneration processes. The relevance of these findings to progressive nephron loss in the CKD patient warrants further study to establish their translational potential.

Funding: Commercial Support - Elanco Animal Health

PUB201

Direct Regulation of FGF23 on Osteoclast Growth and Activity Nan Hu,[2,3] Chuan-Ming Hao,[1] Xin-zhou Zhang.[2,3] *[1]Huashan Hosp., Shanghai, China; [2]Department of Nephrology, Shenzhen People's Hospital, Shenzhen, China; [3]Key Renal Laboratory of Shenzhen, Shenzhen, China.*

Background: In the study of CKD mechanism, FGF23 has been shown to be involved. When the disease occurs, one of the pathological causes is that osteoclasts become hyperactive. We aimed to investigate whether FGF23 can directly regulate on the growth and activity of osteoclasts, which provides another way for FGF23 to participate in CKD.

Methods: Mouse macrophage cell line RAW264.7 was routinely cultured and inducing factor RANKL (25ug/ml) and M-CSF (30ug/ml) were added for 5 days. Then TRAP staining was performed to determine osteoclasts and treatments were carried out using recombinant human FGF23 (Group A:RAW264.7; Group B-E: 1ug/ml, 100ng/ml, 10ng/ml, 1ng/ml, 0ng/ml FGF23). Then we measured the cell survival and apoptosis rate by CCK8 assay and Annexin V-FITC after 24h, 48h and 72h, respectively. Meanwhile, mRNA levels of several key factors (*NFATC1, C-FOS, RANKL, OPG, CATK*) were detected by quantitative RT-PCR after the same treatment.

Results: TRAP staining showed that cells of induced group had positive staining. RAW264.7 cell fusion began and multinucleated giant cells developed in day 5 (Figure 1-a and1-b). Results of CCK8 (Figure 1-c) showed that lower concentrations of Group E and D could promote cell proliferation and higher concentration(Group B and C) inhibited the cell activity. Annexin V-FITC staining showed that compared with control (Group A), the apoptotic rate of each group with FGF23 showed a downward trend in 24h, 48h and 72h. At the same time, mRNA levels of key factors(*NFATC1, C-FOS, RANKL, OPG, CATK*) changed significantly with different concentration of FGF23 and treatment time (Figure 2).

Conclusions: These results indicate that FGF23 can act directly on osteoclasts and provide a theoretical basis for its further involvement in the pathogenesis of CKD.

Funding: Government Support - Non-U.S.

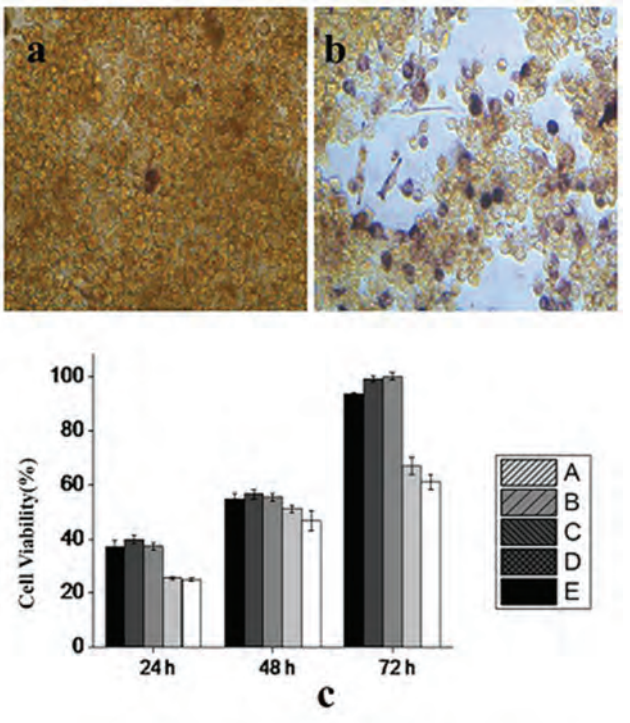


Fig 1: .a: RAW264.7; b: RAW264.7 cells were induced by M-CSF and RANKL (400 x); c: Cell viability of osteoclasts with different treatments after 24 h, 48 h, and 72 h

PUB202

Effects of the Combination of Losartan, Mycophenolate Mofetil, and Tamoxifen on the Development of Albuminuria and Glomerulosclerosis in an Experimental Model of Hypertensive Nephrosclerosis Camilla Fanelli, Humberto Delle, Rita de Cassia Cavaglieri, Wagner Dominguez, Irene L. Noronha. *University of Sao Paulo, Brazil, São Paulo - SP, Brazil.*

Background: The renoprotective effects of tamoxifen (TAM) in CKD induced by chronic inhibition of nitric oxide (L-NAME experimental model) have previously been demonstrated. TAM has been shown to prevent albuminuria, glomerular damage and interstitial fibrosis, despite having no effect on the sustained hypertension. In the present study, we sought to determine whether the addition of an ARB (losartan; LOS) and an immunosuppressor (mycophenolate mofetil; MMF) to TAM treatment could promote further renoprotection in L-NAME-treated animals.

Methods: In 25 male Wistar rats, CKD was induced by oral administration of 70 mg/kg/d of L-NAME, accompanied by a 3.2% high-salt diet. The rats were divided into 5 groups: **L-NAME** (untreated); **LOS** (treated with LOS, 50 mg/kg/d); **MMF** (treated with MMF, 10 mg/kg/d); **TAM,** (treated with TAM, 10 mg/kg/d); and **LOS+MMF+TAM** (treated with all 3). Five additional animals only received the high-salt diet (**Control**). Blood pressure (BP), albuminuria (uALB), glomerular ischemia (GI), glomerular sclerosis (GS), interstitial fibrosis (INT) and αSMA accumulation, as well as renal cortical macrophage (ED1) and T-cell (CD3) infiltration, were evaluated after 30 days of treatment.

Results: Data are presented as Mean ± SE. For One-way ANOVA: $p<0.05$: [a]vs. Control, [b]vs. NAME, [c]vs. LOS, [d]vs. MMF, [e]vs. TAM. For Student's t-test: $p<0.05$: *vs. TAM

Conclusions: The LOS+MMF+TAM combination completely normalized the urinary albumin excretion rate and glomerulosclerosis in L-NAME-treated rats. That combination was also more effective than was TAM monotherapy in reducing hypertension and glomerular ischemia in L-NAME-treated rats. Although the LOS+MMF+TAM combination did not improve interstitial fibrosis or myofibroblast (αSMA) infiltration, it was more efficient than was TAM alone in preventing T-cell infiltration.

Table of Results

	BP (mmHg)	uALB (mg/24h)	GI (%)	GS (%)	INT (%)	αSMA (%)	EDI (cell/mm^2)	CD3 (cell/mm^2)
Control	127±1	1±1	1±1	0.4±0.4	0.3±0.1	1±1	3±1	8±2
NAME	213±11^{a}	147±31^{a}	17±3^{a}	4.2±1.7^{a}	1.7±0.3^{a}	16±4^{a}	29±9^{a}	20±5
LOS	183±12^{ab}	14±10^{ab}	4±1^{b}	0.5±0.2	0.7±0.2^{b}	6±1^{ab}	29±8^{a}	21±4
MMF	173±9^{abc}	11±8^{b}	1±1^{b}	1.6±0.7	0.5±0.3^{b}	7±1^{a}	20±8^{a}	17±5
TAM	208±7^{acd}	23±4^{ab}	5±1^{b}	1.0±0.2	0.4±0.1^{b}	6±1^{ab}	12±4^{a}	21±6
LOS+MMF+TAM	174±2^{abe*}	4±1^{be*}	1±1^{b*}	0.4±0.3^{b*}	0.4±0.1^{b}	5±1^{ab}	14±3^{a}	12±3

PUB203

Unilateral Ureteral Obstruction Induces an Inflammatory Renal Phenotype Along with Sequential Induction of NGAL in Plasma and Peripheral Blood Mononuclear Cells Cristián A. Amador,[2] Carolina A. Lobos,[2] Mauricio A. Lozano,[2] Stefanny M. Figueroa,[2,1] Alexis A. Gonzalez.[1] *[1]Pontificia Universidad Católica de Valparaíso, Valparaíso, Chile; [2]Universidad Autónoma de Chile, Santiago, Chile. Group/ Team: Laboratory of Renal Physiopathology*.

Background: Chronic Kidney Disease (CKD) is a worldwide health problem with poor accurate diagnostic tools, and closely linked to other major diseases. Renal inflammation has been proposed as a relevant mechanism for the CKD development, occurring at early stages of injured kidneys. Studies in patients and experimental animals have shown that the Neutrophil Gelatinase Lipocalin-Associated (NGAL) is increased in the kidney, plasma or urine during CKD progression. Whether NGAL is increased in immune cells during early stages of CKD remains unknown. We performed the unilateral ureteral obstruction (UUO), as a high throughput *in vivo* model of CKD, in order to analyze the NGAL abundance in Peripheral Blood Mononuclear Cells (PBMC) during early inflammatory stage.

Methods: Male C57BL/6 were subjected to a complete UUO (in left kidney) or Sham surgery, and sacrificed after 3 and 7 days (n=8 per group).

Results: We observed tubular dilation in obstructed kidneys sections at day 3 and 7 ($p<0.05$), without changes in plasma creatinine or plasma urea. The left kidney of UUO mice showed augmented mRNA levels of IL-1b, TGF-b1, MCP-1 and CCL5, an inflammatory chemokine, at day 3 and 7. Additionally, we observed an increase in CD68 and IL-12b mRNA levels, as markers of activated macrophages in the left kidney of UUO mice. All these changes were accompanied by the increase of NGAL mRNA abundance in left kidney from 3 to 4-fold, at 3 and 7-days respectively (*vs.* Sham, $p<0.01$), which correlated with protein expression of plasma NGAL in UUO mice (24.1 µg/L in Sham *vs.* 103.8 µg/L and 134.5 µg/L in UUO, at 3 and 7 days respectively). Finally, we observed an induction of NGAL in PBMC after 7-days of UUO, without changes in other pro-inflammatory cytokines/chemokines.

Conclusions: The inflammatory renal phenotype caused by UUO implicates the sequential up-regulation of NGAL; first in kidney and plasma, and later in PBMC. This sequential induction of NGAL suggests a role in inflammatory cells during the early stages of CKD (Supported by FONDECYT 11150542 and Research Project PUCV 039.407/2017).

Funding: Government Support - Non-U.S.

PUB204

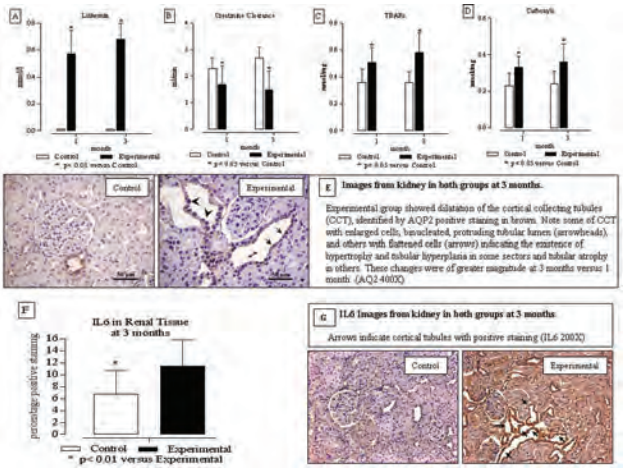
Persistent Oxidative Stress Associated with Lithium-Induced Renal Damage Jorge E. Toblli,[1] Juan M. Acosta,[2] Marisa G. Repetto,[2] Diego J. Martino,[3] Georgina P. Ossani.[1] *[1]Laboratory of Experimental Medicine Hospital Aleman, Buenos Aires, Argentina; [2]University of Buenos Aires, Buenos Aires, Argentina; [3]Institute of Cognitive and Translational Neuroscience, Buenos Aires, Argentina*.

Background: Lithium (Li) is still considered as first-line drug for therapy of bipolar disorder which requires long-term treatment. Interest in the risk of CKD and Li-induced renal failure is renewed due to some findings suggesting that both complications would be more frequent than previously estimated. This study evaluated the effect of oxidative stress on inflammatory response associated with the development of renal damage in rats treated with Li throughout the time.

Methods: Wistar male rats were fed standard diet (Control) or a containing 60 mmol lithium/kg diet (Experimental) ad libitum. This dose resulted in plasma levels of lithium equivalent to therapeutic levels in humans. Rats of each group were sacrificed after 1 or 3 months of treatment. Creatinine clearance (CrCl), lithemia, proteinuria and fractional excretion of sodium (FE_{Na}) were measured. Kidney samples were processed for: 1-oxidative stress (TBARS and carbonyls) evaluation; 2-histology (PAS and H&E); 3- immunohistochemistry: Aquaporin-2 (AQP2) in order to identify cortical collecting tubules and Interleukin-6 (IL6) as inflammatory marker protein.

Results: There were no differences in FE_{Na} and in urine protein excretion between control and experimental group at one and three months. Lithemia reached therapeutic values in the experimental group at 1 and 3 months (Fig 1A). CrCl was markedly reduced in experimental group (Fig1B). A significant increase in TBARs and carbonyls was observed in experimental group at 1 and 3 months, this indicating oxidation of lipids and proteins respectively Fig 1 C and D). Characteristics of the renal damage are shown in Fig 1 panels E, F and G.

Conclusions: Exposure to Li from 1 to 3 months to normal rats induced persistent oxidative stress expressed by lipoperoxidation/protein oxidation resulting in an increase in the inflammatory response with patent tubular damage and reduction in renal function.



PUB205

Renoprotective Effect of DPP-4 Inhibitor in Aging Mice Myung ah Ha, Tae Hyun Ban, Byung ha Chung, Bumsoon Choi, Cheol Whee Park, Chul Woo Yang, Yong-Soo Kim. *The Catholic University of Korea College of Medicine, Seoul, Republic of Korea*.

Background: Dipeptidyl peptidase 4(DPP-4) inhibitor has been increasing evidence of diverse protective effects besides lowering glucose level, including renoprotective effect. However, the pathogenesis of the protective effects have not been clarified yet. We investigated the renoprotective effects of DPP-4 inhibitor via the RAS system in the aging mice model.

Methods: 18 month-old C57BL/6 mice were divided into two groups according to DPP-4 inhibitor administration : LIN (N=8) and CONT (N=8), followed for 24 weeks. The LIN group was administered with linagliptin 5mg/kg per oral daily. Renal function, albuminuria, activities and expressions of DPP-4 and glucagon like peptide-1 in renal tissue, neuropeptide Y and substance P in serum and renal tissue, histologic changes and expressions of angiotensin-converting enzyme (ACE), angiotensin-converting enzyme 2 (ACE2), angiotensin II (Ang II), angiotensin II type 1 receptor (AT1R), angiotensin II type 2 receptor (AT2R), prorenin receptor (PRR), Mas receptor (MasR), endothelial nitric oxide synthase (eNOS), NADPH oxidase 2 and oxidase 4 (Nox2 and Nox4), transforming growth factor-β (TGF-β), collagen IV, fibronectin, and superoxide dismutase 1 and dismutase 2 (SOD1 and SOD2) in renal tissue were analyzed. In renal histology, area of mesangial and tubulointerstitial fibrosis, collagen IV positive area and TGF- β positive area were measured.

Results: Renal function and albuminuria were not different between the two groups. In the LIN group, DPP-4 activities in renal tissue were decreased and serum substance P concentrations were increased. In renal tissue, expressions of ACE, PRR and AT1R were decreased in the LIN group compared to the CON group ($p<0.05$ for both), but ACE2, AT2R and MasR were not different. Nox2 and Nox4, TGF-β, fibronectin and collagen IV were significantly decreased in the LIN group compared to the CON group ($p<0.05$ for both), whereas expressions of phosphorylated $serine^{1177}$-eNOS and SOD1 were significantly increased ($p<0.0001$ and $p<0.05$). Area of mesangial and tubulointerstitial fibrosis, collagen IV positive area and TGF-β positive area were significantly decreased in the LIN group compared to the CON group ($p<0.001$, $p<0.0001$, $p<0.05$ and $p<0.0001$, respectively).

Conclusions: DPP-4 inhibitor may provides renoprotective effects against the aging process of the kidney via reduced PRR-ACE-AT1R axis.

PUB206

Role of Organochlorine Pesticides in Etiopathogenesis of CKD of Unknown Etiology (CKDu) – In-Vivo and In-Vitro Studies Om P. Kalra,[1,5] Rishila Ghosh,[6] Manushi Siddarth,[2] Pawan K. Kare,[3] Basu D. Banerjee,[4] Ashok K. Tripathi.[7] *[1]Nephrology, Pt. B.D. Sharma University of Health Sciences, Rohtak, India; [2]University College of Medical Science (University of Delhi) and GTB hospital, Delhi, India; [3]University College of Medical Sciences, Delhi, India; [4]University College of Medical Sciences and GTB Hospital, Delhi, India; [5]Medicine, University College of Medical Sciences, Delhi, India; [6]Biochemistry, University College of Medical Sciences, Delhi, India; [7]Biochemistry, University College of Medical Sciences, Delhi, India.*

Background: CKDu has emerged as a significant cause of morbidity and mortality and is the second commonest causes of CKD in India. Organochlorine pesticides (OCPs) are nephrotoxic agrochemicals that resist degradation and have been implicated in the etiopathogenesis of various disorders, such as diabetes mellitus, infertility, etc. The present study was designed to investigate the role of OCPs in the etiopathogenesis of CKDu and the possible underlying molecular mechanisms.

Methods: Three groups of subjects were recruited. Group 1: Healthy subjects (n= 60), Group 2: Patients with CKDu (n= 60) and Group 3: Patients with CKD of known etiology (CKDk) (n= 60). Blood OCPs levels of all three study groups were analyzed by

gas chromatography. Various OCPs included: α-HCH, β-HCH, γ-HCH, aldrin, dieldrin, α-endosulfan, β-endosulfan, p,p′-DDT and p,p′-DDE. eGFR was calculated using MDRD method. Effect of OCPs on renal cells was assessed by in-vitro studies using human renal proximal tubular epithelial cells (HK-2). The cultured cell line was treated with α-HCH, β-endosulfan and p,p′-DDE.HK-2 cells were tested for ROS generation and mRNA expression of NADPH oxidase, TGF-β1, α-SMA and E-cadherin gene.

Results: All 9 pesticides were detected in the blood samples of all study subjects; however, α-HCH, aldrin, β-endosulfan, p,p′-DDE were found to be significantly higher in CKDu group as compared to healthy controls. β-endosulfan and p,p′-DDE were found in significantly higher levels in CKDu patients as compared to CKDk patients. Increased levels of these pesticides showed significant positive correlation with urinary albumin excretion and inverse correlation with eGFR. Further, significant increase in ROS generation and increased expression of NADPH, NF- κB and TGF-β1 was observed in HK2 cell lines on exposure to OCPs. In addition to that, decreased expression of E-cadherin and increased expression of α-SMA genes were observed in HK-2 cell lines indicating significant EMT changes on exposure to the OCPs suggestive of fibrotic changes.

Conclusions: Levels of certain organochlorine pesticides, such as α-HCH, aldrin, β-endosulfan, p,p′-DDE were elevated in CKDu. These agents may result in nephrotoxicity through various mechanisms, such as activation of oxidant stress, RAAS, inflammatory and pro-fibrotic pathway.

PUB207

Repeated Dosing of Cisplatin in Mice Leads to Long-Term Loss of Kidney Function and Fibrosis Indicative of CKD Cierra Sharp,[2] Mark A. Doll,[2] Tess Dupre,[2] Levi J. Beverly,[1,3] Leah J. Siskind.[2,3] *[1]University Of Louisville, Louisville, KY; [2]University of Louisville, Louisville, KY; [3]James Graham Brown Cancer Center, Louisville, KY.*

Background: Cisplatin (CDDP) is a potent therapy used for many solid cancers. Its dose-limiting toxicity is nephrotoxicity, leading to acute kidney injury (AKI) in 30% of patients. AKI results in rapid loss of kidney function and an increased mortality rate. Longitudinal studies have indicated that AKI patients are more likely to develop chronic kidney disease (CKD), and other studies have indicated that AKI can progress to CKD. CKD is defined by development of renal fibrosis, renal function loss, and an increased mortality rate. There are no current therapies for CDDP AKI/CKD. This is due to the fact that the mouse model used to study CDDP AKI may not recapitulate the dosing regimen humans receive. Mice are administered one high dose of CDDP that leads to death 3-4 days after treatment. In contrast, patients receive low doses of CDDP over an extended period of time to curtail nephrotoxicity.

Methods: To address the limitation of this mouse model, we developed a repeated dosing regimen of CDDP (mice treated with 7 mg/kg CDDP 1x/wk for 4 wks and sacrificed at Day 24), which induces fibrosis indicative of CKD. However, CKD is a progressive disease that develops over many years in humans. Thus, we wanted to determine long-term renal outcomes of mice treated with our repeated dosing regimen of CDDP. Briefly, 8 wk old FVB mice were treated with our CDDP repeated dosing regimen.

Results: We found that mice were able to survive at least 6 months post-treatment, allowing this model to be used to look at long-term kidney outcomes. Kidney injury NGAL levels returned to baseline 6 months post-treatment in CDDP treated mice, but these mice still had elevated BUN levels compared to vehicle treated mice (1.8-fold). *Mcp-1, Pai-1,* and *Cdkn2a* mRNA levels remained elevated indicative of chronic inflammation and cell cycle arrest (6.7, 2.4, and 6.8-fold, respectively). Furthermore, fibrosis was still present as indicated by Sirius red (SR) stain and α-SMA IHC (35% SR+, 0.5% αSMA+).

Conclusions: These data suggest that while initial injury is resolved 6 months post CDDP treatment, there are long-term effects on renal function and inflammation marked by a trend towards worsened fibrosis, suggesting this model can be used as a *bona fide* model of CKD.

Funding: NIDDK Support

PUB208

The Novel Kinase Inhibitor ANG3070 Improves Renal Injury in the DOCA/Salt Model of CKD Bert Oehlen,[2] Bin Duan,[1] Ping Zhou,[1] Latha Paka,[1] Prakash Narayan,[1] Itzhak D. Goldberg.[2] *[1]Angion Biomedica Corp, Uniondale, NY; [2]Angion Biomedica Corp., Uniondale, NY.*

Background: Aberrant receptor tyrosine kinase signaling has been implicated in development and progression of Chronic Kidney Disease (CKD). We investigated the effects of a novel small molecule receptor tyrosine kinase inhibitor, ANG3070, in *in vitro* and *in vivo* models of CKD.

Methods: We tested the effect of ANG3070 *in vitro* in TGFbeta-stimulated collagen production in renal fibroblasts (NRK49F cells) and on multiple endpoints in a co-culture system of human renal epithelial cells and fibroblasts. For *in vivo* studies, male Sprague-Dawley rats were uni-nephrectomized and received weekly subcutaneous injections of deoxy-corticosterone acetate (DOCA) while drinking water with 1% NaCl. After two weeks, animals were randomized to receive ANG3070 (50 mg/kg, po, bid) or vehicle. At week 6, a comprehensive panel of renal functional and histological endpoints was evaluated to assess the effect of compound treatment.

Results: ANG3070 inhibits TGFbeta-stimulated collagen production in renal fibroblasts and in a co-culture system mimicking the renal milieu, ANG3070 reduced markers of fibroblast activation (e.g. α-SMA and N-cadherin) and of fibrosis (e.g. Collagen III). Uni-nephrectomized rats treated with DOCA and salt after two weeks showed marked kidney histological damage and renal dysfunction, as shown by overt proteinuria and elevated urine levels of kidney injury marker 1 (KIM1). Compared to vehicle treated animals, treatment with ANG3070 for four weeks mitigated kidney damage and reduced renal collagen and α-SMA expression. Proteinuria, Albuminuria and urine KIM1 levels were also reduced as a result of ANG3070 treatment.

Conclusions: In preclinical experiments, the novel receptor tyrosine kinase inhibitor ANG3070 shows promise as a possible treatment for CKD.

Funding: NIDDK Support, Other U.S. Government Support

PUB209

Podocytes and Proximal Tubular Epithelial Cells Participate in ST2 Related Renal Fibrosis Yong Chul Kim,[3] Seung Hee Yang,[1] Ran-hui Cha,[2] Mi-yeon Yu,[6] Hajeong Lee,[5] Jung Pyo Lee,[4] Dong Ki Kim,[6] Suhnggwon Kim,[1] Yon Su Kim.[5,1] *[1]Kidney Research Institute, Seoul National University, Seoul, Republic of Korea; [2]National Medical Center, Seoul, Republic of Korea; [3]SNUH, Seoul, Republic of Korea; [4]Seoul National University Boramae Medical Center, Seoul, Republic of Korea; [5]Seoul National University College of Medicine, Seoul, Republic of Korea; [6]Seoul National University Hospital, Seoul, Republic of Korea.*

Background: Suppression of tumorigenicity 2 (ST2) which is the receptor of IL-33 is involved in renal inflammation and it is also correlated with disease severity in chronic kidney disease (CKD). Here, we report the ameliorating effect of the ST2 blockade as well as the role of ST2 in the progression renal fibrosis.

Methods: Serum and urine levels of sST2 were measured in 296 CKD patients. And ST2 mRNA levels were quantified in blood and urine cells. Immunohistochemistry (IHC) stain of ST2 was performed in kidney biopsy samples of CKD patients. Further, urine cells were co-stained with podocalyxin/aquaporin-1 and ST2 to characterize the cell type. And fibrosis induced by TGF-β in primary cultured podocytes and proximal tubular epithelial cells (PTECs) were evaluated with fibronectin and ST2 mRNA expressions. Anti-ST2 monoclonal antibody (mAb) was treated to evaluate the neutralizing effect of ST2 on renal fibrosis. Finally, ST2 and fibronectin mRNA expression was measured in CKD mouse model (UUO; Unilateral Ureteral Obstruction).

Results: Serum ($P = 0.002$) and urine ($P < 0.001$) sST2 levels increased as renal function deteriorated. Urine ST2 levels adjusted by urine creatinine showed the same pattern ($P < 0.001$). Serum ($P = 0.023$) and urine ($P = 0.03$) ST2 expressions were elevated in CKD stage 5 patients compared with other stages. ST2 IHC stain in CKD stage 5 showed 3-fold increase than CKD stage 1. A large portion of urine cells were ST2-rich podocytes/PTECs and we observed the proportion of these cells increased as renal function decreased in flow-cytometry. When the patients were subdivided by 0.5 g/g proteinuria, patients with more proteinuria had a higher concentration of urine ST2 ($P = 0.02$). After fibrosis induction in primary cultured podocytes/PTECs, mRNA and protein expressions of fibronectin, ST2 showed positive correlation with the fibrosis severity. And anti-ST2 neutralized the fibrosis. In UUO mouse model ST2 and fibronectin expression was increased over time ($P < 0.01$).

Conclusions: Elevated serum and urine ST2 levels are associated with the progression of CKD and podocytes/PTECs involved in this process. ST2-mediated signaling may have a considerable role in the progression renal dysfunction. And ST2 blockade is a potential therapeutic target for renal preservation.

Funding: Government Support - Non-U.S.

PUB210

Abstract Withdrawn

PUB211

High Intensity Interval Training (HIIT) Attenuates Proteinuria in Nephrectomy 5/6 Rats (Nx5/6) Samuel T. Filho,[4] Luciana Jorge,[1] Natalia Reinecke,[2] Alexandre Saud,[2] Rafael Luiz,[1] Wesley Silva,[4] Rodolfo R. Rampaso,[1] Nestor Schor.[3] *[1]None, São Paulo, Brazil; [2]UNIFESP, Sao Paulo, Brazil; [3]Universidade Federal de Sao Paulo/Escola Paulista de Medicina, Sao Paulo, Brazil; [4]Universidade Federal de São Paulo, São Paulo, Brazil.*

Background: HIIT is characterized by intense and intermittent exercises, interspersed with periods of low intensity and / or rest. Recent studies suggest that HIIT stimulates physiological adaptations equal or better comparable to continuous training of moderate intensity. However, the effect of HIIT on renal function and in CKD is not well known. The aim of this study was to evaluate the effects of HIIT on renal function and physical capacity in Nx 5/6 rats.

Methods: Adult Wistar rats, divided into two groups (n=6/group): Nx 5/6 + exercise (NE) and Nx 5/6 sedentary (NS). Physical training protocol started after 7 days of surgical procedures, 3 days/week, 10 sprints at 90% of maximum capacity, 8 weeks total. To evaluate phsycal capacity, all animals underwent a maximal physical capacity test before and after training. The mean arterial pressure (MAP), proteinuria (uProt) as urea nitrogen in the blood (BUN) was evaluated.

Results: HIIT was not able to modify the MAP, but attenuated the increase in the proteinuria rate (38.2±4.4 vs.63.5 ± 1.9mg / 24h, p <0.001). Mean BUN was higher in NS in comparison to NE group. (101.2 ± 10.4 vs 83.1 ± 2.0mg / dl, p <0.01). HIIT also improved physical capacity as seen in maximal physical capacity test (27±2 vs 38±1 m/min).

Conclusions: These results suggests that 8 weeks of HIIT can minimize the impact of CKD, with lower increase of BUN and proteinuria. Thus, HIIT could have a protective effect and may be a time-efficient strategy for non-pharmacological treatment to minimize the complications of CKD.

Funding: Government Support - Non-U.S.

	NX	NE
Weight (g)	402±10	428±9
Serum Creatinine (mg/dL)	1.45±0.1	1.86±0.2
BUN (mg/dL)	101±6	83±9
uProt (mg/24hrs)	63±2	38±8*
MAP (mmHg)	231±8	215±5
Maximal physical capacity test (m/min)	27±2	38±1*

* p < 0.05 vs. NX

PUB212

Immunoglobulin G4 Related Disease with Polycythemia Vinaya R. Soundararajan,[3] Yameen Rashid,[2] Ramesh Soundararajan.[1] *[1]Medicine, Midwestern University College of Medicine, Downers Grove, IL; [2]St James Hospital, Chicago Heights, IL; [3]University of Illinois College of Medicine, Willowbrook, IL.*

Background: (Ig) G4-related disease is a systemic fibro-inflammatory condition characterized by a lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells with elevated IgG4 Levels. The disease presents as involving one organ or may present as a systemic disease affecting multiple organs. We report a case of IgG4-related disease presenting with associated polycythemia. This combination has not been reported in the literature to the best of our knowledge.

Methods: A 41-year-old African-American male construction worker presented with a creatinine of 4.0 mg/dL and was found to have mild microscopic hematuria. His urinalysis showed 5-8 RBCs/HPF and proteinuria. His creatinine was normal 4 years ago. He had a history of hypertension and NSAID usage. Patient also recently was diagnosed with polycythemia, and his hemoglobin was 20 g/dL. Ultrasound of his kidneys suggested bilateral large lobular kidneys. He was otherwise asymptomatic. Workup showed a negative JAK 2 mutation and a urine protein of 600 mg per gram of creatinine. His vasculitis and hepatitis workups were negative, except for a low C3 and C4. The patient also had some enlarged inguinal nodes, which were biopsied but not diagnostic.

Results:

Conclusions: Patient had phlebotomy initially to decrease his hemoglobin. He underwent a kidney biopsy which showed lymphoplasmacytic infiltration of the renal interstitum, with an increased number of IgG4-positive plasma cells. Patient's creatinine decreased to 3.4 mg/dL after stopping his NSAIDs and phlebotomy. After the biopsy, patient was started on 40 mg prednisone a day. The patient's original IgG4 level was 1140 mg/dL. After 4 weeks of prednisone, the level decreased to 260 mg/dL (normal is less than 120 mg/dL). His creatinine also came down to 2.7 and his proteinuria and hematuria resolved. Prednisone is currently being tapered. His Hb decreased to 13 gm/dl IgG 4-related disease is a systemic plasma cell infiltrative disease which can involve multiple organs, including pancreas, lymph nodes and kidneys. It predominantly causes tubular interstitial infiltration in the kidney. Patient is responding well to prednisone. Other treatments including rituximab have been used to treat this disease.

PUB213

Chronic Renal Fibrosis Qualified by Synchrotron Radiation-Fourier Transform Infrared Spectroscopy Jieli Huang,[2] Chen Yu.[1,3] *[1]SHANGHAI TONGJI HOSPITAL, SHANGHAI, China; [2]TONGJI HOSPITAL, SHANGHAI, China; [3]TONGJI UNIVERSITY SCHOOL OF MEDICINE, SHANGHAI, China.*

Background: Renal fibrosis is the main pathology of end stage renal disease. It includes glomerulosclerosis and tubule-interstitial fibrosis, which with the major pathological manifestations of extracellular matrix abnormal increasing and excessive deposition. Fourier transform infrared microspectroscopy and imaging are emerging excellent methodologies for biological analysis and enable nondestructive, label-free analysis of biochemical information towards the assessment of tissue functionality. We will qualify the chronic renal fibrosis by Synchrotron radiation-Fourier transform infrared spectroscopy in this study.

Methods: We used a model of unilateral ureteral obstruction and divided into two groups. Sham and UUO groups. Chronic renal fibrosis was qualified by histological examination and SR-FTIR.

Results: Histologic examination showed there were interstitial fibrosis in UUO rats, with mild or severe glomerular injury in HE staining (Fig1A) and Masson staining (Fig1B). It was found that the bands near 1000-1200 cm^{-1} are main significant differences between the sham and UUO groups. There are three feature bands near 1133.31, 1058.24, 995.2 cm^{-1} in UUO group which reflect the PO2 phosphodiesters stretch from phosphorylated molecules, glycogen and glycoprotein, and reveals that glycoprotein is increased in UUO group (Fig2A). The PCA scores plots showed a clear cluster separation between the sham and the UUO groups(Fig2B), indicating the chemical changes could be assessed by SR-FTIR.

Conclusions: The molecular structural changes of renal fibrosis had been identified and qualifying by the SR-FTIR spectra. These results showed that SR-FTIR would be a useful technique with high sensitivity to tell from the tissue fibrosis.

Funding: Government Support - Non-U.S.

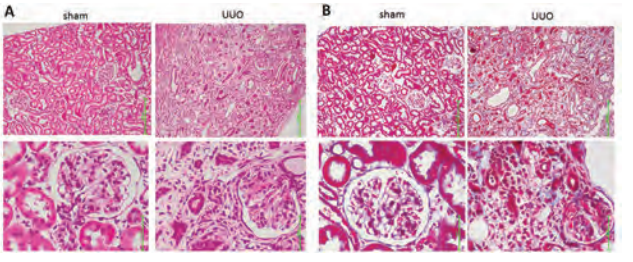


Fig 1. Histology of the kidneys in the sham and the UUO groups (A : HE, B:Masson)

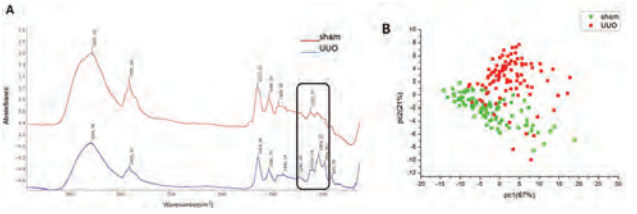


Fig2. SR-FTIR Spectro analysis of the sham and the UUO groups.(A:single spectra analysis, B: PCA analysis)

PUB214

Sulfatide-Selective NKT Cells Mediate M2 to M1 Polarization of Macrophage and Macrophage to Myofibroblast Transition Cell Resulting in Amelioration of Kidney Fibrosis Sunhwa Lee,[6] Hajeong Lee,[5] Jae Wook Lee,[2] Jung Pyo Lee,[4] Ran-hui Cha,[3] Dong Ki Kim,[6] Yon Su Kim,[5] Seung Hee Yang.[1] *[1]Kidney Research Institute, Seoul National University, Seoul, Republic of Korea; [2]National Cancer Center, Seoul, Republic of Korea; [3]National Medical Center, Seoul, Republic of Korea; [4]Seoul National University Boramae Medical Center, Seoul, Republic of Korea; [5]Seoul National University College of Medicine, Seoul, Republic of Korea; [6]Seoul National University Hospital, Jongno-gu, SEOUL, Republic of Korea.*

Background: Macrophage subtype polarization has been suggested as a key player related to kidney fibrosis. Moreover, myofibroblast, the principal cells that produce extracellular matrix in fibrosis, can be originated from macrophage by means of macrophage-myofibroblast transition (MMT). We investigated phenotypic skewing of these cells by sulfatide-selective type II NKT cells and its impact on kidney fibrosis.

Methods: Sulfatide-selective type II NKT cells from B6.Jα281$^{-/-}$ mice were isolated, and co-cultured with primary cultured proximal epithelial cells. In addition, sulfatide [20 or 40μg/300μl IV] was injected before unilateral ureteral obstruction (UUO) operation. Subsequently, total cellular RNA was extracted from minced kidney, lymph nodes, and fresh blood to analyze changes in transcript expression levels using quantitative real-time PCR and microarray. Furthermore, adoptive transfer of type II NKT cells was performed.

Meanwhile, the proportion of infiltrated $\alpha SMA^{+}/CD206^{+}$ double positive cells in sulfatide treated UUO kidney and CKD 3 and 5 patients were investigated.

Results: Severity of renal fibrosis and the proportion of $\alpha SMA^{+}/CD206^{+}$ double positive cells was attenuated after sulfatide injection. At the same time, sulfatide reduced senescence, shown by decreased levels of SA-β-Gal. Sulfatide stimulated polarization from M2 to M1 accompanying by increased iNOS, STAT1, SOCS3 and decreased arginase, STAT3. Pro-fibrotic transcripts, fibronectin and TGFβ, was decreased by adding sulfatide-selective NKT. The expression level of NGAL and IL-1β, a marker of kidney damage and inflammation, was attenuated. Similarly, adoptive transfer of sulfatide-selective type II NKT cells attenuated expression of αSMA and fibronectin. In stage 5 CKD patients, the density of $\alpha SMA^{+}/CD206^{+}$ double positive cells were 3.3 times higher than stage 3.

Conclusions: Sulfatide-selective NKT cell mediates macrophage polarization skewing from M2 to M1 macrophage via switching on STAT1 resulting in ameliorating renal fibrosis. Infiltration of myofibroblast cells co-expressing M2 marker are also decreased by sulfatide accompanying by reduced fibrosis. Inducing the polarization of macrophages by modulation of NKT cells can be suggested as therapeutic target for curbing fibrosis.

PUB215

A Case of Immunoglobulin G4-Related Disease in Association with Polymyalgia Rheumatica Misaki Yoshida, Kiyoaki Ito, Kazunori Yamada, Eiko Shimizu, Nobuhiro Suzuki, Takahiro Matsunaga, Takeshi Zoshima, Satoshi Hara, Ichiro Mizushima, Hiroshi Fujii, Mitsuhiro Kawano. *Kanazawa University Hospital, Ishikawa, Japan.*

Background: Immunoglobulin G4-related disease (IgG4-RD) presents with arthralgias in 10% of patients. Several case reports have described IgG4-RD in association with rheumatoid arthritis, but there has been no report of IgG4-RD in association with polymyalgia rheumatica (PMR). We report a case of IgG4-RD in a patient with PMR.

Methods: A 68-year-old man with a history of lung cancer was admitted with bilateral shoulder, wrist, and pelvic girdle pain for two months. He was found to have elevated C-reactive protein (CRP), hypergammaglobulinemia, hypocomplementemia, and a positive antinuclear antibody (ANA) test during a clinic visit one month prior to admission. The CRP level on admission was 3.7 mg/dl. He not only met the 2012 ACR/EULAR Provisional Classification Criteria for Polymyalgia Rheumatica, but also had unexplained hypocomplementemia (C3, 64 mg/dl; C4, 4 mg/dl; and CH50, 11 U/ml), hypergammaglobulinemia, and a high ANA titer (x20480). Additional blood tests showed an elevated serum IgG4 level (543.0 mg/dl) and IgG4/IgG ratio (23.4%). Computed tomography (CT) revealed swelling of the bilateral submandibular glands and enhanced CT showed multiple low-density lesions in the kidneys. Renal biopsy showed tubulointerstitial nephritis with marked infiltration of IgG4-positive plasma cells (72/high-power field). There was a clear border between affected and unaffected areas in the kidney interstitial lesions. IgG4-RD was diagnosed using comprehensive diagnostic criteria. Prednisolone 30 mg/day was initiated and the PMR symptoms rapidly disappeared.

Results:

Conclusions: This is the first reported case of IgG4-RD in association with PMR. The immunological features of PMR and IgG4-RD are different, but the reason for concurrent presentation in this patient remains unclear. One possibility is that these two diseases are related to malignancy in some cases. Further studies are needed to clarify the pathogenesis of this condition.

PUB216

Difference of Two AKI to CKD Transition Models in Mice Kengo Mayumi,[3] Daisuke Nakano,[1] Tetsushi Yamashita,[3] Yoshifumi Hamasaki,[4] Eisei Noiri,[3] Akira Nishiyama,[2] Masaomi Nangaku,[5] Kent Doi.[4] *[1]Kagawa University, Kagawa, Japan; [2]Kagawa University Medical School, Kita-Gun, Japan; [3]The University of Tokyo, Tokyo, Japan; [4]University of Tokyo, Tokyo, Japan; [5]the University of Tokyo School of Medicine, Tokyo, Japan.*

Background: Recent clinical studies have demonstrated AKI is a major risk factor for CKD. Experimental studies using animal models have been conducted so far to clarify the mechanisms underlying progression from AKI to CKD, but effects of differences between animal models on experimental results has not been sufficiently examined.

Methods: We developed two mouse AKI-to-CKD models by combining renal ischemia reperfusion and nephrectomy; unilateral ischemia-reperfusion injury with contralateral nephrectomy (UIR+UNx) and without nephrectomy (UIR), and evaluated their differences of post-ischemia injury and erythropoietin producing ability.

Results: Renal interstitial fibrosis and erythropoietin producing dysfunction in the UIR+UNx group was significantly milder than that of the UIR group. Intravital multiphoton microscopy revealed contralateral nephrectomy significantly increased blood flow of peritubular capillary (PTC) in post-ischemic kidney. Infrarenal aortic constriction (IRAC) also significantly increased PTC blood flow and reduced G2/M arrest cells and TGF-β1 expression in the ischemic kidney at subacute phase, and reduced interstitial fibrosis in chronic phase. After induction of anemia by phenylhydrazine administration, renal EPO mRNA expression in the post-ischemic kidney is higher in UIR+IRAC group than in UIR group.

Conclusions: Improvement of blood flow in PTCs in UIR+Nx group might have a significant impact on renal interstitial fibrosis and erythropoietin production. These differences suggest that careful interpretation is necessary for animal experiments that evaluate AKI to CKD progression.

PUB217

Abstract Withdrawn

PUB218

Investigating a Ciliopathy – CEP164 Expression throughout Human Embryonic Development Laura A. Devlin,[1] Simon Ramsbottom,[1] Lynne M. Overman,[1,2] Susan Lindsay,[1,2] John Sayer.[1] *[1]Institute of Genetic Medicine, Newcastle University, Newcastle upon tyne, United Kingdom; [2]HDBR, Newcastle University, Newcastle Upon Tyne, United Kingdom.*

Background: Nephronophthisis-related ciliopathies (NPHP-RC) are a collection of disorders that share a common NPHP phenotype, caused by defects in the biogenesis or functioning of primary cilia. NPHP-RC are major contributors to juvenile renal failure and are often associated with neurological, retinal and hepatic abnormalities. Recessive mutations in CEP164 (NPHP15), a distal appendage centrosomal protein, have been identified in some families with NPHP-RC. These patients have a heterogeneous, multi-system phenotype, presenting with features such as retinal degeneration, Leber congenital amaurosis, developmental delay and intellectual disability.

Methods: We utilised the MRC Wellcome Trust Human Development Biology Resource (HDBR) to obtain human embryonic and fetal tissue. Immunohistochemical staining of CEP164 was completed on paraffin embedded tissue sections, from Carnegie stage (CS) 23 (approximately 8 post conception weeks (pcw)) to 19 pcw. Specifically, CEP164 expression in the kidney, eye and brain (hindbrain) were examined.

Results: In human embryonic and fetal tissues, CEP164 had a widespread expression pattern throughout development, with expression in many organs including the kidney, liver, lung and stomach. In all kidney sections analysed, CEP164 was expressed in developing renal tubules; this was maintained throughout development. CEP164 expression was also seen in retinal tissue, during all developmental stages, in defined cell layers. There was strong CEP164 expression in ependymal cells of the choroid plexus as well as cells lining the brain ventricles.

Conclusions: CEP164 has widespread, but defined expression throughout human embryonic development. There is strong expression in the kidney, retina and defined regions of the brain. This supports the multi-system pathology present in patients with Cep164 NPHP-RC.

PUB219

Three-Dimensional Reconstruction of AQP-1 and UT-A2 Expression in a 7-Day-Old Mouse Kidney Ning-Yu Liu,[1] Ling Gu,[1] Shi-Jie Chang,[2] Jie Zhang,[1] Jesper S. Thomsen,[3] Arne A. Andreasen,[3] Erik I. Christensen,[3] Xiao-Yue Zhai.[1] *[1]Department of Histology and Embryology, China Medical University, Shenyang, China; [2]Department of Biomedical Engineering, China Medical University, Shen Yang, China; [3]Department of Biomedicine – Anatomy, Aarhus University, Aarhus C, Denmark.*

Background: Mouse kidneys undergo a couple of weeks of maturation of morphology and transportation mechanisms related to the urine concentration after nephrogenesis ceases at postnatal (P) day 3. The present study investigated the location of AQP-1 and UT-A2 based on three-dimensional reconstruction of nephrons. The aim was to analyze the formation of water and urea transport in Henle's loop in developing kidneys. The morphological basis for mechanism of medullary osmotic gradient formation is discussed.

Methods: Serial 2.5-µm-thick epoxy sections from a 7-day-old mouse kidney were prepared and stained with toluidine blue. Selected sections representing different levels of the kidney were re-embedded, and cut into consecutive 0.5-µm-thick epoxy sections, on which immunohistochemistry was performed for AQP-1 and UT-A2. The location of these membrane proteins was mapped along short and long looped nephrons (SLN, LLN) and descending vasa recta (DVR). The nephrons and blood vessels were identified in 3D by computer assisted tracing on aligned images of the toluidine blue stained sections using custom-made computer software.

Results: Firstly, AQP-1 was, like in the adult kidney, expressed densely along proximal tubules (PT), except the initial part several hundreds micrometers in length. Secondly, AQP-1 were expressed in the entire length of DVR running in vascular bundles (VB) and descending thin limbs (DTL) of LLN running in the interbundle region. Thirdly, the majority of DTL of SLN did not express AQP-1. These SLN DTLs were localized in close proximity to AQP-1 positive DVR in the VB. UT-A2 was expressed alone in the last third of DTL of SLN running also in VB.

Conclusions: The distribution of AQP-1 and UT-A2 in the 7-day-old kidney is mainly consistent with that in adult kidneys. This indicates that the urine concentrating function of the kidney is at least partly established at this time point. This is especially evident in the medulla, suggesting that the morphologic and molecular basis for the intrarenal countercurrent exchange has been set up in the medulla at P7.

Funding: Government Support - Non-U.S.

PUB220

Prediction of Ambulatory Hypertension Based on Clinic Blood Pressure Percentile: The SHIP AHOY Study Gilad Hamdani,[2] Elaine M. Urbina,[1] Marc Lande,[3] Kevin E. Meyers,[5] Joshua A. Samuels,[6] Mark Mitsnefes,[2] Joseph T. Flynn.[4] *[1]Cincinnati Children's Hospital, Cincinnati, OH; [2]Cincinnati Children's Hospital, Cincinnati, OH; [3]Rochester, NY; [4]Seattle Children's Hospital, Seattle, WA; [5]The Children Hospital of Philadelphia and University of Pennsylvania, Philadelphia, PA; [6]University of Texas, Houston, TX. Group/Team: SHIP AHOY Study.*

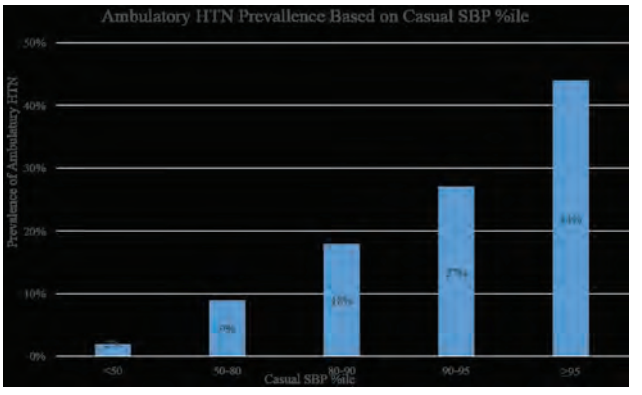
Background: Ambulatory blood pressure (ABP) provides a more precise measure of BP status than clinic BP but ABP adds additional cost to evaluation for HTN. Therefore, our objective was to determine the clinic BP percentile at which the likelihood of ambulatory HTN increases to optimize application of ABP in adolescents.

Methods: We evaluated clinic BP (mean of 6 measures with auscultatory technique) and ABP (Spacelabs OnTrak), anthropometrics, and labs in 132 adolescents (mean 15.8 ± 1.4 years, 66% white, 57% male). Clinic BP percentile and ABP status (normal vs HTN) were determined by age, sex and height-specific pediatric cut-points, and patients were divided into five SBP %ile groups: <50, 50-80, 80-90, 90-95, and ≥95. Association between clinic BP percentile group and ABP status was compared using X^2. Logistic regression and receiver operating characteristics (ROC) analysis were used to determine the clinic systolic BP %ile that best predicted ambulatory HTN.

Results: Eighteen patients (14%) had ambulatory HTN. Prevalence of ambulatory HTN increased according to SBP %ile group, from 2% in subjects with normal clinic BP to 44% in hypertensives ($p<0.0001$). ROC analysis showed that casual SBP %ile predicted ambulatory HTN with an area under the curve of 0.80. The 80th % ile for SBP resulted in the best balance between sensitivity (0.78) and specificity (0.69).

Conclusions: When evaluating adolescents referred to clinic for suspected hypertension, SBP %ile of ≥80 may be the optimal threshold to perform an ABPM.

Funding: Private Foundation Support



PUB221

Patterns of RAAS Blockade Use in Children with CKD Jason T. Lee,[2] Mark Mitsnefes,[1] Charles E. McCulloch,[2] Elaine Ku.[2] *[1]Cincinnati Children's Hospital, Cincinnati, OH; [2]University of California San Francisco, San Francisco, CA.*

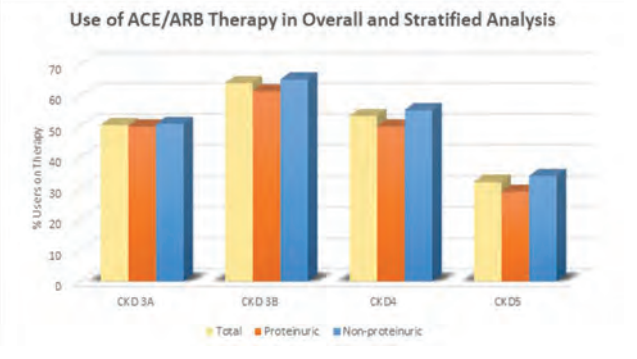
Background: There is limited data on patterns of anti-hypertensive use in children with CKD. RAAS (renin-angiotensin-aldosterone-system) blockade is known to retard progression to ESRD. Our objective was to understand patterns of RAAS blockade use during different stages of CKD.

Methods: We analyzed data from the Chronic Kidney Disease in Children (CKiD) Study, a national observational study of children with CKD. We used mixed models to determine person-specific trajectories of renal function decline using all available eGFR measurements as means of partitioning follow-up time into distinct CKD stages (3a-5). We then determined the prevalence of ACE inhibitor (ACEi)/ARB continuation, discontinuation, or initiation for each CKD stage separately in cross-sectional analysis. We also stratified our analysis by proteinuria level (urine protein creatinine (UPC) ratio of <2.5 and UPC >2.5), using the first available measurement at entry into each CKD stage.

Results: We included 572 CKiD participants, of whom 105 had available data in stage 3a, 175 in stage 3b, 208 in stage 4, and 84 in stage 5. Across CKD stages 3a-5, 52.4%, 65.1% 59.1% and 54.8% of children were treated with ACEi/ARBs. There was significant therapeutic inertia in CKD stage 3 [Figure], whereas in CKD stage 4, 10.5% of children started ACEi/ARBs and 5.7% stopped therapy. In CKD stage 5, 6.0% started ACEi/ARB and 21.4% of children stopped therapy. No differences in potassium level were noted in ACEi/ARB users versus non-users except in CKD stage 5 where hyperkalemia was more prevalent in users of ACEi/ARB (18.8 vs. 3.9%). Patterns of ACEi/ARB use did not differ in stratified analysis by proteinuria [Figure].

Conclusions: ACEi/ARBs appear underused in the pediatric population during early stages of CKD, especially in those with significant proteinuria. Nearly half of children not on ACEi/ARB therapy were proteinuric, and therapy was not initiated until later stages of CKD which may be suboptimal for delaying progression to ESRD.

Funding: Other NIH Support - NHLBI



Prevalence of ACEi/ARB use across CKD stages 3a-5 in those with (red) and without (blue) proteinuria.

PUB222

Pediatric ABPM Program: Utilizing the Electronic Medical Record for Reorganization and Improved Efficiency Monica Casillas,[1] Lieuko Nguyen,[2,1] Meghan M. Cantillon,[1] Jane Goggin,[1] Peter D. Yorgin.[2,1] *[1]Rady Children's Hospital San Diego, San Diego, CA; [2]University of California San Diego, San Diego, CA.*

Background: With increasing incidence of pediatric hypertension (HTN), early recognition and prompt diagnosis of HTN in children are critical. Ambulatory blood

pressure monitoring (ABPM) is utilized to diagnose white coat, masked, and sustained ambulatory HTN.

Methods: Hospital-wide ABPM orders at Rady Children's Hospital are completed by Nephrology department. During 2015, barriers to timely completion of ABPM included: machine malfunctions, mismatch of monitors to referrals, adequate staff time, families not returning machines in <7 days, and complicated hand calculation analysis as ABPM computer program utilized pre-set sleep times of 2200 - 0600 hour. Nephrologists took 20-45 minutes to analyze each ABPM. A new EPIC-based ABPM referral pathway was created. 11 SpaceLab Model 90227 machines were purchased in addition to our 4 models. Medical assistants, RNs, and physicians were re-trained to administer, upload, and analyze the reports. Friday afternoons are dedicated to ABPM appointments. Families sign contracts; we provide mail-in return Fed-Ex boxes. ABPM's were analyzed based on patient's actual sleep and wake times from patient activity logs. An assigned physician for the week analyzes all ABPMs completed. A new EPIC procedure note allowed for easy documentation.

Results: The number of ABPM studies completed per year increased from 280 in 2015 to 350 in 2016. The new pathway via EPIC shortened time from referral to report completion from 146 ± 112 days (March 2015) to 35 ± 14 days (March 2017), $p<0.001$. There was improved machine return rate with utilization of pre-paid Fed-Ex boxes and signed contracts. Physician's time required to analyze each ABPM was significantly decreased to 5-15 minutes.

Conclusions: New procedures for the ABPM program resulted in an improvement in timely diagnosis and workup of pediatric HTN. Improvements in program efficiency can improve patient outcomes, while reducing family and patient anxiety. We recommend working with EPIC/EMR programs to build an interface for scheduling and analyzing, which allows for decreased workload and time commitment. We hypothesize that further improvement in program efficiency can be achieved if we have more monitors, decrease the frequency of machine malfunction, and increase equipment return within 5 days.

PUB223

Impact Cases of Renin–Angiotensin Systems Gene Polymorphisms on Physiological and Pathophysiological Processes in Two Japanese Patients

Kohei Miyazaki,[1] Keisuke Sugimoto,[2] Tomoki Miyazawa,[4] Takuji Enya,[5] Hidehiko Yanagida,[3] Mitsuru Okada,[2] Tsukasa Takemura.[2]
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Background: Renin–angiotensin systems (RAS) play an important role in organ development and the maintenance of physiological functions. Defects in RAS-related genes products may exhibit CAKUT including renal tubule dysplasia (RTD). The majority of children with RTD at birth may present with significantly low blood pressure leading to perinatal death. In contrast, mutations and polymorphism spectrum of the RAS-related genes to clinical outcomes exist. We present two cases of *AGT*- gene related abnormality.

Methods: Case 1 is a 4-year-old boy. He was born at 37 weeks, with a birth weight of 2374 g. After birth, he was treated for hyperventilation and cyanosis without low blood pressure. Renal dysfunction, bilateral kidney atrophy and expansion of the left renal pelvis were observed. He also had delayed mental development, low stature, and low weight. CT showed a thin skull and partial defects of the occipital region. Blood test showed evidence of increased active renin concentration (72 pg/ml [normal: 2.5–21.4 pg/ml]), although the plasma renin activity was normal. Renal biopsy showed immature glomeruli, cystic enlargement of the renal tubules. Gene analysis revealed a heterozygous mutation (C/C→T/T) in the *AGTR1* gene in exon 5. He was diagnosed with RTD caused by *AGTR1* gene abnormality. Case 2 is a 13-year-old boy. No abnormality was found in the perinatal period. Health checkup at 1 month of the age pointed out abnormalities of facial features. Screening test revealed atrophic left kidney with small cysts. Subsequently, mental retardation was recognized. He had small eyeballs and retinal dysplasia, pituitary hyperplasia as revealed in the brain MRI. Evidence of increased active renin concentration (105 pg/ml) was shown. Gene analysis revealed a homogenous M268T mutation in the *AGT* gene in exon 2. A heterozygous mutation in AGT gene was detected in the parents.

Results:

Conclusions: The RAS-related molecule is an essential factor of fetal organ development, and its abnormality shows various symptoms including extrarenal complications. Abnormalities in RAS-related molecules do not necessarily affect the circulating state of RAS-related molecules. Symptoms differ, depending on polymorphisms, suggesting that genetic mutation is potentially present in many asymptomatic patients.

PUB224

RET-Associated Renal and Extrarenal Disease: An Expanding Clinical Spectrum

Keisuke Sugimoto,[4] Tomoki Miyazawa,[5] Kohei Miyazaki,[3] Takuji Enya,[1] Hidehiko Yanagida,[2] Mitsuru Okada,[4] Tsukasa Takemura.[4]
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Background: In *RET* gene abnormality, different symptoms are developed by gain- and loss-of-function. Gain-of-function is involved in multiple endocrine neoplasia type 2 (MEN2). The development of oligomeganephronia (OMN) is the result of loss-of-function. To date, we have reports of simultaneous occurrence of gain- and loss-of-function due to *RET* gene abnormality resulting in the merger of MEN2 in renal dysplasia, but no reports of concomitant thyroid dysfunction.

Methods: We detected two cases of *RET* gene-associated renal and extra-renal disease. Case 1: A 22-year-old woman showed renal dysfunction related to OMN and asymptomatic thyroid dysfunction with elevated thyroid-stimulating hormone (TSH) level. Gene analysis revealed a heterozygous p.T278N mutation in *RET* gene exon 4. This mutation was located in the middle of the extracellular domain of the RET molecule, suggesting the possibility of affecting its binding to GDNF/GFRα1. Case 2: A 17-year-old woman showed congenital sensorineural deafness, renal dysfunction related to OMN, and asymptomatic thyroid dysfunction with elevated TSH level. Gene analysis revealed a heterozygous T/- in *RET* gene intron 1. This mutation was present in the (intron) splice part, and it was abnormal in the polyT region at the 5' end approximately 60 bp upstream from the boundary of the exons/introns, thus possibly causing abnormal splicing of the mRNA precursor.

Results:

Conclusions: Thyroid follicular epithelial cells differentiate from thyroid stem cells, but subsequent cell differentiation is suppressed into cancer due to rearrangement of *RET/PTC* genes. Although latent hypothyroidism may be possible, the likelihood that *RET* gene mutation produces immature follicular cells and thyroid hormone and elevated TSH level as a result of negative feedback was suggested. *RET* gene abnormality in the domain affects the binding between the RET molecule and GDNF/GFRα1. GDNF gene abnormality in glomerular development in the early stage causes low nephron number with thickening of the glomerular basement membrane. In addition to podocyte structural abnormality, interestingly similar findings in the renal specimen were observed in our cases. In summary, these cases more likely caused loss-of-function in both renal and thyroid development. I propose the possibility of a new disease concept due to RET gene abnormality.

PUB225

Nephropathy in STZ-Induced Diabetic Mice: Characterization of Renal Injury and Effects of Standard of Care on Renal Dysfunction

Judi A. Mcnulty,[2] Michael P. Quaile,[2] Kathleen O. Morasco,[1] Erding Hu,[3] Denise d'Epagnier.[2]
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Background: Human diabetic nephropathy (DN) manifests as a complication of chronic diabetes and is characterized by a progressive decline in glomerular filtration rate, histopathologic changes, persistent albuminuria and elevated arterial blood pressure. While many promising murine models of DN populate the literature, no current model of diabetes reliably recapitulates the full spectrum of human DN phenotpye. The aim of the present study was to longitudinally characterize renal dysfunction and injury in a model combining diabetes and hyperlididemia.

Methods: Diabetes was induced in Apolipoprotein E-Knockout (ApoE) mice by multiple injections of streptozotocin (STZ) at 55 mg/kg for 5 days. Mice were considered hyperglycemic when blood glucose levels reached >250 mg/dL. Following induction of diabetes, animals received no treatment or quinapril (10, 30 mg/kg/day) for 20 weeks. Relevant urinary, plasma endpoints as well as renal morphology were evaluated.

Results: ApoE+STZ mice weighed less than ApoE controls, but there was no difference in body weight gain over 20 weeks between groups. ApoE+STZ mice exhibited stable hyperglycemia and polyuria over 20 weeks compared to controls with no quinapril effect on urine output. However, there were no biologically significant differences in renal parameters across groups over the 20 week time course. There were also no significant differences in renal morphology among groups.

Conclusions: Based on the discordance between the phenotype exhibited in this study to that of the human diabetic nephropathy condition as well as previously published literature employing this model, the ApoE-STZ diabetic nephropathy model lacks reproducibility as well as translatability to the human disease state.

PUB226

Urinary Mitochondrial Proteins and Renal Cortical Mitophagy during the Normoalbuminuric Stage of Diabetes Mellitus

Naohito Ishii,[1] Tadachika Ichioka,[1] Akemi Imoto,[1] Yoshifumi Kurosaki,[1] Pamela K. Carmines,[2] Hideki Ikenaga,[3] Yoshio Kodera,[1] Masanori Yokoba,[1] Takafumi Ichikawa,[1] Tsuneo Takenaka,[4] Masato Katagiri.[1]
[1]Kitasato University, Sagamihara, Japan; [2]University of Nebraska College of Medicine, Omaha, NE; [3]Seiikai, Tochigi, Japan; [4]International University of Health and Welfare, Tokyo, Japan.

Background: Renal cortical mitochondria are damaged by oxidative stress even during the normoalbuminuric stage of type 1 diabetes mellitus (DM) (*Clin Sci* 124:543-52, 2013). The goal of this study was to determine if this process results in mitophagy (mitochondrial autophagy) and urinary excretion of mitochondrial proteins.

Methods: Rats were injected with streptozotocin (STZ, *n*=10; 65 mg/kg i.p. to induce DM) or vehicle (Sham, *n*=10), and treatment with the angiotensin receptor blocker telmisartan (TLM; 10 mg/kg/day) was initiated in half of the rats in each group (STZ+TLM; Sham+TLM) to suppress oxidative stress. Two weeks later, blood glucose (BG), blood pressure (BP) and glomerular filtration rate (GFR) were measured in each rat. Production of 3-nitrotyrosine (3-NT; an oxidative stress marker) and levels of mitophagy-related proteins (BNIP3, LC3-II, PINK1, p62) were quantified in renal cortex. Urinary mitochondrial proteins were identified by proteome analysis.

Results: BG levels were higher in STZ rats than in Sham rats ($P<0.05$) and were unaffected by TLM. Compared with Sham, STZ rats displayed significant increases in GFR, as well as renal cortical 3-NT production, LC3-II and PINK1 levels, with these effects prevented by TLM. BNIP3 (dimer) and p62 levels did not differ among groups, nor did BP. LC/MS/MS spectral count analysis of urine from STZ rats identified four mitochondrial proteins that were not detected in urine from Sham, Sham+TLM or STZ+TLM groups: ATP synthase subunit S (ATP5S), adenylate kinase 2 (AK2), O_2-dependent coproporphyrinogen-III oxidase (gene: *Cpox*) and elongation factor Tu (TUFM).

Conclusions: During the normoalbuminuric stage of DM, targeted degradation of oxidative stress-damaged mitochondria is evidenced by a TLM-sensitive elevation in renal cortical levels of the mitophagy-related proteins, LC3-II and PINK1. This results in urinary excretion of four mitochondrial proteins that may represent early diagnostic markers for diabetic nephropathy.

Funding: Government Support - Non-U.S.

PUB227

Huangkui Capsule Attenuates Podocyte Damage in Diabetic Kidney Disease by Regulating NALP3 Inflammasome and Insulin Resistance-Related Signalings Yinglu Liu, Yigang Wan. *Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, Nanjing, China*.

Background: In China, Huangkui capsule (HKC) has been applied extensively for treatment of albuminuria in patients with early diabetic kidney disease (DKD). However, the therapeutic mechanisms still need to be elucidated. In the process of DKD, the activation of NALP3 inflammasome and the inhibition of insulin resistance (IR)-related signalings including MAPK and PI3K/Akt in kidneys lead to podocyte injury, which further result in albuminuria. Therefore this study aimed to investigate effects and mechanisms in vivo of HKC on podocyte lesions, compared with rosiglitazone (ROS) as an insulin sensitizer in clinic, via regulating NALP3 inflammasome and IR-related signalings.

Methods: Rats were randomly divided into 4 groups, the Sham-operated group, the Vehicle-given group, the HKC-treated group and the ROS-treated group. HKC, ROS and saline were daily administrated for 8 weeks after the induction of DKD by high-fat diet, unilateral nephrectomy and streptozotocin injection. Albuminuria, biochemical indicators, NALP3 inflammasome-related factors, IR-related markers (HOMA-IR), glomerular pathological changes, as well as the key signaling molecules in MAPK and PI3K/Akt pathways and podocyte structural molecules in kidneys were examined, respectively.

Results: Results showed that, urinary albumin, HOMA-IR, foot process effacement, glomerularsclerosis, the over-expressions of NALP3, active caspase-1 and active IL-1β and the decreased protein expressions of p-MAPK42/44, p-PI3K, p-Akt2, nephrin and neph1 in kidneys of the DN model rats were ameliorated in different extent after treatment of HKC or ROS. More notably, HKC synchronously inhibited NALP3 inflammasome activation, promoted MAPK42/44 and PI3K/Akt2 signalings and up-regulated nephrin and neph1 protein expressions, which is different from ROS.

Conclusions: In summary, by means of the DN model rats, we demonstrated that NALP3 inflammasome activation and IR-related signalings inhibition contribute to podocyte damage. HKC, as a natural regulator in vivo, can improve podocyte injury by inhibiting NALP3 inflammasome activation and promoting IR-related signalings.

Funding: Government Support - Non-U.S.

PUB228

Lifetime Benefits of Early Detection and Treatment of Diabetic Kidney Disease (DKD) Julia T. Snider,[1] Jeff Sullivan,[1] Emma van Eijndhoven,[1] Michael K. Hansen,[6] Nobel A. Bellosillo,[3] Cheryl Neslusan,[3] Ellen S. O'Brien,[4] Ralph A. Riley,[5] Seth Seabury,[7] Mahlet G. Tebeka,[1] Bertram L. Kasiske.[2] *[1]Precision Health Economics, Los Angeles, CA; [2]Hennepin County Medical Center, Minneapolis, MN; [3]Janssen, Pompano Beach, FL; [4]Janssen Global Services, LLC, Horsham, PA; [5]Janssen Global Services, inc., Titusville, NJ; [6]Janssen Research & Development, Spring House, PA; [7]University of Southern California, Los Angeles, CA.*

Background: DKD is a frequent complication of diabetes. The lifetime health and economic burden of DKD depends on the timing of diagnosis and subsequent management. In this study, we estimated the value that would accrue to current and future diabetes populations from earlier DKD diagnosis and treatment.

Methods: Using The Health Economics Medical Innovation Simulation (THEMIS), we modeled life expectancy and medical spending for people with diabetes. The THEMIS model uses microsimulation techniques to model cohorts aged ≥50 y over their remaining lives and project population-level health and economic outcomes through 2050. The DKD cohort was based on data from the National Health and Nutrition Examination Survey and imputed into the Health and Retirement Study. We simulated the implementation of a new biomarker test that identifies people with diabetes at an elevated risk of DKD and DKD patients at risk of rapid progression. High-risk patients receive treatment that slows the progression toward kidney failure.

Results: Compared to baseline, the prevalence of DKD is reduced 6% with the biomarker test. The test doubles the rate at which people with DKD are diagnosed because it enables identification of at-risk individuals who can be treated when appropriate. Use of the biomarker test also reduces the prevalence of stage 5 chronic kidney disease among people with diabetes by 6%. Due to reduced risk of DKD onset and progression, life expectancy gains among people with diabetes are 0.2 y with the biomarker, while per-capita annual medical spending for people with diabetes falls by 0.3%.

Conclusions: The biomarker test reduces DKD prevalence and increases life expectancy among people with diabetes. Per-capita annual medical spending for people with diabetes falls with the test, demonstrating value. The biomarker test has the potential to be more valuable when combined with more effective DKD treatment. The potential health gains are important given the rising prevalence of diabetes and DKD.

Funding: Other U.S. Government Support, Commercial Support - Janssen, Private Foundation Support

PUB229

High Glucose Induction of the GLUT1 Glucose Transporter and Mechano-Growth Factor (MGF) in Human Mesangial Cells (HMC) Portends Their Roles in Human Diabetic Nephropathy Yongxin Gao,[1] Leighton R. James,[1] Abdalagani A. Abakar Baher,[1] Nanjoo Shin,[2] Emma P. Bueno,[1] Charles W. Heilig.[1] *[1]UF COM- Jacksonville, Jacksonville, FL; [2]Univerfsity of Florida, Jacksonville, FL.*

Background: We previously reported increased mesangial cell (MC) GLUT1 and MGF expression in mouse MC in response to 20 mM (360 mg/dL) high glucose (HG) exposure. This contributed to excess MC extracellular matrix (ECM) production. We also previously reported glomerular GLUT1, NFkB and ECM are increased and/or activated in mouse models of diabetic and nondiabetic glomerulosclerosis (GS). Here, we tested HMC for potential GLUT1 and MGF responses to 20 mM high glucose which might contribute to excessive ECM production in vitro, and by implication human diabetic GS in vivo.

Methods: METHODS: 1. HMC were grown to 80 - 100% confluence at 37C, 5% CO2 in 5 mM glucose medium, then changed to 5 or 20mM glucose medium for 4 days, prior to harvest of total cell proteins or immunofluorescent (IF) staining. 2. Western blotting of HMC proteins and semiquantitation by optical densitometry with normalization of selected proteins to the endogenous housekeeping protein beta-Tubulin. 3. Immunofluorescent staining and semiquantitation of selected proteins in cultured HMC, using Alexa-Red and DAPI nuclear stain. 4. Specific antibodies were obtained against: GLUT1, MGF, fibronectin (FN), NfKB p50, NfKB p65 and CTGF.

Results: RESULTS: 1.GLUT1 protein increased 4-fold in HMC in response to 20 mM glucose, vs control 5 mM glucose, $P < .05$. 2.MGF protein increased 3.9-fold in 20 mM glucose, $P < .05$, while 3.Nuclear NFkB p50 increased 3.3-fold in 20 mM glucose, and nuclear NFkB p65 increased 2.8-fold, $P < .0005$ for both. 4.CTGF increased 3.9-fold in 20 mM glucose, $P < .0005$. 5. Resulting FN protein expression increased 6.8-fold in 20 mM glucose, $P < .05$.

Conclusions: CONCLUSIONS: 1.We found that HMC express both GLUT1 and MGF, which increased in 20 mM glucose, with NFkB activation, increased CTGF and ECM. 2.These mimic the responses we previously observed in mouse MC. 3.Increased GLUT1 and MGF portend important roles in HMC ECM production.

Funding: Commercial Support - Dialysis Clinics Inc., Private Foundation Support

PUB230

Extracellular Vesicles (EV) and Aerobic Exercise Improve Proteinuria in Rats with Diabetic Nephropathy Rodolfo R. Rampaso,[2] Rafael Luiz,[2] Natalia Reinecke,[2] Kleiton A. Silva,[3] Luciana Jorge,[2] Edson A. Pessoa,[1] Nestor Schor.[2] *[1]Universidade Federal de São Paulo, São Paulo, Brazil; [2]Universidade Federal de Sao Paulo/Escola Paulista de Medicina, Sao Paulo, Brazil; [3]University of Missouri, Columbia, AL.*

Background: The aim of this study was to evaluate the effects of application of extracellular vesicles with aerobic exercise training in controlling the progression of diabetic nephropathy, and its possible renoprotective effects

Methods: Adult male Wistar rats divided into 4 groups: Sedentary controls, (SED, n=8), Diabetes+Sedentary (DM-SED, n=8), Diabetes+Exercise (DM-EXE, n=8), Exercise+Controls (EXE,n=8), Extracellular Vesicles/Diabetes-Sedentary (EV/DM-SED, n=8) and Vesicles/Diabetes-Exercise (EV/DM-EXE,n=8). DM was induced with streptozotocin (STZ), 50mg/kg i.v. EV (5 aplication 80µg every 12 days/60 days) was injected into the tail vein. The physical training was done on treadmill 60 min/day, 5 days a week for 8 weeks. Weekly it was determined the Maximal Exercise Test (set at 65-70% of MEtest). Glycemia 24h post training (glycemiapt), MEtest, creatinine clearance/BW (CrCl/BW), mean arterial pressure (MAP), proteinuria (uProt)

Results:

Conclusions: Results of this study show that EV attenuates proteinuria in Diabetic rats. When physical exercise was added to the treatment, this improvement was potentialized. Both, exercise and EV reduced weight loss in Diabetic groups, but only exercised groups prevented increases in glycemia and MAP. Therefore, preliminary data suggest that aerobic exercise and application EV can minimize effects caused by diabetic and could reduce the progression to renal failure.

	SED	DM-SED	DM-EXE	EXE	EV/DM-SED	EV/DM-EXE
uProt (mg/24h)	17 ± 0.88	46 ± 2.05 *#&	18 ± 0.72	16 ± 0.99	33.52 ± 1.16#&$	16.58 ± 0.48
CrCL/ (ml/min/BW)	5.65 ± 0.66	5.02 ± 0.43	4.19 ± 0.37	4.21 ± 0.29	4.86 ± 0.36	4.71 ± 0.15
glycemiapt (mg/dl)	103 ± 2.03	551 ± 7.03*&	491 ± 5.50*&	83 ± 2.57	381.63 ± 13.01	348 ± 11.12
MAP (mmHg)	122 ± 1.89	133.88 ± 1.79*#&$	122 ± 1.35	121 ± 2.11	132.13 ± 1.62*#&$	123.14 ± 1.99
Weight (g)	455 ± 6.00	236 ± 14.41*#&$	324 ± 9.34*&	387 ± 8.71	304.25 ± 9.03	318.75 ± 7.09
MEtest (m/min)	23.2 ± 0.49#&	19.5 ± 0.57*#&$	35.1 ± 0.97	37.5 ± 0.57	22.13 ± 0.77#&$	35.63 ± 0.71

PUB231

Astragaloside IV Synergizes with Captopril in Ameliorating Renal Fibrosis in Uninephrectomized db/db Mice Kam wa Chan, Wai Han Yiu, Haojia Wu, Dickson W. Wong, Bin Li, Ye Li, Loretta Y.Y. Chan, Joseph C K Leung, Kar Neng Lai, Sydney C. Tang. *The University of Hong Kong, Hong Kong, China.*

Background: Astragaloside IV (AS-IV) is an active ingredient of Astragalus membranaceus, the most frequently prescribed Chinese herbal medicine for diabetic kidney disease (DKD). AS-IV monotherapy has been demonstrated to ameliorate podocyte apoptosis, foot process effacement, mesangial expansion, glomerulosclerosis and interstitial fibrosis. Dual renin-angiotensin system (RAS) blockade has not been recommended for DKD due to a lack of efficacy. Since AS-IV is reported to regulate TGF-beta to ameliorate fibrosis, the prospect of combining AS-IV with renin angiotensin blockade warrants investigation.

Methods: Spontaneously diabetic db/db mice and their corresponding non-diabetic db/m littermates were uninephrectomized or sham-operated and received 8 weeks of captopril, AS-IV, combined captopril/AS-IV or vehicle control orally before sacrifice. Urine albumin-to-creatinine ratio (UACR), plasma cystatin C, blood glucose, blood pressure and expression of oxidative stress and fibrosis markers at mRNA and protein levels were determined. Histopathological changes were also examined.

Results: Uninephrectomized db/db mice developed progressive albuminuria, glomerulosclerosis, tubulointerstitial fibrosis and tubular atrophy with dilatation with upregulated cortical expression of TGF-beta, alpha-smooth muscle actin, collagen and fibronectin and NOX4. Mice that received either captopril or AS-IV treatment had ameliorated albuminuria and fibrotic lesions versus control. Mice that received combined treatment displayed the lowest glomerular injury index, tubular injury index, UACR and plasma cystatin C. Blood pressure and glucose were comparable between groups.

Conclusions: Captopril and AS-IV confer synergistic renal anti-fibrotic and anti-oxidative effects in uninephrectomized db/db mice. These findings could potentially be translated into clinical practice. Funding support: Hong Kong Society of Nephrology Research Grant

Funding: Government Support - Non-U.S.

PUB232

Mitochondrial DNA in the Urine: A Potential Biomarker Reflecting Systemic Mitochondrial Stress in Type 2 Diabetes Mellitus Li Fang,[2] Jing Luo,[2] Qi Yuan,[2] Ting Cai,[2] Junwei Yang.[1] *[1]Second Affiliated Hospital, Nanjing Medical University, Nanjing, China; [2]Nanjing Medical University, Nanjing, China.*

Background: Both mitochondrial dysfunction and chronic sterile inflammation were the most common features in type 2 diabetes. Since extracellular mitochondrial DNA (mtDNA) could also be recognized as both a biomarker of mitochondrial dysfunction and a damage-associated molecular pattern agent, our objective was to investigate the clinical significance of mtDNA in type 2 diabetes mellitus.

Methods: In vivo, mtDNA contents extracted from the samples of both diabetic patients and diabetic mice were measured by RT-PCR. In vitro, endothelial cell lines were used to investigate the effect of mitochondrial stress trigged by high glucose on the changes of mtDNA content both inside and outside cells.

Results: As compared to the control group, we found that the plasma mtDNA contents were lower while the creatinine-adjusted urinary mtDNA contents were significantly higher in the diabetic patients. However, in STZ-induced diabetic mice, although mtDNA contents in the plasma did not change significantly, mtDNA contents extracted from the muscle, heart, liver and kidney were significantly decreased in a time-dependent manner while the creatinine-adjusted urinary mtDNA contents were increased. On this basis, the find that mtDNA could be filtrated through the dialysis membrane further suggested that the mtDNA might be released from the diabetic tissues and subsequently filtered into the urine. For exploration of the role of mitochondrial stress, in vivo, we first confirmed that high glucose could induce the increase of extracellular mtDNA contents, meanwhile, the decrease of intracellular mtDNA contents in both dose-dependent and time-dependent manners. Next, by using resveratrol to attenuate the mitochondrial oxidative stress, we found resveratrol could increase the intracellular mitochondrial content and decrease the extracellular mtDNA content.

Conclusions: Our results indicated that mtDNA might be released from the cell as a response of mitochondrial stress under diabetic conditions. Thus, mtDNA which was subsequently filtered into the urine might be a biomarker reflecting systemic mitochondrial stress in type 2 diabetes mellitus.

Funding: Government Support - Non-U.S.

PUB233

Diabetic Myonecrosis: A Rare and Less Known Complication of Diabetes Sherin A. Ahmed,[2] Zeshan sharif Choudhry,[2] Smita Gunda.[1,2] *[1]Cambridge University Hospitals, Cambridge, UK, Kings Lynn, United Kingdom; [2]Renal, Queen Elizabeth hospital, Kings Lynn, United Kingdom.*

Background: We report a case of spontaneous myonecrosis and compartment syndrome involving the upper limb in a poorly controlled type1 diabetic with microvascular complications. Patient had recurrence in left thigh within a month, which was managed conservatively. To our knowledge this is the first report of Diabetic Myonecrosis(DMN) with upper limb as the index site of presentation.

Methods: 39 yr old female type1 diabetic with poor compliance, retinopathy, neuropathy and nephropathy, presented with acute onset pain and swelling of left arm. Clinically had swelling with severe tenderness, skin was intact with no redness. Limb movements were full and pulses intact. Initial bloods showed no evidence of infection Blood Glucose-50.9 mmol/L US Doppler-negative She was treated with antibiotics, anticoagulation and regular opioids for pain. CT showed significant edema with increased suspicion of compartment sydrome. Pain was rapidly worsening with decrease in range of movement and loss of pulse. Hence she was taken up for theatre and intraoperatively deltoid and triceps were found to be necrotic. Histology confirmed necrosis of individual muscle fibres consistent with DMN. Patient recovered well after surgery only to present with pain in thigh muscles within a month, when MRI showed high signal changes and intramuscular fluid consistent with DMN, needing conservative management. At a later date patient presented with fulminant hepatic failure and subsequently died.

Results:

Conclusions: DMN was first described in 1965. It is a rare and under diagnosed complication of long standing and poorly controlled diabetes. DMN is common in females and type1 diabetics, with a predilection for thigh muscles.70% cases have nephropathy. Clinially presents with acute onset pain, swelling and tenderness. Commonly misdiagnosed as cellulitis, thrombosis or fascitis. MRI is the most useful evaluation tool. Responds well to conservative management and can be self limiting but with high recurrence rate. Pathogenesis may involve atherosclerosis, hypoxia-reperfusion injury or atheroembolism. Although short term prognosis is good, long term survival is <5yrs. DMN poses a burden to health service mainly due to lack of early recognition leading to otherwise avoidable investigations and treatment. Hence a high index of suspicion is needed in long standing diabetics with acute muscle pain. Management aiming at strict blood sugar control, rest and analgesics.

PUB234

The Dissociation of Glycated Albumin (GA) and Hemoglobin A1c (HbA1c) Is Associated with Decline of Glomerular Filtration Rate (GFR) Evaluated by Inulin Clearance (Cin) in Type 2 Diabetes Akihiro Tsuda,[1] Eiji Ishimura,[2,1] Hideki Uedono,[3] Shinya Nakatani,[3] Masaaki Inaba,[3] Katsuhito Mori.[3] *[1]Department of Nephrology, Endocrinology, Metabolism, and Molecular Medicine, Osaka City University Graduate School of Medicine, Osaka, Japan; [2]Meijibashi Hospital, Osaka, Japan; [3]Osaka City University Graduate School of Medicine, Osaka, Japan.*

Background: It is well known that GA provides a better measure to estimate glycemic control in hemodialysis patients with diabetes melitus (DM), and that the assessment of glycemic control by HbA1c in those patients might lead to underestimation (Inaba M, et al. J Am Soc Nephrol, 2007). However, to date, no data exists regarding to the question whether and how GA and HbA1c are dissociated in those with non-dialysis chronic kidney disease (CKD) patients with DM and nonDM.

Methods: One hundred forty nine non-dialysis CKD patients (75 DM and 74 nonDM; age, 59.3 ± 13.0 years (diabetics) and 55.4 ± 13.9 years (non-diabetics); 71 males (47.7%)) were enrolled. GFR was evaluated by C_{in}. The factors related to the dissociation between GA and HbA1c in DM patients and nonDM patients were examined.

Results: There was a significant and positive correlation between GA and HbA1c in each stage of CKD in both DM(CKD 1, r=0.906, p<0.0001; CKD 2, r=0.869, p<0.0001; CKD3+4, r=0.809, p<0.0001) and nonDM (CKD 1, r=0.488, p=0.0076; CKD 2, r=0.502, p=0.0075; CKD3+4; r=0.668, p=0.0034). The regression slopes between GA and HbA1c were significantly deeper in advanced CKD stages of DM, but not in nonDM. We next evaluated the factors associated with the dissociation between GA and HbA1c. Since the dissociation of the regression line between GA and HbA1c could be represented by the GA/HbA1c ratio, we performed simple regression analyses of GA/HbA1c ratio with the various clinical parameters. There was a significant and negative correlation between GA/HbA1c ratio and GFR in DM (r=-0.452, p<0.0001), but not in nonDM. Multiple regression analyses revealed that GFR was significantly and independently associated with the GA/HbA1c ratio (ß=-0.244, p=0.0351) after adjustment with the several confounders in diabetics (R^2=0.448, p<0.0001).

Conclusions: GA and HbA1c is dissociated in diabetes, but not in non-diabetes. The dissociation of GA and HbA1c in diabetes is significantly associated with decreased GFR. HbA1c values in diabetic patients underestimate glycemic control index, particularly in those with lower GFR. Thus, evaluation of glycemic control by HbA1c in diabetic CKD patients should be carefully appreciated.

PUB235

The Renal Effect of the SGLT2 Inhibitors on the Japanese Type 2 Diabetes Mellitus Patients With Diabetic Nephropathy Kazuo Kobayashi,[1] Nobuo Hatori,[1] Hiroyuki Sakai,[1] Takayuki Furuki,[1] Masaaki Miyakawa,[1] Masao Toyoda.[2] *[1]Committee of Hypertension and Kidney disease, Kanagawa Physicians Association, Yokohama, Japan; [2]Tokai University School of Medicine, Isehara, Japan.*

Background: Some large-scale clinical trials with SGLT2 inhibitors(SGLT2i) have revealed significant improvements in cardiovascular events and diabetic nephropathy(DMN) in patients with type 2 diabetes mellitus (T2DM). However, it is not clear whether similar results are observed in Japanese patients with T2DM.

Methods: To clarify the renal effects of SGLT2i in Japanese patients, data from T2DM patients with DMN who are visiting members of the Kanagawa Physicians Association, and who were taking SGLT2i were extracted.

Results: We analyzed 592 cases (male: female = 387: 205, age 60.6 ± 12.2 years, BMI 27.7 ± 5.4). The administration period was 14.9 months on average. The distribution of eGFR(mL/min/1.73 m^2) was as follows: ≥60, 76.1%; 30–59, 23.4%; and <30, 0.5%. Six SGLT2i were used: ipragliflozin (n=190), tofogliflozin (n=113), dapagliflozin (n=92), empagliflozin (n=84), canagliflozin (n=61), and luseogliflozin (n=51). Clinical findings at the beginning of administration versus at the time of the survey are shown as mean ± SD. Body weight (kg), 76.5 ± 17.1 vs. 74.4 ± 16.5 (p<0.01); HbA1c (%), 8.1 ± 1.6 vs. 7.4 ± 1.2 (p<0.01); blood pressure (BP) at office(mmHg), 140.2 ± 20.0/79.7 ± 12.6 vs. 133.9 ± 17.2/77.5 ± 11.0 (p<0.01); BP in the early morning at home (n=55; mmHg), 130.2 ± 11.1/76.9± 10.1 vs. 128.3 ± 11.0/73.9 ± 10.2 (p<0.05). eGFR decreased from 78.2 ± 23.4 to 74.9±23.7 mL/min/1.73 m^2 (p<0.01), and the mean value of ACR significantly decreased from 96.8 to 73.9 (p<0.05). The degree of adherence with dietary treatment was divided into four groups (“very good”, ”good”, ”usual”, and ”bad”) and the change of logarithmic value of ACR were -0.43 ± 1.11, -0.20 ± 0.89, -0.19 ± 1.00, and -0.07 ± 0.93, respectively. By multiple linear regression analysis, the age, the usage of aldosterone blocker agent, “very good” adherence with dietary treatment, the usage of empagliflozin, the change of systolic BP at office were independently correlated with the change of ACR.

Conclusions: This retrospective study confirmed that the results of large-scale clinical trials were also observed in the real world. The importance of dietary therapy has also been partially accepted, and further discussion on the relationship between background factors and differences between drug treatments will be considered necessary in the future.

PUB236

Semi-Individualised Chinese Medicine Treatment as an Adjuvant Management for Diabetic Nephropathy – Preliminary Results of an Add-On, Randomised, Controlled, Multi-Centre, Open-Label Pragmatic Trial Kam wa Chan,[4] Alfred Kwong,[1] Sing-Leung Lui,[5] Tai-Pang Ip,[5] Gary Chan,[3] Benjamin J. Cowling,[4] Wai Han Yiu,[4] Dickson W. Wong,[4] Bin Li,[4] Ye Li,[4] Yibin Feng,[4] Kathryn Tan,[6] Loretta Y.Y. Chan,[2] Joseph C K Leung,[4] Kar Neng Lai,[4] Sydney C. Tang.[4] *[1]Hospital Authority, Hong Kong, China; [2]Queen Mary Hospital, Hong Kong, China; [3]Queen Mary Hospital, Hong Kong, Hong Kong, China; [4]The University of Hong Kong, Hong Kong, China; [5]Tung Wah Hospital, Hong Kong, China; [6]University of Hong Kong, Hong Kong, China.*

Background: Conventional treatment for diabetic nephropathy (DN) has achieved limited effect in preserving renal function. Recent big data studies showed that Chinese medicine (CM) could reduce the risk of end-stage kidney disease by 59% percent in a 6-year period. However, existing CM clinical guidelines are weakly evidence-based and the effect of combined Chinese and conventional medicine remains unclear.

Methods: This assessor-blind, add-on, randomized, controlled, multi-center, open-label pilot pragmatic trial evaluates the effect of an add-on semi-individualized CM treatment protocol based on expert consensus. 148 DN patients are being recruited and randomized 1:1 to a 48-week add-on semi-individualized CM treatment or standard medical care. Primary endpoints are changes in estimated glomerular filtration rate (GFR) and spot urine albumin-to-creatinine ratio (UACR) between baseline and endpoint. Outcomes are analyzed as intention-to-treat by regression models.

Results: Recruitment started in July 2015. First 25 patients have completed 24 weeks of study period. The groups are similar for demographics. Mean GFR of intervention and control group decreased by 0.06 and 3.51 mL/min/1.73m^2 respectively (95% CI: -8.08 to 1.19). Mean UACR of intervention and control group increased by 44% and 28% respectively (95% CI: -88.5% to 57%). After adjusting for age, gender, baseline HbA1c, BMI, blood pressures, GFR and UACR, intervention contributes to 3.8 mL/min/1.73m^2 increase (95% CI: -3.9 to 11.4, p=0.30) in 24-week mean GFR in treatment group versus control (47.5 vs 43.8). The model explains 88% of variability and contribution remains similar (mean diff.: 4.1, 95%CI: -4.0 to 12.2, p=0.28) when 24-week UACR is adjusted in sensitivity analysis. Adjusted 24-week mean UACR, HbA1c, blood pressures, AST, ALT levels, and incidence of serious adverse events are comparable between groups.

Conclusions: Our interim analysis suggests that add-on semi-individualized CM treatment may stabilize GFR among DN patients with macroalbuminuria independent of albuminuria, glycemic and blood pressure control. Funding: Health and Medical Research Fund (Ref:12133341)

Funding: Government Support - Non-U.S.

PUB237

Mortality Risk of Renal Glucosuria in a General Screening Participants in Japan Kunitoshi Iseki, Tsuneo Konta, Koichi Asahi, Kunihiro Yamagata, Shouichi Fujimoto, Kazuhiko Tsuruya, Ichiei Narita, Masato Kasahara, Yugo Shibagaki, Toshiki Moriyama, Masahide Kondo, Tsuyoshi Watanabe. *Steering Committee for the Design of the Comprehensive Health Care System for Chronic Kidney Disease (CKD) Based on the Individual Risk Assessment by Specific Health Check, Fukushima, Japan.*

Background: Limited data exist on the association between renal glucosuria and mortality rate in a setting of general screening.

Methods: We followed the screened participants at the2008 specific health check (N=288,528) performed in 6 district in Japan, and identified those who died by 2012. We examined the association between renal glucosuria and mortality. Diabetes Mellitus (DM) was diagnosed either HbA1c≥6.5%, fasting plasma glucose≥126mg/dl, or on medication for DM. Hazard ratio (HR) and 95% confidence interval (CI) was calculated using Cox proportional hazard analysis. Dipstick results of 1+ and higher were defined as glucosuria (+).

Results: Among the total of 294,780 subjects, we identified 3,747 fatal cases by end of 2012. The crude mortality rates were 1.2% in glucosuria (-) and 3.4% in glucosuria (+). In DM subjects with glucosuria (N=4,655), the HR (95% CI) was 1.302 (1.044-1.613, P=0.020) when compared to those without glucosuria (N=20,245). In Non-DM subjects with glucosuria (N=470), it was 2.511 (1.539-3.833, P<0.001) when compared to those without glucosuria (N=183,690).

Conclusions: Glucosuria both DM and non-DM subjects has significant impact on mortality rate among the Japanese community-based screening participants.

PUB238

Diabetic Retinopathy Can Predict the Prognosis of Patients with Type 2 Diabetes and Diabetic Nephropathy Junlin Zhang, Fang Liu, Yiting Wang. *Division of Nephrology, West China Hospital of Sichuan University, Chengdu, China.*

Background: Some patients with type 2 diabetes mellitus (T2DM) do not develop diabetic nephropathy (DN) despite the presence of diabetic retinopathy (DR). We aimed to examine the relationship between DR and the progression of DN in patients with T2DM.

Methods: In the cross-section study, 250 patients with T2DM and biopsy-proven DN were divided into two groups: 130 in the DN without DR group (DN group), and 120 in the DN+DR group. Logistic regression analysis was performed to identify risk factors for DR. Of the above 250 patients, 141 were recruited in the cohort study who received follow-up for at least 1 year and the influence of DR on renal outcome was assessed using Cox regression. Renal outcome was defined as the progression to end-stage renal disease (ESRD) or the initiation of renal replacement therapy.

Results: In the cross-section study, compared with the DN group, patients in DN+DR group had longer duration of T2DM, poorer renal function, more serious glomerular lesions and interstitial inflammation (p<0.05). The logistic regression analysis demonstrated that the severity of glomerular lesions (class IIb + III) and DM history ≥10 years were significantly associated with the odds of DR (OR, 95%CI; 3.568(1.598-7.964); p=0.002 and 2.511(1.217-5.182); p=0.013, respectively) when adjusting for baseline proteinuria, hematuria, e-GFR, interstitial inflammation. In the cohort study, a multivariate COX analysis demonstrated that the DR remained an independent risk factor for progression to ESRD when adjusting for important clinical variables and pathological findings (p < 0.05).

Conclusions: These findings indicated that the severity of glomerular was significantly associated with DR and DR was an independent risk factor for the renal outcomes in patients with DN, which suggested that DR can predict the prognosis of patients with type 2 diabetes and DN.

PUB239

Competing Risk of RRT and Death in Patients with Diabetes and CKD Who Have Undergone Renal Biopsy Ken-Soon Tan,[2] Samantha Ng,[2] Stephen P. McDonald,[1] Wendy E. Hoy.[3] *[1]ANZDATA Registry, Adelaide, SA, Australia; [2]Logan Hospital, Loganholme, NSW, Australia; [3]The University of Queensland, Brisbane, QLD, Australia.*

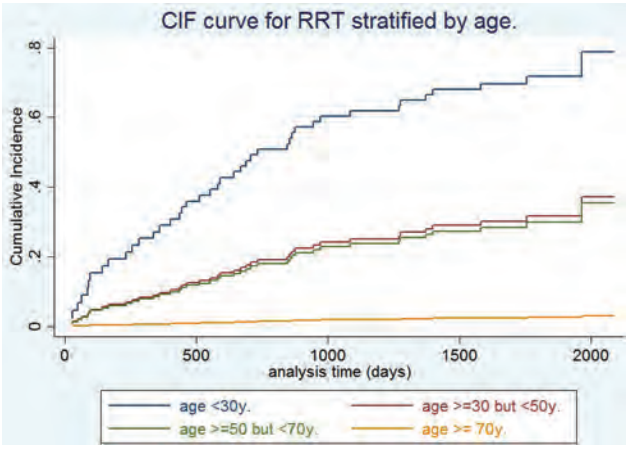
Background: Diabetes mellitus (DM) commonly causes chronic kidney disease (CKD). The CKD.QLD registry is an Australian state-wide registry of patients with CKD followed up in public hospital renal units who have provided informed consent. Enrollment commenced in 2011. We determined competing risk of survival to renal replacement therapy (RRT) and death without RRT in registry patients with DM and CKD who had undergone renal biopsy.

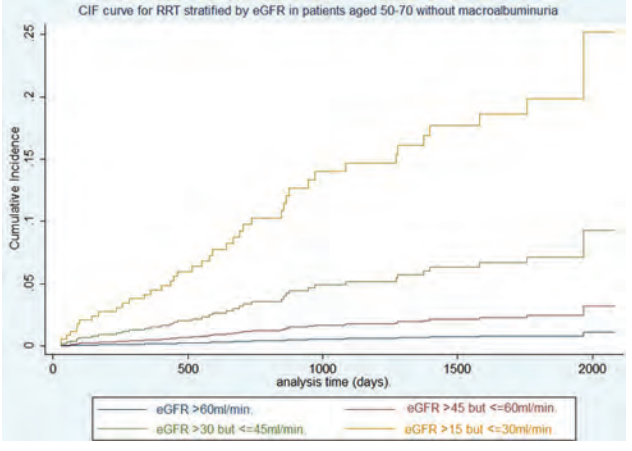
Methods: Patients with DM enrolled from 22/01/2011 - 15/11/2016 inclusive with previous renal biopsy were included. Baseline characteristics, incidence of RRT or death without prior RRT were determined. Censor date was 1/03/2017. Competing risk analysis (Fine and Gray method) was performed with RRT as the event of interest and death as the competing event. Age, eGFR and macroalbuminuria status (y/n) at enrollment were covariates.

Results: 189 patients had previous renal biopsy (58% had diabetic kidney disease present). Mean follow up at censor date was 3.1 years (586 patient-years). Mean age was 60.3years. Mean enrollment eGFR was 36ml/min (SD 17.7). 77% had macroalbuminuria. At censor date, 41 patients had commenced RRT (all dialysis). 29 died without prior RRT. Competing risk analysis revealed that only age (HR 0.94, 95%CI 0.93-0.,96) (fig1) and eGFR (HR 0.92, 95%CI 0.89-0.95) (fig2) contributed to risk of requiring RRT (both p<0.001).

Conclusions: In this high-risk group of patients receiving specialist nephrology care, younger age and lower baseline eGFR were associated with higher risk of requiring RRT.

Funding: Veterans Affairs Support, Government Support - Non-U.S.





PUB240

Changes of Parathyroid Hormone and 25 Hydroxy Vitamin D3 in Diabetic Patients with Maintenance Dialysis (MD) and Their Related Factors Chang Ying Xing, Juan Yang. *First Affiliated Hospital of Nanjing Medical University, Nanjing, China.*

Background: The differences and influences of intact parathyroid hormone (iPTH) and 25 hydroxy vitamin D3[25(OH)D3] in diabetic patients with MD are not clear.

Methods: There were 180 patients underwent maintenance hemodialysis (MHD) and 99 patients underwent peritoneal dialysis (PD). MHD patients were divided into two groups: those with DM as a diabetic hemodialysis group (DH), those without DM as a non-diabetic hemodialysis group (NDH). PD patients with DM as a diabetic peritoneal dialysis group (DP), those without DM as a non-diabetic peritoneal dialysis group (NDP). The clinical data between DH and NDH, DP and NDP were compared respectively, and analysis of possible influencing factors of iPTH and 25(OH) D3 levels were carried out.

Results: The iPTH in DH was lower than that in NDH (P<0.001). 25(OH) D3 in DH was also significantly lower than that in NDH. The level of iPTH was negatively correlated with history of diabetes, and positively correlated with dialysis years, phosphates, alkaline phosphatase (P<0.001) and 25(OH) D3 (P=0.016). The multiple linear regression (MLR) analysis showed history of diabetes (P=0.012) and years of dialysis (P=0.028) were independent factors of iPTH. The concentration of 25(OH) D3 was negatively correlated with history of diabetes (P=0.004), and positively correlated with dialysis years, phosphatase, magnesium, albumin and iPTH (P<0.05). The MLR analysis showed the history of diabetes(P=0.004) was independent factor of 25(OH)D3. The iPTH in DP group was also lower than that in NDP group [(257.7±211.1)pg/ml VS(394.7±338.9)pg/ml. In patients with PD, iPTH was negatively correlated with glycosylated hemoglobin (P<0.003), hemoglobin (P<0.045) and correction of calcium, positively correlated with serum phosphatase(P=0.000), alkaline phosphatase (P=0.013). The MLR analysis showed in patients with PD glycosylated hemoglobin (P=0.040) and serum phosphatase(P=0.024) were independent factors of iPTH. 25(OH) D3 in MPD was negatively correlated with age (P=0.044), and positively correlated with hemoglobin (P=0.007), albumin (P=0.002) and urea nitrogen (P=0.024). The MLR analysis showed that in MPD hemoglobin (P=0.009) was independent factor of 25(OH) D3.

Conclusions: Diabetic patients with dialysis have lower iPTH and 25(OH)D3. Diabetic history, Hb, albumin maybe have some effects on them,should be pay more attension on them.

PUB241

Can HbA1c Be Trusted in Anaemia or CKD? Analyses from the Copenhagen Primary Care Laboratory (CopLab) Database Rikke Borg,[4,5] Frederik Persson,[3] Volkert Siersma,[2] Bent Lind,[1] Niels D. Olivarius,[5] Christen L. Andersen.[5] *[1]Hvidovre Hospital, University of Copenhagen, Hvidovre, Denmark; [2]Research Unit for General Practice, Copenhagen, Denmark; [3]Steno Diabetes Center, Gentofte, Denmark; [4]Nephrology, Zeeland University Hospital, Roskilde, Denmark; [5]University of Copenhagen, Copenhagen, Denmark.*

Background: Glycated hemoglobin (HbA_{1c}) is used to diagnose and evaluate glycemic control in diabetes. Several clinical conditions may alter the blood glucose/HbA_{1c} relationship by affecting erythropoiesis or erythrocyte lifespan. In a large population in primary care, we investigated (1) whether we could confirm the relationship between fasting plasma glucose (FPG) and HbA_{1c} measurements, and (2) the clinical implications of anemia or CKD for the interpretation of HbA_{1c}.

Methods: From a primary care laboratory, we examined valid measurements of both HbA_{1c} and FPG, as well as measurements of hemoglobin (Hb) and eGFR. We stratified our observations according to CKD stage and according to anemia level. The prediction of the mean FPG from HbA1c alone, and jointly from HbA1c and Hb and eGFR respectively was estimated by thin plate regression splines.

Results: In 155.565 individuals (48% men), the FPG/HbA_{1c} relationship imitated the ADAG linear regression equation. The glucose/HbA_{1c} -relationship was unaffected in most patients with mild to moderate CKD and in cases of mild to moderate anemia. Only in severe hyperglycemia (HbA_{1c} >100 mmol/mol) and concurrent anemia or eGFR<45 ml/min the correlation changed, so that glucose concentration was overestimated by HbA_{1c} in anemia and underestimated in CKD (Figure 1). Very few patients in our population had eGFR <30 ml/min (0.82%) or severe anemia (0.11%), demonstrating that HbA_{1c} can be used without adjustment in primary care to estimate glycemic control.

Conclusions:

Funding: Government Support - Non-U.S.

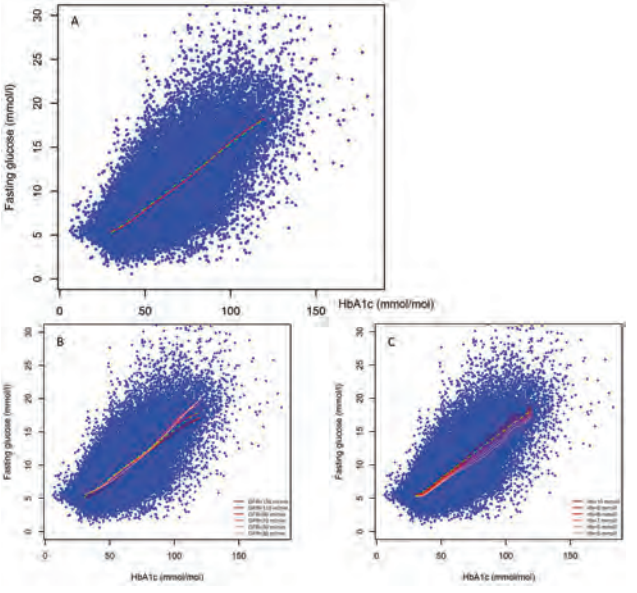


Figure 1. Association between fasting plasma glucose and HbA_{1c} (n, measurements=371,149). The original ADAG study equation for the glucose/HbA1c association shown as dashed line.(A) Overall population; and according to strata of (B) eGFR and (C) haemoglobin.

PUB242

Sodium Intake Does Not Modify the Effect of Silybin and N-AC on Albuminuria in Patients with Diabetic Nephropathy Jeet Gandhi,[4,5] Manoj Bhattarai,[4,5] Subrata Debnath,[2] Sue E. Cunningham,[3,1] Shuko Lee,[1] Chakradhar Velagapudi,[3,5] Shweta Bansal.[3,5] *[1]South Texas Veterans Health Care System, San Antonio, TX; [2]University of Texas Health Science Center at San Anotonio, San Antonio, TX; [3]University of Texas Health Science Center at San Antonio, San Antonio, TX; [4]Nephrology, University of Texas Health Science Center San Antonio, San Antonio, TX; [5]Nephrology, South Texas Veterans Healthcare System, San Antonio, TX.*

Background: Silybin, an active ingredient of Milk Thistle and anti-oxidant, reduced albuminuria in patients with diabetic nephropathy in an Iranian study. However, there was no effect of silybin administration on albuminuria in our study cohort. Dietary sodium intake modifies the effect of angiotensin inhibition on albuminuria. Whether sodium intake can influence the effect of anti-oxidant silybin and N-acetylcysteine (NAC) on

albuminuria needs to be evaluated. We hypothesize that lower sodium intake improves the beneficial effect of silybin and NAC on albuminuria.

Methods: We conducted a sub-analysis of the randomized-controlled trial where 75 subjects with diabetic nephropathy with albumin-creatinine ratio (ACR) of =/>150 mg/g and eGFR 15-60 ml/min on the background of angiotensin inhibition received either placebo or NAC or silybin or combination for 3 months to test their anti-proteinuric effect. Daily sodium intake was estimated by measuring 12-hour urinary Sodium excretion. Urinary ACR and other independent variables were measured at baseline and end of 3-month intervention.

Results: The study population was 62.97±7.48 years old, 89% male, 65% Hispanic, 27% non-Hispanic white and 7% non-Hispanic blacks, had BMI of 35.02±8.54 kg/m^2, eGFR of 36.4±13.3 ml/min, and ACR of 565 [216,1018] mg/g at baseline. None of the interventions reduced the urinary excretion of albumin (post ACR: 638 [243, 1161] mg/g). Mean sodium intake was 4064±2642 mg/d at baseline and 3816±1664 mg/d at 3-month. There was no difference in any of the demographic, clinical and laboratory parameters between the groups categorized by sodium intake. On univariate analysis, ACR correlated positively with systolic BP (r=0.3, p=0.008), and negatively with age (r=-0.25, p=0.03) and eGFR (r=-0.27, p=0.02, only at the end of intervention) but there was no correlation between ACR and daily sodium intake on both the occasions. In multivariable regression model including age, eGFR, sodium intake, use of diuretic and ACEI, different treatment arms, application of interaction term between treatment arms and sodium intake did not predict albuminuria at the end of intervention (p interaction=NS).

Conclusions: There was no modification by the daily sodium intake on the effect of silybin or NAC on albuminuria in patients with diabetic nephropathy.

Funding: Other NIH Support - NIH-NCCAM AT004490 and VA Merit Review 1I01CX000264

PUB243

GLP1RA Facilitate Improved Glycaemia, Reduction in Insulin Requirements, and Weight Loss in Renal Transplant Recipients

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Background: While treatment options for diabetes have increased, there is little experience with these agents in renal transplant recipients. This study examined 13 renal transplant recipients with pre-existing diabetes mellitus (PEDM) or post-transplant diabetes mellitus (PTDM) treated with GLP1 receptor agonists (GLP1RA).

Methods: 7 PEDM & 6 PTDM patients, a mean of 60 months post-transplant were given either a B.D. preparation (Byetta) or weekly preparation (Bydureon) of exenatide.

Results: At baseline, 10 were on insulin (6 PEDM, 4 PTDM) with a mean total daily insulin (TDI) requirement of 100IU/day, 1.6 other glucose lowering agents, mean weight 88.6kg, HbA1c 8.4% and creatinine 120μmol/L. 3 patients were intolerant of Byetta, while all 8 patients on Bydureon tolerated treatment. After a median follow-up of 11 months, 4/10 patients ceased insulin (2/6 PEDM, 2/4 PTDM) with a mean reduction in TDI of 71IU/day. Weight decreased by a mean of 5kg and was greater for those who reduced TDI. Mean HbA1c at follow-up was 7.8%, with a mean reduction of 0.28%. Patients were on an average of 2.2 other agents at follow-up. Of 6 patients with documented NAFLD initially, all had improved liver function on treatment. Patient satisfaction was high, evidenced by continuation of the extra injections even when on insulin.

Conclusions: GLP1RA usage in renal transplant recipients with diabetes enabled significant reduction in TDI, weight; improved glycaemic control, and achieved greater freedom from hypoglycaemia with few adverse effects. These agents prove invaluable in managing abnormal glucose metabolism amongst transplant recipients and warrant further clinical evaluation.

Age (years)	PTDM v PEDM	NAFLD	Years post-transplant	Duration of DM (years)	Follow-up (months)	TDI (IU) prior to GLP1RA	TDI (IU) post GLP1RA	Change in weight (kg)	Change in HbA1c (%)
61	PTDM	Y	8	3	5	0	0	-2.5	N/A
64	PTDM	Y	10	>10	18	200	26	-14	+0.2
42	PTDM	Y	9	3	10	0	0	-9	-2
46	PTDM	N	7	7	6	30	0	-4	-1
55	PEDM	Y	2	4	8	0	0	+1	-1.2
69	PEDM	N	3	>15	18	80	0	-10	-0.2
60	PEDM	N	3	>15	10	70	20	-11	-0.5
53	PEDM	N	6	8	6	40	0	-3	-0.3
66	PEDM	N	3	>15	18	70	24	-6	+2.2
37	PTDM	Y	7	5	9	30	0	-4	-2
42	PEDM	N/A	5	>15	8	110	110	0	0
64	PEDM	Y	4	>15	4	320	90	-8	+1.7
61	PTDM	N/A	4	4	N/A	50	20	+6	N/A

PUB244

Rates of Hypoglycemia in Hospitalized Patients Receiving Hemodialysis

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Background: Because of the link between inadequate nutrition and poor outcomes of hospitalized patients, we established a protocol to permit patients to eat during hemodialysis. Our clinical staff observed frequent episodes of hypoglycemia during and immediately following hemodialysis, resulting in adverse symptoms and interfering with dialysis treatment. A dialysis nurse who is a certified diabetes educator instructed nursing staff on how to calculate the amount of carbohydrate eaten from hospital meal trays. Nurses were instructed to contact physicians for insulin dose adjustments for patients consuming less than 30 grams of carbohydrate.

Methods: We received IRB approval for a retrospective cohort study to identify hypoglycemic episodes defined as any blood glucose (BG) < 90 and severe hypoglycemic episodes as a BG < 54. We reviewed medical records for additional clinical information as well as timing of insulin dosing and administration relative to dialysis. We compared the frequency of hypoglycemia using the reference value of 1-3% in the general population of patients with diabetes and 3-10% in patients admitted to non-ICU hospital settings to our population of hospitalized patients undergoing hemodialysis.

Results: Of 105 dialysis treatments between June and September 2016, 12 patients suffered 16 episodes of hypoglycemia during dialysis (15.2%); in none of these cases was hypoglycemia severe. In 9 of the 16 cases, insulin was administered based on a standard hospital order set; most more than an hour prior to initiating dialysis treatment.

Conclusions: The proportion of our patients who developed hypoglycemia was similar to that seen in a general population of hospitalized patients suggesting that it is safe for hospitalized patients to eat during hemodialysis. We propose that nutrition be more widely provided to hospitalized patients receiving hemodialysis with efforts to base insulin dosing on actual, rather than expected, carbohydrate consumption

Funding: Clinical Revenue Support

PUB245

Levels of Soluble RAGE but Not Endogenous Secretory (ES) RAGE Differ between Type 2 Diabetic versus Control Subjects in the United Arab Emirates

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Background: The United Arab Emirates (UAE) is experiencing increasing rates of obesity, type 2 diabetes (T2D) and its complications. We tested if soluble levels of cell surface-cleaved RAGE (sRAGE) or endogenous secretory RAGE (esRAGE), the product of alternative mRNA splicing of *AGER*, are associated with T2D and obesity in the UAE.

Methods: A case-control study was performed in the Diabetes, Endocrinology and General Medical Clinics of the Sheikh Khalifa Medical City in Abu Dhabi. 216 T2D subjects and 215 controls (mean age 57.4±12.1 vs. 50.7±15.4 years, respectively) were enrolled. Plasma sRAGE and esRAGE levels, anthropomorphic characteristics and routine chemistries were measured. The relationship between sRAGE and esRAGE with obesity and T2D status was tested using a linear regression model.

Results: Univariate analyses comparing T2D case and control subjects revealed differences in sRAGE (1,033±545.3 vs. 1,169±664.1 pg/ml, respectively; p=0.02) but not esRAGE. Covariate adjustment revealed that differences in sRAGE were significant after correction for age and sex and additionally for waist-hip ratio (WHR); total cholesterol (TC), HDL; hsCRP; Vit D; or triglyceride (TG) levels separately. In cases or controls, we tested associations of body mass index (BMI) or WHR with sRAGE and esRAGE. In controls but not T2D cases, sRAGE and esRAGE were significantly associated with BMI, after correction for age and sex and additionally for eGFR; blood pressure; TC, HDL; hsCRP; Vit D; creatinine; TG and HbA1c in a combined model. In the case of WHR, in controls and T2D cases, there were no associations with sRAGE, but only in T2D cases, WHR was associated with esRAGE after correction for age and sex and blood pressure; TC, HDL; hsCRP, HbA1c, creatinine; TG, eGFR, Vit D and TG in a combined model.

Conclusions: Levels of sRAGE but not esRAGE distinguish T2D case vs. controls in the UAE population. Genetic and unique obesity-dependent factors may underlie lack of association between esRAGE in cases vs. controls, which may affect vulnerability to T2D and its complications in the UAE.

Funding: Government Support - Non-U.S.

PUB246

The Cardiometabolic Risk Factor Proneurotensin Is Increased in Renal Dysfunction

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Background: Proneurotensin, the stable N-terminal fragment of the neurotensin precursor hormone, is significantly associated with the development of obesity, diabetes, cardiovascular disease, as well as with total and cardiovascular mortality in the Malmö Diet and Cancer Study and the Framingham Heart Study. In the present study, we investigate the regulation of the cardiometabolic risk factor proneurotensin in human and murine renal dysfunction.

Methods: Circulating proneurotensin levels were quantified by ELISA in 581 patients with chronic kidney disease (CKD cohort) covering the whole spectrum of estimated

glomerular filtration rate (eGFR) categories from G1 to G5. Furthermore, proneurotensin was measured in the German Sorbs population (N = 1041) to validate the associations with renal function in a general cohort. Moreover, *mNts* mRNA expression was investigated in an animal CKD model, i.e. eNOS$^{-/-}$ C57BLKS *db/db* mice, and compared to littermate controls without CKD.

Results: Median circulating proneurotensin levels significantly and continuously increased with deteriorating renal function (eGFR category G1: 129.0; G2: 143.8; G3: 178.3; G4: 224.9; G5: 283.6 pmol/l; $p < 0.001$) in the CKD cohort. Furthermore, proneurotensin was independently associated with eGFR and albumin/creatinine ratio in patients with CKD. In the general cohort of the Sorbs from Germany, impaired renal function remained an independent and positive predictor of proneurotensin levels. In CKD mice, *mNts* mRNA expression in subcutaneous and visceral adipose tissue, as well as in the liver and kidney, was unchanged as compared to controls.

Conclusions: The cardiometabolic risk factor proneurotensin is significantly and independently associated with renal function in both a CKD and a general cohort comprising of >1600 patients. Altered *mNts* mRNA expression might not be the cause for increased proneurotensin levels in CKD. Our results further support proneurotensin as a strong and relevant cardiometabolic risk factor in patients with renal dysfunction.

Funding: Government Support - Non-U.S.

PUB247

Development of a New Mouse Model of Diabetic Kidney Disease Xiaolin He,[2] Tianzhou Zhang,[1,2] Darren A. Yuen.[2] *[1]St. Michael's Hospital, Toronto, ON, Canada; [2]St. Michael's Hospital Keenan Research Centre for Biomedical Science, Toronto, ON, Canada.*

Background: Despite advances in our understanding of its pathogenesis, diabetic nephropathy (DN) remains a common and serious complication of diabetes that can progress to kidney failure, and for which few effective therapies exist. A major barrier to the development of new treatments is the lack of a mouse model that replicates key features of late stage human DN, such as interstitial fibrosis, in part because diabetic mice do not typically develop significant renin-angiotensin system (RAS) activation. **Objectives**: To develop and validate a new mouse model of diabetic nephropathy.

Methods: Mice transgenic for human renin cDNA under the control of the transthyretin promoter (TTRhRen) were employed as a model of RAS hyperactivation. Diabetes was induced in TTRhRen mice by intercrossing with diabetic Akita mice (Akita$^{+/-}$ TTRhRen$^{+/-}$mice).

Results: Both Akita$^{+/-}$ TTRhRen$^{+/-}$ and their non-hypertensive Akita$^{+/-}$ TTRhRen$^{-/-}$ controls developed hyperglycemia beginning at 6 wks of age, although Akita$^{+/-}$ TTRhRen$^{+/-}$ mice also developed increased blood pressure (151±4 vs. 91±1 mmHg), marked albuminuria (urine albumin excretion: 4114±1669 vs. 1197±246 ug/day), and an increase in serum creatinine (69±6 vs. 57±6 umol/L). Structurally, Akita$^{+/-}$ TTRhRen$^{+/-}$ mice displayed markedly increased glomerulosclerosis (glomerular picrosirius red (PSR) score: 0.56±0.11 vs. 0.37±0.06) and interstitial fibrosis (PSR intensity: 0.12±0.03 vs. 0.04±0.01) compared to their Akita$^{+/-}$ TTRhRen$^{-/-}$ controls. Fibrotic gene transcripts (COL1A1 and COL3A1) were also increased in Akita$^{+/-}$ TTRhRen$^{+/-}$ mice.

Conclusions: Taken together our results suggest that Akita$^{+/-}$ TTRhRen$^{+/-}$ mice recapitulate key features of human DN, including glomerular and interstitial fibrosis.

PUB248

Uric Acid and Hemodynamic Responses to Angiotensin II Infusion in Adolescents with T1D Compared to Adults with T1D for ≥ 50 Years Yuliya Lytvyn,[4] Julie A. Lovshin,[5] Genevieve Boulet,[5] Leif E. Lovblom,[5] Hillary A. Keenan,[1] Michael Brent,[6] Narinder Paul,[2] Vera Bril,[3] Bruce A. Perkins,[5] David Cherney.[4] *[1]Joslin Diabetes Center, Boston, MA; [2]Dept. of Medical Imaging, Div. of Cardiothoracic Radiology, University Health Network, Toronto, ON, Canada; [3]Dept. of Medicine, Div. of Neurology, University of Toronto, Toronto, ON, Canada; [4]Dept. of Medicine, Div. of Nephrology, Toronto General Hospital, University of Toronto, Toronto, ON, Canada; [5]Dept. of Medicine, Div. of Endocrinology and Metabolism, Mount Sinai-University Health Network, University of Toronto, Toronto, ON, Canada; [6]Dept. of Medicine, Dept. of Ophthalmology and Vision Sciences, University of Toronto, Toronto, ON, Canada.*

Background: Plasma uric acid (PUA) is associated with activation of the renin-angiotensin-aldosterone system (RAAS), promoting hypertension and kidney disease in patients with type 1 diabetes (T1D). Our aims were to (1) compare blood pressure and renal hemodynamic responses to RAAS activation by angiotensin II (ANGII) infusion in adolescents, young adults, and adults with ≥50 years of T1D, (2) determine if PUA levels modified these responses in such T1D cohorts and (3) study the effect of exogenous ANGII on PUA levels.

Methods: Blood pressure, PUA, GFR_{INULIN} and effective renal plasma flow ($ERPF_{PAH}$) were measured during clamped euglycemia in 28 T1D adolescents, 54 young T1D adults, and 59 adults with ≥50 years of T1D at baseline and after ANGII (3 ng kg^{-1} min^{-1}). Gomez's equations were used to estimate afferent (R_A) and efferent (R_E) arteriolar resistances and glomerular hydrostatic pressure (P_{GLO}).

Results: RAAS activation with ANGII was associated with significantly greater decreases in ERPF and in renal blood flow (RBF) and greater increases in renal vascular resistance (RVR), R_A, SBP, and DBP in adolescents and young adults with T1D compared to patients with ≥50 years T1D (Fig 1). Higher PUA correlated with attenuated increases in DBP in T1D adolescents (p=0.04). ANGII decreased PUA more in those with T1D >50 years vs. adolescent T1D (p=0.02).

Conclusions: Longstanding diabetes modifies the relationship between the RAAS and PUA, resulting in renal and systemic RAAS activation.

Funding: Private Foundation Support, Government Support - Non-U.S.

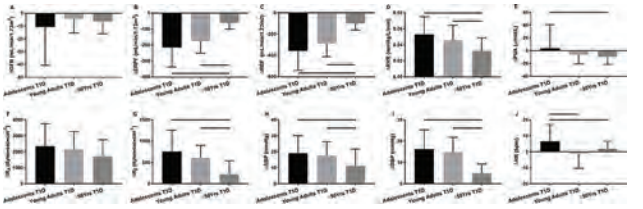


Figure 1. Changes in GFR (A), ERPF (B), RBF (C), RVR (D), plasma uric acid (PUA, E), R_A (F), R_E (G), SBP (H), DBP (I) and HR (J) in response to ANGII (3 ng kg^{-1} min^{-1}) in adolescents, young adults and patients with ≥50 years of T1D. Mean ± SD.

PUB249

Safety and Cost-Effectiveness of In-House Preparation and Centralized Distribution of Acid Dialysis Concentrate Paolo Lentini,[1] Luca Zanoli,[2] Antonio Granata,[3] Carlo Boccato,[4] Roberto Dell'Aquila.[1] *[1]St Bassiano Hospital ULSS 7 Pedemontana, Bassano del Grappa, Italy; [2]University of Catania, Catania, Italy; [3]None, Catania, Italy; [4]Consultant, Milano, Italy.*

Background: It is important to focus the effort of the caregivers on the activities able to generate the most favourable ratio of cost/benefit: during hemodialysis(HD), basic and acid concentrate are used. Making them available at the HD machine requires a considerable efforts in terms of workload and logistic. While basic concentrate is usually provided from a cartridge of dry bicarbonate, acid concentrate is supplied to the machine in a 5-ltr bag(Single-PatientDialysisDeliverySystem-SPDDS). However, the acid concentrate can be supplied to the HD machine via a CentralConcentrateDeliverySystem(CCDS).

Methods: We adopted, 1st Center in Italy, an automated CCDS(*GranumixPlus*®, Fresenius Med. Care-DE) based on a fully mixing unit that performs the dilution of a highly concentrated ingredient in HD water, and a storage and distribution unit that stores the concentrate and distributes it to the HD machines via a dedicated tubing that runs in parallel to the HD water distribution line. Here we evaluated the1-year safety, environmental impact and cost-efficacy ratio ofCCDS.[Fig.1]

Results: CCDS was used in75pts(85%), whereas SPDD was used in10pts that require peculiar treatments with personalized HD fluid composition.11000 treatments/year were performed with CCDS in our center. CCDS was associated with a reduction of staff work-load (avoided movement/management of 59180 kg of material), more space in our storehouse (avoided disposal of 11470 kg of plastic material and 7150 kg of concentrate residuals)and a big money saved ($27544), in absence of any clinical bath-related adverse events[Tab.1].

Conclusions: CCDS is a safe,"green"and cost-effective solution to simplify the preparation of the acid HD concentrate and can reduce costs, storage and transport of the bags and dialysis staff workload.

Fig. 1. CCDS System

* 11,000 treatments/year

	MATERIAL	QUANTITY	WEIGHT PER UNIT	TOTAL WEIGHT	COSTS FOR DISPOSAL
SINGLE USE BAG	CARTON BOX	~5.000	Kg 0,400	Kg 2.300	€ 5.400 ($5520)
	ACID CONCENTRATE RESIDUAL	11.000	~ Kg 0,650*	Kg 7.150**	€ 18.360,00 ($ 18752)
	PLASTIC	11.000	Kg 0,150	Kg 1.650	
	TOTAL PALLET	100	Kg 18	Kg 1.440	€ 900,00 ($ 920)

*Acid Bag: " 500ml+ 500 ml x 1,3 kg/dm³ specific weight = 650 g
** mean cost for disposal of waste (CER 180107/ITALY): € 2,20 ($2,40)

SAVING: €25.220 EURO($27.554) [Total dialysis Unit expense/year]

Tab. 1 Cost-Saving for the disposal of acid concentrate containers and residuals

PUB250

Changes in Biomarkers of Bone and Mineral Metabolism (BMM) Associated with Cross-Over Use of Citrate (CD) and Acetate (AD) Acidified Bicarbonate-Based Dialysates Ludmila Anderson,[1] Linda H. Ficociello,[1] Paul Balter,[2] Alice Topping,[2] Claudy Mullon,[1] Robert J. Kossmann.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Renal Research Institute, New York, NY.*

Background: Dialysates commonly contain acetate or citrate as the acidifying agent. This retrospective analysis of chronic hemodialysis (HD) patients who switched dialysate from AD to CD and back to AD, assessed changes in corrected serum calcium (CSC) and iPTH during these time periods.

Methods: Patients with AD treatment data for 3 months (baseline, [BL]), followed by CD for 9 months (Q1-Q3), and back to AD for 3 months (Q4) were analyzed. Mean pre-HD laboratory values were compared by quarters. Subanalyses were conducted by BL iPTH (<130, 130-600, >600 pg/ml). Changes in medications (Ca-based phosphate binders [CaPB], cinacalcet, in-center vitamin D [VitD]) were explored. Paired t-test, chi^2, α=.05 were used.

Results: Switching dialysate from AD to CD among patients with BL iPTH <= 600 pg/ml was associated with increase in pre-HD iPTH at Q1 that leveled off at Q2-Q3. Among patients with BL iPTH > 600 pg/ml, iPTH decreased (BL: 1,044.1 vs. Q3: 835.3 pg/ml). Switching dialysate from CD to AD was not associated with changes in iPTH. Minor changes in CSC followed AD to CD, and CD to AD, switches (Table). From BL to Q4, % of patients treated with CaPB (32% vs. 34%, p=1.0) and cinacalcet (46% vs. 51%, p=0.7) remained similar, and in-center VitD use increased from 71% to 78% (p<.001).

Conclusions: Clinically modest changes in iPTH and CSC followed AD to CD, and CD to AD, conversion. Patients with BL iPTH <= 600 pg/ml had mean iPTH increase in Q1 and level off at Q2-Q3, and patients with BL iPTH > 600 pg/ml had mean iPTH decrease.

Funding: Commercial Support - Fresenius Medical Care North America

iPTH (pg/ml) CSC (mg/dl)		BL (AD)	Q1	Q2	Q3	Q4
All Patients n=158 Change from prior quarter	iPTH	499.2	541.2 +42.0*	547.6 +6.4	551.6 +4.1	552.2 +0.5
	CSC	8.8	8.7 -0.15*	8.7 +0.04	8.7 -0.06	8.7 +0.17*
BL iPTH < 130 n=9 Change from prior quarter	iPTH	76.2	154.9 +78.7	191.3 +36.4	207.4 +16.2	229.7 +22.2
	CSC	9.0	8.6 -0.4*	8.8 +0.3	8.8 -0.03	8.8 +0.02
BL iPTH 130-600 n=112 Change from prior quarter	iPTH	353.1	411.7 +58.5*	452.6 +40.9*	485.5 +32.9	464.2 -21.3
	CSC	8.9	8.8 -0.14*	8.8 0	8.7 -0.07	8.7 +0.16*
BL iPTH > 600 n=37 Change from prior quarter	iPTH	1,044.1	1,027.2 -16.9	921.6 -105.5	835.3 -86.3	896.7 +61.3
	CSC	8.6	8.5 -0.1	8.6 +0.09	8.5 -0.06	8.5 +0.24*

* p-value < .05 for the change

PUB251

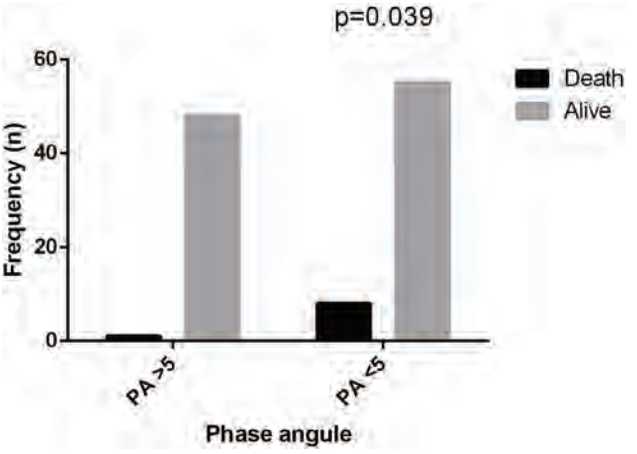
Phase Angle Is Associated with All-Cause Mortality but No Hospitalization in a Cohort of Hemodialysis Patients Javier Soto-Vargas,[1] Anel V. Barbarín vázquez,[2] Sandra L. Báez lópez,[2] Carlos alberto López lozano,[2] Miriam G. Nuño radillo,[2] Itziri P. Preciado,[2] Jesemil Navarro rodríguez,[2] Jorge fernando Topete reyes.[1] *[1]Nephrology, Regional General Hosptial 46, Mexican Institute of Social Security, Guadalajara, Mexico, Guadalajara, Mexico; [2]Clinical Nutrition, Guadalajara University, Guadalajara, Mexico.*

Background: The bioimpedance phase angle (PA) has been associated as a measure of nutritional status in maintenance hemodialysis (MHD) patients. Their relationship with hospitalization and mortality is less well stablished. Our objective is to determine the association between PA and hospitalizations and all-cause mortality in a cohort of MHD patients.

Methods: We included 121 patients in this prospective observational study. The median follow up were 24.9 months (IQR 16.2-34.1). During the follow there were lost 7 (5.8%) patients, because their denial to continue to participate. The PA was measured every 12 weeks in the day between sessions, as well and number and diagnosis of hospitalizations. For all the patients we collected HD session characteristics, demographics and relevant comorbids.

Results: There were a male predominance (60.3%). The mean age was 41 years (IQR 28.2-58.0). The media PA for trimester was 4.8±1.28, 5.1±1.31, 5.3±1.2, 5.2±1.18 and 5.2±1.16. One hundred twelve patients completed one evaluation, 89 two evaluations, 61 three evaluations, 51 four evaluations and only 33 five evaluations. There were 9 (7.4%) deaths and 26 (21.6%) patients were hospitalized during the study, 15 (12.4%) had two or more hospitalizations. The age and initial PA, were associated with mortality (p=0.036, 0.004 respectively). After adjusting for age, the PA <5 remained associated with increased risk of death (RR 1.66 CI 95% 1.24-2.23, p=0.039). The patients with PA <5 were more frequent female, and older (p<0.001 and <0.001 respectively). The change in PA values between evaluations had no impact on mortality.

Conclusions: The bioimpedance PA <5 is associated with an increased risk of death, but no with hospitalization in MHD patients.



PA <5 patients had a higher risk for all-cause death.

PUB252

ESRD and the Risk of Admissions for Recurrent Gastrointestinal Bleeding (GIB): Quality Improvement (QI) Ahmad Anjak,[3,4] Nicole Piero,[1] Charuhas V. Thakar.[2] *[1]Cincinnati VA, Cincinnati, AL; [2]University of Cincinnati, Cincinnati, OH; [3]University of cincinnati, Cincinnati, OH; [4]Cincinnati VA Hospital, Cincinnati, OH.*

Background: ESRD patients face a high risk of readmissions. GI bleed is life-threatening complication in ESRD patients; with the risk of bleeding up to 3-5 folds as compared to non-chronic kidney disease (CKD) patients. Our study aim was to evaluate the characteristics of ESRD patients experiencing GI bleed, including recurrence.

Methods: As a part of QI project, we assessed admissions under renal consult services in ESRD patients admitted to our VA facility from July –December 2016. Clinical operational data included: patients age, cause of ESRD, type of dialysis access, the source of GI bleed, the cause of GI bleed, endoscopy results and intervention, blood products requirement, anticoagulation use with hemodialysis, the use of antiplatelet and proton pump inhibitors (PPI), recurrence of GI bleed, and length of time till recurrence.

Results: During 6 months, there were 50 ESRD patients experiencing 64 admissions. Six patients with ESRD had 10 encounters with GI bleed in the 6 months period, 4 of the 6 patients had recurrent GI bleed, Three patients were diagnosed with arteriovenous malformation (AVM) as the cause of GI bleed, one with polyps and one with gastritis and one the cause of GI bleed was unknown. All patients with AVM had severe acute blood loss that needed blood transfusions, and all of them needed one or more interventions with endoscopy, all patients with AVM had recurrence of GI bleeding. The time for recurrence ranged from 1 to 3 months, recurrence occurred despite PPI use. 2 of the AVM patients also had arterio venous graft as their access, and one with tunneled catheter.

Conclusions: ESRD patients with GI bleed experience frequent recurrence. AVM as the cause of GI bleed had 100% recurrence within 30-90 days. These patients also experienced severe bleeds requiring treatment, and PPI did not reduced the risk of recurrence. Cause of AVM related bleeds in ESRD and prevention of recurrent bleeding need larger studies.

PUB253

Is the Association between Vascular Access by Catheter and Mortality in Incident Hemodialysis Patients Confounded by Sociodemographics and Comorbidities? Marcia T. Martins,[1] Marcelo B. Lopes,[2] Gildete B. Lopes,[2] Antonio A. Lopes.[2] *[1]CLINIRIM, Salvador, Brazil; [2]Federal University of Bahia, Salvador, Brazil.*

Background: Compared with access by arteriovenous fistula (AVF), access of hemodialysis (HD) by catheter for end-stage kidney disease patients has been associated with older age, greater prevalence of comorbidities and higher mortality. The present study investigated if the reported higher mortality in patients receiving HD by venous catheter than AVF could be explained by age, other sociodemographic factors and comorbidities.

Methods: The data are from a propective cohort (PROHEMO) of 421 incident HD patients treated in 4 units of Salvador, BA, Brazil. All patients were on HD for < 6 months (72% < 3 mo). To estimate hazard ratio (HR), Cox's proportional hazard models with cumulative covariate adjustments were used.

Results: Mean age was 51.0±14.9 yr. HD was performed by fistula for 119 and catheter for 302 patients. During a mean follow-up of 2.5 years, 31 deaths occurred in patients with HD by fistula (death rate=8.37/100 person-years) and 99 in patients with HD by catheter (death rate=14.73/100 person-years). The etiologic fraction of death attributed to catheter was 43.2% [(14.73-8.37)/14.73]; 95% confidence interval = 14.1%, 63.3%. The adjusted HRs of death associated with HD by catheter are shown in the Table.

Conclusions: The results of this cohort of incident HD patients add strong support against the use of catheter for vascular access. As shown the association of catheter with higher mortality was only slightly reduced after adjustments for numerous risk factors of death, including age and comorbidities.

Funding: Government Support - Non-U.S.

ADJUSTED HAZARD RATIOS OF DEATH ASSOCIATED WITH HEMODIALYSIS BY CATHETER

ADJUSTED MODELS	HAZARD RATIO (95% CI)	P VALUE
Model 1	2.02 (1.33, 3.09)	0.001
Model 2	1.97 (1.27, 3.05)	0.003
Model 3	1.87 (1.18, 2.98)	0.008

CI = confidence interval; Model 1: Adjusted for age (continuous), sex, race (non-white vs white), economic class (poor/very poor vs higher), education, marital status, living with family, private health insurance and months on dialysis; Model 2: Adjusted for heart failure, ischemic heart disease, cerebrovascular disease, hypertension, diabetes, peripheral vascular disease, cancer, plus variables and model 1; Model 3: Adjusted for hemoglobin, leucocyte count, ferritin, albumin plus variables in model 2.

PUB254

Subclinical Hypothyroidism and Its Associations Observed in ESRD Patients in a Tertiary Care Hospital Sidra Saleem,[1] Syed A. Khalid,[1] Fouzia Ashraf,[2] Syed Rizwan A. Bokhari,[3] Amna Riaz,[4] Shafiq Cheema,[1] Hafiz I. Ahmad.[1] *[1]Nephrology, Allama Iqbal Medical College/Jinnah hospital, Lahore, Pakistan; [2]Pathology, Allama Iqbal Medical College/Jinnah hospital, Lahore, Pakistan; [3]Department of Nephrology and Hypertension, Tulane University, New Orleans, New Orleans, LA; [4]Endocrinology, Allama Iqbal Medical College/Jinnah hospital, Lahore, Pakistan.*

Background: Chronic kidney disease (CKD) has been known to affect thyroid hormone metabolism. End stage renal disease (ESRD) and Subclinical Hypothyroidism (SCH) are independent risk factors for cardiovascular disease (CVD) mortality. There is paucity of data regarding SCH prevalence in patients with ESRD in developing countries. We aimed to study the prevalence of SCH in our ESRD population and its correlation with patient demographics.

Methods: We enrolled all 112 ESRD patients on maintenance hemodialysis at the dialysis center of Jinnah Hospital Lahore. Thyroid function tests were performed on early morning venous samples (fasting) of all patients. Subclinical hypothyroidism (SCH) was labeled when the serum thyroid-stimulating hormone (TSH) level was high (range: 4.2-10 mIU/ml) but the corresponding serum-free thyroxine (FT_4) level was within normal limits (range: 0.93-1.7ng/dl).

Results: The mean age of the patients was 42 ± 10.86 years (range 24-60 years) and 74 (66.1%) were males. The mean duration of ESRD was 4.46 ± 1.42 years (range 1-8 years). SCH was present in 12 (10.7%) of these patients. The mean T3 and T4 values were observed to be 0.246 ± 0.072 ng/dl (range 0.04-0.49 ng/dl) and 1.05 ± 0.25 ng/dl (range 0.4-1.8 ng/dl) respectively. The mean TSH value was 2.60±4.81 mIU/L (range 0.10-40.80 mIU/L). Of these 12 patients with SCH, significant association was found between gender and presence of SCH with p-value 0.011. Eight (67%) patients were females. No significant association of SCH was found between age group and duration of ESRD (p-value 0.186 and 0.287 respectively).

Conclusions: SCH was observed in a small (10.7%) number of ESRD patients in our study and was more prevalent in females. All other variables had no significant association with the presence of SCH. Our study underscores the need to explore the correlation in terms of etiology of SCH in patients with ESRD. Treating these ESRD patients with SCH can improve their morbidity and mortality.

PUB255

Teaching Thinking of Continuing Education in the Implementation of the Integrated Management of Medicine, Nurse, and Technology for Hemodialysis Specialized Nurses Hua Liu,[2] Hongli Jiang.[1] *[1]Dialysis Center of First Affiliated Hospital of Medicine School, Xi?an Jiaotong University, Xi'an, Shaanxi, China; [2]First Affiliated Hospital of Medical College of Xi'an Jiaotong University, Xi'an, China.*

Background: In order to provide good quality service and achieve continuous improvement of medical quality, we carry out the integrated management of medicine, nurse and technology in the department of blood purification of the first affiliated hospital of Xi'an Jiaotong university in 2016. In this paper we discuss the influence factors and methods of the continuing education in integrated management of medicine, nurse and technology for hemodialysis specialist nurses.

Methods: With the problems of daily work and planning training in the implementation of the integrated management of medicine, nurse and technology and the planning training in department, such as, insufficient understanding of their own value, lack of professional knowledge, professional knowledge, scientific research consciousness and communication with patients, and neglect of basic nursing care outside specialist care, etc., we analyzed the influencing factors and methods in the teaching process of continuing education for hemodialysis specialist nurse.

Results: The influencing factors and improvement methods of the continuing education of dialysis specialist nurses include two aspects. The first is nurses' subjective influencing factors which focus on improving the nursing staff's own value awareness level and professional thought training, the function of nursing staff in the quality control system of staff participation, constantly playing subjective initiative, self-learning, improving professional ability knowledge, and their own value and improve the comprehensive quality. The second is continuing education development connotation which focus on the standardized training of basic nursing, professional skills, patients' health education and scientific research consciousness, and the improvement of teaching new methods, active acquisition of knowledge, the ability to analyze problems, solve problems, team collaboration, logical reasoning, literature retrieval, comprehensive evaluation, and communication and expression skills.

Conclusions: In the implementation of the integrated management of blood purification, nurses play an important role, involving all aspects of clinical quality management, we should give improve their quality, and finally implement the continuous improvement of clinical medical quality.

PUB256

The Use of Indices of Volume Status to Predict the Incidence and Severity of Sleep Disordered Breathing in Hemodialysis Patients Matthew C. Breeggemann,[3] Mark S. Bilodeau,[1] William T. Donnelly,[1] James Leiter.[2] *[1]Dartmouth College, Hanover, NH; [2]Dartmouth Medical School, Hanover, NH; [3]Dartmouth-Hitchcock Medical Center, Lebanon, NH.*

Background: Sleep disordered breathing (SDB) is a prevalent condition resulting in a considerable increase in cardiovascular related death (Mooe et al., 2001). Patients with chronic kidney disease (CKD) are known to be at an increased risk for the development of SDB, including obstructive sleep apnea (OSA), for reasons that are not entirely clear (Kimmel et al., 1989). Given the already elevated cardiovascular related morbidity that patients with CKD face, it is especially important to diagnose and treat SDB in this patient population. Defining the predictors of high risk for OSA in patients with CKD would facilitate diagnosis and treatment of OSA. The purpose of this study is to evaluate a variety of physiological factors accessible during hemodialysis to determine which of these factors is most closely associated with incidence and severity of OSA.

Methods: Participants were provided with the Watch-PAT200U Device (Itamar Medical) to assess the occurrence of apneic and hypoxic events. This device can be used to measure the respiratory disturbance index (RDI) during sleep at home. A SFB7 multi-frequency bioelectrical impedance analyzer/monitor from ImpediMed was used to measure changes in tissue water content before, during, and after hemodialysis. This allowed for objective measures of volume status in each patient in order to make indirect assessments of intravascular volume based on changes in the hematocrit during hemodialysis.

Results: All of the patients (n=5) studied have demonstrated evidence of SDB by calculated apnea-hypopnea indices (average AHI=28.50). The average AHI was higher when assessing data from Sunday nights alone (39.75). There were similar findings with oxygen desaturation indices (19.37 vs. 26.95, respectively). Weights above estimated dry weight were slightly higher on Mondays prior to hemodialysis when compared with weekly averages (2.30 vs. 2.15 kg).

Conclusions: This data supports prior findings that CKD patients are at an increased risk for SDB. Initial data from this study demonstrates that apneic and oxygen desaturation events are higher on Sunday nights, supporting the hypothesis that volume overload and potential soft tissue edema of the upper airways may be at play. Further data collection of volume status for correlation with SDB using bioelectrical impedance is underway.

Funding: Private Foundation Support

PUB257

Effect of Anti-HCV Positivity on Nutritional Status and Albumin of Hemodialysis Patients Shafiq Cheema,[2] Faheem U. Sulehri.[1] *[1]Jinnah Hospital Lahore., Lahore, Pakistan; [2]Nephrology & Hypertension, Allama Iqbal Medical College, Lahore, Pakistan.*

Background: Hypoalbuminemia predicts mortality in hemodialysis patients and is assumed to result from malnutrition. The effect of anti-HCV positivity on nutritional status and hence albumin of end stage renal disease (ESRD) patients on hemodialysis (HD) is controversial. We analyzed the effect of anti-HCV positivity on serum albumin among patients with ESRD undergoing maintenance hemodialysis

Methods: All stable HD patients in our dialysis center were included. Thirty five (35) out of 128 total patients were positive for anti-HCV antibody. This included the patients with untreated active disease (positive HCV RNA) and early cirrhosis as well. Patients with decompensated liver disease were excluded. The following lab data was collected for the last 12 months, 1/1/16 till 12/31/2016, among both groups: serum albumin, calcium, phosphorus, parathyroid hormone, uric acid, URR and hemoglobulin. The differences were compared between both groups.

Results: Mean age was 51.8 years in HCV positive group and 47.2 in control group. Similarly the duration on maintenace hemodialysis was 35.6 months and 29.3 months in HCV positive and control group respectively. These differences were not significant We found statistically significant difference in serum albumin and hemoglobin level between hepatitis C positive and control groups, but the difference was non-significant in serum calcium, phosphorus, uric acid, URR and parathyroid hormone level between two groups. Mean albumin in anti-HCV positive patients was 3.55 grams /dl and in control group was 3.77 grams/dl with *p* value of 0.055. Mean hemoglobin in anti-HCV positive patients was 10.62 grams/dl and in control group is 10.02 grams/dl with *p* value of 0.043.

Conclusions: Anti-HCV positivity is associated with low serum albumin and malnutrition in ESRD patient undergoing hemodialysis. The cause of higher hemoglobulin in this group was not clear. This could be attributed to higher dosages of erythropoietin and iron used in this group.

PUB258

The Aggressiveness in Patients with Chronic Renal Failure Tomasz J. Irzyniec.[1,2] *[1]Dept. of Health Promotion and Community Nursing, Medical University of Silesia, Faculty of Health Sciences, Katowice, Poland; [2]Dept. Nephrology/ENDO, MSW i A Hospital, Katowice, Poland. Group/Team: Warchulska-Giergielewicz Team.*

Background: The aggressiveness is perceived as the feature of functioning a clearly evident predisposition to aggression. Its diversity depends on personal and situational factors. The aim was to assess the level of aggressiveness in uremic patients (CRF) and determine risk factors of aggressive behaviors.

Methods: The acceptance of illness, life satisfaction, control of emotions, depression and pain as well as total aggressiveness were examined using psychological tests and scales in 50 non-dialyzed–ND (59±16y) and 100 hemodialyzed-HD (62±14y) patients. The study attempted to select personal, clinical and biochemical features, which apply to patients with aggressiveness higher than the average (AHA) for the general population.

Results: CRF-patients characterized: the mean acceptance of the disease and life satisfaction, higher than the average control of emotions, occurrence of depression and chronic pain. The aggressiveness was similar to observed in general population. HD differed from ND in less percentage of people with depression (41% vs 64% p=0.004), occurrence of pain (38% vs 60% p<0.05) and physical aggression (16±5 vs 20±7pt p<0.007). Women differed from men in an occurrence of pain (ND-79% vs 42% p=0.004), lower suppression of anxiety (HD-20±6 vs 23±5pt p=0.002), greater acceptance of illness (ND-26±11 vs 21±10pt p=0.015 and HD-27±9 vs 21±11pt p=0.038) and less physical aggression (HD-17±5 vs 15±4pt p=0.008). ND with AHA differed from others: in age (45±13 vs 63±15y p<0.001), higher percentages of university educated (46% vs 13.5% p=0.007) and married (38% vs 16% p=0.049), absence of apathy and incidents of nausea and vomiting. A lower concentration of sodium (137±4 vs 141±4 mM/L p<0.001) was observed. HD with AHA differed from others: in percentages of men (75% vs 52%, p=0.035), married (50% vs 30% p=0.046) and time of dialysis (4±4 vs 6±7y p=0.007). They more frequently suffered from a headache (45% vs 20% p=0.02). A lower acceptance of illness (17±9 vs 25±10pt p=0.003) was also a differentiating parameter.

Conclusions: 1.The aggressiveness of uremic patients is not higher than observed among general population 2.The progression of renal insufficiency and implementation of hemodialysis lead to the reduction of aggressive behavior 3.The lower acceptance of the illness differs dialyzed patients with aggressiveness higher than the average from the others.

PUB259

Cardiovascular Autonomic Control during Early Hemodialysis Predicts Hospitalized Cardiovascular Events in Renal Failure Patients Chih-chin Kao.[1,2] *[1]Taipei Medical University Hospital, Taipei, Taiwan; [2]Taipei Medical University, Taipei, Taiwan.*

Background: Labile blood pressure (BP) was associated with increased risk of cardiovascular (CV) mortality. However, the relationship of continuous dynamics of cardiac function during hemodialysis and hospitalized CV events is not known well.

Methods: We enrolled renal failure patients who received chronic hemodialysis in Taipei Medical University Hospital. Each participant received continuous hemodynamic variability exam using ICON® (Osypka Medical. Inc, USA) during hemodialysis. The "beat-to-beat" hemodynamic parameters [heart rate (HR), stroke volume (SV), cardiac output (CO), and systemic vascular resistance index (SVRI)] were recorded. We prospectively followed these patients until the occurrence of hospitalized CV events or the end of study in May, 2017. Analysis was done by hourly basis and several approaches were carried out to explore the dynamical changes of these parameters.

Results: A total of 35 patients were included and the mean age was 57±14 years and 24 (68.6%) were male. 15 patients developed hospitalized CV events (study group), including congestive heart failure (n=5), coronary artery disease (n=8), stroke (n=1), and peripheral arterial occlusive disease (n=1). Patients with hospitalized CV events were compared to those without CV events (control group). There was significant difference in the 2nd, 3rd and 4th hourly averaged coefficient variance (standard deviation/mean) of HR between groups. No significant differences were found in hourly averaged SV, CO, and SVRI. The differences between 2nd and 1st hour coefficient variance of SV and CO was significantly higher in the control group as compared to the study group. **(Figure 1)**

Conclusions: The higher averaged coefficient variance of HR in the 2nd, 3rd, and 4th hour; and the increase of coefficient variance of SV and CO in the early hours of hemodialysis have predictive value for lower hospitalized CV events, which implies that chronic dialysis patients who have better autonomic control system may have better CV outcome.

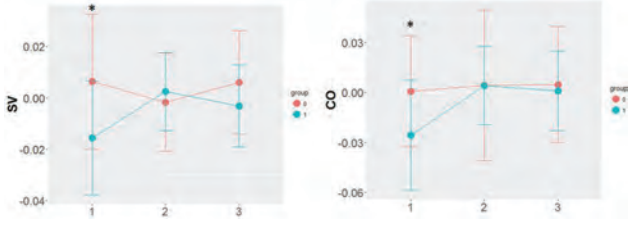


Figure 1. The differences of average [2nd-1st hour (1)], [3rd-2nd hour (2)], and [4th-3rd hour (3)] coefficient variance of SV and CO between groups.(control: 0, study: 1)

PUB260

Associations between Number of Vascular Access Providers by Geography and Catheter Rates Hao Han,[1] Sheetal Chaudhuri,[1] Tommy C. Blanchard,[1] Marta Reviriego-Mendoza,[1] John W. Larkin,[1] Elsie Koh,[2] Murat Sor,[2] Len A. Usvyat,[1] Peter Kotanko,[3] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Fresenius Vascular Care, Malvern, PA; [3]Renal Research Institute, New York, NY.*

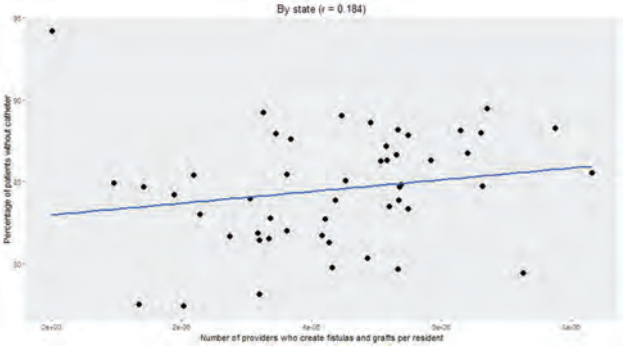
Background: The rates of central venous catheter (CVC) use in hemodialysis (HD) patients has been relatively unaltered over the last decade. In 2016, the United States Renal Data System estimated that about 68% of incident HD patients utilize a CVC at 90 days after starting HD, and approximately 20% of patients never transition to a permanent vascular access. We aimed to study the association between the numbers of vascular access providers in a state versus the catheter rate of patients by state.

Methods: We used publically available 2014 Medicare Provider Utilization and Payment Data to determine vascular access providers who create fistulas and grafts by state. Population data for each state was gathered from 2010 Census data. To perform the analysis a new metric called "Number of Providers/Population" was created. Number of Providers who created fistulas and grafts per resident was correlated to the percentage of patients without a catheter in Fresenius Kidney Care clinics within each respective state.

Results: We found a positive correlation between the number of vascular access providers per resident who create fistulas and grafts to the percentage of patients without a catheter.

Conclusions: Out findings suggest that having access to more vascular access providers has a positive influence on catheter rates in patients. Additional studies are necessary to confirm this observation.

Funding: Commercial Support - Fresenius Medical Care North America



PUB261

Hyperkalemia and Hospitalization Rates in Hemodialysis Patients Sophia Rosen, Marta Reviriego-Mendoza, John W. Larkin, Len A. Usvyat, Jeffrey L. Hymes, Franklin W. Maddux. *Fresenius Medical Care, Waltham, MA.*

Background: Serum potassium (K) levels are important predictors of patient outcomes in dialysis patients. While its association with mortality is well described, the relationship to hospital admissions has not been elucidated. Several methods for detecting elevated K levels include measuring mean K levels over a period of time, and assessing excursions of K levels. We aim to investigate the distribution of K levels in a large cohort of dialysis patients and its relationship to hospital admissions.

Methods: We analyzed all active patients dialyzed in the network of Fresenius Medical Care North America clinics as of Dec 31, 2015, and who were being treated in the clinics for >=6 months. Only patients who had more than six serum K levels were included in this six month analysis and ending on Dec 31, 2015. Hospital admissions data was tracked for six months after Jan 1, 2016.

Results: We analyzed data on 127,213 dialysis patients: 380 patients (0.3%) had a mean K<3.5mmol/L, 115,768 patients (91%) had a mean K>=3.5 to 5.5mmol/L, 9,707 patients (8%) had a mean K>=5.5 to 6 mmol/L, and 1,358 patients (0.7%) had a mean K>=6 mmol/L. Excursions to K>=5.5 mmol/L were more common than mean elevated K levels: 39% of patients had at least one K lab draw>=5.5 mmol/L during a six months observation period. Poisson regression models were used to compare hospital admissions and hospital days rate per patient year. Both hospital admissions and hospital days rate showed a U-shaped relationship to serum K levels, and are lowest in patients with serum K levels of 3.5 to 5.5mmol/L.

Conclusions: In this analysis we observe that, while sustained elevated serum K levels are relatively uncommon in dialysis patients, excursions to serum K levels>=5.5mmol/L are still prevalent, and impact hospitalization rates and days of stay.

Funding: Commercial Support - Fresenius

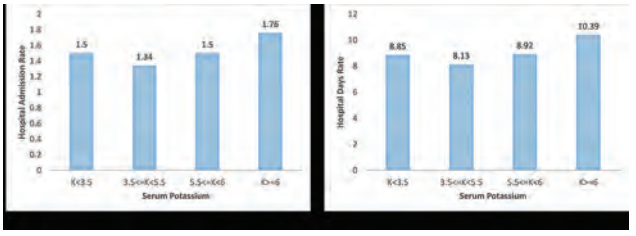


Figure 1. Mean Serum Potassium Levels and Hospitalization Rates

PUB262

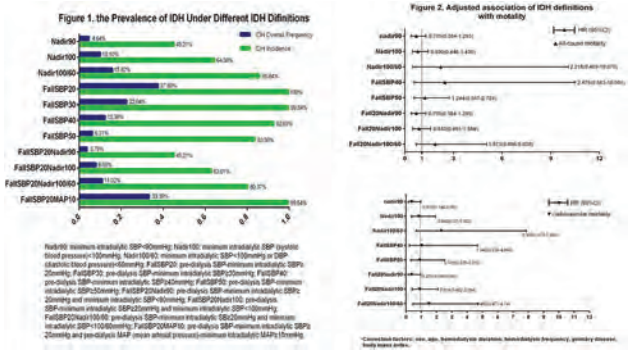
The Prevalence of Intradialytic Hypotension under Different Diagnostic Criteria and the Association with Mortality Zhiyu Wang,[1] Zijin 1. Chen,[1] Zuanhong Jiang,[2] Xiaonong Chen.[2] *[1]Dapartment of Nephrology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China; [2]Division of Nephrology, Division of Nephrology, Ruijin Hospital, Shanghai Jiao Tong University, Shanghai, China, Shanghai, China.*

Background: Intradialytic hypotension (IDH) is one of the common complications during hemodialysis, however its diagnostic criteria are highly controversial. To fully understand the prevalence of IDH in our center and figure out which diagnostic criteria is better for Chinese maintenance hemodialysis (MHD) patients, we choose several IDH definitions and analyze their association with mortality.

Methods: The patients were recruited from Blood Purification Center of Ruijin Hospital undergoing hemodialysis during July 2012. Pre-, intra- and post-dialysis blood pressure were recorded. Patients' clinical characteristics, laboratory results and cardiac ultrasound results were collected. SPSS 23.0 was used to analyze data and conduct survival analysis.

Results: Totally 219 MHD patients underwent 16084 hemodialysis in 6 months. The prevalence rate, overall and individual frequency of IDH fluctuates greatly. For every IDH criteria, the patients was divided into the group IDH(+) and the group IDH(-). Survival analysis found that IDH (an absolute systolic blood pressure (SBP) < 90 mmHg or with a decrease of SBP≥ 20 mmHg) can decrease the risk of patients' cardiovascular mortality but wasn't relevant to all-cause mortality. Further analysis showed these patients had better cardiac functions mainly reflecting in lower Pro-BNP, lower prevalence rate of left ventricular hypertrophy and higher left ventricular ejection fraction than IDH(-) patients. No correlation was found between other IDH criteria and mortality.

Conclusions: The prevalence rate, overall and individual IDH frequency of IDH are of high variability when diagnosed by different IDH criterias. All IDH episodes defined by our selected definitions are of no association with all-cause mortality. An absolute SBP< 90 mmHg or with a decrease of SBP≥ 20 mmHg can decrease the risk of cardiovascular mortality due to their better cardiac function. Large scale researches should be conducted to find optimal IDH definition and explore the association of IDH and mortality.



PUB263

Evaluation of Three Hemodialysis Filters and Their Impact on Kt/V and Anti-Xa Activity in Chronic Hemodialysis Patients Hemodialyzed with Tinzaparin, a Low Molecular Weight Heparin Robert Z. Bell,[1] Michel Korkemaz,[2] Pierre Cartier,[4] Michel Vallee,[4] Naoual Elftouh.[3] *[1]Centre de recherche Hopital Maisonneuve-Rosemont, St. Lambert, QC, Canada; [2]Centre intégré de santé et de services sociaux des Laurentides, Saint-Eustache, QC, Canada; [3]Hôpital Maisonneuve Rosemont, Montreal, QC, Canada; [4]None, Montreal, QC, Canada.*

Background: Optimal usage of anticoagulant in chronic hemodialysis is fundamental in order to prevent catheter dysfunction and ensure adequate dialysis efficacy and safety. We recently switched all our patients from unfractionned heparin to tinzaparin, a low molecular weight heparin, and observed that the type of hemodialysis filter (Phylter 20 and 22) had a substantial impact on the dosage requirement of the low molecular weight heparin. Currently, there are no studies quantifying the impact of a specific hemodialysis filter type on the efficacy and safety of tinzaparin.

Methods: We conducted a subgroup analysis to determine the impact of three different hemodialysis filters on Kt/V and Anti-Xa measurements. Ten patients were hemodialysed with three different hemodialysis filters (Phylter 20 or 22, Revaclear MAX and FX 1000) for six consecutive hemodialysis sessions. The tinzaparin dosage remained the same during the evaluation of the different filters. Primary outcome was the impact of the filter type on Kt/V (efficacy) and the secondary outcome was anti-Xa activity (safety) during the HD session.

Results: The mean Kt/V was 1.30, 1.29 and 1.42 for Phylter 20 or 22, Revaclear Max and FX 1000 respectively. Anti-Xa activity is statistically higher with the FX 1000 (0.42 UI/ml) versus the Phylter 20/22 (0.33 UI/ml) and Revaclear MAX (0.34 UI/ml).

Conclusions: These preliminary results demonstrate that the type of hemodialysis filter used may have a significant impact on the efficacy and safety in regards to the type of anticoagulant that is used for hemodialysis. The data suggests that the FX 1000 filter was the most efficient filter type. We obtained the highest Kt/V (1.42) and anti-Xa activity with the FX 1000 filter. Further evaluations with a larger cohort of patients are warranted to validate our findings. This was an unsponsored study.

PUB264

Correlation of Pulmonary Hypertension with Vitamin D Deficiency in ESRD Patients Firoozeh Farahmand. *Richmond Heights, MO.*

Background: Data regarding incidence of pulmonary hypertension (PH) and its mechanisms in ESRD are scarce. PH is a devastating disease without a cure. Studies suggest oxidative stress as a mediator of PH. Vitamin D is a membrane antioxidant. Low serum vitamin D also stimulates the renin–angiotensin–aldosterone system (RAAS) resulting in vasoconstriction. The aims of this study were to evaluate the incidence of PH among patients with ESRD and its correlation with vitamin D.

Methods: A retrospective cohort of PH in ESRD patients treated with HD for at least 3 months followed in a dialysis unit. Patients without vitamin D assessment were excluded. Subject characteristics were recorded, including age, gender and race. PH was defined as an estimated systolic pulmonary artery pressure (PAP) higher than 25 mm Hg using echocardiograms performed by cardiologist.

Results: A total of 100 HD patients were included in the study. The mean of age of our patients was 59±11.4 years. The mean duration of HD was 28± 14 months. The mean ejection fraction was 45±7%. The prevalence of PHT was 51%. 59% of patients with PH were female that was statisticaly ($p<0.05$). 70% of patients with PH had a 25(OH)D level <30ng/ml ($p<0.05$).

Conclusions: Our findings demonstrate high incidence of PH among ESRD patients under maintenance HD and it is strong association with Suboptimal vitamin D. Further investigations are required to evaluate the beneficial effects of cholecalciferol in PH in ESRD patients.

PUB265

The Clinical Significance of Hyperparathyroidism Detected by Ultrasonography in Hemodialysis Patients and Analysis of Related Factors Zijin Chen,[2] Zuanhong Jiang,[3] Zhiyu Wang,[4] Xiaonong Chen.[1] *[1]Nephrology Department, Ruijin Hospital affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China; [2]Ruijin Hospital affiliated to Shanghai Jiaotong University, Shanghai, China; [3]Shanghai jiaotong university, Shanghai, China; [4]Dapartment of Nephrology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.*

Background: Analysis the prevalence of hyperparathyroidism detected by ultrasonography in hemodialysis patients. Combined with clinical characteristics, analysis of related factors of hyperparathyroidism, and invest the value of intact parathyroid hormone(iPTH) as a predictor of parathyroid hyperplasia.

Methods: Maintenance hemodialysis (MHD) patients were treated in Ruijin Hospital affiliated to Shanghai Jiaotong University School of Medicine in July 1st, 2015 to Dec 31th, 2015. All clinical data, sex, primary disease, dialysis vintage, biochemical data and medication were collected at baseline. Parathyroid hyperplasia was detected by Philips iE33 color Doppler sonography system (transducer with frequency 11 MHz).

Results: Totally 96 MHD patients were enrolled in this study from July 2015 to Dec 2015. Among 96 MHD patients, 54 (57.3%) patients had parathyroid hyperplasia detected by ultrasonography, including 41 (42.7%) patients with left parathyroid hyperplasia and 44(45.8%) patients with right parathyroid hyperplasia. 29 (30.2%) patients had both parathyroid hyperplasia. The prevalence of parathyroid hyperplasia in patients with dialysis vintage <36 months, 36~72months and ≥72months was 34.6%, 54.5% and 68.8%, respectively. Significant difference was between three groups (χ^2=0.018,P=0.018). Compare parathyroid hyperplasia group (n=54) and no parathyroid hyperplasia group (n=42), there was significant difference in dialysis vintage(t=-3.507,P=0.001), serum phosphorus(t=-2.591,P=0.011), intact parathyroid hormone (iPTH)(Z=-4.328,P<0.001) and active Vitamin D treatment(χ^2=11.197,P=0.001). Receiver operating characteristic(ROC) curve showed that iPTH level could predict parathyroid hyperplasia (AUC=0.758,P<0.001,95%CI 0.661-0.855). When iPTH level was over 456.9 pg/ml, the sensitivity and specificity of ultrasonography were 57.4% and 88.1%, respectively.</p>

Conclusions: Parathyroid hyperplasia is one of the common complications in uremic patients. Ultrasonography is one of the effective methods to evaluate the parathyroid gland size. Longer dialysis vintage, higher iPTH level, hyperphosphatemia and active vitamin D treatment are associated with parathyroid hyperplasia. When iPTH > 400pg/ml, it is recommended to evaluate parathyroid hyperplasia by routine parathyroid ultrasonography.

PUB266

A Case of Chronic Cerebral Edema with Recurrent Dialysis Disequilibrium Ugochi A. Osborn, Chinonye C. Ogbonnaya-Odor. *University of Texas Houston, Pearland, TX.*

Background: Introduction Dialysis disequilibrium syndrome can be defined as symptoms occurring during or after intermittent hemodialysis as a result of cerebral edema and increased intracranial pressure. The exact mechanism is unknown. However patients at risk for acute cerebral edema include patients with hepatic encephalopathy, strokes, patients with elevated BUN, hyponatremia, malignant hypertension. We present a patient with chronic cerebral edema which was unmasked by hemodialysis.

Methods: Case 40 y/o female with history of Lupus nephritis leading to End Stage Kidney Disease on hemodialysis three times a week for five years, previous ruptured anterior communicating aneurysm rupture which was surgically treated by clipping 19 years prior and hypertension. She presented after recurrent episodes of severe headaches with nausea and vomiting which was occurring 1hr into dialysis. One month prior she presented with similar intensity headaches. CT imaging revealed cystic mass with vasogenic edema and midline shift. She was initially treated with dexamethasone with mild improvements in headaches but returned after her symptoms initially resolved. Repeat CT head demonstrated radiation necrosis and hydrocephalus without obstruction. Ventriculoperitoneal shunt was placed and symptoms resolved.

Results:

Conclusions: Discussion/Conclusion This case serves as a reminder of the importance of close monitoring of patients on chronic dialysis with history of intracranial instrumentation, as cerebral edema can occur as a consequence leading to dialysis dysequilibrium syndrome.

Funding: Private Foundation Support

PUB267

Practices and Patterns of Hemodialysis in South Asia Sonika Puri, Gaurav Sagar. *Nephrology, Indraprastha Apollo Hospital, Delhi, India.*

Background: South Asian (SA) region faces a high burden of end stage renal disease (ESRD) and has a large gap between demand and supply for renal replacement therapy (RRT). We present the assimilated findings of a survey of nephrologists of the SA region on prevalent hemodialysis (HD) and vascular access (VA) practices in their respective units.

Methods: Nephrologists or Internal Medicine specialists running HD centers in the SA region were sent an online questionnaire. Literature was reviewed to fill gaps for missing data. Responses obtained were then converted into graphs using google survey automated software.

Results: 1700 physicians were contacted. Overall response rate was 10%. Maximum responses were from India and Pakistan (0% from Afghanistan, Bhutan and Maldives). Average cost per HD sessions varies from $10 to $100. Prevalent AV access trend: AV fistula use: 80% (India) to 40% (Myanmar) Temporary catheter use: 30% (Pakistan) to 10% (Sri Lanka). Tunneled catheter use: 30% (Sri Lanka) to 1% (Myanmar) Incident AVF use: 30% (Sri Lanka) to 3% (Bangladesh)

Conclusions: There is evident regional disparity between availability of nephrologists and HD units within this region. Few patients utilize AVF for incident HD or undergo HD three times a week. There is greater need for public-private funding to provide quality ESRD care in this region.

Funding: Clinical Revenue Support

Economic and ESRD indicators in SA Countries

Country	Total Health Expenditure* (% of Gross Domestic Product)	ESRD Prevalence (in p.m.p)	HD patients (in 1000s)	Estimated no. of HD centres	Estimated no. of HD machines	Estimated no. of nephrologists
India	4.7	89	112	3,700	20,000	1,400
Pakistan	2.6	101	20	285	9,250	143
Nepal	5.8	35	1	51	235	40
Bangladesh	2.8	45	8	NA	NA	NA
Sri Lanka	3.5	NA	NA	20	200	20

* Source: WHO and World Bank 2014

NA- Not Available

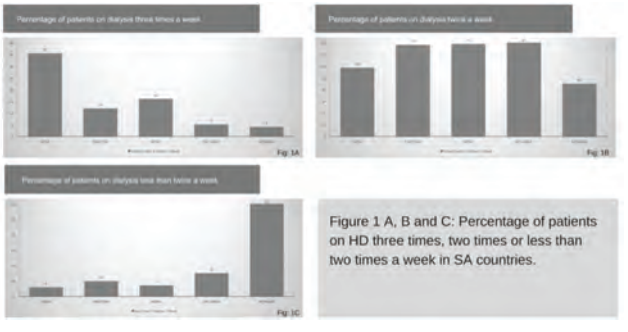


Figure 1 A, B and C: Percentage of patients on HD three times, two times or less than two times a week in SA countries.

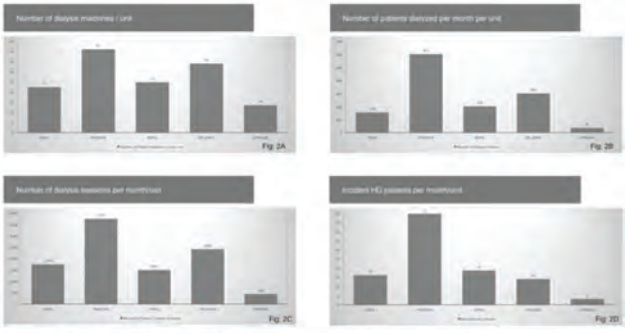


Figure 2 A, B, C and D describe the current status of HD infrastructure and sessions per unit

PUB268

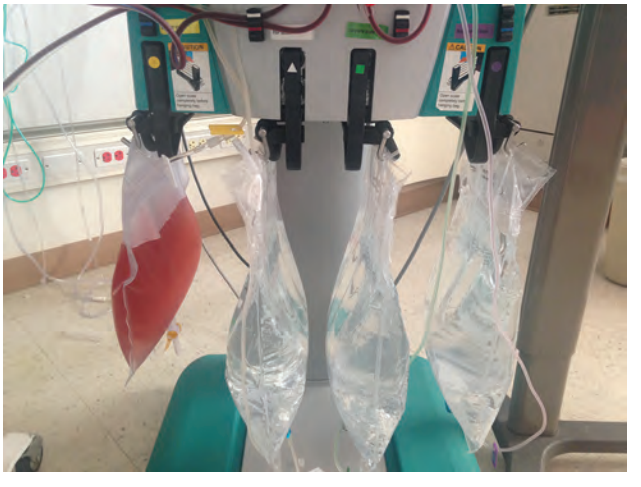
All That Is Red Is Not Blood Fahad Alobaidi, Bijin Thajudeen. *University of Arizona, Tucson, AZ.*

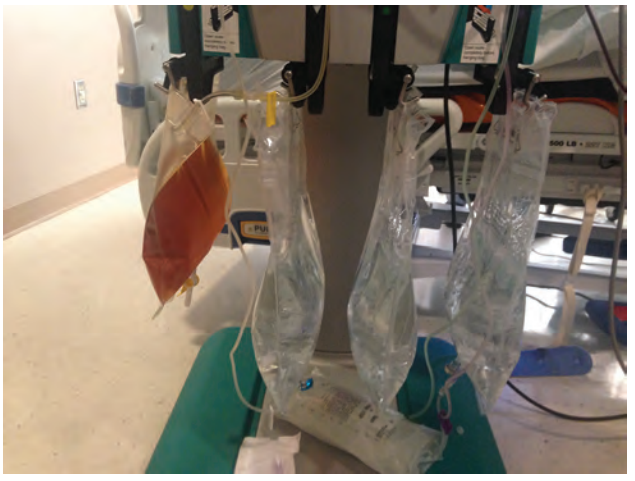
Background: The usual color of effluent fluid is either clear or straw colored. Occasionally there can be reddish discoloration. Common causes of reddish discoloration include hemolysis, blood leak, hyperbilirubinemia and hydroxocobalamin administration. Here we report two scenarios where effluent fluid was discolored.

Methods: 33-year-old male with history of advanced heart disease, left ventricular assist device admitted with fluid overload and acute renal failure. His hemoglobin was 6.5 gm/dl at admission and cause of anemia was thought to be due to chronic hemolysis form use of LVAD. He was started on continuous renal replacement therapy for management of volume overload. The effluent was clear for first two days. On day three he received vitamin B12 injection as part of management of anemia. Few hours following the injection there was reddish discoloration of the effluent fluid [figure 1]. A urine dipstick analysis of the fluid was negative for blood and absence of any blood leak alarm make hemoglobin less likely as the cause of discoloration. The color intensity gradually decreased and was clear by day 7. Case 2 is a 45-year male with history of end stage liver disease admitted with sepsis. He was started on CRRT for AKI, volume overload and anuria. The effluent fluid showed discoloration form the start of CRRT and persisted until CRRT was discontinued [figure 2]. There was also a yellowish discoloration of the CRRT filter. Laboratory tests showed total bilirubin of 45 mg/dl.

Results:

Conclusions: These two cases highlight the importance of checking effluent fluid color and identify the causes of discoloration.





PUB269

Clinical Features of Cardiac Surgery Associated AKI Dependent on Dialysis – A Single Center Retrospective Analysis Hongdi Cao,[1] Hong Ye,[1] Junwei Yang.[2] [1]*Center for kidney disease, Second Affiliated Hospital, Nanjing Medical University, Nanjing, China;* [2]*Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.*

Background: Cardiac surgery associated acute kidney injury (CSA-AKI) is one of the most common postoperative complications. CSA-AKI dependent on dialysis is closely related to the mortality. Previous CSA-AKI, particularly the incidence of dialysis dependence, has been reported differently. This retrospective analysis of the clinical characteristics of CSA-AKI dependent on dialysis is to provide a clinical reference for reducing the incidence of CSA-AKI and improving the prognosis of this population.

Methods: The clinical features of patients with CSA-AKI dependent on dialysis from January 1, 2016 to December 31, 2016 in our hospital were collected and analyzed. The basic characteristics, surgical protocols, dialysis protocols and the follow-up were recorded. Patients with chronic kidney disease were excluded. Dialysis indications were as follows: fluid overload, hyperkalemia, severe metabolic acidosis, diuretic resistance and failure of other organs.

Results: Of the 250 patients who underwent cardiac surgery, 14 with CSA-AKI (5.6%) required continuous renal replacement therapy (CRRT). In addition to a case of child with congenital heart disease, mean age of the other 13 patients was 56±17 years old, and 10 were male (76.9%). 8 patients underwent the combined heart surgery (57.1%), and 3 underwent the most complicated surgery, Bentall, aortic arch replacement, stent atrial trunk and coronary artery bypass grafting (21.4%). 2 of 14 patients were placed with intra-aortic balloon pump and 3 needed extracorporeal membrane oxygenation after operation. 6 patients received CRRT (42.8%) immediately after operation and 8 received CRRT 8-60 hours after operation. 11 patients (78.6%) underwent CRRT for at least 72 hours. 8 patients survived and the rest died in the hospital including the 3 patients who needed ECMO. The survived 8 patients were followed at least three months. 3 of them had complete recovery of renal function, the rest had persistent renal insufficiency, 1 undergoes routine dialysis.

Conclusions: CSA-AKI dependent on dialysis is a common complication after cardiac surgery, especially those undergoing combined cardiac surgery. It is one of the main factors related to the mortality after cardiac surgery.

Funding: Government Support - Non-U.S.

PUB270

Use of CRRT for Myoglobin Clearance in a Patient with Rhabdomyolysis Khaled Boobes,[2] Rebecca Frazier.[1] [1]*Northwestern, Chicago, IL;* [2]*Nephrology, Northwestern University, Chicago, IL.*

Background: Myoglobin pigment released from muscle tissue in rhabdomyolysis is a known cause of acute kidney injury (AKI) in a variety of clinical presentations. Clearance of myoglobin via dialysis has been debatable. We present a case of anuric AKI secondary to rhabdomyolysis in which we used CRRT to assist with myoglobin clearance.

Methods: A 29-year-old male with a history of opioid use for back pain presented with lower extremity pain which was then attributed to a compartment syndrome of unknown etiology. He underwent fasciotomy resulting in a severe rise in his serum creatinine phosphokinase (up to 220200 units/L), with subsequent anuric AKI and hyperkalemia despite aggressive generous hydration with intravenous fluids. We proceeded with continuous renal replacement therapy (CRRT) and elected to do continuous veno-venous hemodiafiltration (CVVHDF) with a high-flux filter for highest possible clearance. We then measured myoglobin in the effluent dialysate fluid as well as in the blood on different time intervals. Myoglobin was indeed filtered into the dialysate fluid. We calculated a clearance of up to 18,000 mcg/hour. Serum CPK level came down to 167,580 units/L within 24 hours, indicating a 25% decrease. Our patient continued to require RRT for 17 days, afterward his renal function started to recover and his urine output increased to the point that he was taken off of RRT.

Results:

Conclusions: In patients with elevated serum myoglobin causing AKI, CRRT could assist in the clearance of myoglobin and other pigments that might be contributing to the renal failure.

PUB271

Cardiac Fistula: A Rare Metastatic Complication of Dialysis Access Infection Hussain Aboud, Abhilash Koratala, Robert Gibson. *University of Florida, Gainesville, FL.*

Background: While infective endocarditis is relatively common in ESRD patients, intra-cardiac fistula associated with catheter-related blood stream infection (CRBSI) is exceedingly rare and we present one such case here.

Methods: A 59-year-old man with history of ESRD on hemodialysis for 2 years has presented with intermittent chest pain and fever for 2 days. He had last hemodialysis session 1 day before via right internal jugular tunneled catheter and complained of 'feeling chilly' while on the machine. He was febrile and hypotensive at presentation. Physical examination revealed a systolic-diastolic apical murmur. Blood cultures were obtained and empiric intravenous antibiotics were started for presumed CRBSI. Cardiac markers were elevated and he was admitted and managed conservatively for non-ST elevation myocardial infarction. Cath was not done, as he was febrile. Blood cultures grew Staphylococcus epidermidis and his antibiotic therapy was adjusted accordingly. On day 5 of admission, he developed ventricular tachycardia and pulseless cardiac arrest. EKG showed ST elevation MI and cardiac catheterization showed non-obstructive coronary artery disease. Trans-esophageal echocardiogram showed findings suggestive of fulminant aortic insufficiency with possible peri-aortic abscess and a fistula connecting left ventricular outflow tract to the right atrium. [Figures 1A and 1B] His dialysis catheter was removed immediately and a temporary catheter was inserted for continuity of hemodialysis. The risks of surgical treatment were deemed to outweigh benefits and he was treated with intravenous vancomycin for 6 weeks followed by Minocycline suppressive therapy. He remained afebrile and asymptomatic throughout the hospital course.

Results:

Conclusions: In some patients with CRBSI, bacteremia leads to metastatic complications, such as endocarditis, osteomyelitis, epidural abscess, septic arthritis or other soft tissue abscesses. As metastatic complications confer high morbidity and mortality, clinicians should pay close attention to patients' symptoms and physical examination findings. In addition, early use of investigations such as trans-esophageal echocardiography whenever applicable may help in early identification of unusual complications and prompt timely interventions.

PUB272

Determinants of Successful Outcomes after Percutaneous Angioplasty of Arteriovenous Fistulas and Grafts Used for Hemodialysis Vipuj Shah,[1] Malgorzata A. Kochanek,[1] Christopher Johnson,[2] Mohammed Khadir,[2] Rakesh Navuluri,[2] Rita L. McGill,[1] Mary S. Hammes.[1] [1]*University of Chicago Medicine, Chicago, IL;* [2]*Interventional Radiology, The University of Chicago, Chicago, IL.*

Background: Arteriovenous fistulas (AVF) and grafts (AVG) may develop venous stenoses caused by neointimal hyperplasia, commonly treated with percutaneous transluminal angioplasty (PTA). We prospectively evaluated the associations of clinical characteristics with one month outcomes of PTA.

Methods: ESRD patients referred for PTA of a patent AVF or AVG from 10/2016 - 4/2017 who consented were included. Demographic, clinical data, indication for PTA and the type and location of each lesion were collected. Each stenosis was evaluated in two orthogonal planes so percentage of stenosis could be calculated as compared to a reference vessel, before and after PTA. Clinical outcomes were ascertained from dialysis unit nurse practitioners one month after PTA. Success was defined as dialyzer blood flows of 450 mL/min during dialysis, without: prolonged bleeding, cannulation pain, high venous pressure, low arterial pressure, pulling clots, infiltrations, poor clearance, infections, or swelling of the arm, neck or head.

Results: We observed 63 stenoses in 46 participants. Success at one month after intervention was seen in 33 patients who had 45 stenoses. Clinical characteristics are presented by outcome in Table.

Conclusions: Success after PTA of a hemodialysis AVF or AVG malfunction was positively associated with use of aspirin, Renin-angiotensin aldosterone inhibitors (RAAS), and referral for high venous pressures. We did not demonstrate any significant associations between procedural success and anatomic features or measurements. Future work is needed to examine longer term outcomes and clarify the role of aspirin in dialysis vascular access.

	ALL (N=46)	FAILURE (N=13)	SUCCESS (N=33)	p-value
Age,mean (std)	59 (14)	60 (16)	59 (14)	0.8
BMI, mean (std)	28.9 (7.1)	28.8 (7.0)	29.0 (7.3)	0.9
Female sex,%	50	54	48	0.7
Diabetes, %	57	38	64	0.1
Tobacco use, %	65	62	67	0.7
RAAS,%	33	8	42	0.04
Statins,%	59	46	64	0.3
Aspirin,%	59	31	70	0.02
Indication:High venous pressure, %	54	15	70	0.0009
Multiple stenosis,%	37	38	36	0.9

PUB273

Resection of Arterial Pseudoaneurysm Followed by a Prosthetic (PTFE) Loop Graft Brachial-Basilic AV Fistula Juan Carlos Garcia Yanez, Jesús A. Nava martínez, Monica L. Mendoza. *Clinica de Accesos Vasculares, Servicios Medicos y de Equipamiento SERME, Tlalnepantla, Mexico.*

Background: This is the first case described in which is detected the presence of a pseudoaneurysm of the humeral artery at the site of anastomosis by Doppler ultrasound, is surgically resected and the same humeral artery is used for the placement of a brachio basilic graft.

Methods: A 32-year-old male patient with chronic renal disease of undetermined etiology who required renal replacement therapy. Initiates conventional hemodialysis with temporary vascular access. History of vascular access: 1. Right Internal jugular venous temporal catheter with duration of 4 months, withdrawn by change to fistula. 2. Left radial-cephalic arteriovenous fistula, which lasted 5 months, currently thrombosed. 3. Right Internal jugular venous temporal catheter placed 8 months ago, current access. 4. Left brachial-cephalic arteriovenus fistula 4 months ago, develops pulse, but does not present thrill. The presence of a pseudoaneurysm in the anastomosis site with the presence of a Ying Yang sign is evidenced by Doppler ultrasonography, and the possibility of rupture is decided to be admitted to the operating room for resection.

Results:

Conclusions: We present the case of a 32-year-old man, who came to the Vascular Access Clinic with suspicion of aneurysm. Doppler ultrasonography was performed, the presence of an arterial pseudoaneurysm was detected at the anastomosis site with a Ying Yang sign, and immediate surgical repair was considered in view of the possibility of rupture. During surgery of resection of the pseudoaneurysm, suitable diameters in the basilic vein and in the brachial artery were evidenced, so that the placement of a synthetic graft 6 mm (Advanta™ VXT PTFE Vascular Graft). The most appropriate treatment should be selected according to the cause, location, size and accessibility of the pseudoaneurysm, as well as the sequential plan of vascular accesses for each individual patient. In view of the growing number of patients with chronic renal disease on hemodialysis with multiple comorbidities, in which the sites for the creation of an arteriovenous fistula are limited, it is of vital importance to choose the optimal treatment of pseudoaneurysm by helping with the technologies available to us. Preserving permeability, decreasing recurrence and prolonging the useful life of vascular access and consequently the quality of life of patients.

PUB274

Outcome and Mechanisms of Central Vein Thrombosis Due to Catheter in Hemodialysis Patients Kazunori Oshima,[1] Naoki Ikegaya,[1] Fumiaki Nogaki,[3] Tatsuo Yamamoto,[4] Hiromichi Kumagai,[5] Takuya Yoshida,[5] George Seki,[2] Akira Hishida.[2] *[1]Dept. of Medicine, Yaizu City Hospital, Yaizu, Japan; [2]Dept. of Nephrology, Yaizu City Hospital, Yaizu, Japan; [3]Dept. of Nephrology, Shimada Municipal Hospital, Shimada, Shizuoka, Japan; [4]Dept. of Nephrology, Fujieda City Hospital, Shizuoka, Japan; [5]Dept. of clinical nutrition, Univ. of Shizuoka, Shizuoka, Japan.*

Background: Though frequent occurrences of central vein thrombosis (VT) due to hemodialysis (HD) catheters have been reported, there are little data about the anticoagulation treatment and outcome of VT. Moreover, patients with uremia exhibit altered coagulation with both increased thrombotic and bleeding risks. We evaluated the outcome of warfarin treatment and mechanisms of VT due to catheters in HD patients.

Methods: Patients requiring temporary HD access were prospectively assessed with ultrasonography prior to catheter insertion and at the time of removal. Patients with VT were treated with warfarin unless otherwise contraindicated, and evaluated with ultrasonography every two weeks after removal. Next, to analyze mechanisms of VT formation in uremia, we retrospectively compared immature platelet counts (IPC) between patients starting HD with arteriovenous fistulas and those with central venous catheters, since immature platelets are activated platelets with an increased prothrombotic potential.

Results: Fifteen jugular and 5 femoral catheters were placed in twenty patients at the induction of HD. Thirteen patients with jugular and 1 patient with femoral catheters presented VT at the time of removal. Nine patients were treated with warfarin, and VT disappeared within 1 month in seven patients and the size of VT decreased in 2 patients. In the next study, 31 patients starting HD with catheters showed significantly increased IPC compared to 17 patients with fistulas (6920 vs. 3840 /μL, $p < 0.05$).

Conclusions: We confirmed the high frequency of VT with HD catheters and observed the possible benefits of warfarin treatment in VT due to HD catheters. Additionally, starting HD with catheters may increase thrombotic events by activating platelets.

PUB275

Patency of Arteriovenous Grafts in Hemodialysis Patients: A Single Center Retrospective Study Xueqin Bian, Hong Ye. *2nd Affiliated Hospital, Nanjing Medical University, Nanjing, China.*

Background: It is difficult to maintain a working access for patients on hemodialysis. Despite current Dialysis Outcome Quality Initiatives recommendations of "Fistula First", not everyone qualifies for a fistula, and those patients undergoing the treatment, a graft, can experience graft failure. The patency of arteriovenous grafts (AVG) and complication of AVG in hemodialysis patients were analysis. This study also examines factors associated with AVG patency.

Methods: From January 2014 to December 2016, maintenance hemodialysis patients underwent arteriovenous graft in our hospital were enrolled in this study. Patency of AVG was examined three times at 3,6 and 12 month after fistulation. Complications, including bleeding, infection, steal syndrome, aneurysm, thrombosis and central venous stenosis were evaluated at 12 month after fistulation. Data were collected from electronic medical records, including date of first and subsequent interventions, salvage technique, medical comorbidities, and use of antiplatelet medications. Logistic regression was used to determine the odds ratio for risk factors associated with patency. Cox proportional hazard models were used statistic analysis.

Results: A total of 155 unique patients had an AVG. Of the 155 patients 68% were female, 70% were hypertensive, and 64% were diabetic. The locations of the grafts were 31% arm and 69% forearm. Configurations, including loop and straight, were 63% and 37%, respectively. The primary patencies were approximately 90%, 69% and 59% at 3, 6 and 12 months, respectively. The cumulative patencies were 92%, 80% and 69% at 3, 6 and 12 months, respectively. The incidence of all complications is 41.9% (65 of 155) at 12 month Primary patency was not found to be different with respect to location and configuration of graft and type of intervention. Primary patency for patients with diabetes and complicated vascular access history were significantly different from other patients, with a P=0.039 and P=0.0431 respectively.

Conclusions: Arteriovenous grafts in hemodialysis patients had excellent patency and some complications. Neither location nor configuration affects the primary patency of AVGs. Diabetes and fistulation history were detrimental factors for patency of AVGs.

Funding: Government Support - Non-U.S.

PUB276

Hypertriglyceridemia Associated Pancreatitis – Is Apheresis Always Required? Krishna K. Manda,[1] Syed H. Jafri,[2] Jagathi Govindu,[1] Talal K. Mahmood.[1] *[1]Swedish American Hospital, Rockford, IL; [2]Swedish American Hospital, Rockford, IL.*

Background: We present two patients with Hypertriglyceridemia associated Pancreatitis (HTGP) who recovered without Apheresis in 3 out of 4 episodes. The first patient is a 52 y/o man with a h/o hypertriglyceridemia presented with abdominal pain in Mar '14. He was diagnosed with HTGP and triglyceride (TG) level was 10186 mg/dl. Apheresis was urgently organized and after one session, TG levels improved to 977 mg/dl. TG level was 262 mg/dl at the time of discharge. He had a similar admission in June '16 and was diagnosed with HTGP and TG level was 9910 mg/dl. He was fluid resuscitated and TG level improved to 373 mg/dl in 36 hours. He did not receive intravenous Insulin or heparin. The second patient is a 32 y/o woman with a h/o poorly controlled Diabetes (HbA1c 12.5%) presented with abdominal pain in Nov '15 and was diagnosed with HTGP and TG level was 12396 mg/dl. She was fluid resuscitated and TG level improved to 4925 in 12 hours and to 1354 in 36 hours. She was discharged on Gemfibrozil but unfortunately stopped taking since Apr '16. She was again admitted in Jun '16 with HTGP and TG level was 9641 mg/dl. She was started on IV Insulin along with fluid resuscitation. TG level dropped to 1816 in 24 hours and to 926 in 48 hours.

Methods:

Results: In patients who develop HTGP, management includes conventional treatment of acute pancreatitis and decreasing the TG levels to <500 mg/dL. Various treatment modalities have been suggested including apheresis, insulin and heparin. No randomized trials have compared the efficacy of Apheresis with that of insulin and heparin for the treatment of HTGP. Many case reports and series have described benefits of apheresis for HTGP. Usual indications are TG level >1000 mg/dL plus lipase >3 times the upper limit of normal and signs of hypocalcemia, lactic acidosis or organ dysfunction. Some have reported a decrease of 41% in TG levels with one session of Apheresis.

Conclusions: As it is elucidated in our experience, HTGP does not always need Apheresis and significant reduction in TG levels can be achieved with supportive management alone. Further studies are needed, before considering Apheresis as the standard of treatment because specially trained multidisciplinary team members are needed to perform the procedure and the resources needed might not be available at all the institutions.

PUB277

Patient Preference Matters: Catheter Patients with a Successful Pregnancy Attiya Haroon,[4] Sushil Mehandru,[3] Avais Masud,[5] Mayurkumar P. Patel,[5] Loay H. Salman,[1] Elmer SADIANG-ABAY,[2] Arif Asif.[3] *[1]Albany Medical College, Albany, NY; [2]JERSEY SHORE UNIVERSITY MEDICAL CENTER, TOMS RIVER, NJ; [3]Jersey Shore University Medical Center, Neptune, NJ; [4]Jersey shore university medical center, Piscataway, NJ; [5]None, Neptune, NJ.*

Background: While an arteriovenous fistula is the best available access, many patients continue to reply on a tunneled hemodialysis catheter (TDC) for dialysis therapy. Despite the highest risk of bacteremia and associated morbidity and mortality, often patients prefer TDC to avoid pain associated with cannulation of an arteriovenous access.

Methods: We report two TDC-dependent patients (age: 33, 35) with end stage renal disease (ESRD) due to polycystic kidney disease and hypertension, respectively; who became pregnant. Pregnancy was discovered at 10 and 12 weeks of gestation. Both patients were switched to daily hemodialysis (6 sessions/week). Both patients had refused the placement of an arteriovenous access and expressed their strong preference for TDC despite vascular access education. Patient preference was acknowledged and therapy continued with TDC. Pregnancy was uneventful and both patients delivered a term healthy baby.

Results:

Conclusions: Patient preference for TDC and satisfaction is important and can result in a successful outcome in pregnant patients. Nonetheless, in keeping with the National Kidney Foundation guidelines as well as the Fistula First, an arteriovenous fistula should be offered to hemodialysis patients.

PUB278

The Use of the Early Cannulation Prosthetic Graft (Gore Acuseal) for 15 Patients as a Lower Extremity Prosthetic Hemodialysis Access

Bing Tang,[1] Yong Xu,[2] Yuanming Li,[2] Xinxin Liu,[1] Bei Hou,[1] Kun Wu.[2] *[1]Renal Division, Carnation Hospital, ChangSha, China; [2]Hemodialysis center, The third affiliated Hospital of Xiang Ya School of Medicine, Central South University, ChangSha, China.*

Background: With the life expectancy of end-stable renal disease increasing, the quality and availability of the native arteriovenous access can be limited and reduced with time, the option of using prosthetic AV will become necessary. The purpose of this study is to report the safety and effectiveness of the Gore Acuseal Graft using as a lower extremity prosthetic vascular access for chronic hemodialysis patients who have exhausted upper extremity vascular access or have central venous stenosis.

Methods: Between December 2016 and May 2017, 15 patients who underwent implantation of the Gore Acuseal prosthetic AV access were included in the study. The graft configuration all were superficial femora-saphenous. follow-up of time to first cannulation, patency rate, rates of seroma, access thrombosis, steal syndrome, pseudo-aneurysm and infection were performed and recorded.

Results: Graft implantation was technically successful in all 15 patients. No patient was lost during a mean follow-up time of 3.6±1.6 months (rang,1.7-6 months;). Mean time to first cannulation was 136.8±97.2hrs (rang, 24-384hrs). Primary functional potency rate was 93.3%. Primary blood flow rate was 200-230ml/min. First puncture time was 136.8 ± 97.2 hrs (24 -384 hrs), an average follow-up of 3.6 ±1.6 months (1.7 -6.0 months). Seroma, thrombosis, pseudo-aneurysm, or graft infection was never observed. Steal syndrome occurred in one patient. Cannulation is easier than other types of regular prosthetic access reported by nurses. Cannulation sites usually stop bleeding in 15 minutes with pressure after treatment, no hematoma was observed .12 patients were removed central venous catheter or ligated dysfunctional fistula at early stage of postoperatively days. Central venous stenosis complications were not observed. Follow-up of blood flow rate all were greater than 250ml/min.

Conclusions: Lower extremity Gore Acuseal graft implantation was safe and effective, with less complications. It can be widely applied for chronic hemodialysis patients who have exhausted upper extremity vascular access or have central venous stenosis.

PUB279

Comparison of the Early Cannulation Graft (Gore Acuseal) and Standard Graft (Gore Intering) for Prosthetic Vascular Access for Haemodialysis

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Background: Background: Gore Acuseal is a new early cannulation prosthetic access, it can be cannulated for dialysis within 3 days. The characteristic of this prothetic access is an attractive alternative to CVC in those requiring urgent dialysis patients. The purpose is to compare the safety and efficacy of early cannulation graft(Gore Acuseal) to standard graft (Gore Intering) for prosthetic vascular access for Haemodialysis.

Methods: This is a prospective observational study of all AVGs placed since December 2016 in our hospital. Outcomes including time to first cannulation, patency rate, rates of seroma, access thrombosis, steal syndrome, pseudo-aneurysm and infection in early cannulation graft (Gore Acuseal) comparison to standard Grafts(Gore Intering).

Results: Sixteen Gore Acuseal grafts and nineteen Gore Intering grafts were implanted in the study period. The Gore Acuseal graft configuration was superficial femora-saphenous(n=15), upper arm axillo-axillary (n= 1); The Gore Intering graft configuration was superficial femora-saphenous(n=15), upper arm brachial-axillary (n=1), brachial-cephalic or basilic (n=3). No patient was lost during a mean follow-up time of 3.6±1.6 months(rang,1.7-6 months;). Primary functional patency (Gore Acuseal 93.8% vs Gore Intering 73%), Secondary patency rate (93.8% vs 89.5%). Mean time to first cannulation was 5.6±4 days(rang, 1-16 days) vs 11 ± 8 days (rang 10-35 days), the differences were statistical significance($p<0.05$). Seroma (0 vs 64.2%, $p<0.05$), AV access infection (0 vs 21%). Steal syndrome occurred in one patient with Gore Acuseal graft. Primary blood flow rate has no difference in both grafts.

Conclusions: Comparing with Gore Interning, Gore Accuseal Graft implantation was safe and effective, early cannulation with higher patency rate, less seroma, thrombosis, and infection. It is a viable option for patients who require urgent hemodialysis instead of temporary or tunneled catheters.

PUB280

Changes in Blood Pressures, Adequacy, and Access Flow Rates before and after Arteriovenous Access Thrombectomy

Sheetal Chaudhuri,[2] Hao Han,[2] Tommy C. Blanchard,[2] Yue Jiao,[2] Marta Reviriego-Mendoza,[2] Hanjie Zhang,[1] Murat Sor,[3] Elsie Koh,[3] John W. Larkin,[2] Len A. Usvyat,[2] Peter Kotanko,[1,4] Franklin W. Maddux.[2] *[1]Renal Research Institute, New York, NY; [2]Fresenius Medical Care North America, Waltham, MA; [3]Fresenius Vascular Care, Malvern, PA; [4]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Thrombotic events are a common complication in hemodialysis (HD) patients with arteriovenous fistulas and grafts (AVFs/AVGs), and are a major cause of dialysis access failure and many negative outcomes. To date, there are no established predictors associated to thrombotic events in AVFs/AVGs. We investigated the trends in levels of pre-dialysis systolic and diastolic blood pressures (preSBP/preDBP), dialysis adequacy, and access flow rates before and after an AVF/AVG thrombectomy in attempt to identify potential predictors of thrombotic events in HD patients.

Methods: We analyzed data from 1,847 Fresenius Medical Care North America HD patients who had an AVF/AVG thrombectomy between Jan 2015 to Jan 2016. The preSBP, preDBP, Kt/V, and access flow rate was tracked in HD patients for 90 days before and after the thrombectomy, and plotted using a penalized B-spline to fit the mean with 95% confidence limits.

Results: During the 90 days prior to an AVF/AVG thrombectomy, HD patients exhibited a slight decline in mean preSBP and preDBP, declining approximately 2.5 mmHg and 2 mmHg respectively. The most precipitous decline for both preSBP and preDBP was in the final 2 weeks prior to thrombectomy. About a week after a thrombectomy, mean preSBP and preDBP increased by approximately 3.5 mmHg and 2 mmHg respectively. The preSBP at 90 days after a thrombectomy was found to increase about 1 mmHg above the levels seen 2 weeks before a thrombectomy. We observed similar findings of decreases before and increases after thrombectomy for Kt/V and access flow rates. The approximate changes after thrombectomy compared to before thrombectomy were: i) average kt/v increased 1%; ii) average access flow rate increased 10%.

Conclusions: These findings indicate that blood pressures, Kt/V, and access flow rates decline before and increase after a thrombectomy. While individual changes may be small, combining multiple variables into a comprehensive model may be useful in predicting AVF/AVG thrombotic events. Further analyses are needed to confirm these observations and assess their usefulness in thrombosis detection.

Funding: Commercial Support - Fresenius Medical Care North America

PUB281

Associations between Arteriovenous Fistula/Graft Failure Rates and Catheter Rates

Sheetal Chaudhuri,[1] Hao Han,[1] Tommy C. Blanchard,[1] Marta Reviriego-Mendoza,[1] John W. Larkin,[1] Elsie Koh,[2] Murat Sor,[2] Len A. Usvyat,[1] Peter Kotanko,[3,4] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Fresenius Vascular Care, Malvern, PA; [3]Renal Research Institute, New York, NY; [4]Ichan School of Medicine, New York, NY.*

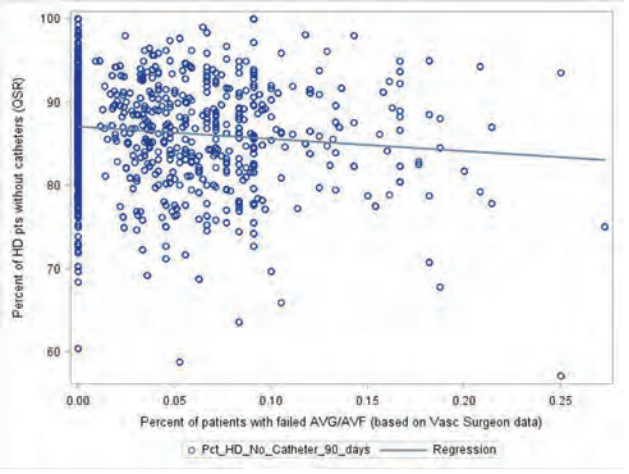
Background: The rates of central venous catheter (CVC) use in hemodialysis (HD) patients have been relatively unaltered over the last decade. In 2016, the United States Renal Data System estimated that about 68% of incident HD patients utilize a CVC at 90 days after starting HD, and approximately 20% of patients never transition to a permanent vascular access (VA). We aimed to study the correlation between vascular access surgeons who have high arteriovenous fistula/graft AVF/AVG failure rates and the catheter rates in patients within the clinics associated with the vascular access surgeons.

Methods: We obtained AVF/AVG creation and failure rates by vascular access surgeon between 2012 and 2016 using Fresenius Medical Care North America access tracking system. We calculated the failure rate for each surgeon by identifying catheter creation after successful AVF/AVG use. We identified the clinics where surgeons had highest number of patients and computed the correlations between the percentage of patients without catheters per clinic and the percentage of patients with a failed AVF/AVG.

Results: We found a negative correlation between the percentage of HD patients without catheters and the percentage of patients with failed AVF/AVG.

Conclusions: Out findings suggest that the quality of AVF/AVG creation is associated with catheter rates and outcomes in HD patients. Additional studies are necessary to confirm this observation.

Funding: Commercial Support - Fresenius Medical Care North America



PUB282

Compare the Influence of Two Kinds of Vascular Accesses on Anemia in Patients on Maintenance Hemodialysis Lirui Wang,[2] Chen Yu.[1] *[1]Shanghai Tongji Hospital, SHANGHAI, China; [2]Tongji Hospital of Tongji University, SHANGHAI, China.*

Background: Previous studies postulate that maintenance hemodialysis (MHD) patients dialyzed with tunneled cuffed catheter (TCC) have poorer outcomes compared to patients using arteriovenous fistula (AVF). This study aimed to compare the effects of two kinds of vascular accesses on anemia of MHD patients.

Methods: Thirty-five MHD patients were recruited from the dialysis center of Tongji Hospital of Tongji University. Patients were classified into two groups according to their different vascular accesses: TCC group (n=15) and AVF group (n=20). Two groups were matched for age, gender, primary disease, duration of dialysis and usage time of access. We compared hemoglobin (Hb), CRP, IL-6, TNF-α and Kt/v between the two groups.

Results: There were no significant difference in the age, gender, blood pressure, BNP, creatinine, blood lipids, albumin, PTH, calcium, phosphorus, ferritin transferrin, TSAT, SF, folic acid, VitB12 and EPO dose between the two groups. Compared to the TCC group, the Hb levels, blood flow and Kt/v in AVF group were significant increased[(112.95±7.52)vs(100.00±13.96)g/L,(215.33±12.46)vs(230.00±17.77)ml/min,(1.40±0.28)vs(1.11±0.12), $P<0.05$], while the CRP, IL-6 and TNF-α levels were significant decreased[(3.59±1.40)vs(7.31±3.41)mg/L,(4.30±2.04)vs(6.93±5.02)pg/ml,(13.70±3.25)vs(17.03±5.60)pg/ml,$P<0.05$]. There was a negative correlation between the CRP, IL-6, TNF-α levels and Hb levels (r= -0.382,-0.376,-0.380,$P<0.05$), and a positive correlation between the Kt/v and Hb levels (r=0.414,$P<0.05$).

Conclusions: Compared to the AVF, the TCC is not good for the improvement of anemia in MHD patients. That may result from increasing microinflammation state and inadequate dialysis.

Funding: Government Support - Non-U.S.

PUB283

Longitudinal Patterns of Quality of Life and Dialysis Modality Use: A National Cohort Study Nwamaka D. Eneanya,[2] Dugan Maddux,[1] Marta Reviriego-Mendoza,[1] John W. Larkin,[1] Len A. Usvyat,[1] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Massachusetts General Hospital, Boston, MA.*

Background: Studies comparing kidney disease quality of life (KDQOL) changes over time between end-stage renal disease patients receiving different renal replacement therapy treatments, have featured small sample sizes, short follow-up times and stable dialysis modality use over time. We investigated patterns of HRQOL by dialysis modality, as well as change in modality over time among a national cohort of dialysis patients.

Methods: We analyzed data from 22,544 PD, home HD, and in-center HD patients of Fresenius Kidney Care clinics between 1/1/2013 and 6/30/2015 who survived the first 485 days on dialysis. Only patients 18 or older years who completed a KDQOL survey during the following two periods: 1) within the first 120 days and 2) within 365 to 485 days of dialysis initiation were included. Peritoneal dialysis (PD) and home hemodialysis (HD) patients were collapsed into one "Home" group. Changes in KDQOL subscale scores were compared between patients who remained on the same modality and for patients who changed modalities between first 120 days of year 1 and year 2 on dialysis. Clinically significant changes in KDQOL domains occur when they are >=3 points.

Results: Compared to in-center HD patients, Home dialysis patients had higher mean (± SD) physical component (PCS; 40.6 ± 10.3 vs. 38 ± 10.4), symptom problem (SPS; 82.5 ± 13.5 vs. 81.0 ± 14.4), burden of kidney disease (BKD; 57.7 ± 27.5 vs. 53.6 ± 28.5) and effects of kidney disease scores (EKD. 79.5 ± 18 vs. 77.2 ± 20.4) in the first 120 days of dialysis. Mental component scores (MCS) were similar between the two groups. Over time, when comparing patients who stayed on the same modality over first 120 days of year 1 and first 120 days of year 2 ("In-center to in-center", "Home to Home") and patients who switched modalities over two periods ("In-center to home", "Home to in-center") no clinically significant changes in Physical and Mental Composite Scores occurred.

Conclusions: We observe that patients treated by a home modality have better baseline HRQOL compared to their in-center HD counterparts. No notable differences in changes in physical and mental composite scores occur between the first and second year of dialysis.

PUB284

Patients Favor Solo Home Hemodialysis to In-Center Hemodialysis – Results of a Patient Preference Survey Paul Kravitz,[1] Eric D. Weinhandl.[1,2] *[1]NxStage Medical, Inc., Lawrence, MA; [2]University of Minnesota, Minneapolis, MN.*

Background: Although many home therapies are done without a partner, there are currently no devices indicated for home hemodialysis (HHD) without a care partner ("Solo HHD") that could help address a commonly reported barrier for HHD – partner requirement. We analyzed data from a patient preference survey to determine which therapy, either Solo HHD or in-center hemodialysis (CHD), that current HHD patients would favor if they no longer had a care partner.

Methods: We designed an online survey to investigate patient preference for Solo HHD. Current HHD patients in the US were invited via unbranded email from a third-party vendor to complete the survey. We used descriptive statistics to report results in 3 groups: respondents currently performing Solo HHD; respondents favoring CHD in absence of a care partner; and respondents favoring Solo HHD in absence of a care partner.

Results: We invited 1049 patients in 129 dialysis centers to participate. The respondent cohort comprised 142 patients (response rate, 13.5%). Age was <60 years in 53% of respondents, 78% were Caucasian, 70% were male, and 31% were employed either full-time or part-time. Respondents were geographically representative. Twenty-two (15%) respondents were already performing Solo HHD. In patients performing HHD with a care partner, 73 (61%) favored Solo HHD over CHD. In those who favored Solo HHD, 40% felt comfortable treating without a care partner immediately after transitioning home, and 62% felt comfortable within 3 months of starting HHD. In patients performing HHD with a care partner, several factors were associated with a preference for either Solo HHD or CHD (table).

Conclusions: A large proportion of HHD patients favored Solo HHD over CHD in absence of a care partner. Many patients would have been comfortable with Solo HHD either immediately or shortly after starting HHD. Patient preference for Solo HHD likely reflects current experience, comfort, and confidence with HHD.

Funding: Commercial Support - NxStage Medical, Inc.

	Favors Solo HHD (N=73)	Favors CHD (N=47)	P-value
Performed a Solo HHD treatment in the past 3 months	16%	4%	0.04
Treats or is very confident in ability to treat without partner present	89%	36%	<0.01
Very confident in ability to handle issues during Solo HHD	67%	13%	<0.01
Age 60 or older	44%	64%	0.03

PUB285

A New Material for Dialysis Fluid Regeneration Dmytro Tymoshenko, Hans De brouwer, David Wimberly. *SABIC, Selkirk, NY.*

Background: Single pass dialysis systems have been used for hemodialysis therapy since they were commercially introduced in the early 1960s. Single pass systems are intrinsically water hungry and require regular and costly fluid pathway maintenance. Additionally, the necessity of "dialysis grade" pure water preparation can result in significant investments in water treatment facilities in hospital environments and stand-alone reverse osmosis units for home dialysis. An alternative therapy is sorbent dialysis, which has re-emerged as a viable water-sparing technological system enabling miniaturization, portability and potential wearability.

Methods:

Results: In this publication, we would like to present a new type of dialysate sorbent material which is under development at SABIC™. We have approached this challenge from both synthetic chemistry and impregnation/coating fronts and made significant progress towards the goal. We have examined several synthetic solutions and developed a series of porous polymer beads as novel adsorbents, which have shown moderate urea and creatinine adsorption capacity. In parallel, we have also explored an innovative impregnation/coating technique providing urea binding capacities comparable to "urease and zirconium ion exchange" technology.

Conclusions: Two innovative approaches to dialysate regeneration sorbent have been developed providing materials comparable to existing enzymatic and sorbent technologies.

Funding: Commercial Support - SABIC

PUB286

The Makings of Successful In-Centre Nocturnal Haemodialysis: Well-Being, Sleep, and Free Time Katherine L. Hull,[2,3] Darren R. Churchward,[3] Suzanne Glover,[2] Warren P. Pickering,[1] Matthew P. Graham-Brown,[3,2] James Burton.[3,2] *[1]Northampton General Hospital, Northampton, United Kingdom; [2]University Hospitals of Leicester NHS Trust, Coventry, United Kingdom; [3]University of Leicester, Leicester, United Kingdom.*

Background: In-centre nocturnal haemodialysis (INHD) provides extended dialysis sessions, for which there is evidence of an array of potential health benefits. To enhance

our patients' experience and dialysis options, we evaluated our INHD service to better understand factors that influence the uptake and adherence.

Methods: An anonymous survey was distributed to current and previous INHD patients. The survey consisted of questions regarding: demographics, length of dialysis, quality of sleep during dialysis, and free text areas for comments regarding facilities, reasons for starting and continuing/stopping INHD, and the impact of INHD. Thematic analysis was conducted on the free text sections.

Results: 58 patients were identified as current INHD (n=24) and previous INHD (n=34) patients. From these 34 patients, 21 discontinued due to: renal transplantation (n=11), transfer to a different unit (n=3), conversion to HHD (n=1) or PD (n=1) and death (n=5). These 21 patients were not included in the survey. From those surveyed (n=36), 27 (75%) were male, the average time on HD was 52 months and the average time on INHD was 9 months. Compared to usual HD, 26 (72.2%) rated INHD as causing less disruption, 25 (69.4%) stated they preferred INHD, and 24 (66.7%) felt better on INHD. The most common reasons to start and continue INHD were to have more time during the day and for the perceived health benefits (changes to medications, better blood results, improved breathlessness and generally feeling better). The main reasons for stopping were the side effects of longer dialysis or daytime tiredness.

Conclusions: Overall patient satisfaction with INHD was high due to the positive impact on lifestyle and perceived health benefits. Those that left the programme did so due to a change in clinical care, side effects of longer dialysis or daytime tiredness. These findings have identified the benefits of INHD from the patient perspective and the modifiable factors to enhance patient experience.

PUB287

Optimal Transitions: A New Approach to Improve Home Dialysis Modality Prevalence Jose A. Morfin,[1] Alex Yang,[2] Elizabeth Wang,[2] Brigitte Schiller.[2,3] *[1]University of California, Davis, Sacramento, CA; [2]Satellite Healthcare, San Jose, CA; [3]Stanford University, Palo Alto, CA.*

Background: Home hemodialysis (HHD) and peritoneal dialysis (PD) result in better clinical outcomes, lower hospitalization rates, and improved quality of life compared to conventional in-center hemodialysis (CHD). Less than 10% of incident patients choose home dialysis, and 70% of patients report not receiving sufficient education on modality options resulting in many patients feeling unprepared to make informed decisions. The Optimal Transitions (OT) program was established to provide in-depth education in all dialysis modalities over a flexible time period. While providing clinical stabilization and self-care management opportunities, patients are empowered to choose the optimal modality based on their life plan. This study aims to determine the effectiveness of the OT program in increasing prevalence of home dialysis modalities by providing sufficient education to prepare patients for transition.

Methods: This study evaluates patients enrolled in the OT program from Oct 2016–Aug 2017. Each patient completes 6 courses over about 4 weeks. OT program consists of 4 chairs within a CHD center, admitting patients screened for their candidacy for home dialysis modalities.

Results: Outcome measures include the proportion of patients who transitioned to home dialysis upon graduation, proportion of patients who reported receiving sufficient education and felt prepared to transition to chosen modality upon graduation. To date, 67% of OT patients have chosen home modalities.

Conclusions: Key unmet needs for patients to successfully undergo home dialysis include psychosocial challenges, suboptimal education, premature decision making, and fear. OT addresses these needs by establishing a life plan, in-depth ongoing education, self-care opportunities to empower patients to choose confidently the most suitable dialysis modality. Preliminary results promise the opportunity to increase the adoption of home/self-care dialysis options.

PUB288

Evaluation of the Quality of eHR Data to Assess the Clinical Features of Anemia in Dialysis Patients Samantha St. Laurent,[1] Rafael Alfonso-Cristancho,[1] Tony Okoro,[1] J. Morel Symons,[1] Kirsten L. Johansen,[2] Laura M. Dember,[3] Vanja Sikirica,[1] Alistair C. Lindsay.[1] *[1]GlaxoSmithKline, Collegeville, PA; [2]University of California, San Franicsco, San Francisco, CA; [3]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA.*

Background: Electronic health records (eHR) have great clinical research potential if the information is sufficiently accurate. Here, we assess the quality and completeness of data in eHR from a large dialysis organization (LDO) in the US, focusing on demographic and clinical variables.

Methods: We used Kahn's framework (*Analytic Methods*, 2012) to assess data quality from ~229,000 de-identified patients across 2,900 US centers in 2015. We focused on the following quality domains: 1) missing values and anomalies in data, 2) accurate relationships between data tables, 3) temporal relationships, and 4) logical events.

Results: Low missingness was seen for age (0.08%), sex (0.04%), and dialysis treatment (0%) data. Hemoglobin (Hb) values were assessed via quality domains 1-4. Hb labs were recorded for 96% of the LDO cohort (range 0-46.8 g/dL; mean 10.9 g/dL, same result obtained with or without zero values). Anemia (defined by Hb <13.0 g/dL for men and <12.0 g/dL for women) was observed in 99% of patients with Hb labs. Extreme Hb values (<5.0 g/dL or >20.0 g/dL) were reported for <0.17% of patients with Hb labs. Among patients with Hb labs, 78% had non-zero Hb values <10.0 g/dL (the KDIGO threshold for anemia of CKD treatment). Of these patients, 11% were below this threshold for a span of at least 90 days based on subsequent lab draw dates, and 3% were below it for 180 days. Of patients with Hb <10 g/dL, 98% were receiving an erythropoietin stimulating agent.

Conclusions: Using Kahn's framework, an objective analysis of eHR from an LDO found that certain demographic features, treatment, and Hb levels were consistently recorded. 99% of all patients were anemic; 78% of patients with Hb labs had a Hb level mandating treatment (<10 g/dL, the KDIGO hemoglobin criteria). Although 98% of these patients were given an erythropoietin stimulating agent, 11% remained anemic for at least 90 days. Future work will assess mortality data linkages, and temporal data relationships between clinical variables, lab tests, and subsequent clinical treatments.

Funding: Commercial Support - GlaxoSmithKline

PUB289

Automation Anemia Management Algorithm System for Hemodialysis Patients Reduces the Staff Resources Yuuki Yoshioka,[1,2] Tadashi Otsuka,[3,2] Ryuzi Aoyagi,[2] Takashi Yokoo.[1] *[1]The Jikei University School of Medicine, Tokyo, Japan; [2]Tachikawa general hospital, Nagaoka, Japan; [3]Niigata University, Niigata, Japan.*

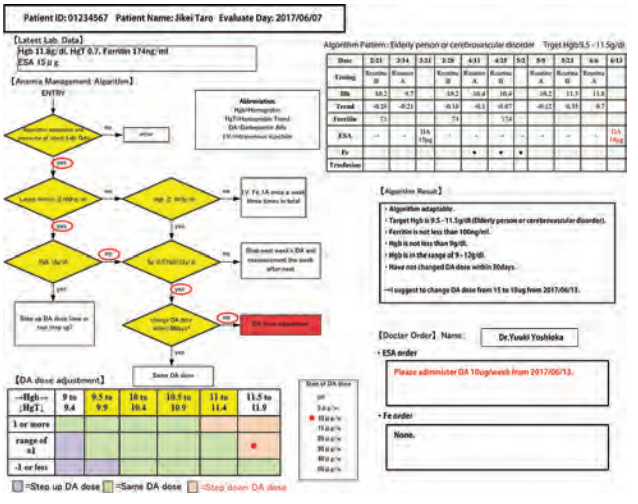
Background: Anemia treatment in hemodialysis(HD) patient involves adequate supply of iron and an erythropoiesis stimulating agent (ESA). We have used Darbepoetin Alfa as ESA from 2007 and managing anemia using an algorithm from 2010. Then facility-level hemoglobin(Hgb) was improved(11.2±0.9g/dl, mean±SD). Our anemia management algorithm requires the following variables: Hgb, ferritine, Hgb Trend (HgT), ESA dose. HgT is calculated as the differential between the average of Hgb during the most recent two months and the two month-period immediately prior to that. All datas were aggregated manually. The doctor confirms the algorithm and sets each patient's next dose. These sequence still influences the potential for human error, inaccuracies, and burden on staff.

Methods: We have designed the Automation Anemia Management Algorithm System(AMAS) which digitalizes the paper-based algorithm. AMAS is connected to the Hospital Information Systems to automatically capture Hgb and ferritin data. HgT is calculated automatically. The doctor verifies the results of AMAS and gives orders via AMAS. The nurse confirms the order on the tablet device.

Results: Before starting AMAS, the nurse evaluated the algorithm of all patients (n=188) using a total average of 168 minutes. The doctor issued dose prescriptions to an average of 98 patients over an average of 83 minutes. The nurse confirmed orders over the total average of 143 minutes(total 394 minutes). There were an average of 0.8 errors per evaluation. After starting AMAS, the doctor verified AMAS results for all patients over an average of 32 minutes. The nurse confirmed orders over the total average of 128 minutes(total 160 minutes). There was no error after the introduction.

Conclusions: Staff resources devoted to anemia management decreased significantly as a result of utilizing AMAS.

Funding: Private Foundation Support



Sample Screen from Automation Anemia Management Algorithm System.

PUB290

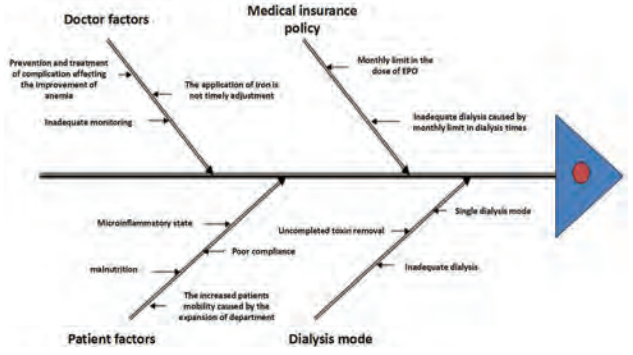
Application of Continuous Quality Improvement in Anemia Management of Maintenance Hemodialysis Patients Hua Liu,[2] Hongli Jiang.[1] *[1]Dialysis Center of First Affiliated Hospital of Medicine School, Xi?an Jiaotong University, Xi'an, Shaanxi, China; [2]First Affiliated Hospital of Medical College of Xi'an Jiaotong University, Xi'an, China.*

Background: In recent years, with the continuous improvement of dialysis technology, the focus of dialysis management is gradually changing over to improve the treatment quality of hemodialysis patients. Plan-do-check-act (PDCA) is the scientific procedures which should be followed by the comprehensive quality management. We used PDCA cycle to explore the clinical effect of the continuous quality improvement on anemia management of the MHD patients.

Methods: After we found the general standard rate of anemia in outpatients in 2014 (37.8%) was lower than that in 2013 (39%), we choose overall anemia (HGB≥100g/L) from 2014 to 2016 for MHD patients in the First Affiliated Hospital of Xi'an Jiaotong University, based on application of PDCA cycle management model, used the fishbone diagram as a management tool to analyze the reasons. Then,we analyzed clinical stage index comparative.

Results: Based on PDCA medical quality improvement for the doctor factors, health care policy, patient factors, dialysis and so on, we adopt the following methods, including strengthening the monitoring efforts, standardizing application of iron; strengthening the follow-up and treatment of new patients, paying attention to prevention and treatment of hyperparathyroidism and other complications, strengthening the patient's propaganda, improving the drug compliance and disease attention, improving malnutrition and the dialysis adequacy, providing different patients with individual dialysis choice, improving the dialysis adequacy and other measures to improve the microinflammatory state in patients. After these methods, the overall standard ratio increased 10.7% in 2015 (48.5%) and 14% in 2016 (51.8%) compared with 2014 (37.8%).

Conclusions: Continuous quality improvement management can promote the improvement of chronic complications in MHD patients such as anemia. We need to continue to make efforts to train staff, technical standards, and quality management in the treatment of MHD patients.



PUB291

The Effect of Ferric Citrate on Inflammation and Lipid Levels in Patients on Hemodialysis Nawsheen Chowdhury,[2] Youngjun Park,[3] Candace D. Grant,[1] Shayan Shirazian.[1] *[1]Winthrop University Hospital, Mineola, NY; [2]Winthrop university hospital, Mineola, NY; [3]Winthrop-University Hospital, Mineola, NY.*

Background: Cardiovascular mortality in hemodialysis patients is up to 20 times that of the general population. This increased mortality has been thought to occur partly due to chronic inflammation and accelerated atherogenesis. The purpose of this ongoing study is to examine the potential of ferric citrate (FC), a recently FDA approved phosphate binder, to improve cardiovascular risk by decreasing inflammatory markers and lipid levels in patients on hemodialysis (HD).

Methods: This is a prospective, non-controlled trial with a target enrollment of 30 participants. Inclusion criteria were HD for ≥ 6 months, phosphate binder use, maintenance intravenous iron (IV Fe) use, dialysis via a fistula, and serum phosphorus (Phos) level between 2.5 to 8.0 mg/dl. Patients with signs of ongoing inflammation, blood transfusion within 3 months, and IV Fe loading within 2 weeks were excluded. After a 2-week wash-out period from their current phosphate binder, FC was initiated and dosed by study investigators according to a previously published protocol. Anemia management was left to the discretion of the subject's nephrologist. Serum levels of ferritin, other inflammatory markers (c-reactive protein, homocysteine, TNF-alpha, IL-6 and IL-8), lipid levels, and Phos were measured at 0 and 6 months. ESA and IVFe requirements in the 6 months prior to the study and during the study period were calculated.

Results: 18 patients have completed the required 6 months. The average age of the completing participants was 58 years, 78% were male, and 61% were white. Phos levels declined significantly from 6.92 ±1.61 to 5.38±1.22 mg/dl (p=0.002). Cumulative IV Fe dose used during the 6 months of the study as compared to the 6 months prior to the study decreased by 46% (p=0.011). There were no significant changes in ferritin levels, inflammatory markers, lipid levels or ESA use.

Conclusions: This study found that while improving Phos, FC significantly decreased the amount of IV Fe used in HD patients during the 6 months of the study as compared to the 6 months prior to the study. Participants were able to maintain their iron stores as there were no significant changes in ferritin levels. Larger trials are needed to confirm these effects.

Funding: Commercial Support - Keryx biopharmaceuticals

PUB292

Quality of Life with Reference to Haemoglobin Levels and Erythropoietin Use in a Rural Tertiary Care Centre Beena Unnikrishnan. *SMIMS, Kulashekaram, Trivandrum, India.*

Background: The relationship between quality of life and anemia has been the subject of recent debates. The study was done in a rural setting where major number of patients cannot afford medications and let alone dialysis. The participants of this study are undergoing twice and thrice weekly hemodialysis. Yet most of them are independent.

Methods: This study examines the relationship between Kidney Disease Quality of Life questionnaire domains(KDQOL) and Hemoglobin (Hgb) levels in 157 patients with ESRD on Hemodialysis followed in Sree Mookambika Institute Of Medical Sciences over the period of six years. QofL measures were compared in a stepwise fashion for Hemoglobin levels of <8, 8- <10, 10 to <12, 12 to 13, and ≥13. Student t test was used to examine the relationship between quality of life scores and Hgb level, age, and albumin level; a history of diabetes, congestive heart failure, or myocardial infarction; use of erythropoetic stimulating agents (ESA); and the level of hemoglobin level and ESA. Out of the 157 patients who participated, only 60 (38%) of them are taking erythropoietin. Even among the 60 only 15 (25%) are taking regularly.

Results: The increasing Hb levels are statistically significant correlation with increases in kidney disease domain scores on the kidney disease component of the questionnaire (p=0.042). About the SF36 component, the difference between 5 groups of Hb levels were significant in the general health (p=0.023), role emotion (p=0.015), social functioning (p=0.008), and mental component summary scores (p=0.039). The most dramatic improvements in these various domains occurred between the 8- <10, and the 10 to <12 group. Quality of life was better among those who are taking erythropoietin compared with the haemoglobin levels but the difference was not statistically significant (P=0.018)

Conclusions: The difference of the Hb levels were statistically significant with differences in the effects of kidney disease, general health, role emotion, and social function scores, and mental component summary scores of the KDQOL-SF questionnaire. Long-term assessment should be considered. These findings have implications for the care of hemodialysis patients in terms of the Hb target and the of erythropoietin (EPO) therapy. It has been suggested that the treatment of anemia of ESRD patients should be individualised.

PUB293

Influence of Iron Deficiency on Contractility in Dialysis Patients Gustavo Laham,[1] Maximo A. Schiavone.[2] *[1]None, Buenos Aires, Argentina; [2]Medicina Interna, Universidad Austral, Pilar, Argentina.*

Background: The major cause of mortality is cardiac arrytmia and sudden death. The key factors are in the cardiac and vascular function. We postulate the rol of anemia and iron load related to this cardiac disfunction. We analyze the prevalence of anemia and iron deficiency on dialysis patient and establish teh rol of iron in ventricular contractility.

Methods: 102 patients attended the interdialysis day to undergo a hemodynamic evaluation. Iron metabolism was measured: serum iron, ferritin and transferrin saturation (TSAT). The patients were then classified into 2 groups according to the presence (Group 1) or not (group 2) of anemia, (hemoglobin (hb) < 13 g / l men and < 12 g / l women, in order to evaluate subgroup separately. In assessing the interaction of iron metabolism on ventricular contractility (d2z / d2t) were considered as dependent variable, adjusting by age, gender, BP, anthropometric variables, TFC, dialysis time and medication to through a multiple regression (Backward Stepwise Regression). Multiple regressions were performed on the total sample and on each subgroups separately

Results: We included 91 patients (age: 58.89, SBP: 143 mmHg, DBP: 80.83 mmHg, women 53.8%, LVMI: 149.63, EPR 0.525,% FEY 63.15, Ferremia 66.44, Ferritin 368.8, TSAT 26.593). 43,96 % patients had anemia, corresponding to group 1. In group 2, 51 patient (56.04%). In the multiple regressions were significant: hb (p = 0.016, serum iron (p = 0.009), TSAT (p=0,038). In the specific analysis of group 1: Hb (p = 0.011), serum iron (p = 0.05), TSAT (p = 0.03). For group 2, Ferritin (p = 0.026), serum iron (p = 0.01) and TSAT (p=0,018) were significant as independent variables for contractility.

Conclusions: In this study we demonstrated the association of iron on contractility regardless of the presence or not of anemia in dialysis patients. These findings correlate with those studies performed in patients with heart failure, except that our population has a conservative ejection fraction, with the majority of studies with patients with decreased ejection fraction.

PUB294

The Relationship between Peripheral Artery Disease and Frailty in Patients with Chorionic Hemodialysis Hidemi Takeuchi,[2] Michihiro Okuyama,[2] Haruhito A. Uchida,[1] Yuki Kakio,[2] Yuka Okuyama,[2] Ryoko Umebayashi,[2] Hitoshi Sugiyama,[3] Jun Wada.[1] *[1]Okayama Univeristy, Okayama, Japan; [2]Okayama University, Okayama, Japan; [3]Okayama University Graduate School, Okayama, Japan.*

Background: The clinical condition of frailty is a common problem in the elderly population. Chronic hemodialysis (HD) patients often have peripheral artery disease (PAD) as a vascular complication. However, the relationship between PAD and frailty in HD patients remains unknown. The aim of this study was to identify the relationships among PAD and risk factors in chronic HD patients.

Methods: This study was a multi-center, cross-sectional and observational investigation which was conducted at 6 institutions. Subjects were all chronic HD patients. To evaluate frailty, we used the modified Fried's frailty phenotype adjusted for Japanese as the self-reported questionnaire, and measured each physical domain. Furthermore, we calculated ankle-brachial index (ABI) to define PAD. PAD was defined according to the definition of TASC II (Trans-Atlantic Inter-Society Consensus II).

Results: Of the 542 patients in all institutions, 362 were enrolled in this study. Sixty-two patients (17.1%) were categorized as PAD group and 300 patients (82.9%) as non-PAD group. In the PAD group, the prevalence of frailty was significantly higher than that in the non-PAD group (34% vs 18%, P = 0.010). Non-shunt side grip strength was

significantly stronger in the non-PAD group compared to PAD group (23.6 kg vs 17.0 kg, P < 0.001). Thigh circumferences (the mean of both sides) were also significantly larger in the non-PAD group compared to PAD group (41.7 cm vs 39.7 cm, P = 0.005). Univariate regression analyses showed that frailty, age, number of oral medicine, and history of myocardial infarction (MI) had significant correlations with PAD. Multivariate logistic regression analysis demonstrated that the factors independently associated with PAD were as follows: frailty (OR = 2.061, 95% C.I. 1.091-3.894, P =0.030) and MI (OR = 3.742, 95% C.I. 2.051-6.831, P < 0.001).

Conclusions: PAD is associated with frailty in HD patients.

PUB295

Assessment of Fluid Shifts of Dialysis Patients Using Plasma Water Index to Predict Intradialytic Hypotension Tadashi Otsuka, Ryohei Kaseda, Yoshikatsu Kaneko, Ichiei Narita, Yuuki Yoshioka. *Niigata University, Chuo-ku, Niigata, Japan.*

Background: Intradialytic hypotension (IDH) is the major risk factor for mortality in hemodialysis (HD), which often occurs when plasma fluid removal outpaces the rate of refilling in the patient whose dry weight (DW) is underestimated to prevent congestive heart failure (CHF). There is no standard measure of ultrafiltration on fluid shifts in the extra- and intracellular fluid spaces. We aimed to put plasma weight index (PWI) into practical use for probing relevant DW, as a marker of plasma refilling rate, and categorized patient's fluid shifts in combination with hANP, an intravascular volume marker. In addition, relationships between those markers and pretibial edema (PTE) just before HD, as an interstitial fluid marker, were examined.

Methods: This study retrospectively examined records of 156 dialysis patients from December 30, 2015, to January 5, 2016 in Tachikawa medical hospital. IDH was defined by current KDOQI guidelines [a decrease in either systolic BP (SBP) ≥ 20 mmHg or mean arterial pressure≥10 mmHg as well as associated symptoms]. CHF group was defined as patients with dyspnea and lower SpO2 level (<96%).

Results: IDH and CHF occurred in 28.2% and 7.7% of all patients respectively. Patients with IDH had higher PWI levels than those without IDH (1.71±2.40 vs. 2.65±1.70, P = 0.007). PWI > 2.0 was predictive of high incidence of IDH (OR = 2.40, 95%CI, 1.12-5.12, P = 0.020), but not associated with incidence of CHF (OR 1.00, 95%CI, 0.30-3.30, P = 1.000). On the other hand, hANP >100 pg/ml was predictive of high incidence of CHF (OR 3.52, 95%CI, 1.06-11.71, P = 0.004), but not associated with incidence of IDH (OR 0.79, 95%CI, 0.37-1.71, P = 0.5504). We subdivided the patients into 4 groups by the two cut-off points of PWI and hANP. In the PWI < 2.0/hANP < 100 pg/ml group, there was no CHF occurrence and incidence of IDH was relatively low (23.7%). PWI of patients with PTE was lower than those without PTE (1.68±2.34 vs. 3.07±1.51, P < 0.001), and hANP had no significant difference between those with or without PTE (62 pg/ml; IQR 39-128 vs. 52 pg/ml; IQR 27-93, P = 0.060).

Conclusions: Assessment of fluid shifts by PWI and hANP would be useful for determination of DW. Moreover, PTE keeps fluid in interstitium and become a reservoir to intravascular volume during HD. Thus, PTE is possible to keep blood pressure during HD.

PUB296

Association of Oral Mucosal Lesions with Mortality in Patients Treated with Hemodialysis: The Oral-D Multinational Cohort Study Marinella Ruospo,[1] Suetonia Palmer,[2] Jorgen B. Hegbrant,[1] Giovanni F. Strippoli.[1,3] *[1]Diaverum, Lund, Sweden; [2]University of Otago, Christchurch, New Zealand; [3]University of Bari, Bari, Italy. Group/Team: ORAL-D investigators.*

Background: Oral mucosal lesions are highly prevalent and frequently severe in patients with CKD, but little is known about the association of oral mucosal lesions such as precancerous or infectious lesions with adverse clinical outcomes in haemodialysis patients. We evaluated the association of oral mucosal lesions with all-cause and cardiovascular mortality in the setting of hemodialysis.

Methods: The ORAL-D study was a multinational prospective cohort study involving haemodialysis patients from 7 countries in Europe and Argentina. Oral and mucosal lesions were evaluated at baseline by trained dentists using calibrated WHO standardized protocols. The association of oral mucosal disease with total and cardiovascular mortality was estimated by random-effect Cox regression models adjusted for age, gender, smoking, MI, stroke, diabetes, albumin, phosphorus, time on dialysis, BMI, blood pressure, occupation, and country. Sensitivity analysis utilized a shared frailty model clustering by country.

Results: The ORAL-D study involved 4,205 patients (61.6±15.6 years, 58% men) during July 2010-February 2012. Median follow up was 23.7 months. Prevalence of pre-malignant lesions was: leukoplakia (3.5%); erythroplakia (4%); neo-formations (2%). Prevalence of oral infections was: thrush (4.6%); herpes (0.5%). Other lesions included scrotal tongue (10.7%), geographical tongue (4.9%), petechial lesions (7.9%), and ulcers (1. 7%). In unadjusted survival analysis, any oral precancerous or infectious mucosal lesion was associated with all-cause mortality (HR 1.32, 95% CI 1.08-1.63 and 1.28, 0.99-1.65) and cardiovascular mortality (1.60, 1.22-2.09 and 1.39, 0.98-1.97). After adjustment, there was no association between oral precancerous lesions and total (HR 0.79, 95% CI 0.53-1.17) and cardiovascular (0.75, 0.42-1.32) mortality. Similarly, no association was found between infectious lesions with total (1.30, 0.81-2.07) or cardiovascular (1.63, 0.87-3.02) mortality. Results were similar when clustered by country.

Conclusions: Oral precancerous or infectious lesions were not associated with all-cause or cardiovascular mortality after 2 years in dialysis patients.

PUB297

Fruit Intake and Cardiovascular and All-Cause Mortality in Adults on Hemodialysis: The DIET-HD Multinational Cohort Study Valeria M. Saglimbene,[1,3] Germaine Wong,[1] Jonathan C. Craig,[2] Jorgen B. Hegbrant,[3] Giovanni F. Strippoli.[4,3] *[1]University of Sydney, Sydney, NSW, Australia; [2]University of Sydney/Children's Hospital, Sydney, NSW, Australia; [3]Diaverum Medical Scientific Office, Lund, Sweden; [4]University of Bari, Bari, Italy. Group/Team: For DIET-HD investigators.*

Background: High fruit intake is associated with reduced cardiovascular risk in the general population, but it is generally discouraged in hemodialysis due to risks associated with hyperkalemia.

Methods: Using data from the DIET-HD study, a prospective cohort study (January 2014-January 2016) in 9757 adults treated with hemodialysis in Europe and South America, fruit intake (portions/day) was measured by the validated GA²LEN food frequency questionnaire. Adjusted cox regression analyses clustered by country were conducted to evaluate the association of fruit intake with cardiovascular and all-cause mortality.

Results: During a median follow up of 1.5 years (8108 person-years), there were 1214 deaths including 515 attributable to cardiovascular causes. Overall there was no association between total fruit intake (one portion (70 g) increase per day) and cardiovascular (adjusted hazards ratio 1.00, 95% confidence interval 0.97-1.02) and all-cause mortality (0.99, 0.97-1.00). Apple consumption (≥ 1 apple per day versus none) was associated with lower risks of cardiovascular (0.67, 0.52-0.88) and all-cause (0.83, 0.69-0.98) mortality. Higher consumption (one fruit increase per day) of avocados (2.75, 1.28-5.91) and apricots (1.84, 1.26-2.69) was associated with increased cardiovascular mortality.

Conclusions: There was no overall association between fruit consumption and all-cause and cardiovascular mortality for patients on hemodialysis, but daily apple consumption may be associated with lower mortality in this clinical setting.

PUB298

Clinical Profile and Survival of Children and Adolescents under Renal Replacement Therapy in a Single Center in Brazil Maria Goretti M. Penido,[2,4] Celina F. Rezende,[3] Andre S. Alvarenga,[3] Mariangela L. Cherchiglia,[1] Viviane L. Nery.[3] *[1]Federal University of Minas Gerais, Belo Horizonte, Brazil; [2]Pediatric Nephrology Unit, Santa Casa de Belo Horizonte Hospital, Belo Horizonte, Brazil; [3]Nephrology Center, Santa Casa de Belo Horizonte Hospital, Belo Horizonte, Brazil; [4]Pediatric Nephrology Unit, Federal University of Minas Gerais, Belo Horizonte, Brazil.*

Background: There are few available data that estimate the clinical profile and survival of pediatric renal replacement therapy (RRT). The aim of this study was to outline the clinical profile and survival of 82 children and adolescents under RRT followed at the Nephrology Center of Santa Casa Hospital in Belo Horizonte, from 2008 to 2016.

Methods: Cohort study with children and adolescents <18 years old with at least 3 months of registration to cohort admission. Patients excluded were those who died in the first 3 months under RRT, acute patients and those ≥18yrs. The databases of the Center as well as patient records were consulted. The following statistic tests were used: Student t, Mann Whitney, Wilcoxon, Fisher exact test and Kaplan-Meyer curves.

Results: We evaluated 82 pediatric patients (52M) with the median age of 9.5 years. 57% showed low height-for-age-and-gender and the BMI was normal in 88%. The primary diagnosis was glomerulonephritis (36.6%), 82% were followed by nephrologists before beginning RRT, and 64.5% presented residual diuresis. Comparison between the admission exams vs 6 and 12 month exams after the beginning of the RRT, showed significant statistical growth of hemoglobin, albumin, alkaline phosphatase, parathyroid hormone and calcium levels. Hemodialysis was the main treatment modality (71%). The long-term double-lumen catheter was the most used vascular access (49%). During the study, 34 patients (41.5%) were transplanted and 94% received the graft from deceased donors. The median waiting time in RRT until the transplant was 20 months, and the median age of transplantation was 12 years of age. The survival rate in 8 years was 80.6%, with sepsis being the main cause of death (56%).

Conclusions: The majority of our patients were male, with glomerulonephritis, followed by nephrologists before starting RRT, on hemodialysis, with the long-term double-lumen catheter for vascular access. 34 patients were transplanted and received the graft from deceased donors. The median time on a waiting list and the age of transplantation was 20 months and 12 years, respectively. The survival in 8 years was 80.6%, with sepsis as the main cause of death. More studies are needed to improve the quality of care provided to pediatric RRT patients.

PUB299

Epidemiological, Social, and Economic Profile of Children and Adolescents under Renal Replacement Therapy in a Single Center in Brazil Maria Goretti M. Penido,[2,3] Celina F. Rezende,[4] Andre S. Alvarenga,[4] Mariangela L. Cherchiglia,[1] Viviane L. Nery.[4] *[1]Federal University of Minas Gerais, Belo Horizonte, Brazil; [2]Pediatric Nephrology Unit, Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; [3]Pediatric Nephrology Unit, Federal University of Minas Gerais, Belo Horizonte, Brazil; [4]Nephrology Center, Santa Casa de Belo Horizonte, Belo Horizonte, Brazil.*

Background: Pediatric chronic kidney disease is a long-term disease and is associated with morbity, premature death and low quality of life. The progressive decline of renal function compromises all organs of the organism as well as psyche, behavior, family dynamics and income. The aim of this study was to outline the epidemiological, social and economic profile of 82 pediatric patients under renal replacement therapy (RRT) followed at the Nephrology Center of Santa Casa Hospital in the city of Belo Horizonte from 2008 to 2016.

Methods: Cohort study with children and adolescents <18 years old with at least 3 months of registration to cohort admission. Patients excluded were those who died in the first 3 months under RRT, acute patients, and those ≥18 years of age. The databases of the Center as well as patient records were consulted. The following statistic tests were used: Student t, Mann Whitney, Wilcoxon and Fisher exact test.

Results: We evaluated 82 pediatric patients (52M) with the median age of 9.5 years and the following age ranges: infants (16%), preschoolers (22%), school-aged (28%), adolescents (34%). Fifty-seven patients did not live in Belo Horizonte and the mother was the caretaker in 80.5%. The *per capita* income was ≤1 minimum wage in 89%, 95% of the patients received RRT from the government, 60% use government transportation for their treatment, and the majority (94%) are enrolled at the primary care unit and received the majority of their medicines from those units. Among those at scholastic age (54), 85% attended school regularly. Fifty-seven percent showed low height-for-age-and-gender and the body mass index was normal in 88%. Hemodialysis was the main treatment modality (71%).

Conclusions: The profile of our pediatric patient was: a boy with low height, on hemodialysis, older than 7 years of age, not living in the city, *per capita* income was ≤1 minimum wage, enrolled at primary care unit, receiving RRT and transportation from the government, attending school regularly, cared for by their mothers. More studies are needed to improve the understanding of the epidemiological, economic and social characteristic of pediatric RRT.

PUB300

Agreeability between Dialysis Unit Blood Pressure and Ambulatory Blood Pressure Monitoring in Dialysis Patients Paras Dedhia, Rachana H. Jasani, Viswanath Billa, SHRIRANG BICHU, Rajesh B. Kumar. *Apex Kidney Foundation, Mumbai, India.*

Background: Hypertension in dialysis population is associated with increased cardiovascular mortality and morbidity. Majority of therapeutic decisions are taken based upon dialysis unit blood pressure (BP) readings.

Methods: Ambulatory BP monitoring (ABPM) was performed for 44 hours in between 2 dialysis sessions beginning immediately post-dialysis. ABPM was recorded every 20 min during the day (7 am to11 pm) and every 30 min during night (11 pm to 7 am) on non-fistula arm. ABPM data with less than 70% readings were excluded from the study. Hourly means were averaged to obtain interdialytic systolic and diastolic blood pressure readings over 44 hours. Pre and post dialysis blood pressure were recorded by dialysis personnel using oscillometric device attached to dialysis machine. These pre and post dialysis unit BP measurements were averaged over one week. Agreement between dialysis unit blood pressure and interdialytic ABPM were assessed by Bland-Altman plot and Lin's concordance correlation coefficient (CCC).

Results: Of 40 patients, 68% were males. Average age was 54.5± 12.3 years. Mean dialysis vintage was 2.85± 2.9 years. About 49% were diabetic, 97% were hypertensive and 23% had IHD. Mean 44 hour ABPM reading was 142.9 ± 18.6/ 82.6±13.8 mm Hg. Limits of agreement between dialysis unit blood pressures and ABPM were wide across all BP parameters by bland-altman plot. Lin's CCC (see table) also showed poor agreement between two readings (ABPM and dialysis unit readings).

Conclusions: There is a disagreement between dialysis unit blood pressure and ABPM. Irrespective of BP parameter, agreement remains poor between 2 measurements. We suggest assessing out of dialysis unit BP readings to make therapeutic decisions in dialysis patients.

Agreement between dialysis unit BP and ABPM

Blood pressure parameters	Limits of agreement	Lin's CCC
Pre dialysis SBP	-31.6 to 25.7	0.70
Pre HD DBP	-16 to 21.7	0.70
Post HD SBP	-36.4 to 32.3	0.64
Post HD DBP	-16.2 to 21.5	0.75
1 week average pre and post HD SBP	-28.7 to 23.6	0.74
1 week average pre and post HD DBP	-11.8 to 17.1	0.81

PUB301

Intradialytic Bioimpedance Cardiography Measurement to Assess Cardiovascular Responses during Hemodialysis Jining Wu, Hong Ye, Junwei Yang. *Second Affiliated Hospital, Nanjing Medical University, Nanjing, China.*

Background: In hemodialysis, extracorporeal circulation is applied to remove accumulated uremic toxins, electrolyte and fluid in plasma into the dialysate through a membrane during a 4h HD session 3 times a week. The rate of exculsion in 4h is approximately 10 times faster than that of previous accumulation for 2 or 3 days. Hemodynamic stress during HD results in recurrent segmental ischemic injury that drives cumulative cardiac damage. We performed an observational study of the cardiovascular effect of dialysis sessions using intradialytic thoracic bioimopedance cardiography to examine the acute effects of standard HD in stable patients.

Methods: In this observational study, we enrolled 114 patients from a single hemodialysis unit. Bioimpedance cardiography measurements included cardiac index, stroke volume index, systemic vascular resistance index, acceleration index and thoracic fluid content.

Results: Patients had mean±SEM ultrafiltration rates of 3.8±2.9 ml/kg per hour during HD. All measures of systolic contractile function fell during HD, with partial recovery after dialysis. Interestingly, during the first 5 mins of hemodialysis, cardiac index and stroke volume index reduced obviously compared to the base lever before dialysis. All patients experienced some degree of segmental left ventricular dysfunction, with severity proportional to ultrafiltration rate and BP reduction.

Conclusions: It suggested that bioimpedance cardiography could assess the acute cardiac effects of dialysis during hemodialysis treatment. And fluid overload could in part explain the fell of cardiac index during dialysis.

Funding: Government Support - Non-U.S.

PUB302

Monitoring Volume Status Using Bioelectrical Impedance Analysis in Chronic Hemodialysis Patients So-hee Jeong, Jin Ho Hwang, Su Hyun Kim, Jung-ho Shin. *Chung-Ang University Hospital, Seoul, Republic of Korea.*

Background: Fluid overload can be an independent risk factor of cardiovascular events and all-cause death in end-stage renal disease (ESRD) patients on chronic hemodialysis. We performed a retrospective study to investigate whether intermittent control of fluid status decreases the rate of these complications using bioelectrical impedance analysis (BIA).

Methods: In ESRD patients on chronic hemodialysis, we identified the ratio of extracellular water to total body water (ECW/TBW) every 6 months using InBody S10 (Biospace, Seoul, Korea), which was measured within 30 minutes after dialysis initiation on the first dialysis day of the week. The uncontrolled group included 57(40.1%) patients with all ECW/TBW measurements ≥0.40; in contrast, the controlled group included 85 (59.9%) with any measured ECW/TBW <0.40.

Results: Included patients were followed for 29 (12, 42) months. The risk of cardiovascular events was higher in the uncontrolled group (HR 2.4, 95% CI 1.2–5.1; $P < 0.05$) than it was in the controlled group; however, this difference disappeared after adjusting for age, sex, and Charlson comorbidity index (not significant). On the other hand, the patients in the uncontrolled group had a higher risk of all-cause death than did those in the controlled group, independent of age, sex, and Charlson comorbidity index (HR 4.7, 95% CI 1.4 – 16.1; $P < 0.05$).

Conclusions: Monitoring volume status using BIA may help to predict all-cause death in chronic hemodialysis patients. Further controlled studies are needed to confirm that strict volume control could reduce the rates of cardiovascular events and mortality in this population.

PUB303

Increased QRS Width Predicts Mortality in Patients on Maintenance Haemodialysis Tony Amin,[4] Lawrence P. McMahon,[3] Matthew A. Roberts,[1] Md nazmul Karim,[2] Catherine Brumby.[3] *[1]Eastern Health, Blackburn, VIC, Australia; [2]Monash University, Melbourne, NSW, Australia; [3]None, Box Hill, VIC, Australia; [4]Renal, Eastern Heath Service, Melbourne, Melbourne, VIC, Australia.*

Background: Cardiovascular mortality is the leading cause of death in haemodialysis patients. We assessed the association of QRS width and corrected QT interval (QTc) on a 12 lead electrocardiography (ECG) with mortality and cardiovascular events (CVE).

Methods: We analysed ECGs performed as part of routine care between March 2013 and June 2014 in 104 maintenance haemodialysis patients. The QRS and QTc duration were calculated by the ECG software and recorded. All-cause-mortality and CVE were determined between December 2013 and December 2015. CVE was defined as a new acute coronary syndrome and or sudden cardiac death. Predictors of mortality and CVE were identified through univariate association and were confirmed by multivariate logistic regression, thus adjusting for possible confounders.

Results: During the 2-year follow-up, 24 deaths and 19 CVE occurred. Patients who died had a significantly higher QRS (119.1 ± 30.8 msec) than patients who survived (99.6±25.0 msec; P=0.002). Similarly, patients with CVE (121.7±35.6 msec) had significantly higher QRS than patients with no CVE (100.1±23.9 msec; P=0.002). QTc Duration did not differ significantly across death or CVE status. The odds of all-cause mortality (OR 1.026, 95% CI 1.006,1.047; p=0.012) and CVE (OR 1.028, 95% CI

1.005,1.051; p=0.016) were increased for each msec increase in QRS width, adjusted for age, gender, duration on dialysis, coronary artery disease status, diabetes status and urea reduction rate (URR).

Conclusions: Prolonged QRS is significantly associated with all-cause mortality and cardiovascular events in patients receiving maintenance haemodialysis.

Funding: Private Foundation Support

PUB304

Stakeholder Priorities for Cardiovascular Outcomes for Trials in Hemodialysis Emma O'Lone,[4,7] Andrea K. Viecelli,[1] Martin Howell,[6] Allison Tong,[2] Jonathan C. Craig,[5] David C. Wheeler.[3] *[1]Sir Charles Gairdner Hospital, Perth, NSW, Australia; [2]The University of Sydney, Sydney, NSW, Australia; [3]University College London, London, United Kingdom; [4]University of Sydney, Sydney, NSW, Australia; [5]University of Sydney/Children's Hospital, Sydney, NSW, Australia; [6]University of Sydney, Sydney, NSW, Australia; [7]Renal Department, Royal North Shore Hospital, Sydney, NSW, Australia. Group/Team: SONG-HD Cardiovascular Disease Expert Working Group.*

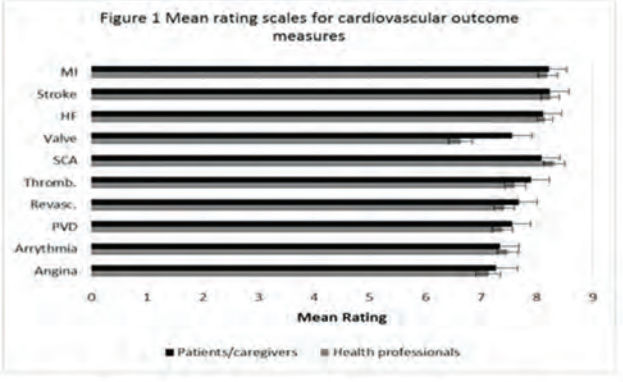
Background: Cardiovascular disease (CVD) is life-threatening and critically important for patients on hemodialysis, their caregivers and health professionals but has been measured inconsistently and variably across trials in hemodialysis.

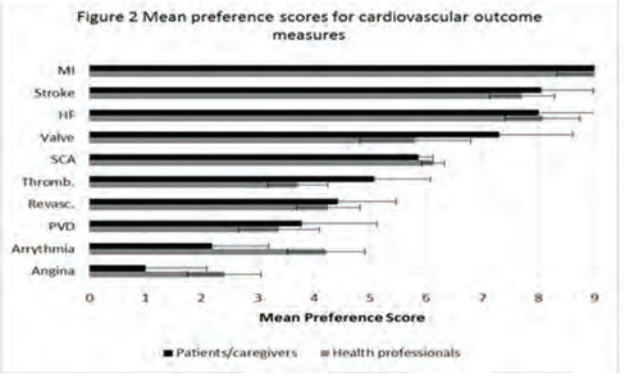
Methods: In an international online survey (available in English, Hindi), participants rated the importance of ten cardiovascular outcomes (derived from a systematic review) on a 9-point Likert Scale, with a score of 7-9 suggesting critical importance. To determine relative importance participants also completed a best-worst scale. Means, medians and proportions were analyzed for each outcome.

Results: In total, 395 participants (including 105 [27%] patients/caregivers) from 51 countries participated. The mean rating and mean preferences scores (both with 95% confidence intervals) are shown in Figure 1 and 2. In absolute terms, all outcomes were rated as critically important (mean score >7), by both patients and healthcare professionals. On relative preference, myocardial infarction was found to be the most important outcome by all stakeholders.

Conclusions: Patients and health professionals identify all cardiovascular outcomes as important but myocardial infarction as the most important outcome to be measured in hemodialysis trials.

Funding: Government Support - Non-U.S.





PUB305

Aldosterone and Insulin Resistance: A Vicious Combination in Patients on Maintenance Hemodialysis Hitoshi Minakuchi,[3] Shu Wakino,[1] Hiroshi Itoh.[2] *[1]Keio University, Tokyo, Japan; [2]Keio University School of Medicine, Tokyo, Japan; [3]school of medicine, Keio University, Tokyo, Japan.*

Background: We recently showed that in patients with chronic kidney disease, insulin resistance (IR) is associated with an increase in plasma aldosterone levels (Kidney Int., 2013). However, the role of this association in patients on maintenance hemodialysis has not been determined.

Methods: A total of 128 patients on hemodialysis were enrolled. The associations of plasma aldosterone or insulin resistance with various parameters were examined. Blood specimens were collected after overnight fasting and IR was evaluated by the homeostasis model of insulin resistance (HOMA-IR). We defined the patients both of whose aldosterone and HOMA-IR were above the tertile of each parameter in this cohort as HH group. Various clinical parameters in HH group were compared to those in control group both of whose aldosterone and HOMA-IR were below the median of each parameter.

Results: Aldosterone levels were associated with age, HbA1c levels, HOMA-IR, and plasma levels of albumin, creatinine, potassium, uric acid, and insulin. Multiple regression analysis showed that the HOMA-IR was independently associated with aldosterone levels. Aldosterone levels were also associated with cardiac hypertrophy and with carotid artery stenosis. The HOMA-IR was associated with age, sex, past history of diabetes or dyslipidemia, body mass index, HbA1c, platelet count, hemoglobin, white blood cell count, and Kt/V, plasma levels of total protein, creatinine, uric acid, phosphorus, high-density lipoprotein, triglycerides, and aldosterone. Multiple regression analysis showed that age, sex, uric acid, body mass index, and aldosterone were independent risk factors. The HOMA-IR was associated with cardiac hypertrophy. HH group exhibited more severe cardiac hypertrophy, contractile dysfunction and carotid artery stenosis as compared with control group.

Conclusions: In patients on maintenance hemodialysis, plasma aldosterone levels and insulin resistance are closely interrelated, each of which is associated with cardiovascular tissue damages. The constellation of increased aldosterone levels and insulin resistance is related to severe cardiovascular damages.

PUB306

Geographical Variations of Comorbidities in ESRD Patients Yue Jiao, Marta Reviriego-Mendoza, John W. Larkin, Len A. Usvyat, Jeffrey L. Hymes, Franklin W. Maddux. *Fresenius Medical Care North America, Waltham, MA.*

Background: Patients with end stage renal disease (ESRD) are known to commonly suffer from several comorbidities including anemia, vascular diseases, and diabetes. National benchmarks exist for many comorbidities in ESRD patients, yet geographical profiles have not been defined. We characterized the prevalence of common comorbidities in dialysis patients by geography in the United States and investigated whether geographical variations exist.

Methods: Data from patients treated at Fresenius Kidney Care clinics in 2016 was analyzed. We characterized the 17 common comorbidities in patients: anemia, cardiac dysrhythmias, diabetes, hepatitis, infection, peripheral or arterial vascular disease, congestive heart failure, hyperparathyroidism, chronic obstructive pulmonary disease, pneumonia, ischemic heart disease, myocardial infarction (including cardiac arrest), cerebrovascular disease, cancer (except skin neoplasm), drug or alcohol dependence, HIV/AIDS and gastrointestinal bleed. Patients were stratified according to the number of comorbidities: ≥1, ≥4, ≥8 or ≥12. We calculated the mean, maximum, and minimum percentages of patients with the selected comorbidities within each of the 50 states in the United States.

Results: Data from 246,903 patients was analyzed. Of the 17 comorbidities investigated, we observed nationally that a mean of 91.2% of patients had ≥1 comorbidity (range: 68.2% to 96.4%), 20.9% had ≥4 comorbidities (range: 4.5% to 35.5%) and 0.81% had ≥8 comorbidities (range: 0% to 2.8%). We identified considerable variations in the number of comorbidities affecting patients in differing states. For instance, in West Virginia 35.52% of patients suffered from ≥4 of the comorbidities, while in North Dakota only 4.55% had ≥4 of the comorbidities. For cardiac dysrhythmias, we found that in patients residing in New Hampshire exhibited the highest prevalence (17.9%) and those in New Mexico (4.3%) had the lowest prevalence. Similar disparities were identified among the 17 comorbidities investigated.

Conclusions: Our analysis indicates that profiles of comorbidities affecting ESRD patients vary by geography. These findings may be useful for the development of improved management strategies that account for regional health disparities.

Funding: Commercial Support - Fresenius Medical Care North America

PUB307

Effect of Albumin on the Efficacy of Fluid Removal in Hypoalbuminemic Patients Donia Ahadian,[1] Etienne Macedo,[1] Bethany E. Karl,[1] Ravindra L. Mehta.[2] *[1]University of California San Diego, San Diego, CA; [2]University of California San Diego Medical Center, San Diego, CA.*

Background: Intradialytic hypotension limits adequate fluid removal in hypoalbuminemic patients with acute kidney injury (AKI) or end stage renal disease (ESRD). Intravenous albumin has been used in such patients with varying results.

Methods: We are conducting a prospective cohort interventional study that included 31 patients with albumin levels less than 3 g/dl with AKI or ESRD who required fluid removal with hemodialysis. In this cross-over design patients were randomized to receive 100mL of either 0.9% sodium chloride or 25% albumin intravenously prior to their first dialysis session and alternated between the two solutions until up to 6 sessions. Patients' vital signs and ultrafiltration removal rate were recorded every 30 minutes during dialysis. 116 dialysis sessions were completed in total, 60 received normal saline and 56 received albumin.

Results: Intradialytic hypotension was defined as a decrease in systolic blood pressure by ≥ 20 mm Hg or a decrease in mean arterial pressure by 10 mm Hg. In total, 77 hypotension episodes (48 in saline and 29 in albumin groups) occured in 39 dialysis sessions (20 in saline and 19 in albumin groups). The median total number of hypotension episodes was 2 for saline and 2 for albumin group (p value=0.68). Hypotension occurred 30 minutes after the start of dialysis in saline versus 37 minutes in the albumin groups (p

value=0.81). The median hypotension duration was 45 minutes for saline and 30 minutes for albumin groups (p value 0.32). In the 48 saline hypotension episodes, 24 (50%) were accompanied by hypotensive symptoms, 11 (22.9%) required saline administration, and 16 (33.3%) required the ultrafiltration rate to decrease or to stop as therapeutic interventions. In the 29 albumin hypotension episodes these numbers were 12 (41.4%), 3 (10.3%), and 8 (27.6%), respectively. In albumin sessions more ultrafiltration fluid was removed compared to saline sessions (-2000 mL in albumin versus -1700 mL in saline).

Conclusions: In hypoalbuminemic patients who need hemodialysis, addition of albumin prior to dialysis results in later onset of hypotension, less incident of hypotensive symptoms, fewer hypotension therapeutic interventions such as saline administration or ultrafiltration rate decrease, shorter duration of intradialytic hypotension, and larger volume of fluid removed. However, these results were not statistically significant.

Funding: Commercial Support - Grifols

PUB308

Associations of Endothelial Function, Arterial Stiffness, and Heart Rate Variability with Physical Activity Anoop Sheshadri,[3] Piyawan Kittiskulnam,[1] Kirsten L. Johansen.[2] *[1]Chulalongkorn university, Bangkok, Thailand; [2]University of California, San Franicsco, San Francisco, CA; [3]University of California, San Francisco, San Francisco, CA.*

Background: In the general population, higher levels of PA are associated with lower cardiovascular risk and better endothelial function, but it is not clear whether the association holds at the lower end of the PA spectrum. We sought to determine whether PA is associated with endothelial function and heart rate variability.

Methods: We recruited 55 dialysis patients ≥18 years of age receiving in-center hemodialysis (HD, n=47) or peritoneal dialysis (PD, n=8), on dialysis for ≥3 months and able to walk. We measured PA by pedometer. We tested endothelial function (reactive hyperemia index or RHI), using the EndoPAT-2000, which measures flow-mediated dilation after a 5-minute arterial occlusion, and also measures arterial stiffness (augmentation index adjusted to heart rate of 75 or AI75), and heart rate variability (standard deviation of NN intervals or SDNN). All measurements were taken before HD sessions for those patients on HD.

Results: Participants' median age was 58 years and 80% were male. Overall, PA was low at 2631, IQR 1361-5176 steps per day. RHI was impaired for the group as a whole (median RHI and IQR 1.57, 1.34 – 1.87), as was SDNN at 20.55, IQR 12.55 – 31.92. AI75 was not substantially impaired at 11, IQR -2 – 22%. After adjusting for age and sex, PA was not statistically significantly associated with endothelial function, augmentation index, or heart rate variability, despite positive associations in the general population and other populations with chronic disease. Adding vintage, diabetic status, and coronary artery disease status to the model did not affect this association.

Conclusions: It is likely that other factors beyond PA dominate in contributing to less traditional cardiac risk factors such as endothelial dysfunction and heart rate variability in patients treated with dialysis, although it is also possible that the majority of patients occupied too low a stratum of PA to generate a meaningful association.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

Association of Average Daily Step Count with Endothelial Function, Augmentation Index, and Heart Rate Variability

	Regression Coefficients adjusted for age and sex (95% CI)
RHI	-0.02 (-0.06 – 0.03)
AI75	-0.51 (-2.47 – 1.46)
SDNN	-2.44 (-5.07 – 0.19)

PUB309

The Relation between Fibroblast Growth Factor 23, Cardiovascular Risk, and Body Composition in Patients Undergoing Hemodialysis Marta Olszewska, Krzysztof Hoppe, Krzysztof Schwermer, Malgorzata Kaluzna, Ewa Baum, Krzysztof Pawlaczyk, Andrzej Oko. *Poznan University of Medical Sciences, Poznan, Poland.*

Background: Fibroblast growth factor 23 (FGF23) is a key player in regulation of bone-mineral homeostasis. Bone mineral disease is associated with negative cardiovascular outcomes in patients with chronic kidney disease. The aim of the study was to assess the relation between FGF23, cardiovascular risk and body composition in patients undergoing hemodialysis (HD).

Methods: This study included a group of 74 HD patients (mean age 62.9±11.8 years, male n=40), divided into 2 subgroups (gr1>1109.88; gr2≤1109.88 [pg/ml]) depending on the median FGF23 value. Serum FGF23 was measured with ELISA. Markers of body composition featured overhydration, adipose and lean tissue mass measured with bioimpedance (BIA, Fresenius BCM). CV injury was assessed with NT-proBNP and troponin T. Other routinely measured laboratory markers featured CRP, hemoglobin, triglicerides, calcium, phosphates (PO4) and PTH. Subjective Global Assessment and Charlson's Comorbidity Score were also carried out. Statistical analysis was performed using Statsoft Statistica 12.5. P-value <0.05 was considered statistically significant.

Results: There were no statistically significant differences in terms of age and sex distribution. The groups differed in terms of residual diuresis (gr1 vs. gr2: 550±800 vs. 150±500 [ml/24h]; p=0.014), HD vintage (2.7±2.7 vs. 5.2±9.2 [years]; p<0.001), NT-proBNP (6130±14056 vs. 9005±30431 [pg/ml]; p=0.040). There were significant differences in PO4 (4.9±1.8 vs. 6.8±2.1 [mg/dl]; p<0.001), ferritin (408.5±840.0 vs. 708.7±674.0; p=0.022) and preHD systolic blood pressure (160±30 vs. 140±35 [mmHg]; p=0.033). FGF23 was correlated with such parameters as: diuresis (r=-0.351, p=0.003), HD vintage (r=0.414, p=0.001), NT-proBNP (r=0.282, p=0.016), PO4 (r=0.658, p<0.001), PTH (r=0.288, p=0.017), and ferritin (r=0.304, p=0.011).

Conclusions: In conclusion, this study seems to confirm the connection between FGF23 and other markers of bone-mineral balance. However, our results may also suggest a potential relation between FGF23 and HD vintage, decreasing residual renal function and it's complications such as iron management dysregulation, blood pressure elevation and cardiac strain. Further research is required to investigate the value of FGF23 as a prognostic marker for patients on maintenance HD.

PUB310

Association between Pre-Dialysis Electrolytes and Incidence of Arrhythmia in Long Interdialytic Interval among Chronic Hemodialysis Patients Kampantong Tangweerapong. *Renal Division, Bhumibol Adulyadej Hospital, Saimai, Thailand.*

Background: End stage renal disease patients have high risk of cardiovascular death. Mortality rate is higher in long interdialytic interval compare to short interdialytic interval and one of the main cause is cardiac arrhythmias.

Methods: A prospective, single-center study was performed among thrice a week-hemodialysis patients without documented arrhythmias to compare the incidence of arrhythmias between long and short interdialytic intervals and determine the associated factors which relate to the events. 24-hour Holter monitoring was done twice in long and short interdialytic intervals within one week. Holter diagnoses were defined by the ACC/AHA guidelines. Patient's baseline data and pre-dialysis serums were collected.

Results: The data analysis of 28 patients who were studied, showed that there were 18 (64.3%) males and 10 (35.7%) females with mean age of 63 years. Non-sustained ventricular tachycardia (VT) was detected in 3 of 28 patients (10.7%) and only occurred in long interdialytic interval. In 8 of 28 patients (28.6%) had higher incidence of overall arrhythmias in long interdialytic interval while the left patients had no significant arrhythmias or no difference of arrhythmias in both intervals. Only male patients had higher incidence of both non-sustained VT and supraventricular arrhythmias in long interdialytic interval. Lower predialysis serum potassium (4.64 ± 0.40 compared to 5.45 ± 1.49, p-value 0.035), lower predialysis calcium (8.26 ± 1.05 compared to 8.95 ± 0.51, p-value 0.027) and lower predialysis serum magnesium (1.91 ± 0.32 compared to 2.34 ± 0.33, p-value 0.004) were found as independent factors for patients who had higher incidence of arrhythmias in long interdialytic interval.

Conclusions: Higher incidences of arrhythmias during long interdialytic interval occasionally occurred in chronic hemodialysis patient. Low serum potassium, low serum calcium and low serum magnesium might be associated factors.

Funding: Government Support - Non-U.S.

PUB311

30-Day Readmissions in ESRD Patients with Heart Failure Linda-Marie Ustaris, Sandeep K. Mallipattu. *Stony Brook Medicine, Stony Brook, NY.*

Background: The overall number of hospitalizations for ESRD on hemodialysis in 2013 was 1.7 admissions per patient year. Rehospitalization rates for Medicare beneficiaries greater than 66 years old without kidney disease compared to those with ESRD are 15.8% and 34.8%, respectively. This study's objective is to identify the modifiable and non-modifiable risk factors associated with increased readmission rates in ESRD patients.

Methods: 1,534 ESRD patients corresponded to 28,695 encounters with an ICD 9 code for ESRD at a university hospital from 2010-2014. Inclusion criteria: more than one inpatient encounter (admission or ER visit) within a 30-day period. Outpatient, ambulance, and duplicate visits were excluded. Each hospital encounter within 30 days from the last discharge was reviewed for reason for admission: dialysis related (HTN, volume overload, electrolyte abnormality and access complication) or non-dialysis related. Baseline demographics and clinical data were collected, including ejection fraction and the presence of left ventricular (LV) dysfunction on echocardiogram. We calculated the proportion of dialysis related visits within each group. Chi square Fisher's exact test calculated the p-value.

Results: 1,184 ESRD (445 females, 739 male) patients and 4,358 encounters met the inclusion criteria. Average number of encounters per patient year was 0.73, with an unadjusted 30-day readmission rate of 0.56 per patient year. Table 1 shows the association of dialysis and non-dialysis related 30-day readmissions with systolic and diastolic dysfunction. There was no statistical significance (p-value: 0.6) between the type of readmission and the subtypes of LV dysfunction.

Conclusions: Our preliminary data suggests that the presence of both systolic and diastolic dysfunction is associated with more dialysis related encounters compared to those without LV dysfunction.

Funding: NIDDK Support

Visit types in ESRD patients with and without LV dysfunction

	No LV dysfunction	Diastolic LV dysfunction	Systolic LV dysfunction	Both systolic and diastolic LV dysfunction
Sex (Male:Female)	1:1	15:12	8:4	5:3
Hemodialysis (N=31)	1	26	12	8
Peritoneal Dialysis (N=1)	0	1	0	0
Transplant (N=1)	1	0	0	0
# of dialysis related visits (N=196)	27 (14%)	173 (88%)	58 (30%)	63 (32%)
# of non-dialysis related visits (N=210)	37 (18%)	195 (93%)	74 (35%)	82 (39%)
Total Visits (N=406)	64 (16%)	368 (91%)	132 (32%)	145 (36%)

PUB312

Correlation Analysis between GNRI and LVMI, RDW, PDW, and OSTA in Maintenance Hemodialysis Patients Wenbo Zhao,[2] Hui-qun Li.[1] *[1]The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China; [2]the Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.*

Background: Malnutrition was a common condition in maintenance hemodialysis patients and increased mortality. The purpose of this study was to investigate the correlation between nutritional risk index (GNRI) and LVMI, RDW, PDW and OSTA in patients with maintenance hemodialysis

Methods: We enrolled 91 cases of maintenance hemodialysis patients (female 42 cases, male 49cases, dialysis time: 3.31±3.34 years). The nutritional risk index (GNRI) was correlated with the red blood cell distribution width (RDW), the platelet distribution width (PDW), the left ventricular mass index (LVMI), Osteoporosis Self-assessment Tool for Asians (OSTA).

Results: GNRI range (93.87 + 7.92), RDW (0.146 + 0.015), PDW (11.46 + 1.65), LVMI (145.23 + 39.56), OSTA, (0.50 + 3.98). GNRI, with a higher risk of RDW, PDW, LVMI, related to the increase of OSTA level ($P < 0.05$), a higher risk of GNRI and RDW ($r=-0.317$, $P=0.002$), PDW ($r=-0.203$, $P=0.045$), LVMI ($r=-0.201$, $P=0.04$), negative correlation, positive correlation with OSTA ($r=0.353$, $P=0.001$)

Conclusions: For maintenance hemodialysis patients, GNRI was closely related to cardiac function, blood cell morphology and degree of osteoporosis. It was important to evaluate the nutritional status of routine hemodialysis patients for routine GNRI to improve the survival state.

PUB313

Mean Platelet Volume as a Determinant of Abdominal Aortic Calcification Myung jin Choi,[2] Jiwon Ryu,[1] Eun young No.[2] *[1]Cheju Halla Hospital, Seoul, Republic of Korea; [2]Chuncheon Sacred Heart Hospital, Chuncheon, Republic of Korea.*

Background: Mean platelet volume (MPV) is a marker of platelet activation. Increased MPV has been reported with the development of thrombotic events such as coronary artery occlusive disease, cardiovascular mortality and vascualr access failure in chronic kidney disease (CKD) patients. However, abdominal aortic calcification (AAC) is also correlated with cardiovascular events in dialysis patients. The effects of MPV on arterial calcification is not known. This study was designed to determine the predictor for AAA in hemodialysis (HD) patients.

Methods: Eighty-nine chronic HD patients (age 59.7 ± 10.4 years, male 51.7 %, diabetes 53.9 %, mean dialysis duration 48.7± 40.9 months) were enrolled. With collection of clinical and laboratory parameters, ambulatory blood pressure monitoring, ankle-brachial index test with pulse wave velocity, echocardiography and lateral lumbar radiography were performed. Quantitative analysis of AAA score was assessed.

Results: Median AAA score were 4.63 ± 4.6. Patients with AAC score (≥ 1) were found in 71 (79.7 %) patients, and they were older ($p=0.000$) and had longer periods of HD ($p=0.018$). They also showed lower levels of pre-HD diastolic blood pressure (BP) and higher levels of sleep diastolic BP and serum ferritin. AAA score showed a significantly positive association with age, HD vintage, diabetes, previous cardiovascular disease, serum calcium and MPV level in univariate analysis. In the multivariate analysis, AAC score was independently associated with MPV level ($\beta=1.466$, $p=0.032$) as well as HD vintage ($\beta=0.028$, $p=0.008$) and serum calcium ($\beta=1.459$, $p=0.004$).

Conclusions: MPV value, HD vintage and serum calcium level are important determinants of AAC in HD patients. MPV may be a potential marker for prediction of not only atherosclerosis but also arterial calcification in dialysis patients.

PUB314

Relationship of Neighborhood Walkability and Dialysis Patient Characteristics and Outcomes John W. Larkin,[1] Maggie Han,[3] Schantel Williams,[3] Xiaoling Ye,[3] Len A. Usvyat,[1] Peter Kotanko,[3] Franklin W. Maddux,[1] Roberto Pecoits-Filho.[2] *[1]Fresenius Medical Care North America, Waltham, MA; [2]Pontificia Universidade Catolica do Parana, Curitiba, Brazil; [3]Renal Research Institute, New York, NY.*

Background: Higher levels of physical activity are known to be associated with dialysis patients achieving better outcomes. A recent study identified that neighborhood walkability scores are positively correlated with the mean daily steps walked by dialysis patients (Han M et al. 2017). We aimed to investigate whether there are correlations in walkability scores and an array of dialysis patient clinical characteristics and outcomes.

Methods: We obtained data on Walk Scores (www.walkscore.com) in 10,000 zip codes in the United States (US) and identified dialysis patients treated at Fresenius Kidney Care (FKC) clinics residing in the same zip codes during June of 2016 to May of 2017. The Walk Score measures neighborhood walkability on a scale of 0 (poorest walkability) to 100 (greatest walkability) based on access to key destinations (e.g. grocery stores, restaurants, retail stores). We calculated the correlation coefficients between the walkability score in the zip code of each patient's residence and 56 clinical and non-clinical variables.

Results: We analyzed data from 89,551 FKC patients living in 8,351 zip codes throughout the US. Of 56 parameters investigated, 17 were positively correlated with higher walkability scores. These included higher KDQOL physical composite scores, albumin, and creatinine levels, and lower rates of infection, rates of hepatitis, potassium levels, a younger dialysis vintage, and others (all $p<0.05$). Black, Asian, and Hispanic patients tend to live in areas with higher walkability. We found 23 parameters negatively correlated with walkability scores, including older age and higher prevalence of cardiac diseases and diabetes, as well as higher intradialytic weight gain. Also, a lower adequacy, treatment time, and body mass index was inversely correlated to walkability scores (all $p<0.05$).

Conclusions: These findings indicate that the walkability score where patients reside is related to physical composite scores, disease states, and many clinical markers of optimal patient management. Identification of surrogate measures of physical activity and overall infrastructure could assist in designing geographically specific support systems.

Funding: Commercial Support - Fresenius Medical Care North America

PUB315

Abstract Withdrawn

PUB316

Treatment of Dialysis-Related Amyloidosis with Lixelle Weeraporn Srisung,[1] David L. Epstein,[2] Jeffrey I. Silberzweig.[2] *[1]New York-Presbyterian, Weill Cornell Medical Center, New York, NY; [2]The Rogosin Institute, New York, NY.*

Background: Dialysis-related amyloidosis (DRA) arises in patients on dialysis, typically for more than 10 years. DRA develops from deposition of amyloid fibrils comprised of beta-2-microglobulin (B2M) primarily in bones and joints of the hips, knees, shoulders, wrists, and spine, but it can also involve visceral organs. In Japan, DRA patients have been treated with Lixelle B2M apheresis columns, which utilize beads with micropores which allow molecules smaller than 30,000 daltons to pass through them. Additionally hydrophobic hexadecyl alkyl ligands on the beads bind B2M. This two-year research trial evaluates the efficacy and side effects of Lixelle in the United States.

Methods: The first US patient treated with Lixelle is a 68 year-old African American man with end-stage renal disease of unclear etiology who started hemodialysis in 1968. A short time later, he underwent bilateral nephrectomy to manage hypertension. He received deceased-donor renal transplants in March 1969, which lasted until February 1970, and in April 1970, which lasted until April 1973. He has been treated by hemodialysis since then except for one year of peritoneal dialysis. He was diagnosed with DRA in 1986. At the time of initiation of Lixelle treatment, he had documented amyloid deposits throughout his body including right shoulder, left hand, colon, small bowel, and buttocks. Due to joint involvement causing weakness, he uses a wheelchair for mobility. He began Lixelle

treatment in August 2016; initial clinical data demonstrated significantly increased removal of B2M with Lixelle (56.7% reduction ratio compared to 27.9% with high flux dialysis alone); he reported reduction in the size of his amyloid deposits. In late April 2017, he developed lightheadedness and hypotension during dialysis. The Lixelle column was held on April 24, 2017. During the course of treatment, his hemoglobin decreased to 9.5 g/dL, and therefore his erythropoietin-stimulating agent dose was increased.

Results:

Conclusions: Our patient started treatment with Lixelle in August 2016 as part of a clinical trial. It is unclear what caused the change in tolerance but the additional extracorporeal volume may contribute to hypotension in predisposed patients. His tolerance of the columns for greater than 7 months suggests that this clinical change is independent of Lixelle.

Funding: Commercial Support - Kaneka Pharma, LLC.

PUB317

Low Triiodothyronine Syndrome Is Associated with High Beta 2 Microglobulin in Hemodialysis Patients Hong joo Lee. *Seoul Red Cross Hospital, Seoul, Republic of Korea.*

Background: Low circulating triiodothyronine (T3) levels, known as the low T3 syndrome, are the most frequently encountered thyroid functional test derangement in end-stage renal disease (ESRD) patients on hemodialysis. Beta-2 microglobulin (β2M) is a prototypical middle molecule uremic toxin that associate with a higher mortality in hemodialysis patients. Hence, we conducted a study to elucidate the interacting factors between β2M and a low T3 level in ESRD patients on hemodialysis.

Methods: All hemodialysis patients in Red Cross Hospital within a period of one year were included in the study. The participants were divided into two groups based on the level of T3. We evaluate relationships between T3 level and the variables showing malnutrition, inflammation, comorbidity, and β2M. Statistical analysis was carried out by using SPSS.

Results: Among the 56 cases, 44.6% of the patients had the low T3 syndrome. The patients with the low T3 syndrome had lower weight and body mass index (BMI) than the patients with normal T3 level. In addition, the T3 level was associated significantly with the level of ferritin, total iron-binding capacity (TIBC) and albumin/globulin (A/G) ratio. We observed a negative correlation between the level of T3 and β2M. However, blood urea nitrogen, creatinine, and lipid profiles including total cholesterol, high density lipoprotein and low density lipoprotein cholesterol, and triglyceride were not related to the level of T3.

Conclusions: Therefore, the intensive hemodialysis for clearing β2M may have an advantage for normal T3 in hemodialysis patients.

PUB318

Lowest Attainment of Guideline Targets Is Associated with Higher Morbimortality in European Haemodialysis Patients (EURODOPPS) Sophie Liabeuf,[4] Ayesha Sajjad,[1] Brian Bieber,[3] Keith McCullough,[3] Ronald L. Pisoni,[3] Fergus J. Caskey,[5] Christian Combe,[6] Bruce M. Robinson,[3] Kitty J. Jager,[1] Ziad Massy.[2] *[1]Academic Medical Center, Amsterdam, Netherlands; [2]Ambroise Pare University Hospital and Inserm U1018 Eq5, Boulogne Billancourt/ Paris cedex, France; [3]Arbor Research Collaborative for Health, Ann Arbor, AL; [4]Clinical research center Amiens University hospital and INSERM U1088, Amiens, France; [5]UK Renal Registry and University of Bristol, Bristol, United Kingdom; [6]CHU de Bordeaux, Bordeaux, France.*

Background: Haemodialysis patients experience a wide variety of intermediate complications, such as anaemia, hypertension and mineral bone disease (MBD). We aimed to compare survival and hospital admissions in patients according to the simultaneous attainment of different guideline targets (hypertension, anaemia and MBD) in a large European cohort of dialysis patients.

Methods: EURODOPPS is part of DOPPS, an international, prospective cohort study of adult, in-centre haemodialysis patients, with clinical data extracted from patient records. For this analysis, 6317 patients from seven European countries were included between 2009 and 201. Quality of guidelines target attainment was considered high if 4 or 5 targets of the 5 evaluated targets were attained, moderate if 2 or 3 targets were attained and low if 0 or 1 target were attained (Table1). Fully adjusted multivariate Cox models investigated the relationship between quality of guideline targets attainment and mortality or first hospital admission.

Results: At baseline, attainment of guidelines was considered as low in 1751 (28%) patients, moderate in 3803 (60%) and high in 763 (12%) patients. In the fully adjusted model using time dependent covariates, low attainment was associated with higher all-cause mortality (Table 2) and with higher risk of hospitalizations (HR = 1.20; 95% CI, 1.11 – 1.30), whereas high attainment was only associated with lower all-cause mortality (Table 2) and not with risk of hospitalization (HR = 1.09; 95% CI, 0.96 – 1.23).

Conclusions: Given the large proportion of patients with low attainment, we may argue that amelioration of guidelines application could improve patient outcomes.

Table 1: Definition of clinical targets, clinical biochemical targets

	Targets
CKD-MBDs	1. A serum phosphate level between 3.5 and 5.5 mg/dl 2. An intact PTH level between 150 and 600 pg/ml 3. A serum calcium level between 8.4 and 10.2 mg/dl
Hypertension	4. A mean of three blood pressure measurements <140/90 mmHg (pre-HD) and <130/80 mmHg (post-HD)
Anaemia	5. A serum Hb level between 11 and 12 g/dl

Table 2 : Association between quality of guidelines attainment and mortality during the study follow up

Target attainment	Baseline No. of observations=6315 HR (95% CI)	Time-varying covariates No. of observations=33,881 HR (95% CI)
Low attainment	1.07 (0.94, 1.21)	**1.19 (1.05, 1.34)**
Moderate attainment	Reference	Reference
High attainment	**0.84 (0.71, 0.99)**	**0.82 (0.68, 0.99)**

Adjusted for age, gender, race, country, dialysis vintage, smoking, body mass index, single pool Kt/V and 13 comorbid diseases

Total number of all-cause mortality n=1328 patients

PUB319

Abstract Withdrawn

PUB320

The Non-Calcium Based Phosphate Binder Ferric Citrate May Increase Serum Calcium in Patients on Hemodialysis (HD) Satoshi Funakoshi,[1] Jyunichiro Hashiguchi,[1] Tayo Kawazu,[1] Osamu Sasaki,[1] Hiroshi Ichinose,[1] Kenji Sawase,[1] Makiko Yamashita,[1] Yoko Obata,[2] Tomoya Nishino,[2] Takashi Harada.[1] *[1]Nagasaki Kidney Center, Nagasaki, Japan; [2]Nagasaki University School of Medicine, Nagasaki, Japan.*

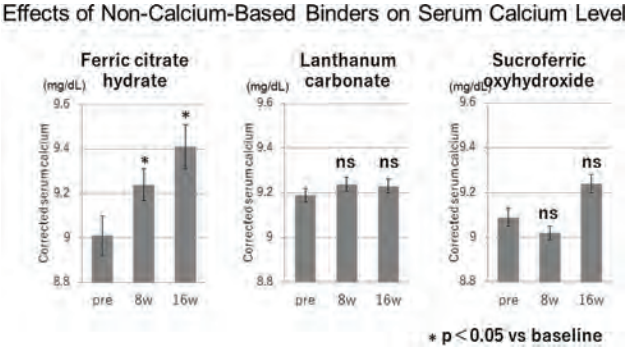
Background: Hypercalcemia caused by calcium overload is associated with mortality and cardiovascular disease in HD patients, and recent studies reported reduction in mortality with non-calcium-based phosphate binders compared with those with calcium-based phosphate binders. We therefore conducted a study to compare ferric citrate and other non-calcium based metal-type phosphate binders for their serum calcium profiles.

Methods: After informed consent was obtained from all subjects, they were adequately informed about the 3 different non-calcium based metal-type phosphate binders to be studied, i.e. lanthanum carbonate, sucroferric oxyhydroxide and ferric citrate, and were asked to choose between these reagents. Relevant serum parameters including calcium were monitored during 16-week follow-up. Their concomitant dosing of calcium basedphosphate binder, vitamin D and HD were not altered.

Results: Thirteen subjects were enrolled in the lanthanum carbonate group, 7 in the sucroferric oxyhydroxide group and 16 in the ferric citrate group. As shown in figure, the serum calcium level was significantly increased only in the ferric citrate group after 8 weeks of treatment.

Conclusions: Of the two intestinal calcium absorption processes involved, an active transcellular process and a passive paracellular process in the small intestines, enhanced calcium chelation and permeation by ferric acid may explain our results.

Funding: Private Foundation Support



PUB321

Relationship Between Vascular Access (VA) Performance Evaluated with a Triage System and Clinical Events in Haemodialysis (HD) Maria luisa Muci,[1] Silverio Rotondi,[4] Lida Tartaglione,[3] Sandro Mazzaferro.[2] *[1]Policlinico Umberto I Roma, Roma, Italy; [2]Sapienza University of Rome, Rome, Italy; [3]sapienza university of rome, Rome, Italy; [4]Nephrology and Dialysis Unit, ICOT hospital, Polo Pontino, Sapienza University, Rome, Italy*.

Background: VA type and performance affect morbidity and mortality in HD. Routine does not allow standard monitoring of VA. We developed a system of VA triage to be representative of average monthly performance. We evaluated the relationship between VA triage and clinical events

Methods: In any session of every patient, nurses report weights, BP, HR, Blood flows, VA pressures, symptoms, clots and, monthly, KT/V. Records generate a score that, according to thresholds, triages the VA as Green (G), Yellow (Y) or Red (R). We retrieved clinical events (admissions and deaths) of those patients whose VA had been triaged for >3 months in the period between 1/1/2014 and 12/31/2016. For each patient we considered the average triage during the whole available follow-up.

Results: We followed 131 patients (78 AVF and 52 CVC) for 21±11 months and recorded 18 deaths and 217 hospital admissions lasting 19±30 days. Prevalence of events was greater in CVC *vs* AVF patients (83% vs 78%, X^2=4,6; p<.05). For statistical purposes, given the unbalanced distribution of triage (70 G; 52 Y; 8 R), we merged the two pathologic classes (Y+R). The incidence rate of events was lower in the G group (1,9/1000 pt/days vs 4,0/1000 pt/days; p<.001)(tab. 1) as compared to the Y+R group, despite similar age, dialysis vintage and diabetes. We confirmed this difference in the two VA subroups (AVF: G=1,1 events/1000pt/days vs Y+R=3,4 events/1000 pt/days; p<.001; CVC (G=2,9 events/1000 pt/days vs Y+R=5,5 events/1000 pt/days; p<.001), separately. CVC patients with G triage had lower death rates than those with the Y-R triage (8% vs 33%; X^2=3,9; p<.05).

Conclusions: We confirm the different impact of VA type on morbidity. Our Triage system allowed to identify patients at increased risk of any clinical event independently of VA type. In patients with CVC VA triage also identifies cases at increased risk of mortality. Our triage is simple and reliable as a sensor of VA performance and labels patients at increased clinical risk.

Tab. 1	Triage Green	Triage Yellow-Red	p<
Patients. (n)	70	60	
Events (n)	94	139	
Age, y.o.	69±14	68±14	n.s.*
Vintage HD, months	28±27	29±34	n.s.*
Diabetes (n)	22	22	n.s.°
Events incidence rate/1000 pt/days	1,91	4,0	.001^
Follow-up, months	23±11	19±11	.04*
Deaths	6	12	n.s.°

•student T test; ^ ; ° Test X^2

Table 1

PUB322

Long-Term Competing Risk for ESKD and Death in a Large Austrian Cohort Emanuel Zitt,[1,2] Constanze Pscheidt,[3] Reinhard Kramar,[4] Raphael S. Peter,[3,5] Hans Concin,[3] Jan Beyersmann,[5] Karl Lhotta,[1,2] Gabriele Nagel.[3,5] *[1]Academic Teaching Hospital Feldkirch, Feldkirch, Austria; [2]VIVIT, Feldkirch, Austria; [3]aks gesundheit GmbH, Bregenz, Austria; [4]Austrian Dialysis and Transplant Registry, Kematen, Austria; [5]Ulm University, Ulm, Germany*.

Background: Knowledge of metabolic risk factors for end-stage kidney disease (ESKD) in the general population is limited, especially when considering the competing event death before ESKD in risk analysis. Aim of our study was to investigate competing risks for ESKD and death in a large general population-based cohort with long-term follow-up.

Methods: In this prospective, longitudinal observational study participants were recruited between 1988 and 2005 within a community-based health monitoring and prevention program (VHM&PP) in the Austrian state of Vorarlberg. This cohort was linked to the Austrian Dialysis and Transplant Registry and the Vorarlberg Mortality Registry. Every adult above the age of 20 years was invited to participate in the program after providing written informed consent. 177,255 participants (53.8% women; mean age 42.5 (SD 15.4) years) were included. Body mass index, fasting blood glucose, systolic and diastolic blood pressure, total cholesterol, triglycerides and γ-glutamyltransferase (GGT) were determined as continuous and obesity, diabetes mellitus, hypertension, hypertriglyceridemia, hypercholesterolemia and GGT elevation as categorized variables. We calculated the risk for ESKD and death applying cause-specific Cox proportional hazards models and subdistributional regression models.

Results: Over a mean follow-up of 16.0 years 358 participants reached ESKD (38% women) and 19,512 participants died. In the fully adjusted cause-specific risk models (HR, 95% confidence interval) diabetes mellitus (4.62, 3.54 -6.03), hypertension (2.89, 2.22-3.77), hypertrigylceridemia (2.08, 1.32-3.28) and hypercholesterolemia (1.61, 1.29-2.00) were associated with a higher risk for ESKD than for death, whereas elevated GGT was associated with an increased all-cause mortality risk (1.49, 1.44-1.54). Subdistribution models supported cause-specific findings.

Conclusions: Components of the metabolic syndrome are associated with a higher risk for ESKD than for its competing event death in a large general population-based cohort of middle-aged adults, whereas elevated GGT levels indicate a higher risk for all-cause mortality. These findings might help improve the design of renal risk factor modification trials and kidney disease awareness and prevention programs in the general population.

PUB323

Elevated Outdoor Temperatures Are Associated with Increased Mortality and Hospitalization Events among Hemodialysis Patients in Northeastern US Cities Richard V. Remigio,[3,5] Alice Topping,[4] Jochen G. Raimann,[4] Peter Kotanko,[4] Franklin W. Maddux,[2] Patrick Kinney.[1] *[1]Boston University School of Public Health, Boston, MA; [2]Fresenius Medical Care, Waltham, MA; [3]Maryland Institute of Applied Environmental Health, School of Public Health, University of Maryland, College Park, College Park, MD; [4]Renal Research Institute, New York, NY; [5]Epidemiology & Biostatistics, Dornsife School of Public Health, Drexel University, Philadelphia, PA.*

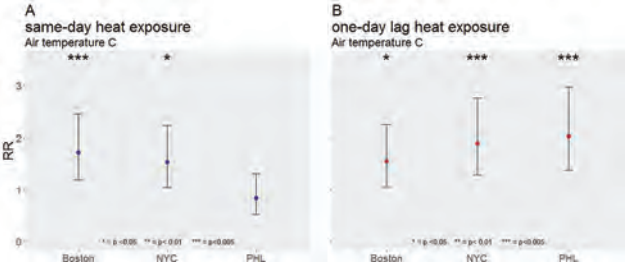
Background: Few studies have focused on the effects of heat-related stress on populations living with chronic diseases, more specifically end-stage renal failure. In this work, we sought to examine the effects of weather conditions on mortality and hospitalization risks among hemodialysis patients treated at Fresenius Medical Care North America (FMC-NA) clinics in Boston MA, New York, NY, and Philadelphia, PA.

Methods: Time-stratified case-crossover analyses were applied to estimate short-term effects of weather on mortality and hospitalization using maximum air and heat index daily temperatures for each city. We considered same-day and one-day lag (before reported event) exposures on patients receiving treatment between 2001 and 2012. We accounted for varying rate denominators inherent with a dynamic cohort. Extreme heat was categorized with respect to upper percentiles of temperature and tested to determine risk.

Results: One-day lag heat wave events (above 97.5th percentile) exhibited statistically significant (p<0.05) associations with mortality across all three cities (Fig 1A). We estimated a 55- to 98-percent increase in the risk of death among patients within a day of a heat wave event. Same-day extreme heat exposures also had a significant effect on mortality rates in Boston and NYC (Fig 1B). On hospitalization, we found that increasing air temperatures had a positive, however modest, effect in all three cities. Extreme heat events demonstrated a null association with hospitalization events.

Conclusions: Heat effects on the mortality and hospitalization of hemodialysis patients varied among the three urban areas. However, extreme heat may have an effect on hemodialysis patients residing in Northeastern USA. The rate of hospitalization does not appear to be associated with extreme heat. Additional factors such as pre-existing co-morbidities and prior infection need to be considered.

Funding: Commercial Support - Renal Research Institute



Mortality risk estimates for same-day (A) and one-day lag (B) heat waves with respect to location

PUB324

National Trends in Medicare Advantage Insurance Coverage for ESRD Jeffrey Pearson,[1,2] Richard A. Hirth,[2] Marc Turenne,[1] Bruce M. Robinson,[1] Rajiv Saran.[2] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]University of Michigan, Ann Arbor, MI*.

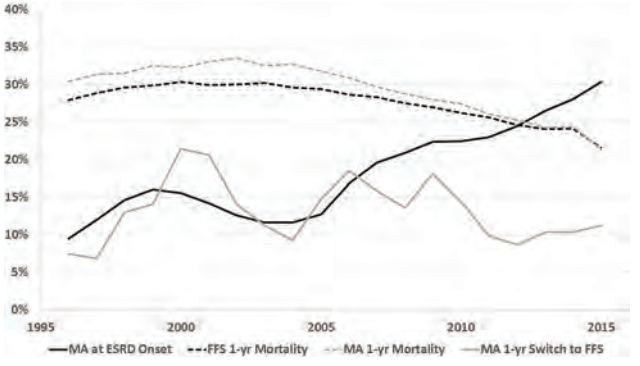
Background: Nearly all ESRD patients are entitled to Medicare coverage, but they have been restricted to traditional fee-for-service (FFS) and barred from Medicare Advantage (MA) health plans, with the exception of beneficiaries who develop ESRD while already in MA. Outside ESRD, the MA program has grown dramatically over the last decade and now covers almost one in three Medicare beneficiaries. Beginning in 2021, the 21st Century Cures Act will allow ESRD patients to join any MA health plan. This study examines recent trends in MA and ESRD.

Methods: USRDS data were analyzed to identify Medicare beneficiaries who had developed ESRD from 1996-2015. MA enrollment at ESRD onset and at one year was obtained from the Medicare Enrollment Database. Multivariate logistic regression was used to identify predictors of MA at incidence (compared to FFS) and predictors of MA beneficiaries switching from MA to FFS.

Results: Out of 1,337,786 patients with Medicare coverage at ESRD onset, 19% were in MA (12% of age <65, 22% of age ≥65). A 2005 change to the Medical Evidence Form (CMS-2728) added MA as a prior insurance choice but since 2006 only 43% of MA enrollees were reported as MA. Patients in MA were more likely to be older, male, black, Hispanic/Latino, and have diabetes as cause of ESRD. At one year after ESRD onset, 28% of MA patients had died, similar to FFS. Among those still alive, 13% have switched to FFS (15% of age <65; 12% of age ≥65). Those more likely to switch to FFS were young, female, from racial/ethnic minorities and with diabetes as cause of ESRD.

Conclusions: Consistent with increasing use of MA in the general Medicare population, an increasing number of patients have MA at the onset of ESRD. Most patients in MA at ESRD onset who survive to one year remain in MA. Patients in MA differ from patients in FFS, and thus any comparisons will need to be risk-adjusted. Policy changes promote additional use of MA for the ESRD population; future research should examine the effect MA plans can have on access, quality, cost, and health outcomes.

Funding: NIDDK Support



PUB325

Demographics and Hospitalization Rates of Dialysis Patients Prescribed the Ten Most Common Drugs Tommy C. Blanchard,[1] Yue Jiao,[1] David A. Hart,[2] Savannah R. Clary,[1] Marta Reviriego-Mendoza,[1] John W. Larkin,[1] Len A. Usvyat,[1] Terry L. Ketchersid,[1] Franklin W. Maddux.[1] *[1]Fresenius Medical Care North America, Waltham, MA; [2]FreseniusRx, Franklin, TN.*

Background: End stage kidney disease patients commonly suffer from multiple comorbidities and are on average prescribed 12 concomitant medications. We aimed to identify the most common drugs prescribed to dialysis patients, and characterize the patient demographics and hospitalization rates by medication type.

Methods: We analyzed data on all dialysis patients treated at Fresenius Kidney Care clinics as of December 2016, and located the ten most common drugs. We then characterized patient demographics by analyzing age, body mass index (BMI), vintage, gender, and hospital admission rate in each drug group and compared them to the whole patient population.

Results: We studied data from 170,560 dialysis patients. We found that the ten most commonly prescribed drugs were: sevelamer carbonate, aspirin, cinacalcet, calcium acetate, amlodipine, carvedilol, atorvastatin, hydralazine, gabapentin, and furosemide. Patients taking aspirin and atorvastatin were the oldest, with a median age of 66. Patients taking cinacalcet had the longest median vintage (4.8 years, compared to 3.1 in the whole population). Hospital admission rate was the lowest for patients taking carvedilol (2.68 per patient year (ppy)) and furosemide (2.96 ppy), and was the highest for those taking hydralazine (4.06 ppy).

Conclusions: Our results indicate that patients on certain medications may have increased hospitalization rates. This worsened morbidity is likely due to indication, yet appears useful for pinpointing patients that might require more attention. More analyses to identify a potential connection between medication utilization and outcomes are warranted.

Funding: Commercial Support - Fresenius Medical Care North America

Drug Name	Proportion of Patients	Median Age	Median BMI	Median Years on Dialysis	Proportion Male	Hospital Admissions Per Patient Year
sevelamer carbonate	0.38	62.8	29	3.77	0.55	3.07
aspirin	0.35	66.4	29.2	3.12	0.57	3.31
cinacalcet	0.3	60.3	29.6	4.88	0.56	3.57
calcium acetate	0.29	62.7	29.1	3.15	0.6	3.11
amlodipine	0.28	62.5	28	3.06	0.55	3.46
carvedilol	0.25	62.7	28.5	2.98	0.58	2.68
atorvastatin	0.22	66.2	29.2	2.75	0.57	3.20
hydralazine	0.17	62.3	27.8	2.84	0.54	4.06
gabapentin	0.16	63.8	30.7	3.36	0.51	3.66
furosemide	0.15	64.7	30.1	2.17	0.56	2.96
all patients		63.7	28.6	3.14	0.57	3.61

Table 1. Cells highlighted green, yellow, and red indicate values higher, equivalent, and low than in the general population, respectively.

PUB326

Changing Burden of Comorbidities Over Last 20 Years among Incident US Hemodialysis Patients and Rate of First-Year Mortality Jennifer L. Bragg-Gresham,[4] Keith McCullough,[1] Rita L. McGill,[3] Kevin He,[2] Rajiv Saran.[4] *[1]Arbor Research Collaborative for Health, Ann Arbor, AL; [2]Kidney Epidemiology and Cost Center, University of Michgian, Ann Arbor, MI; [3]University of Chicago Medicine, Chicago, IL; [4]University of Michigan, Ann Arbor, MI.*

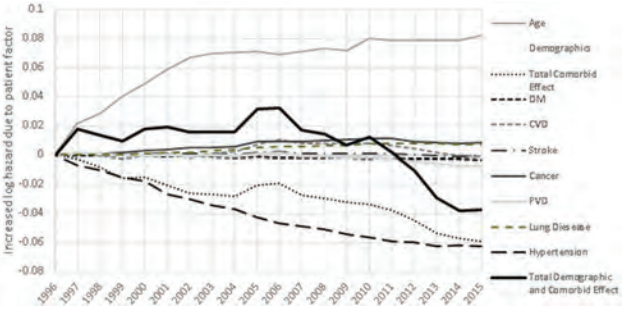
Background: Mortality among HD patients during their first year of renal replacement therapy remains very high, although there is a trend toward declining death rates in recent years. We sought to determine the potential impact of changing patient characteristics and comorbidity burden at initiation of HD on first-year mortality, over the last 20 years.

Methods: A total of 1,885,074 first-time incident HD patients between January 1996 and December 2015 were included and analyzed by year of HD initiation. Age, race, ethnicity, sex, and comorbid conditions were taken from the Medical Evidence Form (MEF), collapsing diabetes and cardiac diagnoses into single variables to align data between the 1995 and 2005 MEF. Cox models, stratified by year, were run to determine the association between each comorbid condition and mortality. The dot product of these model estimates and the means of each covariate by year were used to calculate the log hazard ratios associated with demographic and comorbid differences, versus the reference year 1996. Follow-up was censored at 1 year.

Results: Cardiovascular disease (CVD), stroke, cancer, diabetes (DM), lung disease, and peripheral vascular disease (PVD) showed little change in their impact on mortality over time. Compared to 1996, the aging of the HD population increased the first-year mortality risk 8%, which slowed after 2002. Although the prevalence of hypertension (HTN) rose from 68% to 88% during this period, this increase was associated with lower log hazards of first year mortality over time (HR=0.67, p<0.0001), which drove the overall mortality trend downward.

Conclusions: Increasing age of incident HD patients was associated with an increased risk of first-year mortality, but risk associated with comorbid conditions decreased over time, especially for HTN. The overall risk of first-year mortality decreased from 2010 onwards, suggesting improving health status of incident HD patients over time, which may help explain decreasing first-year mortality rates over the past 2 decades.

Funding: NIDDK Support



PUB327

Sucroferric Oxyhydroxide: A Novel Phosphate Binder Only or Something More? Ioannis Griveas.[1,2] *[1]PRIVATE DIALYSIS UNIT "NEFROIATRIKI", ATHENS, Greece; [2]NEPHROLOGY, 417 VETERANS ARMY ADMINISTRATION HOSPITAL OF ATHENS, ATHENS, Greece. Group/Team: Private Dialysis Unit "NEFROIATRIKI".*

Background: Hyperphosphatemia is a hallmark of advanced chronic kidney disease (CKD). A majority of chronic dialysis patients have also hyperparathyroidism. Different biochemical abnormalities of metabolic bone disease (MBD) have been associated with anemia in hemodialysis (HD) patients. This study was aimed to investigate sucroferric oxyhydroxide (PA21) in terms of efficacy and safety in HD patients with MBD and to assess the relationship between phosphate control, nutrition, anemia, lipids and a set of metabolic bone disease biomarkers in a cohort of adult patients with advanced dialysis-dependent CKD.

Methods: In this study HD patients with hyperphosphataemia were received PA21 for 10 months. The primary outcome was estimation of serum phosphate concentration at the end of treatment. Secondary outcomes were monitoring of haematocrit (Hct), hemoglobin (Hb), corrected serum calcium, albumin, cholesterol, triglycerides, intact-parathyroid hormone (PTH) concentrations. Ferritin levels were monitored also. Adverse events were evaluated.

Results: 31 HD patients were enrolled with mean age 61. 35 years (range: 35-87). 9 patients were naïve regarding phosphate medication, 18 were receiving sevelamer before and 4 lanthanum. All of the patients were taken 2-3 pills of PA21. 6 patients were withdrawn. We noticed significant reduction of the phosphate levels from the first month (from 6.54±1.27 to 5.05±1.01 mg/dl, p<0.05). This trend carried out until the end (4±0.90 mg/dl, p<0.05). PTH levels significantly reduced (PTH at first 698±564 pg/ml, 6th month 433±409 pg/ml, p<0.05) which carried out until the end (383±115 pg/ml). Ferritin levels remained stable. 2 months since the beginning we noticed increase of Hct (35.9% vs 37.41 %, p=0.097) until the end (37.47%). Cholesterol levels tended to reduce (175±34 mg/dl beginning vs 160±15 mg/dl, at the end, p=0.213). Albumin and triglycerides levels remained stable. Calcium levels had also unremarkable differences.

Conclusions: In conclusion, sucroferric oxyhydroxide is a valuable treatment option for hyperphosphataemia in CKD patients on dialysis, providing an effective and generally well tolerated noncalcium-based phosphate binder therapy and the potential for improved treatment adherence in MBD in general. Apart from that, it seems that it helps HD patients holistically since it favours stability of Hct and nutrition improving lipids parameters at the same time.

PUB328

Association between Estimated Glomerular Filtration Rate Equations at Hemodialysis Initiation and Survival in Chinese ESRD Patients YING LIU. *nephrology, The First Affiliatied Hospital of Dalian Medical University, Dalian, China. Group/Team: CHDSE study.*

Background: Accurate estimating glomerular filtration rate (GFR) is one of the important indicators in assessment of dialysis initiation. There are several commonly used GFR estimating equations, while no equation is considered superior for assessing the initiation of dialysis in Chinese end stage renal disease (ESRD) patients. This study aims to examine the association between estimated GFR (eGFR) at the time of hemodialysis initiation and survival using different estimating equations in Chinese ESRD patients.

Methods: 1997 patients with ESRD, commenced hemodialysis between 2008 and 2015 from 24 hemodialysis centers all around mainland China, were enrolled in the study. The eGFR at the initiation of hemodialysis were calculated by the Cockcroft and Gault (CG), the Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and the Chinese-MDRD (C-MDRD) equation. The cohort was respectively grouped by tertiles according to the eGFR calculated by four equations.

Results: The greatest agreement was between the GFR estimated by the CG and CKD-EPI equations with the difference of 0.6 ml/min/1.73m^2 (limits of agreement=-1.1-2.2 ml/min/1.73m^2), and the closest was between the MDRD and CKD-EPI equations, with the difference of 2.6 ml/min/1.73m^2 (limits of agreement=-1.5-6.7 ml/min/1.73m^2). The agreement between the GFR estimated by C-MDRD, MDRD and CKD-EPI equations was similar. After adjustment for age, sex, diabetes mellitus, signs and symptoms at the initiation and laboratory data, there were no significant difference in survival between eGFR tertiles calculated by CG, MDRD, CKD-EPI and C-MDRD.

Conclusions: There were differences between GFR estimated by C-MDRD and other three equations for the assessment of hemodialysis initiation. eGFR at the initiaition of hemodialysis was not associated with patient survival no matter which estimating equation was used.

Funding: Government Support - Non-U.S.

PUB329

Analysis of Factors Regarding Life Prognosis at the Time of Dialysis Initiation among Late-Stage Elderly Patients Starting Hemodialysis Tsutomu Inoue, Ono Atsushi, Koji Tomori, Hirokazu Okada. *Saitama Medical University, Iruma-gun, Saitama, Japan.*

Background: The life prognosis of elderly patients after the initiation of dialysis is not always favorable. Predictive indicators for prognosis provide valuable information for patients and their families when making decisions regarding the initiation of dialysis. The purpose of this study was to investigate the factors regarding life prognosis at the time of dialysis initiation among late-stage elderly patients aged 75 or over starting hemodialysis.

Methods: A single center, retrospective, observational study was conducted. A total of 91 late-stage elderly patients (the mean age: 80.4±1.41 years; the mean observation duration of dialysis: 34.1±24.7 months) who received hemodialysis at our hospital during the period from April 1, 2011 to March 31, 2014 were included in the study. Examination items included age, sex, blood tests at the time of dialysis initiation, ADL at admission and discharge, family structure, as well as all the physical, social, and medical factors.

Results: During the follow-up, 31 patients died (causes of death by fatalities: sepsis, heart disorder, and cancer). With time to death being taken into consideration, a multivariate analysis was performed to identify factors of death using a Cox proportional-hazards model. The followings were found to be significant independent factors: ADL at admission (aHR: 0.36; 95% CI : 0.17~0.73), emergency dialysis initiation (aHR: 3.54; 95% CI: 1.36~6.85), and history of ischemic heart disease (aHR: 2.80; 95% CI : 1.38~5.68) as social and physical factors; serum albumin (aHR: 0.47; 95% CI : 0.282~0.78) and serum phosphorus (aHR: 0.72; 95% CI : 0.54~0.95) as laboratory values at the time of dialysis initiation. In a model wherein the above-mentioned 5 factors as well as age and sex were defined as independent factors, ADL, serum albumin, and serum phosphorus were statistically significant.

Conclusions: ADL independence and nutritional status at the time of dialysis initiation were considered to be independent factors regarding life prognosis after dialysis initiation among late-stage elderly patients. These results suggest that a prospective study is required to further investigate the relevant factors in the future.

PUB330

Efficacy and Safety of Ferric Citrate in Hemodialysis Patients: A 2-Year Retrospective Cohort Study Kazunori Yamada,[5] Mizuho Wada,[3] Minoru Kaneko,[3] Toru Shibata,[3] Satoshi Hara,[4] Ichiro Mizushima,[5] Hiroshi Fujii,[1] Remon Otake,[3] Akira Junicho,[3] Masatsune Hasegawa,[3] Mitsuhiro Kawano,[2] Mikio Namiki,[3] Toru Hasegawa.[3] *[1]Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Kanazawa, Japan; [2]Division of Rheumatology, Kanazawa University Hospital, Kanazawa, Japan; [3]Hasegawa Hospital, Toyama, Japan; [4]Kanazawa Graduate School of Medicine, Kanazawa, Japan; [5]Kanazawa University Graduate School of Medicine, Kanazawa, Japan.*

Background: Long-term effects of ferric citrate (FC) in hemodialysis patients (pts) have not been studied. We evaluated the efficacy and safety of FC in hemodialysis pts.

Methods: We enrolled 132 Japanese hemodialysis pts who underwent HD between July 2014 and October 2016, categorized into two groups: FC group (FCG, n=30) and non-FC group (non-FCG, n=102). All FCG pts discontinued intravenous iron use after FC treatment. Baseline clinical data were obtained between July and September 2014. We retrospectively analyzed serum phosphorus (P), iron, ferritin, hemoglobin (Hb) levels, and the dose of erythropoietin stimulating agent (ESA), which was calculated as darbepoetin a. Bowel movement (BM) disorders were evaluated using Constipation Scoring System (CSS).

Results: Baseline demographics showed that FCG pts were significantly older (60.9 ± 2.7 vs. 66.0 ± 1.3, P=0.020), had a higher serum P level (6.0 ± 0.3 vs. 5.4 ± 0.1, P=0.015), and lower ferritin level (63.6 ± 14.6 vs. 113.1 ± 15.4, P=0.008) compared to non-FCG pts. After FC treatment, serum P level did not significantly differ. Serum ferritin level after 24 weeks (wks) was significantly higher in FCG than in non-FCG (104 wks; 158.7 ± 37.1 vs. 86.5 ± 11.8, P<0.001). Baseline Hb level in both groups was almost the same; however, Hb level in FCG became significantly higher than in the non-FCG between 24 and 72 wks, without a change in the non-FCG. The ESA dose in FCG was significantly lower than in the non-FCG after 24 wks (104 wks; 6.8 ± 1.2 vs. 19.7 ± 1.7, P<0.001), indicating that iron supplied by FC improved anemia, and led to dose reduction of ESA. CSS started to improve at 12 wks in FCG. CSS values at 48, and 104 wks in FCG were significantly lower than in the non-FCG (1.6 ± 0.5 vs. 4.4 ± 0.4, P=0.005, 2.4 ± 0.4 vs. 4.3 ± 0.4, P=0.039, respectively). The most frequent adverse event (AE) was loose stool (n=4). No severe AE was seen.

Conclusions: FC lowered P levels and improved anemia and constipation, indicating that pts with iron deficiency and BM disorder may additionally benefit with use of FC.

PUB331

Effects of a Progressive Inspiratory Muscle Training on Pulmonary Function in Hemodialysis Patients Hsin-Yu Fang, Brett Burrows, Luis M. Perez, Ken Wilund. *University of Illinois at Urbana-Champaign, Urbana, IL.*

Background: Pulmonary abnormalities are prevalent in hemodialysis (HD) patients and the increased pulmonary capillary permeability associated with fluid overload may be one of the causative factors of impaired respiratory function. Inspiratory muscle training (IMT) helps improve respiratory performance in other populations, but there are relatively few studies investigating its treatment effects in patients on HD. This pilot study aimed at assessing the efficacy of a progressive IMT intervention on pulmonary function in HD patients.

Methods: Nine HD patients were recruited from two outpatient clinics in central Illinois with spirometry assessments for pulmonary function at baseline and 8 weeks (immediately post intervention). During the 8-week IMT intervention period participants engaged in thrice weekly training sessions during dialysis by progressively increasing both the training duration and resistance of the IMT breathing device.

Results: All nine patients completed the 8-week intervention for a 100% compliance rate. Baseline patient characteristics were (mean±SD): age = 61±12, BMI = 35.8±19.2 kg/m2, 56% male, 56% AA; 56% smoker. No statistically significant difference was found in patient characteristics from baseline to 8-weeks. For pulmonary function, significant decreases were observed in forced expiratory volume in first second (FEV1, from 2.08 ± 0.506 to 2.01 ± 0.460; p = 0.005) and forced vital capacity (FVC, from 2.60 ± 0.762 to 2.36 ± 0.715; p < 0.005), while a significant increase in peak expiratory flow (PEF, from 311 ± 78.3 to 339 ± 67.7; p = 0.007) was also shown. The FEV1/FVC ratio increased significantly (from 0.813 ± 0.094 to 0.873 ± 0.085; p = 0.017) post training, which was attributed to a decreased FVC level as the denominator.

Conclusions: The present study showed no favorable effects of the 8-week progressive IMT intervention on several pulmonary function test parameters. Because fluid overload is associated with pulmonary malfunction in HD patients, whether IMT intervention is preferable to HD patients with better fluid control remains to be tested. Further studies are needed.

PUB332

The Impact of Patient-Centered Pharmacist Care on Pharmacoadherence in Hemodialysis (HD) Patients: A Quasi-Experimental Study Sherine Ismail,[2,3] Abrar F. Al-Subhi,[2] Eman Y. Ahmed,[2] Medhat S. Ahmed,[2] Abdullah H. Almalki,[2] Diane Seger,[4] Andrew Seger,[1] Earl Francis Cook.[3,1] *[1]Brigham and Women's Hospital, Boston, MA; [2]King Abdullah International Medical Research Center, King Saud Bin Abdulaziz University for Health Sciences, Ministry of National Guard Health Affairs, Ministry of National Guard Health Affairs, King Abdulaziz Medical city, Jeddah, Saudi Arabia; [3]Harvard T.H. Chan School of Public Health, Boston, MA; [4]Partners Healthcare System, Somerville, MA.*

Background: Pharmacoadherence is a public health problem in patients with chronic illness (WHO 2003). Non-Pharmacoadherence in HD patients varies from 12.5-98.6%, which leads to poor clinical outcomes. There is a paucity of data determining the influence of pharmacist on pharmacoadherence in our setting; therefore we aim to assess the impact of patient-centered pharmacist care to improve pharmacoadherence in HD patients.

Methods: The study was conducted at king Abdulaziz Medical City from Oct 2016-Apr 2017. Ambulatory HD patients were included if age ≥18 years and on HD for at least 3 months and excluded if they have no mental capacity to participate. Primary outcome is change in pharmacoadherence assessed by medications' self-report vs. records and pre-dialysis serum phosphorus before and after intervention. Secondary outcomes include changes in systolic blood pressure (SBP), glycosylated hemoglobin (A1c), serum low-density lipoprotein (LDL) and prevalence of Medication-related problems (MRPs) pre and post intervention. Pharmacists interviewed patients monthly and intervention (Medication Therapy Management & motivational interview) occurred at month 3 and 5. An estimated sample of 60-77 patients to provide 20-25% change in adherence from 72 %, power of 80% and alpha 0.05. Linear mixed regression analysis was used to assess mean changes in primary and secondary outcomes and Wilcoxon signed-rank test for assessing prevalence of MRPs pre and post intervention.

Results: A sample of 72/ 98 patients recruited. Median (IQR) of age is 59 (47-67.5), males are (52.8%), mean recorded tablets and median (IQR) self-reported tablets are (11.3 ± 5.5) and 7 (5-11) respectively. Mean changes in self-report medications and serum phosphorus were -0.07, 95% CI [-0.36 - 0.22], *p= 0.348 and -0.01 mmol/L, 95% CI [-0.11-0.09], *p =0.68 respectively. Mean change in SBP and A1c were not significant, *p= 0.08 and *0.11 respectively, however mean change in LDL was -0.2154 mmol/L, 95% CI [-0.35 -(-0.08)], *p=0.0016. There were 4.3 MRPs per 7 medications at month 3 vs. 2.27 at month 5 (p=0.0015). (*p for trends)

Conclusions: Patient-centered pharmacist care may improve pharmacoadherence in HD patients. Although it was not statistically significant, it's crucial to identify and mitigate Medication-related problems.

Funding: Government Support - Non-U.S.

PUB333

Assessing the Microeconomic and Psychosocial Impact of Dialysis for ESRD in Kerala, India Christina L. Bradshaw,[1,2] Shuchi Anand,[1] Noble Gracious,[3] Manjula Kurella Tamura,[1] Glenn M. Chertow.[1] *[1]Nephrology, Stanford University School of Medicine, Palo Alto, CA; [2]Centre for Chronic Disease Control, Gurgaon, India; [3]Nephrology, Government Medical College, Thiruvananthapuram, India.*

Background: A diagnosis of end-stage renal disease (ESRD) carries with it significant financial and psychosocial ramifications, especially in low and middle-income countries where social safety nets are typically limited in scope. In the absence of universal insurance coverage, persons with ESRD often have to resort to extreme measures in order to fund their care, frequently without full understanding of their disease trajectory and prognosis. As one of the most rapidly developing nations in the world with large numbers of persons with chronic kidney diseases, India is at the forefront of this issue. Our study aims to understand the financial and psychosocial burdens experienced by South Asians with ESRD, beginning with preliminary findings from the region of Kerala, India.

Methods: We conducted a cross-sectional multi-site study of persons with ESRD on maintenance hemodialysis in Kerala. Using an interview-based questionnaire, we collected data on demographics, dialysis history, understanding of and engagement in therapy and financial status. The microeconomic impact of dialysis will be quantified in terms of distress financing and catastrophic health spending. We will conduct follow-up interviews at 6 months and one year to determine dialysis status and, if applicable, reason(s) for discontinuation. We will aim to determine significant correlates of dialysis withdrawal, with a focus on financial status and psychosocial needs.

Results: We contacted nephrologists at 12 sites across Kerala and are actively recruiting study participants at 3 sites at this time. We are awaiting ethics approval from 4 other sites. To date, 112 patients have been interviewed. We anticipate available baseline data on 600 persons by November 2017.

Conclusions: Economic development and associated lifestyle changes have shifted the burden of disease in low and middle income countries toward non-communicable diseases, including CKD. Understanding generic and region-specific needs of patients with advanced CKD and ESRD will allow for more compassionate care processes, and could help to promote innovation to reduce the burden of CKD and ESRD worldwide.

Funding: Other NIH Support - Fogarty International Center

PUB334

Gender Difference in the Outcomes of Dialysis Dependent Patients Requiring Hospitalization – A Nationwide Analysis Yumeng Wen,[1,2] Di Pan,[1,2] David Mariuma,[1,2] Marcelo X. Hernandez cuchillas,[1,2] Michael Gramuglia,[3] Ira S. Meisels.[1,2] *[1]Division of Nephrology, Department of Medicine, Mount Sinai St. Luke's and Mount Sinai West Hospitals, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY; [3]Montefiore Medical Center, Scarsdale, NY.*

Background: End Stage Renal Disease (ESRD) is a major cause of worldwide mortality and morbidity. ESRD requiring chronic dialysis is associated with high mortality and morbidity, requiring frequent hospitalization for complications from dialysis and comorbidities. The aim of this study is to determine if gender plays a role with regard to in-hospital outcomes in patients with ESRD on chronic dialysis requiring hospitalization.

Methods: This is a retrospective cohort study using the 2014 National Inpatient Sample, the largest publically available inpatient database in the United States. The inclusion criteria were age>18 years and an ICD-9 CM code for diagnosis of ESRD on chronic dialysis. Patients hospitalized for elective procedures were excluded. The primary outcome was in-hospital mortality. The secondary outcomes were morbidities, as measured by the development of shock and acute respiratory failure, as well as resource utilization including length of hospital stay (LOS) and total hospitalization charges. Analysis was performed by using Stata, version 14.2. Odds ratio (OR) and means were adjusted for the following confounders using multivariate logistic models and multivariate regression models: age, gender, race, Charlson Comorbidity Index, early dialysis in hospital (defined as receiving hemodialysis or peritoneal dialysis within 1 day of admission), primary insurance, hospital region, hospital bed size, household income and admission day.

Results: 934,575 patients with ESRD on chronic dialysis were included in the study. The mean age was 61 years and 47% of patients were female. Female dialysis dependent patients had a reduced in-hospital mortality rate (OR 0.90, p<0.001), lower rates of shock (OR 0.85, p=0.02) and acute respiratory failure (OR 0.85, p<0.001) compared with male patients. There were also a significantly reduced total hospital charges ($69,815 vs $76,025, p<0.001) and a trend in shorter length of hospital stay (6.83 vs 6.95 days, p=0.054) in female patients.

Conclusions: Female patients with ESRD on chronic dialysis requiring hospitalization had lower rates of mortality, shock and acute respiratory failure compared to males. Total hospital charges were also lower in female patients.

PUB335

Association between Physical Activity and Symptoms among Patients on Dialysis Anoop Sheshadri,[2] Piyawan Kittiskulnam,[1] Kirsten L. Johansen.[3] *[1]Chulalongkorn university, Bangkok, Thailand; [2]University of California, San Francisco, San Francisco, CA; [3]University of California, San Franicsco, San Francisco, CA.*

Background: Patients treated with dialysis report very low levels of physical activity (PA) and functional status. Although it is logical to consider that PA might be associated with the heavy burden of symptoms dialysis patients experience, there is little data. We sought to determine whether PA is associated with specific symptoms on a modified version of the Dialysis Symptoms Index (DSI).

Methods: We recruited 55 dialysis patients ≥18 years of age receiving in-center hemodialysis (HD, n=47) or peritoneal dialysis (PD, n=8), on dialysis for ≥3 months and able to walk. We measured PA by pedometer. We administered the DSI, which contains 30 items, each targeting a specific physical or emotional symptom. Patients are asked to report the presence of each symptom at any time during the previous week and if present, report the degree to which the symptom is bothersome on a five-point Likert scale.

Results: Fatigue was the most commonly reported symptom at 71% of patients surveyed, and the most bothersome. After adjusting for age, and sex, PA was inversely associated with the severity of fatigue (-0.24 points per 1,000 daily steps). PA appeared to have a slight negative association with muscle soreness, but this association did not reach statistical significance after adjustment for age and sex. PA did not appear to be associated with insomnia, bone or joint pain, or muscle cramping.

Conclusions: It is possible that improving PA in patients treated with dialysis may improve fatigue, the symptom that is consistently most common and bothersome to patients.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

Table 1. Linear Regression with Average Daily Step Count (per 1,000 steps) and Specific Symptoms on the DSI

Symptom	Unadjusted (95% CI)	Regression Coefficient adjusted for age and sex (95% CI)
Fatigue ("Feeling Tired" or "Having Low Energy")	-0.26 (-0.47 - -0.05)	-0.24 (-0.47 - -0.10)
Muscle Soreness	-0.09 (-0.18 – 0)	-0.09 (-0.18 – 0.01)
Muscle Cramping	0 (-0.11 – 0.12)	0.02 (-0.10 – 0.15)
Insomnia ("Trouble Falling Asleep or "Trouble Staying Asleep")	-0.07 (-0.29 – 0.15)	-0.13 (-0.37 - 0.93)
Bone or Joint Pain	-0.02 (-0.16 – 0.11)	-0.01 (-0.16 – 0.13)

PUB336

Evaluation of Cognitive Functions in Hemodialysis versus Peritoneal Dialysis Treatment Patients in CKD Aclan Ozder,[1] Zeyneb I. Yüksel salduz,[2] Yelda Deligoz bildaci,[1] Rumeyza Kazancioglu.[1] *[1]Bezmialem Vakif University, Istanbul, Turkey; [2]Bezmialem Vakif University, Istanbul, Turkey.*

Background: Chronic kidney disease (CKD) is the disease characterized by the elevation of serum creatinine which had been described in five stages depending of the levels. Renal replacement therapy is required for the patients in last stage which can be done with kidney transplantation, hemodialysis (HD) or peritoneal dialysis (PD). Impaired cognitive function usually accompanies to worsening kidney functions. In this study our aim is to compare cognitive functions of patients which are on either HD or PD versus healthy control groups.

Methods: Our study group was patients who were on renal replacement therapy with either HD or PD in Bezmialem Vakif University Hospital and Haseki Hospital. Patients who did not know reading or writing, who had visional impairment were excluded. Totally 35 (HD:9, PD: 26) patients had Montreal Cognitive Assesment Test (MoCA) with their demographic properties noted as well as their etiology of CKD. Age and gender matched healthy control group also had MoCA test. We compared results renal replacement therapy group vs control group and the differences between dialysis modalities.

Results: Patients on renal replacement therapy showed a rate of mild cognitive impairment (MCI) as 28,57% compared to 8,57 % in control group (p <0,05). There is no difference found between HD versus PD in terms of MCI (p>0,05).

Conclusions: In our study we found that MCI is more often in patients on dialysis therapy compared to patients who are not. There is no differences of MCI scores in between dialysis modalities. We believe that with larger studies to come, our results will be backed up.

PUB337

Outcomes in Patients with Chronic Renal Disease Undergoing Peritoneal Dialysis versus Hemodialysis Fernando R. Aguilar,[2] Ammar Qureshi,[3] Mark A. Nader,[1] Nesreen Benhamed.[2] *[1]None, Germantown, DC; [2]Internal Medicine, Marshall University Medical Center, Huntington, WV; [3]Internal Medicine, Marshall University, Huntington, WV.*

Background: Renal transplant allows a higher life expectancy for patients with end-stage renal disease(ESRD). However, due to the dearth of renal transplant donors, patients with ESRD are treated with dialysis. The 2 most common modalities for dialysis are peritoneal and hemodialysis. Peritoneal dialysis is cheaper, but its use has declined. Some studies have shown that peritoneal dialysis has a higher adjusted mortality rate than hemodialysis and some have shown otherwise. The aim of this study was to compare the demographics and mortality rates between the patients receiving hemodialysis and peritoneal dialysis.

Methods: Data was extracted from the 2005-2012 nationwide sample (NIS) registries. Patients with a diagnosis of Chronic Kidney Disease and ESRD were included in this study. We compared the comorbidities such as diabetes mellitus and hypertension, all-cause mortality, the length of stay between the 2 groups. Pediatric population and those patients who received both hemodialysis and peritoneal dialysis were excluded. The population with chronic kidney disease was stratified based on their glomerular filtration rates and hence stages based on ICD 9 codes and compared the 2 groups.

Results: The NIS registry showed 2.85 million patients diagnosed with ESRD disease between 2005 and2012. Out of this, 1.07 million received either hemodialysis or a peritoneal dialysis. Patients who were receiving a hemodialysis had a higher mortality rate (4.69%) as compared to those receiving peritoneal dialysis (4.69% vs. 3.28%, p<0.0001; OR= 1.45 (95% CI 1.37-1.54). Mean length of stay in patients receiving hemodialysis was significantly higher than those receiving peritoneal dialysis (7.85+/- 10.69 vs. 6.40+/- 6.89, p< 0.0001). More patients in the earlier stages of chronic kidney disease (CKD stages 1-4) received hemodialysis, while peritoneal dialysis was seen to administered more in those diagnosed with stages V and ESRD.

Conclusions: Our results clearly showed that the all crude mortality rate and length of stay were significantly higher in those patients receiving hemodialysis as compared to those receiving peritoneal dialysis. However, since it was also seen that patients with a later stage of chronic kidney disease were more likely to receive hemodialysis, it could explain the higher mortality associated with hemodialysis.

PUB338

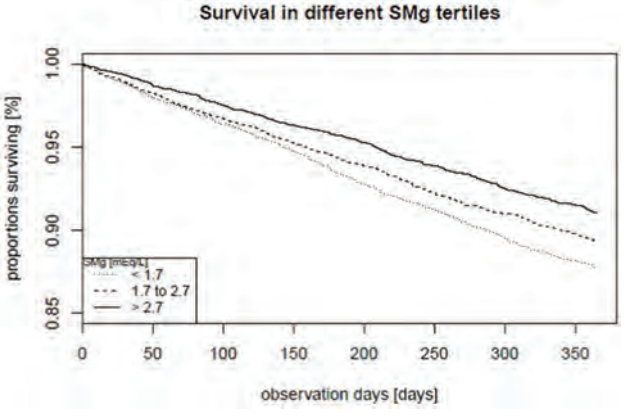
Effects of Dialysate Magnesium Concentration on Serum Magnesium Concentrations and Mortality: A Retrospective Cohort Study of the Monitoring Dialysis Outcomes Initiative Xiaoling Ye,[7] Adrian M. Guinsburg,[2] Cristina Marelli,[3] Bernard J. Canaud,[1] Stefano Stuard,[2] Xiaoqi Xu,[4] Jeroen Kooman,[6] Frank van der Sande,[6] Albert J. Power,[8] Len A. Usvyat,[5] Yuedong Wang,[9] John T. Daugirdas,[10] Peter Kotanko,[7] Jochen G. Raimann.[7] *[1]FMC Deutschland GmbH, Bad Homburg, Germany; [2]Fresenius Medical Care, Moron, Argentina; [3]Fresenius Medical Care Argentina, buenos Aires, Argentina; [4]Fresenius Medical Care Asia Pacific, Hong Kong, China; [5]Fresenius Medical Care North America, Melrose, MA; [6]Maastricht University Medical Centre, Maastricht, Netherlands; [7]Renal Research Institute, New York, NY; [8]Richard Bright Renal Unit, Bristol, United Kingdom; [9]University of California - Santa Barbara, Santa Barbara, CA; [10]University of Illinois College of Medicine, Burr Ridge, IL. Group/Team: MONDO initiative.*

Background: Serum magnesium(SMg) is known to associate with mortality and lower levels, in particular, are associated with a risk of adverse outcomes (Lacson, AJKD 2015). We investigated the relationship between SMg and all-cause mortality in data from the global MONitoring Dialysis Outcomes Initiative.

Methods: For this analysis, we used data from hemodialysis patients between 2000 and 2012 from the international MONDO database initiative. Following the first available data point on SMg we established a 3 month baseline using averages of included parameters for subsequent analyses, and followed outcomes over one year of follow-up. Survival analyses were conducted after stratification of the entire population into tertiles (G1: <1.7, G2 1.7 to 2.7 and G3 >2.7 mEq/L). Kaplan Meier survival curves, Log Rank test and Cox regression analysis adjusted for age, gender, albumin, catheter and dialysis vintage, were employed for the survival analysis.

Results: We studied 20,362 patients (59.0±16.7 years, 58% males, 70% diabetics, 25% catheter. Uni- and multivariate survival analysis showed significant differences in all-cause mortality between the lowest tertile of serum magnesium and the two higher tertiles (**Figure 1**).

Conclusions: Low SMg associates with worse outcomes as compared to higher levels, even after adjustment for relevant parameters possibly confounding the relationship. Frequent magnesium measurements may be indicated and if levels are found to be low and oral or dialytic magnesium supplementation may be beneficial for some patients. Prospective studies investigating the effects of magnesium supplementation on outcomes are needed.



PUB339

Difference in Mortality in Diabetic Patients Receiving Peritoneal versus Hemodialysis Fernando R. Aguilar,[1] Ammar Qureshi,[3] Mark A. Nader,[2] Nesreen Benhamed.[4] *[1]Georgetown University Hospital, Washington, DC; [2]None, Germantown, DC; [3]Internal Medicine, Marshall University, Huntington, WV; [4]in, MUSOM, Barboursville, WV.*

Background: Diabetic patients (DM) often develop end-stage renal disease (ESRD) requiring renal replacement therapy in the form of hemodialysis (HD) or peritoneal dialysis (PD). Studies comparing the outcomes and difference in in-hospital mortality between these 2 groups are sparse. We set our objective to determine the dialysis modality with a better in-hospital survival rate among diabetics with ESRD (ESRD-DM).

Methods: Data was extracted from the 2005 to 2012 Nationwide Inpatient Sample (NIS). Using propensity score matching, ESRD-DM patients on PD were matched with patients on HD at a 1:1 ratio. Analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

Results: Among 586,238 patients with incident ESRD, 568,469(96.97%) and 17,769(3.03%) were initiated on HD and PD, respectively, during the hospitalization. HD-DM patients had a significantly higher in hospital mortality compared with PD, however after matching both groups, it appears PD- DM have a much higher mortality (3.0 % vs 2.52% p<0.0001).

Conclusions: Diabetic patients with ESRD who undergo PD have significantly higher in-hospital mortality, favoring HD as the modality of choice.

PUB340

President Trump's Executive Order 13769: A Nephrology Perspective Scott Reule,[3,2] Mark E. Rosenberg,[2] Paul E. Drawz,[2] Areef Ishani,[1] Robert N. Foley.[2] *[1]None, Minneapolis, MN; [2]University of Minnesota, Minneapolis, MN; [3]Medicine, Veterans Affairs Health Care System, Minneapolis, MN.*

Background: With the recent signing of Executive Order (EO) 13769 restricting travel from 7 designated countries, we set out to describe associations between providers originally from the countries designated (EO providers) and clinical outcomes.

Methods: Physician data obtained from AMA Masterfile combined with USRDS and Medicare claims from 2010-2012 was used to determine associations between providers and outcomes including mortality, listing for, and receipt of kidney transplantation.

Results: A total of 8,025 providers cared for 361,454 patients on renal replacement therapy (RRT), with 7,304 patients receiving care from 174 EO providers compared to 346,450 patients receiving care from the remaining providers. Overall, EO providers were less likely to be female (12.5% vs. 25.2%) and more likely to practice in the Midwest (22.2% vs. 18.8%). EO providers delivered care in less densely populated areas, defined as the highest tertile of population density (32.2% vs. 36.3% for non-EO providers; > 3006.4 people/sq. mi.) and in populated areas with lower median household incomes ($44,126 vs. $49,443 for non-EO providers). Patients receiving care from EO providers were younger than 65 years of age (37% vs. 39.5%), more likely receive care > 12 months prior to initiation of renal replacement therapy (27.9% vs. 25.1%), and more likely to utilize peritoneal dialysis (8.9% vs. 7.9%) as a primary modality. At a mean follow up of 5.8 years, 31.4% of the cohort died. Overall, no significant differences in mortality (AHR 0.97; CI 0.87-1.08), listing for kidney transplantation (AHR 0.95; CI 0.88-1.02), or receipt of kidney transplantation (AHR 0.97; CI 0.84-1.11) were found.

Conclusions: EO providers are tasked with the care of patients in less populated, lower income areas with no impact on important clinical outcomes.

Funding: Clinical Revenue Support

PUB341

Developing an Energy Budgeting Education Program to Improve Fatigue Self-Management in Adults on Chronic Dialysis Janine Farragher,[2,1] Sarbjit V. Jassal,[1,2] Sara Mcewen,[2,3] Helene Polatajko.[2] *[1]University Health Network, Toronto, ON, Canada; [2]University of Toronto, Toronto, ON, Canada; [3]Sunnybrook Health Sciences Centre, Toronto, ON, Canada.*

Background: Fatigue is one of the most common and disabling symptoms found among people with end-stage renal disease on long-term dialysis. Energy budgeting is a novel approach to fatigue self-management, that focuses on strategies such as planning, pacing, and prioritizing to promote optimal use of available energy during everyday tasks. The approach has demonstrated positive effects in other clinical populations, such as multiple sclerosis, but has not yet been tried in the dialysis patient postulation. The objective of this project is to develop an energy budgeting intervention, that limits the deleterious effects of fatigue on life participation for adults on dialysis with fatigue.

Methods: Energy budgeting principles were combined with an established approach to problem-solving (the Cognitive Orientation to Occupational Performance) to form the theoretical framework of the intervention. Learning principles were applied to make educational material concise, simple and easy to learn. Key informant feedback was sought after initial prototype development to guide further program revisions.

Results: The P.E.P. (Personal Energy Planning) program is a two-part fatigue self-management program for adults on dialysis. In Part 1, patients learn general concepts about fatigue and energy budgeting during two concise, self-administered web modules. In Part 2, patients apply the concepts with the guidance of a healthcare professional to create and test personalized energy plans that address their unique goals. The content and design of the program have been largely endorsed by key informants (2 CKD patients, a dialysis nurse coordinator, and a health education specialist), who provided several minor recommendations for further enhancement.

Conclusions: After key informant feedback is implemented, the PEP program will be ready to undergo efficacy testing to explore its effects on fatigue and life participation in adults on chronic dialysis.

Funding: Government Support - Non-U.S.

PUB342

Intra-abdominal Non-Communicating Pseudocyst in a Peritoneal Dialysis Patient Devan Makati,[2] Sana R. Akbar.[1] *[1]None, Morgantown, WV; [2]West Virginia University, Morgantown, WV.*

Background: Introduction Intraperitoneal pseudocyst formation is a rare complication found in peritoneal dialysis (PD) patients. Thus far the cases reported involve the pseudocyst enclosing the Tenchhoff catheter tip (1).

Methods: Case 66 yr old male with a past medical history of Diabetes, cerebral stroke and end stage renal disease on continuous ambulatory PD for 2 years was being treated with intravenous antibiotics for pneumonia. On hospital day 8 due to patient's abdominal pain CT abdomen pelvis was performed showing a 16.1 x 9.0 cm rim-enhancing loculated fluid collection in the right abdomen. Fluid analysis showed creatinine and urea matching serum samples leading to the conclusion that the fluid was fibrin entrapped dialysate. Serum BUN 49mg/dL, creatinine of 7.92mg/dL, fluid BUN was 51mg/dL, fluid creatinine was 8 mg/dL.

Results:

Conclusions: Discussion Our patient's case is rare, due to a lack of communication between the pseudocyst and catheter, making it hard to diagnose as no outflow obstruction was noted. Diagnosis was established only after IR guided fluid drainage due to escalating peritonitis. CT peritoneography is considered superior to traditional CT scans (2). After 24 hours the drain was removed and cultures remained negative. Due to worsening condition and PD cell count the catheter was removed and transitioned to hemodialysis. Patient improved after removal of PD catheter. Non-communicating pseudocyst is a rare complication that occurs in PD patients. We recommend in patients with PD found having loculated fluid collection on imaging; to send cell count, culture and analysis in order to diagnosis a pseudocyst. Our case differ from those reported by Baer et al as there was no outflow obstruction and the signs of peritonitis were masked by the antibiotics for the patient's pneumonia. 1: *Abdominal Pseudocyst following peritoneal dialysis-associated peritonitis: A Report of 3 cases Gernot Baer, MD, Albrecht Wagner, MD, Jochen Selbach, MD, Mike Otto, MD, and Stefan M. Weiner, MD. Am J Kidney Dis 55: e15-e19. 2010* 2: *Complications of Peritoneal Dialysis: Evaluation with CT Peritoneography Sachiko T. Cochran, MD, Huy M Do, MD, Amir Ronaghi, MD, Allen R. Nissenson, MD, Barbara M. Kadell, MD. Scientific Exhibit vol17-number4. Pg. 869-878 July 1997*

PUB343

Abstract Withdrawn

PUB344

Pattern of Late Catheter Dysfunction in Automated Peritoneal Dialysis Patients Detected through Remote Patient Monitoring and Its Impact in Therapy Total Time Mario R. ---,[2] Victor A. Mercado,[2] Manuel Abraham Ramirez Almazan,[1] Manuel G. Lopez de Nava,[1] Pedro Jimenez,[1] Alfonso Ramos.[1] *[1]Baxter Mexico, San Jer?nimo Chicahualco, Mexico; [2]Internal Medicine, Hospital Dr Belisario Domínguez, Mexico, Mexico.*

Background: Despite progress made in the management of patients in peritoneal dialysis and in spite of improvements in technique survival, Tenckhoff catheter dysfunction remains a common problem of peritoneal dialysis. The aim of this report is to show the impact on draining and infusion times as well as on the total therapy time in a group of patients with Tenckhoff catheter dysfunction through remote monitoring and to compare them to a group of patients with functional standard catheters

Methods: A group of patients with an abnormal pattern of drainage time, which affected the total amount of effective therapy time, was detected during the initial assessment. We conducted an evaluation of, 4 patients (3 males, 1 female) (group 1) with an average time on therapy of 24 months. In order to assess the impact, 10 patients (6 male, 4 female) (group 2) who did not show abnormal findings were randomly selected and then, we measured the actual therapy time (min), infusion times (min), drainage times (min), nightly UF (ml) and total UF (ml) in both groups. Descriptive statistics were used, and the differences in the variables between patients in group 1 and 2 were performed using t test for continuous variables and X^2 distributions or Fisher exact test for discrete variables or according its distribution.

Results: The median total therapy time was 335 vs 409 minutes for group 1 and group 2, respectively ($p< 0.02$); the median drainage time was 179 vs 92 minutes ($p< 0.007$); the median infusion times was 46.5 vs 36 minutes ($p< 0.05$); and the median UF was 594 ml vs 1187 ($p=$ NS). A linear regression between UF and total therapy time showed a positive correlation of 0.61. Beta coefficient showed that an increase of one minute in the total therapy time is associated with an increase of the UF of 5.69 ml ($p<0.05$)

Conclusions: Remote patient monitoring in APD patients allows early detection of disturbances in filling and drainage patterns during dialysis. An interesting finding is the correlation between the total time of therapy and the UF

PUB345

Difference in Consideration of Patient Eligibility for Peritoneal Dialysis between Nephrologists and Other Medical Staffs – Using a Conjoint Analysis Hisako Yoshida,[2] Kazuhiko Tsuruya.[1] *[1]Integrated Therapy for Chronic Kidney Disease, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [2]Clinical Research Center, Saga University Hospital, Saga, Japan.*

Background: In patients with incident end-stage renal disease, selection of renal replacement therapy (RRT) modality is affected by consideration of medical staffs. Very few studies have investigated the consideration of medical staffs regarding RRT modality selection. Thus, we conducted a web questionnaire study for nephrologists (Neph) and other medical staffs (OMS) to elucidate their consideration of RRT modality, especially regarding eligibility for peritoneal dialysis (PD), using conjoint analysis (CA).

Methods: CA is a method for understanding the preferences for such as services over a set of multi-attribute alternatives (Clark MD, *et al. NDT* 2016). According to CA procedure, 21 simulation cases were created to quantify the relative importance of hypothetical patient attributes as the 6 categories: sex (male, female); age (40, 55, 70, 85 years old); primary diseases (diabetic nephropathy, chronic glomerulonephritis, polycystic kidney disease); abdominal condition (normal, post-surgery, hernia, diverticulum); necessary for support (independent or dependent of family support); and self-care status (good, poor dietary control, or poor sanitary control). For each case vignette, the Neph and OMS who were working at the PD clinic of Kyushu University Hospital and its related facilities were asked to indicate whether they would recommend PD for their patients using a five-point scale. This research was performed using a web response system (https://questant.jp). Relative importance rates and partial utility scores were calculated via CA. We compared these values between Neph and OMS using Wilcoxon signed-rank test.

Results: A total of 98 respondents (42 Neph and 56 OMS) answered our web questionnaire. We calculated the relative importance which means the strength of influence for respondents' evaluation, and the utility score means weight for decision making within each factor. In Neph compared to OMS, the relative importance was higher in "primary diseases" (p=0.002) and lower in "self-care status" (p=0.023). In "age", the utility score of 85 years old was higher (p<0.001), while in "self-care", good self-care was lower (p=0.041), in Neph than OMS.

Conclusions: The consideration of eligibility for PD was significantly different in age and self-care status between Neph and OMS.

PUB346

Effectiveness of Chlorhexidine, Mupirocin, and Conventional Exit-Site Care for the Prevention of Peritoneal Dialysis-Related Infections (COSMO-PD): A Preliminary Result of a Randomized Trial surapon nochaiwong,[5,6] Chidchanok Ruengorn,[2,6] Kajohnsak Noppakun,[7] Kiatkriangkrai Koyratkoson,[3,6] Chayutthaphong Chaisai,[3,6] Ratanaporn -. Awiphan,[1,6] Wilaiwan -. Chongruksut,[7,6] Sirisak Nanta.[4,6] *[1]Chiangmai University, Chiangmai, Thailand; [2]Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand; [3]Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand; [4]Maesai District Hospital, Chiang Rai, Thailand, Chiang Rai, Thailand; [5]Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand; [6]Pharmacoepidemiology and Statistics Research Center (PESC), Chiang Mai University, Chiang Mai, Thailand; [7]Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand. Group/Team: Thai Renal Outcomes Research (THOR) Investigators.*

Background: Topical antibacterials, antiseptics, and cleansing agents for exit-site care has potential to decrease the risk of PD-related infections-the most common cause of technical failure, morbidity, and mortality in PD patients. Evidence is limited to guide the choice of exit-site care agents for the prevention of PD-related infection. We evaluated whether daily local application of chlorhexidine gluconate (CHG)-impregnated patch would decrease the rate of PD-related infections compared with topical mupirocin ointment or conventional exit-site care.

Methods: In a randomized, double-blind, multicenter trial, we study the effectiveness of three exit-site care agents; 2% CHG-impregnated patch, 2% mupirocin ointment, and conventional exit-site care by normal saline solution among adult PD patients. Participants were recruited from three tertiary PD centers in Thailand, from June 2016 (enrollment is ongoing). The primary pre-specified outcome was a composite of PD-related peritonitis and exit-site infection (ESI). Secondary outcomes included rates of catheter removal, adverse events, and all-cause mortality. The study has been registered as NCT02547103.

Results: Of 215 participants screened, 44, 43, and 43 were randomized to receive CHG, mupirocin, and conventional exit-site care, respectively. No difference of characteristics among groups were observed. With the numbers available, there was no differences of primary and secondary outcomes (all P>0.05) among the study groups, as well as safety profiles.

Conclusions: A preliminary result revealed that no statistically significance in efficacy and safety of three exit-site care agents. However, results may change as the study reaches closure, longer follow-up is warranted.

Funding: Government Support - Non-U.S.

Primary and Secondary Efficacy Outcomes

Outcome	Conventional Exit-Site Care (n=44)		Mupirocin Ointment (n=43)		CHG-Impregnated Patch (n=43)	
	No. of Event	HR (95% CI)	No. of Event	HR (95% CI)	No. of Event	HR (95% CI)
Primary composite PD-related infections	9	Reference	11	1.43 (0.59 – 3.47)	3	0.34 (0.09 – 1.26)
Secondary outcomes						
• Peritonitis	7	Reference	9	1.60 (0.59 – 4.32)	0	NA
• ESI	4	Reference	4	1.04 (0.26 – 4.18)	3	0.82 (0.18 – 3.68)
• Infection-associated catheter removal	1	Reference	1	1.05 (0.66 – 16.85)	0	NA

CI, confidence interval; HR, hazard ratio; NA, not applicable

PUB347

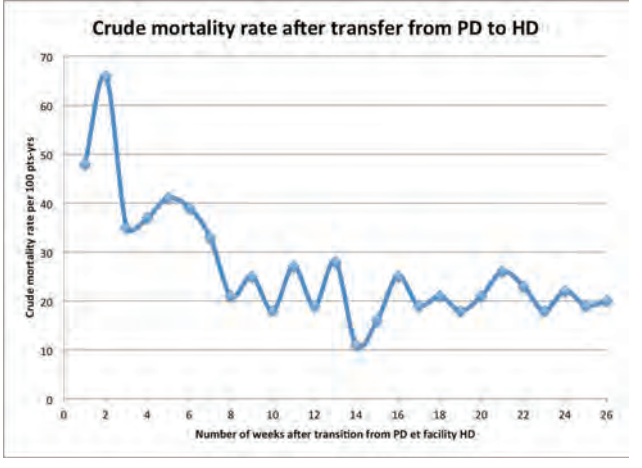
Early Mortality in Patients Transferring from Peritoneal Dialysis to Facility Hemodialysis Annie-Claire Nadeau-Fredette,[5] Christopher T. Chan,[9] Simon J. Davies,[10] Kitty J. Jager,[1] Mark Lambie,[6] Jeffrey Perl,[8] Ronald L. Pisoni,[2] James A. Sloand,[3] Nidhi Sukul,[11] Wim Van Biesen,[4] David W. Johnson.[7] *[1]Academic Medical Center, 1100 DE Amsterdam, Netherlands; [2]Arbor Research Collaborative for Health, Ann Arbor, MI; [3]Baxter Healthcare Corporation, Deerfield, IL; [4]Ghent University, Ghent, Belgium; [5]Hopital Maisonneuve-Rosemont, Montreal, QC, Canada; [6]Keele University, Crewe, United Kingdom; [7]Princess Alexandra Hospital, Brisbane, QLD, Australia; [8]St. Michael's Hospital, Toronto, ON, Canada; [9]Toronto General Hospital, Toronto, ON, Canada; [10]University Hospital of North Midlands, Stoke-on-Trent, United Kingdom; [11]University of Michigan, Ann Arbor, MI. Group/Team: On behalf of INTEGRATED Study Group.*

Background: Transition of patients with end-stage kidney disease (ESKD) between peritoneal dialysis (PD) and hemodialysis (HD) is both common and associated with a heightened risk of adverse events. This study aimed to assess rates and predictors of early death after transfer from PD to facility HD.

Methods: All incident Australian and New Zealand ESKD patients initiated on PD between 2000 and 2014 and with a transition between PD and HD were included. Weekly crude mortality rates were calculated using a Poisson model for the first 26 weeks after the transition and predictors of early death (≤ 50 days after switch to HD) were assessed in an adjusted Cox proportional hazard model, censoring for transplantation, change of modality and end/loss of follow-up.

Results: The study included 5577 patients with a transition from PD to facility HD. Crude mortality rate was highest during the second week after transfer to HD (66 deaths per 100 patient-years, 95% CI 52-84) and stabilized 8 weeks after the switch. (Figure 1). Predictors of early death after transition included older age (HR 1.25, 95% CI 1.18-1.32, per 5 years), diabetic kidney disease (HR 1.41, 95% CI 1.01-2.0 compared to glomerulonephritis), and longer dialysis duration (HR 1.16, 95% CI 1.10-1.24, per year). In contrast, male gender (HR 0.68, 95% CI 0.54-0.85), Asian race (HR 0.58, 95% CI 0.35-0.94 compared to Caucasian), and recent era (HR 0.63, 95% CI 0.43-0.91 for year 2010-2014 compared to 2000-2004) were associated with a lower risk of early death after transition.

Conclusions: The first weeks following transition from PD to HD are associated with a high death rate. Further studies should evaluate whether this vulnerability is mostly related to the reason behind PD completion or to the transition process, and target interventions to mitigate transition-associated risks.



PUB348

Bedside Peritoneal Dialysis Catheter Repositioning – A Novel Technique Santosh Varughese, Suceena Alexander, Anna T. Valson, Shailesh T. Kakde, Anjali Mohapatra, Vinoi G. David. *Christian Medical College, Vellore, India*.

Background: Malfunction of peritoneal dialysis (PD) catheters usually need surgical repositioning, requiring anesthesia, operating time, surgical expertise and longer hospital stay. Where successful, this novel percutaneous technique obviates need for open surgical repositioning.

Methods: The abdomen is scrubbed and cleaned. The PD catheter distal to the exit site is meticulously cleaned, the titanium adaptor and transfer set removed, the former soaked in povidone-iodine. A guide wire is passed through catheter into the peritoneal cavity. After infiltrating skin over the previous healed incision scar with local anesthetic, a 5mm incision is made. The soft tissue is dissected until the deep cuff is visible. With blunt dissection, the cuff is gently separated from the subcutaneous tissue where it had become anchored. Taking care to retain guide wire's position inside the peritoneum, the intra-peritoneal part of the PD catheter is removed. The external portion of the guide wire is advanced through the PD catheter till free from the catheter. The proximal end of the guide wire is thus in the peritoneum and distal end is free. Occluding clots, which may contribute to catheter malfunction, if present, are gently removed and the catheter flushed with saline. A dilator is advanced along the guide wire to ensure adequate space for the PD catheter at the linea alba and below. The peel-away sheath and dilator are then advanced into the peritoneum. The dilator and guide wire are removed leaving only the sheath in place. The catheter is then re-introduced into the peritoneum through the sheath, which is separated leaving the catheter in place. The peritoneal cavity is filled with PD fluid and good inflow and outflow are ensured. The subcutaneous tissue and skin are closed in layers.

Results:

Conclusions: In the 18 patients with PD catheter malfunction in whom percutanous repositioning was done, we had immediate success in 100% and a month later 12 catheters were functioning well. Six months later, they remained functional but one patient had died due to cardiac disease. In a significant proportion of cases, this novel procedure will help to obviate surgical repositioning, saving money, decreasing hospital stay and not necessitating personnel with surgical expertise. This promises to be exceptionally useful in resource-poor settings of South Asia.

PUB349

Abstract Withdrawn

PUB350

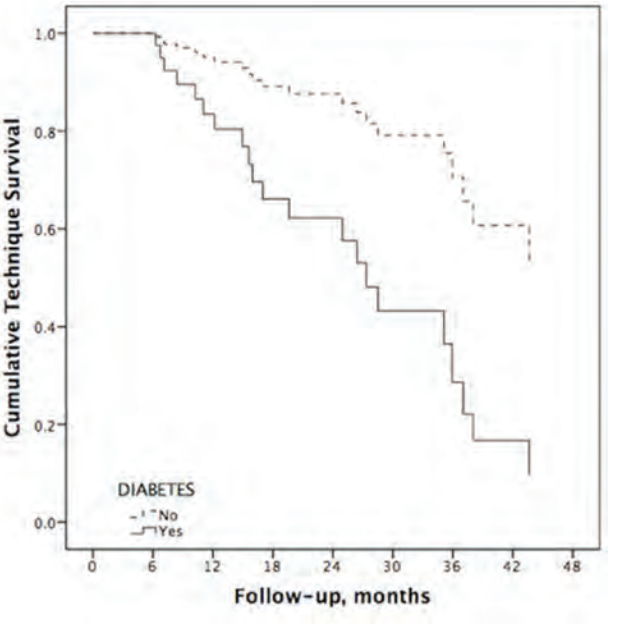
Reasons for Dropout from Peritoneal Dialysis in Contemporary Days Guilherme P. Santa Catharina, Gabriel C. Barsotti, Erica A. Guimarães, Rodrigo S. Adao, Camila Dosse, Bruno C. Silva, Benedito J. Pereira, Rosilene M. Elias, Hugo Abensur. *Universidade de Sao Paulo, Sao Paulo, Brazil*.

Background: Peritoneal dialysis (PD) is a worldwide spread technique that provides comparable mortality with hemodialysis. Technique survival, however, is limited due to patient dropout. Since several advances in peritonitis prevention and treatment occurred over the last few years, we hypothesized that the main patient dropout cause was no longer peritonitis.

Methods: We collected data from patients starting PD between December 2010 and May 2017 in an academic center, including demographic, clinical, and laboratorial variables. Reasons for dropout were classified as catheter-related, PD-related or patient-related problems.

Results: We included 136 patients (age 48±19 years, 51% male, and 29.6% diabetic). During a median follow-up of 10.6 months there were 18 kidney transplants and 67 dropouts: 15 (22.4%) catheter-related, 39 (58.2%) PD-related (20 transfer to hemodialysis due ultrafiltration failure and volume overload and 19 peritonitis), and 13 (19.4%) patient-related (4 recovery of renal function, 2 patient burnout and 7 deaths). Diabetics had a higher technique failure rate (RR 3.6, p=0.008), in a model adjusted for age and renal function at PD entry (Figure 1). Patients with catheter-related problems had a higher body mass index (26.8±4.5 vs. 23.7±4.0 kg/m 2, p=0.017).

Conclusions: Since peritonitis and membrane failure are the main causes for dropout from PD, all efforts should be done in order to preserve renal function and avoid infection. Further investigation is warranted to confirm that overweight patients have more catheter-related problems.



PUB351

Case of Encapsulating Sclerosing Peritonitis in a Renal Transplant Recipient Anam Siddiqui. *Northwell, Elmhurst, NY*.

Background: Encapsulating Sclerosing Peritonitis is an uncommon form of peritoneal inflammation characterized by fibrous thickening of the visceral and parietal surfaces of the peritoneum. PD treatment is the major risk factor for EPS, with specifically the duration of the treatment most crtically linked to EPS development. EPS is categorized by the adhesion of intestines and the subsequent capsule, composed primarily of Fibrin, formed around the adhered lesion. The clinical indicators of patients developing EPS while on PD treatment are ineffective clearance and ultrafiltration failure. Patients who were previously withdrawn from PD treatment and are developing EPS, present with small bowel obstruction.

Methods: We report a case of a 49-year old male, former PD patient of 5 years, with history of HTN, on metoprolol, and a renal transplant recipient. Patient presented 1-2 years after renal transplantation with a month-long history of abdominal discomfort, nausea, and vomiting. CT imaging revealed a small bowel obstruction. Patient received conservative management with an improvement in symptoms and was discharged home. After one week, the patient presented again with similar symptoms. He was again found to have a high-grade small bowel obstruction. Despite the initial conservative treatment, for persistence of symptoms, he underwent surgical treatment. A biopsy then revealed EPS as the cause of his recurrent small bowel obstruction.

Results: Our patient received a diagnosis of EPS, a rare disease which caused him to have SBO. Our patient's history of long term PD treatment was the main cause leading him to develop EPS. Another known contributor to EPS is the use of betablockers. While the specific mechanism remains unclear, one possible explanation is that betablockers have an inhibitory effect on surfactant release. The role of surfactant in the peritoneum may compare to that of surface-active phospholipids, which prevent intra-abdominal adhesions. Surgical treatment is the exclusive recommendation for patients with EPS. This patient population has a relatively poor prognosis with a mortality rate of 25-55%

Conclusions: In more than half of all cases, EPS occurs following PD withdrawal, as was observed with our patient. Thus, despite its rarity, it is imperative to strictly monitor a long-term PD patient upon withdrawal from PD therapy for symptoms of intestinal obstruction.

PUB352

Scope and Heterogeneity of Outcomes Reported in Randomized Trials in Patients Receiving Peritoneal Dialysis Karine E. Manera,[3,5] Allison Tong,[3,5] Jonathan C. Craig,[4,5] Roberto Pecoits-Filho,[1] Benedicte Sautenet,[6] David W. Johnson.[2] *[1]Pontificia Universidade Catolica do Parana, Curitiba, Brazil; [2]Princess Alexandra Hospital, Brisbane, QLD, Australia; [3]The University of Sydney, Westmead, NSW, Australia; [4]University of Sydney/ Children's Hospital, Sydney, NSW, Australia; [5]Centre for Kidney Research, The Children's Hospital at Westmead, Westmead, NSW, Australia; [6]Department of Nephrology and Clinical Immunology, University François Rabelais, Tours, France. Group/Team: On behalf of SONG-PD Steering Group.*

Background: Randomized trials can provide evidence to inform decision-making for improved care and outcomes but this may be limited if the chosen outcomes are not relevant to patients and clinicians, and are reported inconsistently.

Methods: Medline, Embase, the Cochrane Kidney and Transplant Specialized Register and clinicaltrials.gov were searched for RCTs involving adults receiving PD published from 2011 to 2016. All outcome domains and measurements were extracted. The frequency and characteristics of the reported outcome domains and measures were analyzed.

Results: From 85 included trials, 1346 different measurements of 60 different outcome domains were reported, with a median of 5 per trial (interquartile range 3 to 10). Overall, 27 (45%) domains were surrogate, 23 (38%) clinical and 10 (17%) patient-reported. The six most commonly reported domains were PD-related infection (37 [44%]), mortality (32 [38%]), renal function (31 [36%]), dialysis solute clearance (26 [31%]), protein metabolism (25 [29%]) and technique failure (25 [29%]). Quality of life (14%) and fatigue (4%) were reported infrequently. The most frequently reported clinical outcome, PD-related infection, had 69 different outcome measures, with only 11 of these being used in more than one trial.

Conclusions: Trials in PD include important clinical outcomes such as mortality and infection, but these are measured and reported inconsistently; and patient-reported outcomes are infrequently reported. Nearly half of the outcome domains were surrogate or biochemical outcomes.

PUB353

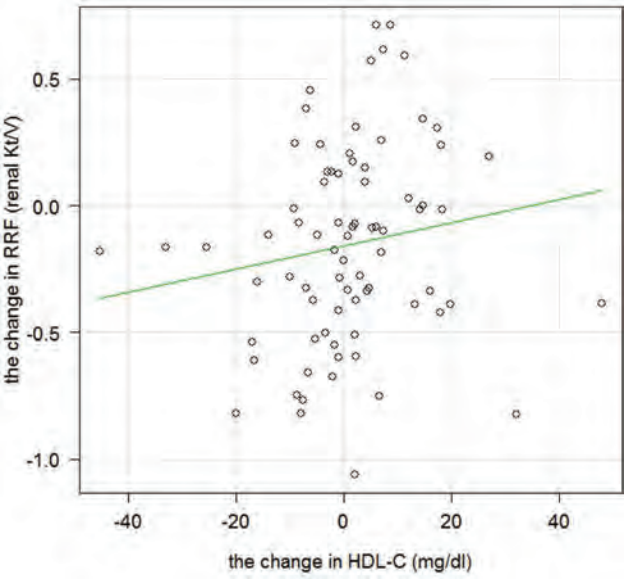
Association between Lipid Profile and Residual Renal Function in Incident Peritoneal Dialysis Patients Yu Honda, Yukio Maruyama, Masatsugu Nakao, Nanae Matsuo, Yudo Tanno, Ichiro Ohkido, Keitaro Yokoyama, Takashi Yokoo. *Division of Nephrology and Hypertension, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan.*

Background: Preserving residual renal function (RRF) is known to be related to mortality in peritoneal dialysis (PD) patients. It has been reported that lipid profile is associated with the incidence and progression of chronic kidney disease, whereas it is not clear whether lipid profile is associated with the decline of RRF in incident PD patients. The aim of this study was to evaluate the association between lipid profile and RRF in incident PD patients.

Methods: This was a retrospective cohort study of 78 patients (58±14 years, male 68%, diabetes 41%) initiating PD between 2006 and 2015 in the three centers. We analyzed the relationship between lipid profile and the alteration of RRF, expressed as renal Kt/V, during 1 year.

Results: The change in renal Kt/V during 1 year was inversely correlated with high-density lipoprotein cholesterol (HDL-C) at PD initiation (rho=-0.28, P<0.05) and positively with the change in HDL-C (rho=0.24, P<0.05) during 1 year. On the other hand, there was no significant correlation between the change in renal Kt/V during 1 year and light-density lipoprotein cholesterol.

Conclusions: Our results demonstrated the association between HDL-C and deterioration of RRF in incident PD patients. Further study is needed to clarify the effect of medication for dyslipidemia on preserving RRF in PD patients.



PUB354

Long-Term PD Patients in Greece: Are There Any Special Characteristics? Emilios Andrikos,[2] Paraskevi Tseke,[3] Olga Balafa,[1] George I. Tsirpanlis,[4] Christina Melexopoulou,[6] Vasileios Liakopoulos,[10] Christos Katsinas,[5] Chrysostomos Dimitriadis,[7] Marios Theodoridis,[8] Ploumis Passadakis.[9] *[1]Nephrology, University Hospital of Ioannina, Ioannina, Greece; [2]Hatzikosta, General Hospital, Ioannina, Greece; [3]MESOGEIOS Dialysis Center, ATHENS, Greece; [4]Nephrology, G.Genimatas, General Hospital Of Athens, Athens, Greece; [5]Nephrology, Bodosakio, General Hospital, Ptolemaida, Greece; [6]Nephrology, Laiko, General Hospital, Athens, Greece; [7]Nephrology, Ippokrateio, General Hospital, Thesaloniki, Greece; [8]Nephrology, University Hospital of Alexandroupolis, Alexandroupolis, Greece; [9]Nephrology, University Hospital of Alexandroupolis, Alexandroupoli, Greece; [10]Nephrology, AXEPA, General Hospital, Thessaloniki, Greece.*

Background: The Hellenic Peritoneal Dialysis (PD) Registry started setting up at the beginning of 2017 in order to evaluate the special characteristics of PD patients (pts) in Greece and to enhance the practical experience of PD physicians and nurses.

Methods: A group of nephrologists with great experience in PD in co-operation with biostatisticians designed a database to record all prevelant PD pts in Greece. All PD physicians were informed for the development of the registry and asked to participate.

Results: Until today, 182 prevalent PD patients from 7 centers have been recorded, 39 of whom are on PD for more than 5 years. Long-term PD survivors (23 male and 16 female) have a median time on PD of 72 months (range from 60-145) and their mean age at start of dialysis was 54.5±15.9. The majority of pts was married (76.3%) and was followed by nephrologists prior to PD initiation (half of them for almost 4.5 years). The educational level was low to basic for 57% of these pts and 1 out of 3 of them lived in islands and rural areas. Training on PD was performed by institutional PD nurses or properly educated employees of PD companies. The latter was significantly associated with longer PD training period (mean training time was 11.5 vs 6.4 days, p=0.004) and shorter time on PD (median time on PD was 60 vs 74 months, p=0.05). Initial PD regimen which was CAPD in 75% and APD in 25% did not significantly affect the total time on PD. However, the odds for peritonitis was significantly reduced in those on APD (OR: 0.12, p=0.023). Noteworthy, 37.5% of the total pts had none or 1 episode of peritonitis in a median time of 67 months and overall peritonitis rate was 3.5 episodes per pt-year. 39.5% of these pts are candidates for kidney transplantation, which is strongly associated with the age at the start of PD treatment (p=0.006) and Charlson's Co-morbidity Index (p=0.008).

Conclusions: As this is the first report of an ongoing study limitations may exist as further findings are expected to fully explore the PD map in Greece.

PUB355

Surgical Outcomes of Tenchkoff Catheter Insertion in a Tertiary Center Gerard Low,[2] Jia rui Kwan,[1] Gabriel W. Low,[2] Chieh-suai Tan,[3] Tze tec Chong.[3] *[1]Nanyang Technological University, Singapore, Singapore; [2]National University of Singapore, Singapore, Singapore; [3]Singapore General Hospital, Singapore, Singapore.*

Background: Peritoneal Dialysis is a cost-effective form of renal replacement therapy. The initiation of PD requires the insertion of a Tenchkoff catheter and this is most commonly performed by a surgeon in our center. We aim to report the surgical outcomes of Tenchkoff catheter insertion in our center and factors affecting outcomes.

Methods: This is a single-centered retrospective study of all patients receiving Tenchkoff catheter between January 2011 and January 2016 in Singapore General Hospital. Electronic medical records of the patients were reviewed and followed up for 1 month after initiation of peritoneal dialysis.

Results: A total of 470 Tenchkoff catheters were inserted. Most were inserted using an open technique (403/470, 85.7%) while the remainder were inserted laparoscopically (67/470, 14.3%). The mean age of the study population was 61.6 ± 14.3 years, 49.8% Male, 75.5% Chinese, 18.9% Malay, 4.9% Indian with a median BMI of 24.0. Diabetes Mellitus (58.5%), Hypertension (87.2%) and Ischemic Heart Disease (41.1%) were the 3 most common comorbidities among patients. Majority of patients did not have any previous abdominal surgery (392/470, 82.6%). More than half of the patients (289/470, 61.5%) were started on hemodialysis before Tenchkoff insertion. Tenchkoff catheter insertion was successful in all patients with no mortality attributable to surgical mishap. Early complications within 30 days of Tenchkoff insertion include bleeding (31/470 with 3 requiring operative hemostasis), leak (3/470 with none requiring operation), flow-related issues requiring re-operation (20/470; migration 3.0%, obstruction 0.8%, poor flow 0.4%) and infection (22/470; PD peritonitis 3.2%, Exit-site infection 3.0%, Tunnel tract infection 0.2%, Incision site infection 0.2%). Early complications were not related to the method of insertion, patient comorbidities or BMI on multivariate analysis.

Conclusions: Tenchkoff catheter can be successfully inserted in majority of patients. Flow-related complications are the most common indication for re-intervention within 30 days. Further studies of composite endpoints are required to improve Tenchkoff insertion outcomes.

PUB356

Icodextrin as an Alternative to Glucose to Evaluate Peritoneal Membrane Transport Pattern Lucas D. Pereira,[2] Rosilene M. Elias,[1] Hugo Abensur,[1] Erica A. Guimarães,[2] Benedito J. Pereira,[3] Rodrigo S. Adao.[2] *[1]Universidade de Sao Paulo, Sao Paulo, Brazil; [2]Universidade de São Paulo, Salvador, Brazil; [3]University of Sao Paulo School of Medicine, Sao Paulo, Brazil.*

Background: Peritoneal equilibration test (PET) is considered the gold standard method to classify transport pattern among patients on peritoneal dialysis (PD). Classically, ultrafiltration (UF) volume obtained after a dwell of 4.25% glucose can estimate peritoneal membrane capacity. Icodextrin is a dialysis solution that promotes UF mainly through the small pores and weather icodextrin can substitute glucose in predicting peritoneal membrane characteristics is unknown. We have compared UF volume with a 4-hour dwell period with icodextrin (UF-ICO) and 4.25% glucose solutions (UF-Glucose), correlating the results with PET.

Methods: We included 35 patients (47±17 years, 51.4% male), on PD for a median time of 9.2 months. Each patient underwent 3 assessments: standard PET, UF-ICO and UF-Glucose.

Results: UF volume, and PET classification according to dialysate 4h/0h glucose and dialysate/plasma creatinine are shown in Table 1. Patients were divided into two groups: low (L) + low average (LA) and high (H) + high average (HA) pattern. Dialysate/plasma creatinine correlated with UF-Glucose (r=-0.383, p=0.023) and with UF-ICO (r=-0.531, p=0.001). ROC estimated the best cut=off point to predict H/HA transport pattern with ICO was 141ml based on PET classification by 4h/0h glucose (sensitivity 69% and specificity 91%) and 141ml based on PET classification by dialysate/plasma creatinine (sensitivity 77% and specificity 95%). (Observe table)

Conclusions: Icodextrin-based solutions promote an equal or better capacity to predict peritoneal membrane pattern. Further studies are warranted to confirm these results in a larger sample size.

PET classification by 4h/0h glucose and dialysate/plasma creatinine

	Glucose 4h/0h		Dialysate/plasma creatinine	
	L/LA N=22	H/HA N=13	L/LA N=22	H/HA N=13
UF-Glucose, ml	793 (574, 898)	613 (475, 719)*	793 (574, 824)	613 (475, 719)
UF-ICO, ml	15 (-19, 85)	236 (25, 444)*	0 (-27, 72)	236 (100, 444)*

*p<0.05 vs. L/LA

PUB357

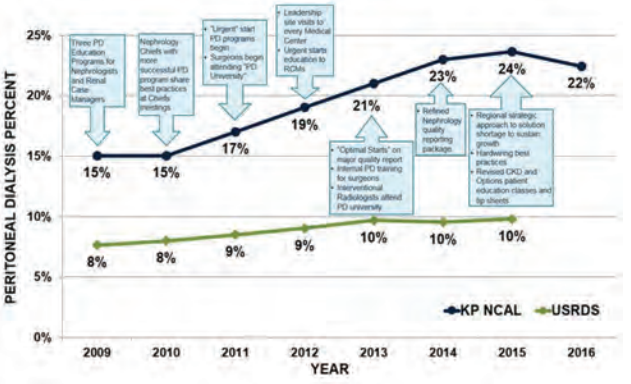
Organizational Performance Improvements in a Successful PD Program Leonid Pravoverov,[1] Sijie Zheng,[3] Joanna Mroz,[3] Neelam M. Bhalla.[2] *[1]Kaiser Permanente, Walnut Creek, CA; [2]None, Fremont, CA; [3]The Permanente Medical Group, Oakland, CA.*

Background: Peritoneal Dialysis (PD) is an underutilized renal replacement modality (RRT) in the United States; currently only 10 % of ESRD patient are on PD (USRDS, 2016). Kaiser Permanente Northern California (KPNC), an integrated health care system consists of 15 Medical Centers with unique Nephrology Departments, providing care to the population of over4 million members. Approximately 1300 KPNC patients initiated dialysis from March 2016 to March 2017. Among them, 27% started on PD and around 24% remained on PD.

Methods: Since 2009, KPNC has developed a multidisciplinary approach to PD promotion including: Patient and Family Education, Provider and Organizational education, multiple operational improvements with monitoring and continuous quality improvement projects. We analyzed the PD incidence and prevalence since 2009 to determine the trend for the past 8 years.

Results: Significantly higher incidence and prevalence of PD in KPNC was achieved by implementation of comprehensive multidisciplinary approach in promotion of home dialysis. Despite our highly effective multi-disciplinary program focusing on "home therapies first", we have recently seen a plateau with our PD penetration.

Conclusions: In a fully integrated health care system, despite continuous organizational efforts to increase PD incidence and prevalence, we observe slowing down of growth in some medical centers. Multiple factors are likely contributing, including socio-economic, demographic, patient composition and changes in healthcare landscape. We evaluate strategies to sustain growth of our home dialysis population by continuous provider education, ongoing evaluation of operational needs of local medical centers and use of technology to support patient education and engagement.



PUB358

Arnos Protein-Energy Wasting Score (ARNOS PEWS): Does It Work in Peritoneal Dialysis (PD) Patients? David Attaf. *Fresenius medical care, Frenes, France.*

Background: A score of PEW named "ARNOs PEWS" is graded from 0 (worse) to 4 (normal) and derived from Alb, BMI, Creat, nPCR. It predicts survival in HD patients. Any increase of the score is associated with increase of survival. It identifies subgroups of patients with higher risk of mortality. We aim to assess retrospectively if the score of PEW is applicable in PD patients

Methods: 76 PD patients (03/05 - 06/16), datas available for 58 patients. We define 4 categories of patients : Score 0-1 (Gr.1:severe wasting); Score 2 (Gr. 2: moderate wasting) ; Score 3 (Gr 3: Slight Wasting) and Score 4 (Gr 4: normal Wasting). We assessed the score changes during the follow-up and analyzed the association with biological and clinical outcomes.

Results: The table below provides clinical and biological parameters according to PEW score. Moderately and severely wasted groups (Gr 1 and 2) included 34 patients i.e. 58% of the global population. All parameters were significantly impaired in Gr 1 versus grp 4, except for the renal Kt/V.

Conclusions: ARNos PEWS is associated with morbidity and survival in PD. Longer follow up and higher number of patients are needed to know if this score will help in PD to identify subgroups of patients with higher risk of mortality in which nutrition support is mandatory.

	Gpe 1	Gpe 2	Grpe 3	Grpe 4	p (Gr 1 vs Gr 4)
Nb	13	21	18	6	< 0,01
Age y	74	69,4	66	59	0,02
Dialysis vintage y	4,5	3	2	1,7	0,03
CRP mg/l	19	14	10	6	< 0,01
Total KT/Vu	1,74	1,65	1,71	1,69	0,9
Residual diuresis ml/d	128	367	835	794	< 0,001
Hospitalisation (%days)	34%	33%	24%	4%	0,01
Death N (%)	4 (30)	5 (23)	3 (16,6)	1 (16,6)	< 0,02

PUB359

Evolution of Small Solute Transport in a Patient Treated for 18 Years with CAPD Restricting Hypertonic Glucose Dominique C. Pagniez, Jean-baptiste Beuscart. *Nephrology, Centre Hospitalier Universitaire, Lille, France.*

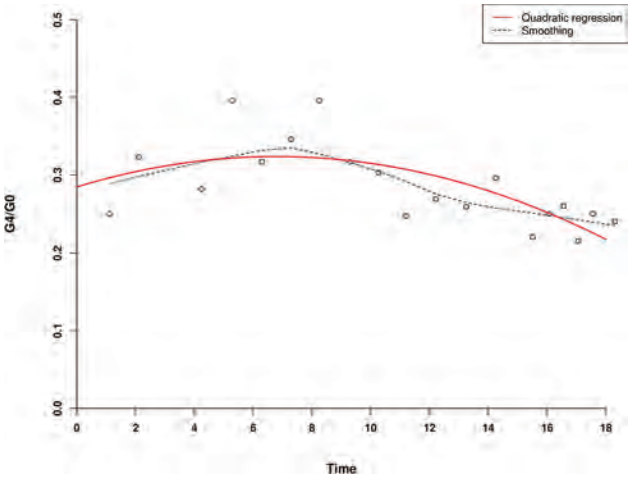
Background: We report on the evolution of Small Solute Transport (SST) in a patient treated for 18 years in our center, where the use of hypertonic (3.86%) glucose solutions has been persistently restricted.

Methods: A 44-year-old female patient started CAPD in August 1994. She used only 1.36% glucose bags until one bag of icodextrin per day was started in December 2006. A second was started in December 2009. She had an early cluster of peritoneal infections leading to a catheter exchange in January 1998, and a late peritoneal infection in September 2009, which was difficult to cure. She received a living donor kidney transplant in January 2013, and is currently doing well. An equivalent of the PET test, using 3.86% glucose, was performed after 6 months of CAPD, and then every 12 months.

Results: As the interference of glucose with creatinine measurement varied widely in the 18-year period, we used the D4/D0 ratio of peritoneal glucose concentrations after

dwell times of 4 and 0 hours as an index of SST. The D4/D0 ratio actually *increased* (SST decreased) until 2004; it then slowly decreased, and was .25 in March 2012, its initial value. There had been a gradual decrease of the effluent volume for both the 1.36% glucose and icodextrin bags since 2010.

Conclusions: This particular case suggests that persistently avoiding exposure to hypertonic glucose may prevent for up to 10 years the increase in SST linked to vascular proliferation.



PUB360

Evaluation of the Nutritional Status in Peritoneal Dialysis Patients: Interactions with Mental Psychological State and Appetite Valerio Vizzardi,[1] Scilla Maghella,[2] Massimo Sandrini.[1] *[1]ASST-Spedali Civili, Brescia, Italy; [2]University of Brescia, Brescia, Italy.*

Background: Malnutrition (MN) is a risk factor in peritoneal dialysis (PD) patients and it's correlated with a major risk of morbidity, mortality and a worsening of quality of life.

Methods: 41 prevalent PD patients were included. The aim was to evaluate nutritional status (NS) testing Malnutrition Inflammation Score (MIS) and correlated it with appetite and mental psychological state (MPS); appetite was assessed by the Council Nutritional Assessment Questionnaire (CNAQ), MPS was assessed by the Mental Component Scale (MCS) of short form-12 (SF-12) questionnaire. MIS and CNAQ were submitted at the first meeting (T_0) and six months later (T_1), MPS at T_1.

Results: The percentage of malnourished depended on the method used for the evaluation both at T_0 and T_1. MIS was negatively correlated with nephelometric albumin and cholesterol at T_0 ($p<0.001$, $p<0.01$) and T_1 ($p<0.001$, $p<0.05$) and with triglyceride at T_0 ($p<0.05$). MIS was positively correlated with C-Reactive Protein (CRP) at T_1 ($p<0.05$). Appetite resulted reduced in 46% at T_0 and 49% at T_1. CNAQ at T_0 didn't correlate with weight loss from T_0 to T_1 and CRP. However higher CNAQ at T_0 (better appetite) correlate with lower MIS at T_1 (better NS) ($p<0,05$). We also studied the relation between MIS and CNAQ at T_0 (Figure 1): we obtained a scatterplot with four boxes: good NS and good appetite (box A), bad NS and good appetite (box B), good NS and bad appetite (box C), bad NS and bad appetite (box D). Analyzing the average CRP value for each box, the highest one was the value of box B. Another factor that can influence the NS is the MPS: lower MCS was related to highest MIS ($p<0,01$), lower nephelometric albumin ($p<0,05$) and lower CNAQ ($p<0,005$).

Conclusions: This study demonstrates that MIS can be used to evaluate the NS of PD patients which resulted influenced by inflammation, appetite and MPS. The latter influenced also the appetite.

PUB361

The Effect of Core Fucosylation on Rat Peritoneal Fibrosis Longkai Li. *First affiliated hospital of Dalian Medical University, China, Dalian, China.*

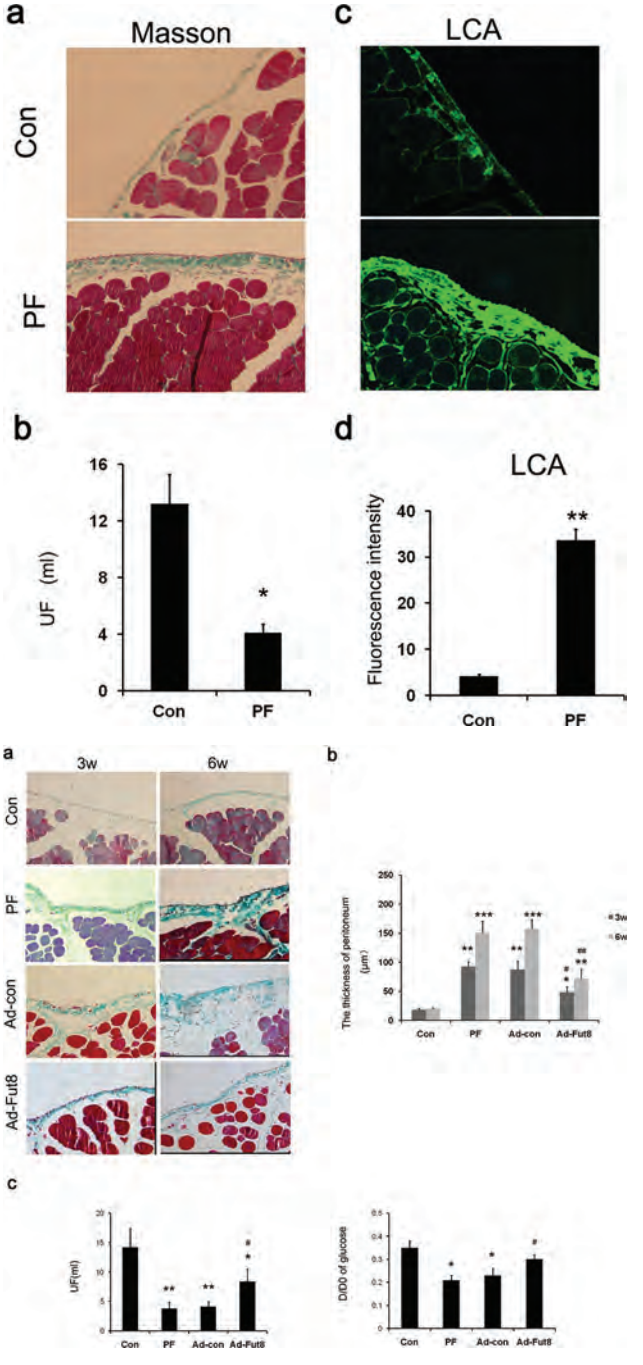
Background: To investigate the effect of core fucosylation (CF) on rat peritoneal fibrosis.

Methods: SD rats were divided into control, peritoneal fibrosis, Ad-Fut8shRNA, Ad-con and imatinib (PDGFR inhibitor) group. We used peritoneal fibrosis rat model induced by peritoneal dialysate. Fut8shRNA recombinant adenovirus was used to inhibit CF. We detected pathologic lesion, observed Collagen I and III, and examined TGFβ and PDGF signaling. We also compared the difference between inhibition of CF and imatinib.

Results: There is increased CF expression in rats with peritoneal fibrosis. After inhibition of CF, pathological lesion and functional changes in Fut8shRNA group were alleviated, compared with peritoneal fibrosis and Ad-con group. Collagen I and III in Fut8shRNA group were also alleviated. In TGFβ signaling, TGFβ receptor I and II and Smad were all increased, p-Smad was significantly decreased in the Fut8shRNA group. In PDGF signaling, PDGF receptor αand βand ERK were all increased, p-ERK was significantly decreased in Fut8shRNA group. Compared with imatinib group, pathological and functional changes, and Collagen I and III were all alleviated in Fut8shRNA group.

Conclusions: Blockage of CF inhibited PF, its effect is better than imatinib.

Funding: Government Support - Non-U.S.



PUB362

Physical Activity in Patients Treated with Peritoneal Dialysis: A Systematic Review Tharshika Thangarasa,[1] Rameez Imtiaz,[3] Swapnil Hiremath,[1] Deborah Lynn Zimmerman.[2] *[1]Ottawa Hospital Research Institute, Ottawa, ON, Canada; [2]Medicine, Ottawa Hospital, Ottawa, ON, Canada; [3]University of Ottawa, Ottawa, ON, Canada.*

Background: End-stage kidney disease (ESKD) treated with peritoneal dialysis (PD) are less active than sedentary individuals in the general population. The actual effects of physical activity with or without structured exercise programs for these patients remain unclear. Our objective was to more completely define the risks and benefits of physical activity in the ESKD population treated with PD.

Methods: With the help of a skilled librarian, a search was conducted using MEDLINE, EMBASE, CINAHL and Cochrane Central Register of Controlled Trials for randomized trials and observational studies to identify research articles examining the effects of physical activity on ESKD patients treated with PD. The primary outcomes of interest were improvements in mental health, physical function, fatigue, quality of life (QOL) and adverse events. Studies reporting adult end-stage kidney disease patients

treated with peritoneal dialysis that have participated in an exercise training program or had their level of physical activity assessed directly or by self-report were included.

Results: A total of 1828 manuscripts were identified; 13 were found to fit the inclusion criteria. Eight of the studies were observational (6 used an accelerometer/ pedometer, 1 used self-reported measures of physical activity and 1 used occupation type as a measure of physical activity), the remaining studies were interventional. Most of the interventional studies assessed aerobic exercise programs. There was evidence from 3 studies to suggest that physical activity resulted in increased levels of physical functioning, 1 study suggested an increased quality of life, and 1 study provided evidence for decreased mortality rates. Biochemical markers improved in majority of studies in which they were measured. However in 1 study, physical activity did not affect fatigue or physical performance.

Conclusions: There is limited evidence to suggest that physical activity in PD patients is associated with important benefits. Most of the studies is small and have important methodological limitations. There is a need for future randomized control trials examining the impact of exercise programs (both aerobic and resistance) in PD patients.

Funding: Clinical Revenue Support

PUB363

Peritonitis in Mexico: Comparison of CAPD and APD Population Ruben G. Roldan. *Instituto Nacional de Cardiologia Ignacio Chávez, Mexico city, Mexico.*

Background: Peritonitis is the major cause of morbidity and mortality in patients on PD. PD infection is associated with peritoneal membrane damage and technique faillure. Following a single episode of peritonitis, the risk of further peritonitis episodes, haemodialysis transfer and death are greatly increased and remain significantly elevated for up to 6 months.

Methods: In this retrospective study we aimed to evaluate patients with peritonitis episode between october 2014 to december 2016 catered in the "National Institute of Cardiology Ignacio Chávez" in Mexico city under continuos ambulatory peritoneal dialysis (CAPD) and automated peritoneal dialysis (APD). Using electronic database we found 71 patients with peritonitis. Clinical and biochemical data were evaluated.

Results: 36 (50.7%) patients were female sex with a median age of 50 years. 54 (76.1%) on CAPD and 17 (23.9%) on APD. The principal etiology of CKD were diabetic nephropathy in 34 (45.1%), 17 (23.9%) with chronic kidney disease of unknow origin and 6 (8.5%) with focal segmental glomerulosclerosis. 28 patients (39.4%) with no history of peritonitis and the principals comorbidities were chronic hypertensión (47.9%), isquemic heart disease (16.9%) and chronic heart faillure (8.5%). The principals organism identified on cultures were S aureus in 23 (32.4%) of patients, E coli in 7 (9.9%), S marcescens in 5 (7%), S epidermidis with 5 (7%) cases and Candida in 5 patients (7%).

Conclusions: The results demostrate a less commonly cases of peritonitis in the APD poblation, with the highest number of cases caused by S. aureus (39.4%). From the patients with mechanical dysfunction (10) only 1 correspond to the APD poblation, and from the deads recorded (5) only 1 was part of the APD modality. We emphasize the results above-mentioned, were the level of albúmin and BUN demonstrated a statistical significance. Posible related to a properly nourished population, whom presented the less mortality and better outcome, in relation to a close follow up in the course of the treatment.

Variable	Outcome	Median	P
Albumin	Alive Dead	3.11 2.3	0.012
BUN	Alive Dead	65.88 36.92	0.02
Leucocytes	Alive Dead	8.47 21.16	0.05
Lymphocytes	Dead Alive	1.21 0.97	0.36
Age	Dead Alive	49.27 57.80	0.62
Cellularity	Dead Alive	2567 2262	0.83

PUB364

Tracheostomy Dependent Long Term Dialysis Patients Jack Rubin,[1] Jacqueline Bogo.[2] *[1]None, Long Beach, CA; [2]none, Los Alamitos, CA.*

Background: Since April 2014 we have been treating tracheostomy dependent patients(pts) at our dialysis unit (ventilator and former continous ventilator). We wish to report salient features of our experience to May 2017.

Methods: Data were retrieved from the dialysis charts. The data from the last available chart entry are presented. All data are presented as mean ± sd unless stated otherwise. Differences between groups were evaluated by 2 tailed t test with Bonferroni correction for multiple comparisons.

Results: There were 38 pts (18F/20M) Their mean age was 68 ± 14 years with a mean time on dialysis at our unit of 171 ± 219 days (median 92). These pts were on dialysis prior to coming to us. They had suffered a medical catastrophe or transferred from a long term acute facility after developing renal failure that did not resolve. KT/V 1.4 ± 0.3, hg 9 ± 1 g%, albumin 3.1 ± 0. 6 g%, calcium 9.3 ± 0.9 mg% and phosphorus 4.3 ± 2.2 mg%. Ten (9F, 1M) (A) are on dialysis 185 ± 300 (median 185) days and 28 have deceased (D) after 112 ± 148 days (median 50). By 2 tailed t test creatinine mg% (A 6.7 ± 1.1;D 4.8 ± 1.4) was significantly lower in those who died (p<0.007). Cholesterol mg% (A 128 ± 50; D 88 ± 31 P<0.009)) and albumin g% (A 3.3 ± 0.6; D 2.9 ± 0.5 P<0.07) almost reached significance (negative after Bonferroni correction). KT/V (A 1.6 ± 0.3; D 1.4 ± 0.3), bun mg% (A 88 ± 39; D 100 ± 34), hemoglobin g% (A 9.9 ± 1.1; D 8.9 ± 1.2), prealbumin mg% (A 20 ± 8; D 16 ± 9), calcium mg% (A 9.5 ±1,1; D 9.4 ±0.8), phosphorus mg% (A 4.6 ± 1.5; D 4.4 ± 2.4) and hg A1c % (A 5.8 ± 1.1; D 6.1 ± 0.9) were not significantly different.

Conclusions: The laboratory differences observed between Alive and Deceased pts may reflect diminished muscle mass (lower creatinine) and malnutrition (lower albumin and cholesterol) as heralds of clinical deterioration prior to death. Upon taking on treatment of this group of pts one must expect a lower star rating as most require catheters and are frequently admitted for infection, bedsores or pulmonary complications. The logistics of transporting patients and ensuing ambulance traffic can be challenging. Funding may be a problem for ambulance service companies. To sustain these selected pts requires a dedicated staff of nurses, respiratory technicians and ambulance services.

PUB365

A Prospective Observational Study on Prevalence of Hepatitis C Virus Infection and Its Risk Factors in CKD Patients on Hemodialysis at Faridabad, Delhi NCR, India Hariharan R. Munganda,[1] Jitendra Kumar,[1] Punit Pruthi.[2] *[1]Asian institute of medical sciences, Faridabad, Haryana, India; [2]internal medicine, Asian Institute of Medical Sciences, Faridabad, India.*

Background: Chronic renal disease patients on haemodialysis are at increased risk of infection by hepatitis C virus (HCV). Subjects undergoing treatment in dialysis centres without nephrologists and improper viral marker screening, dialysis at more than one centre and no separate dialysis machine for HCV positive patients, unscreened blood transfusion are at risk of cross contamination. Thus, there is a need to screen these subjects for prevalence of HCV seropositivity and study the impact of HCV positivity on clinical course of the disease.

Methods: Aim of our study:was to assess prevalence of HCV positivity in CKD on hemodialysis subjects. Also to assess various characteristics of HCV positive subjects compare them with HCV negative CKD subjects.**Methodology**:In our Asian tertiary care hospital dialysis unit a total of 100 CKD subjects were recruited for the study and after informed written consent, further detailed history, socioeconomic and clinical parameters including dialysis related parameters were analysed and compared between the Hepatitis C seropositive and Seronegative subjects. Hepatitis C positivity was assessed using chemoluminiscence.

Results: Prevalence of seropositivity was found to be 16% in CKD subjects. Only 2% of the subjects have turned HCV positive from contaminated blood transfusion and dialysis at multiple centres while 14% have acquired HCV infection from same dialysis centre and by usage of same dialysis machine.

Conclusions: High prevalence of HCV infection exists in CKD subjects. Though CDC doesn't recommend HCV patient isolation/segregation, we in our study strictly recommend use of separate dialyzer for HCV positive patients under expert nephrologists supervision to contain the HCV infection. **References :** 1) CDC may call for HCV screening in hemodialysis, But not likely to recommend patient isolation, Suzanne Cotter, MD, medical epidemiologist in the CDC; https://www.ahcmedia.com/articles/44946-cdc-may-call-for-hcv-screening-in-hemodialysis 2) Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV-related chronic disease. Centers for Disease Control and Prevention. MMWR Recomm Rep. 1998 Oct 16

PUB366

Abstract Withdrawn

PUB367

Reporting Feasibility of the Use of a Real-Time Data Reporting Tool to Improve Outcomes of Haemodialysis Catheter Complications across Australia (REDUCCTION) Sradha S. Kotwal,[7,8] Girish S. Talaulikar,[6] Nicholas A. Gray,[5] Kevan Polkinghorne,[3] Stephen P. McDonald,[1] Alan Cass,[2] Martin P. Gallagher.[4] *[1]ANZDATA Registry, Adelaide, SA, Australia; [2]Menzies School of Health Research, Darwin, NSW, Australia; [3]Monash Medical Centre and Monash University, Melbourne, VIC, Australia; [4]None, Sydney, NSW, Australia; [5]Sunshine Coast University Hospital, Birtinya, NSW, Australia; [6]The Canberra Hospital, Carran Act, NSW, Australia; [7]Renal and Metabolic, The George Institute of Global Health, Sydney, NSW, Australia; [8]Prince of Wales Clinical School, UNSW, Sydney, NSW, Australia.*

Background: Patients with kidney disease are susceptible to healthcare associated infections, especially in association with dialysis catheter use. These catheters are a major driver of blood stream infection and the higher mortality in dialysis patients. Dialysis catheter care in Australia is managed by individual renal units, without real-time reporting and limited national benchmarking. Tools to analyse clinical variation and mount an effective timely response are lacking. Data on the total extent of catheter use and outcomes is limited.

Methods: This project has developed standardised definitions around dialysis catheter usage and complications, validated for accuracy by a central committee. Development of a custom-designed data collection tool used by clinical staff has enabled real-time data collection. The data collection tool was designed and developed using an iterative consultative process with participating renal units. Regular feedback meetings have been conducted since the launch of the data collection tool with changes/updates made using the feedback.

Results: The first phase of this study has involved the design, implementation and uptake of the data collection tool. Of the 36 units involved in the study, 28 are currently entering data. We have data on 696 participants, 427 active catheters with 41033 total catheter days. We expect data on approximately 9000 participants by the end of the study in 2020.

Conclusions: Early involvement of renal units, with regular feedback sessions, is invaluable when pursuing an implementation project at this scale. Meaningful representation with effective engagement from each state is essential to implement change nationally.

PUB368

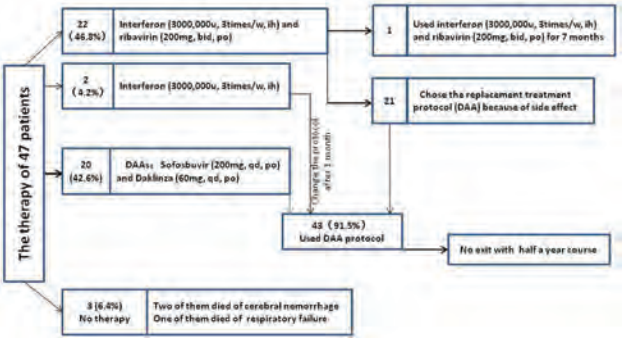
Hepatitis C Virus Outbreak in a Primary Hospital: Infection Investigation and Treatment Follow-Up Hua Liu,[2] Jinhong Xue,[1] Hongli Jiang.[1] *[1]Dialysis Center of First Affiliated Hospital of Medicine School, Xi?an Jiaotong University, Xi'an,Shaanxi, China; [2]First Affiliated Hospital of Medical College of Xi'an Jiaotong University, Xi'an, China.*

Background: To investigate the status of hepatitis C virus (HCV) infection, related factors and treatment follow-up in MHD patients in a primary hospital.

Methods: We monitored the HCV-RNA situation and HCV genotyping of 47 patients with positive anti-HCV antibody. The epidemiological investigation, infection risk factors were analyzed, and treatment response and tolerance of different patients were followd up.

Results: From the analysis of various aspects of HCV transmission in hemodialysis: 1) Regulations on the use of disposable articles are not strictly enforced; 2) The infection consciousness of medical staff is dim, and the conception of asepsis is not strong; 3) the hospital system is not perfect; 4) Infection index monitoring is defective. In the 47 patients, 2 patient were not detected HCV-RNA. The genotype 2a were 32 cases (68.1%), 1b were 9 cases (19.1%), and 2a mixed 1b were 4 cases, 2 (4.25%) patients did not measure genotype has started treatment, overall genotype proportion is different from the common HCV mainly in 1b type. 22 patient (46.8%) used the protocol of interferon and ribavirin (PR protocol) in the beginning, but 21 patients of those were changed to the DAA protocol (Sofobuvir and Daklinza) because of the side effect. 20 cases used the DAA protocol at the beginning. All of the patient used the DAA protocol not only first using but also the replacement, there were no patient exiting because of the intolerance. The negative conversion time of HCV-RNA between the PR and DAA protocol (67.75±8.71 vs 27.93±5.32, P<0.05)was different.

Conclusions: Strengthen the control measures, and strictly implement the infection control system is an important measure to prevent hemodialysis patients from HCV infection. DAAs scheme for MHD patient with HCV-infection has better tolerance, which is a good choice for patients with intolerance of PR protocol, and have better antiviral effect, but also need a lot of guidance for clinical use in clinical data support.



PUB369

Maintaining a Low Peritonitis Rate in Peritoneal Dialysis Patients Sankar Chinnugounder,[2] Stephen B. Craven,[2] Mark E. Stoker,[1] Nishanth Girija kumar,[2] Robert Mark Black.[1] *[1]Reliant Medical Group, Worcester, MA; [2]ST VINCENT HOSPITAL, WORCESTER, MA.*

Background: Peritoneal dialysis (PD) is an efficient, cost effective home modality for renal replacement therapy. In developing countries, PD has increased in numbers possibly due to the lack of hemodialysis (HD) but it has been declining in developed countries (Jain AK et al. J Am Soc Nephrol. 2012 Mar; 23(3): 533–544). The risk and poor outcomes in patients who develop peritonitis may be a major cause of this decline. The International Society of Peritoneal Dialysis (ISPD) position paper (Beth Piraino et al. Peritoneal Dialysis International, Vol. 31, pp. 614–630) considers the difference in incidence rates of peritonitis to be primarily due to disparities in training technique and infection prevention protocols. We strongly concur and propose that the remarkably low peritonitis rate in our program is secondary to a dedicated PD team.

Methods: We conducted an IRB approved retrospective review of data for all patients on PD at our institution between March 2014 and March 2017. Peritonitis during hospitalizations was also included. Our peritonitis rate was expressed as episode per patient per year. We also calculated the peritonitis rate for each organism. We compared the peritonitis rate with the target recommended by ISPD and also with the reported national (United States) level prevalence.

Results: We had an average of 22 patients on PD contributing to a total of 702 patient months. We recorded 7 episodes of peritonitis, which translates to one episode per 100.2 total patient months, which corresponds to 0.12 episodes per patient per year. This is half of the peritonitis rate (0.25 episodes per patient year) in the Unites States (Qamar et al. Advances in Peritoneal Dialysis, Vol. 25, 2009).

Conclusions: We strongly believe that our superior outcomes are due largely to the availability of our PD nurse, our nurse's presence in the operating room at the time of catheter insertion, the use of an experienced surgeon and prompt communication amongst the nephrologist, surgeon and dialysis nurse. We recommend that this process be initiated whenever possible at all PD facilities.

PUB370

Intra-Abdominal Collection and Catheter Removal as a Complication in Mexican Peritoneal Dialysis Patients Guadalupe R. Ramirez,[1] Luis I. Bonilla,[1] Diego E. De la fuente,[2] Elisa M. Guerrero Gonzalez.[1] *[1]Nephrology, University Hospital Dr. José Eleuterio Gonzalez, Monterrey, Mexico; [2]Facultad de Medicina UANL, Monterrey, Mexico.*

Background: Peritonitis continues to be the most frequent cause of Peritoneal dialysis (PD)failure. All dialysis treatments include a certain risk of infection because decreased immune activity in established renal failure. PD is associated with a high risk of infection of the peritoneum, subcutaneous tunnel and exit site. PD patients with severe peritonitis require catheter removal. It is often assumed that this approach, together with antibiotics, would eradicate the infection; however, some patients present further complications despite catheter removal. It is broadly known that developing countries, such as Mexico, are still using proportionally more PD than the rest of the world.

Methods: This was a Retrospective descriptive study about peritonitis on peritoneal dialysis patients. In a period of 40 months nephrology service implanted 238 peritoneal catheters by interventional technique following by predialysis education. Characteristics of the study cohort are described using medians ranges, and moass ranges for the continuous variables and proportions for the categorical variables. The differences between the groups were calculated using chi-square test.

Results: 238 patients were included. The median age was 50.3 years. 12 (52.2%) were male. 62 % were diabetic, 17 (70.8%) had 1 episode and 6 (25%) had 2 episodes of peritonitis. During the study period, 44.1% required catheter removal and 25% developed recurrent peritoneal collection that required percutaneous drainage. In most of cases (85%) the cause of removal catheter was the presence of abdominal collections and 1 patient had several hypoalbuminemia and associated shock, X2[2]= 3,489 p <0.077. *Pseudomonas* species were the microbiological causes of the peritonitis episodes in most of cases (20%). Of the 238 patients, 2 patients died within 24 months, 1 due to pneumonia and 1 due to myocardial infarction.

Conclusions: The formation and the persistence of intra-abdominal fluid collections of different sizes and localizations is not a rarely encountered phenomenon in peritoneal dyalisis patients. Catheter removal represents high cost in developing countries, and implies a low chance of successful return to peritoneal dialysis. Effective education and training in pre - dialysis should improve outcomes and avoid catheter removal.

PUB371

Gram-Negative Bacteraemia (GNB) in Hemodialysis Patients with Tunnelled Dialysis Catheters (TDCs) Quan Yao Ho. *Tan Tock Seng Hospital, Singapore, Singapore.*

Background: The clinical, microbiological characteristics and management of Gram-negative bacteraemia (GNB) in hemodialysis patients with tunnelled dialysis catheters (TDCs) has not been clearly defined.

Methods: Patients who underwent TDC-related procedures from 2014 to 2016 were reviewed and patients who developed GNB while on hemodialysis via TDCs were included.

Results: 599 patients were either newly initiated on dialysis via a TDC (n=424) or converted to hemodialysis via a TDC – either due to failed arterio-venous access (n=138) or conversion from peritoneal dialysis (n=37). On follow-up to 31 March 2017, 121 episodes of GNB developed in 99 patients while on dialysis via TDCs, including 16 episodes of polymicrobial bacteremia, The attributed sources of GNB were TDC (66.9%,n=81), musculoskeletal (6.6%,n=8), respiratory (5.8%,n=7), hepatobiliary (5.0%,n=6), urinary (5.0%,n=6), other gastrointestinal sources (4.1%,n=5) and others (6.7%,n=8) The principal organisms isolated were Pseudomonas (22.4%,n=31), Klebsiella (17.4%,n=24), Escherichia coli (15.9%,n=22), Enterobacter (11.5%,n=16) and Acinetobacter (7.2%,n=11). Among the all isolates tested, 29.1% were resistant to ceftriaxone, 12.6% to ceftazidime, 16.5% to cefepime, 16.5% to piperacillin/tazobactam, 14.1% to carbapenems, 22.7% to gentamicin, 13.6% to amikacin, 23.4% to ciprofloxacin, 32.0% to co-trimoxazole. 82.6%(n=100) of the cases had abdominal imaging (Computer tomography or ultrasound) performed, of which 19.8%(n=24) revealed at least 1 infective focus. 90-day mortality was 17.4%(n=21). 17.4%(n=21) of the cases required Intensive Care Unit (ICU) care; amongst these cases the 90-day mortality rate was 76.2%(n=16). 90-day mortality was associated with ICU admission (OR=15.2, 95%CI 6.28-37.0, p<0.01); a higher median Pitt Bacteraemia Score (3 vs 1; p<0.01); hospital-acquired (>48hours from admission) GNB (OR=3.40, 95%CI 2.13-5.42); source not attributed to TDC (OR=3.18, 95%CI 2.08-4.85, p<0.01) finding of at least 1 infective focus on imaging (OR=2.83, 95%CI 1.48 to 5.41. p<0.01) and management without a line-free period (TDC exchange or no line removal) (OR=1.78, 95%CI 1.18-2.70, p<0.05).

Conclusions: GNB in patients on hemodialysis via TDCs is associated with high morbidity and mortality. Abdominal imaging may be useful in prognostication and TDC removal may be associated with improved survival.

PUB372

Diabetic "MALA"dy – A Tale of a Patient with Diabetes Who Survived Metformin Associated Lactic Acidosis Twice Krishna K. Manda, Sameer Ansar. *OSF St Anthony Medical Center, Rockford, IL.*

Background: We present a case of a 54 y/o man with a h/o Type 2 Diabetes mellitus and Chronic Kidney Disease who was fortunate enough to survive Metformin Associated lactic Acidosis (MALA). He was admitted in June '16 with weakness, nausea and vomiting. Initial investigations revealed Acute Kidney Injury (AKI) with Creatinine (Cr) of 7.3 mg/dl, severe acidosis with Lactic acid greater than 13.3 mmol/L and pH was 7.01. As he was on Metformin, this was thought to be related to MALA amongst other etiologies. He was urgently started on hemodialysis. Renal functions improved and Cr was 1.33 at the time of discharge in July '16. He was again admitted in Feb '17 with increasing lethargy. Labs were notable for AKI with a Cr of 7.1 mg/dl, severe Lactic acidosis >13.3 mmol/L and pH was <6.8. Hemodialysis was emergently initiated. Metformin level was checked which was later found to be elevated at 31 mcg/ml (therapeutic range 1-2). Renal functions gradually recovered and Cr was 1.79 at the time of discharge in March '17.

Methods:

Results: Metformin is one of the most commonly used oral agents in Diabetes. It decreases insulin resistance, decreases hepatic glucose output and increases peripheral glucose uptake. The elimination half-life of Metformin in patients who take multiple doses and have good renal function is approximately 5 hours. Metformin is actively excreted, unmetabolized, via transporters in the proximal tubules of the kidneys and may accumulate in renal failure. The mechanism of MALA is complex. Metformin promotes the conversion of glucose to lactate in the splanchnic bed of the small intestine. Metformin also inhibits mitochondrial respiratory chain complex 1, leading to decreased hepatic gluconeogenesis from lactate, pyruvate, and alanine. This results in additional lactate and substrate for lactate production. Metformin plasma concentrations exceeding 5 mcg/mL are generally associated with MALA. Multiple case series have reported a high rate of mortality with MALA, some approaching 45%. Hemodialysis is indicated if lactate level >20 mmol/L or severe metabolic acidosis (pH ≤7.0)

Conclusions: As Metfomin usage in renal impairment has increased since the removal of rigid serum Cr levels, careful consideration of ongoing usage should be done in order to prevent this potentially life threatening "MALA"dy.

PUB373

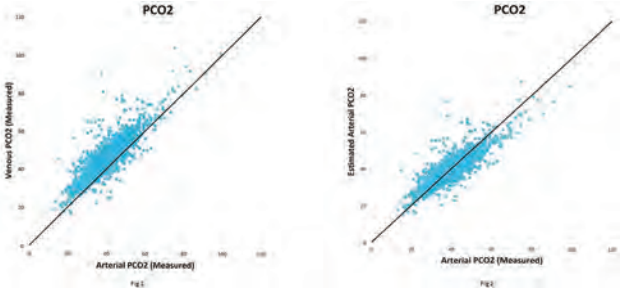
Leveraging "Big Data" Towards a Better Estimation of Arterial pCO2 from Venous pCO2 in the Clinical Settings Sheeba H. Ba aqeel, Alejandro Sanchez, Daniel Batlle. *Northwestern University Feinberg Medical School, Chicago, IL.*

Background: Arterial blood samples are often difficult to obtain owing to technical difficulties and pain associated with the procedure. Venous blood gas is increasingly used instead and there are formulas that transform venous pCO_2 to arterial pCO_2 generated from careful studies which, however, were based on limited data. Moreover, the data originated from specific settings, especially ICU and sometimes obtained using central venous blood etc. In addition, data points from a full spectrum of values within the lower and higher pCO_2 range were usually lacking in previous studies.

Methods: We analyzed a de-identified database of all the venous and arterial blood gases performed in the clinical lab of our hospital (Northwestern Memorial Hospital, Chicago, USA) between November 2003 and November 2016. We selected 3931 values from 11934 observations where both the arterial and venous samples had the same time of blood extraction. These observations were from 2430 males and 1501 females of ages ranging from 17 to 90 yrs and from all clinical settings and departments within the hospital.

Results: The expected relationship between venous and arterial pCO_2 (venous>arterial) was found with r^2= 0.74 (Fig 1). From this relationship the arterial pCO_2 could be recalculated from venous pCO_2 using the least squares formula: $ApCO_2$=0.82 x $VpCO_2$ + 2.19. Based on this relationship the estimated arterial pCO_2 re-plotted as a function of measured arterial pCO_2 was close to the line of identity (Fig 2)

Conclusions: The arterial pCO_2 estimated from venous pCO_2 from thousands of concurrent observations, from different clinical settings, encompassing a wide range of pCO_2 can replace measured arterial pCO_2 with a reasonable level of precision. With this improved estimation of arterial pCO_2 from measured venous pCO_2 the recalculation of arterial pH will likewise also be more accurate.



PUB374

The Pain of Fighting a Shadow: 5-Oxoproline Acidosis as a Clinical Diagnosis Alisha Smith, Franco H. Cabeza Rivera, Desiree Garcia Anton, John Bridges. *University of Mississippi Medical Center, Madison, MS.*

Background: Anion gap metabolic acidosis (AGMA) in the critically ill is a frequent cause of Nephrology consultation. While in most the cause is easily identified, in otherwise unexplained acidosis a high level of suspicion of specific conditions as well as availability of laboratory resources are needed. Despite being recognized as a cause of AGMA for decades, 5-oxoproline (5-OP) acidosis attention seems to have spiked recently with more cases being reported; yet, it is not well characterized and remains underdiagnosed.

Methods: A 79 year-old female with history of anxiety, depression, and COPD was admitted with vertebral and rib fractures after a fall. She was started on scheduled acetaminophen 650 mg PO every six hours for pain. Hospital course was complicated by respiratory failure and hemodynamic instability. Shortly after admission her serum bicarbonate (CO2) level began to fall: from 24 meq/L it decreased daily to a nadir of 14. At the time of consultation, 14.9 g of acetaminophen were administered to the patient over 7 days. ABG: 7.26/35/101; serum chemistry (mEq/L): sodium 137, potassium 4.1, chloride 109, CO2 14, BUN/creatinine 16/0.74 mg/dl (within her baseline), glucose 169 mg/dl, anion gap 17, albumin 2.7 g/dl; lactate normal, no ketones. With negative work-up for common causes of acidosis, discontinuation of acetaminophen was recommended and urine organics acids were ordered. Urine 5-OP level was 17 mmol/molCr. One day after stopping acetaminophen her CO2 improved to 18 and normalized within 72 hours.

Results:

Conclusions: 5-oxyproline acidosis remains a rare cause of AGMA. While mainly diagnosed in women with chronic use of acetaminophen, hospital-acquired cases have been reported. Given the transient nature of the elevation of 5-OP levels and the delay in obtaining confirmatory results, laboratory confirmation should not delay treatment when suspected clinically. In our case, clinical characteristics like gender, age, nutritional status, critical condition and more importantly the temporal correlation between acetaminophen intake and increase in anion gap provided a strong evidence for causality. The resolution of the acidosis after discontinuation of the drug also supports our diagnosis. Even when 5-OP levels in urine were not significantly elevated, its presence represents a pathological condition as it is rarely seen in healthy controls.

PUB375

Easy to Miss but Treatable Cause of High Anion Gap Metabolic Acidosis Priyamvada Singh,[3] Jean M. Francis,[1] Craig E. Gordon.[2] *[1]Boston University Medical Center, West Roxbury, MA; [2]None, Natick, MA; [3]Renal, Boston University, Boston, MA.*

Background: Acquired 5-oxoprolinuria secondary to excessive acetaminophen ingestion is a rare, and underdiagnosed cause of anion gap metabolic acidosis.

Methods: A 59-year-old female with CKD stage 3 (baseline creatinine 1.3 mg/dL, eGFR 41ml/min/1.73m2), diabetes, hypertension, and ischemic heart disease was admitted for bilateral foot gangrene and underwent left saphenofemoral endarterectomy. Her hospital course was complicated by delirium, *Clostridium difficile* colitis, AKI (peak creatinine 1.6mg/dL), and high anion gap metabolic acidosis (AGMA). AKI was attributed to ATN in the setting of high vancomycin levels and hypotension. She was treated with an isotonic bicarbonate infusion. Workup of the etiology of the high AGMA was unrevealing with no evidence of ketoacidosis and normal D and L-lactate values. Additional workup revealed elevated urinary 5-oxoproline (305 mmol/mol of creatinine, normal 15-59) through quantitative urine organic acid testing. In retrospect, we discovered she was treated repeatedly with acetaminophen during the hospital course (total 56 grams over 1 month). We recommended discontinuation of acetaminophen which resulted in improvement in her AGMA and delirium.

Results:

Conclusions: An under-recognized cause of high AGMA is acquired pyroglutamic (5-oxoproline) acidosis due to excessive acetaminophen ingestion. Acetaminophen disrupts the gamma-glutamyl cycle causing depletion of glutathione stores, and leading to accumulation of 5-oxoproline. Normally, glutathione results in a negative feedback by inhibiting gamma-glutamyl cysteine synthetase. With glutathione depletion, the negative feedback is removed resulting in upregulation of this enzyme, leading to increased gamma-glutamyl cysteine, a precursor to 5-oxoproline. Acquired 5-oxoproline acidosis is more common in elderly women with multiple comorbidities, in whom baseline glutathione levels may already be low. This likely is an underdiagnosed condition because measurements of serum and/or urinary 5-oxoproline levels are not readily available. Usually, treatment of the condition is to discontinue acetaminophen. Also, N-acetyl cysteine is shown to be of some benefit likely as it augments glutathione levels. Our case thus illustrates the need for keeping a high clinical suspicion and checking 5-oxoproline levels regularly in patients with unexplained AGMA as it is an easily treatable condition.

PUB376

The Bay Rum Diaries: False Assumptions about Rum and Kidney Function in a Case of Isopropyl Alcohol Ingestion Daniel Corbally, Avrum Gillespie. *Temple Medical School, Philadelphia, PA.*

Background: Isopropyl alcohol ingestion presents with a unique array of clinical and laboratory findings that challenge the understanding of both physiology and clinical chemistry. Isopropyl alcohol is a common ingredient in rubbing alcohol and aftershave products marketed as Bay Rum. Current packaging of Bay Rum often resembles that of common ethanol containing rums. We describe a case of mistaken ingestion of Bay Rum, the multiple abnormalities discovered, and their implications for treatment.

Methods: A Spanish speaking woman was brought to the hospital by her son after she drank Bay Rum. A week prior, the patient had been admitted for a fall related to beer potomania. Her son took away her alcohol so she ingested Bay Rum. On exam she was frail, lethargic, behaving unusually; oriented to only person and place. She was normotensive and euvolemic without neither nystagmus nor flank tenderness. Her Na+ was 123 mEq/L, BUN 47 mg/dl, creatinine 2.54 mg/dl, glucose 75 mg/dl, ethanol < 5 mg/dl, and a calculated osmol gap of 27 mOsm/kg. She was treated with normal saline, thiamine, and folate. Subsequent laboratory results showed osmol gaps of 18 mOsm/kg and 8 mOsm/kg respectively. Pseudo-renal failure was considered as acetone interferes with the creatinine assay, increasing it by 1 mg/dl for every 100 mg/dl of acetone. We calculated serum acetone of 98 mg/dl, which would falsely increase her creatinine by 0.98 mg/dl from her baseline of 0.6 mg/dl. Her elevated creatinine (2.54 mg/dl) cannot be attributed to acetone alone. Her fractional excretion of Na+ was 3.3%, suggesting acute tubular necrosis (ATN). Her creatinine improved slowly to 1.38 mg/dl on discharge.

Results:

Conclusions: This case highlights the importance of understanding and managing the elevated creatinine levels in isopropyl alcohol toxicity. It is critical that kidney function be carefully assessed and the laboratory phenomenon of pseudo-renal failure thought of as a diagnosis of exclusion. When managing toxic alcohol ingestions in the setting of chronic alcohol abuse, volume status and sodium levels must be monitored closely. Furthermore, it is important to understand the toxicity of common household products, and recognize that language barriers may lead to hazardous misunderstandings with such products.

PUB377

Cell Phone Application for Improved Point of Care Urine Concentration Measurement Laura E. Walawender,[3] John Ketz,[1] Vijay Saxena,[3] Andrew L. Schwaderer.[2] *[1]Nationwide Children's Hospital, Columbus, OH; [2]The Ohio State University, Westerville, OH; [3]Nationwide Children's Hospital, Columbus, OH.*

Background: Inadequate hydration may have deleterious effects including cyst progression in ADPKD patients or urinary stone formation. However, markers to evaluate hydration status have not been well studied in children. The objective of this study is to assess pediatric patients' urine osmolality compared to markers of thirst and/or urine concentratrion.

Methods: Children age 12-17 years were eligible for enrollment. Exclusion criteria were CKD > stage 1, concentrating defects, diuretic use, gross hematuria, and medication known to change urine color. Patients reported thirst perception by Visual Analog Scale. Patients and 4 research team members independently matched the patient urine to the urine color scale. Urine specific gravity (SG) was measured by automated dipstick analysis and refractometer. Urine osmolality was measured by osmometer. Linear regression compared urine osmolality to the other hydration markers. The technology department developed a cell phone camera app to to measure light penetrance into urine which was tested on 25 random anonymized urine samples.

Results: Twenty-one patients were enrolled. Linear regression comparing osmolality to hydration markers resulted in the following R squared values: SG (automated dipstick), 0.358; SG refractometer, 0.954; urine color scale (patient), 0.137, urine color scale (research group) 0.026-0.311; and light penetrance, 0.593. The slopes of the SG (automated dipstick), SG refractometer and light penetrance were significantly deviated from a zero-slope line. The refractometer SG had a significantly higher correlation to osmolality than the automated dipstick SG, p= 0.0046. Urine color scales vs. osmolality correlation slopes that significantly deviated from a zero-slope line in 2/4 research team members, but none of the patient or research group member's urine color scale vs. osmolality slopes differed significantly when compared to each other.

Conclusions: Specific gravity by refractometer, but not by urine dipstick correlated closely with urine osmolality. Additionally, there is poor correlation between thirst perception and hydration status. The cell phone application may be a more accurate point of care tool for urine concentration measurement than automated specific gravity dipstick, subjective thirst, and urine color scale, but lags behind specific gravity measured by refractometer.

PUB378

Proteomic Analysis of the Liver with Vacuolar Degeneration from AQP11 Deficient Mice Tatsuya Saito, Sei Sasaki, Kenichi Ishibashi. *Meiji Pharmaceutical university, Tokyo, Japan.*

Background: Aquaporin-11 (AQP11) is expressed at the membrane of intracellular organelles such as endoplasmic reticulum (ER). AQP11-null mice revealed a striking phenotype of multiple large intracellular vacuoles in the proximal tubule and the hepatocyte which are derived mostly from dilated rough ER. However, the mechanism for the vacuole formation is not clear. We employed a proteomic approach to identify key molecules for the hepatic vacuole degeneration before developing kidney dysfunction with polycystic kidneys.

Methods: Mouse livers from three week old AQP11-null mice and their wild-type littermates were compared. Tissue samples were sonicated and digested in sodium deoxycholate buffer to increase hydrophobic protein solubility and trypsin action. After labeling with tandem mass tag (TMT) 6-plex, mixed samples were fractionated by C18-strong cation exchange stop and go extraction tip and separated by nano-flow HPLC followed by mass spectrometer, Q-Exactive.

Results: From the analysis of six livers in each group, 1509 proteins were identified. Around 40 each differently expressed proteins (>1.3 and <0.7 fold) were identified. The enhanced proteins in AQP11-null were Metallothionein2 (binding various heavy metals), Cytochrome P450 4A (20-HETE synthase and fatty acid ω-hydroxylase activities), Thymidine phosphorylase (angiogenic factor), RNA-binding protein3 (anti-apoptotic), Fatty acid-binding protein (cellular antioxidant), Ceruloplasmin (copper-carrying protein), and Calpastatin (membrane fusion inhibitor). The decreased proteins in AQP11-null were RNA helicase DDX39A (cell growth), Cnot3 (cell growth, fat storing), Insulin-like growth factor-binding protein 4 (growth modulator), and Carbonic anhydrase 3 (fat storing). Moreover, KEGG pathway analysis revealed the decreased biosynthesis of antibiotics and nitrogen/lipid metabolism in AQP11-null.

Conclusions: Our proteomic study on AQP11-null liver revealed active cell survival molecules and membrane fusion inhibition with poor growth stimulation and nitrogen/fat metabolisms leading to grown retardation even before kidney failure. The results also

suggested the presence of abnormal heavy metal metabolism relevant to putative metal permeation of AQP11 as some AQPs permeate metals.

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PUB379

Nocturnal Polyuria: An Unusual Cause of Nocturia Umair S. Ahmed. *Lavale, MD.*

Background: Nocturnal polyuria is a syndrome in which more than 33 % of the total daily urine output occurs at night. We present an elderly patient who presented with nocturnal polyuria.

Methods: Patient is a 77 years old female with hypertension who was seen in Nephrology clinic for excessive urination at night. Patient had been experiencing an increased urine frequency and volume overnight for 2 years. Patient kept a voiding diary and was voiding approximately 1.5 liters of urine between midnight and 6:00 in the morning. Urine output during the day was less than 1 liters. Patient denied any consumption of caffeine or alcohol. Work up done included a normal sleep study, no evidence of a urinary tract infection, diabetes mellitus, hypokalemia or hypercalcemia. Transthoracic echocardiogram showed grade 1 diastolic dysfunction. Bilateral lower extremity duplex was unremarkable. Patient was started on Lasix 20 mg every morning without any improvement in symptoms. Desmopressin was discussed as a therapeutic option which was declined by patient due to concerns for hyponatremia, reported to be a risk in elderly patients on Desmopressin.

Results:

Conclusions: Causes of nocturnal polyuria include nephrotic syndrome, congestive heart failure and venous insufficiency which can result in development of interstitial edema during the day. Mobilization of this interstitial fluid can result in nocturia. Patients with chronic kidney disease are unable to maximally concentrate their urine. Neurological diseases including Alzheimer's and Parkinson's disease can result in alterations of the usual diurnal secretion of antidiuretic hormone and natriuretic peptides. Often nocturnal polyuria is idopathic and thought to be related to a decreased production of antidiuretic hormone which is usually elevated at night. Treatment options include non-pharmacological measures such as reducing fluid intake in the evening, avoiding use of caffeine and alcohol and use of compression stockings. Pharmacological options include use of topical estrogen, loop diuretics 6 to 10 hours before sleeping and Desmopressin. Desmopressin is a synthetic analog of anti-diuretic hormone and can reduce nocturnal polyuria by promoting water reabsorption overnight. Side effects of Desmopressin include headache, nausea, peripheral edema and hyponatremia. Severe hyponatremia have been reported in the elderly.

PUB380

Refractory Hypophosphatemia in a Young Asian Man with Cholangiocarcinoma Nattawat Klomjit,[2] Ma Clarisse T. Santos.[1] *[1]Renal Physicians Hawaii, LLC, Honolulu, HI; [2]Medicine, John A. Burns School of Medicine, University of Hawaii., Honolulu, HI.*

Background: Hypophosphatemia is a relatively uncommon electrolytes abnormality in hospitalized patients. Common causes of hypophosphatemia include refeeding syndrome, malnutrition and renal phosphate wasting. Excess parathyroid hormone-related peptide (PTHrP) is one of the causes of renal phosphate wasting. Squamous cell carcinomas are most commonly associated with PTHrP secretion, although there are rare case reports from other solid organ tumors. We present a rare case of refractory hypophosphatemia due to PTHrP from cholangiocarcinoma.

Methods: A 34-year-old man with medical history significant for hypertension and obesity who presented with progressive right upper quadrant pain and significant weight loss. Physical exam was remarkable for hepatomegaly and right upper quadrant tenderness. Initial labs were notable for mild hypercalcemia (13.9 mEq/L), hypophosphatemia (1.8 mEq/L), normal renal function (serum creatinine 0.7 mg/dL) and mildly elevated transaminases. CT pelvis and abdomen showed innumerable hypodense masses in caudate and left lobe of liver. US-guided liver biopsy revealed intrahepatic cholangiocarcinoma. Further work-up showed PTH 7 pg/ml (Low), 25-OH vitamin D 14 ng/ml(Low), 1,25-OH vitamin D 35 pg/ml (Normal) and PTHrP 87 pg/ml (High). Fractional excretion of phosphate was high at 20.46% consistent with urinary phosphate wasting. Hypercalcemia was treated with intravenous fluids, intranasal calcitonin and subsequently IV pamidronate. The patient was also persistently hypophosphatemic despite aggressive phosphorus repletion. He was started on chemotherapy since he was a poor surgical candidate due to an extensive disease. Nonetheless, he developed acute hepatic failure with progressive clinical deterioration. The patient and his family subsequently decided to pursue hospice care and he was then discharged to a nursing home.

Results:

Conclusions: In cancer patients who present with hypercalcemia and hypophosphatemia, excessive PTHrP production should be in the differential regardless of tumor type. Since the identification of PTHrP in 1987, there were less than 15 cases reported and most of them were from Japan. Interestingly, our patient developed cholangiocarcinoma with PTHrP at a relatively young age compared to all prior cases reports wherein patients were older than 50 years old. The presence of excessive PTHrP secretion in cholangiocarcinoma portends dismal prognosis.

PUB381

Acute Intermittent Porphyria as a Cause of Syndrome of Inappropriate Anti-Diuretic Hormone in a Young African American Woman Serena Bhela,[4] Dheeraj Kaul,[2] Gary R. Briefel,[1] Mary C. Mallappallil,[2] Moro O. Salifu.[3] *[1]Kings County Hospital, Brooklyn, NY; [2]Medicine, SUNY Downstate, Brooklyn, NY; [3]SUNY Downstate Medical Center, Brooklyn, NY; [4]Medicine, SUNY Downstate, Brooklyn, NY.*

Background: Acute intermittent porphyria (AIP) is a rare genetic disorder of the synthesis of heme caused by a deficiency in hydroxymethylbilane synthase (HMBS), resulting in the overproduction of the porphyrin precursors δ-aminolevulinic acid and porphobilinogen. When present it can result in hyponatremia and chronic kidney disease. Although identified in all main ethnic groups, it is less common in African Americans.

Methods: A 21 year old African American female with no previous medical history was admitted for three days of vomiting and abdominal pain. Physical exam at the time of admission revealed an elevated blood pressure, normal mental status and bilateral lower quadrant abdominal tenderness. Laboratory data on admission were unremarkable however 2 days into her hospitalization, patient had a witnessed tonic-clonic seizure and repeat lab work was remarkable for severe hyponatremia. She was found to have a normal creatinine with a serum sodium of 113, serum osmolality of 258, urine osmolality 807 and urine sodium of 245. Her TSH and T4 were normal. A diagnosis of SIADH was made and patient started on fluid restriction, Lasix and salt tablets with no improvement in her sodium level. Patient was started on 3% hypertonic saline with correction of her sodium. Given the patients abdominal pain, hypertension and SIADH, the diagnosis of acute intermittent porphyria was suspected. A 24 hour urine sample was collected and she was found to have increased levels of δ-aminolevulinic acid and porphobilinogen. Patient was discharged with labetalol for blood pressure control and advised to avoid medications that precipitate an acute attack. Two years later, the patient had another episode of hyponatremia consistent with SIADH and which responded to Lasix and salt tablets. She has experienced a progressive decline in her renal function, her last estimated glomerular filtration rate was 40ml/min with a serum creatinine of 1.8mg/dL and her urinalysis had mild proteinuria, a finding consistent with tubular damage possibly from porphyrin precursors that result in endoplasmic reticulum stress and apoptosis.

Results:

Conclusions: As there is a low prevalence of acute intermittent porphyria in the United States, the diagnosis should be considered in young females who presents with abdominal pain and SIADH of unclear etiology.

PUB382

An Asian Woman with Chinese Herbal Medicine Induced Transient Fanconi Syndrome Resulting in Rhabdomyolysis and Complicated by Severe Hyponatremia Nattawat Klomjit,[1] Noah M. Solomon,[2] Rick Y. Hayashi.[1,3] *[1]Medicine, John A. Burns School of Medicine, University of Hawaii., Honolulu, HI; [2]Nephrology, Straub Clinics and Hospital, Honlulu, HI; [3]Nephrology, Pali Momi Medical center, Honolulu, HI.*

Background: Fanconi syndrome is a rare disorder with multiple etiologies that is characterized by generalized proximal renal tubular dysfunction. Patients could develop hypophosphatemia, hypokalemia, tubular proteinuria, normoglycemic glycosuria and non-anion gap metabolic acidosis with bicarbonaturia. A potential cause of Fanconi syndrome, more commonly seen in Asia, is Chinese herbal medicine nephropathy.

Methods: A 55 year-old Japanese woman who presented with obtundation, abdominal pain, nausea, and vomiting without history of diarrhea. She was found to have hypotonic hyponatremia with initial serum sodium of 104 mmol/L, hypokalemia (3.3mmol/L), hypophosphatemia (1.1mg/dL) and a non-anion gap metabolic acidosis. Urine studies revealed proteinuria, positive urinary anion gap and glycosuria but with relative normoglycemia. These findings were consistent with generalized proximal renal tubular dysfunction otherwise known as Fanconi syndrome. Renal functions were normal with serum creatinine between 0.5-0.6 mg/dL. However, she had developed rhabdomyolysis with elevated creatine kinase up to 10,586 Units/L. Rhabdomyolysis was likely from hypophosphatemia and hypokalemia as a result of Fanconi syndrome and possible component of severe hyponatremia. The rhabdomyolysis improved after repletion of serum phosphorus and potassium. Possible etiologies of Fanconi syndrome had been ruled out. After an improvement of her mental status, she revealed that she had been taking Chinese herbs with the intention of weight loss starting 1 year prior to the admission. Serum phosphorus and potassium had been improved and were normalized prior to discharge. Sodium level was appropriately improved after 3% NaCL infusion. It is uncommon for Fanconi syndrome to present with severe hyponatremia. Abdominal pain and nausea might contribute to appropriate increased ADH production causing hyponatremia. The temporal relationship between the electrolytes recovery and discontinuation of the Chinese herbs suggests a possible causal role in the patient's transient Fanconi syndrome.

Results:

Conclusions: We reported a rare case of transient Fanconi syndrome associated with Chinese herbal medicine use. Chinese herbs containing aristolochic acid have been known to cause aristolochic nephropathy which could present with Fanconi syndrome.

PUB383

When the Hospitalist Meets the Nephrologist: A Case of a Mixed Acid-Base Disorder in the Ward Alexandra C. Bell,[1] Amr E. Mohamed,[2] Javier A. Neyra,[3] Fabrizio Canepa-Escaro.[2] *[1]Univeristy of Kentucky College of Medicine, Lexington, KY; [2]University of Kentucky, LEXINGTON, KY; [3]University of Kentucky Medical Center, Lexington, KY.*

Background: Mixed acid-base disorders are often found in hospitalized patients. We report a case of non-anion gap metabolic acidosis (NAGMA) resulting from rapid correction of severe metabolic alkalosis in a patient with acute kidney injury (AKI) receiving total parenteral nutrition (TPN).

Methods: A 37-year-old woman with TPN dependency after total small bowel resection and chronic percutaneous gastrostomy (PEG) tube presented with altered mental status. On admission, she had severe metabolic alkalosis with concomitant respiratory acidosis and AKI. Urine electrolytes were obtained after fluid resuscitation with 2.5 L of 0.9% NaCl and a dose of Diamox (250 mg) in the ED. History revealed her PEG tube was placed to continuous drainage for several days. On the wards, the patient continued to receive IV 0.9% NaCl and was briefly on BiPAP. Her mental status, kidney function and metabolic alkalosis improved after IV fluids. Home TPN (amino acids 1.6 g/kg/day) was then resumed without adjustments. Subsequently, the patient's serum $HCO3^-$ trended down with a normal serum anion gap and positive urine anion gap. The patient was diagnosed with post-AKI tubulopathy impairing the ability of the kidney to excrete HCl^- from amino acid metabolism in the context of high-protein TPN and relative dilutional hyperchloremic metabolic acidosis from aggressive administration of chloride-rich solutions. Patient was discharged on Bicitra and follow-up in Renal Clinic.

Results:

Conclusions: Post-AKI tubulopathy may affect acid-base homeostasis in patients exposed to high-protein TPN. Recognition of mixed acid-based disorders is critical for the management of patients with PEG tubes and TPN.

	On admission	At time of metabolic alkalosis resolution	At time of NAGMA diagnosis
SNa	137	143	134
SCl	72	109	107
SHCO3-	53	22	16
Corrected Anion Gap	14	16	15
Arterial pH	7.53	7.38	7.40
PCO2	70	39	28
Urine pH	8.5*		6.0
Urine Na	160*		109
Urine Cl	45*		96
Urine Anion Gap	95*		42
SCr	2.0	1.1	0.9
SBUN	98	44	24

*Post ED fluid resuscitation and Diamox

PUB384

Cases of Obstructive Uropathy Causing Hyponatremia Victoria Gutgarts,[2,1] Ilya Glezerman.[1] *[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Nephrology, Weill Cornell, New York, NY.*

Background: The most common cause of hyponatremia in hospitalized patients is syndrome of inappropriate antidiuretic hormone (SIADH). In older male patients, the etiology may be related to urinary obstruction, with improvement in serum sodium seen after relief of the obstruction.

Methods: Case 1: 63 year old man with prostate cancer and brachytherapy implantation three days prior to admission for altered mental status and penile swelling. He had no focal neurologic deficits on exam. Blood work showed serum osmolarity of 243 mOsm/L and sodium of 116 (136-144) mEq/L. Random urine sodium was 160 mEq/L and osmolarity 500mOsm/L. A urinary catheter was placed and 1600 ml of urine was drained. The serum sodium gradually improved, but patient required 5% continuous dextrose infusion to avoid overcorrection. His mental status improved and returned to baseline. Patient was discharged with indwelling urinary catheter and plan for future trial of void. Case 2: 60 year old man with invasive urothelial cancer who underwent radical cystoprostatectomy, bilateral ureteroileal ureterostomy and creation of neobladder two weeks prior to hospital admission. Patient was brought in for lethargy and poor oral intake. On exam, he was normotensive, lethargic but oriented, and had a urinary catheter draining yellow urine. Blood work notable for serum sodium of 99 mEq/L and creatinine of 4.4 (0.6-1.3) mg/dl from baseline of 0.9mg/dl. Urine studies showed random urinary sodium of 26 mEq/L and osmolarity of 157mOsm/L. Further imaging revealed a large pelvic fluid collection causing displacement of the neobladder and urinary catheter anteriorly. Drainage of the collection improved renal function to 1.3mg/dl with normalization of serum sodium.

Results:

Conclusions: In both cases, urinary retention, either secondary to recent prostate instrumentation or extrinsic compression of the bladder from a pelvic collection, was the direct cause of hyponatremia. Relief of the obstruction with placement of a urinary catheter or drainage of the pelvic collection, respectively, caused improvement in serum sodium. The possible mechanism of SIADH involves antidiuretic hormone release from pain related to distention of the bladder exacerbated by excessive free water intake to counter low urine output. Obstructive uropathy is a reversible cause of hyponatremia that should be considered as part of investigations particularly in the setting of recent urologic procedures.

PUB385

Surreptitious Alcohol Intake in a Hospitalized Patient Victoria Gutgarts,[2,1] Ilya Glezerman.[1] *[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Nephrology, Weill Cornell, New York, NY.*

Background: The serum osmolal gap is a useful tool to evaluate for additional solutes in the blood apart from sodium, glucose, and urea. If the difference between measured and calculated osmolality exceeds 10 mosmol/L, an alternative solute should be considered. Common causes include ethanol intoxication, methanol, ethylene glycol, or isopropyl alcohol. An anion gap can be calculated to differentiate these causes.

Methods: 30 –year-old gentleman with a history of Hodgkin's Lymphoma, Myelodysplastic syndrome, and allogenic stem cell transplant one year ago, presented with bilateral upper extremity tremor and diaphoresis for three days. Tremor was initially thought to be a side effect of cyclosporine, but despite dose reduction and lower serum levels of the cyclosporine, the tremor persisted. Hospital course was complicated by hypernatremia and nephrology was consulted for further evaluation on day 4 of admission. Patient complained of feeling thirsty, and drank two bottles of water daily. He was normotensive, not tachycardic, and afebrile. Physical exam was notable for an essential tremor of the bilateral upper extremities. Otherwise, patient was alert and oriented to person, time, place, but slow to answer and tangential. Recorded urine output was 1.3 liters in 24 hours but patient reported non-compliance with measurement of the output. Blood work was significant for a serum sodium of 154 (136-144) mEq/L and a serum osmolarity of 397 (280-295) mosmol/L. The calculated serum osmolarity was 326 mosmol/L with serum osmolal gap of 71. An anion gap was not present. A more thorough social history was reviewed but patient denied use of alcohol, ingestion of antifreeze, methanol, or alcohol derivatives. Upon further investigation, patient was found to have several empty alcohol containers under his bed.

Results:

Conclusions: Ethanol is the most common cause of an elevated serum osmolal gap. When presented with an elevated serum osmolality, it is important to calculate the osmolarity to investigate whether an osmolal gap is present. Hypernatremia is another clue to ethanol use, since it can cause diabetes insipidus through a transient inhibitory effect on anti-diuretic hormone (ADH) release. When presented with this scenario, a thorough social history and search need to be performed in order to effectively rule out a hazardous cause.

PUB386

Transient Paralysis: Rare Case of Ectopic ACTH Syndrome in Metastatic Prostate Cancer Leading to Severe Hypokalemia Sushma Munugoti, Jennine Michaud. *VA EAST ORANGE, EAST ORANGE, NJ.*

Background: Ectopic ACTH syndrome (EAS), due to malignancy, can lead to severe hypokalemia and metabolic alkalosis. The prognosis depends on tumor type and severity of symptoms. We describe a rare case of transient paralysis due to severe hypokalemia from EAS in metastatic prostate cancer.

Methods: 71 year old African American male with history of hypertension and castration resistant prostate adenocarcinoma, Gleason 9, treated with radical prostatectomy, followed by androgen deprivation therapy and chemotherapy for late recurrence, presented with severe leg weakness. Labs showed serum potassium of 2.2 mEq/L and bicarbonate 33mEq/L. Further studies showed pH of 7.52, PSA 491ng/mL and urine potassium 141mmol/L. Despite initial improvement with potassium repletion, potassium again dropped to 2.2mEq/L resulting in lower extremity paralysis. He concurrently developed progressive lower extremity edema, worsening hypertension, and hyperglycemia. Further work up revealed elevated serum cortisol 47.5 mcg/dL, ACTH 114.4 pg/mL, and 24 hour urine free cortisol 1772 ug. Lack of cortisol suppression after high dose dexamethasone administration confirmed EAS. Ketoconazole was added to potassium supplementation and spironolactone therapy. Paralysis resolved and potassium normalized in just over 24 hours. Ketoconazole was discontinued due to worsening liver function and changed to octreotide. He was discharged on hospice and died 6 weeks after initial evaluation.

Results:

Conclusions: EAS is a clinical state due to prolonged, inappropriate exposure to excessive endogenous secretion of cortisol and excess circulating free cortisol, with loss of the normal feedback mechanisms of the hypothalamo-pituitary-adrenal axis and the normal circadian rhythm of cortisol secretion. Advanced prostate cancer has been shown to dedifferentiate leading to a paraneoplastic syndrome. Inappropriate repression or expression of certain genes, presumably similar to those in normal pituitary corticotropes, can cause tumors to secrete ACTH. Treatment options include ketoconazole, which inhibits adrenal corticosteroid production, and octreotide which has a direct effect on tumor production of ACTH. Despite aggressive therapy, prognosis is poor for unresectable disease.

Funding: Veterans Affairs Support

PUB387

A Curious Course of Hypercalcemia in Rhabdomyolysis Pace Romney,[2] Josephine Abraham.[1] *[1]University of Utah, Holladay, UT; [2]University of Utah Medical Center, Salt Lake City, UT.*

Background: Hypocalcemia and hypercalcemia are common occurrences with rhabdomyolysis, but can mask underlying calcium metabolism disorders.

Methods: A 77 year old white man with a history of atrial fibrillation presented to the emergency department after sustaining a fall and remaining down for an unknown

period of time. He was diagnosed with rhabdomyolysis and was treated with intravenous fluids (CK 28,000 units/L). Despite appropriate interventions, CK continued to increase, hyperkalemia ensued and calcium decreased to 6.5 mg/dL with an ionized calcium 0.91 mmol/L. Intermittent hemodialysis was initiated for progressive renal insufficiency with hyperkalemia and oliguria. After three days of persistently low calcium, the calcium levels started to increase and was within the normal range at day six. However, over the following two weeks, serum calcium elevated to a peak level of 15.8mg/dL. He underwent further investigation. PTH was found to be elevated at 108 pg/mL. 25-OH Vitamin D was 35 ng/mL and 1, 25 Vitamin D was 13 pg/mL. PTHrp was elevated at 5.2pmol/L. Serum and urine were negative for paraprotein. The patient was given calcitonin, cinacalcet, and denosumab and calcium levels improved. In addition, his renal function recovered, and dialysis was discontinued. A tumor evaluation was conducted with a whole body PET scan that revealed increased metabolic activity at the site of muscle injury and ensuing calcinosis. Further review of his chart revealed a previous diagnosis of hyperparathyroidism due to a right inferior parathyroid adenoma seven years before. He declined surgery then and was lost to follow up.

Results:

Conclusions: This case illustrates the difficulties involved in the interpretation and management of calcium levels during acute rhabdomyolysis and ensuing shift of calcium between the muscle and the vascular compartments. Management principles include supportive fluid and calcium management along with renal replacement therapy. In this case, an underlying cause became apparent following correction of the acute metabolic sequelae of rhabdomyolysis. We believe the elevation of PTHrp is unexplained and likely false positive finding.

PUB388

Design and Methods of a Randomized Controlled Trial of Metformin in ADPKD (TAME-PKD) Stephen L. Seliger,[4] Kaleab Z. Abebe,[5] Kenneth R. Hallows,[1] Dana Miskulin,[2] Ronald D. Perrone,[2] Terry J. Watnick,[3] Kyongtae T. Bae.[5] *[1]Keck School of Medicine of USC, Los Angeles, CA; [2]Tufts Medical Center, Boston, MA; [3]University of Maryland School of Medicine, Baltimore, MD; [4]University of Maryland School of Medicine, Baltimore, MD; [5]University of Pittsburgh, Pittsburgh, PA.*

Background: Preclinical studies suggest that metformin may be efficacious for preventing progression in ADPKD by activating the metabolic sensor AMP-activated protein kinase (AMPK). However, the effect of metformin on disease progression in human patients with ADPKD, and the long-term tolerability of this medication in these patients, is unknown.

Methods: This is a phase 2 double-blind placebo-controlled multicenter randomized clinical trial to evaluate the safety, efficacy, and tolerability of metformin in ADPKD patients over a two-year treatment period. Participants (N=96) are adults with ADPKD with estimated GFR ≥50 ml/min/1.73m2, without contraindication to MRI or metformin treatment. Participants are randomized in 1:1 ratio to metformin - beginning at 500mg daily and titrating over 6 weeks to maximally tolerated dose up to 1 gram twice daily - or matching placebo. Follow-up evaluations occur every 2 weeks for 2 months, monthly for 4 more months, and then every 3 months for 24 months total. Metformin dose will be reduced to 500mg twice daily if eGFR declines <45 ml/min/1.73m^2, and will be discontinued if eGFR declines <30 ml/min/1.73m^2 or if increased serum lactate occurs. The primary safety/tolerability outcomes are: proportion of participants experiencing serious adverse events; gastrointestinal symptom rating scale severity; and maximally tolerated dose of study medication. Treatment efficacy is assessed by comparing the annual rate of changes in a) height-adjusted total kidney volume on MRI performed every 6 months and b) eGFR. Mechanistic outcomes include the changes in activity of key glycolytic pathway enzymes, metabolite concentrations, and activity of AMPK pathway enzymes measured in urine. An independent Data Safety Monitoring Board provides study oversight.

Results: Through May 2017, 57 participants have completed screening, of whom 55 were eligible. Of these, 48 were randomized, and 45 remain in active follow-up for a median 4.5 months.

Conclusions: Results of this phase 2 multicenter clinical trial will provide important evidence on the safety, tolerability, efficacy and effects on renal metabolomic biomarkers of metformin in patients with ADPKD. Such evidence will be crucial to support and plan a phase 3 multicenter efficacy trial.

Funding: Other U.S. Government Support

PUB389

Assessment of PROPKD Score in Chilean ADPKD Families to Predict Renal Outcome Paola Krall,[3] Daniela Ubilla,[3] Daniela P. Nualart,[3] Rocio P. Saenz,[1] Claudio A. Flores,[3] Patricio Downey,[2] Leopoldo G. Ardiles,[3] Sergio A. Mezzano.[3] *[1]Centro de Dialisis Dialsur, Osorno, Chile; [2]Pontificia Universidad Catolica, Santiago, Chile; [3]Universidad Austral de Chile, Valdivia, Chile.*

Background: ADPKD is a genetic kidney disease with a highly variable clinical presentation between individuals, even if they share the same mutation within a family. A clinical-genetic prognostic model, PROPKD score, is available to predict renal outcomes in ADPKD patients that needs to be assessed in developing countries with low health care resources.

Methods: 20 unrelated Chilean families with clinical ADPKD diagnosis were recruited between 2015 and 2017. Genetic analysis of *PKD1/PKD2* was performed in the index case and offered to relatives after identification of a pathogenic variant. Clinical data were collected in individuals carrying a pathogenic variant and scored: being male (1pt), hypertension or first urologic event <35 years (2 pt each one), non-truncating (2 pt) or truncating (4 pt) PKD1 mutation. Relationship between risk categories (low, intermediate or high) of progression to ESRD and age of ESRD was analyzed. Association between position of truncating mutations and hypertension was evaluated.

Results: A genetic basis was confirmed in 18 out of 20 Chilean families. 16 different pathogenic PKD1 mutations were identified that predicted protein truncation (n=11), in frame-deletion (n=1) or missense changes (n=4). PROPKD score was estimated in 51 participants (median ESRD age = 49 years) that resulted with low, intermediate or high risk, with median ages for ESRD of 56, 49 and 48 years, respectively (p=NS). 55% (11/20) of patients carrying truncating mutations before exon 26 had hypertension <35 years, whereas only 21% (4/19) of patients carrying truncating mutations after exon 26 had this condition, suggesting that early truncating mutations are associated with early hypertensive phenotype [p=0.048; OR 4.58; 95% CI 1.12-18.8].

Conclusions: Our findings indicate that PROPKD score seems to predict renal outcome in Chilean ADPKD patients, with the same tendency as described in other cohorts. *GANAB* might be considered as third candidate gene in the two families with negative results. Truncating mutations before the first PKD1 TM domain (exon 26) are associated to hypertension and, secondarily, might be important for renal outcome. We expect to recruit more ADPKD families and monitor young affected relatives to be able to predict ESRD with a high predictive value. FONDECYT #11140242

Funding: Government Support - Non-U.S.

PUB390

Overweight and Obesity Are Predictors of Progression in Early Autosomal Dominant Polycystic Kidney Disease Kristen L. Nowak,[8] Zhiying You,[8] Berenice Y. Gitomer,[8] Godela M. Brosnahan,[8] Vicente E. Torres,[3] Arlene B. Chapman,[5] Ronald D. Perrone,[4] Theodore I. Steinman,[1] Kaleab Z. Abebe,[7] Frederic F. Rahbari-Oskoui,[2] Alan S. Yu,[6] Peter C. Harris,[3] Kyongtae T. Bae,[7] Michel Chonchol.[8] *[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]Emory University School of Medicine, Atlanta, GA; [3]Mayo Clinic, Rochester, MN; [4]Tufts Medical Center, Boston, MA; [5]University of Chicago, Chicago, IL; [6]University of Kansas Medical Center, Kansas City, KS; [7]University of Pittsburgh, Pittsburgh, PA; [8]University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: Similar to the general population, body-mass index (BMI) in individuals with autosomal dominant polycystic kidney disease (ADPKD) has been increasing over recent decades. Surprisingly, the association of overweight and obesity with progression in patients with ADPKD has never been described. We hypothesized that overweight and obesity would be associated with faster progression in early-stage ADPKD patients.

Methods: 455 non-diabetic participants with ADPKD and estimated glomerular filtration rate (eGFR) >60 ml/min/1.73m^2 who participated in HALT Study A were categorized based on BMI as normal weight (18.5-24.9 kg/m^2; reference group; n=170), overweight (25.0-29.9 kg/m^2; n=176), or obese (≥30 kg/m^2; n=109). The longitudinal (5-year) association of overweight and obesity with change in height-corrected total kidney volume (htTKV) by magnetic resonance imaging was evaluated using multinomial logistic regression and mixed effects linear regression models.

Results: Mean±s.d. age was 37±8 years, annual percent change in htTKV was 7.4±5.1%, and BMI was 27.1±5.1 kg/m^2. The annual percent change in htTKV was greater with increasing BMI category (normal weight: 5.4±4.2%, overweight: 7.8±4.7%, obese: 9.5±6.0%; p<0.0001). After adjustment for demographics, randomization group, systolic blood pressure, eGFR, urinary albumin excretion, and baseline htTKV and liver volume, overweight and obesity were associated with increased odds of annual percent change in htTKV ≥7% compared to <5% (overweight: OR: 3.07, [95% CI: 1.79, 5.27], obese: OR: 4.86 [2.54, 9.30]). In the fully adjusted mixed effects regression model, htTKV across all time points (0, 24, 48, and 60 months) was greater in both the overweight (p=0.01) and obese (p=0.005) group compared to the normal weight group.

Conclusions: Overweight, and particularly obesity, are strongly and independently associated with rate of htTKV progression in early-stage ADPKD.

Funding: NIDDK Support

PUB391

Adaptations to Increased Flow in Polycystic Kidney Disease Elizabeth Y. Chen,[2] Marcelo F. Cassini,[1] Vijayakumar R. Kakade,[1] Richard Torres,[2] Lloyd G. Cantley.[2] *[1]Yale University, New Haven, CT; [2]Yale University School of Medicine, New Haven, CT.*

Background: Previous studies have demonstrated that the loss of polycystins results in unopposed cilia dependent cyst activating signaling, which leads to pathologic tubule remodeling. Because it has been hypothesized that the polycystin complex can function as a flow sensor in cilia, we evaluated the effect of increased GFR on tubule diameter in mice with either normal PC1 expression or Pkd1 haploinsufficiency.

Methods: We employed a nephrectomy model to induce compensatory hyperfiltration in the remaining kidney in both wild-type and Pkd1 heterozygous mice (which have approximately a 50% reduction of PC1 expression). To analyze tubule morphology we used multiphoton confocal microscopy and optimized the Z-stack image analysis techniques to accurately detect morphological changes in response to hyperfiltration.

Results: One week after unilateral nephrectomy, wild-type mice exhibited a 18.02% increase in tubule diameter (718.84±118.38 um vs. 848.37±119.06 um, $p<0.01$, n=20 tubules). Similarly, Pkd1 heterozygous mice exhibited a 20.45% increase in diameter at the same time point (688.48±102.58 um vs. 829.30±153.41 um, $p<0.01$, n=20 tubules).

Conclusions: These studies support a model of tubular adaptation to increased flow, but demonstrate that Pkd1 haploinsufficiency does not impact the magnitude of external remodeling.

Funding: Private Foundation Support

PUB392

Tuberous Sclerosis: Clinical Characteristics and Renal Management Strategies – A Single Centre Experience Rajkumar Chinnadurai, Peter H. Clough, Jude Allen, Martin N. Punter, David I. New. *SALFORD ROYAL NHS FOUNDATION TRUST, Manchester, United Kingdom.*

Background: Tuberous Sclerosis(TS) is a rare genetic disorder affecting multiple organ systems including Kidneys, where it presents as Angiomyolipoma(AML) and Cysts. With the advent of mTOR inhibitors, the management of this condition has taken a new dimension. As our institution is a tertiary renal and neurological centre, we have a growing cohort of TS patients followed-up in our multi-speciality and multi-disciplinary(MDT) TS clinic.

Methods: A cross-sectional observational study of all patients registered in our TS database. Clinical characteristics and Management strategies were reviewed.

Results: Currently 25 patients are registered in our study database. Mean age of our cohort is 40 with 14 males and 11 females. So far: 22/25 had some form of imaging (MR or CT Scan) of their Abdomen/Kidneys. Of these 22 patients, 13(59%) had a size of AML>3cm and qualified for mTOR inhibitor therapy based on current international guidelines. 5 had AML size <3cm and 4 with no renal involvement. Mean eGFR of our sample was 74.6ml/min/1.73m^2 with the mean haemoglobin 130mg/dl. eGFR did not correlate with the number of AMLs. There a linear increasing trend noted in the size of AMLs with age. Of the 13 eligible for mTOR inhibitor treatment, eight are on sirolimus, one on everolimus and rest under assessment. On review of neurological manifestations, 84%(16 of the available 19) had radiological evidence of cortical tubers in the brain, 11 had Sub Ependymal Nodules, 7 had SEGA(Astrocytoma). Phenotypically, 14 of 25 had an intellectual disability with 23 of the 25 patients having active epilepsy; generalised onset in 18 with co-existent focal onset in 17. The seizure type was unclassified in 5 patients. All 25 were on at least two antiepileptic medications.

Conclusions: Our study and database have given a better insight of our patient characteristics and management strategies, including a plan for timely imaging. With expanding indications of the use of mTOR inhibitors an MDT approach would be the appropriate management strategy. Plans also include the use of Physiologically Based Pharmacokinetic Modelling(PBPK) in guiding mTOR inhibitor dosing to overcome challenges in drug level monitoring due to intellectual disabilities and enzyme inducing anti-epileptic medications.

PUB393

The Effect of Hydration Advice on Urine Specific Gravity as a Marker of Vasopressin Suppression in Polycystic Kidney Disease Ragada El-Damanawi,[3,4] Anita Sarker,[1] Caroline M. Robinson,[2] Richard N. Sandford,[2] Fiona E. Karet,[2,3] Thomas F. Hiemstra.[3,4] *[1]Clinical Biochemistry, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; [2]Medical Genetics, University of Cambridge, Cambridge, United Kingdom; [3]Renal Medicine, Cambridge University Hospital NHS Foundation Trust, Cambridge, United Kingdom; [4]Cambridge Clinical Trials Unit, Cambridge, United Kingdom.*

Background: Vasopressin receptor antagonism (VRA) slows ADPKD progression, but access to this treatment is restricted to a small number of developed economies. High water intake suppresses vasopressin production and may offer an alternative therapeutic approach. Trials of high water intake are needed, but the effectiveness of high water intake advice on urine specific gravity (uSG), a surrogate marker for vasopressin suppression (uSG≤1.010), is unknown.

Methods: We evaluated the effectiveness of high water intake advice in reducing uSG in a cohort of incident patients with ADPKD attending a specialist renal genetics clinic. In this single-centre cohort study, we abstracted data from the health records of all ADPKD patients referred between 2010-2015. We compared uSG after provision of fluid intake advice to baseline values.

Results: Data were available for 77 patients. The mean age (±SD) at baseline was 45±16 y, and 32±16 y at diagnosis. 51% (39) were female, 84% (65) White British, and 49% (38) had a *PKD1* mutation. The mean eGFR was 75±24(SD) ml/min/1.73m^2 and 68% (44/65) of those with imaging data were at high risk of progression (kidney length ≥16cm or Total Kidney Volume ≥750mls). The median uSG at baseline was 1.015 (IQR 1.010-1.020) and 36% (28) had uSG≤1.010. This was not significantly different at follow-up: after high water intake advice 31% (24) achieved uSG≤1.010, p=0.50 (Table). Only 13% (10) had achieved a reduction in uSG from baseline, while uSG increased in 18% (14).

Conclusions: Fluid intake advice was ineffective in increasing the proportion of ADPKD patients attaining dilute urine. Additional strategies that promote adherence to high fluid intake are necessary to achieve vasopressin suppression. This should be taken into account when designing high water intake trials.

Number ± SD	Baseline Visit	Follow-up Visit	P value
Achieved uSG ≤ 1.010	28 (36%)	24 (31%)	0.50
Mean Creatinine umol/L	104±50	106±52	0.21
Mean eGFR ml/min/1.73m2	75±24	73±24	0.32
Mean Arterial Pressure mmHg	101±12	100±11	0.51
Mean Sodium mmol/L	139±3	140±2	1.00

Difference in selected biochemical parameters and mean arterial pressure between baseline and follow-up visits.

PUB394

Clinical Characteristics of ADPKD Patients Requesting Pre-Implantation Genetic Diagnosis Erin L. Murphy, Madeline Droher, Neera K. Dahl. *Yale School of Medicine, New Haven, CT.*

Background: Patients with Autosomal Dominant Polycystic Disease (ADPKD) have a 50% chance of transmitting the disease to their offspring. Preimplantation genetic diagnosis (PGD) reduces this risk to 1-2%. We hypothesized ADPKD patients of childbearing potential who are at high risk of clinical progression are likely to pursue PGD to conceive. Common clinical features that may predict high risk of clinical progression to end stage renal disease (ESRD) in ADPKD patients include genotype, early onset of hypertension, and large kidneys or increased total kidney volume (TKV). In addition, patients may have a family history of intracranial aneurysms or complications of hepatic cysts which may further inform the decision to pursue PGD.

Methods: After IRB approval, we performed a retrospective medical record review of eight patients diagnosed with ADPKD who attempted PGD with IVF. We collected family history and patient characteristics and, including genotype, presence of hypertension, extra-renal manifestations of PKD, and TKV when available.

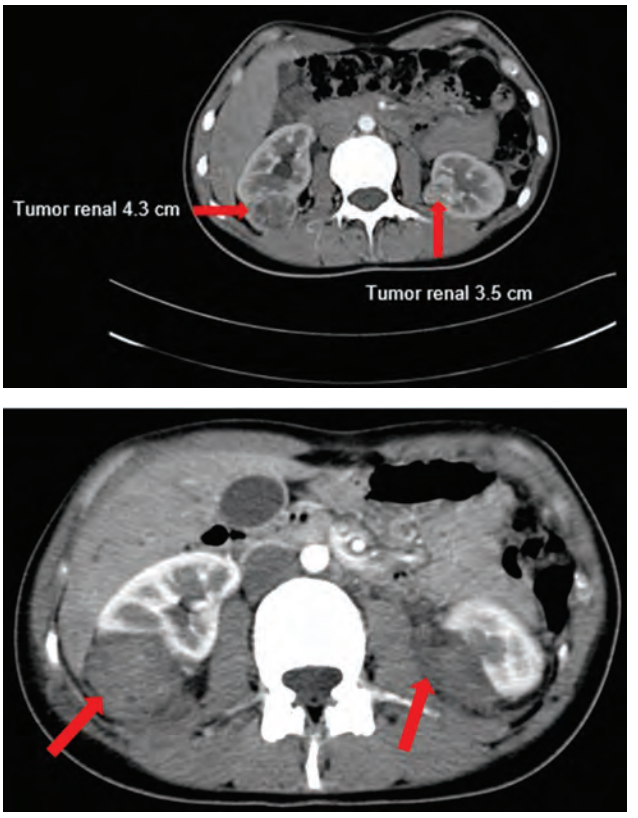
Results: See table.

Conclusions: 7 patients had novel mutations, 4 patients had truncating PKD1 mutations, and 4 patients required additional testing of family members to determine disease associated short tandem repeats (STRs). 1 patient had a mutation near an exome splice site which may cause a truncating mutation, 1 patient had predicted pathogenic mutation in an intronic region. All 8 patients were at high risk of clinical progression, and considered and/or underwent PGD with IVF to conceive.

ADPKD patients requesting PGD

Patient	Pertinent Medical Details: Medical History	Pertinent Medical Details: Family History	Initial Genetic Findings: Genetic Results	Novel Mutation	Mutation Type	Clinical Risk of Progression	Family Linkage Analysis Requirement
1	• 31-year-old female • Abdominal MRI at age 30 revealed 217cc (R) 201cc (L) • TKV: 478 mL • HtTKV: 304.2 mL/m • Head MRI unremarkable for aneurysms • Essential hypertension • Innumerable hepatic cysts	• Maternal grandfather died due to a cerebral hemorrhage, age 48 • Mother diagnosed with advanced renal insufficiency; diagnosed with PKD, mid 20s	Transition: C > T Nucleotide position: 8978 Codon position: 2923 AA change: Gln > Arrh	No	PKD1 truncating	High (G)	Yes
2	• 30 year-old female • Abdominal US revealed 16cm (R) 17cm (L) • Diagnosed with PKD and hypertension at 18 years old • Multiple scattered hepatic cysts	• Father diagnosed with ADPKD, age 40; ESRD, mid 40s; died due to bladder cancer, age 47 • Paternal aunt diagnosed with ADPKD, mid 20s, died due to a cerebral aneurysm, late 40s	Deletion: Exons 27-29	Yes	PKD1 truncating	High (G)	No
3	• 39 year-old female • Abdominal MRI at age 39 revealed 532cc (R) 578cc (L) • TKV: 1110 mL • HtTVK: 750.3 mL/m • Head MRI unremarkable for aneurysms • Hypertension • Innumerable hepatic cysts	• Father diagnosed with ADPKD; ESRD, 60 years old; s/p kidney and liver transplant • Paternal uncle with ADPKD • Brother with ADPKD	Transition: C > T Nucleotide position: 2540 Codon position: 777 AA change: Gln > Arrh	Yes	PKD1 truncating	High (G)	No
4	• 27 year-old female • Abdominal US revealed 13.8cm (R) 14.8cm (L) • Head MRI unremarkable for aneurysms • Hypertension • Persistent left flank pain	• Mother developed ESRD, age 56	c. 8537_8552dup 11 bp duplication Codon position: 2775	Yes	Heterozygous frameshift	High (F)	No
5	• 32 year-old male • Renal US revealed 11.3cm (R) 13.2cm (L) • Hepatic cysts • Head MRA unremarkable for aneurysms	• Mother ADPKD, stage IV CKD, age 60 • Mother's father died from ADPKD complications, age 54 • Father's paternal grandmother died due to ADPKD, age 60 • Maternal grandfather died on dialysis, mid 50's	Transition: G > A Nucleotide position: 9779 Codon position: 3180 AA change: Gly > Arg Transition: C > T Nucleotide position: 8387 Codon position: 2728 AA change: none	Yes No	PKD1 mutation near exonic splice site, likely causing truncating defect Silent, likely benign	High (G) -	Yes -
6	• 32 year-old female • Diagnosed with PKD at 8 months-old following mother's diagnosis during pregnancy • Hypertension	• Mother diagnosed with PKD, age 27; ESRD, age 52 • Maternal uncle PKD s/p transplant • Maternal grandmother diagnosed with PKD; ESRD, age 65	Transversion: C > G Nucleotide position: IVS42-3 Transition: T > C Nucleotide position: 7489 Codon position: 2426 AA change: none	Yes No	Predicted PKD1 truncating Silent, likely benign	High (F) -	Yes -
7	• 37 year-old male • Diagnosed with PKD via US as a teenager • Abdominal MRI revealed 221cc (R) 280cc (L) • TKV: 5090 mL • HtTKV: 2565.2 mL/m • Multiple hepatic cysts • Head MRI unremarkable for aneurysms	• Father diagnosed with PKD; ESRD, age 40, died due to CVA, age 44 • Paternal grandfather, PKD status unknown; died due to CVA, age 45	Transversion: G > C Nucleotide position: 7008 Codon position: 2206 AA change: Arg > Pro Transversion: C > G Nucleotide position: 355 Codon position: 48 AA change: None 10 other PKD1 variants and 1 PKD2 variant were also found for this patient	Yes Yes No	PKD1 non-truncating Silent, likely benign All likely benign	High (F)	Yes
8	• 44 year-old male • Abdominal MRI revealed 1467cc (R) 1846cc (L) • TKV: 3312 mL • HtTKV: 1765.2 mL/m • Hypertension • Upper UTI (kidney/bladder)	• Mother diagnosed with PKD via ultrasound, age 55	Exon 8 - 15 deletion	Yes	PKD2 truncating	High (C)	UNK

G – Genotype
F – Family History
C – Clinical History



PUB395

Thermal Radiofrequency Ablation (RFA) in Renal Cancer of Von Hippel Lindau (VHL) Patients: A Case for Renal Mass Preservation in a Multiple Renal Tumor Setting Javier De Arteaga,[3,4] Pehuén Fernández,[3,4] Jorge De la fuente,[2,4] Walter Douthat.[1] *[1]Hospital Privado Universitario, Córdoba, Argentina; [2]HTAL. PRIVADO DE CORDOBA, BUENOS AIRES, Argentina; [3]Hospital Privado Universitario de Córdoba, Cordoba, Argentina; [4]Universidad Catolica de Cordoba, Cordoba, Argentina.*

Background: VHL can present with a devastating clinical picture that may include ESRD for surgical procedures of multiple renal carcinoma Until not far, open or laparoscopic surgery has been the only therapy considered. Termal RFA is a percutaneous less invasive procedure that allows targeting small nodules (less than 3.5 cm usually) Objective: to perform thermal RFA in VHL patients to avoid open surgery with unnecessary loss of renal tissue.

Methods: 3 VHL patients wih renal nodules between 2.5 (smallest) and 4.2 cm (largest) were subjected to thermal RFA under light sedation and local anaesthesia. A percutaneous tumor biopsy was realized during the procedure.2 patients had a previous unilateral nephrectomy for renal cancer.

Results:

Conclusions: Thermal RFA is a valuable and non agressive alternative therapy to open surgery in the setting of multiple and bilateral kidney cancer of VHL 3 patients that had been previously multioperated with loss of renal parenchima (pts: 2 and 3). and a 3rd one with an extremely fragile condition were treated successfully and without complications with this modality Follow up time was of 2.5 years (pt 1), 9 months (pt 2) and 3 months (pt 3) confirms small changes in renal function (table 1) Percutaneous renal tumor biopsy was a safe procedure and confirmed the diagnosis of clear cell carcinoma in all 3

Patients

Cases	Age	Sex	Tumors (n)	Previous unilateral nefrectomy	CKD-EPI pre RFA (ml/min x 1,73 m2)	CKD-EPI post RFA (ml/min x 1,73 m2)	Follow-up (months)
Case 1	27	F	2	No	122.7	106.6	32.2
Case 2	30	F	1	Yes	63.6	61	9.5
Case 3	35	M	3	Yes	66.9	54.6	3

RFA: Radiofrecuency ablation

PUB396

Urinary Citrate Excretion, a Renal Bioenergetic Source, Is Reduced in Autosomal Dominant Polycystic Kidney Disease Matthew Lanktree,[1] Peili Chen,[2] Anna L. Zisman,[2] Bharathi V. Reddy,[2] Kristin J. Bergsland,[2] Fredric L. Coe,[2] Elaine M. Worcester,[2] Arlene B. Chapman.[2] *[1]Nephrology division, McMaster University, Hamilton, ON, Canada; [2]University of Chicago, Chicago, IL.*

Background: Increased renal metabolism is a feature of autosomal dominant polycystic kidney disease (ADPKD). Hypocitraturia occurs in ADPKD and has been ascribed to reduced glomerular filtration rate (eGFR) and defects in renal tubular acidification. We hypothesize that ADPKD patients have hypocitraturia independent of these abnormalities.

Methods: 16 APDKD and 16 age-, sex-, and eGFR-matched controls with relatively intact kidney function (mean eGFR=64 ml/min/1.73m²) provided a 24-hour and a fasting morning urine and plasma sample in a Clinical Research Center setting. Serum creatinine, electrolytes and citrate, and urine pH, creatinine, electrolytes, and citrate were obtained, and eGFR, fractional excretion of citrate (FE_{Cit}), gastrointestinal alkali absorption (GIAA), net endogenous acid production (NEAP), and net acid excretion (NAE) were calculated.

Results: Unadjusted urinary citrate and FE_{Cit} were significantly lower in ADPKD vs. controls (327 ± 221 vs. 548 ± 199 mEq/day, P=0.006; 4.6 ± 2.4 vs. 11.5 ± 5.4 %, P=0.002). No difference in plasma citrate, GIAA, NEAP, or NAE were observed between ADPKD and controls (3.8 ± 1.1 vs. 3.9 ± 1.2 mmol, P=0.9; 18.5 ± 24.7 vs. 26.2 ± 19.6 mEq/day, P=0.4; 38.5 ± 19.5 vs. 28.8 ± 15.1 mEq/day, P=0.3). No difference in 24-hour urine pH or bicarbonate (5.8 ± 0.5 vs. 6.1 ± 0.5, P=0.2; 3.5 ± 4.8 vs. 3.1 ± 2.7 mEq, P=0.3), serum bicarbonate or potassium concentration (25.0 ± 2.1 vs. 25.2 ± 1.9 mmol/L, P=0.3; 4.2 ± 0.3 vs. 4.3 ± 0.9 mmol/L, P=0.5) were observed. Linear regression modelling demonstrated that ADPKD status contributed independently to 24 hr urinary citrate excretion and FE_{Cit} beyond eGFR, GIAA, NEAP, and urinary potassium, chloride, and ammonium excretion (R^2 = 0.56, F-statistic = 10.0, P<0.001).

Conclusions: ADPKD status associates with decreased urinary citrate excretion. Decreased FE_{Cit} in the setting of unchanged plasma citrate concentration indicates an enhanced proximal tubule uptake of citrate. Citrate provides 10% of energy for renal metabolism under normal conditions. Given epithelial proliferation, cyst growth, expansion and the increased metabolic demands of kidneys in ADPKD, urinary citrate uptake may provide additional epithelial energy substrate.

Funding: NIDDK Support

PUB397

Clinical Outcome of Patients with Autosomal Dominant Polycystic Kidney Disease Receiving Renal Replacement Therapy Seong Sik Kang,[1,2] Hayeon Park,[1] Sang Mok Yeo,[1] Woo Yeong Park,[1,2] Kyubok Jin,[1,2] Sung Bae Park,[1,2] Seungyeup Han.[1,2] *[1]Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Republic of Korea; [2]Keimyung University Kidney Institute, Daegu, Republic of Korea.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of kidney disease in patients receiving renal replacement therapy (RRT). However, there are few reports of clinical outcomes of patients with ADPKD receiving RRT. Herein, we evaluated clinical characteristics and outcomes of patients with ADPKD.

Methods: We retrospectively reviewed the medical records of 253 patients with ADPKD at Keimyung university hospital between January 1989 and January 2017. We analyzed risk factors for renal disease progression and survival rates in patients with ADPKD receiving RRT.

Results: The mean age at diagnosis was 43.2 ± 13.2 years (range, 10-75). Males were 129 (51%) and patients with a family history of ADPKD were 93 (37%). Average duration of follow-up was 76 ± 74.5 months (range, 1-280). Among the 253 patients, 125 (49%) progressed to CKD stage 5 and 100 (40%) received RRT. The mean duration from diagnosis to receiving RRT was 8.8 ± 7.8 years (range, 0-32). In a multivariate analysis, hypertension (HR 2.154, $P = 0.016$), cardiovascular disease (HR 4.325, $P = 0.023$), cyst infection (HR 5.317, $P < 0.001$) were independent risk factors for progression to end-stage renal disease (ESRD). The number of patient receiving hemodialysis, peritoneal dialysis, and kidney transplantation (KT) was 72, 2, and 26, respectively. Twelve (46%) of the 26 KT recipients (KTRs) were treated prior to transplantation. Four underwent simultaneous bilateral nephrectomy and 8 underwent renal artery embolization. The 5-year survival rate of patients without RRT and KTRs were 94.3 ± 2.3% and 96 ± 3.9%, respectively, which was higher than that of 82 ± 5.2% in hemodialysis patients ($P = 0.021$). The 5-year survival rate of allograft kidney in KTRs was 88 ± 8.1%.

Conclusions: Hypertension, cardiovascular disease, and cyst infection were independent risk factors for progression of renal disease in ADPKD. In order to slow the progression to ESRD, best efforts to properly manage hypertension and cardiovascular disease are required. Nevertheless, when progressing to ESRD, KT can be recommended as treatment of choice.

PUB398

ADPKD Prevalence in the Italian Province of Modena Suggests That Is a Rare Condition Francesca Testa,[1] Andrea Solazzo,[1] Marco Busutti,[2] Luciana Furci,[1] Silvia Giovanella,[1] Giulia Ligabue,[1] Giacomo Mori,[1] Gianni Cappelli,[1] Marco Leonelli,[1] Riccardo Magistroni.[1] *[1]Division of Nephrology, Dialysis and Transplant, Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy; [2]UO Nefrologia, Dialisi e Trapianto, Dipartimento di Medicina Specialistica e Sperimentale, Ospedale Sant'Orsola-Malpighi, Alma Master Studiorum Università di Bologna, Bologna, Italy.*

Background: Available estimates of ADPKD's prevalence in literature are conflicting. One of the main difficulties is the complete identification of all affected subjects. The aim of this study was defining the prevalence adjusted for missing diagnosis in a geographically defined population(Province of Modena, Italy). A descriprion of the clinical characteristics of affected subjects is provided.

Methods: The prevalence is calculated considering alive ADPKD patients at the date of 31/Oct/2016. All possible sources of information, including electronic databases, clinical notes of nephrologic clinics, register of RRT patients, have been checked. Index cases were asked to sign the consent and have been clinically evaluated. At risk subjects were invited to partecipate in the study as well. Missing data were imputed through a mixed linear model. The diagnosis of at risk patients without clinical information was predicted through a binary logistic regression. The risk curve was modeled on the population characteristics of the province of Modena extracted from the last census(ISTAT, 2016)

Results: The population of the Province of Modena is 701,642 inhabitants (ISTAT, 2016).254 affected subjects were identified. The point prevalence of ADPKD subjects is 3.63:10,000(IC 95% = 3.010-3.758). Estimated prevalence adjusted for missing diagnosis is 4.82:10,000(IC 95% =4.160- 4.987).81% of patients are in renal replacement therapy (41.9% hemodialysis, 11.6% peritoneal dialysis, 46.5% transplant).42 subjects underwent to a molecular genetic evaluation that showed the involvement of PKD1 in 83% of cases and PKD2 in the remaining 17%.Renal survival is worse in patients with truncated PKD1 mutations(25° survival age 48 years), followed by PKD2 mutations(25° survival age 59 years)and finally by PKD1 missense mutation(25° survival age 64 years).

Conclusions: The prevalence of ADPKD in the Province of Modena is lower than frequently reported in the literature. In our analysis the point prevalence is 3.63:10,000 inhabitants, while predicting missing ADPKD subjects in the cohort of at risk subject produces an estimated prevalence of 4.82:10,000. These estimates are compatible with the definition of rare disease adopted by the European Medicines Agency and Food and Drug Administration.

PUB399

Gastroparesis in Polycystic Kidney Disease – Emphasis on Early Diagnosis Rhea Bhargava,[1] Shradha Gupta,[2] Theodore I. Steinman.[1] *[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]Saint Vincent Hospital, Worcester, MA, Worcester, MA.*

Background: Malnutrition can lead to poor outcomes in renal patients. Early satiety is a well known symptom of polycystic kidney disease. Most of these cases do not undergo an extensive outpatient workup for their GI symptoms and this can lead to unnecessary hospital visits.

Methods: 42 year old male who was diagnosed with polycystic kidney disease at 17 years of age after undergoing a renal ultrasound because of high blood pressure and a history of PKD in the family. His mother developed renal failure and underwent a transplant in 2001. His sister, 2 years older than him is presently on hemodialysis and was also diagnosed with PKD. He has a diagnosis of hypertension since childhood, which has been managed with lisinopril 20 mg daily. Reports decreasing energy levels for the past 2-3 years with associated early satiety and loss of appetite. He was unable to tolerate full meals and had nausea after each meal. Seen by several physicians and had 2 hospital stays for hypovolemia leading to acute kidney injury. No history of hematuria, dysuria, increase in abdominal girth, fever or chills. He has never had any stones or UTIs. He has associated polycystic liver disease as well. Several EGD studies did not reveal any pathology and systemic examination is unremarkable except pallor. He has lost 8 kg over 3 years. Cr has been stable at 1.2 mg/dl for the past 5 years. No other laboratory abnormalities were noted except anemia with a Hb of 11 g/dl. Gastric emptying study showed delayed gastric emptying. Further workup with a CT scan was pursued and this was significant for several right renal cysts providing extrinsic compression on the descending portion of the duodenum. This was thought to be the cause of early satiety. The patient was started on a 6 part small feeding diet and has been followed for 6 months with stable weight and no hospitalizations.

Results:

Conclusions: Mechanical complications of PKD have not been well decsribed and sometimes are undiagnosed. Early screening and close monitoring of these patient with extrinsic bowel compression from cysts can avoid unnecessary procedures and prolonged hospital stays. This can also help in mantaining adequate nutrition which is of utmost importance in these patients. Working in conjuction with urologists to relieve severe symptomatic compression by unroofing cysts has been described.

PUB400

A Rare Case of Distal Renal Tubular Acidosis Complicated with Hypokalemic Nephropathy Xiaoyu Liu, Xuhui Zhong, Jie Ding. *Peking University First Hospital, Beijing, China.*

Background: To report a rare case of distal renal tubular acidosis boy complicated with hypokalemic nephropathy, and analyze the association of hypokalemia, renal tubular acidosis and renal cysts. Detailed clinical data were collected and analyzed. Renal ultrasound and MRI were detected to follow up the change of renal cysts.

Methods: A 9 years old boy, first presented to hospital with a complaint of poor growth and motor retardation at 9 months old. Initial blood investigations showed hypokalemia, hyperchloremic acidosis, with urine PH >5.5. Renal ultrasound showed calcinosis. Renal tubular acidosis and inborn metabolic error were suspected, but no positive was result shown in metabolic screening test. Treatments of sodium bicarbonate, potassium citrate were started, but the follow-up was irregular and the treatment of potassium citrate was not persistent. Other problems, such as growth retardation, rickets, consistent muscle weakness, polyuria and polydipsia developed, and he had experienced several episodes of paralysis which could be relieved by potassium chloride infusion. At the age of 8, urine analysis showed alkalinuria, low titratable acid and FeHCO3. Urine anion gap was 37.39mmol/L. So the diagnosis was type I renal tubular acidosis. But the lab investigation also showed small molecular proteinuria, aminoaciduria and increase of calcium, phosphorus and potassium in urine. Multiple cysts were found in a latest renal ultrasound. In consideration of his long term hypokalemia, a diagnosis of hypokalemic nephropathy was made. After treatment of sodium bicarbonate, potassium citrate and phosphorous salts, his symptom improved with correction of hypokalemia and metabolic acidosis. After 6 months' follow up, his urine protein was negative and the size of renal cysts was decreased.

Results:

Conclusions: Persistent hypokalemia might induce to hypokalemic nephropathy, which manifest as renal tubular injury and renal cysts. Doctors should pay attention to hypokalemia and correct it as soon as possible.

Funding: Government Support - Non-U.S.

PUB401

Prognostic Assessment of Polycystic Kidney Disease by Urine N-Acetylglucosaminidase Excretion Kaori Takayanagi, Yuta Kogure, Hiroaki Hara, Minoru Hatano, Yumiko Nakamura, Saeko Sato, Takatsugu Iwashita, Taisuke Shimizu, Tomonari Ogawa, Koichi Kanozawa, Hajime Hasegawa. *Nephrol and Hypertens, Blood Purification Center, Saitama Med Center, Saitama Med Univ, Kawagoe, Japan.*

Background: For the adequate therapeutic strategy, especially decision of Tolvaptan indication, prognostic assessment of autosomal dominant polycystic kidney disease (ADPKD) is critical. At present, kidney growth rate (KGR)>5%/year is considered as most reliable parameter in this regard, however, repeated CT/MRI scanning with one year

interval is required to assess KGR. This study aimed to investigate the prognostic efficacy of urine N-aithcetylglucosaminidase-to-Cr ratio (NAG index), conventional parameter for tubulo-interstitial nephropathy (TIN), in patients with ADPKD.

Methods: Clinical data of ADPKD patients who received CT scanning twice or more, before beginning to use Tolvaptan in our facility (n=60) were studied by the prospective analysis based on the past time-point. Predictor of latest KGR was explored by focusing clinical data sampled one year prior to the latest CT scanning.ers in one year prior to the latest CT scanning based on the analytical approach of prospective observation from the past.

Results: Average or median value of age, total kidney volume (TKV), KGR, eGFR and NAG index were 50.2 of age, 1351.7 ml of median value, 5.4% per year of median growth, 47.4±20.3 ml/min and 5.47 IU/mgCr. Stratified analysis by the median value of KGR showed the significant difference in NAG index, but not TKV and eGFR. Univariate analysis showed that NAG index, but not TKV nor eGFR, significantly correlated with KGR (R=0.46, p=0.016), and multivariate analysis also showed that the NAG index would be a predictor of future KGR (partial regression coefficient=0.46, standard error=0.76, p=0.015). In addition, ROC analysis showed that the cut-off value of NAG index for the prediction of ≥5%/year of KGR was 5.06 U/mgCr which is almost equivalent to the upper limit of generally accepted normal range of the NAG index (AUC 0.670, 95% CI 0.461-0.880, sensitivity 76.9%, specificity 57.1%).

Conclusions: NAG index might be a useful clinical parameter for the assessment of ADPKD prognosis and indication of Tolvaptan, which might be reasonable when it would be considered that ADPKD is a typical disease setting causing TIN.

PUB402

A Japanese Patient with Autosomal Dominant Polycystic Kidney Disease Suffering Sustained Liver Injury by Tolvaptan Misaki Yoshida,[8] Kazunori Yamada,[4,9] Kiyoaki Ito,[7] Nobuhiro Suzuki,[8] Takahiro Matsunaga,[5] Takeshi Zoshima,[6] Satoshi Hara,[3] Ichiro Mizushima,[4] Hiroshi Fujii,[1] Takeshi Sawada,[9] Mitsuhiro Kawano.[2] *[1]Division of Rheumatology, Department of Internal Medicine, Kanazawa University Graduate School of Medicine, Kanazawa, Kanazawa, Japan; [2]Division of Rheumatology, Kanazawa University Hospital, Kanazawa, Japan; [3]Kanazawa Graduate School of Medicine, Kanazawa, Japan; [4]Kanazawa University Graduate School of Medicine, Kanazawa, Japan; [5]Kanazawa University Hospital, Ishikawa, Japan; [6]Kanazawa university hospital, Kanazawa, Japan; [7]Kanazawa universtiy, Kanazawa, Japan; [8]Kanazawa University, Kanazawa, Japan; [9]Department of Advanced Research in Community Medicine Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan.*

Background: The TEMPO 3:4 Trial described that the elevation of AST and ALT were 3.2% and 4.9%, respectively. However, the whole picture of liver injury by tolvaptan has not been well clarified. Here, we reported an autosomal dominant polycystic disease (ADPKD) patient with drug-induced liver injury (DILI) due to tolvaptan.

Methods: A 37-year-old woman with ADPKD admitted to our hospital due to sustained liver injury. She was administered tolvaptan six months before admission. She had been administered no drug except for tolvaptan. Her hepatic enzymes had been normal for four months after tolvaptan initiation, but they suddenly elevated (ALT 166 IU/L and g-GTP 53 IU/L). Tolvaptan was discontinued, however, her hepatic enzyme had been increasing for two weeks. She was consulted to gerontologist and close examinations were performed. Blood tests showed that hepatitis viruses and auto antibodies were also all negative in addition of normal value of C-reactive protein. Computed tomography showed only a few lever cysts. DILI due to tolvaptan was suspected, although drug lymphocyte stimulation test was negative. Ursodeoxycholic acid was started, but her liver injury did not ameliorate four weeks after discontinuation of tolvaptan (ALT 302 IU/L and g-GTP 180 IU/L). She was admitted our hospital to perform liver biopsy to exclude other disease such as acute onset autoimmune hepatitis. Liver biopsy showed that lymphocytes, neutrophils, a few eosinophil infiltrations were existed. Necrosis with many pigment-phagocyte cells were seen around centrilobular zone. She was diagnosed with acute hepatitis due to tolvaptan. Corticosteroid (30 mg/day) was initiated and her liver function ameliorated. Conclusions: The detail mechanism and the clinical course of liver injury by tolvaptan has not been well understood, and the liver biopsy is ordinary difficult due to liver cysts in ADPKD patients. Therefore, this patient seemed to give some important information to clarify the pathogenesis of liver injury by tolvaptan.

Results:

Conclusions:

PUB403

Experience with Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease Eiichi Sato,[1,2] Tsukasa Nakamura,[2] Takao Ono,[2] Manaka Degawa,[2] Hongmei Lu,[2] Daisuke Matsumura,[2] Mayumi Nomura,[2] Mayuko Amaha,[2] Akiko Fujii,[1] Yuko Ono,[1] Yoshihiko Ueda.[1] *[1]Dokkyo Medical University, Koshigaya Hospital, Koshigaya, Saitama prefecture, Japan; [2]Shinmatsudo Central General Hospital, Matsudo City, Japan.*

Background: The aim of this study was to demonstrate the treatment of autosomal dominant polycystic kidney (ADPKD) with Tolvaptan.

Methods: 15 confirmed cases of ADPKD were included in a cohort between July 2014 to June 2016. Cases were defined according to total kidney volume exceeding 750 ml and with an approximate 5% increase in volume per year by subject. Cases were commenced on 45mg/day of Tolvaptan but the dose was decreased as kidney function deteriorated over time.

Results: Cases were aged between 29-71 years old (average ± standard deviation 52.1 ± 13.1) and comprised 9 males and 6 females. There were 9 patients with a family history of ADPKD. 9 cases were complicated with hypertension, and 5 cases were complicated with cerebral aneurysm including subarachnoid hemorrhage. Hepatic dysfunction, fatty liver, ulcerative colitis, and chronic rheumatism were also observed in this cohort. The eGFR was 54.7 ± 25.6 mL/min/1.73m^2 and the total kidney volume was 1732.7 ± 1052.3 mL at baseline. Cases received a maximum dose of 90 mg/day Tolvaptan and eGFR was recorded as being an average of 49.4 ± 25.6 mL/min/1.73m^2, and mean decrease of 4.99±22.17 % of the total kidney volume/age 6 months after prescription of Tolvaptan.

Conclusions: These cases are typical of patients that are admitted due to kidney disease and are a feature of this cohort. Patients were treated with Tolvaptan for a period of 6 months and we noted a reduction in total kidney volume with Tolvaptan. We also noted that symptoms improved over this 6-month period and we present the effects of this drug on ADPKD including its utility as a biomarker.

PUB404

Predictors of Progression to ESRD in a Cohort of Hispanic Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) Sonia Rodriguez,[1] Jesús A. Cedillo,[1] Ricardo Correa-Rotter,[2] Rodrigo J. Rosado.[1] *[1]Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico; [2]Institutor Nacional de la Nutricion, Mexico City, Mexico.*

Background: Introduction: ADPKD is the most common monogenic kidney disease and one of the most frequent causes of ESRD. Its characteristics in Hispanic population are poorly described.

Methods: Purpose and Methods: To identify the factors associated with advanced chronic kidney disease (CKD), defined as eGFR ≤45 mL/min at the time of presentation and rapid progression of CKD, defined as the fall of GFRe >5 mL/min/y for two consecutives years or 10 mL/min in one year. We employed univariate and multivariate analysis.

Results: Results: Single-center cohort of 222 patients, of whom 139 were women (62%), at a National Institute of Health in Mexico City. Median follow-up of 74 months (24-180 IQR), mean age at diagnosis 41 (SD ±14 y). There were 67 patients (43%) with eGFR <45 mL/min and 17 patients (8%) that had renal replacement therapy requirement (RRT) at diagnosis. In addition, during the follow up period 94 patients (42%) required RRT. The median age at the start of RRT was 63 years old and 68 patients (60%) showed a rapid progression of CKD. The indicators at time of diagnosis that predicted progression to an eGFR <45 employing the univariate analysis were: male sex (p 0.01) and presence of systemic hypertension (p 0.02), while age and tobacco use showed only a trend. In the multivariate analysis, the only factors independently associated to progression were male sex (OR 2.6 CI 95% 1.27 – 5.63, p 0.009) and systemic hypertension (OR 2.4, 95% CI 1.2 – 9.2, p 0.015).

Conclusions: Conclusion. In our cohort, advanced CKD was presented in almost half of patients at the time of diagnosis which may imply a late referral to nephrological care. In addition, we observed a high frequency of rapid progressors to CKD. The hypertension and male sex were associated factors to advanced CKD at diagnosis, more studies are needed to explain this last finding.

PUB405

Developing a Computable Phenotype for Autosomal Dominant Polycystic Kidney Disease (ADPKD) Reem Mustafa,[2,4] Kerri A. McGreal,[1] Alan S. Yu.[3] *[1]None, Prairie Village, KS; [2]Nephrology and Hypertension, Univeristy of Kansas Medical Center, Kansas City, KS; [3]University of Kansas Medical Center, Kansas City, KS; [4]Mcmaster University, Hamilton, ON, Canada.*

Background: Polycystic kidney disease includes inherited diseases that cause chronic kidney disease (CKD) and permanent worsening in kidney function. Autosomal dominant PKD (ADPKD), despite being a rare condition, is the most common genetic cause of CKD. We at University of Kansas Medical Center (KUMC) are leading the ADPKD Research Interest Group (RIG) and aim to develop computable phenotype for ADPKD. This effort is through the PCORNet Kidney Health Collaborative Research Group (CRG).

Methods: We identified patients with potential ADPKD using an algorithm that utilizes ICD9 codes 753.12 and 753.13, and ICD10:Q61.2 and Q61.3. This algorithm was developed through an iterative process by expert clinical nephrologist at KUMC. We used a de-identified patient information in i2b2 data access platform to search for patients with the potential diagnosis of ADPKD. Two reviewers independently determined whether patients had ADPKD or not using strict established criteria.

Results: We identified 496 patients using the ADPKD computable phenotype. we performed chart reviews of a random sample of 283 patients to determine if they had ADPKD or not. ADPKD was confirmed in 236 out of 283 charts reviewed. The ADPKD computable phenotype using ICD9 and 10 codes provides a positive predictive value (PPV) of 83.4 % (95% confidence interval 78%-88%). In four charts the diagnosis of ADPKD was unclear due to missing information. A sensitivity analysis was performed to determine whether classifying the excluded patients as having ADPKD, or as not having ADPKD, and it did not meaningfully change the results.

Conclusions: Identifying ADPKD patients using ICD 9 and 10 code has reasonable PPV. We are in the process of assessing the accuracy of the computable phenotype on a

sample of all patients at KUMC which will allow us to determine other accuracy measures including the Sensitivity, Specificity and Negative Predictive Values of the computable phenotype. We also plan to validate the computable phenotype in other electronic medical record systems. In a condition like ADPKD, future research should focus on developing probabilistic phenotyping which may allow for consideration of radiology reports and/or family history that can enhance and improve the accuracy of the computable phenotype.

Criteria for diagnosing ADPKD

PUB406

Rapid Loss of Kidney Function Due to MYH9 Nephropathy: A Case Report Fellype C. Barreto, Gabriela Sevignani, Sibele S. Milano, Giovana M. Pavanelli, Maria A. Pachaly, Mauricio Carvalho. *Universidade Federal do Paraná, Curitiba, Brazil.*

Background: Mutations in the non-muscle myosin heavy chain gene (*MYH9*) are characterized by congenital macrothrombocytopenia, hearing loss, cataracts and glomerulonephritis. We sought to describe a case of rapid loss of kidney function in a young male patient due to *MYH9* nephropathy.

Methods: Data were extracted from medical records.

Results: A 20-year-old male has been followed up at the Clinic Hospital of Federal University of Paraná due to medical history of epistaxis, ecchymoses and petechiae since infancy. At first, Bernard-Soulier Syndrome was suspected due to macrothrombocytopaenia and tendency of bleeding. When he was 17 years old, hearing loss and hypertension were detected along with mild renal failure [creatinine: 1.2mg/dl; CKD-EPI estimated glomerular filtration rate (eGFR): 88 ml/min/1.73m^2], microhaematuria and nephrotic-range proteinuria (7.5g/24h). Renal biopsy could not be performed due to the risk of bleeding (platelets: 7000/µl). Cataracts were excluded by ophthalmological evaluation. Due to the clinical suspicion of *MYH9* nephropathy, genotyping of the patient and of his parents was performed: a *de novo* missense mutation in exon 1 of *MYH9* [c.287C>T; p.Ser(TCG)96(TTG)Leu] was detected. Enalapril was initiated for renoprotection. The patient did not adhere to treatment and lost follow-up. Two years later, he returned to the Nephrology outpatient clinic complaining of foamy urine, peripheral edema and hypertension (160/120 mmHg). Laboratory tests detected worsening of renal function (creatinine: 3.2 mg/dl; eGFR: 36.4 ml/min/1.73m^2) and persistent proteinuria (9.6g/24h). Table shows the evolution of proteinuria and eGFR.

Conclusions: In conclusion, although *MYH9* mutation is a rare cause of nephropathy, awareness of rare genetic disorders is essential to ensure accurate diagnosis and proper management. There is yet no proved effective treatment for *MYH9* nephropathy. Its early recognition is important to avoid unnecessary diagnostic procedures and potential harmful treatment, such as immunosuppressive agents.

Funding: Private Foundation Support

Table. Laboratory parameters

	March / 2013	June/2015	March/2017
Creatinine (mg/dl)	1.2	1.7	3.2
eGFR (ml/min/1.73m2)	92.5	65.4	36.4
Proteinuria (g/24h)	7.5	5.5	9.6

eGFR - based on CKD-EPI formula

PUB407

Molecular Inversion Probes (MIPs) Are a Highly Scalable, Lower Cost Method for Targeted Sequencing of Kidney Disease Genes Brendan Crawford,[3] V Vega-Warner,[3] D Fermin,[3] Rasheed A. Gbadegesin,[2] Simone Sanna-Cherchi,[1] Jacob O. Kitzman,[3] Matt G. Sampson.[3] *[1]Columbia University, New York, NY; [2]Duke University Medical Center, Durham, NC; [3]University of Michigan, Ann Arbor, MI.*

Background: Targeted sequencing is being used to diagnose patients with putative Mendelian forms of kidney disease. As the number of target genes & patients available for sequencing grows, we are challenged to use affordable and accurate sequencing strategies. Molecular inversion probes (MIPs) is a relatively new method that uses oligonucleotides to perform hybridization-based target capture for subsequent sequencing. MIPs can be massively multiplexed and do not require proprietary technology, thus reducing cost and enhancing scalability. But its performance versus other established methods is less understood. Here, we describe our experience establishing MIPs to screen implicated & candidate Mendelian nephrotic syndrome (NS) genes in a patient cohort.

Methods: We designed an array of 12,000 MIPs for 115 genes (55 previously implicated & 60 candidates). We did a pilot study of 192 NS patients (including 56 previously sequenced) & two 1000 Genomes (1000G) reference samples. Sequences underwent alignment, variant calling, and pathogenicity filtering; Sanger confirmation of qualifying variants was used. We assessed the depth of coverage achieved across the targets, sensitivity in detecting known variants, and depth of coverage needed for acceptable accuracy. We also identified factors impacting acceptable genomic coverage.

Results: The estimated cost was $30/patient, ~5x less expensive than microfluidic based amplification strategies. Sensitivity to detect known variants was 89-94% for 1000G and 100% for previously discovered mutations in NS cases (17/17). Overall, 3.8% of the target region (~23,000 bp) had low coverage, defined as <8X read depth in >10% of samples. Of these regions, 29% also had poor coverage in the Exome Aggregation Consortium dataset, suggesting these are, in general, challenging areas for sequencing. Creating 1500 "rescue" probes resulted in recovery of over 50% of low-coverage regions.

Conclusions: MIPs can be massively multiplexed on arrays, and incorporation of single-molecule tagging permits analysis of unique capture events, reducing the depth necessary at each site to achieve acceptable sensitivity. Provided that there is good DNA quality and rescue of poorly performing regions, MIPs is an accurate and cost-effective method for targeted sequencing studies.

Funding: NIDDK Support

PUB408

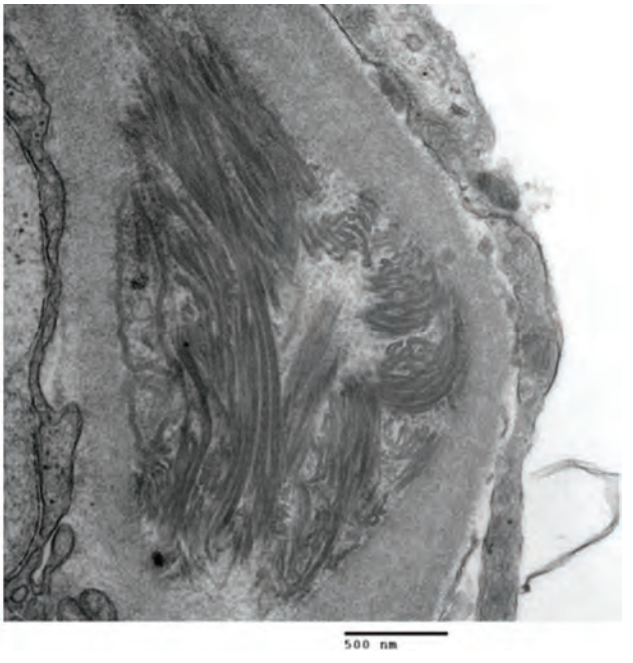
LMX1B Associated Nephropathy with Type III Collagen Deposition in Glomerular and Tubular Basement Membranes Nicole K. Andeen, Jennifer Schleit, Christopher D. Blosser, Fuki M. Hisama, Kelly D. Smith. *University of Washington, Seattle, WA.*

Background: Variants in LIM homeobox transcription factor 1 beta (*LMX1B*) gene cause Nail-Patella Syndrome (NPS). Renal involvement is characterized by incorporation of thick bundles of collagen resembling type III collagen into glomerular basement membranes (GBMs). Recently, variants in *LMX1B* have been associated with renal-limited disease lacking skeletal, joint and nail findings of NPS.

Methods: The patient is a 39 year old man with a family history of kidney disease who presented for transplant evaluation. A kidney biopsy performed 10 years prior when he presented with hypertension, nephrotic syndrome of 5-6 years, and no other physical abnormalities revealed focal and segmental glomerulosclerosis (FSGS). Ultrastructural examination revealed aggregates of electron dense fibrils within thickened GBMs (image) and infrequently in mesangial regions. Some fibrils demonstrated a regular periodicity of 60 nm. Uninvolved GBMs had normal architectural organization and thickness. Several tubular basement membranes were thickened and contained similar fibrils. Immunofluorescence studies were negative. Next generation exome sequencing was performed 10 years later. A total of 66 genes associated with FSGS and steroid resistant nephrotic syndrome were examined. A pathogenic variant in one allele of *LMX1B* (c.737G>A (p.Arg246Gln)) was identified.

Results:

Conclusions: This case highlights the importance of clinical, pathologic, and genomic correlation, and has the novel finding of type III collagen deposition in tubular basement membranes in *LMX1B* associated nephropathy. *LMX1B* variants should be considered as a potential cause of sporadic and hereditary forms of FSGS and steroid resistant nephrotic syndrome, especially in cases where electron microscopy studies reveal incorporation of bundles of type III collagen into basement membranes, regardless of the presence or absence nail or skeletal findings associated with NPS.



PUB409

Autosomal Dominant Interstitial Disease of Kidney – Father and Son Underwent Transplantation Pradeep P. Deshpande. *Hyderabad, India.*

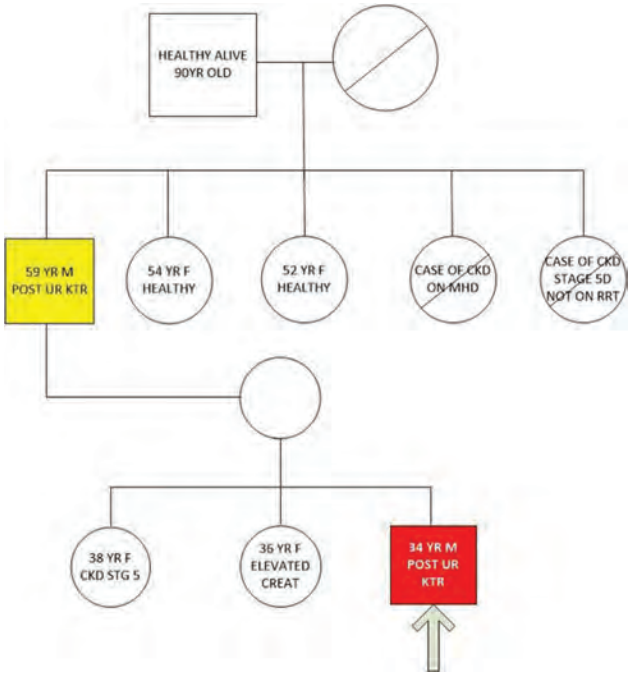
Background: In a village, in India, with 5000 population, around 500 people are suffering from kidney disease. Out of which 100 are on Hemodialysis and 35 underwent kidney transplantation. One family of the same village, in which 6 of the family members are suffering from kidney disease. Father underwent kidney transplantation in 2006 and son underwent kidney transplantation in 2013. Genetic analysis was done for family

members which showed Autosomal Dominant Interstitial Disease of Kidney, mostly due to Mucin -1 gene mutation.

Methods: 34 years old male, kidney transplant recepient, ABO-Compatible(O +ve) on triple drug immunosuppression with Prednisolone 10mg, Tacrolimus 4mg and Mycophenolate 1000mg, on regular follow-up with normal renal functions, serum Creatinine value of 1.3mg/dL. He was initiated on Hemodialysis in February 2013. Underwent unrelated altruistic donor kidney transplantation in July 2013 (due to unsuitability of family members). Family History:Father aged 59 years, underwent kidney transplantation in 2006, doing well and on regular follow-up, with creatinine value of 1.8mg/dL. His two Sisters, 38 and 36 years, who were biopsied and were found to have chronic interstitial disease of the kidney. One having creatinine of 3mg/dl and other having creatinine of 8mg/dl, who has been planned for Deceased donor transplantation. Serum Uric acid levels high in all the affected members.

Results:

Conclusions: To highlight the prevalence of chronic interstitial disease of the kidney in a large population in some districts of India. This family, who had 6 members suffering from chronic interstitial disease, out of which, two, father and son underwent kidney transplantation. Genetic analysis is desirable in such cases to find out the mutation. However, environmental toxins in the soil and water in the villages needs to be studied in detail.



Family Tree of the Index Case

PUB410

Modulation of Angiotensin II Binding and AT1 Receptor Expression in Experimental Alport Mouse Kidney Christopher Neagra,[2,1] Hong weng Pang,[2] Andrea Linares lopez,[2] Judith T. Molina David,[3] Alessia Fornoni,[3] Robert C. Speth.[2,4] *[1]Palmetto General Hospital, Hialeah, FL; [2]College of Pharmacy, Nova Southeastern University, Fort Lauderdale, FL; [3]Katz Family Drug Discovery Center and Division of Nephrology, University of Miami, Miami, FL; [4]Dept. Pharmacology and Physiology, Georgetown University, Washington, DC.*

Background: Alport Syndrome (AS) is a progressive renal glomerular disease that causes kidney failure and hearing and visual impairment, affecting as many as 3% of children and 0.2% of adults with end-stage renal disease (ESRD). It is caused by mutation of a Type IV collagen gene. Angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) are currently the only treatments that slow progression towards ESRD in AS.

Methods: Eight-week-old Col4a3 -/- (KO) and wild-type (WT) mice were utilized. AT_1 receptors were assayed using ^{125}I-sarcosine^1, isoleucine^8 Ang II (^{125}I-SI Ang II) by saturation binding assay and receptor autoradiography to determine receptor density, distribution and binding affinity.

Results: There was a significant 48% decrease ($p < 0.01$) in AT_1 receptor binding in KO compared to WT mouse kidneys (fmole/mg initial wet weight). However, when expressed as fmol/mg protein, the decrease in the Bmax for AT_1 receptor was 31%, which was not significant ($p = 0.11$).). Interestingly, there was a 24% decrease in mg protein/g wet weight in the Col4a3 -/- when compared to WT kidneys ($p < 0.05$). K_D values were not statistically different between the two groups. Receptor autoradiography did not reveal a difference in AT_1 receptor density in KO versus WT kidneys (153 versus 149 fmoles/g wet weight). However the pattern of AT_1 receptors was more diffusely distributed in the Alport model kidney compared to the wild-type kidney.

Conclusions: The density and affinity of AT1 receptors in the whole kidney cortex are reduced or not altered in experimental AS. This suggests that renoprotection with ACEi-ARB in AS is not linked to overexpression of AT_1 receptors in the kidney or to increased receptor binding. If and how the different distribution of AT1R may contribute to disease progression remains to be established.

PUB411

Renal Manifestations of Deficiency of Adenosine Deaminase 2 Marika Manolopoulou, Ed Gould, Julia Lewis. *Vanderbilt University Medical Center, Nashville, TN.*

Background: First described in the literature three years ago, deficiency of adenosine deaminase 2 (DADA2) has since been appreciated to have a myriad of clinical phenotypes. DADA2 is a disease defined by loss of function mutations in the CECR1 gene, leading to inflammatory activation and early-onset vasculopathy. To date, the renal phenotypes observed in this genetic disease have yet to be fully described in the literature. Here, we introduce one patient diagnosed with DADA2 and characterize her renal phenotype.

Methods: An 18-year-old Caucasian female with DADA2 was referred to renal clinic for evaluation of mildly elevated serum creatinine and low serum bicarbonate. She initially developed manifestations of cutaneous polyarteritis nodosa with livedo reticularis at age two. Despite successful remission with methotrexate, she had several periods of disease relapse over the following decade. Her pre-pubertal serum creatinine (sCr) was 0.3 - 0.4 mg/dL. Between the ages of 8 and 10, her sCr rose to 0.8 - 0.9 mg/dL. At age 14 she was recognized to also have neutrophil aberrancies, cytopenias and relative immunodeficiency; she was managed with non-sucrose based IVIg. This constellation of signs and symptoms prompted referral to the NIH for evaluation. At age 17, shortly after DADA2 was described in the literature, she underwent confirmatory genetic testing. Given the complexity of her case, she was referred to renal clinic to consider possible disease manifestations in her kidney. Her renal workup in our clinic – which has been conducted during a period of relative disease quiescence – has demonstrated a stable sCr (0.9-1.0 mg/dL), an inactive urinary sediment, and a mild metabolic acidosis (serum bicarbonate 18-20 mmol/L) likely driven by a distal renal tubular acidosis.

Results:

Conclusions: Adenosine deaminase 2 is primarily active in the extracellular space and seems to have a variety of roles, including serving as a modulator of the extracellular inflammatory milieu. The vasculopathy observed with DAD2 deficiency likely also manifests in the renal vasculature. In our patient, we suspect that her mild renal insufficiency stems from renal vasculopathy during periods of disease activity in her youth. Given the rarity of this disease, we support centralizing a patient database for additional investigation and characterization of the renal specific phenotypes that can be observed.

PUB412

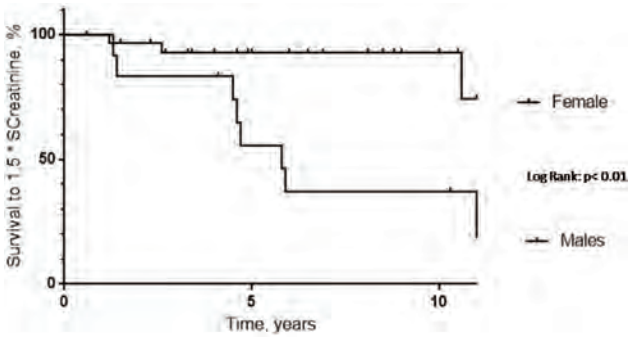
Long Term Renal Function in Patients with Fabry Disease Ricardo M. Heguilen,[3] Juan Politei,[4] Gustavo H. Cabrera,[1] Amelia R. Bernasconi.[2] *[1]Del Viso Medical Group, Buenos Aires, Argentina; [2]Hospital Fernandez, Buenos Aires, Argentina; [3]Hospital Juan A Fernandez, Buenos Aires, Argentina; [4]Department of Neurology, Laboratorio Chamoles, Buenos Aires, Argentina.*

Background: Proteinuria and progressive renal dysfunction, along with cardiovascular and neurological conditions are major findings in patients with Fabry disease (FD). In order to prevent progressive organ failure, enzyme replacement therapy (ERT) should be started early to remove substrate deposition in target tissues. In this study we analyze the renal outcome of a cohort of individuals followed-up throughout a period of almost 15 years from the diagnosis of FD

Methods: Prospective cohort study analyzing the time until an increase in serum creatinina (Screat) 1.5 times from baseline. Proportional hazard (Cox) regression was used to determine whether such outcome was a dependent variable on the following potential covariates: gender, age, hypertension (HTN), diabetes, tobacco use, overweight (OW) or the presence of dyslipemia, Odds ratios with the appropriate 2-sided 95% CI were reported. Kaplan-Meier and the Log-Rank test were used to compare survival curves. All tests were 2 sided, and p values < 0.05 were considered statistically significant.

Results: 44 individuals (13 male) fullfilling the inclusion criteria were followed-up for a time ranging from 1 - 15 years; most of them (80%) receiving ERT from 1 through 13.5 years. The age at diagnosis of FD was 35 ± 2.1 y, baseline creatinine (SCr) was 0.9 ± 0.1 and GFR 89.5 ± 5.0. Ten individuals (6 M) developed the outcome; the median time until the occurrence of the main outcome was 4.6 y, ($p< 0.01$ for gender difference). Male gender (OR 8.9 - 95% CI 1.2-66.8), HTN (10.2; 1.1 – 95.5) and OW (28.7; 1.6 – 50.6) were associated with worsening renal function

Conclusions: Renal involvement in FD is frequent, and the main findings are proteinuria, decreased GFR and tubular dysfunction. ERT may be important to lessen the burden of the disease but is also mandatory to remove other modifiable risk factors that play a major role in the progression of renal involvement



PUB413

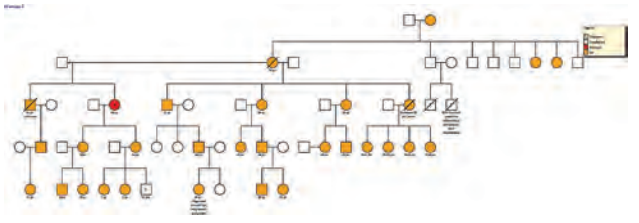
Familial Neurohypophyseal Diabetes Insipidus (FNDI) Spanning Five Generations Denaly S. Chen, Rafia I. Chaudhry, Anum Bilal, Loay H. Salman, Mauricio Monrroy. *Albany Medical College, Albany, NY.*

Background: FNDI is a rare genetic mutation in the AVP gene on chromosome 20p13, resulting in misfolded AVP precursors within the endoplasmic reticulum of hypothalamic neurons, causing cell death. Progressive neuronal degeneration can delay onset of symptoms, however polyuria and polydipsia usually manifest before age 6. Inheritance is autosomal dominant (AD), although autosomal recessive (AR) and X-linked inheritance have been reported. We present a middle-aged patient diagnosed with FNDI, unveiling 5 generations of affected individuals in her family.

Methods: A 56 year old woman with polydipsia and nocturnal enuresis since infancy consulted nephrology following a diagnosis of FNDI in her daughter during pregnancy complicated by dehydration, hypokalemia, and congestive heart failure. Our patient recalled headaches, dizziness, nausea and fatigue with decreased water intake. She had exacerbation of symptoms with limitation of oral intake at the time of a cholecystectomy and ovarian cystectomy. Family hx was positive for polydipsia (siblings) and nocturnal enuresis (daughters). Of note, despite a BMI of 28.8, and full term pregnancies, the patient delivered low birth weight babies (5lb 13 oz and 5 lbs). Initial labs: Cr 0.6 mg/dL, Na 138 meq/L, Ur SG <=1.005. Overnight water deprivation test revealed a Ur osmolality of 398, Sr osmolality 297, serum Na 146 meq/L. Intranasal desmopressin was initiated, Ur SG increased to 1.015, consistent with central DI. Panel gene sequencing of the AQP2 and AVPR2 genes was normal, while the patient was heterozygous in the AVP gene for a sequence variant (c.232_234delGAG), which results in the deletion of one amino acid (p.Glu78del). This mutation is pathogenic for AD FNDI.

Results:

Conclusions: Patients with Central DI have an inability to conserve free water, and FNDI can present with chronic bedwetting, polydipsia and polyuria resulting in growth retardation in childhood, or insidious symptoms with severe electrolyte disturbances during stress (e.g. pregnancy). Genetic screening is essential in patients with Central DI as FNDI affects multiple generations and can have AD, AR or X-linked inheritance.



PUB414

Late Onset Variant N215S GLA Mutation Is Associated with Fabry Nephropathy Behzad Najafian,[2] Mona Maghsoodi-Deerwester,[2] Michael Mauer.[1] *[1]University of Minnesota, Minneapolis, MN; [2]University of Washington, Seattle, WA.*

Background: Fabry disease (FD) is a heterogeneous condition with >700 GLA gene mutations/variants. Characterization of phenotype severity can guide FD treatment. Late onset variants are believed to cause milder phenotypes compared with classical mutations. We compared glomerular lesions, renal function and structural-functional relationships (SFR) in Fabry patients with late onset N215S vs. classical GLA mutations.

Methods: 7 (M/F=4/3) Fabry patients with N215S mutations, age 39(7-54), median (range) years were compared with 7 age and sex matched patients with classical mutations. Fractional volumes of globotriaosylceramide (GL3) inclusions per endothelial [Vv(GL3/Endo)] and mesangial cells [Vv(GL3/Mes)] and podocytes [Vv(GL3/Podo)] were estimated using electron microscopy stereology. Renal function data included urine albumin and protein creatinine ratios (ACR and PCR) and GFR.

Results: All patients had microalbuminuria. GFR, ACR or PCR were not different between classical and N215S patients. N215S was associated with lesser Vv(GL3/Endo) ($p=0.03$) and Vv(GL3/Mes) ($p=0.03$). Vv(GL3/Podo) was numerically greater in classical (0.35±0.16) than in N215S mutations (0.20±0.21) regardless of sex, but the difference was not significant. There was marked variation in Vv(GL3/Podo) among N215S patients regardless of sex, but in patients with classic mutations, variation in Vv(GL3/Podo) was restricted to females. While PCR was strongly associated with Vv(GL3/Podo) ($r=0.78$; $p=0.04$) and Vv(GL3/Endo) ($r=0.86$; $p=0.01$) in the classical group, such SFRs were not seen in the N215S group. Among the clinical symptoms, corneal opacities and gastrointestinal complications were more frequent in the classical compared with the N215S groups.

Conclusions: Late onset N215S variant, typically associated with residual enzyme activity, is associated with less GL3 inclusions in endothelial and mesangial cells, and shows remarkable variation in GL3 content in podocytes compared with classical mutations. This study suggests that, despite delayed onset and milder symptoms with the N215S mutation, these patients may develop substantial Fabry nephropathy with podocyte injury and microalbuminuria.

Funding: Other NIH Support - NINDS, Commercial Support - Sanofi

PUB415

The Distribution Characteristic of Monoclonal Antibody against Triple Helix of Type IV Collagen α Chains in Epidermal and Renal of X-Linked Alport Syndrome Patients with Different Genotypes Xiaoyu Liu, Fang Wang, Jie Ding. *Peking University First Hospital, Beijing, China. Group/Team: National Key Research and Development Program of China.*

Background: To investigate the distribution characteristic of monoclonal antibody against triple helix of type IV collagen α chains in epidermal and renal basement membranes of X-linked Alport syndrome boys with different genotypes.

Methods: Indirect IF staining of monoclonal antibody angainst type IV collagen α5 chain and monoclonal antibody against triple helix of type IV collagenα5α6α5(IV) were performed on the frozen sections of X-linked Alport syndrome boys and nomal controls. And the phenotype and genotype of X-linked Alport syndrome boys were analysed.

Results: In 10 X-linked Alport syndrome boys whose staining of α5(IV) was negative on the EBM, the staining pattern of monoclonal antibodies against triple helix of type IV collagen α5α6α5(IV) on the EBM was negative in 5 patients but positive in the other 5 patients. No definite relationship between genotype and the staining pattern was found. In 5 X-linked Alport syndrome boys whose staining of α5(IV) was positive on their EBM and GBM, the staining pattern of monoclonal antibodies against triple helix of type IV collagen α5α6α5(IV) was positive.

Conclusions: Mutations in the COL4A5 gene producted abnormal α5(V) chain, and the abnormal α5(V) chain can assemble triple helix type IV collagen protomers with other α chains. But the mechanism of how the abnormal protein distribute to the basement membranes and assemble triple helix type IV collagen protomers was still unknown.

Funding: Government Support - Non-U.S.

PUB416

Diffusion Restriction of Kidney Medulla in Gitelman Syndrome Patients Detected by the New Diffusion Kurtosis Imaging of MRI Xiaoyan Peng,[1] Gu-Mu-Yang Zhang,[2] Yan Liu,[1] Dongli Tian,[1] Hao Sun,[2] Limeng Chen.[1] *[1]Department of Nephrology, Chinese Academy of Medical Science, Peking Union Medical College Hospital, Beijing, China; [2]Department of Radiology, Chinese Academy of Medical Science, Peking Union Medical College Hospital, Beijing, China.*

Background: Gitelman syndrome (GS) is an inherited tubulopathy with Na^+-Cl^- cotransporter (NCC) dysfunction. Regular imaging techniques including magnetic resonance imaging (MRI) could not detect any changes in kidney of GS. Diffusion kurtosis imaging (DKI) is a new method of MRI which could disclose more precise tissue structure and non-Gaussian water diffusion. This study first applied this novel technique in GS patients to observe the potential biostructural and functional abnormity of the kidney.

Methods: Sixteen genetically diagnosed GS patients and 24 healthy subjects were enrolled and underwent Diffusion-Weighted imaging of the kidney at a 3 Tesla. Region-of-interest measurements were performed to determine apparent diffusion coefficient (ADC), kurtosis (K) and diffusivity (D) value of the kidney cortex and medulla. Pearson or Spearman correlation was used to evaluate the association between DKI-derived parameters and clinical data, including serum and urine electrolyte levels, plasma upright RAAS levels, and the in vivo NCC function evaluated by the thiazide test.

Results: The mean age of GS patients was 30.0±10.8y and 50% were males, with a mean onset age of 23.4±12.7y. At admission, the median duration of hypokalemia was 24(12, 126) months and the mean serum K^+ was 3.25±0.6 mmol/L, the urinary K^+ excretion was up to 91.1±32.9 mmol/24h. Compared to healthy subjects, lower ADC (1.417±0.189 vs. 1.547±0.115, $P=0.022$) indicating greater diffusion restriction was observed in the renal medulla of GS, but ADC was similar in the cortex. ADC of the cortex was associated with plasma upright AngII concentration ($r=-0.529$, $P=0.035$) and mean blood pressure ($r=-0.598$, $P=0.014$). Among GS patients, D indicating the observed non-Gaussian behavior and K reflecting the more peaked distribution of tissue diffusivities correlated well with serum Cl^- (D: $r=-0.733$, $P=0.001$; K: $r=-0.664$, $P=0.005$), HCO_3^- (D: $r=0.603$, $P=0.014$; K: $r=0.621$, $P=0.010$) and actual base excess. In the medulla, only K value associated with serum Cl^-($r=-0.562$, $P=0.023$). No correlations were observed between DKI-derived parameters and serum potassium or urinary electrolytes excretion.

Conclusions: In GS patients, diffusion restriction of water molecular in kidney medulla was observed by the novel DKI-MRI and associated well with hypochloremia and metabolic alkalosis.

PUB417

Erdheim-Chester: A Rare Multi-System Disease Mohamed Razeem,[2] Smita Gunda.[1] *[1]Cambridge University Hsospitals, Cambridge, UK, Kings Lynn, United Kingdom; [2]Queen Elizabeth Hospital King's Lynn, Swaffham, United Kingdom.*

Background: A case of Erdheim-Chester disease which demonstrates the classic features of the disease including BRAF gene mutation. We have followed up the patient for over 8 years. We aim to demonstrate the challenges in diagnosis and management of a rare disease.

Methods: 55 year old normally fit and well man presented with tiredness and weight loss and underwent investigations for anaemia. Gastroscopy did not find any abnormalities. Upper gastrointenstinal biopsies only showed metaplastic changes. He was then found to be in acute kidney failure with a Creatinine of 199 umol/l but no significant proteinurea or microscopic haematuria. A CT scan of abdomen demonstrated retroperitoneal disease, mesenteric soft tissue mass, left adrenal mass and bilateral hydronephrosis. A laparoscopic biopsy of peritoneal tissue confirmed the suspicion of retroperitoneal fibrosis. Vasculitic screening has been negative. Patient underwent bilateral ureteric stents for urinary obstruction due to fibrosis and kidney function remained stable during this time. Two years after initial presentation, patient developed bilateral exophthalmos with associated double vision. A biopsy of retro-orbital mass was not diagnostic but excluded malignant causes. Patient received various different imuune suppression tretament including rituximab, bot showed no response. A diagnosis of IgG4 was excluded from the differentials and Erdheim-chester disease was considered as a possible differential diagnosis. Based on this, X-rays of limbs showed diffuse medullary and cortical sclerosis within the long bones that is classical of Erdheim-chester disease. An MRI of heart showed a cardiac pseudo-tumour. Since a diagnosis of Erdheim-chester was made, patient was started on treatment with Pegylated Interferon therapy for which a good response was shown clinically and on imaging. unfortunately this had to be discontinued due to drug related hepatitis. Genetic testing came positive for BRAF gv600E mutation that has been associated with Erdheim-chester disease. At present he is off treatment and awaiting funding for Vemurafenib.

Results:

Conclusions: Erdheim-chester is an extremely rare multi-system disease. A little is known about the disease and reported cases in literature is limited. There has been significant chanllenges in diagnosis. Awarenessa and high index of clinical suspicion of disease is helpful in diagnosis and timely management.

PUB418

Fabry Disease Screening: Report of a Hemodialysis Center in Paris - Turin France Nader Bassilios, Angela Balsa, Mahdi Abtahi, Jacques Becart. *CLINIQUE TURIN, PARIS, France.*

Background: Fabry's disease (FD) is an X-linked lysosomal disease due to a deficiency of alpha-galactosidase A, the enzyme responsible for degradation of globotriaosylceramide (Gb3). The accumulation of Gb3 leads to multisystemic deficiency. The renal involvement is a combination of proteinuria and progressive fall in glomerular filtration rate (GFR) resulting in chronic end-stage renal failure in most male patients at around the age of 40 years old, usually requiring haemodialysis (HD). The purpose of the study was to determine the prevalence of FD patients of a hemodialysis center in Paris.

Methods: A total of 51 patients in HD have been included in the study after signing their informed consent. This is a single prospective study. This cohort consisted of 31 male patients aged between 27 and 65 years and 20 female patients aged between 35 and 65 years. 4 patients had past history of renal transplantation (1 male; 3 female). The length of history of dialysis for male patients ranged from 3 to 97 months and from 6 to 159 months for female patients. Residual enzyme activity of α-GAL was tested in men. For women α-GAL activity combined with testing for Lyso Gb3 levels was performed. The genetic test will be performed if the enzyme activity and/or if the Lyso Gb3 value is reduced.

Results: No patient among 51 was diagnosed with FD. In a female patient the α-GAL enzyme activity was extremely low: 1.4 µmol/l/h (cut-off < 2 µmol/l/h). The Lyso Gb3 value was within normal ranges 0.6 ng/ml (normal range 0.00 -3.5). A request for genotyping was made and no mutations were found in the GLA gene.

Conclusions: In this study, 51 patients undergoing HD were included to test for Fabry's disease although no patients were diagnosed. A review of the international literature suggests a prevalence of FD in patients with end-stage renal failure (ESRF) near 1%. However some studies reported a prevalence of 0%. It is important to change our practice and routinely investigate for Fabry's disease in patients in ESRF of indeterminate cause. Multi-disciplinary care is required and particularly a medical visit with geneticists and genetic counsellors in order to establish a family pedigree to screen other members of the family.

Funding: Commercial Support - Sanofi Genzyme Company

PUB419

Hereditary Renal Amyloidosis Caused by Variant Lysozyme W64R in a Chinese Family Hui Xu,[1] Suxia Wang.[2] *[1]Xiamen University Chenggong Hospital, Xiamen, China; [2]Peking University First Hospital, Beijing, China.*

Background: Lysozyme amyloidosis was first described by Pepys in 1993. It is a rare form of hereditary amyloidosis with heterogeneous phenotype including gastrointestinal(GI) symptom, hepatic rupture, sicca syndrome, petechiae and purpura, renal failure and lymphadenopathy, among which gastrointestinal symptom is the most typical manifestation. Here we report a lysozyme amyloidosis caused by variant lysozyme W64R in a Chinese family with renal impairment, whereas GI was not involved.

Methods: A 42-year-old man of Chinese ancestry presented with a 1-year history of hypertension and high creatinine. He denied any gastrointestinal symptoms. He had a family history of renal disease. Physical examinations and laboratory studies revealed an abnormal kidney function. No monoclonal immunoglobulin bands were detected by immunofixation electrophoresis. Renal biopsies were positive for amyloid deposits in the renal glomerulus and blood vessel wall on Congo red staining. Immunohistochemistry(IHC) and proteomic analysis confirmed the deposits was lysozyme. Sequence analysis of exon 2 of the lysozyme gene showed heterozygous double peaks with single base transversion from T to A at the first position of codon 64 (TGG/CGG), indicating a heterozygous W64R mutation in the mature protein.

Results:

Conclusions: According to the family history and the results of IHC, proteomic analysis and DNA sequencing, this patient was diagnosed as hereditary renal amyloidosis caused by variant lysozyme W64R. To date, less than 30 families associated with lysozyme amyloidosis have been reported and the geographic kindreds of these families are United Kingdom, France, Canada, Swedish and Germany. This is the first case report about a Chinese family with lysozyme amyloidosis whose dominant involved organ is renal, whereas GI was not involved.

Funding: Government Support - Non-U.S.

PUB420

Whole Exome Sequencing to Identify Causal Variants for Familial IgA Nephropathy Caragh P. Stapleton,[3] Sharon N. Cox,[2] Claire Kennedy,[1] Neil Fennelly,[1] Gianpiero Cavalleri,[3] Francesco P. Schena,[2] Peter J. Conlon.[1] *[1]Beaumont Hospital, Dublin, Ireland; [2]Department of Emergency and Organ Transplantation, University of Bari Aldo Moro, Bari, Italy; [3]Department of Molecular and Cellular Therapeutics, Royal College of Surgeons, Dublin, Ireland.*

Background: IgA nephropathy (IgAN) is the most common form of glomerular nephritis in the world. Difference in prevalence between ethnicities and familial inheritance patterns indicate a strong genetic component. The advent of next generation sequencing has accelerated the discovery of risk variants underlying familial disorders. We set out test whether damaging variants in known kidney disease genes explain a proportion of cases diagnosed with IgAN.

Methods: We recruited and performed exome sequencing in 8 Italian and 6 Irish families with at least one case of biopsy proven IgAN and at least one other 1st degree relative with either biopsy proven IgAN or end stage renal disease. Candidate causal variants were identified based on 1) being shared between affected family members, 2) frequency in the general population, 3) function and 4) predicted pathogenicity. Qualifying variants were confirmed using Sanger sequencing.

Results: We identified candidate causal variants in three of the Irish families. In one family, we identified a pathogenic variant (according to American College of Medical Genetics standards) in *COL4A5* (known to cause Alport syndrome). The variant was present in two of the three sequenced affected family members and segregated with the disease in five other family members indicating that there may be two similar diseases present in the one family. In another family, we identified a likely pathogenic variant in *COL4A3*. This variant segregated with the disease in two unaffected and two affected family members. In the third family, we identified a variant in *LMX1B*, a gene associated with Nail-patella syndrome. This variant also segregated with the disease however its significance remains uncertain. The same variants associated with kidney disease were not present in the Italian families.

Conclusions: Exome sequencing is a powerful tool for diagnosing unexplained disease. We identified a number of pathogenic and likely pathogenic variants in 14 families who were originally diagnosed with IgAN. This suggests that exome sequence may help improve diagnosis in patients with familial IgAN.

Funding: Government Support - Non-U.S.

PUB421

A Girl with Autosomal Recessive Alport Syndrome Due to Segmental Paternal Isodisomy Zihua Yu,[1,2] Lizhu Chen.[1,2] *[1]Department of Pediatrics, Dongfang Hospital, Fuzhou, China; [2]Department of Pediatrics, Xiamen University Affiliated Dongfang Hospital, Fuzhou, China.*

Background: Autosomal recessive Alport syndrome (ARAS), characterized by hematuria, progressive end-stage renal disease, sensorineural hearing loss and ocular abnormalities, is caused by mutations in either the *COL4A3* gene or the *COL4A4* gene. ARAS may be caused by uniparental disomy, which is composed of two homologous chromosomes from one parent or a duplicate of one chromosome, i.e. isodisomy. A man with ARAS due to segmental maternal isodisomy has been reported. Here we report a girl with ARAS due to segmental paternal isodisomy.

Methods: A four years old girl presented with microhematuria at 25 months old, proteinuria at 28 months old and episodic gross hematuria. Her father age 32 years old and younger brother age 2 years old also presented microhematuia, and her mother had neither hematuria nor proteinuria. Her parents are non consanguineous. A homozygous mutation, 1496G>A (G499E), in exon 21 of the *COL4A3* gene was identified in the girl. The same heterozygous mutation, G499E, was found in both her father and younger brother, but it wasn't detected in her mother. Quantitative PCR analysis showed that she has two copies of exon 21 of the *COL4A3* gene. Chromosomal microarray analysis revealed segmental uniparental isodisomy in her chromosome region 2p25.3-2q37.3 that includes the *COL4A3* gene. She was diagnosed with ARAS due to segmental paternal isodisomy.

Results:

Conclusions: The identification of isodisomy in the patient with ARAS helps to give accurate genetic counseling for the patient's parents. The risk of future child of the patient's parents with affected ARAS is negligible because the recurrence risk for isodisomy is very low.

Funding: Clinical Revenue Support

PUB422

IL-4 Receptor Gene Polymorphism in Childhood Idiopathic Nephrotic Syndrome

Amal A. Al-eisa. *Pediatrics, Kuwait University, Kuwait, Kuwait.*

Background: Idiopathic Nephrotic syndrome (INS) is an immune-mediated disease with a well-documented association with atopy. IL-4 is a vital cytokine involved in atopic symptoms mediated through its receptors (IL-4R). Gene polymorphism of IL-4 receptor (IL-4R) controls the expression and function of IL-4 and therefore might have an effect on the pattern of INS. The aim of this study is to determine the frequency and the association of IL-4R gene polymorphisms with idiopathic nephrotic syndrome (INS) and its effect on the disease pattern in Kuwaiti children.

Methods: Genotypes of the IL-4R gene polymorphisms were analyzed using PCR-RFLP in 151 INS patients and 59 age and sex- matched controls. Clinical data of all subjects were reviewed.

Results: A total of 151 INS (129 steroid-sensitive and 22 steroid- resistant) patients with a mean age was 7.6±4.3 years were studied. Male: Female ratio was 2:1. The CC genotype of IL-4R gene polymorphism was detected in 64% of the INS patients compared to 69.5% of the controls (P=0.57). The heterozygous CT genotype was detected in 30% of INS patients compared 25.5% of the controls (P =0.61). The TT-genotype was detected in 6% of INS patients and 5% of the controls (P =1.00). The C-allele frequency in homozygous and heterozygous forms was found in 94% of INS patients compared to 95% of the controls (P =1.00). The T-allele frequency in homozygous and heterozygous forms was found in 35.7% of INS patients compared to 30.5% of the controls (P =0.57). No significant difference was found in any of the allele frequencies between SS and SR sub-groups when compared with each other or when compared to the controls.

Conclusions: Our data shows no role of IL-4 receptor gene polymorphisms on the clinical pattern or response to steroids in Kuwaiti children with INS

Funding: Government Support - Non-U.S.

PUB423

The Prevalence of Fabry Disease in Hemodialysis Patients of Jeju island

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Background: Fabry disease (FD) is an X-linked genetic disorder, caused by mutation in the GLA gene which encodes lysosomal enzyme, a-galactosidase A (α -Gal A). The deficiency of α-Gal A could cause renal failure, but its diagnosis is completely missed at times. Although the prevalence of FD in dialysis patients are known to be between 0.16% and 1.2%, the higher prevalence was expected in island area in terms of genetic disorder. Therefore, we tried to investigate the prevalence of FD in hemodialysis patients of Jeju island.

Methods: A total of 9 artificial kidney units participated in the study. We measured plasma α-Gal A activity before starting hemodialysis. In patients with low level of plasma α-Gal A activity, we analyzed the GLA gene, under patient's agreement.

Results: A total of 663 patients with hemodialysis were enrolled in the study. The mean age of patients was 57 year, and the male was 64 %. Among them, the 39 (5%) patients showed the low α-Gal A activity with < 0.45 nmol/min/mg protein. The gene analysis was performed in all patients with low α-Gal A activity. In genetic analysis, no definite GLA mutation was found. But E66Q mutation, controversial whether it is a functional variant or FD, was found in 3 female patients. Although their presumptive clinical cause of renal failure was DM in one of the 3 patients, unknown etiology in other 2 patients, the kidney biopsy was not performed.

Conclusions: Although the prevalence of FD was 0%, the E66Q mutation showed 0.04 % in hemodialysis patient of Jeju island. More accurate diagnostic tool for FD and follow-up of prognosis of patient with E66Q mutation are needed.

PUB424

Saudi Children Have High Prevalence of Genetic Related Atypical Hemolytic Uremic Syndrome and Better Renal Recovery with Eculizumab Therapy

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Background: Atpical hemolytic uremic syndrome (aHUS) is ultra-rare disease, characterized by microangiopathy hemolytic anemia, thrombocytopenia and renal impairment. Genetic defects that determine uncontrolled activation of the alternative complement pathway have been well documented, it accounts for about 40%–60% of the cases. Recent studies demonstrate the effectiveness of Eculizumab in aHUS treatment. In Saudi Arabia, there is up to 56% of consanguinity marriage resulting in higher prevalence of genetic diseases. We are reporting the experience of a tertiary care center in Saudia for children with aHUS who were treated with plasma therapy and or Eculizumab, their outcome and genetic background.

Methods: This is a retrospective study, from January 2010 till May 2017 in a tertiary care center comparing children with aHUS who had received plasma therapy to those received Eculizumab therapy which was introduced at our center in 2014. We report our data in regard to demographic, clinical presentation, the length of hospital stay, need for dialysis, renal recovery and genetic mutations.

Results: 21 Saudi children who have similar demographic background diagnosed with aHUS, 12 (57%) of them showed complete renal and hematologic recovery (67% in the Eculizumab group versus 33 % in plasma therapy group). Six cases (29 %) reached End Stage Renal Disease (ESRD), four patients (67 %) of these cases from the plasma therapy group; two patients (33%) from Eculizumab group reached ESRD, their genetic mutations were not related to complement dysregulation system. Two of the 21 cases (17%) developed disease recurrence while receiving plasma therapy but no recurrence developed after using Eculizumab. Hospitalization was reduced by 10.6 days in Eculizumab group. 11 (69%) of the 16 cases who underwent genetic testing have identified gene mutations.

Conclusions: In our 21 cases with aHUS, Eculizumab was superior to plasma therapy in inducing, maintaining remission, and associated with better renal recovery. Genetic mutations detected among our patients were higher than reported for this ultra-rare disease, most probably related to the high prevalence of consanguinity marriage.

PUB425

Prohibitin-2 Gene Polymorphism and ROS Tolerance in Frequent Relapsing Nephrotic Syndrome

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Background: Patients with minimal change nephrotic syndrome (MCNS) often also have allergic diseases. Imbalances between reactive oxygen species (ROS) and antioxidants have been implicated in MCNS and progression of atopic dermatitis (AD). ROS, produced mainly within mitochondria, subject cells to oxidative stress, while prohibitin 2 protects mitochondria by increasing tolerance to ROS.

Methods: An 18-year-old male patient who developed nephrotic syndrome at 3 years of age subsequently was diagnosed with MCNS by histologic examination. Disease manifestations have recurred 12 times. He had given the various immunosuppressants. At present, proteinuria has abated during treatment with prednisolone and MMF. Eczema has appeared on the patient's face, trunk, and 4 limbs, beginning at 2 months after birth, and worsening of intractable skin eruptions has accompanied or preceded increases in proteinuria. The serum IgE concentration was 18670 IU/L, representing a marked increase. Sensitization to fungi and staphylococcal enterotoxin was detected by ImmunoCAP-specific IgE. Among Th2 cytokines, increases in IL-4 and IL-13 were marked. High value of the dROM represent high oxidative stress and slight reduction of BAP, indicating low antioxidant activity. On exome sequencing analysis detected a heterozygous *prohibitin 2* polymorphism, c.873-3_873-2 delCA (rs111523336). This mutation in exon 9 located on chromosome 12 caused frameshifts in regions connected to splicing sites, where they could disrupt transcription of *prohibitin 2*. Frequency of this polymorphism in exon 9 is 7.3% among Japanese.

Results:

Conclusions: Increase in peripheral blood ROS even MCNS remission state suggests the heterozygous prohibitin 2 variant may contribute to give more susceptibility towards the recurrence of MCNS as well as AD. This increase may have progression of AD, which sometimes heralded. The prohibitin-2 polymorphism may reduce ROS tolerance in glomerular epithelium and led to high local exposure to ROS, increasing permeability of the GBM to result in proteinuria. Imbalance between ROS and antioxidants together with failure of signal transduction in the glomerular slit membrane caused by prohibitin 2 abnormality could have contributed to NS patients. Prohibitin 2 analysis is needed in additional MCNS patients with concomitant allergic disease.

PUB426

The Interaction Effect of rs4077515 and rs17019602 Increases the Susceptibility to IgA Nephropathy

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Background: Immunoglobulin A nephropathy (IgAN), the most common form of primary glomerular diseases worldwide, is a complex multifactorial disease. Previous genome wide association studies (GWAS) reported that variants CARD9 and VAV3 genes were associated with immunoregulation and susceptibility to IgAN.

Methods: In this study, we further validated the associations and explored the interaction effect of rs4077515 and rs17019602 in IgAN patients.

Results: There was no significant correlation between the two variants and IgAN (P>0.05). The analysis of disease risk score showed that rs4077515 and rs17019602 had interaction effect on the susceptibility to IgAN, and the more the number of risk alleles, the higher the risk of IgAN. For additive interaction, the CT or TT of rs4077515 and GG of 17019602 genotype combination conferred a 2.556-fold risk of IgAN reference to CC

of 4077515 and AA of 17019602 (OR=2.556, 95% CI: 0.976-6.694, P=0.049). There was no significant association between genotype distribution and clinical characteristics in IgAN patients (P>0.05).

Conclusions: The interaction effect of the variants of CARD9 and VAV3 genesincreases the susceptibility to IgAN.

PUB427

The Association Between Frailty and Quality of Life in CKD Andrew Nixon,[1,2] Theodoros M. Bampouras,[3] Alastair R. Petrie,[3] Atinuke J. Afolabi,[3] Neil Pendleton,[1] Sandip Mitra,[4] Ajay P. Dhaygude.[2] *[1]University of Manchester, Manchester, United Kingdom; [2]Lancashire Teaching Hospitals NHS Foundation Trust, Preston, United Kingdom; [3]University of Cumbria, Lancaster, United Kingdom; [4]Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom*.

Background: Frailty is associated with an increased mortality in chronic kidney disease (CKD). Smaller studies that used modified versions of the frailty phenotype have demonstrated that frailty is also associated with a worse quality of life (QoL) in CKD. Further studies are needed to validate this association.

Methods: Fifty-eight patients with dialysis-dependent CKD and pre-dialysis stage 4 and 5 CKD were recruited. Frailty was assessed using the original frailty phenotype (FP). Patients were categorised as robust, pre-frail or frail. QoL was assessed using the 36-Item Short Form Survey (SF36). Between group differences in SF36 scores were assessed using the Kruskal–Wallis test. A p value of <0.05 was considered statistically significant. Linear regression analysis was performed to assess the magnitude of associations between FP scores and SF36 domains.

Results: Median age was 70 years old (IQR: 58.75-77.00) with 28 male participants. Half were receiving haemodialysis. Mean Charlson Comorbidity Index (CCI) score was 3.12 (SD: 1.29). Frailty and pre-frailty prevalence was 24% and 47%, respectively. The frail group had the lowest median scores across all SF36 domains. There were significant differences between FP categories for all SF36 domains except 'emotional well-being'. Table 1 demonstrates linear regression coefficients. Adjusting for age, CCI score and CKD stage did not substantially alter coefficients. An increase in frailty score by 1 point had the greatest effect on the 'physical functioning', 'role limitations due to emotional problems' and 'pain' SF36 domains.

Conclusions: Frailty is associated with a worse QoL in CKD and influences both physical and emotional aspects of QoL. Nephrology services should routinely assess frailty and offer additional support for those considered frail.

Table 1. Frailty and Quality of Life: Linear Regression Analysis.

SF36 Domain	Regression Coefficient	95% Confidence Intervals	p value	Adjusted Regression Coefficient	95% Confidence Intervals	p value
Physical Functioning	-14.95	-19.18 to -10.71	0.00	-13.98	-18.45 to -9.52	0.00
Role Limitations due to Physical Health	-11.98	-18.82 to -5.13	0.00	-11.43	-18.96 to -3.90	0.00
Role Limitations due to Emotional Problems	-9.76	-17.30 to -2.22	0.01	-12.90	-21.05 to -4.75	0.00
Energy/Fatigue	-9.86	-13.12 to -6.60	0.00	-10.61	-14.16 to -7.06	0.00
Emotional Well-Being	-3.75	-7.58 to 0.09	0.06	-5.53	-9.69 to -1.37	0.01
Social Functioning	-8.66	-13.40 to -3.93	0.00	-9.14	-14.15 to -4.12	0.01
Pain	-12.33	-16.26 to -8.40	0.00	-11.76	-16.13 to -7.39	0.00
General Health	-5.66	-9.03 to -2.30	0.00	-6.47	-9.84 to -3.11	0.00

PUB428

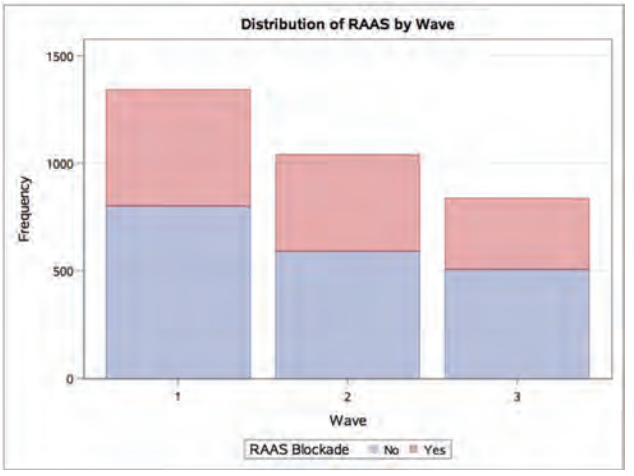
RAAS Blockade in Community Dwelling Elders and the Importance of "Sick Day Rules" Donal J. Sexton,[2,1] Mark Canney,[2] Rose Anne M. Kenny,[2] Mark A. Little,[3] Conall M. O'Seaghdha.[2,1] *[1]Nephrology Department, Beaumont Hospital, Dublin, Ireland; [2]The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin., Dublin, Ireland; [3]Trinity Health Kidney Center, Trinity College Dublin, Dublin, Ireland*.

Background: Acute kidney injury contributed to by continued RAAS blockade during episodes of intercurrent illness is common. We set out to define the size of the population denominator for AKI due to ACE inhibitors or ARBs by defining the frequency of their use in community dwelling individuals ≥ 75.

Methods: TILDA is a nationally representative prospective longitudinal cohort study of community-dwelling adults aged ≥ 50 years resident in the Republic of Ireland. Random sampling of geographical clusters was used to select households. Data collection involved an in-home interview (CAPI) (N=8175) and a health assessment undertaken in the health center or in the respondent's home (N=5751). Mean follow up for TILDA was 3.4 years. Our study-utilised data from wave 1 (completed July 2011), wave 2 (March 2013) and wave 3 (December 2015) TILDA.

Results: In those aged ≥ 75 yrs (N=1342), mean age 80.2 (4.36), 598 Male, 745 female. At wave 1 TILDA (of 218,309 population) 41% were on some form of RAAS blockade, 7.1% were taking prescription NSAIDS, 3% were taking both RAAS blockade and NSAIDS. At wave 3 follow up, 20% were on an ACE, 18.9% were on an ARB, 38.4% on any RAAS blockade. 53.9% had hypertension, 9.2% previous MI, 11.2% diabetes, 3.2% stroke, 5.2% TIA, 1.7% CHF. Of those aged ≥ 75 and eGFR < 60 ml/min, 38.4% were on some form of RAAS blockade, 15.2% were on both RAAS blockade and diuretics.

Conclusions: The prescription of RAAS blockade medication is widespread in community dwelling elders. Given the prevalence of CHF, previous myocardial infarction and CKD in the population, it is likely that the majority of RAAS blockade prescribing is related to hypertension treatment in the community. Awareness of the importance of sick-day rules in primary care merits emphasis.



Cross sectional prevalence of RAAS blockade prescriptions in community dwelling individuals aged ≥ 75 years over the first three waves of TILDA.

PUB429

Erythropoietin Resistance May Just Be Diagnostic Complacency Jack Rubin,[1] Lihong Wu.[2] *[1]None, Long Beach, CA; [2]none, LOS ALAMITOS, CA*.

Background: We reviewed our dialysis units data to identify patients (pts) whose hemoglobin (hg) did not increase with increasing doses of erythropoietin (epo)(our functional definition of epo resistance). 21 of 123 patients fulfilled this criteria. 8 of the 21 are pts who came to dialysis after medical catastrophes requiring feeding tubes and tracheostomies, 1 patient is noncompliant with dialysis, 1 has short bowel and cardiomyopathy and 2 had hematologic illness. The rest remained unexplained. We wish to report on the pts with hematologic illness.

Methods: Mr. Y, aged_75 developed membranous nephropathy and eventually required dialysis. He was started on peritoneal dialysis and converted to hemodialysis after he developed an inguinal hernia (9/12-3/15). He has coronary artery disease with past bypass surgery and a recent stent placement. His main complaint is the sensation that he is cold all the time and has no energy, especially when his hg is less than 9 g %. He remained throughout the course requiring large doses of erythropoietin up to 10000 units thrice weekly. After 4 years we requested a hematology consult because he developed thrombocytopenia. Bone marrow found myelodysplastic syndrome with a 20q deletion. Chemotherapy was started with Dacogen. After 2 cycles of treatment hg and platelet count improved. Mrs. X, An 82 year old pt with renal insufficiency secondary to diabetes mellitus and congestive heart failure started hemodialysis 9/2015 initially to control congestive heart failure. Within a month she developed facial zoster. She has been maintained on dialysis twice weekly. She remained anemic. After 18 months she had a sudden marked drop in hemoglobin from 9 to 6 g% with associated rectal bleeding. A gastrointestinal workup was unrevealing. A hemolytic anemia was eventually diagnosed and thrombocytopenia noted culminating in a bone marrow biopsy diagnosing mantle cell lymphoma. Chemotherapy was started with single agent Rituxin and after 4 doses she is in remission.

Results:

Conclusions: In summary 17% of our pts (21/123) failed to respond to increasing doses of epo. Of these 21 pts a satisfactory explanation could be found for 11 of the 21 pts. When pts are found to have epo resistance differential diagnosis needs to be broadened beyond iron deficiency, bleeding without a source or an "inflammatory state" causing anemia of chronic disease.

PUB430

Frailty Is Predictive of Future Adverse Outcome in Incident Elder Patients with ESRD: A Prospective Cohort Study in Korea Soojin Lee,[1] Sung Woo Lee,[2] Anna Lee,[3] Ho Jun Chin.[3] *[1]Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea; [2]Eulji General Hospital, Seoul, Republic of Korea; [3]Seoul National University Bundang Hospital, Seong nam, Republic of Korea*.

Background: Little is known for the clinical significance of frailty in elderly patients with end stage renal disease (ESRD).

Methods: We prospectively enrolled 46 elder patients with incident ESRD in a dialysis center of tertiary hospital between May 2013 and March 2015. Frailty was assessed using comprehensive geriatric assessment protocol and was defined as ≥ 10 of the multidimensional frailty score. The main outcome was composites of all-cause death or cardiovascular hospitalization determined at June 2016.

Results: Of 46 participants, median age was 71.5 years and 63.0% was men. During median 17.7 months' follow-up, the rate of composite outcome was 17.4%. In

multivariate logistic regression analysis, after adjusting for age, sex, diabetes, body mass index (BMI) and time of pre-dialytic nephrologic care, women and increased BMI were associated with increased and decreased odds of frailty, respectively. In multivariate Cox proportional hazard analysis, after adjusting for age, sex, diabetes, BMI and time of pre-dialytic nephrologic care, frailty was significantly associated with composite adverse outcome. In repeated frailty assessment, the multidimensional frailty score was significantly improved 12 months after dialysis initiated, which was largely relied on the improved alimentation.

Conclusions: Frailty is associated with increased risk of adverse outcome in elder patients with incident ESRD. Dialysis may improve frailty, particularly relying on the improved alimentation in elder ESRD patients. Future large studies need to confirm our study results.

PUB431

Coordinating Values for Shared Decision Making in Dialysis: Patient and Provider Perspectives Ann E. Vandenberg,[2] C. Barrett Bowling,[1] Janice P. Lea,[2] Leigh Nadel,[2] David Byrd,[3] Amelia Lambeth,[3] Brian D. Jones,[3] Laura Plantinga.[2] *[1]Durham VA Medical Center, Decatur, GA; [2]Emory University, Atlanta, GA; [3]Georgia Institute of Technology, Atlanta, GA.*

Background: Patient values are a core component of shared decision making (SDM). Less often identified, provider values also influence SDM. Little is known about dialysis patient or provider values. As part of the development of a report on dialysis patient functional status using geriatric assessments to facilitate SDM, we examined patient and provider values with respect to dialysis care.

Methods: Four 90-minute focus groups were conducted, two with patients (n=17, patient group) and two with providers (n=9, MD group – physicians and physician-extenders; n=8, non-MD group – social workers, registered nurses, and dietitians). Transcripts were analyzed within and across stakeholder groups for concordance and discordance of expressed values.

Results: All groups shared the values of patient function, individualized care, social service support, and patient personal responsibility in treatment. All attributed the value of efficiency to other groups to explain a streamlined, non-individualistic approach to dialysis care. The patients and the non-MD group shared many values, including access to quality patient-provider meetings, family support in care, cost-savings within the medical system, and patient family responsibility, work, independence, effort, and hope. Hope, or focusing on possibilities rather than limitations in function, was repeatedly expressed by both patient groups. Patients but not providers emphasized the importance of their own physical comfort within and outside the clinic; using knowledge of their own body to inform treatment, including medication adherence; and freedom away from dialysis. Providers but not patients valued objectivity in functional assessment and biomedical knowledge (i.e., lab results, medications) for treatment decisions. The MD group attributed the value of body knowledge to patients and saw it as a barrier to patient adherence to treatment recommendations.

Conclusions: These findings may facilitate SDM by informing dialysis providers about the presence of and allegiance to values across stakeholder groups in dialysis clinics. By attending to the values of patient hope, effort, and family responsibility, nephrologists might increase their persuasiveness with patients with regard to the shared value of personal responsibility in adhering to treatment recommendations.

Funding: Commercial Support - Satellite Healthcare

PUB432

Six-Month Impact on Quality of Life and Functional Assessment of Elder Patients with ESRD Undergoing Hemodialysis David Escamilla-Illescas,[4] Jorge Rivera reyes,[5] Mario A. Sebastian-Diaz,[2] Michael E. Wasung,[3] Mario A. Cerecedo rosendo,[6] Guillermo Cardenas.[1] *[1]General Hospital Manuel Gea Gonzalez, Mexico, Mexico; [2]None, MEXICO, DF, Mexico; [3]Hospital Angeles de Acoxpa, Mexico City, Mexico; [4]Hospital Central del Sur de Alta Especialidad PEMEX, Mexico City, Mexico; [5]PEMEX, Mexico City, Mexico; [6]PEMEX SERVICIOS MEDICOS, Mexico City, Mexico.*

Background: Hemodialysis improving survival rates of Chronic Kidney Disease (CKD) patients but not Quality of Life (QoL) is an important problem. This aggravates in the elder. We describe the impact in QoL and functional assessment of 6-months hemodialysis treatment.

Methods: Single center prospective study, applying the Kidney Disease Quality of Life (KDOQOL-36™) in Spanish, Katz Index, Barthel Index, Lawton and Brody Scale and Karnofsky Performance Status to patients with CKD KDIGO 5D, aged 65 years or older at Hospital Central Sur de Alta Especialidad PEMEX (Mexico) on October 2016. We applied the surveys again on May 2017 to the same population. We presented the general view in mean and standard deviation and analyzed with Studen's t-test.

Results: At the beginning of the study there were 22 elder patients in hemodialysis, 59% men with an average age of 72.9 (±5.9) years old and a time in hemodialysis of 27.1 (±24.1) months. Six-months later we had 18% deaths, 9% changed their residency and 73% were still active, 62.5% men. Mean values from the different scales are represented in Table 1. We compared the media of each subscale after six months with Student's t-test but there were no significant variables.

Conclusions: We observed a decrease in all subscales of KDOQOL-36™ and functional assessment evaluation with no statistical differences. The first evaluation was higher than previous hemodialysis reports on QoL in Mexico, but it turned out to be quite similar in the second analysis. One important limitation is that we don't know the bias of applying the same survey, also the proper means of measuring QoL in chronically patients are unclear. We suggest the continuous evaluation of QoL in geriatric population to get a global perspective.

Scale	2016 Mean (SD) / Mode	2017 Mean (SD) / Mode
Symptom/problem list	84.6 (±10.5)	80.4 (± 17.2)
Effects of kidney disease	84.9 (±17.9)	75.2 (±23.6)
Burden of kidney disease	61.6 (±25.6)	49.2 (±18.4)
SF-12 Physical Composite	41.5 (±8.7)	39.1 (±8.4)
SF-12 Mental Composite	49.8 (±11)	45.7 (±12.1)
Karnofsky Performance Status	78.6 (±17.2)	76.2 (±16.2)
Barthel Index	85.2 (±18.8)	80.9 (±17.9)
Katz Index	A (77%)	A (62%)
Lawton and Brody Scale	5.1 (±2.7)	5 (±3)

PUB433

Effects of Global TRPC6 Knockout on Passive Anti-GBM Nephritis in Sprague-Dawley Rats: No Effects on Renal Fibrosis or Overall Renal Function but Reduced Glomerulosclerosis Stuart E. Dryer, Eunyoung Kim. *University of Houston, Houston, TX.*

Background: TRPC6 channels have been implicated in familial forms of FSGS. There are reports that TRPC6 knockout in mice reduces renal fibrosis[1]. Here we examined this question in a global constitutive TRPC6 knockout in Sprague-Dawley rats using a model of immune complex nephritis.

Methods: Nephritis was induced by a single i.v. injection of sheep anti-rat GBM (Probetex, San Antonio, TX). Rats were not previously immunized with anti-sheep IgG. Renal phenotypes were characterized by standard biochemical and histological methods. All experiments were approved by the University of Houston IACUC.

Results: Rats injected with nephrotoxic serum had robust IgG and complement deposition within glomeruli measured 28 days after injection. This was the same in $TRPC6^{+/+}$ and $TRPC6^{-/-}$ littermates. TRPC6 knockout had no effect on 24-hr urine albumin excretion measured 4, 18 or 28 days after immunization. At 28 days after immunization, TRPC6 knockout had no effect on serum creatinine, BUN or circulating procollagen type I peptide, all of which were significantly elevated in immunized animals, and which reflected a decline in renal function and an ongoing fibrotic process. TRPC6 knockout also had no effect on the abundance of CD68, vimentin, or α-smooth muscle actin in renal cortex, or on kidney weight: body weight ratio. Tubulointerstitial fibrosis as assessed by PAS and Masson's trichrome staining was severe in this model, and there was no protective effect of TRPC6 knockout on tubules or in the interstitium. However, close examination of glomeruli in PAS-stained sections showed less severe glomerular disease and a reduced percentage of glomeruli with crescentic lesions in $TRPC6^{-/-}$ rats ($P < 0.05$). Basal TRPC3 abundance in renal cortex was increased in $TRPC6^{-/-}$ rats compared to $TRPC6^{+/+}$ controls. However TRPC3 did not increase further during anti-GBM nephritis. None of the manipulations in this study affected TRPC5 channels.

Conclusions: TRPC6 knockout had a partial protective effect on glomeruli in Sprague-Dawley rats during anti-GBM glomerulonephritis. However, it failed to reduce tubulointerstitial fibrosis and did not have any effect on the decline of overall renal function in this model. 1. Wu et al. *Kidney Int.* 91: 830-841, 2017.

Funding: NIDDK Support

PUB434

Detection of Convertase-Stabilizing Factors in Patients with Complement-Mediated Renal Diseases Marloes Michels,[1] Marcin Okroj,[2] Sanne van Kraaij,[3] Nicole Van De Kar,[1] Elena Volokhina,[1,3] Bert Van den heuvel.[1,4] *[1]Pediatric Nephrology, Radboud university medical center, Nijmegen, Netherlands; [2]Medical Biotechnology, Intercollegiate Faculty of Biotechnology, Medical University of Gdansk, Gdansk, Poland; [3]Laboratory Medicine, Radboud university medical center, Nijmegen, Netherlands; [4]Pediatrics, University Hospitals Leuven, Leuven, Belgium.*

Background: The autoantibody C3 nephritic factor (C3NeF) plays a pathogenic role in C3 glomerulopathy (C3G) by stabilizing the key enzyme of complement activation, the C3 convertase. However, reliability of currently used assays to detect C3NeF is limited. Recently, we developed a method to measure convertase stability in human serum. We now optimized the method for simple detection of convertase-stabilizing factors such as C3NeF in large patient cohorts.

Methods: Convertase stability was measured in a hemolytic assay using the C5-blocking agent eculizumab to separate the alternative pathway (AP) into two steps: formation of C3/C5 convertases by test sera in a time-variable step 1 and formation of lytic membrane attack complexes in a standardized step 2 for readout. Samples of 15 controls and 29 patients with C3G were analyzed. In addition, convertase stability was assessed in a family with complement Factor B (FB) mutation (p.Lys323Glu) and atypical hemolytic uremic syndrome (aHUS), a complement-mediated disease not associated with C3NeF.

Results: Healthy controls were tested to define the normal convertase activity profile: maximal convertase activity was observed after 10-15 min and after 30 min the activity of all controls had returned to background levels. When serum or purified Ig fraction containing C3NeF was added to control serum, convertase activity was increased at t=30 ($P<0.001$). Thus, detectable convertase activity at t=30 min or later was chosen as a marker for presence of convertase-stabilizing factors such as C3NeF. In our cohort, 16 out of 29 (55%) patients showed increased convertase stability. Interestingly, prolonged convertase activity was also detected in an aHUS family and segregated with the FB mutation in affected and non-affected family members.

Conclusions: We present optimization of a simple, reliable, and cost- and time-effective assay for detecting convertase-stabilizing factors (C3NeF and some mutations) in patients with various complement-mediated renal diseases. This study may give insight in disease pathogenesis and treatment strategies in these patients.

PUB435

Alterations in Circulating Lymphoid Cell Populations in Systemic Small Vessel Vasculitis Are Non-Specific Manifestations of Renal Injury Barbara Fazekas,[7] Ana D. Moreno,[6] Yvelynne P. Kelly,[1] Paul O'Hara,[3] Susan L. Murray,[4] Alan Kennedy,[6] Niall P. Conlon,[5] Dearbhaile Dooley,[8] Eóin O'Brien,[2] Sarah M. Moran,[4] Derek G. Doherty,[6] Mark A. Little.[6] *[1]Beaumont Hospital, Dublin 9, Co. Cork, Ireland; [2]St. James' Hospital, Dublin, Ireland; [3]HSE, Limerick, Ireland; [4]None, Dublin 8, Ireland; [5]St. James's Hospital, Dublin, Ireland; [6]Trinity College Dublin, Dublin, Ireland; [7]Trinity Health Kidney Centre, Trinity College Dublin, Dublin 8, Ireland; [8]Trinity Health Kidney Centre, Trinity College Dublin, Dublin, Ireland.*

Background: Innate lymphocyte populations, such as innate lymphoid cells (ILCs), γδ T cells, invariant natural killer T (iNKT) cells and mucosal associated invariant T (MAIT) cells are emerging as important effectors of innate immunity and are involved in various inflammatory and autoimmune diseases. The aim of this study was to assess the frequencies and absolute numbers of innate lymphocytes in peripheral blood from a cohort of ANCA associated vasculitis (AAV) patients.

Methods: Flow cytometry was used to enumerate circulating ILC subsets (ILC1, ILC2, ILC3, LTi), γδ T cell subsets (Vδ1, Vδ2, Vδ3), iNKT cells, MAIT cells, $CD4^+$, $CD8^+$ and $CD4^-CD8^-$ T cells, B cells, natural killer (NK) cells and monocytes in 29 AAV patients and 19 healthy and disease controls. Recruited patients with AAV were sampled both with and without immunosuppressive treatment, and in the setting of both active and remission disease.

Results: The frequencies of MAIT and ILC2 cells were significantly decreased in all disease groups, including the disease control group, compared to healthy controls. These reductions in the AAV patients remained during remission. B cell numbers and frequencies were significantly lower in AAV in remission compared to patients with active disease and disease controls. Despite the strong Th2 preponderance of eosinophilic granulomatosis with polyangiitis, we did not observe increased ILC2 frequency in this cohort of patients. The frequencies of other cell types were similar in all groups studied.

Conclusions: Reduction in circulating ILC2 and MAIT cells seen in patients with AAV are not specific for AAV, but are more likely to be due to non-specific manifestations of renal impairment and chronic illness. Reduction in B cells in remission AAV is almost certainly therapy related.

Funding: Government Support - Non-U.S.

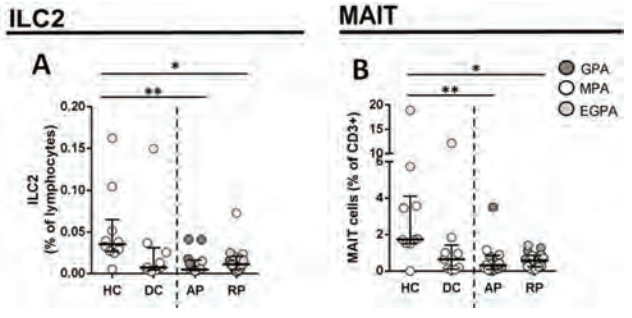


Figure 1. ILC2 and MAIT cells are persistently depleted in AAV patients and disease controls.

PUB436

Renal CD141+ Dendritic Cell Infiltration in Crescentic Glomerulonephritis in Humans and Mice Titi Chen,[6,7] Qi Cao,[1] Padmashree Rao,[5,3] Guoping Zheng,[4,7] Yiping Wang,[2] David C. Harris.[3,7] *[1]Centre for Transplant and Renal Research, Westmead Millennium Institute, University of Sydney, Sydney, NSW, Australia; [2]Centre for Transplantation and Renal Research, Westmead Millennium Institute, The University of Sydney, Westmead, NSW, NSW, Australia; [3]Sydney Medical School - University of Sydney, Terrey Hills, NSW, Australia; [4]The University of Sydney, Sydney, NSW, Australia; [5]Westmead Millenium Institute for Medical Research, Parramatta, NSW, Australia; [6]School of Medicine, University of Sydney, Westmead, NSW, Australia; [7]Centre for Transplant and Renal Research, Westmead Institute for Medical Research, Westmead, NSW, Australia.*

Background: CD141+ dendritic cells (DCs) have recently been identified as a unique myeloid DC subset that play a significant role in immune regulation. CD103+ DCs, their murine homologue, have been shown to play an important role in murine crescentic glomerulonephritis (GN). However, little is known about expression of CD141+ DC in human crescentic GN. We aim to investigate the relationship between CD141+ DC infiltration and clinicopathologic features in human crescentic GN, and to investigate possible underlying mechanisms of injury in a murine model.

Methods: Adult patients with a sole diagnosis of crescentic GN were enrolled in the study. Patients were excluded if they received immunosuppressant therapy before renal biopsy. Anti-GBM disease was induced in C57BL/6 mice by injection of sheep anti-mouse glomerular basement membrane serum. Mice were examined at week 1 and week 3.

Results: In normal human kidney, CD141+DCs were rarely present. However, the number significantly increased in patients with crescentic GN (P=0.021). Higher CD141+ DC density was associated with worse serum creatinine (P=0.029) and proteinuria (P=0.038). In contrast to previous studies, which showed myeloid DCs were mainly present in the interstitium, we also found a high number of CD141+ DCs in glomeruli. Similar to humans, we found CD103+ DCs constituted only 2% of total leucocytes in normal murine kidneys. In murine anti-GBM disease, the number and proportion of kidney CD103+ DCs was significantly increased (P=0.021), and CD103+ DCs were mainly present in the interstitium. We are examining pathological correlations and pathogenic mechanisms of CD 103+ DCs in this model.

Conclusions: Our data suggest that CD141+ DCs may play an important role in crescentic GN.

PUB437

Urinary Cytokines/Chemokines as Prognostic Markers in Crescentic Glomerulonephritis Patients Receiving Immunosuppressive Therapy Junseok Jeon,[1] Minjung Kim,[1] Do Hee Kim,[2] Jung eun Lee,[1] Wooseong Huh,[1] Dae Joong Kim,[1] Yoon-Goo Kim,[1] Ha Young Oh,[1] Hye Ryoun Jang.[1] *[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [2]Chungbuk National University College of Medicine, Cheongju, Republic of Korea.*

Background: Immunosuppressive therapy is considered to be the standard treatment for crescentic glomerulonephritis (CrGN). However, timely kidney biopsy and initiation of aggressive immunosuppressive therapy is not always feasible in cases such as very old age or serious comorbidities. In this study, we investigated the clinical usefulness of urinary cytokines / chemokines as non-invasive prognostic markers for predicting the treatment response in patients with CrGN.

Methods: A total of 87 patients with biopsy-proven CrGN from 2002 to 2015 were included. In 38 patients, both urine and serum samples were collected on the day of kidney biopsy. A panel of cytokines / chemokines were measured as follows: regulated on activation, normal T cell expressed and secreted (RANTES), fractalkine, interferon-γ, interleukin (IL)-4, IL-6, IL-10, monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-α (TNF-α), and vascular endothelial growth factor (VEGF). Urine cytokine / chemokine levels were adjusted with urinary creatinine levels. Baseline estimated glomerular filtration rate (eGFR), urinary protein to creatinine ratio (uPCR), and the proportion of non-albumin proteinuria were also analyzed in all patients. The primary outcome was uPCR and renal function at 1 year after kidney biopsy. Good response was defined as a decrease in proteinuria to < 50% without significant renal function deterioration. Mann Whitney U-test and logistic regression analysis were used as appropriate.

Results: The median age of patients was 65 years and 47% were male. Baseline eGFR was 18.7 ml/min/1.73m^2 and uPCR was 1.87 mg/mg Cr. The proportion of the good response group was 50%. In all patients, baseline eGFR was identified as a predictor of good response to immunosuppressive treatment. In 38 patients whose urinary and serum cytokines / chemokines were analyzed, baseline urinary RANTES (P = 0.016), fractalkine (P = 0.044), and MCP-1 (P = 0.041) levels were higher in the good response group

Conclusions: Our study demonstrated the importance of early initiation of immunosuppressive treatment before renal function deterioration in patients with CrGN for improving renal outcome. Urinary MCP-1, RANTES and fractalkine may be of prognostic value as non-invasive markers predicting treatment response.

PUB438

Cross-Reactivity of Neutralizing Anti-Rituximab Antibodies and New Anti-CD20 Monoclonal Antibodies: An Alternative Therapy in Primary Membranous Nephropathy? Sonia B. Boyer,[1] Sylvia Benzaken,[2] Ghislaine Bernard,[2] Vincent L. Esnault,[1] Barbara Seitz-Polski.[2,1] *[1]Nephrology, Nice University Hospital, Nice, France; [2]Immunology, Nice Univertsity Hospital, Nice, France.*

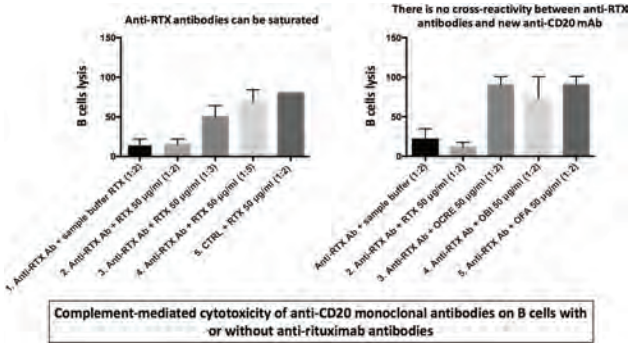
Background: Rituximab (RTX) is a murine / human chimeric monoclonal antibody (mAb) directed against CD20, a surface marker expressed on B cells (BC). RTX induced clinical remission in 60 to 80% of patients with primary membranous nephropathy (MN) in several non-randomized studies. However, mAb as RTX can elicit an unwanted antibody response in a substantial number of patients, resulting in a loss of efficacy of treatment. In MN, we showed that some patients develop neutralizing anti-RTX antibodies. We therefore investigated whether a cross-reactivity existed with new anti-CD20 mAb (humanized or fully human).

Methods: We studied complement-mediated cytotoxicity of anti-CD20 mAb on BC in the presence or absence of anti-RTX antibodies. Tested anti-CD20 mAb were: RTX with increasing concentrations, ocrelizumab (OCR) and obitunuzumab (OBI) (humanized anti-CD20 mAb), ofatumumab (OFA) (fully human anti-CD20 mAb).

Results: In presence of anti-RTX antibodies, RTX cytotoxicity is close to zero, demonstrating the neutralizing character of these antibodies. We observe a dose-response effect in RTX cytotoxicity, related to anti-RTX antibodies saturation. In the case of OCR, OBI and OFA, cytotoxicity is evaluated above 80-100% in the presence of anti-RTX antibodies. There is no neutralizing effect of anti-RTX antibodies on the three new anti-

CD20 mAb tested, even for low dose tested. Our work demonstrates the absence of cross-reactivity with three anti-CD20 mAb currently studied: OCR, OBI and OFA. Moreover, these third-generation mAb might be less immunogenic and less responsible for treatment resistance.

Conclusions: We find no cross-reactivity of anti-RTX antibodies with last-generation of anti-CD20 mAb. These humanized or fully human anti-CD20 mAb could be an alternative therapy to RTX in MN for patients with anti-RTX antibodies. Searching for neutralizing anti-RTX antibodies could also be extended to other autoimmune diseases.



Complement-mediated cytotoxicity of anti-CD20 monoclonal antibodies on B cells with or without anti-rituximab antibodies

PUB439

Zebrafish Embryos and ANCA-Associated Glomerulonephritis: Initial Steps towards a New Animal Model Malu Zandbergen, Hans J. Baelde, Jan A. Bruijn, Ingeborg M. Bajema. *Leiden University Medical Center, Dept. Pathology, Leiden, Netherlands.*

Background: The titre of Antineutrophil Cytoplasmic Autoantibodies (ANCAs) in the serum of patients with ANCA associated vasculitis (AAV) does not always correspond to clinical disease activity, although a pathogenic role for these antibodies has been described in several studies. Currently, there is no model available to predict the disease activity in patients with AAV. The zebrafish (*Danio rerio*) embryo model has been used successfully to study leukocyte migration and inflammatory processes *in vivo.* Here, we report our initial proceedings into investigating whether the zebrafish embryo model can be used to predict disease activity in patients with AAV.

Methods: Frozen sections of 4dpf zMPO:GFP transgenic zebrafish embryos were stained with polyclonal anti-human MPO antibody. 4dpf zMPO:GFP transgenic zebrafish embryos were injected with sera from AAV patients with high anti-MPO levels. Zebrafish embryos injected with sera from healthy controls and PBS served as controls. A local inflammation was induced 1 hour after injection by tail transection. At different time points, ~30 embryos were fixed and the number of zMPO:GFP cells responding to the site of injury was scored.

Results: The zebrafish myeloperoxidase (zMPO) and human MPO protein, one of the best-documented autoantigen targets of ANCA, share 76,5% similarity. However, there was no substantial binding detectable of conventional MPO-ANCA assays on zebrafish zMPO:GFP positive cells. An increased number of zMPO:GFP cells was observed at the site of injury from 2 to 6 hours after tail transection, however, there was no statistically significant difference over the groups (controls versus those injected with AAV serum).

Conclusions: Although we have been able to replicate in our zebrafish model previous findings of leucocyte migration to sites of injury, we have not been able to enhance this effect by injection of human AAV sera. We are currently focussing on leucocyte priming in parallel to previously described animal models of AAV where this was a major component for optimization of the model.

PUB440

Effects of Classical CKD Treatments and Quantification of Inflammatory Cell Infiltrates in the Nephrotoxic Nephritis Model Maria K. Ougaard,[1,2] Henrik Søndergaard,[1] Henrik E. Jensen,[2] Peter H. Kvist.[1] *[1]Novo Nordisk A/S, Måløv, Denmark; [2]University of Copenhagen, Frederiksberg, Denmark.*

Background: Renal inflammation is central in the pathogenesis of chronic kidney disease (CKD) and studies of renal inflammation and its treatment response might clarify the impact of the infiltrating cell types during disease development and could help improve therapy of CKD. The nephrotoxic nephritis (NTN) model is a model of CKD which could provide a robust inducible model where significant inflammation is associated with CKD. In this study, the inflammatory cell infiltration in the kidney in the NTN model was quantified over time and the effect of the ACE-inhibitor; enalapril and the angiotensin receptor blocker; losartan were evaluated.

Methods: NTN was induced by injecting CD1 female mice with 50 µl nephrotoxic serum containing anti-GBM sheep IgG on day 0, 1, and 2. Sheep IgG and inflammatory cell infiltrates (CD45+, CD3+, and F4/80+) were visualised by IHC on day 7, 42, 63, and 77 and quantified with Visiopharm software. In a 6 week study, enalapril (15, 30 mg/kg/day) and losartan (15, 30 mg/kg/day) were administrated via the drinking water from day -1, and their effect on CKD readouts was evaluated.

Results: In the NTN model a significant infiltration of CD45+, CD3+, and F4/80+ cells were present in the kidneys on day 7, 42, 63, and 77 compared to the controls. The CD3+ and F4/80+ cells comprised approximately 25% of the CD45+ cells indicating an infiltration also of other hemopoietic cells. The renal inflammatory cells were significantly reduced on day 63 and 77 compared to day 42 which was associated with a decrease of GBM-bound sheep IgG observed post day 42. Treatment with enalapril ($p<0.0001$) and losartan ($p<0.0001$) significantly reduced UAER on day 7-8 and 36-37 after NTN induction compared to the vehicle group, suggesting an important effect of the renin-angiotensin axis in preservation of protein-loss in the NTN model in the context of inflammation. Further analysis is currently ongoing to evaluate effects on mesangial expansion and the inflammatory response.

Conclusions: The NTN model of CKD shows significant inflammatory infiltration of CD3+, F4/80 and other hemopoietic cells which appear to follow the presence of GBM-bound IgG. Treatment with enalapril and losartan significantly reduced UAER, suggesting a key role of RAS-blockade in inflammation-associated CKD.

PUB441

The Presence and Function of Anti-Neutrophil Extracellular Trap Antibody in Patients with Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis Fumihiko Hattanda,[1] Kanako Watanabe,[1] Daigo Nakazawa,[1] Saori Nishio,[1] Tatsuya Atsumi,[1] Akihiro Ishizu.[2] *[1]Department of Rheumatology, Endocrinology and Nephrology Faculty of Medicine and Graduate School of Medicine Hokkaido University, Sapporo, Japan; [2]Faculty of Health Sciences, Hokkaido University, Sapporp-shi, Japan.*

Background: Although anti-neutrophil cytoplasm antibody (ANCA) is the major autoantibody in patients with ANCA-associated vasculitis (AAV), previous studies have suggested the presence of anti-neutrophil extracellular trap (NET) antibody in some AAV patients. However, the prevalence and function of anti-NET antibody in AAV patients remain elusive. The aim of this study is to determine the prevalence and function of anti-NET antibody in AAV patients.

Methods: We determined the presence or absence of anti-NET antibody in 11 AAV patients by indirect immunofluorescence, and assessed the relationship of anti-NET antibody with the serum abilities of NET induction and degradation.

Results: Anti-NET antibody was present in 6 out of 11 AAV patents. Since anti-NET antibody was not absorbed by myeloperoxidase (MPO), anti-NET antibody seemed to be distinct from MPO-ANCA. NET induction and degradation abilities were not different between the anti-NET antibody-positive sera and anti-NET antibody-negative sera. Although NET degradation ability in the sera without anti-NET antibody was significantly increased by addition of DNase I, the increase was not observed in some sera with anti-NET antibody. In addition, NET degradation ability in some sera with anti-NET antibody was markedly increased by depletion of IgG from the serum.

Conclusions: The collective findings demonstrate that a part of AAV patients produce anti-NET antibody and suggest that some of them possess the inhibitory function against DNase I.

PUB442

Tissue Resident Macrophage in the Kidney Kazunori Karasawa, Takahito Moriyama, Ken Tsuchiya, Kosaku Nitta, Keiko Uchida. *Tokyo Women's Medical University, Tokyo, Japan.*

Background: Tissue resident macrophages are subset of macrophages that are present at steady state. It is considered to be a heterogeneous population of immune cells having tissue-specific functions including Kupffer cells, Langerhans cells of the skin, and alveolar macrophages. In the kidney, we have several subsets of tissue resident macrophages, but their pathological roles are not fully understood. We are trying to reveal the role of novel subset macrophage in kidney.

Methods: Wild type mouse kidney was analyzed using immunohistochemical stainning and flowcytometer.

Results: Previously, we reported that the localization of $F4/80^+$ macrophage, $CD169^+$ macrophages, $CX3CR1^+$ macrophage, respectively, was clarified by immunohistochemical staining at steady state in kidney interstitium. Furthermore, we found that $CD206^+$ macrophages are localized in the mesangial region of glomeruli. To ensure that these $CD206^+$ macrophages are resident macrophages in the mesangial region, we co-stained with CD140b, which is a pericyte marker that lines blood vessels from the outside. Most of the $CD206^+$ macrophages co-localized with CD140b. From the staining results, we hypothesized that mesangial cells are heterogenous even at steady state. We decided to focus on CD206 and CD140b double positive resident macrophages in glomeruli. For further analysis, we isolated the glomeruli using Dynabeads and then analyzed using flowcytometer. Flowcytometry analysis with CD206 and CD140b antibody revealed that mesangial cells were distinguished into three fractions. However, expression of molecules characteristic of macrophages such as F4/80 and CD11b was not recognized in CD206 and CD140b double positive macrophages.

Conclusions: Our results suggest that mesangial cells are heterogenous even at steady state. CD206 and CD140b double positive cells in mesagial region may be a very specific tissue resident macrophage subset having the functions of macrophage and pericyte.

Funding: Government Support - Non-U.S.

PUB443

Timing the Effect of Rituximab on Peripheral CD 20+B cells: An In Vivo Experience Dario Roccatello,[1] Savino Sciascia,[2] Roberta Fenoglio.[1] *[1]Ospedale San GIovanni Bosco, Torino, Italy; [2]Center of Research of Immunopathology and Rare Diseases (CMID), Division of Clinical Immunology, Giovanni Bosco Hospital and University of Turin, Ita, Torino, Italy*.

Background: B-lymphocyte antigen CD20 is an activated-glycosylated phosphoprotein expressed on the surface of all B-cells starting at the pro-B phase and progressively increasing in concentration until maturity. CD20 is the target of the monoclonal antibodies (mAb) rituximab (RTX), which is an active agent in the treatment of many immuno-mediate diseases. RTX can induce killing of CD20+ cells through multiple mechanisms. RTX direct effects include complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity; the indirect effects include structural changes and apoptosis. In all disease states in which RTX has been given, there has been a rapid elimination of circulating B cells. However, the timing of the complete depletion of CD19/CD20+ after RTX administration is still unknown. In this study, we aimed to investigate in vivo the timing of the effect of rituximab on peripheral CD 20+B cells during the first infusion of RTX

Methods: We evaluated 8 pts during the first infusion of RTX at the dosage of 375 mg/m^2 or 1 gr. B-cell levels (CD19/CD20+cells) were measured by flow cytometry in peripheral bloodat various intervals after initiation of treatment (baseline, 10, 20, 60, and 180 minutes). The depletion was defined as a number of CD19/CD20+<10 cell/mm^3.

Results: White blood cells (n.v. 4000-9000 x 10^3) and lymphocytes counts were normal at baseline. B-cells expressing CD19/CD20+ were not detectable in the peripheral blood in any pts within 1 h after initial treatment with Rituximab; in 5 pts (62.5%) they were not detectable within 20 minutes. The complete depletion of CD19/CD20+ was confirmed in all pts after 180 minutes.

Conclusions: This is the first study investigating in vivo the timing of the effect of RTX on peripheral CD CD19/CD20+ B during RTX therapy. Of high interest, we observed a very rapid B-cells depletion during RTX administration. The association of peripheral CD CD19/CD20+ B depletion with tissue levels of still remain to be investigated.

PUB444

IRF5 Polymorphisms Do Not Predict Interferon Signature nor the Presence of Tubuloreticular Inclusions within the Glomerulus in Patients with Biopsy Proven Lupus Nephritis Romy C. Lawrence,[1] Britte C. Beaudette-Zlatanova,[1] Hanni Menn-Josephy,[3] Ramon G. Bonegio.[2] *[1]Boston Medical Center, Roxbury, Boston, MA; [2]Boston University School of Medicine, Boston, MA; [3]None, Newton, MA.*

Background: Several Interferon Regulatory Factor 5 (IRF5) polymorphisms have been shown to be associated with the development of autoimmune diseases including systemic lupus erythematous (SLE). The polymorphism rs77571059 is thought to be a gain of function variant and is reported to cause higher levels of IRF5 and type 1 interferons. Tubuloreticular inclusions (TRI) are distinctive intracellular structures found in the cytoplasm of endothelial cells and lymphocytes within the glomerulus. These structures are markers of systemic stimulation by interferons and their presence raise diagnostic suspicion for autoimmune disease or viral infections. We hypothesized that patients who are homozygous for the rs77571059 SLE risk polymorphism would have a higher rate of TRI within their glomeruli and this could serve as a predictor of their interferon signature and thus response to treatment with interferon inhibition.

Methods: The authors extracted DNA from 59 patients with SLE and amplified the rs77571059 polymorphism using PCR. This DNA was sequenced and patients were divided based on their genotyping results into those who are homozygous for the risk allele, homozygous for the protective allele, and heterozygous patients. The presence of TRI was recorded from previous renal biopsies and compared to patients within these 3 groups.

Results: The risk allele frequency in SLE patients was 39%. Patients with nephritis had a similar risk allele frequency (36%) to those without (40%). Seventy two percent of patients with nephritis had tubular reticular structures reported on biopsy. The genotype of the patients at the rs77571059 locus was not associated with the presence of TRI as similar rates of TRIs were found in patients who were homozygous for the SLE risk allele (100%), homozygous for the protective allele (71%) and heterozygous patients (67%).

Conclusions: TRI are common in the biopsies of lupus patients, occurring in about 72% of lupus patients. This is in keeping with the reported rate of high interferon signature within lupus patients. IRF5 variants may influence the level of type 1 interferon but do not predict the presence of TRI in the glomeruli. Therefore, we propose that IRF5 genotyping alone may not be sufficient to predict response to interferon inhibition.

PUB445

Abstract Withdrawn

PUB446

Butyrate Ameliorates CKD by Improving Gut Permeability and Inflammation Austin J. Gonzalez,[3] Siddhartha S. Ghosh,[2] Daniel E. Carl,[2] Richard Krieg,[1] Shobha Ghosh,[1] Todd W. Gehr.[3] *[1]VCU, Richmond, VA; [2]VCU Medical Ctr, Richmond, VA; [3]Virginia Commonwealth University, Fredericksburg, VA.*

Background: Changes in intestinal microbiota in CKD alters intestinal permeability. This change increases paracellular transport of inflammatory toxins such as lipopolysaccharide (LPS). LPS in the circulation leads to inflammation which aggravates CKD. Short chain fatty acids such as butyrate produced by colonic bacteria have anti-inflammatory properties and may correct intestinal permeability. We hypothesized that butyrate treatment in CKD animals can improve gut permeability and will alleviate renal failure.

Methods: 5/6 nephrectomy was done in ten Sprague dawley rats to induce CKD and divided into 2 groups, untreated (CKD) and butyrate treated (CKD+BU). Control were sham operated. Na Butyrate (250 mg/100ml) was given in drinking water for 6 weeks to BU. After 6 weeks animals were sacrificed. Plasma was used measure renal function, LPS, and TNF∝. Kidney and colon were collected for western blots for NFkB, IL-10, Colon was stained with alacian blue to determine mucin expression.

Results: Our results show that butyrate improves renal function, sclerosis and inflammation in CKD animals. Although butyrate improved tubular dilatation it was not significant.

Conclusions: Mucins protects the gut from bacteria and inflammation and is regulated by anti-inflammatory cytokine IL-10. We show that in CKD animals there is lowering of IL-10 and mucin production which results in loss of colonic tight-junction protein ZO1 leading to increased LPS in circulation and inflammation. Butyrate's modulation of biomolecules of colonic mucosa may contribute to its anti-inflammatory and reno-protective effect.

	Control	CKD	CKD+BU
Serum Urea (mg/dl)	34±4	121±23*	85±11#
Urinary protein/creatinine ratio (Fold Change)	1±0.02	1.74±0.2	1.12±0.2
%Segmental Sclerosis	-	35±4.1*	21.4±3.6 #
%Tubular Dilatation	-	18±3.6*	10.1±4.8
Mucin (Fold Change)	1.0±0.1	0.67±0.06*	0.89±0.09 #
IL-10 -Colon (Fold change)	1.0±0.15	0.48±0.07*	0.74±.09 #
ZO-1- Colon (Fold Change)	1.0+0.19	0.14±0.1*	0.49±.08#
Plasma LPS (EU /ml)	0.31±0.04	1.2±0.22*	0.77±0.15
Plasma TNFα (pg/ml)	52.6±7.7	194±20.1*	114.8±21.1#
NFkB- Kidney (Fold Change)	1.0±0.24	2.90.47*	1.6±0.33#

*P<0.05 compared to Control; #p<0.05 compared to CKD.

PUB447

Differential Effects of Acthar® Gel and Methylprednisolone in a Preclinical Rodent Model of FSGS Kyle Hayes, Elizabeth A. Warner, Chris Bollinger, Dale Wright, Richard M. Fitch. *Mallinckrodt Pharmaceuticals, Hazelwood, MO.*

Background: Repository corticotropin injection (RCI: H.P. Acthar® gel) contains a purified porcine pituitary ACTH-analogue, and is an FDA-approved treatment to induce remission of proteinuria in idiopathic nephrotic syndrome. The hypothesis that RCI (30IU/kg) treatment may be effective on progressive glomerulosclerosis was evaluated in a rat puromycin (PAN) induced model of FSGS. Effects of RCI or methylprednisolone (2mg/kg/day) on proteinuria, kidney histopathology, serum and urine biomarkers, were compared to treatment with placebo gel, saline or Enalapril (ACEi). RCI treatment was beneficial for expression of previously reported biomarkers of podocyte injury, podoplanin (Pdpn) and Wilms tumor-1 (Wt1), as determined by IHC and quantitative image analysis. A certified pathology read demonstrated treatment with RCI notably decreased renal fibrosis, tubular degeneration, and glomerular injury, compared to saline controls and steroid treatment (Severity Score= 0-5, Mean +/- SD).

Methods:

Results:

Conclusions: Compared to saline, RCI significantly reduced overall proteinuria and serum creatinine at all time-points, at day-28 ($p< 0.05$). In addition, RCI reduced serum creatinine ($p<0.05$, day-28), cholesterol ($p< 0.05$, day-28 and 56), and urine kidney injury molecule (Kim-1) ($p< 0.05$, day-28). In contrast, treatment with methylprednisolone resulted in overall increased proteinuria, serum creatinine, serum cholesterol and triglycerides, compared to saline. Methylprednisolone treatment had no effect on disease induced tubular injury, and resulted in increases in renal fibrosis and glomerular injury, as determined by the pathologist. In this rat model of FSGS, RCI suppressed disease endpoints compared to saline, while treatment with methylprednisolone was associated with increased disease severity, biomarkers, and progression.

Funding: Commercial Support - Mallinckrodt Pharmaceuticals

Histology Scoring Summary	Fibrosis	Interstitial Inflammation	Tubular Injury	Glomerular Changes
Saline	2.3 +/- 0.2	1.4 +/- 0.2	2.6 +/- 0.2	2.5 +/- 0.3
Placebo Gel	2.3 +/- 0.3	1.6 +/- 0.2	2.0 +/- 0.2	2.5 +/- 0.3
RCI	1.6 +/- 0.2	1.0 +/- 0.0	1.5 +/- 0.2	1.8 +/- 0.2
Enalapril	2.1 +/- 0.2	1.6 +/- 0.2	1.6 +/- 0.2	1.8 +/- 0.3
MethylPred	2.9 +/- 0.3	1.3 +/- 0.2	2.8 +/- 0.3	3.3 +/- 0.3

PUB448

Activation of Mineralocorticoid Receptor by the Adaptogenic Ecdysteroids Promotes Glomerular Injury Minglei Lu,[1,2] Zhangsuo Liu,[1] Rujun Gong.[2] *[1]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [2]Brown Medical School, Providence, RI.*

Background: Anabolic steroids are commonly used by bodybuilders to achieve impressive muscular physiques. Among these, ecdysteroids, represented by ecdysone, are insect molting hormones and have been marked as natural anabolic agents and popularly used as adaptogenic dietary supplements. However, ecdysone is likely problematic for health as indicated by occasional case reports associating its use with disorders manifested as proteinuria or renal impairment. The renal effect of ecdysone and related mechanisms were examined here.

Methods: The renal effect of ecdysone was examined *in vivo and in vitro*. *In-silico* modeling system was applied to screen proteins with the highest probability of interacting with ecdysone.

Results: In mice, daily treatment with ecdysone for 2 weeks incurred an increasingly elevated albuminuria, associated with glomerular injury, marked by glomerular cell apoptosis, mesangial expansion, podocyte injury featured by a variable degree of foot process effacement on electron microscopy, diminished glomerular expression of podocyte marker proteins like podocin and synaptopodin, and augmented expression of desmin. This pathogenic effect was likely due to an autonomous glomerular injury, because addition of ecdysone to cultured glomerular cells caused substantial cytopathic changes, including cellular hypertrophy, increased apoptosis, lessened expression of podocyte differentiation proteins like WT-1, and activation of mesangial cells as evidenced by increased expression of α-smooth muscle actin and extracellular matrix. To explore the molecular target of ecdysone, *in-silico* modeling system of compound–protein interaction was carried out and identified mineralocorticoid receptor (MR) as one of the top-ranking proteins with putative interactions with ecdysone. In consistency, the molecular structure of ecdysone was found to be highly homologous to mineralocorticoids, like aldosterone. Indeed, ecdysone was capable of activating MR, as probed by MR nuclear translocation in glomerular podocytes and mesangial cells both *in vitro* and *in vivo*. Conversely, spironolactone, a selective blockade of MR, largely abolished the cytopathic effect of ecdysone in glomerular cells *in vitro* and attenuated albuminuria and glomerular lesions in ecdysone-treated mice.

Conclusions: The adaptogenic ecdysone is able to activate MR and thereby promote glomerular injury and proteinuria.

PUB449

Is Histone Deacetylases 2 Associated with Steroid Resistance in Childhood Nephrotic Syndrome? Narayan Prasad,[1] Harshit Singh,[1] Vikas Agarwal,[3] Saurabh Chaturvedi,[3] Akhilesh Jaiswal.[2] *[1]NEPHROLOGY, SGPGIMS, Lucknow, India; [2]Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India; [3]CLINICAL IMMUNOLOGY, SGPGIMS, LUCKNOW, India.*

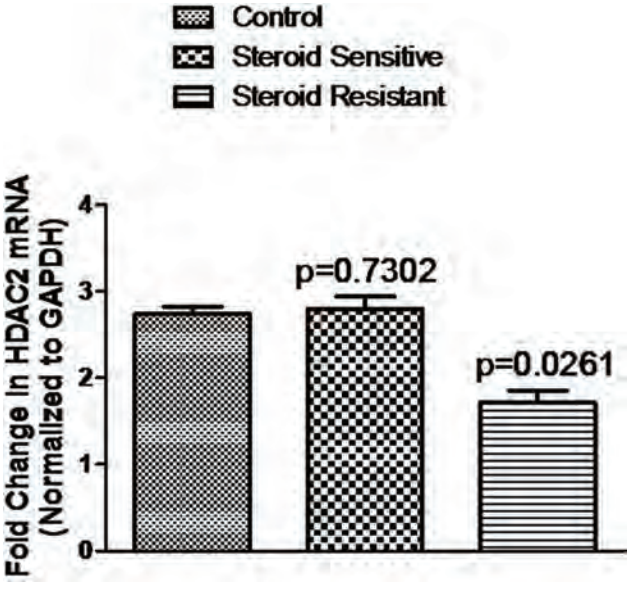
Background: Glucocorticoids (GCs) are first line therapy for Nephrotic Syndome(NS). The activated glucocorticoid receptors interact with co-repressor molecules to impair NFκB-associated coactivator activity, which reduces histone acetylation. Reduction in histone acetylation occurs through recruitment of histone deacetylase HDAC 2 to activated inflammatory gene complex by activated glucocorticoid receptor, resulting in suppression of activated inflammatory genes within the nucleus. Epigenetic phenomenon may be associated with steroid response. We hypothesize that reduction in HDAC2 may lead to steroid resistance.

Methods: Immunohistochemical HDAC-2 expression was analyzed on renal biopsy samples in SRNS patients (n=15, M=9, mean age 8.4±2.59), and healthy control (n=6, M=3, mean age 12.14± 5.26). Controls were biopsy proven Nephrectomy samples. Remission (SSNS) (n=25, M=15, mean age 9.85±3.08) for at least 6 months without steroid were recruited. All definitions are as per the criteria of International Study of Kidney Diseases in Childhood. RNA was isolated from Peripheral blood mononuclear cells (PBMCs) using trizol method. Real time quantitative PCR was performed using SYBR green.

Results: S.Albumin (SSNS=2.87±.98, SRNS=2.27±.79, p=0.012) was lower and proteinuria (SSNS=13.18±3.09, SRNS=284±193.45, p<0.001) was higher in SRNS as compared to SSNS. HDAC2 nuclear expression was significantly lower in SRNS group as compared to control and steroid dependent group(86.67%), (p=0.002). HDAC2 mRNA expression was also significantly lower in SRNS- fig.1.

Conclusions: Lower HDAC2 nuclear and gene expression is associated within steroid resistance in NS. The inducers of HDAC 2 may lead to restoration of glucocorticoid response and prevent GCs resistance.

Funding: Government Support - Non-U.S.



PUB450

Endostatin Concentration in Mice with Advanced Glomerulonephritis Phenotype Measured with a Specific and Robust ELISA Jacqueline Wallwitz,[2] Gabriela Berg,[3] Dagmar Stoiber.[1] *[1]Ludwig Boltzmann Institute of Cancer Research, Vienna, Austria; [2]The Antibody Lab GmbH, Vienna, Austria; [3]Biomedica, Vienna, Austria.*

Background: Endostatin is a 20 kDa protein produced by proteolytic cleavage of collagen XVIII. It is one of the most potent endothelial cell-specific inhibitors of angiogenesis with influence on proliferation, migration and apoptosis. Vav-BCL2 transgenic mice (BCL2tg) are prone to suffer from follicular lymphoma with age and can develop kidney disease, i.e. glomerulonephritis. A synergism between the ETV6/RUNX1 fusion product and BCL2 was identified by intercrossing single transgenic mice for BCL2 and ETV6/RUNX1.

Methods: We developed an immunoassay for the detection of mouse and rat endostatin. The assay was validated according to ICH and EMEA guidelines. Serum concentration of endostatin and also blood urea nitrogen as an established kidney marker were measured in mouse samples with impaired kidney function caused by glomerulonephritis.

Results: The novel endostatin ELISA is optimized for 1 µl mouse serum or plasma and all validation parameters like specificity (>98%), precision (<10% CV), dilution linearity (88-109%), accuracy (91-97%), sample stability, LOD (0.24 nmol/l) and LLOQ (0.5 nmol/l) meet the quality standards. The glomerulonephritis phenotype of ETV6/RUNX1 and BCL2 transgenic mice is accompanied with higher endostatin serum concentration, which seem to better reflect progression of impaired kidney function than the established kidney biomarker BUN.

Conclusions: Detection of endostatin with a reliable and accurate ELISA may give new perspectives within the biomarker research in the field of kidney disease progression.

PUB451

Transcutaneous Measurement of Glomerular Filtration Rate in a Mouse Model of Diabetic Kidney Disease Asim B. Dey, Leah L. Porras, Shannon M. Harlan, Josef G. Heuer, Mark Kowala, Matthew D. Breyer, Mark Rekhter. *Eli Lilly and Company, Indianapolis, IN.*

Background: ReninAAV treated unilaterally nephrectomized (uNx) *db/db* mice is a novel model of progressive diabetic kidney disease (Abstract MP16: SM Harlan, AHA 2015). It features major risk factors: type 2 diabetes (db/db mice), nephron loss (uni-nephrectomy) and arterial hypertension (over-expression of human renin delivered by adeno-associated virus). The model is characterized by proteinuria, increased serum creatinine and renal pathology reminiscent of human DKD. In addition, previous characterization has also demonstrated reduced glomerular filtration rate (GFR) by analysis of FITC inulin clearance. In this study, we applied novel non-invasive technology to analyze longitudinal changes of GFR in this model.

Methods: 20 week-old, unilaterally nephrectomized female db/db mice received single retro-orbital injection of AAV-Renin or LacZ (mock-transfection). The animals were randomized to two groups: vehicle and Lisinopril (30mg/L) in the drinking water. GFR was analyzed every two weeks. The mice were injected FITC-sinistrin (a polysaccharide exclusively eliminated through the kidneys). Plasma disappearance curve, reflecting glomerular filtration, was measured by a skin-mounted detector (Medibeacon).

Results: Significant hyperfiltration (31%) has been observed in db/db uninephrectomized mice compared to the age-matched lean animals. While lacZ injected mice continued hyperfiltering, GFR was decreased by 22% in hypertensive (renin-overexpressing) animals. Progressive GFR decline was accompanied by proteinuria and

increase in serum creatinine. After 4 weeks of drug treatment, Lisinopril significantly reduced proteinuria and serum creatinine and inhibited GFR decline.

Conclusions: Novel method of GFR analysis can be used for animal model characterization and analysis of pharmacological treatment.

Funding: Commercial Support - Eli Lilly and Co

PUB452

Renal Thrombotic Microangiopathy in Rat Models after Bone Marrow Transplantation and Irradiation Sae Aratani,[3,1] Takafumi Kanemitsu,[2] Shinya Nagasaka,[1] Shuichi Tsuruoka,[3] Akira Shimizu.[1] *[1]Analytic Human Pathology, Nippion Medical School, Tokyo, Japan; [2]University of Tokyo, Bunkyo-ku, Japan; [3]Nephrology, Nippon Medical School Hospital, Tokyo, Japan.*

Background: Thrombotic microangiopathy (TMA) is a renal complication after allogenic hematopoietic stem cell transplantation. We previously established a rat model of renal TMA after bone marrow transplantation (BMT), and concluded that chronic graft versus host disease could induce renal TMA. However, the influence of irradiation on the development of TMA has not been fully evaluated. In this study, we used radiation nephropathy model to investigate the role of irradiation in developing TMA, and compared the clinical and pathological characteristics to renal TMA after BMT.

Methods: According to the previous methods, TMA after BMT was induced in DA rats. In brief, bone marrow cells ($6x10^{-7}$ cells) from Lewis rats were transplanted to DA rats, which received 10 Gy of whole body irradiation before BMT. Radiation nephropathy was induced in DA rats by irradiation of 10 Gy (low dose irradiation) or 18-20 Gy (high dose irradiation) with shielding of hind legs and sternal bone by lead block. The clinical and pathological findings were examined at 36 weeks after BMT or irradiation.

Results: In rat with BMT, pathological renal TMA was observed, as previously reported. On the contrary, rat with high dose irradiation (18-20 Gy), but not low dose (10 Gy), developed proteinuria, hematuria, and increased serum Cr level. Hemolytic anemia and hypertension were not evident. Pathological findings revealed diffuse endothelial cell injuries, including swollen endothelial cells with loss of fenestra and diffuse double contour of glomerular basement membrane (GBM) with widening subendothelial spaces. The pathological findings were most consistent with renal TMA. Notably, these clinical and pathological characteristics observed in high dose irradiation were quite similar to those seen in renal TMA after BMT. In high dose irradiation, loss of capillaries was seen concomitant with podocyte injury which was indicated by positive stain for Desmin.

Conclusions: High dose irradiation could cause renal TMA with proteinuria, hematuria, and renal dysfunction, but without hemolytic anemia and hypertension, as similar as TMA after BMT. However, low dose irradiation (10 Gy) alone, which was used in BMT, did not contribute to the development of renal TMA. Irradiation might induce a direct endothelial injury, developing pathological renal TMA.

PUB453

Glomerular Volume Does Not Increase with Age after Accounting for Comorbidities Aleksandar Denic, Jerry Mathew, Mariam P. Alexander, R. houston Thompson, Bradley Leibovich, Walter K. Kremers, John C. Lieske, Lilach O. Lerman, Andrew D. Rule. *Mayo Clinic, Rochester, MN.*

Background: A stipulation that glomerular volume increases with aging has been largely based on studies that included patients with comorbidities. Conversely, we and others have observed no change in glomerular volume with aging among healthy living kidney donors. We hypothesized that an increased prevalence of comorbidities with age may account for this discrepancy.

Methods: We studied biopsies from living kidney donors (n=2054) and patients who underwent a radical nephrectomy for a renal tumor (n=749). Periodic acid-Schiff stained kidney biopsy sections were scanned into high-resolution images. Non-sclerotic glomeruli (NSG) profiles were manually traced and mean NSG volume calculated using the Weibel-Gomez stereological formula. NSG volume was regressed on age and comorbidities known to affect glomerular volume.

Results: Compared to donors, nephrectomy patients were older, more male, obese, diabetic, hypertensive, and had a 12% larger NSG. In both populations male gender, obesity, taller height, and hypertension were associated with larger NSG. In the combined dataset, independent predictors of larger NSG were male sex, obesity, diabetes, and hypertension. After adjusting for comorbidities, the NSG volume did not significantly differ between donors and tumor nephrectomy patients and instead of increasing with age trended towards decreasing with age (**Table**).

Conclusions: Older age alone is not an independent determinant of increasing glomerular volume, while several comorbidities increase it. A decrease in metabolic demand for glomerular function with age may explain the lack of compensatory increase in glomerular volume with age-related nephron loss.

Funding: NIDDK Support

Characteristics associated with NSG volume

Characteristic	Unadjusted		Adjusted for each other characteristic	
	% Change	P Value	% Change	P Value
Age per 10 years	1.4%	0.006	-1.5%	0.06
Male sex	19.1%	<0.001	10.5%	<0.001
Height per SD	7.6%	<0.001	2.0%	0.08
BMI per SD	11.4%	<0.001	9.0%	<0.001
Hypertension	15.2%	<0.001	4.9%	0.04
Diabetes	32.8%	<0.001	15.7%	0.001
eGFR per SD	-3.0%	0.0001	0.7%	0.52
24hr Urine Protein per Doubling	3.0%	<0.0001	1.1%	0.11
Tumor Size per Doubling	1.7%	<0.0001	1.2%	0.12
Nephrectomy Pts. compared to Donors	12.1%	<0.0001	-7.0%	0.19

PUB454

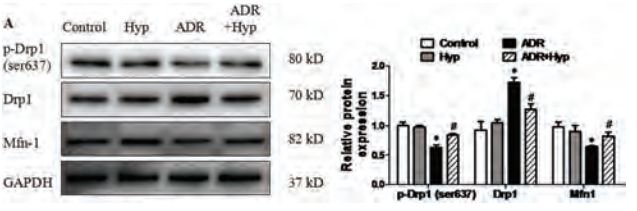
The Protective Role of Hyperoside in Adriamycin-Induced Nephropathy in Mice Chang Ying Xing,[2] Zhuyun Chen.[1] *[1]First Affiliated Hospital of Nanjing Medical University, Nanjing, China; [2]Department of Nephrology, First Affiliated Hospital of Nanjing Medical University, Nanjing, China.*

Background: Hyperoside (HYP) is a major active flavonoid glycoside extracting from *Abelmoschus manihot (L.) Medik.* which is a traditional Chinese medicine. Hyperoside has various effects on several diseases, like antidiabetic, antioxidant, anti-inflammatory, anticancer and anticoagulant. In vivo and vitro study showed that HYP can reduce myocardial cell ischemia-reperfusion injury through decrease reactive oxygen species (ROS) and improve the activity of antioxidant enzymes. The balance of mitochondrial fission/fusion is very important. Unbalanced fission or fusion led to mitochondria injury. Mitochondrial fission usually observed at the early stage of mito MtD. We assume that HYP has protective effect to podocyte through inhibiting mitochondrial fission and dysfunction.

Methods: Balb/c mice(22-28g,aged 8 weeks) were randomly divided into 4 groups: Control group, HYP group, ADR group and ADR+HYP group. ADR group and ADR+HYP group were injected with 10 mg/kg of Adriamycin through tail vein at day 0. HYP group and ADR+HYP group were treated by hyperoside by intraperitoneal injection for 14 days. Urine were collected by metabolic cage at day 14 after the injection of adriamycin. All mice were sacrificed on day 15 after the injection. Drp1 expression was detected by western blot and real-time PCR and located by laser scanning confocal microscopy. Other proteins were measured by western blot.

Results: ADR increased mice urine microalbumin and decreased the expression of nephrin and podocin. Glomerular sclerosis and protein casts were markedly increased under light microscopy. As observed via transmission electron microscope(TEM) foot process effacement was extensive. Drp1 expression was increased and Mfn-1 was decreased on the contrary. Hyperoside treatment can reverse part of kidney injury. The expression of podocyte markers like nephrin and podocin were increased compared with ADR group. And Drp1 decreased, Mfn-1increased(Fig A). Drp1 fluorescence was collocated with Synapotodin, and markedly increased in ADR group. After treatment of hyperoside the fluorescence was reduced.

Conclusions: ADR causes mice podocyte injury and increased mitochondrial fission. The injury can be reversed by hyperoside.



PUB455

Optimizing Experimental Animal Models of Nephrotic Syndrome Jiro Kino,[1] Melinda A. Chanley,[1] William E. Smoyer,[1,2] Shipra Agrawal.[1,2] *[1]CCTR, The Research Institute at Nationwide Children's Hospital, Columbus, OH; [2]Pediatrics, The Ohio State University, Columbus, OH.*

Background: Puromycin aminonucleoside (PAN)- induced nephropathy has become the animal model of choice for minimal change nephrotic syndrome, due to its hallmarks of podocyte flattening and nephrotic-range proteinuria. However, there is no standard way to use this model and it exhibits many inherent variabilities leading to wide-ranging results. The aim of this study was to optimize PAN utilization with respect to species, strain, dosage, administration and treatment response.

Methods: Wistar and Sprague Dawley (SD) rats were injected with PAN (i.v.; tail vein) in saline at 0, 50, 75 and 100 mg/kg (N=3-15/group). Wistar rats were additionally injected with PAN (i.p.) at 0, 75, 100 and 150 mg/kg. Steroid efficacy was measured in PAN- injected (i.v. and i.p.) Wistar rats by treating them with glucocorticoids (GC) (15 mg/kg/d i.p.). Proteinuria (spot urine protein/creatinine ratio) was measured at baseline and days 7 and 11 by Antech (GLP lab). Additionally, sv129 mice were injected with vehicle, 150 mg/kg PAN (i.v.) alone or in combination with albumin overload (400mg/day, i.p.) for 4 days and proteinuria analyzed till day 5.

Results: Comparable proteinuria was induced in both SD (Day11;UPC=39.7±5.5mg/mg,$P<0.01$) and Wistar (Day11;UPC=56.3±10.5mg/mg,$P<0.01$) rats with a single dose

of PAN (i.v.) at 75 mg/kg. Proteinuria varied in range but increased with PAN dosing i.v. [50, 75 and 100 mg/kg; UPC=28.0±9.0, 56.3±10.5 and 101.0±11.2mg/mg, respectively] as well as i.p from 75 to 100 mg/kg (UPC=14.6±10.2, 83.4±16.9mg/mg) which plateaued at 150 mg/kg (UPC=73.3±35.7mg/mg) in Wistar rats. Notably, higher i.p. doses produced similar result as lower i.v. doses (i.v. 75mg/kg vs i.p. 100mg/kg,*P*=0.13). Moreover, GC treatment reduced proteinuria significantly in i.v. PAN at 50 and 75 mg/kg (74%,*P*<0.01 and 78%,*P*<0.01 respectively), moderately in i.p. PAN at 75 mg/kg (75%,*P*=NS), but significantly in i.p. PAN at 100 mg/kg (70%,*P*=0.04). Additionally, PAN injection + albumin overload resulted in massive proteinuria in PAN-resistant mice.

Conclusions: Strain differences play a minimal role in PAN sensitivity in rats. Moreover, although i.v. PAN injection leads to a wider range of proteinuria, it is more responsive to GC than i.p. PAN. Finally, PAN resistant mice can be made susceptible by a second insult with albumin overload which may create useful models to study genetic deletions.

Funding: NIDDK Support

PUB456

The Inhibition of D-Site Binding Protein (DBP) Contributes to the Proliferation of Mesangial Cells in Experimental Anti-Thy1 Glomerulonephritis

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Background: Mesangial proliferative glomerulonephritis (MsPGN) is one of the most common glomerular diseases worldwide. It is characterized by mesangial cell proliferation accompanied by ECM expansion. Anti-Thy1 antibody-induced glomerulonephritis is a classical experimental model of MesGN. Our previous study demonstrated that D-site binding protein (DBP) was involved in the inflammatory response at the early stage of the anti-Thy1 nephritis. However, the role of DBP on the proliferation of mesangial cells (MCs) remains unclear.

Methods: 8-week old SD rats were injected with anti-Thy1 antibody (2.5 mg/kg body weight) though tail venous to induce anti-Thy1 nephritis. The rats in negative control (NC) group were received PBS injection. Specimens of the NC group were collected at 0d after the injection, while those of other groups were collected at 7d and 14d after the injection, respectively. Renal cortex slices were obtained for histological and immunohistochemistry assessment. Glomeruli were isolated by the differential-sieving method. The expression of DBP in tissues was detected by Westen blotting. In vitro study, RMCs with DBP overexpression and DBP knockdown were conducted by DBP plasmid and siRNA transfection, respectively. Cell cycles were examined by flow cytometry. Westernblotting were used for detecting the expression of DBP, p27, p21 and Cyclin D1.

Results: In the anti-Thy 1 nephritis, mesangial proliferation and ECM accumulation peaked at 7d and decreased subsequently at 14d after anti-Thy1 antibody injection. The positive rates of PCNA in glomerulus were also significant rised at 7d and then decreased 14d. Compared with NC group, the expression of DBP at 7d in glomerulus was significantly reduced at 7d and then increased at 14d. Flow cytometry results demonstrated that the knockdown of DBP promoted G0/G1-G2/S transition in RMCs, whereas, the overexpression of DBP arrested cell cycle at G0/G1 phase. Furthermore, we found the knockdown of DBP reduced the expression of p27 and p21,and increased the expression of Cyclin D1. The complete contrary results were observed in the DBP-overexpressed RMCs.

Conclusions: DBP has an effect on the G1 phase to G2/S phase transition in RMCs though regulating the expression of p27, p21 and Cyclin D1, and finally affects the proliferation of RMCs.

PUB457

Endothelial Cell Injury Plays an Important Role in the Mechanism Developing Nephrotic Syndrome in Proliferative Lupus Nephritis: Immunohistochemical and Messenger RNA Analysis

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Background: Nephrotic syndrome (NS) is a major feature of lupus nephritis (LN) and reflects podocyte injury. Although slit diaphgram protein molecules are important for the integrity of the filtration barrier in NS, these studies in lupus nephritis are lacking. The aim of our study is to clarify whether the damage of podocyte or slit diaphragm protein molecules or endothelial cell injury plays a central role in developing nephrotic syndrome in proliferative LN (lupus III/IV) and membranous LN (lupus V).

Methods: Sixty-six patients with nephrotic syndrome including minimal change nephrotic syndrome (MCNS), primary membranous nephropathy (PMN), lupus III/IV and lupus V were enrolled in the study. Glomerular expression of podocyte or slit diaphragm molecules including Wilms tumor protein 1 (WT1), nephrin, synaptopodin and podocalyxin was evaluated in renal tissue by immunohistochemistry (IHC) and quantitative RT-PCR. Endothelial cell injury was evaluated by electron microscopy (EM) and CD31-immunostaining. In EM study, the number of capillary loop which shows subendothelial space enlargement was counted.

Results: WT1, nephrin and synaptopodin expression were reduced in PMN, lupus III/IV and lupus V by IHC and mRNA analysis. Podocalyxin expression was reduced in MCNS, lupus III/IV and lupus V. CD31-expression was significantly reduced alone in lupus III/IV. The percentage of endothelial cell injury with subendothelial space enlargement was significantly higher in lupus III/IV group than lupus V group on EM. Foot process effacement was found only along the glomerular loop showing endothelial cell injury in lupus III/IV.

Conclusions: Our results first demonstrate that endothelial cell injury plays a pivotal role in nephrotic syndrome of lupus III/IV. In lupus V, reduction of slit membrane protein molecules of synaptopodin, nephrin and podocalyxin may be associated with developing nephrotic syndrome.

PUB458

Effect of Long-Term Rapamycin Treatment on Kidney Parameters in Mice

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Background: Podocyte depletion causes glomerulosclerosis. Age-associated glomerulosclerosis in humans is also associated with decreasing podocyte density caused by glomerular volume increase and podocyte number reduction (Hodgin, Bitzer et al JASN 2015). Rapamycin (RAPA), like calorie intake reduction, extends lifespan in nematodes and mice and slows the rate of glomerular hypertrophy in rodent models. We therefore evaluated kidney and glomerular parameters in a large cohort of mice (n=152) aged to >22 months to compare the effects of rapamycin and calorie restriction initiated at 4 months.

Methods: A four-way cross of genetically heterogeneous mice (UM-HET3) was used to reduce impact of strain-specific characteristics on outcome. Treatments included ad-libitum fed (ad-lib), rapamycin-treated (RAPA), and caloric restricted (CR) (PMID27923560). A pilot cohort of 5 male mice per group was assessed. 50 randomly selected glomeruli were analyzed per mouse using FFPE tissue sections stained with PAS and WT1 IHC, computer-assisted image analysis was used to estimate glomerular volume and podocyte density.

Results: Kidney to body weight ratio is highly preserved in nature and remains so in this study (n=152, r=.54, p<0.0001) with the notable exception of the RAPA-treated cohort where this relationship was lost (n=21, r=-.09, p=0.69). During aging the rate of body weight gain of ad-lib and RAPA groups were not different, although both were greater than the CR group (p<0.01). In parallel, ad-lib and RAPA groups had significantly increased kidney weight compared to the CR group (P=0.01). Glomerular volume correlated with kidney weight (p=0.002, r=.65) and was highest in RAPA-treated mice and statistically increased in both ad-lib and RAPA groups compared with the CR group (P<0.05). As a result of the RAPA-associated glomerular volume increase this group also showed a significantly lower podocyte density compared to either ad-lib (p=0.02) or CR (p=0.008) groups.

Conclusions: Reduction in podocyte density during aging is predicted to be associated with increased prevalence of glomerulosclerosis. Therefore, the observation that glomerular volume is increased in association with long term rapamycin treatment in adult mice raises a question about the potential use of rapamycin to prevent aging in humans. Additional quantitative morphometric and transcriptomic studies are planned.

Funding: Veterans Affairs Support

PUB459

Nicotine Induces Podocyte Apoptosis through Increasing Mitochondrial Pro-Apoptotic Proteins

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Background: Cigarette smoking is considered to be the most important cause of preventable mortality in many developed countries, including the United States. It is also an independent risk factor for chronic kidney disease (CKD) including diabetic nephropathy (DN). Nicotine, one of the highly active compounds in cigarette smoke, is required for smoking-accelerated CKD. Our previous studies have confirmed that nicotine causes podocyte apoptosis; however, the underlying detailed molecular mechanisms are still poorly understood. In this study, we examined the effect of nicotine on mitochondrial pro-apoptotic proteins.

Methods: We cultured human podocytes in both normal (5mM) and high glucose (25 mM) medium, and then treated them with nicotine at different concentrations (0.1, 1, and 10 μM). Occurrence of cell apoptosis was determined with morphologic assays (condensed and fragmented nucleus), and the expression of mitochondrial pro-apoptotic proteins was determined with real-time PCR and Western blotting.

Results: Nicotine significantly induced podocyte apoptosis in a dose-dependent manner in both normal and high glucose milieus. It also increased the expression of mitochondrial pro-apoptotic molecules such as Bax, Bim, and Nox4, at both RNA and protein levels.

Conclusions: Nicotine may induce podocyte apoptosis through enhancing the expression of pro-apoptotic proteins in mitochondria. The present study provides insight for further studies on the molecular mechanisms involved in smoking associated progression of chronic kidney disease.

PUB460

Role of SMPDL3b in Sphingolipid Biosynthesis and in Glomerular Diseases Shamroop Kumar Mallela,[1] Alla Mitrofanova,[1] Eden Rosenfeld-Gur,[2] Tony Futerman,[2] Alessia Fornoni.[1] *[1]Katz Family Division of Nephrology and Hypertension, University of Miami Miller school of medicine, Miami, FL; [2]Weizmann Institute of Science, Rehovot, Israel.*

Background: Research suggests an important role of sphingolipids in the pathogenesis of kidney diseases. We demonstrated that decreased Sphingomyelinase phosphodiesterase like 3b (SMPDL3b) expression in post reperfusion kidney biopsies from patients with focal segmental glomerulosclerosis (FSGS) predicted recurrence of nephrotic range proteinuria suggesting that SMPDL3b may be a susceptibility factor contributing to the pathogenesis of FSGS. Others have shown that in macrophages, SMPDL3b is a glycosylphosphatidylinositol (GPI) anchored protein that is localized to lipid rafts and affects ceramide species composition of the plasma membrane thus regulating the inflammatory response. However, if SMPDL3b affects the ceramide species composition of the plasma membrane in podocytes thus contributing to podocyte injury remains to be established. Sphingolipids have various cellular functions. Ceramide and sphingosine can induce cell cycle arrest and promote apoptosis whereas ceramide-1-phosphate (C1P) and sphingosine-1-phosphate (S1P) promote cell survival and proliferation. Similarly to SMPDL3b, C1P was also shown to regulate inflammatory processes. We have generated preliminary data supporting the fact that SMPDL3b expression in podocytes regulates C1P levels, an observation that led us to test the hypothesis that SMPDL3b regulates C1P levels by directly dephosphorylating C1P or by inhibiting the activity of ceramide kinase (CERK).

Methods: Mass spectrometry analysis of lipids was performed. Phosphatase activity of SMPDL3b was determined *in vitro*. Co- and endogenous immunoprecipitation experiments were used to investigate a potential interaction of CERK and SMPDL3b.

Results: We observed an increase in C1P levels in siSMP podocytes when compared to SMPDL3b overexpressing podocytes. We show that CERK and SMPDL3b interact in transfected HEK293 cells and in glomeruli isolated from mice. Finally, we demonstrate that SMPDL3B can dephosphorylate C1P *in vitro*.

Conclusions: Our results identify an important role of SMPDL3b in regulating podocyte C1P levels. Further experiments to understand the exact mechanism by which SMPDL3b controls C1P levels in podocytes are underway.

Funding: Other NIH Support - DK090316, DK104753, U24DK076169, U54DK083912, UM1DK100846 and 1UL1TR000460

PUB461

A High Degree of Sulfation of Heparin Triggers Differentiation of Cultured Podocytes Eishin Yaoita,[1] Yutaka Yoshida,[2] Hiroki Takimoto.[1] *[1]Department of Structural Pathology, Kidney Research Center, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan; [2]Institute for Research Promotion, Niigata University, Niigata, Japan.*

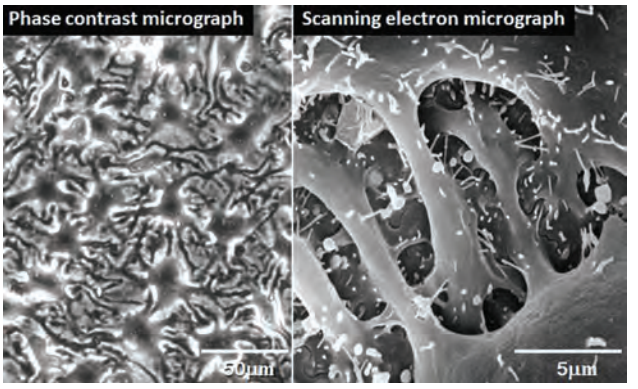
Background: We have succeeded in establishing culture conditions in which cultured podocytes exhibit phenotypes close to those *in vivo* morphologically and in gene expression (JASN 2016; 27: 153A). Heparin is indispensable to the culture conditions. In this study, we have tried to clarify the role of heparin more precisely.

Methods: Rat primary cultured podocytes were subcultured and used for experiments. The effect of heparin was examined by changing the period of addition to culture media or comparing with effects of other polysaccharides having some structural similarities to heparin.

Results: When the presence of heparin was limited to the first 24 hours after subculture instead of the entire time during culture, interdigitating cell processes and foot process-like staining of podocin were also formed five days after as shown by the figures below. Changes of gene expression consistent with differentiation *in vivo*, marked upregulation of podocyte-specific genes and downregulation of classic cadherins, were completed within the first 24 hours. Without heparin, such phenotypic changes were not observed. It is likely that heparin serves as a trigger for phenotypic changes. Heparan sulfate is less sulfated than heparin, but has the same polysaccharide structure as heparin. Sulfated dextran is highly sulfated, but has polysaccharides different from heparin. Sulfated dextran substituted for heparin, but heparan sulfate did not show such trigger effects.

Conclusions: A high degree of sulfation is crucial for the effect of heparin to trigger differentiation of cultured podocytes.

Funding: Government Support - Non-U.S.



PUB462

Ultra-Miniaturized Podocyte Cell-Based High-Content Screening (HCS) Assay Ha Won Lee,[2] Jean-Michel Saffin,[3] Mehmet M. Altintas,[1] Jochen Reiser,[2] Vineet Gupta.[2] *[1]Rush University, Chicago, IL; [2]Rush University Medical Center, Chicago, IL; [3]Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA.*

Background: Podocytes are established targets for therapeutic development for glomerular diseases. Podocyte morphology is essential for their physiological functions. We have previously shown that automated high-content imaging based assays can quantitatively discriminate between healthy and damaged podocytes. We also utilized this methodology to screen a library of ~2000 compounds with podocytes in a 96-well format and identified novel podocyte-protective compounds. However, the 96-well format is not ideal for screening larger chemical libraries, thus necessitating further miniaturization. Here, we describe our efforts towards miniaturization of the cell-based phenotypic assay to 384- and 1536-well formats.

Methods: Differentiated mouse podocytes were seeded in collagen-I coated multi-well plates. Cells were fixed with paraformaldehyde, permeabilized with Triton X-100, and blocked with donkey serum. Then, cells were stained with CellMask Blue, anti-paxillin antibody, and phalloidin. Images were taken using Opera HCS system. Morphologic parameters were quantified using Columbus software and analyzed by Genedata Screener software.

Results: Optimization of seeding density and culture conditions of podocytes in 384- and 1536-well plate formats provided reproducible results. Quantification of cellular phenotypes showed dose-dependent changes in cellular parameters upon treatment with puromycin aminonucleoside (podocyte injury-inducing agent). Co-treatment with mizoribine (podocyte protective compound) showed dose-dependent protection of podocytes from injury, as observed in the 96-well plate format. The assay also showed *Z'*-values similar to those in 96-well format, indicating the robustness of our assay.

Conclusions: We have optimized our podocyte based HCS assay in the ultraminiaturized 1536-well format for high throughput screening. This miniaturized HCS format quantitatively discriminates between healthy and injured podocytes. The ultraminiaturized assay will allow us to screen large and diverse chemical libraries to identify novel podocyte-protective compounds. With the miniaturized format, an in-house library of >300,000 compounds will be screened.

Funding: NIDDK Support

PUB463

Concurrent Treatment with Growth Hormone and Transforming Growth Factor Beta Exacerbates the Epithelial-to-Mesenchymal Transition in Mouse and Human Podocytes Alison L. Brittain. *Biological Sciences, Ohio University, Athens, OH.*

Background: Previous research has indicated that both growth hormone (GH) and transforming growth factor beta (TGFβ) can individually promote the epithelial-to-mesenchymal transition (EMT) in several different cell types. One such cell type is the podocyte. Podocyte EMT enhances foot process effacement and causes loss of podocytes from the basement membrane, ultimately leading to glomerular dysfunction and albuminuria. The purpose of this research was to test the effect of combined GH and TGFβ on mouse and human podocytes in terms of the EMT process.

Methods: To test the relationship between GH, TGFβ and the EMT process, we administered these two growth-promoting peptides individually or concurrently to immortalized mouse podocytes and primary human podocytes. We performed qPCR to evaluate EMT-related gene regulation, Western blotting to evaluate relevant second messengers, immunofluorescence and confocal microscopy to view structural proteins, and colony and scratch assays to evaluate cell phenotype.

Results: Our results show that individual administration of either GH or TGFβ causes an increase in markers of EMT and promotes a mesenchymal phenotype in both cell lines. Our results also show that compared to GH and TGFβ administration alone, combined administration of these growth factors results in further enhancement of EMT, as evidenced by regulation of EMT-specific genes and proteins such as E-cadherin, N-cadherin and Vimentin. Our results also suggest dual GH or TGFβ administration

results in significant actin rearrangement, as well as enhanced cell migration and colony formation.

Conclusions: These results suggest that GH administration may exacerbate preexisting kidney disease, as would be the case in pediatric patients with chronic kidney disease who are given GH to treat short stature.

Funding: Private Foundation Support

PUB464

COL4A Immunofluorescent Staining in the Diagnosis of Autosomal Alport Syndrome

Abdurrahman M. Hamadah, Samih H. Nasr, Kamel A. Gharaibeh, Ziad El-Zoghby. *Mayo Clinic, Rochester, MN*.

Background: Alport syndrome (AS) is an inherited disorder due to mutations in genes *COL4A1 -5* encoding type IV collagen alpha chains. Transmission of AS is mainly X-linked (*COL4A5* gene on X chromosome) (80% of cases), and less commonly autosomal (*COL4A3* or *COL4A4* genes) (20% of cases). We present a case of AS where we established the mode of inheritance by staining pattern of COL4A.

Methods: A 24-year-old woman, with history of microscopic hematuria since age of three presented with worsening renal function. She was thought to have benign hematuria and did not undergo kidney biopsy previously. She had a recent creatinine of 1.5 mg/dL, hematuria on urinalysis, and proteinuria of 5 grams/24 hours. She denied systemic symptoms such as hearing or eye complaints. Family history was significant for hematuria in paternal grandmother, father, and sister, but none had kidney failure. Physical exam was unremarkable. Workup revealed a creatinine of 1.3 mg/dL. Urinalysis showed hematuria and lipiduria. A 24-hour urine revealed 3.2 g of protein. She underwent kidney biopsy with light microscopy showing mild thickening of the glomerular basement membranes (GBM). No significant abnormalities were seen on Immunofluorescence (IF). Electron microscopy revealed thickened GBM with scalloping and lamellation. IF staining with antibody to COL4A5 was negative in glomeruli and positive in tubular basement membranes (TBM) and Bowman's capsule (BC), suggesting autosomal Alport disease due to a mutation in *COL4A3* or *COL4A4* genes. Normal IF staining for COL4A2 was observed in GBM, TBM, and BC. She was initiated on ACE inhibitor.

Results:

Conclusions: The history and biopsy findings of this patient are consistent with AS, with a pattern of staining with antibodies against alpha 5 of collagen IV consistent with autosomal type. In X-linked AS, there is loss of COL4A5 staining of GBM, BC, and distal TBM, whereas in autosomal AS, there is loss of COL4A5 staining of GBM with intact staining of BC and distal TBM. Because of the large size of the COL4 genes and many disease-causing mutations (1900 variants in COL4A5), staining for COL4 chains maybe a useful adjunct for diagnosis and determination of mode of inheritance. In summary, this case illustrates the unique ability of specific alpha chain staining in identifying the underlying defect in AS and its associated mode of inheritance.

PUB465

Clinico-Pathologic Scoring System Predicting Renal Outcome in IgA Nephropathy

Kornchanok Vareesangthip,[1] Ngoentra Tantranont,[3] Boonyarit Cheunsuchon,[4] Ratana Chawanasuntorapoj.[2] *[1]Division of Nephrology, Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand; [2]Division of Nephrology, Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand; [3]Department of Pathology, Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand; [4]Department of Pathology, Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand*.

Background: Prediction of prognosis in IgA nephropathy (IgAN) is still limited and the Oxford classification of IgAN is required the validation in different ethnicity. This study aimed to establish the predictors of renal outcome in IgAN in Thai patients.

Methods: The 327 patients diagnosed IgAN by renal biopsy in Siriraj Hospital between the year 1996-2014 were retrospectively followed. The clinical parameters were collected and the pathologic lesions were evaluated and scored with the Oxford classification.

Results: At the time of renal biopsy, the patients' mean age was 39 years, 64.5% was female and the median creatinine was 1.4 mg/dL. The median renal survival was 155 months, and 114 of 327 patients developed ESRD during the median follow up time of 89 months. From multivariate analysis, age (≤ 30 years: HR 2.28, 95%CI 1.24 to 4.19), serum creatinine at 6 months follow up (Cr 1.2-2.99 mg/dL: HR 4.77, 95%CI 1.96 to 11.59; Cr ≥ 3 mg/dL: HR 16.94, 95%CI 5.73 to 50.12), proteinuria at 6 months follow up (HR 2.03, 95%CI 1.17 to 3.52), tubular atrophy/interstitial fibrosis (T2: HR 3.80, 95%CI 1.54 to 9.38) and ≥ 30% crescent (HR 4.32, 95%CI 1.77 to 10.55) were independent risk factors for the time to ESRD. These variables were used to create a clinico-pathologic scoring system for 5-year ESRD risk. This scoring system demonstrated a good discrimination with a c-statistic of 0.85 (95%CI 0.79 to 0.89).

Conclusions: Our study showed that IgAN in Thailand had a rather high ESRD outcome. The risks of ESRD were young age, high serum creatinine, high proteinuria, high T score from the Oxford classification and high percentage of crescent. With these factors included in the scoring system, 5-year ESRD risk score can be predicted. Further study to validate this clinico-pathologic scoring system is being investigated.

PUB466

Characterization of a Sandwich ELISA for the Quantification of Total Soluble Human Neuropilin-1

Gabriela Berg,[1] Elisabeth Gadermaier,[2] Jacqueline Wallwitz.[2] *[1]Biomedica, Vienna, Austria; [2]The Antibody Lab GmbH, Vienna, Austria*.

Background: Neuropilin-1 (NRP1) functions as co-receptor for several extracellular ligands. It exists as 103 kDa transmembrane NRP1 isoform 1, and as 72 and 68 kDa soluble NRP1 (sNRP1) isoforms 2 and 3, that are generated by alternative splicing. NRP1 and sNRP1 expression was demonstrated in the kidney, e.g. in visceral glomerular epithelial cells. An alteration of NRP1 expression with reduced NRP1 levels was described in diabetes and diabetic nephropathy. The measurement of circulating levels of the soluble forms of NRP1 have proven to be difficult due to the lack of a reliable technique to accurately quantify the analyte. In addition, to our knowledge, it is also not yet known if soluble NRP1 circulates free or as a ligand-bound form. In order to investigate the potential of sNRP1 as a renal biomarker we developed a highly specific and sensitive assay for the quantification of total soluble Neuropilin-1 in peripheral blood.

Methods: We developed a sandwich ELISA that is able to detect total sNRP1 employing polyclonal and monoclonal anti-human NRP1 antibodies. Linear epitopes were mapped with microarray technology and compared between the soluble NRP1 isoforms. Assay parameters like specificity, dilution linearity, and spike recovery were assessed.

Results: The monoclonal detection antibody binds to a linear epitope located in the N-terminal CUB 1 domain of human NRP1. The multiple linear epitopes recognized by the polyclonal coating antibody are distributed over the whole NRP1 sequence. All mapped linear epitopes are conserved between the two known human sNRP1 isoforms. The assay is calibrated with sNRP1 isoform 2, and it detects total sNRP1 in human serum and plasma (heparin, EDTA, citrate) samples. All assay characteristics (specificity, dilution linearity, spike recovery) meet the international standards of acceptance.

Conclusions: Our novel ELISA provides a reliable and accurate tool for the quantitative determination of total soluble human Neuropilin-1 in healthy and diseased samples and it could help to investigate the role of this biomarker in chronic kidney disease.

PUB467

A Spectrum and Clinical Course of Focal Segmental Glomerulosclerosis Variants by Colombia Classification in Japanese Patients

Akihiro Tsuchimoto,[3] Yuta Matsukuma,[3] Kosuke Masutani,[3] Kazuhiko Tsuruya,[4] Shigeru Tanaka,[2] Takanari Kitazono.[1] *[1]Department of Medicine and Clinical Science, Fukuoka, Japan; [2]Fukuoka Dental College, Fukuoka, Japan; [3]Kyushu University, Fukuoka, Japan; [4]None, Fukuoka, Japan*.

Background: Focal segmental glomerulosclerosis (FSGS) is divided into 5 pathological variants by Columbia classification. A spectrum of FSGS variants and the utility of this classification to predict a response to treatment and patient outcome have not been fully investigated in Asian patients.

Methods: This is a retrospective cohort study consisted of 151 patients aged 1–87 years who were diagnosed as FSGS from 1993 through 2016 in 9 nephrology centers in Japan. The patients were divided into 5 subgroups according to the Columbia classification. Interobserver reproducibility of pathological diagnosis was tested using kappa statics by two independent observers, blinded for clinical courses. We compared patients' clinical characteristics and renal composite outcome defined serum creatinine doubling and/or development of end-stage kidney disease.

Results: A distribution of FSGS variant was as follows: not otherwise specified (NOS), 60% (n = 90); perihilar, 15% (n = 23); cellular, 13% (n = 19); tip, 7% (n = 11); and collapsing, 5% (n = 8). Interobserver reproducibility of pathological diagnosis was good (kappa statics 0.71). Urinary protein excretion at kidney biopsy was severer in the tip and collapsing variants than the other three subtypes. Renal function was comparable among the five subtypes. With regard to the response to treatment, proteinuria and serum creatinine at 6 months were lower in patients with tip variant. In the collapsing group, renal composite outcome was significantly worse than NOS variant [adjusted hazard ratio (95% confidence interval), 5.05 (1.42–18.0); p=0.024), while it was similar among the other three groups.

Conclusions: In this study, a frequency of collapsing variant was lower and cellular variant was higher as compared with previous studies reported from the United States and Europe. Good treatment responsiveness of tip variant and poor prognosis of collapsing variant were similar with previous studies.

Funding: Government Support - Non-U.S.

PUB468

Myeloma Cast Nephropathy with Light Chain Proximal Tubulopathy, Renal Extramedullary Hematopoiesis, and Collapsing FSGS Virginie Royal,[1,2] Richard Leblanc,[1,2] Annie-Claire Nadeau-Fredette,[1,2] Louis-Philippe Laurin.[1,2] *[1]Hopital Maisonneuve-Rosemont, Montreal, QC, Canada; [2]University of Montreal, Montreal, QC, Canada.*

Background: Light chain cast nephropathy is a common etiology of acute kidney injury associated with multiple myeloma. Presence of albuminuria in patients with multiple myeloma is usually related to a concomitant glomerulopathy such as AL amyloidosis or MIDD. Collapsing FSGS has been caused by various etiologies, including infections (e.g. HIV, CMV), lupus and pamidronate therapy, but has not been frequently described in patients with myeloma with proximal tubular injury.

Methods: We described a 45-year Caucasian woman who presented with severe renal failure, albuminuria (1364 mg/mmol) and severe hypercalcemia (17.1 mg/dL), requiring dialysis therapy. Serum kappa/lambda ratio was 2632 at initial presentation. Kidney biopsy showed extensive light chain cast nephropathy (Figure 1A), light chain proximal tubulopathy (Figure 1B) along with extramedullary hematopoiesis. Collapsing FSGS was also seen on light microscopy (Figure 1C). Kappa staining was observed on pronase-digested paraffin sections. EM showed intraluminal cast formation and intracytoplasmic electron dense crystals in proximal tubular cells only. Bone marrow biopsy showed 80% plasma cells. The patient was treated with cyclophosphamide, bortezomib and dexamethasone with significant improvement of renal function which resulted in end of dialysis therapy.

Results:

Conclusions: We describe an unusual case of light chain cast nephropathy and proximal tubulopathy with extramedullary hematopoiesis, and concomitant collapsing FSGS. There was no direct light chain deposition in podocytes to explain collapsing FSGS.

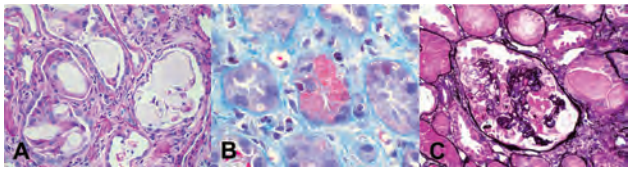


Figure 1. A) Myeloma cast nephropathy: fractured, PAS negative casts, surrounded by cellular reaction, 400x. B) Light chain proximal tubulopathy: Trichrome red intracytoplasmic crystals in proximal tubular cells, 60x. C) Collapsing FSGS: Silver stain showing collapsus associated with podocyte hypertrophy and hyperplasia, 40x.

PUB469

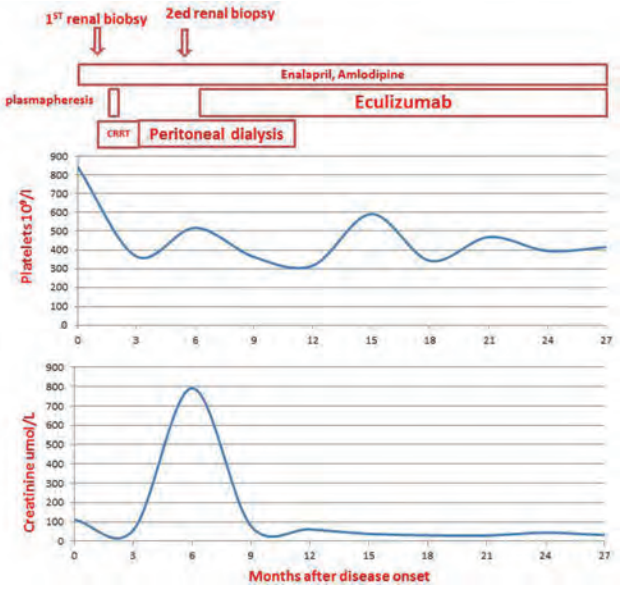
Eculizumab Resulted in Complete Renal Recovery after 9 Months of Dialysis in a Child with Atypical Hemolytic Uremic Syndrome Saeed M. Al zabli,[2] Khawla A. Rahim,[1] Abdulkarim S. Alanazi.[1] *[1]King Fahad Medical City, Riyadh, Saudi Arabia; [2]King Fahed Medical City, Riyah, Saudi Arabia.*

Background: Atypical haemolytic uraemic syndrome (aHUS) is rare, life-threatening, genetic disease characterized by microangiopathic hemolytic anemia, thrombocytopenia, and renal injury. Plasma therapy was the mainstay of treatment, with over 50 % of patients either died or developed permanent kidney damage within the first year. Eculizumab is a monoclonal antibody that blocks the cleavage of C5. Prospective trials demonstrated its effectiveness in management of aHUS

Methods: We report a 3 year old boy, with partial aHUS presented with renal impairment, anemia, normal platelets, low C3, low Complement Factor I and B (CFI & CFB). First kidney biopsy showed proliferative glomerulonephritis, vascular changes without obvious thrombosis. Genetic analysis came positive for mutations in CFI and C3 genes. Second biopsy while on dialysis was consistent with aHUS Steroid pulse therapy and plasmapheresis were ineffective to control the disease, peritoneal dialysis then started. Despite vigorous antihypertensive treatment and improved fluid overload with dialysis, HTN persisted. Eculizumab was given after 4 months of dialysis

Results:

Conclusions: Eculizumab resulted in renal recovery and cessation of prolonged dialysis. Renal function improved after the second dose. PD catheter was removed after 9 months of dialysis. Currently, after 24 months of Eculizumab therapy, disease is in remission and renal function is normal Partial HUS to be considered; diagnosis to be confirmed by biopsy and or gene mutations



PUB470

Atypical Hemolytic Syndrome (aHUS) Presenting as Acute Pulmonary-Renal Syndrome Preceded by Ocular Manifestation: A Very Rare Presentation Sanjeev Gupta,[1] Savneek S. Chugh,[2] Magdi H. Abdelrahman,[1] Anastasios Papanagnou,[1] Praveen N. Chander.[3] *[1]Dept. of Nephrology, Westchester Medical Center, Valhalla, NY; [2]Dept. of Nephrology, New York Medical College, Valhalla, NY; [3]Dept. Of Pathology, New York Medical College, Valhalla, NY.*

Background: Atypical hemolytic uremic syndrome (aHUS) is a systemic disease characterized by excessive complement activation in the microvasculature. Kidneys are most commonly involved organ while pulmonary and retinal involvement is very rare and usually discovered at autopsy. We present a case of aHUS mediated acute pulmonary-renal syndrome with ocular involvement.

Methods: A 32-year-old man with a history of Crohn's disease s/p bowel resection was admitted with seizures, acute respiratory failure and acute kidney injury (creatinine-8.5 mg/dl). He also had a very recent history of bilateral eye blindness, resolved with steroid treatment. Laboratory findings showed hemoglobin 6.8 g/dl and platelet count 96,000). Chest X-ray showed diffuse bilateral interstitial infiltrate; bronchoscopy revealed diffuse pulmonary hemorrhage with a normal ejection fraction noted on echocardiogram. A diagnosis of pulmonary-renal syndrome was considered and he was started on IV steroids, Cytoxan, plasmapheresis, and hemodialysis. Further workup revealed low C3 at 57, normal C4 and negative MPO Ab, PR3 Ab, ANA, hepatitis panel, anti-GBM Ab, anticardiolipin Ab, SSA Ab, SSB Ab and blood cultures. ADAMTS-13 activity was 43. Renal biopsy showed changes of thrombotic microangiopathy (TMA) with glomerular immunofluorescence staining strongly for C3 compatible with a diagnosis of possible C3 nephropathy (GN). Given his multi-organ involvement, low serum C3, TMA and C3 GN on renal biopsy, and hematologic findings, a diagnosis of aHUS was made. The patient was lost to follow-up so genetic testing and complement blockade therapy could not be initiated.

Results:

Conclusions: Diagnosis of aHUS is based on clinical and laboratory findings. Extrarenal manifestations of aHUS are seen in about 20% of cases and often involve the skin, cardiovascular, and central nervous system. To our knowledge, there is only one case reported thus far of aHUS presenting as an acute pulmonary-renal syndrome; this was successfully treated with steroid and plasmapheresis. Although renal involvement with pulmonary hemorrhage is a rare manifestation of aHUS, it should be included in the differential diagnosis of pulmonary-renal syndrome, as early treatment is crucial for the better clinical outcome.

PUB471

Immunotactoid Glomerulopathy with Masked Monotypic Immunoglobulin Deposition Tsubasa Fukuoka,[2] Shunichi Shibazaki,[2] Makoto Araki,[2] Katuji Tuda,[2] Takashi Ehara.[1] [1]*Matsumoto University Graduate School of Medicine, Nagano, Japan;* [2]*Suwa Central Hospital, Nagano Pref., Japan.*

Background: Immunotactoid glomerulopathy (ITG) is a rare disease characterized by organized, Congo red-negative immunoglobulin deposits. ITG often has a monotypic light chain restriction because of a possible association with lymphoproliferative disorders, but 31% of ITGs are kappa and lambda immunoglobulin positive.

Methods: An 80-year-old woman with deteriorating renal function since 6 months presented with proteinuria of 1.5 g/day, creatinine levels, 0.92 mg/dl, and a mild decrease in C3 (76 mg/dl). Serology and urine protein electrophoresis assay and anti-nuclear antibody were normal. A renal biopsy revealed membranoproliferative glomerulonephritis. Congo red staining was negative. Immunofluorescence staining of the frozen tissue was IgG and C3 positive in the mesangial and subendothelial regions, with no differences in kappa/lambda. Electron microscopy revealed a 30-nm deposition of microtubules with a hollow core. The diagnosis was ITG. As additional checks, Serum immunofixation indicated trace amounts of IgG-kappa M protein and a normal serum free kappa/lambda light chain ratio of 1.99, (65.2/32.8). Serum cryoglobulin was negative on quintuplicate assay; bone marrow aspiration did not show excess plasma cells. Computed tomography findings were normal. Because it has recently been reported that monoclonal proteins occasionally show false negative staining by routine immunofluorescence of the frozen tissue, we tried to study light microscopic immunohistochemistry of trypsin-digested section from epon-embedded tissue. As a result, it revealed obvious subepithelial deposition of kappa. After 6 months of immunosuppressive therapy, creatinine level was 1.21 mg/dl and urinary protein concentration was 1.3 g/g Cr without any evidence of lymphoproliferative disorders.

Results:

Conclusions: ITG is a monoclonal gammopathy of renal significance, but monoclonal deposition may not be confirmed if the three-dimensional structure of the antigenic site is masked. In this patient, light microscopic immunohistochemistry of trypsin-digested section revealed monotypic kappa deposition, even though direct immunofluorescence staining of frozen tissue was both kappa and lambda positive. This would provide evidence that the monoclonal protein is the cause of ITG and would justify treating with chemotherapy

PUB472

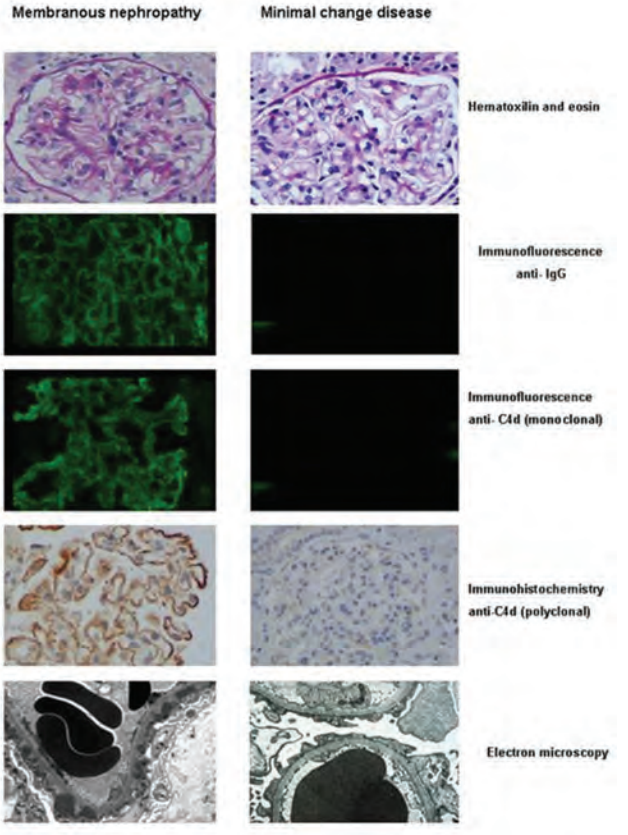
C4d Is an Important Diagnostic Tool in Membranous Nephropathy Cristina Rabasco, Mario Espinosa. *UGC Nephrology, University hospital Reina Sofía, Cordoba, Spain.*

Background: Idiopathic membranous nephropathy (MN) is the most frequent cause of the nephrotic syndrome in adults. The diagnosis is based on typical findings observed via electron microscopy (EM) and immunofluorescence (IF) studies. Recent advances have shown that MN is a kidney specific autoimmune disease induced by antibodies specific for podocyte antigens. Complement plays an important role, even if mechanisms of activation have not been clarified yet. C4d is a fragment of C4 that is produced during activation of the classical or lectin complement pathway. We might therefore expect to find C4d deposition as a marker of complement activation in MN. The aim of our study was to determine whether immunohistochemical detection of C4d in patients with MN could be useful as a diagnostic tool.

Methods: All adult patients diagnosed with idiopathic minimal change disease (MCD) and MN biopsied in our unit between January 2001-December 2016 were considered for inclusion in the study. Diagnoses of MCD and MN were based on histological assessment of renal biopsy tissue with LM, IF and EM studies. 51 patients with MCD and 91 with MN were finally included.

Results: No C4d deposition was observed in any of the glomeruli of patients with MCD, and 100% of these patients were classified as "negative". C4d was detected in 100% of patients with NM in the form of a uniform granular distribution that outlined all the capillary loops and spared the mesangium. Detectable C1q deposits by IF were detected in only two patients with MN.

Conclusions: The demonstration of C4d by means of immunohistochemical techniques can thus be used as a tool for the differential diagnosis of MN and MCD. The deposit of C4d and no C1q deposit suggest that the alternative and/or lectin pathways might be predominantly involved in complement activation and formation of the C5b-9 complex in MN.



PUB473

Atypical Myeloperoxidase Anti-Neutrophil Cytoplasmic Antibody (MPO-ANCA) Associated Crescentic Glomerulonephritis (GN) with Immune Deposits Overlap with CREST Celeste S. Chang, Yorg Al Azzi. *Nephrology, NY medical college at Westchester Medical Center, Valhalla, NY.*

Background: Pauci-immune crescentic GN is defined as few or no immune deposits on renal biopsy. However, some reported an overlap of pauci-immune pathology with immune deposits in the setting of anti-MPO-ANCA. CREST is typically associated with thrombotic microangiopathy (TMA) like renal lesion and only a handful of case reports associated between ANCA vasculitis and CREST. Here, we present a rare case of atypical MPO-ANCA associated crescentic GN on light microscopy with immune deposits on electron microscopy, overlap with CREST.

Methods: 74 F from El Salvador presented with tea-colored urine, proteinuria (Urine protein/Cr ratio: 8) and AKI with positive ANA (centromere), Anti- MPO Ab, negative HbsAg, reactive Anti-Hbs and Anti-Hbc. History of HTN, pulmonary nodules, mild restrictive pulmonary disease, pulmonary HTN, arthralgia and latent syphilis. Renal biopsy revealed crescentic and focal necrotizing GN with mesangial and subendothelial deposits on EM. There are IgG, IgA, C3, fibrillary segment, both kappa and lambda light chains on IF staining. Thrombi are present in some glomeruli, suggestive of TMA with possibility of overlapping with autoimmune disease. She was started on steroid and cyclophosphamide, required hemodialysis for fluid overload and worsening of AKI. However, she recovered renal function and came off from dialysis without any plasmapheresis. Her HbsAg became positive after cyclophosphamide.

Results:

Conclusions: This is a very unusual and rare case of pauci-immune GN with evidence of immune deposits on EM which could be related to atypical lupus nephritis with positive ANCA vs ANCA vasculitis with unusual immune deposits from possible contribution of latent syphilis and latent hepatitis B infection, the latter was unmasked by immunosuppression. All these superimposed on an element of thrombotic microangiopathy, probably secondary to CREST.

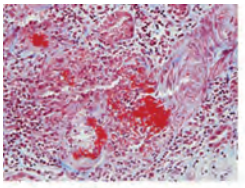


Fig 1: Necrotizing Crescentic Glomerulonephritis

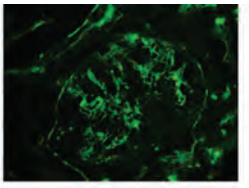


Fig 2: C3 deposit on immunofluorescent microscopy

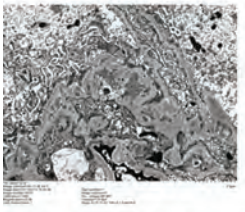
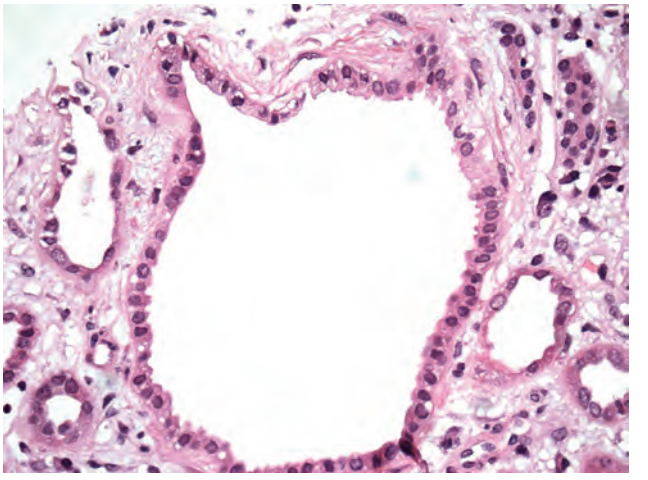


Fig 3: Mesangial and subendothelial deposits on electron microscopy



Dilated tubule with surrounding interstitial fibrosis

PUB474

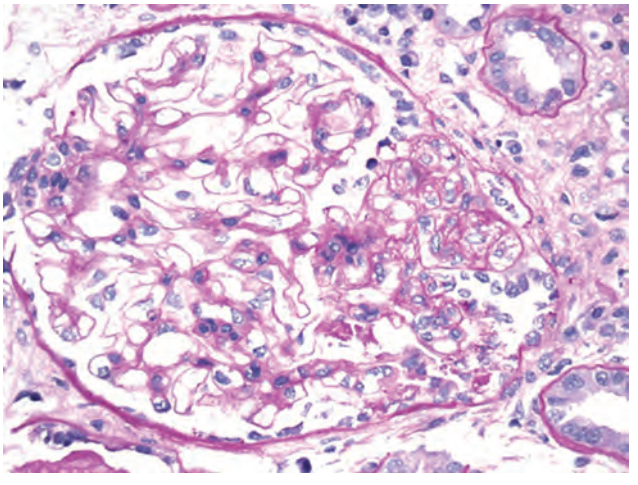
Lithium: Mood Stabilizer That Made Us Dialyze Her Anna S. Gutman, Shimshon Wiesel, Madeeha Abdul Ghaffar, Militza K. Kiroycheva. *Staten Island University Hospital, Staten island, NY.*

Background: Despite its toxic effects, lithium continues to be used for the management of bipolar disorder. We present a case of acute and chronic lithium nephrotoxicity.

Methods: A 43-year-old woman with bipolar disorder, who had been taking lithium for over 11 years, presented with lethargy and decreased oral intake. She was alert but disoriented, and had bilateral lower extremity edema. Serum creatinine was 3.5 mg/dL, from a normal baseline, with large proteinuria. Her spot urine total protein:creatinine was 54g/mg, albumin 2.0 g/dL, and serum Li^+ 3.2mmol/L, which did not improve with intravenous fluids. Intermittent hemodialysis was started, with frequent monitoring of her Li^+ levels. A renal biopsy showed focal segmental and global glomerulosclerosis, interstitial fibrosis, and multiple distal tubular cysts. Li^+ was discontinued, but the patient remained hemodialysis dependent.

Results:

Conclusions: Renal biopsies of patients with chronic lithium use and nephrotic range proteinuria show tubulointerstitial nephropathy, minimal change disease, focal segmental, and global glomerulosclerosis. Despite discontinuing lithium, as many as 75% of patients progress to end stage renal disease. Our patient had routine monitoring of her serum lithium and creatinine levels, however she progressed to ESRD. We recommend frequent quantification of proteinuria for closer monitoring of lithium induced nephrotoxicity.



Glomerulus with FSGS tip variant

PUB475

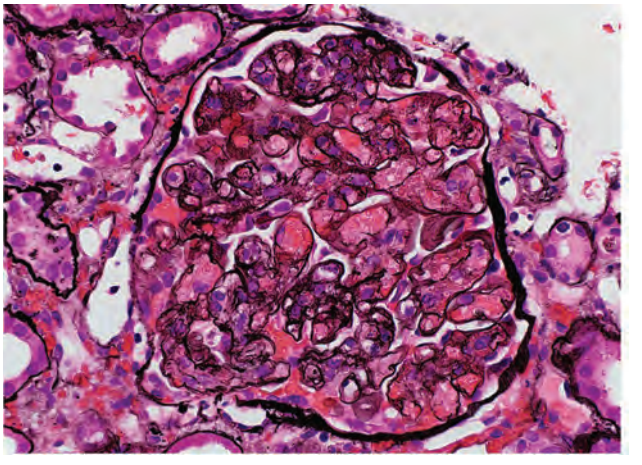
Rare Case of Catastrophic Anti-Phospholipid Syndrome Iyad S. Mansour. *Banner university medical center/ university of arizona, Tucson, AZ.*

Background: Catastrophic Anti-Phospholipid Syndrome (CAPS) is a rare life threatening form of APS. Acute thrombotic microangiopathy is the most common histological finding on kidney biopsy in this disease

Methods: A 48 year old male with PMH of Idiopathic thrombocytopenic purpura, pulmonary embolism, and recent diagnosis of arthritis, presented with 4 day history of lower back and left flank pain. P/E: vitals are stable, lung exam: scattered crackles, mild left flank and left mid- abdomen tenderness, +1 lower extremities edema, intermittent confusion, patient has been oliguric. Labs showed Hb: 13.2, WBC 10.7, plat:85,000, serum Cr: 2.8 mg/dl, AST:71, ALT:57, D.D:16.6, PT:15, PTT:39.9, blood smear showed thrombocytopenia with normocytic RBC, no hemolysis, MRI abdomen showed left adrenal hematoma. Urine AX: 100 mg/dl protein, 41 RBC and 4 WBC, 2 granular cast, serological For HIV,HCV,HBV,ANA, ASMA, Anti-DsDna, ANCA were negative, anticardiolipin antibody IgG: 18, lupus anticoagulant :2.02 (High). ADAMTS13 activity: 54%, C3, C4: both low, Kidney biopsy showed acute and chronic thrombotic microangiopathy, acute tubular injury, negative immune fixation. This patient had involvement in kidneys, adrenal glands, liver and probable CNS involvement. So he fulfilled the criteria of probable CAPS. He was treated with steroids, anticoagulation, plasma exchange and rituximab, with good response

Results:

Conclusions: APS is autoimmune disease, characterized by arterial and venous thrombosis, Catastrophic antiphospholipid syndrome (CAPS) is a rare life threatening form associated with disseminated vascular thrombosis results in multiorgan ischemia and failure. Kidney are involved in 73% of patient with CAPS, TMA is the most common histological finding in this disease. It is a life threatening disease that requires aggressive treatment strategies, and all patient with CAPS should be treated with steroids, anticoagulation, and possibly plasma exchange, in refractory and relapsing cases, Rituximab and Eculizumab may be an option.



PUB476

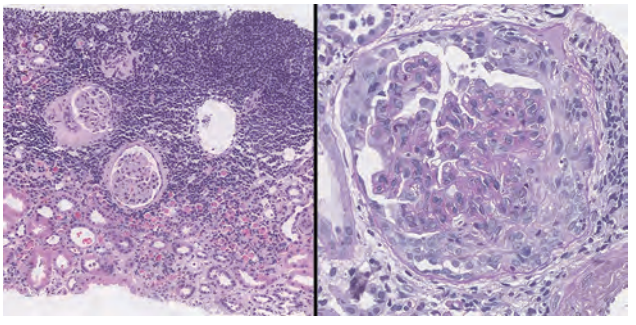
Unusual Cause of Nephrotic Syndrome with AKI: Membranoproliferative Glomerulonephritis (MPGN) with Concurrent Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) Infiltration in Kidney Shubha Ananthakrishnan,[1] Kuang-Yu Jen,[3] Kevin D. Marquez.[2] *[1]UC Davis, Sacramento, CA; [2]University of California Davis Medical Center, Sacramento, CA; [3]University of California, Davis, Sacramento, CA.*

Background: Renal manifestations in patients with CLL/SLL have been reported, with MPGN being the most common glomerular finding. Here we describe a patient with history of CLL/SLL who presented with new onset nephrotic syndrome and renal impairment.

Methods: The patient is a 74-year-old Caucasian male, previously treated for CLL/SLL with a rituximab-based regimen. He was off treatment for 2 years but presented with new onset ascites, requiring frequent paracentesis. On exam, he was chronically ill-appearing with marked ascites but had no peripheral edema. Labs were significant for rise in serum creatinine to 2.6 mg/dl (baseline of 1 mg/dl) and low albumin of 1.7 g/dl. Liver enzymes were normal and he had no evidence of viral hepatitis. Ascitic fluid cytology was negative for malignancy. Urine protein excretion was ~10 grams/24 hrs. Urine microscopy showed many dysmorphic red blood cells. A renal biopsy was performed that revealed CLL/SLL infiltrating the renal parenchyma with concurrent MPGN showing focal crescent formation. MPGN deposits displayed IgG1-kappa restriction, correlating to the phenotype of the patient's malignancy.

Results:

Conclusions: This is an unusual case of a patient with a history of CLL/SLL with multiple simultaneous renal manifestations - ascites related to nephrotic syndrome that was caused by MPGN secondary to CLL/SLL and AKI related to crescent formation and parenchymal infilration by CLL/SLL.



Kidney biopsy showing infiltration of parenchyma by CLL/SLL as well as MPGN with crescent formation.

PUB477

Membranous Nephropathy Secondary to Syphilis Deepa Nagaraja, Himanshu Vashistha, Shirisha Bodana, Damodar R. Kumbala. *Ochsner Health System, New Orleans, LA.*

Background: Membranous nephropathy is one of the most common causes of nephrotic syndrome in the adult population. Although in the majority of cases an inciting event can't be identified, in about a third, an association with autoimmune disease, drugs, or infections is usually found. Syphilis is a rare infectious cause of membranous nephropathy and usually presents nephrotic range proteinuria (X). In the last fifteen years, there has been a reemergence in the cases of primary and secondary syphilis in the United States (CDC), which could lead to a greater number of patients affected by this sexually transmitted disease seeking medical help due to renal involvement.

Methods:

Results: We described the case of a 41 year-old African American man without known prior medical history that presented to the hospital with the chief complaint of one-week history of gradual, incapacitating, bilateral lower extremity edema. High-risk conduct for sexually transmitted disease was identified during the history. A physical exam revealed a maculopapular rash on his palms and soles. Initial laboratories showed rapid plasma regain dilution of 1:128, serum creatinine of 1.2mg/dl, and spot urine to protein creatinine ratio of 5.7. Kidney biopsy was consistent with membranous nephropathy. After four weeks of antibiotic treatment for secondary syphilis, there was a complete resolution of his nephrotic picture.

Conclusions: Although syphilis is rarely associated with membranous nephropathy, the increasing incidence of secondary syphilis will invariably lead to a greater number of patients that are present with renal involvement. Healthcare providers must remain aware of the association of syphilis with renal disease and its possible presentations. History and physical findings suggestive of this sexually transmitted disease in a patient presenting with proteinuria and/or nephrotic syndrome should point towards accurate diagnosis. Resolution of the associated nephropathy is seen after antibiotic treatment against *Treponema pallidum*.

PUB478

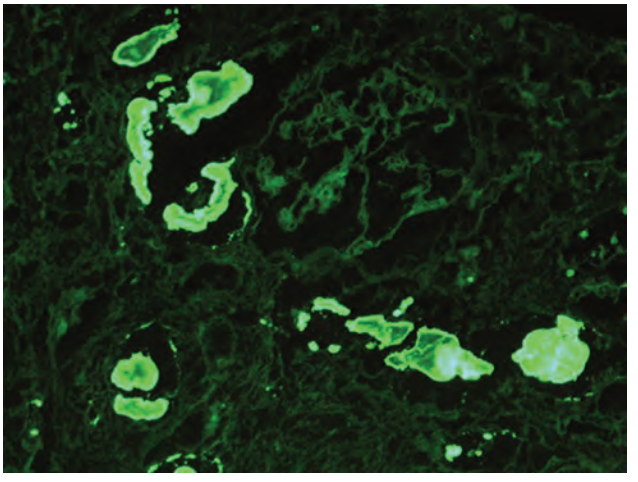
A Case of Myeloma Kidney with Glomerular C3 Deposition Asif Khan, Suzanne E. El Sayegh, Elie El-Charabaty. *Medicine, Staten Island University Hospital, Staten Island, NY.*

Background: Myeloma cast nephropathy and monoclonal immunoglobulin deposition disease are the most common renal complications of multiple myeloma (MM). Up to 50% of MM patients present with renal impairment at diagnosis: 20% may present with acute kidney injury, and 10% require dialysis. Light chains can precipitate in the proximal and distal tubules causing inflammation leading to secondary interstitial fluid involvement. Moreover, mutations or autoantibodies such as C3 nephritic factor (C3Nef) against complement regulatory proteins promote the erratic activity of the complement cascade, causing glomerular deposition of C3 without marked deposition of classical complement components and with minimal, or no immunoglobulin deposits resulting in tissue damage. These disorders are described as C3 glomerulopathy(C3G).

Methods: We report the case of a 59-year-old man Trinidadian man who presented to the emergency with acute kidney injury, hyperkalemia, anemia, serology positive for anti-dsDNA antibody and low levels of C3 with normal C4. Kidney biopsy showed cast nephropathy with mesangial staining for C3. A bone marrow biopsy showed CD56 positive plasma cell myeloma (42% IgG Lambda). Four months after the initial biopsy, the patient remained dependent on hemodialysis therapy and required multiple blood transfusions. Evaluation of the alternative complement pathway showed normal activity level.

Results:

Conclusions: Currently, there are no effective disease-specific treatments for C3G. Clinicians should be aware of isolated glomerular deposits that stain weakly or dominantly for C3 might represent an unusual complication of plasma cell dyscrasia, related to complement activation through an autoantibody activity of the monoclonal Ig against complement regulatory proteins.



Immunofluorescent revealed 3+ staining for lambda in the distribution of the atypical casts with weak granular mesangial staining for C3. Staining for IgA, IgG and C1 were negative.

PUB479

Podocytic Infolding Glomerulopathy: A Case Report Pin Zhang,[2] Daqing Hong,[3] Yurong Zou,[4] Guisen Li.[1] *[1]Renal Division and Institute of Nephrology, Sichuan Academy of Medical Sciences and Sichuan Provincial People?s Hospital, Chengdu, China; [2]Sichuan Provincal People's Hospital, Chengdu, China; [3]Sichuan Provincial People's Hospital, CHENGDU, China; [4]Sichuan provincial people's hospital, Chengdu, China.*

Background: Podocytic infolding glomerulopathy (PIG) has recently been proposed as a possible new pathological entity. In PIG, microtubules or microspheres, or both, are associated with the infolding of cytoplasmic processes of podocytes into the glomerular basement membrane (GBM). Most of PIG cases have been reported in Japan, and it is unclear whether this lesion indicates a new disease entity or a transient morphological finding of a well-known disease.

Methods: Here, we report a PIG case of a 57-year-old Chinese female. The patient presented nephrotic syndrome without renal functional impairment or other systemic diseases. Glomeruli were normocellular, but GBMs were diffusely and mildly thickened. Immunofluorescent staining was negative for immunoglobulin, complements, fibrinogen and light chain. Electron microscopy showed diffuse distribution of microtubules and microspheres within thickened GBM in association with segmental infolding of cytoplasmic processes of podocytes into the GBM. The patient was treated with steroids for 6 weeks, resulting in proteinuria less than 1 g/day.

Results:

Conclusions: The presented case demonstrates a rare and peculiar glomerulopathy, the podocytic infolding glomerulopathy. The pathogenic mechanism of PIG should be multiple, more cases of PIG are needed to be analyzed in order to better understand this lesion.

PUB480

Abstract Withdrawn

PUB481

Early Recognition and Intervention Improves Outcome in HELLP-HUS: A Case Report Rakesh Kumar,[1] Dhanashri Kohok,[3] Ramesh Adhikari,[2] Manish Gera.[1] *[1]Internal Medicine Nephrology, INC, Terre Haute, IN; [2]Union Hospital, Terre Haute, IN; [3]Internal medicine, Union Hospital, Terre Haute, IN.*

Background: Atypical hemolytic uremic syndrome (aHUS) with Hemolysis elevated liver enzyme and low platelet (HELLP) syndrome is a rare complication of pregnancy. It is associated with high morbidity and mortality. Renal survival is dismal and renal dysfunction is the rule.

Methods: A 23-year-old Caucasian female pregnant at 32 weeks gestation age was admitted with epigastric pain. She was hypertensive at presentation and had proteinuria. Fetal distress led to an emergent cesarean section. Post delivery of fetus her vital signs stabilized. She had hemolysis, elevated liver enzymes, and low platelets. At the time of presentation serum creatinine was 0.6 mg/dL. Preeclampsia with HELLP syndrome was diagnosed. Post-partum she became oliguric and had renal failure. Haptoglobin and Lactate dehydrogenase (LDH) were < 10 mg/dL and 2450 U/L respectively. Schistocytes were present in peripheral blood smear. Urinalysis showed hematuria and proteinuria (greater than 3 grams/day). She was diagnosed with preeclampsia with HELLP syndrome and post-partum atypical HUS. Deregulated alternative pathway has been implicated in the pathogenesis of HELLP and aHUS so plasmapheresis was given within a few hours of diagnosis and eculizumab was given within twenty-four hours of diagnosis. Her urine output slightly improved with first session of plasmapheresis. Her serum creatinine trended up to 5.5 mg/dL. She needed 3rd session of plasmapheresis on 7th day due to worsening renal function. Supplemental dose of eculizumab was given after 3rd plasmapheresis. None of the genetic variants of 10 genes associated with aHUS were present. Lupus anticoagulants and Hepatitis screen were negative. After 2 weeks of hospital stay, her serum creatinine improved to 1.2 mg/dL and LDH started trending down but remained high at 539 U/L. Platelets improved from 53000 /uL to 386000 /uL. Hemoglobin levels also started improving but she remained anemic. She never required dialysis.

Results:

Conclusions: The association of preeclampsia, HELLP syndrome and post-partum aHUS suggest that these may be a spectrum of single disease process i.e. abnormal alternative complement activation. Early recognition of HELLP/ aHUS and treatment with plasmapheresis and eculizumab may improve renal outcome.

PUB482

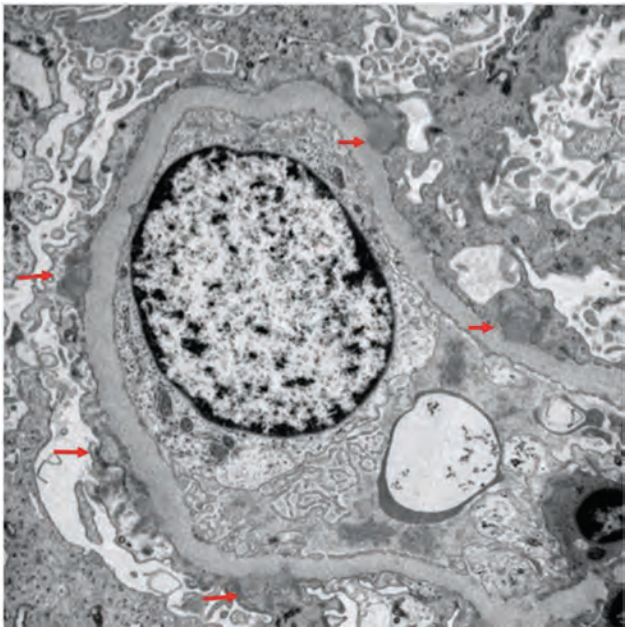
The Great Imitator: An Unusual Cause of Reversible Nephrotic Syndrome Arundati Rao,[2] Sarthak Virmani,[2] Christine B. Vigneault,[1] Michael N. Moustakakis.[1] *[1]Greater Hartford Nephrology, Bloomfield, CT; [2]University of Connecticut, Hartford, CT.*

Background: Sudden onset of nephrotic syndrome in HIV infected patients has a broad differential including HIV associated nephropathy/FSGS. Immune deposition mediated nephrotic syndrome due to co-infections is an unusual etiology in such patients.

Methods: A 52-year-old male with PMH of HIV infection on HAART presented with a 3 day history of periorbital edema, bilateral lower extremity swelling, weight gain and a urine dipstick showing 3 + proteinuria. Exam was notable for a BP of 140/85mmHg and anasarca. Investigations revealed BUN 21mg/dL, S.Cr. 1.3mg/dL, albumin 1.7g/dL, total cholesterol 422mg/dL and Triglycerides 374mg/dL. A urine protein:creatinine ratio was 5266.75mg/g and the 24 hour urine protein was quantified at 13.3g. He was diagnosed with nephrotic syndrome and started on an ACE inhibitor. Workup revealed normal levels of ANA, ANCA, complements and negative hepatitis serologies. FSGS was the working diagnosis and a renal biopsy was performed that showed immune complex GN suggestive of an infectious etiology. On further questioning, he reported a 1 day history of self limiting rash and fever following treatment with ceftriaxone for recently diagnosed gonorrhea 2 weeks prior to presentation. This was presumed to be a Jarisch-Herxheimer reaction. Subsequently, RPR and FTA-ABS were found to be positive and he was treated for secondary syphilis with penicillin. This led to complete resolution of his nephrotic syndrome clinically with a S.Cr. of 0.8mg/dL, albumin 3.2g/dL and an undetectable urine:protein creatinine ratio.

Results:

Conclusions: Syphilitic infection causing nephrotic syndrome in HIV infected patients is unusual but completely treatable and reversible. It is recommended that patients with a similar clinical picture be tested for co-infection with syphilis.



Sub-epithelial immune complex deposits on EM

PUB483

A Case of Cronkhite-Canada Syndrome Complicated by Membranous Nephropathy Christine Parsons,[1] Leslie F. Thomas,[2] Lucinda A. Harris,[1] Maxwell L. Smith.[1] *[1]Mayo Clinic, Scottsdale, AZ; [2]Mayo Clinic Arizona, Phoenix, AZ.*

Background: Cronkhite-Canada syndrome (CCS) is a very rare disorder with less than 500 reported cases. It is characterized by extensive gastrointestinal polyposis and various ectodermal anomalies including alopecia, cutaneous hyperpigmentation, and onychodystrophy. Only a few cases of associated kidney disorders (namely membranous nephropathy) have been reported.

Methods: A 71-year-old male with a history of calcium pyrophosphate deposition disease and recently diagnosed CCS presented for evaluation of proteinuria. The patient initially presented with abdominal discomfort, a 45-pound weight loss, dysgeusia, skin hyperpigmentation, alopecia and dystrophic nails. Radiologic and endoscopic evaluation was significant for widespread gastrointestinal nodular inflammation and colonic polyps. Histopathology was consistent with CCS. He was treated with prednisone and antacids, followed by steroid sparing therapy with azathioprine. He had moderate clinical improvement, but developed proteinuria, which progressed to nephrotic-range (4.4 grams on 24-hour urine collection). Renal biopsy showed membranous glomerulonephritis, and cyclosporine and losartan were initiated. The patient had significant improvement in his CCS manifestations; however, his proteinuria did not resolve and eventually worsened

coincident with declining glomerular filtration rate. Rituximab was added to his regimen of cyclosporine and azathioprine, which resulted in remission of his MN, marked improvement in his polyposis, and near resolution of his cutaneous symptoms.

Results:

Conclusions: CCS is a rarely encountered disorder in which associated renal disease, such as membranous nephropathy, uncommonly manifests. After a careful review of the literature, only three cases of CCS have been associated with MN. To our knowledge, this is the first reported case of CCS with MN as well as any case of CCS treated with rituximab. The excellent response observed for both CCS and MN recommends consideration of this treatment, especially for resistant disease. The use of cyclosporine was reported as successful in another case of CCS with MN. Steroid-resistant CCS is scarcely reported, but some success has been noted with cyclosporine, azathioprine, and infliximab. Cyclosporine in the present case evoked a response superior to azathioprine.

PUB484

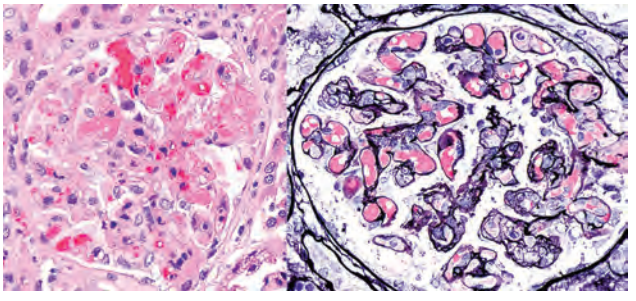
Combined Tacrolimus and Sorafenib-Associated Thrombotic Microangiopathy Voravech Nissaisorakarn,[1] Weeraporn Srisung,[1] Steven Salvatore,[1] Vesh Srivatana.[2] *[1]Weill Cornell Medical Center, New York, NY; [2]The Rogosin Institute, New York, NY.*

Background: Thrombotic microangiopathy (TMA) is an inflammatory and thrombotic disease of the microvasculature, which often occurs in hematopoietic stem cell transplantation (HSCT) population. Risk factors of TMA in HSCT include chemotherapy, radiation, calcineurin inhibitors (CNI), anti-vascular endothelial growth factor (anti-VEGF) therapies, graft-versus-host disease, and infections. Tacrolimus and sorafenib have been individually associated with TMA, however, to our knowledge there have been no reports of TMA with the combination of the two drugs. We report the first case of tacrolimus and sorafenib-associated TMA.

Methods: Our patient is a 57-year-old woman with acute myeloid leukemia who underwent HSCT. She had been taking sorafenib for seven weeks and stopped one week prior to HSCT. The post-HSCT immunosuppression consisted of antithymocyte globulin, mycophenolate mofetil, and tacrolimus. Thirteen weeks after HSCT, she had an acute kidney injury (AKI) from tacrolimus toxicity. The renal function improved after a temporary discontinuation of tacrolimus. Seventeen weeks after HSCT, sorafenib was started on top of concomitant use of tacrolimus. Two weeks later she developed severe oliguric AKI from biopsy-proven TMA (figure 1). Despite therapy with eculizumab, she died from complications of sepsis after a prolonged hospital course. Autopsy confirmed the diagnosis of TMA involving the cardiac and renal tissue.

Results:

Conclusions: We observed that TMA developed when the patient was taking both tacrolimus and sorafenib but not when they were taken individually. The concept of two drugs having synergistic effects to cause TMA has been demonstrated in dual anti-VEGF inhibition but not with the combination of CNI and anti-VEGF therapy. We hypothesize that tacrolimus and sorafenib combined may have caused a severe endothelial injury initiating the pathogenesis of systemic TMA. Despite early and aggressive therapy, the patient died. Due to emerging indications for combined use of these drugs in HSCT population, intensive monitoring for early signs of TMA is critical for optimizing outcomes.



PUB485

A Case of Sjogren Syndrome Related Cryoglobulinemic Glomerulonephritis Tramanh Phan, David Levy, Rickinder Grewal, Bruce Goldman, Scott E. Liebman. *University of Rochester Medical Center, Rochester, NY.*

Background: Sjogren syndrome is the most common cause of non-hepatitis C virus (HCV)-related cryoglobulinemia. Here, we report a case of Sjogren syndrome associated cryoglobulinemic glomerulonephritis (GN) that responded to treatment with steroids, rituximab and mycophenolate.

Methods: A 43 year-old woman with Sjogren syndrome (with hypocomplementemia, positive cryoglobulins, ANA, anti-Ro and anti-La antibodies and on hydroxychloroquine) presented with nephrotic syndrome (protein to creatinine ratio of 3.7 g/g, albumin of 2.5 g/dL). Other than peripheral edema, the physical exam was unremarkable. Further workup revealed an elevated serum free light chain (FLC) ratio of 5.78, and serum immunofixation was positive for IgM kappa. CT of the neck, chest, abdomen and pelvis did not reveal lymphadenopathy. Bone marrow aspirate was negative for multiple myeloma. Renal biopsy showed type II cryoglobulinemic GN (Fig.1). Congo red stain was negative. There was no evidence of HCV or current or previous hepatitis B infection. Thus, she was diagnosed with Sjogren syndrome associated cryoglobulinemic GN. Initial treatment was with high dose steroids followed by rituximab infusion. She continued hydroxychloroquine and was on lisinopril as tolerated by kidney function. Several months later the patient developed myopathy. Steroids were tapered off in favor of mycophenolate and continued rituximab. The protein to creatinine ratio peaked at 13.36 g/g but decreased to 0.23 g/g at six months. Serum cryoglobulins are no longer detectable, FLC ratio has decreased to 1.77 and serum creatinine is normal.

Results:

Conclusions: Although rare, cryoglobulinemic GN should be considered in Sjogren syndrome patients with nephrotic syndrome. The combination of steroids, rituximab and mycophenolate is a potential therapy for biopsy proven cryoglobulinemic GN in this setting.

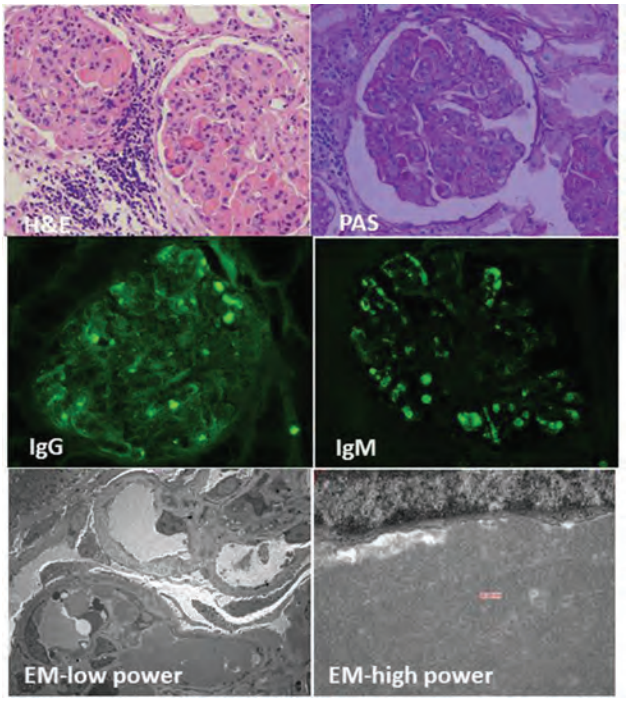


Fig.1. Renal biopsy: light microscopy (H&E,PAS), immunofluorescence (IgG, IgM), and electron microscopy (EM)

PUB486

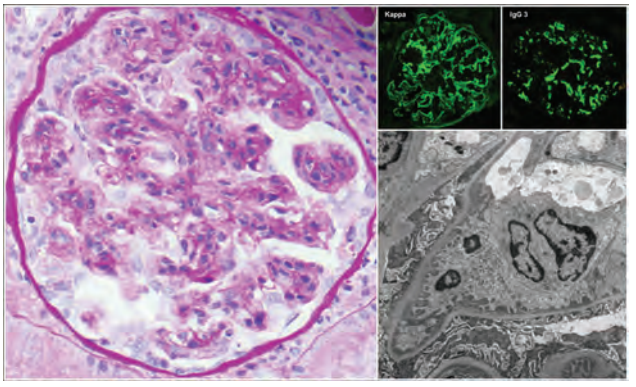
A Case of Proliferative Glomerulonephritis with Monoclonal IgG Deposits Early after Renal Transplantation Yasir Alfi, Scott D. Cohen, Muralidharan Jagadeesan. *Division of Renal Diseases & Hypertension, George Washington University, Washington, DC.*

Background: Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) was first described by Nasr et al. in 2004 as a form of renal involvement by monoclonal gammopathy resembling immune-complex glomerulonephritis. Here we describe a case of PGNMID early after renal transplantation in a patient with a prior history of multiple myeloma in remission.

Methods: A 66 year old male with a past history of treated IgG lambda multiple myeloma who presented with abnormal renal function 5 months after a deceased donor renal transplant with a serum Cr of 1.3 mg/dl up from a baseline Cr of 0.9 mg/dl and a new nephrotic range proteinuria with a spot UPCR of 9.5 g/g. The patient was first diagnosed with MM 13 years prior to kidney transplant and achieved remission following autologous stem cell transplant. His native kidney biopsy at that time showed lambda light chain cast nephropathy and amyloidosis. Serological workup showed no evidence of a monoclonal paraprotein. A kidney biopsy was remarkable for glomerular mesangial matrix expansion with increased cellularity and segmental double contours. IF stained for IgG3 and kappa light chains, but not for lambda light chains. EM showed subendothelial and mesangial electron dense deposits. The patient was subsequently treated with Bortezomib and Dexamethasone with improvement of GFR to baseline and slight improvement in proteinuria to 4.1 g/g.

Results:

Conclusions: There are only limited case reports of PGNMID in renal allografts. It can present as a recurrence of the native kidney disease usually early after the transplantation or as a *de novo* glomerulonephritis years after the kidney transplant. We report a case of PGNMID that presented early after kidney transplantation in a patient who had myeloma cast nephropathy and amyloidosis on his native renal biopsy. The optimal treatment of PGNMID is unclear with mixed results using Rituximab. Early treatment with Bortezomib and high-dose Dexamethasone may be effective for the treatment of PGNMID but needs further study.



PUB487

Three Year Follow Up Results of Severe IgAN with CKD Treated by MP-Pulse Therapy and Autologous Adipose Derived SVF Byoung-Soo Cho,[1] Hyaejin Yun,[1] Sung min Jung,[1] Wang kwang Hong,[2] Daeyoung Kim.[3] *[1]Mirae Kidney Center, Seoul, Republic of Korea; [2]ByulE plastic surgery, Seoul, Republic of Korea; [3]N-biotek, Seoul, Republic of Korea.*

Background: As yet there is no specific method of treatment in severe IgAN associated with CKD, but giving ACEi, ARB, Omega-3, etc., however most patients eventually progress to ESRD and need RRT. Recently stem cell/SVF(stromal vascular fraction) therapy has been suggested as a promising option for CKD, attenuation of renal ischemia and reperfusion injury especially by SVF and adipose-derived mesenchymal stem cells. Our group have been reported a shorterm result of MP pulse therapy and adipose derived SVF at the ASN(2015,2016) in IgAN with CKD3. The mechanisms underlying this beneficial effect are still a matter of debate, therapeutic strategies aimed at correcting the potential of stem cells based on the administration of SVF. In this report we summarized 3 years follow up results as follows.

Methods: Case 1. : A 27-year-old male was diagnosed as IgAN with 24% glomerulosclerosis. Follow up renal biopsy after 10 cycles of MP followed by SVF in 1 year showed markedly decreased immune deposits without lesions of sclerosis. Laboratory results showed BUN/Cr 6.9/1.08, urine protein/Cr 0.974. Follow up lab after 2 years showed BUN/Cr 16.5/1.04, urine protein/Cr 0.145. Case 2. : A 45-year-old female was diagnosed as IgAN grade IV(HS Lee Classification) with 61% sclerotic glomeruli. Follow up renal biopsy after 10 cycles of MP followed by SVF in 1 year showed 41% sclerotic glomeruli with disappearance of IgA and C3 deposition. Initial serum Cr and GFR was 1.77mg/dl and 35ml/min. Follow up lab after 3 years showed 1.03mg/dl and 61ml/min. Case 3. : A 36-year-old female was diagnosed as IgAN grade V with 67% glomerular sclerosis. Follow up renal biopsy after 10 cycles of MP pulse followed by SVF in 1 year showed stage IV with 33% glomerulosclerosis. Initial serum Cr and GFR was 1.39mg/dl and 43ml/min. Follow up lab after 3 years showed 1.32mg/dl and 48ml/min.

Results:

Conclusions: In conclusion, although further longterm studies are needed, 3 years follow up of MP pulse followed by SVF treatment in severe IgAN with CKD might be promising new therapeutic strategies without noticeable side-effects or complications.

PUB488

State of Rituximab in Treatment of Minimal Change Disease: A Systematic Review Chandra M. Jha,[1] Hormaz D. Dastoor,[3] Ehab A. Elshukri,[4] Alind Kumar.[2] *[1]Nephrology, Gulf Diagnostic Center Hospital, Abu Dhabi, United Arab Emirates; [2]Nephrology, Julekha Hospital, Dubai, United Arab Emirates; [3]Nephrology, Rahba Hospital- Johns Hopkins International, ABU DHABI, United Arab Emirates; [4]Nephrology, Burjeel Hospital, Abu Dhabi, United Arab Emirates. Group/Team: ADHARR.*

Background: 90% of childhood &10-15% of adult Nephrotic Syndrome is caused by primary minimal change disease (MCD). Corticosteroid has remarkable success. Around 25% of patients have frequently relapse & 30% become steroid dependent. Chimeric monoclonal antibody Rituximab (RTX) induces B cell depletion. The pathophysiology & mechanistic involvement of B cells in MCD is poorly understood. Yet Rituximabb is reported to be used in its management. We aimed to review the literature to find answers about: 1. Efficacy of Rituximab in Frequently relapsing Nephrotic syndrrome due to MCD / FSGS in children and adult; 2. Dose & duration of RTX used for MCD; 3. Side effects / complications associated with its use.

Methods: We searched PUBMED, Chochrane Review Database and Govt. Trial Registry for the search term “rituximab in minimal change disease”, “rituximab in proteinuria” and “Rituximab in Glomerular diseases” during the period 1st January 1998 to 31st March 2017. We excluded the publications for membranous nephropathy, IgA nephropathy and secondary MCD. All publications including case reports, prospective and retrospective cohorts studies were included. Data was pulled from full text articles by lead author and independently verified by 2nd author. Revman 5 was used for review.

Results: There were 11 case reports & 3 case series (25 patients), two retrospective cohort studies (total 29 patients) and 16 prospective cohort studies (309 patients). There was one prospective randomized control study involving 48 patients. Few cases of FSGS in some studies were not excluded. RTX dose employed varied from single dose of 375 mg/M² two such doses, to 500 ng every sixth month for duration of two years. Rituximab was effective in bringing remission, reducing requirement of immunosupressives and reducing the recurrences. Treatment with mycophenolate was associated with poor response to Rituximab. FSGS was more prone to early relapse. Commonest side effect was infusion reaction, hypopropeinemia, lymphopenia & neutropenia, rash & fever.

Conclusions: Rituximab appears to be effective treatment without any serious complication in relapse or steroid dependent MCD. RTX requires to be evaluated as a second line of therapy if it could bring permanent or prolonged remission & less steroid dependence. Long term effect of RTX if any is unknown and observation in this direction is very much required.

PUB489

An Unusual Case of Unilateral Sensorineural Hearing Loss Associated with IgA Vasculitis Chuan Jiang, Jordan L. Rosenstock. *Nephrology, Lenox Hill - Northwell Health, New York, NY.*

Background: Immunoglobulin A vasculitis (IgAV), also known as Henoch-Schonlein Purpura, is a systemic disorder characterized by immune complex glomerulonephritis, arthalgias, leukocytoclastic vasculitis manifesting as palpable purpura, and abdominal pain. There are case reports and series in the pediatric literature highlight neurological manifestations such as headaches, seizures, central and peripheral neuropathies. We describe a case with unilateral sensorineural hearing loss associated with onset of renal biopsy proven IgAV. This association has not been previously reported.

Methods: A 28 year old Caucasian male without significant medical history was evaluated for renal insufficiency and edema. Clinical history revealed the patient had an upper respiratory infection about one month prior to evaluation that was treated with amoxicillin and followed by an extensive palpable purple leg rash associated with arthralgia, nausea, and anasarca. Concurrently, the patient also reported sudden hearing loss in his right ear associated with tinnitus. Workup revealed creatinine of 1.38g/dL, albumin 2.1 g/dL, and nephritic urine sediment (10 RBC/hpf) with 8.4g/g of proteinuria. Serologic evaluation was unrevealing. Renal biopsy revealed diffuse endocapillary proliferative glomerulonephritis, acute tubular injury, diffuse granular mesangial and glomerular capillary wall staining for IgA and C3, and electron microscopy demonstrated 70% podocyte foot process effacement. MEST scores M1, E1, S0, T0, C0. He also received ENT evaluation that identified severe sensorineural hearing loss in his right ear. MRI was unrevealing for intracranial pathology. Creatinine rose to 2.4mg/dL that likely reflected tubular injury due to the severe podocytopathy. High dose prednisone (1mg/kg dosing) and aggressive diuresis were initiated with improvement in renal function but the hearing loss has not yet improved.

Results:

Conclusions: Neurological manifestations are known sequelae of small vessel vasculitis such as IgAV. However, there are no cases in the literature describing an association with unilateral sensorineural hearing loss. This report extends the observed constellation of symptoms with IgAV to include unilateral sensorineural hearing loss, which has not yet resolved in our patient.

PUB490

Unusual Presentation of Secondary Syphilis Syed Rizwan A. Bokhari,[1] Adrian J. Baudy,[2] Myra A. Kleinpeter,[4] Laura R. Kidd,[3] Eric E. Simon.[2] *[1]Tulane School of Medicine, New Orleans, LA; [2]Tulane University, New Orleans, LA; [3]Tulane University Medical School, New Orleans, LA; [4]Tulane University School of Medicine, New Orleans, LA.*

Background: Nephrotic syndrome with secondary Membranous glomerulonephritis (MGN) is frequently encountered with autoimmune diseases, diabetes mellitus, exposure to toxins, malignancies and infectious agents. Infection-related MGN, secondary to syphilis is rarely seen with advancement of healthcare in developed countries.

Methods: We describe a case of 21-year-old African American HIV positive male with severe renal dysfunction and no known co-morbidities admitted with a 1 week complaints of epigastric pain, nausea, vomiting and diarrhea. Review of systems, family and allergic history were insignificant. Sexual history was positive for a single male partner of less than a year. Examination revealed maculopapular rash on trunk, few small axillary and inguinal lymph nodes, epigastric tenderness and perianal tenderness on palpation. Labs showed normal complete blood count, BUN and creatinine of 53 mg/dl and 7.1 mg/dl (baseline 1.1) respectively, with no electrolyte or liver function test abnormalities. Urinalysis showed 4+ protein, 2+ blood, negative for nitrite and bacteria. Urine microscopy and culture were unremarkable. Urine protein/creatinine was 7.3 g/g, Infectious profile was positive for HIV with viral load 1917 copies/mL, CD 4 count 306 cells/mm³ and strongly positive RPR. Autoimmune profile, complement levels, thyroid function tests, lipid profile, coagulation profile, serum and urine electrophoresis were all within normal limits. Renal ultrasound and CT abdomen were unremarkable, except for few abdominal lymph nodes. Patient received penicillin G benzathine 2.4 M units IM and percutaneous renal biopsy was consistent with early MGN and a patchy interstitial mononuclear cell infiltrate composed of predominately plasma cells. A treponemal (spirochete) immunohistochemical stain was very focally positive for spirochetes within the areas of plasma cell-rich interstitial infiltrate. Significant improvement in renal function was noted in a week with complete return to baseline within one month of discharge.

Results:

Conclusions: Syphilis has been traditionally associated with MGN with infrequent presentation in the current era, our case described the rare biopsy features of tubular involvement and interstitial inflammation. These findings are not always seen in the MGN

secondary to syphilis, however, if present, they are almost always associated with plasma cell rich infiltrate.

PUB491

Predictive Significance of Indicated Repeat Biopsy in Patients with Lupus Nephritis Krishan Lal L. Gupta, Joyita Bharati, Hari A. Prasad, Raja Ramachandran, Manish Rathi, Aman Sharma, Ritambhra Nada. *Postgraduate Institute of Medical Education & Research, Chandigarh, India.*

Background: Lupus nephritis, an important cause for morbidity and mortality in systemic lupus erythematosus, is characterized by remissions and relapses. Although repeat renal biopsy in a flare/resistant disease is suggested in almost all guidelines, few conclusive studies have investigated its role. We analysed the contribution of repeat renal biopsy in treatment decision and assessed various predictors of renal outcome.

Methods: Sixty-four patients who underwent repeat renal biopsy from January 2013 to January 2017 were included. Renal biopsy was done only when clinically indicated. The clinical and histological parameters at initial biopsy and repeat biopsy were compared. Multivariate regression analysis was used to determine factors significantly affecting renal outcome at last visit. Renal relapse and outcome (complete remission, partial remission, resistant) were defined based on KDIGO (Kidney Disease: Improving Global Outcomes) guideline.

Results: Repeat biopsy was done for relapse in 56% and for resistant disease in 44% of patients (56/64 underwent one repeat biopsy, 8/64 underwent 2 repeat biopsies). The median age of patients was 29 ± 9.6 years at initial biopsy and male to female ratio is 1:3. Nine (17%) out of 52 patients with baseline proliferative histology converted to non-proliferative disease while 3/12 (25%) with non-proliferative lesion converted to proliferative disease. After the second biopsy, 84% of patients had therapy changed. In multivariate analysis, the factors statistically significant for non-response at last visit are non-responsive disease to second line of therapy, non-nephrotic severe relapse, presence of IFTA (Interstitial fibrosis/tubular atrophy) at first biopsy, IFTA >25% at second biopsy, presence of diffuse glomerular basement membrane thickening and TMA (thrombotic microangiopathy) at second biopsy. With a median follow-up of 146 months, 48/64 (75%) patients have responded to therapy after the second biopsy, with 17/64 (26.5%) in complete remission and 5/64 (7.8%) needing renal replacement therapy.

Conclusions: Tubulointerstitial and vascular involvement in repeat biopsy were associated with poor response to therapy. This indicates ineffectiveness of current induction therapy in lupus nephritis. The practice of repeat renal biopsy is still an important and decisive tool.

PUB492

Survey of Deceased Children with Shiga Toxin-Associated Hemolytic Uremic Syndrome in Japan Shuichi Ito,[1] Mayumi Sako,[2] Takashi Igarashi.[2] *[1]Department of Pediatrics, Graduate School of Medicine, Yokohama City University, Yokohama, Japan; [2]National Center for Child Health and Development, Setagaya-ku, Japan.*

Background: In patients with Shiga toxin-producing *Escherichia coli* (STEC)-related hemolytic uremic syndrome (HUS), known major causes of death are encephalitis or intestinal perforation, but few studies have analyzed clinical features of deceased children.

Methods: We conducted a nation-wide retrospective survey of deceased children due to STEC-HUS between 2000 and 2014. We sent a questionnaire to 1100 institutes in Japan. We analyzed collected data.

Results: Eighteen patients (males 11; females 7) were studied. The median age at onset was 4 years (2.2-14.6 years) and the median weight was 13.5 kg (12–47 kg). O antigens of *E. coli* were O157 (n=10), O111 (n=4), O26 (n=2), and unknown (n=2). All patients developed AKI and thrombocytopenia. Convulsion and conscious disturbance were observed in 18 and 14 patients, respectively. Six patients developed acute cardiac failure and 5 had arrhythmia. The median day of death was 3 days from the onset of HUS (1-181days). Primary causes of death were encephalopathy (n=12), encephalopathy with acute cardiac failure (n=1), cardiac failure (n=4), and AKI (n=1). Types of intervention were dialysis (n=11), plasma exchange or infusion (n=8), anticoagulation (n=14), methylprednisolone pulse therapy (n=1), and antibiotics (n=14). The median day from onset of diarrhea to death was 20.7 days in patients treated with antibiotics (n=14), but 4 days in those who were not (n=4) (p=0.047). There were no significant differences in laboratory data and characteristics of patients at the diagnosis of HUS between those who died within 3 days (n=10) and after 3 days (n=8).

Conclusions: Most patients had rapid and devastating clinical course, and the median day from onset of HUS to death was only 3 days. The second main cause of death was acute cardiac failure. The time from onset of diarrhea to death was significantly longer in antibiotic-treated patients than in non-treated patients. Risks and benefits of antibiotics have not been clarified, but survival was improved in antibiotic-treated patients in an outbreak of O104:H4 in Germany (BMJ 2012). Significant efficacy of methylprednisolone pulse therapy against STEC-HUS encephalopathy was recently reported (Neurology 2014). A combination of antibiotics and methylprednisolone pulse therapy may improve outcome of patients with severe STEC-HUS.

PUB493

Hydroxychloroquine Induced Phospholipidosis Satya Sai V. Bhupathi,[1] Franco H. Cabeza Rivera,[2] Jorge L. Castaneda.[1] *[1]University Of Mississippi Medical Center, Madison, MS; [2]University of Mississippi Medical Center, Ridgeland, MS.*

Background: Systemic Lupus Erythematosus (SLE) is a systemic disease, can manifest as Lupus Nephritis and shown to overlap with other diseases. SLE is treated by a combination of steroids, immune-suppression and anti-malarial like Chloroquine (CQ) and Hydroxychloroquine (HCQ). Fabry is a X-Linked disease due to inactivation of Lysosomal Alpha-galactosidase (GAL) enzyme, renal biopsy is characterized by Zebra bodies on electron microscopy. We report a case of SLE on HCQ with zebra bodies and negative genetic testing.

Methods: A 35 y.o. AA woman is known to have SLE for 17 years, with Asthma, Myositis, HTN, Lupus Anticoagulant, PE on Warfarin. SLE treated with Azathioprine, Prednisone and HCQ. Noted to have increased proteinuria and hematuria. FH significant for SLE. She is non-smoker, no alcohol/drug use. Exam only positive for leg edema. Labs showed normal blood counts, sCr 0.8, electrolytes and C3/C4. Urine showed protein >300 mg/dL and RBC 50-100, 24 hr collection showed 2.42 gm of protein. HIV, Hepatitis B/C were negative and ANA/dsDNA positive. Protein electrophoresis and light chains were normal. Renal Biopsy showed areas of Mesangial depostis, rare sub-epithelial deposits and tubulo-reticular inclusion consistent with Class I LN. Abundant Zebra Bodies of varying sizes were noted in the visceral epithelial cell cytoplasm, characteristic of Fabry Disease. Further tests showed normal Plasma Lyso-Gb3 level and negative genetic GLA sequencing, ruled out Fabry. After discontinuation of HCQ, proteinuria improved and renal function stable.

Results:

Conclusions: Zebra bodies are mostly seen in primary renal phospholipidosis but described with various drugs like CQ, amiodarone and silicon. CQ induced Phospholipidosis was first described as CQ Keratopathy in 1977. CQ Cardiotoxicity was describe in a Mayo study in 2002. The first description of CQ Renal Phospholipidosis was reported in German in 2002. More recently HCQ has been associated with similar findings. Being a weak base HCQ is concentrated in lysosomes and inhibits enzymes like alpha-galactosidase, cathepsin, acid hydroxylase and phospholipases leading to Iatrogenic Phospholipidosis. Accumulation is higher in patients on higher doses of HCQ, prolonged exposure and renal failure. Fabry needs to be ruled out to establish diagnosis. Only few case reports of this association are reported and clinicians need to be aware of Drug Induced Phospholipidosis.

PUB494

Complete Remission of Severe Nephrotic Syndrome and AKI in Collapsing FSGS with a Combination of ACTH Gel and Abatacept – A Case Report Rebeca D. Monk. *University of Rochester, Rochester, NY.*

Background: Focal segmental glomerulosclerosis (FSGS) is now the most prevalent primary nephrotic disorder. The collapsing variant of FSGS often portends a poor prognosis. Patients develop severe nephrotic syndrome (NS) with ensuing kidney failure despite therapy. This case demonstrates success using combination therapy with Abatacept and ACTH gel.

Methods: A previously healthy 32 year old florist presented with 3+ leg edema. Initial creatinine (Cr) was 0.99. Alb 2.0, Cholesterol 404, 24h urine, protein:creat ratio were both consistent with 8 g of proteinuria. Kidney biopsy revealed FSGS-- collapsing variant with Ki-67 immunostaining. She was treated with 1 mg/kg prednisone, lisinopril and furosemide. She developed AKI and hyperkalemia with no improvement in anasarca. Due to high K (5.9) and Cr (to 2' s), calcineurin inhibitors were not felt safe to use. Cellcept was initiated with iv diuretics in the hospital. Steroids were continued. She suffered numerous medications side effects including proximal myopathy, severe anemia on cellcept and methemoglobinemia from Dapsone. Months later she was 45 lbs greater than baseline weight of 100 lbs. Cr was 3 (GFR 19) and protein:creatinine ratio remained 30 to 50. B7-1 stain was ordered and Abatacept was started. 3 weeks later insurance for ACTH gel (Acthar ®) was approved. B7-1 staining was negative but both medications were continued for 9 months. Over the first 2 months she lost 40 lbs. One months later, Cr decreased to 0.83, MA:creat ratio 766. Eight months after initiation MA:creat ratio was 255. 3 years later she remains disease free and pregnant with her first child.

Results:

Conclusions: This patient with no response to prior therapy of collapsing FSGS had a surprising full recovery of disease with combined ACTH gel and Abatacept. ACTH stimuates melanocortin receptors including MC1R on podocytes. Activation of MC1R may have a variety of podocyte protective effects but few pts with FSGS have had complete remissions with ACTH. Theoretically, Abatacept inhibits B7-1 binding to β-1 integrin, an action that prevents podocyte migration and proteinuria. However, our patient was B7-1 negative. The mechanism by which one or both of these drugs led to complete remission in this case is not clear. Further studies may elucidate the benefits of this therapy.

PUB495

Spontaneous Resolution of Histiocytic Glomerulopathy in a Patient with Secondary HLH after a Presumed Acute Viral Illness Bhavin Chokshi, Kisra Anis. *Jacobi Hospital Medical Center, Bronx, NY.*

Background: Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of excessive immune activation leading to massive infiltration of activated macrophages.

Following first description in 1939, substantial advances have been achieved in the understanding the pathophysiology and clinical course leading to identification of growing number of cases. Despite this, renal complications of HLH remain poorly documented. Immunosuppression remains the mainstay of treatment and spontaneous resolution have not been shown so far.

Methods: Our patient is a 33-year-old female with history of hypothyroidism, who was admitted with puffiness of face, fever and pitting leg edema. Laboratory work up revealed acute kidney injury with albuminuria of 5.1 grams, elevated liver transaminase, bicytopenia, elevated ferritin, low fibrinogen and active urine sediments with granular and hyaline casts and oval fat bodies. Ultrasound showed normal sized kidneys with normal echogenicity. The kidney biopsy revealed glomeruli with prominent infiltrating monocytes/histiocytes & endothelial swelling, most consistent with histiocytic glomerulopathy. Following kidney biopsy, she received supportive care as her renal function started to improve. She was discharged home six days after biopsy with clinical improvement and kidney function reaching baseline and albuminuria of 123 mg. She was followed up in the out patient clinic and has normal GFR with no albuminuria six months post discharge.

Results:

Conclusions: HLH is often triggered by infectious, autoimmune, neoplastic diseases and sometimes multiple causes exist. Most recent modification of diagnostic criteria include three of four clinical findings (fever, splenomegaly, cytopenia, hepatitis) plus one of four immune markers (hemophagocytosis, increased ferritin, hypofibrinogenemia, absent or very decreased NK cell function). We report a case of HLH after a presumed acute viral illness, who fulfilled criteria of HLH with histiocytic glomerulopathy and had spontaneous, rapid resolution of nephrotic syndrome and renal insufficiency in the absence of immunosuppressive therapy. Our case highlights the potential reversibility of the secondary HLH in clinically stable patient. Further research is needed to understand more about this rare disease and reporting of clinical presentations and outcomes of all cases are recommended.

PUB496

Glomerular Inflammatory and Lipid Related Genes Correlate with Clinical Variables in Patients with FSGS Undergoing a Kidney Transplant Sandra M. Merscher,[1] Lilian A. Otalora,[1] Efren A. Chavez,[2] Daniel J. Watford,[2] Lissett Tueros,[3] Mayrin Correa,[4] Viji Nair,[5] Phillip Ruiz,[3] Sean Eddy,[5] Matthias Kretzler,[5] George W. Burke,[3] Alessia Fornoni.[1] *[1]Katz Family Division of Nephrology and Katz Family Drug Discovery Center, University of Miami, Miami, FL; [2]Jackson Memorial Hospital, Miami, FL; [3]Department of Surgery, University of Miami, Miami, FL; [4]Department of Pathology, University of Miami, Miami, FL; [5]Dept. of Internal Medicine and Computational Medicine and Bioinformatics, University of Michigan, Ann Arbor, MI.*

Background: Focal segmental glomerulosclerosis (FSGS) is a common glomerular disorder and recurrence of nephrotic range proteinuria (REC) post transplantation (PT) occurs in up to 70% of high risk patients. Podocyte foot process effacement (FPE) in post-reperfusion (PostR) biopsies can be detected early and correlates with REC. We previoulsy showed that decreased Sphingomyelinase phosphodiesterase-like 3b (SMPDL3b) expression in PostR kidney biopsies predicted REC and was associated with foot process effacement (FPE) suggesting that SMPDL3b may be a susceptibility factor intrinsic to podocytes contributing to the pathogenesis of FSGS. The current study was aimed at confirming our previous observations and at identifying mechanisms by which SMPDL3b may contribute to the REC in FSGS.

Methods: Serum, urine and glomerular biopsies from forty-six patients with FSGS undergoing kidney transplantation were obtained. Microarray analysis, immunohistochemistry (IHC) and electron microscopy (EM) were performed using Pre (PreR) and PostR biopsy samples. Serum samples were also used for *in vitro* studies. Correlation analysis between genes important in modulating lipid metabolism and the immune response and morphometric variables such as FPE in PT kidney biopsies and clinical variables (proteinuria, estimated GFR) was performed.

Results: SMPDL3b expression was not significantly modulated in PostR kidney biopsies but weakly correlated with eGFR at 1 year. Inflammatory and lipid related pathways were highly regulated in glomeruli of PostR kidney biopsies and in podocytes exposed to the sera obtained from a subset of patients with FSGS.

Conclusions: We identified a small set of glomerular inflammatory and lipid related genes that correlated with clinical variables and may be utilized to stratify patients for PT REC and decline of GFR.

Funding: NIDDK Support, Private Foundation Support

PUB497

Proliferative Glomerulonephritis with Monoclonal Immune Deposits Associated with a Bladder Mass Ranine Ghamrawi,[2] Arjun Sekar.[1] *[1]Cleveland Clinic Foundation, University Heights, OH; [2]Hurley Medical Center/Michigan State University, Flint, MI.*

Background: A new entity called proliferative glomerulonephritis with monoclonal immune deposits (PGNMID) has been added to the spectrum of monoclonal gammopathies of renal significance (MGRS). The pathogenesis and management of this entity have not yet been clearly described. We report a case of PGNMID with an associated bladder mass.

Methods: 76 y old male patient with hypertension and diabetes mellitus type 2 presented with dyspnea, generalized swelling of the body and acute kidney injury (AKI). Physical examination was significant for confusion, edema and asterixis with stable vitals. Creatinine(Crea) was 3.7 up from a baseline of 1.1. Complete blood count(CBC), and electrolytes were within normal limit. Protein/Crea ratio was 4.4. Serology for hepatitis B and C, anti- neutrophilic cytoplasmic antibodies (ANCA), anti-nuclear antibody (ANA), anti-histones, anti – double stranded DNA were all negative. C3, and C4 and serum cryoglobulins were normal. Serum kappa and lambda, and M proteins were not elevated. Renal ultrasound and chest x- ray were normal. Renal biopsy was done and showed 19 glomeruli with 5 sclerosed. There was marked endocapillary hypercellularity with subepithelial and subendothelial immune complex deposits and 10-20% fibrosis. Immunofluorescence (IF) was positive for IgG3, C3c, C1q, and kappa light chains. Electron Microscopy (EM) showed focal subendothelial and subepithelial electron dense immune complex deposits. The biopsy was suggestive of PGNMID as there was IgG3 staining of mesangium and capillary loops. The patient was started on steroids, with improvement in the confusion, dyspnea and kidney function (Crea down to 1). Work up for malignancy included CT scan which showed a large bladder mass. Biopsy of the mass was deferred as the patient was later switched as per request to palliative care.

Results:

Conclusions: PGNMID is a newly recognized entity caused by monoclonal deposition of IgG. The diagnosis and treatment is made by histology and robust data is lacking. Different immunomodulators particularly steroids have been tried successfully and some cases reported complete remission. PGNMID has also been occasionally associated with different malignancies, mostly hematological. This case demonstrates a case of PGNMID associated with a solid bladder mass that showed initial improvement by steroids within one week of treatment.

PUB498

Association of Mesangial IgM Deposits with Rapidly Progressive Diabetic Nephropathy Bronwyn Leblanc,[4] Juan Carlos Q. Velez,[5] Mark Lusco,[1] Meghan E. Kapp,[2] Ivo Lukitsch.[3] *[1]Pathology, Vanderbilt University School of Medicine, Nashville, TN; [2]Pathology, Vanderbilt University Medical Center, Nashville, TN; [3]Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA; [4]Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA; [5]Department of Nephrology, Ochsner Clinic Foundation, New Orleans, LA.*

Background: Classic diabetic nephropathy (DN) is characterized by progressive proteinuria and decline in kidney function over a period of 10-15 years. However, when the clinical course does not fit the norm, a kidney biopsy is often performed to confirm the diagnosis. Whether the tissue specimens of those who require kidney biopsy and are found to have DN disclose additional unique pathological findings is not well established.

Methods: We performed a retrospective review of clinical data and kidney biopsy results from patients with long-standing type 2 diabetes mellitus who underwent kidney biopsy for the following indications: 1) rapid onset or worsening of proteinuria uncharacteristic for DN (n=5) and 2) positive serum protein electrophoresis for monoclonal gammopathy (n=3) suspicious for plasma dyscrasia; and were found to have pathologic evidence of DN.

Results: Eight cases were identified. The mean age of the cohort was 62 years, predominantly African American (62%), with equal percentage of men and women. The mean serum creatinine, estimated glomerular filtration rate (eGFR) and urine protein-to-creatinine ratio values at the time of the biopsy were 2.39 mg/dL, 30.1 ml/min and 8.7 g/g, respectively. Glomerular findings consistent with DN and arterionephrosclerosis were present in all cases. In addition, varying degrees of mesangiopathic changes were noted by light microscopy, along with mesangial IgM deposition by immunofluorescence and electron microscopy. Five patients had a rapidly progressive course (decline in eGFR > 10ml/min/year) and three of them required renal replacement therapy within one year post biopsy. The median rate of decline of kidney function was estimated at -11 ml/min/year (range: +3.2 to -28.0).

Conclusions: Although IgM mesangial deposition is often associated with minimal change disease or focal segmental glomerulosclerosis, evidence of its association with DN is sparse. Our results suggest that mesangial IgM deposition may be found in individuals with DN exhibiting an unusual clinical course and this finding could be associated with an accelerated course of DN. Further investigation is warranted to better characterize this entity.

PUB499

All the Right Hits: APOL1, CMV, and Collapsing Focal Segmental Glomerulosclerosis Stephenie Le, Ritu Modi, Anum Bilal, Rafia I. Chaudhry, Richard J. Blinkhorn, Loay H. Salman, Krishnakumar D. Hongalgi. *Albany Medical College, Albany, NY.*

Background: Collapsing focal segmental glomerulosclerosis (FSGS) is the main pathologic feature of HIV associated nephropathy. Non-HIV collapsing FSGS is much less common, but increasingly recognized. We present a case of collapsing FSGS in a patient, 11 months postpartum, with sickle hemoglobinopathy, APOL1 gene mutation, and cytomegalovirus (CMV) viremia.

Methods: A 31 year old African American female with SC hemoglobinopathy presented with fever, sore throat, sinus congestion, myalgia, vomiting, and dark urine. There was no illicit drug or NSAID use. Creatinine (Cr) 2.3 mg/dL, hemoglobin 9.5 g/dL, respiratory viral panel positive for parainfluenza virus. Spot urine protein/Cr was 9.8 g/g. Cr eventually peaked at 7.2 mg/dL. Plasma CMV by PCR was 2594 IU/mL, and CMV IgM antibody titer was >240 AU/mL. Tests for HIV, hepatitis B, hepatitis C, and parvovirus B19 were negative. Renal biopsy showed collapsing of capillary loops, prominent overlying epithelial cells, and extensive foot process effacement on

EM, without endothelial deposits. Immunostaining was negative for viral inclusions in glomeruli. APOL1 genotyping showed heterozygosity for G1 and G2 alleles. The patient was treated with corticosteroids and ganciclovir, with subsequent improvement: Cr to 1.1 mg/dL (without renal replacement therapy), CMV by PCR became undetectable, and proteinuria declined to 3 g/g.

Results:

Conclusions: While collapsing FSGS is traditionally associated with HIV, non-HIV viruses are now emerging as potential triggers. A "two hit" mechanism has been proposed; wherein genetically susceptible hosts with the APOL1 gene polymorphism, subsequently exposed to an environmental trigger, such as viral infection, results in activation of the immune system and local podocyte destruction. Our patient had heterozygous APOL1 genotype and CMV viremia leading to collapsing FSGS. Collapsing FSGS is typically associated with poor renal outcomes and progression to end stage renal disease, however, early recognition and prompt treatment of CMV with ganciclovir and corticosteroids for FSGS resulted in clearance of viremia and renal recovery in our patient.

PUB500

Fibrillary Glomerulonephritis (FGN): A Rare Clinical-Pathologic Entity, Not Always with Poor Renal Outcomes! Swati Mehta,[1] Anum Bilal,[1] Arif Asif,[4] Llewellyn A. Foulke,[2] Adam Austin,[3] Rafia I. Chaudhry.[5] *[1]AMC, Albany, NY; [2]Albany Medical Center, Albany, NY; [3]Albany Medical College, Albany, NY; [4]Jersey Shore University Medical Center, Neptune, NJ; [5]None, Albany, NY.*

Background: FGN is a renal deposition disease characterized by 10-30 nm thickness, disorganized, straight fibrils in the mesangium and glomerular basement membrane (GBM) on electron microscopy (EM). FGN is reported in 0.5-1% of native renal biopsies.

Methods: 5 cases of FGN presented to Albany Medical Center (AMC) over the last 12 years.986 native renal biopsies were performed in this period, confirming an incidence of 0.5% of FGN amongst native renal biopsies at AMC. We present 3 cases (follow-up data missing in the remaining 2).

Results: Mean age of diagnosis was 66 years, 2 Caucasians, with male to female ratio 2:1. Presenting features: nephrotic syndrome (2/3), AKI (2/3) with mean Cr 1.4mg/dL, hematuria (3/3) and hypertension (3/3). 1 patient (Pt) was diagnosed with Multiple Myeloma. LM revealed mesangial GN (1/3), membranous GN (1/3), and membranoproliferative GN (1/3), with polyclonal IgG and C3 on IF for all 3, and IgG4 subclass in 1. EM was diagnostic with 10-30 nm fibrils in mesangium and GBM, and sub epithelial deposits. All 3 patients received RAS blockade, and during a 35 month follow up: Pt 1(initial Cr 1 mg/dL, 11 gms proteinuria): progressed to ESRD despite immunosuppression (IS) with rituximab. Pt 2 (initial Cr 0.6 mg/dL, 6.8 gms proteinuria): partial remission with corticosteroids and tacrolimus. Pt 3 (initial Cr 2.7): did not receive IS, and Cr stabilized at 2.7.

Conclusions: FGN predominates in Caucasians, and most patients are 40-60 yrs old, presenting with nephrotic range proteinuria, with or without renal insufficiency and hematuria. Previously considered an idiopathic disease, FGN may herald systemic illnesses, with autoimmune conditions or malignancy found in a third of cases in a large Mayo clinic series. Histologic findings are widely variable, although mesangial GN and MPGN are reported in most cases, along with diagnostic fibril deposits. The therapeutic strategy remains poorly defined, and renal survival is poor, with 50% patients reaching ESRD despite RAS blockade and IS. Prospective, controlled studies are limited by the rarity of the disease, and data on optimal therapeutic regimen is lacking.

PUB501

Unusual Presentations of Anti-GBM Disease: A Case Series Anum Bilal,[1] Adam Austin,[1] Loay H. Salman,[1] Arif Asif,[2] Swati Mehta,[1] Llewellyn A. Foulke,[1] Roman Zuckerman,[2] Rafia I. Chaudhry.[1] *[1]Albany Medical College, Albany, NY; [2]Jersey Shore University Medical Center, Neptune, NJ.*

Background: Anti glomerular basement membrane (anti-GBM) disease is a small vessel vasculitis with antibodies (Ab) to the basement membrane of pulmonary and renal capillaries. The prevalence of anti-neutrophil cytoplasm antibodies (ANCA) with anti-GBM, i.e. double positive disease, is estimated at 30%.

Methods: We present 10 cases of anti-GBM disease diagnosed by renal biopsy for RPGN from 2009-2017 at Albany Medical Center. 60% were male, 90% Caucasian, aged 15-82 yrs. 2 patients had pulmonary hemorrhage; both non-smokers, with prior history of asthma in 1. 40% tested positive for ANCA (all P-ANCA: 3 MPO, 1 PR3), consistent with the reported prevalence of double positive disease. 8 of 10 patients required hemodialysis (HD) and only 1 had renal recovery, while 7 progressed to ESRD. Both cases that did not require HD, and the only case of renal recovery, had double positive disease. All patients received cyclophosphamide, corticosteroids and plasmapheresis. One patient was switched to rituximab due to pancytopenia, and a subsequent diagnosis of multiple myeloma. Anti-GBM titers decreased with plasmapheresis in all cases. 5 patients received renal transplants without recurrence of anti-GBM disease. Anti-GBM Ab prior to transplantation were negative in all cases, consistent with data suggestive of decreased risk of recurrence post-transplant with low pre-transplant anti-GBM Ab titers.

Results:

Conclusions: Anti-GBM classically has a bimodal age distribution with peak incidence in the 3rd and 6th decades. Our series does not support this pattern, with at least 1 case in every decade of life (between age 10-90), except the 8th (70-79 yrs). Prior reports demonstrate mixed renal outcomes in double positive disease, including a correlation with poor renal prognosis in some studies. However, the 30% renal survival in our series was amongst double positive cases. The low incidence of pulmonary hemorrhage may be due to screening based on renal biopsy, while notably both cases were non-smokers. We did not note a seasonal pattern to the disease (only 50% presented in the warmer months). Despite the severity of anti-GBM disease, and associated high mortality, we have 100% patient survival to date.

PUB502

A Rare Etiology of Renal Failure in Chronic Hepatitis C Viral Infection Arun Rajasekaran,[1] Mario A. Mendoza,[2] Edward T. Casey.[2] *[1]University of Central Florida College of Medicine, Kissimmee, FL; [2]Nephrology, Orlando VA Medical Center, Orlando, FL.*

Background: Chronic hepatitis C viral (HCV) infection is strongly associated with immune mediated glomerular diseases, including membranoproliferative glomerulonephritis (MPGN), and rarely fibrillary glomerulonephritis. We describe a case of fibrillary MPGN in a patient with HCV infection, with no improvement in renal function despite achieving sustained virologic response after anti-viral therapy.

Methods: A 60-year-old white male with treatment-naïve HCV infection presented with a four month history of progressive leg swelling. He was taking high doses of non-steroidal anti-inflammatory (NSAIDs) agents for pain relief. On examination, there was pitting edema in the legs. Serum creatinine was 4.1 mg/dl (1.2 mg/dl a year ago), urine studies showed hematuria and nephrotic range proteinuria. HCV RT-PCR returned at 405,073 IU/ml (normal <12), and testing revealed genotype-1a. Serology revealed normal ESR and complement levels. HIV, ANA, ANCA, and cryoglobulins were negative. NSAIDs were stopped and his hypertension treated. A kidney biopsy showed normal sized glomeruli with a mesangial matrix expansion that stained positive for H&E and PAS. There was severe widespread tubular atrophy and interstitial fibrosis, along with severe intimal fibrosis of blood vessels. On immunofluorescence, there was global mesangial and capillary wall "smudged" deposits staining 3+ for IgG, 2+ for C3 and 2-3+ for kappa and lambda light chains. Electron microscopy showed ill-defined fibrillary deposits within an expansile mesangium, and glomerular basement membrane global thickening with severe foot process effacement of the visceral epithelial cells. These findings were consistent with a fibrillary MPGN. 12 week treatment with elbasvir-grazoprevir lead to undetectable viral loads; however his renal function progressively worsened to chronic kidney disease stage V.

Results:

Conclusions: Fibrillary MPGN is a rare cause of renal failure, manifestations range from nephrotic syndrome to overt renal failure. Few cases of this renal disease have been associated with HCV infection and elevated viral titers. The patient's kidney biopsy showed severe glomerular sclerosis, tubular atrophy and interstitial fibrosis that predicted a poor renal response to treatment of his HCV. This case highlights an unusual renal manifestation of HCV infection, along with the need for early recognition and treatment of HCV.

PUB503

Persistent, Heavy Proteinuria Despite Discontinuation of VEGF Inhibitors for Renal Cell Carcinoma Dheeraj Kaul,[3] Himabindu Valluru,[2] Philip Goldwasser,[2] Gary R. Briefel,[1] Man S. Oh,[2] Ian L. Provancha.[4] *[1]Kings County Hospital, Brooklyn, NY; [2]None, Brooklyn, NY; [3]Nephrology, SUNY Downstate Medical Center, Brooklyn, NY; [4]SUNY Downstate Medical Center, Brooklyn, NY.*

Background: Axitinib is an antineoplastic tyrosine kinase inhibitor targeting VGEF receptors used against renal cell carcinoma. Proteinuria, hypertension and renal dysfunction are known adverse effects, but nephrotic range proteinuria rarely continues after the medication is discontinued. We report a case of nephrotic range proteinuria within 10 days after initiation of axitinib.

Methods: A 66 year old man with type 2 diabetes, hypertension, hyperlipidemia and obstructive sleep apnea and stage 3b CKD with a diagnosis of renal cell cancer treated with left nephrectomy in 2001. In 2015, lung metastases from renal cell cancer were found, for which sunitinib was started. Prior to the start of sunitinib, a 24 h urine albumin was 383 mg/day and protein 754 mg/day. Because of neutropenia, sunitinib was discontinued on October 2015. Axitinib 5 mg daily was started on 1/1/16. On 2/29/16, protein excretion was 16.7 g/day. Axitinib was increased to 5mg BID on 3/16/16. On 3/31/16, albumin excretion was 18.0 g/day and urine protein 23.3 g/day. Although Axitinib was discontinued that day, the heavy proteinuria persisted: 15.2 g/day (Apr. '16), 11.1 g/day (Nov '16), 16.3 g/day (Feb '17).

Results:

Conclusions: Proteinuria induced by tyrosine kinase inhibitors directed against VGEF receptors is usually mild to moderate, but occasionally severe enough to cause nephrotic syndrome. Proteinuria usually improves upon discontinuation of the drug. The persistence of severe proteinuria could be due to another mechanism, but a solitary kidney prevented diagnostic biopsy.

PUB504

Membranoproliferative Glomerulonephritis and the "Lollipop" Lymph Node Follicles Manish K. Saha,[4] Ritika Ohri,[2] Denyse Thornley-Brown,[1] Huma Fatima.[3] *[1]UAB, Birmingham, AL; [2]University Of Alabama at Birmingham, Hoover, AL; [3]University of Alabama at Birmingham (UAB), Birmingham, AL; [4]Medicine, University of Alabama at Birmingham, Birmingham, AL.*

Background: Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury which is either immune-complex or complement mediated, based on immunofluorescence (IF). We describe a rare case of MPGN with a negative IF for any immunoreactant.

Methods: A 44-yr-old woman presented with abdominal distension and anasarca. Physical examination revealed ascites, lower extremity edema, parotid enlargement, and diffuse adenopathy. Hemoglobin was 7.7 gm/dL, platelet count 110-192 x 10^3 /μL, serum creatinine 2.3 mg/dL, spot urine protein/creatinine ratio 0.4 mg/mg; urinalysis showed 3-10 red blood cells per high-power field. Serum LDH, complements and haptoglobin levels were normal. Significant radiographic findings included: diffuse lymph node enlargement in the neck, chest, abdomen and pelvis, hepatomegaly, and ascites. Ultrasound of the kidneys was normal. Immunoelectrophoretic studies, autoimmune and infectious disorders were negative. The kidney biopsy showed a classic membranoproliferative pattern of glomerular injury (MPGN) by light microscopy. No specific staining for immunoglobulins or complements was identified by immunofluorescence. Electron microscopy was negative for immune-complex deposits. These morphologic features in the absence of immune-complex deposits were consistent with chronic thrombotic microangiopathy (TMA). Lymph node biopsy showed "lollipop" appearance of lymph node follicles: concentric layers of small lymphocytes in the mantle zone penetrated by a hyalinized blood vessel. Multicentric Castleman's Disease (MCD) was diagnosed based on systemic findings, lymph node and renal histology.

Results: .

Conclusions: MCD is a group of lymphoproliferative disorders which may have renal involvement due to amyloidosis, MPGN, and interstitial nephritis. Circulating levels of IL-6 and VEGF were elevated in our patient, which are thought to be the mediators of inflammation and microangiopathy, respectively. Our patient was initially treated with the IL-6 inhibitor siltuximab; however, creatinine continued to rise, and peaked at 4.8 mg/dL. She was subsequently treated with rituximab, with improvement of creatinine to 1.0 mg/dL. Although uncommon, MCD should be on the differential diagnosis of a patient with immunoglobulin and complement negative MPGN and systemic findings of lymphadenopathy, fever and hepato-splenomegaly .

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PUB505

Leukocytoclastic Vasculitis Heralding Immunoglobulin G4-Related Kidney Disease Anubhav Kumar, Jia hwei Ng, Jehan Z. Bahrainwala. *Nephrology, Penn-Presbyterian Medical Center, Philadelphia, PA.*

Background: Immunoglobulin G4-related disease (IgG4-RD) is a systemic inflammatory disorder that can affect multiple organs. IgG4 related kidney disease (IgG4-RKD) is a rare cause of kidney disease, though it is becoming more widely recognized as a cause of serious renal morbidity. It most commonly manifests as tubulointerstitial nephritis. We describe a case of IgG4-RKD preceded by leukocytoclastic vasculitis of the skin.

Methods: A 70 year-old Caucasian female with no prior history of kidney disease was directly admitted to our institution for acute kidney injury. Over the course of one year prior to admission, she experienced unintentional weight loss, lower extremity purpuric macules and submandibular swelling. Her serologies were notable for low C4 (11 mg/dl) and C3 (75mg/dl), high RF (>600 IU/ml). She had negative SSA/SSB, ANCA, Hepatitis B, Hepatitis C and HIV serologies. A skin biopsy was consistent with leukocytoclastic vasculitis. A salivary gland biopsy was not diagnostic. She was treated briefly with prednisone that improved her symptoms. On routine blood work prior to admission, her creatinine was 3.8 mg/dl; an increase from 1 mg/dl two months prior. She was admitted for urgent work up. Her creatinine peaked at 4 mg/dl. Her repeat serologies were negative. Her spot urine to protein creatinine ratio was 1.4 g/g. Her IgG4 levels were elevated at 419 mg/dL (1-123). Renal imaging showed large kidneys, 15 cm each, without hydronephrosis. Her kidney biopsy showed a diffuse dense infiltrate of plasma cells and lymphocytes; > 50 IgG4-positive cells in a single high-powered field, without evidence of lymphoproliferative or plasma cell disorders, consistent with IgG4-RKD. She was pulsed with methylprednisolone and discharged on high dose oral prednisone with a plan to taper over 12 weeks. Her creatinine decreased to 1.86 mg/dL within two weeks of diagnosis.

Results:

Conclusions: IgG4 related skin disease is typically due to IgG4 plasma cell infiltration in the skin lesions but other non-specific, inflammatory skin lesions have been described. This case represents a rare case of IgG4-RKD associated with leukocytoclastic vasculitis. Early recognition of the disease is important as it commonly responds rapidly to steroid therapy.

PUB506

ANCA Associated Vasculitis: Experience of a Tertiary Care Referral Center Rafia I. Chaudhry,[1] Anum Bilal,[1] Adam Austin,[1] Swati Mehta,[1] Loay H. Salman,[1] Paul J. Feustel,[1] Llewellyn A. Foulke,[1] Roman Zuckerman,[2] Arif Asif.[2] *[1]Albany Medical College, Albany, NY; [2]Jersey Shore University Medical Center, Neptune City, NJ.*

Background: Anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV) is a small-vessel vasculitis that encompasses Granulomatosis Polyangitis (GPA), Microscopic Polyangitis (MPA) and Eosinophilic GPA. U.S. incidence estimates are limited, and European data suggest 10-20 cases per million per year. Renal manifestations of AAV include rapidly progressive glomerulonephritis. While the gold standard for diagnosis is pauci immune glomerulonephritis on renal biopsy, the term AAV is coined from associated circulating antibodies detected by neutrophil immunofluorescence demonstrating cytoplasmic (cANCA), perinuclear (PANCA) or atypical patterns in a majority of these vasculitides.

Methods: We identified 54 cases of AAV from 986 renal biopsies (5.47% of total biopsies) performed at Albany Medical Center (AMC) from January 2005 to April 2017. 41 cases met inclusion criteria: 18 GPA, 19 MPA and 4 Dual Positives, i.e. anti-GBM with ANCA positivity.

Results: 90% were Caucasians, 56% male, and mean age 52.41. The mean values for laboratory data were: Sr creatinine 3.9 mg/dL, albumin 2.7 g/dL, and hemoglobin 9.7 g/dL. 73% of the cases had hypertension, 17% had nephrotic range proteinuria, and hematuria was present in 100%. 32% (13 cases) required hemodialysis (HD), and of these, 7 came off HD by week 24. Statistical significance: C-ANCA positivity in GPA vs MPA ($p<0.001$), P-ANCA in MPA vs GPA ($p<0.001$), C-ANCA-PR3 pairing in GPA ($p=0.003$), P-ANCA-MPO in MPA ($p=0.003$). All 4 Dual Positive cases were seropositive for P-ANCA. 4 cases did not have ANCA positivity, and met criteria for AAV based on biopsy and clinical features. Of note, 8 of the 41 cases presented in 2016, and 16 presented from within a 15-mile radius.

Conclusions: Our data suggests that AAV is seen at a significantly higher rate in patients meeting criteria for renal biopsy at AMC. We postulate that this may reflect an increased regional incidence of AAV in the Capital District. In addition to the clustering of AAV, there appears to be a temporal relationship, with a higher number of cases in certain years. Prior studies suggest interplay of environmental and genetic factors resulting in varying incidence of AAV, which may explain the higher numbers of AAV presenting to our hospital.

PUB507

Recurrent Atypical Anti-Glomerular Basement Disease in a Kidney Transplant Patient Samir A. Brahmbhatt,[3] Basheer A. Kummangal,[1] Leal C. Herlitz,[1] Richard A. Fatica,[4] Saul Nurko.[2] *[1]Cleveland Clinic, Cleveland Heights, OH; [2]Cleveland Clinic Foundation, Cleveland, OH; [3]Cleveland Clinic Foundation, Cleveland, Ohio, Beachwood, OH; [4]The Cleveland Clinic, Cleveland, OH.*

Background: Atypical anti-glomerular basement disease (anti-GBM) is a rare variant of anti-GBM disease characterized clinically by an indolent course usually. Compared to typical anti-GBM, there is no circulating alpha-3NC1 antibody, no diffuse crescentic and necrotizing glomerulonephritis, and quasi-linear IgG staining on a kidney biopsy. Here we report a case of a recurrence in a renal transplant.

Methods: 23 year old Caucasian female with end-stage renal disease attributed to membranoproliferative glomerulonephritis, status post living related donor kidney transplant, on Tacrolimus, Mycophenolate Mofetil, Prednisone, with last known stable graft function with serum creatinine (SCr) 1.8 mg/dL one year ago. After 5 years and 1 month of her transplant, she presented with nausea, vomiting x 3 days, low-grade fever and acute kidney injury with SCr 5.88 mg/dL. Initial basic work up showed no evidence of obstruction and there was no significant improvement in graft function after intravenous hydration. There was a high suspicion of a rejection as she was found to have 2 ng/mL Tacrolimus trough levels, so a transplant kidney biopsy was performed. It showed diffuse endocapillary proliferative with membranoproliferative features and focal crescentic formations. Immunofluorescence showed diffuse linear positivity of GBM with IgG, kappa and lambda, suggestive of atypical anti-GBM nephritis. In addition, there was Banff Grade 1B acute cellular rejection and acute antibody-mediated rejection. She had a negative serum anti-GBM antibody. She was treated with plasmapheresis, intravenous Methylprednisone, then 60 mg Prednisone orally daily and Rituximab infusions, continued on Tacrolimus and stopped Mycophenolate Mofetil. She did not require dialysis. Her SCr improved to 3.53 mg/dL with estimated glomerular filtration rate 16 mL/min/1.73m2 on 2 months follow up.

Results:

Conclusions: This is the only 3rd reported case of recurrent atypical anti-GBM disease in a renal transplant patient. Optimal therapy for atypical anti-GBM disease in both native kidneys and after recurrence in the transplant remains controversial, as this is a rare disease entity. Further studies are needed to characterize the molecular architecture of GBM auto-antigens in these patients and establish optimal therapy.

PUB508

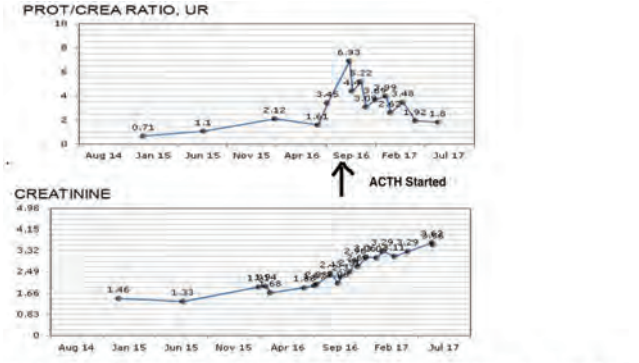
Acthar® (ACTH) Therapy in Post-Transplant De Novo IgA Nephropathy (IgAN) Asma Hasan, Nelson P. Kopyt. *Lehigh Valley Hospital, Allentown, PA.*

Background: IgAN has been reported to recur Post-Transplant as well as De Novo. We present a case of De Novo IgAN treated with 6 months of ACTH.

Methods: 32 YO F presented with AKI at age 18 due to Hemolytic Uremic Syndrome: native renal biopsy revealed acute thrombotic microangiopathy with extensive ATN. Immunofloresence (IF) staining was negative for IgA. Despite aggressive treatment with pulse steroids/plasmapheresis (pre eculizumab) failed to recover and started HD until receiving a LRKT from mother in 2004. Induction: Basiliximab & steroids, maintenance Tacrolimus (Tacro), Steroids, and MMF with steroid taper a year later. Creatinine (Cr) stable (1–1.4) with urine Protein/Cr ratio (UPCR) 0.5 g/g. In 2013 developed progressive Proteinuria (Pr) (See graph) and Cr ↑ to 2.26 mg/dL. Serological w/u negative. Biopsy showed FSGS changes with 1+ IgA / 2+ IgM deposits in mesangium (20% tubular atrophy & interstitial fibrosis along with ATN and vacuolization of tubules (possible calcineuronal effect). No rejection. Suggestive but not diagnostic of IgAN. Tacro dose adjusted to keep level 3-5 ng/ml. Started Losartan titrated to 100 mg daily. MMF stopped for a year due to gastroparesis, able to resume low dose a year later. On Losartan UPCR ↓ to 0.71 g/g and Cr stabilized at 1.4 mg/dL. In 2016 Cr again worsened to 1.9 mg/dL and UPCR ↑ to 2.12 g/g so repeat biopsy done, revealing IgAN, global sclerosis (4/8 glomeruli) and worsening parenchymal chronicity from 20 to 50-70%. Of note, biopsies prior to 2014 showed no IgA positivity. Donor (mother) was rechecked and again had no microhematuria or Pr. May 2016, she stopped losartan trying to conceive. Her status worsened and UPCR ↑ as noted below to a peak of 6.9 g/g. Cr ↑ to 2.6-3.3 mg/dL, losartan restarted. After lengthy discussion with patient regarding options, started on ACTH therapy for 6 months with a partial remission as noted below in Pr and stabilization in the Cr. Pr continues to improve despite being off ACTH since March most recently 1.37 g/g. She is currently undergoing a w/u for a second transplant and remains Dialysis free.

Results:

Conclusions:



We have demonstrated a significant improvement in Pr and stabilization of Cr with ACTH in this young woman with De Novo IgAN with primary disease HUS.

PUB509

Lung Involvement on Patients with ANCA Associated Renal Disease Hiroki Mizuno, Yoshifumi Ubara, Akinari Sekine, Yoichi Oshima, Masahiko Oguro, Masayuki Yamanouchi, Keiichi Sumida, Junichi Hoshino. *Nephrology Center, Toranomon Hosp., Tokyo, Japan.*

Background: ANCA-associated vasculitis is a systemic vasculitis affecting multi-organ systems. Although analyses of each organ damage has already been published, the interaction between kidney and lung involvement has not been analyzed in detail.

Methods: We reviewed clinical data and high resolution lung CT (HRCT) on forty eight patients who were diagnosed as ANCA-associated renal disease by the kidney biopsy between April 2007 and December 2015. Glomerular lesions were classified according to the classification published by Berden *et al.* in 2012 and lung involvements were classified into 5 categories; (1) airway lesion; bronchial wall thickening, bronchiectasis, bronchiolitis, (2) pleural lesion; pleural thickening, pleural effusion, (3) alveolar lesion; pure ground-glass opacity, mixed ground-glass opacity, consolidation, (4) focal lesion; nodular lesion, cavity, (5) interstitial lung disease. We conducted statistically analysis about the association between those findings and clinical data.

Results: Median age was 72 (IQR: 60.5-78.5) years old, and eighteen cases were men. Forty-four (91.7%) were MPO-ANCA positive. Serum creatinine level was 1.525 (0.75-3.51) mg/dL, urine protein excretion was 0.715 (0.335-1.895) g/day. Glomerular lesion was seen in forty-six (95.8%). Eight (16.7%) cases were classified as sclerotic type; twelve (25%) cases, crescentic type; seven (14.6%) cases; focal type; nineteen (39.6%) cases, mixed type. On 95.8 percent of total patients with ANCA-associated renal disease, lung involvement including five categories (category 1; 62.5%, 2; 62.5%, 3; 41.7%, 4; 31.3%, 5; 43.8%) were detected. Median BVAS was 18(IQR: 15-24). Although there is no statistical association between renal and lung lesion categories, the alveolar lesion was significantly associated with heart failure($p<0.01$); the nodular lesion, the glomerular fibrinoid necrosis($p=0.01$); the interstitial pneumonitis, hematuria ($p=0.02$). In patients with interstitial pneumonitis, lung involvements proceeded renal dysfunction.

Conclusions: Almost of all patients diagnosed as ANCA-associated renal disease by the kidney biopsy had some lung involvements detected by HRCT, dividing into 5 categories. Though 50% of patients with AAV in Japan is renal-limited type, ANCA-associated renal disease was considered to have some relation with lung involvement.

PUB510

The Significance of Renal Repeat-Biopsy in Non-Remitting IgA Nephropathy to Navigate Treatment Shinako Miyano,[2] Tomo Suzuki,[1] Mikako Hisamichi,[1] Daisuke Ichikawa,[1] Sayuri Shirai,[1] Yugo Shibagaki.[1] *[1]Division of Nephrology and Hypertension, St Marianna University Hospital, Kawasaki, Japan; [2]St. Marianna University School of Medicine, Tokyo, Japan.*

Background: The renal outcome of Immunoglobulin A nephropathy (IgAN) depends on clinical features (impaired renal function, hypertension, proteinuria etc.), and a renal biopsy (Glomerular mesangial hypercellularity, atorophy/interstitial fibrosis etc.). After a long-term treatment of IgAN, some patients do not lead to a remission. It is uncertain that a renal repeat-biopsy is useful to get a further prognosis prediction and a decision of treatment. Aim: The significance of a repeat-biopsy in non-remitting IgAN was evaluated by comparing 1st biopsy and re-biopsy specimen in those received steroid + tonsillectomy and those only with conservative treatment.

Methods: We retrospectively observed 13 non remitting IgAN patients who had received a re-biopsy followed more than 1 year from their initial biopsy at our hospital. Six patients received only with renin-angiotensin system (R group) and seven patients experienced steroid therapy with tonsillectomy (A group). With two classification (Japan and Oxford), we compared clinical changes with historical grade between R and A groups.

Results: Both A and R groups were not significantly different clinically (proteinuria: A group 2.6 ±1.4 g/g Cre R group 2.6 ± 1.5 g/g Cre, eGFR : A group 51.8 ± 6.1 ml/min/1.72m^2 R group 50.6 ± 6.6 ml/min/1.73m^2). With The Oxford classification, the specimen in both groups appeared to recover by C score and to worsen by S and T scores. However, with Japanese classification, it seems that the re-biopsy specimen of A group do not tend to reflect clinical stages directly The concordance rate was 42.9% in A group and 66.7% in R group. In A group, in particular, two cases showed totally opposite results (worse clinical staging with good histological staging.

Conclusions: Impressive: The discordant results between clinical prognostic parameters and pathological findings indicated the significance of a repeat biopsy to better navigate appropriate treatment. We suggest that a repeat biopsy in R group may be unnecessary.

PUB511

Efficacy of Induction Immunosuppression in Ethnic Minorities with Membranous Lupus Nephritis Aniesh Bobba, Jayasree Krishnan, Ambarish Athavale, Amit J. Joshi, Setri Fugar, Peter D. Hart. *John H stroger hospital of cook county, Chicago, IL.*

Background: Thirty eight percent of patients with systemic lupus have kidney disease, 20% of those with membranous lupus nephritis (Class V LN) experience decreased GFR after 7-12 years. Current guidelines recommend treating Class V LN in the presence of nephrotic range proteinuria with immunosuppressant in addition to steroids. We investigated the 6 months clinical outcome of induction treatment with Cyclophosphamide or Mycophenolate Mofetil (MMF) in patients with Class V LN.

Methods: Retrospective review of kidney biopsy database at Stroger Cook County Hospital from Jan 2000- April 2017 identified 28 patients with class V LN. Baseline characteristics including age, gender, race, serum creatinine(sCr) and urine protein/creatinine ratio(uP/Cr) at the time of initiation of therapy and after 6 months of therapy were obtained. Baseline characteristics were compared using descriptive statistics and categorical variables were compared using Chi-square analysis.

Results: There was no difference in sCr or proteinuria at 6 months in patients receiving induction treatment with MMF or cyclophosphamide (Table 1). After 6 months of therapy, MMF group (4/22) and cyclophosphamide group (3/6) had either partial or complete response. 50% patients in cyclophosphamide group had partial or complete response however only 6 patients received cyclophosphamide. Complete response was defined as sCr to baseline plus Pr/Cr < 500 mg/g. Partial response is sCr improve >25% plus 50% reduction in P/Cr and Pr/Cr < 3000 mg/g.

Conclusions: Mycophenolate is less effective than Cyclosphosphamide for inducing remission in ethnic minority patients with class V LN. An RCT is needed to compare MMF to cyclophosphamide for induction of remission in this patient population.

Table 1

Induction therapy	MMF(n=22)	Cyclophosphamide(n=6)	p value
Age (years)	38±2.5	38±4.8	p=0.8
Male: Female	5:17	2:4	p=0.6
Ethnicity	AA 11 Hispanic 10 Unknown 1	AA 2 Hispanic 4	
S. Creatinine at biopsy: mg/dl	1.1±0.2	1.1±0.8	p=0.9
S. Creatinine at 6 months: mg/dl	1.1±0.1	1.2±0.7	p=0.8
Pr/Cr ratio at biopsy (g/g)	3.5±0.5	4.4±1.1	p=0.5
Pr/Cr ratio at 6 months (g/g)	3.2±0.6	3.5±1.2	p=0.8
Change in sCr	0.03(-0.2 to 0.1)	0.03(95% CI -0.3 to 0.4)	p=0.7
Change in uP/Cr	0.4(-1.2 to 0.5)	0.8(-2.5 to 0.9)	p=0.6

PUB512

Renal and Cutaneous ANCA Positive Vasculitis: Be Aware to Illicit Cocaine-Levamisole Use Even Though the Patient Denies Elvino J. Guardao barros,[3,2] Veronica V. Antunes,[2] Gustavo G. Thomé,[2] Joao B. Saldanha de castro filho,[2] Fernando S. Thomé,[2] Dirceu R. Da silva,[2] Pedro E. Schaefer,[2] Viviane Sebben,[1] Alberto Nicolella,[1] Francisco V. Veronese.[2] *[1]Centro de Informações Toxicológicas do Rio Grande do Sul, Porto Alegre, Brazil; [2]Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil; [3]Nephrology Division, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil.*

Background: Adulterated cocaine with levamisole in different concentrations has been increasingly used during the last decades. Levamisole can cause skin lesions, intravascular thrombosis, neutropenia, and crescentic nephritis. Physician awareness is essential for ensuring a proper diagnosis, because patients frequently deny the use of illicit drugs.

Methods: We describe a series of five patients with anti-neutrophil cytoplasmic antibody (ANCA)- associated vasculitis secondary to levamisole-adulterated cocaine, which were prospectively followed at a single hospital. Demographics and clinical characteristics are presented.

Results: Urine toxicology was all positive for cocaine and levamisole, tested by immunochromatography and gas chromatography-mass spectrometry. Three patients brought a sample of the cocaine powder (1 g), in which the presence of cocaine and levamisole was confirmed (levamisole: 32%, 1,2% and 0,5% in each powder). Demographics and clinical characteristics are presented in Figure 1. No patient quit cocaine use. End-stage renal disease (ESRD) developed in one patient; the worst outcome was death due to vasculitic mesenteric necrosis and sepsis, that occurred in another patient.

Conclusions: In conclusion, cocaine/levamisole-induced vasculitis should be suspected in patients with renal and skin lesions, even when illicit drug use is denied. A urine drug toxicology screen is necessary to confirm the diagnosis and must be done during follow-up to ascertain drug abstinence. This condition can induce poor outcomes, as ESRD and death.

	Female, 46y	Male, 48y	Male, 48y	Male, 50y	Female, 22y
Renal manifestations	None	Dialysis dependent / pauci-immune crescentic glomerulonephritis (PICG)	Creatinine (Cr): 2,7 mg/dL / PICG	Cr 4,8 mg/dL / PIGC	Cr 3,4 mg/dL / PICG
Skin manifestations	Retiform purpura (RP)/ leukocytoclastic vasculitis (LV)	RP/ neutrophilic vasculitis of small vessels		RP/ LV	RP
Serology markers	pANCA >1/320	pANCA 1/320	pANCA >1/320	pANCA >1/320 Anti-MPO and anti-PR3 positive	pANCA >1/320
Treatment	Oral prednisone	Corticosteroids (CC) Cyclophospha-mide (CYC) Plasmapheresis	CC	CC CYC	CC CYC
Outcome	Death (sepsis)	Chronic hemodialysis No skin lesions	Cr: 1,2 mg/dL No proteinuria	Cr: 1,5 mg/dL No skin lesions	Cr: 0,9 mg/dL Proteinuria: 3,0

PUB513

A Case of Familial Type III Hyperlipoproteinemia with Severe Foam Cell Mesangial Infiltration and Endothelial Injury Hirokazu Marumoto, Kentaro Koike, Naoko Nakaosa, Akihiro Shimizu, Nobuo Tsuboi, Yoichi Miyazaki, Tetsuya Kawamura, Makoto Ogura, Takashi Yokoo. *Division of nephrology and hypertension, The Jikei university school of medicine, Tokyo, Japan.*

Background: Apolipoprotein E (apoE) serves as a ligand for the low-density lipoprotein (LDL) receptor and other cell-surface receptors of the LDL receptor gene family. Type III hyperlipoproteinemia in patients homozygous for *apoE2* is associated with increased levels of apoE, but there are few reports on the occurrence of glomerulopathy in *apoE2* homozygotes.

Methods: A 67-year-old female was admitted to our hospital with renal insufficiency and abnormal urine test results. Her laboratory data on admission were as follows: serum creatinine level, 1.69 mg/dl; urinary protein excretion, 2.7 g/24 h; urinary red blood cell, 0-1/high-power field; LDL-cholesterol level, 44 mg/dl; and triglyceride level, 346 mg/dl. Her family history included an older brother with renal insufficiency who had been on hemodialysis since the age of 34 years. In a genetic screening, a genetic mutation was not detected in *apoE*. Thus, the genotype was apoE2/E2, and the patient was diagnosed with familial type III hyperlipoproteinemia. Of the seven glomeruli evaluated in the renal biopsy specimen, none showed global sclerosis; rather, most were hypertrophic and infiltrated by numerous foam cells, which were immunohistochemically positive for CD68. The capillary walls showed segmental duplication. Electron microscopy revealed endothelial cell injury and lipid deposition in the mesangial area. Mild thickening of the glomerular basement membrane was also seen. There were no electron-dense deposits, and an immunofluorescence analysis showed no significant glomerular deposits.

Results:

Conclusions: The glomerulopathy seen in our patient was characterized by abundant foam cell infiltration of the glomeruli and endothelial damage. Unlike in lipoprotein glomerulopathy, however, lipoprotein thrombi with lamella formation were not observed. Although the mechanism remains to be elusive, this case is an important cue to better understand the pathogenesis of glomerulopathy related to familial type III hyperlipoproteinemia.

PUB514

Nephrotic Syndrome Secondary to Chronic Thrombotic Microangiopathy without Pathognomonic Clinical or Laboratory Features Arun Rajasekaran,[2] Najam A. Siddiqui,[1] Pran M. Kar.[3] *[1]Lake Erie College of Osteopathic Medicine, Lake Worth, FL; [2]University of Central Florida College of Medicine, Kissimmee, FL; [3]Nephrology, Orlando VA Medical Center, Orlando, FL.*

Background: Thrombotic microangiopathy (TMA) encompasses small-vessel thrombosis, consumptive thrombocytopenia, and microangiopathic hemolytic anemia (MAHA) that leads to global ischemia. Severe hypertension may promote TMA within the renal vasculature. We describe the first case of chronic thrombotic microangiopathy as a cause of nephrotic syndrome, not associated with clinical or laboratory features suggestive of TMA.

Methods: A 71-year-old Arab male with well-controlled hypertension (on amlodipine), CKD stage 4 (baseline serum creatinine 1.4 mg/dl), and anemia of chronic disease (baseline hemoglobin 12 mg/dl) presented with a one-month history of worsening lower extremity swelling. He was alert, afebrile, normotensive, and had pitting edema in his legs. Hemoglobin was 12 mg/dl, albumin 2.1 mg/dl, and serum creatinine 1.4 mg/dl. A 24-hour-urine collection revealed 10 grams of protein. Platelet counts, liver enzymes, coagulation parameters, lactate dehydrogenase, haptoglobin, ESR, serum complements and immunoglobulins were normal. HIV, ANA, ANCA, RF, hepatitis B and C serologies, cryoglobulins, anti-GBM and antiphospholipid antibodies, and direct Coombs test were negative. No schistocytes were seen in the blood smear. Renal biopsy revealed glomeruli with extensive double-contour formation, mesangiolysis, and severe interstitial fibrosis and tubular atrophy. Severe arteriosclerosis and arteriolar hyalinosis were seen. Immunofluorescence revealed negative staining for IgG, IgM, IgA, C3, C4, C1q, albumin, fibrinogen, and kappa and lambda light chains. Electron microscopy depicted thickened and irregular basement membranes due to extensive double-contour formation. These features suggested a chronic TMA. Workup for an occult malignancy was negative. He was given intravenous albumin for the next 3 days and low-dose Lisinopril was added. After a month, his proteinuria markedly improved with a spot urine protein-to-creatinine ratio being 0.455.

Results:

Conclusions: We report the first case of biopsy-proven chronic TMA as a cause of nephrotic syndrome with significant improvement of proteinuria, in an individual with well-controlled hypertension, not associated with clinical or laboratory features suggestive of TMA. Further studies on this phenomenon are warranted to better understand the pathophysiology of renal damage in TMA.

PUB515

Treatment of Proteinuria Due to Treatment Resistant or Treatment Intolerant Idiopathic Focal Segmental Glomerulosclerosis: A 2 Part Prospective Study of H.P. Acthar® Gel (PODOCYTE) James A. Tumlin,[4] Brad H. Rovin,[2] Richard A. Lafayette,[3] Enxu Zhao,[1] Patrice Becker,[1] Leah Patel,[1] Susan Vanmeter.[1] *[1]Mallinckrodt Pharmaceuticals, Ellicott City, MD; [2]Ohio State University Wexner Medical Center, Columbus, OH; [3]Stanford University, Stanford, CA; [4]University of Tennessee College of Medicine, Chattanooga, TN.*

Background: Focal segmental glomerulosclerosis (FSGS) is a glomerulopathy with a high rate of progression to end stage renal disease; prior FSGS studies show that 16 weeks of therapy with glucocorticoids (GCs), calcineurin inhibitors (CNIs) and other agents have a limited ability to induce sustained remission. H.P. Acthar® Gel (repository corticotropin injection, RCI) contains a highly purified porcine ACTH analogue, and is indicated to induce remission of proteinuria in idiopathic nephrotic syndrome. Its mechanism of action is incompletely understood, though preclinical studies suggest activation of melanocortin receptors in the kidney and modification of circulating immune cells may reduce proteinuria via steroid-dependent and independent pathways.

Methods: Approximately 236 patients with FSGS, nephrotic range proteinuria (urine protein to creatinine ratio [uPCR] > 3.5 g/g) who are refractory or intolerant to GCs or CNIs will start open-label RCI 80 units (U) subcutaneously 3x/week. After 24 weeks, patients taper to 80 U 2x/week; those with complete (CR), partial (PR) or fractional remission of proteinuria (uPCR ≤ 0.3 g/g; uPCR ≤ 3.5 g/g and ≥ 50% reduction from baseline; uPCR > 3.5 g/g and ≥ 50% reduction from baseline, respectively) at Week 24 are randomized 1:1 to RCI 80 U 2x/week or placebo for 24 weeks. Subjects who do not achieve remission may continue RCI in an open-label extension to investigate possible delayed response. Efficacy will be assessed by change in proteinuria at Weeks 24 and 50; safety will be assessed by collection of AEs, changes in vital signs and labs.

Results:

Conclusions: This is the largest study to date in refractory FSGS patients and will investigate the efficacy of RCI to induce CR or PR; also, it will determine the efficacy of prolonged therapy on response rates.

Funding: Commercial Support - Mallinckrodt ARD, Inc.

PUB516

Improvement of Clinical Outcome in Kidney Diseases via the On-line Thai Glomerular Disease Registry: Lupus Nephritis Ratana Chawanasuntorapoj,[5] Boonyarit Cheunsuchon,[4] Warangkana Pichaiwong,[3] Bancha Satirapoj,[2] Siribha Changsirikulchai.[1] *[1]Medicine, Srinakharinwirot University, Bangkok, Thailand; [2]Medicine, Phramongkutklao hospital, Bangkok, Thailand; [3]Medicine, RAJAVITHI HOSPITAL, Bangkok, Thailand; [4]Pathology, Siriraj hospital, Bangkok, Thailand; [5]Medicine, Siriraj Hospital, Bangkok, Thailand. Group/Team: Thai Glomerular Disease Collaborative Network (TGCN).*

Background: Lupus nephritis (LN) is the most common glomerular disease causing the end stage renal disease (ESRD) in Thailand. The data on epidemiology and outcomes of LN are limited in few medical schools. Thai Glomerular Disease Collaborative Network (TGCN) was established to investigate the epidemiology and clinical outcomes in Thai glomerular disease patients.

Methods: The data collected prospectively from TGCN included adult patients with biopsy-proven LN during July 2014 to March 2017. The clinical, laboratory and renal pathology data were obtained via online record.

Results: We found that LN was the most common pathological finding from TGCN (522 from 1,556 cases, 33.5%). Female was 89.3%. The median serum creatinine(sCr) was 1.06 mg/dL(0.7-9.2), and median urine protein creatinine ratio(UPCR) was 3.72 g/g.Cr(0.1-24.7). The percentage of class I, II, III, IV, V, III+V, IV+V, and VI was 0.4, 2.1, 15.5, 42.9, 15.7, 10.9, 11.1, and 1.3. The initial sCr≥1.2 mg/dL was found in class IV 60.7, VI 57, IV+V 53.4, III 37, III+V 29.8%. Crescentic formation>50% was found in class IV 11.2% and IV+V 10.3%. The median activity index (AI) in class III, IV, V, III+V, IV+V, and VI was 5, 8, 1, 3, 9 and 2, whereas the median chronicity index(CI) in class class III, IV, V, III+V, and IV+V was 3, 3, 2, 3, 3 and 10, respectively. During 32 months follow-up period, overall clinical response was not different among LN class. The % of partial response/complete response in proliferative LN (III, IV), V, and III+V, IV+V were 34.8/41.2, 39.2/27.5, and 38.7/40.7. Focus on LN III and IV, the multivariate analysis showed that sCr≥1.2 mg/dL, and CI≥4 were the independent factors of none renal response with HR (95%CI) of 0.48 (0.29,0.82), 0.44 (0.21, 0.91). Additionally, the predicting factor for renal response in LN V was only the interstitial fibrosis. During this period, ESRD was found 6.1% in class III and IV.

Conclusions: Our study described the LN class IV was the most common renal findings and severe renal impairment at the time of biopsy in SLE patients. The clinical manifestation and renal response were comparable with the other studies. The independent unfavorable factors for renal response in LN III, IV were sCr≥1.2 mg/dL, and CI≥4, whilst in LN V was the high interstitial fibrosis.

Funding: Private Foundation Support

PUB517

An Unkind Cut: A Case of Pauci-Immune Crescentic Glomerulonephritis Associated with Suspected Exposure to Levamisole-Adulterated Cocaine Robert Lorch,[1] Susanne F. Mclaughlin,[2] Sreedhar A. Mandayam.[1] *[1]Baylor College of Medicine, Houston, TX; [2]None, Bellaire, TX.*

Background: Levamisole (LEV) is a ubiquitous cocaine adulterant in the United States and has been implicated in an ANCA-associated vasculitis syndrome which commonly manifests as purpuric skin lesions, agranulocytosis, and thrombocytopenia. An increasingly recognized effect of LEV is kidney injury in the form of pauci-immune glomerulonephritis (GN). Our understanding of LEV-induced kidney injury is limited, and it can be difficult to differentiate ANCA-associated GN secondary to LEV from primary ANCA-associated vasculitis based on serology and biopsy. The implications for prognosis and treatment in this scenario are unclear.

Methods: We present the case of a 57-year-old man with stage 3 CKD and an approximately 20-year history of regular intranasal cocaine use, who presented with 8 weeks of myalgias and chills, as well as several days of new-onset dyspnea. He had last used cocaine 2 days prior. Physical exam was remarkable only for bibasilar crackles and bilateral scattered rhonchi in the lungs, mild abdominal distension, and no abnormal skin findings. Initial laboratory testing revealed a creatinine of 5.1 mg/dL (baseline creatinine of approximately 2 mg/dL), blood urea nitrogen of 66 mg/dL, and urine testing positive for cocaine. Bilateral patchy airspace opacities were seen on chest CT. Renal biopsy demonstrated pauci-immune crescentic GN, and serologic testing was suggestive of microscopic polyangiitis (anti-MPO positive, anti-PR3 negative). Due to his significant history of cocaine use, LEV-induced vasculitis could not be ruled out as a cause of rapidly progressive GN. He was treated with corticosteroids, rituximab, and plasma exchange; although he ultimately progressed to dialysis-dependent renal failure.

Results:

Conclusions: Up to 80% of cocaine in the United States now contains LEV, and this case highlights the growing public health concern of LEV exposure. Our current knowledge of the clinical, laboratory, and biopsy findings specific for LEV-induced GN is often too limited to differentiate this form of drug-induced vasculitis from primary vasculitis, especially in otherwise medically complicated cases and when clinical stakes are high. A better understanding of the effects of LEV on the kidney is needed so that improved methods to diagnose and treat levamisole-induced glomerulonephritis may be developed.

PUB518

Improvement of Clinical Outcome in Kidney Diseases via the On-line Thai Glomerular Disease Registry: The Third-Year Report Ratana Chawanasuntorapoj,[6] Boonyarit Cheunsuchon,[5] Ngoentra Tantranont,[4] Warangkana Pichaiwong,[3] Bancha Satirapoj,[2] Siribha Changsirikulchai.[1] *[1]Medicine, Srinakharinwirot University, Bangkok, Thailand; [2]Medicine, Phramongkutklao hospital, Bangkok, Thailand; [3]Medicine, Rajavithi hospital, Bangkok, Thailand; [4]Pathology, Siriraj Hospital, Mahidol University, Bangkok, Thailand; [5]Pathology, Siriraj hospital, Bangkok, Thailand; [6]Medicine, Siriraj Hospital, Bangkok, Thailand. Group/Team: Thai Glomerular Disease Collaborative Network (TGCN).*

Background: End stage renal disease (ESRD) affects the quality of life and causes the high cost in health care system. The prevention of ESRD is the early recognition and appropriate treatment. Glomerulonephritis is the third most common cause of ESRD in Thailand. Thai Glomerular Disease Collaborative Network (TGCN) was established to evaluate the epidemiology and clinical outcomes in the glomerular diseases and helped to promote the good system to taking care of these patients.

Methods: TGCN originally consists of 9 tertiary care centers and expands to 20 hospitals. We conducted a prospective cohort study in the adults' native kidney biopsy proven glomerular diseases between July 2014 and Mar 2017. The clinical and laboratory parameters at the time of biopsy, pathologic findings, treatment regimens and clinical outcomes were recorded via on-line registry.

Results: We recruited 1,556 patients performed native kidney biopsy during Jul 1, 2014 to Mar, 2017. The female to male ratio was 1.88:1. The average age, creatinine, albumin, and cholesterol were 43.4 (18-87) years, 1.48 (0.4-16.2) mg/dL, 2.9±0.8 g/dL, and 294±131 mg/dL in respectively. The median proteinuria was 3.7 (0.02-25.3) g/day. The patients presented with 40% of nephrotic syndrome, 21.7% of nephritis, 19.4% of nephrotic nephritis, and 60.8% of renal impairment (creatinine≥1.2 mg/dL). The renal pathological findings showed 33.9% of LN, 13.5% of IgAN, 10.9% of FSGS, 7.4% of minimal change disease(MCD), and 7.1% of membranous nephropathy (MN). The mean age of LN, IgAN, FSGS, MCD, and MN were 34.9, 39.4, 47.3, 46.5 and 52.6 years. The median creatinine at biopsy of LN, IgAN, FSGS, MCD, and MN were 1.08, 1.76, 1.7, 1.02 and 0.98 mg/dL.

Conclusions: Our study described the common renal pathological findings including LN, IgAN, FSGS, MCD, and MN. The clinical outcomes and predicting factors of renal response were described in the separate articles. *Funding: Health Systems Research Institute, and Nephrology Society of Thailand support*

Funding: Private Foundation Support

PUB519

Renal Complications of Hematopoietic Stem Cell Transplantation (SCT) and Glomerulopathies in Patients with Leukemia Receiving SCT: MD Anderson Cancer Center's Experience Ali Ziaolhagh,[6] Umut Selamet,[1] Laila S. Lakhani,[5] Amanda Tchakarov,[2] William F. Glass,[3] Ala Abudayyeh.[4] *[1]MD Anderson Cancer Center, Houston, TX; [2]University of Texas Medical School at Houston, Houston, TX; [3]University of Texas – Houston Medical School, Houston, TX; [4]The University of Texas MD Anderson Cancer Center, Houston, TX; [5]UT Houston, Houston, TX; [6]University of Texas health science center at Houston, Housotn, TX.*

Background: Variety of kidney diseases as such as nephrotic range proteinuria and glomerulonephritis, acute and chronic kidney disease are associated with Hemoatopoeitic stem cell transplant. We present our experience in our Institute in patients with undelying leukemia who were managed with hematopoetic stem cell transplant. Glomerular diseases were confirmed by renal biopsy. Reason for biopsy were acute kidney injury and in some patients were nephrotic range proteinuria.

Methods: After we obtained IRB (institutional review board) approval, renal biopsy reports from year 2000- 2017 were obtained from pathology department. Patients with leukemia who had stem cell transplant were selected. Medical charts were reviewed. We collected date on base line serum creatinine, serum creatinine at the time of biopsy, degree of proteinuria, urinalysis and renal pathology report.

Results: We reviewed 15 cases with leukemia including AML, ALL, CLL, and diffuse large B-cell lymphoma. We had 3 cases with BK nephropathy, 3 cases with thrombotic microangiopathy which might represent graft-versus-host disease, 1 case with membranous nephropathy, 1 with mesangioproliferative glomerulopathy, 3 with Acute Tubular Necrosis, 1 with FSGS and 1 with moderate to severe chronic interstitial fibrosis. 1 specimen was disregarded due to inadequate sample. 5 patient had nephrotic range proteinuria between 3-20 g proteinuria.

Conclusions: Hematopoietic stem cell transplant is associated with variety of kidney diseases. Some patients develop nephrotic range proteinuria with different glomerulopathies.

PUB520

Novel Approaches Based in Current Evidence in ANCA-Associated Vasculitis with Renal Involvement Treatment Vanina Vazquez,[2] Gabriela González,[3] Javier E. Robaina Sindin.[3] *[2]Simplemente Evita Hospital, Buenos Aires, Argentina; [3]División Nefrología, Hospital de Clínicas José de San Martín, Universidad de Buenos Aires, Buenos Aires, Argentina.*

Background: ANCA-associated vasculits (AAV) are a group of autoinmune diseases characterized by inflamation and necrosis in small and medium vessels. AAV could respond to diferent therapeutics protocols depends on levels of clinical severity. Early treatment could improve the outcome. In spite of recognized efficay of regimens with cyclophosphamide and corticosteroids to control the AAV, efforts to minimize drugs-related toxicity led to consider targeted therapies. Considering novely and currently therapies evidence proposed to AAV and severity of renal presentation, we suggest new rational approaches emphasizing targeting B-cells therapy and preventing disease relapse.

Methods: Latest quality evidence was identified by methodological search filters, assessed evidence quality with Cochrane Renal Goup check list, determinated the strenght of recommendations by Levels of Evidence (Oxford Centre for Evidence-based Medicine)

Results: Rituximab (RTX), a monoclonal anti-CD 20antibody, is the biologic agent more using in AAV in current evidences. Unlike latest Guides and Recommendations published, RTX would be recommended in induction and maintenance AAV with renal involvement treatment (Table 1)

Conclusions: Current therapies for AVV with renal involvement shows that emerging therapies like RTX could improve rates of relapses and treatment-related toxicity. Further studies would provide target-therapeutical options. **References:** Vazquez V et al. Medicina (Buenos Aires)2015;75 Suppl 1:1-38;Mukhtyar C et al. Ann Rheum Dis 2009;68:310-317;Guillevin L et al. N Engl J Med 2014;371:1771-80

AAV Induction Therapy	Early systemic (GF>60 ml`):MTX + GC (Ib,B) Severe generalised (Cr>5.68 mg/dl):CFM IV/PO + MPS (Ia,A) Generalised with contraindication to CFM:RTX + GC (Ib,B) Prophylaxis against Pneumocystis jirovecii (in CFM or RTX therapy):Cotrimoxazol PO (IIb,B) Severe with RPGN:Plasma Exchange-adjuvant therapy (Ia, B)
AAV Maintenance Therapy	Low-dose GC + AZA up 18 months (IIb,B) Low-dose GC + LF (less safer) (Ib,B) Low-dose GC + MTX with GF >60 ml/` (Ib,B) Avoid use CFM long-term (higher relapse risk) (Ia,A) In GPA:RTX + GC low-dose each 6 months up18 months (Ib, B)
AAV Relapse	Minor Relapse:increase GC dose (IIb,C) Major Relapse:RTX + GC (Ia,A) Major Relapse with CFM cumulative dose < 36 gr:CFM + GC (Ib,B) Plasma Exchange and/or MPS (IIb,C)
VAA Refractaria	RTX + GC,specially patients whose never recived RTX (II,B) Plasma Exchange in RPGN and/or dialysis-dependen (Ia,B)

GF:glomerular filtrate, MTX:metotrexate, GV:glucocorticoids, Cr: creatinine, CFM:ciclophosphamide, IV:intravenous, PO:oral, MPS:metilprednisolone, RTX:rituximab, RPGN:rapidly progressive glomerulonephritis, AZA:azathioprine, LF:leflunomide, GPA:granulomatosis with polyangiitis

PUB521

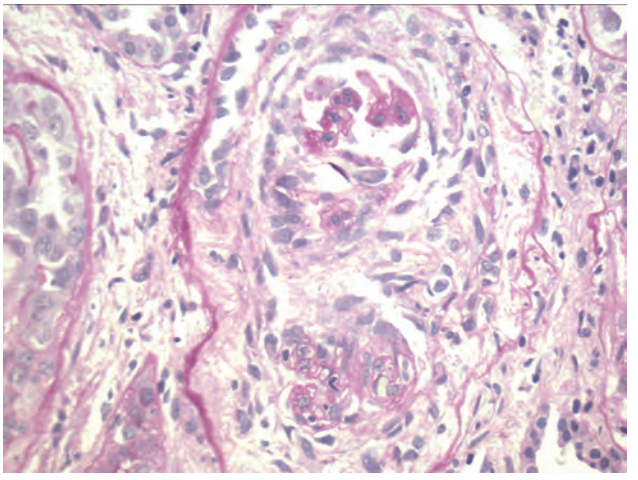
ANCA Associated Crescentic GN with Infective Endocarditis: Hold the Immunosuppression and Treat the Cause Pradeep Chaganti,[2] Mubasshar Rehman,[2] Purva D. Sharma,[2] Ira S. Meisels,[3] Steven D. Smith.[1] *[1]Icahn School of Medicine at Mount Sinai/St Luke's-Roosevelt Hospital Center, New York, NY; [2]Mount Sinai Saint Luke's and mount Sinai West, Bronx, NY; [3]None, Brooklyn, NY.*

Background: Infective endocarditis can mimic ANCA associated vasculitis with positive serological markers. We report a case of infective endocarditis associated pauci-immune crescentic glomerulonephritis with positive PR3, which improved clinically and serologically with treatment of endocarditis, without any immunosuppression

Methods: 63 y/o man with AIDS on ART, HCV+ (treated and HCV RNA negative), ex-IVDU, CKD III (baseline creat 1.6 mg/dl), h/o epistaxis, first presented to an outside hospital with fever and was found to have Granulicatella adiacens MV endocarditis and AKI with high titer cANCA (PR3-Ab) requiring hemodialysis, transferred to our hospital for MVR. At the time, his urine sediment was active with multiple dysmorphic RBCs and RBC casts along with granular casts. He received antibiotics and underwent successful bioprosthetic MVR. His renal function improved and he was able to come off dialysis in 2 weeks without any immunosuppressive therapy with a creatinine of 4.5 on discharge. He presented again after 3 weeks to the outside hospital with epistaxis without any other symptoms. Creatinine at the time was 2.6 with persistent subnephrotic proteinuria. ENT evaluation revealed multiple telangiectasias and a nasal biopsy showed inflammation without any granulomas/micro abscess, followed by a renal biopsy that showed a pauci-immune focal crescentic GN with moderate IFTA. On completion of 6 weeks of antibiotics and negative blood cultures, his acute kidney injury resolved with resolution of proteinuria. His last labs showed PR-3 Ab levels decreased from 76 AU/ml to 33 AU/ml, no proteinuria and a Cr of 1.74.

Results:

Conclusions: Infective endocarditis associated GN can present as diffuse necrotizing and crescentic GN with or without associated ANCA positivity and its recognition is crucial to prevent inadvertent therapy with immunosuppressive medications



Fibrocellular crescent [“pauci immune” on IF]

PUB522

A New Kid in the Paraffin Block R hea Bhargava,[3] Isaac E. Stillman,[3] Nikhil Agrawal,[3] Himmat Grewal,[2] Christina Chen,[1] Samer S. Nasser.[1] *[1]None, Watertown, MA; [2]Saint Vincent Hospital, Worcester, MA, Watertown, MA; [3]Beth Israel Deaconess Medical Center, Boston, MA.*

Background: ‘MGRS’ (monoclonal gammopathy of renal significance) is a newly described entity. This is thought to be from a non malignant cell clone. ESRD and recurrence after kidney transplantation has been described.

Methods: 68 year old female presented with lower extremity edema for 6 months. Trialed on diuretics as an outpatient with inadequate response prompting inpatient admission. Cr increased from 0.7 to 4.5 mg/dl over 7 months with a urine protein/cr ratio of ~12mg/mg. Systemic examination was unremarkable except for 2+ pitting edema in bilateral lower extremities. Urine sediment demonstrated red cells with several acanthocytes, multiple granular and hyaline casts. She underwent a kidney biopsy which demonstrated endocapillary proliferative glomerulonephritis with substructured deposits suggestive of paraprotein deposition. Pronase digested paraffin sections showed capillary wall staining for kappa while IgG and lambda were negative. Prior to admission, was on losartan with inadequate improvement in proteinuria and persistent lower extremity edema. Serology showed a negative anti GBM, ANCA, ANA, SPEP/UPEP, cryoglobulins, hepatitis panel and a normal rheumatoid factor. Further studies showed a negative PET scan, bone marrow biopsy and peripheral flow cytometry. The decision to start immunosuppressive therapy was made. IV cyclophosphamide(300mg/m2- 50% reduced dose) with mesna was initiated along with prednisone 60 mg daily with a taper. She has recieved 3 IV cytoxan infusions and is presently on 20 mg daily prednisone with a Cr of 1.7 mg/dl and a urine protein/cr ration of 4.4 mg/mg.

Results:

Conclusions: MGRS is diagnosed by the presence of monoclonal immunoglobulin deposition in the kidney. Since the treatment can vary depending on the cell clone identified and the type of immunoglobulin found (IgG versus IgM) it is imperative to do a thorough workup including peripheral flowcytometry, PET scan and bone marrow biopsy if protein electrophoresis is negative. In our patient, no single cell clone was indentified and non-IgM deposits were present. Cyclophosphamide was initiated since it targets both B-cells and plasma cells and a good response has been noted. Early diagnosis and treatment may prevent poor renal outcomes that have been reported in literature. A collabrative approach and further prospective trials will be helpful to further elucidate treatment options in this disorder.

PUB523

Abstract Withdrawn

PUB524

Clinical Utility and Prognosis of Standardizing Chronic Changes in Renal Biopsies with CKD Laura Fuentes, Ivan Rosero. *Hospital General de Mexico, Distrito Federal, Mexico*.

Background: Renal biopsy still is controversy in patients with chronic kidney disease, chronic changes are predictors of renal outcomes because predicts prognosis, guides and assess treatment. We correlate the histological findings classiffied with severe damage by interstitial fibrosis and tubular atrophy (IFTA) and add the proposed in a previous consensus (glomeruloesclerosis, arterioesclerosis) with outcomes such as improve in renal function, CKD, ERSD, renal replacement therapy and mortality.

Methods: We retrospectively reviewed the records of 348 adult patients who underwent kidney biopsies between 01/01/12 and 06/01/17, focused only in patients with IFTA >50% including demographic, clinical, laboratory, ultrasonography and renal histopathological characteristics.

Results: The population was 49 men and 45 women, age 41.5± 14.2 years, kidney size 97.78 ± 12.3 mm for right and 98.72 ± 12.0 left, nephrotic in 37.2% and rapidly progressive syndrome in 28.7%, 22.3% patients were in RRT before the biopsy, and the main comorbidities were HTA, DM, SLE, at the diagnosis 97.9% were in CKD and 46.8% in ESRD, we found SGN in 61.7% (n:58), diabetic nephropathy in 22 (23.4%), lupus 19 (20.2%), vasculitis 11 (11.7%), GSFS as the main cause in PGN in 13.8%, followed by IgAN and membranous, there were and overlap seen in diabetics and FSGS and also PGN with tubulointersticial nephritis in 25%, 22 patients received inmunossupresive therapy because the underlaying cause with recovery and withadrawal of renal replacement therapy in 28.7%, using the classification with the glomerular and vascular damage can classify the patient to offer treatment or delay progression factors with more accuracy compared to previous classification for mortality and progression to ESRD in 19.5%.

Conclusions: The renal biopsy in CKD patients is still debated but it is a irrepleaceable tool that may help clinicians stablish a therapeutic strategy to slow down progression of kidney injury, in previous studies don't take the overlap between PGN and SGN with another pattern of glomerular damage and it is very important to differenciate it because the prognosis in renal outcome treating both diseases. Also a postbiopsy treatment change in 25% of CKD patients. Therefore, even if only speculative, it indicates that biopsy has been useful to decide the therapy for these patients so the criteria should be expanded.

PUB525

Minimal Renal Affection in Patients with Systemic Lupus Erythematosus: Characteristics and Evolution Eva Rodriguez,[5] Tarek C. Salman,[2] Maria Jose Soler,[6] Clara Barrios,[4] Jordi Abelló,[1] Julio Pascual.[3] *[1]Hospital del Mar, Barcelona, Spain; [2]Rheumatologist, Hospital del Mar, Barcelona, Spain; [3]Hospital del Mar, Parc de Salut Mar, Barcelona, Spain; [4]Hospital del Mar. Institut Mar d?Investigacions Mediques. Barcelona. Spain., Barcelona, Spain; [5]Nephrology, Parc de Salut Mar, BARCELONA, Spain; [6]Parc de Salut Mar. Fundació IMIM, Barcelona, Spain.*

Background: Lupus nephritis (LN) is the most common organ involvement in Systemic Lupus Erythematosus (SLE). Indications of renal biopsy (RB) are deterioration of renal function and / or activity in sediment and / or proteinuria> 0.5g / 24h or urine protein: creatinine ratio (P:C ratio) > 0.5 (SEN consensus 2012). There are patients who show data of "minimal renal involvement" (MRI) without indication of RB. Our objective is determine if these patients present clinical and analytical characteristics that allow them to differentiate from patients with LN.

Methods: We reviewed 171 patients with SLE diagnosis, classifying them as MRI if they showed> 3 occasions at least 1 year, proteinuria determinations = 0.3 g / 24h or P:C ratio= 0.3, ruling out urologic pathology. We have compared clinical and analytical variables of MRI vs LN at the time of SLE diagnosis, at renal involvement diagnosis and last visit.

Results: We identified 38 (18.7%) patients with MRI and 41 (24%) patients with LN. At the time of SLE diagnosis, the MRI group had a lower titer of anti-DNAds (14.8% vs 42.1%, p = 0.01), anti-Sm (12% vs 32.2%, p = 0.04), lupus anticoagulant (38%, p = 0.01) and anticardiolipin IgG (11% vs 38%, p = 0.01), less severe C3 hypocomplementemia (70 ± 34 vs 86.9 ± 32.7 mg / dl, p = 0.04), C4 (14 ± 10 vs 17 (p = 0.04) and CH50 (33.3 ± 15 vs 49.6 ± 17.4 mg / dl, p = 0.04); and lower inflammatory parameters: ESR (23.1 ± 20 vs 58.9 ± 42 mg / dl, p = 0.01), CRP (12.7±11.8 vs 27.3±17 mg/dl, p=0.02). At the diagnosis of the renal involvement, these results were confirmed (Table) and we observed that, in MRI patients, proteinuria appeared at an older age, with a higher evolution of SLE (12.7 ± 11.8 vs 27.3 ± 17 mg / dl, p = 0.02) and with absence of previous immunosuppressant therapy. After a mean follow-up of 10 ± 6.6 years, no MRI patient presented a renal flare, maintaining stable the renal function.

Conclusions: Our results showed that patients with MRI had a lower clinical and biological SLE activity, both at SLE diagnosis and at the diagnosis of renal involvement. No MRI patients presented a LN flare during the follow-up although it is difficult to know the role played by the immunosuppressant treatment

PUB526

Proliferative Glomerulonephritis with Monoclonal IgG Deposits: Successful Treatment with Steroids, Bortezomib, and Plasma Exchange Olga Baraldi, Giorgia Comai, Vania Cuna, Matteo Ravaioli, Maria Cappuccilli, Gaetano La Manna. *University of Bologna, Bologna, Italy*.

Background: Kidney impairment is frequent in plasma cell dyscrasias and it is characterized by polymorphic histology mainly related to the physicochemical properties of the pathological monoclonal component. Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a newly discovered pathological entity. The diagnosis of renal alterations is based on histology, and the patients with compromised renal function are commonly treated with standard hematology chemotherapy protocols.

Methods: Case description. We report a case of a 64-year-old man with nephrotic syndrome, normal renal function, negative immunological and viral tests (in particular anti-PLA2R antibodies). Serum electrophoresis for detection of IgG light chain monoclonal proteins revealed: monoclonal component 3.4%, kappa 92.6 mg/L, lambda 23.7 mg/L, kappa/lambda ratio 3.7. Magnetic resonance was negative for spine injuries. Bone-marrow biopsy revealed a monoclonal gammopathy of undetermined significance (MGUS) with an IgG/kappa clone. Echocardiogram showed no features of cardiac amyloidosis. Renal biopsy histology displayed diffuse and global membranoproliferative glomerulonephritis with linear single IgG monoclonal deposition at immunofluorescence. Electron microscopy disclosed the presence of subendothelial deposits with granular and non-organized morphology. The patient was treated with steroids (dexamethasone 40 mg for 3 days), bortezomib (1.3 mg/m^2, weekly) and plasma exchange with albumin reinfusion. ACE-inhibitor and furosemide therapy was also administered. After 2 months, the clinical conditions were better, renal indices were slightly improved (creatinine 1.2 mg/dL, eGFR 47 mL/min/1.73m^2), urine protein excretion was 2 g/day, and kappa chains levels dropped to half of the initial level (44.9 mg/dL).

Results:

Conclusions: In patients with multiple myeloma (MM) or amyloidosis, established chemotherapy protocols are regularly used, whereas no consolidated therapy exists for the treatment of MGUS with renal impairment. The described patient affected by PGNMID with MGUS was successfully treated with a therapy regimen associated with plasma exchange consistent with those used in MM.

PUB527

Critical Value of Early Diagnosis to Restore Renal Function in Thrombotic Microangiopathy Induced by Severe Lupus Nephritis: A Case Report Haijing Hou,[3] Jiasheng Huang,[2] Jiawei He,[2] Suyuan Peng,[2] Guobin Su,[1] Chuan Zou,[3] Fuhua Lu.[3] *[1]Karolinska Institutet, Stockholm, Sweden; [2]The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China; [3]Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China*.

Background: Thrombotic microangiopathy (TMA) is a pathological process based on microangiopathic hemolytic anemia, thrombocytopenia and microvascular occlusion, with an incidence of 0.5/100000 in adults. It is rare but severe in lupus nephritis (LN).

Methods: A 28-year-old Chinese woman with a previous history of anemia was admitted with swelling legs and recurring fever for a month. Initial lab findings indicated acute renal failure, thrombocytopenia, infection and severe LN with the high SLEDAI scoring of 20, ruling out antiphospholipid syndrome and thalassemia. After receiving sufficient dose of cyclophosphamide (accumulated to 1.8g), methylprednisolone therapy (0.5g/qd*3d) and hemodialysis for 2 weeks. her renal function was still progressively declining (Scr 6.04mg/dL VS 1.99mg/dL at baseline) with a low count of platelet (62*10^9/L, baseline 113*10^9/L) and anuria. Bearing the risk of uncontrolled bleeding due to thrombocytopenia, a renal biopsy was performed to guide the treatment. The renal biopsy showed endocapillary fibrin thrombi and crescent. The diagnosis of TMA was established based on renal biopsy, the ADAMTS13 activity level of 50.4% and RBC schistocytes of the peripheral blood smear. Plasmapheresis was initiated, combined with Traditional Chinese Medicine (TCM), which aimed to reduce the risk of infection during the CTX therapy. At discharge, her urine output improved and did not require dialysis (ADAMTS13: above 100%, Scr: 1.93 mg/dL and platelet counts: 164*10^9/L). In 6 months follow-up, she reports improvement in symptoms with stable renal function.

Results:

Conclusions: TMA is an uncommon LN-related disorder, early diagnosis of patients is critically important for treatment and prognosis of LN patients. This case highlights the need to have a broad differential diagnosis for hematological system damage of LN and TMA. Plasmapheresis combined with TCM in the treatment of LN with TMA deserved further study.

PUB528

Complete Remission of Immunotactoid Glomerulopathy Following Rituximab Jacqueline Raicek,[1] Jason R. Pettus,[2] Elizabeth J. Brant.[2] *[1]Dartmouth Hitchcock Medical Center, Hanover, NH; [2]Dartmouth-Hitchcock Medical Center, Lebanon, NH.*

Background: Immunotactoid glomerulopathy (ITG) is a rare cause of glomerular disease characterized by large (30-50 nm) non-amyloid microtubule-like ultrastructural deposits in glomeruli. It can be associated with a lymphoproliferative disorder but is usually idiopathic. Optimal treatment is not defined.

Methods:

Results: The patient was a 68-year-old woman with no significant medical history who presented in 9/2015 with a 5-month history of proteinuria and gross hematuria. Prior cystourethroscopy and CT urography were negative. Physical examination was unremarkable. Dysmorphic hematuria and oval fat bodies were seen on urine microscopy. Serum creatinine was 0.57, urine protein-to-creatinine ratio 10.6 (13.1 in 10/2015), total cholesterol >400 and LDL >200 (previously normal). SPEP showed two faint IgG kappa restrictions; UPEP was negative. Kidney biopsy revealed a diffuse segmental proliferative glomerulonephritis on light microscopy; global staining for IgG(1+), C3(2-3+), trace IgA, kappa(1+), and lambda(1+) on immunofluorescence. Electron microscopy showed predominantly subepithelial electron-dense deposits in the mesangium and periphery of glomeruli, which were characterized by discrete microtubule-like organization (~30-35 nm in diameter), consistent with a diagnosis of ITG. Bone marrow biopsy demonstrated normocellular marrow with trilineage hematopoiesis and <0.1% of clonal B-cells. PET scan was negative. She was treated with rituximab 1g IV in 10/2015 and 11/2015 with prompt resolution of hematuria. Proteinuria was 5g, less than one month after rituximab and has remained <1g since 6/2016. She received rituximab 500 mg IV in 8/2016 upon repopulation of B cells. Creatinine has been stable.

Conclusions: Immunotactoid glomerulopathy is a rare cause of kidney disease that is associated with microtubule-like organized deposits in glomeruli. It can be associated with a lymphoproliferative disorder but is often idiopathic, as in our patient. Prognosis is often poor, with as many as 50% of patients progressing to end-stage renal disease. Optimal treatment has not been defined. Rituximab may be an effective therapy, as demonstrated in our case. Normal renal function at presentation may have played a role in the overall positive outcome. Thus, early diagnosis and treatment are important in potentially changing the course of the disease.

PUB529

Association between Cardio-Ankle Vascular Index and Various Pathological Lesions in Patients with IgA Nephropathy Hideo Okonogi, Tetsuya Kawamura, Akihiro Shimizu, Shinya Yokote, Masahiro Suyama, Kei Matsumoto, Kentaro Koike, Nobuo Tsuboi, Yoichi Miyazaki, Masato Ikeda, Makoto Ogura, Takashi Yokoo. *Division of Nephrology and Hypertension, Department of Internal Medicine, Jikei University School of Medicine, Tokyo, Japan.*

Background: Cardio-ankle vascular index (CAVI) is a non-invasive index of arterial stiffness and, theoretically, independent of blood pressure at the time of measurement. Recently, association of arterial stiffness with decline in renal function has discussed, however, few studies have examined the association between arterial stiffness and pathological lesions. Therefore, we examined the association between CAVI at the time of renal biopsy (RBx) and pathological lesions in patients with IgA nephropathy (IgAN).

Methods: We included 27 IgAN patients, who were diagnosed by first time RBx and whose renal biopsy specimens contained afferent arterioles and ≥6 glomeruli. The presence of mesangial hypercellularity (MH), endocapillary hypercellularity (EH), segmental glomerulosclerosis (SG), tubular atrophy or interstitial fibrosis (≥20%) (TI), and hyaline change of afferent arterioles (HA) were analyzed.

Results: As a result, the percentage of patients who had MH, EH, SG, TI and HA lesion were 37%, 11%, 19%, 56% and 63%, respectively. In SG, TI and HA lesions, CAVI value of lesion-positive groups were significantly higher than those of lesion-negative groups ($p<0.05$, $p<0.05$ and $p<0.05$, respectively). However, in MH and EH lesions, there was no significant difference of CAVI value between lesion-positive groups and lesion-negative groups. Relative cumulative frequency of the presence of SG, TI, and HA lesions became higher in accordance with increase of CAVI value. Furthermore, the forms of three graphs closely resembled each other, and 58%, 53% and 53% of SG, TI and HA lesion-positive patients had CAVI value below 8.

Conclusions: These results indicate that CAVI reflects the presence of SG, TI and HA lesions in IgAN patients. Moreover, these pathological legions have begun to appear in kidney of IgAN patients with relatively low CAVI value which correspond to systemically normal value.

PUB530

LECT2 Renal-Hepatic Amyloid with Associated Primary Biliary Cholangitis and Rheumatoid Arthritis Sabitha Eppanapally. *kern medical, Bakersfield, CA.*

Background: Introduction: Amyloidosis represents a varied group of diseases which result from the misfolding and aggregation of autologous proteins which are deposited in diverse tissues in the form of amyloid fibrils; one of the most recently recognized of these is Amyloid Leukocyte Chemotactic Factor 2 (LECT2). In LECT2 amyloidosis, leukocyte chemotactic factor 2 is the precursor protein, which is involved in chemotaxis, cell proliferation, inflammation, immunomodulation and carcinogenesis. We present a case with primary biliary cholangitis and rheumatoid arthritis that subsequently was diagnosed with LECT2 amyloidosis with demonstrated liver, renal and bone marrow involvement.

Methods: Case Report: The patient is a 70-year old Hispanic female with history of rheumatoid arthritis and primary biliary cholangitis. Due to complaints of persistent hematuria and worsening renal function, patient underwent a renal biopsy which showed amyloidosis which involved the interstitium and arterioles, which may represent leukocyte chemotactic factor 2 associated amyloidosis (LECT2); biopsy was negative for light chains. Liver biopsy showed features consistent with primary biliary cholangitis with bridging fibrosis and amyloid deposition; the globular amyloid pattern with LECT2 amyloidosis; no features of plasma cell neoplasm identified. Bone marrow biopsy was also positive for Congo red stain for amyloid, indicating the possibility of LECT2 associated amyloidosis. Patient is also followed by hematology for plasma cell dyscrasia-related amyloidosis with plans to start immunomodulatary therapy. She has family history significant for renal disease in her sister, who died from lupus nephritis requiring dialysis complications; also, patient's mother who had renal failure of unknown etiology.

Results:

Conclusions: Conclusion: LECT2 is a multifunctional cytokine and its precise functions and mechanisms are unclear and currently being investigated. LECT2 has been linked to multiple pathologic conditions such as liver disease. Globular amyloid consists of large circular globules with extracellular deposits within the sinusoids or as intracellular deposits within hepatocytes. Our patient had this globular amyloid deposition confirming the diagnosis of ALECT2 amyloidosis, involving the liver and kidney.

PUB531

A Comparative Study of Lupus Podocytopathy versus Primary MCD or FSGS Jason Cobb,[2] Titilayo O. Ilori.[1] *[1]Nephrology, University of Arizona, Tucson, AZ; [2]Nephrology, Emory University School of Medicine, Atlanta, GA.*

Background: Lupus podocytopathy has been described as minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS) in patients with SLE with or without mesangial involvement but without proliferative or membranous lupus nephritis features. Outcomes of patients with lupus podocytopathy (a secondary podocytopathy) have not been compared to patients with idiopathic or primary MCD and FSGS. We present a retrospective comparison of lupus podocytopathy patients and primary MCD/FSGS patients in our institution.

Methods: We collected kidney biopsies from our academic system from 2000-2016. We identified fifteen patients with lupus podocytopathy and randomly chose sixteen patients with primary MCD or FSGS. We collected demographic variables (age, gender, race, duration of SLE), laboratory data (serum creatinine, albumin, degree of proteinuria, presence of hematuria, complement levels), pathology data (light microscopy, immunofluorescence, and electron microscopy) and clinical data (treatment, treatment response, duration of follow-up).

Results: In the lupus podocytopathy group of patients there were 14 females and 1 male patient. In the primary MCD/FSGS group there were 8 females and 8 males. In the lupus podocytopathy group there were 10 black, 3 Caucasian, 1 hispanic, and 1 middle eastern patient. In the primary MCD/FSGS group there were 8 black and 8 Caucasian patients. In the lupus podocytopathy group 6 of the patients were FSGS and in the other group 5 of the patients had FSGS. The average initial peaked creatinine was 3.08 mg/dL in the lupus podocytopathy group and 1.72 mg/dL in the primary MCD/FSGS group ($p=.037$). The average final creatinine was 1.25 mg/dL in lupus podocytopathy (excluding one ESRD patient) and the average final creatinine was 1.64 mg/dL in the primary MCD/FSGS patients ($p=0.16$). The average protein per day was 9.3 g/day in the lupus podocytopathy and 9.4 g/day in the primary MCD/FSGS group ($p=0.19$). The average age was 36.2 years in the lupus podocytopathy group and 42.6 years in the primary MCD/FSGS group ($p=0.15$).

Conclusions: We presented the first comparative study of lupus podocytopathy patients and patients with primary MCD/FSGS. The lupus podocytopathy group was more likely to be female and had a higher initial peaked creatinine in comparison to primary MCD/FSGS patients. There were similar levels of proteinuria (average > 9 g/day) and age.

PUB532

Renal Biopsy Should Not Delay Treatment Initiation in Suspected Lupus Nephritis Astrid Baumann, Ravindra Rajakariar. *Renal, Royal London Hospital, London, United Kingdom.*

Background: Renal biopsies are considered the gold standard in diagnosing lupus nephritis (LN). Since the publication of ALMS, the largest randomized trial in LN, Mycophenolate Mofetil (MMF) has been standard therapy in proliferative LN, but there may be delays in obtaining a histological diagnosis due to practical considerations. Renal biopsy also has a recognized complication rate. We therefore investigated whether histological findings influenced treatment in patients with SLE and clinical features consistent with LN.

Methods: Histopathology and renal databases were used to identify all cases of new biopsy-proven active LN, diagnosed between Feb 2012 and Nov 2016 and managed at the Barts Lupus Centre (n=62). Patients were divided into subgroups based on their renal function (eGFR > or ≤50 ml/min/).

Results: The mean age at LN diagnosis was 37 years (+-13 SD). 55 patients were female (88%) whilst 7 were male (12%). The ethnic distribution: 46% South Asian, 34% Black, and 11% Caucasian. The histological class was either pure proliferative (class III or IV) or mixed proliferative (with additional class V) in 24 cases (39%). 42 (68%) patients had an eGFR > 50mL/min at presentation with a mean albumin and urine PCR of

30 g/dL and 520 mg/mmol respectively. Of this group, 37 patients (88%) received MMF, 3 patients were treated with cyclophosphamide (1- clinician decision, 2- severe extra renal manifestations) and the remaining two patients received Azathioprine (sub-nephrotic proteinuria). At six months 85% of LN patients were either in partial remission defined as proteinuria below 200 mg/mmol (44%) or complete remission defined as proteinuria below 50 mg/mmol (41%). The treatment choice was different in the group with eGFR ≤50mL/min, with 13 (65%) of these patients receiving cyclophosphamide.

Conclusions: Current guidelines strongly recommend performing a kidney biopsy in every patient presenting with suspected LN. Our findings indicate that in patients with preserved renal function and significant proteinuria, treatment decision is not influenced by biopsy result. We therefore propose, that induction treatment with MMF should not be delayed until a renal biopsy result is available. This study also questions the necessity of baseline histology in LN patients with preserved renal function and raises the possibility that biopsy could be reserved for patients who are resistant to induction therapy.

PUB533

Retrospective Review of Lupus Nephritis in African Americans from an Academic Hospital Ravi K. Thimmisetty,[1] Obead Y. Yaseen,[2] Zeenat Y. Bhat,[1] Yahya M. Osman Malik.[3] *[1]Wayne State University, Detroit, MI; [2]Wayne State University/ Detroit Medical Centre, LaSalle, ON, Canada; [3]Wayne State University Medical School, Detroit, MI.*

Background: Lupus Nephritis is one of the most common forms of secondary glomerulonephritis causing nephrotic syndrome and progressive loss of renal function. We examined the relation between proteinuria class of nephritis and level of chronicity in renal biopsies. We also evaluated the response to therapy as well as one year's outcome.

Methods: We reviewed medical records of biopsy proven lupus nephritis (n= 26, ISN/RPS 2003 class I-VI) from the year 2012 to 2016 with one year follow-up after initiation of immune-suppressive therapy. This included correlation between proteinuria, histological class, severity and chronicity on renal biopsies, as well as one year follow-up of proteinuria and eGFR following initiation of immuno-suppressive therapy.

Results: The mean follow up was 12 months. The population was predominantly African American groups (92% were African American groups, and 92% female). Baseline mean proteinuria was 4.97 ± 4.75 g/24h and eGFR was 74.19 ± 41 ml/min/1.73m2. Majority received cyclophosphamide as an induction therapy. Out of 26 patients, most of them were found to have class III to V at the time of diagnosis. The mean proteinuria following immune-suppressive therapy has dropped to 2.08 g/24 h, This is more than 50% reduction with a p-value of 0.006. However, there was a weak correlation between proteinuria and the histological classes of lupus (correlation coefficient is 0.201; p- value 0.324) and also to disease activity index (correlation coefficient is 0.353; p- value 0.07). A moderate correlation was found between chronicity and degree of proteinuria and this was statistically significant (correlation coefficient is 0.528; p- value 0.006). Pre-treatment eGFR and one-year post-treatment, did not demonstrate any significant change[75.5,78.9 ml/minute respectively]with a p-value of 0.409.)

Conclusions: The magnitude of proteinuria is a reasonable predictor of severity of chronicity, among other factors. Measurement of eGFR may not be a sensitive parameter to monitor the response to immune-suppressive therapy when compared with proteinuria. Our results showed that reduction of proteinuria within one year of therapy was statistically significant and may be a good prognostic marker for monitoring lupus nephritis.

PUB534

Successful Treatment of Membranous Lupus Nephritis with Rituximab Andres Serrano. *Mount Sinai Hospital, Chicago, IL.*

Background: Rituximab has been proven to be a safe and effective therapy for idiopathic membranous nephropathy. In regards of lupus nephritis, there have been reports of rituximab to be efficacious when used as a combined therapy. However, in a large randomized study, rituximab did not improve the response of mycophenolate mofetil. I am reporting a case of membranous lupus nephropathy successfully treated with rituximab alone.

Methods: The patient is a 38 year-old African-American woman who was sent for evaluation of nephrotic syndrome. At the initial visit her only symptom was progressive peripheral edema, which advanced over the course of 4 weeks. Her past medical history included intra-cranial hemorrhage, seizure disorder and sickle cell trait. The only medication she was taking was levetiracetam for her seizure disorder. On physical exam her blood pressure was normal, and she had severe lower extremities edema. Work up ordered showed a serum creatinine of 0.5 mg/dl, and a serum albumin of 1.5 mg/dl. The urinalysis reported >500 mg/dl of protein, and the urine protein/creatinine was 5.1 gm/gm. A complete serological work up was negative. Patient underwent a transcutaneous ultrasound-guided kidney biopsy, which revealed membranous lupus nephritis. Because of lack of symptoms suggestive of systemic lupus erythematous and a negative serological work up, I decided to treat the patient with rituximab 1 gm IV every 14 days for a total of 2 doses, along with oral prednisone. Patient had a mild allergic reaction during the first dose. Two months after completing the last dose of rituximab, the urine protein/creatinine decreased to 1.0 gm/gm and the serum albumin increased to 2.3 mg/dl. Six months later the patient was in complete remission, urine protein/creatinine decreased to 0.1 gm/gm, and serum albumin increased to 3.8 mg/dl.

Results:

Conclusions: In patients with lupus nephritis rituximab does not add any additional benefit when used as a combined therapy. The case I presented achieved a full remission using rituximab alone. The patient had serological-negative membranous lupus nephritis. It is possible this group of patients have a clinical course similar to idiopathic membranous nephropathy. Hence, the response to Rituximab.

PUB535

Single Centre Report of Outcomes of Treatment of ANCA Vasculitis from a Large Cohort of Patients David Makanjuola,[1] Eirini LIOUDAKI.[2] *[1]St. Helier Hospital, Carshalton, United Kingdom; [2]ST HELIER HOSPITAL, Surrey, United Kingdom.*

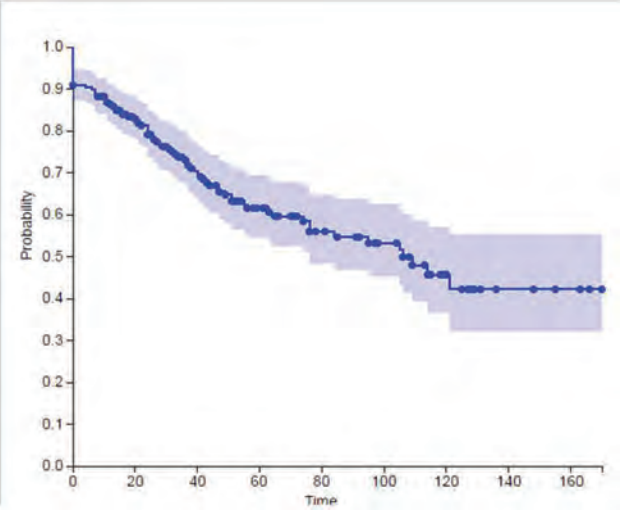
Background: The aim of treatment of patients with ANCA associated vasculitis is to induce a remission and then to maintain it. The challenge then is to wean the dose of immunosuppression to minimise toxicity from exposure to the immunosuppressive therapy, and balance this against the risk of relapse. We present the outcomes following treatment in a cohort of patients in whom remission was achieved with standard induction treatment, followed by maintenance therapy with Azathioprine (Aza) as first line agent, or Mycophenolate mofetil (MMF).

Methods: Data were collected from paper and electronic medical records of patients over a 13 year period.

Results: 220 patients with ANCA associated vasculitis successfully completed induction treatment and started maintenance treatment. 45% female, 91% Caucasian, age range 19 – 89 yrs (median 68). 112 (51%) had PR3 antibodies and 108 (49%) had MPO antibodies. 55 (25%) had a creatinine of > 500μmol/l at presentation. 27 (12.2%) patients died. 154 (70%) patients were relapse free at median follow up of 57 months (range 6-170). 66 (30%) experienced 1 or more relapses; data were available on 62 (Table 1). The presence of PR3 was more frequently associated with relapse - odds ratio (OR) 2.523 (95% CI 1.362 to 4.676) compared to MPO (p=0.004). MMF as maintenance treatment was also more frequently associated with relapse compared with Aza (OR 2.733; 95% CI 1.328 to 5.626, p=0.0068). The probability of event free survival (censored for death and/or relapse) is shown in figure 1.

Conclusions: Using our treatment protocol, 70% of patients had no relapse during the follow up period. In those who relapsed, we found, as has been described in other studies, that PR3 positivity was associated with an increased risk of relapse and that MMF also was inferior to Aza at maintaining remission.

Treatment at time of relapse	Prednisolone only	Aza or MMF only	Prednisolone and Aza or MMF	None
Number who relapsed	6 (9.5%)	14 (22.5%)	34 (55%)	8 (13%)
Average time (months) to relapse	38 (18-51)	38 (4-84)	29 (7-109)	89 (51-121)



PUB536

The Circadian Clock Provides Beneficial Effects against the Endothelial Dysfunction to Promote Atherogenesis by Regulating LKB1/AMP-Activated Protein Kinase Activation Hideyuki Negoro. *Harvard Medical School, The Graduate School of Project Design, Tokyo, Japan.*

Background: The circadian clock is a molecular mechanism that confers 24 hour variations in gene expression and function to regulate number of physiological functions in humans. Disruption of the clock is associated with pathological remodeling in the arterial structure and vascular stiffness. Chronic circadian clock disruption is also associated with dysfunction in endothelial signaling and responses. In this study, we observed if the deletion of Bmal1, a critical component of the circadian clock, can influence the protein levels of LKB1, a serine/threonine kinase, the phosphorylation of its downstream target AMP-activated protein kinase (AMPK) and plasminogen activator inhibitor (PAI)-1 generation which play an important part in the progression of vascular diseases.

Methods: Congenic 12- to 16-week-old male, wild-type and Bmal1-KO littermate mice were generated from heterozygote breedings to be used for these studies. We also knocked down Bmal1 to evaluate the protein levels of LKB1, AMPK and PAI-1 in the knocked down cells.

Results: Endothelial function was reduced in aorta from Bmal1-KO mice. In aorta from Bmal1 KO mice, there was an increase in LKB1, AMPK and PAI-1 expression in mice with a dysfunctional circadian rhythm. Moreover, Bmal1 KO mice display premature aging to have a dramatic prothrombotic phenotype. This phenotype is linked to changes in the regulation of key risk factors for cardiovascular disease. These include LKB1, AMPK and PAI-1, which are significantly elevated in Bmal1 KO mice. We also confirmed that LKB1, AMPK and PAI-1 levels follow a circadian pattern and this pattern was absent in Bmal1 KO mice.

Conclusions: These findings indicate that circadian clock provides beneficial effects against the endothelial dysfunction to promote atherogenesis by regulating LKB1, AMPK activation and PAI-1 generation. This study establishes a mechanistic connection between Bmal1 and cardiovascular phenotype.

Funding: Government Support - Non-U.S.

PUB537

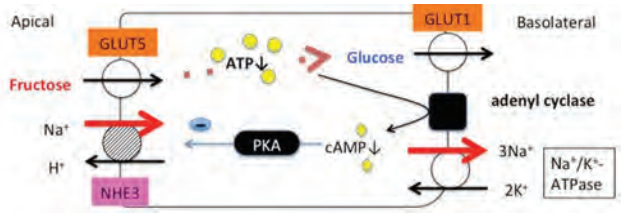
High-Fructose Diet Induces the Dysfunction of Energy Metabolism (ATP Depletion) and Hypertension Hiroaki Hara, Kaori Takayanagi, Minoru Hatano, Kento Hirose, Takatsugu Iwashita, Taisuke Shimizu, Tomonari Ogawa, Koichi Kanozawa, Hajime Hasegawa. *Department of Nephrology, Hypertension, Blood Purification, Saitama Medical center, Saitama Medical University, Kawagoe, Japan.*

Background: Consumption of fructose is revealed to evoke an acceleration of obesity, hypertension, insulin resistance, and uric acid production. Recently, it is known that fructose activates sodium–hydrogen exchanger 3 (NHE3) through the reduction of cyclic AMP in the proximal tubule. It would be highly assumed that the uni-directional fructose metabolism-induced ATP-consumption may be involved in the development of energy dysfunction, however, it has not been directly demonstrated yet. Here, we investigated the fructose-induced changes in the renal salt handling and ATP levels.

Methods: Male SD rats (7 weeks old) were fed by food containing 60% glucose (GLU) and food containing 60% fructose (FRU) for 3 and 6 and 12weeks (n=5 in each group). Calorie per unit-weight was adjusted in all three kinds of food. Tissue ATP concentration was assayed by use of assay kit (Abcam plc, Cambridge, UK). No difference of calorie and salt intake of individual animal was daily confirmed by the measured weight of remaining food.

Results: Body weight was not different in both groups at all time-points. Mean blood pressure of FRU was significantly higher than that of GLU at 6 and 12-weeks (6w-GLU: 85.9 ± 1.2 mmHg, 6w-FRU: 90.1 ± 1.4 mmHg, 12w-GLU: 94.8 ± 3.4 mmHg, 12w-FRU: 103.7 ± 1.2 mmHg), however, it was not different at 3-week. Fractional excretion of sodium (FENa) of FRU at 6-weeks was significantly higher than that of GLU (6w-GLU: 0.100 ± 0.016%, 6w-FRU: 0.042 ± 0.09%, 12w-GLU: 0.084 ± 0.011%, 12w-FRU: 0.059 ± 0.08%). The NHE3 immunostaining positive area of FRU at 12-weeks was significantly higher than that of GLU (12w-GLU: 5.31±0.490%, 12w-FRU:6.55±0.369%). Renal cortical ATP concentrations of FRU was significantly low comparing to GLU at 6 and 12-week (12w-FRU: 6.15 ± 1.11 nmol/mg protein, 12w-GLU: 10.81 ± 1.99 nmol/mg protein) whereas no significant difference was observed at 3-weeks.

Conclusions: We demonstrated that fructose intake might cause the elevation of blood pressure and salt reabsorption through the ATP consumption being independent on calorie and salt intake in the present study.



PUB538

Inhibition of Both NFκB and NLRP3/IL1β Pathways Affords Better Renoprotection in Chronic NO Blockade/Salt Overload Fernanda F. Zambom, Karin C. Oliveira, Viviane D. Faustino, Orestes Foresto-Neto, Victor F. Avila, Simone C. Arias, Flavia G. Machado, Camilla Fanelli, Claudia R. Sena, Vivian L. Viana, Denise M. Malheiros, Niels O. Camara, Roberto Zatz, Clarice K. Fujihara. *Univ Sao Paulo, SP, Brazil.*

Background: NO inhibition with L-NAME along with salt overload (HS) lead to severe hypertension (HT), albuminuria (ALB), glomerulosclerosis (GS) and interstitial fibrosis. We investigated whether activation of the NFκB and/or NLRP3 pathways is involved in the pathogenesis of renal injury in this model.

Methods: Adult male Munich-Wistar rats receiving oral NAME (32 mg/kg/d) and HS (HS+N) were given Allopurinol (Allo) as NLRP3 inhibitor, 36 mg/kg/d ($HS+N_{Allo}$), or Pyrrolidine Dithiocarbamate (PDTC), a NFκB inhibitor, 60 mg/kg/d ($HS+N_{PDTC}$). After 4 wk, we assessed: tail-cuff pressure (TCP, mmHg), ALB (mg/d), GS (%), renal uric acid (rUA, mg/g), interstitial collagen 1 (COLL, %), macrophages (MΦ, cells/mm²), NLRP3+ cells (/mm²) and the renal content of IL1β (pg/mg), TLR4, nuclear p65 (NFκB) and Superoxide Dismutase (SOD2) (xHS).

Results: HS+N rats developed HT, ALB and renal injury, along with inflammation, oxidative stress (OS), TLR4/NFκB and NLRP3/IL1β activation. Allo lowered rUA and inhibited NLRP3/IL1β, without changing OS, in association with amelioration of HT, ALB and interstitial inflammation/fibrosis, but not GS. Besides diminishing rUA and NLRP3/IL1β, PDTC prevented OS and NFκB, and exerted a more efficient antiinflammatory and nephroprotective effect than Allo.

Conclusions: NLRP3/IL1β and NFκB act in parallel to promote renal injury/inflammation and must be simultaneously inhibited for best nephroprotection in the chronic NO blockade/salt overload model. FAPESP/CNPq

Funding: Government Support - Non-U.S.

	TCP	ALB	GS	COLL	MΦ	TLR4	NFκB	rUA	NLRP3	IL1β	SOD2
HS	149±2	9±3	1±1	1.0±0.1	23±2	1.0±0.1	1.0±0.1	1±1	3±1	1±1	1.0±0.1
HS+N	209±4 ^{a}	147±12 ^{a}	4±1 ^{a}	2.8±0.1 ^{a}	131±7 ^{a}	2.6±0.4 ^{a}	2.9±0.3 ^{a}	2±1 ^{a}	8±1 ^{a}	4±1 ^{a}	0.6±0.1 ^{a}
$HS+N_{Allo}$	190±4 ^{ab}	80±17 ^{ab}	4±1 ^{a}	2.2±0.1 ^{ab}	88±8 ^{ab}	1.8±0.2	2.7±0.3 ^{a}	1±1 ^{b}	5±1 ^{ab}	2±1 ^{b}	0.6±0.1 ^{a}
$HS+N_{PDTC}$	174±4 ^{abc}	37±8 ^{bc}	1±1 ^{bc}	1.6±0.1 ^{abc}	37±6 ^{bc}	1.3±0.2 ^{b}	1.4±0.3 ^{bc}	1±1 ^{b}	5±1 ^{ab}	2±1 ^{b}	0.9±0.1 ^{bc}

Mean±SE;^{a}p<0,05 vs HS;^{b}p<0,05 vs HS+N;^{c}p<0,05 vs $HS+N_{Allo}$

PUB539

Evaluation of Further Cardiovascular and CKD Risk Factors Screening in an Apparently Healthy Population Attilio Di Benedetto,[3] Annalisa Ciotola,[3] Fabrizio Cerino,[3] Annamaria Colao,[4] Stefano Stuard,[2] Bernard J. Canaud.[1] *[1]FMC Deutschland GmbH, Bad Homburg, Germany; [2]Fresenius Medical Care, Bad Homburg, Germany; [3]NephroCare, Naples, Italy; [4]University Federico II Naples, Naples, Italy.*

Background: Cardiovascular disease(CVD) prevalence is on the rise in industrialized countries, presenting a significant societal and economic burden. We report the results of a screening program in an apparently healthy population

Methods: In 2013,2014 and 2015, during prevention events, a large sample of apparently healthy people were evaluated for cardiovascular and kidney risk factors. The following parameters were assessed:blood pressure, weight, height, waist circumference, BMI and Body Composition (BC). Lean(LTI) and Fat(FTI) tissue indexes and ECFO were evaluated by multi-frequency bioimpedance spectroscopy(BIS). Results are reported as mean and standard deviations or percentages for continuous and categorical variables in different age group and gender, respectively.

Results: 1081subjects were evaluated: 416(38.5%)were male(m),665(61,5%)were female(f);mean age was 54.46(±15.9) years in m, 50.17 (±15.2) years in f;5.5% m and 6.8% f referred dyslipidemia;4.3%m and 2.4%f referred diabetes;21.6%m and 13.4%f were hypertensive;2.6% m and 0.5% f referred heart disease;0% m and 2.6% f referred hypothyroidism;1.2% m and 1.5% f referred CKD.Mean systolic blood pressure(SBP)was 125.38(±19.18)mmHg, mean diastolic blood pressure (DBP)was 75.85 (±11.3)mmHg. BMI levels were: <20 kg/m²: 2(0.5%) in m and 30 (4.5%) f ; 20-24 kg/m²: 104(25.0%) m and 276(41.5%) f; 25-29 kg/m²: 208 (50.0%) m and 210 (31.6%) f; >30 kg/m²:102 (24.5%)m and 149 (22.4%) f.FTI and LTI were evaluated according to normal distribution adjusted by age and gender.

Conclusions: In a large sample of apparently healthy population a relevant proportion of male compared to female had more risk factors as higher SBP, ECFO, FTI, but also additional CVD/CKD risk factors such as obesity, dislipidemia, smoke, diabetes. In stratifying general population for risk factors, body composition appears to be an important method to evaluate FTI and ECFO risk factors.

Funding: Private Foundation Support

Mean SBP, DBP, proportion of patients with ECFO, FTI, LTI in both gender

Gender	SBP mmHg	DBP mmHg	ECFO<-1L	ECFO>-1<1L	ECFO>1L	FTI low	FTI Normal	FTI high	LTI low	LTI normal	LTI high
Male	133.25 (18.4)	80.11(11.3)	8.8%	43.7%	47.6%	9.5%	78.3%	12.2%	18.5%	71.5%	10%
Female	120.44(17.9)	73.20 (10.4)	15.9%	52.7%	31.4%	7.3%	80.4%	12%	16%	75.1%	8.9%

PUB540

Effect of Aliskiren on Arterial Stiffness, Compared with Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Antagonists in Hypertensive Patients: A Meta-Analysis Georgios Spanos,[1] Rigas Kalaitzidis,[2] Evangelos Evangelou,[3] Kostas Siamopoulos.[2] *[1]Department of Nephrology & Renal Transplantation Unit, Laiko General Hospital, National & Kapodistrian University of Athens, Medical School, Athens, Greece; [2]Department of Nephrology, University Hospital of Ioannina, Ioannina, Greece; [3]Department of Hygiene and Epidemiology, University of Ioannina, Medical School, Ioannina, Greece.*

Background: The degree of arterial stiffness (AS) is correlated with the risk of cardiovascular disease and it is a powerful predictor for morbidity and mortality. Inhibition of the renin-angiotensin system (RAS) is associated with an important decrease in cardiovascular risk, while classic RAS inhibitors have shown to improve AS indices. We sought to compare the relationship of direct renin inhibitor aliskiren versus classic RAS inhibitors on AS in mild to moderate hypertensive patients.

Methods: PUBMED, MEDLINE, and Cochrane library searches were performed until March 1st, 2017 for potential related articles. Inclusion criteria were i) randomized controlled trials in adult hypertensive patients, ii) comparison of aliskiren with other agents that inhibit the RAS, iii) reported data for blood pressure, pulse wave velocity (PWV), augmentation index (AIx) and iv) Study duration over 4 weeks. We calculated the summary standardized mean difference (SMD) from all studies using a random-effects

model using an inverse variance approach. Heterogeneity was quantified using the I^2 which ranges between 0-100% and describes the percentage of the variability in the effect estimates (e.g standardized mean differences in our case) that is due to heterogeneity rather than chance. Values >50% represent substantial heterogeneity.

Results: A total of 40 articles were found through database searches. These articles included 4 randomized controlled studies involving a total of 160 participants who met all pre-defined criteria. The SMD calculated did not indicated any significant differences with summary estimates including the null. Specifically, for PWV the summary effect size derived from the random effects model was 0.01 (95% CI: -1.00- 1.02) with no observed heterogeneity (I^2=0%). For AIx the summary effect was -0.21 (95% CI: -5.14-4.72) with no observed heterogeneity ((I^2=0%)

Conclusions: Aliskiren when compared to other RAS inhibitors have similar effect on arterial stiffness indices in hypertensive patients.

PUB541

Anti-Vascular Endothelial Growth Factor Agent Bevacizumab Use for Diabetic Retinopathy in a Hemodialysis Patient Dheeraj Kaul,[3] Serena Bhela,[1] Moro O. Salifu,[2] Mary C. Mallappallil.[1] *[1]None, Brooklyn, NY; [2]SUNY Downstate Medical Center, Brooklyn, NY; [3]Nephrology, SUNNY Downstate Medical Center, Brooklyn, NY.*

Background: In diabetic patients microvascular disease could present as diabetic retinopathy, nephropathy and or neuropathy. Among diabetics, diabetic macular edema (DME) is the most common cause of vision loss. While in the past, laser photocoagulation significantly reduced moderate vision loss and was the gold standard treatment for DME. Recently, with the use of anti-Vascular Endothelial Growth Factor drugs (Bevacizumab, Ranibizumab, and Aflibercept), better outcomes were obtained in terms of visual acuity gain and decrease in macular thickness as monotherapy. As the dose of the agent used in intravitreal injection is small the systemic side effects of progression of thrombosis is rare.

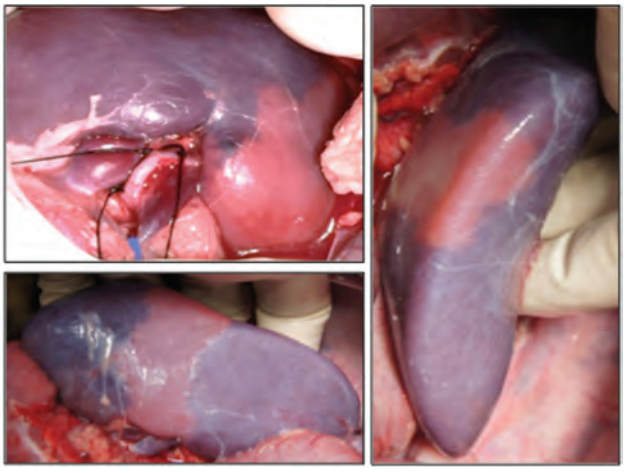
Methods: We present a case of a woman with primary open angle glaucoma, diabetic retinopathy and nephropathy who presented with diabetic retinopathy since 2006. She developed diabetic macular edema and successfully treated with focal laser photocoagulation with repeated treatments of both eyes in 2008, 2010, 2012 and intravitreal bevacizumab in 2008, 2010, 2011 and 2012. Pan retinal photocoagulation was performed in 2012. With the progression of her diabetic nephropathy, chronic hemodialysis was initiated in April 2016. She continued her treatment of diabetic retinopathy safely with bevacizumab in July 2016 and got repeated treatments for her non proliferative diabetic retinopathy with the agent in 2017 without any systemic side effects. With the treatments her visual acuity and optical coherence tomography showed improvement with as objective measures being a decrease in macular thickness in both eyes (512 to 412 and 610 to 440 Micrometers).

Results:

Conclusions: Macular laser therapy may still play an important role as an adjuvant treatment because it is able to improve macular thickness outcomes and reduce the number of injections needed. There are no case reports in the literature of the use of anti-VEGF intraocular injection therapy in hemodialysis for diabetic retinopathy either as monotherapy or combination with focal or pan retinal laser therapy.

PUB542

Abstract Withdrawn



PUB543

Better Late Than Never Anjuman A. Howlader, Bijin Thajudeen. *University of Arizona, Tucson, AZ.*

Background: Acute renal arterial occlusion due to a stent thrombosis is common. The management options include endovascular or surgical revascularization. When the renal artery is occluded, a revascularization decision is sometimes deferred depending on the size of the kidney or extent of chronicity based on imaging or biopsy. Here we present the case of a patient who had total occlusion of renal artery in the presence of solitary kidney and who responded to revascularization.

Methods: 73-year-old female with history of right renal arterial stenosis, status post stent placement, congenital atrophic left kidney, hypertension, and chronic kidney disease presented with reduced urine output of 3 days duration. She also has a history of chronic kidney disease. Laboratory tests showed serum creatinine of 17 mg/dl and potassium of 7.4 meq/L. Emergency hemodialysis was started. Subsequent evaluation showed occlusion of right renal arterial stent. A renal angiogram revealed total occlusion of the renal arterial stent and attempt for revascularization failed. In view of the small size of kidneys (8.5 cm), thin cortex and loss of corticomedullary differentiation it was deemed that a surgical vascularization may not be of benefit. Hence, she was discharged home with recommendations to continue the hemodialysis. But 2 weeks later she presented to the ER with back pain and was found to have a ruptured aortic aneurysm on CT angiogram. CT angiogram also showed presence of contrast in the mid renal artery despite the total occlusion which suggested ongoing perfusion of the kidney. An endovascular repair of the aortic aneurysm was done using a synthetic graft. Since there were some signs of perfusion to that kidney a revascularization bypass procedure was done using PTFE graft connecting the aortic graft used for repairing the aortic aneurysm and renal artery distal to the thrombosed stent. Following the bypass procedure there was reestablishment of circulation to the kidney and improvement in urine output. Hemodialysis was discontinued. Serum creatinine was 1.8 mg/dl 2 weeks after the procedure. A post procedure duplex showed heterogenous perfusion to the kidney although a similar study was not available prior to procedure to compare.

Results:

Conclusions: This case highlights the importance of considering revascularization procedure in presence of renal vascular occlusion irrespective of the size of the kidney especially in patients with solitary kidney.

PUB544

Uremia Alters Vascular Gene Expression in Pig Carotid Artery and Jugular Vein Jaroslav Janda,[2] Begoña Campos,[4] Frank C. Brosius,[2] Aous Jarrouj,[1] Keith L. Saum,[4] Lindsay N. Kohler,[2] Prabir Roy-Chaudhury,[2,5] Diego Celdran-Bonafonte.[3] *[1]Banner-University of Arizona, Tucson, AZ; [2]University of Arizona, Tucson, AZ; [3]University of Arizona / BIO 5 Institute, Tucson, AZ; [4]University of Cincinnati, Cincinnati, OH; [5]Southern Arizona VA Healthcare System, Tucson, AZ.*

Background: Uremia induces multiple pathologic changes in vascular tissues leading to enhanced cardiovascular disease and increased mortality in patients with advanced chronic kidney disease and end-stage kidney disease. To identify key pathogenic molecules in this process we have utilized a uremic pig model and have specifically determined the expression of 8 genes associated with endothelial and vascular dysfunction, at different arterial and venous sites.

Methods: Yorkshire pigs (n = 4 in each group) were made uremic by 5/6 nephrectomy]. Arterial (carotid, aorta) and venous (jugular, inferior vena cava) segments were removed under anesthesia 6 wk post-surgery and processed for total RNA isolation and cDNA synthesis. Quantitative real time-PCR was performed for ICAM, VCAM, NOS3, NOX4, KLF2, CCL2, MMP2, and MMP9.

Results: NOX4 and MMP2 expression was reduced ~2-fold in uremic vs. normal carotid artery ($p < 0.05$). NOS3, CCL2 and VCAM demonstrated non-significant reductions in gene expression in uremic carotid artery vs. non-uremic carotid artery.

In jugular vein, KLF2 and ICAM were reduced ~7-fold ($p<0.05$) in uremic veins. No significant changes in gene expression were found in the 8 genes studied in uremic aortas or inferior vena cavas vs. their non-uremic counterparts.

Conclusions: Uremia is associated with a reduction in expression of vascular genes in both carotid artery and jugular vein. Such reductions may alter signaling and vascular adaptation in uremia. Ongoing and future studies will characterize the functional effect of these gene changes through a systematic evaluation of genome-wide expression in uremic vessels, together with an evaluation of changes in uremic and non-uremic vessels in response to vascular stress/injury.

Funding: NIDDK Support, Veterans Affairs Support

PUB545

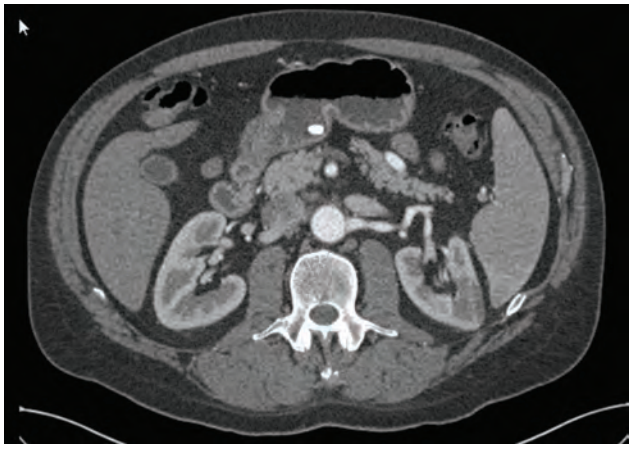
A Case of Renal Artery Dissection in a Patient with Fibromuscular Dysplasia and Rheumatoid Arthritis Aditya S. Pawar,[2] Stephen B. Erickson.[1] *[1]Mayo Clinic, Rochester, MN; [2]Mayo Clinic, Rochester, MN, ROCHESTER, MN.*

Background: Fibromuscular dysplasia (FMD) is a non-inflammatory and non-atherosclerotic angiopathy, most commonly seen in renal arteries. Here, we present a case of renal artery dissection in a patient with FMD and Rheumatoid Arthritis (RA) presenting with flank pain.

Methods: 59-year-old male with past medical history of RA and HTN controlled with hydrochlorothiazide presented to emergency room with severe flank pain. His vitals were stableand had no prior history of kidney disease. EKG and echocardiogram were unremarkable. Laboratory test showed hemoglobin of 13 g/dL, WBC 6.8 x 10^9/L, serum creatinine 1mg/dL. Electrolyte panel, ESR, CRP, UA and microscopy were unremarkable. CT angio showed a dissection of the left mid renal artery with wedge shaped infarction of lateral upper/mid left kidney (Figure1). Additionally, beaded irregularity was seen in the mid and distal renal arteries, which supported diagnosis of FMD. MRA of neck and brain was unremarkable. Kidney function remained stable during his hospital stay. He was discharged on low dose aspirin with outpatient follow up with Nephrology and hypertension.

Results:

Conclusions: Flank Pain can be one of the presenting symptom of FMD (17%). FMD can mimic atherosclerotic disease and vasculitis. Minority of FMD patients develop aneurysm and dissection. Treatment is focussed on control of hypertension and anti-platelet therapy. The next most common arterial bed involvement after renal arteries is cerebral and vertebral arteries. RA, which is a pro-inflammatory condition and has been shown to accelerate atherogenesis from endothelial dysfunction may predispose to a dissection of FMD involved arteries. In our case, having RA might have predisposed our patient to develop a dissection and subsequent infarction. It is important for physcians to be aware of the complications of FMD as timely intervention can prevent further damage.



PUB546

Physicians' Perception of Blood Pressure Control in Patients with CKD and the Target BP Achievement Rate Ran-hui Cha,[2] Hajeong Lee,[4] Jung Pyo Lee,[3] Young rim Song,[1] Yon Su Kim.[4] *[1]Hallym Univ. Sacred Heart Hospital, Anyang, Republic of Korea; [2]National Medical Center, Seoul, Republic of Korea; [3]Seoul National University Boramae Medical Center, Seoul, Republic of Korea; [4]Seoul National University College of Medicine, Seoul, Republic of Korea.*

Background: Blood pressure (BP) control is the most-established method for the prevention of chronic kidney disease (CKD) progression. However, the ideal BP target for CKD patients is still in debate.

Methods: We performed a questionnaire survey of regular members registered in the Korean Society of Nephrology to determine the physicians' perception of BP control in patients with CKD. And we evaluated the target BP achievement rate using data from the APrODiTe-2 study.

Results: Two-thirds of physicians considered the target BP for CKD to be < 130/85 mmHg. The SBP thresholds for diabetic CKD, proteinuria ≥ 300 mg/day, 30 ≤ GFR < 60 ml/min/1.73 m^2, age < 60 years, and the presence of atherosclerotic (ASO) complications were significantly lower than the SBP thresholds of the opposite parameters. The four major hurdles to controlling BP were non-compliance to life-style modification and medications, self-report of well-controlled home BP, and co-prescription from other specialties. 78.6% and 97.3% of physicians prescribed home and ambulatory BP monitoring to less than 50% of their patients, respectively. The target BP achievement rates using the SBP thresholds in this survey were as follows: non-diabetic (69.3%); diabetic (29.5%); proteinuria < 300 mg/day (72.3%); proteinuria > 300 mg/day (33.7%); GFR ≥ 60 (76.4%); GFR < 30 (47.8%); no evidence of ASO (67.8%); and the presence of ASO (42.9%).

Conclusions: The target BP was lower in patients with higher cerebro-cardiovascular risks, including diabetic CKD, lower GFR, higher proteinuria, and the presence of ASO. These patient groups also showed lower target BP achievement rates. We also found a relatively lower application and clinical reflection rate of home or ambulatory BP monitoring.

PUB547

A Pharmacist-Guided Patient-Driven Interdisciplinary Program to Improve Blood Pressure Control in Patients with Hypertension Charles W. Hopley,[6] Emily Andrews,[3] Patrick M. Klem,[5] Zhiying You,[1] Michelle Jonjak,[2] Diana I. Jalal.[4] *[1]UC Denver, Aurora, CO; [2]University of Colorado, Aurora, CO; [3]University of Colorado Denver, Aurora, CO; [4]University of Colorado Denver Health Science Center, Aurora, CO; [5]University of Colorado Heospital, Aurora, CO; [6]University of Colorado SOM, Denver, CO.*

Background: Hypertension is a major risk factor for kidney and cardiovascular disease and mortality. Yet, approximately 2/3rds of patients treated for hypertension do not meet blood pressure goals. Patient-driven self-titration of blood pressure (BP) medications and lifestyle modifications are both reportedly effective and safe in the management of hypertension. We launched a quality improvement project implementing a pharmacist-guided patient-driven self-titration protocol and standardized dietary counseling to improve BP control in the chronic kidney disease (CKD) clinic.

Methods: Patients with uncontrolled hypertension on 3 or fewer antihypertensive agents were included. BP goals were established based on individual risk factors. Patients were referred to the clinical pharmacist who devised a personalized plan for BP medication titration based on home BP monitoring and provided dietary education. Patients were required to enter their BP readings via electronic medical records (EMR) every 2 weeks. The following outcomes were evaluated: adherence and effectiveness (entry of home BP readings via EMR), adverse events, and appeal to patients and providers.

Results: Nineteen patients have been enrolled and 3 patients have completed 6 month follow-up visits. 72.2% have entered home BP readings regularly in EMR. 2 of the 3 patients completing 6 month follow-up had significant improvement in blood pressure (avg 16.26 mmHG). Preliminary assessment of current patients demonstrates that of 13 patients actively entering readings, six patients have already met pre-specified blood pressure goals. One patient has reported episode of hypotension associated with a transient increase in serum creatinine, the patient was instructed to withhold diuretics and the symptoms resolved without further intervention. No other adverse events have been reported. Program provider surveys suggest favorable acceptance by the renal providers.

Conclusions: Patient-driven self-titration of BP medications and dietary counseling is feasible, safe, and well received from providers. Early results from patients completing the protocol appear to be promising and future plans include transitioning recruitment to the clinic staff, expanding it to all patients with hypertension, and expanding it to the primary care setting.

Funding: Clinical Revenue Support

PUB548

Prevalence and Treatment of Hypertension in Hemodialysis Patients in Three Time Points – 2006, 2011, and 2016 Piotr Skonieczny,[1,2] Zbigniew Heleniak,[1] Klaudia Piechowska,[1] Bartosz Pakula,[1] Marta Ksi??ek,[1] Monika Michalczuk,[1] Marek Karowiec,[1] Przemyslaw Rutkowski,[3,4] Leszek Tylicki,[1] Alicja Debska-Slizien.[1] *[1]Department of Nephrology, Transplantology and Internal Diseases, Medical Univeristy of Gdansk, Gdansk, Poland; [2]Department of Physiology, Medical University of Gdansk, Gdansk, Poland; [3]Department of General Nursery, Medical University of Gdansk, Gdansk, Poland; [4]Diaverum Poland, Gdansk, Poland.*

Background: Hypertension is a major problem among hemodialysis patients. The aim of the cross-sectional, observational study was to evaluate the prevalence, antihypertensive treatment and control of blood pressure according to JNC and K/DOQI recommendations in hemodialysis patients.

Methods: 227 patients hemodialyzed in Diaverum Dialysis Unit in three distinct periods of time 2006,2011 and 2016 were enrolled to the study. The analysis of the antihypertensive treatment was based on the medical files and it consisted of a comparison of the mean blood pressure results reported during the six consecutive HD sessions.

Results: The characteristic of study popualtion was showed in table 1. The mean blood pressure before HD session was 133/77,130/74 and 140/76mmHg, after HD session was 123/73,126/72 and 139/77mmHg in 2006,2011 and 2016 respectively and the values differed in three distinct periods of time. Percentage of patients using single, double, triple and multidrug therapy (4-6) were 23.6,18.2,28,12.5 in 2006, 14.8,34.6,24.7,17.2 in 2011 and 12.8,18.7,29,23.3 in 2016. The differences between single and double therapy were statistically significant. The most often used drugs were ß-blockers, diuretics and calcium channel blockers.

Conclusions: 1.Target of blood pressure control according to recommendations was achieved more often in 2006 probable as a result of differences in group characteristics 2.ß-blockers, diuretics and calcium channel blockers were the most common hypertensive drugs used in 2006,2011 and 2016 3.Percentage of patients using triple and multidrug therapy increased in 2016 in comparison to 2006 and 2011

Table 1 Characteristic of the study population

	2006	2011	2016	p
Number of participants (n)	59	82	86	<0.05
Man n(%)	38 (64,4)	49 (59,7)	50 (58,1)	<0.05
Mean age (years)	61,0	64,4	66,1	ns
Hypertension n(%)	55 (93,1)	81 (98,8)	80 (93)	ns
Cardiovascular disease n(%)	42 (71,2)	64 (79)	57 (66,3)	<0.05*
Diabetes n(%)	22 (37,3)	33 (40,7)	29 (33,7)	<0.05*
Duration of hypertension diagnosis (years)	10,2	11,0	14,5	<0.05
Duration of dialysis treatment (months)	25,2	33,6	44,7	<0.05
Blood pressure <140/80 before HD n(%)	41 (69,5)	52 (64,2)	44 (51,2)	<0.05
Blood pressure post HD <130/80 n(%)	37 (67,2)	47 (58)	24 (27,9)	<0.05

ANOVA variation linear

*ANOVA variation quadratic

PUB549

Changes in Day- and Night-Time HRV during Acute Phase of ARB Therapy Masashi Mizuno,[1] Michio Fukuda,[1] Yoshiaki Ogiyama,[1] Hiroko Shibata,[1] Tetsuhei Matsuoka,[1] Ken Mizuguchi,[1] Hiroya Shimogushi,[1] Ken Kiyono,[3] Yoshiharu Yamamoto,[4] Hiroyuki Kobori,[5] Junichiro Hayano,[2] Nobuyuki Ohte.[1] *[1]Department of Cardio-Renal Medicine and Hypertension, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [2]Department of Medical Education, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [3]Department of Mechanical Science and Bioengineering, Osaka University, Osaka, Japan; [4]Department of Physical and Health Education, University of Tokyo Graduate School of Education, Tokyo, Japan; [5]International University of Health and Welfare, Tokyo, Japan.*

Background: Enhanced renal tubular absorption (tNa) cause sodium sensitivity of BP and non-dipper circadian BP rhythm. We had clarified that angiotensin receptor blockers (ARBs) can suppress “inappropriately increased intrarenal RAAS” to inhibit tNa, resulting in increase of daytime natriuresis and restoration of circadian BP rhythm. Recently, we have reported that the increase in daytime natriuresis with ARB treatment was accompanied by intrarenal dopamine secretion. However, in that study some individuals demonstrated restoration of circadian BP rhythm without alteration of natriuresis.

Methods: 24h-holter ECG data was analysis to investigate changes in sympathetic (non-Gaussianity index λ2s) and parasympathetic (HF and deceleration capacity, DC) nervous activity in 20 patients with CKD during acute phase (2 days) of ARB (azilsartan).

Results: At baseline, 5 patients had dipper and 15 nondipper BP rhythm. HF was a determinant of night/day BP ratio (β = -0.50, F = 5.8), rather than DC or λ2s. Five patients out of 15 non-dipper patients had decrease in daytime λ2s. (0.49±0.50→0.47±0.05, p=0.04). Other 5 patients of 15 nondippers, who did not get decrease in night/day BP ratio, nighttime λ2s augmented.

Conclusions: In summary, diminished parasympathetic nervous activity was related to nondipper BP rhythm in CKD, but restoration of the BP rhythm with ARB was derived from its sympathoinhibitory effect.

PUB550

Saving the Pulseless Kidney! Rahul Kumar,[1] Ali Mehdi,[1] Georges Nakhoul.[2] *[1]Internal Medicine, Cleveland Clinic Foundation, Cleveland, OH; [2]Nephrology, Cleveland Clinic Foundation, Cleveland, OH.*

Background: Takayasu’s arteritis (TAK) also known as the pulseless disease, is a granulomatous large-vessel vasculitis. It primarily affects women of age 10 to 40 years. In patients with TAK, the prevalence of hypertension varies from 23% to 76% across the world and about half of them are secondary to renal artery involvement. In this case report, we present a patient with difficult to control hypertension and worsening renal function due to TAK induced bilateral renal artery stenosis refractory to medical therapy.

Methods: A 39-year-old Caucasian female presented with sudden onset chest pain. The patient was found to have an anterior ST-elevation myocardial infarction. Coronary angiography revealed 99% ostial stenosis of the left anterior descending as well as high-grade stenosis of the proximal left subclavian and bilateral renal artery. The patient underwent an urgent coronary artery bypass graft. On detailed history, she reported intermittent left arm shooting pain, muscle ache, fatigue, poor appetite and 50-pound weight loss over the past year. She has a past medical history of multiple sclerosis, ulcerative colitis, and cigarette smoking. On exam, blood pressure was 110/72 mmHg in the right arm and 88/70 mmHg in left arm, heart rate 86 bmp. A left subclavian bruit was present. Patient has a normal right radial pulse but a feeble left radial pulse. Patient labs showed ESR 59 and CRP 1.1. A CT angiogram showed severe stenosis of the proximal left subclavian artery, SMA, IMA, celiac and bilateral renal artery (80% RRA and 90% LRA). A clinical diagnosis of Takayasu’s arteritis was made. The patient was discharged on prednisone and methotrexate. At a six-month follow-up visit, MRA abdomen showed a completely occluded RRA with atrophied right kidney. Renal Duplex US showed an occluded RRA and 60-99% LRA proximal stenosis with a PSV of 768 cm/sec. An aortogram confirmed the RRA occlusion. The patient underwent a left aorto-renal bypass graft of her solitary kidney. A six-month follow-up showed stable kidney function with better control of blood pressure.

Results:

Conclusions: Takayasu’s arteritis is a rare cause of renovascular hypertension. Our patient was prevented from becoming dialysis dependent by timely recognition and intervention. In TAK with advanced renal artery stenosis refractory to medical therapy, surgical revascularization is the treatment of choice. Patient management must include a well-coordinated multidisciplinary approach.

PUB551

Rapid Progressive Visual Loss Due to Macular Edema and Cotton Wool Spots in a Pediatric Patient Receiving Peritoneal Dialysis Takahiro Namba,[1] Akira Ashida,[1] Hideki Matsumura,[1] Yuko Fujii,[1] Hyogo Nakakura,[1] Akihiko Shirasu,[1] Satoshi Yamazaki,[1] Tsunehiko Ikeda,[2] Motoshi Hattori,[3] Hiroshi Tamai.[1] *[1]Pediatrics, Osaka Medical College, Takatsuki, Japan; [2]Ophthalmology, Osaka Medical College, Takatsuki, Japan; [3]Pediatric Nephrology, Tokyo Women’s Medical University, Tokyo, Japan.*

Background: End-stage renal disease (ESRD) may lead to unique ocular complaints or exacerbate any underlying ocular disease. These ocular manifestations are a result of uremia, abnormal electrolyte balance, loss of fluid homeostasis, anemia, and hypertension. Although typical ocular symptoms in pediatric patients with ESRD include red, irritated eyes, ocular pain and changes in visual acuity, rapid progressive vision loss is relatively rare. Here, we report an unusual case of acute bilateral vision loss due to bilateral macular edema and cotton wool spots in a patient receiving peritoneal dialysis for ESRD.

Methods: A 15-year-old boy visited our clinic because of rapidly progressive blurring of his central vision. The patient had no history of diabetes, and had end-stage renal disease caused by focal glomerulosclerosis. Peritoneal dialysis had been started at the age of 14 years, and then six months later he had been admitted for readjustment of his dialysis conditions due to hypertension. However, because of non-adherence to dialysis, his blood pressure continued to increase. After a further two months, rapid progressive blurring of his central vision occured. On examination, his visual acuity was 0.5 in the right eye and 0.35 in the left. An ocular fundus examination revealed bilateral disk edema, macular edema, and cotton wool spots. Macular edema was confirmed by optical coherence tomography. As the patient’s blood pressure was found to have increased to 197/114 mmHg on admission, we changed the conditions of his peritoneal dialysis to improve water overload and administered additional antihypertensive drugs. After one month of treatment, his blood pressure was reduced to 100/60 mmHg and his visual acuity was improved to 1.5 in both eyes.

Results:

Conclusions: Irrespective of whether ocular symptoms are present, ophthalmological screening is necessary for pediatric patients with ESRD, as early ophthalmological diagnosis and treatment may restore vision and reverse any retinal anatomic changes without the need for surgical intervention.

PUB552

Frequency of Multi-Drug Treatment for Pediatric Hypertension Bethany Crawford,[2] Christopher Cates,[2] John Lin,[4] Nichaela A. Hoffman,[1] Thomas K. Davis,[3] Vikas R. Dharnidharka,[3] Laura Hesemann.[2] *[1]Barnes Jewish Hospital, St. Louis, MO; [2]University of Missouri School of Medicine, Columbia, MO; [3]Washington University School of Medicine, St Louis, MO; [4]Washington University in St. Louis, St. Louis, MO.*

Background: Hypertension (HTN) is increasingly prevalent among children and adolescents. Data regarding treatment of pediatric HTN is increasing but remains limited. Up to 75% of adult patients require multiple medications for blood pressure (BP) control. Knowledge of this guides adult practitioners regarding expected outcomes and gives a rationale for rapid titration of medication. The goals of this study were to determine the frequency with which children require multi-drug therapy to attain BP control and to identify risk factors for needing multiple BP medications.

Methods: All patients with HTN seen between May 2012 and April 2013 at a pediatric nephrology clinic in an academic center were evaluated. Patients with resolved HTN, ESRD, or history of kidney transplant were excluded. Data were collected for BP control as assessed by the treating physician, number of medications needed to achieve control, and risk factors including race, gender, BMI, CKD, and diabetes mellitus.

Results: Of 126 subjects, 92 (73%) were prescribed 1 medication. The remaining 34 (27%) were prescribed 2 or more medications. The groups were not significantly different with regard to the presence of any of the identified risk factors (table 1). Adequate BP control was achieved in 81% of subjects on 1 medication, which was not statistically different from the 82% who required multiple medications (p=0.883). In logistic regression, none of the identified risk factors correlated with the need for multiple anti-hypertensive medications.

Conclusions: Similar to findings in adult patients, a significant proportion of hypertensive children require multi-drug therapy to achieve BP control. The need for multi-drug therapy was independent of the evaluated risk factors and may not be an indication for more intensive evaluation. None of the factors evaluated predicted the need for multi-drug therapy. Further studies are needed to validate these findings in larger cohorts.

HTN risk factor assessment by number of medications used

	1 medication (N=93)	2+ medications (N=33)	p-value
male	61%	64%	0.812
AA	35%	24%	0.236
CKD	24%	33%	0.277
DM	6%	15%	0.134
BMI > 85%	63%	61%	0.906

Pearson Chi-Square or Fisher's Exact Test as appropriate

PUB553

Relationship between Angiogenesis Inhibitors and Pediatric Hypertension: A Case-Series Marissa Lipton,[4] Laura jane Pehrson,[3] Suzanne M. Vento,[2] Howard Trachtman,[1] Laura Malaga-Dieguez.[4] *[1]NYU Langone Med Ctr, New York City, NY; [2]NYU Langone Medical Center, New York, NY; [3]NYU School of Medicine, New York, NY; [4]New York University School of Medicine, New York, NY.*

Background: Angiogenesis inhibitors have an emerging role in the treatment of pediatric cancers. CNS tumors have high concentrations of pro-angiogenic factors and neo-vascularization. Much of what is known about angiogenesis inhibitors comes from adult studies, where they have been more widely used. Hypertension is a common side effect of this new drug class in adults. Limited information is available about the safety of these medications in children.

Methods: A single center, retrospective chart review was conducted. Twenty-eight patients under 25 years of age with CNS tumors, who were followed by the Division of Pediatric Hematology and Oncology at NYU Medical Center, were identified who had received angiogenesis inhibitors developed hypertension. Chart review was conducted in 12 cases. The other cases met exclusion criteria or access to full EMR was unavailable.

Results: Seven (56%) patients developed hypertension within 9 months of initiation of the drugs, with most occurring in the first 3 months. Four were treated with bevacizumab, 2 axitinib, and 1 pazopanib. While one patient's symptoms resolved, the remaining 6 children required treatment with anti-hypertensive agents. Only two patients were referred to pediatric nephrology and were treated with amlodipine. The remaining patients were all given diuretics by the oncology team, with 3 requiring use of a second antihypertensive agent (ACE inhibitors).

Conclusions: Our findings are consistent with the adult literature and indicate that secondary hypertension is a frequent complication of angiogenesis inhibitor therapy. Poorly controlled hypertension in children has the potential to track into adulthood and is a major risk factor for cardiovascular morbidity and mortality. Identification and treatment of pediatric hypertension is an important health focus for pediatric oncology patients. Timely referral to a pediatric nephrologist should be coinsidered for treatment of angiogenesis inhibitor-associated hypertension.

PUB554

Identification of Factors Modulating Hypertension in CKD: A Pilot Study Mochammad Thaha,[6] Maulana A. Empitu,[5] Ika N. Kadariswantiningsih,[1] Cahyo wibisono Nugroho,[4] Muhammad Amin,[7] Haerani Rashid,[3] Muhammad Yusuf.[2] *[1]Department of Microbiology, Airlangga University School of Medicine, Surabaya, Indonesia; [2]Department of Cardiology, Airlangga University School of Medicine, Surabaya, Indonesia; [3]Department of Internal Medicine, Hasanuddin University, Makassar, Indonesia; [4]Department of Internal Medicine, Airlangga University Hospital, Surabaya, Indonesia; [5]Department of Pharmacology, Airlangga University School of Medicine, Surabaya, Indonesia; [6]Department of Internal Medicine - Nephrology Division, Airlangga University School of Medicine, Surabaya, Indonesia; [7]Institute of Tropical Disease, Airlangga University, Surabaya, Indonesia.*

Background: Hypertension and chronic kidney disease interact in multifaceted dimension. Hypertension is regarded amongst leading causes of CKD. In contrast, hypertension is frequently developed in previously normotensive CKD patients. As hypertension also progress with kidney disease, it becomes urgent to identify factors which modulate the development of hypertension in CKD patients. Therefore, we conduct an observational study to investigate the contribution of nutritional status, quality of sleep, inflammation, and oxidative stress to the progression of hypertension in CKD.

Methods: During the first phase of recruitment, 35 consented stable CKD patients who enrolled in outpatient or haemodialysis clinics at a private and a government hospital in Surabaya, Indonesia were included. The nutritional status were evaluated using anthropometric measurement, Malnutrition-Inflammation Score (MIS) and Dialysis Malnutrition Score (DMS), while sleep quality were examined using Pittsburgh Sleep Quality Index (PSQI). Blood biochemical and cytological parameters represented with inflammation and oxidative stress were measured at baseline level. The medication and medical history were documented.

Results: The baseline characteristics of the study participants were aged 52.6±14.3 years with Cystatin-C adjusted eGFR 36.6±43.2 ml/minute per 1.73 m^2. Partial least squares - discriminant analysis on 49 different factors including clinical and biochemical parameters, revealed that 21 measured parameters significantly contributed ($Qi^2 > 0.8$, CI 95%) to the projection of hypertension. Among factors those significantly contributed in this model were eosinophil counts (VIP=2.27), renal function (VIP=1.80), Total Iron Binding Capacity (VIP=1.12), percentage of body weight change during the last 3 months (VIP=1.10), MIS score (VIP=1.06), the presence of sleep disturbance (VIP=0.91), and sleep latency (VIP=0.89±0.63).

Conclusions: The analysis result might consist of factors related to hypertension in CKD. However due to the limited numbers of data, the model used in this study needs to be validated along with this ongoing study recruiting more subjects.

Funding: Government Support - Non-U.S.

PUB555

Evaluation of Blood Bicarbonate Levels and Gas Analysis in Hemodialysis Patients Who Switch from Lanthanum Carbonate to Sucroferric Oxyhydroxide Aristeidis Stavroulopoulos,[1,2] Vasiliki V. Aresti,[1,2] Christoforos Papadopoulos,[3,2] Panagiotis Nennes,[2] Polyxeni G. Metaxaki,[2] Anastasios Galinas.[4,2] *[1]IASIO Hospital - General Clinic of Kallithea, Athens, Greece; [2]Dialysis Unit "ATTIKOS NEPHROS", Athens, Greece; [3]Dialysis Unit "ATHINAIKO KENTRO NEFROU", Athens, Greece; [4]417 NMTS Hospital, Athens, Greece.*

Background: Different phosphate binders have different effects on acid-base status of hemodialysis patients. We sought to examine possible alterations in acid-base parameters in patients switching from lanthanum carbonate (LC) to sucroferric oxyhydroxide (SOH).

Methods: Fifteen stable patients, on bicarbonate hemodialysis, switched from LC to SOH. However, only 9 continued on SOH; 3 returned to LC and the other 3 switched to sevelamer carbonate due to side effects of SOH. The later 6 patients served as a control group to the SOH group of 9 patients. Blood was sampled from the "arterial needle" of the vascular access, on the 3-day and the last 2-day interval of the week prior to switching and 6 weeks after, at the same intervals. Bicarbonate levels (HCO_3), pH, pO_2, pCO_2 were measured, and the mean of the 2 measurements (3-day and 2-day interval) was calculated. Dialysate, medications and hemodialysis prescription (except of ultrafiltration) were remained unchanged throughout the study.

Results: Comparing pre-switching to post-switching measurements in the SOH group, no statistically significant differences were found in any of the parameters studied. Mean pre-switching HCO_3 levels were 22.41 ± 1.66 mmol/L and post-switching 22.62 ± 2.25 mmol/l (P=0.743). Respectively, mean pH= 7.384 ± 0.028 vs. 7.388 ± 0.03 (P=0.723), mean pCO_2= 38.41 ± 3.29 vs. 38.37 ± 3.62 mmHg (P=0.971), Phosphate = 4.65 ± 0.85 vs. 4.21 ± 1.19 mg/dL (P=0.194) etc. No significant differences were found even when we analyzed the data for the 3-day and the 2-day intervals. There were not any significant differences when we performed the same analyses in the control group, or between SOH and control group. In addition, no correlations were found, either between pre-switching daily LC daily dose, or between post-switching daily dose of the new binder and the measured parameters. Only, pH and HCO_3 were significantly lower at the 3-day vs. 2-day interval, as expected.

Conclusions: In our small study, switching from LC to SOH did not have any significant effect on blood bicarbonate levels and gas analysis, indicating that there is no need to change hemodialysis prescription regarding these parameters. However, monitoring of serum bicarbonate levels is part of good clinical practice.

PUB556

Does Intravenous Iron Therapy Decrease Serum Phosphorus Levels? Frieda Wolf, Vladimir Poletaev, Mazen Elias. *Emek Medical Center, Afula, Israel.*

Background: Several intravenous iron formulations have been reported to increase phosphaturia, causing dangerously low serum phosphorus levels. This may lead to osteomalacia and fractures, more so in people with vitamin D deficiency. This phenomenon has been observed with saccharated ferric oxide, a preparation commonly used in Japan, and with iron polymaltose. It has also been observed with iron carboxymaltose There is no information in the literature about phosphorus levels after treatment with iron sucrose or ferric gluconate, which we use most frequently for individuals with iron deficiency anemia, with or without kidney disease.

Methods: . We checked serum phosphorus levels in 48 individuals with iron deficiency anemia, before and after iron treatment. Comparisons of phosphorus levels prior to and after treatment were done using students' t-test.

Results: Forty seven received iron sucrose. Only three individuals had vitamin D deficiency. Average phosphorus level pre- treatment was 3.46±0.5 mg/dL, with a mean PTH level of 62.59 pg/mL and mean vitamin D level of 40.67 nmol/L. Average phosphorus level was 3.47±0.55 mg/dL post-treatment.

Conclusions: We conclude that iron sucrose is a safe and effective treatment for iron deficiency, and does not reduce serum phosphorus levels.

Funding: Clinical Revenue Support

Laboratory values before and after iron treatment

	N	Mean value ±SD before iron	N	Mean value ±SD after iron
Phosphorus mg/dL	48	3.46 ±0.5	48	3.47 ±0.55
Hemoglobin g/dL	46	9.33 ±1.5	30	11.79 ±1.33
Albumin g/dL	34	3.9 ±0.33	32	3.88 ±0.45
Creatinine mg/dL	46	0.77 ±0.35	45	0.78 ±0.4
eGFR (MDRD)	25	113 ±44.4	23	109.85 ±38.2
PTH pg/mL	46	62.59 ±27.75	19	57.9 ±33.8
Vitamin D-25OH nmol/L	43	40.67 ±23.4	19	57.82 ±29.5

PUB557

Nephrocalcinosis Secondary to Total Parenteral Nutrition Gayatri D. Nair,[2] Laura Ferreira Provenzano,[1] Leal C. Herlitz.[1] *[1]Cleveland Clinic, Cleveland, OH; [2]Cleveland Clinic, Cleveland, OH.*

Background: Nephrocalcinosis is a rare complication of TPN and has only been reported in prenatal infants to date. Here we report a case of a middle aged woman who was found to have microscopic nephrocalcinosis with calcium phosphate deposition seen on renal biopsy which was due to high amounts of phosphorus she was receiving via TPN.

Methods: A 55 year old female with a history of Ulcerative colitis and total colectomy at the age of 6 followed by a diverting loop jejunostomy and end ileostomy in 2012 requiring TPN since then, presented to nephrology clinic in 2016 for elevated serum creatinine (SCr). Her baseline SCr was 0.6-0.8 mg/dL a year prior to presentation and had been slowly rising to a SCr of 1.8 mg/dL on initial evaluation. She had a history of recurrent episodes of dehydration secondary to high ostomy output which was an ongoing problem at the time of presentation. Her intake was adjusted to match output and protein content of TPN was decreased but SCr continued to rise and reached 2.29 mg/dL. Further labs showed an elevated phosphorous of 6.9mg/dL, PTH 329 pg/mL and low normal calcium, suggesting secondary hyperparathyroidism. Urine analysis showed no significant proteinuria or hematuria with some amorphous crystals seen on microscopy. 24 hour urine showed elevated phosphorus (1300 mg/24hr). Renal ultrasound was normal. Biopsy revealed chronic tubulointerstitial inflammation with moderate interstitial fibrosis and tubular atrophy. Moderate amounts of crystals consistent with calcium phosphate deposition were scattered throughout the interstitium. On further investigation it was found that the patient was receiving very high levels of phosphorus via TPN and had intermittent episodes of hyperphosphatemia in the prior year. The phosphorus content of TPN was substantially decreased and over the next few months SCr improved to 1.4mg/dL.

Results:

Conclusions: The mechanism of nephrocalcinosis due to TPN is related to the calcium phosphate ratio required for maintaining a neutral or positive calcium balance in order to prevent bone disease. Usual adult parenteral dose of phosphorus is 27-53 meq/day, our patient was receiving very high levels of phosphorous(95-180meq/day) for an extended period of time which led to calcium phosphate crystal deposition causing renal injury. Thus, in patients with renal dysfunction receiving TPN this is an important consideration.

PUB558

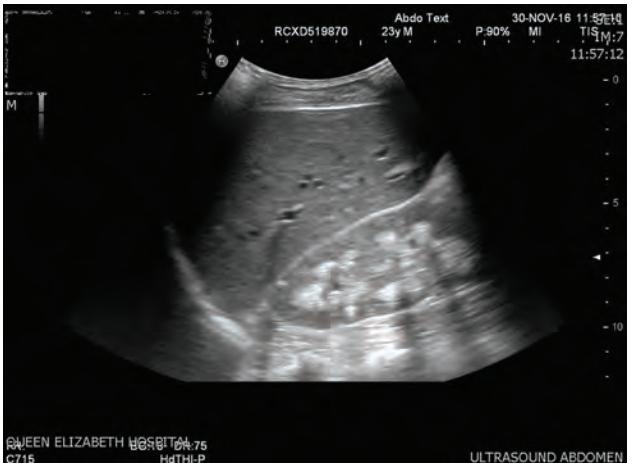
Medullary Sponge Kidney and Primary Hyperparathyroidism – An Enigma Zeshan sharif Choudhry,[2] Sherin A. Ahmed,[3] Smita Gunda.[1] *[1]Cambridge University Hsospitals, Cambridge, UK, Kings Lynn, United Kingdom; [2]NATIONAL HEALTH SERVICES, Kings Lynn, United Kingdom; [3]NHS, Cambridgeshire, United Kingdom.*

Background: Medullary sponge kidney is considered as congenital disorder usually characterised by malformation of collecting ducts which manifest as medullary cysts with sparing of cortex. It is thought to be a developmental abnormality with limited evidence of genetic transmission. It is usually asymptomatic and picked up as incidental finding on imaging but some times presents with hematuria, UTIs and renal colic with overall good prognosis with preserved renal function.

Methods: 23 year old gentleman with no past medical history. Presented to GP with 12 months history of increasing tiredness and fatigue, negative family history of any endocrinopathy. Normal physical examination. Routine blood tests revelaed raised alkaline phosphatase and therefore an abdominal ultrasound was arranged. This was suggestive of medullary sponge kidney and he was referred for nephrology review. Nephrology review and subsequent investigations showed a raised calcium 3.42mmol/l, high parathyroid hormone 28.7 pmol/l, urinary calcium 2.87 mmol/l, negative myeloma screen, normal ACE/vitamin D levels, normal range urinary metanephrines, normal pituitary profile and no symptoms of hypercalcaemia. CT urogram did not show renal stones and confirmed medullary sponge kidney. Clinical impression was of primary hyperparathyroidism which was treated with fluids and pamidronate. MIBI scan later confirmed right sided parathyroid adenoma which was surgically excised.

Results:

Conclusions: There is limited evidence in literature regarding association of primary hyperparathyroidism with medullary sponge kidney. There are suggestions that primary hyperparathyroidism can cause medullary sponge kidney but on other hand it is well proven fact that naphrocalcinosis can cause medullary sponge kidney. Association and mechanism of primary hypeparathyroidism as causative factor for medullary sponge kidney still remains an enigma.



PUB559

A Case Study of a Patient with CKD-Metabolic Bone Disorder with Concomitant Ectopic Primary Parathyroid Adenoma Joseph T. Leeds,[2] Abubakr Abdelaziz,[2] Tushar Chopra.[1] *[1]None, Nashville, TN; [2]University of Virginia, Charlottesville, VA.*

Background: We report an outpatient referral of a patient with chronic kidney disease (CKD) and normal to borderline elevated Calcium (Ca) with elevated PTH who presented to our outpatient clinic being referred by his Primary Physician.

Methods: 65-year-old Caucasian male with a past medical history of CKD Stage 3 likely secondary to presumed underlying type II diabetes mellitus (DM), and hypertension (HTN) who presents with fatigue, constipation and cold intolerance. Physical examination was unremarkable. Serum creatinine (Cr) had been elevated at 1.4-1.6 mg/dl since August of 2015 along with intermittent hypercalcemia since 2012 with peak Ca of 11.9mg/dl in January 2013. Most recent labs revealed serum PTH of 174 pg/ml, calcium of 11.1 mg/dL, 25-Hydroxy Vitamin D of 16ng/ml, and phosphorus of 1.8 mg/dL. Renal ultrasound was inconclusive. A sestamibi scan revealed an abnormal uptake due to an ectopic retrosternal parathyroid. A diagnosis of primary hyperparathyroidism (HPT) along with some element of secondary hyperparathyroidism related to renal insufficiency was made. Subsequently, he was referred for a surgical excision, while being medically managed with cinacalcet.

Results:

Conclusions: Ectopic parathyroid adenoma has a prevalence of 5%[1-3]. Common locations include mediastinum, retropharyngeal, carotid sheath, and intrathyroidal. Most common symptoms include renal colic, frequent urination, abdominal pain, nausea, vomiting, impaired memory, personality changes, and constipation. Primary HPT is often overlooked in Chronic Kidney Disease patients. Our case highlights the importance of persistent hypercalcemia with normal or low serum phosphorus levels as a biochemical clue in diagnosing primary HPT with ectopia in patients with suspected secondary hyperparathyroidism from CKD and Vitamin D deficiency. Imaging approach includes a sestamibi scan which is not necessary in all cases. It is important to remember the need for a sestamibi or 4-dimensional CT as ultrasound alone could miss ectopic adenomas, especially with inexperienced ultrasonographers.[5] Treatment approach includes surgery. The indication for parathyroidectomy in our case was elevated calcium values 1mg/dl above normal along with CKD. Whether the ectopic parathyroid is the hyper-functioning nodule can only be confirmed by excision and following PTH levels.

PUB560

Rebound Hypercalcemia Post Denosumab Exposure Mohammed Z. Mohialdeen,[1] Karim M. Soliman.[2] *[1]NEPHROLOGY, MUSC, Charleston, SC; [2]Medical University of South Carolina, Charleston, SC.*

Background: Hypercalcemia is an oncological emergency with an estimated incidence of 10–20% in adult patients with cancer. Denosumab is a humanized monoclonal antibody to RANKL approved for treatment of osteoporosis and prevention of skeletal-related events from bone metastases. RANK ligand (RANKL) is a cell surface protein involved in many cellular processes, including osteoclastogenesis. Receptor activator of nuclear factor κ-B ligand (RANKL) is a cell surface molecule that plays an important role in bone resorption and bone remodeling through its effect on osteoclasts.

Methods: We describe a 68 year old female with a pmhx of polymyalgia rheumatic (PMR), hypothyroidism, osteoarthritis, osteopenia, liver cirrhosis with Bx proven NASH, right breast cancer without bone metastasis, diagnoised 3 years earlier, who underwent bilateral mastectomy. She did not undergo chemo- or radiation therapy. She adjuvant therapy initially with letrozole which was changed to tamoxifen. Patient presented with generalized weakness and change in mental status. One week earlier, she was found to have a Ca2+ of 12. On admission, Ca2+ was 14 with albumin of 3.1. She received one dose of Denosumab for her known osteoporosis 6 month ago. Other outpatient medications included vit d 2000 U and Centrum silver once Labs:- CBC: Hgb 9.3, wbc 3.6, plt 76. BMP :- Na 144, k 2.8, Cl: 108, HCo3 27, AG 9, BUN: 16, CR: 1.3 BS: 107, EGFR:42,

Ca: 14., ALB: 3.1, Ionized Ca 1.35, PTH: 21.1. MG: 0.9 BIL/T 2.2, AST 29, ALT 11, ALK: 53, P: 6.1. UPEP:NL, SPEP:NL, K/LCR: 2.05, ACE: 66, 25-Hydroxy: 9.6,25, D3:30.3, 25-D : 39.9. AMMONIA: 15.1, VIT A: 0.07, PTH-RP: 0.8, CALCIUM, URINE: 14.6 Radiology:- Skeletal survey : Neg. Bone scan :Neg. Sestamibi scan: neg During her hospitalization course, she was treated with IV hydration, calcitonin. We stopped her vit D and supplement since admission. Corrected her Mg level and re-measure PTH with no significant changes. After that we re-introduce her Denosumab with significant improvement in her calcium level and PTH was up to 54.7 from 21

Results:

Conclusions: In previous case reports Denosumab was associated with clinically significant disturbances of mineral metabolism both while on treatment and after discontinuation. In all reported cases hypercalcemia was due to increased bone resorption from osteoclast activity following loss of denosumab inhibitory effect. in our case there was no bone metastasis

Funding: Private Foundation Support

PUB561

Sevelamer Crystals in Injured Colonic Mucosa – Causative Agent or an Innocent Bystander?

Antonin Jaros,[3] Fazia Mir,[2] Susan Hudson,[1] Saeed K. Shaffi.[4] *[1]DCI, Albuquerque, NM; [2]Presbyterian Hospital, Albuquerque, NM; [3]UNM, Albuquerque, NM; [4]University of New Mexico, Albuquerque, NM.*

Background: Sevelamer carbonate is a polymeric amine that is used as a phosphorus binder in patients with advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD). We report a case of colitis in a patient with ESRD where sevelamer may have been responsible for colonic mucosal injury.

Methods: A 48 year old female with ESRD on hemodialysis presented to the hospital with abdominal pain, nausea and diarrhea. Laboratory evaluation revealed leukocytosis. A Computed Tomography(CT) scan of abdomen and pelvis was notable for right sided colonic wall thickening with associated luminal narrowing. Initial colonoscopy revealed severely edematous bluish mucosa of the cecum and ascending colon. Pathology report on obtained biopsy was consistent with ischemic colitis. Abdominal CT angiogram showed patent vasculature. She received supportive care and was discharged home with improvement in her symptoms. Two weeks after discharge, she presented to the hospital with epigastric and left sided abdominal pain, nausea and dark stools. Evaluation revealed hypotension, anemia and leukocytosis. Patient underwent colonoscopy with finding of ulcerated, friable mucosa from cecum to splenic flexure. Pathology report was notable for presence of granulation tissue, sevelamer crystals and associated foreign body inflammatory response. No features of acute ischemia were found. Sevelamer was discontinued with improvement in her symptoms. Repeat colonoscopy 18 months later revealed ulcerated long stricture in ascending colon preventing passage of 10mm colonoscope. Biopsy showed chronic colitis with mild activity.

Results:

Conclusions: Sevelamer induced colitis can be a cause of chronic diarrhea in selected cases resulting in stricturing disease over time. This has been reported previously in the literature. Further studies are needed to establish whether sevelamer is responsible for mucosal injury or whether sevelamer can exacerbate injury in an already damaged colonic mucosa. This infrequent adverse effect should be kept in mind in any patient treated with sevelamer having otherwise unexplained colitis.

PUB562

Hypercalcemia in a Patient with Cholangiocarcinoma (CC): Diagnosis and Management (CC)

Pablo Garcia,[1] Kartik Kalra,[1] Nabil Ghani,[1] Simranjit S. Randhawa,[2] Ayan De.[1] *[1]Saint Peter's University Hospital, New Brunswick, NJ; [2]Sir Ganga Ram Hospital, New Delhi, India.*

Background: Hypercalcemia is a common problem. It can occur when there is an increase in bone resorption, excessive GI absorption, or decreased renal excretion of calcium. Primary hyperparathyroidism comprises the majority of hypercalcemic patients among the ambulatory population, but malignancy accounts for up to 65% of such patients in the hospital. Humoral hypercalcemia of malignancy (HHM) has been rarely documented in patients with CC. Here we present an unusual case of hypercalcemia secondary to cholangiocarcinoma.

Methods: 62 year-old female, was admitted with weakness, constipation, 20 pound weight loss, and decrease oral intake for about two months. PMH of HTN, DM, HLD and restless leg syndrome. Medications as outpatient were diltiazem, colace, losartan, tramadol and alogliptin. In the ER the initial blood work showed serum Ca of 15.4 mg/dl, creatinine of 2 mg/dl and magnesium of 1.4 mg/dl. She was admitted for further investigation. On further investigation PTH was 22 pg/ml and ionized calcium was 14 mg/dl. CT scan of the abdomen showed multiple metastatic lesions in the liver. Liver biopsy was done on day 3 of hospitalization, it showed morphologic and immunohistochemical features of cholangiocarcinoma. PTHrP levels were elevated which is consistent with HHM secondary to cholangiocarcinoma. Multiple myeloma and metastatic disease workup was negative. Patient was treated with intravenous hydration, calcitonin and zolendronic acid. On day 3 of hospitalization calcium was 10. 7 and patient was discharge with a calcium level of 8.4. Patient symptoms resolved, and it was discharge on calcitonin and we have been following as outpatient with calcium levels 8.2 – 9 mg/dl.

Results:

Conclusions: Increased calcium levels, decreased PTH levels and absence of metastatic bone disease in the setting of CC suggest the diagnosis of HHM. Management of hypercalcemia due to HHM should be started as soon as possible to improve the symptoms.

PUB563

Report of Recombinant Parathyroid Hormone Therapy (Forteo) in a 18 Year Old Patient with Fanconi Syndrome and Osteomalacia

Ivie O. Okundaye, Aparna Natarajan, Julia Schneider. *Loyola University Medical Center, Maywood, IL.*

Background: An 18-year old woman with Fanconi Syndrome due to an unknown genetic mutation initially presented with proximal renal tubular acidosis, hypokalemia and hypophoshatemia resulting in osteomalacia and pathologic fractures. Patient presented to the ER with sudden onset right leg pain and inability to bear weight. Imaging showed diffuse osteopenia, left transverse femoral shaft fracture, multiple prior stress fractures and a right ulnar fracture. Labs notable for K 3.0, Phos 1.7, HCO3 16, Ca 7.7, Ionized Ca 1.15 PTH 129, and normal serum creatinine. There was no evidence of nephrolithiasis. 24 hour urine did not show hypercalciuria. Alkaline Phosphatase 1004, Vitamin D 25-OH 16. Vitamin D- 1,25 within normal limits. Dexa Scan revealed Z score -5.5 consistent with osteomalacia for her age.

Methods: Vitamin D was repleted but due to severe chronic bone pain and poor fracture healing, use of recombinant parathyroid hormone analogue, Forteo was initiated. Interestingly, alkaline phosphatase, bone alkaline phosphatase, levels improved after Forteo therapy, and patient has not had additional fractures after therapy. She also reports marked pain improvement. Patient remains on calcium 600 mg, calcitriol 1ug BID, and ergocalciferol 50,000 IU every other week, kphos packets TID.

Results:

Conclusions: Forteo is known to expedite bone healing however its use in young patients with Fanconi syndrome and hypophosphatemic rickets has not been studied. This drug is typically used for treatment of osteoporosis in elderly patients or those taking corticosteroid medications. Some studies show acceleration of bone healing from fractures in patients with osteoporosis. Here we present a case of hypophosphatemic rickets resulting in debilitating bone fractures successfully treated with Forteo. Forteo in combination with calcium and phosphorous replacement therapy demonstrates a novel approach in treatment of Fanconi syndrome associated hypophosphatemic rickets with pathologic fractures.

PUB564

A Case of Sagliker Syndrome

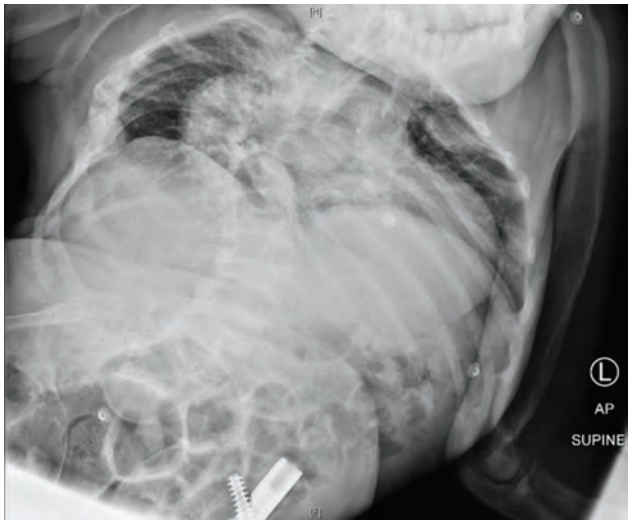
Julia Brown,[2] Rebecca Frazier.[1] *[1]Northwestern, Chicago, IL; [2]Nephrology, McGaw Medical Center of Northwestern University, Chicago, IL.*

Background: Sagliker Syndrome is a recently described entity in which patients with chronic renal failure and uncontrolled hyperparathyroidism develop severe bone deformities including teeth, maxillary and mandibular bone, skull, finger, and height changes. These abnormalities are more severe than expected with high parathyroid hormone levels. It is often associated with lack of medical care. This syndrome likely has an underlying genetic basis although the genes are not yet identified.

Methods: A 36-year-old male on dialysis for 11 years presented with progressive skeletal abnormalities and bone pain. He had normal stature and musculoskeletal development until he developed renal failure in his early 20s. Over the next few years, he developed many deformities including bilateral leg fractures, bowing of the legs and arms, curvature of the spine, mandibular hypertrophy, and angulation of the distal phalanges. These changes caused progressive immobility; on presentation he was bedridden. He was found to have a parathyroid hormone level of 2410 pg/mL, phosphorus 6.8 mg/dL, calcium 9.4 mg/dL, and alkaline phosphatase 727 U/L. X-rays revealed diffuse demineralization, cystic changes, and cortical sclerosis consistent with severe osteitis fibrosa cystica. Parathyroid ultrasound demonstrated enlarged parathyroids, and sestamibi scan revealed parathyroid hyperplasia. His case is consistent with Sagliker Syndrome. The patient was treated with subtotal parathyroidectomy with forearm autotransplatation of 3 mm^3 of parathyroid gland. Bone pain resolved post-operatively, however, he developed hungry bone syndrome requiring a total of 67g of intravenous calcium and 24g of oral calcium in the first 72 hours post-operatively. His PTH level after parathyroidectomy was 8 pg/mL.

Results:

Conclusions: Early recognition of skeletal changes and strict control of hyperparathyroidism is crucial in preventing devastating bony deformities in those predisposed to Sagliker Syndrome.



PUB565

Serum Calcitriol Concentrations and Kidney Function Decline, Heart Failure, and Mortality in Community-Living Persons: The Health, Aging, and Body Composition Study Umut Selamet,[1] Ronit Katz,[2] Dena E. Rifkin,[1] Linda F. Fried,[3] Stephen Kritchevsky,[4] Andrew N. Hoofnagle,[2] David A. Drew,[5] Tamara Harris,[6] Anne B. Newman,[3] Orlando M. Gutierrez,[7] Mark J. Sarnak,[5] Michael Shlipak,[8] Joachim H. Ix.[1] *[1]UCSD, San Diego, CA; [2]Univ of Washington, Seattle, WA; [3]Univ of Pittsburgh, Pittsburgh, PA; [4]Wake Forest Sch of Med, Winston-Salem, NC; [5]Tufts Med Center, Boston, MA; [6]NIA, Bethesda, MD; [7]UAB Sch of Med, Birmingham, AL; [8]UCSF, San Francisco, CA.*

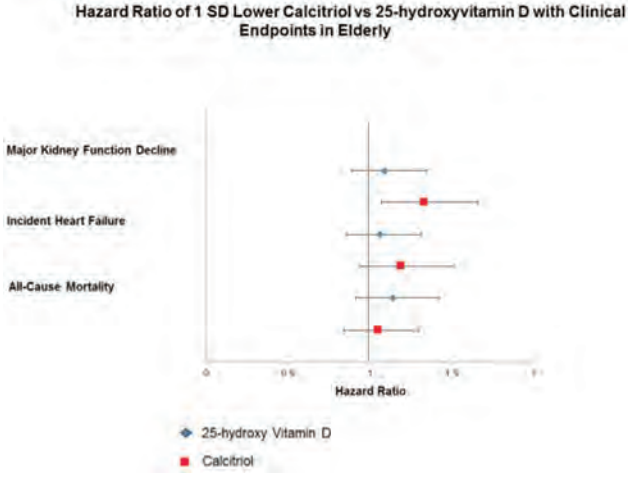
Background: Lower 25-hydroxyvitamin D concentrations have been associated with kidney function decline, heart failure (HF), and mortality, but calcitriol has been less studied as a risk factor in community-living individuals. We evaluated the associations of plasma calcitriol concentrations with kidney function decline, HF, and mortality in the Health ABC Study of participants aged 70 to 79 years.

Methods: We used a case-cohort design and we measured baseline calcitriol in a random sub-cohort of 479 participants, and also among incident cases with kidney function decline (≥ 30% decline in eGFR from baseline [n=397]) and HF (n=207). In addition, 136 of the 479 participants in the sub-cohort died during 8.6 years mean follow-up.

Results: After adjusting for demographics, kidney function, traditional cardiovascular risk factors, calcium, phosphate, intact parathyroid hormone (iPTH) and fibroblast growth factor (FGF)-23 concentrations, each standard deviation (SD) lower calcitriol concentration was associated with 33% higher risk of kidney function decline (95% CI 1.07, 1.66; p=0.012) during 10 years follow-up. Calcitriol was not significantly associated with incident HF (HR 1.19 [0.94, 1.51]) or mortality (HR 1.05 [0.84, 1.30]) in adjusted analyses. We observed no significant interactions by chronic kidney disease status, or baseline iPTH and FGF-23 levels. We also evaluated associations of 25-hydroxyvitamin D with the same clinical end-points and in fully adjusted models, we did not observe statistically significant associations of 25-hydroxyvitamin D levels with any of the outcomes.

Conclusions: Lower concentrations of calcitriol were independently associated with kidney function decline but not with incident HF or mortality among community-living older adults.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIA



PUB566

The Impact of Smoking on the CKD-MBD Biomarkers Geuza D. Dos santos,[2] Rosilene M. Elias,[3] Emilia M. Soeiro,[2] Camila Dosse,[3] Luciene dos Reis,[3] Wagner Dominguez,[3] Fabiana Graciolli,[3] Giovanio V. da Silva,[3] Ivone B. Oliveira,[3] Vanda Jorgetti,[3] Maria Dalboni,[1,2] Rosa M. Moyses.[2,3] *[1]Universidade Federal de São Paulo, São Paulo, Brazil; [2]Universidade Nove de Julho, São Paulo, Brazil; [3]Nephrology, Universidade de São Paulo, São Paulo, Brazil.*

Background: Chronic kidney disease and smoking are considered a public health problem and are associated with an increased risk of cardiovascular disease. CKD-BMD also presents a high cardiovascular risk for CKD patients. However, the potential association of smoking and CKD-MBD is unknown. A previous study has shown that smoking habits among CKD patients is associated with higher serum c-terminal FGF-23, although the mechanism has not been elucidated. In this study, we aimed to confirm whether intact FGF-23 would be elevated in CKD patients who smoke. We hypothesized that an elevation of FGF-23 would be related to a decrease in serum Klotho or an increase in hypoxia inducible factor 1α (HIF1α). The latter is usually increased among smokers and has been recently described as a regulator of FGF-23 production, in experimental models.

Methods: We have evaluated 92 patients divided into three groups: Control without CKD, CKD stages III and IV on conservative treatment, and dialytic group, with smokers and non-smokers. We collected data from August 2016 to January 2017. Measurements of HIF-1α, Intact FGF-23 and Klotho were performed using commercial ELISA assays, according to manufacturers' protocols.

Results: Smokers performed less time of physical activity than the other groups. Serum phosphate was lower among patients on conservative treatment with smoking habits (3.10 ± 0.5 vs. 3.6 ± 06 mg/dl; $p < 0.05$). Serum uric acid was also lower in smokers, regardless the CKD stage (6.1± 1.5 vs. 6.8 ± 1.6 mg/dl; $p < 0.05$). No differences were found for calcium, 25-vitamin D, parathormone or alkaline phosphatase. FGF-23 was higher in dialysis patients than in conservative patients, but no differences were found between smokers and non-smokers. There were not any significant differences in Klotho and HIF1α levels among these groups.

Conclusions: We found no argument to support our preliminary hypotheis, as there were no significant differences in FGF-23, Klotho and HIF1α levels when comparing patients with and without smoking habits. As an aditional finding however, the effect of cigarette smoking on plasma uric acid and phosphate levels deserves further investigation.

Funding: Government Support - Non-U.S.

PUB567

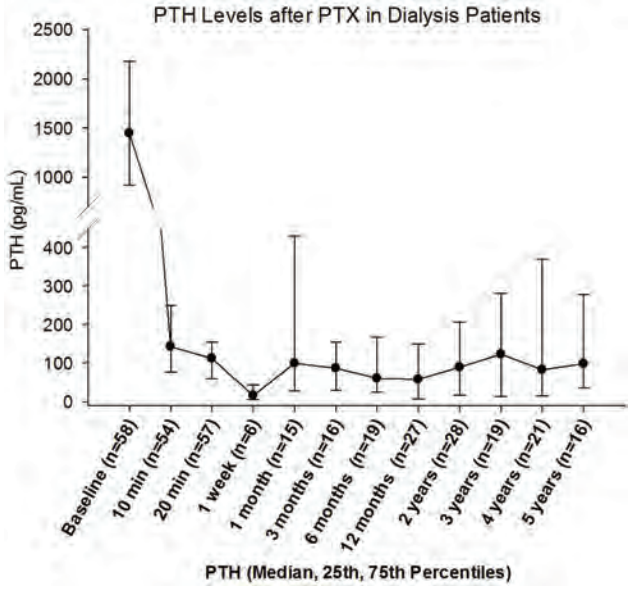
The Value of Intra-Operative PTH Assay during Parathyroidectomy in Dialysis Patients with Refractory Hyperparathyroidism Adeleye A. Edon, Kevin Wang, David Saxon, Florence Lima, David Sloan, B. Peter E. Sawaya, Amr E. Mohamed. *University of Kentucky, LEXINGTON, KY.*

Background: In dialysis patients with secondary and tertiary hyperparathyroidism (HPT), the correlation of intra-operative parathyroid hormone (ioPTH) measurement during parathyroidectomy (PTX) with long-term PTH level is unknown. The present study aims at evaluating the value of ioPTH measurements on long-term outcome of PTX in dialysis patients in a single center study.

Methods: The ioPTH was measured in 57 hemodialysis patients (33 females and 24 males) who underwent PTX between 2005 and 2015 because of refractory HPT. Near-total PTX was performed in 43 patients, total PTX in 15 patients (one patient underwent second PTX within 3 months because of failure of the first PTX). The ioPTH monitoring included 3 samples: pre-intubation (pre-ioPTH), 10- and 20-minute post PTX (10- ioPTH and 20-ioPTH). The patients were followed for up to 5 years (mean ± SD: 2.2 ± 2.1 years.

Results: The median (25th-75th percentile) pre-, 10- and 20-ioPTH levels were: 1447 pg/ml (969-2168), 143 pg/ml (78-244) and 112 pg/ml (59-153), respectively. There was no significant difference between 20-ioPTH and any subsequent PTH measurements (P=0.8, Figure). Sixteen patients (28%) were readmitted within 90 days due to significant hypocalcemia. One patient was readmitted for post-PTX hematoma evacuation. No patient required repeat PTX because of recurrent HPT.

Conclusions: The 20-ioPTH is a good indicator of long-term PTH values. Hypocalcemia is a common complication and the main reason for readmission after PTX. No patient required second PTX due to recurrent HPT.



PUB568

A Three-Year Experience with 201 Cases of Denosumab: Risk Factors and Precautions of Severe Hypocalcemia, Particularly in CKD Patients Rio Noto,[1] Hideki Yokoi,[2] Akihiro Yoshimoto,[1] Motoko Yanagita.[2] *[1]Kobe City Medical Center General Hospital, Kobe, Japan; [2]Kyoto University Graduate School of Medicine, Kyoto City, Japan.*

Background: Denosumab, a human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL), has good evidence for preventing osteoporotic fragility fractures, so that the demand increases. On the other hand, cases of denosumab-associated hypocalcemia are reported more frequently.

Methods: We searched patients receiving denosumab from August 2013 to December 2016 in our hospital, and verified the frequency and risk factors of hypocalcemia.

Results: A total of 201 patients, including 84% female and 16% male, were treated by denosumab. The mean (±SD) age was 73.0 (±12.6) years, 28% of patients took steroid and 37% suffered from systemic autoimmune diseases. The baseline estimated GFR (eGFR, mL/min/1.73 m2) was as follows; ≧60 (67%), ≧45 to <60 (18%), ≧30 to <45 (8%) and <30 (7%). Adjusted calcium level decreased in 48%, increased or unchanged in 36%, and could not be compared in 16%. In 43 cases who underwent the second blood test within 2 weeks after injection of denosumab, lower baseline eGFR and steroid use were significantly associated with the decline of adjusted calcium levels (eGFR; p=0.0082, steroids; p=0.0157). Among them, 4 patients had side effects. eGFR of these patients was under 30 in 3 of 4 cases, one of which underwent intensive care, including artificial ventilator and intermittent hemodialysis, because of coma and acute respiratory failure induced by severe hypocalcemia. In every 4 cases, there was room for improvement for prescription. For example, a CKD patient was prescribed with natural vitamin D and calcium compounds as preventive medicine for hypocalcemia.

Conclusions: Renal dysfunction and steroid therapy were risk factors of denosumab-associated hypocalcemia. If denosumab is administered to patients with severe CKD, close monitoring and adequate supplementation of active vitamin D and calcium compounds is required to avoid the development of hypocalcemia.

PUB569

Is the Efficacy of Nutritional Vitamin D (Cholecalciferol) Comparable to Active Vitamin D (Calcitriol) as Maintenance Therapy in Dialysis Dependent CKD Patients? (CHOLCAL) Chau Wang Ng,[1,2] Mathew C. Mathew,[1] Rajesh Raj.[1] *[1]Nephrology, Peninsula Health, Frankston, VIC, Australia; [2]Medicine, Launceston General Hospital, Launceston, TAS, Australia.*

Background: Dialysis dependent chronic kidney disease patients have reduced renal 1-α-hydroxylase and consequently insufficient active vitamin D activity, which is often manifested as hypocalcaemia. Calcitriol is traditionally used as not needing further renal conversion. However, it can cause increased phosphate absorption from gut. There is evidence of persistent extra-renal 1-α-hydroxylase activity in these patients. Hence, cholecalciferol has been proposed as potential alternative therapy. This study investigated cholecalciferol's efficacy in maintaining serum calcium in adult dialysis dependent chronic kidney disease patients.

Methods: This twelve-week pilot prospective interventional cohort study was conducted across three dialysis units in Northern Tasmania, Australia. Adult dialysis patients on pre-existing calcitriol with normal serum calcium were enrolled. Their calcitriol was then changed to cholecalciferol. Bloods including calcium, phosphate, parathyroid hormone, alkaline phosphatase, 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D_3 were sampled at baseline, 4-week, 8-week and 12-week post therapy change. Therapy success was defined as ability of cholecalciferol to maintain serum calcium, and the successful proportion was calculated.

Results: From February till April 2016, 112 patients were screened and total 13 patients were enrolled. 12 of 13 participants succeeded cholecalciferol therapy at end of study. When compared to baseline, there was no significant difference to serum calcium, phosphate and parathyroid hormone at end of study. There was statistically significant rise in serum alkaline phosphatase (mean increase 19.1 U/L, P=0.004) and 25-hydroxyvitamin D_3 (mean increase 24.7 nmol/L, P<0.001) at week 12. Serum 1,25-dihydroxyvitamin D_3 showed significant initial drop at week 4 (mean reduction 28.1 pmol/L, P<0.001) and week 8 (mean reduction 20.2 pmol/L, P<0.001), but exhibited no significant difference by week 12.

Conclusions: Cholecalciferol can maintain serum calcium in a worthwhile proportion of adult dialysis dependent chronic kidney disease patients.

Funding: Private Foundation Support

PUB570

Ultrasound Guided Ablation Therapy for Treatment of Severe Secondary Hyperparathyroidism Elias J. Baied, Marc J. Alonzo, Stuart M. Sprague. *NorthShore University HealthSystem University of Chicago Pritzker School of Medicine, Chicago, IL.*

Background: The successful management of severe secondary hyperparathyroidism in patients with chronic kidney disease (CKD) is difficult to accomplish with medical therapy alone due to complications of drug treatment, medication intolerance and non-compliance. Thus, many patients still require surgical parathyroidectomy. Ultrasound guided percutaneous ethanol (US-EtOH) injection has been successfully used in a few centers, especially in Japan, however, widespread acceptance of this procedure has not yet occurred. The aim of this analysis is to review patients in our center who underwent US-EtOH therapy.

Methods: Charts of patients who underwent US-EtOH therapy between 2013 and 2017 were reviewed. Data analyzed included basic demographic information, pre-ablation parathyroid hormone (PTH), calcium (Ca), number of ablations, and 6-9 month follow up PTH and Ca concentrations.

Results: A total of 20 patients were identified, however, data was only available on 16 (5 males). Four of the patients were post-transplant, 1 undergoing hemodialysis and 11 with CKD. In 56%, PTH concentrations decreased by > 25 % at 8 ± 2 month. Mean Ca decreased from 10.4 ± 1.9 to 9.9 ± 0.07, p< 0.05.

Conclusions: US-EtOH therapy may be helpful in controlling secondary hyperparathyroidism in selected patients with CKD. Further experience and prospective studies are needed.

Funding: Clinical Revenue Support

PUB571

The Contralateral Kidney Is Protected against Fibrosis in Unilateral Ureter Obstructed (UUO) Rats Anders Nordholm,[1] Maria L. Mace,[1] Eva Gravesen,[2] Jacob Hofman-Bang,[2] Klaus Olgaard,[2] Ewa Lewin.[1] *[1]Department of Nephrology, Herlev Hospital, University of Copenhagen, Copenhagen, Denmark; [2]Department of Nephrology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark.*

Background: Emerging concepts propose that circulating factors released from an injured kidney, might cause vasculopathy, bone disease, and kidney fibrosis. We examined the expression of genes related to fibrosis and Wnt signaling in the contralateral, untouched kidney (CON) to unilateral obstructed kidney (OBS) in UUO rats with unilateral nephrectomized (UNX) and normal rats as controls.

Methods: UUO rats (n=48) were studied at 0, 2, 4, 6 hr, 1, 3, 4 and 10 days (D) in parallel with UNX control rats (n=30) and normal rats (n=6). Kidney expression *of Klotho, BMP7, TGF-β, Periostin, Sclerostin, DKK-1 and ActivinA* were examined as well as plasma (p) levels of Sclerostin and ActivinA.

Results: *ActivinA* mRNA was undetectable in normal kidney but highly induced in OBS (Baseline:0.09±0.01, D3:1.38±0.22, D10:2.94±0.55, p<0.01). However gene expressions in CON were similar to that of UNX and normal kidney. P-ActivinA doubled at day 10 in UUO rats compared to baseline and UNX (B:217±14, UNX 10D:254±18, UUO 10D:413±44, p<0.001) indicating that ActivinA is released from the injured kidney. P-sclerostin was similar in UNX and UUO rats (B:142±18, UNX 10D:284±42, UUO 10D:313±60, p<0.05). Kidney *sclerostin* mRNA was undetectable in all groups indicating non-renal source of sclerostin. *DKK-1* mRNA was similar in OBS and CON. In the OBS kidney there was a down-regulation of anti-fibrotic factors *Klotho* and *BMP7* already at day 1 (p<0.001) but not at 0-6 hr. Simultaneously in the OBS kidney a progressive up-regulation of pro-fibrotic *TGF-β* and induction of *Periostin* were evident from day 1 (p<0.01). All genes were similar in CON, UNX and normal kidneys at all time points.

Conclusions: A rapid decrease in anti-fibrotic factors and an increase in pro-fibrotic factors is observed in the OBS kidney of UUO rats. Induction of ActivinA in OBS kidney may contribute to its elevated plasma levels and could potentially represent a circulating factor that drives kidney fibrosis. However, gene expressions of pro - and anti-fibrotic factors in the CON kidney are maintained normal, indicating protection against circulating fibrotic factors.

PUB572

Increased Bioactive Sclerostin Levels in Kidney Transplant Recipients Detected with a New and Well-Characterized ELISA Jacqueline Wallwitz,[1] Gabriela Berg,[2] Elisabeth Gadermaier.[1] [1]*The Antibody Lab GmbH, Vienna, Austria;* [2]*Biomedica, Vienna, Austria.*

Background: Over the past years there is an increasing knowledge about the relationship between mineral and bone disorder (MBD) and cardiovascular diseases in patients with chronic kidney disease (CKD). One of the key regulators identified in CKD-MBD is sclerostin a 190-amino acid glycoprotein, which is mainly secreted by osteocytes. It was shown that circulating sclerostin levels are increased in CKD-MBD patients. Sclerostin is an inhibitor of the osteoanabolic Wnt signaling pathway achieved by binding with its second loop to the LRP5/6 complex. The measurement of this bioactive site of sclerostin may be helpful to further investigate its role within CKD-MBD disease progression and in the assessment of therapeutic effectiveness.

Methods: We have developed an immunoassay for the detection of the bioactive binding site of sclerostin in human serum and plasma samples. The antibodies were characterized and assay performance was validated according to ICH and EMEA guidelines. Plasma concentration of bioactive sclerostin was measured in apparently healthy controls and renal transplant recipients.

Results: The recombinant monoclonal coating antibody recognizes an epitope within the second loop of sclerostin, whereas the polyclonal detection antibody has five linear epitopes distributed throughout the molecule. Both antibodies have good binding kinetics of k_{dis} of <1.0E-07 s^{-1} for the monoclonal antibody and 1.19E-05 s^{-1} for the polyclonal antibody, respectively. The validation parameters were within the required quality standards. Bioactive sclerostin concentration was significantly increased from 87 +/- 41.7 pmol/l (apparently healthy) to 166.5 +/- 68.0 pmol/l in renal transplant recipients.

Conclusions: This ELISA provides a reliable and accurate tool for the quantification of the bioactive site of the sclerostin molecule in healthy and diseased human and may give a new perspective within CKD-MBD research.

PUB573

Abstract Withdrawn

PUB574

Two-Year Cortical and Trabecular Bone Loss in CKD-5D: Biochemical and Clinical Predictors Hartmut H. Malluche, Florence Lima, Marie-Claude M. Faugere, Conor Lowry, Daniel Davenport. *University of Kentucky, Lexington, KY.*

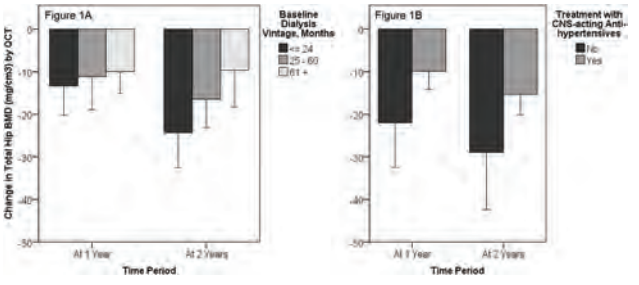
Background: This prospective two-year study of CKD-5D patients assessed cortical and trabecular bone loss at the hip and spine and examined potential demographic, clinical and serum biochemical predictors of bone loss.

Methods: Eighty-nine CKD-5D patients had baseline, year 1 and year 2 bone mineral density (BMD) measurements using dual X-ray absorptiometry (DXA) and quantitative computed tomography (QCT); concurrent blood samples were drawn and clinical variables recorded. No study treatments occurred.

Results: The two-year total hip BMD changes were -5.9% by QCT and -2.7% by DXA ($p < .001$). Spinal BMD was unchanged. QCT total hip cortical mass and volume decreased by -7.3% and -10.0%; trabecular volume increased by 5.9% (all $p < .001$). BMD changes did not vary with age, BMI, race, diabetes, smoking, or exercise. Patients with longer dialysis vintage and more negative baseline t-scores lost less BMD ($p < .05$, Figure 1A). Vitamin D analogs and phosphate binders were not protective against bone loss; cinacalcet was protective by univariate but not by multivariable analysis. CNS-affecting anti-hypertensives were protective against loss of BMD, cortical mass, cortical volume and trabecular mass (all $p < .05$, Figure 1B). These effects remained after adjustment for baseline t-score and dialysis vintage. BSAP correlated with changes in BMD, cortical mass and volume (all $p < .01$) as did sclerostin (inversely, all $p < .01$).

Conclusions: In CKD-5D patients, there is severe cortical bone loss at the hip best recognized by QCT. Patients with shorter dialysis vintage and less pre-existing bone loss lose more bone, calling for early diagnosis and treatment. BSAP and sclerostin are useful markers of bone loss. These are the first data showing a protective effect of CNS-acting anti-hypertensives against bone loss in these patients.

Funding: NIDDK Support, Other NIH Support - CTSA, Private Foundation Support



PUB575

Secondary Hyperparathyroidism Treated with a Novel Vitamin D Prohormone, Extended-Release Calcifediol, in a Renal Allograft Patient with CKD Jack E. Rubin. *Encino, CA.*

Background: Patients with advanced CKD have secondary hyperparathyroidism (SHPT), arising from vitamin D insufficiency and derangements of mineral and bone parameters such as caclicum, (CA), phosphorus (P). PTH elevation in these patients causes demineralization of bone and increases the risk of cardiovascular morvidity and mortality. While calcitriol and active vitamin D analogs are effective in lowering elevated PTH levels, they are associated with increased risk of hypecalcemia and hyperphosphatemia and increased FGF-23 levels. Addtionally, the problem of correcting vitamin D insufficiency remains unaddressed with these therapies. Rayaldee (extended-relase calcifediol, 25-OH-D3), a prohormone of the active form of Vitamin D3, has recently been approved by the FDA for the treatment of SHPT and vitamin D insufficiency in CKD stages 3 or 4, the only vitamin D producted indicated to treat elevated PTH and insufficient Vitamin D levels, correcting both disorders.

Methods: Here, I present a 57 year old African-American male who had a renal allograft placed 8 years ago and now has stage 4 CKD due to chronic allograft nephropathy. He also has type 2 diabetes mellitus, hypertension, hyperlipidemia, pulomonary artery hypertension, anemia of CKD and hypertension.

Results: His PTH reached its apex of 266 pg/ml on 11/7/16 and his Vitamin D level was at its nadir then at 20.1 ng/dl. He was then taken off calcitriol 0.25 mg and placed on Rayaldee, calcifediol ER (CER) 30 mcg hs. After 4 months of treatment on CER, on 4/27/17, his PTH fell to 97.2 ng/dl, a 36% reduction. His Vitamin D level rose to 36.7, a 83% increase. During this time period his serum creatinine increased from 3.3 mg/dl to 3.6 mg/dl, a 9% increase.

Conclusions: There are no case reports of CER being used to treat SHPT in renal allograft recpients with CKD in the literature. This patient had a reduction of his elevated PTH level of 36% with no untoward clinical events. As his PTH was significantly reduced, an expected amelioration of his bone-induced SHPT bone disease would occur. This case report shows that CER is a safe and more effective option to treat SHPT in renal allograft patients with CKD. However, a large randomized controlled study utilizing calcifediol ER for the treatment of SHPT in patients with renal allografts is needed.

PUB576

Effect of Cinacalcet Combined with Low Dose Calcitriol on Clinical Outcome and Bone Metabolism in Patients on Hemodialysis with Severe Secondary Hyperparathyroidism Fang Yuan,[1] Hong Liu,[3] Xing Chen,[1] Fu-You Liu.[2] *[1]Department of Nephrology, The Second Xiangya Hospital, Central South University, Changsha, China; [2]The Second Xiangya Hospital, Changsha, China; [3]Departments of nephrology, Second Xiangya Hospital Central South University, Changsha, China.*

Background: Secondary hyperparathyroidism(SHPT) is a common complication observed in maintenance hemodialysis (MHD) patients, characterized by multi system damage, calcium-phosphorus metabolism disorders and bone disease. Several clinical studies have confirmed that SHPT is closely related to the high risk of cardiovascular disease and mortality. Our study is To observe the clinical outcome and the effect of bone metabolism of cinacalcet hydrochloride combined with low dose calcitriol in MHD patients with severe SHPT.

Methods: Thirty MHD patients were enrolled to receive treatment of cinacalcet combined with low dose calcitriol, with inclusion criteria as follows: maintenance on HD>6 months;serum intact parathyroid hormone(iPTH)>600 pg/ml; parathyroid glands had more than 1 nodules by ultrasonography; traditional therapy is not effective. All patients were given cinacalcet 25-75 mg and 0.5 μg calcitrol dialy. Serum Ca, P, iPTH, bone metabolic markers and bone density were measured before and after treatment. The clinical symptoms and their improvement were investigated.

Results: The baseline levels of iPTH,Ca,and P were 1787.3±1321pg/mL, 2.54±0.19 mmol/L, and 2.06±0.15 mmol/L, respectively. After 2 weeks of treatment, serum phosphorus decreased by 20%; after one and three month, iPTH decreased by 35% and 70% compared with before treatment. Ca and P fell to 2.39±0.17mmol/L and 1.56 ±0.50mmol/L(P<0.05) after one month, respectively. The symptoms of the patients relieved. The above indicators remained stable after one year. Moreover, the bone metabolism index showed alkaline phosphatase, osteocalcin and β-Cross levels were decreased by 50%, 37% and 49% respectively than that before treatment after 6 months. Patients' bone density decline was inhibited. No severe adverse events were observed.

Conclusions: Cinacalcet hydrochloride combined with low dose calcitriol can improve high calcium, high phosphorus and high iPTH in MHD patients with severe SHPT, relieve symptoms, improve bone metabolism. It can be used as a favorable choice for the treatment of SHPT.

PUB577

Predictive Factors for PTH Control in Hemodialysis Patients with Secondary Hyperparathyroidism Treated with Cinacalcet in Real-World Clinical Practice: MIMOSA Study Pablo A. Urena,[3] Jacques B. Rottembourg,[5] Catherine Michel,[1] Abdelaziz Hamani,[4] HEBIBI Hedia,[2] Thomas Guincestre.[6] *[1]AURA, Paris, France; [2]nephrologist, THIAIS, France; [3]Dialysis, Clinique du Landy, Saint Ouen, France; [4]Hôpital privé Athis Mons, Athis Mons, France; [5]Paris, France; [6]Hopital Victor Provo, Roubaix, France. Group/Team: Study Group MIMOSA.*

Background: Secondary hyperparathyroidism (SHPT) is frequent in hemodialysis (HD) patients. Oral cinacalcet provides a way to decrease and control PTH but we lack real-life data based on KDIGO guidelines. Our goal is to assess the percentage of cinacalcet-treated HD patients for 12 months (M12) with controlled SHPT (PTH < 9xULN).

Methods: We performed a retrospective observational study in HD patients with SHPT treated by cinacalcet between 2005 and 2015 and dialyzed in 7 French HD centers using the HEMODIAL database.

Results: The study includes 1,268 patients with a mean follow-up of 21±12 months. Their mean dialysis vintage was 4.3±5.6 years. Phosphate binders were used in 335 (52%), active vitamin D in 289 (45%) patients throughout the study. Among the 645 patients with PTH values available at M12, 58.9% had controlled SHPT and 41.1% uncontrolled.

Conclusions: In this real-life study, 41% of HD patients with SHPT treated with cinacalcet retained a PTH above the KDIGO recommended target after 12 months of treatment. Apart from the possibility of non-compliance, the severity of SHPT appears to be a major factor, reinforcing the importance to treat SHPT at earlier stages.

Funding: Commercial Support - Amgen

	Controlled N=380		Uncontrolled N=265		p-value *	
Age (year)	65.5±14.7		60.6±16.5		0.0001	
Male (%)	60.8		59.6		NS	
Diabetes (%)	26.3		24.2		-	
	M0	M12	M0	M12	p-value M0*	p-value M12*
PTH (pg/mL)	831±346	304±158	1057±480	1084±543	<0.001	<0.001
Calcemia (mmol/L)	2.18±0.20	2.19±0.23	2.22±0.19	2.19±0.20	0.0213	0.9430
Phosphatemia (mmol/L)	1.63±0.56	1.40±0.56	1.73±0.57	1.55±0.63	0.0351	0.0013
25OHD (ng/mL)	33±21	34±18	30±18	29±16	0.4435	0.0034
Alkaline Phosphatase (UI/L)	145±106	122±94	187±234	205±218	0.0714	<0.001
Active vitamin D (%)	7.1%	31.1%	6.8%	29.1%	0.8781	0.5871
Cinacalcet dosage (mg/day)	34±13	50±26	34±12	59±32	<0.001	0.45

*Data are expressed as mean±SD or %. *Student t test, Wilcoxon or Chi2 test between controlled and uncontrolled patients*

In multivariate analysis, older age, baseline lower calcemia and PTH were predictive factors for uncontrolled SHPT.

PUB578

Possible Role of Hydroclorotiazide Suppressing PTH on Peritoneal Dialysis Antonio A. Portela Neto,[2] Lilian Cordeiro,[2] Erica A. Guimarães,[3] Benedito J. Pereira,[2] Hugo Abensur,[2] Rosa M. Moyses,[1,2] Rosilene M. Elias.[2] *[1]Universidade Nove de Julho, São Paulo, Brazil; [2]Universidade de Sao Paulo, Sao Paulo, Brazil; [3]Universidade de São Paulo, São Paulo, Brazil.*

Background: In peritoneal dialysis (PD), there is a safety concern regarding influx of calcium (Ca), which becomes challenging while treating patients starting therapy with low parathyroid hormone (PTH). The use of low dialysate calcium concentration [Ca]d and the avoidance of Ca-based binders are recommended. Despite this, PD patients are more prone to have adynamic bone disease. We have assessed the behaviour of CKD-MBD markers in patients on PD, focusing on incident patients with PTH <150pg/ml.

Methods: Patients starting PD between January 2009 and December 2016 in an academic center, with demographic, clinical and laboratorial data available on alkaline phosphatase(AP), PTH, Ca, 25vitamin D and phosphate(P) were included.

Results: Sixty-nine patients (47±18 years, 46.4% male, 80% hypertensive, 23% diabetic) were included. Mean ionized and total Ca, and phosphate were 4.8±0.4mg/dl, 8.8±0.8mg/dl, and 4.7±1.2mg/dl, respectively. AP was 81 (67,119)UI/l and PTH was 226(98, 461)pg/ml. 25vitamin D was 19.9±9.6ng/ml (59.4% had levels <15ng/ml).[RC1] Patients who started PD with PTH<150pg/ml (N=28, 40.6%) presented higher iCa (p=0.036), higher glicemia (0.027), lower P (p=0.0001), lower AP (p=0.004), and a similar percentage of vitamin D deficiency (0.373) and diabetes (p=0.322), as compared to those with PTH>150pg/ml. None of the patients with low PTH were taking calcium-based binder and 3 have received low d[Ca]; after a median of 26 months of follow-up, 11 patients (39.3%) remained with PTH <150pg/ml. This subset of patients differed from those whose PTH increased because a higher percentage of patients were taking hydrochlotiazide (p=0.040) and because of a tendency toward avoiding low d[Ca] (p=0.06). Another additional 18 patients reduced PTH to as low as <150pg/ml, because hyperparathyroidism treatment. Neither clinical nor demographic characteristics, including the use of hydrochlotiazide differed patients whose PTH decreased overtime.

Conclusions: Besides traditional factors such as Ca-based phosphate binders, calcitriol and high d[Ca], hydroclorotiazide seems to supress PTH in patients on PD. Although this finding is already described in CKD on conservative management, further studies are warranted to confirm the mechanism in PD.

PUB579

The Usefulness of Fracture Risk Assessment through FRAX without BMD in Hemodialysis Patients Heeryong Lee, Woochul Lee. *Good Samsun Hospital, Busan, Busan, Republic of Korea.*

Background: According to the Improving Global Outcomes (KDIGO) CKD-MBD (chronic kidney disease-mineral and bone disorder) guideline update 2017, there is a recommendation that the risk of fractures in CKD 3a-5 stage patients can be evaluated by BMD (bone mineral density). The Fracture Risk Assessment Tool (FRAX) is a computerized algorithm that determines fracture probability by integrating important individual risk factors for fracture and mortality, with or without the addition of femoral neck BMD. We would like to evaluate whether FRAX without BMD can replace BMD in fracture risk assessment.

Methods: Total 56 dialysis patients aged 40 years or older were included in the study. The mean age was 61.06 ± 11.39 years and the duration of hemodialysis was 57.11 ± 57.33 months. We calculated the 10-year probabilities of fracture (%) using the Korean FRAX models with or without femoral neck BMD. We then performed comparative analyses 10-year probabilities of major/hip osteoporotic fractures depending on BMD values.

Results: The mean 10-year probabilities of major osteoporotic fractures and hip fractures using the FRAX model without BMD were 4.63 ± 3.08 % and 1.37 ± 1.48 %. When the BMD value was assigned to the FRAX, the 10-year probabilities of fracture were 5.31 ± 4.57 % and 1.90 ± 2.64 %. A statistically significant difference in major osteoporotic fractures was not observed for FRAX in individuals with femoral neck BMD versus without femoral neck BMD. Also there was no statistical significance in hip fracture (95% confidence intervals; p=0.22 and p=0.23).

Conclusions: This study showed that Even if BMD is not measured in hemodialysis patients, the risk of 10-year bone fracture can be predicted only through FRAX.

Baseline characteristics of the 56 subjects

Characteristic	N=56
Age(years)	61.06 ± 11.39
Height(cm)	161.88 ± 9.02
Weight(kg)	56.9 ± 10.21
Male sex, n(%)	28(50%)
Previous fracture	10(17.9%)
Parent fractured hip	1(1.8%)
Current smoking	8(14.3%)
Glucocorticoids	6(10.7%)
Rheumatoid arthritis	0(0%)
Secondary osteoporosis	2(3.6%)
Alcohol 3 or more units/day	0(0%)
Femoral neck BMD(g/cm2)	-1.13 ± 1.38

PUB580

Mineral and Bone Disease Management in the Hemodialysis Unit: Improvement Care Model Fadwa S. Al-Ali,[2] Tarek A. Fouda,[2] Mohamed amin Khalil elesnawi,[2] Saifatullah Khan,[1] Tarek A. Ghonimi,[1] Abdullah Hamad,[1] Khulood Kasem,[1] Khulood Awadh,[3] Fadumo Y. Yasin,[4] Aisha Abdulla,[5] Rania A. Ibrahim,[1] Mohamed Y. Mohamed.[1] *[1]Hamad Medical Corporation, Doha, Qatar; [2]Hamad medical cooporation, Doha, Qatar; [3]Hamad Medical corporation, Doha, Qatar; [4]Hamad medical coorporation, Doha, Qatar; [5]HMC, Doha, Qatar*.

Background: Chronic kidney disease affects mineral and bone metabolism in Hemodialysis(HD) patients, so patients are often vulnerable to deterioration of mineral and bone disorder (MBD) long term complications that influencing morbidity and mortality. We developed a proactive interventional protocol to improve MBD management to achieve better PTH level control in HD population as per KDOQI/ KDIGO recommendation

Methods: We developed a new care model for MBD management (Nurse based model under nephrologist supervision)HD patients were selected randomly and gradually from Fahad Bin Jassim Kidney Center over 12 month of period. MBD blood laboratory parameter monitored (PTH, Ca, Po4 level as per protocol. Assigned dialysis nurse played important active role in the care coordination, planning, communication and education

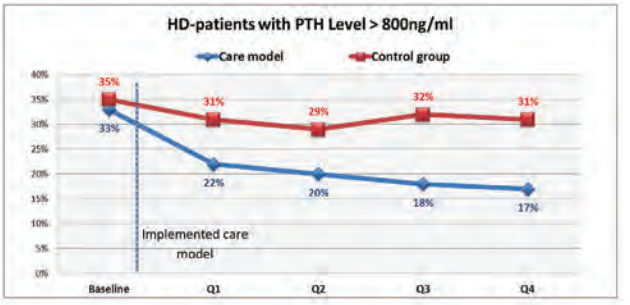
Results: In March 2016 we started with 23 pts. And gradually increased number to 152 in March 2017. Percentage of pts. With target PTH level (150-300 ng/ml) increased by 23%. And the extreme PTH level (>800 ng/ml) decreased by 16%. The new care model also controlled the other parameters (Ca, Po4, and CPP). Minimize the utilization of special calcium dialysate bath

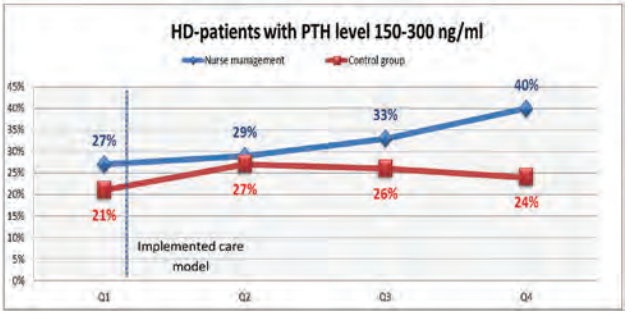
Conclusions: The new MBD care model was developed and implemented successfully. We achieved, and maintained patients within target PTH level (150-300 ng/ml)

Funding: Government Support - Non-U.S.

MBD care model

Criteria	care model (152 pts.)	control group (152 pts.)
Pts. in target PTH level (150-300 ng/ml)	40%	24%
Pts. in target carcium level (2.1-2.37 mmol/l)	68%	52%
Pts. in target phosphorus level (1.13-1.8 mmol/l)	59%	52%
Pts.in target CPP level (<4.4)	84%	76%
Special calcium bath	9%	20%
Median PTH	312	528





PUB581

Iliac Crest Biopsy Performed by Interventional Radiologists: A New Way to Improve Access to Bone Biopsy in Patients with CKD Lori Asselin-Thompstone, Fabrice Mac-Way. *Qu?bec, QC, Canada*.

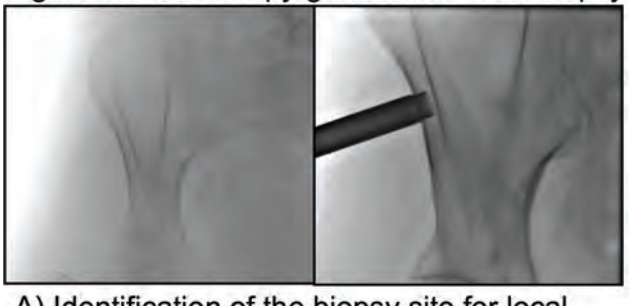
Background: Mineral and bone disorder (MBD) is a major health issue among patients with chronic kidney disease (CKD). It is associated with an increased risk of fracture, cardiovascular disease and mortality. The 2009 Kidney Disease Improving Global Outcomes guidelines recommend performing iliac crest biopsies to aid in the diagnosis and management of CKD-MBD. Unfortunately, the procedure is rarely performed because many clinicians lack the technical ability required to carry out the intervention. In order to increase access to this procedure, we suggest that it be performed by interventional radiologists rather than nephrologists.

Methods: A nephrologist familiar with the procedure first trained two interventional radiologists at CHU de Québec - Hôtel-Dieu de Québec Hospital in November 2016. The Rochester bone biopsy kit was used and the samples were sent for bone histomorphometric analysis. In contrast to the traditional blind technique, radiologists used a new fluoroscopy-guided approach. This novel procedure provided direct visualization of the outer and inner cortical bone during the intervention (Figure 1). This standardized technique allowed for easier identification of the preferred bone biopsy site.

Results: All of the iliac crest biopsies currently being performed at Hôtel-Dieu de Québec Hospital are being carried out by interventional radiologists. So far, more than 10 fluoroscopy-guided biopsies have been obtained and no complications have been observed. There were no cases of pain, hematoma, infection or neuropathy following the intervention. Furthermore, all of the bone specimens were adequate and sufficient for analysis.

Conclusions: Iliac crest biopsies performed by interventional radiologists will increase nephrologists' access to bone specimens in patients with CKD-MBD. Moreover, the addition of a standardized, image-guided technique will lower the risk of possible complications.

Figure 1. Fluoroscopy-guided iliac crest biopsy



A) Identification of the biopsy site for local anesthesia; B) Trans-iliac Rochester trocar insertion

PUB582

Renal Osteodistrophy: A Weird Case of Leontiasis Ossea Emiliana Ferramosca,[2] Annarita Valletta,[1] Vilma Martella,[1] Marcello Napoli.[1] *[1]ASL Lecce - V. Fazzi Hospital, Lecce, Italy; [2]Nephrology Dialysis and Transplantation, ASL Lecce - V. Fazzi Hospital, Lecce, Italy.*

Background: Renal osteodystrophy (ROD) is a common complication in dialysis patients (pt), due to disorders of mineral and bone metabolism secondary to a longstanding hyperparathyroidism (HPT), resulting in both skeletal and extraskeletal consequences. The combination between high bone turnover and mineralization defects lead to an increased risk of bone fractures and deformities. ROD affects several sites (long bones, ribs, spine), but the cranio-facial localization is rather rare. At this site, the more dramatic pattern is *leontiasis ossea.* Radiological examination of the skeleton is a non-invasive tool for the identification of ODR, with high specificity but low sensitivity, since it only recognizes the advanced forms of the disease.

Methods: We report a case of a 45 y/o man on regular HD. History: coronary artery disease treated with CABG, hypertension, COPD, severe secondary HPT non responder to medical therapy, with parathyroid gland hyperplasia detected by ultrasound and scintigram. The pt presented vertebral osteoporosis with multiple vertebral collapses. His high cardiovascular risk contraindicated a parathyroidectomy. Due to the rapid onset of facies alterations, with macrognathia and severe facial deformity, the pt underwent cranio-facial CT. This test showed marked morphostructural bone alterations, with symmetrical bone remodelling, affecting both the trabecular structure and cortical one. At this level we found widespread erosions with symmetrical involvement of bone structures. Multiple lytic and sclerotic areas representing brown tumourss were also observed in the maxilla and mandible. This aspect was compatible with fibrocystic osteitis. Extensive vascular and soft tissue calcification were also found.

Results:

Conclusions: Todate, despite the numerous therapeutic options, high-efficiency dialysis, and parathyroidectomy, ODR still remains a complication in dialysis pt. Leontiasis ossea is a rare or maybe undiagnosed condition. Its early recognition is fundamental in order to intensify intervention strategies and improve pt outcome.

PUB583

Vitamin D and Stone Burden in Calcium Phosphorus Kidney Stone Formers Xuerong Wen,[2] Jie Tang.[1] *[1]University Medicine - Nephrology, Brown University, Providence, RI; [2]University of Rhode Island, Kingston, RI.*

Background: Vitamin D is important in regulating calcium and phosphorus homeostasis, but its effects on the risk of kidney stone and stone burden among calcium phosphorus (CaP) stone formers are not clear.

Methods: We conducted a retrospective cross-sectional study of a cohort of prevalent CaP stone formers, from a large academic hospital in Rhode Island. Both plasma 25-hydroxy-vitamin D (25D) and 1,25-dihydroxy-vitamin D (1,25D) were measured and the stone burden (calculated as the cumulative stone size) was assessed by ultrasound. The associations between plasma vitamin D measurements and kidney stone burden were assessed after adjusting for demographic and other clinical characteristics.

Results: A total of 36 CaP stone formers were identified for the study. Among them, 18 (50%) were female, 30 (83%) were caucasian, 14 (39%) had history of hypertension, 8 (22%) had diabetes, 14 (39%) had hyperlipidemia, 2 (6%) were taking allopurinol, 6 (18%) were taking potassium citrate, and 6 (18%) were taking thiazide diuretic. Mean body mass index (standard deviation (SD)) was 30.3 (6.9). The stone burden were higher in older subjects (p=0.003), among women (p=0.004), in those without hypertension (p=0.001), in those with hyperlipidemia (p=0.02), in those not taking allopurinol (p=0.001) or thiazide (p=0.006), and in those had either higher urine phosphorus (p=0.04) or lower urine citrate (p=0.001). For the final analyses, we included a total of 66 laboratory measurements of vitamin D, with corresponding other blood and urine tests as well as stone burden assessment. Mean plasma 25D (SD) was 26.4 ng/ml (9.9), mean plasma 1,25D (SD) was 58.1 pg/ml (16.6), and median stone burden was 6.6 mm (Interquartile range: 2.5 - 11.0 mm). Plasma 25D did not associate significantly with plasma 1,25D (p=0.7). Neither plasma 25D nor 1,25D showed significant associations with measurements of blood intact parathyroid hormone (p=0.8, 0.9 respectively), 24-hour urine calcium (p=0.5, 0.7 respectively) and phosphorus (p=0.8, 0.1 respectively), as well as CaP supersaturation (p=0.7, 0.3 respectively). Finally, neither plasma 25D nor 1,25D had significant effect on stone burden after adjustment for demographics and 24-hour urine sodium, potassium, pH, citrate, volume, and medication use (allopurinol, thiazide), p=0.3 and 0.4 respectively.

Conclusions: Neither 25D nor 1,25D, appears to affect kidney stone burden among prevalent CaP stone formers

Funding: Clinical Revenue Support

PUB584

MCP-1 and NGAL-Positive Urinary Extracellular Vesicles Associate with Calcium Oxalate Stone Former Status Robin S. Chirackal, Xiangling Wang, Muthuvel Jayachandran, Samuel Edeh, Zejfa Haskic, Majuran Perinpam, Timothy M. Halling, Ramila A. Mehta, John C. Lieske. *Mayo Clinic, Rochester, MN, Rochester, MN.*

Background: Randall's plaque (RP) appears to be an important precursor of kidney stone disease. However, RP cannot be noninvasively detected. Thus we investigated potential biomarkers on urinary extracellular vesicles (EVs) of stone formers (SFs) with high (≥ 5% papillary surface with plaque) and low (< 5% surface area) amounts of RP compared to controls.

Methods: RP were assessed via videotaping and quantitative image processing in 64 consecutive idiopathic calcium oxalate SFs undergoing percutaneous surgery for stone removal. Cell-free urinary EVs from SFs and controls (n=40) derived from different segments of the nephron were quantified in bio- banked urine by digital flow cytometry using fluorophore conjugated antibodies. Candidate protein biomarkers of renal fibrosis (MCP-1), injury (NGAL) and RP (OPN) were selected for study.

Results: Data are presented as median (25th, 75th percentile). Overall the number of EVs positive for MCP-1 and NGAL differed significantly in SFs compared to controls (Table), but not between low and high plaque SF. OPN-positive vesicles were similar in all 3 groups.

Conclusions: EVs carrying MCP-1 and NGAL may contribute to stone pathogenesis and /or reflect inflammatory or injury processes ongoing during stone formation. Hence further validation of EV associated biomarkers including MCP-1 and NGAL as a noninvasive tool to access those at risk of urinary stone disease are warranted.

Expression of urinary EVs positive for MCP-1 & NGAL among Controls vs Cases.

Nephron Segment	Marker 1	Marker 2	Controls (n-40)	Cases (n-64)	P-value
Proximal	MCP-1	URAT1	13.2 (3.4, 44.9)	4.6 (1, 21.1)	0.05
Thin Loop	MCP-1	AQ1	29.2 (7.6, 96.3)	5.0 (0.2, 26.0)	<0.01
Thick Loop	MCP-1	UROM	3.7 (1.5, 19.7)	3.4 (1, 12.2)	0.40
Distal	MCP-1	SLC12A3	2.1 (0.6, 10.2)	2.8 (0.6, 11.9)	0.96
Collecting Duct	MCP-1	AQ2	26 (8.3, 93.5)	16.2 (3.6, 67.3)	0.15
Renal Pelvis	MCP-1	CK-19	14.5 (3.2, 48.4)	2.5 (0.7, 12.2)	<0.01
Proximal	NGAL	URAT1	19.1 (5.1, 59.2)	8.3 (2.3, 43.8)	0.03
Thin Loop	NGAL	AQ1	50.7 (22.5, 172.5)	8.0 (0.4, 54.5)	<0.01
Thick Loop	NGAL	UROM	62.8 (19.3, 198)	35.4 (9.5, 130.2)	0.13
Distal	NGAL	SLC12A3	4 (1.9, 16.1)	4.6 (1.5, 17.2)	0.94
Collecting Duct	NGAL	AQ2	77.3 (27, 219.4)	38.7 (11.6, 139.5)	0.03
Renal Pelvis	NGAL	CK-19	30.8 (5.9, 111.1)	5.8 (1.2, 25.7)	<0.01

Data is represented as median (25%, 75%) EVs/mg creatinine × 10000.

PUB585

Clinical Characteristics and Tolerability of ALLN-177 in Phase 2 Studies of Patients with Secondary Hyperoxaluria Sagar U. Nigwekar,[3] James E. Lingeman,[2] Gyan Pareek,[1] Annamaria T. Kausz.[4] *[1]Brown University, Providence, RI; [2]IU Health Physicians Urology, Indianapolis, IN; [3]Massachusetts General Hospital, Boston, MA; [4]Allena Pharmaceuticals, Newton, MA.*

Background: Secondary (2°) HOx is caused by excess oxalate absorption from diet due to enteric disorders (enteric HOx, EH) or is unexplained (idiopathic, IH), and can lead to kidney stones and other sequelae including oxalate nephropathy. Presently there are no approved pharmacotherapies for HOx. ALLN-177 is a novel oral formulation of crystalline oxalate decarboxylase that degrades oxalate in the gastrointestinal (GI) tract, thereby reducing urinary oxalate (UOx).

Methods: Three phase 2 trials have been conducted in patients with 2°HOx and history of kidney stones to evaluate effect of ALLN-177 on 24-hour UOx. In study 396, 16 subjects received 7500 u/meal of ALLN-177 3x/d for 4d. In study 649, 32 subjects were randomized to 1500, 3000 or 7500 u/meal ALLN-177 or placebo 3x/d for 7d, then crossed over to an alternate arm for 7d. In Study 713, 67 subjects were randomized to 7500 u/meal ALLN-177 or placebo 3x/d for 28d. In Studies 649 and 713, CT scans were obtained at baseline to assess kidney stone burden.

Results: A total of 115 subjects were enrolled across the three studies; mean age range was 54 -61 years; 70.4% were male and 33 (28.7%) had EH. Across Studies 649 and 713, subjects reported on average 7.6 stones in the past 5 years and had 2.3 stones on CT scan. Compared with IH, subjects with EH had higher baseline UOx (mean 98.9 vs 57.5 mg/24h) despite lower dietary oxalate intake (mean 248 vs 315 mg/d). EH patients also had more kidney stones on CT (2.85 vs 2.02). Across the studies, adverse events (AE) were reported in 50-56.3% of ALLN-177 subjects vs. 25-62.9% placebo. The most frequently reported AEs were GI AEs, with no notable difference in rates between ALLN-177 and placebo. There were no drug-related serious AEs or drug-related AEs that led to withdrawal in the ALLN-177.

Conclusions: Despite lower dietary oxalate intake, EH patients have higher UOx and more kidney stones than IH patients. The characteristics of subjects in ALLN-177 clinical trials highlight the need for an effective therapy, especially in EH patients. ALLN-177 was well-tolerated and has the potential to address this unmet need.

Funding: Commercial Support - Allena Pharmaceuticals

PUB586

Polycystic Ovary Syndrome, Testosterone, and Urinary Stone Risk: A Matched Case Comparative Study Donald C. Fedrigon, Kareem Alazem, Sri Sivalingam, Juan C. Calle. *Glickman Urological & Kidney Institute, Cleveland Clinic, Cleveland, OH.*

Background: Polycystic ovary syndrome (PCOS), a common endocrine disorder characterized by androgen excess, has been suggested as a potential risk factor for kidney stone formation based on past evidence indicating a relationship between elevated testosterone and urinary stone risk. Our goal was to evaluate the relationship between PCOS, elevated testosterone, and stone formation from the perspective of stone composition and 24-hour urine metabolic stone risk.

Methods: We retrospectively identified 74 patients diagnosed with PCOS. A matched case cohort of female stone formers in our stone registry was generated at a 3:1 ratio, matched by age and BMI for a total of 222 control patients. Additionally, PCOS patient

data was compared based on normal and high testosterone categorization. Primary endpoints were 24-hour urinary metabolic panels and stone composition and both cohorts were compared using Pearson chi-square and Student T-tests. The PCOS-testosterone cohort was also compared using multivariable analysis adjusted for age, BMI, and metformin status.

Results: For the case-control cohort PCOS patients had both significantly lower urinary sodium excretion (p=0.015) and lower frequency of hypernatriuria (28.9% vs 50.9%, p=0.009). Within the PCOS-testosterone cohort, high testosterone patients had both significantly higher urinary citrate values (p=0.041, table 3) and significantly lower odds of having hypocitraturia (36.7% vs 54.2%, OR=0.2, p=0.042). These patients also had higher urinary sodium (p=0.058) with significantly higher odds of having hypernatriuria (40.0% vs 13.6%, OR=13.3, p=0.021). Stone composition analysis for either cohort did not reveal any statistically significant patterns.

Conclusions: When compared to matched cohort of healthy stone formers PCOS patients did not demonstrate significant enough changes in 24-hour urine and stone composition to indicate PCOS is an independent risk factor for stone formation. Elevated free testosterone in PCOS patients has a significant association with higher urinary citrate and sodium values; findings that in and of themselves do not confirm the hypothesized increased risk of stone formation. This patient cohort may provide deeper insight into the interplay between androgens and stone risk, however, further study is needed to fully confirm any hypothesized increased risk of stone formation in PCOS.

PUB587

A Pilot Randomized Study Comparing Blumea Balsamifera (Sambong) and Terpenes on Ureterolithiasis Rommel P. Bataclan. *Medicine, San Antonio District Hospital, San Antonio, Philippines.*

Background: Other agents have been proposed to be given in the management of kidney or ureteral stones. This study aims to investigate the safety and efficacy of *Blumea balsamifera* (Sambong) in comparison with a terpene combination drug as treatment for ureterolithiasis.

Methods: Patients with clinically stable kidney function and ureter stones of ≤5mm were randomised to receive a special terpene combination (Rowatinex®; 2 capsules three times daily) or Blumea balsamifera 500mg tablet (2 tablets three times daily). The study consisted of a 12-week active treatment phase, in addition to standard management. All patients had a physical examination, and diagnosis of kidney stones was made by ultrasound at baseline and after 6 and 12 weeks of treatment. Primary outcomes are change in stone size and stone-free status, defined as obviously successful expulsion of calculi/fragments, documented by ultrasound.

Results: After 6 weeks, 5 patients in the Sambong group and 6 individuals in the Terpene group were stone free (p-value 0.90). After 12 weeks, 6 in Sambong group and 8 in the Terpene group were stone free (p-value 0.31). In terms of stone size, there was significant decrease in the mean value of stone size after 6 weeks (1.81+2.01mm, p-value 0.008) and 12 weeks (1.12+1.43mm p<0.005) in the Sambong group, and also with the Terpene group (At 6 weeks 1.24+1.43mm, p<0.005; at 12 weeks 0.74+0.70, p<0.005). However, there were no differences between the two groups. Urine pH also significantly increased in both groups compared to baseline but no statistical difference when comparing both arms, Frequency of pain, hematuria, change in serum parameters were also not statistically significant and no other adverse events were noted.

Conclusions: Treatment with Blumea balsamifera and Terpene combination are well tolerated and safe in patients with Urolithiasis. Further studies may be warranted, with inclusion of other urine parameters.

	Stone Size (mm)		Stone Free		Stone Unchanged		Stone Decrease Size		Urine pH	
	Sambong	Terpene	Sambong	Terpene	Sambong	Terpene	Sambong	Terpene	Sambong	Terpene
Baseline	2.98±1.02	3.01±0.88							5.82±0.34	5.85±0.55
6 weeks (p vs baseline)	1.81±2.01 (0.008)	1.24±1.43 (<0.005)	5	6	3	1	9	11	6.64±0.30 (<0.005)	6.41±0.35 (0.02)
P-value in 2 groups	0.22				0.9				0.23	
12 weeks (p vs baseline)	1.12±1.43 (<0.005)	0.74±0.70 (<0.005)	7	8	3	3	8	6	6.64±0.14 (<0.005)	6.58±0.19
P-value in 2 groups	0.30				0.31				0.68	

Results of Primary Outcome after 6 and 12 weeks of Treatment

PUB588

Oxalate Nephropathy: A Systematic Review and Individual Patient Data Meta-Analysis of Case Reports and Case Series Nuttha Lumlertgul,[1] Monchai Siribumrungwong,[2] Paweena Susantitaphong,[1] Bertrand L. Jaber.[3] *[1]Chulalongkorn University, Bangkok, Thailand; [2]Lerdsin Hospital, Bangkok, Thailand; [3]St. Elizabeth's Medical Center, Boston, MA.*

Background: Little is known of oxalate nephropathy. The aim of this systematic review and individual patient data meta-analysis is to perform an in-depth review on the state of the evidence on oxalate nephropathy and its association with oxalate intake, and provide a more precise estimate of clinical characteristics and outcomes through pooling of aggregate data and analysis of individual patient data.

Methods: The following electronic databases were searched for relevant citations: PubMed, Ovid, and the Cochrane Central Register of Controlled Trials (inception to November 2016). We included case reports, case series, case control studies, and retrospective and prospective cohort studies that describe individual cases or cohorts of patients with evidence of biopsy-proven oxalate nephropathy in the setting of native or transplanted kidneys.

Results: Seventy-nine case report and case series (150 patients) were included. Twenty-three (15%) cases involved kidney transplant recipients. The mean age was 51.3±17.0 years. Increased dietary oxalate intake through excessive consumption is the most common cause (52%) followed by increased oxalate availability in the colon due to decreased intestinal calcium availability from fat malabsorption (47%), 3% resulted from decreased intestinal oxalate degradation due to decreased intestinal colonization with oxalate-degrading bacteria and only 1% resulted from increased colonic permeability to oxalate. Seventy-seven percent had acute kidney injury, 9% had acute-on-chronic kidney disease, 3% had chronic kidney disease and 11% had stones. Sixty percent needed dialysis and 29% had complete recovery, 25 % had partial recovery, 46% had non-recovery of kidney function and 31% required dialysis dependence. The mortality rate was 22%.

Conclusions: The main etiology cause was the increased dietary oxalate intake through excessive consumption. Most people had acute kidney injury, needed dialysis requirement, and did not have renal recovery. Therefore, the prevention should be considered.

PUB589

A Systematic Literature Review to Understand the Impact of Calcium-Containing Phosphate Binders and Sevelamer on Mortality and Cardiovascular Calcification in Patients with Kidney Disease Charles Piwko,[3] Elizabeth M. Uleryk,[4] Leora Kurtz,[1] Philip McFarlane.[2] *[1]CHP Pharma Inc, Thornhill, ON, Canada; [2]St. Michael's Hospital, Toronto, AB, Canada; [3]CHP Pharma Inc, Thornhill, ON, Canada; [4]E.M. Uleryk Consulting, Mississauga, ON, Canada.*

Background: Phosphate binders are pivotal in managing hyperphosphatemia in patients with kidney disease. Calcium containing phosphate binders (CPBs) may be effective and perceived to be less expensive but more likely to cause hypercalcemia, vascular calcification (VC) and mortality compared with non-CPBs, such as sevelamer. The objective was to compare the effects of phosphate binders on patients with chronic kidney disease and bone mineral disorders (CKD-MBD) in regard to VC and mortality.

Methods: A systematic literature search was conducted. Two independent reviewers identified and reviewed relevant references. Included were any peer-reviewed randomized studies that presented research on the impact of CPBs and sevelamer (hydrochloride or carbonate) on VC and mortality. Patients had to be >18 years. Papers in any language published after 1995 were accepted. Studies where outcomes of interest were part of pooled analyses or post-hoc analyses were excluded.

Results: From the 1,690 identified references, 17 and 5 studies that reported outcomes for VC and mortality, respectively, were included for data summary. Only 3 studies did not report advantages of sevelamer concerning CV calcification. In regard to (all-cause) mortality, all studies reported advantages of sevelamer versus CPBs.

Conclusions: Based on this literature review it can be concluded that sevelamer has advantages versus CPBs with respect to vascular calcification and mortality and should therefore be considered preferentially to CPBs for the management of hyperphosphatemia in CKD patients. Furthermore, a Rapid Response published by the Canadian Agency for Drugs and Technologies in Health suggests that sevelamer is less costly and more clinically effective than calcium-carbonate in all scenarios involving a subset of pre-dialysis or non-dialysis-dependent CKD patients.

Funding: Commercial Support - SANOFI-AVENTIS CANADA INC

PUB590

Atypical Case of Calciphylaxis in a Renal Transplant Recipient Brittany L. Schreiber, Muhammad A. Mujtaba. *University of Texas Medical Branch, Galveston, TX.*

Background: Calciphylaxis is a rare, life-threatening condition with insidious onset and significant mobidity and mortality. Traditionally, it is associated with chronic kidney disease-mineral bone disease, hyperparathyroidism, high calcium phosphate product, and vitamin D administration. We present a unique case of calciphylaxis in a renal transplant recipient with normal renal function.

Methods: A 42-year-old female with a history of secondary hyperparathyroidism status-post parathyroidectomy and ESRD on hemodialysis for 10 years status-post renal transplant with normal renal function presented with a few week history of intractable lower extremity pain followed by a non-healing cutaneous ulcers 4 months after transplantation. Initially she was referred to dermatology and underwent a punch biopsy which showed epidermal and dermal necrosis with acute inflammation and leukocytoclasia. Infectious work up was negative. One week later she was admitted to the hospital for worsening pain and presence of new ulcerations. Repeat punch biopsy at that time showed results consistent with prior biopsy. She received a taper of steroids and was discharged with wound care and analgesics. For the next 2 months, she was admitted multiple times with extensive work-up including vascular studies, bone scan, and EMG/Nerve conduction studies performed for lower extremity pain and weakness, all of which were unremarkable. Despite low intact-PTH and calcium-phosphate product levels ranging from 13.7 to 20.4 pg/mL and 20.8 to 36.5 respectively, based upon high clinical suspicion a diagnoses of calciphylaxis was entertained and the patient was started on sodium thiosulfate. A repeat punch biopsy was performed which revealed vascular congestion in the dermis and subcutis with focal calcification consistent with a diagnosis of calciphylaxis.

Results:

Conclusions: A diagnosis of calciphylaxis should be considered as part of the differential for ulcer in post transplant patients despite normal renal function and calcium phosphate product. Recognition and diagnosis with prompt initiation of therapy in a setting with high clinical suspicion is crucial in patients with atypical mineral profiles or negative biopsy as delay in therapy can lead to worse outcomes with increased morbidity and mortality.

PUB591

Calciphylaxis in Patients after Bariatric Surgery Charbel C. Khoury,[3,1] Lauren N. Ko,[4] Ravi I. Thadhani,[3,4] Sagar U. Nigwekar,[3,4] Daniela Kroshinsky,[2,4] Malcolm K. Robnson.[1,4] *[1]Brigham and Women's Hospital, Boston, MA; [2]Massachusetts General Hospital, Harvard Medical School, Boston, MA; [3]Massachusetts General Hospital, Boston, MA; [4]Harvard Medical School, Boston, MA.*

Background: Calciphylaxis is a rare disease of dysregulated calcium-phosphorous metabolism predominantly seen in patients (pts) with CKD/ESRD. Recent observational studies have identified potential risk factors such as hypercoagulability, warfarin intake, as well as diabetes and obesity. However, calciphylaxis has rarely been reported in pts after bariatric surgery.

Methods: This study includes 9 pts with a history of bariatric surgery who were referred to the calciphylaxis clinic or admitted to the inpatient service at the Massachusetts General Hospital from 2012-2017. Data was abstracted from electronic medical records.

Results: Median age was 49 (IQR 44,65) years, 4 pts were women, and 8 were white. At the time of diagnosis, 1 pt had normal kidney function, 1 had AKI, 4 pts had CKD stage 2-3, and 3 pts were on maintenance dialysis (with a vintage of 6 months, 3 years, and 4 years). Bariatric surgery consisted of Roux-en-Y gastric bypass (n=6), sleeve gastrectomy (n=2), and laparoscopic banding (n=1). The mean (SD) maximal weight loss was 45.6 (3.7)%, excess body weight loss was 81.8 (8.1)%. Comorbidities included diabetes (n=5), NAFLD (n=5), hypercoagulable state (n=3). No pts were on warfarin. Laboratory testing was notable for a mean serum(SD) calcium level of 8.8 (1.4)mg/dL, phosphate 4 (1.2)mg/dL, 25-HO vitamin D 21.7 (13.9)ng/mL, and parathyroid hormone 173 (203.2)pg/mL. Calciphylaxis ulcers were located mainly on the abdomen, breast, and thighs. The lesions of 3 pts resolved following intralesional/intravenous sodium thiosulfate, 2 pts required surgical debridement. Three pts died; however the causes of death were unrelated to infection of their ulcers.

Conclusions: To our knowledge this is the largest series of pts with calciphylaxis following bariatric surgery. While calciphylaxis is thought to occur more commonly in women, our series had almost equal number of men and women. There were more pts with normal kidney function or early stages of CKD, and bone mineral disease markers did not reflect the nutritional vitamin D deficiency recorded. These findings, along with the significant weight loss noted suggests a potential role for nutritional deficiencies in the pathogenesis of calciphylaxis. Sample size and characteristics of pts included in our study limit generalizability to overall bariatric population and warrant examination in larger independent studies.

Funding: Private Foundation Support

PUB592

Ginkgo Biloba Extract Inhibits High-Phosphorus-Induced VSMC Calcification by Interfering with Sclerostin/Lrp4 Li Yao,[1] Jian Wang,[1] Tianhua Xu,[1] Zitong Sheng,[1] Lining Wang.[2] *[1]The First Affiliated Hospital of China Medical University, Shenyang, China; [2]The First Hospital of China Medical University, ShenYang, China.*

Background: To investigate whether Ginkgo biloba extract(GBE) inhibits high calcium-induced calcification of VSMC by interfering with sclerostin/Lrp4.

Methods: Extraction of SD rat aortic vascular smooth muscle cells(VSMCs) and identification. Divided into normal control group, high phosphorus induced calcification group(10mmol/Lβ-glycerophosphate + 50ug/ml ascorbic acid),high phosphorus induced calcification+GBE intervention group(10mmol/Lβ-glycerophosphate+50ug/ml ascorbic acid+0.5mg/ml GBE),and the medium was induced for 14 days. Vonkossa staining and alizarin red staining were used to detect the calcification of VSMCs. The expression of BGP mRNA was detected by real time PCR, the expression of sclerostin and Low density lipoprotein receptor relatd protein 4(Lrp4) was detected by western blot.

Results: Vonkossa staining and alizarin red staining showed that there was significant calcium deposition in VSMC calcification group compared with normal control group, and calcium salt deposition in GBE was significantly reduced compared with calcification group. The mRNA expression of BGP in VSMC calcified group was significantly higher than that in other groups ($P<0.05$) and it was significantly lower in GBE than that in calcification group ($P<0.05$). Western Blot showed that the expression of sclerostin protein in VSMC calcified group was significantly higher than that in other groups ($P<0.05$), and the expression of Lrp4 protein was significantly lower than that of other groups ($P<0.05$). The expression of sclerostin protein in GBE was significantly lower than that in calcified group ($P<0.05$), and the expression of Lrp4 protein was significantly higher than that of calcification group ($P<0.05$).

Conclusions: High phosphorus can induce VSMC calcification. Sclerostin/Lrp4 is involved in hyperphosphine-induced VSMC calcification and plays an important role. GBE can inhibit high phosphorus induced VSMC calcification by interfering with Sclerostin/Lrp4.

PUB593

Establishment of Novel Mouse Model to Exhibit CKD – Mineral and Bone Disorder Associated with Hyperphosphatemia Takashi Tani,[3,1] Hideo Orimo,[1] Akira Shimizu,[2] Shuichi Tsuruoka.[3] *[1]Department of Metabolism and Nutrition, Nippon Medical School, Bunkyo-ku, Japan; [2]Department of Analytic Human Pathology, Nippion Medical School, Bunkyo-ku, Japan; [3]Department of Nephrology, Nippon Medical School, Bunkyo-ku, Japan.*

Background: CKD - mineral bone disorder (CKD-MBD), which mainly represents medial arterial calcification (MAC) and renal osteodystrophy, is a serious complication and risk factor of CKD-related mortality. Our aim was to develop a novel mouse model of CKD using an adenine-fed procedure to investigate the clinical course of MBD.

Methods: Eight-week-old C57BL/6J male mice were assigned to the following groups: the control group, fed a standard chow for 6 or 12 weeks (C6 an C12); the CKD-normal phosphorus (NP) group, fed a chow containing 0.2% adenine, with normal (0.8%) phosphorus, for 6 or 12 weeks (A6 and A12); and the CKD-high phosphorus (HP) group, fed 6 weeks with the 0.2% adenine/0.8% phosphorus diet, followed by a chow with 1.8% phosphorus for 2 weeks, 4 weeks or 6 weeks (A6P2, A6P4 and A6P6). At sacrifice, aorta and femur bone were scanned by computed tomography (CT) imaging and were evaluated histologically, while plasma was drawn for biochemical findings. mRNA expressions of aortic lysates were quantified by qRT-PCR analysis.

Results: Blood levels of urea nitrogen and serum creatinine were elevated in both CKD-NP and CKD-HP group than control, while serum phosphorus and intact parathyroid hormone were significantly increased in the CKD-HP than CKD-NP mice and control. MAC was confirmed only in CKD-HP mice by histological (positive Von-Kossa and Alizarin Red staining) and CT imaging, and the volume of MAC increased with longer exposure to the high phosphorus feed. MAC formation in CKD-HP mice was associated with upregulation in runt-related transcription factor 2 (Runx2), tissue non-specific alkaline phosphatase (TNAP) and osteopontin (OPN), indicative of osteoblastic trans-differentiation of vascular smooth muscle cells. CT and histological imaging revealed that the cortex of the femur was particularly thinned in CKD-HP mice; significant depletion in mineral density/volume of the cortical bone of the femur in CKD-HP mice was observed.

Conclusions: Our results support a previously-reported strong influence of hyperphosphatemia for the formation of CKD-MBD. Our novel CKD-MBD model is enhanced by its recapitulation of CKD-MBD in patients with end-stage renal disease in practice, without any surgical or transgenic interventions. We expect this model to be of value advancing research in the field of CKD.

PUB594

Vascular Calcification and Cardiac Function According to Residual Renal Function in Patients on Hemodialysis with Urination Dong Ho Shin,[1] Jung-woo Noh,[3] Jeonghwan Lee.[2] *[1]College of Medicine, Hallym University, Seoul, Republic of Korea; [2]Hallym University Hangang Sacred Heart Hospital, Seoul, Republic of Korea; [3]Hallym University, Seoul, Republic of Korea.*

Background: Vascular calcification (VC) is common and may affect cardiac function in patients with end-stage renal disease (ESRD). However, little is known about the effect of residual renal function (RRF) on VC and cardiac function in patients on hemodialysis (HD).

Methods: This study was conducted between January 2014 and January 2017. One hundred six patients with RRF on maintenance HD for 3 months were recruited. We used residual renal urea clearance (KRU) to measure RRF. First, abdominal aortic calcification score (AACS) and brachial-ankle pulse wave velocity (baPWV) were measured in patients on HD. Second, we performed echocardiography and investigated new cardiovascular events after study enrollment.

Results: The median KRU was 0.9 (0.3 – 2.5) mL/min/1.73m^2. AACS (4.0 [1.0 – 10.0] vs. 3.0 [0.0 – 8.0], $p = 0.05$) and baPWV (1836.1 ± 250.4 vs. 1676.8 ± 311.0 cm/s, $p = 0.01$) were significantly higher in patients with a KRU < 0.9 mL/min/1.73m^2 than a KRU ≥ 0.9 mL/min/1.73m^2. Log-KRU significantly correlated with log-AACS (ß = -0.33, $p < 0.001$) and baPWV (ß = -0.23, P = 0.01) after factor adjustment. The proportion of left ventricular diastolic dysfunction (LVDD) was significantly higher in patients with a KRU < 0.9 mL/min/1.73m^2 than with a KRU > 0.9 mL/min/1.73m^2 (67.9 % vs. 49.1%, $p = 0.05$). Patients with a KRU < 0.9 mL/min/1.73m^2 showed a higher tendency of cumulative cardiovascular events compared to those with a KRU > 0.9 ml/min/1.73m^2 ($P = 0.08$).

Conclusions: RRF was significantly associated with VC and LVDD in patients on HD.

PUB595

Evaluation of Major Factors for Vascular Calcification in Patients with Hemodialysis Yoshihito Nihei, Hitoshi Suzuki, Masao Kihara, Yusuke Suzuki. *Nephrology, Juntendo University Faculty of Medicine, Tokyo, Japan.*

Background: Vascular calcification is the common complication in patients with end-stage of kidney disease (ESKD) and is high risk of cardiovascular disease and stroke. In present study, we investigated the clinical parameters for vascular calcification in patients with hemodialysis.

Methods: The vascular calcification was quantified as an Aortic Arch Calcification Score (AoACS) by chest X-ray, as previously reported (Hemodial Int 2009). AoACS was measured in forty hospitalized patients with hemodialysis. Forty patients were divided into two groups depending on the AoACS; high AoACS group as ≥ mean + 1SD, low

AoACS group as < mean -1SD. The cause of ESKD, complications, age, duration of hemodialysis, serological data including Ca, P and intact PTH were analysed its association with AoACS.

Results: In high AoACS group, major causes of ESKD were mainly diabetes and nephrosclerosis. Meanwhile, the major cause in low AoACS group was glomerulonephritis. The high AoACS group had a long history of smoking, dialysis treatment, and hypertension. In addition, higher levels of P as well as product of Ca and P was significantly higher in the high AoACS group (P<0.05).

Conclusions: Vascular calcification is one of the major risks of cardiovascular diseases in hemodialysis patients and well associate with mortality. The strict management of hypertension and arteriosclerosis in addition to treatment of Ca and P are necessary to prevent the vascular calcification.

PUB596

1.25-VitD Is Independently Associated to CAC in CKD Patients

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Background: Vascular calcification (VC) is highly prevalent in CKD patients and is an independent predictor of cardiovascular morbidity and mortality. CKD-MBD may contribute to VC. Although several studies have addressed the association of 25-VitD with VC, 1.25-VitD has been less studied.

Methods: CKD-MBD measurements and clinical data from 372 participants in the Progredir Study were used. CAC was assessed by CT. Univariable and multivariable logistic regression models on the risk of Agatston score ≥ 400 and gamma models using CAC as a continuous variable were built.

Results: Mean eGFR was 36 (IQR 26 – 46) ml/min/1.73m^2 and median CAC was 165 (IQR 7 – 784), with only 17% of participants with CAC of zero. As expected, higher CAC was associated to age, sex, race, diabetes, lipids and smoking. In the logistic regression and gamma models, 1.25-VitD (inversely) was significantly associated with CAC, while other CKD-MBD biomarkers like PTH and FGF-23 were not, even after adjustments for age, sex, race, diabetes and smoking. 1.25-VitD remained significantly and inversely associated with CAC after additional adjustment for 25-Vit D (Table1).

Conclusions: Our results demonstrate that 1.25-VitD is inversely related to CAC in CKD patients not on dialysis. The identification of ideal ranges of 1.25-VitD and the benefits of strategies to achieve those levels in preventing and treating VC should be explored in future studies.

Funding: Government Support - Non-U.S.

Table 1. Gamma Models

	Estimate	SE	p value
Univariable			
1.25-vitD	-0.04	0.01	<0.001
FGF23	3.00E-04	4.00E-04	0.46
1.25-VitDModel 1 (age, sex, diabetes, smoking, race)			
1.25-VitD	-0.03	0.01	0.002
Model 2 (age, sex, diabetes, smoking, race, 25-vitD)			
1.25-vitD	-0.03	0.008	<0.001

PUB597

Carotid Calcium Score Is Associated with Coronary Calcium Score in Patients with ESRD on Hemodialysis

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Background: In patients with end-stage renal disease (ESRD) on hemodialysis (HD), the degree of coronary calcium score is associated with cardiovascular risk and mortality. Those with higher degree of carotid calcium score are known to have higher cerebrovascular risk and mortality. However, there is no study which evaluates a correlation between coronary artery calcium score and carotid calcium score

Methods: This is a cross-sectional study involving ESRD patients who were dialyzed in Soonchunhyang Cheonan Hospital and agreed to participate in the study. Brain computed tomography (CT) and heart CT were performed to evaluate the carotid and coronary calcium score, and the routine laboratory data in artificial kidney center were analyzed.

Results: Total 49 patients were included. A mean age of the group was 58.5 ± 12.1 year, and a mean duration of HD 67.7 ± 44.2 months. Serum calcium, phosphorus, intact parathyroid hormone, and alkaline phosphatase (ALP) levels were 8.9 (8.6 – 9.1) mg/dL, 4.1 ± 1.4 mg/dL, 241.5 ± 173.9 pg/mL, and 63 (46 – 87) IU/L, respectively. Carotid and coronary calcium score were noted as 125.7 (23.3 – 366.7) and 172.6 (7.2 – 798.7), respectively. The patients were divided into two groups, < 50 or ≥ 50 percentile, based on carotid calcium score. Among the variables, there was a significant difference in age (< 50 percentile, 51.5 ± 8.9; ≥ 50 percentile, 65.2 ± 10.9 year) between the two groups. The partial correlation analysis showed that a correlation between coronary calcium score and carotid calcium score was statistically significant (r = 0.556, p < 0.001), when the age was set as confounding variables.

Conclusions: In patients with ESRD on HD, coronary calcium score was correlated with carotid calcium score in patients with ESRD on HD

Funding: Government Support - Non-U.S.

PUB598

Prevalence of CKD-Mineral Bone Disorder (CKD-MBD) in Mexico

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Background: CKD-MBD includes bone alterations (remodeling/mineralization), biochemical, (calcium, phosphorus, 25-OH-vitamin D, parathormone), and presence of extra bone calcifications. It is not completely known the epidemiology of MBD-CKD in México. Aim: To determinate the prevalence of MBD-CKD in our country.

Methods: Cross-sectional analytical study, performed in 333 patients with diagnosis of Chronic Kidney Disease with renal function replacement therapy whit hemodialysis or peritoneal dialysis, between January of 2014-June of 2016. There was no distinction between gender or causes of CKD. The comparisons were performed with c^2 or Student's T. A *p* value <0.05 was considered adequate.

Results: Fifty one percent (n 168) was men, 38% in hemodialysis and 62% in peritoneal dialysis. The prevalence of vascular calcification was 48%; hyperparathyroidism (PTH >300 pg/mL) was 62%, and the prevalence of deficiency of vitamin D (<15 ng/ml) was 27%.

Conclusions: The prevalence of vascular calcification was similar to the results of other national studies. The prevalence of hyperparathyroidism was close to two thirds. The deficiency of vitamin D was just in one of each four patients.

Variable	Men (51%)	Women (49%)	p value
Age (years)	35 ± 15	36 ± 15	0.49
Treatment time (years)	23 (10-36)	18 (6-37)	0.59
Albumin (g/dL)	3 ± 0	3 ± 0	0.63
C reactive protein (mg/L)	3 (3-11)	4 (3-8)	0.97
Cholesterol (mg/dL)	153 (130-176)	159 (135-187)	0.39
Triglycerides (mg/dL)	118 (84-167)	130 (96-191)	**0.04**
Phosphorus (mg/dL)	3 ± 2	4 ± 2	**<0.001**
Corrected calcium (mg/dL)	9 ± 1	9 ± 0	0.38
Alkaline phosphatase (U/L)	108 (76-189)	137 (84-295)	0.06
PTHi (pg/mL)	312 (124-815)	589 (192-1,117)	**<0.001**
VC score	0 (0-2)	1 (0-6)	**0.04**
Variable	**Hemodialysis (38%**	**Peritoneal dialysis (62%)**	**p value**
Age (years)	31 ± 9	35 ± 16	**0.008**
Treatment time (years)	15 (4-36)	24 (11-36)	**0.04**
Albumin (g/dL)	4 ± 0	3 ± 0	**<0.001**
C reactive protein (mg/L)	4 (3-9)	3 (3-7)	0.34
Cholesterol (mg/dL)	148 (128-170)	163 (141-187)	**<0.001**
Triglycerides (mg/dL)	129 (92-190)	131 (93-179)	0.96
Phosphorus (mg/dL)	4 ± 2	4 ± 2	0.57
Corrected calcium (mg/dL)	9 ± 1	9 ± 1	0.96
Alkaline phosphatase (U/L)	138 (92-294)	93 (75-156)	**<0.001**
PTHi (pg/mL)	548 (162-1,022)	436 (125-1052)	0.52
VC score	1 (0-7)	0 (0-2)	**<0.001**

Table 1. Compairson betwen gender and renal function replacement therapy.

Compairson betwen gender and renal function replacement therapy

PUB599

Coronary Artery Calcium (CAC) Score, CAC Volume, and CAC Density in Relation to Cardiovascular Disease (CVD) and Mortality in CKD Patients

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Background: A high content of CAC measured by computed tomography (CT) associates with increased mortality with Agatston score of CAC being weighted upward for greater calcium density. However, increased calcium density in plaques may be CVD protective. Here we investigated association of CAC score, CAC volume and CAC density with presence of CVD and all-cause mortality risk in CKD patients (pts).

Methods: In 201 CKD pts (median age 56 years old, 66% male, 22% diabetes; 97 non-dialyzed, 104 on dialysis) who underwent multi-slice CT, CAC parameters (CACP) were estimated by *Calcium Scoring* (S). Framingham's CVD risk score (FRS) and CACP were analyzed as classifiers of CVD and as predictors of all-cause mortality. Agreement between CAC score and FRS was assessed by weighted kappa calculation. Kaplan Meier and multivariate Cox models evaluated association of mortality with CACP and FRS. During follow-up for a median of 25 months, there were 34 deaths.

Results: CAC score (S) and CAC volume (S) associated with FRS (rho=0.72), CVD (rho=0.43), hsCRP (rho=0.37) and IGF-1 (rho=-0.38; n=149) and various nutritional markers. CAC density was associated with male sex (rho=-0.20). In AUC calculation, classifier of CVD by CAC score (S) (AUC=81), Volume (S) (AUC=0.81) and Density (S) (AUC=0.70). AUC for predictor of all-cause mortality CAC score (S) (AUC=0.81), Volume (S) (AUC=0.81) and Density (S)(AUC=0.62). The ln(log) CAC volume and density scores in the same multivariate model, the lnCAC volume showed an independent association with all-cause mortality, with a HR of 6.93 (95%CI, 2.25-21.33) per 1-SD increase. Conversely, CAC density showed an independent inverse association, with an HR of 0.27 (0.08-0.93) per 1-SD increase.

Conclusions: Whereas high CAC volume predicted increased mortality, high CAC density independently associated with decreased mortality suggesting that CAC density should be considered in evaluations of CAC scoring.

Funding: Commercial Support - Baxter Healthcare Corporation, Government Support - Non-U.S.

PUB600

Professionalism and Privacy of Pediatric Residents' Facebook Profiles Melinda Carpenter,[1] Katherine W. Herbst,[1] Cynthia J. D'Alessandri-Silva.[1,2] *[1]Connecticut Children's Medical Center, Hartford, CT; [2]Pediatrics, University of Connecticut Health Center, Farmington, CT.*

Background: Social media has progressed more rapidly than regulatory guidelines have emerged. Professional, regulatory and educational organizations have started to disseminate social media guidelines. This study's aim was to rate pediatric residents' Facebook profiles on privacy and professionalism.

Methods: Pediatric residency programs were randomly selected from the 2016-2017 ACGME list. Facebook was queried in May 2017 to determine if residents had private or public profiles. If public, profiles were reviewed for gender, residency year (PGY), residency program affiliation, and professional rating. Professionalism was rated as: 1) Professional (P)-no evidence of unprofessional content; 2) Potentially unprofessional (PU)-images of alcohol/tobacco in hand, political commentary, religious statements, or weapons; or 2) Clearly unprofessional (CU)-HIPAA violation, inappropriate language, binge drinking, drug use, racist or sexist content, and sexual content.

Results: Of 327 resident names searched, 232 (71%) had a Facebook profile. Neither gender nor year of residency was associated with having a profile (p>0.05). The majority (96%) of profiles were public with information from the bio "info" section, photo albums, friends, likes, groups and locations viewable. Almost half of residents (48%; n=111) affiliated with their current residency program. Three-quarters of the profiles were rated as professional (n=174). Of 55 profiles rated as unprofessional, over half (n=29) were holding an alcoholic drink and one quarter had images of alcohol. Three profiles were rated clearly unprofessional due to sexual and alcohol-related content.

Conclusions: Social media guidelines and institutional policies are needed in order to guide resident behavior as public posts could pose risk to themselves and their affiliated institutions. Facebook privacy features need to be reviewed and judiciously applied given the widespread popularity in current culture.

Funding: Clinical Revenue Support

	n(%)	P	PU	CU
Total	232	174(75)	55(24)	3(1)
Topic: Holding Alcohol			29	3
Alcohol Image			13	1
Political			13	0
Religious			2	0
Weapons			2	0
Sexual			0	1
Binge Drinking			0	1

PUB601

CT-Guided Renal Biopsy: A Useful Technique in the Hands of Trained Nephrologists Sadiq Ahmed,[1] Hani Alkhankan.[2] *[1]University of Kentucky, Lexington, KY; [2]University of Kentucky Medical Center, Lexington, KY.*

Background: Percutaneous kidney biopsy has a crucial role in the diagnosis & management of renal diseases. Nephrologists typically perform the biopsies with ultrasound but it is often difficult to biopsy the native kidney of an obese patient. On the other hand the CT-guided renal biopsies are much more precise. As obesity becomes an epidemic it is important for more nephrologists to learn the techniques of CT-guided renal biopsy. Here we share the experience of 42 consecutive CT guided native kidney biopsies performed by nephrologists in our center

Methods: The patient is placed in prone position. With a CT scanner the kidney is localized, overlying skin is marked and the distance to the surface of the kidney is measured. Skin is cleaned with antiseptic solution & draped. The skin and track to the renal surface is anesthetized with 1% Lidocaine. A 15G introducer is inserted up to the surface of the kidney with CT guidance. A 16G Biopsy gun is inserted through the introducer & 2-3 cores are collected. Post-biopsy patient rested for 8 hours with vitals monitored.

Results: All 42 patients had adequate samples. (Table) In 32 out of 42 Patients post-biopsy mean arterial pressure (MAP) remained unchanged compared to pre-biopsy. In 8 out of 42 Patients MAP dropped 10 mmHg post-biopsy and in 2 Patients it dropped 20 mmHg. Out of these 42 Patients 35 (> 83%) had less than 1 g/dl drop of hemoglobin (Hgb) measured on the following morning post biopsy. In 7 Patients Hgb dropped 1-2g/dl & in 1 other Patient it dropped > 2 g/dl. 2 Patients needed PRBC transfusion (4.7%) & 1 of them needed coiling of the bleeding vessel by the interventional radiologist. There was no loss of kidneys, injury to the adjacent organs or death. Average radiation exposure is 350-380 DLP.

Conclusions: CT-guided renal biopsies yield adequate tissue with acceptable complication rate even in morbidly obese patients. More nephrologists are encouraged to learn this technique as obese patients are commonly encountered. The renal fellowship training programs should incorporate performing CT-guided kidney biopsies in training of future nephrologists.

BMI(No. of Patients)	>35(n=12)	30-34.9(n=11)	25-29.9(n=13)	<25(n=6)
Median No. of Glomeruli (min-max)	27(7-45)	20(6-32)	13(4-32)	14(10-35)
MAP drop >10mmhg	3	3	1	1
MAP drop >20 mmhg	0	0	1	1
Hgb Drop <1-2 g/dl	3	1	1	2
Hgb Drop> 2 g/dl	0	1	0	0

PUB602

Awareness of AKI Risk Factors and Perspective toward Its Practice Guideline Numan Alabdan,[3,5] Abdelhameed Mohammed,[2] Rami Bustami,[4] Yousef A. Alrajhi.[1] *[1]KAMC-MNHGA-ksa, Riyadh, Saudi Arabia; [2]KSAU-HS, Riyadh, Saudi Arabia; [3]Pharmaceutical care, King Abdulaziz Medical City, Riyadh, Saudi Arabia; [4]King Saud Bin Abdul-Aziz University for Health Sciences (KSAU-HS), Riyadh, Saudi Arabia; [5]College of Pharmacy, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.*

Background: There is an increasing need for awareness of acute kidney injury (AKI) risk factors and its risk assessment because it is a crucial step towards early detection and possible intervention to prevent or minimize AKI and its associated adverse outcomes. Our aim is to assess awareness, and risk assessment of healthcare professionals regarding AKI risk factors. Also, to assess perspective toward Kidney Disease Improving Global Outcomes (KDIGO) AKI Practice Guidelines.

Methods: Cross sectional survey-based by using online survey program which let us to create a link that can be electronically mail it to a healthcare professionals (physicians and pharmacists) during Dec 2016 – Feb 2017 at King Abdulaziz Medical City (KAMC), Riyadh, Saudi Arabia

Results: 117 physicians and 135 pharmacists completed the survey. The vast majority of respondents were aged ≤ 38 years (78%), 57% were males, and had < 9 years of experience (70%). Among 25 risk factors of AKI and 15 drugs may cause AKI, there was a large variation between respondents in term of awareness of AKI risk factors and the drugs that may cause AKI e.g.96% were aware of nephrotoxic medication whereas 20% agreed on female gender and 92% agreed on aminoglycoside but 47% agreed on ciprofloxacin. In general, significantly higher percentage of physicians identified individual AKI risk factors than pharmacists, however significantly higher percentage of pharmacists identified individual AKI causing drugs than physicians. Variations were observed between the 2 professions and the profession level. Although the majorities face AKI cases in their practice (77%), only half of them do AKI risk assessment, 42% stratify patients' AKI risk according to their offending risk factors, or document AKI as past medical history. 71% agreed that practice guidelines improve patient outcome and 69% thought that these guidelines help standardized care and ensure that patients are treated in a consistent way.only 69 % defined AKI as per KDIGO AKI criteria. 87% did not receive any continuous medical educations hours on AKI.

Conclusions: While the majority of respondents had a positive perspective toward AKI guidelines, a large variation in awareness of AKI risk factors, risk assessment, and the drugs that may cause it was detected. Educational efforts are needed to raise awareness and knowledge to reduce the variation.

PUB603

Formative Learning in Medicine Integrated to the Primary Health Care: Pedagogical Innovation for the Prevention of CKD in Brazil Joao M. Penido,[3] Adriana M. Figueiredo,[3] Maria Goretti M. Penido,[1] Thaís B. Finotti,[2] Allana S. Mamedio,[2] Aline S. Oliveira.[2] *[1]Pediatric Nephrology Unit, Department of Pediatrics, Federal University of Minas Geraisl, Belo Horizonte, Brazil; [2]Universidade Federal de Ouro Preto, Carangola, Brazil; [3]Federal University of Ouro Preto, Ouro Preto, Brazil.*

Background: Health education practices reflect the pillars of Primary Health Care. Health teams need to develop strategies to assist families and communities in understanding mechanisms for health assurance and disease prevention. The aim of this study is to present a educational strategy to prepare medical students and all health team to identify individuals at risk for developing chronic kidney disease (CKD).

Methods: Teachers from medical public school located in southeast of Brazil developed integrated teaching strategies to primary care units for CKD prevention. Those strategies were: health team training, education of the local community on CKD and its risk factors, a survey of the population at risk of becoming ill was conducted, educational videos and booklet for the population and health team on CKD and its risk factors.

Results: Medical students have learned on an integrated and contextualized situation how to clinically to identify kidney disease in the community, focusing on early detection and combining educational practices to promote family health as prevention of disease. Learning was meaningful and collaborative. Also, the medical team learned how to identify individuals at risk to developed chronic kidney disease.

Conclusions: Integrated and collaborative learning between medical students and the health team could be an essential tool for reducing the incidence of CKD in low-income population with difficult access to more developed centers. More studies are necessary to

improve the understanding about how to prevent the CKD and how to identify early risk factors for developing CKD.

Funding: Government Support - Non-U.S.

PUB604

Lifestyle Management for People with CKD Suyuan Peng, Jiasheng Huang, Jiawei He, Yifan Wu. *The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China. Group/Team: Second Clinical College of Guangdong Provincial Hospital of Chinese Medicine.*

Background: Self-management program involves initiative participation in the daily care of their discomforted symptoms, medical treatments, as well as maintainance healthy lifestyles and prevention of progression of diseases for the patients with chronic diseases. Patient engagement and self-management are the cornerstones of optimal chronic disease management. These programs are designed to encourage patients to be expert patients so as to improve outcomes.

Methods: The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, PubMed, Chinese National Knowledge Infrastructure(CNKI), China Biology Medicine disc(CBM), and China Biology Medicine disc and Chinese Scientific Journals full text database (CQVIP) were searched(up to January 2017) for randomized controlled trials (RCTs)assessing the effectiveness of lifestyles related self-management programs for people with chronic kidney disease(CKD) by two independent authors. Meta-analysis was conducted to compare the effects of interventions.

Results: Eight studies (n=585 patients) were included. Across these trials, Self-management programs resulted in a significant difference in glomerular filtration rate(GFR, Mean Difference 2.27, 95% CI 1.90 to 2.65 ml/min; I^2=4%). Compared with usual care only, the intervention resulted in -7.97(95% CI -1.82 to -1.58) and -2.98(95% CI -3.28 to -2.69)mmHg mean changes in systolic and diastolic BPs, with moderate heterogeneity across the included studies(I^2 = 42%, P = 0.18) and a mean change of -2.80(95% CI -3.31 to -2.28)mg/L in C-reactive protein(CRP) with no evidence of heterogeneity (I^2 = 0.0%, P =0.58). Meta-analysis results for total cholesterol(TC), low-density cholesterol(LDL-C) and hemoglobin failed to show a difference between the lifestyle related self-management intervention of CKD and the usual standard care.

Conclusions: To date, there have been very few randomized trials testing Self-management interventions targeting lifestyle care with the goal of delaying the progression of CKD. Those conducted to date have shown a clinically moderate but significant impact, longer follow-up is needed to determine if these findings will translate into delaying the progression of CKD. Suggesting that other strategies, or multi-faceted interventions, may be required to enhance the management of risk factors for patients with CKD in the community.

Funding: Government Support - Non-U.S.

PUB605

Abstract Withdrawn

PUB606

Winning the Fight against a Progressive Hereditary Disease: An 87-Year-Old Patient with ADPKD Freddy R. Malpartida, Abhilash Koratala, Amir Kazory. *University of Florida, Gainesville, FL.*

Background: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common inherited diseases that frequently progresses to end-stage renal disease (ESRD) at a relatively young age. Herein, we present a case of an 87-year old man with ADPKD in whom optimal management of risk factors for progression of chronic kidney disease (CKD) has halted the progression of his disease.

Methods: In 2001, a 71-year old Caucasian man was seen for flank pain after a fall. He was found with hypertension, renal dysfunction, and enlarged kidneys that were filled with innumerable cysts on the ultrasound as well as multiple cysts in the liver. Family history was positive for ADPKD; at least 2 of the siblings were known to have renal cysts (father had died at the age of 55 in an accident). He had no children. At that time, no family members were diagnosed with ESRD but over the next 10 years, one brother and one sister started dialysis. He quit smoking, was advised to increase his water intake to suppress cyst formation, and his hypertension was treated with an angiotensin-converting enzyme inhibitor (ACE-I) and a thiazide diuretic with optimal control. Three years later, he developed a hemorrhagic cyst that could be managed conservatively. Since then, the patient has been doing excellent: although he is 87 years old, the rate of progression of his CKD could be significantly reduced due to optimal management of risk factors (e.g. blood pressure 120-140/60-70, albuminuria 180 mg/g of creatinine, and bicarbonate level 25 mmol/L). His estimated glomerular filtration rate has reached 21 ml/min.

Results:

Conclusions: The severity of renal involvement varies considerably among ADPKD patients implying the importance of factors that are independently associated with worse renal outcomes (e.g. male gender and hypertension). Although clinical symptoms of renal disease can appear at any age, the first symptoms most often appear in the 4th or 5th decade and then progress rapidly; the mean age of ESRD has been reported between 56 and 69. This case represents one of the oldest patients with ADPKD whose CKD progression rate could be successfully reduced, underscoring the importance of modifiable risk factors in management of this hereditary disease that is known to be progressive.

PUB607

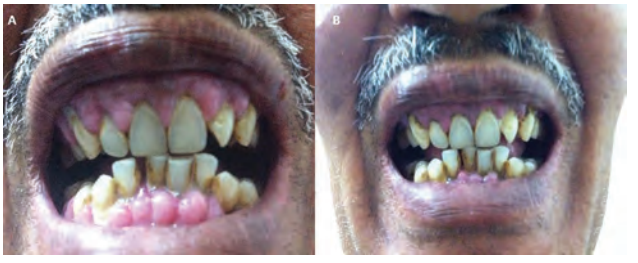
A Rare Side Effect of the Commonly Used Anti-Hypertensive Medication Indirakshi Jamalpur,[1] Abhilash Koratala.[2] *[1]Sri Padmavathi Medical College for Women, Tirupati, India; [2]University of Florida, Gainesville, FL.*

Background: Drug-induced gingival enlargement (DIGE) was first described in patients taking anti-convulsive drug, Phenytoin. The three most common classes of medications implicated are anti-convulsives, calcineurin inhibitors and calcium channel blockers (CCBs). In patients who are on predisposing medications, DIGE should be suspected when they present with enlarged gums.

Methods: A 50-year-old male has presented to the clinic complaining of enlarged gums in the upper and lower front jaws for 2 months. His medical history was significant for hypertension and diabetes mellitus type 2. He denied any fever, bleeding from the gums, loosening of the teeth, use of any prosthesis or dental braces. He did not have any history of dental procedures in the recent past. His medications included enalapril 10mg bid, amlodipine 10mg per day (for 6 months), sitagliptin 100mg per day and glipizide 20mg per day. Oral examination revealed marginal and interdental gingival enlargement, predominantly involving maxillary and mandibular anterior teeth [Figure 1A]. The enlargement was firm, non-tender with no bleeding on probing. Poor dental hygiene was noted. Laboratory tests were unremarkable including a negative HIV test. We diagnosed Amlodipine induced gingival enlargement and the patient showed slight but notable improvement in 4 weeks after switching amlodipine to long acting thiazide diuretic [Figure 1B].

Results:

Conclusions: While DIGE is a well-known side effect of CCBs, the incidence varies among different agents. For example, in a study by Ellis et al., the risk for developing clinically significant gingival enlargement was found to be higher in those treated with nifedipine (6.3%), compared to patients taking either amlodipine (1.7%) or diltiazem (2.2%). Treatment primarily consists of withdrawing the offending agent whenever possible in addition to maintenance of good oral hygiene. It may take from 1 -8 weeks for resolution of gingival overgrowth after discontinuing the drug.



PUB608

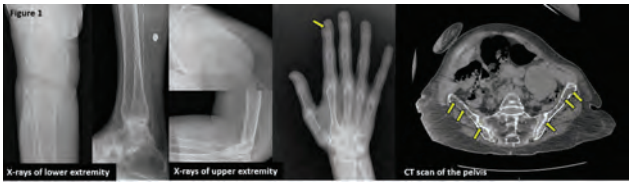
Forgotten, but Not Gone: Bone Manifestations of Secondary Hyperparathyroidism Muhannad Leghrouz, Abhilash Koratala, Amir Kazory. *University of Florida, Gainesville, FL.*

Background: In the current era of early detection of chronic kidney disease and efficient therapeutic options for management of its complications, skeletal manifestations of renal hyperparathyroidism are increasingly rare. Herein, we present a case of secondary hyperparathyroidism that presented with brittle bones and characteristic radiographic changes.

Methods: A 31-year-old female patient presented for evaluation of pain in the left forearm, right hand, right knee, right hip and lower back following a fall sustained 3 days prior to presentation. She had a past medical history notable for ESRD on hemodialysis for the past 15 years, hypertension, diabetes, and congestive heart failure. She was wheelchair bound due to disabling diabetic neuropathy and chronic leg pain. She reported multiple prior fractures that were managed conservatively. Review of the medical records revealed that she had poor compliance with her diet, medications, and dialysis treatments. Labs were significant for marked elevation in serum parathyroid hormone level (1735 pg/mL) as well as hyperphosphatemia and normal serum calcium levels. X-ray images showed generalized severe demineralization of the extremities with the pelvic CT scan revealing presence of diffuse brown tumors [Figure 1]. In addition, she had insufficiency fractures of the extremities that left her incapacitated and had to be managed conservatively due to her poor functional status and ongoing severe hyperparathyroidism. Unfortunately, the patient refused surgical removal of the parathyroid glands and was hence treated with a high dose phosphate binder and a calcimimetic agent together with reinforcement of compliance.

Results:

Conclusions: Our case highlights the importance of metabolic assessment of patients presenting with unexpected bone complications and can be used to raise awareness of the physicians on the extreme cases of mineral bone complications secondary to renal disease that are observed rarely.



PUB609

Silent Hyperoxaluria Contributes to CKD Progression in a Patient with Short Bowel Myriam C. Vela-Ortiz,[2] Li Li,[4] Suzanne Boyle,[3] Suganthi Soundararajan.[1] *[1]Drexe lUniversity, Philadelphia, PA; [2]Nephrology, Drexel University, Philadelphia, PA; [3]Drexel University College of Medicine, Philadelphia, PA; [4]DrexelUiversity Colleg of Medicie, Philadelphia, PA.*

Background: Hyperoxaluria is common in patients with short bowel syndromes due to enhanced colonic resorption of soluble oxalate, which can result in symptomatic calcium-oxalate nephrolithiasis and nephrocalcinosis. There are also reports of subtle calcium oxalate crystal deposition contributing to progressive CKD.

Methods: A 75 year-old white female presented with elevated creatinine. She had a history of left nephrouretectomy and ileal resection secondary to urothelial carcinoma and carcinoid syndrome; HTN; and anxiety/depression. She reported frequent loose stools following meals for which she took diphenoxylate-atropine. She denied flank pain, dysuria, and kidney stones. She limited her liquid intake in order to reduce the frequency of bowel movements. Creatinine was 1.4 mg/dl prior to nephrouretectomy and gradually rose to 2.5 mg/dl over 4 years. Renal ultrasound revealed a 9.6 cm right kidney with normal echotexture and no nephrolithiasis. The left renal fossa was replaced by scar tissue. Kidney biopsy had hypertensive glomerular changes with moderate interstitial fibrosis and tubular atrophy. Few tubular oxalate crystals were present with focal extravasation into the interstitium with granulomatous inflammation. No immune complexes were detected. Discontinuation of a PPI, chlorthalidone, and fluoxetine and addition of a short course of steroids for the nephritis failed to improve the creatinine. A 24-hour urine assessment showed hypocalciuria; hyperoxaluria (63 mg/day; normal < 45); hypocitraturia; urine pH of 5.7; volume of 1.4 L.

Results:

Conclusions: Chronic calcium oxalate deposition in the tublointerstitium can lead to nephritis. While this patient's progressive CKD was multi-factorial, including hyperfiltration of a solitary kidney and HTN, the calcium oxalate crystal deposition was likely contributing. Despite a significantly reduced GFR, hyperoxaluria was evident on 24 hour urine collection. Due to the absence of symptomatic and radiologic nephrolithiasis, interstitial calcium oxalate deposition might otherwise be excluded from the differential diagnosis in this setting. This underscores that with ileal resection and CKD, hyperoxaluria should be considered. Early implementation of hyperoxaluric therapy might mitigate CKD progression

PUB610

Water Is Toxic Kartik Kalra,[1] Nabil Ghani,[1] Simranjit S. Randhawa.[2] *[1]Internal Medicine, Saint Peters University Hospital, New Brunswick, NJ; [2]Sir Ganga Ram Hospital, New Delhi, India.*

Background: Water intoxication can occur in a variety of clinical settings but is more commonly associated with chronic schizophrenics. The condition may go unrecognized in the initial stages when the patient may have symptoms of confusion, syncope and changes in psychotic symptoms. Early detection is crucial to prevent severe hyponatremia, which can be life-threatening. This is a case of a young schizophrenic male who had hyponatremia secondary to Psychogenic Polydipsia (PPD).

Methods: A 38 year old male with a 5 year history of seizure disorder currently on Levetiracetam/Oxcarbazepine and Citalopram, past history of schizophrenia admitted after syncope while micturition and mild confusion. Vitals and Physical examination on arrival in ER were not suggestive of volume depletion. Further questioning revealed patient had been drinking >5 liters water/day for a week. Labs revealed serum sodium(Na)-123 mEq/L, Creatinine-0.7 mg/dL, Serum osmolality(osm)-275 mOSm/kg, Urine osm-106 mOsm/kg, and Urine Na-18mEq/L. Given his labs, clinical history, and physical exam findings, hyponatremia was attributed to PPD. Water restriction was started and sodium corrected to 134mEq/L within 8 hrs. Patient was given DDAVP and D5W to reverse rapid correction. On day 2 sodium was stable at 134mEq/L, and patient was discharged home with education about need to avoid excess water.

Results:

Conclusions: PPD occurs in 25% of patients with schizophrenia. Pathophysiology is complex and multifactorial - malfunction of the hypothalamic thirst center likely contributes. It usually occurs in three phases- Beginning with polydipsia and polyuria, followed by hyponatremia (water is retained as the kidneys fail to excrete the excess fluid) and finally water intoxication leading to symptoms secondary to movement of fluid into brain cells. Symptoms range from confusion, vomiting, syncope and can eventually lead to seizures, coma and death. Differentials include other cause of hyponatremia especially SIADH. PPD usually has low urine osmolality in contrast to SIADH (Urine osm>100). Water restriction remains main stay of treatment. In severe cases, however, hypertonic saline solution is recommended. Sodium should be closely followed and rapid correction may have to be reversed with DDAVP to prevent osmotic demyelination syndrome. PPD thus is an unusual cause of hyponatremia that may go unnoticed without an appropriate clinical history that carries high mortality.

PUB611

Granulomatous Interstitial Nephritis in Diet-Controlled Crohn's Disease Kabir O. Olaniran,[2] Ivy A. Rosales,[2] Astrid Weins,[1] Nwamaka D. Eneanya.[2] *[1]Brigham & Women's Hospital, Boston, MA; [2]Massachusetts General Hospital, Boston, MA.*

Background: Crohn's disease (CD) is a chronic recurrent inflammatory condition with rare renal involvement. CD associated granulomatous interstitial nephritis (GIN) is even more rare and has only been described in a few case series and reports. CD associated GIN typically occurs in the setting of recent mesalamine exposure, new onset CD, or exacerbation of existing CD. We report a case of GIN due to CD in the absence of clinically apparent GI symptoms.

Methods: A 19-year-old male with a history of biopsy-proven CD and hypertension (HTN), both well controlled with dietary modifications, presented for a second opinion regarding acute kidney injury (AKI). One month prior, his serum creatinine (Cr) had increased from a baseline of 1.3mg/dL to 2.6mg/dL. He did not have recent nephrotoxin exposure, new or chronic medication use, chronic cough or acute illnesses. His physical exam was unremarkable, he was asymptomatic and normotensive (not on medications). Urine studies showed microscopic hematuria (1+) and microalbuminuria (48.7mg/g). Serum calcium, sedimentation rate and calcitriol levels were normal. Renal imaging with Doppler analysis was unremarkable. Serologic work-up for a nephritic process was negative. The kidney biopsy showed diffuse non-caseating granulomatous inflammation with no immune complex deposition or microorganisms. Vessels were unremarkable. Based on these findings, we determined that his GIN was due to CD. He received pulse steroids and his serum Cr decreased to 2.04 mg/dL. Due to steroid dependence, adalimumab was initiated. Steroids were tapered off and his serum Cr decreased to 1.6mg/dL after 5 months on adalimumab.

Results:

Conclusions: This case emphasizes the need to recognize and further explore the association between CD and GIN given the potential long term adverse renal outcomes if treatment is delayed. Early nephrology consultation may be advisable in CD patients with mild renal dysfunction or abnormal urine studies regardless of CD symptom control.

PUB612

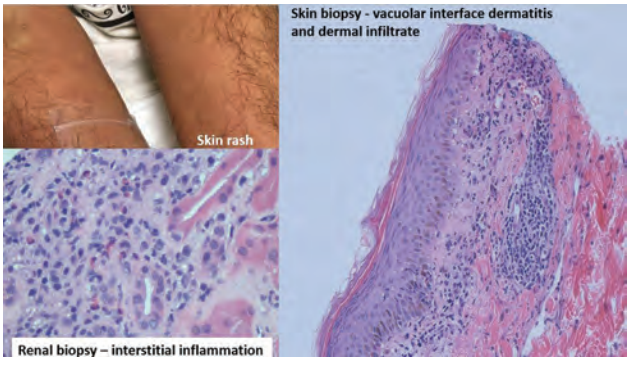
Cefepime Induced DRESS Syndrome without Eosinophilia S. Irfan Qadri, Xu Zeng, Abhilash Koratala. *University of Florida, Gainesville, FL.*

Background: Approximately 60-70% cases of acute interstitial nephritis (AIN) are drug-induced. Multiple agents from different drug classes can cause AIN and the clinical presentation and laboratory findings vary based on the class of drug. We report a case of AKI and drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome without eosinophilia, associated with cefepime.

Methods: A 62-year-old man with poorly controlled diabetes mellitus developed osteomyelitis of the foot and was prescribed intravenous antibiotic therapy with vancomycin 1g every 12 hours and cefepime 6g continuous infusion for an intended duration of 6 weeks. The patient tolerated this regimen well until a few days prior to the end of therapy. He presented to the hospital with fatigue, anorexia, morbilliform rash and fever. Labs demonstrated AKI with a SCr of 3.6 mg/dL (baseline 0.8), transaminitis and leukocytosis. Peripheral smear revealed vacuolated neutrophils and atypical lymphocytes, but no eosinophilia. Urine microscopy revealed multiple WBC casts. He was diagnosed with DRESS. Serum complements were normal and was started on empiric steroid therapy with prednisone 1mg/kg/day. SCr continued to worsen requiring dialysis. After 10 days of prednisone therapy, the patient's renal function began to improve and he is currently off dialysis. Renal biopsy was consistent with AIN and skin biopsy with DRESS [Figure 1].

Results:

Conclusions: DRESS is an idiosyncratic hypersensitivity response to drugs defined by presence of at least 3 of the following findings: cutaneous eruption, fever, lymphadenopathy, systemic symptoms involving internal organs, hematologic abnormalities (atypical lymphocytes, eosinophilia). Cefepime is a rare cause of DRESS syndrome and can present without eosinophilia. Although there are no clear guidelines regarding dose and duration of steroid therapy, early initiation of steroid therapy has been shown to hasten recovery of renal function in drug-induced AIN.



PUB613

Adult Diagnosed Tuberous Sclerosis Complex with Renal Cell Carcinoma Amit Reddy,[2] John C. Henegan,[1] Teja Poosarla.[1] *[1]Hematology/ Oncology, University of Mississippi Medical Center, Jackson, MS; [2]Pathology, University of Mississippi Medical Center, Jackson, MS.*

Background: Tuberous sclerosis complex (TSC) is a rare autosomal dominant connective tissue disorder involving multiple systems that affects roughly 1 in 10,000 live births. Approximately 2-4% of people with TSC are diagnosed with renal cell carcinoma (RCC), typically with an onset 20 to 30 years earlier than in the general population. The diagnosis of TSC is established by either clinical findings (i.e. physical examination and/or radiological imaging) or the identification of a pathogenic variant in either *TSC1* or *TSC2*. The presentation of the disease varies substantially and because of this the diagnosis of TSC can be missed during childhood. Here we present a case of TSC diagnosed in an adult.

Methods: A 56-year-old African American female with history of end stage renal disease on intermittent hemodialysis, coronary artery disease, and RCC with a right nephrectomy 14 years earlier presented for a routine follow up. Physical examination showed multiple small lesions on her bilateral cheeks consistent with angiofibromas. CT scan showed multiple bilateral 2-3 mm scattered stable pulmonary nodules, evidence of a prior right nephrectomy, stable extensive mixed density masses in the left kidney, and persistent edematous changes with soft tissue infiltration into the left renal pelvis and proximal ureter with enlargement of a left retroperitoneal lymph node. Previous magnetic resonance imaging of the brain revealed a subependymal nodule. The presence of both the subependymal nodule and angiofibromas are major criteria for TSC, confirming its clinical diagnosis. Subsequently, the patient was referred for an echocardiogram and ophthalmic evaluation based on this new diagnosis.

Results:

Conclusions: Certain findings should prompt testing for hereditary syndromes when assessing patients with RCC, including bilateral/multifocal RCC, family history of RCC, certain renal tumor histologies, and clinical manifestations of known hereditary RCC syndromes. Clinicians should also consider hereditary RCC syndromes such as TSC in all patients with RCC diagnosed at an age less than 47 years-old, like the case presented. Many hereditary RCC syndromes have a subtle presentation which may delay their diagnosis. Identifying hereditary RCC syndromes is important as their diagnosis may lead to downstream testing for associated clinical manifestations as well as cascade family testing with appropriate genetic counseling.

PUB614

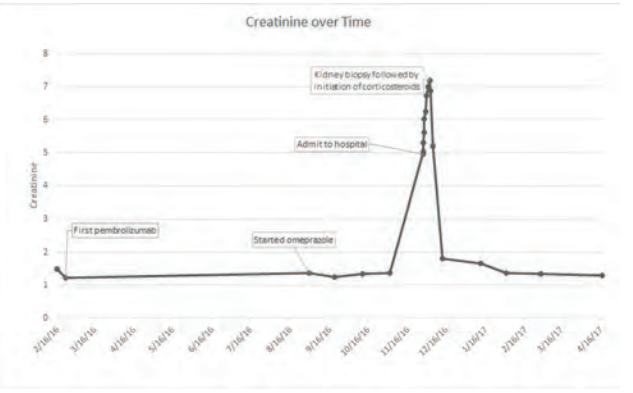
Acute Interstitial Nephritis in a Patient with Urothelial Carcinoma on Pembrolizumab: A Programmed Cell Death 1 Inhibitor Anthony N. Muiru, Patrick Ahearn, Thuy M. Nguyen, Santhi Voora, Diana Mina, Christopher A. Carlos, Yuenting D. Kwong, Terence W. Friedlander, Lawrence Fong, Meyeon Park. *UCSF, San Francisco, CA. Group/Team: UCSF First Year Fellows.*

Background: Pembrolizumab, a PD-1 inhibitor was recently approved for all solid tumors with a specific genetic biomarker. There are several case reports of PD-1 inhibitors induced acute interstitial nephritis (AIN) in the setting of lung, melanoma, and pancreatic cancers. We present a patient with AIN while being treated with pembrolizumab for urothelial carcinoma.

Methods: A 61-year-old man with a history of atrophic left kidney, CKD 3a, and urothelial carcinoma developed AKI. Nine months after starting Pembrolizumab serum creatinine increased from 1.3 mg/dl to 5 mg/dl (figure). His 14th cycle was held due to vomiting, diarrhea, and AKI, and he was hospitalized. Examination was notable for BP of 103/59 mm hg, HR 59 beats/min, and dry mucous membranes. Urine sediment showed non-dysmorphic RBCs, clumps of WBC, and no casts. Renal ultrasound showed mild right hydronephrosis and atrophic left kidney. A Foley catheter was placed for decompression. He was volume resuscitated, omeprazole and losartan were discontinued, but creatinine continued to rise. After discussion regarding the higher than typical risk, a kidney biopsy was performed. The biopsy revealed AIN. Corticosteroids were started with improvement in serum creatinine (figure).

Results:

Conclusions: Although rare, treatment with PD-1 inhibitors has been associated with AIN. Similar to previous case reports, our patient was also taking a second medication associated with AIN, omeprazole. Researchers hypothesize that PD-1 inhibition may lower the threshold for concomitant immunogenic agents like proton pump inhibitors to cause AIN. Despite high risk, biopsy was especially necessary prior to treatment of AIN in setting of chronic sterile pyuria related to urothelial carcinoma. Steroids and discontinuation of the PD-1 inhibitor have been shown to be effective in management of PD-1 induced AIN.



Creatinine prior to, during, and after hospitalization

PUB615

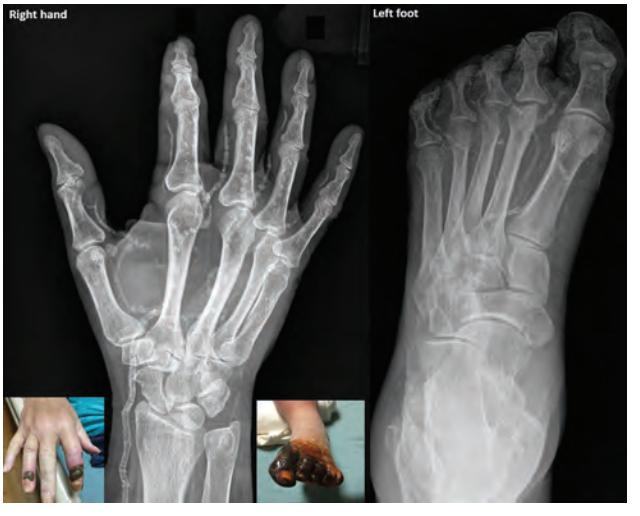
Calcified Vessels: A Disastrous Complication of ESRD S. Irfan Qadri, Abhilash Koratala. *University of Florida, Gainesville, FL.*

Background: Calciphylaxis is a clinical syndrome of arterial calcification with resultant tissue necrosis, most commonly seen in patients with end-stage renal disease (ESRD) on dialysis. This condition carries a high mortality rate mainly due to infection. Helpful interventions include adequate dialytic therapy, medical management of hyperparathyroidism, hyperphosphatemia and intravenous sodium thiosulfate therapy. Herein we present a case with extensive arterial calcification associated with calciphylaxis.

Methods: A 54-year-old woman with obesity, diabetes mellitus and ESRD on hemodialysis presented with exquisitely painful lesions on her extremities. Examination revealed necrotic lesions at the tips of right index and ring fingers and toes, with surrounding inflammation. There was no obvious infection. Labs demonstrated serum calcium of 8.3 mg/dL (8.4-10.2), albumin 3.0 g/dL (3.5-5.0), phosphorus 7.7 mg/dL (2.7-4.5), and parathyroid-hormone (PTH) 348 pg/ml (150-300 for ESRD). Her PTH was apparently 'very high' several months ago. X-rays of the hand and foot revealed extensive arterial calcifications suggestive of calciphylaxis [Figure 1].

Results:

Conclusions: Risk factors for calciphylaxis include high calcium-phosphate product, elevated PTH, hypoalbuminemia, diabetes, obesity, warfarin use, female sex and protein C or S deficiency. Most lesions occur in legs though uncommon sites such as breast have been reported. It has been proposed that calciphylaxis and vascular calcification are a continuum of extra-skeletal osteogenesis and the clinical manifestations depend upon the location of the affected artery. Our patient was treated with sodium thiosulfate and intensification of dialysis regimen which resulted in modest improvement of the lesions.



PUB616

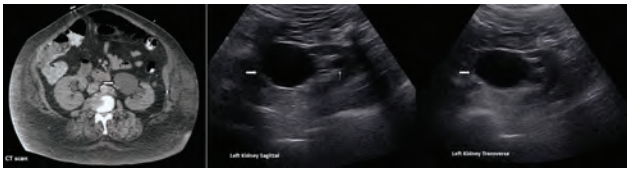
Not All That Is Black on Kidney Ultrasound Is Hydronephrosis Abhilash Koratala,[2] Deepti Bhattacharya.[1] *[1]University of Florida, Gainesville, FL; [2]Nephrology, Hypertension and Renal Transplantation, University of Florida, Gainesville, FL.*

Background: As point-of-care renal ultrasound is being increasingly performed by Nephrologists, it is important to have a thorough understanding of renal anatomy and the sonographic appearance of normal kidneys, including normal anatomical variants.

Methods: A 73-year-old woman with hypertension and heart failure has presented with generalized weakness for about 2 weeks leading to a fall at home. She was found to have severe hypercalcemia with a serum calcium of 16 mg/dl and acute kidney injury. CT scan of the chest was obtained to exclude malignancy. In addition to multiple pulmonary nodules, the upper abdominal slices of the scan demonstrated fullness of the left renal pelvis suspicious for hydronephrosis. Renal ultrasound was obtained to evaluate this finding, which demonstrated a large hypoechoic mass just outside the renal sinus but with no distension of the calyces or the ureter [Figure]. This finding was consistent with extrarenal pelvis, which is often confused with hydronephrosis.

Results:

Conclusions: An extrarenal pelvis is a normal anatomical variant that is predominantly outside the renal sinus and is larger and more distensible than an intrarenal pelvis that is surrounded by sinus fat. Extrarenal pelvis can easily be misinterpreted as hydronephrosis, especially on a quick bedside exam as it appears as a black mass. Close attention to detail can help differentiate between these two conditions. Hydronephrosis appears as branching, 'interconnected' areas of decreased echogenicity that show sonographic evidence of fluid. As the obstruction continues, renal parenchyma becomes compressed with loss of corticomedullary differentiation. On the other hand, extrarenal pelvis is not associated with dilated calyces, parenchymal thinning or hydroureter as in our case. In the figure, a medullary pyramid (line arrow) can be seen just above the central echogenic portion of the kidney suggestive of preserved corticomedullary differentiation and absence of compression. While extrarenal pelvis is asymptomatic in most cases, complications such as infection and stone formation have been reported.



PUB617

Escitalopram Induced Hyponatremia in a Young Post-Surgical Patient: Case Report Rommel P. Bataclan. *Medicine, University of the East Ramon Magsaysay Medical Center, Quezon City, Philippines.*

Background: Hyponatremia is a rare adverse effect of Selective Serotonin Reuptake Inhibitors (SSRI). These are medications given to individuals with Depressive Disorders and Panic Disorders. This presentation highlights the association of hyponatremia and use of Escitalopram in a post-surgical young patient without medical co-morbidities.

Methods: Patient is a 28-year old male who was admitted due to abdominal surgery from injuries incurred in a vehicular accident. Patient had panic attacks and was given Escitalopram. He was referred post-surgical due to restlessness and change of sensorium. Physical exam reveals a pale-looking patient with multiple abrasions and hematoma. He was drowsy, unable to respond from verbal cues. No focal deficits were noted. Serum Sodium was 121 mmol/l, Serum Osmolality 265 mOsm/kg, Urine Sodium 56 mmol/l and Urine Osmolality was 210 mOsm/kg. Rest of bloodworks and Cranial CT Scan were unremarkable. Escitalopram was discontinued, advised fluid restriction and 0.9% saline solution intravenously was given. Serum Osmolality was noted to be 265 mOsm/kg, Urine Sodium was 56mmol/l and Urine Osmolality was 210 mOsm/kg. On the initial 24 hours Escitalopram was discontinued, Serum Sodium was monitored three times, with values of 122, 124 & 125 mmol/l. Serum Sodium was normal (135 mmol/l), 72 hours after Escitalopram was discontinued. Diazepam was started as the anxiolytic drug, and patient's subsequent course was unremarkable and discharged on 15th hospital day.

Results:

Conclusions: SSRI-induced hyponatremia is attributed to a syndrome of inappropriate antidiuretic hormone (SIADH) secretion induced by a non-osmotic release of anti- diuretic hormone. Risk factors for SSRI-induced SIADH include advanced age, female gender, concomitant diuretics, hyperkalemia, baseline hyponatremia, and lower body mass index, all of which are not present in our patient. The only definitive treatment for drug-induced SIADH is removal of the offending agent. Most cases resolve promptly upon drug discontinuation. This case, together with the other previous reports highlight the need to monitor serum sodium and other electrolytes when anti-psychotic medications is started. Monitoring of serum sodium concentrations at baseline and 1 to 2 weeks after initiation of SSRIs may be warranted in individuals at risk of SIADH.

PUB618

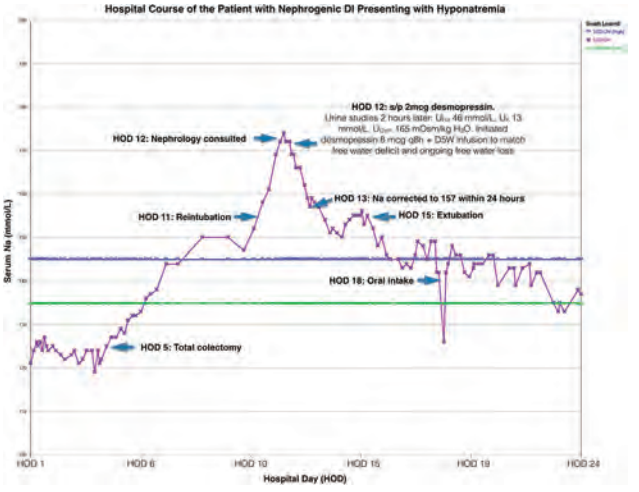
Hypovolemic Hyponatremia Masking Nephrogenic Diabetes Insipidus (DI) Maria Clarissa Tio,[1] Jiten Patel.[2] [1]*Department of Medicine, University of Texas Southwestern Medical Center, Dallas, TX;* [2]*Division of Nephrology, University of Texas Southwestern Medical Center, Dallas, TX.*

Background: DI typically presents with hypernatremia and polyuria. We report a unique case of a patient with an unknown history of DI presenting with hyponatremia in the setting of abdominal compartment syndrome and septic shock.

Methods: A 50-year old white female with bipolar disorder, remotely treated with lithium, presented with a week of bloody diarrhea. She was found to be in severe septic shock from *C. difficile* colitis and AKI. On admission: Na 121 mmol/L, Cr 4.63 mg/dL, Serum osmolality 280 mOsm/kg H_2O, Urine Na (U_{Na}) <20 mmol/L, Urine osmolality (U_{Osm}) 298 mOsm/kg H_2O. She developed oliguria, acidemia, increasing pressor requirements, and respiratory failure. Bladder pressure was 21 cm H_2O. She underwent emergent total colectomy on hospital day (HOD) 5. Post-op, her renal function improved and urine output (UOP) increased to 4ml/kg/hr. Serum Na rose from 130s to 152 mmol/L and was managed with fluids and free water. On HOD 11, she aspirated and was reintubated. Serum Na increased from 152 to 174 mmol/L within 24 hours with concurrent 8L of UOP. Cr 1.14 mg/dL, U_{Na} 32 mmol/L, U_K 6 mmol/L, Uosm 107 mOsm/kg H_2O. Desmopressin (2 mcg IV) was given, 2 hours later: U_{Na} 46 mmol/L, U_K 13 mmol/L, U_{Osm} 165 mOsm/kg H_2O. Nephrogenic DI was diagnosed. Given the acute rise in Na, we lowered it equally rapidly to 157 with 5% dextrose (D5W) and supraphysiologic desmopressin (4 mcg q8h). Daily U_{Osm} measurements thereafter ranged from 120-180 mOsm/kg H_2O. The patient was successfully extubated on HOD 15 and tolerated oral intake on HOD 18. On HOD 20, serum Na was 142 mmol/L, desmopressin was stopped, and D5W was weaned off. Hydrochlorothiazide was initiated.

Results:

Conclusions: We report a case of nephrogenic DI presenting with hyponatremia from abdominal compartment syndrome and septic shock. Subsequent abdominal decompression, resolution of sepsis, and eventual loss of free water access from reintubation unmasked this previously unknown history of nephrogenic DI.



PUB619

Granulomatosis with Polyangiitis (GPA) Presenting as Renal Vasculitis in a Patient with Crohn's Disease Judi M. Graham,[1,2] Melissa S. Nataatmadja,[1,2] Linda G. DeLuca.[2] [1]*Nephrology, University of British Columbia, Vancouver, BC, Canada;* [2]*Nephrology, St Paul's Hospital, Vancouver, BC, Canada.*

Background: Anti-neutrophil cytoplasmic antibodies (ANCA), most commonly perinuclear ANCA (P-ANCA), is associated with inflammatory bowel disease (IBD), usually without evidence of systemic vasculitis. We describe a case of GPA with Crohn's disease (CD) presenting as rapidly progressive glomerulonephritis.

Methods:

Results: A 51 year old man presented with fever and headache. Past history included chronic kidney disease with creatinine 120umol/L and normal urinalysis 6 months prior. CD was diagnosed 30 years earlier but had been quiescent for many years. On presentation, blood pressure was 187/87mmHg, creatinine 454umol/L, urine albumin/creatinine ratio (ACR) 66mg/mmol and dysmorphic erythrocytes seen in urine. C-ANCA was 160 and PR3 115U. Renal biopsy showed pauci-immune proliferative glomerulonephritis with a cellular crescent. Treatment commenced with intravenous then oral steroids, and oral cyclophosphamide- later replaced by rituximab due to bone marrow toxicity. Ten weeks later, creatinine was 197umol/L, PR3 10U, ACR 4.6mg/mmol with no urine erythrocytes.

Conclusions: CD, a granulomatous disease of the gut, may manifest extraintestinally as musculoskeletal, ocular, mucocutaneous and lung disease. In GPA, granulomas typically form in the respiratory tract and kidneys but involve the gut in 20-30% of cases. Thus, extra-intestinal CD may masquerade as GPA, and extra-pulmonary GPA as CD. ANCA, without evidence of ANCA-associated vasculitis (AAV), is well described in IBD however rare cases of these diseases occurring together have been reported; mostly with pulmonary involvement. One group reported coexistence of eosinophilic granulomatosis with polyangiitis (EGPA) with UC, and GPA with CD, but no cases of EGPA with CD, or GPA with UC. As with other autoimmune diseases, they may coexist in "clusters", thus there may be a yet unknown immune or genetic predisposition in affected individuals. Data suggests that EGPA and UC are both mediated by Th2. Conversely, both GPA and CKD are considered granulomatous diseases and primarily mediated by Th1. Future research may reveal more about the relationship of these diseases and could provide opportunities for gene based therapy. Currently, immunosuppression is the mainstay of therapy in both CD and AAV, however differentiating the two diseases is important to guide treatment, prognosis and risk of relapse.

PUB620

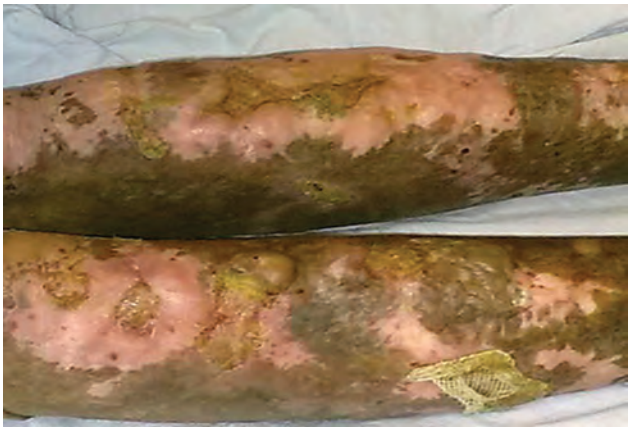
Diffuse Membranoproliferative Glomerulonephritis with Focal Sclerosis and Renal Amyloidosis in an Adult Male with Autosomal Dominant Dystrophic Epidermolysis Bullosa Karim M. Soliman,[1,2] David W. Ploth.[1] *[1]Medical University of South Carolina, Charleston, SC; [2]Nephrology, Cairo University, Cairo, Egypt.*

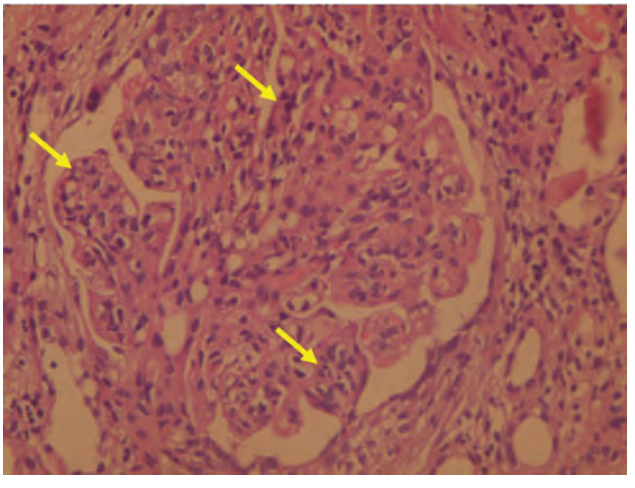
Background: Previous reports of glomerular disease in adult patients with autosomal dominant dystrophic epidermolysis bullosa are limited and include post-infectious glomerulonephritis, IgA nephropathy, amyloidosis and leukocytoclastic vasculitis. To our knowledge, membranoproliferative glomerulonephritis (MPGN) has not been described.

Methods: A 39 year old male with autosomal dominant dystrophic epidermolysis bullosa, presented with leg swelling of one week duration. There was no other significant past medical history. Physical examination was remarkable for scars and erosions over all body areas, all extremities with blisters and ulcers, bilateral lower extremity edema (Fig.1) and absent finger and toenails. Serum creatinine (Cr) was 0.9 mg/dl, albumin 1.3 gm/dL, and urine protein excretion 3.7 gm/24hr. Viral markers (Hepatitis B, C and HIV), C3, C4 and immune profile were all negative. Renal ultrasound and echocardiogram were normal. Renal biopsy showed fourteen glomeruli, all with proliferation of mesangial and endothelial cells and expansion of the mesangial matrix (arrows in Fig.2), focal segmental sclerosis, and amorphous homogeneous eosinophilic deposits which were positive with Congo red staining.

Results:

Conclusions: We recommend physicians consider the possibility of MPGN and secondary amyloidosis in patients with epidermolysis bullosa especially with the availability of new treatment modalities for the latter.





PUB621

Steroid-Free Regimen for Primary Membranous Nephropathy with High Antibody Titer Roxana A. Jurubita, Bogdan Obrisca, Bogdan M. Sorohan, Vlad T. Berbecar, Andreea Andronesi, Gener Ismail. *Fundeni Clinical Institute, Bucharest, Romania.*

Background: Primary membranous nephropathy (pMN) remains a leading cause of adult nephrotic syndrome (NS). Multidrug regimens in patients with contraindications to corticosteroid therapy have never been evaluated. Additionally, patients with high antibody titer are less likely to obtain a spontaneous remission and would benefit from early immunosuppressive therapy (IS). Therefore, we report a case of pMN treated with cyclophosphamide and low-dose cyclosporine.

Methods: A 34-years old male is admitted with a relapse of the NS. His past medical history included pMN diagnosed 2 years ago and bipolar disorder that precluded the use of corticosteroids. Therefore the patient was started on cyclosporine (5 mg/kg/day), while being on adequate RAS blockade, and the clinical course was fluctuating with partial remissions and relapses of the NS (proteinuria levels between 3 and 10 g/day). However after 18 months of therapy the patient voluntarily stopped the cyclosporine and soon after the NS relapsed. At the time of admission he presented edemas, normal BP, while the laboratory results showed hypoalbuminemia (1,9 g/dl), proteinuria 8g/day and eGFR of 87 ml/min. The patient was started on monthly cyclophosphamide pulse-therapy (0.75 g/m2) and low-dose cyclosporine (100 mg/d), while being on adequate RAS blockade for the past 18 months. After 2 months of multidrug regimen, proteinuria and antibody titer significantly decreased to 1,3 g/day and 210 IU/ml, respectively. Subsequent check-ups are shown in the table.

Results:

Conclusions: The podocyte targeted effect of low-dose cyclosporine (rapid decline of proteinuria) in addition to the immunosuppressive effect of cyclophosphamide (decreased antibody titer) is associated with a rapid response in this particular patient. This multidrug regimen could be useful in patients with contraindications to corticosteroids and high antibody titer, but it needs to be validated in large clinical trials.

Patient Follow-up

Variable	Baseline	Month 1	Month 2	Month 3
eGFR (ml/min)	97	70	102	97
Serum Albumin (g/dl)	1.9	3.3	3.3	3.6
Proteinuria (g/day)	8	3.84	1.3	1.2
Anti-PLA2R antibody titer (IU/ml)	1041	770	210	198
Cyclosporine level (ng/ml)	30	26	28	21

PUB622

Oxalate Nephropathy Leading to ESRD Following Roux-en-Y Gastric Bypass Erika Drury, Ali Poyan-Mehr. *BIDMC- Division of Nephrology, Boston, MA.*

Background: Hyperoxaluria is a common and underappreciated complication of gastro-intestinal bypass surgeries. Calcium oxalate nephropathy is known to occur following jejunoilial bypass, and case series have reported oxalate nephropathy after Roux-en-Y gastric bypass. Here we report a case of calcium oxalate nephropathy occurring after Roux-en-Y gastric bypass for gastric adenocarcinoma leading to severe renal failure and end stage renal disease and outline potential strategies for prevention of future events.

Methods: An 83-year-old male with hypertension, type 2 diabetes mellitus, systolic heart failure (EF 45%), stage III CKD, and gastric adenocarcinoma status-post gastrectomy and Roux-en-Y esophagojejunostomy four months prior was admitted to our hospital with acute renal failure. He described new weakness, dysphagia, and loose stool. His creatinine was 9.3 mg/dL and arterial pH was 7.07. Renal ultrasound demonstrated a left-sided 1.3 cm non-obstructing stone. Urinary sediment showed rare renal tubular epithelial cells and granular casts. ANA, ANCA, C3, C4, SPEP, and UPEP were normal. He rapidly developed oliguria and uremia and was initiated on hemodialysis. Renal biopsy demonstrated advanced interstitial fibrosis, tubular atrophy, and calcium oxalate and calcium phosphate deposition. He never recovered renal function and was discharged on dialysis.

Results:

Conclusions: While hyperoxaluria is known to occur after gastric bypass, oxalate nephropathy and severe renal failure are less frequently reported. Our patient developed ESRD four months after surgery. Prior series have reported acute renal failure developing at a mean of thirty-three weeks after surgery. One study reported progression to ESRD within three months of identification of renal failure in 72% of patients. We identified several factors that may have contributed to this rapid and severe course including underlying CKD, diuretic use, post-operative AKI, diarrhea, and poor oral intake. In light of this case and prior reports, we propose the following considerations for patients undergoing gastric bypass: a) heightened clinical suspicion post-operatively, b) patient and provider education on the risks of hyperoxaluria and oxalate nephropathy, particularly in states of volume depletion, c) close monitoring of volume status and post-operative renal function, and d) early referral to nephrology, particularly for at-risk patients.

PUB623

Idiopathic Acute Renal Infarction Sandheep Venkataraman, Shruti Polu, Lin N. Lwin. *Montefiore Medical Center, Bronx, NY.*

Background: Renal infarction (RI) is a rare and under-diagnosed condition resulting from a sudden disruption of blood flow in the renal artery. Estimated incidence is about 0.004%– 0.007%. We report a case of RI presenting with no identifiable cause.

Methods: A 51 year old man with a history of hypertension, diabetes, and nephrolithiasis, presented with sudden onset, severe left flank pain radiating to the left groin. He had never smoked/used illicit drugs. He was afebrile and hypertensive(181/104 mm Hg) on presentation. EKG was normal. Labs: leukocytosis, high LDH(730 U/L) and CRP(33 mg/L). Urinalysis showed proteinuria and small blood. CT abdomen with contrast showed a region of non-enhancement in the left upper renal pole, suggestive of infarction. No aorto-renal vascular pathology was noted. Trans-esophageal echo was normal. Holter monitoring was uneventful. He had severe uncontrolled hypertension, requiring 4 medications including a calcium channel blocker. He was subsequently discharged on oral anti-coagulation.

Results:

Conclusions: RI usually occurs between the 6th and 8th decades of life. It commonly presents as abdominal/flank pain, nausea and vomiting, with leukocytosis, elevated LDH, and microscopic hematuria. Severe and difficult-to-control hypertension is often seen in these patients, which is thought to be renin-dependent due to renal ischemia. Most patients have a history of prior cardio-embolic events such as atrial fibrillation(AF), valvular heart disease, ventricular aneurysm, endocarditis, and dilated cardiomyopathy. AF is the most common risk factor, found in about 64% cases. Other possible etiologies include vasculitis, coagulopathies, aorto-renal vascular pathology, and trauma. However, the cause may remain undetermined in up to 29% of the cases. Clinical diagnosis of RI is difficult due to its non-specific presentation. Ultrasound is very low yield. Contrast-enhanced CT is the gold standard, which shows a wedge-shaped area of low attenuation within an otherwise normal appearing kidney. No clear treatment strategy for RI has yet been established. The current practice is to anticoagulate these patients similar to a patient with AF. However, the duration and mortality benefit is unknown given the scarcity of data available about this condition. In conclusion, RI must be considered in a patient with acute flank pain, and high levels of LDH, especially in the presence of risk factors for thromboembolic events.

PUB624

Malignant Hypertension/Thrombotic Microangiopathy: The Basis for Irretrievable Renal Failure in a Patient with SLE Brian R. Stotter,[1,2] Lisa Teot,[4] Ghaleb H. Daouk,[1] Seymour Rosen.[3,4] *[1]Div of Nephrology, Boston Children's Hospital, Harvard Medical School, Boston, MA; [2]Div of Nephrology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; [3]Dept of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; [4]Dept of Pathology, Boston Children's Hospital, Harvard Medical School, Boston, MA.*

Background: Renal vascular abnormalities are common in systemic lupus erythematosus (SLE) nephritis, but not part of the ISN/RPS 2003 classification. We present a case of SLE nephritis in a girl whose renal biopsies showed endocapillary proliferative glomerulonephritis, glomerular ischemia, and evolving vascular injury from acute phase intimal edema to occlusive intimal fibrous obliteration. These changes reflect injury from severe malignant hypertension/TMA.

Methods: A 16-year-old girl of African ancestry was admitted with arthralgias, blurry vision, edema, and BPs in the 190s/110s. Ophthalmologic exam revealed hypertensive retinopathy. She had anemia, thrombocytopenia, low C3 and C4, elevated anti-dsDNA titers, and AKI with sCr 1.7 mg/dL. She received steroids, MMF, and Cytoxan for induction. After two weeks, sCr peaked at 5.3 mg/dL and she started HD. Her first renal biopsy showed endocapillary proliferative glomerulonephritis with low level immune complex (IC) deposition consistent with SLE nephritis, but with extensive glomerular ischemia, intimal edema of the vasculature, and myofibroblastic proliferation in the interlobular arteries **(Figure A)**, consistent with malignant hypertension/TMA. A repeat biopsy after a course of eculizumab had similar glomerulonephritis, but the arterial changes became chronic and occlusive **(Figure B)**. Her BPs remained poorly controlled, despite maximizing five antihypertensive agents, and she underwent bilateral nephrectomy.

Results:

Conclusions: Disease burden in SLE nephritis is commonly classified by glomerular pathology and IC deposition. This case illustrates that in rare situations, malignant hypertension/TMA can drive disease progression and lead to chronic, irreversible renal vascular changes with poor renal outcomes.

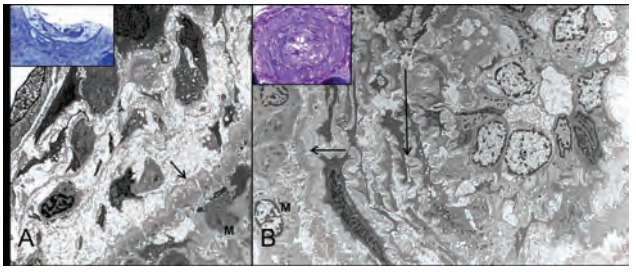


Figure A: First biopsy. Larger interlobular artery with edematous intima (arrow – internal elastic lamina; M – media). EM, inset 1 micron section.**Figure B:** Second biopsy. Interlobular artery with thickened occlusive intima (horizontal arrow – internal elastic lamina; vertical arrow – reduplicated elastica; M – media). EM, inset 1 micron section.

PUB625

Renal Limited TMA in Patients with HSCT: Endothelial Variant of Graft versus Host Disease Nupur N. Uppal,[1] Rimda Wanchoo,[1] Douglas H. Allison,[3] Cristie Scott,[2] Meina Fung,[2] Richard L. Barnett,[1] Ruthee Bayer,[2] James M. Pullman,[3] Kenar D. Jhaveri.[1] *[1]Nephrology, Hofstra Northwell School of Medicine, Great Neck, NY; [2]Hematology/Oncology, Hofstra Northwell School of Medicine and Northwell Health, Lake Success, NY; [3]Pathology, Montefiore Medical Center, Bronx, NY.*

Background: Thrombotic microangiopathy (TMA) and graft versus host disease (GVHD) are well-recognized complications of hematopoietic stem cell transplantation (HSCT). TMA in HSCT (TA-TMA) is preceded by endothelial injury triggered by chemo-radiotherapy, infections or immunosuppressive drugs. Recent data suggests that GVHD itself may be a trigger of TA-TMA. We report 2 cases where GVHD in HSCT was associated with renal-limited TMA.

Methods: A 58-year-old female with a second allogenic HSCT one year ago, and on cyclosporine treatment for gastrointestinal GVHD was admitted with acute kidney injury (AKI), worsening hypertension (HTN), nephrotic range proteinuria and early hemolysis. Serum creatinine (Scr) increased from 1 to 1.8mg/dl over 4 months. AKI worsened requiring dialysis despite discontinuation of cyclosporine. A kidney biopsy confirmed acute on chronic TMA with minimal fibrosis, and she received 2 doses of rituximab. AKI resolved over the course of 6 weeks. However, she expired due to sepsis. Another patient, a 58-year-old-female with a second HSCT on tacrolimus therapy for skin GVHD, had AKI 1 year after transplant with HTN, proteinuria, and signs of hemolysis. Scr worsened from 1.1 to 3.8mg/dl despite discontinuation of tacrolimus. A kidney biopsy revealed chronic TMA, with tubular reticular inclusion bodies (TRIs) without any viral etiology demonstrable by serology or immunohistochemistry.

Results:

Conclusions: A relationship between GVHD and TA-TMA has been previously described but is confounded by calcineurin inhibitor use, infections, heterogeneous study populations, and retrospective study designs. Our findings suggest a possible link between GVHD and TA-TMA. One patient's GVHD and TA-TMA improved following anti-B cell therapy (rituximab) and the other showed evidence of a high interferon state (TRIs), as seen in GVHD. Our results suggest that TA-TMA represents a form of "renal GVHD" or "endothelial GVHD". However, more research is needed to understand the exact mechanism of development of GVHD associated TA-TMA

PUB626

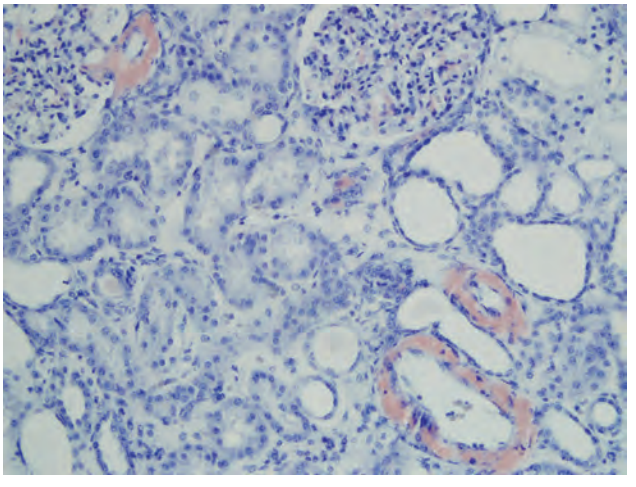
An Unusual Cause of Gross Hematuria Divya Raghavan, Monica P. Revelo Penafiel, Frederic Clayton, Mazdak A. Khalighi, Josephine Abraham. *University of Utah, Murray, UT.*

Background: Amyloidosis refers to the deposition of amyloid fibrils in various tissues. AL amyloidosis is seen in plasma cell dyscrasias.

Methods: A 42-year-old man was transferred from an outside hospital for persistent hematuria after a fall which had resulted in splenic laceration and proximal ureteral injury. He had undergone cystoscopy, embolization, and finally nephrectomy. His serum creatinine rose from 1.8 mg/dl on admission to 4.4 mg/dl by day 4. Urine dipstick was positive for protein and blood. Ultrasound showed right hydronephrosis and he underwent cystoscopy, bladder biopsy and ureteric stent placement. His renal function worsened, necessitating dialysis. Immunofixation electrophoresis revealed an M-spike. Echocardiogram showed infiltrative cardiomyopathy. Bladder biopsy revealed vascular AL amyloidosis. Patient underwent endomyocardial biopsy followed by bone marrow biopsy. Renal function eventually improved and dialysis was stopped. The endomyocardial biopsy showed AL-lambda type amyloidosis. Nephrectomy tissue obtained from the outside hospital showed vascular amyloidosis. Bone marrow aspirate showed 10-15% plasma cells and focal vascular amyloid deposition. Patient was started on chemotherapy. He was readmitted a week later with a gastrointestinal bleed. He developed a cardiac arrest requiring resuscitation. Angiography showed bleeding from a branch of the inferior mesenteric artery and left renal stump. His condition worsened despite aggressive therapies, and the patient was transitioned to comfort care per family wishes. A post mortem demonstrated amyloidosis in the brain, lungs, lymph nodes, thyroid, stomach, bowel, liver, spleen, adrenals and testes in addition to the heart, kidney and bladder.

Results:

Conclusions: Gross hematuria is a relatively rare presentation of renal amyloidosis. Proteinuria (often nephrotic range) is the most common manifestation.



Kidney specimen with Congo red positive vascular deposits

PUB627

Tumor Lysis Syndrome with Extremely High Serum Uric Acid and Phosphate Abhilash Koratala, Hussain Aboud. *University of Florida, Gainesville, FL.*

Background: The tumor lysis syndrome (TLS) occurs when tumor cells release their contents into the bloodstream, typically in response to chemotherapy, leading to the characteristic findings of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. We report a case of TLS who presented with extremely high serum uric acid (34.6 mg/dL) and phosphate (32 mg/dL) and to the best of our knowledge, such high numbers were never reported before.

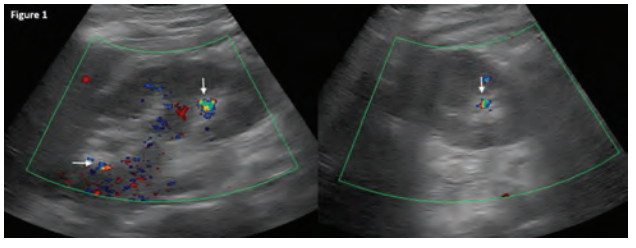
Methods: A 51-year-old woman with history of chronic lymphocytic leukemia (CLL) and hypertension has presented to the hospital with fatigue, nausea, vomiting and decreased urine output. She received the first cycle of chemotherapy one week ago, which consisted of Fludarabine and Cyclophosphamide. She was not taking her allopurinol and not able to stay hydrated because of vomiting. The patient was found to be having acute kidney injury with a serum creatinine of 12.3 mg/L (baseline <1) and was slightly hypervolemic. Other labs were suggestive of TLS [Table1]. In response to chemotherapy, the WBC count has dropped from 165 thou/mm^3 a month ago to 3.5. Interestingly, review of her renal ultrasound images revealed twinkle artefacts on color doppler, which possibly represent calcium phosphate deposits [Figure1, arrows]. She later improved with hemodialysis.

Results:

Conclusions: Patients at high risk for the tumor lysis syndrome need to be closely monitored with labs and should be instructed to seek medical attention immediately if they do not feel well. Initial low-intensity chemotherapy may be considered in suitable individuals for slower lysis of the cancer cells allowing renal homeostatic mechanisms to clear metabolites before they accumulate and cause organ damage.

Table 1: Labs at presentation

	Results	Reference range
White blood cell count (thou/mm^3)	3.5	4-10
White blood cell count (thou/mm^3) – one month prior to presentation	165.6	4-10
Hemoglobin (g/dL)	8.8	12-16
Platelets (thou/mm^3)	220	150-450
Sodium (mmol/L)	124	136-145
Potassium (mmol/L)	7.8	3.4-5.1
Chloride (mmol/L)	81	98-107
Bicarbonate (mmol/L)	8	22-30
Urea nitrogen (mg/dL)	134	6-20
Creatinine (mg/dL)	12.27	0.4-0.9
Calcium (mg/dL)	6.2	8.0-10.6
Phosphate (mg/dL)	32	2.7-4.5
Uric acid (mg/dL)	34.6	2.6-6.8
LDH (U/L)	804	135-225
Total CPK (U/L)	87	30-223



PUB628

A "Muddy Brown" Herring Mona Shaban,[1] Jeremy J. Sorkin,[2] Gerald A. Hladik,[3] Alexei V. Mikhailov,[1] Kawan A. Swain.[2] *[1]University of North Carolina, Chapel Hill, NC; [2]University of North Carolina, Chapel Hill, NC; [3]University of North Carolina at Chapel Hill Kidney Center, Chapel Hill, NC.*

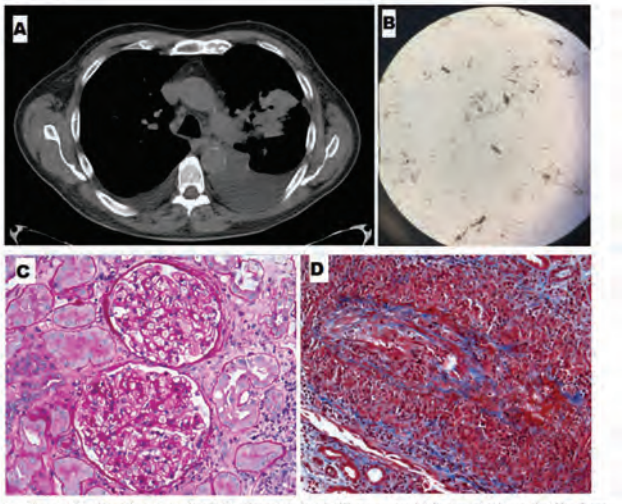
Background: Examination of the urinary sediment is a powerful tool in the diagnostic evaluation of acute kidney injury (AKI). However, the specificity of the urinary sediment exam is imperfect and can dissuade clinicians from considering alternative diagnoses. We present a case of ANCA-associated vasculitis manifest as AKI associated with muddy brown casts.

Methods: A 73-year-old man was seen in consultation for AKI. His serum creatinine (SCr) had risen from 1.2 mg/dl to 2.6 mg/dl. He was recently hospitalized with fever, hypoxia, and multifocal pulmonary infiltrates that initially improved with antibiotic therapy, however symptoms recurred. Follow up imaging revealed persistent multifocal infiltrates and bilateral pleural effusions (Figure 1A). Bronchoscopy demonstrated purulent exudate emanating from the left upper lobe without hemorrhage. The urinary sediment revealed 6 to 10 "muddy brown" casts per low power field (Figure 1B). PR3-ANCA was positive at >200 U/ml. Kidney biopsy showed severe, widespread necrotizing vasculitis, but minimal glomerular changes and only one small, segmental cellular crescent (Figure 1C/D). Immunofluorescence microscopy showed mesangial C3 deposition, but otherwise negative. These findings were in the spectrum of a pauci-immune ANCA-associated small vessel vasculitis. The SCr peaked at 4.2 mg/dl and patient required one hemodialysis treatment for hypervolemia. The patient gradually improved after implementation of corticosteroids, plasmapheresis, and IV cyclophosphamide. The SCr was 1.7 mg/dl at discharge and 1.4 mg/dl 6 months later.

Results:

Conclusions: ANCA-associated vasculitis can present with minimal glomerular involvement. In this case, the "muddy brown" casts were most likely indicative of "downstream" ischemic tubular injury resulting from severe vasculitis. This case highlights the importance of maintaining a high index of suspicion for underlying vasculitis in patients with persistent pulmonary renal syndrome even in the absence of glomerular hematuria.

Figure 1



A. Chest CT showing patchy left upper lobe infiltrate and bilateral pleural effusions.
B. "Muddy brown" casts seen on wet prep of urine sediment. Magnification × 100
C. Glomeruli with only minimal changes with minimal mesangial matrix expansion. One glomerulus of 28 showed a small segmental cellular crescent (not shown).
D. Dramatic segmental fibrinoid vascular wall necrosis and segmentally accentuated transmural inflammation with circumferential intimal lymphocytic infiltrates consistent with small vessel vasculitis. The lumen is obliterated by edematous intimal thickening.

PUB629

Light Chain Deposition Disease (LCCD) Manifesting as Monoclonal Gammopathy of Renal Significance (MGRS) in a Patient with B-cell Marginal Cell Lymphoma Leah M. McIntosh,[2] Barry M. Wall,[1] Geeta G. Gyamlani.[1] *[1]Veterans Affairs Medical Center, Memphis, TN; [2]University of Tennessee Health Science Center, Memphis, TN.*

Background: MGRS includes renal disorders caused by monoclonal immunoglobulin (MIg) secreted by a a clonal population of plasma cells or B-cells. Athough patients with MGRS often do not meet criteria for overt multiple myeloma or lymphoma, they can have significant renal disease due to MIg deposition. MGRS is associated with a wide spectrum of glomerulopathies, classified by type, localization, and organization of the deposited MIg. Kidney biopsy is indicated to determine the exact lesion and to evaluate its severity. Early recognition is crucial, as suppression of Mig secretion by chemotherapy often improves outcomes. We present a case of LCCD, manifesting as MGRS in a patient with B-cell marginal cell lymphoma.

Methods: 74-year-old male presented with progressive renal dysfunction: baseline creatinine 2.0 mg/dL in 2014 which increased to 2.4 mg/dL in 2017. Blood pressure was normal and there was no edema. Urinalysis was bland with no protein on qualitative exam. Urine protein creatinine ratio was 292 mg/g. Viral and autoimmune etiologies were ruled out. Renal ultrasound was unremarkable. Serum protein electrophoresis revealed a monoclonal spike in the gamma region, immunofixation electrophoresis showing IgG kappa. Serum free light chain (K/L) ratio was 9 and 24 hour urine free light chain (K/L) ratio was 100. Flow cytometry on bone marrow aspirate was positive for malignant low-grade B cell lymphoma. Bone marrow biopsy showed an indolent marginal zone lymphoma. Kidney biopsy showed mesangial expansion without nodules, IF showed linear kappa light chain deposition along glomerular and tubular basement membranes. He was treated with rituximab weekly for 4 weeks along with oral chlorambucil. Susequently, creatinine has improved to 2.1 mg/dL and serum free light chain ratio has improved 4.5.

Results:

Conclusions: The association of marginal zone B cell lymphoma with LCDD is extremely uncommon. Kidney biopsy is indicated in patients with renal impairment and MIg to diagnose MGRS. There may be a benefit of plasma cell or lymphoma directed therapy for decreasing the risk of chronic kidney disease, even in the presence of low levels of clonal cells. This case highlights the importance of diagnosing MGRS and related kidney disease, such that the paraprotein secreting clone can be optimally treated.

PUB630

Unmasking the Culprit: Valproic Acid Induced Thrombotic Microangiopathy Sean Hebert, Rita Swinford, Christian L. Erikson. *McGovern Medical School at The University of Texas Health Science Center at Houston (UTHealth), Houston, TX.*

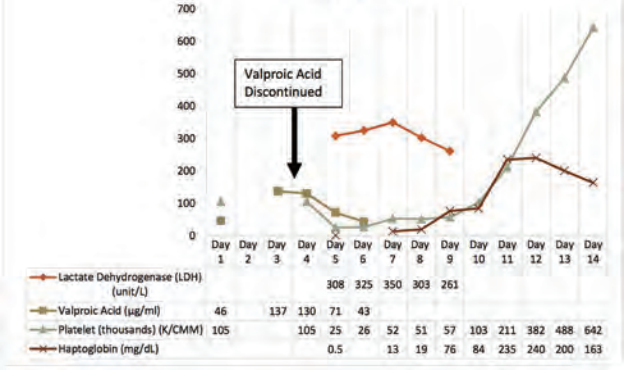
Background: Thrombotic microangiopathy (TMA) is a serious, sometimes life-threatening disorder marked by the presence of endothelial injury and microvascular thrombi. One specific TMA syndrome, Drug-induced TMA (DI-TMA) can occur following drug exposure via drug-dependent antibodies or direct tissue toxicity. Examples include TMA secondary to calcineurin inhibitors Tacrolimus and Cyclosporine and the antineoplastic Gemcitabine. To the best of our knowledge, this is the first reported case of DI-TMA from VPA toxicity.

Methods: An adolescent male with difficult to control epilepsy was admitted for impaired hepatic function while on valproic acid therapy. On the third hospital day, he developed severe metabolic lactic acidosis and multiorgan failure, prompting transfer to the pediatric intensive care unit. Progressive anemia and thrombocytopenia instigated an evaluation for thrombotic microangiopathy, where confirmed by hemolysis with schistocytes, elevated lactate dehydrogenase (LDH), low haptoglobin, and oliguric acute kidney injury. Thrombotic thrombocytopenic purpura was less likely with adequate ADAMTS13. Discontinuing valproic acid reversed the anemia, thrombocytopenia, and normalized the LDH and haptoglobin, supporting a drug-induced cause for the TMA.

Results:

Conclusions: TMA syndromes are extraordinarily diverse. Universally, they are incited by microvascular endothelial cell injury leading to arteriolar and capillary thrombosis and subsequent organ injury. We propose VPA's ability to modify cellular membranes served as the nidus for DI-TMA. Swift recognition and VPA discontinuation likely saved this patient from escalation to plasma exchange and/or hemodialysis. Our case features the first reported case of DI-TMA with VPA toxicity. We suggest increasing awareness of VPA as a TMA culprit will assist in identifying future cases.

FIGURE 1



PUB631

Sterile Peritonitis with Monocytic Predominance in a Peritoneal Dialysis Patient Ryan Spiardi,[2] Myriam C. Vela-Ortiz,[1] Jaime A. Baynes-Fields,[1] Lissa B. Levin Mizrahi,[3] Sandeep Aggarwal,[2] Rebecca K. Seshasai.[3] *[1]Drexel University, Philadelphia, PA; [2]Drexel University College of Medicine, Philadelphia, PA; [3]None, Philadelphia, PA.*

Background: PD peritonitis presents with cloudy fluid, abdominal pain, and dialysis effluent WBC > 100/ml with > 50% neutrophils (PMNs). In sterile peritonitis, infectious and non-infectious causes must be considered. We present a PD patient with sterile peritonitis with monocytic predominance of cells.

Methods:

Results: 53 year old female with history of kidney-pancreas transplant in 1999 with bladder exocrine drainage. Renal allograft failed, she began PD in 2016. She continued low dose tacrolimus and cellcept. Pancreas allograft showed reduced function: elevated serum amylase (176 IU/l) and lipase (102 IU/l), fasting hyperglycemia, HgA1C 6.2% and C-peptide level 5.2 ng/ml. She used both CCPD and CAPD and did not use icodextrin. She first presented with cloudy PD fluid and abdominal pain with effluent WBC 335 with 42% PMNs and 44% monos. She received IP antibiotics. Cultures were negative and repeat fluid cell count at one week showed WBC 71 with 23% PMNs and 64% monos. Empirically she received two weeks antibiotics for sterile peritonitis and symptoms resolved. Six weeks later she again presented with cloudy effluent and cell count showed WBC 150 with 25% PMNs and 67% monos. She received antibiotics initially but they were stopped at 3 days when cultures were again negative and repeat cell count was WBC 153 with 5% PMNs and 75% monos. All bacterial, fungal and mycobacterial cultures were negative. CT abdomen showed heterogenous pancreas, possibly consistent with pancreatitis, kidney allograft anatomy and blood flow normal. PD fluid amylase was not elevated (27 IU/l), making pancreaticoduodenocystostomy leak in the setting of bladder drained pancreas unlikely. Symptoms improved without antibiotics and have not recurred after 3 months. Differential includes inflammation of juxtaperitoneal organ, mild graft rejection of pancreas and presence of intraperitoneal air. On review of patient technique, we found she was not properly priming the line during CAPD and infusing air into her peritoneal cavity.

Conclusions: There is a wide differential for sterile monocytic peritonitis. The patient is now asymptomatic and doing well. One must consider less common infectious causes as well as non-infectious causes in complicated patients who are immunosuppressed and have multiple organ transplants.

PUB632

The Man with the Large Tongue – A Case Report Kyrstin Alexander, Sathish Karmegam, Renuka Chowdhury. *Methodist Dallas Medical Center, Dallas, TX.*

Background: Introduction: AL amyloidosis is a clonal plasma cell disorder that causes systemic symptoms secondary to deposition of amyloid in multiple organs. AL amyloidosis can present with abnormalities, such as macroglossia, carpal tunnel syndrome, hepatosplenomegaly, heart failure, nephrotic range proteinuria, neuropathy and bleeding diathesis.

Methods: Case Description: A 78-year-old Hispanic man presented with progressive fatigue, SOB and lower extremity edema. PMH included DM, CAD, diastolic heart failure, recurrent pleural effusions, and BPH. He further complained of poor oral intake because of difficulty swallowing. He was hypotensive and hyponatremic at 127 mmol/L prompting a nephrology consultation. He appeared chronically ill with significant difficulty in articulation. He had significant macroglossia with ulcers along the margins of the tongue and stigmata of multiple biopsies to rule out malignancy. His teeth had been "shaved to fit the big tongue better" by an OMF surgeon. His urine protein was >600 mg/dL and protein/creatinine ratio of 20 grams. Given the macroglossia, proteinuria and diastolic CHF, amyloidosis was suspected. Serological work up including hepatitis, ANA, RPR, HIV, ANCA, SPEP and UPEP were unremarkable. Free light chain analysis showed IgG Lambda chain of 30.60 mg/dL and a kappa/lambda ratio of 0.05. BM Bx did not indicate a plasma cell dyscrasia but there were abnormal cytogenetic findings by FISH. Amyloidosis was diagnosed on kidney and tongue biopsies as Congo red staining resulted positive. Liquid chromatography tandem mass spectrometry was performed on peptides extracted from Congo red positive micro-dissected areas of kidney specimen to diagnose AL amyloidosis. He was started on Dexamethasone and Bortezomib but continued to become progressively weaker and was placed on hospice.

Results:

Conclusions: Discussion: AL amyloidosis has a poor prognosis when detected at an advanced stage. Treatment varies with the eligibility of the patient to pursue high dose melphalan followed by autologous hemopoietic cell transplantation. Our patient did not meet the eligibility criteria. Despite his macroglossia for more than one year and multiple biopsies to rule out malignancy, amyloidosis was not considered. High clinical suspicion is required to diagnose this rare life threatening disorder.

PUB633

Hemolysis Associated with Continuous Renal Replacement Therapy Aala Jaberi,[2] Samer Abujaber.[1] *[1]Mount Auburn Hospital, Cambridge, MA; [2]Internal Medicine, Mount Auburn Hospital, Harvard Teaching Hospital, Cambridge, MA.*

Background: Hemolysis is a rare, but potentially life-threatening complication of hemodialysis. Patients undergoing long-term hemodialysis seldom develop this complication, and even less so in critically ill patients undergoing Continuous Veno-Venous Hemofiltration (CVVH). We present a case of a critically ill patient undergoing CVVH who developed acute hemolytic anemia.

Methods: A 65-year-old female was admitted to the intensive care unit with severe pancreatitis, with progression to multiorgan failure, including acute kidney injury (AKI), requiring CVVH. After 48 hours from CVVH initiation, high return circuit pressure developed with significant clot burden in the circuit. The dialysis catheter was exchanged confirming adequate flow; however, elevated return pressures and filter pressures persisted. Nursing staff noted blood in the effluent fluid with continuous system alarm signals. The circuit was disconnected without blood return to the patient. Hemolysis labs were urgently drawn and the dialysate filter was sent to the manufacturer for analysis. CVVH was reinitiated with a new filter pending; however, within an hour of treatment the effluent fluid demonstrated blood and the treatment was discontinued. Laboratory studies revealed: significant drop in hemoglobin to 7g/dL and significant thrombocytopenia to 50 K/UL. elevated LDH at 600 U/L with low to normal haptoglobin. While CVVH was on hold, the patient received a Furosemide infusion for management of volume overload, with improvement in urine output and electrolyte abnormalities. After 24 hours from CVVH discontinuation, the patient's hemoglobin level rose to 8.9g/dL and her platelets to 105 K/UL, with further improvement noted at 48 hours.

Results:

Conclusions: The diagnosis of CVVH induced hemolysis, although rare, requires a high level of suspicious in critically ill patient, given their increased propensity for pro-inflammatory and hypercoagulable states. Thrombus formation and cytokine aggregation can result in filter clot formation and elevated circuit pressures. This clot burden can result in significant hemolysis due to the shearing forces on red blood cells as they travel throughout the extracorporeal circuit and roller pump. Hemolysis can also result from treatment-induced electrolyte abnormalities, such as hypophosphatemia, hyponatremia, and hypokalemia. With significant hemolysis, pigment-induced nephropathy can occur causing further renal injury.

PUB634

Granulicatella adiacens Causing Infective Endocarditis with Crescentic Glomerulonephritis Bhupinder K. Prajapati,[1] Katie Bean,[3] Manoj Das,[1] Imran F. Fatani,[2] Daniel E. Carl,[1] Jason M. Kidd.[2] *[1]VCU, Henrico, VA; [2]VCU Medical Center, Richmond, VA; [3]Virginia Commonwealth University Health Systems, Richmond, VA. Group/Team: VCUrine.*

Background: Rapid progressive glomerulonephritis is manifested by evidence of glomerular disease in the urine, rapid progressive deterioration renal function and is characterised morphologically by formation of crescents. Granulicatella Adiacens(GA) is designated as a nutritionally variant streptococci (NVS) the transmission of which from mouth is a noted cause of infective endocarditis(IE). NVS can cause severe infections in immunocompetent and immunosuppressed hosts.

Methods: A 32 year old white male with history of congenital heart defect presented with fevers, chills, night sweats for 6 months. Recently, he noted decreased urine output and 30 pound weight loss. On admission, he was febrile. Initial labs were significant for a creatinine of 7 mg/dl (previously normal). His urinalysis was significant for hemautria and proteinuria. Blood cultures grew Granulicatella Adiacens and transesophageal echocardiography showed vegetation on the pulmonary valve. Renal biopsy was performed which showed crescentic glomerulonephritis. Electron microscopy showed sub-endothelial electron dense deposits. His crescentic glomerulonephritis was attributed to infectious endocarditis. His renal function began to slowly improve with the initiation of antibiotics and he never required renal replacement therapy. With treatment, his serum creatinine was steadily improving, and was 3.8mg/dL at discharge.

Results:

Conclusions: This case highlights two unique features. First, GN associated with IE historically occurred with Streptococcus viridans but with the advent of prophylactic antibiotic coverage in IE, it is currently most commonly seen in Staph aureus IE. Antibiotics are the cornerstone of treatment for these patients, but in some cases, immunosuppression has been utilized. Granulicatella Adiacens is a rare cause of infective endocarditis. In 2015 Eduardo et al found only 25 cases of IE caused by granulicatella species and none of them were associated with nephritis. We present the first reported case of post infectious glomerulonephritis related to this uncommon organism. Secondly, this case highlights the diverse glomerular pathological patterns associated with Infectious GN, as crescentic glomerular lesions are uncommonly seen with PIGN but are typical for GN with IE.

PUB635

A Case of Water Intoxication with Transient SIADH After Seizure Shinichi Tanaka,[1] Takaya Sasaki,[1,2] Masahiro Okabe,[1,2] Yu Honda,[1,2] Masahiro Ishikawa,[1,2] Takashi Yokoo.[2] *[1]KAWAGUCHI MUNICIPAL MEDICAL CENTER, Saitama, Japan; [2]The Jikei University School of Medicine, Tokyo, Japan.*

Background: Water intoxication is caused by excessive water ingestion and a fatal disorder and usually shows hypotonic urine. We report a case of water intoxication with transient hypertonic urine and a relatively high antidiuretic hormone (ADH) level.

Methods: A 54-year-old Japanese man presented to our hospital with seizure and unconsciousness. After cessation of seizure, his Glasgow Coma Scale score was 11(E2V4M5). Blood pressure, heart rate, and body temperature are 136/67 mmHg, 90 / min, and 36.4 degrees centigrade, respectively. Blood tests revealed hyponatremia (108 mmol/L) and hypo-osmolality (227 mOsm/L). Urinalysis showed hypertonic urine (U-Na 97 mmol/L, U-K 18 mmol/L, and U-osm 416 mOsm/L). He was treated with 3% sodium chloride solution for about 36 hours until hypotonic urine (U-Na 32 mmol/L and U-K 9 mmol/L) was observed. Subsequent treatment with half normal saline to prevent overcorrection gradually improved hyponatremia. After regaining consciousness he had consumed at least 6 liters of water over 3 hours due to adaptation disorder. His blood ADH concentration was relatively high (3.1 pg/mL). Magnetic resonance imaging focusing on pituitary and laboratory tests for pituitary hormones indicated no other clinically significant pituitary abnormalities. He was diagnosed with water intoxication augmented by secondary syndrome of inappropriate secretion of ADH (SIADH) after seizure. He was discharged without abnormal neurological findings on the 14th day.

Results:

Conclusions: Water intoxication often occurs in patients with psychiatric disorders in a setting of abnormal thirst or SIADH caused by antipsychotics. While water intoxication is usually associated with hypotonic urine, patients with SIADH administered antipsychotics, often show hypertonic urine. Our patient showed a transiently high ADH level and hypertonic urine despite hypotonic hyponatremia with euvolemia. Because he had no history of antipsychotic medication intake, it was assumed that he demonstrated a transient secondary SIADH after seizure. Hyponatremia rapidly improved after his urine changed from hypertonic to hypotonic. A rapid increase of serum sodium concentration predisposes to osmotic demyelination syndrome. Thus it is necessary to frequently confirm serum and urinary electrolytes and promptly adjust the content of infusion therapy.

PUB636

A Case of Severe Hyponatremia Managed with Prolonged 3% Saline in a Patient with Acute Intermittent Porphyria Sayed S. Ahmed,[2] Dia R. Waguespack.[1] *[1]UTHealth, Houston, TX; [2]Renal Diseases and Hypertension, McGovern Medical School at UTHealth, Houston, TX.*

Background: Acute Intermittent Porphyria (AIP) results from partial deficiency of heme biosynthetic enzyme porphobilinogen deaminase. Among various clinical manifestations, severe hyponatremia is a possible clinical presentation. Hyponatremia can occur from variety of entities including syndrome of inapprpriate antiduretic hormone (SIADH), losses from the gastrointestinal tract and renal sodium wasting. We report a case of severe hyponatremia in patient with AIP managed with aggressive and prolonged 3% saline replacement.

Methods: A 21 year old woman presented with generalized body pain. She had a history of rhabdomyolysis one month ago. During that admission she was managed with intravenous fluid and pain control. This admission she presented with similar symptoms, however her creatinine phosphokinase level was normal. Nephrology was consulted for severe hyponatremia (serum sodium level of 116 meq/L) that was consistent with SIADH on laboratory work up. She was initially treated with 3% saline boluses. Despite this her sodium level continued to decline. She was then transitioned to a continous 3% saline infusion at 25-30 ml/hr. The treatment goal was to maintain goal sodium correction of 6 meq/24hrs. During this time confirmatory tests for the diagnosis of AIP returned. She was started on directed treatment of AIP. Over next several days hypertonic saline therapy was discontinued as sodium level stabilized between 130-140 meq range with the treatment of her AIP.

Results:

Conclusions: This case was notable because of continued use of 3% saline over approximately 2 week period due to SIADH/salt wasting etiology. This case also demonstrates refractory hyponatremia in AIP requiring aggressive and prolonged repletion with 3% saline and eventual stabilization of sodium level after treating underlying etiology.

PUB637

From an Implantable Venous Access Device to the Kidneys: Staphylococcus Infection-Associated Glomerulonephritis Fatima B. Cintron-Rosa,[1] Martin Gorrochategui,[1] Ileana E. Ocasio Melendez,[1] Jannice M. Arroyo,[1] Krystahl Z. Andujar,[1] Sulimar Rodriguez.[2] *[1]Nephrology, University of Puerto Rico, San Juan, PR; [2]Gastroenterology, University of Puerto Rico School of Medicine, Guaynabo, PR.*

Background: IgA nephropathy (IgAN) is a mesangial proliferative glomerulonephritis characterized by diffuse mesangial deposition of IgA. It has been associated with inflammatory bowel disease (IBD); in addition, IgA-dominant glomerular deposition occurs with Staphylococcus infection-associated glomerulonephritis (SAGN). We present a case of a patient with IBD and staphylococcal infection with nephritic syndrome and acute kidney injury (AKI).

Methods: A 57-year-old female with perianal Crohn's disease receiving infliximab infusions via an implantable venous port presented with a two-week history of diarrhea. She was admitted and her evaluation was significant for a prerenal AKI. Urinalysis was positive for protein, leukocyte esterase, white blood cells and red blood cells. Urine culture and blood cultures were remarkable for methicillin sensitive staphylococcus aureus (MSSA). Renal sonogram and echocardiogram were negative for obstruction and endocarditis, respectively. She was initiated on intravenous fluids and piperacillin-tazobactam for urinary tract infection and bacteremia and showed clinical improvement from kidney function and infection. Two weeks later, she developed nephritic syndrome. Laboratory workup for glomerular disease with low complement C3 levels, suggestive of infectious glomerulonephritis. The implantable port was removed and its culture yielded MSSA. New echocardiogram was negative for endocarditis. The kidney biopsy reported immune complex mesangial glomerulonephritis with IgA deposition suggestive of IgAN. SAGN was diagnosed and antibiotic therapy was completed. Bacteremia was eradicated with further improvement of AKI.

Results:

Conclusions: SAGN is an unusual immune complex-mediated disease that presents with a *Staphylococcal* infection associated with edema, hematuria, leukocyturia, proteinuria, hypocomplementemia and AKI. The infection site may be the skin, heart, lung or indwelling catheter. Recently, a SAGN study showed a wide spectrum of IgA staining, trace or negative C3 staining and a much lower prevalence of subepithelial "humps". This case represented a diagnostic challenge due to biopsy features of two entities, SAGN versus IgAN secondary to IBD. In SAGN, infection needs to be appropriately treated with antibiotic therapy instead of immunosuppression.

PUB638

Is There a Role for High Intensive Angiotensin Blockade in Mesangial Proliferative Glomerulonephritis? Ana F. Gomes da silva, Maria N. Pestana, Miguel Goncalves, Pedro M. Vieira, José M. Durães, Luís Resende, Jose N. Guimaraes Rosa, José Teixeira, Gil Silva. *Hospital Central do Funchal, Funchal, Portugal.*

Background: Idiopathic mesangial proliferative glomerulonephritis (MPGN) may represent a variant of minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS), but some believe that they are separate conditions.

Methods: A 38 year old male was referred to our nephrology department consultation with non-nephrotic proteinuria and serum creatinine (sCr) of 1.26mg/dL. He was assimptomatic and had no personal or family history of kidney disease. Laboratory findings revealed sCr level of 1.31 mg/dL and urinary albuminuria and proteinuria levels were 2.535 g/24h and 3.61 g/24h, respectively. Creatinine clearance (CrCl) was 103.6 ml/min. A renal biopsy was performed and its histological analysis revealed mesangial cell proliferation with mesangial granular deposits of IgG (+), IgA (-), IgM (-), C3 (+/-), C1q (+), kappa (+/-) and lambda (+/-). The patient was treated with prednisolone (PDN) 60 mg/day and ramipril 5 mg/day. The initial response was oscillating with the need for successive increases in ramipril dose up to 40mg/day. 2 years later, with PDN progressive

reduction and suspension, he presented with persistent cough and ramipril was replaced with losartan 50mg/day. In the following months there was a new rise in albuminuria requiring increasing doses of losartan up to 200mg/day and currently the patient remains clinically stable with this therapy.

Results:

Conclusions: MPGN can be secundary to a variety of diseases including lupus nephritis, IgA nephropathy, and mild postinfectious glomerulonephritis. In this case report, no cause was found responsible for mesangial proliferation. The immunofluorescence microscopy revealed deposits of IgG (+) and C1q (+) without the predominance of one of them, which excluded C1q nephropathy. The majority of patients with MPGN respond initially to PDN and an antiproteinuric drug. The treatment of our patient was particularly challenging since he needed a prolonged corticotherapy (during 2 years) and the use of high doses of angiotensin blockers.

PUB639

A Case of Concurrent Catastrophic Antiphospholipid Syndrome and IGA Nephropathy Kristine Soltanpour, Tiffany N. Caza, Paul F. Shanley, Apurv Khanna. *SUNY Upstate Medical University, Clay, NY.*

Background: Antiphospholipid syndrome (APS) can be a cause of CKD over time due to repeated formation of microthrombi and their dissolution. Although an association of antiphospholipid antibodies and Henoch-Schonlein purpura has been recognized, few cases of APS and IgA nephropathy have been reported. Here we show a rare case of concurrent thrombotic microangiopathy (TMA) due to catastrophic antiphospholipid syndrome (CAPS) and IgA nephropathy.

Methods: A 42 year old morbidly obese male patient with an 18 year history of antiphospholipid syndrome due to B2 glycoprotein and anti-cardiolipin antibodies, complicated by bilateral deep venous thromboses on warfarin, presented with abdominal pain, AKI, and acute hypoxic respiratory failure. A prior episode of CAPS resulted in AKI due to TMA and required dialysis and plasmapheresis. After recovery from this episode, he had CKD stage III with his baseline creatinine being in the mid-1 range. Upon admission, he was found to have acute pancreatitis with a lipase of 764 and AKI on CKD with a serum creatinine of 4.5 g/dL. Review of systems was positive for mouth sores, dry eyes, nausea, abdominal pain, 100 lb weight loss, and arthralgias. Physical exam was significant for left lower quadrant tenderness. He had a nephritic presentation with microscopic hematuria with 25-50 RBC/hpf, 3+ hemoglobinuria, and a protein-to-creatinine ratio of 2.34. He had anemia and thrombocytopenia. A CT of the abdomen showed splenomegaly and no obstructive uropathy. His clinical presentation was concerning for recurrent catastrophic antiphospholipid syndrome requiring a renal biopsy. Biopsy showed both evidence of TMA and a mesangiocapillary proliferative glomerulonephritis with IgA-containing immune complexes consistent with IgA nephropathy. There was acute on chronic TMA with severe ischemic tubulointerstitial damage, interstitial hemorrhage, infarction, occlusion of glomerular capillaries, endothelial damage, and subendothelial widening. He was treated with plasmapheresis and high dose steroids, discharged with a steroid taper and hydroxychloroquine, and recovered with a creatinine of 1.9.

Results:

Conclusions: Here we present a case of catastrophic antiphospholipid syndrome and IgA nephropathy overlap treated successfully with plasmapheresis, anticoagulation, and steroids.

PUB640

Severe AKI in a Sickle Cell Patient Taking Deferasirox Bair Cadet,[1] Amarpali Brar,[1] Okwudili Nnaji,[3] Mary C. Mallappallil,[1] Hanan K. Tawadrous,[1] Moro O. Salifu.[2] *[1]Nephrology, SUNY- Downstate School of Medicine, Brooklyn, NY; [2]SUNY Downstate Medical Center, Valley stream, NY; [3]SUNY downstatemedicsl center, Brooklyn, NY.*

Background: Introduction Acute kidney injury (AKI) occurs in five to seven percent of hospitalized patients. Deferasirox is an iron chelating agent used in treatment of chronic iron overload. Here we report a case of severe AKI associated with use of Deferasirox in a patient with sickle cell disease and iron overload.

Methods: Case description A 24-year-old man with Moya Moya disease, sickle cell disease who was dependent on chronic blood transfusions, stroke associated with bilateral extremities weakness presented with 3 days of non-bloody diarrhea and vomiting. He was found to have AKI on admission. His medications at home included lisinopril, deferasirox, levetiracetam, carbamazepine and folic acid. Laboratory investigation revealed calculated fractional excretion of sodium to be 1.7 %, creatinine on the day of admission was 7.18 mg/dl with baseline creatinine of 0.83 mg/dl recorded 2 weeks prior. Urinalysis was noted for a pH 6.0, RBCs <1, WBCs 3 and negative for protein. Renal ultrasound showed normal echogenicity without any acute renal pathology.

Results:

Conclusions: Discussion In this case, the patient who was treated with deferasirox for iron overload developed AKI. Recognized mechanism of renal injury include decrease prostaglandin synthesis, inhibition of tubular reabsorption of solute and direct mitochondrial injury. The discontinuation of the deferasirox and lisinopril resulted in the serum creatinine decreasing to 0.88 mg/dl. Deferasirox should be used with caution in patient on ACE inhibitor with rapid discontinuation in the setting of dehydration.

PUB641

Biopsy-Proven HIV-Associated Nephropathy in a Patient with Untreated HIV/AIDS and Non-Nephrotic-Range Proteinuria Diana Mina. *UCSF Division of Nephrology, San Francisco, CA.*

Background: Renal involvement in patients with HIV/AIDS has been described since the mid-1980s, and can directly cause glomerular and tubulointerstitial injury, or can be associated with renal infection, renal involvement by neoplasm, or can be secondary to anti-retroviral medications. The histopathologic lesion termed HIV-associated nephropathy (HIVAN) is characterized by a collapsing form of focal and segmental glomerulosclerosis (FSGS) with coexistent tubulointerstitial disease and classically presents with heavy proteinuria and chronic renal failure, but must be considered in the differential diagnosis for all patients with HIV/AIDS who present with renal failure.

Methods: A 37 year old male with HIV/AIDS, not taking anti-retroviral medications, was brought to the hospital by family members due to several days of altered mental status. Cerebral spinal fluid studies revealed CNS lymphoma and the patient was treated with anti-retroviral medications, high dose steroids, and rituximab. Records from the 4 months prior to admission suggested a baseline creatinine of 1.5, with several prior episodes of acute kidney injury during hospitalization for opportunistic infections, but degree of albuminuria (0.6 g/g) and proteinuria (1.5 g/g) on admission made sepsis-related ATN or possible renal infection, such as by CMV, appear to be more plausible etiologies for renal failure than HIVAN per se. Complete serologic work-up was unremarkable and renal ultrasound revealed large kidneys with increased echogenicity. Renal biopsy revealed collapsing FSGS with coexistent tubulointerstitial disease. Interestingly, after several weeks on anti-retroviral therapy and continuous renal replacement therapy, renal function improved significantly, though patient remained dialysis dependent in the context of a CMV-related gastrointestinal bleed and clinical deterioration. The patient remains critically ill and dialysis-dependent.

Results:

Conclusions: Though anti-retroviral treatment has significantly reduced the prevalence of HIVAN, and though it classically presents with high-grade proteinuria, it must be considered in the differential diagnosis of all HIV/AIDS patients presenting with renal failure. The degree of recovery depends on the extent of the renal injury, and prompt recognition of HIVAN and initiation of anti-retroviral therapy is critical for preventing progression to end-stage renal disease.

PUB642

AKI Secondary to Sunitinib in a Renal Allograft Patient Sean Verma, Kayla Shirley, Claude Bassil. *University of South Florida, Tampa, FL.*

Background: Sunitinib is a multiple tyrosine kinase inhibitor used in advanced renal cell carcinoma (RCC) and gastrointestinal stromal tumor. Nephrotoxicity is a rare side effect that was not reported during clinical trials

Methods: A 64-year-old man with a living related donor renal transplant due to focal segmental glomerulosclerosis and stage 4 metastatic RCC of native left kidney was found to have acute kidney injury (AKI) with creatinine of 3.5 mg/dL (baseline 1.4 mg/dL). He was on cyclosporine and prednisone, while myceophenolate mofetil was held over last 3 months with the discovery of RCC. He completed a 14 day course of sunitinib 4 days prior to routine labs showing AKI. Labs showed potassium 6.1 meq/L, bicarbonate 14 meq/L, albumin 2 mg/dL. A cyclosporine trough was within normal limits. Urinalysis showed 100 mg/dL protein. Urine eosinophils, BK, and JC viruses were negative. Renal ultrasound of the transplant showed no hydronephrosis and patent vasculature. Creatinine peaked at 3.7 mg/dL the next day. A spot protein/creatinine ratio showed nephrotic range proteinuria at 4.75 g protein/g creatinine. Over the following days his creatinine remained stable at 3.5-3.7 mg/dL but he became oliguric. After discussion, he declined renal replacement therapy and opted for palliative care. He was discharged with hospice and passed away 15 days after admission.

Results:

Conclusions: Sunitinib targets multiple cell factor receptors that are involved in growth regulation, neoangiogenesis, differentiation, and cell survival, most notably vascular endothelial growth factor receptor (VEGFR). Renal side effects seldomly implicated with sunitinib include, acute interstitial nephritis, thrombotic microangiopathy, tumor lysis syndrome, new or worsening hypertension, edema, and proteinuria. 7 case reports describe a pre-eclamptic like condition, in which patients developed hypertension, edema and proteinuria. VEGFR is important in the function of podocytes and glomerular epithelial cells. VEGFR inhibition may result in decreased endothelial fenestration formation, effacement of podocyte foot processes, and disturbance of the glomerular filtration barrier leading to proteinuria, hypertension, and AKI. Treatment is supportive with intravenous fluids, stopping the sunitinib, and avoiding any additional renal insults. Sunitinib is not cleared through hemodialysis. Renal biopsy can be considered if safe to proceed.

PUB643

Valerian Root Interaction with Statins: Another Cause of Rhabdomyolysis-Associated AKI Alexander Borrero-Arvelo,[7] Enrique E. Acosta Oruna,[1] Stefano Coppola fasick,[3] Jacobo J. Loyola,[7] Eddie M. Rodriguez,[7] Migdoel Cruz rodriguez,[6] Carlos J. Perez-Lopez,[5] Lorena D. Morales,[4] Elvin Soto,[2] Carlos S. Rosado-Rodriguez.[7] *[1]Internal Medicine Resident, San Juan, PR; [2]VA Caribbean Healthcare System, San Juan, PR; [3]VA Caribbean healthcare system, Guaynabo, PR; [4]VA caribbean Healthcare System, San Juan, PR; [5]VA caribbean Healthcare sytem, San juan, PR; [6]VA healthcare system, Patillas, PR; [7]Veterans Affairs Caribbean Healthcare System, Toa Baja, PR.*

Background: Valerian root is an herbal supplement used to treat insomnia, anxiety and muscle tension. It has a complex mixture of chemical compounds including valeric acid and its derivatives. Valeriana root has been shown to decreased the CYP3A gene expression by nuclear receptors in an experimental model but interactions with drugs metabolized by the CYP450 has not been clearly established. We report a patient who presented with severe rhabdomyolysis and oliguric acute renal failure coincident with the use of Valerian root and Rosuvastatin.

Methods: An 88 year old man was brought to the ED with 3 day history of general malaise, hypoactivity, poor oral intake and decrease urine output. He had history of CKD Stage 3b associated to HTN, T2DM, CVA with residual right hemiparesis, prostate hypertrophy, and hyperlipidemia. He was on Rosuvastatin, Losartan and Terazosin. No recent medication dose changes was documented. He was also taking Melatonin and Valerian root herbal supplement for insomnia. Vital signs: BP: 110/70 HR: 60/min. The patient was alert, but disoriented. Physical exam was remarkable for bilateral leg pitting edema. Initial laboratory data at the ED revealed: S Creat: 14.9, BUN 118 mg/dl, and Glucose: 216 mg/dl; Na: 123 K: 8.6, Cl: 90, TCO2: 15 meq/l. Blood pH: 7.20 pCO2: 37.3. Elevated total CPK(See Table). Urinalysis was not taken since anuria. A diagnosis of acute kidney injury due to rhabdomyolysis was made. The patient required acute RRT. There were no signs of urinary tract obstruction in imaging studies. Clinical picture was complicated by development of respiratory failure due to bilateral pneumonia. He also had episode of allergic reaction to Sulfa. The patient was discharged home 3 weeks later on hemodialysis treatments since there no significant recovery of renal function.

Results:

Conclusions: Development of acute renal failure due to rhabdomyolysis may have been precipitated by Valerian root interaction with hepatic metabolism of Rosuvastatin.

Funding: Veterans Affairs Support

Day	S Creat (mg/dl)	Total CPK (IU/L)	Total Bilirubin (mg/dl)
1	14.9	>20,000	0.29
5	2.04	6441	1.18
16	5.10	182	0.48

PUB644

Two Cases of Successful Percutaneous Transluminal Angioplasty to Treat Immature Arteriovenous Fistulas Due to Non-Thrombotic Occlusions Takeshi Tosaki,[1] Takaya Sasaki,[1,2] Yu Honda,[1,2] Masahiro Okabe,[1,2] Masahiro Ishikawa,[1,2] Takashi Yokoo.[2] *[1]Kawaguchi Municipal Medical Center, Kawaguchi-shi, Saitama, Japan; [2]The Jikei University School of Medicine, Minato-ku Tokyo-to, Japan.*

Background: Percutaneous transluminal angioplasty (PTA) to stenosis of an immature arteriovenous fistula (AVF) serves as an effective treatment. A non-thrombotic occlusion of a mature AVF is also treated with PTA, and a high patency rate has been reported. However, the effectiveness of PTA for the treatment of an immature AVF due to non-thrombotic occlusion is still unknown. We report two cases of successful PTA for treatment of immature AVF caused by non-thrombotic occlusion.

Methods: Case 1 examines a 75-year-old man with end-stage renal failure due to benign nephrosclerosis. The patient underwent an AVF operation on his left forearm, and dialysis was started. The main trunk of the AVF in the cephalic vein was poorly developed, and a collateral vein was used for dialysis. Arteriography was performed one month after the operation because of insufficient blood flow for dialysis, showing a non-thrombotic complete obstruction in the main trunk. The main trunk was expanded completely without any complications, and blood flow became sufficient. Case 2 involves a 79-year-old man with end-stage renal failure due to diabetic nephropathy who underwent an AVF operation on the left tobacco fossa. Seven months later, pulsation of the AVF in the cephalic vein and hand edema appeared, and venous hypertension syndrome and an immature AVF were suggested. Arteriography showed a complete non-thrombotic occlusion of the main trunk of AVF; thus, PTA was performed on the occlusion. After the PTA, the pulsation of the AVF and hand edema disappeared. The expanded vein has been fully patent in both patients.

Results:

Conclusions: Although PTA is usually performed for complete non-thrombotic occlusions, few studies have been reported. Especially, there is no evidence for the developmental failure of the AVF due to non-thrombotic obstructions. We have reported here that PTA could be effective for immature AVF treatment due to complete non-thrombotic occlusion of the main trunk.

PUB645

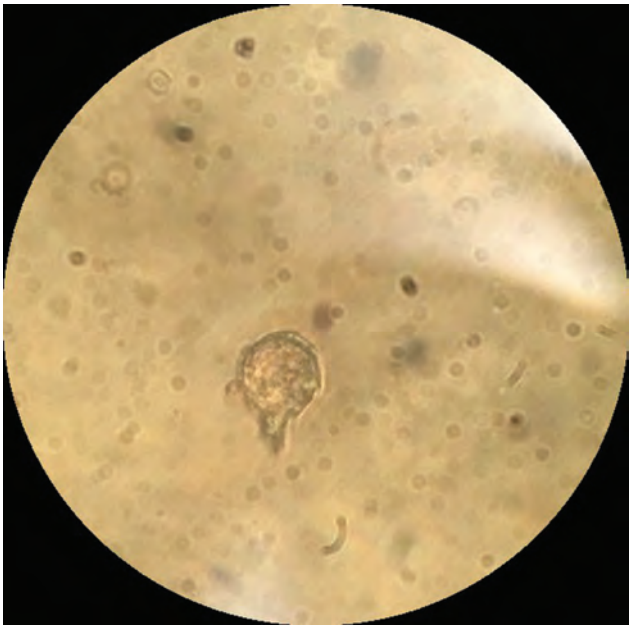
Urinary Schistosomiasis Aala Jaberi,[2,3] Jasvinder S. Bhatia.[1] *[1]Boston University Medical Center, Brookline, MA; [2]Nephrology, Boston Medical Center, Boston, MA; [3]Internal Médicine, Mount Auburn Hospital, Cambridge, MA.*

Background: Schistosomiasis, also commonly known as bilharzia, is a water-born parasitic infection most common in developing countries. It has been estimated that more than 97% of all schistosomiasis cases occur in Africa. In areas endemic for urinary schistosomiasis, bladder cancer is the most commonly diagnosed malignant neoplasm. Genitourinary schistosomiasis can present early with microscopic hematuria. In chronic infection, granulomatous inflammation leading to fibrosis and calcification of the bladder wall with the development of pseudopolyps can result. Early diagnosis of S. haematobium is based on identification of embryonated ova in the urine. The eggs are elongated at 110 μm to 170 μm in length by 40 μm to 70 μm in width. Here we present a case of a 24-year-old male with history of chronic hematuria.

Methods: 24-year-old Egyptian male with no significant past medical history, presented for evaluation of two-year history of terminal painless gross hematuria. He was a recent immigrant to the united states from Egypt, however he denied illicit drug use. He smoked cigarettes occasionally. Lab studies were significant for 16%eosinophils, creatinine 0.74mg/dL, normal C3, C4, undetectable Hepatitis C RNA. Urine sediment revealed nondysmorphic RBCs and the egg of Schistosoma hematobium. Further lab studies revealed positive IgG antibodies to both Schistosoma hematobium and Schistosoma Mansoni. Renal ultrasound revealed a 1.2cm bladder mass, which was resected on cystoscopy. The patient was treated with Praziquantel, with complete resolution of his gross and microscopic hematuria.

Results:

Conclusions: Urine microscopy is an essential tool in the diagnosis of urinary schistosomiasis. Prompt recognition can result in early referral for further investigations and expedited treatment and management.



PUB646

Monoclonal Gammopathy of Renal Significance: An Unresolved Dilemma Abhilash Koratala,[3] Don H. Esprit,[2] Volodymyr Chornyy.[1] *[1]UF Department of Nephrology, Gainesville, FL; [2]University of Florida, Gainesville, FL; [3]University of Florida, Gainesville, FL.*

Background: Monoclonal gammopathy of renal significance (MGRS) encompasses all renal disorders caused by a monoclonal immunoglobulin secreted by a nonmalignant B-cell clone. Patients with MGRS do not meet the criteria for overt multiple myeloma by definition. Management of these patients remains a clinical dilemma at this time.

Methods: A 33-year-old woman was referred for evaluation of CKD. She did not have any significant medical history except for hypokalemia and hypophosphatemia, noted about a year ago, requiring supplements. Vital signs were stable and the laboratory data at presentation is shown in figure1. In brief, she had mild reduction in GFR, hypokalemia, hypophosphatemia, non-anion gap metabolic acidosis and glycosuria without hyperglycemia suggestive of proximal renal tubular acidosis with Fanconi syndrome. In addition, there was discrepancy between urine protein and albumin excretion. Serum protein electrophoresis revealed an M-spike in the gamma region (2 g/dL). Bone marrow biopsy demonstrated hypercellular marrow (70%) with 20% of plasma cells with abnormal phenotype. Congo red stain was negative for amyloid. Skeletal survey was negative for lytic bone lesions. Based on current definitions, she was labelled as ‘smoldering myeloma’. We chose to monitor her renal function expectantly for now

without chemotherapy based on the fact that baseline GFR is a major determinant of renal outcome in most types of MGRS.

Results:

Conclusions: While the pathologic spectrum of renal diseases in MGRS is wide, the role of a kidney biopsy in changing the management is questionable. Moreover, the benefit of early initiation of chemotherapy in patients with 'stable' renal function is not established and chemotherapy has significant side effects on the other hand. There is no one-size-fits-all approach for the treatment of this entity at present and consensus on the pathological definition of the MGRS spectrum is needed in order to design future collaborative studies.

Figure 1: Laboratory data at presentation

Blood	Results	Reference range
White blood cell count (thou/mm^3)	7.4	4-10
Hemoglobin (g/dL)	12.1	12-16
Platelets (thou/mm^3)	102	150-450
Sodium (mmol/L)	135	136-145
Potassium (mmol/L)	3.1	3.4-5.1
Chloride (mmol/L)	108	98-107
Bicarbonate (mmol/L)	16	22-30
Urea nitrogen (mg/dL)	6	6-20
Creatinine (mg/dL)	1.1	0.4-0.9
eGFR (ml/min/1.73m2)	58	>90
Glucose (mg/dL)	98	65-99 fasting
Calcium (mg/dL)	8.2	8.0-10.6
Phosphate (mg/dL)	2.2	2.7-4.5
Urine		
Ph	6.5	5-8
Glucose	3+	Negative
Protein-creatinine ratio (mg/g)	2100	<150
Albumin-creatinine ratio (mg/g)	360	<30
Renal ultrasound: Kidney length 11.5/11 cm on the right and left respectively. No major structural abnormalities.		

PUB647

Thrombotic Microangiopathy: The Importance of Early Identification and Differentiation Otis H. Brunson,[2] Christopher T. Perry,[1] Sabrina G. Bessette.[2] *[1]University of South Alabama, Mobile, AL; [2]University of South Alabama College of Medicine, Daphne, AL.*

Background: The differentiation of Thrombotic Microangiopathy (TMA) is difficult due to overlapping features in presentation. Malignant hypertension-induced TMA (MH TMA) and atypical Hemolytic Uremic Syndrome (aHUS) are two of the more difficult etiologies of TMA to distinguish. Both can present with severely elevated blood pressures and classic TMA features: microangiopathic hemolytic anemia, thrombocytopenia, and renal failure. Rapid recognition of aHUS is important due to the vast improvement in prognosis with early Eculizumab initiation.

Methods: Presentation: A 59-year-old African American Female with PMH of hypertension presented with renal failure, anemia, and thrombocytopenia. Diagnosis: A diagnosis of TMA was made based on lab findings and schistocytes on peripheral smear. Intervention: Patient was initially treated for HTN emergency due to BP 181/115 mmHg on admission. She was then started on plasma exchange therapy, while ADAMSTS13 level was sent to rule out TTP. After ADAMSTS13 returned normal, an additional diagnosis of aHUS was considered. The decision was made to start Eculizumab while awaiting confirmatory aHUS genetic panel. The patient was treated with five weekly doses of Eculizumab. Outcomes: Hematologic parameters and renal function improved on Eculizumab. Genetic panel returned normal, thus aHUS ruled less likely. The patient's TMA was thus determined to be solely due to severe hypertension. The patient was discharged after blood pressure control and stabilization of Creatinine.

Results:

Conclusions: Our case highlights an important clinical point; in patients presenting with TMA and severe hypertension it is important to consider aHUS as a potential underlying diagnosis. Research shows that a subset of patients diagnosed with MH TMA have proven complement dysfunction, suggesting a close association between MH TMA and aHUS. Early treatment with Eculizumab is warranted due to better outcomes in kidney function and decreased progression to ESRD. Treatment with Eculizumab should be initiated as early as possible and before confirmatory genetic testing is completed.

PUB648

Recurrence of Primary FSGS in Renal Allograft Kartik Kalra,[1] Nabil Ghani,[1] Simranjit S. Randhawa.[2] *[1]Internal Medicine, Saint Peter's University Hospital, New Brunswick, NJ; [2]Sir Ganga Ram Hospital, New Delhi, India.*

Background: Focal segmental glomerulosclerosis (FSGS) refers to a histologic pattern that is a characteristic of various distinct underlying etiologies sharing a common theme of podocyte injury and depletion. Recurrent FSGS usually presents in the early post-transplantation period with re-emergence of proteinuria and progressive graft dysfunction. This is a case of a 52-year-old gentleman with progressive renal failure secondary to FSGS in renal allograft.

Methods: 52-year-old gentleman with past medical history of Left Nephrectomy (1981), End-stage renal disease (ESRD) secondary to primary FSGS status post (s/p) Living donor transplant (2016) currently on Tacrolimus, Mycophenolic Acid and Prednisone presented with 1 week history of progressive bilateral lower extremity swelling, and orthopnea (5 months s/p transplant). Vitals and Physical Examination were significant for Blood Pressure 172/100 mm Hg, +3 pitting pedal edema. Labs revealed Creatinine(Cr) 5.15 mg/dL (Baseline 2.3 - 2.5 mg/dL), Albumin 2.8 g/dL, Total Cholesterol 280 mg/dL, Spot Urine Protein:Cr Ratio 4.87 gram/gram. Subsequently, renal biopsy showed progressive scarring of glomeruli suggestive of FSGS. Histologic Variant - Not otherwise specified. The patient was managed conservatively on renin-angiotensin blockade and dietary sodium restriction. Corticosteroid and immunosuppressive therapy were continued.

Results:

Conclusions: Recurrence of primary FSGS is remarkably common in transplanted kidneys and may recur in up to 50% of the cases. Factors thought be associated with higher risk of recurrence include: Rapid progression of initial disease, White race, history of recurrence in a prior allograft. Case reports of recurrence have been reported for podocin and TRP6 mutations. The pathogenesis is thought to be possibly related to a circulating factor in majority of the cases. No definite treatment is available yet, though usual strategies include plasmapheresis to remove the "possible circulating factor", calcineurin inhibitors for their anti-proteinuric effects by stabilizing actin cytoskeleton in podocytes. Rituximab use has also been reported and is thought to have a direct action on the podocytes in addition to interference with the presentation of B cell antigens. Future research exploring pathogenic molecular pathways will lead to more insight into pathophysiology and FSGS classification and thus will lead way for improved treatment strategies.

PUB649

An Old Friend Strikes Again: A Rare Case of CMV Acute Tubulointerstitial Nephritis in a Transplant Recipient with AKI Sathish Karmegam,[2] Kosunarty Fa,[2,1] Jose A. Castillo-Lugo.[2,1] *[1]Dallas Nephrology Associates, Dallas, TX; [2]Nephrology, Methodist Dallas Medical Center, Dallas, TX.*

Background: Introduction: Cytomegalovirus (CMV) infection remains one of the most important etiology for the morbidity and mortality of transplantation patients. The impact on patients depends on the form of CMV infection. About 10% to 50% develop symptomatic disease while solid organ involvement (e.g. CMV nephritis) have a deleterious outcome and requires histopathology testing. This is a rare case of CMV presenting as acute tubulointerstitial nephritis.

Methods: Case Description: A 65 y/o male, recipient of a deceased-donor kidney transplant 8 months prior to admission presented with progressively worsening diffuse abdominal pain for 3 days, associated with nausea, vomiting, and diarrhea. CMV status at transplantation was CMV D+/R+, and baseline serum Cr was 1.2 mg/dl. Immunosuppression regimen consisted of tacrolimus, MMF, and prednisone. He received valgancyclovir prophylaxis for 3 months post-transplant, after which it was discontinued as per protocol. CT of abdomen/pelvis on admission was unremarkable. An US of the transplanted kidney showed some fullness around the allograft. Stool workup was negative. His tacrolimus level was elevated at 19 ng/mL and it was held. He became febrile and CXR showed RML infiltrate prompting the use of broad spectrum antibiotics. His CMV viral load returned at 2.9 million copies/ml. He was started on IV ganciclovir for CMV disease. All cultures and cytology were unremarkable. On day 8, his Cr started to increase up to 5.0 mg/dl with a benign sediment and therapeutic tacrolimus levels. A kidney biopsy revealed acute interstitial nephritis with viral inclusions but no signs of rejection. He was started on IV methylprednisolone 500 mg daily and his Cr started to downtrend to 0.9 after 5 days. His CMV viral load dropped to 9492 copies/mL. He received a total of 25 days of IV ganciclovir and then transitioned to oral route to be continued for a total of 6 months as ID recommended a long duration of induction therapy.

Results:

Conclusions: Discussion: CMV infections in renal allograft recipients constitute an important cause of renal graft dysfunction. There is an increasing incidence coinciding with more potent immunosuppression regimens. CMV nephritis can present as glomerulopathy and tubulointerstitial disease. High clinical suspicion and vigilance required for diagnosis and prompt treatment.

PUB650

An Interesting Case of Hypercalcemia from HTLV-1 Associated Adult T-Cell Lymphoma Krishna Sury,[1] Namrata Krishnan.[1,2] *[1]Section of Nephrology, Yale University School of Medicine, New Haven, CT; [2]Section of Nephrology, Department of Veterans Affairs, West Haven, CT.*

Background: Adult T-cell leukemia/lymphoma (ATL) is a rare form of non-Hodgkin lymphoma involving regulatory T cells. Human T-cell lymphotropic virus type 1 (HTLV-1) is a known risk factor. ATL is rarely seen in the United States, but is prevalent in endemic areas such as Japan, South America, Central Africa, and the Caribbean islands. We present a case of severe, symptomatic hypercalcemia in a Jamaican man who was ultimately diagnosed with HTLV-1 associated ATL.

Methods: A 71-year old Jamaican man with hypertension, diabetes, and stage 2 chronic kidney disease presented with one month of fatigue, unintentional sixteen-pound weight loss, and polyuria. Laboratory data showed an elevated creatinine of 3.1 mg/dl (from baseline 1.5 mg/dl), and hypercalcemia (ionized calcium 8.53 mg/dl) that was unchanged after saline therapy and required calcitonin and intravenous pamidronate. Workup included negative SPEP/UPEP, normal angiotensin converting enzyme level (28 mg/l), low Vitamin D (<13 ng/ml), suppressed PTH (12 pg/ml), and elevated PTHrP (40 pg/ml). Total-body CT scan showed no adenopathy, but FDG-PET revealed increased metabolic activity in lymph nodes throughout the neck, chest, abdomen, and pelvis. On biopsy, the bone marrow was hypercellular with atypical lymphocytes. Peripheral blood flow cytometry showed T cells with an abnormal immunophenotype, and a T-cell

gene rearrangement study confirmed monoclonality. HTLV-1 IgG antibody testing was positive. Final diagnosis was HTLV-1 associated adult T-cell leukemia/lymphoma. Sadly, due to distrust of the medical system, the patient refused care. Weeks later, he was found dead in his home.

Results:

Conclusions: Severe hypercalcemia is present in less than 4% of lymphomas, yet 70% of acute ATL cases are complicated by severe (often resistant) life-threatening hypercalcemia. PTHrP plays a pathologic role. Although HTLV-1 associated ATL is rare in the United States, given the high frequency of international travel, diseases endemic to other parts of the world must be considered during diagnostic evaluation. The asymptomatic carrier state and long latency period (decades) between infection with HTLV-1 and onset of ATL makes the diagnosis challenging and requires a high index of suspicion.

PUB651

Dense Deposit Disease – A Clinical Case Report Sofia S. Coelho, Ana Fernandes, Elsa S. Soares, Patrícia V. Santos, Ana Farinha, Ana Natario. *Nephrology, Centro Hospitalar de Setúbal, Setubal, Portugal.*

Background: Dense deposit disease (DDD) and C3 glomerulonephritis (GN) are rare forms of renal disease both in children and adults. Initially classified as a subgroup of membranoproliferative GN type II, these conditions have recently been re-classified as *complement-associated glomerular disease*. Both DDD and GN result from an abnormal regulation of the alternative complement pathway, with variable pathological mechanism and clinical presentations.

Methods: We report the case of a 48-year-old Caucasian man with smoking habits and a 2 years history of arterial hypertension. No individual or family history of kidney disease was known. The patient was referred to the Nephrology department 2 months after the detection of rapidly progressive kidney failure, nephrotic syndrome, hematuria and poorly controlled hypertension. At physical examination, acquired partial lipodystrophy was observed, and the ophthalmologic observation revealed a macular drusen suggestive of DDD. The blood tests revealed a quite frankly low C3, with the remaining being negative for autoimmune disease, monoclonal gammopathy or viral infection. The renal ultrasound showed normal kidneys' features. In order to clarify the etiology of the renal disease, a renal biopsy was taken, which showed glomerulonephritis associated with dense deposits, exclusively of C3; cellular crescents, endocapillary proliferation, moderate interstitial fibrosis and tubular atrophy were also present. A rapid worsening of renal function, requiring hemodialysis, followed. Given the presence of active lesions in the histology, combined immunosuppression therapy with steroids plus mycophenolate mofetil, was started. Later on, the the complement analisys revealed a nonsense pathogenic mutation of the complement factor B gene (c.1424dupT, p.Ser476Glufs*43) not previously described and a homozygous haplotype for the complement factor H gene, known to confer risk for atypical haemolytic uraemic syndrome (CFH3-tgtgt).

Results:

Conclusions: DDD is a rare disease with a poor renal prognosis; renal failure requiring dialysis at the time of presentation is a predictor of progression to end stage renal disease. Randomized clinical trials designed to establish the better therapeutic options are needed.

PUB652

Podocytopathy in Anabolic Steroid User Rapidly Responsive to Steroids Melissa C. Fajardo,[1] Beenish Noor,[2,1] Suhaib A. Andrabi,[1] Jeffrey D. Wallach,[1] Sudhanshu Jain.[1] *[1]Harlem Hospital, New York, NY; [2]Harlem Hospital Centre, NY, NY.*

Background: Focal segmental glomerulosclerosis (FSGS) is a commonly found histologic lesion that underlies nephrotic syndrome in adults. It can be classified into primary and secondary variants. Primary FSGS, is thought to be a result of injury to the podocyte, with involvement of parietal epithelial cells. Secondary FSGS, is usually a result of an adaptive response to hyperfiltration and glomerular hypertrophy that comes about from scarring from previous injury or from another glomerular abnormality. Secondary FSGS has been well linked to obesity, drugs, infections amongst other things. Recently, a link to long term anabolic steroid use and development of secondary FSGS was identified. Our case describes a patient who was on chronic anabolic steroids and presented with nephrotic syndrome.

Methods: 29 y/o AAM with no known past medical history who presented with complaints of progressive B/L LE swelling, scrotal swelling and abdominal distention for 2 weeks. He denied any recent illness, previous similar episode, sick contacts, recent travel. He c/o increased urinary frequency, foamy urine, vomiting and DOE. He had taken a supplement called Halo X, to build muscle for 6 months intermittently amongst other supplements years before. Negative family history, no toxic habits, was a body builder. O/E- BP-142/80, HR-70 RR- 16, he was afebrile;he had bilateral gynecomastia; abdomen was distended, soft; there was ++scrotal/penis edema, LE- 4+edema B/L to upper thigh, erythema,+tenderness. Investigations-K- 5.2, BUN/creatinine were 24/1.6, total protein-4.1 and albumin-1.5, UA-3+ protein, CK-1167, UACR-3938mg/g UPCR-4.2g/g;urine sediment was bland. CystatinC-0.98 Initial management-IV diuretics and albumin infusion;serologic studies were sent and were negative, kidney biopsy was scheduled but not done. Later, he came to clinic c/o of worsening LE swelling and pain. O/E-edematous, tense, erythematous LE, scrotal swelling. He was admitted, given IV diuretics. Labs- BUN/creatinine of 39/2.2, albumi n 1.0; UACR-3995 and UPCR-4.0 Renal bx- 80% foot process effacement, consistent with primary FSGS, tubular atrophy.

Results:

Conclusions: Management- 120mg of prednisone qod, diuretics; No ACE/ARB-high K. Initial outpatient follow up (3 weeks) showed- 31kg weight loss, no cushingoid features, BUN/Creat-20/1.71UACR-267, UPCR-0.4;albumin-4.5 K was normal, ARB was initiated.

PUB653

Isolated Renal Injury: A Case of Monoclonal Light Chain Deposition Disease Enrique E. Acosta Oruna,[7] Alexander Borrero-Arvelo,[7] Stefano Coppola fasick,[4] Jacobo J. Loyola,[2] Elvin Soto,[3] Eddie M. Rodriguez,[1] Lorena D. Morales,[5] Carlos S. Rosado-Rodriguez.[6] *[1]None, San Juan, PR; [2]VA Caribbean Health Care System, Camuy, PR; [3]VA Caribbean Healthcare System, San Juan, PR; [4]VA Caribbean healthcare system, Guaynabo, PR; [5]VA caribbean Healthcare System, San Juan, PR; [6]Veterans Affairs CAribbean Healthcare System, Guaynabo, PR; [7]Veterans Affairs Caribbean Healthcare System, San Juan, PR.*

Background: Monoclonal light-chain deposition disease (MLCDD) is a systemic disease that typically presents initially with isolated renal injury related to a glomerular lesion associated with nonamyloid electron-dense granular deposits of monoclonal light chains with or without heavy chains.

Methods: A 69 year-old male was brought to the emergency department with the chief complaint of combined lower extremity, scrotal, and penile swelling of one week of evolution. Past medical history includes HTN, obesity, dyslipidemia, prostate cancer treated with local radiotherapy, radiation cystitis, and GERD. His medication profile included nifedipine, atorvastatin, and omeprazole. Physical examination revealed elevated blood pressure 169/75mmHg and anasarca. Laboratories showed AKI with an increase in creatinine from 1.2mg/dl to 2.0mg/dl, anemia of 8.3g/dl, proteinuria of >500mg/dl by dipstick, and microscopic hematuria. A urine 24-hour collection was performed and showed nephrotic range proteinuria. Further lab results reported hypocomplementemia, elevated rheumatoid factor, and positive IgG schistosoma titers. In view of this, patient was trated with praziquantel. However, eosinophilia, anasarca, and elevation in serum creatinine persisted despite treatment. Secondary causes of nephrotic syndrome were ruled out. Hepatitis workup, Strongyloides, and HIV with negative results. SPEP and UPEP without monoclonal spikes. Renal biopsy was requested and light microscopy remarkable for thickened capillary loops and membranes which suggested a membranoproliferative pattern. Electron microscopy revealed subendothelial deposits with mesangial widening and diffuse efacement of podocyte foot processes. Immunofluorescence positive focal granular deposits of low intensity for IgG and lambda light chains, moderate intensity for IgM, and high intensity for C3. All deposits were mesangial and subendothelial in origin. Bone marrow biopsy negative for multiple myeloma. PET scan negative. Serum free light chains were elevated with a high kappa/lambda ratio. Patient was diagnosed with MLCDD.

Results:

Conclusions: MLCDD is a rare entity that should be considered in the differential diagnosis of patients with nephrotic syndrome. A delay in diagnosis worsen renal outcomes due to the rapid progression of disease.

PUB654

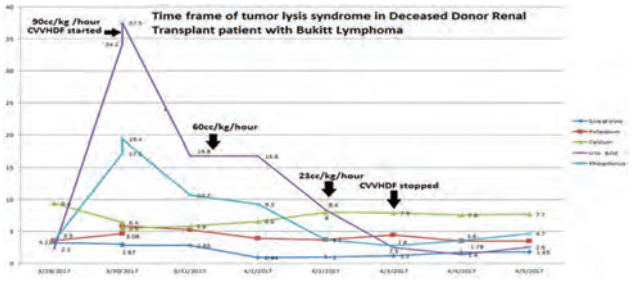
Successful Treatment of Severe Tumor Lysis Syndrome in a Deceased Donor Renal Transplant Recipient Massini Merzkani, Jamil Ibrahim, Richard L. Barnett, Vinay Nair. *Northwell, Mineola, NY.*

Background: The recent use of more effective targeted agents enhances the risk of developing Tumor Lysis Syndrome(TLS). The mortality in TLS is 66% in patients who present with AKI. Few cases has been reported in patients with renal transplantation. We present a case in a patient with deceased donor renal transplantation(DDRT) with severe TLS refractory to medical management which was successfully treated with CVVHDF.

Methods: A 39 year old female with history of DDRT 15 years ago, diabetes mellitus and recent pregnancy 4 months ago presenting with abdominal pain and AKI. Initial creatinine was 3.7 mg/dL. The CT abdomen revealed multiple lymph nodes in the peritoneum. A biopsy revealed Burkitt lymphoma. Epstein Barr serum PCR was 195322 IU/ml. Her immunosuppression was changed, by increasing prednisone to 10 mg PO daily and discontinuing tacrolimus. The patient initiated chemotherapy with rituximab (678 mg). The following day the patient had oliguria. Her serum calcium decreased to 6.4 mg/dL, uric acid increased to 34.3 mg/dL, serum phosphorus increased to 19.2 mg/dl and serum potassium rised up to 5.9mmol/L. Her EKG revealed peaked T waves, widening QRS 0.15 sec and prolonged QTc 0.55 sec. She received multiple infusions of calcium gluconate, fluids and rasburicase 6mg. EKG changes and electrolyte abnormalities did not reverse with medical management. High dose CVVHDF was initiated (90cc/ kg / hour) with immediate improvement of electrolytes (figure). Subsequent CVVHDF dose was decreased to 60 cc/kg/hour on day 2 and 3 then 23cc/kg/hour on day 4. On day 5 urine output increased and CVVHDF was discontinued. Serum Creatinine normalized to 1mg/dL

Results:

Conclusions: This is one of the few cases reported with TLS in a renal transplantation recipient. This case showed severe hyperkalemic EKG changes despite mild hyperkalemia enhanced by hypocalcemia. In this case high dose CVVHDF was started immediately as she was refractory to medical management. High clearance CVVHDF may not only be lifesaving but was associated with excellent recovery in the renal transplant.



PUB655

Thrombotic Microangiopathy in the Kidney Transplant Population: An Emergency That Requires a Quick Diagnosis and Treatment Hassaan Rasheed,[1] Aleksandra De Golovine.[2] *[1]UT Houston, Houston, TX; [2]UTHSC-H, Houston, TX.*

Background: Thrombotic microangiopathy (TMA) is a histopathological term that describes glomerular, arteriolar or interlobular artery lesions, characterized by patchy distribution, with intimal cell proliferation, thickening and necrosis of the wall, thrombi and narrowed lumens.(1) These lesions are rare, but can be devastating in kidney transplants if the processes that cause them are not stopped. Post kidney transplant TMAs can be recurrent, often the result of genetic mutations or de novo, attributed to drugs, infections or rejection. Quick diagnosis is key to the survival of the graft. We describe three cases of TMA in renal transplant recipients.

Methods: The first case is a 35-year-old African American man who underwent a living unrelated kidney transplant complicated by delayed graft function. A kidney biopsy was done and showed no evidence of rejection. He was readmitted 4 months later for sepsis secondary to a urinary tract infection and CMV colitis. He also had severe acute kidney injury requiring temporary hemodialysis. A kidney transplant biopsy was repeated which revealed focal segmental glomerular platelet thrombi, consistent with disseminated intravascular coagulation. Electron microscopy showed segmental intracapillary platelet aggregates consistent with microthrombin and TMA. The infections were treated and his kidney function recovered. The second case is a 40-year-old white female with atypical hemolytic uremic syndrome on eculizumab, who underwent a living unrelated kidney transplant. She was found to have a rising creatinine and a transplant kidney biopsy revealed TMA, likely secondary to atypical hemolytic uremic syndrome despite being on eculizumab. She was found to have CMV colitis. She was treated and her calcineurin inhibitor was discontinued. Her kidney function stabilized. The third case is a 60 -year- old African American female with a history of active hepatitis C who underwent a deceased donor kidney transplant from a hepatitis C positive donor and developed acute kidney injury. Transplant kidney biopsy revealed HCV related cryoglobulinemia and TMA. Her hepatitis C was treated and her kidney injury resolved.

Results:

Conclusions: Discussion: Early recognition and accurate diagnosis of TMA in kidney transplant recipients improves graft survival. 1) Ponticelli C, Banfi Giovanni. Thrombotic microangiopathy. *Transplant Int*

PUB656

An Unusual Case of Membranoproliferative Glomerulonephritis Due to Culture Negative Peritonitis Ahmed O. Giwa,[2] Silvi Shah.[1] *[1]University of Cincinnati, Cincinnati, OH; [2]Internal Medicine, University of Cincinnati, Cincinnati, OH.*

Background: Membranoproliferative glomerunephritis (MPGN) is a type of chronic nephritis. Viral infections (e.g. hepatitis C) and chronic bacterial infections (e.g. endocarditis) are the most common reported infectious causes. We report a rare case of MPGN due to culture negative peritonitis.

Methods: 41-year-old female initially presented with a 3-day history of diffuse abdominal pain, abdominal swelling and acute kidney injury (AKI). Her medical history was significant for orthotropic liver transplant 13 years back complicated by chronic rejection, cirrhosis and ascites requiring frequent paracentesis. Vitals were stable. Physical examination revealed ascites and bilateral lower extremity swelling. Blood work showed a white cell count of 3.8 10E3/microL and elevated creatinine of 3.5 mg/dl (baseline creatinine of 1.2 mg/dl). Urinalysis showed 100 RBC's with dysmorphic RBC's seen on urine microscopy. Spot urine protein/creatinine ratio was 8.4. Albumin was 3.2g/dl. Complement C3 was low (57mg/dl) but C4 was normal (22mg/dl). Workup for Hepatitis and HIV were negative. No monoclonal or cyroglobulins were detected. Renal ultrasound showed normal sized kidneys with no hydronephrosis. Paracentesis revealed 372 TNC's and 75% neutrophils. A diagnosis of spontaneous peritonitis was made and patient was started on broad-spectrum antibiotics. Both ascitic fluid culture and blood culture remained negative. Due to worsening oliguric AKI (creatinine peaked to 4.3mg/dl on day five of admission), renal biopsy was done; that showed a proliferative glomerular lesion with evidence of immune complex deposits, predominantly IgG and C3 in the mesangial region and the capillary walls, representing features consistent with MPGN. Etiology of MPGN was attributed to culture negative peritonitis. Patient was started on dialysis, but was dialysis free at time of discharge with creatinine of 3.3mg/dl and stable electrolytes.

Results:

Conclusions: This case underscores an unusual cause of MPGN due to culture negative peritonitis, as compared to the well-documented cases secondary to Hepatitis C, bacterial endocarditis and fungal infections. Clinicians should be mindful of this to avert renal complication of peritonitis.

PUB657

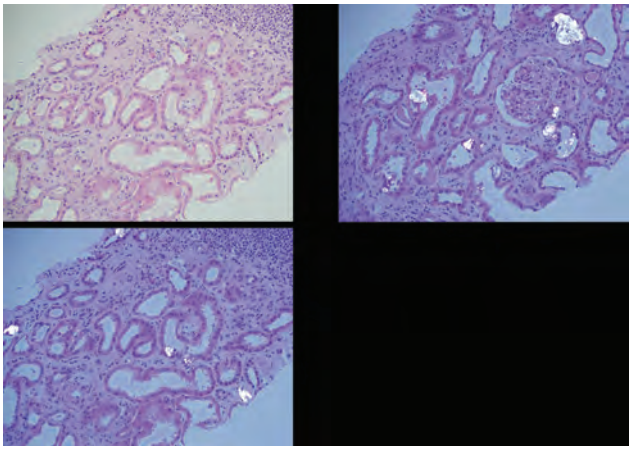
Oxalate Nephropathy: A Case of Acute Renal Failure from Chronic Pancreatitis Trevor R. Smith,[2] Monica P. Revelo Penafiel,[1] Josephine Abraham.[1] *[1]University of Utah, Holladay, UT; [2]Nephrology, University of Utah, Salt Lake City, UT.*

Background: Acute oxalate nephropathy (AON) is a rare form of secondary enteric hyperoxaluria that can result in renal failure.

Methods: A 78 year old white male presented with an elevated creatinine from a baseline of 1.8 mg/dL. He has a history of acute gallstone pancreatitis with necrosis and pseudocysts; acquired diabetes; hypertension; and carcinoid tumor of the appendix status-post resection 5 years prior. He was complaining of chronic explosive watery diarrhea for 2 months associated with a 70 lb weight loss over 12 months. Physical exam was significant for mild abdominal distension and no fluid wave, and non-blanching purpuritic rash on the bilateral lower extremities. Urinalysis was unremarkable. Serologic studies revealed a creatinine of 4.98 mg/dL, cystatin C of 3.1 mg/L, phosphate 6.1 mEq/L, total calcium 8.5 mg/dL. Monoclonal spike of 0.59 g was found on serum protein electrophoresis with kappa/lambda serum free light chain ratio of 2.15. CT of the abdomen and pelvis showed pancreatic calcifications, but was otherwise negative. Renal biopsy showed diffuse oxalate crystals with associated tubular damage, AIN with scattered eosinophils, 30% interstitial fibrosis and tubular atrophy, moderate hypertensive nephrosclerosis. Additionally, basement membrane thickening and mesangial expansion was found. Immunofluorescence was negative for kappa or lambda light chains or IgG4. Congo red stain was negative. Bone marrow biopsy showed plasma cell dyscrasia (5% plasma cells), and a small population of monoclonal B-cells (1.5% by flow cytometry). The patient was treated with pancrealipase enzyme replacement with improvement of his diarrhea. His creatinine stabilized to ~ 4.

Results:

Conclusions: Case series of acute oxalate nephropathy with pancreatic insufficiency have been described. Here we describe a case of unknown exocrine pancreatic insufficiency where the diagnosis of oxalate nephropathy lead to alternative treatment of his pancreatic disease.



PUB658

A Case of Asymptomatic Hydralazine-Induced ANCA Vasculitis Eric Chang, Jeffrey M. Turner. *Yale University, New Haven, CT.*

Background: ANCA vasculitis covers a wide spectrum of different disorders, typically microscopic polyangiitis, granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis. Less commonly seen is drug-induced vasculitis. We report a case of asymptomatic hydralazine-induced ANCA vasculitis.

Methods: A 32-year-old female with history for viral cardiomyopathy with past cardiogenic shock and subsequent recovery of heart function, who presented with new, progressive renal dysfunction. Renal injury occurred within 6 months of presentation with creatinine increasing from 0.85 mg/dL to 1.96 mg/dL and then 2.32 mg/dL. She had no significant symptoms at time of presentation, only seasonal allergy symptoms of itchy eyes and rhinorrhea. She was exposed to antibiotics for a root canal procedure 3 months prior to presentation. She recently had several medications tapered off by her cardiologist, including hydralazine, isosorbide dinitrate, losartan and carvedilol. Review of systems was negative for chest pain, shortness of breath, nausea, vomiting, diarrhea, muscle aches, joint pains and rashes. Urine sediment revealed several dysmorphic RBCs and >300 proteinuria on dipstick. Further diagnostic testing showed normal C3/C4, negative hepatitis B/C and HIV, positive ANA at 1:320, elevated dsDNA antibody level of 252 IU/mL, elevated anti-histone antibody of 3.4, positive p-ANCA with anti-MPO level of 553.6 CU, and 8.66 g/g proteinuria with normal urine immunofixation. Renal biopsy demonstrated necrotizing glomerulonephritis with chronicity consistent with

pauci-immune crescentic glomerulonephritis, and presence of acute interstitial nephritis. Treatment to date has included prednisone, resumption of losartan and rituximab.

Results:

Conclusions: Hydralazine has been associated with two rheumatic syndromes: drug-induced lupus and ANCA vasculitis. Drug-induced lupus rarely involves the kidneys, and our patient did not exhibit any symptoms suggesting lupus. On the other hand, hydralazine-induced ANCA vasculitis frequently has renal involvement. Notable differences between hydralazine-induced ANCA vasculitis and idiopathic ANCA vasculitis include presence of several different antibodies: anti-histone, anti-lactoferrin, anti-elastase and antiphospholipid. This case serves to shed light on a rare condition, and to highlight the importance of rigorous review of patient medications for potential sources for renal disease.

PUB659

Men in Our Own Backyard: Case Reports of ESRD from Suspected Mesoamerican Nephropathy Susanne F. Mclaughlin,[2] Sreedhar A. Mandayam.[1] *[1]None, Missouri City, TX; [2]Nephrology, Baylor College of Medicine, Houston, TX.*

Background: There is a mysterious cluster of renal failure without obvious etiology in young agricultural workers from Central America. Potential risk factors including pesticide exposure, heat stress, NSAID use, and contaminated water are being implicated. As part of a larger study at Baylor College of Medicine investigating Mesoamerican Nephropathy, we are conducting demographic surveys on immigrant patients with ESRD who come to our ER for dialysis. Here we present a selection of case reports illustrative of Mesoamerican Nephropathy.

Methods: ESRD patients who have emigrated from Mexico or Central America volunteer for a survey about their work and living conditions in their native country. Those with a known cause of ESRD are excluded. Data is then compiled to look for commonalities in their environmental exposures. The following are representative cases from our study population. A 54 y/o M from Guatemala, who spent 30 years working as a banana farmer, developed ESRD at the age of 48. He reports chemical exposures, NSAID use, drinking home-brewed liquor, and several incidences of heat stress. His water source was unfiltered irrigation tubes in the fields. He rarely washed his hands prior to eating. His father, who was also a banana farmer, died from renal failure at the age of 80. A 37 y/o M from El Salvador, who spent 13 years working in sugar cane and cotton fields, developed ESRD at the age of 34. He reports chemical exposures, NSAID use, and dehydration. His water was unfiltered from a spigot at home. His father and uncle, both of whom worked cutting sugar cane, died from renal failure, both at the age of 56. A 53 y/o M from Mexico, who spent 25 years working in fields growing corn, tomatoes, and bananas, developed ESRD at the age of 40. He reports chemical exposures, NSAID use, local herbal use, and several incidence of heat stress.

Results:

Conclusions: Unfortunately there is no known treatment for Mesoamerican Nephropathy. The suspected pathogenesis of ESRD is progressive damage from repeated episodes of acute kidney injury. It is our hope that our work will contribute to the body of evidence that elucidates definitive risk factors for Mesoamerican Nephropathy. Intervention strategies directed at environmental and occupational exposures can then be implemented in efforts to prevent this malady, which is demonstrating increasing prevalence, morbidity, and mortality.

PUB660

IgA Nephropathy: A Diagnostic Dilemma Roshni Radhakrishna,[3] Manish K. Saha,[2] Volker Nickeleit,[1] Patrick H. Nachman.[4] *[1]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [2]UNC Kidney Center, Chapel Hill, NC; [3]University of North Carolina, Carrboro, NC; [4]University of North Carolina School of Medicine, Chapel Hill, NC.*

Background: Primary IgA Nephropathy (IgAN) is the most common form of glomerulopathy, while secondary causes of IgAN include inflammatory bowel diseases (IBD), infections and liver disease among others. It usually presents as glomerular hematuria and proteinuria with variable progression of kidney disease; crescentic rapidly progressive glomerulonephritis (RPGN) is an uncommon presentation. Other possible differential diagnoses in this setting include IgA ANCA vasculitis, IgA dominant infectious glomerulonephritis (AIGN) and lupus nephritis.

Methods: 67 year old female with Ulcerative colitis with complex surgical history including total colectomy, partial small bowel resection, multiple infections and fistulas was admitted with poor oral intake and abdominal pain. She was found to have septic shock from enterocutaneous fistula and Enterococcal UTI which was treated with antibiotics. Subsequently, she was found to have a gradual rise in creatinine from baseline of 0.6-0.8 to 3.8 mg/dl with an active urinary sediment with acanthocytes and UPCR of 12mg/mg. Review of past records since 2012 showed low grade proteinuria and microscopic hematuria which had not been evaluated. C3 was low at 80 mg/dl with elevated circulatory IgA levels at 855 mg/dl. Kidney biopsy revealed diffuse proliferative IgA glomerulonephritis with features of MPGN and associated focal and segmental cellular and fibrocellular crescents. She was subsequently started on steroids. For progressive renal failure she was initiated on dialysis.

Results:

Conclusions: This case highlights the dilemma in diagnosis of a RPGN presentation of IgAN in the setting of systemic infections. Our patient has had multiple infections with gram-negative organisms prior to this presentation, although not diabetic or elderly. She had evidence of consistent low grade hematuria and proteinuria, years before this presentation, pointing towards possible underlying secondary IgA nephropathy associated with IBD; in addition, the elevated ratio of IgA: C3 (ratio>10) was consistent with this diagnosis. The lack of C3 predominance staining over IgA, maintenance of lambda/kappa staining, absence of subepithelial humps may suggest crescentic IgAN rather than AIGN. It is essential to differentiate these two conditions as treatment differs. We propose that presence of low grade hematuria and proteinuria be evaluated for underlying glomerular diseases in patients with IBD.

PUB661

Smoldering C3 Glomerulonephritis Exacerbated by Blood Transfusion and Inactivated after Immunosuppression Therapy Hatem Elabd, Rushi K. Nayak, Tarek Rashid. *Jacobi Medical Center, New York, NY.*

Background: C3 glomerulonephritis (C3GN) is a separate form of proliferative glomerulopathy under category of C3 glomerulopathies, which is characterized by isolated or predominantly C3 deposits. It is associated with dysregulation of the complement alternative pathway (AP) secondary to acquired autoantibodies and/or genetic mutation of complement proteins.

Methods: We report a case of a 49-year-old male, presenting with bilateral lower extremity swelling, hypertension, plasma creatinine of 1.2mg/dl, protein-to-creatinine ratio 5.4 gm/g and bland urine, markedly depressed C3 level of 7mg/dl [90-180], normal C4, and normal ASO titer. A renal biopsy was planned. In the meantime, the patient received a blood transfusion, after which he became acutely febrile, developed a non-oliguric acute kidney injury (AKI) with creatinine peak of 3.1mg/dl, worsened proteinuria, and dark urine with an active sediment. Therefore pulse steroids were commenced then oral steroid 1mg/kg maintained. Renal pathology shows evidence of C3 glomerulonephritis. Further AP workup revealed presence of Factor H autoantibodies 28 Unit/mL [<=22], C3 nephritic factor (C3NeF) 38 units/ml [<=0] and markedly elevated soluble membrane attack complex serum C5b-9 >1700 [Reference Range: <=244 ng/mL]. Patient underwent Plasma exchange for 7 sessions, then rituximab two weekly doses (0.5 and 1 gm), and maintained on prednisone. Patient improved clinically, creatinine stabilized at 1.2mg/dl, proteinuria decreased. In addition factor H autoantibodies normalized, C3NeF decreased to 6 units/ml, serum C5b-9 went to 546 ng/ml and C3 increased to 55mg/dl. Mycophenolate introduced at this time and steroids tapered.

Results:

Conclusions: An underlying genetic or acquired complement alternative pathway abnormality can be possibly exacerbated by triggering immune complement system which subsequently triggers an unbalanced excessive continual driving of complement terminal pathway activation. In our case, blood transfusion might have led to induction of complement cascade activity either through classical or alteranative pathway dysregulation. There is limited evidence and no randomized trials to inform therapeutic decisions in C3GN. In our case, the therapeutic regimen may mitigate AP pathway activity and normalize factor H autoantibodies.

PUB662

Complications of Therapy for Pauci-Immune Rapidly Progressive Glomerulonephritis Syeda A. Raza,[1] Melanie Powell,[2] Leigh K. Hunter.[3] *[1]Methodist Health System, Dallas, TX; [2]Methodist Dallas Medical Center, Dallas, TX; [3]Methodist Hospitals of Dallas, Dallas, TX.*

Background: Rapidly progressive glomerulonephritis (RPGN) is a clinical syndrome resulting from damage to the glomeruli and is characterized by progressive loss of renal function over a short period of time. RPGN is classified into three categories, each based upon the immunofluorescence patterns. Type III, also known as pauci-immune RPGN, accounts for about 50% of RPGN cases.

Methods: A 68-year-old Hispanic female with history significant for P-ANCA-associated pauci-immune RPGN and Type II Diabetes Mellitus presented with complaints of weakness, worsening lower extremity edema that was refractory to outpatient diuretics and dysuria. Patient had been on an immunosuppresant (Rituxan) and steroids (Prednisone 40mg/day) with plans to taper. On physical examination, the patient was noted to have Cushingoid features (moon facies) along with 3+ pitting edema to the mid shins bilaterally with bruising apparent in the bilateral feet and ankles. Lab work was notable for leukocytosis and urinalysis positive for urinary tract infection. Patient was admitted for management of the multiple side effects related to prednisone therapy including marked edema refractory to oral diuretics, muscle weakness, and urinary tract infection. Patient was treated with IV diuretics for the lower extremity edema and antibiotics for the urinary tract infection. Patient had improvement of her symptoms and was sent home with a steroid taper to follow up with nephrology outpatient.

Results:

Conclusions: Treatment of RPGN relies on the use of corticosteroids. This case illustrates the importance of recognizing side effects seen with therapy and assessing the short-and long-term effects of such therapy.

PUB663

ACEI Induced Anaphylactoid Reactions in Polysulfone Dialyzers Anthony F. Iluyomade,[2] Hema Manickam.[1] *[1]None, Granite Bay, CA; [2]University of California Davis Medical Center, Sacramento, CA.*

Background: Gone are the days of severe anaphylactic reactions to Ethylene oxide and non-biocompatible membrane dialyzers; with the new era of using polysulfone and other synthetic dialyzers. Hypersensitivity reactions to these synthetic dialyzers are also on the rise. Reports of Anaphylactoid reactions in patients on ACEI dialyzing via PAN (AN69) dialyzer is widely known to occur from bradykinin effects but similar reactions

in patients on ACEI's using non – PAN (AN69) is not well known. We hereby present a case of anaphylactoid reaction to two different manufacters polysulfone dialyzers in a patient on ACEI.

Methods: A 53 year old male with a history of ESRD on HD for 3 years, HTN on Lisinopril 10mg daily, CAD S/P CABG X 3 stents and type 2 DM with retinopathy, transferred to the ER from his HD unit due to sudden shortness of breath symptoms with 86% O2sats and becoming restless about 12 minutes after starting his regular dialysis session. He was dialyzed on rexeed - 18R, a reusable dialyzer and was on the 9th re-use that day. He also endorsed similar symptoms about 3 days prior to presentation by the 8th use but these were self limiting. Patient had always tolerated his HD sessions and was initially on Revaclear polysulfone dialyzer briefly. He had been on Lisinopril treatment for hypertension management for years. No prior allergy to food or medications. Chest xray evaluation showed mild pulmonary edema, cardiac work up including an ECHO and Cardiac Cath were negative. Patient had similar reactions the next day after hospital admission when revaclear polysulfone dialyzer was used. His symptoms resolved with supplemental O2 treatment and was able to complete his dialysis session. He had not received his Lisinopril since admission given hyperkalemia and was able to tolerate dialysis from the 3rd day onward. Patient's Lisinopril was eventually discontinued and he is back to his outpatient HD unit using the same rexeed polysulfone dialyzer and has not had any recurrent symptoms.

Results:

Conclusions: ACEI triggered anaphylactoid reactions have not been commonly reported in patients using non-PAN dialyzers and literature review shows very few cases of similar reactions in ACEI and Polysulfone dialyzers. With the wide spread use of both Polysulfone dialyzers in HD units and increasing number of dialysis patients on ACEI, knowledge of such possible reactions can help in the management of our dialysis patients.

PUB664

Histoplasmosis in a Renal Transplant Patient: A Case Report Fernanda T. Ferreira,[2] Antonio A. Portela Neto,[7] Laura Onuchic,[6] Marcella M. Frediani,[1] Precil D. Neves,[3] Flavio De paula,[4] Elias David-Neto.[5] *[1]USP, Sao Paulo, Brazil; [2]University State of São Paulo, São Paulo, Brazil; [3]University of S?o Paulo, S?o Paulo, Brazil; [4]University of Sao Paulo School of Medicine, Sao Paulo, Brazil; [5]University of São Paulo School of Medicine, São Paulo, Brazil; [6]Universidade de São Paulo, São Paulo, Brazil; [7]University State of São Paulo, São Paulo, Brazil.*

Background: Transplant success depends on achieving the ideal doses of immunosuppressants capable of avoiding rejection while still maintaing sufficient immune level to prevent opportunistic infections. Histoplasmosis is a fungal disease, with a incidence <0.5% in transplant patients and clinical manifestation may vary from common cold-like symptoms to generalized systemic infections, lethal if left untreated

Methods: A 39-year-old female kidney transplant recipient due to lupus nephritis, underwent a second unrelated live donor transplant 12 years ago. Initial immunosuppression include thymoglobulin and maintenance consisted on everolimo, mycophenolate mofetila and prednisone. She had been recently diagnosed with transplant glomerulopathy during investigation of chronic graft dysfunction. She presented enterorrhagia 4 days after admission and a significant fall in hemoglobina: 8.5-> 5.0 g/dL and was, therefore, hospitalized. She was investigated with upper digestive endoscopy, abdominal and chest tomography and blood cultures; all normal. She underwent colonoscopy, which revealed an ulcerated lesion in the ascending colon, compromising ¾ of the colon circumference and biopsies were performed. During hospitalization, the patient progressed with worsening of renal function and infectious parameters, returning to the chronic hemodialysis program and starting treatment with Levofloxacin, Clarithromycin, Etambutol and Amphotericin B, according to our infectology guidelines for empiric coverage, without effective clinical improvement, and maintenance therapy was scheduled for 12 months. Although digestive haemorrhages caused by intestinal infections are most commonly associated with cytomegalovirus or herpes simplex, in our patient such agents were not identified. The colonic biopsy showed active granulomatous colitis with fungal structures of Histoplasma sp, as well as a positive BAAR. Treatment was modified to Itraconazole. The patient was discharged from hospital using this medication after clinical improvement.

Results:

Conclusions: We described a very rare case that shows the importance of extensive investigation in the presence of renal dysfunction, fever or other systemic manifestations in immunosuppressed patients, since they may present atypical pathologies and clinical manifestations, with potentially tragic evolution.

PUB665

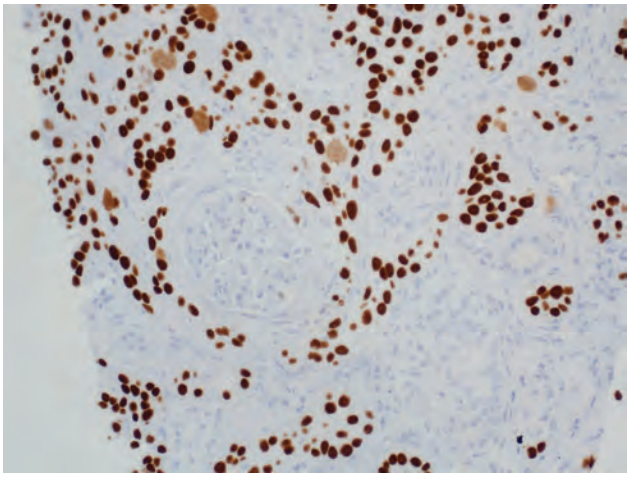
Lung Cancer in the Kidneys, Blood in the Urine Brad Long, Mazdak A. Khalighi, Josephine Abraham. *University of Utah, Salt Lake City, UT.*

Background: Metastatic squamous cell lung cancer is a lethal disease that can involve any organ in the body. Most frequent sites of metastases are bone, liver, brain, and adrenal glands. Rarely, the kidney is involved. We present a case of metastatic SCC of the lung involving the kidneys presenting with gross hematuria and AKI.

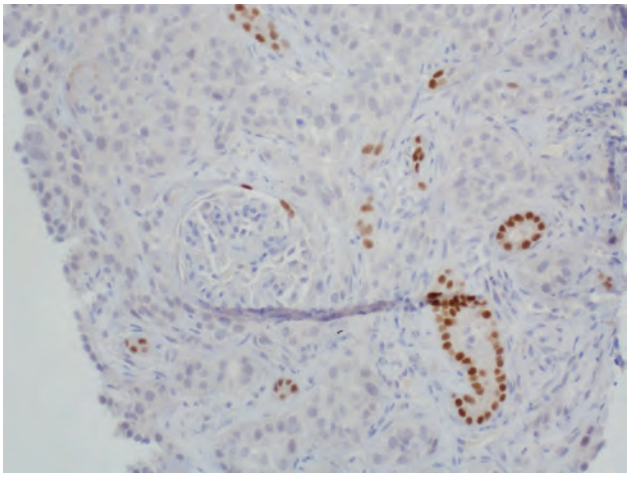
Methods: A 68 year old male with metastatic squamous cell lung carcinoma admitted to the acute care oncology clinic with four days' progressive shortness of breath and gross hematuria and passage of a large clot. Creatinine was elevated to 2.75mg/dL from a baseline of 1.0mg/dL. Renal ultrasound showed enlarged kidneys bilaterally, with loss of normal corticomedullary differentiation and small bilateral cystic structures. CT scan from four months prior showed large kidneys with infiltrative process present in the right kidney, with obliteration of the superior pole collecting system.

Results: Recent kidney biopsy revealed poorly differentiated squamous cell carcinoma metastatic from the lung. AKI during this admission was felt to be due to infiltration of the renal parenchyma by tumor cells. Glomerulonephritis due to chemotherapy was considered though felt unlikely.

Conclusions: Renal invasion by primary lung cancer is rare and can present with hemorrhage leading to gross hematuria and impaired renal function. Hematuria and acute kidney injury should also prompt consideration of chemotherapy-related effects. In any event, lung cancer that invades the kidneys carries a very poor prognosis.



P63 stain highlighting carcinoma cells



PAX 8 stain highlighting residual tubules

PUB666

IgA-Dominant Post Infectious Glomerulonephritis and IgA Nephropathy: Different Diseases with Similar Mechanisms? Brenden D. Connor,[1] Swati Rao,[1] Duncan B. Johnstone,[1] Manjula Balasubramanian,[2] Iris J. Lee.[1] *[1]Temple University School of Medicine, Philadelphia, PA; [2]Einstein Medical Center, Philadelphia, PA.*

Background: IgA glomerular deposition is a hallmark of IgA nephropathy (IgAN). Rarely, isolated IgA- deposition is observed in post infectious glomerulonephritis (PIGN) instead of IgG. IgA-dominant PIGN, more common in elderly with diabetes mellitus (DM), has a guarded prognosis with 40% progression to ESRD. Due to similar findings in clinical and histological presentations, the differentiation of IgA dominant PIGN from IgAN can be challenging. Both diseases can present with hematuria, proteinuria, acute kidney injury, and have mesangial and endocapillary proliferation with IgA and C3 deposits on biopsy. When present, evidence of staphylococcal infection, low complements, large subepithelial deposits and polymorphonuclear (PMN) cellular infiltrates on biopsy favor IgA dominant PIGN. We report a case of IgA dominant PIGN with challenging diagnostic features.

Methods: A 75 y/o Cuban female with DM presented with gross hematuria and 2 weeks of fatigue and weight loss, without other symptoms. No findings were notable on physical exam. Labs demonstrated creatinine (Cr) of 5.3mg/dL (baseline 0.9mg/dl), hemoglobin 8.3g/dL, normal platelets, 1 gm proteinuria and dysmorphic RBC on urine microscopy. There was no clinical or laboratory evidence of infection. Ultrasound of the kidneys was normal. Serologic work up was negative and complement levels were normal.

Renal biopsy demonstrated glomerulitis, with infiltrating PMN in multiple glomeruli, mild mesangial proliferative disease, interstitial inflammation and acute tubular necrosis. Immunofluorescence was positive for IgA and C3. Electron microscopy showed mild effacement of podocyte foot processes, PMN in glomerular capillary loops, and minimal electron dense deposits in the mesangium. The lack of classic clinical and histological features of PIGN in our patient presented a diagnostic dilemma. The acute presentation with no prior known renal disease and striking glomerulitis led us to a diagnosis of IgA-dominant PIGN. After a steroid pulse, hematuria resolved and Cr improved from 6.7mg/dl to 2.63mg/dl.

Results:

Conclusions: IgA dominant PIGN is an uncommon disease and is very challenging to diagnose and manage. Interestingly, both IgA and IgA dominant PIGN can be triggered by infection, supporting similar underlying pathological mechanism but different clinical disease patterns.

PUB667

Minimal Change Disease Relapse after Influenza Vaccination Olusola Isikalu, Ruth C. Campbell, Roberto Pisoni. *Medical University of South Carolina, Charleston, SC.*

Background: Minimal change disease (MCD) is a major cause of idiopathic nephrotic syndrome (NS) accounting for 15% of idiopathic NS cases in adults. It is characterized by severe proteinuria, hypoalbuminemia, and hypercholesterolemia leading to edema. MCD onset and relapse following vaccinations has been described in the literature since 1966, but only few cases due to influenza vaccination are reported.

Methods: We report a case of MCD relapse after influenza virus immunization. Patient was a 45-year-old white woman with MCD diagnosed in December 2014 after presenting with abrupt onset of bilateral hand, facial, and lower extremity edema, and frothy urine. She had no significant past medical or allergy history and no signs of systemic infection. She was normotensive. Urinalysis (UA) showed 3+ protein and urine protein-to-creatinine (UPCR) was 6.5 g/g. Serum albumin was 1.5g/dL, total cholesterol 465 mg/dL, WBC 6.79K/mm^3, hemoglobin (Hgb) 14.5 g/dL, platelets 417K/mm^3, BUN 20 mg/dL, creatinine 1.0 mg/dL, AST 29IU/L, ALT 20 IUL/L, C3 155mg/dL, and C4 29.3mg/dL. RPR, hepatitis B & C serologies, and ANA were negative. After approximately 2 weeks, UPCR worsened to 12 g/g. A kidney biopsy showed MCD and oral prednisone 1mg/kg daily was started in addition to torsemide 5mg/day and rosuvastatin 5mg/day. Complete remission of proteinuria was documented 2 weeks later and persisted after completing a 6-month course of prednisone. Patient remained in complete remission until October 2016 when, just after receiving influenza vaccine, she developed periorbital edema and frothy urine. She denied recent infections or NSAID use. She was normotensive. Renal and hepatic chemistries were normal with creatinine 0.7 mg/dL except for serum albumin of 3.0 g/dL. UA showed protein 100 mg/dL and 24 hour proteinuria was 1.5 g. Relapse of MCD was attributed to recent influenza vaccination in the absence of other potential triggers of MCD. She was treated with oral prednisone 50mg/day and proteinuria resolved within 21 days.

Results:

Conclusions: Our case as well as previous anecdotal reports suggest that influenza vaccination and the resulting stimulation of the immune system may cause MCD. This finding demands further investigation in the pathophysiology of MCD and also requires consideration of further vaccinations in this patient population.

PUB668

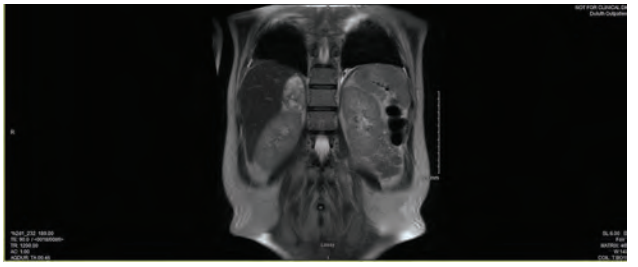
An Uncommon Cause of Hypertension in Sepsis Jin Lee,[1] Sharad Virmani.[2] *[1]Gwinnett Medical Center Internal Medicine Residency Program, Lawrenceville, GA; [2]Georgia Nephrology, LLC, Lawrenceville, GA.*

Background: Pheochromocytoma is responsible for 0.1% of hypertension cases. Oftentimes, the classic triad of palpitations, headache, and diaphoresis can be overlooked or even absent. Pheochromocytoma should be considered in patients presenting with resistant hypertension, paroxysmal hypertension or labile blood pressure. We present a case pheochromocytoma masked by sepsis.

Methods: A 52 year-old Korean female with no past medical history presented to Gwinnett Medical Center with sepsis secondary to pneumonia. On admission, BP was 86/43mmHg and pulse was 124bpm. The patient was started on broad spectrum antibiotics with IV fluid resuscitation. The patient clinically improved with resolution of pneumonia but she remained tachycardic with labile blood pressure (SBP 68-200, DBP 37-93mmHg). She required intermittent Norepinephrine and Nicardipine for management of her dramatic BP fluctuations. Further questioning of her medical history revealed two years of intermittent episodes of flushing and palpitations which she believed to be related to menopause, thus she did not seek medical assistance. Evaluation for secondary causes of hypertension revealed a 4.8x4x5.37cm right adrenal mass on renal duplex. This raised a suspicion for pheochromocytoma and a 24 hour urine metanephrine analysis was performed resulting in normetanephrine levels of 5208mcg/24h, metanephrine levels of 11807mcg/24h, and vanillymadelic acid levels of 51.4mcg/24h, all elevated. Confirmatory MRI with gadolinium showed a 5cm heterogenous, cystic supra-renal mass with central necrosis. She was immediately started on phenoxybenzamine. Optimization of BP was achieved and was deemed stable for discharge with plans for operative removal of the tumor after two weeks of alpha blockade.

Results:

Conclusions: Pheochromocytoma can be an underdiagnosed condition due to nonspecific historical and physical exam findings. Upon diagnosis, initiation of alpha blockade to stabilize blood pressure prior to resection of the adrenal tumor is critical to avoid lethal intraoperative blood pressure fluctuation. Our case highlights the importance of a thorough history to identify a rare disorder overlapped by a common presentation of sepsis.



MR abdomen, saggital

PUB669

Crescentic IgA Nephropathy (IgAN) in a Patient with Underlying Crohn's Disease – A Treatment Challenge Alinda M. Sarma,[1] Anca C. Vlasie.[2] *[1]Cleveland Clinic, Cleveland, OH; [2]Comprehensive Kidney Care, Westlake, OH.*

Background: Crescentic IgA Nephropathy (IgAN), defined as >50% crescentic glomeruli on kidney biopsy, is a common cause of rapidly progressive glomerulonephritis (GN), but a rare manifestation of IgA vasculitis. We present a case of IgAN in a chronically immunosuppressed patient.

Methods: A 49 year old female was admitted for profound malaise, found to severe acute kidney injury (AKI). Her past medical history was significant for Crohn's disease and secondary inflammatory arthritis treated with prednisone, mesalamine, 6-mercaptopurine, methotrexate and infliximab over the years, recurrent skin rash with biopsy suggestive of leucocytoclastic vasculitis, chronic sinusitis. Physical examination was significant for purpuric rash on lower extremities. Laboratory work-up revealed serum creatinine of 2.9 mg/dl, BUN of 57 mg/dl, WBC of 13.06 k/ul, ESR of 111 mm/hr and CRP of 20.6 mg/dl, urinalysis with dysmorphic RBCs and RBC casts. P-ANCA, C-ANCA, Anti-proteinase 3, Anti-myeloperoxidase, ANA were all negative, and serum complement levels were normal. Kidney biopsy showed focal endocapillary proliferative and crescentic GN with IgA-dominant deposits, and electron microscopy confirmed the presence of mesangial and peripheral capillary wall immune deposits. Differential diagnoses included large vessel vasculitis/cutaneous vasculitis in setting of Chrohn's disease, cutaneous vasculitis and GN secondary to medications (infliximab or TNF alpha inhibitor), and IgA vasculitis. Patient was started on pulse dose steroids and oral cyclophosphamide. After three months, creatinine was 1.5 mg/dl, with resolution of hematuria and rash.

Results:

Conclusions: The Oxford Classification of IgAN does not account for glomerular crescents and there are no specific guidelines for treating crescentic IgAN. Crescentic GN is usually associated with ANCA – associated vasculitis or anti-GBM disease. While isolated case reports suggest good response to treatment that includes pulse steroids, cyclophosphamide and plasma exchange, others show no benefit from aggressive treatment. Our patient presented with all the acknowledged risk factors for IgA progressive disease: serum creatinine >1.35 mg/dL, proteinuria >1 g/day, fibrinoid necrosis, and responded well to aggressive treatment. Further guidelines on managing crescentic IgAN would greatly improve the care of these challenging patients.

PUB670

Antiphospholipid Syndrome Started with Microangiopathy and Developed Right Renal Infarction and Left Renal Artery Stenosis Maiko Nagata, Takayuki Fujii, Kaiji Saito, Mizuki Shinozaki, Mayu Morimoto, Noriko Terasaki, Hiroaki Tanaka, Satoshi Suzuki. *Seirei Sakura Citizen Hospital, Chiba, Japan.*

Background: The kidney is one of the organs that is involved in patients with primary antiphospholipid syndrome (APS). Renal involvement in APS is characterized by non-inflammatory occlusion of renal vessels ranging in size from large vessels to intrarenal microvasculature. However, there are no reports of these lesions over time.

Methods: This is a case of a 48-year-old woman, who was previously in good health presented to our department for the investigation of proteinuria when she was 44 years old. She did not have hypertension. The serum creatinine level was 0.5 mg/dl. Urinalysis showed no microscopic hematuria and mild proteinuria (0.5 g/day). Imaging did not show renal artery stenosis. When she was 45 years old, renal biopsy was performed for continuous mild proteinuria (0.5 g/day). Renal biopsy showed fibrous intimal hyperplasia of arterioles and segmental glomerular basement membrane reduplication. Immunofluorescence showed IgG deposits in her capillaries. She was suspected of membranous nephropathy and prescribed angiotensin receptor blocker. Three years later, she admitted to our hospital due to right back pain, and her contrast computerized tomography (CT) scan revealed right renal infarction and left renal artery stenosis. APS was considered the most likely diagnosis because her lupus anticoagulant, anticardiolipin antibody, and anti-β2 glycoprotein I antibody were positive. There was no thrombosis in other organs. Because she was not suspected systemic lupus erythematosus, only anticoagulation treatment was started. A retrospective analysis shows that renal biopsy three years ago showed microangiopathy which might be a pathological feature of APS nephropathy.

Results:

Conclusions: This is a rare case that we were able to observe APS started with microangiopathy and developed right renal infarction and left renal artery stenosis. This might be a process of development from intrarenal microvasculature to large vessels in renal involvement in APS.

PUB671

A Case of Bilateral Renal Artery Thromboembolic Disease of Unknown Etiology Franklin Lam,[1] Samah Musa,[1] Matthew J. Bruha,[2] Krishnakumar D. Hongalgi.[1] *[1]Albany medical center, Albany, NY; [2]Albany Medical College, Albany, NY.*

Background: Renal artery thrombosis usually presents unilaterally and is treated with anticoagulation therapy or endovascular repair. We present a case of bilateral renal artery thromboembolic disease of unknown etiology.

Methods: This patient is a 56 year old female with history of COPD and current smoker who presented with hemoptysis and hematuria. She had no other complaints. Lab work showed elevated creatinine of 3.5 mg/dL. Baseline creatinine was normal. Urinalysis was noteable for 3+ protein and RBCs and WBCs in urine sediment. Twenty four hour protein was 1.7gm A renal ultrasound showed absent vascular flow suggestive for renal vein thrombus. Anticoagulation was initiated with IV heparin and was also started on Coumadin. Her renal function continued to decline and creatinine increased to 6.8 mg/dL. On day 4 MRI of abdomen which showed striking bilateral heterogeneous signal abnormality involving half of the left kidney and a third of the right kidney which represents multiple embolic infarcts of the kidneys in setting of an infrarenal aortic thrombus. On day 6 a right renal biopsy was obtained which revealed diffuse tubular degenerative changes consistent with ATN. When correlated with the MRI, the possibility of unsampled renal vascular injury including thromboembolic processes vs. structural, vasoactive or inflammatory vascular insults should be considered. Patient required hemodialysis on day 5. She developed intracranial hemorrhage and status epilepticus requiring intensive care unit stay and intubation for a period of time. Anticoagulation was stopped and she was extubated and has been hemodialysis dependant Work up for cause of thromboembolic state so far revealed no evidence of atrial fibrillation, and TTE was negative for thrombus or valvular disease. Further investigation yielded the following results: positive ANA, C3 & C4 were normal, pANCA & cANCA negative, Hepatitis panel negative, negative Factor V Leiden, and negative antiphospholipid syndrome. The patient also demonstrated an elevated homocysteine level. JAK 2 mutation is negative.

Results:

Conclusions: This is a case of bilateral renal artery thromboembolic disease of unclear etiology. Once the patients intracranial hemorrhage resolved by CT imaging she was initiated on IV heparin and her neurological status was monitored closely.

PUB672

TINU Syndrome: A Diagnosis of Exclusion Malavika Kapuria, Natasha N. Dave, Rajeev Raghavan. *Baylor College of Medicine, Spring, TX.*

Background: With little over 250 cases reported, the diagnosis of Tubulointerstitial Nephritis and Uveitis (TINU) syndrome requires a high index of suspicion. Variable clinical presentations, poorly understood underlying mechanisms and lack of specific laboratory markers make its diagnosis all the more complex. We report the case of a young female who presented with AKI, anterior uveitis and systemic symptoms, initially misdiagnosed as pyelonephritis, and subsequently diagnosed and treated for TINU syndrome.

Methods: A 33 year-old Hispanic female with no significant past medical history presented with an 11 days history of fever, fatigue, headache, epigastric pain, dysuria, polyarthralgias and bilateral conjunctival injection. CT scan showed bilateral striated nephrogram with perinephric stranding. She was diagnosed with pyelonephritis and discharged on empiric antibiotics. She presented again 2 days later with no improvement in symptoms. Physical examination was notable for bilateral conjunctival erythema without drainage, epigastric tenderness and wrist synovitis. Serum creatinine was 2.5 mg/dl increased from 1.5 mg/dl 2 days prior (baseline Cr 0.8). Further work-up including urinalysis revealed a loss of concentrating ability (specific gravity 1.005 decreased from previous 1.023 in 2011) with 'few' urine eosinophils. Urine microscopy revealed WBC casts. Renal ultrasound showed preserved kidney sizes with bilateral heterogeneous poor corticomedullary differentiation. Other pertinent labs included elevated CRP (8.94) and ESR (76), negative ANA, and mildly elevated C3 (154) and C4 (46.9). Ophthalmologic evaluation found anterior uveitis with conjunctival injection. A kidney biopsy showed acute TIN with eosinophils and non-caseating granulomas. Additional work-up for syphilis, tuberculosis, Sjogren's, HLA-B27, MPO/PR3 ANCA and chest x-ray were negative. The patient had excellent response to steroids (pulse dose IV steroids for 3 days, followed by PO steroid taper) with improvement in renal function back to baseline within 14 days. She was treated for a total of 6 weeks and remains asymptomatic 2 months post-hospitalization.

Results:

Conclusions: TINU is a rare, idiopathic syndrome and remains a diagnosis of exclusion. This case exemplifies the variety of presenting signs/symptoms and the degree of renal dysfunction associated with TINU, and highlights the need for a systematic approach to ruling out alternative diagnoses.

PUB673

Underdiagnosis of Adrenocortical Adenoma Franklin Lam,[2] Rafia I. Chaudhry,[2] Loay H. Salman,[1] Mauricio Monrroy.[2] *[1]Albany Medical College, Albany, NY; [2]None, Providence, RI.*

Background: Primary hyperaldosteronism, described by Conn in 1956 as an aldosterone-secreting adrenal adenoma results in resistant HTN. Less than 1% of cases with HTN were initially attributed to Conn's syndrome. Recent data indicates a higher incidence of Conn's syndrome of up to 5-15% in pts with HTN, suggesting considerable underdiagnoses.

Methods: 33 yr-old Caucasian male, with PMHx of obesity and HTN, referred for HTN, hypokalemia in 2013. BP 178/100 mmHg on Amlodipine 10 mg. Funduscopic exam revealed bilateral retinal AV nicking. Sr Cr 1.0 mg/dL, K 3.3 mmol/L, and CO_2 32 mmol/L. Renal US unremarkable, doppler US negative for renal vein stenosis. Plasma aldosterone concentration (PAC) 7.7 ng/dL, plasma renin activity (PRA) 0.86, 24-hr Ur aldosterone (ALD) 40.50, Ur Na 182. MRI negative for adrenal abnormality. BP remained marginally controlled on Amlodipine, Telmisartan, and Amiloride. CPAP was started for OSA. HTN remained sub optimally controlled HTN 3 yrs later, and repeat studies consistent with hyperaldosteronism (PAC 37.8, 24-hr Ur ALD 40.50, PRA 4.81 and 6.17). CT adrenal mass protocol revealed 1.1-cm left adrenal nodule. Adrenal venous sampling (AVS) confirmed lateralization to left adrenal gland, and adrenalectomy will be pursued.

Results:

Conclusions: Adrenal CT scan has superior spatial resolution than MRI to detect adrenal adenoma. If CT scan is negative, or demonstrates bilateral abnormalities, or unilateral abnormality in pt > age 35, AVS can confirm unilateral disease to explore the role of surgical intervention for primary hyperaldosteronism.

Time (minutes)	Left AV Aldosterone	Right AV Aldosterone
Baseline	166 ng/dL	26 ng/dL
5	4310 ng/dL	42 ng/dL
10	2990 ng/dL	48 ng/dL
15	2930 ng/dL	60 ng/dL

PUB674

The Role of Continuous Renal Replacement in the Management of Type B Lactic Acidosis Due to Hemophagocytic Lymphohistiocytosis Ryan Mullane, Scott G. Westphal. *University of Nebraska Medical Center, Omaha, NE.*

Background: Hemophagocytic Lymphohistiocytosis (HLH) is a rare, life-threatening complication of excessive immune activation caused by uncontrolled release of inflammatory cytokines from activated macrophages and T lymphocytes. Type B lactic acidosis due to HLH is extremely rare with few case reports; therefore, the optimal treatment strategy is unknown. We present a case of type B lactic acidosis due to HLH where continuous renal replacement therapy (CRRT) and sodium bicarbonate infusion were incorporated in the successful management of the lactic acidosis.

Methods: A 64-year-old female with chronic lymphocytic leukemia and anaplastic large cell lymphoma was admitted for pancytopenia and hyponatremia. Examination was notable for splenomegaly and recurrent fevers. Extensive evaluation into an infectious etiology was unremarkable. Further testing revealed hypertriglyceridemia (triglyceride level of 362 mg/dL), hyperferritinemia (ferritin level of 60,917 ng/mL), transaminitis, and an elevated soluble IL-2 receptor level (111,000 pg/mL); given her presentation, she was diagnosed with HLH. Over the next 24 hours, despite remaining normotensive with relatively unchanged renal function, she developed lactic acidosis with a maximum lactate level of 16.6 mmol/L and profound acidemia. She was started on CHOP chemotherapy and we initiated treatment for her lactic acidosis with IV sodium bicarbonate and continuous venovenous hemodialysis (CVVHD) with a high dialysate flow rate of 5,000 mL/hour (~60 mL/kg/hour) to control the acidosis. The patient's lactic acidosis resolved over the following days and her sodium bicarbonate infusion and CRRT were both discontinued.

Results:

Conclusions: Type B lactic acidosis and HLH both have poor survival rates. Historically, the use of renal replacement therapy and bicarbonate infusion for lactic acidosis is controversial with limited evidence of benefit in Type B lactic acidosis. Our patient had resolution of lactic acidosis due to HLH following chemotherapy initiation and treatment with CRRT and sodium bicarbonate infusion. Concurrent with chemotherapy, sodium bicarbonate infusion with CRRT may be a potential novel management approach for type B lactic acidosis due to HLH.

PUB675

Cases of Intimal Arteritis with Phantom Etiology John T. Nguyen,[2] Aleksandra De Golovine.[1] *[1]UTHSC-H, Houston, TX; [2]University of Texas Houston Medical School, Houston, TX.*

Background: V lesions in transplant renal biopsy have shown to be important in our ability to diagnose and prognosticate graft failure. The conventional thought is that V lesions represent T cell-mediated rejection however there is concern that V lesions may be present in antibodymediated rejection as well. We report three cases of renal transplant patients who underwent indicated renal biopsy that demonstrated isolated intimal arteritis.

Methods: The first case is a 55 year old male with end stage renal disease after he donated a kidney and developed renal cell carcinoma in his remaining kidney. He underwent deceased donor transplant on 10/31/2016. The patient had delayed graft function which resulted in a biopsy on 11/3/2016 that showed 3 arteries with intimal arteritis that was almost obliterative. The patient was clinically diagnosed with atypical HUS and started on eculizumab shortly after. The patient's renal function stabilized but

worsened three months later. Repeat transplant renal biopsy on 3/3/2016 that revealed isolated V lesion of a single artery with no significant tubulointerstial inflammation, tubulitis or peritubular capillaritis, no interstitial fibrosis and C4d was negative. The second case involves a 41 year old male with a history of dilated cardiomyopathy status post heterotypic transplant in 1992. The patients was admitted in 05/2016 for decompensated heart failure and developed acute on chronic kidney disease requiring hemodialysis. The patient underwent simultaneous heart and kidney transplant on 1/22/2017. Post operative course was complicated by respiratory failure, recurrent C. difficile colitis, influenza and renal graft insufficiency. Patient had a transplant renal biopsy on 2/17/2017 that showed isolated intimal arteritis, no tubulitis, no peritubular capillarities, and no C4d positivity. The third case involves a 49 year old male with a medical history of end stage renal disease, congestive heart failure, and hypertension. He underwent living unrelated transplant on 12/09/2016. There was delay of graft function and transplant renal biopsy was performed on 12/16/2016 which showed intimal arteritis in four arteries but with negative C4d and no tubulitis.

Results:

Conclusions: These cases are notable because they demonstrate how isolated V lesions are present in acute rejection but there needs to be continued efforts to further define their role in diagnosis and prognostication of graft failure.

PUB676

Hypophosphatemia and Cardiac Arrest in an Elderly Hemodialysis Patient Joanne Cooke, Amina Khan, Munis A. Mattu, David E. Webb, Virginia J. Savin. *Kansas City VA Medical Center, Kansas City, MO.*

Background: About 40% of hemodialysis (HD) patients funded by Medicare are ≧ 65 years old. Both hyper- and hypo-phosphatemia are associated with increased mortality in HD patients. Hyperphosphatemia is the primary concern for younger patients, while hypophosphatemia is more common in elderly patients and is associated with higher all-cause and cardiovascular mortality.

Methods: A 77 yo man with malnutrition and hypophosphatemia prior to starting HD received a liberal diet, nutrition supplement (Nepro) and tid oral NA/K/PO_4 (Neutraphos) and no PO_4 binders. Dialysis was 3.5 h tiw. 18 months later he had asystole at the end of HD. Plasma PO_4 after cardiac arrest was 1.8 mg/dl. He was hospitalized for 26 days and DC'd on dialysis 3 h tiw, with a Life Vest ™ and plan for ICD. He received IV $NaPO_4$, 30 mM at each HD for 4 months (~1350 mM total). Predialysis PO_4 rose from 2.5 to 4.5.

Results:

Conclusions: Of 34 HD patients in our VA HD unit, 7 (21%) had pre-dialysis PO_4 ≦3.5. Pre- and post-dialysis PO_4 were 3.1±0.7and 1.2±0.5 (Mean±SD), respectively. Decrease in PO_4 during dialysis was 1.9±0.9 (59±18%). Hypophosphatemic patients had lower Hgb and BUN than others. Each had lost weight in prior 3 months (2.2±1.9%). Five were hospitalized in the prior month. After recognizing low PO_4 as a potential risk, PO_4 binders were stopped in these patients. Predialysis PO_4 increased by a mean of 0.75 mg/dL within 30 days. Two patients resumed PO_4 binder at a lower dose and have maintained predialysis PO_4 ≧ 3.5. Hypophosphatemia increases mortality in continuous and intermittent therapies. It is a challenge in geriatric care as well as during intensive treatments in acutely ill persons. Measurements of dialysis adequacy focus on removal of organic compounds, but depletion of inorganic compounds occurs simultaneously. PO_4 drops during HD and, although it rebounds within 5 hours, dynamic changes may increase the risk of cardiac events. Increasing predialysis PO_4 by including foods with intrinsically higher nutrient:PO_4 ratio (dairy, legumes) and limiting PO_4 binders can increase predialysis PO_4 and reduce risk. Recognizing the high incidence of hypophosphatemia may alter prescriptions and improve outcomes in the elderly.

Funding: Veterans Affairs Support

PUB677

A Variability Study of Two Leading Metabolomics Platforms in CKD Eugene P. Rhee,[3] Sushrut S. Waikar,[1] Casey Rebholz,[2] Regis Perichon,[4] Clary B. Clish,[10] Julian R. Avila-Pacheco,[6] Michelle Denburg,[7] Amanda H. Anderson,[8] Harold I. Feldman,[8] Paul L. Kimmel,[5] Josef Coresh.[9] *[1]Harvard Medical School, Boston, MA; [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [3]Massachusetts General Hospital, Boston, MA; [4]Metabolon, Durham, NC; [5]National Institute of Diabetes and Digestive Kidney Diseases (NIDDK), Bethesda, MD; [6]The Broad Institute of MIT and Harvard, Cambridge, MA; [7]The Children's Hospital of Philadelphia, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; [8]University of Pennsylvania, Philadelphia, PA; [9]Welch Center for Prevention, Epidemiology & Clinical Research, Baltimore, MD; [10]Broad Institute of MIT and Harvard, Cambridge, MA. Group/Team: On behalf of NIDDK CKD Biomarkers Consortium.*

Background: Non-targeted metabolomics can measure thousands of low molecular weight biochemicals, but important gaps limit its utility for biomarker discovery in CKD. These include the need to characterize technical and intraperson analyte variation, to pool data across metabolomics platforms, and to outline relationships between the metabolome and GFR.

Methods: Plasma from 49 individuals with CKD (eGFR <60 mL/min/1.73m2 and/or ≥1g proteinuria) was examined over two study visits; 20 samples were repeated as blind replicates. To enable comparison and synthesis across two non-targeted metabolomics platforms, samples were profiled at the Broad Institute and Metabolon.

Results: The Broad (B) platform reported 681 known metabolites and 28,630 unknown ion features. The Metabolon (M) platform reported 896 known metabolites and 46,212 unknown ion features. Median CVs across blind replicates were 6.3% (B) and 14.6% (M) for knowns, and 24.5% (B) and 35.1% (M) for unknowns. Median CVs for day-to-day variability were 24.9% (B) and 29.0% (M) for knowns, and 36.7% (B) and 40.9% (M) for unknowns. 343 knowns were shared across platforms, with a median Pearson correlation of 0.91. Many metabolites were negatively correlated with eGFR-Cr at p<0.001: 8.8% (B) and 19.1% (M) of knowns, and 12.4% (B) and 9.0% (M) of unknowns.

Conclusions: Nontargeted metabolomics quantifies thousands of analytes with low technical CVs (lower for known metabolites than unknown ion features). Substantial intraperson variation and correlation with eGFR underscore the need for careful selection of potential metabolite biomarkers. Agreement for overlapping metabolites across two leading platforms is excellent, setting the stage for future cross-platform meta-analyses.

Funding: NIDDK Support

Table. CVs for blind replicates and day-to-day variation

			N	Median (%)	25%tile	75%tile	CV<20%
Blind duplicates (N=20)	Broad	known	594	6.3	4.8	10.6	523 (88.1%)
		unknown	26106	24.5	12.0	63.7	11344 (43.5%)
	Metabolon	known	837	14.6	9.1	24.4	557 (66.6%)
		unknown	45436	35.1	19.5	65.2	11728 (25.8%)
Day-to-day variability (N=49)	Broad	known	593	24.9	14.0	56.1	241 (40.6%)
		unknown	26096	40.9	16.8	155.7	7908 (30.3%)
	Metabolon	known	837	29.0	17.2	61.6	275 (32.9%)
		unknown	45607	36.7	23.4	61.0	8347 (18.3%)

PUB678

A Simplified Protein-Energy Wasting Scoring System for Survival Prediction in Korean Incident Hemodialysis Patients Young Eun Kwon,[1] Hye Min Choi,[1] Dong-jin Oh,[1] Shin-Wook Kang.[2] *[1]Department of Internal Medicine, Myoungji hospital, Seonam University College of Medicine, Goyang-si, Gyeonggi-do, Republic of Korea; [2]Department of Internal Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea.*

Background: Even though protein-energy wasting (PEW) is a crucial risk factor for survival in end-stage renal disease (ESRD) patients, a convenient and reliable assessment method to determine PEW in ESRD patients has not been established. However, a recent study proposed a simplified PEW scoring system based on the PEW diagnostic criteria, which was predictive for European ESRD patients' survival. This study aimed to validate the prognostic significance of the simplified PEW score in Korean incident hemodialysis patients.

Methods: Data were retrieved from a prospective cohort study from the Clinical Research Center for ESRD in Korea. The simplified PEW scoring system is graded from 0 (the worst) to 4 (the best), which consists of four components: serum albumin, body mass index, serum creatinine/body surface area, and normalized protein nitrogen appearance. Since the number of patients in the PEW score 0 group was too small (n=14), the PEW score 0 and 1 groups were combined into a same group. The survivals of the four groups (PEW score 0~1, 2, 3, and 4) were compared by Kaplan-Meier plot, and multiple Cox regression analysis was performed to identify the association between the PEW score and patients' survival.

Results: A total number of 430 patients were included in this study. The numbers of patients in the four score groups were 77 (score 0~1), 158 (score 2), 145 (score 3), and 50 patients (score 4). The mean age was 61.1 years and male was 59.8%. Kaplan-Meier plot revealed that the lowest PEW score group had the worst cumulative survival or there was a significant difference in patient survival across the groups (log-rank test, P<0.001); 2-year mortality rates of 15.6% in the score 0~1 group, 8.2% in the score 2 group, 1.4% in the score 3 group, and 2.0% in the score 4 group. In multiple Cox regression analysis, moreover, PEW score was a significantly independent factor for mortality even after adjusting for confounding variables (PEW score 0~1 as a reference; PEW score 2, hazard ratio [HR] 0.450, 95% confidence interval [CI] 0.262–0.772, P=0.004; PEW score 3, HR 0.165, 95% CI 0.070–0.385, P<0.001; and PEW score 4, HR 0.101, 95% CI 0.013–0.760, P=0.026).

Conclusions: A simplified PEW scoring system is a practical and reliable method for predicting mortality in Korean incident hemodialysis patients.

PUB679

Short and Long Term Effects of Renal Rehabilitation on Oxidative Stress Aki Hirayama,[1] Misa Miura,[1] Yo Hirayama,[2] Go Yasuda,[3] Yumiko Nagano,[3] Atsushi Ueda,[4] Akihito Nishida,[1] Hirofumi Matsui,[3] Kazumasa Aoyagi,[1] Masahiro Kohzuki,[5] Shigeru Oowada.[6] *[1]Tsukuba University of Technology, Tsukuba, Japan; [2]HIRAYAMA HOSPITAL, Chiba, Japan; [3]University of Tsukuba, Ibaraki, Japan; [4]Tsukuba University Hospital Hitachi Medical Education and Research Center, Hitachi, Ibaraki, Japan; [5]Tohoku University Graduate School of Medicine, Sendai, Japan; [6]Asao Clinic, Kawasaki, Japan.*

Background: To evaluate the risk of renal rehabilitation, we investigated short (3 months) and long (6 to 9 months) term effect of exercise program for hemodialysis (HD) patients on oxidative stress

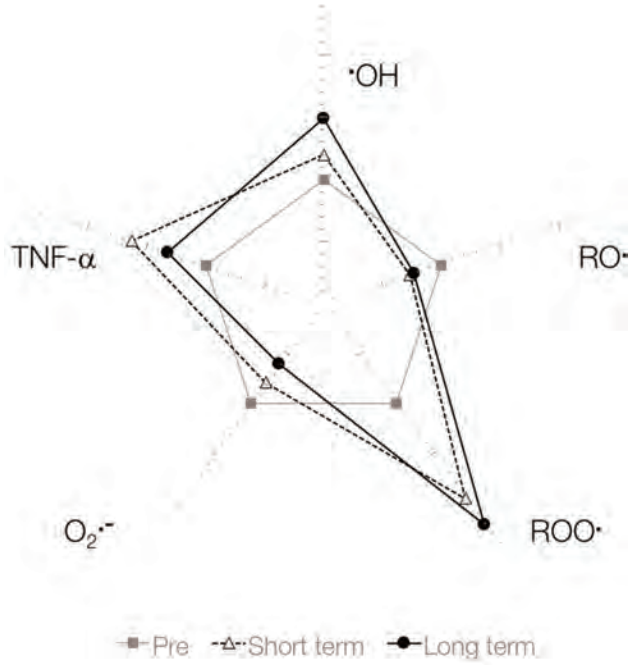
Methods: Total 39 stable HD patients, 22 with and 17 without the exercise program, were examined. The renal rehabilitation program was; aerobic training with lower limb ergo-meter, Borg scale 11 to 13, twice a week during HD, and the work time15 to 60 min. Oxidative stress was evaluated by serum scavenging activities against multiple reactive

oxygen species, measured by an electric spin resonance-based method, and inflammatory cytokines.

Results: No severe unfavorable effects were confirmed during the program. The patients received the renal rehabilitation showed significant increase of daily activity, exercise tolerance and muscular strength, and decrease of blood pressure, LDL and HDL. The program significantly increased serum scavenging activity against alkylperoxyl radical ($ROO^{\cdot}$) within the first 3 months, then against hydroxyl radical ($^{\cdot}OH$) within the next 6 months. Contrary, superoxide ($O_2^{\cdot-}$) scavenging activity was decreased within the first 3 months, and then alkoxyl radical ($RO^{\cdot}$) scavenging activity was decreased within 9 months. An increase of TNF-α was detected in the patients with the exercise program.

Conclusions: Our study revealed that the renal rehabilitation gradually improved oxidative stress over time. The effects on antioxidant system are not uniform and their timing window are various. Most of these results are favorable, while there still remains negative effects including TNF-α and $RO^{\cdot}$ scavenging activity. The change of $O_2^{\cdot-}$-scavenging activity may be the result of an adaptation against already increased oxidative stress in HD patients.

Funding: Government Support - Non-U.S.



PUB681

Evaluation of Peridialytic Change in Body Composition Using Three Bioimpedance Devices Ohnmar Thwin,[1] Fansan Zhu,[1] Priscila Preciado,[1] Xia Tao,[1] Laura Rosales,[1] Jochen G. Raimann,[1] Stephan Thijssen,[1] Peter Kotanko.[1,2] *[1]Renal Research Institute, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Body mass (BM) can be divided into fat mass (FM) and lean body mass (LBM). Skeletal muscle mass (SMM) is a major component of LBM. In general, the ratio of LBM to total body water (TBW) is approximately 0.73. LBM can be calculated if TBW is known. The aim of this study was compare 3 commercially available bioimpedance devices with respect to (1) measurements of peridialytic BC changes and (2) BC measurements in healthy subjects (HS).

Methods: Ten HD patients (8 males, age 58.1±12 years) and 12 HS (7 females, 33.3±5.6 years) were studied. Measurements were performed pre and post HD in patients and once in HS. We used three multi-frequency bioimpedance devices: InBody 770 (InBody USA, Cerritos, CA), Seca mBCA 514 (Seca North America, Chino, CA), and Hydra 4200 (Xitron Technologies, San Diego, CA). InBody and Seca report TBW, FM, LBM, and SMM. Hydra provides FM, LBM, and SMM using a model (Chamney, Am J Clin Nutr, 2007). We analyzed peridialytic BC changes and BC in HS.

Results: All devices reported a significant peridialytic decrease in BM, TBW and LBM (**Fig.1 a, c, d**). However, FM results differed between the devices: InBody reported no change, while Seca reported increased with a high variability and Hydra found decreased (**Fig 1 b**). The pre HD FM-to-BM ratio (%FM) was higher with Hydra compared to InBody and Seca, respectively (**Table 1**). In HS, however, %FM was significantly higher with Seca compared to Hydra and InBody, respectively. In both HD and HS LBM was reported lower with Hydra compared to InBody and Seca, respectively. In HD patients and HS SMM was reported lower with Hydra compared to InBody.

Conclusions: In this pilot study the peridialytic FM increase suggests that LBM may be underestimated due to use of a constant TBW/LBM ratio (0.73). This ratio may not correct in dialysis patients.

Table 1

	Pre FM (kg)	Pre %FM (%)	Pre LBM (kg)	Pre SMM (kg)	FM-HS (kg)	%FM-HS (%)	LBM-HS (kg)	SMM-HS (kg)
InBody	21.37 12	27.5 12	51.7 8.6	29.3 5.1*	21.7 11.8	28.6 10	52 13.7	28.9 8.3
Seca	22.7 11.9	29.2 12	52.3 9.6	24.0 5.6	33.5 24.3*	44.4 29*	70.2 29.5	33.4 15.2
Hydra	23.8 10.3	31.3 10*	40.8 12.6*	21.7 4.9*	20.8 9.4	28.2 10	45.3 15.6*	25.9 6.0*

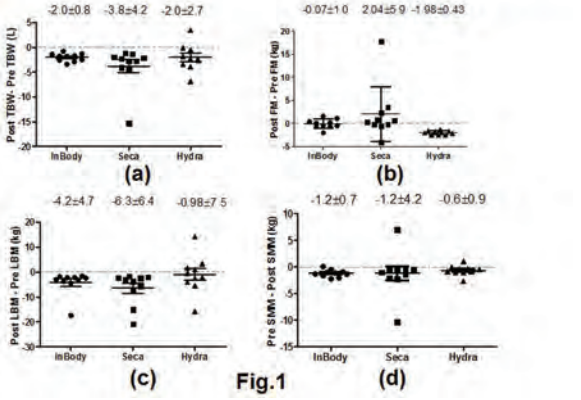


Fig.1

PUB682

Status of Nutrition in Hemodialysis Patients Survey: SNIPS Talia R. Weinstein,[2,3] Odile Azoulay,[4] Mona Boaz.[1] *[1]Ariel University, Ariel, Israel; [2]Tel Aviv Medical Center, Tel-Aviv, Israel; [3]Tel Aviv University, Tel Aviv, Israel; [4]Rabin Medical Center, Petach Tikva, Israel.*

Background: Protein-energy wasting (PEW) is prevalent in hemodialysis (HD) patients, due to inadequate dietary intake and an increased catabolic state. Adverse outcomes include increased hospitalization, morbidity and death. The prevalence ranges from 18-70%, depending on the method used for PEW definition. Expert panels have recommended dietary modifications intended to prevent PEW in this population. The primary objective of this study was to survey nutrition intake in Israeli HD patients and to estimate the PEW prevalence; additionally, the study measured patients' mean energy and nutrient intake, and their adherence to dietary recommendations.

Methods: This multi-center, cross-sectional study included a representative sample of HD patients treated at 9 hospitals throughout the country. At each center, the population was stratified for age; sex; ethnicity; dialysis vintage (< 1 year >); dialysis shift; and diabetes. Patients were proportionally randomly sampled from each strata. Dietary intake was assessed using the 24-hour recall. Biochemistry, demographic data, prescription list and anthropometric data were extracted from the electronic medical record.

Results: The study included 378 HD patients, mean age 64.8±12.7 years, mean dialysis vintage 2.4±4.9 years, Kt/V 1.4±0.29, 52% female, 80% Jews. Comorbidities included hypertension (65%); dyslipidemia (35%) and diabetes (33%). Serum albumin was 3.7±0.4 g/L, serum phosphorous was 5.1±1.5 mg/dl and c-reactive protein was 11.7±25.9 mg/dl. Total energy intake, energy intake per kg/ideal body weight and protein per kg/ideal body weight were all significantly below recommendations. Only 19% consumed adequate calories, 29% consumed adequate protein. Almost 70% of patients had below-normal serum albumin levels; 58% of the study population was classified as having PEW. Only 8.2% of the study population overall and only 15.5% of patients with PEW received nutrition supplementation. Almost 50% of patients were categorized as overweight or obese.

Conclusions: PEW is common in Israeli HD patients. Compliance with nutrition recommendations and guidelines is poor. Despite this, use of nutrition supplementation was limited. Paradoxically, almost half of the patients were overweight or obese. Further studies must be conducted to reconcile these seemingly incongruous states; additionally, studies investigating methods to enhance dietary compliance must be carried out.

Funding: Commercial Support - Abbott Nutrition

PUB683

Biomarker Profiling in Stage 5 CKD Hemodialysis Patients with Reference to Apparent Metabolic Syndrome and Vascular Manifestations Vinod K. Bansal,[1] Leonidas Skiadopolous,[1] Ryan Mcmillan,[1] Debra Hoppensteadt,[1] Jawed Fareed.[2] *[1]Loyola University Medical Center, Maywood, IL; [2]Loyola University medical center, Maywood, IL.*

Background: Stage 5 Chronic Kidney Disease Hemodialysis (CKD5-HD) represents a complex syndrome in which a variety of inflammatory factors contribute to its pathogenesis and progression. Vascular disorders and metabolic syndrome are common comorbidities in CKD5-HD patients. The purpose of this study is to profile inflammatory biomarkers to determine their role in pathogenesis of CKD5-HD and how they relate to apparent metabolic syndrome and vascular disorders.

Methods: Ninety patients (45 male, 45 female) with documented CKD5-HD on maintenance hemodialysis were included in the study. The control group consisted of 50 healthy individuals (25 male, 25 female; George King Biomedical, Overland, KS). Plasma from the CKD5-HD and control groups were used to measure levels of Vitamin

D, PTH, Endocan, Endothelin-1, NGAL, PDGF-BB, IL-18, NT-proBNP, MPTF, KIM-1, Lp(a), Heparin anti-Xa, and PF4.

Results: All biomarker levels were elevated in the CKD5-HD cohort compared to the healthy controls, except for Vitamin D. Of the 90 CKD5-HD patients, 48 (53%) were found to have a history of vascular disease, of CKD5-HD which 36 (40%) had coronary artery disease and 19 (21%) had peripheral vascular disease; 38 (42%) were determined to have apparent metabolic syndrome. A correlation was found between Vitamin D and Endothelin-1 ($p=0.037$, $r= 0.220$) in all 90 CKD5-HD patients as well as in the vascular disease group ($p=0.023$, $r= 0.328$). Lp(a) levels were significantly elevated in the vascular disease patients ($p=0.032$, % change =21.2%) and in the PVD patients ($p=0.002$, % change=35.9%). Endothelin-1 was also found to be statistically significantly increased in the 38 patients with apparent metabolic syndrome ($p=0.002$, % change =42.9%) as was PF4 ($p=0.005$, % change=16.8%) and platelet count ($p=0.025$, % change= 24%).

Conclusions: Decreased plasma Vitamin D levels, along with increased PTH, Endocan, and Endothelin-1 levels in the CKD5-HD patients compared to the healthy controls suggests that these biomarkers may play a role in the pathogenesis of CKD5-HD. The correlation found between Vitamin D and Endothelin-1 in the CKD5-HD cohort as well as in the vascular disease group suggests that the mechanism behind this vascular endothelial dysfunction may in part occur through the upregulation of Endothelin-1 levels.

PUB684

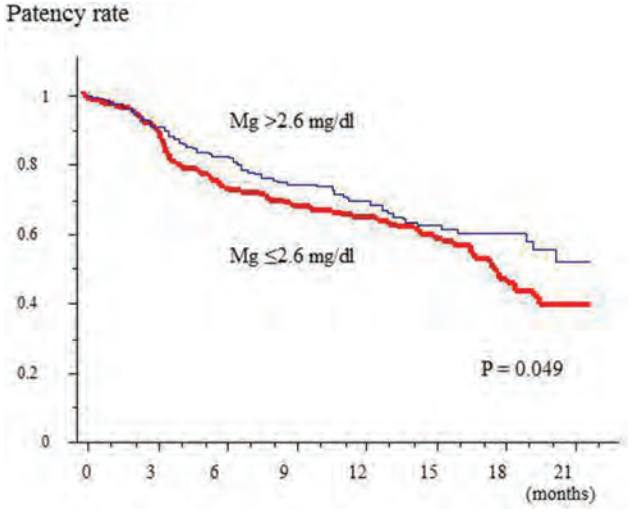
Higher Serum Magnesium Effect on Second Patency Rates of Vascular Access in Patients on Hemodialysis Yukiko Hasuike, Naoto Kakita, Kiyoko Yamamoto, Kosuke Mizusaki, Takahiro Kuragano, Takeshi Nakanishi. *Internal Medicine, Division of Kidney and Dialysis, Nishinomiya, Japan.*

Background: Vascular access (VA) is essential for the patients on HD. However, VA failure is often occurred even after VA intervention therapy (VAIVT). Several studies suggested a possible association between hypomagnesemia and vascular change. The purpose of this study was to examine the factors affecting VA patency after VAIVT, including Mg, and factors related to oxidative stress, inflammation, and uremia.

Methods: Blood samples were taken from 518 HD patients at the VAIVT. Among them, 391 patients (75.5%) had native arteriovenous fistula. Routine blood chemistries and factors related to mineral-bone metabolism (Mg (xylidyl blue method, 1.9 to 2.6 mg/dl), corrected calcium, phosphate, parathyroid hormone-intact), oxidative stress (8-hydroxy-2'-deoxyguanosine, GSH/GSSG), inflammation (CRP, interleukin-6, tumor necrosis factor-α), and uremia (body mass index, albumin, urea nitrogen, hemoglobin) were measured. The end point of study was the re-vascularization or re-operation of VA during the observational period after VAIVT (mean follow-up periods 289 days). Cox proportional hazards models for the end point was used.

Results: During follow-up period, re-vascularization was performed in 96 patients and re-operation in 88 patients. The median value of serum Mg concentration was 2.5 mg/dl in all patients. The patients with VA failure had lower serum Mg compared with the patients without VA failure. There was no significant difference in other factors. The Kaplan-Meier analysis showed that the patents with lower Mg (≤2.6 mg/dl) was associated with higher incidence of VA failure ($p=0.049$, [figure1]). Cox regression analysis also revealed that lower Mg (adjusted hazard ratio 1.365, 95% confidential interval 1.013 to 1.839, $p=0.041$) was linked to VA failure.

Conclusions: Lower serum Mg was associated with the poor event-free patency of VA after VAIVT, and affected the second patency rates of VA.



PUB685

Effect of Gender on Obesity-Associated Renal Dysfunction and Involvement of Adipokines Blanche Martin,[1] Chloé Wilkin,[1] Inès Jadot,[1] Olivia Botton,[1] Anne-Emilie Decleves,[2] Nathalie Caron.[1] *[1]Laboratory of General Physiology - URPHYM, University of Namur, Namur, Belgium; [2]Laboratory of Molecular Biology, University of Mons, Belgium, NIMY (MONS), Belgium.*

Background: Obesity incidence has dramatically increased during the last few years. This disease, characterized by an excessive fat accumulation, has for consequences an alteration of adipose tissue function and a chronic inflammation status, leading to metabolic disturbances. It is also well described that an excess of fat can be considered as a risk factor for kidney disease development. Today, most researches focus on males. However, it is imperative to determine how the sex difference can affect metabolic homeostasis and obesity syndrome. Indeed, differences, such as adipose tissue distribution, have been highlighted between sexes. Moreover, sexual hormones are involved in lipid and glucose metabolism. Adipose tissue has been to shown to play endocrine functions by the secretion of adipokines, such as chemerin, adiponectin, leptin and TNF-α. In obese patients, secretion of these adipokines is impaired. In the present study, we investigated the role of adipokines in obesity progression in males and in females and its impact on obesity-induced kidney alterations.

Methods: C57BL/6 male and female mice were randomized to a low fat diet (LFD) or a high fat diet (HFD) for 16 weeks.

Results: We demonstrated that male mice fed a HFD developed obesity, as illustrated by an increase in body weight, kidney hypertrophy and glucose metabolism disorders. Regarding kidney function, we observed that HFD mice tend to develop renal functional impairment as they exhibited proteinuria and a slight increase in albuminuria. These observations were associated with a mesangial matrix expansion in glomeruli and vacuolated tubular cells. We also observed effects of HFD on adipokine concentrations, inflammation and fibrosis process in kidney. Finally, HFD mice presented a moderated oxidative stress. Female mice, on the other hand, seem less affected by HFD according to metabolic data. Moreover, kidney lesions were less important than in male. However, female mice exhibited important inflammation, fibrosis and oxidative stress modifications compared with male fed a HFD and LFD.

Conclusions: In summary, we demonstrated appearance of obesity as well as associated kidney failure in HFD male and female mice. However, according to our results, gender seems to influence the obtained data, highlighting roles of sexual hormones in obesity physiopathological mechanisms.

Funding: Government Support - Non-U.S.

PUB686

Hepatocyte Nuclear Factors as Possible Mediators of Inflammation in Experimental Chronic Renal Failure Elzbieta Sucajtys-Szulc, Marek Szolkiewicz, Boleslaw Rutkowski, Ryszard Milczarek, Alicja Debska-Slizien. *Medical University of Gdansk, Gdansk, Poland.*

Background: The molecular background of CKD-related inflammatory state is rather obscure, though the most potent inflammatory biomarkers (CRP, IL-6) are linked with the pathogenesis of many CKD-related disorders, including cardiovascular diseases. Recently, we found that hepatocyte nuclear factors (HNFs) involved in the transcriptional regulation of large number of genes, were up-regulated in liver of CRF rats. In this paper, we analyze the interplay between HNFs, IL-6 and CRP synthesis in experimental CRF.

Methods: Rats with experimentally induced CRF (5/6 nephrectomy), pair-feds and controls (sham-operated) were used in the study. Persistent inflammation was induced in additional group of healthy animals by implanting a subcutaneous slow-release ALZET osmotic pump to infuse 1 mg/kg/d of lipopolysaccharide (LPS). *Crp, Il-6, Hnf1α* and *Hnf4α* genes expression in liver and WAT were determined using real-time RT-PCR (mRNA) and Western blotting analysis (protein). Serum level of CRP and IL-6 were estimated by immunoassay.

Results: We found a significant up-regulation of *Crp, Il-6* and *Hnf1α* and *Hnf4α* genes expression (mRNA and protein amount) in liver and WAT of CRF rats, when compared with pair-feds and controls. This was accompanied by the elevated CRP and IL-6 serum levels in animals with CRF. We also observed significant positive correlations between serum CRP or IL-6 and creatinine levels. Moreover, *Crp* gene expression (at the level of mRNA, protein amount and serum level) significantly positively correlated with *Hnf*s (mRNA and protein amount) gene expression in both liver and WAT. And finally, a serum creatinine concentration in LPS-treated healthy rats remain low, but we found the identical pattern of changes concerning liver and WAT *Crp, Il-6, Hnf1α* and *Hnf4α* genes expression (mRNA, protein amount, serum level) like in rats with CRF, and the same correlations between these genes expressions and circulating CRP.

Conclusions: The presented results suggest that overexpression of genes encoding *Crp, Il-6* and *Hnf1α* and *Hnf4α* are linked to each other, and are tightly associated with kidney function. It seems that CRF-related inflammatory state is a crucial these genes up-regulator, and HNFs may be an essential element of its molecular background.

PUB687

Interventions to Increase Nutrition Referrals in Patients with CKD Stefan C. Hemmings, Haldane Porteous, Daphne H. Knicely. *Johns Hopkins University School of Medicine, Baltimore, MD.*

Background: The prevalence of malnutrition in patients with chronic kidney disease (CKD) is high. Nephrologists are inadequately trained in nutrition education and lack

the time during clinic visits to adequately address the nutrition aspects of patient care. Inadequate documentation of nutrition status of patients with CKD in our Nephrology fellows' clinic lead to the design of a quality improvement (QI) project to improve documentation of nutrition status for CKD patients and making appropriate referrals to nutrition services.

Methods: Charts for patients with CKD stage G3a to G5 seen in the Nephrology fellows' clinic during December 2016 were audited by peer review to assess nutritional status within this population. Clinic notes were reviewed for documentation of nutrition data and referrals. Late December 2016, fellows were given a CKD nutrition lecture addressing clinical indicators for nutrition and an electronic health record (EHR) template or "smart phrase" for nutrition was designed to capture surrogates of nutritional status. In January and February 2017, charts were audited to determine nutrition referral rates. After completion of the project, fellows were sent a survey regarding the nutrition QI project and dilemmas with managing nutrition.

Results: A total of 80 charts were reviewed pre-intervention, and 121 charts were reviewed post-intervention. 49.5% of patients were either obese with BMI ≥30 kg/m² or undernourished with BMI <18.5kg/m². Serum albumin was documented in 150 charts, 23% of which had an albumin level <3.5mg/dL. The pre-intervention nutrition referral rate was 5%. Post-intervention, nutrition referrals were higher in each of the two subsequent months at 15% and 33%, respectively. The fellow survey identified major barriers to nutrition referrals, including lack of clinic time, low importance of nutrition compared to other clinical measures, and insurance coverage for referrals.

Conclusions: Obesity and hypoalbuminemia indicating poor nutritional status is prevalent in CKD patients. This QI project demonstrated that fellow education and an EHR "smart phrase" was associated with a sustained improvement in nutrition referrals. Further study is needed to determine what parameters increase a patient's chance of nutrition referral and if such referrals and adherence to diet plans improve patient outcomes.

PUB688

Profile of High Sensitivity C Reactive Protein in AKI and CKD Abhishek Goel, Tushar A. Dighe, Atul Mulay, Charan B. Bale, Ashwini Sharma, Jayraj Korpe, Nilesh Shinde, Vajed Mogal, Pratik Shete, Atul Sajgure. *Nephrology, Dr. D Y Patil Medical College, Pune, India.*

Background: Prevalence of chronic kidney disease (CKD) is around 10% worldwide, while that of acute kidney injury (AKI) has not been systematically examined. Inflammation has been identified as an important factor of co morbidities in AKI and CKD. High sensitivity C reactive protein (hsCRP) assay is useful for detection of inflammatory state. We studied the profile of serum hsCRP in patients of AKI and CKD on hemodialysis (CKD_{5D}) and the correlation of hsCRP with other inflammatory markers.

Methods: A prospective observational single tertiary care centre study from western India. Serum hsCRP, serum ferritin and serum albumin levels were checked on initiation of hemodialysis for both AKI and CKD subjects. All were dialyzed with a low flux dialyzer. Sample was collected for hsCRP, pre and post hemodialysis. All subjects were divided into AKI, CKD and Acute on CKD groups. HsCRP was analyzed using the Immuno Turbidimetry method with Cobas Integra 400 plus fully automatic analyzer. Unpaired t test was used to denote the statistical significance. Correlation between different inflammatory markers was calculated using the Pearson's correlation coefficient.

Results: A total of 106 subjects were enrolled, which included 78 (73.6%) males. The mean age of participants was 49.90±15.22 years. 74 (69.8%) were CKD, 17 (16%) in Acute on CKD and 15 (14.2%) subjects in AKI group. Serum hsCRP in AKI group (65.23±47.25 mg/l) was significantly higher (p=0.023) compared to CKD (31.93±52.60 mg/l). On comparing AKI with Acute on CKD (39.87±37.11 mg/l, p=0.106) and Acute on CKD with CKD (p=0.47), were not statistically significant. Serum hsCRP was not found to correlate with serum ferritin level in AKI (R=0.43, p=0.11), Acute on CKD (R=0.23, p=0.37) and CKD groups (R= -0.04, p=0.73). Correlation was also not found with serum albumin levels in AKI (R= -0.9,p=0.73), Acute on CKD (R= -0.33, p=0.198) and CKD (R= -0.13, p=0.26). A two tailed paired samples t test on pre and post hemodialysis values of hsCRP revealed that the hsCRP level does not change with hemodialysis (p=0.128).

Conclusions: Serum hsCRP is higher in subjects with AKI as compared to CKD, while no difference was found on comparing both the groups with acute on CKD. Serum hsCRP does not correlate with other inflammatory markers and is not dialyzable.

PUB689

Sources of Dietary Phosphorus in Patients on Dialysis Margareth L. Fornasari,[1,2] Yvoty A. Sens.[1] *[1]Santa Casa de São Paulo School of Medical Sciences, São Paulo, Brazil; [2]Nutrition, Sao Judas Tadeu University, Sao Paulo, Brazil.*

Background: Phosphorus control in the diet of end stage renal disease patients involves restriction of foods that contains phosphorus additives, processed foods with inorganic phosphorus that has high bioavailability. Dietary counseling focuses on education as a key component of hyperphosphatemia management. However, despite long-standing recommendations to limit phosphorus additives from foods most patients consume too much. The purpose of the study was to verify the contribution of foods with natural phosphorus versus foods with phosphorus additives.

Methods: A total of 67 adults with hyperphosphatemia and end-stage renal disease patients on hemodialysis for ≥6 months at a single center were evaluated. Three record-assisted 24-hour dietary recalls were collected from each participant to capture eating for a weekday on dialysis, and one recall for a weekday without dialysis. Post recall included calculating the total phosphorus amount in the diet and the identification of sources of processed foods with phosphorus additives. To verify if processed foods contained phosphorus additives food labels of each food referred was observed.

Results: The mean age were 56±13 years; 32(47%) were women and 35 (53%) were men. Phosphorus-containing foods additives contributed to 23% of the total sources of phosphorus in the diet on dialysis day and 21% on weekday without dialysis. Total phosphorus intake on dialysis day was 789±298 mg/d for total sample and was statistically different between women 789±298 mg/d and men 803±301 mg/d (p<0.001) while in a weekday without dialysis was 811±260 mg/d and was statistically different between women 811±259 mg/d and men 822±263 (p<0.001). There weren't differences between women and men and day of the week concerning foods with phosphorus additives; women 2.4±1.4 foods and men 2.4±1.4 foods on dialysis day ((p=0.87); and women 2.4±1.5 foods and men 2.4±1.5 foods (p=0.81) with phosphorus additives on a day without dialysis.

Conclusions: Foods that have natural phosphorus were the highest contributor to phosphorus in the diet but phosphorus-containing foods additives were present in the diet of all patients of this study regarding educational tools.

PUB690

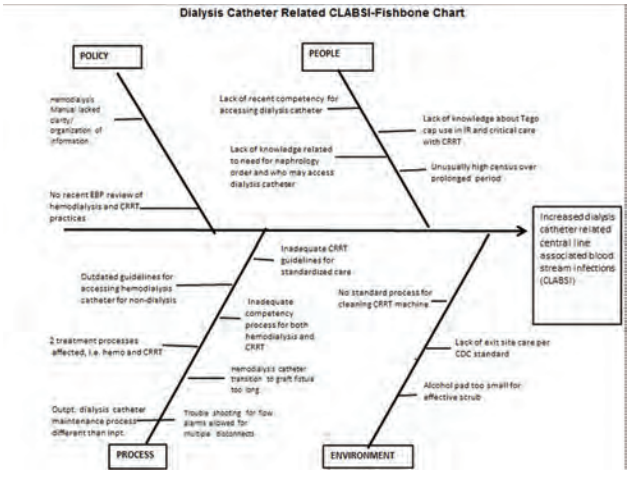
Interdisciplinary Approach to Mitigate Harm Related to Dialysis CLABSIs Robert S. Gayner. *Nephrology, St Lukes University Health Network, Bethlehem, PA.*

Background: Central Line Associated Blood Stream Infections (CLABSI) are associated with increased mortality, morbidity and cost. CLABSIs result annually in 84,551-203,916 preventable infections, 10,426-25,145 preventable deaths, and 1.7-21.4 billion dollars in avoidable cost. CLABSIs are preventable when EBM guidelines are followed. In the 1st quarter of CY 2015, we experienced a sudden increase in dialysis CLABSIs. The goal of our project was to reduce dialysis CLABSIs by 50% within 6 months and achieve sustained results.

Methods: EBM literature review, CLABSI task force creation, root cause analysis, benchmarking, human factor learning, developing clinical competencies, education and guidelines for catheter care were methods used to decrease dialysis CLABSIs

Results: Achievement: We met and surpassed our goal to reduce CLABSIs related to dialysis catheters by 50% within 6 months and achieve sustained results over time. Financial Implications: For CY2016 2016 we had 3 dialysis CLABSIs versus a spike of six in the 1st quarter of 2015. Annual cost saving is estimated at $137,442 (3 x $45,814 compared to CLABSI spike, $962,094 if initial CLABSI spike was pro-rated over 1 year. Another financial component to be considered is avoidance of Hospital-Acquired Condition (HAC) penalties. Statistical Significance: Calculating a p value would not add to what was an obvious and clinically significant reduction.

Conclusions: Hemodialysis associated CLABSIs are a significant contributor to patient associated morbidity and cost of care. This will become particularly important with Pay for Value Reimbursement and HAC penalties. Despite establishing a program of low CLABSI rates, this can change at anytime and needs to be constantly moniotred. Establishing a rapid cycle task force, updating EBM guidelines, employing human factor learing and updating clinical competencies are some core factors in preventing dialysis associated CLABSIs



PUB691

Renal Failure and Death by Hydrogen Peroxide Lori Shah,[3] Neil S. Sanghani,[2] Amit K. Rajput.[1] *[1]None, Nashville, TN; [2]Vanderbilt Nephrology, Nashville, TN; [3]Vanderbilt University Medical Center, Nashville, TN.*

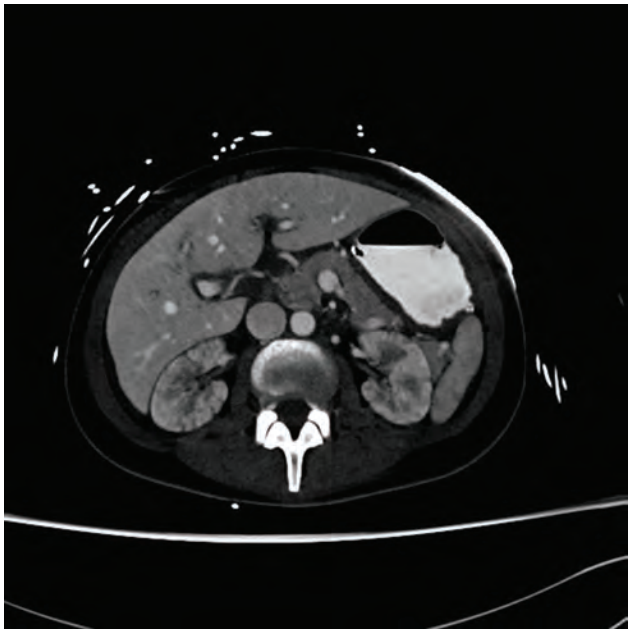
Background: Hydrogen peroxide is frequently used in alternative medicine as a treatment for autoimmune disease, infections including HIV, atherosclerotic plaques, cancers, and COPD.

Methods: A 43 year old female with scleroderma and Sjogren's presented with lethargy, vomiting, and diarrhea and was found to have multi-organ failure after use of 3% IV hydrogen peroxide infusions as therapy for her autoimmune disease. She had received

2 one-liter infusions over the preceding 3 weeks. CRRT was started for acute renal failure found to be due to multiple renal microinfarctions. Splenic and pulmonary microinfarcts were also noted on CT. She had hypertensive emergency, subarachnoid hemorrhage, DIC, severe lactic acidosis, and respiratory failure. After suffering one PEA arrest with successful CPR, she had a second arrest from which she was not resuscitated.

Results:

Conclusions: Hydrogen peroxide is a caustic oxidizing agent which can cause severe damage when infused, ingested, or inhaled. The more commonly used 3% solutions cause mild inflammation when ingested, however when used in an infusion form they can cause oxygen gas embolization to the brain and other organs, compromised cardiac output due to excessive oxidation, and disseminated intravascular coagulation. Public education on the risks of hydrogen peroxide is needed, as this toxic agent is often recommended in alternative medicine treatment regimens.



Visible renal, splenic, and occasional hepatic microinfarcts caused by hydrogen peroxide. These microinfarcts were the cause of renal failure.

PUB692

Perception of Quality of Life in Patients with Lupus Nephritis Gustavo Aroca Martinez,[3,4] Alvaro A. Martinez Bayona,[1] Henry J. Gonzalez Torres,[2] Alex Domínguez,[5] Santos Depine.[2] *[1]Fundación de Lupus del Caribe, Barranquilla, Colombia; [2]Universidad Simon Bolivar, Barranquilla, Colombia; [3]Medicine, Universidad Simón Bolívar, Barranquilla, Colombia; [4]Nephrology, Clínica de la Costa, Barranquilla, Colombia; [5]Universidad Simón Bolívar, Buenos Aires, Argentina.*

Background: Patients with Lupus Nephritis (LN), in addition to the pathophysiological factors associated with the disease, present other aspects that are of clinical interest, such as their Quality of Life - QL. Objective: to perceive the QL of 30 patients under follow-up under the risk management model of LN at an institution in the Colombian Caribbean region.

Methods: Analytical, longitudinal and retrospective study. Patients with a diagnosis of LN were included. To measure the quality of life of the patients, the GENCAT quality of life instrument was used, which evaluates eight dimensions. Emotional Well-Being, Interpersonal Relations, Material Well-being, Personal Development, Physical Well-Being, Self-Determination, Social Inclusion and Rights. For the application of the instrument, 3 controls were performed, first control at the time of being diagnosed with LN and each year during two years follow-up.

Results: 30 LN patients that were controlled, 28(93%) were women and 2(7%) were men. The results found in the different dimensions of the scale allowed us to determine that patients with LN did not obtain a high level of quality of life (Material Welfare (16.9%), Interpersonal Relations (66.7%), Personal Development (50.7%), Physical Well-being (10.9%), Self-Determination (69.1%), Social Inclusion (33.9%). From the first control the overall scores increased, being more noticeable; In those where the score was higher than the average, that improvement in the other aspects of their quality of life was also significant, especially for Emotional Welfare, Interpersonal Relations, Physical Well-Being and personal rigth.

Conclusions: The quality of life studied with the Gencat scale showed at the beginning the presence of depression and low self-esteem. Many of them failed to maintain good interpersonal relationships, they can not project their goals for their future, associated with poor self-care. From the third controls, the change was significant. Patients reported achieving and maintaining better self-esteem and self-perception. These findings could be related to a good response to treatment. At the beginning, the stress situation that affected the patients, motivated by their illness, their precarious economic situation and the deterioration of interpersonal relations, generated a vicious circle of psychological affectation.

PUB693

Upper Extremity Weight Lifting by Hemodialysis Patients with Mature Upper Extremity Arteriovenous Fistulas: Safety Considerations and the State of the Science Randi Bates.[1,2] *[1]Dennison Renal Care, Inc., Columbus, OH; [2]The Ohio State University, Columbus, OH.*

Background: Exercise, including resistance training and weight lifting, has been demonstrated to provide hemodialysis patients with mature arteriovenous fistulas (AVFs) with numerous health-related benefits. However, it is not known how much weight these patients can safely lift with their upper extremities while simultaneously having a mature upper extremity AVF. To better understand this patient safety concern and state of the science, I conducted a comprehensive review of published, empirical research.

Methods: I comprehensively searched Cochrane Central Register of Controlled Trials, Embase, and MEDLINE using the following search phrase "(arteriovenous AND fistula) AND exercise AND dialysis." I also searched the bibliography of relevant articles. I then scanned articles' title, abstract, and/or full-text for relevance.

Results: A total of three empirical studies resulted from the search, but two studies described the same results from the same population. Thus, two empirical studies with a total of 71 patients were identified for this review. One study was a randomized control trial and reported no serious adverse events, but did not report how much weight the dialysis patients lifted. The other study was a non-randomized controlled crossover trial, but did not discern exactly how many patients had an AVF. This study found that patients lifted up to 8.8 +/- 4.5kg (mean +/- SD) on the chest press and up to 6.7 +/- 1.1kg on the biceps curl with three sets of 12-15 repetitions each, three times per week (up to 26 weeks) without experiencing any serious adverse events.

Conclusions: A lack of well-defined randomized controlled trials limit the ability to conclude how much weight a hemodialysis patient with a mature upper extreimity AVF can safely lift with their upper extremities. Further trials are needed to better investigate this patient safety concern.

Funding: Commercial Support - Dennison Renal Care, Inc.

PUB694

The Causes of Dysuria after Renal Biopsy Hui-qun Li. *The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China.*

Background: Background: To prevent the risk of bleeding, routine care after renal biopsy requires that the patients should be in bed rest for 24 hours, and at the initial 6 hours the patients are required to be in supine position. Patients often suffer from dysuria during bed rest. Nurses can use the quality control circle (QCC) to analyze the causes of dysuria and to carry out continuous quality improvement of nursing care.

Methods: Methods: Retrospective analysis of 288 cases with renal biopsy was involved (149 male, 139 female). Urination status of the patients undergoing renal biopsy was analyzed, including preoperative training, postoperative urination, induced urination and the time of postoperative urination. QCC activity was used in this survey.

Results: Results: This retrospective survey showed that the incidence of dysuria after renal biopsy was 14.5%, training implementation rate of the preoperative supine urination was only 46.7%. 35.7% patients with hot compress and glycerol enema were still unable to urinate, eventually indwelling catheter was carry out. Pareto Chart analysis showed three major causes of dysuria after renal biopsy, including poor preoperative education, supine position and back pain. Among them, the reasons of poor preoperative education mainly included nurses' education methods, busy tasks and patients causes (such as the training was not been carried out or ignored). And sometimes bad privacy ward environment and the lack of standard health education materials were the reasons. Finally, the forced supine position after renal biopsy, and patients failed to complete the bed urination training also led to dysuria operation; in addition, postoperative puncture site pain and back pain were the reasons of dysuria.

Conclusions: Conclusion: Many causes of dysuria after renal biopsy were founded in this survey. The nurse's efforts can be carried to reduce the incidence of dysuria after renal biopsy.

PUB695

Effect Bisection Time and Administration Interval of Evolocumab Frieder Keller. *University Hospital, Ulm, Germany.*

Background: In the FOURIER trial, subcutaneous evolocumab was given with 140 mg every 14 days or with the pharmacodynamic equivalent of 420 mg every 28 days. The pharmacokinetic equivalent of 280 mg every 28 days was found less efficient. The effect of evolocumab is measured by the decrease in circulating proprotein convertase subtilisin/ kexin type 9 concentrations (PCSK9). This direct effect on circulating PCSK9 concentrations is immediate and lasts for 20 days until 50 % of initial concentrations are restored. The PCSK9 inhibition translates into an indirect response by the decrease in LDL cholesterol with a time delay of 10 days for the strongest effect.

Methods: With 140 mg, the maximum unbound evolocumab concentration is 20 μg/ml but with 420 mg the C_{max} is 50 μg/ml. Since the systemic clearance is 0.26 l/day and the apparent volume 2.6 liters, the elimination half-life ($T_{1/2}$) can be estimated with 7.5 days. Based on the published data, the perplexing dosing experience with evolocumab can be explained by the effect bisection time (TED_{50}). The TED_{50} is a new pharmacodynamic parameter that relates the time of effect duration to the elimination half-life (T1/2), the Hill coefficient (H) and the concentration producing 50 % of maximum effect (CE_{50})

according to the pharmacodynamic E_{max} model. $TED_{50} = T_{1/2} \times (1.44 / H) \times \ln[2 + (C_{max} / CE_{50})^H]$

Results: The TED_{50} equation was used to find a numerical solution for the pharmacodynamic parameters H with 1.4 and for CE_{50} with 4 μg/ml. The low Hill coefficient might indicate that evolocumab action is concentration-dependent and not time-dependent, allowing for an administration interval longer than the half-life. From our parameter estimates the TED_{50} is calculated with 19 days for the 140 mg evolocumab dose, but with 28 days for the 3-fold higher dose of 420 mg in complete agreement with the published 28 days administration interval. With the only two-fold higher dose of 280 mg, however, the effect bisection time will be estimated with 25 days and less than twice the normal 14 days administration interval.

Conclusions: The present formula for the effect bisection time TED_{50} allows to estimate exact pharmacodynamic parameters that could be used for the most rational evolocumab dosing.

PUB696

Automated Approach to Calculating Total Daily Dose of Tacrolimus in the Million Veteran Program Using the Electronic Health Record Adriana Hung,[1,2] Cecilia P. Chung,[2] Victoria Whitfield,[2] Csaba P. Kovesdy,[3] Christianne Roumie,[1] Todd L. Edwards,[2] Edward D. Siew,[1,2] Digna R. Velez edwards,[2] Ayush Giri,[2] Michael E. Matheny,[1] Kelly A. Birdwell.[2,1] *[1]TVHS Veterans Administration, Nashville, TN; [2]Vanderbilt University Medical Center, Nashville, TN; [3]Memphis VA Medical Center, Memphis, TN. Group/Team: On behalf of VA Million Veteran Program.*

Background: Tacrolimus dosing is complex, often requiring the combination of two pills of two different strengths that are generated concurrently with the same date/time stamp. For a study of tacrolimus pharmacogenomics in the Veterans Affairs Million Veteran Program (MVP), we aimed to develop informatics algorithms to abstract accurate dosing of tacrolimus.

Methods: Using the VA corporate data warehouse we assembled a retrospective cohort of veterans with a prescription of tacrolimus following kidney transplant. We used pharmacy files to identify dispensed prescriptions, date filled, days supplied, number of pills and dosage, and the printed bottle instructions. We built two automated algorithms to ascertain the number of pills per day per prescription and calculate the total daily dose of tacrolimus, confirming 10% by manual chart review. We then used them to confirm each other for accuracy.

Results: We identified 28,081 prescriptions of tacrolimus. **Method 1:** used the automatically printed bottle instructions prescription instructions to generate a repository of distinct text. We found 2612 distinct texts and converted them into their numeric equivalent of pills per day. **Method 2:** used structured data to identify the pill strengths, number of pills dispensed, and the number of days' supply. We divided the number of pills by the number of days supplied to get the number of pills per day. Methods 1 and 2 were compared to verify if the number of pills per day matched for each individual prescription and 90% perfectly matched, with Method 1 being the most accurate. Discrepancies were primarily caused by providers adjusting doses in the clinic without writing a new prescription.

Conclusions: Method 1, a repository of distinct texts of automatically printed bottle instructions, allowed more accurate recognition of complex prescriptions. Printed instructions are generic and can be used in the context of any prescription and will be of great use for pharmacoepidemiological and pharmacogenomics studies of other drugs.

Funding: Veterans Affairs Support

PUB697

Pharmacokinetics of Vancomycin in Pediatric Patients Receiving Hemodialysis and Hemodiafiltration Erin Chung,[1,3] James A. Tjon,[1,3] Rosaleen M. Nemec,[2,5] Nadya Nalli,[1,3] Elizabeth A. Harvey,[2,6] Christoph Licht,[2,4] Winnie Seto.[1,3] *[1]Department of Pharmacy, The Hospital for Sick Children, Toronto, ON, Canada; [2]Division of Nephrology, The Hospital for Sick Children, Toronto, ON, Canada; [3]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada; [4]Institute of Medical Sciences, University of Toronto, Toronto, ON, Canada; [5]Division of Nephrology, University Health Network (Toronto General Hospital), Toronto, ON, Canada; [6]Faculty of Medicine, Department of Paediatrics, University of Toronto, Toronto, ON, Canada.*

Background: Vancomycin is commonly used for bacteremia, but optimal dosing in pediatric patients requiring hemodialysis (HD) or hemodiafiltration (HDF) remains unknown. This study aims to characterize vancomycin pharmacokinetics, monitor its efficacy and safety, explore effects of various factors on vancomycin pharmacokinetics and derive an optimal vancomycin dosing regimen for pediatric patients on HD/HDF.

Methods: A therapeutic drug monitoring (TDM) guideline was implemented for pediatric patients on HD/HDF. Eligible patients received vancomycin 10mg/kg/dose post-dialysis and a series of serum vancomycin concentrations were collected pre-, immediately-post-, 1-h-post- and 4-h-post-dialysis. The pharmacokinetic parameters were estimated using a single compartment model and nonlinear least-squares algorithm. Monte Carlo simulations (MCS) were performed to assess dosing regimen of vancomycin.

Results: 42 courses from 16 patients were included. The average drug removal was 56.38%, rebound was 23% and net drug removal was 43% using HD/HDF. Nine courses from 6 patients with pharmacokinetic profiles were included in our pharmacokinetic model. While on HD/HDF, the median elimination constant (k_e) was $0.32h^{-1}$, and clearance was 0.18L/kg/h. When off dialysis, the median k_e was $0.013h^{-1}$, clearance was 0.0066L/kg/h and volume of distribution was 0.64L/kg. We found that duration of HD/HDF session, and type of dialysis (HD vs. HDF) may be important determinants of vancomycin pharmacokinetics. All vancomycin courses dosed at 10mg/kg/dose post-dialysis followed by TDM to assess re-dosing appeared effective based on white blood cell count, temperature and culture results. No adverse effects were reported except for one case of Redman syndrome. MCS demonstrated that the current regimen is optimal to reach therapeutic range for 4-hour post-dialysis concentrations (for central nervous system infections: 10-15mg/L or other: 5-12mg/L) and 24-hour area under the curve over minimum inhibitory concentration (AUC/MIC) ≥400 if MIC is 0.5mg/L.

Conclusions: Vancomycin is significantly removed by HD/HDF with rebound occurring at 4 hours post-dialysis. However, time to maximum rebound remains unknown due to sparse blood sampling. The current vancomycin dosing regimen is optimal for pediatric patients on HD or HDF at this institution.

PUB698

A Case of Levofloxacin Induced Choreiform Movements in a Hemodialysis Patient Muhammad Saad,[1] Shehryar Mehershahi,[1] Kalpana A. Uday,[2] Rabih Nasr.[1] *[1]Bronx Lebanon Hospital Centre, Bronx, NY; [2]Bronx-Lebanon Hospital Center, Irvington, NY.*

Background: Neurotoxic effects of quinolones have been described and are considered as second most common adverse effects after gastrointestinal side effects. Risk factors associated with enhanced adverse effects are renal impairment, old age, higher doses and interaction with other medications especially theophylline. We report a case of reversible involuntary movement (choreiform movements) in end stage renal disease (ESRD) patient secondary to levofloxacin.

Methods: 63-year-old man with known history of hypertension, end stage renal disease (ESRD), on alternate day dialysis schedule, diastolic heart failure presented with complain of generalized tremors and intermittent twitching of face and extremities for the past 2 days. Patient was compliant to his usual anti-hypertensive medications and dialysis. Four days prior to his presentation patient was started on levofloxacin 750 mg daily for treatment of upper respiratory tract infection. No history of fever, headache, photophobia, sensory or motor deficit, new medication, alcohol/drug exposure, recent travel was reported. On physical examination, his vitals were within normal limits. He was fully alert and oriented with no neurological deficit. Of significance, he was noted to have coarse tremors in all his extremities. Choreiform movements of face and tongue tremor on protrusion were also identified. No nystagmus or cerebellar signs were found. His Laboratory tests including cell count, electrolytes were completely normal and renal functions were stable. Computed Tomography(CT) head did not show any acute abnormality. Levofloxacin was stopped and hemodialysis was given as per his regular schedule. His tremors drastically improved with complete resolution within one week.

Results:

Conclusions: Although rare, Central Nervous System (CNS) toxicities such as orofacial dyskinesia, choreiform movements, myoclonus and Chorea Like movement have been reported with levofloxacin. Clinicians should be vigilant of renal adjusted doses in treating infections especially in the setting of renal failure. Conservative management with treatment of symptoms has been suggested.

PUB699

Dialysis-Induced Ventricular Tachycardia? A Reappraisal of Quinidine Clearance with Modern Dialyzers Graham T. Gipson,[2] Daniel E. Carl,[2] Jason M. Kidd.[1] *[1]VCU Medical Center, Richmond, VA; [2]Virginia Commonwealth University, Richmond, VA.*

Background: We studied the pharmacokinetics of quinidine in order to establish or refute its culpability in hemodialysis-associated breakthrough ventricular tachycardia.

Methods: 74-year-old white gentleman who was admitted to the ICU for management of recurrent ventricular tachycardia (VT). He required intermittent hemodialysis (HD) for acute kidney injury. A pattern developed wherein each HD treatment was associated with breakthrough VT despite treatment with quinidine. After determining that electrolyte and hemodynamic abnormalities were not likely the cause of this breakthrough VT, we hypothesized that intradialytic quinidine clearance might drop the blood quinidine concentration outside of the therapeutic range. Little data is available regarding the transport characteristics of quinidine with newer generation hemodialysis membranes like Revaclear MAX (used for this patient). Thus we performed a quinidine pharmacokinetic study during HD. Venous blood quinidine concentrations were assessed under steady-state conditions immediately prior to an oral maintenance dose (300 mg), thereby providing "trough" concentrations. The quinidine trough concentration for this patient was reliably 3.5 μg/mL. The patient then received a routine oral maintenance dose (300 mg), a venous blood sample was collected, and HD was started. The peak blood quinidine concentration was 4 μg/mL. Paired inflow and outflow venous blood samples were collected hourly for the duration of the HD treatment. Dialysate flow rate was set at 600 mL/min, and blood flow rate was 350 mL/min. Quinidine clearance, computed using the Fick method for blood clearance, was 25.6 mL/min, or 0.179 mL/min/kg (using an average body weight during HD equal to 142.7 kg). This computation does not account for the effect of convective clearance driven by ultrafiltration. The final venous blood quinidine concentration was 3.2 μg/mL, well within the accepted therapeutic range. The patient did not suffer breakthrough VT during this HD treatment.

Results:

Conclusions: Reported quinidine hemodialysis clearances are quite variable and our data does neither accords with nor stands out from previously published data. While older drugs find increased use in modern clinical practice we should reappraise the historical

dialyzability data for these drugs in light of the transport characteristics of newer hemodialysis membranes.

PUB700

Pharmacokinetics of Oral ZYAN1 across Indian and Australian Healthy Subjects Kevinkumar A. Kansagra,[4] Deven Parmar,[5] Mukul R. Jain,[6] Devang P. Parikh,[2] Harilal V. Patel,[3] Nuggehally R. Srinivas,[1] Vrajesh B. Pandya.[5] *[1]Cadila Health Care Ltd, Ahmedabad, India; [2]Cadila Healthcare Ltd., Ahmedabad, India; [3]Cadila Healthcare limited, Ahmedabad, India; [4]Cadila healthcare lmt, Ahmedabad, India; [5]Zydus Cadila, Ahmedabad, India; [6]Zydus Research Centre, Ahmedabad, India.*

Background: Hypoxia inducible factor (HIF)-prolyl hydroxylase inhibitors are being developed for the treatment of anaemia in chronic diseases. ZYAN1- a HIF prolyl hydroxylase inhibitor stabilized the HIF alpha and stimulated endogenous erythropoietin production and raise HB level in preclinical studies. This study was conducted to evaluate safety and compare the pharmacokinetics of ZYAN1 at an oral dose of 150 mg in Indian and Australian healthy human subjects.

Methods: Randomized, double-blind, placebo-controlled, single dose study included a total of 16 subjects; 6 subjects in each Indian and Australian group received ZYAN1 150 mg and 2 subjects in each group received matching placebo. The data were evaluated based on the blood concentration vs. time profile of ZYAN1 and the pharmacokinetic parameters were estimated using non-compartmental model.

Results: Mean age (years) and BMI (kg/m²) of Indian and Australian subjects were 28.00±4.00, 22.90±3.04 and 30.88±12.38, 22.91±1.77, respectively. There was no statistically significant difference in pharmacokinetic parameters of Indian subjects compared to Australian subjects with 150 mg dose as presented in Table.

Conclusions: Pharmacokinetics of ZYAN1 150 mg was comparable between Indian and Australian subjects. ZYAN1 150 mg was safe and well tolerated in healthy volunteers.

Funding: Commercial Support - Cadila healthcare ltd., Clinical Revenue Support

Pharmacokinetic comparison of ZYAN1 Single dose (150 mg) study between Indian and Australian healthy human Subjects

PK Parameters	Indian Subjects Single Dose 150 mg	Australian Subjects Single Dose 150 mg
n	6	6
Tmax (hr)*	2.000 (1.000 -4.000)	3.000 (2.500 -5.000)
Cmax (ng/mL)	10431.490±2519.259	8119.333±1269.627
AUC0-t(hr*ng/mL)	66278.794±20200.065	54401.071±12592.181
AUC0-∞(hr*ng/mL)	66628.622±20453.358	54672.481±12686.075
Elimination rate constant λz (1/hr)	0.069±0.025	0.062±0.008
Half life t1/2 (hr)	10.899±2.912	11.357±1.616
Volume of distribution Vd (mL)	36170.710±7431.492	46536.434±9434.457
Clearance Cl (mL/hr)	2440.574±753.217	2891.042±782.208

Note: *median (range), n=number of subjects

PUB701

Vancomycin Dosing in Short Daily Hemodialysis (SDHD) Using the NxStage System One Machine Mohan Ramkumar,[2,1] Brooke K. Decker,[2,1] Paul M. Palevsky.[2,1] *[1]University of Pittsburgh, Pittsburgh, PA; [2]Medicine Specialty, VA Pittsburgh HCS, Pittsburgh, PA.*

Background: Vancomycin is a glycopeptide antibiotic that is commonly used for treatment of Gram-positive pathogens. Both renal and non-renal clearance of vancomycin is markedly diminished in patients with decreased kidney function. Its molecular weight (~ 1450 KD), volume of distribution (~0.4-1 L/kg) and limited binding to protein (~50%) allow for significant clearance during hemodialysis using modern high flux dialyzers. Use of SDHD as a modality of home dialysis is increasing; however there are no published data to guide vancomycin dosing in patients on SDHD using the NxStage System One machine.

Methods: We evaluated the pharmacokinetics of intravenous vancomycin in an anephric patient on SDHD (30L/session, dialysate flow~ 200 ml/min, 6 days a week) using the NxStage System One machine at home. We measured vancomycin levels pre- and post- hemodialysis (HD) on numerous occasions. The volume of distribution (V), clearance (K) and half-life on HD($T_{1/2}$) were calculated assuming a single compartment model (C_0 is the pre-HD vancomycin concentration, C_t is the post-HD concentration and t is the time on dialysis): $C_t = C_0 e^{-Kt/V}$ $C_t = C_0 e^{-0.693/T½}$ Dose = V. C_0

Results: Using a loading dose of 20mg/kg followed by a maintenance dose of 500mg (~ 6mg/kg) after each SDHD session pre-HD vancomycin levels were 23-30 mg/L with post-HD (trough) levels of 15-20 mg/L. V = 0.76L/kg, K = 192 ml/min, $T_{1/2}$ = 226 minutes. Limitations: This is a limited pharmacokinetic study with data from a single anephric patient; these data will need to be confirmed in additional patients. For logistical reasons, peak vancomycin levels were not obtained 1-2 hours after vancomycin infusion; in this anephric patient we used pre-HD levels as a surrogate for peak levels.

Conclusions: To our knowledge, this is the first published report of vancomycin pharmacokinetics in patients on SDHD using the NxStage System One machine. Although the results need to be confirmed in a larger number of patients, our data provide a basis for prescription of vancomycin in patients treated with SDHD.

Funding: Veterans Affairs Support

PUB702

Toxic Epidermal Necrolysis Induced by Febuxostat: A Case Report Xiaoxuan Hu,[1] Jiawei He,[2] Jiasheng Huang,[3] Suyuan Peng,[3] Haijing Hou,[1] La Zhang,[1] Fuhua Lu.[1] *[1]Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China; [2]The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China; [3]The Second Affiliated Hospital of Guangzhou University of Chinese Medicine, Guangzhou, China.*

Background: Toxic epidermal necrolysis (TEN) is a rare, life-threatening drug-induced skin disease with a mortality rate of 25-70%. The precise mechanism is still unclear. Clinically, the Nikolsky's sign, erosions of the mucous membranes and extensive detachment of the epidermis should be an alarm for us. Specific drugs like nonsteroidal anti-inflammatory, antimicrobial drugs and allopurinol seem to be the main predisposing factors for TEN. Additionally, population's genetic background such as human leukocyte antigen (HLA) status is associated with the disease. The purpose is to describe a hyperuricemia woman, with HLA-B*5801 negative, developing the TEN after using Febuxostat.

Methods: A 64-year-old Asian woman was hospitalized with proteinuria and high serum creatinine level. Referring to her medical history, urinary color Doppler ultrasound as well as some laboratory findings, we argued that renal dysfunction was caused by chronic glomerulonephritis by the means of exclusion. She was initially treated with Febuxostat-a potent non-purine selective xanthine oxidase inhibitor against her high level of serum uric acid. However, erythematous plaques first appeared on her buttocks soon afterward. Lesions rapidly coalesced and became tense bullae. With the progression of the disease, they formed large confluent areas of epidermal detachment. Mucosal involvement occurred in her oral cavity simultaneously. All the suspect drugs were erythematous discontinued immediately. She was treated with the corticosteroid, intravenous immunoglobulins, blood transfusions, and antibiotics, along with other supportive therapies. Eventually, extensive epidermal detachment improved. It was a pity that because of the heart failure and sustained limb swelling, she accepted hemodialysis from then on.

Results:

Conclusions: What depress us most is the mortality of the disease. The most important therapeutic measures are identification and withdrawal of the suspect drugs. In this case, our patient used various kinds of medicine including traditional Chinese medicine. We listed all the medicines and sorted them according to the literature review and other drug-induced adverse reactions reports. Additionally, a genetic test was arranged but what surprised us was that her HLA-B*5801 negative, which meant drugs causing allergies'mechanism between Febuxostat and Allopurinol was different.

PUB703

Decreased Tremor and Improvement of Quality of Life after Switching to Prolonged Release Formulation of Tacrolimus in Kidney Transplant Patients Marisol Poma tapia,[2] Natividad Calvo,[2] Fernando F. Hadad-Arrascue,[3] Ana Sanchez fructuoso,[2] Isabel I. Perez-Flores.[1] *[1]Hospital Clinico San Carlos, Madrid, Spain; [2]Hospital Clínico San Carlos, MADRID, Spain; [3]Clinica RTS Murcia VII, Murcia, Spain.*

Background: Tacrolimus is the immunosuppressant of choice in kidney transplant patients, one of the most common side effects is tremor occurring at peak serum tacrolimus blood concentrations. Tremor is associated with a significant decrease in the quality of life (QOL) of transplant patient. Our objective was to determine the change in tremor severity using the Fahn-Tolosa-Marín (TMF) scale and QOL using the quality of life questionnaire (QUEST), after switching from immediate release formulation of tacrolimus to prolonged release formulation of tacrolimus.

Methods: There were 11 stable Kidney transplant patients. They had tremors that affected their QOL. Tremor pre and one month post conversion was evaluated using the FTM scale, patients completed the QUEST. We measure levels Cmin (minimum concentration) and Cmax (maximum concentration) pre and after switching from immediate release to prolonged release formulation of tacrolimus.

Results: The mean age of patients was 58 +/- 11 y. After switching from immediate release tacrolimus to prolonged release tacrolimus there was a decrease in tremor in the absolute FTM test from 26.82 to 18.36 (-8.46 P <0.012) as an improvement in the parts of the FTM test: tremor location/severity 9.45 to 5.64 (-3-81P <0.07), specific motor tasks 12.9 to 10.2 (-2.6P <0.04), functional disability as a consequence of tremor 4.4 to 2.6 (-1.81P <0.1). Regarding the QUEST QOL test in the self-evaluation, there was a subjective decrease in tremor from 7.45 to 4.18 (-3.27 P <0.03) and an increase in the quality of life assessment from 58.6 to 65.9 (-7.2P<0.027). As for immediate release tacrolimus levels in Cmin 8.1 ng/ml and Cmax (at 2 hours) 13.6 ng/ml, unlike prolonged-release tacrolimus with Cmin 7.1 and Cmax (at 8 hours) 10.8 ng/ml. There was a 30% reduction in the total dose of tacrolimus when switching to prolonged-release tacrolimus. The renal function, serum and urinary magnesium levels did not produce statistically significant differences.

Conclusions: Results suggest after switching from immediate release formulation of tacrolimus to prolonged release formulation of tacrolimus there is decrease objectively and subjectively in the tremor and there is an improvement in the quality of life of Kidney transplant patients affected by tremor.

PUB704

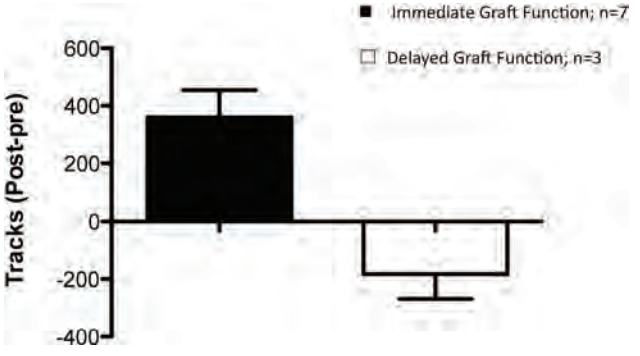
Successful Kidney Transplantation Normalizes Platelet Function Claire Kennedy,[4,5] Limy Wong,[4] Donal J. Sexton,[3] Jonathan J. Cowman,[2] Martin Kenny,[5] Peter J. Conlon,[1] Dermot Kenny.[2] *[1]Beaumont Hospital, Dublin 9, Co Dublin, Ireland; [2]RCSI, Dublin, Ireland; [3]The Irish Longitudinal Study on Ageing (TILDA), Trinity College Dublin., Dublin, Ireland; [4]Nephrology, Beaumont Hospital, Dublin, Ireland; [5]Royal College of Surgeons in Ireland, Dublin, Ireland.*

Background: Uremic platelet dysfunction is poorly understood largely because of inadequate platelet function assays. We have developed an assay of platelet function that accurately measures platelets translocating across von Willebrand factor (VWF) at arterial shear rates (DPFA). The aim of this study was to investigate the impact of kidney transplantation (KTX) on platelet function using the DPFA.

Methods: Blood samples from ten patients before and after KTX surgery and nine healthy controls at two different time points were assayed using the DPFA. Multiple parameters of platelet behavior and platelet-VWF interactions were recorded using customized platelet tracking software. The assay was repeated 3-8 weeks post-transplant.

Results: Platelet-VWF interactions were markedly reduced in the ten pre-transplant patients compared to the healthy controls. They normalized post-transplant in the seven patients with immediate graft function (despite a small drop in hemoglobin and hematocrit) but remained markedly abnormal in the three patients with delayed graft function (DGF).

Conclusions: This is the first demonstration of normalization of platelet function with reversal of uremia by KTX. Early normalization of platelet-endothelial interactions did not occur in those with DGF. This has important clinical consequences, as patients with DGF are more likely to undergo invasive procedures including transplant biopsies and insertion of central venous catheters.



Change in platelet interactions following transplantation as measured by differences between post-transplant and pre-transplant platelet tracks (ie the number of platelets interacting with VWF over the course of 500 frames)

PUB705

Value of the Immune Cell Function Assay in Pediatric Kidney Transplantation Lokesh N. Shah,[2] Joann M. Carlson,[1] Lynne S. Weiss,[1] Anna Petrova.[1] *[1]Rutgers RWJMS, New Brunswick, NJ; [2]Thomas Jefferson University Hospital, AI DuPont Hospital for Children, Wilmington, DE.*

Background: End-stage renal disease (ESRD) is associated with long-term complications and alteration of quality of life in affected children. Kidney transplantation is widely accepted for the management of ESRD in pediatric patients. The immune cell function (ICF) assay that measures CD4 lymphocyte ATP activation has been suggested to assess the level of immunosuppression, which is essential to reduce the risk for both rejection and complications of immune dysfunction.

Methods: We analyzed ICF level and clinical data on 20 children aged 3 to 20 years who underwent kidney transplantation. A total number of 75 ICF levels were analyzed to identify an association with the white blood counts (WBC), blood level of tacrolimus, and month after renal transplant (from 1 to 145). In addition, the ICF level was analyzed with respect to the therapeutic regiments: Group 1 (tacrolimus, mycophenolate/mycophenolic acid, and prednisone and Group 2 (tacrolimus and prednisone). Data is presented as mean with 95% Confidence Interval (95%CI) and correlation coefficient (r). *P*-value <0.05 was considered significant.

Results: A total number of 56 ICF levels were measured in Group 1 and 19 in Group 2 of studied patients. We found no difference in ICF levels [Group 1 (336.5, 95% CI 288.6-384.7) vs. Group 2 (359.4, 95%CI 248.8-469.9), P=0.65]. The ICF was correlated with WBC (r=0.66, P<0.01). There was no correlation with ICF and tacrolimus levels, nor was there an association between the ICF and the month after transplantation. ICF measures analyzed during post-transplantation follow-up were low, moderate and high in 23.2%, 64.3%, and 12.5% in Group 1 and in 42.1%, 31.6%, and 26.3% of those in Group 2 (P<0.05).

Conclusions: Immunosuppression therapy including mycophenolate or mycophenolic acid is more likely to maintain a moderate immunosuppression status, and the WBC may be used as surrogate measurement of immune-suppression in pediatric patients followed kidney transplantation.

PUB706

Predictors of Persistent Hyperparathyroidism Post Renal Transplantation – A Single Centre Experience Mayank Chawla,[1] Sobhana Thangaraju.[2] *[1]singapore general hospital, SINGAPORE, Singapore; [2]renal medicine, singapore general hospital, SINGAPORE, Singapore.*

Background: Hyperparathyroidism improves after kidney transplantation (KTR). However, persistent- hyperparathyroidism (PH) may occur and is associated with a higher risk of cardiovascular events, fractures, allograft failure, and all-cause mortality. Pre-transplant parathyroidectomy (PTX) has been advocated to prevent the risk of PH and complications of post-transplant PTX. However, there is no defined criteria for the timing of pre-transplant PTX. This study seeks to identify predictors of PH following transplantation to guide timely intervention

Methods: All first KTR performed in our tertiary care center, between January 2005 and July 2015 with follow-up of until 12 months and pre-transplant dialysis of more than 3 months were recruited for analysis (n=169). PH was defined as serum corrected calcium (cCA) of > 2.50 mmol/L and serum iPTH > 6.5pmol/L at 12 months post-transplant Baseline demographic and biochemical data were compared between groups with and without PH. Univariate analysis was performed and significant predictors of PH were further analyzed with multivariate regression analysis

Results: Mean age of study population was 45.8 years. The mean dalysis vintage was 88 months (36-140) and 84% were on hemodialysis. 68% of patients received deceased donor KTR. PH was diagnosed in 65 patients (38 %). On univariate analysis, patients with PH were older (48 (7.9) vs 44.4 (10.8), p=0.025), had longer dialysis vintage (108 vs 77 months p= 0.002), and higher pre-transplant cCA (2.51 (2.34, 2.68) vs. 2.29 (2.07, 2.51), p<0.0001), alkaline phosphatase (127.0 (114.0, 140.0) vs. 88.0 (38.0, 105.0), p=0.016), iPTH (90.2 (29.0, 127.2) vs. 38.0 (11.7, 49.9), P=0.0002), and phosphate (1.90(1.38,2.42) vs 1.66(1.14,2.18), P=0.0056) levels. Estimated GFR was lower in patients with PH at 12 months (54.5 (34.5, 75.0) vs. 61.0 (42.0, 80.0), P=0.0001). Following multivariate adjustment, longer dialysis vintage (HR = 1.011, 95% CI=(1.001,1.021)), higher pre-transplant cCa (HR=1.647, 95% CI=(1.296, 2.177)), and higher pre transplant iPTH (HR=1.015, 95% CI=(1.006,1.026)) remained significant

Conclusions: Longer dialysis vintage, higher pre-transplant iPTH and pre-transplant hypercalcemia are important predictors of PH following kidney transplantation

PUB707

A Unique Case of Disseminated Nocardia Infection and Post Transplant Lymphoproliferative Disorder in a Renal Allograft Recipient Dilini M. Daswatta,[1] Rohan V. Mehta,[1] Stephen O. Pastan,[1] Rahul Mehta.[2] *[1]Emory University School of Medicine, Atlanta, GA; [2]University of Virginia, Charlottesville, VA.*

Background: Nocardia infections most commonly present 1 to 6 months after solid organ transplantation with acute or subacute pneumonia, but hematogenous spread to brain, bone, eye and rarely skin and subcutaneous tissue have been reported. Inhanced Immunosupression, particular exposure to antilymphocytic antibody preparations may potentially increase the risk of such infections.

Methods: A 55 year old asian man with a history of Deceased Donor Renal Transplant of 2 years and stable Post Transplant Lymphoproliferative Disorder(PTLD) presented with left leg swelling for 2 weeks. About 6 months prior, he was diagnosed with biopsy proven metastatic CNS PTLD managed with systemic Rituximab, Intracranial radiation and Decadron. His maintenace immunosupression which included Belatacept was held and the dose of Cellcept was reduced after the diagnosis. The right parietal brain lesion was stable and liver metastasis had resolved after completion of therapy. He also had a history of Acute Rejections managed with Predniosne and Thymoglobulin in the past.

Results: CT scan of the leg reveals intramuscular fluid collection in the adductor and vastus group of muscle suggeting cellulitis / abscess, while Chest CT shows consolidation of the right upper and lower lobes. A new ring enhancing lesion suggestive of infection is discovered in the right temporal lobe of the brain on MRI, after the patient develpos altered mental status. Tissue biopsy from the leg grows Nocardia Farcinica. A CT guided drain is placed in the leg. The patient is started on Bactrim and Meropenem. Bactrim is later replaced with Linezolid. A repeat CT of the leg is suggestive of reduction in the fluid collection and the patient shows clinical improvement.

Conclusions: We present a case of Disseminated Nocardia Farcinica Infection in the setting of PTLD complicating a Deceased Donor Renal Transplant. We highlight the risk factors leading to these complications and discuss potential therapeutic options.

PUB708

Clinical Predictors of Recurrent Focal Segmental Glomerulosclerosis in Renal Transplantation Anita Shah,[3] Juan M. Gonzalez,[1,2] Sandra Barrow.[2,3] *[1]Houston Methodist Hospital, Houston, TX; [2]Nephrology, Dialysis & Transplantation Associates PA, Houston, TX; [3]J. C. Walter Jr. Transplant Center, Houston Methodist Hospital, Houston, TX.*

Background: Focal segmental glomerulosclerosis (FSGS) is a clinicopathologic syndrome involving scarring of the glomerulus and nephrotic range proteinuria[1]. Approximately 30% of patients have recurrent FSGS after renal transplantation[1], and these patients are at high risk of losing their graft. This recurrence, if not halted, ultimately leads to failure of the renal transplant and either dialysis or retransplantation. While some studies have shown risk factors associated with recurrence, there is no consensus on which patients are at greatest risk[1-3]. Our aim is to describe factors that help predict FSGS recurrence in transplant recipients.

Methods: A retrospective, observational case-control study was conducted on 24 patients (15 males) with idiopathic FSGS who had received a renal transplant at the Methodist Hospital between 2011 to 2015. All patients underwent a renal transplant biopsy. Baseline characteristics such as age at transplant, sex, race, immunosuppressive regimen, donor type, proteinuria, and creatinine were compared between those with and without FSGS recurrence. Continuous data were expressed as mean ± standard deviation (range) and analyzed with a Mann-Whitney test, while categorical data was analyzed by Fisher's exact test.

Results: At the time of biopsy, patients with FSGS recurrence illustrated, as expected, a significantly higher creatinine (p=0.010) and amount of proteinuria (p=0.001). However, no significant difference in age, sex, race, immunosuppressive regimen, or donor type could be identified between the two groups.

Conclusions: Surprisingly, there was no association between age, sex, race, immunosuppressive regimen, or donor type and recurrence, which differs from prior studies[1-3]. Future longitudinal studies monitoring idiopathic FSGS patients prior to and after transplantation can lead to proper screening of high-risk patients. 1. Shimizu, A, Higo, S, Fujita, E, et al. Focal segmental glomerulosclerosis after renal transplantation. Clin Transplant 2011; 25(Suppl. 23): 6-14. 2. Vinai, M, Waber, P, Seikaly, MG. Recurrence of focal segmental glomerulosclerosis in renal allograft: An in-depth review. Pediatric Transplantation 2010; 14: 314-25. 3. Abbott, KC, Sawyers, ES, Oliver, JD, et al. Graft loss due to recurrent focal segmental glomerulosclerosis in renal transplant recipients in the United States. Am J of Kidney Diseases 2001; 37(2): 366-73.

PUB709

Severe AKI Due to AMR Rescued with Eculizumab Mark J. Lerman,[1] Michael B. Kuperman,[3] Afzal Nikaein,[2] Judson M. Hunt,[1] Salman Khan.[1] *[1]Dallas Nephrology Associates, Dallas, TX; [2]Texas Medical Specialty, Dallas, TX; [3]Johns Hopkins, Baltimore, MD.*

Background: Antibody mediated rejection (AMR) in transplant recipients may cause graft dysfunction and decreased graft survival. Current treatment options for AMR include plasma exchange (PP), intravenous immunoglobulin (IVIG), and anti--CD 20 therapy. Patient's with severe forms of AMR usually do not respond to these treatments. We present one case of very severe acute antibody mediated rejection which was resistant to conventional therapy but responded to Eculizumab.

Methods: 45-year-old AA man status post deceased donor kidney transplant in 2013, baseline creatinine 1.2. Patient presented with a serum creatinine > 20 in 2015. A biopsy revealed severe diffuse peritubular capillary C4d staining. Donor specific antibodies were present against DQ9 MFI 13153 at 1:32 dilution. Hemodialysis was initiated. A repeat renal biopsy after 5 doses of IV SoluMedrol and 5 treatments of plasma exchange and low-dose IV IgG continued to show diffuse peritubular capillary C4d deposition. Light microscopy remained essentially unremarkable. DSA to DQ9 remained high at MFI 12837 at 1:32 dilution. He remained on tacrolimus and mychophenolate. Eculizumab was begun at 1200 mg IV every week x 4. After 4 weeks and 4 doses of Eculizumab, renal function was clearly improving with a serum creatinine of 3 and a GFR of 25 mL/min/1.73m2. Dialysis was discontinued and a third renal biopsy showed complete resolution of C4d staining and very mild tubulitis with about 30% interstitial fibrosis. Patient received Eculizumab 900 mg every 2 weeks for another 4 doses. He has remained dialysis free for the last 19 months.

Results:

Conclusions: To our knowledge, prior to this case, no patient with a serum creatinine above 20 has responded to antirejection therapy and been able to discontinue dialysis. Our patient remains stable with serum creatinine 2.5 and has not required dialysis after almost 19 months. We believe even severe acute renal failure due to AMR requiring dialysis, may respond to Eculizumab. Allograft biopsy demonstrating absence of chronic changes and particularly thombosis maybe an important predictor for responsive patients regardless of renal dysfunction.

DATA

date	MFI	Scr	date	MFI	Scr
8/10/17	1:32 13152	20	12/22/15	1:32 11506	3.2
8/19/15	1:32 12837	5.4	3/18/16	1:32 2561	3.6
9/1/15	1:32 16178	4	3/15/17	1:32 1191	2.5

PUB710

The Risk of Inadequately Low First Tacrolimus Trough Level with Currently Recommended Reduced Drug Dosing in Kidney Transplant Recipients Aureliusz Kolonko, Andrzej Wiecek, Jerzy Chudek. *Medical University of Silesia, Katowice, Poland.*

Background: Nowadays, reduced tacrolimus (Tc) initial daily dose (0.1-0.15 mg/kg) is recommended for the majority of kidney transplant recipients (KTR). The aim of the study was to check the safety of such a regimen including the risk of first inadequately low tacrolimus blood level, acute rejection occurrence and delayed graft function (DGF).

Methods: In 2011, we introduced a modified (reduced from 0.2 to 0.1-0.15 mg/kg/day) initial tacrolimus dosing regimen in older (>55 years) and/or overweight KTR. To assure the safety of this protocol we have monitored the risk of inadequately low blood Tc level (<6 ng/ml) and incidence of acute rejection or DGF. The historical cohort (n=319) served as a control group.

Results: The mean Tc daily dose in 79 KTR (group with reduced dosing) was 0.13±0.02 mg/kg and was significantly lower than the standard, previously prescribed dose (0.19±0.02 mg/kg). The dose reduction resulted in slight, nonsignificant decrease in first blood Tc trough level (15.6±7.8 vs. 16.1±7.2 ng/ml). There were 6.3% (n=5) versus 5.3% (n=17) first Tc trough levels below 6 ng/ml and 45.6% (n=36) versus 48.9% (n=156) above 15 ng/ml in reduced and standard dosing groups, respectively. These differences were not significant. The incidence of acute rejection (7.6 vs. 6.0%) and DGF (26.6 vs. 28.5%) was similar in both groups.

Conclusions: 1. The currently recommended reduction in Tc initial dosing does not increase the risk of inadequate immunosuppression and does not affect the early graft function. 2. Regardless of Tc dose reduction, there is still a greater risk for Tc overdosing in older and overweight kidney transplant recipients.

PUB711

Rapid Graft Loss Due Recurrence of Undiagnosed Primary Hyperoxaluria Saffa M. El awad.[1,2] *[1]NEPHROLOGY, HAMAD MEDICAL COORPORATION, DOHA, Qatar; [2]TRANSPLANTATION, UNIVERSITY OF LIVERPOOL, LIVERPOOL, United Kingdom.*

Background: Primary hyperoxaluria (PH) is a rare autosomal recessive disorder leading to systemic deposition of calcium oxalate crystal causing nephrocalcinosis, nephrolithiasis, and chronic kidney disease. A case record of a young woman with end-stage renal disease is being presented who underwent paid organ transplantation and developed allograft loss at two weeks due to recurrence of undiagnosed PH.

Methods: Case Records: The patient is a 28-year-old female patient, was known to have hypertension and hyperlipidaemia for few years. She presented with end-stage renal disease and commenced on haemodialysis in December 2014. She was found to have bilaterally small kidneys; hence kidney biopsy was not performed. In February 2016, she received kidney transplantation from donor a 38 years old paid male donor (no further information available). Post-operative period was complicated with severe bacterial sepsis and development of a lymphocele. Two weeks later there was a consistent decline in graft function, and eventually, she required maintenance haemodialysis. Renal allograft biopsy showed extensive calcium oxalate crystals deposition, suggestive of recurrence of primary hyperoxaluria. Genetic studies confirmed the diagnosis of primary hyperoxaluria type 1. Moreover, patient contracted hepatitis C and developed severe erythropoietin-resistant anaemia

Results:

Conclusions: Recurrence of PH is recognised, leading to graft loss. Despite this in 10% of patient diagnosis is done retrospectively. This case demonstrated the need for careful screening of PH in young patients prior to transplantation. There is a dire need for pre-transplant counselling to increase awareness of life-threatening situations in unregulated health care sector, where money is the sole aim. The exploitation of donors and recipient is rampant and unabated where cross-infections are common. Acquisition of hepatitis C is not surprising.

PUB712

Urinary Tract Infection in Kidney Transplant Recipients, Experience of the Hospital Specialties, Western National Medical Center, Mexican Institute of Social Security Victor M. Martinez-Mejia,[1] Jorge Andrade-Sierra,[1,2] Benjamin Gomez-Navarro,[1] Milagros M. Flores fonseca.[1] *[1]Nephrology, Instituto Mexicano Del Seguro Social. Centro Medico Nacional de Occidente, Guadalajara, Mexico; [2]Physiology, University of Guadalajara, Guadalajara, Mexico.*

Background: URINARY TRACT INFECTIONS (UTI) ARE THE MAIN CAUSE OF INFECTIOUS COMPLICATIONS AFTER KIDNEY TRASPLANT. THE INCIDENCE REPORTED OF UTIs RANGES FROM 21% TO 79%. GRAM NEGATIVE BACTERIA ACCOUNT FOR MOST OF 70% OF UTI; E. COLI IS THE MOST UROPAHOGEN. THE RISK FACTORS FOR THE DEVELOPMENT OF POSTTRANSPLANT UTIS ARE MULTIFACTORIAL AND ARE DETERMINED BY THE INTERACTION BETWEEN HOST FACTORS, PATHOLOGIC AGENTS AND ANATOMICAL ABNORMALITIES.

Methods: WE PERFORMED COHORT STUDY INCLUDING ALL THE ADULT PATIENTS WHO RECEIVED A RENAL TRANSPLANT AT HOSPITAL OF SPECIALTIES, WESTERN NATIONAL MEDICAL CENTER, MEXICAN INSTITUTE OF SOCIAL SECURITY FROM JANUARY 2013 TO APRIL 2015. WE DEFINED AS UTI PATIENTS WITH URINE CULTURE WITH >10 5 CFU/ML. PRINCIPAL OUTCOME: TO DETERMINE THE INCIDENCE OF UTIs IN THE FIRST YEAR POSTTRANSPLANT. SPECIFIC OUTCOMES. TO RECOGNIZE RISK FACTORS, PATHOLOGIC AGENTS.

Results: THE POPULATION CONSISTED OF 631 PATIENTS, WITH MAJORITY RECEIVING ALLOGRAFT FROM LIVING DONORS (86%). A TOTAL OF 192 PATIENTS (30.4%) DEVELOPED AT LEAST ONE EPISODE OF UTI. SIGNIFICANT RISK FATORS FOR POSTTRASPLANT UTIs WERE FEMALE GENDER (OR 2.8; CI 95%:1.7-4.3; P <0.001) CADAVERIC DONOR (OR 2.2; CI 95%:1.4-3.6; P <0.001), DIABETES MELLITUS 2 (OR 2.8; CI 95%:1.3-6.0; P <0.001), DURATION BLADDER CATHETERIZATION MORE THAN FOUR DAYS (OR 6.4; CI 95%:3.1-13.3; P <0.001)URETERAL CATHETER PLACEMENT(OR 3.1; CI 95%:1.9-5.1; P <0.001) AND ANATOMICAL ALTERATIONS (OR 9.7; CI 95%:4.86-19.5; P <0.001).

Conclusions: IN THIS COHORT OF PREDOMINANTLY LIVING DONOR RENAL TRANSPLANT RECIPIENTS, THE INCIDENCE OF UTI IS SIMILAR TO THAT REPORTED IN OTHER STUDIES. ISOLATED PATHOGENS AS IN OTHER REPORTS CORRESPOND TO GRAM-NEGATIVE BACILLI. RISK FACTORS THAT WE COULD DETERMINED WERE FEMALE SEX, CADAVERIC DONOR, PROLONGED URETHRAL CATHETER STAY, URETERAL CATHETER PLACEMENT AND ANATOMICAL ALTERATIONS.

PUB713

Procalcitonin for Diagnosis of Bacterial Infections and Rejection in the Early Post-Renal Transplant Period Shefali Gupta,[3] Pradeep Jaswani,[2] Kashi nath Prasad,[2] Narayan Prasad,[2] Amit Gupta,[1] Chinmoy Sahu.[2] *[1]Department of Nephrology, Lucknow, India; [2]SGPGI, Lucknow, India; [3]Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India.*

Background: Infection and rejection are leading causes of morbidity and mortality in renal transplant recipients. Since patients with infection and rejection have similar clinical presentation, differentiating the two can pose a diagnostic challenge for transplant clinicians. We evaluated the utility of PCT in differential diagnosis of rejection and infection in renal transplant recipients.

Methods: In this study, serum PCT concentrations were monitored in 146 renal transplant recipients from the day of transplant to 15 days after transplant. The PCT estimation was done using ELECSYS BRAHMS PCT kit. Recipients were grouped into Group 1: non-infectious and Group 2: infectious group. Group 2 was further subdivided into: graft rejection (Group 2a) and non-rejection (Group 2b) cases. SPSS (V.20) was used for statistical analysis. PCT levels > 0.5 ng/ml were consideredclinically significant. Rejection was proven with biopsy.

Results: Out of the total 146 patients, 111 (group 1) did not develop a bacterial infection while 35 (group 2) suffered bacterial infections within 15 days of renal transplant. Among the group 2 patients, 13 (group 2a) suffered acute graft rejection while 22 (group 2b) did not. Receiver operating characteristic (ROC) analysis showed the area under thecurve (AUC) for predicting infection above PCT level of 1.9 ng/ml was 0.89, (95% confidence interval [CI]: 0.83-0.94; p = <0.0001). For differentiating group 2a patients from group 2b, AUC was 0.65 (95% CI: 0.46-0.83; p = 0.1).

Conclusions: PCT levels can improve diagnostic accuracy of bacterial infections in patients in the early post–renal transplant period with adequate sensitivity and specificity. It does not, however, reliably exclude the co-occurrence of rejection in patients who have also developed bacterial infections. Larger, multicenter studies would be useful to validate the PCT cutoff values.

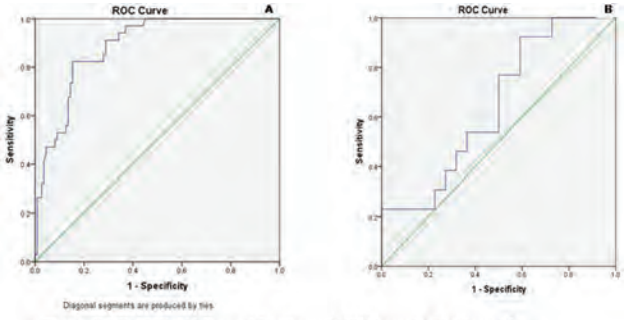


Figure: ROC-AUC (A) Group 1 Vs Group 2, (B) Group 2a Vs Group 2b

PUB714

A Case of Immune Complex Membranoproliferative Glomerulonephritis (IC-MPGN) and De Novo Donor Specific Antibodies (dnDSA) after Kidney Transplantation in a Patient with Polycystic Kidney Disease Syed Hammad Alam,[4] John E. Leggat,[2] Paul F. Shanley,[2] Vikram Aggarwal,[1] Oleh G. Pankewycz.[3] *[1]SUNY UPSTATE MEDICAL UNIVERSITY, NEW YORK, Syracuse, NY; [2]SUNY Upstate Medical University, Syracuse, NY; [3]SUNY, Upstate Medical University, Syracuse, NY; [4]Upstate Medical University, Syracuse, NY.*

Background: Immune mediated glomerular disorders in transplant recipients include recurrent GN, post-infectious GN and antibody mediated rejection. Different GNs usually do not occur simultaneously as they imply either over-immunosuppression (IS) i.e. infection or under-IS i.e. alloantibodies. We now describe an unusual case of IC-MPGN with concurrent dnDSA in a patient with ESRD due to APKD.

Methods: A 61 year old man with a panel reactive antibody level of 0% received a kidney transplant from a non-Public Health Service defined high risk donor. Both recipient and donor were negative for hepatitis C virus (HCV). Rabbit anti-thymocyte globulin was given with maintenance IS on cyclosporine, mycophenolate and prednisone. Allograft function was excellent with creatinine levels of 1.0-1.2 mg/dl. The patient was often noncompliant with therapy due to adverse drug effects. Fourteen months after transplant the patient developed nephrotic range proteinuria (4.6-6.9 gr), microscopic hematuria and a creatinine of 1.4 mg/dl. Allograft biopsy showed typical changes of IC-MPGN with double contouring of glomerular basement membrane accompanied by glomerular and mesangial dense deposits, C3, C1q, IgG, IgA and IgM staining by immunofluorescence and microtubular aggregates by EM. An evaluation revealed the presence of anti-HCV antibodies, serum cryoglobulins and a low C3 level, however HCV viral copies were undetected. Peritubular capillaritis and C4d staining were also observed. The recipient was also found to have anti-Class II dnDSA (DR1, DQ2 and DQA105) and anti-Class I (A1) dnDSA. High dose steroid therapy, apheresis and IVIG were started with resultant improvement in proteinuria and return of serum creatinine to prior baseline. Anti-HCV antibodies and cryoglobulins were negative on repeat testing.

Results:

Conclusions: Without anti-viral therapy, post-transplant HCV infection is associated with IC-MPGN and the HCV infection by itself rarely remits and leads to high rates of graft loss and patient mortality. Our patient represents an unusual case of a presumed spontaneously resolved HCV infection with cryoglobulins due to under-IS as evidenced by the presence of dnDSA.

PUB715

Long-Term Outcome of Renal Transplantations in Two Patients with ADCK4-Associated Glomerulopathy Zihua Yu,[1,2] Si Wang.[1] *[1]Department of Pediatrics, Dongfang Hospital, Fuzhou, China; [2]Department of Pediatrics, Xiamen University Affiliated Dongfang Hospital, Fuzhou, China.*

Background: Mutations in the *ADCK4* gene can cause *ADCK4*-associated glomerulopathy. Patients with *ADCK4*-associated glomerulopathy can be treatable with CoQ10 at the early stage because the transcript of *ADCK4* encodes a protein of the CoQ10 biosynthetic pathway, which localizes to the mitochondria in podocytes. The patients with *ADCK4*-associated glomerulopathy who progress to end-stage renal disease (ESRD) require dialysis or renal transplantation. It has reported that some patients with *ADCK4*-associated glomerulopathy received renal transplantations. However, long-term outcome of transplantations in the patients with *ADCK4*-associated glomerulopathy is unknown. Here, we report the long-term outcome of two cases with *ADCK4*-associated glomerulopathy who received cadaveric renal transplantations at more than 10 years of follow up.

Methods: The two patients harbor a compound heterozygous mutation (532 C>T; R178W and 748 G>C; D250H) in the *ADCK4* gene. Case 1, a boy presented with steroid-resistant nephrotic syndrome (SRNS) at 7 years old and had mesangial proliferative glomerulonephritis lesions on renal biopsy at 8 years old. He received a cadaveric renal transplantation at 16 years old when he progressed to ESRD. The avenues in the immunosuppressive treatment included the use of mycophenolate mofetil, tacrolimus plus prednisone. His renal examination retained normal at 11 years of follow-up. His last urinalysis showed normal. His serum creatinine was 114 μmol/L and urea nitrogen 7.9 mmol/L. Case 2 (older sister of case 1), a girl presented with SRNS and had focal segmental glomerulosclerosis on renal biopsy at 10 years old. She received a cadaveric renal transplantation at 14 years old when she progressed to ESRD. She received the same avenues after transplantation. Her renal examination also retained normal at 15 years of follow-up. Her last urinalysis also showed normal. Her serum creatinine was 81μmol/L and urea nitrogen 5.5mmol/L.

Results:

Conclusions: Long-term outcome of renal transplantations is good in the patients with *ADCK4*-associated glomerulopathy who progress to ESRD.

Funding: Clinical Revenue Support

PUB716

Triglyceride Metabolism in Japanese Kidney Transplant Recipients Makoto Tsujita. *Nagoya Daini Red Cross Hospital, Nagoya, Japan.*

Background: Residual risk factors such as triglyceride (TG) cause cardiovascular disease. TG metabolism after kidney transplantation remains unclear.

Methods: Sixty-three consecutive stable recipients just one year after kidney transplantation were included in the study at Nagoya Daini Red Cross Hospital from January to September in 2014. We performed cookie test(this cookie consists of 75 g carbohydrate and 25 g fat) to evaluate TG metabolism. TG, Blood sugar (BS), remnant like particle-choresterol (RLP-C), serum insulin were measured at fasting (f) and 2 and 4 hours (h) after ingestion. Low density lipoprotein cholesterol (LDL-C) and high desity lipoprotein cholesterol (HDL-C) and apoB were measured at fasting.

Results: Figure 1 summarizes the clinical and metabolic characteristics of this study. Mean TGf and RLP-Cf were 139.4±62.6 mg/dl and 5.6±3.4 mg/dl within normal range, however, both mean TG2h and TG4h were above 200 mg dl, and both mean RLP-C 2h and RLP-C 4h were above 9 mg/dl. A negative correlation was seen between TGf and eGFR (r=-0.48 p<0.001). TGf had positive correlation with RLP-C, non HDL-C, LDL-C/apoB ratio, BMI (r=0.80 p<0.001, r=0.47 p<0.001, r=0.48 p<0.001, r=0.38 p=0.002, respectively). BMI had positive correlations with RLP-C (r=0.35, p<0.001) and a negative correlation with HDL-C and LDL-C/apoB ratio (r=0.48 p<0.001, r=0.30 p=0.016, respectively). LDL-C levels were under control because of statin use, but LDL-C/apoB ratio levels in 50% of recipients were below 1.2, meaning the rate of small dense LDL-C in LDL-C increased. TG metabolism in non DM group was similar with that in DM group. In Everolimus (EVR) group, TGf levels were higher than that in non EVR group (p=0.04).

Conclusions: Prevalence of postprandial hypertriglyceride among kidney transplant recipients was high, however, whether it should be treated remained unknown.

Table 1 Patients' characteristics of this study(n=63)

Variable	All patients (n=63)	DM group (n=10)	non DM group (n=53)	P value	EVR group (n=18)	non EVR group (n=45)	P value
Gender(male),n	29	4	25	0.68	11	23	0.58
age, years	47.7±13.0	53.9±8.1	46.5±13.5	0.10	48.4±9.7	47.4±14.2	0.80
Total-cholestrol, mg/dL	181.0±24.6	182.2±28.3	46.5±13.5	0.86	188.9±25.4	177.8±23.7	0.10
Low density lipoprotein-cholesterol, mg/dl	95.1±18.0	98.7±19.0	94.4±18.0	0.49	55.5±11.6	56.4±14.4	0.81
High density lipoprotein-cholesterol, mg/dL	56.2±13.5	54.9±11.4	56.4±14.0	0.75	133.0±23.7	121.4±20.0	0.05
Non high denstty lipoprotein-cholesterol, mg/dL	124.7±21.6	127.3±27.5	124.2±20.6	0.68	98.2±18.7	93.9±17.8	0.39
Low density lipoprotein-cholesterol/apoB ratio	1.2±0.2	1.25±0.17	1.21±0.15	0.40	1.19±0.17	1.23±0.14	0.36
Triglyceride fasting, mg/dL	139.4±62.6	144.4±45.3	138.5±65.7	0.79	165.2±68.9	129.1±57.5	0.04
2hours, mg/dL	212.2±90.1	191.4±87.5	216.1±90.8	0.43	237.9±103.8	201,9±83.0	0.15
4hours, mg/dL	206.3±105.2	174.7±49.2	212.3±112.0	0.30	235.4±116.2	194.7±99.4	0.17
Remnant-like particle-choresterol fasting, mg/dL	5.6±3.4	6.1±2.8	5.5±3.5	0.62	6.6±3.8	5.2±3.2	0.34
2hours, mg/dL	9.7±4.7	10.9±4.3	9.5±4.8	0.52	10.2±5.2	9.5±4.6	0.65
4hours, mg/dL	9.1±5.6	9.6±4.9	9.0±5.8	0.76	9.5±5.8	8.9±5.6	0.71
Blood sugar fasting, mg/dL	97.5±34.8	145.7±52.8	88.4±20.8	<0.001	101.4±41.8	96.0±32.1	0.58
2hours, mg/dL	130.7±48.3	150.3±90.7	127.1±35.6	0.16	136.4±42.7	128.5±50.6	0.56
4hours, mg/dL	135.9±57.8	213.8±94.5	121.2±35.6	<0.001	135.2±53.0	136.1±60.2	0.96
HbA1c, %	5.9±1.1	7.7±1.8	5.6±0.4	<0.001	5.9±0.7	6.0±1.2	0.92
eGFR, ml/min/m2	46.6±11.4	48.1±10.8	46.3±11.6	0.65	42.2±14.3	48.4±9.6	0.05
CyA use,n	27	5	22	0.73	16	11	<0.001
Tac use,n	35	9	26	0.73	2	34	<0.001
EVR use,n	18	2	16	0.70	18	0	-
statin use,n	35	9	26	0.03	15	20	0.01
Original disease of diabetes nephropathy,n	10	10	0	-	2	8	0.71
BMI	22.2±3.7	24.3±1.4	21.9±0.5	0.06	21.8±0.9	22.4±0.6	0.58

Values were expressed as number and mean (standard deviation) when appropriate
eGFR : estimated glomerular filtration rate, DM : diabetes mellitus
CyA : cyclosporine, Tac : tacrolimus
MMF : mycophenolate mofetil, PSL : predonisolone, EVR : everolimus

PUB717

The Relationship Between Intra-Patient Tacrolimus Variability and Immunosuppression Regimens in Kidney Transplant Patients: A Comparative Multi-Centre Retrospective Study Vitaliy Androshchuk. *Oxford University Hospitals NHS Foundation Trust, Bristol, United Kingdom. Group/Team: Transplant Audit Collaborative (UK).*

Background: It is increasingly recognised that high tacrolimus trough level intra-patient variability (IPV) is a predictor for poor long-term outcome after renal transplant. The relationship between IPV and the use of induction and maintenance immunosuppressive agents has not been previously evaluated.

Methods: Database records of all kidney transplant recipients on standard-release Tacrolimus were interrogated across 5 UK transplant centres (Oxford, Manchester, Liverpool, Glasgow and King's College London) between 2009 and 2014. Each centre compared trough level IPV in patients on different immunosuppression during the 6-12 month post-transplant (T1) and the last 12 months of follow-up (T2) using Kruskal-Wallis analysis. Patients were excluded if they received dual-organ transplants or modified release tacrolimus and if death or graft loss occurred within two years of transplantation.

Results: 1066 patients were included from 5 UK centres (Table 1). There was no significant difference in tacrolimus IPV between patients receiving induction with basiliximab or alemtuzumab and those on maintenance mycophenolate and Azathioprine during T1 and T2 (p>0.05 for all comparisons). In Oxford and King's College London, patients receiving steroids had significantly higher IPV in T2 (p=0.0001 and p=0.013 respectively) compared to those on steroid-free regimen. A similar trend was seen in other centres but the difference in IPV did not reach significance.

Conclusions: This study represents the first multicentre comparative evaluation of tacrolimus IPV in kidney transplant patients on different immunosuppression across the UK. Our results demonstrate an association between the use of steroids and higher tacrolimus IPV in 2 out of 5 centres. Further study of pooled data is awaiting ethical approval.

Funding: Commercial Support - Educational grant from Astellas Pharma Ltd

Table 1. Comparison of Median (IQR) Tacrolimus IPV in Patients on Different Immunosuppression Agents across 5 UK Renal Transplant Centres.

Agent	Oxford IPV (%) (n=284)	King's College IPV (%) (n=132)	Manchester IPV (%) (n=312)	Glasgow IPV (%) (n=167)	Liverpool IPV (%) (n=171)
Basiliximab T1	15.0 (9.73, 21.2)	15.2 (10.3, 21.0)	15.9 (11.9, 22.4)	16.0 (12.3, 24.4)	16.5 (12.6, 24.6)
Alemtuzumab T1	15.6 (10.6, 22.0)	(-)	(-)	(-)	16.5 (11.4, 22.2)
Basiliximab T2	15.5 (9.50, 22.7)	14.8 (10.0, 24.0)	15.6 (10.7, 24.2)	14.0 (9.11, 19.5)	14.6 (8.29, 20.5)
Alemtuzumab T2	16.4 (11.1, 27.9)	(-)	(-)	(-)	15.6 (11.4, 21.6)
Steroids T1	17.3 (12.4, 24.1)	15.0 (10.6, 21.1)	16.4 (12.8, 22.8)	15.3 (12.3, 22.6)	16.9 (13.4, 23.0)
Steroid Naïve T1	15.2 (10.4, 21.3)	(-)	15.4 (11.1, 22.2)	(-)	16.0 (11.5, 23.8)
Steroids T2	22.1 (13.6, 34.0)*	16.7 (10.2, 26.7)*	16.2 (11.6, 25.2)	14.1 (9.60, 19.5)	15.8 (9.85, 24.4)
Steroid Naïve T2	15.1 (9.50, 22.2)	12.3 (7.84, 19.5)	15.2 (10.2, 24.0)	(-)	14.6 (8.61, 20.8)
Mycophenolate T1	15.1 (9.80, 21.3)	15.2 (10.6, 21.6)	15.6 (11.6, 22.0)	15.8 (12.5, 23.3)	16.1 (12.2, 22.4)
Azathioprine T1	15.7 (12.0, 22.8)	(-)	16.1 (12.3, 21.6)	(-)	18.3 (11.7, 28.7)
Mycophenolate T2	14.7 (9.50, 23.3)	13.7 (9.70, 23.0)	15.4 (10.6, 23.3)	14.0 (9.52, 19.5)	13.8 (8.62, 20.4)
Azathioprine T2	16.5 (11.3, 23.2)	(-)	14.3 (10.6, 22.2)	(-)	18.0 (10.8, 28.7)

*p<0.05, (-) no/insufficient data

PUB718

Five Year Outcomes of Adult and Pediatric Kidney Transplantation: A Single Center Experience from Guatemala Alejandro Lucas. *Tlalpan, Mexico.*

Background: The Latin American Dialysis and Transplant Registy, indicates that the overall kidney tranplant rate increased from 3.7 per million population (pmp) in 1987 to 19.4 pmp in 2013, neverthless Guatemala is a country with very low rate of kidney transplant (5.6 pmp), and this rate has not changed during the last ten years. This study presents the experience of kidney transplants from foundation Amor, this is a nongovernmental and noprofit institution that provides renal transplants in adults and childrens without social security. This is the first report of long term follow up kidney tranplants to our country. The objetive is determine 5 years graft and patient survival and factors asociated to graft lost.

Methods: It includies all transplants peformed between December 2011 to December 2016. Data were expressed as mean ± s.d. or medians, percentages. Patient and graft survival rates were estimated by theKaplan–Meier method. Log rank test were used to compare graft and patient survival rates. Cox regression analisys used to determine hazard ratio to graft failure. The SPSS 18 was used to analize the data.

Results: A total of 131 kidney transplants were performed between observation period, the distribution was 82 adults(62.6%) and 49 pediatrics(37.4%). Mean follow-up time adult graft survival was 28.5 months DE ± 19.9 (0-65), in pediatrics was 32.3 months DE ±19.5 (1-63). A total of 30 grafts were losts in the follow-up time, 19 (23.2%) in adults, in pediatrics were 11 (22.4%). Graft adult survival at 1, 3 and 5 yeas was 87%, 71% and 71% respectly. In pediatric group the graft survival at 1,3 and 5 years was 92%, 80% y 69% respectly Klaplan meier analisys of patients survaivor showed no diferences between adulst an pediatric (p:0.2). Adult patient survaivor was at 1 year 97 % and 5 year 94%. Pediatric patient survaivor was at 1 year 96% and 5 year 91%. Analisys of Cox regresión to determine hazard ratio of factors associates to graft lost showed in adult patients, got social security in follow-up is a protector factor to lost, Hazard ratio 0.2 IC 95% (0.06-0.60) p: 0.006.

Conclusions: Kidney transplants in adults and pediatrics patientes had good outcomes at 5 year follow up time in our center.

PUB719

Access to Kidney Transplant: Limitations from the Patient's Perspective in Jalisco, México Daniel Murillo brambila,[1,2] Monica C. Jimenez cornejo,[1,2] Karina Renoirte,[1,2] Gabriela J. Abundis Mora,[1,2] Guillermo Garcia-Garcia.[1] *[1]Hospital Civil De Guadalajara, University of Guadalajara, Guadalajara, Mexico; [2]PISA SANEFRO, Guadalajara, Mexico.*

Background: CKD is a major public health problem in Mexico, the incidence is 421 per million inhabitants according to the latest 2016 USRDS report. Renal replacement therapy is expensive and in the majority of low and middle-income countries is prohibitive. Renal transplantation is the treatment of choice for patients with ESRD. Objetive is evaluate the main obstacles encountered by prevalent hemodialysis patients to undergo a kidney transplant.

Methods: A cross-sectional study of 200 prevalent hemodialysis patients in Jalisco. Insured and uninsured patients were included. Demographic variables, time on hemodialysis, social security status and main reasons to undergo or refuse the kidney transplant protocol, The data are shown in numbers, percentages, mean and standard deviation.

Results: Only 72 (36%) patients were under a kidney transplant protocol; 78% of these patients belonged to the Social Security: 32 (44.4%) had completed the protocol, with an average time of 8.8 months for completion, and an average waiting time for surgery of 12.4 months. 128 (64%) patients were not on the transplant protocol; 103 (80.4%) of patients are insured. Main reasons were 46 (36%) were medically unsuitable candidates, 21(16.4%) did not have a compatible living-related donor, 20 (15.6%) were afraid of being transplanted; 20 (15.6%) were not offered transplant, 18 (14.1%) lacked financial resources

Conclusions: Being medically unsuitable candidate, lack of a compatible living-related donor, fear of transplantation, not offered the option of transplantation, lack of financial resources, and lack of relatives not willing to donate were the most commonly identified obstacles to kidney transplantation. The findings were similar among the insured and non insured populations.

Table 1: Baseline characteristic

	Overall	Under transplant protocol (group A)	No protocol (group B)	A vs B
	n= 200	n= 72	n= 128	p
Age, (y) (SD)	43.5(19,02)	34.3 (14.06)	48.7(19.4)	0.94
Male (%)	134(67)	21 (29.2)	83(64.8)	0.38
Current worker, (%)	66(33)	35 (48.6)	31(24.2)	<0.01
Currently studying, (%)	13(6.5)	6(8.3)	7(5.5)	0.43
Urban housing, (%)	154(77)	53 (73.6)	90(70.3)	0.39
Rural housing(%)	46(23)	19 (26.4)	38(29.7)	
Hypertension, (%)	141(70.5)	51 (70.8)	90(70.3)	0.93
Diabetes, (%)	73(36.5)	13 (18.1)	60(46.9)	<0.01
Average HD vintage, (months) (SD)	36(32.6)	37.1 (32.9)	35.7(32.6)	0.68
Type of insurance				
None, (%)	2(1)	0	2(1.6)	0.28
IMSS (%)	135(67.5)	56(77.8)	75(58.6)	<0.01
Popular Health Insurance (%)	34(17)	14(19.4)	23(18)	0.62
IPEJAL (%)	29(14.5)	2(2.8)	28(21.9)	<0.01
Type of donor				
Deceased donor, (%)	NA	44(61.1)	NA	NA
Living related donor, (%)	NA	22(30.6)	NA	NA
Living unrelated donor, (%)	NA	6(8.3)	NA	NA

Chi Square and hosmer and lemeshow test, SD standar desviation, HD hemodialysis, IMSS Instituto Mexicano del Seguro Social, IPEJAL Instituto de Pensiones del Estado de Jalisco, NA Non-Application

PUB720

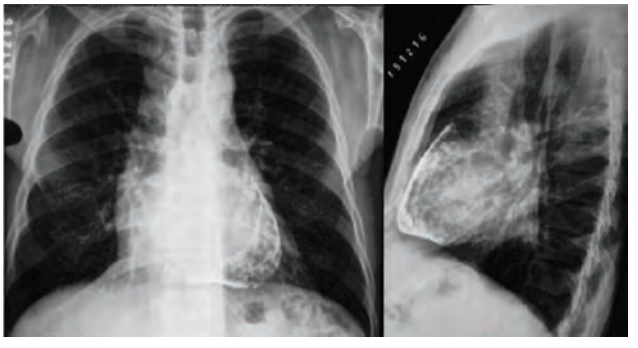
Tuberculous Constrictive Pericarditis after Renal Transplantation: Case Report Larissa G. Andrade,[6] Alexandre D. Pinto,[6] Diogo B. Cabral,[4] Gisele Vajgel,[6] Guilherme G. Danzi,[6] Joaquim O. Borba,[5] Marclebio M. Dourado,[3] Maria carolina R. Coêlho,[2] Zaira R. Menezes,[6] Filipe C. Aguiar.[1] *[1]Federal University Of Pernambuco, Recife, Brazil; [2]Hospital das Clínicas HC - UFPE, Recife, Brazil; [3]UFPE, Recife, Brazil; [4]UNIVERSIDADE FEDERAL DE PERNAMBUCO, RECIFE, Brazil; [5]Ufpe, Recife, Brazil; [6]Universidade Federal de Pernambuco, Recife, Brazil.*

Background: Constrictive pericarditis (CP) results from chronic scarring caused by inflammation of pericardium. The main causes of CP are idiopathic, viral, or after cardiac surgery, acute pericarditis or radiation therapy. Tuberculosis (TB) is still an important cause of pericarditis in developing countries and imunossuppressed patients.

Methods: A 35-year-old male patient with end-stage renal failure of unknown etiology received a live donor renal transplant(Tx) in 2001 after 3 years undergoing hemodialysis. His tuberculin skin test was negative before Tx. He received cyclosporine, prednisone and azathioprine as maintenance medications and no induction. Baseline serum creatinine was 1,4mg/dL. In 2012 changed to sirolimus and prednisone due to pelvic chondrosarcoma. In 2016 the patient was admitted to Hospital with dyspnea. Physical examination revealed hepatomegaly and distended jugular veins. Chest X-ray revealed pericardial calcification (figure 1). Echocardiogram showed increased brightness of the pericardium and biatrial dilatation. Polymerase Chain Reaction (PCR) to TB were positive in blood and urine. He started rifampicin, isoniazid, pyrazinamide and ethambutol. Despite initial treatment, symptoms worsened and he underwent anterior pericardiectomy. Histopathological examination showed diffuse fibrosis, but PCR to TB was negative. Patient improved symptoms and was discharged under antituberculous drugs.

Results:

Conclusions: TB has a high incidence in Brazil and is 14 times more common in Tx patients. The incidence of CP following kidney Tx is unknown, and there are only few case reports in literature. CP is a serious sequel of TB pericarditis. CP has progressive course causing congestive heart failure and high cardiovascular mortality risk. This patient had a good response after surgery. Pericardiectomy is indicated once the diagnosis of CP is made.



PUB721

Warfarin Related Nephropathy Complicating Management of IgA Nephropathy in a Patient with Cirrhosis Leading to Combined Liver and Kidney Transplant: A Case Report Yougandhar Akula,[2] Satya Sai V. Bhupathi,[1] Juan A. Medaura.[2,1] *[1]University Of Mississippi Medical Center, Madison, MS; [2]Nephrology, Univ of mississippi medical ctr, JACKSON, MS.*

Background: Warfarin related nephropathy or its broader term Anticoagulant related nephropathy is known to cause AKI in patients with supratherapeutic INR. The predominant mechanism seems to involve hemorrhage, heme induced free radical injury and inflammation. We report a case of AKI in a pt with cirrhosis caused by Warfarin in a pt with IgA nephropathy leading to combined kidney, liver transplant

Methods: Pt is a 47 y/o white male with PMH of Liver Cirrhosis and Hepatitis C, who was transferred from community hospital for the management of SBP. In spite of treatment of SBP his creatinine continued to rise. Pt had red cells in his urinalysis. This was thought to be secondary to Warfarin for portal vein thrombosis. Due to concern for IgA nephropathy versus membranoproliferative glomerulonephritis a kidney biopsy was done. The biopsy was complicated by post biopsy hemorrhage. He was discharged and later readmitted for combined liver and kidney transplant. His kidney biopsy revealed IgA nephropathy, probably secondary to the patient's hepatitis C related cirrhosis, with focal segmental endocapillary proliferative glomerulonephritis (in 2 of 15 glomeruli). No segmental or global glomerulosclerosis present. No significant interstitial fibrosis. Erythrocytes were present within a number of tubular lumen some of which are degenerate. There is one small focus in which the tubules show mild thickening of their basement membranes compatible with some early tubular atrophy.

Results:

Conclusions: Anticoagulant-related nephropathy has been associated with warfarin and dabigatran use. The mechanism of AKI was shown to be secondary to 1) injury to tubular epithelial cells caused by reactive oxygen species and lipid peroxidation generated by free hemoglobin in the tubular lumen 2) intracellular uptake of hemoglobin by tubular epithelial cells leading to activation of caspases and induction of apoptosis 3) intracellular hemoglobin activates proinfalmmatory pathways. The risk of AKI occurs at an INR threshold of >3; It appears that supratherapeutic INR alone may not be sufficient. AKI is more likely to occur in the setting of pre-existing glomerular damage like IgA nephropathy as in our patient.

PUB722

The Role of Resilience in Healthcare Transitions among Adolescent and Young Adult Kidney Transplant Recipients Sheila M. Quinn,[3] Hilda E. Fernandez,[1] Frances K. Barg,[2] Kenneth R. Ginsburg,[3] Sandra Amaral.[3] *[1]NYP-CUMC, NYC, NY; [2]University of Pennsylvania, Philadelphia, PA; [3]The Children's Hospital of Philadelphia, Philadelphia, PA.*

Background: Adolescent and young adult (AYA) kidney transplant (KT) recipients experience high rates of premature allograft loss, believed in part to be due to the healthcare transition (HCT) process. Yet, most AYA with KT navigate the HCT successfully. There is a critical need to identify the protective factors associated with stable HCT. Resilience--the ability to thrive in the setting of adversity-- is a learned and dynamic process with known positive impact on health outcomes. This study is the first to examine the novel role of resilience as a protective factor in securing stable HCT.

Methods: This is a retrospective mixed methods study of AYA with KT who transitioned from a single pediatric center between 2008-2016 to adult nephrology care. Medical record data stratified participants into stable or unstable HCT groups. (Unstable = loss-to-follow-up, missing ≥50% of adult nephrology visits in the first 12 months (mo) post-transfer, or unexpected dialysis initiation in 12 mo post-transfer). Semi-structured interviews were conducted in adult clinics at least 6 mo post-transfer to investigate the role of key constructs of the American Academy of Pediatrics Resilience Framework (confidence, competence, connection, character, contribution, coping, control). Qualitative analysis used a grounded theory approach, with transcripts coded in a blinded fashion using NVivo11Pro.

Results: 23 of an estimated 30 necessary participants (55% male, median age 24.4 years (yrs), median time since KT 10.6 yrs, median 3.2 yrs since transfer) have enrolled. 16 participants with stable HCT endorsed strong character and personal control over their medical condition. Thematic saturation is not yet achieved in the 7 participants with unstable HCT, but they preliminarily seem to lack the aforementioned character and control, and instead emphasize competence as a leading mediator in HCT. Coping skills and a meaningful connection with an adult appear salient in both groups.

Conclusions: Resilience constructs can be supported and enhanced, and therefore are potentially modifiable mediators of HCT. Here, AYA with KT endorsing a strong sense of character and personal control over their medical condition appear to have more stable HCT. Our findings suggest that enhancing sense of personal control while finding supportive connections may support stable HCT.

PUB723

Have Kidney Transplants from Uncontrolled Donation after Circulatory Death (uDCD) Different Cardiovascular Risk Factors after Transplantation? Maria Molina, Enrique Morales, Manuel Praga, Esther Gonzalez monte, Amado Andres. *Nephrology Department, Hospital Universitario 12 de Octubre, Madrid, Spain.*

Background: Cardiovascular diseases (CVD) are the most frequent cause of mortality in kidney transplant (KT) recipients, and 50% of these deaths are due to ischemic heart disease (IHD). The recipients of KT from uDCD received more frequently induction therapy with lymphocytes depleting antibodies and higher dose of inhibitor of calcineurin. The incidence of CVD after this kind of KT is unknown. **Aim**: To analyse the prevalence and the incidence of CVD events in our program of KT from uDCD after 100 months of follow up and to determinate the risk factors that are involved in the development of this complication.

Methods: We included 237 RT from uDCD between 2005 and 2013. We reviewed donors, recipients, procurement and evolution characteristics. We reported CVD eventes: IHD, cerebrovascular accidents and peripheral vascular disease (PVD) or death attributable to CVD.

Results: Recipient's age was 48±11 y and 141 (59.5%) were male. Pretransplantation cardiovascular risk factors were: 77.2% (183) hypertension, 22.8% (54) diabetes mellitus and 39.2% (93) dyslipidemia. CVD pretransplantation were: 5.5% (13) IHD, 4.6% (11) stroke and 3.8% (9) PVD. Mean follow up was 44±27 (25-63) months. The prevalence of CVD was 8.8% and the incidence was 27 cases/1000 patient-years. Of the 21 CVD events in 20 patients, 55% (11) were IHD, 35% (7) stroke and 10% (3) PVD. Multivariable analysis shown the following risk factors to develop for any CVD event: pretransplantation IHD (HR: 9.2 (3.2-26.8) p<0.001), pretransplantation PVD (HR: 4.2 (1.1-15.4) 0=0.02), previous cerebrovascular accidents (HR: 4.2 (1.4-12) p=0.008), recipient's age at transplantation (HR: 1.05 (1.006-1.1) p=0.04), body mass index of recipient at transplantation (HR: 1.12 (1.004-1.2) p=0.04), diabetes mellitus (HR: 2.8 (1.03-7.9) p=0.04), dyslipidaemia (HR: 2.5 (1-6.1) p=0.05) and serum creatinine at 6 month (HR: 2 (1.1-3.5) p=0.02). Hepatitis C, donor gender or proteinuria … didn't increase CDV risk.

Conclusions: The incidence of CVC events following renal transplantation of uDCD donors is low and is related to the previous CVD factors and renal function at 6 months. Then, renal transplant recipients with pre-KT CVC events require a wide pre-transplant vascular study and a close post KT follow-up.

PUB724

Hypophosphatemia Post Kidney Transplant – A Single Centre Experience Pablo Justo avila,[3] Terrina Abd rahim,[2] Shafi Malik.[1] *[1]Renal Medicine, Leicester General Hospital, Leicester, United Kingdom; [2]Kettering General Hospital, Leicester, United Kingdom; [3]Renal, Royal Derby Hospital NHS Trust, Derby, United Kingdom.*

Background: Hypophosphatemia (HP) is a common complication after kidney transplant (Tx). It requires correction by either oral or intravenous phosphate (PO_4). We aim to identify predisposing factors for developing HP post-Tx.

Methods: We identified 57 kidney Tx recipients from Nov14 to Dec15. We collated demographics, cause of ESRD, prevalent RRT pre-Tx, type of Tx, duration of admission, serum phosphate (SPO_4) levels 3 days post-Tx and at discharge, requirement of PO_4 supplementation and Tx function for the period of 6 months. We defined HP as SPO_4 levels <0.8 mmol/L and delayed graft function (DGF) as requiring RRT 7 days post-Tx.

Results: Mean age was 47.2 years. Causes for ESRD were GN (31.6%), unknown aetiology (22.8%), hereditary (19.3%), interstitial nephritis (14%), renovascular (7%) and DM nephropathy (5.3%). Prior to Tx, 47.4% and 29.8% were on HD or PD respectively. 10 patients received a living donor Tx (LD) (17.5%), 32 deceased brain-death Tx (DBD) (56.1%) and 14 deceased cardiac-death Tx (DCD) (24.6%). Mean duration of admission was 9.4 days (SD 9.3). 28 presented with drop in SPO_4 levels of >0.3 mmol/L 3 days post-Tx. Mean SPO_4 at discharge was 0.94 mmol/L (SD 0.3). 10 (17.5%) had normal graft function, 45 (78.9%) had DGF and 2 (3.5%) had primary graft dysfunction. Mean SCr at Day 1, 1,3 and 6 months post-Tx were 561.7 μmol/L (SD 248.2), 150.3 μmol/L (SD 102.4), 159.1 μmol/L (SD 100) and 147.5 μmol/L (SD 71.7) respectively. At the end of follow-up, 37 patients presented HP. 27 (47.37%) required oral PO_4, 3 (5.26%) required IV PO_4 while 7 (12.28%) required both. Mean dose of PO_4 supplementation was 44.34 mmol/day (SD 44.74) for oral and 130 mmol (SD 48.3) for IV. There is a correlation between HP and type of Tx (p 0.018); (LD 70%, DBD 78%, DCD 35.7%); SPO_4 level at discharge ($p < 0.01$) and Tx function in the 1st, 3rd and 6th months post-Tx (p values 0.023, 0.021, 0.05). We found no correlation between HP and cause of ESRD, prevalent RRT, Tx function 1 day post-Tx, initial drop of PO_4 levels 3 days post-Tx and presence of DGF.

Conclusions: 1. Probably, DBD and LD Tx are more likely to develop HypoP in comparison with DCD Tx. 2. Improved Tx function is associated with higher incidence of HypoP, close monitoring of these patients is advisable to prevent complications. 3. The presence of DGF and initial monitoring of renal function are not reliable factors to predict the onset of HypoP.

PUB725

The Coefficient of Variation (CV) and the Mean Absolute Deviation (MAD) Are Both Acceptable Measures of Intrapatient Variability (IPV) in Tacrolimus Trough Levels Petra M. Goldsmith. *Royal Liverpool Hospital, Lymm, United Kingdom. Group/Team: UK Transplant Audit Collaborative.*

Background: Tacrolimus is the preferred first line immunosuppressant following renal transplant in the UK. It has a narrow therapeutic index which is measured by serum trough levels. Studies have shown that a high IPV (the variability observed in a patient's trough level over time) is associated with poorer outcomes post-transplant. In previous studies IPV has been inconsistently calculated using CV or MAD. CV is calculated using the square value of differences from the mean whereas the MAD uses the absolute difference. We hypothesised that because of this difference in formula, the CV method would overestimate IPV when compared with MAD.

Methods: Patients transplanted in 5 UK centres between 2009-2014 and who were taking standard release Tacrolimus preparations were included in the study. IPV data was captured for each patient from 2 predetermined time points – 6-12months post-transplant and the most recent 12 months, with a minimum of four separate trough levels for each time point. MAD and CV were calculated for both time points and a rank correlation performed using Spearman's Rho Test.

Results: The results are shown in table 1: Although the values calculated for IPV are higher using CV when compared to MAD, there is a very high rank correlation observed in all centres between both tests.

Conclusions: We conclude either method is a valid measure of IPV. In practical terms CV is generally simpler to calculate, especially using an automated reporting system. However, CV would need to be used with caution where there are isolated high outlying values, such as a mistimed post-dose sample.

Comparison of CV versus MAD in 5 UK Renal Transplant Centres

Hospital	N= IPV Calculations (Participants)	Median (IQR) CV	Median (IQR) MAD	Spearman's Rank Order Correlation
Liverpool	342 (171)	20 (13.62, 28.45)	15.64 (11.11, 22.03)	Rs=0.9847 P <0.0001
Glasgow	334 (167)	17.96 (13.02, 26.31)	14.76 (10.89, 21.25)	Rs=0.9827 P <0.0001
Oxford	568 (284)	20.7 (14.01, 29.52)	15.6 (10.4, 23.15)	Rs=0.9839 P <0.0001
King's College (London)	264 (132)	20.22 (13.77, 29.97)	14.82 (10, 22.21)	Rs=0.964 P <0.0001
Manchester	624 (312)	20.47 (14.74, 30.41)	15.57 (11.11, 23.04)	Rs=0.983 P <0.0001

PUB726

Intrapatient Tacrolimus Level Variability Can Vary Significantly During Separate Time Periods, Depending on Transplant Centre: A Multicentre UK Retrospective Study Philip Nash. *King's College Hospital NHS Trust, London, United Kingdom. Group/Team: UK Tacrolimus Audit Collaborative.*

Background: Tacrolimus is the first choice primary immunosuppressant used after kidney transplantation in the UK. It has a narrow therapeutic range, and its successful use requires regular monitoring of serum trough levels. There is emerging evidence that low levels of intra-patient variability (IPV) in tacrolimus levels during the first year after kidney transplantation are associated with improved outcomes in the short term. Longer term data examining IPV and its association with outcomes is limited. It is also not known whether transplant recipients tend to maintain a consistent IPV over longer time periods or not.

Methods: Five UK Transplant Centres calculated IPV from trough tacrolimus levels during two separate time periods; months 6-12 after transplantation (T1) and the most recent 12 months of follow up (T2). Hospital databases were interrogated to provide demographic details and laboratory results for all recipients of kidney transplants between 1 January 2009 and 31 December 2014. Patients were excluded if they received duel-organ transplants, if they died or lost graft function within two years of transplantation, if their immunosuppression regimens were not based on tacrolimus or if they were given modified release tacrolimus preparations. Each centre examined the correlation of IPV during the two time periods and results between centres were compared. The means from each time period were compared using a paired t test.

Results: Data from 1063 eligible transplant recipients were included. Follow up periods ranged from two to five years. Results are summarised in table 1.

Conclusions: This unique national retrospective study demonstrates that at 3 centres there was no significant difference between the tacrolimus IPV during T1 and T2. However, recipients from Glasgow and Oxford had statistically significant differences in IPV during the two time periods. These results are inconsistent across centres, and this prompts further study. Relatively small sample sizes limit the power of the inidividual analyses. We propose to combine the data after gaining ethical approval, which we hope will expand upon these findings.

Funding: Commercial Support - Educational grant from Astellas Pharma Ltd

Table 1

	King's London (n=129)	Oxford (n=284)	Liverpool (n=171)	Glasgow (n=168)	Manchester (n=311)
Mean (SD) T1 Tacrolimus IPV	17.0% (9.9%)	17.9% (10.9%)	19.1% (10.4%)	18.1% (9.0%)	17.9% (9.4%)
Mean (SD) T2 Tacrolimus IPV	18.0% (11.8%)	20.1% (17.1%)	17.7% (13.7%)	15.8% (9.0%)	18.6% (11.7%)
Two-tailed P Value	0.3803	0.0448	0.3022	0.0085	0.4018

PUB727

Adenovirus Nephritis in Kidney Transplant Recipients: Features of Clinical Presentation and Management Shalini Bumb, Varun K. Phadke, Carla L. Ellis. *Emory University, Atlanta, GA.*

Background: Adenoviruses (AdV) are double-stranded DNA viruses that are rare, but well recognized causes of morbidity and allograft dysfunction in transplant recipients. We have previously shown that adenovirus nephritis (AdN) can present with granulomatous or neutrophilic tubulointerstitial nephritis in kidney biopsies. There are many options to management, ranging from supportive therapy to the use of AdV-directed therapy. Here we report 7 cases of AdN in kidney transplant recipients and their associated clinical outcomes.

Methods: We performed a retrospective search to identify cases of AdN in renal transplant recipients from 2009-2016 at our institution.

Results: The diagnosis of AdN was confirmed by immunostaining of kidney transplant biopsies in 6/7 cases. The diagnosis of AdN was made serologically in the remaining case as the biopsy was not an adequate sample. The median time from transplant to the development of AdN was 50 days. All patients presented with complaints of dysuria, hematuria, and proteinuria. Additionally, 5 presented with fever, 5 with diarrhea, and 2 with respiratory symptoms. The peak serum creatinine increased by a median of 83% from baseline. Treatment in these cases varied from supportive care (2), ribavirin (3), ribavirin/IVIG (1), and brincidofovir (1). Of the 2 that did not receive AdV-directed therapy, 1 had resolution of the viremia after 42 days. Viremia clearance was not documented for the second, although the clinical course was benign. The 4 who received ribavirin cleared at a median of 78 days. The 1 who received brincidofovir cleared at 22 days. Proteinuria and hematuria improved or resolved in all patients. 3 of the 7 were treated for rejection. As such, the immunosuppression regimens were titrated and quite variable. 6 of the 7 cases were also noted to have CMV, BK, EBV, or parvovirus at the time of their management for AdN.

Conclusions: Our case series summarizes the clinical features and management of AdN. Treatment varies, but clinical resolution was noted in all cases and was most profound with brincidofovir. Despite the morbidity of AdN, if managed and monitored closely, resolution can be achieved with good outcomes in renal function in kidney transplant recipients. Additional study of cases of AdN without AdV-directed therapy are required before supportive therapy can be considered a universally viable option.

PUB728

JC Nephropathy in Renal Transplant Patients: Review of Two Cases Harleen Aujla,[4] Jose A. Morfin,[2] Ling-Xin Chen,[1] Kuang-Yu Jen.[3] *[1]None, West Sacramento, CA; [2]University of California Davis, El Dorado Hills, CA; [3]University of California, Davis, Sacramento, CA; [4]UC Davis, Sacramento, CA.*

Background: JC and BK viruses are polyomaviruses that commonly infect humans but become latent in immunocompetent individuals. In immunocompromised patients such as transplant recipients, polyomavirus can become reactivated and result in infection of the renal parenchyma with associated allograft dysfunction. Polyomavirus nephropathy (PVAN) is primarily associated with BK virus while JC nephropathy is a very rare complication in transplant patients. Here we report two transplant patients with evidence of JC nephropathy.

Methods: Review of transplant biopsy records from our institution from 07/2016-05/2017 showed three cases with biopsy-proven PVAN but without significant plasma BK viral loads. Subsequent plasma JC viral load was quantified and two of the cases exhibited substantial JC DNA levels.

Results: The two renal transplant patients were noted to have rises in serum creatinine from baseline several years post-transplant. Both underwent allograft biopsies, which revealed evidence of PVAN with positive SV40 immunohistochemical (IHC) staining in tubular epithelial cells. One case showed viral cytopathic changes including viral inclusions. The other case did not show definitive viral cytopathic changes. Moderate to severe chronicity and severe chronic vascular disease were noted in the biopsies as well. No evidence of rejection was identified. Serologically, neither patient had BK viremia but JC viral loads were found to be elevated. Subsequent JC virus in situ hybridization (ISH) on the biopsy material was positive. Each patient underwent reduction in immunosuppression regimen with decreased JC viral loads.

Conclusions: JC nephropathy may be missed both clinically and on biopsy if one is not aware of this entity. In some cases, no viral cytopathic changes are identified on biopsy although SV40 IHC may reveal allograft infection. Although BK nephropathy typically occurs early in the post-transplant period, our cases of JC nephropathy were detected late in the transplant course. JC virus screening should be considered in patients with PVAN and negative BK serologies.

	Time post-transplant	Immunosuppression	Plasma BK viral load	SV40 IHC	JCV ISH	Plasma JCV DNA
Case 1	6.0 years	Tacrolimus Myfortic Prednisone	<500 copies/mL	Positive	Positive	75,046 copies/mL
Case 2	6.5 years	Tacrolimus Mycophenolate	<500 copies/mL	Positive	Positive	48,387 copies/mL

PUB729

Belatacept Conversion and Improved eGFR in Transplant Recipients with Calcineurin Inhibitor Intolerance Harleen Aujla, Andrew I. Chin, Victoria Chung, Brian J. Gallay. *UC Davis Medical Center, Sacramento, CA.*

Background: Calcineurin inhibitors (CNIs) are the mainstay of immunosuppressive therapy after renal transplant, but nephrotoxicity has been thought to limit long term allograft survival. Belatacept, a chimeric CTLA4-IgG fusion protein which blocks T cell costimulation has been shown to afford superior composite patient and graft survival after transplant when used de novo after kidney transplant. We report our experience with 19 patients converted from CNI-based maintenance immunosuppression to belatacept for CNI intolerance.

Methods: Nineteen transplant patients from 2009 to 2016 underwent conversion from tacrolimus or cyclosporine to belatacept.

Results: The majority of patients (68%, n=13) were switched to belatacept due to biopsy-proven or suspected CNI renal toxicity. Excluding 3 patients with eGFR of >60 mL/min/1.73 m^2 before and after conversion, eGFR increased after the switch (30.9 ± 11.1 vs 36.1 ± 13.8, p=0.031) at a median of 43 months from initial transplantation.

Conclusions: In patients with CNI intolerance or renal toxicity, our series suggest an improvement in short and long-term eGFR for most patients converted to belatacept. This warrants a randomized trial comparing late conversion to belatacept to continued maintenance of CNI in recipients with evidence of chronic allograft injury.

Age/Sex	Initial Immunosuppression	Reason for switching	eGFR before switch mL/min	eGFR after switch (mL/min)
52, F	TAC/MMF/pred	Suspected CNI renal toxicity	13	18
68, F	CSA/Azathioprine/pred	Suspected CNI renal toxicity	18	22
53, M	TAC/Myfortic	CNI renal toxicity on biopsy	39	27
69, M	TAC/MMF/pred	severe arteriosclerosis on biopsy	>60	>60
49, F	TAC/MMF/pred	CNI renal toxicity on biopsy	30	31
77, F	TAC/Myfortic/pred	Suspected CNI renal toxicity	51	45
49, F	CSA/myfortic	other CNI side effect	>60	>60
63, M	CSA/MMF/pred	CNI renal toxicity on biopsy	20	28
62, M	TAC/MMF	suspected CNI renal toxicity	35	50
31, F	TAC/Myfortic	CNI renal toxicity on biopsy	35	45
26, M	CSA/MMF/pred	CNI toxicity	13	5
78, M	TAC/Myfortic	CNI renal toxicity on biopsy	30	49
71, M	TAC/MMF	CNI renal toxicity on biopsy	29	39
53, F	CSA/azathioprine	other CNI side effect	48	50
63, F	TAC/MMF/pred	myopathy from CNI	38	48
74, M	CSA/MMF	suspected CNI renal toxicity	30	32
80, M	CSA/Azathioprine	severe gout	39	54
43, F	TAC/MMF	CNI renal toxicity on biopsy	25	34
43, F	TAC/MMF	severe gout	>60	>60

PUB730

GFR and Biomarkers of CKD in Diabetic and Prediabetic Rhesus Monkeys Yinan Liang,[1] Zhenyan Yang,[1] Zunyuan Yang,[1] Bc Hansen,[2] Li Gong,[1] Wen Zeng.[1] *[1]Chengdu Primed Huaying Bio-tech Co., Ltd., Chengdu, China; [2]Dept Int Med, Univ of So Florida, Tampa, FL.*

Background: In view of the known similar renal physiology and fundamental mechanisms of diabetic kidney disease between humans and nonhuman primates, rhesus monkeys with chronic kidney disease (CKD) have been proven to provide an excellent large animal model to validate the efficacy of drugs targeting nephropathy. Research on biomarkers is providing improved experimental methods to assess early stage CKD status before the disease becomes irreversible.

Methods: Forty one adult male rhesus monkeys were studied for the purpose of examining the relationships between glomerular filtration rate (GFR determined by the Iohexol clearance with five-point plasma method) and plasma biomarkers that may detect early CKD. Creatinine (Cr), receptor for advanced glycation end products (RAGE), kallikrein B1 (KLKB1), vascular endothelial growth factor (VEGF), homocysteine (HCYS), Cystatin-C (CYSC), high sensitivity C reactive protein (hsCRP) were measured. Pearson's correlation was performed.

Results: GFR was significantly negatively correlated with Cr (r=-0.599, p<0.01), HCYS (r=-0.319, p<0.05) and CYSC (r=-0.478, p<0.01). Cr was moderately correlated with CYSC (r=0.312, p<0.05). RAGE, KLKB1 and VEGF were highly correlated between each pair (RAGE vs KLKB1, r=0.998, p<0.01; RAGE vs VEGF, r=0.995, p<0.01; and KLKB1 vs VEGF, r=0.996, p<0.01).

Conclusions: Cr and CYSC were broadly used in both the MDRD and CKD EPI equations to calculate the estimated GFR in patients. Cr, HCYS and CYSC were all significantly negatively related to GFR. These biomarkers will help to diagnose early stage CDK in monkeys.

Correlation between GFR and biomarkers of CKD (n=41)

	GFR (ml/min/1.73m2)	Cr (μmol/L)	HCYS (μmol/L)	CYSC (mg/L)	hsCRP (mg/L)	RAGE (ng/ml)	KLKB1 (ng/ml)
Cr (μmol/L)	-0.599**						
HCYS (μmol/L)	-0.319*	0.239					
CYSC (mg/L)	-0.478**	0.312*	0.090				
hsCRP (mg/L)	0.221	0.046	-0.284	-0.306			
RAGE (ng/ml)	0.103	-0.010	-0.009	0.050	-0.029		
KLKB1 (ng/ml)	0.122	-0.019	-0.021	0.042	-0.012	0.998**	
VEGF (pg/ml)	0.120	-0.036	-0.025	0.046	-0.015	0.995**	0.996**

*p value<0.05, **p value<0.01

PUB731

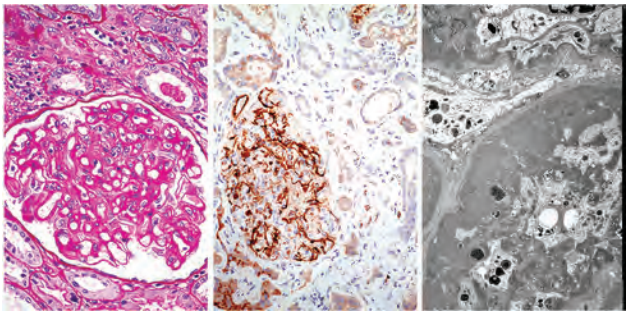
Coexisting Recurrent Lupus Nephritis and Chronic Antibody-Mediated Rejection in Renal Allograft: A Case Report Watcharapong Treesinchai, Bunyong Phakdeekitcharoen, Suchin Worawichawong, Punlop Wiwattanathum. *Ramathibodi Hospital, Mahidol university, Ratchatewi, Thailand.*

Background: Chronic antibody-mediated rejection (ABMR) is one of the common causes of late allograft dysfunction and play a major role in allograft loss. On the other hand recurrent lupus nephritis (RLN) is uncommon but it also causes allograft dysfunction and failure. There have been limited reports about these two distinct processes on the same allograft. Herein we reported a case that had two concurrent diseases on allograft.

Methods: A 32 year-old female with ERSD from lupus nephritis (LN) underwent a kidney transplantation from her mother in July 2010. Serum creatinine was 1.0 mg/dl at discharge. Five years after KT, she developed progressive increase proteinuria and serum creatinine to 2.7 mg/dL while having good compliance and tacrolimus level was in target range. The allograft biopsy revealed diffuse endocapillary proliferation, wire-loop lesion and focal basement membrane reduplication in glomeruli with focal tubulitis and peritubular capillaritis. The immunofluorescence (IF) showed full house pattern. Electron microscopy (EM) demonstrated electron dense deposits in subendothelium and mesangium with focal basement membrane reduplication. The immunoperoxidase staining for C4D was positive in glomeruli and peritubular capillaries. These findings were compatible with lupus nephritis class IV-G (A/C) combined with chronic antibody-mediated rejection. The blood tests showed positive for donor specific antibody Class I&II but negative for ANA and anti-DNA and complement within normal range. Therapies were offered with methyl prednisolone and plasmapheresis in keeping with raise level of tacrolimus and mycophenolate mofetil. Serum creatinine was stable of 2.2 mg/dl.

Results:

Conclusions: The additional tests including IF, EM and serologic markers may helping for diagnosis these overlapping histological finding.



PUB732

Impact of Prostate Cancer (PCa) on Waiting Time for Transplant and Mortality in ESRD Nagaraju Sarabu,[3] Nicholas K. Schiltz,[1] Donald E. Hricik.[2] *[1]Case Western Reserve University, Cleveland, OH; [2]University Hospitals Case Medical Center, Rocky River, OH; [3]Medicine, University Hospitals Cleveland, Cleveland, OH.*

Background: Prostate cancer is a very slow growing cancer with a low mortality. It is unclear if kidney transplant should be delayed after a diagnosis of prostate cancer and how it affects mortality post-transplant.

Methods: This study included incident cases of end-stage renal disease for males 40-79 years old from the 1999-2012 United States Renal Data System, linked with Medicare claims data. Our main study variable of interest was prostate cancer as indicated through an ICD-9-CM diagnosis code. Primary outcomes of interest were time to kidney transplant and mortality. We used propensity score matching control to for selection bias, and Cox proportional hazards models and Kaplan Meier curves to compare the risk between men with prostate cancer and those without.

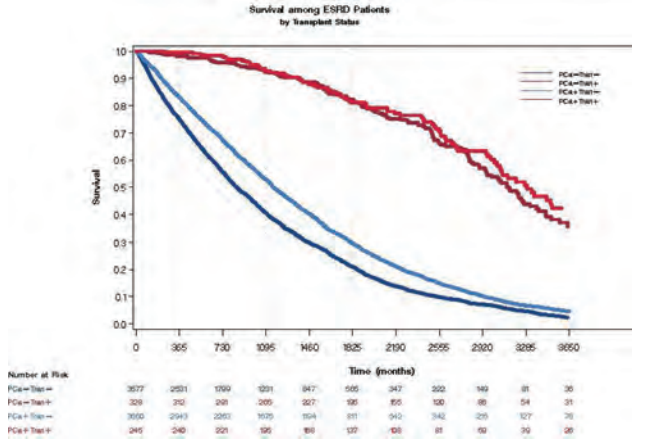
Results: Figure 1 shows that the baseline characteristics are all well matched between prostate cancer group, and the control group except that the prostate cancer has slightly more patients in the older age groups. Prostate cancer was associated with a better survival compared to controls (HR:0.82; CI:0.78-0.86), and signifcantly chances of transplant (HR:0.61; CI:0.52-0.72). Kidney transplantation significantly reduced the mortality regardless of prostate cancer status, figure 2.

Conclusions: Kidney transplant improves survival in prostate cancer patients and should not be delayed.

Funding: Commercial Support - University Hospitals Cleveland Medical Center

Characteristic	No Prostate Cancer 3905		Prostate Cancer 3905		p-value
Agegroup					0.009
40-44	32	1%	27	1%	
45-49	72	2%	57	1%	
50-54	134	3%	133	3%	
55-59	268	7%	271	7%	
60-64	425	11%	488	12%	
65-69	813	21%	882	23%	
70-74	1,003	26%	1,030	26%	
75-79	1,158	30%	1,017	26%	
Race					0.964
Black	1,215	31%	1,226	31%	
White	2,595	66%	2,584	66%	
Other	95	2%	95	2%	
Hispanic ethnicity	272	7%	282	7%	0.692
Dialysis Type					0.842
CAPD	179	5%	175	4%	
CCPD	97	2%	88	2%	
Hemo	3,617	93%	3,627	93%	
Inability to ambulate	82	2%	112	3%	0.035
Inabilty to transfer	32	1%	46	1%	0.139
Comorbidities					
Atherosclerotic heart disease	531	14%	532	14%	0.999
Alcohol dependence	48	1%	53	1%	0.689
Cancer	1,029	26%	1,086	28%	0.154
Congestive heart failure	1,136	29%	1,098	28%	0.354
COPD	370	9%	393	10%	0.402
Cerebrovascular disease	324	8%	325	8%	0.999
Diabetes	1,313	34%	1,316	34%	0.962
Hypertension	3,286	84%	3,287	84%	0.999
Needs assistance with ADL	143	4%	148	4%	0.811
Peripheral vascular disease	561	14%	545	14%	0.626
Current tobacco user	249	6%	221	6%	0.199
Employment Status					0.861
Employed	316	8%	334	9%	
Retired	3,082	79%	3,056	78%	
Unemployed	444	11%	454	12%	
Other	63	2%	61	2%	
Insurance					
Medicare Advantage	48	1%	43	1%	0.673
Employer Group Plan	808	21%	827	21%	0.617
VA	69	2%	59	2%	0.423
Medicaid	568	15%	599	15%	0.341
Medicare	3,182	81%	3,128	80%	0.128
None	166	4%	199	5%	0.086
Other	1,449	37%	1,405	36%	0.312

All cells reflect counts. For binary variable comparisons, p values obtained by Fisher's Exact Test. For multicategorical variables, p values from Likehood Ratio Chi-Square Test.



Transplant Improves Survival regardless of Prostate Cancer status

PUB733

Acute Brucellosis in Renal Transplant Patient Muddassar Mahboob,[4] Sana Hasan,[1] Ebadur Rahman,[4] Mohammed F. Akhtar,[5] Ashraf A. Attia,[3] Syed Rizwan A. Bokhari.[2] *[1]Prince Sultan Military Medical City, Riyadh, Saudi Arabia; [2]Tulane School of Medicine, New Orleans, LA; [3]kfsh&rc, Riyadh, Saudi Arabia; [4]Prince Sultan Military Medical City(PSMMC), Riyadh, Saudi Arabia; [5]Prince Sultan military Medical City, Riyadh, Saudi Arabia.*

Background: Brucellosis is common in developing countries and is usually transmitted by the consumption of unpasteurized milk or direct exposure with the infected animals. Very few cases have beed reported regarding the incidence of Brucellosis in the renal transplant patients. We are reporting a case of Brucellosis in the renal transplant patient presenting to Prince Sultan Militart Medical City, Riyadh.

Methods: We report a case of 61-year-old male, known case of living related kidney transplant 7 years ago with co-morbid conditions including Diabetes (DM), Hypertension (HTN) and Coronary Artery Disease (CAD). Presented to emergency department with constitutional symptoms of fever, burning micturation, dizziness and headache. Examination was positive for epigastric tenderness only. Labortary workup showed normal complete blood count, ESR 167, CRP 10, BUN 60 mg/dl and Creatinine 3.3 mg/dl, with no other electrolyte or liver function test abnormalities. Urinalysis, microscopy and culture were negative. Acute rejection panel was unremarkable. Infectious profile revealed Blood culture positive for gram-negative Coccobacillus with negative viral studies. Renal Doppler ultrasound was unremarkable. Patient recieved empirical antibiotics in addition to his routine immunosuppression, while mycophenolate mofetil (MMF) was held for three days. Further work up showed positive Brucellosis titre 1:10240, which was negative before kidney transplant. Patient was treated with doxycycline and ciprofloxacin with marked clinical improvement and biochemistry returned to normal in a week.

Results:

Conclusions: Brucellosis is a rare zoonotic disease in renal transplant recpients especially in endemic areas however timely diagnosis and appropriate treatment results in complete recovery.

PUB734

Results of a Pediatric Kidney Transplantation Cohort in Brazil Maria Goretti M. Penido,[2,3] Karina C. Zocrato,[2] Andre S. Alvarenga,[1] Carolina M. Leite,[1] João vitor S. Cortez,[2] Mariana G. Paula,[2] Marcelo S. Tavares.[2] *[1]Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; [2]Pediatric Nephrology Unit, Santa Casa de Belo Horizonte, Belo Horizonte, Brazil; [3]Pediatric Nephrology Unit, Federal University of Minas Gerais, Belo Horizonte, Brazil.*

Background: Pediatric kidney transplantation (TxPed) is the renal replacement therapy (RRT) of choice in pediatrics. The aim of this study was to outline the results of the pediatric kidney transplantation in a single center in Brazil.

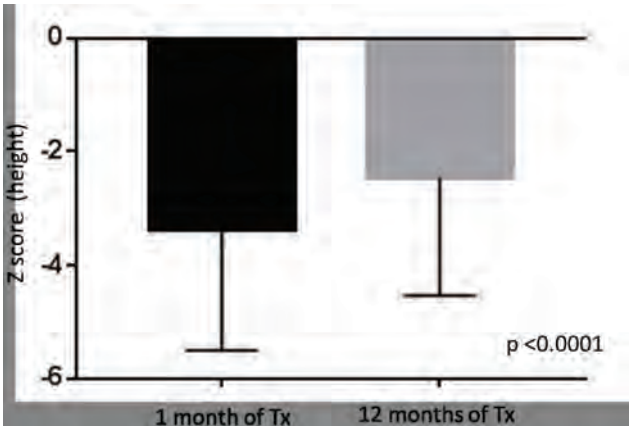
Methods: Analysis of a retrospective cohort of 48 TxPed conducted between 2011 and 2017.

Results: There were 47 TxPed with deceased donors and 1 with living donor, and their main results are shown in table 1. There was signficant increase of the mean z score for height with 1 month of Tx (Z = -3,3) and after 12 months of Tx (Z = -2,3) (Figure 1). Graft survival was 82.5% at 30 months. There was no difference between the patients with and without graft failure regarded age, sex of the recipient, type of RRT before trasnplantation, type of induction, delayed graft function, KDPI or preemptive TxPed. AUROC of KDPI for graft lost was 0,54. Interestingly, linear regression analysis showed an inverse correlation between KDPI and 3 months eGFR(p=0,037).

Conclusions: The graft survival rate of pediatric TxPed at the analyzed center is similar to other centers. KDPI was not a valuable index to predict graft loss in children. There was significant improvement in stature with 1 year of TxPed.

TxPed data

Data	TxPed (n=48)
Age (years) - mean	11
Waiting time in List (days) - median	58
Cold ischemia time (hours) - median	11.5
Donor creatinine (mg/dl) - median	0.72
KDPI (%) - median	21
Delayed graft function (%)	21
3 months eGFR (ml/min/1.73m2) - median	64
12 months eGFR (ml/min/1.73m2) - mean	67
Allograft acute rejection (%)	20.8
CMV infection (%)	16
Deaths (%)	0



Z score for height evolution in first year after TxPed

PUB735

BK Virus in Renal Transplantation Patients Using Alemtuzumab for Induction Immunosuppression Katie L. Korneffel, Bradley B. Gehring. *University of Toledo College of Medicine, Toledo, OH.*

Background: Alemtuzumab (Ale) is a monoclonal antibody that targets CD52+ lymphocytes, causing profound B- and T-cell depletion. The use of potent immunosuppressive agents poses an increased threat of BK virus infection in organ transplants. We sought to determine the impact of Ale immunodepletion, with steroid freedom for low risk patients, on the incidence of BK virus viremia and associated patient outcomes.

Methods: An IRB-approved retrospective analysis was performed on 676 patients at the University of Toledo Medical Center who underwent renal transplantation between 3/06 and 11/15. All patients were induced with Ale. BK Viremia was defined as clinically significant BK infection confirmed by PCR.

Results: Median patient age was greater for BK (53.3 years vs 60.5 years, p=0.041). Median patient BMI was not significant (28.2 without BK and 27.7 with BK, p=0.743). A greater percent of elderly patients (defined as >65 years) had BK (8.2% vs 3.8%; p=0.035). No other demographic factors were significant for BK. BK was associated with increased 1 year rejection (21.2% vs. 34.5%; p=0.049). However, clinically positive BK was not significantly associated with overall increased rejection, although it was close (OR 2.01, 95% CI 0.96-4.19, p=0.064). There was no association of BK with death-censored graft survival (DCGS) or patient survival. (Table 2)

Conclusions: The median age of patients with BK was greater than patients without BK. A greater percent of elderly patients than non-elderly patients had BK. Overall, clinically positive BK was not associated with increased rejection. BK was not associated with increased DCGS or patient survival.

Incidence of Rejection, DCGS, and Patient Survival in BK and No BK Patients

	BK Viremia (n, % of total)	Control (n, % of total)	Significance
Rejected (total)	13 (41.9%)	169 (26.2%)	0.063
90 day rejection	6 (19.4%)	94 (14.6%)	0.44
1 year rejection	10 (34.5%)	130 (21.1%)	0.049
3 year rejection	13 (47.2%)	154 (25.9%)	0.104
5 year rejection	13 (47.2%)	165 (29%)	0.143
1 year DCGS	27 (100%)	499 (93.9%)	0.39
3 year DCGS	14 (91.8%)	342 (87.8%)	0.381
5 year DCGS	8 (78.2%)	253 (83.5%)	0.671
1 year patient survival	27 (100%)	584 (95.6%)	0.622
3 year patient survival	14 (100%)	371 (89.5%)	0.38
5 year patient survival	10 (100%)	313 (84.2%)	0.375

PUB736

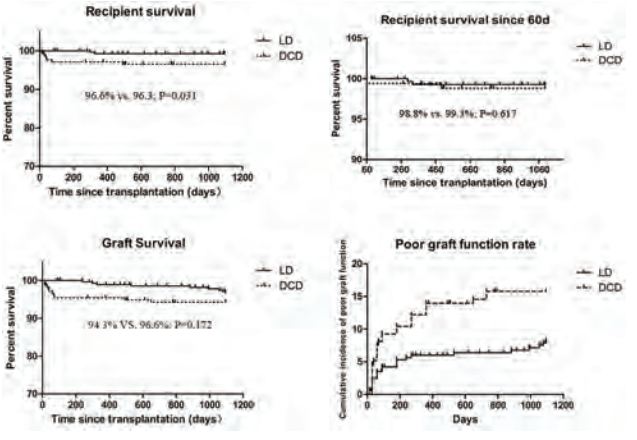
Comparison of 3-Year Graft Outcome between Donation after Cardiac Death (DCD) and Living Donor Kidney Transplantation Xing Zhang,[2] Jianyong Wu.[1] *[1]The First Affiliated hospital of Zhejiang University School of Medicine, Hangzhou, China; [2]Kidney disease center, The First Affiliated hospital of Zhejiang University School of Medicine, Hangzhou, China.*

Background: DCD and living donor kidney transplantation become main kidney transplant forms in China at present. There is few study special focusing on comparison of graft outcome between DCD and living donor kidney transplantation.

Methods: We retrospectively compared graft outcome between 176 DCD and 284 living donor kidney transplant recipients. 3-year graft survival, death-censored graft survival, recipient survival and graft function were compared. The relationship of DCD kidney transplantation with poor kidney function defined as the composite of death censored graft failure or two consecutive eGFRs less than 45 mL/min/1.73m2 occurring within 3 years was evaluated.

Results: Delayed graft function (DGF) was more common in DCD kidney transplantation (14.20% vs. 0.35%; P<0.001). 3-year graft survival (94.3% vs. 96.6%; P=0.172) and death-censored graft survival (97.1% vs. 97.3%; P=0.757) were similar between DCD and living donor kidney transplantation. The recipient survival was similar between two groups once DCD kidney transplantation recipients survived over 2 months (98.8% vs. 99.3%; P=0.617). The graft function assessed by eGFR at 3 years after transplantation for DCD kidney transplantation was better than living donor kidney transplantation (mean, 71.08 vs. 62.72 ml/min/1.73m2; P<0.001). DCD kidney transplantation was an independent risk factor of poor kidney function in multiple-variables analysis of Cox proportional hazards regression models, although it had similar 3-year graft survival and superior 3-year gaft function compared with living donor kidney transplantation.

Conclusions: In spite of higher DGF rate, 3-year kidney survival of DCD is comparable with that of living kidney transplantations. And 3-year graft function for DCD is superior to living donor kiney transplantation. DCD kidney transplantation remained to be an independent risk factor of poor kidney function.



Comparison of outcome between DCD and living donor kidney ransplantation

PUB737

Page Kidney after Kidney Transplant Biopsy: A Case Series Camilo Cortesi, Mai Sedki, Giselle Guerra, Adela D. Mattiazzi. *University of Miami/Jackson Memorial Hospital, Miami, FL.*

Background: Page Kidney (PK) is a rare but serious complication that is seen in kidney transplant (KT) recipients after renal allograft biopsy. PK results from a large perinephric collection compressing the allograft parenchyma, characterized by a triad of hypertension (HTN), perinephric collection, and creatinine (Cr) elevation. This condition has been poorly described in KT recipients with a few cases reported in the literature. This is a case series of 3 patients that developed PK after KT biopsy (KTb). We provide a full demographic description of each patient in Table1.

Methods: Case 1: 66-year-old (yo) woman with deceased donor kidney transplant (DDKT) due to ESRD from HTN and diabetes mellitus (DM) was admitted with elevated Cr. Ultrasound (US)-guided KTb was done, the next day she developed HTN up to 205/95 mmHg, lower abdominal pain and anuria. US of the KT revealed a large hematoma measuring 7x4cm. Patient was taken to the OR for exploratory surgery with drainage of 500mL of blood. After the procedure, Cr was 6.08mg/dL resolving 2 weeks later at 1.6mg/dL. Case 2: 45 yo man with DDKT due to ESRD from FSGS underwent US-KTb given high donor specific antibodies. Three days after biopsy he presented with diffuse abdominal pain, HTN up to 192/83 mmHg, and Cr elevation from 2.54 to 11.41mg/dL. CT scan showed a subcapsular hematoma of the KT measuring 6.7x2.5x10.1cm and 17.5x10.9x16.4cm retroperitoneal collection. Patient underwent exploratory surgery with removal of 3L; one month later Cr was 3.4mg/dL. Case 3: 56 yo man with DDKT due to ESRD from HTN and DM had an elevated Cr, he underwent US-KTb to rule out allograft rejection. Immediately after, he had pain at the site of KT and HTN up to 202/82 mmHg. Subsequently patient became anuric and Cr rose from 2.1 to 13.2mg/dL. CT scan unveiled

a perinephric hematoma measuring 8.7x4.5x10.9cm which was then percutaneously drained. Patient required dialysis indefinitely after this event.

Results:

Conclusions: PK diagnosis relies mainly on clinical suspicion and the use of appropriate imaging. Once PK is diagnosed, aggressive management is often necessary to ensure optimal viability of the allograft. This highlights the importance of identifying risk factors associated with this complication. Large cohort studies are needed to adequately assess the risk.

Demographics at the time of biopsy	Case 1	Case 2	Case 3
Age (years)	67	45	57
Gender	Female	Male	Male
Race	African-American	African-American	African-American
BMI	24.5	36	37
Blood Pressure (mmHg)	147/86	174/92	176/90
Hemoglobin (g/dL)	9.7	10.4	13.7
Creatinine (mg/dL)	1.17	2.58	2.1
BUN (mg/dL)	62	33	25
Platelets (K/uL)	183	161	205
INR	0.96	0.89	1.02
Antiplatelet therapy	No	Yes	No
Anticoagulation	No	No	No
Transplant type	DDKT	DDKT	DDKT
Number of Cores	3	3	3
Needle Gauge (G)	18	18	18
Biopsy Performer	Mild	Mild	Mild
Outcome	Graft Survival	Graft Survival	Graft Loss

PUB738

Characterization of H2-Blocker and Proton Pump Inhibitor Prescribing Practices in Maintenance Care of Kidney Transplant Recipients Vicki K. Sandys, Amy Hudson, Catherine M. Brown, Sean F. Leavey. *Nephrology, University Hospital Waterford, Waterford, Ireland.*

Background: Antacids, either histamine type 2 receptor-blockers (H2Bs) or proton pump inhibitors (PPIs) are routinely prescribed post-transplant. Interactions with immunosuppressants occur in the case of PPIs, through the inhibition of cytochrome P-450 and alteration of the gastric milieu. Of concern, evidence linking PPIs to acute interstitial nephritis now shows an association with progressive chronic kidney disease.

Methods: Active prescriptions for patients attending transplant clinic at UHW on Jan 15 th 2017, were extracted from the electronic health record (EMedrenal), with demographic, clinical and laboratory covariates. A variable describing the sum of all non-immunosuppressive medications per patient (excluding antacids)was created as an indicator for polypharmacy. Descriptive and both univariate and multivariate inferential analysis was undertaken using SPSS (version 23).

Results: 1540 prescriptions identified in 168 patients. 75% of patients were on antacids (41.7% (70) on H2B; 33.3% (56) on PPI). Significant positive associations with any antacid use ($p<0.05$) were found in univariate analysis for older age, male gender, immunosuppressant type, anticoagulant, statin and polypharmacy. Lower eGFR indicated preference for PPI over H2B ($p<0.05$). In multivariate modelling, the prescription of prednisone, MMF and each additional non-immunosuppressant independently increased the Odds of antacid prescribing by 4.7, 3.8 and 1.4 fold.

Conclusions: There is a high prevalence of antacid use. Polypharmacy and immunosuppressant use independently influence prescribing. The use of PPIs long-term, post-transplant may have clinical implications for graft survival. The factors influencing the indication for and choice of antacid post-transplant merits further study.

Multivariate Logistic Regression: Predictors of Antacid Prescribing

	B	S.E.	p-value	Adj. Odds Ratio (95% CI)
Age	.018	.016	.287	1.0 (0.99-1.05)
Tx Vintage	.022	.036	.537	1.0 (0.95-1.10)
eGFR	-.004	.012	.766	1.0 (0.97-1.02)
Polypharmacy*	.301	.115	.009	1.4 (1.08-1.69)
MMF	1.344	.475	.005	3.8 (1.51-9.73)
Prednisolone	1.557	.530	.003	4.7 (1.68-13.4)
Tacrolimus	1.387	.761	.068	4.0 (0.90-17.8)
Constant	-4.444	1.616	.006	0.0

*Sum of all non-immunosuppressive drugs (excl antacids)

PUB739

Association between Vascular Access Type in Hemodialysis Patients and Subsequent Kidney Transplant Outcomes Medha Airy,[1] Colin R. Lenihan,[3] Monnie Wasse,[2] Wolfgang C. Winkelmayer.[1] *[1]Baylor College of Medicine, Houston, TX; [2]Rush University Medical Center, Chicago, IL; [3]Stanford University School of Medicine, Palo Alto, CA.*

Background: Type of vascular access is associated with outcomes in patients with end-stage kidney disease undergoing hemodialysis. Whether associations exist with outcomes after kidney transplant is unknown. Potential mechanisms towards worse outcomes include patency of residual peripheral accesses potentially contributing to heart failure as well as retained vascular grafts that may cause chronic inflammation.

Methods: A retrospective cohort study of hemodialysis patients receiving a first kidney transplant was done using merged data from the US Renal Data System and a large dialysis organization. We ascertained the access used for the last hemodialysis prior to transplantation: arteriovenous fistula (AVF); arteriovenous graft (AVG); central venous catheter (CVC). Patients were followed from kidney transplant for all-cause mortality, kidney allograft loss from any cause, and allograft loss not from death.

Results: Among 9291 patients who underwent kidney transplantation between 2006-2011, 65.3% had an AVF and 20.4% had an AVG and 14.3% used a CVC. Cox proportional hazards regression models adjusted for demographic, comorbidity, and transplant characteristics, as well as laboratory parameters indicated no associations between vascular access type and all-cause mortality or all-cause allograft loss (Table). Central venous catheter use was associated with a 30% higher risk of allograft loss from causes other than death compared to use of an arteriovenous fistula (HR=1.30; 95% CI, 1.06-1.57).

Conclusions: No clear associations between vascular access use for dialysis and subsequent transplant outcomes were identified. The association of central venous catheter use with allograft loss from all causes other than death lacks a plausible explanation and requires confirmation.

*Adjusted HR (95% CI)	AVG vs AVF	CVC vs AVF
All-cause mortality	1.13 (0.97, 1.33)	1.00 (0.83, 1.21)
Allograft loss	1.13 (1.00, 1.28)	1.12 (0.96, 1.29)
Allograft loss from cause other than death	1.17 (0.98, 1.39)	1.30 (1.06, 1.57)

*Adjusted for demographic variables, comorbidities, transplant characteristics, and laboratory parameters

PUB740

Twelve-Year Experience in ABO Incompatible Kidney Transplantation: Differences in Infection Rate and Short-Term Outcomes between Hemodialysis and Peritoneal Dialysis Patients Georgios Spanos,[1] Christina Melexopoulou,[1] Chrysanthi Skalioti,[1] Smaragdi Marinaki,[1] John Bokos,[2] Georgios Zavos,[2] John N. Boletis.[1] *[1]Nephrology Department & Renal Transplantation Unit, Laiko General Hospital, National & Kapodistrian University of Athens, Medical School, Athens, Greece; [2]Renal Transplantation Unit, Laiko General Hospital, National & Kapodistrian University of Athens, Medical School, Athens, Greece.*

Background: The use of intensfied desensitization protocols in ABO-incompatible kidney transplantation (ABOi KTx) seems to increase postoperative infection rates. Currently, no clear consensus has emerged regarding whether the peritoneal dialysis (PD) catheter should be removed at the time of transplant surgery or not, in the event dialysis is required in the immediate post-transplant period. The purpose of this study was to audit infectious complications and outcomes in ABOi KTx in PD patients and compare them with heamodialysis (HD) patients.

Methods: A single centre prospective cohort of ABOi KTx patients from June 2005 till May 2017 with a desensitization protocol including the use of rituximab 30 days pre-KTx, immunoadsorptions, intravenous immunoglobulin and double oral immunosuppression administered 15 days pre-KTx was followed up for one year post KTx.

Results: The cohort included 42 patients (14% PD patients, 76% HD patients and two preemptive) with a mean age of 37.4 ± 10.8 years, 26% female. No significant difference was observed in baseline characteristics between two groups. One episode of peritonitis during desensitization period was successfully treated causing rescheduling the KTx date, while one episode of central venous catheter related septicemia was observed during follow up. The incidence of post-KTx bacterial infections leading to hospitalization, viral infections (cytomegalovirus and polyoma virus) and surgical complications were similar between the two groups. There was no significant difference in serum creatinine at the end of follow up (1.73±0.5 vs 1.51±0.35, p=ns), and patient and graft survival was 100% vs 100% and 100% vs 97.6% in the PD vs HD group, respectively (p=ns). Furthermore, the rate of biopsy-proven acute rejection was comparable. Two patients in the PD group and 3 in the HD group had acute cellular rejection, treated successfully. Only one HD patient developed acute antibody-mediated rejection and graft loss in the immediate post KTx period.

Conclusions: Peritoneal dialysis and hemodialysis patients undergoing ABO incompatible kidney transplantation have comparable infectious complication rate and short term outcomes.

PUB741

Kidney Autotransplantation as an Effective Alternative to Percutaneous Transluminal Renal Angioplasty for Renal Artery Stenosis: A Case Report Hirofumi Sumi, Atsuko Uehara, Tsutomu Sakurada, Yugo Shibagaki. *St. Marianna University School of Medicine, Kawasaki, Japan.*

Background: Acute kidney injury (AKI) caused by renal artery stenosis is common. The most common treatment is percutaneous transluminal renal angioplasty (PTRA); however, this procedure is technically difficult in some cases. In these cases, the indications and effectiveness of kidney autotransplantation (AutoTx) remain unclear. We describe the case of a patient with renal artery in-stent restenosis successfully treated with kidney AutoTx.

Methods: The patient was a 76-year-old woman with a right solitary kidney attributable to left renal thromboembolism. Two years prior to admission, she underwent an endovascular aortic aneurysm repair with a stent graft for infrarenal aortic aneurysm, which led to ostial occlusion of the right renal artery. She underwent PTRA and stenting. Two days prior to admission, she developed leg edema and hypertension, and thus visited the hospital. Her serum creatinine level was 2.4 mg/dL (baseline, 1.0 mg/dL). AKI due to renal artery in-stent restenosis was suspected, and re-angioplasty was attempted on hospital day 2 but was unsuccessful because of technical failure. Her renal function did

not improve, and anuria persisted, so hemodialysis was initiated on the same day. The size of the right kidney was preserved (8.6 cm) relative to her body size, with only mild cortical atrophy and Doppler ultrasonography and mercaptoacetylgriglycine scan showing a minimal but significant perfusion of the right kidney. Thus, we considered that the kidney perfusion was not arrested and that renal function could be reversed. On hospital day 25, we proceeded with right kidney AutoTx to the right iliac fossa to reestablish an adequate renal perfusion and reverse the need for dialysis. Soon after the procedure, the patient started passing urine. Her renal function improved and serum creatinine level decreased to 1.0 mg/dL on hospital day 33. Hemodialysis was discontinued after the surgery.

Results:

Conclusions: Our findings indicate that kidney AutoTx can be a treatment option for patients with renal artery stenosis who have undergone an unsuccessful PTRA.

PUB742

Acute Tacrolimus Toxicity Successfully Treated with Phenytoin Tasleem Katchi,[2] Kavneet Kaur,[1] Savneek S. Chugh,[1] Sanjeev Gupta,[3] Muhammad R. Mustafa.[2] *[1]New York Medical College, White Plains, NY; [2]Westchester Medical Center, White Plains, NY; [3]Westchester county medical center, White Plains, NY.*

Background: Tacrolimus is an integral part of immunosuppression following solid organ transplantation. We present a case of acute tacrolimus toxicity in a renal transplant recipient successfully treated with phenytoin.

Methods: A 55-year old male with history of end-stage renal disease due to tuberous sclerosis and polycystic kidney disease who had undergone a living related renal transplant 17 years ago was transferred to our facility for evaluation of acute kidney injury (AKI). The patient was admitted to a psychiatric facility for suicidal ideations and had recently been initiated on multiple psychotropic drugs including haloperidol, quetiapine, benztropine, hydroxyzine, citalopram and fluoxetine. Anti-psychotic therapy was held due to AKI. Upon arrival, the patient had progressive worsening of generalized body tremors. Vitals signs were normal and physical examination was unremarkable. Laboratory results revealed a serum chloride concentration of 113 mEq/L, bicarbonate 11 mEq/L, blood urea nitrogen 98 mg/dl, creatinine 3.42 mg/dl (increased from baseline of 1.7 mg/dl). Serum trough tacrolimus level was >30 ng/ml. Within a few hours, the patient had worsening mental status and was intubated for airway protection. Tacrolimus was held and he was started on phenytoin 100 mg every 8 hours. On hospital day 3, tacrolimus levels dropped to 7.5 ng/ml and creatinine was 1.7 mg/dl. The patient became more alert, his tremors resolved and he tolerated extubation. Phenytoin was stopped and tacrolimus was restarted at a dose of 2 mg twice daily.

Results:

Conclusions: Calcineurin inhibitors form the backbone of immunosuppression in solid organ transplant recipients. Tacrolimus is metabolized by the Cytochrome P450 (CYP) 3A4 enzyme and levels ranging from 5-15 ng/ml are recommended post-transplant. Clinical features of tacrolimus toxicity can vary from complete absence of symptoms to renal failure and neurotoxicity. Our patient developed tacrolimus toxicity likely due to drug interactions with multiple psychotropic drugs given without checking tacrolimus levels. This in turn led to the AKI and worsening body tremors. Very few cases of tacrolimus toxicity treated with phenytoin have been reported in the literature. Phenytoin is an inducer of the CYP system. It increases the metabolism of tacrolimus, and can be considered in cases where rapid decrease in tacrolimus levels is desired.

PUB743

Hyperammonemia after Lung Transplant, an Often Fatal Complication Pace Romney,[2] Laith Al-Rabadi,[3] Nirupama Ramkumar,[1] Josephine Abraham.[1] *[1]University of Utah, Holladay, UT; [2]University of Utah Medical Center, Salt Lake City, UT; [3]University of Utah hospital, Salt Lake, UT.*

Background: Hyperammonemia after lung transplantation is a rare complication which is frequently fatal. The etiology is unclear and early recognition is important for survival.

Methods: A 69 year old man with a history of alpha-1 antitrypsin deficiency underwent lung transplantant with an initial uneventful post operative course and discharge on day 14. He was induced with basiliximab and maintained on mycophenolate, tacrolimus, corticosteroids, with routine antimicrobial prophylaxis. Day 17 he complained of fatigue, lightheadedness, and decreased mental acuity. Day 23 he had hyponatremia but improved mentation and energy. However day 31 he was unable to ambulate, was admitted to the hospital, and was found to have continued hyponatremia and an ammonia level of 200. Due to worsening encephalopathy, he was intubated shortly after admission. Management for hyperammonemia included broad-spectrum antibiotics, hemodialysis, bowel decontamination, amino acid supplementation, and nitrogen scavengers. Tacrolimus and mycophenolate were stopped. Ammonia levels and mentation improved and he was extubated, but despite this improvement and ongoing therapy, hyperammonemia recurred. He was reintubated due to worsening hypoxia and initiated on pressors for hypotension. Despite aggressive hemodialysis, ammonia levels continued to increase. Palliative consult followed due to the patient's continued decline and care was withdrawn. Consent for autopsy was obtained and a lung sample was notably positive for Ureaplasma parvum.

Results:

Conclusions: Hyperammonemia is a rare occurrence after lung transplant affecting 1-4% of these patients and the etiology is unknown. Proposed mechanisms include unmasking of partial urea cycle disorders, immunosuppressive agents, and infection with urea-splitting organisms such as Ureaplasma or Mycoplasma. Goals of treatment include minimization of ammoniagenesis and increased nitrogen removal. Strategies to reduce ammonia production include protein restriction, bowel decontamination and amino acid supplementation. Nitrogen removal is achieved through hemodialysis and use of nitrogen scavengers such as sodium benzoate and sodium phenylacetate. Empiric treatment for urea-splitting organisms with a fluoroquinolone and macrolide is recommended. Despite therapy, mortality is high and a high index of suspicion is required for early diagnosis and prompt initiation of therapy.

PUB744

Monoclonal IgG4/2-Kappa Deposition Following Eculizumab Therapy for Recurrent Atypical Hemolytic Uremic Syndrome (aHUS) in Kidney Transplantation Priyamvada Singh,[5] Hui Chen,[1] Craig E. Gordon,[7] John M. Sloan,[2] Karen Quillen,[4] Vipul C. Chitalia,[6] Amitabh Gautam,[3] Joel M. Henderson,[4] Jean M. Francis.[4] *[1]BMC, Boston, MA; [2]Boston MEdical Center, Boston, MA; [3]Boston Medical Center, Boston, MA; [4]Boston University Medical Center, Boston, MA; [5]Renal, Boston University Medical Center, Boston, MA; [6]Boston University School of Medicine, Boston, MA; [7]None, Natick, MA.*

Background: Eculizumab is emerging as a promising therapy for aHUS. We present a patient with rapid resolution of recurrent aHUS after kidney transplantation following eculizumab therapy but with evidence of monoclonal IgG4/2-kappa deposition on repeat kidney biopsy

Methods: A 22-year-old male with CKD stage 5 of unknown etiology underwent preemptive living related kidney transplantation from his sister. His post-operative course was complicated by thrombocytopenia on day 3 after transplant (nadir platelet count: 36k/ul) and delayed graft function. Testing revealed elevated LDH (673 U/L, normal 171-308), low haptoglobin (<7 mg/dL, normal 44-184), and schistocytosis on peripheral blood smear. Eculizumab was initiated for possible recurrent aHUS on day 3 post-transplant. Kidney biopsy performed on day 5 post-transplant following a recovery of thrombocytopenia confirmed the diagnosis of acute thrombotic microangiopathy (TMA). Hematological parameters improved rapidly following treatment but the renal function did not improve as expected. A repeat kidney biopsy performed after 5 doses of eculizumab demonstrated complete resolution of TMA features on a background of essentially normal renal parenchyma. Interestingly, immunofluorescence microscopy revealed monoclonal staining for IgG4/2-kappa in glomeruli, vasculature, and focally in tubular basement membranes. The deposits suggest eculizumab deposition because eculizumab is a hybrid monoclonal immunoglobulin comprised of IgG4/2-kappa chains. IgG4/2-kappa deposits are rare pathological findings seen following eculizumab therapy.

Results:

Conclusions: Early identification and treatment of recurrent TMA after transplantation require a high clinical suspicion but result in improved graft function and patient outcome. IgG4/2-kappa deposits are a rare pathological finding following effective eculizumab therapy but the long-term effects of these deposits on renal function remain unknown.

PUB745

Cytomegalovirus Infection and Hemophagocytic Lymphohistiocytosis in a Renal Transplant Recipient Brittany L. Schreiber, Muhammad A. Mujtaba. *University of Texas Medical Branch, Galveston, TX.*

Background: Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening hyper-inflammatory syndrome characterized by hypercytokinemia, histiocytic proliferation and hematophagocytosis. Renal transplant recipients (RTRs) are at increased risk of developing HLH due to chronic immunosuppression and high prevalence of opportunistic infections including cytomegalovirus (CMV). We present a unique case of HLH due to CMV infection in a renal transplant recipient.

Methods: A 75-year-old female with a history of polycystic kidney disease status post renal transplantation 12 years prior to presentation, maintained on tacrolimus, mycophenolate mofetil, and prednisone presented with watery diarrhea and generalized weakness. Initial work-up revealed thrombocytopenia, acute kidney injury and tacrolimus toxicity with a serum level of 29 ng/mL. Tacrolimus was held and levels returned to therapeutic range after administration of rifampin. After 7 days of hospitalization, the patient became lethargic, febrile and hypotensive. Mycophenolate was held, empiric antibiotics were started, and the patient was resuscitated with intravenous fluids. Laboratory work-up at that time showed worsening pancytopenia, rising transaminases, elevated ferritin and coagulopathy with hypofibrinogenemia. Despite multiple blood product transfusions the pancytopenia persisted and hematology was consulted and a bone marrow biopsy was performed revealing hemophagocytosis, dyserythropoiesis and dysgranulopoiesis. CMV polymerase chain reaction returned showing over 33 million viral copies/mL. The patient was diagnosed with HLH secondary to disseminated CMV infection and was started on intravenous ganciclovir with resolution of viremia and improvement in clinical condition.

Results:

Conclusions: RTRs are at high risk for CMV infection, a known precipitant of HLH. These patients are most susceptible during periods of intense immunosuppression, particularly in the early post-transplantation period. Unlike HLH in non-transplant patients, etoposide is not a mainstay of therapy and treatment remains controversial with little consensus on the role of immunosuppression. Intensive supportive care and organism-directed antimicrobials are essential in patient survival. Prognosis remains poor despite therapy making early diagnosis and prompt initiation of directed therapy crucial in this population.

PUB746

Is There an Association between Frailty and Relative Telomere Length in Pre-Renal Transplant Recipients? Vasantha M. Muthuppalaniappan,[2] Kieran Mccafferty,[1] Muhammad M. Yaqoob.[2] *[1]NHS, LONDON, United Kingdom; [2]William Harvey Research Institute, London, United Kingdom.*

Background: Both telomere length (TL) and frailty is associated with aging. Frailty is emerging as an important risk factor for adverse renal transplant (RT) outcomes and increasingly recognized as potential tools in risk stratifying RT candidates. Strong associations between frailty and relative TL (rTL) have been reported but sparse data is found in renal transplantation. The aim of the study was to assess the association of frailty in RT recipients with rTL and outcome in this cohort.

Methods: This was a single centre prospective study from October 2016 - April 2017. Frailty was measured as defined and validated by Fried based on 5 components at admission for RT. Non-frail was defined as a score of 0 or 1; intermediate frailty as a score of 2 and frail if the score was ≥3. TL was measured from peripheral white blood cell pre-transplant using quantitative PCR (T/S ratio) using a modified Cawthon protocol. Data on co-morbidities, complications, and length of stay in hospital and readmissions were recorded.

Results: 33 recipients (14 male, 19 female) were recruited prior to RT. Ages ranged from 26-77 year with a median age of 47.97 ± 12.84. Cadaveric transplantation was performed in 66.7% of patients and 33.3% had living donor transplant. 66.7% of patients were non-frail (68.2% cadaveric, 63.6% living donor); 24.2% were intermediately frail (18.2% cadaveric, 36.4% living donor) and 9.1% were frail (13.6% cadaveric) at the time of RT. There was no correlation between age and length of stay (R^2= 0.03). A higher Charlson co-morbidity index was strongly associated with longer length of stay post RT (p=0.001). Length of stay post RT was increased with shorter rTL but this was subsequently found not to be significant (p=0.392). There was no significant association with raised frailty scores and increased hospital admissions (p= 0.35). There was no association between frailty score and rTL was found in this study. Dialysis vintage was inversely proportional to RTL (p=0.046). rTL was also significantly shorter in RT recipients on haemodialysis in comparison to peritoneal dialysis (p< 0.001).

Conclusions: Despite literature suggesting a correlation between frailty and shorter rTL, our study failed to replicate these findings. There was no significant association between frailty index and rTL, however a small sample size may be the limiting factor.

PUB747

Clinical Features, Treatment, and Outcomes of Kidney Transplant-Associated Thrombotic Microangiopathy: A Single-Center Experience Kohei Unagami,[2] Masayoshi Okumi,[2] Hideki Ishida,[1] Kosaku Nitta,[2] Kazunari Tanabe.[2] *[1]Tokyo Women's Meedical University, Tokyo, Japan; [2]Tokyo Women's Medical University, Tokyo, Japan.*

Background: Thrombotic microangiopathy (TMA) is a dangerous disorder characterized by fragmented red blood cells, decreased platelet count, and organ failure due to thrombosis. In recent years, atypical HUS has been reported to present such a state. Furthermore, TMA was also considered to present the same state, so strict differentiation between the two conditions is difficult. Kidney transplant-associated TMA (TA-TMA) presents a severe state; thus, rapid differential diagnosis is required.

Methods: We conducted a retrospective study of kidney transplantations performed between January 1999 and December 2015 at our institution, and investigated and evaluated diagnoses, treatment, and graft survival.

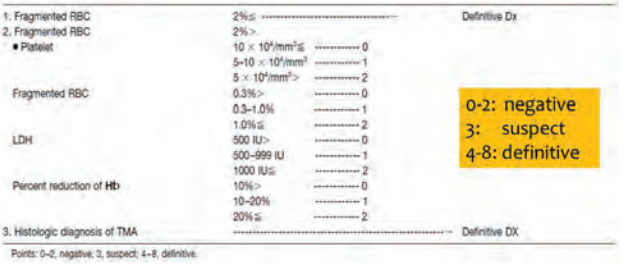
Results: 1,109 renal transplantations were performed, and 24 recipients were diagnosed as having TA-TMA (Table1). The prevalence of ABO incompatible cases with TA-TMA was higher than that of ABO compatible cases (odds ratio, 2.39; p = 0.03). We confirmed pathological findings of TMA in 23 cases, including rejection in 11 cases. Using our proposed TA-TMA diagnostic scoring system (Table2), 23 cases were diagnosed as TMA (95.8%). By contrast, the positivity rate without TMA was 0%. As treatments, plasma exchange therapies were performed in almost all the cases. In 3 cases, eculizumab infusion was given. We confirmed the disappearance of TMA in 13 (54.2%) of the 24 cases via biopsy examination. Except 2 cases, all cases showed good graft survival, with a creatinine level of 1.87 ± 0.81 mg/dL.

Conclusions: Prompt diagnosis and treatment based on diagnostic criteria may lead to good treatment results.

TMA (Jan/1999-Dec/2015)

Case	Year	Age	Sex	Etiology		Donor	Compatibility	Anti-Blood Ab IgM/IgG	DSA
1	1999	23	male	Unknown	living	Father	Incompatible	X8 X16	unknown
2	1999	32	female	Unknown	living	Father	Minor mismatch	none	unknown
3	1999	36	female	HSPN	living	Father	Minor mismatch	none	unknown
4	1999	56	female	Unknown	living	Daughter	Compatible	none	unknown
5	2000	42	male	Unknown	living	Mother	Incompatible	X32 X32	unknown
6	2000	57	male	RPGN	living	Mother	Minor mismatch	none	unknown
7	2000	40	male	Unknown	living	Mother	Incompatible	X8 X32	unknown
8	2001	48	male	Unknown	living	Mother	Minor mismatch	none	unknown
9	2002	60	female	Unknown	deceased	unknown	Compatible	none	unknown
10	2005	42	female	IgAN	living	Mother	Incompatible	X16 X32	unknown
11	2006	52	female	Unknown	living	Mother	Incompatible	X4 X128	negative
12	2007	27	male	IgAN	living	Mother	Minor mismatch	none	negative
13	2009	33	male	IgAN	living	Mother	Compatible	none	negative
14	2010	51	female	VUR	living	Husband	Minor mismatch	none	positive
15	2011	75	male	IgAN	living	Sister	Compatible	none	unknown
16	2011	63	male	ADPKD	deceased	Male	Compatible	none	unknown
17	2011	30	male	FSGS	deceased	Male	Compatible	none	unknown
18	2013	33	male	IgAN	living	Father	Incompatible	X32 X64	negative
19	2013	61	male	DMN	living	Wife	Incompatible	X32 X2	negative
20	2014	66	male	Unknown	living	Wife	Incompatible	X16 X64	negative
21	2014	59	male	DMN	living	Brother	Compatible	none	positive
22	2014	68	male	Unknown	living	Wife	Incompatible	X16 X4	negative
23	2015	27	Female	SLE	living	Father	Incompatible	X32 X2	negative
24	2015	50	Male	unknown	living	Wife	Incompatible	X8 X2	negative

Diagnostic Criteria of TMA



PUB748

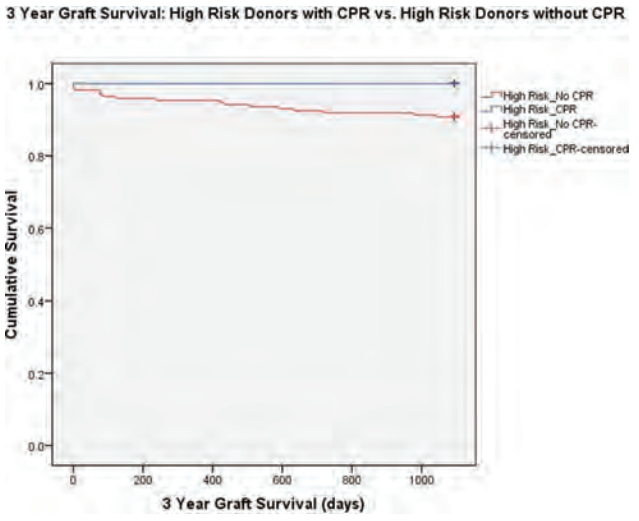
CPR in High-Risk DCD and ECD Donors for Kidney Transplantation Jacentha L. Buggs,[1] Victor Bowers.[2] *[1]Transplant Surgery, Tampa General Medical Group, Tampa, FL; [2]Transplant Surgery, Tampa General Medical Group, Tampa, FL.*

Background: The demand for organs for kidney transplantation compels the use of high risk (HR), donation after circulatory death (DCD) and extended criteria donors (ECD) in addition to standard criteria and living donors to expand the donor pool. Most studies suggest DCD and ECD kidney transplants (KTX) may be associated with inferior graft survival. Many cadaveric donors receive CPR as a lifesaving method to return the patient to baseline function but the literature does not address the consideration of donor CPR as an additional tangible benefit to graft survival when selecting donors for KTX. We hypothesize that donor CPR correlates with improved graft survival with HR DCD and ECD KTX thus providing additional information when evaluating a potential donor.

Methods: We retrospectively analyzed consecutive cadaveric KTX recipients and their donor data from January 1, 2008 to December 31, 2013.

Results: A total of 646 cadaveric donors (498 SCD, 55 DCD, and 93 ECD) facilitated 910 cadaveric KTX. Within the 148 HR donors, 31 received CPR and 117 did not. There were 223 cadaveric KTX performed at our center from HR donors. The mean age of HR donors was 45 yrs. with CPR and 53 yrs. without CPR (p-value 0.010). There was no difference in HR donor gender, race, and BMI with or without CPR. The KTX recipients of HR donors revealed no significant difference in BMI, LOS, discharge Cr, CIT or DGF with and without CPR although the LOS and discharge Cr were lower, and the CIT was greater with CPR vs. without CPR. Graft survival at 3 years was significant with 0 failures out of 50 KTX from HR donors with CPR vs. 16 graft failures out of 173 KTX from HR donors without CPR (p-value 0.026).

Conclusions: Our study is limited as a single center retrospective study, however the result of significant 3 year graft survival in high-risk donors who received CPR suggests donor CPR should be considered when assessing organs for transplantation.



PUB749

Acute Antibody Mediated Rejection Associated With the Use of the New Anti-HCV Medications – A Case Report Khaled Karkout,[1] Saleema Sharief,[2] Qutaiba Hussain,[1] Yousef Boobes.[1] *[1]Tawam hospital, Al Ain, United Arab Emirates; [2]Tawam Hospital, Al Ain, United Arab Emirates.*

Background: Hepatitis C virus (HCV) infection is prevalent in renal allograft recipient and associated with increased morbidity and mortality. The new direct acting antiviral agents (DAAs) are highly effective in clearing the virus and considered safe for use in kidney transplant patients, no acute graft rejection has been reported so far after their use. Here we are reporting for the first time a case of biopsy-proven acute graft rejection after the use of DAAs.

Methods: We report a case of a 47-year-old, type 1 diabetic male, who had a living unrelated kidney transplant in 2006. Prior to his transplant, he acquired HCV infection. In 2009, he was found to have 12 million copies of HCV, with a deranged liver function test. In 2015, the patient showed F3 fibrosis on fibro-scan. However, due to the risk of graft rejection he wasn't started on INF therapy, he was kept on low immunosuppressive treatment consists of cyclosporine (CYC) 75/50 mg daily, mycophenolic acid 180 mg twice daily and prednisolone 5 mg daily. Recently, DAAs became available and he was started on Daclatasvir 60 mg daily with Sofosbuvir 400 mg daily. Creatinine level (Cr) was maintained mostly around 1.4-1.5 mg/dL. About 3 months after initiating anti-HCV treatment, his Cr raised to 2.4 mg/dL, and kept rising steadily reaching 4.78 mg/dL. During the course DAAs treatment CYC trough level was kept always therapeutic (140-180 ng/mL), a renal biopsy was done almost three month after starting DAAs, and revealed the presence of acute anti-body mediated rejection (AMR) as well as features of advanced diabetic nephropathy and severe interstitial fibrosis and tubular atrophy. He received methylprednisolone IV pulses and CYC was replaced by tacrolimus together with increasing the dose of mycophenolic acid. The AMR responded with gradual improvement of his serum Cr

Results:

Conclusions: In our patient, the use of DAAs was associated with biopsy proven acute AMR raising the need to be more cautious when using these medications in kidney transplant patients. More studies are needed to establish the link between this treatment and graft rejection.

PUB750

Long-Term Spontaneous Operational Tolerance after Deceased-Donor Kidney Transplantation: A Case Report Denaly S. Chen, Loay H. Salman, Rafia I. Chaudhry, Mauricio Monrroy. *Albany Medical College, Albany, NY.*

Background: Operational Tolerance (OT) is defined by the maintenance of stable allograft function in the absence of immunosuppressive drugs for at least one year in kidney transplant recipients. OT does not imply a complete paucity of anti-donor reactivity, but the absence of clinically detectable, deleterious immune responses directed against the allograft. This highly desirable phenomenon has been linked to an increase in expression of B cell associated genes, and changes in B cell subsets, with an increase in naïve and decrease in memory B cells. Less than 200 kidney transplant recipients have been reported to develop spontaneous OT after discontinuing immunosuppressive medications, and these patients maintained allograft function without rejection for years. Almost all of the reported cases were living-donor kidney recipients.

Methods: A 25yo WM presented to the ED for left flank pain. He had a history of ESRD due to bilateral congenital kidney dysplasia and underwent living donor kidney transplant from his mother at age 4, with early graft failure due to vascular thrombosis. He underwent a second kidney transplant from a cadaveric donor at the age of 7, and was followed at our institution until 19 yrs of age. His baseline creatinine was 1.9 mg/dL, immunosuppressive regimen included Prednisone, Myfortic and Rapamune. The patient was then lost to follow-up and eventually stopped all immunosuppressive therapy at the age of 20 due to noncompliance. 5 years after discontinuing immunosuppressive agents, the patient remained normotensive, with an unremarkable physical exam. His creatinine impressively remained at 1.8 mg/dL, UA was positive for trace protein only.

Results:

Conclusions: Although factors such as pre-sensitization against HLA antigens and previous rejection episodes have not prevented the subsequent emergence of spontaneous tolerance, most reported cases of OT are recipients well matched to their donor. In this case, the development of OT to a cadaveric donor kidney is remarkable, with an impressively stable renal function, and urine sediment without evidence of ongoing kidney injury after 5 years off immunosuppression.

PUB751

Impact of Pre-Implant Biopsy Findings on Short-Term Kidney Graft Function and Maintenance Immunosuppression Management Sanjeev Akkina, Ewa Borys, Amishi S. Desai, Raviprasenna K. Parasuraman. *Loyola University Medical Center, Chicago, IL.*

Background: The role of procurement biopsies or pre-implant biopsies on renal allograft outcomes is unclear. Altering maintenance immunosuppression (IS) by calcineurin-inhibitor (CNI) reduction or conversion to non-CNI regimens based on donor histology may improve allograft function. In this study, we hypothesize that pre-implant biopsy (bx) histology may predict the need for changes in maintenance IS early after transplant.

Methods: In this retrospective, single-center review, we have 24 individuals had a pre-implant bx between January 2016 and March 2017. We collected donor characteristics including the reported histological findings from the donor bx prior to procurement. We assessed for glomerulosclerosis, tubular atrophy, interstitial fibrosis, and arterial hyalinosis as the primary predictors. Our outcomes of interest were serum creatinine at 1, 4, and 8 weeks after transplant and changes that occurred in maintenance IS. Linear and logistic regression was used to determine which factors were associated with allograft function and changes in maintenance IS.

Results: Of the 24 individuals that had a pre-implant bx, 18 had a donor bx prior to procurement. The mean donor age was 42±15 years with a mean KDPI of 57±25. Cause of death was anoxia or trauma in 71% of the donors while 50% had hypertension and an additional 17% had both hypertension and diabetes. Mean terminal creatinine was 1.6±1.2mg/dL with a cold ischemia time of 17±5 hours. Of the 24 recipients, 4 had alterations in their maintenance IS within the first 8 weeks after transplantation (CNI reduction for 2, conversion to belatacept for 2) with an average reduction of 40% in creatinine within 4 weeks after the change. Creatinine at 8 weeks was associated with arteriolar hyalinosis on the pre-implant bx (2.8±3.4 vs 1.2±0.3mg/dL, p=0.076). Creatinine was not associated with other histological parameters or donor KDPI. Logistic regression of bx findings did not predict alterations in maintenance IS.

Conclusions: In our study, we found that arterial hyalinosis on pre-implant biopsies was associated with higher 8 week creatinine level but there were insufficient data to predict who would benefit from early changes in maintenance IS.

PUB752

Drug Resistant CMV Infection in Post Kidney Transplant Recipients – High Dose Gancyclovir as a Safe Treatment Option Swetha Rani Kanduri,[2] Desiree Garcia Anton,[1] Pradeep Vaitla.[2] *[1]University of Mississippi Medical Center, Ridgeland, MS; [2]Nephrology, University of Mississippi Medical Center, Jackson, MS.*

Background: Resistant cytomegalovirus infection (CMV) is a significant problem in kidney transplant recipients with an incidence of 0.54%–1%. The factors that promote the emergence of resistance include CMV donor-positive recipient-negative status. (D+/R–), receipt of potent immunosuppression, prolonged exposure to anti-CMV agents and high CMV virus load. There are multiple reports of poor graft survival and increased mortality with resistant CMV infections noted in literature. Here we present a case of gancyclovir (GCV) resistant CMV infection and its successful treatment.

Methods: 28-year-old African American female, with end stage renal disease underwent disease donor renal transplant secondary to hypertensive nephrosclerosis. She received thymoglobulin induction along with Mycophenolate mofetil, Tacrolimus and Prednisone. She is low risk for CMV with both donor and recipient being positive for CMV IgG. 3 months post-transplant, patient was diagnosed with CMV colitis after she completed valgancylovir prophylaxis. Received treatment with high dose oral valgancyclovir. CMV PCR levels initially decreased however trended back up and had persistent leukopenia. Genetic testing noted to have GCV resistant CMV viremia. Resistance testing showed mixed CMV population with resistance at UL97 gene target. Available treatment options were induction with Foscarnet vs Cidofovir vs high dose Gancyclovir. Foscarnet and Cidofovir have adverse nephrotoxic profiles along with electrolyte abnormalities and Fanconi picture. They also cause significant disease burden with need for IV fluids and close monitoring of labs. Option of high dose GCV induction was chosen for two weeks followed by high dose oral valgancyclovir. Colitis and leukopenia improved along with significant decrease in CMV PCR levels.

Results:

Conclusions: Resistance to GCV can be explained by mutations in two CMV genes: UL97, encoding a kinase responsible for the initial phosphorylation and activation of GCV; and UL54, encoding the viral DNA polymerase. Therapeutic options for GCV-resistant CMV are limited and with some therapeutic options being extremely toxic. So far, we have no controlled trial data to support the best alternative therapy. The use of

higher doses of IV GCV 10 mg/kg twice daily has been been one of the successful options considering side effect patterns of other options.

PUB753

Utility of Day 0 Urine Screening Protocol in Predicting Early Onset Urinary Tract Infection after Renal Transplantation Anil Mishra, Olanrewaju Aboderin, Bradley B. Gehring, Katie L. Korneffel, Graham Mitro. *University of Toledo College of Medicine, Toledo, OH.*

Background: Urinary tract infection (UTI) limits allograft survival and is the most common form of bacterial infection in patients who undergo renal transplantation. Many hospitals including the University of Toledo Medical Center routinely screen patients via urinalysis (UA) and/or urine culture (UC) for nitrites or bacteria prior to operation (Day 0) in order to address this issue. Our study investigates the utility of this protocol in predicting the onset of UTI within two weeks of transplantation (early onset UTI).

Methods: An IRB-approved retrospective cohort study was conducted on 675 patients who received renal transplantation between 03/2006 and 11/2015 at the University of Toledo Medical Center. Day 0 through Day 14 UA and UC data were collected and analyzed. A positive UA was defined as a UA containing nitrites and positive UC as a UC containing greater than or equal to 10^5 colony forming units per milliliter (Cfu/mL). All patients were induced with Alemtuzumab.

Results: Of the 675 patients, 227 (33.3%) received screening on Day 0. Eleven of these patients (1.6% of total) had a positive UA and/or positive UC within two weeks of transplantation. Only one patient (0.15% of total) was positive on Day 0, and this patient did not have another positive result within two weeks of transplant. 448 patients (66.4%) did not receive Day 0 screening, and this group was used as a control. Twelve of these patients (1.8% of total) had a positive UA and/or positive UC within two weeks of transplantation. Day 0 urine screening was not a significant predictor of early onset UTI in patients (p=0.143).

Conclusions: Based on our single-center study at UTMC, the practice of Day 0 Urine screening is not a significant predictor of UTI within two weeks of renal transplantation. Hospitals should re-evaluate this protocol and further investigate its utility at their local site before permanently implementing.

Day 0 Urine Screen and the Development of UTI (14 days after Transplant)

	No UTI	UTI	Total
Without Day 0 Urine Screen	436 (64.6%)	12 (1.8%)	448 (66.4%)
With Day 0 Urine Screen	216 (32.0%)	11 (1.6%)	227 (33.6%)
Total	652 (96.6%)	23 (3.4%)	675 (100%)

PUB754

Abstract Withdrawn

PUB755

Early Acute Antibody Mediated Rejection in a Simultaneous Liver Kidney Transplant Patient Requiring Bortezomib Therapy Winston A. Ally,[2] Gayle M. Vranic,[2] Karen M. Warburton,[2] Angie G. Nishio-Lucar,[2] Peter I. Lobo,[2] Alden M. Doyle.[1] *[1]University of Virginia, Charlottesvillle, VA; [2]University of Virginia Health System, Charlottesville, VA.*

Background: In simultaneous liver kidney transplantation, the liver is traditionally thought to be protective of the kidney. Herein, we present the case of early acute antibody mediated rejection in a simulatenous liver kidney transplant patient.

Methods: A 61 year old female with a history of hepatitis C cirrhosis and type 2 hepatorenal syndrome on hemodialysis was admitted for deceased donor simultaneous liver kidney transplantation. This was a donation after brain death donor with a positive low level donor specific antibodies (DSA) at the time of transplant (MFI: A68=1487, A24=343, B61=280, B35=269 DR4=3044, DR11=1360, DR52=1243, DR53=544, DQ7=136, DP4=2080). The patient received induction immunosuppression with 1.5 mg/kg rabbit anti-thymocyte globulin, methylprednisolone 500 mg IV and 3 g/kg IVIG (2g/kg in OR and 0.5 g/kg on POD1 and 4). Maintenance immunosuppression included steroid taper and mycophenolate with tacrolimus initiated on POD5. The patient had delayed graft function of the kidney requiring renal replacement therapy (RRT). On POD 11, the kidney allograft biopsy revealed marked peritubular capilliritis and robust C4D staining associated with elevated DSAs (DQ7=9977 on POD 11 vs. 150 on POD4) consistent with antibody mediated rejection. Therapy was initiated including 9 sessions of plasmapheresis followed by IVIG 0.5 g/kg. Although the patient no longer required RRT by POD 35, kidney function remained poor with serum creatinine ranging from 3.1 to 3.9 mg/dl. Repeat biopsy on POD 47 was significant for ongoing antibody mediated rejection, DSAs remained elevated (DQ7=14011 on POD 47 vs. 11500 on POD 40). Due to the lack of response, treatment with four sessions of plasmapheresis and bortezomib therapy (4 doses of 1.3 mg/m^2) was initiated on POD48 with continued improvement in renal allograft function.

Results:

Conclusions: This represents a case of early acute antibody mediated rejection in a simultaneous liver kidney transplant patient non-responsive to extended IVIG/plasmapheresis therapy, now requiring treatment with bortezomib, a proteasome inhibitor targeting plasma cells. Although the liver is thought to be protective in simultaneous liver kidney transplantation, close monitoring and careful consideration of induction therapy as warranted, as this is not always the case.

PUB756

Hemophagocytic Syndrome Associated with Acute Renal Allograft Dysfunction Milagros M. Flores fonseca,[1] Claudia A. Mendoza cerpa,[1] Sandra F. Velasco,[2] Benjamin Gomez-Navarro,[1] Viridiana Rodriguez,[1] Jorge Andrade-Sierra.[1] *[1]Nefrologia y Trasplantes, Centro Medico Nacional de Occidente. Instituto Mexicano de Seguridad Social., Guadalajara, Mexico; [2]Quimica, Universidad de Guadalajara, Guadalajara, Mexico.*

Background: Although there are few reports of hemophagocytic syndrome (HPS) and histoplasmosis infection, we present two cases of renal allografts that developed acute allograft dysfunction.

Methods: **Case 1.** A 31-year-old male with chronic kidney disease (CKD) of unknown etiology, kidney transplant recipient, kidney biopsy with an acute cellular rejection (ACR) 1A receiving IV methylprednisolone, hospitalized with fever and diarrhea, paraclinical exams with pancytopenia, serum creatinine (SCr) 3.7mg/dl, hyperferritinemia, hypertriglyceridemia, hypofibrinogenemia and abdomen tomography showed hepatosplenomegaly. Bone marrow reports sporadic hemophagocytosis (Figure 1). Discontinuing immunosuppresive therapy, followed by amphotericin and itraconazole. He clinically improves, discharged SCr 2.3mg/dl, and restarting immunosuppressive therapy. **Case 2.** A 25-year-old male with CKD of unknown etiology, kidney transplant recipient, kidney biopsy with an ACR 1A receiving thymoglobulin, hospitalized complaining of fever and productive sputum, bicytopenia, SCr 2.2 mg/dl, hyperferritinemia, hypertriglyceridemia, chest tomography with areas of consolidation, and abdominal ultrasound with hepatosplenomegaly. Positive culture for Histoplasma capsulatum. Peripheral blood smear revealed megaloblastic changes and hemophagocytosis. Immunosuppressive therapy was suspended, administer amphotericin and itraconazole. Clinically improving and discharged SCr 1.7 mg/dl.

Results:

Conclusions: We report two cases of HPS with acute allograft dysfunction, followed by ramped up immunosuppressive treatment after ACR episodes, initially unfavorable evolution, discharged patients with a partially recovered renal function. These findings suggests a reasonable management strategy might be discontinued immunosuppressive drugs and considering additional treatment with antifungals, IVIg or high-dose steroids.

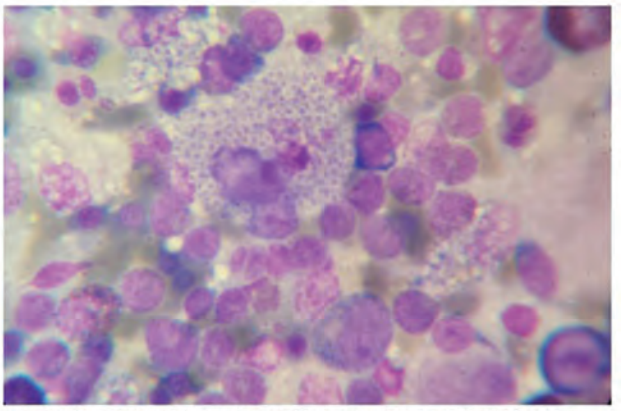


Figure 1: Bone marrow biopsy pronormoblasts with intracytoplasmic inclusions in phagocytes. (Giemsa, 1000×). Case 1.

PUB757

Posttransplant Hypercalcemia Associated with Cryptococcal Pneumonia Katherine I. Lemming,[1] Winston A. Ally,[2] Gayle M. Vranic,[2] Karen M. Warburton,[1] Angie G. Nishio-Lucar,[1] Alden M. Doyle.[1] *[1]University of Virginia Health System, Charlottesville, VA; [2]University of Virginia Health System, Charlottesville, VA.*

Background: Hypercalcemia associated with cryptococcal infections is a rarely reported complication. Herein, a kidney transplant patient with cryptococcal pneumonia who develops significant hypercalcemia post-transplant is presented.

Methods: A 64-year-old male with a history of hypertension, focal segmental glomerulosclerosis, and end-stage kidney disease presented 8 months after successful deceased donor kidney transplant with cough, malaise, and low grade fever. Patient had been maintained on tacrolimus, mycophenolate mofetil, and prednisone with stable kidney allograft function and a baseline creatinine of around 1.7 mg/dl. During his initial posttransplant period he had been maintained on low dose calcitriol with PTH values of 300-500, and serum calcium of 9.5-10.1 and serum phosphorus of 2.2-3.1. Patient was found to have right middle and lower lobe opacities and was started on antibiotics. Work up revealed a positive Cryptococcal antigen (1:160), the diagnosis of Cryptococcal pneumonia was confirmed by bronchoscopy. During his admission, his calcium levels rose. Despite discontinuation of his vitamin D supplementation and administration of IV fluids and furosemide, his calcium level rose to a zenith of 12.9 mg/dl associated with an ionized calcium of 6.9 mg/dl and a marked fall in his PTH levels. His vitamin D 1,25-dihydroxy level was found to be 85 pg/ml. Patient received hydrocortisone, calcitonin, and a single dose of pamidronate with improvement to a current serum calcium level to 10.6.

Results:

Conclusions: Cryptococcal infections are a rare but important cause of posttransplant hypercalcemia that are felt to be related to 1-hydroxylation of vitamin D.

PUB758

Long-Term Outcome after Multimodal Treatment of Kidney Transplant Rejection with Microvascular Injury Ksenija Vucur,[3] Bojana Maksimovic,[3] Zeljka Jurekovic,[3] Danica G. Ljubanovic,[2] Mladen Knotek,[3] Stela Bulimbasic.[1] *[1]University Hospital Center Zagreb, Zagreb, Croatia; [2]University of Zagreb School of Medicine, Clinical Hospital Dubrava, Zagreb, Croatia; [3]Department of Nephrology, University of Zagreb School of Medicine and University Hospital Merkur, Zagreb, Croatia.*

Background: Microvascular injury (MVI) (peritubular capillaritis (ptc) and/or glomerulitis (g) with DSA is common histopathological feature of acute and chronic active AMR, but MVI can also be found in TCR. Some studies reported that MVI was independently associated with graft loss. The aim of the study was to analyze patient (pt) survival, death-censored graft survival, and overall graft survival after treatment of kidney rejection with MVI.

Methods: Retrospective analysis included all pts who had kidney tx (KT) or simultaneous pancreas and kidney tx (SPKT) at Merkur hospital between 2007 and 2016. We found 75 pts (68 KT and 7 SPKT) who had a rejection episode with MVI. 87% KT were from deceased donors. In induction, 75% pts received anti IL-2 receptor antibody, with TAC, MMF ± steroid maintenance.

Results: The mean time from tx to index bx was 1.1±4.1 mos (median 0.3 mos). 64% pts experienced early graft rejection (within 90 d from tx). Index biopsies were classified as: TCR (49%), borderline (28%), and AMR (23%). Cumulative treatment included steroids (79%), plasmapheresis (27%), anti-thymocyte globulin (23%), IVIG (15%), bortezomib (13%), and rituximab (6%). Last follow-up bx after the treatment revealed persisting rejection in 42% pts (borderline 32%, TCR 4%, and AMR 6%). Average number of bx per pt was three. Time from index to last bx was 6.2±9.6 mos (median 3.9 mos). During follow up period of 33.3±27.4 mos pt survival was 93.3%, death-censored graft survival was 78.4%, and overall graft survival was 74.3%. In univariate analysis v-score in the index bx, ptc in the last bx, i-score in the last bx, steroids, and rituximab were associated with death censored graft survival, but none of these factors was found to be significant in multivariate analysis (Tbl).

Conclusions: Neither MVI, nor Banff classification of rejection was independently associated with long-term death-censored graft loss regardless of the onset and the type of the rejection, possibly reflecting effect of a multimodal cumulative rejection treatment pts have received based on follow up bx.

Univariate and multivariate Cox proportional-hazards regression analysis for death-censored graft surival

	Univariate		Multivariate	
Variable	HR (95% CI)	p-value	HR (95% CI)	p-value
v-score	2.1 (1.3-3.5)	0.002	-	-
ptc	1.9 (1.1-3.3)	0.03	-	-
i-score	2.2 (1.3-3.7)	0.003	-	-
steroid tretament	3.1 (1.1-8.8)	0.032	-	-
rituximab treatment	0.1 (0.03-0.4)	< 0.001	-	-

HR = hazard ratio; CI = confidence interval

AUTHOR INDEX

The number refers to the location of the body of the abstract in the publication section

KEYWORD INDEX

The number refers to the location of the body of the abstract in the publication section

SA-OR121

Tolvaptan Slows eGFR Decline in Later-Stage ADPKD Vicente E. Torres,[1] Arlene B. Chapman,[8] Olivier Devuyst,[10] Ron T. Gansevoort,[7] Ronald D. Perrone,[6] Gary G. Koch,[9] John Ouyang,[2] Robert D. Mcquade,[11] Jaime Blais,[4] Frank S. Czerwiec,[3] Olga Sergeyeva.[5] *[1]Mayo Clinic, Rochester, MN; [2]Otsuka Pharm. Dev. & Comm., Rockville, MD; [3]Otsuka Pharma. Devel. & Comm., Inc., Rockville, MD; [4]Otsuka Pharmaceutical Development and Commercialization, Princeton, NJ; [5]Otsuka Pharmaceuticals, Princeton, NJ; [6]Tufts Medical Center, Boston, MA; [7]UMC Groningen, Groningen, Netherlands; [8]University of Chicago, Chicago, IL; [9]University of North Carolina at Chapel Hill, Chapel Hill, NC; [10]University of Zurich, Zurich, Switzerland; [11]Otsuka Pharmaceutical Development and Commercialization Inc, Rockville, MD. Group/Team: REPRISE Trial Investigators.*

Background: In subjects with autosomal dominant polycystic kidney disease (ADPKD) and relatively early disease (estimated creatinine clearance ≥60 mL/min) the vasopressin V2 receptor antagonist tolvaptan slowed kidney growth and estimated glomerular filtration rate (eGFR) decline, but also caused more frequently transaminase and bilirubin elevations. Tolvaptan efficacy and safety in later-stage ADPKD are unknown.

Methods: REPRISE is a phase 3, multi-center, randomized withdrawal, placebo controlled, double-blind trial. After an 8-week pre-randomization period including sequential placebo and tolvaptan treatments, 1,370 ADPKD subjects, 18–55 years with eGFR 25-65 mL/min/1.73 m^2 or 56–65 years with eGFR 25-44 mL/min/1.73 m^2, were randomized 1:1 to tolvaptan or placebo and treated for 12 months. Safety assessments were conducted monthly.

Results: The primary endpoint, annualized eGFR change from pre-treatment baseline to post-treatment follow-up, was -2.34 mL/min/1.73 m^2 with tolvaptan versus -3.61 mL/min/1.73 m^2 with placebo, indicating a 35% reduction in rate of eGFR decline (P<0.001). The secondary endpoint, annualized eGFR slope was -3.16 mL/min/1.73 m^2 versus -4.17 mL/min/1.73 m^2 (P<0.001). Alanine aminotransferase elevations (>3 x upper limit of normal, ULN) occurred in 5.6% or 1.2% of subjects receiving tolvaptan or placebo, respectively. Transaminase elevations were reversible and no subjects showed bilirubin elevations >2 x ULN.

Conclusions: Compared with placebo, tolvaptan slowed eGFR decline by 35% over 1-year in subjects with later-stage ADPKD. While transaminase elevations occurred more frequently with tolvaptan treatment, these were reversible after withdrawal of tolvaptan, without concurrent bilirubin elevation, and none met Hy's laboratory criteria, likely due to more frequent transaminase monitoring and earlier discontinuation.

Funding: Commercial Support - Otsuka Pharmaceuticals

SA-OR122

Bardoxolone Methyl Improved GFR Measured by Standard Inulin Clearance: The TSUBAKI Study Masaomi Nangaku,[1] Ryutaro Shimazaki,[2] Tadao Akizawa.[3] *[1]the University of Tokyo School of Medicine, Tokyo, Japan; [2]Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan; [3]Showa University School of Medicine, Tokyo, Japan.*

Background: Bardoxolone methyl (BARD), an Nrf2 activator, consistently and significantly increased the estimated glomerular filtration rate (eGFR) in multiple clinical studies in patients with diabetic kidney disease (DKD). A prior Phase 3 study (BEACON) was terminated prematurely due to early-onset fluid overload, however, post-hoc analyses identified risk factors for fluid overload. We have therefore conducted a study that excluded at-risk DKD patients, known as the TSUBAKI study. In the study, we used the inulin clearance method, which is the gold standard for measuring GFR, to determine if changes in eGFR were reflective of true changes in GFR.

Methods: This was a randomized, double-blind, placebo-controlled, multi-center Phase 2 trial in patients with stages G3 and G4 DKD without identified risk factors for fluid overload such as baseline BNP > 200 pg/ml and prior history of heart failure. Patients were administered BARD or placebo with a titration scheme from 5 to 15 mg orally once daily for 16 weeks. Primary efficacy endpoint was the change in GFR measured by standard inulin clearance after 16 weeks of treatment in patients with stage G3 in a pre-specified interim analysis. The safety of BARD was evaluated in patients with both stages.

Results: A total of 120 patients with stages G3 and G4 were treated. In patients with stage G3, 85 patients were randomly assigned to either BARD or placebo with a 1:1 allocation; three patients discontinued before treatment started. GFR was evaluated in 40 patients (BARD: n=17; placebo: n=23). The mean eGFR and GFR at baseline were 46.7 (32.9 to 58.8) and 48.5 (27.9 to 64.8) ml/min/1.73 m^2, respectively. A significant improvement in GFR was seen in the BARD compared to the placebo group (6.6 ml/min/1.73 m^2, p=0.008). Data also showed that BARD significantly improved eGFR compared to placebo. In patients with stage G4, all 38 patients completed their treatment period. For patients with both stages, BARD was well tolerated, and no signs or symptoms of fluid overload were observed.

Conclusions: BARD improved renal function assessed by inulin clearance. The results suggest among preselected patients, BARD may yield significant treatment benefits without safety concerns.

SA-OR123

Kidney Injury After Intravenous or Intracoronary Contrast Agents for Noninvasive or Invasive Coronary Angiography: An Industry-Independent, Phase 3, Randomized Controlled Trial Marc Dewey,[1] Peter Martus,[2] Maria Bosserdt,[1] Elke Zimmermann,[1] Michael Laule,[1] Eva Schönenberger.[1] *[1]Charité, Berlin, Germany; [2]UKT Tübingen, Tübingen, Germany. Group/Team: CAD-Man Study Group.*

Background: X-ray contrast agents can have nephrotoxic effects, while it is unknown whether acute kidney injury is more likely after intracoronary or intravenous administration of these agents and whether contrast-induced acute kidney injury is associated with impaired chronic kidney function.

Methods: In this randomized controlled trial, patients with suspected coronary artery disease were recruited. Patients without known coronary artery disease and a clinical indication for invasive coronary angiography (ICA) based on atypical chest pain were eligible. Patients were randomly assigned (1:1) to ICA with intracoronary contrast or coronary computed tomography angiography (CTA) with intravenous contrast. The same low-osmolar non-ionic contrast agent was used for ICA and CTA. The primary outcome of this analysis was contrast-induced acute kidney injury within 3 days following contrast agent administration defined as an increase in serum creatinine of ≥0.5 mg/dL or 25% after 18-24 hours or 46-50 hours. Laboratory investigators were masked to randomization group.

Results: Between February 18, 2009, and August 2, 2015, 162 and 165 patients were randomly assigned and underwent ICA and CTA. Follow-up creatinine after 18-24 hours or 46-50 hours was available for 159 patients (98%) in the ICA group and 161 (98%) in the CTA group. Baseline estimated glomerular filtration rates were not significantly different between patients in the CTA (84.3±17.2 mL/min/1.73 m^2) and the ICA group (87.1±16.7 mL/min/1.73 m^2; p=0.14). There were 30 cases of contrast-induced acute kidney injury overall: 9 in the CTA group (6%, 95% CI 3-10%) and 21 in the ICA group (13%, 95% CI 8-19%, p=0.023; OR 2.57, 95% CI 1.14-5.80). Long-term serum creatinine follow-up was available in 97% of patients (311 of 320) after a median duration of 1.9 years, and a greater proportion of patients with acute kidney injury still had increased creatinine (38%) compared with those without acute kidney injury (6%; p<0.001).

Conclusions: In patients with suspected coronary artery disease, acute kidney injury seems to be less likely after intravenous than after intracoronary contrast agent administration and contrast-induced acute kidney injury was associated with impaired chronic kidney function.

Funding: Government Support - Non-U.S.

SA-OR124

Efficacy and Safety of QPI-1002 (QPI) for Prevention of AKI Following Cardiac Surgery David Corteville,[5] Robert J. Still,[9] Gabor Szabo,[7] Madhav Swaminathan,[3] Vasant Jayasankar,[1] Andre Lamy,[6] Lukas J. Lehner,[10] Matthias Thielmann,[8] Craig D. Brown,[4] Ec Squiers,[2] U Schwertschlag,[2] A Potts,[2] A Patel,[2] E K. Messersmith,[2] D Rothenstein,[2] D J. Odenheimer,[2] S Erlich.[2] *[1]Cardiothoracic and Vascular Surgical Assoc, Jacksonville, FL; [2]Quark Pharmaceuticals, Inc., Fremont, CA; [3]Duke University Medical Center, Durham, NC; [4]New Brunswick Heart Centre, Saint John, NB, Canada; [5]McLaren Northern Michigan, Petoskey, MI; [6]McMaster University, Hamilton, ON, Canada; [7]University of Heidelberg, Heidelberg, Germany; [8]West-German Heart and Vascular Center Essen, University Duisburg-Essen, Essen, Germany; [9]JCCR, Jacksonville, FL; [10]Department of Nephrology and Medical Intensive Care, Charité - Universitätsmedizin Berlin, Berlin, Germany. Group/Team: QRK209 AKI Study Group.*

Background: QPI, a siRNA targeting p53, is being developed for prevention of Delayed Graft Function (DGF) following renal transplantation (ReGIFT Phase 3 Study, NCT#02610296) and for acute kidney injury (AKI). AKI is a major complication of cardiac surgery (CS) that increases morbidity and mortality. No treatments are approved for the prevention of AKI following CS.

Methods: The efficacy and safety of QPI, was studied in a global Phase 2 double-blind study (N=341: QPI=165, Placebo (PL)=176) undergoing CS at 41 sites (NCT#02610283). Subjects undergoing non-emergent CS at risk for AKI were enrolled (risk factors included: Age ≥ 70 years; eGFR ≤ 60 mL/min/1.73m^2, diabetes, proteinuria, congestive heart failure). Subjects were stratified by eGFR (≥ vs < 60mL/min/1.73m^2). A single IV dose of either QPI (10mg/kg) or PL was given 4 hours post-CS. Safety assessments included clinical and laboratory exams and adverse events (AEs). Efficacy endpoints included the rate of AKI determined by serum creatinine according to AKIN (primary), RIFLE and KDIGO (secondary) criteria assessed through Day 5. Secondary endpoints also included duration and grade of AKI, and the composite of death, renal replacement therapy (RRT) and 25% reduction of eGFR at Day 90.

Results: Demographics and AE profiles were similar between treatment groups and consistent with CS. QPI treatment resulted in a 26% relative risk reduction (RRR) of AKI (AKIN): (37% QPI vs. 50% PL; p=0.020). Risk reductions were consistently observed across predefined populations (age, diabetes, CS type, gender, baseline eGFR). Treatment with QPI improved AKI across all AKIN grades (by 18%–61%; p=0.012). Duration of AKIN AKI from Days 0-5 was shorter with QPI (p=0.013). QPI significantly impacted AKI incidence, grade and duration by RIFLE and KDIGO criteria. The composite of Death, RRT and Reduction of eGFR by 25% at Day 90 favored QPI in a subpopulation (N=241) with either proteinuria, and/or low base line eGFR, and/or diabetes, (37% QPI vs 51% PL; RRR=29%; p=0.024).

Conclusions: In this study, QPI reduced the incidence, grade and duration of AKI in high risk subjects following CS. Further development of QPI for the prevention of AKI is warranted.

Funding: Commercial Support - Quark Pharmaceuticals, Inc.

SA-OR125

The Pivotal Multicenter Trial of Ultrasound Guided Percutaneous Arteriovenous Fistulae for Hemodialysis Access Jeffrey E. Hull,[1] William C. Jennings,[2] Randy I. Cooper,[3] Umar Waheed,[3] Matthew E. Schaefer,[4] Rajeev Narayan.[4] *[1]Richmond Vascular Center, North Chesterfield, VA; [2]Univ OK Med Col, Tulsa OK, Tulsa, OK; [3]Southwest Kidney Institute, PLC, Tempe, AZ; [4]San Antonio Kidney Disease Center, San Antonio, TX.*

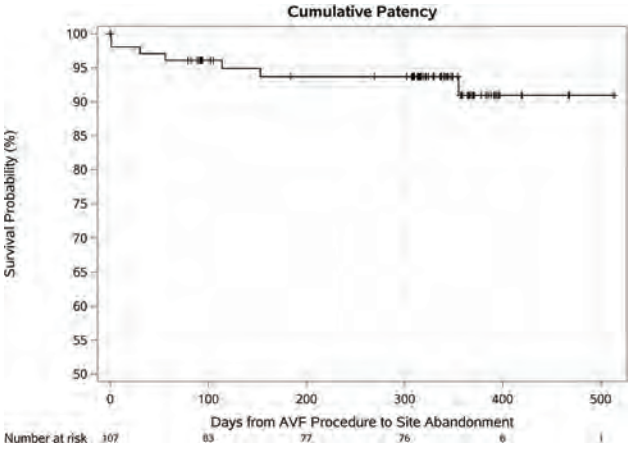
Background: Arteriovenous fistulae for hemodialysis are usually created by a surgical procedure. Percutaneous creation of an arteriovenous fistulae with a thermal resistance anastomosis device (TRAD) in an office based vascular center is emerging as an alternative to surgery.

Methods: One hundred seven patients were enrolled in a prospective, non-inferiority trial at 5 sites. Patients underwent ultrasound guided anastomosis creation between the proximal radial artery and perforating vein with the Ellipsys® Vascular Access System followed by seperate maturation procedures. All procedures were performed in outpatient vascular centers. The primary endpoints were brachial artery flow volume ≥ 500 mL/min and vein diameter ≥ 4 mm in > 49% of patients, and absence of device related complications at 90 days.

Results: Arteriovenous fistulae with fused anastomoses were created in 95% (102/107) patients. Maturation procedures included anastomotic balloon dilation in 72% (77/107), brachial vein embolization in 32% (34/107), cubital vein ligation in 27% (29/107), and surgical transposition in 26% (28/107). The primary flow and diameter endpoints were achieved in 86.0% (92/107) of the patients exceeding the performance goal of 49% ($p < 0.0001$). There were no major adverse events attributed to the device. Cumulative patency was 96.1%, 93.7%, 91.0 % at 90, 180, and 360 days, respectively. The target dialysis vein was the cephalic, basilic, and brachial veins in 74% (73/99), 24% (24/99), 2% (2/99), respectively. 2-needle dialysis was achieved in 88% (71/81) of patients on hemodialysis at a mean 113.1 ± 72.0 days. Functional patency was 98.4%, 98.4%, and 92.3% at 90, 180, and 360 days, respectively.

Conclusions: The Ellipsys® Vascular Access System met the primary safety, and efficacy endpoint goals in the United States pivotal trial.

Funding: Commercial Support - Avenu Medical Inc.



SA-OR126

Primary Results of the Time to Reduce Mortality in End-Stage Renal Disease (TiME) Trial: A Pragmatic Trial Demonstration Project of the NIH Health Care Systems Research Collaboratory Laura M. Dember,[12] Eduardo K. Lacson,[9] Steven M. Brunelli,[2] Jesse Y. Hsu,[11] Alfred K. Cheung,[14] John T. Daugirdas,[10] Tom Greene,[14] Csaba P. Kovesdy,[13] Dana Miskulin,[8] Ravi I. Thadhani,[5] Wolfgang C. Winkelmayer,[1] Allen R. Nissenson,[3] Franklin W. Maddux,[4] Michael F. Flessner,[6] Kevin C. Abbott,[7] J. R. Landis.[11] *[1]Baylor College of Medicine, Houston, TX; [2]DaVita Clinical Research, Needham, MA; [3]DaVita Healthcare Partners Inc., El Segundo, CA; [4]Fresenius Medical Care, Waltham, MA; [5]Massachusetts General Hospital, Boston, MA; [6]NIDDK, NIH, Bethesda, MD; [7]The National Institutes of Health, NIDDK, Bethesda, MD; [8]Tufts Medical Center, Sommerville, MA; [9]Tufts University School of Medicine, Boston, MA; [10]University of Illinois College of Medicine, Burr Ridge, IL; [11]University of Pennsylvania, Philadelphia, PA; [12]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [13]University of Tennessee Health Science Center, Memphis, TN; [14]University of Utah, Salt Lake City, UT. Group/Team: TiME Trial Study Group.*

Background: Observational studies of patients receiving maintenance hemodialysis suggest that mortality is lower with dialysis sessions longer than 4 hours but this hypothesis has not been evaluated in a randomized trial, and broad acceptability of longer treatments has not been established.

Methods: Cluster-randomized trial fully embedded in clinical care delivery with no on-site research staff or primary data collection. 266 dialysis units operated by two US dialysis providers were randomized to Intervention or Usual Care. Intervention units were to adopt a default hemodialysis session duration of ≥4.25 hours (255 minutes) for incident patients. Usual Care units had no trial-driven approach to duration. The primary outcome was mortality. The major secondary outcome was hospitalization rate.

Results: 7035 incident patients highly representative of the US dialysis population were enrolled between 12/18/13 and 9/30/16. The trial was discontinued at a median follow-up of 1.1 years after an interim analysis showed a smaller than targeted group difference in session duration and no difference in outcomes. For the primary analysis population (patients with Watson V≤42.5L), per-patient mean session durations were 219 and 210 minutes for Intervention and Usual Care, respectively, and there was no difference in mortality (HR 0.97, 95% CI 0.84, 1.12; p=0.69) or hospitalization rate (204 vs 213 per 100 patient-yrs, p=0.44). Findings were similar for the full analysis population (all patients).

Conclusions: A partnership between academic investigators and multiple dialysis providers and a highly pragmatic design resulted in successful and efficient participant enrollment, data acquisition, and trial monitoring but uptake of the intervention was insufficient to determine whether longer hemodialysis sessions improve clinical outcomes. The TiME trial results demonstrate feasibility of several aspects of large-scale pragmatic trials in dialysis. However, effective strategies for engaging clinicians and patients are required to evaluate interventions fully incorporated into routine care delivery. NCT02019225

Funding: NIDDK Support, Other NIH Support - NIH Common Fund

SA-OR127

A Multi-Center Randomized Controlled Trial of Rituximab versus Cyclosporine in the Treatment of Idiopathic Membranous Nephropathy (MENTOR) Fernando C. Fervenza,[4] Pietro A. Canetta,[7] Sean Barbour,[13] Richard A. Lafayette,[10] Brad H. Rovin,[9] Nabeel Aslam,[6] Michelle A. Hladunewich,[16] Heather N. Reich,[11] Paul E. Brenchley,[3] Debbie S. Gipson,[15] Matthias Kretzler,[12] Jai Radhakrishnan,[2] Lee A. Hebert,[8] Patrick E. Gipson,[15] Leslie F. Thomas,[5] Ellen T. McCarthy,[14] Gerald B. Appel,[1] J. Ashley Jefferson,[17] Nelson Leung,[4] Daniel C. Cattran.[11] *[1]Columbia University College of Physicians and Surgeons, Scarsdale, NY; [2]Columbia University Medical Center, New York, NY; [3]Manchester Royal Infirmary, Manchester, United Kingdom; [4]Mayo Clinic, Rochester, MN; [5]Mayo Clinic Arizona, Phoenix, AZ; [6]Mayo Clinic Florida, Jacksonville, FL; [7]None, New York, NY; [8]Ohio State University Medical Center, Columbus, OH; [9]Ohio State University Wexner Medical Center, Columbus, OH; [10]Stanford University, Stanford, CA; [11]Toronto General Hospital, Toronto, ON, Canada; [12]U.Michigan, Ann Arbor, MI; [13]University of British Columbia, Vancouver, BC, Canada; [14]University of Kansas Medical Center, Kansas City, KS; [15]University of Michigan, Ann Arbor, MI; [16]University of Toronto, Toronto, ON, Canada; [17]University of Washington, Seattle, WA.*

Background: Membranous nephropathy (MN) remains the leading cause of nephrotic syndrome in Caucasian adults. Cyclosporine (CSA) is successful in reducing proteinuria, but its use is associated with a high relapse rate. Rituximab (RTX) is effective in reducing proteinuria but whether RTX is as effective as CSA in inducing and maintaining complete (C) or partial remission (PR) of proteinuria in MN is unknown. The MENTOR trial hypothesized that B-cell targeting with RTX is non-inferior to CSA in inducing long-term remission of proteinuria.

Methods: Patients with proteinuria ≥5g/24h, estimated GFR ≥ 40 ml/min/1.73m2 and ≥3-months of AII blockade were randomized into a 12-month treatment period with IV RTX, 1000 mg (2 infusions, 14 days apart; repeated at 6 months if proteinuria reduction >25% at 6-months or oral cyclosporine 3.5-5mg/kg/day for 6-months (continued for another 6-months if a substantial reduction in proteinuria (equal to or >25%) is seen at 6-months). Treatment efficacy was assessed by an intention-to-treat analysis of remission status (C or PR) at 24-months post-randomization. At the 6-month post-randomization, patients who did not have proteinuria reduction ≥25% were considered treatment failures and exit the study. Follow up was at 3, 6, 9, 12, 18 and 24 months, and included quantification of creatinine clearance, serum albumin, 24h proteinuria, anti-PLA2R antibodies levels as well as quality of life assessment.

Results: One hundred and eighty one were screened and 130 patients (mean age 52 ± 12.4 SD; 76.9% male) were randomized. Mean BP 125/76 ± 14 mmHg. Median SCr 1.2 mg/dl (range 0.5-2.5), serum albumin 2.6 g/dl (range 1.6-4.1), proteinuria 10.3 g/24h (range 8.9-27-5).

Conclusions: Last patient randomized was September 2015 and follow-up will be completed on 9/11/2017. We guarantee that will be able to present preliminary results by the time of the ASN.

Funding: Commercial Support - Genentech Inc, South San Francisco, CA, Private Foundation Support

FR-PO1053

Initial Data Report from "CARDINAL": A Phase 2/3 Study of Bardoxolone Methyl in Patients with Alport Syndrome Geoffrey A. Block,[1] Pablo E. Pergola,[2] Lesley Inker,[3] Peter A. McCullough,[4] Melanie Chin,[5] Colin J. Meyer,[5] Michelle N. Rheault,[6] Clifford E. Kashtan,[6] David G. Warnock.[7] *[1]Denver Nephrology, Denver, CO; [2]Renal Associates PA, San Antonio, TX; [3]Tufts Medical Center, Boston, MA; [4]Baylor University Medical Center, Dallas, TX; [5]Reata Pharmaceuticals, Irving, TX; [6]University of Minnesota, Minneapolis, MN; [7]UAB, Birmingham, AL.*

Background: In previous studies that enrolled over 2,600 patients, primarily including patients with CKD caused by type 2 diabetes, bardoxolone methyl (BARD) improved estimated GFR (eGFR) and inulin clearance. A Phase 2/3 trial (CARDINAL, NCT03019185) was initiated to test the hypothesis that BARD will improve eGFR in patients with Alport syndrome (AS).

Methods: The Phase 2 open-label portion of the study was designed to enroll 30 patients on stable RAAS blockade, ages 12 to 60 years, with confirmed diagnosis of AS, eGFR values from 30 to 90 mL/min/1.73 m^2 [calculated using CKD-EPI or Bedside Schwartz (age < 18 years) equations], and urinary albumin to creatinine ratio (UACR) ≤ 3500 mg/g. Patients received BARD at 5 mg, to dose-escalate as tolerated to 10 mg at Week 2, 20 mg at Week 4, and for patients with baseline UACR > 300 mg/g, to 30 mg at Week 6. The primary efficacy endpoint was change from baseline in eGFR after 12 weeks of treatment. Interim results are described herein.

Results: 30 patients were enrolled (mean age 44 years, 60% female, 73% X-linked AS). Data were extracted after the first 8 patients had received 12 weeks of treatment. From a mean baseline eGFR of 54.7 mL/min/1.73 m^2, treatment with BARD produced mean improvements of 6.9 mL/min/1.73 m^2 at Week 4 (n=19; p<0.0005), which further increased to 12.7 mL/min/1.73 m^2 at Week 12 (n=8; p<0.00005), as of July 24th, 2017. Over 80% of patients demonstrated clinically meaningful improvement in eGFR of at least 3.0 mL/min/1.73 m^2 by Week 8. eGFR improvements were associated with mean decreases in BUN, uric acid, and phosphorous. Median UACR increased, however, UACR/eGFR ratios were unchanged from baseline. Blood pressure was unchanged. The most commonly reported adverse event (AE) was muscle spasms, which were generally mild to moderate in severity, with no laboratory evidence of muscle toxicity. No patients have discontinued from the study and no serious AEs have been reported so far, in this ongoing trial.

Conclusions: BARD was generally well tolerated and improved kidney function in patients with AS. The Phase 3 double-blind, randomized, placebo-controlled portion of the trial that will enroll up to 150 patients has been initiated.

Funding: Commercial Support - Reata Pharmaceuticals

FR-PO1054

A Phase 1/2 Trial of ALN-GO1: An Investigational RNAi Therapeutic for Primary Hyperoxaluria Type 1 Yaacov Frishberg,[1] William van't Hoff,[2] Sally Hulton,[3] Patrick Haslett,[4] David V. Erbe,[4] Tracy Mcgregor,[4] Georges Deschênes.[5] *[1]Shaare Zedek Medical Center, Jerusalem, Israel; [2]Great Ormond Street Hospital, London, United Kingdom; [3]Birmingham Childrens' Hospital, Birmingham, United Kingdom; [4]Alnylam Pharmaceuticals, Cambridge, MA; [5]Hospital Robert Debre, Paris, France.*

Background: In Primary Hyperoxaluria Type 1 (PH1) alanine-glyoxylate aminotransferase deficiency leads to excessive hepatic oxalate production. This results in nephrocalcinosis, recurrent calcium oxalate stones, and progressive renal impairment, ultimately with multi-organ damage from systemic oxalosis. ALN-GO1 is an investigational RNAi therapeutic which suppresses hepatic glycolate oxidase, decreasing the conversion of glycolate to glyoxylate, a required substrate for oxalate production. Previously released study data from healthy adult volunteers showed that single dose ALN-GO1 was well tolerated with dose-dependent elevations in plasma glycolate. Here we report initial outcomes of patients with PH1 in the Phase 2 portion of the study.

Methods: This randomized, placebo controlled, single blind, multicenter trial is ongoing (ClinicalTrials.gov: NCT02706886). To be eligible, patients with PH1 must have urinary oxalate ≥0.7 mmol/24h/1.73m^2 and eGFR >45 ml/min/1.73m^2. One of four patients in each cohort is randomized to 3 doses of placebo prior to dosing with ALN-GO1. The first cohort received 1 mg/kg ALN-GO1 subcutaneously every 28 days x 3 doses, with the second cohort receiving 3 mg/kg ALN-GO1. The primary endpoint is safety, and secondary endpoints include change in 24 hour urinary oxalate excretion from baseline.

Results: ALN-GO1 has demonstrated acceptable safety and tolerability to date with no treatment related serious adverse events or discontinuations from the study. Preliminary results reveal that all three patients randomized to ALN-GO1 in the first cohort experienced >50% decrease in urinary oxalate excretion from baseline. Two of the three patients achieved levels within the normal range. The patient randomized to placebo in the first cohort shows a similar trend after initial dosing with ALN-GO1. Data from the second cohort are forthcoming.

Conclusions: ALN-GO1 is an investigational RNAi therapy which has been well tolerated while showing promising activity in lowering urinary oxalate excretion in patients with PH1. These preliminary data support continued development of ALN-GO1 as a potential therapeutic approach to alleviating the pathologic overproduction of oxalate in this devastating disease.

Funding: Commercial Support - Study funded by Alnylam Pharmaceuticals

FR-PO1055

Abstract Withdrawn

FR-PO1056

IV Cyclophosphamide vs Tacrolimus and Azathioprine as Induction in Proliferative Lupus Nephritis: A Randomized Controlled Trial Arpita Roychowdhury,[2] Dipankar Sircar.[1] *[1]IPGMER, SSKM HOSPITAL, KOLKATA, India; [2]Nephrology, IPGMER, Kolkata, India.*

Background: Therapy for proliferative lupus nephritis is limited to cyclophosphamide or mycophenolate as induction regimens. We present a randomized controlled trial of a regimen comprising of tacrolimus, azathioprine and steroids compared to IV cyclophosphamide and steroids for induction of lupus nephritis.

Methods: Patients of lupus nephritis (classes III, IV, V+III or V+IV), age 15-60 years were included. Exclusion criteria included patients with biopsy proven class IIIC/IV C lupus nephritis, an estimated glomerular filtration rate (eGFR) of <30ml/min/1.73m^2, severe infections or contraindications to any drugs. All patients received 3 pulses of methylprednisolone (500 mg). Subsequently, prednisolone was given at doses of 0.5 mg/kg/day and tapered. The Triple Drug regimen group received tacrolimus (0.075 mg/kg; trough 5-10 ng/ml) and azathioprine (2mg/kg). The control group received IV cyclophosphamide, 500 mg/m^2 monthly. All patients received hydroxychloroquine. The primary end point was achievement of complete renal remission. Secondary end points included decrease of proteinuria, decrease in disease activity scoring(SLEDAI Score) and incidence of severe adverse events.

Results: 137 patients were screened and 92 patients were randomly assigned to both arms and of them 65 completed the study for first 6 months induction phase. There were 33 patients in group 1and 32 patients in group 2. Complete remission occurred in 22/33 patients in the triple drug group and 22/32 patients in the IV Cyc group (p=0.857). Secondary end points were also similar between treatment groups- Group1 & Group2. Major infective complications requiring hospital admission in the Group1 (2/33) were less in number than in group 2 (5/32) had significant adverse effect but it did not reach significance (p= 0.183)

Conclusions: The novel triple therapy comprising of TAC-AZA-PRED as induction therapy in proliferative lupus nephritis is comparable to IV cyclophosphamide with respect to efficacy and safety.

Funding: Government Support - Non-U.S.

Triple drug regimen vs IV Cyc

	Tac-Aza:baseline	Cyc Baseline	P value	Tac aza 6 months	Cyc 6months	p value
SLEDAI	16.60±6.09	19.78±7.80	0.066	3.20±3.77	1.96±2.66	0.144
24 Hr urine protein (g/day)	2.658±1.623	3.249±2.212	0.214	0.388±0.441	0.530±0.631	0.417
Serum creatinine (mg/dl)	1.003±0.436	1.062±0.408	0.571	0.886±0.415	0.829±0.366	0.559
C3 (mg/dl)	63.53±32.06	57.99±32.38	0.488	96.29±26.52	116.65±28.18	0.007
Response (present)				22/33	22/32	0.857

All figures are mean ± standard deviation

FR-PO1057

Rituximab (RTX) Treatment of Fibrillary Glomerulonephritis (FGN): A Pilot Study Stephen B. Erickson,[1] Mariam P. Alexander,[2] Samih H. Nasr,[2] Fernando C. Fervenza.[1] *[1]Division of Nephrology, Mayo Clinic, Rochester, MN; [2]Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN.*

Background: FGN is a rare glomerular disease for which no standard treatment is available. Renal survival is poor with nearly 50% of patients progressing to ESRD within 4 yrs.

Methods: We recruited 11 patients with biopsy proven idiopathic FGNs into an open-label study testing the efficacy of RTX in reduction of proteinuria and preservation of kidney function. Patients' age ranged from 35 to 77 yrs, mean 58.5. Eight were females. All patients received 2 doses of RTX 1 gm each, at day 1 and day 14 with identical retreatment at 6 mos. Prespecified end points included 24 hr creatinine clearance (CrCl) and proteinuria at 12 mos. A logarithmic transformation was applied to CrCl values at each time point prior to comparing the values using a paired t-test. No serious adverse events.

Results: All patients completed 12 mos of the study. There was no significant change in CrCl: 47.73 (SD 24.02) at baseline, 43.73 (SD 23.08) ml/min/SA at 12 mos, p=0.21 [Fig 1]. Proteinuria decreased from 3824.7 (SD 1468.8) to 2650.5 (SD 1692.2) mg/24h, or nephrotic to non-nephrotic p=0.068. A subgroup of 3 (27%) patients had a dramatic response[Fig 2]. CD-19 B cells, the RTX target, dropped from an avg of 158.9 cells/mcL pre-RTX to nearly 0 at day 28 post-RTX. With the exception of patients 1 and 6 who had rebound by day 180 after both RTX treatments, all patients remained CD-19 cell depleted throughout the study.

Conclusions: Following 4 doses of RTX, patients had stable renal function. There was a tendency for proteinuria to decrease although it did not quite meet statistical significance(p= 0.068). A subgroup of patients showed remarkable reduction in proteinuria. For a previously untreatable disease, this is good news.

Funding: Commercial Support - Genentech

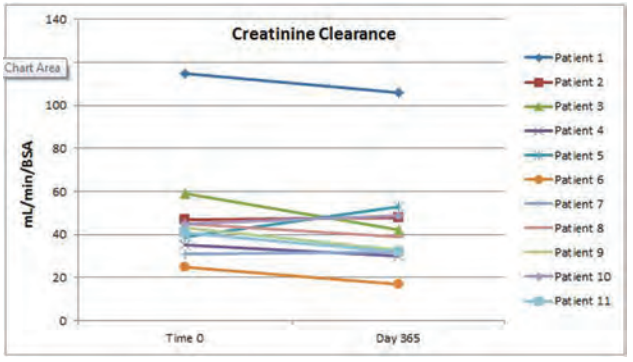


Figure 1

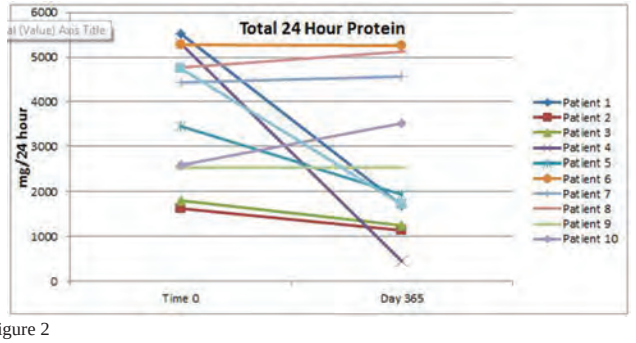


Figure 2

FR-PO1058

Canagliflozin and Renal Outcomes in Type 2 Diabetes: Data from the CANVAS Program Vlado Perkovic,[1,2] Dick de Zeeuw,[3] Kenneth W. Mahaffey,[4] Greg Fulcher,[2] Ngozi Erondu,[5] Wayne Shaw,[5] Terrance D. Barrett,[5] Michele Weidner-Wells,[5] Hsiaowei Deng,[5] Norm Rosenthal,[5] Mehul Desai,[5] David R. Matthews,[6] Bruce Neal.[1] *[1]The George Institute for Global Health, UNSW Sydney, Sydney, NSW, Australia; [2]The Royal North Shore Hospital and University of Sydney, Sydney, NSW, Australia; [3]University of Groningen, University Medical Center Groningen, Groningen, Netherlands; [4]Stanford Center for Clinical Research (SCCR), Stanford University, Department of Medicine, Stanford, CA; [5]Janssen Research & Development, LLC, Raritan, NJ; [6]University of Oxford, Oxford, United Kingdom. Group/Team: CANVAS Program collaborative group.*

Background: Canagliflozin (CANA) is an SGLT2 inhibitor that may have beneficial effects on the kidney in people with diabetes. The effects of CANA on prespecified renal outcomes in people with type 2 diabetes (T2D) and an elevated risk of cardiovascular (CV) disease were assessed in the CANagliflozin cardioVascular Assessment Study (CANVAS) Program.

Methods: The CANVAS Program consists of 2 double-blind, randomized trials conducted in 10,142 people with T2D and elevated CV risk (defined by the presence of documented CV disease or ≥2 risk factors), who received CANA (pooled analysis of 100 and 300 mg doses) or matching placebo (PBO). The prespecified exploratory renal outcomes were changes in urinary albumin:creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), and composite clinical outcomes.

Results: At baseline, median UACR was 12.3 mg/g and mean eGFR was 76.5 mL/min/ 1.73 m^2. Urinary albumin excretion was 18% lower in participants treated with CANA versus PBO overall (95% CI 16%-20%), and 34% (95% CI 29%-38%) and 36% (95% CI 28%-43%) lower in participants with micro- and macroalbuminuria, respectively. Annual rate of eGFR decline was also reduced (difference 1.31 mL/min/1.73 m^2/year, 95% CI 1.15-1.48). The composite outcome of end-stage kidney disease, doubled serum creatinine, or renal death occurred less frequently in the CANA group (hazard ratio 0.53, 95% CI 0.33-0.84). Rates of renal adverse events were similar with CANA and PBO.

Conclusions: CANA reduced urinary albumin excretion, slowed eGFR decline, and reduced the risk of substantial loss of kidney function.

Funding: Commercial Support - Janssen Research & Development, LLC

FR-PO1059

Vascular Adhesion Protein-1 Inhibitor (VAP-1i) Reduces Albuminuria in Diabetic Kidney Disease Dick de Zeeuw,[2] Ronny Renfurm,[1] Tobias E. Larsson.[1] *[1]Astellas Pharma Europe B.V., Leiden, Netherlands; 2University Medical Center Groningen, Groningen, Netherlands. Group/Team: ALBUM investigators.*

Background: Many diabetic kidney disease (DKD) patients treated with Angiotensin Converting Enzyme inhibitors (ACEi) or Angiotensin Receptor Blockers (ARB) have residual albuminuria and high risk for disease progression. We investigated the efficacy of a novel and specific VAP-1i, ASP8232, for reducing albuminuria on top of ACEi or ARB treatment in DKD. VAP-1 is an amine-oxidase with pro-inflammatory and pro-oxidative stress actions that is elevated and predicts cardiovascular risk in diabetes.

Methods: ALBUM was a randomized, double-blind, placebo-controlled, Phase 2 study in 45 European centers, enrolling 125 patients with type 2 diabetes and DKD. Inclusion criteria included Urinary Albumin Creatinine Ratio (UACR) ≥200 mg/g, eGFR 25-75 ml/min/1.73 m^2, and stable ACEi or ARB and anti-diabetic treatment for ≥3 months. After a 5-week screening/run-in, patients were randomized to ASP8232 40mg or placebo once daily for 12 weeks. Primary endpoint was change from baseline to end of treatment in first morning void (FMV) UACR. Secondary endpoint was change in 24-h albuminuria. A sample size of 110 was sufficient to detect 30% UACR reduction vs placebo with 80% power at a significance level of 5%.

Results: Of 406 patients screened, 125 were randomized and 120 were included in the analysis. Mean age was 69 yr, BMI 32 kg/m^2, HbA_{1c} 7.5%, BP 139/75 mmHg, eGFR 39.7 ml/min/1.73m^2, UACR 715 mg/g. Randomization was balanced. Use of ACEi (48.3% vs 53.3%), ARB (50.0% vs 43.3%), and combination (1.7% vs 3.3%) therapy was similar among ASP8232 vs placebo groups, respectively. Effects of ASP8232 vs placebo are shown in the table. ASP8232 reduced $UACR_{FMV}$ by 19.5% (p=0.033), $albuminuria_{FMV}$ by 26% (p=0.004), and 24h albuminuria by 20.0% (p=0.094). Reduction in UACR of ≥30% was observed in 37% of ASP8232 vs 22% of placebo patients (p=0.109). ASP8232 was safe and well tolerated; no serious drug-related adverse events were reported.

Conclusions: The VAP-1i ASP8232 yielded a clinically meaningful reduction of residual albuminuria in patients with DKD on stable ACEi/ARB treatment compared with placebo after 12 weeks of treatment.

Funding: Commercial Support - Astellas Pharma Inc

	ASP8232 Baseline	ASP8232 12 weeks	Placebo Baseline	Placebo 12 weeks	ASP8232 vs Placebo
UACR (mg/g) (geometric mean)	745	617	687	721	P=0.033
BP (mmHg)	139.6/75.4	141.9/73.7	138.7/75.0	140.5/75.9	P=0.974/0.116
Weight (kg)	92.8	92.7	94.7	95.2	P=0.926
$eGFR_{cystatinC}$ (ml/min/1.73m^2)	38.8	35.8	40.6	39.7	P=0.009

FR-PO1060

Abstract Withdrawn

FR-PO1061

Abstract Withdrawn

FR-PO1062

A Multicentre, Stepped-Wedge Cluster Randomised Trial of a Complex Intervention to Reduce Harm Associated with AKI Nicholas M. Selby,[6,8] Anna Casula,[5] Laura Lamming,[9] John Stoves,[3] Yohan P. Samarasinghe,[2] Andrew J. Lewington,[4] Russell Roberts,[3] Nikunj Shah,[1] Richard J. Fluck,[8] Mel J. Johnson,[7] Natalie Jackson,[7] Carol A. Jones,[1] Fergus J. Caskey.[5] *[1]Ashford & St Peters Hospitals NHS Foundation Trust, Chertsey, United Kingdom; [2]Frimley Park Hospital, Camberley, United Kingdom; [3]Bradford Teaching Hospitals NHS Foundation Trust, Bradford, United Kingdom; [4]Leeds Teaching Hospitals, Leeds, United Kingdom; [5]UK Renal Registry, Bristol, United Kingdom; [6]Centre for Kidney Research and Innovation, University of Nottingham, Nottingham, United Kingdom; [7]Yorkshire & Humber Improvement Academy, Bradford, United Kingdom; [8]Department of Renal Medicine, Royal Derby Hospital, Derby, United Kingdom; [9]University of Bradford, Bradford, United Kingdom. Group/Team: Tackling AKI investigators.*

Background: Acute kidney injury (AKI) is common and associated with poor outcomes. We sought to evaluate the effectiveness, at the hospital level, of a package of measures to reduce harm associated with AKI.

Methods: A multi-centre, pragmatic, stepped-wedge cluster randomised trial (SWCRT) was performed in five UK hospitals. The organisation-wide intervention consisted of AKI alerts, a care bundle and an educational program that was introduced sequentially across fixed three month periods until all hospitals were ultimately exposed to the intervention. The sequence was determined by random number generation. All patients with AKI aged ≥18 years hospitalised for >1day were included. Chronic dialysis was the only exclusion criterion. Data were collected in 3 month periods, with a minimum of 2 pre-exposure (control), one transition and a minimum of one exposed periods per site. The primary outcome was 30-day mortality associated with AKI, with pre-specified secondary endpoints and a nested evaluation of care process delivery.

Results: 24,059 AKI episodes were studied (incidence 7.6 cases/100 admissions); mean age was 72±17yrs; 62% had AKI stage 1, 21% AKI stage 2, 17% AKI stage 3. Overall 30d mortality was 24.5%, with no difference between control and intervention periods (OR 1.07, 95% CI 0.93-1.24). Hospital length of stay (LoS) was reduced in the intervention period; -0.2days (95% CI -0.4 to 0.1), -0.7days (-1.3 to -0.1) and -1.3days (-2.7 to 0.1) for tertiles with low, middle and high LoS, respectively. The incidence of AKI increased in the intervention period, likely reflecting improved AKI detection. Process measures were assessed in 1042 patients. In the intervention period, improvements were seen in several metrics including AKI recognition, medication optimization, fluid assessment and urinalysis; care bundle usage was 40% with variation between centres

(range 15-68%). The degree of improvement differed between centres, which will be explored in a qualitative analysis.

Conclusions: A complex, hospital-wide intervention to reduce harm associated with AKI resulted in improvements in delivery of care, improved AKI detection and a modest reduction in LoS, but did not alter AKI mortality.

Funding: Private Foundation Support

FR-PO1063

Fenoldopam in in Shiga Toxin-Related Hemolytic Uremic Syndrome

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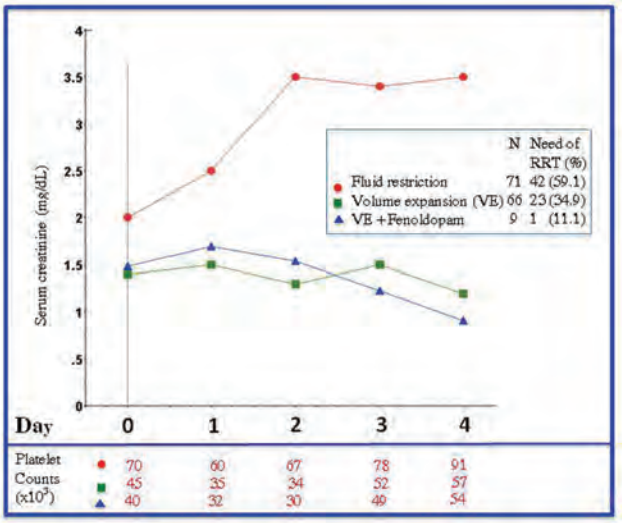
Background: The pathogenic sequence leading to renal damage in Shiga toxin-related hemolytic uremic syndrome (eHUS) includes endothelial injury, intravascular thrombi formation, microvascular occlusion and ischemic tissue injury. Early volume expansion (VE) reduces the number and severity of complication most likely by increasing organ perfusion. Fenoldopam (F), a dopamine-1 receptor agonist, is being widely used as an off-label treatment (T) for AKI as it induces renal vasodilation and favours perfusion, but we are unaware of its assessment in eHUS.

Methods: We describe our experience with F, in combination with VE, to treat 9 children with eHUS. FT was started immediately after eHUS was diagnosed. Renal resistance index (RRI) was measured on and off F. The disease course was compared with that observed in a cohort of patients receiving standard T(n=71) or early VE(n=66).

Results: Mean (SD) RRI decreased from 0.82(0.04) to 0.73(0.06) on F(-10.4%;p<0.00001). The figure compares the time-course of median serum creatinine during the initial 5 days of disease with the 3 T strategies, together with the platelet counts and the rate of RRT. An important reduction to 11.1% of the need of RRT was observed in patients treated with F(actually, a single patient required a single dialysis session) compared to either the standard T(59.1%) or the VE(34.9%) group. No patient treated with F showed signs of central nervous system involvement or any other complication and renal fuction quikly and fully recovered in all of them without sequels. No adverse event was observed. Despite the clearly ongoing and severe thrombotic microangiopathy (as evidenced by platelets count), combined T with F and VE was associated with an impressive favourable outcome.

Conclusions: If confirmed on a larger scale, FT may become an important addition to VE for improving the outcome of eHUS with important lifesaving potentials.



FR-PO1064

Results of a Randomized Multicentre Pilot Study of Sacubitril/Valsartan versus Irbesartan in Patients with CKD: United Kingdom Heart and Renal Protection (UK HARP)-III Trial

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Background: Angiotensin Receptor Neprilysin Inhibitor (ARNI) therapy inhibits the renin-angiotensin system (RAS) and increases concentrations of natriuretic and other vasoactive peptides. ARNI therapy may delay progression of kidney disease and prevent cardiovascular events. Trials among patients with heart failure have shown that treatment with ARNI significantly reduces the risk of cardiovascular events. However, the potential benefits in patients with CKD have not been studied. UK HARP-III is a randomized trial comparing the effects on kidney function, safety and tolerability of the ARNI sacubitril/valsartan (S/V) versus irbesartan (IRB) in patients with CKD.

Methods: Patients ≥18 years of age with either (i) an estimated glomerular filtration rate (eGFR) of ≥45 <60 mL/min/1.73m̊ and urine albumin:creatinine ratio (uACR) >20 mg/mmol; or (ii) eGFR ≥20 <45 mL/min/1.73 m² (regardless of uACR) were eligible to participate. After 4-7 week placebo run-in (including washout of RAS inhibitors), participants were randomly assigned S/V 97/103 mg twice daily or IRB 300 mg once daily. The primary outcome was measured glomerular filtration rate (mGFR) at 12 months. Other outcomes include effects on uACR, change in eGFR over time and the short-term safety and tolerability of S/V.

Results: 414 participants were randomized. Mean eGFR was 35.4 ml/min/1.73m² and median uACR was 54 mg/mmol. Allocation to S/V had no effect on mGFR at 12 months (difference -0.1 [SE 0.7] ml/min/1.73m²) nor eGFR at any time point. Allocation to S/V led to a non-significant 9% (95% CI -1 to 18) reduction in uACR. S/V was well-tolerated and was not associated with excess of any serious adverse events. Allocation to S/V reduced study average systolic and diastolic blood pressure by 5.4 (3.4-7.4) and 2.1 (1.0-3.3) mmHg respectively. There was a non-significant excess of hyperkalaemia (>5.5 mmol/l) among those allocated S/V vs IRB (32% vs 24%; p=0.10).

Conclusions: Compared to irbesartan, S/V had no measurable effect on GFR or uACR. S/V was well-tolerated and no major hazards were observed. A large randomized trial is required to assess the effects of S/V on cardiovascular and renal outcomes.

Funding: Commercial Support - Novartis Pharma AG

FR-PO1065

Aspirin Treatment in Primary Cardiovascular Prevention and Renal Disease Progression in CKD Patients: A Randomized Clinical Trials (AASER Study)

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Background: Aspirin (ASA) use for primary cardiovascular disease (CV) prevention is controversial in general population. Chronic kidney disease (CKD) patients have a high CV risk but no evidence is available about the use of aspirin in CKD patients to decrease CV risk and to reduce renal disease progression.

Methods: We conducted a prospective, multicentric open randomized trial that included 111 patients with estimated GFR (eGFR) <60 ml/min (stage 3 and 4) without previous CV events. Patients were randomly assigned to treatment with aspirin 100 mg/day (*n*: 50) or to continue the usual therapy (*n:61*). Mean follow up time was: 63.6±16.4 months. Outcomes: The primary end-point was a composite of non-fatal cardiovascular events and mortality. Secondary end-points included progression of renal disease doubling of serum creatinine, ≥50% decrease in estimated glomerular filtration rate or renal replacement therapy and bleeding episodes

Results: During long-term follow-up, 16 and 5 participants in control and ASA groups respectively suffered from a CV event (p=0.05). Eight patients suffered from a fatal or non-fatal coronary event in the control group and no patient in the ASA group experienced a coronary event (log rank 5.997, p=0.014). Seventeen patients in the control group reached the renal outcome in comparison with 3 patients in the ASA group (log rank: 5.849 p=0.016). Aspirin treatment decreased renal disease progression in a model adjusted for age, baseline kidney function and diabetes mellitus (HR, 0.272; 95% CI, 0.075-0.955; p= 0.045). No differences were found in bleeding episodes (2 in standard and 3 in ASA group) Limitations: Small sample size and not double blind trial.

Conclusions: Long-term treatment with low dose aspirin decreases coronary events and may slow the rate of progression of kidney disease.

FR-PO1066

CKD Antidepressant Sertraline Trial (CAST) Susan Hedayati,[5] Lucile Parker Gregg,[5] Thomas Carmody,[4] Nishank Jain,[2] Marisa S. Toups,[3] Augustus J. Rush,[1] Robert D. Toto,[6] Madhukar Trivedi.[4] *[1]Duke-NUS, Santa Fe, NM; [2]Little Rock VA Hospital, Little Rock, AR; [3]UT Dell Medical School, Austin, TX; [4]UT Southwestern Medical Center, Dallas, TX; [5]University of Texas Southwestern, Dallas, TX; [6]University of Texas Southwestern Medical Center, Dallas, TX*.

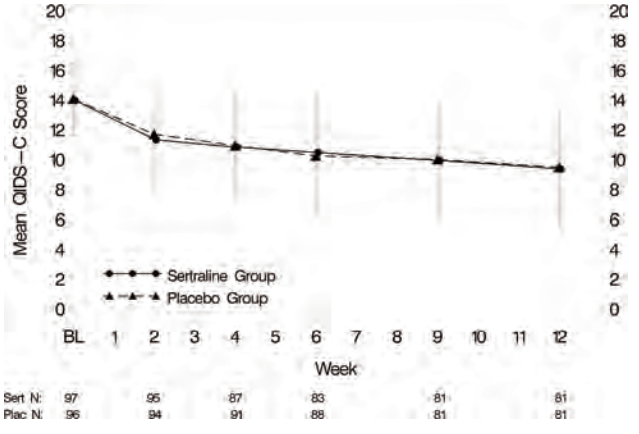
Background: Major Depressive Disorder (MDD) is prevalent in CKD patients and associated with morbidity and mortality. Efficacy and safety of selective serotonin reuptake inhibitors in these patients are unknown. CAST (Clinicaltrials.gov NCT00946998) is the first well-powered, randomized, double-blinded, placebo-controlled trial in nondialysis stages 3-5 CKD patients to determine if treatment with sertraline improves depression and quality of life (QOL) and is safe and tolerable.

Methods: After a 1-week placebo run-in, 201 patients with MDD, established by the Mini Neuropsychiatric Interview, were randomized to 12 weeks of 50 mg/day of sertraline or matching placebo, escalated to a maximum tolerated dose of 200 mg/day. The primary prespecified outcome was improvement in depression severity from baseline by the Quick Inventory of Depression Symptomatology Clinician-Rated scale (QIDS). Secondary outcomes were safety and improvement in QOL.

Results: Intention-to-treat analysis included 193 patients (CKD stages 3a, 3b, 4, and 5: 11%, 36%, 36%, 17%) who received at least one post-randomization outcome assessment. The baseline QIDS score was 14.0 ±2.4 in the sertraline (N=97) and 14.1 ±2.4 in the placebo (N=96) group. The median participation time was 12.0 weeks and median achieved dose 150 mg/day, not different between groups. The QIDS score changed by -4.1, 95% CI (-5.1, -3.1) in the sertraline and -4.2 (-5.0, -3.5) in the placebo group; between-group difference, -0.1 (-1.3 to 1.1), *P*=.82 (Figure). Serious adverse events and changes in QOL were comparable between groups. Nausea or vomiting (23 vs. 10%, *P*=.03) and diarrhea (13 vs. 3%, *P*=.02) occurred more frequently in the sertraline vs. placebo arm.

Conclusions: In nondialysis CKD patients, treatment with sertraline did not improve depression or QOL and increased adverse events. These data do not support the use of sertraline to treat depression in CKD, which can have significant impact on clinical practice. (Funding: 1R01DK085512)

Funding: NIDDK Support, Veterans Affairs Support



FR-PO1067

Rapid Bedside Plasma Volume (PV) and Measured GFR (mGFR) in Normal and CKD Subjects Dana Rizk,[4] Daniel Meier,[1] Ruben M. Sandoval,[3] Teresa Chacana,[5] Erinn S. Reilly,[1] Jesse C. Seegmiller,[6] Emanuel Denoia,[2] James S. Strickland,[1] Joseph Muldoon,[1] Bruce A. Molitoris.[3] *[1]FAST BioMedical, Carmel, IN; [2]Icon, San Antonio, TX; [3]Indiana University School of Medicine, Indianapolis, IN; [4]University of Alabama, Birmingham, AL; [5]University of Alabama at Birmingham, Birmingham, AL; [6]University of Minnesota, Minneapolis, MN*.

Background: Quantitative measurement of plasma volume (PV) and glomerular filtration rate (mGFR) remain arduous clinical tasks having wide ranges for individual subjects. Estimated GFRs (eGFRs), derived from endogenous markers such as creatinine, are commonly employed in both clinical AKI and CKD studies to evaluate severity of injury and disease progression. However, at the present time the eGFR results typically suffer in the healthy and end stage renal disease populations.

Methods: FAST BioMedical has developed a rapid PV and mGFR technique based on the plasma disappearance following a single IV injection containing a large 150kDa (12 mg) rhodamine derivative monitored as a signature of PV and small 5kDa fluorescein carboxy methylated dextrans (35mg) for mGFR determination, respectively. PV is quantified after only 15 minutes following injection by dilution of the large dextran which is stable for over 6 hours allowing repeat determinations without redosing.

Results: In a recently finished phase 2b study, involving 16 normal subjects and 8 CKD III and 8 CKD IV patients, injections were well tolerated and no SAEs were reported. A 24 hour repeat dose measurement in 8 healthy subjects showed PV reproducibility of better than +/- 5% and mGFR within 5%. In response to intravenous infusion of a 350 ml 5% albumin over 30 minutes the increase in PV, measured using dilution principles of the 150kd carboxy methylated dextran, was on average plus 290ml at 30 minutes post infusion. mGFR determination required three 0.5 ml blood draws over 2.5 hours and values compared well, +/- 5%, with standard Iohexol plasma disappearance studies using samples taken over 6 hours for all patients.

Conclusions: Use of this FAST BioMedical approach allows for the rapid bedside determination of PV, changes in PV with clinical maneuvers, accurate measurement of GFR and renal reserve (stimulated maximal GFR) while maintaining patient safety, measurement accuracy and reproducibility.

Funding: NIDDK Support

FR-PO1068

Effect of Drinking More Water on Kidney Function Decline in Adults with CKD: A Randomized Clinical Trial William F. Clark. *London Health Sciences Center, London, ON, Canada. Group/Team: Water Intake Trial (WIT) Investigators*.

Background: Drinking more water is associated with a slower rate of kidney function decline in animal experiments and human observational studies. We conducted a clinical trial to determine whether drinking more water slows the decline in estimated glomerular filtration rate (eGFR) over one year in patients with chronic kidney disease (CKD).

Methods: Design: Randomized controlled trial. **Setting**: Nine centers in Ontario, Canada (2013–17). **Participants**: Adults with stage 3 CKD and microalbuminuria. **Intervention**: The hydration group was coached to drink more water above their usual fluid intake and the control group to maintain usual fluid intake. **Analysis:** The primary outcome was the one-year change in eGFR. Secondary outcomes included the one-year change in plasma copeptin, 24-hr urine albumin, 24-hr creatinine clearance, and health-related quality of life. In the primary analysis patients were analyzed according to random assignment (intention to treat), and in additional analyses by protocol adherence, defined using 24-hr urine volume (per-protocol).

Results: Of 631 randomized patients (mean age 65, men [63%], diabetes [48%], mean eGFR 43 mL/min/1.73m^2) 2% died within one year and 95% of survivors provided one-year follow-up measurements. At 12 months, the 24-hr urine volume was 0.6 L/day higher in the hydration group than the control group (95% CI, 0.5 to 0.7; p<0.001). The average one-year decline in eGFR was 2.2 mL/min/1.73m^2 in the hydration group and 1.9 mL/min/1.73m^2 in the control group, and the adjusted between-group difference in change was -0.3 mL/min/1.73m^2 (95% CI, -1.7 to 1.2; p=0.74). Results were similar in the per-protocol analysis. No significant between-group difference in one-year change was seen for 24-hour urine albumin or health-related quality of life. However, at one year, plasma copeptin concentrations were lower in the hydration group than the control group (the between-group difference in one-year change was -2.3 pmol/L [95% CI, -3.9 to -0.6; p=0.009]), while 24-hr creatinine clearance was higher in the hydration group compared to the control group (the between-group difference in one-year change was 3.6 mL/min/1.73m^2 [95% CI, 0.8 to 6.5; p=0.012]).

Conclusions: Among patients with stage 3 CKD, the average one-year change in eGFR did not differ in patients who drank more water compared with those who continued their usual fluid intake.

Funding: Commercial Support - Danone Research

FR-PO1069

An Integrated Smartphone Application Improves Patient Safety and Intervention Adherence: A Randomized Controlled Trial (RCT) with an Active Control Group Sarbjit V. Jassal,[3,2] Stephanie W. Ong,[3] Kelly Min,[3] Akib Uddin,[3] Eveline C. Porter,[3] Joseph A. Cafazzo,[3] Emily Seto,[2] George Tomlinson,[3,2] Alexander G. Logan.[1,2] *[1]Mount Sinai Hospital, Toronto, ON, Canada; [2]University of Toronto, Toronto, ON, Canada; [3]University Health Network, Toronto, ON, Canada*.

Background: There are a large number of applications (apps) available for chronic kidney disease (CKD) management, but few have been rigorously evaluated in a RCT. We previously published the efficacy of the eKidneyCare App when used to monitor blood pressure (BP), medications, labs and symptoms (CJASN 2016). To establish the clinical effectiveness of using an integrated app system and including customizable algorithms to send real-time feedback we completed a 1-year prospective RCT comparing eKidneyCare (Active) to MyMedRec (Active Control), a widely-recommended, commercially available app that records similar medical information without providing feedback.

Methods: We randomly assigned patients with CKD 3b-5 or 5D, attending an outpatient renal clinic at UHN, to a mobile-health monitoring kit consisting of a Bluetooth-enabled home blood pressure(BP) monitor, and a smartphone preloaded with either the eKidneyCare or MyMedRec app. The primary outcome was the number of medication discrepancies at 1 year. Secondary outcomes included adherence to monitoring regime, use of the app over time, BP at study exit and feedback from patient-questionnaires.

Results: Between May and Sept 2016, a total of 182 adults (mean age, 57 years; 65% (n=118) men; 31% (n=57) diabetics) underwent randomization (93 MyMedRec; 89 eKidneyCare). Median follow up was 11.4 months (84% completed, 10% medical exit, 6% patient withdrawal). Medication discrepancies were more common in the MyMedRec group (mean 7.3, 5.1 in MyMedRec and eKidneyCare respectively; difference -2.2, 95% CI, -3.8 to -1.1). The number of BP readings taken per month was sustained longer and at significantly higher rates in the eKidneyCare group (median readings per month 16.8 vs 8.6, p<0.0001).

Conclusions: In this study, patients allocated to the eKidneyCare app participated more in self-monitoring behaviours and had fewer medication discrepancies than those

using the commercially available app. Our results suggest that integration and real-time feedback features in the app are critical components for success.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO1070

DIALOGUE Phase 2 Extension Studies of BAY 85-3934, Molidustat, a HIF-PH Inhibitor with Daily Oral Treatment in Anemic Subjects with CKD Tadao Akizawa,[2] Iain C. Macdougall,[3] Jeffrey S. Berns,[4] Thomas Bernhardt,[5] Thilo Krueger,[5] Megumi Taguchi,[1] Eriko Ogura,[1] Kazuma Iekushi.[6] *[1]Bayer Yakuhin, Ltd., Osaka, Japan; [2]Showa University School of Medicine, Tokyo, Japan; [3]King's College Hospital, London, United Kingdom; [4]University of Pennsylvania School of Medicine, Philadelphia, PA; [5]Bayer AG, 13353 Berlin, Germany; [6]Bayer Yakuhin, Ltd, Osaka, Japan.*

Background: Renal anemia is one of the most frequent complications of chronic kidney disease (CKD). Traditionally renal anemia is treated with erythropoiesis stimulating agents. The Hypoxia-inducible factor (HIF)-prolyl hydroxylase (PH) inhibitor, molidustat (BAY 85-3934), is developed for the oral treatment of anemia in subjects with CKD.

Methods: The clinical program included 3 randomized, multicenter main studies and 2 controlled, parallel group, open-label, multicenter extension studies, one in non-dialysis and one in dialysis subjects with anemia associated with CKD. Subjects enrolled in the main studies were planned to enter the 2 extension studies to prove long-term safety and efficacy of molidustat for a period of up to 36 months as measured by the change from baseline to post-baseline time points in Hb levels.

Results: In the hemodialysis study, mean Hb values at baseline were similar in the molidustat group (10.40 g/dL) and in the epoetin group (10.52 g/dL). Mean (SD) Hb values during treatment were 10.52 (0.557) g/dL in the molidustat group and 10.37 (0.471) g/dL in the epoetin group. Similar rates of subjects reported a TEAE in the molidustat group (91.2%) compared with the epoetin group (93.3%). In the non-dialysis study, mean Hb values at baseline were similar in the molidustat group (11.28 g/dL) and in the darbepoetin group (11.08 g/dL). Mean (SD) Hb values during treatment were 11.10 (0.508) g/dL in the molidustat group and 10.98 (0.571) g/dL in the darbepoetin group. Similar rates of subjects reported a TEAE in the molidustat group (85.6%) compared with the darbepoetin group (85.7%).

Conclusions: The oral HIF-PH inhibitor, molidustat may offer potential benefits for managing anemia in both dialysis and non-dialysis subjects. Future Phase 3 studies of larger size will be executed to further assess the effects of molidustat.

Funding: Commercial Support - Bayer AG

FR-PO1071

Head-to-Head Efficacy and Safety Comparisons of a Novel Calcimimetic Agent (Evocalcet) with Cinacalcet in Japanese Hemodialysis Patients with Secondary Hyperparathyroidism: A Randomized Clinical Trial Masafumi Fukagawa,[1] Ryutaro Shimazaki,[2] Tadao Akizawa.[3] *[1]Tokai University School of Medicine, Kanagawa, Japan; [2]Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan; [3]Showa University School of Medicine, Tokyo, Japan. Group/Team: the Evocalcet Study Group.*

Background: Cinacalcet is a potent calcimimetic agent used to treat secondary hyperparathyroidism (SHPT) in hemodialysis (HD) patients. Because there are many refractory patients who cannot tolerate cinacalcet owing to gastrointestinal (GI) symptoms, we developed evocalcet, a new oral calcimimetic agent. Here, we compared the efficacy and safety between evocalcet and cinacalcet in Japanese HD patients with SHPT.

Methods: This was a multicenter, randomized, double-blind, double-dummy, parallel-group, phase 3 trial. Evocalcet and cinacalcet were administered within the dose ranges of 1–8 mg/day and 12.5–100 mg/day, respectively. The primary efficacy endpoint was the non-inferiority of evocalcet to cinacalcet at achieving the target intact parathyroid hormone (iPTH) level of 60–240 pg/mL (target range in Japan) during weeks 28–30 (non-inferiority margin, 15% in the per protocol set (PPS)). For safety, adverse events (AEs) related to GI symptoms (abdominal discomfort, nausea, vomiting, abdominal distension, and decreased appetite) and serum calcium levels were evaluated.

Results: In total, 639 subjects were randomized. Among 519 patients in the PPS, the proportion of patients who achieved the target iPTH level was 72.7% (184/253) and 76.7% (204/266) in the evocalcet and cinacalcet groups, respectively. The estimated intergroup difference in the achievement rate was −4.0% (95% CI −11.4%, 3.5%, p=0.002 for non-inferiority). The proportion of patients who achieved a ≥30% reduction in iPTH level from baseline was comparable. GI AEs were observed in 18.6% (evocalcet) vs 32.8% (cinacalcet) of patients (difference −14.2% [95% CI −20.9%, −7.5%], p<0.001). The rates for decreased serum calcium level from baseline were comparable.

Conclusions: Non-inferiority of evocalcet to cinacalcet was verified in terms of PTH suppression, with a lower incidence of GI AEs in the evocalcet group. Our results suggest that evocalcet may be a potent alternative to existing calcimimetics with a wider safety margin for management of SHPT.

Funding: Commercial Support - Kyowa Hakko Kirin Co., Ltd.

FR-PO1072

Effect of Phosphate Binders on Biochemical and Vascular Outcomes in Patients with Non-Dialysis Dependent CKD Csaba P. Kovesdy,[1] Jun Ling Lu,[1] Zhongji Han,[1] Fridtjof Thomas,[1] Leigh D. Quarles,[1] Nabil Jarmukli.[2] *[1]University of Tennessee Health Science Center, Memphis, TN; [2]Salem VAMC, Salem, VA.*

Background: Abnormal phosphate (P) homeostasis develops early in CKD and is associated with adverse clinical outcomes. It is unclear if normalization of P homeostasis results in improved clinical outcomes in patients with non-dialysis dependent (NDD) CKD.

Methods: We randomized 120 patients with CKD stages 3-4 in a 1:1:1 ratio to open-label lanthanum carbonate, calcium acetate or dietary phosphorus restriction for one year (3 months titration and 9 months maintenance). The co-primary outcomes were month 12 (vs. baseline) biochemical (serum and urinary P, PTH, calcium, bone-specific alkaline phosphatase [bALP], and FGF-23) and vascular parameters (coronary artery calcium [Agatson score], arterial stiffness [pulse wave velocity, PWV] and endothelial dysfunction [reactive hyperemia index, RHI]) in all patients. Secondary outcomes were between-treatment differences in change for each parameter between month 12 and baseline. All analyses were intention-to-treat.

Results: Patients were 66.1±11.4 years old, 87% male, 52% African American, 55% diabetic, and their baseline eGFR was 32±10 ml/min/1.73m^2. Baseline characteristics were similar between the intervention arms (p>0.5). 107 of 120 (89%) randomized patients completed 12 months of follow-up. Differences were not significant at month 12 (vs. baseline) for any of the outcomes (**Table**) except bALP and FGF-23. Changes for all outcomes were similar in the three arms except for PTH, which was suppressed more effectively by calcium acetate (p<0.001, data not shown).

Conclusions: A 1-year intervention to limit P absorption using dietary restriction or two different P binders resulted in decreased bALP suggesting improvement in bone turnover, but no other significant changes in biochemical or vascular parameters in patients with NDD CKD. (NCT01357317)

Funding: Veterans Affairs Support, Commercial Support - Shire

	Baseline	Month 12	p
Phosphorus (mg/dl)	3.8±0.6	3.7±0.8	0.15
PTH (pg/ml)	141 (105, 203)	146 (92,204)	0.5
TRP (%)	0.63±0.14	0.64±0.16	0.5
Calcium (mg/dl)	9.2±0.5	9.1±0.6	0.15
Bone-specific ALP (mcg/L)	15.8 (12.1, 21.1)	13.8 (10.6, 17.6)	<0.001
FGF-23 (pg/ml)	133 (86, 189)	132 (99, 216)	0.002
PWV (m/sec)	11.5 (8.7, 13.1)	10.7 (8.5, 13.7)	0.4
CAC (Agatson score)	356 (40,1016)	309 (51,1048)	0.5
RHI	2.03±0.59	2.05±0.61	0.8

P values are for paired t tests

FR-PO1073

Comparison of Lanthanum Carbonate with Calcium Carbonate for the Progression of Coronary Artery Calcification in Hemodialysis Patients Hiroaki Ogata,[2] Masafumi Fukagawa,[3] Hideki N. Hirakata,[1] Tatsuo Kagimura,[4] Tadao Akizawa.[2] *[1]Fukuoka Renal Clinic, Fukuoka City, Japan; [2]Showa University School of Medicine, Yokohama, Japan; [3]Tokai University School of Medicine, Isehara, Japan; [4]Translational Research Informatics Center, Kobe, Japan. Group/Team: On behalf of the LANDMARK Study Group.*

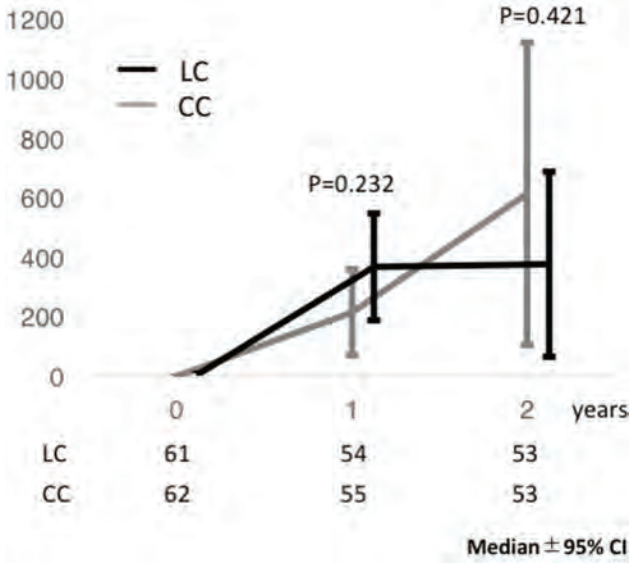
Background: The LANDMARK study is a multicenter, randomized, open-label, parallel assignment study comparing the effects on cardiovascular mortality and morbidity of a non-calcium phosphate (P) binder, lanthanum carbonate (LC), with calcium carbonate (CC) in hemodialysis patients. This adjunct study (LANDMARK-SS) investigated whether LC delayed the progression of coronary artery calcification compared with CC.

Methods: Adult hemodialysis patients with at least one risk factor for vascular calcification (age >65 years, postmenopausal women, type 2 diabetes mellitus), were randomly assigned to receive LC or CC. Doses of LC and CC were titrated to achieve target serum P levels of 3.5–6.0 mg/dL. If this was not achieved with the maximum tolerated dose, other non-calcium-based P binders were added in the LC group and P binders other than LC in the CC group. The primary endpoint was the change in Agatston coronary artery calcification score (CACS) from baseline.

Results: Median changes in CACS in the LC and CC groups were 360 (95% confidence interval [CI], 180–541) and 211 (95%CI 77–366), respectively, at 1 year, and 368 (95%CI 57–680) and 611 (95%CI 105–1118) at the end of the 2-year study. The increase in CACS appeared to lessen after 1 year with LC, but these differences were not statistically significant, and stratified analysis based on concomitant treatment, age, and baseline CACS also showed no significant differences in CACS progression between groups.

Conclusions: We conclude that LC did not significantly attenuate calcification in comparison with CC over 2 years in hemodialysis patients.

Funding: Commercial Support - Bayer Yakuhin, Ltd.



Changes in total Agatston CACS from baseline

FR-PO1074

Efficacy and Safety of Short-Term Treatment with Sodium Zirconium Cyclosilicate (ZS-9) for Hyperkalemia: Open-Label, Phase 3 Trial David K. Packham,[1] Steven Fishbane,[2] Pablo E. Pergola,[3] Edgar V. Lerma,[4] Javed Butler,[5] Stephan Von haehling,[6] Scott H. Adler,[7] Bhupinder Singh,[8,9] Philip T. Lavin,[10] Peter A. McCullough,[11] Mikhail Kosiborod,[12] Bruce S. Spinowitz.[13] *[1]U. of Melbourne, Melbourne, NSW, Australia; [2]Hofstra Northwell Health School of Med., Great Neck, NY; [3]Renal Associates PA, San Antonio, TX; [4]UIC/ Advocate Christ, Oak Lawn, IL; [5]Stony Brook U., Stony Brook, NY; [6]U. of Göttingen Medical Centre, Göttingen, Germany; [7]AstraZeneca, Gaithersburg, MD; [8]ZS Pharma Inc., part of AstraZeneca, San Mateo, CA; [9]University of California, Irvine, Irvine, CA; [10]Boston Biostatistics Research Foundation, Framingham, MA; [11]Baylor U. Medical Center, Dallas, TX; [12]Saint Luke's Mid America Heart Institute, Kansas City, MO; [13]New York Presbyterian Queens, New York, NY.*

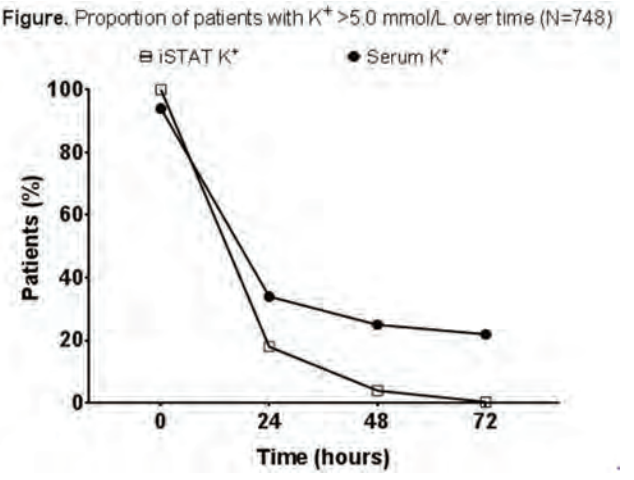
Background: Correction of hyperkalemia (HK) is important for the clinical management of patients (pts). Sodium zirconium cyclosilicate (ZS-9) is a selective, inorganic, potassium (K)-binder. We report results of ≤72h of ZS-9 treatment from the largest study of treated HK pts to date.

Methods: This international, open-label, single-arm trial with no dietary K or RAASi restrictions enrolled 751 outpatients (≥18y) with HK (K≥5.1mmol/L). Pts received 10g ZS-9 TID for 24–72h until normokalemic (K3.5–5.0 mmol/L; blood K measured by point-of-care device [iSTAT]). Treatment decisions were based on iSTAT K, generally considered to be highly accurate; efficacy endpoints were based on serum K from central lab per usual practice. Endpoints were achievement of normokalemia, overall response rate (%), change in K from baseline (ΔK), and adverse events (AE).

Results: 99.3% of pts completed. By 24h, ΔK was -0.8 mmol/L (iSTAT, -14.9%; from 5.5 to 4.7 mmol/L) and -0.7 mmol/L (serum, -12.7%; from 5.6 to 4.9 mmol/L). Overall, 99.5% (95% CI [99%, 100%]) of pts achieved normokalemia by iSTAT and 77.9% (95% CI [75%, 81%]) by serum K. 100% of pts experienced a reduction in K (regardless of measurement method) with 92% having K reductions ≥0.5 mmol/L; 0.4% of pts had iSTAT K>5.0mmol/L and 22% had serum K>5.0mmol/L (Figure). 4.1% of pts experienced an AE. Most common were nausea (0.5%) and urinary tract infection (UTI; 0.5%); 1 pt each had peripheral edema and serum K3.0-<3.5mmol/L. UTI was the 1 SAE (resulting in the only hospitalization), and 2 pts discontinued due to AEs (UTI, flatulence, and upper abdominal pain). No deaths occurred.

Conclusions: ZS-9 rapidly and reliably normalized K in nearly all HK pts, with a safety profile similar to prior studies.

Funding: Commercial Support - AstraZeneca



FR-PO1075

Novel Intermittent Pneumatic Compression Device Promotes Early Cannulation Tej M. Singh.[1,2] *[1]Palo Alto Medical Foundation, Los Altos Hills, CA; [2]Fist Assist Devices, LLC, Los Altos Hills, CA.*

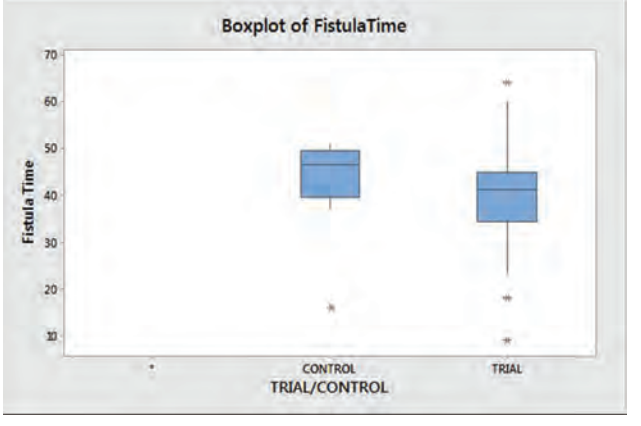
Background: Arteriovenous fistulas (AVF) are the preferred for hemodilaysis access. However, AVF maturation has been poor globally. Poor maturation often leads to increased catheter contact time and costs. Intermittent compression of upper arm veins may aid in forearm vein dilation. Early use of non-invasive devices may help in maturation and possible early AVF needle cannulation.

Methods: After AVF creation, an intermittent pneumatic compression device [Fist Assist® (FA)] was applied to allow cyclic compression of 60 mm Hg daily for 90 days. Fourty (n=40) AVF patients were in the study arm to test vein dilation with FA and needle cannulation time. Of these patients, twenty-four (n=24) had brachiocephalic fistulas (BCF), while seventeen (n=16) had radiocephalic fistulas (RCF). Controls (n=16) used a sham device. Vein size was measured and recorded at baseline and after 90 days by duplex measurement. Clinical results (percentage increase) were recorded and tested for significance. Time to fistula cannulation was recorded as the difference between surgery date and needle placement.

Results: After three months, the mean percentage increase in vein diameter in the FA treatment group with RCF was significantly larger than those with BCF at proximal locations of 5 cm, 10 cm, and 15 cm from the anastomosis (p=0.000, 0.000, and 0.017, respectively) compared to the control group. Fistulas treated with the FA device were cannulated sooner by 4 days in the clinic (Control: 43.8±8/7 days vs. FA: 39.2±9.6) [Table 1]. All fistulas treated with FA are still functional with no reported thrombosis or extravasations.

Conclusions: Improved AVF maturation is important for vascular access care and has been an important goal. Early application of an intermittent pneumatic compression may be successful in AVF maturation at longer time points as demonstrated in this comparative study. Pneumatic devices may assist in early cannulation of AVF.

Funding: Private Foundation Support



MEAN FISTULA TIME A significant decrease in mean fistula time was observed for the Treatment group vs. Control group

FR-PO1076

Prospective, Randomized, Multi-Center, Double-Blind, Controlled, Two-Period, Two-Treatment, Crossover, Phase II Trial to Evaluate the Safety and Efficacy of Alanyl-Glutamine in Peritoneal Dialysis

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Background: Recent meta-analyses concluded that the past 20 years development of dialysis fluids with low concentration of glucose degradation products did not lead to improved peritonitis rates, membrane failure or technique drop out of peritoneal dialysis (PD) patients. In early clinical testing, addition of alanyl-glutamine (AlaGln) to a single dwell of glucose-based PD fluids restored peritoneal cellular stress responses and leukocyte function. This study tests effects of a novel AlaGln supplemented PD fluid on relevant biomarkers in a nation-wide trial.

Methods: In a prospective, double-blinded, cross-over design (EudraCT-2013-000400-42) stable PD outpatients were enrolled to undergo 16 weeks of treatment, 8 weeks with standard PD fluid (Physioneal 40, Baxter) and 8 weeks with AlaGln supplemented standard PD fluid (Physioneal 40 and Dipetiven [Fresenius-Kabi]), in a randomized order. As primary outcome parameters cancer-antigen 125 (CA-125) appearance rate as marker of peritoneal cell mass and ex-vivo stimulated interleukin 6 (IL-6) release as marker of peritoneal immune competence were assessed in effluents of standard peritoneal equilibration tests at 1h (IL-6 release) and 4h (CA-125).

Results: Out of 54 enrolled PD patients in 8 Austrian centers, 50 patients were randomized. In the full analysis set (n=41), addition of AlaGln significantly increased CA-125 appearance rate (mean treatment difference: 46.7 U/min [95% CI: 23.5-69.9], p=0.0001) and log 10 of ex-vivo stimulated IL-6 release (mean treatment difference: 0.15 [95% CI: 0.04-0.26], p=0.004). Higher levels of stimulated TNFα release and lower levels of peritoneal protein loss supported the beneficial effect of intraperitoneal AlaGln supplementation. No adverse events or safety signals were observed with AlaGln, all peritonitis episodes in the safety population (n=47) occurred during standard PD fluid treatment.

Conclusions: A novel AlaGln-supplemented PD fluid improves important biomarkers of mesothelial cell status and peritoneal immune competence compared to treatment with a standard dual-chamber PD fluid.

Funding: Commercial Support - Zytoprotec GmbH

FR-PO1077

Twelve Weeks of Home-Based Exercise Training Improves Strength, Function and Quality-of-Life Measures in Elderly Hemodialysis Patients

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Background: Maintenance hemodialysis (MHD) patients exhibit significantly impaired physical function and skeletal muscle wasting. We examined whether 12 weeks of home-based exercise training improves cardiopulmonary function, muscle mass, strength, QOL, and cognitive function in elderly MHD patients.

Methods: Twenty-three elderly MHD patients (66 ± 7.7 yrs) were randomized to either a 12-week home-based exercise program (n=9) or usual care (n=14). Measures of peak VO_2, thigh muscle quality (percentage intramuscular fat [IMF]) evaluated by magnetic resonance imaging (MRI), body composition by DXA scan, upper and lower body strength, six-minute walk test (6MWT), and QoL were determined.

Results: Peak VO_2 (ml/kg/min) increased 13% in the exercise group while no significant changes occurred among controls. Exercise time improved 44% in the exercise group while there was 14% reduction among controls (p=0.06). There were no significant changes in thigh muscle IMF % by MRI or leg fat % by DXA in either group. Distance covered during the 6MWT was marginally improved in both groups. Number of sit-to-stand repetitions in 1 minute was improved by 10% in the exercise group and was unchanged in usual care. Exercised patients improved 12 % in lower body strength. Both physical and mental component scores were improved by approximately 12% in the exercise group.

Conclusions: In this interim analysis, we observed that 12 weeks of exercise training is potentially effective in improving cardiopulmonary function, strength and quality of life in elderly MHD patients.

Funding: Veterans Affairs Support

Table1. Exercise capacity, strength, and quality of life measures in the exercise and control groups before and after the 12-week period.

Variables	Ex (*n*=9)			UA (*n*=14)			*p*-value Interaction
	Baseline	12 week	Δ (%)	Baseline	12 week	Δ (%)	
Peak VO_2 (ml/kg/min)	14.0±3	16.8±3	13±13	15.2±3.4	14.7±4	-3±14	0.28
Estimated METs	4.8 ±2	5.7±2	21±23	4.5±1.5	4.3±2	-6±17	0.32
Exercise time (seconds)	528±210	722±238	44±36	479±164	455±162	-1.4±25	0.06
6MWT (meters)	353±72	362±84	4±16	312±67	324±53	5±10	0.94
1 sit-stand # of repetitions	22±7	24±8	10±30	18±8	18±7	0.3±35	0.71
Left leg % IMF	18±5	18.3±4	2±22	18.5±5	18±3	0.5±24	0.76
Right leg % IMF	15.7±4	16.8±3	9±23	18.5±5	18.6±6	4±25	0.77
% Leg Fat (DXA)	28.1±7	28.3±8	0.2±7	33±9	35.6±8	2±6	0.68
Upper body strength (lbs.)	65±16	67±20	3±11	59±32	58±32	-1.4±19	0.85
Lower body strength (lbs.)	68±20	77±26	12±17	70±27	69±28	0±29	0.57
PCS	42±10	49 ± 9	14±26	43±6.6	42±7	0.5±13	0.14
MCS	50±15	55±5.5	7±20	53 ±10	53±11	-1.3±13	0.42

PCS=Physical component score, MCS= Mental component score

Table 1. Exercise capacity, strength, and quality of life measures in the exercise and control groups before and after the 12-week period.

FR-PO1078

Safety and Cardiovascular Efficacy of Spironolactone (SPL) in Dialysis-Dependent ESRD (SPin-D): A Pilot Trial of the NIDDK Hemodialysis Novel Therapies Consortium

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Background: Small trials suggest that SPL reduces cardiovascular events in maintenance hemodialysis patients but the optimal dose for a large, clinical outcomes trial is unknown.

Methods: Multicenter, randomized, double-blind placebo(PL)-controlled trial of SPL at 12.5, 25, or 50 mg per day for 36 weeks for patients receiving maintenance hemodialysis. The trial aimed to evaluate safety (primary) and generate estimates of efficacy on cardiac structure and function. Randomization was based on a 2:1 ratio for PL vs each SPL dose.

Results: 129 patients were randomized. Hyperkalemia and hypotension events were more frequent with SPL 50 mg/day than with lower doses, but did not result in more frequent study drug reduction or discontinuation than PL (Table). There were no differences in change from baseline to week 36 in the primary efficacy measure of diastolic function.

Conclusions: SPL appears to be reasonably safe at doses ranging from 12.5 to 50 mg per day in a clinical trial setting with regular monitoring. The greater rate of hyperkalemia at 50 mg suggests that safety measures such as dose titration/reduction algorithms should be incorporated in a clinical outcomes trial if a 50 mg dose is used.

Funding: NIDDK Support

Safety Outcomes

	Placebo N=51	SPL 12.5 mg N=27	SPL 25 mg N=26	SPL 50 mg N=25	P value for trend	P value SPL vs Placebo
Primary						
K >6.5 mEq/L, # per 100 pt-wk	1.20	0.71	0.55	2.42	0.08	0.90
Serious hypotension[1], # per 100 pt-wk	0	0.30	0	0.30	NE[6]	NE[6]
Secondary						
Serious hyperkalemia[2], # per 100 pt-wk	0.30	0.20	0	1.51	NE[6]	0.16
K >6.0 mEq/L, # per 100 pt-wk	3.50	2.12	2.18	5.04	0.08	0.50
Per-patient K, mEq/L, mean (SD)	4.84 (0.50)	4.85 (0.44)	4.76 (0.43)	4.96 (0.43)	0.47	0.84
Recurrent intra-dialytic hypotension[3], # per 100 pt-wk	4.14	3.94	4.25	6.75	0.01	0.17
Inter-dialytic hypotension[4], # per 100 pt-wk	0.85	0.81	0.87	0.91	0.59	0.73
Study drug reduction or discontinuation, # (%)	15 (29.4)	4 (14.8)	6 (23.1)	8 (32.0)	0.60	0.42
Death[5], # (%)	2 (3.9)	0	2 (7.7)	1 (4.0)	NE[6]	>0.99

[1]Requiring hospitalization or ER visit. [2]Requiring hospitalization, extra dialysis, or resin. [3]Systolic bp<80 or treatment for hypotension during 3 dialysis sessions within 30 days. [4]Systolic bp <90 or change in bp medication for hypotension between dialysis sessions. [5]No deaths due to hyperkalemia. [6]Non-estimable due to 0 values in ≥1 group.

FR-PO1079

Effect of Hemodialyzer Characteristics on the Prognosis of Elder Dialysis Patients with Early Dialysis Stage (E-HOPED Study)

Ikuto Masakane,[1] Jun Minakuchi,[2] Hideki Kawanishi,[4] Kosaku Nitta.[3] *[1]Honcho-Yabuki Clinic, Yamagata, Japan; [2]Kawashima Hospital, Tokushima, Japan; [3]Tokyo Women's Medical University, Shinjuku-ku, Japan; [4]Tsuchiya General Hospital, Hiroshima, Japan. Group/Team: E-HOPED Study Group.*

Background: Increasing older dialysis patients have to continue dialysis because of few chances of renal transplantation so that it has been an urgent issue what kind of

dialysis prescription could ameliorate QOL and survival rate of them. In recent years high flux dialysis have been universally performed, however, its evidences have not been established especially for elder dialysis patients.

Methods: Eight hundred and two incident dialysis patients as greater than 70 years old were recruited to the study. The patients were randomly assigned to the following 2 groups; Group A as treated with low flux ethylenevinylalcohol (EVAL) membrane, Group B as treated with high flux synthetic membranes mainly of polysulfone (PS). 5-year survival rate as the primary outcome was compared between Group A and Group B by Kaplan-Meier Analysis. Secondary outcomes such as body weight, serum creatinine, serum albumin and hemodynamic indices during dialysis were also evaluated. Safety evaluation were performed on cause of death, CVD event, hosipitalization and vascular access failure.

Results: Seven hundred thirty-four patients, 363 patients in Group A and 371 patients in Group B, were analyzed for survival rate as a full analysis set. The mean age in each group was 78.1 in Group A and 77.9 in Group B. One-year, 2-year, 3-year, 4-year and 5-year survival rates in each group were 95.6%, 87.1%, 80.1%, 67.7% and 60.9% respectively in Group A; 95.3%, 89.3%, 84.9%, 79.4% and 68.9% in Group B. There were no differences between Group A and Group by Kaplan Meier analysis (Log-rank P value, 0.089). Secondary outcomes and safe aspects were not different between Group A and Group B.

Conclusions: In the current study, we did not find beneficial effects of high flux dialysis on the elder dialysis patients survival. Recently several adverse effects of PS membrane have been reported such as anaphylaxis, thrombocytopenia and deterioration in peripheral circulation during dialysis session and these could be recognized to be related to the bioimcopmpatibility of PS membrane. EVAL membrane is biocompatible especially for hemodynamic stability during dialysis session. Biocompatible aspect of EVAL membrane might have modified the outcome of elder dialysis patients even if it is a low flux membrane.